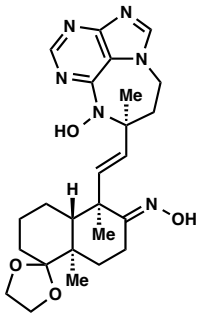
Table of Contents of Supporting Information:

Table of cytotoxicity data of the asmarines

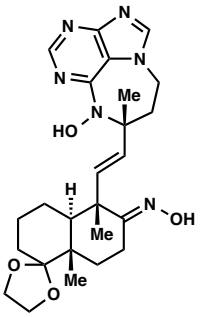
	48 hr IC50 (uM)			
Compound	**HT29**	**Jurkat**	**Hela**	**HL60**
26	8.6 ± 0.9	14.4 ± 0.9	~60 (no effect)	8.5 ± 1.3
***ent*-26**	9.3 ± 0.6	9.8 ± 0.5	~56 (no effect)	12.7 ± 0.9
37	1.9 +/-0.3	1.2 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
56	607 nM ± 90 nM	472 nM ± 50 nM	714 nM ± 100 nM	199 nM ± 11 nM
57	590 nM ± 70 nM	471 nM ± 37 nM	572 nM ± 98 nM	270 nM ± 45 nM

	48 hr IC50 (uM)		
Compound	**HEK 293**	**MCF 7**	**MDA-MB 231**
26	12.2 ± 1.4	15.5 ± 2.6	17.7 ± 2.4
***ent*-26**	12.5 ± 1.3	20.8 ± 2.1	15.9 ± 1.6
37	1.8 ± 0.3	2.2 ± 0.1	2.8 ± 0.8
56	455 nM ± 16 nM	455 nM ± 80 nM	511 nM ± 46 nM
57	295 nM ± 43 nM	312 nM ± 47 nM	455 nM ± 15 nM

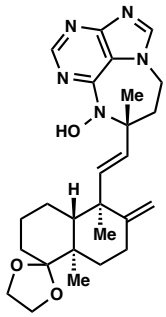
	48 hr IC50 (uM)		
Compound	**HT29**	**Jurkat**	**Hela**
19	~113 (no effect)	~82 (no effect)	~54 (no effect)
***ent*-19**	~86 (no effect)	~61 (no effect)	~52 (no effect)
22	no effect	no effect	26.2 ± 1.0
24	24.7 ± 5.0	25.9 ± 4.4	21.6 ± 2.7
34	21.3 ± 1.2	19.6 ± 0.9	~106 (no effect)
***ent*-34**	11.8 ± 0.7	21.6 ± 1.0	31.83 ± 3.9
35	~52 (no effect)	~70 (no effect)	~50 (no effect)
***ent*-35**	21.23 ± 0.8	35.9 ± 1.5	36.6 ± 1.5
36	5.6 ± 1.1	6.1 ± 0.3	12.9 ± 1.9
38	~100 (no effect)	~74 (no effect)	~47 (no effect)
49	24.7 ± 3.9	22.6 ± 3.6	35.4 ± 3.3
50	21.1 ± 6.0	15.4 ± 0.5	21.2 ± 2.5
51	~260 (no effect)	~40 (no effect)	~61 (no effect)
52	32.6 ± 2.4	32.2 ± 3.6	21.4 ± 2.1
53	no effect	no effect	~58 (no effect)
54	1.1 ± 0.2	1.6 ± 0.1	1.7 ± 0.2
55	1.5 ± 0.3	1.3 ± 0.03	1.2 ± 0.1
59	no effect	no effect	27.1 ± 1.1
SI-5	30.9 ± 0.5	36.2 ± 1.5	~45 (no effect)
SI-6	32.7 ± 0.9	36.8 ± 1.3	33.2 ± 1.2
SI-13	~57 (no effect)	~270 (no effect)	~77 (no effect)
SI-14	~264 (no effect)	~121 (no effect)	~76 (no effect)



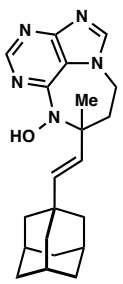
26



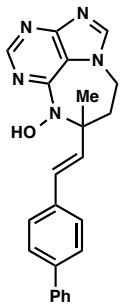
ent-26



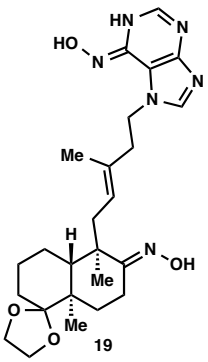
37



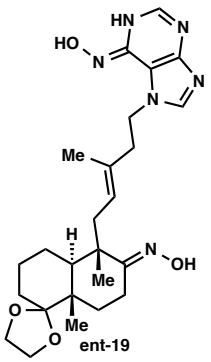
56



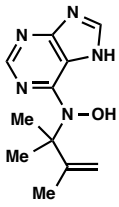
57



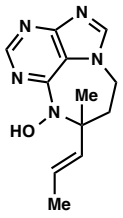
19



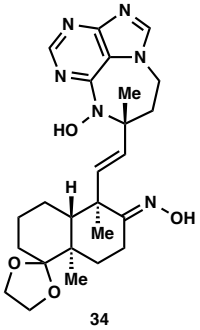
ent-19



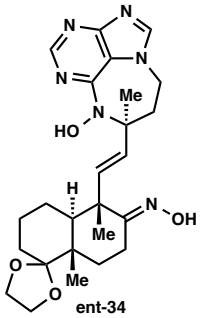
22



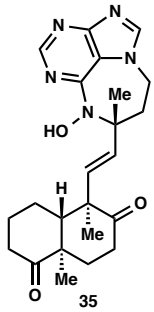
24



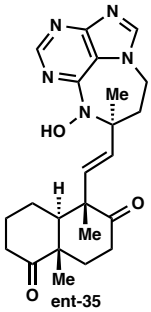
34



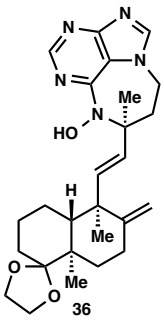
ent-34



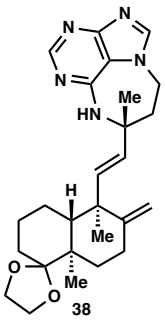
35



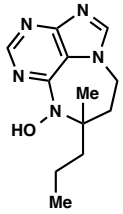
ent-35



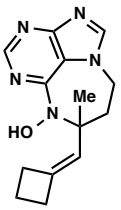
36



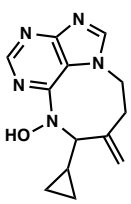
38



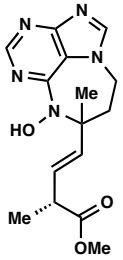
49



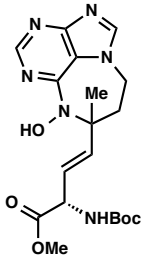
50



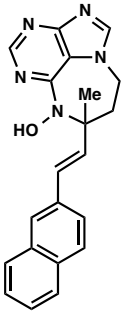
51



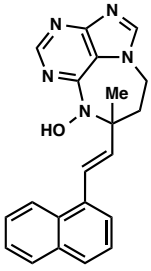
52



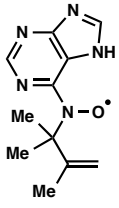
53



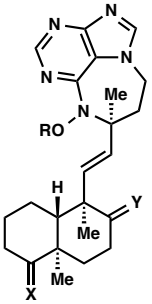
54



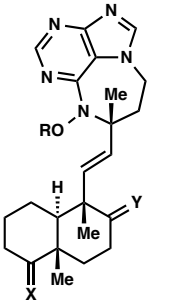
55



59



SI-5:X=Y=O; R = H
SI-13 X=(-OC_2H_4O-),
Y = CH_2,
R = OTIPS



SI-6: X=Y=O; R = H
SI-14 X=(-OC_2H_4O-),
Y = CH_2,
R = OTIPS

Materials and methods

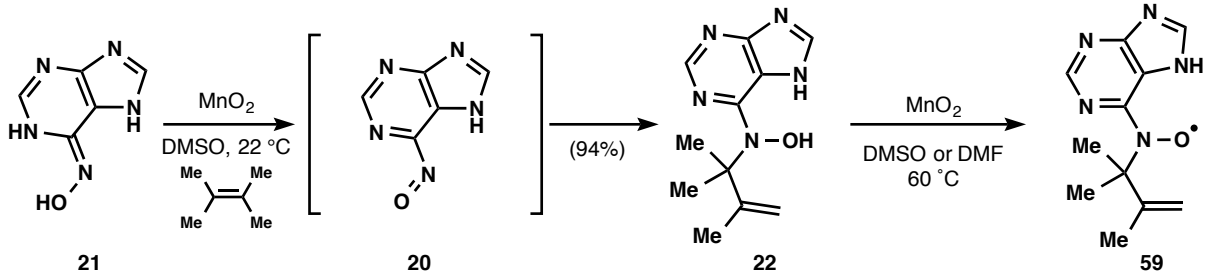
All reactions were carried out under positive pressure of nitrogen unless otherwise noted. Pentane, hexanes, dichloromethane (DCM), toluene, ethyl acetate (EtOAc), and diethyl ether were purchased from Fisher Chemicals or Sigma Aldrich and used without further purification, unless otherwise noted. Benzene, dimethylsulfoxide (DMSO), methanol (MeOH), *N*-dimethylformamide (DMF), dichloroethane (DCE), α, α, α –trifluorotoluene and triethylamine were purchased from Sigma Aldrich, EMD Chemicals, Fisher Chemicals or Acros Organics and used without further purification. Anhydrous dichloromethane was distilled from calcium hydride (10 % w/v) under positive pressure of nitrogen. Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under positive pressure of nitrogen. All other anhydrous solvents were purchased from Fisher Chemicals, Sigma Aldrich or Arcos Organics and used without further purification, unless otherwise stated. All other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated.

Reactions were monitored by thin layer chromatography (TLC) with precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F_{254}, 250 µm thickness) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, iodine vapor, or basic aqueous potassium permanganate (KMnO4), and heat as developing agents. Preparatory thin layer chromatography (PTLC) was performed using the aforementioned silica gel plates. Flash column chromatography was performed over silica gel 60 (particle size 0.035-0.07 mm) from Acros Organics. Compounds with solubility issues (ie. most purines) were dry-loaded onto silica prior to column chromatography. NMR spectra were recorded on Bruker AV-600 (equipped with a Cryoprobe), DRX-600 (equipped with a Cryoprobe), DRX-500 or DPX-400 and calibrated using residual non-deuterated solvent as an internal reference ($CHCl_3$: 7.26 ppm(^{1}H), 77.16 ppm(^{13}C); Methanol-d_4: 3.31 ppm(^{1}H), 49.0 ppm(^{13}C); iPrOH-D_8: 5.12 ppm(^{1}H); DMSO-d_6: 39.52 (^{1}H), 2.50 (^{13}C)). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = 1quintet, h = hextet, m = multiplet, br = broad. LC/MS analysis was performed on Agilent 1100 series HPLC/MSD A61946D system or an Agilent 1260 series HPLC/MSD (G6120BSQ ESI) LCMS system with ACN and 0.01% TFA in H_2O as eluents. GC/MS analysis was performed on Agilent 7820A/5975 GC/MSD system with helium as a carrier gas. Unless otherwise specified, GC runs were preformed with the following method: GC/MSD; HP-5MS UI; 139 KPa; flow rate 2 mL/min; inlet temperature 200 °C; column temperature 50 °C for 0 min, then 20 °C/min to 280 °C, then hold 2 min. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

Experimental procedures

1. Model studies to build the asmarine scaffold

a. Model nitroso-ene reaction



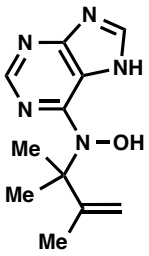
21 20 22 59

Procedure for selective formation of 22:

Hydroxylamine **21**[1] (100 mg, 0.66 mmol) and iodobenzene diacateate (220 mg, 0.68 mmol, 1.0 equiv.) were dissolved in MeOH (8.0 mL) under air. Tetramethylethylene (4.0 mL, 2.82 g, 33.5 mmol, 50 equiv.) was added to the stirring solution and the reaction was stirred for 1 hr. Upon verification of complete conversion by LCMS, the reaction was concentrated and purified via column chromatography (10% MeOH in $CHCl_3$ -> 15% MeOH in $CHCl_3$, R_f = 0.30 10% MeOH in $CHCl_3$) to give 145.4 mg of **22** (94%, 0.62 mmol) as a white solid.

Procedure for formation of 22 and 59:

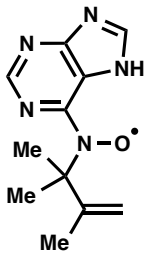
Hydroxylamine **21** (5 mg, 0.033 mmol) was dissolved in DMF (2.0 mL) under air. To this reaction was added MnO_2 (3 mg, 0.035 mmol) and the mixture was heated to 40 ˚C for 2 hours under air. LCMS analysis after 2 hours of heating showed that there was 2:1 of **22**:**59** in the reaction mixture. The reaction was then concentrated and purified via preparative thin layer chromatography (10% MeOH in $CHCl_3$, loaded onto one 10 x 10 cm TLC plate, R_f = 0.70, 10% MeOH in $CHCl_3$ – orange band, UV active) to give 2 mg of **59** (32%) as a bright orange solid. Alternatively, **59** can also be formed from **22** under the same conditions.



22: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.25 (s, 1H), 8.17 (s, 1H), 4.92 (s, 1H), 4.77 (s, 1H), 1.81 (s, 3H), 1.63 (s, 6H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 159.84, 156.11, 153.69, 152.12, 152.02, 143.61, 109.31, 69.13, 25.95, 20.03.

LCMS (APCI): Calculated $[M+H]^+$: 234.1; Found 234.1

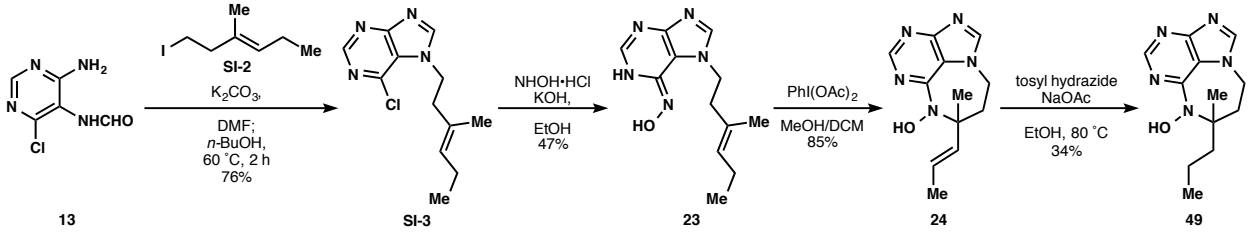


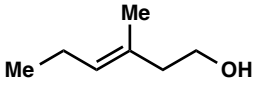
59: LCMS (APCI): Calculated $[M+H]^+$: 233.1; Found 233.1

The material gives very broad signals in NMR, and thus X-ray crystallography was utilized to confirm the radical structure.
(.cif crystal file available from the Cambridge Crystallographic Data Centre: CCDC 1036478. See: www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx)

Empirical formula : C13.50 H20 N5 O
Formula weight : 268.35
Temperature : 100(2) K
Wavelength : 1.54178 Å
Crystal system : Triclinic
Space group : P-1
Unit cell dimensions: a = 9.4698(6) Å, a= 91.493(3)°. b = 10.4699(7) Å, b= 91.953(2)°. c = 28.2764(17) Å, g = 100.509(3)°.
Volume: 2753.4(3) Å3
Z: 8
Density (calculated): 1.295 Mg/m^3
Absorption coefficient: 0.696 mm^{-1}
F(000): 1152
Crystal size: 0.15 x 0.11 x 0.10 mm^3
Crystal color, habit: Red-Orange Block
Theta range for data collection: 1.56 to 68.52°.
Index ranges: -11<=h<=11, -12<=k<=12, 0<=l<=34
Reflections collected: 9368
Independent reflections: 9368 [R(int) = 0.0535]
Completeness to theta = 65.00°: 96.9 %
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.9337 and 0.9028
Refinement method: Full-matrix least-squares on F2
Data / restraints / parameters: 9368 / 134 / 697
Goodness-of-fit on F2: 1.039
Final R indices [I>2sigma(I)]: R1 = 0.0922, wR2 = 0.2703
R indices (all data): R1 = 0.1003, wR2 = 0.2799
Extinction coefficient: not measured
Largest diff. peak and hole: 0.471 and -0.390 $e.Å^{-3}$

b. Model intramolecular nitroso-ene reaction



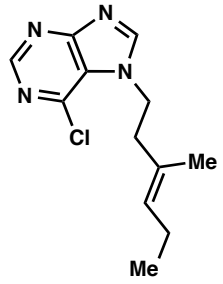


SI-1: To a flamed-dried flask, (*E*)-4-iodo-3-methylbut-3-en-1-ol (3.18 g, 15 mmol) [prepared from one step from butynol] [2] and $Pd(PPh_3)_4$ (1.04 g, 0.9 mmol, 0.06 equiv.) were dissolved in THF (300 mL) and cooled to 0˚C. To the stirring solution was added, dropwise, a 1.0 M solution of Et_2Zn in hexanes (45 mL, 45 mmol, 3 equiv.) and then the reaction was warmed to room temperature. After stirring for 3 hours at rt, TLC indicated complete consumption of starting material and the resulting solution was quenched with brine (300 mL) and diluted with 10% Et_2O in pentane (300 mL). The aqueous layer was extracted with 10% Et_2O in pentane (3 x 200 mL), and the combined organics were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated in vacuo [caution: compound is volatile – evaporated at 250 torr.] to give the crude mixture. Purification via column chromatography (2:1 -> 1:1 pentane: Et_2O, R_f = 0.35 with 3:1 hexanes:EtOAc) gave 1.2 g of the clean title compound (70% yield, 10.5 mmol) as a pale yellow oil.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.22 – 5.28(m, 1H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.24 (t, *J* = 6.1 Hz, 2H), 2.03 (quint, *J* = 7.2 Hz, 2H), 1.63 (s, 3H), 1.47 (s, 1H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 130.62, 130.21, 60.18, 42.75, 21.42, 15.67, 14.47.

GCMS (EI 70 eV) m/z (%): 53.0 (12), 55.1 (60), 56.0 (14), 67.0 (23), 68.0 (11), 69.0 (27), 70.0 (10), 79.0 (12), 81.1 (100), 82.1 (8), 96.2 (10), 114.0 (6).



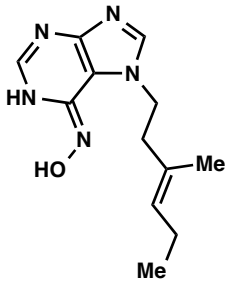
SI-3: To a flask protected from light with foil, alcohol **SI-1** (1.2 g, 10.5 mmol), imidazole (2.14g, 31.8 mmol, 3.0 equiv.) and Ph_3P (8.26 g, 31.2 mmol, 3.0 equiv.) were dissolved anhydrous DCM (93 mL). The mixture was then cooled to 0 ˚C (with ice bath), and iodine (7.92 g, 31.5 mmol, 3.0 equiv.) was added portion-wise into the stirring solution. The reaction was stirred for 10 minutes before it was warmed to room temperature. After 2 hours (and confirmation of reaction completion via TLC), the reaction was quenched with sodium thiosulfate (sat. aq.) solution (50 mL). The aqueous layer was extracted with pentane (3 x 30 mL), the organics were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in vacuo [caution: compound is volatile – concentrated at 250 torr.]. Purification via a short silica plug (100% pentane, R_f = 0.95 with 3:1 hexanes: EtOAc) gave 0.95 g of mostly pure (*E*)-1-iodo-3-methylhex-3-ene (**SI-2**) as a pale yellow oil (40% yield, 4.25 mmol). [Note: the low yield due to the volatility of the compound.] The crude compound was taken onto the next step without further purification or characterization.

To a flask protected from light, iodide **SI-2** (1.93 g, 17.2 mmol, 2.5 equiv.), *N*-(5-amino-6-chloropyrimidin-4-yl)formamide **13** [obtained in 2 steps from 5-amino-4,6-dichloropyrimidine, see Montgomery *et al.* for procedure] [3] (797 mg, 7.1 mmol) and potassium carbonate (2.56 g, 18.5 mmol, 2.6 equiv.) were dissolved in DMF (12.8 mL, 0.55 M). The reaction was left stirring overnight (20 hours). Upon verification that the alkylation had completed via LCMS, *n*-BuOH (12.8 mL) was added to the reaction and the mixture was heated to 60 ˚C for 2 hours [reaction was monitored carefully – heating for an extended period of time will result in the chloride being displaced by butanol]. The reaction was then cooled to room temperature and diluted with DCM (30 mL) and quenched with NH_4Cl (30 mL). The aqueous layer was extracted with 10% MeOH in DCM (3 x 30 mL). The combined organics were concentrated and purified via column chromatography (1:1 hexanes:EtOAc -> 1:2 hexanes:EtOAc -> 100% EtOAc, R_f = 0.26 with 1:1 hexanes:EtOAc) to yield 812 mg of the title compound (76% yield, 5.4 mmol) as a white solid.

^{1}H NMR (600 MHz, Methanol-d_4) δ 8.78 (s, 1H), 8.57 (s, 1H), 4.81 (t, *J* = 7.2 Hz, 1H), 4.65 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 1.90 (quint, *J* = 7.5 Hz, 2H), 1.73 (s, 3H), 0.74 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 162.64, 152.99, 152.17, 144.63, 131.86, 130.59, 123.61, 46.91, 42.42, 22.06, 15.73, 14.14.

LCMS (APCI): Calculated $[M+H]^+$: 251.1; Found 251.1

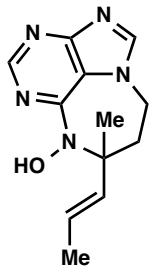


23: Chloropurine **SI-3** (812 mg, 3.25 mmol) and hydroxylamine hydrochloride (2.971 g, 42.3 mmol, 13 equiv.) were dissolved in anhydrous ethanol (32.5 mL). To the stirring solution was added anhydrous triethylamine (4.5 mL, 32.5 mmol, 10 equiv.). The reaction was left stirring for 2 days, and upon verification of depletion of starting material by LCMS the reaction was quenched with $NaCO_3$ (sat. aq.) (30 mL). DCM (50 mL) was added and the aqueous layer was extracted with 10% MeOH in DCM (3 x 50 mL). The combined organics were concentrated in vacuo and purified via column chromatography (10% MeOH in $CHCl_3$, R_f = 0.26 with 10% MeOH and 1% NH_4OH in $CHCl_3$) to yield 378 mg of the title compound as a white solid (47% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (s, 1H), 7.56 (s, 1H), 4.95 (t, *J* = 7.2 Hz, 1H), 4.33 (t, *J* = 6.8 Hz, 2H), 2.46 (t, *J* = 6.7 Hz, 2H), 1.91 (quint, *J* = 7.4 Hz, 3H), 1.67 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, CD3OD) δ 149.92, 145.16, 141.46, 141.10, 131.09, 130.94, 112.09, 47.11, 42.15, 22.10, 15.79, 14.29.

LCMS (APCI): Calculated $[M+H]^+$: 248.1; Found 248.1

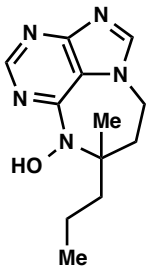


24: Hydroxylamine **23** (1.36 g, 5.5 mmol) and iodosobenzene diacetate (1.75 g, 5.5 mmol, 1.0 equiv.) were dissolved in DCM (120 mL) and MeOH (65 mL) under air. The reaction mixture was stirred for 30 minutes, and upon verification of complete cyclization via LCMS, the reaction was quenched with $NaHCO_3$ (sat. aq.) (50 mL). The aqueous layer was extracted with 10% MeOH in DCM (5 x 50 mL), and the organics were washed with brine and concentrated in vacuo. Purification via column chromatography (10% MeOH and 1% NH_4OH in $CHCl_3$ -> 20% MeOH and 1% NH_4OH in $CHCl_3$) 1.15 g gave of the title compound (85% yield) as a purple solid.

^{1}H NMR (400 MHz, Methanol-d_4) δ 8.38 (s, 1H), 8.24 (s, 1H), 5.48 – 5.66 (m, 2H), 4.38 – 4.66 (m, 2H), 4.28 (ddd, *J* = 13.7, 10.3, 3.2 Hz, 4H), 2.38 – 2.55 (m, 2H), 1.66 – 1.69(m, 6H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 158.90, 153.08, 152.96, 145.51, 132.58, 127.65, 110.86, 68.60, 44.17, 39.98, 26.68, 17.84.

LCMS (APCI): Calculated $[M+H]^+$: 246.1; Found 246.1



49: Alkene **24** (15 mg, 0.06 mmol), *p*-Toluenesulfonyl hydrazide (900 mg, 4.8 mmol, 80 equiv.) and NaOAc (400 mg, 4.8 mmol, 80 equiv.) were dissolved in EtOH (3 mL). The resulting mixture was heated to reflux for 2 hours. The reaction was then cooled and quenched with $NaHCO_3$ (sat. aq.) solution (5 mL). The mixture was extracted with 10% MeOH in DCM (6 x 5 mL), concentrated in vacuo and purified via preparative thin layer chromatography (10% MeOH and 1% NH_4OH in $CHCl_3$, loaded onto three 10 x 10 cm TLC plates, ran 3x per plate for clean separation) to yield 5 mg of the title compound (34% yield) as a purple solid. The data reported is consistent with those reported by Pappo *et al.* [4]

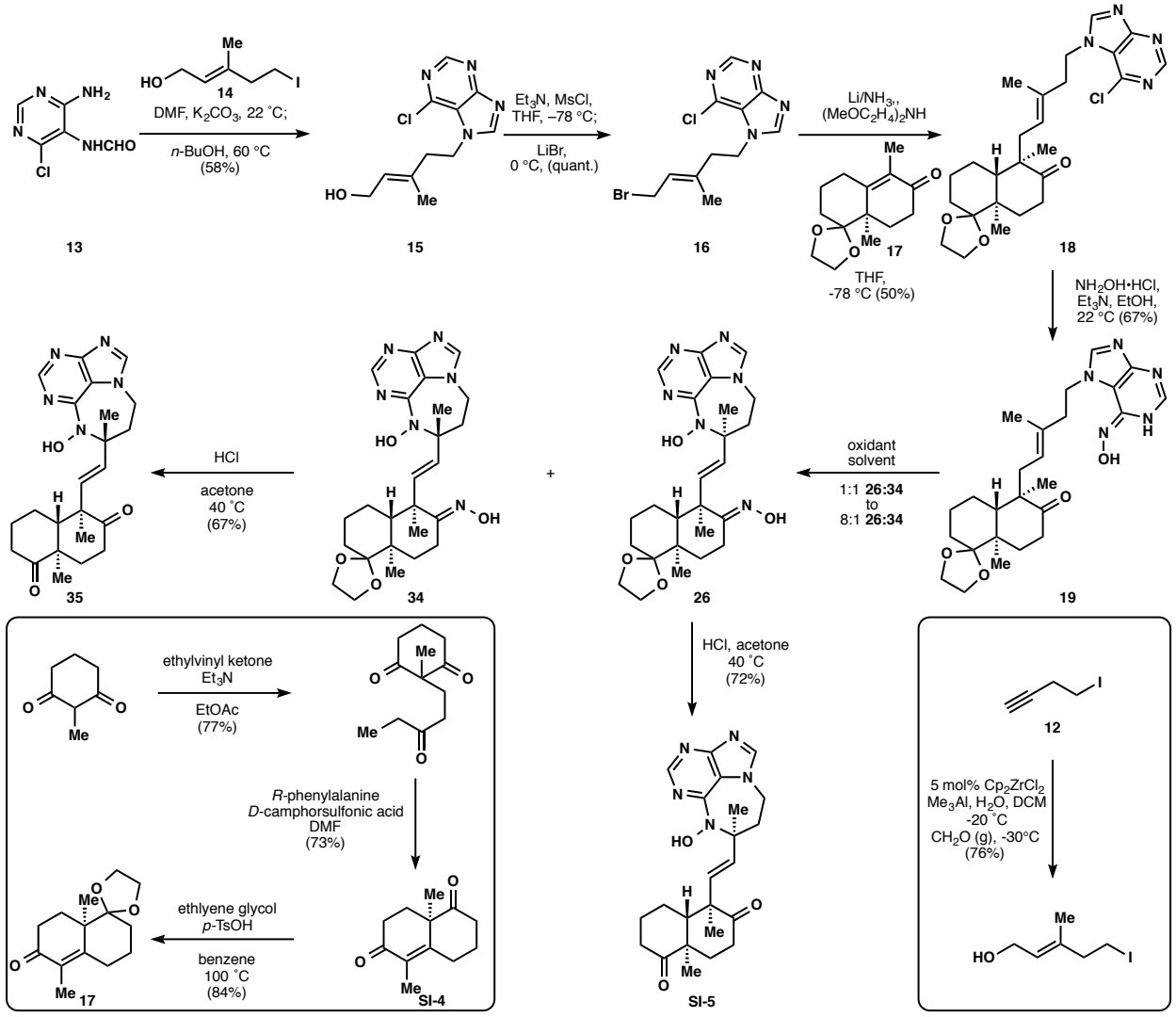
LCMS (APCI): Calculated $[M+H]^+$: 248.1; Found 248.2

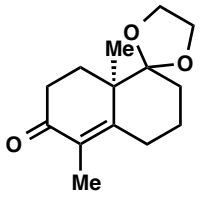
The NMR peaks of the title compound were broad, so 20 μL of HBr was added to form the HBR salt for characterization instead:

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.49 (s, 1H), 4.43 (dt, J = 23.5, 14.3 Hz, 2H), 2.50 – 2.55 (1H – under DMSO), 2.41 (dd, J = 14.2, 8.3 Hz, 1H), 1.88 (ddt, J = 14.3, 11.3, 4.8 Hz, 1H), 1.73 (td, J = 13.5, 12.5, 5.6 Hz, 1H), 1.47 (s, 3H), 1.26 – 1.38 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).

^{13}C NMR (151 MHz, DMSO-d_6) δ 154.29, 147.24, 145.56, 144.04, 108.15, 68.84, 48.61, 42.35, 34.86, 23.48, 16.71, 14.26.

2. Route to (–)–clerdoane asmarines through oxime





17: Adapting the procedure provided by Ling *et al.,*[5] the title compound was obtained in 3 steps from 2-methyl-1,3-cyclohexadione:

Triethylamine (13 mL, 93.2 mmol, 1.3 equiv.), 2-methyl-1,3-cyclohexadione (9.0 g, 71.3 mmol, 1 eq.), ethyl vinyl ketone (9.2 g, 7.8 mL, 78.9 mmol, 1.1 eq.) and EtOAc (500 mL) were mixed in a 1L flask in open air. The resulting opaque solution was then heated under nitrogen (and a reflux condenser) at 75 ˚C, and after an hour the solution turned to a clear dirty yellow liquid. The mixture was further heated at the same temperature overnight (10 hours). It was then cooled to room temperature and the reaction was judged to be complete by TLC (R_f = 0.73 in 1:1 hexane:EtOAc). The solvent was then removed on a rotary evaporator and the resulting crude mixture was purified via column chromatography (4:1 hexanes:EtOAc) to afford the pure triketone as a colorless oil, which crystalizes into long off-white needles upon cooling to -20 ˚C (11.5 g, 77% yield).

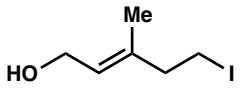
The resulting triketone (7.1g, 33.8 mmol), *D*-phenylalanine (5.53g, 33.8 mmol, 1.0 equiv.) and *D*-camphor sulfonic acid (3.87g, 33.8 mmol, 0.5 equiv.) were dissolved in 500 mL of DMF (0.07M). The resulting orange solution was stirred overnight (8-16 hours) at room temperature. The reaction was then heated for 24 hours at 30 ˚C, and the temperature was continually raised 10˚C at 24 hours intervals until the reaction was judged to be complete by TLC (usually in 6 days). The reaction was then quenched by cold $NaHCO_3$ (300 mL) and extracted with Et_2O (200 mL x3). The resulting extract was washed with water (100 mL x 5), brine (100 mL), dried with $MgSO_4$ and concentrated. The crude mixture was purified via column chromatography (4:1 hexanes:EtOAc) to afford 4.73 g of the decalin as a yellow oil (73% yield, 89%ee*, $[\alpha]_D^{25}$ = -125.0 (10 mg/ 1 mL MeOH)). The enantiomeric ratio was then enriched by serial recrystallizations: the decalin was first dissolved 5:1 hexanes: Et_2O and recrystallized at -20 ˚C (10 min – 2 hrs). The supernatant was then removed, and the crystals were washed with Et_2O and re-subjected to the same crystallization conditions until the specific rotation matches that of the desired enantiopurity (100% ee, $[\alpha]_D^{25}$ = -140.0). The number of recrystallizations could be shortened with the use of enantiopure seed crystals and recrystallization in Et_2O at -20 ˚C (10 min – 12 hrs). Using these conditions, 3.0 g of the Wieland Mischer ketone **SI-4** was obtained (46% yield, 99% ee, $[\alpha]_D^{25}$ = -139.0 (10 mg/ 1 mL MeOH)).

[It should be noted that a typo was made in Ling et al.'s procedure – D-phenylalanine should be used in the cyclization to obtain the Wieland-Mischer ketone with the above-drawn (-)-stereochemistry, The use of L-phenylalanine, as indicated by Ling et al.'s procedure, would result in the enantiomer, the (+)-ketone.]

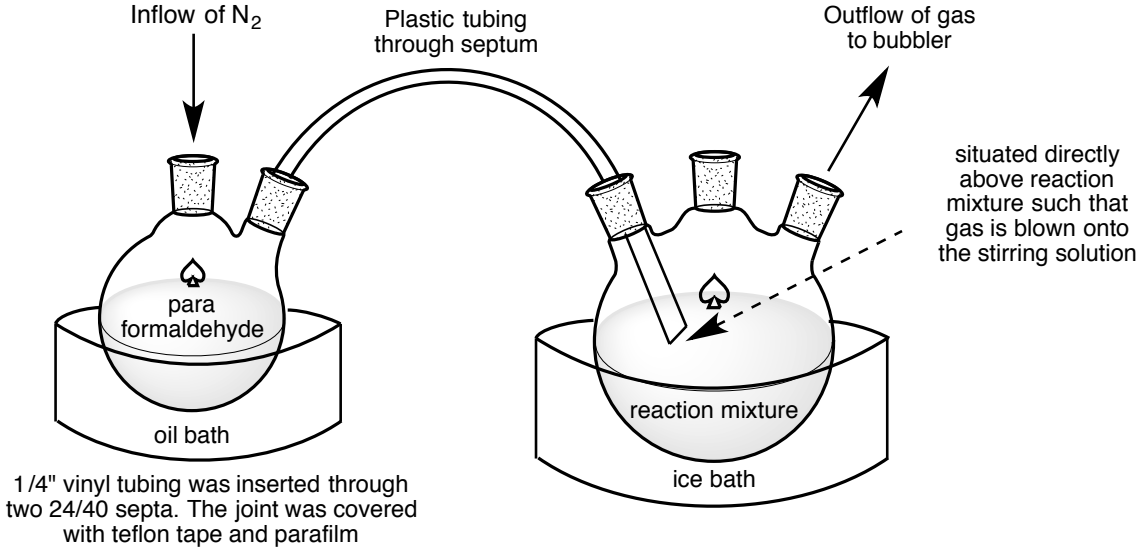
*[It should also be noted that the authors had no luck reproducing **SI-4** in high ee% with the procedure from Lanfranchi et al.* [6] *Following their reported procedure exactly, we could only obtain the Wieland-Miescher diketone analog in 45% ee instead of the 82% ee as described in the paper. While with seed crystals we were able to ultimately enrich the material to 99% ee after 8-10 sequential crystallizations with pure seed crystals, we recommend using the longer route that is described above to generate the diketone.]*

*Hagiwara *et al.* [7] reported that 100% ee **SI-4** should have specific rotation of -140 and *ent*-**SI-4** of +140, so the ee% of the sample was calculated from this number.

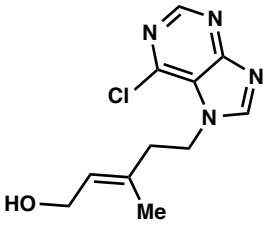
Using a Dean-Stark trap, ethylene glycol (6.16 mL, 106 mmol, 14.5 equiv.) was refluxed in benzene (50 mL) for 2 hours. Upon cooling, Wieland Miescher ketone (1.4 g, 7.3 mmol) in benzene (4.7 mL) and *p*-toluene sulfonic acid (29 mg, 0.16 mmol, 0.02 equiv.) were added to the solution and the resulting mixture was heated to reflux under a condenser for 2 hours (heating for more than 2 hours will result in diketal formation). The solution was then cooled and quenched with $NaHCO_3$ (50 mL). The resulting mixture was extracted with Et_2O (30 mL x3), washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography (4:1 hexanes: Et_2O) to obtain 1.4g of the pure ketal (84% yield, $[\alpha]_D^{25}$ = -128.5 (10 mg/ 1 mL MeOH) as a clear oil.
The spectroscopic data and R_f of these compounds matched those reported by Ling *et al.*[5]



14: To a 3 neck flame-dried flask under argon atmosphere, zirconocene dichloride (1.75 g, 6.0 mmol, 0.05 equiv.) was dissolved in dry DCM (50 mL), and the resulting solution was stirred vigorously at -20 ˚C with acetone and dry ice bath. A 2.0M solution of trimethyl aluminum in toluene (15 mL, 30 mmol, 2 equiv.) was added dropwise to this flask over 20 minutes. The resulting mixture was stirred for 10 minutes, and then water (0.15 mL, 1 equiv.) was added very slowly (1 drop per 30 seconds – CAUTION – reacts violently, do not add faster than this rate!) to the flask. The resulting mixture was stirred for 10 minutes, and a solution of 4-iodobut-1-yne [obtained from 3-butyn-1ol through the mesylate in 2 steps] in pentane (15 mmol, 1: 2.8 iodide : pentane) dissolved in DCM (12 mL) was added dropwise over 20 minutes. After stirring for an addition 10 minutes, the reaction was warmed to room temperature and stirred for 2 hours. Upon TLC verification that the carboalumination was completed, the reaction mixture was cooled to – 30˚C with acetone and dry ice bath. A separate 2-neck flask with paraformaldehyde (3.6 g, 120 mmol, 8 equiv.) connected (see below illustration and explanation for set up) was connected to the reaction flask, and formaldehyde gas (cracked from the flask with paraformaldehyde being heated to 150 ˚C, until all the solid had been cracked) was blown onto the surface of the solution. The resulting solution was stirred for 15 minutes, and upon verification of complete conversion by TLC, the reaction was quenched slowly with water (7.5 mL) and the reaction was warmed to room temperature. Rochelle's salt (sat. aq.) (50 mL) and Et_2O (150 mL) were added to the reaction mixture, which was then stirred overnight (12 hours). The reaction mixture was then filtered through a fritted funnel to remove aluminum salts, extracted with Et_2O (3 x 150 mL), washed with brine (300 mL) and dried with $MgSO_4$. The crude product was purified via chromatography (1:4 EtOAc: hexanes, R_f = 0.31 with 3:1 hexanes: EtOAc) to yield 3.4 g of the title compound (76% yield) as a clear oil.



The spectroscopic data of these compounds matched those reported by Bergman *et al.* [8]



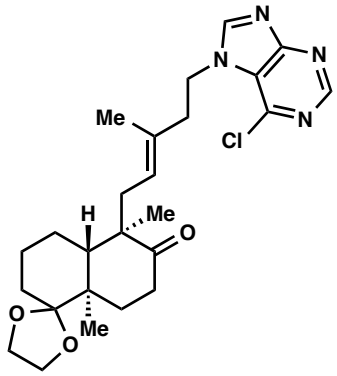
15: To a flask protected from light, iodide **14** (459 mg, 2.0 mmol, 1.5 equiv.), *N*-(5-amino-6-chloropyrimidin-4-yl)formamide **13**[3] (238 mg, 1.4 mmol) and potassium carbonate (760 mg, 5.5 mmol, 4.0 equiv.) were dissolved in DMF (4 mL, 0.4 M). The reaction was left stirring overnight (15 hours). Upon verification that the alkylation had completed via LCMS, n-BuOH (4 mL) was added to the reaction and the mixture was heated to 60 ˚C for 2 hours [reaction was monitored carefully – heating for an extended period of time will result in the chloride being displaced by butanol]. The solvent was then removed under pressure (~5 torr) at 60 ˚C via rotovap and the resulting crude mixture was subjected to column chromatography (5% MeOH in EtOAc ->8% MeOH in EtOAc, R_f = 0.28 with 5% MeOH in EtOAc) twice to yield 203 mg of the title compound (58% yield) as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.88 (s, 1H), 8.16 (s, 1H), 5.24 – 5.30 (m, 1 H), 4.58 (t, 2H, *J* = 7.2 Hz), 4.13 (d, 2H, , *J* = 6.0 Hz), 2.62 (t, 2H, *J* = 7.2 Hz), 1.77 (s, 3H).

^{1}H NMR (400 MHz, Methanol-d_4): δ 8.79 (s, 1H), 8.62 (s, 1H), 5.18 (t, *J* = 6.0 Hz, 1H), 4.67 (t, *J* = 7.1 Hz, 2H), 4.01 (d, *J* = 6.6 Hz, 2H), 2.64 (s, 1H), 1.78 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 162.15, 152.64, 149.28, 143.08, 133.31, 133.03, 128.37, 59.05, 46.01, 41.42, 16.62.

LCMS (APCI): Calculated $[M+H]^+$: 253.1; Found 253.1



18: In a flamed dried flask, alcohol **15** (114 mg, 0.45 mmol) and triethylamine (0.9 mL, 0.63 mmol, 1.4 equiv.) were dissolved in anhydrous THF (22.5 mL). The reaction was cooled to -40 ˚C, and methanesulfonyl chloride (0.45 mL, 0.59 mmol, 1.3 equiv.) was added to the reaction and the mixture was stirred for one hour. Upon verification of the complete formation of mesylate via TLC, a 2.0M lithium bromide solution in THF (1.13 mL, 2.25 mmol, 5 equiv.) was added into the reaction mixture and it was stirred for another 45 minutes. The reaction was then quenched with a mixture of cold DCM (113 mL) and cold $NaHCO_3$ (sat. aq.) (90 mL) [Note: the product is unstable and polymerized easily at room temperature – it needs to be kept cold (-20 ˚C or lower) and preferably in a dilute solution of THF]. The phase was separated in a pre-cooled separatory funnel and the aqueous phase was quickly extracted (3 x 50 mL cold DCM). The resulting organic phase was dried over $MgSO_4$ and filtered through a pre-cooled fritted funnel, and the liquid was concentrated under reduced pressure via rotovap at 0 ˚C. The product was then transferred onto the high vacuum (~0.3 torr) at 0 ˚C and quickly warmed to rt for 30 seconds to ensure complete solvent evaporation. The flask was then subjected to an argon atmosphere and cold anhydrous THF (3 mL) was then added to the flask to give (*E*)-7-(5-bromo-3-methylpent-3-en-1-yl)-6-chloro-7*H*-purine as an orange solution in THF. This solution needed to be kept at -20 ˚C and was used in the next step immediately.

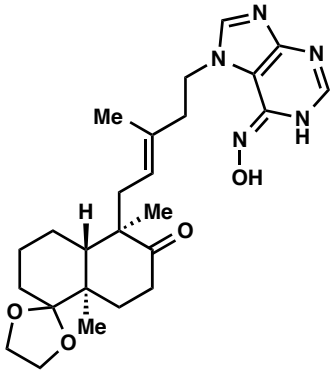
To a flame-dried 3-neck flask fitted with an oven-dried cold-finger condenser cooled to -78 ˚C (dry ice/acetone), ammonium gas was condensed into the liquid state (30 mL). To this stirring ammonia solution were added THF (3 mL) and lithium (11 mg, 1.5 mmol, 5 equiv.). The resulting blue solution was vigorously stirred for 10 minutes. To a separate flame-dried flask, ketal **17** (71 mg, 0.3 mmol) was dried by azeotropic removal of water three times with toluene under high vacuum. Freshly distilled bis(2-methoxyethyl)amine (0.42 mL, 2.8 mmol, 9.3 equiv.) and THF (12 mL) was added to this flask. This resulting solution was then added drop-wised into the reaction vessel. [Note: the color of the reaction should remain blue throughout the addition – more lithium was added if the mixture turned clear]. The resulting blue solution was stirred for 15 minutes, and then freshly distilled isoprene was added dropwise (3 drops, or until the blue solution turns clear) until the reaction turned clear. The allylic bromide solution in THF (see above) was then added dropwise into the reaction, and the resulting mixture was stirred for 1 hour. Upon verification of complete alkylation by LCMS, the reaction was quenched with NH_4Cl (sat. aq.) (5 mL) at -78 ˚C and the reaction was slowly warmed to -30 ˚C. The ammonia was then slowly evaporated, and the reaction was warmed to room temperature and DCM (30 mL) and more NH_4Cl (sat. aq.) (20 mL) was added. The aqueous phase was extracted DCM (3 x 30 mL) and the combined organics were washed with brine. The crude mixture was then concentrated in vacuo and purified via column chromatography (100% EtOAc, R_f = 0.30 with EtOAc) to yield 70 mg of the title compound as a white solid (50% yield).

^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.83 (s, 1H), 8.23 (s, 1H), 5.00-5.06 (m, 1H), 4.50 (t, *J* = 7.4 Hz, 2H), 3.80 – 3.93 (m, 4H), 2.42 – 2.59 (m, 3H), 2.37 (dd, *J* = 14.4, 5.8 Hz, 1H), 2.25 – 2.32 (m, 1H), 1.96 – 2.05 (m, 2H), 1.85 (td, *J* = 13.3, 5.5 Hz, 1H), 1.58 – 1.53 (m, 3 H), 1.64 (s, 3H), 1.48 – 1.58 (m, 1H), 1.29 – 1.43 (m, 3H), 1.17 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 216.03, 162.15, 152.41, 149.31, 142.99, 131.92, 125.76, 122.31, 112.83, 65.30, 64.98, 51.34, 46.71, 44.52, 42.46, 41.95, 36.55, 35.12, 30.28, 28.75, 22.98, 22.01, 21.93, 16.58, 16.28.

LCMS (APCI): Calculated $[M+H]^+$: 473.2; Found 473.3

$[\alpha]_D^{25}$ = +6.9 (10 mg/ 1 mL DCM)



19: Chloropurine **18** (70 mg, 0.15 mmol) and hydroxylamine hydrochloride (128 mg, 1.8 mmol, 12 equiv.) were dissolved in anhydrous ethanol (1.4 mL). To the stirring solution was added anhydrous triethylamine (0.21 mL, 1.5 mmol, 10 equiv.). The reaction was left stirring for 3 days, and upon verification of depletion of starting material by LCMS the reaction was quenched with $NaCO_3$ (sat. aq.) (5 mL). DCM (5 mL) was added and the aqueous layer was extracted with 10% MeOH in DCM (3 x 5 mL). The combined organics were concentrated in vacuo and purified via

column chromatography (8% MeOH in $CHCl_3$, R_f = 0.26 with 10% MeOH and 1% NH_4OH in $CHCl_3$) to yield 48 mg of the title compound as a white solid (67% yield).

^{1}H NMR (600 MHz, Methanol-d_4): δ 7.76 (s, 1H), 7.56 (s, 1H), 5.12-5.19 (m, 1H), 4.32 (t, *J* = 7.2 Hz, 2H), 3.79 – 3.94 (m, 4H), 2.88 – 2.94 (m, 1H), 2.48 (t, *J* = 6.8 Hz, 2H), 2.34 (dd, *J* = 14.3, 4.7 Hz, 1H), 2.07 – 2.20 (m, 2H), 1.87 (d, *J* = 10.2 Hz, 1H), 1.64 (s, 3H), 1.50 – 1.67 (m, 4 H), 1.27 – 1.45 (m, 4H), 1.09 (s, 3H), 1.02 (s, 3H).

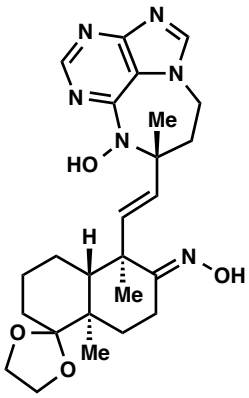
^{13}C NMR (151 MHz, Methanol-d_4): δ 164.69, 150.00, 145.18, 141.37, 141.09, 133.01, 126.84, 114.12, 112.04, 66.22, 65.86, 47.87, 45.23, 44.23, 43.81, 42.59, 38.88, 31.31, 28.76, 24.64, 23.95, 22.78, 18.70, 16.57, 16.54.

LCMS (APCI): Calculated $[M+H]^+$: 485.3; Found 485.3

$[\alpha]_D^{25}$ = -15.9 (10 mg/ 1 mL MeOH)

Non-stereoselective nitroso-ene cyclization procedure:
Hydroxylamine **19** (200 mg, 0.41 mmol) and iodosobenzene diacetate (132 mg, 0.41 mmol, 1.0 equiv.) were dissolved in DCM (4 mL) under air. The reaction mixture was stirred for 30 minutes, and upon verification of complete cyclization via LCMS (1:1 mixture of 2 diastereomers), the mixture was concentrated in vacuo and purified via preparative thin layer chromatography (10% MeOH and 1% NH_4OH in $CHCl_3$, loaded onto thirty 10 x 10 cm TLC plates, ran 3x per plate for clean separation) to yield 40 mg of **26** and 40 mg of **34** (20% yield per diastereomer, 40% total yield) as brown-green solids. [Note: a variety of oxidants and solvents could be used for this reaction. See section below for further discussion of stereoselectivity of this cyclization]

[See **ent-26 and ent-34** in the section below for stereoselective nitroso-ene cyclization procedure from **ent-27.]**

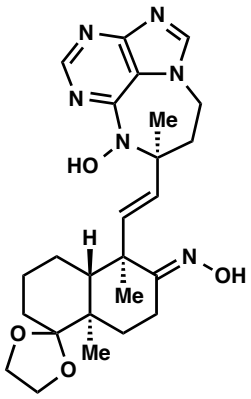


34: R_f = 0.38 with 10% MeOH and 1% NH_4OH in $CHCl_3$
^{1}H NMR (400 MHz, Methanol-d_4): δ 8.42 (s, 1H), 8.27 (s, 1H), 5.54 (s, 2H), 4.35 – 4.52 (m, 2H), 3.72 – 3.97 (m, 4H), 3.26 (d, *J* = 14.8 Hz, 1H), 2.42 – 2.67 (m, 2H), 1.88 – 2.00 (m, 1H), 1.69 (s, 3H), 1.35 – 1.60 (m, 6H), 1.20 – 1.33 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 0.97 – 1.06 (m, 1 H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 166.52, 158.96, 153.17, 153.03, 145.69, 141.60, 131.04, 113.83, 111.03, 68.60, 66.29, 65.89, 49.08, 47.22, 44.15, 44.13, 39.82, 31.44, 30.24, 25.61, 23.61, 22.66, 18.72, 17.67, 16.51.

LCMS (APCI): Calculated $[M+H]^+$: 483.6; Found 483.3

$[\alpha]_D^{25}$ = -50.0 (10 mg/ 1 mL MeOH)



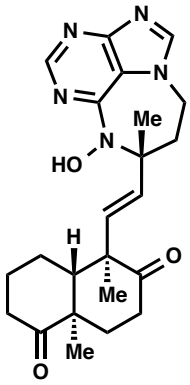
26: R_f = 0.35 with 10% MeOH and 1% NH_4OH in $CHCl_3$

^{1}H NMR (400 MHz, Methanol-d_4): δ 8.38 (s, 1H), 8.22 (s, 1H), 5.35 (s, 2H), 4.48 – 4.58 (m, 1H), 4.34 – 4.43 (m, 1H), 3.72 – 3.95 (m, 4H), 3.15 (d, J = 14.0 Hz, 1H), 2.42 – 2.56 (m, 2H), 1.85 – 2.00 (m, 1H), 1.72 (s, 3H), 1.323 – 1.70 (m, 9H), 1.17 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 165.68, 158.64, 152.87, 152.86, 145.45, 140.94, 128.42, 113.91, 110.86, 69.41, 66.26, 65.90, 49.85, 47.03, 44.27, 44.03, 39.92, 31.49, 29.80, 27.41, 23.70, 22.57, 19.52, 17.54, 16.49.

LCMS (APCI): Calculated $[M+H]^+$: 483.6; Found 483.3

$[\alpha]_D^{25}$ = +72.6 (3.3 mg/ 1 mL MeOH)



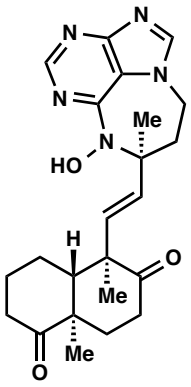
35: Oxime **34** (10 mg, 0.021 mmol) was dissolved in acetone (1 mL), and a 1M HCl solution (0.12 mL, 0.12 mmol, 5.7 equiv.) was added to the reaction. The reaction was then heated to 40 ˚C for 3 hours, and upon verification of complete hydrolysis via LCMS, DCM (5 mL) was added to the reaction and a 0.1M pH 8 phosphate buffer (5 mL) was then used to neutralize the acid. The aqueous phase was then extracted with 10% MeOH in DCM (7 x 5 mL), and the organic phase was concentrated to yield the crude product which was then purified via preparative thin layer chromatography (10% MeOH and 1% NH_4OH in $CHCl_3$, loaded onto one 10 x 10 cm TLC plate, R_f = 0.30 with 10% MeOH and 1% NH_4OH in $CHCl_3$) to yield 6 mg of the title compound (68%) as a purple solid. [Note: it is crucial to add DCM to the reaction prior to quenching and to quench with this exact amount of phosphate buffer – deviation will lead to lower yields]

^{1}H NMR (600 MHz, Methanol-d_4): δ 8.40 (s, 1H), 8.29 (s, 1H), 5.69 (d, J = 16.0 Hz, 1H), 5.38 (d, J = 16.0 Hz, 1H), 4.33 – 4.49 (m, 2H), 2.67 – 2.77 (m, 1H), 2.57 – 2.66 (m, 2H), 2.46 – 2.56 (m, 1H), 2.32 (d, J = 14.5 Hz, 1H), 2.09 (d, J = 14.8 Hz, 1H), 1.81 – 1.97 (m, 3H), 1.73 (s, 3H), 1.66 – 1.72 (m, 1H), 1.50 (d, J = 12.1 Hz, 1H), 1.32 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 215.42, 214.90, 158.87, 153.17, 152.76, 145.73, 137.19, 132.64, 111.23, 68.83, 55.48, 53.12, 49.57, 44.32, 40.03, 38.37, 35.35, 33.20, 26.65, 26.64, 22.68, 18.66, 18.29. (peaks @ 158.87, 152.76 and 145.73 are broadened out)

LCMS (APCI): Calculated $[M+H]^+$: 424.2; Found 424.3

$[\alpha]_D^{25}$ = -17.1 (1.3 mg/ 1 mL MeOH)



SI-5: Following the same procedure as **35**, 4 mg of the title compound (0.010mmol, 72% yield) as a purple solid was obtained from 6 mg (0.013 mmol) of the starting diketone.

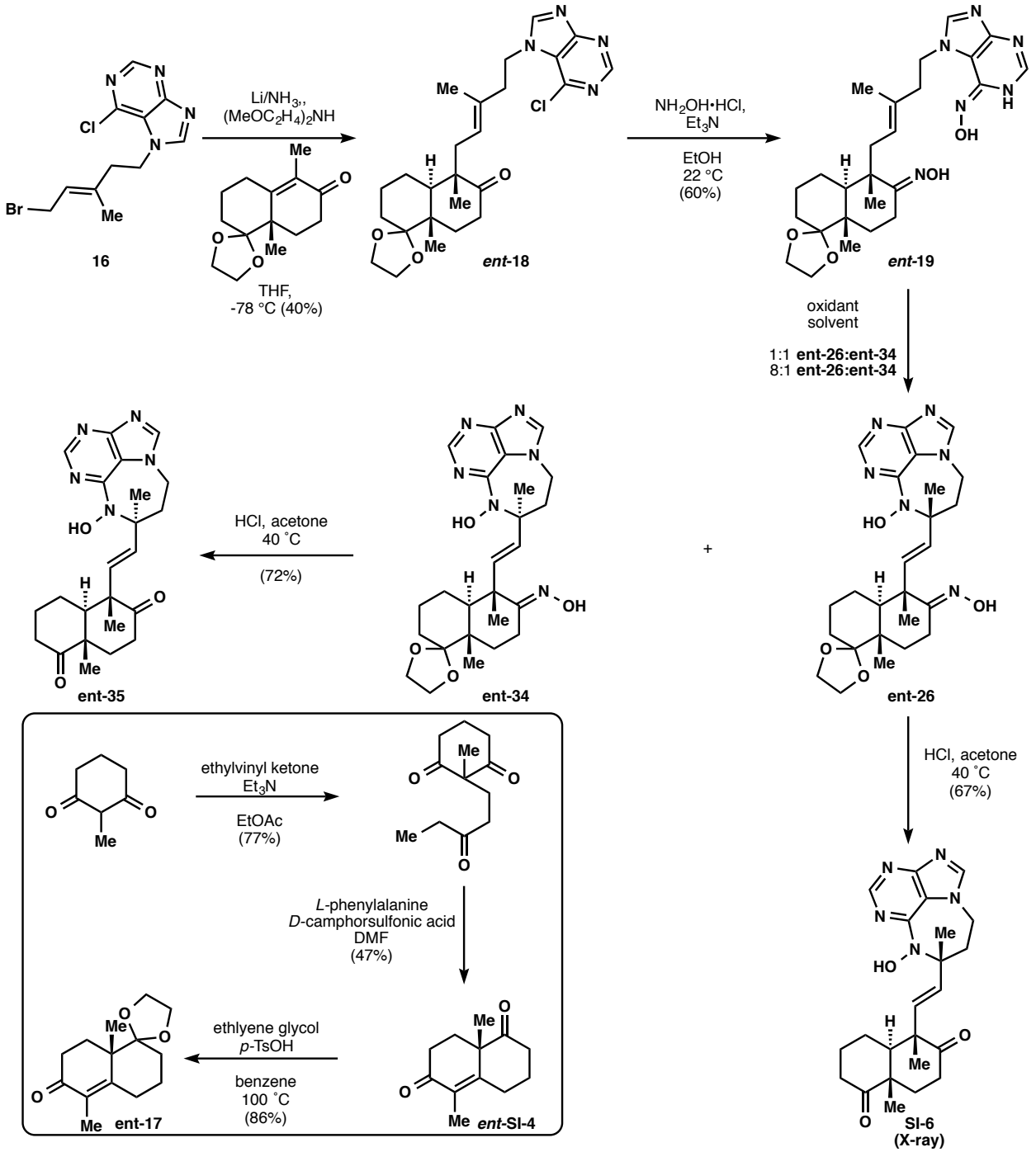
^{1}H NMR (600 MHz, Methanol-d_4): δ 8.37 (s, 1H), 8.25 (s, 1H), 5.53 (d, J = 15.8 Hz, 1H), 5.22 (d, J = 15.8 Hz, 1H), 4.38 – 4.44 (m, 2H), 2.61 – 2.73 (m, 2H), 2.52 – 2.58 (m, 1H), 2.43 – 2.50 (m, 1H), 2.16 (d, J = 14.0 Hz, 2H), 2.00 – 2.08 (m, 1H), 1.79 – 1.89 (m, 3H), 1.74 (s, 3H), 1.69 (d, J = 12.2 Hz, 1H), 1.55 (d, J = 12.4 Hz, 1H), 1.43 – 1.50 (m, 1H), 1.35 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4): δ 215.61, 214.54, 158.76, 153.08, 152.13, 145.34, 137.03, 131.59, 111.01, 69.34, 55.52, 52.94, 48.92, 44.27, 39.84, 38.44, 35.18, 33.09, 27.90, 26.70, 22.83, 18.67, 18.39. (peaks @ 158.77, 152.13 and 145.34 are broadened out)

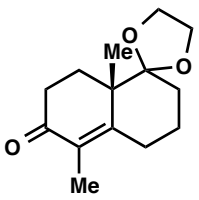
LCMS (APCI): Calculated $[M+H]^+$: 424.2; Found 424.3

$[\alpha]_D^{25}$ = +138.9 (1.3 mg/ 1 mL MeOH)

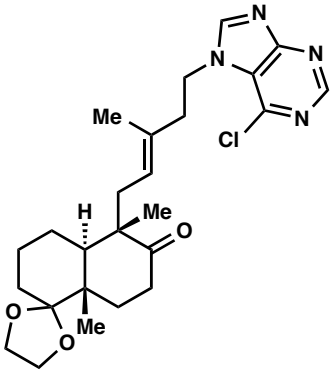
3. Route to (+)-clerdoane-core asmarines through oxime



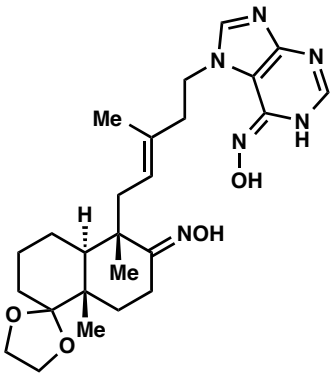
The compounds listed below are obtained, unless otherwise noted, following the same procedures described for their enantiomers in the section immediately above (Experimental procedure, section 1 - First generation route to (-) -clerdoane-core asmarines).



ent-17: Following the same procedure as **19**, except with use of *L*-phenylalanine, 1.86 g of the title compound (86% yield, $[\alpha]_D^{25}$ = +128.5 (10 mg/ 1 mL MeOH)) was obtained. All the spectroscopic data and R_f were identical to that of the enantiomer **17** reported above, except for specific rotation of ***ent*-SI-4**: (96% ee, $[\alpha]_D^{25}$ = +134.2 (10 mg/ 1 mL MeOH)).



ent-18: 150 mg of the title compound was obtained (40% yield, $[\alpha]_D^{25}$ = -6.5 (10 mg/ 1 mL DCM)). The spectroscopic data and R_f were identical to that of the enantiomer **18** reported above.



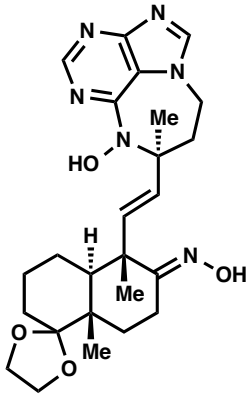
ent-19: 92 mg of the title compound was obtained (60% yield, $[\alpha]_D^{25}$ = +10.9 (10 mg/ 1 mL MeOH)). The spectroscopic data and R_f were identical to that of the enantiomer **19** reported above.

Nitroso-ene cyclizations of hydroxylamine *ent*-19:

Stereoselective nitroso-ene cyclization procedure:
Hydroxylamine ***ent*-19** (50 mg, 0.10 mmol) was dissolved in 3.25:1 H_2O: EtOH (6.8 mL) under air. To this stirring solution was added MnO_2 (9 mg, 0.10 mmol, 1.0 equiv.) and the reaction was sonicated to ensure complete solubility of the substrate. After 12 hours, the solvent was removed in vacuo and re-dissolved in 1:1 MeOH:DCM (3 mL). The mixture was filtered through a short silica plug (eluted with 1:1 DCM: MeOH ->100% MeOH) to remove MnO_2, and the ratios of the two diastereomers were evaluated by ^{1}H NMR to be 8:1 (**ent-26**:**ent-34**). Upon purification via preparative thin layer chromatography (10% MeOH and 1% NH_4OH in $CHCl_3$, loaded onto thirty 10 x 10 cm TLC plates, ran 3x per plate for clean separation), 22 mg of **ent-26** (45% yield) and 2 mg of **ent-34** (4% yield) were obtained (49% total yield) as white solids.

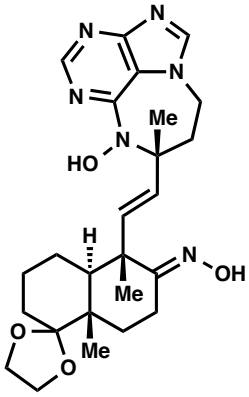
[Note: the major product of this stereoselective cyclization was deprotected with acid (see **35** for procedure). X-ray crystallography analysis revealed the structure to be **SI-6** (see below), leading us to conclude that the major diastereomer formed from the nitroso-ene cyclization was **ent-26** and the minor diastereomer was **ent-34**.]

Non-stereoselective nitroso-ene cyclization procedure:
Using the non-stereoselective cyclization procedure outlined for **26** and **34** above, 20 mg of **ent-34** and 35 mg of **ent-26** (21% yield of **ent-34**, 37% yield of **ent-26**, 58% total yield) were obtained as brown-green solids.



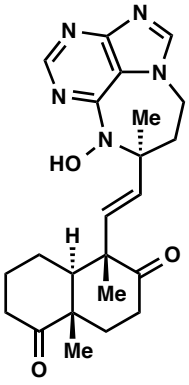
ent-34: The spectroscopic data and R_f were identical to that of the enantiomer **42** reported above.

$[\alpha]_D^{25}$ = +43.2 (2.5 mg/ 1 mL MeOH)



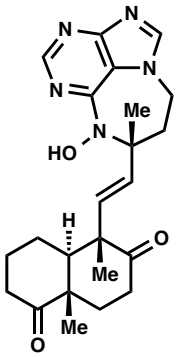
ent-26: The spectroscopic data and R_f were identical to that of the enantiomer **34** reported above.

$[\alpha]_D^{25}$ = -60.6 (4.3 mg/ 1 mL MeOH)



ent-35: 5 mg of the title compound (64% yield) as a purple solid was obtained. The spectroscopic data and R_f were identical to that of the enantiomer **43** reported above.

$[\alpha]_D^{25}$ = +18.8 (0.5 mg/ 1 mL MeOH)



SI-6: 6 mg of the title compound (68% yield) as a purple solid was obtained. The spectroscopic data and R_f were identical to that of the enantiomer **SI-4** reported above.

$[\alpha]_D^{25}$ = -307.2 (0.8 mg/ 1 mL MeOH)

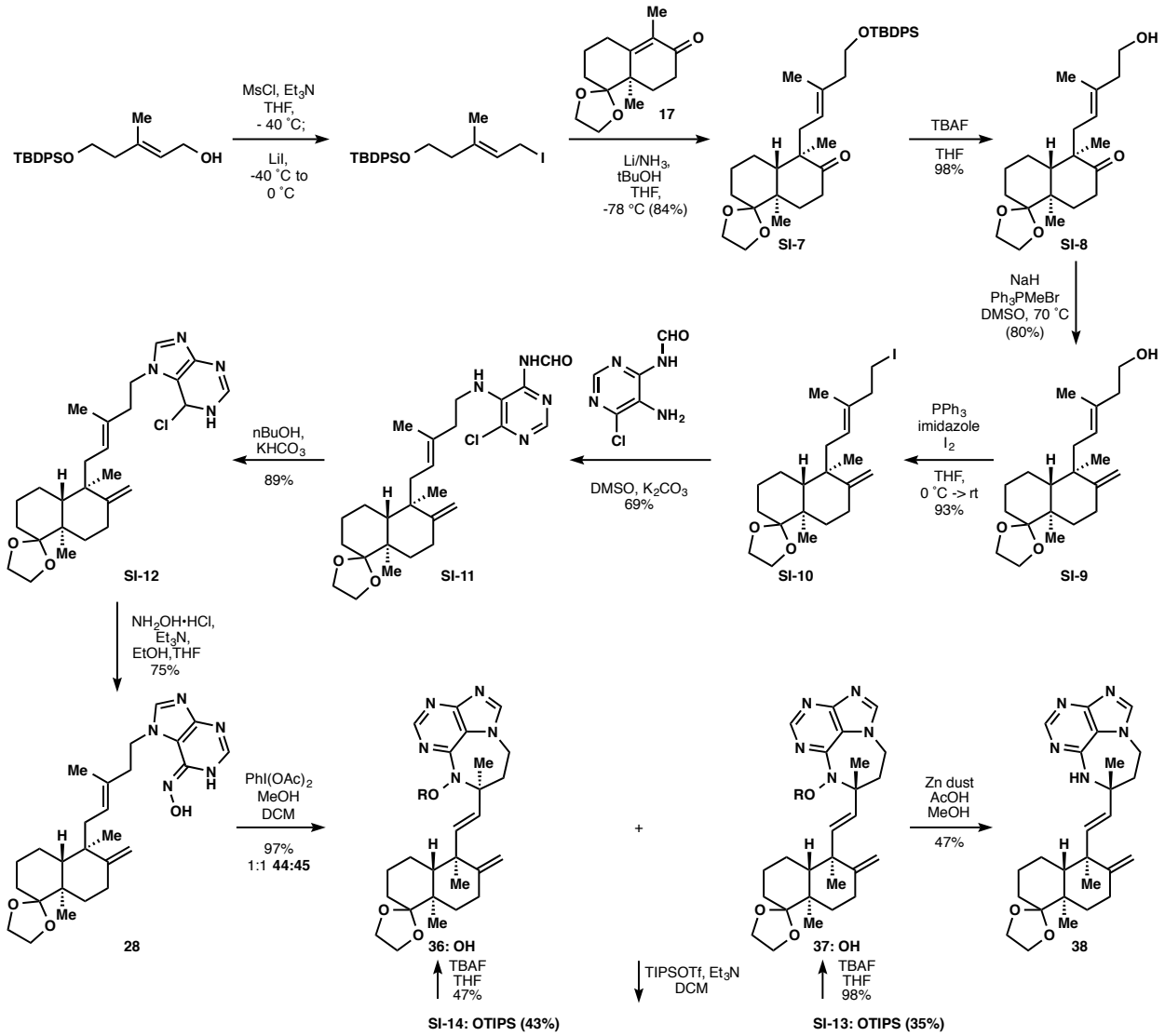
X-ray crystal (.cif crystal file available from the Cambridge Crystallographic Data Centre: CCDC 1036462. See: www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx)

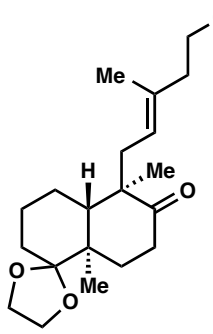
Empirical formula : C23 H33.50 N5 O5.25
Molecular formula :
C23 H29 N5 O3, 2.25(H2O)
Formula weight : 464.05
Temperature : 100(2) K
Wavelength : 1.54178 Å
Crystal system : Orthorhombic
Space group : P2(1)2(1)2
Unit cell dimensions:
a = 11.9694(5) Å, a= 90°. b = 46.2965(16) Å,
b= 90°. c = 8.6754(3) Å, g = 90°.
Volume: 4807.4(3) $Å^3$
Z: 8
Density (calculated): 1.282 Mg/m^3
Absorption coefficient: 0.757 mm^{-1}
F(000): 1988
Crystal size: 0.15 x 0.08 x 0.05 mm3
Crystal color, habit: Colorless Block
Theta range for data collection:
1.91 to 69.18°.
Index ranges:
-14<=h<=14, -55<=k<=55, -7<=l<=10

Reflections collected: 25313
Independent reflections:
8274 [R(int) = 0.0267]
Completeness to theta = 68.00°: 96.5 %
Absorption correction:
Semi-empirical from equivalents
Max. and min. transmission:
0.9631 and 0.8949
Refinement method:
Full-matrix least-squares on F2
Data / restraints / parameters:
8274 / 11 / 650
Goodness-of-fit on F2: 1.031
Final R indices [I>2sigma(I)]:
R1 = 0.0496, wR2 = 0.1364
R indices (all data):
R1 = 0.0536, wR2 = 0.1399
Absolute structure parameter: -0.01(19)
Extinction coefficient: not measured
Largest diff. peak and hole:
0.678 and -0.271 $e.Å^{-3}$

4. Route to (–)–clerodane-asmarines through olefin

Installation of a methylene subsequent to the appendage of the purine ring was not possible, so a second approach to the union of the decalin and purine was developed and is described below. This route leads to exo-methylene asmarines, but the nitrosopurine-ene reaction was not stereoselective with this substrate. This route could also be modified to converge with the oxime route described above.





