Total synthesis of structurally-diverse pleuromutilin antibiotics.

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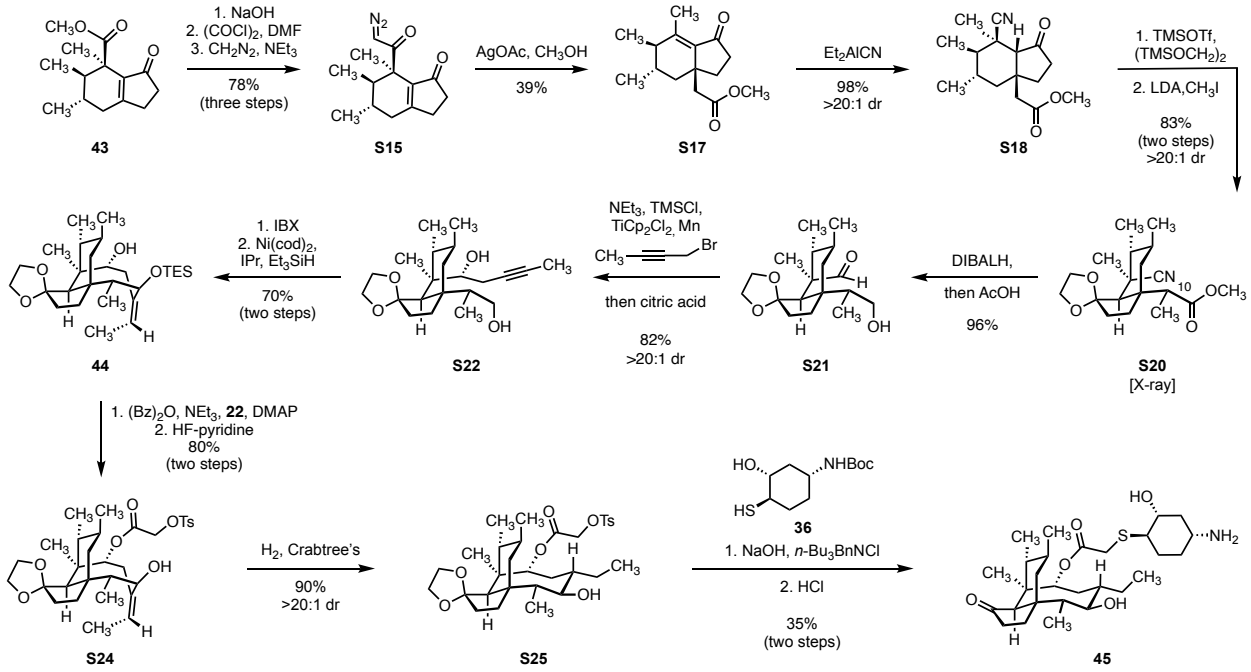


Figure S1. Preparation of the C7-substituted analog **45**.

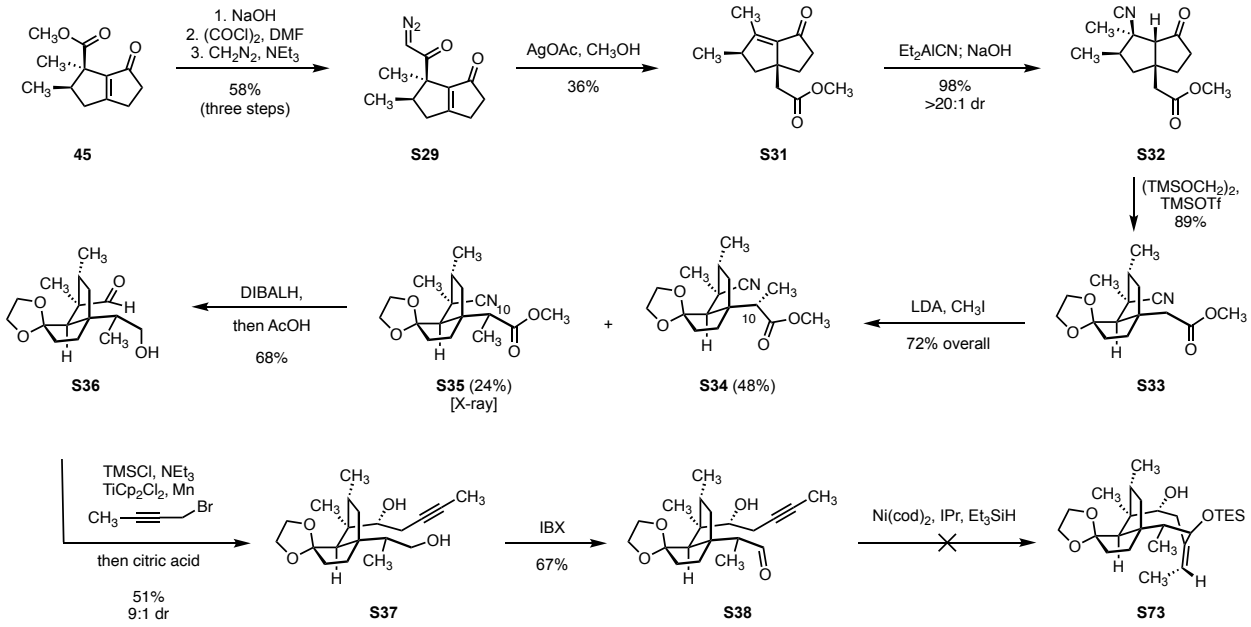


Figure S2. Preparation of the ring-contracted cyclization precursor **S38** and attempted ring closure.

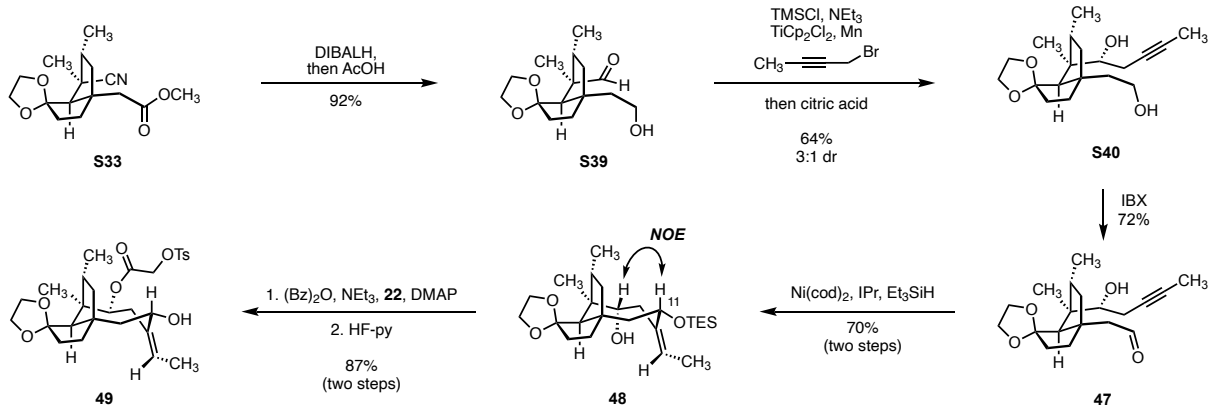


Figure S3. Elaboration of the C10 normethyl cyanoester **S33** to the tosylate **49**.

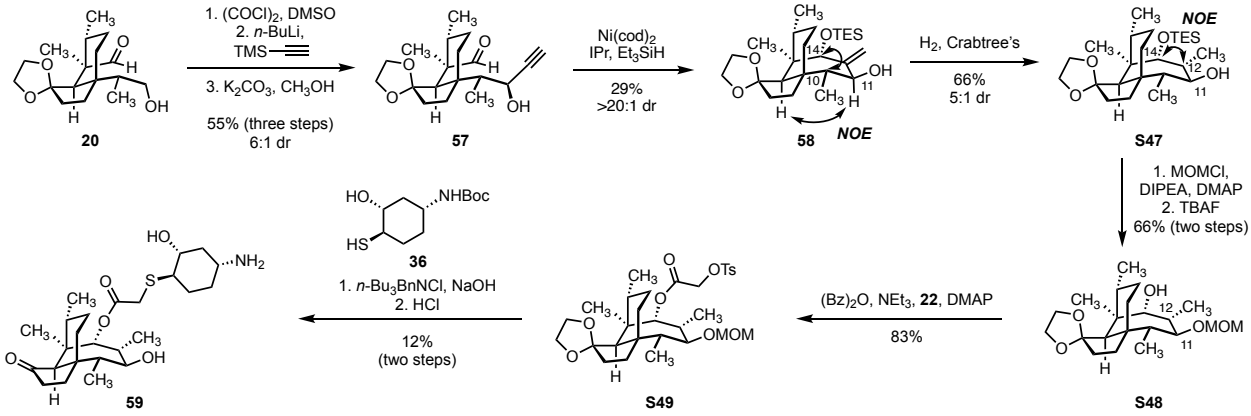


Figure S4. Synthesis of the seven-membered ring derivative **59** from the common precursor **20**.

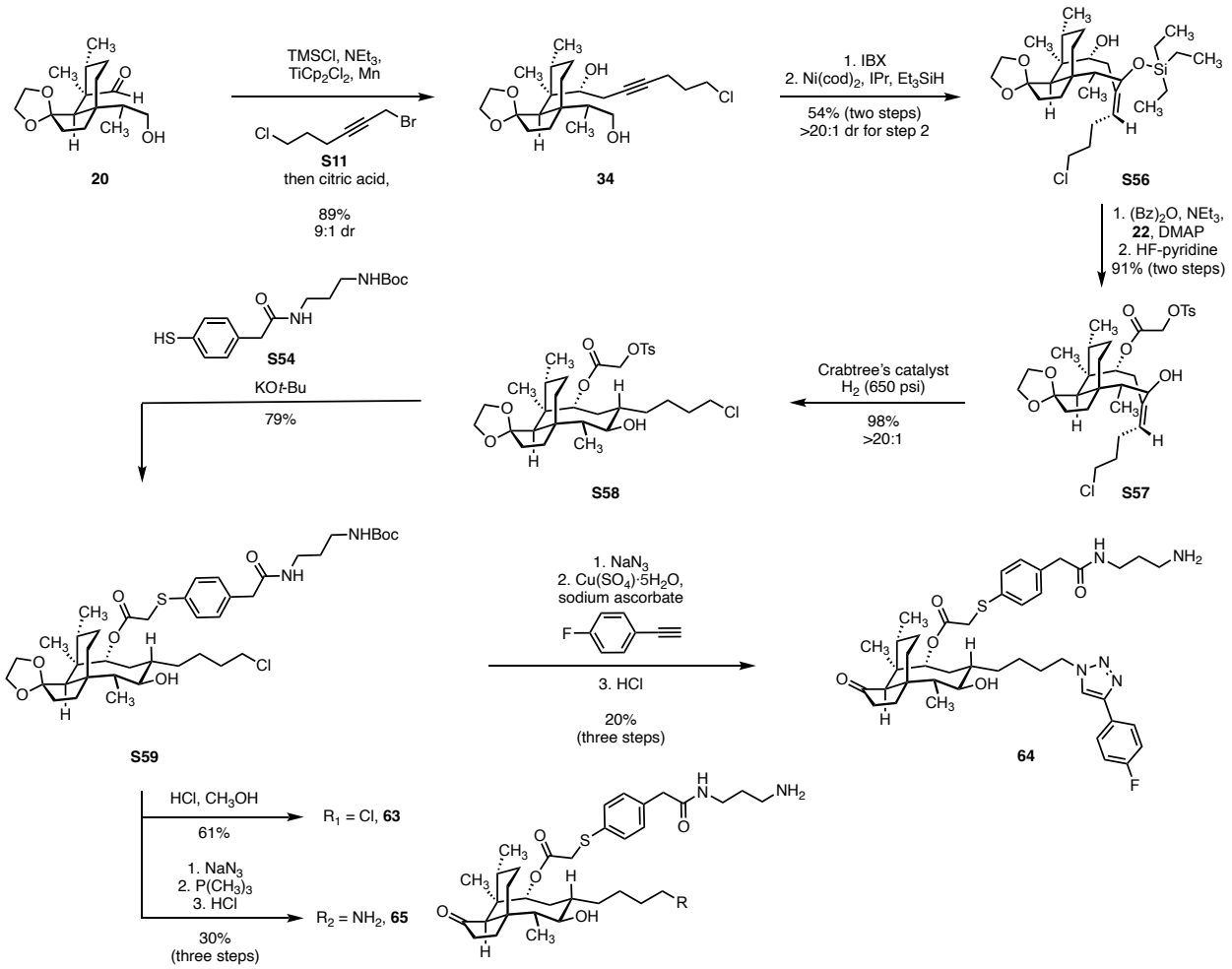


Figure S5. Preparation of the analogs **63**, **64** and **65** from the common precursor **20**.

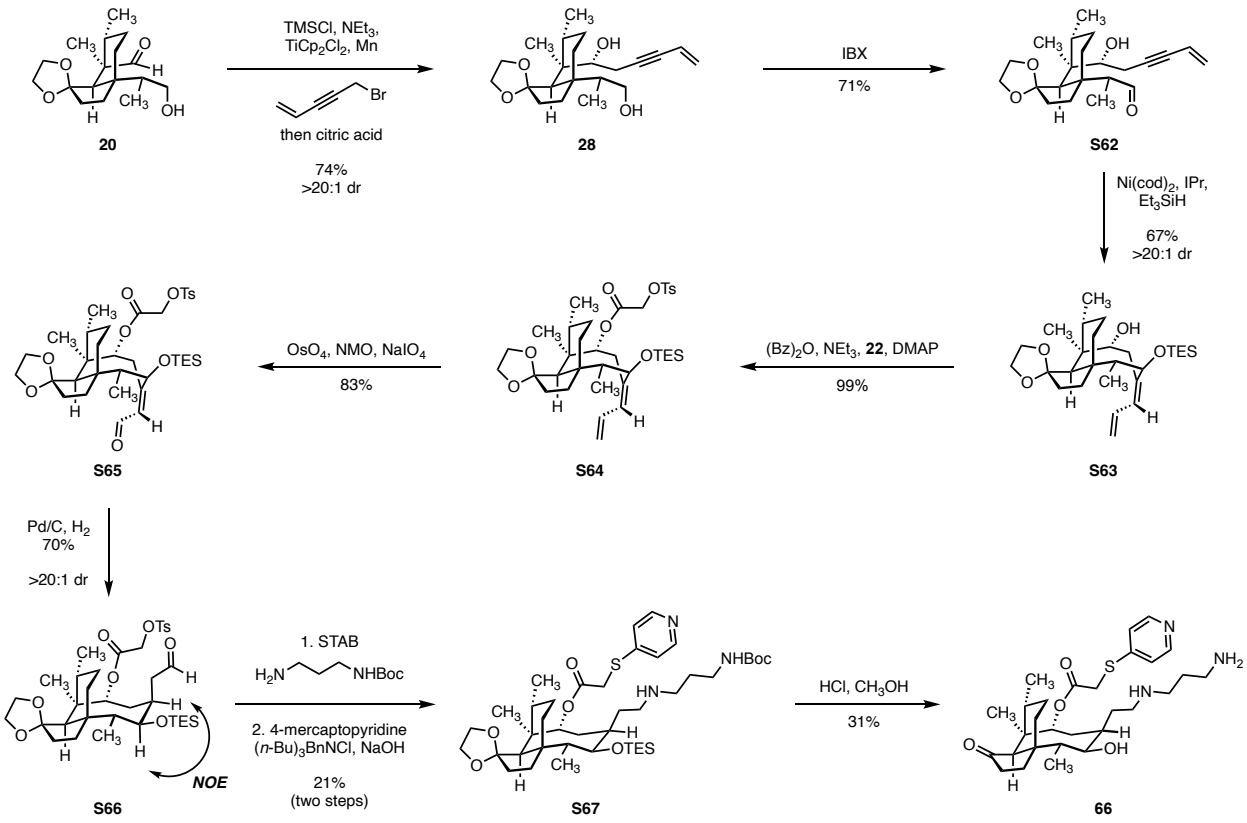


Figure S6. Synthesis of the analog **66** from the common precursor **20**.

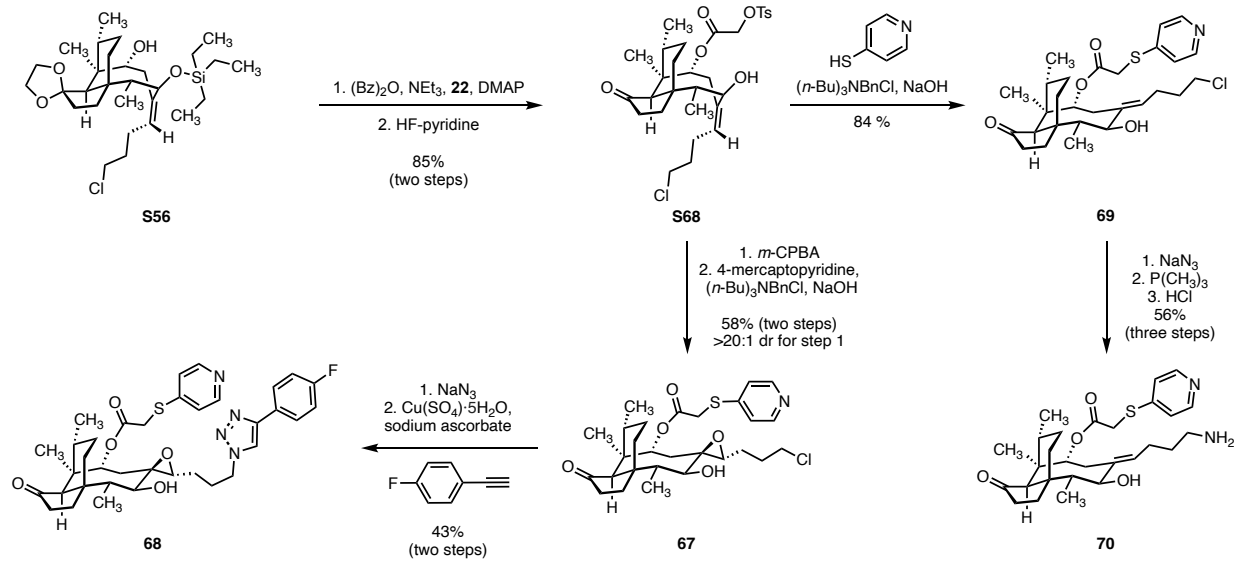
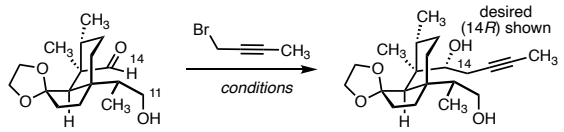


Figure S7. Preparation of the C12 modified analogs **67**, **68**, **69** and **70** from the macrocyclization product **S56**.

Table S1. Optimization of the butynylation of **20**.[a]



20 **21**

entry	conditions	yield[b]	dr (*R*:*S*)[c]
1	Mg, ether	30%	1:3
2	Mg, glyme	33%	1:1.5
3	$TiCp_2Cl_2$ (1.0 equiv), Mn, collidine, TMSCl	21%	>20:1
4	$TiCp_2Cl_2$ (3.0 equiv), Mn, NEt_3, TMSCl (dilute with citric acid)	46%	>20:1
5	$TiCp_2Cl_2$ (3.0 equiv), Mn, NEt_3, TMSCl (reverse addition)	81%	37:1

[a]General reaction conditions: **20** (33.7 μmol), TMSCl (1.00 equiv), collidine or NEt_3 (2.00 equiv), $TiCp_2Cl_2$ (3.00 equiv), Mn (12.0 equiv), propargyl bromide (3.50 equiv), THF (40 mM), 22 °C, 3h. [b]Isolated yields of **21** after purification by flash-column chromatography. [c]Determined by ^{1}H NMR spectroscopy of the unpurified product mixture.

General experimental procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,[1] employing silica gel ('SiliaFlash® P60', 60 Å, 40–63 μm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (250 μm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM), *p*-anisaldehyde (PAA), or aqueous potassium permanganate solution ($KMnO_4$), followed by brief heating on a hot plate (120 °C, 10–15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), *N*,*N*-dimethylformamide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.[2] Triethylamine was distilled from calcium hydride immediately prior to use. Di-*iso*-propylethylamine was distilled from calcium hydride and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon. The molarities of *n*-butyllithium and methyllithium solutions were determined by titration against a standard solution of menthol and 1,10-phenanthroline in tetrahydrofuran (average of three determinations).[3] Trimethylsilyl trifluoromethanesulfonate was purified by vacuum distillation and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon at –20 °C. Triethylsilane were purified by fractional distillation and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon. Diazomethane,[4] 2-iodoxybenzoic acid,[5] (1-but-2-ynyl)magnesium bromide,[6] diethyl allyl phosphate,[7] 6-bromohex-1-en-4-yne,[8] pent-4-en-2-yn-1-ol,[9] 2-((5-bromopent-3-yn-1-yl)oxy)tetrahydro-2*H*-pyran,[10] 1-(allyloxy)-4-bromobut-2-yne,[11] the hydrindenone **6**,[12] *O*-(tosyloxy)acetic acid (**22**),[13] *tert*-butyl-((1*R*,3*R*,4*R*)-3-hydroxy-4-mercaptocyclohexyl) carbamate (**36**),[14] the β-keto ester **38**,[15] pleuromutilin-22-*O*-tosylate (**S1**),[14] 4-(trimethylsilyl)but-2-yn-1-ol (**S8**),[17] 6-chlorohex-2-yn-1-ol (**S10**),[18] *O*-[(*tert*-butyldiphenyl)-silyl]-12-*epi*-pleuromutilin (**S51**),[16] (+)-12-*epi*-pleuromutilin (**S52**),[16] and *tert*-butyl (3-(2-(4-mercaptophenyl)acetamido)propyl) carbamate (**S54**)[19] were prepared according to published procedures. (+)-Pleuromutilin (**1**) was purchased from Toronto Research Chemicals.

Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400, 500, or 600 megahertz (MHz) at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.16; CD_2HOD, δ 3.31; DHO, δ 4.79; C_2D_6OS, δ 2.50). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100, 125, or 150 MHz at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.1; CD_3OD, δ 49.0). Distortionless enhancement by polarization transfer [DEPT (135)], heteronuclear single quantum coherence (HSQC), and hetereonuclear multiple bond

correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. ^{13}C NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) or HSQC experiments]. Proton-decoupled fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 376 or 470 MHz at 23 °C. ^{19}F NMR data are represented as follows: chemical shift. Two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) experiments were performed at 500 MHz at 23 ºC, unless otherwise noted. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra-high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C_{18} column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 μL/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C18 column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 μL/min. Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ($[\alpha]_\lambda^T$), concentration (g/mL), and solvent.

Methods for measuring minimum inhibitory concentrations (MICs). MICs were determined by Micromyx LLC (Kalamazoo, MI) using the broth microdilution method as recommended by the Clinical and Laboratory Standards Institute (CLSI).[20-21] The test agents and lefamulin were provided by Yale University and were stored at –20 °C prior to use. The comparator compound and quality control agent levofloxacin (Sigma 28266, Lot No. BCBF7004V) was supplied by Micromyx. The mass of the test agents was determined by quantitative ^1H NMR analysis using (1,3,5-trimethyl)benzene as an internal standard. Stock solutions of all compounds were prepared on the day of testing. The compounds were dissolved in 100% DMSO (Sigma 472301) to a stock concentration of 40X the final testing concentration (640 μg/mL or 1280 μg/mL). Lefamulin, was dissolved in 50% DMSO due to insolubility in water, as recommended by the CLSI guidelines.[21] The concentration range evaluated for each of the compounds was 32–0.03 μg/mL or 16–0.015 μg/mL.

Test organisms. The test organisms evaluated in this study consisted of clinical isolates from the Micromyx Repository (MMX; Kalamazoo, MI) and reference isolates from the American Type Culture Collection (ATCC; Manassas, VA). Upon initial receipt at Micromyx, the organisms were sub-cultured onto an appropriate agar medium. Following incubation, colonies were harvested from these plates and cell suspensions prepared and frozen at –80 ºC with a cryoprotectant. Prior to testing, the isolates were streaked from frozen vials onto trypticase soy agar with 5% sheep blood (Becton Dickenson BD/BBL; Sparks, MD, Lot No. 1057393) and incubated at 37 ºC for 24

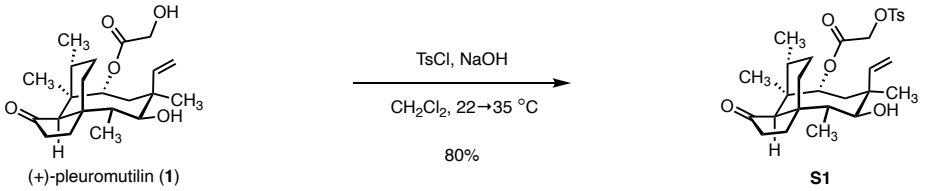
hr. *Haemophilus influenzae* was streaked onto Chocolate Agar (BD; Lot No.1057195). Additionally, *Streptococcus pneumoniae* and *H. influenzae* were incubated in 5% carbon dioxide.

Test media. Cation-adjusted Mueller Hinton broth (CaMHB II; BD; Lot No. 0286591) was used for MIC testing of aerobic organisms. For *Streptococcus* isolates, this medium was supplemented with 3% laked horse blood (LHB; Hemostat, Dixon, CA; Lot No. 474990). MIC testing of *H. influenzae* was performed in Haemophilus Test Medium Broth (HTM) which was made by supplementing CaMHB with 15 μg/mL nicotinamide adenine dinucleotide (NAD; Sigma; St. Louis, MO; Lot. No. SLBX4629), 15 μg/mL porcine hematin (Sigmas; Lot. No. SLBD4979V), and 5 g/L yeast extract (Sigma; Lot. No. 7179579).

Broth microdilution susceptibility testing. MIC values were determined using a broth microdilution procedure described by CLSI.[20-21] Automated liquid handlers (Biomek 3000 and Biomek FX, Beckman Coulter, Fullerton CA) were used to conduct serial dilutions and liquid transfers. All wells in column 2 through 12 of a standard 96-well microdilution plate (Costar 3795) were filled with 150 μL of the appropriate diluent. Then, 300 μL of the tested agents were added to the wells of column 1 of the plates at 40X the highest final concentration to be tested. Serial two-fold dilutions were made across the rows through column 11 using the Biomek 3000. The wells of column 12 contained no testing agent and served as the growth control wells. This plate served as the "mother plate" from which MIC assay plates or "daughter plates" were made. The daughter plates were loaded with 185 μL per well of the appropriate test medium for the tested organism using the Biomek FX or by hand. The daughter plates were completed on the Biomek FX instrument which transferred 5 μL of tested agent solution from each well of a mother plate to the corresponding well of each daughter plate in a single step. Due to volume constraints, a few daughter plates were created by transferring 5 μL from the mother plate by hand with a multichannel pipet. A standardized inoculum of each test organism was prepared per CLSI methods.[20-21] The inoculum for each organism was dispensed into sterile reservoirs divided by length (Beckman Coulter), and the Biomek 3000 was used to inoculate the plates. Daughter plates were placed on the Biomek 3000 work surface in reverse orientation so that inoculation took place from low to high drug concentration. Daughters were then inoculated with 10 μL of the inoculum resulting in a final cell density of approximately 5×10^5 CFU/mL. Plates were stacked 3–4 high, covered with a lid on the top plate, placed in plastic bags, and incubated at 35 ºC for approximately 20 h. Following incubation, the microplates were removed from the incubator and viewed from the bottom using a plate viewer. For each test media and each drug, an un-inoculated solubility control plate was observed for evidence of tested agent precipitation. The MIC was read and recorded as the lowest concentration of drug that inhibited visible growth of the organism. The MIC values for lefamulin and levofloxacin were within CLSI established QC ranges,[21] thus validating the study.

Synthetic procedures.

*Synthesis of pleuromutilin-22-O-tosylate (**S1**).*

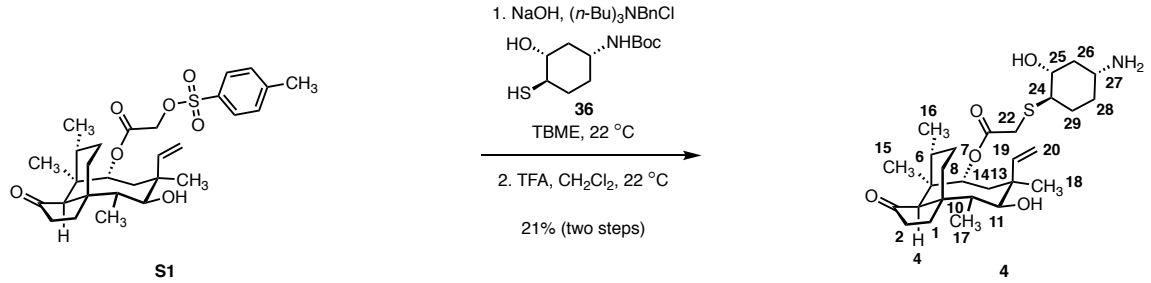


Aqueous sodium hydroxide solution (5.7 N, 204 mL, 1.16 mmol, 1.10 equiv) was added in one portion to a solution of tosyl chloride (202 mg, 1.06 mmol, 1.00 equiv) and (+)-pleuromutilin (**1**) (400 mg, 1.06 mmol, 1 equiv) in dichloromethane (1.6 mL) at 22 ºC. The reaction vessel was transferred to an oil bath that had been preheated to 35 ºC. The reaction mixture was stirred and heated for 16 h at 35 ºC. The product mixture was cooled to 22 ºC over 20 min. The cooled product mixture was diluted sequentially with ether (3.0 mL) and saturated aqueous ammonium chloride solution (2.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 2.0 mL). The organic layers were combined and the combined organic layers were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, four steps) to provide the pleuromutilin-22-*O*-tosylate **S1** as a white foam (450 mg, 80%).

Spectroscopic data for the pleuromutilin-22-*O*-tosylate **S1** obtained in this way were identical to those previously reported.[14]

^{1}H NMR (500 MHz, C_2D_6OS) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 6.05 (dd, *J* = 17.7, 11.3 Hz, 1H), 5.53 (d, *J* = 8.4 Hz, 1H), 5.09 – 4.97 (m, 2H), 4.77 (d, *J* = 16.2 Hz, 1H), 4.64 (d, *J* = 16.3 Hz, 1H), 3.40 (d, *J* = 5.9 Hz, 1H), 2.41 (s, 4H), 2.28 (s, 1H), 2.18 (dd, *J* = 19.4, 11.3 Hz, 1H), 2.09 (t, *J* = 9.3 Hz, 1H), 2.06 – 1.96 (m, 2H), 1.61 (dt, *J* = 20.1, 12.5 Hz, 2H), 1.49 – 1.40 (m, 1H), 1.31 (s, 3H), 1.26 – 1.18 (m, 4H), 1.03 (s, 4H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.50 (d, *J* = 7.1 Hz, 3H).

*Synthesis of lefamulin (**4**).*



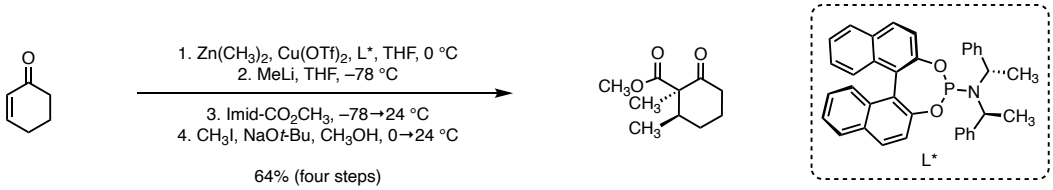
Aqueous sodium hydroxide solution (1 N, 49.0 μL, 48.8 μmol, 1.30 equiv) was added to a solution of the thiol **36** (12.1 mg, 48.8 μmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (2.30 mg, 7.50 μmol, 0.20 equiv), and pleuromutilin-22-*O*-tosylate (**S1**, 20.0 mg, 37.5 μmol, 1 equiv) in *tert*-butyl methyl ether (380 μL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 80% ethyl acetate–hexanes). The filtrate was collected and concentrated. The residue obtained was used directly in the following step.

Trifluoroacetic acid (35.0 μL, 461 μmol, 16.0 equiv) was added to a solution of the displacement product obtained in the preceding step (nominally 48.8 μmol, 1 equiv) in dichloromethane (300 μL) at 22 °C. The reaction mixture was stirred for 4 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and aqueous potassium carbonate solution (10% w/v, 1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to provide lefamulin (**4**) as a fine, white solid (4.00 mg, 21% over two steps).

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (dd, J = 17.4, 11.2 Hz, 1H, H_{19}), 5.76 (dd, J = 8.5, 3.5 Hz, 1H, H_{14}), 5.36 (d, J = 11.0 Hz, 1H, H_{20a}), 5.21 (d, J = 17.4 Hz, 1H, H_{20b}), 3.47 (td, J = 9.5, 3.7 Hz, 1H, H_{25}), 3.36 (d, J = 6.4 Hz, 1H, H_{11}), 3.35 – 3.22 (m, 1H, H_{22a}), 3.21 (d, J = 15.6 Hz, 1H, H_{22b}), 2.99 (t, J = 10.2 Hz, 1H, H_{27}), 2.65 – 2.52 (m, 1H, H_{24}), 2.39 – 2.03 (m, 7H, H_2, H_4, H_{10}, H_{13a}, H_{26a}, H_{29a}), 2.00 – 1.91 (m, 1H, H_{28a}), 1.82 – 1.72 (m, 1H, H_{8a}), 1.65 (q, J = 11.3, 10.6 Hz, 2H, H_{1a}, H_6), 1.59 – 1.23 (m, 10H, H_{1b}, H_7, H_{13b}, H_{18}, H_{26b}, H_{28b}, H_{29b}), 1.17 (s, 4H, H_{8b}, H_{15}), 0.88 (d, J = 6.8 Hz, 3H, H_{17}), 0.72 (d, J = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.2 (C), 170.1 (C), 139.1 (CH), 117.5 (CH_2), 74.8 (CH), 71.3 (CH), 70.0 (CH), 58.3 (CH), 51.9 (CH), 48.4 (CH), 45.6 (C), 45.0 (CH_2), 44.1 (C), 41.9 (C), 40.6 (CH_2), 36.9 (CH), 36.1 (CH), 34.6 (CH_2), 33.5 (CH_2), 33.1 (CH_2), 30.5 (CH_2), 28.1 (CH_2), 27.0 (CH_2), 26.5 (CH_3), 25.0 (CH_2), 17.0 (CH_3), 15.0 (CH_3), 11.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 3435 (w),

2936 (m), 2163 (m), 1720 (s), 1697 (s), 1283 (m), 1167 (m), 755 (m). HRMS-ESI (m/z): [M + H]$^+$ calcd for [$C_{28}H_{46}NO_5S$]$^+$ 508.3097; found 508.3099. $[a]_D^{20}$ = +15.5 (c = 0.100, $CHCl_3$).

Synthesis of the α-methyl-β-ketoester.



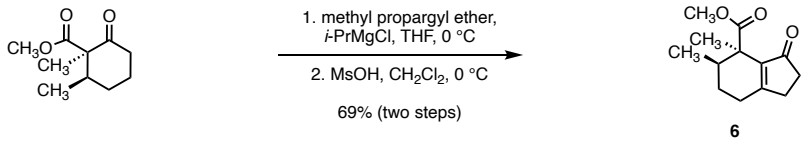
Copper(II) triflate (56.4 mg, 156 mmol, 500 ppm) and (11b*R*)-*N*,*N*-bis[(*S*)-1-phenylethyl]dinaphtho(1,3,2)dioxaphosphepin-4-amine (L*, 168 mg, 312 mmol, 1000 ppm) were added to a 2 L three-neck round-bottom flask in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The center septum was exchanged with a mechanical stir bar and the reaction vessel was equipped with an argon inlet and gas outlet in the remaining two septa. The reaction vessel was purged with a stream of argon for 30 min. Toluene (420 mL) was added to the reaction vessel via cannula and the resulting mixture was stirred for 1 h at 24 °C. The mixture was then cooled over 1 h to 0 °C. Cyclohex-2-en-1-one (30.2 mL, 312 mmol, 1 equiv) was added dropwise to the catalyst mixture at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. A solution of dimethylzinc in toluene (1.2 M, 281 mL, 337 mmol, 1.08 equiv) was then added dropwise via syringe pump over 3 h into the reaction mixture at 0 °C. The resulting mixture was stirred for 36 h at 0 °C. The mixture was then cooled to –78 °C over 2 h and stirred for an additional 2 h at this temperature. A solution of methyllithium in ether (1.6 M, 211 mL, 337 mmol, 1.08 equiv) was then added dropwise via syringe pump over 1.5 h. Upon completion of the addition, the reaction mixture was stirred for 30 min at –78 °C. A solution of methyl 1*H*-imidazole-1-carboxylate [49.2 g, 390 mmol, 1.25 equiv; dried by azeotropic distillation from benzene (500 mL)] in toluene (90 mL) was then added dropwise via cannula over 30 min at –78 °C. Upon completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm to 24 °C over 6 h. Aqueous citric acid solution (10% w/w, 200 mL) was then added dropwise over 30 min to the product mixture. The diluted product mixture was transferred to a separatory funnel that had been charged with ether (500 mL). The layers that formed were separated and the aqueous layer was extracted with ether (5 × 1.0 L). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to afford a brown residue that was used immediately in the next step.

Sodium *tert*-butoxide (60.0 g, 624 mmol, 2.00 equiv) was added in one portion to a solution of iodomethane (97.1 mL, 1.56 mmol, 5.00 equiv) and the unpurified product obtained in the preceding step (nominally 312 mmol, 1 equiv) in methanol (600 mL) at 0 °C. Upon completion of the addition the cooling bath was removed and the reaction mixture was allowed to warm to 24 °C over 2 h. The warmed reaction mixture was stirred for 48 h at 24 °C. The product mixture was diluted with aqueous acid solution (10% w/w, 200 mL). The diluted product mixture was transferred to a separatory funnel that had been charged with ether (500 mL). The layers that formed were separated and the aqueous layer was extracted with ether (5 × 1.0 L). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with hexanes initially, grading to 30% ether–hexanes, four steps) to afford the α-methyl-β-ketoester as a light-yellow oil (37.1 g, 64%).

Spectroscopic data for the α-methyl-β-ketoester obtained in this way were identical to those previously reported.[12]

R*f* = 0.30 (5% ethyl acetate–hexanes; $KMnO_4$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.72 (td, *J* = 14, 6.8 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.08 – 1.97 (m, 1H), 1.97 – 1.83 (m, 1H), 1.72 – 1.58 (m, 3H), 1.34 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.2, 171.7, 60.8, 51.8, 43.7, 39.7, 30.1, 25.3, 18.7, 16.9.

*Synthesis of the methyl ester **6**.*



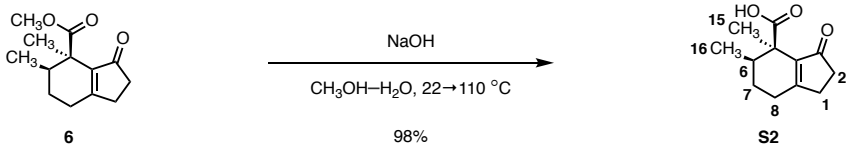
A solution of *iso*-propylmagnesium chloride in tetrahydrofuran (2.0 M, 120 mL, 240 mmol, 1.30 equiv) was added dropwise over 20 min to a solution of methyl propargyl ether (20.3 mL, 240 mmol, 1.30 equiv) in tetrahydrofuran (250 mL) under argon at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. The resulting alkynyl Grignard solution was added dropwise into a solution of the α-methyl-β-ketoester (34.0 g, 185 mmol, 1 equiv) in tetrahydrofuran (750 mL) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. The cold product mixture was diluted with saturated aqueous ammonium chloride solution (600 mL). The resulting biphasic mixture was stirred for 10 min at 0 °C. The cooling bath was removed, and the product mixture was allowed to warm to 24 °C over 30 min. The warmed product mixture was transferred to a separatory funnel that had been charged with ether (500 mL). The layers that formed were separated and the aqueous layer was extracted with ether (5 × 1.0 L). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used immediately in the next step.

Methanesulfonic acid (60.0 mL, 923 mmol, 5.00 equiv) was added dropwise over 20 min to a solution of the unpurified propargyl ether obtained in the preceding step (nominally 185 mmol, 1 equiv) in dichloromethane (170 mL) at 0 °C. Upon completion of the addition, the cooling bathw was removed, and the reaction mixture was allowed to warm to 22 °C over 4 h. The product mixture was diluted sequentially with ether (200 mL) and water (200 mL). The diluted product mixture was cooled to 0 °C. The cooled product mixture was carefully basified with aqueous sodium hydroxide solution (10% w/w, 400 mL) at 0 °C. The resulting basified mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 300 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with hexanes initially, grading to 50% ether–hexanes, four steps) to afford the methyl ester **6** as an orange solid (31.0 g, 69% over two steps).

Spectroscopic data for the methyl ester **6** obtained in this way were identical to those previously reported.[12]

R*f* = 0.38 (30% ethyl acetate–hexanes; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.61 (s, 3H), 2.51 (t, *J* = 4.7 Hz, 2H), 2.42 – 2.27 (m, 4H), 1.72 – 1.62 (m, 3H), 1.41 (s, 3H), 0.90 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.3, 174.3, 173.5, 140.9, 51.8, 45.5, 39.2, 34.8, 29.9, 27.8, 27.12, 21.5, 16.2.

*Synthesis of the carboxylic acid **S2**.*

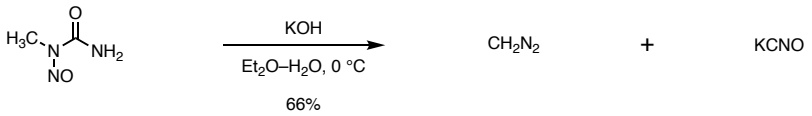


6 S2

Aqueous sodium hydroxide solution (2N, 600 mL, 1.20 mol, 16.7 equiv) was added to a solution of the methyl ester **6** (16.0 g, 71.9 mmol, 1 equiv) in methanol (600 mL) at 22 °C. The reaction vessel was fitted with a reflux condenser and then placed in an oil bath that had been preheated to 110 °C. The reaction mixture was stirred for 15 h at 110 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted sequentially with water (600 mL) and ether (500 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 500 mL, discarded). The washed aqueous layer was cooled to 0 °C over 20 min. The cooled aqueous layer acidified to pH ~ 1 by the dropwise addition of 12 N concentrated hydrochloric acid solution over 20 min at 0 °C. The acidified aqueous phase was diluted with ether (500 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The layers that formed were separated. The aqueous layer was extracted with ether (2 × 500 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the carboxylic acid **S2** as a yellow foam (14.6 g, 98%). The product obtained was judged to be of >95% purity (600 MHz, ^{1}H NMR analysis) used without further purification.

R_f = 0.19 (1% acetic acid–50% ethyl acetate–hexanes; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.53 (t, J = 4.9 Hz, 2H, H_1), 2.47 – 2.23 (m, 4H, H_2, H_8), 1.97 – 1.75 (m, 1H, H_{7a}), 1.75 – 1.60 (m, 2H, H_{7b}, H_6), 1.46 (s, 3H, H_{15}), 1.03 (d, J = 6.5 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8 (C), 177.9 (C), 174.7 (C), 140.3 (C), 45.4 (C), 39.0 (CH), 34.6 (CH_2), 29.8 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 21.2 (CH_3), 16.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 2929 (w), 1681 (s), 1631 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{12}H_{16}O_3Na]^+$ 231.0992; found 231.1001. $[\alpha]_D^{20}$ = +156.4 (c = 1.13, $CHCl_3$).

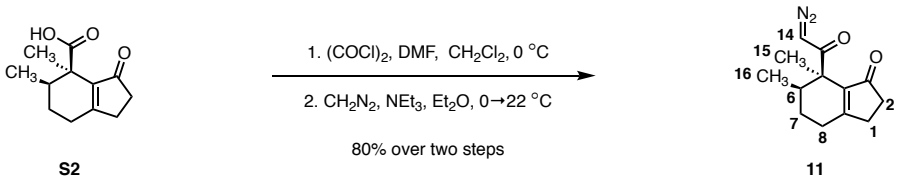
Preparation of diazomethane.



CAUTION: Explosion and shock hazard. Needles should be avoided and unscratched glassware should be used. Perform reagent preparation, aqueous workup, and all reactions in a well-ventilated fume hood behind a blast shield. All glassware and waste solutions should be quenched extremely carefully with dilute acid before removing from fume hood.

Diazomethane was prepared according to the method of Arndt.[4] *N*-nitroso-*N*-methylurea (64.7 g, 628 mmol, 1 equiv) was added in five portions over 15 min to a stirring biphasic mixture of ether (630 mL) and aqueous potassium hydroxide solution (50% w/w, 140 mL) at 0 °C. The resulting yellow biphasic mixture was stirred for 30 min at 0 °C. The yellow organic layer was carefully decanted into a 2 L Erlenmeyer flask and dried over potassium hydroxide. Titration with benzoic acid was used to determine the concentration of the solution of diazomethane in ether as 0.66 M (66%). The diazomethane solution was used immediately in the next step without further purification.

*Synthesis of the α-diazoketone **11**.*

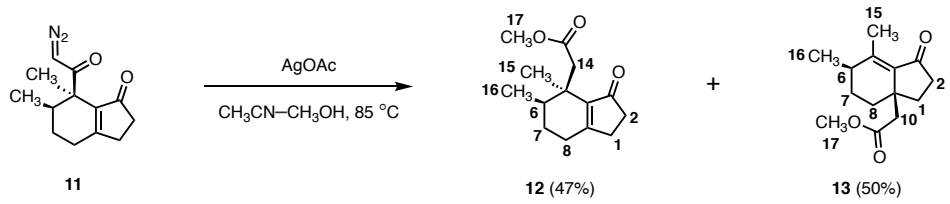


Oxalyl chloride (3.17 mL, 36.9 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of the carboxylic acid **S2** [7.00 g, 33.6 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 20 mL)] and *N,N*-dimethylformamide (5.51 mL, 67.2 mmol, 2.00 equiv) in dichloromethane (56 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was concentrated. The residue obtained was dissolved in dichloromethane (20 mL) and the resulting solution was eluted over a plug of silica gel (5.0 cm × 5.0 cm). The silica gel plug was washed with 50% ether–hexanes (100 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

A solution of the unpurified acid chloride obtained in the preceding step (nominally 33.6 mmol, 1 equiv) in ether (75 mL) was added dropwise over 20 min to a solution of diazomethane in ether (ca. 0.66 M, 226 mL, 7.00 equiv) and triethylamine (14.1 mL, 101 mmol, 3.00 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was allowed to warm to 22 °C over 1 h. The warmed reaction mixture was stirred for 12 h at 22 °C. The product mixture was cooled to 0 °C over 20 min. The cooled product mixture was diluted slowly with aqueous potassium phosphate buffer solution (pH 7, 200 mL). The resulting biphasic mixture was stirred for 2 h at 0 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 200 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (300 mL) and saturated aqueous sodium chloride solution (300 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, four steps) to provide the diazoketone **11** as a yellow solid (6.21 g, 80% over two steps).

R_f = 0.25 (50% ethyl acetate–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 1H, H_{14}), 2.57 – 2.50 (m, 2H, H_1), 2.49 – 2.34 (m, 4H, H_2, H_8), 1.98 – 1.78 (m, 1H, H_{7a}), 1.68 (ddd, J = 13.6, 5.8, 3.0 Hz, 1H, H_{7b}), 1.63 – 1.53 (m, 1H, H_6), 1.43 (s, 3H, H_{15}), 0.99 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3 (C), 196.0 (C), 175.3 (C), 141.2 (C), 54.8 (CH), 48.8 (C), 40.0 (CH), 34.9 (CH_2), 29.8 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 20.5 (CH_3), 16.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 2930 (w), 2097 (s), 1691 (s), 1631 (m), 1347 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{13}H_{16}N_2O_2Na]^+$ 255.1109; found 255.1115. $[a]_D^{20}$ = +385.2 (c = 0.880, $CHCl_3$).

*Synthesis of the Arndt–Eistert homologation products **12** and **13**.*



11 **12** (47%) **13** (50%)

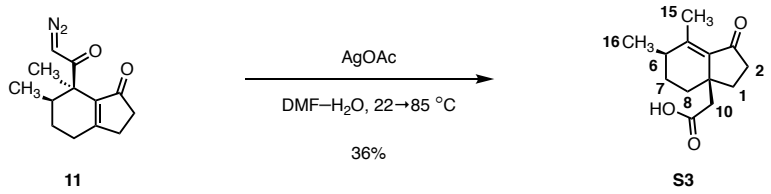
A solution of the diazoketone **11** (2.30 g, 8.91 mmol, 1 equiv) in acetonitrile (100 mL) was added rapidly over 1 min via additional funnel to a suspension of silver acetate (446 mg, 2.67 mmol, 0.30 equiv) in methanol (72 mL) and acetonitrile (400 mL) that had been preheated to 85 °C. The reaction mixture was stirred for 1 h at 85 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was filtered through a pad of Celite. The Celite pad was rinsed with ethyl acetate (2 × 100 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide separately the homologation product **12** (pale yellow oil, 990 mg, 47%) and the rearranged ester **13** (pale yellow oil, 1.05 g, 50%).

Within the limits of detection (400 MHz ^{1}H NMR analysis), the rearranged product **13** was formed as a single diastereomer. The relative stereochemistry of **13** was established via X-ray analysis of the corresponding carboxylic acid **S3** (see page S152).

12: R_f = 0.51 (50% ethyl acetate–hexanes; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (s, 3H, H_{17}), 2.62 – 2.51 (m, 2H, H_{14}), 2.43 (q, J = 4.1, 3.2 Hz, 2H, H_1), 2.33 (dt, J = 9.0, 4.9 Hz, 2H, H_2), 2.31 – 2.22 (m, 2H, H_8), 1.74 – 1.63 (m, 2H, H_{7a}, H_6), 1.50 – 1.38 (m, 1H, H_{7b}), 1.33 (s, 3H, H_{15}), 0.96 (d, J = 6.6 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3 (C), 173.0 (C), 172.9 (C), 142.1 (C), 51.2 (CH_3), 39.0 (CH), 38.6 (CH_2), 37.1 (C), 35.1 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 24.3 (CH_3), 14.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 3366 (w), 2951 (w), 1731 (s), 1708 (s), 1629 (m), 1216 (m) 1168 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{14}H_{21}O_3]^+$ 237.1412, found 237.1496. $[a]_D^{20}$ = +42.9 (c = 1.28, $CHCl_3$).

13: R_f = 0.79 (50% ethyl acetate–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H, H_{17}), 2.51 – 2.33 (m, 2H, H_{1a}, H_{2a}), 2.31 (s, 2H, H_{10}), 2.25 – 2.16 (m, 2H, H_6, H_{1b}), 2.11 (dt, J = 13.0, 3.4 Hz, 1H, H_{8a}), 2.05 (s, 3H, H_{15}), 1.83 (ddt, J = 13.9, 6.8, 3.4 Hz, 1H, H_{7a}), 1.54 – 1.36 (m, 2H, H_{2b}, H_{7b}), 1.33 – 1.21 (m, 1H, H_{8b}), 1.11 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (C), 171.8 (C), 151.8 (C), 137.2 (C), 51.4 (CH_3), 42.6 (C), 40.2 (CH_2), 37.4 (CH), 35.6 (CH_2), 33.4 (CH_2), 32.1 (CH_2), 28.3 (CH_2), 19.7 (CH_3), 16.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 2932 (w), 1732 (m), 1688 (s), 1634 (m), 1202 (m), 1146 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{14}H_{21}O_3]^+$ 237.1412; found 237.1494. $[a]_D^{20}$ = +49.4 (c = 0.720, $CHCl_3$).

*Synthesis of the carboxylic acid **S3**.*



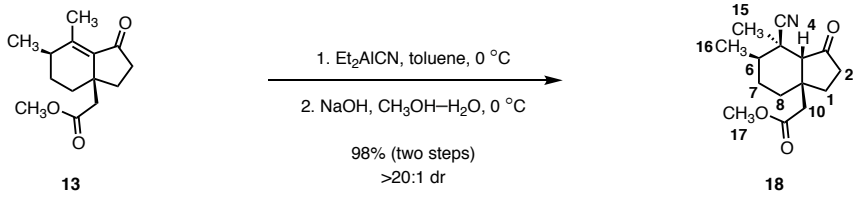
11 **S3**

Silver acetate (4.30 mg, 25.8 μmol, 0.30 equiv) was added to a solution of the diazoketone **11** (20.0 mg, 86.1 μmol, 1 equiv) in a mixture of *N,N*-dimethylformamide and water (2:1 v/v, 4.4 mL) at 22 °C. The reaction vessel was placed in an oil bath that had been preheated to 85 °C. The reaction mixture was stirred for 40 min at 85 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted sequentially with ether (5.0 mL) and 2 N aqueous sodium hydroxide solution (6.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was washed with ether (2 × 10 mL). The washed aqueous layer was separated and the pH of the separated aqueous layer was adjusted to ~1 by the dropwise addition of 1 N aqueous hydrochloric acid solution at 22 °C. Ether (10 mL) was then added and the resulting biphasic mixture was transferred to a separatory funnel. The layers that formed were separated and the aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid–33% ether–hexanes initially, grading to 1% acetic acid–50% ether–hexanes, two steps) to provide the rearranged acid **S3** as a pale yellow oil (7.00 mg, 36%).

The relative stereochemistry of the carboxylic acid **S3** was determined by X-ray analysis (see page S152).

R_f = 0.65 (1% acetic acid–50% ether–hexanes; UV). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 – 2.35 (m, 4H, H_{2a}, H_{7a}, H_{10}), 2.33 – 2.18 (m, 3H, H_{2b}, H_6, H_{8a}, 2.09 (s, 3H, H_{15}), 1.88 (ddt, J = 13.9, 6.7, 3.3 Hz, 1H, H_{1a}), 1.59 – 1.41 (m, 2H, H_{1b}, H_{7b}), 1.31 (td, J = 13.7, 3.4 Hz, 1H, H_{8b}), 1.15 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8 (C), 176.7 (C), 152.5 (C), 137.2 (C), 42.8 (C), 40.0 (CH_2), 37.6 (CH), 35.8 (CH_2), 33.4 (CH_2), 32.2 (CH_2), 28.4 (CH_2), 19.9 (CH_3), 17.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 2931 (w), 2872 (w), 1702 (s), 1622 (s), 1459 (w), 1217 (m), 1081 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{13}H_{19}O_3]^+$ 223.1334; found 223.1327.

*Synthesis of the cyanoester **18**.*



13 18

CAUTION: Cyanide hazard! Perform reaction, aqueous workup, and purification in a well-ventilated fume hood. All glassware and waste solutions should be washed with bleach prior to removing from fume hood.

A solution of diethylaluminum cyanide solution in toluene (1.0 M, 14.6 mL, 14.6 mmol, 1.50 equiv) was added dropwise over 2 min to a solution of the enone **13** (2.50 g, 9.73 mmol, 1 equiv) in toluene (100 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The product mixture was diluted with saturated aqueous potassium sodium tartrate solution (60 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 80 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

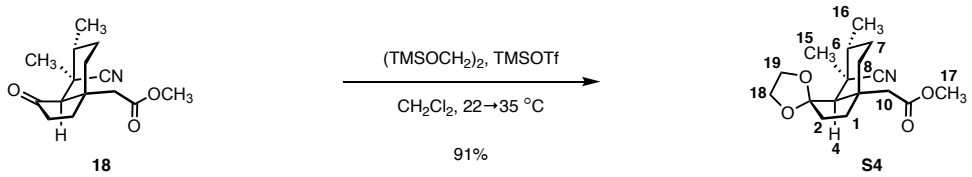
Aqueous sodium hydroxide solution (13 mL) was added dropwise over 1 min to a solution of the cyanoester **18** obtained in the preceding step (nominally 9.73 mmol, 1 equiv) in methanol (65 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The product mixture was diluted sequentially with ether (100 mL) and saturated aqueous ammonium chloride solution (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ether–hexanes) to provide the cyanoester **18** as a pale yellow oil (2.55 g, 98% over two steps).

^{1}H NMR analysis (500 MHz) of the unpurified product indicated a >20:1 mixture of diastereomers. The relative stereochemistry of the cyanoester **18** was established via X-ray analysis of the methylation product **19** (see page S154).

R_f = 0.31 (50% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.69 (s, 3H, H_{17}), 2.95 (s, 1H, H_4), 2.87 (dd, J = 98.7, 16.4 Hz, 2H, H_{10}), 2.30 (dddd, J = 19.8, 10.8, 2.3, 1.2 Hz, 1H, H_{2a}), 2.22 (dt, J = 19.6, 9.6 Hz, 1H, H_{2b}), 2.04 (dt, J = 13.0, 10.4 Hz, 1H, H_{1a}), 1.74 (s, 3H, H_{15}), 1.69 (ddd, J = 13.1, 9.4, 2.2 Hz, 1H, H_{1b}), 1.64 (dd, J = 14.4, 2.8 Hz, 1H, H_{7a}), 1.59 – 1.50 (m, 3H, H_6, H_8), 1.26 (ddd, J = 13.8, 9.3, 7.4 Hz, 1H, H_{7b}), 1.06 (d, J = 5.8 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.4 (C), 172.0 (C), 122.9 (C), 57.4 (CH), 51.5 (CH_3), 41.8 (C), 40.2 (CH_2), 39.0 (C), 36.1 (CH), 34.0 (CH_2), 31.9 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 22.6 (CH_3), 16.8 (CH_3). IR (ATR-

FTIR), cm^{-1}: 3323 (w), 2937 (w), 2360 (s), 2338 (s), 1734 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{15}H_{21}NO_3Na]^+$ 286.1419; found 286.1426. $[a]_D^{20}$ = +45.3 (c = 0.576, CH_3OH).

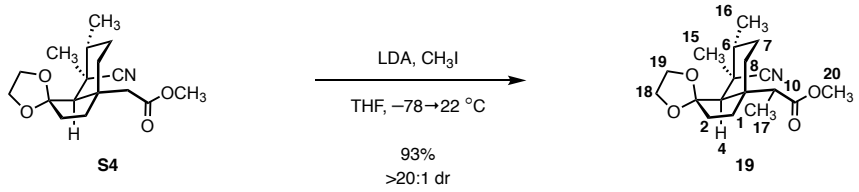
*Synthesis of the ketal **S4**.*



Trimethylsilyl trifluoromethanesulfonate (1.10 mL, 6.08 mmol, 2.00 equiv) was added to a solution of 1,2-bis(trimethylsiloxy)ethane (2.92 mL, 15.2 mmol, 5.00 equiv) and the cyanoester **18** [801 mg, 3.04 mmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 5.0 mL)] in dichloromethane (15 mL) at 22 °C. The reaction vessel was placed in an oil bath that had been preheated to 35 °C. The reaction mixture was stirred for 4 d at 35 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted with ether (20 mL) and carefully poured into saturated aqueous sodium bicarbonate solution (35 mL) at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the ketal **S4** as a pale yellow oil (853 mg, 91%).

R_f = 0.35 (50% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (q, *J* = 8.9, 8.0 Hz, 1H, $H_{18a\text{ or }19a}$), 3.91 – 3.83 (m, 2H, H_{18b}, H_{19b}), 3.78 (td, *J* = 8.5, 7.3, 5.8 Hz, 1H, $H_{18a\text{ or }19a}$), 3.65 (s, 3H, H_{17}), 2.80 (dd, *J* = 261.2 15.0 Hz, 2H, H_{10}), 2.48 (d, *J* = 1.9 Hz, 1H, H_4), 2.13 (ddt, *J* = 11.3, 6.8, 3.3 Hz, 1H, H_6), 1.87 – 1.81 (m, 2H, H_2), 1.76 (ddt, *J* = 15.7, 11.2, 5.6, 1H, H_{1a}), 1.71 – 1.47 (m, 5H, H_{1b}, H_8, H_7), 1.45 (s, 3H, H_{15}), 1.05 (d, *J* = 6.7 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3 (C), 124.0 (C), 118.7 (C), 63.7 (CH_2), 62.1 (CH_2), 54.7 (CH), 51.2 (CH_3), 42.8 (C), 42.0 (CH_2), 39.0 (C), 35.2 (CH_2), 35.1 (CH), 33.8 (CH_2), 30.1 (CH_2), 28.5 (CH_2), 22.1 (CH_3), 17.2 (CH_3). IR (AT-FTIR), cm^{-1}: 2947 (w), 2889 (w), 1735 (s), 1153 (m). HRMS-ESI (m/z): [M + Na]$^+$ calcd for $[C_{17}H_{25}NO_4Na]^+$ 330.1681; found 330.1691. $[a]_D^{20}$ = –28.7 (*c* = 0.465, CH_3OH).

*Synthesis of the methylation product **19**.*

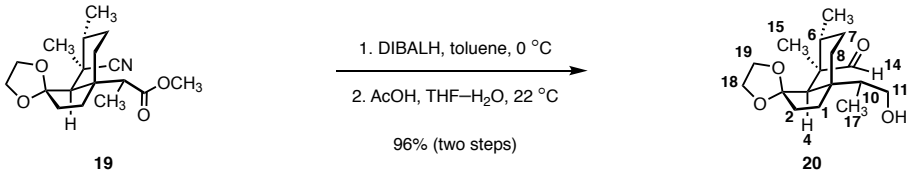


A solution of lithium diisopropylamide in tetrahydrofuran (1.3 M, 15.6 mL, 19.5 mmol, 2.40 equiv) was added to the solution of the ketal **S4** [2.50 g, 8.13 mmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 5.0 mL)] in tetrahydrofuran (41 mL) at –78 °C. The reaction mixture was stirred for 2 h at –78 °C. The reaction mixture was warmed to 0 °C over 10 min and stirred for an additional 1 h at 0 °C. The reaction mixture was cooled to –78 °C over 30 min. Iodomethane (1.52 mL, 24.4 mmol, 3.00 equiv) was then added dropwise over 5 min to the cooled reaction mixture. The reaction mixture was stirred for 1 h at –78 °C and then was warmed to 22 °C over 2 h. The warmed reaction mixture was stirred for 15 h at 22 °C. The product mixture was diluted sequentially with ether (50 mL) and saturated aqueous ammonium chloride solution (50 mL). The resulting biphasic mixture was stirred for 15 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (60 mL) and saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ether–hexanes initially, grading to 30% ether–hexanes, two steps) to provide the methylation product **19** as a white, crystalline solid (2.40 g, 93%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the methylation product **19** was formed as a single diastereomer. The relative stereochemistry of **19** was established via X-ray analysis (see page S161).

R_f = 0.34 (50% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 – 3.94 (m, 1H, H_{18a}, H_{19a}), 3.94 – 3.74 (m, 3H, $H_{18a\text{ or }19a}$, H_{18b}, H_{19b}), 3.70 (s, 3H, H_{20}), 3.39 (q, J = 7.1 Hz, 1H, H_{10}), 2.89 (s, 1H, H_4), 2.21 – 2.08 (m, 2H, H_{1a}, H_6), 1.89 – 1.75 (m, 2H, H_2), 1.71 – 1.63 (m, 1H, H_{8a}), 1.59 (dd, J = 13.2, 3.5, 1H, H_{8b}), 1.50 – 1.43 (m, 1H, H_{7a}), 1.45 (s, 3H, H_{15}), 1.43 – 1.34 (m, 1H, H_{7b}), 1.29 (ddd, J = 12.7, 8.8, 5.9 Hz, 1H, H_{1b}), 1.16 (d, J = 7.3 Hz, 3H, H_{17}), 1.05 (d, J = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0 (C), 123.9 (C), 119.1 (C), 63.7 (CH_2), 62.1 (CH_2), 51.4 (CH_3), 51.0 (CH), 45.0 (C), 41.1 (CH), 39.0 (C), 35.5 (CH), 34.6 (CH_2), 30.4 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 22.5 (CH_3), 17.3 (CH_3), 13.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2443 (m), 2348 (m), 1738 (s), 1371 (s), 1210 (s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{18}H_{27}NO_4Na]^+$ 344.1838; found 344.1849. $[a]_D^{20}$ = –123.8 (c = 0.285, $CHCl_3$).

*Synthesis of the aldehyde **20**.*



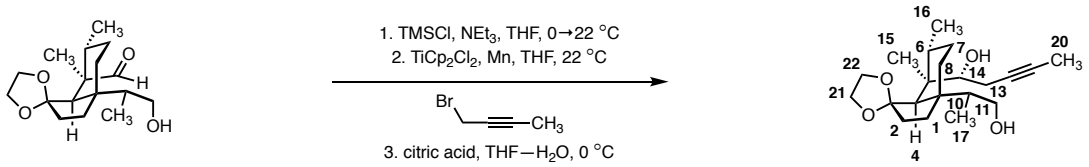
19 **20**

A solution of diisobutylaluminum hydride toluene (1.0 M, 8.71 mL, 8.71 mmol, 3.50 equiv) was added over 1 min to a solution of the cyanoester **19** [800 mg, 2.49 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 10 mL)] in toluene (17 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL) and saturated aqueous potassium sodium tartrate solution (30 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Acetic acid (286 μL, 4.98 mmol, 2.00 equiv) was added to a solution of the imine obtained in the preceding step (nominally 2.49 mmol, 1 equiv) in 4:1 tetrahydrofuran–water (v/v, 18 mL) at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 40 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the aldehyde **20** as a colorless oil (770 mg, 96%, two steps). The aldehyde **20** was determined to be >95% pure by quantitative ^{1}H NMR analysis (500 MHz) and was used directly in the following step.

R_f = 0.46 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H, H_{14}), 4.07 – 3.73 (m, 5H, H_{18}, H_{19}, H_{11a}), 3.24 (t, J = 9.4 Hz, 1H, H_{11b}), 2.75 (s, 1H, H_4), 2.21 – 2.09 (m, 1H, H_6), 1.84 (ddt, J = 24.1, 14.1. 9.4 Hz, 2H, H_2), 1.72 – 1.37 (m, 6H, H_{1a}, H_7, H_8, H_{10}), 1.31 (ddd, J = 17.5, 7.9, 3.3 Hz, 1H, H_{1b}), 1.17 (s, 3H, H_{15}), 1.07 (d, J = 7.2 Hz, 3H, H_{16}), 0.94 (d, J = 6.7 Hz, 3H, H_{17}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1 (CH), 119.8 (C), 65.0 (CH_2), 63.9 (CH_2), 62.3 (CH_2), 49.6 (C), 48.8 (CH), 45.6 (C), 38.0 (CH), 35.8 (CH_2), 35.0 (CH), 29.0 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 18.9 (CH_3), 15.5 (CH_3), 12.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 3414 (w), 2941 (s), 2878 (m), 1699 (m), 1457 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{17}H_{28}O_4Na]^+$ 319.1885; found 319.1894. $[a]_D^{20}$ = –72.9 (c = 0.750, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **21**.*



Trimethylsilyl chloride (152 μL, 1.19 mmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (303 μL, 2.17 mmol, 2.00 equiv) and the aldehyde **20** (321 mg, 1.09 mmol, 1 equiv) in tetrahydrofuran (11 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 20 min and the cooled product mixture was diluted sequentially with ether (10 mL) and aqueous potassium phosphate buffer solution (pH 7, 10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

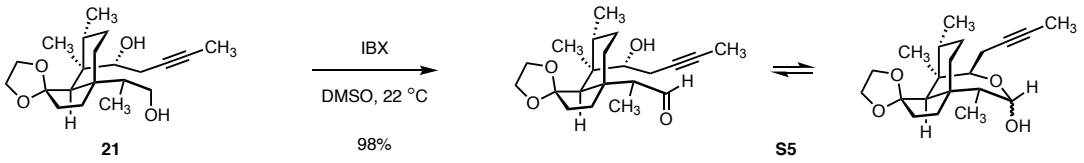
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (811 mg, 3.26 mmol, 3.00 equiv) and manganese powder (715 mg, 13.0 mmol, 12.0 equiv) in tetrahydrofuran (13 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the protected alcohol obtained in the preceding step (nominally 1.09 mmol, 1 equiv) and 1-bromobut-2-yne (577 mg, 4.34 mmol, 4.00 equiv) in tetrahydrofuran (13 mL) was added dropwise over 40 min at 22 °C using a syringe pump. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted with hexanes (20 mL) the diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 6.3 mL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 1.09 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (40 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 60 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (90 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **21** as an off-white foam (325 mg, 81% over three steps).

^{1}H NMR analysis (400 MHz) of the unpurified product mixture indicated a >20:1 mixture of diastereomers. The relative stereochemistry of the homopropargylic alcohol **21** was later determined by NOE correlations in the cyclization product **S6**.

R_f = 0.34 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6) δ 4.22 (dt, *J* = 10.5, 2.9 Hz, 1H, H_{14}), 3.62 – 3.50 (m, 2H, H_{11a}, $H_{21a\ or\ 22a}$), 3.44 – 3.34 (m, 2H, H_{21b}, H_{22b}), 3.34 – 3.23 (m, 1H, $H_{21a\ or\ 22a}$), 3.10 (td, *J* = 9.9, 5.7 Hz, 1H, H_{11b}), 2.72 (s, 1H, H_4), 2.44 (dt, *J* = 16.4, 2.5 Hz, 1H, H_{13a}), 2.31 (ddq, *J* = 15.8, 10.6, 2.5 Hz, 1H, H_{13b}), 2.14 (ddt, *J* = 15.8, 10.6, 2.5 Hz, 1H, H_{10}), 1.93 (d, *J* = 3.3 Hz, 1H, OH), 1.90 – 1.78 (m, 2H, H_2), 1.59 – 1.45 (m, 3H, H_{1a}, H_6, H_{8a}), 1.43 (t, *J* = 2.5 Hz, 3H, H_{20}), 1.35 (dt, *J* = 13.3, 9.3 Hz, 3H, H_{1b}, H_7), 1.17 – 1.04 (m, 10H, H_{15}, H_{16}, H_{17}, H_{8b}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.4 (C), 77.8 (C), 77.6 (C), 76.0 (CH), 64.9 (CH_2), 63.8 (CH_2), 62.9 (CH_2), 46.0 (C), 45.5 (CH), 42.7 (CH), 41.1 (C), 36.5 (CH), 35.8 (CH_2), 30.5 (CH_2), 29.8 (broad, CH_2), 25.7 (CH_2), 22.8 (CH_2), 20.5 (CH_3), 17.0 (CH_3), 13.1 (CH_3), 2.9 (CH_3). IR (AT-FTIR), cm^{-1}: 2952 (w), 1715 (s), 1396 (m), 1299 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{21}H_{34}O_4Na]^+$ 373.2355; found 373.2366. $[\alpha]_D^{20}$ = +156.4 (*c* = 1.13, $CHCl_3$).

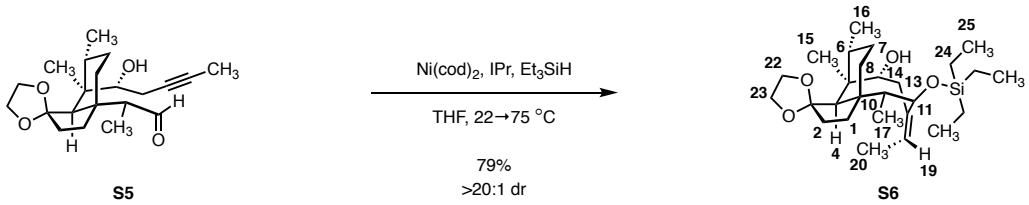
*Synthesis of the lactol **S5**.*



2-Iodoxybenzoic acid (IBX, 265 mg, 899 μmol, 1.05 equiv) was added in one portion to a solution of the homopropargylic alcohol **21** (300 mg, 856 μmol, 1 equiv) in dimethylsulfoxide (12 mL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (20 mL), saturated aqueous sodium bicarbonate solution (10 mL), and saturated aqueous sodium thiosulfate solution (10 mL) at 22 °C. The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the lactol **S5** as a white foam (292 mg, 98%). The lactol **S5** was used immediately in the following step.

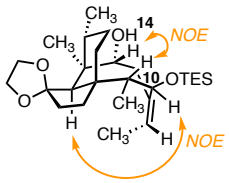
^{1}H NMR analysis (400 MHz) of the purified product mixture indicated the presence of a 1:1 mixture of hydroxyaldehyde and lactol isomers.

Synthesis of the allylic silyl ether ***S6****.*



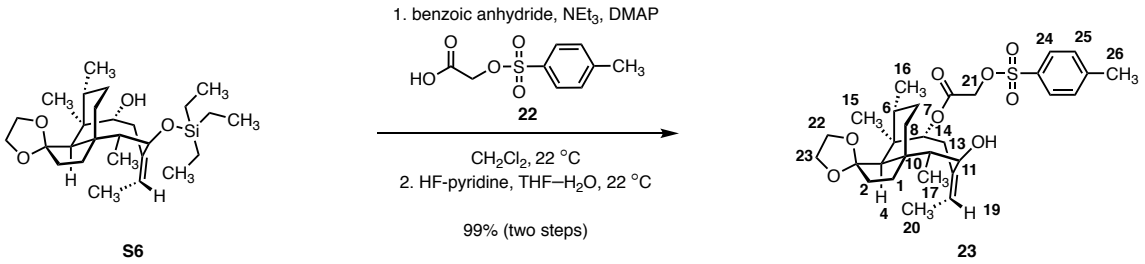
A solution of bis(cyclooctadiene)nickel(0) (5.50 mg, 20.1 μmol, 0.20 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 7.80 mg, 20.1 μmol, 0.20 equiv) in tetrahydrofuran (200 μL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. The resulting solution was added to a solution of triethylsilane (47.9 μL, 301 μmol, 3.00 equiv) and the alkynyl aldehyde **S5** (35.0 mg, 101 μmol, 1 equiv) in tetrahydrofuran (1.7 mL) in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 75 °C. The reaction mixture was stirred for 3 h at 75 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was eluted over a pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the allylic silyl ether **S6** as a clear oil (34.0 mg, 79%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the allylic silyl ether **S6** was formed as a single diastereomer. The relative stereochemistry of the C14 alcohol was determined by NOE correlations between H14 and H10. The relative stereochemistry of the C11 alcohol was determined by NOE correlations between H11 and H4. The relative stereochemistry was later confirmed by X-ray analysis of the mutilin derivative **26** (see page S163).



R_f = 0.72 (33% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (qd, J = 6.7, 2.6 Hz, 1H, H_{19}), 4.78 (dt, J = 11.3, 4.3 Hz, 1H, H_{14}), 4.01 – 3.91 (m, 1H, $H_{22a \text{ or } 23a}$), 3.90 (d, J = 8.8 Hz, 1H, H_{11}), 3.83 (ddt, J = 19.2, 13.4, 6.6 Hz, 2H, H_{22b}, H_{23b}), 3.71 – 3.63 (m, 1H, $H_{22a \text{ or } 23a}$), 3.14 (d, J = 2.3 Hz, 1H, H_4), 2.58 (dd, J = 15.1, 11.5 Hz, 1H, H_{13a}), 2.33 (ddt, J = 15.0, 4.6, 2.4, 1H, H_{13b}), 2.26 – 2.12 (m, 2H, H_6, H_{10}), 1.85 – 1.16 (m, 11H, H_1, H_2, H_7, H_8, H_{20}), 1.06 – 0.99 (m, 6H, H_{15}, H_{17}), 0.97 – 0.88 (m, 12H, H_{16}, H_{25}), 0.64 – 0.50 (m, 6H, H_{24}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5 (C), 121.2 (CH), 119.9 (C), 84.9 (CH), 69.1 (CH), 63.7 (CH_2), 61.4 (CH_2), 50.6 (CH), 45.6 (C), 43.2 (C), 42.0 (CH), 36.0 (CH_2), 35.9 (CH), 33.6 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 18.6 (CH_3), 15.9 (CH_3), 14.1 (CH_3), 13.3 (CH_3), 7.0 (3 × CH_3), 5.1 (3 × CH_2). IR (AT-FTIR), cm^{-1}: 2951 (m), 2875 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{27}H_{49}O_4Si]^+$ 465.3400; found 465.3417. $[\alpha]_D^{20}$ = +1.19 (c = 0.156, $CHCl_3$).

*Synthesis of the ester **23**.*



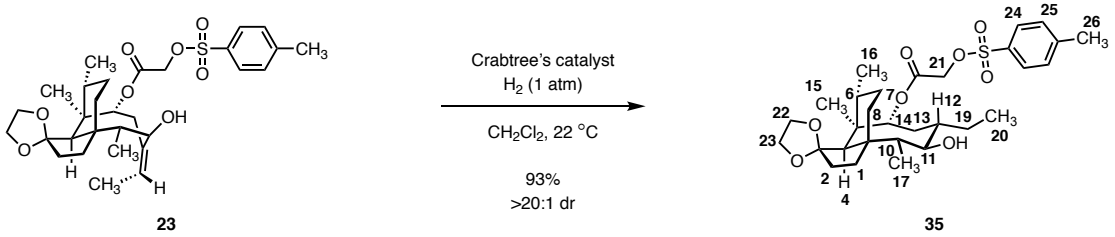
4-Dimethylaminopyridine (800 μg, 6.50 μmol, 0.10 equiv) was added to a solution of the sulfonated glycolic acid **22** (89.2 mg, 387 μmol, 6.00 equiv), benzoic anhydride (87.6 mg, 387 μmol, 6.00 equiv), triethylamine (63 μL, 452 μmol, 7.00 equiv) and the allylic silyl ether **S6** [30.0 mg, 64.5 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)], in dichloromethane (650 μL) at 22 ˚C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (4.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Hydrogen fluoride–pyridine complex (16.0 μL, 129 μmol, 2.00 equiv) was added to a solution of the product obtained in the proceeding step (nominally 64.5 μmol, 1 equiv) in 2:1 tetrahydrofuran–water (v/v, 650 μL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the ester **23** as a white foam (44.0 mg, 99%, two steps).

R_f = 0.43 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H, H_{24}), 7.35 (d, *J* = 8.0 Hz, 2H, H_{25}), 5.93 (dd, *J* = 11.7, 4.6 Hz, 1H, H_{14}), 5.43 (qd, *J* = 6.7, 2.6 Hz, 1H, H_{19}), 4.48 – 4.49 (m, 2H, H_{21}), 4.01 – 3.93 (m, 1H, $H_{22a\ or\ 23a}$), 3.90 (d, *J* = 9.2 Hz, 1H, H_{11}), 3.84 (tq, *J* = 13.6, 6.6 Hz, 2H, H_{22b}, H_{23b}), 3.73 – 3.65 (m, 1H, $H_{22a\ or\ 23a}$), 3.03 (s, 1H, H_4), 2.66 (dd, *J* = 15.4, 11.7 Hz, 1H, H_{13a}), 2.45 (s, 3H, H_{26}), 2.27 – 2.18 (m, 3H, H_6, H_{10}, H_{13b}), 1.95 – 1.69 (m, 2H, H_2), 1.65 (dd, *J* = 6.7, 1.8 Hz, 3H, H_{20}), 1.62 – 1.32 (m, 5H, H_{1a}, H_7, H_8), 1.32 – 1.27 (m, 1H, H_{1b}), 1.13 – 1.07 (m, 6H, H_{15}, H_{17}), 0.62 (d, *J* = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3 (C), 145.2 (C), 141.0 (C), 132.6 (C), 129.9 (2 × CH), 128.1 (2 × CH), 122.7 (CH), 119.5 (C), 83.6 (CH), 73.4 (CH), 65.0 (CH_2), 63.8 (CH_2), 61.4 (CH_2), 50.6 (CH), 45.6 (C), 42.4 (C), 41.4 (CH), 35.9 (CH_2), 35.5 (CH), 29.3 (CH_2), 28.5 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 21.7

(CH_3), 17.2 (CH_3), 15.8 (CH_3), 15.4 (CH_3), 13.5 (CH_3). IR (AT-FTIR), cm^{-1}: 2946 (m), 2864 (w), 1757 (w), 1371 (m), 1177 (s), 1036 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{30}H_{42}O_8SNa]^+$ 585.2498; found 585.2492. $[a]_D^{20}$ = –0.37 (c = 0.322, $CHCl_3$).

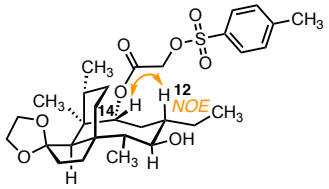
*Synthesis of the reduction product **35**.*



23 **35**

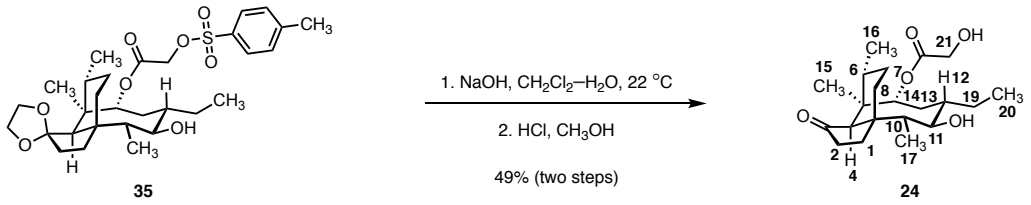
Crabtree's catalyst (1.00 mg, 1.2 μmol, 0.05 equiv) was added to a solution of the alkene **23** [12.0 mg, 24.1 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (1.2 mL) at 22 °C. The reaction vessel was purged with dihydrogen and placed under a balloon of dihydrogen. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the reduction product **35** as a clear oil (11.2 mg, 93%).

Within the limits of detection (600 MHz ^{1}H NMR analysis), **35** was formed as a single diastereomer. NOE correlations between H14 and H1, as well as X-ray analysis of the mutilin derivative **26** (see page S163), support the relative stereochemical assignment depicted.



R_f = 0.44 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H, H_{24}), 7.35 (d, J = 7.9 Hz, 2H, H_{25}), 5.34 (d, J = 8.2 Hz, 1H, H_{14}), 4.52 (s, 2H, H_{21}), 4.07 – 4.01 (m, 1H, $H_{22a\ or\ 23a}$), 3.94 – 3.85 (m, 2H, H_{22b}, H_{23b}), 3.80 – 3.73 (m, 1H, $H_{22a\ or\ 23a}$), 3.34 (dd, J = 10.1, 6.8 Hz, 1H, H_{11}), 2.45 (s, 3H, H_{26}), 2.24 (h, J = 7.2 Hz, 1H, H_6), 2.12 (p, J = 7.1, 6.5 Hz, 1H, H_{10}), 1.96 (s, 1H, H_4), 1.93 – 1.77 (m, 3H, H_2, H_{13a}), 1.77 – 1.66 (m, 2H, H_{12}, H_{19a}), 1.60 – 1.53 (m, 2H, H_8), 1.42 (dt, J = 13.2, 10.5 Hz, 1H, H_{1a}), 1.38 – 1.24 (m, 5H, H_{1b}, H_7, H_{13b}, H_{19b}), 1.05 (s, 3H, H_{15}), 0.90 (d, J = 7.0 Hz, 3H, H_{17}), 0.87 (t, J = 7.5 Hz, 3H, H_{20}), 0.62 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6 (C), 145.2 (C), 132.7 (C), 129.9 (2 × CH), 128.1 (2 × CH), 120.4 (C), 76.2 (CH), 71.5 (CH), 65.2 (CH_2), 63.8 (CH_2), 61.5 (CH_2), 50.9 (CH), 47.8 (CH), 46.1 (C), 41.6 (C), 40.0 (CH), 36.5 (CH_2), 35.8 (CH_2), 35.5 (CH), 29.2 (CH_2), 28.7 (CH_2), 27.1 (CH_2), 25.7 (CH_2), 21.7 (CH_3), 17.5 (CH_3), 14.6 (CH_3), 11.5 (CH_3), 10.5 (CH_3). IR (AT-FTIR), cm^{-1}: 2938 (m), 2879 (w), 2361 (w), 1752 (w), 1372 (m), 1177 (s), 1035 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{30}H_{44}NaO_8S]^+$ 587.2655; found 587.2641. $[a]_D^{20}$ = –4.19 (c = 0.172, $CHCl_3$).

*Synthesis of the normethyl derivative **24**.*

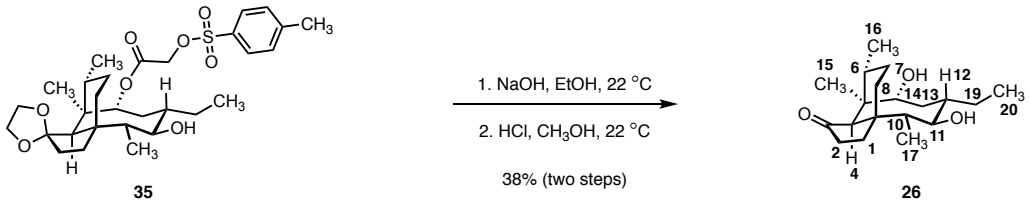


Aqueous sodium hydroxide solution (2 N, 28.0 μL, 56.0 μmol, 10.0 equiv) was added to a solution of the sulfonate **35** (3.20 mg, 5.60 μmol, 1 equiv) in dichloromethane (200 μL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated. The residue obtained was used directly in the following step.

Aqueous hydrochloric acid solution (12 N, 9.30 μL, 112 μmol, 20.0 equiv) was added to a solution of the product obtained in the preceding step (nominally, 5.60 μmol, 1 equiv) in methanol (200 μL) at 22 °C. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, two steps) to provide the normethyl derivative **24** as a clear oil (1.00 mg, 49% over two steps).

R_f = 0.54 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (d, J = 6.7 Hz, 1H, H_{14}), 4.08 (qd, J = 17.1, 5.3 Hz, 2H, H_{21}), 3.40 (s, 1H, H_{11}), 2.42 – 2.12 (m, 4H, H_2, H_{10}, OH), 2.04 (d, J = 2.7 Hz, 1H, H_4), 1.88 – 1.57 (m, 6H, H_{1a}, H_6, H_{8a}, H_{12}, H_{13a}, H_{19a}), 1.46 – 1.36 (m, 8H, H_{1b}, H_7, H_{15}, H_{13b} H_{19a}), 1.14 (td, J = 13.9, 4.5 Hz, 1H, H_{8b}), 1.01 (d, J = 7.0 Hz, 3H, H_{17}), 0.90 (t, J = 7.5 Hz, 3H, H_{20}), 0.73 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.1 (C), 173.0 (C), 74.5 (CH), 71.8 (CH), 61.4 (CH_2), 58.3 (CH), 47.5 (CH), 45.7 (C), 41.8 (C), 41.0 (CH), 36.8 (CH), 36.6 (CH_2), 34.5 (CH_2), 30.7 (CH_2), 27.2 (CH_2), 25.9 (CH_2), 25.6 (CH_2), 17.4 (CH_3), 15.1 (CH_3), 11.4 (CH_3), 10.3 (CH_3). IR (AT-FTIR), cm^{-1}: 3730 (w), 3383 (w), 2361 (s), 2341 (s), 1718 (w), 1648 (w), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{21}H_{35}O_5]^+$ 367.2484; found 367.2479.

*Synthesis of the mutilin derivative **26**.*



35 26

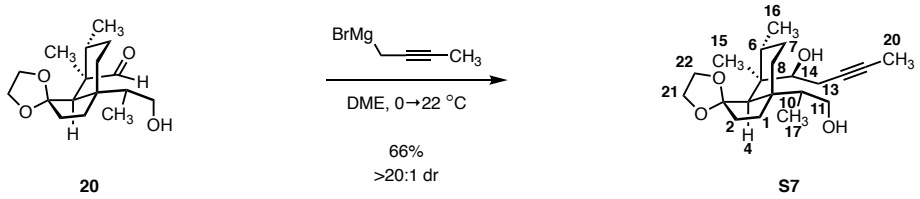
Aqueous sodium hydroxide solution (2 N, 35.0 μL, 69.1 μmol, 10.0 equiv) was added to a solution of the sulfonate **35** (3.90 mg, 6.90 μmol, 1 equiv) in ethanol (200 μL) at 22 °C. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was concentrated. The residue obtained was used directly in the following step.

Aqueous hydrochloric acid solution (12 N, 5.80 μL, 69.1 μmol, 10.0 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally, 6.90 μmol, 1 equiv) in methanol (200 μL) at 22 °C. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, two steps) to provide the mutilin derivative **26** as white solid (830 μg, 38% over two steps).

The relative stereochemistry of the mutilin derivative **26** was established by X-ray analysis (see page S163).

R_f = 0.53 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.37 – 4.22 (m, 1H, H_{14}), 3.40 (dt, J = 10.0, 6.4 Hz, 1H, H_{11}), 2.28 – 2.14 (m, 3H, H_2, H_{10}), 2.02 – 1.99 (m, 1H, H_4), 1.84 – 1.73 (m, 3H, H_{8a}, H_{13a}, H_{19a}), 1.71 – 1.45 (m, 6H, H_1, H_6, H_{7a}, H_{12}, H_{13b}), 1.43 – 1.35 (m, 5H, H_{7b}, H_{15}, H_{19b}), 1.33 – 1.29 (m, 2H, 2 × OH), 1.14 (td, J = 14.0, 4.3 Hz, 1H, H_{8b}), 1.00 – 0.95 (m, 6H, H_{16}, H_{17}), 0.94 (td, J = 7.5, 1.0 Hz, 3H, H_{20}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.9 (C), 72.0 (CH), 70.5 (CH), 59.1 (CH), 48.2 (CH), 45.7 (C), 42.9 (C), 40.8 (CH), 39.1 (CH_2), 37.1 (CH), 34.6 (CH_2), 30.8 (CH_2), 27.3 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 18.4 (CH_3), 13.6 (CH_3), 11.2 (CH_3), 10.5 (CH_3). IR (AT-FTIR), cm^{-1}: 3401 (w), 2923 (w), 2357 (m), 1725 (m), 662 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{19}H_{33}O_3]^+$ 309.2430; found 309.2420.

*Synthesis of the homopropargylic alcohol **S7**.*

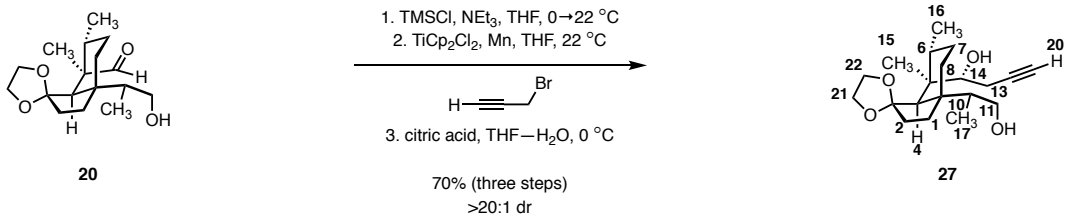


A solution of (1-but-2-ynyl)magnesium bromide in ether (30 mM, 1.6 mL, 486 μmol, 3.00 equiv) was added dropwise to a solution of the aldehyde **20** [60.0 mg, 162 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dimethoxyethane (2.3 mL) at 0 °C. The reaction mixture was allowed to warm to 22 °C over 10 min. The warmed reaction mixture was stirred for 20 min at 22 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (6.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **S7** as an off-white foam (37.0 mg, 66%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the homopropargylic alcohol **S7** was formed as a single diastereomer. The relative stereochemistry was determined by comparison of $^3J_{H–H}$ coupling constants to the diastereomeric addition product **21**.

R_f = 0.32 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6) δ 4.00 (dd, J = 9.0, 3.0 Hz, 1H, H_{14}), 3.89 (ddd, J = 13.8, 9.4, 4.1 Hz, 1H, H_{11a}), 3.52 (ddt, J = 10.4, 6.1, 3.7 Hz, 1H, $H_{21a \text{ or } 22a}$), 3.48 – 3.29 (m, 3H, $H_{21a \text{ or } 22a}$, H_{21b}, H_{22b}), 3.24 (ddd, J = 10.1, 7.0, 2.7 Hz, 1H, H_{11b}), 2.98 (s, 1H, H_4), 2.57 (dq, J = 16.5, 2.7 Hz, 1H, H_{13a}), 2.47 (dtt, J = 19.7, 7.2, 2.9 Hz, 2H, H_{10}, H_{13b}), 2.14 (ddq, J = 11.6, 8.0, 4.1 Hz, 1H, H_6), 1.66 (dddd, J = 27.1, 21.0, 10.2, 6.5 Hz, 4H, H_1, H_2), 1.48 (d, J = 2.6 Hz, 5H, H_{7a}, H_{8a}, H_{20}), 1.33 – 1.23 (m, 1H, H_{7b}), 1.19 – 1.09 (m, 4H, H_{8b}, H_{15}), 1.03 – 0.86 (m, 6H, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 120.8 (C), 83.6 (C), 74.3 (CH), 70.5 (C), 66.7 (CH_2), 63.5 (CH_2), 61.9 (CH_2), 47.7 (CH), 45.8 (C), 43.5 (C), 39.4 (CH), 38.9 (CH), 35.4 (CH_2), 33.0 (CH_2), 29.7 (CH_2), 28.0 (CH_2), 25.7 (CH_2), 20.6 (CH_3), 18.8 (CH_3), 17.8 (CH_3), 14.7 (CH_3). IR (AT-FTIR), cm^{-1}: 2953 (w), 1715 (m), 1396 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{21}H_{34}O_4Na]^+$ 373.2355; found 373.2356.

*Synthesis of the homopropargylic alcohol **27**.*



20 **27**

Trimethylsilyl chloride (45.0 μL, 355 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (90.0 μL, 646 μmol, 2.00 equiv) and the aldehyde **20** (96.0 mg, 323 μmol, 1 equiv) in tetrahydrofuran (3.2 mL) at 0 °C. The reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min. The cooled product mixture was diluted sequentially with ether (4.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 2.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

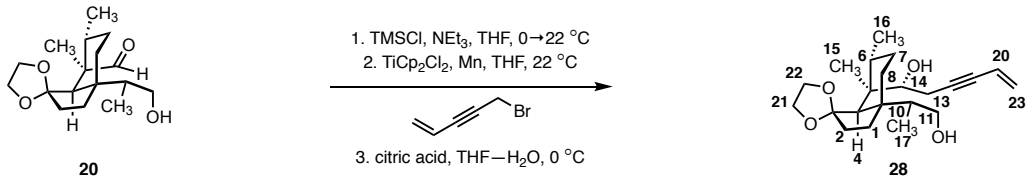
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (241 mg, 969 μmol, 3.00 equiv) and manganese powder (213 mg, 3.87 mmol, 12.0 equiv) in tetrahydrofuran (4.0 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of propargyl bromide in toluene (80% w/w, 122 μL, 1.29 mmol, 4.00 equiv) and the protected alcohol obtained in the preceding step (nominally 323 μmol, 1 equiv) in tetrahydrofuran (4.0 mL) was then added dropwise over 2 min at 22 °C. The reaction mixture was stirred for 15 min at 22 °C. The product mixture was diluted with hexanes (8.0 mL). The diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 400 μL) was added dropwise to a solution of the unpurified addition product obtained in the preceding step (nominally 323 μmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and saturated aqueous sodium bicarbonate solution (3.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 4.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **27** as an off-white foam (75.0 mg, 70% over three steps).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the homopropargylic alcohol **27** was formed as a single diastereomer. The relative stereochemistry was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.41 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 4.23 (ddd, J = 10.5, 3.8, 2.2 Hz, 1H, H_{14}), 3.60 (dd, J = 10.4, 3.1 Hz, 1H, H_{11a}), 3.55 (q, J = 7.4 Hz, 1H, $H_{21a\ or\ 22a}$), 3.43 (td, J = 7.4, 4.6 Hz, 1H, $H_{21b\ or\ 22b}$), 3.39 – 3.29 (m, 2H, $H_{21a\ or\ 22a}$, $H_{21b\ or\ 22b}$), 3.14 (dd, J = 10.4, 8.8 Hz, 1H, H_{11b}), 2.72 (s, 1H, H_4), 2.39 (dt, J = 16.6, 2.5 Hz, 1H, H_{13a}), 2.26 (ddd, J = 16.7, 10.5, 2.6 Hz, 1H, H_{13b}), 2.17 (dtp, J = 9.8, 6.3, 3.1 Hz, 1H, H_{10}), 1.96 – 1.82 (m, 2H, H_2), 1.73 (t, J = 2.6 Hz, 1H, H_{20}), 1.63 – 1.45 (m, 4H, H_{1a}, H_6, H_7), 1.45 – 1.36 (m, 1H, H_{1b}), 1.15 – 0.91 (m, 11H, H_8, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.3 (C), 83.3 (C), 76.0 (CH), 70.2 (CH), 64.8 (CH_2), 63.7 (CH_2), 62.9 (CH_2), 45.9 (C), 45.3 (CH), 42.7 (CH), 41.1 (C), 36.3 (CH), 35.8 (CH_2), 30.6 (CH_2), 25.6 (CH_2), 25.6 (CH_2), 22.4 (CH_2), 20.6 (CH_3), 16.7 (CH_3), 13.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3416 (w), 2937 (m), 2883 (m), 2361 (s), 2339 (s), 1100 (m), 1021 (m), 772 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{20}H_{33}O_4]^+$ 337.2379; found 337.2373. $[a]_D^{20}$ = –24.8 (c = 0.205, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **28**.*



Trimethylsilyl chloride (18.0 μL, 141 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (303 μL, 2.17 mmol, 2.00 equiv) and the aldehyde **20** (36.1 mg, 128 μmol, 1 equiv) in tetrahydrofuran (1.3 mL) at 0 °C. The reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min. The cooled product mixture was diluted sequentially with ether (10 mL) and aqueous potassium phosphate buffer solution (pH 7, 10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

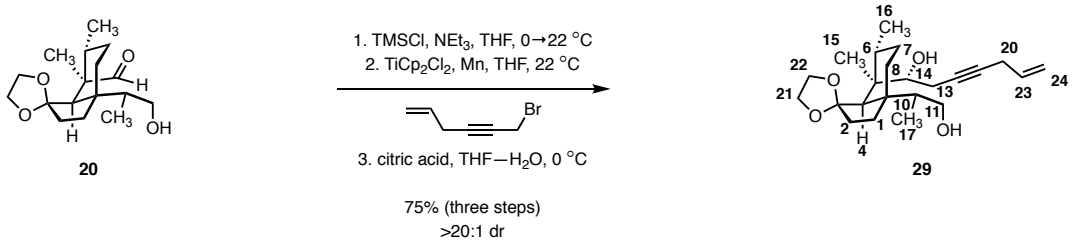
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (95.2 mg, 383 μmol, 3.00 equiv) and manganese powder (84.1 mg, 1.53 mmol, 12.0 equiv) in tetrahydrofuran (650 μL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the protected alcohol obtained in the preceding step (nominally 128 μmol, 1 equiv) and 5-bromopent-1-en-3-yne (76.1 mg, 446 μmol, 3.50 equiv) in tetrahydrofuran (650 μL) was added dropwise over 5 min at 22 °C. The reaction mixture was stirred for 30 min at 22 °C. The product mixture was diluted with hexanes (1.0 mL). The diluted product mixture was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 200 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 128 μmol, 1 equiv) in tetrahydrofuran (2.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (4.0 mL) and saturated aqueous sodium bicarbonate solution (4.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 6.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (9.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **28** as a yellow foam (34.0 mg, 74% over three steps).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the homopropargylic alcohol **28** was formed as a single diastereomer. The relative stereochemistry was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.34 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 5.70 (ddt, *J* = 17.6, 11.0, 2.2 Hz, 1H, H_{20}), 5.54 (dd, *J* = 17.5, 2.2 Hz, 1H, H_{23a}), 5.12 (dd, *J* = 11.1, 2.2 Hz, 1H, H_{23b}), 4.27 (dt, *J* = 10.5, 2.6 Hz, 1H, H_{14}), 3.61 (dd, *J* = 10.4, 3.0 Hz, 1H, H_{11a}), 3.54 (q, *J* = 7.3 Hz, 1H, $H_{20a\ or\ 21a}$), 3.42 (td, *J* = 7.4, 4.5 Hz, 1H, $H_{20b\ or\ 21b}$), 3.37 – 3.26 (m, 2H, $H_{20a\ or\ 21a}$, $H_{20b\ or\ 21b}$), 3.15 (dd, *J* = 10.4, 8.8 Hz, 1H, H_{11b}), 2.74 (s, 1H, H_4), 2.59 (dt, *J* = 16.8, 2.4 Hz, 1H, H_{13a}), 2.46 (ddd, *J* = 16.8, 10.4, 2.2 Hz, 1H, H_{13b}), 2.18 (dqd, *J* = 9.5, 6.6, 2.9 Hz, 1H, H_{10}), 1.97 – 1.84 (m, 2H, H_2), 1.67 – 1.35 (m, 5H, H_1, H_6, H_{7a}, H_{8a}), 1.20 – 1.06 (m, 11H, H_{7b}, H_{8b}, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 126.2 (CH_2), 121.7 (C), 117.9 (CH), 90.3 (C), 81.7 (C), 76.5 (CH), 65.3 (CH_2), 64.1 (CH_2), 63.3 (CH_2), 46.4 (C), 45.7 (CH), 43.1 (CH), 41.6 (C), 36.8 (CH), 36.2 (CH_2), 31.0 (CH_2), 30.2 (CH_2), 26.0 (CH_2), 23.8 (CH_2), 21.1 (CH_3), 17.2 (CH_3), 13.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 2940 (w), 2362 (m), 2343 (m), 1541 (w), 1020 (w), 773 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{22}H_{34}NaO_4]^+$ 385.2355; found 385.2346. $[a]_D^{20}$ = –3.68 (*c* = 0.200, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **29**.*



Trimethylsilyl chloride (88.0 μL, 695 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (176 μL, 1.26 mmol, 2.00 equiv) and the aldehyde **20** (187 mg, 632 μmol, 1 equiv) in tetrahydrofuran (6.3 mL) at 0 °C. Upon completion of the addition the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min. The cooled product mixture was diluted sequentially with ether (6.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 6.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

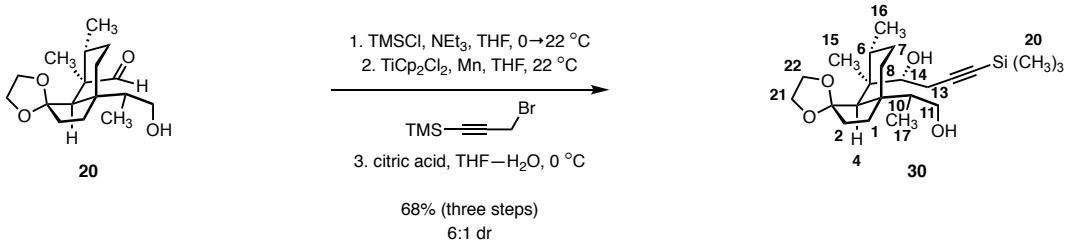
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (488 mg, 1.89 mmol, 3.00 equiv) and manganese powder (417 mg, 7.58 mmol, 12.0 equiv) in tetrahydrofuran (4.5 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of 6-bromohex-1-en-4-yne (503 mg, 2.21 mmol, 3.50 equiv) and the protected alcohol obtained in the preceding step (nominally 632 μmol, 1 equiv) in tetrahydrofuran (4.5 mL) was added dropwise over 1 h at 22 °C. The reaction mixture was stirred for 4 h at 22 °C. The product mixture was diluted with hexanes (6.0 mL). The diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 900 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 632 μmol, 1 equiv) in tetrahydrofuran (2.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (4.0 mL) and saturated aqueous sodium bicarbonate solution (4.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **29** as an off-white foam (178 mg, 75% over three steps).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the homopropargylic alcohol **29** was formed as a single diastereomer. The relative stereochemistry was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.44 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 5.64 (ddt, *J* = 16.9, 10.1, 5.2 Hz, 1H, H_{23}), 5.37 (dq, *J* = 17.0, 1.9 Hz, 1H, H_{24a}), 5.02 (dq, *J* = 10.0, 1.8 Hz, 1H, H_{24b}), 4.29 (dt, *J* = 10.6, 2.8 Hz, 1H, H_{14}), 3.66 – 3.55 (m, 2H, H_{11a}, $H_{21a\ or\ 22a}$), 3.48 – 3.41 (m, 2H, H_{21b}, H_{22b}), 3.39 – 3.33 (m, 1H, $H_{21a\ or\ 22a}$), 3.19 – 3.12 (m, 1H, H_{11b}), 2.77 (s, 1H, H_4), 2.72 (dt, *J* = 5.2, 2.1 Hz, 2H, H_{20}), 2.53 (dq, *J* = 16.5, 2.4 Hz, 1H, H_{13a}), 2.40 (ddt, *J* = 16.4, 10.6, 2.4 Hz, 1H, H_{13b}), 2.20 (ddp, *J* = 9.5, 6.6, 3.3 Hz, 1H, H_{10}), 1.99 (d, *J* = 3.6 Hz, 1H, OH), 1.96 – 1.85 (m, 2H, H_2), 1.65 – 1.49 (m, 4H, H_{1a}, H_6, H_7), 1.46 – 1.38 (m, 1H, H_{1b}), 1.18 – 0.96 (m, 11H, H_8, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 133.0 (CH), 121.4 (C), 115.4 (CH_2), 81.5 (C), 78.8 (C), 76.1 (CH), 64.9 (CH_2), 63.8 (CH_2), 62.9 (CH_2), 46.0 (C), 45.4 (CH), 42.7 (CH), 41.1 (C), 36.5 (CH), 35.8 (CH_2), 30.6 (CH_2), 25.7 (CH_2), 25.7 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 20.6 (CH_3), 16.9 (CH_3), 13.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3417 (w), 2947 (m), 2360 (s), 2332 (m), 1456 (w), 1100 (m), 1019 (m), 772 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{23}H_{37}O_4]^+$ 377.2692; found 377.2686. $[a]_D^{20}$ = –972.3 (*c* = 0.200, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **30**.*



Trimethylsilyl chloride (6.00 μL, 44.8 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (11.0 μL, 81.4 μmol, 2.00 equiv) and the aldehyde **20** (12.0 mg, 40.7 μmol, 1 equiv) in tetrahydrofuran (400 μL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (1.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

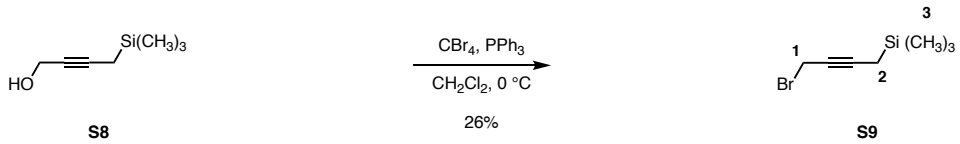
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (30.4 mg, 122 μmol, 3.00 equiv) and manganese powder (26.8 mg, 488 μmol, 12.0 equiv) in tetrahydrofuran (250 μL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of (3-bromoprop-1-yn-1-yl)trimethylsilane (38.9 mg, 162 μmol, 3.50 equiv) and the protected alcohol obtained in the preceding step (nominally 40.7 μmol, 1 equiv) in tetrahydrofuran (250 μL) was added dropwise over 1 h at 22 °C. The reaction mixture was stirred for 4 h at 22 °C. The product mixture was diluted with hexanes (1.0 mL). The diluted product mixture was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 100 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 40.7 μmol, 1 equiv) in tetrahydrofuran (500 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.5 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **30** as an off-white foam (11.3 mg, 68% over three steps).

^{1}H NMR (500 MHz) analysis of the unpurified product mixture indicated the presence of a 6:1 mixture of diastereomers. The relative configuration of the major diastereomer was determined by comparison to the diastereomeric addition product **21**.

R_f = 0.48 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 4.32 (dt, *J* = 10.3, 3.1 Hz, 1H, H_{14}), 3.64 (dd, *J* = 10.5, 2.9 Hz, 1H, H_{11a}), 3.58 – 3.51 (m, 1H, $H_{21a\ or\ 22a}$), 3.45 – 3.37 (m, 2H, H_{21b}, H_{22b}), 3.37 – 3.27 (m, 1H, $H_{21a\ or\ 22a}$), 3.19 – 3.12 (m, 1H, H_{11b}), 2.72 (s, 1H, H_4), 2.55 (dd, *J* = 16.9, 2.4 Hz, 1H, H_{13a}), 2.42 (dd, *J* = 16.8, 10.4 Hz, 1H, H_{13b}), 2.18 (tt, *J* = 9.3, 6.5 Hz, 1H, H_{10}), 2.04 (d, *J* = 3.9 Hz, 1H, OH), 1.91 – 1.80 (m, 2H, H_2), 1.70 – 1.43 (m, 4H, H_{1a}, H_6, H_7), 1.44 –1.34 (m, 1H, H_{1b}), 1.16 – 1.00 (m, 11H, H_8, H_{15}, H_{16}, H_{17}), 0.19 (d, *J* = 2.1 Hz, 9H, H_{20}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.7 (C), 107.0 (C), 87.0 (C), 76.1 (CH), 65.3 (CH_2), 64.1 (CH_2), 63.2 (CH_2), 46.4 (C), 46.1 (CH), 43.1 (CH), 41.7 (C), 37.0 (CH), 36.1 (CH_2), 30.9 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 24.5 (CH_2), 20.7 (CH_3), 17.4 (CH_3), 13.4 (CH_3), 0.2 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 3416 (w), 2955 (m), 2885 (m), 2361 (w), 2172 (w), 1250 (m), 1017 (m), 843 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{23}H_{41}O_4Si]^+$ 409.2774; found 409.2768. $[a]_D^{20}$ = –15.0 (*c* = 0.570, $CHCl_3$).

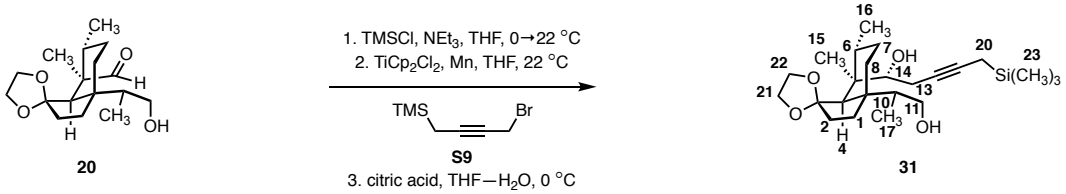
Synthesis of (*4-bromobut-2-yn-1-yl)trimethylsilane* (***S9***).



Triphenylphosphine (619 mg, 2.36 mmol, 1.05 equiv) was added in three portions over 30 min to a solution of tetrabromomethane (783 mg, 2.36 mmol, 1.05 equiv) and 4-(trimethylsilyl)but-2-yn-1-ol (**S8**, 320 mg, 2.25 mmol, 1 equiv) in dichloromethane (11 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted with pentane (50 mL) and the diluted product mixture was filtered through a pad of Celite. The Celite pad was rinsed with pentane (50 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with pentane) to provide (4-bromobut-2-yn-1-yl)trimethylsilane (**S9**) as a colorless oil (120 mg, 26%).

R_f = 0.88 (1% ether–hexanes; $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (t, *J* = 2.8 Hz, 2H, H_1), 1.52 (t, *J* = 2.8 Hz, 2H, H_2), 0.10 (s, 9H, H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.9 (C), 74.1 (C), 16.8 (CH_2), 7.6 (CH_2), –2.0 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 2956 (w), 2223 (w), 1249 (m), 1217 (w), 640 (s), 787 (w), 698 (w), 599 (m).

*Synthesis of the homopropargylic alcohol **31**.*



Trimethylsilyl chloride (27.0 μL, 209 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (53.0 μL, 380 μmol, 2.00 equiv) and the aldehyde **20** (56.0 mg, 190 μmol, 1 equiv) in tetrahydrofuran (1.9 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (2.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 2.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

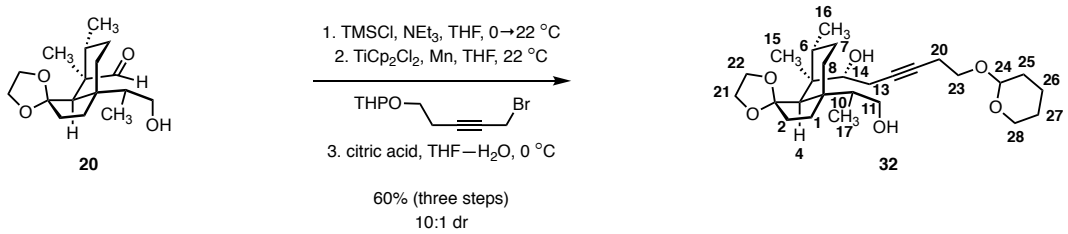
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (142 mg, 570 μmol, 3.00 equiv) and manganese powder (125 mg, 2.28 mmol, 12.0 equiv) in tetrahydrofuran (2.4 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of (4-bromobut-2-yn-1-yl)trimethylsilane (**S9**, 155 mg, 665 μmol, 3.50 equiv) and the protected alcohol obtained in the preceding step (nominally 190 μmol, 1 equiv) in tetrahydrofuran (2.4 mL) was then added dropwise over 1 h at 22 °C. The reaction mixture was stirred for 6 h at 22 °C. The product mixture was diluted with hexanes (3.0 mL). The diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 500 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 190 μmol, 1 equiv) in tetrahydrofuran (1.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.5 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **31** as an off-white foam (52.0 mg, 65% over three steps).

^{1}H NMR (500 MHz) analysis of the unpurified product mixture indicated the presence of a 3:1 mixture of diastereomers. The relative configuration of the major diastereomer was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.48 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 4.32 (d, *J* = 10.6 Hz, 1H, H_{14}), 3.72 – 3.62 (m, 2H, H_{11a}, $H_{21a\ or\ 22a}$), 3.56 (td, *J* = 6.7, 4.4 Hz, 1H, $H_{21b\ or\ 22b}$), 3.49 (td, *J* = 7.2, 4.4 Hz, 1H, $H_{21a\ or\ 22a}$), 3.43 (q, *J* = 6.9 Hz, 1H, $H_{21b\ or\ 22b}$), 3.17 (td, *J* = 9.8, 4.3 Hz, 1H, H_{11b}), 2.82 (s, 1H, H_4), 2.55 (dq, *J* = 16.5, 2.6 Hz, 1H, H_{13a}), 2.42 (ddt, *J* = 16.3, 10.6, 2.8 Hz, 1H, H_{13b}), 2.23 (dqd, *J* = 9.3, 6.5, 2.7 Hz, 1H, H_{10}), 2.12 (d, *J* = 2.9 Hz, 1H, OH), 1.95 (dd, *J* = 10.3, 6.1 Hz, 2H, H_2), 1.71 – 1.51 (m, 4H, H_{1a}, H_6, H_7), 1.47 – 1.38 (m, 1H, H_{1b}), 1.36 (t, *J* = 2.7 Hz, 2H, H_{20}), 1.21 – 1.06 (m, 11H, H_8, H_{15}, H_{16}, H_{17}), 0.05 (s, 9H, H_{23}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.9 (C), 80.4 (C), 77.7 (C), 76.6 (CH), 65.4 (CH_2), 64.3 (CH_2), 63.4 (CH_2), 46.4 (C), 45.9 (CH), 43.2 (CH), 41.4 (C), 36.9 (CH), 36.3 (CH_2), 31.0 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 23.4 (CH_2), 21.0 (CH_3), 17.4 (CH_3), 13.5 (CH_3), 7.2 (CH_2), –2.1 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 2996 (m), 2359 (w), 2341 (w), 1424 (m), 1401 (m), 1135 (s), 944 (s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{24}H_{42}NaO_4Si]^+$ 445.2750; found 445.2738. $[\alpha]_D^{20}$ = –4.66 (*c* = 0.313, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **32**.*



Trimethylsilyl chloride (5.00 μL, 36.0 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (9.00 μL, 65.2 μmol, 2.00 equiv) and the aldehyde **20** (9.70 mg, 32.6 μmol, 1 equiv) in tetrahydrofuran (320 μL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (1.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

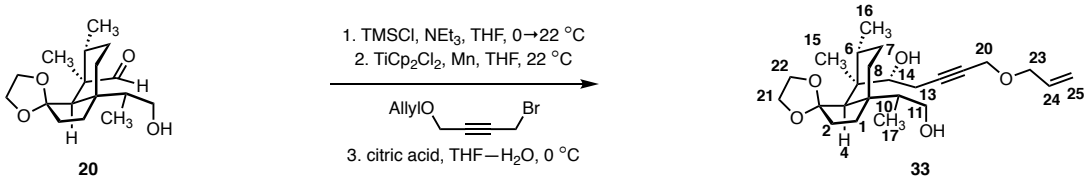
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (24.3 mg, 97.7 μmol, 3.00 equiv) and manganese powder (21.5 mg, 391 μmol, 12.0 equiv) in tetrahydrofuran (550 μL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of 2-((5-bromopent-3-yn-1-yl)oxy)tetrahydro-2*H*-pyran (32.2 mg, 130 μmol, 4.00 equiv) and the protected alcohol obtained in the preceding step (nominally 32.6 μmol, 1 equiv) in tetrahydrofuran (550 μL) was added dropwise over 45 min at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted with hexanes (2.0 mL). The diluted product mixture was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 100 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 32.6 μmol, 1 equiv) in tetrahydrofuran (500 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.5 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **32** as an off-white foam (9.00 mg, 60% over three steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 10:1 mixture of diastereomers. The relative configuration of the major diastereomer was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.39 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 4.54 (q, *J* = 3.6 Hz, 1H, H_{24}), 4.31 (dd, *J* = 10.4, 2.4 Hz, 1H, H_{14}), 3.79 (tdd, *J* = 13.4, 8.1, 3.4 Hz, 2H, H_{23a}, H_{28a}), 3.71 – 3.60 (m, 2H, H_{11a}, $H_{21a\ or\ 22a}$), 3.54 – 3.44 (m, 2H, H_{21b}, H_{22b}), 3.43 – 3.31 (m, 3H, $H_{21a\ or\ 22a}$, H_{23b}, H_{28b}), 3.18 (ddd, *J* = 10.7, 8.9, 2.1 Hz, 1H, H_{11b}), 2.77 (d, *J* = 7.5 Hz, 1H, H_4), 2.51 (ddq, *J* = 16.4, 4.8, 2.4 Hz, 1H, H_{13a}), 2.37 (ddddt, *J* = 29.4, 23.0, 20.2, 6.9, 2.9 Hz, 4H, H_{13b}, H_{20}, OH), 2.23 (tdt, *J* = 11.4, 6.6, 3.0 Hz, 1H, H_{10}), 1.91 (dd, *J* = 9.3, 6.3, 2H, H_2), 1.80 – 1.49 (m, 7H, H_{1a}, H_6, H_7, H_{25}, H_{26a}), 1.45 – 1.22 (m, 4H, H_{1b}, H_{26b}, H_{27}), 1.22 – 1.00 (m, 11H, H_8, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.8 (C), 98.8 (d, *J* = 14.7 Hz, CH), 80.3 (C), 76.3 (C), 76.1 (CH), 66.2 (CH_2), 65.3 (CH_2), 64.2 (CH_2), 63.3 (CH_2), 61.9 (CH_2), 46.4 (C), 46.1 (CH), 43.0 (CH), 41.6 (C), 37.1 (CH), 36.2 (CH_2), 30.9 (CH_2), 30.9 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 23.3 (CH_2), 20.8 (CH_2), 20.7 (CH_2), 20.7 (CH_3), 19.6 (CH_2), 17.5 (CH_3), 13.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2928 (w), 2357 (m), 2019 (w), 1219 (w), 773 (s). HRMS-ESI (m/z): $[M+H]^+$ calcd for $[C_{27}H_{45}O_6]^+$ 465.3216; found 465.3211. $[\alpha]_D^{20}$ = –17.4 (*c* = 0.055, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **33**.*



Trimethylsilyl chloride (14.0 μL, 108 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (27.0 μL, 195 μmol, 2.00 equiv) and the aldehyde **20** (29.0 mg, 97.7 μmol, 1 equiv) in tetrahydrofuran (970 μL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (2.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

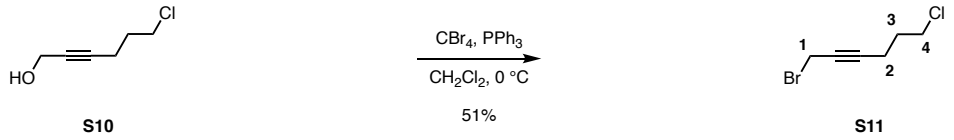
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (72.9 mg, 293 μmol, 3.00 equiv) and manganese powder (64.4 mg, 1.17 mmol, 12.0 equiv) in tetrahydrofuran (1.0 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of 1-(allyloxy)-4-bromobut-2-yne (73.9 mg, 391 μmol, 4.00 equiv) and the protected alcohol obtained in the preceding step (nominally 97.7 μmol, 1 equiv) in tetrahydrofuran (1.0 mL) was added dropwise over 15 min at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted with hexanes (3.0 mL). The diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 300 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 97.7 μmol, 1 equiv) in tetrahydrofuran (1.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.5 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **33** as an off-white foam (22.0 mg, 55% over three steps).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the homopropargylic alcohol **33** was formed as a single diastereomer. The relative stereochemistry was determined by comparison to the diastereomeric addition product **21**.

R_f = 0.40 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 5.81 (ddt, *J* = 17.3, 10.7, 5.4 Hz, 1H, H_{24}), 5.24 (dq, *J* = 17.2, 1.8 Hz, 1H, H_{25a}), 5.02 (dq, *J* = 10.4, 1.5 Hz, 1H, H_{25b}), 4.28 (dd, *J* = 10.4, 2.4 Hz, 1H, H_{14}), 3.98 (t, *J* = 2.1 Hz, 2H, H_{20}), 3.91 (dt, *J* = 5.4, 1.6 Hz, 2H, H_{23}), 3.64 (dt, *J* = 10.4, 2.6 Hz, 1H, H_{11a}), 3.56 (tdd, *J* = 9.0, 6.8, 1.6 Hz, 1H, $H_{21a\ or\ 22a}$), 3.45 – 3.39 (m, 2H, H_{21b}, H_{22b}), 3.38 – 3.32 (m, 1H, $H_{21a\ or\ 22a}$), 3.16 (ddd, *J* = 10.7, 8.8, 2.0 Hz, 1H, H_{11b}), 2.71 (s, 1H, H_4), 2.52 (dq, *J* = 16.6, 2.2 Hz, 1H, H_{13a}), 2.36 (ddt, *J* = 16.7, 10.4, 2.1 Hz, 1H, H_{13b}), 2.20 (dqd, *J* = 9.4, 6.5, 2.9 Hz, 1H, H_{10}), 1.94 – 1.82 (m, 2H, H_2), 1.60 (ddd, *J* = 14.2, 8.9, 5.5 Hz, 2H, H_{1a}, H_6), 1.57 – 1.49 (m, 2H, H_7), 1.45 – 1.35 (m, 1H, H_{1b}), 1.17 – 0.98 (m, 11H, H_8, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 134.5 (CH), 121.3 (C), 116.5 (CH_2), 85.5 (C), 78.4 (C), 76.1 (CH), 70.2 (CH_2), 64.7 (CH_2), 63.7 (CH_2), 62.8 (CH_2), 57.5 (CH_2), 46.0 (C), 45.6 (CH), 42.6 (CH), 41.3 (C), 36.6 (CH), 35.7 (CH_2), 30.5 (CH_2), 25.7 (CH_2), 25.7 (CH_2), 23.0 (CH_2), 20.4 (CH_3), 17.0 (CH_3), 13.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3461 (w), 2940 (m), 2883 (m), 2361 (m), 1454 (w), 1073 (m), 1021 (m), 773 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{24}H_{39}O_5]^+$ 407.2797; found 407.2792. $[a]_D^{20}$ = –15.1 (c = 0.160, $CHCl_3$).

*Synthesis of 1-bromo-6-chlorohex-2-yne (**S11**).*

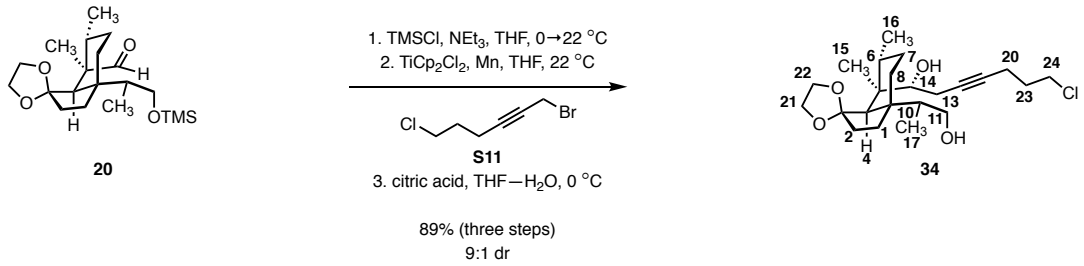


S10 **S11**

Triphenylphosphine (10.9 g, 41.8 mmol, 1.10 equiv) was added in three portions over 30 min to a solution of tetrabromomethane (13.8 g, 41.8 mmol, 1.10 equiv) and 6-chlorohex-2-yn-1-ol (**S10**, 5.04 g, 38.0 mmol, 1 equiv) in dichloromethane (190 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted with pentane (500 mL) and the diluted product mixture was filtered through a pad of Celite. The Celite pad was rinsed with pentane (100 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 100% pentane) to provide 1-bromo-6-chlorohex-2-yne (**S11**) as a colorless oil (3.80 g, 51%).

R_f = 0.75 (1% ether–hexanes; $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$) δ 3.91 (t, J = 2.4 Hz, 2H, H_1), 3.63 (t, J = 6.3 Hz, 2H, H_4), 2.44 (tt, J = 6.8, 2.4 Hz, 2H, H_2), 1.96 (p, J = 6.6 Hz, 2H, H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0 (C), 76.3 (C), 43.5 (CH_2), 31.0 (CH_2), 16.4 (CH_2), 15.2 (CH_2). IR (ATR-FTIR), cm^{-1}: 2958 (w), 2362 (w), 2234 (w), 1429 (w), 1239 (w), 1206 (m), 859 (w), 723 (w), 652 (m), 608 (s).

