Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Enantioselective Total Synthesis of Virosaine A and Bubbialidine

Hideki Miyatake-Ondozabal, Linda M. Bannwart and Karl Gademann*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

E-mail: Karl.gademann@unibas.ch

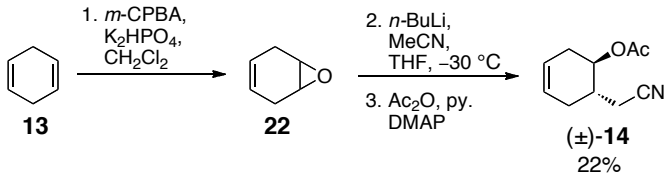
Table of contents

General remarks

All reactions were performed in flame-dried round-bottomed flasks under a positive pressure of argon. The following anhydrous reaction solvents were obtained by filtration and passing through activated anhydrous alumina columns (Innovative Technology solvent purification system); THF, CH_2Cl_2, Et_2O, PhMe. All other solvents (DMF, MeOH, MeCN, $CHCl_3$, EtOH) and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Syringes or stainless steel cannula were used to transfer air and moisture sensitive liquids and solutions. Analytical thin layer chromatography (Merck silica gel 60 F254 plates) was utilized for monitoring reactions and visualized by UV light (254 nm and 350nm) or by staining using vanillin or potassium permanganate solution followed by gentle heating with a heat gun. Flash Chromatography was performed using SiliCycle silica gel 60 (230-400 Mesh) and R_f values of compounds are indicated. ^{1}H NMR spectra were recorded on Varian Gemini Bruker DPX 400 MHz or Bruker DRX 500 MHz spectrometers at 298K in the indicated deuterated solvent, unless otherwise stated. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak (δ 7.26 ppm for $CHCl_3$, δ 3.31 ppm for MeOH). ^{13}C NMR spectra were recorded with ^{1}H-decoupling on Varian Gemini Bruker DPX 100 MHz or Bruker DRX 125 MHz spectrometers at 298K in the indicated deuterated solvent, unless otherwise stated. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak (δ 77.16 ppm for $CHCl_3$, δ 49.00 ppm for MeOH). Melting points (Mp) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Varian 800 FT-IR ATR spectrometer and data are reported in terms of frequency of absorption (v, cm^{-1}). Optical rotations $[\alpha]_D$ were recorded at 24.5 °C on a Jasco P-2000 digital polarimeter with a path length of 1 dm, using the 589.3nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. All mass spectra (HRMS-ESI) were recorded by the Mass spectrometry service of University of Bern on Sciex QSTAR Pulsar mass spectrometer using electrospray ionization.

Experimentals and Procedures

*Synthesis of acetate (±)-**14***[1]



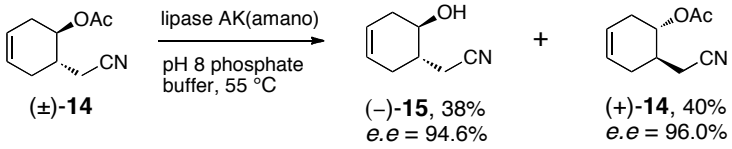
To a stirred solution of 1,4-cyclohexadiene (22 g, 267 mmol) in CH_2Cl_2 (1 L) at 0 °C, K_2HPO_4 (108 g, 600 mmol) was added followed by the portion-wise addition of *m*-CPBA (90 g, 353 mmol). The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (800 mL) and the aqueous layer was extracted with Et_2O (2 x 1.5 L). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give epoxide **22** as a yellow liquid (13 g, 50%). This material was used in the following step without further purification.

n-BuLi in hexane (2.5 M; 73 mL) was added drop-wise to a solution of acetonitrile (10 mL, 196 mmol) in THF (300 mL) at –30 °C and the resulting yellow solution was stirred for 30 min. Epoxide **22** (13 g, 135 mmol) in THF (85 mL) was then added over 25 min and the resulting mixture was stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (500 mL) and the aqueous layer was extracted with Et_2O (2 x 600 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a crude alcohol (18 g) as a yellow-brown oil. This material was used in the following step without further purification.

To a stirred solution of crude alcohol (18 g) in CH_2Cl_2 (45 mL), pyridine (16 mL) and DMAP (82 mg) were added and stirred for 5 min. Acetic anhydride (25 mL) was then added drop-wise over 25 min and stirred for 20 h at room temperature. The reaction was quenched with H_2O (800 mL) and the aqueous layer was extracted with Et_2O (2 x 800 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ solution (2 x 500 mL) and dried ($MgSO_4$). Rotary evaporation followed by silica gel column chromatography (Et_2O : pentane 1 : 4 to 2 : 3) gave acetate (±)-**14** (8.8 g, 22% over three steps) as a colourless oil: $\mathbf{R_f}$ 0.65 (Et_2O : pentane 1 : 1); **IR (film)** 3035, 2927, 2246, 1729, 1436, 1372, 1234, 1035, 985 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.66 – 5.57 (m, 2H), 4.86 – 4.80 (m, 1H), 2.57 – 2.42 (m, 2H), 2.51 (dd, J = 16.7, 5.2 Hz, 1H), 2.32 (dd, J = 16.7, 7.7 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.12 – 2.00 (m, 2H), 2.09 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.6, 124.7, 124.3, 118.2, 72.4, 35.2, 30.9, 30.3, 21.2, 20.3; ***m/z* (ESI)** 180 $(M + H)^+$. The provided reference does not report the corresponding experimental data.

[1] Kato, N.; Inada, M.; Sato, H.; Ito, S.; Shoji, M.; Ueda, M. *Tetrahedron Lett.* **2007**, *48*, 7702.

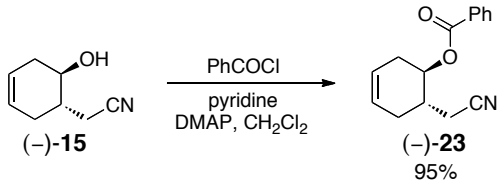
*Synthesis of alcohol (–)-**15** and acetate (+)-**14***[1]



A stirred solution of acetate (±)-**14** (8.8 g, 49.1 mmol) and amanolipase AK (2.87 g) in phosphate buffer solution (pH-8; 176 mL) was heated at 55 °C for 21 h. The reaction was diluted with H_2O (300 mL) and the aqueous layer was extracted with Et_2O (2 x 300 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 2 : 3 to 1 : 1) to give alcohol (–)-**15** (2.56 g, 38%, e.e = 94.6%) and acetate (+)-**14** (4.40 g, 49%, e.e = 77%) as colouress oil. Acetate (+)-**14** (4.40 g, e.e = 77%) was re-submitted to enzymatic kinetic resolution conditions (44 h at 55 °C) to give acetate (+)-**14** (3.54 g, 40%, e.e = 96.0%): alcohol (–)-**15** - $\mathbf{R}_f$ 0.48 (EtOAc : pentane 1 : 1); $[\alpha]_D$ −135.8° (*c* 0.52, MeOH); **IR (film)** 3426, 3031, 2912, 2247, 1435, 1342, 1068, 1050, 968 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.64 – 5.57 (m, 2H), 3.76 – 3.70 (m, 1H), 2.63 (dd, *J* = 16.7, 4.3 Hz, 1H), 2.55 (dd, *J* = 16.8, 6.9 Hz, 1H), 2.46 – 2.35 (m, 2H), 2.09 – 1.95 (m, 3H), 1.92 (*br*. s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 125.3, 124.6, 118.8, 69.6, 37.7, 34.9, 30.5, 20.1; ***m/z* (ESI)** 138 $(M + H)^+$. For acetate (+)-**14** – $[\alpha]_D$ +111.4° (*c* 0.53, MeOH). The provided reference does not report the corresponding experimental data.

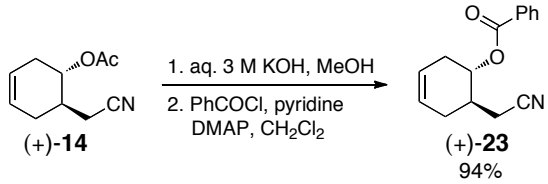
Enantiomeric excess determination

The enantiomeric excess was determined on their benzoate derivatives as followed.



To a stirred solution of alcohol (–)-**15** (25 mg, 0.18 mmol) and pyridine (0.045 mL, 0.57 mmol) in CH_2Cl_2 (1 mL), benzoyl chloride (0.037 mL, 0.32 mmol) was added and the resulting mixture was stirred for 15 h at room temperature. The reaction was quenched with H_2O (3 mL) and the aqueous layer was extracted with Et_2O (2 x 3 mL). The combined organic layers were washed with saturated aqueous $CuSO_4$ solution (2 x 3 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 1 : 4 to 2 : 3) to give benzoate (–)-**23** (42 mg, 95%) as a colourless oil: $\mathbf{R}_f$ 0.63 (Et_2O : pentane 1 : 1); $[\alpha]_D$ −153.9° (*c* 0.54, MeOH); **IR (film)** 3034, 2922, 2246, 1714, 1601, 1451, 1312, 1268, 1111, 1026 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.06 – 8.04 (m, 2H), 7.59 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.48 – 7.44 (m, 2H), 5.72 – 5.63 (m, 2H), 5.13 – 5.07 (m,

1H), 2.71 – 2.54 (m, 3H), 2.43 – 2.40 (m, 1H), 2.37 (dd, J = 13.7, 7.9 Hz, 1H), 2.27 – 2.09 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.0, 133.4, 129.9, 129.7 (2C), 128.6 (2C), 124.8, 124.3, 118.2, 72.8, 35.4, 30.9, 30.3, 20.4; **HRMS (ESI)** calc. for $C_{15}H_{16}NO_2^+$: $(M + H)^+$, 242.1176; Found: $(M + H)^+$, 242.1182.



(+)-**14** (+)-**23** 94%

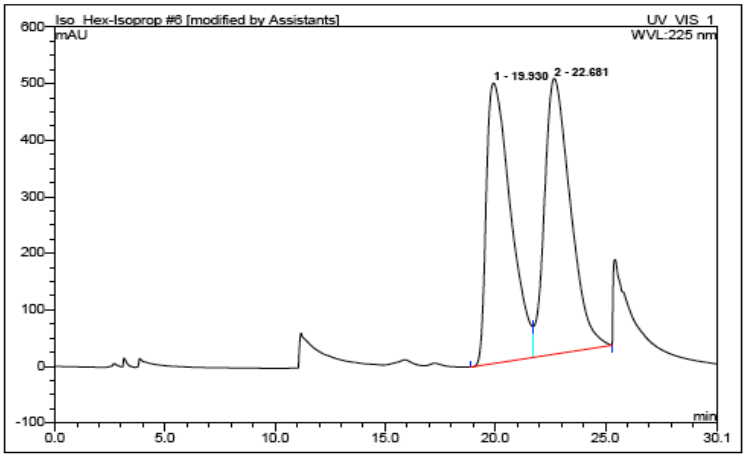
To a stirred solution of acetate (+)-**14** (50 mg, 0.28 mmol) in MeOH (0.3 mL), aqueous KOH (3 M; 0.65 mL) was added and stirred for 40 min at room temperature. The reaction mixture was diluted with Et_2O (3 mL) and the organic layer was washed with H_2O (3 mL) and brine (3 mL). The organic layer was then dried ($MgSO_4$) and rotary evaporated to give the corresponding alcohol. The crude material was used in the next step following identical protocol described in the previous page to furnish benzoate (+)-**23** as a colourless oil: **$[\alpha]_D$** +175.9° (*c* 0.51, MeOH)

Chiral HPLC analysis was performed on a Dionex HPLC with a UV-detector using a Chiralpak IA column with isocratic solvent mixture of n-hexane:i-PrOH 99.5:0.5, with a flowrate of 1.3 mL/min at 25 °C where UV = 254 nm.

Operator:Assistants Timebase:HPLC-1 Sequence:Iso_Hex-Isoprop
Page 1-1
5.12.2012 10:39 AM

6 Compound 23 (racemate)

Sample Name:	**Compound 23 (racemate)**	*Injection Volume:*	**5.0**
Vial Number:	**2**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**Iso_Hex-isoprop_99,5_0,5_1,3mL**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**9.10.2012 17:17**	*Sample Weight:*	**1.0000**
Run Time (min):	**30.09**	*Sample Amount:*	**1.0000**

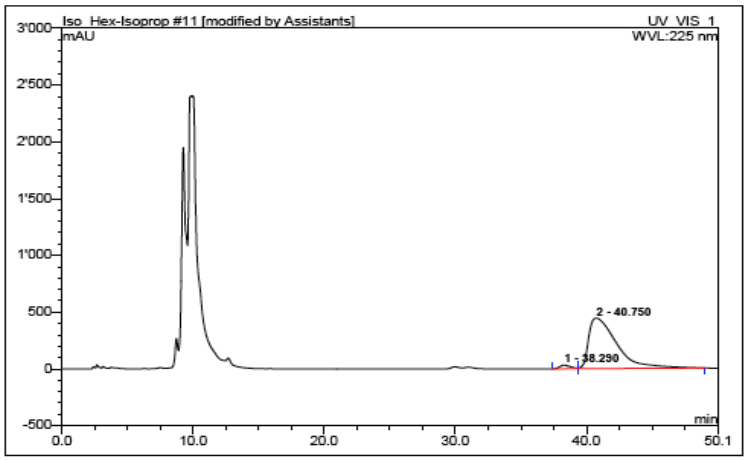


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.93	n.a.	495.842	634.137	48.72	n.a.	BM *
2	22.68	n.a.	487.455	667.564	51.28	n.a.	MB*
Total:			983.297	1301.701	100.00	0.000	

Operator:Assistants Timebase:HPLC-1 Sequence:Iso_Hex-Isoprop Page 1-1
5.12.2012 10:46 AM

11 Compound (-)23 94 % ee

Sample Name:	**Compound (-)23 94 % ee**	*Injection Volume:*	**5.0**
Vial Number:	**7**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**Iso_Hex-isoprop_99,5_0,5_1,3mL**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**23.10.2012 16:29**	*Sample Weight:*	**1.0000**
Run Time (min):	**50.06**	*Sample Amount:*	**1.0000**

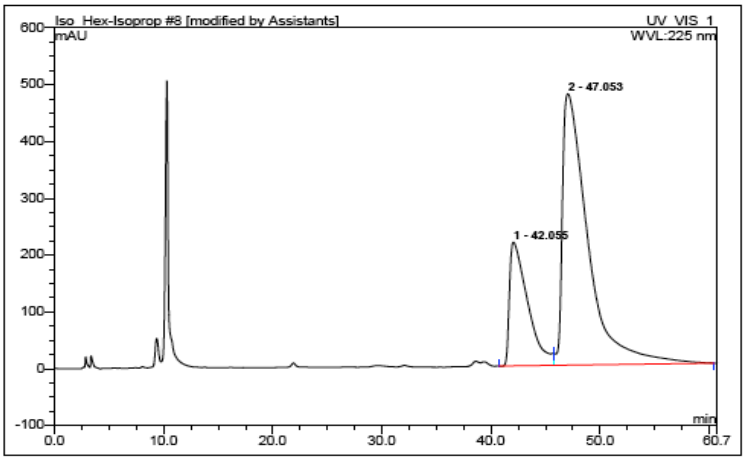


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	38.29	n.a.	31.406	30.720	2.71	n.a.	BM *
2	40.75	n.a.	444.397	1103.532	97.29	n.a.	MB*
Total:			475.803	1134.252	100.00	0.000	

Operator:Assistants Timebase:HPLC-1 Sequence:Iso_Hex-Isoprop Page 1-1
5.12.2012 10:45 AM

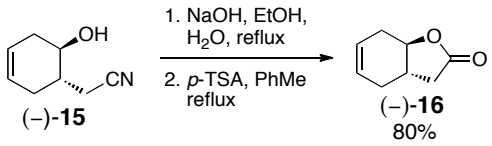
8 Compound 23 (racemate and (-) 1to1)

Sample Name:	**Compound 23 (racemate and (-) 1to1)**	*Injection Volume:*	**5.0**
Vial Number:	**4**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**Iso_Hex-isoprop_99,5_0,5_1,3mL**	*Bandwidth:*	**1**
Quantif. Method:	**default**	*Dilution Factor:*	**1.0000**
Recording Time:	**16.10.2012 14:54**	*Sample Weight:*	**1.0000**
Run Time (min):	**60.70**	*Sample Amount:*	**1.0000**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	42.06	n.a.	217.573	420.455	24.49	n.a.	BM *
2	47.05	n.a.	477.420	1296.400	75.51	n.a.	MB*
Total:			694.994	1716.855	100.00	0.000	

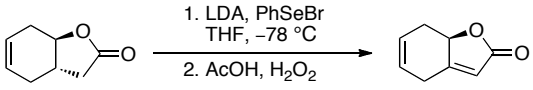
*Synthesis of lactone (–)-**16***[1]



To a stirred solution of NaOH (6 g, 145 mmol) in EtOH/H_2O (144 mL; 3 : 1) was added alcohol (–)-**15** (2.3 g, 16.8 mmol) in EtOH (12 mL). The resulting mixture was heated at reflux for 18 h and then cooled to 0 °C. The reaction mixture was acidified using aqueous HCl solution (1 M) and volatiles were removed by rotary evaporation. The remaining solution was extracted with Et_2O (2 x 350 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to give the corresponding carboxylic acid. This material was subsequently used in the next step without further purification.

To a stirred solution of crude carboxylic acid in benzene (120 mL) was added *p*-TSA (96 mg, 0.5 mmol) and the resulting mixture was heated at reflux with azeotropic removal of H_2O using a Dean-Stark apparatus for 3 h. The reaction mixture was cooled to room temperature and the volatiles were removed by rotary evaporation. The residue was chromatographed (Et_2O : pentane 1 : 4 to 1 : 1) to give lactone (–)-**16** (1.83 g, 80 % over 2 steps) as a white solid: $\mathbf{R_f}$ 0.68 (Et_2O : pentane 1 : 1); **Mp** 54.8 – 55.5 °C; $\mathbf{[\alpha]_D}$ −101.2° (*c* 0.53, MeOH); **IR (film)** 2919, 1763, 1432, 1292, 1237, 1191, 1122, 1019 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.74 – 5.65 (m, 2H), 4.10 (td, J = 10.4, 5.5 Hz, 1H), 2.65 – 2.58 (m, 2H), 2.45 – 2.38 (m, 1H), 2.35 – 2.15 (m, 3H), 2.10 – 2.02 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 176.5, 127.1, 124.4, 81.5, 40.3, 35.6, 30.8, 29.9; **HRMS (ESI)** calc. for $C_8H_{11}O_2^+$: $(M + H)^+$, 139.0754; Found: $(M + H)^+$, 139.0755. The provided reference does not report the corresponding experimental data.

*Synthesis of butenolide (–)-**17***[2]



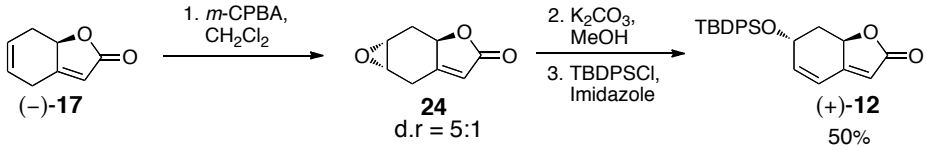
(–)-**16** (–)-**17** 48%

A solution of lactone (–)-**16** (1.6 g, 11.6 mmol) in THF (10 mL) was added drop-wise to a solution of freshly prepared lithium di-*iso*propylamide (15.6 mmol) in THF (26 mL) at −78 °C and the resulting mixture was stirred for 1 h. PhSeBr (3.55 g, 15.1 mmol) in THF (9 mL) was then added and further stirred for an hour. The reaction was allowed to warm to room temperature and quenched with aqueous HCl solution (1 M; 64.5 mL) and the resulting aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed sequentially with H_2O (80 mL), saturated aqueous $NaHCO_3$ solution (80 mL) and brine (80 mL). The resulting organic layer was dried ($MgSO_4$) and rotary evaporated to give an amber oil (3.4 g). This crude material was used in the following step without further purification.

To an iced-cooled solution of selenide intermediate (3.4 g as a crude) and AcOH (0.60 mL) in THF (80 mL), 35% H_2O_2 solution (4.13 mL, 51 mmol) was added at 4 °C. After 2 h of stirring, saturated aqueous $NaHCO_3$ solution (90 mL) was added and the mixture was stirred at room temperature for an hour. Precipitate was formed and the solution was diluted with Et_2O (150 mL). The solid was decanted and the filtrate was partitioned. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). The resulting organic layer was dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 1 : 9 to 2 : 3) to give butenolide (–)-**17** (750 mg, 48% over 2 steps) as an amber oil. Unreacted starting material (–)-**16** (200 mg, 13%) was recovered: $\mathbf{R}_f$ 0.47 (Et_2O : pentane 1 : 1); $[\alpha]_D$ −269.5° (*c* 0.42, MeOH); **IR (film)** 2919, 2851, 1742, 1648, 1282, 1130, 1031, 840 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.85 – 5.83 (m, 1H), 5.76 – 5.68 (m, 2H), 4.97 (t, J = 8.8 Hz, 1H), 3.37 – 3.30 (m, 1H), 3.23 – 3.16 (m, 1H), 2.97 – 2.90 (m, 1H), 2.19 – 2.10 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.5, 168.2, 123.8, 123.2, 113.5, 78.5, 32.7, 28.3; ***m/z* (ESI)** 137 $(M + H)^+$.