SI-7: (*E*)-5-((*tert*-butyldiphenylsilyl)oxy)-3-methylpent-2-en-1-ol (3.90 g, 11.0 mmol, prepared by the reported conditions[9] from butynol in 2 steps) was dried by azeotropic removal of water twice with THF (8 mL) prior to being dissolved in anhydrous THF (35 mL) and cooled to -40 °C. To this stirring solution, Et_3N (4.3 mL, 31 mmol, 2.8 equiv.) and MsCl (2.3 mL, 29 mmol, 2.6 equiv.) were added successively and the resulting mixture was stirred for 45 minutes. The reaction flask was then protected from light with foil and a solution of lithium iodide (4.56 g, 34 mmol, 3.0 equiv.) in THF (30 mL) was then added over 2 minutes. After stirring at -40 ˚C for 10 minutes, the reaction mixture was warmed to 0 ˚C and stirred for another 30 minutes at 0 ˚C. The reaction was then diluted with Et_2O (100 mL) quenched with sodium thiosulfate (sat. aq.) (100 mL). The aqueous phase was extracted with Et_2O (3 x 100 mL), and the organics were combined and dried over $MgSO_4$ and concentrated in

vacuo to give 4.7g of (*E*)-*tert*-butyl((5-iodo-3-methylpent-3-en-1-yl)oxy)diphenylsilane as a pale yellow oil (92% crude yield). Since (*E*)-*tert*-butyl((5-iodo-3-methylpent-3-en-1-yl)oxy)diphenylsilane was not very stable, the crude compound was used in the next step without further purification.

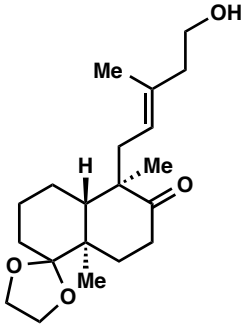
To a flame-dried 3-neck flask fitted with an oven-dried cold-finger condenser cooled to -78 ˚C (dry ice/acetone), gaseous ammonia was condensed to liquid (30 mL). Lithium (190 mg, 27 mmol, 3 equiv.) was then added and the resulting blue solution was vigorously stirred for 10 minutes. To a separate flame-dried flask, ketal **17** (2.16 g, 9.14 mmol) was dried by azeotropic removal of water three times with toluene under high vacuum and then dissolved in anhydrous THF (6 mL) and *t*-BuOH (1.7 mL). This resulting solution was then added drop-wised into the reaction vessel over 15 minutes. [Note: the color of the reaction should remain blue throughout the addition – more lithium was added if the mixture turned clear]. The resulting blue solution was stirred for 1 hour, and then freshly distilled isoprene was added dropwise (0.92 mL, 9.2 mmol, 1.0 equiv. or until the blue solution turns clear) until the reaction turned clear. (*E*)-*tert*-butyl((5-iodo-3-methylpent-3-en-1-yl)oxy)diphenylsilane (4.25 g, 9.14 mmol, 1.0 equiv.) [dried by azeotropic removal of water 3 times with toluene] dissolved in anhydrous THF (6.0 mL) was then added dropwise into the reaction, and the resulting mixture was stirred for at -78 ˚C for 10 minutes. The reaction was then protected from light with foil and slowly warmed to room temperature (allowing ammonia to evaporate). The reaction was then stirred at room temperature for 1 hour. Upon verification of complete alkylation by LCMS, the reaction was then diluted with EtOAc (50 mL) quenched with NH_4Cl (sat. aq.) (30 mL). The aqueous phase was extracted EtOAc (3 x 30 mL) and the combined organics were washed with brine. The crude mixture was then concentrated in vacuo and purified via column chromatography (10% EtOAc in hexanes, R_f = 0.32 with 3:1 Hexanes: Et_2O) to yield 4.40 g of the title compound as a colorless oil (84% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.61 – 7.67 (m, 4H), 7.34 - 7.43 (m, 6H), 4.98 (t, *J* = 7.2 Hz, 1H), 3.60 – 3.92 (m, 6H), 3.37 – 3.49 (m, 1H), 3.22 – 3.36 (m, 4H), 1.95 – 2.13 (m, 2H), 1.82 (td, *J* = 12.7, 6.3 Hz, 1H), 1.54 – 1.69 (m, 4H), 1.52 (s, 3H), 1.46 – 1.49 (m, 1H), 1.32 – 1.39 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 1H), 1.12 (s, 3H), 1.04 (s, 9H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 216.41, 135.54, 134.35, 134.08, 134.04, 129.51, 127.59, 123.03, 112.66, 64.96, 64.86, 63.75, 51.12, 43.93, 43.28, 42.24, 37.28, 35.19, 30.24, 28.18, 26.88, 22.87, 22.13, 21.94, 19.14, 16.63, 16.11.

LCMS (APCI): Calculated $[M+H]^+$: 575.4; Found 575.4

$[\alpha]_D^{25}$ = -3.2 (1.0 mg/ 10 mL DCM)



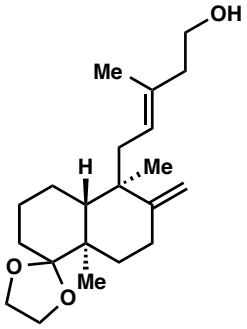
SI-8: A solution of silylether **SI-7** (3.92 g, 6.82 mmol) in THF (14 mL) was treated with a 1.0M solution of TBAF in THF (10 mL, 10.0 mmol, 1.5 equiv.) at room temperature. The reaction was stirred for 3 hours, and upon verification of completion of reaction via TLC, the reaction mixture was diluted with EtOAc (50 mL) and quenched with brine (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) three times. The combined organics were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield the crude mixture. Purification via column chromatography (2 : 1 hexanes : EtOAc, R_f = 0.24 with 2 : 1 Hexanes : EtOAc) gave 2.24 g of the title compound as a colorless oil (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.08 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.83 – 3.96 (m, 4H), 3.57 – 3.76 (m, 2H), 2.24 – 2.55 (m, 4H), 2.06 – 2.22 (m, 4H), 1.85 (td, *J* = 13.2, 5.8 Hz, 1H), 1.51 – 1.77 (m, 4H), 1.61 (s, 3H), 1.32 – 1.48 (m, 3H), 1.19 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 216.16, 133.90, 124.34, 112.68, 64.94, 64.79, 60.17, 50.93, 43.71, 43.23, 42.01, 36.99, 34.99, 29.98, 27.94, 22.87, 21.92, 15.90, 15.76.

LCMS (APCI): Calculated $[M+H]^+$: 337.2; Found 337.3

$[\alpha]_D^{25}$ = -8.3 (4.0 mg/ 1 mL DCM)



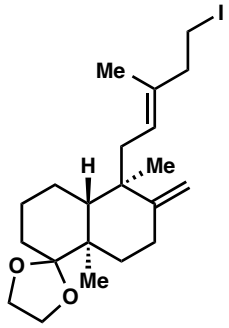
SI-9: Sodium hydride (4.23 g, 106 mmol, 20.0 equiv.) [washed with anhydrous Et_2O (3x 20 mL) before use] was dissolved in anhydrous DMSO (160 mL) and stirring mixture was heated to 75 °C for 80 minutes. After cooling to room temperature, Ph_3PMeBr (37.8 g, 106 mmol, 20.0 eqiuv.) was added to the reaction mixture in portions and stirred for 30 min. A solution of ketoalcohol **SI-8** (1.78 g, 5.29 mmol) [dried by azeotropic removal of water with benzene (2 x 2 mL) before use] in DMSO (14.0 mL) was then added to the reaction, and the resultant mixture was heated to 75 °C for 5 hours. The reaction was then cooled back to room temperature, diluted with EtOAc (500 mL) and quenched with NH_4Cl (sat. aq.) (300 mL). The aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organics were washed with brine (5 x 100 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Purification via column chromatography (10% EtOAc in hexanes -> 20% EtOAc in hexanes, R_f = 0.38 (10% MeOH in EtOAc) gave 1.78 g of the title compound as a pale yellow oil (80% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.28 – 5.38 (m, 1H), 4.77 (s, 1 H), 4.65 (s, 1H), 3.78 – 3.96 (m, 4H), 3.57 – 3.66 (m, 2H), 2.08 – 2.43 (m, 6H), 1.76 (d, *J* = 8.7 Hz, 1H), 1.54 – 1.66 (m, 3H), 1.62 (s, 3H), 1.45 – 1.54 (m, 1H), 1.21 – 1.44 (m, 4H), 1.12 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.17, 132.01, 125.34, 113.49, 107.08, 65.20, 65.00, 60.24, 44.16, 43.35, 43.30, 42.55, 37.60, 31.19, 30.35, 29.62, 24.47, 23.13, 21.49, 17.41, 16.21.

LCMS (APCI): Calculated $[M+H]^+$: 335.3; Found 335.3

$[\alpha]_D^{25}$ = -45.9 (4.3 mg/ 1 mL DCM)



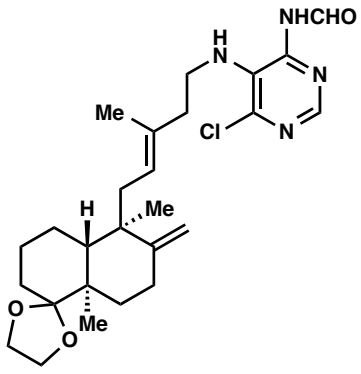
SI-10: To a flask protected from light with foil, ketoalcohol **SI-9** (1.73 g, 5.17 mmol), imidazole (1.05g, 15.6 mmol, 3.0 equiv.) and Ph_3P (2.06g, 7.78 mmol, 1.5 equiv.) were dissolved anhydrous THF (15 mL). The mixture was then cooled to 0 ˚C (with ice bath), and iodine (2.02g, 8.02 mmol, 1.55 equiv.) was added portion-wise into the stirring solution. The reaction was stirred for 10 minutes before it was warmed to room temperature. After 2 hours (and confirmation of reaction completion via TLC), the reaction was diluted with Et_2O (30 mL) and quenched with sodium thiosulfate (sat. aq.) (30 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL), the organics were combined and washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via column chromatography (10% EtOAc in hexanes, R_f = 0.80 (10% EtOAc in hexanes) gave 2.14 g of the title compound as a pale yellow oil (93% yield).

^{1}H NMR (400 MHz, Chloroform-*d*): δ 5.28 (t, *J* = 6.7 Hz, 1H), 4.76 (s, 1H), 4.62 (s, 1H), 3.78 – 3.99 (m, 4H), 3.20 (t, *J* = 7.9 Hz, 2H), 2.48 – 2.62 (m, 2H), 2.30 – 2.41 (m, 1H), 2.08 – 2.22 (m, 3H), 1.77 (d, *J* = 10.7 Hz, 1H), 1.58 – 1.71 (m, 3H), 1.62 (s, 3H), 1.44 – 1.52 (m, 1H), 1.21 – 1.44 (m, 4 H), 1.13 (s, 3 H), 0.98 (s, 3 H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.22, 134.11, 124.85, 113.41, 107.03, 65.26, 64.87, 44.49, 44.45, 43.36, 42.62, 37.42, 31.51, 30.37, 29.65, 23.93, 22.99, 21.45, 17.68, 15.81, 5.25.

LCMS (APCI): Calculated $[M+H]^+$: 445.2; Found 445.2

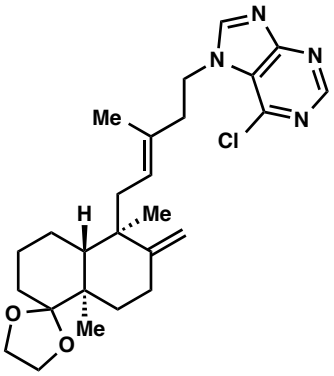
$[\alpha]_D^{25}$ = -20.8 (5.8 mg/ mL DCM)



SI-11: To a flask protected from light, iodide **SI-10** (557 mg, 1.40 mmol, 1.0 equiv.), *N*-(5-amino-6-chloropyrimidin-4-yl)formamide (241 mg, 1.4 mmol) and potassium carbonate (773 mg, 5.60 mmol, 2.86 equiv.) were dissolved in DMSO (3.5 mL, 0.4 M). The reaction was left stirring overnight (12 hours). Upon verification that the alkylation had completed via LCMS, the reaction was diluted with EtOAc (10 mL) and quenched with NH_4Cl (sat. aq.) (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL), the organics were combined and washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via column chromatography (10% acetone in hexanes -> 40% acetone in hexanes, R_f = 0.43 (40% EtOAc in hexanes) gave 425.2 mg of the title compound as an off-white amorphous solid

(69% yield). Since the isolated compound was a mixture of rotamers, it was taken to the next step without NMR characterization.

LCMS (APCI): Calculated $[M+H]^+$: 491.3 Found 491.4



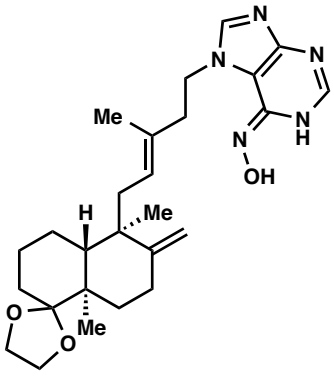
SI-12: Formamide **SI-11** (471 mg, 0.96 mmol) and potassium bicarbonate (384 mg, 3.84 mmol, 4.0 equiv.) were dissolved in *n*-BuOH (6.4 mL, 0.15M) and the stirring mixture was heated to 85 °C for 100 minutes. After confirming depletion of starting material by LCMS, the reaction mixture was cooled to room temperature. [Reaction was monitored carefully – heating for an extended period of time will result in the chloride being displaced by butanol.] The reaction was diluted with EtOAc (10 mL) and quenched with NH_4Cl (sat. aq.)(10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL), the organics were combined and washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.48 (10% MeOH and 1% NH_4OH in $CHCl_3$)) gave 403 mg of the title compound as an off-white amorphous solid (89% yield). [Note: the crude compound was pure enough to be taken through the next step without purification if desired.]

^{1}H NMR (600 MHz, Methanol-d_4) δ 8.79 (s, 1H), 8.61 (s, 1H), 5.00 (t, J = 6.6 Hz, 1H), 4.64 (t, J = 7.5 Hz, 2H), 4.56 (s, 1H), 4.24 (s, 1H), 3.84 – 3.93 (m, 3H), 3.76 – 3.82 (m, 1H), 2.61 (t, J = 6.9 Hz, 2H), 2.33 (td, J = 13.6, 4.7 Hz, 1H), 2.13 – 2.20 (m, 1H), 2.04 (dt, J = 13.8, 4.4 Hz, 2H), 1.75 (s, 3H), 1.66 (dd, J = 10.2, 4.6 Hz, 1H), 1.45 – 1.63 (m, 4H), 1.23 – 1.35 (m, 4H), 1.10 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 162.68, 155.35, 152.97, 151.94, 144.67, 131.49, 127.03, 123.68, 114.39, 107.22, 66.26, 65.78, 47.24, 45.37, 44.44, 43.49, 42.78, 38.18, 32.55, 31.20, 30.43, 24.72, 23.98, 22.27, 17.73, 16.31.

LCMS (APCI): Calculated $[M+H]^+$: 471.2 Found 471.3

$[\alpha]_D^{25}$ = -24.2 (4.2 mg/ mL DCM)



28: Chloropurine **SI-11** (1.41 g, 3.0 mmol) and hydroxylamine hydrochloride (2.54 g, 36.6 mmol, 12.2 equiv.) were dissolved in anhydrous ethanol (9 mL) and THF (8 mL). To the stirring cloudy solution was added anhydrous triethylamine (5.1 mL, 36.6 mmol, 12.2 equiv.). The reaction was left stirring for 2 days at room temperature, and upon verification of depletion of starting material by LCMS the reaction was quenched with $NaCO_3$ (sat. aq.)(15 mL). 10% MeOH in DCM (20 mL) was added and the aqueous layer was

extracted with 10% MeOH in DCM (5 x 10 mL). The combined organics were concentrated in vacuo and purified via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.55 with 10% MeOH and 1% NH_4OH in $CHCl_3$) to yield 1.05 g of the title compound as a white solid (75% yield).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.70 (s, 1H), 7.56 (s, 1H), 5.02 (t, J = 5.9 Hz, 1H), 4.63 (s, 1H), 4.27 – 4.37(m, 3H), 3.74 – 3.99 (m, 4H), 2.40 – 2.59 (m, 2H), 2.32 (t, J = 12.2 Hz, 1H), 1.97 – 2.20 (m, 3H), 1.68 (s, 3H), 1.64 – 1.74 (m, 1H), 1.45 – 1.64 (m, 4H), 1.24 – 1.39 (m, 4H), 1.10 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 155.19, 149.95, 145.11, 141.30, 141.11, 132.02, 126.24, 114.43, 112.05, 107.50, 66.19, 65.70, 47.36, 45.62, 44.39, 43.43, 42.45, 38.44, 32.61, 31.14, 30.47, 24.35, 23.92, 22.39, 18.06, 16.32.

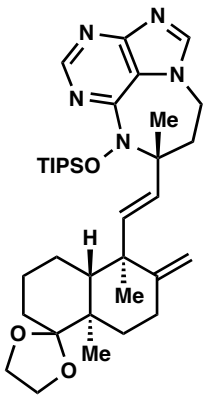
LCMS (APCI): Calculated $[M+H]^+$: 468.3 Found 468.3

$[\alpha]_D^{25}$ = -41.5 (10 mg/ mL MeOH)

Nitroso-ene cyclization of hydroxylamine 28

Using the non-stereoselective cyclization procedure outlined for **26** and **34** above, 155 mg of a mixture of **36** and **37** (97% total yield) was isolated as purple solids upon purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.62 with 10% MeOH and 1% NH_4OH in $CHCl_3$). [Note: These diastereomers are inseparable by silica, but can be separated after TIPS protection. The crude material could be taken onto the TIPS protection step if desired.]

The mixture of **36** and **37** (56 mg, 0.12 mmol) were dissolved in DCM (3.2 mL) and cooled to 0 ˚C. Et_3N (75.4 mL, 0.54 mmol, 4.5 equiv.) and TIPSOTf (100 mL, 0.36 mmol, 3.0 equiv.) were added and the reaction was stirred for 40 min at 0 ˚C. Upon verification of completion of reaction by TLC, the reaction was quenched $NaHCO_3$ (sat. aq.)(3 mL). The aqueous layer was extracted with 10% MeOH in DCM (3 x 5 mL). The combined organic extracts was concentrated in vacuo, and purification by preparative TLC (2% MeOH and 2% NH_4OH in 96% EtOAc, loaded onto ten10 x 10 cm TLC plates, ran 1x -2x per plate for clean separation) afforded 32 mg (43% yield) of less polar **SI-13** as a white solid and 26 mg (35% yield) of more polar **SI-14** as a colorless oil.



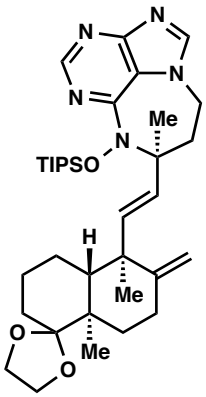
SI-13: R_f = 0.53 with 10% MeOH and 1% NH_4OH in $CHCl_3$

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.96 (s, 1H), 5.23 – 5.40 (m, 2H), 4.14 – 4.33 (m, 3H), 3.70 – 3.82 (m, 4H), 3.40 (s, 1H), 2.40 – 2.52 (m, 2H), 2.28 (t, J = 13.9 Hz, 1H), 2.01 (d, J = 14.2 Hz, 1H), 1.79 (s, 3H), 1.32 – 1.66 (m, 8H), 1.17 – 1.30 (m, 5H), 1.15 (d, J = 7.4 Hz, 8H), 1.05 – 1.11 (m, 12 H), 0.98 (s, 3 H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 159.17, 155.19, 152.84, 152.03, 143.36, 143.29, 126.41, 113.13, 110.17, 107.47, 68.01, 65.41, 65.06, 47.47, 46.25, 43.17, 43.05, 39.47, 31.18, 30.81, 29.85, 29.47, 28.60, 22.81, 22.10, 19.28, 18.91, 18.84, 16.49, 15.02.

LCMS (APCI): Calculated $[M+H]^+$: 622.4 Found 622.6

$[\alpha]_D^{25}$ = +37.9 (3.1 mg/ mL MeOH)



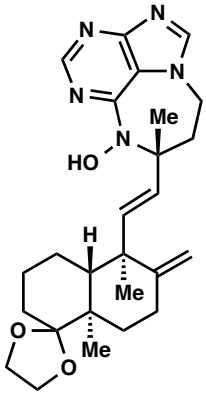
SI-14: R_f = 0.43 with 10% MeOH and 1% NH_4OH in $CHCl_3$

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.96 (s, 1H), 5.30 – 5.55 (m, 2H), 4.59 (s, 1 H), 4.47 (s, 1H), 4.16 – 4.32 (m, 3H), 3.69 – 3.88 (m, 4H), 2.53 (ddd, *J* = 15.8, 12.4, 3.4 Hz, 1H), 2.43 (dt, *J* = 15.6, 2.7 Hz, 1H), 2.34 (td, *J* = 13.5, 3.8 Hz, 1H), 2.12 (dt, *J* = 14.1, 3.4 Hz, 1H), 1.80 (s, 3 H), 1.33 – 1.56 (m, 8H), 1.18 – 1.32 (m, 4H), 1.14 (d, *J* = 7.5 Hz, 9H), 1.10 (d, *J* = 7.5 Hz, 9H), 1.06 (s. 3 H), 0.97 (dd, *J* = 12.9, 3.5 Hz, 1H), 0.93 (s, 3 H), 0.79 – 0.90 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 159.37, 155.40, 152.85, 152.08, 143.80, 143.38, 126.80, 113.05, 110.39, 108.01, 67.55, 65.36, 64.93, 47.88, 46.22, 43.13, 42.99, 39.89, 31.42, 30.62, 29.84, 28.89, 28.73, 22.67, 21.86, 19.22, 18.87, 18.83, 16.46, 14.97.

LCMS (APCI): Calculated $[M+H]^+$: 622.4 Found 622.6

$[\alpha]_D^{25}$ = -32.8 (3.1 mg/ mL MeOH)



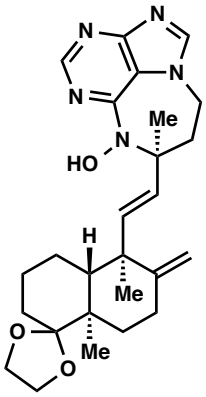
37: A solution of silylether **SI-13**(15 mg, 0.024 mmol) in THF (2 mL) was treated with a 1.0M solution of TBAF in THF (50 μL, 0.05 mmol, 2 equiv.) at room temperature. The reaction was stirred for 5 minutes, and upon verification of completion of reaction via TLC, the reaction mixture was diluted with DCM (5 mL) and quenched with $NaHCO_3$ (sat. aq.)(5 mL). The aqueous layer was extracted with 10% MeOH in DCM (4 x 5 mL). The combined organic extracts were concentrated in vacuo to yield the crude mixture. Purification by preparative TLC (10% MeOH and 1% NH_4OH in $CHCl_3$, loaded onto four 10 x 10 cm TLC plates) afforded 11 mg (98% yield) of the title compound as a white solid (R_f = 0.62 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 8.40 (s, 1H), 8.26 (s, 1H), 5.39 (dd, *J* = 132.5, 16.1 Hz, 1H), 4.59 (s, 1 H), 4.46 (ddd, *J* = 13.4, 4.7, 2.6 Hz, 1H), 4.27 (t, *J* = 8.4 Hz, 1H), 4.19 (s, 1H), 3.72 – 3.91 (m, 4H), 2.55 – 2.62 (m, 1H), 2.46 – 2.53 (m, 1H), 2.32 – 2.40 (m, 1H), 2.03 (d, *J* = 14.3 Hz, 1H), 1.75 (s, 3H), 1.32 – 1.65 (m, 9H), 1.15 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 159.20, 157.19, 153.93, 153.22, 145.56, 142.80, 129.20, 114.22, 111.17, 107.59, 69.28, 66.26, 65.92, 47.23, 44.57, 44.14, 39.98, 32.46, 31.54, 30.76, 29.53, 27.81, 23.81, 22.99, 19.73, 16.77.

LCMS (APCI): Calculated $[M+H]^+$: 466.3 Found 466.3

$[\alpha]_D^{25}$ = +45.8 (1.0 mg/ mL MeOH)



36: Following the procedure for **37**, 1.4 mg of **36** was obtained as a white solid from 4 mg of **SI-14** (47% yield).

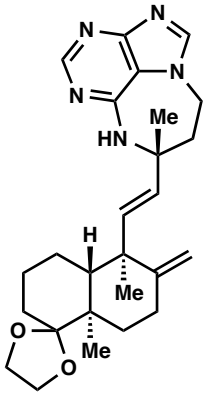
R_f = 0.62 with 10% MeOH and 1% NH_4OH in $CHCl_3$

^{1}H NMR (600 MHz, Methanol-d_4) δ 8.43 (s, 1H), 8.26 (s, 1H), 5.37 (dd, *J* = 162.1, 16.2 Hz, 1H), 4.61 (m, 2H), 4.47 (d, *J* = 13.9 Hz, 1H), 4.28 (t, *J* = 12.9 Hz, 1H), 3.67 – 3.87 (m, 4H), 2.58 – 2.64 (m, 1H), 2.52 (t, *J* = 13.9 Hz, 1H), 2.34 – 2.42 (m, 1H), 2.11 (d, *J* = 14.1 Hz, 1H), 1.77 (s, 3H), 1.31 – 1.47 (m, 5H), 1.10 – 1.21 (m, 1H), 1.06 – 1.07 (m, 6H), 0.93 – 1.03 (m, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 158.88, 156.40, 154.43, 153.16, 145.58, 143.37, 128.73, 113.95, 111.38, 108.88, 69.27, 66.21, 65.82, 47.05, 44.72, 44.12, 40.09, 32.58, 31.43, 30.75, 29.56, 28.31, 23.59, 23.00, 19.46, 16.69.

LCMS (APCI): Calculated $[M+H]^+$: 466.3 Found 466.3

$[\alpha]_D^{25}$ = -70.0 (0.5 mg/ mL MeOH)



38: Zinc dust (16 g) was first activated with HCl (2.7M, or 10% v/v) by stirring in the acidic solution for 2 minutes. The solid was then filtered and washed with H_2O (12 mL), acetone (4 mL) and Et_2O (4 mL). The zinc dust was then dried on high vacuum for 2 hours.

MeOH (1 mL) was added to a flask with activated zinc dust (50 mg, 0.76 mmol, 40 equiv.) and **37** (8.9 m, 0.019 mmol). AcOH (0.04 mL, 0.70 mmol, 37 equiv.) was then added and the resulting solution was stirred for 24 hours. The reaction was then quenched by adding the reaction mixture into a stirring solution of 0.1M pH 8 phosphate buffer (20 mL) and 10% MeOH in DCM (20 mL). The aqueous layer was extracted with 10% MeOH in DCM (8 x 20 mL). The combined organics were washed with brine (5 mL) and concentrated in vacuo. Purification by preparative TLC (10% MeOH and 1% NH_4OH in DCM, loaded onto two 10 x 10 cm TLC plates) afforded 4 mg (47% yield) of the title compound as a white solid (R_f = 0.62 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

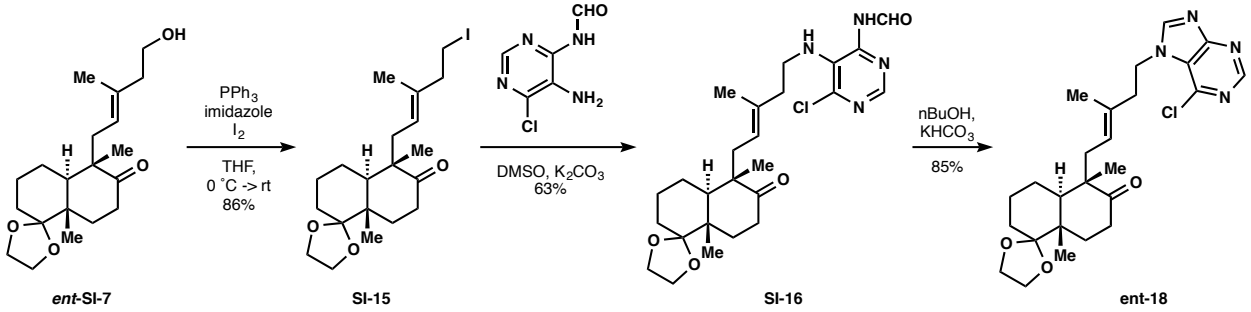
^{1}H NMR (600 MHz, Methanol-d_4) δ 8.28 (s, 1H), 8.23 (s, 1H), 5.51 (dd, J = 125.7, 16.0 Hz, 1H), 4.50 (dt, J = 13.7, 3.1 Hz, 1H), 4.32 – 4.25 (m, 1H), 4.16 (s, 1H), 3.76 – 3.92 (m, 4H), 3.44 (s, 1H), 2.54 (ddd, J = 15.4, 12.6, 2.9 Hz, 1H), 2.45 (ddd, J = 15.4, 4.1, 2.3 Hz, 1H), 2.38 (td, J = 13.8, 5.2 Hz, 1H), 2.04 (dt, J = 14.2, 3.5 Hz, 1H), 1.60 – 1.68 (m, 1H), 1.58 (s, 3H), 1.32 – 1.55 (m, 8H), 1.17 (s, 3H), 1.12 (s, 3H).

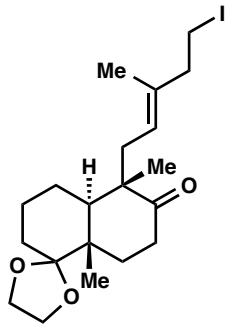
^{13}C NMR (151 MHz, Methanol-d_4) δ 159.55, 157.30, 153.85, 153.81, 145.65, 141.87, 132.43, 114.25, 110.89, 107.43, 66.29, 65.93, 59.65, 47.05, 45.77, 44.17, 40.35, 32.46, 31.54, 31.26, 30.75, 29.53, 23.84, 22.95, 19.89, 16.79.

LCMS (APCI): Calculated $[M+H]^+$: 450.3 Found 450.3

$[\alpha]_D^{25}$ = +52.7 (2.3 mg/ mL DCM)

5. Alternative route to (+)-clerodane asmarines





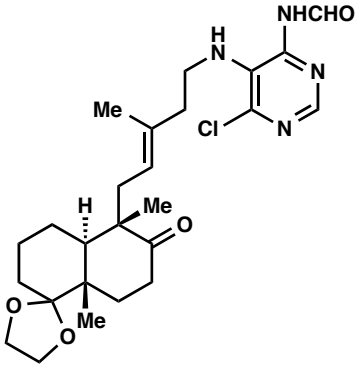
SI-15: Following the same procedure as **SI-10**, with purification via column chromatography (5% EtOAc in hexanes -> 15% EtOAC in hexanes, R_f = 0.20 with 10% EtOAc in hexanes), 329 mg of **SI-15** (0.73 mmol, 86% yield) was obtained from 300 mg of ***ent*-SI-7** (0.89 mmol) as a clear oil.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.00 – 5.06 (m, 1H), 3.75 – 3.95 (m, 4H), 3.09 – 3.23 (m, 2H), 2.41 – 2.57 (m, 3H), 2.27 – 2.38 (m, 2 H), 2.10 – 2.17 (m, 1H), 2.01 (dd, J = 14.3, 9.3 Hz, 1H), 1.89 (td, J = 13.2, 5.8 Hz, 1H), 1.59 – 1.70 (m, 2H), 1.58 (s, 3H), 1.35 – 1.54 (m, 5H), 1.15 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 216.33, 135.95, 124.19, 112.86, 65.25, 64.99, 51.29, 44.40, 44.14, 42.45, 36.92, 35.23, 30.35, 28.51, 22.95, 22.11, 22.08, 16.23, 15.68, 4.67.

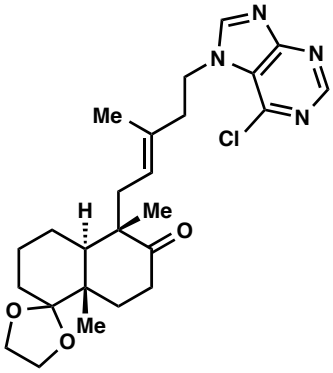
LCMS (APCI): Calculated $[M+H]^+$: 447.2 Found 447.2

$[\alpha]_D^{25}$ = -5.4 (10 mg/ mL DCM)



SI-16: Following the same procedure as **SI-11**, with purification via column chromatography (30% acetone in hexanes -> 40% acetone in hexanes, R_f = 0.26 (40% EtOAc in hexanes) gave 199 mg of the title compound as an off-white solid (63% yield) from 288 mg of iodide **SI-15** (0.67 mmol). Since the isolated compound was a mixture of rotamers, it was taken to the next step without NMR characterization.

LCMS (APCI): Calculated $[M+H]^+$: 493.3 Found 493.4



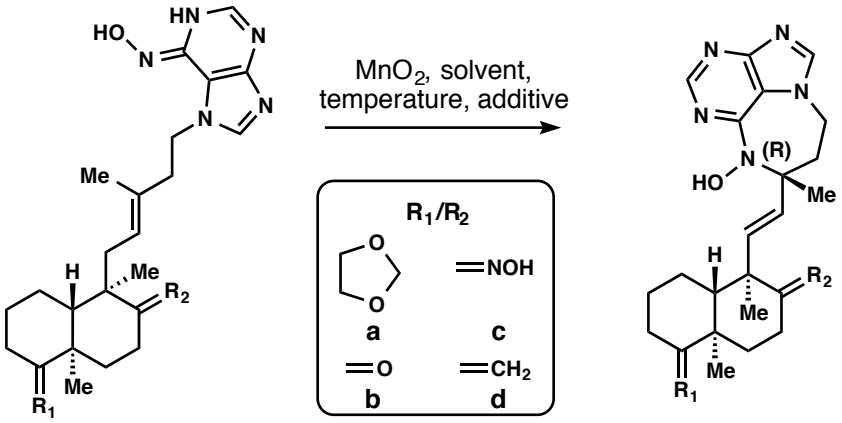
ent-18: Following the same procedure as **SI-12**, with purification via column chromatography (100% EtOAc, R_f = 0.30 with EtOAc) to yield 132 mg of the title compound (0.28 mmol, 85% yield) as a white solid from 160 mg of **SI-16** (0.32 mmol). All data matched that previous reported above.

5. Stereoselectivity of the nitroso-ene reaction

Selective stereoselectivities from our studies and optimization of the nitroso-ene cyclization is listed in the tables below.

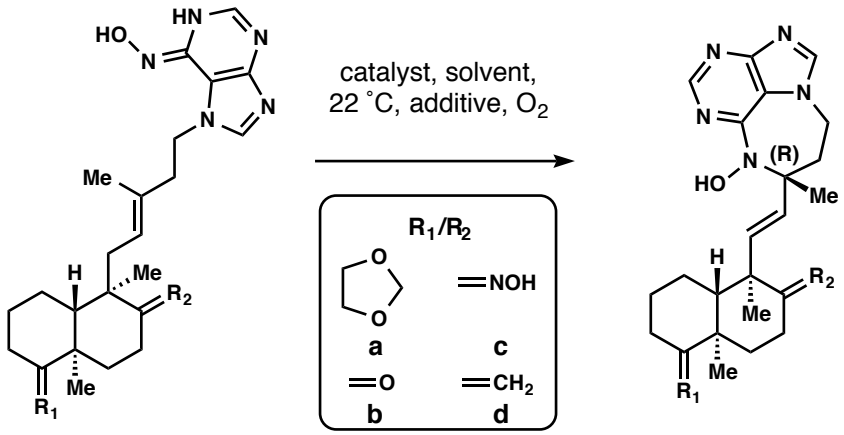
Representative procedure:

To a mixture of hydroxylamine (1.0 equiv.) and oxidant (1.0 equiv.) [and additive if applicable] were added solvent (0.1M). The reaction progress was monitored via LCMS and the ratio of the two diasteromeric products was obtained either by LCMS or ^{1}H NMR. [Reactions with MnO_2 were done under normal air, and all the other reactions are done under an oxygen atmosphere.]



R_1/R_2	Solvent	Temperature	Additive	**(S) : (R)**
a/c	**DMF**	22 °C	–	1.5 : 1.0
a/c	**CH_2Cl_2**	22 °C	–	1.5 : 1.0
a/c	**1:9 MeOH/ CH_2Cl_2**	22 °C	**NH_4OH (1%)**	2.1 : 1.0
a/c	**EtOH**	22 °C	–	3.8 : 1.0
a/c	**EtOH**	–20 °C	–	3.0 : 1.0
a/c	**EtOH**	22 °C	**AcOH (1 equiv.)**	2.7 : 1.0
a/c	**TFE**	22 °C	–	2.3 : 1.0
a/c	**1:1 EtOH/ H_2O**	22 °C	–	4.7 : 1.0
a/c	**H_2O**	22 °C	–	6.0 : 1.0
a/c	**1:4 EtOH/ H_2O**	22 °C	–	7.9 : 1.0
b/b	**1:4 EtOH/ H_2O**	22 °C	–	1.2 : 1.0
a/d	**1:4 EtOH/ H_2O**	22 °C	–	1.1 : 1.0
d/d	**1:4 EtOH/ H_2O**	22 °C	–	1.1 : 1.0

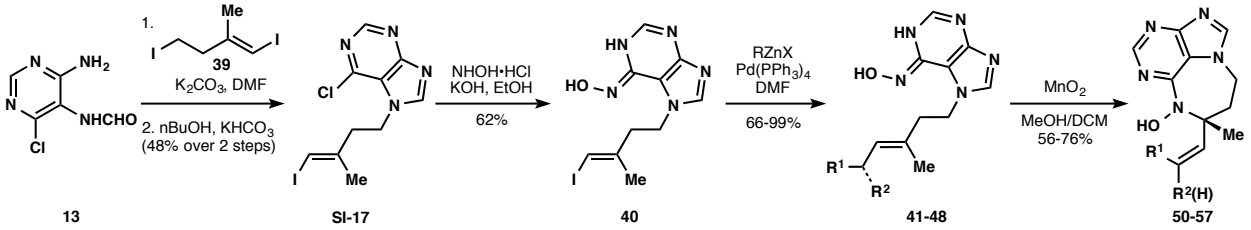
Table 1. Example selectivity of the nitroso-ene reactions with MnO_2 as oxidant.

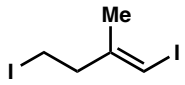


R_1/R_2	Solvent	Catalyst	Additive	**(S) : (R)** * low conversion
a/c	**DCM**	**$Mn(acac)_3$**	–	1.4 : 1.0
a/c	**THF**	**$Mn(acac)_3$**	–	2.0 : 1.0
a/c	**THF**	**$Mn(acac)_3$**	**Et_3N (1 equiv.)**	1.6 : 1.0
a/c	**EtOH**	**$Mn(acac)_3$**	–	4.0 : 1.0
a/c	**benzene**	**$Mn(acac)_3$**	–	4.0 : 1.0*
a/c	**F_6-benzene**	**$Mn(acac)_3$**	–	2.0 : 1.0*
a/c	**DCM**	**$Mn(OAc)_3$**	–	1.5 : 1.0
a/c	**DCM**	**$Mn(OAc)_3$**	**AcOH (1 equiv.)**	1.1 : 1.0
a/c	**DCM**	**$Mn(OAc)_3$**	**Et_3N (1 equiv.)**	1.6 : 1.0
a/c	**THF**	**$Mn(OAc)_3$**	–	1.4 : 1.0
a/c	**EtOH**	**$Mn(OAc)_3$**	–	3.6 : 1.0
a/c	**CCl_4**	**$Mn(OAc)_3$**	–	4.0 : 1.0*
a/c	**DCM**	**$Co(acac)_2$**	–	1.0 : 1.0*
a/c	**DCM**	–	–	1.5 : 1.0*
a/c	**DCM**	**Mn(3-(perflurorbutyryl)-(+)-camphor)$_2$**	–	1.3 : 1.0
d/d	**DCM**	**$Mn(OAc)_3$**	–	1.1 : 1.0
d/d	**THF**	**$Mn(OAc)_3$**	–	1.7 : 1.0
d/d	**EtOH**	**$Mn(OAc)_3$**	–	1.5 : 1.0

Table 2. Example selectivity of the nitroso-ene reactions with other oxidants.

6. Synthesis of asmarine analogs



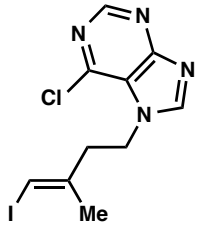


39: To a flask protected from light with foil, *(E)*-4-iodo-3-methylbut-3-en-1-ol (5.2 g, 24.5 mmol) [prepared from one step from butynol][2], imidazole (2.5 g, 36.8 mmol, 1.5 equiv.) and Ph_3P (9.62 g, 36.8 mmol, 1.5 equiv.) were dissolved anhydrous DCM (20 mL). The mixture was then cooled to 0 ˚C (with ice bath), and iodine (9.36 g, 36.8 mmol, 1.5 equiv.) was added portion-wise into the stirring solution. The reaction was stirred for 10 minutes before it was warmed to room temperature. After 1 hour (and confirmation of reaction completion via TLC), the reaction was quenched with sodium thiosulfate (sat. aq.)(20 mL). The aqueous layer was extracted with pentane (3 x 20 mL), the organics were washed with brine (75 mL), dried over $MgSO_4$, filtered and concentrated in vacuo [caution: compound is volatile: evaporated at 250 torr]. The crude material was purified through a short silica plug (100% pentane, R_f = 0.35 in pentane) gave 7.50 g of the title compound as a pale yellow oil (95% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.06 (q, *J* = 1.1 Hz, 1H), 3.22 (t, *J* = 7.5 Hz, 2H), 2.76 (td, *J* = 7.6, 1.0 Hz, 2H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.08, 110.14, 43.44, 23.26, 2.35.

GCMS (EI 70 eV) m/z (%): 53.0 (6), 65.0 (5), 67.0 (27), 68.1 (28), 126.9 (11), 154.9 (6), 166.9 (4), 194.9 (100), 195.9 (5), 321.8 (20).



SI-17: To a flask protected from light, iodide **39** (3.22 g, 10 mmol, 4.0 equiv.), *N*-(5-amino-6-chloropyrimidin-4-yl)formamide (431 mg, 2.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol, 3.0 equiv.) were dissolved in DMF (6 mL). The reaction was left stirring for 24 hours. Upon verification that the alkylation had completed via LCMS, the reaction was diluted with 10% MeOH in DCM (10 mL) and quenched with NH_4Cl (sat. aq.)(5 mL). The aqueous layer was extracted with 10% MeOH in DCM (8 x 6 mL) and the organics were combined and concentrated in vacuo. The crude material was then taken onto the next step without further purification. [Note: The aqueous work-up was necessary prior to cyclization because otherwise the next step will have significant solvent alkylated by-products.]

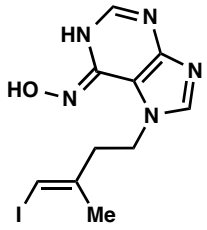
The crude material was then dissolved in *n*-BuOH (16 mL) with $KHCO_3$ (990 mg, 9.9 mmol, 4.0 equiv.) and the reaction was heated to 85˚C for 1 hour. [Reaction was monitored carefully – heating for an extended period of time will result in the chloride being displaced by butanol.]

After confirming depletion of starting material by LCMS, the reaction mixture was cooled to room temperature. The reaction was diluted with 10% MeOH in DCM (15 mL) and quenched with NH_4Cl (sat. aq.) (10 mL). The aqueous layer was extracted with 10% MeOH in DCM (5 x 10 mL), the organics were combined and concentrated in vacuo. Purification via column chromatography (3% MeOH & 0.3% NH_4OH in $CHCl_3$ -> 5% MeOH and 0.5% NH_4OH in $CHCl_3$, R_f = 0.32 in 4% MeOH and 0.4% NH_4OH in $CHCl_3$) gave 418 mg of the title compound as a white solid (48% yield over 2 steps).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.90 (s, 1H), 8.23 (s, 1H), 5.96 (s, 1H), 4.59 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 1.95 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 161.52, 152.90, 148.94, 143.16, 142.25, 122.14, 79.61, 45.77, 41.39, 24.13.

LCMS (APCI): Calculated $[M+H]^+$: 348.96 Found 348.9

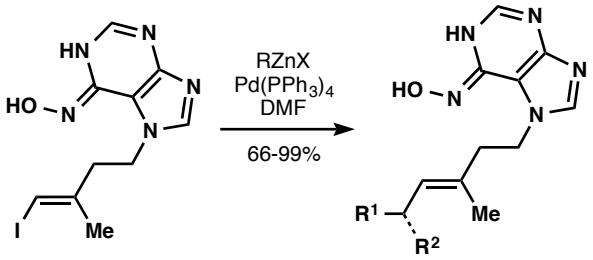


40: Chloropurine **SI-17** (424 mg, 1.21 mmol) and hydroxylamine hydrochloride (1.77 g, 16.9 mmol, 14 equiv.) were dissolved in anhydrous ethanol (12.8 mL). The reaction was sonicated for 5 minutes to help solubilize the substrate. To the stirring cloudy solution was added anhydrous triethylamine (1.78 mL, 12.8 mmol, 10.5 equiv.). The reaction was left stirring for 4 days at room temperature, and upon verification of depletion of starting material by LCMS the cloudy reaction was quenched with a $NaCO_3$ (sat. aq.)(10 mL). 10% MeOH in DCM (10 mL) was added and the aqueous layer was extracted with 10% MeOH in DCM (10 x 10 mL). The combined organics were concentrated in vacuo and purified via column chromatography (10% MeOH & 1% NH_4OH in $CHCl_3$, R_f = 0.27 with 10% MeOH and 1% NH_4OH in $CHCl_3$) to yield 260 of the title compound as a white solid (62% yield). [Note: solubility sometimes is an issue with purification – sometimes the crude material will not dissolve to be loaded onto silica. In that case simply washing the substrate with water repeatedly will purify the title compound from the impurities, though the yield may be lower (ca. 30%-60%) with this method.]

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.73 (s, 1H), 7.56 (s, 1H), 5.94 (s, 1H), 4.37 (t, *J* = 6.9 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.91 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 150.08, 145.35, 145.18, 141.24, 140.92, 112.04, 77.99, 46.69, 41.59, 23.99.

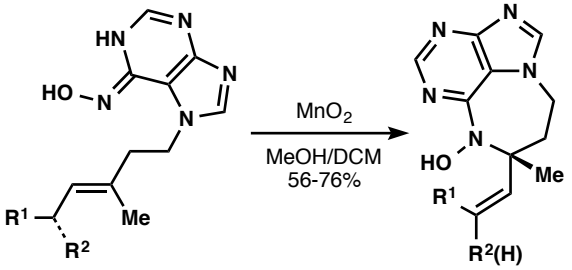
LCMS (APCI): Calculated $[M+H]^+$: 346.0 Found 346.0



40 41-48

General Procedure A: Negishi Coupling

Under nitrogen atmosphere, vinyliodide **40** (1 equiv.) was dried by azeotropic removal of water twice with toluene under high vacuum. $Pd(PPh_3)_4$ (5 mol%) was then added to the flask, and the flask was evacuated under high vacuum and backfilled with nitrogen twice. The flask was then transferred to an argon atmosphere, and the solution of organozinchalide (ca. 17 – 20 equiv., usually 0.5M) was added to the flask. [If the solvent of the organozinc was DMF, then no other solvent was added. Otherwise, an equal volume of DMF to the volume of organozinc added was introduced to the reaction.] The reaction was then degassed by bubbling argon through the solution while sonicating for 1 minute. The reaction was then stirred for typically 5 hours (unless otherwise noted) and upon verification of completion of reaction by LCMS the reaction was quenched with 10% sodium thiosulfate (sat. aq.) in $NaHCO_3$ (sat. aq.) and extracted with 10% MeOH in DCM (8x). Purification by column chromatography gave the coupling product **41-48**.



41-48 50-57

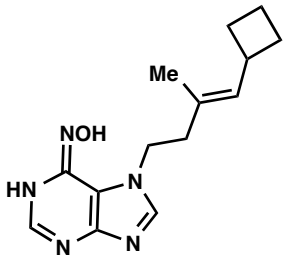
General Procedure B: Nitroso-ene cyclization for analogs

Hydroxylamine **41-48** (1 equiv.) was dissolved in DCM/MeOH (1:1, 0.05M) [unless otherwised noted] under air. MnO_2 (1 equiv.) was then added and the reaction mixture was typically stirred for 30 minutes, and upon verification of complete cyclization via LCMS), the mixture was filtered through a celite plug (MeOH), redissolved in DCM (add up to 10% MeOH if necessary for solubility) and stirred with a 0.75 mL pH 8 EDTA solution until solution becomes clear or a pale yellow. The EDTA washes were back extracted with 10%MeOH in DCM (3x). Purification by column chromatography (unless otherwise noted) gave the cyclized product **50-57**.

General Procedure C: Generation or alkylzinchalide

Zinc dust (1.5 equiv.) was added to a flame-dried flask and it was flame-dried for 30 seconds on high vacuum. Once the flask content had cooled, it was transferred to an argon atmosphere and DMF (1.0 M) was added to the flask. To this vigorously stirring solution was added I_2 (0.05 equiv.), and the resulting yellow solution, which turned clear in 1-2 minutes, was stirred for 5 minutes. The halide-substrate (1 equiv.) was then added to the solution neat, and the resulting

mixture was degassed for 1 minute by bubbling argon gas through the sonicating solution. The reaction was then heated at 65 ˚C (unless otherwise noted) for typically 12 hours. The reaction was then cooled and the excess zinc dust allowed to settle, and its conversion was verified by titration – (12.7 mg I_2 in 0.5 mL THF, titrate with organozinchalide until clear). The organozinchalide solution was then used as is [note: it is important to let the zinc dust settle and be sure that zinc is not transferred to either the titration or the reaction. If zinc dust is present in the Negishi coupling it will deoxygenate the N-OH bond.]

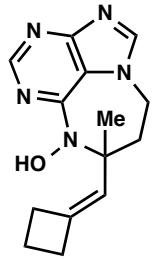


41: Following general procedure A, using a 0.34 M solution of cyclobutylzinc bromide in THF [purchased from Rieke Metals Inc.] and 1.6 mL of DMF as solvent, 17 mg of the title compound (95% yield, 0.055 mmol) was obtained from 20 mg of **40** (0.058 mmol) as a white solid upon purification via chromatography (4% MeOH & 0.4% NH_4OH in $CHCl_3$, R_f = 0.29 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.65 (s, 1H), 7.56 (s, 1H), 5.02 (d, *J* = 8.2 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.05 (h, *J* = 8.2 Hz, 1H), 2.43 (t, *J* = 6.7 Hz, 2H), 2.04 (tdd, *J* = 11.1, 5.5, 2.8 Hz, 2H), 1.82 (td, *J* = 17.8, 8.9 Hz, 2H), 1.65 – 1.74 (m, 2H), 1.63 (d, *J* = 1.1 Hz, 3H), 1.59 – 1.63 (m, 2H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 149.79, 145.03, 141.30, 141.10, 134.96, 130.17, 112.04, 46.99, 41.93, 35.49, 30.37, 19.56, 16.30.

LCMS (APCI): Calculated $[M+H]^+$: 274.2 Found 274.1

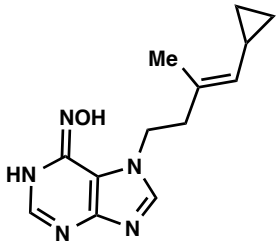


50: Following general procedure B, 7 mg of the title compound (60% yield, 0.0251 mmol) was obtained from 11 mg (0.042 mmol) of hydroxylamine **41** as a white solid upon purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.27 with 5% MeOH and 0.5% NH_4OH in $CHCl_3$).

^{1}H NMR (500 MHz, 10% Chloroform-*d* in Methanol-d_4) δ 8.37 (s, 1H), 8.21 (s, 1H), 5.17 (s, 1H), 4.39 – 4.45 (m, 1H), 4.34 (ddd, *J* = 13.4, 9.6, 3.6 Hz, 1H), 2.66 – 2.80 (m, 3H), 2.39 – 2.52 (m, 2H), 2.23 – 2.35 (m, 1H), 1.89 – 2.01 (m, 1H), 1.78 – 1.90 (m, 1H), 1.69 (s, 3H).

^{13}C NMR (151 MHz, 10% Chloroform-*d* in Methanol-d_4) δ 158.70, 152.88, 152.00, 145.00, 144.50, 122.33, 110.38, 68.25, 49.00, 44.02, 39.56, 32.48, 31.64, 27.34, 17.93.

LCMS (APCI): Calculated $[M+H]^+$: 272.1 Found 272.2

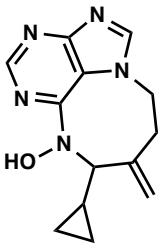


42: Following general procedure A, using a 0.50 M solution of cyclopropyl bromide in THF [purchased from Sigma-Alrich] and 1.0 mL of DMF as solvent, 15 mg of the title compound (99% yield, 0.058 mmol) was obtained from 20 mg of **40** (0.058 mmol) as a white solid upon purification via chromatography (4% MeOH & 0.4% NH_4OH in $CHCl_3$, R_f = 0.30 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.69 (s, 1H), 7.56 (s, 1H), 4.32 (q, *J* = 7.5, 6.8 Hz, 3H), 2.43 (t, *J* = 6.8 Hz, 2H), 1.79 (s, 3H), 1.35 – 1.42 (m, 1H), 056 – 0.64 (m, 2H), 0.06 – 0.13 (m, 2H).

^{13}C NMR (151 MHz, Methanol-d_4) δ149.90, 145.20, 141.50, 141.14, 133.30, 130.13, 112.08, 49.00, 47.16, 42.03, 16.41, 10.72, 6.83.

LCMS (APCI): Calculated $[M+H]^+$: 260.1 Found 260.1

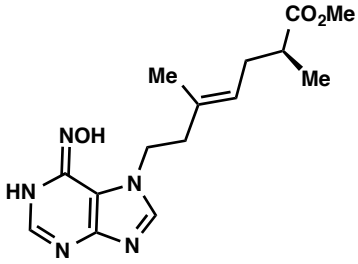


51: Following general procedure B, 9 mg of the title compound (59% yield, 0.0251 mmol) was obtained as the exclusive product from 15 mg (0.058 mmol) of hydroxylamine **42** as a white solid upon purification via column chromatography (4% MeOH & 0.4% NH_4OH in $CHCl_3$, R_f = 0.22 with 8% MeOH and 0.8% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 8.59 (s, 1H), 8.35 (s, 1H), 4.81 (s, 1H), 4.70 – 4.77 (m, 1H), 4.61 (s, 1H), 4.56 (dd, *J* = 14.1, 5.6 Hz, 1H), 3.15 (dd, *J* = 19.7, 12.6 Hz, 2H), 2.70 (dt, *J* = 19.7, 6.1 Hz, 1H), 1.39 – 1.45 (m, 1H), 0.93 – 1.01 (m, 1H), 0.78 – 0.85 (m, 1H), 0.60 (dt, *J* = 14.0, 9.1 Hz, 1H), 0.09 (dt, *J* = 14.6, 4.7 Hz, 1H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 159.55, 152.88, 146.89, 144.00, 124.09, 117.97, 111.40, 81.97, 49.00, 45.90, 36.69, 14.74, 8.69, 1.43.

LCMS (APCI): Calculated $[M+H]^+$: 258.1 Found 258.1

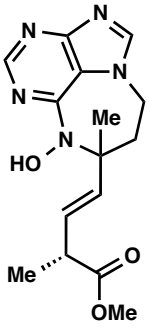


43: Following general procedure A, using a 0.41M solution of (*S*)-(3-methoxy-2-methyl-3-oxopropyl)zinc(II) bromide in THF [purchased from Rieke Metals Inc.] and 1.0 mL of DMF as solvent, 18 mg of the title compound (95% yield, 0.055 mmol) was obtained from 20 mg of **40** (0.058 mmol) as a white solid upon purification via chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.24 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, 10% Chloroform-*d* in Methanol-d_4) δ 7.64 (s, 1H), 7.55 (s, 1H), 4.97 (t, *J* = 7.1 Hz, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.62 (s, 3H), 2.51 (t, *J* = 6.8 Hz, 2H), 2.35 (h, *J* = 7.0 Hz, 1H), 2.24 (dt, *J* = 14.1, 7.0 Hz, 1H), 2.05 (dt, *J* = 14.4, 7.3 Hz, 1H), 1.68 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, 10% Chloroform-*d* in Methanol-d_4) δ 178.25, 149.76, 144.93, 140.95, 133.99, 125.64, 111.89, 52.11, 49.00, 46.94, 41.98, 40.50, 32.77, 16.83, 16.17.

LCMS (APCI): Calculated $[M+H]^+$: 320.2 Found 320.1

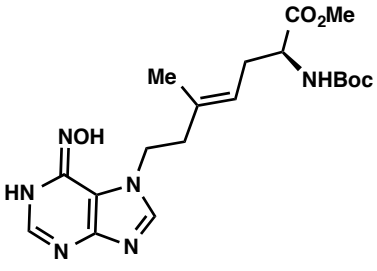


52: Following general procedure B except with the use of 4:1 H_2O:EtOH as solvent, 12 mg of the title compound (70% yield, 0.0381 mmol) as a 1:1 diastereomer was obtained from 17 mg (0.058 mmol) of hydroxylamine **43** as a white solid upon purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.31 with 10% MeOH and 1% NH_4OH in $CHCl_3$). The diastereomeric ratio was determined by the integration of the methyl ester peaks in the ^{1}H NMR.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 7.99 (s, 1H), 5.56 – 5.74 (m, 2H), 4.29 (b. s, 2H), 3.58 (2 s, 1:1, 3H), 3.12 – 3.18 (m, 1H), 2.42 – 2.55 (m, 2H), 1.78 (s, 3H), 1.21 – 1.25 (2 d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.71, 174.55, 159.06, 159.00, 151.83, 150.16, 150.14, 143.67, 143.56, 131.67, 131.60, 131.34, 131.25, 109.75, 109.72, 66.10, 52.15, 42.96, 42.94, 42.40, 42.30, 39.37, 39.34, 25.96, 25.73, 17.34, 17.16.

LCMS (APCI): Calculated $[M+H]^+$: 318.2 Found 318.1



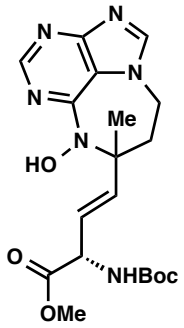
44: Following general procedure A, using a 0.35 M solution of (*S*)-(2((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl) zinc(II) bromide in DMF [generated according to Danner *et al.*[10]], 16 mg of the title compound (66% yield, 0.039 mmol) was obtained from 20 mg of **40** (0.058 mmol) as a white solid upon purification via chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.31 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.72 (s, 1H), 7.56 (s, 1H), 5.06 (s, 1H), 4.33 (s, 2H), 4.08 (s, 1H), 3.68 (s, 3H), 2.51 (t, *J* = 6.1 Hz, 2H), 2.44 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.33 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.69 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 174.19, 157.83, 150.07, 145.23, 141.34, 141.06, 136.06, 123.23, 112.06, 80.66, 55.00, 52.65, 49.00, 47.29, 42.16, 31.36, 28.70, 16.30.

LCMS (APCI): Calculated $[M+H]^+$: 421.2 Found 421.2

$[\alpha]_D^{25}$ = +7.9 (1.9 mg/ mL MeOH)



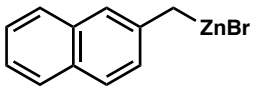
53: Following general procedure B except with the use of 4:1 H_2O:EtOH as solvent, 6 mg of the title compound (76% yield, 0.014 mmol) as a 2.2:1 diastereomer was obtained from 8 mg (0.019 mmol) of hydroxylamine **44** as a white solid. The product proved to be unstable on silica or alumina, but it turned out no purification was needed – the compound was mostly pure after the EDTA washes. The diastereomeric ratio was determined by the integration of the methyl ester peaks in the ^{1}H NMR – the peaks provided optimal separation with isopropanol-d_8.

R_f = 0.30 with 10% MeOH and 1% NH_4OH in $CHCl_3$

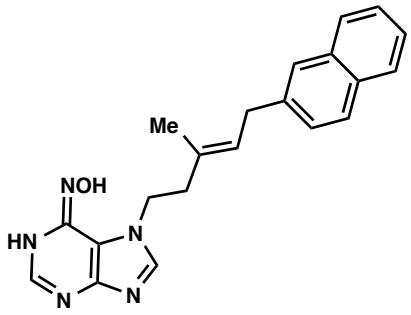
^{1}H NMR (600 MHz, isopropanol-d_8) δ 8.32 (s, 1H), 8.09 (m, 1H), 5.80 – 5.84 (m, 1H), 5.45 – 5.52 (m, 1 H), 4.58 (2 d, J = 5.9 Hz, 1H), 4.15 – 4.35 (m, 3 H), 3.45 (2 s, 2.2:1, 3 H), 2.26 – 2.48 (m, 2H), 1.62 (s, 3H), 1.25 (s, 9H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 172.59, 172.45, 159.39, 157.57, 157.43, 153.13, 145.80, 135.43, 135.36, 127.16, 126.98, 115.06, 111.07, 80.75, 68.54, 68.50, 56.59, 52.93, 44.11, 39.83, 28.61, 26.52.

LCMS (APCI): Calculated $[M+H]^+$: 419.2 Found 419.2



SI-18: Following general procedure C, a 0.55 M solution of the title compound in DMF was generated from 2.66 g of 2-(bromomethyl)naphthalene (12 mmol).

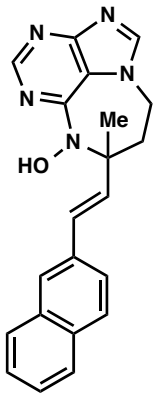


45: Following general procedure A, using a 0.55 M solution of **SI-18** in DMF, 23 mg of the title compound (77% yield, 0.066 mmol) was obtained from 30 mg of **40** as a white solid (0.086 mmol) upon purification via chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.28 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (600 MHz, Methanol-d_4) δ 7.74 – 7.80 (m, 3H), 7.71 (d, J = 8.4 Hz, 1H), 7.50 (s, 1H), 7.35 – 7.45 (m, 3H), 7.11 (dd, J = 8.3, 1.6 Hz, 1H), 5.28 (t, J = 7.0 Hz, 1H), 4.41 (t, J = 6.8 Hz, 2H), 3.44 (d, J = 7.3 Hz, 2H), 2.60 (t, J = 6.7 Hz, 2H), 1.85 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 149.92, 145.12, 141.36, 141.10, 139.83, 135.14, 133.49, 133.30, 128.95, 128.54, 128.51, 128.09, 127.76, 126.94, 126.82, 126.10, 112.19, 46.96, 42.16, 35.23, 16.23.

LCMS (APCI): Calculated $[M+H]^+$: 360.2 Found 360.2



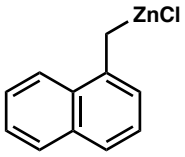
54: Following general procedure B, 17 mg of the title compound (71% yield, 0.047 mmol) was obtained from 24 mg (0.066 mmol) of hydroxylamine **45** as a white solid. The product proved to be unstable on silica or alumina, but it turned out no purification was needed – the compound was mostly pure after the EDTA washes.

R_f = 0.28 with 10% MeOH and 1% NH_4OH in $CHCl_3$

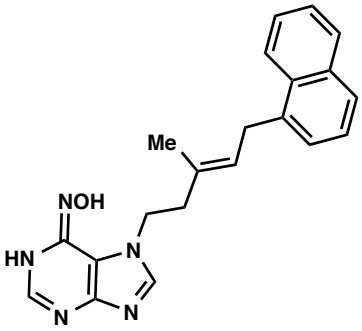
^1H NMR (600 MHz, Methanol-d_4) δ 8.47 (s, 1H), 8.24 (s, 1H), 7.76 (t, J = 7.2 Hz, 3H), 7.68 (s, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.39 – 7.45 (m, 2H), 6.60 (dd, J = 16.1 Hz, 112.2 Hz, 2H), 4.48 (dd, J = 13.0, 5.1 Hz, 1H), 4.36 (t, J = 12.0 Hz, 1H), 2.69 (dd, J = 15.5, 5.7 Hz, 1H), 2.53 – 2.62 (m, 1H), 1.86 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 153.31, 153.09, 135.07, 135.02, 134.56, 132.02, 131.76, 129.25, 129.02, 128.59, 127.64, 127.33, 127.05, 124.44, 111.38, 69.24, 53.69, 49.00, 44.34, 40.15, 26.42.

LCMS (APCI): Calculated $[M+H]^+$: 358.2 Found 358.1



SI-19: Following general procedure C, a 0.63 M solution of the title compound in DMF was generated from 2.23 g of 1-(chloromethyl)naphthalene (1.80 mL, 12 mmol).

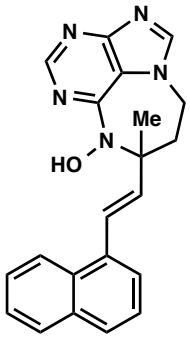


46: Following general procedure A, using a 0.63 M solution of **SI-19** in DMF, 12 mg of the title compound (79% yield, 0.034 mmol) was obtained from 15 mg of **40** (0.043 mmol) as a white solid upon purification via chromatography (6% MeOH & 0.6% NH_4OH in $CHCl_3$, R_f = 0.34 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^1H NMR (500 MHz, Methanol-d_4) δ 7.82 (dd, J = 17.0, 8.2 Hz, 2H), 7.71 (s, 1H), 7.67 (s, 1H), 7.54 (s, 1H), 7.39 – 7.49 (m, 2H), 7.30 – 7.35 (m, 1H), 7.03 – 7.08 (m, 1H), 5.23 (t, J = 6.4 Hz, 1H), 4.26 – 4.42 (m, 2H), 3.68 (d, J = 6.8 Hz, 1H), 2.56 (t, J = 6.4 Hz, 2H), 1.87 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 149.92, 145.15, 141.34, 141.10, 138.10, 135.32, 133.19, 133.10, 129.60, 127.72, 127.64, 126.85, 126.61, 126.51, 126.46, 124.71, 112.14, 47.00, 42.07, 32.47, 16.24.

LCMS (APCI): Calculated $[M+H]^+$: 360.2 Found 360.2

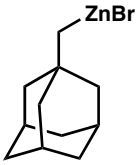


55: Following general procedure B, 7 mg of the title compound (73% yield, 0.025 mmol) was obtained from 12 mg (0.034 mmol) of hydroxylamine **46** as a white solid upon purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.35 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

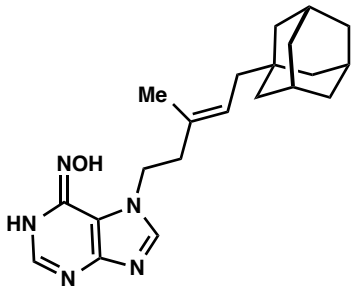
^{1}H NMR (500 MHz, Methanol-d_4) δ 8.50 (s, 1H), 8.26 (s, 1H), 7.89 (s, 1H), 7.77 (dd, J = 25.2, 8.1 Hz, 2H), 7.61 (dd, J = 25.5, 7.6 Hz, 2H), 7.32 – 7.48 (m, 3H), 7.18 (d, J = 15.8 Hz, 1H), 6.38 (d, J = 15.7 Hz, 1H), 4.50 (dd, J = 12.9, 3.9 Hz, 1H), 4.37 (t, J = 12.4 Hz, 1H), 2.73 (dd, J = 15.2, 4.7 Hz, 1H), 2.55 – 2.68 (m, 1H), 1.90 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 159.19, 153.52, 153.31, 145.82, 135.20, 135.02, 134.52, 132.41, 129.51, 129.20, 127.12, 126.83, 126.61, 124.76, 124.27, 111.17, 79.47, 69.42, 44.41, 40.11, 26.75.