*Synthesis of the homopropargylic alcohol **34**.*



Trimethylsilyl chloride (264 μL, 2.08 mmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (526 μL, 3.78 mmol, 2.00 equiv) and the aldehyde **20** (560 mg, 1.89 mmol, 1 equiv) in tetrahydrofuran (19 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (30 mL) and aqueous potassium phosphate buffer solution (pH 7, 25 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

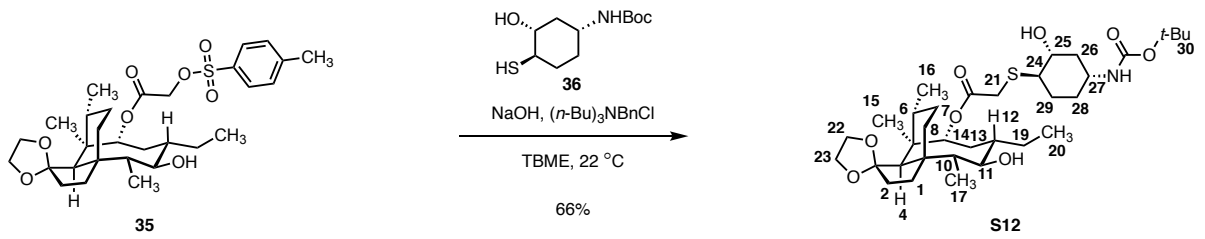
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (1.41 g, 5.70 mmol, 3.00 equiv) and manganese powder (1.25 g, 22.8 mmol, 12.0 equiv) in tetrahydrofuran (24 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the propargyl bromide **S11** (1.49 g, 7.59 mmol, 4.00 equiv) and the protected alcohol obtained in the preceding step (nominally 1.89 mmol, 1 equiv) in tetrahydrofuran (24 mL) was added dropwise over 70 min at 22 °C using a syringe pump. The reaction mixture was stirred for 2.5 h at 22 °C. The product mixture was diluted with hexanes (40 mL). The diluted product mixture was eluted over a plug of silica gel (4.0 cm × 4.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 15 mL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 1.89 mmol, 1 equiv) in tetrahydrofuran (60 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 150 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **34** as an off-white foam (700 mg, 89% over three steps).

^{1}H NMR (500 MHz) analysis of the unpurified product mixture indicated the presence of a 9:1 mixture of diastereomers. The relative configuration of the major diastereomer was determined by comparison to the diastereomeric homopropargylic alcohol **21**.

R_f = 0.41 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 4.27 (d, *J* = 10.2 Hz, 1H, H_{14}), 3.66 (d, *J* = 10.6 Hz, 1H, H_{11a}), 3.64 – 3.58 (m, 1H, $H_{21a\ or\ 22a}$), 3.47 (tq, *J* = 15.3, 9.6, 7.7 Hz, 2H, H_{21b}, H_{22b}), 3.38 (q, *J* = 10.0, 8.4 Hz, 1H, $H_{21a\ or\ 22a}$), 3.25 (t, *J* = 6.5 Hz, 2H, H_{24}), 3.18 (t, *J* = 9.6 Hz, 1H, H_{11b}), 2.77 (s, 1H, H_4), 2.49 (d, *J* = 16.3, 1H, H_{13a}), 2.35 (dd, *J* = 16.2, 10.8 Hz, 1H, H_{13b}), 2.21 (t, *J* = 7.6 Hz, 1H, H_{10}), 2.06 (q, *J* = 7.8 Hz, 2H, H_{20}), 1.91 (q, *J* =7.1, 5.8 Hz, 2H, H_2), 1.69 – 1.49 (m, 6H, H_{1a}, H_6, H_7, H_{23}), 1.42 (dt, *J* = 20.3, 9.7 Hz, 1H, H_{1b}), 1.15 (dd, *J* = 12.2, 4.9 Hz, 11H, H_8, H_{15}, H_{16}, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 121.8 (C), 80.7 (C), 80.3 (C), 76.5 (CH), 65.3 (CH_2), 64.2 (CH_2), 63.3 (CH_2), 46.4 (C), 45.9 (CH), 43.7 (CH_2), 43.1 (CH), 41.6 (C), 37.0 (CH), 36.2 (CH_2), 31.8 (CH_2), 31.0 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 23.2 (CH_2), 20.9 (CH_3), 17.3 (CH_3), 16.4 (CH_2), 13.5 (CH_3). IR (AT-FTIR), cm^{-1}: 3410 (w), 2945 (m), 2884 (w), 1020 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{23}H_{38}ClO_4]^+$ 413.2459; found 413.2461. $[a]_D^{20}$ = –94.7 (*c* = 0.350, $CHCl_3$).

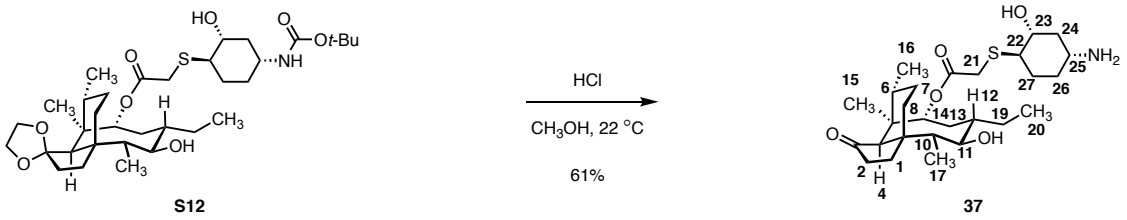
*Synthesis of the sulfide **S12**.*



Aqueous sodium hydroxide solution (1 N, 11.8 µL, 11.8 µmol, 1.66 equiv) was added to a solution of the thiol **36** (5.80 mg, 11.7 µmol, 1.66 equiv), benzyl tri-*n*-butylammonium chloride (440 µg, 1.40 µmol, 0.20 equiv) and the sulfonate **35** (4.00 mg, 7.10 µmol, 1 equiv) in *tert*-butyl methyl ether (320 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), aqueous phosphoric acid solution (0.1 N, 1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the displacement product **S12** as a white foam (3.00 mg, 66%).

R_f = 0.21 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.33 (d, J = 8.2 Hz, 1H, H_{14}), 4.44 (s, 1H, NH), 4.03 (q, J = 6.3, 5.4 Hz, 1H, $H_{22a\ or\ 23a}$), 3.89 (tt, J = 13.7, 7.0 Hz, 2H, H_{22b}, H_{23b}), 3.75 (q, J = 7.3, 6.4 Hz, 1H, $H_{22a\ or\ 23a}$), 3.51 (s, 2H, H_{27}, OH), 3.40 – 3.28 (m, 3H, H_{11}, H_{21a}, H_{25}), 3.26 – 3.19 (m, 1H, H_{21b}), 2.44 (ddd, J = 13.6, 9.9, 3.9 Hz, 1H, H_{24}), 2.34 (d, J = 12.2 Hz, 1H, H_{26a}), 2.24 (dt, J = 10.9, 5.8 Hz, 1H, H_6), 2.15 (q, J = 6.9 Hz, 1H, H_{10}), 2.08 – 2.00 (m, 2H, H_{28a}, H_{29a}), 1.98 (s, 1H, H_4), 1.93 – 1.69 (m, 5H, H_2, H_{12}, H_{13a}, H_{19a}), 1.62 – 1.50 (m, 2H, H_8), 1.49 – 1.09 (m, 18H, H_1, H_7, H_{13b}, H_{19b}, H_{26b}, H_{28b}, H_{29b}, H_{30}), 1.07 (s, 3H, H_{15}), 0.92 – 0.84 (m, 6H, H_{17}, H_{20}), 0.69 (d, J = 7.3 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C), 155.0 (C), 120.4 (C), 79.4 (C), 75.9 (CH), 71.7 (CH), 71.4 (CH), 63.8 (CH_2), 61.5 (CH_2), 52.9 (CH), 51.0 (CH), 48.0 (CH), 47.7 (CH), 46.2 (C), 41.6 (C), 40.5 (CH_2), 40.0 (CH), 36.6 (CH_2), 35.8 (CH_2), 35.4 (CH), 33.2 (CH_2), 33.1 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 28.4 (3 × CH_3), 27.2 (CH_2), 25.8 (CH_2), 17.7 (CH_3), 14.7 (CH_3), 11.5 (CH_3), 10.6 (CH_3). IR (AT-FTIR), cm^{-1}: 2933 (w), 2358 (s), 2342 (m), 1696 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{34}H_{57}NNaO_8S]^+$ 662.3703; found 662.3686. $[a]_D^{20}$ = –11.1 (c = 0.063, $CHCl_3$).

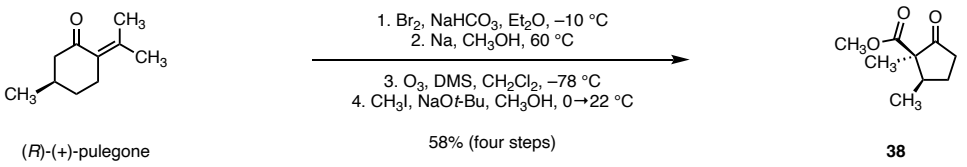
*Synthesis of the lefamulin derivative **37**.*



Concentrated aqueous hydrochloric acid solution (12 N, 1.30 μL, 16.0 μmol, 10.0 equiv) was added to a solution of the thioglycolic ester **S12** (1.00 mg, 1.60 μmol, 1 equiv) in methanol (200 μL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the lefamulin derivative **37** as a white solid (510 μg, 61%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 5.39 (d, J = 8.2 Hz, 1H, H_{14}), 3.59 – 3.46 (m, 2H, H_{21a}, H_{23}), 3.37 (ddd, J = 25.5, 10.9, 7.0 Hz, 1H, H_{11}), 3.33 – 3.29 (m, 1H, H_{21b}), 3.24 – 3.14 (m, 1H, H_{25}), 2.69 (td, J = 10.1, 4.1 Hz, 1H, H_{22}), 2.31 – 2.09 (m, 7H, H_{1a}, H_2, H_4, H_{10}, H_{24a}, H_{27a}), 2.04 – 2.00 (m, 1H, H_{26a}), 1.89 – 1.77 (m, 3H, H_{8a}, H_{13a}, H_{19a}), 1.76 – 1.58 (m, 3H, H_6, H_{7a}, H_{12}), 1.51 – 1.40 (m, 8H, H_{1b}, H_{7b}, H_{13b}, H_{15}, H_{24b}, H_{26b}), 1.40 – 1.26 (m, 2H, H_{19b}, H_{27b}), 1.21 – 1.07 (m, 1H, H_{8b}), 0.97 (d, J = 7.0 Hz, 3H, H_{17}), 0.88 (t, J = 7.4 Hz, 3H, H_{20}), 0.78 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.2 (C), 170.9 (C), 73.9 (CH), 71.6 (CH), 70.8 (CH), 57.7 (CH), 49.8 (CH), 47.8 (CH), 47.4 (CH; detected by HSQC), 45.4 (C), 41.3 (C), 41.2 (CH), 37.9 (CH_2), 36.7 (CH), 35.9 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 30.4 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 26.9 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 16.7 (CH_3), 14.2 (CH_3), 10.3 (CH_3), 9.5 (CH_3). IR (AT-FTIR), cm^{-1}: 3734 (w), 2359 (s), 2431 (m), 1717 (w), 668 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{27}H_{46}NO_5S]^+$ 496.3097; found 496.3090. $[a]_D^{20}$ = +25.7 (c = 0.035, CH_3OH).

*Synthesis of the β-keto ester **38**.*



Bromine (19.5 mL, 380 mmol, 1.10 equiv) was added dropwise over 20 min via addition funnel to a suspension of sodium bicarbonate (8.72 g, 104 mmol, 0.30 equiv) and (*R*)-(+)-pulegone (57.2 g, 346 mmol, 1 equiv) in ether (430 mL) at –10 °C. The reaction mixture was stirred for 3 h at –10 °C. The stirred reaction mixture was transferred via cannula to a solution of sodium metal (19.5 g, 847 mmol. 2.45 equiv) in methanol (350 mL) at 22 °C. The reaction vessel was placed in a heating mantle that had been preheated to 60 °C. The reaction mixture for stirred and heated for 2 h at 60 °C. The product mixture was cooled to 20 °C over 20 min. The cooled product mixture was diluted sequentially with ether (500 mL) and saturated aqueous ammonium chloride solution (500 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 400 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (800 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

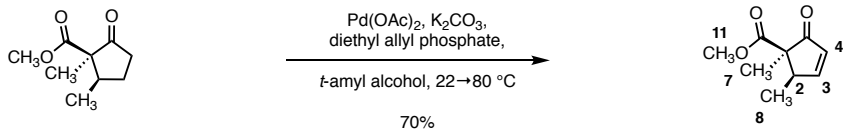
Ozone was passed through a solution of the unpurified olefin obtained in the previous step (nominally 346 mmol, 1 equiv) in dichloromethane (230 mL) at –78 °C. The addition of ozone was continued until a blue color persisted (~4 h). Nitrogen was then passed through the solution to remove any dissolved ozone, resulting in a colorless solution. Dimethyl sulfide (30.7 mL, 415 mmol, 1.20 equiv) was then added to the cold mixture. Upon completion of the addition, the cooling bath was removed and the product mixture was allowed to warm to 22 °C over 16 h. The warmed product mixture was concentrated. The residue obtained was purified by fractional distillation at 100 Torr (collecting the fraction boiling between 100–120 °C) to obtain the intermediate β-keto ester as a yellow oil (36.5 g, 234 mmol).

Sodium *tert*-butoxide (33.8 g, 352 mmol, 1.50 equiv) was added in four portions over 1 h to a solution of methyl iodide (29.2 mL, 469 mmol, 2.00 equiv) and the unpurified β-keto ester obtained in the preceding step (36.5 g, 234 mmol) in methanol (270 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm to 22 °C over 30 min. The warmed reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ether (600 mL) and saturated aqueous ammonium chloride solution (500 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 400 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (800 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained wsa purified by fractional distillation at 100 Torr (collecting the fraction boiling between between 120–140 °C) to provide the β-keto ester **38** as a yellow oil (34.2 g, 58% over four steps).

^{1}H NMR analysis (400 MHz) of the unpurified product mixture indicated the presence of a >20:1 mixture of diastereomers. Spectroscopic data for the β-keto ester **38** obtained in this way were identical to those previously reported. [15]

R_f = 0.65 (55% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.58 (ddd, *J* = 19.3, 8.9, 1.4 Hz, 1H), 2.26 (ddd, *J* = 19.4, 11.1, 8.7 Hz, 1H), 2.09 – 1.97 (m, 2H), 1.88 – 1.73 (m, 1H), 1.26 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H).

*Synthesis of the enone **39**.*

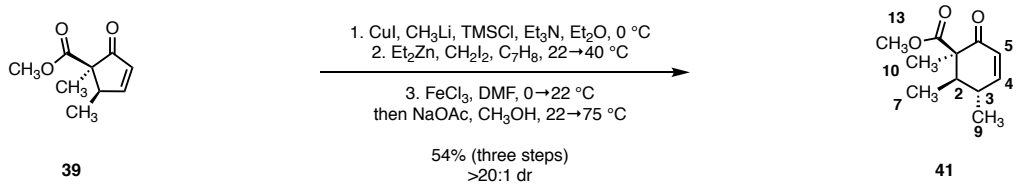


38 **39**

Palladium acetate (10% w/w, 1.50 g) was added to a mixture of diethyl allyl phosphate (29.2 g, 150 mmol, 1.80 equiv), potassium carbonate (15.0 g, 108 mmol, 1.30 equiv) and the β-keto ester **38** (14.1 g, 83.1 mmol, 1 equiv) in *tert*-amyl alcohol (110 mL) at 22 °C. The reaction vessel was placed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred for 16 h at 80 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted with acetone (50 mL). The diluted product mixture was filtered through a pad of Celite. The Celite pad was rinsed with acetone (50 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the enone **39** as a dark yellow oil (9.78 g, 70%).

R_f = 0.35 (20% ethyl acetate–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 5.7, 2.4 Hz, 1H, H_3), 6.19 (dd, J = 5.7, 2.1 Hz, 1H, H_4), 3.66 (s, 3H, H_{11}), 2.82 (qt, J = 7.5, 2.3 Hz, 1H, H_2), 1.40 (s, 3H, H_7), 1.15 (d, J = 7.5 Hz, 3H, H_8). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.5 (C), 171.9 (C), 166.7 (CH), 131.9 (CH), 58.0 (C), 52.0 (CH_3), 48.5 (CH), 20.2 (CH_3), 14.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 2970 (w), 2359 (s), 2342 (m), 1737 (s), 1711 (s), 1456 (w), 1375 (w), 1216 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_9H_{13}O_3]^+$ 169.0865; found 169.0859. $[a]_D^{20}$ = –407.3 (c = 0.21, $CHCl_3$).

*Synthesis of the enone **41**.*



39 **41**

A solution of methyllithium in ether (1.60 M, 26.6 mL, 42.6 mmol, 3.00 equiv) was added to a solution of copper (I) iodide (4.06 g, 21.3 mmol, 1.50 equiv) in ether (31 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C. A solution of the enone **39** (2.39 g, 14.2 mmol, 1.00 equiv) in ether (31 mL) was then added dropwise. The reaction mixture was stirred for 10 min at 0 °C. Trimethylsilyl chloride (14.4 mL, 114 mmol, 8.00 equiv) and triethylamine (15.8 mL, 114 mmol, 8.00 equiv) were then added sequentially to the stirred mixture. The reaction mixture was stirred for 10 min at 0 °C. The product mixture was diluted sequentially with hexanes (25 mL), ether (25 mL), and aqueous potassium phosphate buffer solution (pH 7, 60 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (2 × 60 mL) and saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

A solution of diethylzinc in toluene (15% w/w, 38.8 mL, 42.7 mmol, 3.00 equiv) and diiodomethane (3.40 mL, 42.7 mmol, 3.00 equiv) were added in sequence to a solution of the unpurified enoxysilane obtained in the preceding step (nominally 14.2 mmol, 1 equiv) in toluene (40 mL) at 22 °C. Upon completion of the addition, the reaction vessel was transferred to an oil bath that had been preheated to 40 °C. The reaction mixture was stirred for 2 d at 40 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted with saturated aqueous ammonium chloride solution (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 80 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

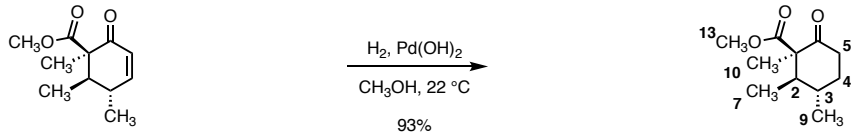
A solution of the unpurified cyclopropanol obtained in the preceding step (nominally 14.2 mmol, 1 equiv) in *N*,*N*-dimethylformamide (10 mL) was added dropwise over 20 min to a solution of iron (III) chloride (4.62 g, 28.5 mmol, 2.20 equiv) in *N*,*N*-dimethylformamide (13 mL) at 0 °C. The reaction mixture was stirred for 2 h at 22 °C. A saturated solution of sodium acetate in methanol (80 mL) was then added. The reaction vessel was transferred to an oil bath that had been preheated to 75 °C. The warmed reaction mixture was stirred for 3 h at 75 °C. The product mixture was diluted sequentially with ether (100 mL) and aqueous hydrochloric acid solution (1 N, 50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried

solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes, grading up to 20% ethyl acetate–hexanes, three steps) to provide the enone **41** as a yellow oil (1.50 g, 54% over three steps).

^{1}H NMR analysis (400 MHz) of the unpurified product mixture indicated the presence of a >20:1 mixture of diastereomers. The relative stereochemistry of **41** was established by X-ray analysis of the methylation product **S20** (see page S165).

R_f = 0.33 (10% ethyl acetate–hexanes; UV, PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 10.2, 2.1 Hz, 1H, H_5), 6.02 (dd, *J* = 10.2, 2.7 Hz, 1H, H_4), 3.63 (s, 3H, H_{13}), 2.54 – 2.47 (m, 1H, H_3), 1.64 (dd, *J* = 6.3, 3.6 Hz, 1H, H_2), 1.42 (s, 3H, H_{10}), 1.14 (t, *J* = 7.5 Hz, 6H, H_7, H_9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1 (C), 171.5 (C), 156.1 (CH), 127.4 (CH), 57.1 (C), 52.2 (CH_3), 45.8 (CH), 35.7 (CH), 19.4 (CH_3), 19.2 (CH_3), 14.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 2983 (w), 2881 (w), 2359 (m), 2341 (w), 1736 (s), 1675 (s), 1454 (w)1376 (w) 1218 (m), 1165 (w), 1111 (w), 1088 (w), 773 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{11}H_{17}O_3]^+$ 197.1178; found 197.1172. $[a]_D^{20}$ = +77.4 (*c* = 0.395, $CHCl_3$).

*Synthesis of the cyclohexanone **42**.*

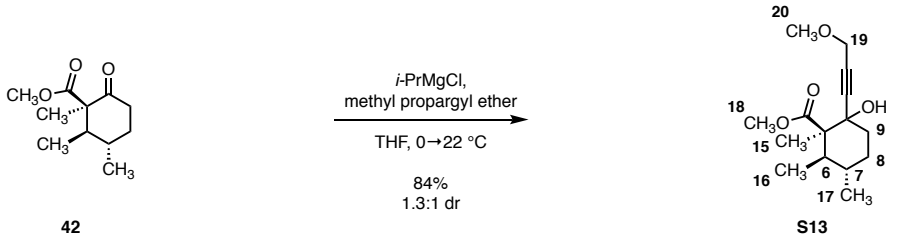


41 **42**

Palladium hydroxide (10% w/w, 120 mg) was added to a solution of the enone **41** (1.20 g, 6.12 mmol, 1 equiv) in methanol (50 mL) at 22 °C. The reaction vessel was sparged with a balloon of dihydrogen. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was filtered through a pad of Celite. The Celite pad was rinsed with dichloromethane (100 mL). The filtrates were combined and the combined filtrates were concentrated to provide the cyclohexanone **42** as a pale yellow oil (1.12 g, 93%). The product obtained in this way was judged to be of >95% purity (400 MHz ^{1}H NMR analysis) and was used without further purification.

R_f = 0.36 (10% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H, H_{13}), 2.80 (td, J = 14.1, 6.2 Hz, 1H, H_{5a}), 2.43 (ddd, J = 14.1, 4.5, 2.6 Hz, 1H, H_{5b}), 2.10 – 1.92 (m, 2H, H_2, H_{4a}), 1.44 – 1.35 (m, 1H, H_{4b}), 1.34 (s, 3H, H_{10}), 1.30 – 1.20 (m, 1H, H_3), 1.10 (d, J = 6.8 Hz, 3H, H_9), 0.96 (d, J = 6.4 Hz, 3H, H_7). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5 (C), 172.0 (C), 60.5 (C), 52.1 (CH_3), 49.6 (CH), 40.0 (CH_2), 34.8 (CH_2), 33.6 (CH), 20.0 (CH_3), 19.4 (CH_3), 14.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2922 (w), 2852 (w), 2360 (s), 2341 (m), 1720 (w), 1461 (w), 1221 (w), 773 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{11}H_{19}O_3]^+$ 199.1334; found 199.1329. $[a]_D^{20}$ = –41.2 (c = 0.195, $CHCl_3$).

*Synthesis of the alcohol **S13**.*

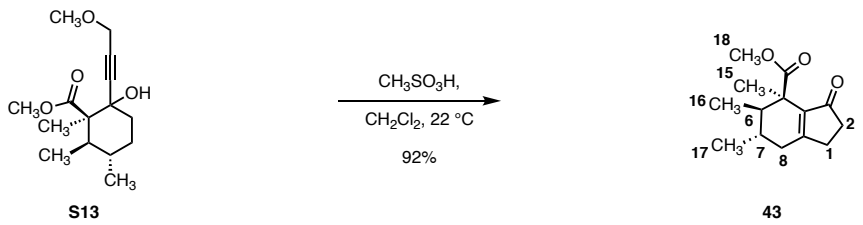


42 **S13**

A solution of *iso*-propyl magnesium chloride in tetrahydrofuran (2.0 M, 3.50 mL, 7.02 mmol, 1.30 equiv) was added dropwise to a solution of methyl propargyl ether (592 μL, 7.02 mmol, 1.30 equiv) in tetrahydrofuran (7.2 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The resulting mixture was added dropwise to a solution of the cyclohexanone **42** (1.01 g, 5.40 mmol, 1 equiv) in tetrahydrofuran (11 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 20 min. The warmed reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL) and saturated aqueous ammonium chloride solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the alkylation product **S13** as a yellow oil (1.21 g, 84%).

^{1}H NMR analysis (400 MHz) of the unpurified product mixture indicated the presence of a 1.3:1 mixture of diastereomers (stereochemistry not assigned). The unpurified product was employed in the following step.

*Synthesis of the enone **43**.*

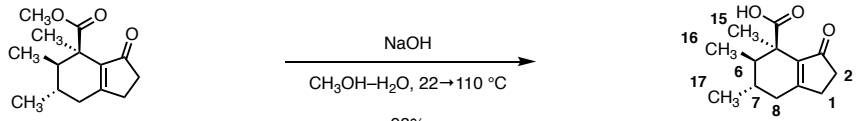


S13 **43**

A solution of the alcohol **S13** (650 mg, 2.42 mmol, 1 equiv) in dichloromethane (2.4 mL) was added dropwise to a solution of methanesulfonic acid (3.10 mL, 48.4 mmol, 20.0 equiv) at 22 °C. The reaction mixture was stirred at 22 °C for 1 h. The product mixture was carefully poured into water (40 mL) that had been cooled to <5 °C. Ether (30 mL) was added and the resulting biphasic mixture was transferred to a separatory funnel. The layers that formed were separated. The aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes, four steps) to provide the enone **43** as a yellow oil (530 mg, 92%).

R_f = 0.22 (20% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H, H_{18}), 2.52 (q, J = 3.0 Hz, 2H, H_2), 2.42 (d, J = 4.5, 1H, H_{8a}), 2.40 – 2.33 (m, 2H, H_1), 2.03 (dd, J = 18.6, 11.0, 1H, H_{8b}), 1.86 (tdd, J = 11.1, 6.7, 4.6 Hz, 1H, H_7), 1.43 (s, 3H, H_{15}), 1.24 (dq, J = 10.8, 6.9 Hz, 1H, H_6), 0.98 (d, J = 6.6 Hz, 3H, H_{17}), 0.93 (d, J = 6.9 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3 (C), 174.2 (C), 173.5 (C), 141.2 (C), 51.9 (CH_3), 46.3 (C), 46.0 (CH), 37.9 (CH_2), 34.8 (CH_2), 31.0 (CH), 29.8 (CH_2), 21.4 (CH_3), 19.7 (CH_3), 13.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 2918 (w), 2851 (w), 2363 (s), 2342 (m), 1699 (w), 1652 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{14}H_{21}O_3]^+$ 237.1491; found 237.1485. $[a]_D^{20}$ = +186.6 (c = 0.035, $CHCl_3$).

*Synthesis of the carboxylic acid **S14**.*

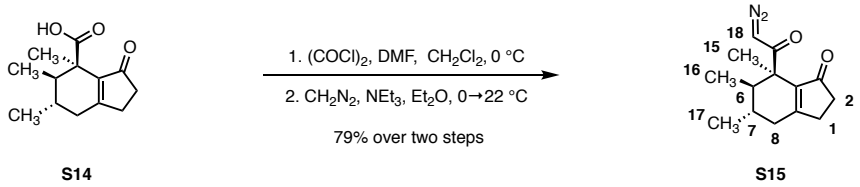


43 **S14**

Aqueous sodium hydroxide solution (2 N, 320 mL, 640 mmol, 20.0 equiv) was added to a solution of the methyl ester **43** (7.50 g, 31.7 mmol, 1 equiv) in methanol (320 mL) at 22 °C. The reaction vessel was equipped with a reflux condenser and then placed in an oil bath that had been preheated to 110 °C. The reaction mixture was stirred for 48 h at 110 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted sequentially with water (300 mL) and ether (300 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was washed with ether (2 × 300 mL, discarded). The washed aqueous layer was cooled to 0 °C over 10 min. The pH of the cooled aqueous layer was adjusted to 1 by the dropwise addition of 12 N concentrated hydrochloric acid solution over 20 min at 0 °C. The acidified aqueous phase was diluted with ether (300 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The layers that formed were separated. The aqueous layer was extracted with ether (2 × 300 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to obtain the carboxylic acid **S14** as a yellow foam (6.88 g, 98%). The product so obtained was judged to be of >95% purity (400 MHz ^{1}H NMR analysis) and was used without further purification.

R_f = 0.04 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (q, J = 4.9 Hz, 2H, H_2), 2.44 – 2.32 (m, 3H, H_{8a}, H_1), 2.09 – 1.98 (m, 1H, H_{8b}), 1.99 – 1.85 (m, 1H, H_7), 1.46 (s, 3H, H_{15}), 1.32 – 1.21 (m, 1H, H_6), 1.04 (d, J = 7.0 Hz, 3H, H_{16}), 1.00 (d, J = 6.5 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.7 (C), 178.1 (C), 174.6 (C), 140.6 (C), 46.1 (C), 45.9 (CH), 38.0 (CH_2), 34.9 (CH_2), 30.7 (CH), 29.8 (CH_2), 21.1 (CH_3), 19.7 (CH_3), 12.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 2361 (s), 2341 (m), 771 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{13}H_{19}O_3]^+$ 223.1334; found 223.1329. $[a]_D^{20}$ = +356.8 (c = 0.025, $CHCl_3$).

*Synthesis of the diazoketone **S15**.*



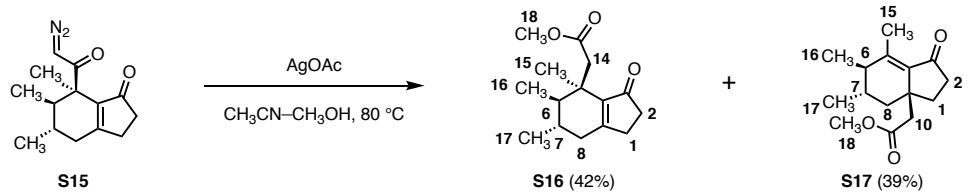
S14 **S15**

Oxalyl chloride (190 μL, 2.23 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of the carboxylic acid **S14** [450 mg, 2.02 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 5.0 mL)] and *N,N*-dimethylformamide (312 μL, 4.05 mmol, 2.00 equiv) in dichloromethane (3.4 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was concentrated. The residue obtained was dissolved in dichloromethane (20 mL) and the resulting solution was eluted over a plug of silica gel (4.0 cm × 3.0 cm). The silica gel plug was washed with 50% ether–hexanes (100 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

A solution of the unpurified acid chloride obtained in the preceding step (nominally 2.02 mmol, 1 equiv) in ether (14 mL) was added dropwise over 20 min to a solution of diazomethane in ether (ca. 0.66 M, 14.0 mL, 7.00 equiv) and triethylamine (850 μL, 6.07 mmol, 3.00 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 22 °C over 1 h. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was cooled to 0 °C over 20 min. The cooled product mixture was slowly diluted with aqueous potassium phosphate buffer solution (pH 7, 20 mL). The resulting biphasic mixture was stirred for 2 h at 0 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 20 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, four steps) to provide the diazoketone **S15** as a yellow solid (395 mg, 79% over two steps).

R_f = 0.39 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1H, H_{18}), 2.56 – 2.50 (m, 2H, H_2), 2.50 – 2.39 (m, 1H, H_{8a}), 2.39 – 2.33 (m, 2H, H_1), 2.10 – 1.95 (m, 2H, H_{8b}, H_7), 1.44 (s, 3H, H_{15}), 1.20 (dq, J = 9.8, 7.3 Hz, 1H, H_6), 0.98 (d, J = 6.1 Hz, 6H, H_{16}, H_{17}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4 (C), 196.4 (C), 175.1 (C), 141.4 (C), 55.2 (CH), 49.7 (C), 46.7 (CH), 38.1 (CH_2), 35.0 (CH_2), 30.9 (CH), 29.8 (CH_2), 20.8 (CH_3), 19.8 (CH_3), 12.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 3087 (w), 2973 (w), 2929 (w), 2380 (w), 2341 (w), 2099 (s), 1695 (s), 1648 (m), 1625 (m), 1454 (w), 1344 (m), 1304 (w), 1152 (w), 1121 (w), 1026 (w), 979 (w), 775 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{14}H_{18}N_2O_2Na]^+$ 269.1266; found 269.1261. $[\alpha]_D^{20}$ = +336.9 (c = 0.235, $CHCl_3$).

*Synthesis of the Arndt–Eistert homologation products **S16** and **S17**.*



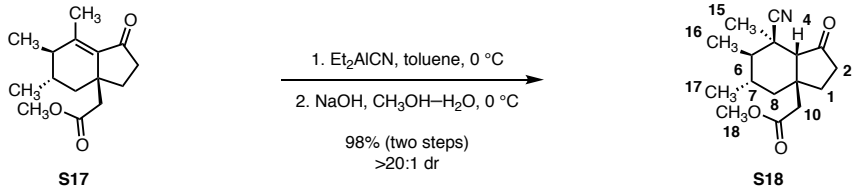
A solution of the diazoketone **S15** (2.15 g, 8.29 mmol, 1 equiv) in acetonitrile (100 mL) was added rapidly over 1 min via additional funnel to a suspension of silver acetate (415 mg, 2.49 mmol, 0.30 equiv) in methanol (64 mL) and acetonitrile (450 mL) that had been preheated to 80 °C. The reaction mixture was stirred for 1 h at 80 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was filtered through a pad of Celite. The Celite pad was rinsed with ethyl acetate (2 × 100 mL). The filtrates were combined, and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 40% ether–hexanes, four steps) to provide separately the homologation product **S16** (pale yellow oil, 870 mg, 42%) and the rearranged ester **S17** (pale yellow oil, 799 mg, 39%).

The relative stereochemistry of **S17** was determined by X-ray analysis of the methylation product **S20** (see page S165).

S16: R_f = 0.39 (20% ethyl acetate–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 3H, H_{18}), 2.65 (d, J = 12.9 Hz, 1H, H_{14a}), 2.48 – 2.40 (m, 2H, H_{1a}, H_{2a}), 2.40 – 2.29 (m, 3H, H_{8a}, H_{1b}, H_{2b}), 2.27 (d, J = 12.9 Hz, 1H, H_{14b}), 2.01 – 1.89 (m, 1H, H_{8b}), 1.58 – 1.44 (m, 1H, H_7), 1.35 (s, 3H, H_{15}), 1.21 (dq, J = 11.2, 6.8 Hz, 1H, H_6), 1.00 (d, J = 6.9 Hz, 3H, H_{16}), 0.96 (d, J = 6.5 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3 (C), 173.1 (C), 172.9 (C), 142.2 (C), 51.5 (CH_3), 47.0 (CH), 39.1 (CH_2), 38.4 (CH_2), 38.3 (C), 35.3 (CH_2), 30.4 (CH), 29.4 (CH_2), 24.5 (CH_3), 20.1 (CH_3), 11.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 2975 (w), 2362 (w), 2325 (w), 1733 (m), 1696 (s), 1645 (s), 1438 (w), 1383 (w), 1263 (w), 1211 (w), 1143 (w), 1119 (w), 1017 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{15}H_{23}O_3]^+$ 251.1647; found 251.1642. $[a]_D^{20}$ = +152.5 (c = 0.445, $CHCl_3$).

S17: R_f = 0.58 (20% ethyl acetate–hexanes; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67 (s, 3H, H_{18}), 2.46 – 2.21 (m, 5H, H_1, H_2, H_{10a}), 2.07 (s, 3H, H_{15}), 2.07 – 2.02 (m, 1H, H_{8a}), 1.77 – 1.70 (m, 1H, H_6), 1.66 – 1.58 (m, 1H, H_7), 1.47 (dd, J = 9.0, 1.7 Hz, 1H, H_{10b}), 1.16, (d, J = 7.0 Hz, 3H, H_{16}), 1.04 (d, J = 6.6 Hz, 4H, H_{17}, H_{8b}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8 (C), 172.0 (C), 152.2 (C), 137.1 (C), 51.6 (CH_3), 45.7 (CH), 43.1 (C), 42.1 (CH_2), 40.7 (CH_2), 36.0 (CH_2), 33.1 (CH), 32.2 (CH_2), 21.1 (CH_3), 17.9 (CH_3), 17.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2955 (w), 1734 (s), 1707 (s), 1629 (m), 1435 (w), 1215 (w), 1172 (w), 1084 (w), 1008 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{15}H_{23}O_3]^+$ 251.1647; found 251.1642. $[a]_D^{20}$ = –273.6 (c = 0.385, $CHCl_3$).

*Synthesis of the hydrocyanation product **S18**.*



*CAUTION***:** Cyanide hazard! Perform reaction, aqueous workup, and purification in a well-ventilated fume hood. All glassware and waste solutions should be washed with bleach prior to removing from fume hood.

A solution of diethylaluminum cyanide solution in toluene (1.0 M, 2.90 mL, 2.86 mmol, 1.10 equiv) was added dropwise over 2 min to a solution of the enone **S17** (650 mg, 2.60 mmol, 1 equiv) in toluene (17 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 ˚C. The product mixture was diluted with saturated aqueous potassium sodium tartrate solution (20 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 40 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

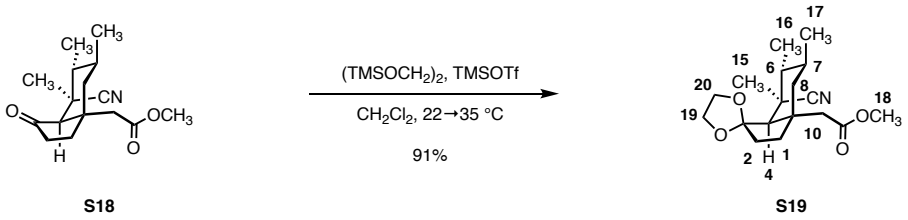
Aqueous sodium hydroxide solution (0.1 N, 3.2 mL) was added dropwise over 1 min to a solution of the unpurified product obtained in the preceding step (nominally 2.60 mmol, 1 equiv) in methanol (16 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The product mixture was diluted sequentially with ether (20 mL) and saturated aqueous ammonium chloride solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (60 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the hydrocyanation product **S18** as a pale yellow oil (702 mg, 98% over two steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated a >20:1 mixture of diastereomers. The relative stereochemistry of **S18** was established by X-ray analysis of the methylation product **S20** (see page S165).

R_f = 0.30 (20% ethyl acetate–hexanes; CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H, H_{18}), 3.04 – 2.96 (m, 2H, H_4, H_{10a}), 2.81 (d, J = 16.5 Hz, 1H, H_{10b}), 2.37 – 2.13 (m, 2H, H_2), 2.04 (dt, J = 12.9, 10.2 Hz, 1H, H_{1a}), 1.77 (s, 3H, H_{15}), 1.74 – 1.63 (m, 2H, H_7, H_{1b}), 1.60 (dt, J = 14.4, 3.0 Hz, 1H, H_{8a}), 1.27 – 1.16 (m, 1H, H_6), 1.09 (d, J = 6.6 Hz, 3H, H_{16}), 0.98 (dd, J = 14.3, 12.4 Hz, 1H, H_{8b}), 0.93 (d, J = 6.3 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.6 (C), 172.2 (C), 123.1 (C), 57.7 (CH), 51.6 (CH_3), 42.5 (CH), 41.8 (C), 41.5 (CH_2), 40.9 (CH_2), 39.1 (C), 34.1 (CH_2), 31.9 (CH), 30.6 (CH_2), 23.5 (CH_3), 20.1 (CH_3), 13.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 2953 (w), 1735

(s), 1454 (w), 1369 (w), 1243 (w), 1203 (w), 1160 (w), 1004 (w), 773 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for [$C_{16}H_{24}NO_3$]$^+$ 278.1756; found 278.1751. $[a]_D^{20}$ = +65.6 (c = 0.470, $CHCl_3$).

*Synthesis of the ketal **S19**.*

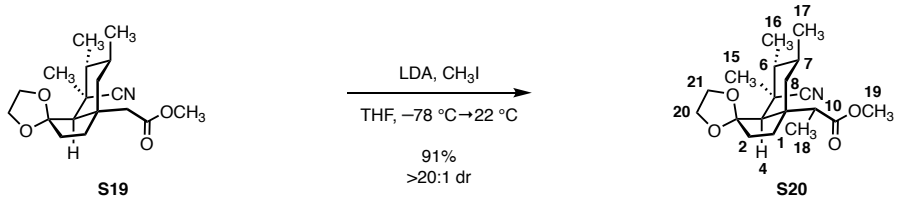


S18 **S19**

Trimethylsilyl trifluoromethanesulfonate (131 μL, 721 μmol, 2.00 equiv) was added rapidly via syringe to a solution of 1,2-bis(trimethylsiloxy)ethane (442 μL, 1.80 mmol, 5.00 equiv) and the cyanoester **S18** [100 mg, 360 μmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 2.0 mL)] in dichloromethane (1.8 mL) at 22 °C. The reaction vessel was placed in an oil bath that had been preheated to 35 °C. The reaction mixture was stirred for 4 d at 35 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted with ether (10 mL). The diluted solution was carefully poured into saturated aqueous sodium bicarbonate solution (15 mL) that had been precooled to 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes, three steps) to provide the ketal **S19** as a pale yellow oil (105 mg, 91%).

R_f = 0.37 (20% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 – 3.73 (m, 4H, H_{19}, H_{20}), 3.65 (s, 3H, H_{18}), 3.07 (d, J = 15.0 Hz, 1H, H_{10a}), 2.57 (d, J = 15.0 Hz, 1H, H_{10b}), 2.50 (d, J = 2.0 Hz, 1H, H_4), 1.88 – 1.80 (m, 2H, H_2), 1.80 – 1.68 (m, 2H, H_{1a}, H_6), 1.67 – 1.54 (m, 3H, H_{1b}, H_7, H_{8a}), 1.47 (s, 3H, H_{15}), 1.40 – 1.30 (m, 1H, H_{8b}), 1.07 (d, J = 6.6 Hz, 3H, H_{16}), 0.96 (d, J = 6.2 Hz, 3H, H_{17}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C), 124.6 (C), 118.9 (C), 63.9 (CH_2), 62.2 (CH_2), 55.0 (CH), 51.4 (CH), 42.8 (CH_2), 42.8 (C), 41.8 (CH), 39.5 (CH_2), 39.2 (C), 35.3 (CH_2), 34.1 (CH_2), 31.7 (CH), 22.8 (CH_3), 20.4 (CH_3), 13.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 2951 (w), 2884 (w), 2359 (w), 1736 (s), 1457 (w), 1331 (w), 1164 (m), 1101 (w), 1066 (w), 1027 (w), 948 (w), 772 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{18}H_{28}NO_4]^+$ 322.2018; found 322.2013. $[a]_D^{20}$ = –15.7 (c = 0.340, $CHCl_3$).

*Synthesis of the methylation product **S20**.*

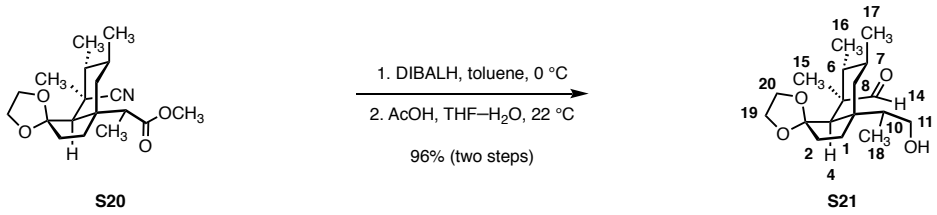


A solution of lithium diisopropylamide in tetrahydrofuran (1.2 M, 1.50 mL, 1.75 mmol, 1.20 equiv) was added to the solution of the ketal **S19** [468 mg, 1.46 mmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 5.0 mL)] in tetrahydrofuran (7.0 mL) at –78 °C. The reaction mixture was stirred for 2 h at –78 °C. The reaction mixture was warmed to 0 °C over 10 min and stirred for an additional 1 h at 0 °C. The reaction mixture was cooled to –78 °C over 30 min. Iodomethane (272 μL, 4.37 mmol, 3.00 equiv) was added dropwise over 5 min to the cooled reaction mixture. The reaction mixture was stirred for 1 h at –78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 22 °C over 2 h. The warmed reaction mixture was stirred for 15 h at 22 °C. The product mixture was diluted sequentially with ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL). The resulting biphasic mixture was stirred for 15 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (30 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 25% ethyl acetate–hexanes, three steps) to provide the methylation product **S20** as a white, crystalline solid (445 mg, 91%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the methylation product **S20** was formed as a single diastereomer. The relative stereochemistry of **S20** was determined by X-ray analysis (see page S165).

R_f = 0.44 (20% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.01 – 3.94 (m, 1H, $H_{20a\text{ or }21a}$), 3.92 – 3.76 (m, 3H, $H_{20a\text{ or }21a}$, H_{20b}, H_{21b}), 3.71 (s, 3H, H_{19}), 3.42 (q, J = 7.2 Hz, 1H, H_{10}), 2.92 (s, 1H, H_4), 2.11 (ddd, J = 12.7, 10.3, 8.4 Hz, 1H, H_{2a}), 1.84 – 1.78 (m, 2H, H_1), 1.75 (ddd, J = 13.3, 8.4, 5.7 Hz, 1H, H_6), 1.56 – 1.50 (m, 1H, H_{8a}), 1.48 (s, 4H, H_7, H_{15}), 1.37 (dd, J = 13.9, 12.2 Hz, 1H, H_{8b}), 1.28 (ddd, J = 14.4, 8.5, 6.3 Hz, 1H, H_{2b}), 1.17 (d, J = 7.2 Hz, 3H, H_{18}), 1.07 (d, J = 6.7 Hz, 3H, H_{16}), 0.94 (d, J = 6.2 Hz, 3H, H_{17}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1 (C), 124.5 (C), 119.3 (C), 63.9 (CH_2), 62.2 (CH_2), 51.6 (CH_3), 51.5 (CH), 45.1 (C), 42.2 (CH), 41.7 (CH), 39.9 (CH_2), 39.3 (C), 34.7 (CH_2), 31.2 (CH), 29.5 (CH_2), 23.1 (CH_3), 20.5 (CH_3), 13.9 (CH_3), 13.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2951 (w), 2882 (w), 2360 (s), 2340 (m), 2162 (w), 2005 (w), 1731 (m), 1457 (w), 1196 (w), 1158 (w), 1096 (w), 1027 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{19}H_{30}NO_4]^+$ 336.2175; found 336.2169. $[a]_D^{20}$ = –45.8 (c = 0.230, $CHCl_3$).

*Synthesis of the aldehyde **S21**.*



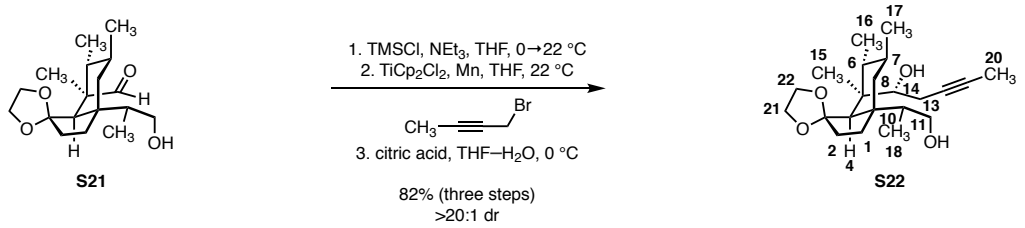
S20 **S21**

A solution of diisobutylaluminum hydride solution in toluene (1.0 M, 2.20 mL, 2.19 mmol, 3.50 equiv) was added over 1 min via syringe to a solution of the ester **S20** [210 mg, 630 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 5.0 mL)] in toluene (3.0 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous potassium sodium tartrate solution (10 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Acetic acid (36.0 μL, 630 μmol, 1.00 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally 630 μmol, 1 equiv) in 4:1 tetrahydrofuran–water (v/v, 18 mL) at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the aldehyde **S21** as a colorless oil (186 mg, 96% over two steps). The purity of the aldehyde **S21** was determined to be >95% by quantitative ^{1}H NMR analysis (600 MHz).

R_f = 0.32 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 9.67 (s, 1H, H_{14}), 3.82 (dd, J = 10.6, 3.2 Hz, 1H, H_{11a}), 3.46 – 3.35 (m, 2H, H_{19a}, H_{20a}), 3.33 (q, J = 6.5, 5.8 Hz, 1H, $H_{19b\ or\ 20b}$), 3.27 (q, J = 6.2 Hz, 1H, $H_{19b\ or\ 20b}$), 3.19 (dd, J = 10.6, 7.9 Hz, 1H, H_{11b}), 2.95 (s, 1H, H_4), 1.91 (dp, J = 15.7, 7.6 Hz, 1H, H_6), 1.71 – 1.61 (m, 2H, H_2), 1.58 (ddq, J = 10.8, 6.7, 3.6 Hz, 1H, H_{10}), 1.47 – 1.27 (m, 4H, H_{1a}, H_7, H_8), 1.18 (s, 3H, H_{15}), 1.12 – 1.01 (m, 1H, H_{1b}), 0.99 (d, J = 7.0 Hz, 3H, H_{16}), 0.92 (d, J = 6.6 Hz, 3H, H_{18}), 0.87 (d, J = 5.9 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 206.2 (CH), 120.2 (C), 64.5 (CH_2), 63.8 (CH_2), 62.0 (CH_2), 50.9 (C), 50.0 (CH), 46.0 (C), 41.8 (CH), 40.3 (CH_2), 37.9 (CH), 35.9 (CH_2), 30.7 (CH), 28.4 (CH_2), 21.2 (CH_3), 19.4 (CH_3), 13.2 (CH_3), 12.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 3480 (w), 2971 (m), 2946 (m), 2886 (m), 1452 (w) 1378 (w), 1312 (w), 1232 (w), 1144 (w), 1107 (m), 1085 (s), 1044 (s), 1022 (s), 949 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{18}H_{31}O_4]^+$ 311.2222; found 311.2217. $[\alpha]_D^{20}$ = –85.9 (c = 0.040, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **S22**.*



Trimethylsilyl chloride (45.0 μL, 354 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (358 μL, 2.58 mmol, 4.00 equiv) and the aldehyde **S21** (100 mg, 322 μmol, 1 equiv) in tetrahydrofuran (6.0 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 2 h. The product mixture was cooled to 0 °C over 10 min and the cooled product mixture was diluted sequentially with ether (10 mL) and aqueous potassium phosphate buffer solution (pH 7, 10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

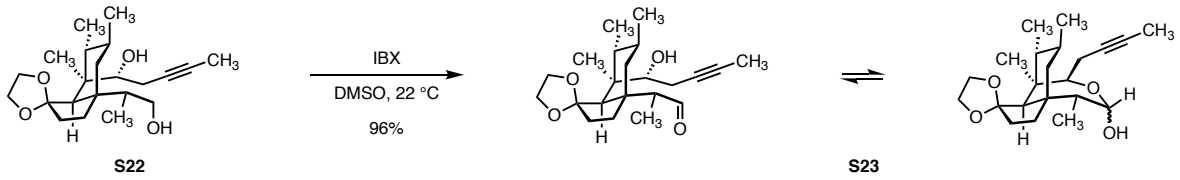
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (234 mg, 940 μmol, 3.00 equiv) and manganese powder (207 mg, 3.77 mmol, 12.0 quiv) in tetrahydrofuran (4.0 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the protected alcohol obtained in the preceding step (nominally 314 μmol, 1 equiv) and 1-bromobut-2-yne (170 mg, 1.26 mmol, 4.00 equiv) in tetrahydrofuran (4.0 mL) was added dropwise over 40 min at 22 °C via syringe pump. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted with hexanes (10 mL). The diluted product mixture was eluted over a plug of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 2.1 mL) was added dropwise to a solution of the unpurified addition product obtained in the preceding step (nominally 314 μmol, 1 equiv) in tetrahydrofuran (7.0 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes, five steps) to provide the homopropargylic alcohol **S22** as an off-white foam (93.2 mg, 82% over three steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a >20:1 mixture of diastereomers.

R_f = 0.31 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6) δ 4.28 (dt, *J* = 10.1, 2.5 Hz, 1H, H_{14}), 3.74 (dd, *J* = 11.2, 2.7 Hz, 1H, H_{11a}), 3.52 – 3.40 (m, 2H, H_{21a}, H_{22a}), 3.40 – 3.32 (m, 2H, H_{11b}, $H_{21b\ or\ 22b}$), 3.27 (td, *J* = 7.1, 5.1 Hz, 1H, $H_{21b\ or\ 22b}$), 2.63 (dp, *J* = 16.6, 2.4 Hz, 1H, H_{13a}), 2.45 (s, 1H, H_4), 2.42 – 2.32 (m, 1H, H_{13b}), 2.02 – 1.88 (m, 2H, H_6, H_{10}), 1.71 – 1.62 (m, 2H, H_{2a}, H_{8a}), 1.60 – 1.51 (m, 1H, H_{2b}), 1.51 – 1.40 (m, 5H, H_{1a}, H_7, H_{20}), 1.36 (dd, *J* = 13.6, 12.3 Hz, 1H, H_{8b}), 1.27 (t, *J* = 3.7 Hz, 6H, H_{15}, H_{18}), 1.09 – 0.98 (m, 4H, H_{1b}, H_{16}), 0.95 (d, *J* = 6.5 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 120.6 (C), 78.4 (C), 78.1 (C), 74.8 (CH), 65.6 (CH_2), 64.0 (CH_2), 62.1 (CH_2), 49.1 (CH), 46.1 (C), 45.2 (CH), 44.1 (C), 43.0 (CH_2), 40.9 (CH), 35.5 (CH_2), 30.3 (CH), 29.9 (CH_2), 24.7 (CH_2), 22.1 (CH_3), 17.8 (CH_3), 17.1 (CH_3), 14.0 (CH_3), 3.3 (CH_3). IR (ATR-FTIR), cm^{-1}, 3496 (w), 2951 (s), 2884 (m), 1456 (w), 1373 (w), 1338 (w), 1186 (w), 1159 (w), 1103 (w), 1022 (s), 940 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{22}H_{37}O_4]^+$ 365.2692, found 365.2686. $[\alpha]_D^{20}$ = –4.39 (*c* = 0.175, $CHCl_3$).

*Synthesis of the aldehyde **S23**.*

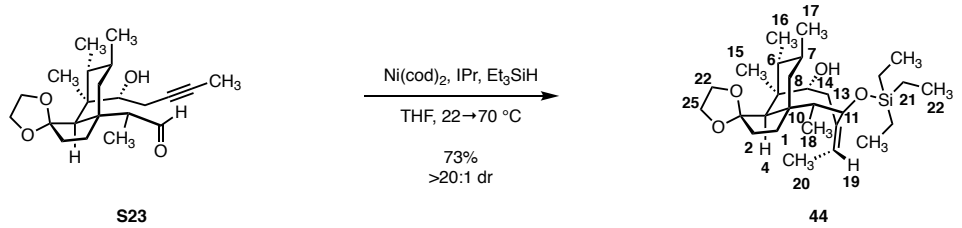


S22 **S23**

2-Iodoxybenzoic acid (36.9 mg, 132 μmol, 1.00 equiv) was added in one portion to a solution of the homopropargylic alcohol **S22** (48.0 mg, 132 μmol, 1.00 equiv) in dimethylsulfoxide (1.6 mL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (5.0 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and saturated aqueous sodium thiosulfate solution (5.0 mL) at 22 °C. The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous phase was extracted with ether (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the aldehyde **S23** as a white foam (46.0 mg, 96%). The product **S23** was used immediately in the following step.

^{1}H NMR analysis (400 MHz) of the purified product mixture indicated the presence of a 1:1 mixture of hydroxyaldehyde and hemiketal.

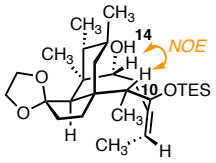
*Synthesis of the allylic ether **44**.*



S23 **44**

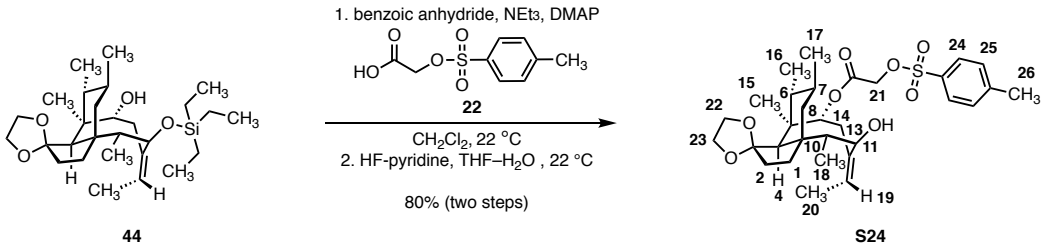
A solution of bis(cyclooctadiene)nickel(0) (4.90 mg, 17.9 µmol, 0.20 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 7.00 mg, 17.9 µmol, 0.20 equiv) in tetrahydrofuran (230 µL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. The resulting solution was added to a solution of triethylsilane (43.0 µL, 269 µmol, 3.00 equiv) and the alkynyl aldehyde **S23** (36.1 mg, 86.9 µmol, 1 equiv) in tetrahydrofuran (2.2 mL) in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred at 3 h at 70 °C. The product mixture was cooled to 22 °C over 15 min. The cooled product mixture was eluted over a short pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, four steps) to provide the allylic ether **44** as a clear oil (31 mg, 73%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the allylic ether **44** was formed as a single diastereomer. The relative stereochemistry of the C14 alcohol was determined by NOE correlations between H14 and H10.



R_f = 0.64 (30% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 – 5.25 (m, 1H, H_{19}), 4.81 (dd, J = 11.5, 4.6 Hz, 1H, H_{14}), 3.96 (q, J = 6.4, 5.7 Hz, 1H, $H_{23a\ or\ 24a}$), 3.89 (d, J = 8.7 Hz, 1H, H_{11}), 3.81 (tt, J = 13.5, 6.8 Hz, 2H, $H_{23b\ or\ 24b}$), 3.67 (p, J = 7.3, 6.6 Hz, 1H, $H_{23a\ or\ 24a}$), 3.16 (s, 1H, H_4), 2.58 (dd, J = 15.1, 11.4 Hz, 1H, H_{13a}), 2.31 (d, J = 15.2 Hz, 1H, H_{13b}), 2.21 – 2.12 (m, 1H, H_{10}), 1.85 (dd, J = 10.9, 7.0 Hz, 1H, H_6), 1.79 – 1.66 (m, 3H, H_2, H_7), 1.64 (dd, J = 6.7, 1.8 Hz, 3H, H_{20}), 1.45 – 1.37 (m, 1H, H_{8a}), 1.26 (td, J = 24.2, 22.7, 10.9 Hz, 3H, H_1, H_{8b}), 1.08 – 0.99 (m, 6H, H_{15}, H_{18}), 0.97 (d, J = 7.0 Hz, 3H, H_{16}), 0.92 (dd, J = 9.9, 6.4 Hz, 12H, H_{17}, H_{22}), 0.57 (p, J = 8.7, 7.9 Hz, 6H, H_{21}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7 (C), 121.3 (CH), 120.1 (C), 85.0 (CH), 70.3 (CH), 64.0 (CH_2), 61.6 (CH_2), 51.0 (CH), 45.7 (C), 44.0 (C), 43.1 (CH), 42.9 (CH), 38.9 (CH_2), 36.1 (CH_2), 33.9 (CH_2), 30.6 (CH), 28.7 (CH_2), 21.4 (CH_3), 16.2 (CH_3), 15.4 (CH_3), 14.4 (CH_3), 13.5 (CH_3), 7.2 (3 × CH_3), 5.3 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 3392 (w), 2923 (s), 2853 (m), 1725 (w), 1670 (w), 1457 (w), 1375 (w), 1261 (m), 1094 (s), 1016 (s), 800 (s), 725 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{28}H_{50}O_4SiNa]^+$ 501.3376; found 501.3371. $[a]_D^{20}$ = –15.6 (c = 0.030, $CHCl_3$).

*Synthesis of the sulfonate **S24**.*



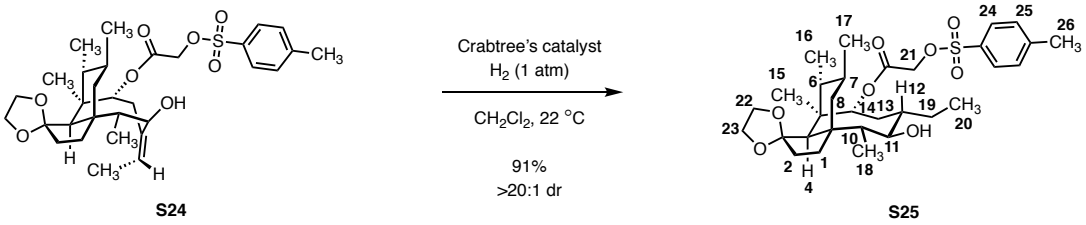
(4-Dimethylamino)pyridine (300 μg, 2.50 μmol, 0.10 equiv) was added to a solution of the sulfonate **22** (31.7 mg, 138 μmol, 5.50 equiv), benzoic anhydride (31.2 mg, 138 μmol, 5.50 equiv), triethylamine (23.0 μL, 163 μmol, 6.50 equiv), and the allylic ether **44** [12.0 mg, 25.1 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (250 μL) at 22 ˚C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (4.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Hydrogen fluoride–pyridine complex (21.0 μL, 50.2 μmol, 2.00 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally 25.1 μmol, 1 equiv) in 2:1 tetrahydrofuran–water (v/v, 500 μL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, four steps) to provide the sulfonate **S24** as a white foam (44.0 mg, 80% over two steps).

R_f = 0.49 (30% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H, H_{24}), 7.33 (d, J = 8.0 Hz, 2H, H_{25}), 5.95 (dd, J = 11.8, 4.6 Hz, 1H, H_{14}), 5.41 (qd, J = 6.7, 2.6 Hz, 1H, H_{19}), 4.52 (s, 2H, H_{21}), 3.99 – 3.90 (m, 1H, $H_{22a\ or\ 23a}$), 3.87 (d, J = 9.3 Hz, 1H, H_{11}), 3.85 – 3.69 (m, 2H, H_{22b}, H_{23b}), 3.71 – 3.61 (m, 1H, $H_{22a\ or\ 23a}$), 3.03 (d, J = 2.6 Hz, 1H, H_4), 2.64 (dd, J = 15.4, 11.7 Hz, 1H, H_{13a}), 2.43 (s, 3H, H_{26}), 2.37 – 1.99 (m, 2H, H_{10}, H_{13b}), 1.84 (dq, J = 11.0, 7.4 Hz, 1H, H_6), 1.79 – 1.66 (m, 2H, H_1), 1.63 (dd, J = 6.7, 1.8 Hz, 3H, H_{20}), 1.62 – 1.47 (m, 1H, H_7), 1.48 – 1.14 (m, 4H, H_2, H_8), 1.09 (d, J = 6.1 Hz, 6H, H_{15}, H_{18}), 0.83 (d, J = 6.3 Hz, 3H, H_{17}), 0.62 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (C), 145.4 (C), 141.2 (C), 132.8 (C), 130.0 (2 × CH), 128.3 (2 × CH), 122.9 (CH), 119.8 (C), 83.7 (CH), 74.4 (CH), 65.2 (CH_2), 64.0 (CH_2), 61.6 (CH_2), 51.0 (CH), 45.7 (C), 43.2 (C), 42.5 (CH), 42.4 (CH), 38.5 (CH_2), 36.0 (CH_2), 30.6 (CH), 29.7 (CH_2), 28.8 (CH_2), 21.8 (CH_3), 21.1 (CH_3), 16.1 (CH_3), 15.7 (CH_3),

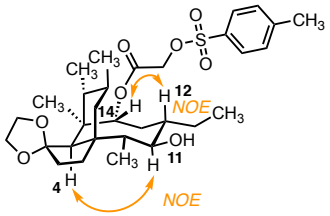
14.1 (CH_3), 13.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2927 (m), 2881 (w), 2365 (m), 2338 (m), 1759 (w), 1733 (w), 1454 (w), 1371 (m), 1298 (w), 1221 (w), 1178 (s), 1096 (w), 1038 (m), 816 (w), 773 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{31}H_{44}O_8SNa]^+$ 599.2655; found 599.2649. $[a]_D^{20}$ = +2.65 (c = 0.205, $CHCl_3$).

*Synthesis of the reduction product **S25**.*



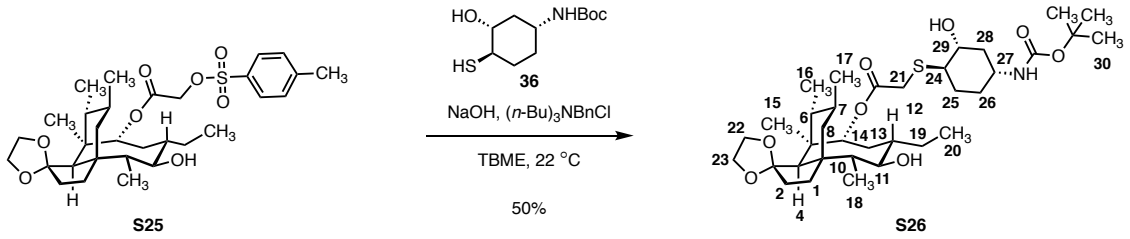
Crabtree's catalyst (400 µg, 0.50 µmol, 0.05 equiv) was added to a solution of the alkene **S24** [5.50 mg, 9.50 µmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (950 µL) at 22 °C. The reaction vessel was purged with dihydrogen and placed under a balloon of dihydrogen. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the reduction product **S25** as a clear oil (5.00 mg, 91%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), **S25** was formed as a single diastereomer. The C12 configuration depicted is supported by NOE correlations between H14 and H12. The C11 configuration depicted is supported by NOE correlations between H11 and H4.



R_f = 0.45 (30% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H, H_{24}), 7.35 (d, J = 7.9 Hz, 2H, H_{25}), 5.39 (d, J = 8.3 Hz, 1H, H_{14}), 4.52 (s, 2H, H_{21}), 4.02 (q, J = 6.0, 4.8 Hz, 1H, H_{22a} or H_{23a}), 3.88 (tt, J = 13.2, 6.7 Hz, 2H, H_{22b} or H_{23b}), 3.75 (q, J = 7.6, 6.4 Hz, 1H, H_{22a} or H_{23a}), 3.37 – 3.31 (m, 1H, H_{11}), 2.45 (s, 3H, H_{26}), 2.15 – 2.06 (m, 1H, H_{10}), 1.98 (s, 1H, H_4), 1.95 – 1.84 (m, 2H, H_6, H_{13a}), 1.82 – 1.77 (m, 2H, H_1), 1.76 – 1.35 (m, 5H, H_{2a}, H_7, H_{8a}, H_{12}, H_{19a}), 1.27 (d, J = 15.9 Hz, 4H, H_{2b}, H_{8b}, H_{13b}, H_{19b}), 1.06 (s, 3H, H_{15}), 0.91 (d, J = 7.0 Hz, 3H, H_{18}), 0.86 (t, J = 7.0 Hz, 6H, H_{17}, H_{20}), 0.64 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7 (C), 145.4 (C), 132.8 (C), 130.0 (2 × CH), 128.3 (2 × CH), 120.6 (C), 77.0 (CH), 71.7 (CH), 65.3 (CH_2), 64.0 (CH_2), 61.7 (CH_2), 51.3 (CH), 47.9 (CH), 46.2 (C), 42.4 (C), 42.0 (CH), 41.0 (CH), 39.3 (CH_2), 36.8 (CH_2), 35.9 (CH_2), 30.1 (CH), 28.9 (CH_2), 25.9 (CH_2), 21.8 (CH_3), 21.1 (CH_3), 15.0 (CH_3), 14.3 (CH_3), 11.8 (CH_3), 10.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2974 (m), 2883 (w), 1754 (m), 1733 (m), 1371 (m), 1178 (s), 1036 (m), 818 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{31}H_{47}O_8S]^+$ 579.2992; found 579.2986. $[a]_D^{20}$ = +21.6 (c = 0.063, $CHCl_3$).

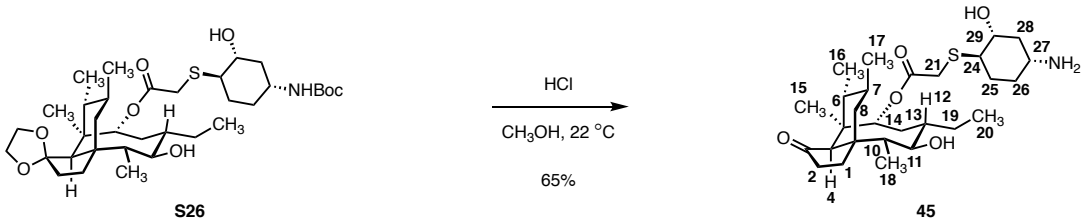
*Synthesis of the sulfide **S26**.*



Aqueous sodium hydroxide solution (1 N, 13.8 μL, 13.8 μmol, 1.60 equiv) was added to a solution of the thiol **36** (3.40 mg, 13.8 μmol, 1.6 equiv), benzyl tri-*n*-butylammonium chloride (539 μg, 1.70 μmol, 0.20 equiv) and the sulfonate **S25** (4.00 mg, 7.10 μmol, 1 equiv) in *tert*-butyl methyl ether (200 μL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), 0.1 N aqueous phosphoric acid solution (1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the sulfide **S26** as a white foam (2.80 mg, 50%).

R_f = 0.16 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.37 (d, J = 8.1 Hz, 1H, H_{14}), 4.45 (s, 1H, NH), 4.02 (q, J = 6.3, 5.5 Hz, 1H, $H_{22a\ or\ 23a}$), 3.94 – 3.83 (m, 2H, H_{22b}, H_{23b}), 3.79 – 3.71 (m, 1H, $H_{22a\ or\ 23a}$), 3.52 (d, J = 14.8 Hz, 2H, H_{27}, OH), 3.43 – 3.30 (m, 3H, H_{11}, H_{21a}, H_{29}), 3.28 – 3.20 (m, 1H, H_{21b}), 2.46 (ddt, J = 13.3, 10.0, 4.9 Hz, 1H, H_{24}), 2.36 (dd, J = 11.8, 5.5 Hz, 1H, H_{28a}), 2.17 (p, J = 7.2 Hz, 1H, H_{10}), 2.06 (td, J = 14.2, 3.9 Hz, 2H, H_{25a}, H_{26a}), 2.01 (s, 1H, H_4), 1.96 – 1.86 (m, 2H, H_6, H_{13a}), 1.86 – 1.68 (m, 4H, H_2, H_{12}, H_{19a}), 1.53 (d, J = 14.2 Hz, 2H, H_7, H_{8a}), 1.47 – 1.10 (m, 17H, H_1, H_{8b}, H_{12b}, H_{19b}, H_{25b}, H_{26b}, H_{28b}, H_{30}), 1.10 (s, 3H, H_{15}), 0.90 (dt, J = 21.0, 6.5 Hz, 9H, H_{17}, H_{18}, H_{20}), 0.72 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C), 155.0 (C), 120.5 (C), 79.4 (C), 76.8 (CH), 71.8 (CH), 71.5 (CH), 63.8 (CH_2), 61.5 (CH_2), 52.9 (CH), 51.2 (CH), 48.0 (CH), 47.7 (CH), 46.1 (C), 42.2 (C), 42.0 (CH), 40.9 (CH), 40.5 (CH_2), 39.1 (CH_2), 36.7 (CH_2), 35.8 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 30.0 (CH), 29.4 (CH_2), 28.8 (CH_2), 28.4 (3 × CH_3), 25.8 (CH_2), 21.0 (CH_3), 14.9 (CH_3), 14.4 (CH_3), 11.6 (CH_3), 10.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2927 (w), 2360 (s), 2341 (m), 1698 (w), 1508 (w), 1169 (w), 772 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{35}H_{60}NO_8S]^+$ 654.4040; found 654.4034. $[a]_D^{20}$ = –35.0 (c = 0.025, $CHCl_3$).

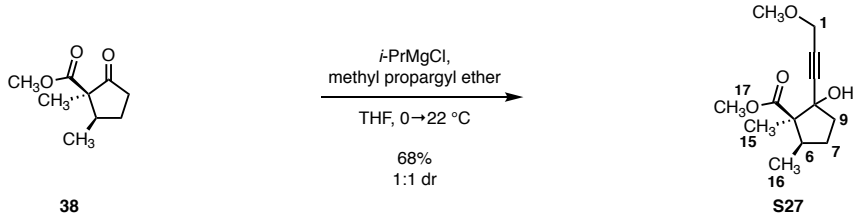
*Synthesis of the lefamulin derivative **45**.*



Aqueous hydrochloric acid solution (12 N, 1.60 µL, 18.6 µmol, 20.0 equiv) was added to a solution of the sulfide **S26** (610 µg, 0.93 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the lefamulin derivative **45** as a white solid (310 µg, 65%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.04 (90% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 5.45 (d, J = 7.6 Hz, 1H, H_{14}), 3.72 (s, 1H, NH), 3.58 – 3.51 (m, 2H, H_{21a}, H_{29}), 3.44 – 3.34 (m, 2H, H_{11}, H_{21b}), 3.24 – 3.18 (m, 1H, H_{27}), 2.71 (td, J = 10.0, 9.3, 3.7 Hz, 1H, H_{24}), 2.31 – 2.25 (m, 3H, H_{2a}, H_4, H_{28a}), 2.21 (td, J = 11.1, 10.3, 4.6 Hz, 2H, H_{10}, H_{25a}), 2.14 (dd, J = 19.1, 9.4 Hz, 1H, H_{2b}), 2.03 (d, J = 8.3 Hz, 1H, H_{26a}), 1.95 – 1.79 (m, 2H, H_{13a}, H_{19a}), 1.78 (dd, J = 14.8, 3.1 Hz, 1H, H_{8a}), 1.70 (qd, J = 12.0, 8.8 Hz, 2H, H_{1a}, H_{12}), 1.57 (dp, J = 16.3, 5.5, 5.0 Hz, 1H, H_7), 1.52 – 1.40 (m, 8H, H_{1b}, H_{15}, H_{13b}, H_{25b}, H_{26b}, H_{28b}), 1.36 – 1.22 (m, 2H, H_6, H_{19b}), 1.00 (d, J = 7.0 Hz, 3H, H_{18}), 0.92 – 0.85 (m, 6H, H_{17}, H_{20}), 0.83 (d, J = 7.3 Hz, 4H, H_{8b}, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.3 (C), 170.9 (C), 74.8 (CH), 71.6 (CH), 70.8 (CH), 57.9 (CH), 49.8 (CH), 48.1 (CH), 47.4 (CH), 45.2 (C), 43.2 (CH), 42.1 (CH), 41.8 (C), 40.3 (CH_2), 37.9 (CH_2), 36.0 (CH_2), 33.7 (CH_2), 33.3 (CH_2), 30.1 (CH), 29.2 (CH_2), 27.6 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 19.6 (CH_3), 14.7 (CH_3), 13.5 (CH_3), 10.4 (CH_3), 9.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 3361 (w), 2925 (m), 2360 (s), 2341 (m), 1718 (m), 1456 (w), 1285 (w), 1019 (w), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{48}NO_5S]^+$ 510.3253; found 510.3248. $[a]_D^{20}$ = +33.8 (c = 0.045, CH_3OH).

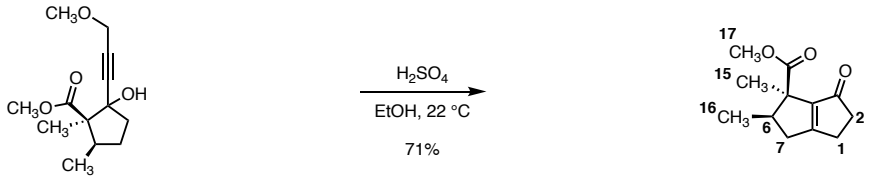
*Synthesis of the propargylic alcohol **S27**.*



A solution of *iso*-propyl magnesium chloride in tetrahydrofuran (2.0 M, 136 mL, 272 mmol, 1.30 equiv) was added dropwise to a solution of methyl propargyl ether (23.0 mL, 272 mmol, 1.30 equiv) in tetrahydrofuran (280 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The resulting mixture was then added to a solution of the β-ketoester **38** [35.6 g, 209 mmol, 1 equiv; dried by azeotropic distillation from benzene (1 × 50 mL)] in tetrahydrofuran (420 mL) at 0 °C. The reaction mixture was warmed to 22 °C and stirred for 2 h at 22 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (600 mL) and ethyl acetate (600 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes, grading to 50% ethyl acetate–hexanes, three steps) to provide the propargylic alcohol **S27** as a pale yellow oil (34.2 g, 68%).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 1:1 mixture of diastereomers.

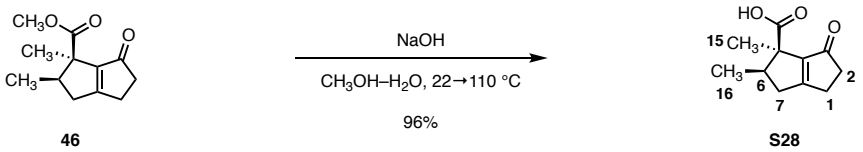
*Synthesis of the bicyclic ketone **46**.*



Concentrated sulfuric acid solution (18 N, 6.40 mL, 119 mmol, 11.3 equiv) was added dropwise over 2 min to a solution of the propargylic alcohol **S27** (2.54 g, 11.0 mmol mol, 1 equiv) in ethanol (6.4 mL) at 22 °C. The reaction mixture was stirred at 22 °C for 20 min. The product mixture was cooled to 0 °C and the cooled product mixture was diluted sequentially with ether (10 mL) and water (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified be flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes, three steps) to provide the bicyclic ketone **46** as a pale orange solid (1.56 g, 71%).

R_f = 0.25 (60% ethyl acetate–hexanes, UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.65 (s, 3H, H_{17}), 2.79 – 2.50 (m, 6H, H_1, H_2, H_6, H_{7a}), 2.31 (dd, J = 17.6, 8.3 Hz, 1H, H_{7b}), 1.43 (s, 3H, H_{15}), 1.05 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6 (C), 186.5 (C), 173.9 (C), 150.3 (C), 53.2 (C), 51.9 (CH_3), 51.6 (CH), 40.6 (CH_2), 39.1 (CH_2), 25.9 (CH_2), 21.2 (CH_3), 15.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2957 (w), 2361 (w), 2338 (w), 1733 (m), 1696 (s), 1231 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{12}H_{17}O_3]^+$ 209.1178; found 209.1172. $[a]_D^{20}$ = +75.6 (c = 0.795, $CHCl_3$).

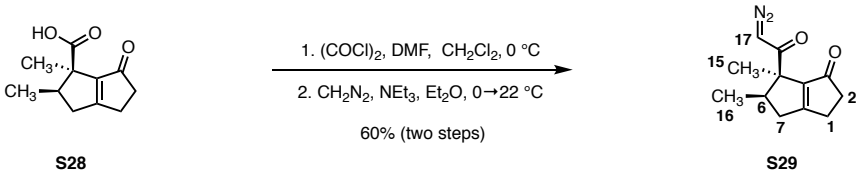
*Synthesis of the carboxylic acid **S28**.*



Aqueous sodium hydroxide solution (2 N, 890 mL, 1.78 mol, 20.0 equiv) was added to a solution of the methyl ester **46** (18.5 g, 88.8 mmol, 1 equiv) in methanol (890 mL) at 22 °C. The reaction vessel was equipped with a reflux condenser and then placed in an oil bath that had been preheated to 110 °C. The reaction mixture was stirred for 15 h at 110 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted sequentially with water (600 mL) and ether (500 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was washed with ether (2 × 500 mL, discarded). The washed aqueous layer was cooled to 0 °C over 10 min. The pH of the cooled aqueous layer was adjusted to ~1 by dropwise addition of 12 N concentrated hydrochloric acid solution over 20 min at 0 °C. The acidified aqueous phase was diluted with ether (500 mL) and the resulting biphasic mixture was transferred to a separatory funnel. The layers that formed were separated. The aqueous layer was extracted with ether (2 × 500 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the carboxylic acid **S28** as a yellow foam (16.5 g, 96%). The product so obtained was judged to be of >95% purity (400 MHz ^{1}H NMR analysis) and was used without further purification.

R*f* = 0.12 (1% acetic acid–50% ethyl acetate–hexanes; UV). ^{1}H NMR (400 MHz, C_6D_6) δ 2.73 – 2.67 (m, 2H, H_2), 2.66 – 2.58 (m, 2H, H_6, H_{7a}), 2.58 – 2.52 (m, 2H, H_1), 2.35 (q, J = 6.7 Hz, 1H, H_{7b}), 1.41 (s, 3H, H_{15}), 1.14 (d, J = 6.7 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, C_6D_6) δ 203.2 (C), 187.8 (C), 179.0 (C), 149.7 (C), 52.9 (C), 51.4 (CH), 40.4 (CH_2), 38.9 (CH_2), 25.9 (CH_2), 20.6 (CH_3), 15.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2919 (w), 1692 (s), 1631 (m), 1232 (w). HRMS-ESI (m/z): calcd for $[C_{11}H_{15}O_3]^+$ 195.1021; found 195.1016. $[a]_D^{20}$ = +56.2 (c = 0.930, $CHCl_3$).

*Synthesis of the α-diazoketone **S29**.*



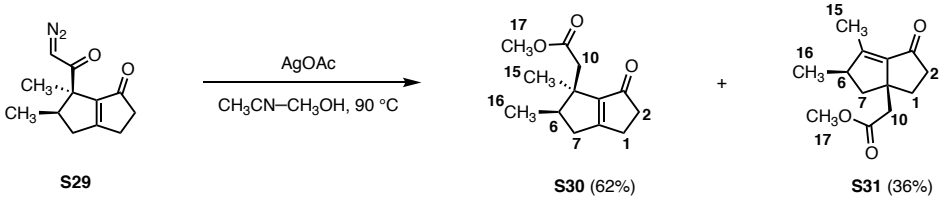
S28 **S29**

Oxalyl chloride (1.16 mL, 13.6 mmol, 1.10 equiv) was added dropwise over 5 min to a solution of the carboxylic acid **S28** [2.40 g, 12.4 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 10 mL)] and *N,N*-dimethylformamide (1.90 mL, 24.7 mmol, 2.00 equiv) in dichloromethane (21 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was concentrated. The residue obtained was dissolved in dichloromethane (20 mL) and the resulting solution was eluted over a plug of silica gel (5.0 cm × 5.0 cm). The silica gel plug was washed with 50% ether–hexanes (100 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

A solution of the unpurified acid chloride obtained in the preceding step (nominally 12.4 mmol, 1 equiv) in ether (25 mL) was added dropwise over 20 min to a solution of diazomethane in ether (ca. 0.66 M, 130 mL, 7.00 equiv) and triethylamine (5.16 mL, 37.1 mmol, 3.00 equiv) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 1 h. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was cooled to 0 °C over 20 min. The cooled product mixture was slowly diluted with aqueous potassium phosphate buffer solution (pH 7, 100 mL). The resulting biphasic mixture was stirred for 2 h at 0 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 150 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, four steps) to provide the α-diazoketone **S29** as a yellow solid (1.90 g, 60% over two steps).

R_f = 0.32 (66% ethyl acetate–hexanes; UV). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.38 (s, 1H, H_{17}), 2.74 – 2.70 (m, 2H, H_2), 2.67 (dd, J = 17.9, 7.8 Hz, 1H, H_{7a}), 2.62 – 2.58 (m, 2H, H_1), 2.57 (d, J = 7.6 Hz, 1H, H_6), 2.35 (ddtd, J = 17.9, 8.3, 1.8, 0.8 Hz, 1H, H_{7b}), 1.40 (s, 3H, H_{15}), 1.11 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8 (C), 195.6 (C), 188.1 (C), 150.7 (C), 57.0 (C), 54.5 (CH), 51.8 (CH), 40.7 (CH_2), 39.3 (CH_2), 26.1 (CH_2), 21.1 (CH_3), 15.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2929 (w), 2130 (s), 1691 (s), 1631 (m), 1351 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{12}H_{15}N_2O_2]^+$ 219.1134; found 219.1128. $[\alpha]_D^{20}$ = –12.5 (c = 0.290, $CHCl_3$).

*Synthesis of the Arndt–Eistert homologation products **S30** and **S31**.*



S29 **S30** (62%) **S31** (36%)

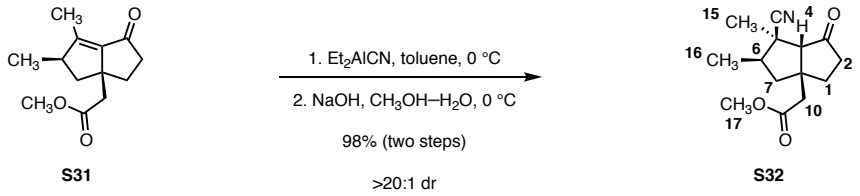
A solution of the α-diazoketone **S29** (1.37 g, 6.28 mmol, 1 equiv) in acetonitrile (64 mL) was added rapidly over 1 min via additional funnel to a suspension of silver acetate (314 mg, 1.88 mmol, 0.30 equiv) in methanol (35 mL) and acetonitrile (250 mL) that had been preheated to 85 °C. The reaction mixture was stirred for 1 h at 85 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was filtered over a pad of Celite. The Celite pad was rinsed with ethyl acetate (2 × 200 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 30% ether–hexanes, four steps) to provide separately the homologation product **S30** (pale yellow oil, 800 mg, 62%) and the rearranged ester **S31** (pale yellow oil, 495 mg, 36%).

The relative stereochemistry of **S31** was established by X-ray analysis of the methylation product **S35** (see page S167).

S30: R_f: 0.52 (60% ether–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H, H_{17}), 2.70 – 2.61 (m, 2H, H_7), 2.61 – 2.42 (m, 4H, H_1, H_{2a}, H_6,), 2.36 (q, J = 13.6 Hz, 2H, H_{10}), 2.21 (dd, J = 17.1, 8.1 Hz, 1H, H_{2b}), 1.31 (s, 3H, H_{15}), 1.06 (d, J = 6.9 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4 (C), 184.3 (C), 172.8 (C), 152.5 (C), 51.7 (CH_3), 50.3 (CH), 44.8 (C), 40.7 (CH_2), 39.2 (CH_2), 38.5 (CH_2), 25.9 (CH_2), 24.1 (CH_3), 14.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 2955 (w), 1732 (m), 1691 (s), 1635 (w), 1436 (w), 1376 (w), 1319 (w), 1195 (w), 1165 (w), 1091 (w), 1013 (w), 970 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{13}H_{19}O_3]^+$ 223.1334; found 223.1329. $[a]_D^{20}$ = –12.3 (c = 3.25, $CHCl_3$).

S31: R_f: 0.72 (60% ether–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H, H_{17}), 2.89 (p, J = 7.8 Hz, 1H, H_6), 2.62 – 2.38 (m, 4H, H_1, H_2), 2.34 (dd, J = 12.6, 7.9 Hz, 1H, H_{10a}), 2.17 (dd, J = 13.8, 9.4 Hz, 1H, H_{7a}), 2.04 – 1.94 (m, 4H, H_{7b}, H_{15}), 1.65 (td, J = 12.2, 8.4 Hz, 1H, H_{10b}), 1.22 (d, J = 7.4 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (C), 172.4 (C), 154.4 (C), 143.2 (C), 54.3 (C), 51.6 (CH_3), 49.8 (CH), 44.5 (CH_2), 43.2 (CH_2), 40.8 (CH_2), 34.3 (CH_2), 20.0 (CH_3), 13.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2957 (w), 1734 (s), 1708 (s), 1655 (m), 1436 (w), 1260 (w), 1201 (w), 1167 (w), 1093 (w), 1009 (w), 773 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{13}H_{19}O_3]^+$ 223.1334; found 223.1329. $[a]_D^{20}$ = –8.92 (c = 0.935, $CHCl_3$).

*Synthesis of the nitrile **S32**.*



S31 **S32**

*CAUTION***:** Cyanide hazard! Perform reaction, aqueous workup, and purification in a well-ventilated fume hood. All glassware and waste solutions should be washed with bleach prior to removing from fume hood.

A solution of diethylaluminum cyanide solution in toluene (1.0 M, 8.7 mL, 8.69 mmol, 1.40 equiv) was added dropwise over 2 min to a solution of the enone **S31** (1.50 g, 6.40 mmol, 1 equiv) in toluene (62 mL) at 0 °C. The reaction mixture was stirred for 20 min at 0 °C. The product mixture was diluted with saturated aqueous potassium sodium tartrate solution (60 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 80 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

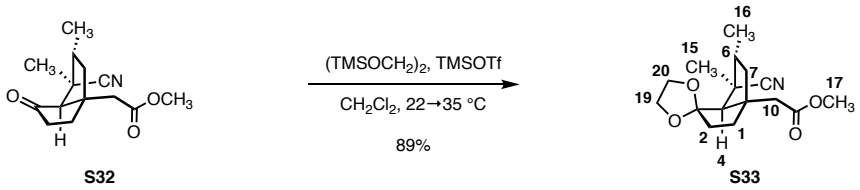
Aqueous sodium hydroxide solution (0.1 N, 7.7 mL) was added dropwise over 1 min to a solution of the nitrile **18** obtained in the preceding step (nominally 6.40 mmol, 1 equiv) in methanol (65 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The product mixture was diluted sequentially with ether (100 mL) and saturated aqueous ammonium chloride solution (100 mL). The resulting biphasic solution was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ether–hexanes) to provide the nitrile **S32** as a pale yellow oil (1.51 g, 98% over two steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated that the product **S32** had been formed as a >20:1 mixture of diastereomers. The relative stereochemistry of the nitrile **S32** was established by X-ray analysis of the methylation product **S35** (see page S167).

R_f = 0.61 (60% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H, H_{17}), 2.80 (d, J = 15.8 Hz, 1H, H_{10a}), 2.75 (s, 1H, H_4), 2.68 (d, J = 15.9 Hz, 1H, H_{10b}), 2.42 (dddd, J = 18.6, 9.5, 6.2, 1.7 Hz, 1H, H_{2a}), 2.25 (ddd, J = 18.5, 10.1, 8.1, 1H, H_{2b}), 2.11 – 2.02 (m, 2H, H_{1a}, H_{7a}), 1.96, ddd, J = 13.7, 10.1, 6.2 Hz, 1H, H_{1b}), 1.86 (t, J = 13.0 Hz, 1H, H_{7b}), 1.77 (dp, J = 12.8, 6.3 Hz, 1H, H_6), 1.41 (s, 3H, H_{15}), 1.17 (d, J = 6.3 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4 (C), 171.7 (C), 122.3 (C), 63.4 (CH), 51.7 (CH_3), 48.0 (CH_2), 47.3 (C), 46.9 (C), 45.8 (CH_2), 44.5 (CH), 39.6 (CH_2), 34.0 (CH_2), 19.2 (CH_3), 14.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2961 (w), 2360 (w), 2338

(w), 1734 (s), 1456 (w), 1218 (w), 1174 (w), 773 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{14}H_{20}NO_3]^+$ 250.1443; found 250.1438. $[a]_D^{20} = +10.9$ ($c = 0.455$, $CHCl_3$).

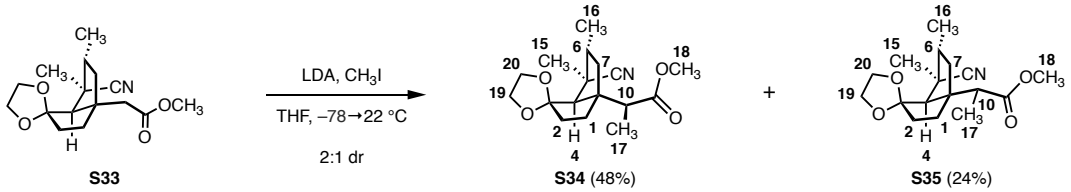
*Synthesis of the ketal **S33**.*



Trimethylsilyl trifluoromethanesulfonate (2.18 mL, 12.0 mmol, 2.00 equiv) was added rapidly to a solution of 1,2-bis(trimethylsiloxy)ethane (5.79 mL, 30.1 mmol, 5.00 equiv) and the nitrile **S32** [1.50 g, 6.02 mmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 5.0 mL)] in dichloromethane (30 mL) at 22 °C. The reaction vessel was placed in an oil bath that had been preheated to 35 °C. The reaction mixture was stirred for 4 d at 35 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted with ether (20 mL). The diluted mixture was slowly poured into saturated aqueous sodium bicarbonate solution (60 mL) that had been precooled to 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (70 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the ketal **S33** as a pale yellow oil (1.56 g, 89%).

R_f = 0.69 (60% ether–hexanes; PAA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 – 3.84 (m, 4H, H_{19}, H_{20}), 3.66 (s, 3H, H_{18}), 2.63 (d, J = 3.5 Hz, 2H, H_{10}), 2.54 (s, 1H, H_4), 2.39 – 2.23 (m, 1H, H_6), 2.02 (dt, J = 7.8, 2.0 Hz, 1H, H_{2a}), 1.95 (dd, J = 13.6, 6.4 Hz, 1H, H_{7a}), 1.69 (dt, J = 7.7, 2.2 Hz, 1H, H_{2b}), 1.61 (dd, J = 13.5, 12.5 Hz, 1H, H_{7b}), 1.57 – 1.51 (m, 2H, H_1), 1.46 (s, 3H, H_{15}), 1.08 (d, J = 6.6 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3 (C), 124.0 (C), 118.2 (C), 63.9 (CH_2), 63.9 (CH_2), 61.9 (CH), 51.6 (CH_3), 47.4 (C), 46.6 (C), 46.1 (CH_2), 45.9 (CH_2), 41.9 (CH), 35.6 (CH_2), 35.5 (CH_2), 17.4 (CH_3), 14.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2961 (w), 2364 (w), 1736 (s), 1439 (w), 1310 (w), 1259 (w), 1168 (s), 1117 (s), 1079 (w), 1029 (s), 956 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{16}H_{24}NO_4]^+$ 294.1705; found 294.1700. $[a]_D^{20}$ = –67.8 (c = 0.235, $CHCl_3$).

*Synthesis of the methylation products **S34** and **S35**.*



A solution of lithium diisopropylamide in tetrahydrofuran (1.3 M, 660 μL, 825 μmol, 2.20 equiv) was added to the solution of the ketal **S33** [110 mg, 375 μmol, 1 equiv; dried by azeotropic distillation from benzene (3 × 5.0 mL)] in tetrahydrofuran (1.2 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C. The reaction mixture was warmed to 0 °C over 10 min and stirred for an additional 3 h at 0 °C. The reaction mixture was cooled to –78 °C over 30 min. Iodomethane (70.0 μL, 1.13 mmol, 3.00 equiv) was added dropwise over 2 min to the cooled reaction mixture. The reaction mixture was stirred for 1 h at –78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 22 °C over 2 h. The warmed reaction mixture was stirred for 15 h at 22 °C. The product mixture was diluted sequentially with ether (5.0 mL) and saturated aqueous ammonium chloride solution (5.0 mL). The resulting biphasic mixture was stirred for 15 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (6.0 mL) and saturated aqueous sodium chloride solution (6.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, six steps) to provide separately the (10*S*) methylation product **S34** (white solid, 55.0 mg, 48%) and the (10*R*) methylation product **S35** (white solid, 28.0 mg, 24%).

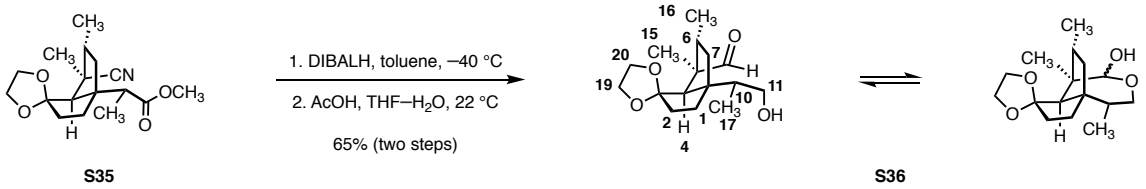
^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 2:1 mixture of **S34** and **S35**. The relative stereochemistry of the minor product **S35** was established by X-ray analysis (see page S167).

S34: R_f = 0.61 (60% ether–hexanes; CAM). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.03 – 3.93 (m, 1H, $H_{19a\text{ or }20a}$), 3.88 (dddd, *J* = 10.9, 7.8, 5.6, 3.1 Hz, 3H, $H_{19a\text{ or }20a}$, H_{19b}, H_{20b}), 3.86 (s, 3H, H_{18}), 2.79 (q, *J* = 7.2 Hz, 1H, H_{10}), 2.68 (s, 1H, H_4), 2.34 – 2.25 (m, 2H, H_{1a}, H_6), 1.76 (dd, *J* = 13.4, 6.5 Hz, 1H, H_{7a}), 1,69 (ddd, *J* = 12.5, 7.0, 3.2 Hz, 1H, H_{2a}), 1.63 (d, *J* = 12.9 Hz, 1H, H_{7b}), 1.54 (dt, *J* = 12.3, 6.0 Hz, 1H, H_{2b}), 1.47 (s, 3H, H_{15}), 1.45 – 1.37 (m, 1H, H_{1b}), 1.21 (d, *J* = 7.2 Hz, 3H, H_{17}), 1.06 (d, *J* = 6.6 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6 (C), 123.9 (C), 118.2 (C), 63.9 (CH_2), 63.5 (CH_2), 58.9 (CH), 51.5 (CH_3), 51.2 (C), 48.8 (CH), 46.2 (CH_2), 46.1 (C), 41.3 (CH), 36.9 (CH_2), 33.3 (CH_2), 17.7 (CH_3), 14.4 (CH_3), 14.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2959 (m), 2360 (s), 2341 (m), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{17}H_{26}NO_4]^+$ 308.1862; found 308.1856. $[\alpha]_D^{20}$ = –19.52 (*c* = 1.031, $CHCl_3$).

S35: R_f = 0.59 (60% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 – 3.90 (m, 1H, $H_{19a\text{ or }20a}$), 3.91 – 3.83 (m, 3H, $H_{19a\text{ or }20a}$, H_{19b}, H_{20b}), 3.69 (s, 3H, H_{18}), 2.98 (s, 1H, H_4), 2.75 (q, *J* = 6.9 Hz, 1H, H_{10}), 2.30 (dt, *J* = 12.8, 6.4 Hz, 1H, H_6), 2.16 – 2.09 (m, 1H, H_{1a}), 1.76 (dd, *J* = 13.3,

6.3 Hz, 1H, H_{7a}), 1.67 – 1.52 (m, 2H, H_{2a}, H_{7b}), 1.49 (s, 3H, H_{15}), 1.39 – 1.27 (m, 2H, H_{1b}, H_{2b}), 1.19 (d, J = 6.9 Hz, 3H, H_{17}), 1.09 (d, J = 6.5 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8 (C), 123.9 (C), 118.1 (C), 63.8 (CH_2), 63.6 (CH_2), 58.7 (CH), 51.9 (C), 51.5 (CH_3), 47.6 (CH), 46.3 (CH_2), 46.1 (C), 41.0 (CH), 36.1 (CH_2), 32.3 (CH_2), 17.5 (CH_3), 14.3 (CH_3), 13.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2960 (m), 1732 (s), 1167 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{17}H_{26}NO_4]^+$ 308.1862; found 308.1856. $[a]_D^{20}$ = –68.1 (c = 1.582, $CHCl_3$).

*Synthesis of the aldehyde **S36**.*



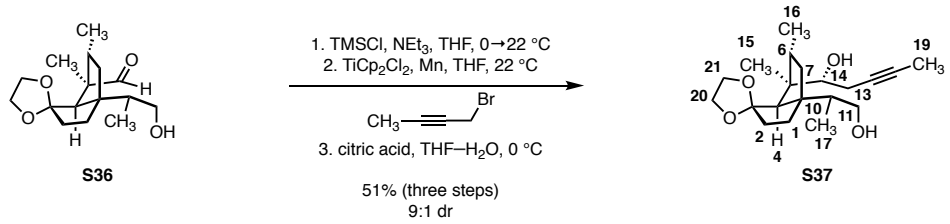
S35 **S36**

A solution of diisobutylaluminum hydride solution in toluene (1.0 M, 146 μL, 244 μmol, 3.00 equiv) was added over 10 s to a solution of the nitrile **S35** [15.0 mg, 48.8 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in toluene (330 μL) at –40 °C. The reaction mixture was stirred for 15 min at –40 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous potassium sodium tartrate solution (1.0 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Acetic acid (14.0 μL, 244 μmol, 5.00 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally 48.8 μmol, 1 equiv) in 4:1 tetrahydrofuran–water (v/v, 18 mL) at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the aldehyde **S36** as a colorless oil (9.00 mg, 65% over two steps). The product **S36** was formed as an 2.6:1 mixture of hydroxyaldehyde and hemiketal isomers (600 MHz ^{1}H NMR analysis). The product **S36** was determined to be >95% pure by quantitative ^{1}H NMR analysis (600 MHz) and was used directly in the following step.

R_f = 0.31 (60% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6, hydroxyaldehyde only) δ 9.44 (s, 1H, H_{14}), 3.64 (dd, J = 10.9, 4.5 Hz, 1H, H_{11a}), 3.46 – 3.40 (m, 1H, $H_{19a\text{ or }20a}$), 3.39 – 3.27 (m, 4H, H_{11b}, $H_{19a\text{ or }20a}$, H_{19b}, H_{20b}), 3.00 (s, 1H, H_4), 2.10 – 1.87 (m, 2H, H_{1a}, H_6), 1.86 – 1.77 (m, 1H, H_{10}), 1.63 – 1.51 (m, 2H, H_2), 1.51 – 1.35 (m, 1H, H_{7a}), 1.25 (s, 3H, H_{15}), 1.22–1.13 (m, 2H, H_{1b}, H_{7b}), 0.97 (d, J = 6.8 Hz, 3H, H_{17}), 0.87 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 204.1 (CH), 119.2 (C), 65.5 (CH_2), 63.9 (CH_2), 62.6 (CH_2), 57.7 (C), 53.5 (CH), 52.6 (C), 47.7 (CH_2), 44.8 (CH), 42.3 (CH), 36.4 (CH_2), 32.9 (CH_2), 15.0 (CH_3), 13.2 (CH_3), 13.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 3423 (w), 2957 (s), 2878 (m), 2360 (m), 2336 (m), 1717 (m), 1458 (w), 1117 (s), 1027 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{16}H_{27}O_4]^+$ 283.1909; found 283.1903. $[a]_D^{20}$ = –84.3 (c = 0.075, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **S37**.*



Trimethylsilyl chloride (4.00 μL, 35.1 μmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (18.0 μL, 128 μmol, 4.00 equiv) and the aldehyde **S36** (9.00 mg, 31.9 μmol, 1 equiv) in tetrahydrofuran (320 μL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with ether (1.0 mL) and aqueous potassium phosphate buffer solution (pH 7, 1.5 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

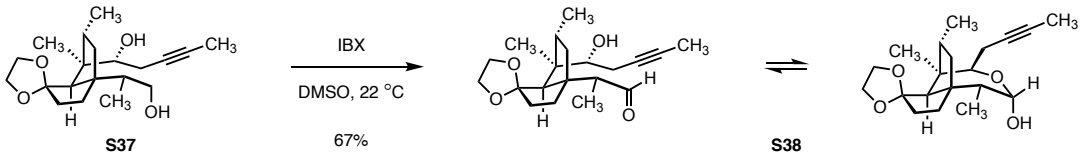
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (11.4 mg, 45.7 μmol, 3.00 equiv) and manganese powder (10.0 mg, 19.3 mmol, 12.0 equiv) in tetrahydrofuran (190 μL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the protected alcohol obtained in the preceding step (nominally 31.9 μmol, 1 equiv) and 1-bromobut-2-yne (8.30 mg, 53.5 μmol, 3.50 equiv) in tetrahydrofuran (190 μL) was added dropwise over 5 min at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted with hexanes (2.0 mL). The diluted product mixture was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 100 μL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 31.9 μmol, 1 equiv) in tetrahydrofuran (500 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (2.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **S37** as a colorless oil (2.60 mg, 51% over 3 steps).

^{1}H NMR analysis (400 MHz) of the unpurified product mixture indicated the presence of a 9:1 mixture of diastereomers. The relative stereochemistry of the major diastereomer was assigned by comparison of $^3J_{H–H}$ coupling constants to the addition product **S40**.

R_f = 0.32 (60% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6) δ 3.81 (dt, *J* = 10.1, 2.4 Hz, 1H, H_{14}), 3.61 (dd, *J* = 11.1, 5.3 Hz, 1H, H_{11a}), 3.47 (dd, *J* = 11.3, 5.4 Hz, 1H, H_{11b}), 3.39 – 3.16 (m, 4H, H_{20}, H_{21}), 2.63 (dt, *J* = 16.5, 2.7 Hz, 1H, H_{13a}), 2.57 – 2.41 (m, 2H, H_4, H_{13b}), 2.17 (d, *J* = 2.5 Hz, 1H, OH), 2.11 (q, *J* = 7.5 Hz, 1H, H_6), 1.87 (ddd, *J* = 13.1, 9.1, 7.8 Hz, 1H, H_{1a}), 1.79 (dt, *J* = 6.9, 5.6 Hz, 1H, H_{10}), 1.72 – 1.60 (m, 2H, H_2), 1.58 – 1.50 (m, 3H, H_{1b}, H_7), 1.46 (t, *J* = 2.5 Hz, 3H, H_{19}), 1.38 (s, 3H, H_{15}), 1.22 (d, *J* = 7.3 Hz, 3H, H_{17}), 0.96 (d, *J* = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, C_6D_6) δ 119.7 (C), 78.5 (C), 77.4 (C), 73.8 (CH), 65.6 (CH_2), 64.3 (CH_2), 62.4 (CH_2), 56.8 (CH), 53.8 (C), 51.2 (C), 47.2 (CH_2), 45.3 (CH), 44.9 (CH), 35.7 (CH_2), 32.1 (CH_2), 25.0 (CH_2), 16.6 (CH_3), 16.0 (CH_3), 13.8 (CH_3), 3.11 (CH_3). IR (ATR-FTIR), cm^{-1}: 3397 (w), 2918 (m), 2874 (m), 2361 (s), 2341 (s), 1027 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{20}H_{32}NaO_4]^+$ 359.2198; found 359.2198. $[a]_D^{20}$ = –142.9 (*c* = 0.014, $CHCl_3$).

*Synthesis of the aldehyde **S38**.*

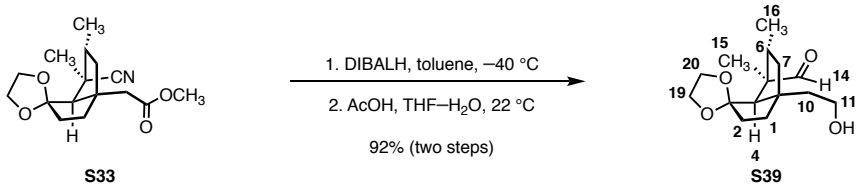


S37 **S38**

2-Iodoxybenzoic acid (1.40 mg, 4.71 μmol, 1.05 equiv) was added in one portion to a solution of the homopropargyl alcohol **S37** (1.50 mg, 4.50 μmol, 1 equiv) in dimethylsulfoxide (200 μL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium thiosulfate solution (1.0 mL) C. The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the aldehyde **S38** as a white foam (1.00 mg, 67%).

^{1}H NMR analysis (500 MHz) of the purified product mixture indicated the presence of a 1:1 mixture of hydroxyaldeyde and hemiketal isomers.

*Synthesis of the aldehyde **S39**.*



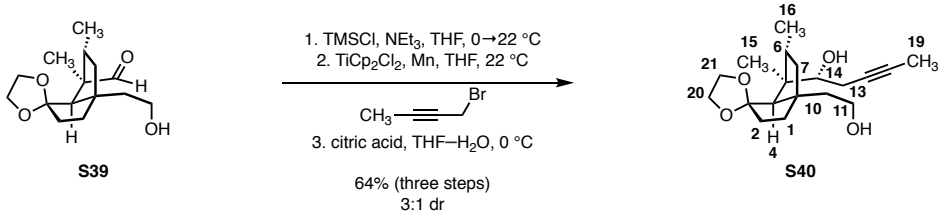
S33 **S39**

A solution of diisobutylaluminum hydride solution in toluene (1.0 M, 3.3 mL, 3.26 mmol, 4.00 equiv) was added over 10 s to a solution of the nitrile **S33** [239 mg, 815 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 2.0 mL)] in toluene (4.1 mL) at –40 °C. The reaction mixture was stirred for 15 min at –40 °C. The product mixture was diluted sequentially with ethyl acetate (4.0 mL) and saturated aqueous potassium sodium tartrate solution (4.0 mL). The resulting biphasic mixture was stirred vigorously for 2 h at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 8.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The aldehyde **S39** was determined to be >95% pure by quantitative ^{1}H NMR analysis (400 MHz) and was used directly in the following step.

Acetic acid (234 μL, 4.07 mmol, 5.00 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally 815 μmol, 1 equiv) in 4:1 tetrahydrofuran–water (v/v, 18 mL) at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (5.0 mL) and saturated aqueous sodium bicarbonate solution (7.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the aldehyde **S39** as a colorless oil (200 mg, 92% over two steps). The purity of the aldehyde **S39** was determined to be >95% by ^{1}H NMR analysis (400 MHz).

R_f = 0.41 (70% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6) δ 9.44 (s, 1H, H_{14}), 3.53 (td, J = 7.3, 1.9 Hz, 2H, H_{11}), 3.47 – 3.28 (m, 4H, H_{19}, H_{20}), 2.69 (s, 1H, H_4), 2.09 (dp, J = 13.8, 7.0 Hz, 1H, H_6), 1.90 – 1.74 (m, 3H, H_{1a}, H_{10}), 1.71 – 1.48 (m, 2H, H_2), 1.44 (dd, J = 12.9, 6.4 Hz, 1H, H_{1b}), 1.36 – 1.13 (m, 5H, H_7, H_{15}), 0.87 (d, J = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, C_6D_6) δ 205.1 (CH), 119.2 (C), 64.1 (CH_2), 63.3 (CH_2), 60.5 (CH_2), 57.7 (C), 57.5 (CH), 48.7 (C), 47.1 (CH_2), 44.7 (CH_2), 43.4 (CH), 36.3 (CH_2), 35.6 (CH_2), 14.9 (CH_3), 13.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 3406 (w), 2956 (m), 2936 (m), 2879 (m), 2359 (w), 2342 (w), 1717 (s), 1456 (w), 1353 (w), 1320 (w), 1260 (w), 1182 (w), 1116 (m), 1032 (s), 949 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{15}H_{25}O_4]^+$ 269.1753; found 269.1747. $[\alpha]_D^{20}$ = –53.7 (c = 1.000, $CHCl_3$).

*Synthesis of the homopropargylic alcohol **S40**.*



Trimethylsilyl chloride (230 μL, 1.19 mmol, 1.10 equiv) was added dropwise over 1 min to a solution of triethylamine (688 μL, 4.95 mmol, 2.00 equiv) and the aldehyde **S39** (442 mg, 1.65 mmol, 1 equiv) in tetrahydrofuran (16 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with ether (10 mL) and aqueous potassium phosphate buffer solution (pH 7, 15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

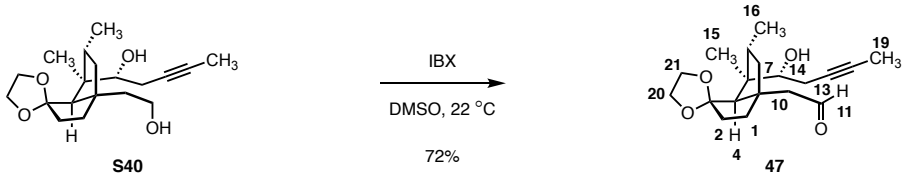
A mixture of bis(cyclopentyldienyl)titanium(IV) dichloride (1.21 g, 4.84 mmol, 3.00 equiv) and manganese powder (1.06 g, 19.3 mmol, 12.0 equiv) in tetrahydrofuran (20 mL) was stirred vigorously at 22 °C until a light green color persisted (approximately 30 min). A solution of the unpurified product obtained in the preceding step (nominally 1.65 mmol, 1 equiv) and 1-bromobut-2-yne (752 mg, 5.65 mmol, 3.50 equiv) in tetrahydrofuran (20 mL) was added dropwise over 40 min at 22 °C via syringe pump. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted with hexanes (40 mL). The diluted product mixture was eluted over a plug of silica gel (4.0 cm × 4.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Aqueous citric acid solution (10% w/v, 9.0 mL) was added dropwise to a solution of the addition product obtained in the preceding step (nominally 1.65 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the homopropargylic alcohol **S40** as an off-white foam (340 mg, 64% over three steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 3:1 mixture of diastereomers. The relative stereochemistry of major diastereomer was established by NOE analysis of **48**.

R_f = 0.25 (30% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 3.78 (dd, *J* = 10.3, 2.7 Hz, 1H, H_{14}), 3.53 (t, *J* = 7.2 Hz, 2H, H_{11}), 3.44 – 3.29 (m, 4H, H_{20}, H_{21}), 2.57 (dt, *J* = 16.4, 2.7 Hz, 1H, H_{13a}), 2.47 (ddd, *J* = 16.5, 10.1, 2.7 Hz, 1H, H_{13b}), 2.12 (p, *J* = 7.3 Hz, 1H, H_6), 2.03 (s, 1H, H_4), 1.89 (dt, *J* = 13.4, 6.7 Hz, 1H, H_{10a}), 1.71 (td, *J* = 15.2, 7.7 Hz, 2H, H_{1a}, H_{2a}), 1.63 (tt, *J* = 13.5, 6.8 Hz, 1H, H_{10b}), 1.57 (dd, *J* = 6.7, 4.3 Hz, 1H, H_{2b}), 1.55 (d, *J* = 6.5 Hz, 1H, H_{7a}), 1.49 – 1.43 (m, 4H, H_{7b}, H_{19}), 1.34 (s, 3H, H_{15}), 1.29 (dd, *J* = 11.7, 6.7 Hz, 1H, H_{1b}), 1.20 (d, *J* = 7.3 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 119.4 (C), 78.5 (C), 77.6 (C), 74.3 (CH), 64.4 (CH_2), 62.8 (CH_2), 60.7 (CH), 60.4 (CH_2), 50.8 (C), 49.7 (C), 46.5 (CH_2), 46.5 (CH_2), 45.7 (CH), 35.8 (CH_2), 35.5 (CH_2), 25.1 (CH_2), 16.5 (CH_3), 16.2 (CH_3), 3.3 (CH_3). IR (ATR-FTIR), cm^{-1}, 3429 (w), 2925 (s), 2879 (m), 2360 (m), 2336 (w), 1456 (w), 1336 (w), 1222 (w), 1112 (m), 1027 (s), 949 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{19}H_{31}O_4]^+$ 323.2222; found 323.2217. $[\alpha]_D^{20}$ = –5.58 (*c* = 0.165, $CHCl_3$).

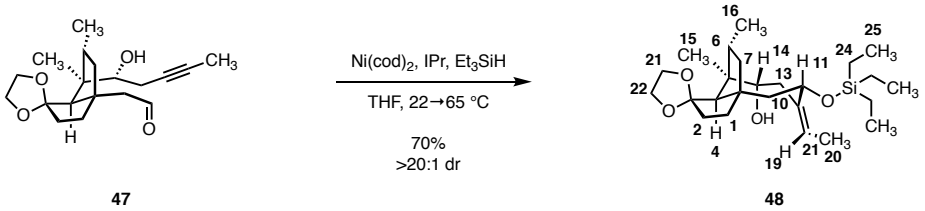
*Synthesis of the aldehyde **47**.*



2-Iodoxybenzoic acid (351 mg, 1.19 mmol, 1.01 equiv) was added in one portion to a solution of the homopropargylic alcohol **S40** (380 mg, 1.18 mmol, 1 equiv) in dimethylsulfoxide (15 mL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (20 mL), saturated aqueous sodium bicarbonate solution (10 mL), and saturated aqueous sodium thiosulfate solution (10 mL). The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the hydroxyaldehyde **47** as a white foam (274 mg, 72%). The product **47** was used immediately in the following step.

R_f = 0.43 (33% ether–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 9.50 (d, J = 2.2 Hz, 1H, H_{11}), 3.64 (dd, J = 10.1, 2.7 Hz, 1H, H_{14}), 3.43 – 3.26 (m, 4H, H_{20}, H_{21}), 2.59 – 2.53 (m, 1H, H_{10a}), 2.52 – 2.45 (m, 1H, H_{13a}), 2.43 – 2.33 (m, 1H, H_{13b}), 2.25 (dd, J = 15.9, 2.1 Hz, 1H, H_{10b}), 2.12 (s, 1H, OH), 2.03 (p, J = 7.3, 6.8 Hz, 1H, H_6), 1.87 (s, 1H, H_4), 1.78 – 1.73 (m, 1H, H_{7a}), 1.70 – 1.58 (m, 2H, H_{1a}, H_{2a}), 1.56 – 1.40 (m, 6H, H_{1b}, H_{2b}, H_{7b}, H_{19}), 1.29 – 1.22 (m, 3H, H_{15}), 1.08 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 201.3 (CH), 118.9 (C), 78.6 (C), 77.4 (C), 74.5 (CH), 64.6 (CH_2), 62.8 (CH_2), 60.8 (CH), 57.6 (CH_2), 50.5 (C), 48.5 (C), 46.6 (CH_2), 45.8 (CH), 36.5 (CH_2), 35.8 (CH_2), 25.1 (CH_2), 16.6 (CH_3), 16.4 (CH_3), 3.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2922.0 (w), 2359.7 (s), 2341.1 (m), 1716.8 (w), 1028.9 (w), 772.5 (w). HRMS-ESI (m/z): calcd for $[C_{19}H_{29}O_4]^+$ 321.2066; found 321.2060. $[\alpha]_D^{20}$ = –4.89 (c = 0.185, $CHCl_3$)

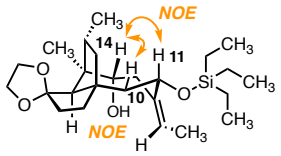
*Synthesis of the allylic silyl ether **48**.*



47 **48**

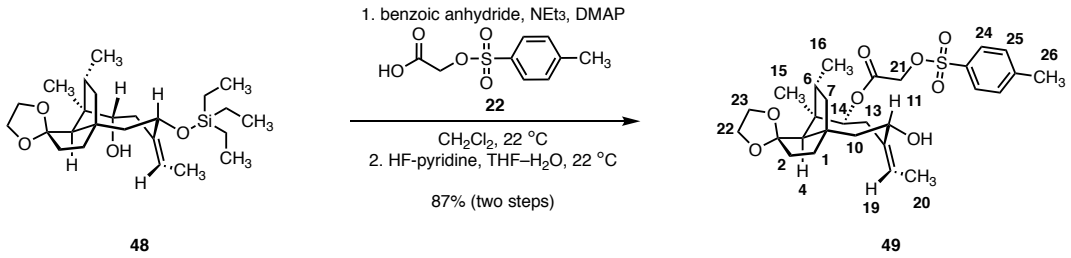
A solution of bis(cyclooctadiene)nickel(0) (23.5 mg, 85.5 μmol, 0.20 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 33.2 mg, 85.5 μmol, 0.20 equiv) in tetrahydrofuran (1.0 mL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. The resulting mixture was added to a solution of triethylsilane (35.0 mg, 301 μmol, 3.00 equiv) and the alkynyl aldehyde **47** (274 mg, 428 μmol, 1 equiv) in tetrahydrofuran (14 mL) at 22 °C in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 65 °C. The reaction mixture was stirred at 3 h at 65 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was eluted over a short pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the allylic silyl ether **48** as a clear oil (130 mg, 70%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the allylic ether **48** was formed as a single diastereomer. NOE correlations between H11 and H14, and H10 and H14, support the configuration of the C11 and C14 centers, respectively, as that shown.



R_f = 0.61 (33% ether–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6, 77 °C) δ 6.04 (q, J = 7.1 Hz, 1H, H_{19}), 4.45 (dd, J = 10.6, 4.6 Hz, 1H, H_{14}), 3.85 (d, J = 8.7 Hz, 1H, H_{11}), 3.55 (dq, J = 18.3, 6.6, 2H, H_{21a}, H_{22a}), 3.43 (dq, J = 12.6, 6.8, 2H, H_{21b}, H_{22b}), 2.91 (dd, J = 15.7, 8.8 Hz, 1H, H_{10a}), 2.63 (s, 1H, H_4), 2.46 (dq, J = 13.3, 7.3 Hz, 1H, H_6), 2.17 (dd, J = 13.2, 4.7 Hz, 1H, H_{13a}), 2.08 (d, J = 15.6 Hz, 1H, H_{10b}), 1.85 (dd, J = 13.2, 10.4 Hz, 1H, H_{13b}), 1.77 – 1.47 (m, 9H, H_1, H_2, H_7, H_{20}), 1.30 (s, 3H, H_{15}), 1.08 – 0.99 (m, 9H, H_{25}), 0.95 (d, J = 7.1 Hz, 3H, H_{16}), 0.64 (q, J = 7.6 Hz, 6H, H_{24}). ^{13}C NMR (150 MHz, C_6D_6) δ 120.3 (C), 63.6 (CH_2), 63.4 (CH_2), 55.4 (CH), 53.9 (CH_2), 51.3 (C), 47.0 (C), 45.6 (CH_2), 43.0 (C), 42.4 (CH_2), 36.1 (CH_2), 35.9 (CH_2), 14.0 (CH_3), 13.5 (CH_3), 7.3 (3 × CH_3), 5.3 (3 × CH_2). IR (AT-FTIR), cm^{-1}: 2954 (m), 2875 (m), 2358 (w), 1040 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{25}H_{45}O_4Si]^+$ 437.3087; found 437.3082. $[\alpha]_D^{20}$ = –862.9 (c = 0.265, $CHCl_3$). Note: Owing to conformational equilibria of the eight-membered ring, extensive line broadening was observed in the ^{13}C NMR spectrum of **48** and the ^{13}C shifts of C6, C11, C14, C19, and C21 could not be resolved.

*Synthesis of the sulfonate **49**.*



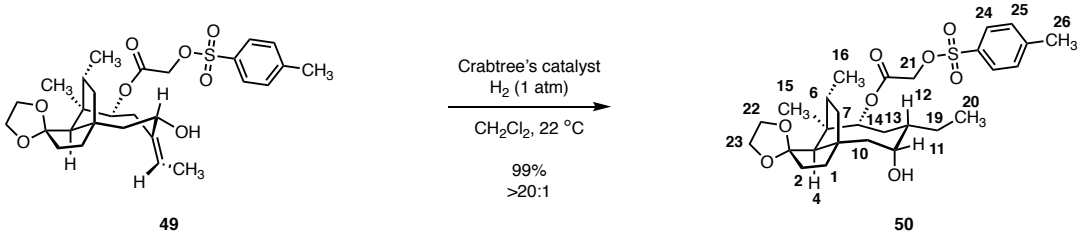
(4-Dimethylamino)pyridine (400 µg, 3.40 µmol, 0.10 equiv) was added to a solution of the sulfonate **22** (39.5 mg, 172 µmol, 5.00 equiv), benzoic anhydride (38.9 mg, 172 µmol, 5.00 equiv), triethylamine (33.0 µL, 240 µmol, 7.00 equiv), and the allylic ether **48** [20.0 mg, 34.3 µmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (270 µL) at 22 ˚C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (4.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used in directly in the following step.

Hydrogen fluoride–pyridine complex (12.0 µL, 68.6 µmol, 2.00 equiv) was added to a solution of the unpurified product obtained in the proceeding step (nominally 34.3 µmol, 1 equiv) in 2:1 tetrahydrofuran–water (v/v, 690 µL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the sulfonate **49** as a white foam (16.0 mg, 87% over two steps).

R_f = 0.35 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6, 77 °C) δ 7.81 (d, J = 8.3 Hz, 2H, H_{24}), 6.65 (d, J = 8.0 Hz, 2H, H_{25}), 5.77 (q, J = 7.0 Hz, 1H, H_{19}), 5.35 (dd, J = 10.0, 2.2 Hz, 1H, H_{14}), 4.39 (s, 2H, H_{21}), 4.30 (d, J = 10.4 Hz, 1H, H_{11}), 3.56 – 3.46 (m, 2H, $H_{22\ or\ 23}$), 3.40 – 3.29 (m, 2H, $H_{22\ or\ 23}$), 2.84 (dd, J = 16.2, 10.2 Hz, 1H, H_{13a}), 2.59 (s, 1H, H_4), 2.46 (q, J = 8.7 Hz, 1H, H_6), 2.07 (dd, J = 12.9, 4.2 Hz, 1H, H_{10a}), 1.97 (d, J = 16.2 Hz, 1H, H_{13b}), 1.78 (s, 3H, H_{26}), 1.59 – 1.50 (m, 2H, H_{1a}, H_{10b}), 1.47 – 1.36 (m, 8H, H_{1b}, H_2, H_7, H_{20}), 1.33 (s, 3H, H_{15}), 0.79 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 165.5 (C), 144.2 (C), 141.5 (C), 133.6 (C), 129.4 (2 × CH), 128.0 (2 × CH), 119.5 (C), 119.0 (CH), 75.3 (CH), 69.6 (CH), 64.6 (CH_2), 63.3 (CH_2), 62.9 (CH_2), 54.7 (CH), 51.5 (CH_2), 49.7 (C), 45.8 (C), 45.3 (CH_2), 41.8 (CH), 41.4 (CH_2), 35.3 (CH_2), 32.6 (CH_2), 20.7 (CH_3), 13.1 (CH_3), 12.7 (CH_3). IR (AT-FTIR), cm^{-1}: 2935 (w), 2877

(w), 1757 (w), 1372 (m), 1190 (m), 1177 (s), 1033 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{39}O_8S]^+$ 535.2366; found 535.2360. $[a]_D^{20} = -47.3$ (c = 0.119, $CHCl_3$). Note: Owing to the conformational equilibria of the eight-membered ring, extensive line broadening was observed in the ^{13}C NMR spectrum of **49** and the ^{13}C shift of C15 could not be resolved.

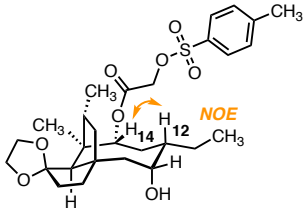
*Synthesis of the reduction product **50**.*



49 **50**

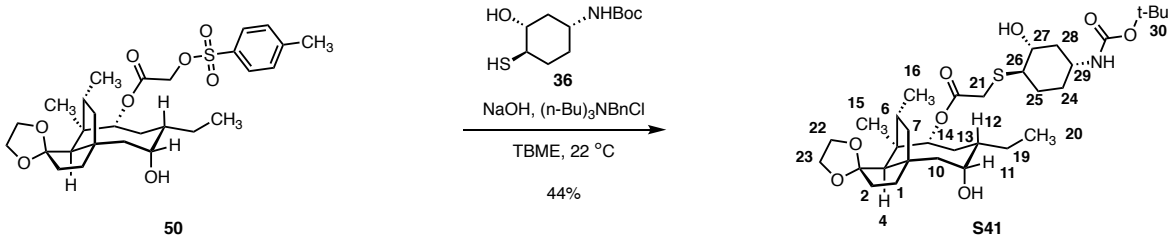
Crabtree's catalyst (600 μg, 750 nmol, 5.0 mol%) was added to a solution of the alkene **49** [8.00 mg, 15.0 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (750 μL) at 22 °C. The reaction vessel was purged with dihydrogen and placed under a balloon of dihydrogen. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the reduction product **50** as a clear oil (8.00 mg, 99%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), the reduction product **50** was formed as a single diastereomer. The relative stereochemistry of the ethyl substituent was determined by NOE correlations between H14 and H12.