[2] Audran, G.; Mori, K. Eur. *J. Org. Chem.* **1998**, 57.

*Synthesis of silyl-protected aquilegiolide (+)-**12***[2,3]



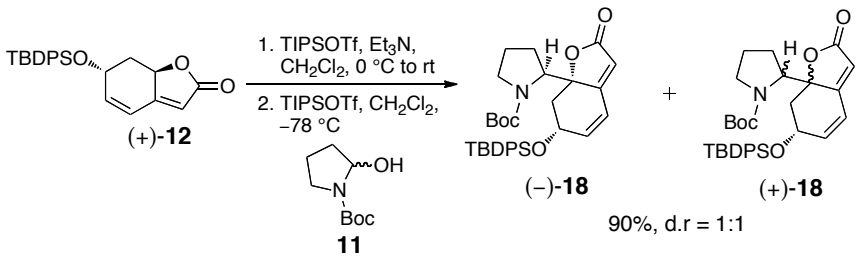
To a solution of *m*-CPBA (1.9 g, 7.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C, butenolide (–)-**17** (700 mg, 5.14 mmol) in CH_2Cl_2 (6 mL) was added and stirred for 24 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 1 : 1 to 1 : 0) to give the *trans*-epoxide **24** (530 mg, 67%, white solid) and the *cis*-epoxide (110 mg, 14%, colourless oil). The spectra data of these compounds were identical to those reported in the literature.[2]

To a stirred solution of epoxide **24** (500 mg, 3.29 mmol) in MeOH (35 mL) at 4 °C, K_2CO_3 (68 mg, 0.49 mmol) was added and stirred for 1 h at 4 °C. The reaction was quenched with excess of NH_4Cl (powder). The solvent was removed by rotary evaporation and the crude product was suspended in CH_2Cl_2. The mixture was filtered and the filtrate was rotary evaporated to give aquilegiolide as a white solid. This material was subsequently used in the following step.

To a stirred solution of aquilegiolide (3.29 mmol), imidazole (784 mg, 11.5 mmol) and DMAP (80.4 mg, 0.66 mmol) in CH_2Cl_2 (40 mL), TBDPSCl (1.71 mL, 6.58 mmol) was added and stirred for 32 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 1 : 9 to 2 : 3) to give silyl-protected aquilegiolide (+)-**12** (1 g, 50% over 3 steps) as a colourless solid. This compound can be easily re-crystallized from Et_2O/pentane to give colourless needles: $\mathbf{R_f}$ 0.52 (CH_2Cl_2 : pentane 1 : 1); **Mp** 103 – 105 °C; $\mathbf{[\alpha]_D}$ +217.3° (*c* 0.52, MeOH); **IR (film)** 3066, 2961, 2858, 1743, 1639, 1426, 1332, 1108, 1062, 1020, 897 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.68 (dd, J = 8.0, 1.5 Hz, 2H), 7.66 (dd, J = 7.8, 1.3 Hz, 2H), 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 4H), 6.48 (d, J = 9.7 Hz, 1H), 5.96 (dd, J = 9.6, 5.1 Hz, 1H), 5.78 (d, J = 1.2 Hz, 1H), 5.46 (ddd, J = 12.6, 5.0, 1.9 Hz, 1H), 4.52 – 4.49 (m, 1H), 2.58 – 2.53 (m, 1H), 1.64 – 1.59 (m, 1H), 1.08 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.5, 163.2, 138.2, 135.9 (2C), 135.8 (2C), 133.5, 133.0, 130.3, 130.2, 128.1 (2C), 127.9 (2C), 121.2, 112.3, 76.8, 65.8, 37.8, 27.0 (3C), 19.3; ***m/z* (ESI)** 391 $(M + H)^+$.

[3] Bardaji, G. G.; Canto, M.; Alibes, R.; Bayon, P.; Busqué, F.; De March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 7657.

*Synthesis of pyrrolidinyl-furanone (–)-**18***



To a stirred solution of (+)-**12** (890 mg, 2.28 mmol) in CH_2Cl_2 (15 mL) at 0 °C, triethylamine (0.93 mL, 6.61 mmol) was added drop-wise and the resulting mixture was stirred for 45 min. TIPSOTf (0.7 mL, 2.51 mmol) was then added and further stirred for 18 h at room temperature. The reaction mixture was cooled to −78 °C and aminol **11**[4] (640 mg, 3.42 mmol) in CH_2Cl_2 (12 mL) was added. TIPSOTf (1.43 mL, 5.13 mmol) was then added drop-wise and stirred further for 1.5 h at aforementioned temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (45 mL) and allowed to warm to room temperature. The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL) and the combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2 : EtOAc : pentane 10 : 1 : 10) to give solely two diastereoisomers.

(–)-**18** (573 mg, 45%, colourless foam);

R_f 0.45 (CH_2Cl_2 : EtOAc : pentane 10 : 1 : 10); **Mp** 62 – 65 °C; **$[\alpha]_D$** −33.5° (*c* 0.35, MeOH); **IR (film)** 3070, 2933, 2858, 1756, 1692, 1644, 1472, 1386, 1162, 1108, 1077, 1010, 844 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 (d, J = 7.0 Hz, 4H), 7.48 – 7.38 (m, 6H), 6.55 (dd, J = 9.9, 1.2 Hz, 1H), 6.21 (d, J = 10 Hz, 1H), 5.62 (s, 1H), 4.54 – 4.50 (*br.* m, 1H), 3.71 – 3.68 (m, 1H), 3.39 – 3.33 (*br.* m, 1H), 3.12 – 3.05 (m, 1H), 2.34 (dd, J = 12.4, 5.6 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.87 (dd, J = 12.3, 10.2 Hz, 1H), 1.62 – 1.59 (m, 1H), 1.51 – 1.40 (m, 2H), 1.32 (s, 9H), 1.07 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.6, 165.7, 155.1, 139.7, 135.9 (2C), 135.8 (2C), 133.5, 133.1, 130.2 (2C), 128.0 (4C), 122.2, 110.9, 88.4, 79.7, 67.3, 59.1, 47.4, 41.4, 28.3 (3C), 27.0 (3C), 26.0, 24.6, 19.2; **HRMS (ESI)** calc. for $C_{33}H_{42}NO_5Si^+$: $(M + H)^+$, 560.2827; Found: $(M + H)^+$, 560.2836.

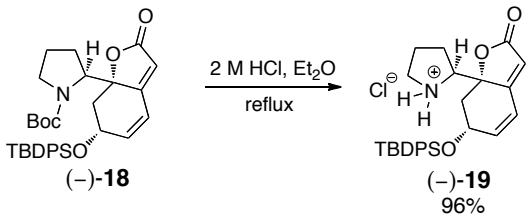
(+)-**18** (575 mg, 45%, colourless foam);

R_f 0.40 (CH_2Cl_2 : EtOAc : pentane 10 : 1 : 10); **Mp** 75 – 78 °C; **$[\alpha]_D$** +112.6° (*c* 0.35, MeOH); **IR (film)** 3049, 2932, 2858, 1755, 1691, 1472, 1387, 1166, 1107, 1059, 1002, 925, 856 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 – 7.66 (m, 4H), 7.47 – 7.38 (m, 6H), 6.50 (d, J = 9.8 Hz, 1H), 5.75 – 5.67 (*br.* m, 1H), 5.57 (s, 1H), 4.81 – 4.72 (*br.* m, 1H), 4.56 – 4.53 (m, 1H), 3.71 – 3.69 (m, 0.2H), 3.51 – 3.49 (m, 0.8H), 3.27 – 3.23 (*br.* m, 1H), 2.44 (*br.* d, J = 14.0 Hz, 1H), 2.19 – 2.10

[4] Peixoto, S.; Nguyen, T. M.; Crich, D.; Delpech, B.; Marazano, C. *Org. Lett.* **2010**, *12*, 4760.

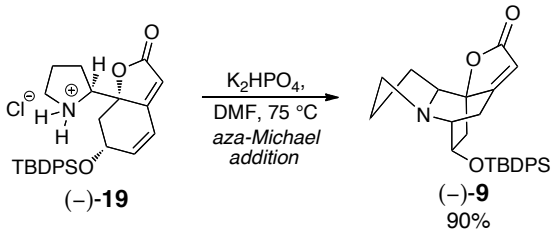
(m, 2H), 1.85 – 1.80 (m, 2H), 1.48 – 1.35 (m, 1H), 1.40 (s, 9H), 1.10 (s, 9H) – rotamers present in 4:1 ratio; **^{13}C NMR (100 MHz, $CDCl_3$)** δ 172.9, 165.8, 155.0, 136.1 (2C), 135.9 (2C), 134.3, 133.4, 133.1, 130.3, 130.2, 128.1 (2C), 128.0 (2C), 123.0, 111.4, 87.6, 79.3, 65.8, 60.6, 47.8, 38.1, 28.4 (3C), 27.4, 27.2 (3C), 24.5, 19.3; **HRMS (ESI)** calc. for $C_{33}H_{42}NO_5Si^+$: $(M + H)^+$, 560.2827; Found: $(M + H)^+$, 560.2835.

*Synthesis of HCl salt (–)-**19***



A stirred solution of Boc-pyrrolidine (–)-**18** (230 mg, 0.41 mmol) in HCl in Et_2O (2 M; 5.2 mL) was heated at reflux for 15 h. The volatiles were removed by rotary evaporation and the resulting white solid was triturated with pentane to give the hydrochloride salt (–)-**19** (195 mg, 96%) as a white powder: **Mp** 209 °C (decomp.); **$[\alpha]_D$** −7.3° (*c* 0.34, MeOH); **IR (film)** 3048, 2932, 2856, 1759, 1643, 1410, 1361, 1113, 1047, 1020, 912 cm^{-1}; **^{1}H NMR (400 MHz, CD_3OD)** δ 7.72 (*br.* d, J = 7.8 Hz, 4H), 7.54 – 7.45 (m, 6H), 6.71 (dd, J = 10.1, 2.2 Hz, 1H), 6.40 (d, J = 10.1 Hz, 1H), 6.06 (s, 1H), 4.62 – 4.58 (*br.* m, 1H), 3.62 – 3.58 (m, 1H), 3.26 – 3.19 (m, 1H), 3.14 – 3.08 (m, 1H), 2.38 (dd, J = 12.4, 5.6 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.85 (dd, J = 12.4, 9.8 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.55 – 1.47 (m, 1H), 1.34 – 1.29 (m, 1H), 1.08 (s, 9H); **^{13}C NMR (100 MHz, CD_3OD)** δ 171.6, 164.7, 143.6, 137.1 (2C), 137.0 (2C), 134.2, 134.0, 131.5, 131.4, 129.2 (2C), 129.1 (2C), 120.9, 114.3, 84.6, 68.3, 62.1, 47.2, 43.9, 27.3 (3C), 25.6, 23.2, 19.8; **HRMS (ESI)** calc. for $C_{28}H_{34}NO_3Si^+$: $(M – HCl + H)^+$, 460.2302; Found: $(M – HCl + H)^+$, 460.2296.

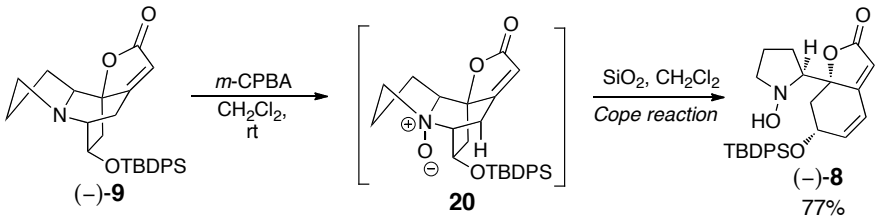
*Synthesis of tetracycle (–)-**9***



(–)-**19** (–)-**9** 90%

To a stirred mixture of K_2HPO_4 (70 mg, 0.4 mmol) in DMF (20 mL) at room temperature, HCl salt (–)-**19** (80 mg, 0.16 mmol) in DMF (5 mL) was added in one portion. The resulting solution was heated at 75 °C for 15 h. The reaction was allowed to cool to room temperature and quenched with H_2O (40 mL) and diluted with EtOAc (40 mL). The contents were stirred vigorously for several min. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 x 25 mL) and water (2 x 25 mL). The resulting organic layer was dried ($MgSO_4$), rotary evaporated and chromatographed (Et_2O : pentane 1 : 1) to give the tetracycle (–)-**9** (66.6 mg, 90%) as a pale yellow oil: $\mathbf{R_f}$ 0.30 (Et_2O : pentane 1 : 1); $\mathbf{[\alpha]_D}$ –88.4° (*c* 0.35, MeOH); **IR (film)** 2931, 2857, 1764, 1667, 1386, 1256, 1090, 1062, 918 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.61 – 7.58 (m, 4H), 7.46 – 7.41 (m, 2H), 7.39 – 7.35 (m, 4H), 5.82 (t, *J* = 1.9 Hz, 1H), 4.40 – 4.37 (m, 1H), 3.34 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.11 (dt, *J* = 20.2, 2.1 Hz, 1H), 3.00 – 2.95 (m, 2H), 2.94 – 2.90 (m, 1H), 2.63 (td, *J* = 9.9, 6.0 Hz, 1H), 2.32 (dd, *J* = 12.9, 9.2 Hz, 1H), 1.77 – 1.69 (m, 2H), 1.68 – 1.60 (m, 1H), 1.52 (dd, *J* = 12.9, 2.8 Hz, 1H), 1.06 (s, 9H), 1.05 – 0.98 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.6, 171.7, 135.8 (2C), 135.7 (2C), 133.5, 133.4, 130.1, 130.0, 127.9 (4C), 112.7, 84.2, 68.8, 62.9, 55.5, 50.9, 41.6, 27.1, 27.0 (3C), 25.1, 22.0, 19.2; **HRMS (ESI)** calc. for $C_{28}H_{34}NO_3Si^+$: $(M + H)^+$, 460.2302; Found: $(M + H)^+$, 460.2300.

*Synthesis of N-hydroxy-pyrrolidine(–)-**8***

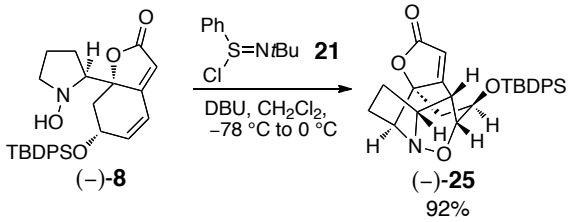


(–)-**9** **20** (–)-**8** 77%

To a stirred solution of tetracycle (–)-**9** (35 mg, 0.076 mmol) in CH_2Cl_2 (6 mL) at room temperature, *m*-CPBA (24 mg, 0.10 mmol) was added and the resulting mixture was stirred for 1 h. The reaction was quenched with H_2O (30 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and rotary evaporated to give a mixture of *N*-oxide **20** and *m*-chlorobenzoic acid. This material was dissolved in EtOAc (40 mL)

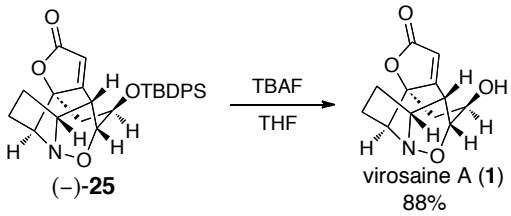
and washed with saturated aqueous $NaHCO_3$ (30 mL). The resulting organic layer was dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2 : MeOH 15 : 1 to 10 : 1) to give *N*-hydroxy-pyrrolidine (–)-**8** (28.5 mg, 77 %) as a crystalline solid: $\mathbf{R_f}$ 0.72 (CH_2Cl_2 : MeOH 10 : 1); **Mp** 89 – 91 °C; $[\alpha]_D$ –9.8° (*c* 0.21, MeOH); **IR (film)** 3364, 2961, 2931, 2857, 1732, 1638, 1427, 1105, 1080, 1012, 850, 701 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.68 – 7.65 (m, 4H), 7.50 – 7.45 (m, 2H), 7.44 – 7.39 (m, 4H), 6.51 (dd, *J* = 10.0, 2.2 Hz, 1H), 6.18 (d, *J* = 10.3 Hz, 1H), 5.75 (s, 1H), 4.46 – 4.42 (m, 1H), 3.11 – 3.07 (m, 1H), 2.74 (dd, *J* = 10.1, 6.7 Hz, 1H), 2.69 (td, *J* = 9.7, 7.7 Hz, 1H), 2.28 (dd, *J* = 12.3, 5.6 Hz, 1H), 1.85 (dd, *J* = 12.3, 10.0 Hz, 1H), 1.66 – 1.55 (m, 3H), 1.47 – 1.39 (m, 1H), 1.07 (s, 9H) – OH not visible; **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.9, 165.0, 141.2, 135.9 (2C), 135.8 (2C), 133.2, 133.1, 130.3, 130.2, 128.0 (4C), 120.6, 111.9, 86.1, 69.9, 67.6, 58.7, 42.1, 27.0 (3C), 24.0, 21.2, 19.2; **HRMS (ESI)** calc. for $C_{28}H_{34}NO_4Si^+$: $(M + H)^+$, 476.2252; Found: $(M + H)^+$, 476.2246.

*Synthesis of (–)-**25***



To a stirred solution of hydroxylamine (–)-**8** (25 mg, 0.053 mmol) and DBU (0.016 mL, 0.11 mmol) in CH_2Cl_2 (3.5 mL) at –78 °C, a solution of *N*-*t*-butylbenzenesulfinimidoyl chloride (17 mg, 0.08 mmol) in CH_2Cl_2 (2.0 mL) was added and stirring was continued for 2 h. The reaction mixture was allowed to warm to 0 °C and the reaction was quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 8 mL) and the combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (EtOAc : pentane 1 : 3 to 1 : 1) to give the virosaine A precursor (–)-**25** (23 mg, 92%) as a colourless oil: $\mathbf{R_f}$ 0.63 (EtOAc : pentane 7 : 3); $[\alpha]_D$ –25.2° (*c* 0.32, MeOH); **IR (film)** 3071, 2957, 2932, 2857, 1749, 1656, 1471, 1427, 1109, 1064, 1047, 901 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.52 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.40 – 7.36 (m, 4H), 5.88 (s, 1H), 4.44 – 4.41 (m, 1H), 4.35 – 4.32 (m, 1H), 3.95 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.87 (d, *J* = 5.8 Hz, 1H), 3.82 (dd, *J* = 5.7, 4.7 Hz, 1H), 2.78 (dd, *J* = 14.2, 5.4 Hz, 1H), 1.96 (d, *J* = 14.0 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.77 – 1.67 (m, 1H), 1.48 – 1.42 (m, 1H), 1.34 – 1.25 (m, 1H), 1.00 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.2, 169.7, 135.8 (2C), 135.7 (2C), 133.3, 132.9, 130.3, 130.2, 128.1 (4C), 86.7, 84.1, 77.4, 73.1, 69.7, 66.3, 49.5, 43.9, 26.9 (3C), 21.4, 20.2, 19.3; ***m/z* (ESI)** 474 $(M + H)^+$, 496 $(M + Na)^+$, 512 $(M + K)^+$, 969 $(2M + Na)^+$.

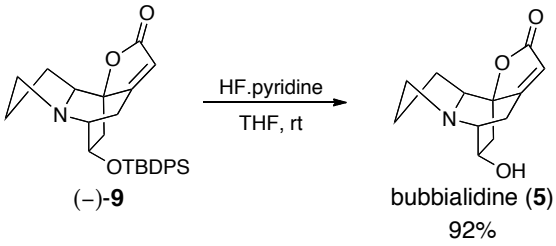
*Synthesis of virosaine A (**1**)*



A solution of (–)-**25** (22.5 mg, 0.048 mmol) in THF (1.5 mL) was treated with TBAF in THF (1 M; 0.1 mL) at room temperature and stirred for 2 h. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2 : MeOH 10 : 1) to give virosaine A (**1**) (8.8 mg, 88%) as a crystalline solid: $\mathbf{R_f}$ 0.40 (CH_2Cl_2 : MeOH 9 : 1); **Mp** 178 – 179 °C, lit.[5] 177 – 178 °C; $\mathbf{[\alpha]_D}$ –44.8° (*c* 0.14, MeOH), lit.[5] $\mathbf{[\alpha]_D}$ –51.6° (*c* 0.50, MeOH); **IR (film)** 3418, 2949, 2921, 1720, 1646, 1626, 1465, 1404, 1288, 1215, 1113, 1062, 876 cm^{-1}; **^{1}H NMR (500 MHz, CD_3OD)** δ 5.85 (*br.* s, 1H), 4.68 (ddd, *J* = 5.9, 4.8, 1.1 Hz, 1H), 4.31 – 4.28 (m, 1H), 4.02 (dd, *J* = 6.8, 4.8 Hz, 1H), 3.91 – 3.89 (m, 2H), 2.93 (dd, *J* = 14.2, 5.6 Hz, 1H), 1.94 – 1.89 (m, 1H), 1.84 (dd, *J* = 14.1, 1.1 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.49 (ddd, *J* = 13.4, 10.6, 6.0 Hz, 1H), 1.21 (ddd, *J* = 13.9, 10.6, 3.1 Hz, 1H) – OH not visible; **^{13}C NMR (125 MHz, CD_3OD)** δ 175.5, 171.9, 110.8, 88.0, 85.4, 74.1, 70.9, 65.4, 50.3, 44.7, 22.2, 20.8; ***m/z* (ESI)** 236 $(M + H)^+$; **HRMS (ESI)** calc. for $C_{12}H_{14}NO_4^+$: $(M + H)^+$, 236.0917.; Found: $(M + H)^+$, 236.0917.