LCMS (APCI): Calculated $[M+H]^+$: 358.2 Found 358.1



SI-20: Following general procedure C, a 0.27 M solution of the title compound in DMF was generated from 2.78 g of (3*r*,5*r*,7*r*)-1-(bromomethyl)adamantane (12 mmol) with heating to 80˚C for 12 hours.

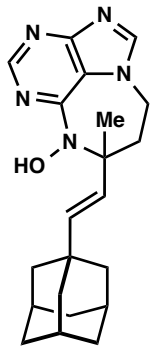


47: Following general procedure A, using a 0.27 M solution of **SI-20** in DMF, 13 mg of the title compound (60% yield, 0.035 mmol) was obtained from 20 mg of **40** (0.058 mmol) as a white solid upon purification via chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.34 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.75 (s, 1H), 7.54 (s, 1H), 5.05 (t, J = 7.4 Hz, 1H), 4.39 (t, J = 6.5 Hz, 2H), 2.57 (t, J = 6.5 Hz, 2H), 1.70 – 1.89 (m, 3H), 1.53 – 1.72 (m, 11H), 1.29 (d, J = 2.8 Hz, 6H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 149.85, 145.05, 141.33, 141.18, 133.00, 125.24, 112.28, 46.70, 43.63, 43.37, 42.32, 38.17, 34.51, 30.15, 16.05.

LCMS (APCI): Calculated $[M+H]^+$: 368.2 Found 368.2

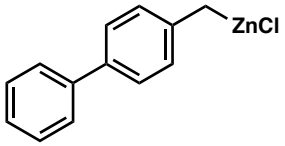


56: Following general procedure B, 8 mg of the title compound (70% yield, 0.022 mmol) was obtained from 12 mg (0.031 mmol) of hydroxylamine **47** as a purple solid upon purification via column chromatography (4% MeOH & 0.4% NH_4OH in $CHCl_3$, R_f = 0.35 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

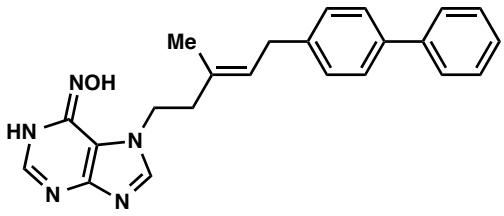
^{1}H NMR (600 MHz, Methanol-d_4) δ 8.38 (s, 1H), 8.22 (s, 1H), 5.43 (d, J = 16.0 Hz, 1H), 5.34 (d, J = 16.0 Hz, 1H), 4.41 (ddd, J = 13.2, 5.1, 2.2 Hz, 1H), 4.22 – 4.32 (m, 1H), 2.39 – 2.58 (m, 2H), 1.91 (m, 3H), 1.71 (m, 6H), 1.63 (d, J = 11.7 Hz, 3H), 1.49 (s, 6H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 158.39, 153.23, 152.52, 145.10, 143.90, 126.36, 110.92, 68.83, 44.19, 43.32, 40.17, 37.80, 35.84, 29.85, 27.22.

LCMS (APCI): Calculated $[M+H]^+$: 365.2 Found 365.2



SI-21: Following general procedure C, a 0.50 M solution of the title compound in DMF was generated from 2.43 g of 4-(chloromethyl)-1,1'-biphenyl (12 mmol).

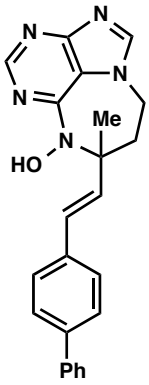


48: Following general procedure A, using a 0.63 M solution of **SI-21** in DMF, 15 mg of the title compound (87% yield, 0.038 mmol) was obtained from 15 mg of **40** (0.043 mmol) as a white solid upon purification via chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.28 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^{1}H NMR (500 MHz, 1:1 Chloroform-d: Methanol-d_4) δ 7.54 (s, 1H), 7.49 (s, 1H), 7.45 (d, J = 7.9 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 5.25 (t, J = 7.2 Hz, 1H), 4.33 (t, J = 7.0 Hz, 2H), 3.30 (s, 1H), 2.54 (t, J = 6.8 Hz, 2H), 1.78 (s, 3H).

^{13}C NMR (151 MHz, 1:1 Chloroform-d: Methanol-d_4) δ 149.39, 144.16, 140.72, 140.48, 140.09, 139.26, 132.10, 129.09, 129.00, 127.46, 127.41, 127.28, 127.22, 111.41, 46.67, 41.46, 34.16, 16.19.

LCMS (APCI): Calculated $[M+H]^+$: 386.2 Found 386.1



57: Following general procedure B, 8 mg of the title compound (56% yield, 0.021 mmol) was obtained from 15 mg (0.038 mmol) of hydroxylamine **48** as a white solid upon purification via column chromatography (5% MeOH & 0.5% NH_4OH in $CHCl_3$, R_f = 0.28 with 10% MeOH and 1% NH_4OH in $CHCl_3$).

^1H NMR (500 MHz, Methanol-d_4) δ 8.46 (s, 1H), 8.25 (s, 1H), 7.56 (dd, *J* = 18.3, 6.2 Hz, 4H), 7.36 – 7.47 (m, 4H), 7.25 – 7.35 (m, 1H), 6.41 – 6.59 (m, 2H), 4.44 – 4.52 (m, 1H), 4.30 – 4.40 (m, 1H), 2.68 (dd, *J* = 15.9, 4.3 Hz, 1H), 2.56 (dd, *J* = 15.4, 10.9 Hz, 1H), 1.84 (s, 3H).

^{13}C NMR (151 MHz, Methanol-d_4) δ 159.13, 153.27, 153.02, 145.68, 141.86, 141.79, 136.68, 131.64, 131.27, 129.86, 128.41, 128.11, 128.05, 127.74, 110.95, 69.18, 44.28, 40.14, 26.37.

LCMS (APCI): Calculated $[M+H]^+$: 384.2 Found 384.2

Biological experimental procedure and data

Procedure for cell viability assays using CellTiter-Glo®

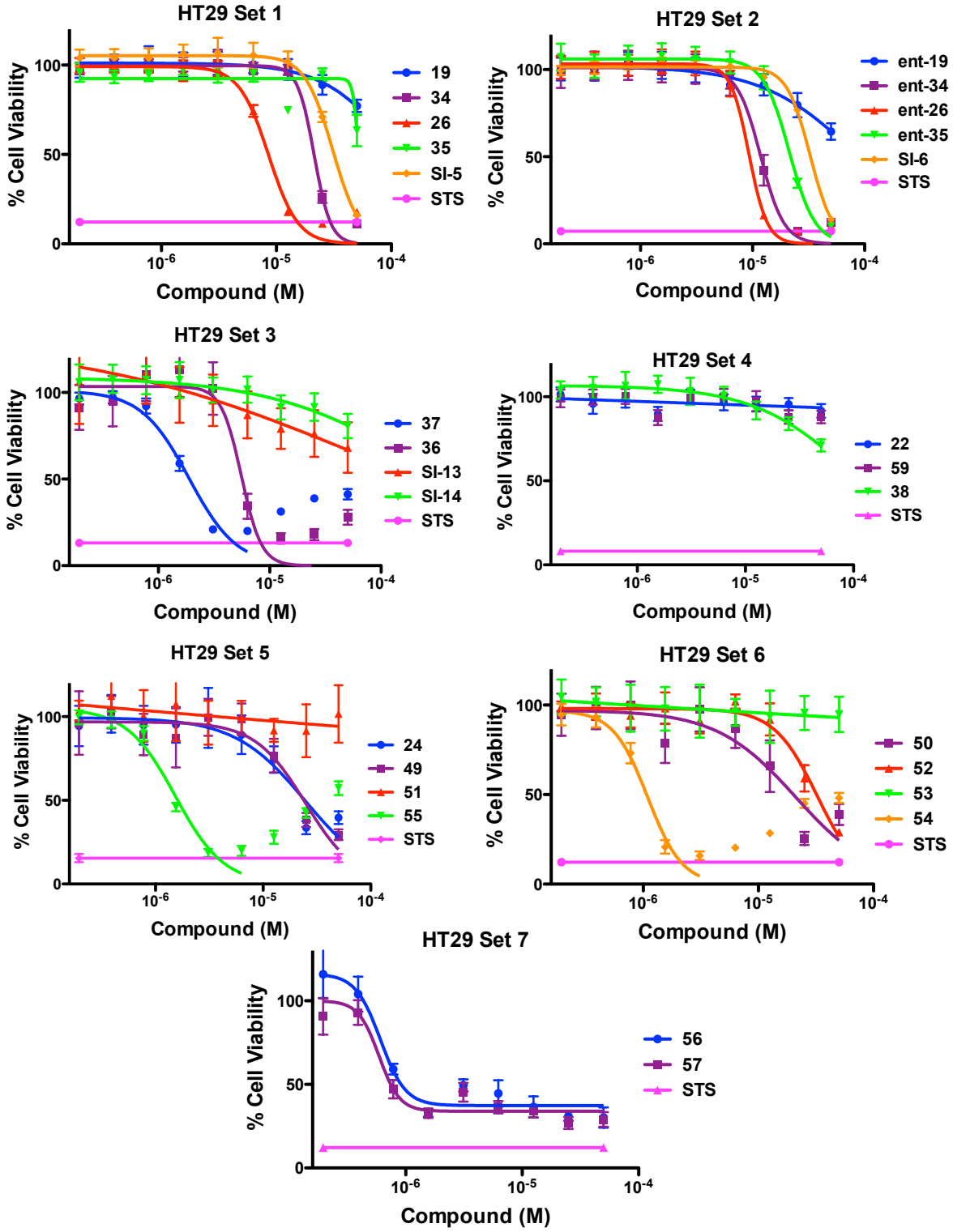
HT29, Jurkat, HeLa, HL60, HEK293, MCF7, MDA-MB-231 cells were maintained in the optimal media as suggested by ATCC. 14 hours prior to addition of asmarine derivatives, cells were plated into sterile 96-well tissue culture-treated plates (50 µL total volume) at a density of 5000 (HT29, HeLa, HEK293, MCF-7, MDA-MB-231) or 7500 (Jurkat, HL60) cells/well.

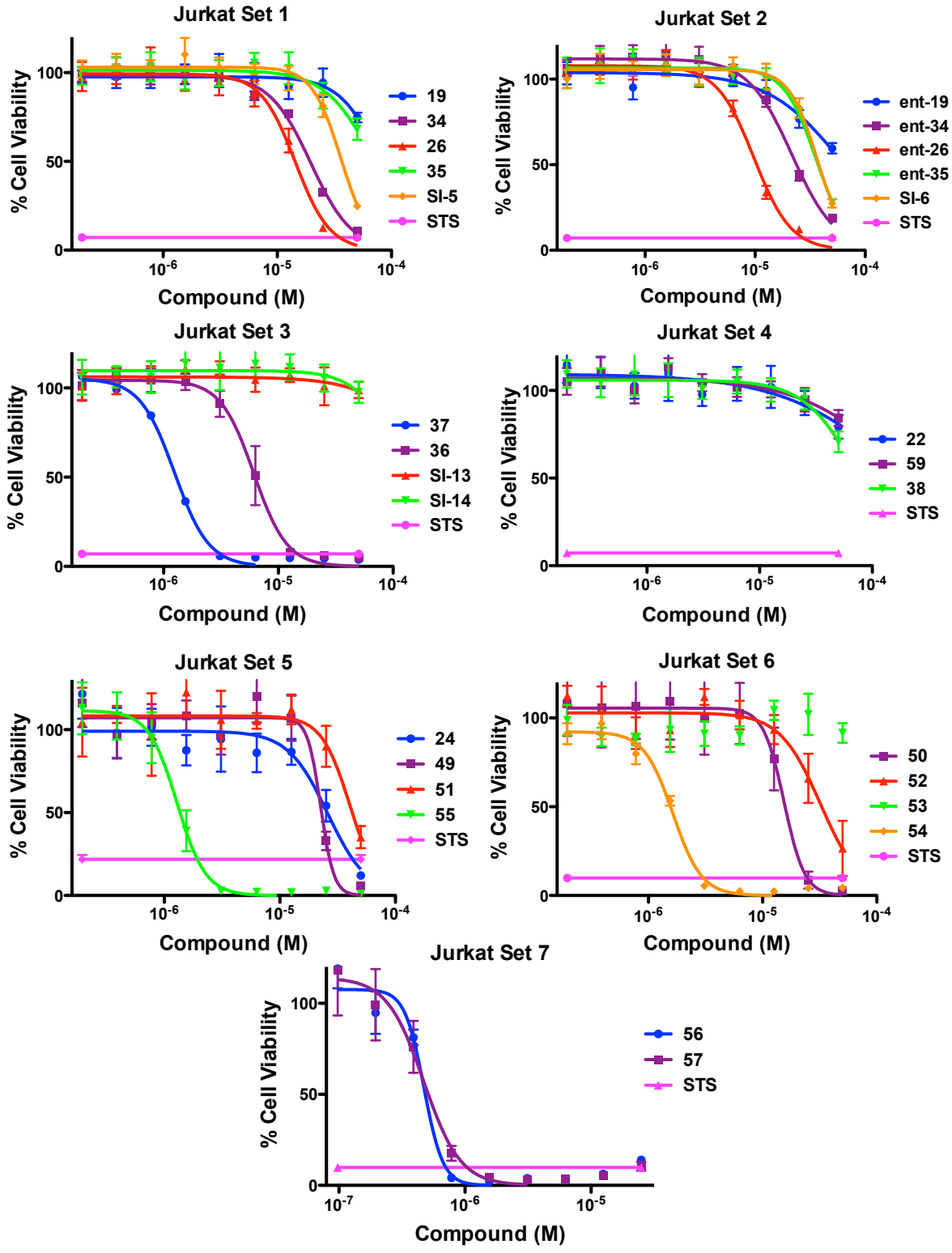
Cell viability EC_{50} experiments were performed in a final volume of 50 µL with 0.05 – 50 µM asmarine compounds (0.5% DMSO). 1 µM staurosporine (Trevigen) and 0.5% DMSO were used as the positive and negative controls, respectively. The cells were incubated at 37 °C in the presence of 5% CO_2 and assessed for viability by the addition of 50 µL of CellTiter-Glo® (Promega) at 24, 48, and 72 h (HT29) or after a 48 h incubation (Jurkat, HeLa, HL60, HEK293, MCF7, MDA-MB-231). After a 10-min incubation at room temperature, luminescence was measured on a PerkinElmer EnVision plate reader. All assay data was collected in triplicate with EC_{50} values determined using GraphPad Prism.

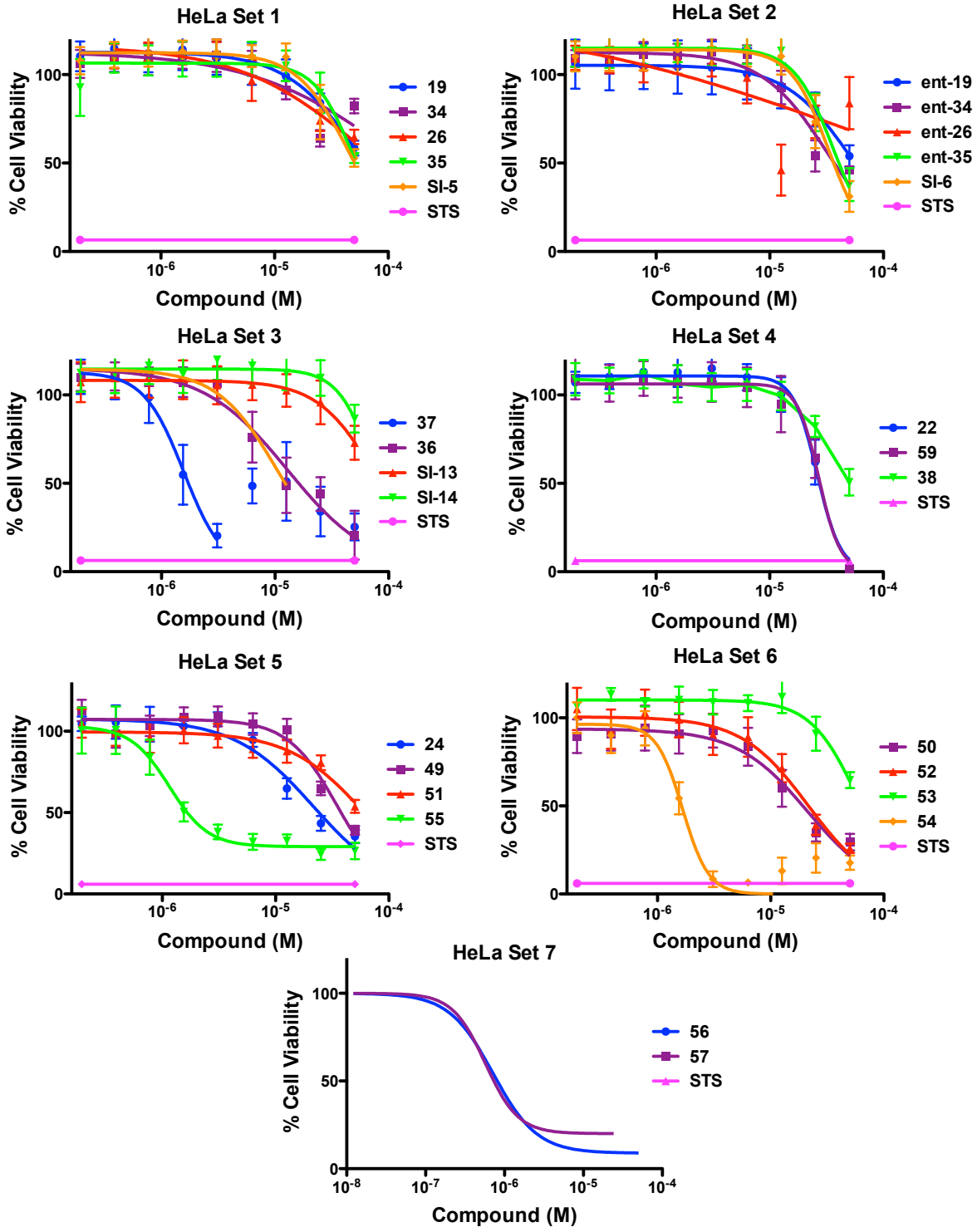
Discussion on cell death responses

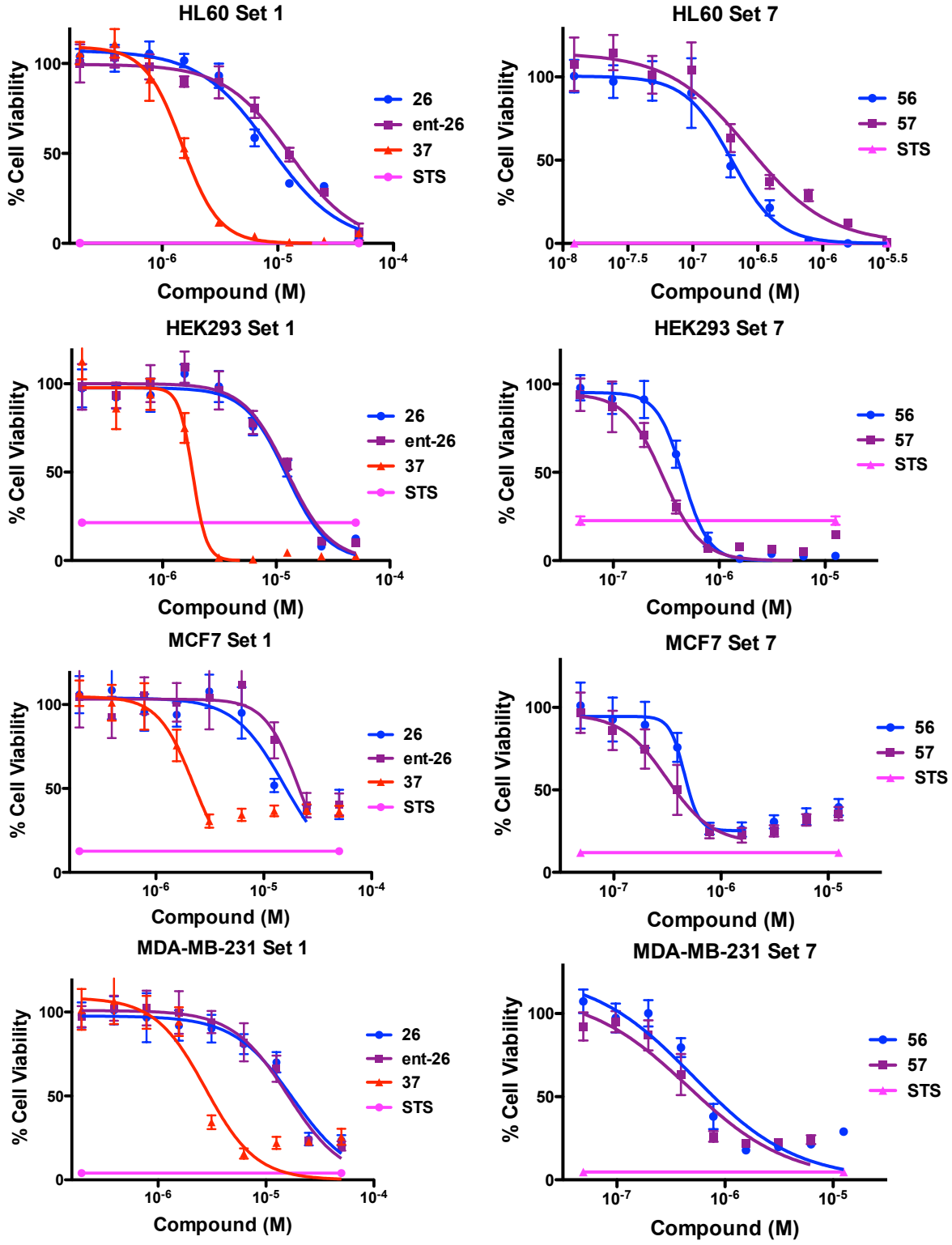
Asmarine analogs that promote cytotoxicity within the high nM to low mM (i.e., compounds 44, 45, 63, 64, and 65) across the cell line panel demonstrate a unique dose-response as an increase in compound concentration promotes a decrease in cell death. This behavior is likely due to the limited solubility of these compounds within the cell media, as precipitation and/or aggregation at higher concentrations will significantly reduce the percentage of monomeric active compound.[11] Importantly, the likelihood that the asmarine analogs promote cell death by a non-specific mechanism, such as membrane disruption via colloidal aggregates is unlikely.[11,12] Firstly, while many of the highly cytotoxic compounds have predicted logP values within the range of known small molecule aggregators (64, logP 3.8; 65, logP 4.5), several inactive analogs also have high logP (e.g., 46, logP 4.3 - calculated with Shoichet lab's http://advisor.bkslab.org/search/). Secondly, the extensive incubation time of 48 h required to induce cell death negates the possibility of promiscuous cytotoxicity via membrane disruption as observed for the rapid induction of cell death by mild detergents.[13] We are actively pursuing the biological targets of our highly cytotoxic asmarine analogs.

Cell death assays for compounds reported in “Table of cytotoxicity data of the asmarines” above




Jurkat Set 1
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
19
34
26
35
SI-5
STS
Jurkat Set 2
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
ent-19
ent-34
ent-26
ent-35
SI-6
STS
Jurkat Set 3
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
37
36
SI-13
SI-14
STS
Jurkat Set 4
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
22
59
38
STS
Jurkat Set 5
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
24
49
51
55
STS
Jurkat Set 6
% Cell Viability
100
50
0
10-6
10-5
10-4
Compound (M)
50
52
53
54
STS
Jurkat Set 7
% Cell Viability
100
50
0
10-7
10-6
10-5
Compound (M)
56
57
STS


HeLa Set 1
% Cell Viability
Compound (M)
19
34
26
35
SI-5
STS
HeLa Set 2
ent-19
ent-34
ent-26
ent-35
SI-6
STS
HeLa Set 3
37
36
SI-13
SI-14
STS
HeLa Set 4
22
59
38
STS
HeLa Set 5
24
49
51
55
STS
HeLa Set 6
50
52
53
54
STS
HeLa Set 7
56
57
STS


HL60 Set 1
% Cell Viability
Compound (M)
26
ent-26
37
STS
HL60 Set 7
56
57
STS
HEK293 Set 1
HEK293 Set 7
MCF7 Set 1
MCF7 Set 7
MDA-MB-231 Set 1
MDA-MB-231 Set 7

References

[1] A. Giner-Sorolla, A. Bendich, *J. Am. Chem. Soc.,* **1958,** *80(15)*, 3932-3937.

[2] C. Cook, X. Guinchard, F. Liron, E. Roulland, *Org. Lett.* **2010**, *12(4),* 744-747.

[3] J. A. Montgomery, K. Hewson, *J. Org. Chem.* **1961,** *26(11)*, 4469-4472.

[4] D. Pappo, S. Shimony, Y. Kashman, *J. Org. Chem.* **2005**, *70(1)*, 199-206

[5] T. Ling, J. Xu, R. Smith, A. Ali, C. L. Cantrell, E. A. Theodorakis, *Tetrahedron*, **2011,** *67 (17),* 3023 – 3029.

[6] D. A. Lanfranchi, N. Baldovini, G. Hanquet, *Synthesis* **2008**, *23,* 3775-3778.

[7] H. Hagiwara, H. Uda, *J. Org. Chem.* **1988,** *53,* 2306-2311.

[8] J. A. Bergman, K. Hahne, J. Song, C. A. Hrycyna, R. A. Gibbs, *Medicinal Chemistry Letters,* **2012,** *3(1),* 15-19.

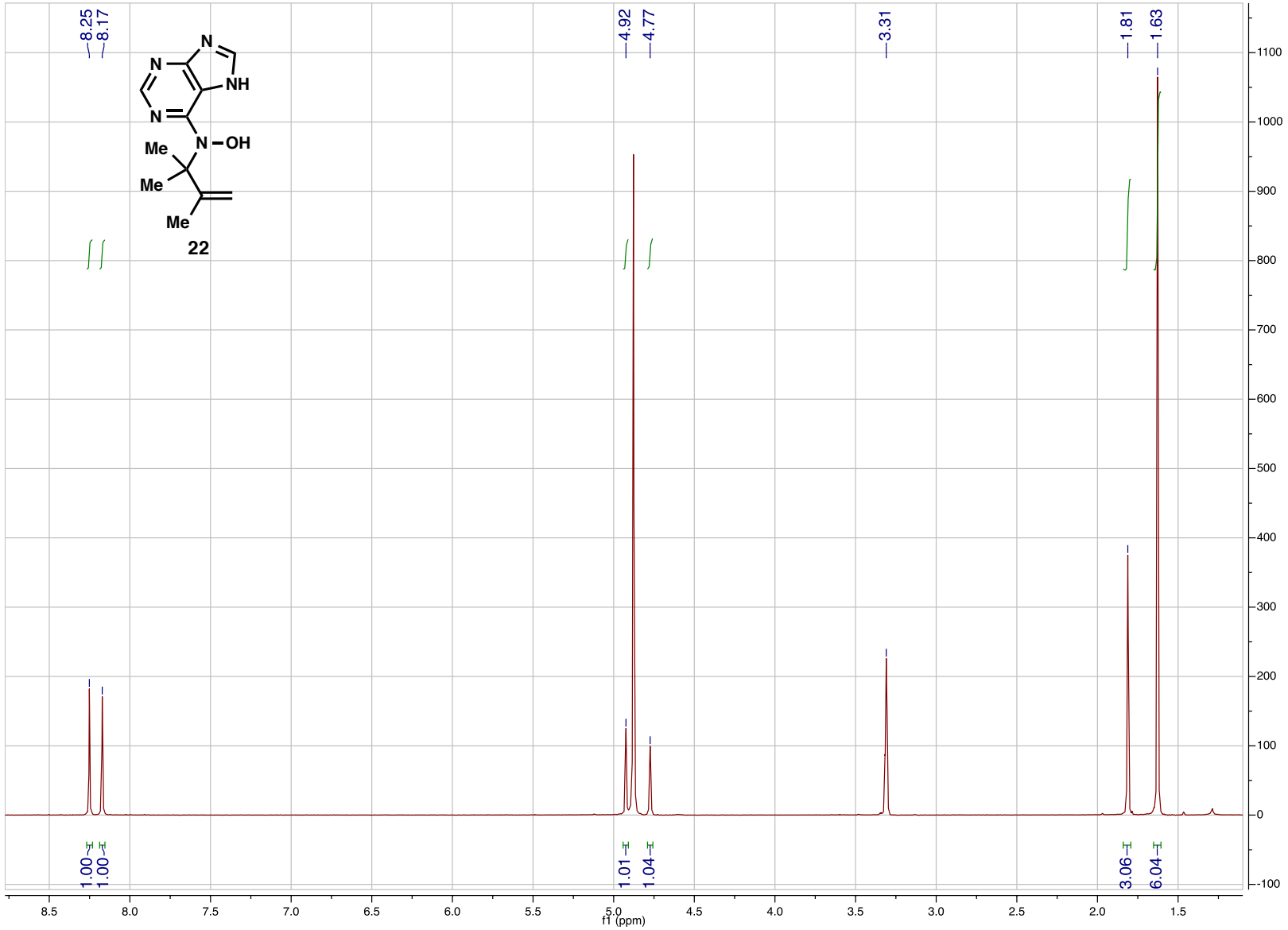
[9] K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley, R. A. Shenvi. *J. Am. Chem. Soc.* **2014,** *136(4)*, 1300 – 1303.

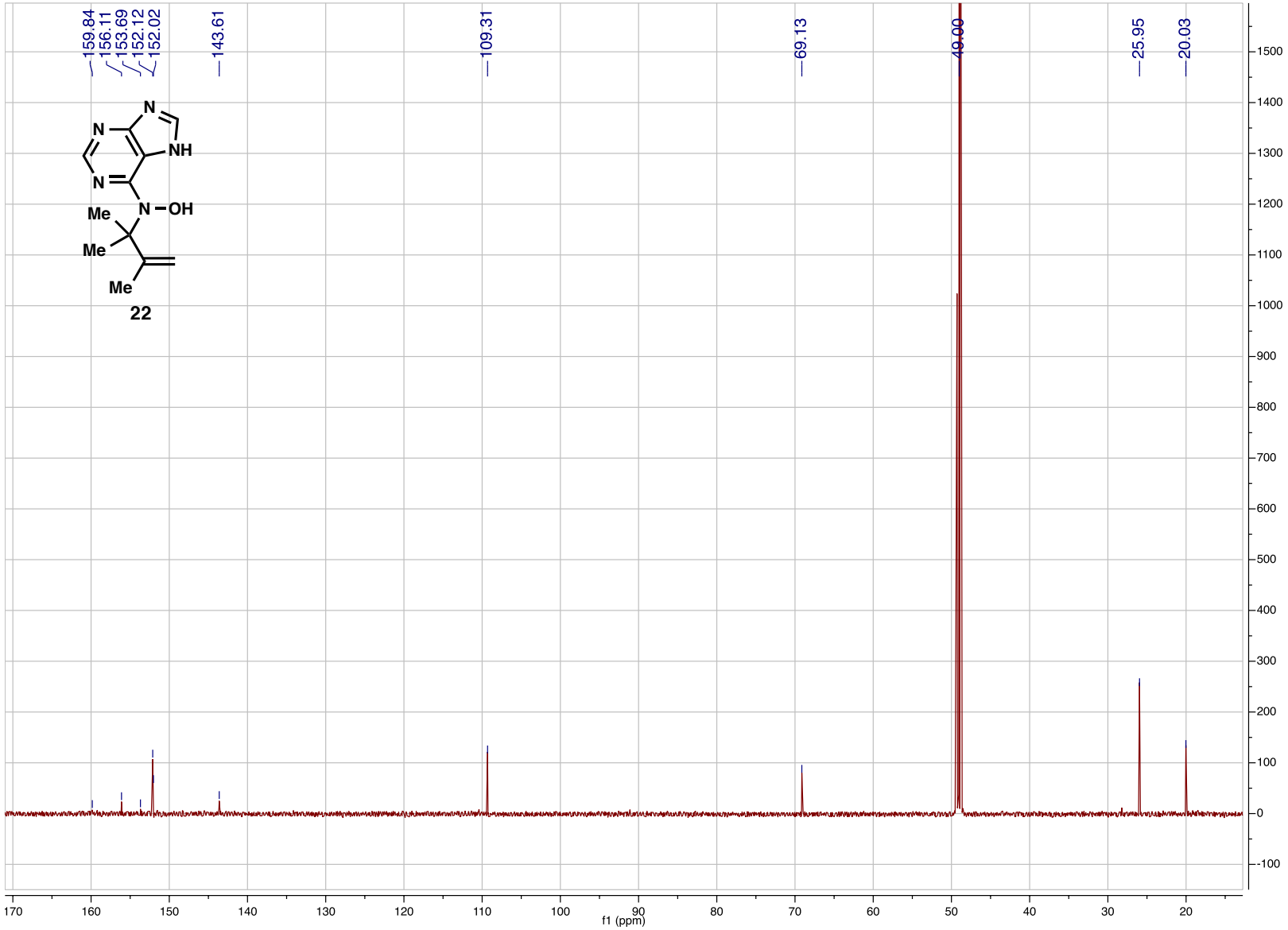
[10] P. Danner, M. Morkunas, M. E. Maier, *Org. lett.* **2013,** *15(10)*, 2474- 2477.

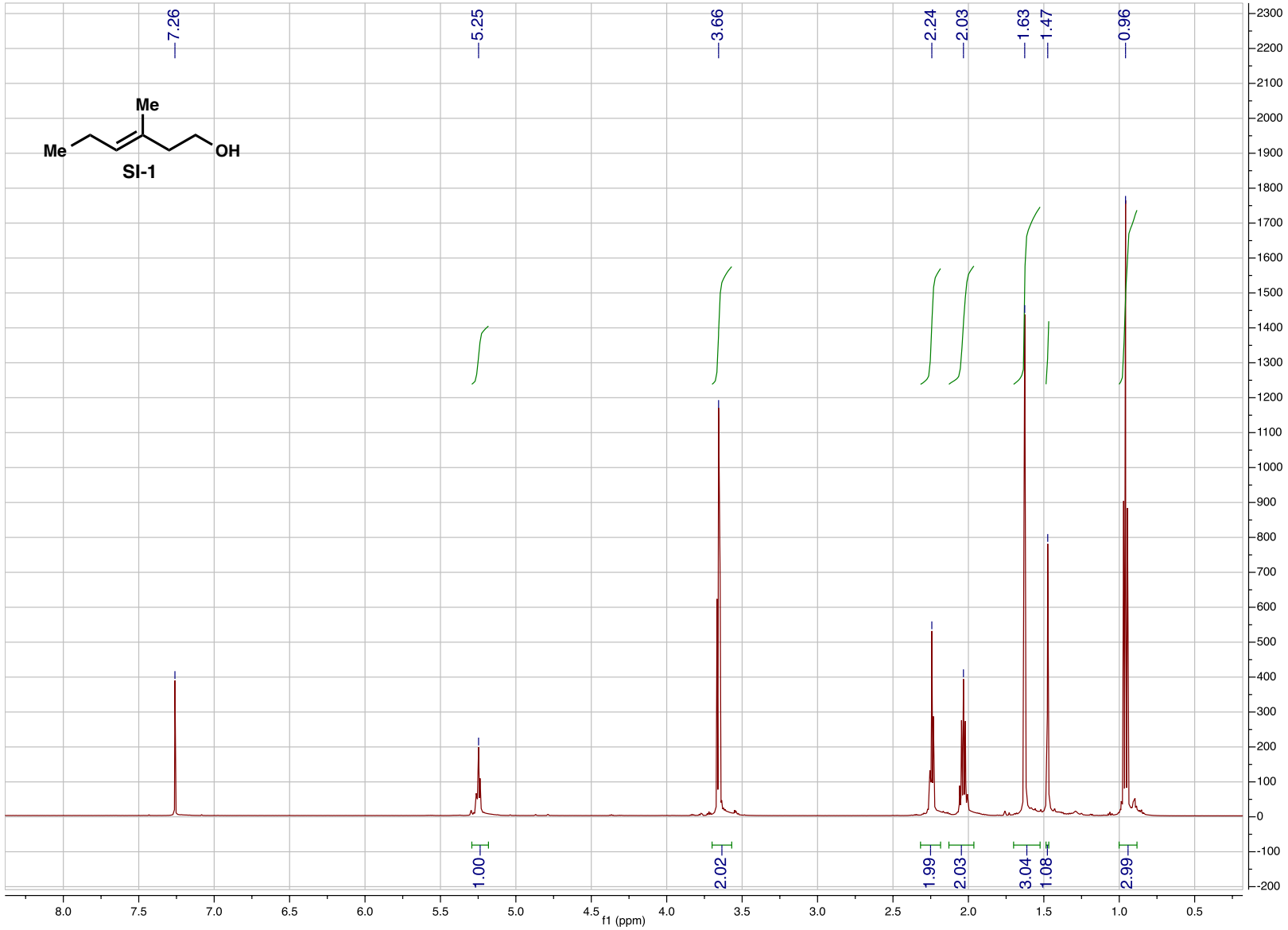
[11] B. K. Shoichet, *Drug Discovery Today*, **2006,** *11*(13-14), 607–615.

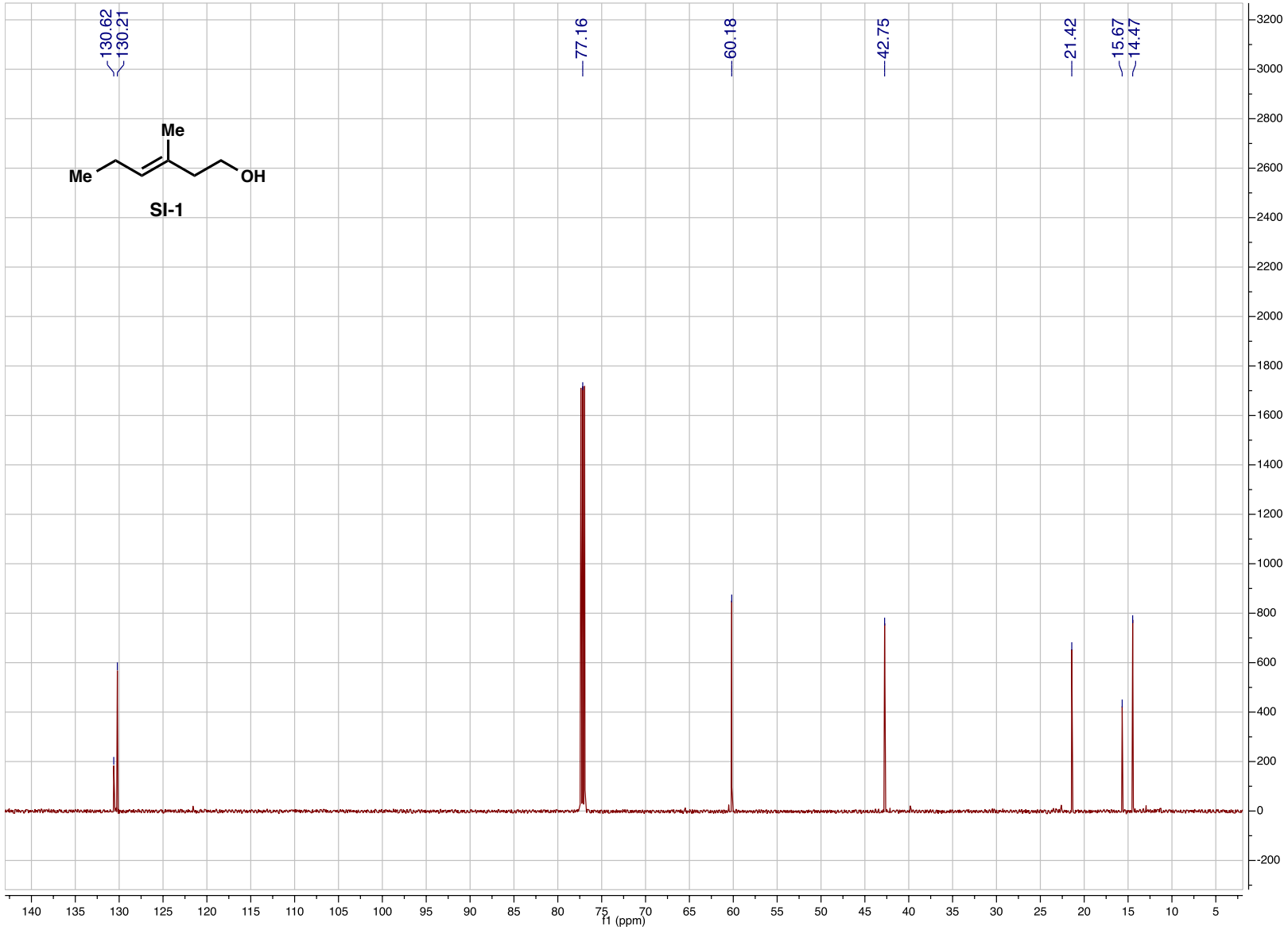
[12] R. F. Bruns, I. A. Watson, *Journal of Medicinal Chemistry*, **2012,** *55*(22), 9763–9772.

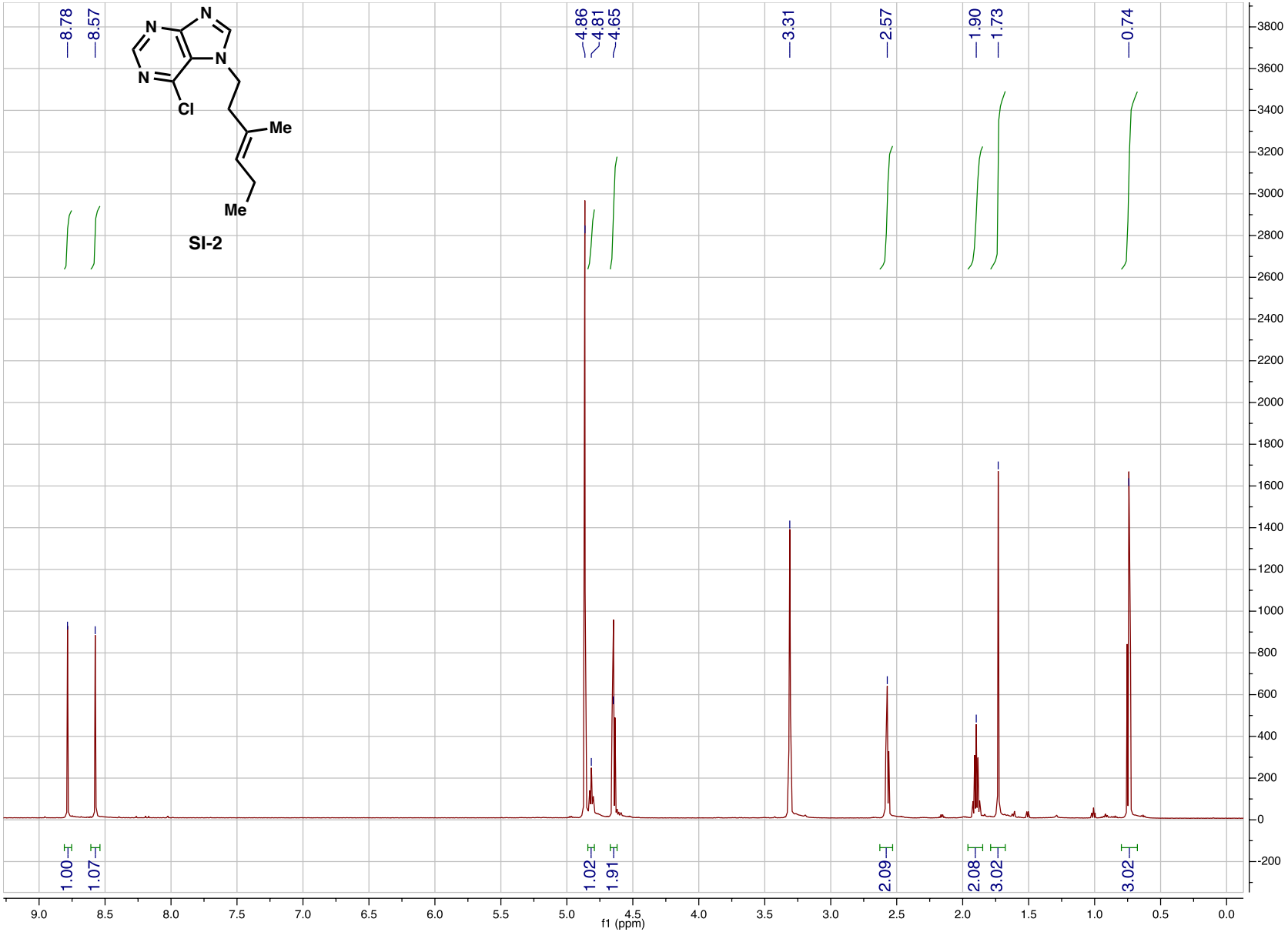
[13] W. Strupp, G. Weidinger, C. Scheller, R. Ehret, H. Ohnimus, H. Girschick, P. Tas, E. Flory, M. Heinkelein, C. Jassoy, *J. Membrane Biol.*, **2000,** *175,* 181–189.

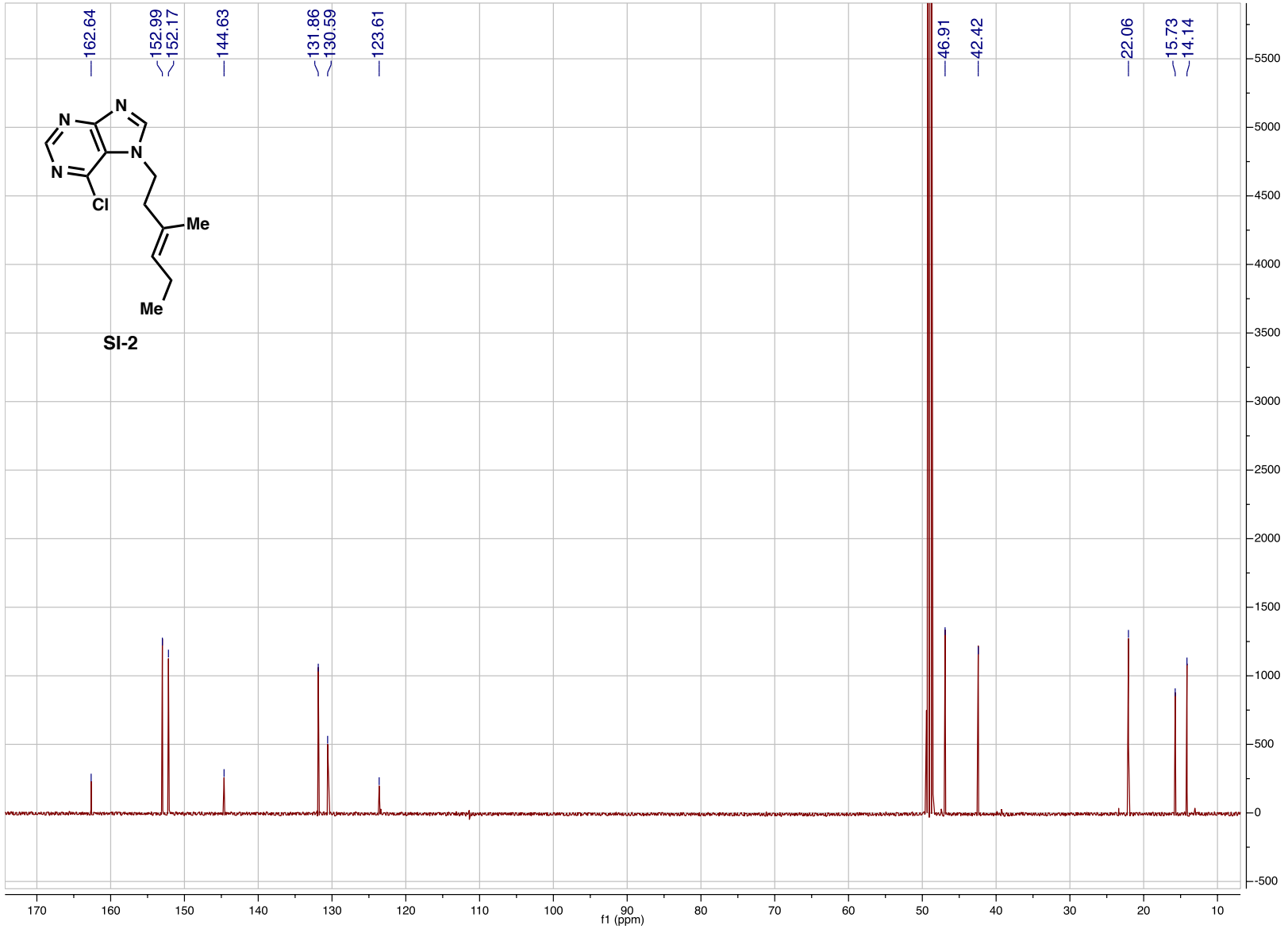

8.25
8.17
4.92
4.77
3.31
1.81
1.63
N
N
NH
N
N–OH
Me
Me
Me
22
1.00
1.00
1.01
1.04
3.06
6.04
f1 (ppm)

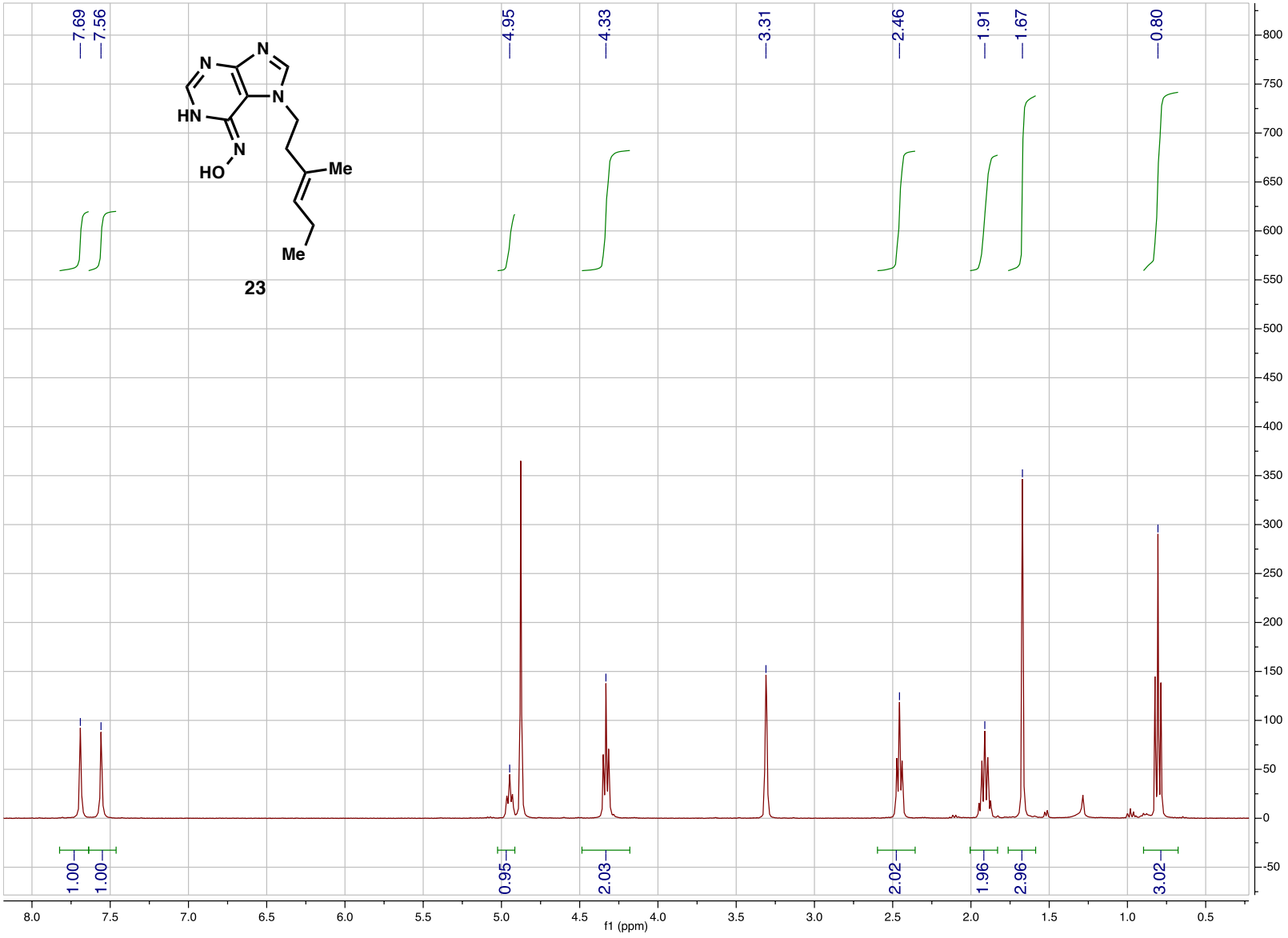

159.84
156.11
153.69
152.12
152.02
143.61
109.31
69.13
49.00
25.95
20.03
N
N
NH
N
N
OH
Me
Me
Me
22
f1 (ppm)

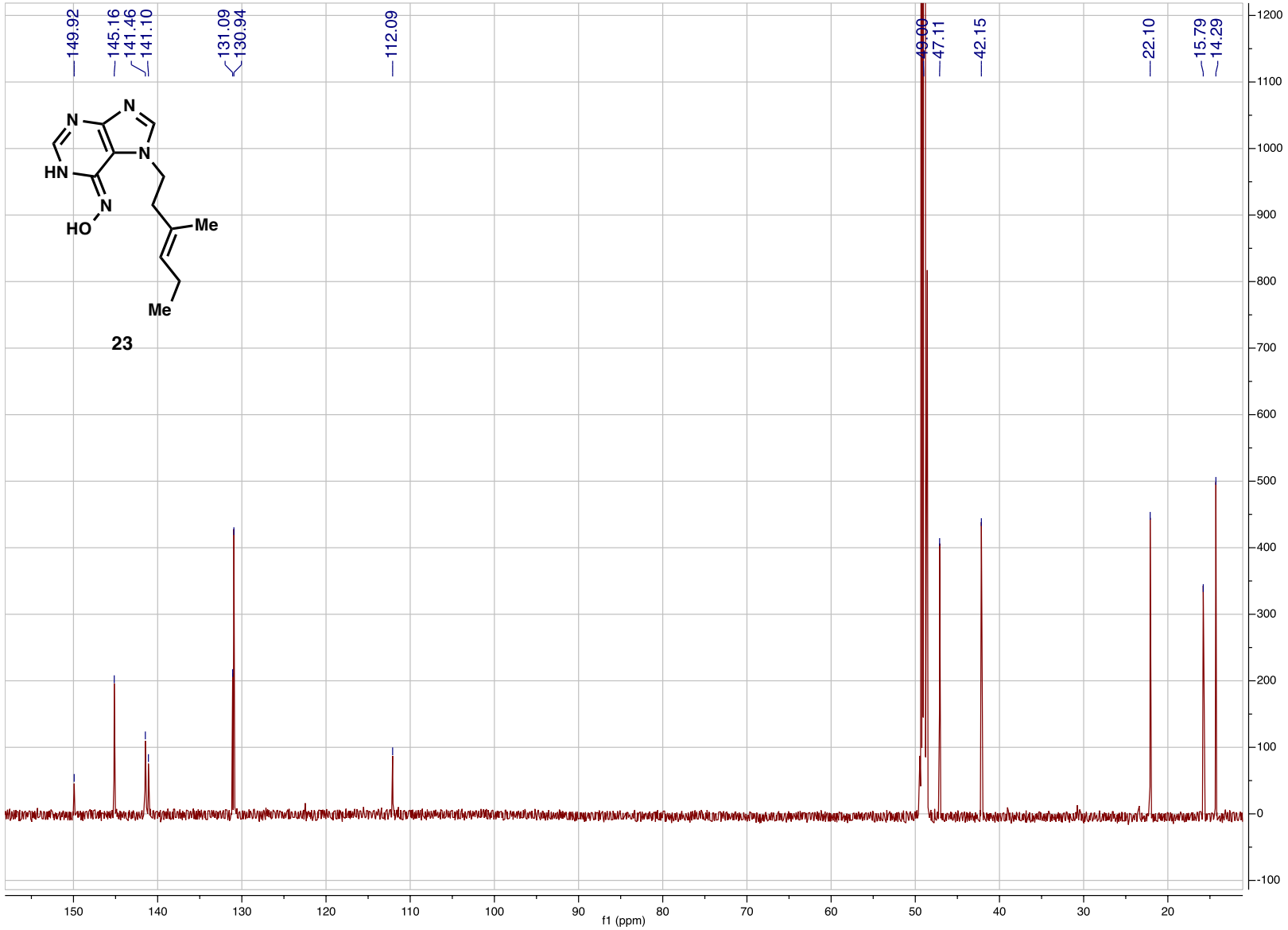

7.26
5.25
3.66
2.24
2.03
1.63
1.47
0.96
Me
Me
OH
SI-1
1.00
2.02
1.99
2.03
3.04
1.08
2.99
f1 (ppm)

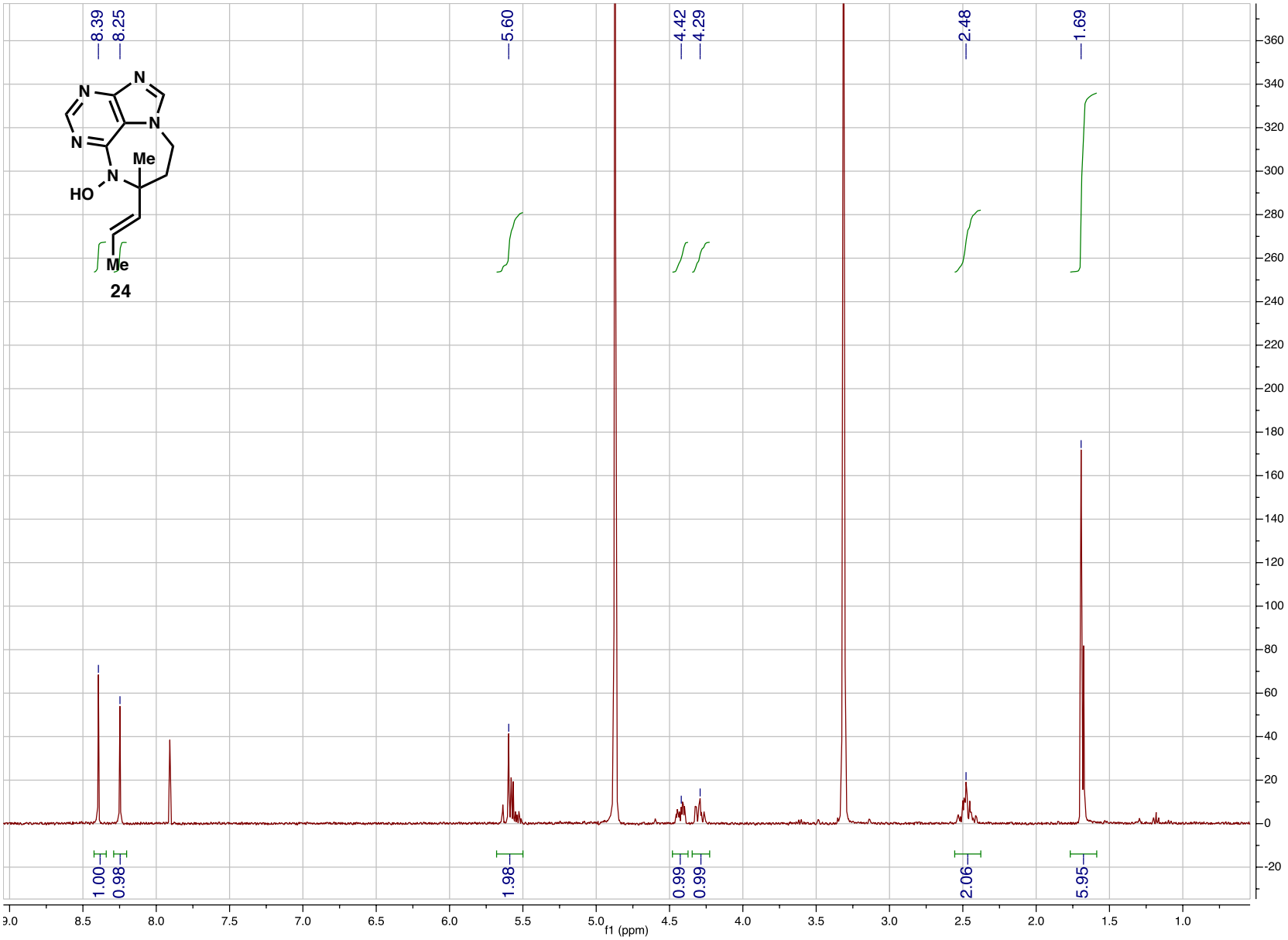

130.62
130.21
77.16
60.18
42.75
21.42
15.67
14.47
Me
Me
OH
SI-1
f1 (ppm)

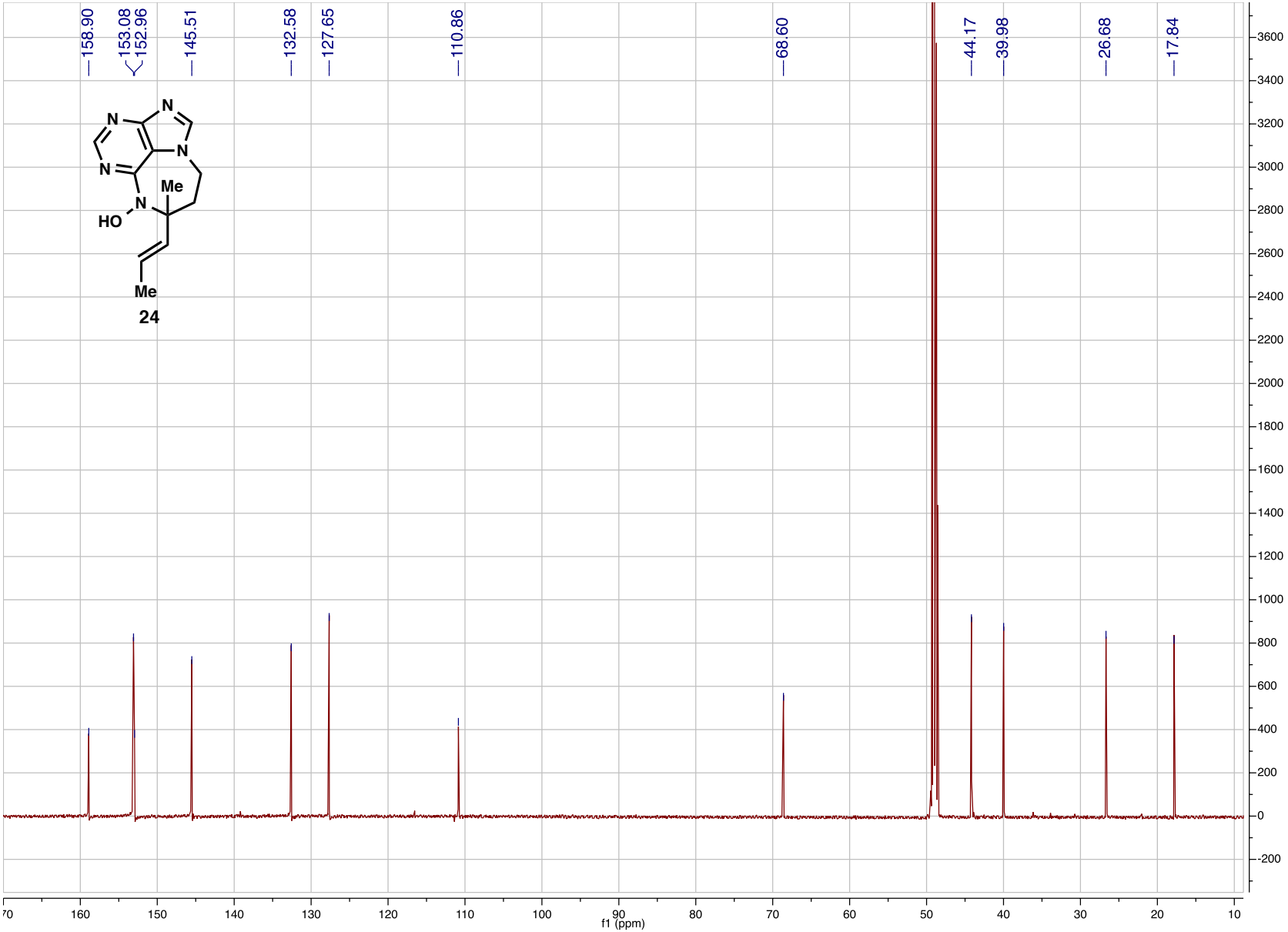

8.78
8.57
4.86
4.81
4.65
3.31
2.57
1.90
1.73
0.74
N
N
N
N
Cl
Me
Me
SI-2
1.00
1.07
1.02
1.91
2.09
2.08
3.02
3.02
f1 (ppm)

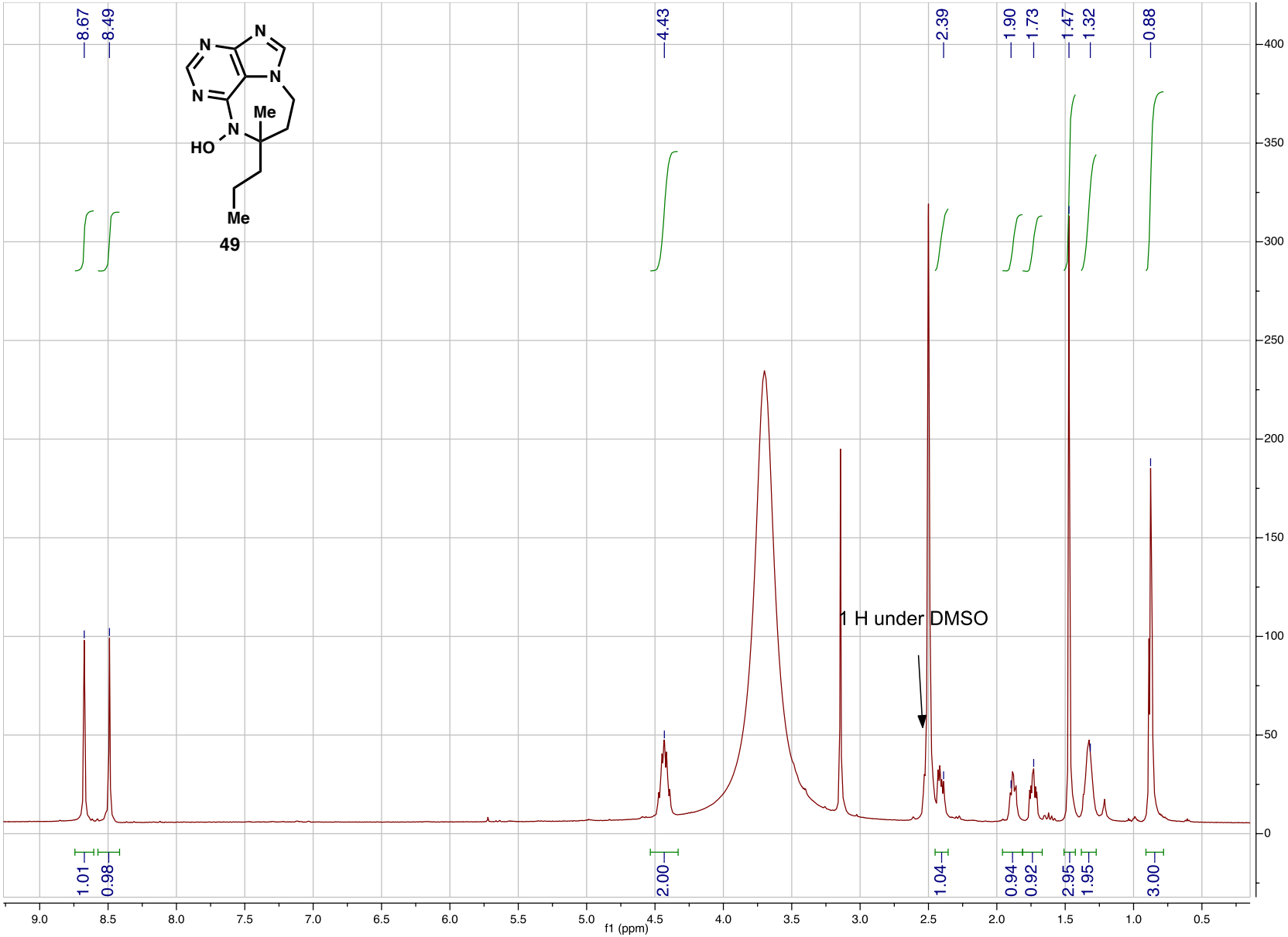

162.64
152.99
152.17
144.63
131.86
130.59
123.61
46.91
42.42
22.06
15.73
14.14
N
N
N
N
Cl
Me
Me
SI-2
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