R_f = 0.36 (40% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6, 77 °C) δ 7.77 (d, J = 8.0 Hz, 2H, H_{24}), 6.74 (d, J = 7.9 Hz, 2H, H_{25}), 5.08 (d, J = 8.5 Hz, 1H, H_{14}), 4.39 (q, J = 15.6 Hz, 2H, H_{21}), 3.98 (d, J = 9.8 Hz, 1H, H_{11}), 3.57 (p, J = 6.4, 5.0 Hz, 2H, $H_{22\text{ or }23}$), 3.46 (p, J = 7.8, 6.9 Hz, 2H, $H_{22\text{ or }23}$), 2.59 (s, 1H, H_4), 2.51 (s, 1H, H_6), 2.05 – 1.76 (m, 6H, H_{10a}, H_{12}, H_{13a}, H_{26}), 1.75 – 1.48 (m, 8H, H_1, H_2, H_7, H_{10b}, H_{13b}), 1.32 (s, 4H, H_{15}, H_{19a}), 1.17 (s, 1H, H_{19b}), 0.85 – 0.77 (m, 6H, H_{16}, H_{20}). ^{13}C NMR (150 MHz, C_6D_6) δ 165.5 (C), 144.1 (C), 133.7 (C), 129.4 (2 × CH), 127.9 (2 × CH), 120.1 (C), 74.7 (CH), 69.3 (CH), 64.6 (CH_2), 63.4 (CH_2), 62.9 (CH_2), 56.8 (CH), 49.1 (C), 47.4 (CH), 45.2 (C), 43.8 (CH), 41.7 (CH_2), 41.4 (CH), 35.7 (CH_2), 35.7 (CH_2), 34.4 (CH_2), 29.8 (CH_2), 23.6 (broad, CH_2), 20.7 (CH_3), 13.4 (CH_3), 11.2 (CH_3). IR (AT-FTIR), cm^{-1}: 2931 (w), 2876 (w), 2360 (m), 2340 (m), 1756 (w), 1371 (w), 1177 (s), 1042 (m). HRMS-ESI (m/z): [M + Na]$^+$ calcd for $[C_{28}H_{40}NaO_8S]^+$ 559.2342; found $[a]_D^{20}$ = +0.23 (c = 0.088, $CHCl_3$).

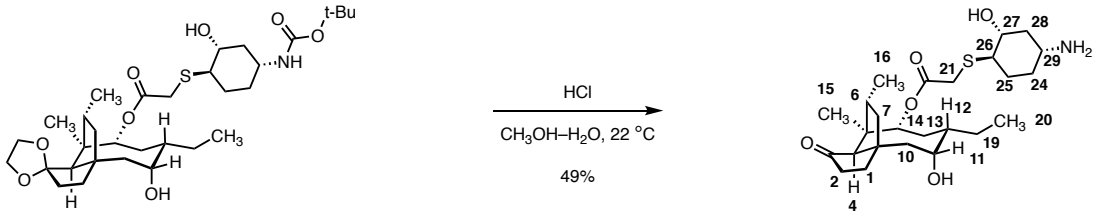
*Synthesis of the sulfide **S41**.*



Aqueous sodium hydroxide solution (1.0 M, 5.00 µL, 4.80 µmol, 1.30 equiv) was added to a solution of the thiol **36** (2.40 mg, 4.80 µmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (230 µg, 0.75 µmol, 0.20 equiv), and the sulfonate **50** (2.00 mg, 3.70 µmol, 1 equiv) in *tert*-butyl methyl ether (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), 0.1 N aqueous phosphoric acid solution (1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the displacement product **S41** as a white foam (1.00 mg, 44%).

R_f = 0.21 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, C_6D_6, 77 °C) δ 5.11 (d, J = 8.5 Hz, 1H, H_{14}), 4.07 – 3.99 (m, 2H, NH, H_{11}), 3.65 – 3.55 (m, 2H, $H_{22\text{ or }23}$), 3.52 – 3.37 (m, 3H, $H_{22\text{ or }23}$, H_{29}), 3.22 (s, 1H, H_{27}), 3.15 (d, J = 15.0 Hz, 1H, H_{21a}), 3.04 (d, J = 14.9 Hz, 1H, H_{21b}), 2.85 (s, 1H, OH), 2.67 (s, 1H, H_4), 2.56 (s, 1H, H_6), 2.35 (td, J = 11.0, 9.4, 3.9 Hz, 1H, H_{26}), 2.20 (dd, J = 12.4, 2.4 Hz, 1H, H_{28a}), 1.95 (dd, J = 14.7, 9.9 Hz, 2H, H_{12}, H_{13a}), 1.83 (dd, J = 13.7, 4.0 Hz, 1H, H_{25a}), 1.79 – 1.54 (m, 12H, H_1, H_2, H_7, H_{10}, H_{13b}, H_{19}, H_{24a}), 1.45 (s, 9H, H_{30}), 1.38 (s, 3H, H_{15}), 1.19 – 1.08 (m, 1H, H_{24b}), 0.98 (q, J = 11.5 Hz, 1H, H_{28b}), 0.93 – 0.84 (m, 6H, H_{16}, H_{20}), 0.76 (t, J = 12.1 Hz, 1H, H_{25b}). ^{13}C NMR (150 MHz, C_6D_6) δ 170.7 (C), 154.5 (C), 120.2 (C), 78.2 (C), 74.7 (CH), 71.6 (CH), 71.6 (CH), 63.4 (CH_2), 62.9 (CH_2), 56.9 (CH), 52.4 (CH), 49.0 (C), 47.5 (CH_2), 47.3 (CH), 45.3 (C), 44.0 (CH), 41.8 (CH_2), 41.6 (CH), 40.3 (CH_2), 35.7 (CH_2), 34.6 (CH_2), 32.5 (CH_2), 32.5 (CH_2), 29.8 (CH_2), 28.8 (CH_2), 28.1 (3 × CH_3), 23.7 (CH_2), 13.7 (CH_3), 12.6 (CH_3), 11.3 (CH_3). IR (AT-FTIR), cm^{-1}: 2935 (w), 1696 (w), 1288 (w), 1172 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{32}H_{53}NNaO_8S]^+$ 634.3390; found 634.3378. $[a]_D^{20}$ = –7.74 (c = 0.031, $CHCl_3$).

*Synthesis of the lefamulin derivative **51**.*

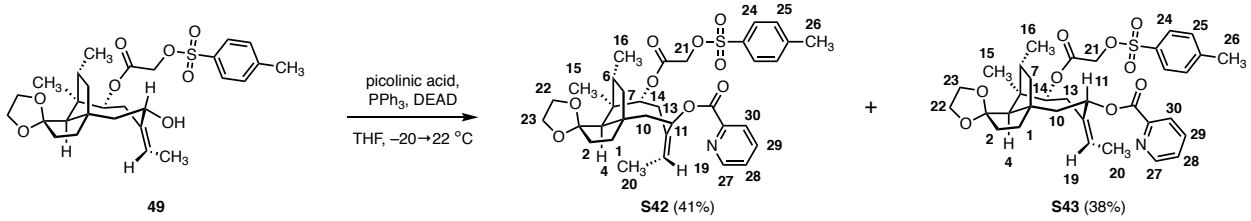


S41 **51**

Aqueous hydrochloric acid solution (12 N, 1.50 µL, 19.5 µmol, 15.0 equiv) was added to a solution of the sulfide **S41** (800 µg, 1.30 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the lefamulin derivative **51** as a fine, white solid (300 µg, 49%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 4.11 (d, J = 9.7 Hz, 1H, H_{11}), 3.61 – 3.48 (m, 3H, H_{21a}, H_{27}, NH), 3.35 – 3.30 (m, 1H, H_{21b}), 3.20 (s, 1H, H_{29}), 2.91 (s, 1H, H_4), 2.70 (s, 1H, H_{26}), 2.49 (s, 1H, OH), 2.26 (qd, J = 11.1, 10.2, 7.0 Hz, 2H, H_{2a}, H_{28a}), 2.16 (td, J = 18.3, 16.9, 6.5 Hz, 3H, H_{2b}, H_{24a}, H_{25a}), 2.02 (s, 1H, H_{24b}), 1.91 (dd, J = 29.7, 10.8 Hz, 2H, H_{1a}, H_{13a}), 1.73 (d, J = 15.4 Hz, 1H, H_{10a}), 1.70 – 1.62 (m, 2H, H_{10b}, H_{12}), 1.62 – 1.38 (m, 7H, H_{1b}, H_6, H_7, H_{19a}, H_{24b}, H_{25b}), 1.37 – 1.17 (m, 6H, H_{13b}, H_{19b}, H_{15}, H_{28a}), 0.90 (t, J = 7.4 Hz, 3H, H_{20}), 0.80 (d, J = 6.6 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 222.8 (C), 171.0 (C), 75.7 (broad, CH), 71.8 (CH), 70.7 (CH), 60.8 (CH), 52.7 (C), 49.7 (CH), 48.7 (CH_2), 47.7 (CH), 45.8 (C), 45.1 (CH), 45.1 (CH), 38.8 (CH_2), 38.1 (CH_2), 38.1 (CH_2), 35.0 (CH_2), 33.2 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 27.6 (CH_2), 26.1 (CH_2), 13.8 (CH_3), 12.1 (CH_3), 11.3 (CH_3). IR (AT-FTIR), cm^{-1}: 3015 (w), 2359 (w), 2341 (w), 1412 (w), 1139 (s), 944 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{25}H_{42}NO_5S]^+$ 468.2784; found 468.2774. $[a]_D^{20}$ = +278.7 (c = 0.015, CH_3OH).

*Synthesis of the esters **S42** and **S43**.*



A solution of diethyl azodicarboxylate in tetrahydrofuran (1.0 M, 185 µL, 1.50 equiv) was added dropwise over 1 min to a solution of picolinic acid (22.8 mg, 185 µmol, 1.50 equiv), triphenylphosphine (32.2 mg, 185 µmol, 1.50 equiv) and the allylic alcohol **49** [66.0 mg, 123 µmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)], in tetrahydrofuran (820 µL) at –20 °C. The reaction mixture was stirred for 5 h at –20 °C. The reaction vessel was removed from the cooling bath and allowed to warm to 22 °C over 20 min. The reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, three steps) to provide separately the ester **S42** (white solid, 32.6 mg, 41%) and the ester **S43** (white solid, 30.0 mg, 38%).

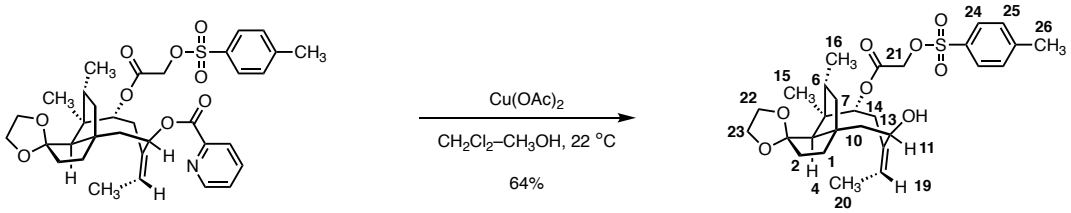
^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 1.1:1 mixture of C11 diastereomers. The relative stereochemistry of the C11 alcohol of **S42** was determined by NOE analysis of the allylic alcohol **52**.

S42: R_f = 0.65 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (600 MHz, C_6D_6) δ 8.43 (d, J = 3.8 Hz, 1H, H_{27}), 8.05 (d, J = 7.8 Hz, 1H, H_{30}), 7.80 (d, J = 8.3 Hz, 2H, H_{24}), 6.98 (td, J = 7.7, 1.8 Hz, 1H, H_{29}), 6.66 (d, J = 8.0 Hz, 2H, H_{25}), 6.58 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H, H_{28}), 5.99 (dd, J = 5.0, 3.1 Hz, 1H, H_{11}), 5.61 (q, J = 6.9 Hz, 1H, H_{19}), 5.51 (dd, J = 6.7, 2.4 Hz, 1H, H_{14}), 4.53 – 4.42 (m, 2H, H_{21}), 3.65 – 3.53 (m, 2H, $H_{22\text{ or }23}$), 3.46 – 3.37 (m, 2H, $H_{22\text{ or }23}$), 2.91 – 2.67 (m, 2H, H_4, H_{13a}), 2.44 – 2.34 (m, 1H, H_6), 2.17 (dd, J = 15.3, 3.2 Hz, 1H, H_{10a}), 2.11 – 2.01 (m, 1H, H_{10b}), 1.80 (s, 3H, H_{26}), 1.70 – 1.43 (m, 5H, H_1, H_2, H_{13b}), 1.41 – 1.14 (m, 8H, H_7, H_{15}, H_{20}), 0.99 (d, J = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 165.2 (C), 164.0 (C), 149.5 (CH), 149.3 (C), 144.1 (C), 132.9 (C), 129.4 (2 × CH), 128.4 (broad, CH), 128.1 (2 × CH), 128.1 (CH), 125.8 (CH), 124.6 (CH), 119.6 (C), 81.3 (CH), 80.1 (CH), 64.6 (CH_2), 63.4 (CH_2), 63.1 (CH_2), 56.0 (CH), 50.3 (C), 47.8 (C), 46.7 (CH_2), 44.6 (CH_2), 43.8 (CH), 42.1 (CH_2), 35.6 (CH_2), 29.8 (CH_2), 20.7 (CH_3), 19.7 (broad, CH_3), 13.8 (CH_3), 12.6 (CH_3). IR (AT-FTIR), cm^{-1}: 3733 (w), 3628 (w), 2360 (s), 2340 (m), 1733 (w), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{34}H_{41}NNaO_9S]^+$ 662.2400; found 662.2388. $[\alpha]_D^{20}$ = –6.98 (c = 0.063, $CHCl_3$).

S43: R_f = 0.60 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (500 MHz, C_6D_6, 77 °C) δ 8.45 – 8.41 (m, 1H, H_{27}), 7.89 (dd, J = 8.1, 6.4 Hz, 3H, H_{24}, H_{30}), 7.04 (td, J = 7.7, 1.7 Hz, 1H, H_{29}), 6.77 (d,

J = 8.1 Hz, 2H, H_{25}), 6.67 (dd, J = 7.7, 4.7 Hz, 1H, H_{28}), 5.97 (d, J = 7.8 Hz, 1H, H_{11}), 5.45 (q, J = 6.5 Hz, 1H, H_{19}), 5.21 (d, J = 7.7 Hz, 1H, H_{14}), 5.05 (d, J = 15.7 Hz, 1H, H_{21a}), 4.75 (d, J = 15.6 Hz, 1H, H_{21b}), 3.58 – 3.50 (m, 2H, $H_{22\ or\ 23}$), 3.44 – 3.37 (m, 2H, $H_{22\ or\ 23}$), 2.80 (s, 1H, H_4), 2.63 (dd, J = 16.2, 7.8 Hz, 1H, H_{13a}), 2.48 – 2.36 (m, 2H, H_6, H_{13b}), 2.25 (d, J = 18.1 Hz, 1H, H_{10a}), 2.08 (dd, J = 18.1, 7.9 Hz, 1H, H_{10b}), 1.87 (s, 3H, H_{26}), 1.70 – 1.28 (m, 6H, H_1, H_2, H_7), 1.26 (d, J = 6.5 Hz, 3H, H_{20}), 1.23 (s, 3H, H_{15}), 0.78 (d, J = 7.4 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 166.2 (C), 164.3 (C), 149.3 (CH), 149.0 (C), 143.8 (C), 135.9 (CH), 133.9 (C), 132.8 (C), 129.3 (2 × CH), 128.3 (2 × CH; detected by HSQC), 127.2 (CH), 125.9 (CH), 124.8 (CH), 119.5 (C), 78.4 (CH), 77.0 (CH), 64.9 (CH_2), 63.4 (CH_2), 62.9 (CH_2), 53.9 (CH), 49.9 (C), 49.1 (CH_2), 47.4 (C), 43.0 (CH), 42.9 (CH_2), 42.2 (CH_2), 35.5 (CH_2), 30.6 (CH_2), 20.8 (CH_3), 19.8 (CH_3), 19.8 (CH_3), 11.5 (CH_3). IR (AT-FTIR), cm^{-1}: 2362 (s), 2341 (m), 773 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{34}H_{41}NNaO_9S]^+$ 662.2400; found 662.2390. $[a]_D^{20}$ = –62.4 (c = 0.050, $CHCl_3$).

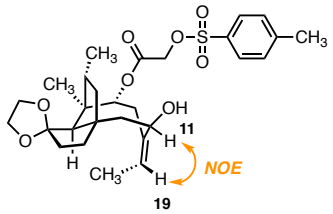
Synthesis of the allylic alcohol ***52****.*



S42 **52**

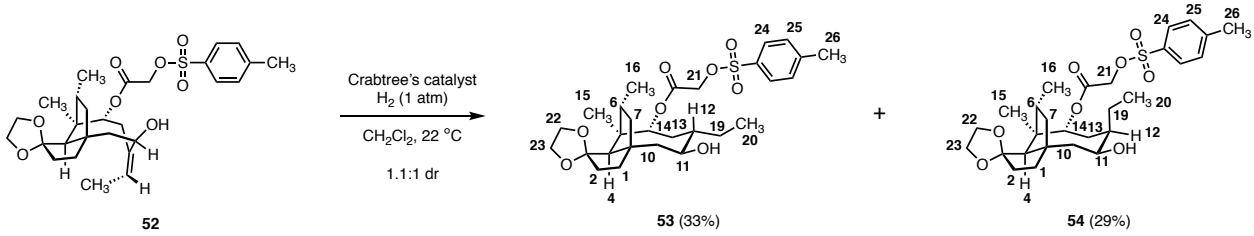
Copper acetate (4.50 mg, 25.0 µmol, 0.50 equiv) was added to a solution of methanol (20.0 µL, 500 µmol, 10.0 equiv) and the picolinic ester **S42** (32.0 mg, 50.0 µmol, 1 equiv) in dichloromethane (500 µL) at 22 °C. The reaction mixture was placed in an oil bath that had been preheated to 30 °C. The reaction mixture was stirred for 4 h at 30 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted with dichloromethane (1.0 mL) and 0.1 N aqueous ethylenediaminetetraacetic acid solution (1.0 mL). The resulting biphasic mixture was stirred for 10 min at 22 °C. The stirred biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, three steps) to provide the allylic alcohol **52** as a colorless foam (17.0 mg, 64%).

The relative stereochemistry of the (11*S*) alcohol was determined by NOE correlations between H11 and H19 and further supported by comparison to the (11*R*) diastereomer **49**.



R_f = 0.62 (60% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, C_6D_6) δ 7.77 (d, J = 8.3 Hz, 2H, H_{24}), 6.66 (d, J = 8.0 Hz, 2H, H_{25}), 5.68 (dd, J = 7.3, 6.2 Hz, 1H, H_{14}), 5.24 (q, J = 6.9 Hz, 1H, H_{19}), 4.49 (d, J = 1.5 Hz, 2H, H_{21}), 4.17 (dt, J = 5.4, 2.7 Hz, 1H, H_{11}), 3.57 (dd, J = 6.1, 3.9 Hz, 2H, $H_{22\text{ or }23}$), 3.47 – 3.38 (m, 2H, $H_{22\text{ or }23}$), 2.69 – 2.63 (m, 2H, H_4, H_{13a}), 2.40 – 2.29 (m, 1H, H_6), 1.96 (dd, J = 14.7, 2.7 Hz, 1H, H_{10a}), 1.88 – 1.82 (m, 1H, H_{10b}), 1.79 (s, 3H, H_{26}), 1.69 – 1.44 (m, 7H, H_1, H_2, H_7, H_{13b}), 1.32 (d, J = 6.9 Hz, 3H, H_{20}), 1.27 (s, 3H, H_{15}), 0.88 (d, J = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, C_6D_6) δ 165.5 (C), 144.1 (C), 137.0 (C), 133.6 (C), 129.4 (2 × CH), 127.2 (2 × CH), 125.2 (CH), 119.7 (C), 79.6 (CH), 79.3 (CH), 64.6 (CH_2), 63.4 (CH_2), 63.0 (CH_2), 55.9 (CH), 50.1 (C), 48.4 (CH_2), 48.0 (C), 44.9 (CH_2), 43.8 (CH_2), 42.3 (CH_2), 35.6 (CH), 29.8 (CH_2), 20.7 (CH_3), 18.6 (broad, CH_3), 13.8 (CH_3), 12.7 (CH_3). IR (AT-FTIR), cm^{-1}: 2916 (s), 2849 (m), 2362 (m), 2338 (m), 1732 (w), 1040 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{38}NaO_8S]^+$ 557.2185; found 557.2177. $[a]_D^{20}$ = –948.4 (c = 0.031, $CHCl_3$).

*Synthesis of the reduction products **53** and **54**.*

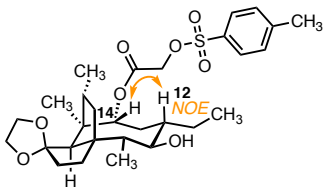


Crabtree's catalyst (600 μg, 0.75 μmol, 0.05 equiv) was added to a solution of the alkene **52** [8.00 mg, 15.0 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (750 μL) at 22 °C. The reaction vessel was purged with dihydrogen and placed under a balloon of dihydrogen. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 75% ethyl acetate–hexanes) to provide separately the (12*S*) reduction product **53** (clear oil, 2.20 mg, 33%) and the (12*R*) reduction product **54** (clear oil, 2.00 mg, 29%)

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated the presence of a 1:1 mixture of C12 diastereomers.

53: R_f = 0.53 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H, H_{24}), 7.35 (d, *J* = 8.0 Hz, 2H, H_{25}), 5.00 (d, *J* = 8.0 Hz, 1H, H_{14}), 4.55 (s, 2H, H_{21}), 3.85 (dddd, *J* = 44.4, 24.7, 12.7, 6.2 Hz, 4H, H_{22}, H_{23}), 3.45 (t, *J* = 9.9 Hz, 1H, H_{11}), 2.45 (s, 3H, H_{26}), 2.25 – 2.13 (m, 2H, H_6, H_{10a}), 1.97 (dd, *J* = 14.0, 9.9 Hz, 1H, H_{13a}), 1.89 – 1.81 (m, 3H, H_4, H_{7a}, H_{10b}), 1.76 – 1.47 (m, 6H, H_1, H_2, H_{12}, H_{19a}), 1.42 – 1.28 (m, 3H, H_{7b}, H_{13b}, H_{19b}), 1.14 (s, 3H, H_{15}), 0.88 (t, *J* = 7.5 Hz, 3H, H_{20}), 0.70 (d, *J* = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9 (C), 145.4 (C), 132.8 (C), 130.1 (2 × CH), 128.3 (2 × CH), 120.5 (C), 76.4 (CH), 72.0 (CH), 65.1 (CH_2), 64.5 (CH_2), 63.4 (CH_2), 58.9 (CH), 54.0 (CH_2), 51.4 (CH_2), 51.3 (C), 47.6 (CH), 47.1 (C), 42.2 (CH), 39.0 (CH_2), 37.1 (CH_2), 36.1 (CH_2), 25.9 (CH_2), 21.8 (CH_3), 14.7 (CH_3), 11.4 (CH_3), 10.9 (CH_3). IR (AT-FTIR), cm^{-1}: 2957 (w), 2361 (m), 2340 (m), 1756 (s), 1040 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{40}NaO_8S]^+$ 559.2342; found 559.2332. $[a]_D^{20}$ = –19.4 (*c* = 0.063, $CHCl_3$).

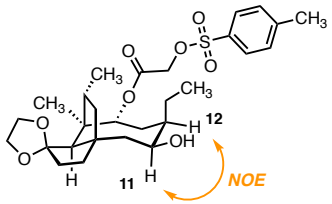
The relative stereochemistry of (12*S*) diastereomer **53** is supported by an NOE correlation between H12 and H14.



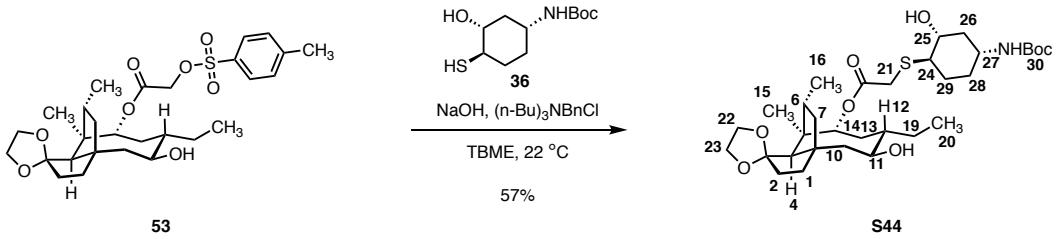
54: R_f = 0.65 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (600 MHz, C_6D_6) δ 7.86 (d, *J* = 8.0 Hz, 2H, H_{24}), 6.68 (d, *J* = 8.0 Hz, 2H, H_{25}), 5.19 (d, *J* = 6.6 Hz, 1H, H_{14}), 4.98 – 4.34 (m, 2H, H_{21}), 3.64 (q, *J* = 6.6, 6.2 Hz, 1H, $H_{22a\ or\ 23a}$), 3.54 (q, *J* = 7.1, 6.5 Hz, 1H, $H_{22a\ or\ 23a}$), 3.51 (s, 1H, H_{11}), 3.50 – 3.40 (m, 2H, H_{22b}, H_{23b}), 2.69 (s, 1H, H_4), 2.59 – 2.46 (m, 2H, H_{7a}, H_{13a}), 2.43 – 2.32 (m,

1H, H_6), 1.80 (s, 4H, H_{10a}, H_{26}), 1.75 – 1.43 (m, 7H, H_1, H_2, H_{7b}, H_{10b}, H_{12}, H_{13b}), 1.24 (s, 3H, H_{15}), 1.08 (ddd, J = 13.3, 9.3, 7.0 Hz, 1H, H_{19a}), 1.04 – 0.95 (m, 1H, H_{19b}), 0.87 (d, J = 7.2 Hz, 3H, H_{16}), 0.66 (t, J = 7.3 Hz, 3H, H_{20}). ^{13}C NMR (150 MHz, C_6D_6) δ 165.2 (C), 144.0 (C), 133.7 (C), 129.4 (2 × CH), 128.2 (2 × CH), 119.9 (C), 81.2 (CH), 74.9 (CH), 64.5 (CH_2), 63.3 (CH_2), 63.2 (CH_2), 56.7 (CH), 49.5 (C), 49.0 (CH_2), 48.3 (C), 44.4 (CH_2), 41.4 (CH), 43.6 (CH_2), 35.9 (CH_2), 35.5 (CH), 31.9 (CH_2), 28.0 (CH_2), 21.2 (CH_3), 20.7 (CH_3), 12.0 (CH_3), 11.7 (CH_3). IR (AT-FTIR), cm^{-1}: 2955 (w), 2360 (s), 2340 (m), 1757 (s), 1177 (m), 1040 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{40}NaO_8S]^+$ 559.2342; found 559.2340. $[a]_D^{20}$ = –27.9 (c = 0.094, $CHCl_3$).

The relative stereochemistry of (12*R*) diastereomer **54** is supported by an NOE correlation between H11 and H12.



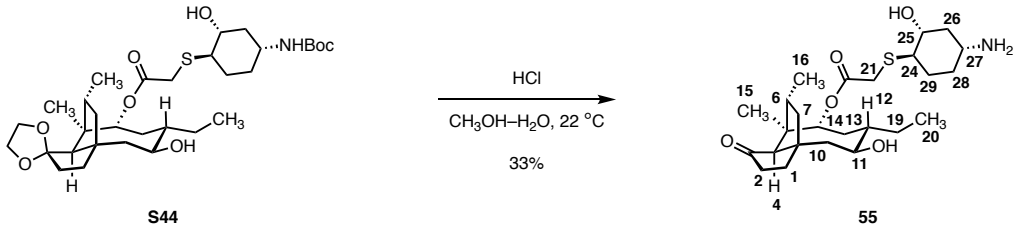
*Synthesis of the sulfide **S44**.*



Aqueous sodium hydroxide solution (1 N, 4.70 µL, 4.70 µmol, 1.30 equiv) was added to a solution of the thiol **36** (1.50 mg, 4.70 µmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (177 µg, 570 nmol, 0.20 equiv), and the sulfonate **53** (1.50 mg, 2.80 µmol, 1 equiv) in *tert*-butyl methyl ether (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), aqueous phosphoric acid solution (10 mM, 1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the displacement product **S44** as a white solid (1.00 mg, 57%).

R_f = 0.53 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (d, J = 7.9 Hz, 1H, H_{14}), 4.45 (s, 1H, NH), 3.98 – 3.76 (m, 4H, H_{22}, H_{23}), 3.60 – 3.33 (m, 4H, H_{11}, H_{21a}, H_{25}, H_{27}), 3.26 (d, J = 15.6 Hz, 1H, H_{21b}), 2.54 – 2.43 (m, 1H, H_{24}), 2.36 (d, J = 12.3 Hz, 1H, H_{26a}), 2.25 – 2.14 (m, 2H, H_6, H_{10a}), 2.11 – 1.95 (m, 3H, H_{7a}, H_{28a}, H_{29a}), 1.95 – 1.83 (m, 3H, H_4, H_{10b}, H_{13a}), 1.81 – 1.57 (m, 7H, H_1, H_2, H_{12}, H_{13b}, H_{19a}), 1.44 (s, 10H, H_{7b}, H_{30}), 1.38 – 1.06 (m, 7H, H_{15}, H_{19b}, H_{26b}, H_{28b}, H_{29b}), 0.91 (t, J = 7.5 Hz, 3H, H_{20}), 0.77 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 155.2 (C), 120.5 (C), 79.7 (broad, C), 76.1 (CH), 72.2 (CH), 71.7 (CH), 64.5 (CH_2), 63.4 (CH_2), 59.0 (CH), 54.1 (CH_2), 53.0 (CH), 51.5 (C), 51.3 (CH_2), 47.8 (CH), 47.8 (CH), 47.2 (C), 42.3 (CH), 40.7 (CH_2), 39.0 (CH_2), 37.1 (CH_2), 36.2 (CH_2), 33.2 (CH_2), 33.1 (CH_2), 29.6 (CH_2), 28.5 (3 × CH_3), 26.0 (CH_2), 15.0 (CH_3), 11.6 (CH_3), 11.1 (CH_3). IR (AT-FTIR), cm^{-1}: 3357 (w), 2926 (s), 2856 (w), 2361 (s), 2341 (m), 1686 (m), 1170 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{32}H_{53}NNaO_8S]^+$ 634.3390; found 634.3379. $[a]_D^{20}$ = –7.23 (c = 0.047, $CHCl_3$).

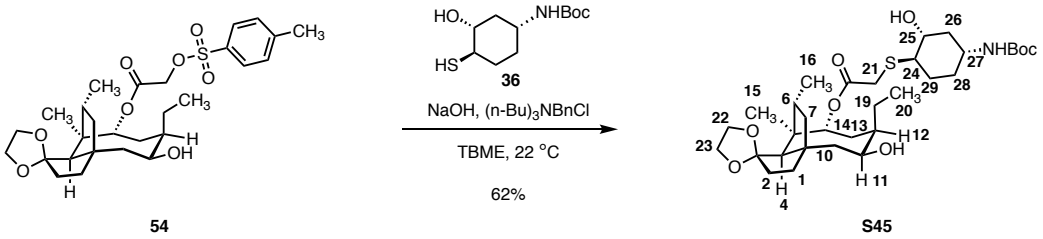
*Synthesis of the lefamulin derivative **55**.*



12 N concentrated hydrochloric acid solution (2.00 µL, 24.0 µmol, 15.0 equiv) was added to a solution of the ester **S44** (1.00 mg, 1.60 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the lefamulin derivative **55** as a fine white solid (260 µg, 33%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 4.98 (dd, J = 7.7, 2.0 Hz, 1H, H_{14}), 3.59 – 3.52 (m, 2H, H_{21a}, H_{25}), 3.44 – 3.34 (m, 2H, H_{11}, H_{21b}), 3.23 – 3.18 (m, 1H, H_{27}), 2.71 (s, 1H, H_{24}), 2.39 – 2.14 (m, 6H, H_2, H_{7a}, H_{10a}, H_{26a}, H_{29a}), 2.09 – 1.77 (m, 8H, H_1, H_4, H_{10b}, H_{13}, H_{19a}, H_{28a}), 1.69 – 1.28 (m, 7H, H_6, H_{7b}, H_{12}, H_{19b}, H_{26b}, H_{28b}, H_{29b}), 1.25 (s, 3H, H_{15}), 0.89 (td, J = 7.5, 1.7 Hz, 3H, H_{20}), 0.83 (d, J = 6.7 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 222.7 (C), 172.3 (C), 75.5 (CH), 73.1 (CH), 71.5 (CH), 61.4 (CH), 55.0 (CH_2), 54.5 (C), 51.5 (CH_2), 51.1 (CH), 49.6 (CH), 49.0 (CH; detected by HSQC), 46.9 (C), 46.0 (CH), 40.7 (CH_2), 39.7 (CH_2), 39.4 (CH_2), 37.4 (CH_2), 34.5 (CH_2), 30.6 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 15.4 (CH_3), 13.0 (CH_3), 11.2 (CH_3). IR (AT-FTIR), cm^{-1}: 2942 (w), 2358 (s), 2341 (m), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{25}H_{42}NO_5S]^+$ 468.2784; found 468.2775. $[a]_D^{20}$ = +458.6 (c = 0.014, $CHCl_3$).

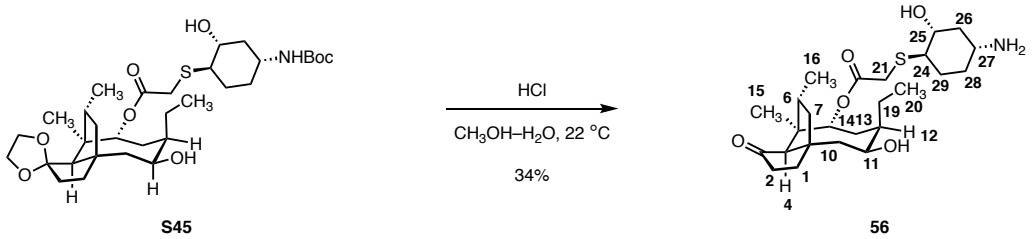
*Synthesis of the sulfide **S45**.*



Aqueous sodium hydroxide solution (1 N, 4.40 µL, 4.40 µmol, 1.66 equiv) was added to a solution of the thiol **36** (2.20 mg, 4.40 µmol, 1.66 equiv), benzyl tri-*n*-butylammonium chloride (165 µg, 530 nmol, 0.20 equiv), and the sulfonate **54** (1.40 mg, 2.70 µmol, 1 equiv) in *tert*-butyl methyl ether (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), 0.1 N aqueous phosphoric acid solution (1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the sulfide **S45** as a white solid (1.00 mg, 62%).

R_f = 0.53 (75% ethyl acetate–hexanes; PAA).^{1}H NMR (600 MHz, C_6D_6) δ 5.20 (d, J = 6.7 Hz 1H, H_{14}), 4.34 (s, 1H, NH), 3.65 – 3.54 (m, 3H, H_{11}, $H_{22a\ or\ 23a}$, H_{27}), 3.49 (p, J = 7.8, 7.3 Hz, 1H, $H_{22a\ or\ 23a}$), 3.44 – 3.33 (m, 3H, H_{22b}, H_{23b}, H_{25}), 3.27 (dd, J = 30.6, 15.4 Hz, 1H, H_{21a}), 3.13 (dd, J = 24.8, 15.3 Hz, 1H, H_{21b}), 2.74 (s, 1H, H_4), 2.57 (dt, J = 24.2, 10.2 Hz, 3H, H_{7a}, H_{24}, H_{29a}), 2.43 (dp, J = 14.9, 7.4 Hz, 1H, H_6), 2.27 – 2.20 (m, 1H, H_6), 1.91 – 1.60 (m, 8H, H_{1a}, H_{10}, H_{12}, H_{13}, H_{28a}, H_{29b}), 1.58 – 1.43 (m, 12H, H_2, H_{7b}, H_{30}), 1.38 – 1.28 (m, 4H, H_{1a}, H_{15}), 1.23 – 1.05 (m, 4H, H_{19}, H_{26b}, H_{28b}), 0.93 (d, J = 7.1 Hz, 3H, H_{16}), 0.84 (t, J = 7.4 Hz, 3H, H_{20}). ^{13}C NMR (150 MHz, C_6D_6) δ 170.2 (C), 154.6 (C), 120.0 (C), 80.7 (CH), 78.2 (C), 74.4 (CH), 71.3 (CH), 63.3 (CH_2), 62.9 (CH_2), 57.0 (CH), 51.4 (CH), 49.5 (C), 49.2 (CH_2), 48.3 (C), 47.2 (CH), 44.3 (CH_2), 44.0 (CH), 43.7 (CH_2), 39.5 (broad, CH_2), 35.7 (CH_2), 35.6 (CH), 32.1(CH_2), 32.0 (CH_2), 31.7 (broad, CH_2), 29.8 (CH_2), 28.1 (3 × CH_3), 27.7 (CH_2), 21.2 (CH_3), 12.1 (CH_3), 12.1 (CH_3). IR (AT-FTIR), cm^{-1}: 3727 (w), 2360 (s), 2340 (m), 669 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{32}H_{53}NNaO_8S]^+$ 634.3390; found 634.3375. $[a]_D^{20}$ = –12.8 (c = 0.100, $CHCl_3$).

*Synthesis of the lefamulin derivative **56**.*

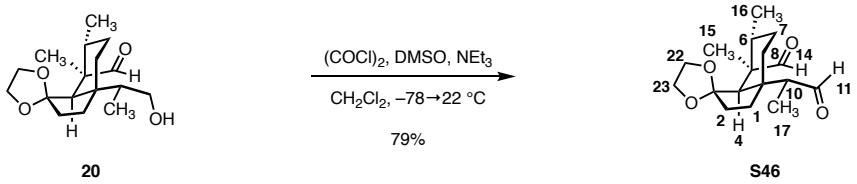


S45 56

Aqueous hydrochloric acid solution (12 N, 2.00 µL, 24.0 µmol, 15.0 equiv) was added to a solution of the thioglycolic ester **S45** (1.00 mg, 1.60 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the lefamulin derivative **56** as a fine, white solid (280 µg, 34%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA).^{1}H NMR (600 MHz, CD_3OD) δ 4.96 (d, J = 6.7 Hz, 1H, H_{14}), 3.97 (t, J = 3.6 Hz, 1H, H_{11}), 3.64 – 3.55 (m, 2H, H_{21a}, H_{25}), 3.49 (d, J = 15.5 Hz, 1H, H_{21b}), 3.24 – 3.18 (m, 1H, H_{27}), 2.97 (t, J = 13.7 Hz, 1H, H_{7a}), 2.79 (td, J = 9.9, 9.4, 3.8 Hz, 1H, H_{24}), 2.59 (s, 1H, H_4), 2.56 – 2.50 (m, 1H, H_{13a}), 2.37 (dddd, J = 16.6, 13.6, 9.5, 3.0 Hz, 1H, H_{2a}), 2.32 – 2.19 (m, 2H, H_{26a}, H_{29a}), 2.15 (dd, J = 15.6, 3.0 Hz, 2H, H_{2b}, H_{10a}), 2.09 – 1.98 (m, 3H, H_{1a}, H_6, H_{28a}), 1.89 (q, J = 7.3 Hz, 1H, H_{12}), 1.79 (ddd, J = 32.7, 14.8, 7.0 Hz, 2H, H_{7b}, H_{10b}), 1.64 – 1.42 (m, 4H, H_{1b}, H_{13b}, H_{26b}, H_{29b}), 1.42 – 1.23 (m, 3H, H_{19}, H_{28b}), 1.02 (d, J = 7.1 Hz, 3H, H_{16}), 0.94 (s, 3H, H_{15}), 0.85 (t, J = 7.4 Hz, 3H, H_{20}). ^{13}C NMR (150 MHz, CD_3OD) δ 221.2 (C), 170.6 (C), 78.0 (CH), 73.5 (CH), 71.9 (CH), 61.5 (CH), 52.5 (C), 49.5 (CH), 49.2 (CH_2), 48.1 (C), 47.8 (CH; detected by HSQC), 46.8 (CH), 45.5 (CH_2), 40.1 (CH_2), 39.3 (CH_2), 37.8 (CH_2), 36.0 (CH), 33.0 (CH_2), 31.8 (CH_2), 29.0 (CH_2), 27.9 (CH_2), 27.3 (CH_2), 22.3 (CH_3), 11.6 (CH_3), 11.3 (CH_3). IR (AT-FTIR), cm^{-1}: 3733 (w), 2360 (s), 2341 (m), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{25}H_{42}NO_5S]^+$ 468.2784; found 468.2771. $[a]_D^{20}$ = –9.47 (c = 0.019, CH_3OH).

*Synthesis of the dialdehyde **S46**.*

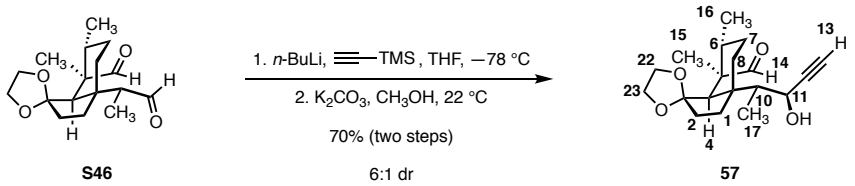


20 **S46**

Oxalyl chloride (149 μL, 1.74 mmol, 1.20 equiv) was added to a solution of dimethylsulfoxide (134 μL, 1.89 mmol, 1.30 equiv) in dichloromethane (7.3 mL) at –78 °C. The resulting solution was stirred for 15 min at –78 °C. A solution of the hydroxyaldehyde **20** [430 mg, 1.45 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (1.0 mL) was added dropwise over 5 min at –78 °C. The reaction mixture was stirred for 30 min at –78 °C. Triethylamine (605 μL, 4.35 mmol, 3.00 equiv) was then added dropwise over 2 min at –78 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 22 °C over 30 min. The product mixture was diluted sequentially with ether (10 mL) and saturated aqueous ammonium chloride solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the dialdehyde **S46** as a colorless oil (338 mg, 79%).

R_f = 0.31 (43% ether–hexanes; PAA). ^{1}H NMR (400 MHz, C_6D_6) δ 9.76 (d, J = 1.6 Hz, 1H, H_{11}), 9.40 (s, 1H, H_{14}), 3.46 – 3.34 (m, 2H, H_{22a}, H_{23a}), 3.34 – 3.24 (m, 2H, H_{22b}, H_{23b}), 2.95 (s, 1H, H_4), 2.61 (q, J = 6.7 Hz, 1H, H_{10}), 1.93 (s, 1H, H_6), 1.85 – 1.61 (m, 6H, H_1, H_2, H_8), 1.34 (qd, J = 6.4, 4.3, 3.3 Hz, 2H, H_7), 1.15 (s, 3H, H_{15}), 0.92 (d, J = 7.2 Hz, 3H, H_{16}), 0.84 (d, J = 7.0 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, C_6D_6) δ 204.9 (CH), 204.7 (CH), 119.9 (C), 63.9 (CH_2), 62.8 (CH_2), 49.6 (C), 47.6 (CH), 45.6 (C), 35.6 (CH_2), 35.6 (CH_2), 35.0 (CH), 30.5 (CH_2), 26.7 (CH_2), 19.0 (CH_3), 15.3 (CH_3), 9.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2943 (m), 2880 (w), 2360 (s), 2341 (m), 2330 (m), 1716 (m), 772 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{17}H_{26}NaO_4]^+$ 317.1729; found 317.1729. $[a]_D^{20}$ = –92.7 (c = 0.118, $CHCl_3$). Note: Owing to the presence of conformational equilibria, extensive line broadening was observed in the ^{13}C NMR spectrum of **S46** and the ^{13}C shift of C10 could not be resolved.

*Synthesis of the propargylic alcohol **57**.*



S46 **57**

A solution of *n*-butyllithium in hexanes (1.8 M, 694 μL, 1.26 mmol, 1.10 equiv) was added dropwise to a solution of trimethylsilylacetylene (178 μL, 1.26 mmol, 1.10 equiv) in tetrahydrofuran (1.7 mL) at –78 °C. The resulting solution was stirred for 1 h at –78 °C. The stirred solution was added dropwise over 5 min to a solution of the dialdehyde **S46** [338 mg, 1.15 mmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 2.0 mL)]) in tetrahydrofuran (4.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 20 min. The product mixture was diluted sequentially with ether (5.0 mL) and saturated aqueous ammonium chloride solution (4.0 mL). The resulting biphasic was allowed to warm to 22 °C over 20 min. The warmed mixture was stirred for 15 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

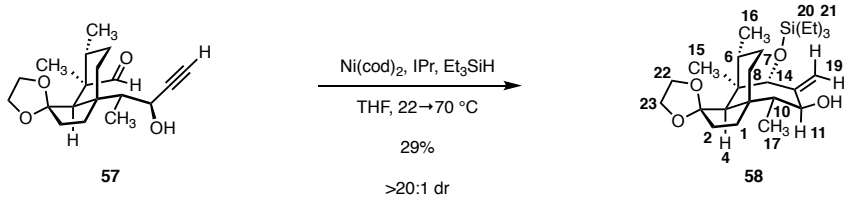
Potassium carbonate (238 mg, 1.72 mmol, 1.50 equiv) was added to a solution of the unpurified product obtained in the preceding step (nominally 1.15 mmol, 1 equiv) in methanol (5.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The product mixture was diluted sequentially with ether (10 mL) and saturated aqueous ammonium chloride solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, four steps) to provide the propargylic alcohol **57** as an off-white foam (257 mg, 70% over two steps).

^{1}H NMR analysis (500 MHz) of the unpurified product mixture indicated a 6:1 mixture of C11 diastereomers. The major diastereomer was assigned as the (11*S*) isomer by NOE analysis of the allylic alcohol **58**.

R_f = 0.48 (30% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.57 (s, 1H, H_{14}), 4.62 (s, 1H, H_{11}), 3.46 – 3.36 (m, 2H, H_{22a}, H_{23a}), 3.36 – 3.27 (m, 3H, H_{13}, H_{22b}, H_{23b}), 2.75 (s, 1H, H_4), 2.23 – 2.15 (m, 1H, H_{8a}), 2.12 – 2.04 (m, 1H, H_{10}), 2.04 – 1.97 (m, 1H, H_{16}), 1.81 – 1.41 (m, 3H, H_2, H_6), 1.39 – 1.23 (m, 4H, H_1, H_7), 1.21 (s, 3H, H_{15}), 1.16 (d, J = 6.9 Hz, 4H, H_{8b}, H_{16}), 0.92 (d, J = 7.2 Hz, 3H, H_{17}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.1 (CH), 120.2 (C), 86.5 (C), 72.2 (CH), 63.9 (CH_2), 62.7 (CH_2), 62.5 (CH), 49.7 (C), 49.0 (CH), 46.8 (C), 40.7 (CH), 35.7 (CH_2), 35.0 (CH), 30.2 (CH_2), 29.7 (CH_2) 27.1 (CH_2), 19.4 (CH_3), 15.7 (CH_3), 9.3 (CH_3). IR (ATR-

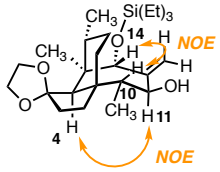
FTIR), cm^{-1}: 2922 (m), 2359 (s), 2331 (w), 1716 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{19}H_{28}NaO_4]^+$ 343.1885; found 343.1883. $[a]_D^{20} = -10.3$ ($c = 0.094$, $CHCl_3$).

Synthesis of the allylic alcohol ***58****.*



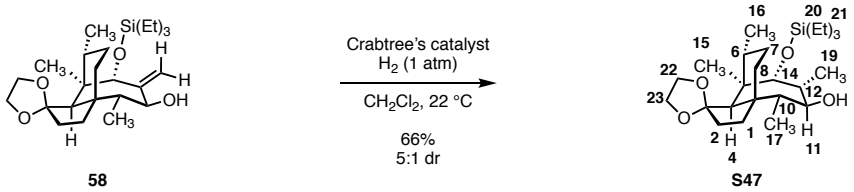
A solution of bis(cyclooctadiene)nickel(0) (44.1 mg, 160 μmol, 0.20 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 62.3 mg, 160 μmol, 0.20 equiv) in tetrahydrofuran (1.0 mL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. The catalyst solution was added to a solution of triethylsilane (383 μL, 2.41 mmol, 3.00 equiv) and the alkynyl aldehyde **57** (257 mg, 802 μmol, 1 equiv) in tetrahydrofuran (15 mL) in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox and placed in an oil bath that had been preheated to 75 °C. The reaction mixture was stirred at 2 h at 75 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was eluted over a short pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the allylic alcohol **58** as a clear oil (99.0 mg, 29%).

Within the limits of detection (500 MHz ^{1}H NMR analysis), **58** was formed as a single diastereomer. The relative stereochemistry of the C11 alcohol was determined by NOE correlations between H11 and H4. The relative stereochemistry of the C14 alcohol was determined by NOE correlations between H14 and H10.



R_f = 0.31 (45% ether–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, J = 9.2 Hz, 2H, H_{19}), 4.74 (s, 1H, H_{14}), 4.00 (q, J = 6.8 Hz, 1H, $H_{22a\text{ or }23a}$), 3.94 – 3.78 (m, 3H, H_{11}, H_{22b}, H_{23b}), 3.78 – 3.66 (m, 1H, $H_{22a\text{ or }23b}$), 2.31 – 2.19 (m, 1H, 1H, H_6), 2.11 – 2.03 (m, 1H, H_{10}), 1.86 – 1.75 (m, 3H, H_2, H_4), 1.58 – 1.13 (m, 18H, H_1, H_7, H_8, H_{17}, H_{21}), 1.01 – 0.82 (m, 6H, H_{15}, H_{16}), 0.62 (q, J = 7.9 Hz, 6H, H_{20}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4 (C), 119.6 (C), 113.3 (CH_2), 75.1 (CH), 69.9 (CH), 64.2 (CH_2), 61.7 (CH_2), 54.1 (CH), 44.3 (C), 43.8 (C), 37.1 (CH), 36.8 (CH_2), 34.5 (CH), 30.4 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 17.5 (CH_3), 13.8 (CH_3), 13.6 (CH_3), 7.3 (3 × CH_3), 5.7 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 2941 (m), 2359 (s), 2339 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{25}H_{45}O_4Si]^+$ 437.3087; found 437.3082. $[\alpha]_D^{20}$ = –7.97 (c = 2.063, $CHCl_3$).

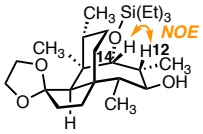
*Synthesis of the hydrogenation product **S47**.*



58 S47

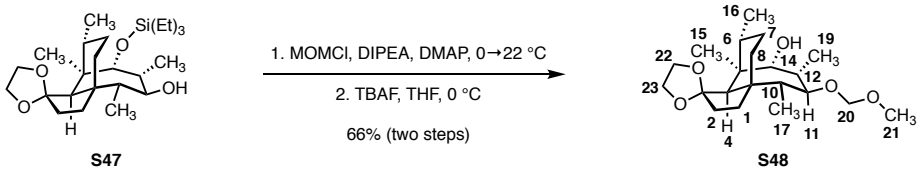
Crabtree's catalyst (1.70 mg, 2.10 μmol, 5.0 mol%) was added to a solution of the alkene **58** [18.0 mg, 41.2 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (2.1 mL) at 22 °C. The reaction vessel was purged with dihydrogen and placed under a balloon of dihydrogen. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the hydrogenated product **S47** as a clear oil (12.0 mg, 66%).

^{1}H NMR (500 MHz) analysis of the unpurified product mixture indicated the presence of a 5:1 mixture of diastereomers. The relative configuration of the major diastereomer was determined by NOE correlations between H14 and H12.



R_f = 0.25 (33% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.34 (d, J = 5.0 Hz, 1H, H_{14}), 4.00 (p, J = 6.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.87 (tq, J = 13.4, 6.5 Hz, 2H, H_{22b}, H_{23b}), 3.76 – 3.69 (m, 1H, $H_{22a\ or\ 23a}$), 3.27 (dt, J = 11.6, 4.6 Hz, 1H, H_{11}), 2.09 (ddq, J = 32.5, 13.2, 6.9 Hz, 2H, H_6, H_{10}), 1.93 – 1.85 (m, 1H, H_{12}), 1.83 – 1.77 (m, 3H, H_2, H_4), 1.57 – 1.23 (m, 6H, H_1, H_7, H_8), 1.21 (d, J = 7.4 Hz, 3H, H_{19}), 1.03 (s, 3H, H_{15}), 0.99 (t, J = 7.9 Hz, 9H, H_{21}), 0.87 (d, J = 6.8 Hz, 3H, H_{17}), 0.82 (d, J = 7.0 Hz, 3H, H_{16}), 0.64 (qd, J = 7.9, 1.5 Hz, 6H, H_{20}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 119.7 (C), 76.8 (CH), 71.1 (CH), 64.3 (CH_2), 61.8 (CH_2), 52.4 (CH), 50.5 (CH), 44.7 (C), 41.7 (C), 37.2 (CH), 36.7 (CH_2), 36.0 (CH), 29.6 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 17.6 (CH_3), 17.5 (CH_3), 14.5 (CH_3), 13.0 (CH_3), 7.4 (3 × CH_3), 5.9 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 3437 (w), 2953 (s), 2876 (m), 2362 (s), 2341 (m), 1089 (m), 1019 (m), 737 (m). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{25}H_{47}O_4Si]^+$ 439.3244; found 439.3238. $[a]_D^{20}$ = –36.2 (c = 0.063, $CHCl_3$).

*Synthesis of the protected alcohol **S48**.*

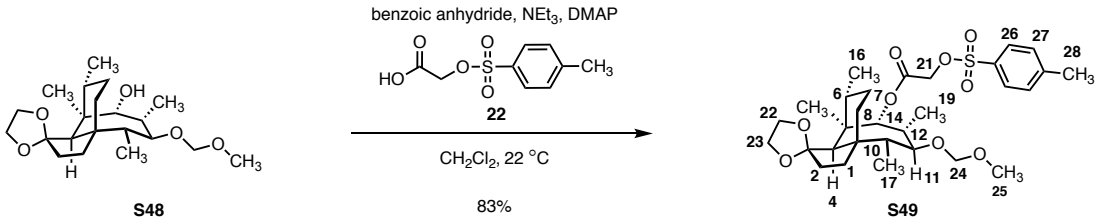


4-Dimethylaminopyridine (1.00 mg, 8.20 μmol, 0.10 equiv) was added to a solution of chloromethyl methyl ether (43.0 μL, 571 μmol, 7.00 equiv), diisopropylethylamine (199 μL, 1.14 mmol, 14.0 equiv), and the alcohol **S47** [35.8 mg, 81.6 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (270 μL) at 0 °C. The reaction mixture was allowed to warm to 22 °C over 15 h. The product mixture was diluted sequentially with ether (2.0 mL) and saturated aqueous ammonium chloride solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 245 μL, 245 μmol, 3.00 equiv) was added dropwise over 2 min to a solution of the unpurified product obtained in the preceding step (nominally 81.6 μmol, 1 equiv) in tetrahydrofuran (400 μL) at 0 °C. The reaction mixture was stirred for 30 min at 22 °C. The product mixture was diluted sequentially with ether (2.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 60% ethyl acetate–hexanes, three steps) to provide the protected product **S48** as a clear oil (20.0 mg, 66% over two steps).

R_f = 0.38 (33% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (d, J = 6.9 Hz, 1H, H_{20a}), 4.60 (d, J = 6.9 Hz, 1H, H_{20b}), 4.25 (d, J = 4.8 Hz, 1H, H_{14}), 4.01 (p, J = 6.5, 6.0 Hz, 1H, $H_{22a\ or\ 23a}$), 3.88 (tq, J = 13.4, 6.4 Hz, 2H, H_{22b}, H_{23b}), 3.78 – 3.70 (m, 1H, $H_{22a\ or\ 23a}$), 3.37 (s, 3H, H_{21}), 3.14 (dd, J = 11.8, 4.6 Hz, 1H, H_{11}), 2.16 (dtt, J = 36.4, 12.2, 6.6 Hz, 3H, H_6, H_{10}, H_{12}), 1.85 – 1.78 (m, 3H, H_2, H_4), 1.61 – 1.27 (m, 6H, H_1, H_7, H_8), 1.24 (d, J = 7.5 Hz, 3H, H_{19}), 1.04 (s, 3H, H_{15}), 0.87 (d, J = 7.0 Hz, 3H, H_{17}), 0.85 (d, J = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 119.5 (C), 97.2 (CH_2), 83.6 (CH), 70.3 (CH), 64.2 (CH_2), 61.7 (CH_2), 55.7 (CH), 52.4 (CH), 48.0 (CH), 44.4 (C), 41.0 (C), 37.1 (CH), 36.5 (CH_2), 35.7 (CH), 29.7 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 17.2 (CH_3), 16.9 (CH_3), 13.3 (CH_3), 13.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2960 (m), 2582 (w), 1007 (m), 772 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{21}H_{36}NaO_5]^+$ 391.2460; found 391.2454. $[\alpha]_D^{20}$ = –5.06 (c = 0.181, $CHCl_3$).

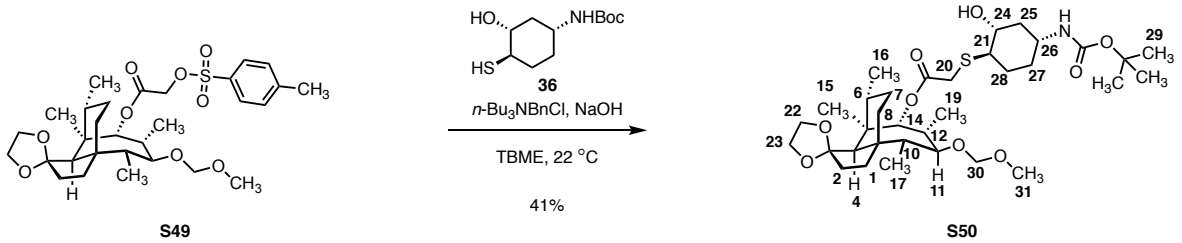
*Synthesis of the ester **S49**.*



4-Dimethylaminopyridine (300 µg, 2.70 µmol, 0.10 equiv) was added to a solution of the protected glycolic acid **22** (62.5 mg, 271 µmol, 10.0 equiv), benzoic anhydride (61.4 mg, 271 µmol, 10.0 equiv), triethylamine (53.0 µL, 380 µmol, 14.0 equiv), and the alcohol **S48** [10.0 mg, 64.5 µmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (4.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the ester **S49** as a white foam (13.1 mg, 83%).

R_f = 0.41 (33% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H, H_{26}), 7.36 (d, J = 7.9 Hz, 2H, H_{27}), 5.45 (d, J = 5.0 Hz, 1H, H_{14}), 4.63 (t, J = 5.3 Hz, 3H, H_{21}, H_{24a}), 4.61 – 4.51 (m, 1H, H_{24b}), 4.01 (q, J = 6.5, 5.9 Hz, 1H, $H_{22a\ or\ 23a}$), 3.88 (tt, J = 13.5, 6.9 Hz, 2H, H_{22b}, H_{23b}), 3.79 – 3.70 (m, 1H, $H_{22a\ or\ 23a}$), 3.34 (s, 3H, H_{25}), 3.12 (dd, J = 11.8, 4.8 Hz, 1H, H_{11}), 2.46 (s, 3H, H_{28}), 2.30 – 2.22 (m, 1H, H_{10}), 2.14 (ddt, J = 42.3, 12.0, 5.4 Hz, 2H, H_6, H_{12}), 1.91 – 1.76 (m, 3H, H_2, H_4), 1.56 – 1.23 (m, 6H, H_1, H_7, H_8), 1.17 (d, J = 7.3 Hz, 3H, H_{19}), 1.06 (s, 3H, H_{15}), 0.85 (d, J = 6.8 Hz, 3H, H_{17}), 0.60 (d, J = 7.4 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6 (C), 145.6 (C), 132.5 (C), 130.1 (2 × CH), 128.3 (2 × CH), 119.3 (C), 97.2 (CH_2), 83.0 (CH), 74.6 (CH), 64.2 (CH_2), 61.8 (CH_2), 61.7 (CH_2), 55.8 (CH_3), 51.9 (CH), 44.3 (C), 44.3 (CH), 40.6 (C), 37.2 (CH), 36.4 (CH_2), 35.6 (CH), 29.6 (CH_2), 28.1 (CH_2), 27.6 (CH_2), 21.9 (CH_3), 17.7 (CH_3), 15.9 (CH_3), 13.8 (CH_3), 13.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2924 (m), 1759 (m), 1732 (m), 1372 (m), 1178 (m), 1034 (s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{30}H_{44}NaO_9S]^+$ 603.2604; found 603.2592. $[a]_D^{20}$ = –32.3 (c = 0.065, $CHCl_3$).

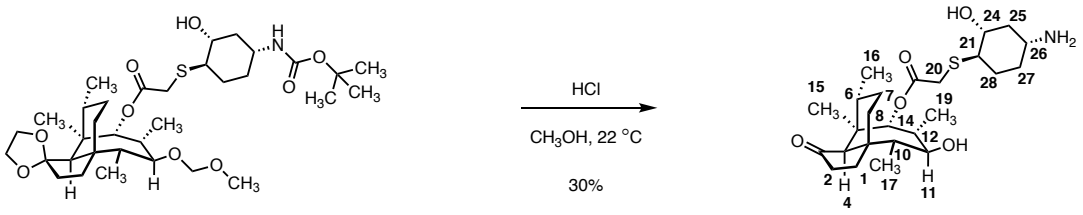
*Synthesis of the sulfide **S50**.*



Aqueous sodium hydroxide solution (1 N, 29.0 μL, 29.3 μmol, 1.30 equiv) was added to a solution of the thiol **36** (14.5 mg, 29.3 μmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (1.40 mg, 4.50 μmol, 0.20 equiv), and the sulfonate **S49** (13.1 mg, 22.5 μmol, 1 equiv) in *tert*-butyl methyl ether (230 μL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), 0.1 N aqueous phosphoric acid solution (1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% acetone–hexanes initially, grading to 80% acetone–hexanes, three steps) to provide the displacement product **S50** as a white solid (6.00 mg, 41%).

R_f = 0.19 (33% acetone–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (d, *J* = 4.9 Hz, 1H, H_{14}), 4.64 (dd, *J* = 7.0, 3.4 Hz, 1H, H_{30a}), 4.57 (dd, *J* = 7.0, 3.7 Hz, 1H, H_{30b}), 4.47 (s, 1H, NH), 4.00 (p, *J* = 6.3, 5.4 Hz, 1H, $H_{22a\ or\ 23a}$), 3.89 (td, *J* = 12.7, 11.6, 6.7 Hz, 2H, H_{22b}, H_{23b}), 3.79 – 3.70 (m, 1H, $H_{22a\ or\ 23a}$), 3.52 (s, 1H, H_{26}), 3.47 – 3.37 (m, 1H, H_{24}), 3.37 – 3.23 (m, 5H, H_{20}, H_{31}), 3.13 (dd, *J* = 11.8, 4.7 Hz, 1H, H_{11}), 2.49 (ddd, *J* = 13.3, 9.7, 3.8 Hz, 1H, H_{21}), 2.38 – 2.23 (m, 2H, H_{10}, H_{25a}), 2.23 – 1.99 (m, 4H, H_6, H_{12}, H_{27a}, H_{28a}), 1.96 – 1.77 (m, 3H, H_2, H_4), 1.59 – 1.40 (m, 13H, H_1, H_{7a}, H_{8a}, H_{29}), 1.38 – 1.02 (m, 10H, H_{7b}, $H_{8b,}$ H_{15}, H_{19}, H_{25b}, H_{28b}), 0.85 (d, *J* = 6.8 Hz, 3H, H_{17}), 0.65 (dd, *J* = 16.0, 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2 (C), 155.2 (C), 119.4 (C), 97.2 (CH_2), 83.1 (CH), 79.6 (C), 74.4 (CH), 71.8 (CH), 64.2 (CH_2), 61.7 (CH_2), 55.8 (CH_3), 52.7 (CH), 52.0 (CH), 47.8 (CH), 44.3 (C), 44.2 (CH), 40.6 (C), 40.5 (CH_2), 37.1 (CH), 36.5 (CH_2), 35.7 (CH), 33.1 (CH_2), 32.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.5 (3 × CH_3), 28.1 (CH_2), 27.6 (CH_2), 17.9 (CH_3), 16.1 (CH_3), 14.0 (CH_3), 13.2 (CH_3). IR (ATR-FTIR), cm^{-1}: HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{34}H_{57}NNaO_9S]^+$ 678.3652; found 678.3648. $[\alpha]_D^{20}$ = +27.1 (*c* = 0.031, $CHCl_3$).

*Synthesis of the lefamulin derivative **59**.*

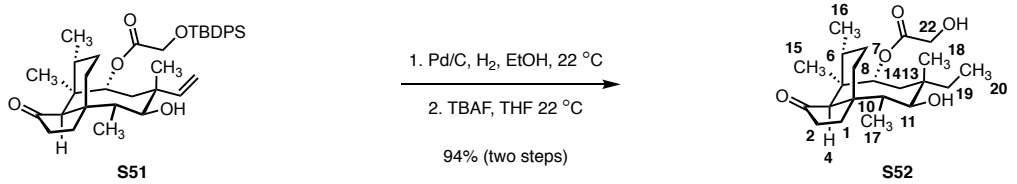


S50 **59**

Aqueous hydrochloric acid solution (12 N, 7.50 μL, 91.0 μmol, 10.0 equiv) was added to a solution of the thioglycolic ester **S50** (6.00 mg, 9.10 μmol, 1 equiv) in methanol (200 μL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the analytically pure analog **59** as a fine, white solid (1.30 mg, 30%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (80% acetone–hexanes; PAA). ^{1}H NMR (500 MHz, CD_2Cl_2) δ = 5.44 (d, J = 5.0 Hz, 1H, H_{14}), 3.55 – 3.36 (m, 2H, H_{20a}, H_{24}), 3.29 (td, J = 15.4, 14.0, 8.8 Hz, 2H, H_{11}, H_{20b}), 2.90 (s, 1H, H_{26}), 2.58 (s, 1H, H_{21}), 2.30 – 2.05 (m, 3H, H_1, H_{10}), 2.05 – 1.79 (m, 2H, H_4, H_{12}), 1.71 – 1.40 (m, 10H, H_2, H_6, H_7, H_{15}, H_{27}), 1.35 – 1.06 (m, 9H, H_8, H_{19}, H_{25}, H_{28}), 0.96 (d, J = 6.7 Hz, 3H, H_{17}), 0.68 (d, J = 5.8 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 216.0 (C), 170.6 (C), 76.3 (CH), 72.6 (CH), 71.9 (CH), 58.9 (CH), 56.2 (CH), 48.7 (CH), 46.5 (CH), 44.0 (C), 40.6 (C), 37.9 (CH), 36.9 (CH), 34.9 (CH_2), 33.4 (CH_2), 30.1 (CH_2), 29.9 (CH_2), 29.9 (CH_2), 28.3 (CH_2), 27.7 (CH_2), 26.4 (CH_2), 17.8 (CH_3), 16.1 (CH_3), 15.0 (CH_3), 12.4 (CH_3). IR (ATR-FTIR), cm^{-1}: 3728 (w), 2361 (s), 2341 (s), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{25}H_{42}NO_5S]^+$ 468.2784; found 468.2783. $[a]_D^{20}$ = +16.0 (c = 0.025, CH_3OH).

*Synthesis of the hydrogenated derivative **S52**.*



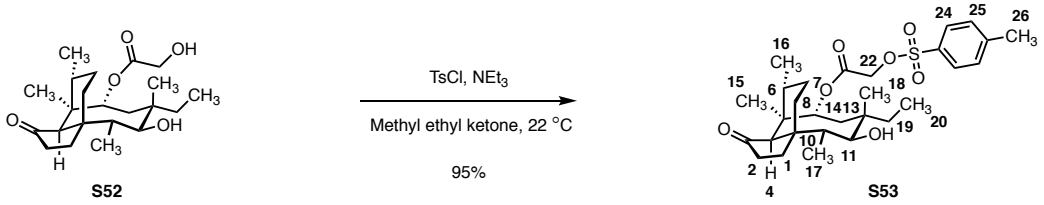
S51 **S52**

Palladium on carbon (5% w/w, 20.0 mg) was added to a solution of *O*22-[(*tert*-butyldiphenyl)-silyl]-12-*epi*-pleuromutilin (**S51**, 400 mg, 648 μmol, 1 equiv) in ethanol (4.1 mL) at 22 °C. The reaction vessel was sparged using a balloon of dihydrogen. The reaction mixture was stirred for 12 h at 22 °C. The product mixture was filtered through a pad of Celite. The Celite pad was rinsed with dichloromethane (2 × 10 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 840 μL, 840 μmol, 1.30 equiv) was added to a solution of the residue obtained in the preceding step (nominally 648 μmol, 1 equiv) in tetrahydrofuran (6.5 mL) at 22 °C. The reaction mixture was stirred for 15 min at 22 °C. The product mixture was diluted sequentially with ethyl acetate (15 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to provide the hydrogenated product **S52** as an amorphous white solid (230 mg, 94% over two steps).

R_f = 0.30 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.70 (d, *J* = 8.3 Hz, 1H, H_{14}), 4.06 (d, *J* = 17.0 Hz, 1H, H_{22a}), 3.99 (d, *J* = 17.0 Hz, 1H, H_{22b}), 3.40 (d, *J* = 6.1 Hz, 1H, H_{11}), 2.39 (p, *J* = 7.0 Hz, 1H, H_{10}), 2.28 – 2.12 (m, 2H, H_2), 2.09 (s, 1H, H_4), 1.81 – 1.68 (m, 3H, H_{8a}, H_{13a}, H_{19a}), 1.68 – 1.41 (m, 5H, H_1, H_6, H_{7a}, H_{19b}), 1.41 – 1.28 (m, 5H, H_{7b}, H_{13b}, H_{18}), 1.11 (td, *J* = 14.0, 4.4 Hz, 1H, H_{8b}), 0.98 – 0.91 (m, 6H, H_{15}, H_{17}), 0.74 (t, *J* = 7.4 Hz, 3H, H_{20}), 0.66 (d, *J* = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.0 (C), 172.3 (C), 76.4 (CH), 70.1 (CH), 61.3 (CH_2), 58.4 (CH), 45.5 (C), 41.8 (C), 41.0 (CH_2), 40.9 (C), 36.5 (CH), 34.4 (CH_2), 34.3 (CH), 30.2 (CH_2), 26.8 (CH_2), 26.3 (CH_3), 24.9 (CH_2), 20.6 (CH_2), 16.4 (CH_3), 14.7 (CH_3), 11.1 (CH_3), 8.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 3460 (w), 2961 (m), 1731 (s), 1221 (m), 1099 (m), 756 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{22}H_{37}O_5]^+$ 381.2641; found 381.2636. $[a]_D^{20}$ = +11.9 (*c* = 0.850, $CHCl_3$).

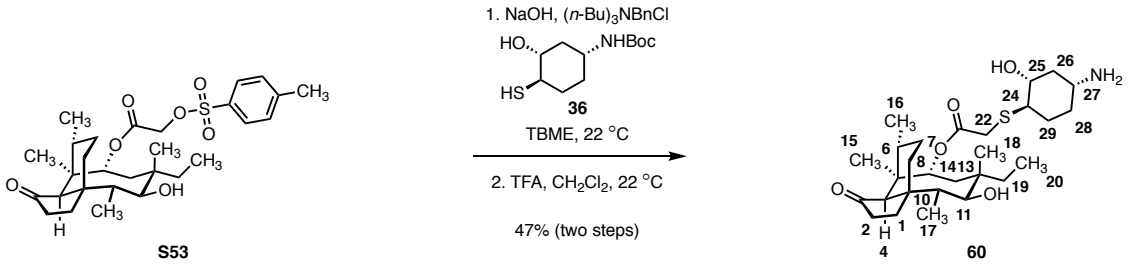
*Synthesis of the sulfonate **S53**.*



4-Toluenesulfonyl chloride (48.6 mg, 255 μmol, 1.00 equiv) was added to a solution of triethylamine (39.0 μL, 280 μmol, 1.10 equiv) and the glycolic ester **S52** (97.0 mg, 255 μmol, 1 equiv) in methyl ethyl ketone (2.0 mL) at 22 °C. The reaction mixture was stirred for 24 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL) and saturated aqueous ammonium chloride solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 30% ethyl acetate–hexanes, three steps) to provide the sulfonate **S53** as an amorphous white solid (130 mg, 95%).

R_f = 0.31 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2H, H_{24}), 7.35 (d, J = 8.0 Hz, 2H, H_{25}), 5.60 (d, J = 8.6 Hz, 1H, H_{14}), 4.48 (s, 2H, H_{22}), 3.49 (d, J = 6.2 Hz, 1H, H_{11}), 2.45 (s, 3H, H_{26}), 2.34 – 2.14 (m, 3H, H_2, H_{10}), 2.06 – 1.97 (m, 2H, H_4, H_{13a}), 1.75 (dd, J = 14.6, 3.2 Hz, 1H, H_{8a}), 1.64 – 1.43 (m, 5H, H_1, H_6, H_{7a}, H_{19a}), 1.41 – 1.23 (m, 5H, H_{7b}, H_{18}, H_{19b}), 1.10 (td, J = 14.1, 4.3 Hz, 1H, H_{8b}), 0.98 (s, 3H, H_{15}), 0.96 – 0.90 (m, 4H, H_{13b}, H_{17}), 0.86 (t, J = 7.5 Hz, 3H, H_{20}), 0.61 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.1 (C), 165.0 (C), 145.5 (C), 132.8 (C), 130.1 (2 × CH), 128.3 (2 × CH), 72.0 (CH), 71.1 (CH), 65.2 (CH_2), 58.2 (CH_2), 45.5 (C), 42.0 (C), 41.6 (CH_2), 40.4 (C), 36.7 (CH), 34.8 (CH), 34.6 (CH_2), 34.6 (CH_2), 30.4 (CH_2), 26.9 (CH_2), 25.1 (CH_2), 21.8 (CH_3), 17.7 (CH_3), 16.8 (CH_3), 15.0 (CH_3), 11.1 (CH_3), 8.0 (CH_3). IR (ATR-FTIR), cm^{-1}: 3568 (w), 2957 (m), 2365 (w), 1732 (s), 1371 (m), 1176 (s), 1042 (m), 760 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{29}H_{42}NaO_7S]^+$ 557.2549; found 557.2541. $[a]_D^{20}$ = +4.48 (c = 0.530, $CHCl_3$).

*Synthesis of the lefamulin derivative **60**.*

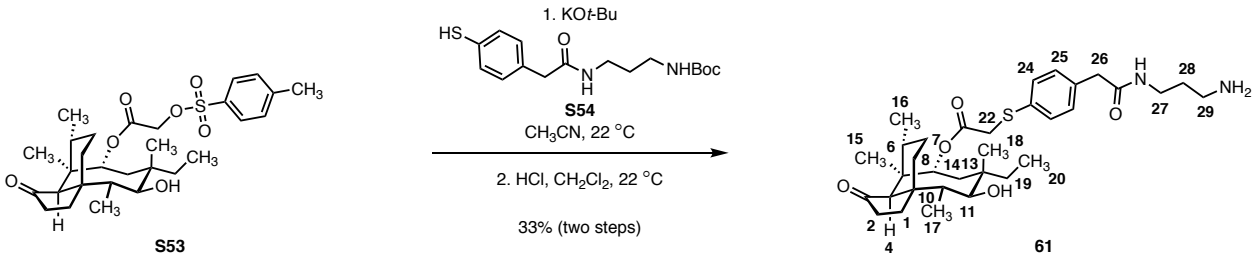


Aqueous sodium hydroxide solution (1 N, 49.0 μL, 48.6 μmol, 1.30 equiv) was added to a solution of the thiol **36** (12.0 mg, 48.6 μmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (2.30 mg, 7.50 μmol, 0.20 equiv), and the sulfonate **S53** (20.0 mg, 37.4 μmol, 1 equiv) in *tert*-butyl methyl ether (410 μL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 80% ethyl acetate–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

Trifluoroacetic acid (40.0 μL, 525 μmol, 16.0 equiv) was added to a solution of the thioglycolic ester obtained in the preceding step (nominally 37.4 μmol, 1 equiv) in dichloromethane (330 μL) at 22 °C. The reaction mixture was stirred for 4 h at 22 °C. The product mixture was concentrated to provide the analytically lefamulin derivative **60** as a fine, white solid (8.90 mg, 47% over two steps). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.58 (d, J = 8.6 Hz, 1H, H_{14}), 3.51 (d, J = 6.2 Hz, 1H, H_{11}), 3.43 (ddd, J = 12.9, 7.7, 3.6 Hz, 1H, H_{25}), 3.31 (d, J = 15.7 Hz, 1H, H_{22a}), 3.21 (d, J = 15.6 Hz, 1H, H_{22b}), 2.92 (d, J = 11.1 Hz, 2H, H_{27}, NH), 2.61 – 2.52 (m, 1H, H_{24}), 2.34 (p, J = 6.9 Hz, 1H, H_{10}), 2.28 – 2.04 (m, 6H, H_2, H_4, H_{13a}, H_{26a}, H_{29a}), 1.94 – 1.86 (m, 1H, H_{28a}), 1.78 (dq, J = 14.5, 3.2 Hz, 1H, H_{8a}), 1.65 – 1.40 (m, 10H, H_1, H_6, H_{7a}, H_{18}, H_{19a}, H_{29b}), 1.39 – 1.22 (m, 4H, H_{7b}, H_{19b}, H_{26b}, H_{28b}), 1.19 – 1.08 (m, 1H, H_{8b}), 1.00 (s, 3H, H_{15}), 0.93 (d, J = 7.1 Hz, 3H, H_{17}), 0.87 (t, J = 7.5 Hz, 3H, H_{20}), 0.71 (d, J = 6.9 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 216.9 (C), 169.9 (C), 71.7 (CH), 71.1 (CH), 70.5 (CH), 57.9 (CH), 51.9 (CH), 48.3 (CH), 45.4 (C), 41.8 (C), 41.5 (CH_2), 40.8 (CH_2), 40.1 (C), 36.8 (CH), 34.7 (CH), 34.5 (CH_2), 34.4 (CH_2), 33.3 (broad, CH_2), 33.3 (CH_2), 30.2 (CH_2), 27.9 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 17.4 (CH_3), 16.7 (CH_3), 14.6 (CH_3), 10.7 (CH_3), 7.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 3436 (w), 2940 (m), 1694 (s), 1282 (m), 1167 (m), 754 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{48}NO_5S]^+$ 510.3253; found 510.3248.

*Synthesis of the aminoamide **61**.*

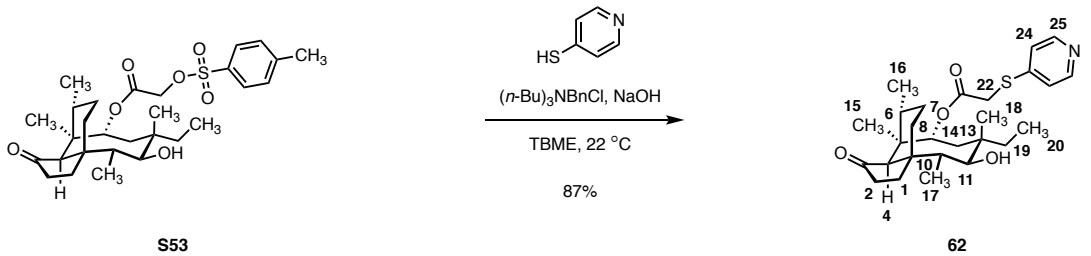


A solution of potassium *tert*-butoxide solution in tetrahydrofuran (50.0 mM, 33.0 µL, 16.7 µmol, 0.80 equiv) was added dropwise to a solution of the was added to a solution of the thiol **S54** (5.40 mg, 16.7 µmol, 0.80 equiv), and the sulfonate **S53** (11.1 mg, 20.8 µmol, 1 equiv) in acetonitrile (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was eluted over a plug of silica gel (1.0 cm × 1.0 cm, eluting with 85% ethyl acetate–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was used directly in the following step.

A solution of hydrogen chloride in dioxane (4.0 M, 83.0 µL, 333 µmol, 16.0 equiv) was added to a solution of the unpurified ester obtained in the preceding step (nominally 20.8 µmol, 1 equiv) in dichloromethane (190 µL) at 22 °C. The reaction mixture was stirred for 4 h at 22 °C. The product mixture was concentrated to provide the aminoamide **61** as a fine, white solid (4.30 mg, 33% over two steps). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (d, J = 7.8 Hz, 2H, H_{25}), 7.26 (d, J = 7.9 Hz, 2H, H_{24}), 5.57 (d, J = 8.4 Hz, 1H, H_{14}), 3.68 (d, J = 15.3 Hz, 1H, H_{22a}), 3.61 (d, J = 15.3 Hz, 1H, H_{22b}), 3.48 (d, J = 9.7 Hz, 3H, H_{11}, H_{26}), 3.28 (m, 2H, H_{27}), 2.88 (t, J = 7.2 Hz, 2H, H_{29}), 2.26 (dq, J = 17.3, 10.7, 8.4 Hz, 2H, H_{2a}, H_{10}), 2.14 (q, J = 9.8, 9.0 Hz, 2H, H_{2b}, H_4), 1.99 (dd, J = 15.7, 8.4 Hz, 1H, H_{13a}), 1.81 (dt, J = 19.5, 9.8 Hz, 3H, H_{8a}, H_{28}), 1.73 – 1.64 (m, 1H, H_{1a}), 1.63 – 1.40 (m, 4H, H_{1b}, H_6, H_{7a}, H_{19a}), 1.38 – 1.20 (m, 5H, H_{7b}, H_{18}, H_{19b}), 1.12 (td, J = 13.9, 4.2 Hz, 1H, H_{8b}), 0.91 (d, J = 6.9 Hz, 3H, H_{17}), 0.87 (s, 3H, H_{15}), 0.84 – 0.79 (m, 4H, H_{13b}, H_{20}), 0.67 (d, J = 6.9 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 219.6 (C), 174.7 (C), 170.1 (C), 135.6 (C), 135.2 (C), 130.9 (2 × CH), 130.8 (2 × CH), 72.4 (CH), 71.7 (CH), 59.1 (CH), 46.7 (C), 43.2 (CH_2), 43.0 (CH_2), 42.8 (C), 41.1 (C), 38.2 (CH_2), 38.1 (CH), 37.5 (CH_2), 37.0 (CH_2), 36.4 (CH), 35.6 (CH_2), 35.3 (CH_2), 31.5 (CH_2), 28.8 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 18.2 (CH_3), 17.3 (CH_3), 15.5 (CH_3), 11.6 (CH_3), 8.2 (CH_3). IR (ATR-FTIR), cm^{-1}: 2952 (w), 2360 (s), 2341 (m), 1729 (w), 1523 (w), 1277 (w), 1169 (w), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{33}H_{51}N_2O_5S]^+$ 587.3519; found 587.3515.

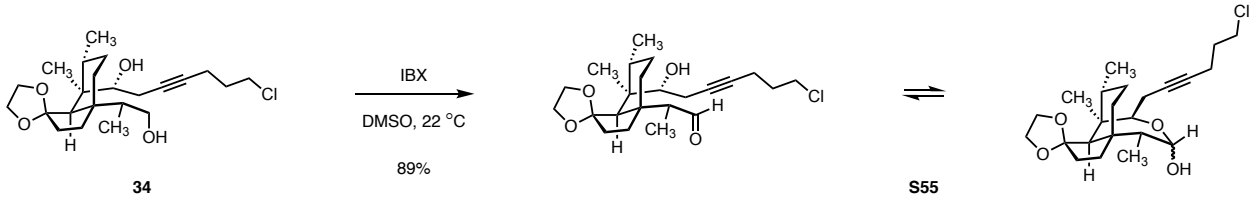
*Synthesis of the pyridyl sulfide **62**.*



Aqueous sodium hydroxide solution (1 N, 49.0 µL, 48.6 µmol, 1.30 equiv) was added to a solution of 4-mercaptopyridine (5.40 mg, 48.6 µmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (2.30 mg, 7.50 µmol, 0.20 equiv), and the sulfonate **S53** (20.0 mg, 37.4 µmol, 1 equiv) in *tert*-butyl methyl ether (370 µL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the pyridyl sulfide **62** as a white solid (15.3 mg, 87%).

R_f = 0.15 (75% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 2H, H_{25}), 7.17 (d, J = 5.2 Hz, 2H, H_{24}), 5.58 (d, J = 8.5 Hz, 1H, H_{14}), 3.70 – 3.62 (m, 2H, H_{22}), 3.45 (d, J = 6.2 Hz, 1H, H_{11}), 2.29 (t, J = 6.9 Hz, 1H, H_{10}), 2.25 – 2.13 (m, 2H, H_2), 2.02 – 1.95 (m, 2H, H_4, H_{13a}), 1.75 (dq, J = 14.6, 3.2 Hz, 1H, H_{8a}), 1.68 – 1.54 (m, 2H, H_{1a}, H_6), 1.53 – 1.39 (m, 6H, H_{1b}, H_{7a}, H_{18}, H_{19a}), 1.34 (dq, J = 14.5, 3.7 Hz, 1H, H_{7b}), 1.30 – 1.17 (m, 1H, H_{19b}), 1.10 (td, J = 14.1, 4.4 Hz, 1H, H_{8b}), 0.93 – 0.88 (m, 6H, H_{15}, H_{17}), 0.85 (d, J = 15.9 Hz, 1H, H_{13b}), 0.79 (t, J = 7.5 Hz, 3H, H_{20}), 0.69 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 216.9 (C), 167.1 (C), 149.0 (2 × CH), 147.9 (C), 120.8 (2 × CH), 72.0 (CH), 71.1 (CH), 58.0 (CH), 45.4 (C), 41.8 (C), 41.7 (CH_2), 40.1 (C), 36.6 (CH), 34.7 (CH), 34.5 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 30.2 (CH_2), 26.8 (CH_2), 25.0 (CH_2), 17.4 (CH_3), 16.9 (CH_3), 14.9 (CH_3), 10.9 (CH_3), 7.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 3422 (w), 2956 (m), 2362 (m), 1727 (s), 1580 (m), 1276 (m), 1116 (m), 755 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{27}H_{40}NO_4S]^+$ 474.2678; found 474.2677. $[\alpha]_D^{20}$ = +10.1 (c = 0.975, $CHCl_3$).

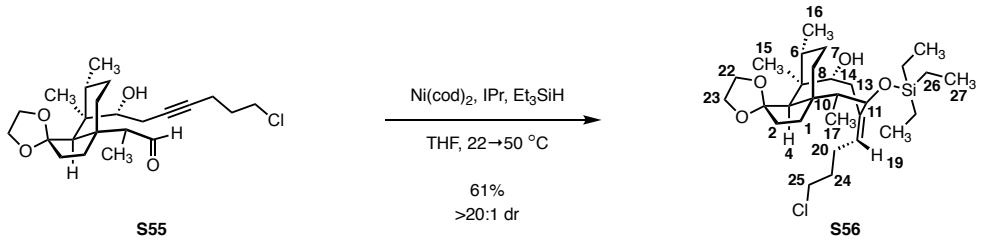
*Synthesis of the lactol **S55**.*



2-Iodoxybenzoic acid (199 mg, 674 μmol, 1.05 equiv) was added in one portion to a solution of the homopropargyl alcohol **34** (265 mg, 642 μmol, 1 equiv) in dimethylsulfoxide (8.2 mL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (20 mL), saturated aqueous sodium bicarbonate solution (10 mL), and saturated aqueous sodium thiosulfate solution (10 mL) at 22 °C. The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the product **S55** as a white foam (229 mg, 89%). The product **S55** was used immediately in the following step.

^{1}H NMR analysis (400 MHz) of the purified product mixture indicated the presence of a 1:1 mixture of hydroxyaldeyde and hemiketal.

*Synthesis of the allylic silyl ether **S56**.*

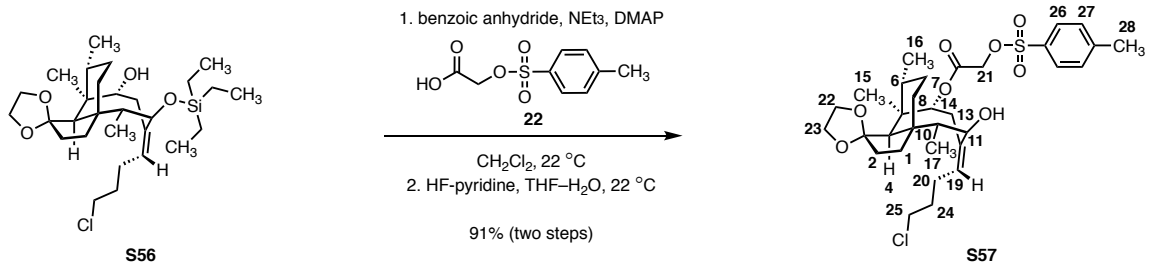


A solution of bis(cyclooctadiene)nickel(0) (10.3 mg, 34.1 μmol, 1.00 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 13.2 mg, 34.1 μmol, 1.00 equiv) in tetrahydrofuran (300 μL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. A portion of this solution (60.0 μL, 6.82 μmol, 0.20 equiv of nickel and ligand) was added to a solution of triethylsilane (16.3 μL, 102 μmol, 3.00 equiv) and the alkynyl aldehyde **S55** (14.0 mg, 34.1 μmol, 1 equiv) in tetrahydrofuran (1.1 mL) in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The sealed vessel was placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred for 3 h at 50 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was eluted over a short pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the allylic silyl ether **S56** as a clear oil (11.0 mg, 61%).

Within the limits of detection (600 MHz, ^{1}H NMR analysis), the allylic silyl ether **S56** was formed as a single diastereomer. The relative stereochemistry was assigned by comparison of $^3J_{H–H}$ coupling constants to the allylic silyl ether **S6**.

R_f = 0.73 (30% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.17 (t, J =7.1 Hz, 1H, H_{19}), 4.78 (dt, J = 11.1, 5.2 Hz, 1H, H_{14}), 3.97 (dt, J = 8.9, 6.0 Hz, 1H, $H_{22a\text{ or }23a}$), 3.90 (d, J = 8.6 Hz, 1H, H_{11}), 3.87 – 3.78 (m, 2H, H_{22b}, H_{23b}), 3.66 (ddd, J = 7.9, 5.7, 2.1 Hz, 1H, $H_{22a\text{ or }23a}$), 3.56 (tdd, J = 6.8, 4.2, 2,1 Hz, 2H, H_{25}), 3.12 (s, 1H, H_4), 2.69 – 2.54 (m, 1H, H_{13a}), 2.38 (d, J = 15.0 Hz, 1H, H_{13b}), 2.30 – 2.13 (m, 4H, H_6, H_{10}, H_{20}), 1.97 – 1.87 (m, 2H, H_{24}), 1.75 (dddd, J = 13.5, 11.1, 9.0, 2.0 Hz, 1H, H_{2a}), 1.69 – 1.62 (m, 1H, H_{2b}), 1.62 – 1.39 (m, 4H, H_7, H_8), 1.38 – 1.30 (m, 1H, H_{1a}), 1.29 – 1.20 (m, 1H, H_{1b}), 1.04 – 0.99 (m, 6H, H_{15}, $H_{16\text{ or }17}$), 0.97 – 0.88 (m, 12H, $H_{16\text{ or }17}$, H_{27}), 0.55 (qd, J = 8.1, 1.6 Hz, 6H, H_{26}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9 (C), 125.0 (CH), 119.8 (C), 84.9 (CH), 69.0 (CH), 63.7 (CH_2), 61.3 (CH_2), 50.7 (CH), 45.6 (C), 45.0 (CH_2), 43.2 (C), 42.1 (CH), 36.0 (CH_2), 36.0 (CH), 33.9 (CH_2), 31.6 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 25.2 (CH_2), 18.6 (CH_3), 15.9 (CH_3), 14.1 (CH_3), 7.0 (3 × CH_3), 5.2 (3 × CH_2). IR(ATR-FTIR), cm^{-1}: 2953 (s), 2875 (s) 1036 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{29}H_{52}ClNO_4Si]^+$ 527.3325; found 527.3318. $[a]_D^{20}$ = –10.9 (c = 0.760, $CHCl_3$).

*Synthesis of the ester **S57**.*



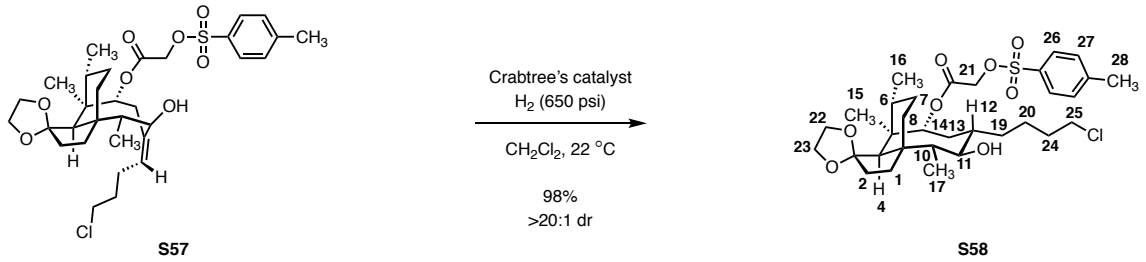
4-Dimethylaminepyridine (5.80 mg, 47.4 μmol, 0.10 equiv) was added to a solution of the sulfonate **22** (600 mg, 2.61 mmol, 5.50 equiv), benzoic anhydride (590 mg, 2.61 mmol, 5.50 equiv), triethylamine (429 μL, 3.08 mmol, 6.50 equiv), and the allylic silyl ether **S56** [250 mg, 474 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (4.7 mL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (6.0 mL) and 1 N aqueous sodium hydroxide solution (4.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (4 × 6.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (12 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used direcly in the following step.

Hydrogen fluoride–pyridine complex (119 μL, 948 μmol, 2.00 equiv) was added to a solution of the unpurified product obtained in the proceeding step (nominally 474 μmol, 1 equiv) in 2:1 tetrahydrofuran–water (9.5 mL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (6.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the ester **S57** as a white foam (271 mg, 91% over two steps).

R_f = 0.45 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H, H_{26}), 7.35 (d, J = 8.0 Hz, 2H, H_{27}), 5.93 (dd, J = 11.7, 4.5 Hz, 1H, H_{14}), 5.30 (ddd, J =7.7, 6.5, 2.6, 1H, H_{19}), 4.58 – 4.47 (m, 2H, H_{21}), 4.00 – 3.93 (m, 1H, $H_{22a\ or\ 23a}$), 3.89 (d, J = 9.2 Hz, 1H, H_{11}), 3.88–3.76 (m, 2H, H_{22b}, H_{23b}), 3.70 – 3.63 (m, 1H, $H_{22a\ or\ 23a}$), 3.60 – 3.50 (m, 2H, H_{25}), 3.03 (s, 1H, H_4), 2.68 (dd, J = 15.4, 11.7 Hz, 1H, H_{13a}), 2.45 (s, 3H, H_{28}), 2.34 – 2.12 (m, 5H, H_6, H_{10}, H_{13b}, H_{20}), 1.98 – 1.83 (m, 2H, H_{24}), 1.76 (ddd, J = 14.0, 11.4, 8.9 Hz, 1H, H_{2a}),1.69 (ddd, J = 14.0, 10.0, 1.5 Hz, 1H, H_{2b}), 1.52 – 1.43 (m, 3H, H_7, H_{8a}), 1.40 – 1.33 (m, 2H, H_{1a}, H_{8b}), 1.29 – 1.21 (m, 1H, H_{1b}), 1.10 – 1.07 (m, 6H, H_{15}, H_{17}), 0.61 (d, J = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4 (C), 145.3 (C), 141.4 (C), 132.6 (C), 129.9 (2 × CH), 127.9 (2 × CH), 126.7 (CH), 119.5 (C), 83.7 (CH), 73.2. (CH), 65.0 (CH_2), 63.7 (CH_2), 61.4 (CH_2), 50.6 (CH), 45.5 (C), 44.8 (CH_2),

42.4 (C), 41.5 (CH), 35.9 (CH_2), 35.6 (CH), 31.5 (CH_2), 29.7 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 25.2 (CH_2), 21.7 (CH_3), 17.1 (CH_3), 15.9 (CH_3), 15.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 2949 (w), 2361 (w), 2337 (w), 1757 (w), 1372 (m), 1190 (m), 1177 (s), 1037 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{32}H_{45}ClNaO_8S]^+$ 647.2421; found 647.2416. $[a]_D^{20}$ = –73.6 (c = 0.205, $CHCl_3$).

*Synthesis of the hydrogenation product **S58**.*



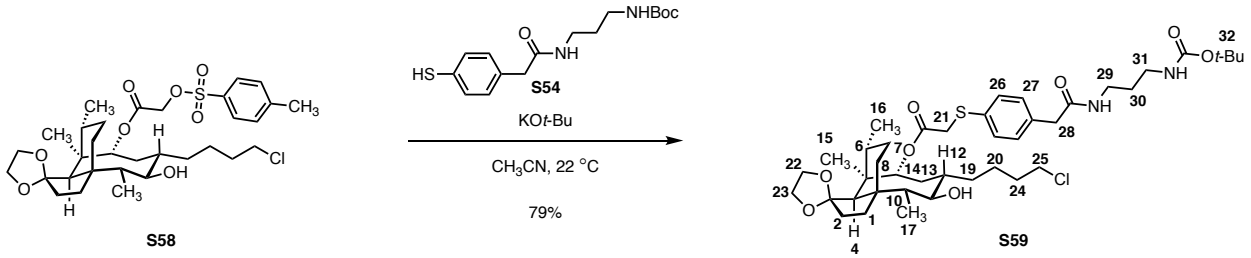
S57 **S58**

Crabtree's catalyst (1.00 mg, 1.20 μmol, 5 mol%) was added to a solution of the allylic alcohol **S57** (15.0 mg, 24.0 μmol, 1 equiv) in dichloromethane (2.4 mL) at 22 °C in a nitrogen-filled drybox. The reaction vessel was then transferred to a stainless-steel hydrogenation apparatus. The apparatus was sealed and removed from the drybox. The apparatus was purged with dihydrogen by pressurizing to 200 psi and venting. This process was repeated three times. The vessel was then pressurized to 650 psi dihydrogen and sealed. The reaction mixture was stirred at 22 °C for 15 h. The apparatus was then slowly vented. The product mixture was concentrated and the residue was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the alcohol **S58** as a colorless oil (14.8 mg, 98%).

Within the limits of detection (600 MHz, ^{1}H NMR analysis), the hydrogenation product **S56** was formed as a single diastereomer. The relative stereochemistry was assigned by comparison of $^3J_{H–H}$ coupling constants to the hydrogenation product **35**.

R_f = 0.45 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H, H_{26}), 7.35 (d, J = 8.2 Hz, 2H, H_{27}), 5.33 (dd, J =7.9, 1H, H_{14}), 4.50 (d, J = 1.7 Hz, 2H, H_{21}), 4.08 – 3.98 (m, 1H, $H_{22a\ or\ 23a}$), 3.90 (tq, J = 13.7, 6.6 Hz, 2H, H_{22b}, H_{23b}), 3.81 – 3.71 (m, 1H, $H_{22a\ or\ 23a}$), 3.53 (t, J = 6.7 Hz, 2H, H_{25}), 3.32 (dd, J = 9.7, 6.7 Hz, 1H, H_{11}), 2.45 (s, 3H, H_{28}), 2.23 (dh, J = 9.4, 6.8 Hz, 1H, H_6), 2.12 (p, J = 7.1 Hz, 1H, H_{10}), 1.95 (s, 1H, H_4), 1.89 – 1.67 (m, 7H, H_2, H_{12}, H_{13}, H_{24}), 1.61 – 1.42 (m, 3H, H_7, H_{19a}), 1.50 – 1.22 (m, 7H, H_1, H_8, H_{19b}, H_{20}), 1.04 (s, 3H, H_{15}), 0.90 (d, J = 7.0 Hz, 3H, H_{17}), 0.62 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7 (C), 145.2 (C), 132.6 (C), 129.9 (2 × CH), 128.1 (2 × CH), 120.3 (C), 76.1 (CH), 71.9 (CH), 65.1 (CH_2), 63.8 (CH_2), 61.5 (CH_2), 50.9 (CH), 46.4 (CH), 46.1 (C), 45.0 (CH_2), 41.6 (C), 40.1 (CH), 37.0 (CH_2), 35.8 (CH_2), 35.3 (CH), 32.8 (CH_2), 32.4 (CH_2), 29.2 (CH_2), 28.7 (CH_2), 28.7 (CH_2), 23.4 (CH_2), 21.7 (CH_3), 17.5 (CH_3), 14.6 (CH_3), 11.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2936 (m), 1754 (w), 1372 (m), 1199 (m), 1177 (s), 1035 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{32}H_{47}ClNaO_8S]^+$ 649.2578; found 649.2590. $[a]_D^{20}$ = –15.6 (c = 0.440, $CHCl_3$).

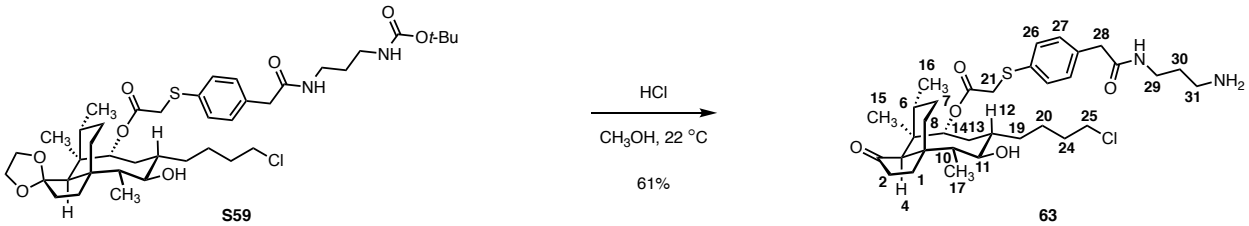
*Synthesis of the thioglycolic ester **S59**.*



A solution potassium *tert*-butoxide in tetrahydrofuran (1.0 M, 22.0 µL, 21.9 µmol, 1.72 equiv) and the thiol **S54** (7.10 mg, 21.9 µmol, 1.72 equiv) in acetonitrile (200 µL) was stirred for 5 min at 22 °C. A portion of this solution (116 µL, 12.8 µmol, 1.00 equiv) was added to a solution of the sulfonate **S58** [8.00 mg, 12.8 µmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in acetonitrile (200 µL) at 22 °C. The reaction mixture was stirred for 1 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was stirred for 5 min at 22 °C. The stirred biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous phase was extracted with ethyl acetate (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% acetone–hexanes initially, grading to 60% acetone–hexanes, four steps) to provide the sulfide **S59** as a fine, white solid (7.90 mg, 79%).

R_f = 0.15 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2H, H_{27}), 7.21 (d, J = 7.8 Hz, 2H, H_{26}), 6.07 (s, 1H, NH), 5.29 (d, J =7.9 Hz, 1H, H_{14}), 4.90 (s, 1H, NH), 4.03 (p, J = 6.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.89 (tt, J = 13.7, 7.2 Hz, 2H, H_{22b}, H_{23b}), 3.76 (q, J = 7.3, 6.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.63 – 3.54 (m, 2H, H_{28}), 3.53 – 3.46 (m, 4H, H_{21}, H_{25}), 3.31 (dd, J = 9.7, 6.8 Hz, 1H, H_{11}), 3.25 (q, J = 6.4 Hz, 2H, H_{31}), 3.09 (q, J = 6.4 Hz, 2H, H_{29}), 2.23 (ddd, J = 17.5, 13.5, 8.8 Hz, 1H, H_6), 2.18 – 2.10 (m, 1H, H_{10}), 1.94 (s, 1H, H_4), 1.88 – 1.66 (m, 5H, H_2, H_{12}, H_{13}), 1.57 (dt, J = 12.5, 7.2 Hz, 2H, H_{30}), 1.45 – 1.19 (m, 21H, H_1, H_7, H_8, H_{19}, H_{20}, H_{24}, H_{32}), 1.04 (s, 3H, H_{15}), 0.90 (d, J = 7.1 Hz, 3H, H_{17}), 0.68 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C), 169.1 (C), 156.5 (C), 134.3 (C), 133.6 (C), 130.0 (2 × CH), 129.9 (2 × CH), 120.4 (C), 79.3 (C), 75.5 (CH), 72.1 (CH), 63.8 (CH_2), 61.5 (CH_2), 51.0 (CH), 46.5 (CH), 46.1 (C), 45.0 (CH_2), 43.3 (CH_2), 41.5 (C), 40.1 (CH), 37.1 (CH_2), 37.1 (CH_2), 37.0 (CH_2), 36.1 (CH_2), 35.8 (CH_2), 35.4 (CH), 32.7 (CH_2), 32.4 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 28.4 (3 × CH_3), 27.2 (CH_2), 23.5 (CH_2), 17.7 (CH_3), 14.7 (CH_3), 11.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 3303 (w), 2937 (w), 2359 (m). HRMS-ESI (m/z): [M + Na]$^+$ calcd for $[C_{41}H_{63}N_2NaO_8S]^+$ 801.3891; found 801.3886. $[a]_D^{20}$ = +4.29 (c = 0.190, $CHCl_3$).

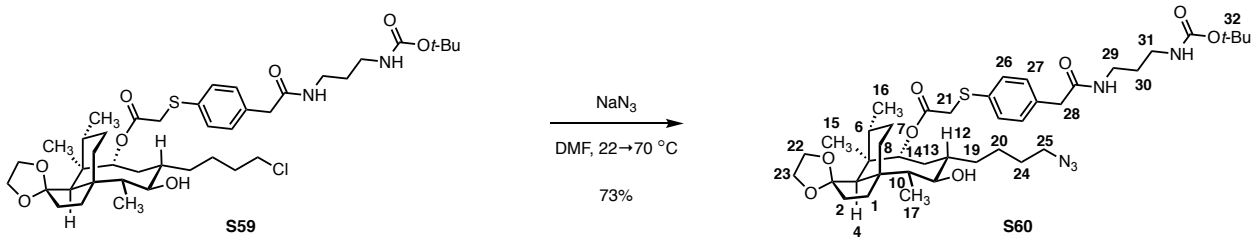
*Synthesis of the amino amide **63**.*



Aqueous hydrochloric acid solution (12 N, 3.20 µL, 38.0 µmol, 10.0 equiv) was added to a solution of the thioglycolic ester **S59** (1.00 mg, 3.80 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provde the amino amide **63** as a fine, white solid (1.58 mg, 61%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (d, J = 8.3 Hz, 2H, H_{27}), 7.25 (d, J = 8.2 Hz, 2H, H_{26}), 5.32 (d, J = 6.5 Hz, 1H, H_{14}), 3.69 (d, J = 15.1 Hz, 1H, H_{21a}), 3.60 (d, J = 15.2 Hz, 1H, H_{21b}), 3.51 (t, J = 6.7 Hz, 2H, H_{25}), 3.48 (s, 2H, H_{28}), 3.31 (m, 1H, H_{11}; detected by HSQC), 3.26 (t, J = 6.7 Hz, 2H, H_{29}), 2.87 (dd, J = 8.5, 6.1 Hz, 2H, H_{31}), 2.33 – 2.07 (m, 4H, H_2, H_4, H_{10}), 1.86 – 1.62 (m, 7H, H_{8a}, H_{12}, H_{13a}, H_{24}, H_{30}), 1.58 (ddt, J = 11.5, 7.1, 3.5 Hz, 1H, H_6), 1.49 – 1.23 (m, 11H, H_1, H_7, H_{13b}, H_{15}, H_{19a}, H_{20}), 1.23 – 1.07 (m, 2H, H_{8b}, H_{19b}), 0.95 (d, J = 7.0 Hz, 3H, H_{17}), 0.70 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.3 (C), 173.2 (C), 169.7 (C), 134.1 (C), 133.8 (C), 129.4 (2 × CH), 129.4 (2 × CH), 74.0 (CH), 71.2 (CH), 57.7 (CH), 45.8 (CH), 45.3 (C), 44.4 (CH_2), 41.8 (CH_2), 41.3 (C), 41.3 (CH), 36.7 (CH_2), 36.7 (CH), 36.4 (CH_2), 35.9 (CH_2), 35.6 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 30.3 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 24.8 (CH_2), 23.2 (CH_2), 16.5 (CH_3), 14.1 (CH_3), 10.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 3285 (m), 1643 (w), 1014 (s) 514 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{34}H_{51}ClN_2NaO_5S]^+$ 657.3105; found 657.3099. $[a]_D^{20}$ = +74.4 (c = 0.063, CH_3OH).

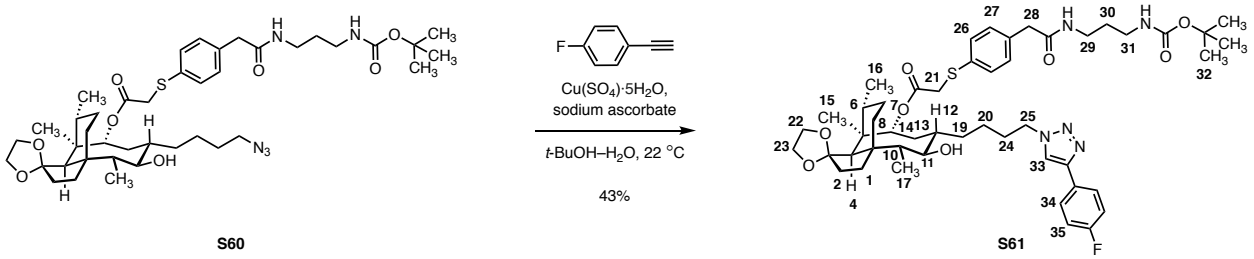
*Synthesis of the azide **S60**.*



Sodium azide (2.40 mg, 37.6 μmol, 3.00 equiv) was added to a solution of the alkyl chloride **S59** (12.2 mg, 12.5 μmol, 1 equiv) in *N,N*-dimethylformamide (200 μL) at 22 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred at 3 h at 70 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted sequentially with ethyl acetate (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The organic layer was washed sequentially with water (2 × 1.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% acetone–hexanes) to provide the azide **S60** as a fine, white solid (7.20 mg, 73%).

R_f = 0.15 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.2 Hz, 2H, H_{26}), 7.20 (d, J = 7.9 Hz, 2H, H_{27}), 6.08 (s, 1H, NH), 5.29 (d, J = 7.7 Hz, 1H, H_{14}), 4.89 (s, 1H, NH), 4.03 (q, J = 6.0, 4.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.94 – 3.82 (m, 2H H_{22b}, H_{23b}), 3.80 – 3.72 (m, 1H, $H_{22a\ or\ 23a}$), 3.64 – 3.54 (m, 2H, H_{21}), 3.51 (s, 2H, H_{28}), 3.31 (dd, J = 9.6, 6.7, 1H, H_{11}), 3.24 (p, J = 6.7 Hz, 4H, H_{25}, H_{31}), 3.09 (q, J = 6.4 Hz, 2H, H_{29}), 2.23 (q, J = 8.3, 6.8 Hz, 1H, H_6), 2.15 (p, J = 6.7 Hz, 1H, H_{10}), 1.95 (s, 1H, H_4), 1.89 – 1.69 (m, 5H, H_2, H_{12}, H_{13a}, H_{8a}), 1.65 – 1.16 (m, 23H, H_1, H_7, H_{8b}, H_{13b}, H_{19}, H_{20}, H_{24}, H_{30}, H_{32}), 1.04 (s, 3H, H_{15}), 0.90 (d, J = 6.9 Hz, 3H, H_{17}), 0.67 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0 (C), 169.1 (C), 156.5 (C), 134.3 (C), 133.6 (C), 130.0 (2 × CH), 129.9 (2 × CH), 120.4 (C), 79.3 (C), 75.5 (CH), 72.0 (CH), 63.8 (CH_2), 61.5 (CH_2), 51.3 (CH_2), 51.0 (CH), 46.6 (CH), 46.1 (C), 43.3 (CH_2), 41.5 (C), 40.1 (CH), 37.2 (CH_2), 37.1 (CH_2), 37.0 (CH_2), 36.1 (CH_2), 35.8 (CH_2), 35.4 (CH), 32.7 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.4 (3 × CH_3), 27.2 (CH_2), 23.3 (CH_2), 17.7 (CH_3), 14.7 (CH_3), 11.5 (CH_3). IR (ATR-FTIR), cm^{-1}: 2931 (m), 2359 (s), 2341 (m), 2096 (m), 1695 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{41}H_{63}N_5NaO_8S]^+$ 808.4295; found 808.4290. $[\alpha]_D^{20}$ = +7.04 (c = 0.112, $CHCl_3$).

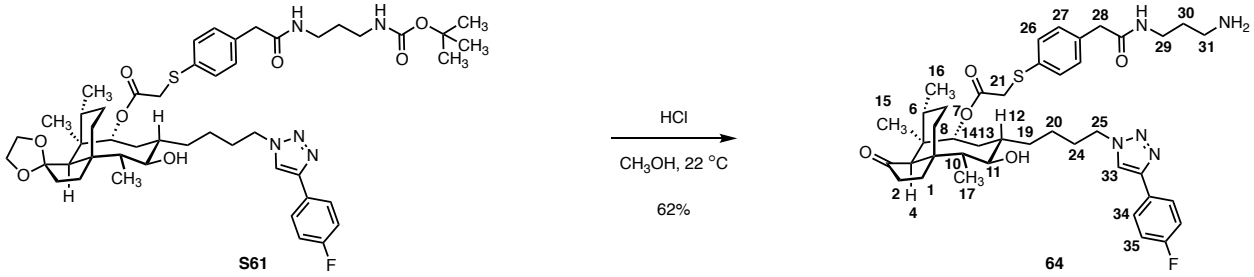
*Synthesis of the triazole **S61**.*



A solution of copper sulfate in water (2.5 mM, 61.0 µL, 150 nmol, 3.0 mol%) and a solution of sodium ascorbate in water (25.0 mM, 61.0 µL, 1.50 µmol, 0.30 equiv) were added to a solution of 1-ethynyl-4-fluorobenzene (1.00 mg, 8.70 µmol, 1.70 equiv) and the azide **S60** (4.00 mg, 5.10 µmol, 1 equiv) in *tert*-butanol (200 µL) at 22 °C. The reaction mixture was stirred for 2 d at 22 °C. The product mixture was diluted sequentially with ethyl acetate (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (2 × 1.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 80% ethyl acetate–hexanes) to provide the triazole **S61** as a fine white solid (2.00 mg, 43%).

R_f = 0.25 (90% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.85 (s, 1H, H_{33}), 7.82 (dd, J = 8.6, 5.5 Hz, 2H, H_{34}), 7.31 (d, J = 8.2 Hz, 2H, H_{27}), 7.20 (d, J = 7.9 Hz, 2H, H_{26}), 7.13 (t, J = 8.8 Hz, 2H, H_{35}), 6.32 (s, 1H, NH), 5.25 (d, J = 7.8 Hz, 1H, H_{14}), 5.05 (s, 1H, NH), 4.38 – 4.26 (m, 2H, H_{25}), 4.01 (td, J = 7.3, 5.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.92 – 3.80 (m, 2H, H_{22b}, H_{23b}), 3.72 (td, J = 7.6, 5.8 Hz, 1H, $H_{22a\ or\ 23a}$), 3.59 (q, J = 15.4 Hz, 2H, H_{21}), 3.47 (s, 2H, H_{28}), 3.29 (dt, J = 9.7, 6.6 Hz, 1H, H_{11}), 3.23 (q, J = 6.3 Hz, 2H, H_{29}), 3.07 (q, J = 6.3 Hz, 2H, H_{31}), 2.24 (tt, J = 13.4, 6.1 Hz, 1H, H_6), 2.16 – 2.09 (m, 1H, H_{10}), 2.00 – 1.89 (m, 2H, H_4, H_{24a}), 1.88 – 1.19 (m, 27H, H_1, H_2, H_7, H_8, H_{12}, H_{13}, H_{19}, H_{20}, H_{24b}, H_{30}, H_{32}), 1.04 (s, 3H, H_{15}), 0.89 (d, J = 7.0 Hz, 3H, H_{17}), 0.68 (d, J = 7.2 Hz, 3H, H_{16}). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 171.1 (C), 169.5 (C), 163.9 (C), 156.7 (broad, C), 147.0 (C), 134.6 (C), 134.4 (C), 130.3 (2 × CH), 129.9 (2 × CH), 127.8 (2 × CH), 120.7 (C), 120.2 (CH), 116.1 (d, J = 21.8 Hz, 2 × CH), 79.3 (C), 75.9 (CH), 72.2 (CH), 64.2 (CH_2), 61.9 (CH_2), 51.3 (CH), 50.5 (CH_2), 46.8 (CH), 46.5 (C), 43.5 (CH_2), 42.0 (C), 40.7 (CH), 37.5 (CH_2), 37.3 (CH_2), 36.5 (CH_2), 36.1 (CH_2), 35.8 (CH_2), 35.4 (broad, CH), 32.6 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 30.5 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 28.5 (3 × CH_3), 27.7 (CH_2), 23.4 (CH_2), 17.9 (CH_3), 14.9 (CH_3), 11.7 (CH_3). ^{19}F NMR (470 MHz, CD_2Cl_2) δ – 114.8. IR (ATR-FTIR), cm^{-1}: 2931 (w), 2360 (m), 2339 (w), 1714 (m). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{49}H_{68}FN_5NaO_8S]^+$ 928.4670; found 928.4665. $[a]_D^{20}$ = +14.8 (c = 0.027, $CHCl_3$).

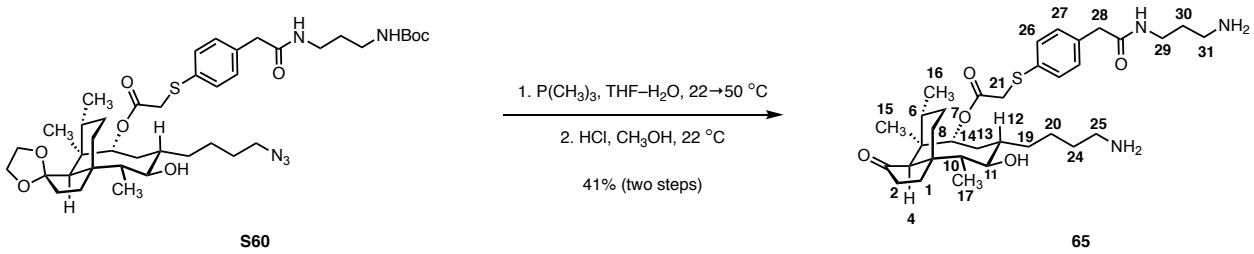
*Synthesis of the triazole **64**.*



Aqueous hydrochloric acid solution (12 N, 2.80 µL, 33.1 µmol, 20.0 equiv) was added to a solution of the ketal **S61** (1.50 mg, 1.70 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 2 d at 22 °C. The product mixture was concentrated to provide the triazole **64** as a fine, white solid (810 µg, 62%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 8.36 (s, 1H, H_{33}), 7.82 (dd, *J* = 8.7, 5.4 Hz, 2H, H_{34}), 7.29 (d, *J* = 8.3 Hz, 2H, H_{27}), 7.21 (d, *J* = 8.3 Hz, 2H, H_{26}), 7.17 (t, *J* = 8.8 Hz, 2H, H_{35}), 5.29 (d, *J* = 6.4 Hz, 1H, H_{14}), 4.45 – 4.33 (m, 2H, H_{25}), 3.68 – 3.53 (m, 2H, H_{21}), 3.46 (s, 2H, H_{28}), 3.29 (1H, H_{11}; detected by HSQC), 3.25 (t, *J* = 6.7 Hz, 2H, H_{29}), 2.88 (t, *J* = 7.3 Hz, 2H, H_{31}), 2.26 – 2.18 (m, 2H, H_{2a}, H_4), 2.18 – 2.06 (m, 2H, H_{2b}, H_{10}), 1.97 – 1.53 (m, 10H, H_{1a}, H_6, H_{8a}, H_{12}, H_{13a}, H_{19a}, H_{24}, H_{30}), 1.50 – 1.17 (m, 10H, H_{1b}, H_7, H_{13b}, H_{15}, H_{19b}, H_{20}), 1.10 (td, *J* = 14.0, 4.5 Hz, 1H, H_{8b}), 0.95 (d, *J* = 7.0 Hz, 3H, H_{17}), 0.69 (d, *J* = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.3 (C), 173.1 (C), 169.8 (C), 163.7 (C), 162.0 (C), 146.1 (C), 134.1 (C), 133.8 (C), 129.4 (2 × CH), 129.3 (2 × CH), 127.4 (d, *J* = 8.2 Hz, 2 × CH), 121.2 (CH), 115.5 (d, *J* = 22.0 Hz, 2 × CH), 74.2 (CH), 71.2 (CH), 57.6 (CH), 50.3 (CH_2), 45.7 (CH), 45.3 (C), 41.8 (CH_2), 41.3 (CH), 41.2 (C), 36.8 (CH_2), 36.6 (CH), 36.3 (CH_2), 35.8 (CH_2), 35.6 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 16.6 (CH_3), 14.1 (CH_3), 10.3 (CH_3). ^{19}F NMR (375 MHz, CD_3OD) δ –115.5 IR (ATR-FTIR), cm^{-1}: 3317 (w), 2369 (m), 2340 (w), 1014 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{42}H_{57}FN_5O_5S]^+$ 762.4064; found 762.4059. $[a]_D^{20}$ = +127.7 (*c* = 0.031, CH_3OH).

*Synthesis of the amine **65**.*



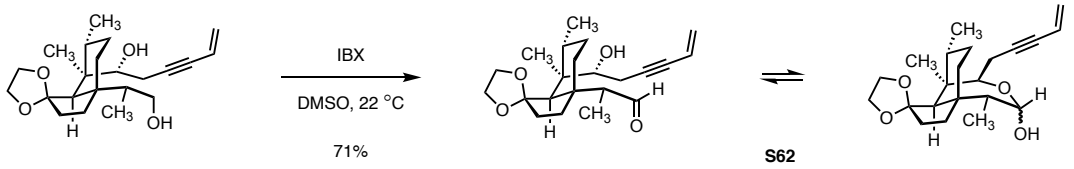
S60 **65**

A solution of trimethylphosphine in tetrahydrofuran (100 mM, 10.0 µL, 12.7 µmol, 5.00 equiv) was added to a solution of the azide **S60** (2.00 mg, 2.50 µmol, 1 equiv) in tetrahydrofuran–water (4:1 v/v, 200 µL) at 22 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred and heated for 3 h at 50 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted sequentially with dichloromethane (1.0 mL) and aqueous sodium thiosulfate solution (10% w/v, 1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Aqueous hydrochloric acid solution (12 N, 2.10 µL, 25.0 µmol, 10.0 equiv) was added to a solution of the unpurified product obtained in the proceeding step (nominally 2.50 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 2 d at 22 °C. The product mixture was concentrated to provide the amine **65** as a fine, white solid (700 µg, 41% over two steps). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 7.37 (d, J = 7.7 Hz, 2H, H_{26}), 7.27 (dd, J = 8.4, 3.2 Hz, 2H, H_{27}), 5.36 – 5.29 (m, 1H, H_{14}), 3.77 – 3.59 (m, 2H, H_{21}), 3.51 (d, J = 5.7 Hz, 2H, H_{28}), 3.35 (s, 1H, H_{11}; detected by HSQC), 3.28 (s, 2H, H_{29}; detected by HSQC), 2.92 – 2.82 (m, 4H, H_{25}, H_{31}), 2.34 – 2.09 (m, 4H, H_2, H_4, H_{10}), 1.97 – 1.56 (m, 10H, H_{1a}, H_6, H_{8a}, H_{12}, H_{13a}, H_{19a}, H_{24}, H_{30}), 1.54 – 1.06 (m, 11H, H_{1b}, H_7, H_{8b}, H_{13b}, H_{15}, H_{19b}, H_{20}), 0.98 (d, J = 7.0 Hz, 3H, H_{17}), 0.71 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.2 (C), 173.1 (C), 169.9 (C), 134.2 (C), 133.7 (C), 129.5 (2 × CH), 129.3 (2 × CH), 74.3 (CH), 71.0 (CH), 57.7 (CH), 45.6 (CH), 45.3 (C), 41.8 (CH_2), 41.4 (CH), 41.3 (C), 39.3 (CH_2), 36.8 (CH_2), 36.7 (CH), 36.4 (CH_2), 36.0 (CH_2), 35.7 (CH_2), 33.8 (CH_2), 32.0 (CH_2), 30.3 (CH_2), 27.4 (CH_2), 27.2 (CH_2), 26.8 (CH), 24.8 (CH_2), 22.7 (CH_2), 16.6 (CH_3), 14.1 (CH_3), 10.3 (CH_3). IR (ATR-FTIR), cm^{-1}: 3734 (w), 2359 (s), 2341 (m), 668 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{34}H_{54}N_3O_5S]^+$, 616.3784; found 616.3795. $[\alpha]_D^{20}$ = +44.6 (c = 0.044, CH_3OH).