[5] Zhao, B.-X.; Wang, Y.; Zhang, D.-M.; Huang, X.-J.; Bai, L.-L.; Yan Y.; Chen, J.-M.; Lu, T.-B.; Wang, Y.-T.; Zhang, Q.-W.; Ye, W.-C. *Org. Lett.* **2012**, *14*, 3096.

*Synthesis of bubbialidine (**5**)*

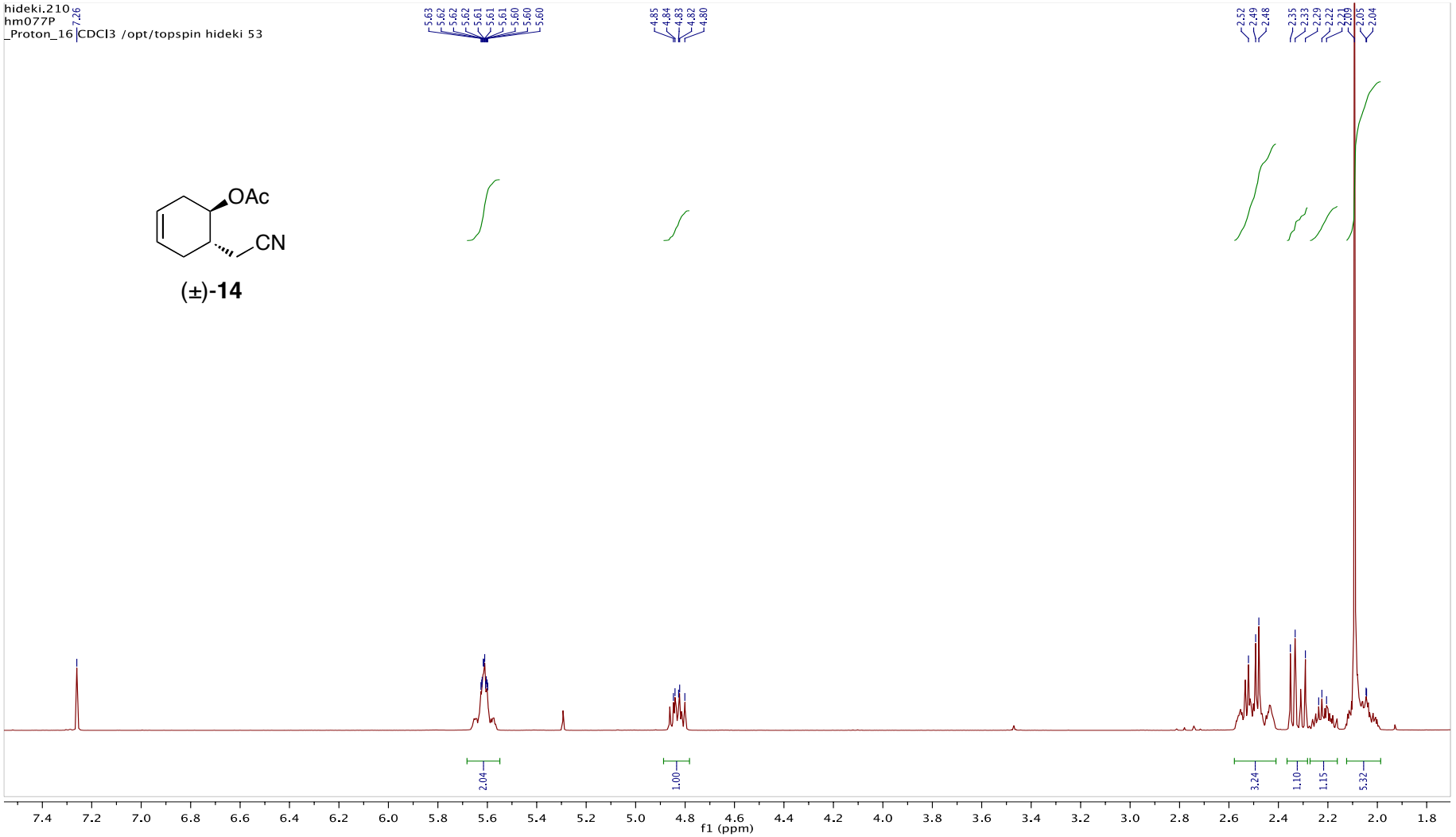


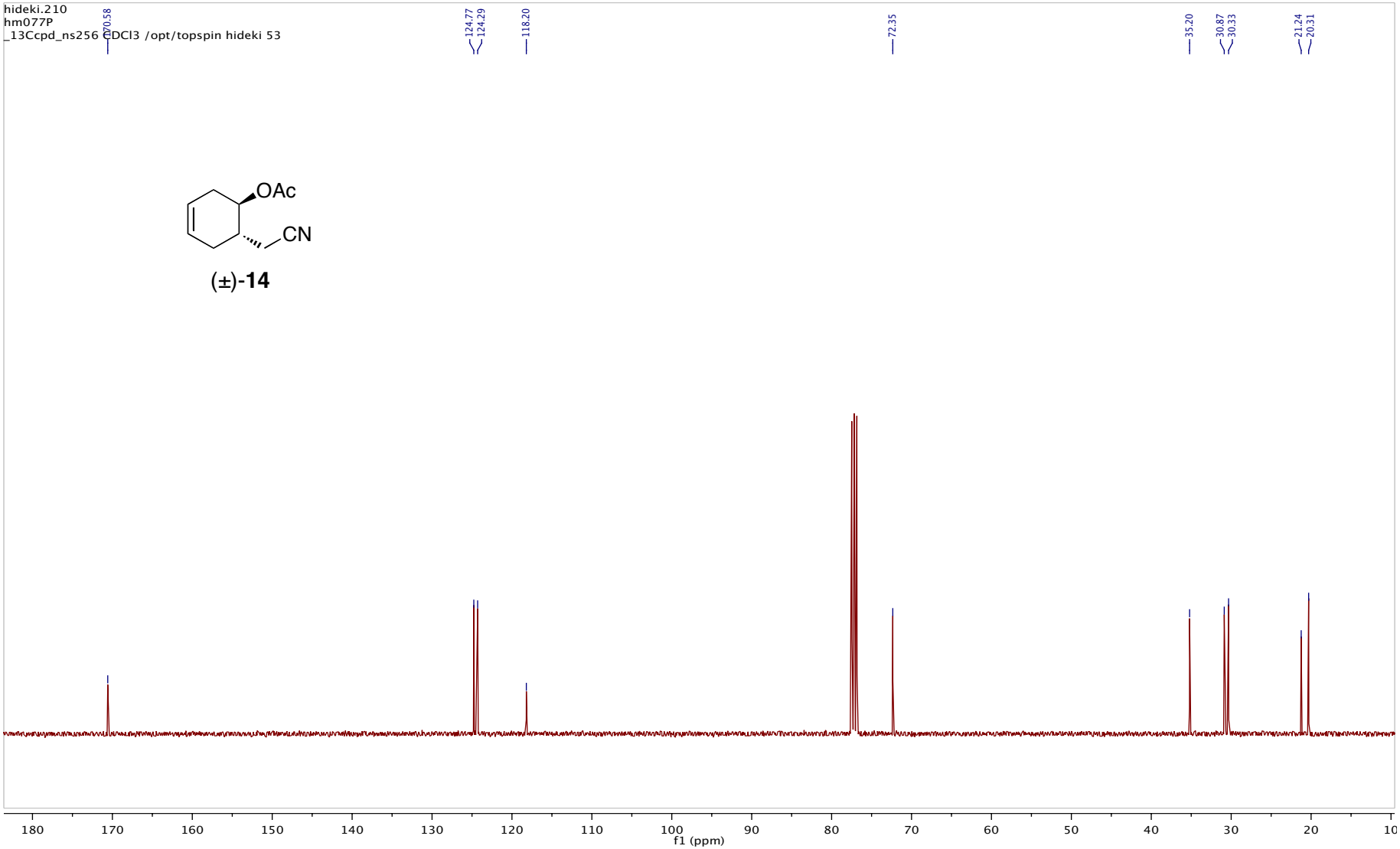
(–)-**9** bubbialidine (**5**) 92%

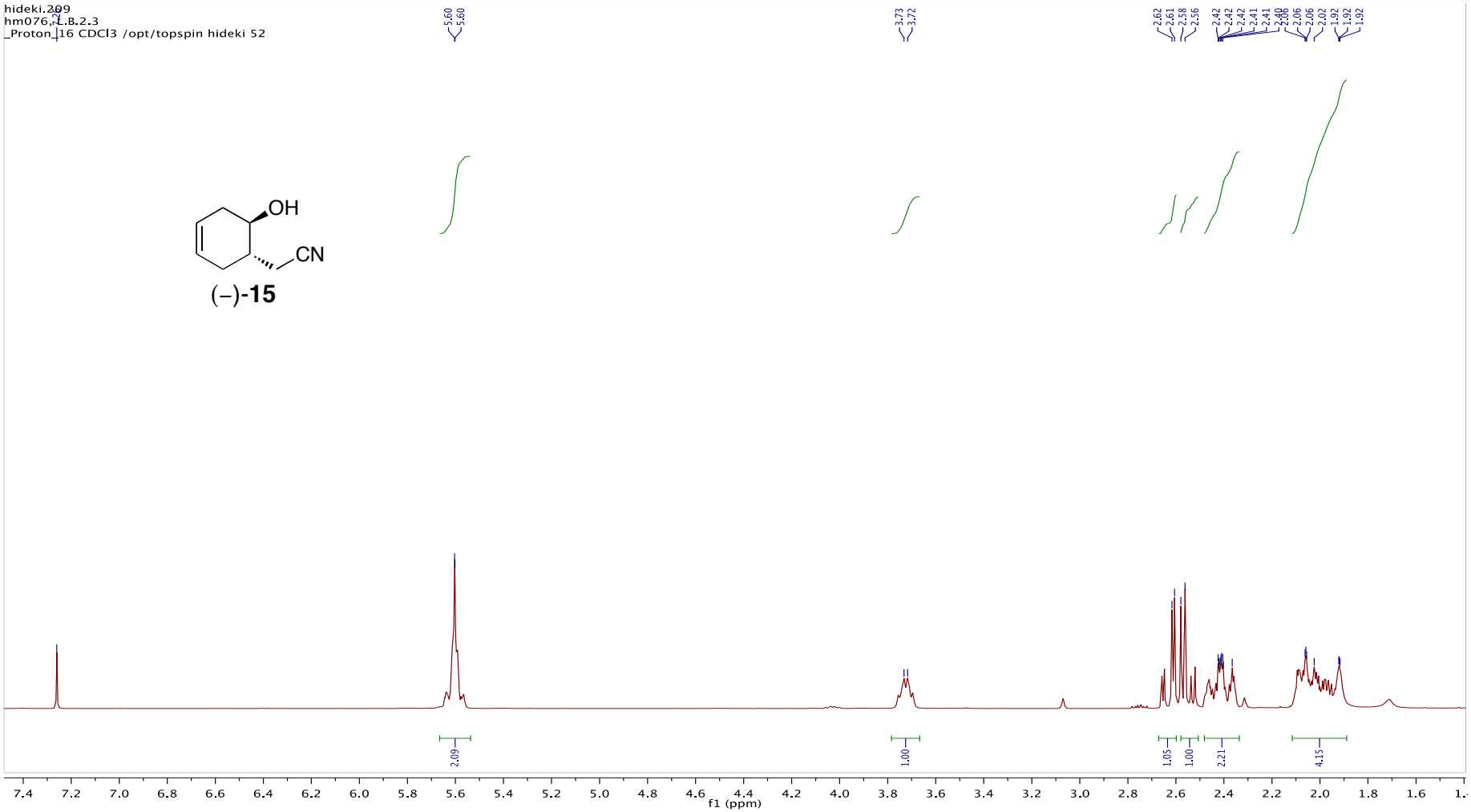
To a solution of tetracycle (–)-**9** (140 mg, 0.3 mmol) in THF (4 mL), HF.pyridine (65 - 70%; 0.5 mL, excess) was added at room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), rotary evaporated and chromatographed (CH_2Cl_2 : MeOH 10 : 1) to give bubbialidine (**5**) (62 mg, 92%) as a colourless solid: $\mathbf{R_f}$ 0.30 (CH_2Cl_2 : MeOH 10 : 1); **Mp** 127 – 130 °C; $\mathbf{[\alpha]_D}$ –72.4° (*c* 0.11, MeOH), lit.[6] $\mathbf{[\alpha]_D}$ –85.0° (*c* 1.47, MeOH); **IR (film)** 3505, 2967, 2919, 2870, 1749, 1652, 1410, 1348, 1256, 1140, 1081, 1043, 919 cm^{-1}; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.78 (t, *J* = 2.0 Hz, 1H), 4.44 (dt, *J* = 9.5, 3.3 Hz, 1H), 3.51 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.09 – 3.08 (m, 1H), 3.04 – 3.01 (m, 1H), 2.99 – 2.98 (m, 2H), 2.91 – 2.90 (*br.* s, OH), 2.70 (td, *J* = 9.8, 5.8 Hz, 1H), 2.66 (dd, *J* = 12.9, 9.5 Hz, 1H), 1.83 – 1.73 (m, 2H), 1.72 – 1.67 (m, 1H), 1.50 (dd, *J* = 12.9, 3.1 Hz, 1H), 1.10 – 1.04 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.6, 171.4, 112.8, 84.1, 67.4, 62.9, 55.5, 50.8, 40.4, 27.0, 25.1, 21.8; ***m/z* (ESI)** 222 $(M + H)^+$; **HRMS (ESI)** calc. for $C_{12}H_{16}NO_3^+$: $(M + H)^+$, 222.1125.; Found: $(M + H)^+$, 222.1128.

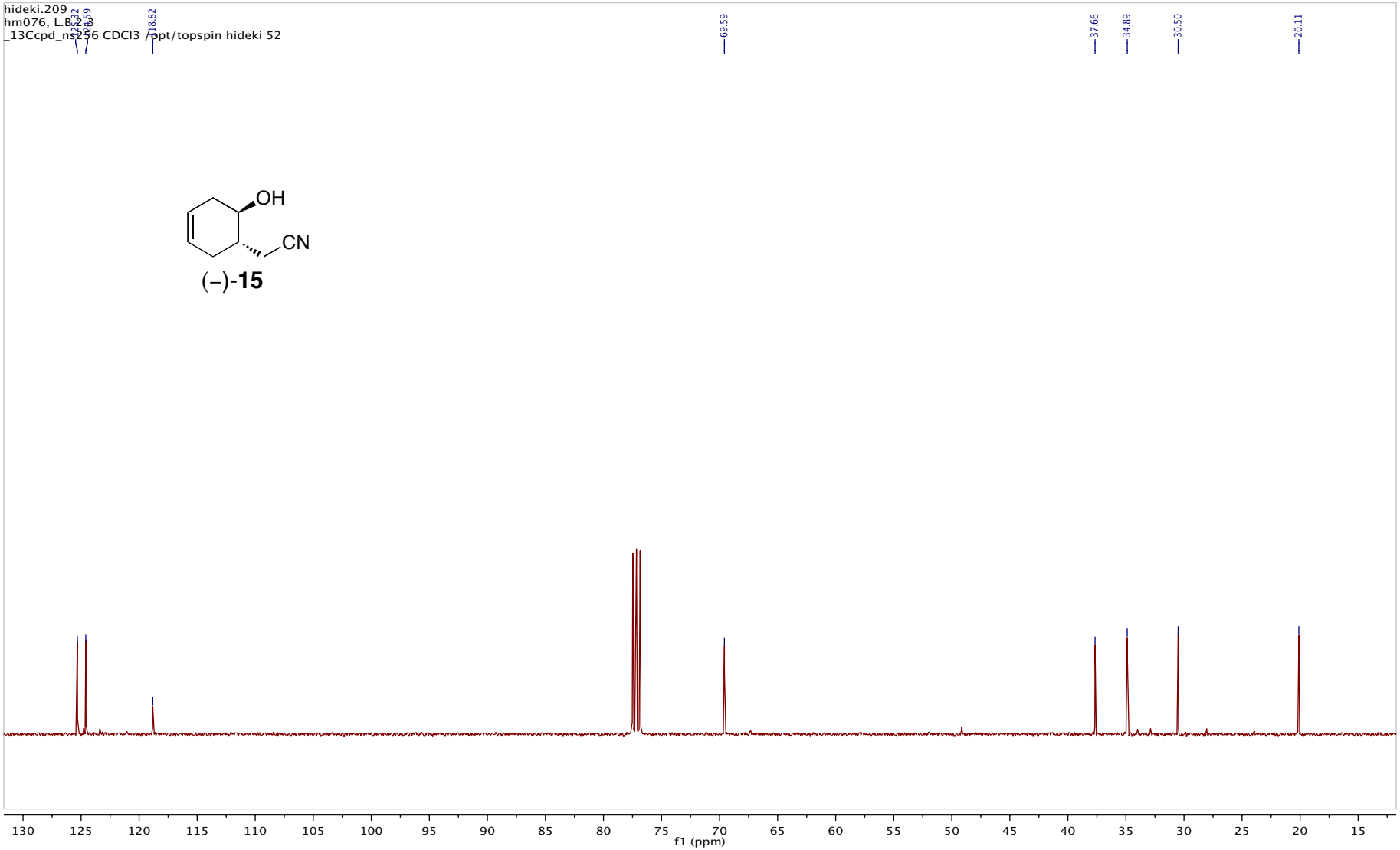
[6] Ahond, A.; Guilhem, J.; Hamon, J.; Hurtado, J.; Poupat, C.; Pusset, J.; Pusset, M.; Sévenet, T.; Potier, P. *J. Nat. Prod.* **1990**, *53*, 875.