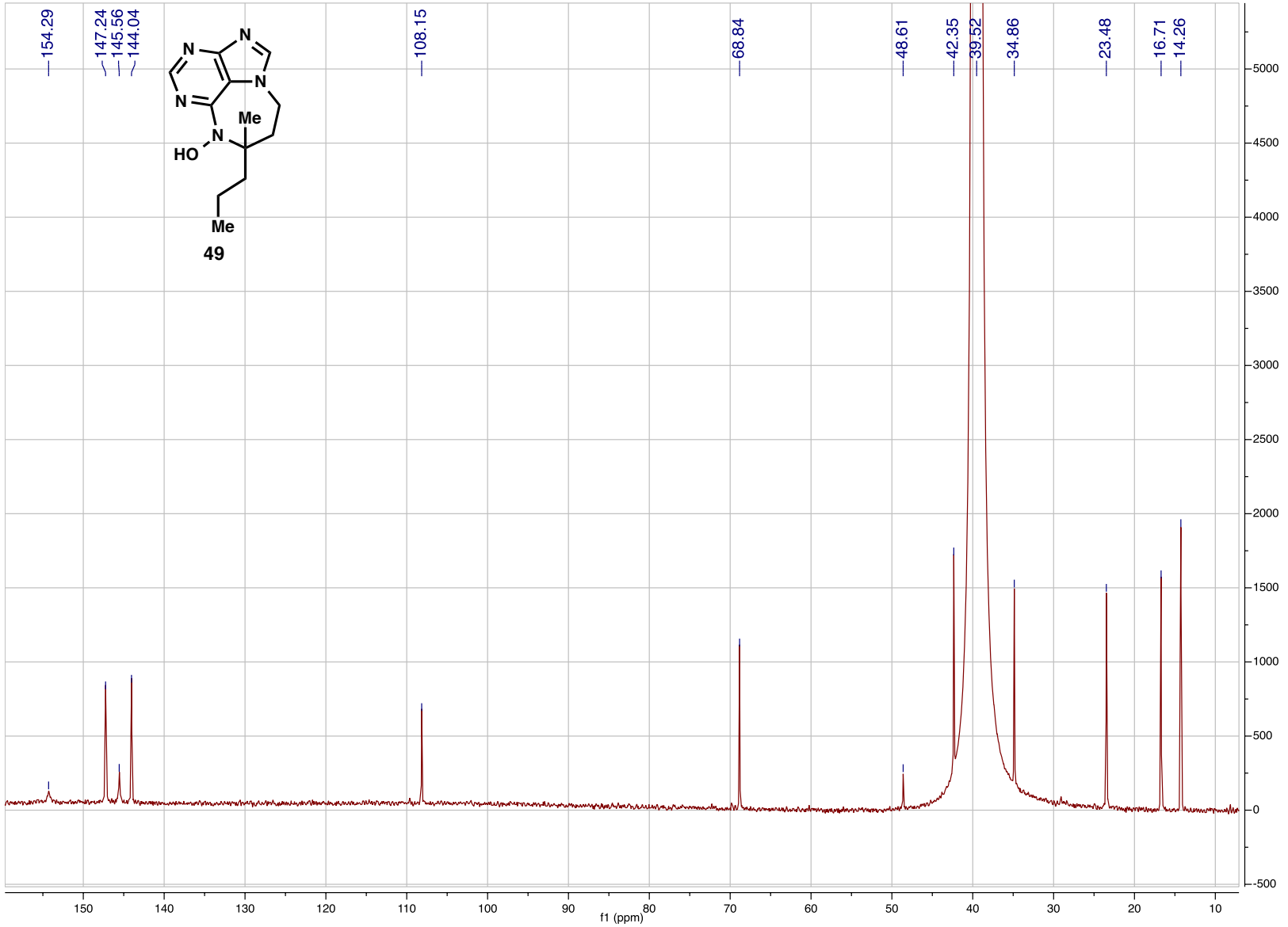

7.69
7.56
4.95
4.33
3.31
2.46
1.91
1.67
0.80
HN
N
HO
Me
Me
23
1.00
1.00
0.95
2.03
2.02
1.96
2.96
3.02
f1 (ppm)

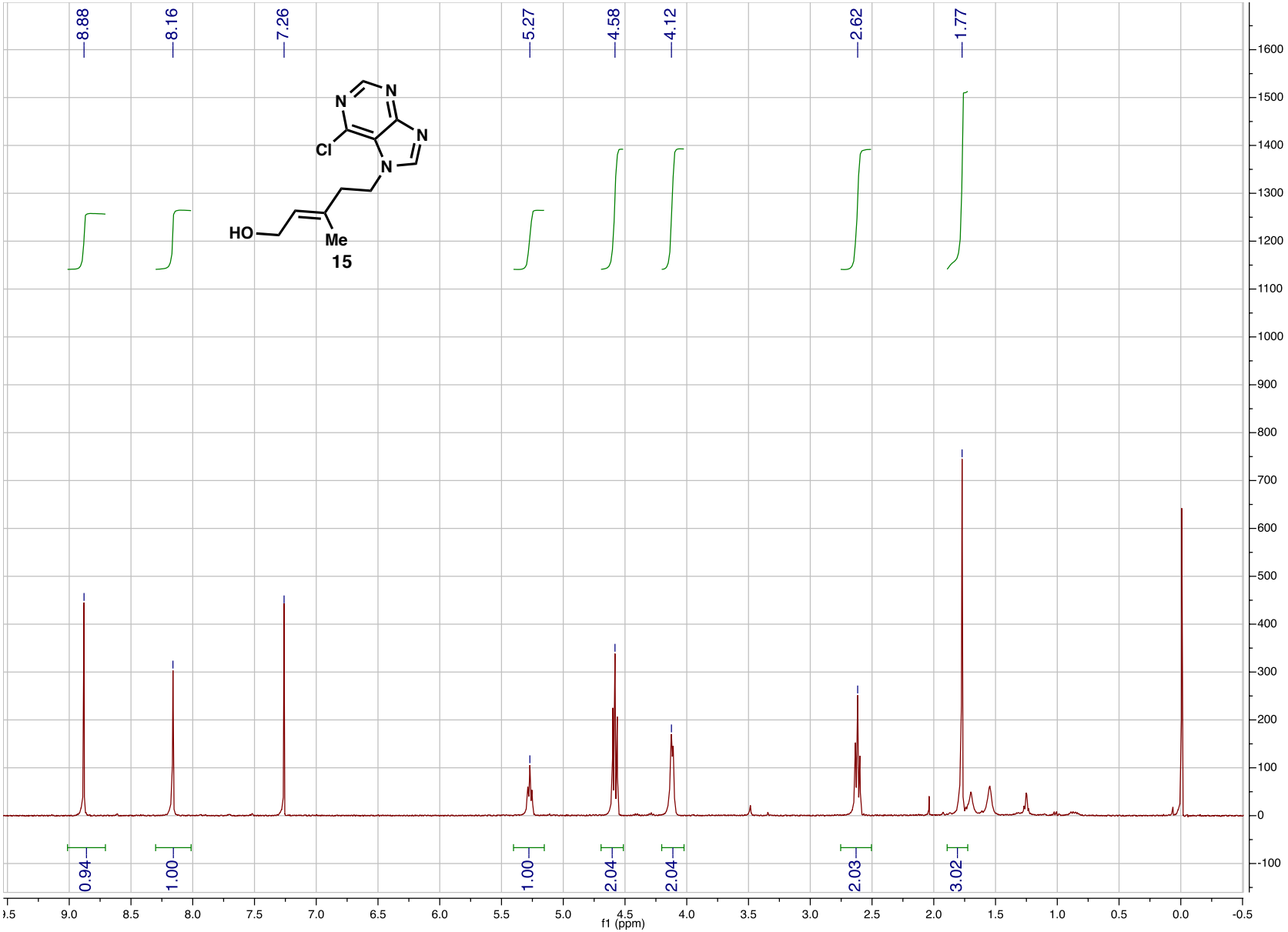

149.92
145.16
141.46
141.10
131.09
130.94
112.09
49.00
47.11
42.15
22.10
15.79
14.29
HN
N
N
N
HO
Me
Me
23
f1 (ppm)

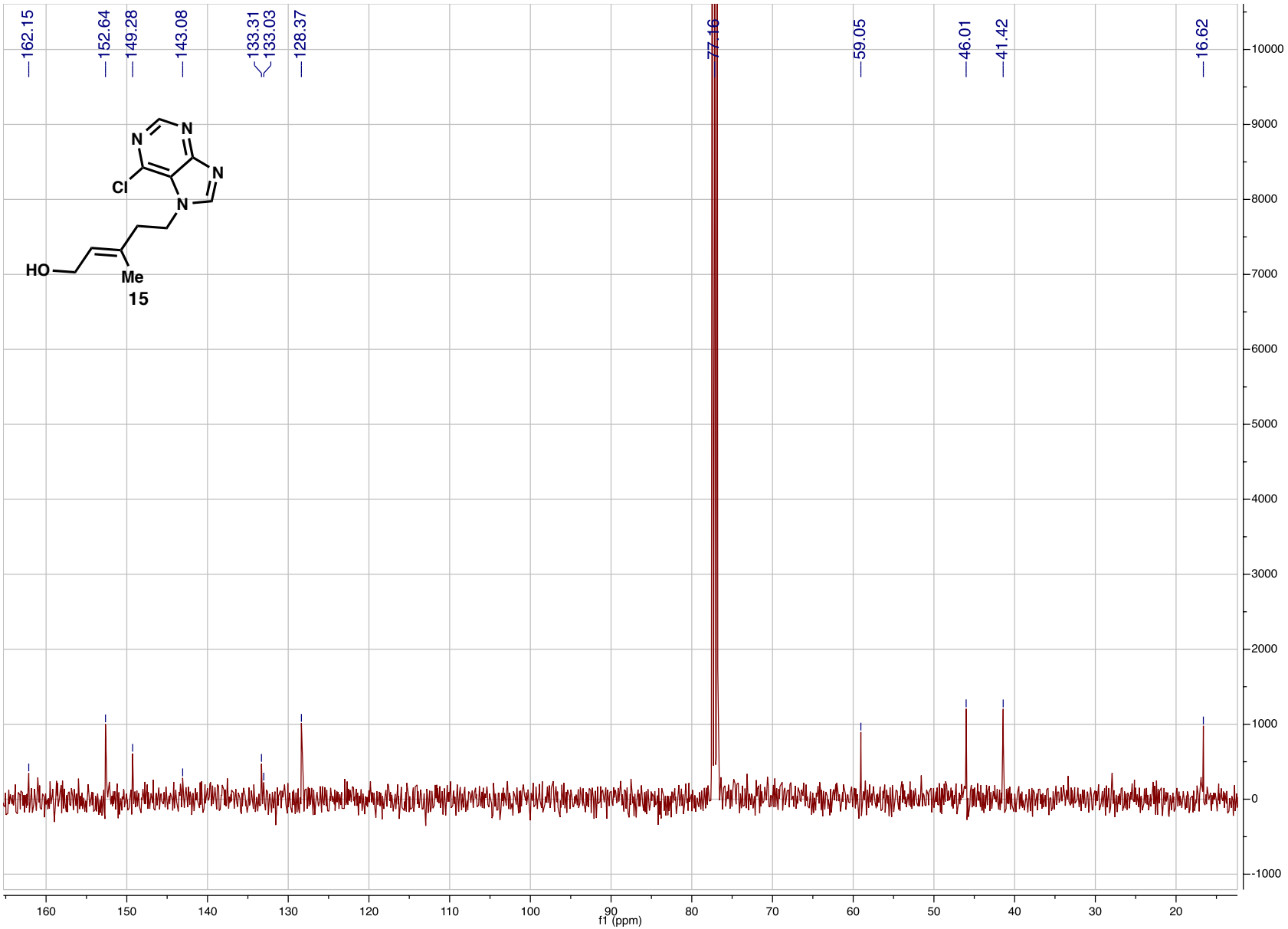

8.39
8.25
5.60
4.42
4.29
2.48
1.69
N
N
N
N
N
Me
HO
Me
24
1.00
0.98
1.98
0.99
0.99
2.06
5.95
f1 (ppm)

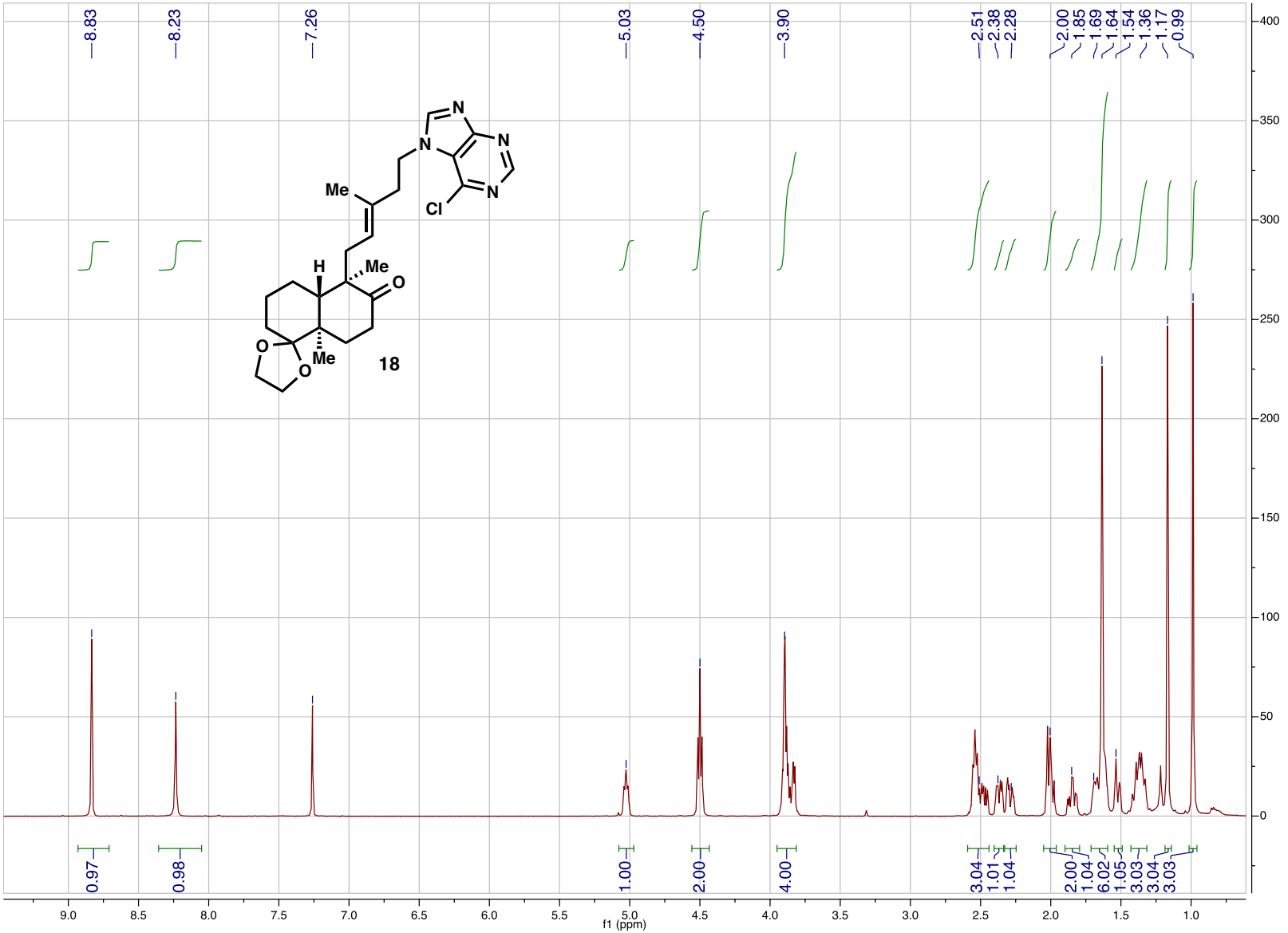

158.90
153.08
152.96
145.51
132.58
127.65
110.86
68.60
44.17
39.98
26.68
17.84
N
N
N
N
N
Me
HO
Me
24
f1 (ppm)

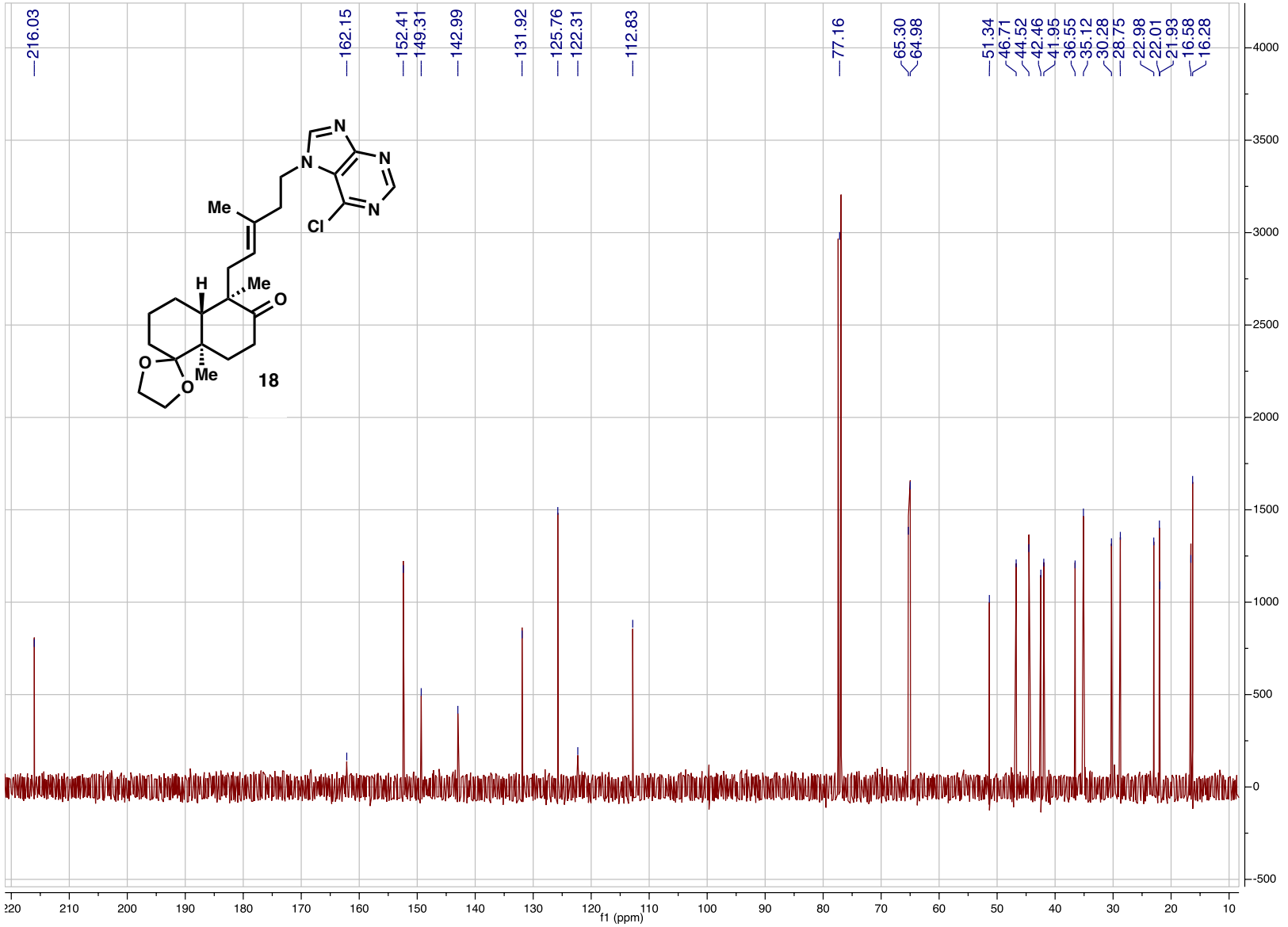

8.67
8.49
4.43
2.39
1.90
1.73
1.47
1.32
0.88
N
N
N
N
N
Me
HO
Me
49
1 H under DMSO
1.01
0.98
2.00
1.04
0.94
0.92
2.95
1.95
3.00
f1 (ppm)

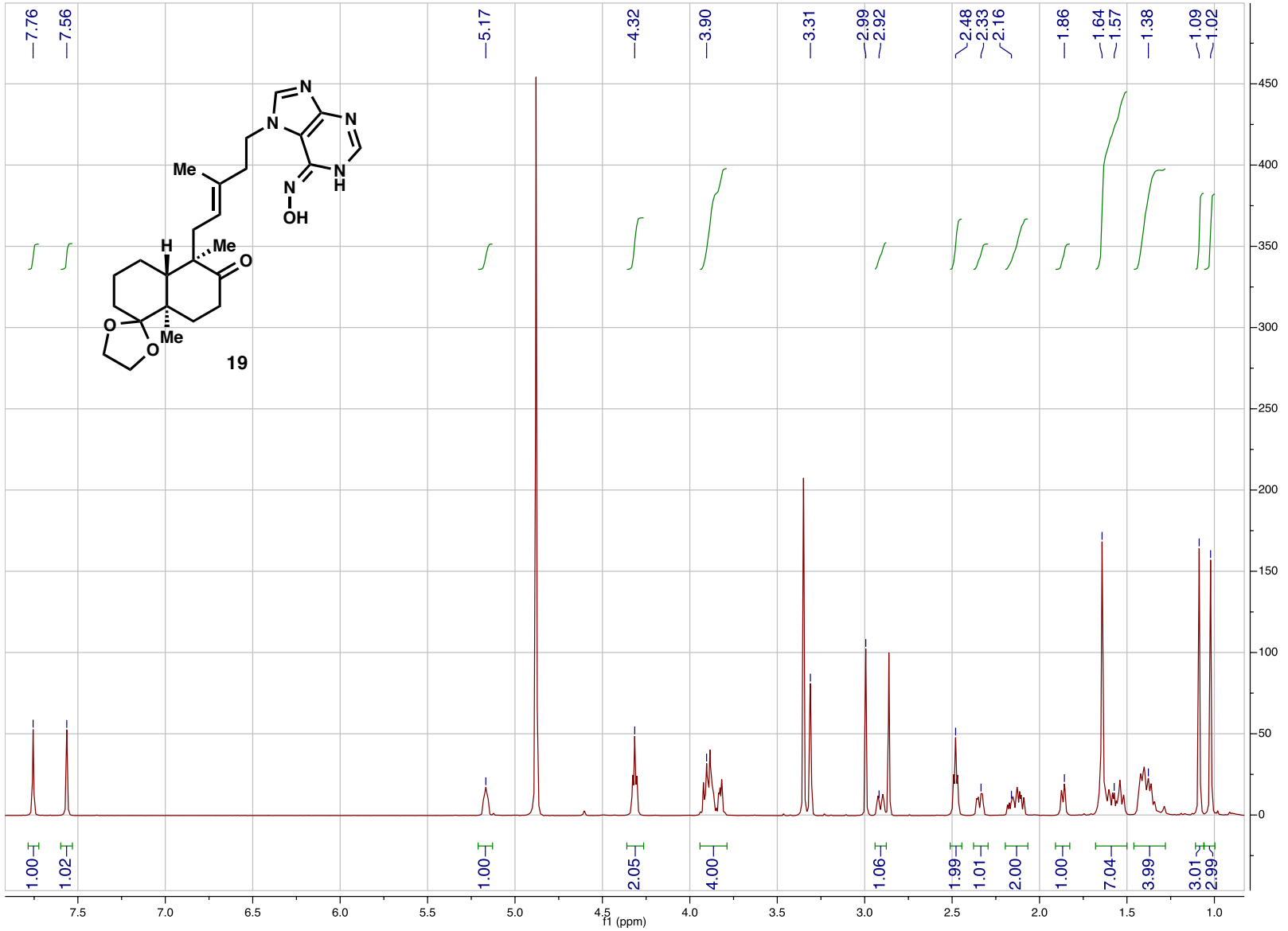

154.29
147.24
145.56
144.04
108.15
68.84
48.61
42.35
39.52
34.86
23.48
16.71
14.26
N
N
N
N
N
HO
Me
Me
49
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

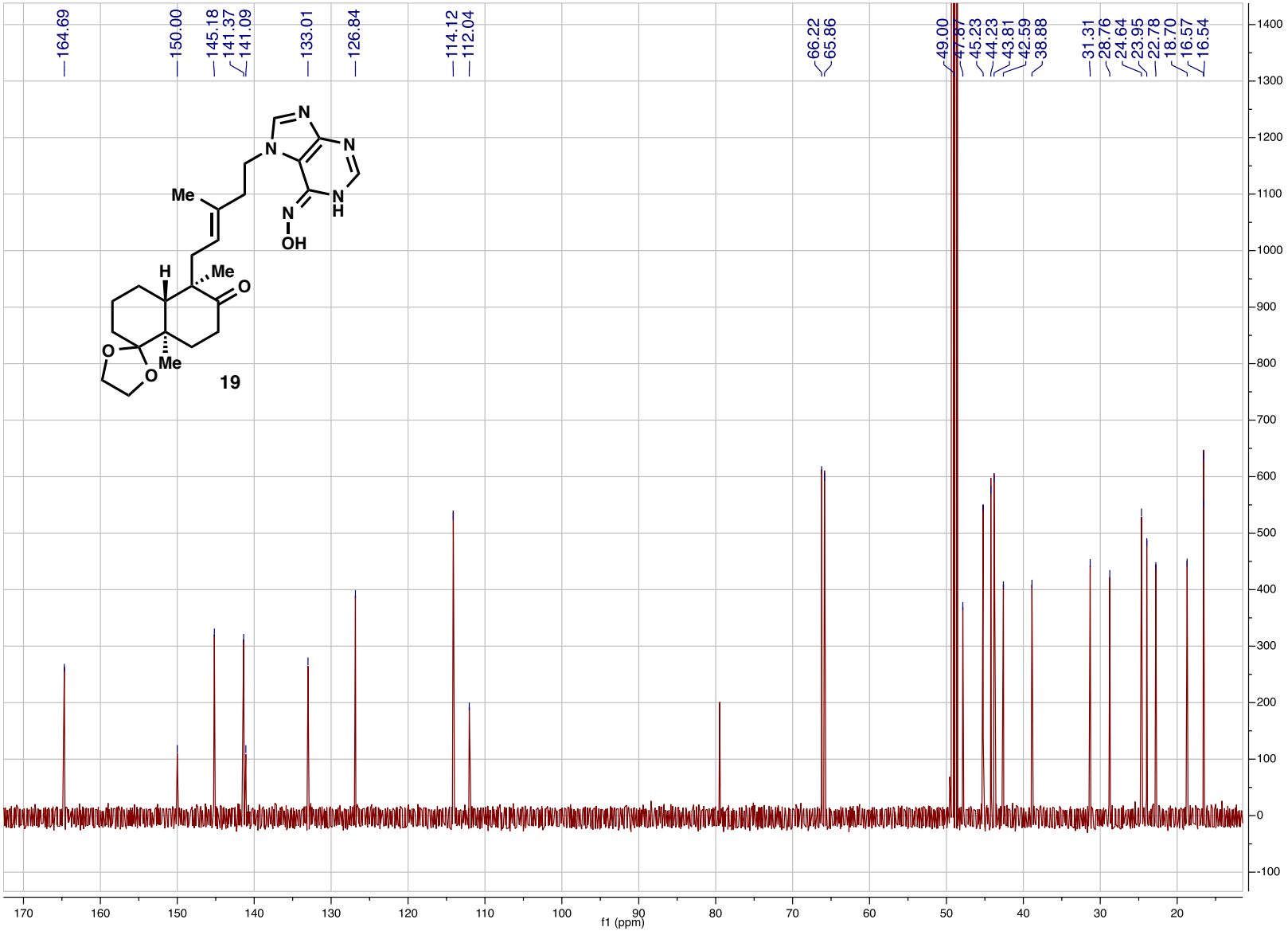

8.88
8.16
7.26
5.27
4.58
4.12
2.62
1.77
Cl
HO
Me
15
0.94
1.00
1.00
2.04
2.04
2.03
3.02
f1 (ppm)

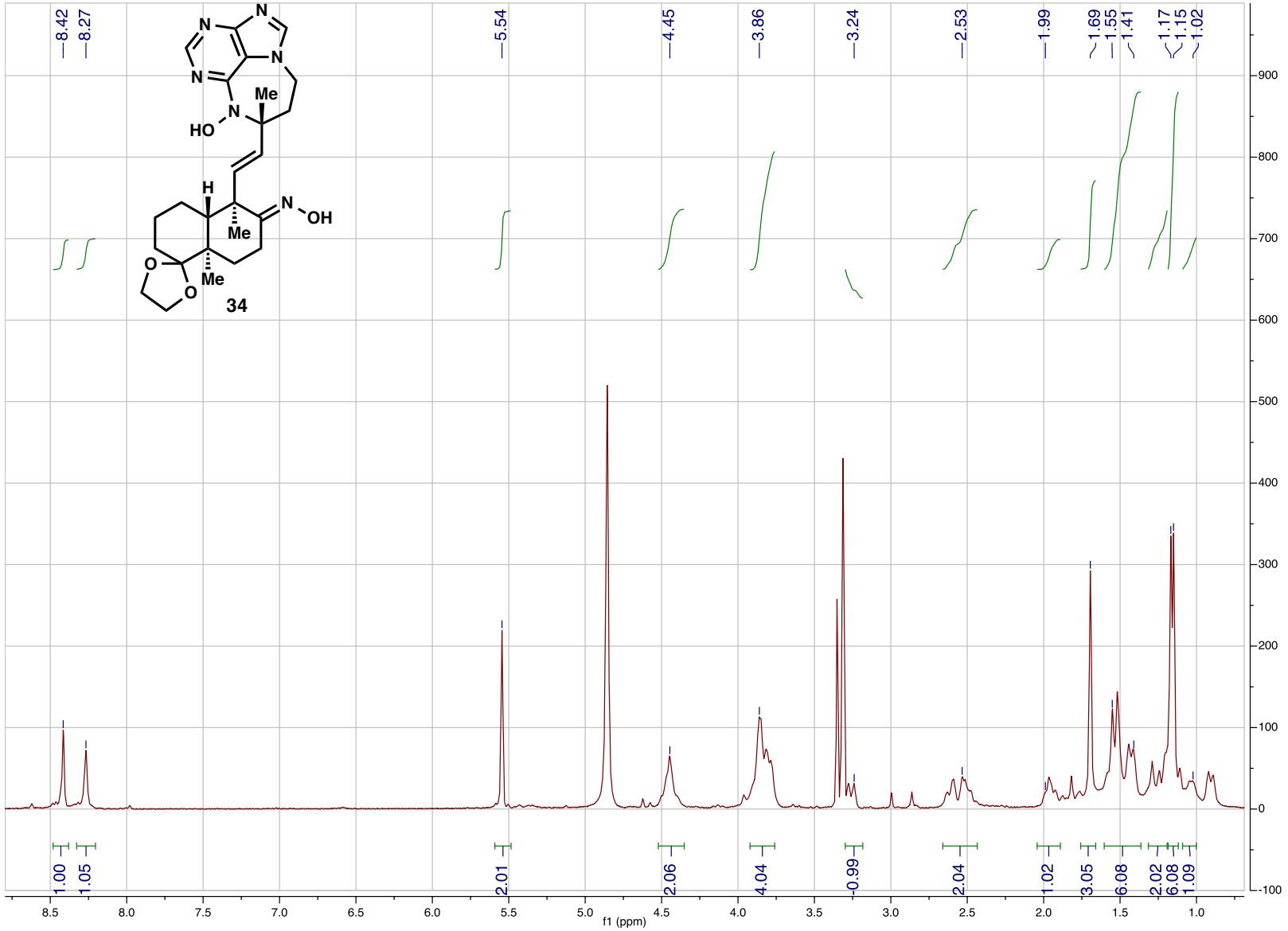

162.15
152.64
149.28
143.08
133.31
133.03
128.37
77.16
59.05
46.01
41.42
16.62
N
N
N
Cl
N
HO
Me
15
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

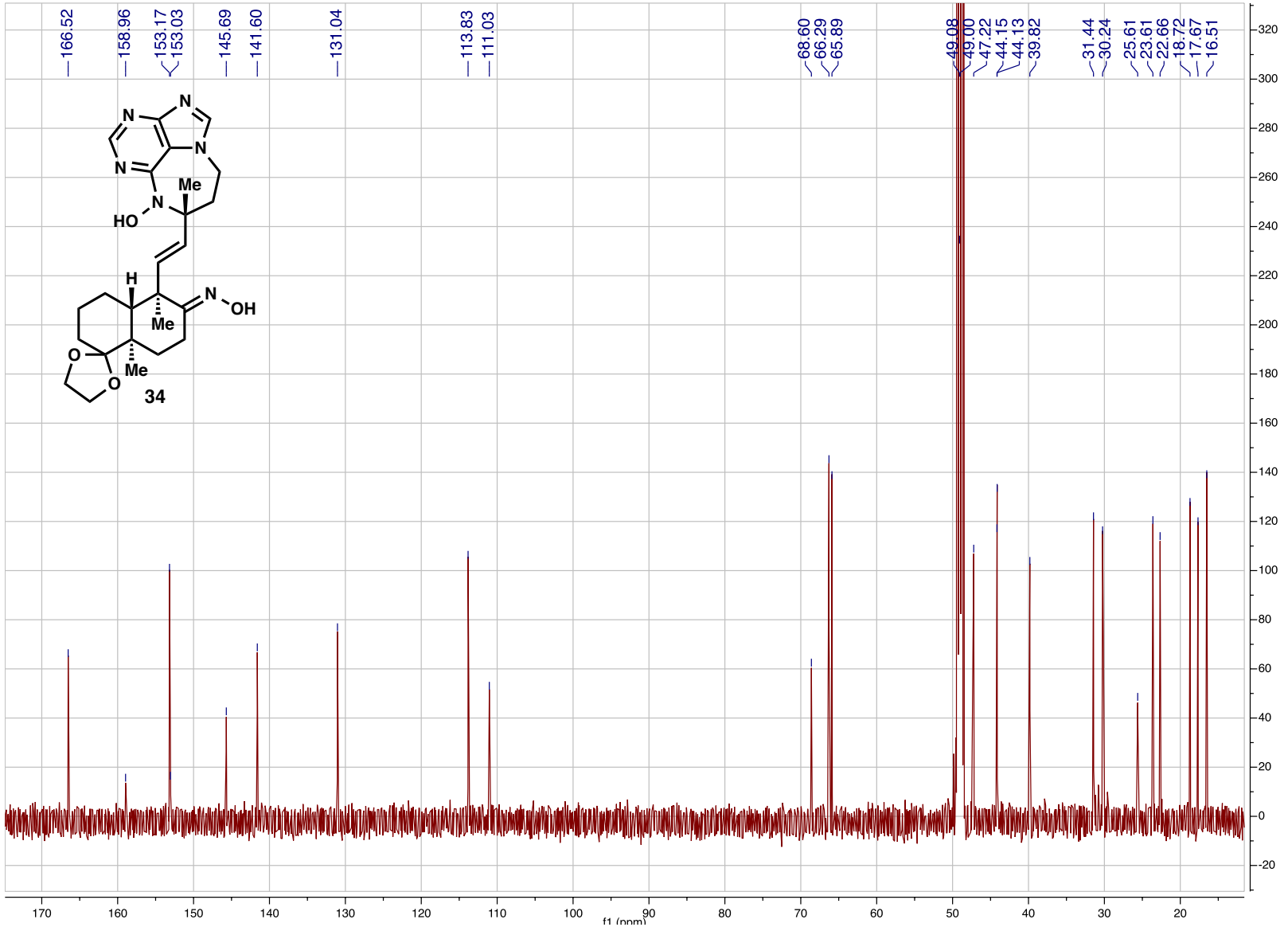

8.83
8.23
7.26
5.03
4.50
3.90
2.51
2.38
2.28
2.00
1.85
1.69
1.64
1.54
1.36
1.17
0.99
N
N
N
N
Cl
Me
H
Me
O
O
O
Me
18
0.97
0.98
1.00
2.00
4.00
3.04
1.01
1.04
2.00
1.04
6.02
1.05
3.03
3.04
3.03
f1 (ppm)

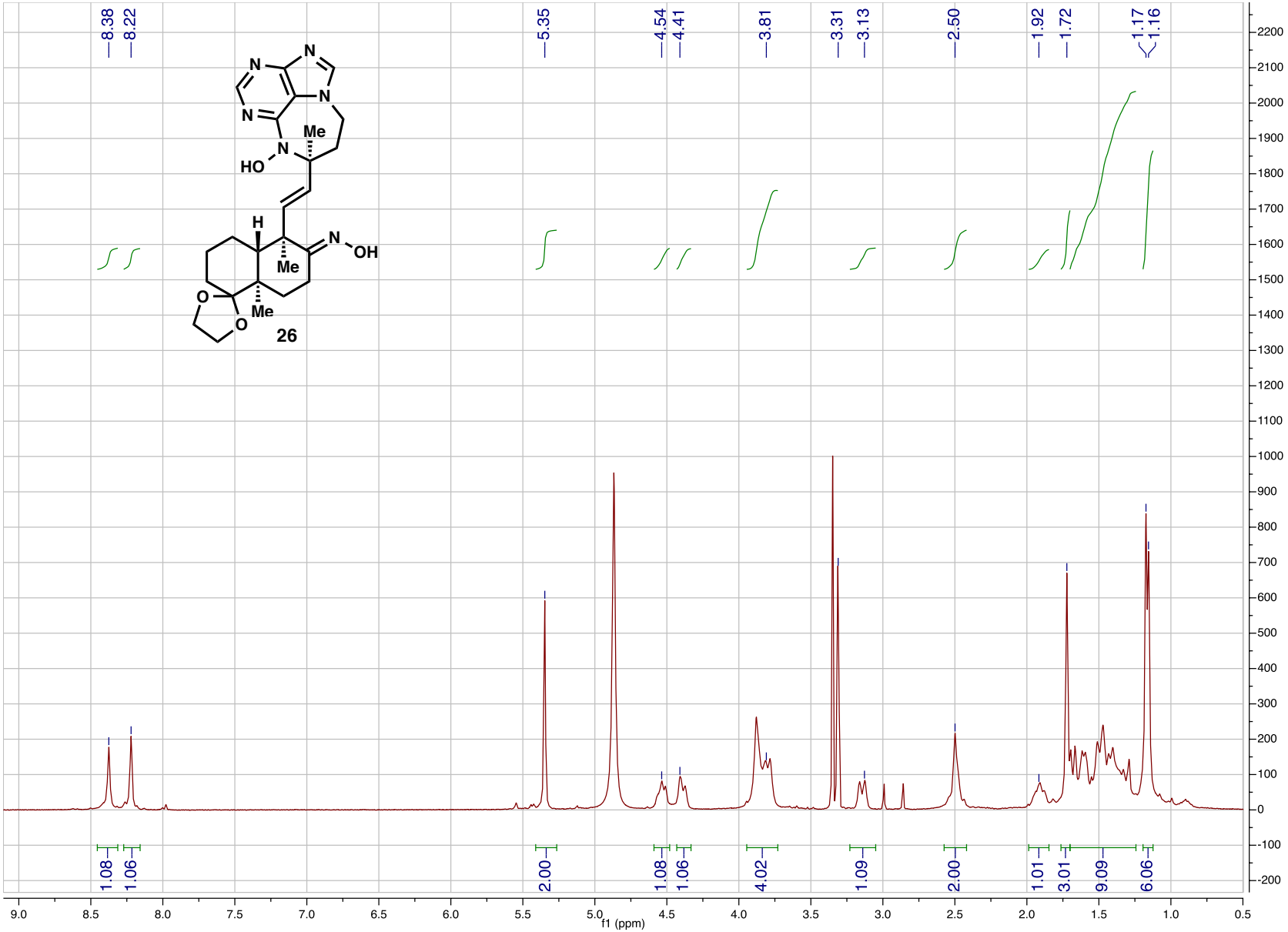

216.03
162.15
152.41
149.31
142.99
131.92
125.76
122.31
112.83
77.16
65.30
64.98
51.34
46.71
44.52
42.46
41.95
36.55
35.12
30.28
28.75
22.98
22.01
21.93
16.58
16.28
Me
Cl
H
Me
O
O
Me
O
18
f1 (ppm)

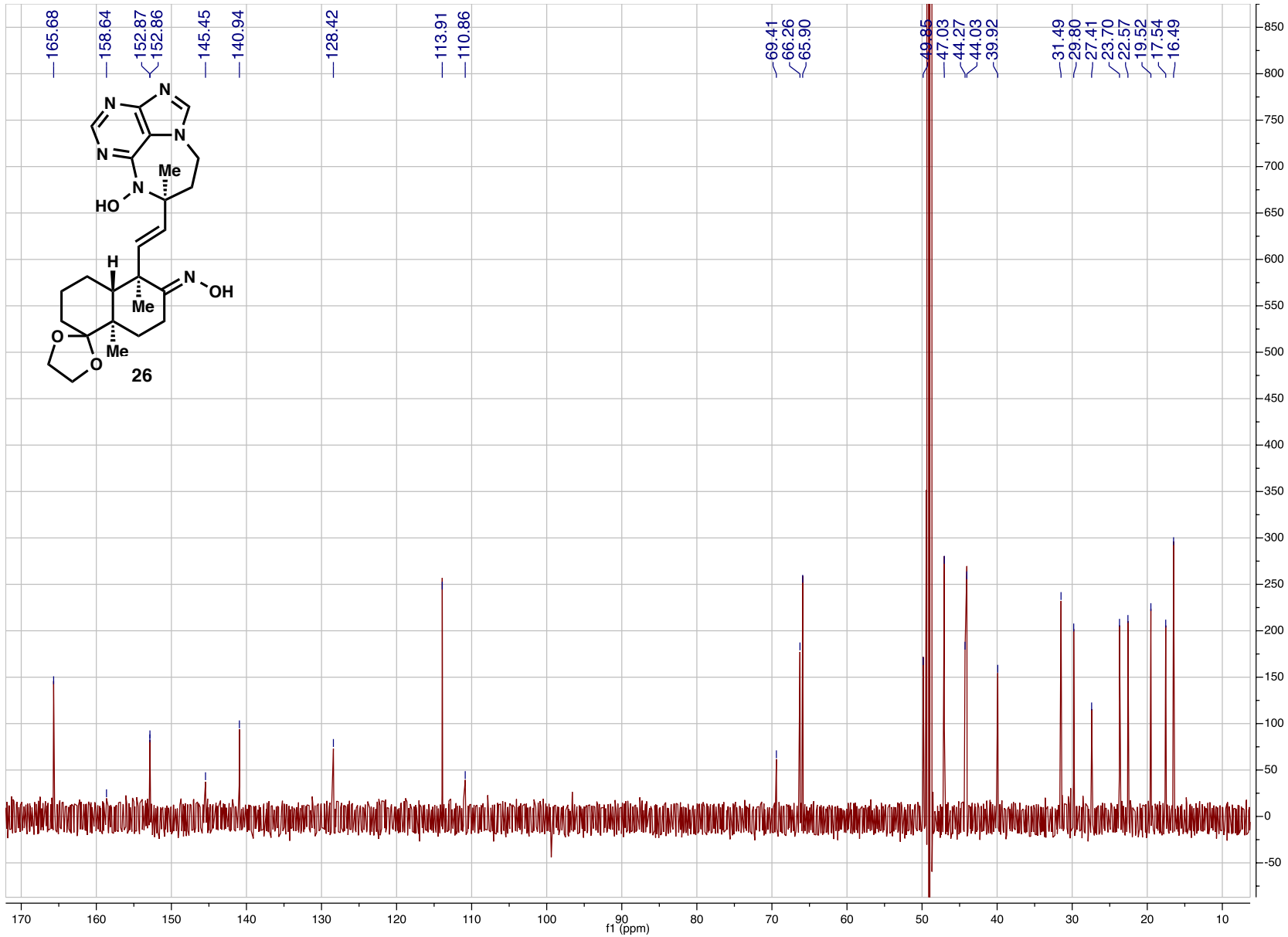

7.76
7.56
5.17
4.32
3.90
3.31
2.99
2.92
2.48
2.33
2.16
1.86
1.64
1.57
1.38
1.09
1.02
Me
N
N
N
N
H
N
OH
H
Me
O
O
O
Me
19
1.00
1.02
1.00
2.05
4.00
1.06
1.99
1.01
2.00
1.00
7.04
3.99
3.01
2.99
f1 (ppm)

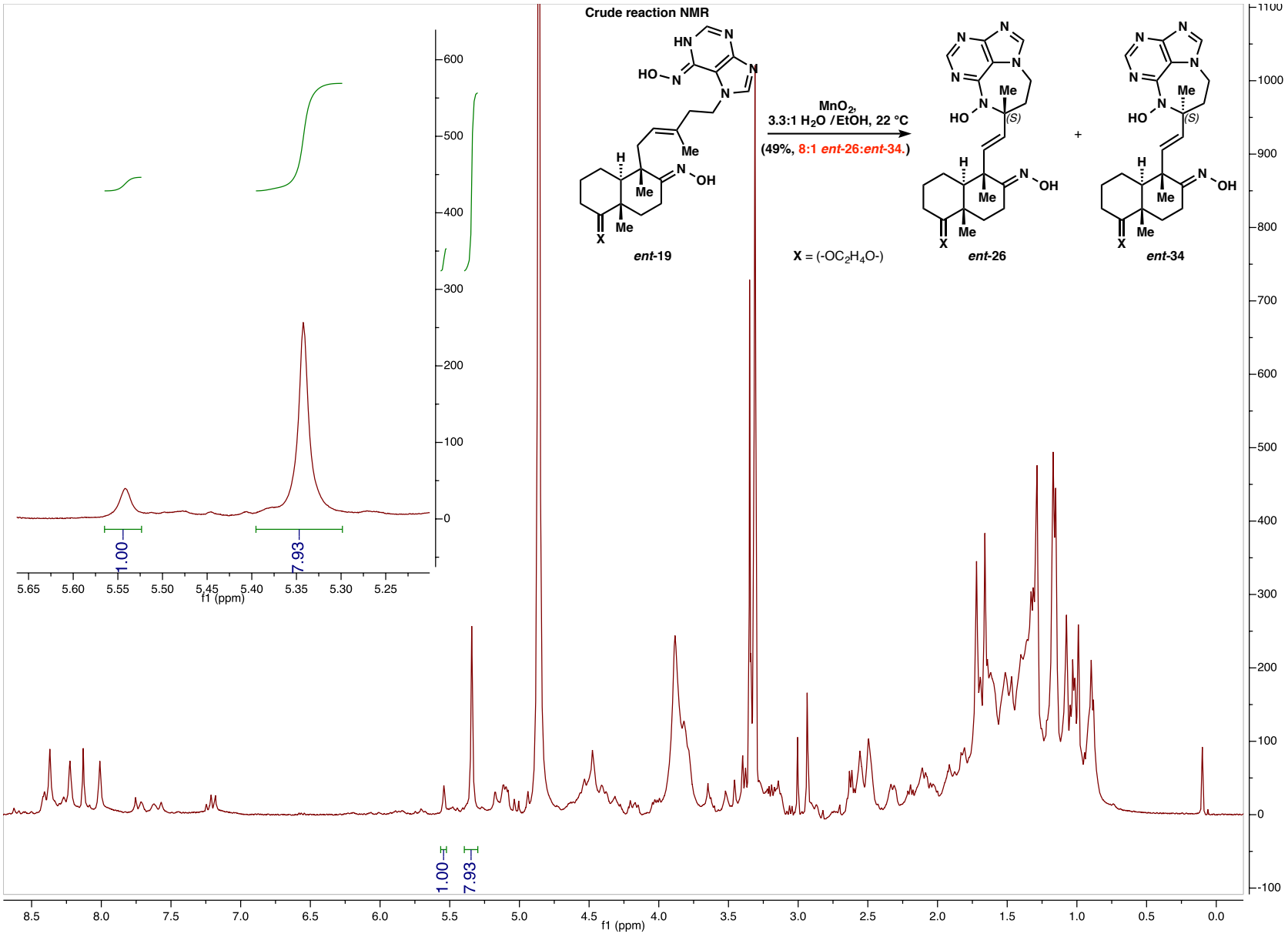

164.69
150.00
145.18
141.37
141.09
133.01
126.84
114.12
112.04
66.22
65.86
49.00
47.87
45.23
44.23
43.81
42.59
38.88
31.31
28.76
24.64
23.95
22.78
18.70
16.57
16.54
Me
N
N
N
N
H
N
OH
H
Me
O
O
O
Me
19
f1 (ppm)

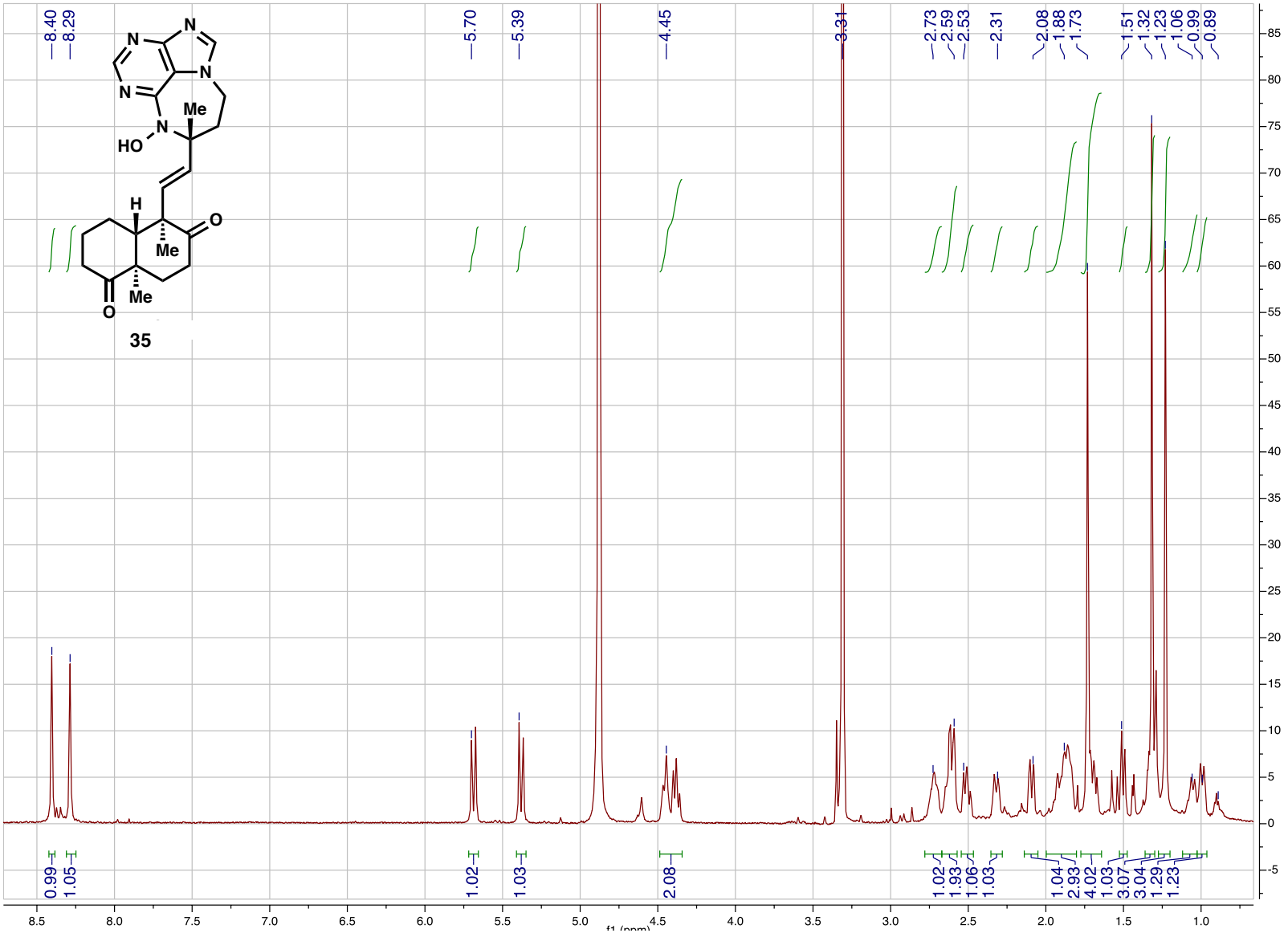

8.42
8.27
5.54
4.45
3.86
3.24
2.53
1.99
1.69
1.55
1.41
1.17
1.15
1.02
Me
HO
N
H
Me
N
OH
O
Me
O
34
1.00
1.05
2.01
2.06
4.04
0.99
2.04
1.02
3.05
6.08
2.02
6.08
1.09
f1 (ppm)

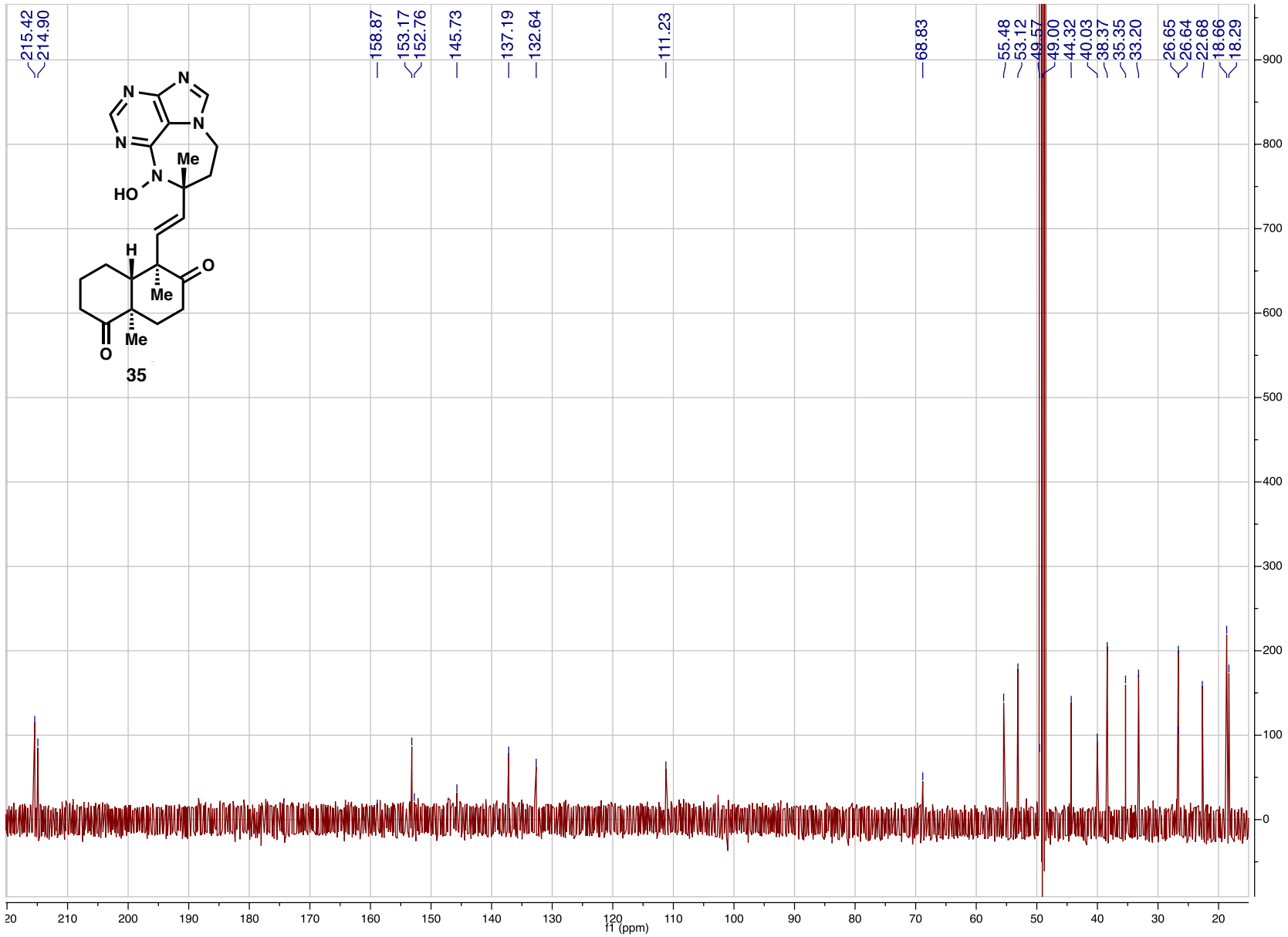

166.52
158.96
153.17
153.03
145.69
141.60
131.04
113.83
111.03
68.60
66.29
65.89
49.08
49.00
47.22
44.15
44.13
39.82
31.44
30.24
25.61
23.61
22.66
18.72
17.67
16.51
N
N
N
N
N
Me
HO
H
N
OH
Me
O
O
Me
34
f1 (ppm)

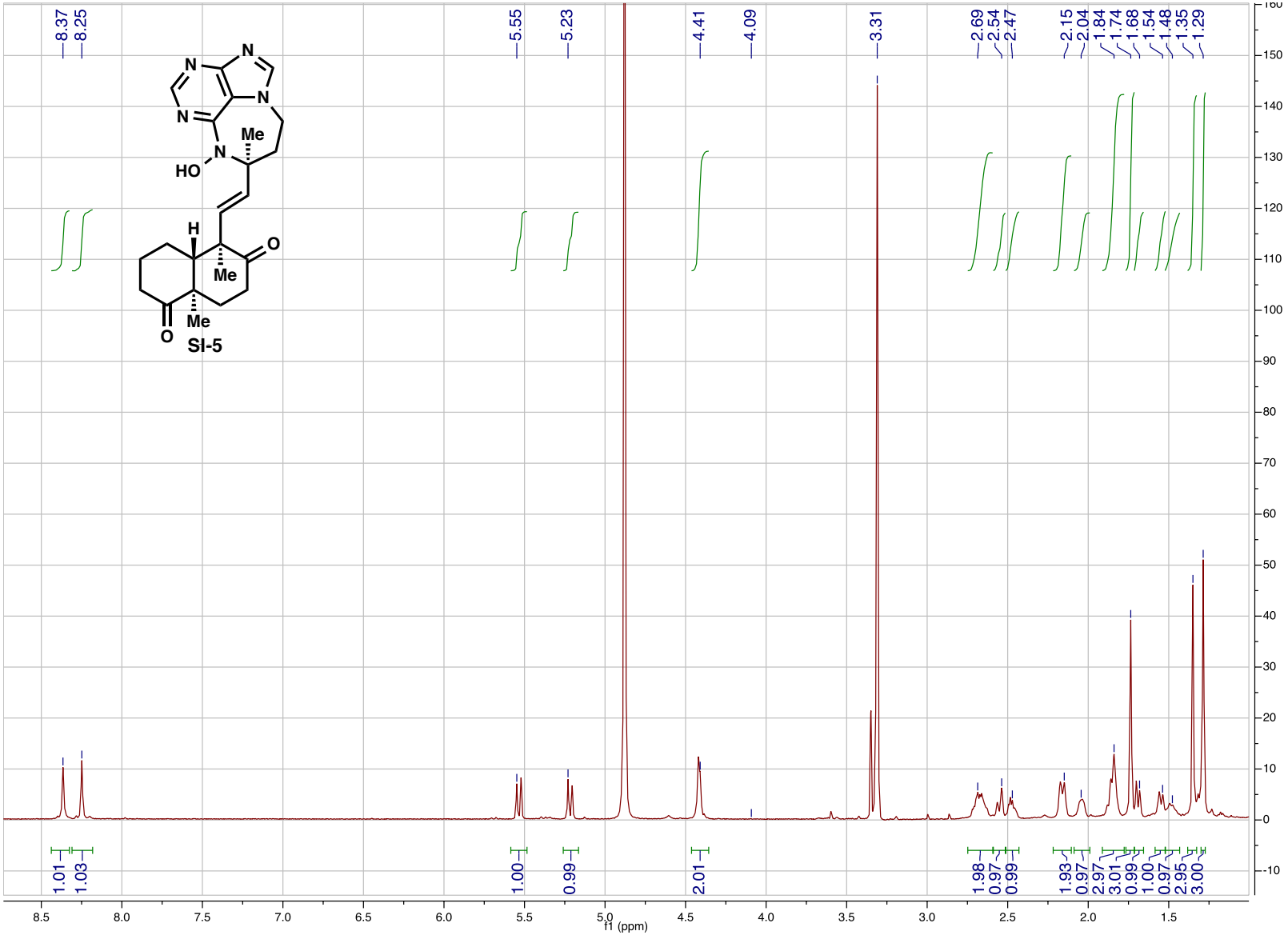

8.38
8.22
5.35
4.54
4.41
3.81
3.31
3.13
2.50
1.92
1.72
1.17
1.16
Me
HO
N
H
Me
N
OH
O
Me
O
26
1.08
1.06
2.00
1.08
1.06
4.02
1.09
2.00
1.01
3.01
9.09
6.06
f1 (ppm)

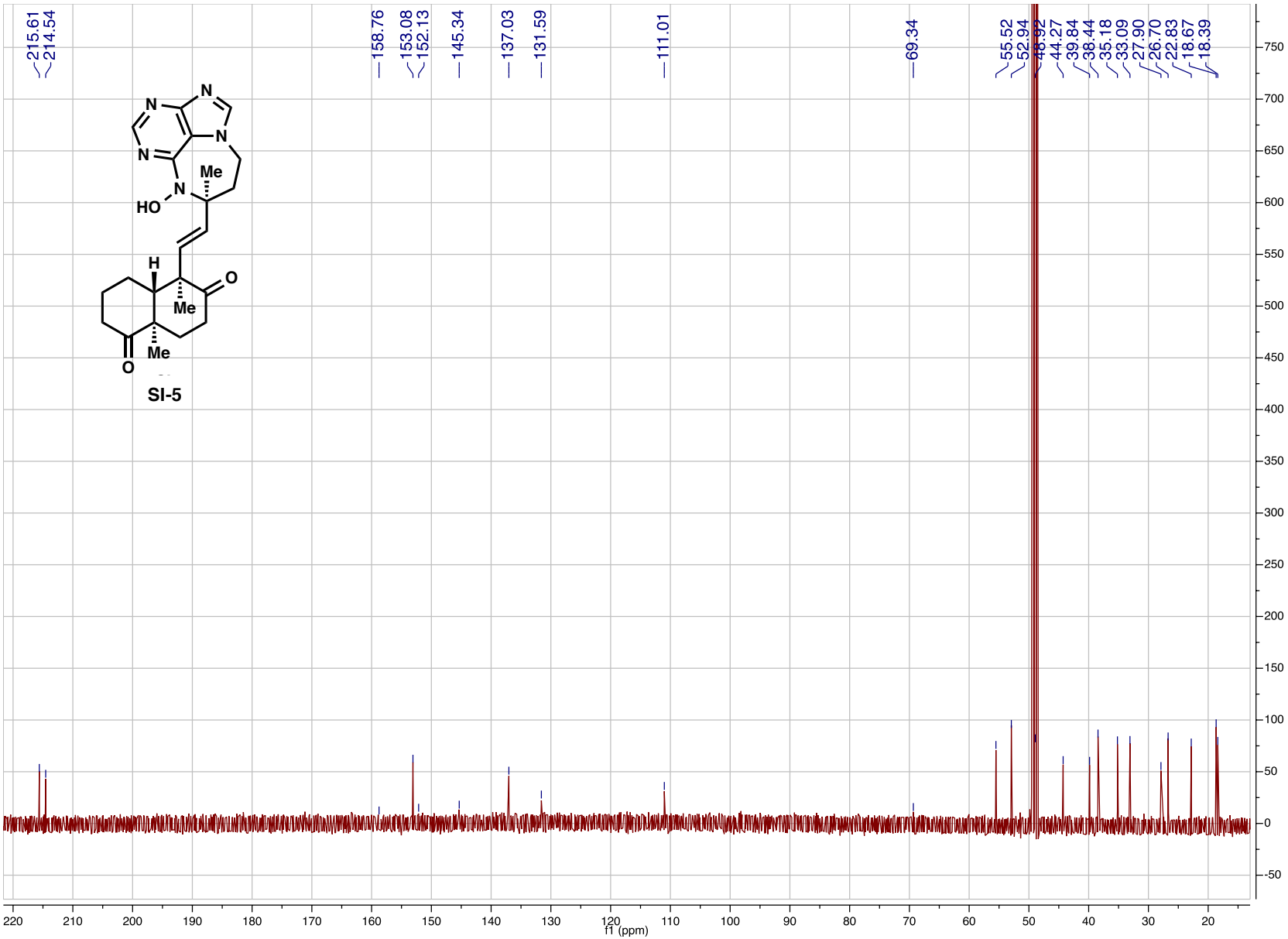

165.68
158.64
152.87
152.86
145.45
140.94
128.42
113.91
110.86
69.41
66.26
65.90
49.85
47.03
44.27
44.03
39.92
31.49
29.80
27.41
23.70
22.57
19.52
17.54
16.49
N
N
N
N
N
Me
HO
H
N
OH
Me
O
O
Me
26
f1 (ppm)

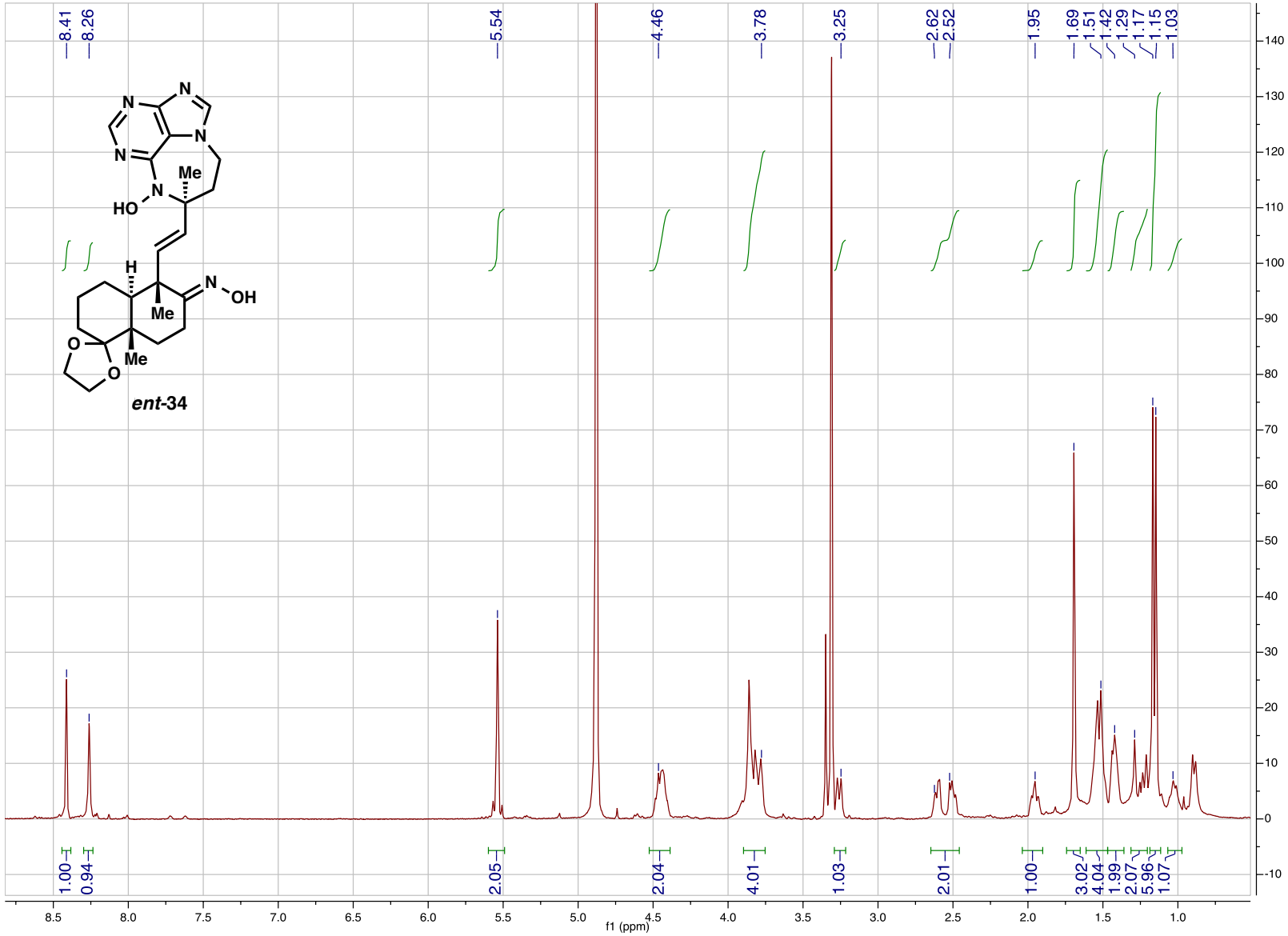

Crude reaction NMR
MnO2,
3.3:1 H2O /EtOH, 22 °C
(49%, 8:1 ent-26:ent-34.)
X = (-OC2H4O-)
ent-19
ent-26
ent-34
1.00
7.93
f1 (ppm)

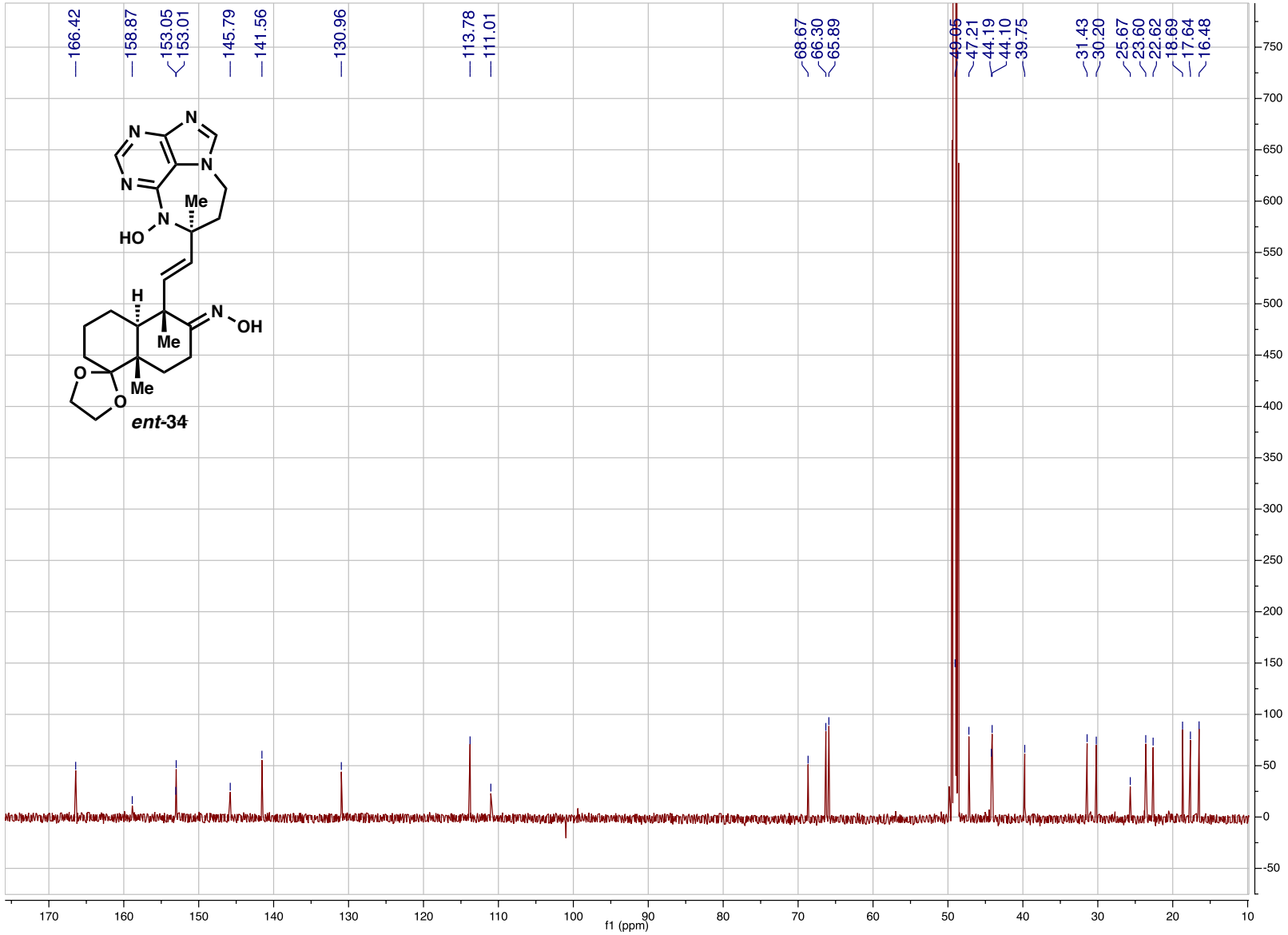

8.40
8.29
5.70
5.39
4.45
3.31
2.73
2.59
2.53
2.31
2.08
1.88
1.73
1.51
1.32
1.23
1.06
0.99
0.89
N
N
N
N
N
Me
HO
H
O
Me
Me
O
35
0.99
1.05
1.02
1.03
2.08
1.02
1.93
1.06
1.03
1.04
2.93
4.02
1.03
3.07
3.04
1.29
1.23
f1 (ppm)