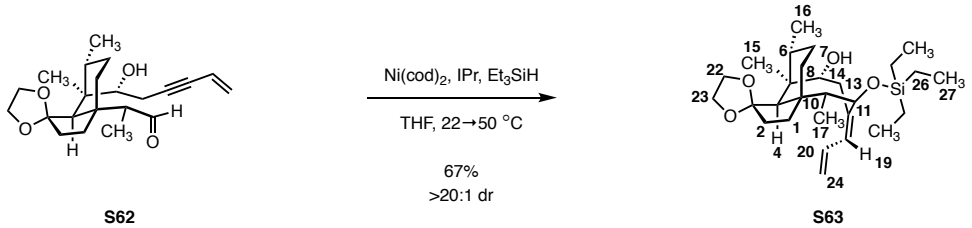
*Synthesis of the aldehyde **S62**.*



2-Iodoxybenzoic acid (171 mg, 579 μmol, 1.05 equiv) was added in one portion to a solution of the homopropargyl alcohol **28** (200 mg, 552 μmol, 1 equiv) in dimethylsulfoxide (5.5 mL) at 22 °C. The reaction mixture was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ether (20 mL), saturated aqueous sodium bicarbonate solution (10 mL), and saturated aqueous sodium thiosulfate solution (10 mL) at 22 °C. The resulting biphasic mixture was stirred vigorously for 30 min at 22 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous phase was extracted with ether (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, three steps) to provide the product **S62** as a white foam (142 mg, 71%). The product **S62** was used immediately in the following step.

^{1}H NMR analysis (400 MHz) of the purified product indicated the presence of a 1:1 mixture of hydroxyaldeyde and hemiketal. The product was used immediately in the following step.

*Synthesis of allylic silyl ether **S63**.*

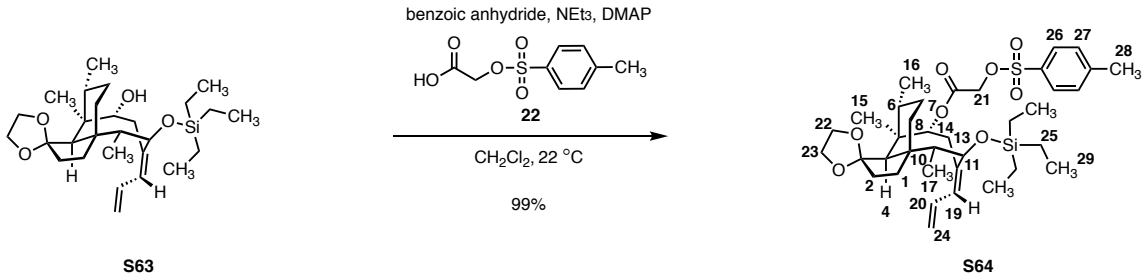


A solution of bis(cyclooctadiene)nickel(0) (19.5 mg, 70.9 μmol, 0.20 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 27.6 mg, 70.9 μmol, 0.20 equiv) in tetrahydrofuran (600 μL) was stirred for 30 min at 22 °C in a nitrogen-filled glovebox. The resulting solution was added to a solution of triethylsilane (169 μl, 102 μmol, 3.00 equiv) and the alkynyl aldehyde **S62** (142 mg, 355 μmol, 1 equiv) in tetrahydrofuran (6.5 mL) in a round-bottomed flask fused to a Teflon-coated valve at 22 °C in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed reaction vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred for 3 h at 50 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was eluted over a short pad of silica gel (2.0 cm × 2.0 cm, eluting with 30% ether–hexanes). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes initially, grading to 30% ether–hexanes, three steps) to provide the allylic silyl ether **S63** as a clear oil (114 mg, 67%).

Within the limits of detection (600 MHz ^{1}H NMR analysis), the allylic silyl ether **S63** was formed as a single diastereomer. The relative stereochemistry was assigned by comparison of $^3J_{H–H}$ coupling constants to the allylic silyl ether **S6**.

R_f = 0.71 (30% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.65 (dt, J = 16.8, 10.5 Hz, 1H, H_{20}), 5.84 (d, J = 10.7 Hz, 1H, H_{19}), 5.21 (d, J = 16.7 Hz, 1H, H_{24a}), 5.14 (d, J = 10.1 Hz, 1H, H_{24b}), 4.77 (dt, J = 10.7, 5.0 Hz, 1H, H_{14}), 4.06 – 3.94 (m, 1H, $H_{22a\ or\ 23b}$), 3.91 (d, J = 8.7 Hz, 1H, H_{11}), 3.81 (dq, J = 13.6, 6.9, 2H, H_{22b}, H_{23b}), 3.65 (q, J = 7.4, 6.8 1H, $H_{22a\ or\ 23a}$), 3.02 (s, 1H, H_4), 2.76 (dd, J = 15.4, 11.2 Hz, 1H, H_{13a}), 2.48 (dt, J = 15.4, 3.4 Hz, 1H, H_{13b}), 2.30 – 2.10 (m, 2H, H_6, H_{10}), 1.86 – 1.66 (m, 2H, H_2), 1.64 – 1.20 (m, 6H, H_1, H_7, H_8), 1.01 (s, 6H, H_{15}, $H_{16\ or\ 17}$), 0.95 – 0.88 (m, 12H, $H_{16\ or\ 17}$, H_{27}), 0.56 (q, J = 7.9 Hz, 6H, H_{26}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.3 (C), 132.3 (CH), 127.1 (CH), 119.8 (C), 117.9 (CH_2), 84.3 (CH), 69.3 (CH), 63.6 (CH_2), 61.4 (CH_2), 51.0 (CH), 45.5 (C), 43.1 (C), 42.5 (CH), 35.9 (CH_2), 35.9 (CH), 34.3 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 18.6 (CH_3), 15.7 (CH_3), 13.9 (CH_3), 7.0 (3 × CH_3), 5.1 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 2953 (m), 2876 (m), 2360 (s), 2340 (m), 1035 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{28}H_{49}O_4Si]^+$ 477.3400; found 477.3468. $[a]_D^{20}$ = +23.5 (c = 0.255, $CHCl_3$).

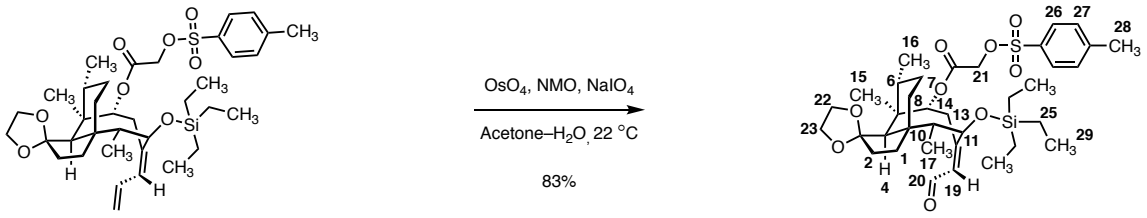
*Synthesis of ester **S64**.*



(4-Dimethylamino)pyridine (600 μg, 5.20 μmol, 0.10 equiv) was added to a solution of the sulfonate **22** (60.4 mg, 262 μmol, 5.00 equiv), benzoic anhydride (59.3 mg, 262 μmol, 5.00 equiv), triethylamine (44.0 μL, 315 μmol, 6.00 equiv), and the allylic silyl ether **S63** [25.0 mg, 52.4 μmol, 1 equiv; dried by azeotropic distillation with benzene (3 × 1.0 mL)] in dichloromethane (350 μL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with ether (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes initially, grading to 50% ether–hexanes, three steps) to provide the ester **S64** as a clear oil (36.0 mg, 99%).

R_f = 0.71 (30% ether–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H, H_{26}), 7.34 (d, J = 7.8 Hz, 2H, H_{27}), 6.57 (dt, J = 16.7, 10.5 Hz, 1H, H_{20}), 5.91 (dd, J = 11.3, 4.8 Hz, 1H, H_{14}), 5.87 (dd, J = 10.9, 2.3 Hz, 1H, H_{19}), 5.31 – 5.05 (m, 2H, H_{24}), 4.56 – 4.47 (m, 2H, H_{21}), 3.94 (q, J = 6.6, 6.2 Hz, 1H, $H_{22a\ or\ 23a}$), 3.90 (d, J = 8.7 Hz, 1H, H_{11}), 3.85 – 3.75 (m, 2H, H, $H_{22a\ or\ 23a}$, $H_{22b\ or\ 23b}$), 3.69 – 3.62 (m, 1H, $H_{22b\ or\ 23b}$), 3.04 (d, J = 2.3 Hz, 1H, H_4), 2.71 (dd, J = 15.1, 11.3 Hz, 1H, H_{13a}), 2.43 (s, 3H, H_{28}), 2.37 (ddd, J = 15.2, 4.8, 2.5 Hz, 1H, H_{13b}), 2.26 – 2.14 (m, 2H, H_6, H_{10}), 1.77 – 1.66 (m, 2H, H_2), 1.55 – 1.40 (m, 3H, H_{7a}, H_8), 1.37 – 1.31 (m, 2H, H_{1a}, H_{7b}), 1.29 – 1.20 (m, 1H, H_{1b}), 1.07 (s, 3H, H_{15}), 1.01 (d, J = 6.4 Hz, 3H, H_{17}), 0.90 (t, J = 7.9 Hz, 9H, H_{29}), 0.59 (d, J = 7.2 Hz, 3H, H_{16}), 0.53 (q, J = 8.0 Hz, 6H, H_{25}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8 (C), 145.1 (C), 142.1 (C), 132.8 (C), 131.9 (2 × CH), 129.8 (2 × CH), 128.1 (CH), 127.5 (CH), 119.7 (C), 118.4 (CH_2), 83.6 (CH), 73.6 (CH), 65.1 (CH_2), 63.7 (CH_2), 61.4 (CH_2), 50.7 (CH), 45.4 (C), 42.4 (C), 42.4 (CH), 35.9 (CH_2), 35.5 (CH), 30.3 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 21.7 (CH_3), 17.0 (CH_3), 15.7 (CH_3), 15.4 (CH_3), 7.0 (3 × CH_3), 5.0 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 2953 (m), 2877 (m), 2362 (m), 2340 (m), 1761 (m), 1372 (m), 1190 (m), 1043 (s). HRMS-ESI (m/z): [M + Na]$^+$ calcd for $[C_{37}H_{56}NaO_8SSi]^+$ 711.3363; found 711.3348. $[\alpha]_D^{20}$ = –21.5 (c = 0.981, $CHCl_3$).

*Synthesis of the enal **S65**.*

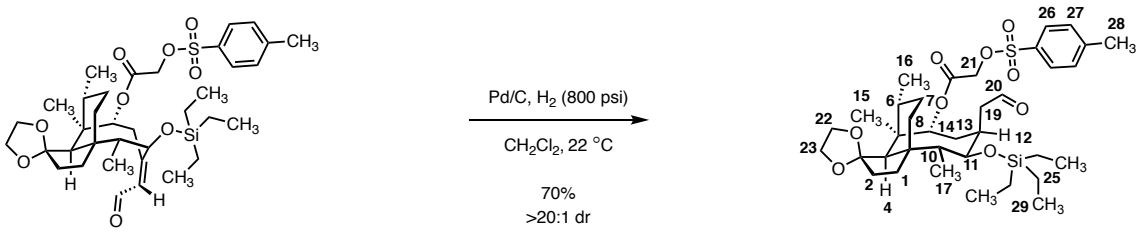


S64 **S65**

Aqueous osmium tetroxide solution (80 mM, 11.0 μL, 870 nmol, 2.0 mol%) was added to a solution of 4-methylmorpholine *N*-oxide (10.5 mg, 87.1 μmol, 2.00 equiv) and the diene **S64** (30.0 mg, 43.5 μmol, 1 equiv) in acetone–water (2:1 v/v, 1.0 mL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. Sodium metaperiodate (18.6 mg, 87.1 μmol, 2.00 equiv) was added to the reaction mixture at 22 °C and the resulting solution was stirred for 3 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 2.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes initially, grading to 50% ether–hexanes, three steps) to provide the enal **S65** as a clear oil (25.0 mg, 83%).

R_f = 0.41 (30% ether–hexanes; UV). ^{1}H NMR (400 MHz, C_6D_6) δ 10.08 (dd, *J* = 7.2, 1.9 Hz, 1H, H_{20}), 7.79 (dd, *J* = 8.4, 2.0 Hz, 2H, H_{26}), 6.72 – 6.64 (m, 2H, H_{27}), 6.11 – 5.97 (m, 2H, H_{14}, H_{19}), 4.40 – 4.19 (m, 2H, H_{21}), 3.91 (d, *J* = 7.9 Hz, 1H, H_{11}), 3.52 – 3.25 (m, 4H, H_{13a}, $H_{22a\ or\ 23a}$, H_{22b}, H_{23b}), 3.16 (qd, *J* = 6.3, 5.2, 2.6 Hz, 1H, $H_{22a\ or\ 23a}$), 2.96 – 2.81 (m, 2H, H_4, H_{13b}), 2.39 (dd, *J* = 18.7, 11.8 Hz, 2H, H_6, H_{10}), 1.81 (s, 3H, H_{28}), 1.67 – 1.06 (m, 11H, H_1, H_2, H_7, H_8, H_{15}), 0.96 (td, *J* = 7.9, 1.9 Hz, 12H, H_{17}, H_{29}), 0.78 (dd, *J* = 7.2, 2.0 Hz, 3H, H_{16}), 0.56 (qd, *J* = 7.9, 1.9 Hz, 6H, H_{25}). ^{13}C NMR (100 MHz, C_6D_6) δ 189.5 (CH), 165.2 (C), 162.4 (C), 144.3 (C), 133.5 (C), 129.5 (2 × CH), 128.0 (2 × CH), 126.5 (CH), 119.3 (C), 81.9 (CH), 72.9 (CH), 64.6 (CH_2), 63.4 (CH_2), 61.1 (CH_2), 51.9 (CH), 45.3 (C), 43.3 (CH), 42.4 (C), 35.6 (CH), 35.6 (CH_2), 30.6 (CH_2), 29.8 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 27.3 (CH_2), 20.7 (CH_3), 17.0 (CH_3), 15.3 (CH_3), 15.0 (CH_3), 6.8 (3 × CH_3), 5.0 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 2953 (m), 2877 (m), 2362 (m), 2341 (m), 1762 (m), 1372 (m), 1178 (m), 1043 (s). HRMS-ESI (m/z): [M + Na]$^+$ calcd for $[C_{37}H_{54}NaO_9SSi]^+$ 713.3156; found 713.3153. $[a]_D^{20}$ = –26.0 (*c* = 0.769, $CHCl_3$).

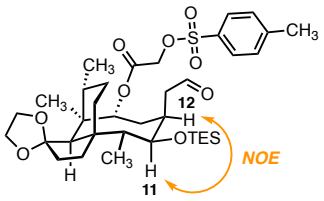
Synthesis of the aldehyde ***S66****.*



S65 **S66**

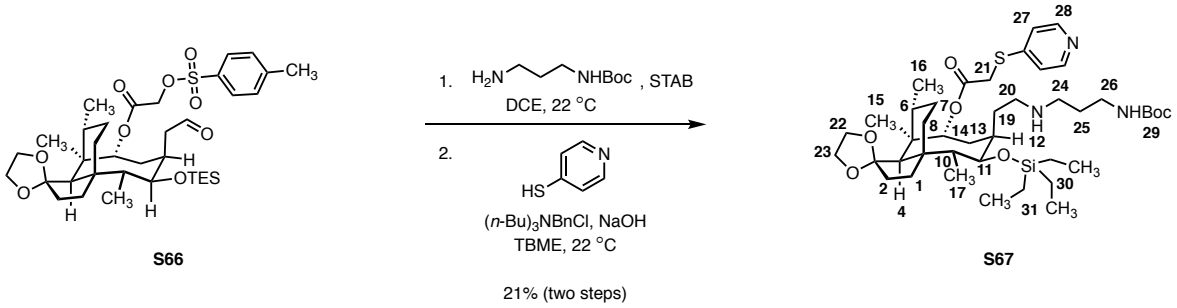
Palladium on carbon (10% w/w, 600 μg) was added to a solution of the enal **S65** (6.00 mg, 10.4 μmol, 1 equiv) in dichloromethane (800 μL) at 22 °C. The reaction vessel was then transferred to a stainless-steel hydrogenation apparatus. The apparatus was purged with dihydrogen by pressurizing to 200 psi and venting. This process was repeated three times. The vessel was then pressurized to 800 psi dihydrogen and sealed. The reaction mixture was stirred at 22 °C for 15 h. The apparatus was then slowly vented. The product mixture was filtered over a pad of Celite. The Celite pad was rinsed with dichloromethane (5.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether–hexanes) to provide the aldehyde **S66** as a colorless oil (4.20 mg, 70%).

Within the limits of detection (400 MHz ^{1}H NMR analysis), the hydrogenation product **S66** was formed as a single diastereomer. The relative stereochemistry of the hydrogenation product was determined by NOE correlations between H11 and H12.



R_f = 0.48 (50% ether–hexanes; PAA). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.72 (s, 1H, H_{20}), 7.77 (d, J = 8.3 Hz, 2H, H_{26}), 7.38 (d, J = 8.1 Hz, 2H, H_{27}), 5.28 (d, J = 8.9 Hz, 1H, H_{14}), 4.41 (d, J = 0.7 Hz, 2H, H_{21}), 4.01 (q, J = 6.3, 5.3 Hz, 1H, $H_{22a\ or\ 23a}$), 3.86 (qt, J = 12.5, 5.9 Hz, 2H, H_{22b}, H_{23b}), 3.79 – 3.68 (m, 2H, H_{11}, $H_{22a\ or\ 23a}$), 2.95 (dd, J = 18.0, 9.3 Hz, 1H, H_{19a}), 2.79 (dd, J = 18.1, 3.8 Hz, 1H, H_{19b}), 2.52 (dt, J = 8.7, 3.9 Hz, 1H, H_{12}), 2.45 (s, 3H, H_{28}), 2.31 – 2.15 (m, 2H, H_6, H_{13a}), 1.99 (q, J = 6.8 Hz, 2H, H_4, H_{10}), 1.82 (td, J = 11.2, 10.5, 3.3 Hz, 2H, H_2), 1.58 – 1.52 (m, 2H, H_8), 1.44 – 1.17 (m, 5H, H_1, H_7, H_{13b}), 1.02 (s, 3H, H_{15}), 0.93 (t, J = 7.9 Hz, 9H, H_{29}), 0.80 (d, J = 7.0 Hz, 3H, H_{17}), 0.63 – 0.54 (m, 9H, H_{16}, H_{25}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 202.0 (CH), 165.2 (C), 145.6 (C), 132.4 (C), 130.0 (2 × CH), 127.9 (2 × CH), 120.3 (C), 72.0 (CH), 70.9 (CH), 65.3 (CH_2), 63.7 (CH_2), 61.5 (CH_2), 50.6 (CH), 45.9 (C), 41.8 (C), 40.4 (CH_2), 38.7 (CH), 35.6 (CH_2), 35.2 (CH), 35.1 (CH), 34.0 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 21.4 (CH_3), 16.9 (CH_3), 14.4 (CH_3), 12.0 (CH_3), 6.7 (3 × CH_3), 4.9 (3 × CH_2). IR (ATR-FTIR), cm^{-1}: 2952 (m), 2878 (w), 2365 (w), 1732 (s), 1178 (m), 1047 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{37}H_{56}NaO_9SSi]^+$ 715.3312; found 715.3300. $[\alpha]_D^{20}$ = –5.11 (c = 0.219, $CHCl_3$).

*Synthesis of the pyridyl sulfide **S67**.*



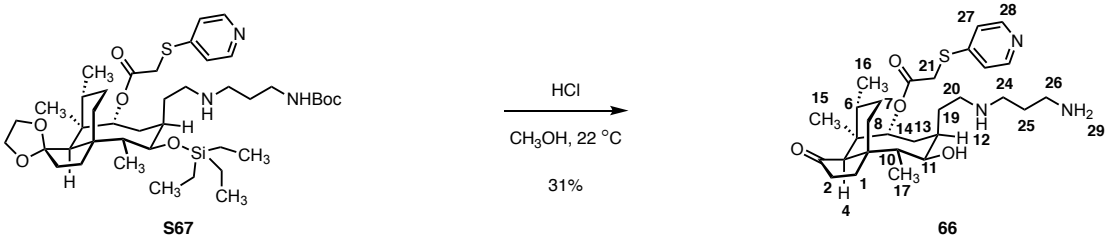
N-(*tert*-Butoxycarbonyl)-1,3-propanediamine (2.10 mg, 12.1 μmol, 2.00 equiv) was added to a suspension of magnesium sulfate (1.46 mg, 12.1 μmol, 2.00 equiv) and the aldehyde **S66** (4.20 mg, 6.11 μmol, 1 equiv) in dichloroethane (250 μL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. Sodium triacetoxyborohydride (2.60 mg, 24.2 μmol, 2.00 equiv) was then added at 22 °C. The reaction mixture was stirred for 8 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Aqueous sodium hydroxide solution (0.1 N, 8.00 μL, 7.90 μmol, 1.30 equiv) was added to a solution of 4-mercaptopyridine (900 μg, 7.90 μmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (100 μg, 610 nmol, 0.10 equiv), and the unpurified product obtained in the preceding step (nominally 6.10 μmol, 1 equiv) in *tert*-butyl methyl ether (230 μL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the pyridyl sulfide **S67** as a white solid (1.00 mg, 21% over two steps).

R_f = 0.15 (70% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.39 (d, *J* = 6.3 Hz, 2H, H_{28}), 7.18 (d, *J* = 6.3 Hz, 2H, H_{27}), 5.44 (d, *J* = 8.8 Hz, 1H, H_{14}), 4.05 – 3.95 (m, 1H, $H_{22a\text{ or }23a}$), 3.94 – 3.80 (m, 2H, H_{22b}, H_{23b}), 3.77 – 3.56 (m, 4H, H_{11}, H_{21}, $H_{22a\text{ or }23a}$), 3.17 – 3.10 (m, 2H, H_{26}), 2.51 (s, 2H, H_{24}), 2.36 (s, 2H, H_{20}), 2.23 (ddd, *J* = 11.5, 7.1, 4.1 Hz, 1H, H_6), 2.15 – 1.98 (m, 4H, H_4, H_{10}, H_{13}), 1.92 – 1.48 (m, 7H, H_2, H_{12}, H_{19}, H_{25}), 1.45 – 1.20 (m, 16H, H_1, H_7, H_8, H_{13b}, H_{29}), 1.06 (s, 3H, H_{15}), 0.95 (td, *J* = 8.0, 5.0 Hz, 9H, H_{31}), 0.78 (d, *J* = 7.1 Hz, 3H, H_{17}), 0.65 (d, *J* = 7.2 Hz, 3H, H_{16}), 0.58 (q, *J* = 7.9 Hz, 6H, H_{30}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 168.0 (C), 156.4

(C), 149.8 (2 × CH), 147.8 (C), 121.0 (2 × CH), 120.8 (C), 78.9 (C), 72.5 (CH), 72.1 (CH), 64.1 (CH_2), 61.9 (CH_2), 51.2 (CH), 49.4 (CH_2), 48.1 (CH_2), 46.4 (C), 43.2 (CH), 42.3 (C), 39.8 (CH_2), 36.1 (CH_2), 35.8 (CH), 35.0 (CH), 34.3 (CH_2), 33.9 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 28.8 (CH_2), 28.6 (3 × CH_3), 27.7 (CH_2), 24.6 (CH_2), 17.3 (CH_3), 15.0 (CH_3), 12.5 (CH_3), 7.3 (3 × CH_3), 5.5 (3 × CH_3). IR (ATR-FTIR), cm^{-1}: 2949 (m), 2876 (m), 2360 (m), 2339 (w), 1714 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{42}H_{72}NaN_3O_7SSi]^+$ 790.4860; found 790.4842. $[a]_D^{20}$ = +1.50 (c = 0.080, $CHCl_3$).

*Synthesis of the amine **66**.*

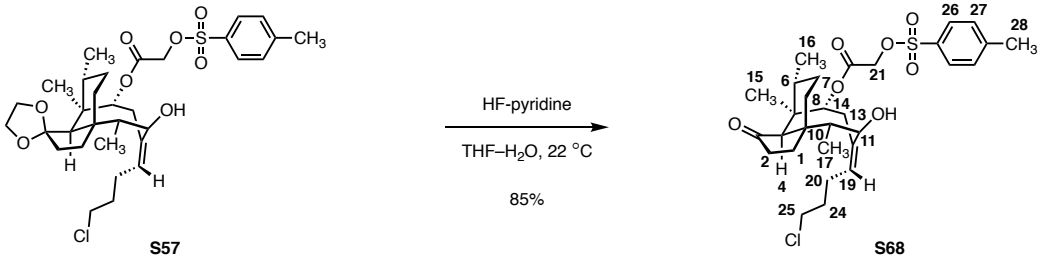


S67 **66**

Aqueous hydrochloric acid solution (12 N, 2.10 µL, 25.3 µmol, 20.0 equiv) was added to a solution of the ketal **S67** (1.00 mg, 1.30 µmol, 1 equiv) in methanol (200 µL) at 22 °C. The reaction mixture was stirred for 4 d at 22 °C. The product mixture was concentrated to provide the amine **66** as a fine, white solid (240 µg, 31%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.15 (70% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 8.57 (d, J = 6.2 Hz, 2H, H_{28}), 7.95 (d, J = 6.3 Hz, 2H, H_{27}), 5.47 (d, J = 8.5 Hz, 1H, H_{14}), 4.38 – 4.15 (m, 2H, H_{21}), 3.90 (t, J = 8.4 Hz, 1H, H_{11}), 3.17 – 3.10 (m, 2H, H_{24}), 3.06 (q, J = 8.7, 8.2 Hz, 2H, H_{26}), 2.45 – 2.22 (m, 4H, H_4, H_{13}, H_{20a}), 2.17 – 1.96 (m, 8H, H_2, H_{10}, H_{12}, H_{19a}, H_{20b}, H_{25}), 1.79 – 1.58 (m, 3H, H_6, H_{8a}, H_{19b}), 1.53 – 1.23 (m, 7H, H_1, H_7, H_{15}), 1.14 (qd, J = 14.0, 12.2, 3.8 Hz, 1H, H_{8b}), 0.95 (d, J = 7.1 Hz, 3H, H_{17}), 0.73 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.9 (C), 168.4 (C), 165.2 (C), 140.9 (2 × CH), 123.8 (2 × CH), 72.8 (CH), 70.5 (CH), 58.6 (CH), 46.6 (C), 45.7 (CH_2), 43.2 (C), 42.8 (CH), 38.0 (CH), 38.0 (CH_2), 36.2 (CH_2), 35.4 (CH_2), 35.1 (CH_2), 35.0 (CH_2), 35.0 (CH), 31.2 (CH_2), 30.3 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 17.9 (CH_3), 15.3 (CH_3), 11.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 2924 (m), 2360 (s), 2341 (m), 1725 (w), 1624 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{29}H_{46}N_3O_5S]^+$ 531.3131; found 531.3192. $[a]_D^{20}$ = –906.7 (c = 0.015, CH_3OH).

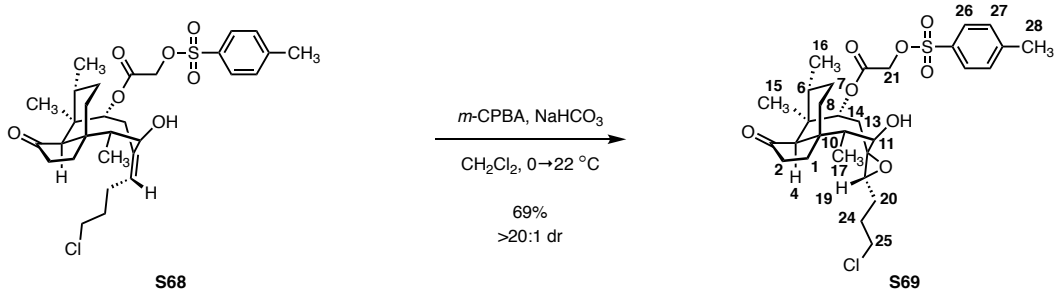
*Synthesis of the ketone **S68**.*



Hydrogen fluoride–pyridine complex (120 μL 811 μmol, 2.00 equiv) was added to a solution of the ester **S57** (253 mg, 406 μmol, 1 equiv) in tetrahydrofuran–water (2:1 v/v, 24 mL) at 22 °C. The reaction mixture was stirred for 16 h at 22 °C. A second portion of hydrogen fluoride–pyridine complex (376 mg, 811 μmol, 2.00 equiv) was then added at 22 °C. The reaction mixture was stirred at 22 °C for 4 d. The product mixture was diluted with ethyl acetate (20 mL). The diluted product mixture was cooled to 0 °C over 20 min. Saturated aqueous sodium bicarbonate solution (20 mL) was then added dropwise over 5 min at 0 °C. The resulting biphasic mixture was warmed to 22 °C over 10 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous later was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (40 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, four steps) to provide the ketone **S68** as a white solid (200 mg, 85%).

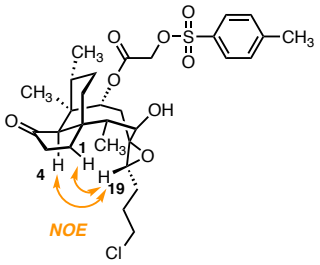
R_f = 0.45 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1 Hz, 2H, H_{26}), 7.36 (d, J = 8.0 Hz, 2H, H_{27}), 6.00 (dd, J = 11.6, 5.1 Hz, 1H, H_{14}), 5.38 (td, J = 7.0, 2.4, 1H, H_{19}), 4.57 – 4.47 (m, 2H, H_{21}), 3.99 (d, J = 9.4 Hz, 1H, H_{11}), 3.52 (t, J = 6.3 Hz, 2H, H_{25}), 3.14 (s, 1H, H_4), 2.67 (dd, J = 15.3, 11.5 Hz, 1H, H_{13a}), 2.45 (s, 3H, H_{28}), 2.41 (ddd, J = 15.3, 5.0, 2.6 Hz, 1H, H_{13b}), 2.30 (dq, J = 9.3, 6.4 Hz, 1H, H_{10}), 2.24 (q, J = 7.5 Hz, 2H, H_{20}), 2.11 (dd, J = 10.0, 5.8 Hz, 2H, H_2), 1.85 (p, J = 6.9 Hz, 2H, H_{24}), 1.71 – 1.46 (m, 5H, H_1, H_6, H_{7a}, H_{8a}), 1.44 (s, 3H, H_{15}), 1.43 – 1.33 (m, 1H, H_{7b}), 1.17 (d, J = 6.3 Hz, 3H, H_{17}), 1.03 (td, J = 14.0, 4.6 Hz, 1H, H_{8b}), 0.65 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.5 (C), 165.4 (C), 145.3 (C), 141.5 (C), 132.6 (C), 129.9 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 83.3 (CH), 71.7 (CH), 64.8 (CH_2), 59.5 (CH), 44.7 (C), 44.3 (CH_2), 42.1 (C), 41.5 (CH), 36.7 (CH), 34.2 (CH_2), 31.6 (CH_2), 30.3 (CH_2), 29.1 (CH_2), 27.1 (CH_2), 25.4 (CH_2), 25.2 (CH_2), 21.7 (CH_3), 16.9 (CH_3), 15.8 (CH_3), 15.1 (CH_3). IR (ATR-FTIR), cm^{-1}: 2924 (w), 1729 (w), 1190 (w), 1368 (w), 1024 (w). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{30}H_{41}ClNaO_7S]^+$ 603.2159 found 603.2154. $[\alpha]_D^{20}$ = +9.15 (c = 0.260, $CHCl_3$).

*Synthesis of the epoxide **S69**.*



Meta-chloroperbenzoic acid (5.20 mg, 30.3 µmol, 1.10 equiv) was added to a solution of sodium bicarbonate (4.60 mg, 55.1 µmol, 2.00 equiv) and the alkene **S68** (16.0 mg, 27.5 µmol, 1 equiv) in dichloromethane (1.1 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and was then allowed to warm to 22 °C over 1 h. The warmed reaction mixture was stirred for 16 h at 22 °C. The product mixture was diluted sequentially with ether (3.0 mL) and saturated aqueous sodium bicarbonate solution (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ether (3 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, three steps) to provide the epoxide **S69** as a colorless oil (11.4 mg, 69%).

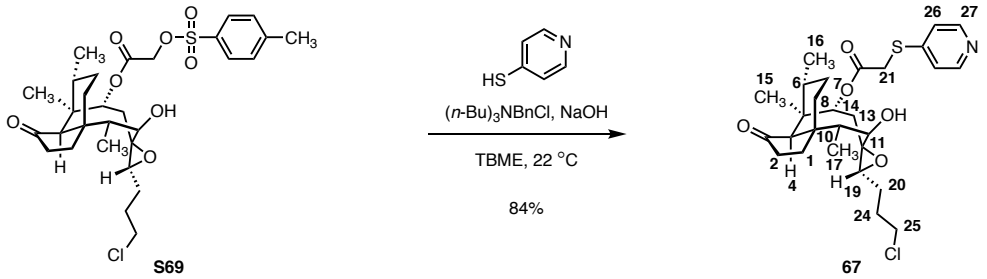
Within the limits of detection (600 MHz ^{1}H analysis), the epoxide **S69** was formed as a single diastereomer. The relative stereochemistry of the C12 epoxide was determined by NOE correlations between H19 and H4 and NOE correlations between H19 and H1.



R_f = 0.42 (50% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 2H, H_{26}), 7.35 (d, J = 8.0 Hz, 2H, H_{27}), 5.99 (dd, J = 11.3, 4.8 Hz, 1H, H_{14}), 4.52 (s, 2H, H_{21}), 3.68 – 3.57 (m, 2H, H_{25}), 3.07 (dd, J = 9.4, 3.2 Hz, 1H, H_{11}), 2.98 (dd, J = 9.0, 3.0 Hz, 1H, H_{19}), 2.46 (d, J = 6.4 Hz, 4H, H_4, H_{28}), 2.41 (dq, J = 9.4, 6.5 Hz, 1H, H_{10}), 2.32 – 2.24 (m, 2H, H_{13a}, OH), 2.21 (dd, J = 10.1, 5.9 Hz, 2H, H_2), 2.05 – 1.93 (m, 2H, H_{24}), 1.89 (dddd, J = 14.6, 8.9, 5.9, 3.1 Hz, 1H, H_{20a}), 1.75 – 1.50 (m, 6H, H_{1a}, H_6, H_{7a}, H_{8a}, H_{13b}, H_{20b}), 1.50 – 1.42 (m, 4H, H_{1b}, H_{15}), 1.42 – 1.37 (m, 1H, H_{7b}), 1.12 (d, J = 6.4 Hz, 3H, H_{17}), 1.08 (td, J = 14.0, 4.4 Hz, 1H, H_{8b}), 0.67 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.9 (C), 165.0 (C), 145.4 (C), 132.5 (C), 129.9 (2 × CH), 128.1 (2 × CH), 81.0 (CH), 71.0 (CH), 67.5 (CH), 64.8 (CH_2), 64.5 (C), 60.0

(CH), 44.5 (C), 44.1 (CH_2), 41.3 (C), 40.7 (CH), 36.7 (CH), 34.2 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 26.9 (CH_2), 26.4 (CH_2), 25.3 (CH_2), 21.7 (CH_3), 16.7 (CH_3), 15.6 (CH_3), 14.9 (CH_3). IR (ATR-FTIR), cm^{-1}: 2917 (w), 2356 (w), 2341 (w), 1733 (w), 1041 (m), 800 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{30}H_{42}ClO_8S]^+$ 597.2289; found 597.2283. $[a]_D^{20}$ = +5.83 (c = 0.096, $CHCl_3$).

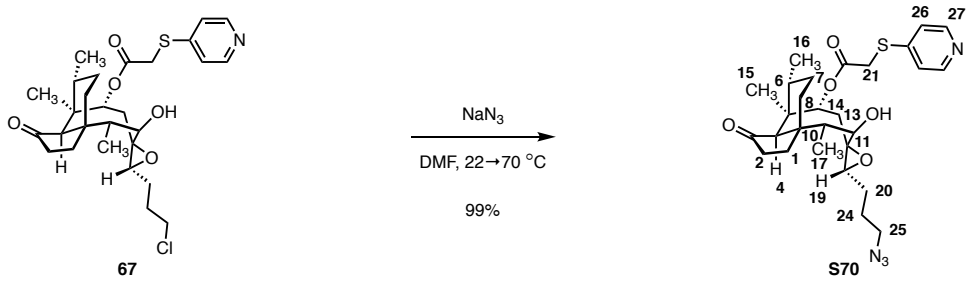
*Synthesis of the pyridyl sulfide **67**.*



Aqueous sodium hydroxide solution (1 N, 22.0 μL, 21.8 μmol, 1.30 equiv) was added to a solution of 4-mercaptopyridine (2.40 mg, 21.8 μmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (400 μg, 1.70 μmol, 0.10 equiv), and the sulfonate **S69** (10.0 mg, 16.7 μmol, 1 equiv) in *tert*-butyl methyl ether (260 μL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the pyridyl sulfide **67** as a colorless foam (7.70 mg, 84%).

R_f = 0.36 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.39 (d, J = 6.4 Hz, 2H, H_{27}), 7.17 (d, J = 6.4 Hz, 2H, H_{26}), 5.93 (dd, J = 11.4, 4.9 Hz, 1H, H_{14}), 3.71 (d, J = 2.4 Hz, 2H, H_{21}), 3.69 – 3.55 (m, 2H, H_{25}), 3.06 (dd, J = 9.4, 3.1 Hz, 1H, H_{11}), 2.98 (dd, J = 9.1, 3.0 Hz, 1H, H_{19}), 2.45 (d, J = 3.0 Hz, 1H, H_4), 2.42 – 2.31 (m, 2H, H_{10}, OH), 2.28 – 2.13 (m, 3H, H_{13a}, H_2), 2.04 – 1.90 (m, 2H, H_{24}), 1.90 – 1.77 (m, 1H, H_{20a}), 1.75 – 1.60 (m, 3H, H_{1a}, H_6, H_{8a}), 1.60 – 1.33 (m, 8H, H_{1b}, H_7, H_{13b}, H_{15}, H_{20b}), 1.14 – 1.01 (m, 4H, H_{8b}, H_{17}), 0.73 (d, J = 7.0 Hz, 3H, H_{16}). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 214.7 (C), 167.5 (C), 149.5 (2 × CH), 147.0 (C), 120.7 (2 × CH), 81.0 (CH), 71.1 (CH), 67.6 (CH), 64.3 (C), 59.9 (CH), 44.4 (C), 44.4 (CH_2), 41.3 (C), 40.7 (CH), 36.8 (CH), 34.1 (CH_2), 33.7 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 16.8 (CH_3), 15.4 (CH_3), 14.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2926 (m), 1730 (m), 1276 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{39}ClNO_5S]^+$ 536.2237; found 536.2232. $[\alpha]_D^{20}$ = +8.60 (c = 0.272, $CHCl_3$).

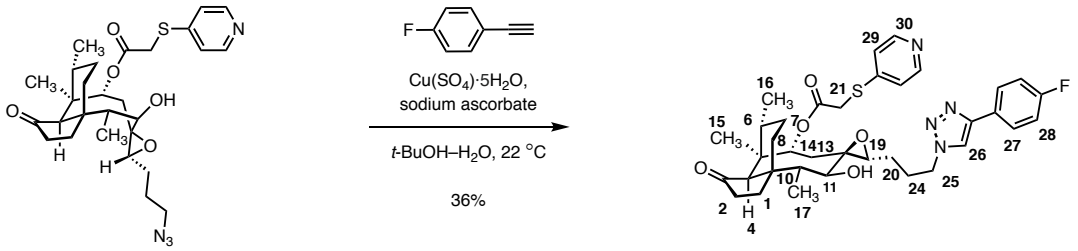
*Synthesis of the azide **S70**.*



Sodium azide (1.00 mg, 15.4 μmol, 3.40 equiv) was added to a solution of alkyl chloride **67** (3.00 mg, 4.50 μmol, 1 equiv) in *N,N*-dimethylformamide (200 μL) at 22 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred for 3 h at 70 °C. The product mixture was cooled to 22 °C over 20 min. The cooled product mixture was diluted sequentially with ethyl acetate (3.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The organic layer was washed sequentially with water (2 × 1.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% acetone–hexanes) to provide the azide **S70** as a fine white solid (2.50 mg, 99%).

R_f = 0.36 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.40 (d, J = 4.4 Hz, 2H, H_{27}), 7.18 (d, J = 4.4 Hz, 2H, H_{26}), 5.94 (dd, J = 11.5, 4.8 Hz, 1H, H_{14}), 3.72 (dd, J = 5.7, 1.7 Hz, 2H, H_{21}), 3.43 – 3.31 (m, 2H, H_{25}), 3.06 (d, J = 9.4 Hz, 1H, H_{11}), 2.97 (d, J = 9.06, 1H, H_{19}), 2.45 (d, J = 2.9 Hz, 1H, H_4), 2.40 – 2.34 (m, 2H, H_{10}, OH), 2.29 – 2.15 (m, 3H, H_2, H_{13a}), 1.86 – 1.62 (m, 5H, H_{1a}, H_6, H_{8a}, H_{24}), 1.56 – 1.36 (m, 9H, H_{1b}, H_7, H_{13b}, H_{15}, H_{20}), 1.17 – 1.04 (m, 4H, H_{8b}, H_{17}), 0.74 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 214.7 (C), 167.5 (C), 149.4 (2 × CH), 147.0 (C), 120.7 (2 × CH), 81.1 (CH), 71.1 (CH), 67.8 (CH), 64.3 (C), 59.9 (CH), 50.9 (CH_2), 44.4 (C), 41.3 (C), 40.7 (CH), 36.8 (CH), 34.1 (CH_2), 33.7 (CH_2), 30.1 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 25.3 (CH_2), 16.8 (CH_3), 15.4 (CH_3), 14.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 2361 (w), 2341 (w), 1731 (w), 772 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{39}N_4O_5S]^+$ 543.2641; found 543.2636. $[a]_D^{20}$ = +8.53 (c = 0.150, $CHCl_3$).

*Synthesis of the triazole **68**.*

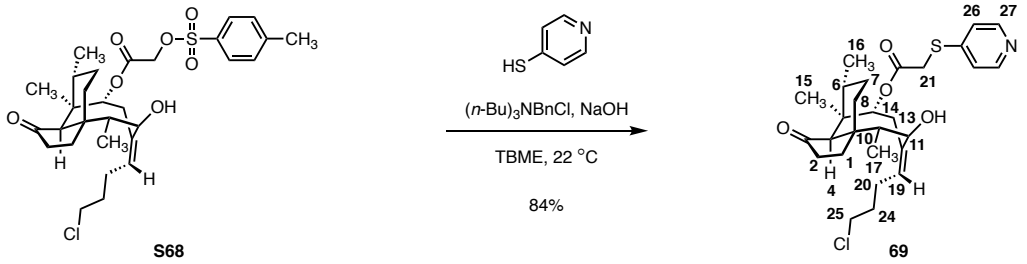


S70 **68**

A solution of copper sulfate in water (10.0 mM, 13.0 μL, 130 nmol, 3.0 mol%) and a solution of sodium ascorbate in water (100 mM, 13.0 μL, 1.30 μmol, 0.30 equiv) were added in sequence to a solution of 1-ethynyl-4-fluorobenzene (1.50 mg, 12.7 μmol, 3.00 equiv) and the azide **S70** (2.30 mg, 4.20 μmol, 1 equiv) in *tert*-butanol (200 μL) at 22 °C. The reaction mixture was stirred for 2 d at 22 °C. The product mixture was diluted sequentially with ethyl acetate (2.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (2 × 1.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 80 % ethyl acetate–hexanes) to provide the triazole **68** as a fine white solid (1.00 mg, 36%).

R_f = 0.37 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.39 (d, J = 6.3 Hz, 2H, H_{30}), 7.86 – 7.80 (m, 3H, H_{26}, H_{27}), 7.19 – 7.11 (m, 4H, H_{28}, H_{29}), 5.90 (dd, J = 11.3, 4.7 Hz, 1H, H_{14}), 4.51 (dt, J = 13.9, 7.0 Hz, 1H, H_{25a}), 4.42 (dt, J = 14.1, 7.2 Hz, 1H, H_{25b}), 3.73 – 3.63 (m, 2H, H_{21}), 3.08 (dd, J = 9.3, 2.3 Hz, 1H, H_{11}), 3.02 (dd, J = 9.0, 3.0 Hz, 1H, H_{19}), 2.40 – 2.32 (m, 2H, H_4, H_{10}), 2.26 – 2.09 (m, 5H, H_2, H_{13a}, H_{24}), 1.80 – 1.51 (m, 5H, H_{1a}, H_6, H_{8a}, H_{13b}, H_{20a}), 1.50 – 1.36 (m, 7H, H_{1a}, H_7, H_{15}, H_{20b}), 1.13 – 1.04 (m, 4H, H_{8b}, H_{17}), 0.72 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 214.8 (C), 167.4 (C), 163.4 (C), 161.7 (C), 149.4 (2 × CH), 147.0 (C), 146.6 (C), 127.3 (d, J = 8.1 Hz, 2 × CH), 120.8 (2 × CH), 119.7 (CH), 115.7 (d, J = 21.9 Hz, 2 × CH), 80.6 (CH), 71.0 (CH), 67.2 (CH), 64.4 (C), 59.9 (CH), 49.4 (CH_2), 44.5 (C), 41.3 (C), 40.6 (CH), 36.8 (CH), 34.1 (CH_2), 33.7 (CH_2), 30.1 (CH_2), 29.4 (CH_2), 27.7 (CH_2), 26.9 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 16.8 (CH_3), 15.4 (CH_3), 14.4 (CH_3). ^{19}F NMR (470 MHz, CD_2Cl_2) δ –114.7. IR (ATR-FTIR), cm^{-1}: 2362 (m), 2341 (m), 1732 (w), 773 (w). HRMS-ESI (m/z): [M + H]$^+$ calcd for $[C_{36}H_{44}FN_4O_5S]^+$ 663.3016; found 663.3015. $[a]_D^{20}$ = +18.0 (c = 0.051, $CHCl_3$).

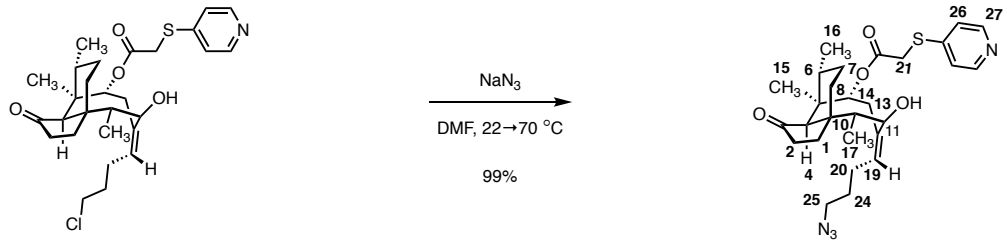
*Synthesis of the pyridyl sulfide **69**.*



Aqueous sodium hydroxide solution (1 N, 54.0 µL, 53.7 µmol, 1.30 equiv) was added to a solution of 4-mercaptopyridine (6.00 mg, 53.7 µmol, 1.30 equiv), benzyl tri-*n*-butylammonium chloride (900 µg, 4.10 µmol, 0.10 equiv) and the sulfonate **S68** (24.0 mg, 41.3 µmol, 1 equiv) in *tert*-butyl methyl ether (1.0 mL) at 22 °C. The reaction mixture was stirred for 5 h at 22 °C. The product mixture was diluted sequentially with ethyl acetate (3.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with 0.1 N aqueous phosphoric acid solution (3.0 mL), saturated aqueous sodium bicarbonate solution (3.0 mL), and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes initially, grading to 80% ethyl acetate–hexanes, three steps) to provide the pyridyl sulfide **69** as a colorless foam (18.0 mg, 84 %).

R_f = 0.25 (70% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.40 (d, *J* = 6.3 Hz, 2H, H_{27}), 7.19 (d, *J* = 6.3 Hz, 2H, H_{26}), 5.95 (dd, *J* = 11.5, 5.2 Hz, 1H, H_{14}), 5.36 (td, *J* = 6.9, 2.6 Hz, 1H, H_{19}), 3.99 (d, *J* = 9.5 Hz, 1H, H_{11}), 3.82 – 3.68 (m, 2H, H_{21}), 3.53 (t, *J* = 6.4 Hz, 2H, H_{25}), 3.12 (d, *J* = 2.9 Hz, 1H, H_4), 2.57 (dd, *J* = 15.2, 11.5 Hz, 1H, H_{13a}), 2.35 (dd, *J* = 16.2. 4.1 Hz, 1H, H_{13b}), 2.28 (dq, *J* = 9.5, 6.5 Hz, 1H, H_{10}), 2.23 – 2.13 (m, 2H, H_{20}), 2.08 (dd, *J* = 9.8, 6.0 Hz, 2H, H_2), 1.95 (s, 1H, OH), 1.87 – 1.76 (m, 2H, H_{24}), 1.72 – 1.48 (m, 5H, H_1, H_6, H_{7a}, H_{8a}), 1.45 (s, 3H, H_{15}), 1.44 – 1.32 (m, 1H, H_{7b}), 1.15 (d, *J* = 6.3 Hz, 3H, H_{17}), 1.10 – 0.97 (m, 1H, H_{8b}), 0.73 (d, *J* = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 215.2 (C), 167.8 (C), 149.4 (2 × CH), 147.2 (C), 141.6 (C), 128.2 (2 × CH), 120.7 (CH), 83.1 (CH), 71.7 (CH), 59.3 (CH), 44.6 (CH_2), 44.6 (C), 42.1 (C), 41.2 (CH), 36.8 (CH), 34.1 (CH_2), 33.8 (CH_2), 31.6 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 16.9 (CH_3), 15.6 (CH_3), 14.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2360 (s), 2341 (m), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{39}ClNO_4S]^+$, 520.2288 found 520.2283. $[a]_D^{20}$ = –725.2 (*c* = 0.260, $CHCl_3$).

*Synthesis of the azide **S71**.*

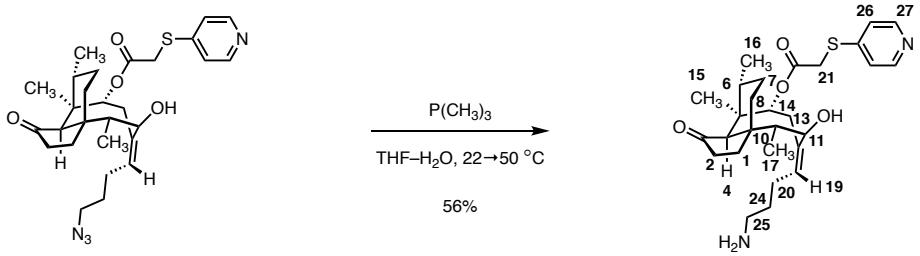


69 **S71**

Sodium azide (3.00 mg, 46.1 μmol, 5.00 equiv) was added to a solution of alkyl chloride **69** (6.00 mg, 9.20 μmol, 1 equiv) in *N,N*-dimethylformamide (200 μL) at 22 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 70 °C. The reaction mixture was stirred at 3 h at 70 °C. The product mixture was cooled to 22 °C over 10 min. The cooled product mixture was diluted sequentially with ethyl acetate (4.0 mL) and water (1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The organic layer was washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (1.5 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% acetone–hexanes) to provide the azide **S71** as a fine, white solid (4.90 mg, 99%).

R_f = 0.25 (70% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.41 (s, 2H, H_{27}), 7.19 (d, *J* = 5.4 Hz, 2H, H_{26}), 5.95 (dd, *J* = 11.4, 5.3 Hz, 1H, H_{14}), 5.37 (td, *J* = 7.0, 2.6 Hz 1H, H_{19}), 3.99 (d, *J* = 9.5 Hz, 1H, H_{11}), 3.81 – 3.67 (m, 2H, H_{21}), 3.26 (td, *J* = 6.6, 3.0 Hz, 2H, H_{25}), 3.12 (d, *J* = 2.9 Hz, 1H, H_4), 2.62 – 2.49 (m, 1H, H_{13a}), 2.41 – 2.31 (m, 1H, H_{13b}), 2.27 (dq, *J* = 9.5, 6.5 Hz, 1H, H_{10}), 2.10 (ddd, *J* = 15.9, 10.0, 7.2 Hz, 4H, H_2, H_{20}), 1.76 – 1.20 (m, 7H, H_1, H_6, H_{7a}, H_{8a}, H_{24}), 1.48 – 1.20 (m, 4H, H_{7b}, H_{15}), 1.15 (d, *J* = 6.4 Hz, 3H, H_{17}), 1.03 (td, *J* = 6.8 Hz, 1H, H_{8b}), 0.73 (d, *J* = 6.8 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 215.3 (C), 167.8 (C), 149.4 (2 × CH), 147.2 (C), 141.4 (C), 128.5 (2 × CH), 120.8 (CH), 83.1 (CH), 71.7 (CH), 59.3 (CH), 51.0 (CH_2), 44.6 (C), 42.1 (C), 41.1 (CH), 36.8 (CH), 34.1 (CH_2), 33.8 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 16.9 (CH_3), 15.6 (CH_3), 14.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2936 (w), 2360 (s), 2340 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{39}N_4O_4S]$ 527.2692; found 527.2687. $[a]_D^{20}$ = –25.3 (*c* = 0.117, $CHCl_3$).

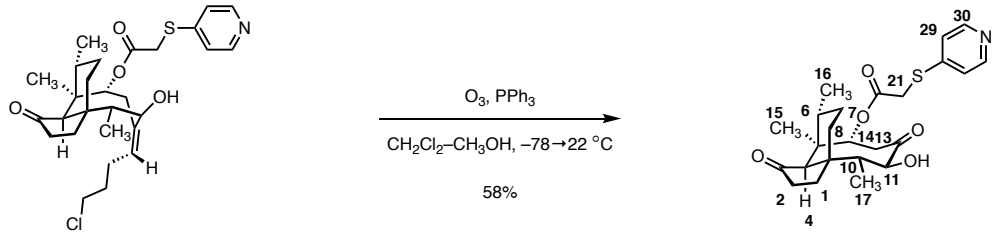
*Synthesis of the amine **70**.*



A solution trimethylphosphine in tetrahydrofuran (1.0 M, 19.0 μL, 18.6 μmol, 2.00 equiv) was added to a solution of the azide **S71** (4.90 mg, 9.30 μmol, 1 equiv) in tetrahydrofuran–water (4:1 v/v, 200 μL) at 22 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred for 3 h at 50 °C. The product mixture was cooled to 22 °C over 5 min. The cooled product mixture was diluted sequentially with ethyl acetate (1.0 mL) and aqueous sodium thiosulfate solution (10% w/v, 1.0 mL). The resulting biphasic mixture was transferred to a borosilicate test tube and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated to provide the amine **70** as a fine white solid (2.60 mg, 56%). The product obtained in this way was judged to be of >95% purity (400 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.39 (d, J = 6.3 Hz, 2H, H_{27}), 7.19 (d, J = 6.3 Hz, 2H, H_{26}), 5.95 (dd, J = 11.5, 5.2 Hz, 1H, H_{14}), 5.38 (td, J = 7.1, 2.7 Hz, 1H, H_{19}), 3.98 (d, J = 9.5 Hz, 1H, H_{11}), 3.80 – 3.67 (m, 2H, H_{21}), 3.18 (d, J = 2.9 Hz, 1H, H_4), 2.62 (t, J = 7.0 Hz, 2H, H_{25}), 2.54 (dd, J = 5.1, 11.5 Hz, 1H, H_{13a}), 2.39 – 2.14 (m, 2H, H_{10}, H_{13b}), 2.11 – 1.98 (m, 4H, H_2, H_{20}), 1.86 – 1.21 (m, 11H, H_1, H_6, H_7, H_{8a}, H_{15}, H_{24}), 1.15 (d, J = 6.4 Hz, 3H, H_{17}), 1.09 – 0.96 (m, 1H, H_{8b}), 0.72 (d, J = 6.6 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 215.4 (C), 167.8 (C), 149.4 (2 × CH), 147.3 (C), 140.4 (C), 129.8 (CH), 120.7 (2 × CH), 83.2 (CH), 71.8 (CH), 59.2 (CH), 44.6 (C), 42.1 (C), 41.7 (CH_2), 41.1 (CH), 36.8 (CH), 34.1 (CH_2), 33.8 (CH_2), 32.7 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 27.2 (CH_2), 25.3 (CH_2), 25.3 (CH_2), 16.9 (CH_3), 15.6 (CH_3), 14.7 (CH_3). IR (ATR-FTIR), cm^{-1}: 2921 (w), 2360 (s), 2341 (m), 1732 (w), 1219 (w), 772 (s). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{28}H_{41}N_2O_4S]^+$ 501.2787; found 501.2775. $[a]_D^{20}$ = –5.71 (c = 0.063, $CHCl_3$).

*Synthesis of the ketone **71**.*

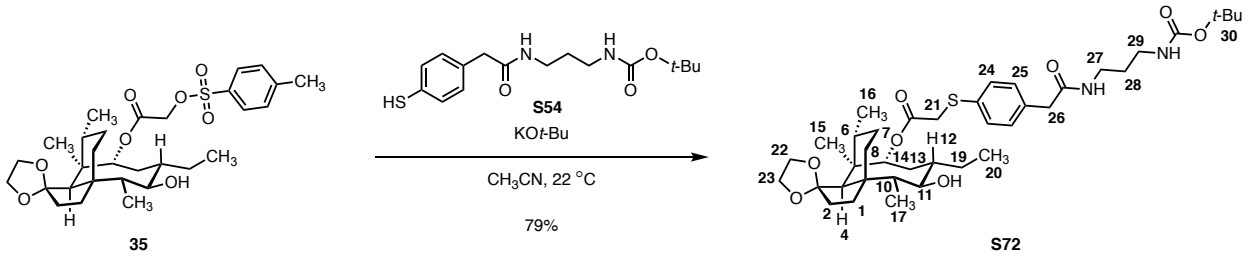


69 **71**

Ozone was passed through a solution of the allylic alcohol **69** (4.00 mg, 7.72 μmol, 1 equiv) in dichloromethane–methanol (2:1 v/v, 800 μL) at –78 °C. The addition of ozone was continued until a blue color persisted. Dioxygen was then passed through the solution to remove any dissolved ozone, resulting in a colorless solution. Triphenylphosphine (4.04 mg, 15.4 μmol, 2.00 equiv) was then added to the cold mixture. Upon completion of the addition, the cooling bath was removed and the product mixture was allowed to warm to 22 °C over 1 h. The warmed product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 70% ethyl acetate–hexanes) to provide the ketone **71** as a white solid (2.00 mg, 58%).

R_f = 0.25 (80% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.41 (d, J = 6.3 Hz, 2H, H_{30}), 7.18 (d, J = 6.4 Hz, 2H, H_{29}), 5.81 (dd, J = 10.3, 3.2 Hz, 1H, H_{14}), 3.97 (dd, J = 9.8, 4.9 Hz, 1H, H_{11}), 3.74 (d, J = 5.2 Hz, 2H, H_{21}), 3.16 (d, J = 5.5 Hz, 1H, OH), 2.82 – 2.66 (m, 2H, H_{13}), 2.42 (dd, J = 9.7, 6.7 Hz, 1H, H_{10}), 2.21 (dr, J = 19.6, 10.6 Hz, 2H, H_2), 2.07 (d, J = 3.0 Hz, 1H, H_4), 1.88 – 1.62 (m, 3H, H_{1a}, H_6, H_{8a}), 1.61 – 1.57 (m, 1H, H_{1b}), 1.45 (s, 5H, H_7, H_{15}), 1.20 – 1.12 (m, 1H, H_{8b}), 1.06 (d, J = 6.7 Hz, 3H, H_{17}), 0.76 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 215.1 (C), 207.6 (C), 168.1 (C), 149.9 (C), 147.7 (2 × CH), 121.1 (2 × CH), 78.3 (CH), 70.1 (CH), 59.8 (CH), 45.3 (C), 44.6 (CH_2), 42.4 (C), 39.5 (CH), 37.1 (CH), 34.5 (CH_2), 34.1 (CH_2), 30.5 (CH_2), 27.3 (CH_2), 25.6 (CH_2), 17.5 CH_3), 15.1 (CH_3), 12.8 (CH_3). IR (ATR-FTIR), cm^{-1}: 2919 (m), 2367 (s), 1736 (m), 1190 (m), 1044 (w), 772 (m). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{24}H_{32}NO_5S]^+$ 446.2001; found 446.1996. $[a]_D^{20}$ = +45.0 (c = 0.016, $CHCl_3$).

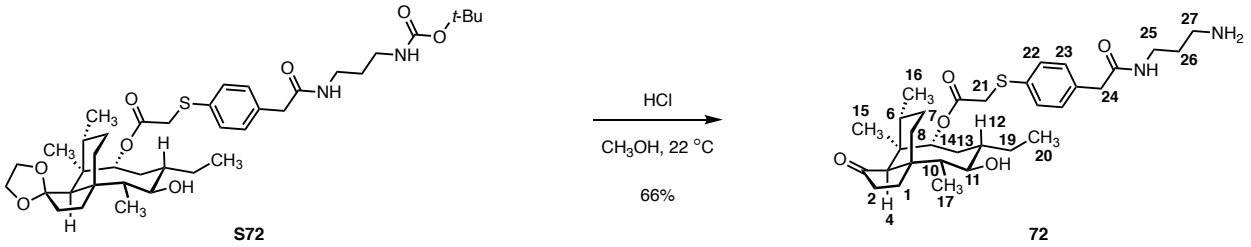
*Synthesis of the sulfide **S72**.*



A solution of potassium *tert*-butoxide in tetrahydrofuran (50 mM, 28.0 µL, 14.2 µmol, 0.80 equiv) was added dropwise to a solution of the thiol **S54** (4.60 mg, 14.2 µmol, 0.80 equiv), and the sulfonate **35** (14.0 mg, 24.8 µmol, 1 equiv) in acetonitrile (200 µL) at 22 °C. The reaction mixture was stirred for 2 h at 22 °C. The product mixture was diluted sequentially with dichloromethane (1.0 mL) and 1 N aqueous sodium hydroxide solution (1.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 1.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with aqueous sodium thiosulfate solution (10% w/v, 1.0 mL), saturated aqueous sodium bicarbonate solution (1.0 mL), and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% acetone–hexanes initially, grading to 80% acetone–hexanes, three steps) to provide the sulfide **S72** as a white foam (8.00 mg, 79%).

R_f = 0.25 (65% acetone–hexanes; PAA). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 2H, H_{24}), 7.19 (d, *J* = 7.8 Hz, 2H, H_{25}), 6.11 (s, 1H, NH), 5.29 (d, *J* = 8.1 Hz, 1H, H_{14}), 4.88 (s, 1H, NH), 4.02 (q, *J* = 6.6, 5.9 Hz, 1H, $H_{22a\ or\ 23a}$), 3.88 (tq, *J* = 13.7, 6.9 Hz, 2H, H_{22b}, H_{23b}), 3.77 – 3.71 (m, 1H, $H_{22a\ or\ 23a}$), 3.58 (s, 2H, H_{21}), 3.51 (s, 2H, H_{26}), 3.31 (dd, *J* = 10.1, 6.9 Hz, 1H, H_{11}), 3.24 (q, *J* = 6.3 Hz, 2H, H_{27}), 3.08 (d, *J* = 6.5 Hz, 2H, H_{29}), 2.21 (ddd, *J* = 11.7, 7.2, 4.9 Hz, 1H, H_6), 2.18 – 2.07 (m, 1H, H_{10}), 1.95 (s, 1H, H_4), 1.81 (qtd, *J* = 14.5, 9.4, 5.1 Hz, 3H, H_2, H_{13a}), 1.76 – 1.64 (m, 2H, H_{12}, H_{19a}), 1.56 (dp, *J* = 10.4, 5.8, 5.2 Hz, 5H, H_1, H_{7a}, H_{28}), 1.49 – 1.20 (m, 14H, H_{7b}, H_8, H_{13b}, H_{19b}, H_{30}), 1.03 (s, 3H, H_{15}), 0.88 (d, *J* = 6.8 Hz, 3H, H_{17}), 0.81 (t, *J* = 7.4 Hz, 3H, H_{20}), 0.66 (d, *J* = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1 (C), 169.0 (C), 156.5 (C), 134.3 (C), 133.5 (C), 130.1 (2 × CH), 130.0 (2 × CH), 120.4 (C), 79.4 (C), 75.5 (CH), 71.7 (CH), 63.8 (CH_2), 61.5 (CH_2), 51.0 (CH), 47.9 (CH), 46.2 (C), 43.3 (CH_2), 41.6 (C), 40.0 (CH), 37.1 (CH_2), 36.6 (CH_2), 36.2 (CH_2), 35.8 (CH_2), 35.4 (CH), 30.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 28.4 (3 × CH_3), 27.2 (CH_2), 25.8 (CH_2), 17.7 (CH_3), 14.7 (CH_3), 11.5 (CH_3), 10.5 (CH_3). IR (AT-FTIR), cm^{-1}: 3324 (w), 2936 (m), 2876 (w), 1695 (m), 1655 (m), 1278 (m), 1162 (m), 755 (s). HRMS-ESI (m/z): $[M + Na]^+$ calcd for $[C_{39}H_{60}N_2NaO_8S]^+$ 739.3968; found 739.3958. $[\alpha]_D^{20}$ = +10.4 (*c* = 0.425, $CHCl_3$).

*Synthesis of the amido amine **72**.*



Aqueous hydrochloric acid solution (12 N, 11.8 μL, 142 μmol, 10.0 equiv) was added to a solution of the ester **S72** (8.00 mg, 14.2 μmol, 1 equiv) in methanol (200 μL) at 22 °C. The reaction mixture was stirred for 72 h at 22 °C. The product mixture was concentrated to provide the amido amine **72** as a fine, white solid (4.20 mg, 66%). The product obtained in this way was judged to be of >95% purity (600 MHz ^{1}H NMR analysis) and was used in susceptibility testing without further purification.

R_f = 0.05 (95% ethyl acetate–hexanes; PAA). ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (d, J = 8.1 Hz, 2H, H_{22}), 7.24 (d, J = 8.0 Hz, 2H, H_{23}), 5.33 (d, J = 7.5 Hz, 1H, H_{14}), 3.69 (d, J = 15.1 Hz, 1H, H_{21a}), 3.61 (d, J = 15.2 Hz, 1H, H_{21b}), 3.48 (s, 2H, H_{24}), 3.35 – 3.23 (m, 3H, H_{11}, H_{25}), 2.87 (t, J = 7.3 Hz, 2H, H_{27}), 2.33 – 2.05 (m, 4H, H_2, H_4, H_{10}), 1.88 – 1.53 (m, 8H, H_{1a}, H_6, H_{8a}, H_{12}, H_{13a}, H_{19a}, H_{26}), 1.49 – 1.20 (m, 8H, H_{1b}, H_7, H_{13b}, H_{15}, H_{19b}), 1.17 – 1.06 (m, 1H, H_{8b}), 0.95 (d, J = 7.0 Hz, 3H, H_{17}), 0.80 (t, J = 7.4 Hz, 3H, H_{20}), 0.70 (d, J = 7.1 Hz, 3H, H_{16}). ^{13}C NMR (150 MHz, CD_3OD) δ 218.3 (C), 173.2 (C), 169.6 (C), 134.2 (C), 133.7 (C), 129.6 (2 × CH), 129.4 (2 × CH), 74.0 (CH), 70.8 (CH), 57.7 (CH), 47.3 (CH), 45.3 (C), 41.8 (CH_2), 41.3 (CH), 41.2 (C), 36.8 (CH_2), 36.7 (CH), 36.1 (CH_2), 35.9 (CH_2), 35.6 (CH_2), 33.8 (CH_2), 30.3 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 16.5 (CH_3), 14.1 (CH_3), 10.3 (CH_3), 9.4 (CH_3). IR (AT-FTIR), cm^{-1}: 3730 (w), 3383 (w), 2361 (s), 2341 (s), 1718 (w), 1648 (w), 669 (w). HRMS-ESI (m/z): $[M + H]^+$ calcd for $[C_{32}H_{49}N_2O_5S]^+$ 573.3362; found 573.3355. $[a]_D^{20}$ = +39.9 (c = 0.263, CH_3OH).

Crystallographic analysis of the enone S3.

Single crystals of the enone **S3** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **S3** in *n*-hexanes at 22 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-17125. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exception is H3, which was found in the difference map and freely refined. The full numbering scheme of compound 007b-17125 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2114513 (007b-17125) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

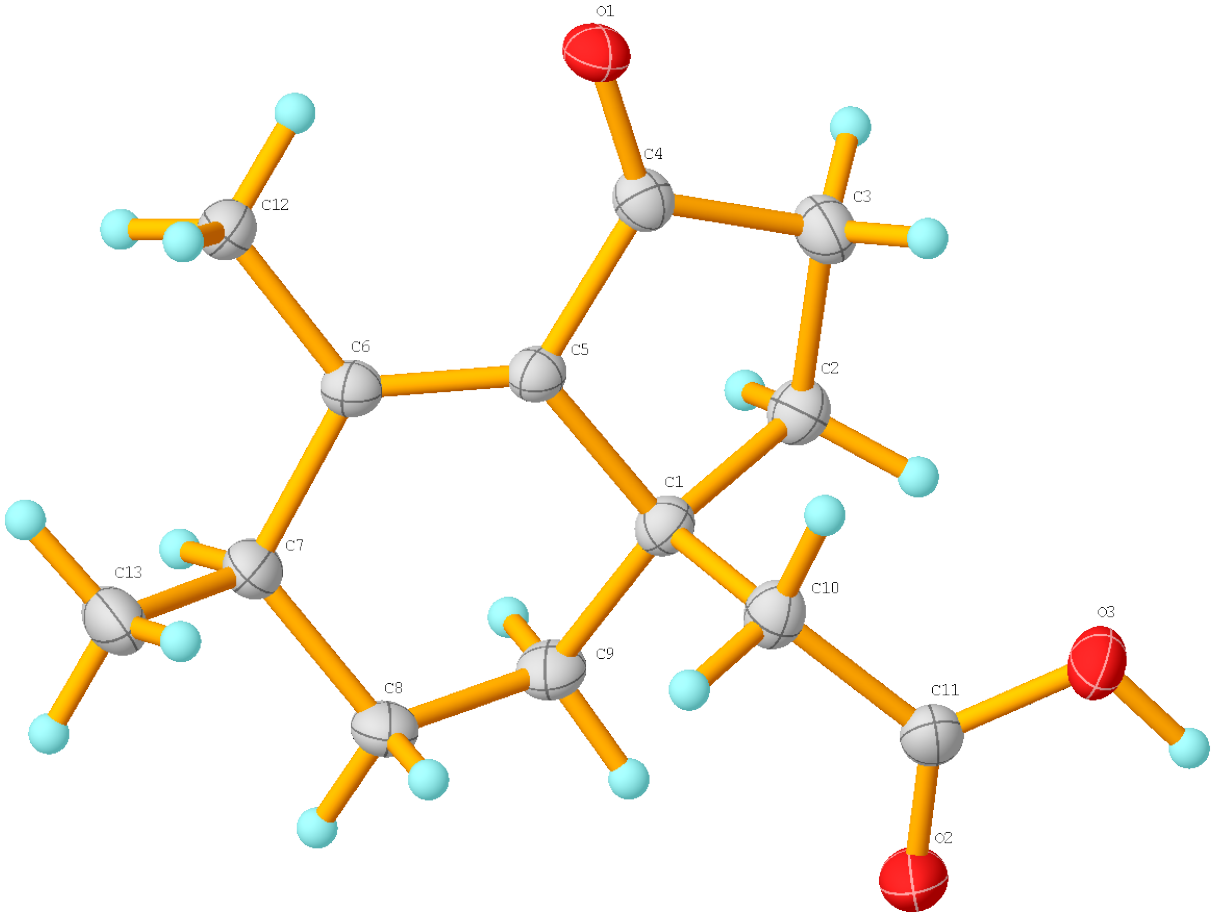


Figure S8. The complete numbering scheme of the enone **S3** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Crystal data and structure refinement for the enone **S3**:

Identification code	007b-17125	
Empirical formula	C13 H18 O3	
Formula weight	222.27	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.75320(10) Å	α = 90°.
	b = 9.34860(10) Å	β = 90°.
	c = 14.2570(2) Å	γ = 90°.
Volume	1166.65(2) $Å^3$	
Z	4	
Density (calculated)	1.265 Mg/m^3	
Absorption coefficient	0.717 mm^{-1}	
F(000)	480	
Crystal size	0.200 x 0.100 x 0.030 mm^3	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	5.659 to 66.585°.	
Index ranges	-10<=h<=10, -11<=k<=11, -16<=l<=16	
Reflections collected	41576	
Independent reflections	2052 [R(int) = 0.0331]	
Observed reflections (I > 2sigma(I))	2027	
Completeness to theta = 66.585°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.70996	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	2052 / 0 / 152	
Goodness-of-fit on F^2	1.100	
Final R indices [I>2sigma(I)]	R1 = 0.0289, wR2 = 0.0724	
R indices (all data)	R1 = 0.0292, wR2 = 0.0727	
Absolute structure parameter	0.03(4)	
Extinction coefficient	0.0105(10)	
Largest diff. peak and hole	0.261 and -0.170 $e.Å^{-3}$	

Crystallographic analysis of the cyanoester 19.

Single crystals of the ester **19** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **19** in *n*-hexanes at 22 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-18129. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-18129 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2114514 (007b-18129) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

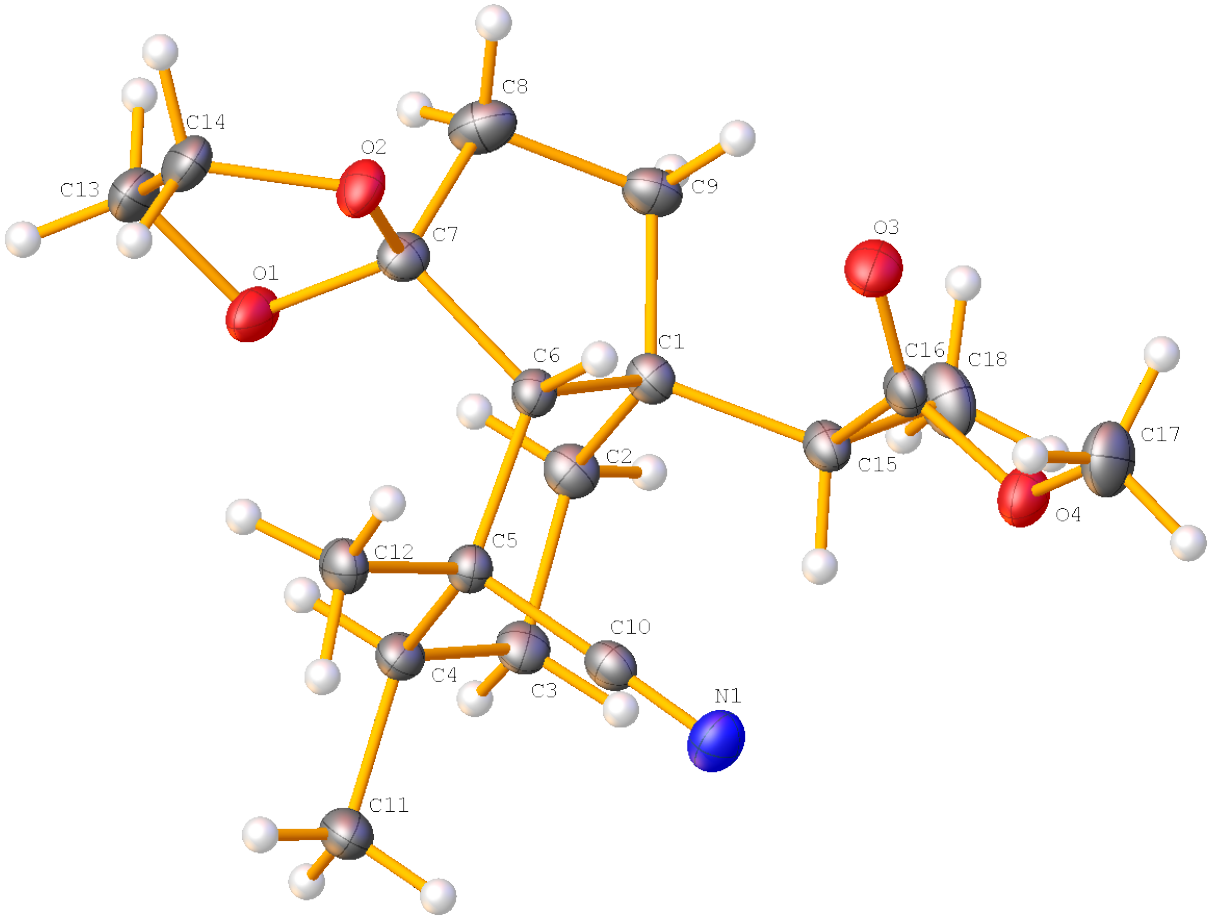


Figure S9. The complete numbering scheme of the cyanoester **19** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Crystal data and structure refinement for the cyanoester **19**.

Identification code	007b-18129	
Empirical formula	C18 H27 N O4	
Formula weight	321.40	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.04910(10) Å	α = 90°.
	b = 8.26590(10) Å	β = 103.3330(10)°.
	c = 11.43230(10) Å	γ = 90°.
Volume	832.075(16) $Å^3$	
Z	2	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.727 mm^{-1}	
F(000)	348	
Crystal size	0.200 x 0.100 x 0.060 mm^3	
Crystal color and habit	Yellow Plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	3.974 to 66.576°.	
Index ranges	-10<=h<=10, -9<=k<=9, -13<=l<=13	
Reflections collected	29673	
Independent reflections	2867 [R(int) = 0.0219]	
Observed reflections (I > 2sigma(I))	2850	
Completeness to theta = 66.576°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.82417	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	2867 / 1 / 213	
Goodness-of-fit on F^2	1.129	
Final R indices [I>2sigma(I)]	R1 = 0.0273, wR2 = 0.0677	
R indices (all data)	R1 = 0.0275, wR2 = 0.0679	
Absolute structure parameter	-0.04(4)	
Extinction coefficient	0.0324(19)	
Largest diff. peak and hole	0.169 and -0.176 $e.Å^{-3}$	

Crystallographic analysis of the diol 26.

Single crystals of the diol **26** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **26** in *n*-hexanes at 22 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-19061. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl and alcohol groups). The full numbering scheme of compound 007b-19061 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2114515 (007b-19061) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

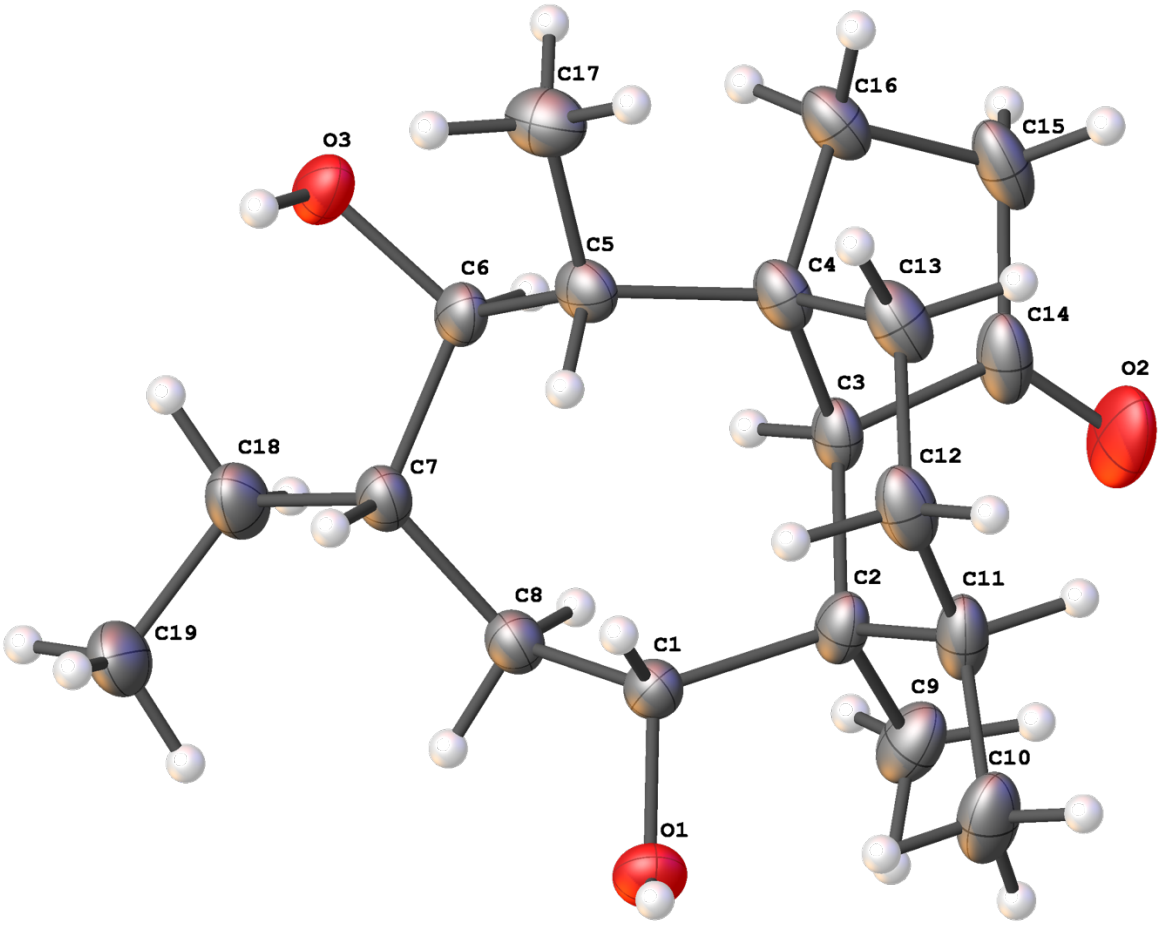


Figure S10. The complete numbering scheme of the diol **26** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Crystal data and structure refinement for the diol **26**.

Identification code	007b-19061	
Empirical formula	C19 H32 O3	
Formula weight	308.44	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.4440(3) Å	α = 90°.
	b = 22.9025(6) Å	β = 97.093(2)°.
	c = 8.6536(2) Å	γ = 90°.
Volume	1660.70(8) $Å^3$	
Z	4	
Density (calculated)	1.234 Mg/m^3	
Absorption coefficient	0.636 mm^{-1}	
F(000)	680	
Crystal size	0.200 x 0.040 x 0.040 mm^3	
Crystal color and habit	Colorless Needle	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	3.860 to 66.589°.	
Index ranges	-10<=h<=10, -27<=k<=26, -10<=l<=10	
Reflections collected	58395	
Independent reflections	2932 [R(int) = 0.0605]	
Observed reflections (I > 2sigma(I))	2568	
Completeness to theta = 66.589°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.69350	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	2932 / 0 / 205	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1045	
R indices (all data)	R1 = 0.0498, wR2 = 0.1089	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.193 and -0.313 $e.Å^{-3}$	

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Author Response: The H1 is likely disordered about the C1-O1 bond. There is a hydrogen bond between O1 and its symmetry equivalent position. The atom was placed geometrically and refined as a riding atom with the special position constraints suppressed

Crystallographic analysis of the C7-methyl substituted cyanoester S20.

Single crystals of the ester **S20** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **S20** in *n*-hexanes at 22 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007a-20033. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). Atom C19 is disordered over two positions. The site occupancies were freely refined to values of 0.81/0.19. Due to the small amount of electron density in the minor site, the thermal parameter was restrained to be identical to its major counterpart. The full numbering scheme of compound 007a-20033 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2114516 (007a-20033) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

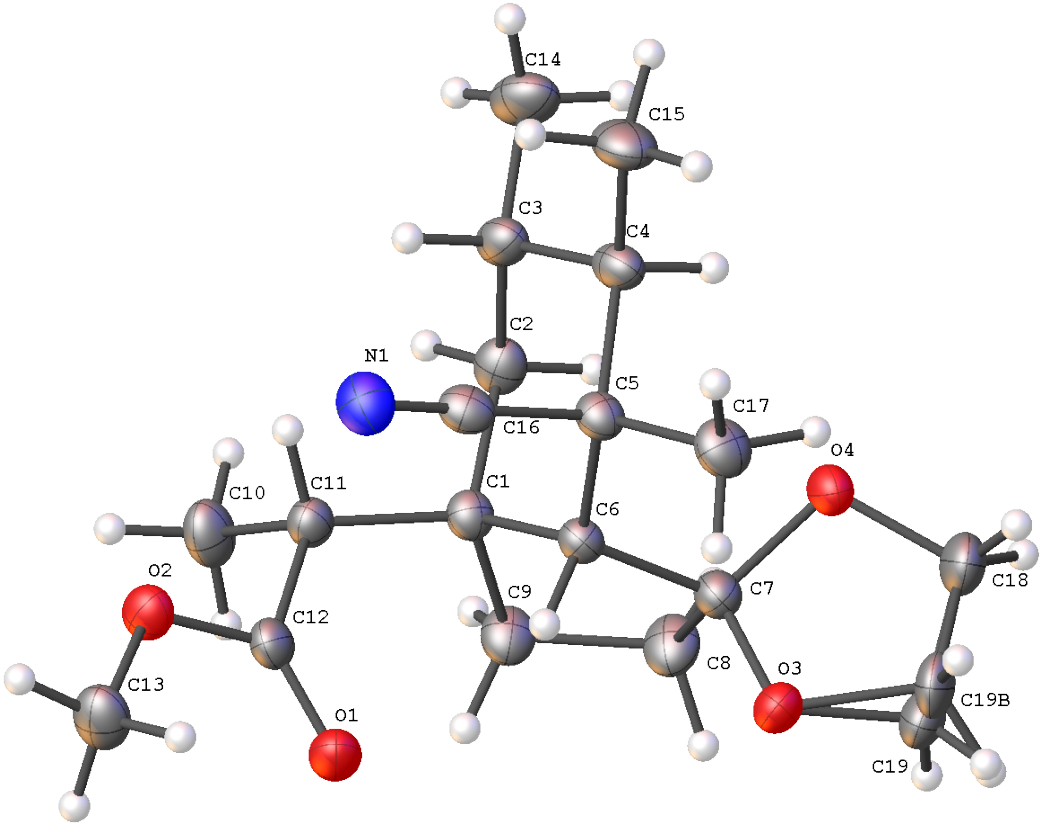


Figure S11. The complete numbering scheme of the cyanoester **S20** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Crystal data and structure refinement for the cyanoester **S20**.

Identification code	007a-20033	
Empirical formula	C19 H29 N O4	
Formula weight	335.43	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.28320(10) Å	α = 90°.
	b = 10.92690(10) Å	β = 90°.
	c = 19.5262(2) Å	γ = 90°.
Volume	1767.31(3) $Å^3$	
Z	4	
Density (calculated)	1.261 Mg/m^3	
Absorption coefficient	0.705 mm^{-1}	
F(000)	728	
Crystal size	0.100 x 0.080 x 0.040 mm^3	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	4.529 to 66.576°.	
Index ranges	-9<=h<=9, -13<=k<=13, -23<=l<=23	
Reflections collected	62899	
Independent reflections	3101 [R(int) = 0.0421]	
Observed reflections (I > 2sigma(I))	3071	
Completeness to theta = 66.576°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.85408	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	3101 / 0 / 232	
Goodness-of-fit on F^2	1.062	
Final R indices [I>2sigma(I)]	R1 = 0.0245, wR2 = 0.0661	
R indices (all data)	R1 = 0.0247, wR2 = 0.0663	
Absolute structure parameter	0.01(4)	
Largest diff. peak and hole	0.175 and -0.135 $e.Å^{-3}$	

Crystallographic analysis of the ring-contracted cyanoester S35.

Single crystals of the ester **S35** suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound **S35** in *n*-hexanes at 22 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-21112. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-21112 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2114517 (007b-21112) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

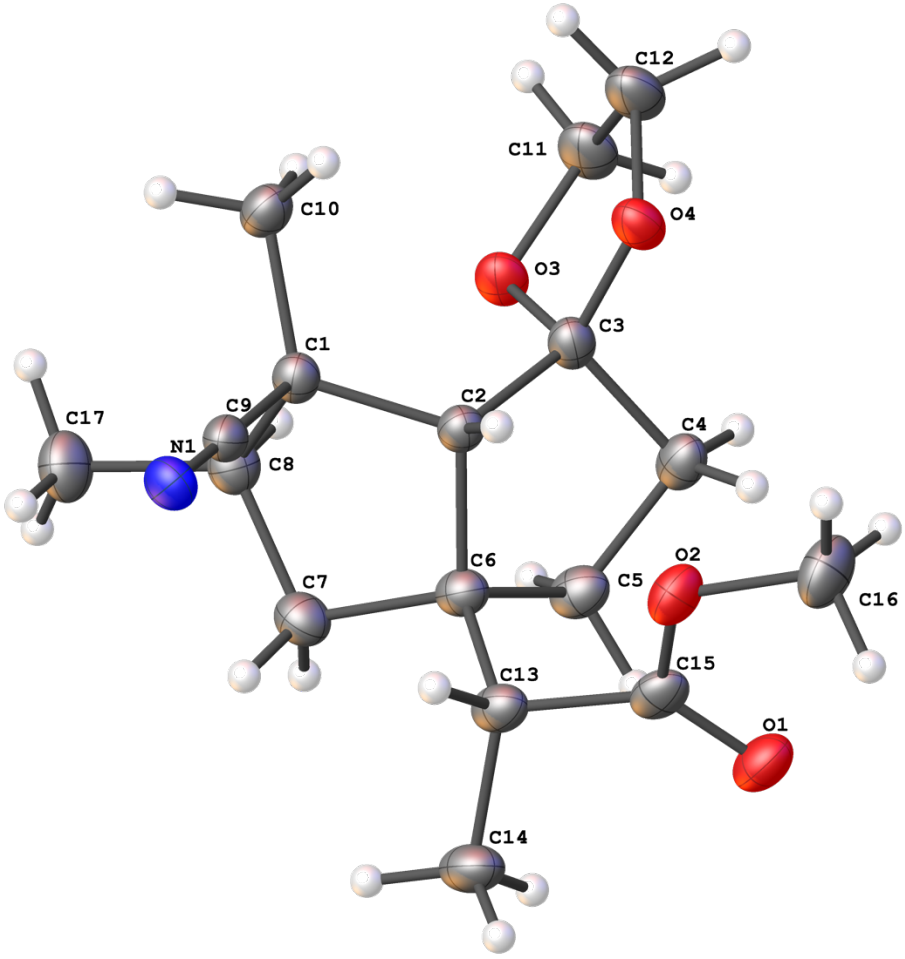
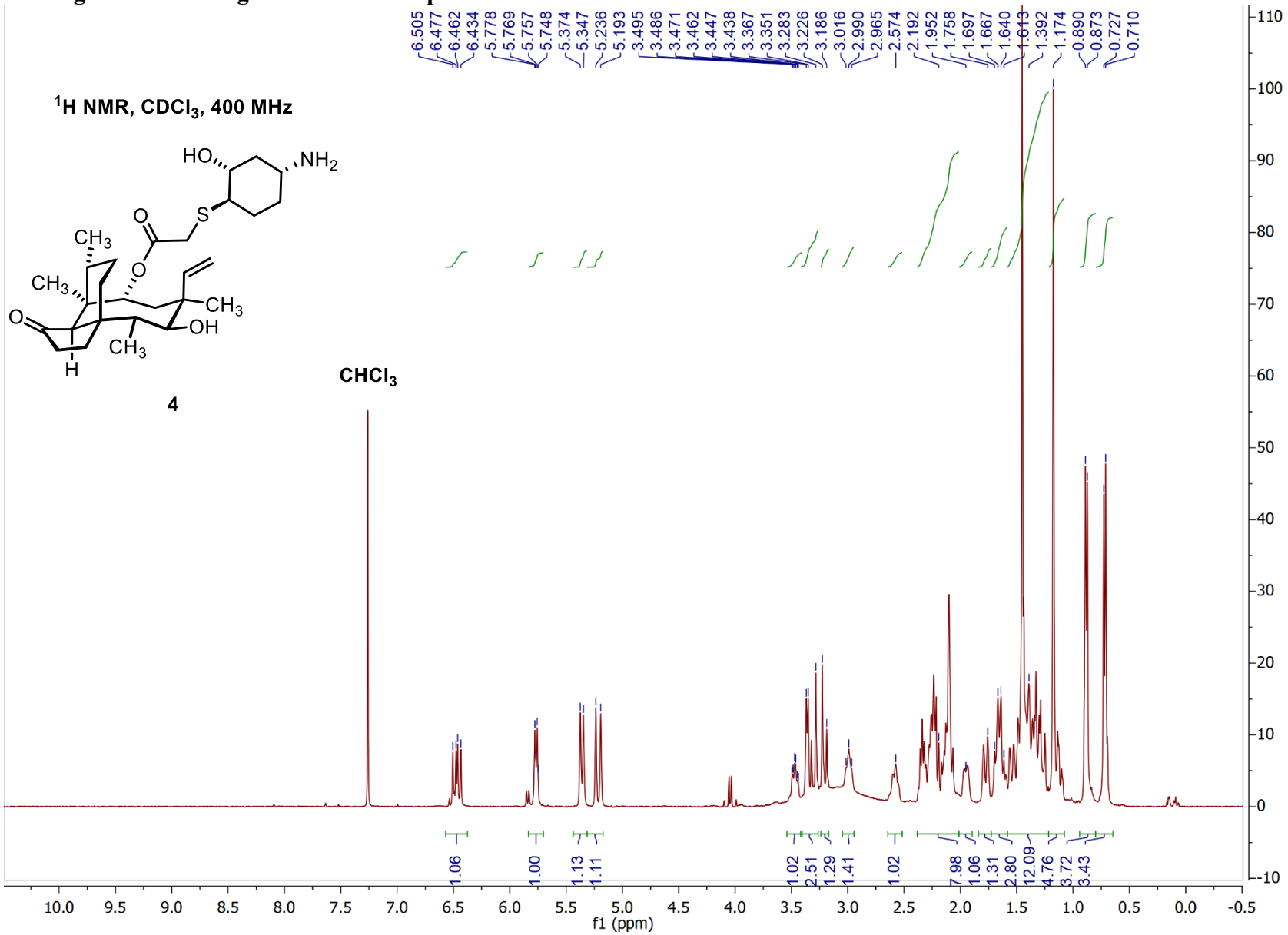


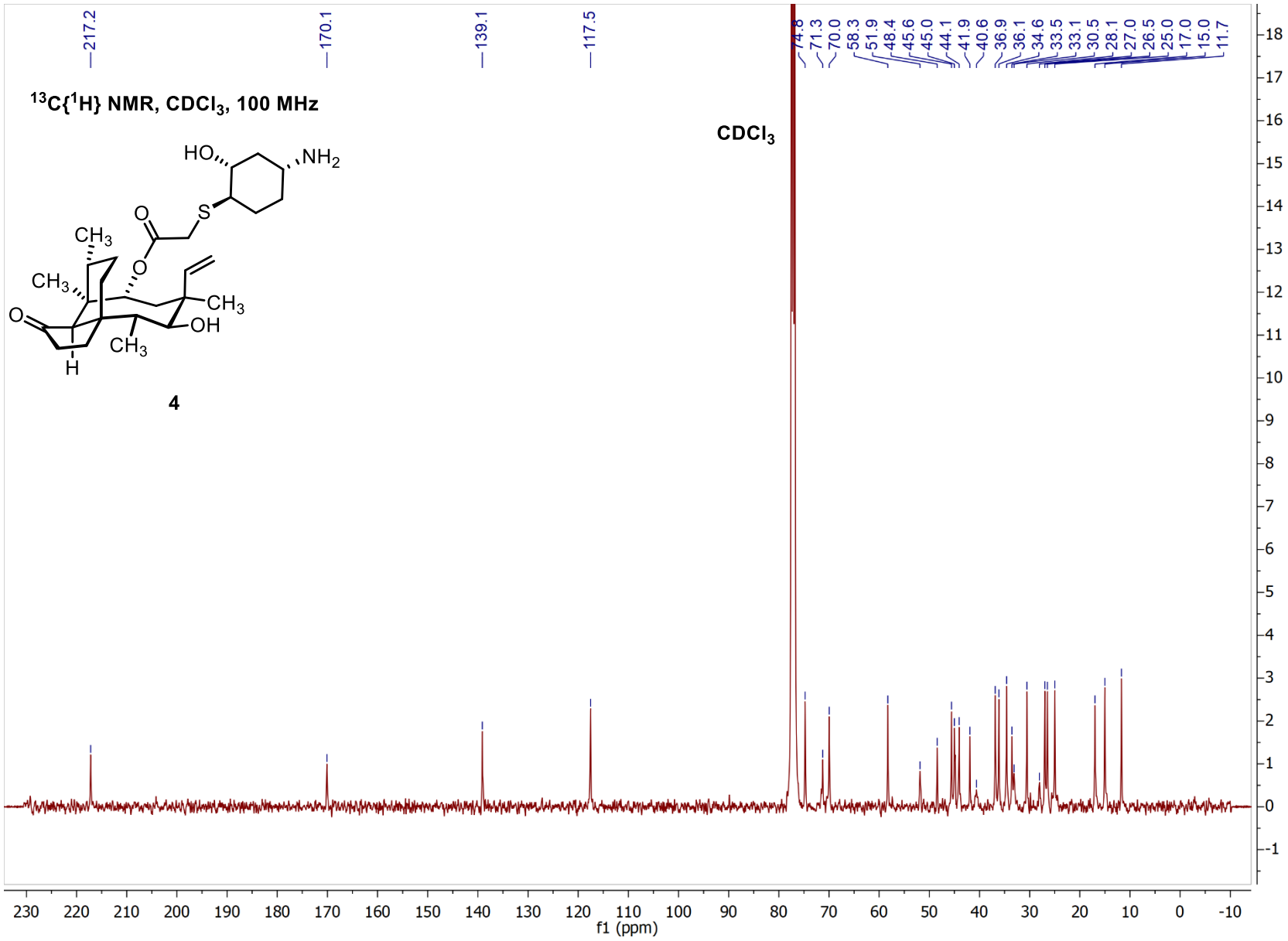
Figure S12. The complete numbering scheme of the cyanoester **S35** with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

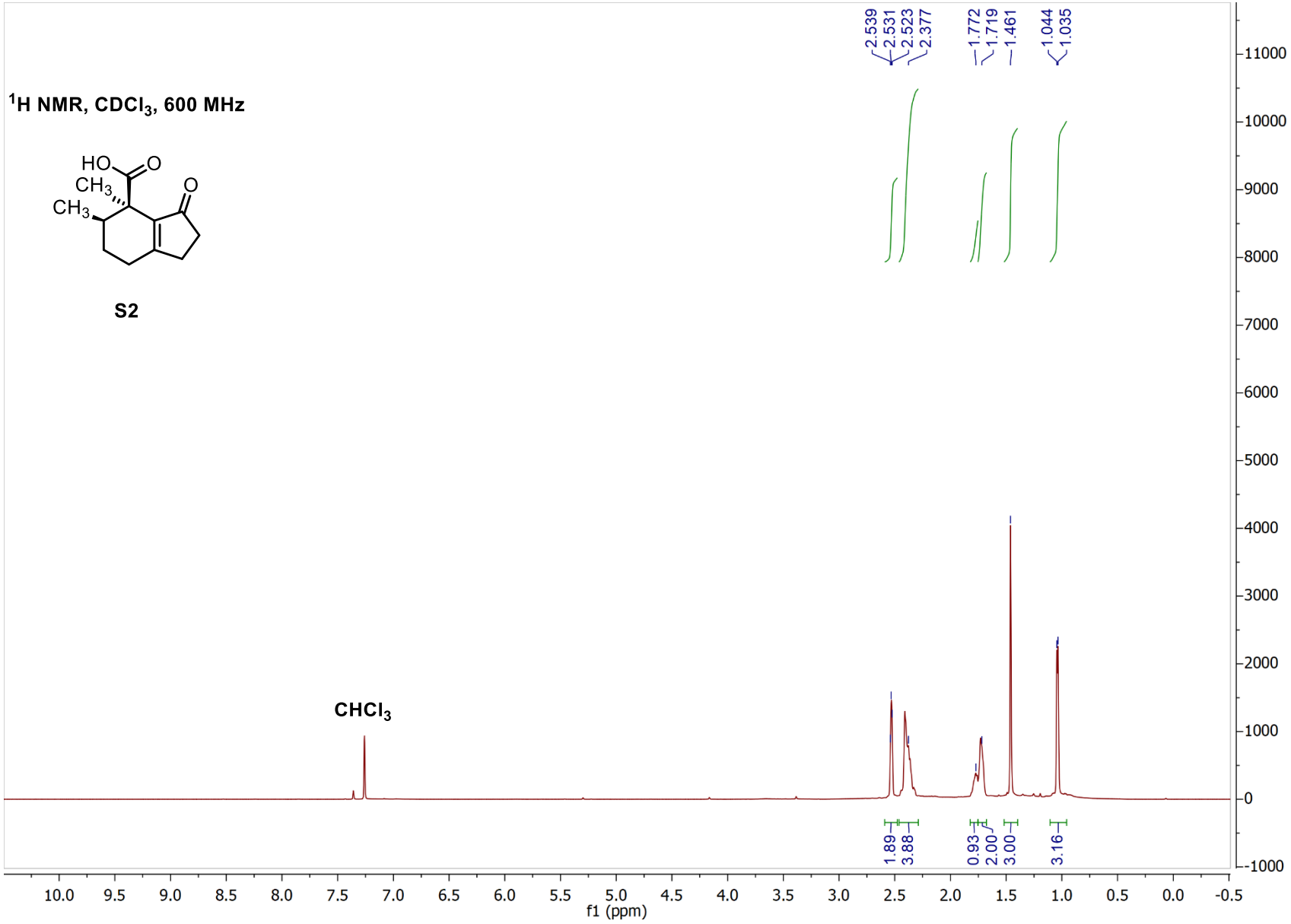
Crystal data and structure refinement for the cyanoester **S35**.

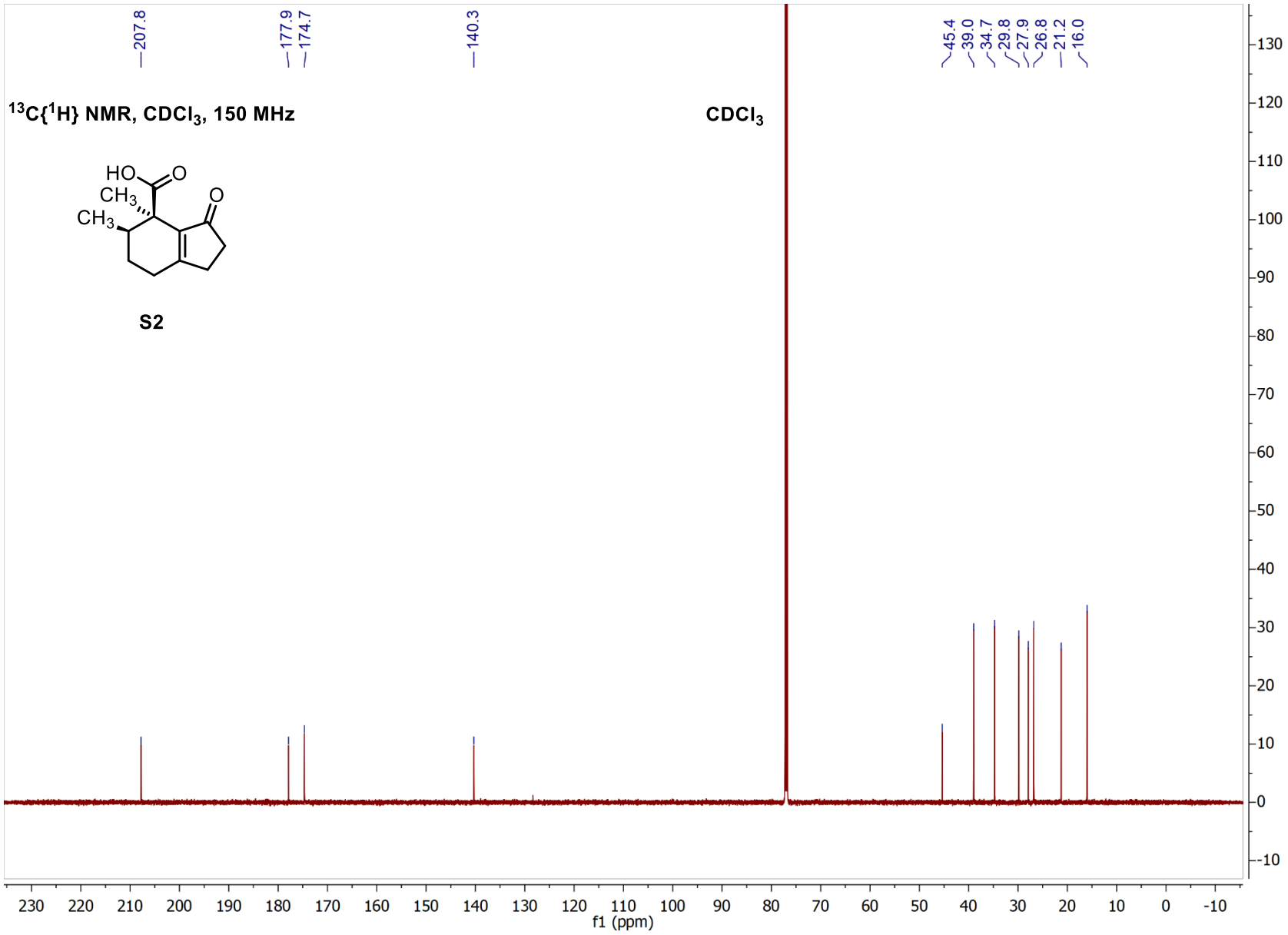
Identification code	007b-21112	
Empirical formula	C17 H25 N O4	
Formula weight	307.38	
Temperature	93(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.23790(10) Å	α = 90°.
	b = 8.89490(10) Å	β = 91.1470(10)°.
	c = 14.8286(2) Å	γ = 90°.
Volume	822.61(2) $Å^3$	
Z	2	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	0.713 mm^{-1}	
F(000)	332	
Crystal size	0.200 x 0.200 x 0.020 mm^3	
Crystal color and habit	Colorless Block	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	2.981 to 66.584°.	
Index ranges	-7<=h<=7, -10<=k<=10, -17<=l<=17	
Reflections collected	28682	
Independent reflections	2883 [R(int) = 0.0392]	
Observed reflections (I > 2sigma(I))	2834	
Completeness to theta = 66.584°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.59439	
Solution method	SHELXT-2014/5 (Sheldrick, 2014)	
Refinement method	SHELXL-2014/7 (Sheldrick, 2014)	
Data / restraints / parameters	2883 / 1 / 204	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0666	
R indices (all data)	R1 = 0.0274, wR2 = 0.0672	
Absolute structure parameter	-0.06(6)	
Extinction coefficient	0.0205(13)	
Largest diff. peak and hole	0.145 and -0.146 $e.Å^{-3}$	

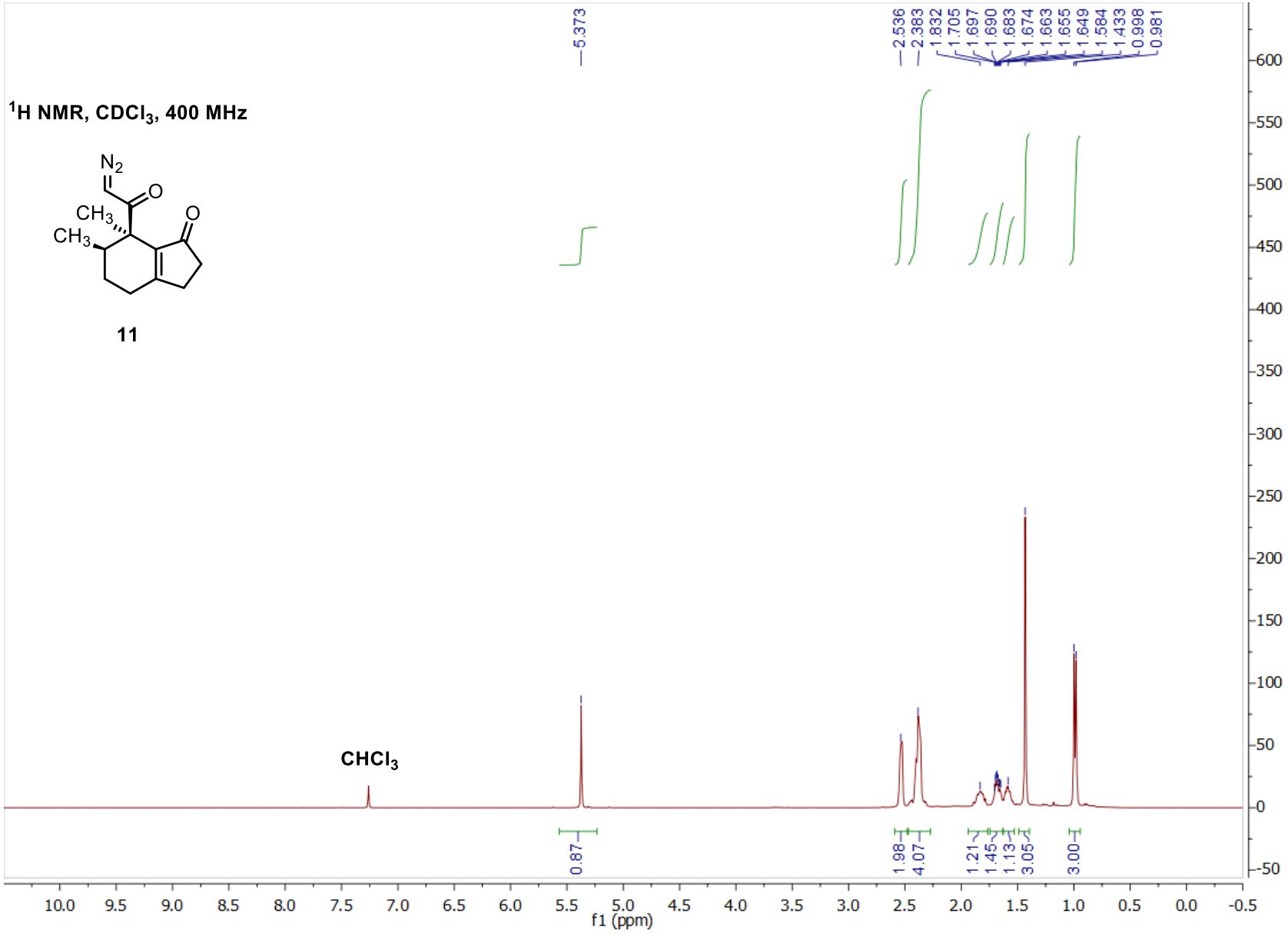
Catalog of nuclear magnetic resonance spectra.