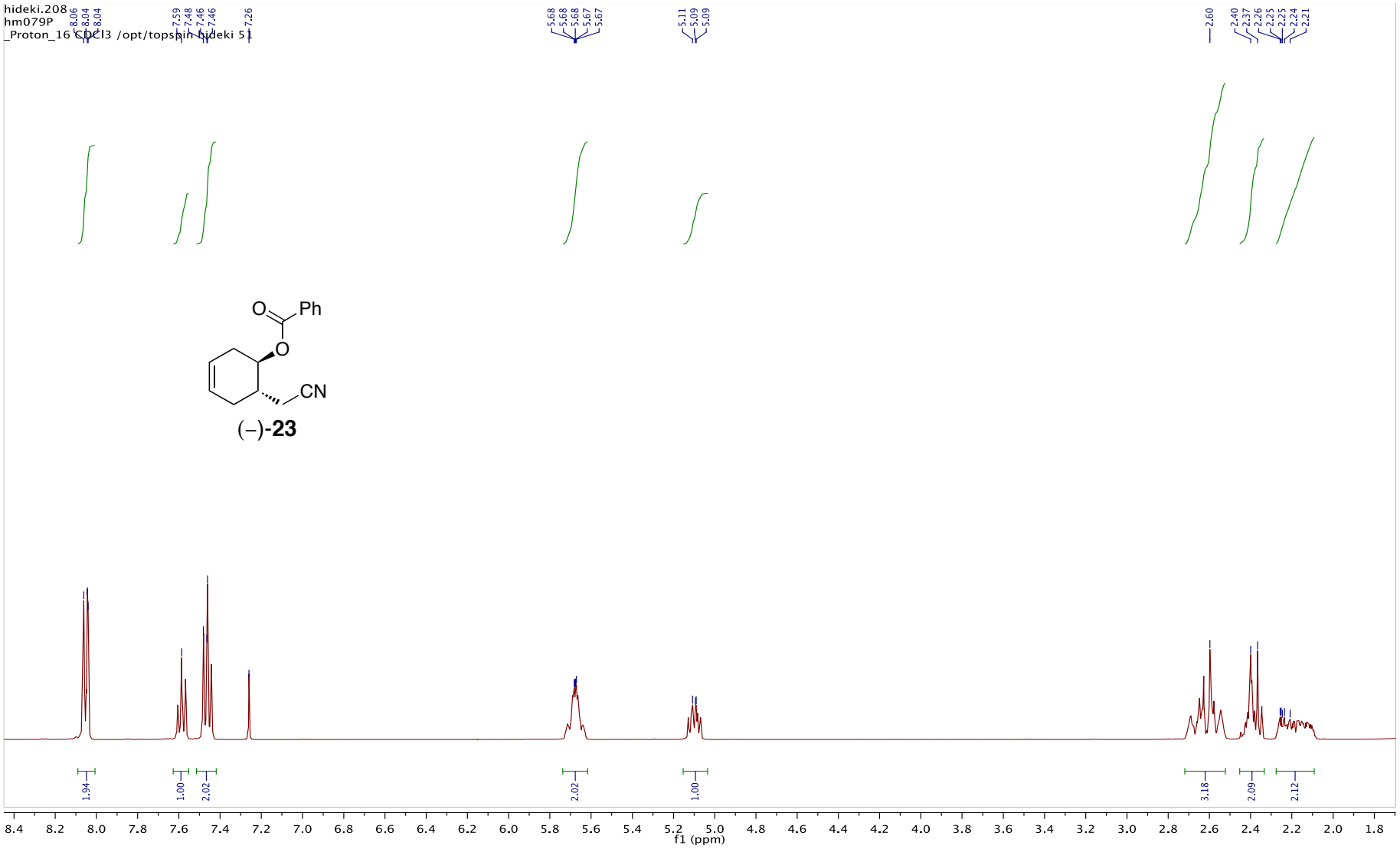
^{1}H NMR and ^{13}C NMR spectra

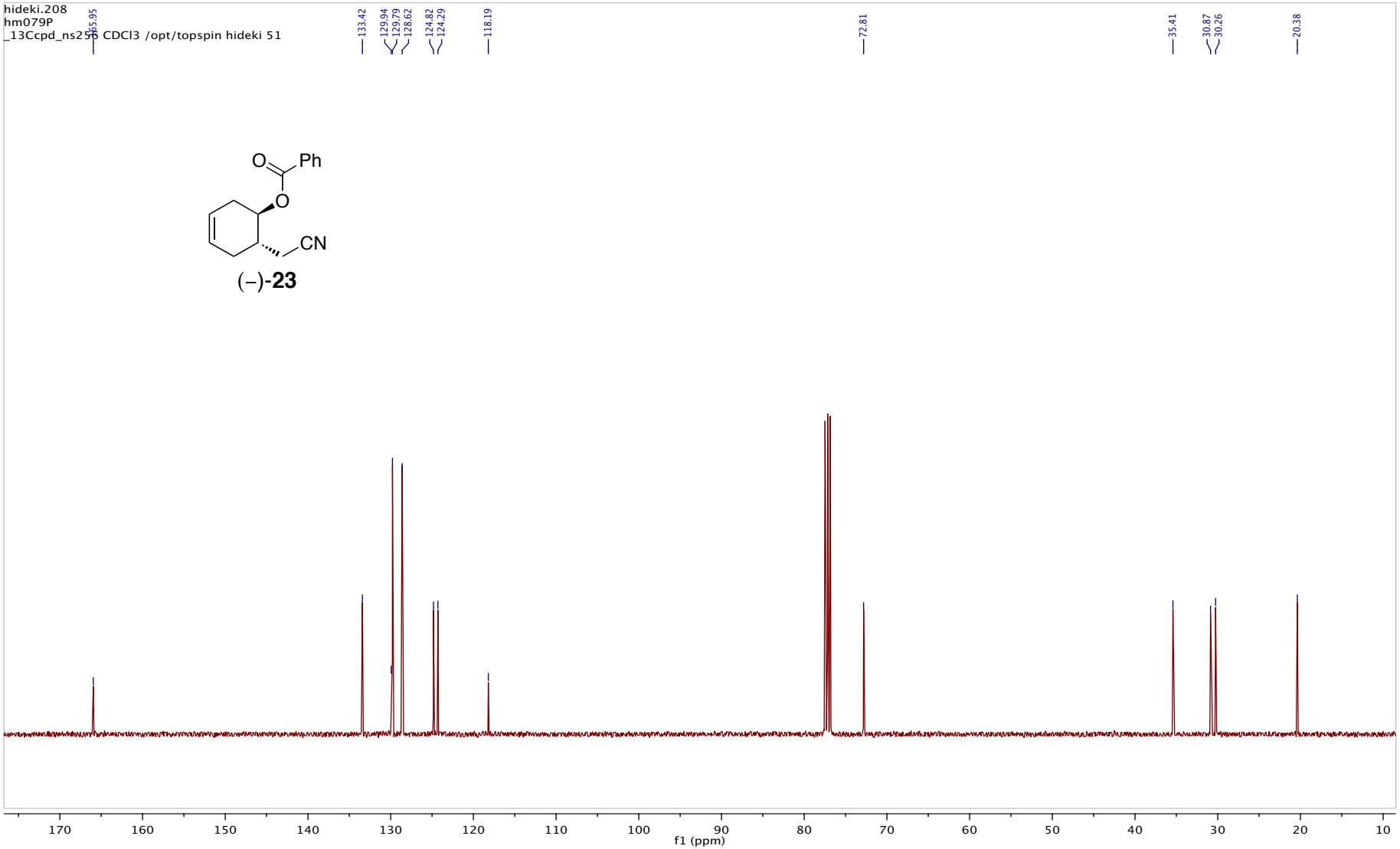


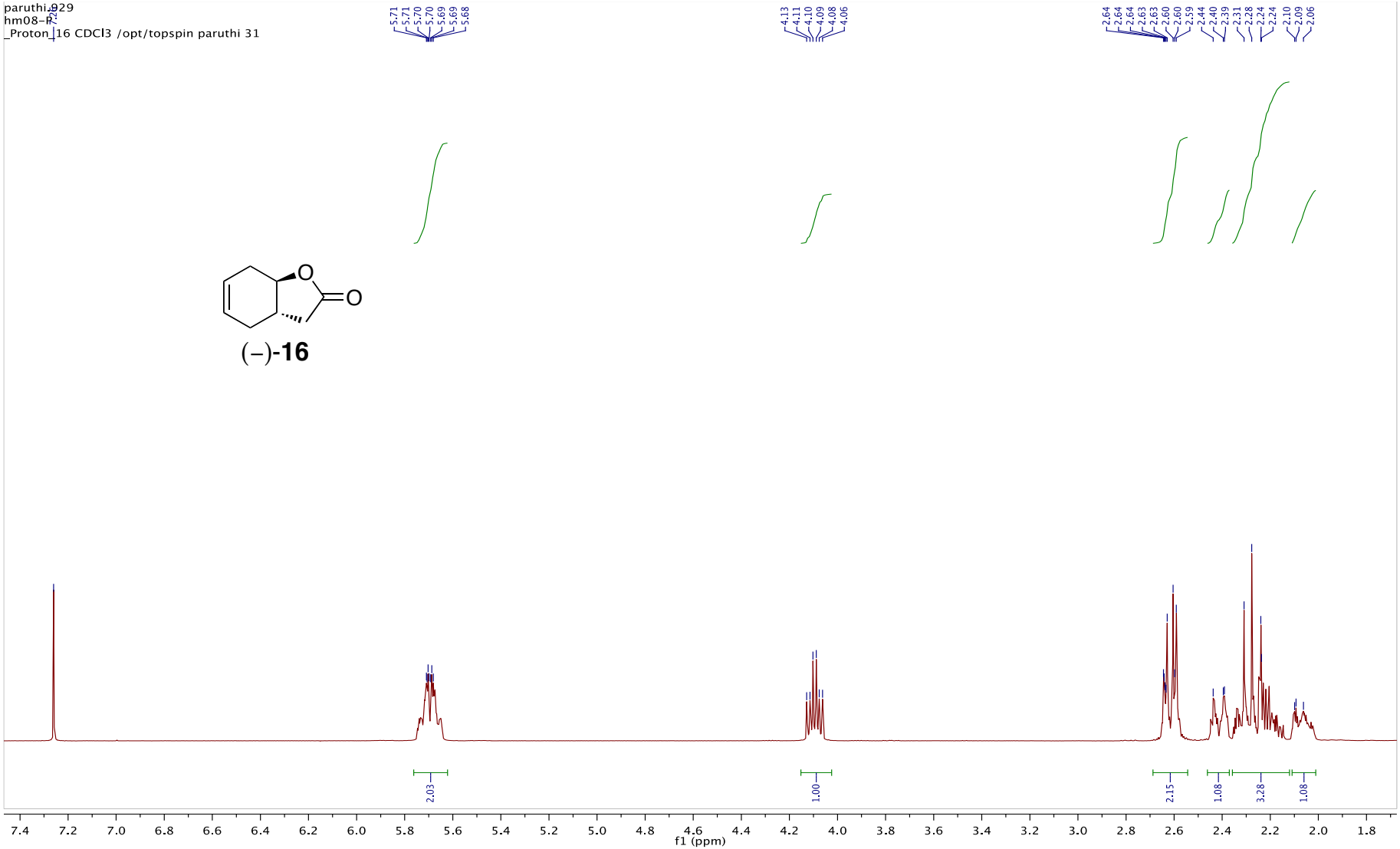

hideki.210
hm077P
_13Ccpd_ns256 CDCl3 /opt/topspin hideki 53
170.58
124.77
124.29
118.20
72.35
35.20
30.87
30.33
21.24
20.31
OAc
CN
(±)-14
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

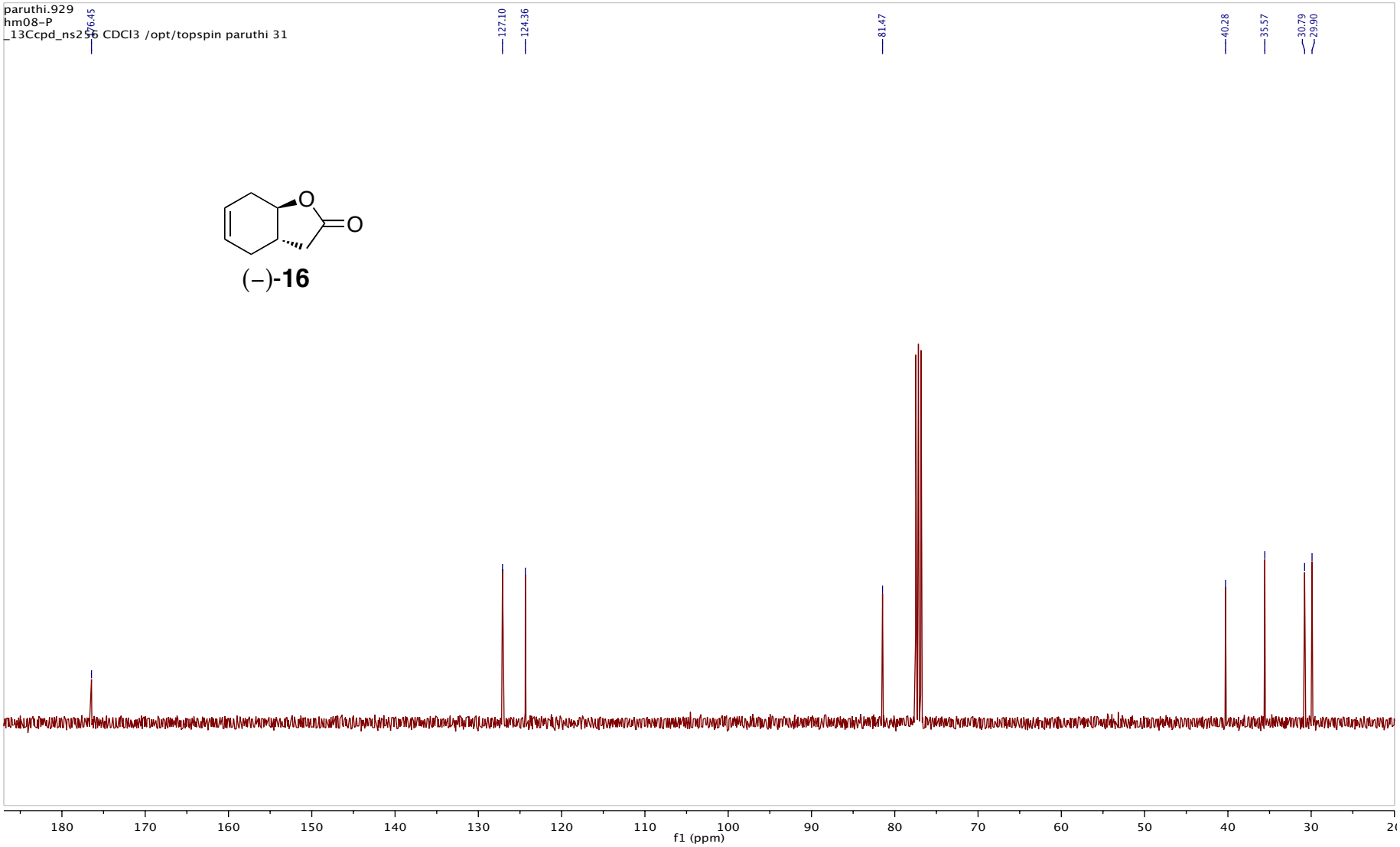

hideki.209
hm076_1.8.2.3
_Proton_16 CDCl3 /opt/topspin hideki 52
OH
CN
(–)-15
f1 (ppm)

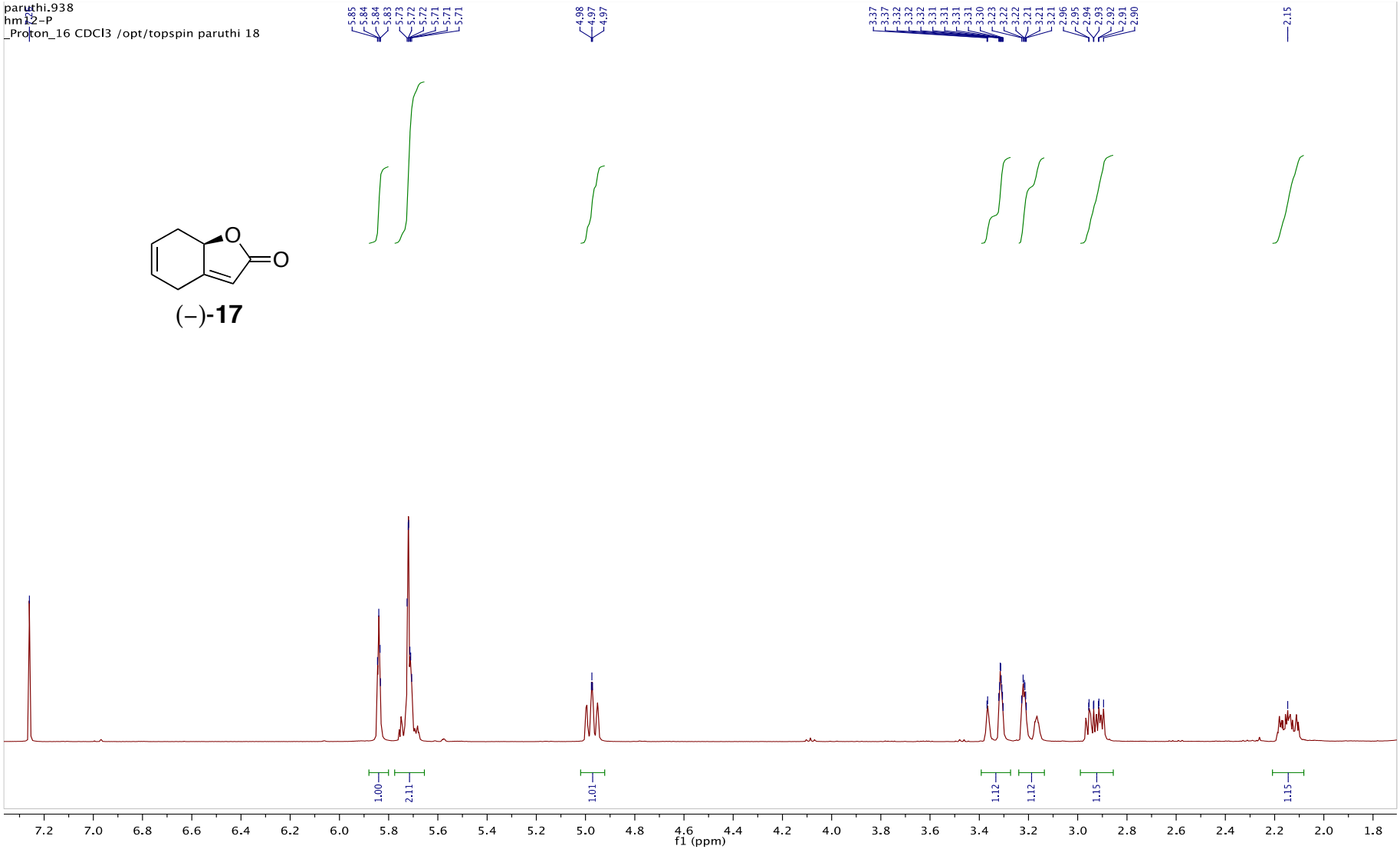

hideki.209
hm076, L.B.2.3.8
_13Ccpd_ns256 CDCl3 /ppt/topspin hideki 52
118.82
69.59
37.66
34.89
30.50
20.11
OH
CN
(–)-15
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
f1 (ppm)

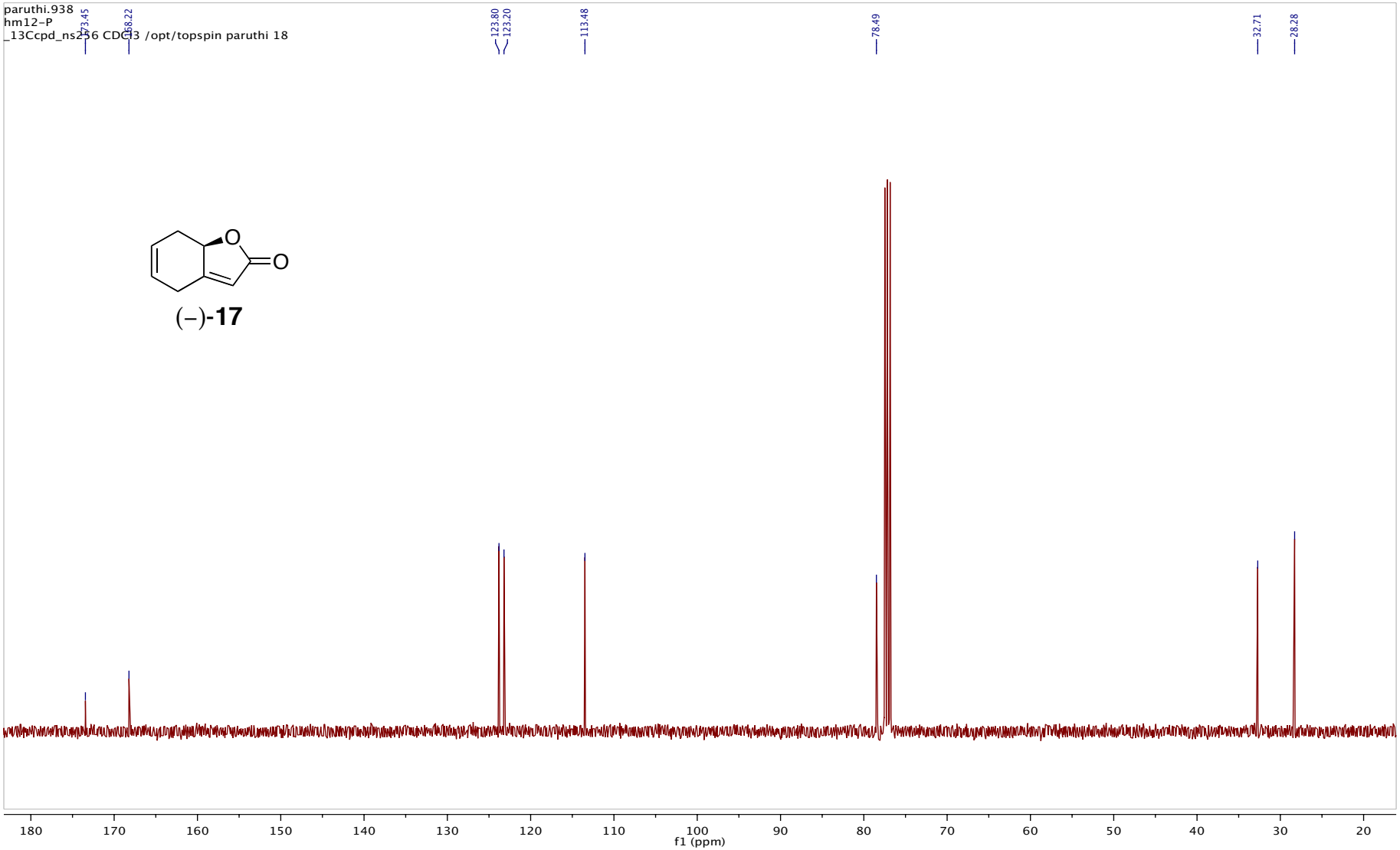

hideki.208
hm079P
_Proton_16 CDCl3 /opt/topspin hideki 51
8.06
8.04
8.04
7.59
7.48
7.46
7.46
7.26
5.68
5.68
5.68
5.67
5.67
5.11
5.09
5.09
2.60
2.40
2.37
2.26
2.25
2.25
2.24
2.21
O
Ph
O
CN
(–)-23
1.94
1.00
2.02
2.02
1.00
3.18
2.09
2.12
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