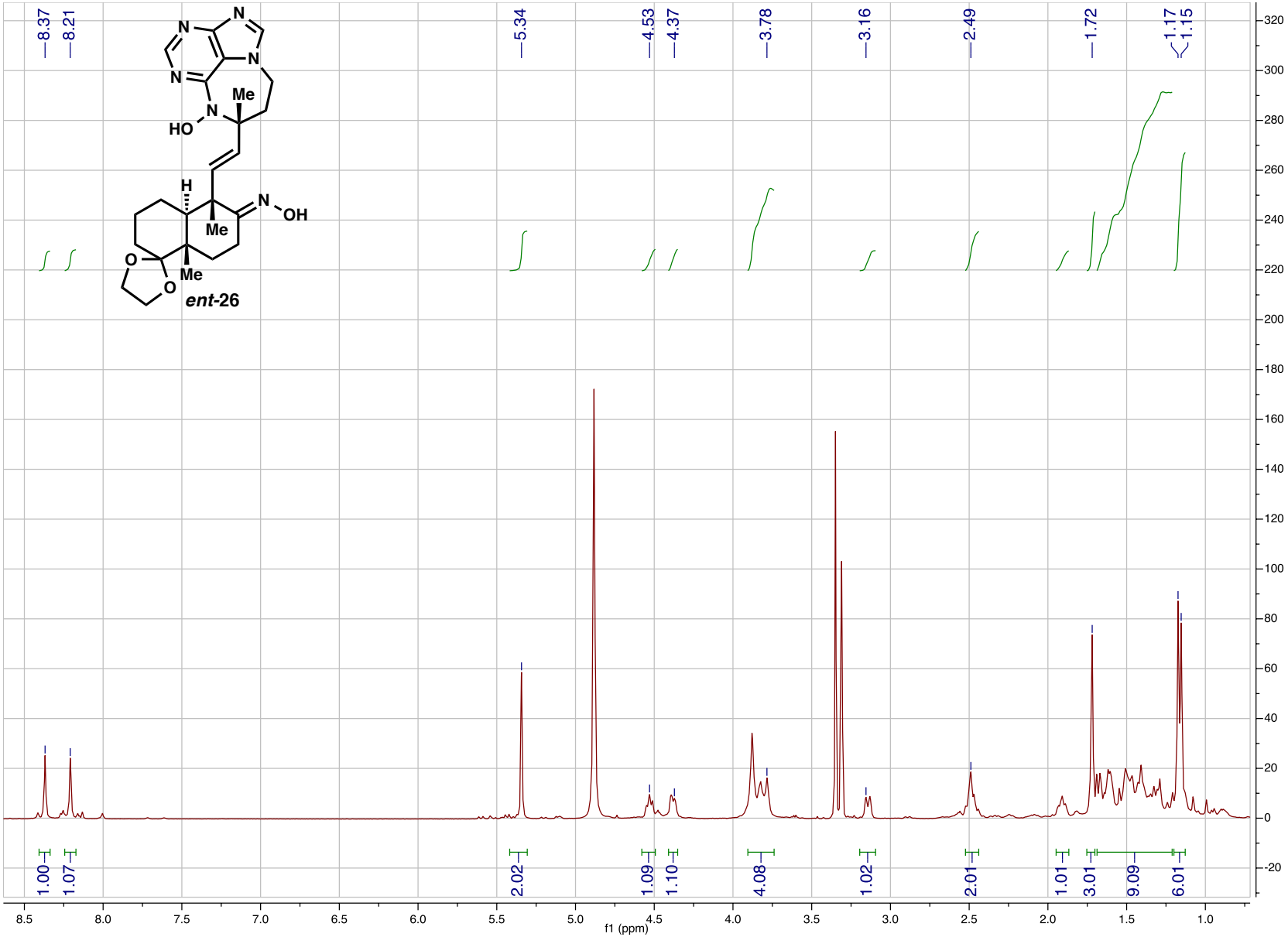

215.42
214.90
158.87
153.17
152.76
145.73
137.19
132.64
111.23
68.83
55.48
53.12
49.57
49.00
44.32
40.03
38.37
35.35
33.20
26.65
26.64
22.68
18.66
18.29
N
N
N
N
N
HO
Me
H
O
Me
Me
O
35
f1 (ppm)

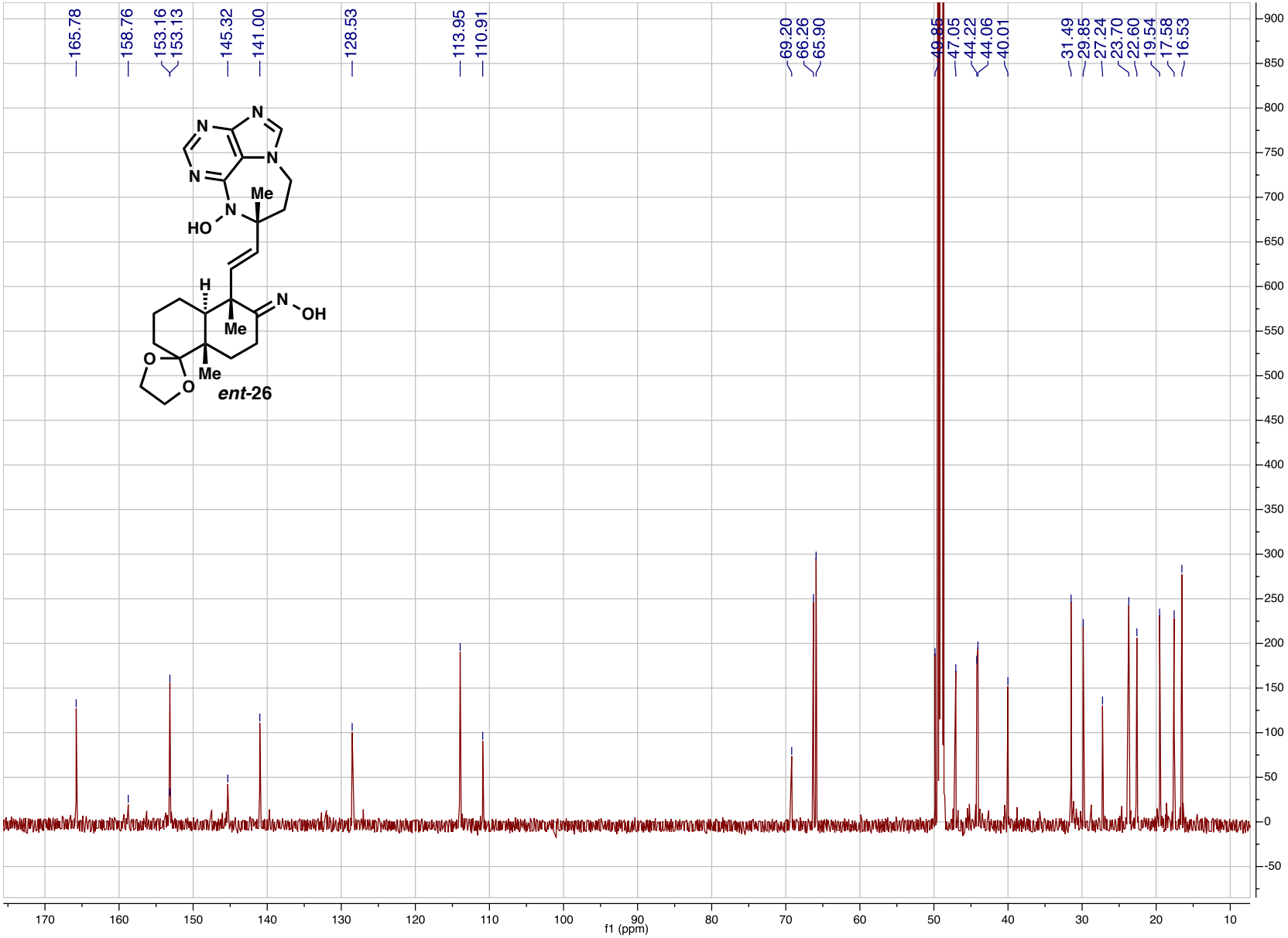

8.37
8.25
5.55
5.23
4.41
4.09
3.31
2.69
2.54
2.47
2.15
2.04
1.84
1.74
1.68
1.54
1.48
1.35
1.29
Me
HO
H
Me
Me
O
O
O
SI-5
1.01
1.03
1.00
0.99
2.01
1.98
0.97
0.99
1.93
0.97
2.97
3.01
0.99
1.00
0.97
2.95
3.00
f1 (ppm)

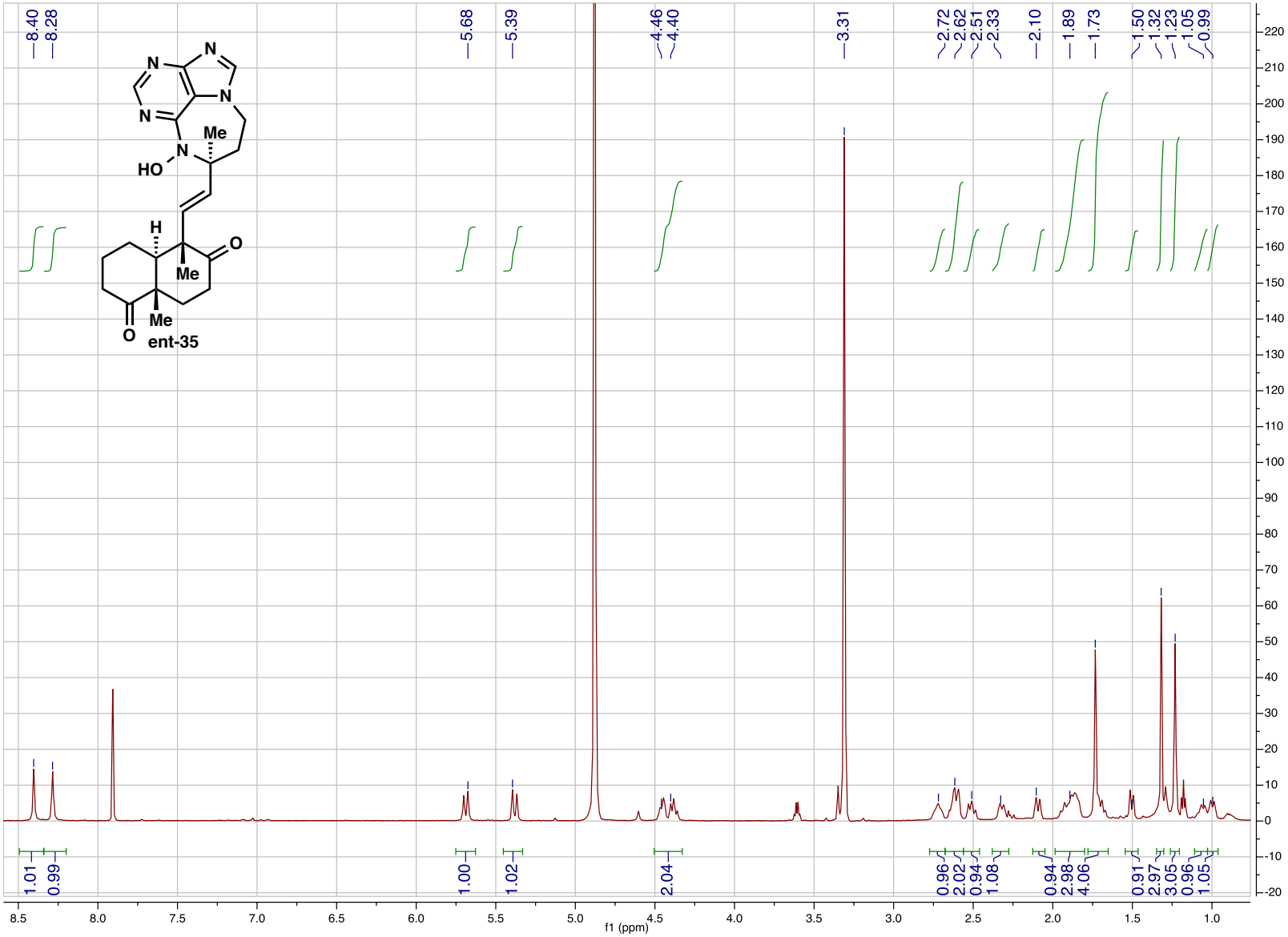

215.61
214.54
158.76
153.08
152.13
145.34
137.03
131.59
111.01
69.34
55.52
52.94
48.92
44.27
39.84
38.44
35.18
33.09
27.90
26.70
22.83
18.67
18.39
SI-5
f1 (ppm)

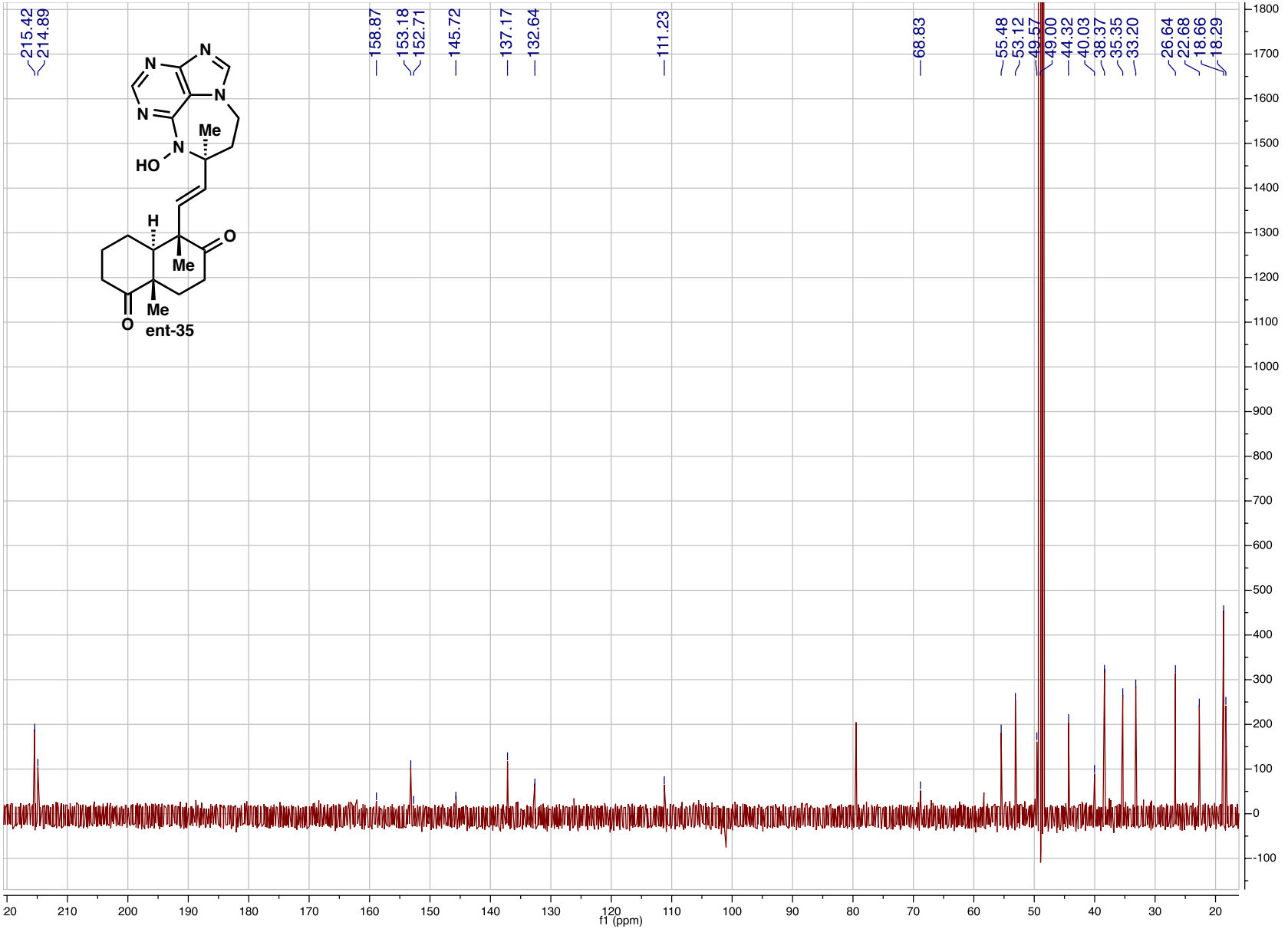

8.41
8.26
5.54
4.46
3.78
3.25
2.62
2.52
1.95
1.69
1.51
1.42
1.29
1.17
1.15
1.03
Me
HO
N
H
Me
N
OH
O
O
Me
ent-34
1.00
0.94
2.05
2.04
4.01
1.03
2.01
1.00
3.02
4.04
1.99
2.07
5.96
1.07
f1 (ppm)

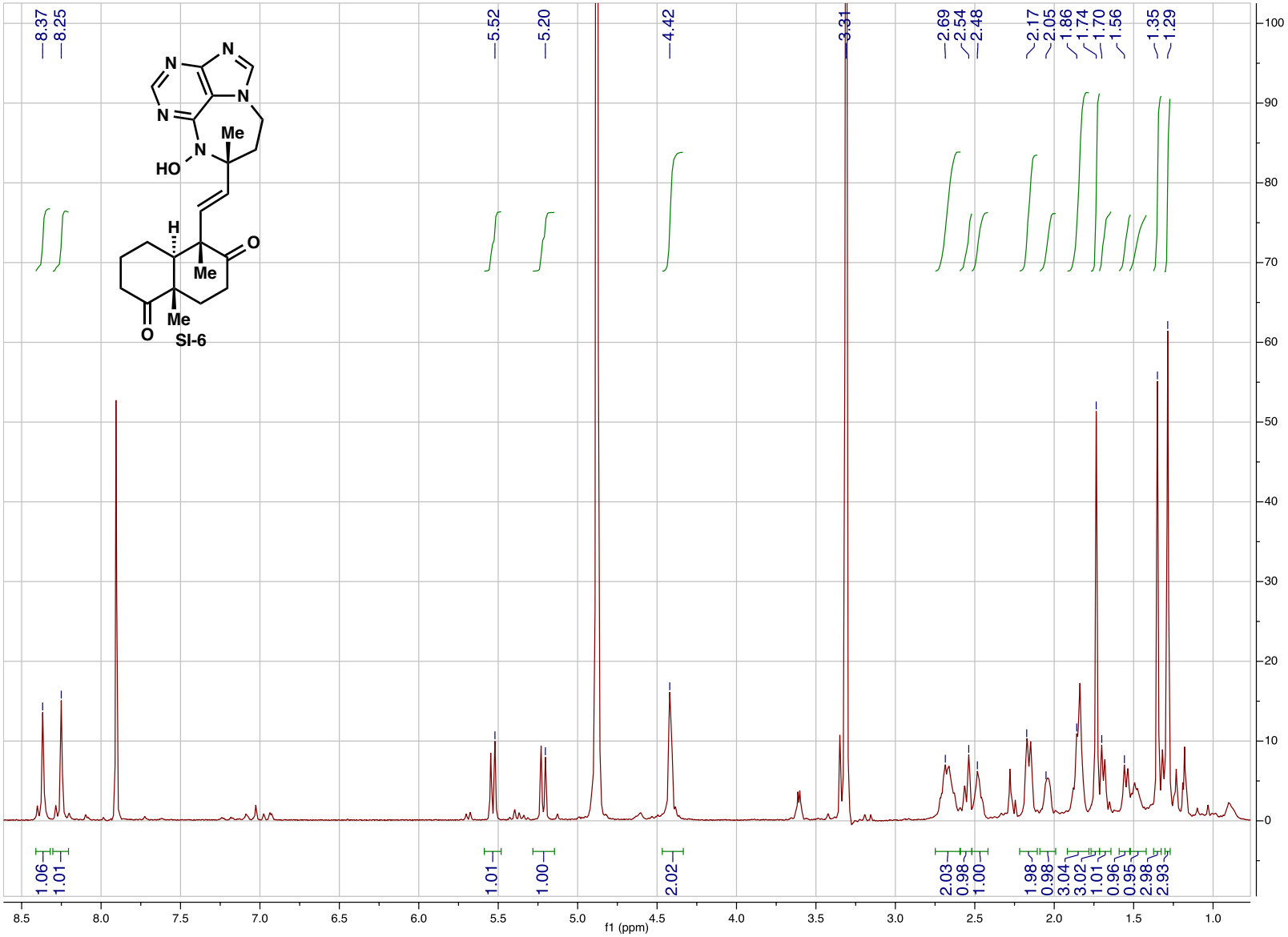

166.42
158.87
153.05
153.01
145.79
141.56
130.96
113.78
111.01
68.67
66.30
65.89
49.05
47.21
44.19
44.10
39.75
31.43
30.20
25.67
23.60
22.62
18.69
17.64
16.48
ent-34
f1 (ppm)

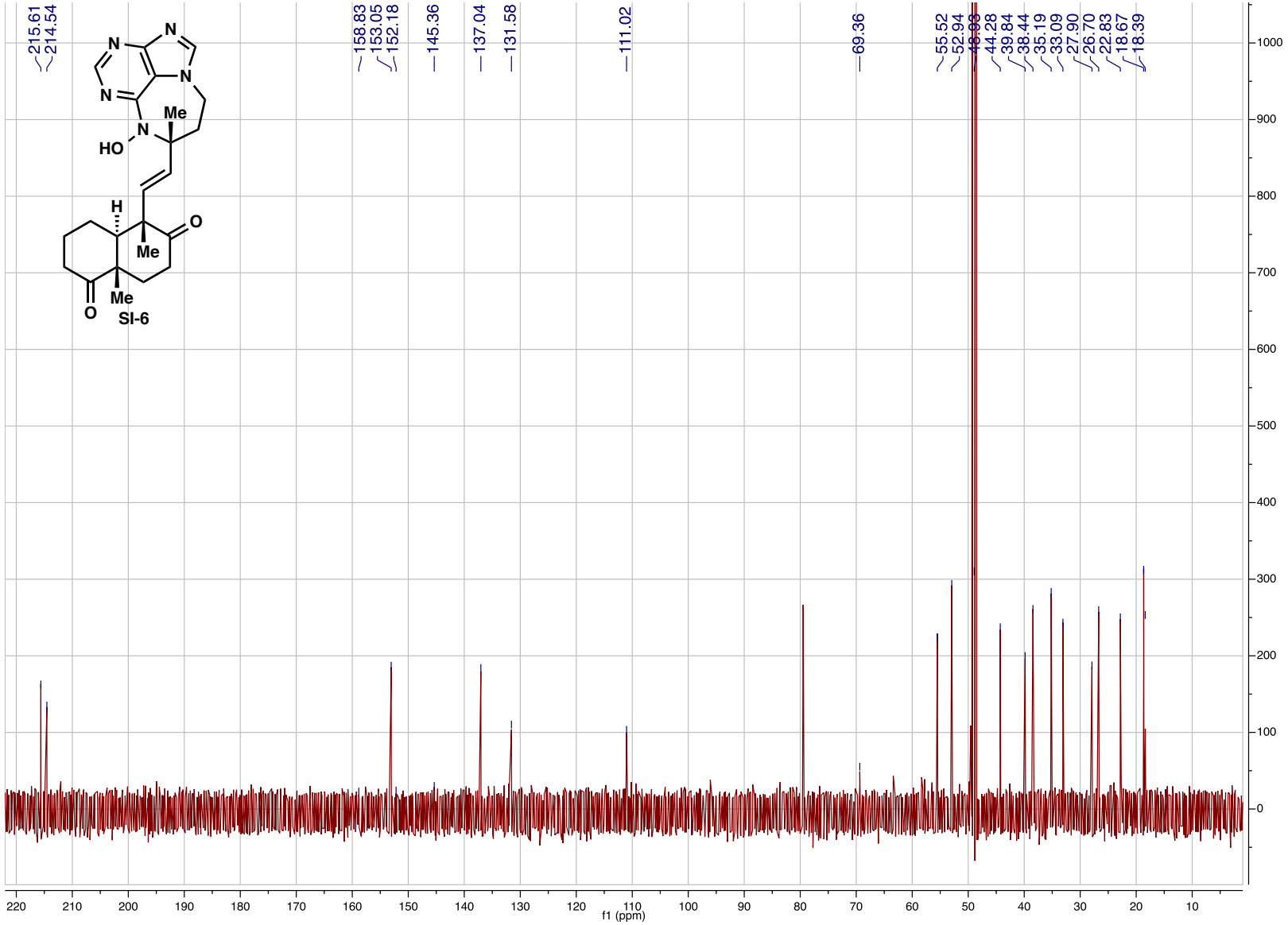

8.37
8.21
5.34
4.53
4.37
3.78
3.16
2.49
1.72
1.17
1.15
Me
HO
N
H
Me
N
OH
O
Me
O
ent-26
1.00
1.07
2.02
1.09
1.10
4.08
1.02
2.01
1.01
3.01
9.09
6.01
f1 (ppm)

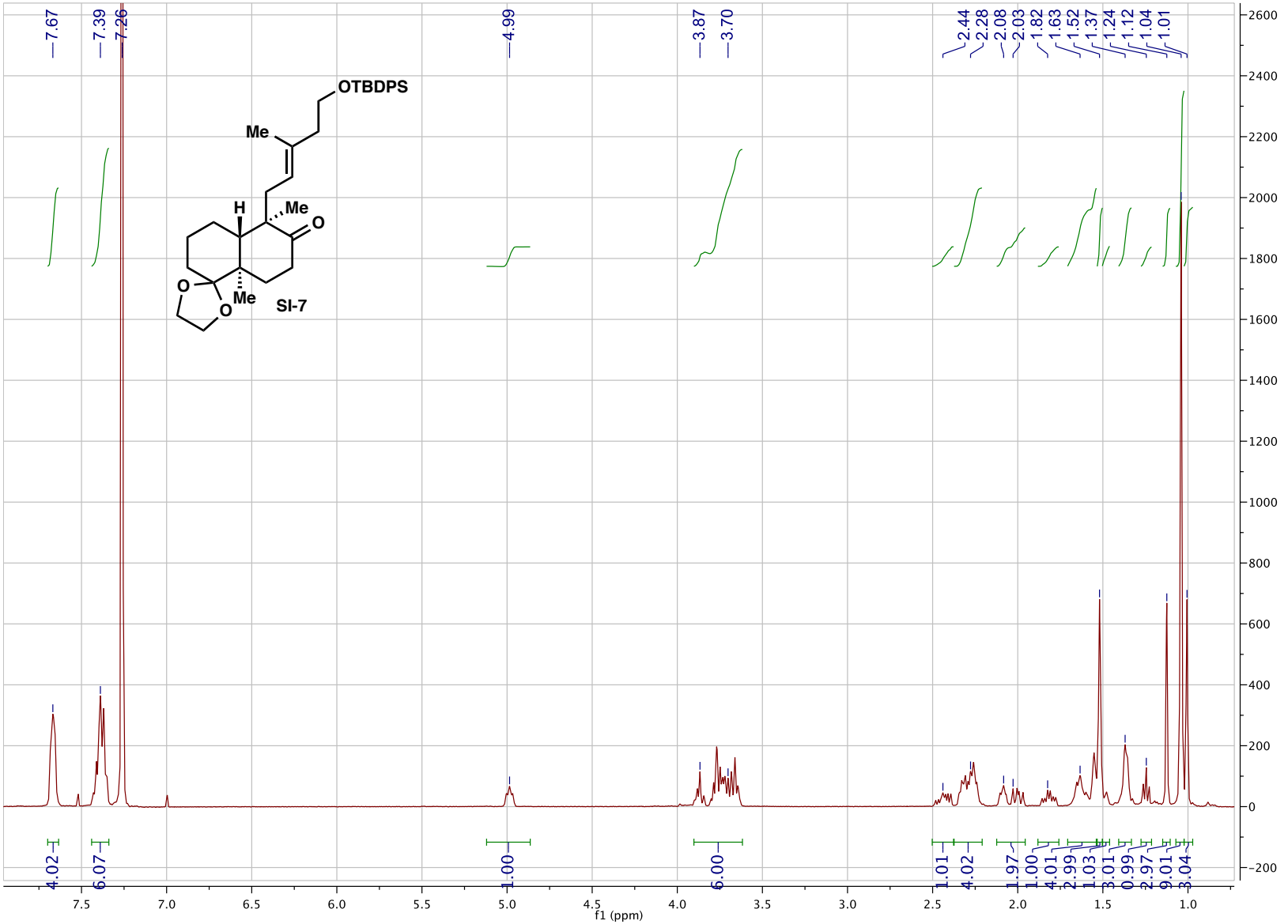

165.78
158.76
153.16
153.13
145.32
141.00
128.53
113.95
110.91
69.20
66.26
65.90
49.85
47.05
44.22
44.06
40.01
31.49
29.85
27.24
23.70
22.60
19.54
17.58
16.53
ent-26
f1 (ppm)

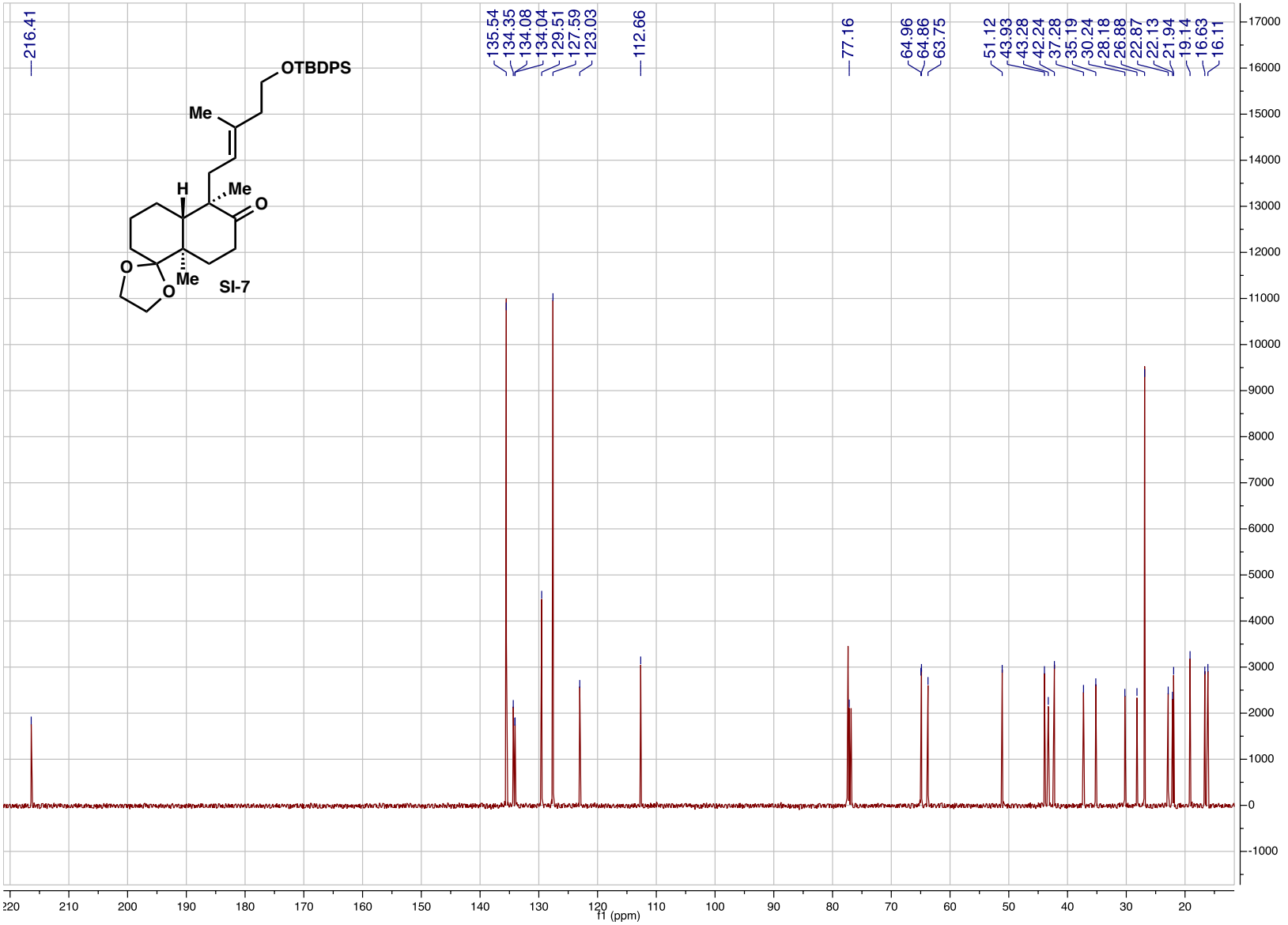

8.40
8.28
5.68
5.39
4.46
4.40
3.31
2.72
2.62
2.51
2.33
2.10
1.89
1.73
1.50
1.32
1.23
1.05
0.99
Me
HO
N
H
O
Me
Me
O
ent-35
1.01
0.99
1.00
1.02
2.04
0.96
2.02
0.94
1.08
0.94
2.98
4.06
0.91
2.97
3.05
0.96
1.05
f1 (ppm)

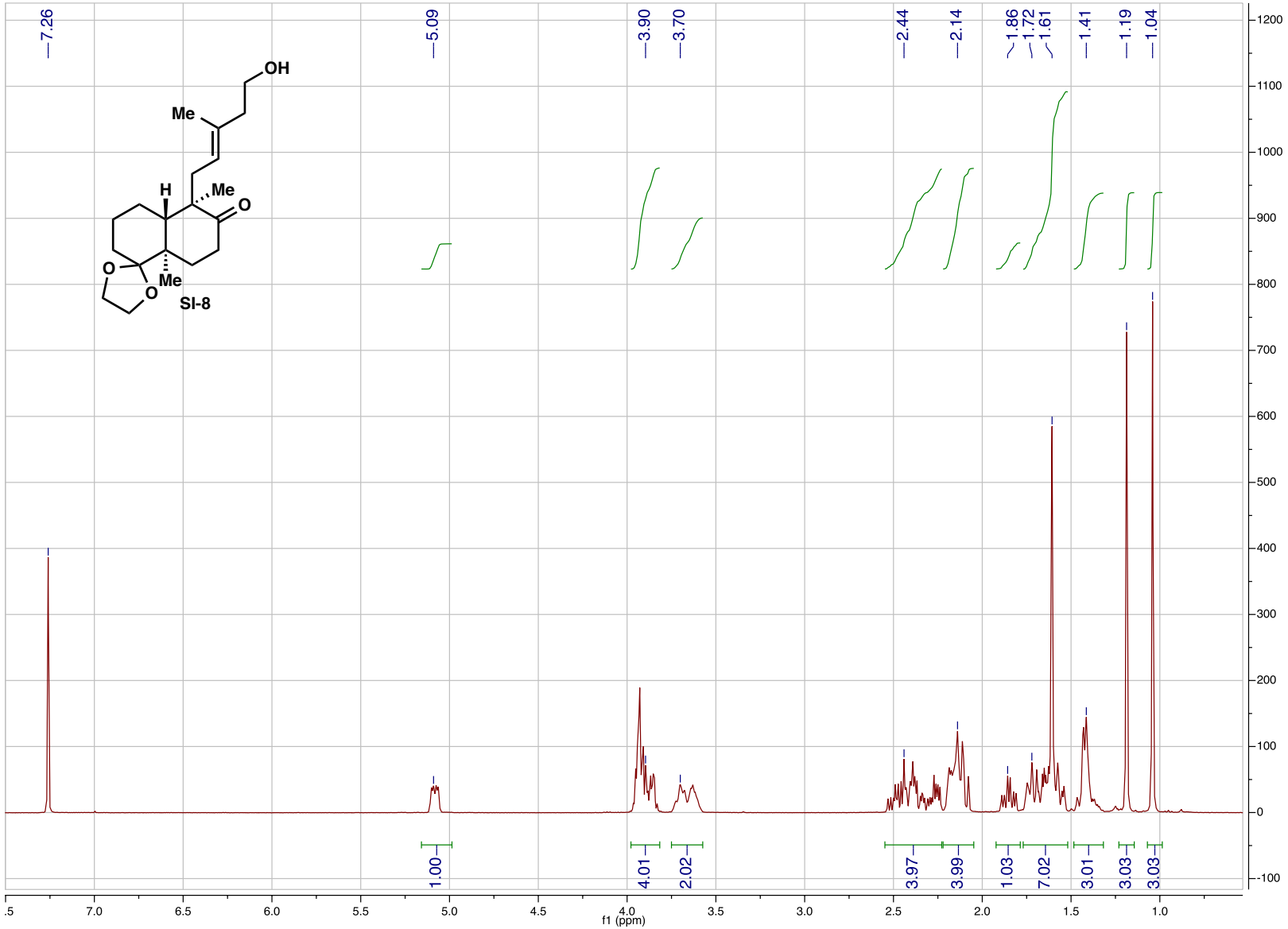

215.42
214.89
158.87
153.18
152.71
145.72
137.17
132.64
111.23
68.83
55.48
53.12
49.57
49.00
44.32
40.03
38.37
35.35
33.20
26.64
22.68
18.66
18.29
N
N
N
N
N
Me
HO
H
O
Me
Me
O
ent-35
f1 (ppm)

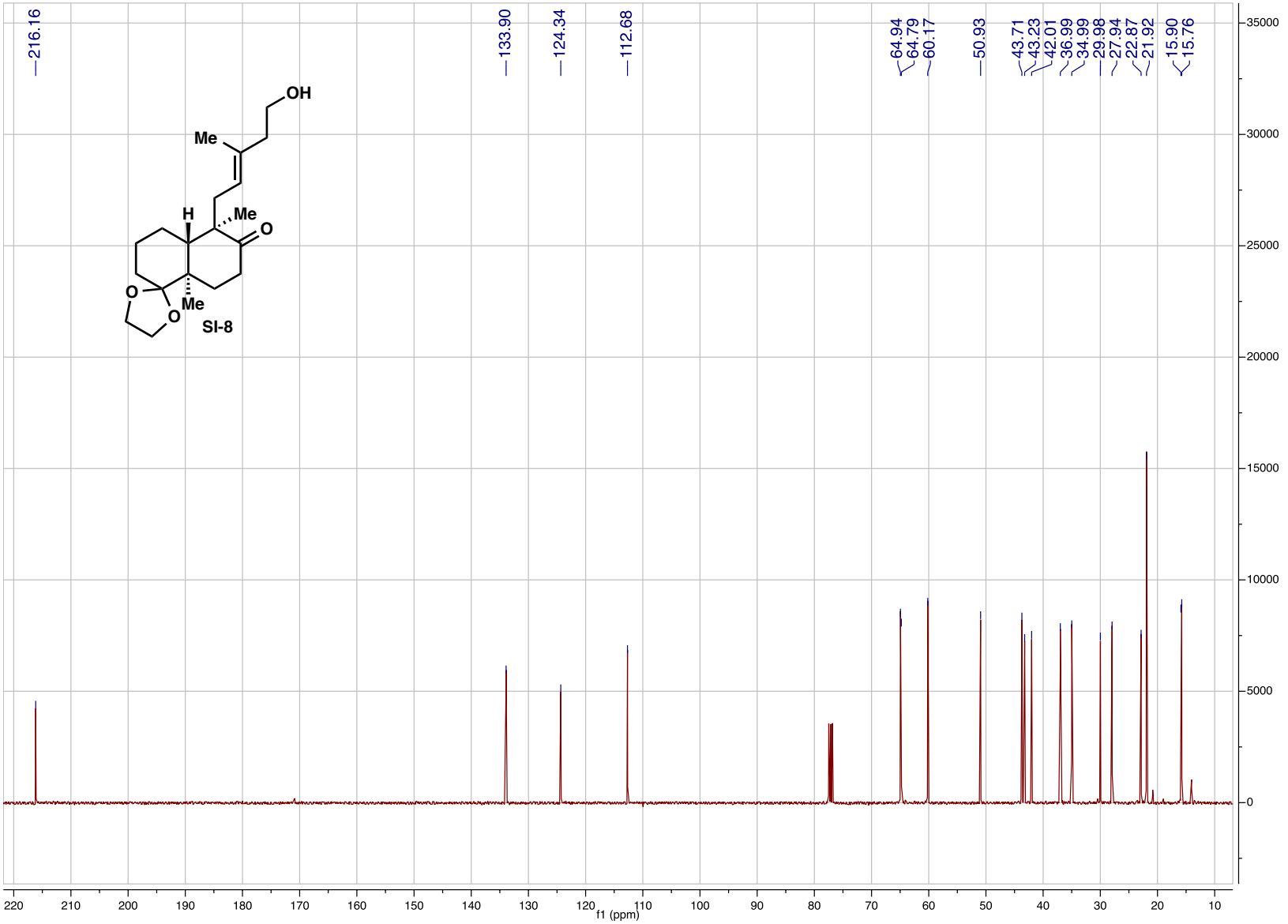

8.37
8.25
5.52
5.20
4.42
3.31
2.69
2.54
2.48
2.17
2.05
1.86
1.74
1.70
1.56
1.35
1.29
Me
HO
N
H
O
Me
Me
O
SI-6
1.06
1.01
1.01
1.00
2.02
2.03
0.98
1.00
1.98
0.98
3.04
3.02
1.01
0.96
0.95
2.98
2.93
f1 (ppm)

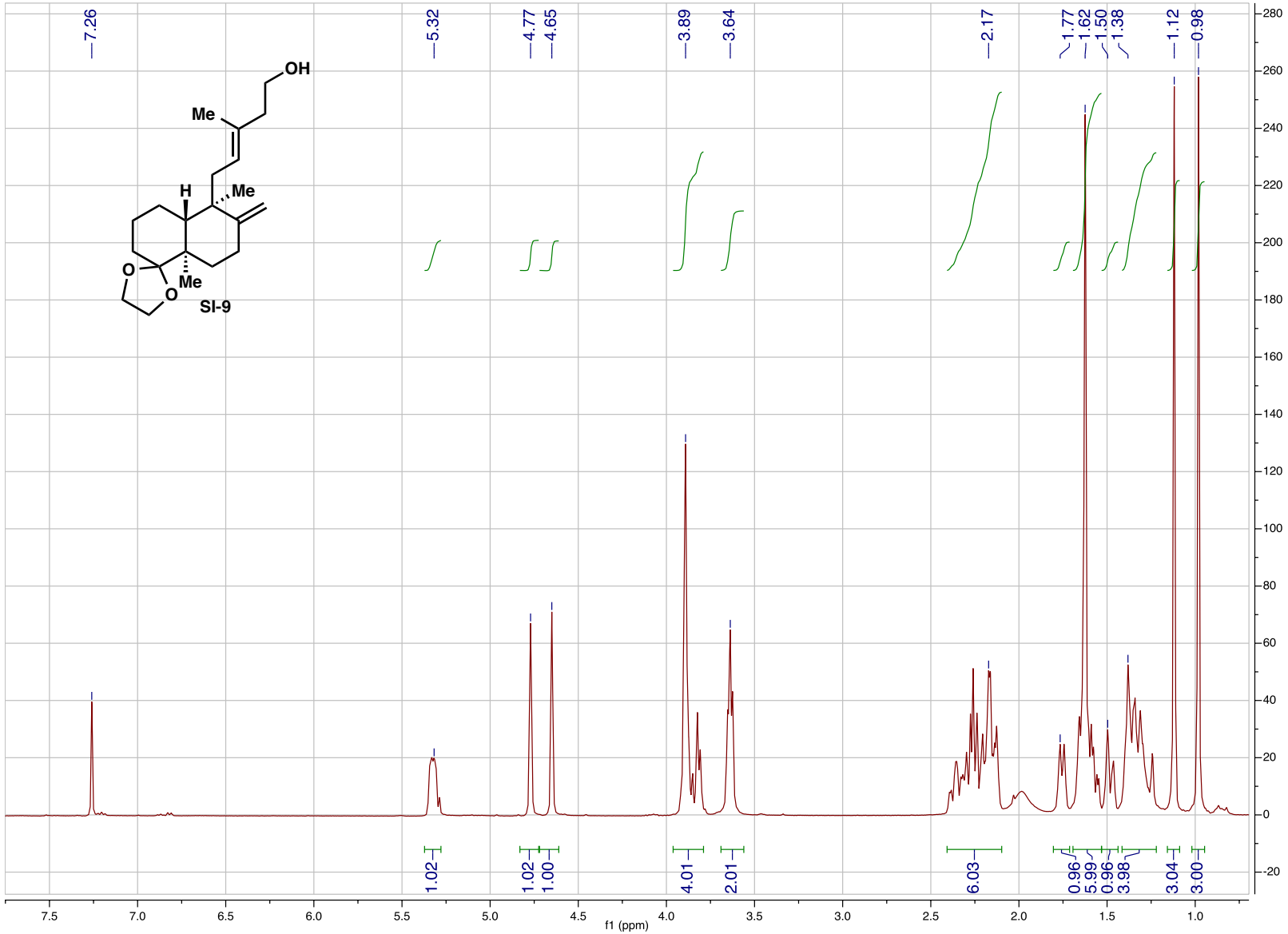

215.61
214.54
158.83
153.05
152.18
145.36
137.04
131.58
111.02
69.36
55.52
52.94
48.93
44.28
39.84
38.44
35.19
33.09
27.90
26.70
22.83
18.67
18.39
HO
Me
Me
Me
H
O
O
SI-6
f1 (ppm)

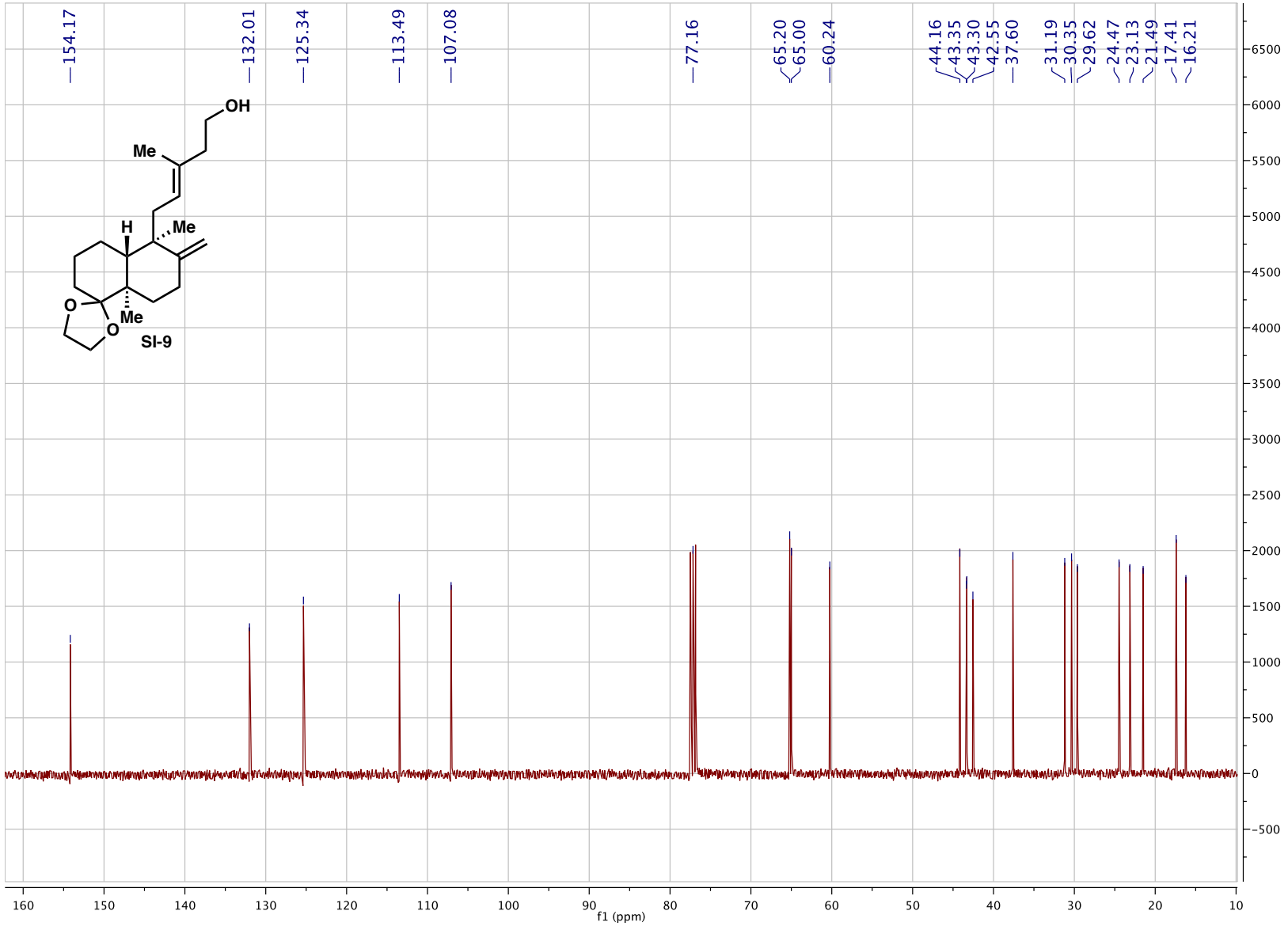

7.67
7.39
7.26
4.99
3.87
3.70
2.44
2.28
2.08
2.03
1.82
1.63
1.52
1.37
1.24
1.12
1.04
1.01
OTBDPS
Me
H
Me
O
O
O
Me
SI-7
4.02
6.07
1.00
6.00
1.01
4.02
1.97
1.00
4.01
2.99
1.03
3.01
0.99
2.97
9.01
3.04
f1 (ppm)

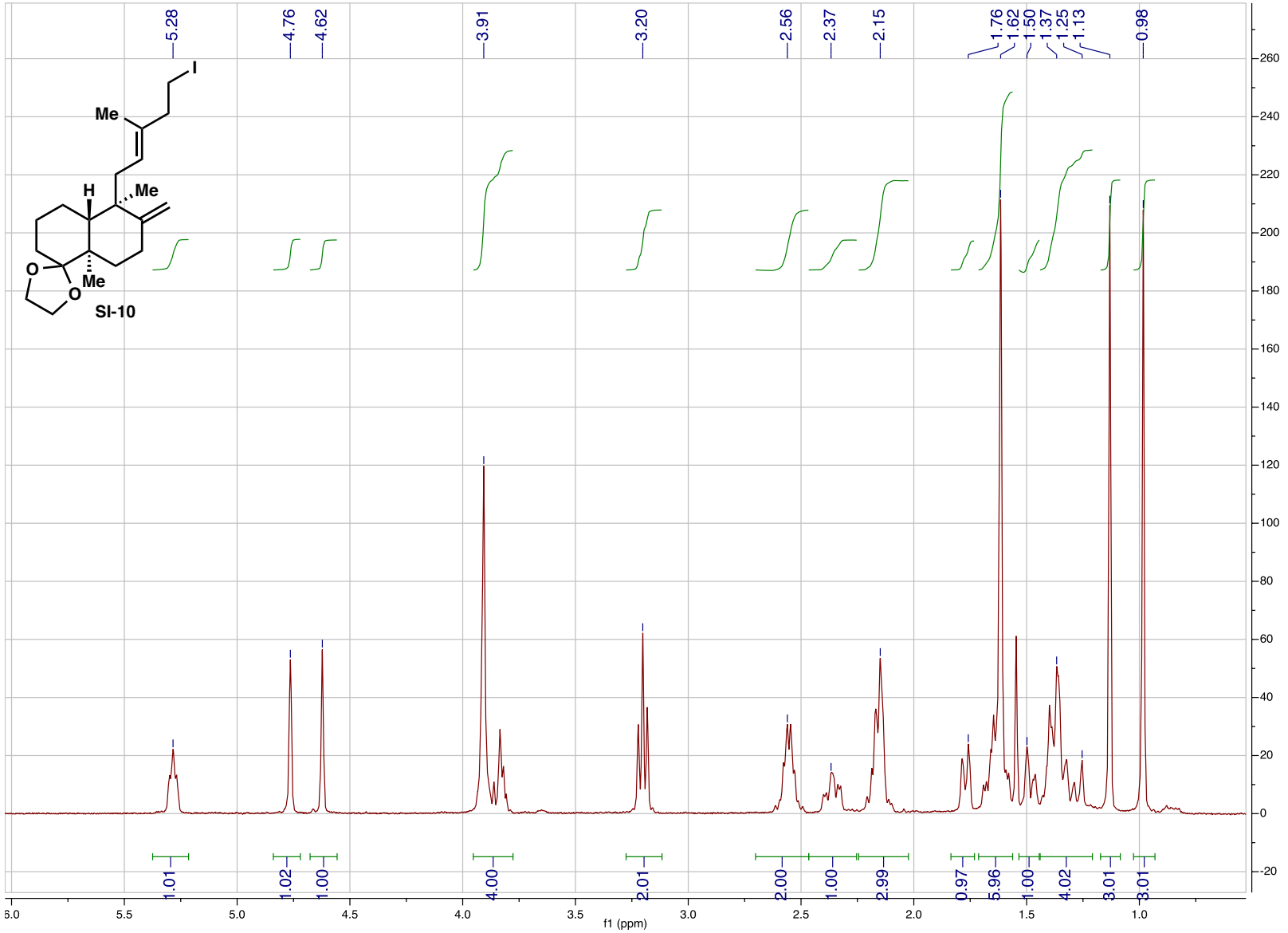

216.41
135.54
134.35
134.08
134.04
129.51
127.59
123.03
112.66
77.16
64.96
64.86
63.75
51.12
43.93
43.28
42.24
37.28
35.19
30.24
28.18
26.88
22.87
22.13
21.94
19.14
16.63
16.11
OTBDPS
Me
H
Me
O
O
Me
O
SI-7
f1 (ppm)

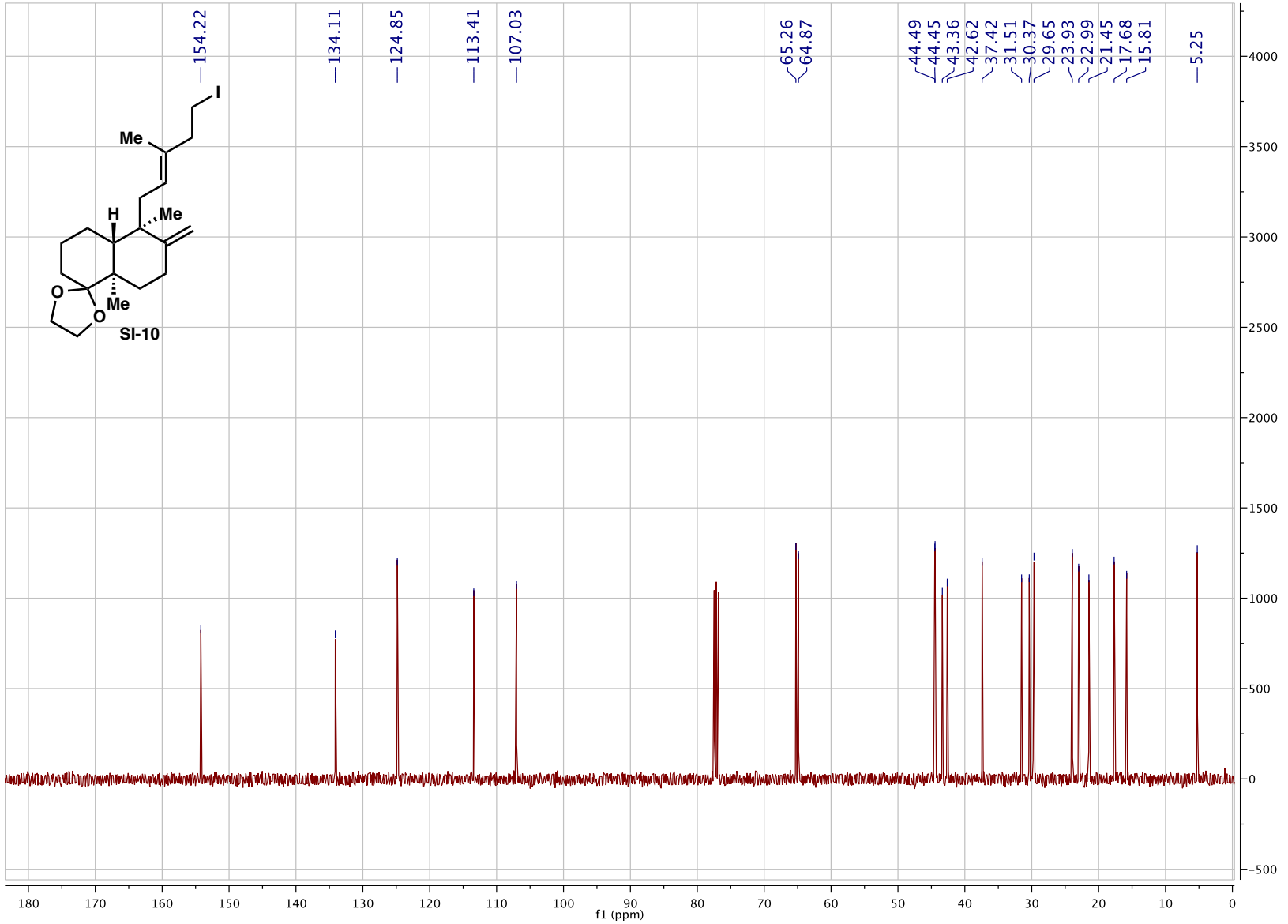

7.26
5.09
3.90
3.70
2.44
2.14
1.86
1.72
1.61
1.41
1.19
1.04
OH
Me
H
Me
O
O
Me
O
SI-8
1.00
4.01
2.02
3.97
3.99
1.03
7.02
3.01
3.03
3.03
f1 (ppm)

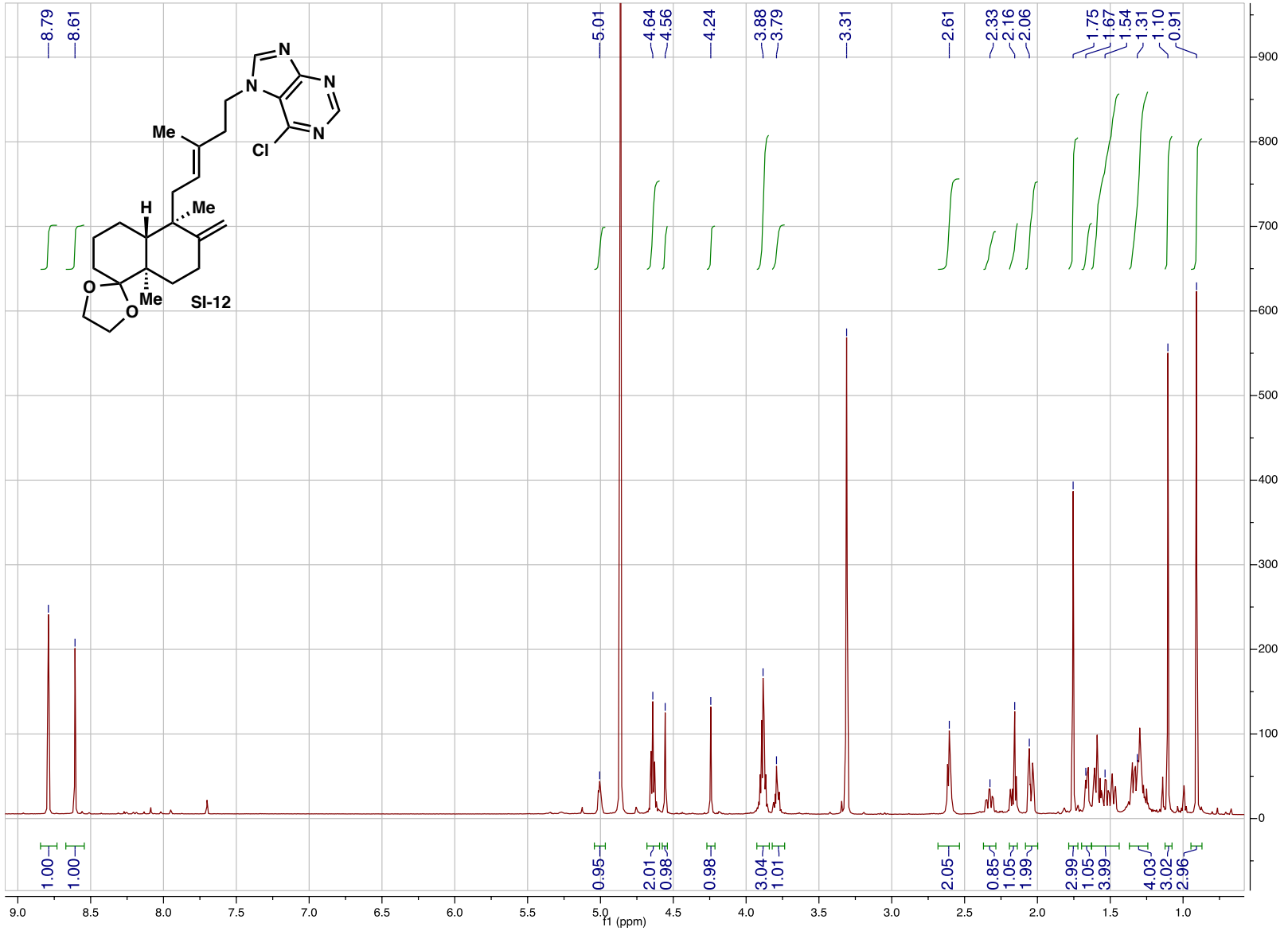

216.16
133.90
124.34
112.68
64.94
64.79
60.17
50.93
43.71
43.23
42.01
36.99
34.99
29.98
27.94
22.87
21.92
15.90
15.76
OH
Me
H
Me
O
O
O
Me
SI-8
35000
30000
25000
20000
15000
10000
5000
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

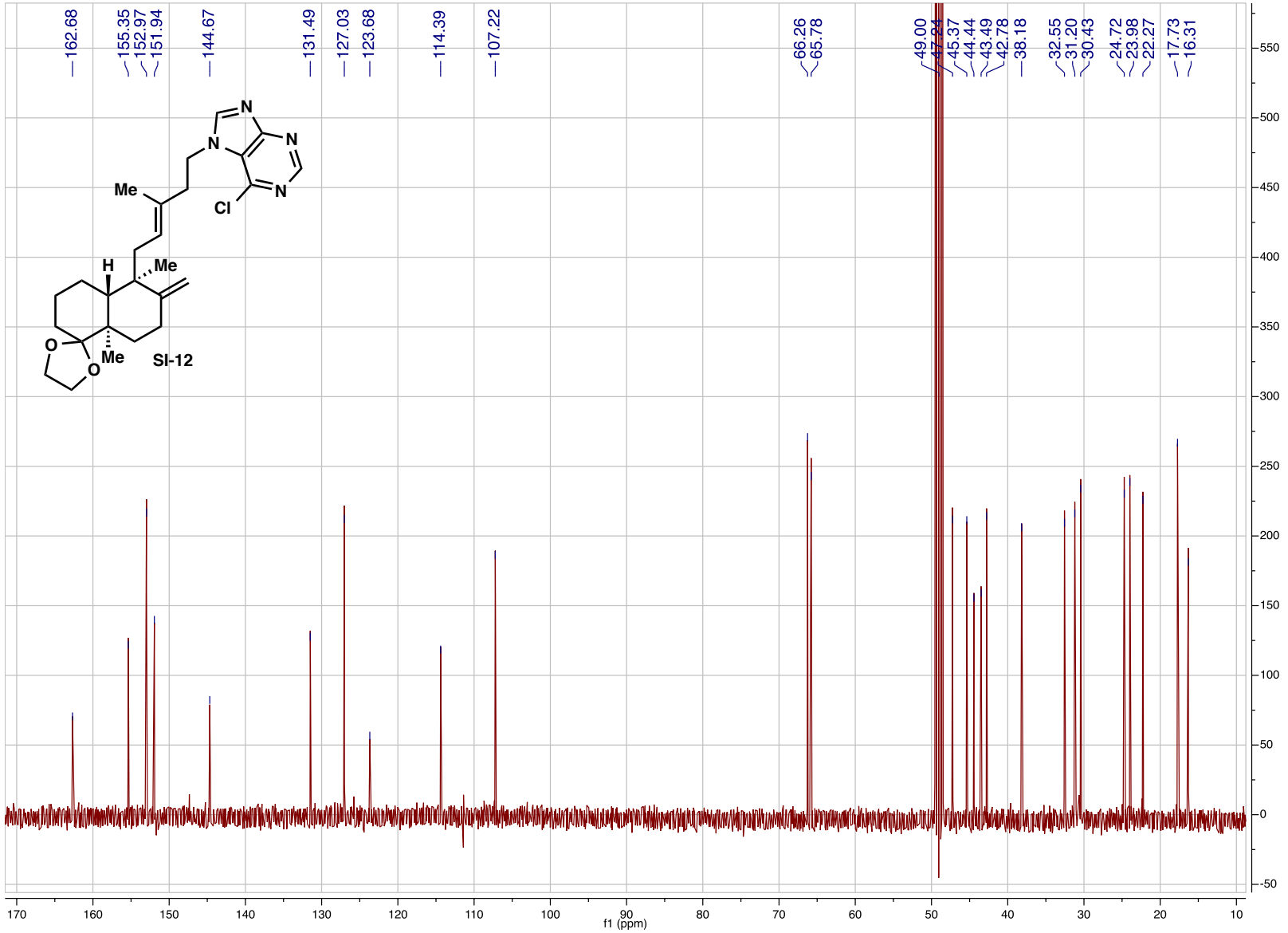

7.26
5.32
4.77
4.65
3.89
3.64
2.17
1.77
1.62
1.50
1.38
1.12
0.98
OH
Me
H
Me
O
O
Me
SI-9
1.02
1.02
1.00
4.01
2.01
6.03
0.96
5.99
0.96
3.98
3.04
3.00
f1 (ppm)

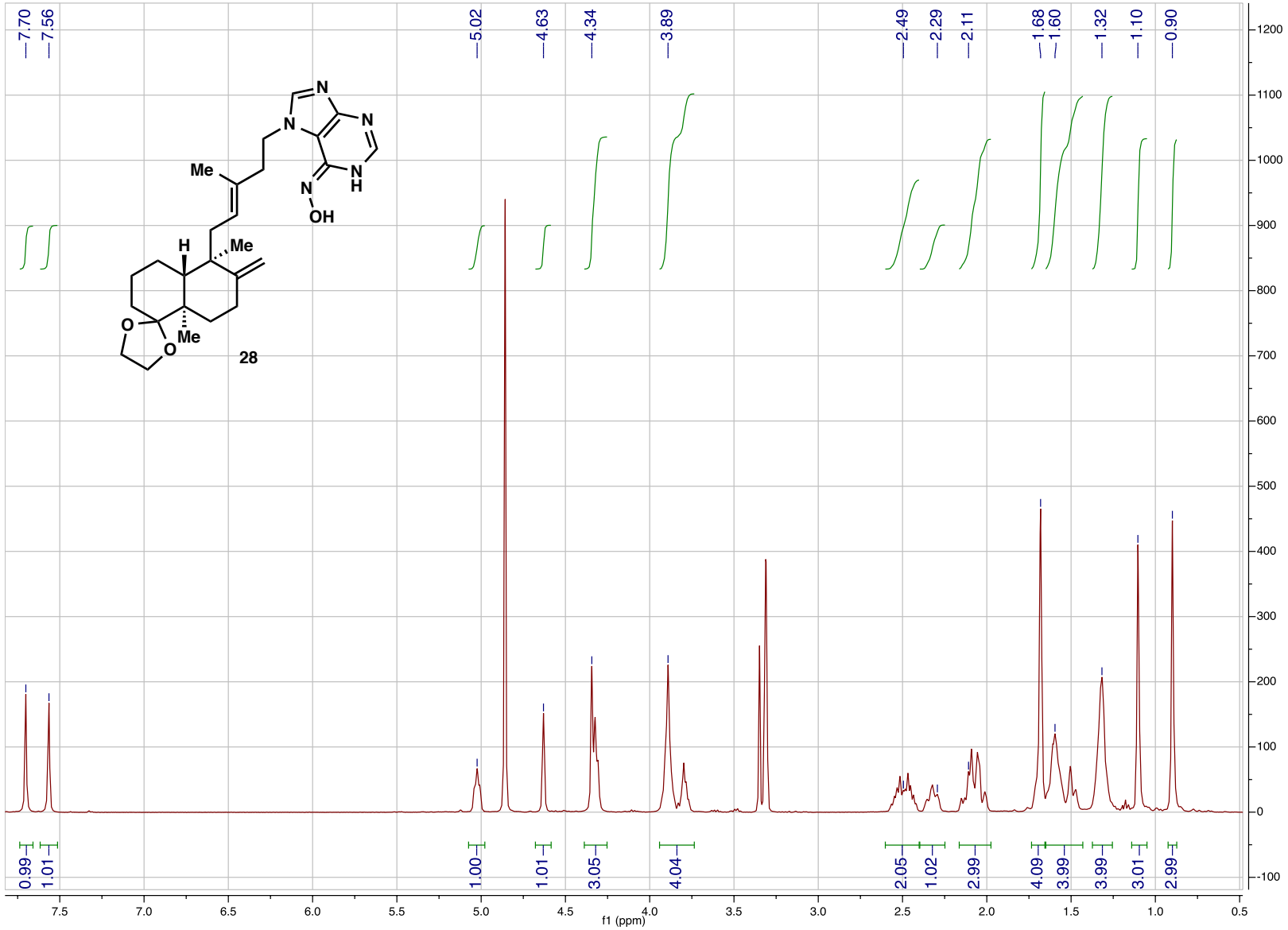

154.17
132.01
125.34
113.49
107.08
77.16
65.20
65.00
60.24
44.16
43.35
43.30
42.55
37.60
31.19
30.35
29.62
24.47
23.13
21.49
17.41
16.21
OH
Me
H
Me
O
Me
O
SI-9
f1 (ppm)