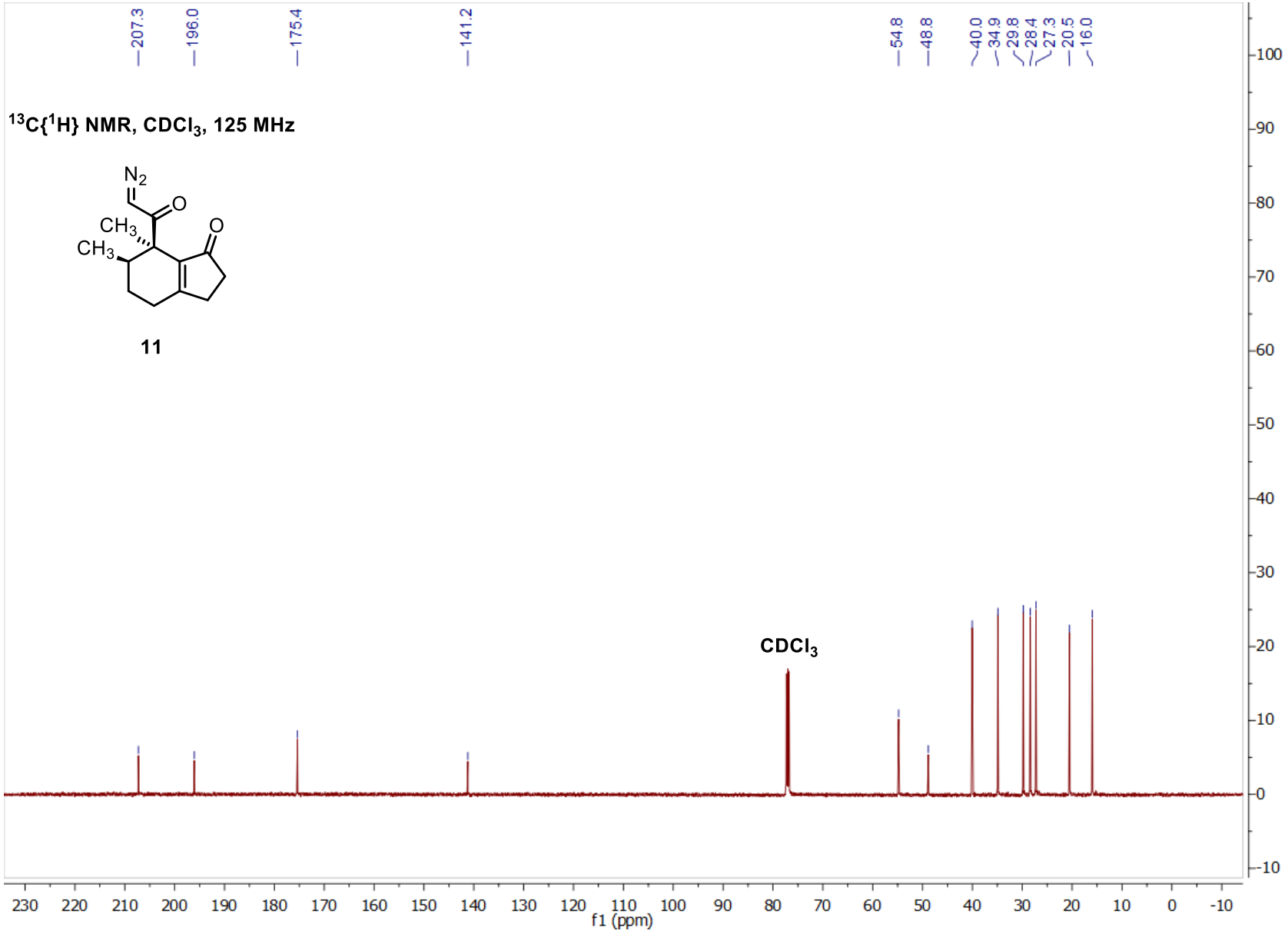


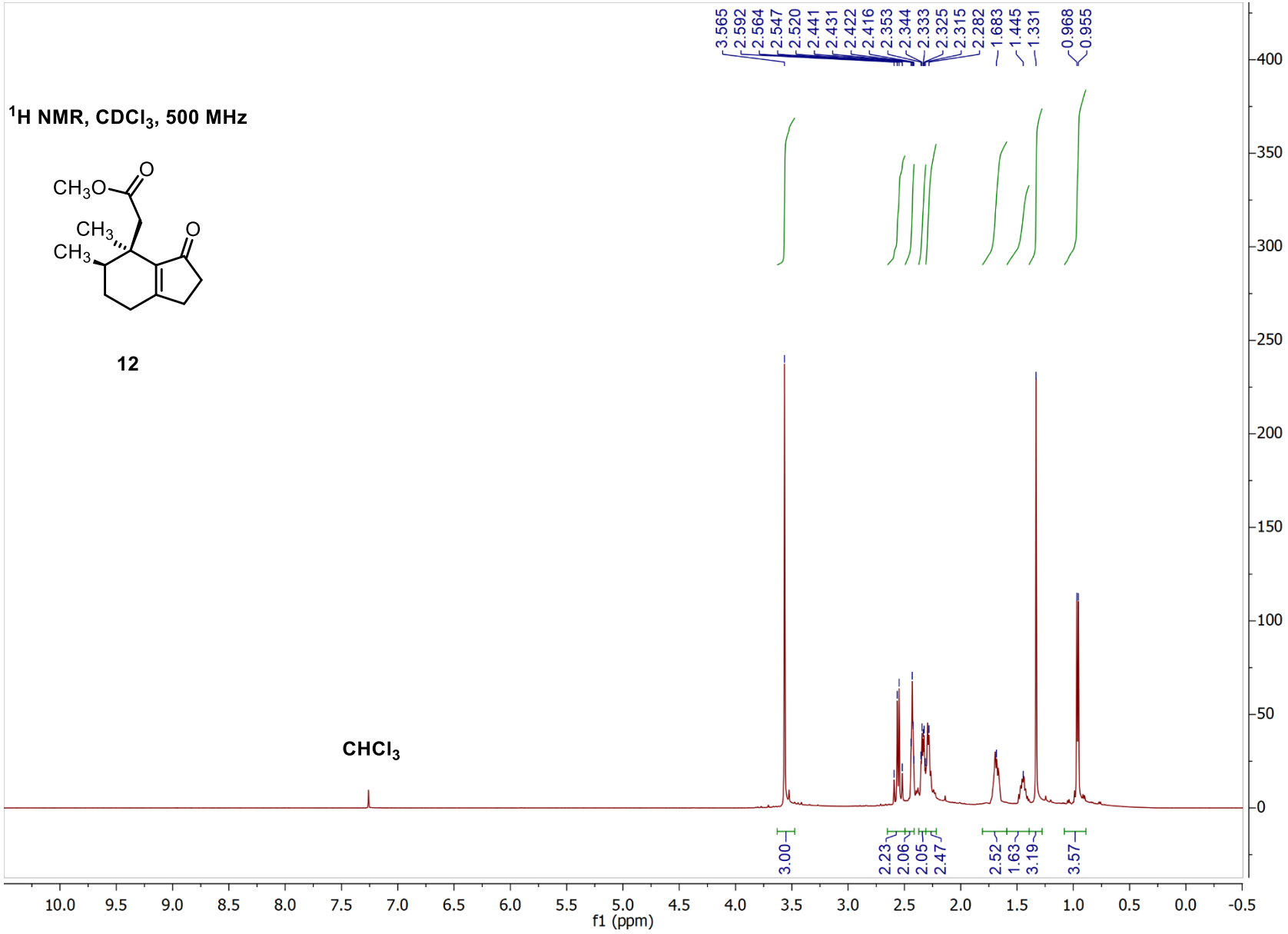

217.2
170.1
139.1
117.5
74.8
71.3
70.0
58.3
51.9
48.4
45.6
45.0
44.1
41.9
40.6
36.9
36.1
34.6
33.5
33.1
30.5
28.1
27.0
26.5
25.0
17.0
15.0
11.7
13C{1H} NMR, CDCl3, 100 MHz
CDCl3
HO
NH2
O
S
CH3
CH3
O
CH3
CH3
OH
O
H
4
f1 (ppm)

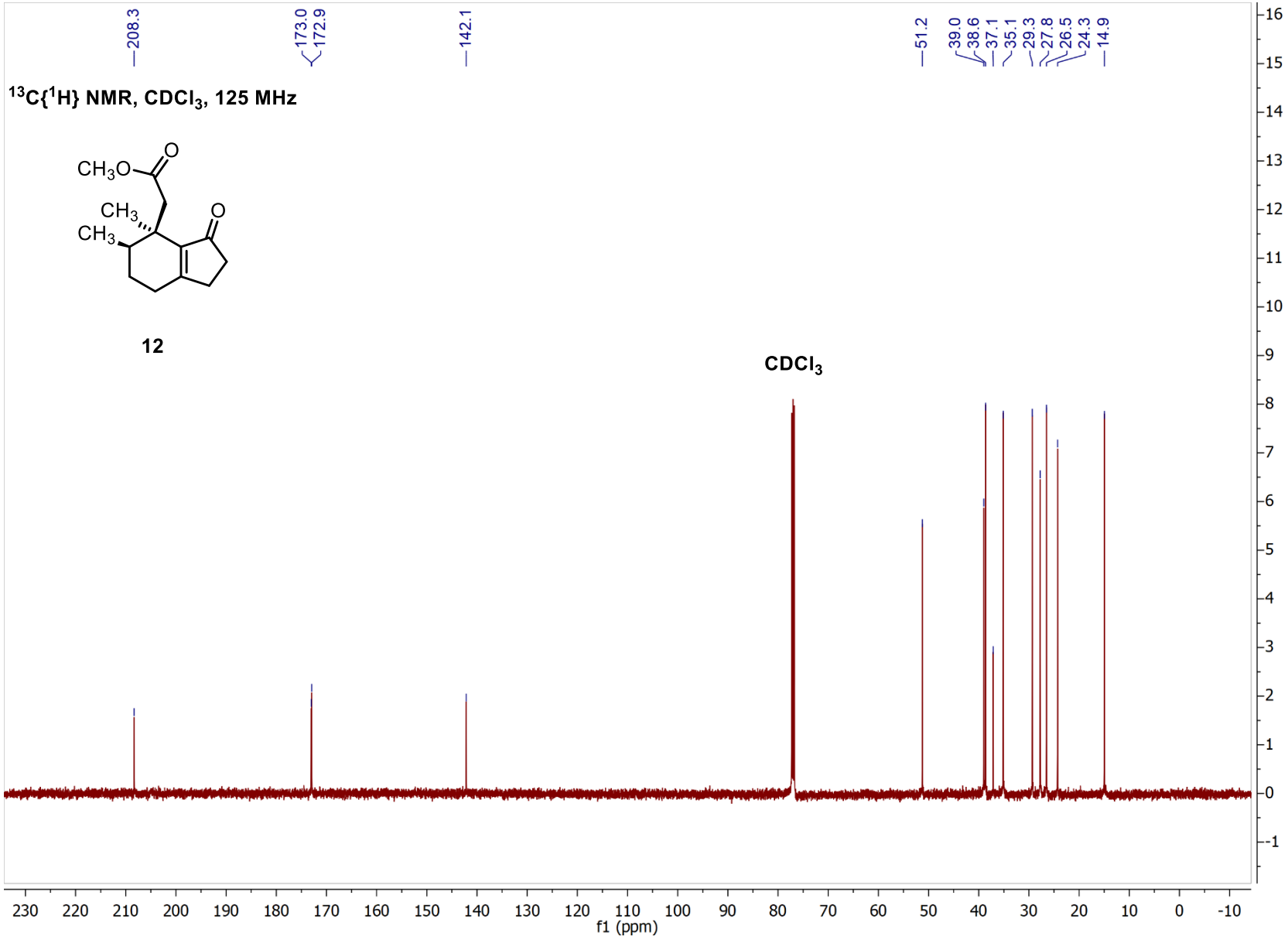

^{1}H NMR, $CDCl_3$, 600 MHz
HO
O
CH_3
CH_3
O
S2
2.539
2.531
2.523
2.377
1.772
1.719
1.461
1.044
1.035
$CHCl_3$
1.89
3.88
0.93
2.00
3.00
3.16
f1 (ppm)

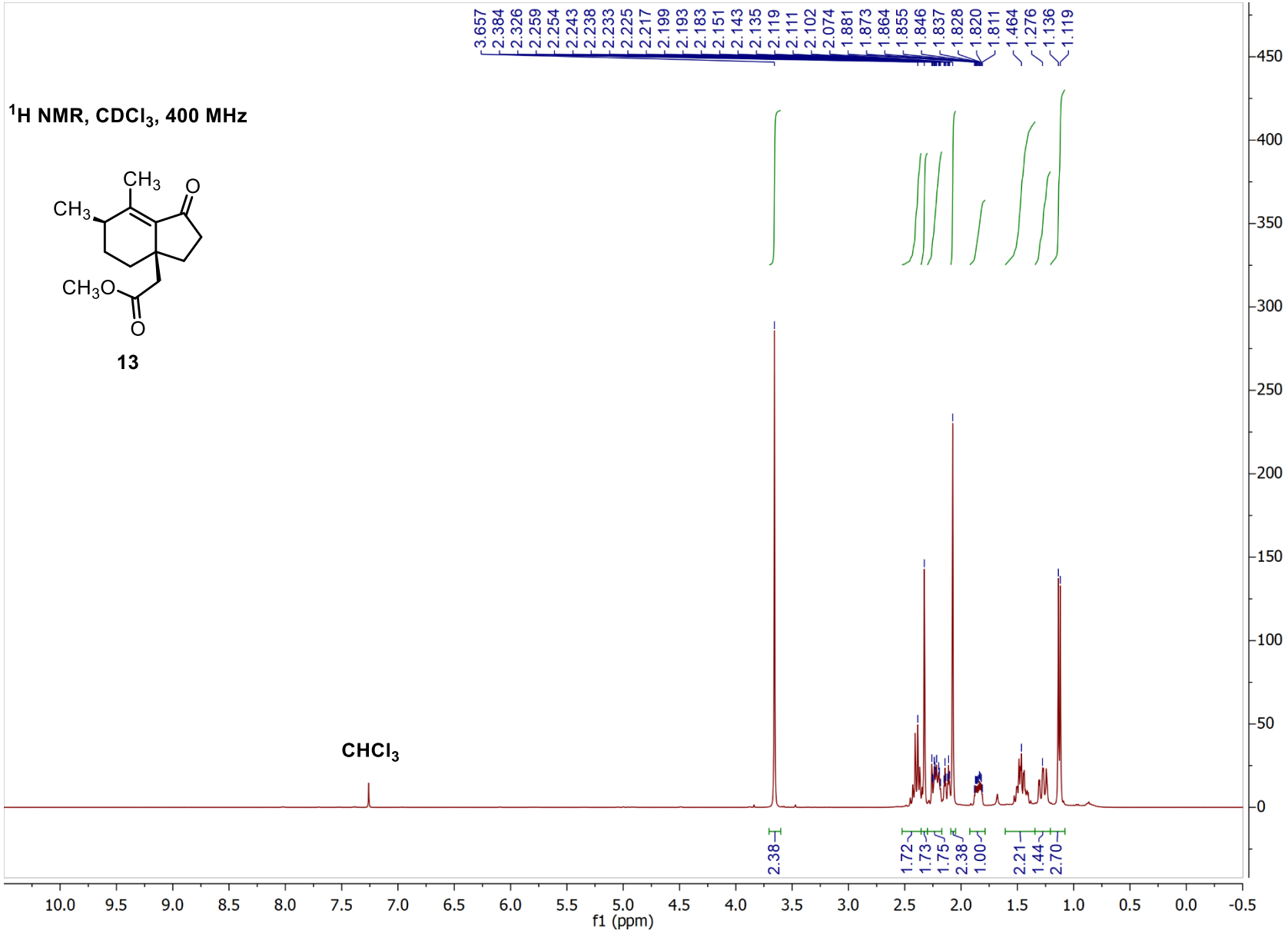

207.8
177.9
174.7
140.3
45.4
39.0
34.7
29.8
27.9
26.8
21.2
16.0
$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
$CDCl_3$
HO
O
CH_3
CH_3
O
S2
f1 (ppm)

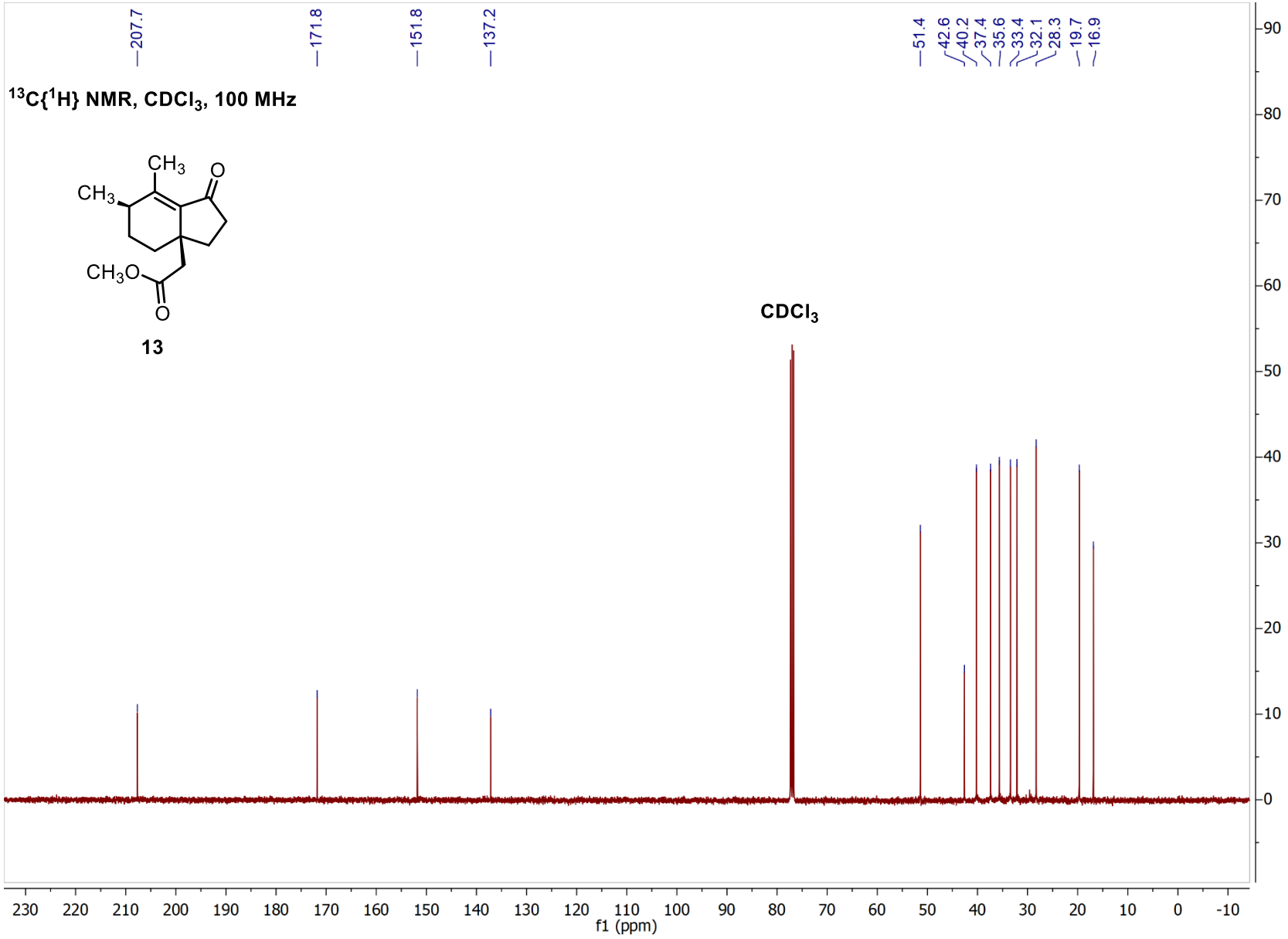

^{1}H NMR, $CDCl_3$, 400 MHz
N_2
O
CH_3
O
CH_3
11
5.373
2.536
2.383
1.832
1.705
1.697
1.690
1.683
1.674
1.663
1.655
1.649
1.584
1.433
0.998
0.981
$CHCl_3$
0.87
1.98
4.07
1.21
1.45
1.13
3.05
3.00
f1 (ppm)

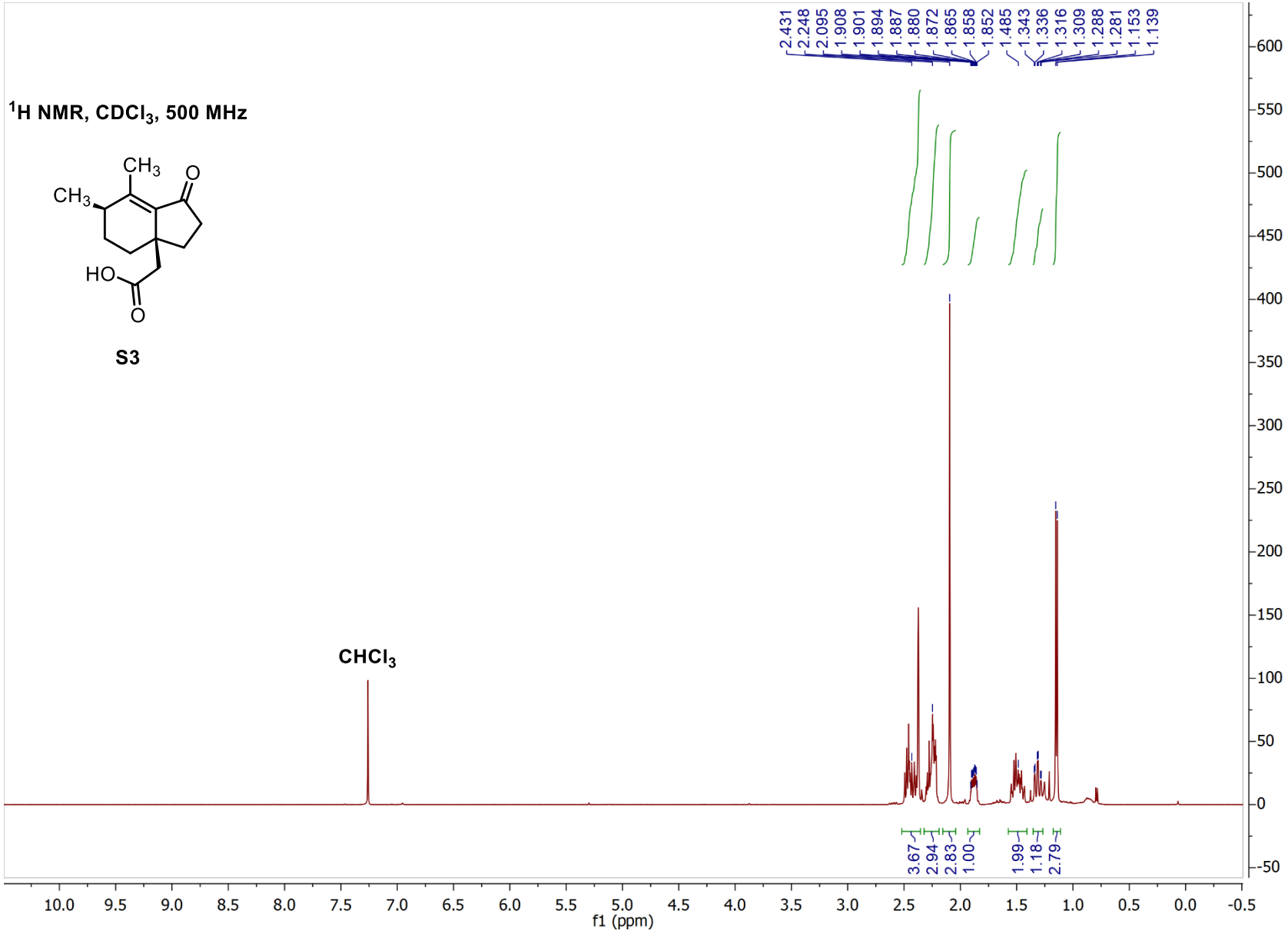

207.3
196.0
175.4
141.2
54.8
48.8
40.0
34.9
29.8
28.4
27.3
20.5
16.0
13C{1H} NMR, CDCl3, 125 MHz
N2
O
CH3
CH3
O
11
CDCl3
f1 (ppm)

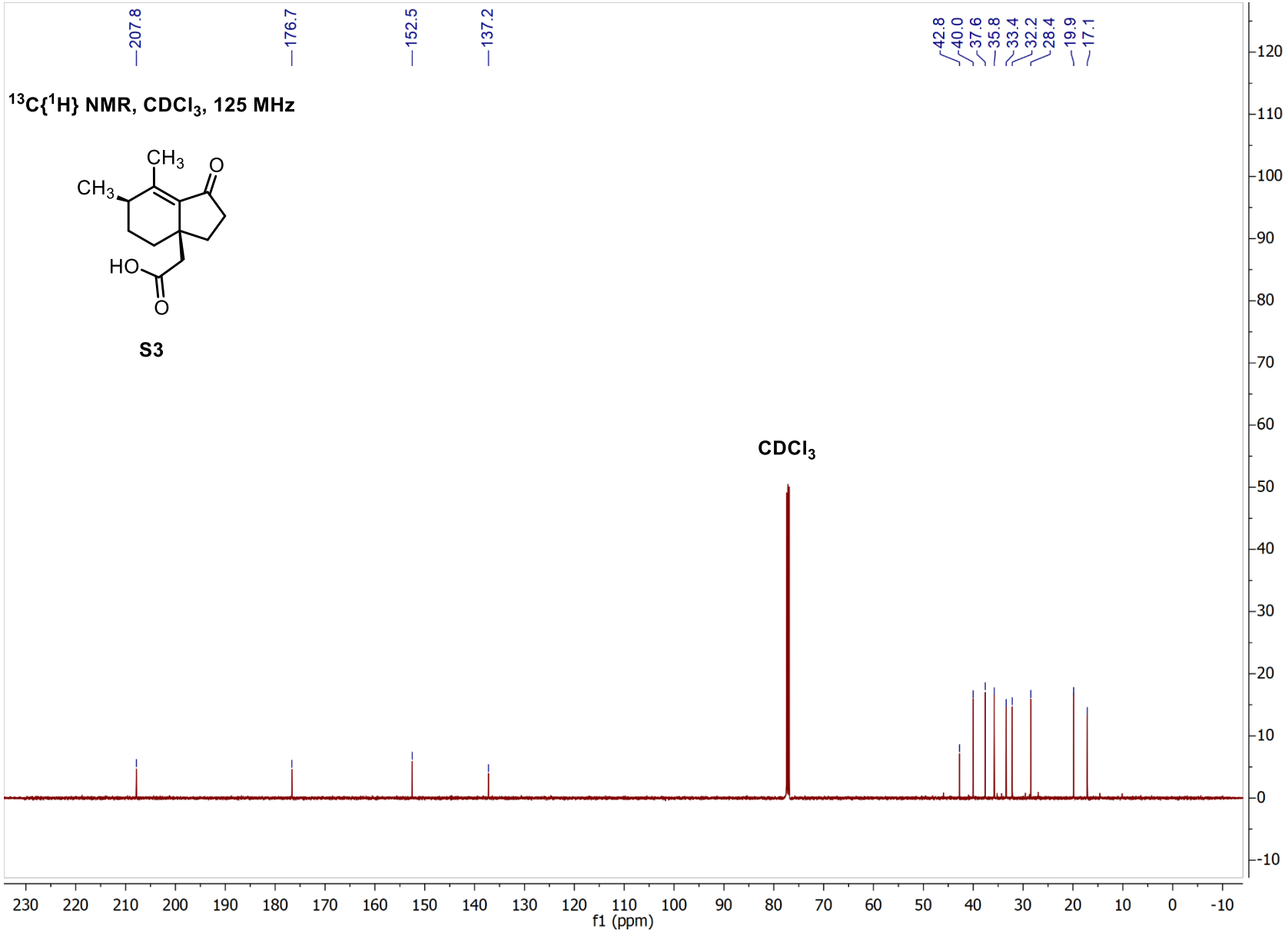

^{1}H NMR, $CDCl_3$, 500 MHz
CH_3O
O
CH_3
CH_3
O
12
3.565
2.592
2.564
2.547
2.520
2.441
2.431
2.422
2.416
2.353
2.344
2.333
2.325
2.315
2.282
1.683
1.445
1.331
0.968
0.955
$CHCl_3$
3.00
2.23
2.06
2.05
2.47
2.52
1.63
3.19
3.57
f1 (ppm)

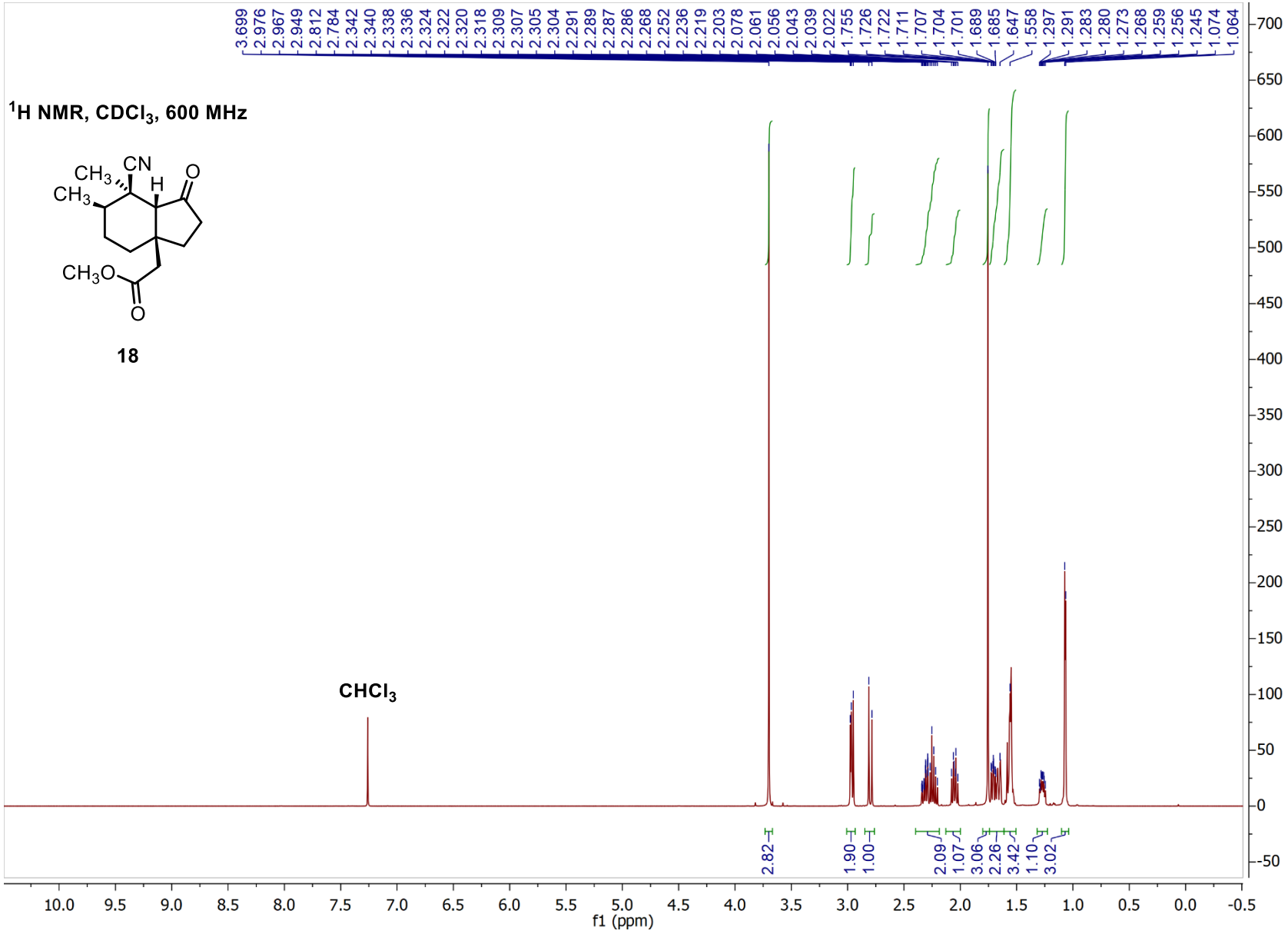

208.3
173.0
172.9
142.1
51.2
39.0
38.6
37.1
35.1
29.3
27.8
26.5
24.3
14.9
13C{1H} NMR, CDCl3, 125 MHz
CH3O
O
CH3
CH3
O
12
CDCl3
f1 (ppm)

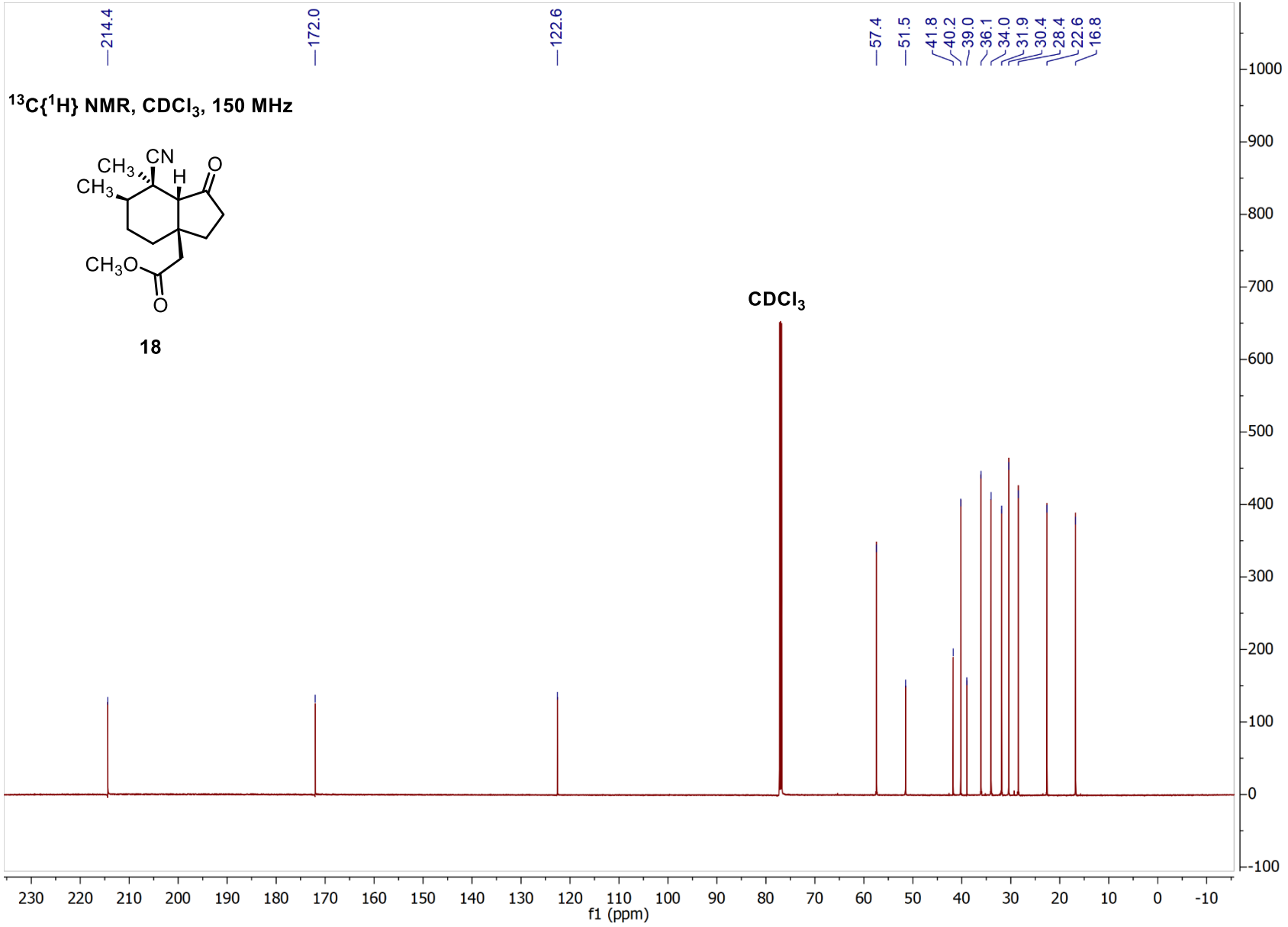

^{1}H NMR, $CDCl_3$, 400 MHz
13
$CHCl_3$
f1 (ppm)

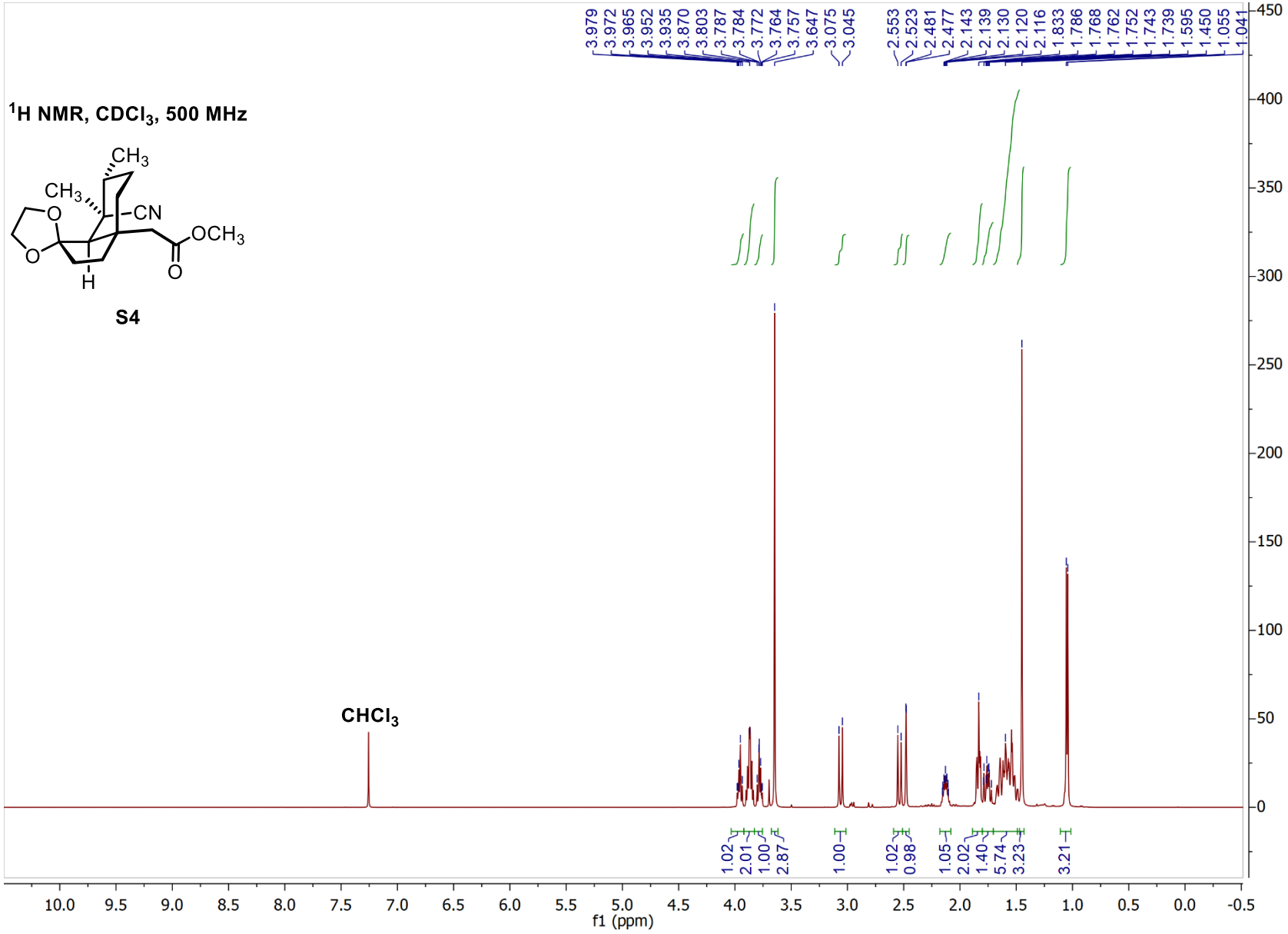

207.7
171.8
151.8
137.2
51.4
42.6
40.2
37.4
35.6
33.4
32.1
28.3
19.7
16.9
13C{1H} NMR, CDCl3, 100 MHz
CH3
CH3
O
CH3O
O
13
CDCl3
f1 (ppm)

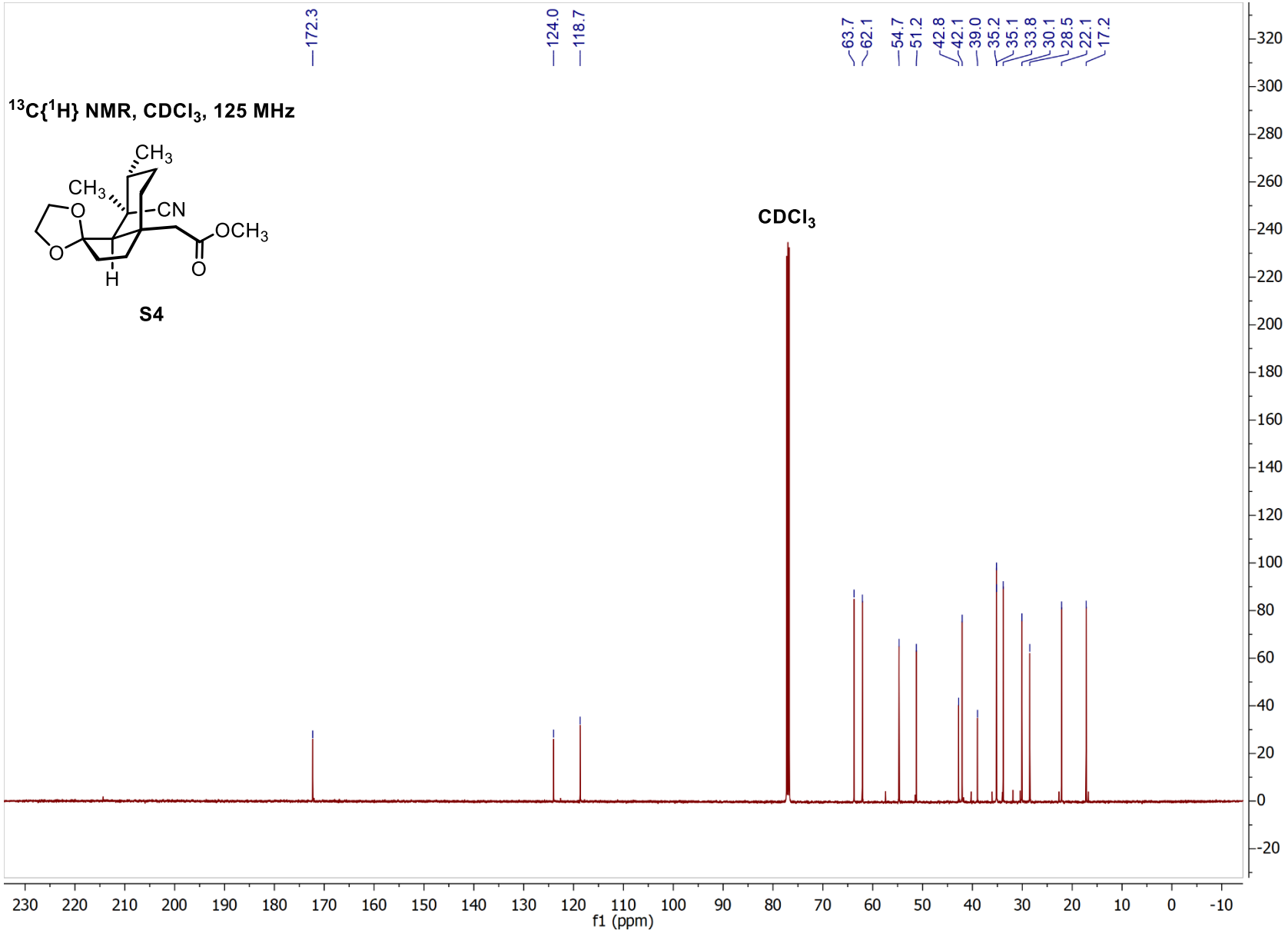

^{1}H NMR, CDCl$_3$, 500 MHz
CH3
CH3
O
HO
O
S3
2.431
2.248
2.095
1.908
1.901
1.894
1.887
1.880
1.872
1.865
1.858
1.852
1.485
1.343
1.336
1.316
1.309
1.288
1.281
1.153
1.139
CHCl3
3.67
2.94
2.83
1.00
1.99
1.18
2.79
f1 (ppm)

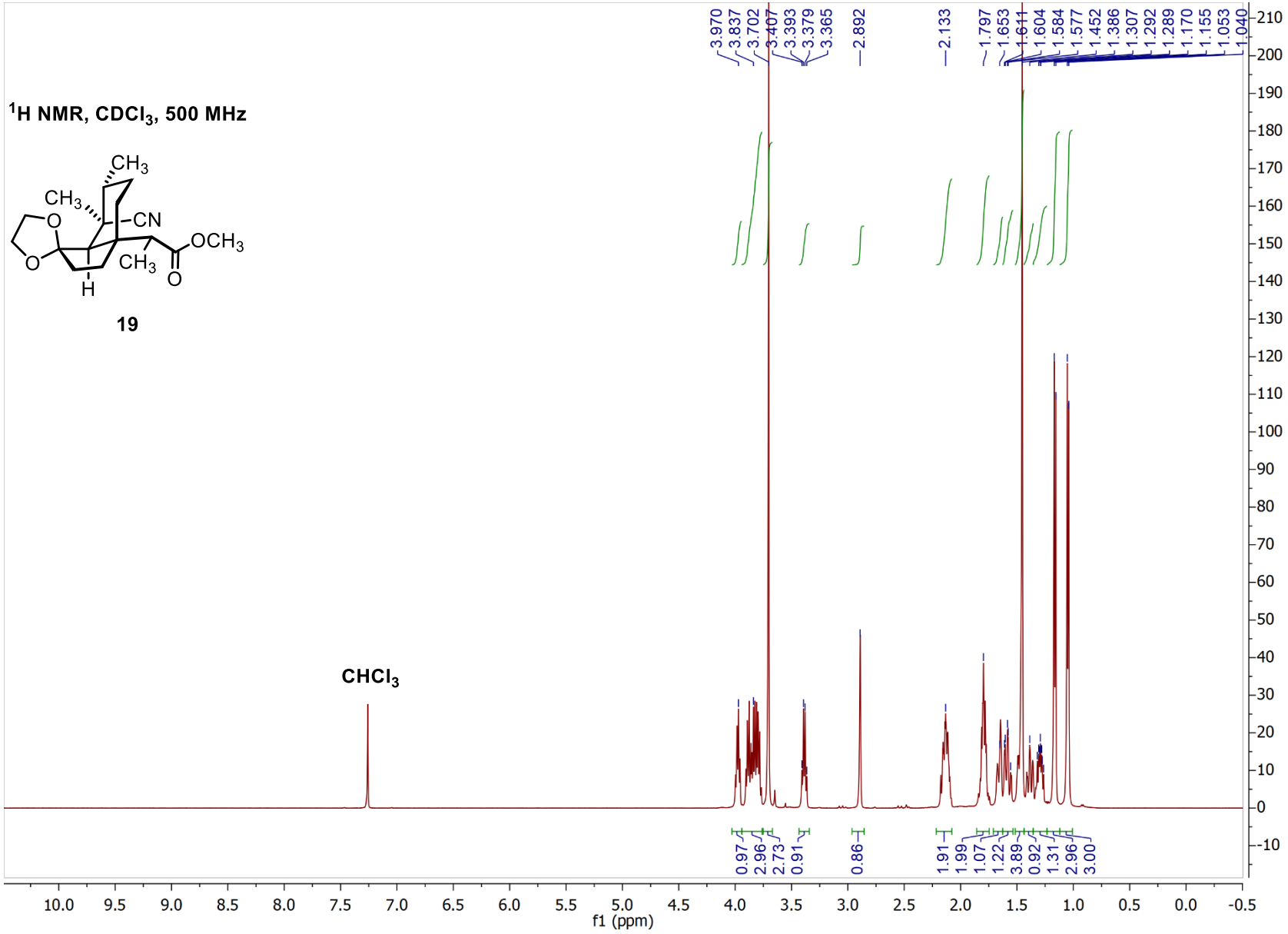

207.8
176.7
152.5
137.2
42.8
40.0
37.6
35.8
33.4
32.2
28.4
19.9
17.1
13C{1H} NMR, CDCl3, 125 MHz
CH3
CH3
O
HO
O
S3
CDCl3
f1 (ppm)

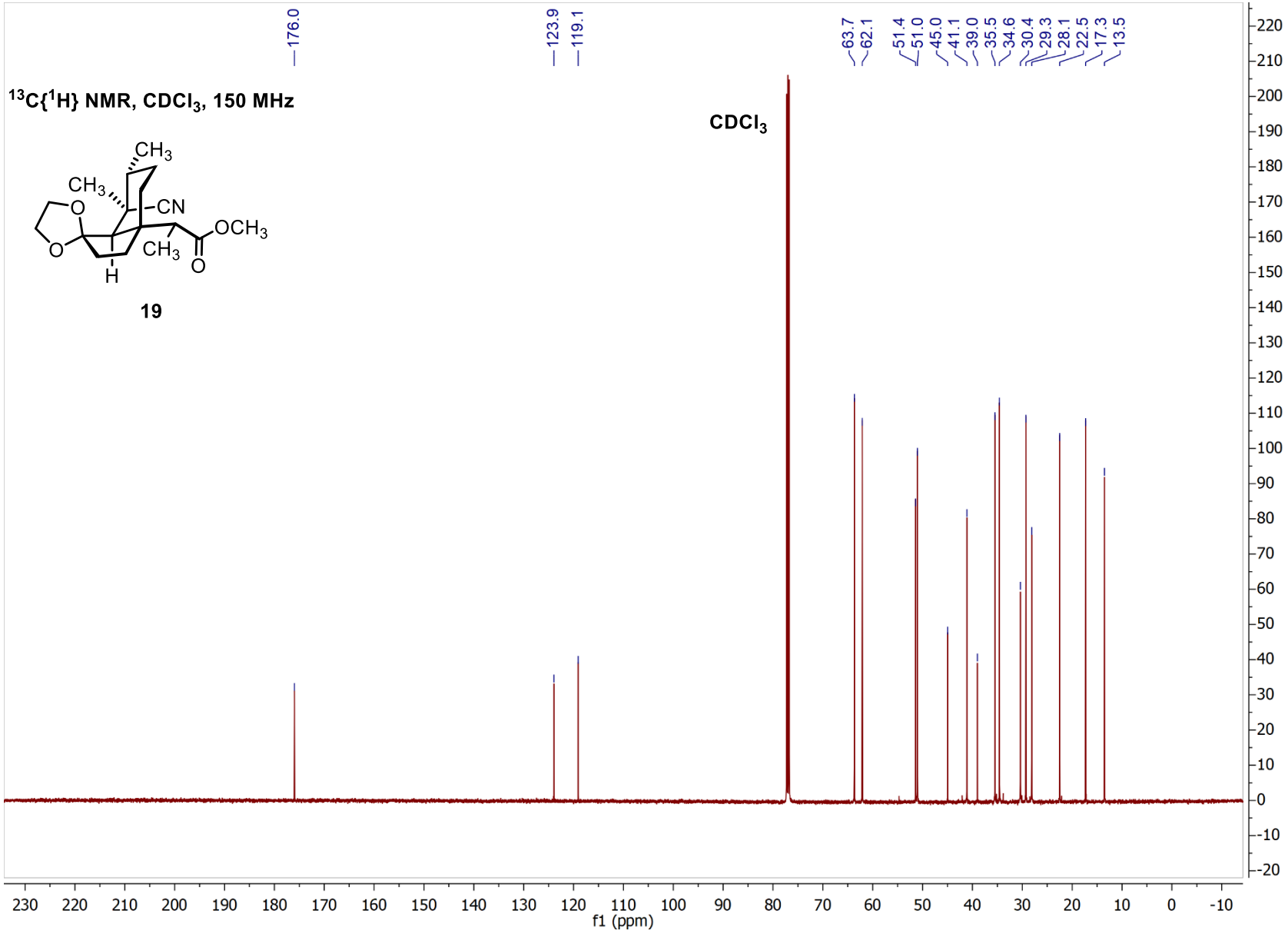

^{1}H NMR, $CDCl_3$, 600 MHz
18
$CHCl_3$
f1 (ppm)

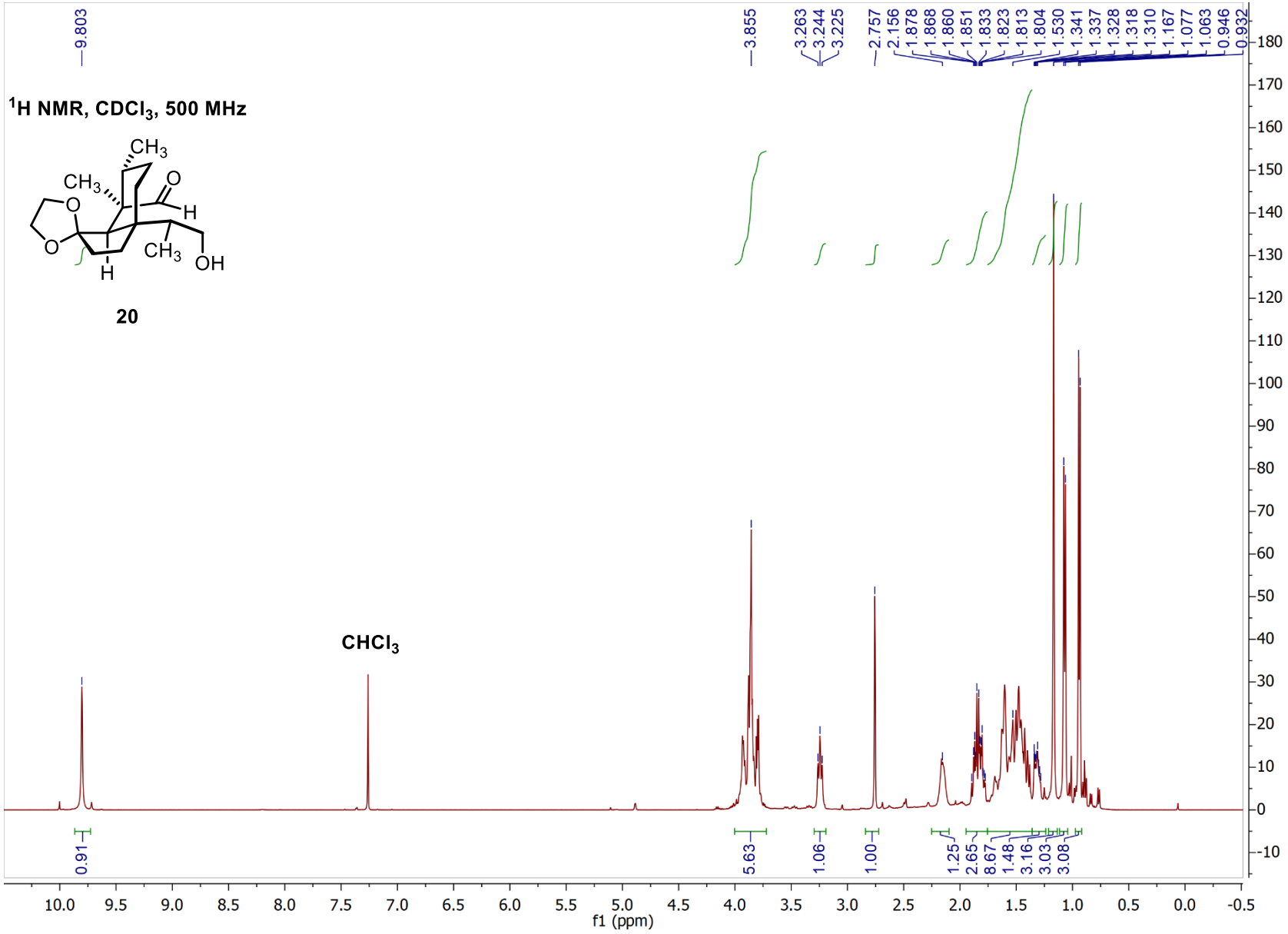

214.4
172.0
122.6
57.4
51.5
41.8
40.2
39.0
36.1
34.0
31.9
30.4
28.4
22.6
16.8
13C{1H} NMR, CDCl3, 150 MHz
CH3
CN
H
O
CH3
CH3O
O
18
CDCl3
f1 (ppm)

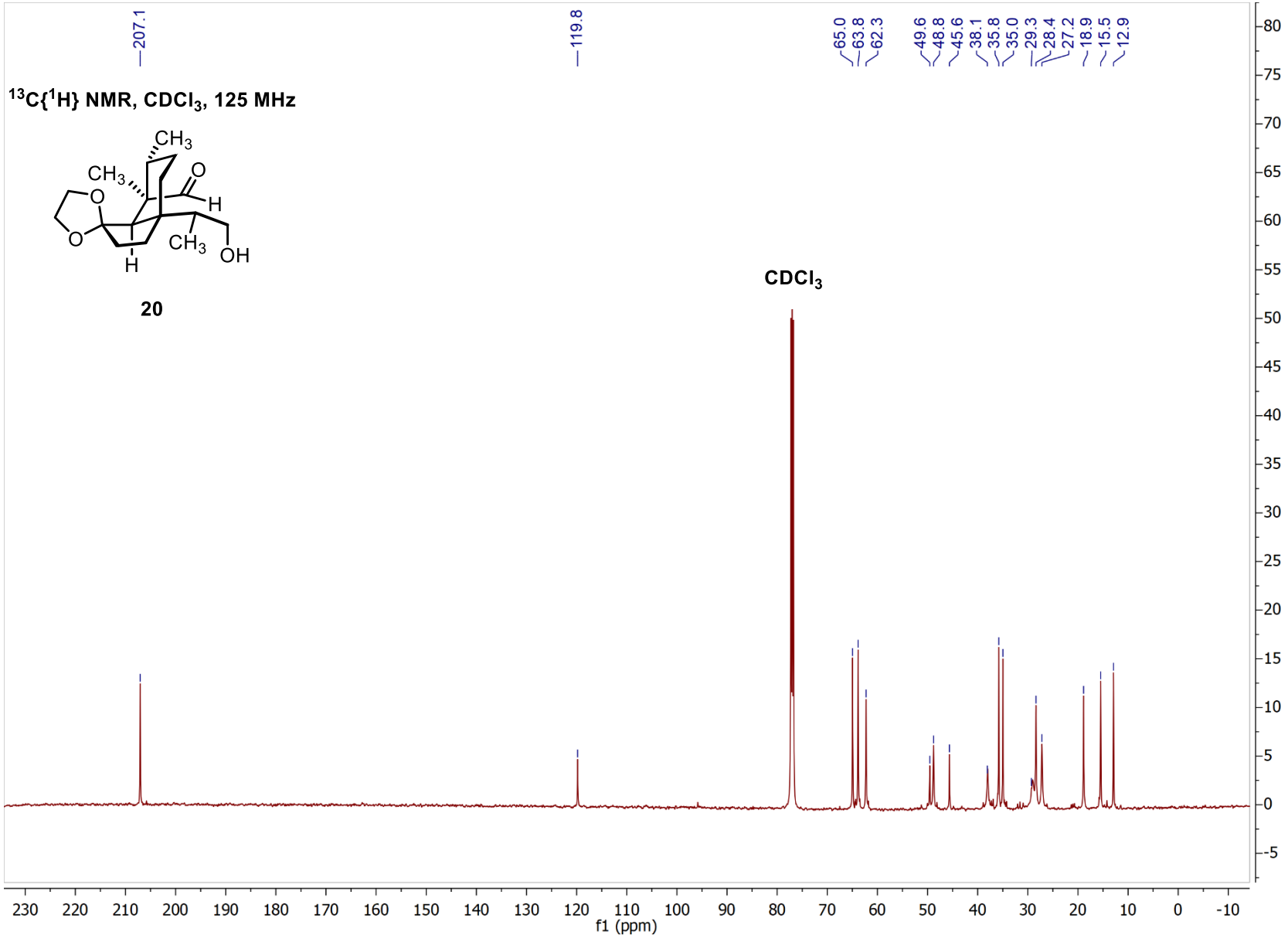

^{1}H NMR, $CDCl_3$, 500 MHz
S4
$CHCl_3$
f1 (ppm)

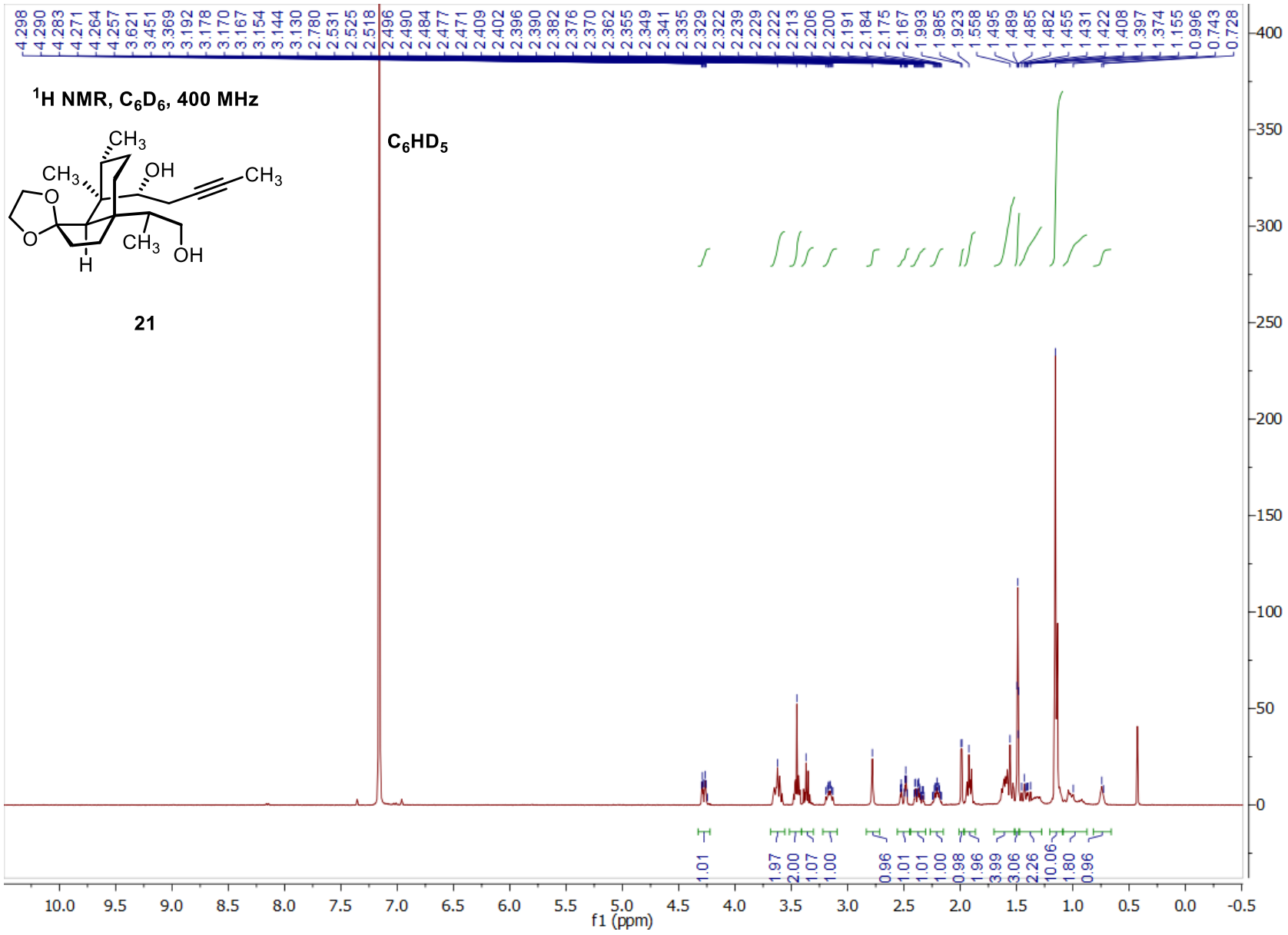

172.3
124.0
118.7
63.7
62.1
54.7
51.2
42.8
42.1
39.0
35.2
35.1
33.8
30.1
28.5
22.1
17.2
13C{1H} NMR, CDCl3, 125 MHz
CH3
CH3
CN
OCH3
O
O
O
H
S4
CDCl3
f1 (ppm)

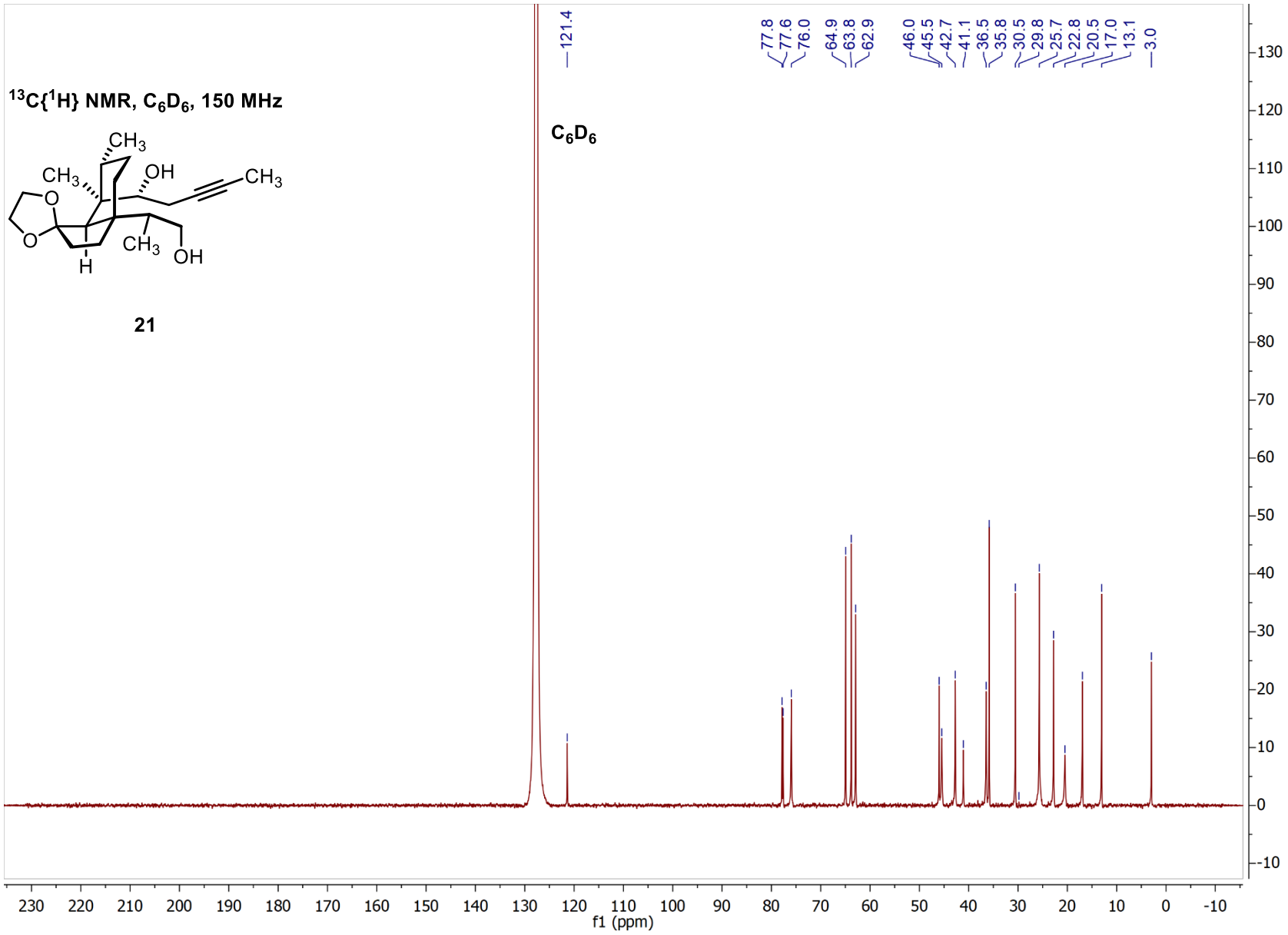

^{1}H NMR, $CDCl_3$, 500 MHz
19
$CHCl_3$
f1 (ppm)


$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
$CDCl_3$
176.0
123.9
119.1
63.7
62.1
51.4
51.0
45.0
41.1
39.0
35.5
34.6
30.4
29.3
28.1
22.5
17.3
13.5
CH3
CH3
CN
OCH3
CH3
O
O
O
H
19
f1 (ppm)

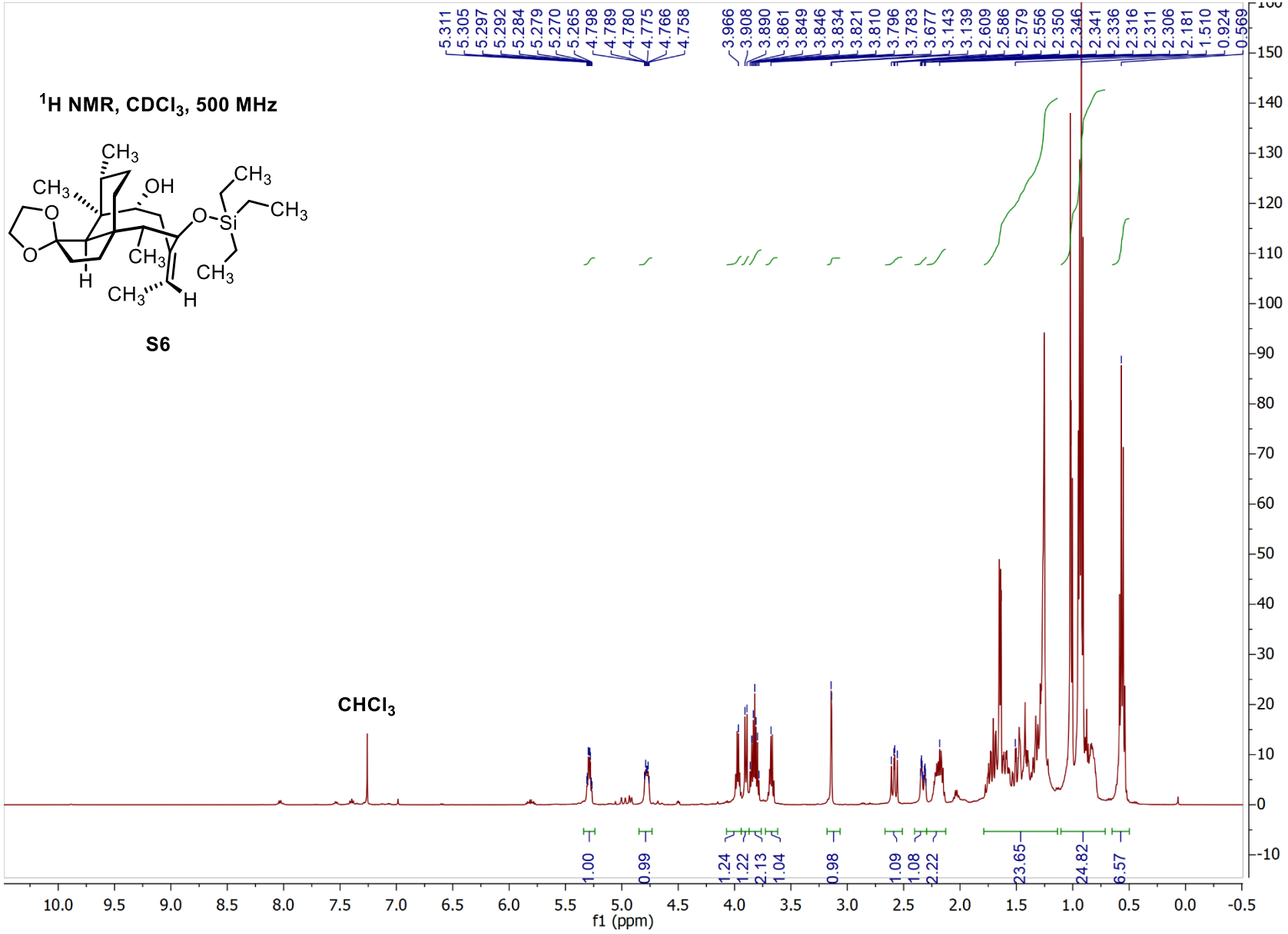

^{1}H NMR, $CDCl_3$, 500 MHz
20
$CHCl_3$
f1 (ppm)

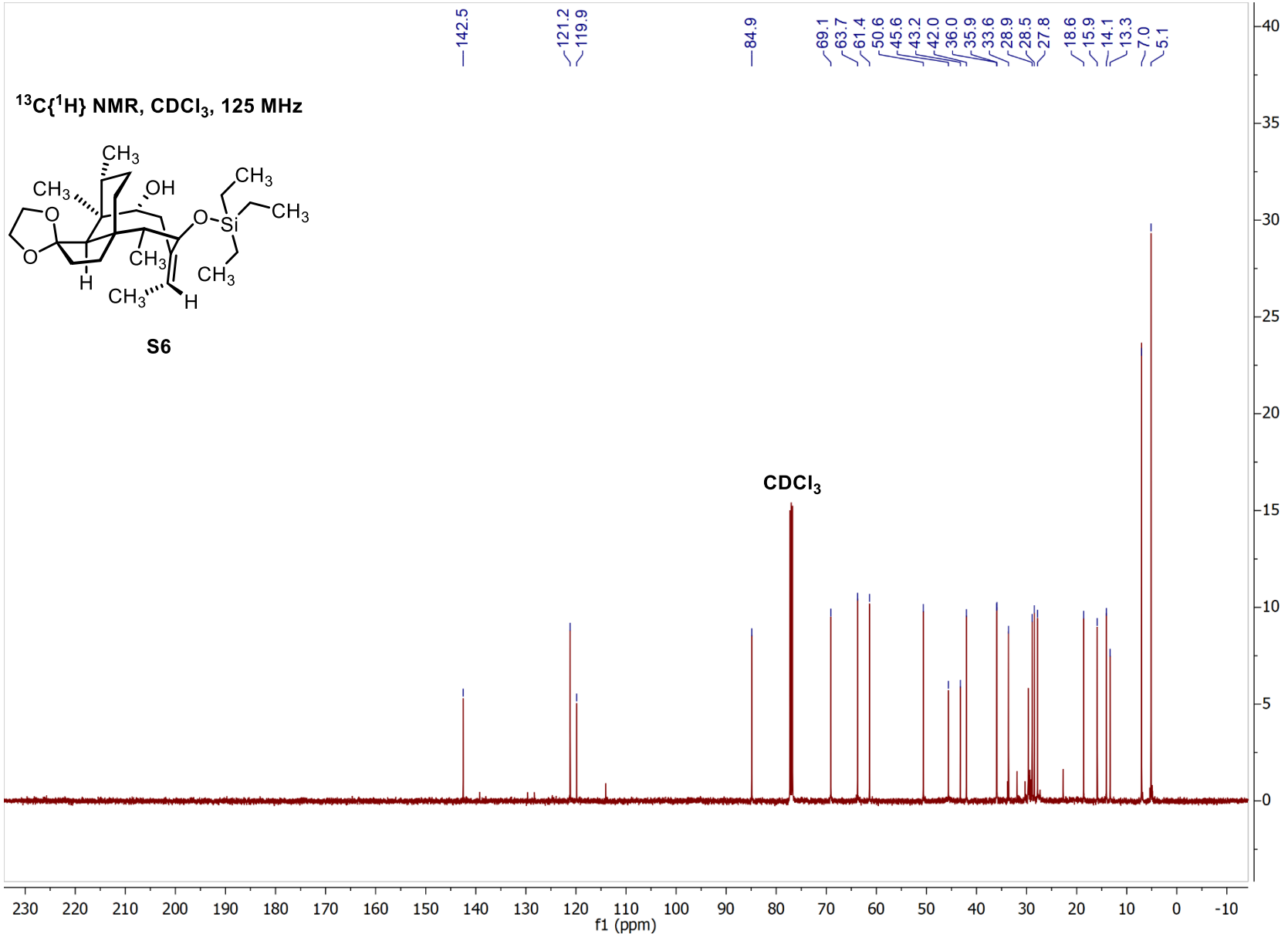

207.1
119.8
65.0
63.8
62.3
49.6
48.8
45.6
38.1
35.8
35.0
29.3
28.4
27.2
18.9
15.5
12.9
13C{1H} NMR, CDCl3, 125 MHz
CH3
CH3
O
O
O
H
CH3
OH
H
20
CDCl3
f1 (ppm)

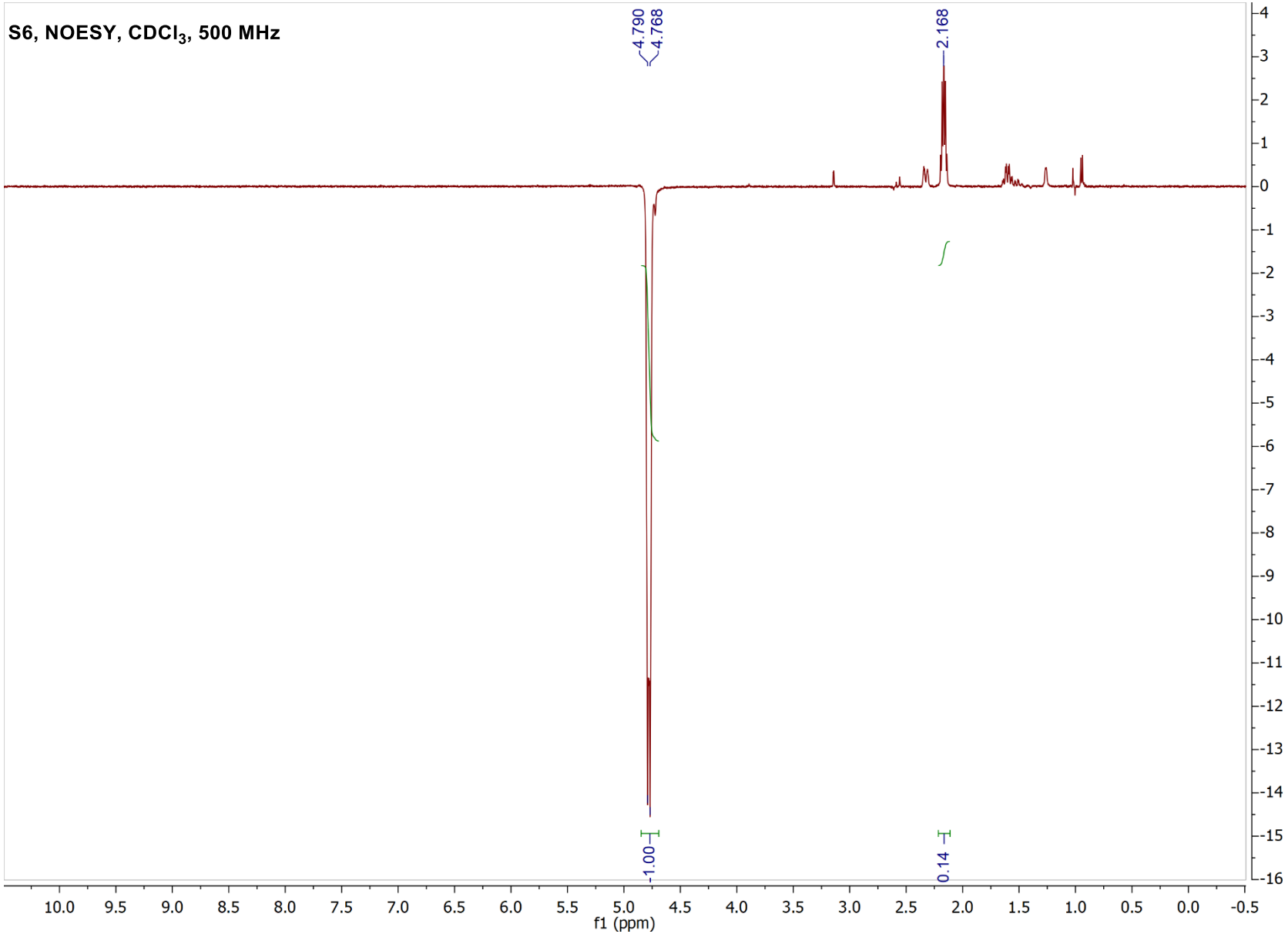

^{1}H NMR, C_6D_6, 400 MHz
C_6HD_5
21
f1 (ppm)

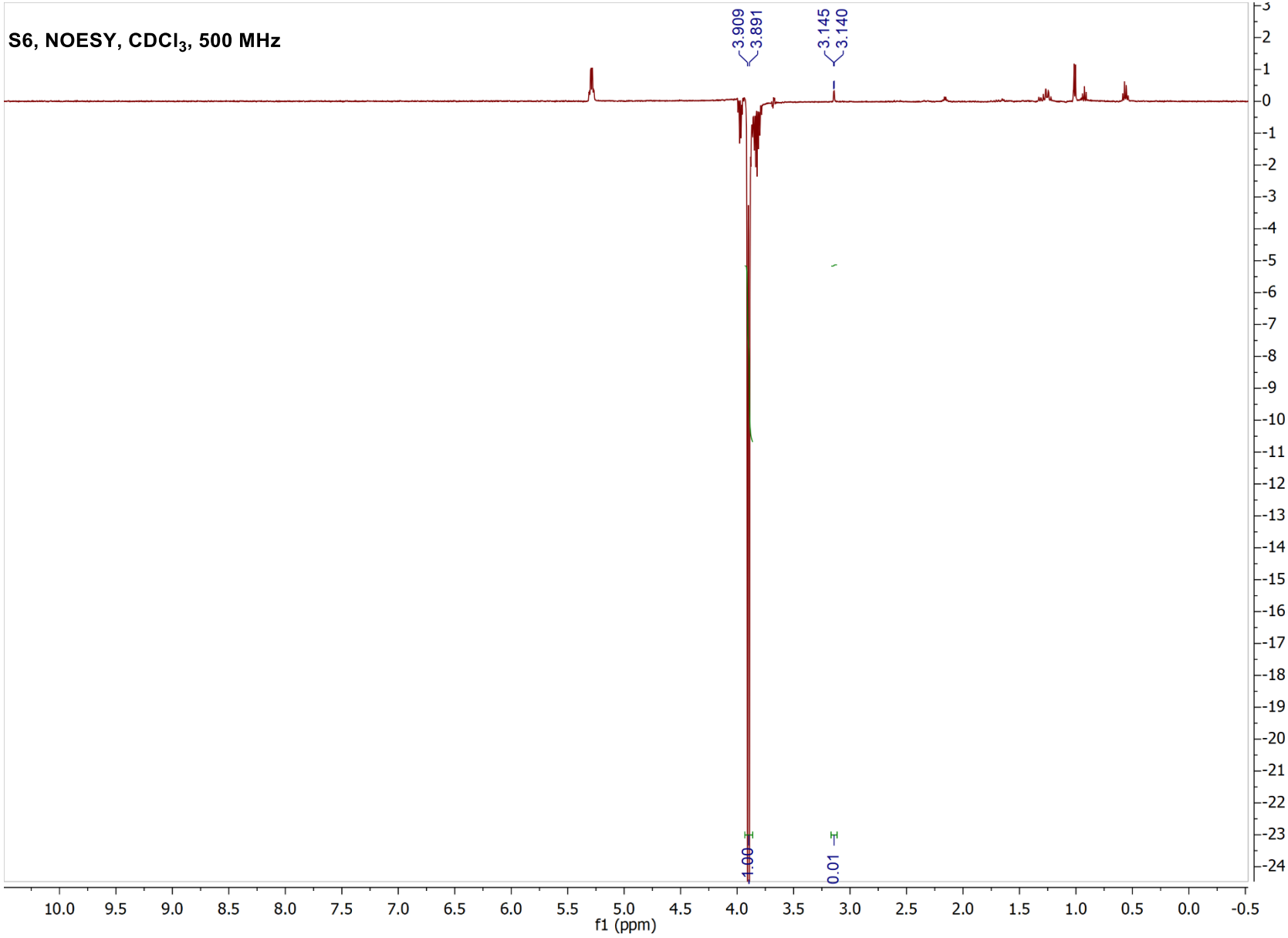

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
121.4
77.8
77.6
76.0
64.9
63.8
62.9
46.0
45.5
42.7
41.1
36.5
35.8
30.5
29.8
25.7
22.8
20.5
17.0
13.1
3.0
f1 (ppm)

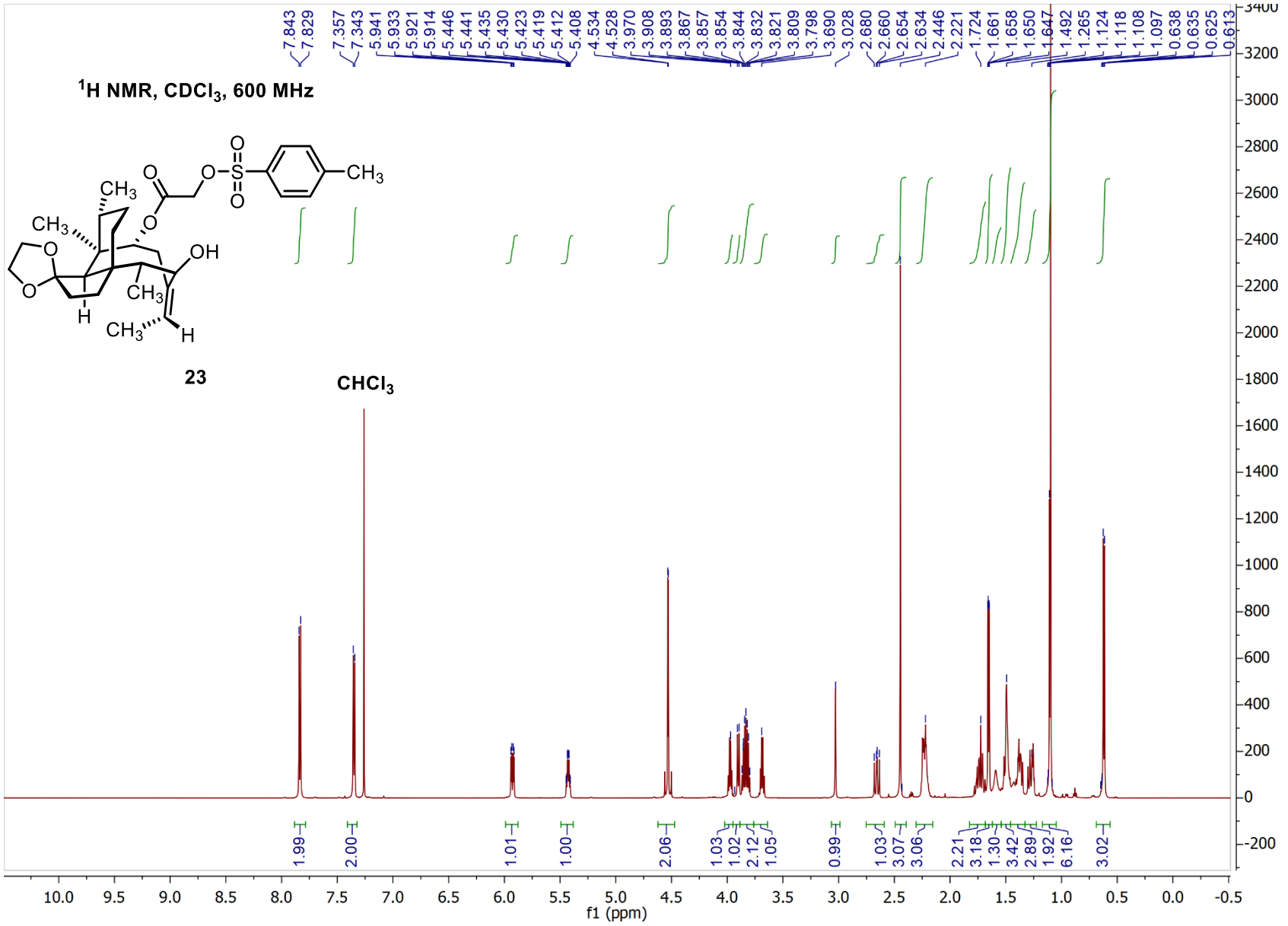
21

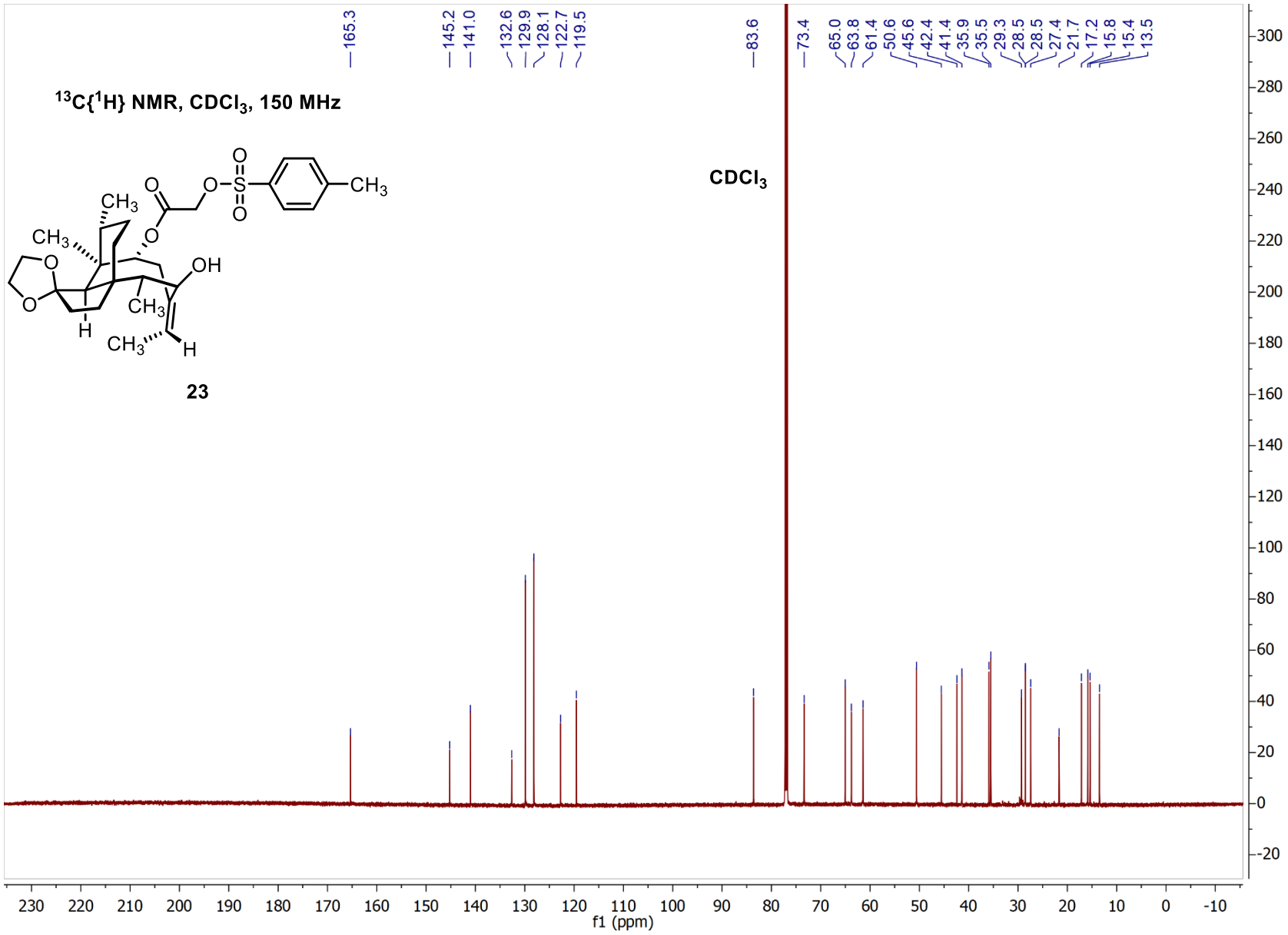

^{1}H NMR, $CDCl_3$, 500 MHz
S6
$CHCl_3$
f1 (ppm)

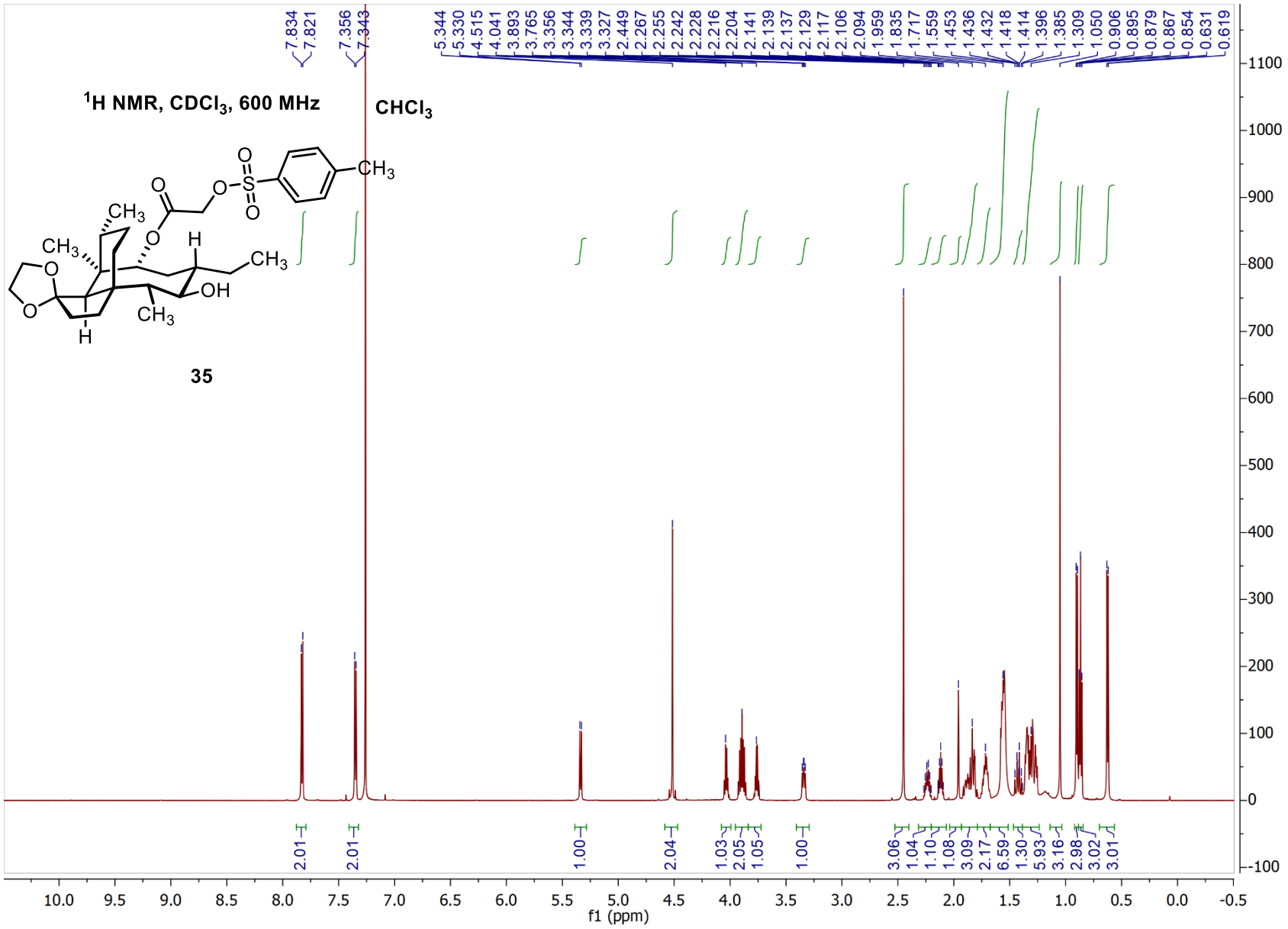

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 125 MHz
S6
142.5
121.2
119.9
84.9
69.1
63.7
61.4
50.6
45.6
43.2
42.0
36.0
35.9
33.6
28.9
28.5
27.8
18.6
15.9
14.1
13.3
7.0
5.1
$CDCl_3$
f1 (ppm)

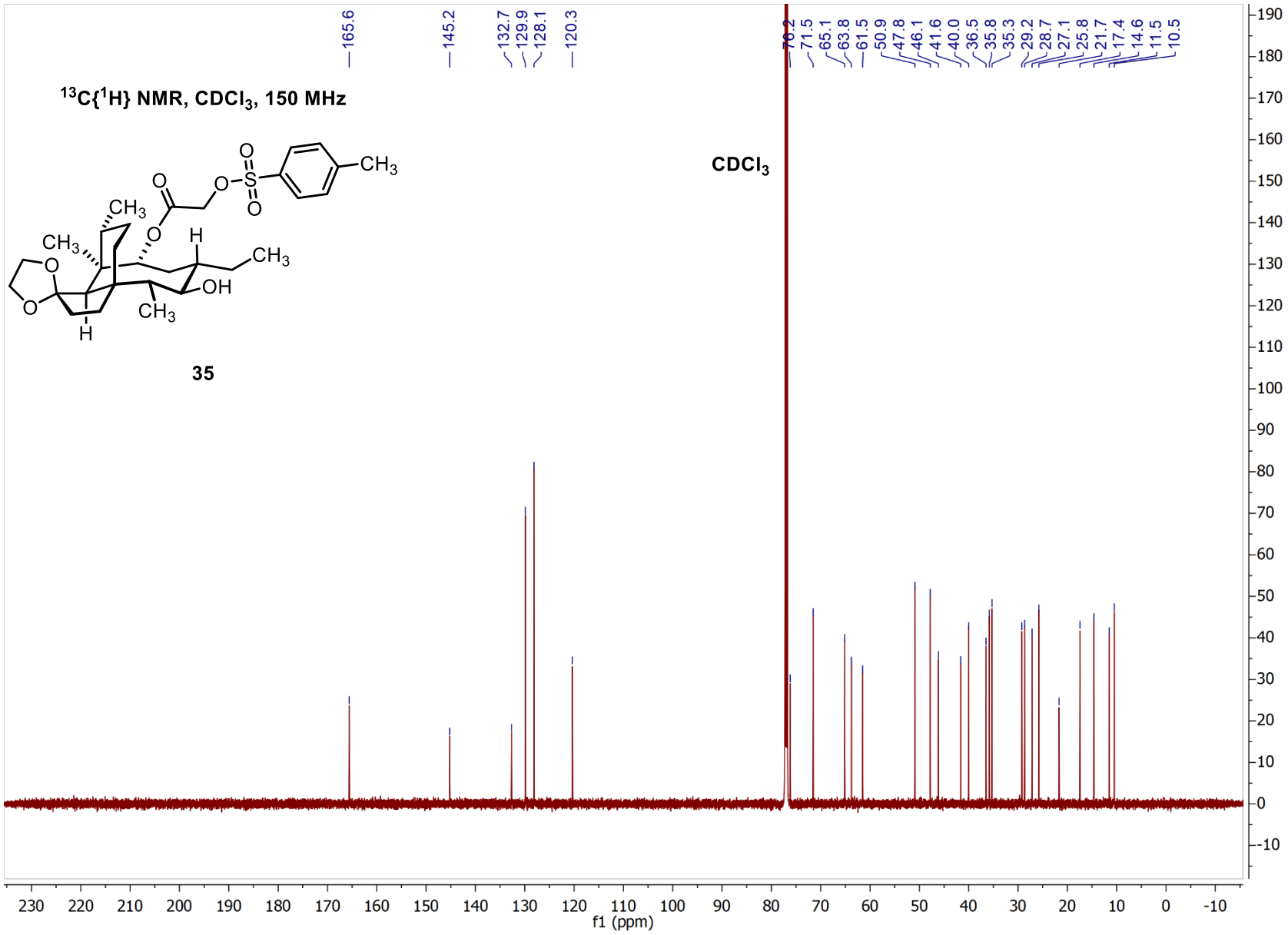

S6, NOESY, CDCl3, 500 MHz
4.790
4.768
2.168
1.00
0.14
f1 (ppm)

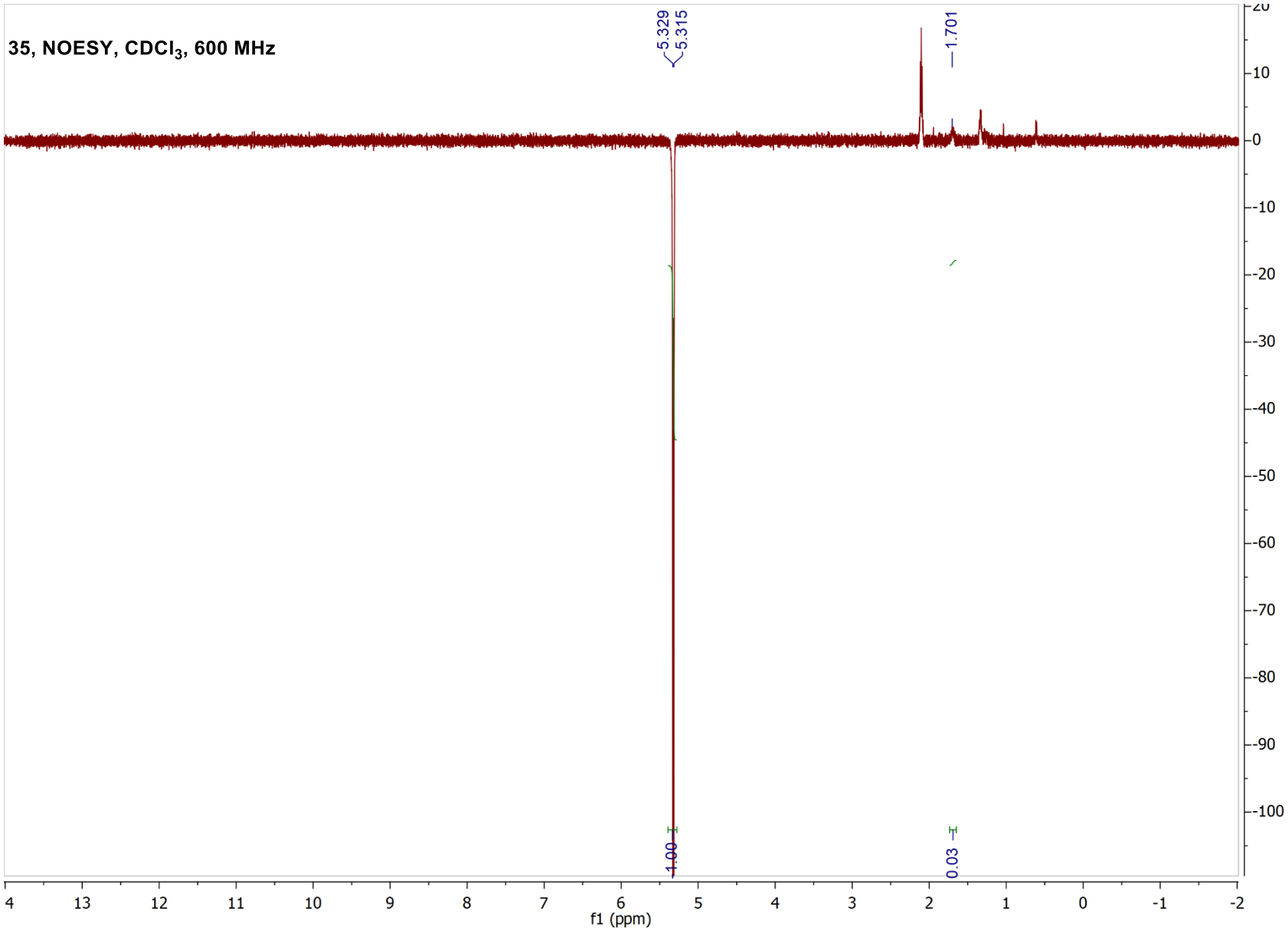

S6, NOESY, CDCl3, 500 MHz
3.909
3.891
3.145
3.140
1.00
0.01
f1 (ppm)

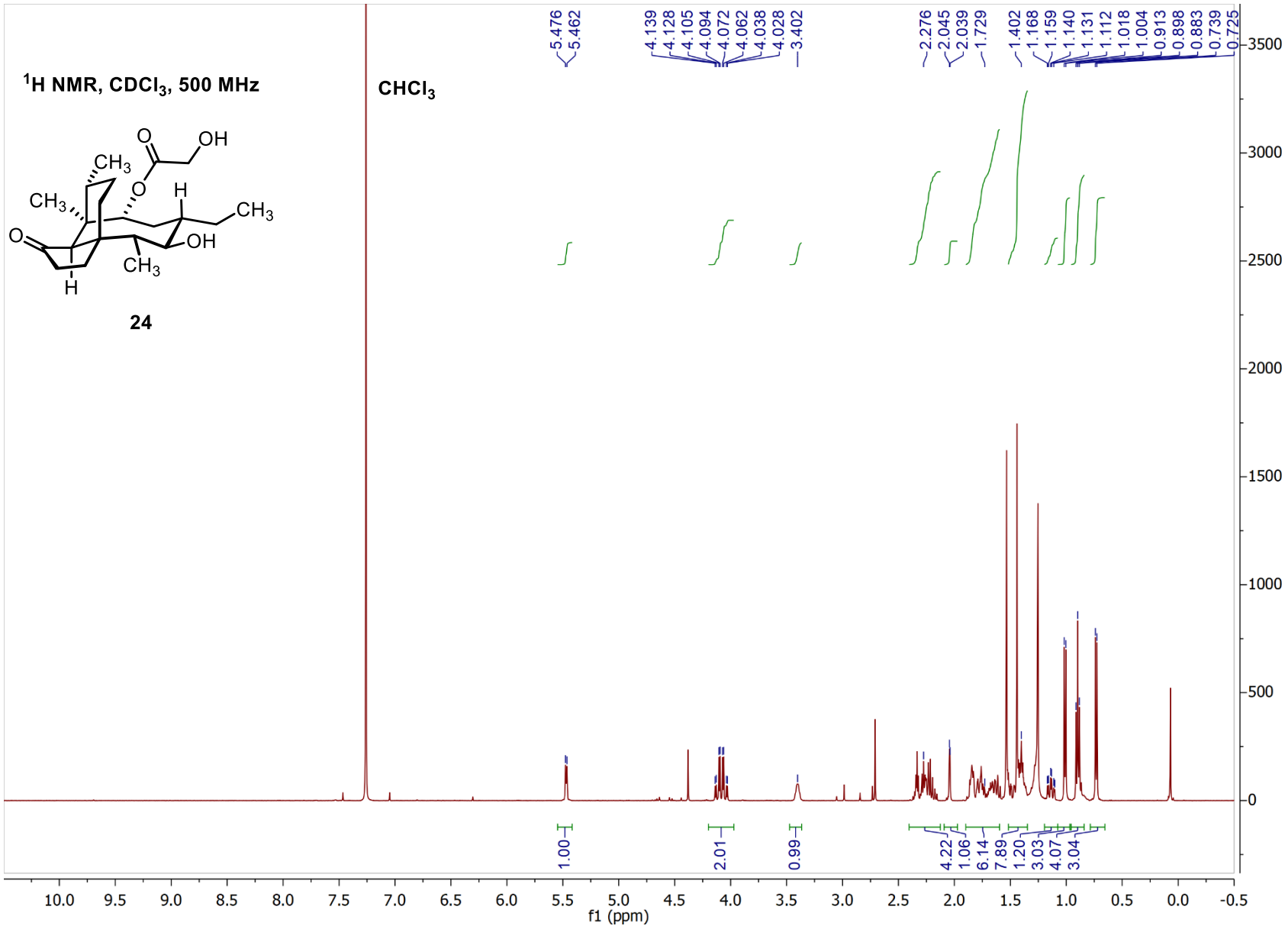

^{1}H NMR, $CDCl_3$, 600 MHz
23
$CHCl_3$
f1 (ppm)

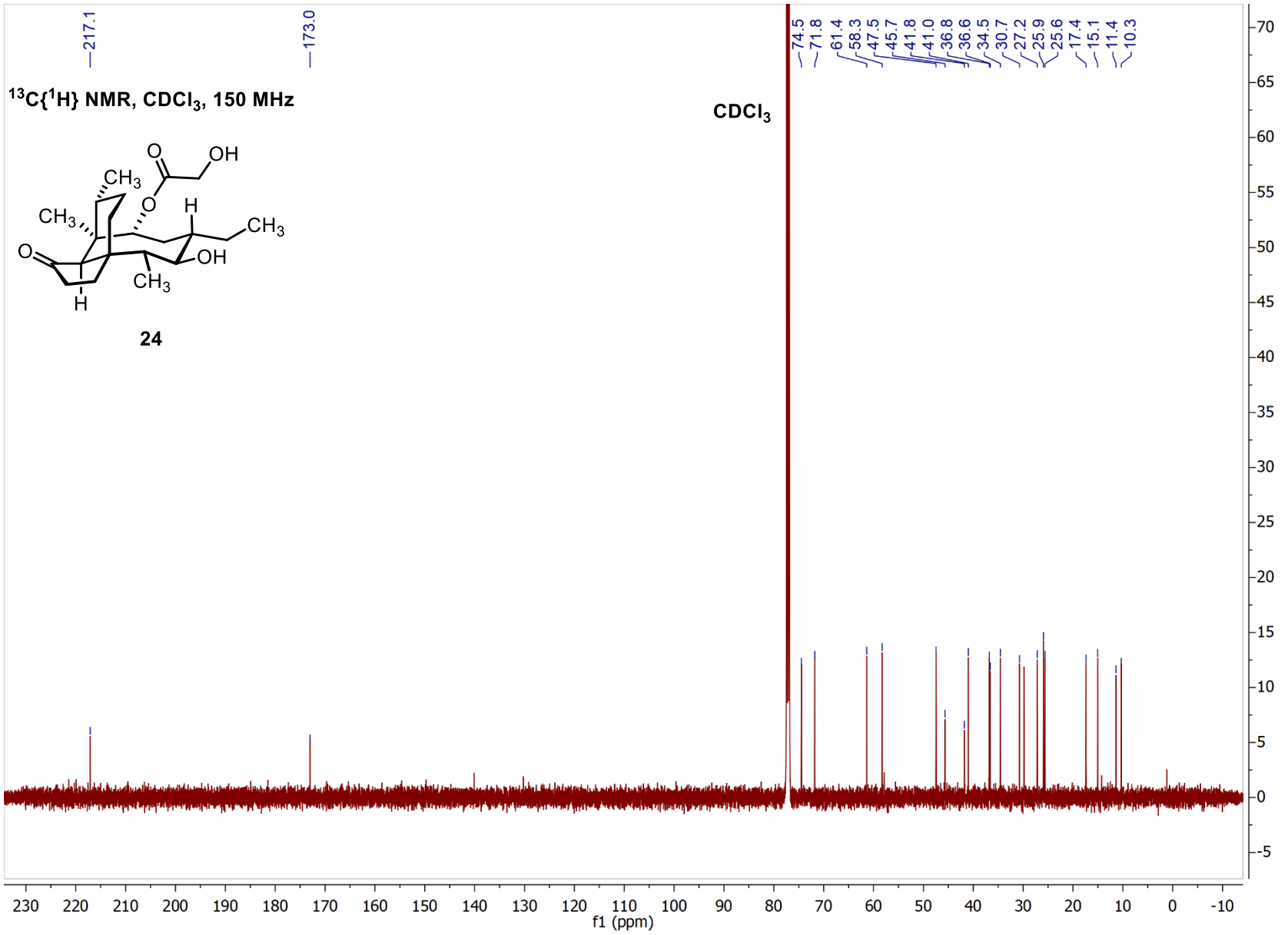

165.3
145.2
141.0
132.6
129.9
128.1
122.7
119.5
83.6
73.4
65.0
63.8
61.4
50.6
45.6
42.4
41.4
35.9
35.5
29.3
28.5
28.5
27.4
21.7
17.2
15.8
15.4
13.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
23
f1 (ppm)

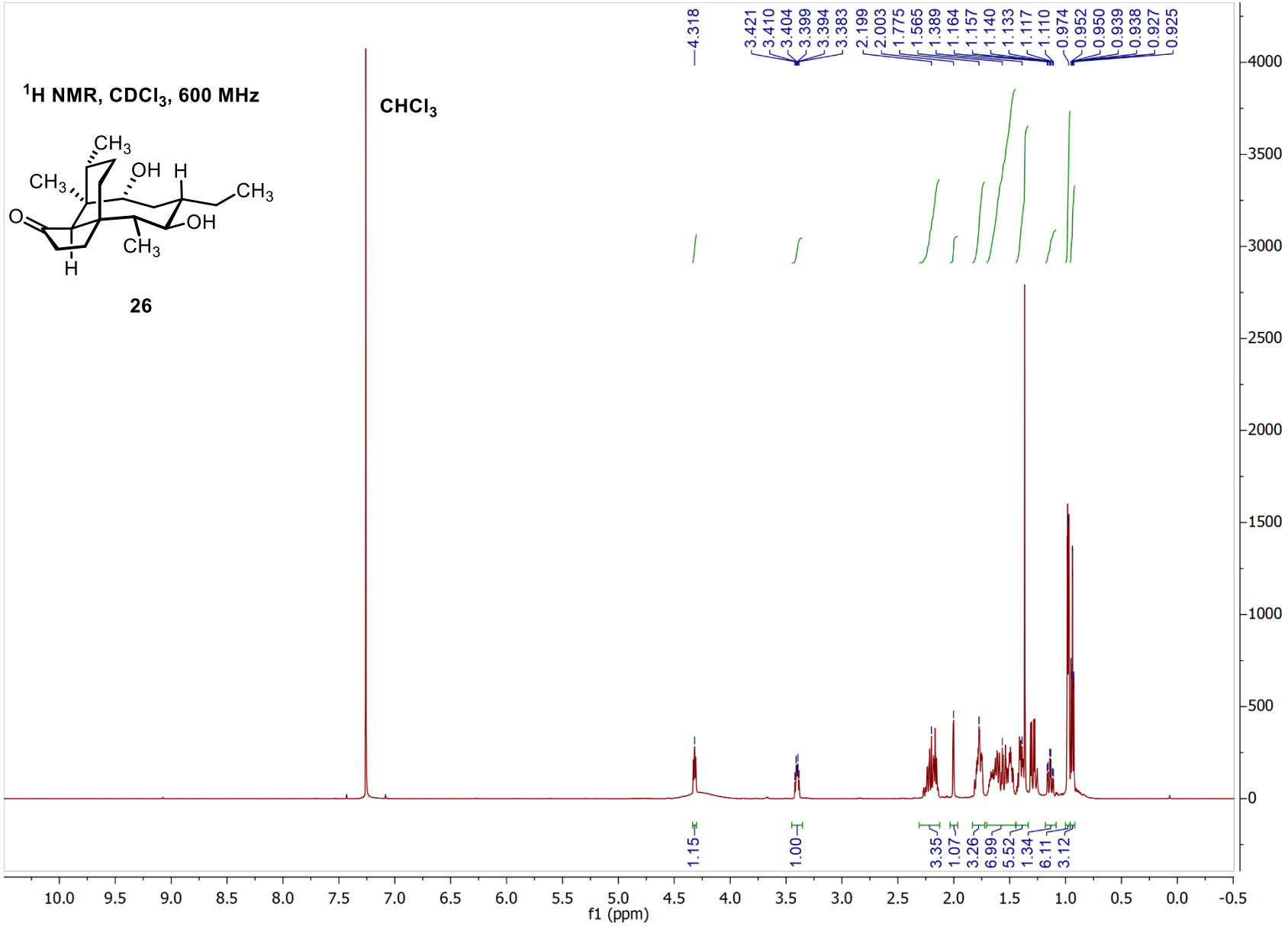

1H NMR, CDCl3, 600 MHz
CHCl3
35
7.834
7.821
7.356
7.343
5.344
5.330
4.515
4.041
3.893
3.765
3.356
3.344
3.339
3.327
2.449
2.267
2.255
2.242
2.228
2.216
2.204
2.141
2.139
2.137
2.129
2.117
2.106
2.094
1.959
1.835
1.717
1.559
1.453
1.436
1.432
1.418
1.414
1.396
1.385
1.309
1.050
0.906
0.895
0.879
0.867
0.854
0.631
0.619
2.01
2.01
1.00
2.04
1.03
2.05
1.05
1.00
3.06
1.04
1.10
1.08
3.09
2.17
6.59
1.30
5.93
3.16
2.98
3.02
3.01
f1 (ppm)

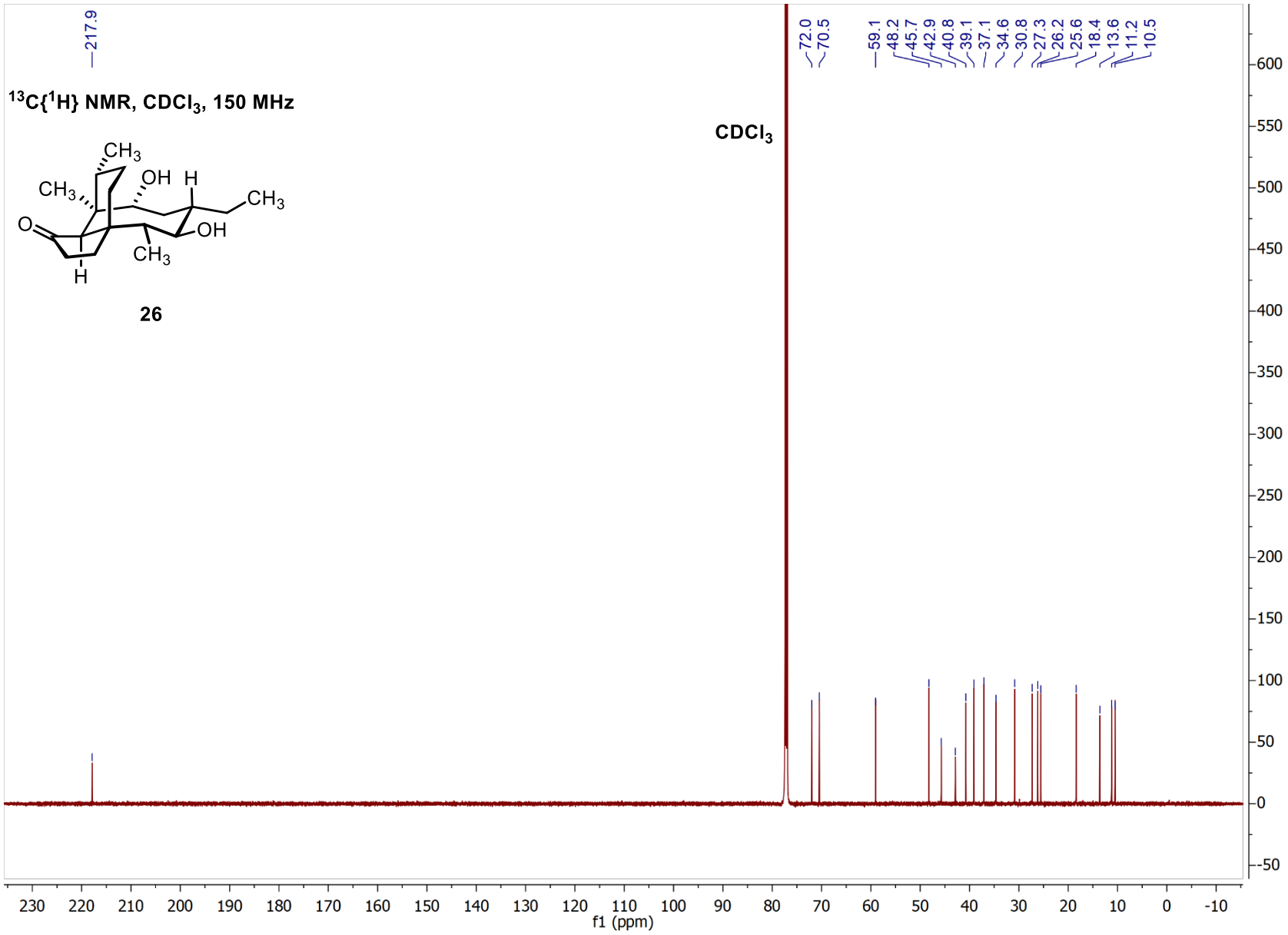

165.6
145.2
132.7
129.9
128.1
120.3
70.2
71.5
65.1
63.8
61.5
50.9
47.8
46.1
41.6
40.0
36.5
35.8
35.3
29.2
28.7
27.1
25.8
21.7
17.4
14.6
11.5
10.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
35
f1 (ppm)

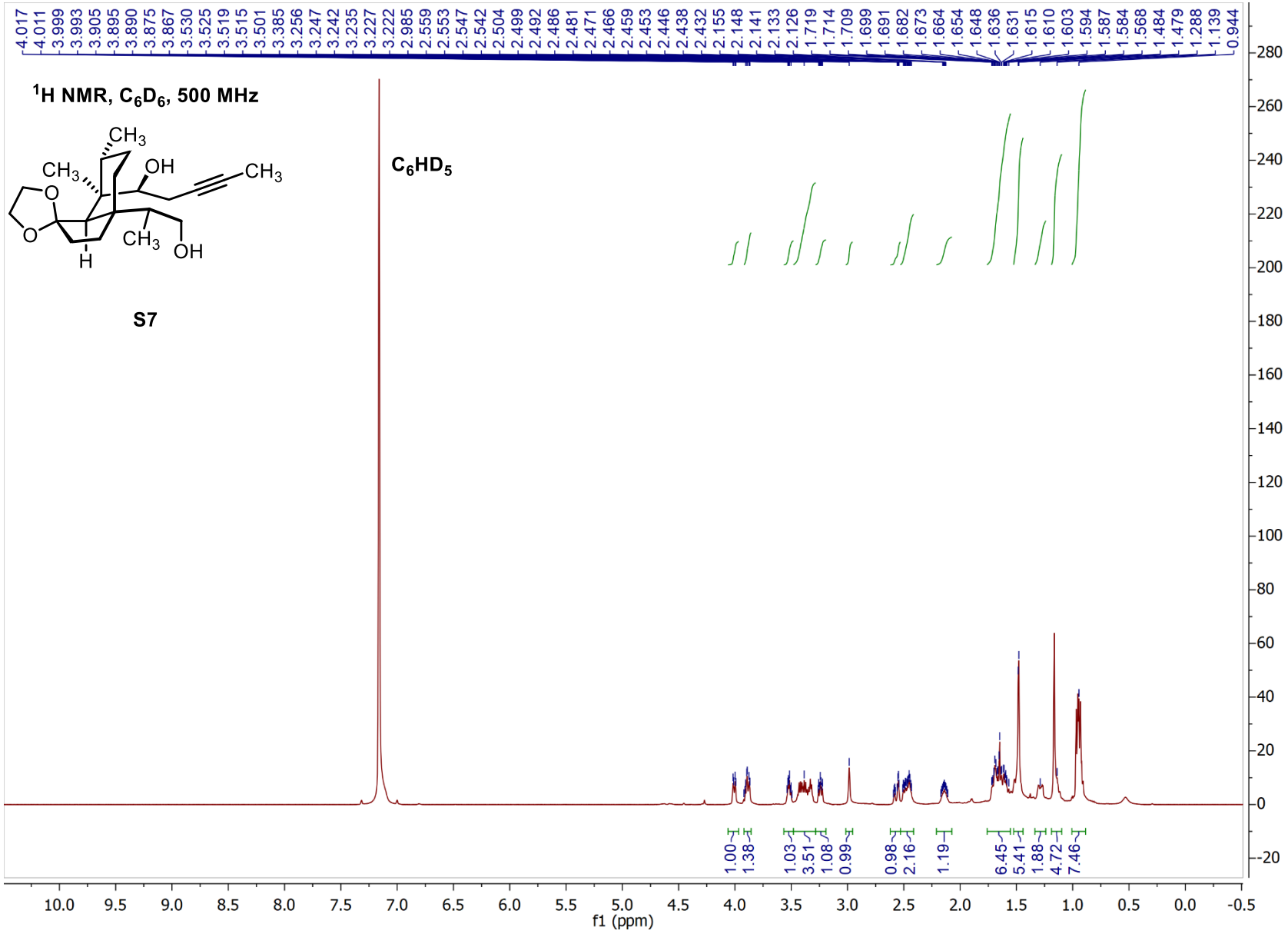

35, NOESY, CDCl3, 600 MHz
5.329
5.315
1.701
1.00
0.03
f1 (ppm)

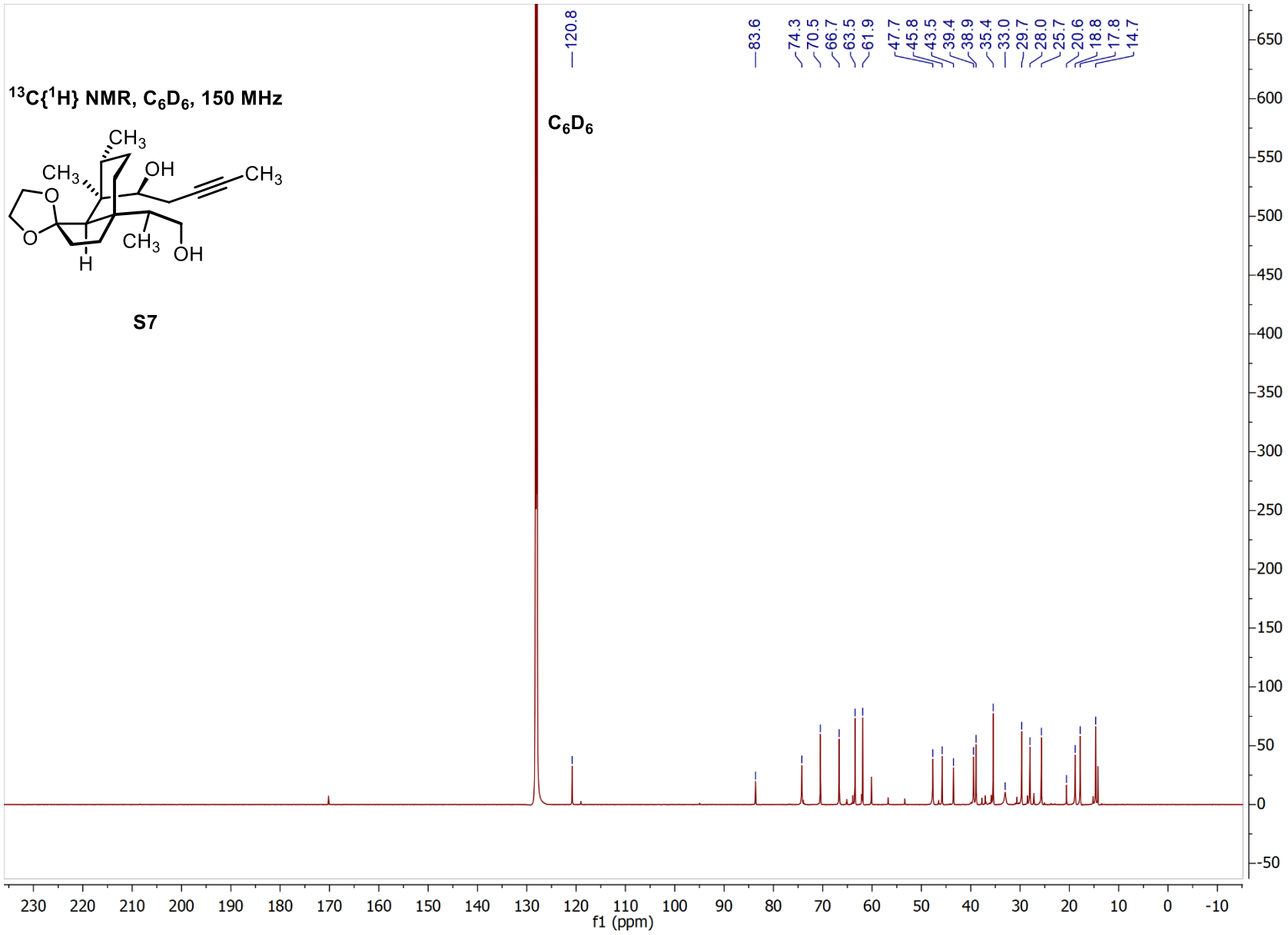

^{1}H NMR, $CDCl_3$, 500 MHz
$CHCl_3$
24
5.476
5.462
4.139
4.128
4.105
4.094
4.072
4.062
4.038
4.028
3.402
2.276
2.045
2.039
1.729
1.402
1.168
1.159
1.140
1.131
1.112
1.018
1.004
0.913
0.898
0.883
0.739
0.725
1.00
2.01
0.99
4.22
1.06
6.14
7.89
1.20
3.03
4.07
3.04
f1 (ppm)

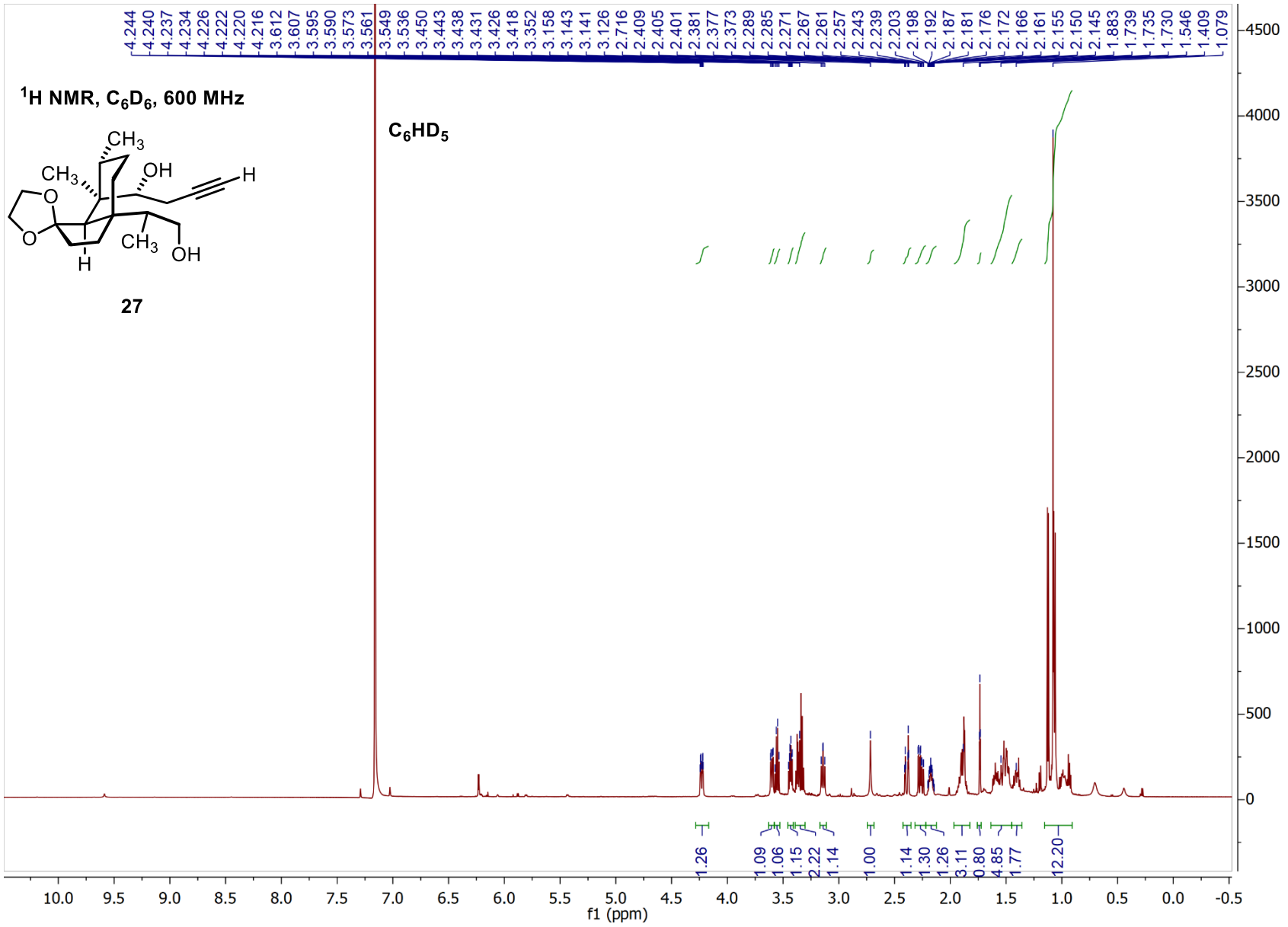

217.1
173.0
74.5
71.8
61.4
58.3
47.5
45.7
41.8
41.0
36.8
36.6
34.5
30.7
27.2
25.9
25.6
17.4
15.1
11.4
10.3
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
24
f1 (ppm)

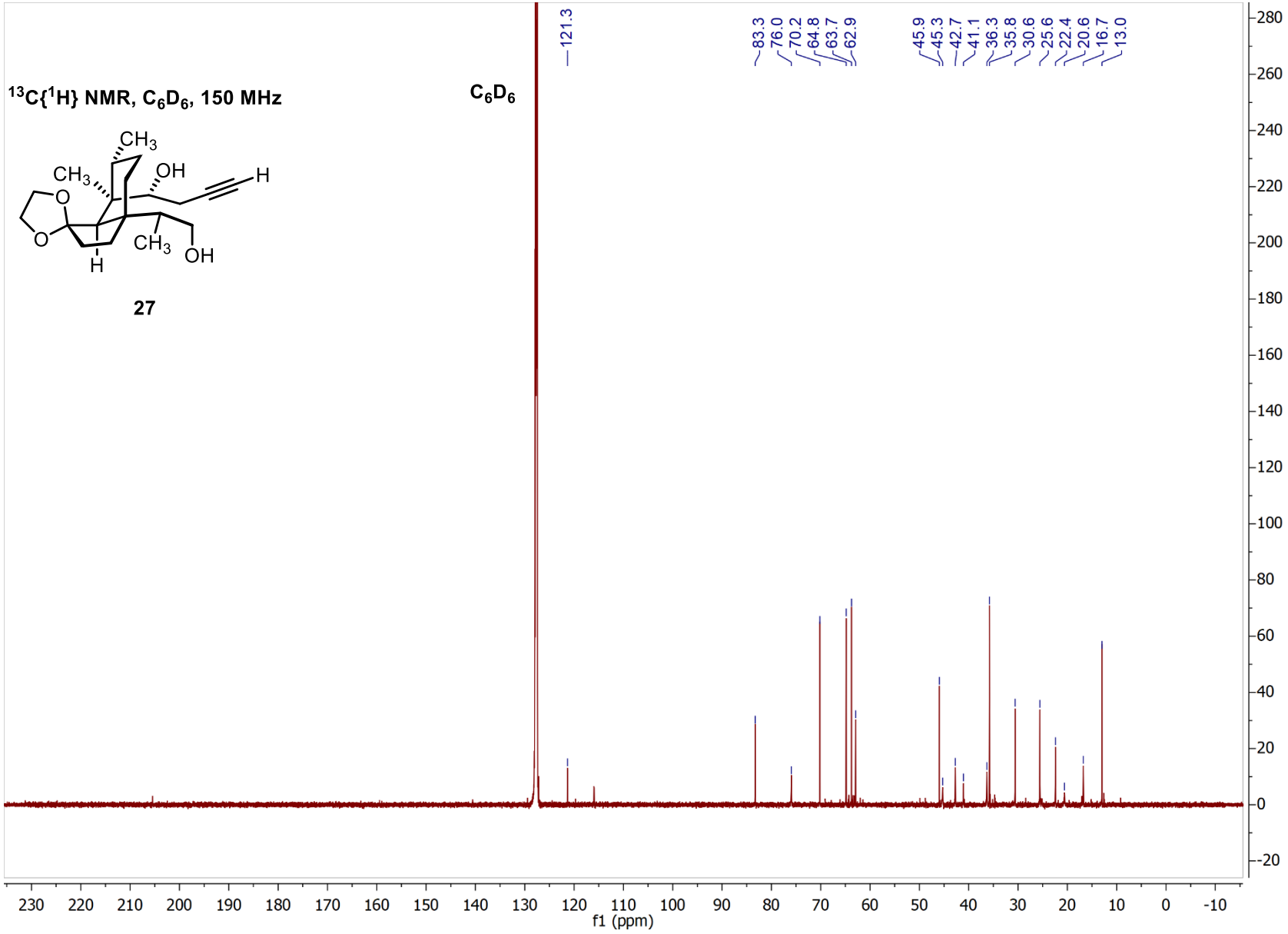

^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
26
4.318
3.421
3.410
3.404
3.399
3.394
3.383
2.199
2.003
1.775
1.565
1.389
1.164
1.157
1.140
1.133
1.117
1.110
0.974
0.952
0.950
0.939
0.938
0.927
0.925
1.15
1.00
3.35
1.07
3.26
6.99
5.52
1.34
6.11
3.12
f1 (ppm)

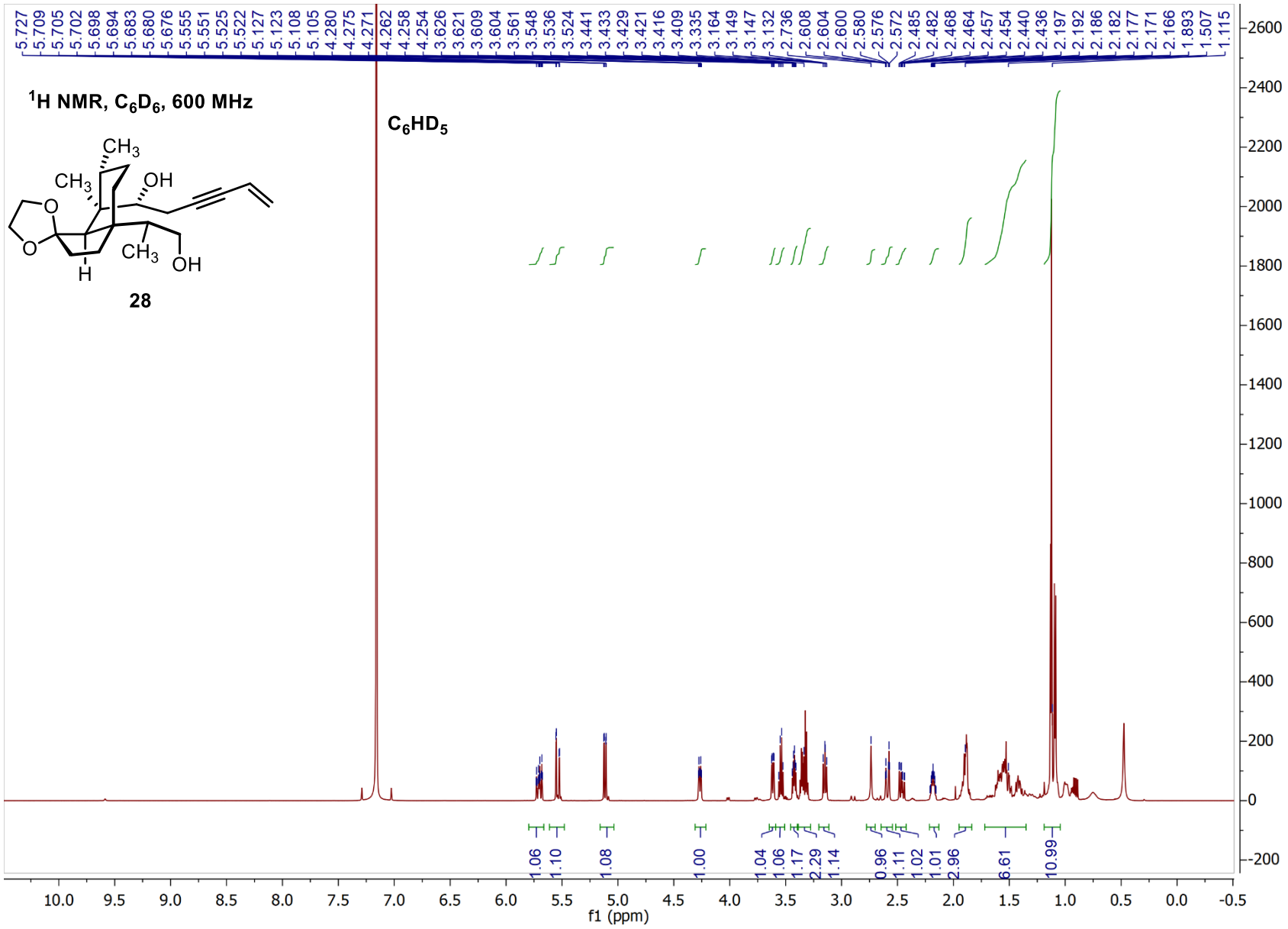

217.9
72.0
70.5
59.1
48.2
45.7
42.9
40.8
39.1
37.1
34.6
30.8
27.3
26.2
25.6
18.4
13.6
11.2
10.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
CH3
OH
H
CH3
CH3
O
OH
CH3
H
26
f1 (ppm)