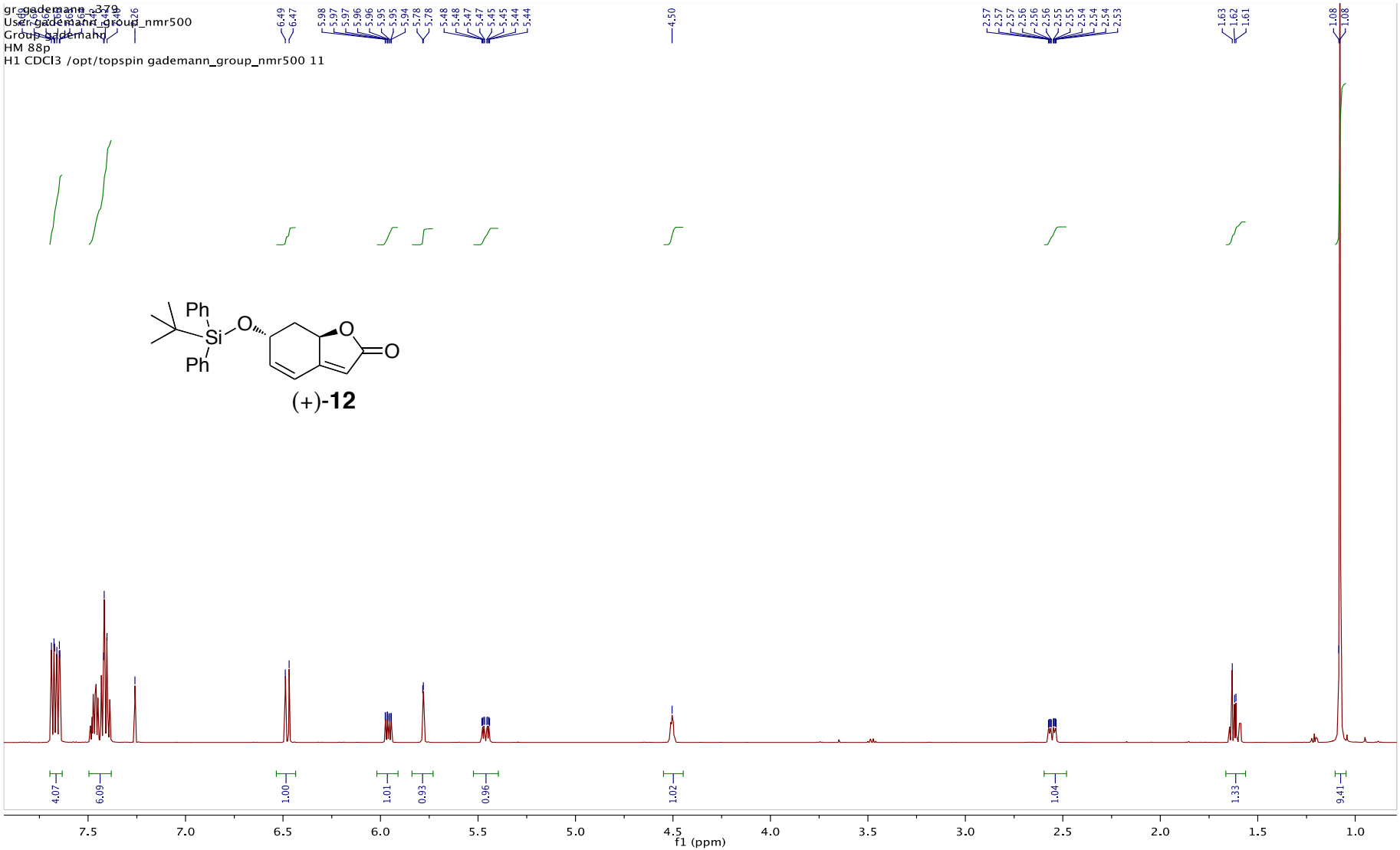

hideki.208
hm079P
_13Ccpd_ns256 CDCl3 /opt/topspin hideki 51
165.95
133.42
129.94
129.79
128.62
124.82
124.29
118.19
72.81
35.41
30.87
30.26
20.38
O
Ph
O
CN
(–)-23
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

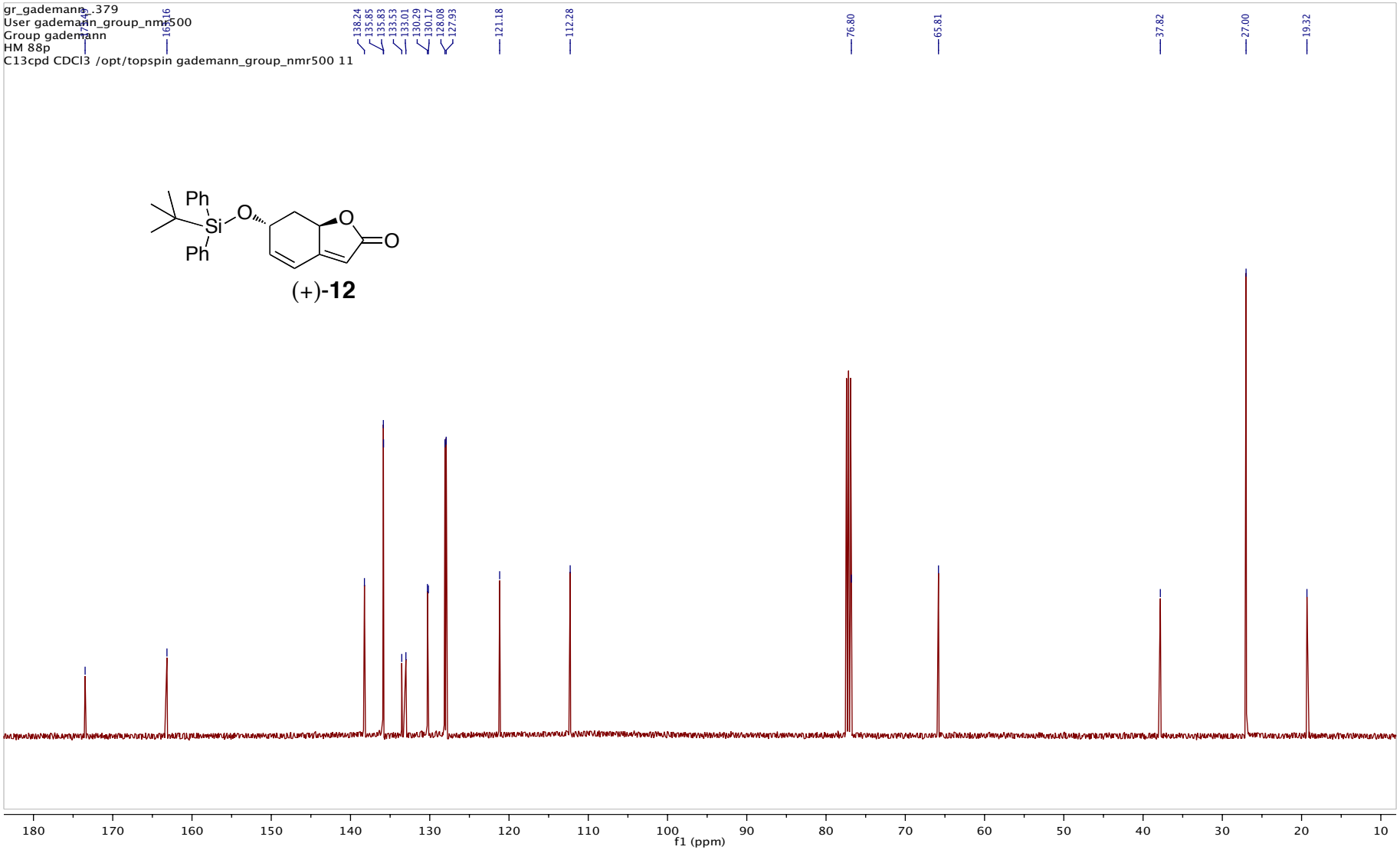

paruthi-929
hm08-P
_Proton_16 CDCl3 /opt/topspin paruthi 31
5.71
5.71
5.70
5.70
5.69
5.69
5.68
4.13
4.11
4.10
4.09
4.08
4.06
2.64
2.64
2.64
2.63
2.63
2.60
2.60
2.59
2.44
2.40
2.39
2.31
2.28
2.24
2.24
2.10
2.09
2.06
O
O
(–)-16
2.03
1.00
2.15
1.08
3.28
1.08
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

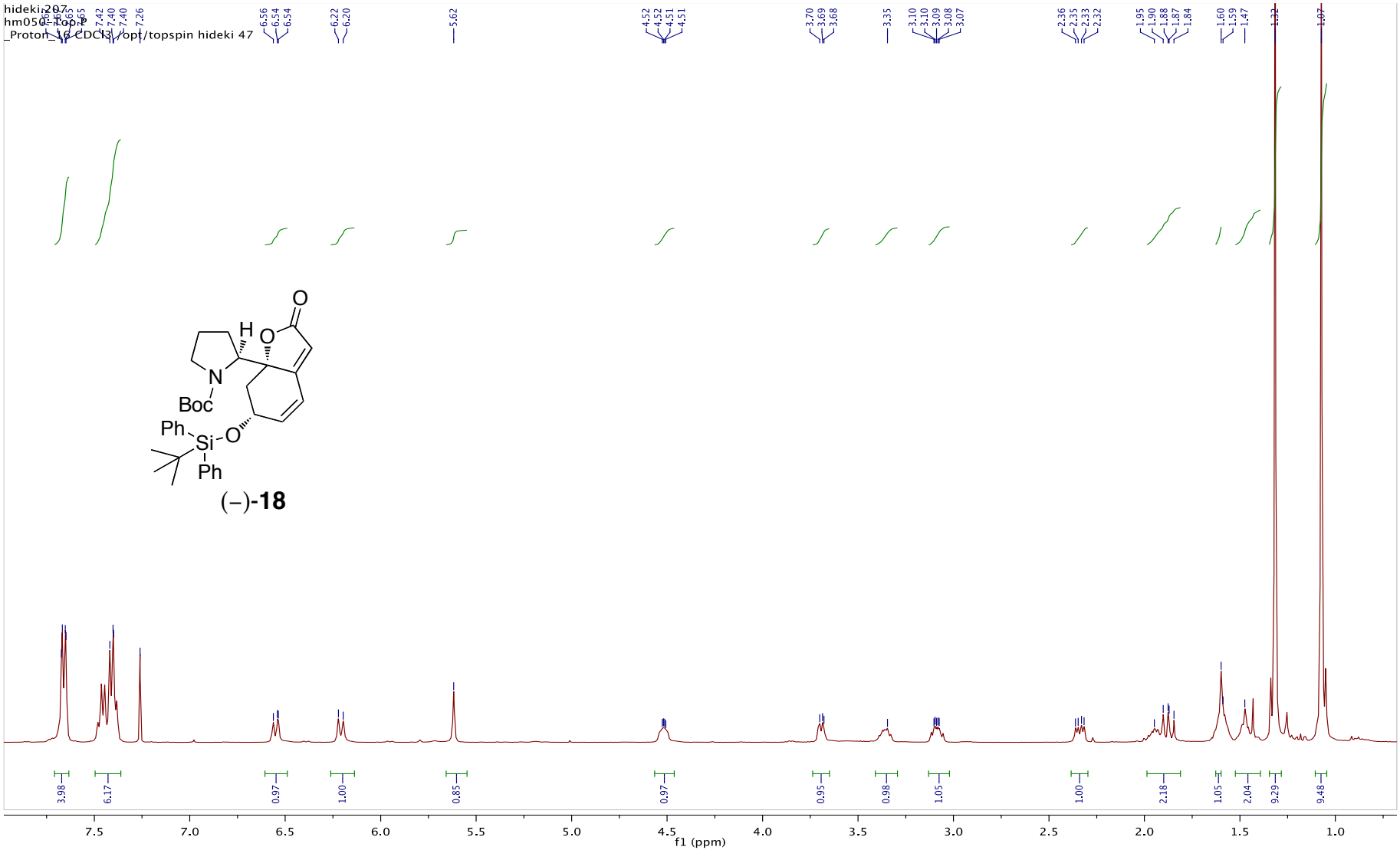

paruthi.929
hm08-P
_13Ccpd_ns256 CDCl3 /opt/topspin paruthi 31
176.45
127.10
124.36
81.47
40.28
35.57
30.79
29.90
O
O
(–)-16
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

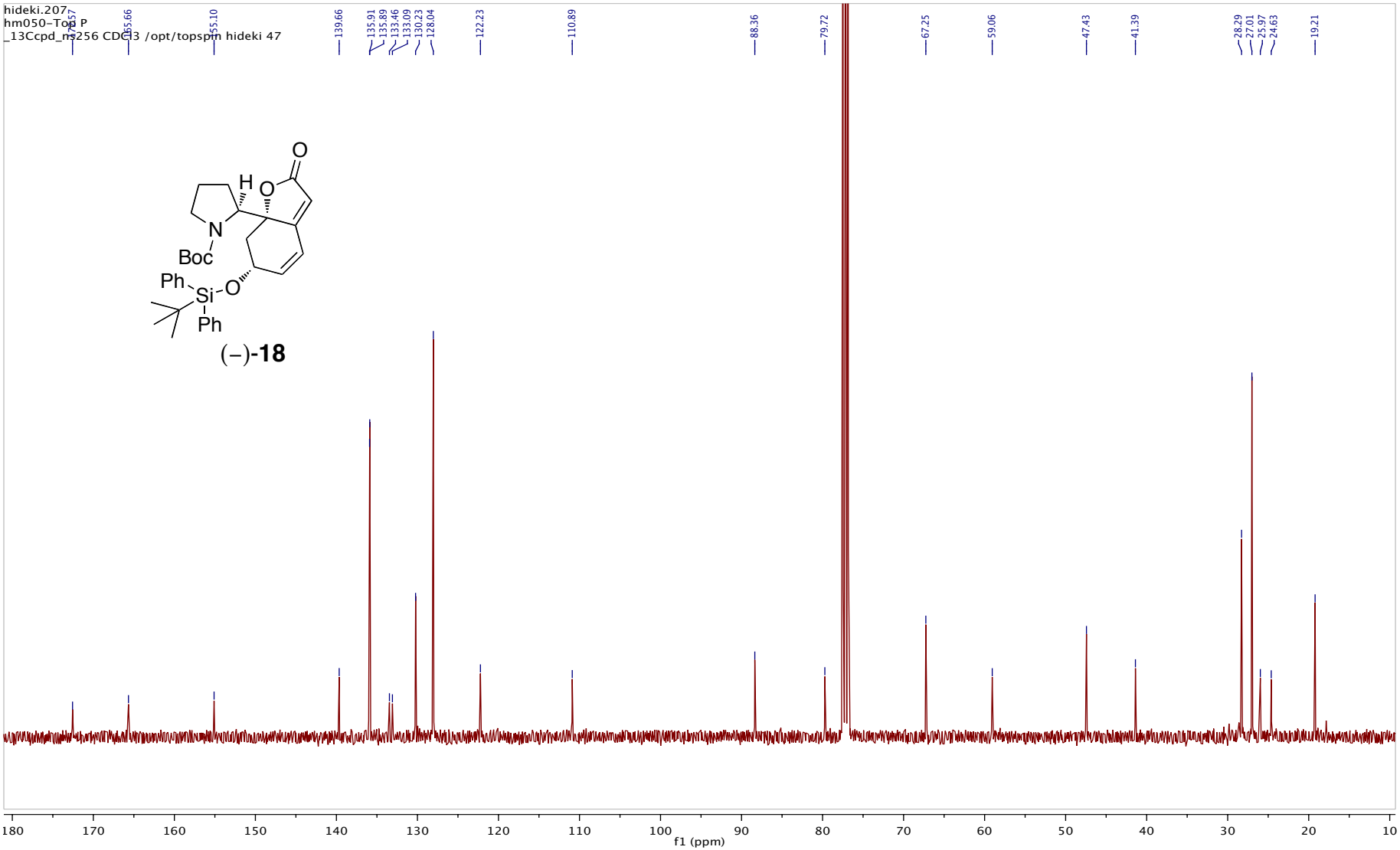

paruthi-938
hm12-P
_Proton_16 CDCl3 /opt/topspin paruthi 18
5.85
5.84
5.84
5.83
5.73
5.72
5.72
5.71
5.71
5.71
4.98
4.97
4.97
3.37
3.37
3.32
3.32
3.32
3.31
3.31
3.31
3.31
3.30
3.23
3.22
3.22
3.21
3.21
3.21
2.96
2.95
2.94
2.93
2.92
2.91
2.90
2.15
O
O
(–)-17
1.00
2.11
1.01
1.12
1.12
1.15
1.15
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
f1 (ppm)

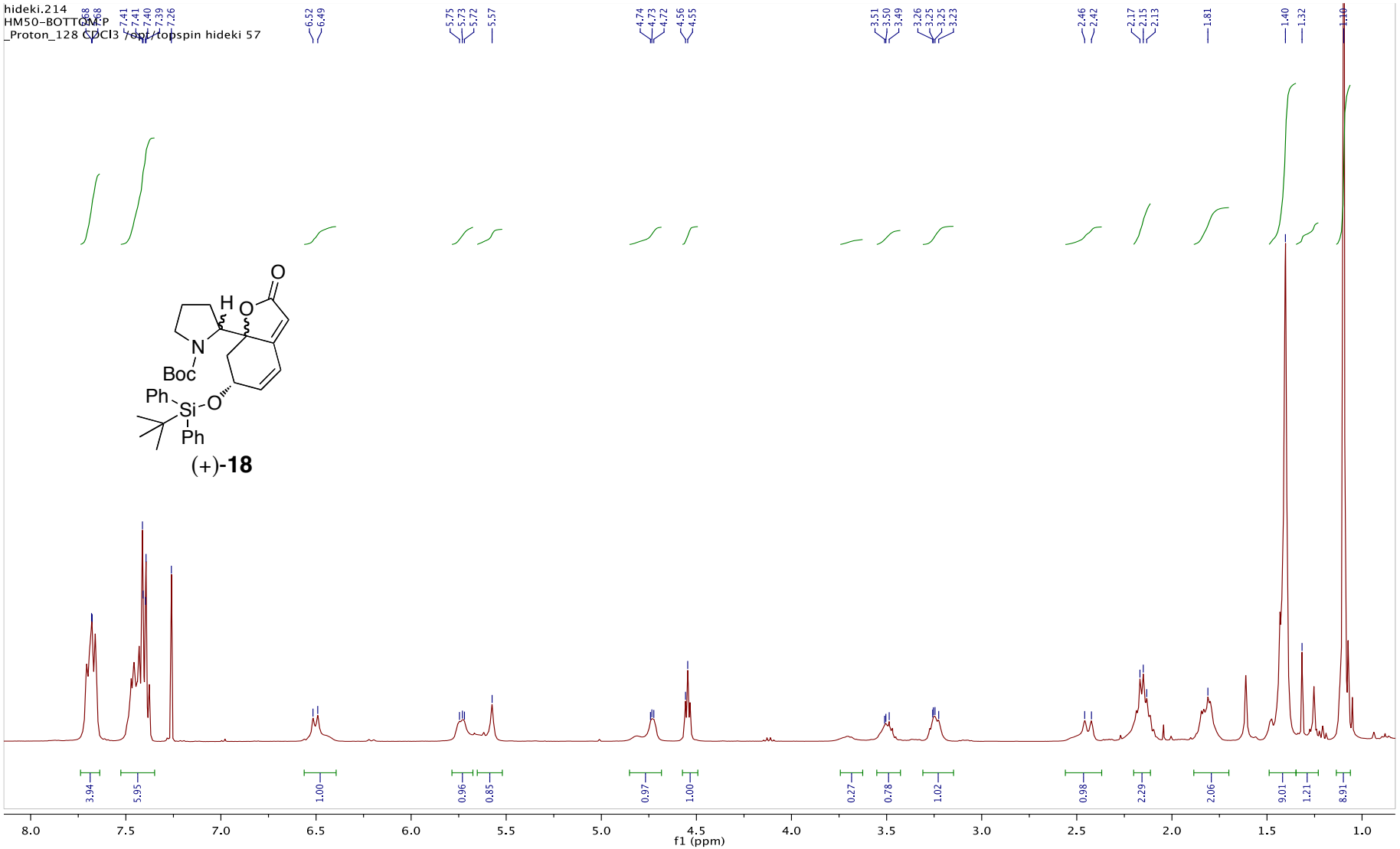

paruthi.938
hm12-P
_13Ccpd_ns256 CDCl3 /opt/topspin paruthi 18
173.45
168.22
123.80
123.20
113.48
78.49
32.71
28.28
O
O
(–)-17
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