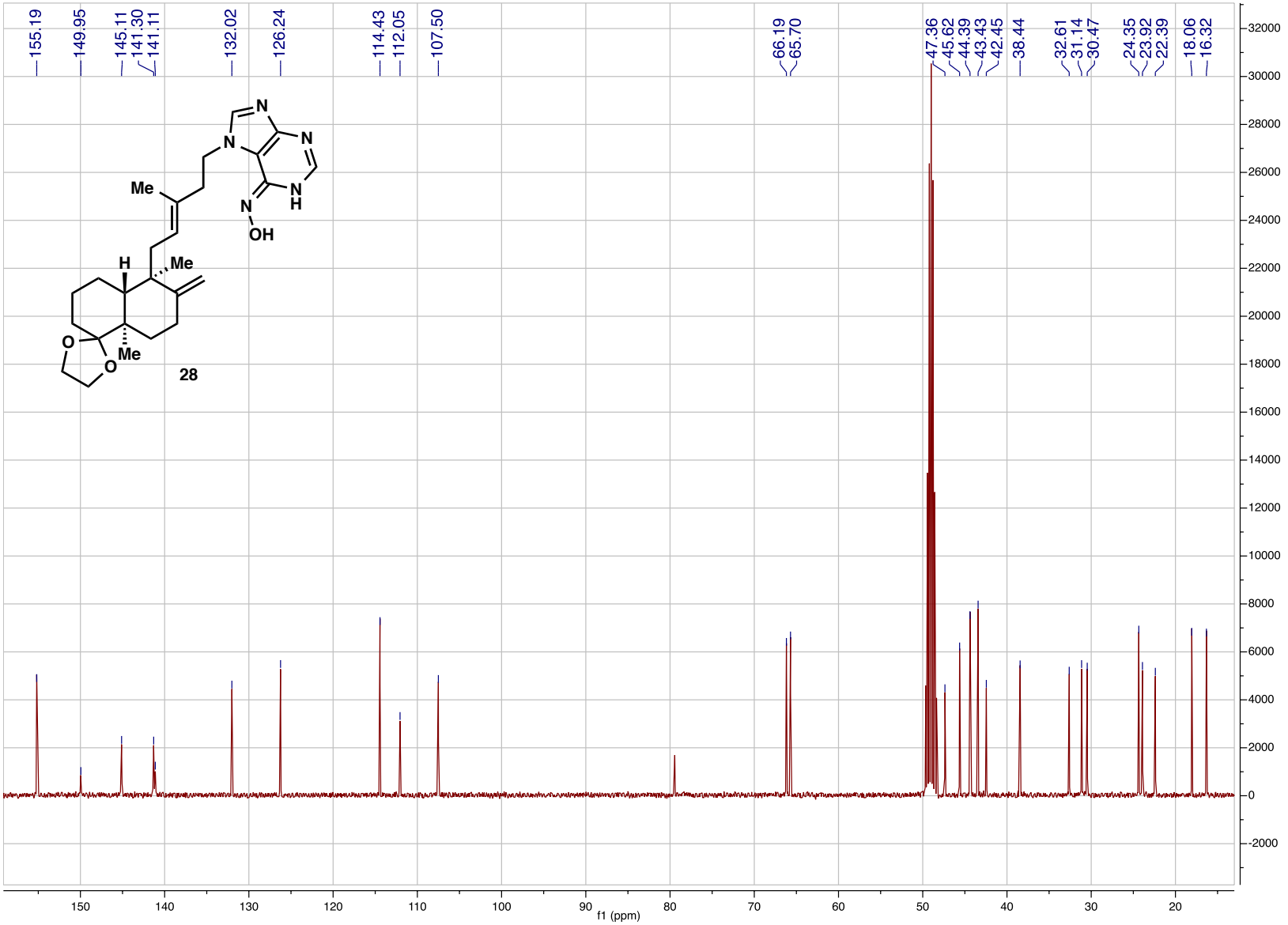

5.28
4.76
4.62
3.91
3.20
2.56
2.37
2.15
1.76
1.62
1.50
1.37
1.25
1.13
0.98
I
Me
H
Me
O
O
Me
SI-10
1.01
1.02
1.00
4.00
2.01
2.00
1.00
2.99
0.97
5.96
1.00
4.02
3.01
3.01
f1 (ppm)

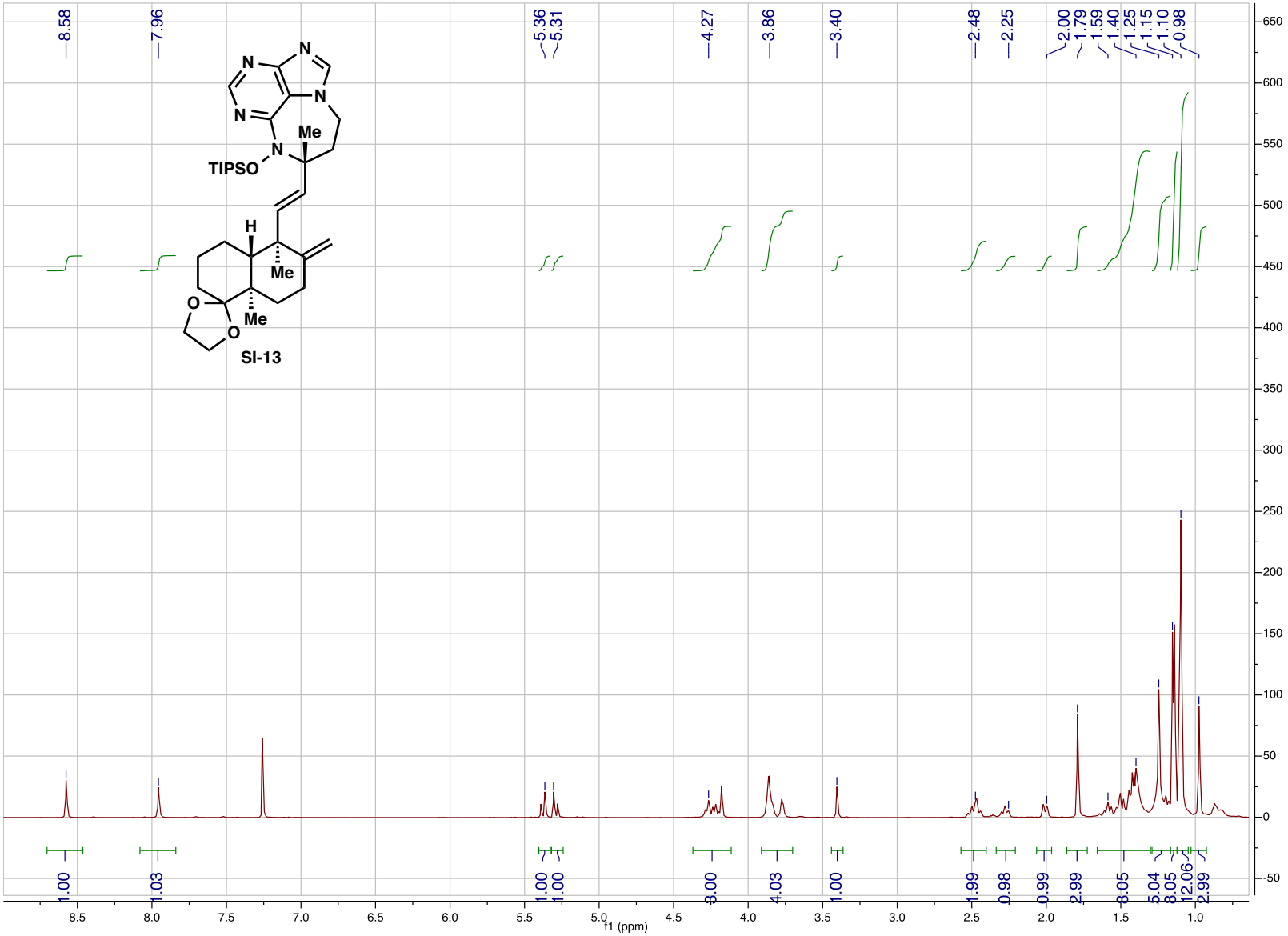

154.22
134.11
124.85
113.41
107.03
65.26
64.87
44.49
44.45
43.36
42.62
37.42
31.51
30.37
29.65
23.93
22.99
21.45
17.68
15.81
5.25
I
Me
H
Me
O
Me
O
SI-10
f1 (ppm)

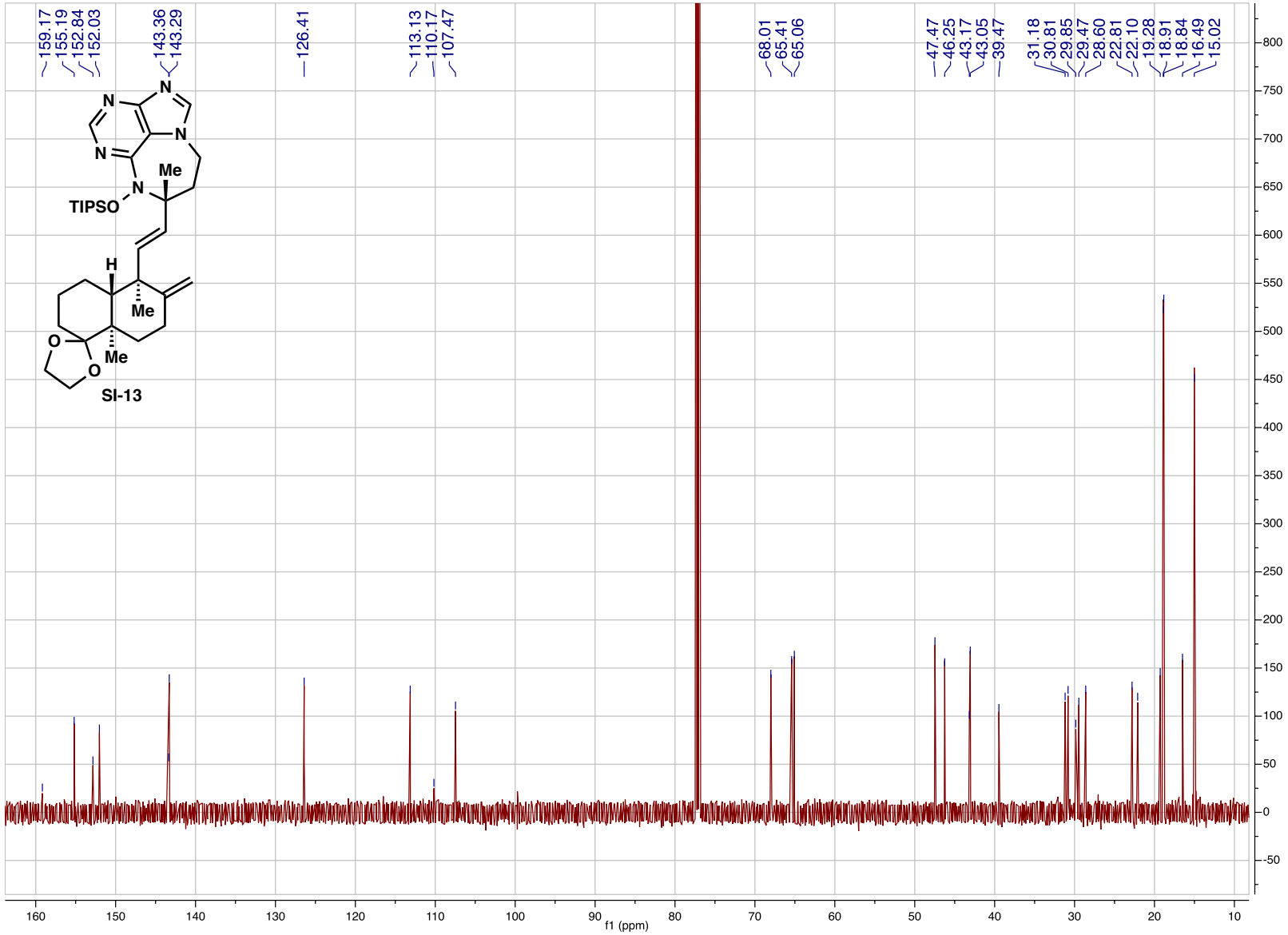

8.79
8.61
5.01
4.64
4.56
4.24
3.88
3.79
3.31
2.61
2.33
2.16
2.06
1.75
1.67
1.54
1.31
1.10
0.91
Me
Cl
H
Me
O
Me
O
SI-12
1.00
1.00
0.95
2.01
0.98
0.98
3.04
1.01
2.05
0.85
1.05
1.99
2.99
1.05
3.99
4.03
3.02
2.96
f1 (ppm)

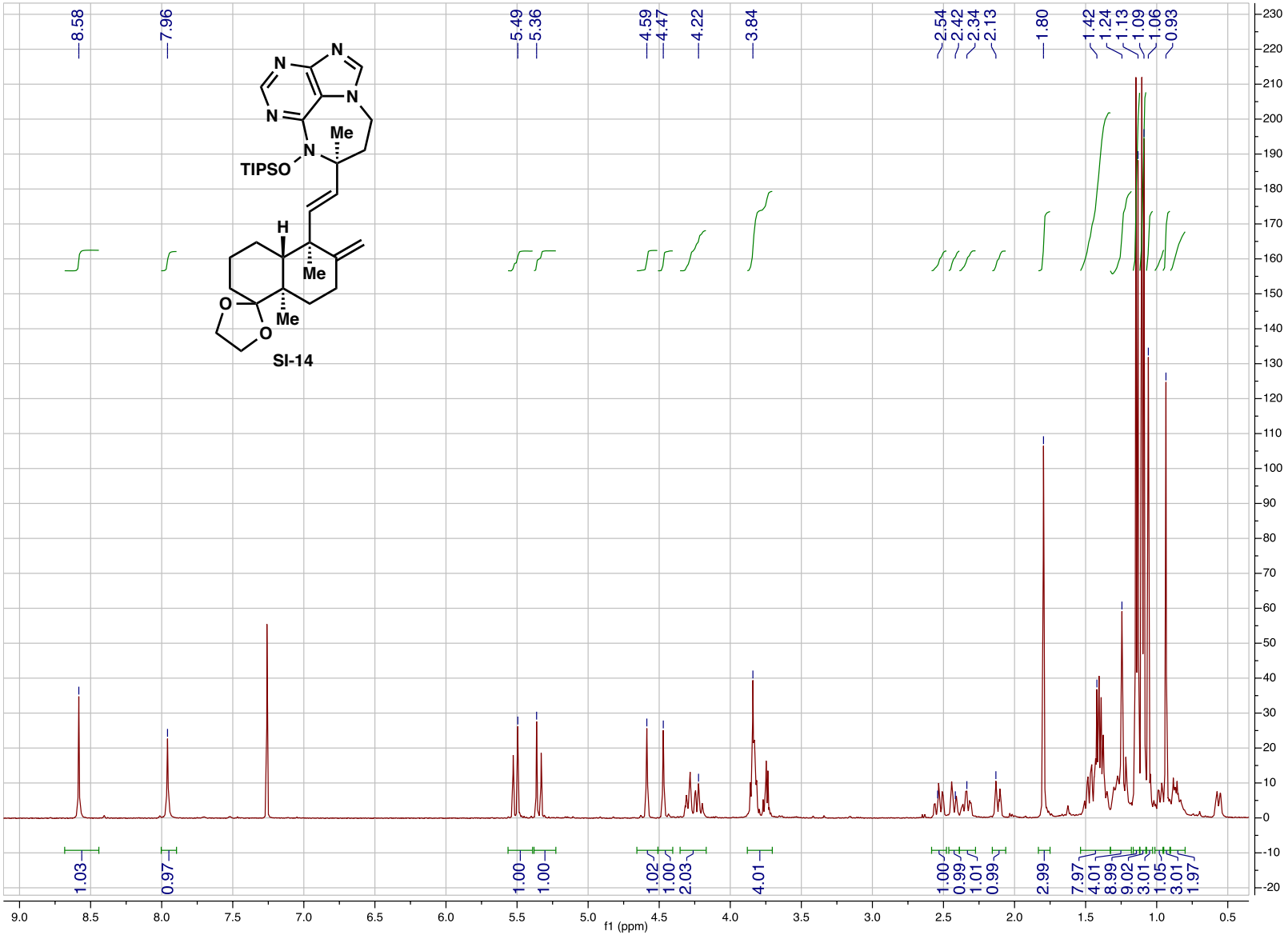

162.68
155.35
152.97
151.94
144.67
131.49
127.03
123.68
114.39
107.22
66.26
65.78
49.00
47.24
45.37
44.44
43.49
42.78
38.18
32.55
31.20
30.43
24.72
23.98
22.27
17.73
16.31
N
N
N
N
Cl
Me
H
Me
Me
O
O
SI-12
f1 (ppm)

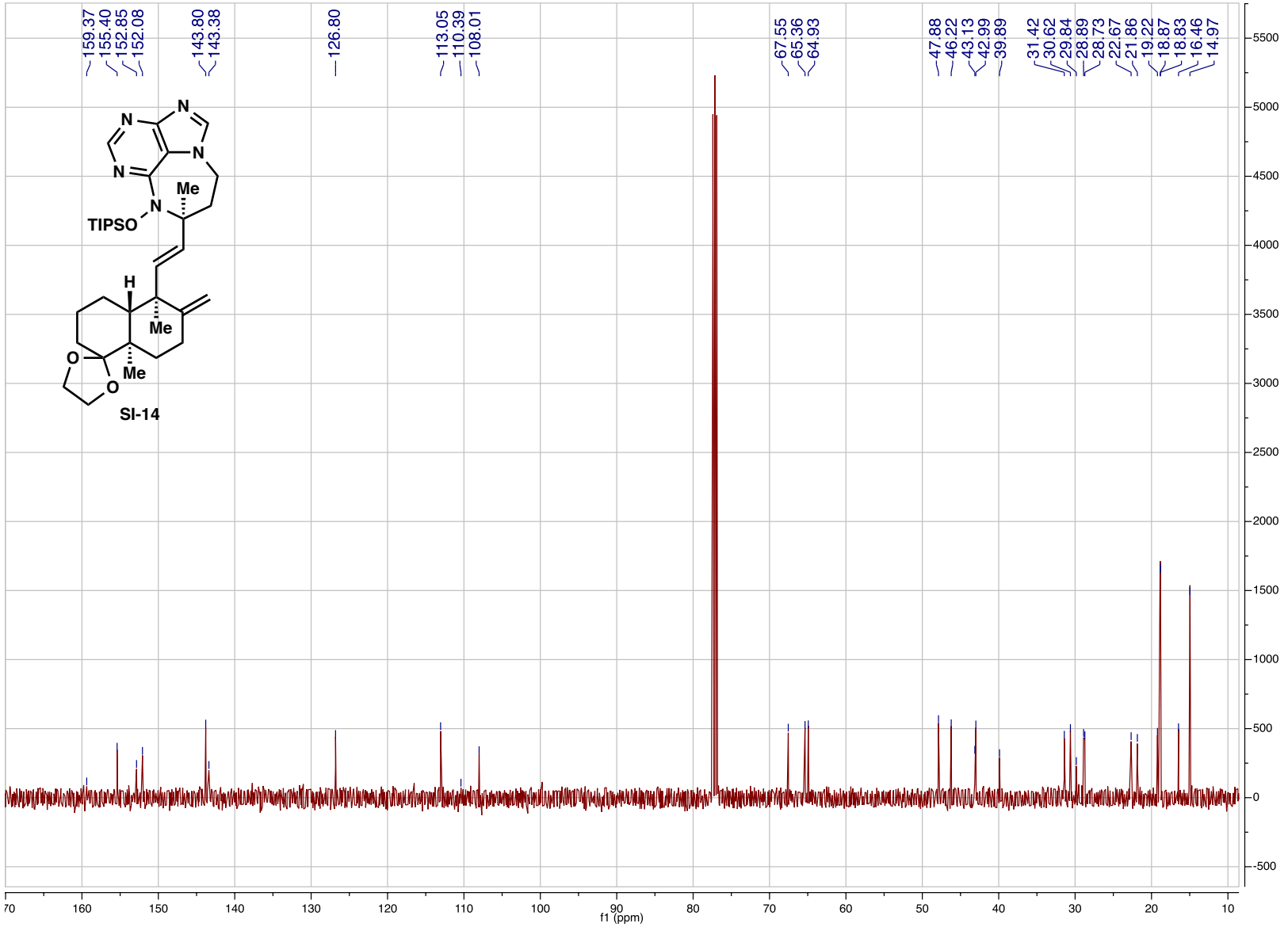

7.70
7.56
5.02
4.63
4.34
3.89
2.49
2.29
2.11
1.68
1.60
1.32
1.10
0.90
Me
H
Me
Me
O
O
N
N
N
N
H
N
OH
28
0.99
1.01
1.00
1.01
3.05
4.04
2.05
1.02
2.99
4.09
3.99
3.99
3.01
2.99
f1 (ppm)

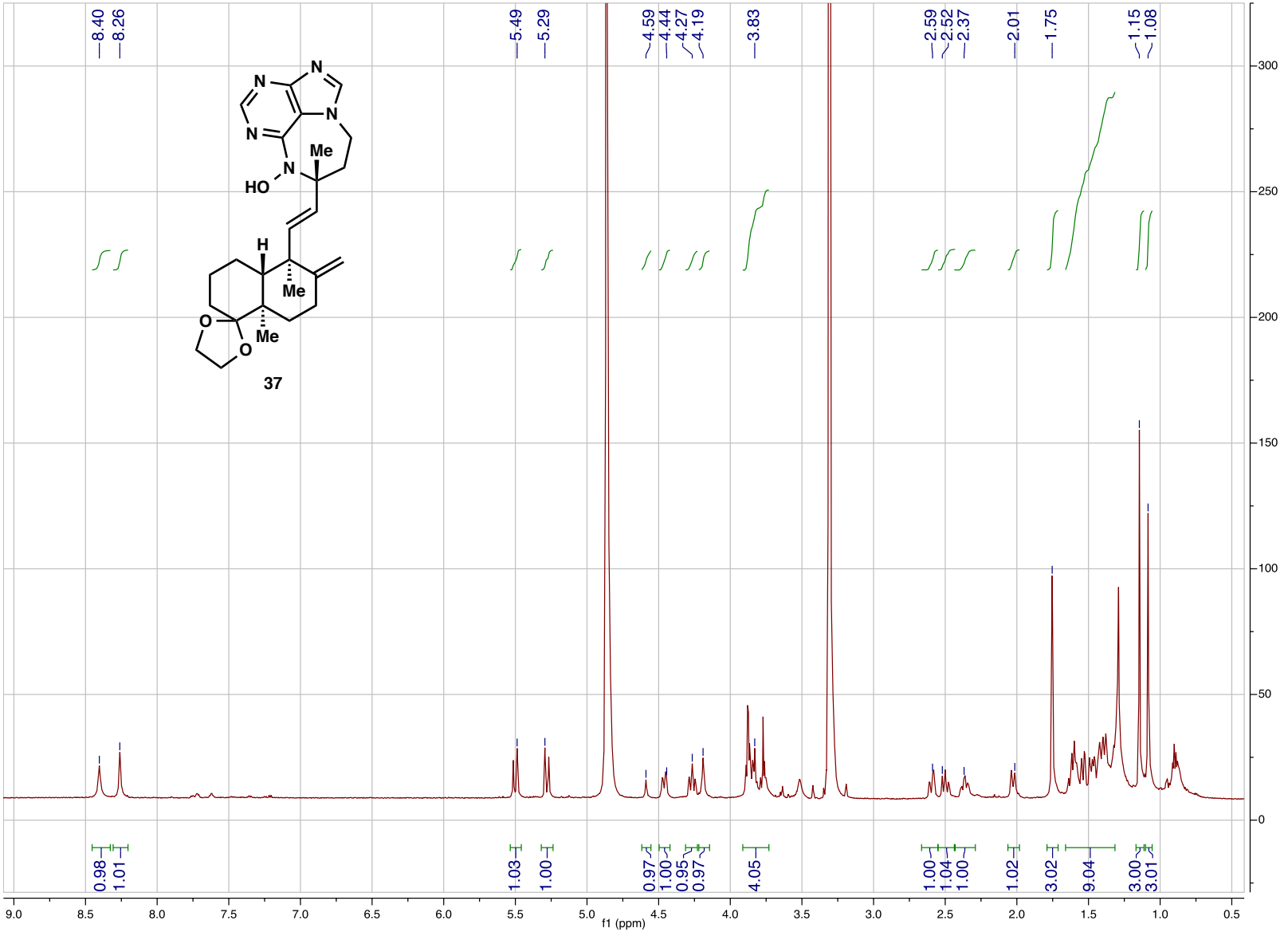

155.19
149.95
145.11
141.30
141.11
132.02
126.24
114.43
112.05
107.50
66.19
65.70
47.36
45.62
44.39
43.43
42.45
38.44
32.61
31.14
30.47
24.35
23.92
22.39
18.06
16.32
N
N
N
N
H
N
OH
Me
H
Me
O
O
Me
28
f1 (ppm)

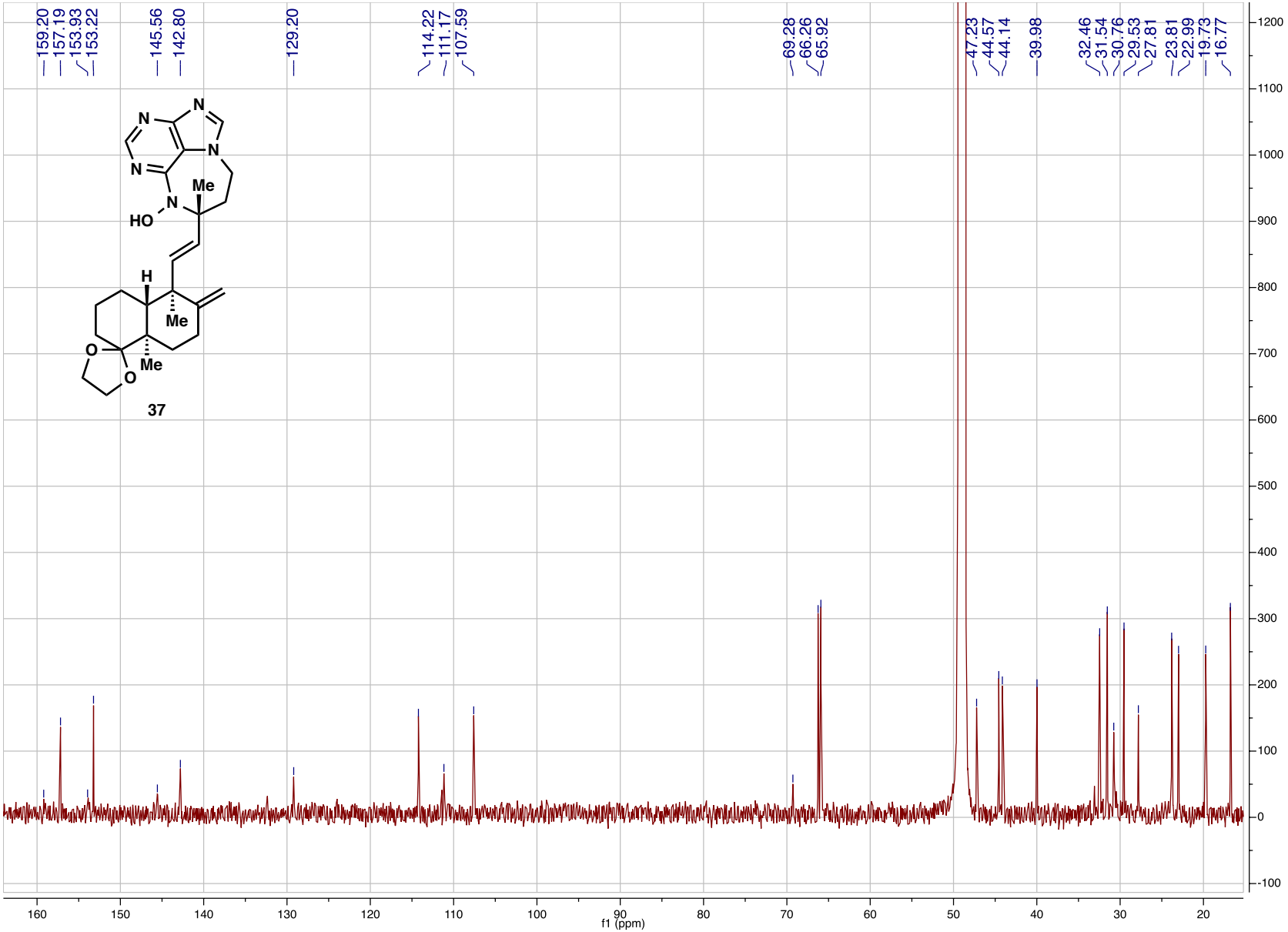

8.58
7.96
5.36
5.31
4.27
3.86
3.40
2.48
2.25
2.00
1.79
1.59
1.40
1.25
1.15
1.10
0.98
TIPSO
Me
H
Me
O
Me
O
SI-13
1.00
1.03
1.00
1.00
3.00
4.03
1.00
1.99
0.98
0.99
2.99
8.05
5.04
8.05
12.06
2.99
f1 (ppm)

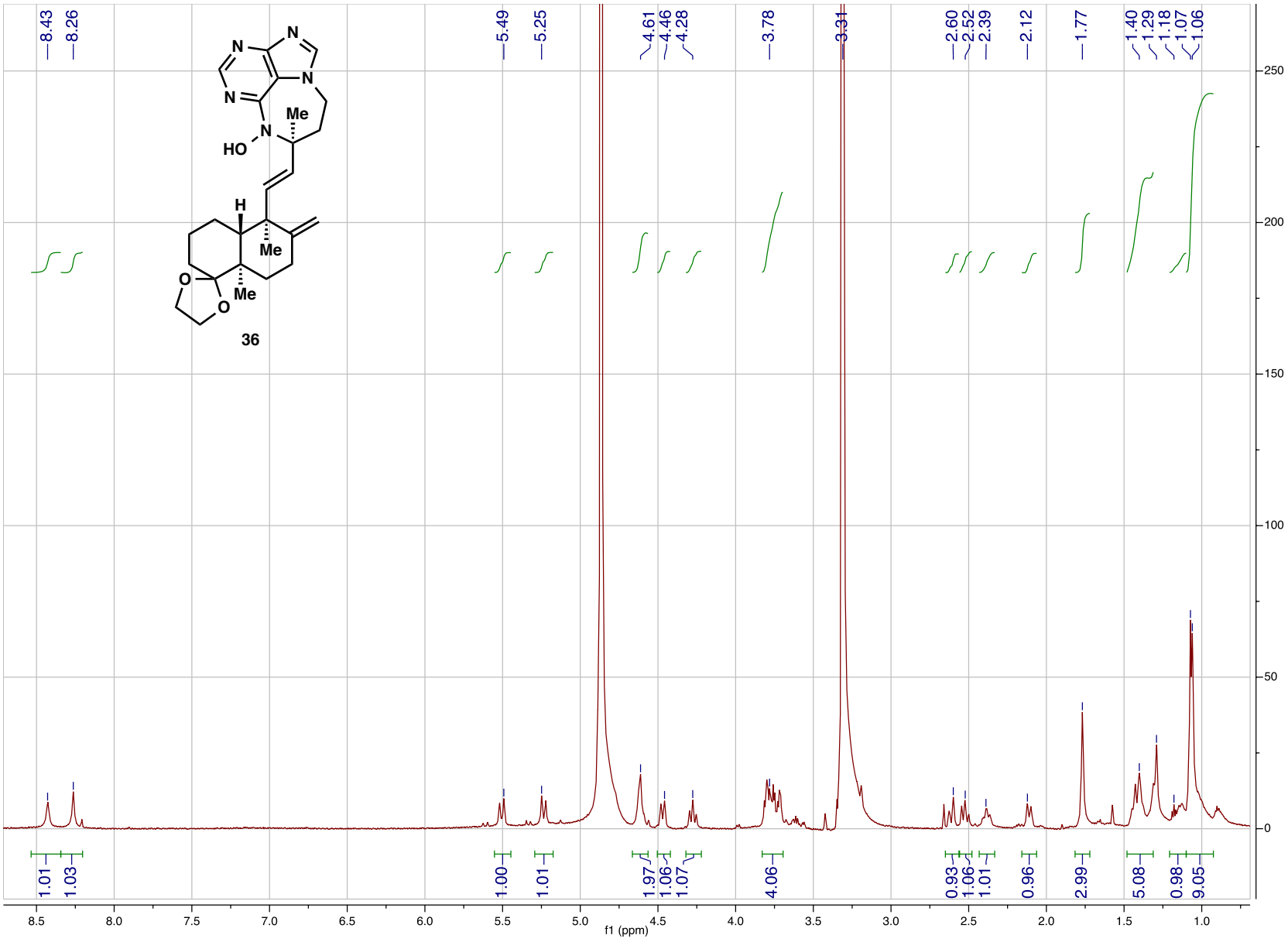

159.17
155.19
152.84
152.03
143.36
143.29
126.41
113.13
110.17
107.47
68.01
65.41
65.06
47.47
46.25
43.17
43.05
39.47
31.18
30.81
29.85
29.47
28.60
22.81
22.10
19.28
18.91
18.84
16.49
15.02
TIPSO
Me
H
Me
O
Me
O
SI-13
f1 (ppm)

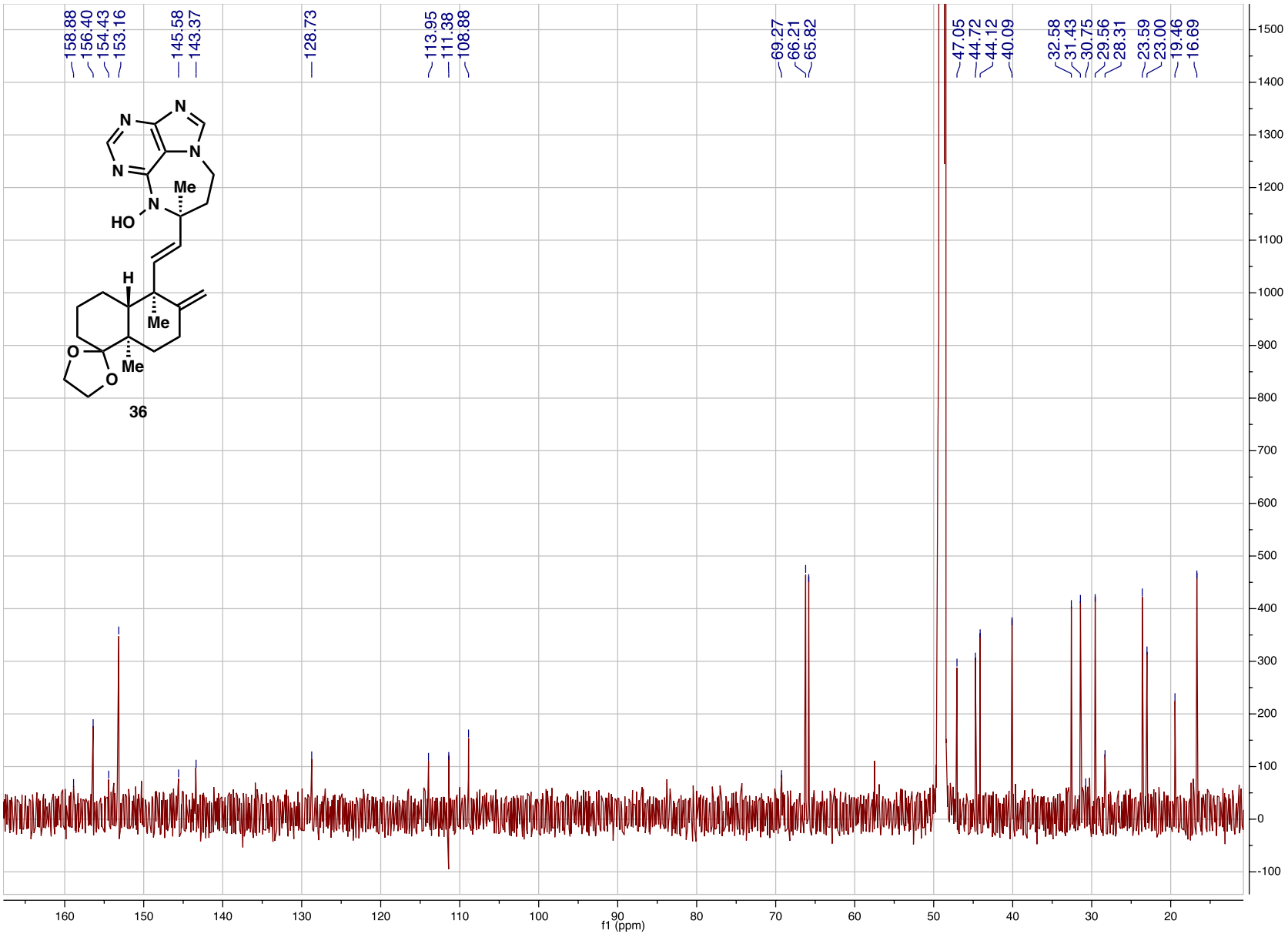

8.58
7.96
5.49
5.36
4.59
4.47
4.22
3.84
2.54
2.42
2.34
2.13
1.80
1.42
1.24
1.13
1.09
1.06
0.93
TIPSO
Me
H
Me
Me
O
O
SI-14
1.03
0.97
1.00
1.00
1.02
1.00
2.03
4.01
1.00
0.99
1.01
0.99
2.99
7.97
4.01
8.99
9.02
3.01
1.05
3.01
1.97
f1 (ppm)

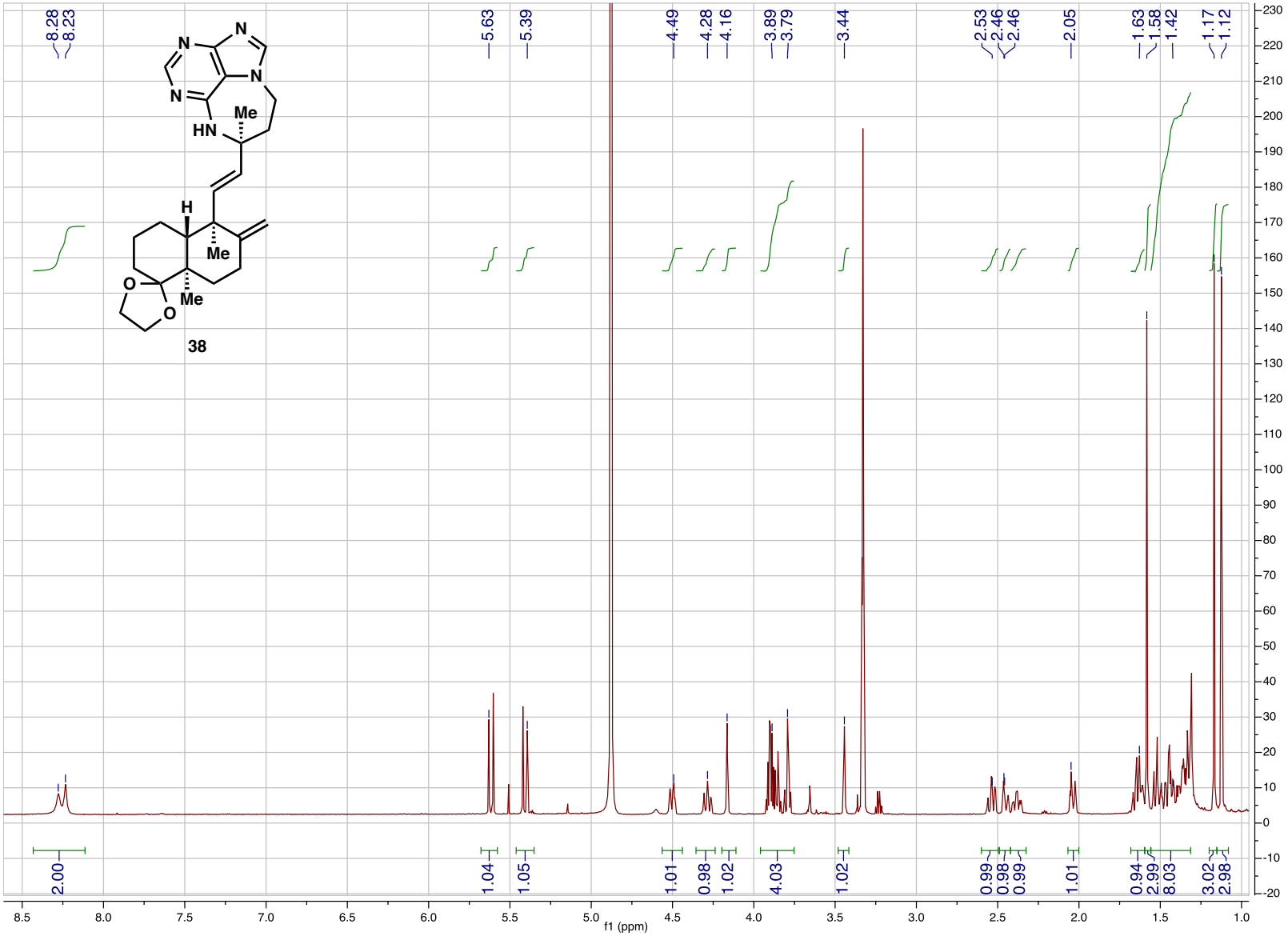

159.37
155.40
152.85
152.08
143.80
143.38
126.80
113.05
110.39
108.01
67.55
65.36
64.93
47.88
46.22
43.13
42.99
39.89
31.42
30.62
29.84
28.89
28.73
22.67
21.86
19.22
18.87
18.83
16.46
14.97
TIPSO
Me
H
Me
Me
O
O
SI-14
f1 (ppm)

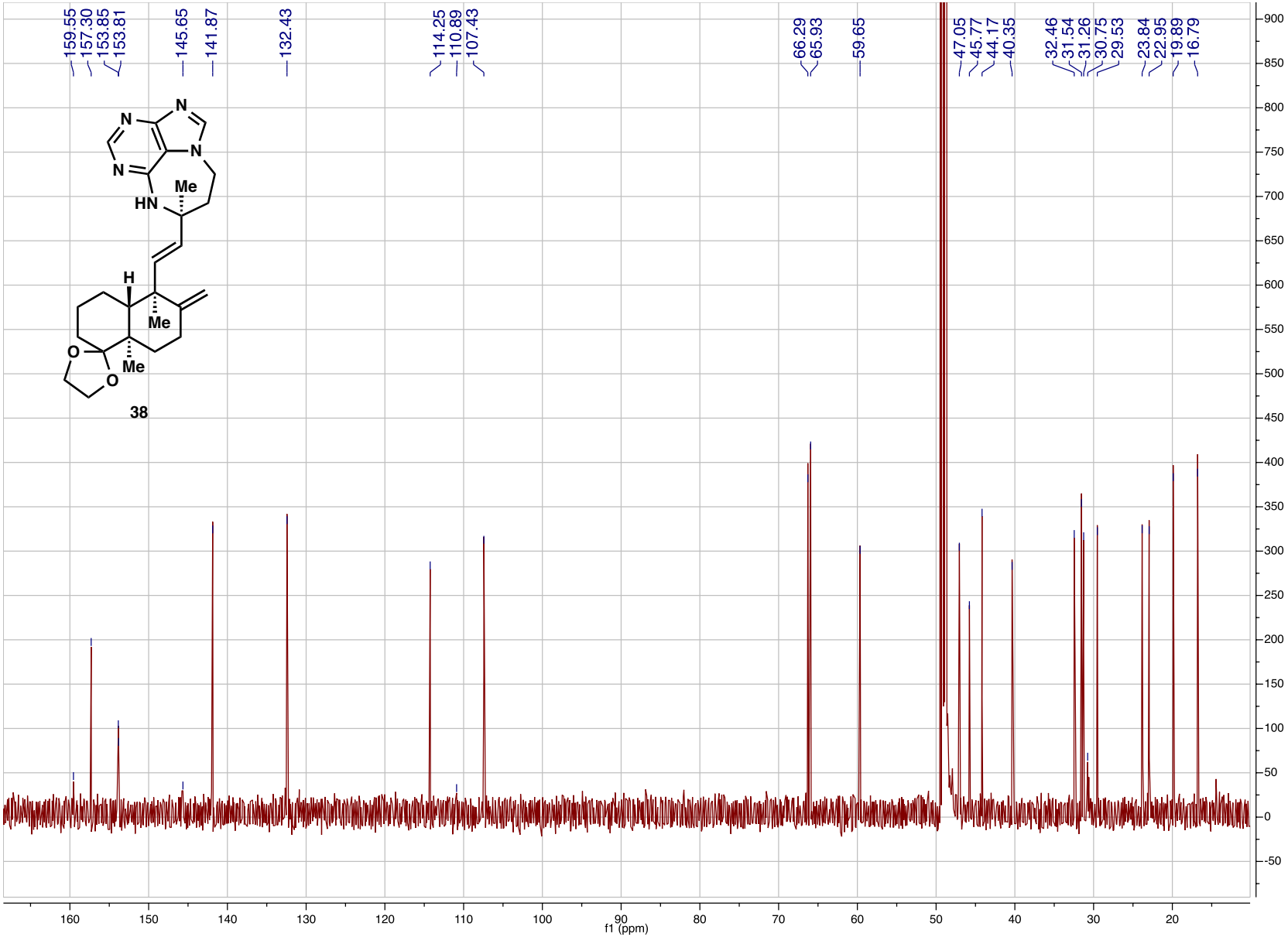

8.40
8.26
5.49
5.29
4.59
4.44
4.27
4.19
3.83
2.59
2.52
2.37
2.01
1.75
1.15
1.08
Me
HO
H
Me
Me
O
O
37
0.98
1.01
1.03
1.00
0.97
1.00
0.95
0.97
4.05
1.00
1.04
1.00
1.02
3.02
9.04
3.00
3.01
f1 (ppm)

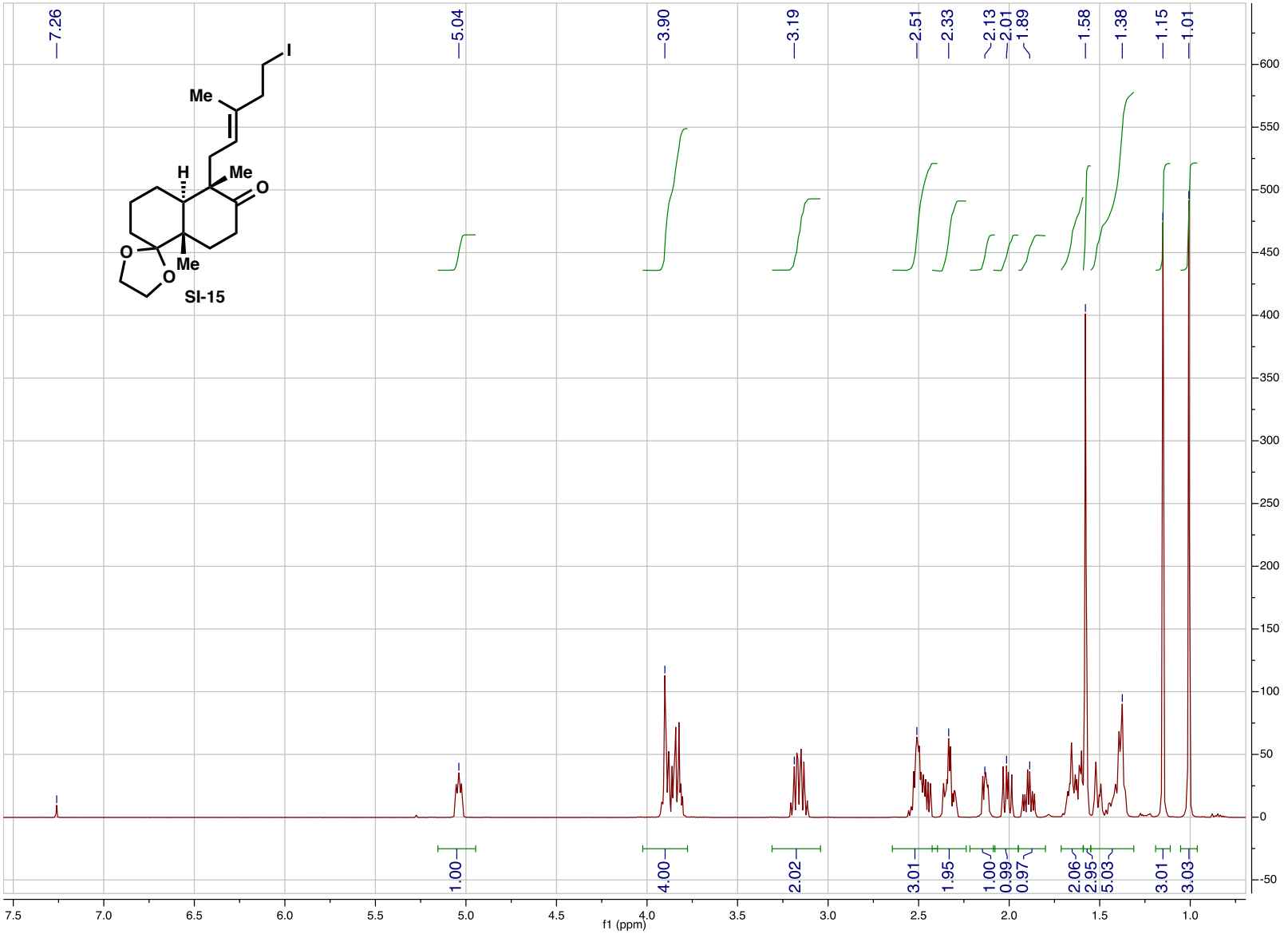

159.20
157.19
153.93
153.22
145.56
142.80
129.20
114.22
111.17
107.59
69.28
66.26
65.92
47.23
44.57
44.14
39.98
32.46
31.54
30.76
29.53
27.81
23.81
22.99
19.73
16.77
N
N
N
N
N
Me
HO
H
Me
O
Me
O
37
f1 (ppm)

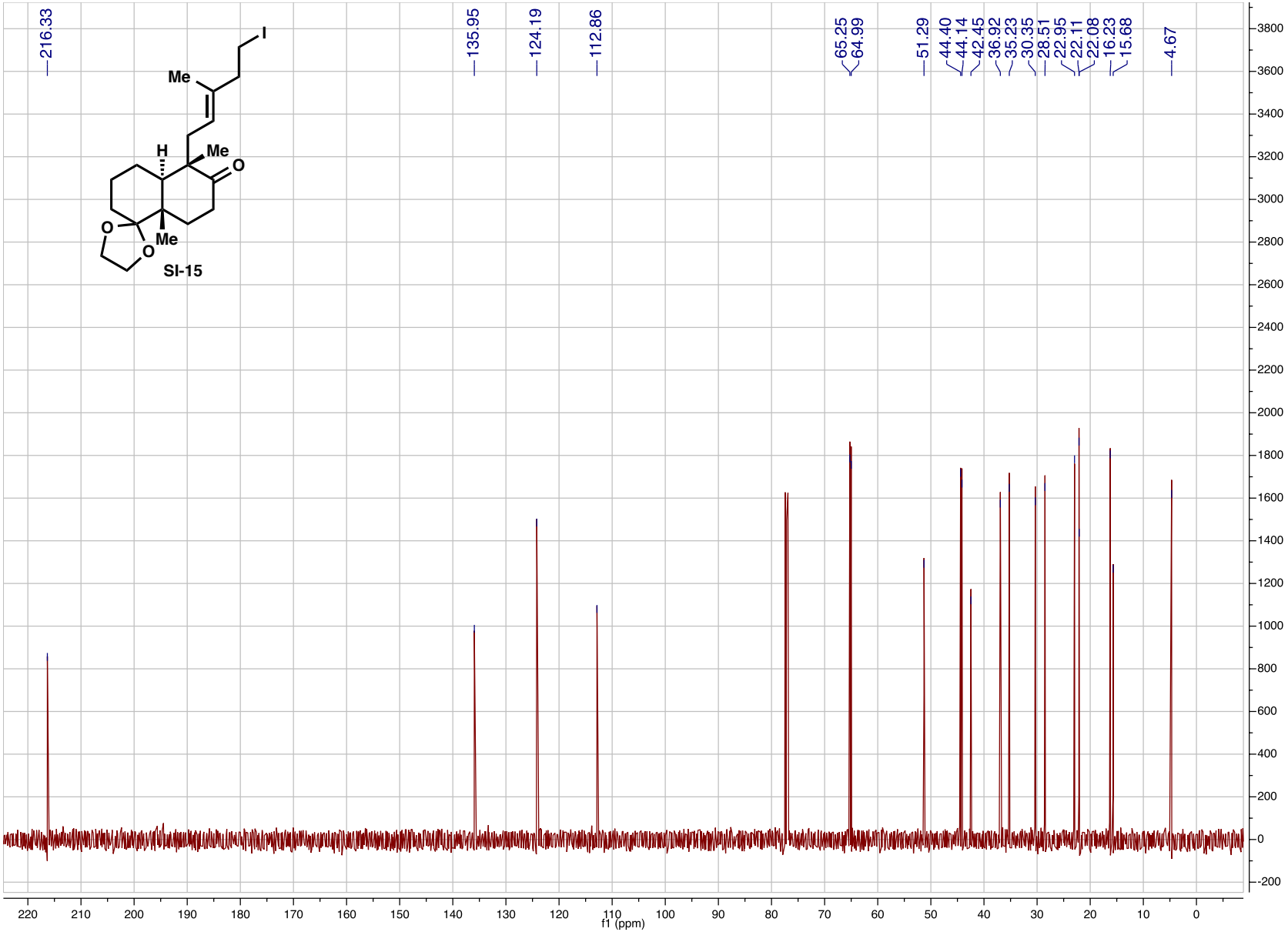

8.43
8.26
5.49
5.25
4.61
4.46
4.28
3.78
3.31
2.60
2.52
2.39
2.12
1.77
1.40
1.29
1.18
1.07
1.06
Me
HO
H
Me
Me
O
O
36
1.01
1.03
1.00
1.01
1.97
1.06
1.07
4.06
0.93
1.06
1.01
0.96
2.99
5.08
0.98
9.05
f1 (ppm)

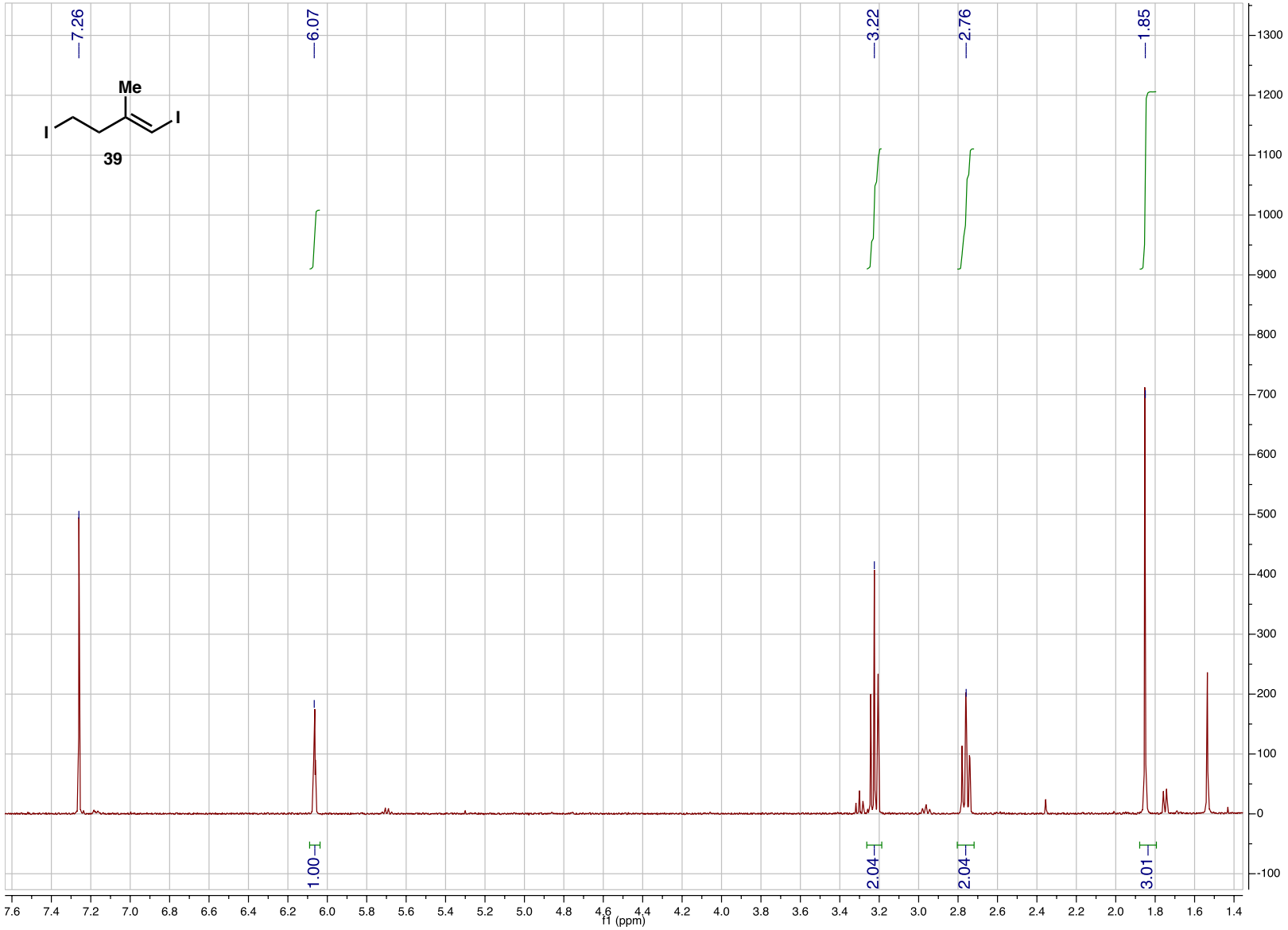

158.88
156.40
154.43
153.16
145.58
143.37
128.73
113.95
111.38
108.88
69.27
66.21
65.82
47.05
44.72
44.12
40.09
32.58
31.43
30.75
29.56
28.31
23.59
23.00
19.46
16.69
Me
HO
H
Me
Me
O
O
36
f1 (ppm)

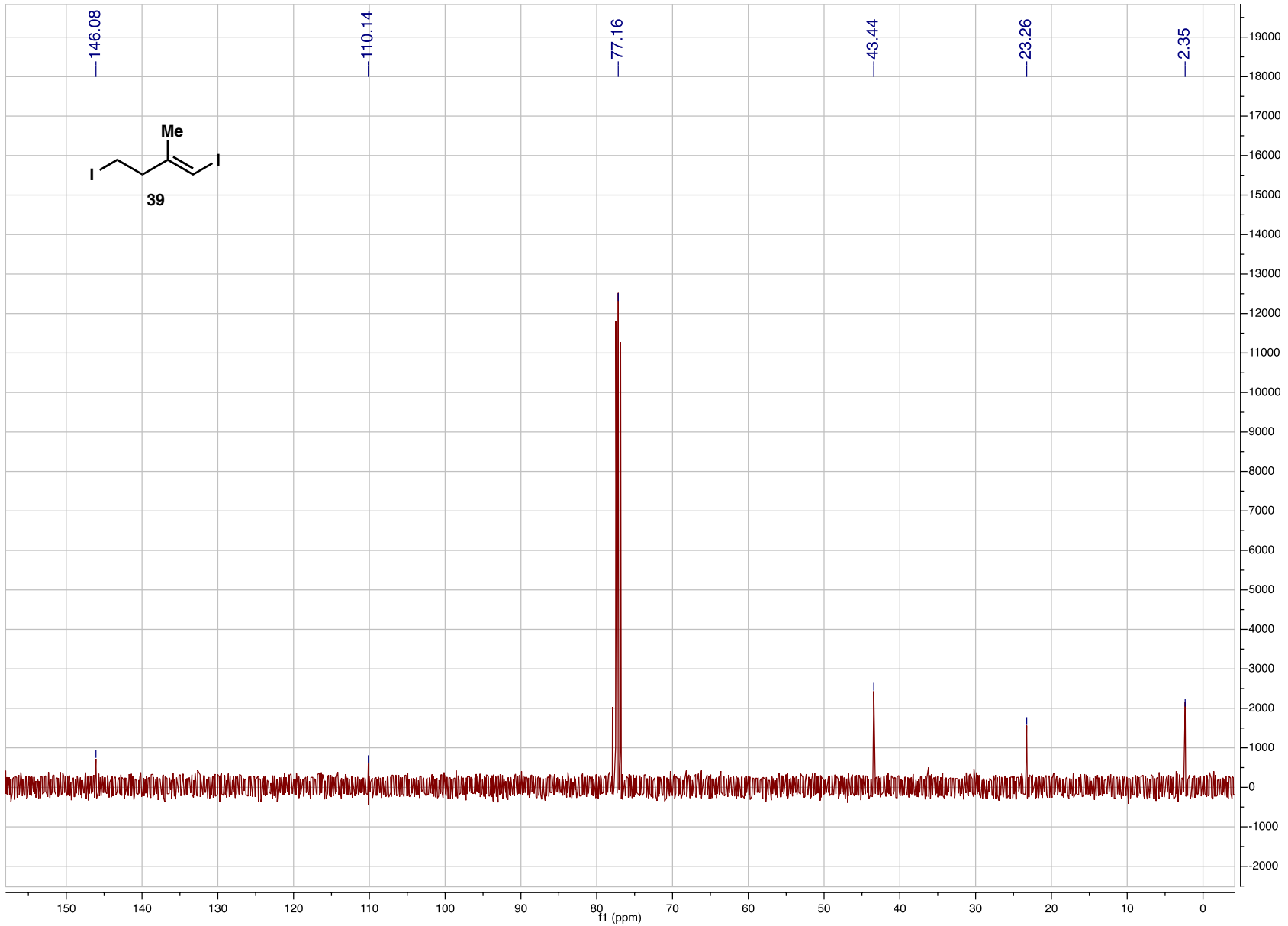

8.28
8.23
5.63
5.39
4.49
4.28
4.16
3.89
3.79
3.44
2.53
2.46
2.46
2.05
1.63
1.58
1.42
1.17
1.12
N
N
N
N
HN
Me
H
Me
O
Me
O
38
2.00
1.04
1.05
1.01
0.98
1.02
4.03
1.02
0.99
0.98
0.99
1.01
0.94
2.99
8.03
3.02
2.98
f1 (ppm)

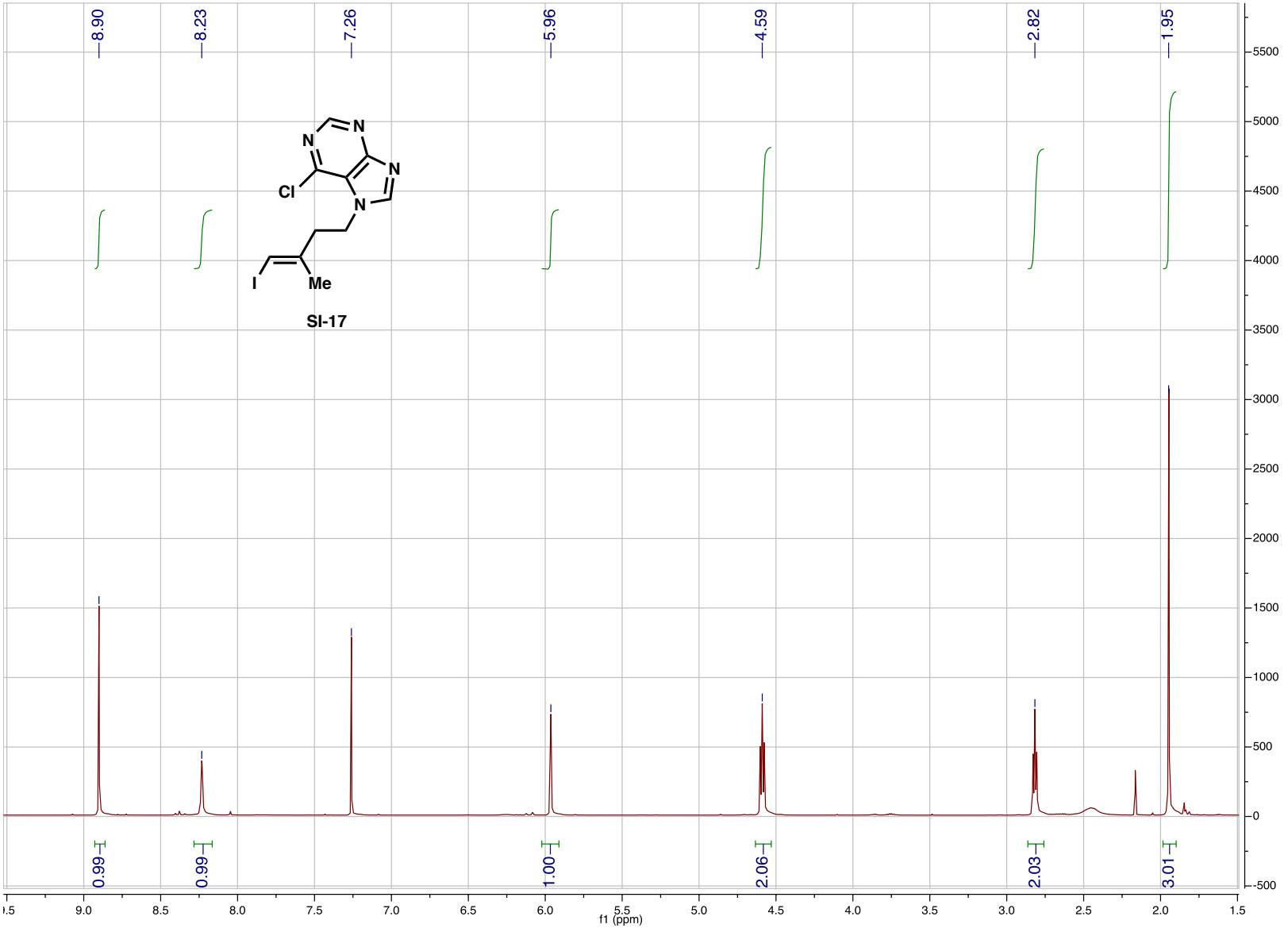

159.55
157.30
153.85
153.81
145.65
141.87
132.43
114.25
110.89
107.43
66.29
65.93
59.65
47.05
45.77
44.17
40.35
32.46
31.54
31.26
30.75
29.53
23.84
22.95
19.89
16.79
N
N
N
N
HN
Me
H
Me
O
Me
O
38
f1 (ppm)

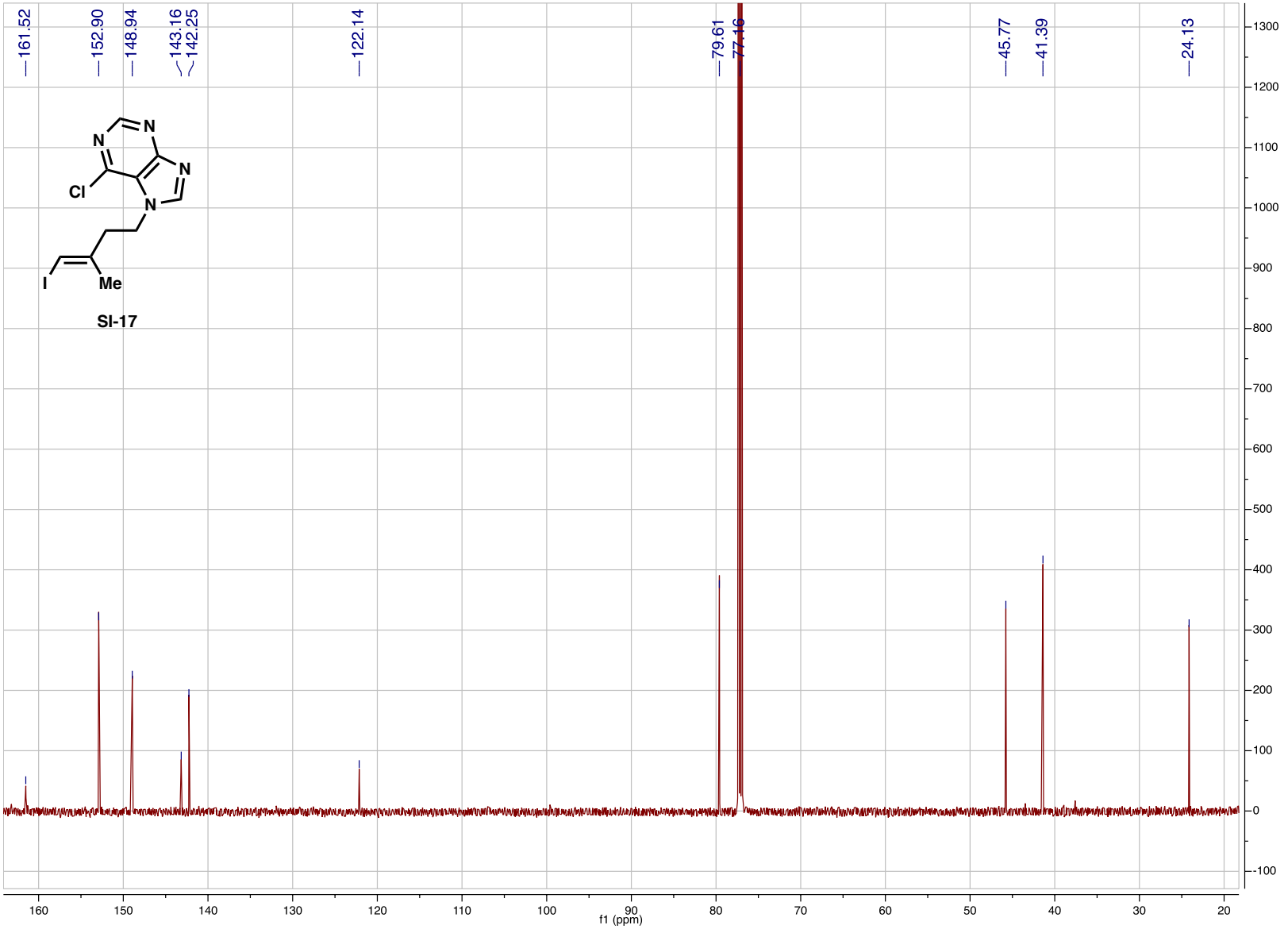

7.26
5.04
3.90
3.19
2.51
2.33
2.13
2.01
1.89
1.58
1.38
1.15
1.01
I
Me
H
Me
O
O
Me
O
SI-15
1.00
4.00
2.02
3.01
1.95
1.00
0.99
0.97
2.06
2.95
5.03
3.01
3.03
f1 (ppm)