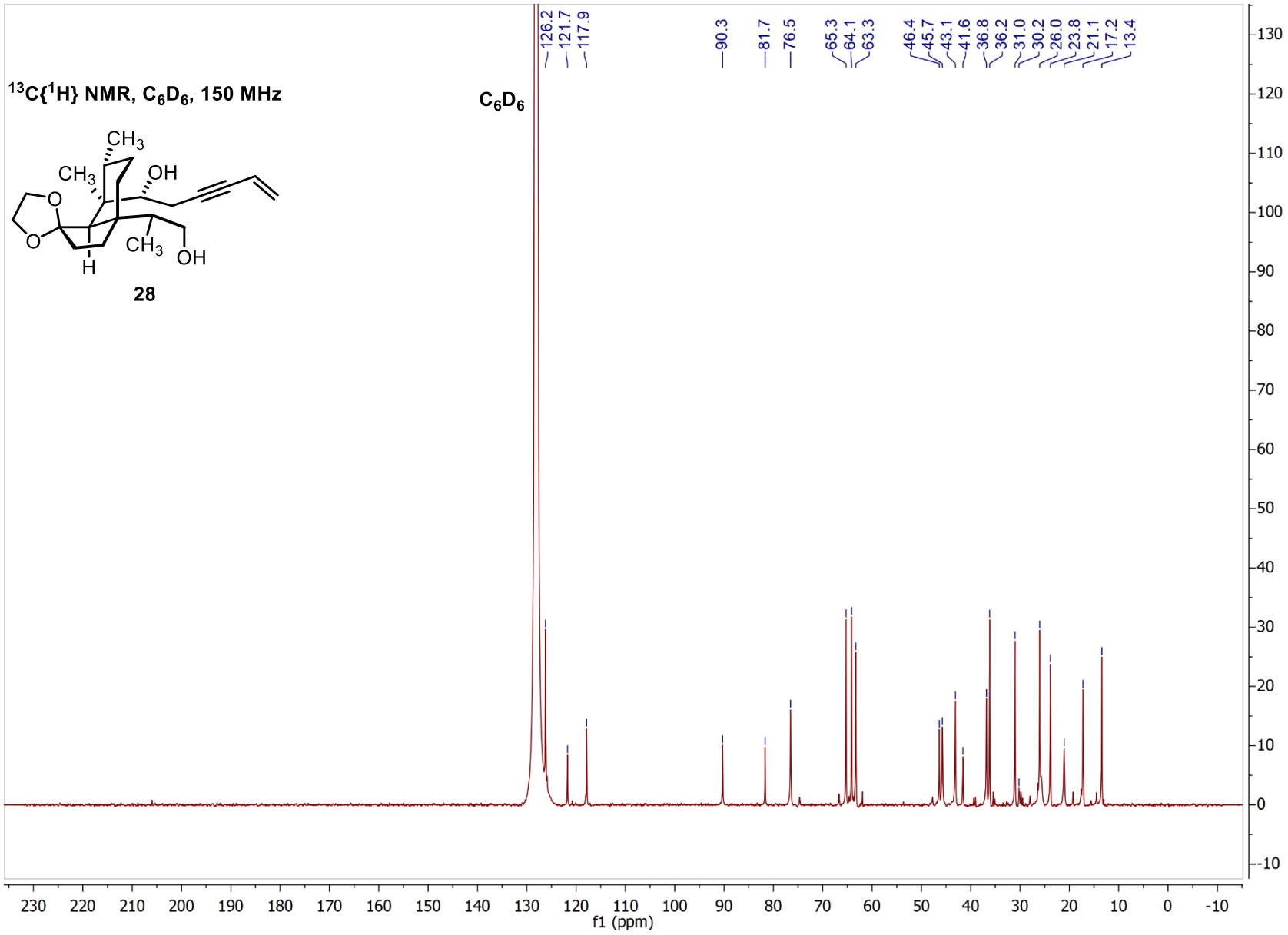

4.017 4.011 3.999 3.993 3.905 3.895 3.890 3.875 3.867 3.530 3.525 3.519 3.515 3.501 3.385 3.256 3.247 3.242 3.235 3.227 3.222 2.985 2.559 2.553 2.547 2.542 2.504 2.499 2.492 2.486 2.481 2.471 2.466 2.459 2.453 2.446 2.438 2.432 2.155 2.148 2.141 2.133 2.126 1.719 1.714 1.709 1.699 1.691 1.682 1.673 1.664 1.654 1.648 1.636 1.631 1.615 1.610 1.603 1.594 1.587 1.584 1.568 1.484 1.479 1.288 1.139 0.944
^{1}H NMR, C_6D_6, 500 MHz
CH3
CH3
OH
CH3
O
O
CH3
OH
H
S7
C6HD5
1.00 1.38 1.03 3.51 1.08 0.99 0.98 2.16 1.19 6.45 5.41 1.88 4.72 7.46
f1 (ppm)


13C{1H} NMR, C6D6, 150 MHz
S7
C6D6
120.8
83.6
74.3
70.5
66.7
63.5
61.9
47.7
45.8
43.5
39.4
38.9
35.4
33.0
29.7
28.0
25.7
20.6
18.8
17.8
14.7
f1 (ppm)

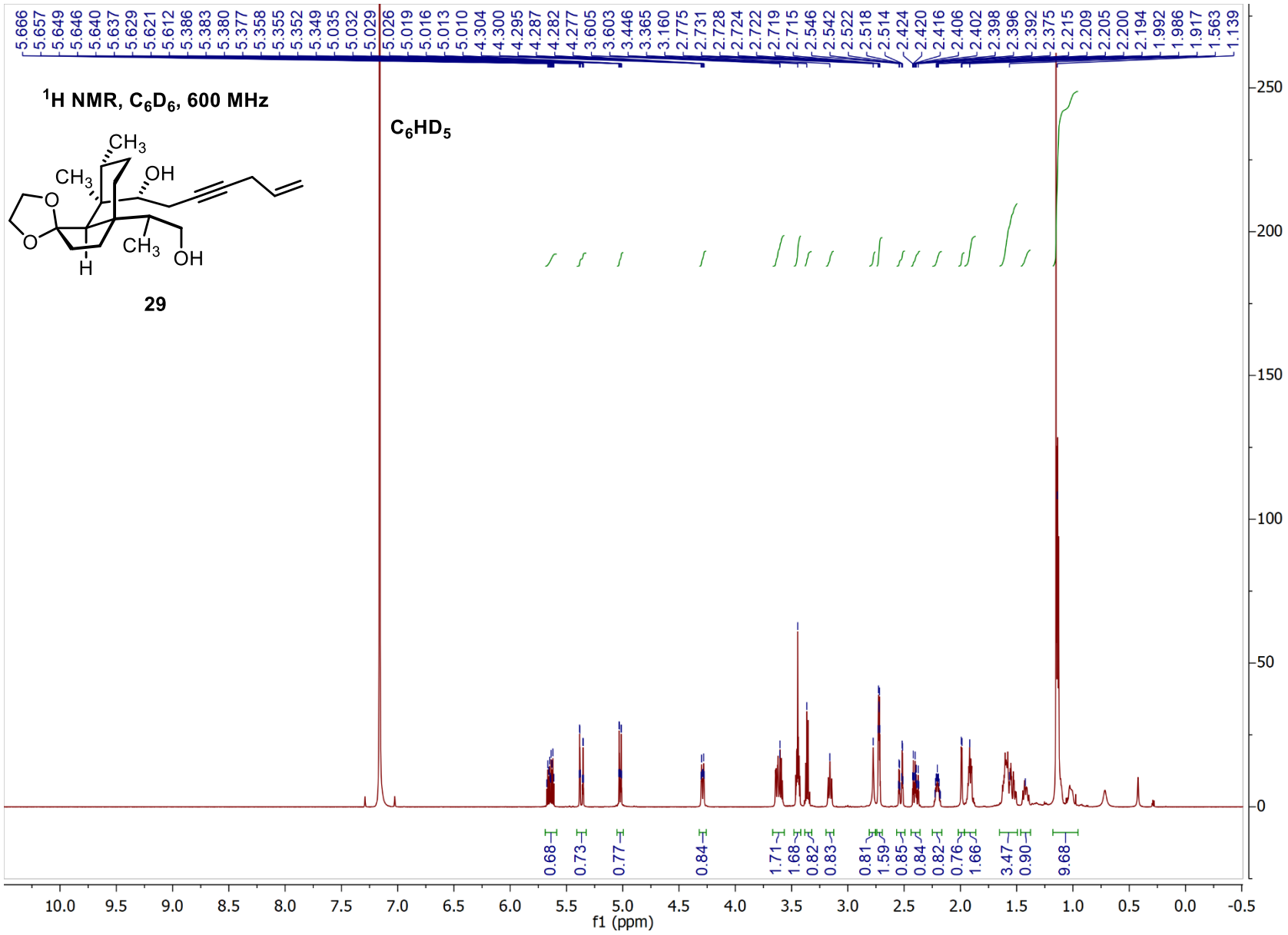

4.244 4.240 4.237 4.234 4.226 4.222 4.220 4.216 3.612 3.607 3.595 3.590 3.573 3.561 3.549 3.536 3.450 3.443 3.438 3.431 3.426 3.418 3.352 3.158 3.143 3.141 3.126 2.716 2.409 2.405 2.401 2.381 2.377 2.373 2.289 2.285 2.271 2.267 2.261 2.257 2.243 2.239 2.203 2.198 2.192 2.187 2.181 2.176 2.172 2.166 2.161 2.155 2.150 2.145 1.883 1.739 1.735 1.730 1.546 1.409 1.079
1H NMR, C6D6, 600 MHz
C6HD5
CH3
CH3
OH
H
O
O
CH3
OH
H
27
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.26
1.09
1.06
1.15
2.22
1.14
1.00
1.14
1.30
1.26
3.11
0.80
4.85
1.77
12.20
10.0 9.5 9.0 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 1.0 0.5 0.0 -0.5
f1 (ppm)

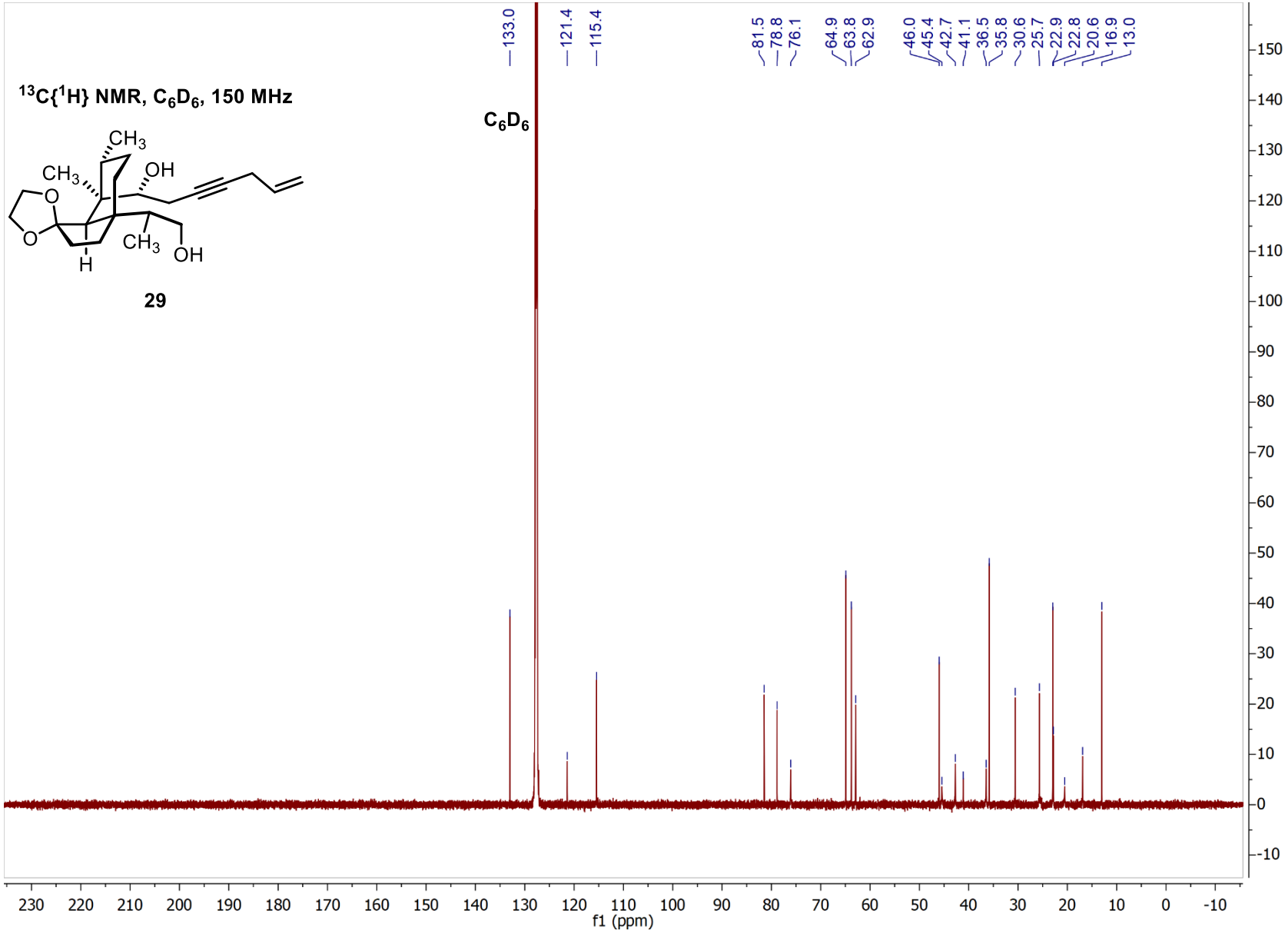

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
27
121.3
83.3
76.0
70.2
64.8
63.7
62.9
45.9
45.3
42.7
41.1
36.3
35.8
30.6
25.6
22.4
20.6
16.7
13.0
f1 (ppm)

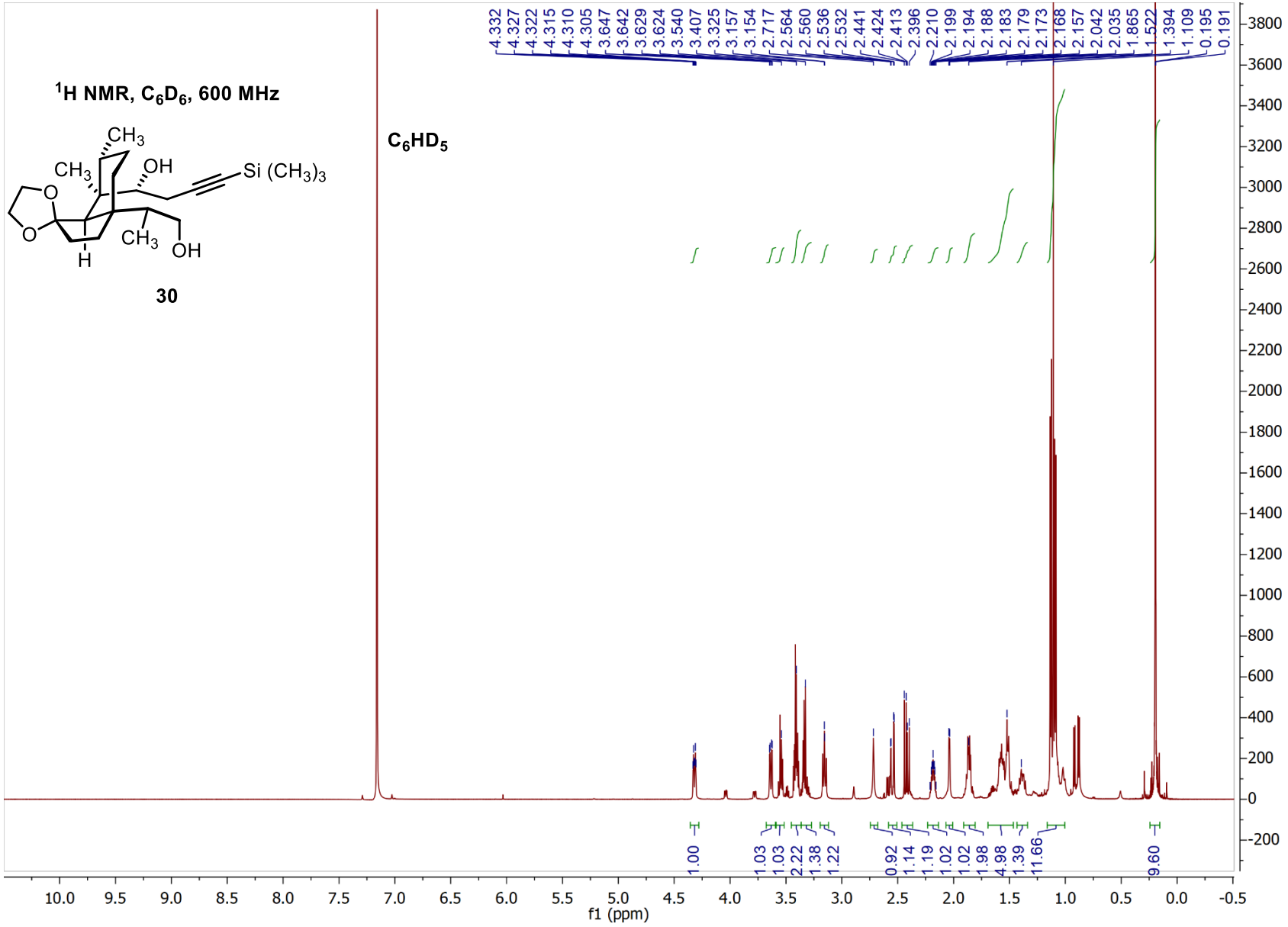

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
28
f1 (ppm)

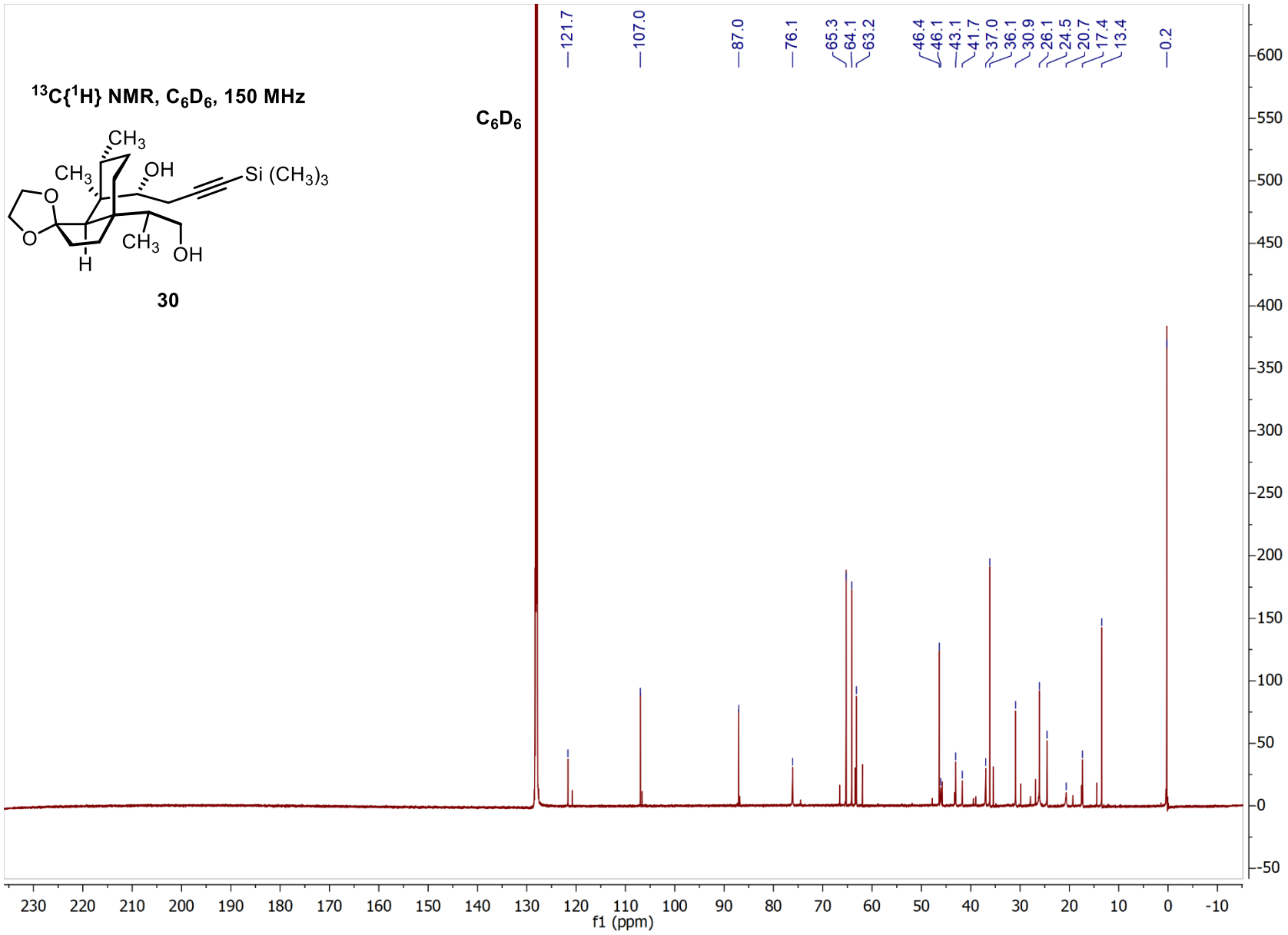

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
126.2
121.7
117.9
90.3
81.7
76.5
65.3
64.1
63.3
46.4
45.7
43.1
41.6
36.8
36.2
31.0
30.2
26.0
23.8
21.1
17.2
13.4
f1 (ppm)

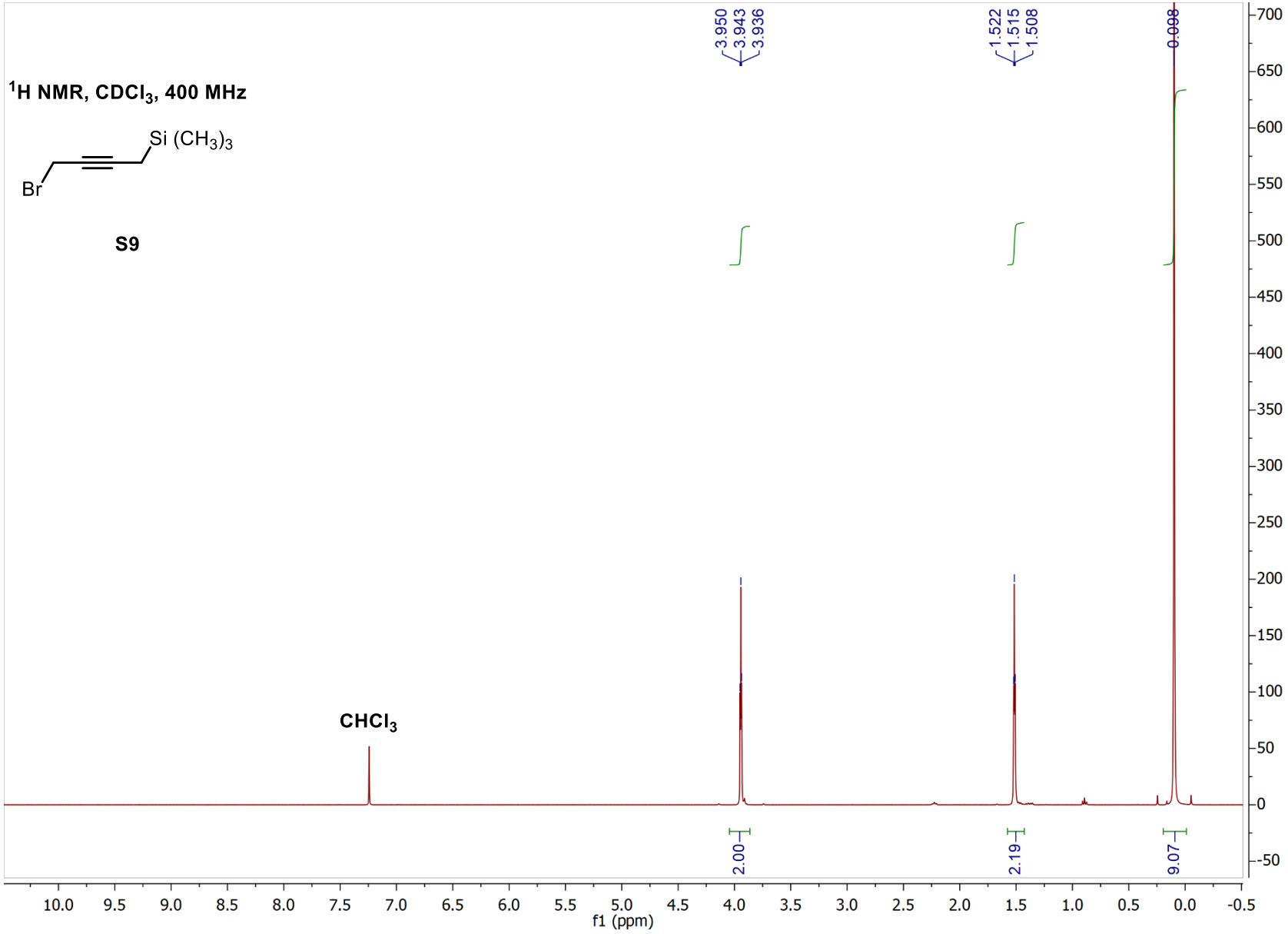
28

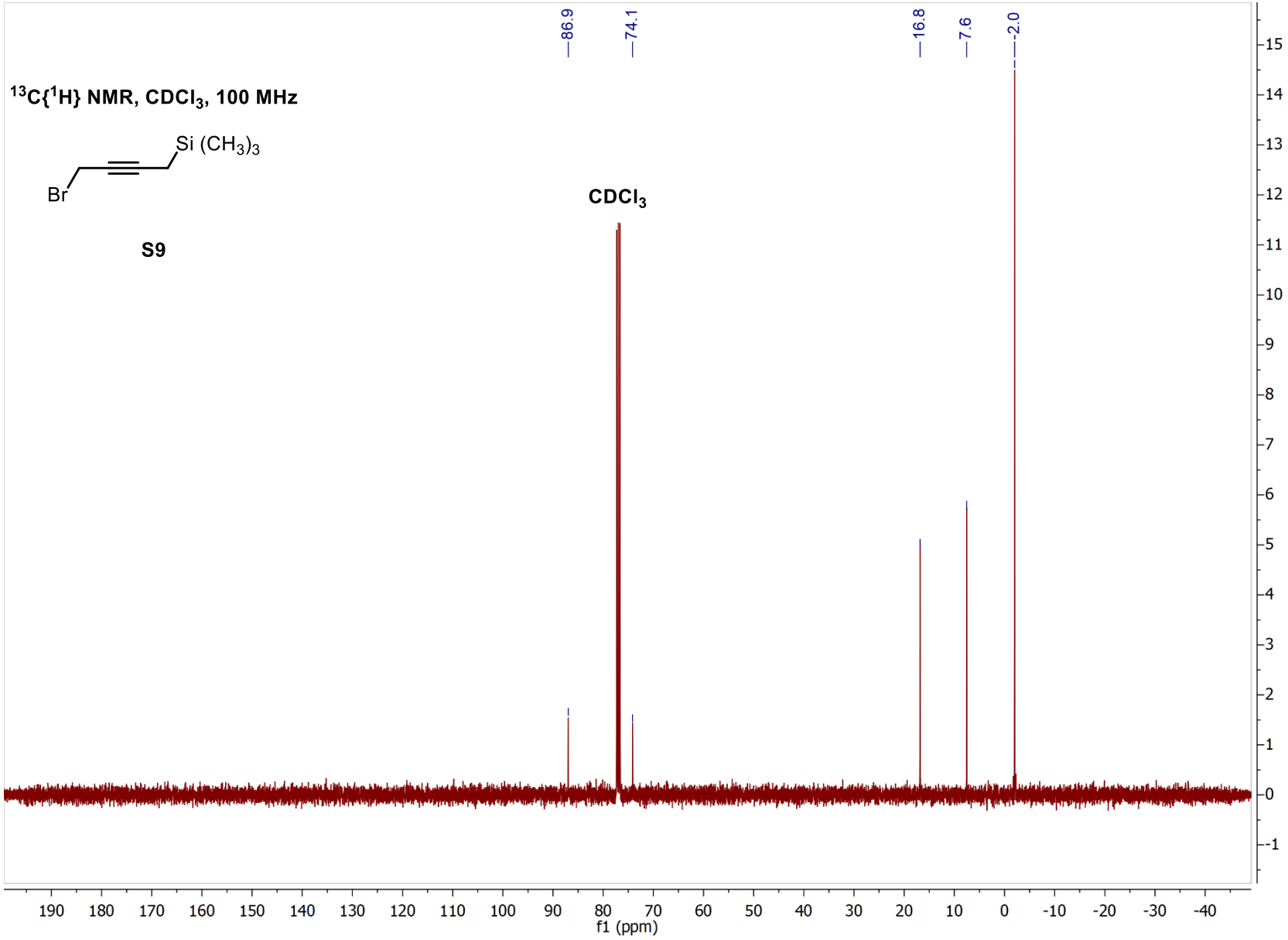

5.666 5.657 5.649 5.646 5.640 5.637 5.629 5.621 5.612 5.386 5.383 5.380 5.377 5.358 5.355 5.352 5.349 5.035 5.032 5.029 5.026 5.019 5.016 5.013 5.010 4.304 4.300 4.295 4.287 4.282 4.277 3.605 3.603 3.446 3.365 3.160 2.775 2.731 2.728 2.724 2.722 2.719 2.715 2.546 2.542 2.522 2.518 2.514 2.424 2.420 2.416 2.406 2.402 2.398 2.396 2.392 2.375 2.215 2.209 2.205 2.200 2.194 1.992 1.986 1.917 1.563 1.139
^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
CH3
CH3
OH
O
O
CH3
OH
H
29
0.68 0.73 0.77 0.84 1.71 1.68 0.82 0.83 0.81 1.59 0.85 0.84 0.82 0.76 1.66 3.47 0.90 9.68
250
200
150
100
50
0
10.0 9.5 9.0 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 1.0 0.5 0.0 -0.5
f1 (ppm)

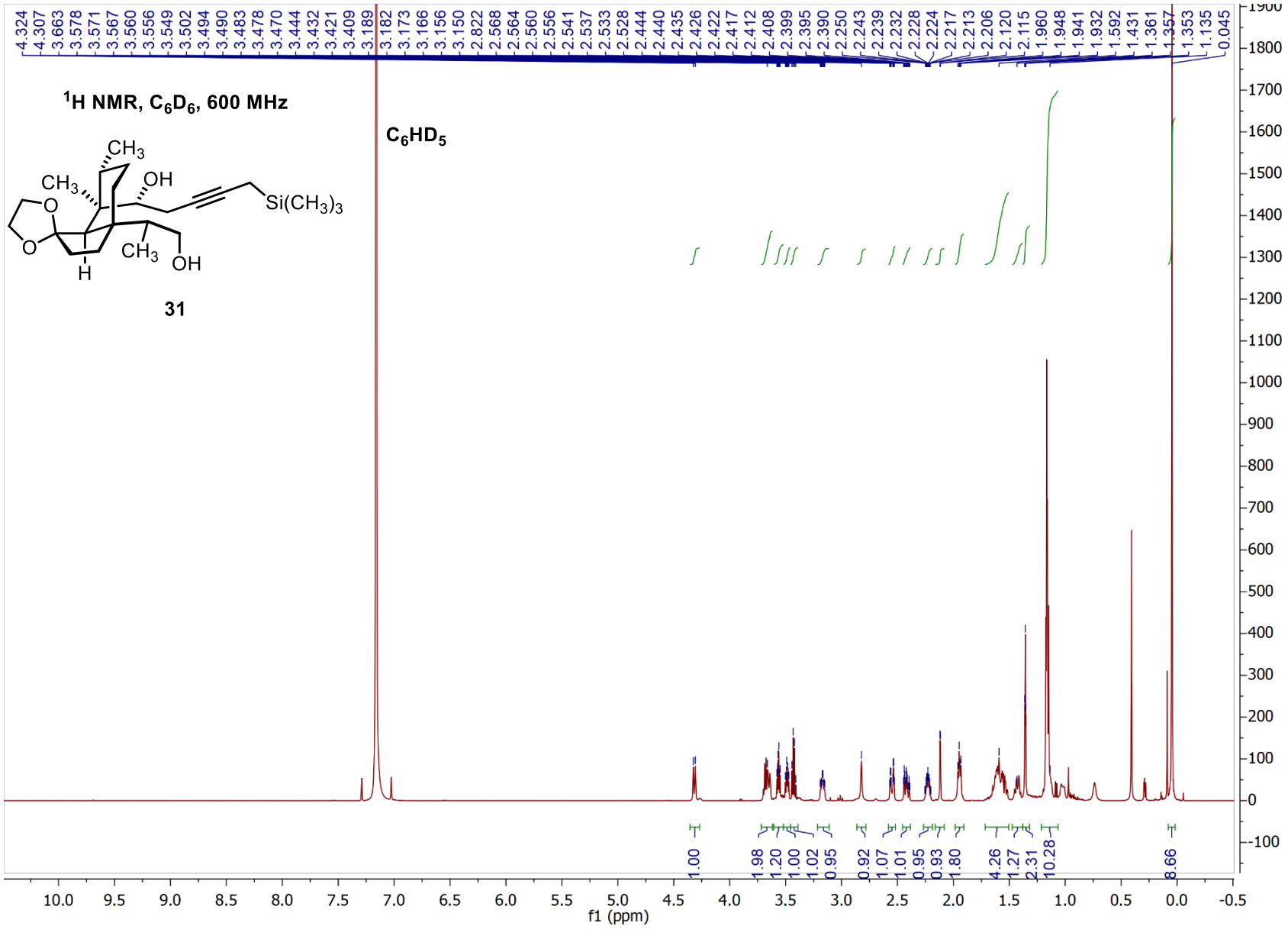

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
133.0
121.4
115.4
81.5
78.8
76.1
64.9
63.8
62.9
46.0
45.4
42.7
41.1
36.5
35.8
30.6
25.7
22.9
22.8
20.6
16.9
13.0
CH3
CH3
OH
O
O
CH3
OH
H
29
f1 (ppm)

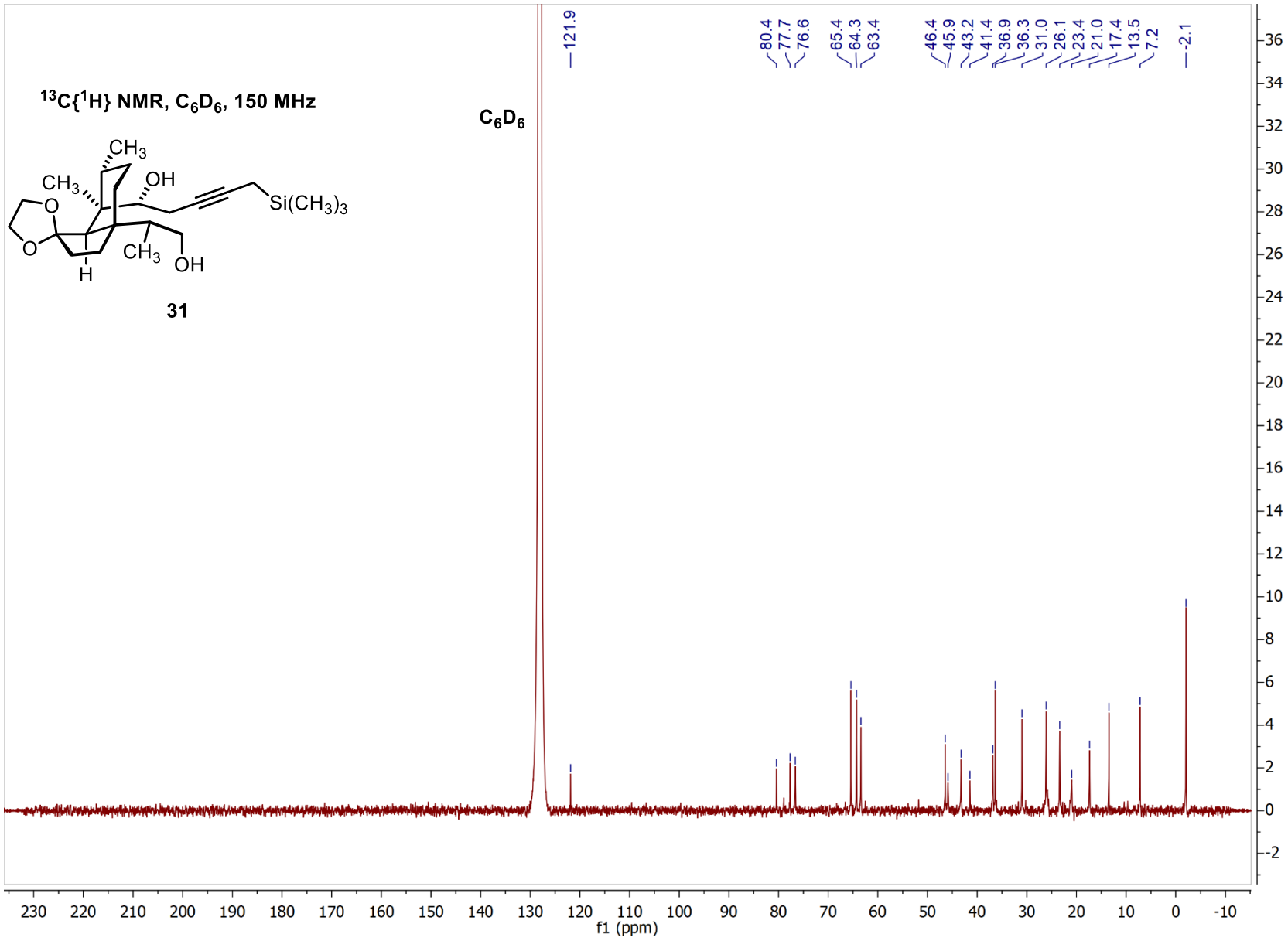

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
30
f1 (ppm)

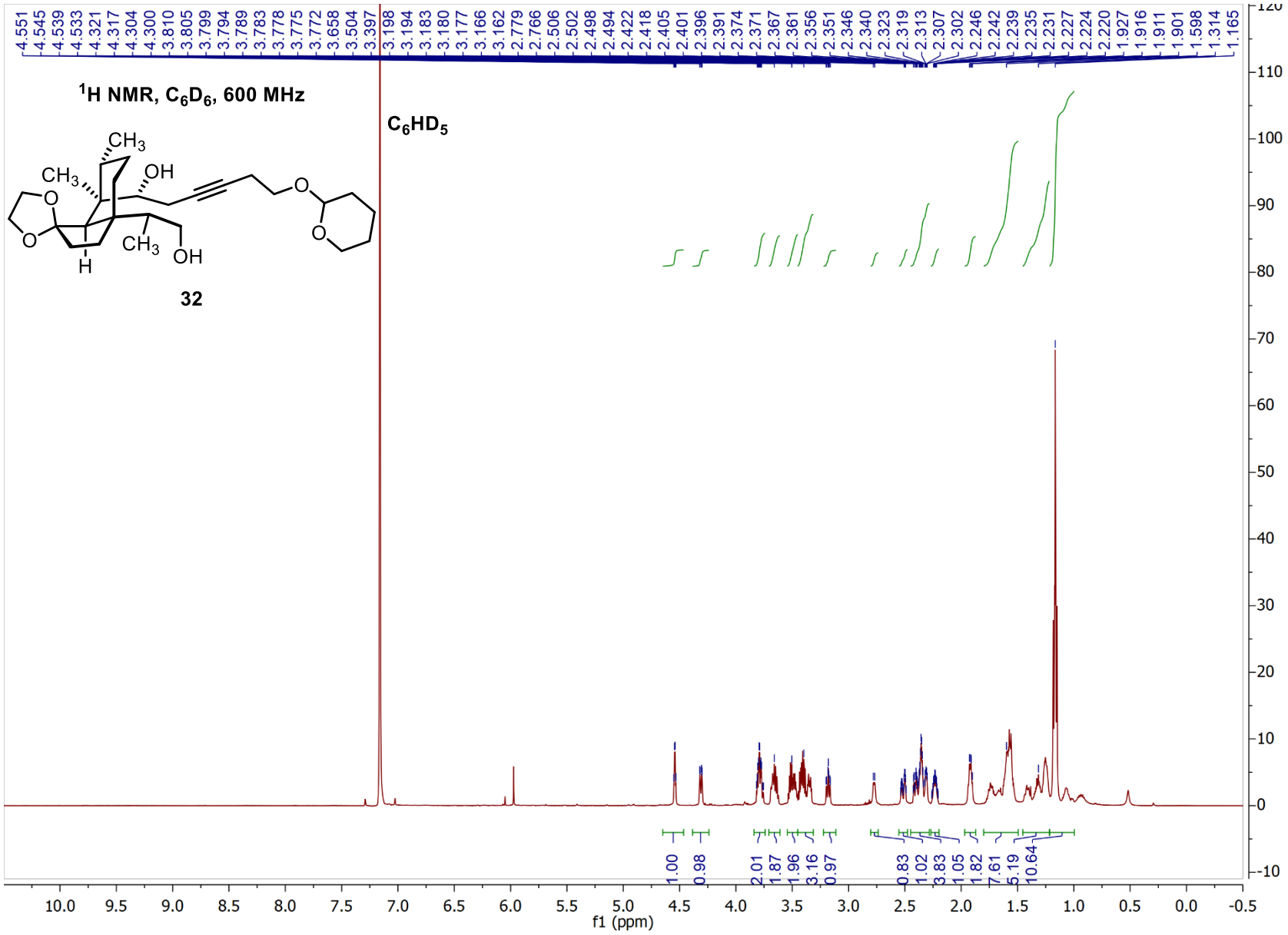

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
121.7
107.0
87.0
76.1
65.3
64.1
63.2
46.4
46.1
43.1
41.7
37.0
36.1
30.9
26.1
24.5
20.7
17.4
13.4
0.2
CH3
CH3
OH
Si (CH3)3
O
O
CH3
OH
H
30
f1 (ppm)

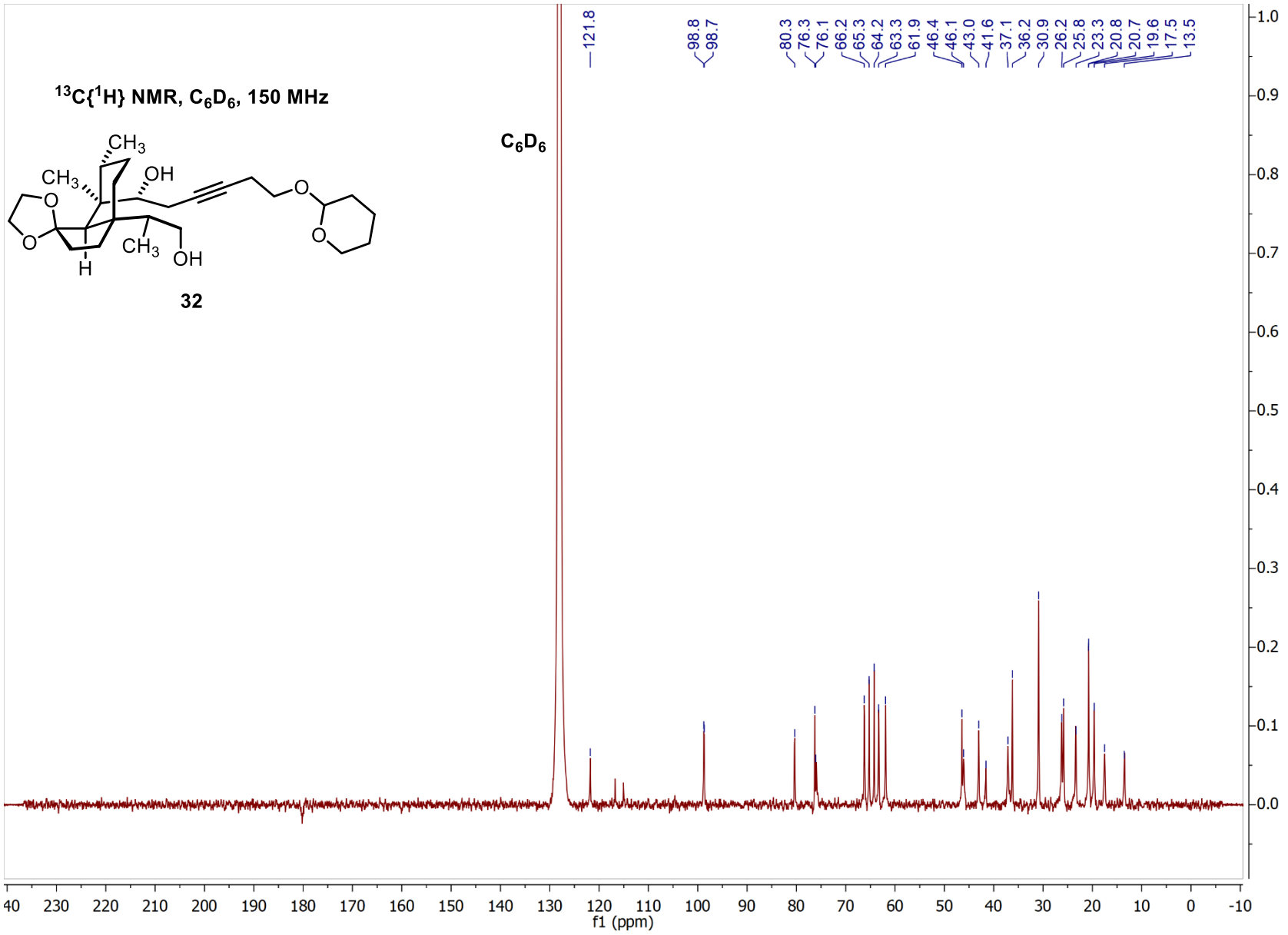

1H NMR, CDCl3, 400 MHz
Si (CH3)3
Br
S9
CHCl3
3.950
3.943
3.936
1.522
1.515
1.508
0.008
2.00
2.19
9.07
f1 (ppm)

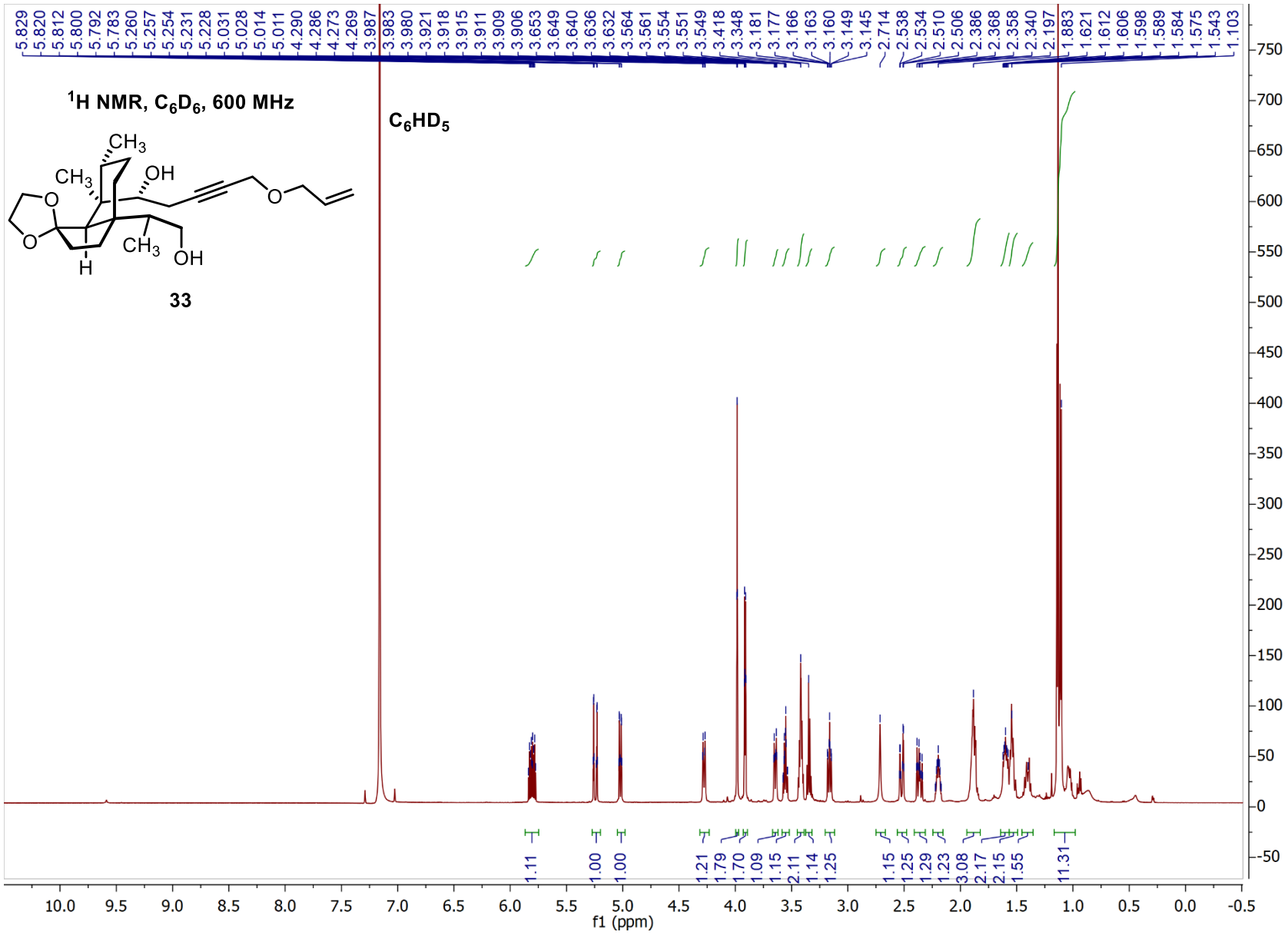

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100 MHz
Si $(CH_3)_3$
Br
S9
$CDCl_3$
86.9
74.1
16.8
7.6
-2.0
f1 (ppm)

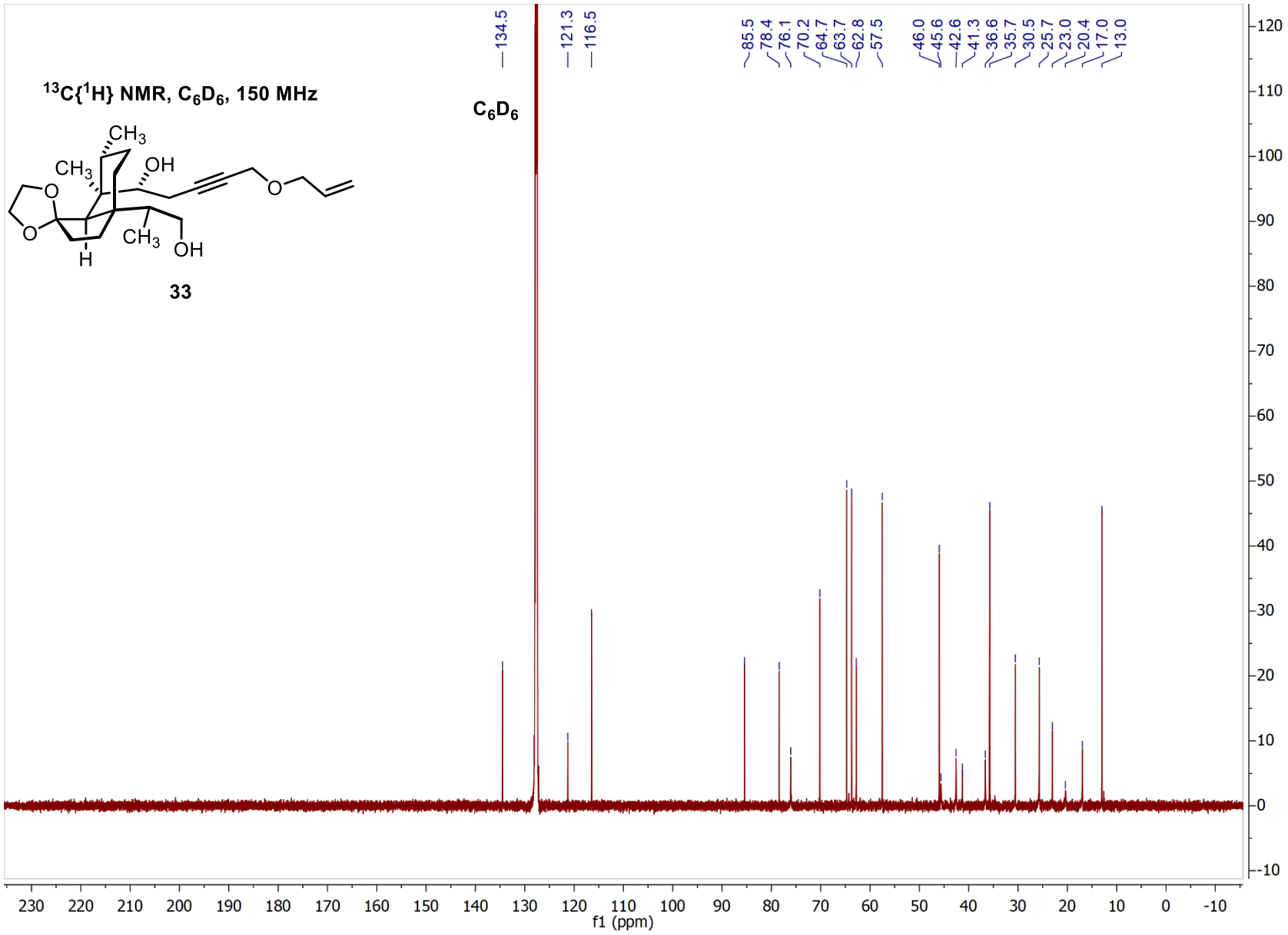

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
31
f1 (ppm)

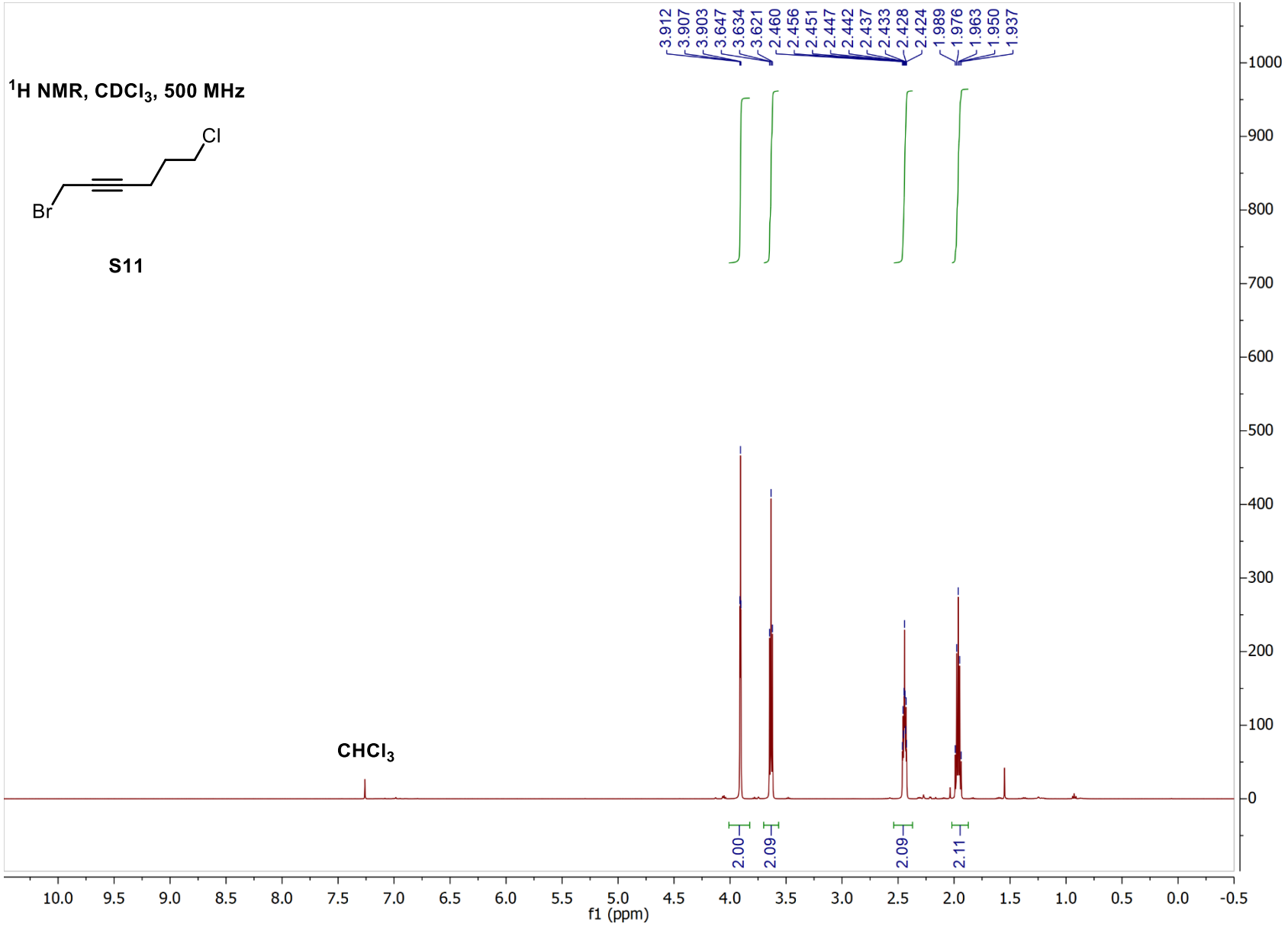

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
121.9
80.4
77.7
76.6
65.4
64.3
63.4
46.4
45.9
43.2
41.4
36.9
36.3
31.0
26.1
23.4
21.0
17.4
13.5
7.2
-2.1
CH3
CH3
OH
Si(CH3)3
O
O
CH3
OH
H
31
f1 (ppm)

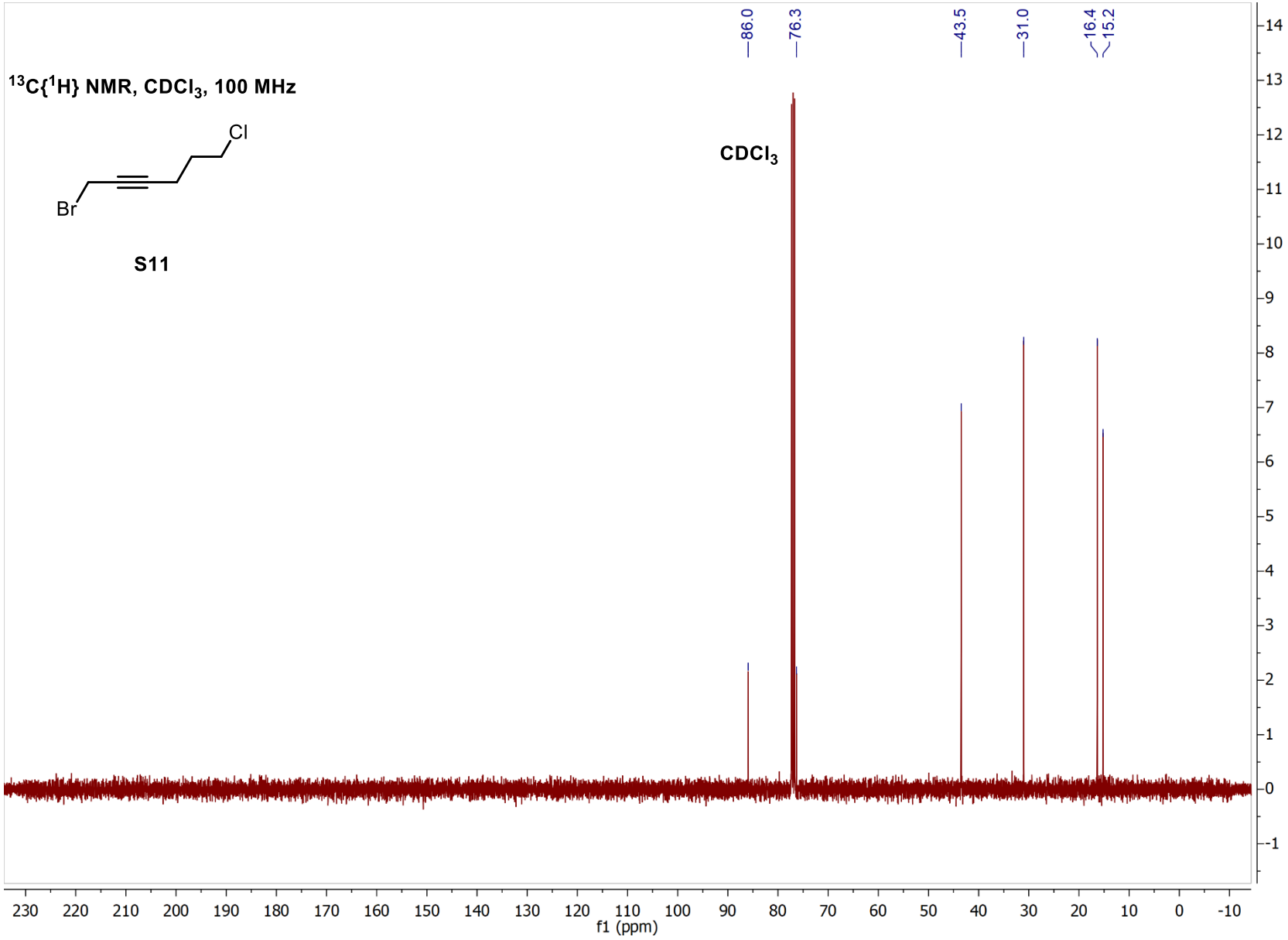

4.551 4.545 4.539 4.533 4.321 4.317 4.304 4.300 3.810 3.805 3.799 3.794 3.789 3.783 3.778 3.775 3.772 3.658 3.504 3.397 3.198 3.194 3.183 3.180 3.177 3.166 3.162 2.779 2.766 2.506 2.502 2.498 2.494 2.422 2.418 2.405 2.401 2.396 2.391 2.374 2.371 2.367 2.361 2.356 2.351 2.346 2.340 2.323 2.319 2.313 2.307 2.302 2.246 2.242 2.239 2.235 2.231 2.227 2.224 2.220 1.927 1.916 1.911 1.901 1.598 1.314 1.165
^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
CH3
CH3
OH
O
O
O
O
CH3
OH
H
32
1.00 0.98 2.01 1.87 1.96 3.16 0.97 0.83 1.02 3.83 1.05 1.82 7.61 5.19 10.64
f1 (ppm)

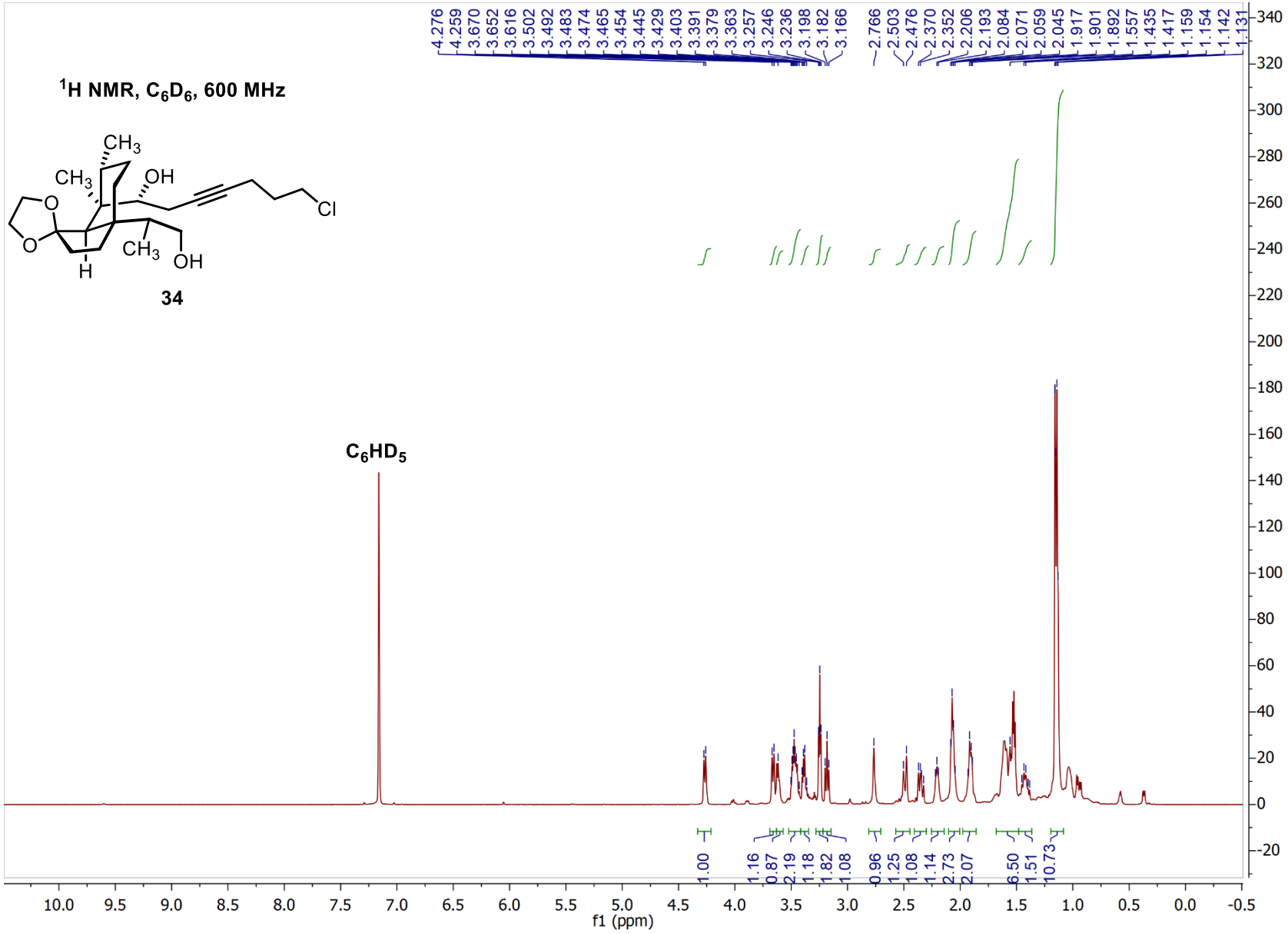

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
32
121.8
98.8
98.7
80.3
76.3
76.1
66.2
65.3
64.2
63.3
61.9
46.4
46.1
43.0
41.6
37.1
36.2
30.9
26.2
25.8
23.3
20.8
20.7
19.6
17.5
13.5
f1 (ppm)

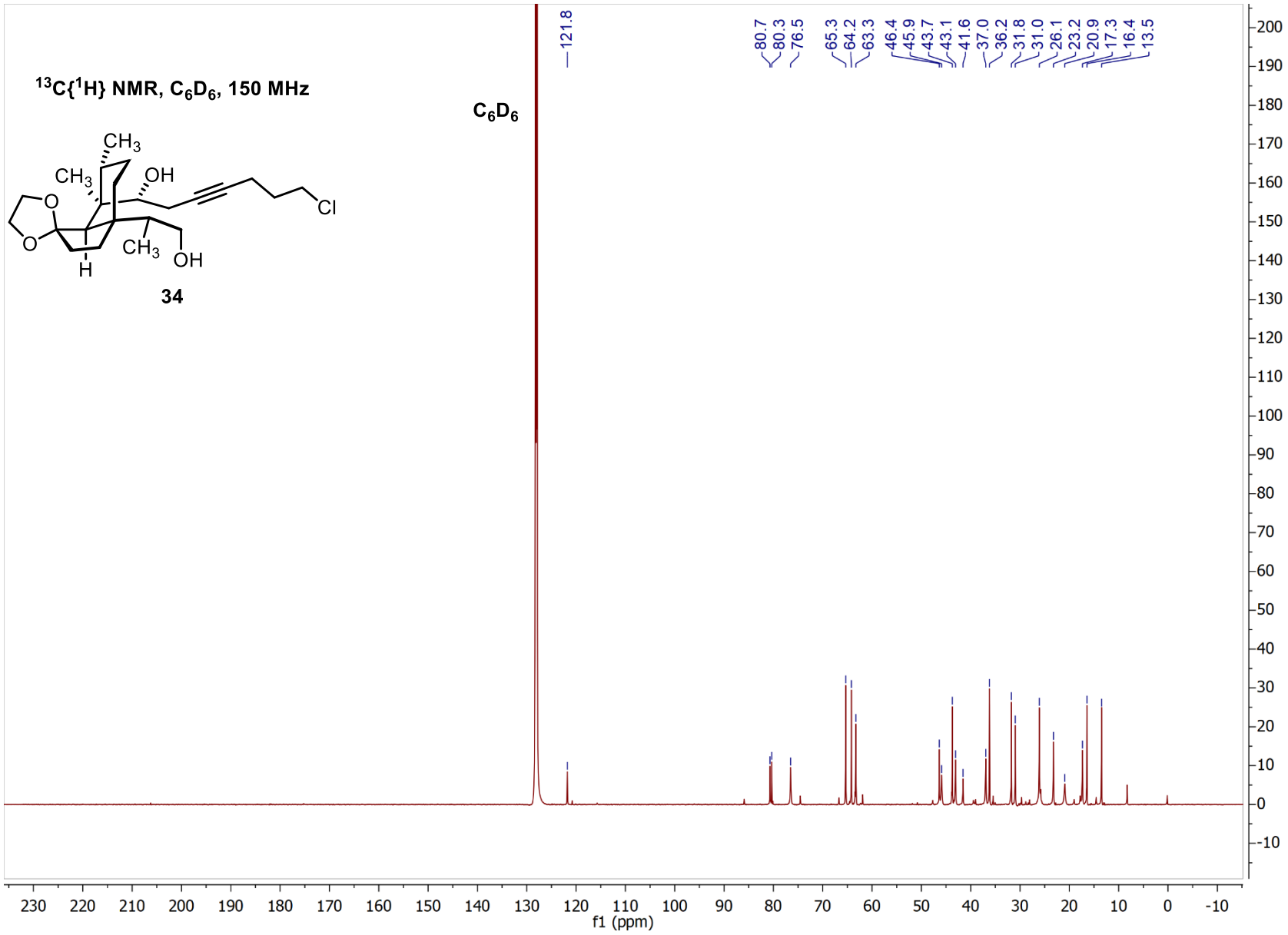

5.829 5.820 5.812 5.800 5.792 5.783 5.260 5.257 5.254 5.231 5.228 5.031 5.028 5.014 5.011 4.290 4.286 4.273 4.269 3.987 3.983 3.980 3.921 3.918 3.915 3.911 3.909 3.906 3.653 3.649 3.640 3.636 3.632 3.564 3.561 3.554 3.551 3.549 3.418 3.348 3.181 3.177 3.166 3.163 3.160 3.149 3.145 2.714 2.538 2.534 2.510 2.506 2.386 2.368 2.358 2.340 2.197 1.883 1.621 1.612 1.606 1.598 1.589 1.584 1.575 1.543 1.103
^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
CH3
CH3
OH
O
O
O
CH3
OH
H
33
1.11 1.00 1.00 1.21 1.79 1.70 1.09 1.15 2.11 1.14 1.25 1.15 1.25 1.29 1.23 3.08 2.17 2.15 1.55 11.31
f1 (ppm)

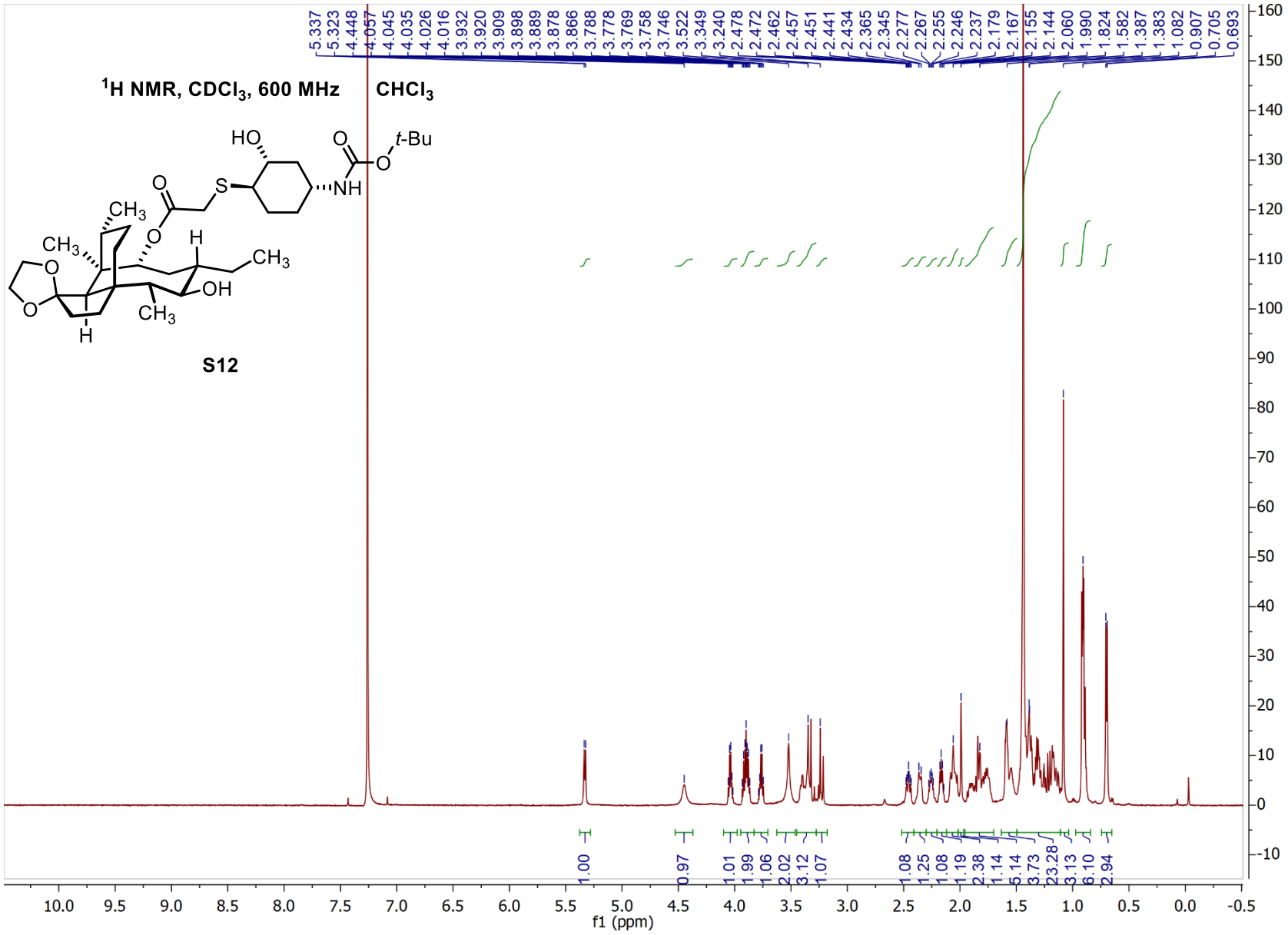

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
33
134.5
121.3
116.5
85.5
78.4
76.1
70.2
64.7
63.7
62.8
57.5
46.0
45.6
42.6
41.3
36.6
35.7
30.5
25.7
23.0
20.4
17.0
13.0
f1 (ppm)

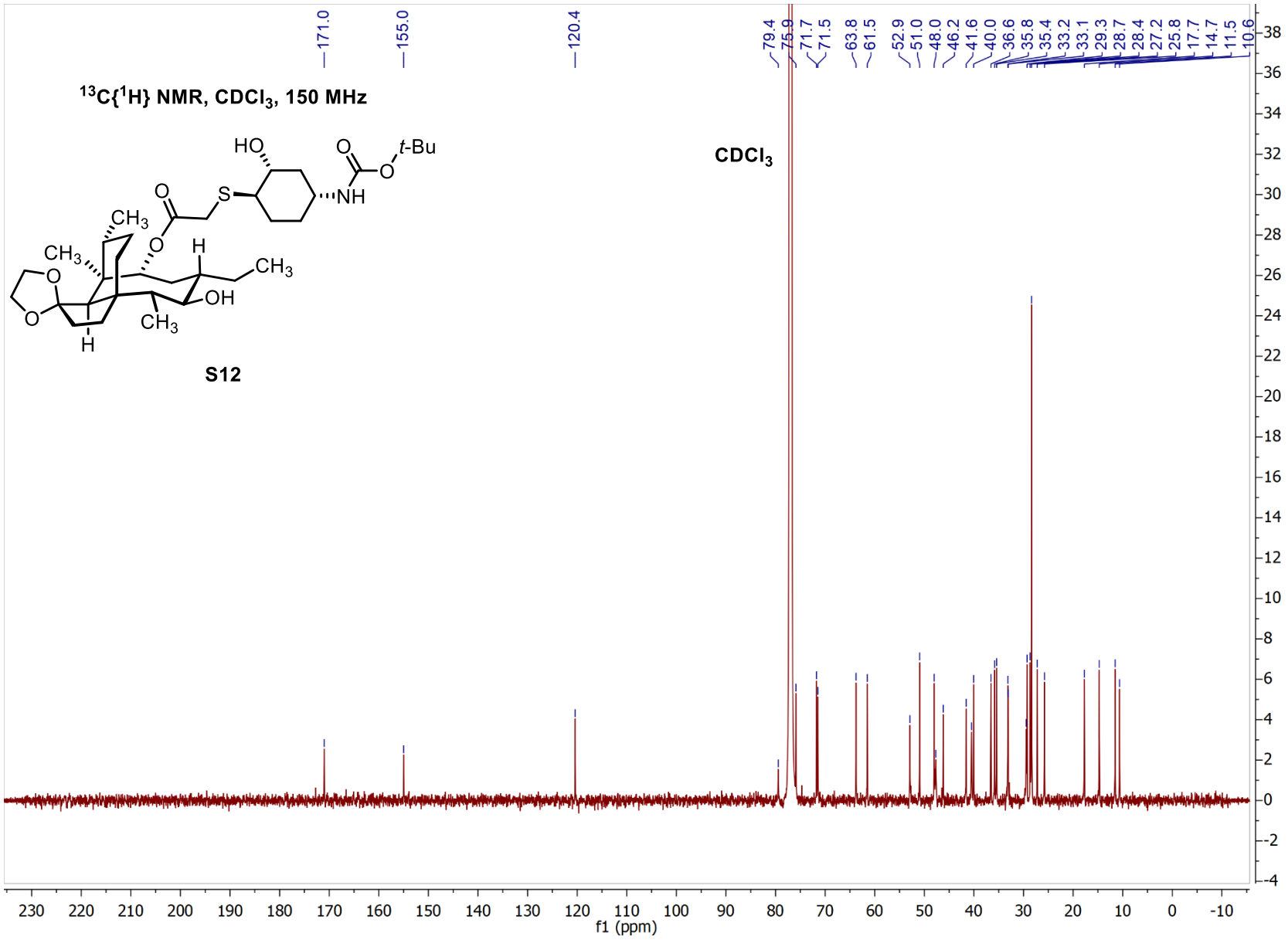

^{1}H NMR, $CDCl_3$, 500 MHz
Cl
Br
S11
3.912
3.907
3.903
3.647
3.634
3.621
2.460
2.456
2.451
2.447
2.442
2.437
2.433
2.428
2.424
1.989
1.976
1.963
1.950
1.937
$CHCl_3$
2.00
2.09
2.09
2.11
f1 (ppm)

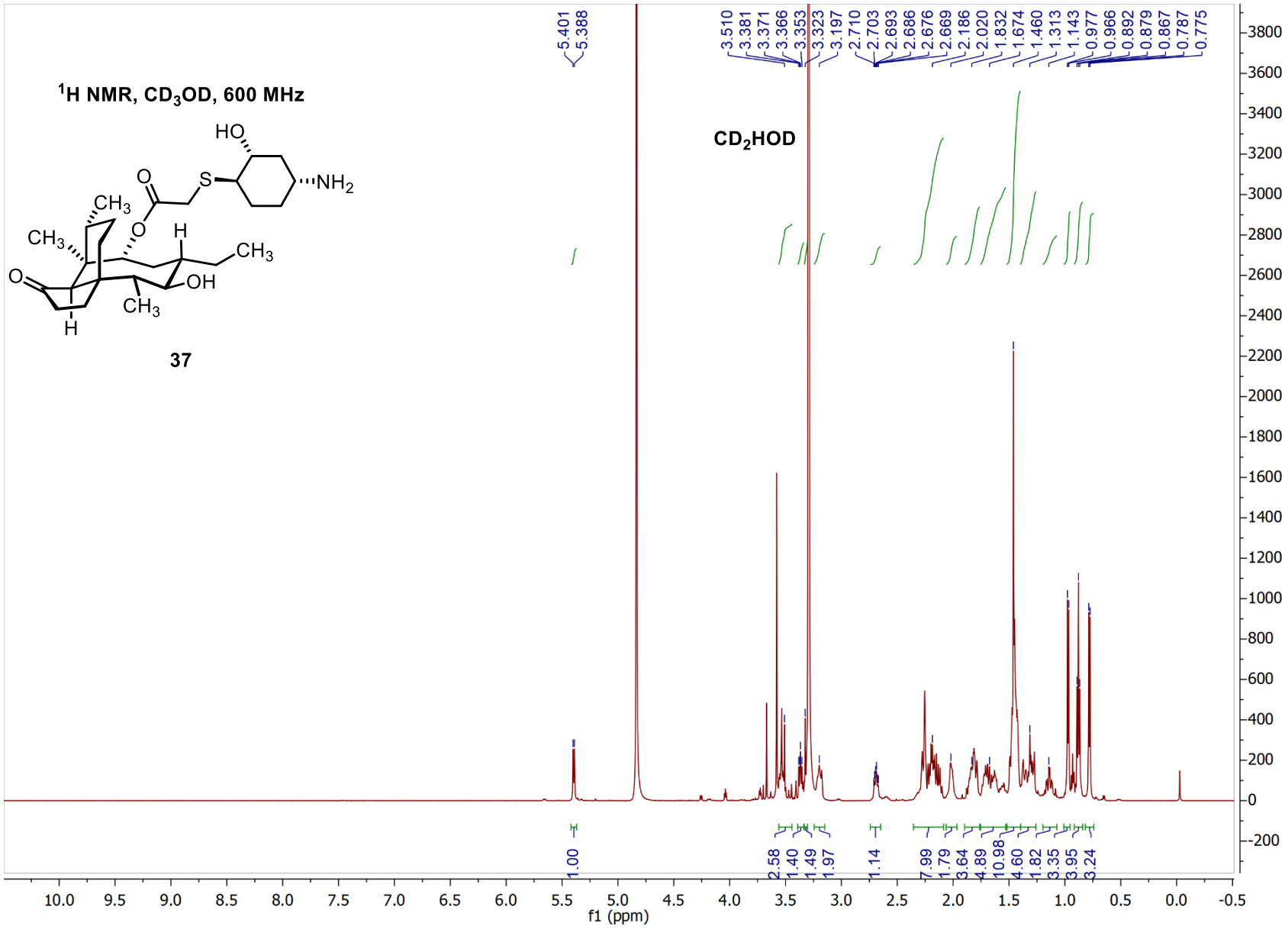

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100 MHz
Cl
Br
S11
$CDCl_3$
86.0
76.3
43.5
31.0
16.4
15.2
f1 (ppm)

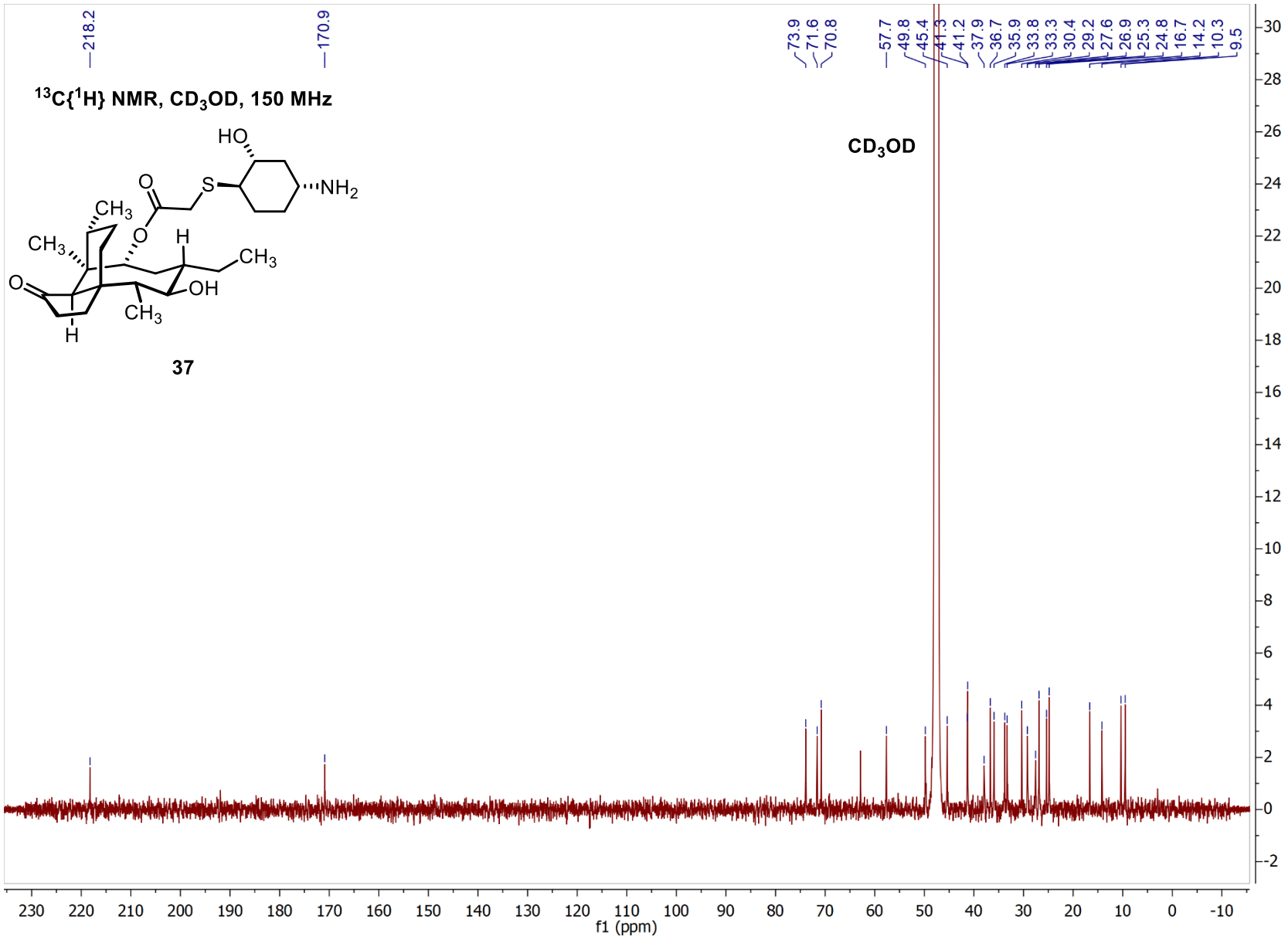

^{1}H NMR, C_6D_6, 600 MHz
34
C_6HD_5
f1 (ppm)

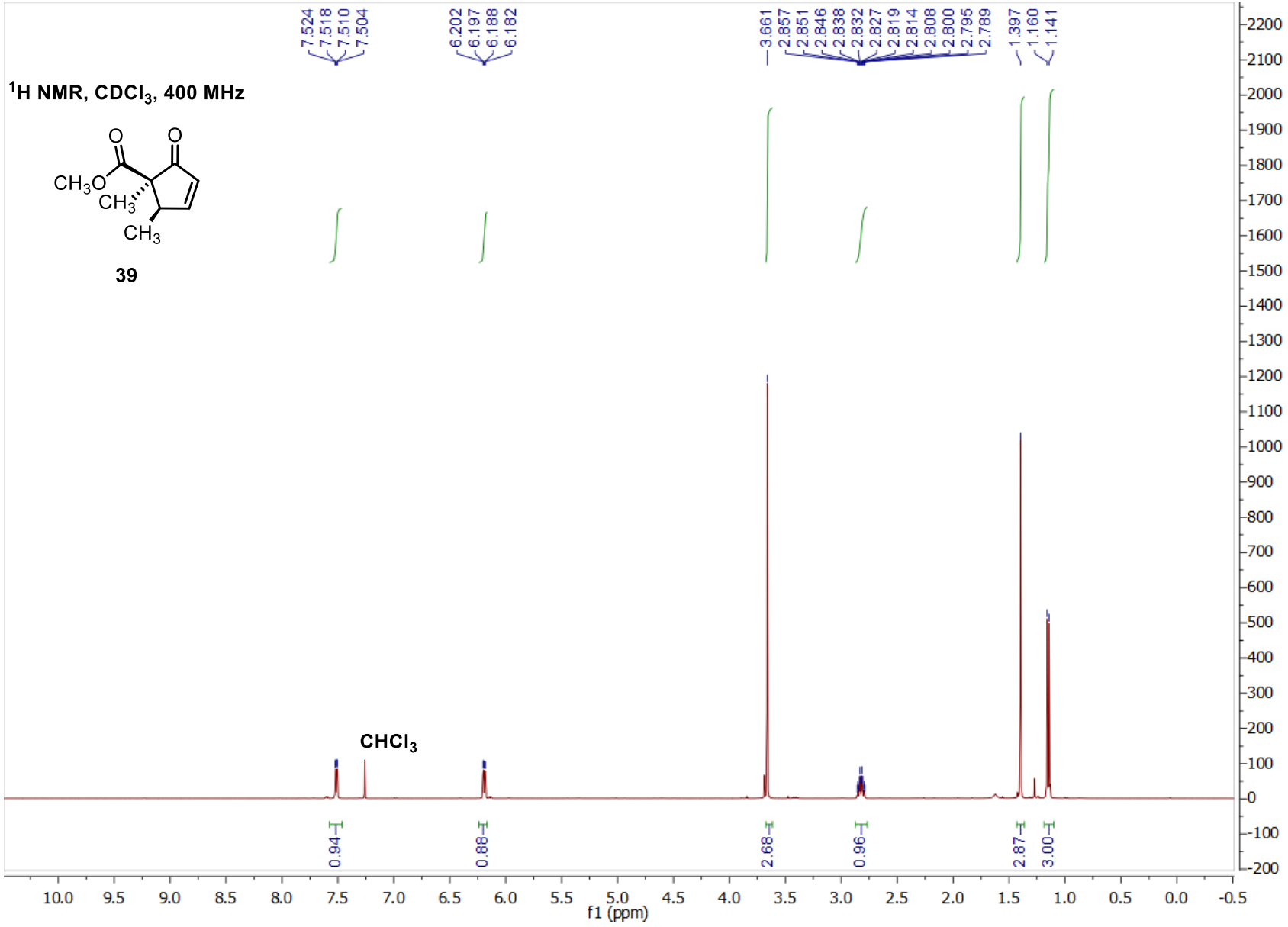

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
34
121.8
80.7
80.3
76.5
65.3
64.2
63.3
46.4
45.9
43.7
43.1
41.6
37.0
36.2
31.8
31.0
26.1
23.2
20.9
17.3
16.4
13.5
f1 (ppm)

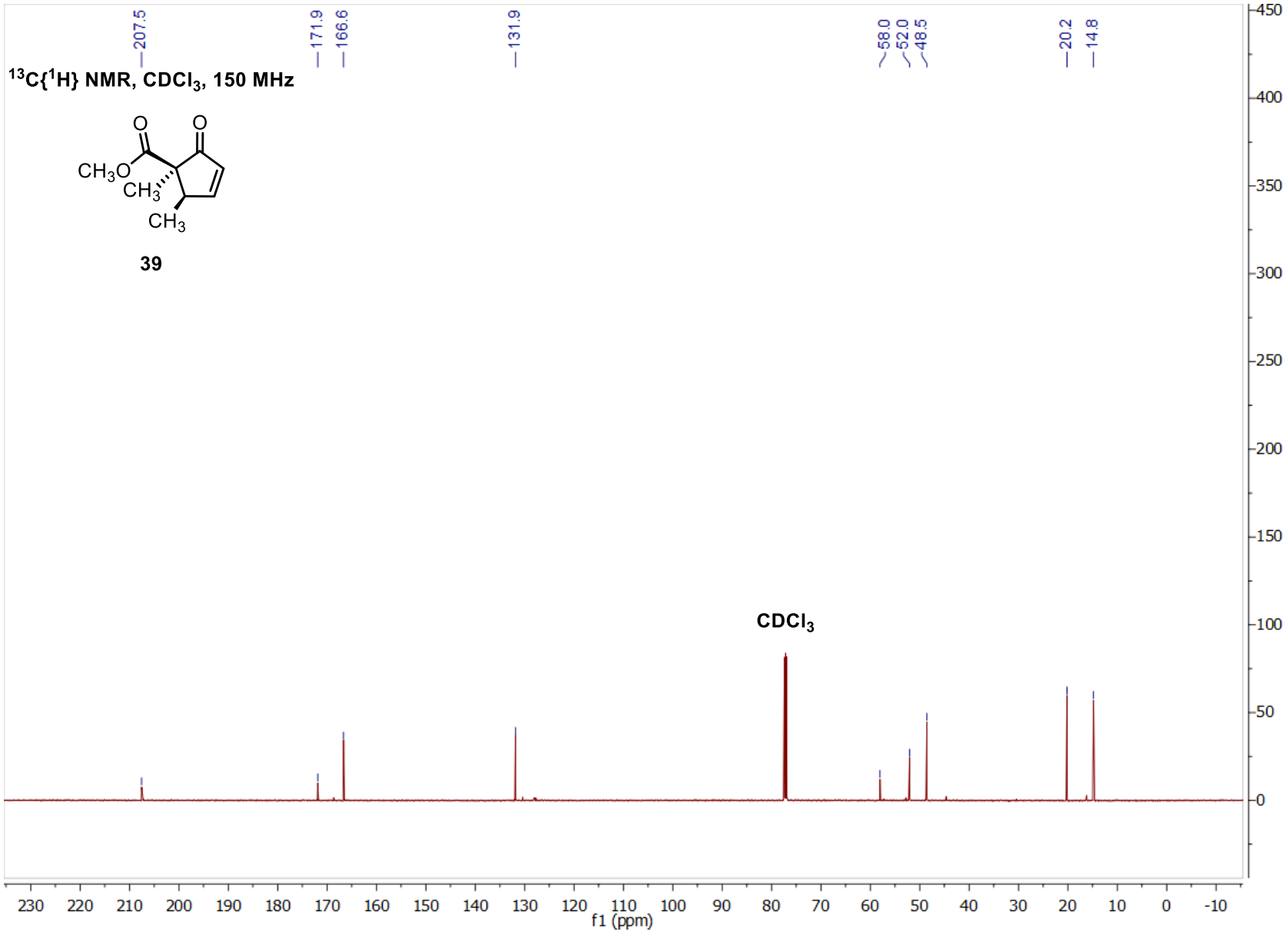

^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
S12
f1 (ppm)

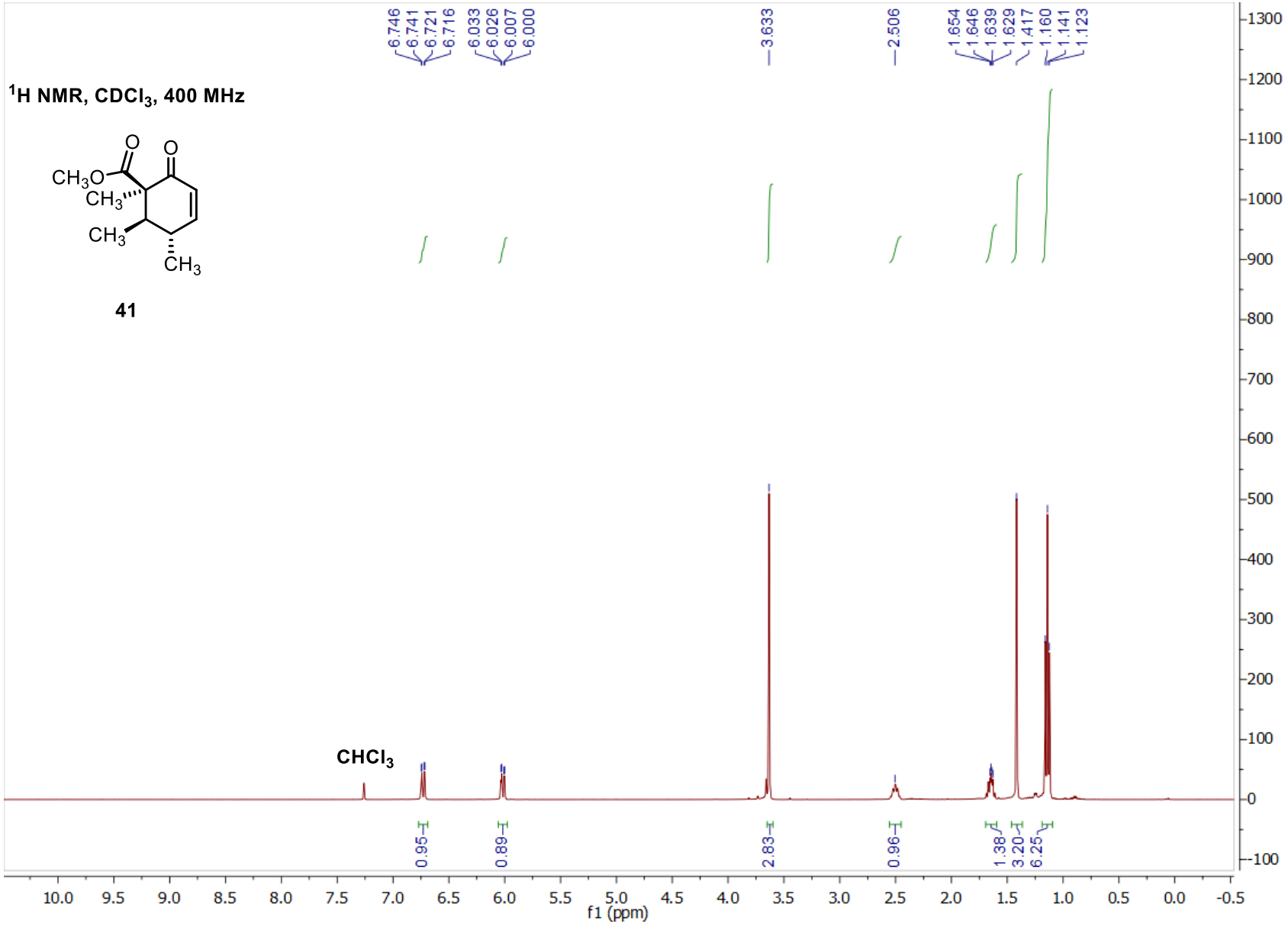

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S12
$CDCl_3$
171.0
155.0
120.4
79.4
75.9
71.7
71.5
63.8
61.5
52.9
51.0
48.0
46.2
41.6
40.0
36.6
35.8
35.4
33.2
33.1
29.3
28.7
28.4
27.2
25.8
17.7
14.7
11.5
10.6
f1 (ppm)

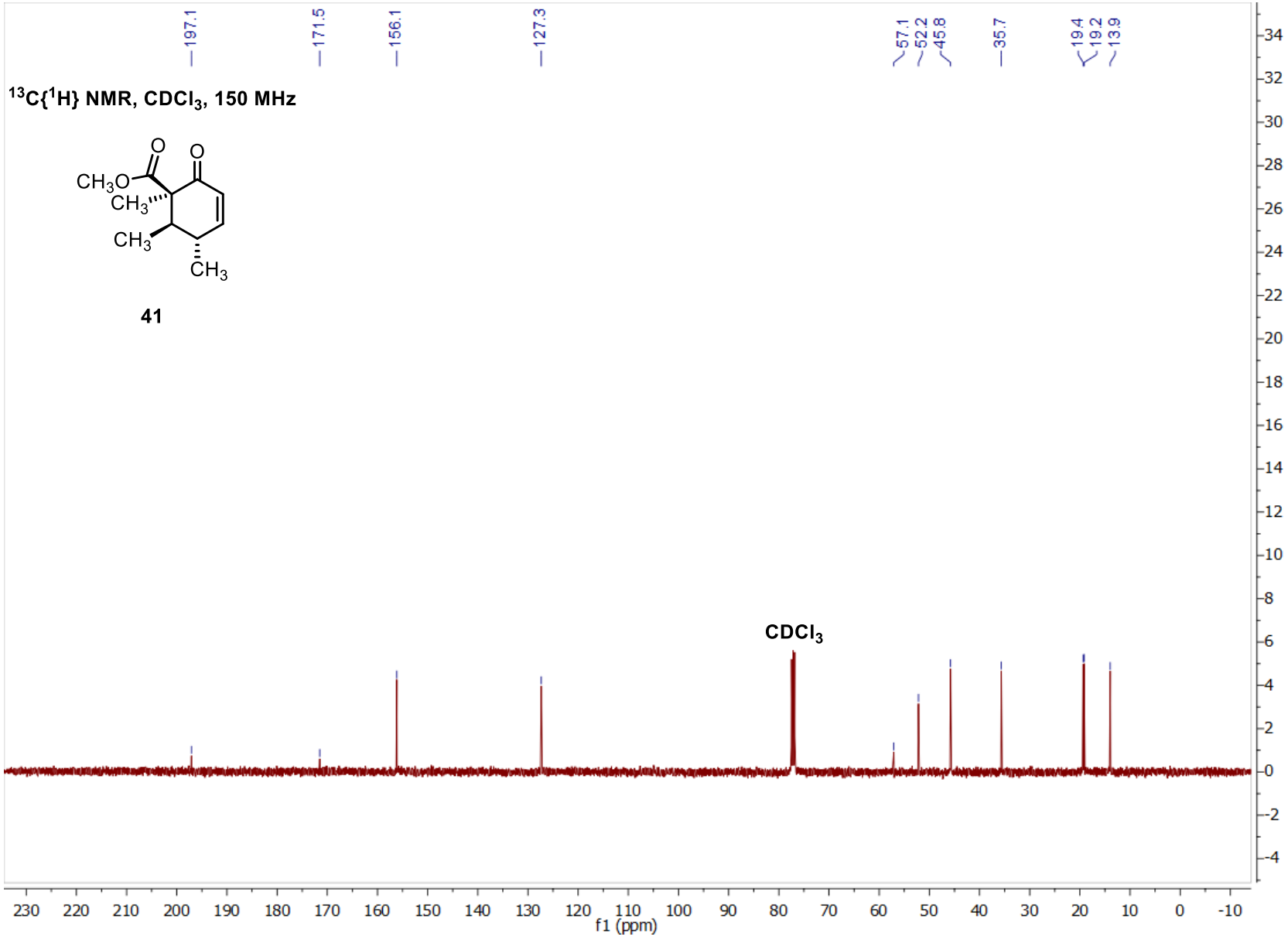

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
37
5.401
5.388
3.510
3.381
3.371
3.366
3.353
3.323
3.197
2.710
2.703
2.693
2.686
2.676
2.669
2.186
2.020
1.832
1.674
1.460
1.313
1.143
0.977
0.966
0.892
0.879
0.867
0.787
0.775
1.00
2.58
1.40
1.49
1.97
1.14
7.99
1.79
3.64
4.89
10.98
4.60
1.82
3.35
3.95
3.24
f1 (ppm)

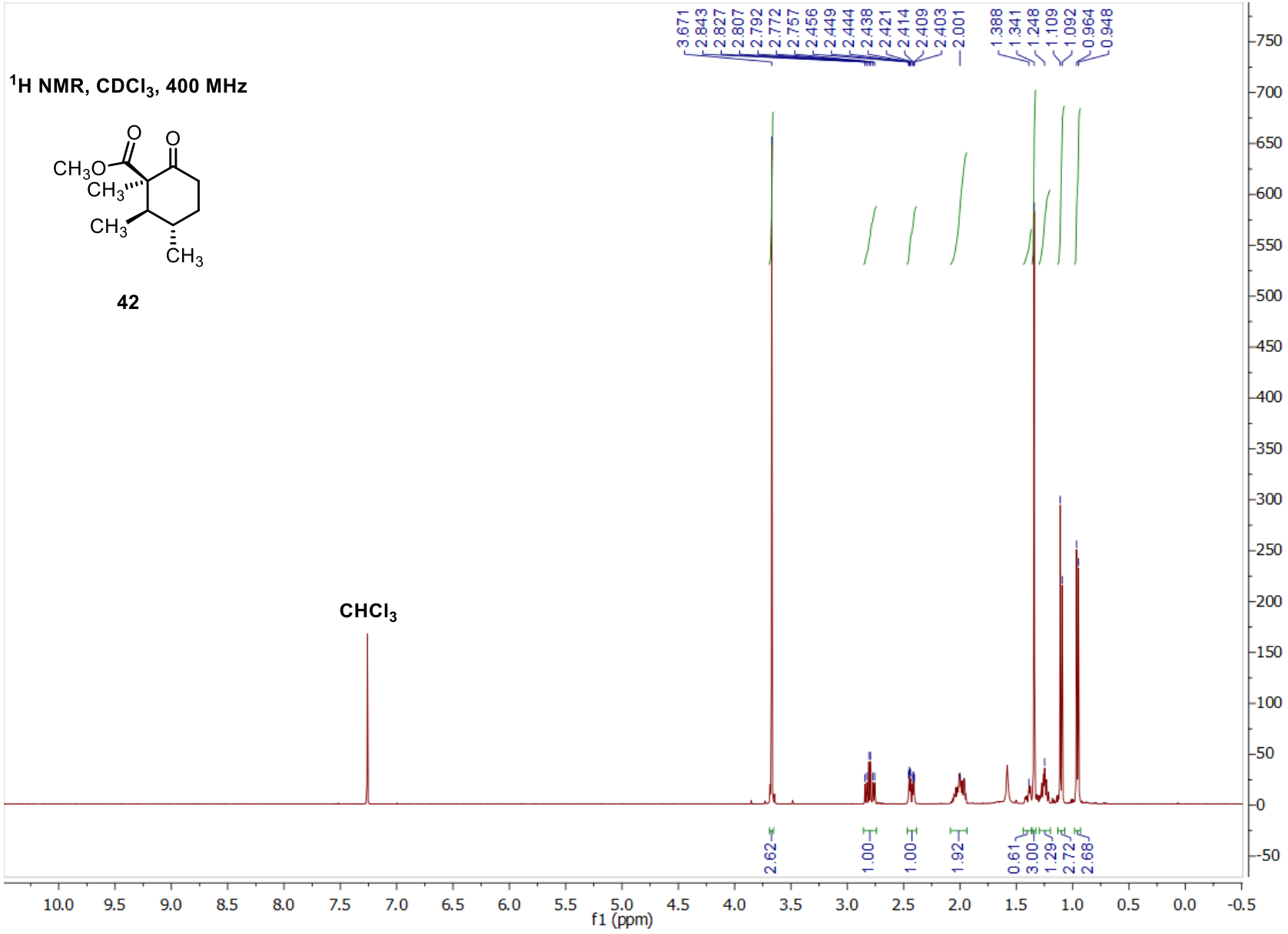

218.2
170.9
73.9
71.6
70.8
57.7
49.8
45.4
41.3
41.2
37.9
36.7
35.9
33.8
33.3
30.4
29.2
27.6
26.9
25.3
24.8
16.7
14.2
10.3
9.5
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
HO
NH2
S
O
CH3
CH3
O
H
CH3
O
OH
CH3
H
37
f1 (ppm)

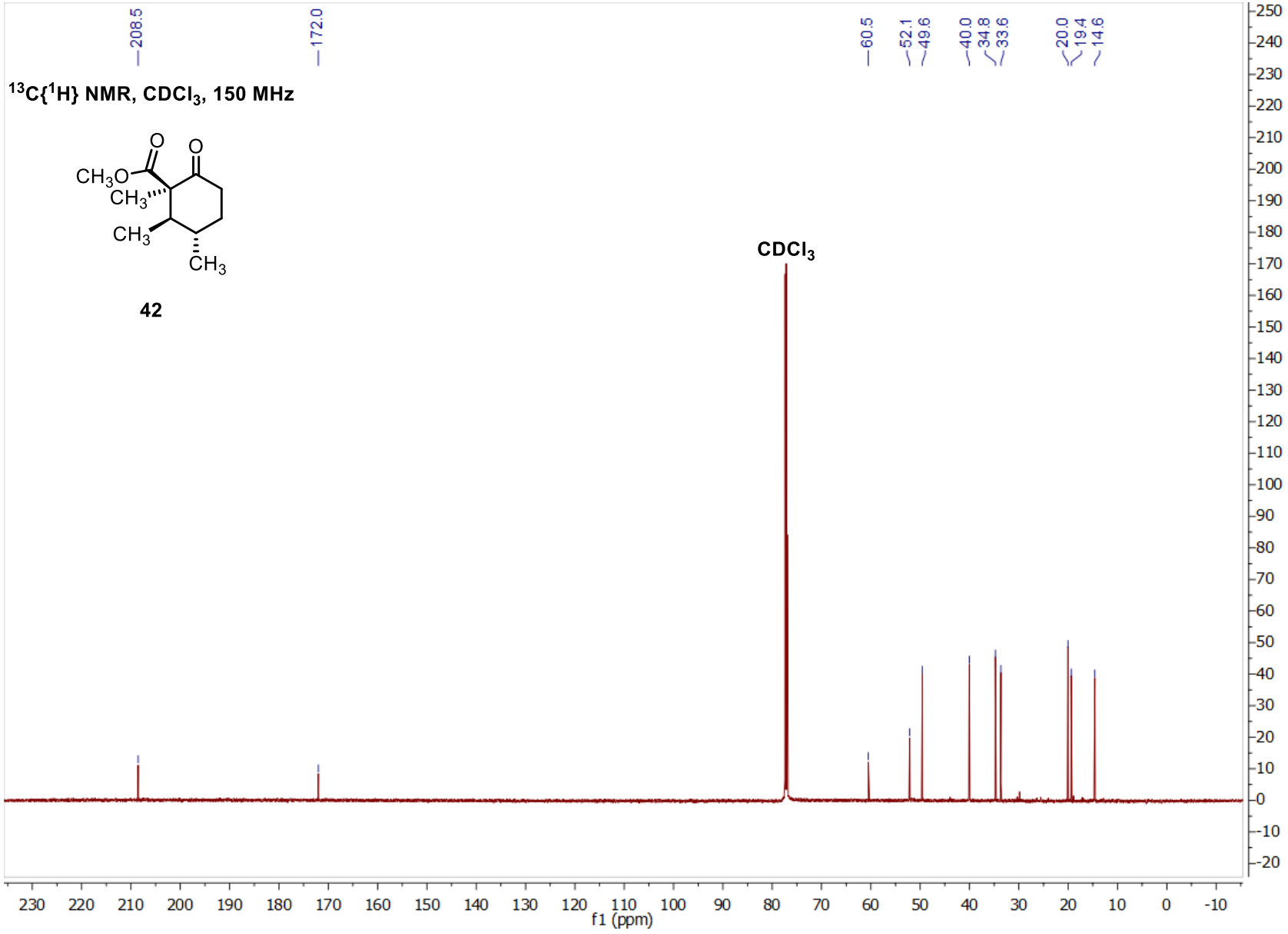

^{1}H NMR, $CDCl_3$, 400 MHz
39
7.524
7.518
7.510
7.504
6.202
6.197
6.188
6.182
3.661
2.857
2.851
2.846
2.838
2.832
2.827
2.819
2.814
2.808
2.800
2.795
2.789
1.397
1.160
1.141
$CHCl_3$
0.94
0.88
2.68
0.96
2.87
3.00
f1 (ppm)

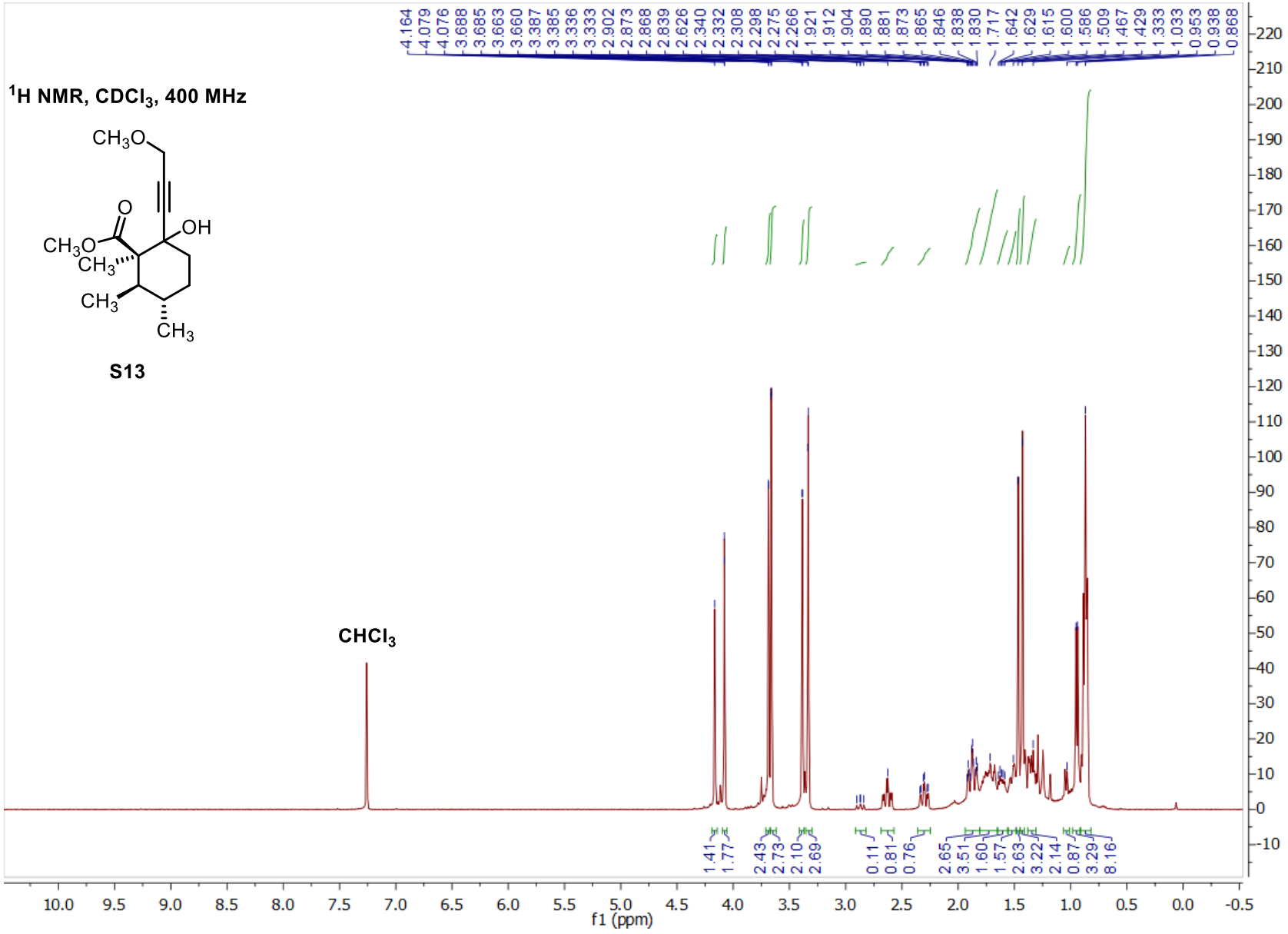

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
207.5
171.9
166.6
131.9
58.0
52.0
48.5
20.2
14.8
CH_3O
CH_3
CH_3
O
O
39
$CDCl_3$
f1 (ppm)

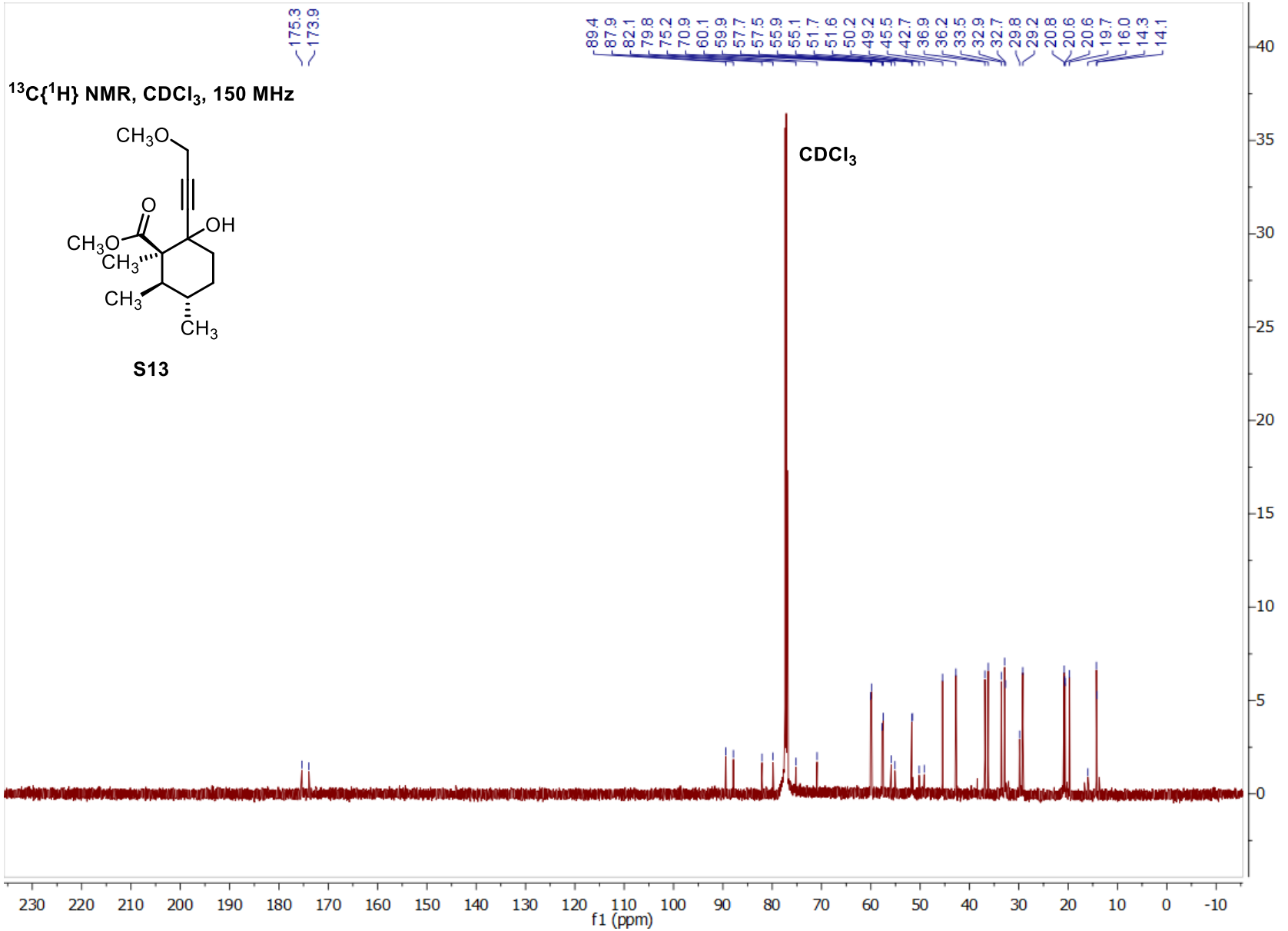

1H NMR, CDCl3, 400 MHz
41
CHCl3
6.746
6.741
6.721
6.716
6.033
6.026
6.007
6.000
3.633
2.506
1.654
1.646
1.639
1.629
1.417
1.160
1.141
1.123
0.95
0.89
2.83
0.96
1.38
3.20
6.25
f1 (ppm)

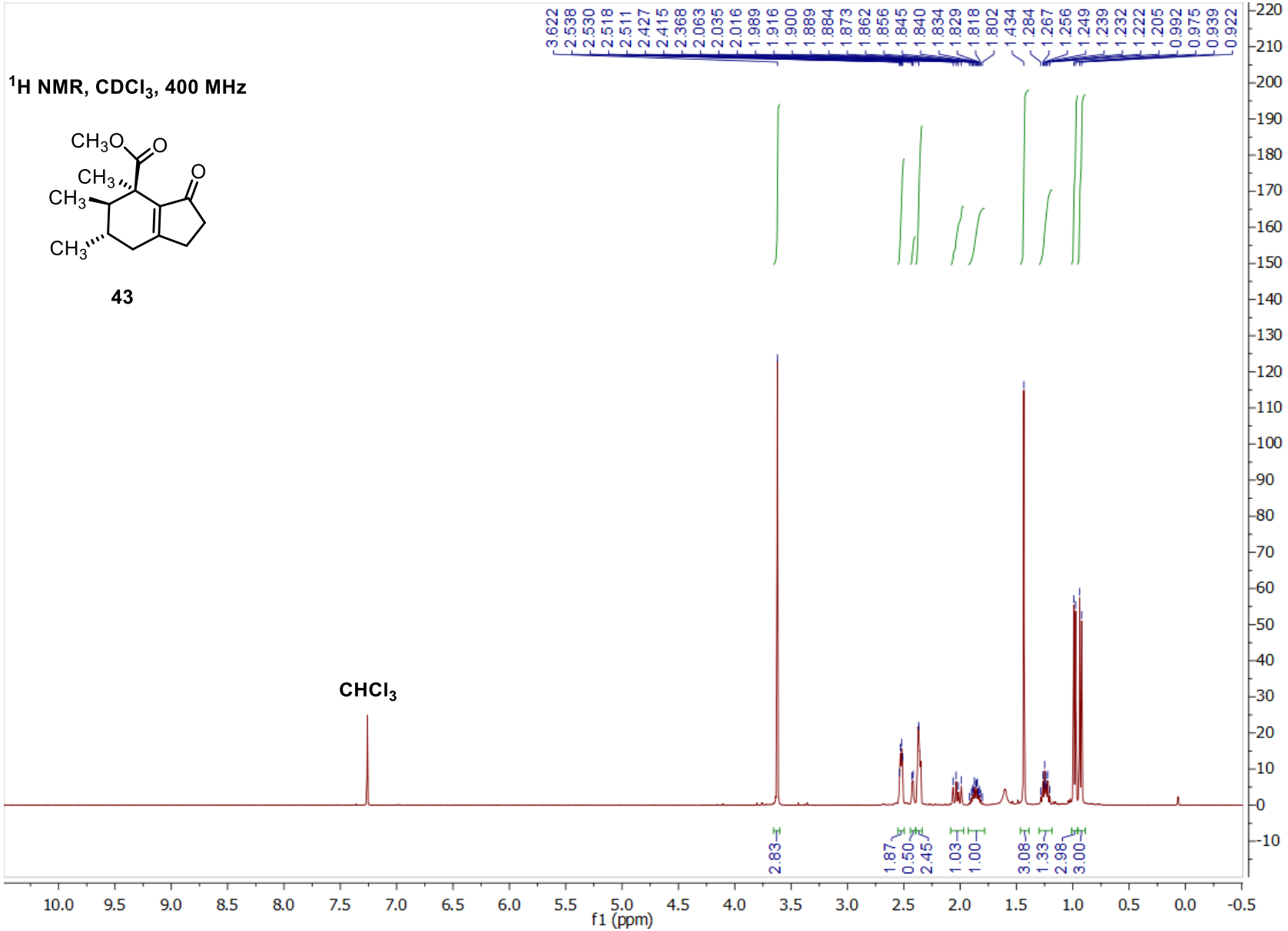

197.1
171.5
156.1
127.3
57.1
52.2
45.8
35.7
19.4
19.2
13.9
13C{1H} NMR, CDCl3, 150 MHz
O
O
CH3O
CH3
CH3
CH3
41
CDCl3
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
-2
-4
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

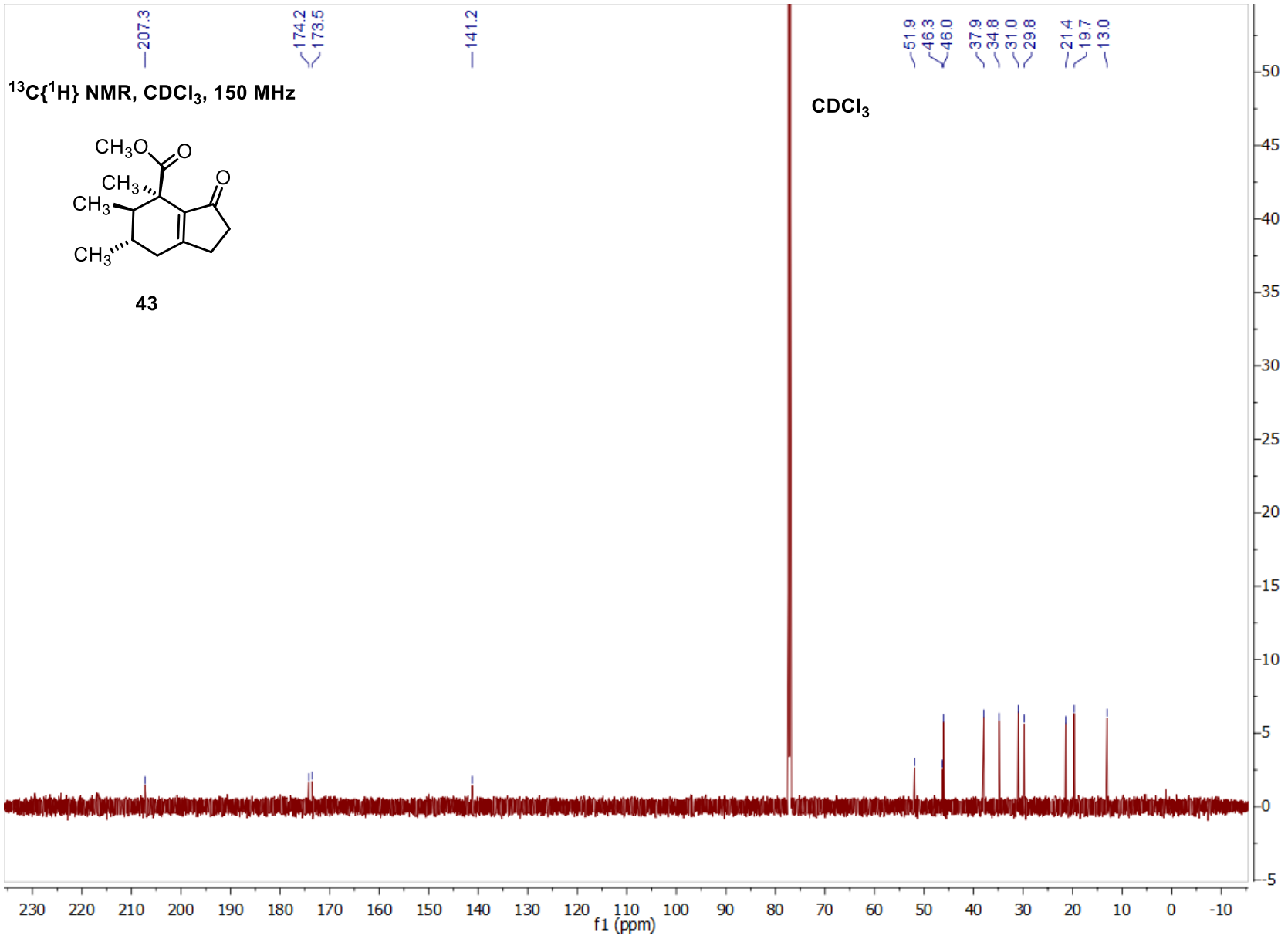

^{1}H NMR, $CDCl_3$, 400 MHz
42
$CHCl_3$
3.671
2.843
2.827
2.807
2.792
2.772
2.757
2.456
2.449
2.444
2.438
2.421
2.414
2.409
2.403
2.001
1.388
1.341
1.248
1.109
1.092
0.964
0.948
2.62
1.00
1.00
1.92
0.61
3.00
1.29
2.72
2.68
f1 (ppm)