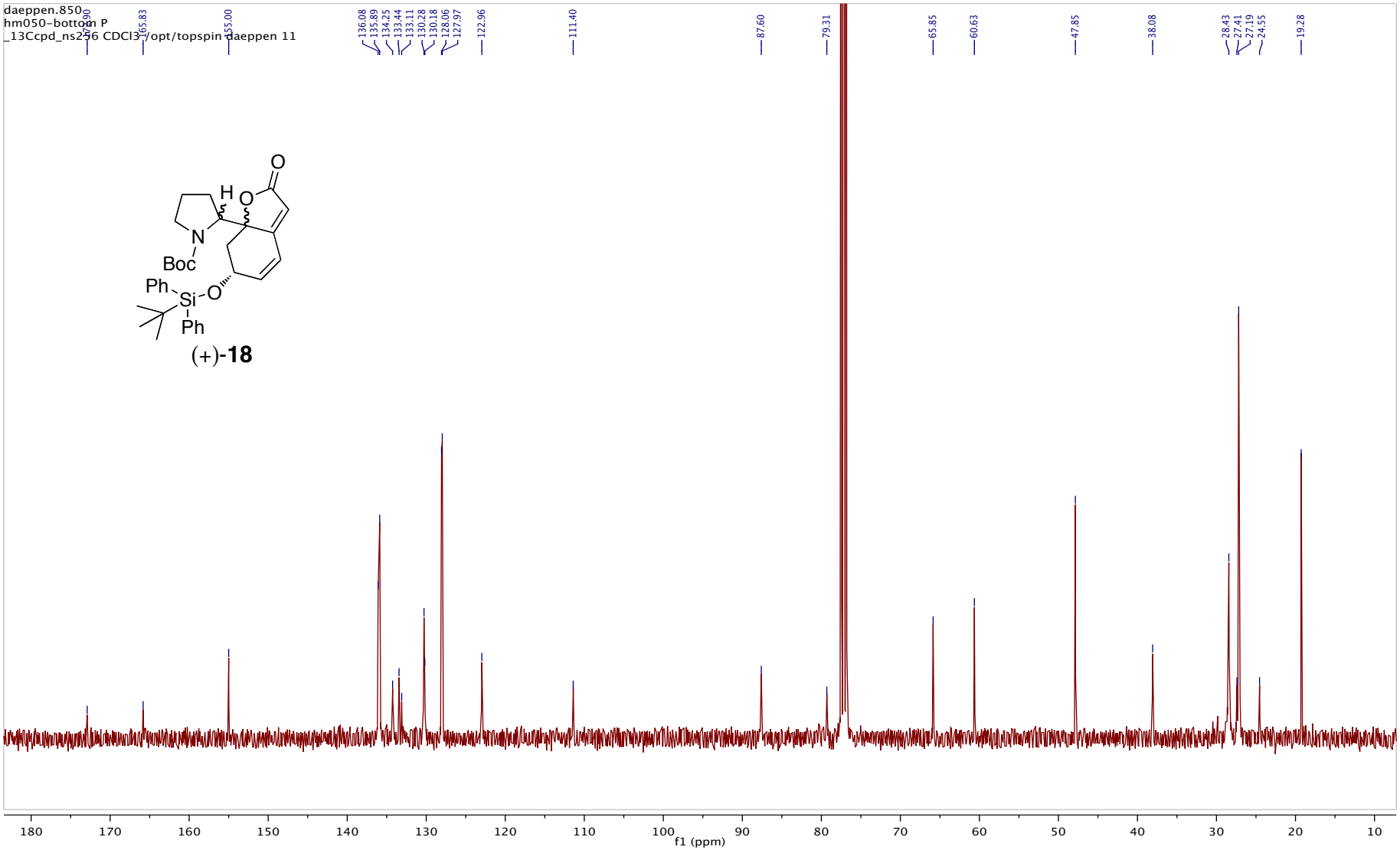

gr-gademann -379
User-gademann_group_nmr500
Group gademann
HM 88p
H1 CDCl3 /opt/topspin gademann_group_nmr500 11
Ph
Si
O
O
O
Ph
(+)-12
f1 (ppm)

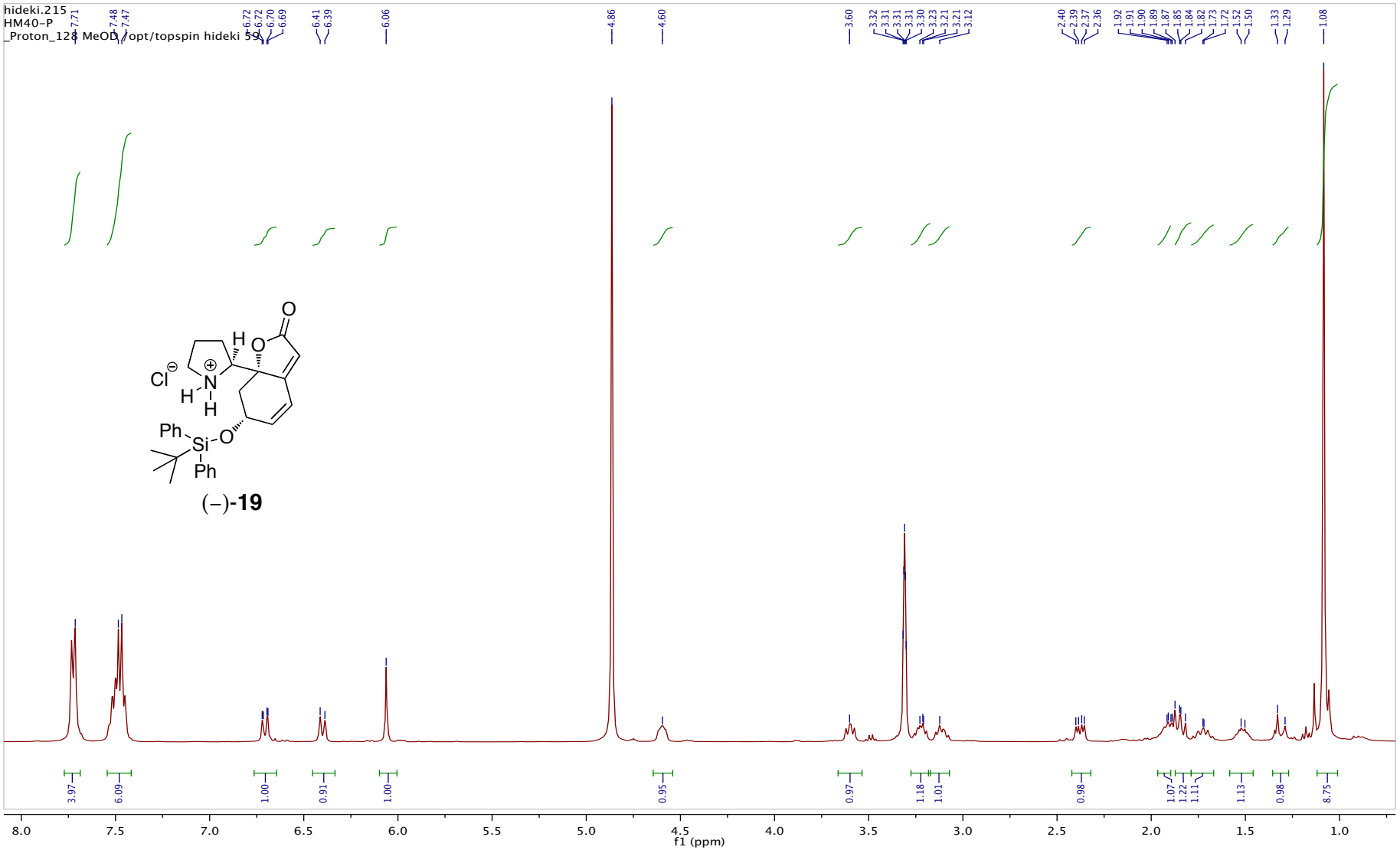

gr_gademann_c.379
User gademann_group_nmr500
Group gademann
HM 88p
C13cpd CDCl3 /opt/topspin gademann_group_nmr500 11
174.47
165.16
138.24
135.85
135.83
133.53
133.01
130.29
130.17
128.08
127.93
121.18
112.28
76.80
65.81
37.82
27.00
19.32
Ph
Si
Ph
O
O
O
(+)-12
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


hideki-207
hm050_top1
_Proton_1d CDCl3 /opt/topspin hideki 47
7.42
7.40
7.40
7.26
6.56
6.54
6.54
6.22
6.20
5.62
4.52
4.52
4.51
4.51
3.70
3.69
3.68
3.35
3.10
3.10
3.09
3.08
3.07
2.36
2.35
2.33
2.32
1.95
1.90
1.88
1.87
1.84
1.60
1.59
1.47
1.32
1.07
O
H
O
N
Boc
Ph
Si
O
Ph
(–)-18
3.98
6.17
0.97
1.00
0.85
0.97
0.95
0.98
1.05
1.00
2.18
1.05
2.04
9.29
9.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

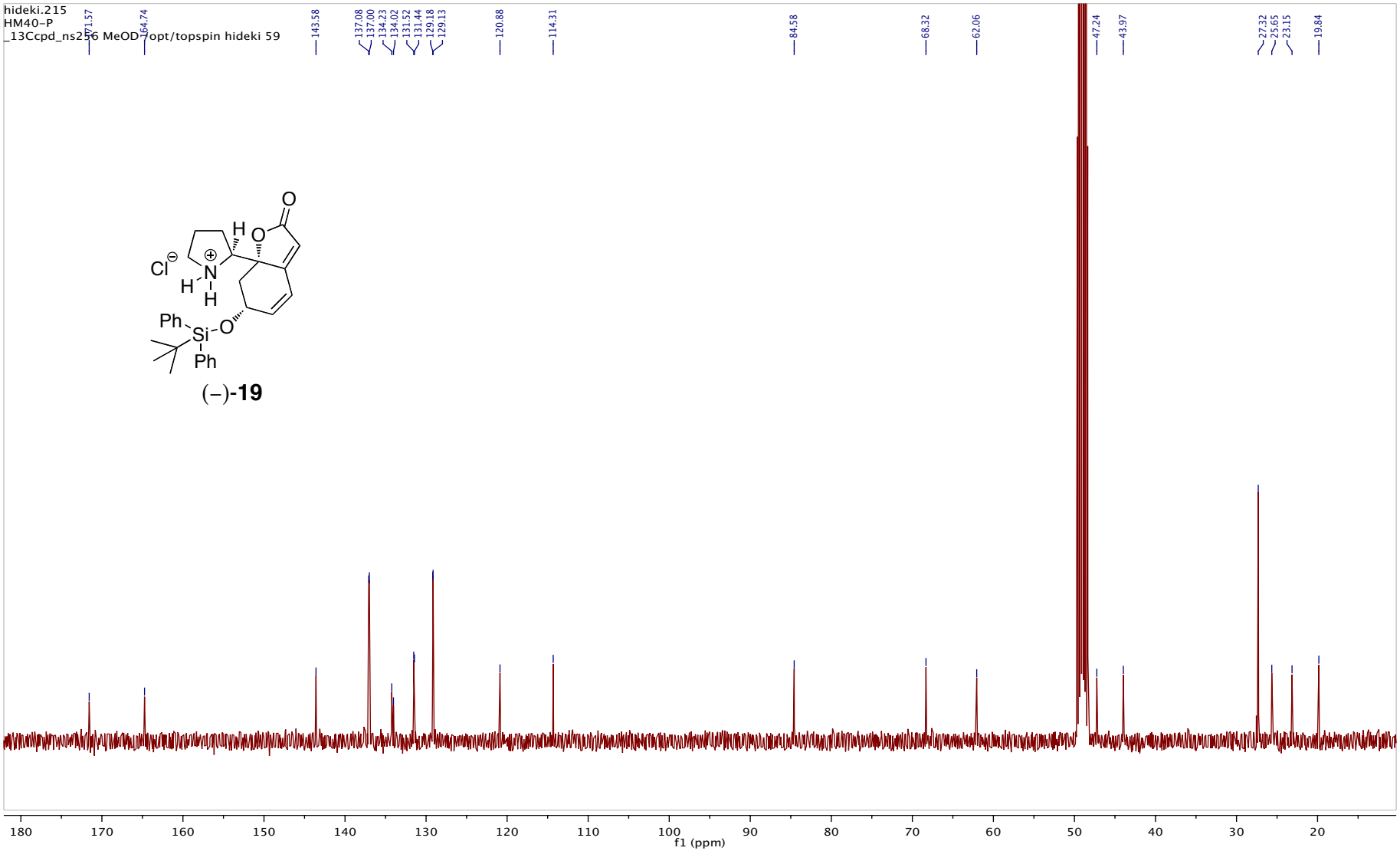

hideki.207
hm050-Top P
_13Ccpd_ns256 CDCl3 /opt/topspin hideki 47
155.57
155.66
155.10
139.66
135.91
135.89
133.46
133.09
130.23
128.04
122.23
110.89
88.36
79.72
67.25
59.06
47.43
41.39
28.29
27.01
25.97
24.63
19.21
O
H
O
N
Boc
Ph
Si
O
Ph
(–)-18
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


hideki.214
HM50-BOTTOM-P
_Proton_128 CDCl3 /opt/topspin hideki 57
6.52
6.49
5.75
5.73
5.72
5.57
4.74
4.73
4.72
4.56
4.55
3.51
3.50
3.49
3.26
3.25
3.25
3.23
2.46
2.42
2.17
2.15
2.13
1.81
1.40
1.32
1.10
O
H
O
N
Boc
Ph
Si
O
Ph
Ph
(+)-18
3.94
5.95
1.00
0.96
0.85
0.97
1.00
0.27
0.78
1.02
0.98
2.29
2.06
9.01
1.21
8.91
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

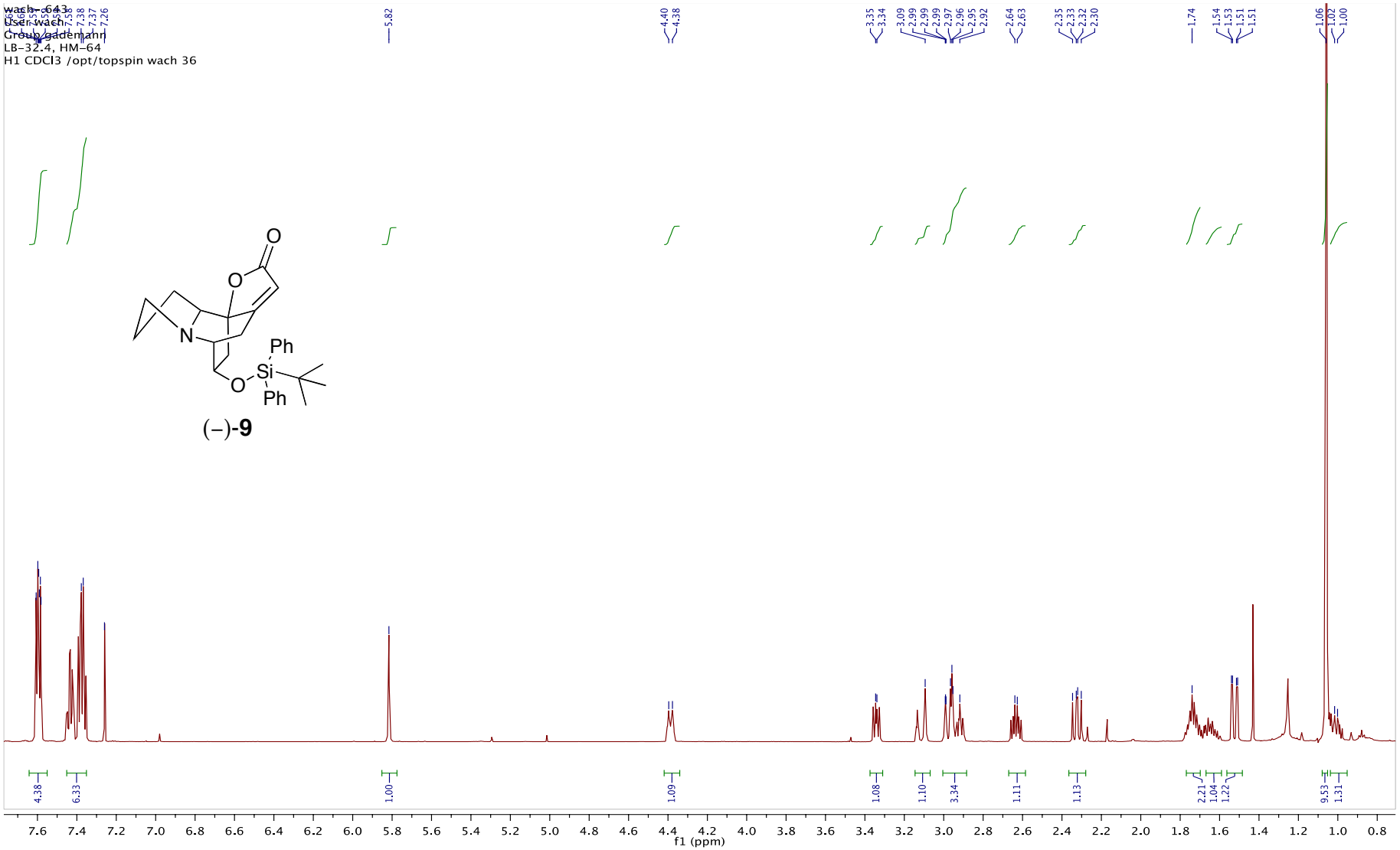

daeppen.850
hm050-bottom P
_13Ccpd_ns256 CDCl3 /opt/topspin daeppen 11
175.90
165.83
155.00
136.08
135.89
134.25
133.44
133.11
130.28
130.18
128.06
127.97
122.96
111.40
87.60
79.31
65.85
60.63
47.85
38.08
28.43
27.41
27.19
24.55
19.28
O
H
O
N
Boc
Ph
Si
O
Ph
(+)-18
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

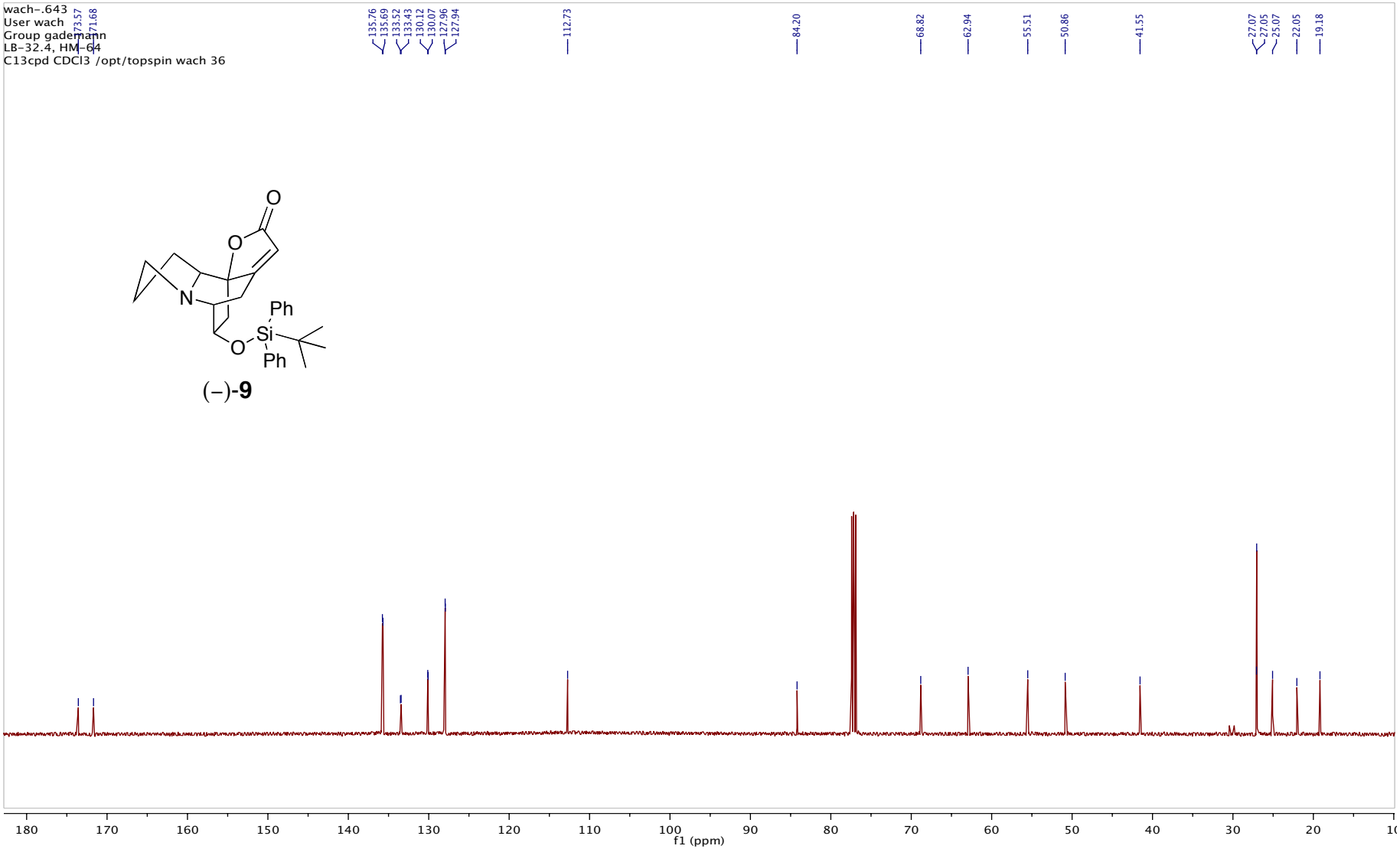

hideki.215
HM40-P
_Proton_128 MeOD //opt/topspin hideki 59
7.71
7.48
7.47
6.72
6.72
6.70
6.69
6.41
6.39
6.06
4.86
4.60
3.60
3.32
3.31
3.31
3.31
3.30
3.23
3.21
3.21
3.12
2.40
2.39
2.37
2.36
1.92
1.91
1.90
1.89
1.87
1.85
1.84
1.82
1.73
1.72
1.52
1.50
1.33
1.29
1.08
3.97
6.09
1.00
0.91
1.00
0.95
0.97
1.18
1.01
0.98
1.07
1.22
1.11
1.13
0.98
8.75
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