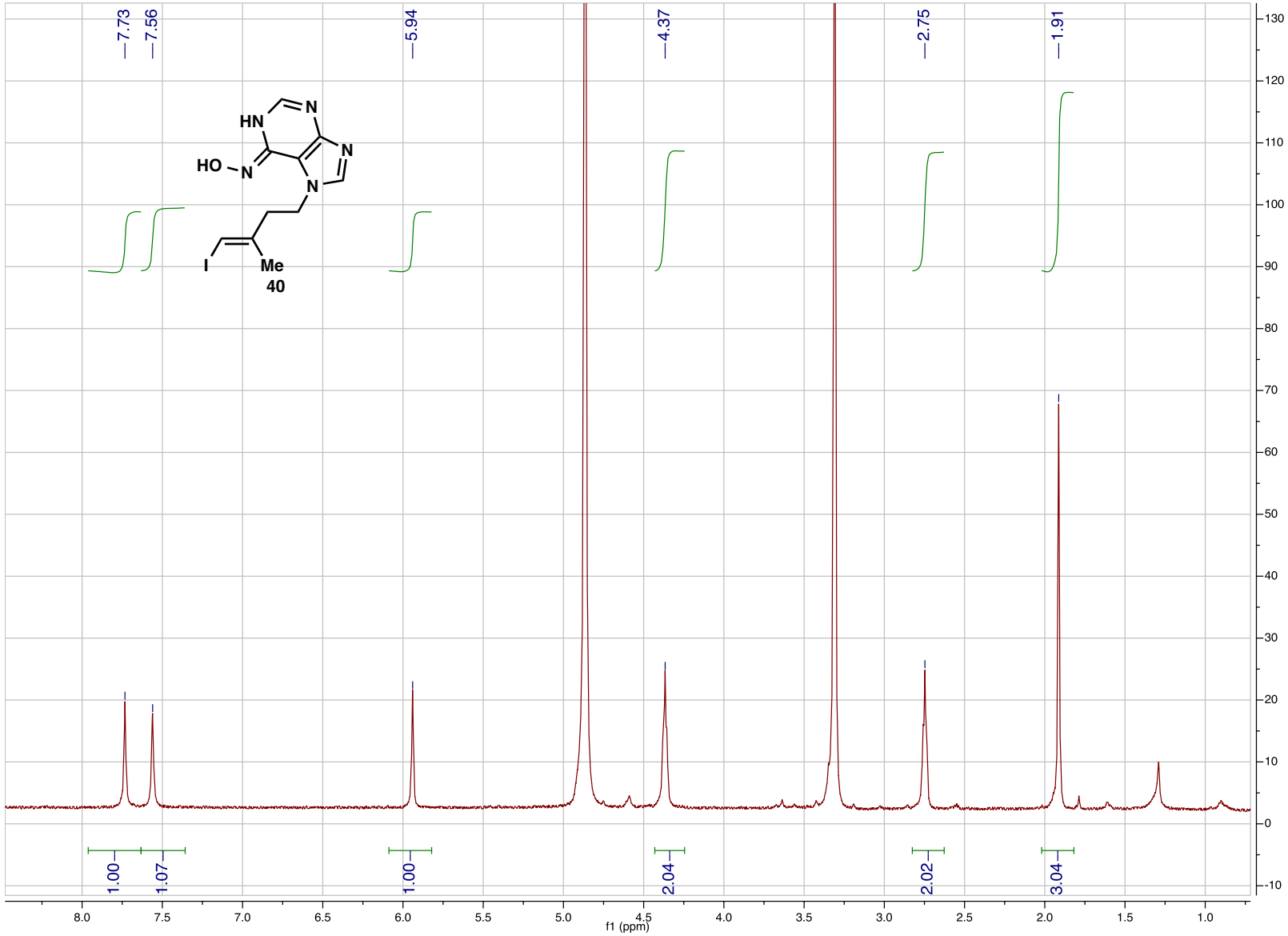

216.33
135.95
124.19
112.86
65.25
64.99
51.29
44.40
44.14
42.45
36.92
35.23
30.35
28.51
22.95
22.11
22.08
16.23
15.68
4.67
Me
I
H
Me
O
O
Me
O
SI-15
f1 (ppm)

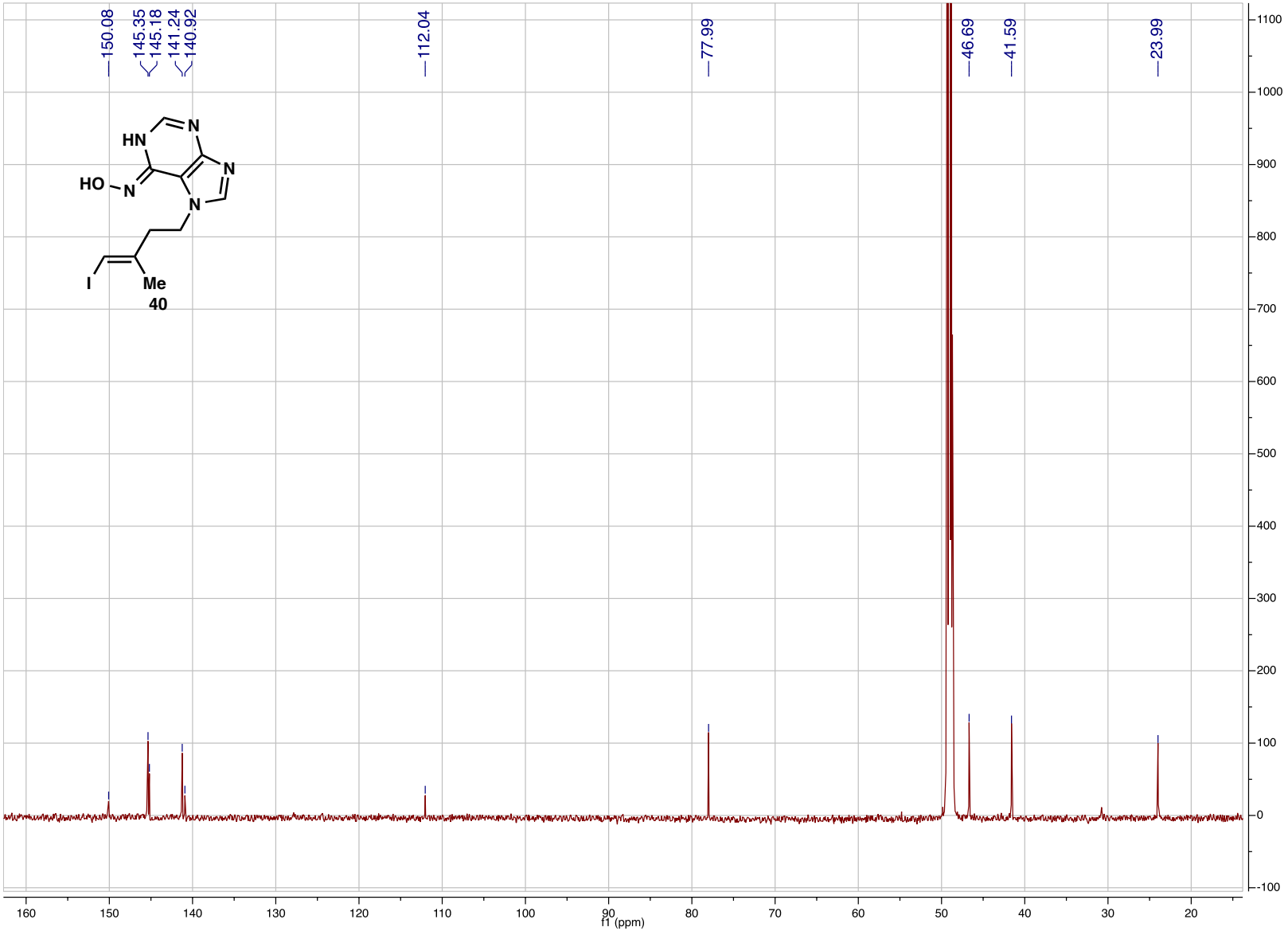

7.26
6.07
3.22
2.76
1.85
Me
I
I
39
1.00
2.04
2.04
3.01
f1 (ppm)

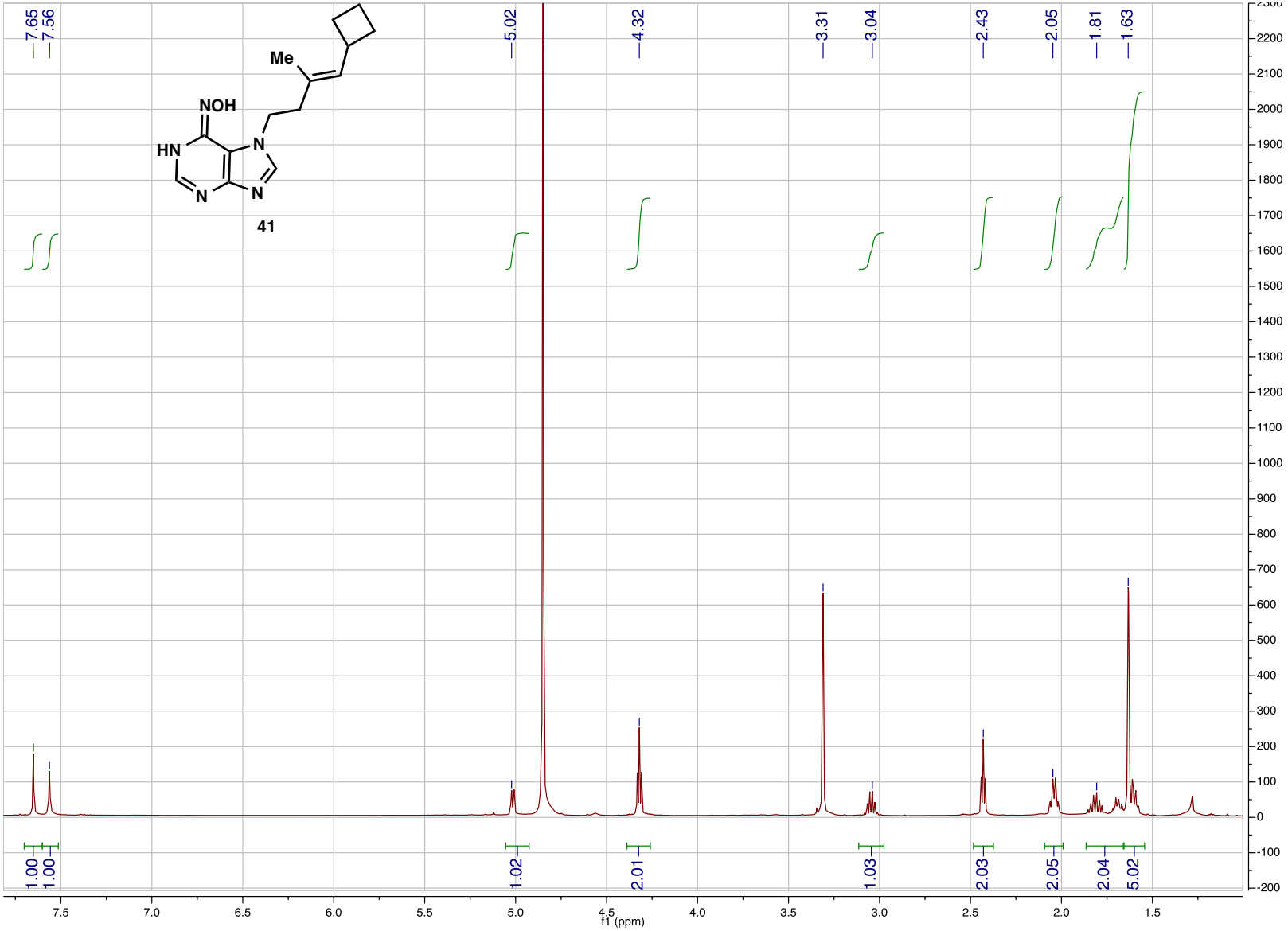

146.08
110.14
77.16
43.44
23.26
2.35
Me
I
I
39
f1 (ppm)

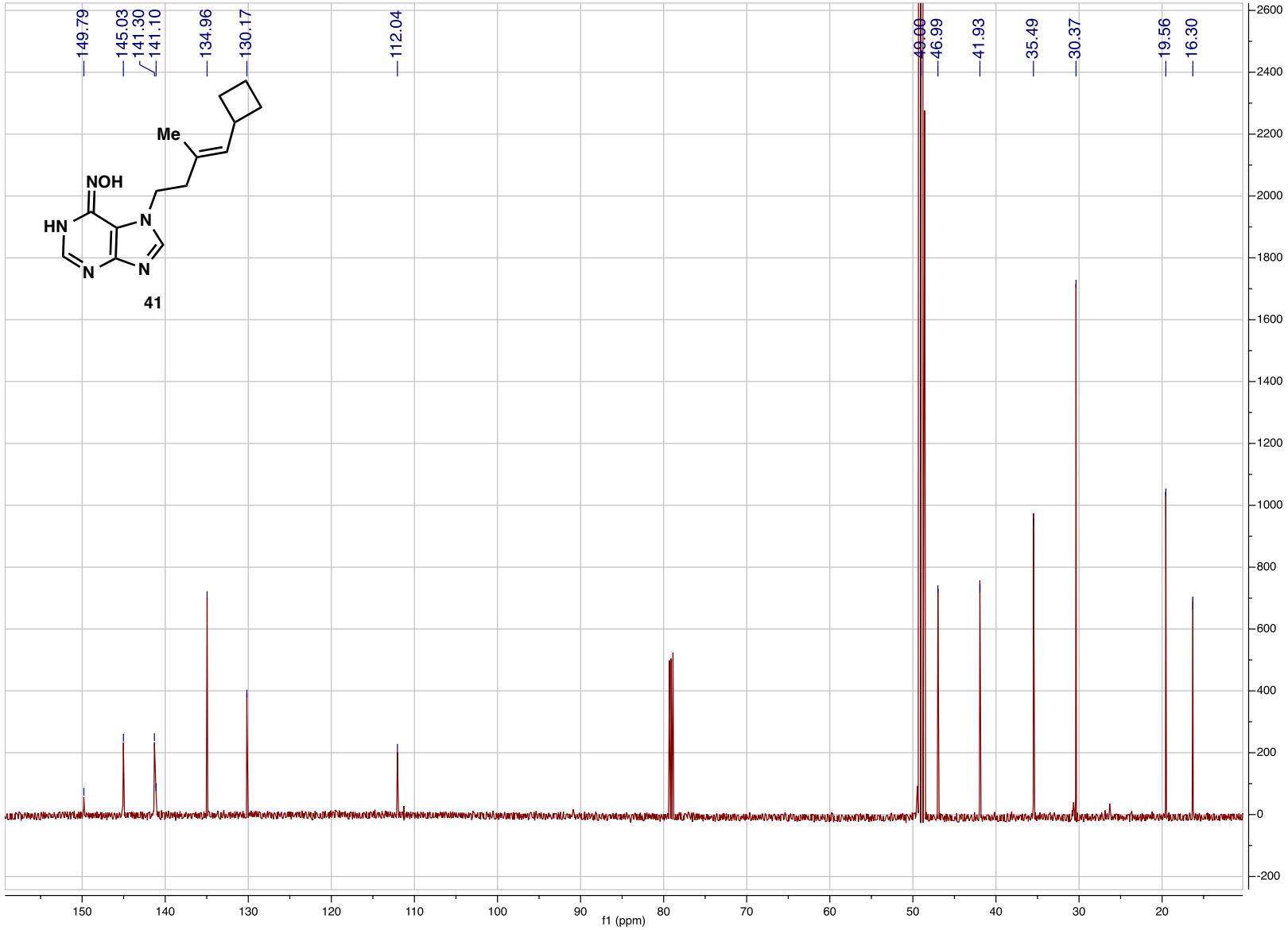

8.90
8.23
7.26
5.96
4.59
2.82
1.95
N
N
N
N
Cl
I
Me
SI-17
0.99
0.99
1.00
2.06
2.03
3.01
f1 (ppm)

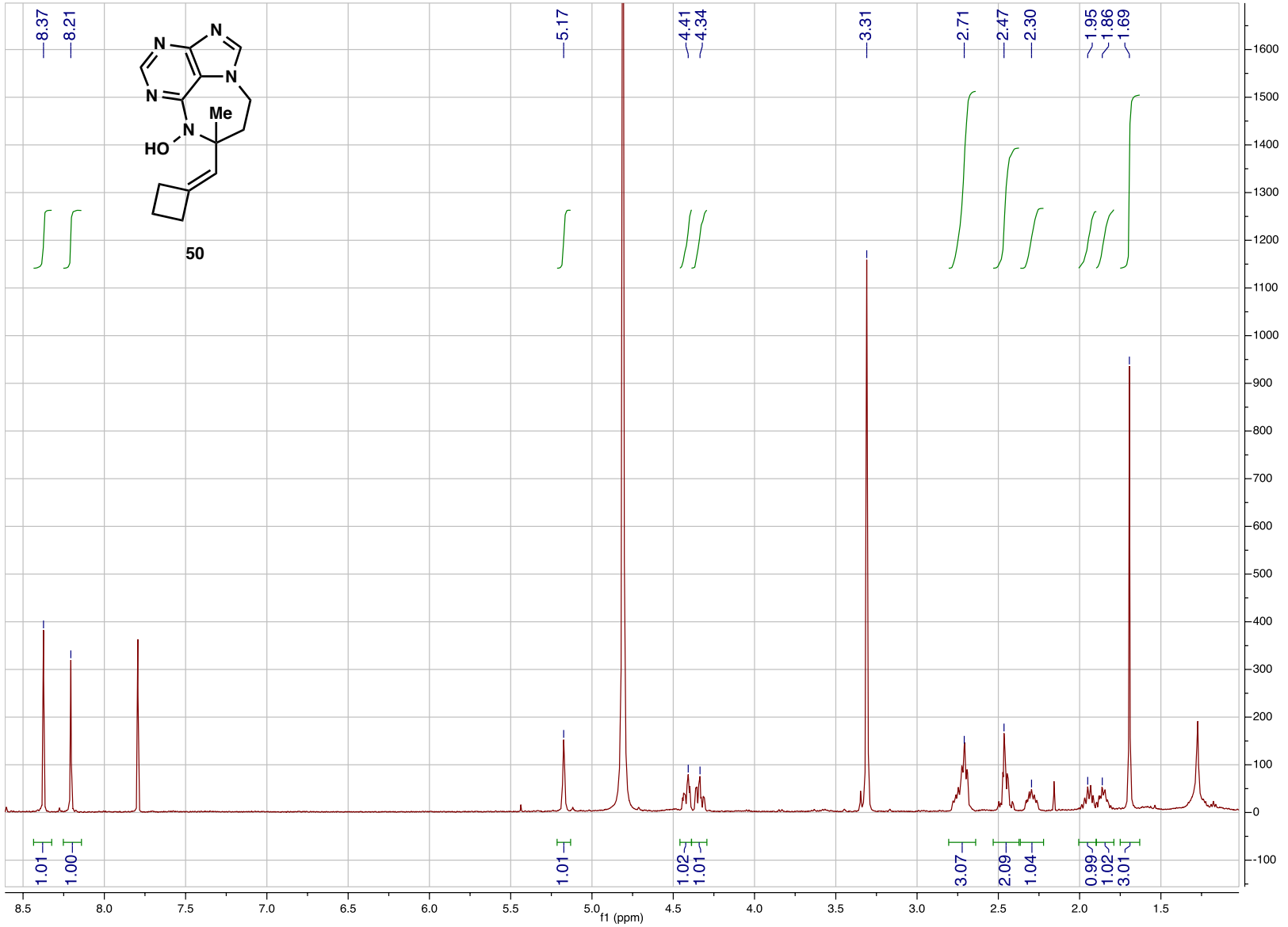

161.52
152.90
148.94
143.16
142.25
122.14
79.61
77.16
45.77
41.39
24.13
N
N
N
N
Cl
I
Me
SI-17
f1 (ppm)

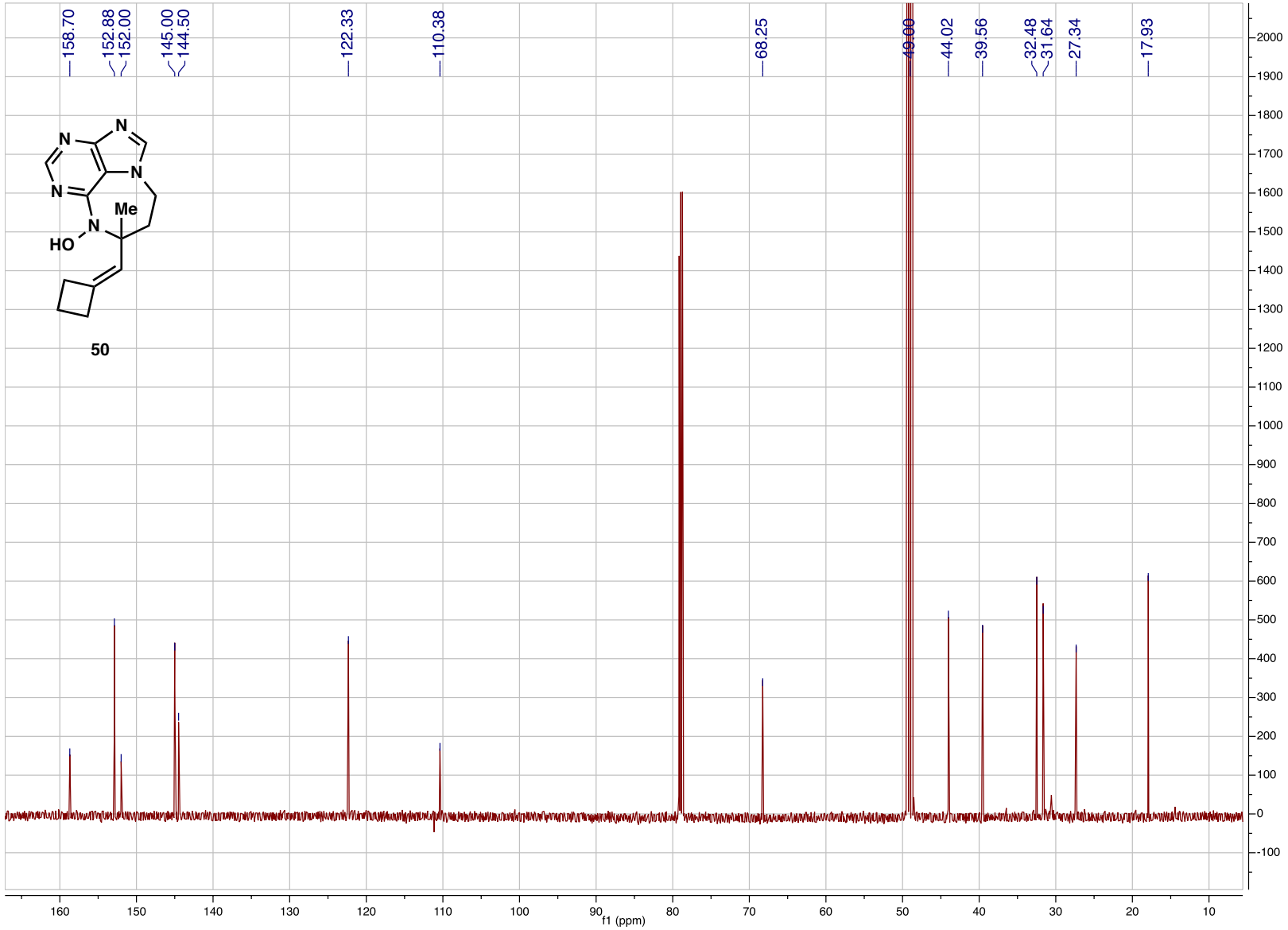

7.73
7.56
5.94
4.37
2.75
1.91
HN
N
HO
N
N
N
I
Me
40
1.00
1.07
1.00
2.04
2.02
3.04
f1 (ppm)

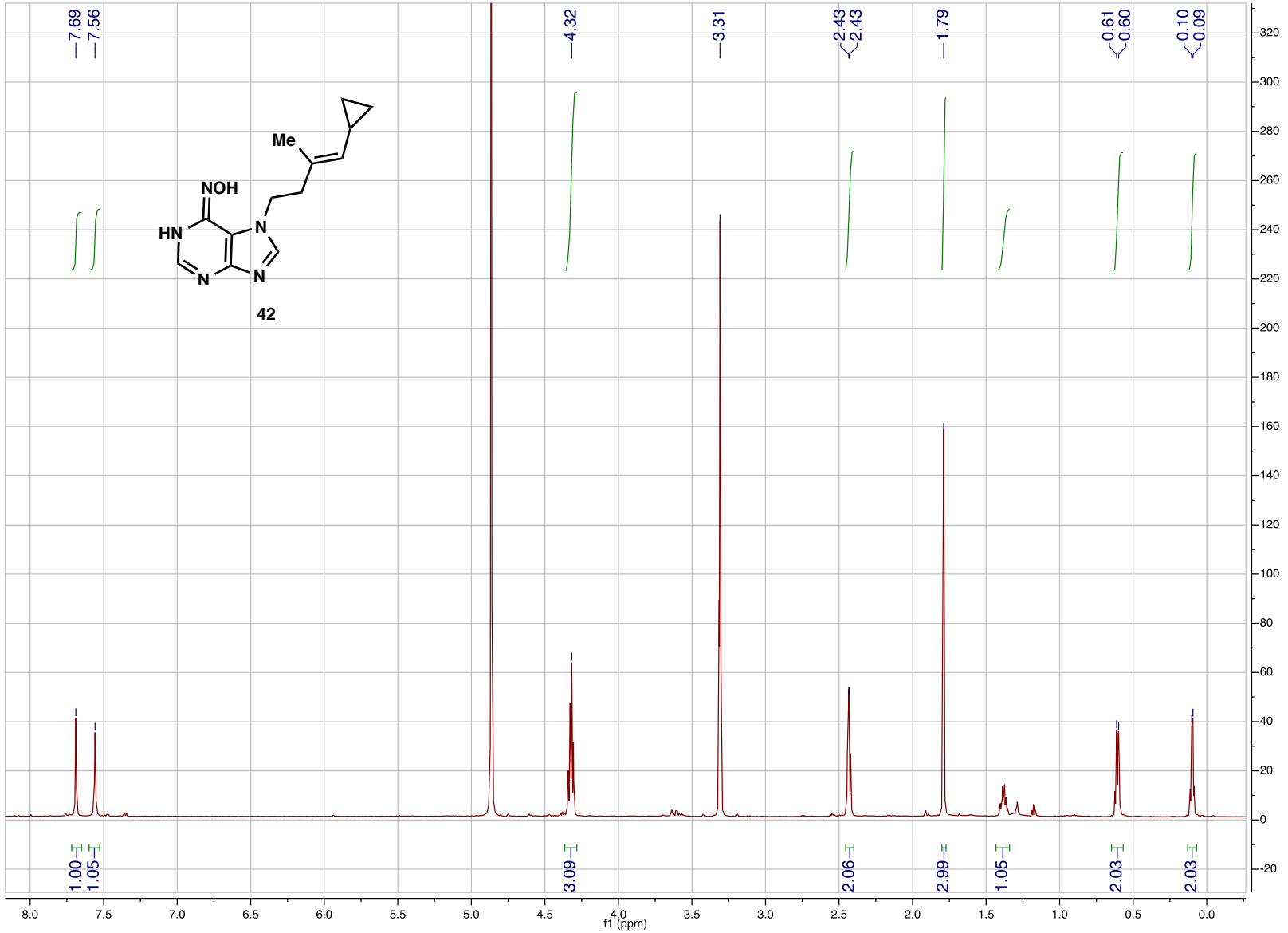

150.08
145.35
145.18
141.24
140.92
112.04
77.99
46.69
41.59
23.99
HN
N
HO
N
N
N
I
Me
40
f1 (ppm)

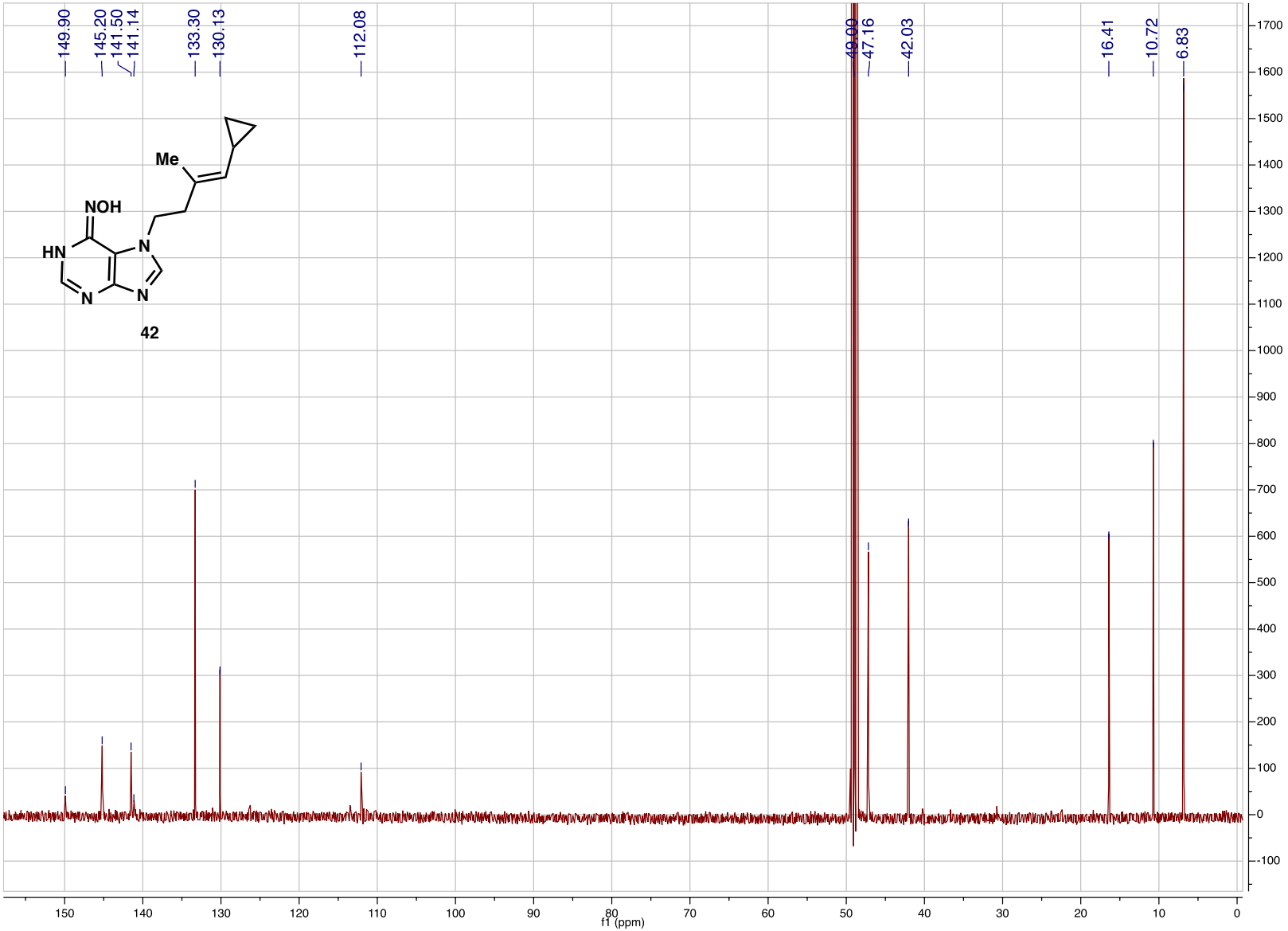

7.65
7.56
5.02
4.32
3.31
3.04
2.43
2.05
1.81
1.63
Me
NOH
HN
N
N
N
41
1.00
1.00
1.02
2.01
1.03
2.03
2.05
2.04
5.02
f1 (ppm)

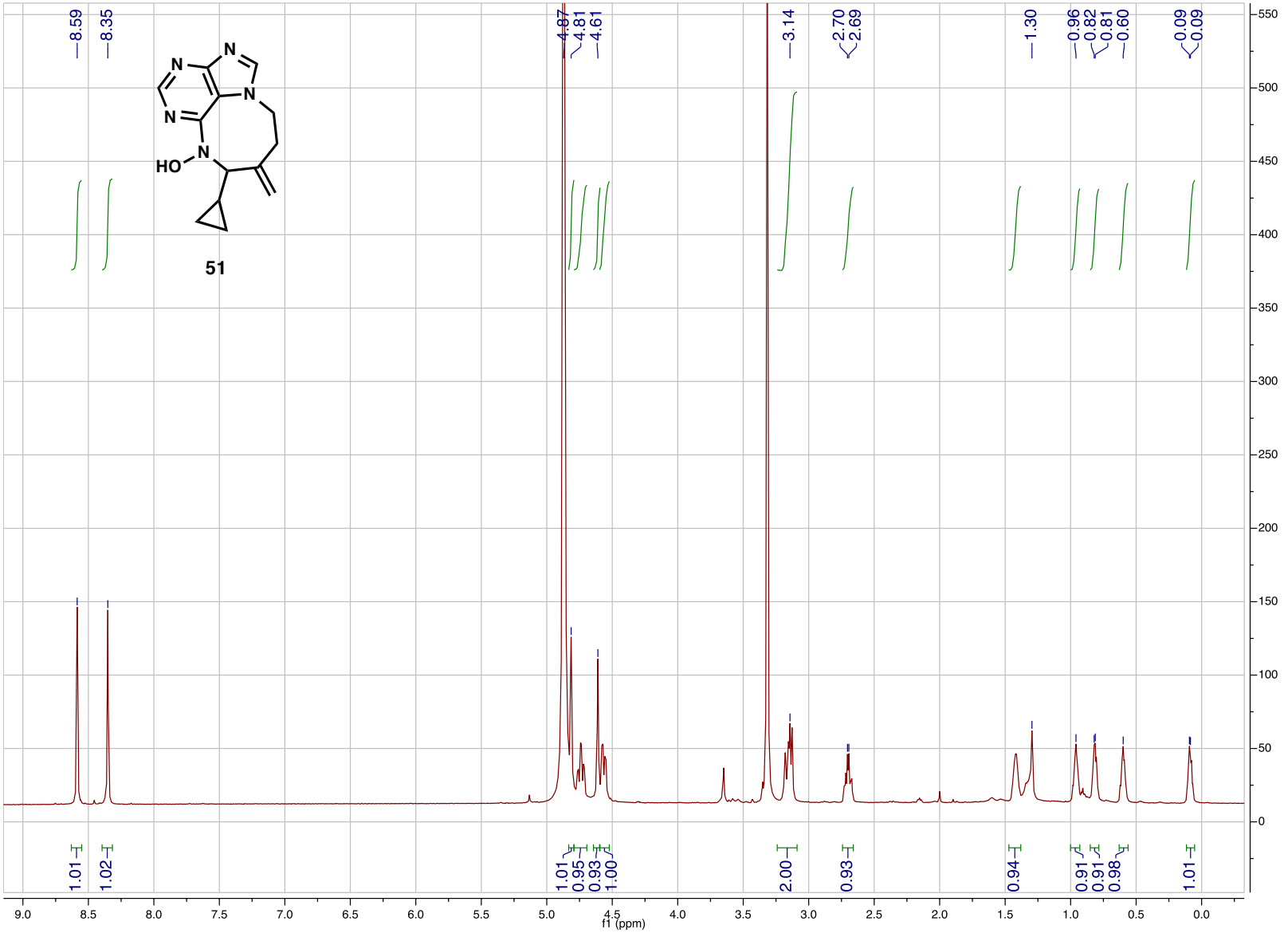

149.79
145.03
141.30
141.10
134.96
130.17
112.04
49.00
46.99
41.93
35.49
30.37
19.56
16.30
Me
NOH
HN
N
N
N
41
f1 (ppm)

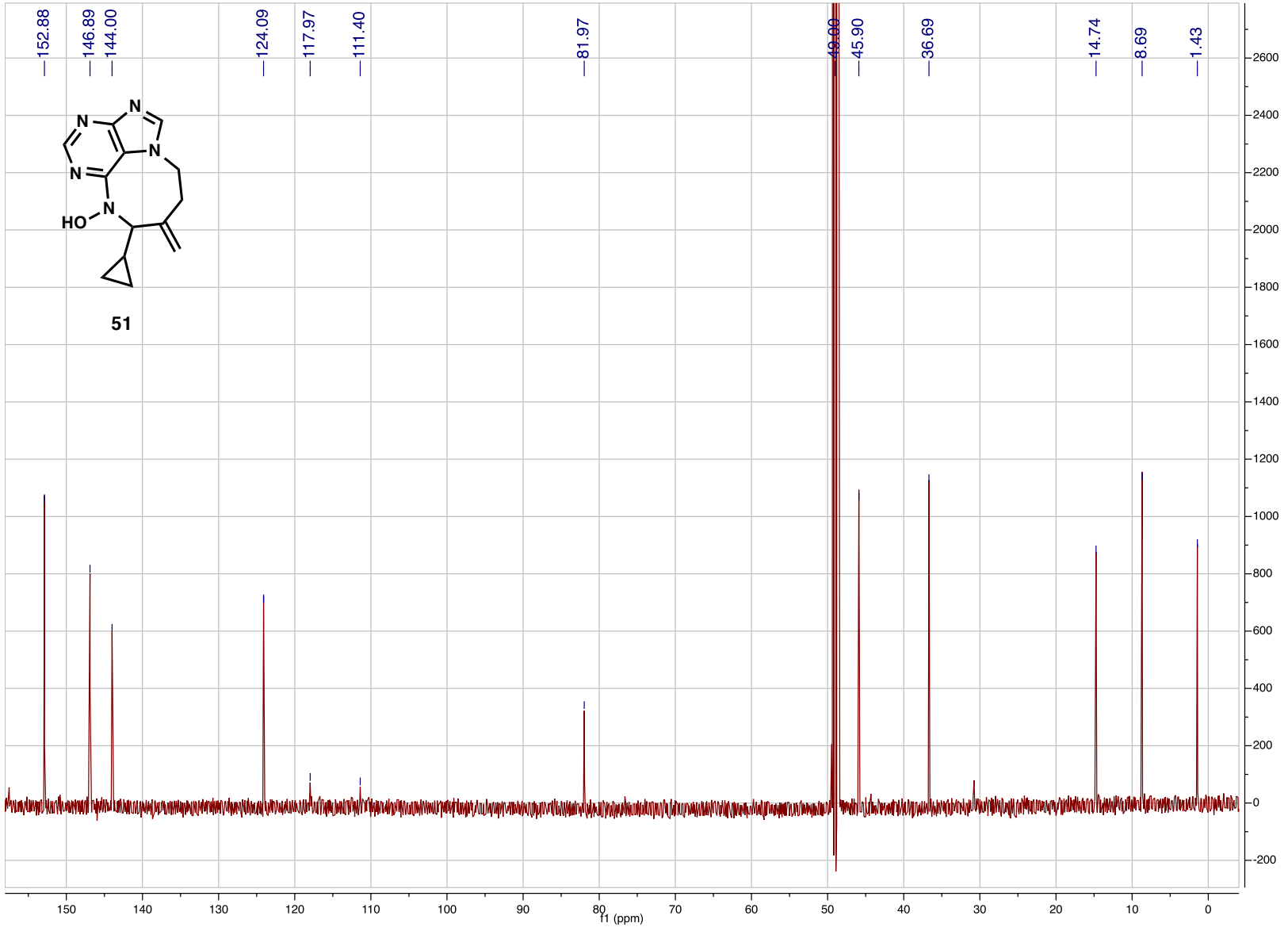

8.37
8.21
5.17
4.41
4.34
3.31
2.71
2.47
2.30
1.95
1.86
1.69
N
N
N
N
N
Me
HO
50
1.01
1.00
1.01
1.02
1.01
3.07
2.09
1.04
0.99
1.02
3.01
f1 (ppm)

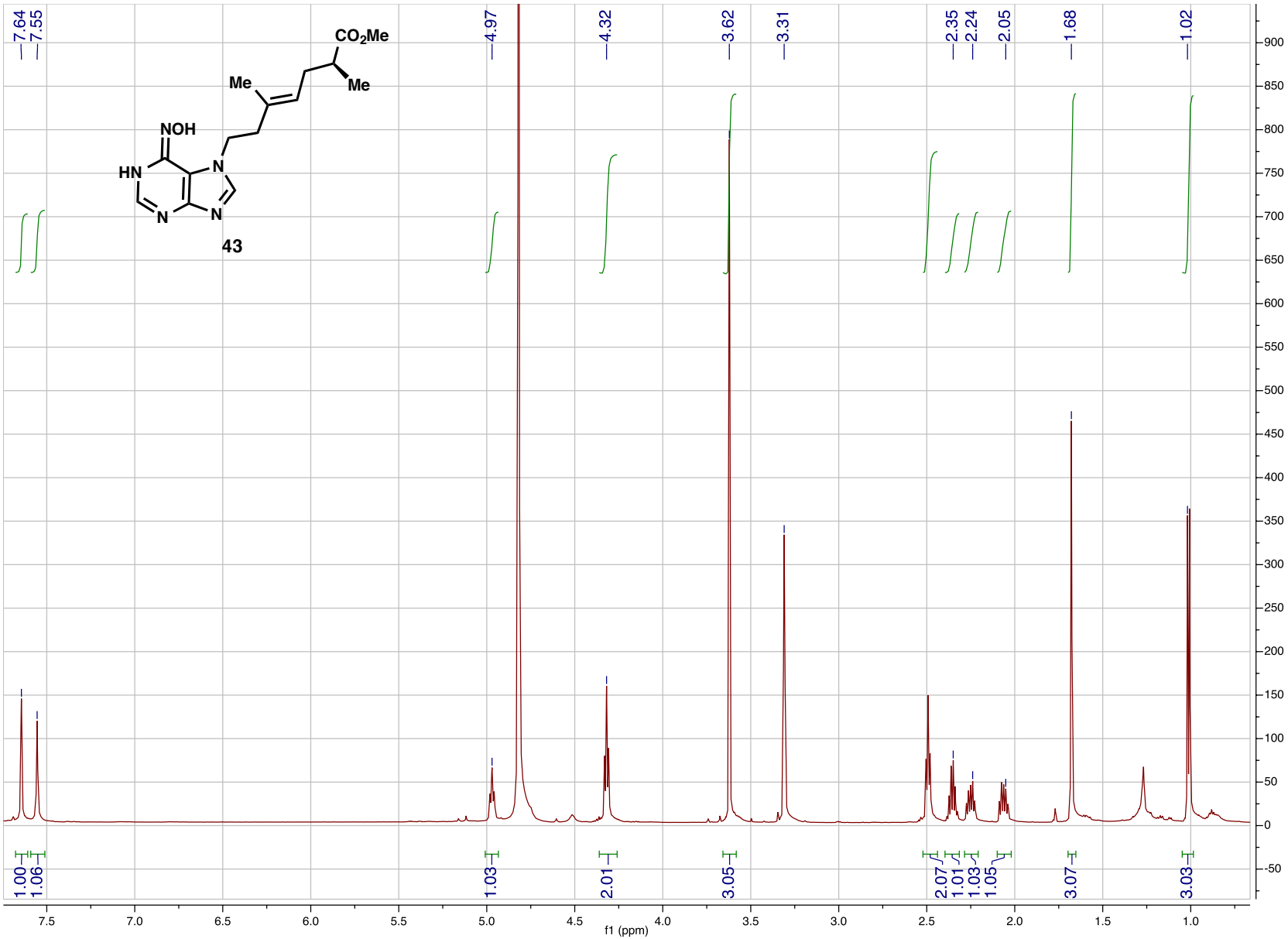

158.70
152.88
152.00
145.00
144.50
122.33
110.38
68.25
49.00
44.02
39.56
32.48
31.64
27.34
17.93
N
N
N
N
N
Me
HO
50
f1 (ppm)

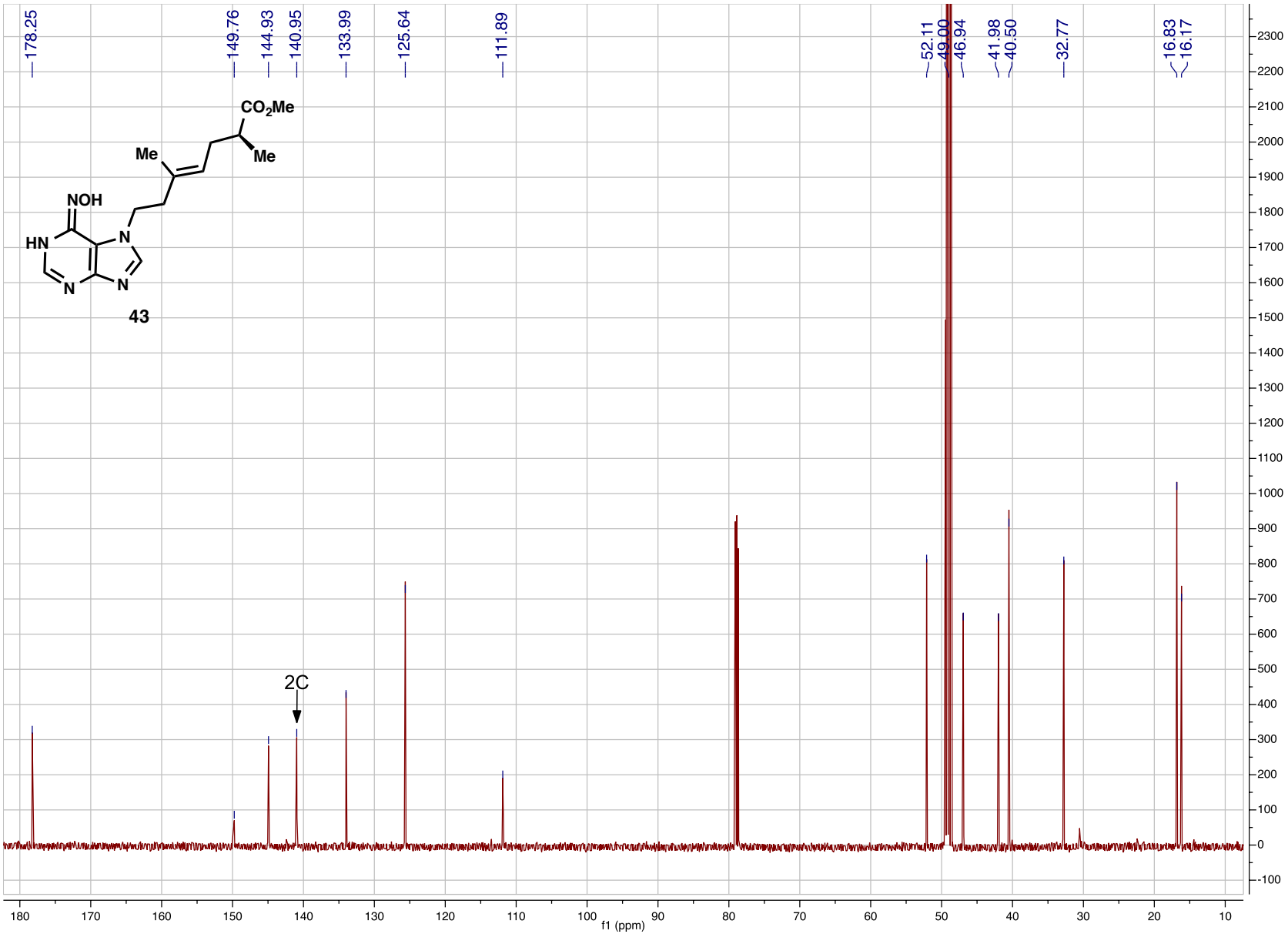

7.69
7.56
4.32
3.31
2.43
2.43
1.79
0.61
0.60
0.10
0.09
NOH
HN
N
N
N
Me
42
1.00
1.05
3.09
2.06
2.99
1.05
2.03
2.03
f1 (ppm)

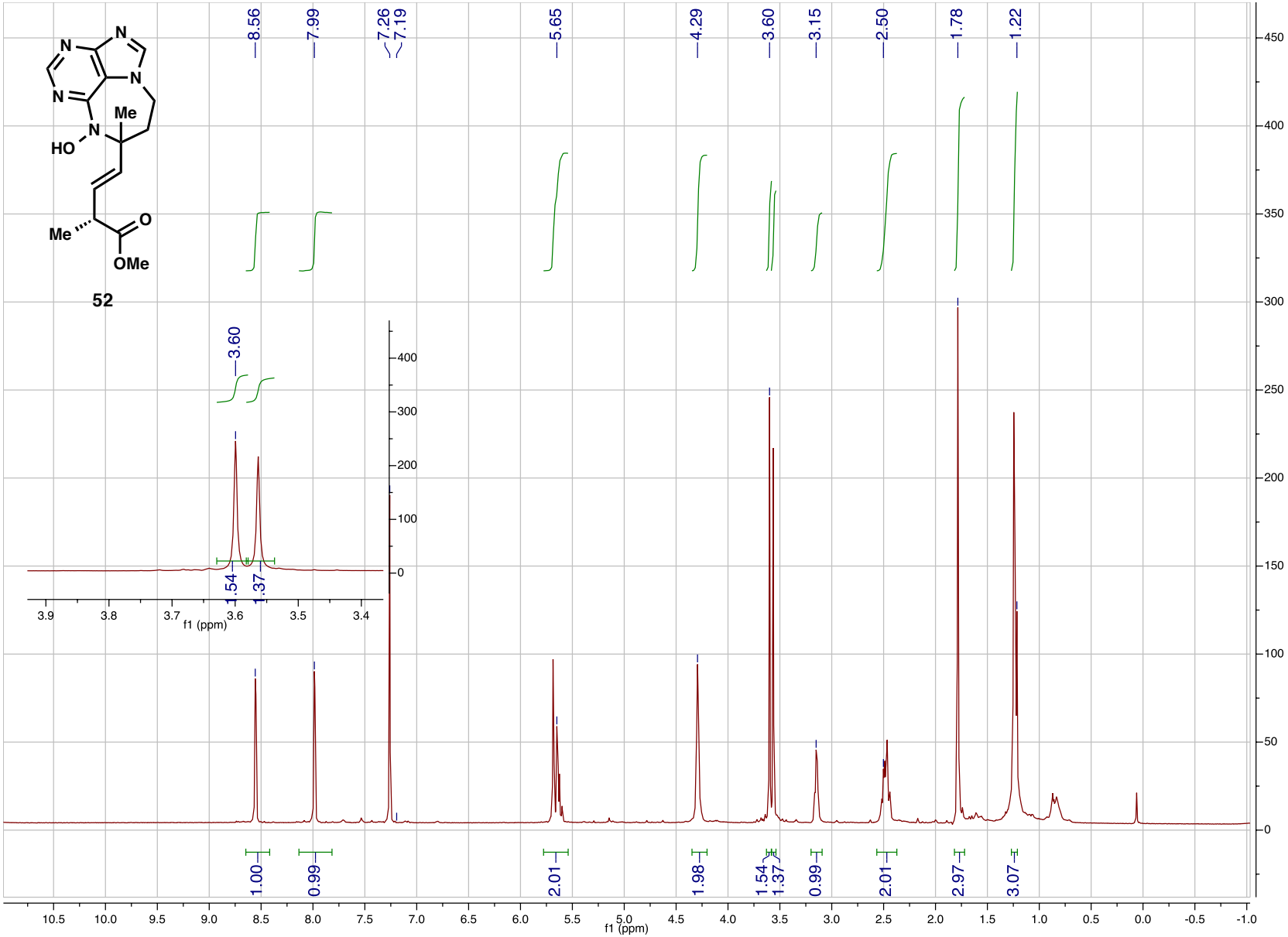

149.90
145.20
141.50
141.14
133.30
130.13
112.08
49.00
47.16
42.03
16.41
10.72
6.83
Me
NOH
HN
N
N
N
42
f1 (ppm)

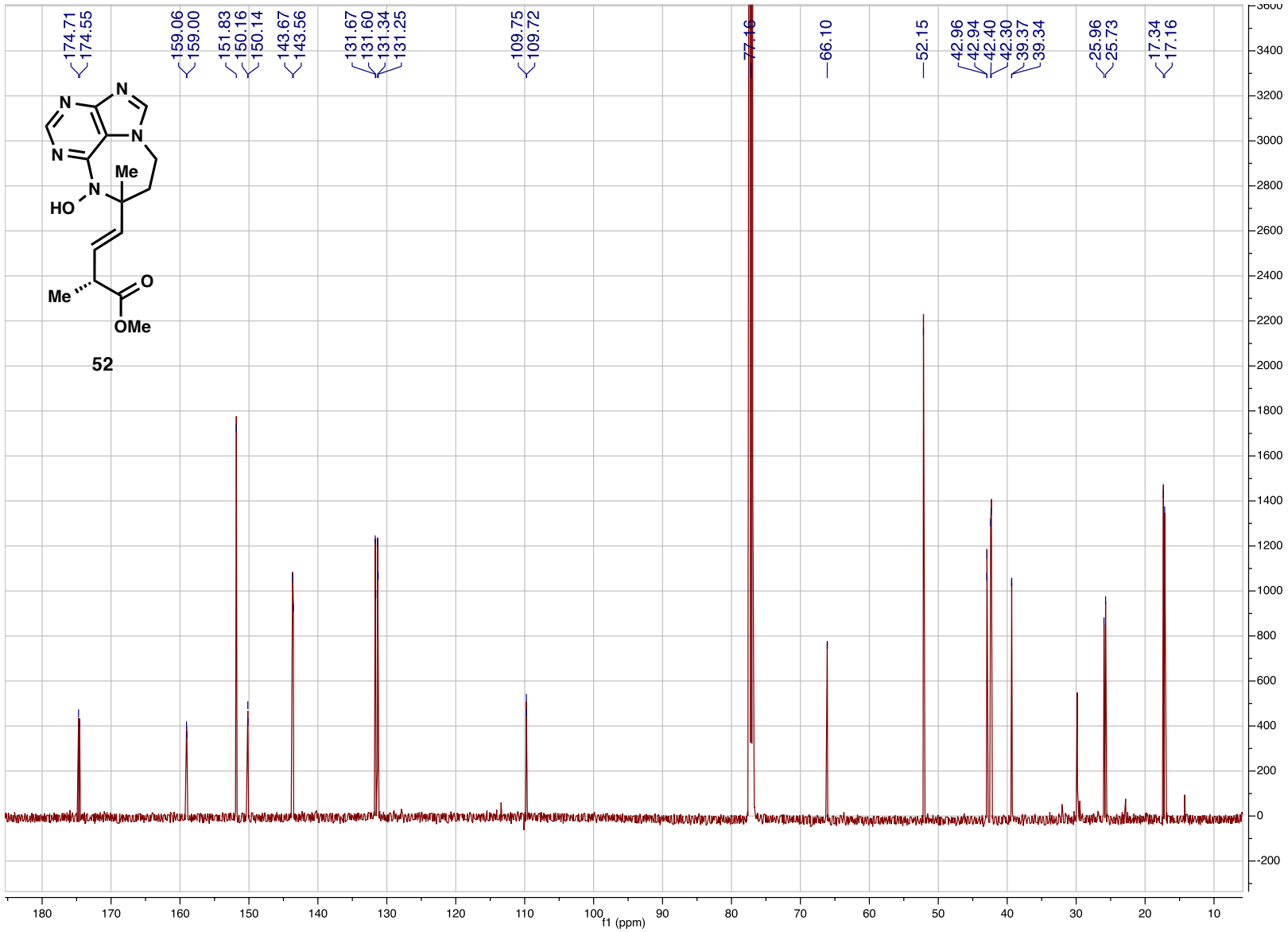

8.59
8.35
4.87
4.81
4.61
3.14
2.70
2.69
1.30
0.96
0.82
0.81
0.60
0.09
0.09
HO
N
51
1.01
1.02
1.01
0.95
0.93
1.00
2.00
0.93
0.94
0.91
0.91
0.98
1.01
f1 (ppm)

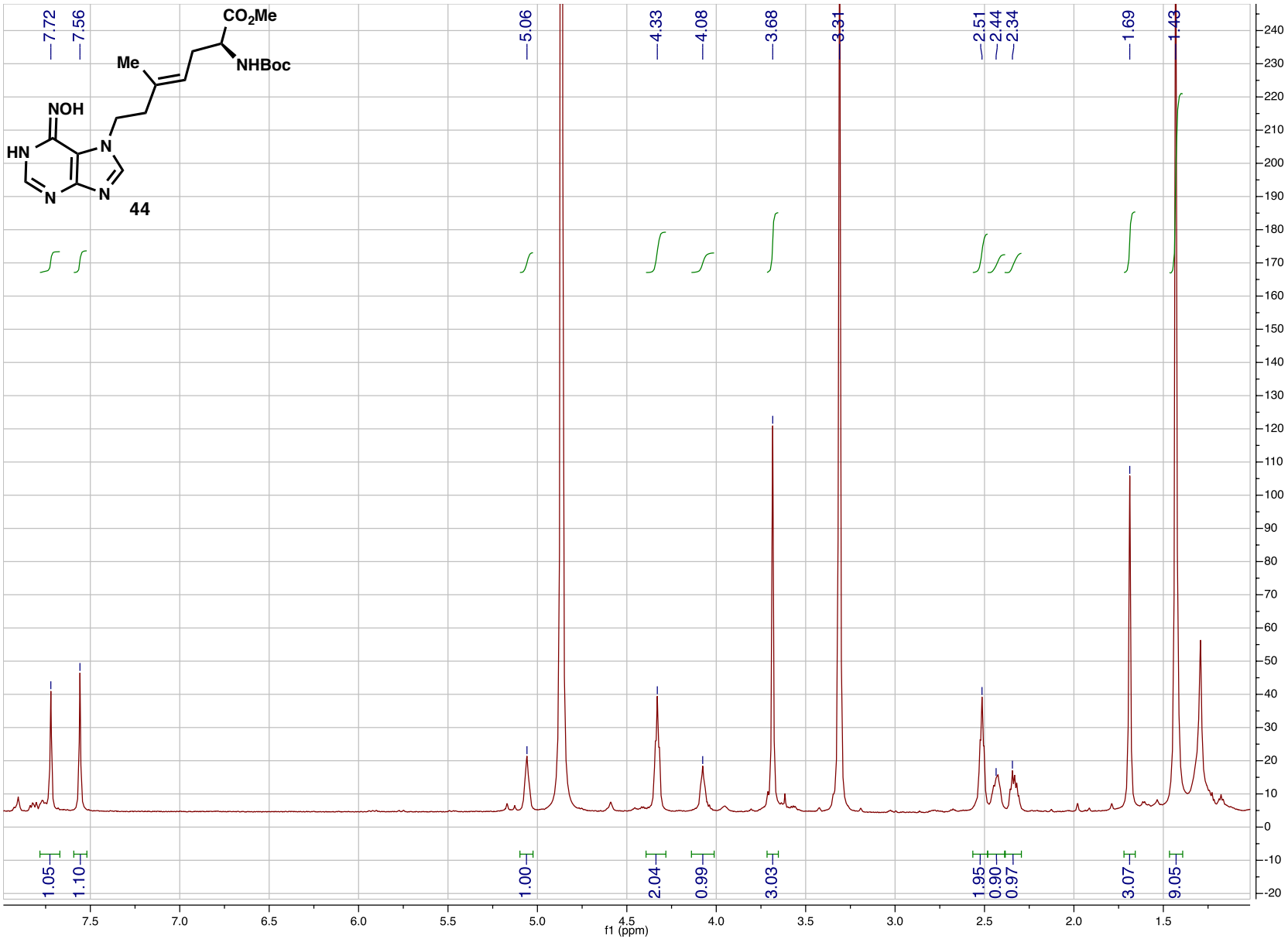

152.88
146.89
144.00
124.09
117.97
111.40
81.97
49.00
45.90
36.69
14.74
8.69
1.43
HO
N
51
f1 (ppm)

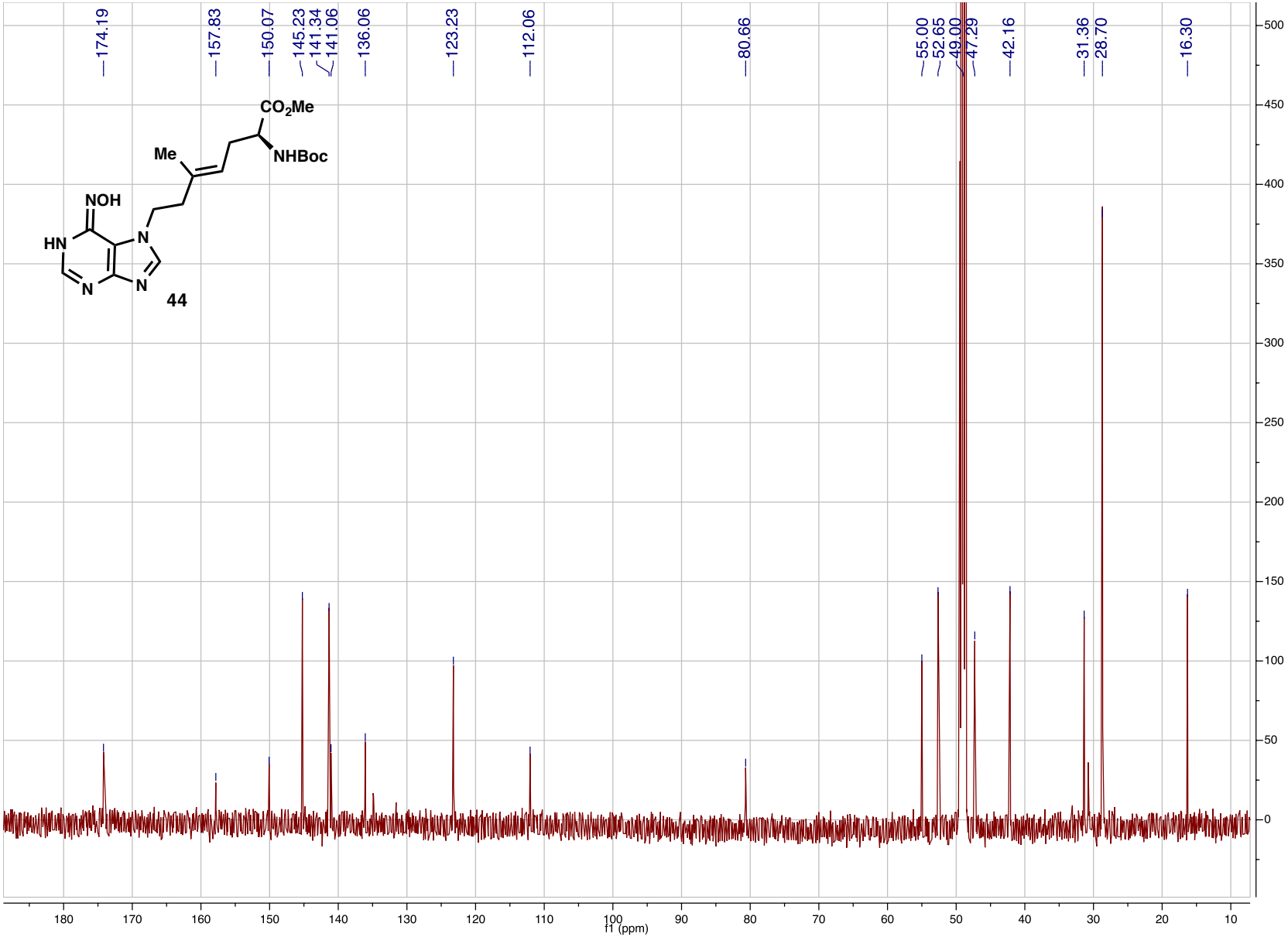

7.64
7.55
4.97
4.32
3.62
3.31
2.35
2.24
2.05
1.68
1.02
CO2Me
Me
Me
NOH
HN
N
N
N
43
1.00
1.06
1.03
2.01
3.05
2.07
1.01
1.03
1.05
3.07
3.03
f1 (ppm)

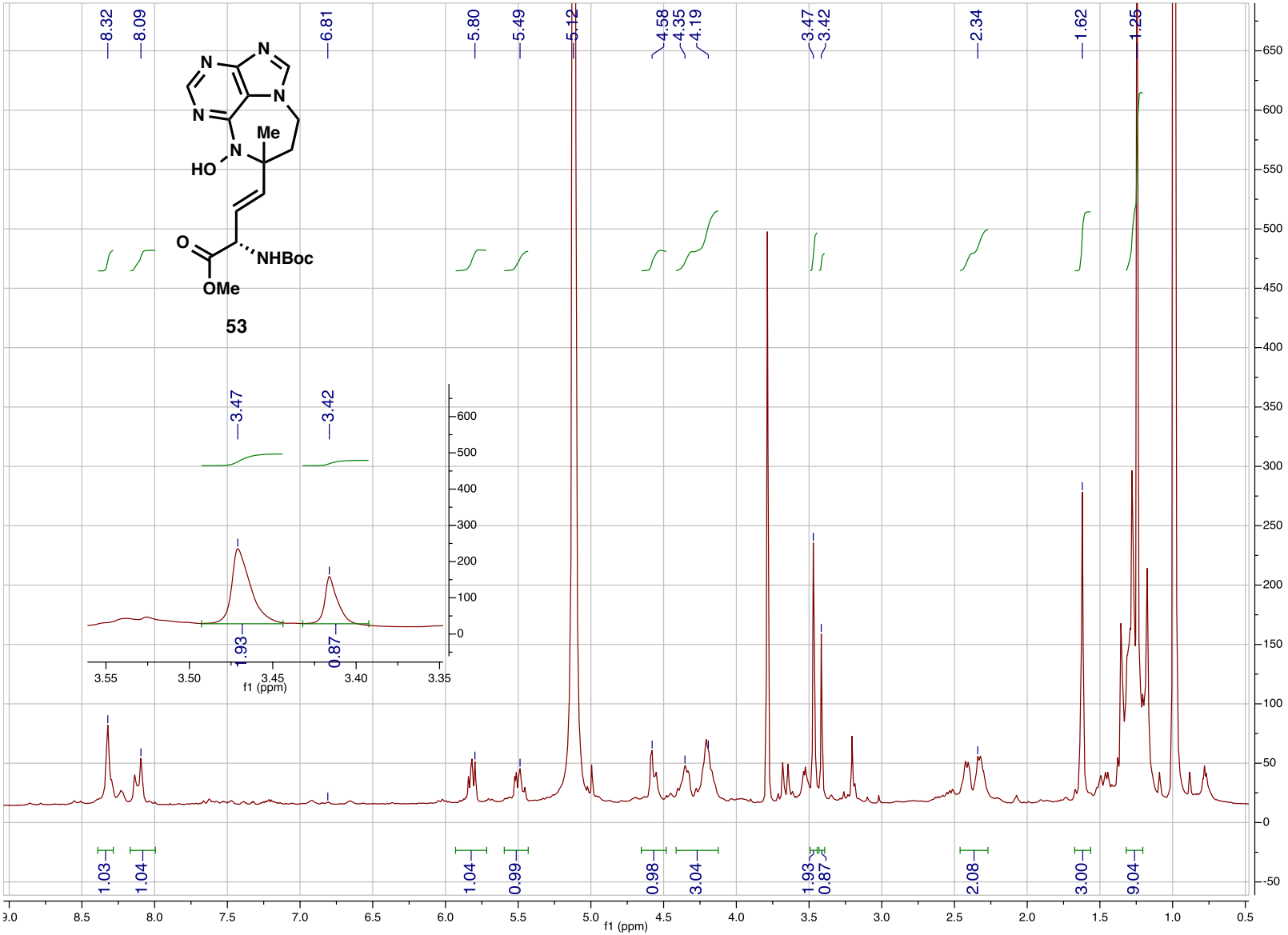

178.25
149.76
144.93
140.95
133.99
125.64
111.89
52.11
49.00
46.94
41.98
40.50
32.77
16.83
16.17
CO2Me
Me
Me
NOH
HN
N
N
N
43
2C
f1 (ppm)