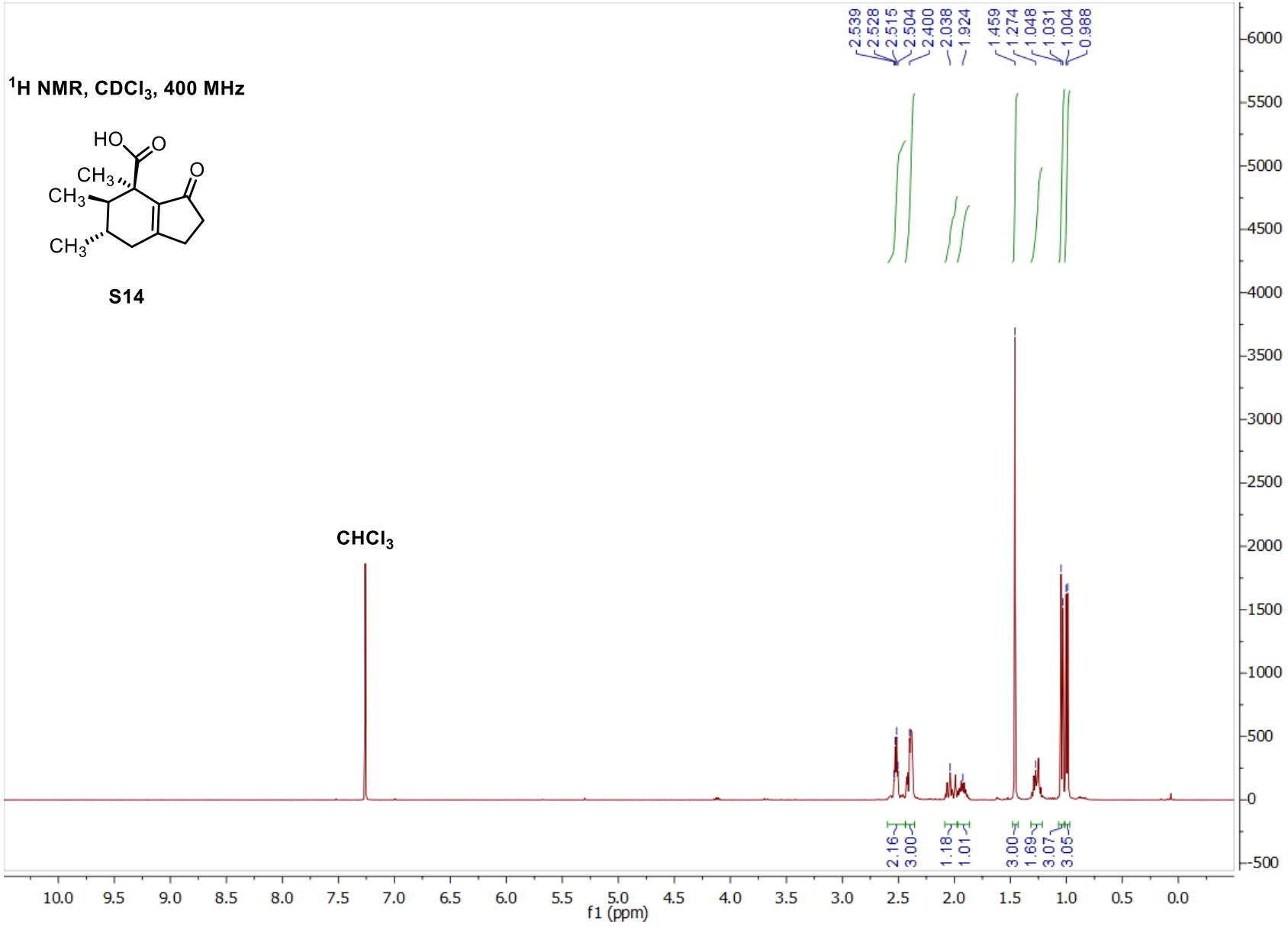

208.5
172.0
60.5
52.1
49.6
40.0
34.8
33.6
20.0
19.4
14.6
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
42
f1 (ppm)

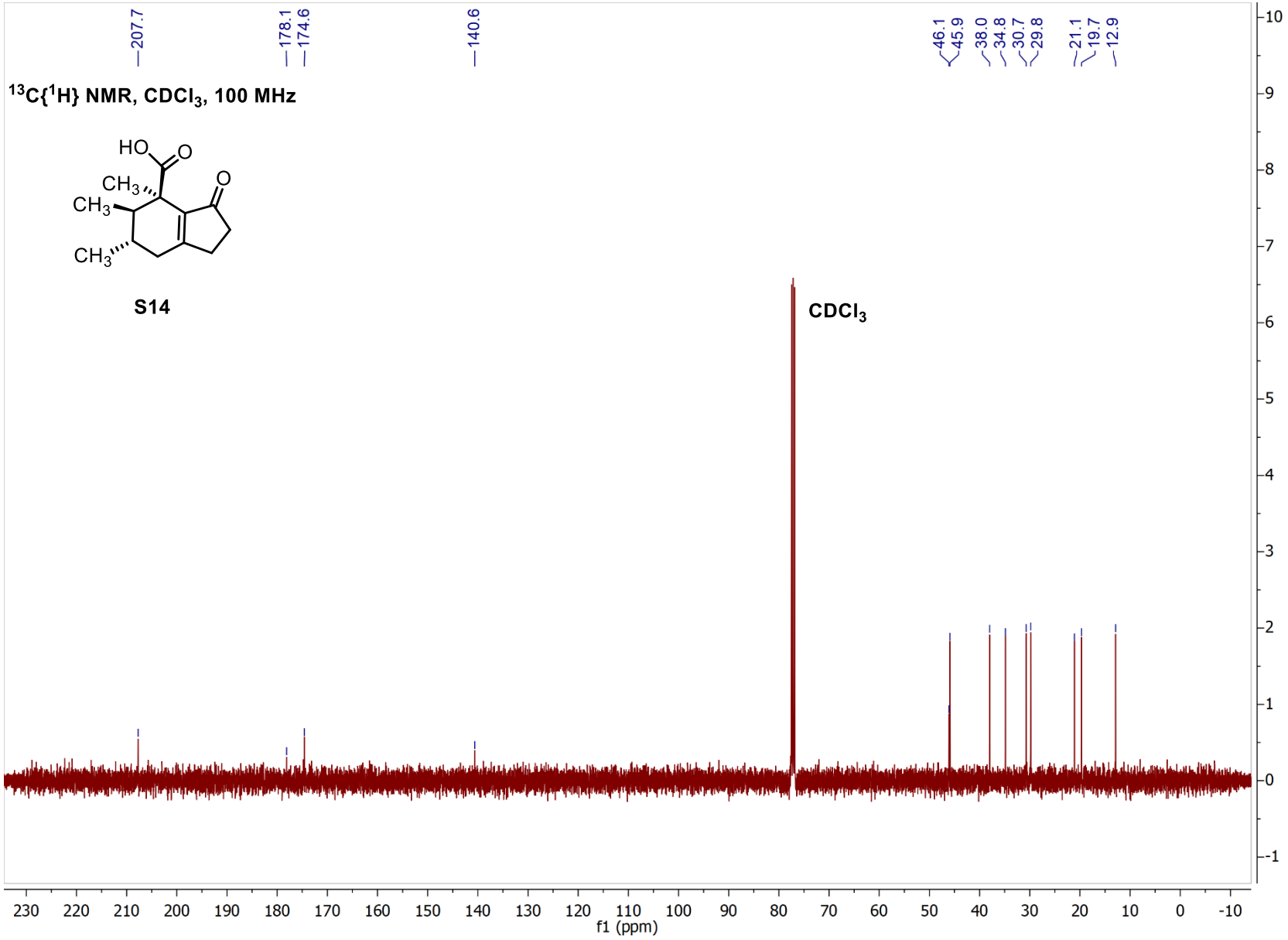

^{1}H NMR, $CDCl_3$, 400 MHz
S13
$CHCl_3$
f1 (ppm)

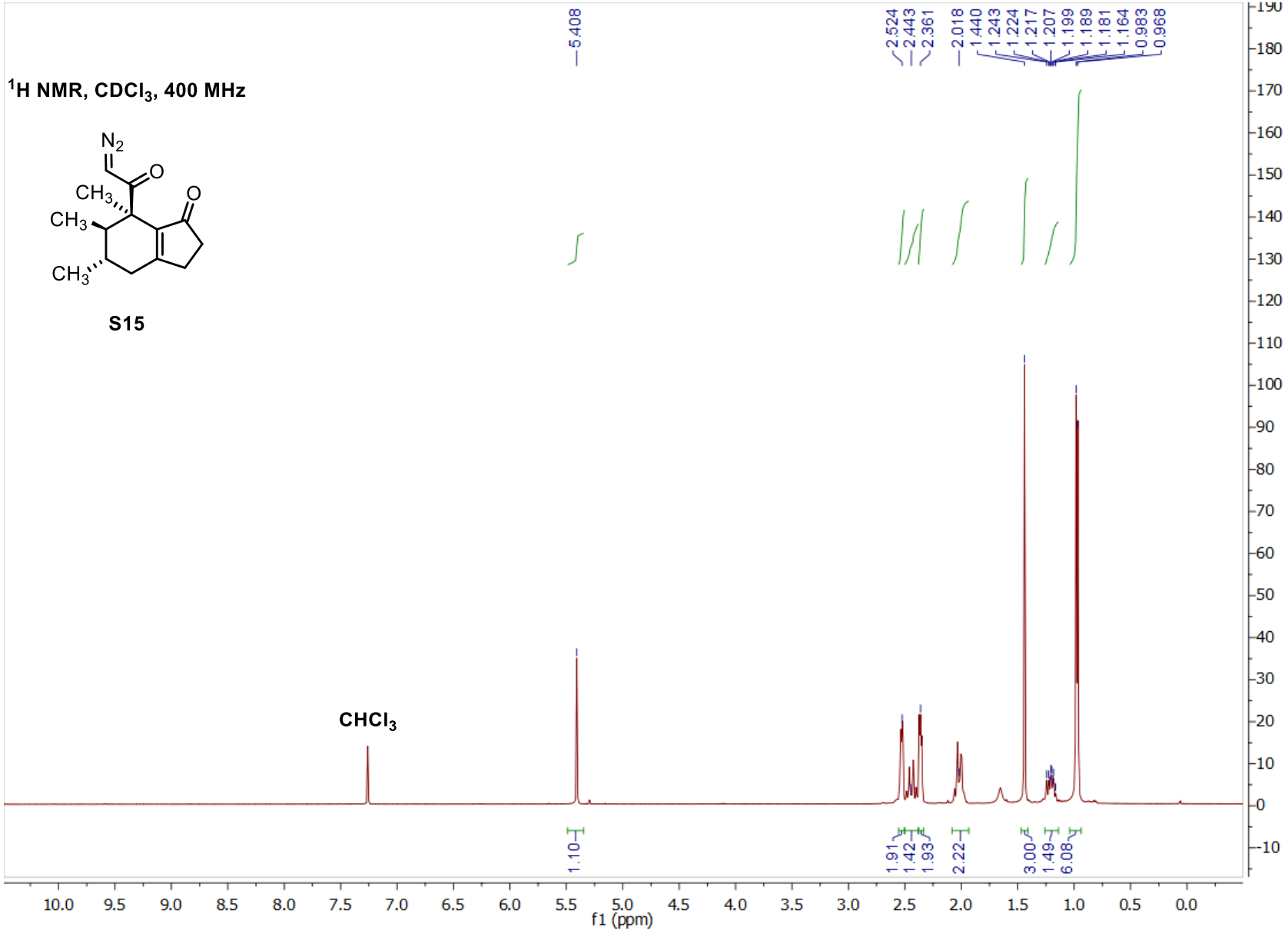

175.3
173.9
89.4
87.9
82.1
79.8
75.2
70.9
60.1
59.9
57.7
57.5
55.9
55.1
51.7
51.6
50.2
49.2
45.5
42.7
36.9
36.2
33.5
32.9
32.7
29.8
29.2
20.8
20.6
20.6
19.7
16.0
14.3
14.1
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
CH3O
O
OH
CH3O
CH3
CH3
CH3
S13
f1 (ppm)

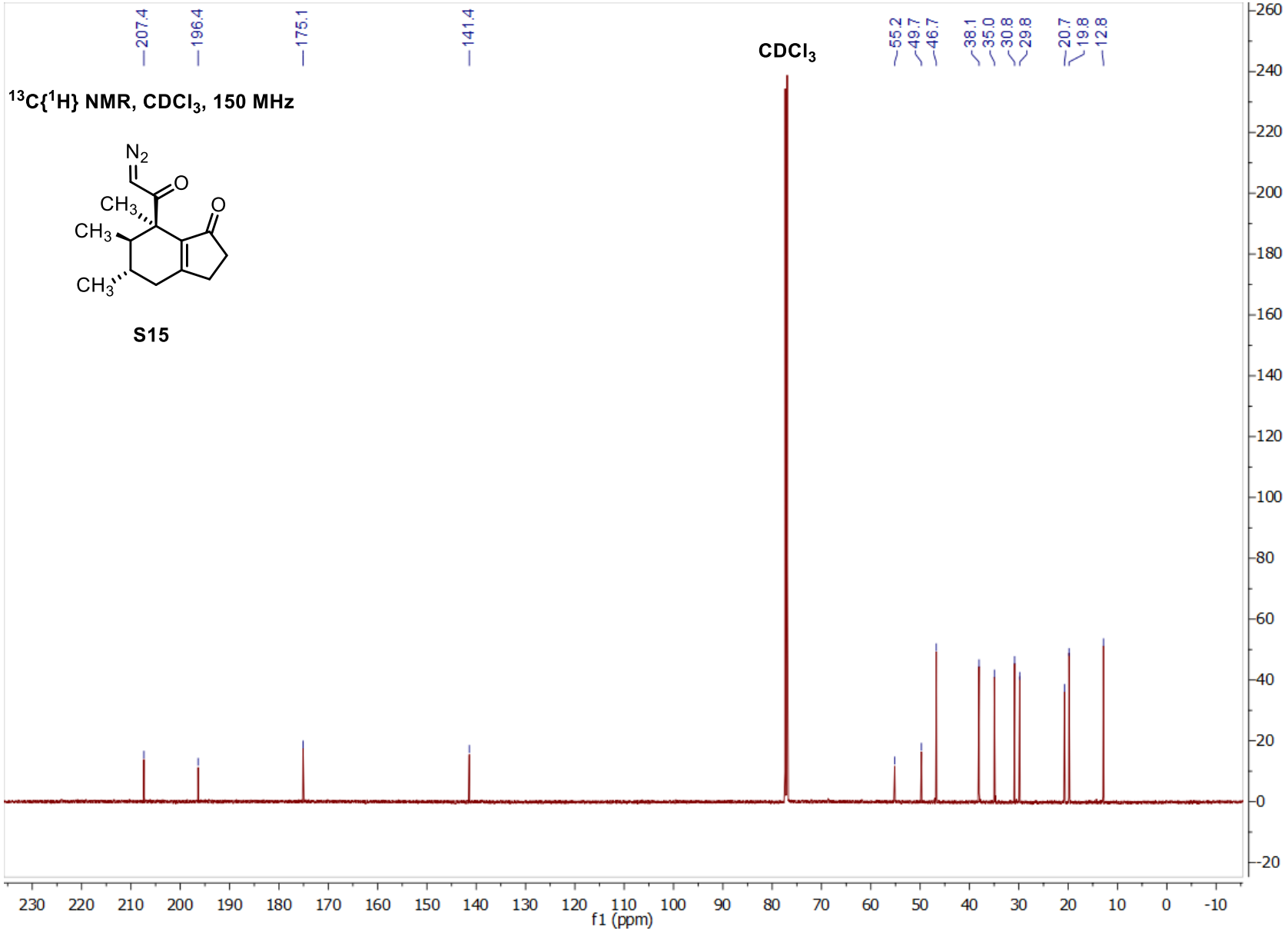

^{1}H NMR, $CDCl_3$, 400 MHz
43
$CHCl_3$
f1 (ppm)

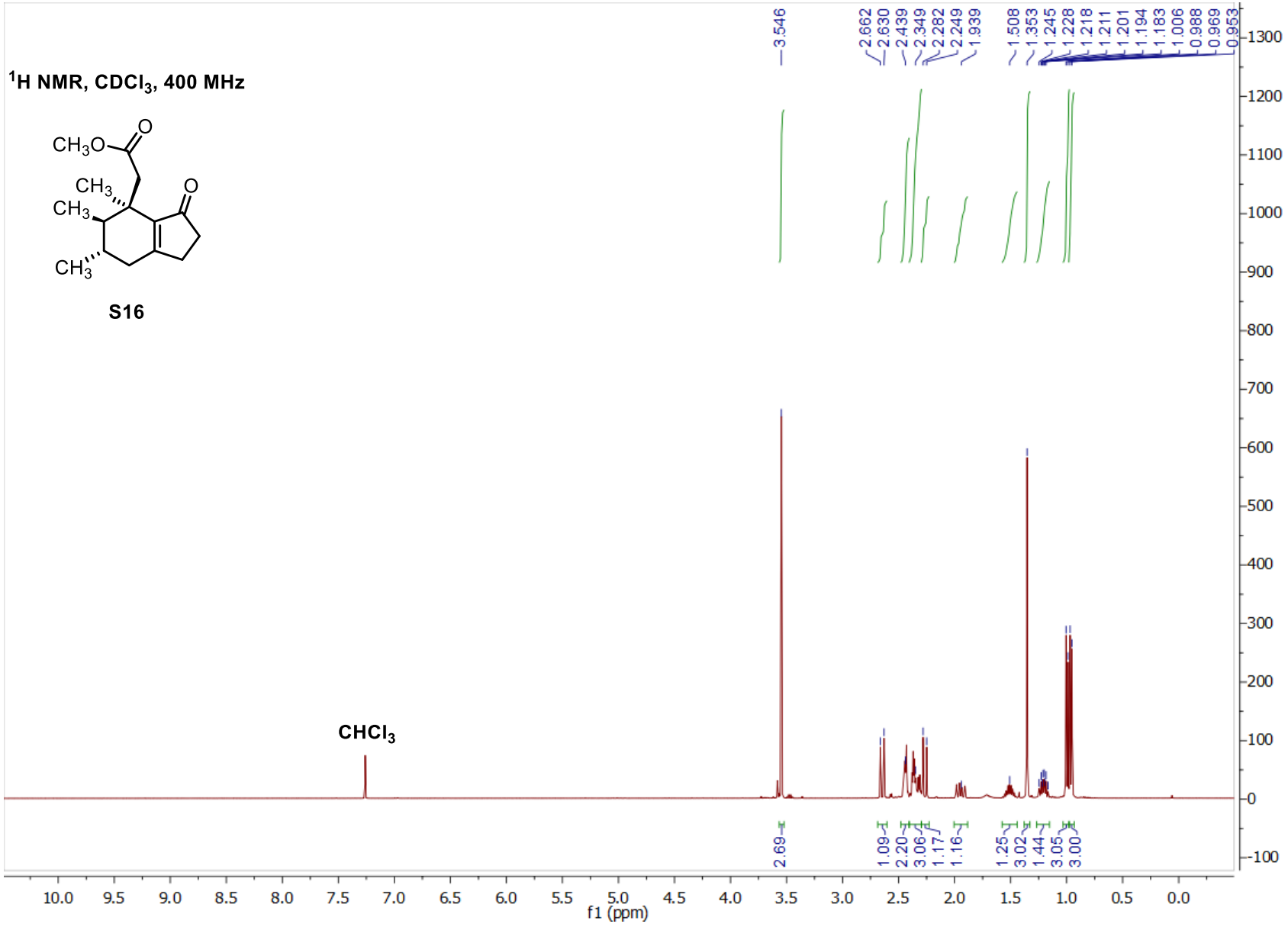

207.3
174.2
173.5
141.2
51.9
46.3
46.0
37.9
34.8
31.0
29.8
21.4
19.7
13.0
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
CH3O
O
CH3
CH3
O
CH3
43
f1 (ppm)

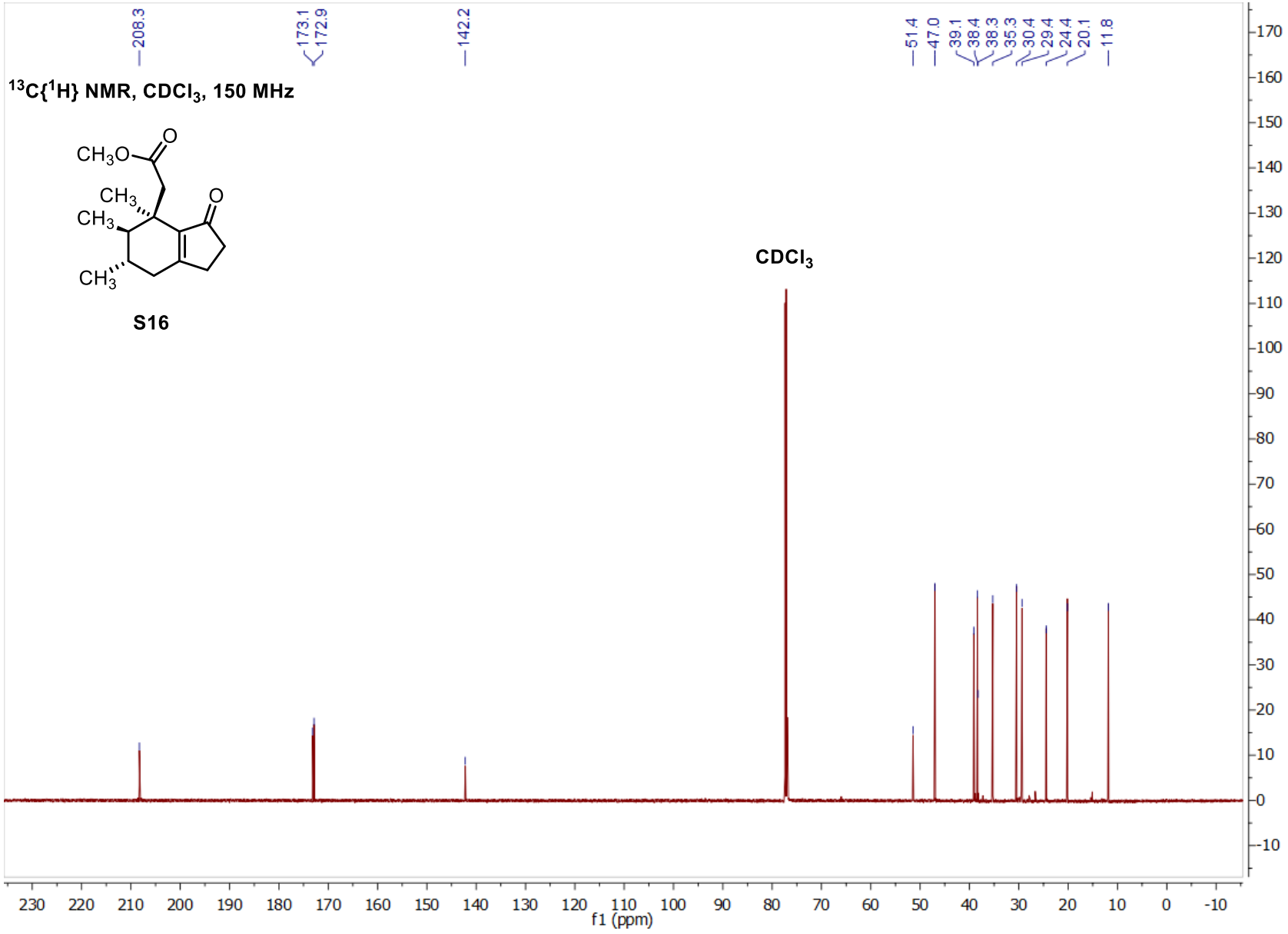

^{1}H NMR, $CDCl_3$, 400 MHz
HO
O
CH_3
CH_3
O
CH_3
S14
$CHCl_3$
2.539
2.528
2.515
2.504
2.400
2.038
1.924
1.459
1.274
1.048
1.031
1.004
0.988
2.16
3.00
1.18
1.01
3.00
1.69
3.07
3.05
f1 (ppm)

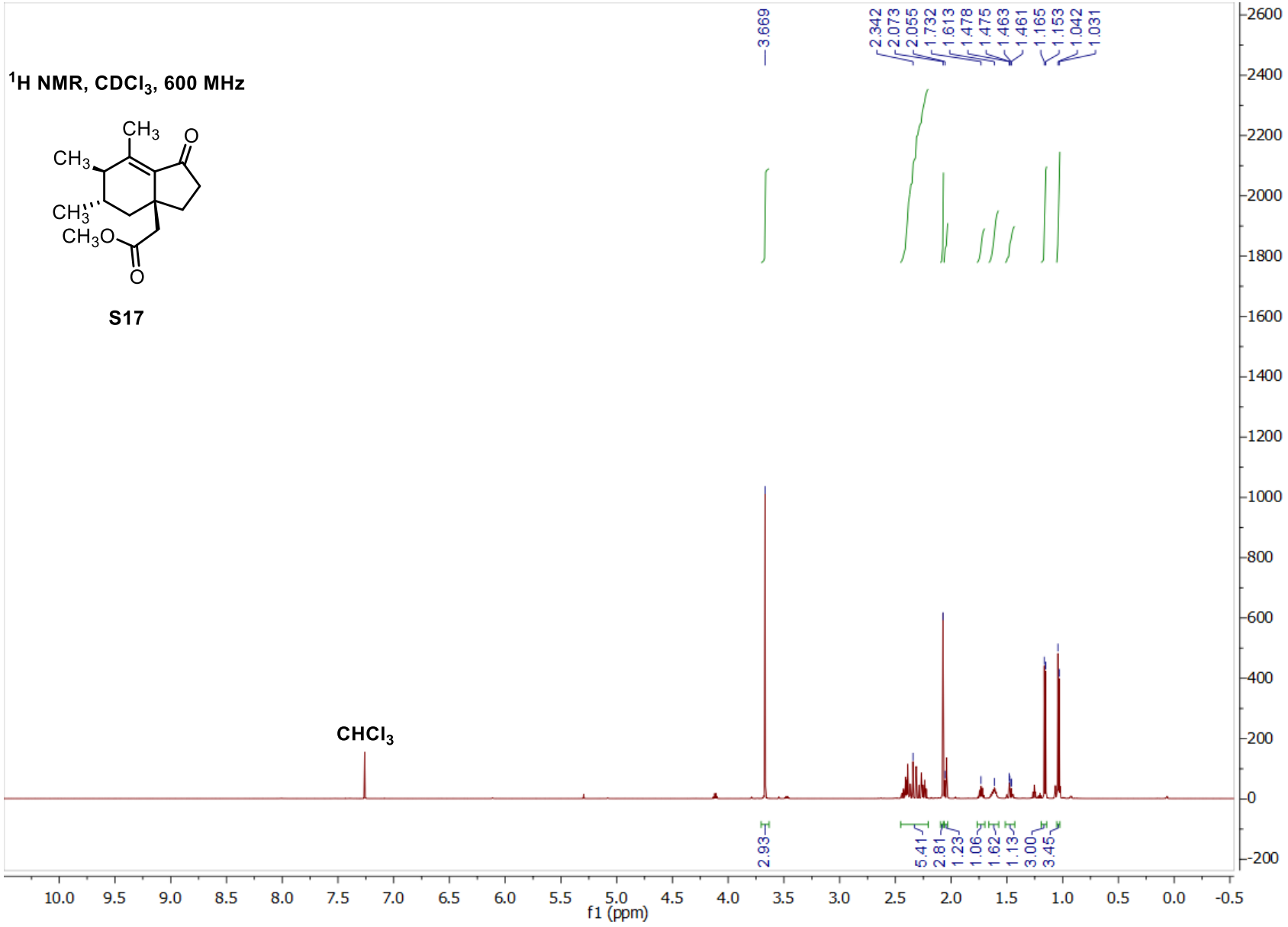

207.7
178.1
174.6
140.6
46.1
45.9
38.0
34.8
30.7
29.8
21.1
19.7
12.9
13C{1H} NMR, CDCl3, 100 MHz
HO
O
O
CH3
CH3
CH3
S14
CDCl3
f1 (ppm)

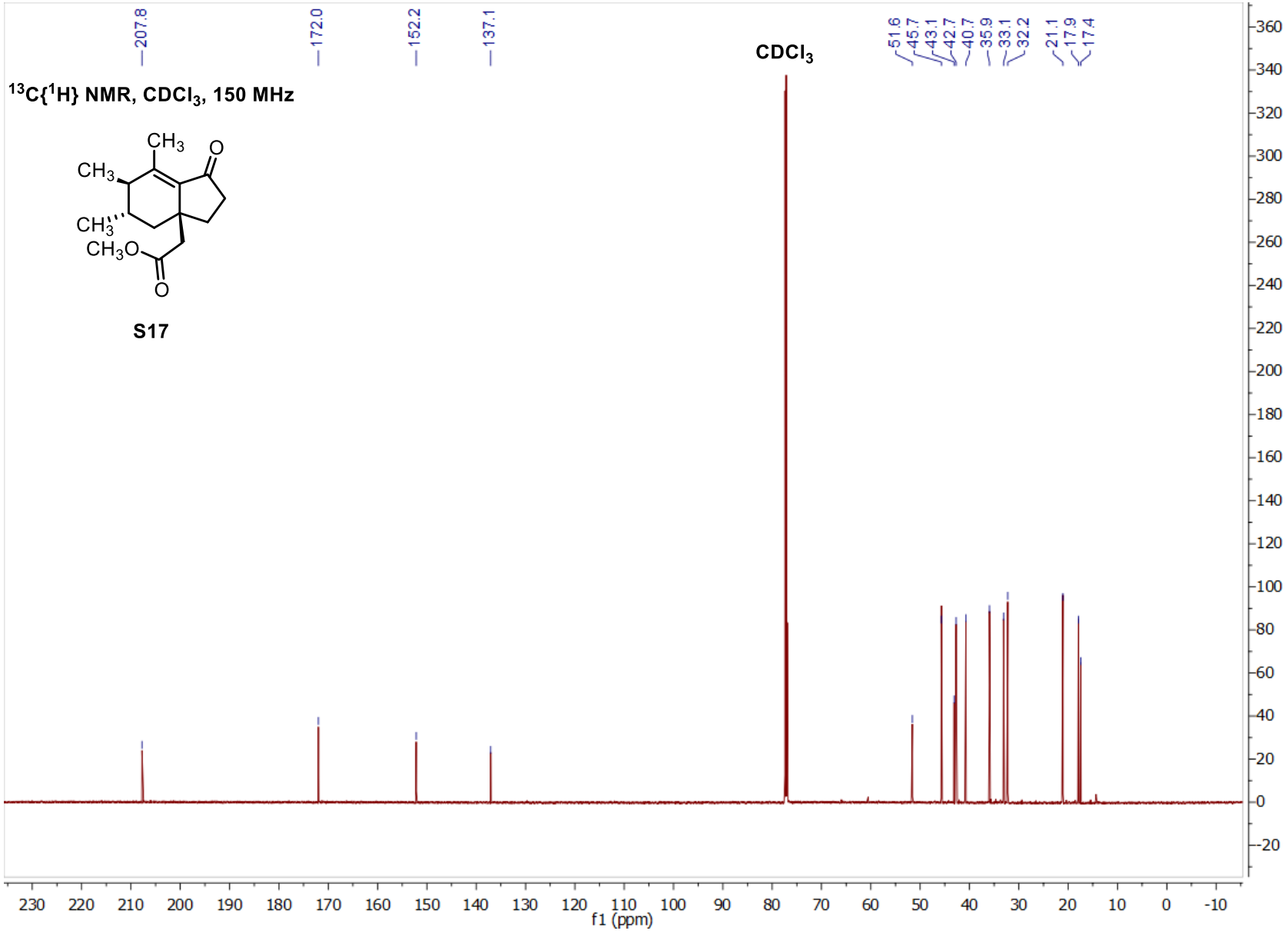

1H NMR, CDCl3, 400 MHz
S15
CHCl3
5.408
2.524
2.443
2.361
2.018
1.440
1.243
1.224
1.217
1.207
1.199
1.189
1.181
1.164
0.983
0.968
1.10
1.91
1.42
1.93
2.22
3.00
1.49
6.08
f1 (ppm)

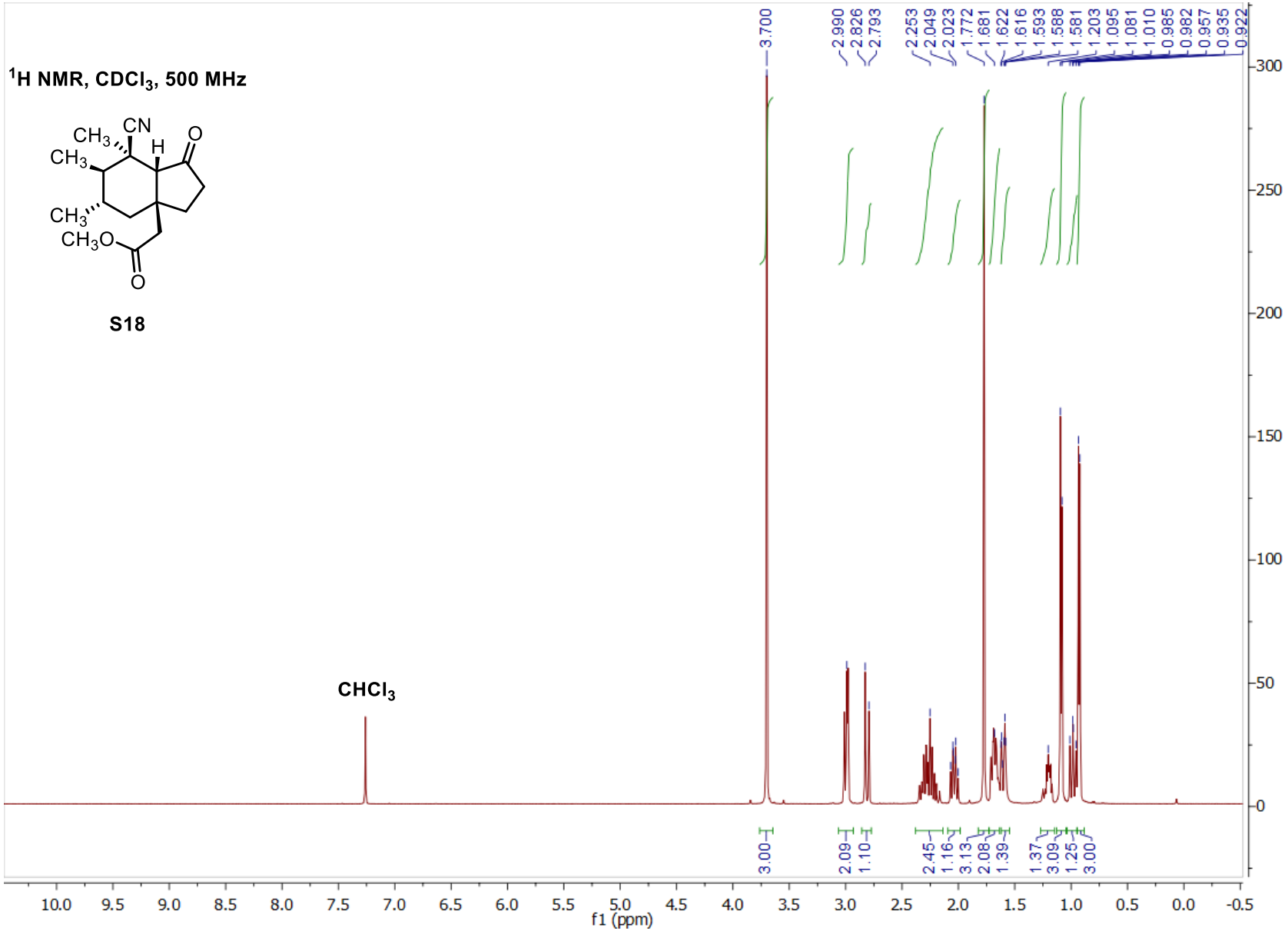

207.4
196.4
175.1
141.4
CDCl3
55.2
49.7
46.7
38.1
35.0
30.8
29.8
20.7
19.8
12.8
13C{1H} NMR, CDCl3, 150 MHz
N2
O
CH3
CH3
CH3
O
S15
f1 (ppm)

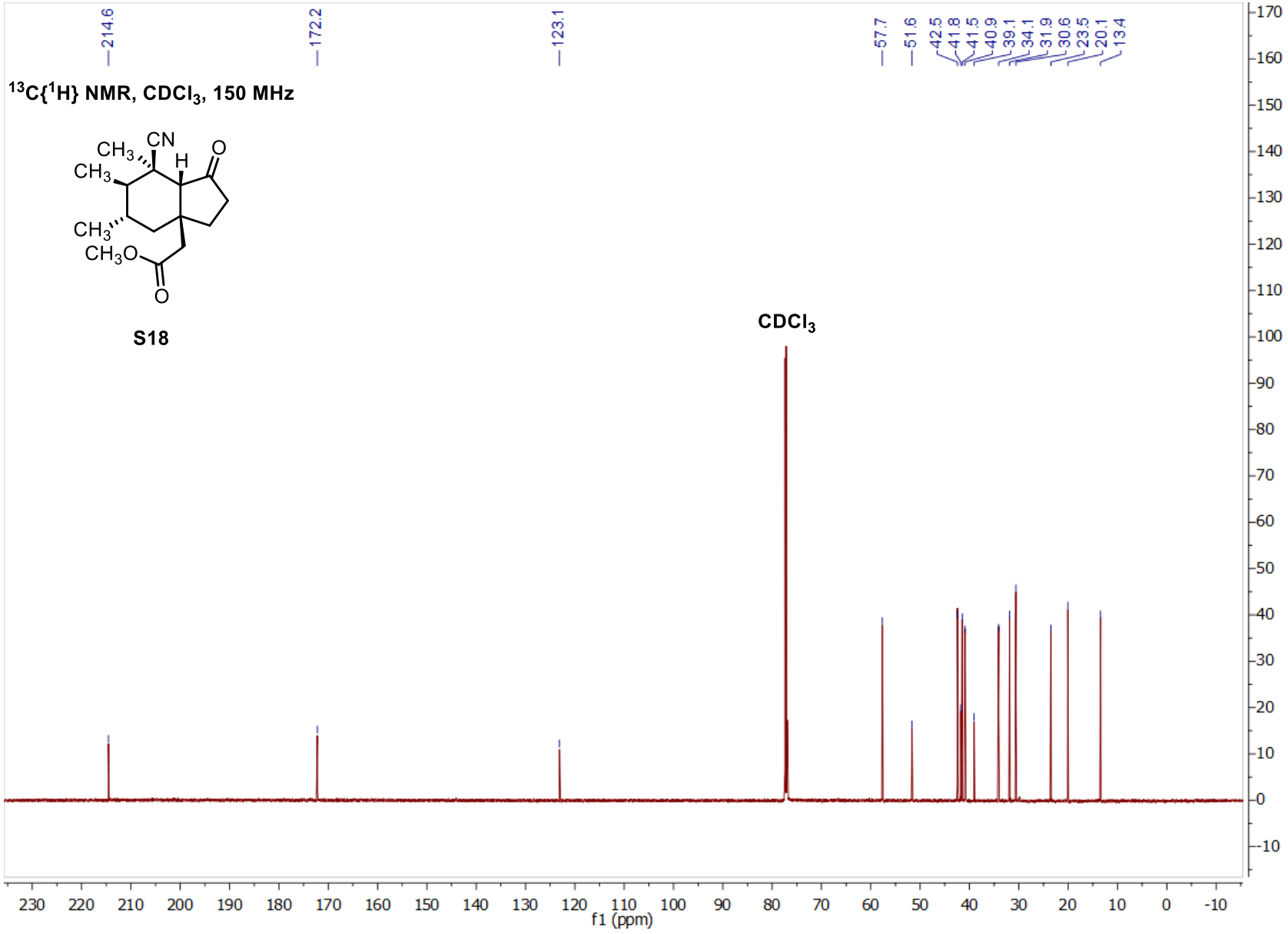

1H NMR, CDCl3, 400 MHz
S16
CHCl3
f1 (ppm)

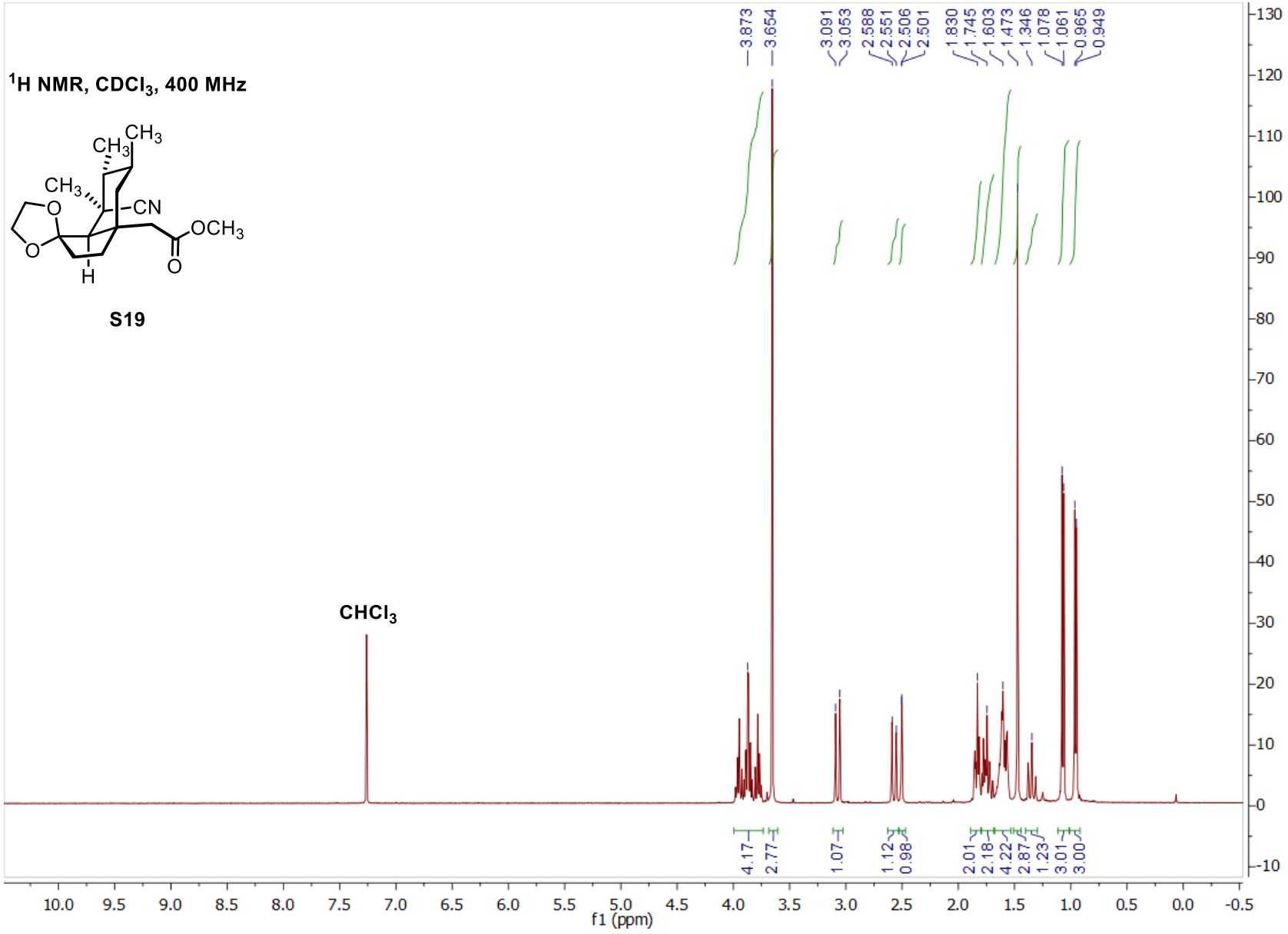

208.3
173.1
172.9
142.2
51.4
47.0
39.1
38.4
38.3
35.3
30.4
29.4
24.4
20.1
11.8
13C{1H} NMR, CDCl3, 150 MHz
CH3O
O
CH3
CH3
O
CH3
S16
CDCl3
f1 (ppm)

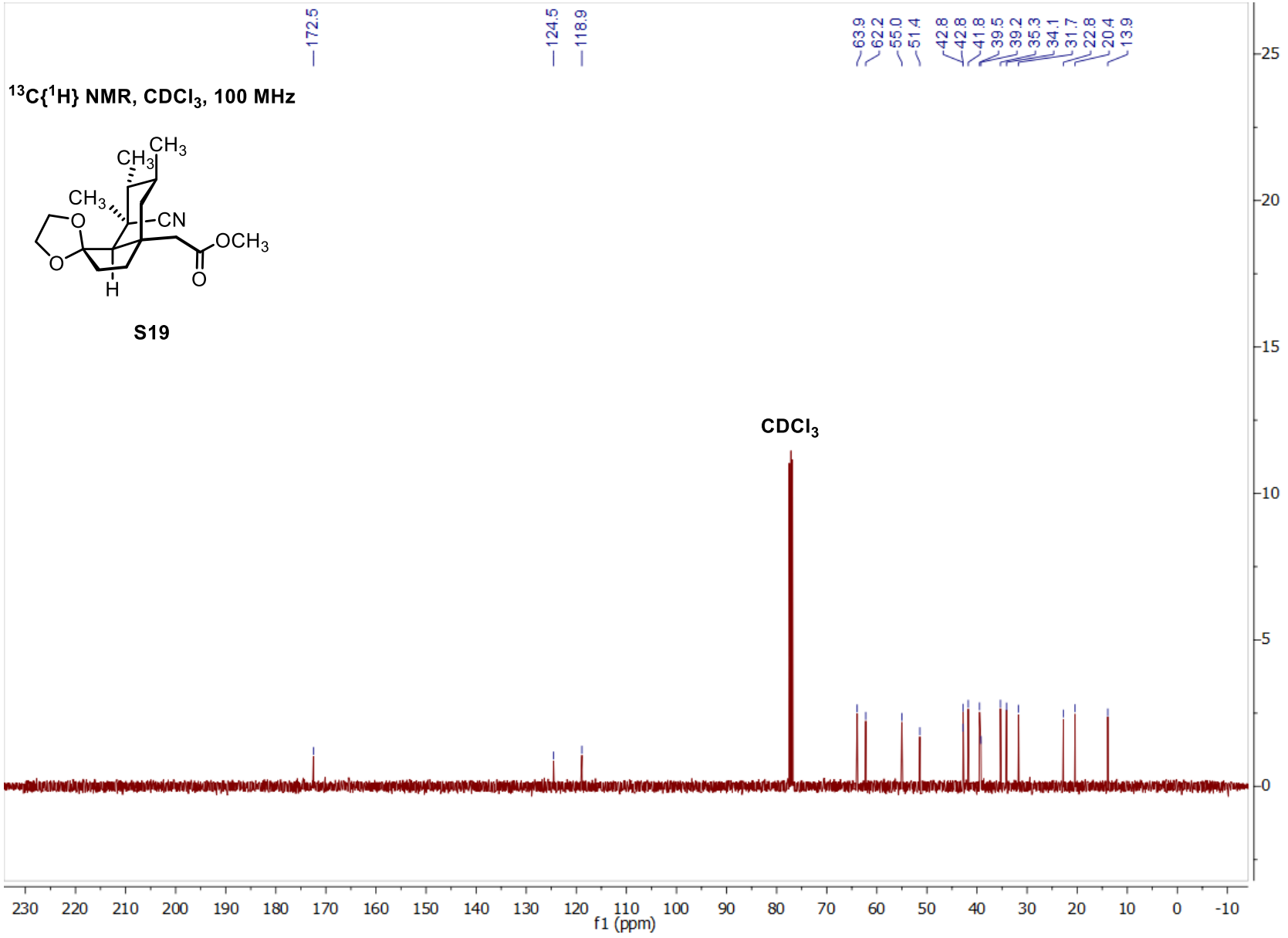

1H NMR, CDCl3, 600 MHz
S17
CHCl3
3.669
2.342
2.073
2.055
1.732
1.613
1.478
1.475
1.463
1.461
1.165
1.153
1.042
1.031
2.93
5.41
2.81
1.23
1.06
1.62
1.13
3.00
3.45
f1 (ppm)

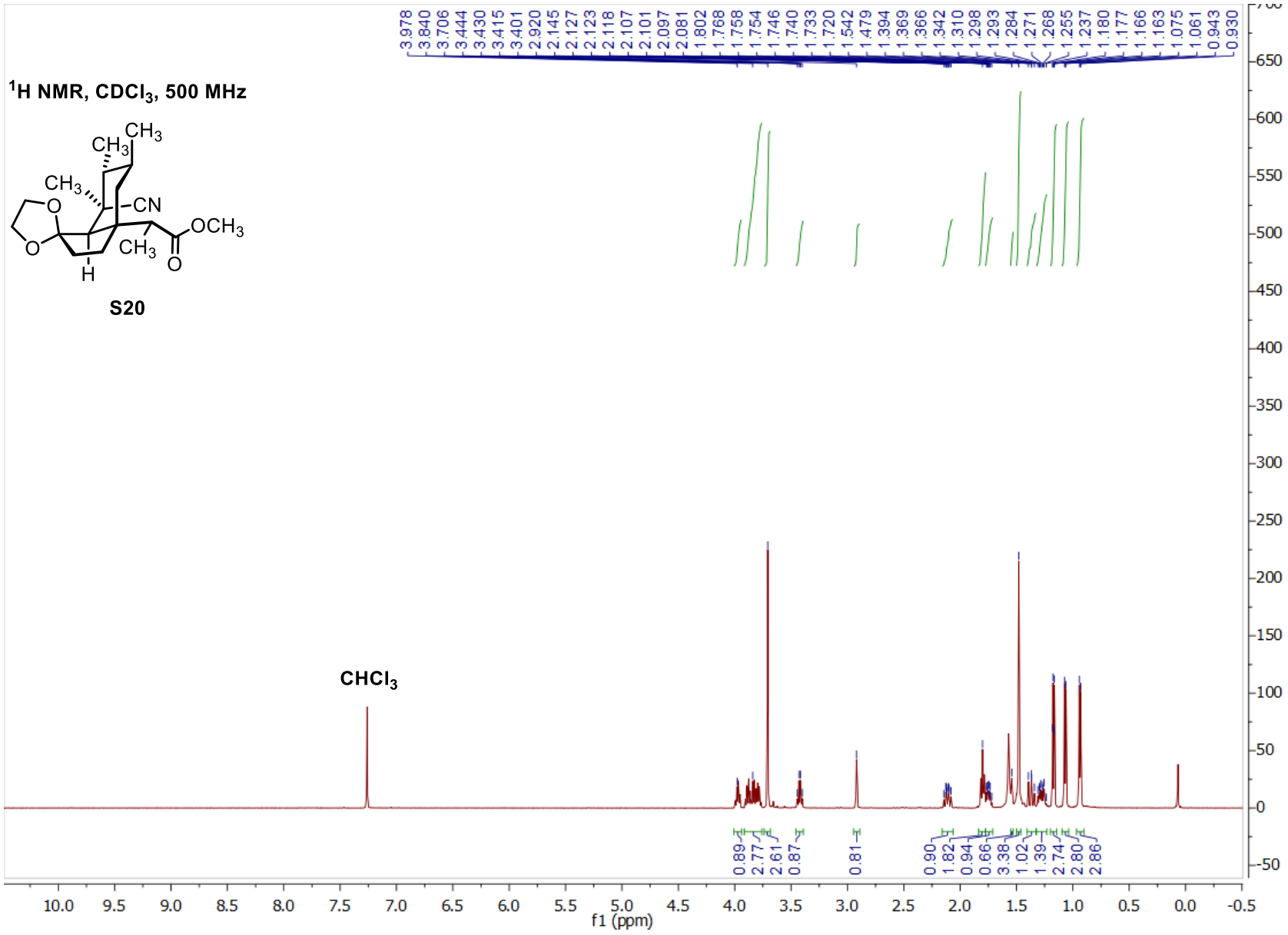

207.8
172.0
152.2
137.1
CDCl3
51.6
45.7
43.1
42.7
40.7
35.9
33.1
32.2
21.1
17.9
17.4
13C{1H} NMR, CDCl3, 150 MHz
CH3
O
CH3
CH3
CH3O
O
S17
f1 (ppm)

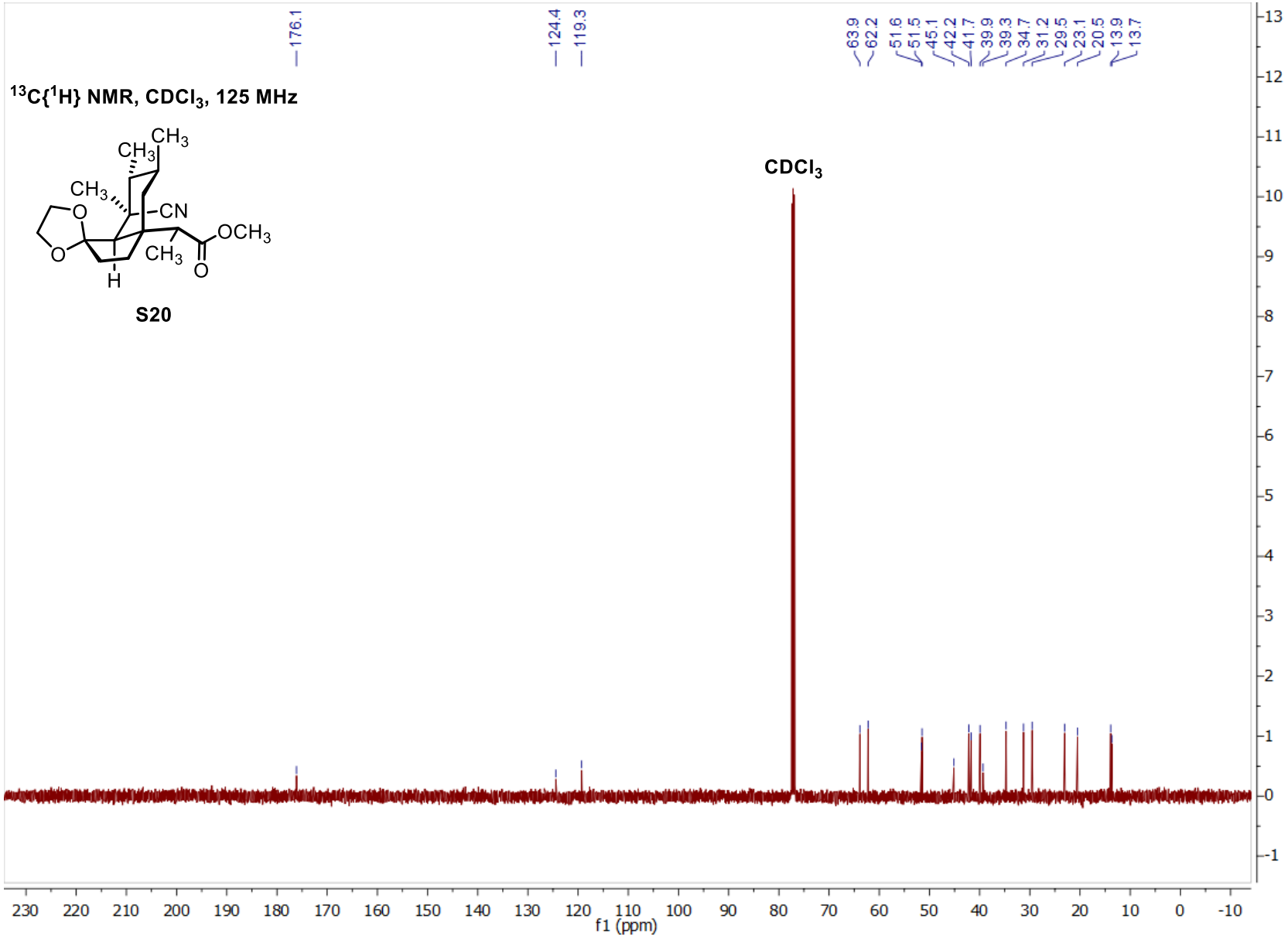

1H NMR, CDCl3, 500 MHz
CH3
CN
H
O
CH3
CH3
CH3O
O
S18
CHCl3
3.700
2.990
2.826
2.793
2.253
2.049
2.023
1.772
1.681
1.622
1.616
1.593
1.588
1.581
1.203
1.095
1.081
1.010
0.985
0.982
0.957
0.935
0.922
3.00
2.09
1.10
2.45
1.16
3.13
2.08
1.39
1.37
3.09
1.25
3.00
f1 (ppm)

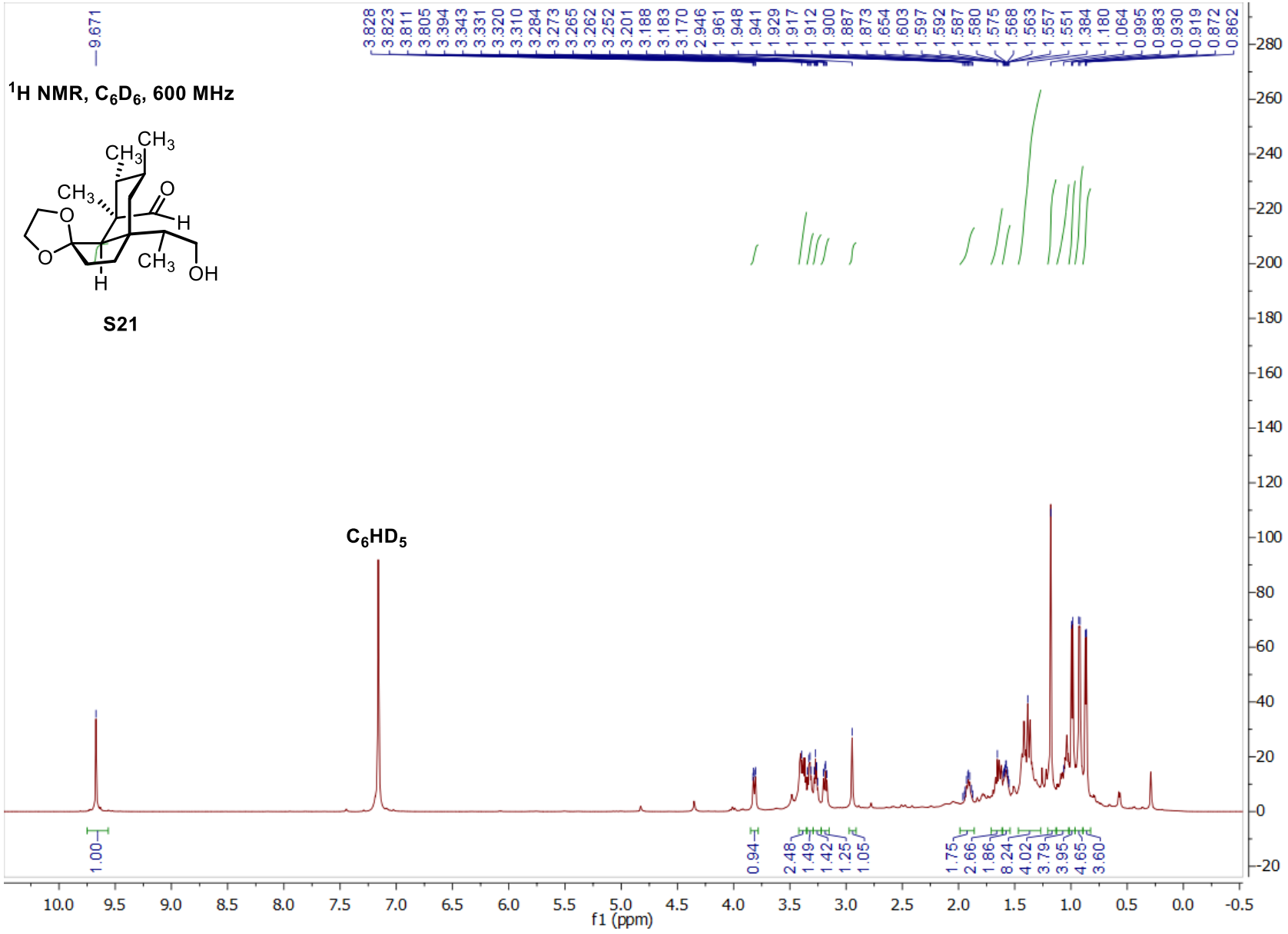

214.6
172.2
123.1
57.7
51.6
42.5
41.8
41.5
40.9
39.1
34.1
31.9
30.6
23.5
20.1
13.4
13C{1H} NMR, CDCl3, 150 MHz
CH3
CN
H
O
CH3
CH3
CH3O
O
S18
CDCl3
f1 (ppm)

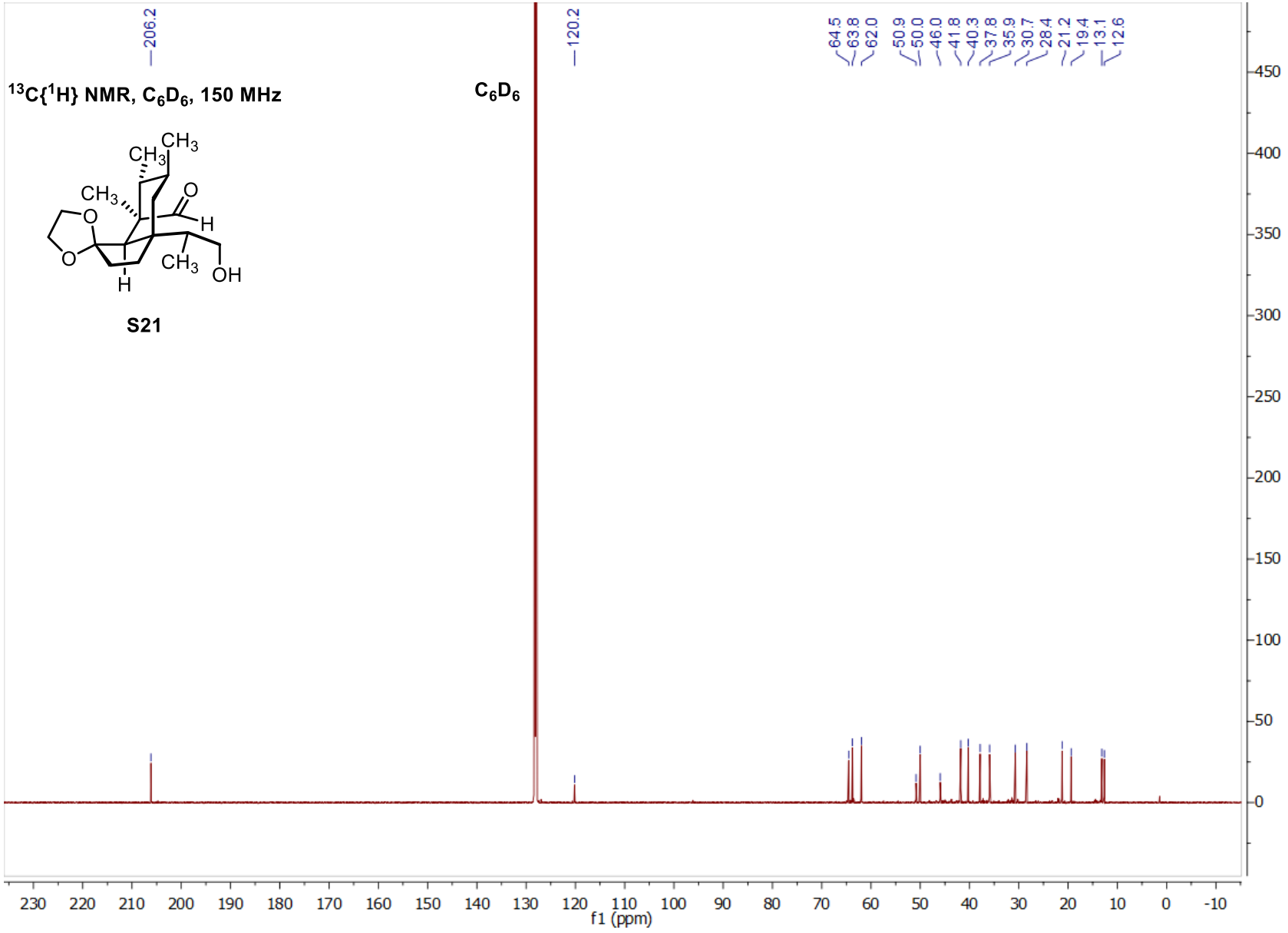

1H NMR, CDCl3, 400 MHz
CH3
CH3
CH3
CN
OCH3
O
O
O
H
S19
CHCl3
3.873
3.654
3.091
3.053
2.588
2.551
2.506
2.501
1.830
1.745
1.603
1.473
1.346
1.078
1.061
0.965
0.949
4.17
2.77
1.07
1.12
0.98
2.01
2.18
4.22
2.87
1.23
3.01
3.00
f1 (ppm)

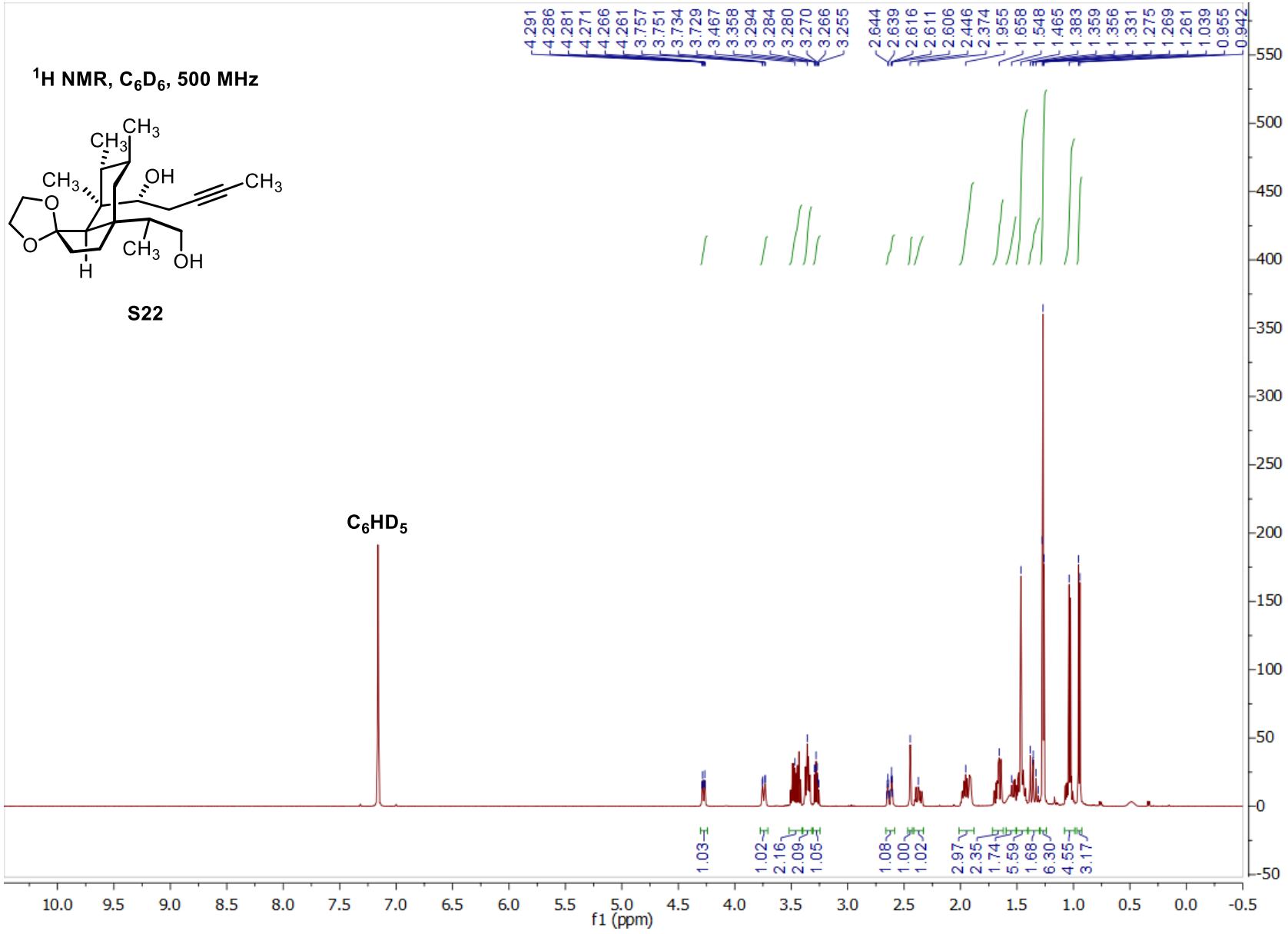

172.5
124.5
118.9
63.9
62.2
55.0
51.4
42.8
42.8
41.8
39.5
39.2
35.3
34.1
31.7
22.8
20.4
13.9
13C{1H} NMR, CDCl3, 100 MHz
CH3
CH3
CH3
CN
OCH3
O
O
O
H
S19
CDCl3
25
20
15
10
5
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

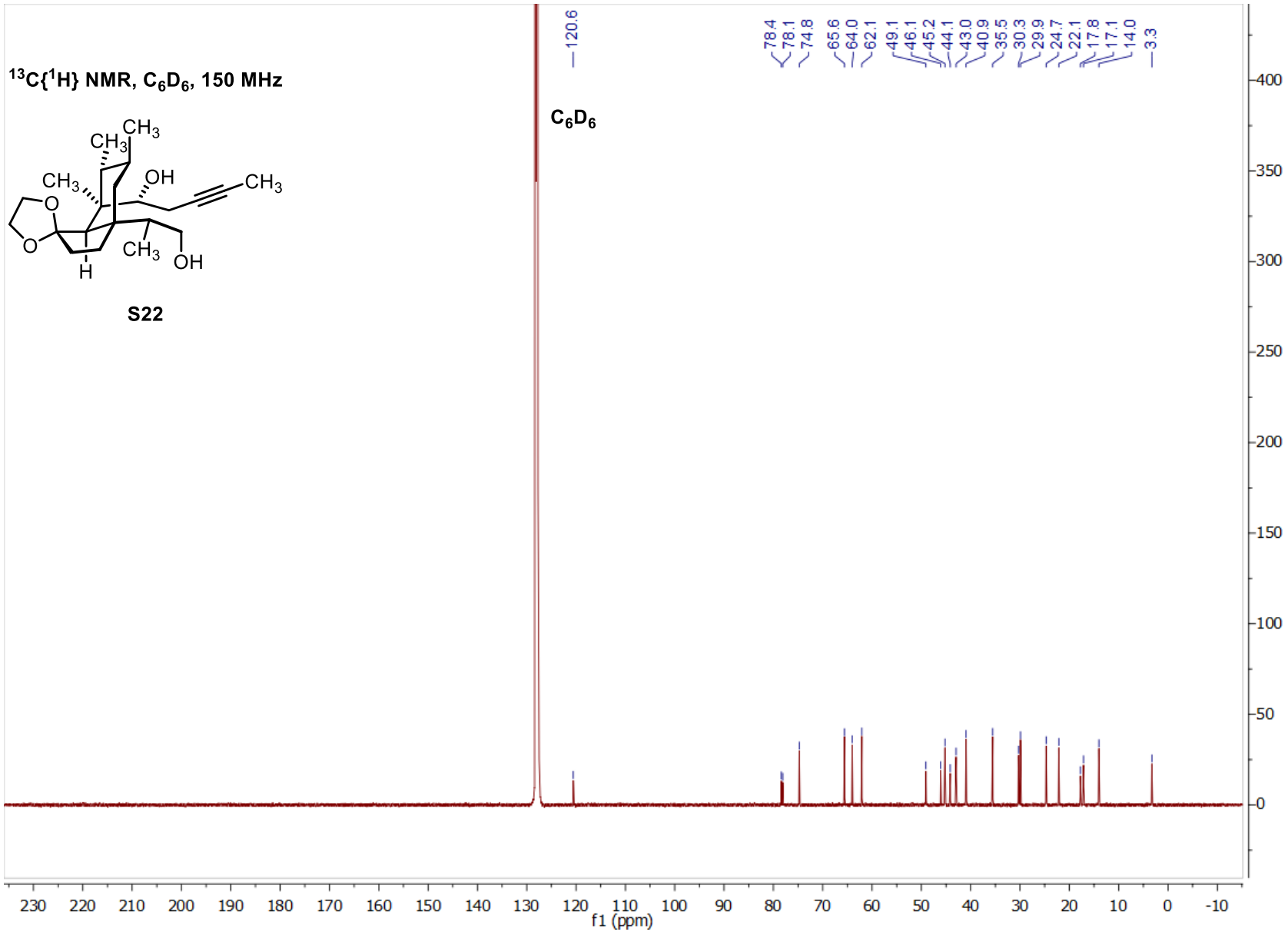

1H NMR, CDCl3, 500 MHz
S20
CHCl3
f1 (ppm)

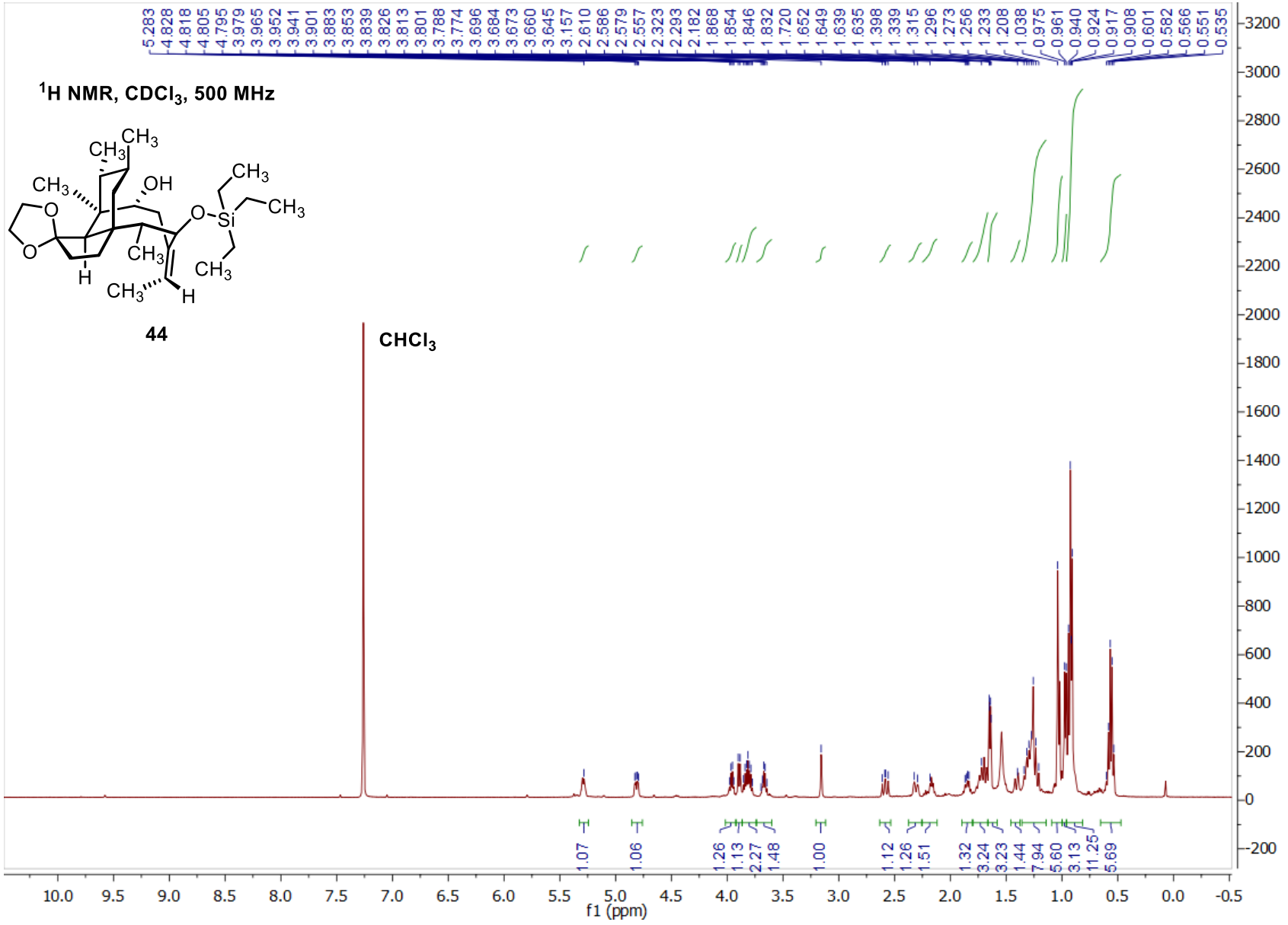

13C{1H} NMR, CDCl3, 125 MHz
S20
CDCl3
176.1
124.4
119.3
63.9
62.2
51.6
51.5
45.1
42.2
41.7
39.9
39.3
34.7
31.2
29.5
23.1
20.5
13.9
13.7
f1 (ppm)

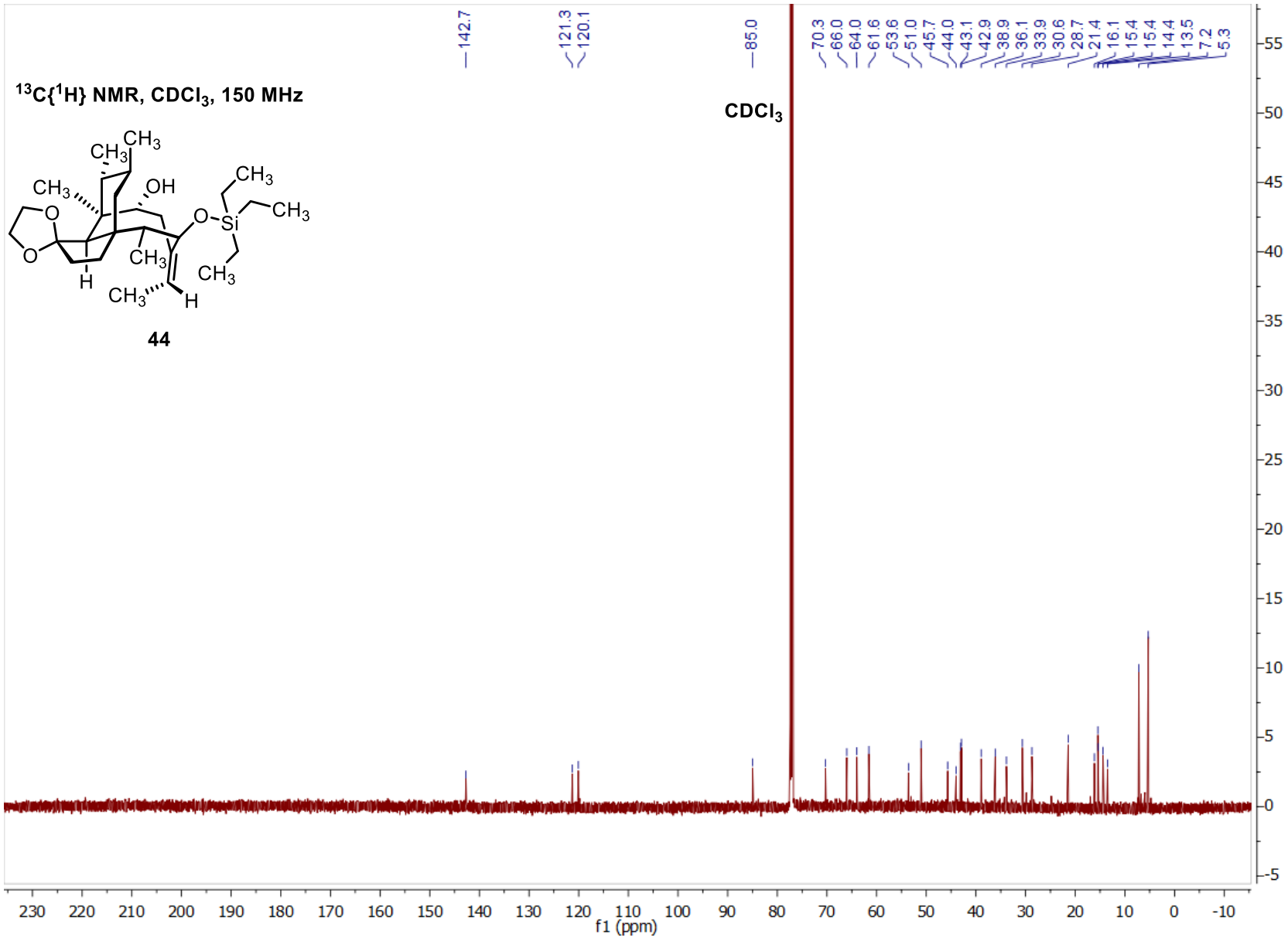

^{1}H NMR, C_6D_6, 600 MHz
S21
C_6HD_5
f1 (ppm)


206.2
120.2
64.5
63.8
62.0
50.9
50.0
46.0
41.8
40.3
37.8
35.9
30.7
28.4
21.2
19.4
13.1
12.6
13C{1H} NMR, C6D6, 150 MHz
C6D6
CH3
CH3
CH3
O
O
O
H
CH3
OH
H
S21
450
400
350
300
250
200
150
100
50
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

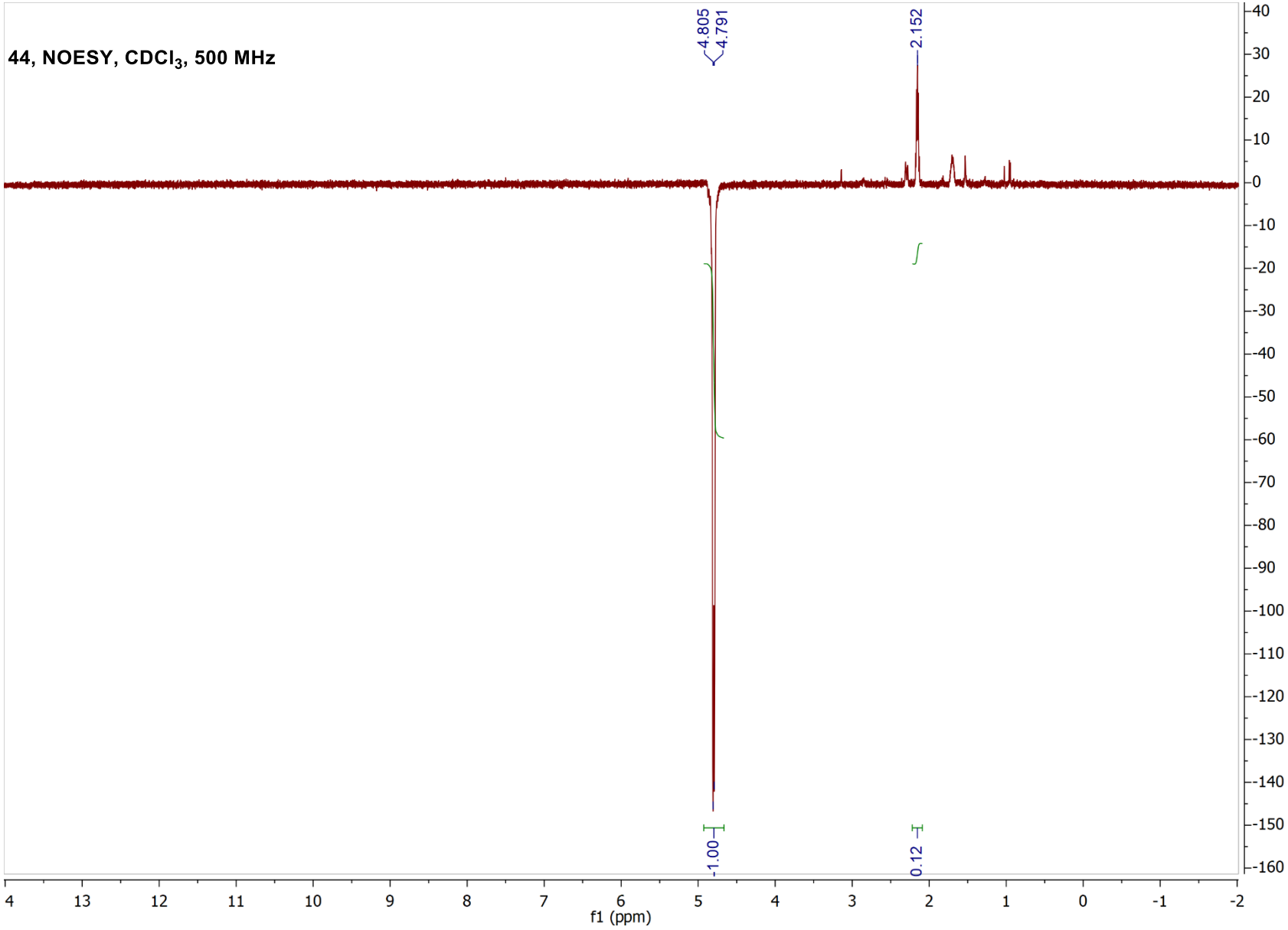

1H NMR, C6D6, 500 MHz
S22
C6HD5
f1 (ppm)

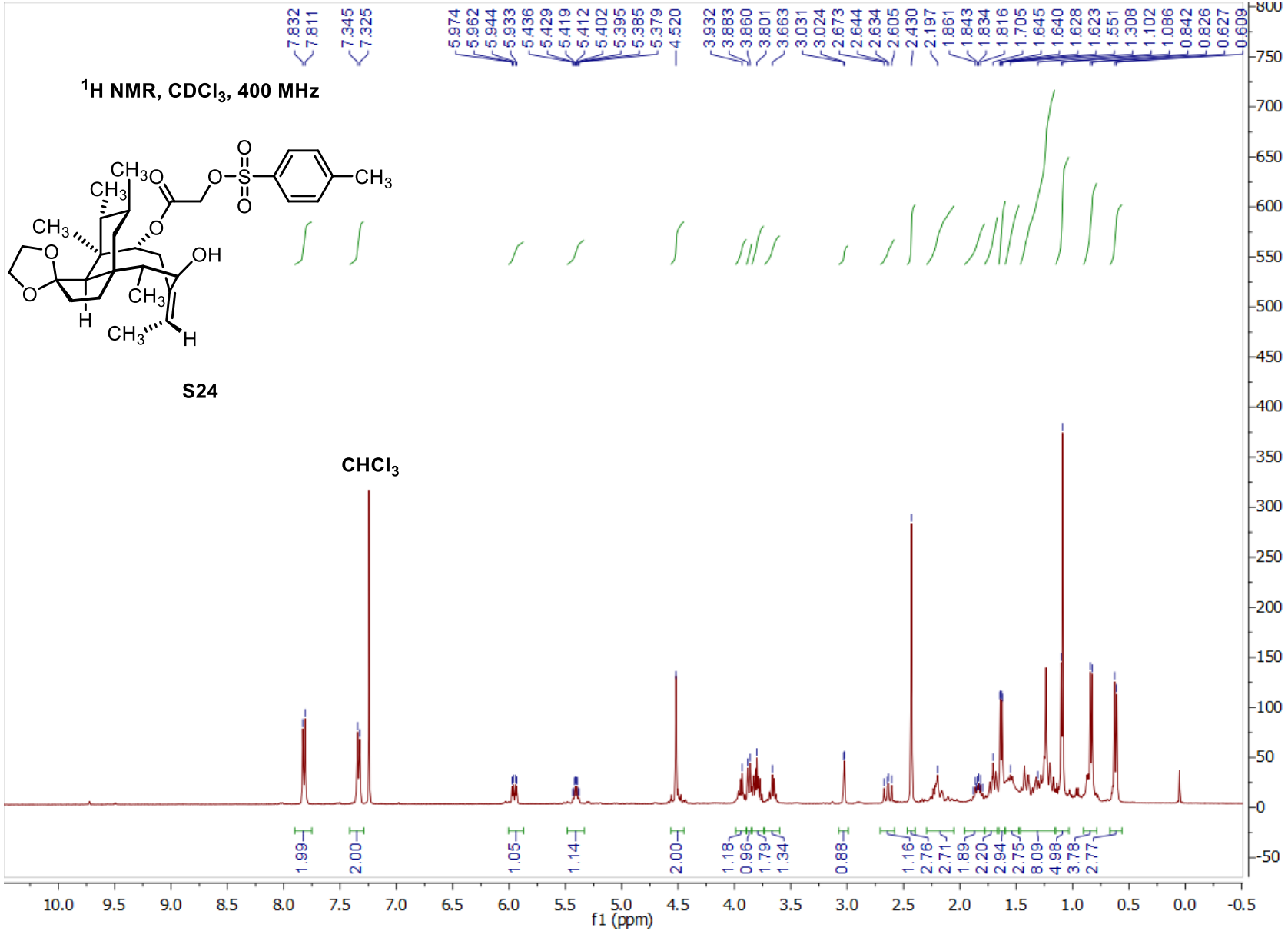

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
S22
C_6D_6
120.6
78.4
78.1
74.8
65.6
64.0
62.1
49.1
46.1
45.2
44.1
43.0
40.9
35.5
30.3
29.9
24.7
22.1
17.8
17.1
14.0
3.3
f1 (ppm)

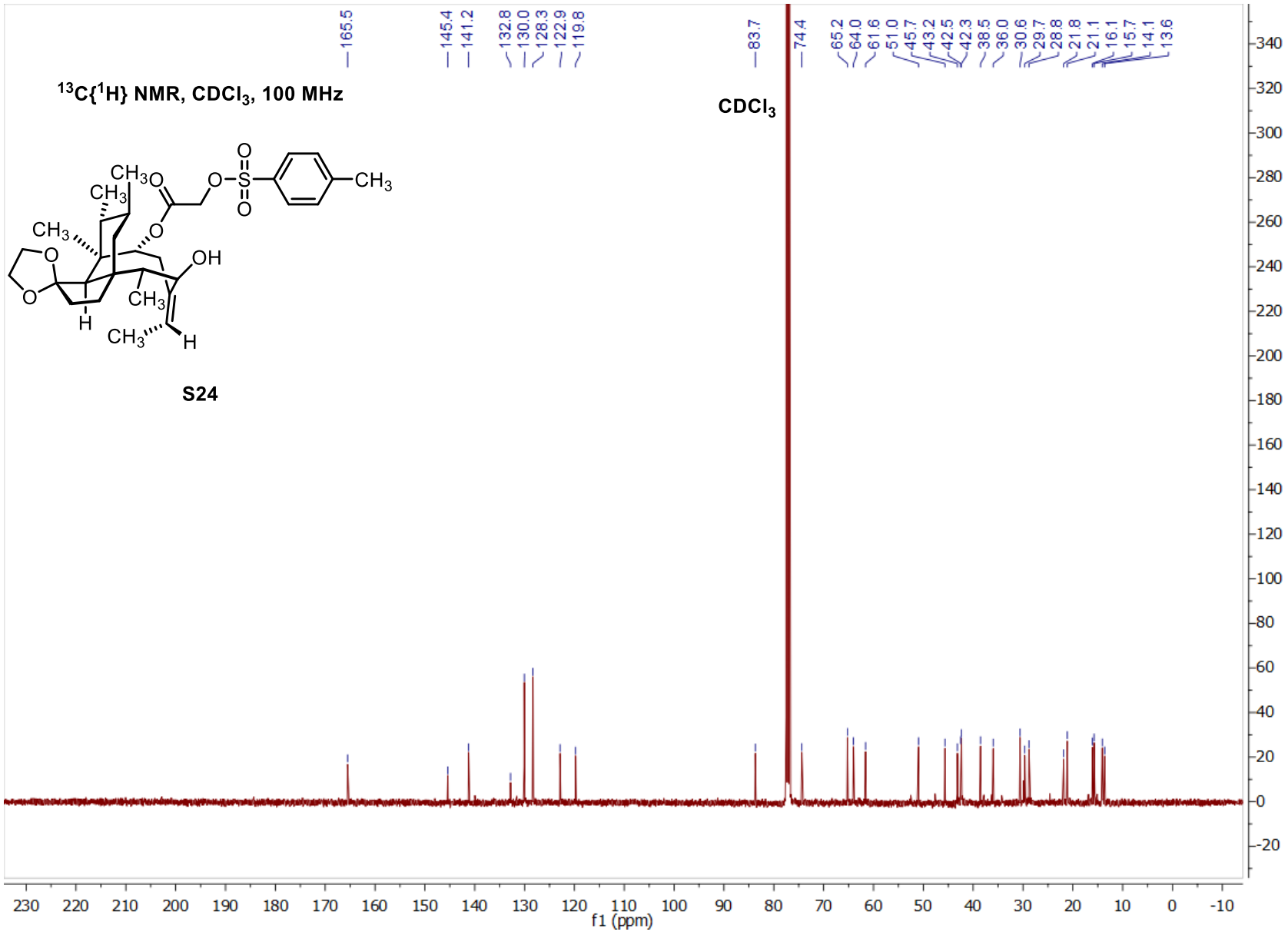

5.283
4.828
4.818
4.805
4.795
3.979
3.965
3.952
3.941
3.901
3.883
3.853
3.839
3.826
3.813
3.801
3.788
3.774
3.696
3.684
3.673
3.660
3.645
3.157
2.610
2.586
2.579
2.557
2.323
2.293
2.182
1.868
1.854
1.846
1.832
1.720
1.652
1.649
1.639
1.635
1.398
1.339
1.315
1.296
1.273
1.256
1.233
1.208
1.038
0.975
0.961
0.940
0.924
0.917
0.908
0.601
0.582
0.566
0.551
0.535
^{1}H NMR, $CDCl_3$, 500 MHz
CH3
CH3
CH3
OH
O
O
Si
CH3
CH3
CH3
CH3
H
H
44
$CHCl_3$
1.07
1.06
1.26
1.13
2.27
1.48
1.00
1.12
1.26
1.51
1.32
3.24
3.23
1.44
7.94
5.60
3.13
11.25
5.69
f1 (ppm)

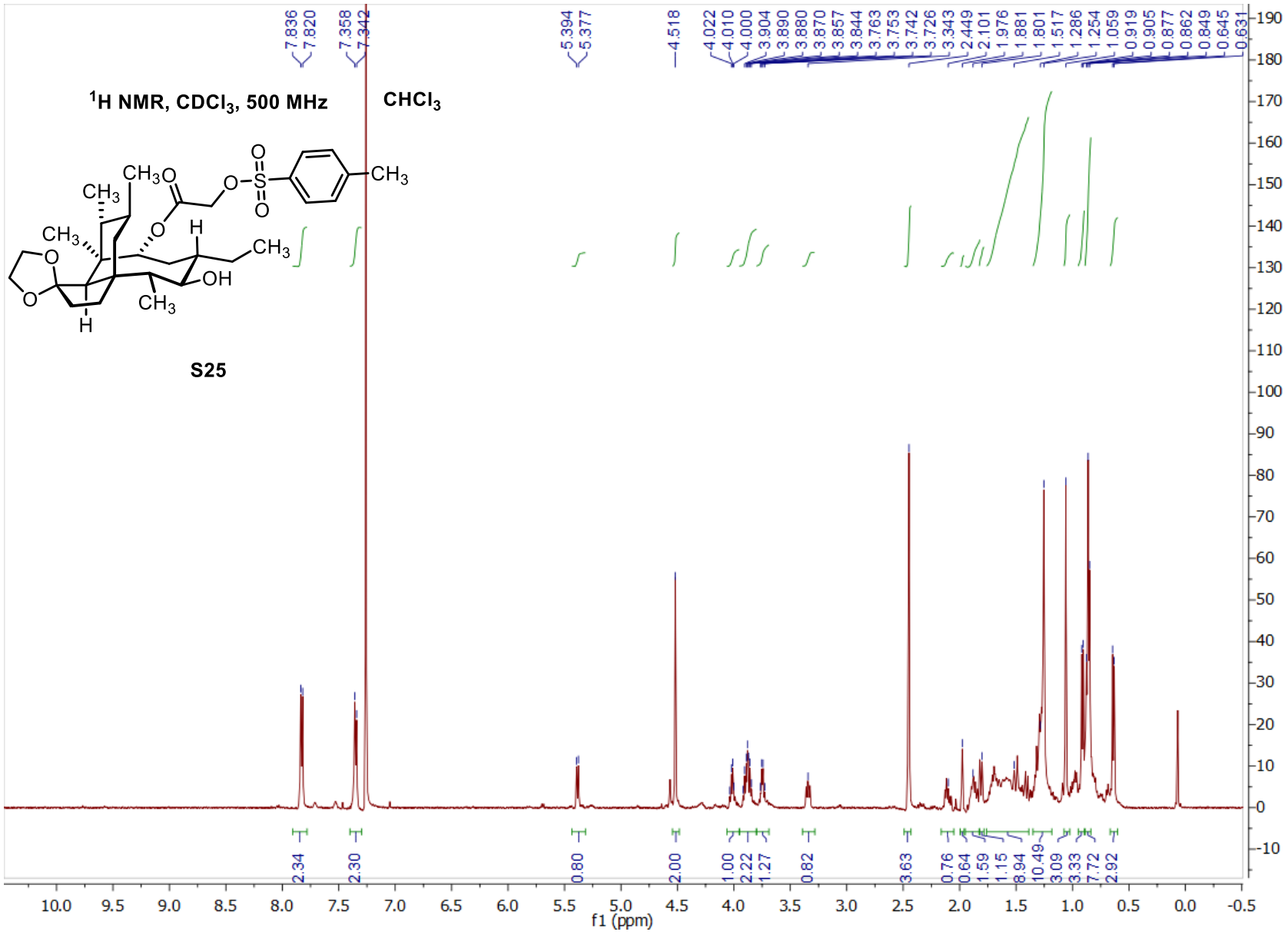

13C{1H} NMR, CDCl3, 150 MHz
CDCl3
142.7
121.3
120.1
85.0
70.3
66.0
64.0
61.6
53.6
51.0
45.7
44.0
43.1
42.9
38.9
36.1
33.9
30.6
28.7
21.4
16.1
15.4
15.4
14.4
13.5
7.2
5.3
f1 (ppm)

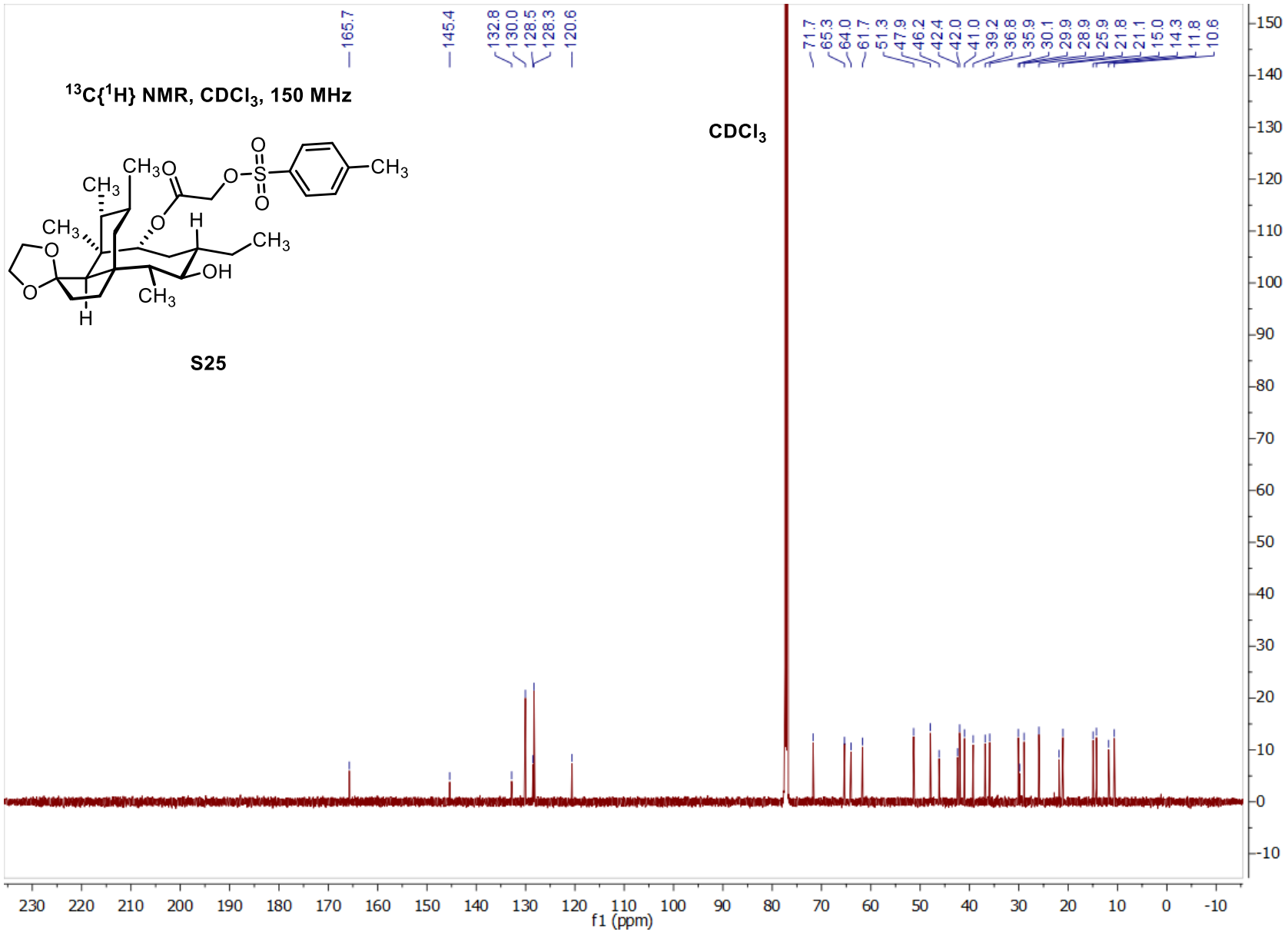
44

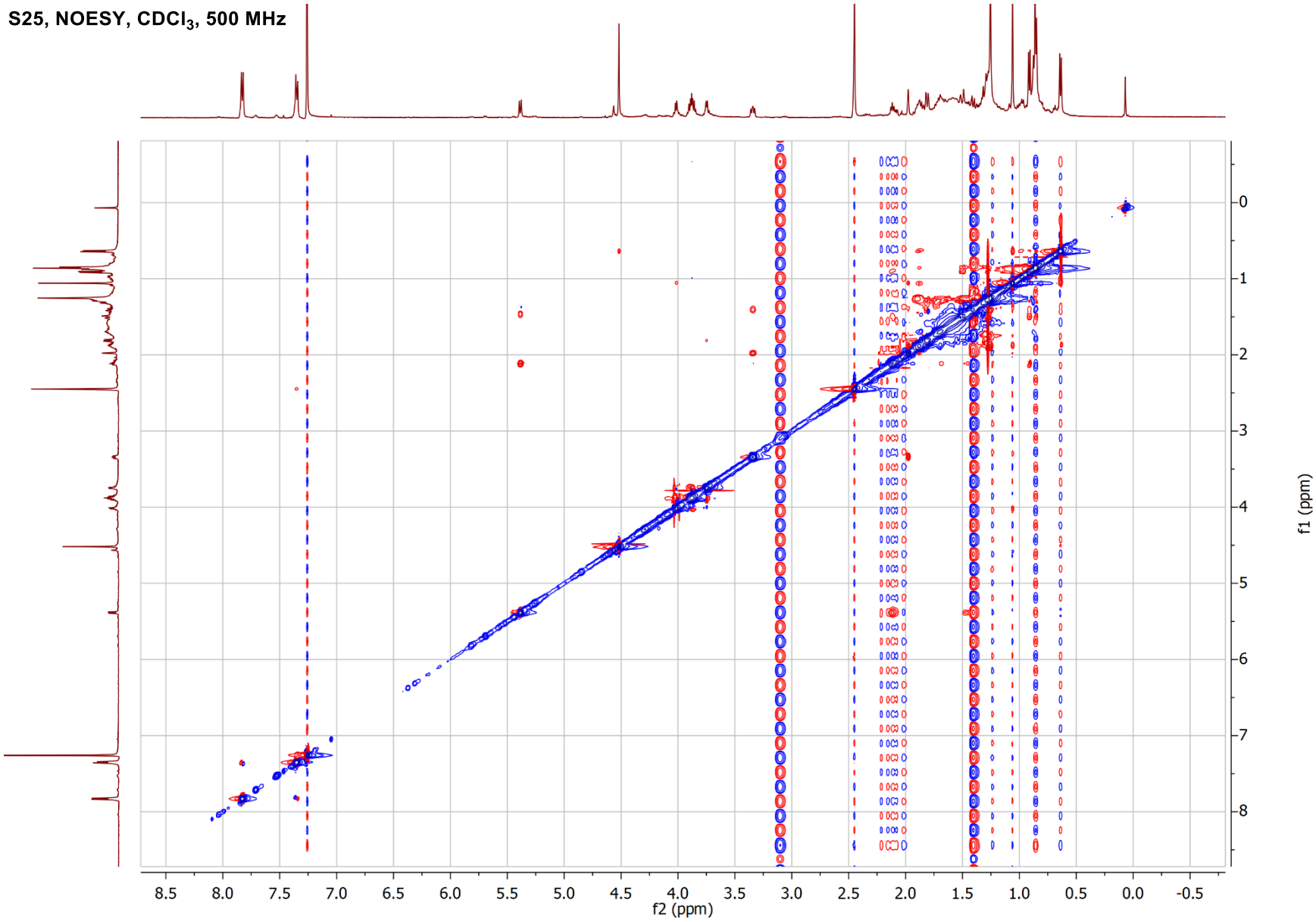

44, NOESY, CDCl3, 500 MHz
4.805
4.791
2.152
1.00
0.12
f1 (ppm)

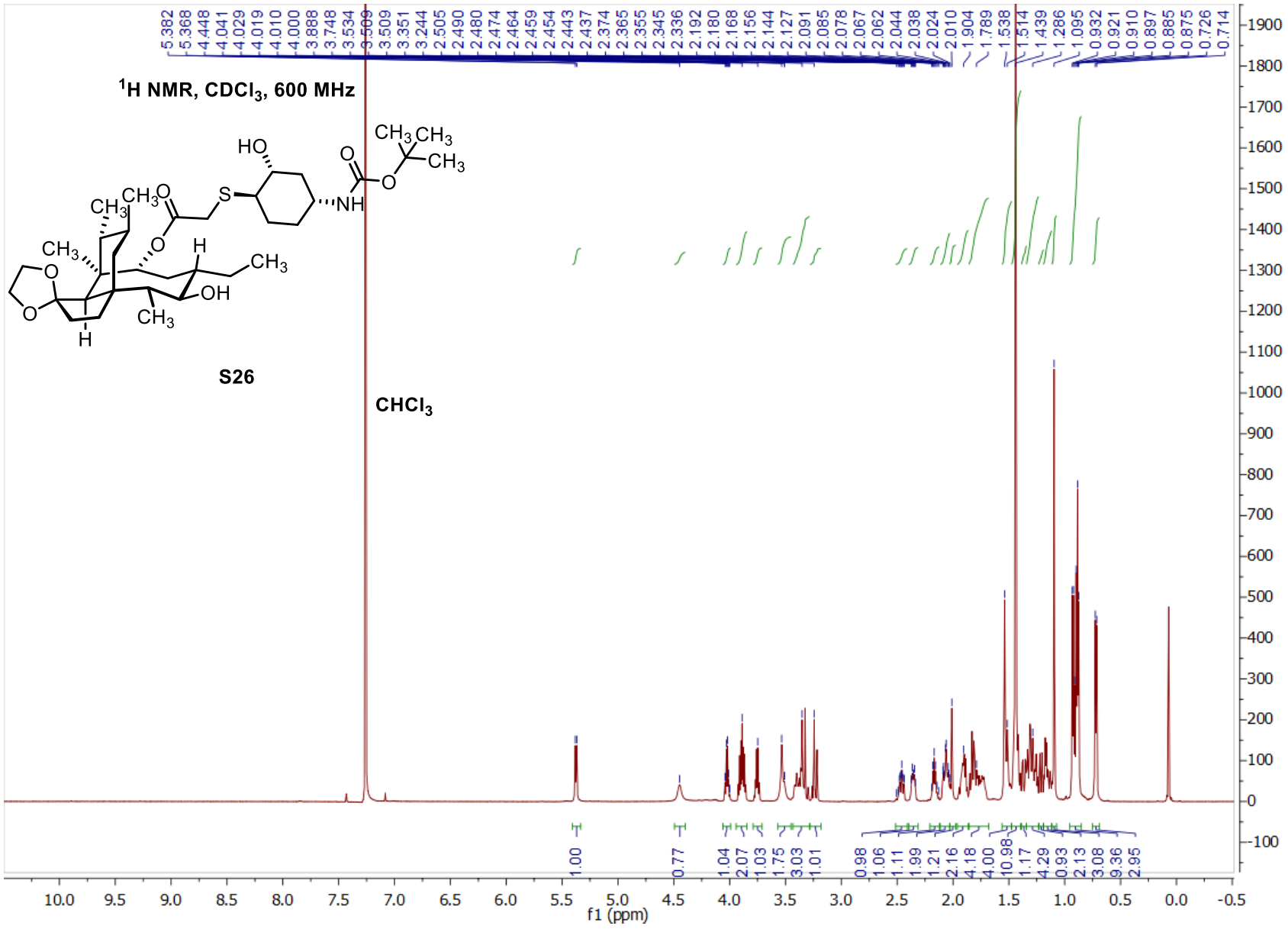

^{1}H NMR, $CDCl_3$, 400 MHz
S24
$CHCl_3$
f1 (ppm)

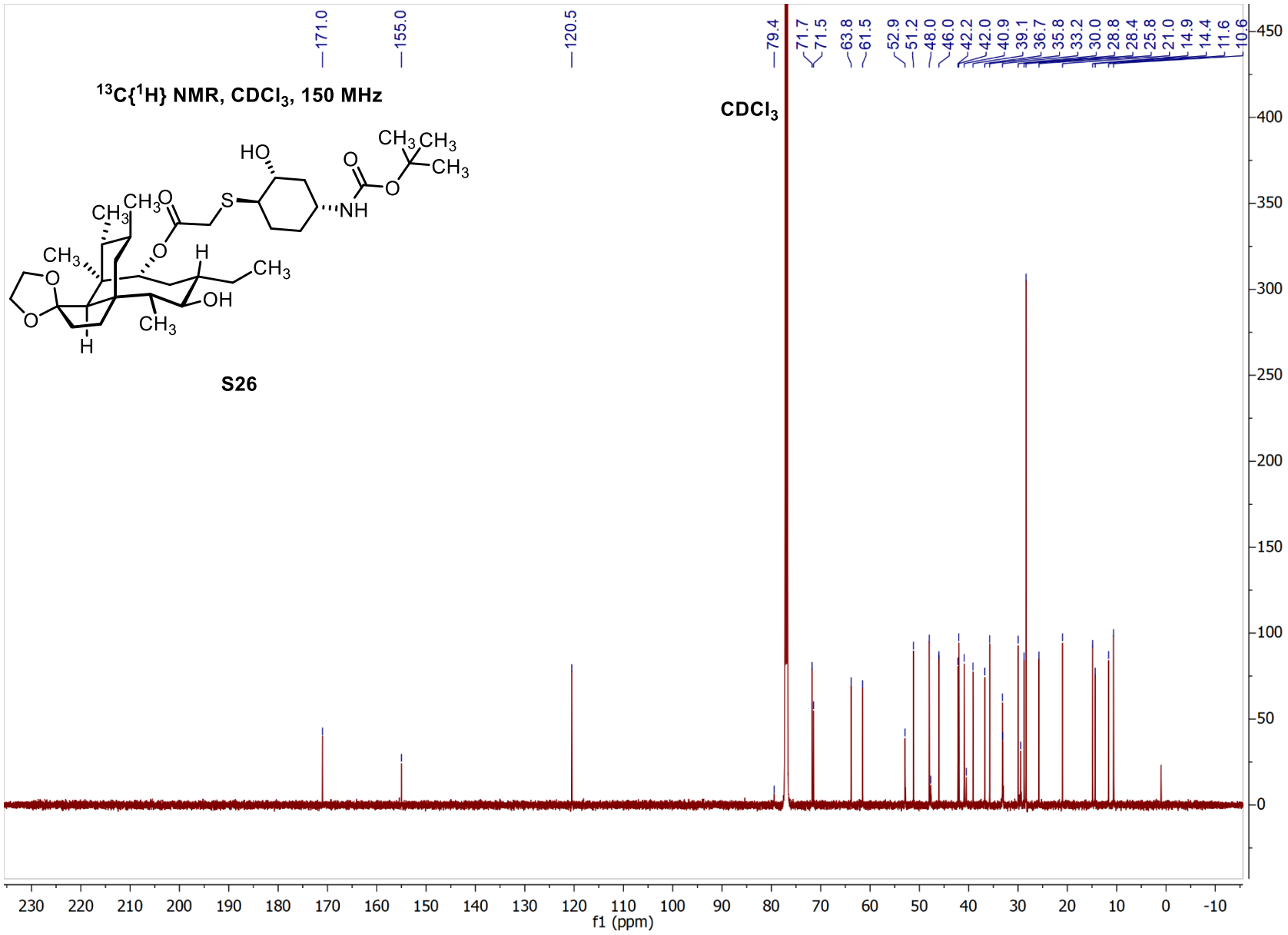

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 100 MHz
$CDCl_3$
S24
165.5
145.4
141.2
132.8
130.0
128.3
122.9
119.8
83.7
74.4
65.2
64.0
61.6
51.0
45.7
43.2
42.5
42.3
38.5
36.0
30.6
29.7
28.8
21.8
21.1
16.1
15.7
14.1
13.6
f1 (ppm)

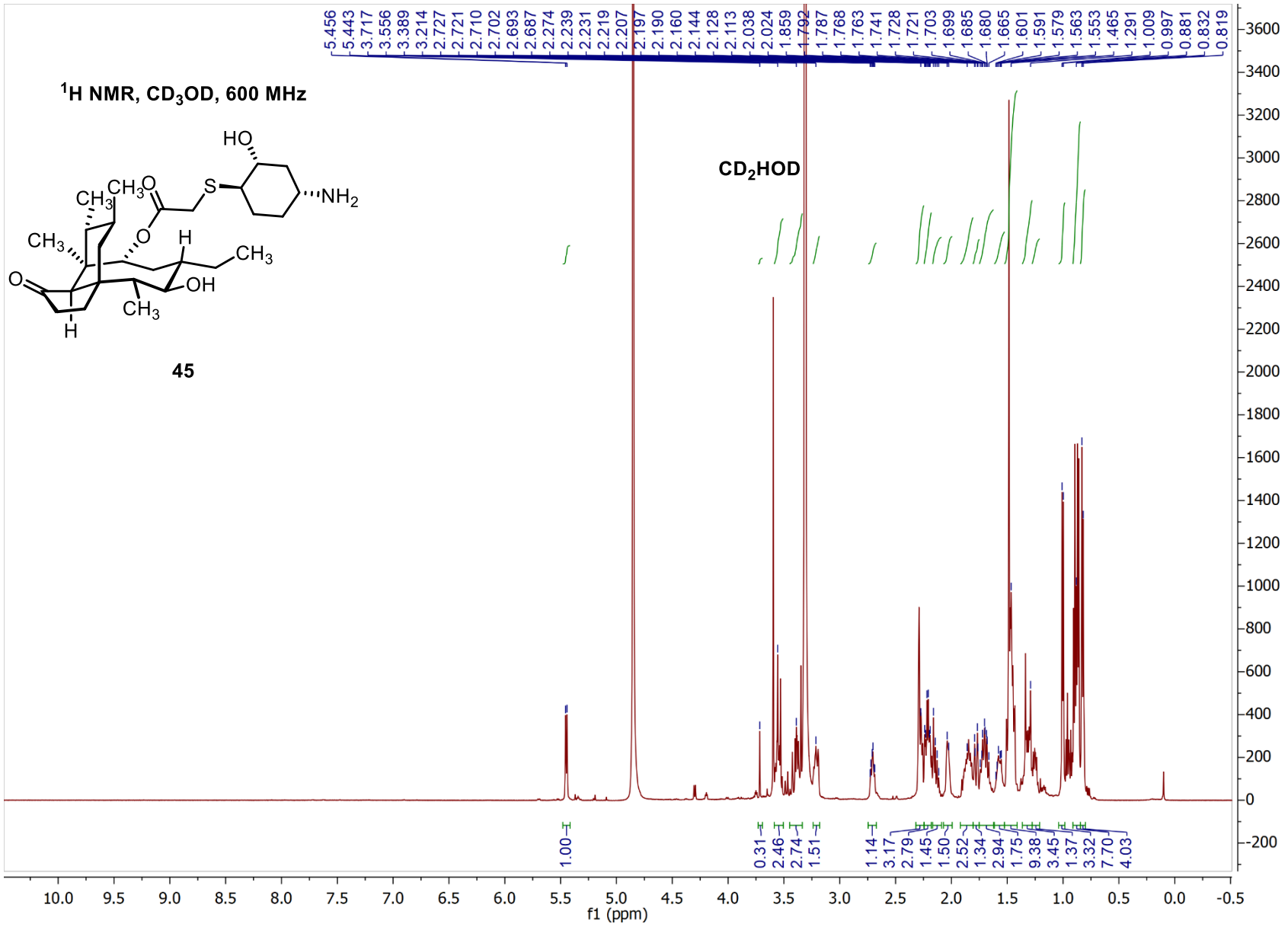

^{1}H NMR, $CDCl_3$, 500 MHz
$CHCl_3$
S25
f1 (ppm)

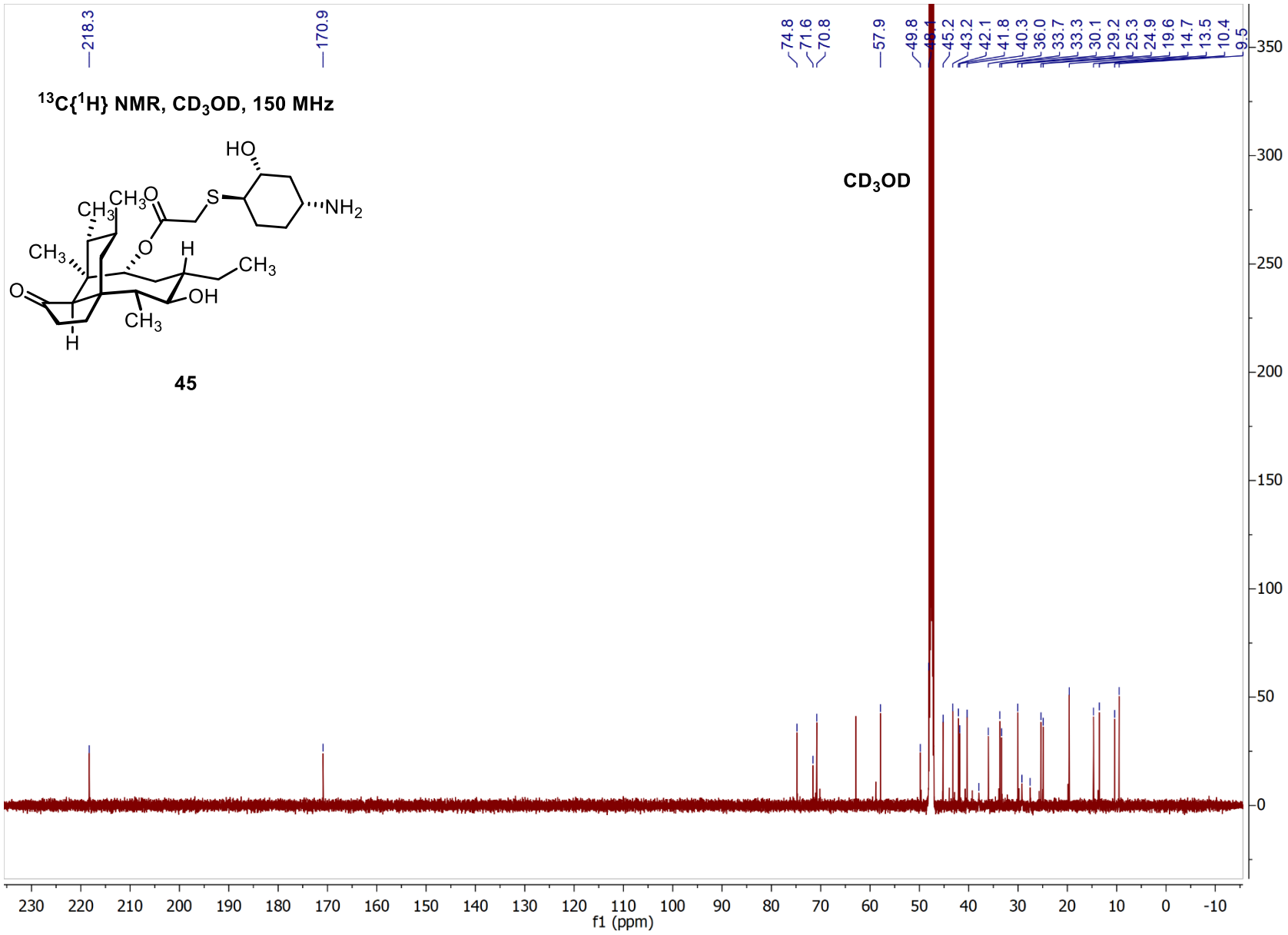

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S25
$CDCl_3$
165.7
145.4
132.8
130.0
128.5
128.3
120.6
71.7
65.3
64.0
61.7
51.3
47.9
46.2
42.4
42.0
41.0
39.2
36.8
35.9
30.1
29.9
28.9
25.9
21.8
21.1
15.0
14.3
11.8
10.6
f1 (ppm)

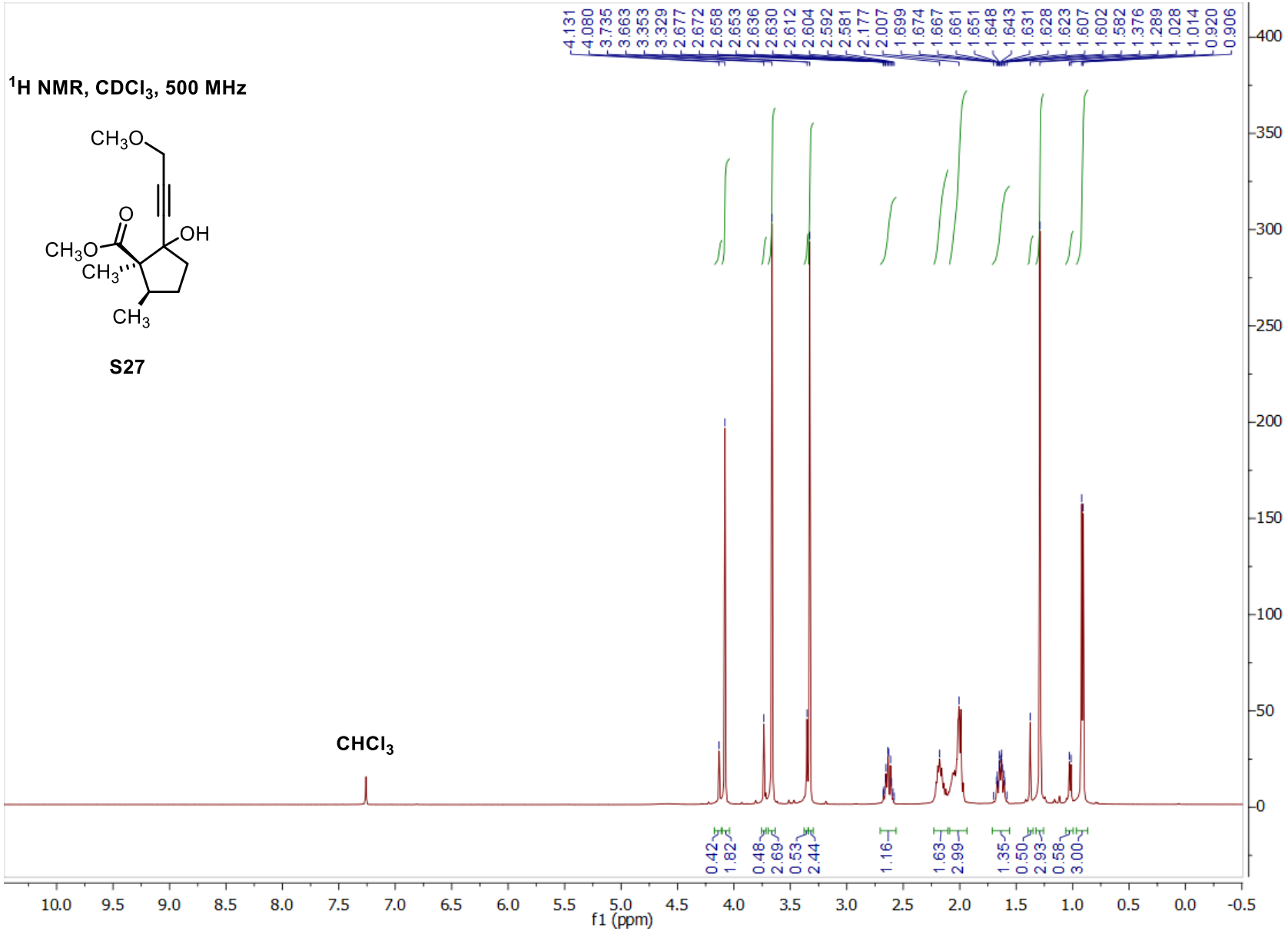

S25, NOESY, CDCl3, 500 MHz
f2 (ppm)
f1 (ppm)