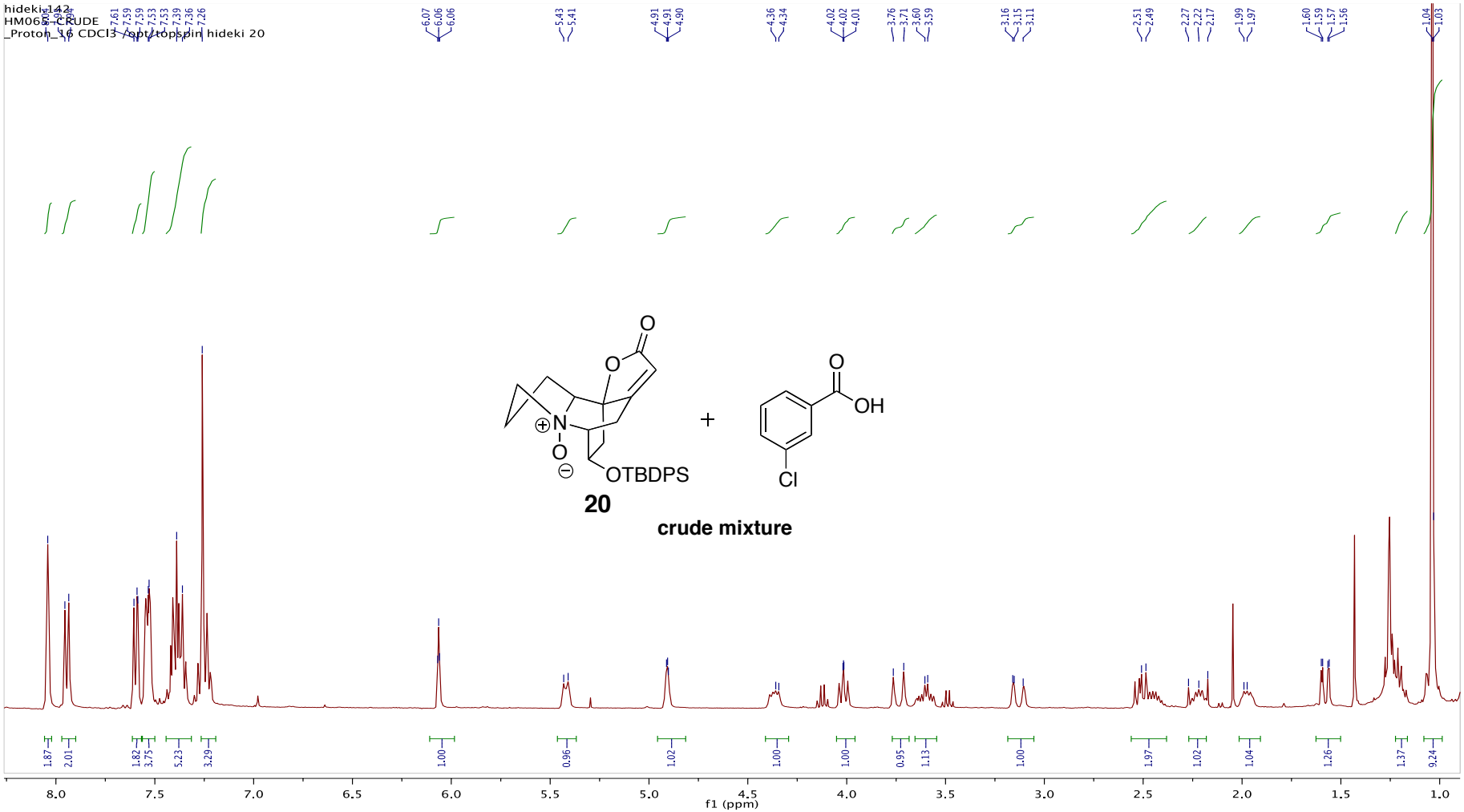
(–)-**19**

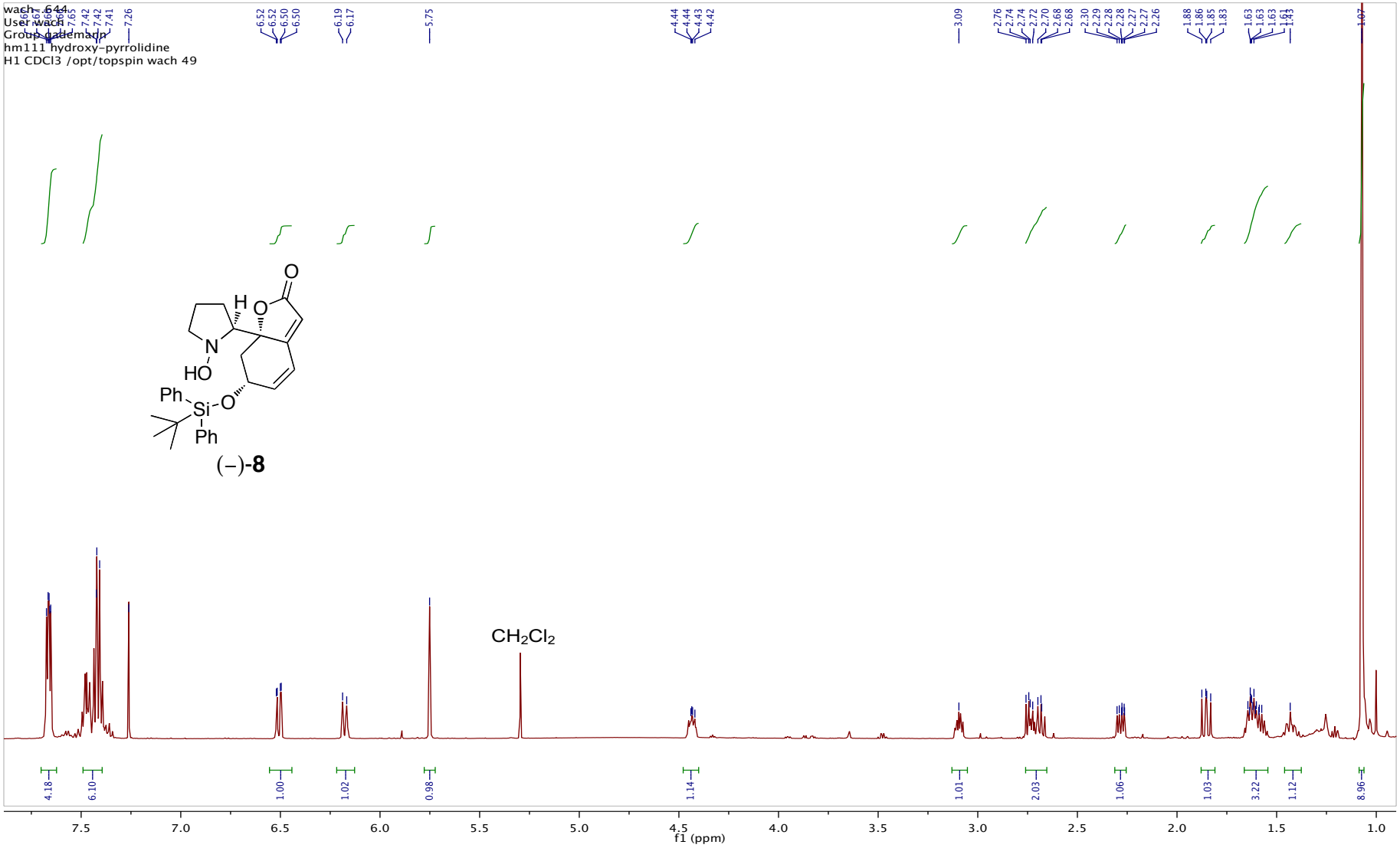

hideki.215
HM40-P
_13Ccpd_ns256 MeOD-7opt/topspin hideki 59
171.57
164.74
143.58
137.08
137.00
134.23
134.02
131.52
131.44
129.18
129.13
120.88
114.31
84.58
68.32
62.06
47.24
43.97
27.32
25.65
23.15
19.84
f1 (ppm)

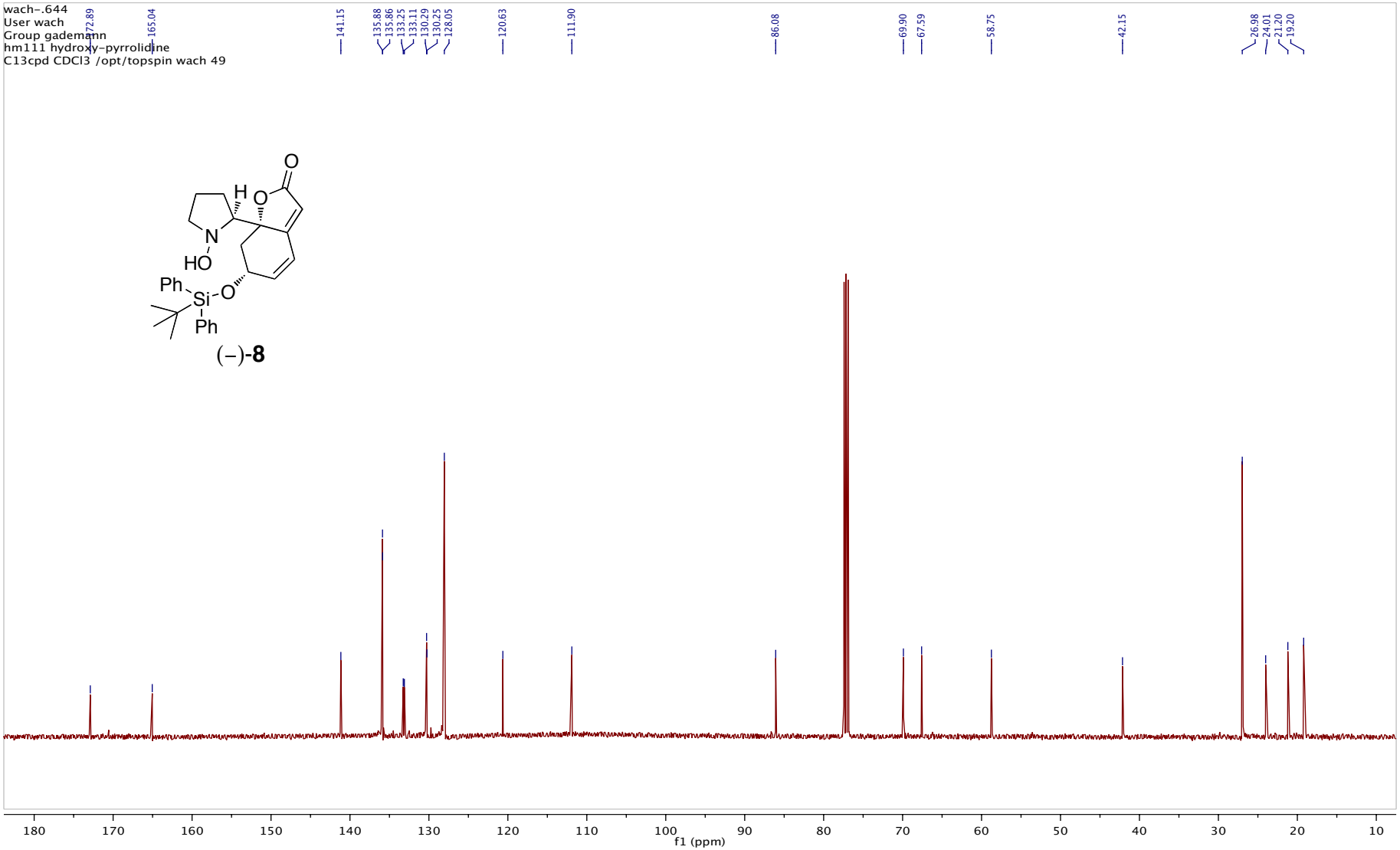
(–)-**19**

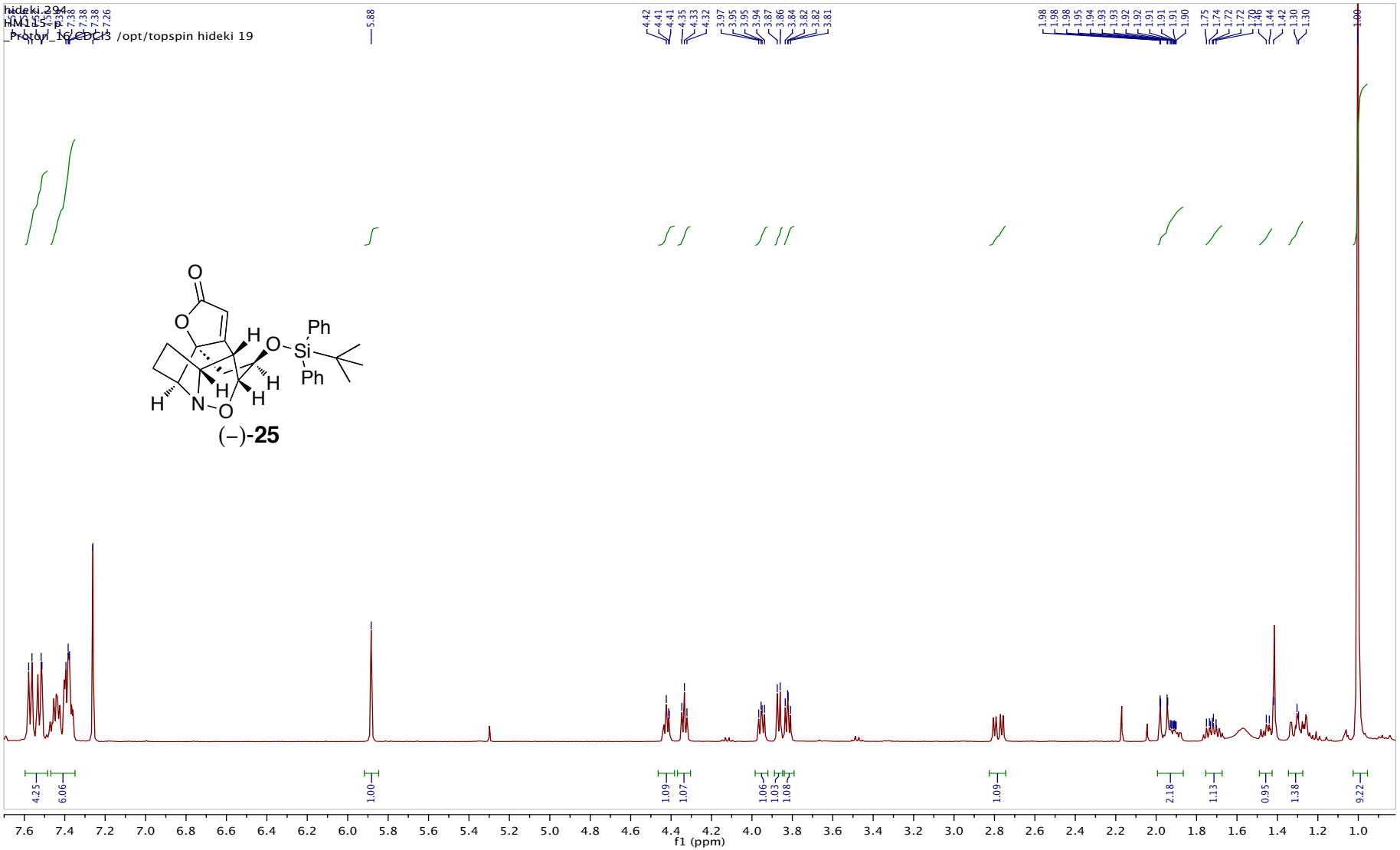

wach-643
User: wach
Group: gademann
LB-32.4, HM-64
H1 CDCl3 /opt/topspin wach 36
7.66 7.65 7.58 7.38 7.37 7.26
5.82
4.40 4.38
3.35 3.34 3.09 2.99 2.99 2.99 2.97 2.96 2.95 2.92
2.64 2.63
2.35 2.33 2.32 2.30
1.74
1.54 1.53 1.51 1.51
1.06 1.02 1.00
O
O
N
Ph
Si
O
Ph
(–)-9
4.38 6.33 1.00 1.09 1.08 1.10 3.34 1.11 1.13 2.21 1.04 1.22 9.53 1.31
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

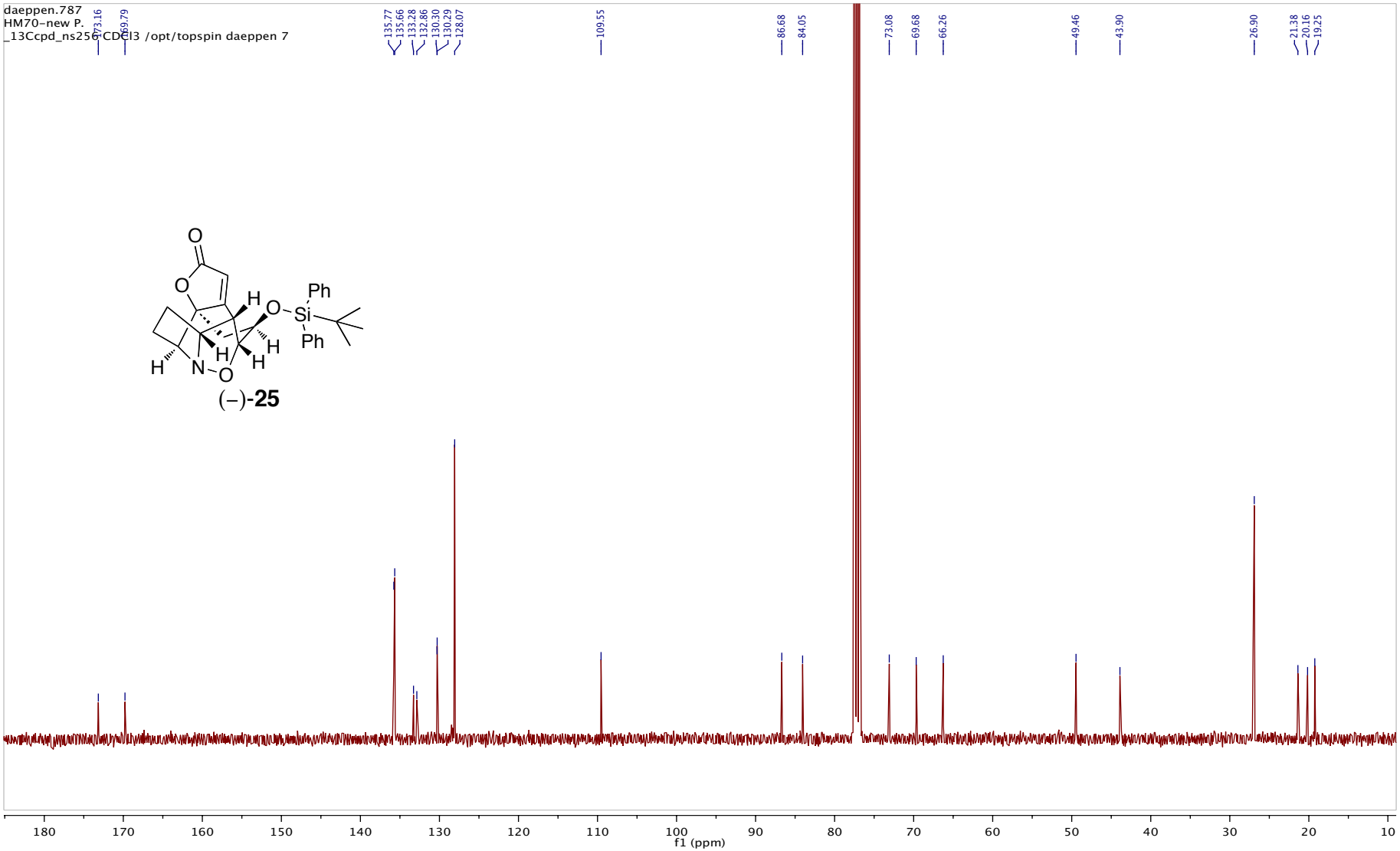

wach-.643
User wach
Group gademann
LB-32.4, HM-64
C13cpd CDCl3 /opt/topspin wach 36
73.57
71.68
135.76
135.69
133.52
133.43
130.12
130.07
127.96
127.94
112.73
84.20
68.82
62.94
55.51
50.86
41.55
27.07
27.05
25.07
22.05
19.18
O
O
N
Ph
Si
O
Ph
(–)-9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