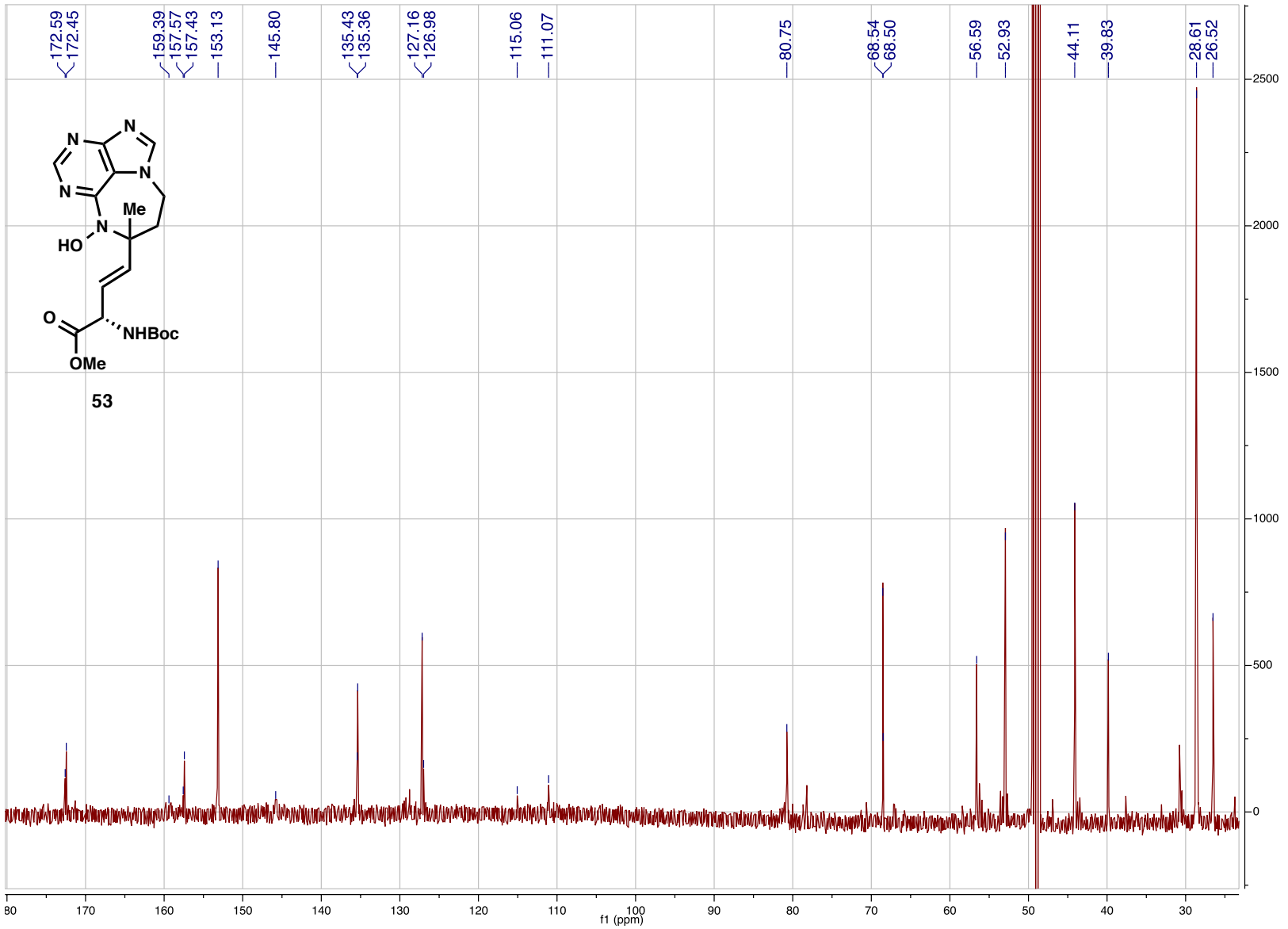

8.56
7.99
7.26
7.19
5.65
4.29
3.60
3.15
2.50
1.78
1.22
Me
HO
Me
O
OMe
52
1.00
0.99
2.01
1.98
1.54
1.37
0.99
2.01
2.97
3.07
f1 (ppm)

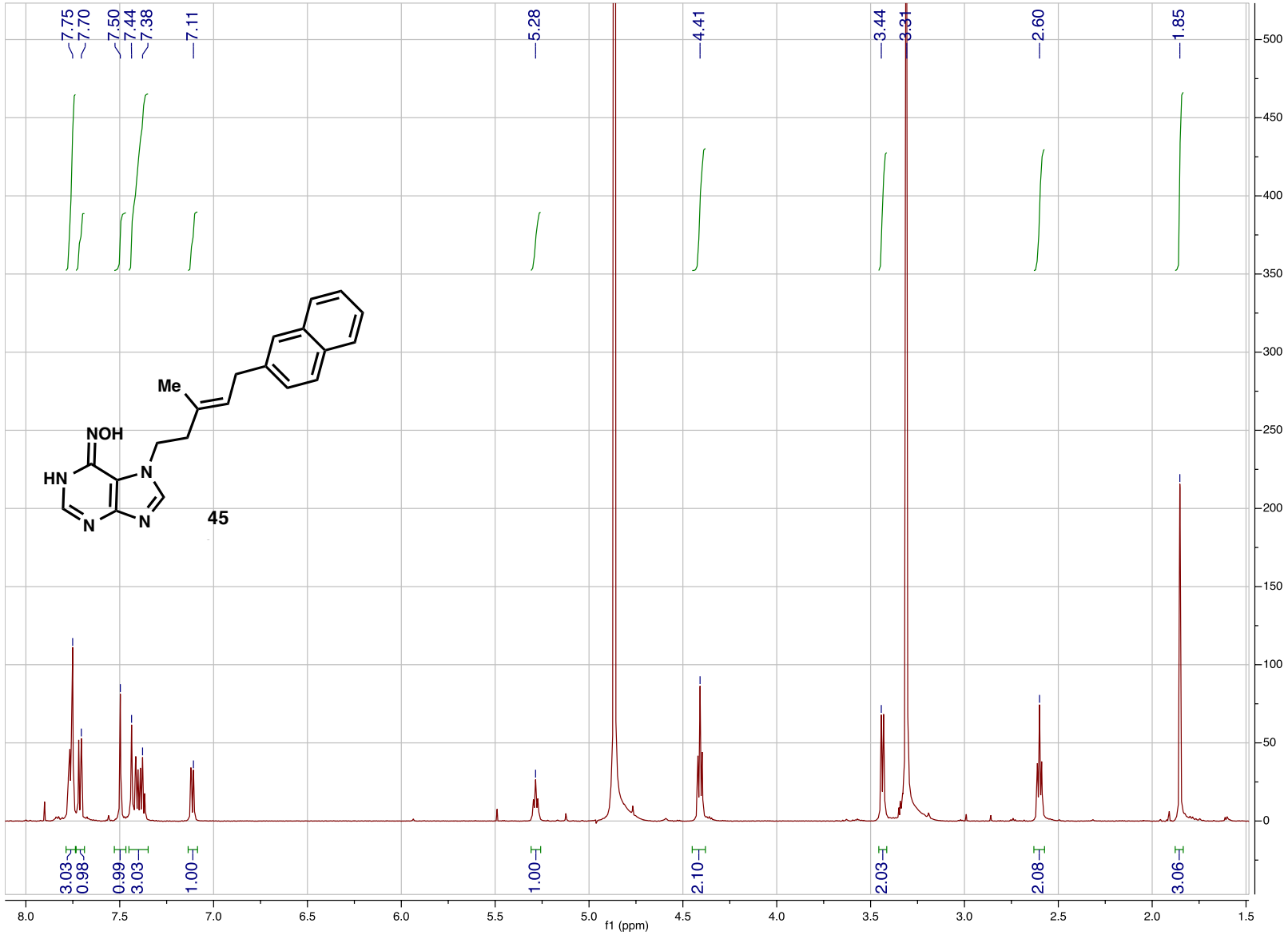

174.71
174.55
159.06
159.00
151.83
150.16
150.14
143.67
143.56
131.67
131.60
131.34
131.25
109.75
109.72
77.16
66.10
52.15
42.96
42.94
42.40
42.30
39.37
39.34
25.96
25.73
17.34
17.16
N
N
N
N
N
Me
HO
Me
O
OMe
52
f1 (ppm)

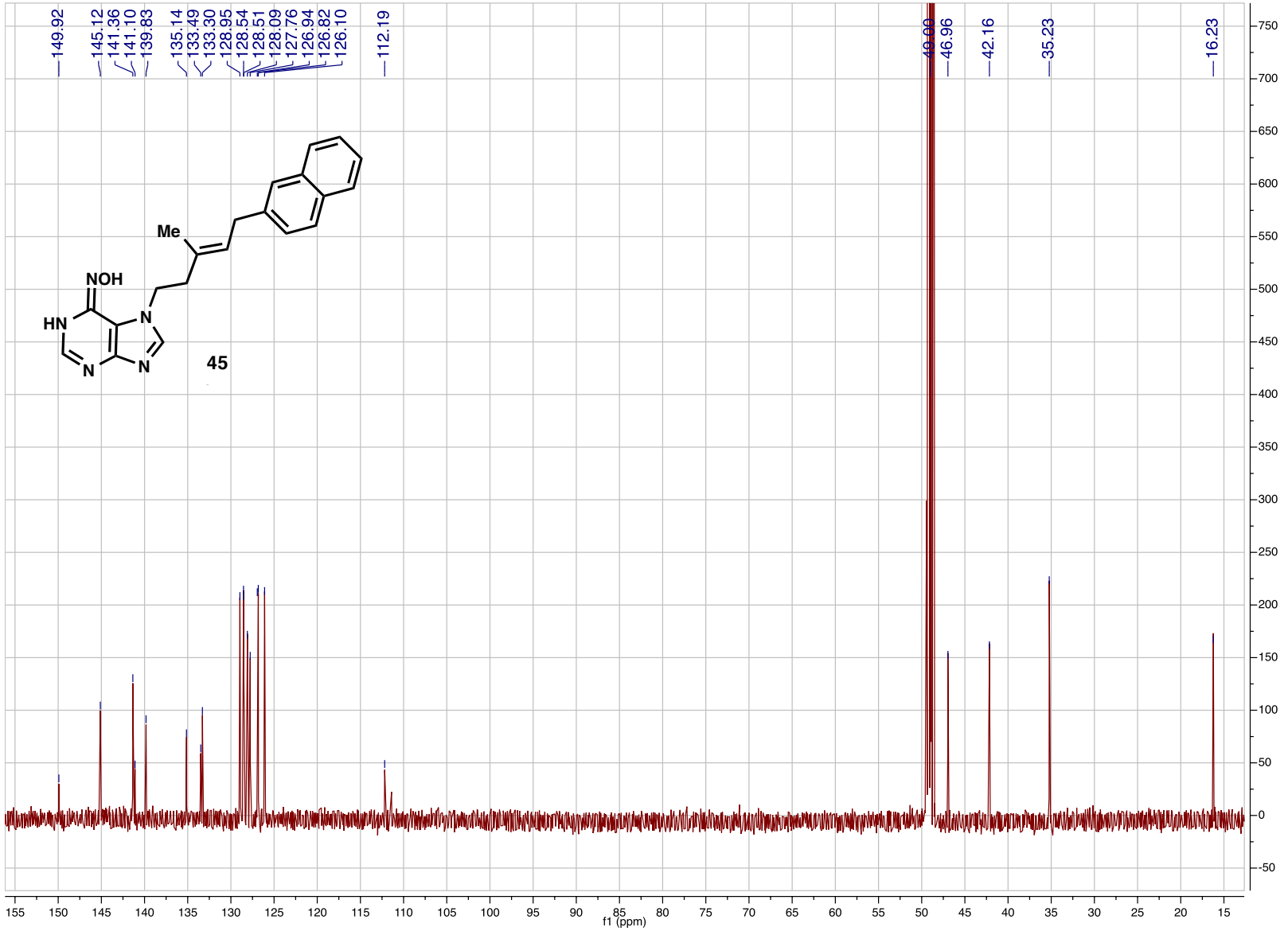

7.72
7.56
5.06
4.33
4.08
3.68
3.31
2.51
2.44
2.34
1.69
1.43
CO2Me
NHBoc
Me
NOH
HN
N
N
N
44
1.05
1.10
1.00
2.04
0.99
3.03
1.95
0.90
0.97
3.07
9.05
f1 (ppm)

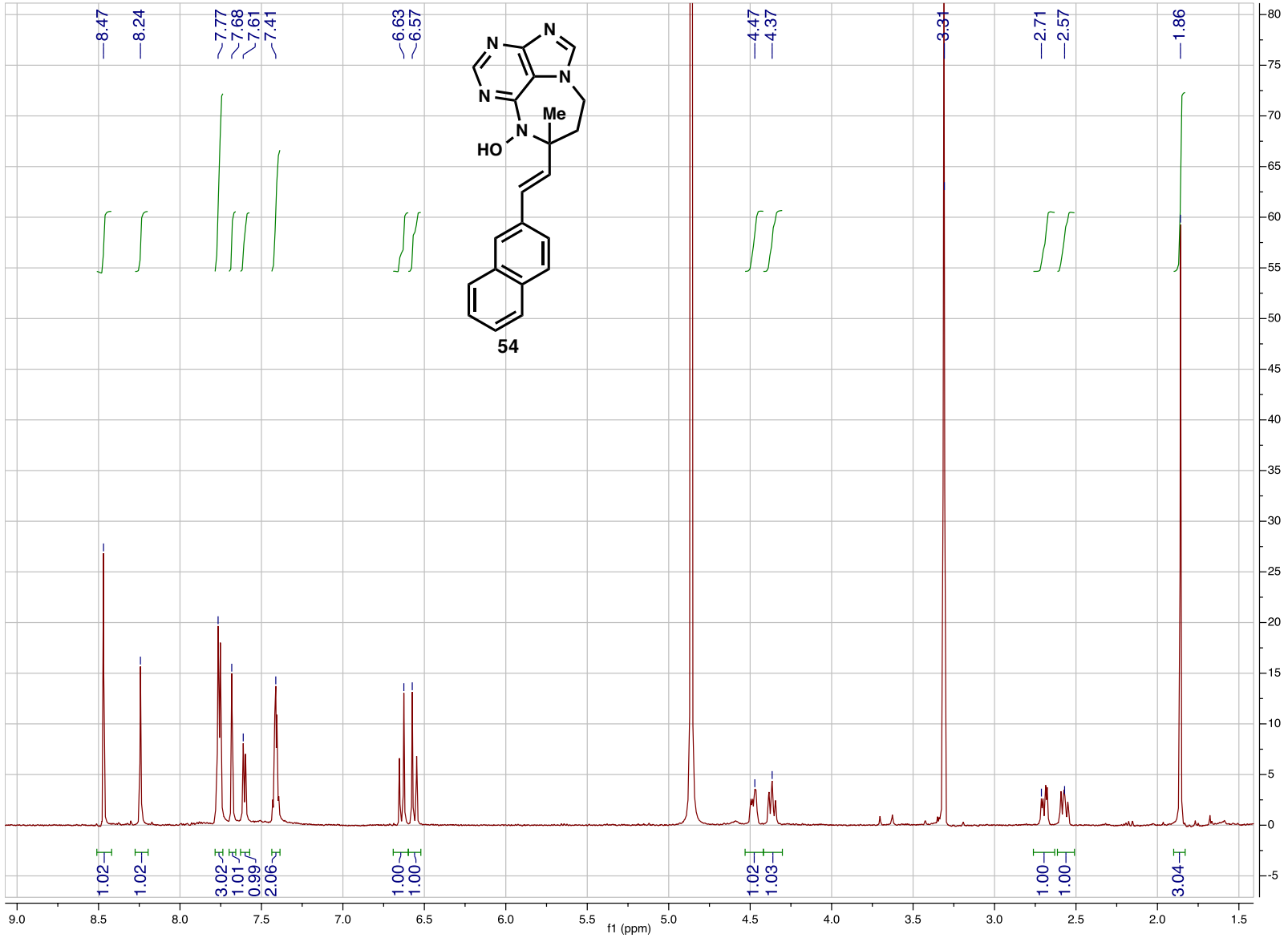

174.19
157.83
150.07
145.23
141.34
141.06
136.06
123.23
112.06
80.66
55.00
52.65
49.00
47.29
42.16
31.36
28.70
16.30
CO2Me
NHBoc
Me
NOH
HN
N
N
N
44
f1 (ppm)

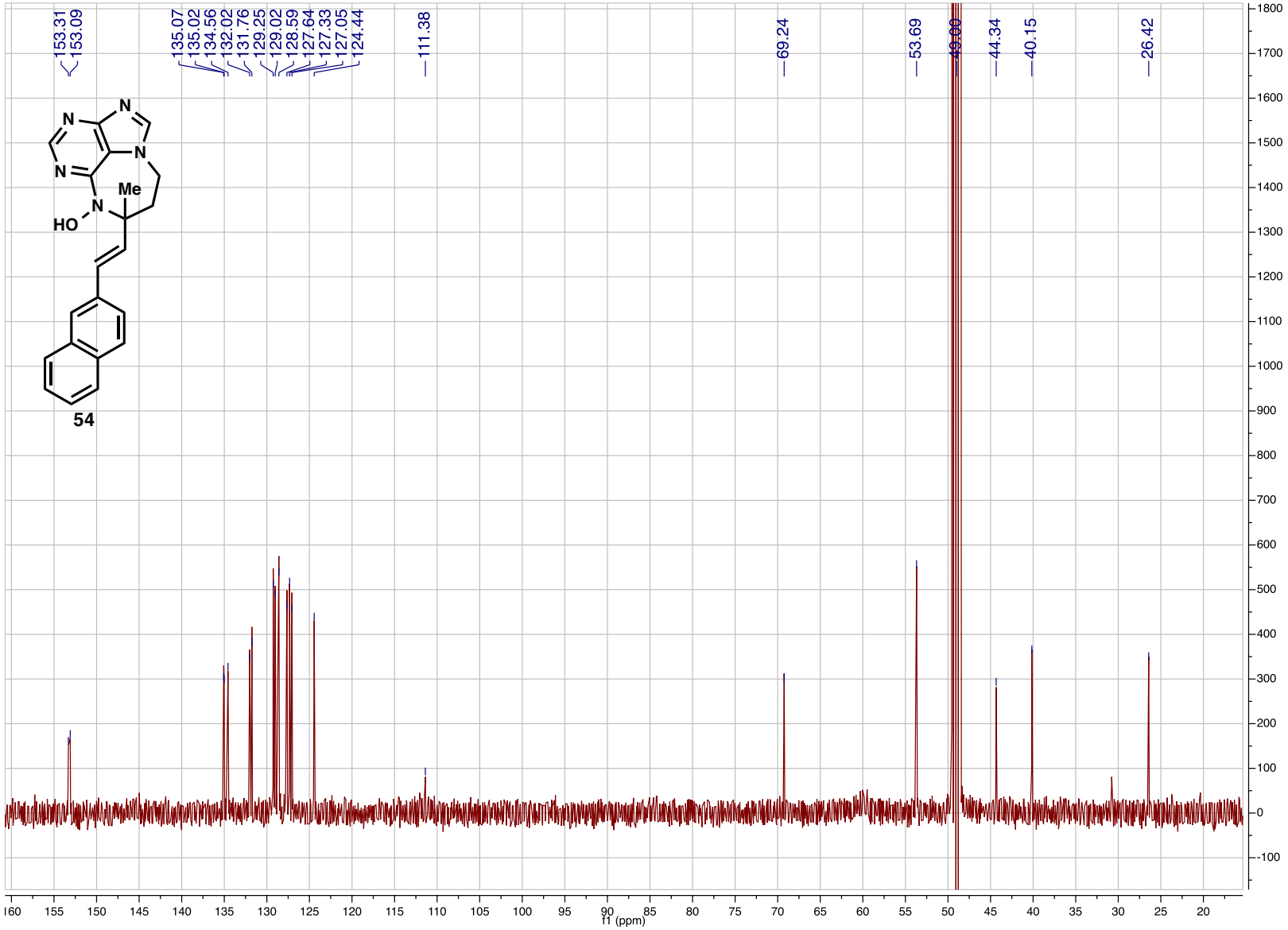

8.32
8.09
6.81
5.80
5.49
5.12
4.58
4.35
4.19
3.47
3.42
2.34
1.62
1.25
N
N
N
N
N
Me
HO
O
NHBoc
OMe
53
1.03
1.04
1.04
0.99
0.98
3.04
1.93
0.87
2.08
3.00
9.04
f1 (ppm)

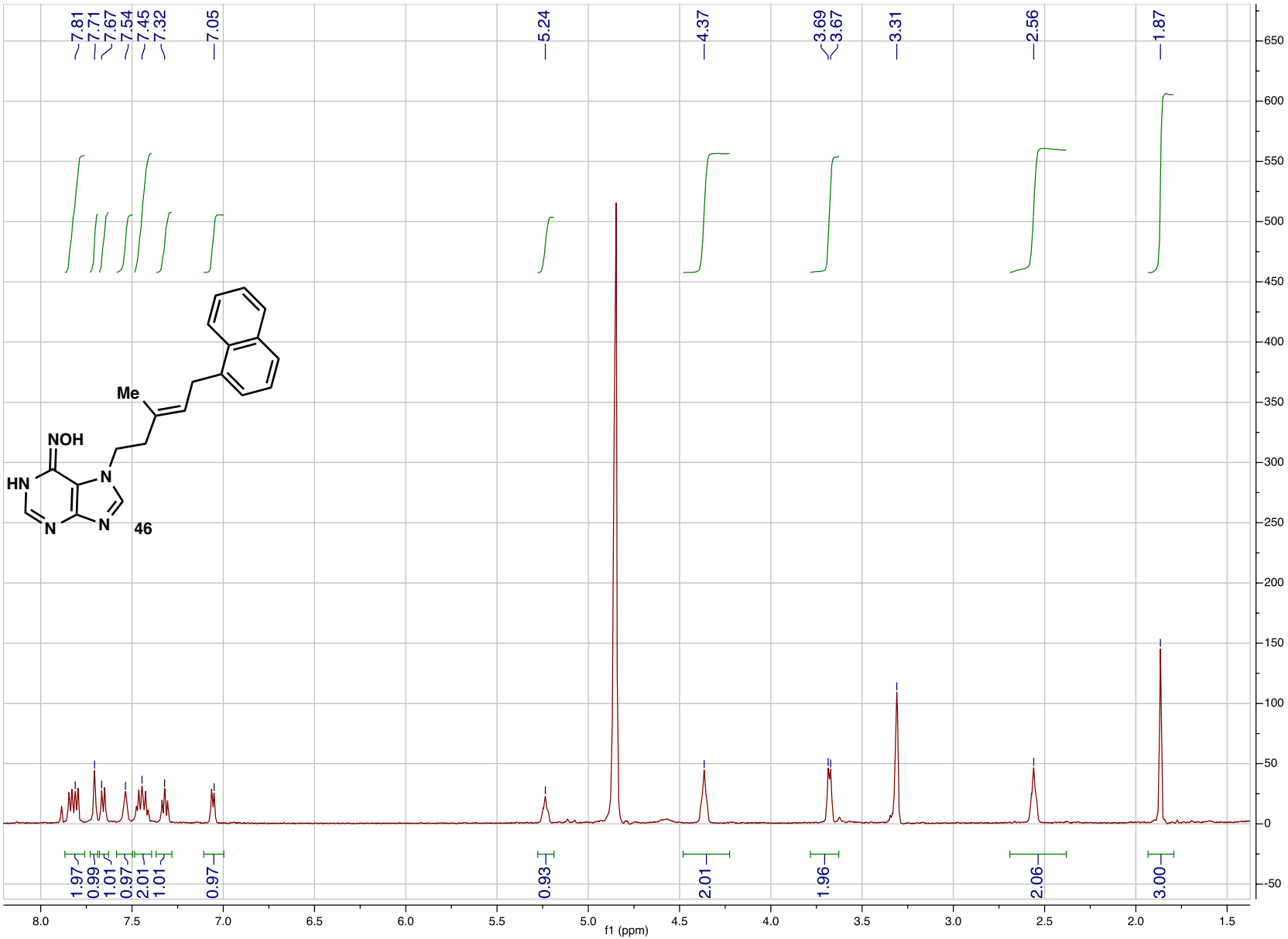

172.59
172.45
159.39
157.57
157.43
153.13
145.80
135.43
135.36
127.16
126.98
115.06
111.07
80.75
68.54
68.50
56.59
52.93
44.11
39.83
28.61
26.52
N
N
N
N
N
Me
HO
O
NHBoc
OMe
53
2500
2000
1500
1000
500
0
f1 (ppm)

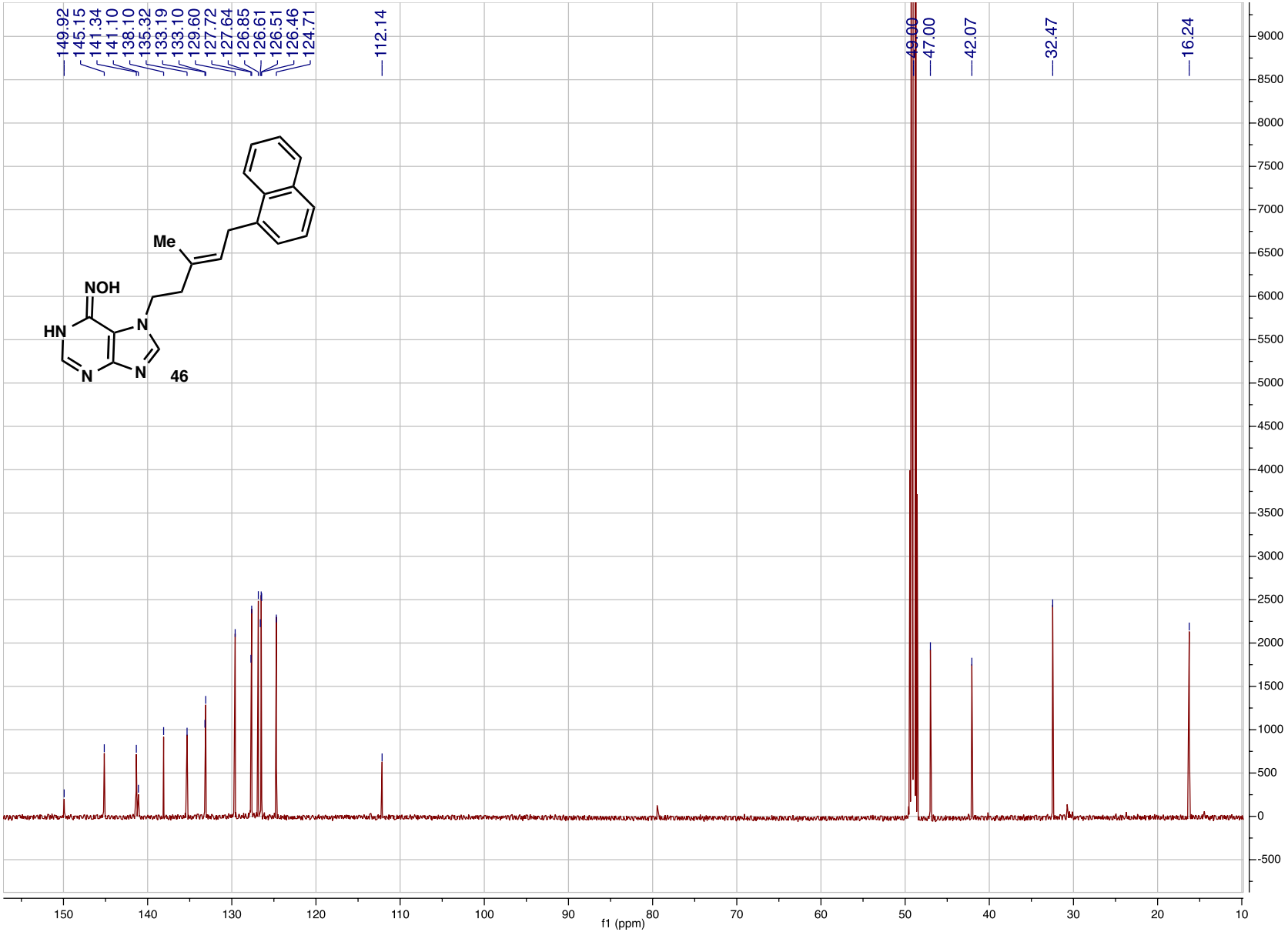

7.75
7.70
7.50
7.44
7.38
7.11
5.28
4.41
3.44
3.31
2.60
1.85
Me
NOH
HN
N
N
N
45
3.03
0.98
0.99
3.03
1.00
1.00
2.10
2.03
2.08
3.06
f1 (ppm)

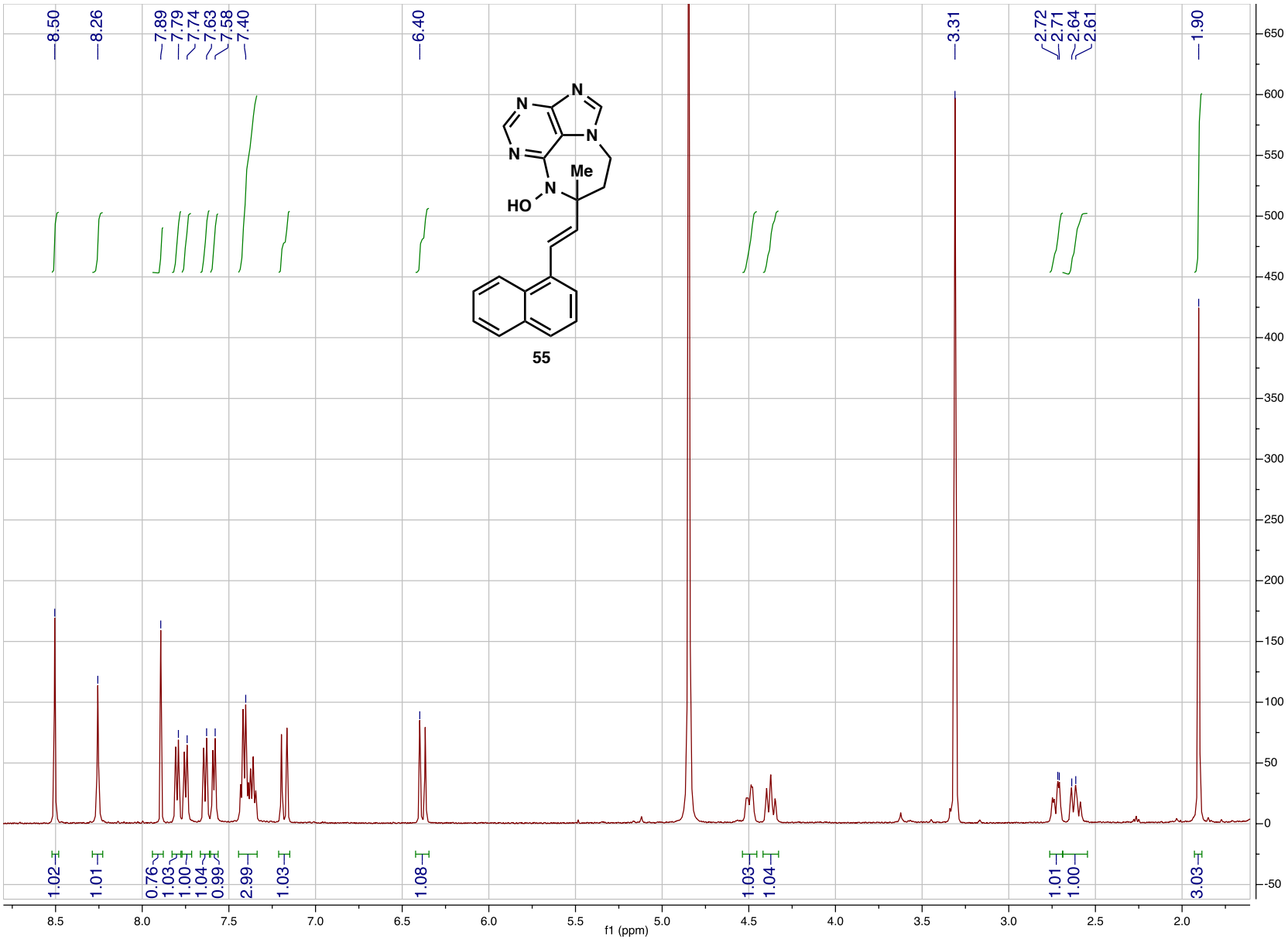

149.92
145.12
141.36
141.10
139.83
135.14
133.49
133.30
128.95
128.54
128.51
128.09
127.76
126.94
126.82
126.10
112.19
49.00
46.96
42.16
35.23
16.23
Me
NOH
HN
N
N
N
45
f1 (ppm)

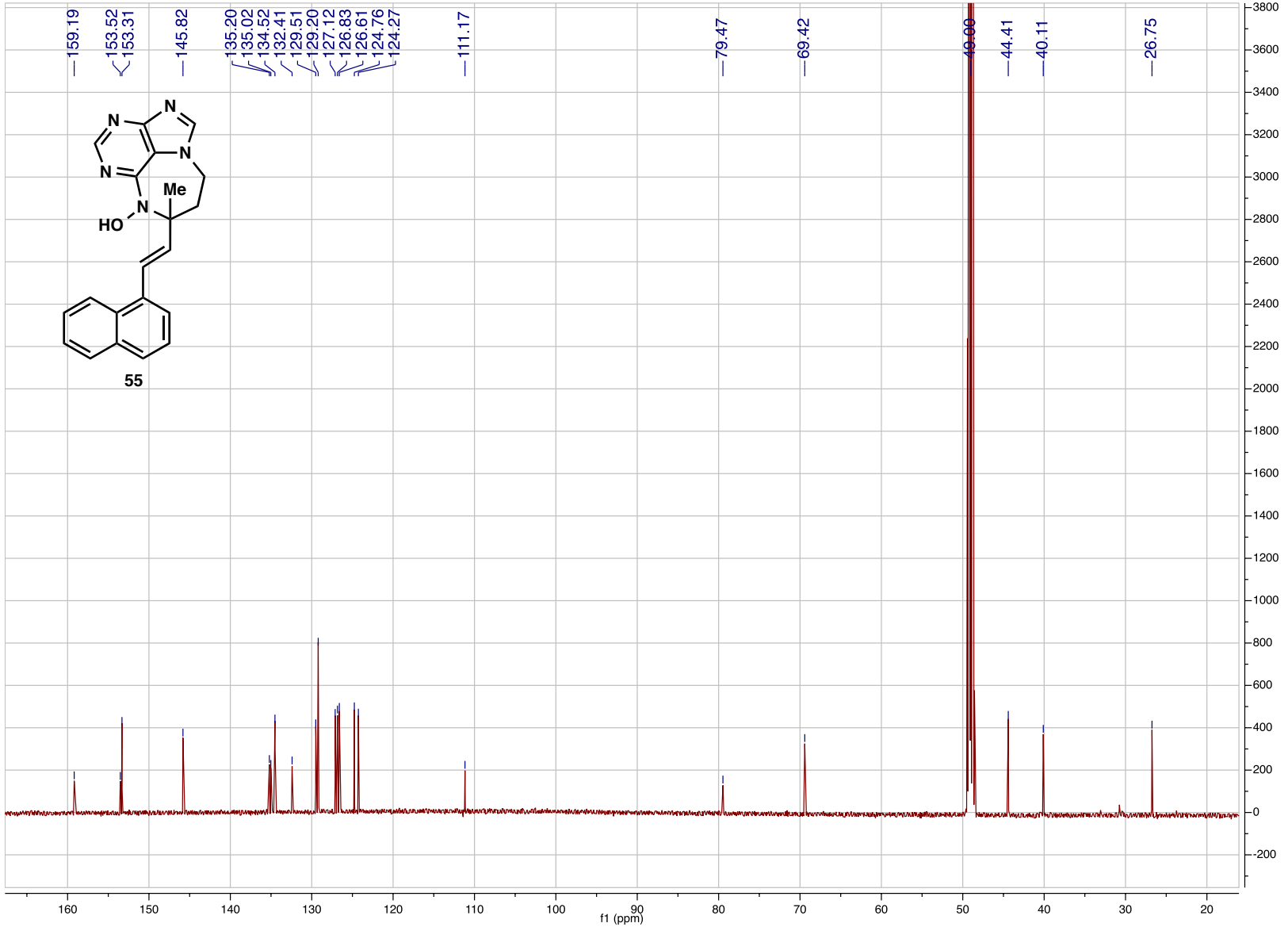

8.47
8.24
7.77
7.68
7.61
7.41
6.63
6.57
4.47
4.37
3.31
2.71
2.57
1.86
Me
HO
N
54
1.02
1.02
3.02
1.01
0.99
2.06
1.00
1.00
1.02
1.03
1.00
1.00
3.04
f1 (ppm)

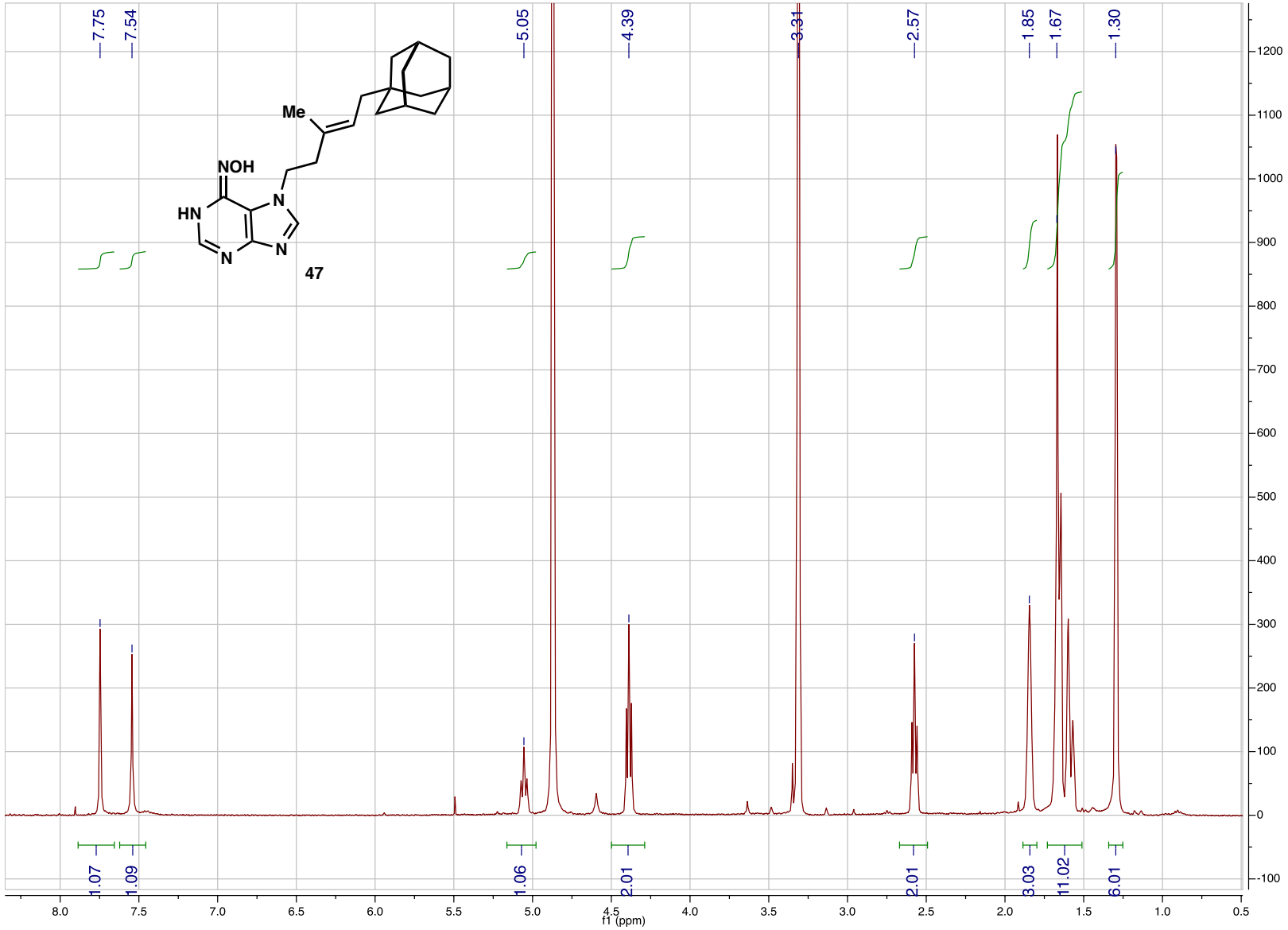

153.31
153.09
135.07
135.02
134.56
132.02
131.76
129.25
129.02
128.59
127.64
127.33
127.05
124.44
111.38
69.24
53.69
49.00
44.34
40.15
26.42
Me
HO
54
f1 (ppm)

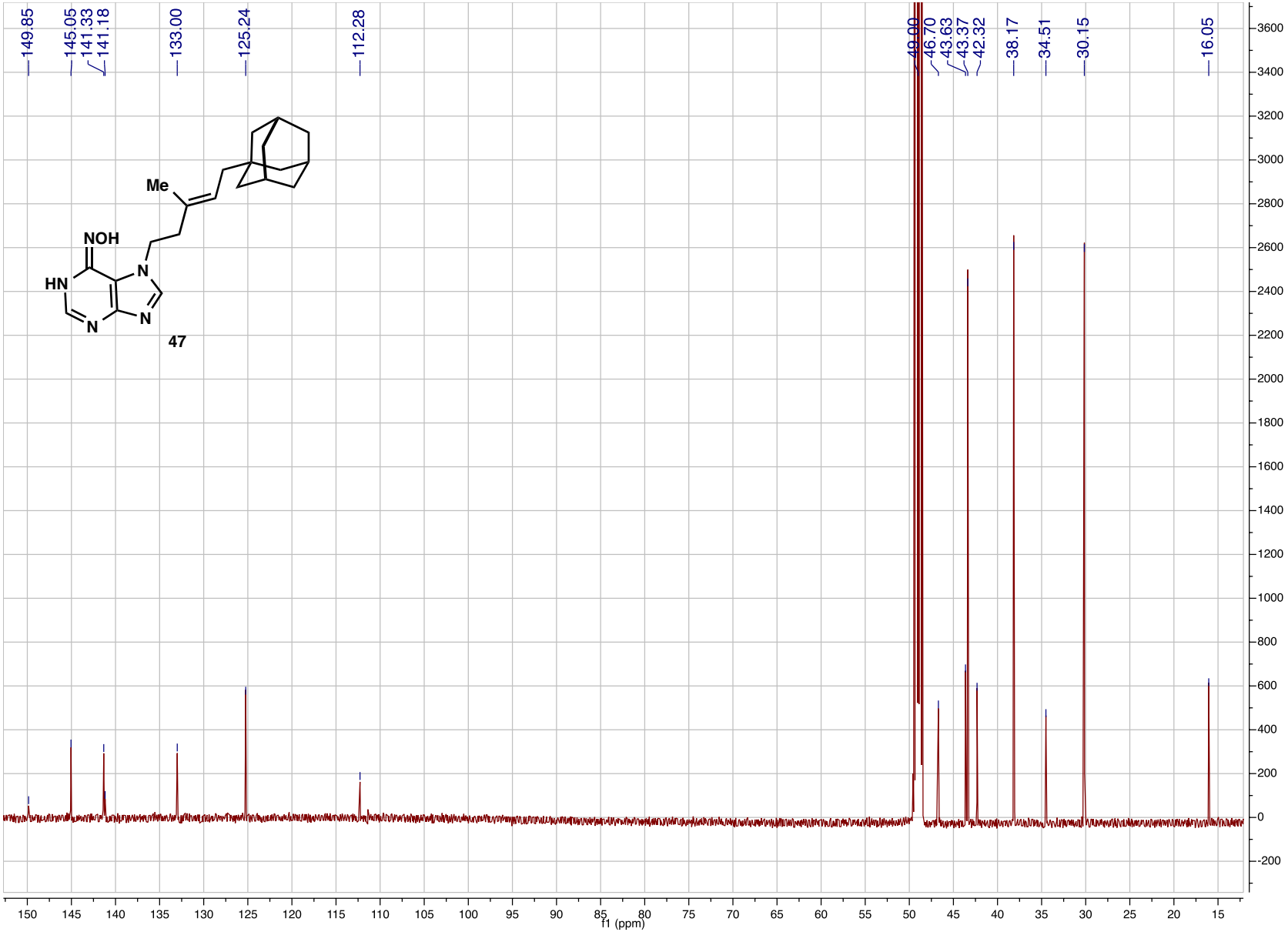

7.81
7.71
7.67
7.54
7.45
7.32
7.05
5.24
4.37
3.69
3.67
3.31
2.56
1.87
Me
NOH
HN
N
N
N
46
1.97
0.99
1.01
0.97
2.01
1.01
0.97
0.93
2.01
1.96
2.06
3.00
f1 (ppm)

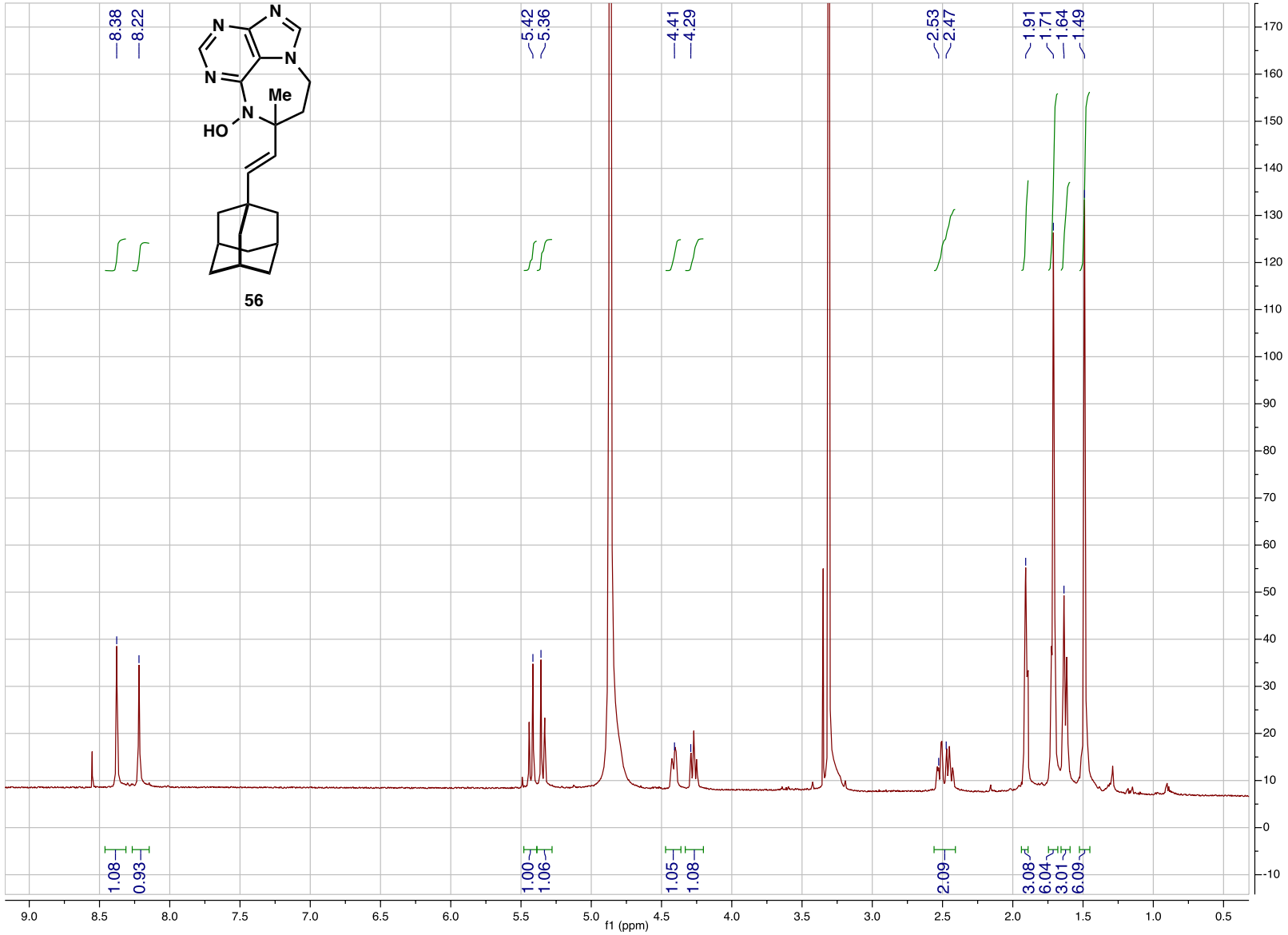

149.92
145.15
141.34
141.10
138.10
135.32
133.19
133.10
129.60
127.72
127.64
126.85
126.61
126.51
126.46
124.71
112.14
49.00
47.00
42.07
32.47
16.24
Me
NOH
HN
N
N
N
46
f1 (ppm)

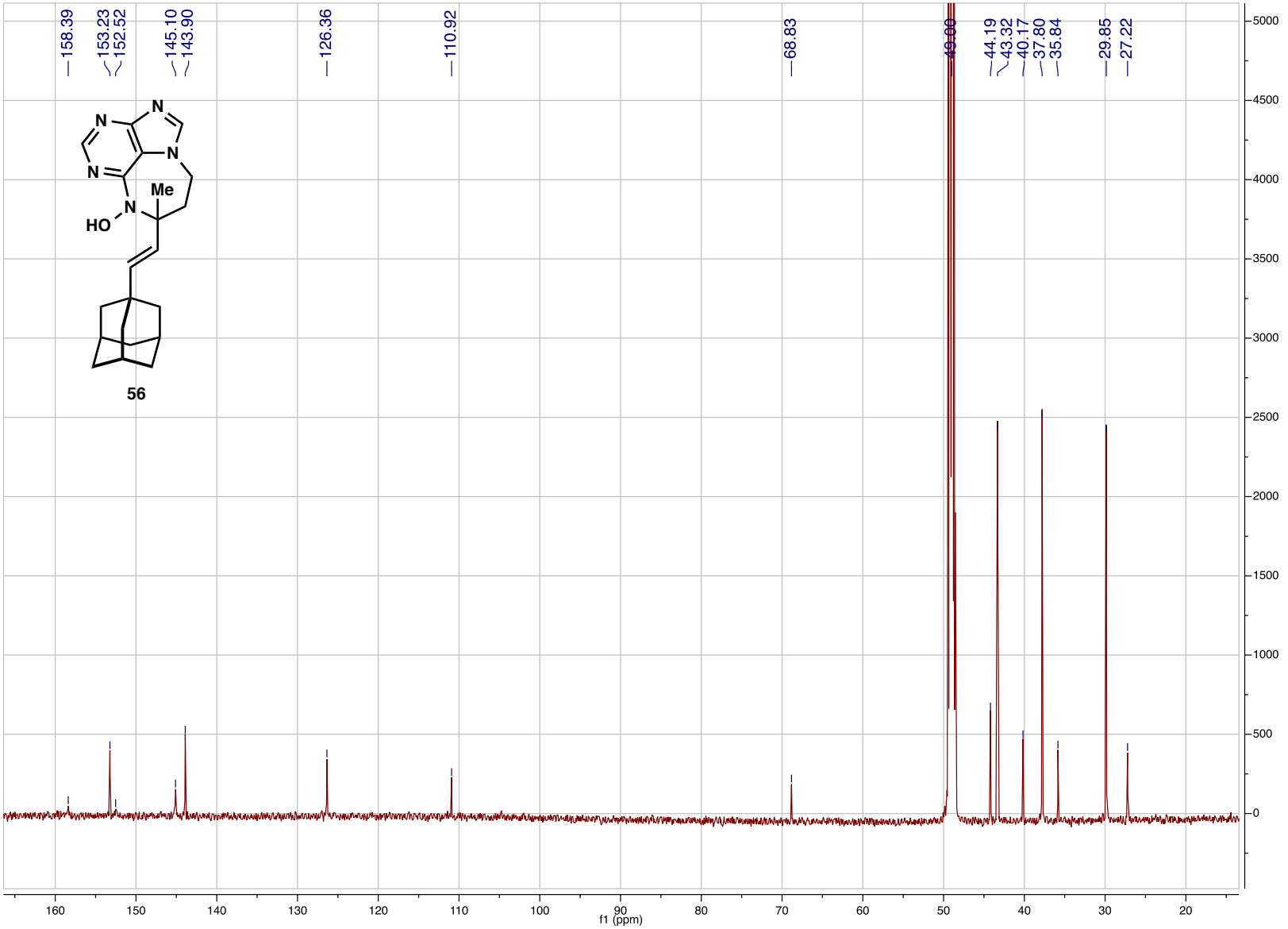

8.50
8.26
7.89
7.79
7.74
7.63
7.58
7.40
6.40
3.31
2.72
2.71
2.64
2.61
1.90
N
N
N
N
N
Me
HO
55
1.02
1.01
0.76
1.03
1.00
1.04
0.99
2.99
1.03
1.08
1.03
1.04
1.01
1.00
3.03
f1 (ppm)

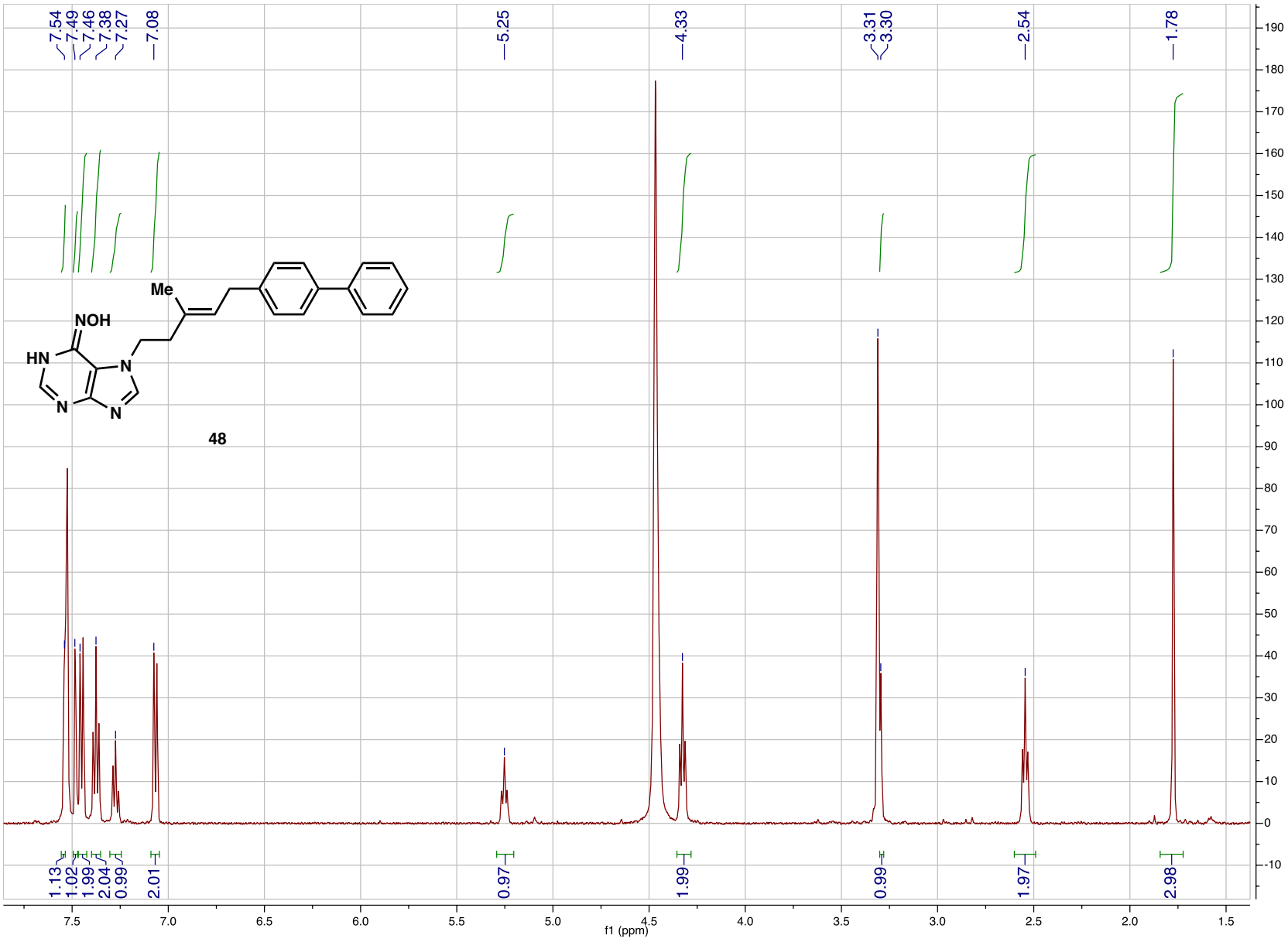

159.19
153.52
153.31
145.82
135.20
135.02
134.52
132.41
129.51
129.20
127.12
126.83
126.61
124.76
124.27
111.17
79.47
69.42
49.00
44.41
40.11
26.75
N
N
N
N
N
Me
HO
55
f1 (ppm)

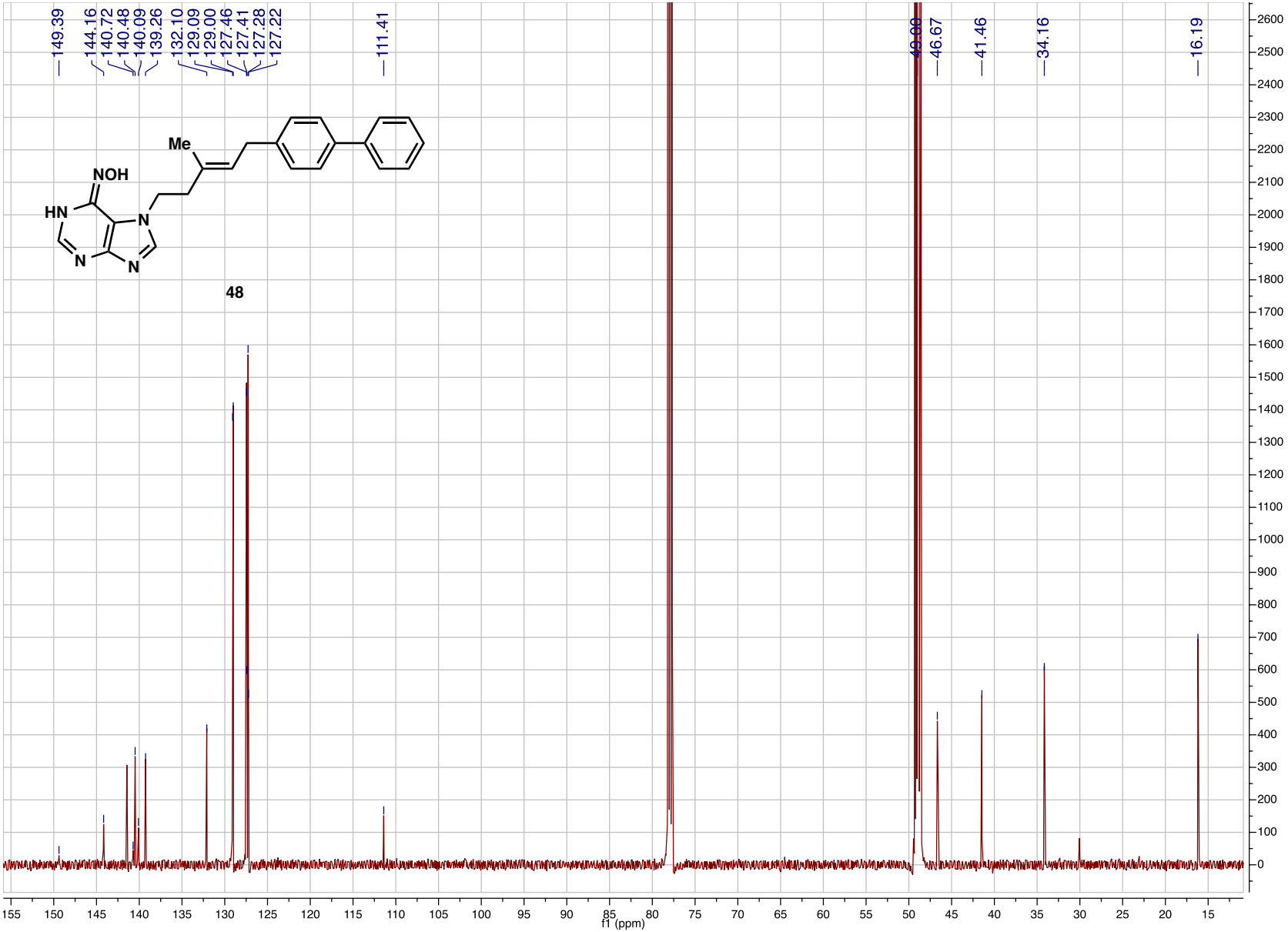

7.75
7.54
5.05
4.39
3.31
2.57
1.85
1.67
1.30
Me
NOH
HN
N
N
N
47
1.07
1.09
1.06
2.01
2.01
3.03
11.02
6.01
f1 (ppm)

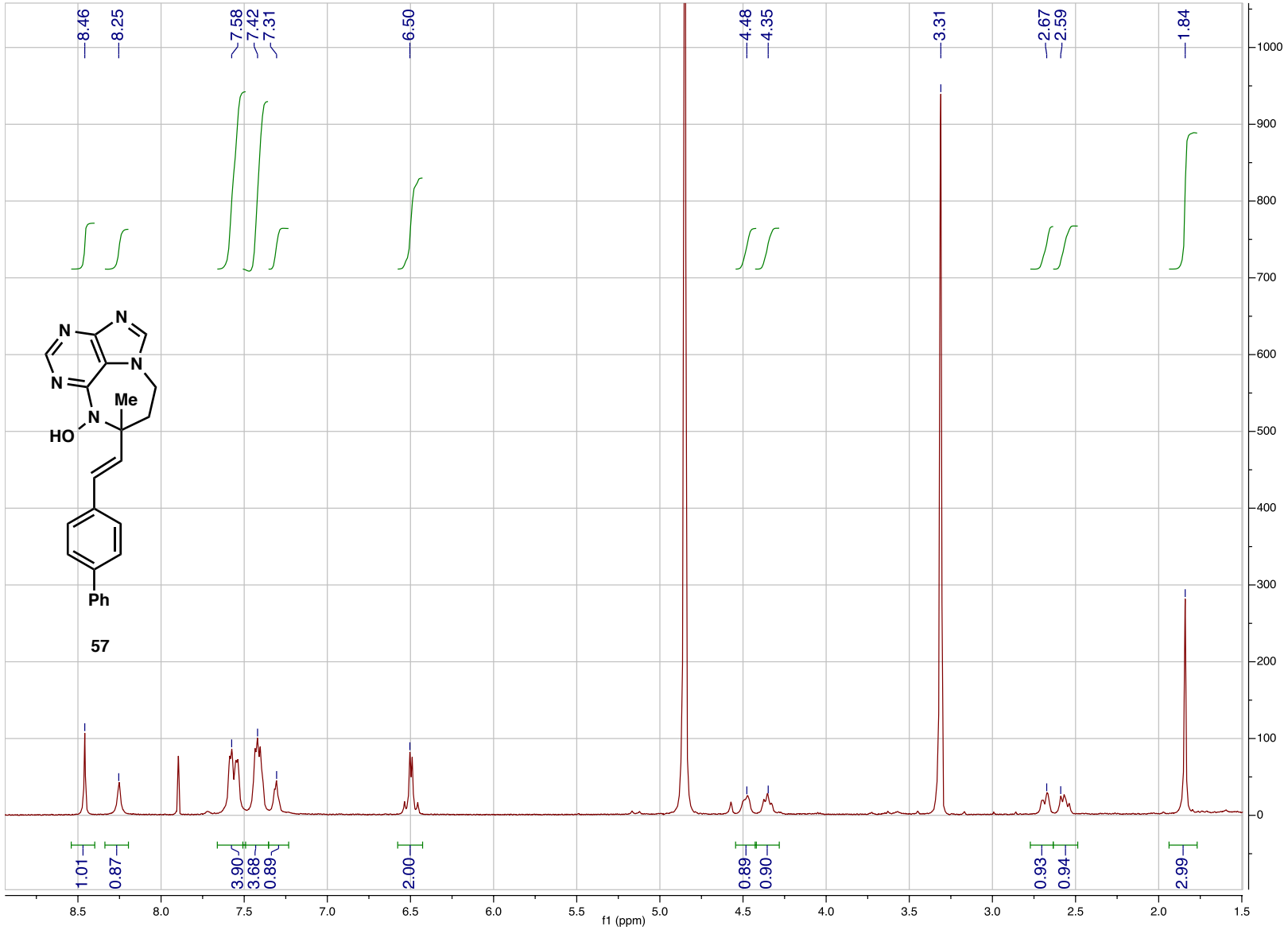

149.85
145.05
141.33
141.18
133.00
125.24
112.28
49.00
46.70
43.63
43.37
42.32
38.17
34.51
30.15
16.05
Me
NOH
HN
N
N
N
47
f1 (ppm)

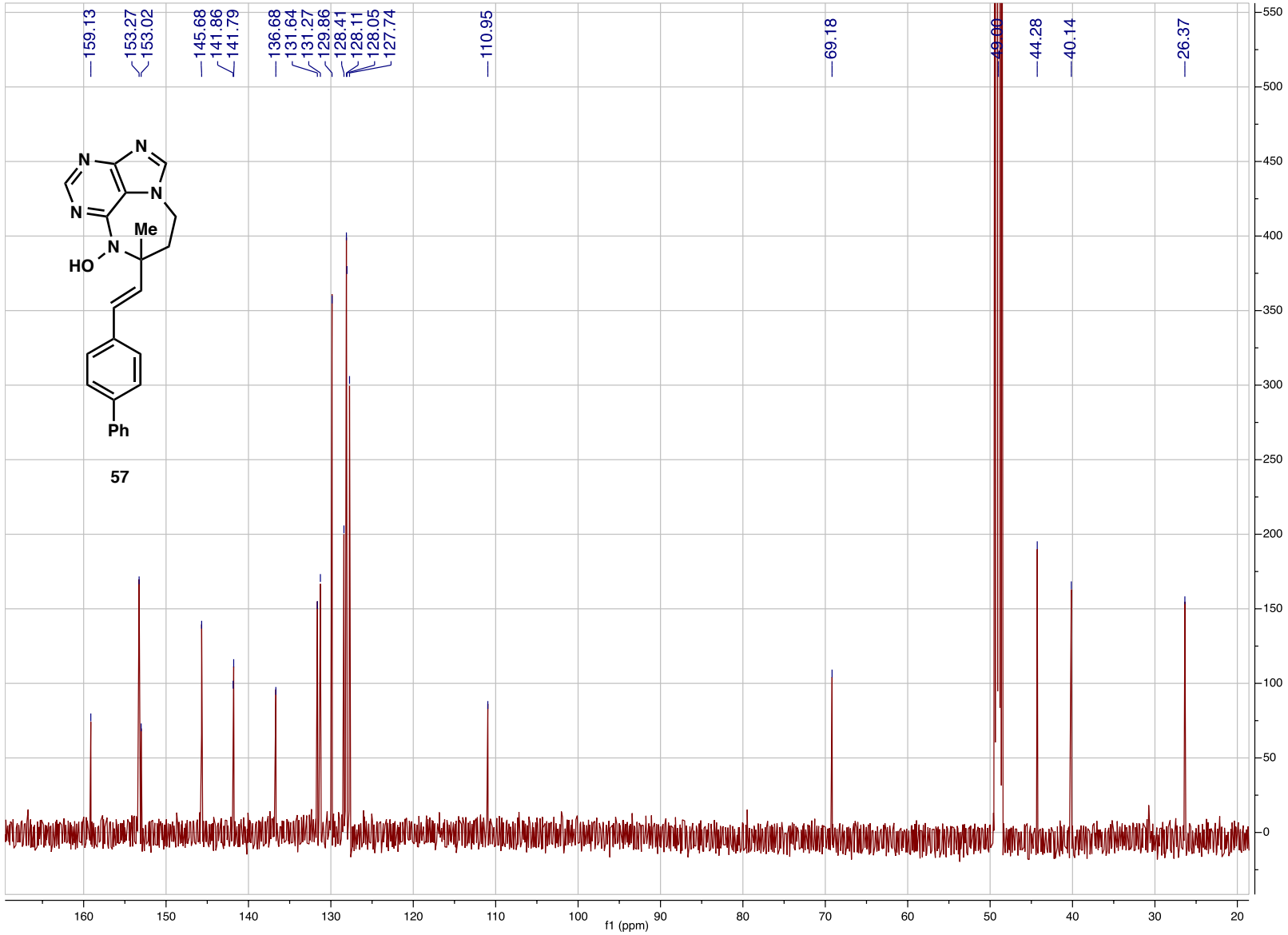

8.38
8.22
5.42
5.36
4.41
4.29
2.53
2.47
1.91
1.71
1.64
1.49
N
N
N
N
N
Me
HO
56
1.08
0.93
1.00
1.06
1.05
1.08
2.09
3.08
6.04
3.01
6.09
f1 (ppm)


158.39
153.23
152.52
145.10
143.90
126.36
110.92
68.83
49.00
44.19
43.32
40.17
37.80
35.84
29.85
27.22
N
N
N
N
N
Me
HO
56
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


7.54
7.49
7.46
7.38
7.27
7.08
5.25
4.33
3.31
3.30
2.54
1.78
Me
NOH
HN
N
N
N
48
1.13
1.02
1.99
2.04
0.99
2.01
0.97
1.99
0.99
1.97
2.98
f1 (ppm)


149.39
144.16
140.72
140.48
140.09
139.26
132.10
129.09
129.00
127.46
127.41
127.28
127.22
111.41
49.00
46.67
41.46
34.16
16.19
Me
NOH
HN
N
N
N
48
f1 (ppm)


8.46
8.25
7.58
7.42
7.31
6.50
4.48
4.35
3.31
2.67
2.59
1.84
1000
900
800
700
600
500
400
300
200
100
0
N
N
N
N
N
Me
HO
Ph
57
1.01
0.87
3.90
3.68
0.89
2.00
0.89
0.90
0.93
0.94
2.99
8.5
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
f1 (ppm)


159.13
153.27
153.02
145.68
141.86
141.79
136.68
131.64
131.27
129.86
128.41
128.11
128.05
127.74
110.95
69.18
49.00
44.28
40.14
26.37
N
N
N
N
N
Me
HO
Ph
57
f1 (ppm)