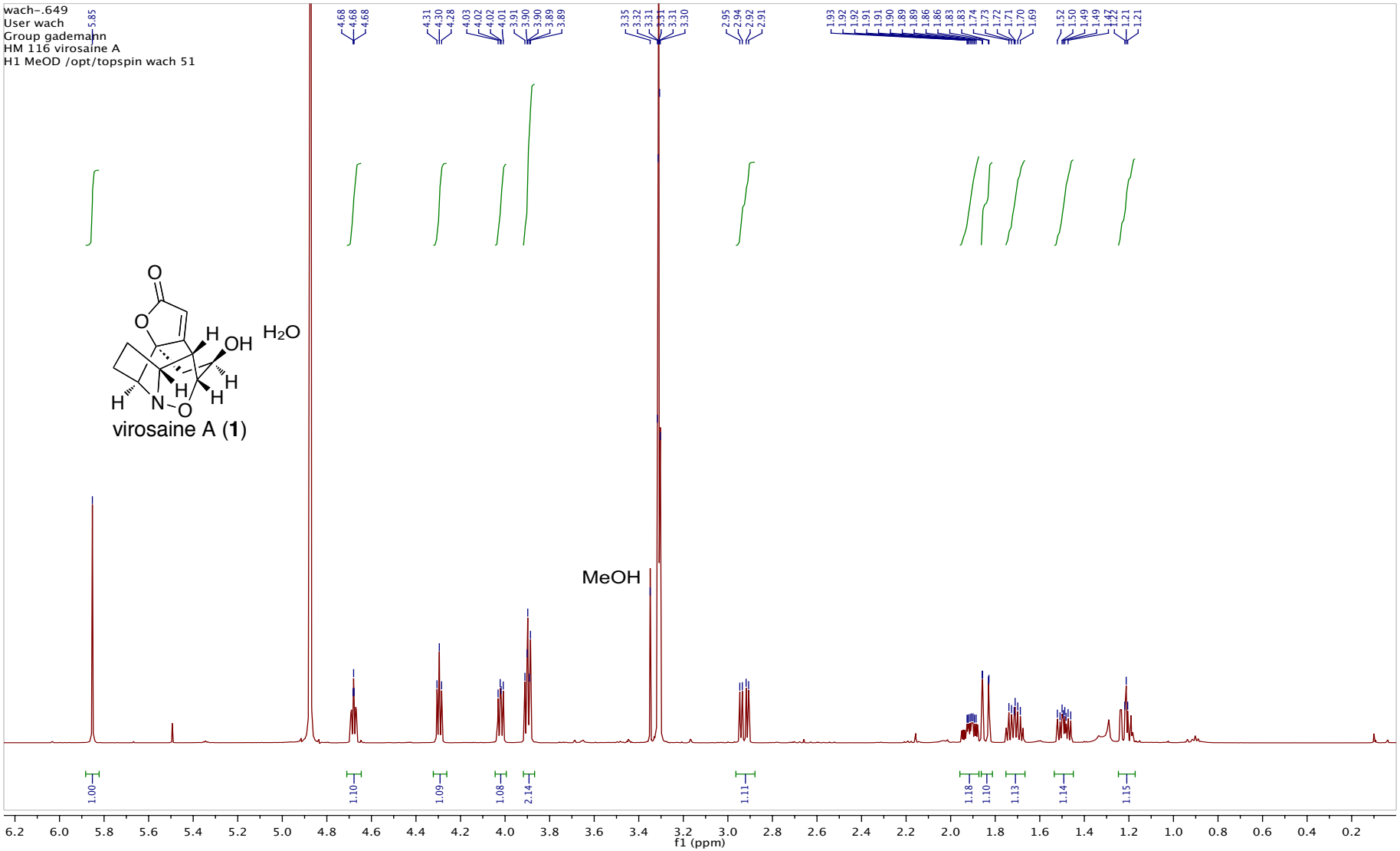

hideki-142
HM065-CRUDE
_Proton_16 CDCl3 /apt/cropsdin hideki 20
7.61
7.59
7.59
7.53
7.53
7.39
7.36
7.26
6.07
6.06
6.06
5.43
5.41
4.91
4.91
4.90
4.36
4.34
4.02
4.02
4.01
3.76
3.71
3.60
3.59
3.16
3.15
3.11
2.51
2.49
2.27
2.22
2.17
1.99
1.97
1.60
1.59
1.57
1.56
1.04
1.03
O
O
N
O
OTBDPS
20
+
O
OH
Cl
crude mixture
1.87
2.01
1.82
3.75
5.23
3.29
1.00
0.96
1.02
1.00
1.00
0.95
1.13
1.00
1.97
1.02
1.04
1.26
1.37
9.24
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

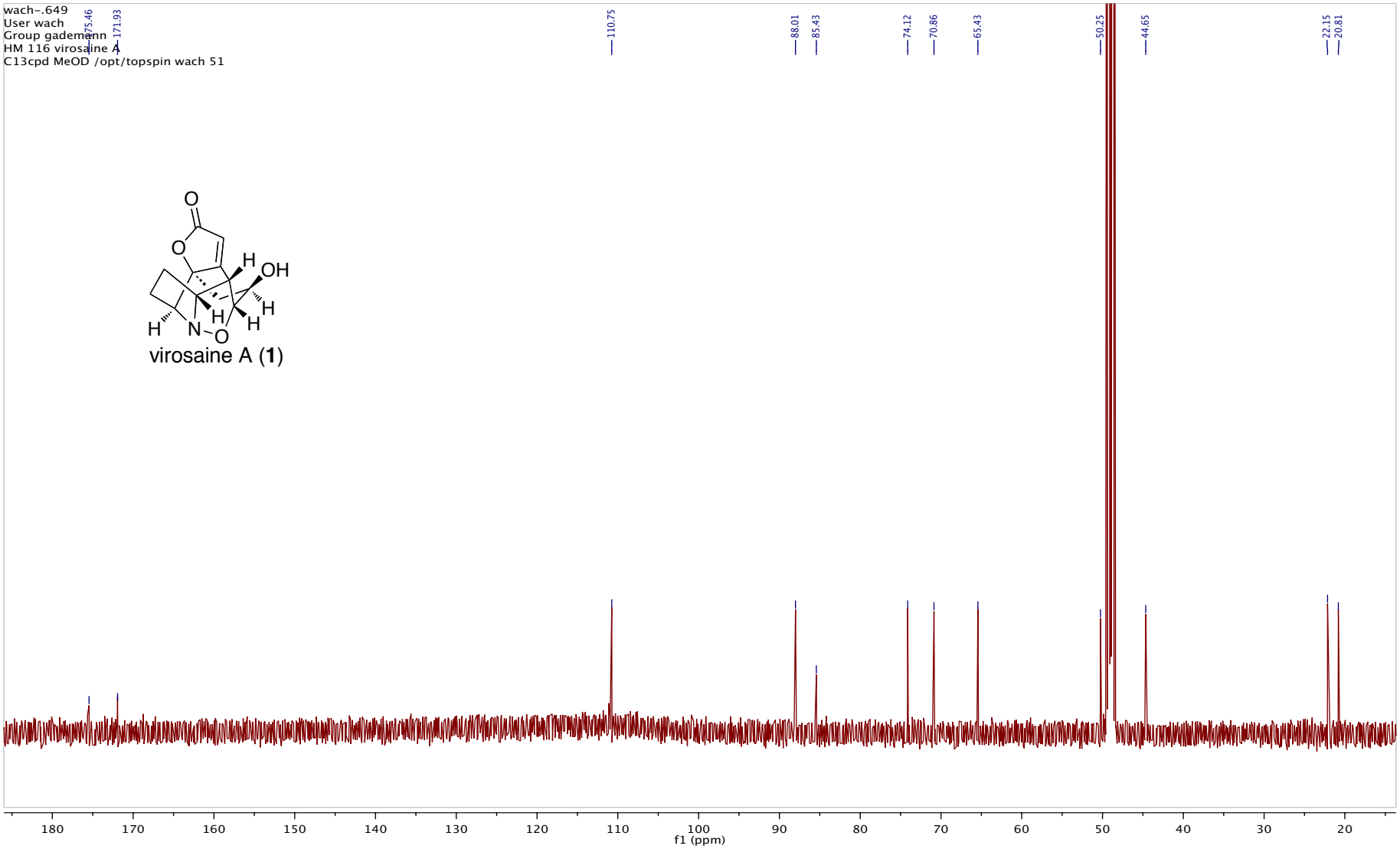

wach-644
User wach
Group dademann
hm111 hydroxy-pyrrolidine
H1 CDCl3 /opt/topspin wach 49
(–)-8
CH2Cl2
f1 (ppm)


wach-.644
User wach
Group gademann
hm111 hydroxy-pyrrolidine
C13cpd CDCl3 /opt/topspin wach 49
172.89
165.04
141.15
135.88
135.86
133.25
133.11
130.29
130.25
128.05
120.63
111.90
86.08
69.90
67.59
58.75
42.15
26.98
24.01
21.20
19.20
O
H
O
N
HO
Ph
Si
O
Ph
Ph
(–)-8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


hideki 294
HM115 p
Proton_1c/CDCl3 /opt/topspin hideki 19
(–)-25
f1 (ppm)

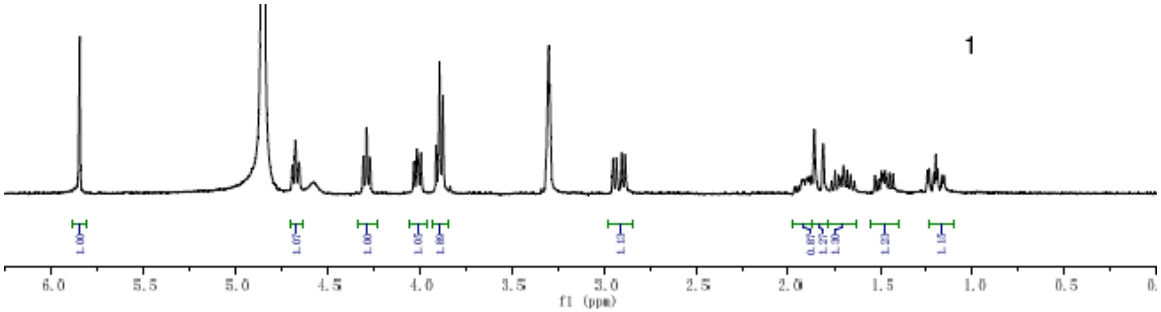

daeppen.787
HM70-new P.
_13Ccpd_ns256_CDCl3 /opt/topspin daeppen 7
173.16
169.79
135.77
135.66
133.28
132.86
130.30
130.29
128.07
109.55
86.68
84.05
73.08
69.68
66.26
49.46
43.90
26.90
21.38
20.16
19.25
O
O
H
O
Si
Ph
Ph
H
H
H
H
N
O
(–)-25
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



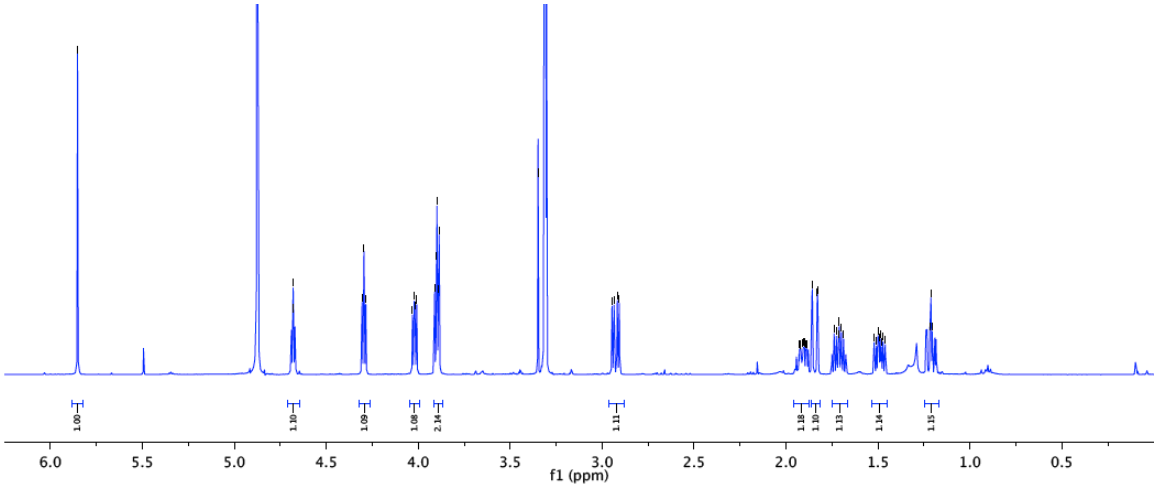

wach-.649
User wach
Group gademann
HM 116 virosaine A
C13cpd MeOD /opt/topspin wach 51
175.46
171.93
110.75
88.01
85.43
74.12
70.86
65.43
50.25
44.65
22.15
20.81
O
O
H
OH
H
H
H
N
O
H
virosaine A (1)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{1}H-NMR Comparison

Natural

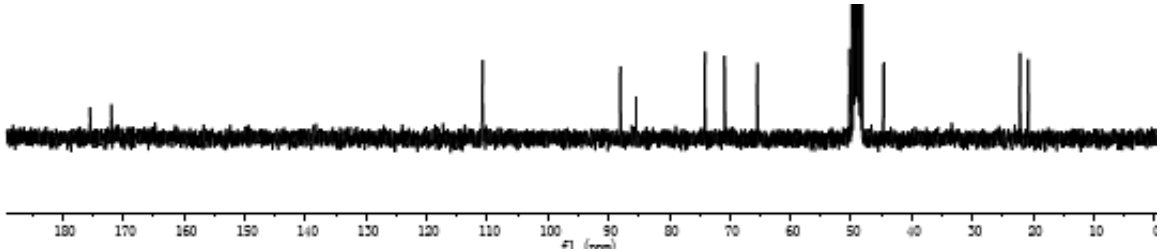


Synthetic

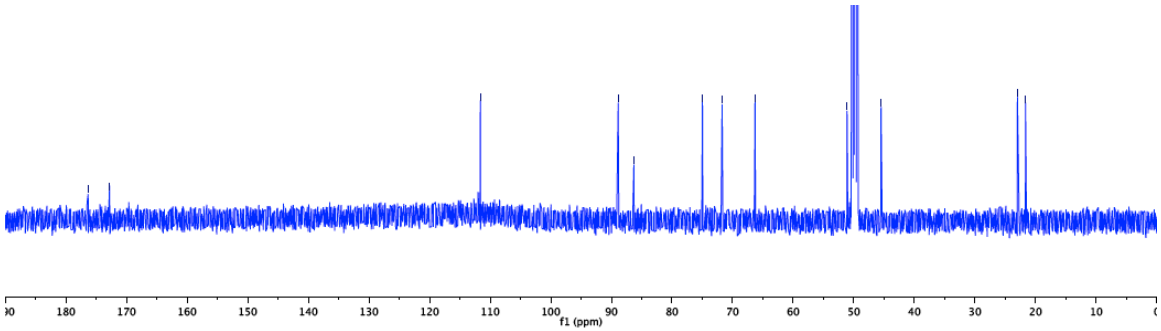


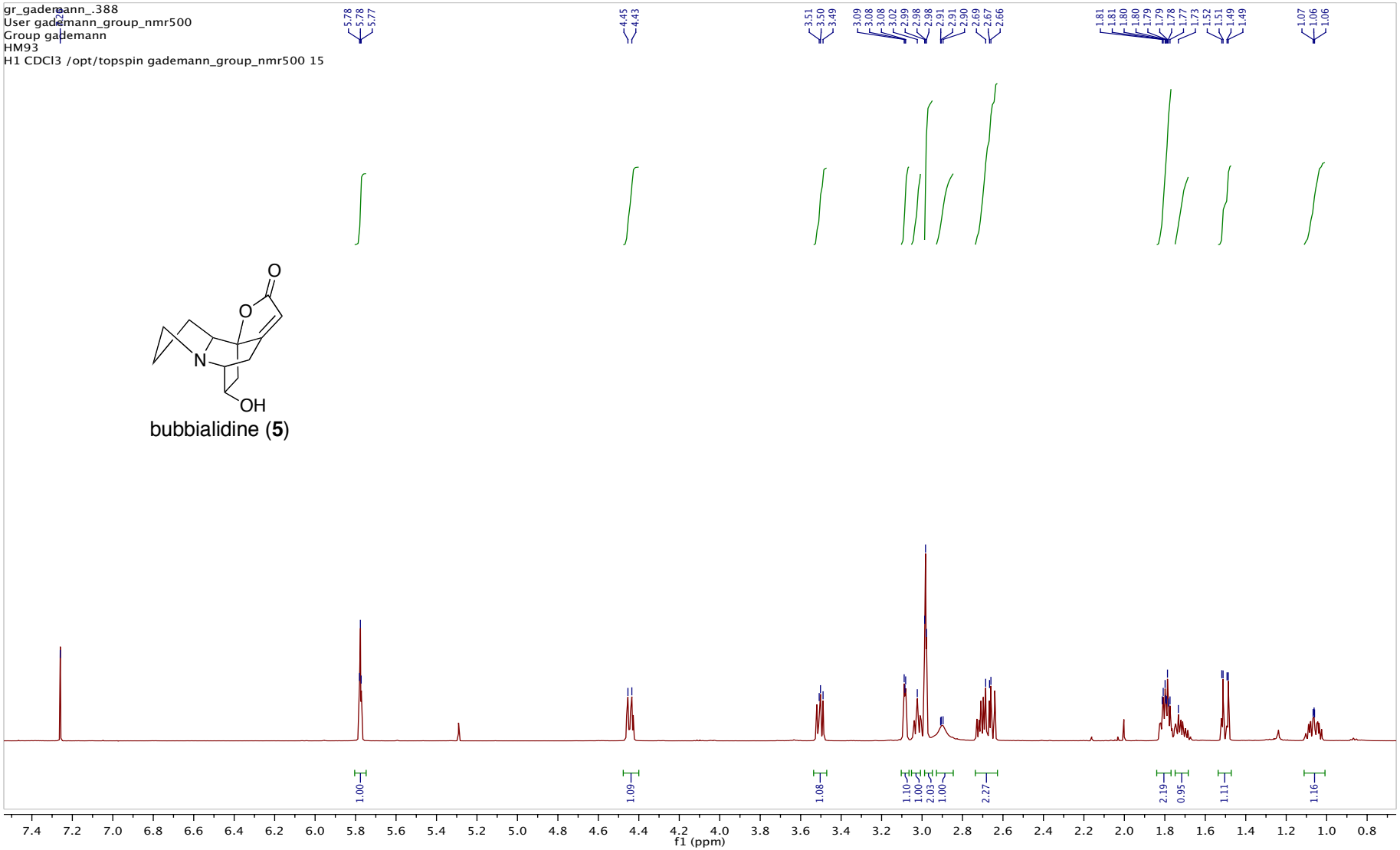
^{13}C-NMR comparison

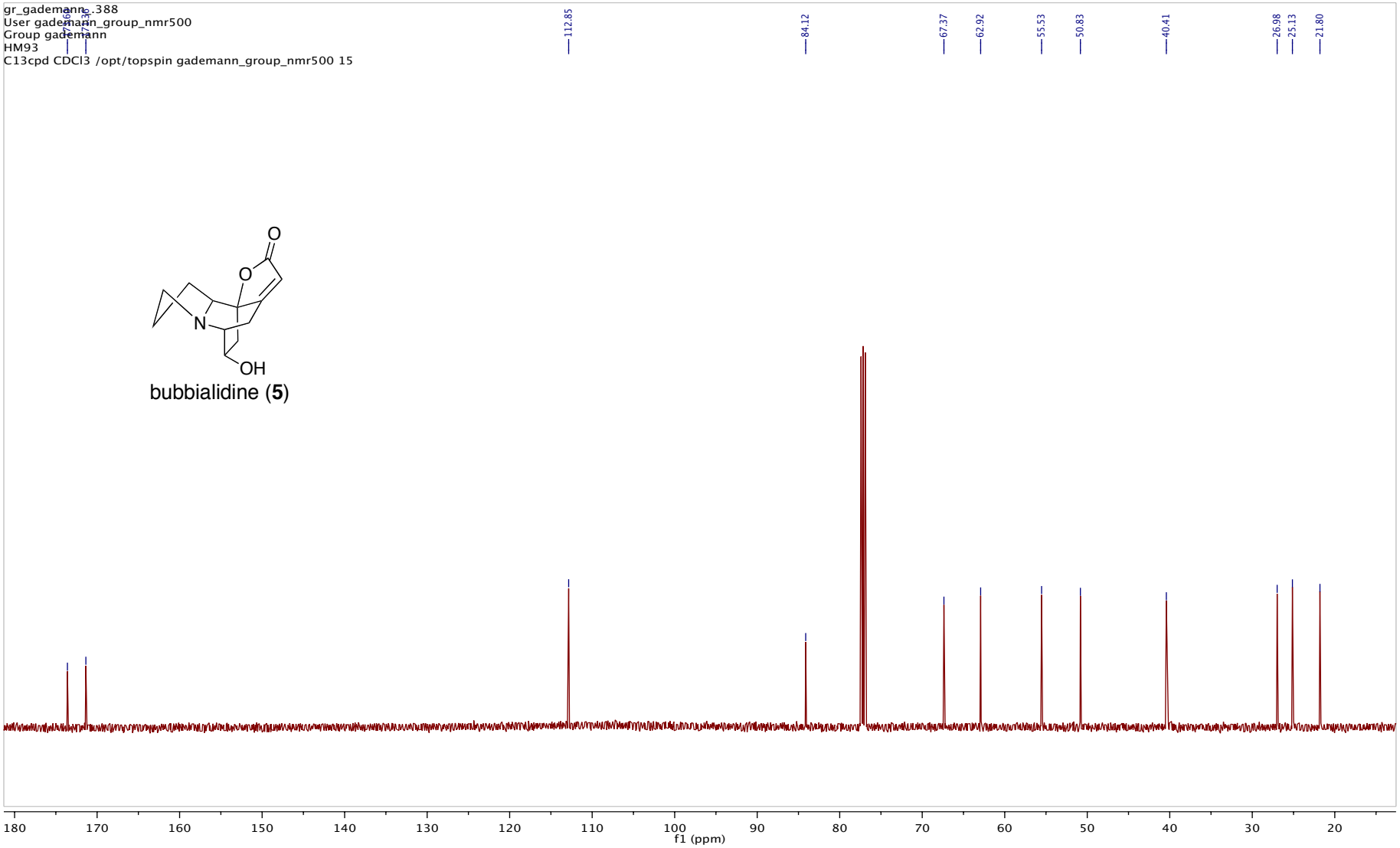
Natural



Synthetic




gr_gademann_.388
User gademann_group_nmr500
Group gademann
HM93
H1 CDCl3 /opt/topspin gademann_group_nmr500 15
O
O
N
OH
bubbialidine (5)
f1 (ppm)


gr_gademann_c.388
User gademann_group_nmr500
Group gademann
HM93
C13cpd CDCl3 /opt/topspin gademann_group_nmr500 15
176.66
173.38
112.85
84.12
67.37
62.92
55.53
50.83
40.41
26.98
25.13
21.80
O
O
N
OH
bubbialidine (5)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)