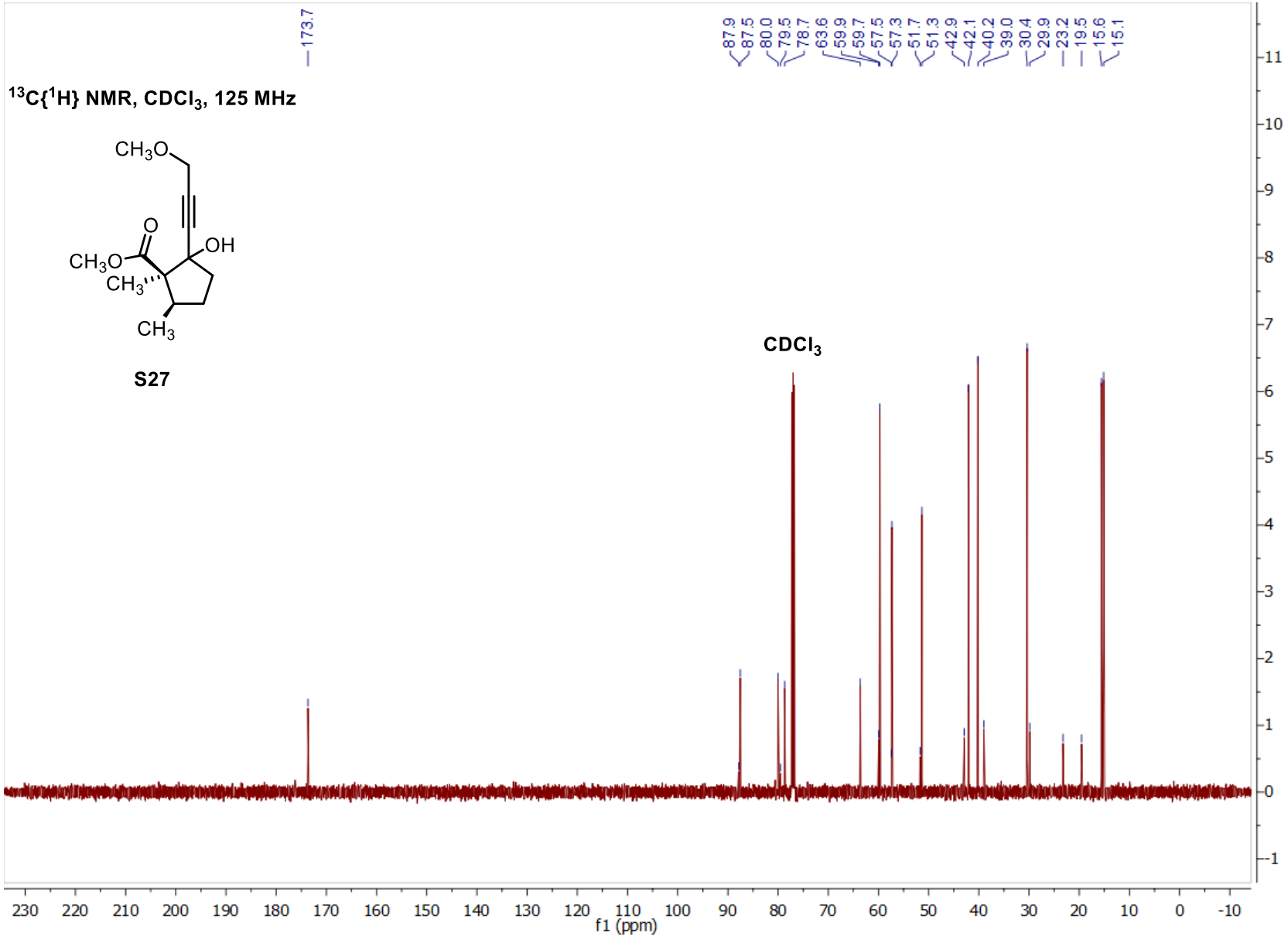

1H NMR, CDCl3, 600 MHz
S26
CHCl3
f1 (ppm)

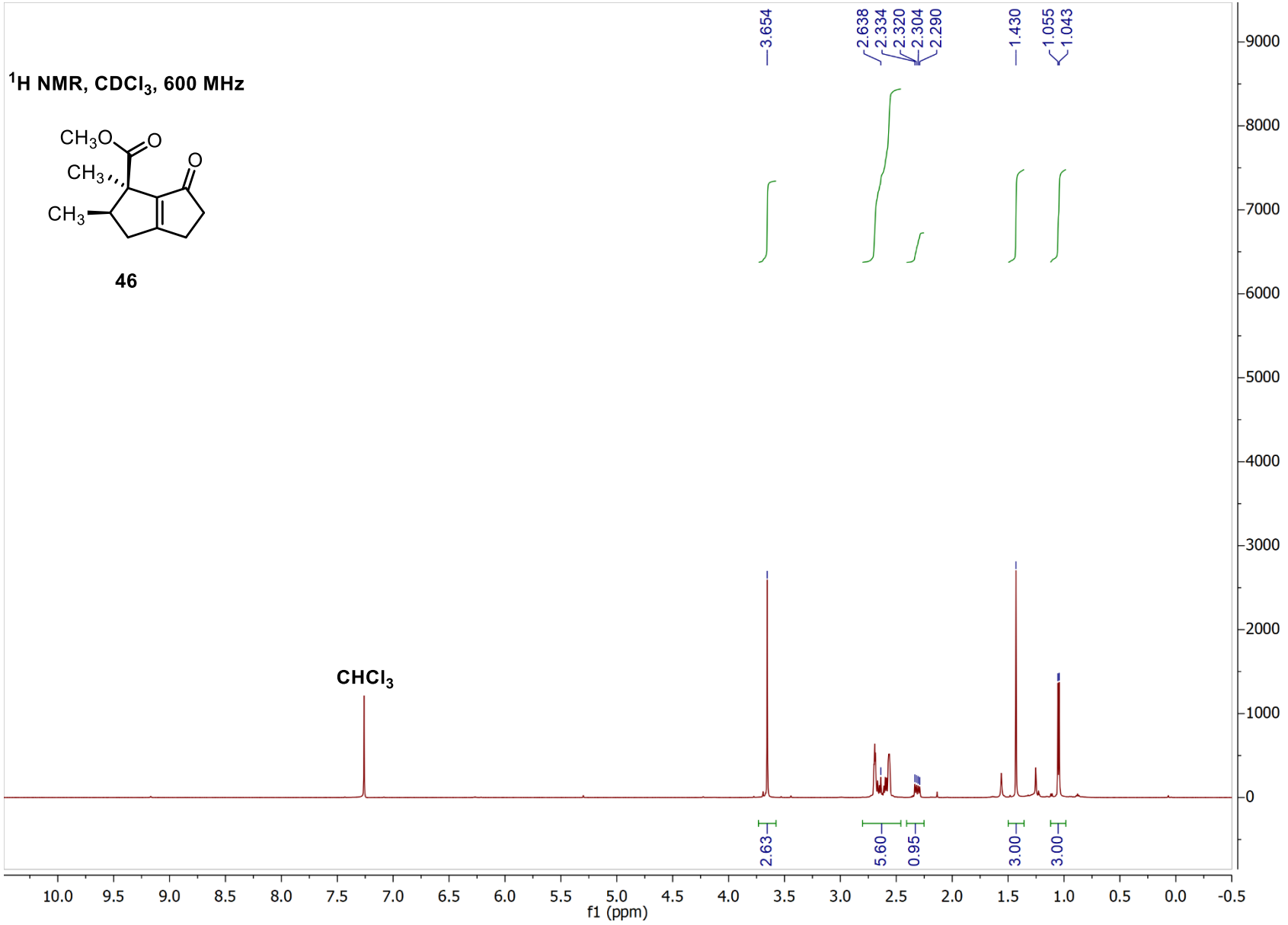

13C{1H} NMR, CDCl3, 150 MHz
CDCl3
171.0
155.0
120.5
79.4
71.7
71.5
63.8
61.5
52.9
51.2
48.0
46.0
42.2
42.0
40.9
39.1
36.7
35.8
33.2
30.0
28.8
28.4
25.8
21.0
14.9
14.4
11.6
10.6
S26
f1 (ppm)

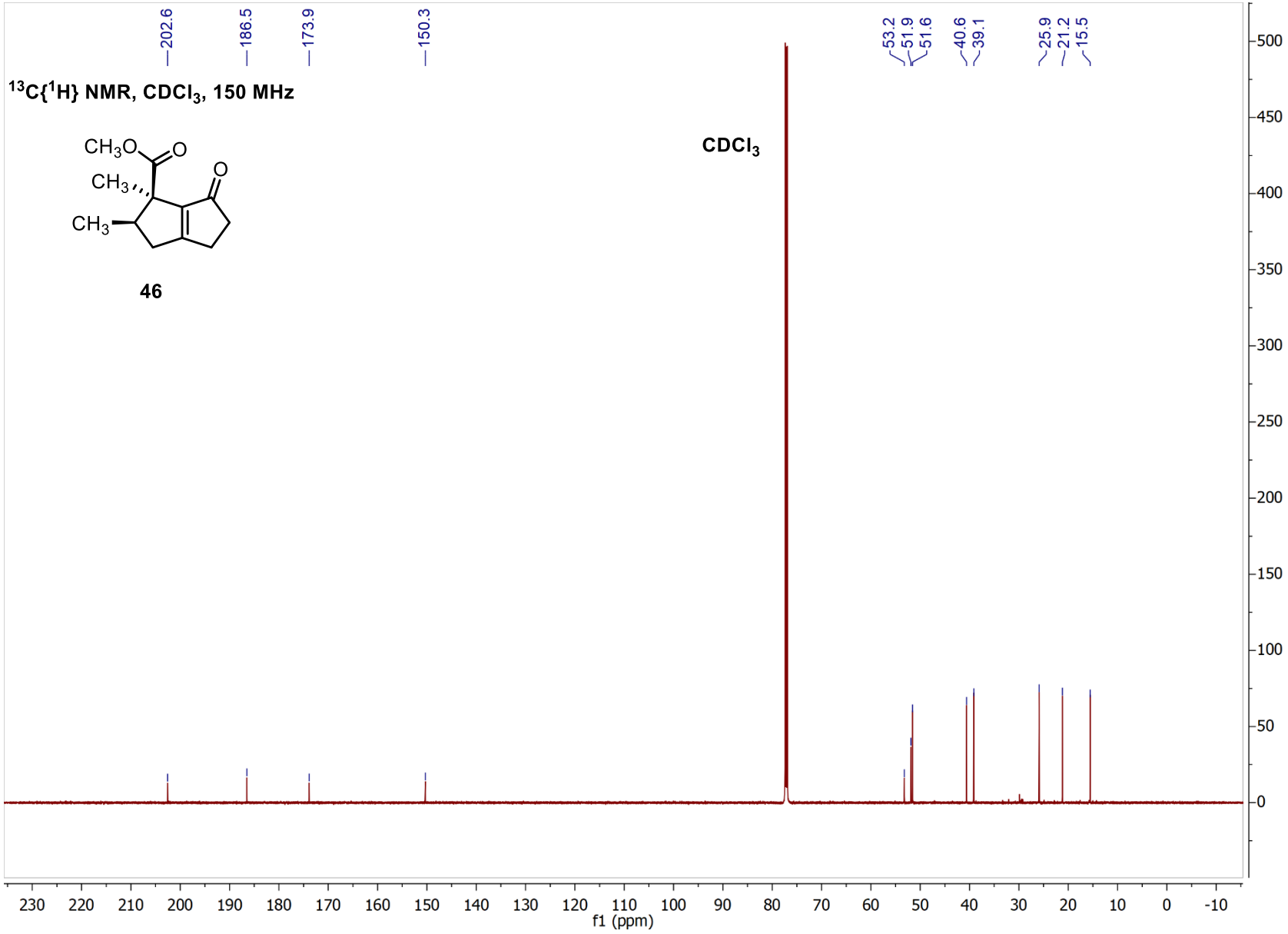

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
45

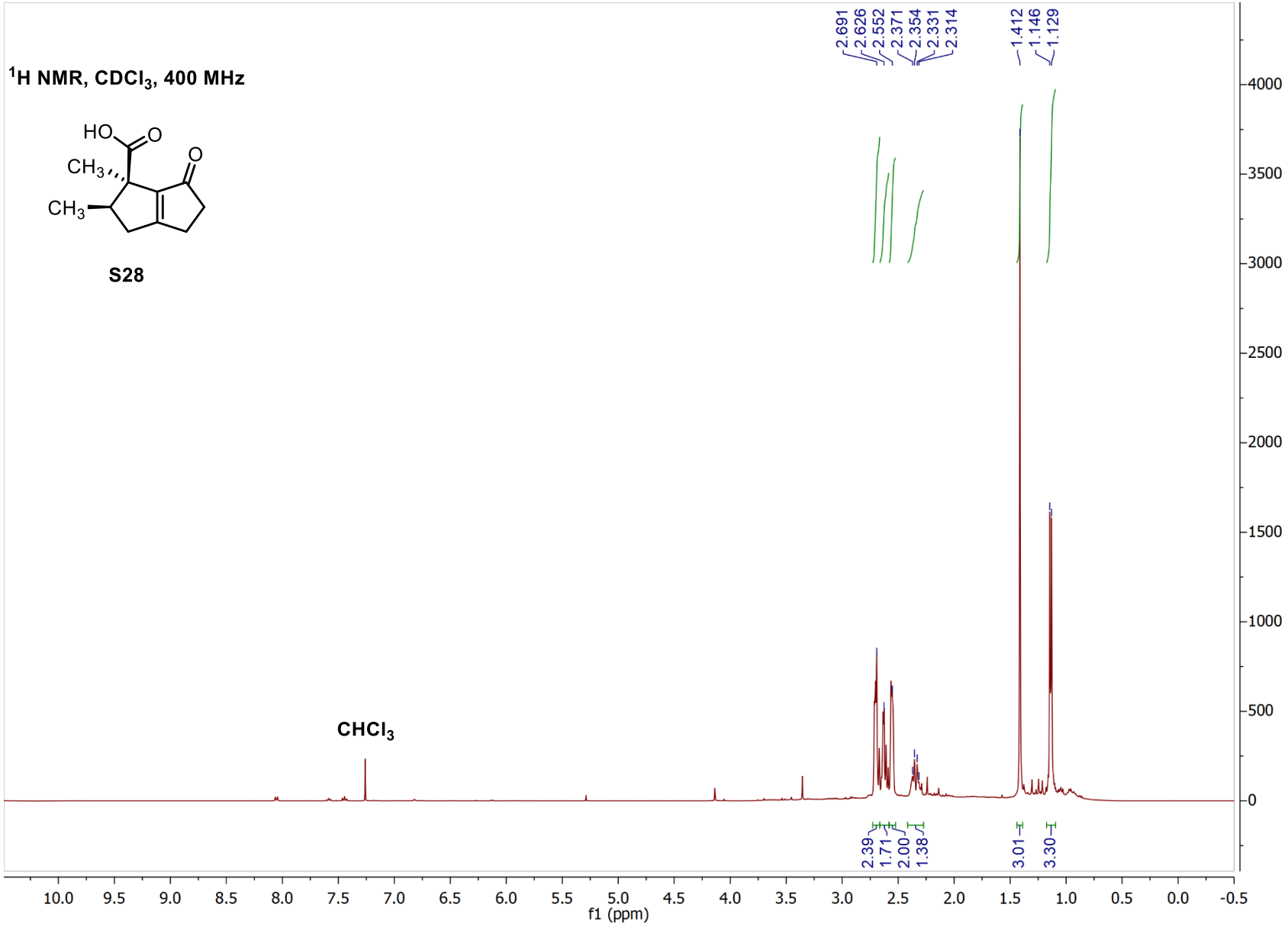

218.3
170.9
74.8
71.6
70.8
57.9
49.8
49.1
45.2
43.2
42.1
41.8
40.3
36.0
33.7
33.3
30.1
29.2
25.3
24.9
19.6
14.7
13.5
10.4
9.5
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
45
f1 (ppm)

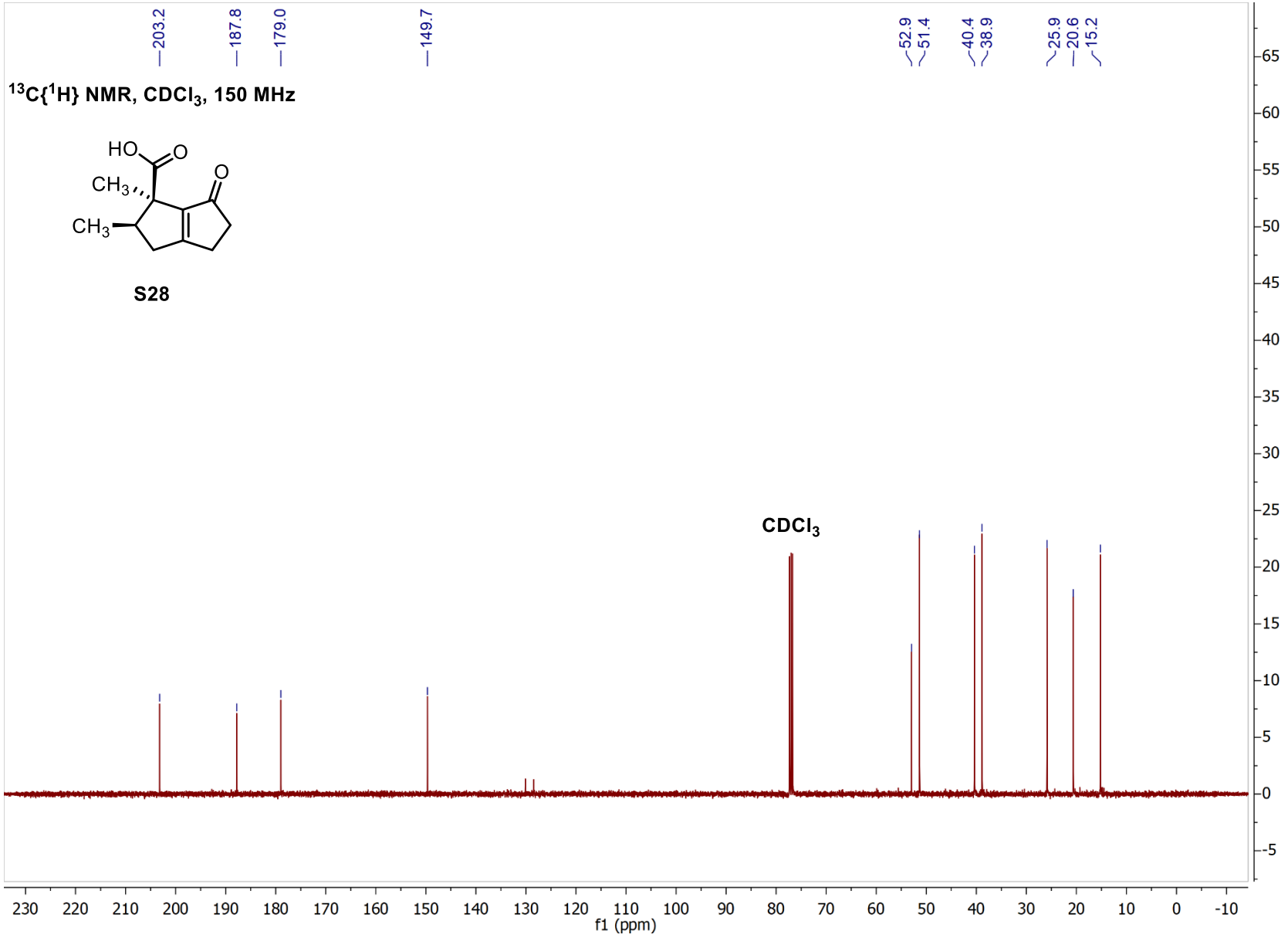

1H NMR, CDCl3, 500 MHz
CH3O
O
CH3O
OH
CH3
CH3
S27
CHCl3
4.131
4.080
3.735
3.663
3.353
3.329
2.677
2.672
2.658
2.653
2.636
2.630
2.612
2.604
2.592
2.581
2.177
2.007
1.699
1.674
1.667
1.661
1.651
1.648
1.643
1.631
1.628
1.623
1.607
1.602
1.582
1.376
1.289
1.028
1.014
0.920
0.906
0.42
1.82
0.48
2.69
0.53
2.44
1.16
1.63
2.99
1.35
0.50
2.93
0.58
3.00
f1 (ppm)

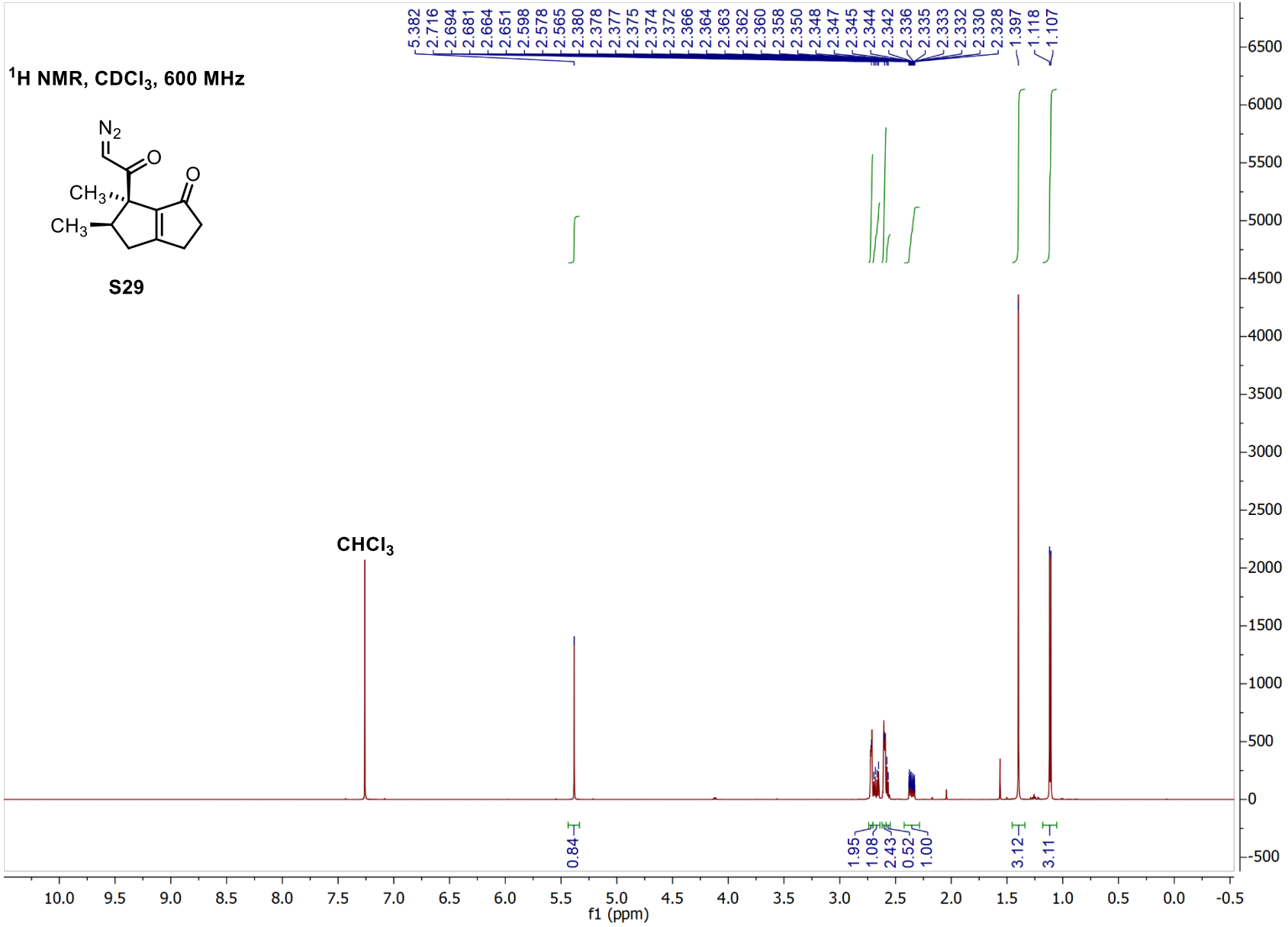

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 125 MHz
S27
$CDCl_3$
173.7
87.9
87.5
80.0
79.5
78.7
63.6
59.9
59.7
57.5
57.3
51.7
51.3
42.9
42.1
40.2
39.0
30.4
29.9
23.2
19.5
15.6
15.1
f1 (ppm)

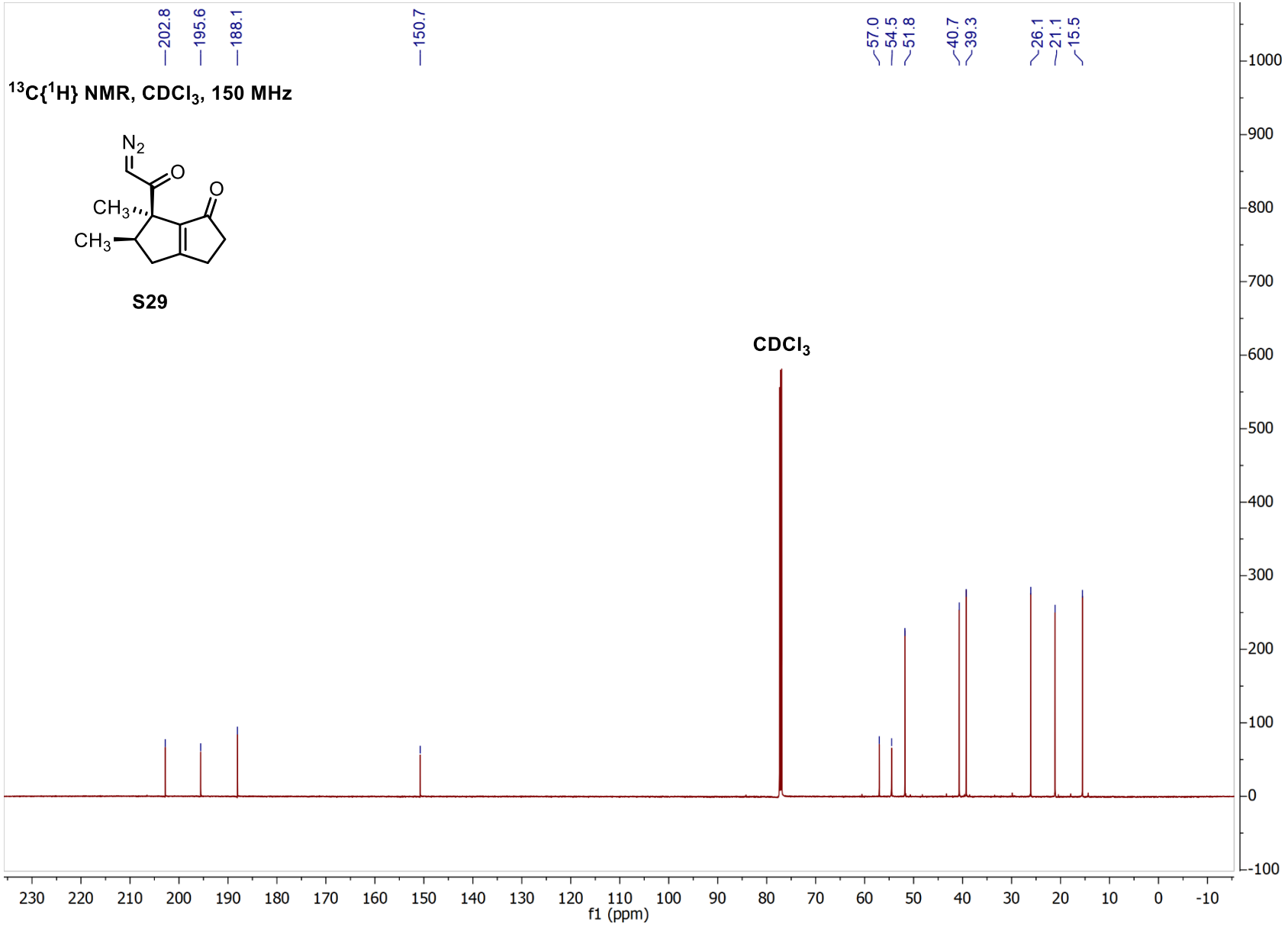

1H NMR, CDCl3, 600 MHz
CH3O
O
CH3
O
CH3
46
3.654
2.638
2.334
2.320
2.304
2.290
1.430
1.055
1.043
CHCl3
2.63
5.60
0.95
3.00
3.00
f1 (ppm)

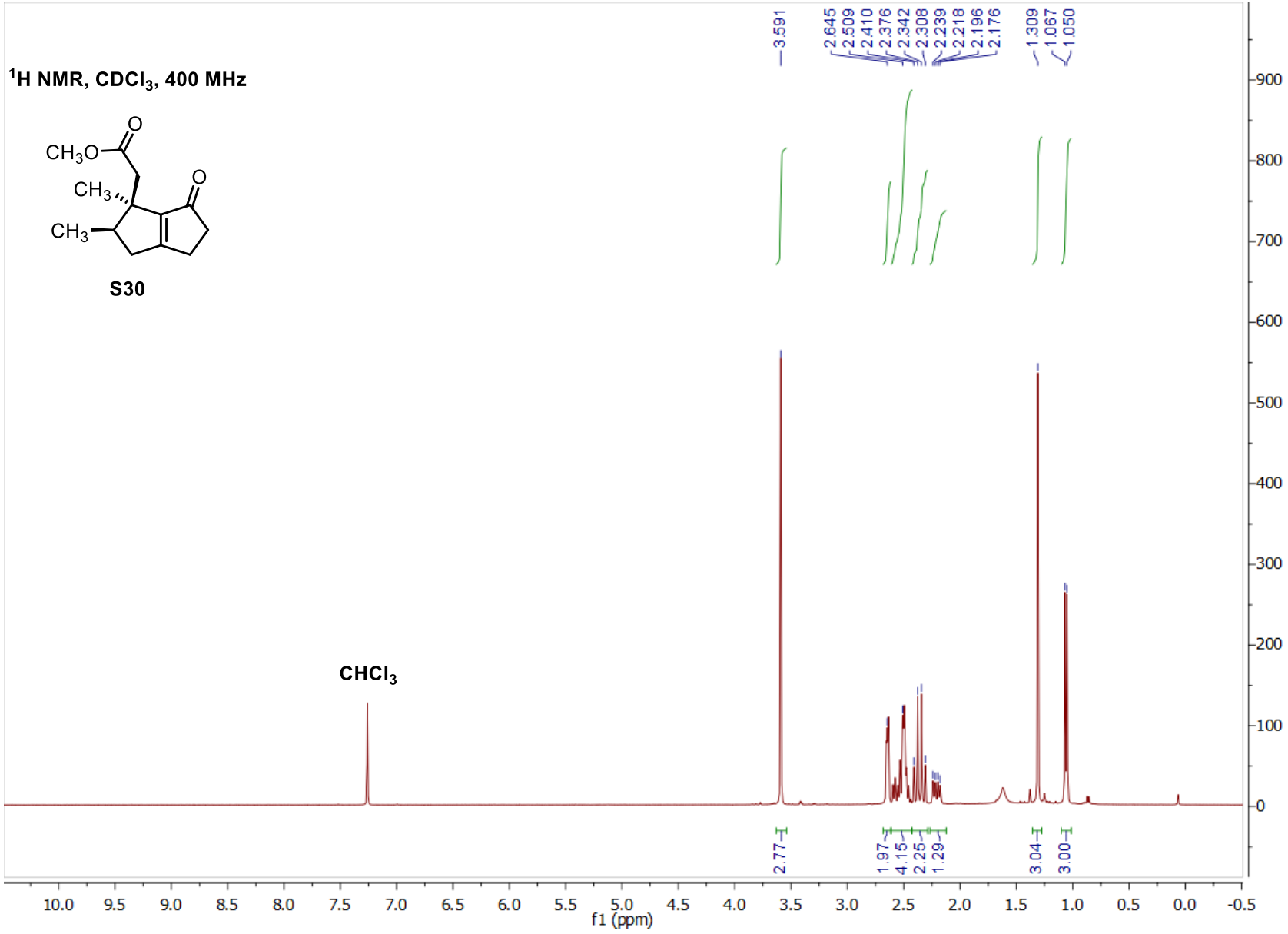

202.6
186.5
173.9
150.3
53.2
51.9
51.6
40.6
39.1
25.9
21.2
15.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
CH3O
O
CH3
O
CH3
46
500
450
400
350
300
250
200
150
100
50
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

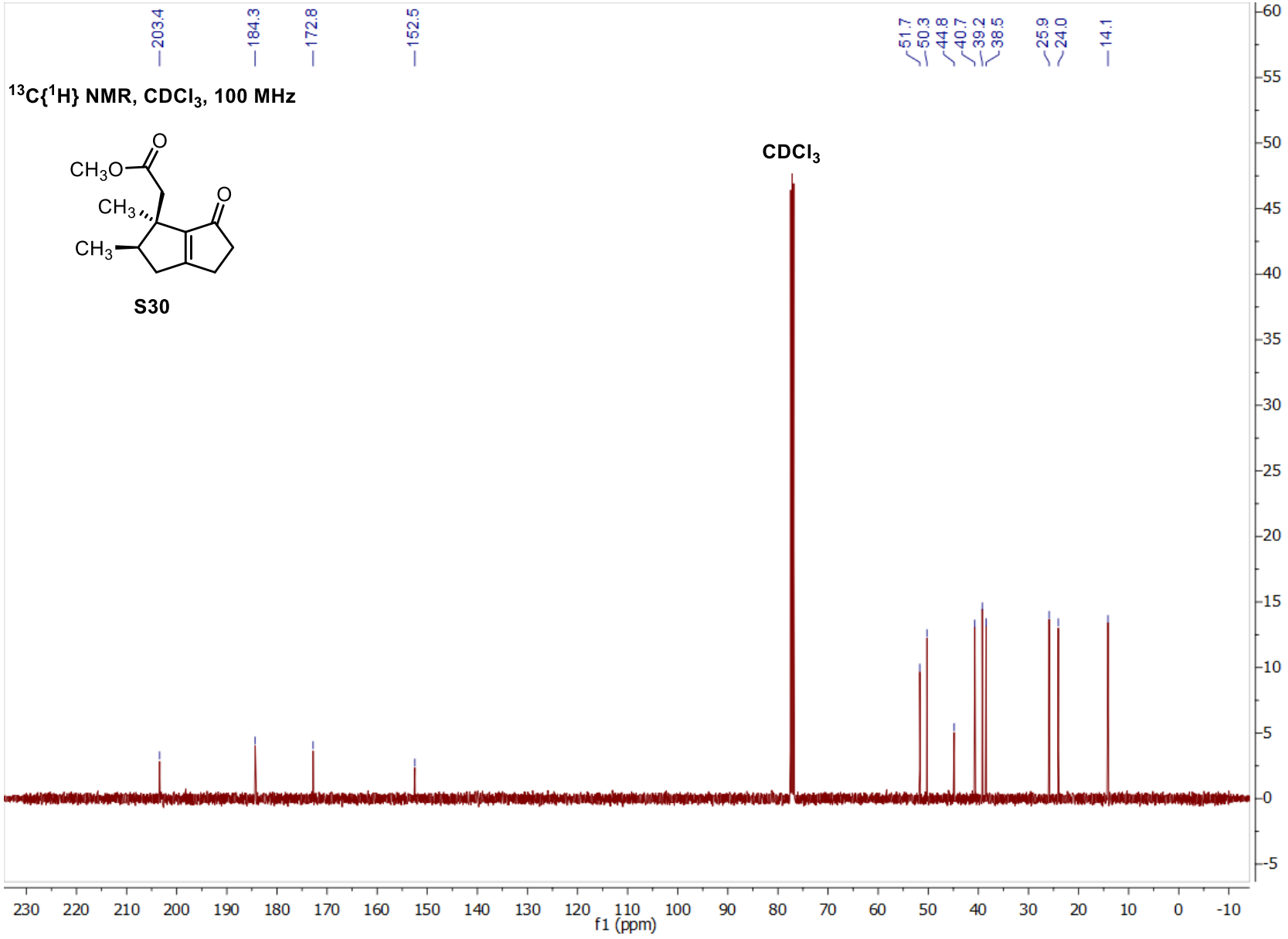

1H NMR, CDCl3, 400 MHz
HO
O
CH3
O
CH3
S28
2.691
2.626
2.552
2.371
2.354
2.331
2.314
1.412
1.146
1.129
CHCl3
2.39
1.71
2.00
1.38
3.01
3.30
f1 (ppm)

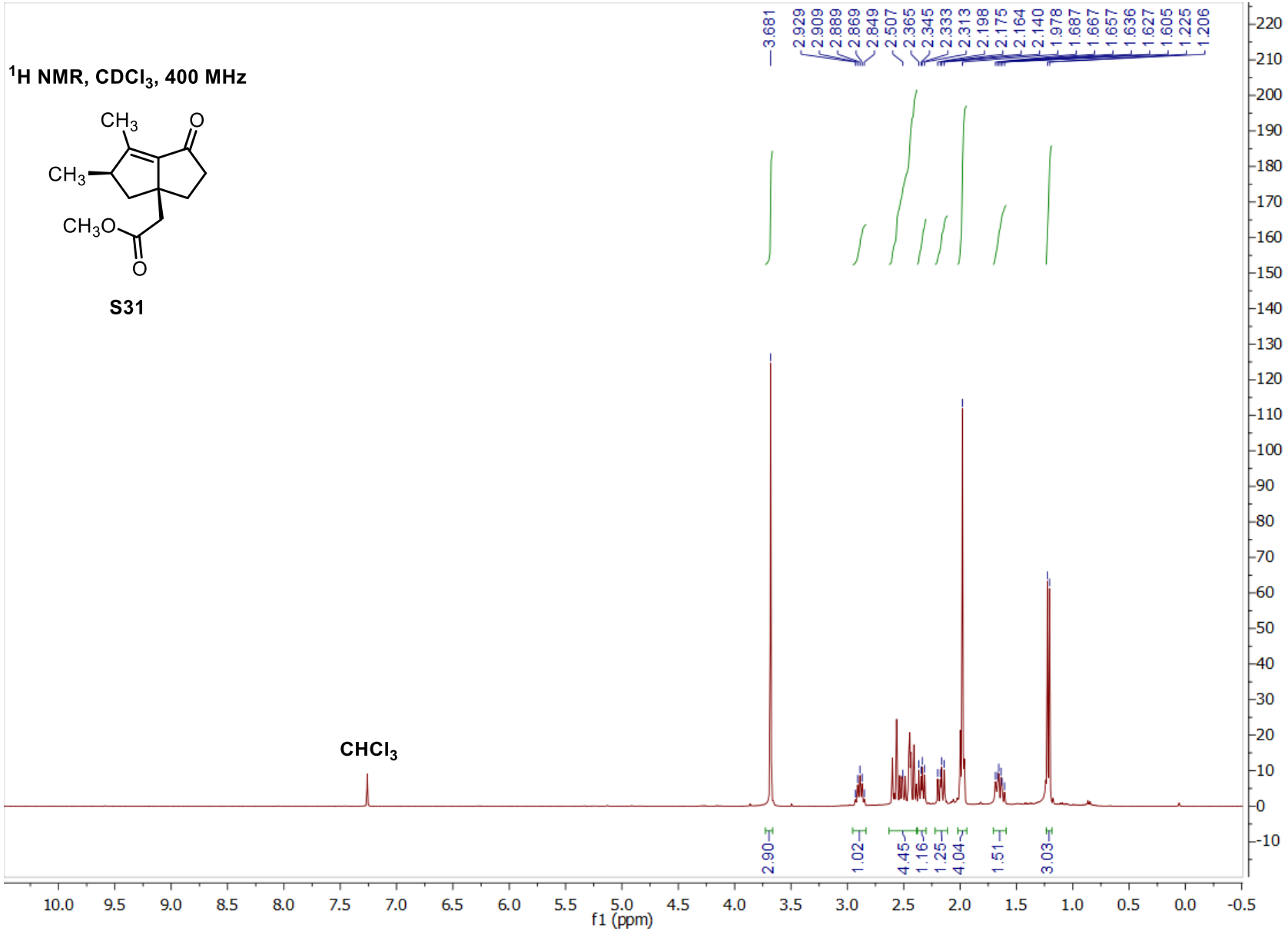

203.2
187.8
179.0
149.7
52.9
51.4
40.4
38.9
25.9
20.6
15.2
13C{1H} NMR, CDCl3, 150 MHz
HO
O
O
CH3
CH3
S28
CDCl3
f1 (ppm)

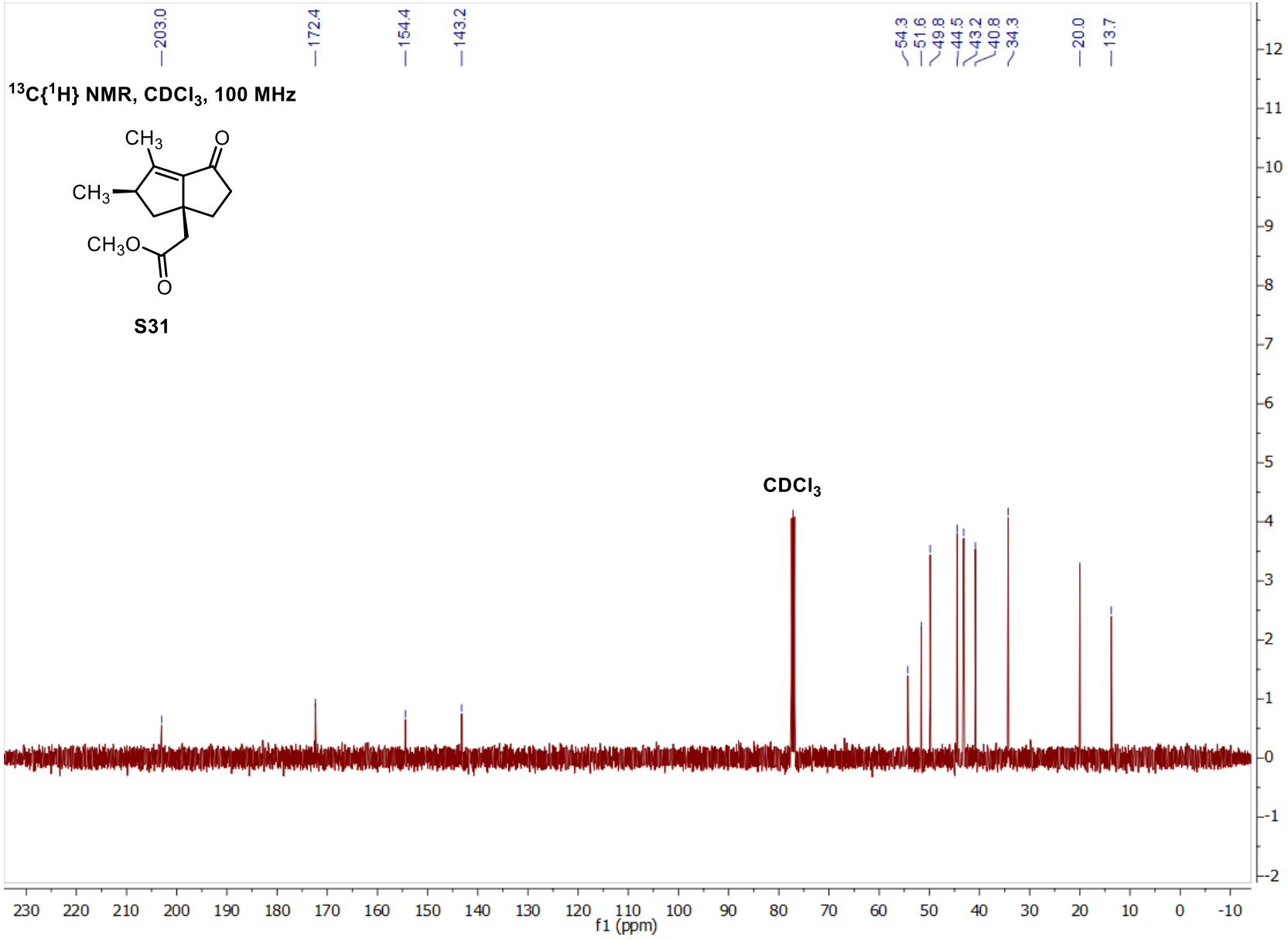

1H NMR, CDCl3, 600 MHz
S29
CHCl3
5.382
2.716
2.694
2.681
2.664
2.651
2.598
2.578
2.565
2.380
2.378
2.377
2.375
2.374
2.372
2.366
2.364
2.363
2.362
2.360
2.358
2.350
2.348
2.347
2.345
2.344
2.342
2.336
2.335
2.333
2.332
2.330
2.328
1.397
1.118
1.107
0.84
1.95
1.08
2.43
0.52
1.00
3.12
3.11
f1 (ppm)

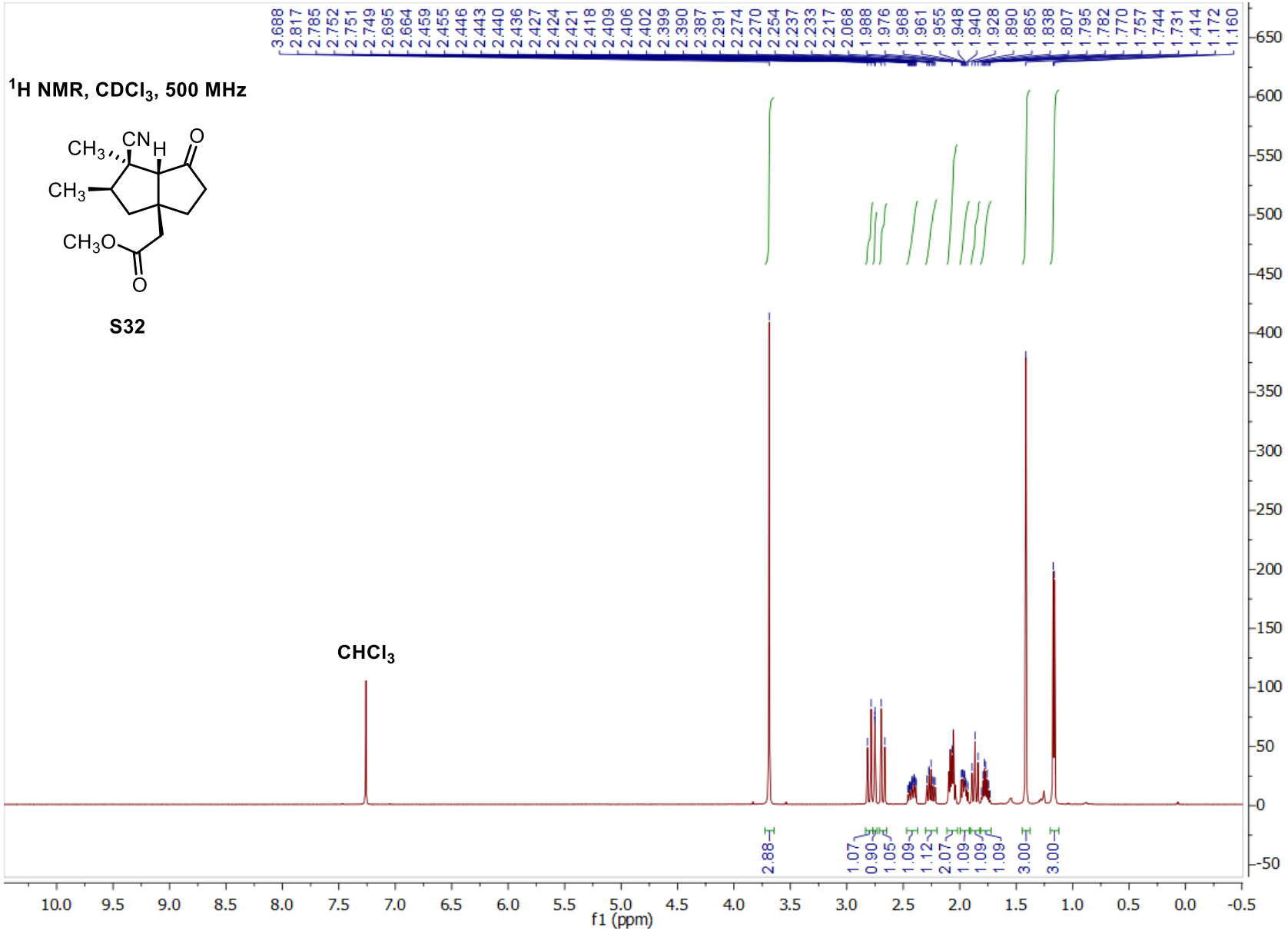

202.8
195.6
188.1
150.7
57.0
54.5
51.8
40.7
39.3
26.1
21.1
15.5
13C{1H} NMR, CDCl3, 150 MHz
N2
O
O
CH3
CH3
S29
CDCl3
f1 (ppm)

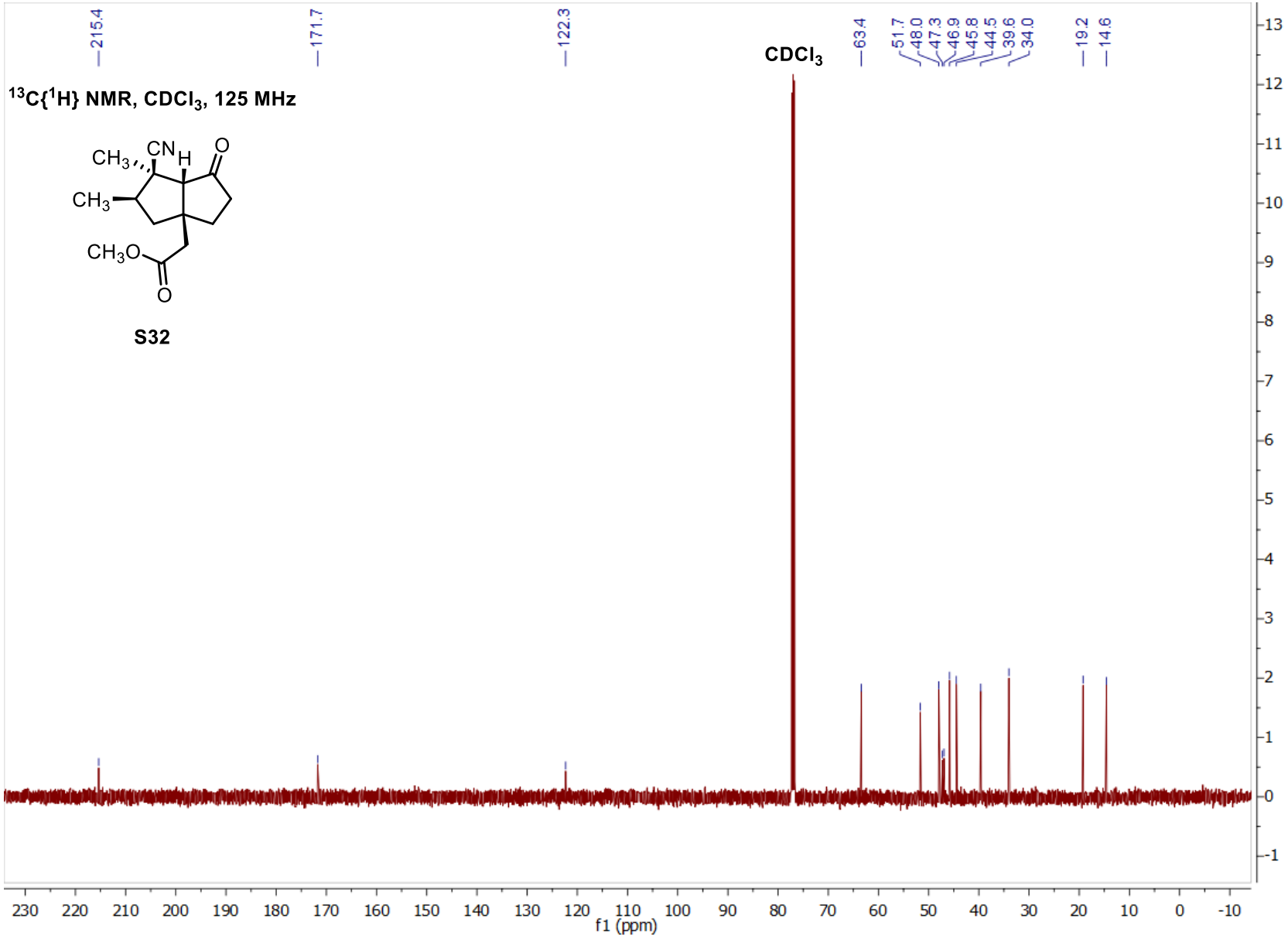

1H NMR, CDCl3, 400 MHz
S30
CHCl3
3.591
2.645
2.509
2.410
2.376
2.342
2.308
2.239
2.218
2.196
2.176
1.309
1.067
1.050
2.77
1.97
4.15
2.25
1.29
3.04
3.00
f1 (ppm)

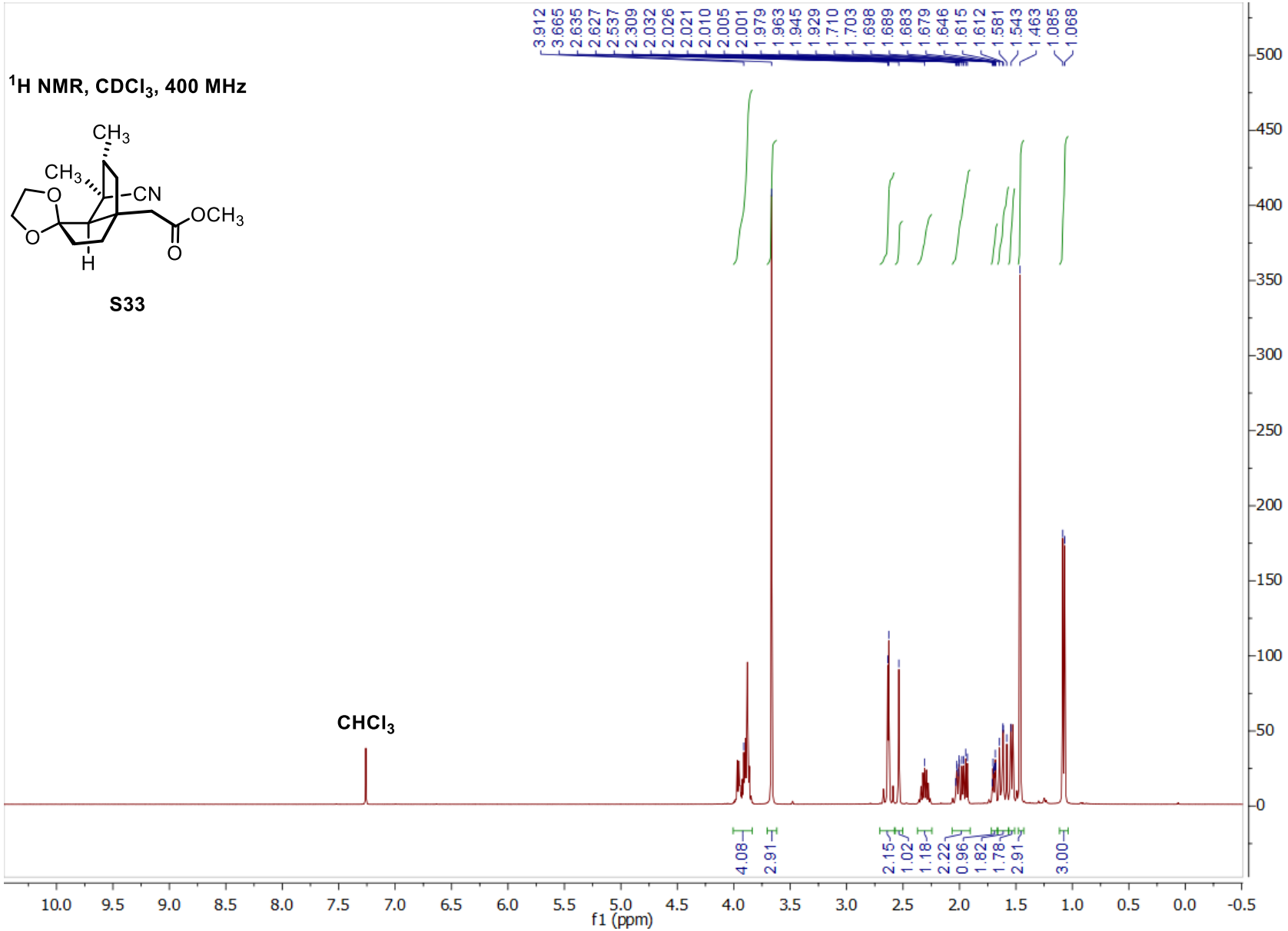

203.4
184.3
172.8
152.5
51.7
50.3
44.8
40.7
39.2
38.5
25.9
24.0
14.1
13C{1H} NMR, CDCl3, 100 MHz
CDCl3
S30
f1 (ppm)

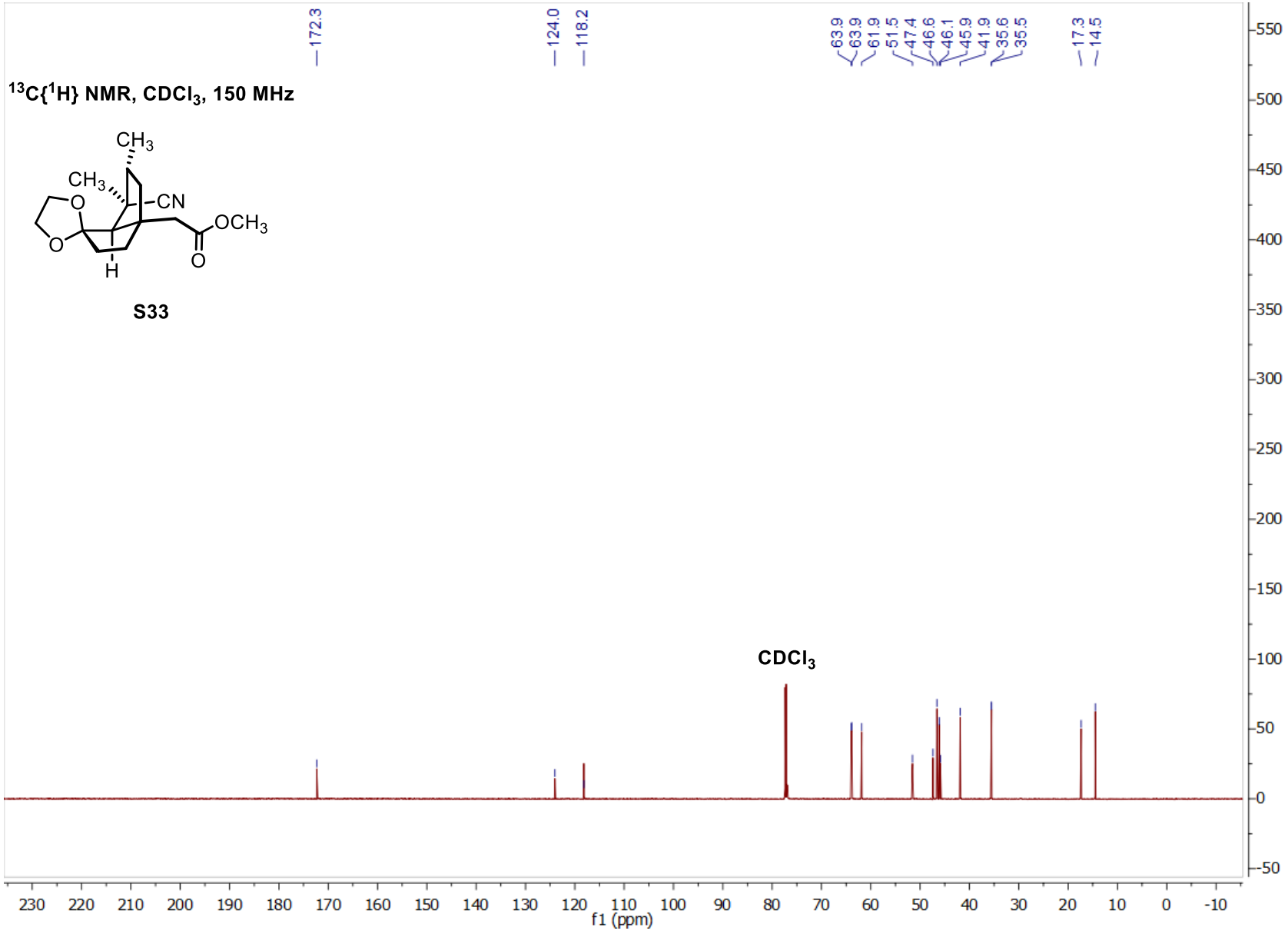

1H NMR, CDCl3, 400 MHz
CH3
O
CH3
CH3O
O
S31
3.681
2.929
2.909
2.889
2.869
2.849
2.507
2.365
2.345
2.333
2.313
2.198
2.175
2.164
2.140
1.978
1.687
1.667
1.657
1.636
1.627
1.605
1.225
1.206
CHCl3
2.90
1.02
4.45
1.16
1.25
4.04
1.51
3.03
f1 (ppm)

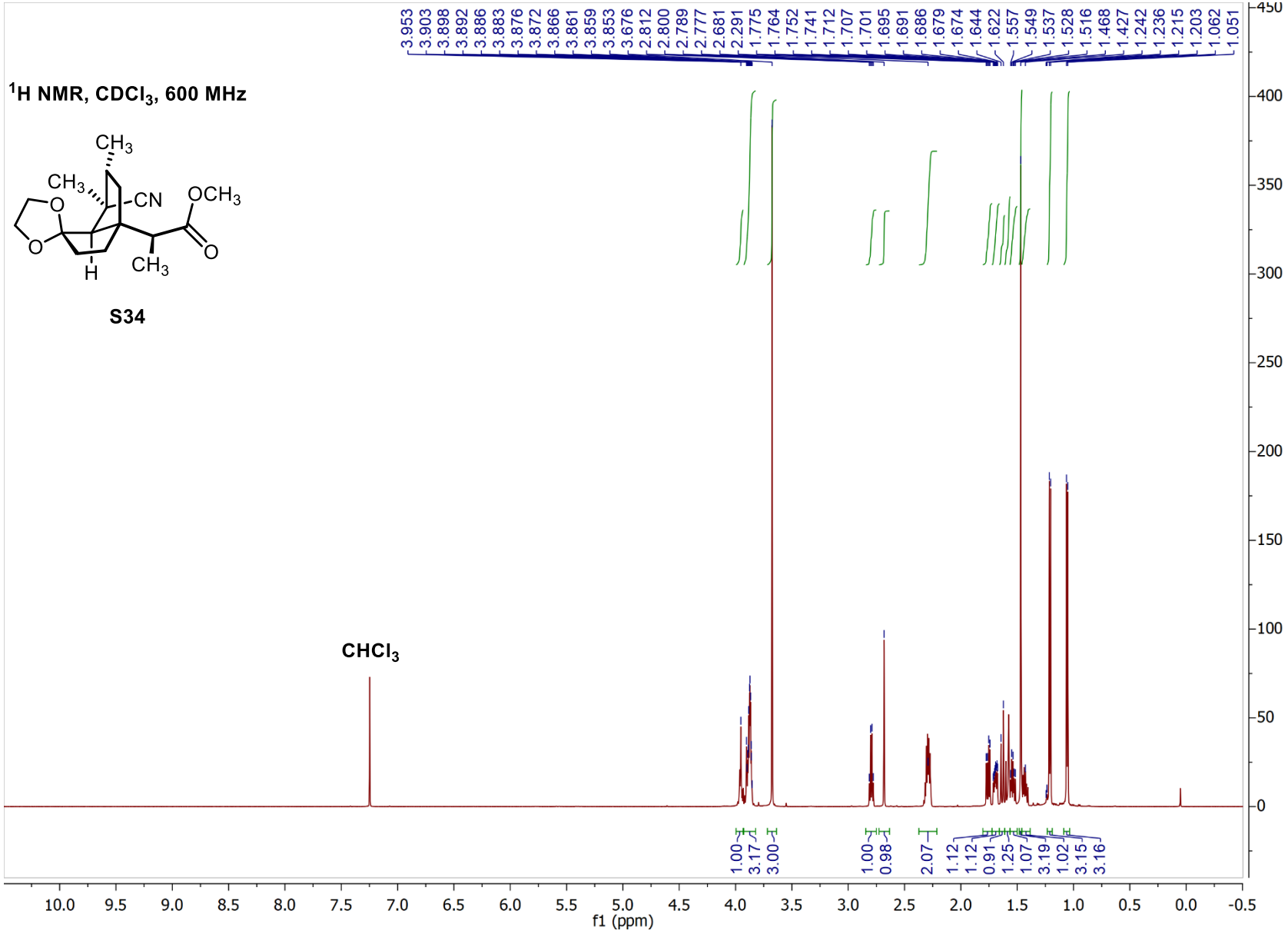

203.0
172.4
154.4
143.2
54.3
51.6
49.8
44.5
43.2
40.8
34.3
20.0
13.7
13C{1H} NMR, CDCl3, 100 MHz
CH3
O
CH3
CH3O
O
S31
CDCl3
f1 (ppm)

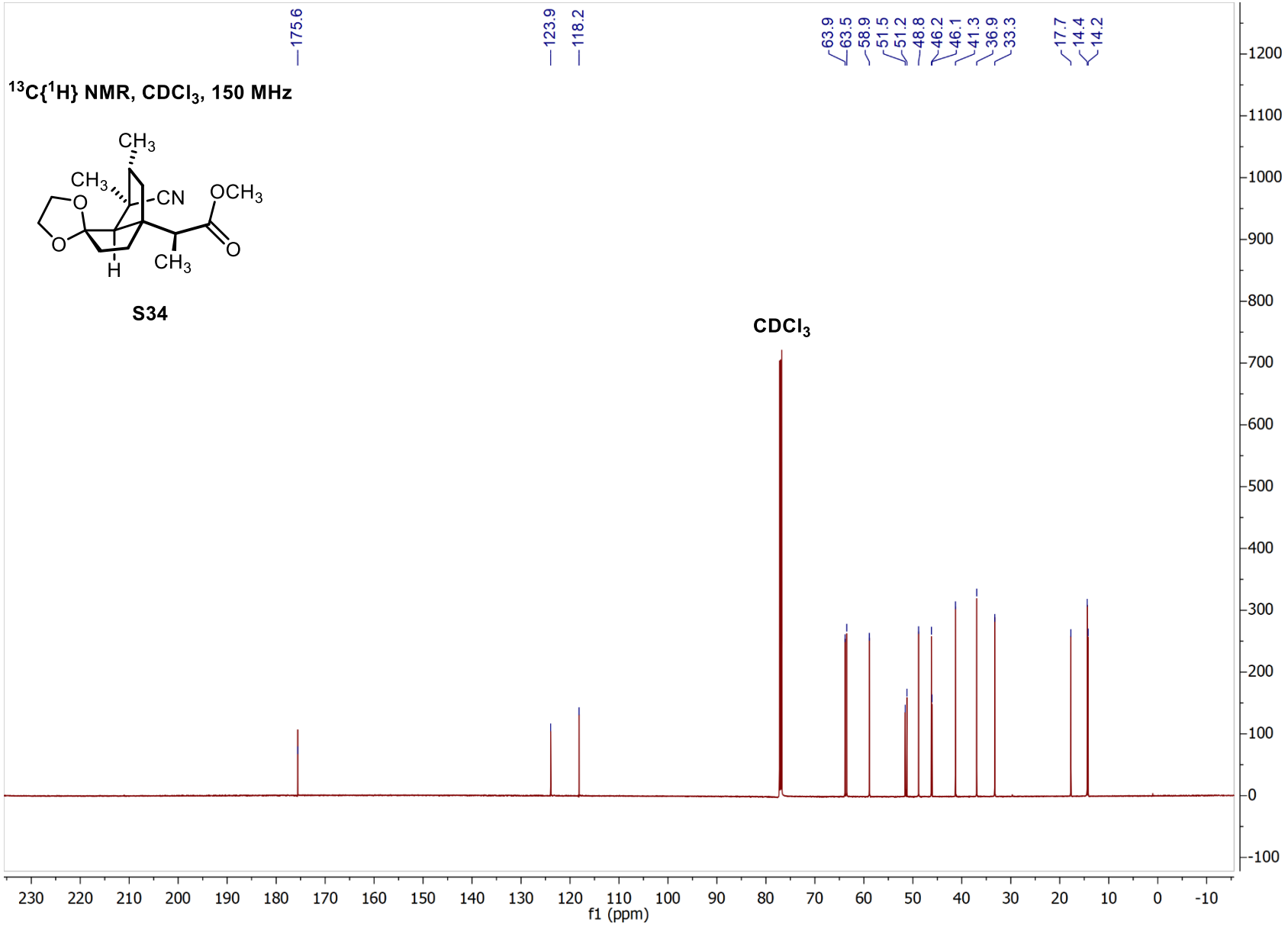

^{1}H NMR, $CDCl_3$, 500 MHz
S32
$CHCl_3$
f1 (ppm)

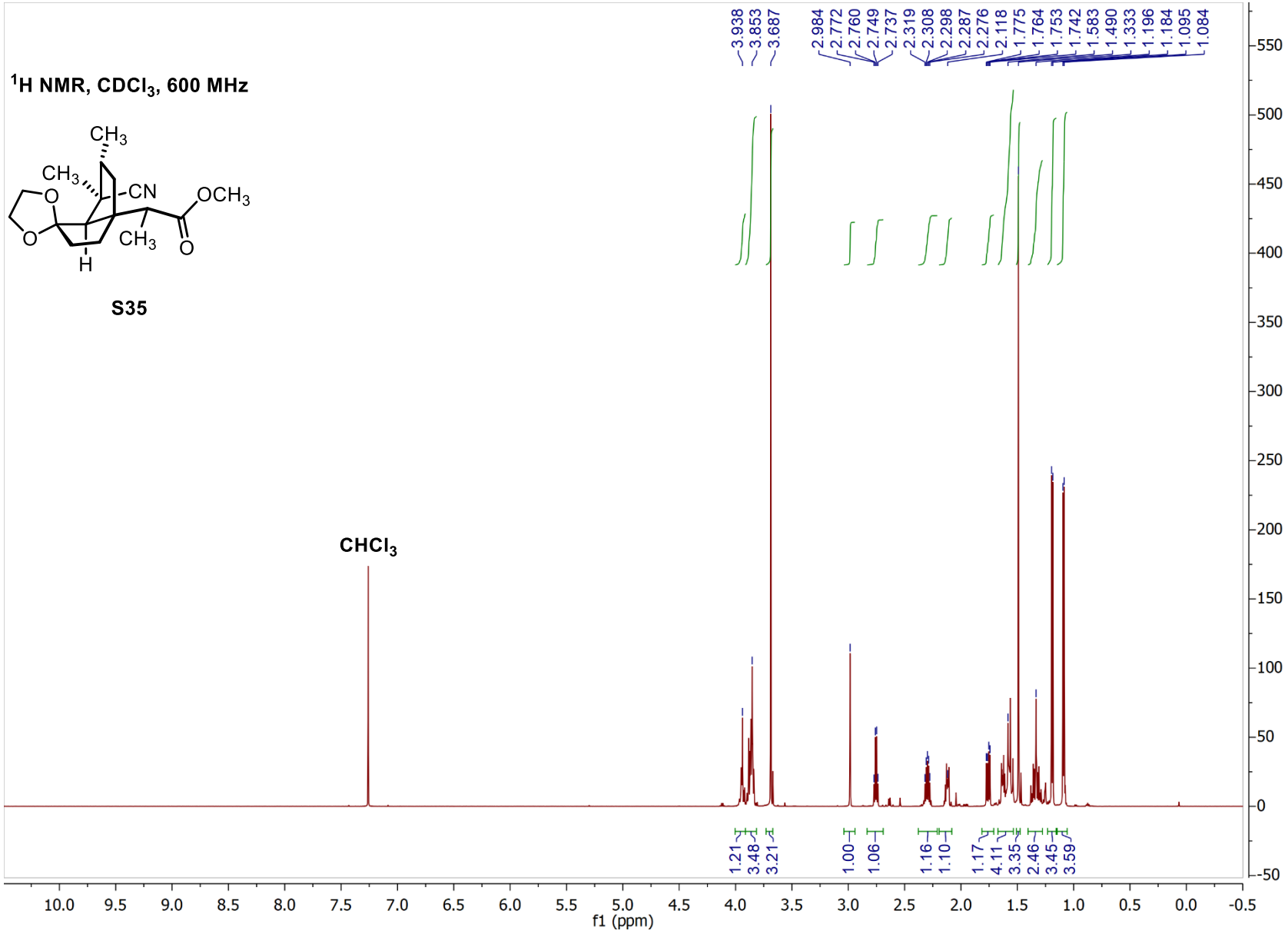

215.4
171.7
122.3
CDCl3
63.4
51.7
48.0
47.3
46.9
45.8
44.5
39.6
34.0
19.2
14.6
13C{1H} NMR, CDCl3, 125 MHz
CH3
CN
H
O
CH3
CH3O
O
S32
f1 (ppm)

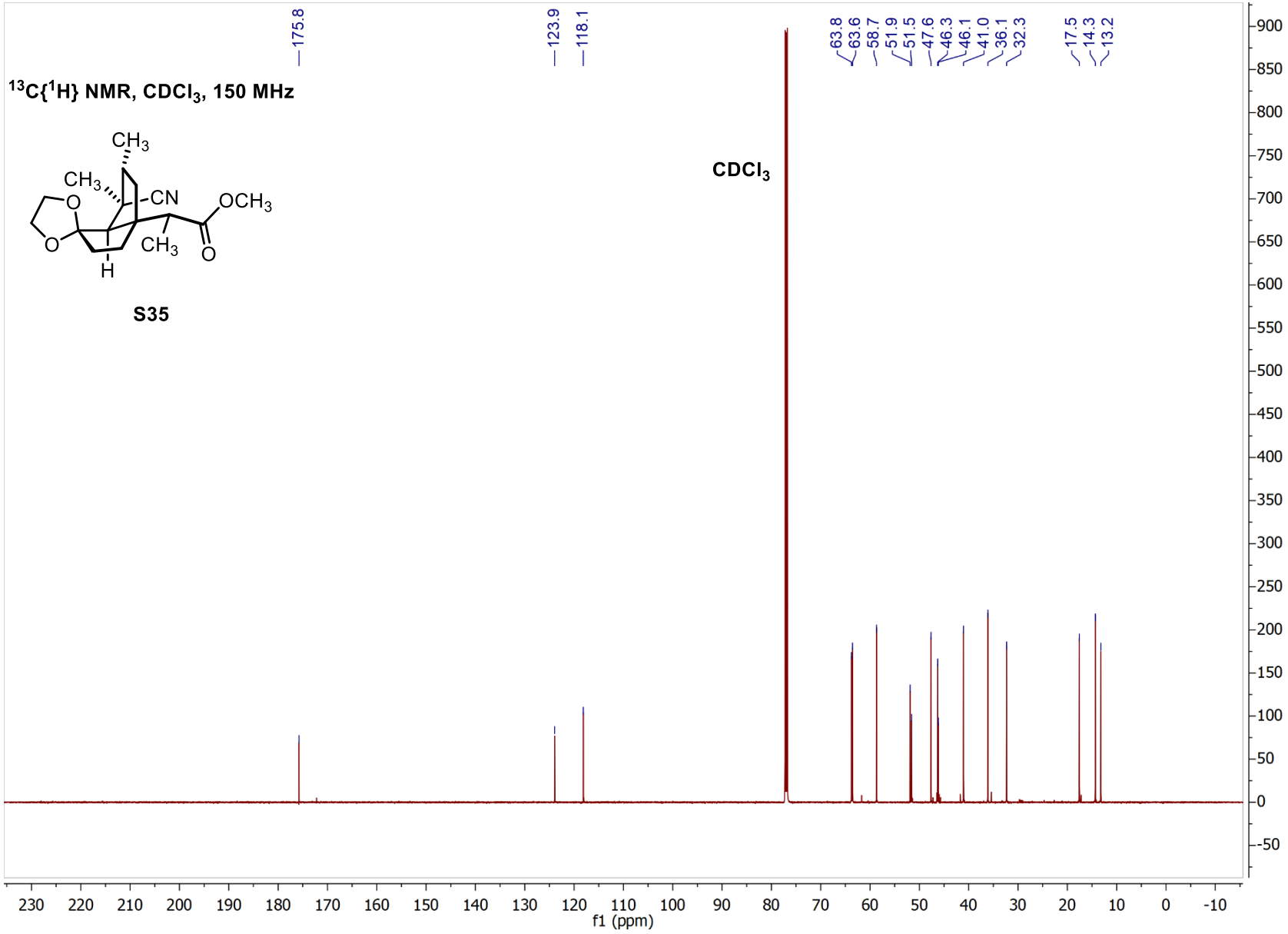

1H NMR, CDCl3, 400 MHz
CH3
CH3
CN
OCH3
O
O
O
H
S33
CHCl3
3.912
3.665
2.635
2.627
2.537
2.309
2.032
2.026
2.021
2.010
2.005
2.001
1.979
1.963
1.945
1.929
1.710
1.703
1.698
1.689
1.683
1.679
1.646
1.615
1.612
1.581
1.543
1.463
1.085
1.068
4.08
2.91
2.15
1.02
1.18
2.22
0.96
1.82
1.78
2.91
3.00
f1 (ppm)

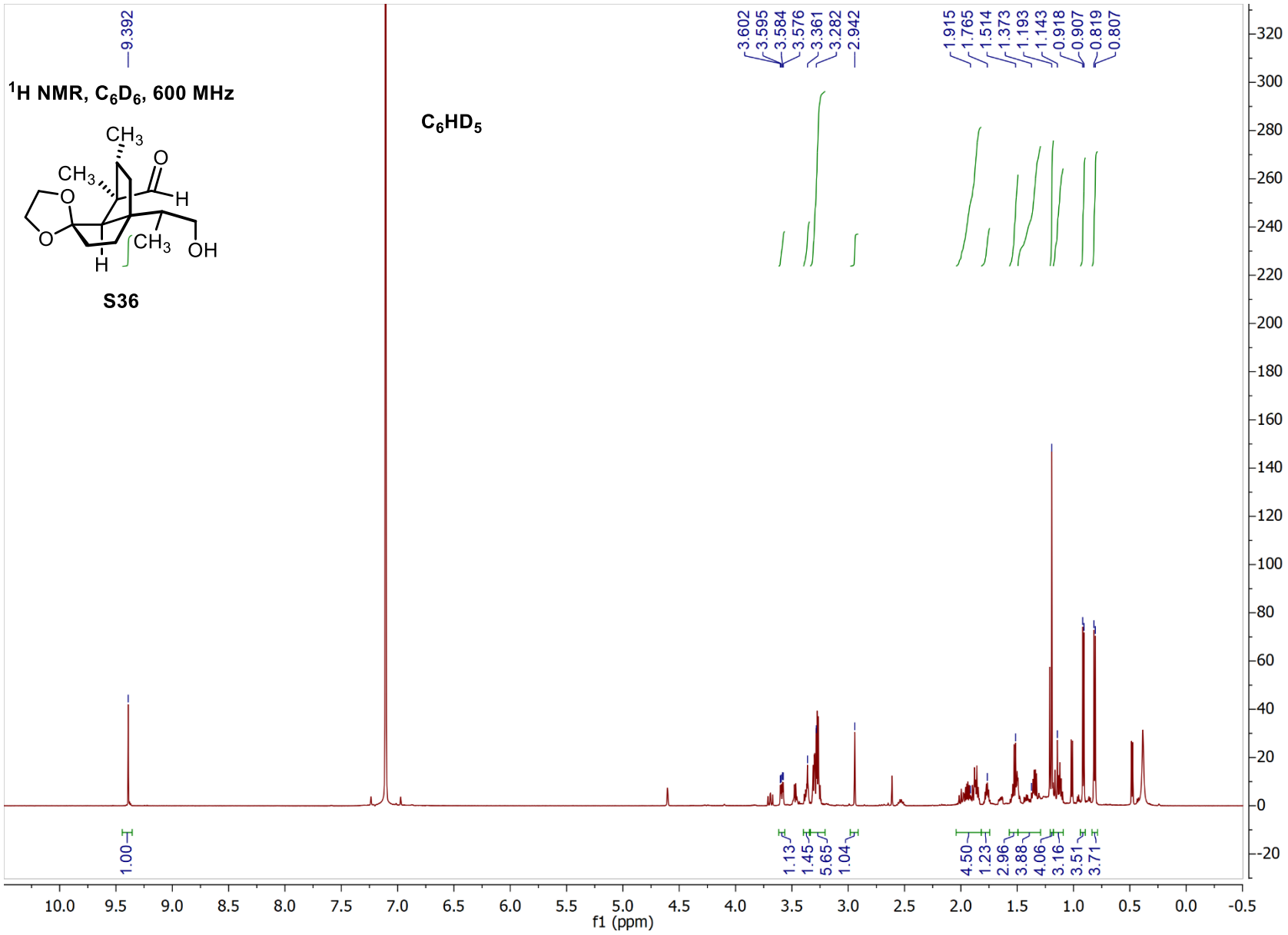

13C{1H} NMR, CDCl3, 150 MHz
CH3
CH3
O
CN
OCH3
O
O
H
S33
172.3
124.0
118.2
63.9
63.9
61.9
51.5
47.4
46.6
46.1
45.9
41.9
35.6
35.5
17.3
14.5
CDCl3
f1 (ppm)

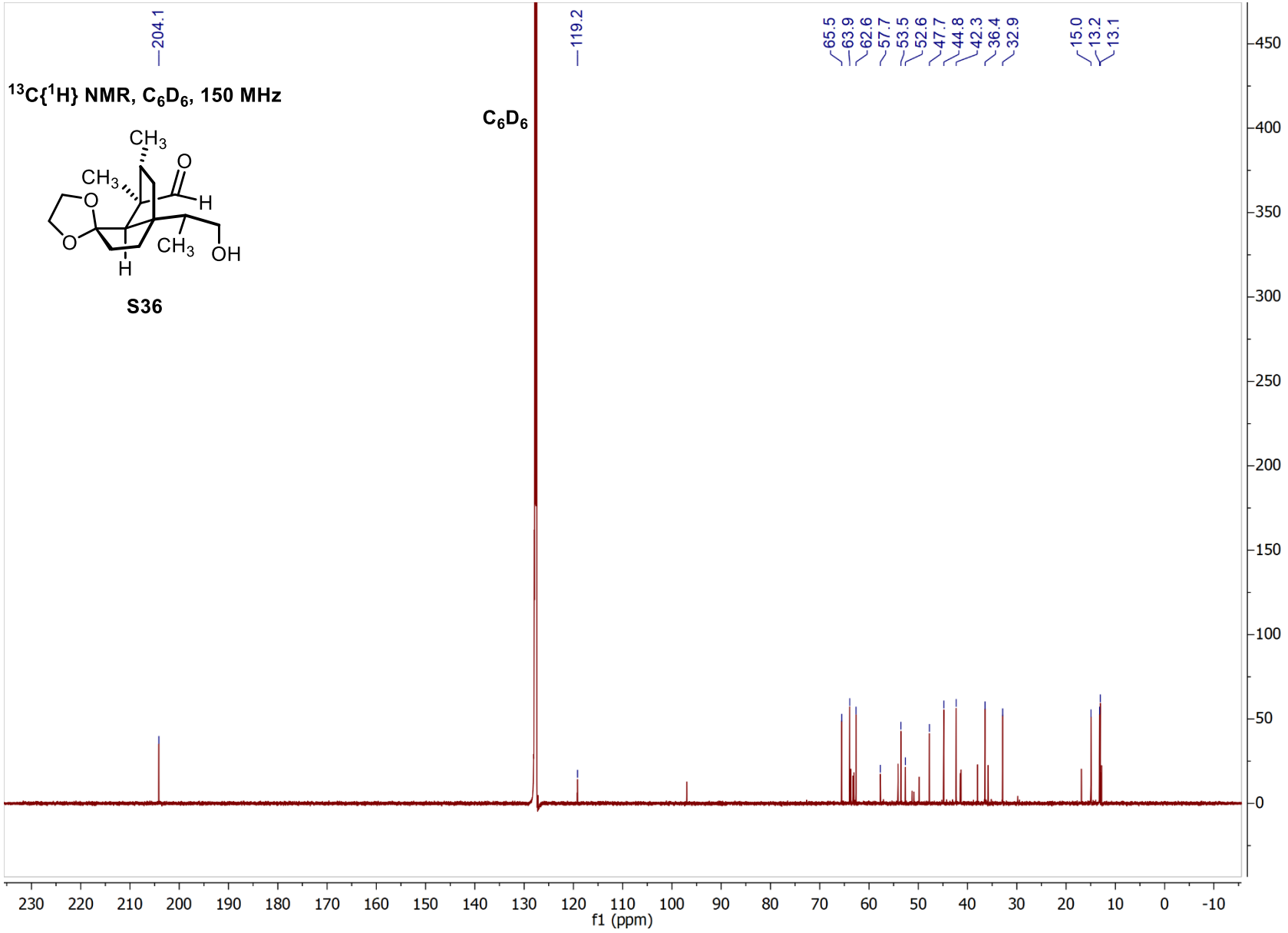

1H NMR, CDCl3, 600 MHz
CH3
CH3
CN
OCH3
O
O
O
H
CH3
S34
CHCl3
3.953
3.903
3.898
3.892
3.886
3.883
3.876
3.872
3.866
3.861
3.859
3.853
3.676
2.812
2.800
2.789
2.777
2.681
2.291
1.775
1.764
1.752
1.741
1.712
1.707
1.701
1.695
1.691
1.686
1.679
1.674
1.644
1.622
1.557
1.549
1.537
1.528
1.516
1.468
1.427
1.242
1.236
1.215
1.203
1.062
1.051
1.00
3.17
3.00
1.00
0.98
2.07
1.12
1.12
0.91
1.25
1.07
3.19
1.02
3.15
3.16
f1 (ppm)

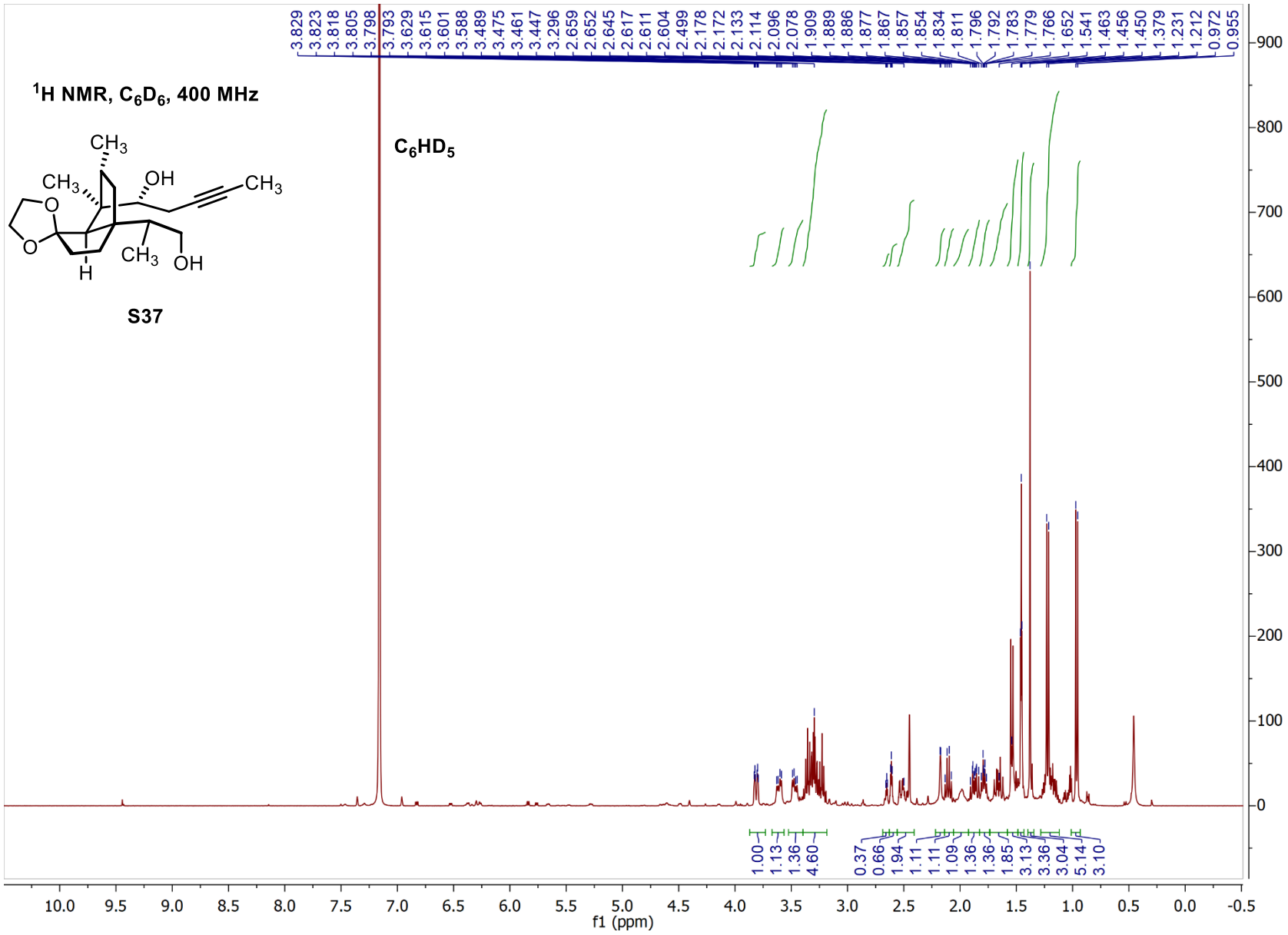

175.6
123.9
118.2
63.9
63.5
58.9
51.5
51.2
48.8
46.2
46.1
41.3
36.9
33.3
17.7
14.4
14.2
13C{1H} NMR, CDCl3, 150 MHz
CH3
CH3
CN
OCH3
O
O
O
H
CH3
S34
CDCl3
f1 (ppm)

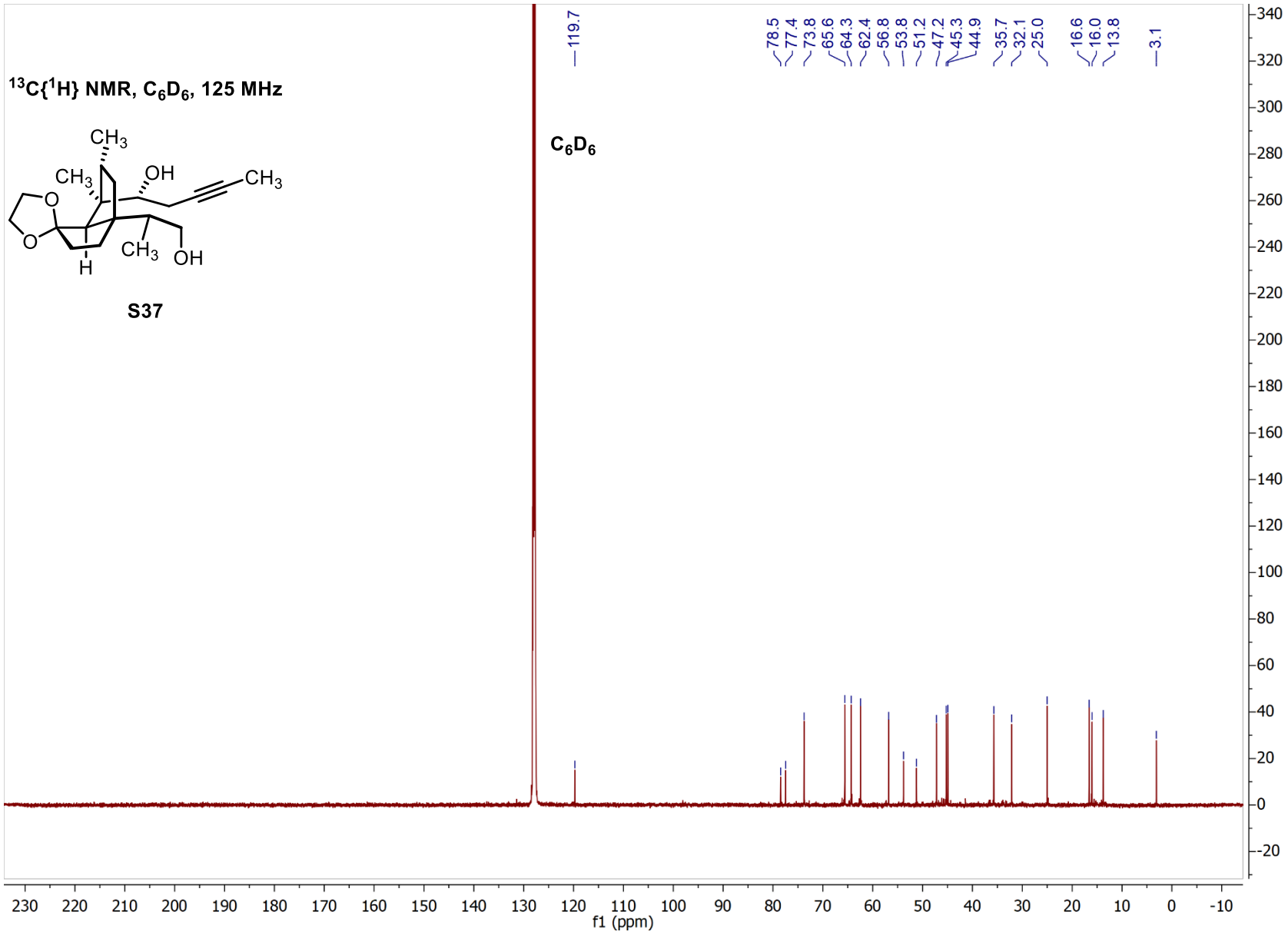

1H NMR, CDCl3, 600 MHz
CH3
CH3
CN
OCH3
O
O
CH3
O
H
S35
CHCl3
3.938
3.853
3.687
2.984
2.772
2.760
2.749
2.737
2.319
2.308
2.298
2.287
2.276
2.118
1.775
1.764
1.753
1.742
1.583
1.490
1.333
1.196
1.184
1.095
1.084
1.21
3.48
3.21
1.00
1.06
1.16
1.10
1.17
4.11
3.35
2.46
3.45
3.59
f1 (ppm)

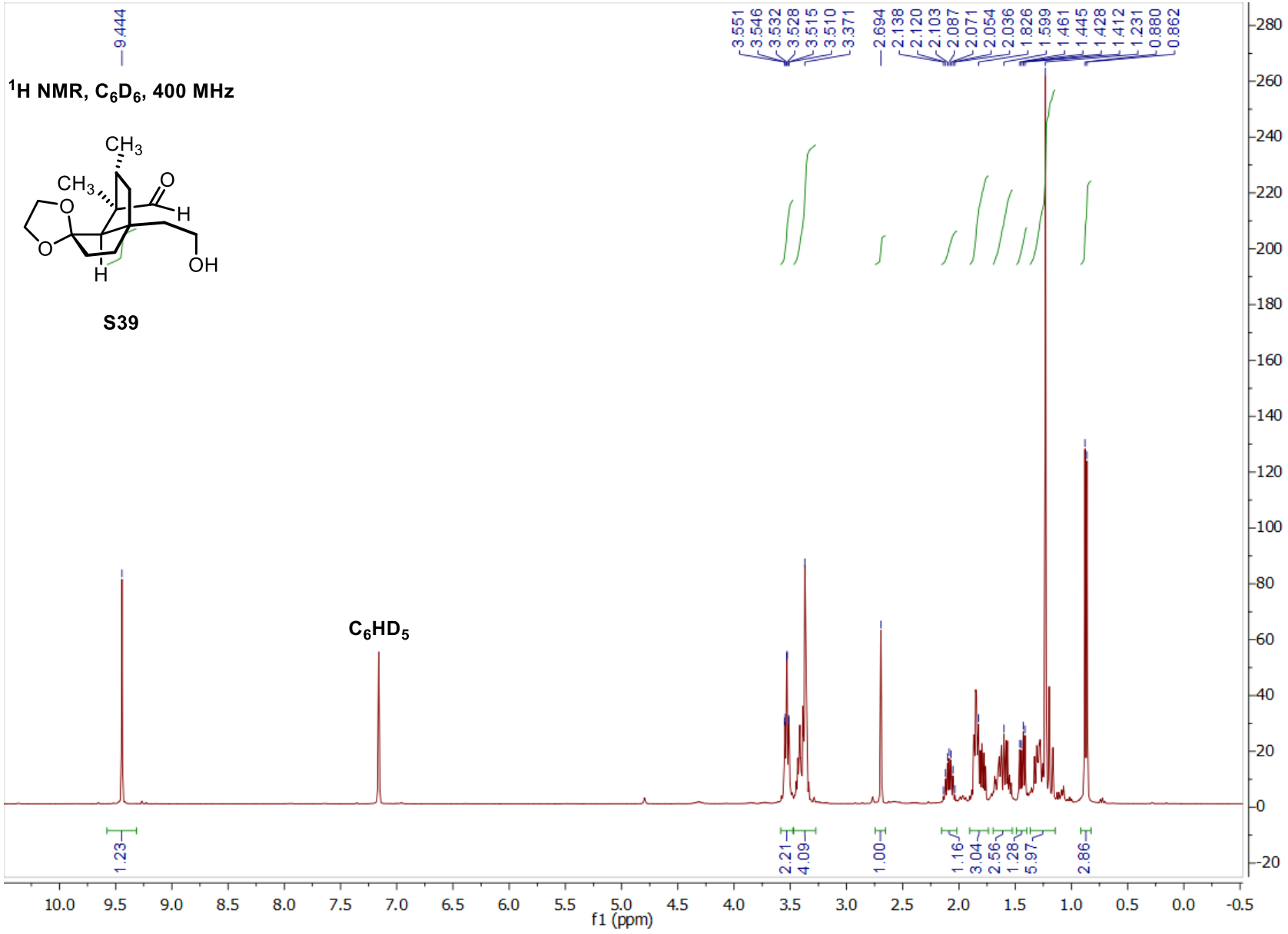

13C{1H} NMR, CDCl3, 150 MHz
CH3
CH3
CN
OCH3
O
O
CH3
O
H
S35
CDCl3
175.8
123.9
118.1
63.8
63.6
58.7
51.9
51.5
47.6
46.3
46.1
41.0
36.1
32.3
17.5
14.3
13.2
f1 (ppm)

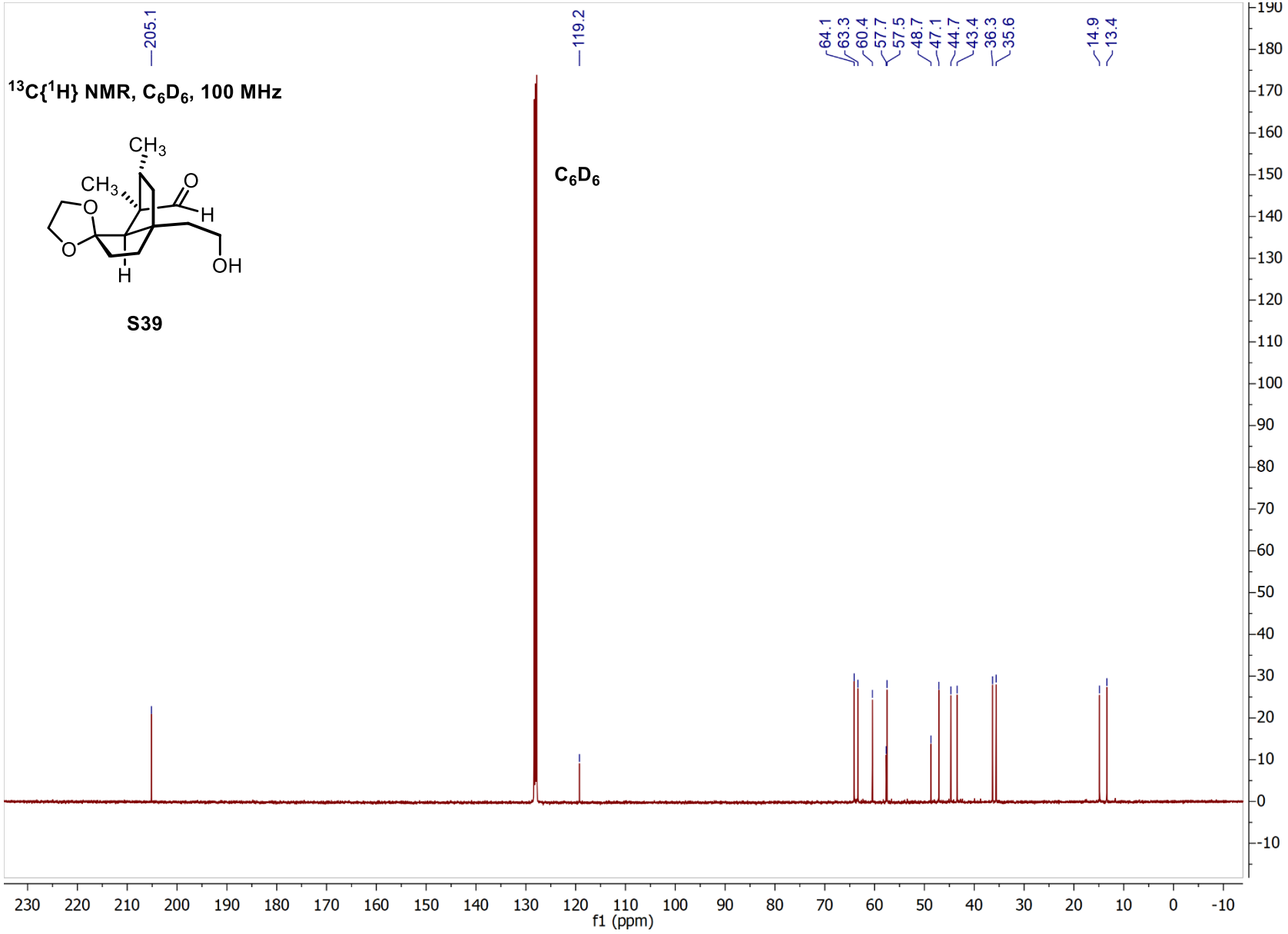

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
S36
9.392
3.602
3.595
3.584
3.576
3.361
3.282
2.942
1.915
1.765
1.514
1.373
1.193
1.143
0.918
0.907
0.819
0.807
1.00
1.13
1.45
5.65
1.04
4.50
1.23
2.96
3.88
4.06
3.16
3.51
3.71
f1 (ppm)

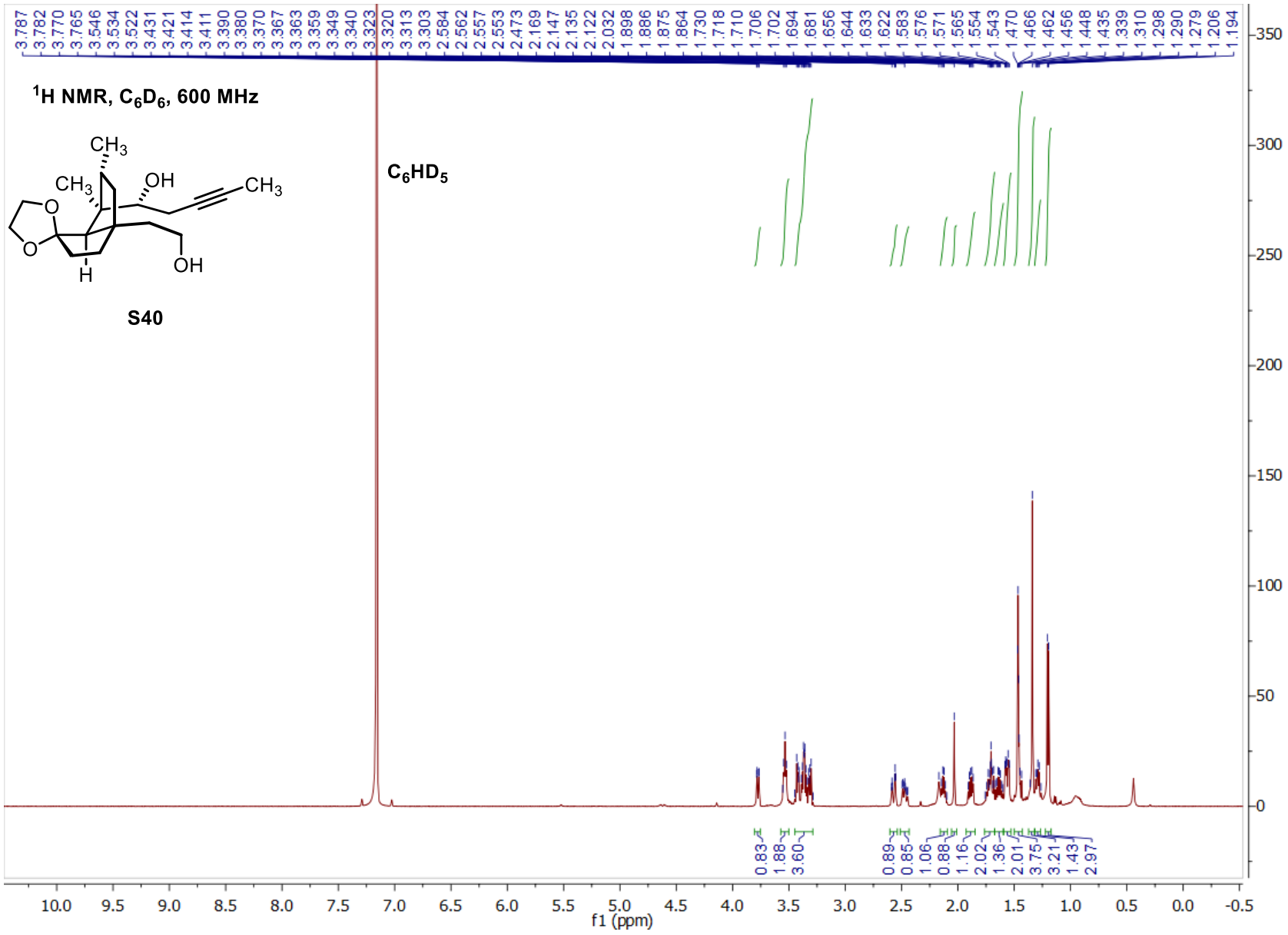

204.1
119.2
65.5
63.9
62.6
57.7
53.5
52.6
47.7
44.8
42.3
36.4
32.9
15.0
13.2
13.1
13C{1H} NMR, C6D6, 150 MHz
C6D6
CH3
O
CH3
H
O
O
CH3
OH
H
S36
450
400
350
300
250
200
150
100
50
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

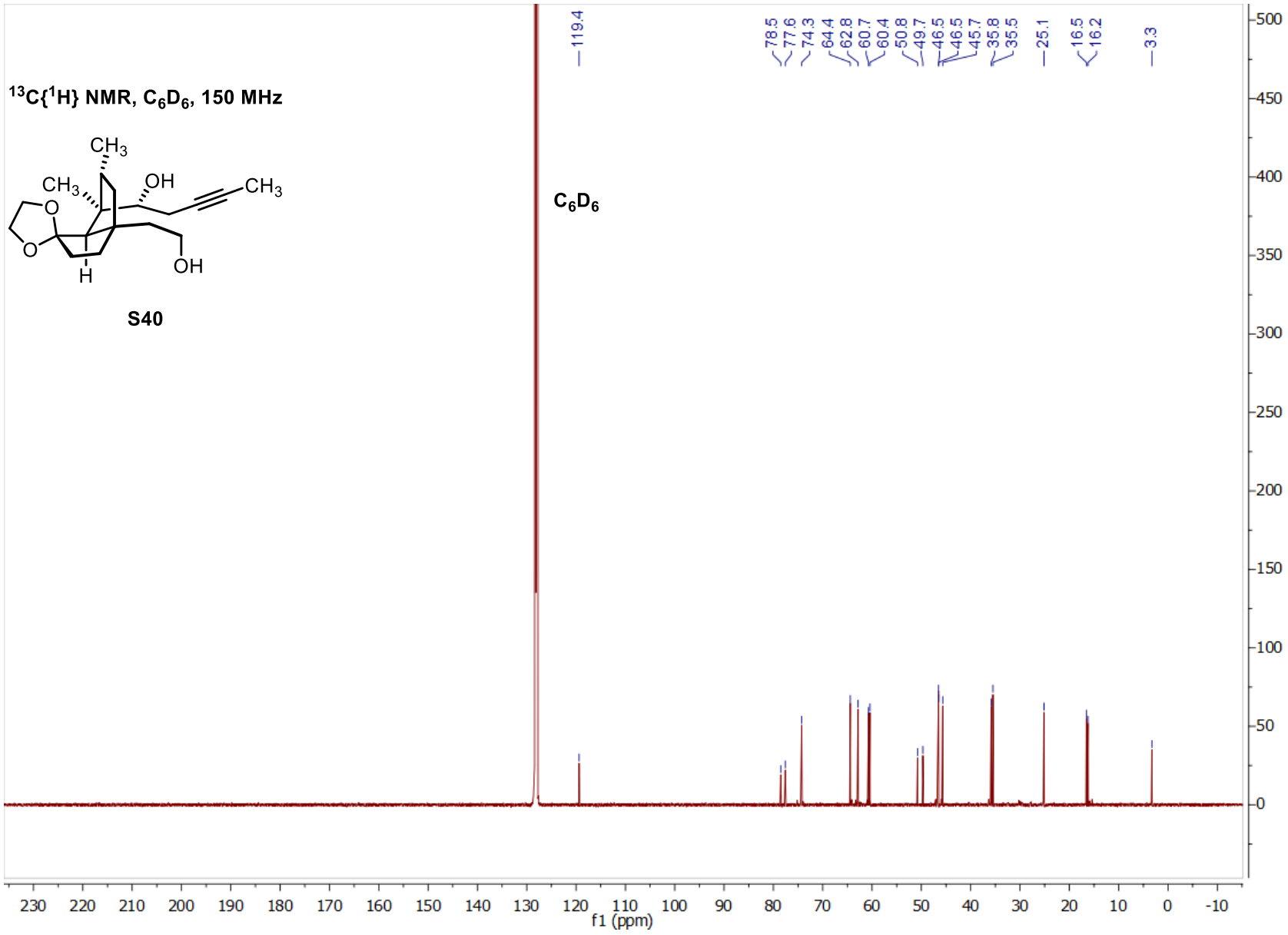

3.829
3.823
3.818
3.805
3.798
3.793
3.629
3.615
3.601
3.588
3.489
3.475
3.461
3.447
3.296
2.659
2.652
2.645
2.617
2.611
2.604
2.499
2.178
2.172
2.133
2.114
2.096
2.078
1.909
1.889
1.886
1.877
1.867
1.857
1.854
1.834
1.811
1.796
1.792
1.783
1.779
1.766
1.652
1.541
1.463
1.456
1.450
1.379
1.231
1.212
0.972
0.955
^{1}H NMR, C_6D_6, 400 MHz
C_6HD_5
CH3
CH3
OH
CH3
O
O
CH3
OH
H
S37
1.00
1.13
1.36
4.60
0.37
0.66
1.94
1.11
1.11
1.09
1.36
1.36
1.85
3.13
3.36
3.04
5.14
3.10
f1 (ppm)

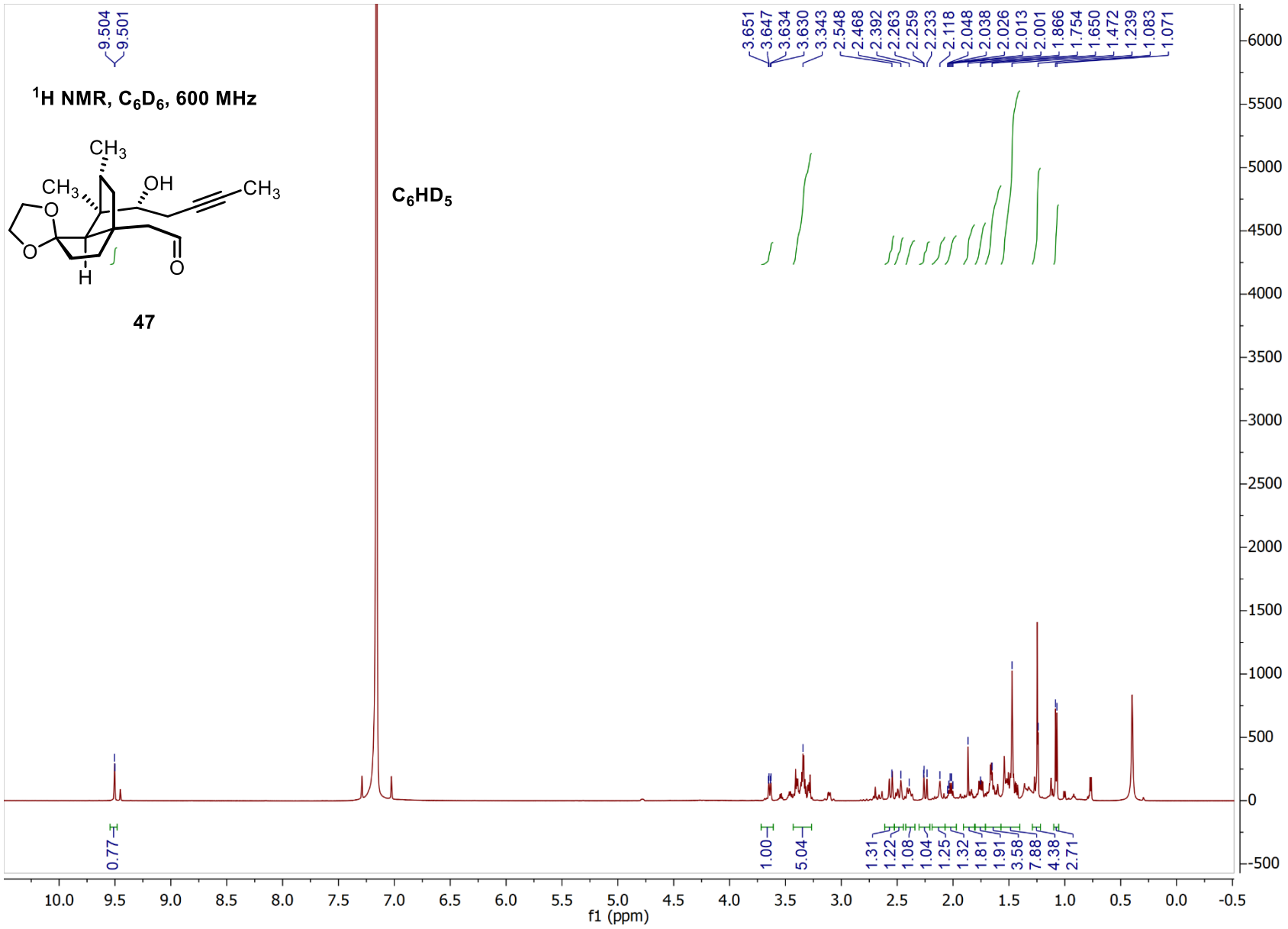

13C{1H} NMR, C6D6, 125 MHz
CH3
CH3
OH
CH3
O
O
CH3
OH
H
S37
C6D6
119.7
78.5
77.4
73.8
65.6
64.3
62.4
56.8
53.8
51.2
47.2
45.3
44.9
35.7
32.1
25.0
16.6
16.0
13.8
3.1
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

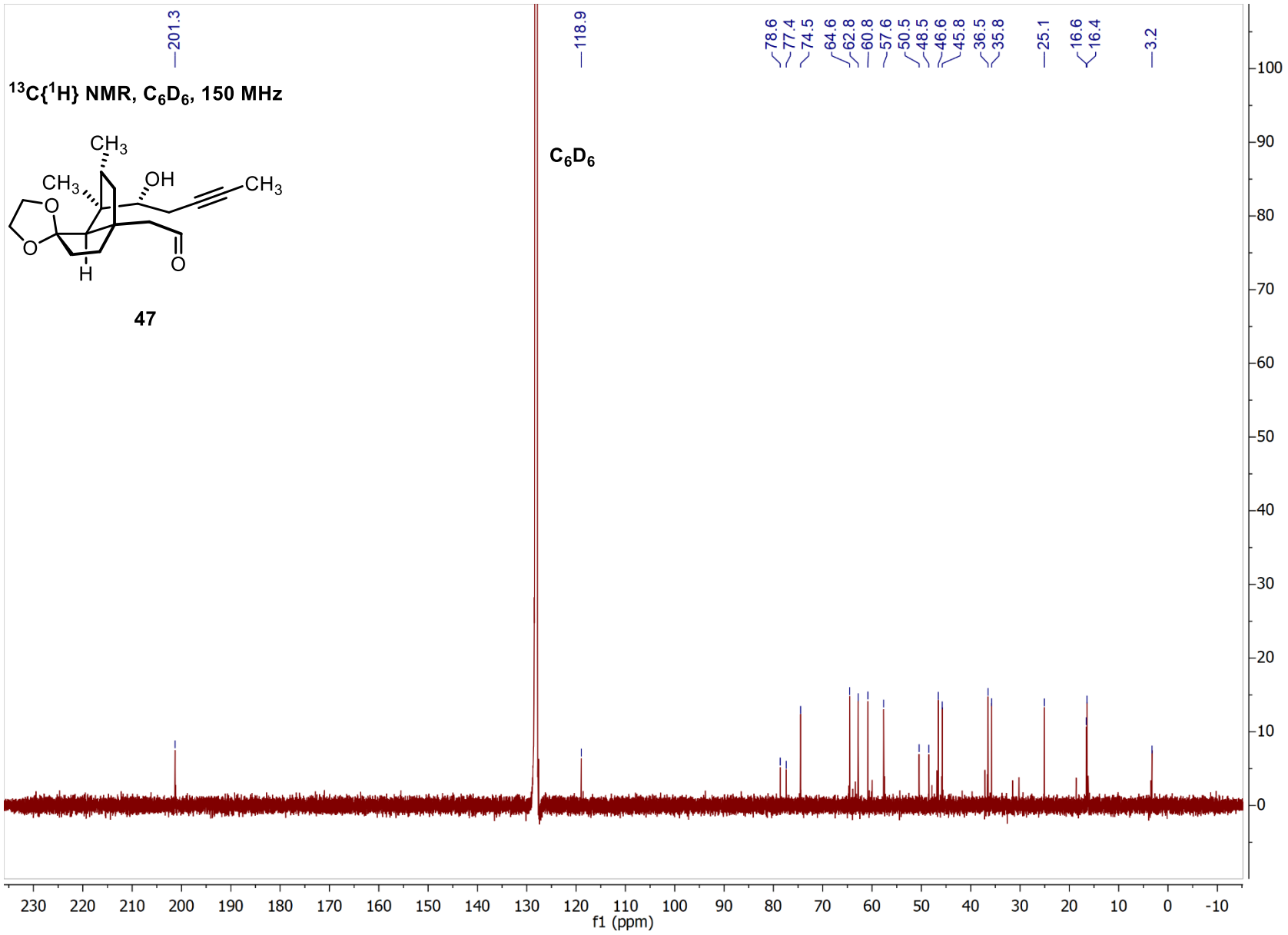

9.444
3.551
3.546
3.532
3.528
3.515
3.510
3.371
2.694
2.138
2.120
2.103
2.087
2.071
2.054
2.036
1.826
1.599
1.461
1.445
1.428
1.412
1.231
0.880
0.862
1H NMR, C6D6, 400 MHz
CH3
CH3
O
O
O
H
H
OH
S39
C6HD5
1.23
2.21
4.09
1.00
1.16
3.04
2.56
1.28
5.97
2.86
f1 (ppm)

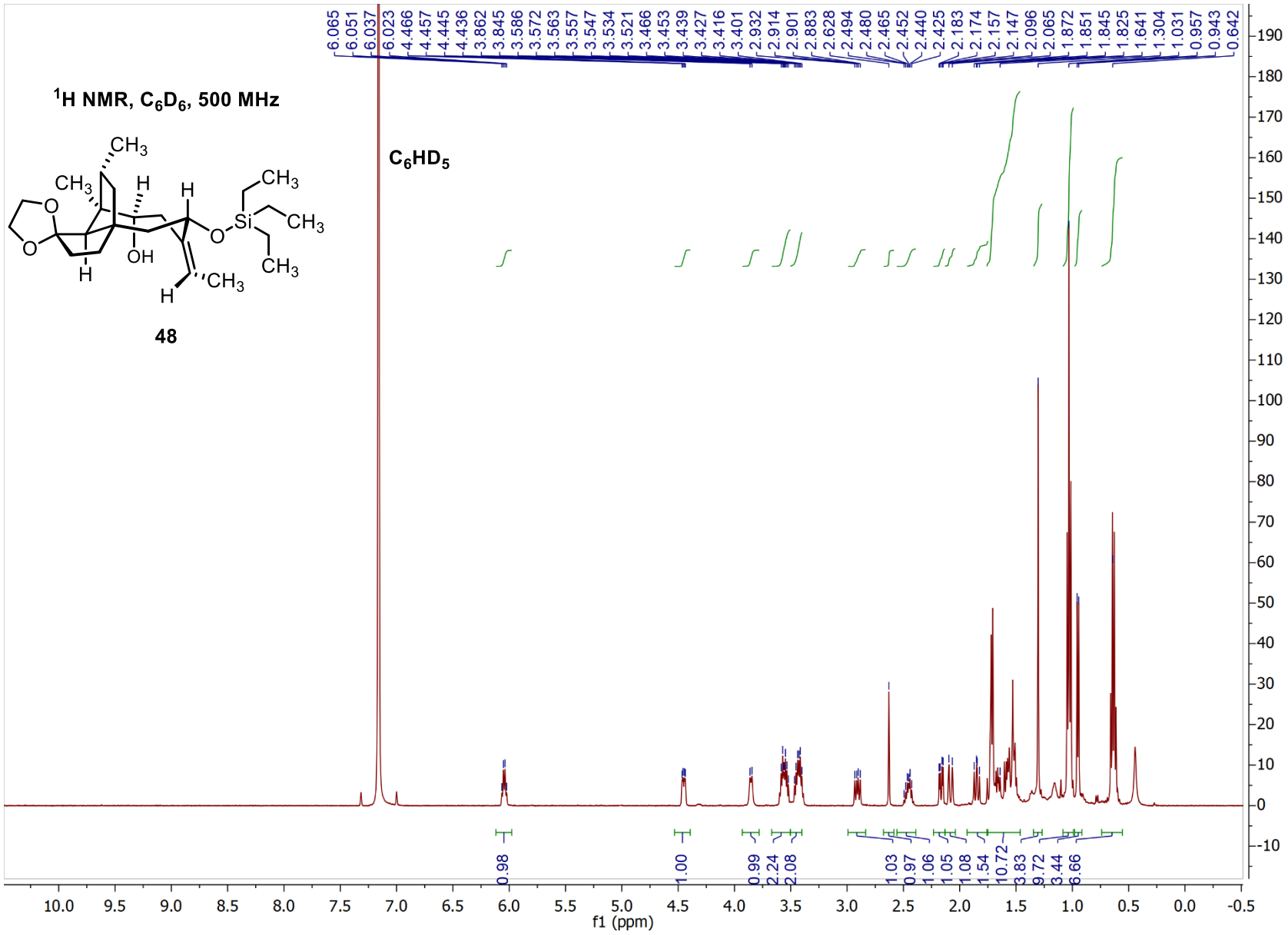

205.1
119.2
64.1
63.3
60.4
57.7
57.5
48.7
47.1
44.7
43.4
36.3
35.6
14.9
13.4
13C{1H} NMR, C6D6, 100 MHz
CH3
CH3
O
O
O
H
H
OH
C6D6
S39
f1 (ppm)

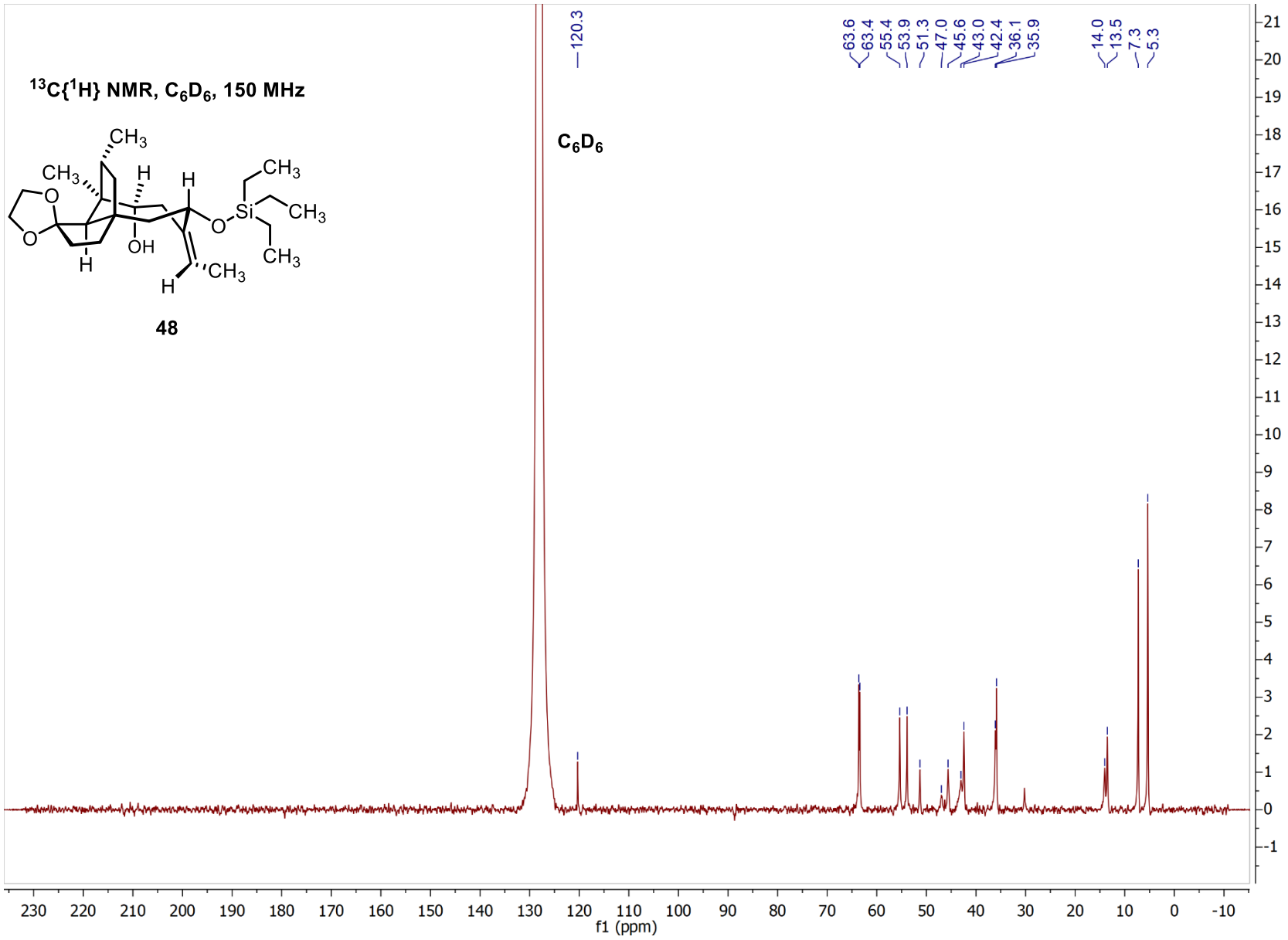

3.787 3.782 3.770 3.765 3.546 3.534 3.522 3.431 3.421 3.414 3.411 3.390 3.380 3.370 3.367 3.363 3.359 3.349 3.340 3.323 3.320 3.313 3.303 2.584 2.562 2.557 2.553 2.473 2.169 2.147 2.135 2.122 2.032 1.898 1.886 1.875 1.864 1.730 1.718 1.710 1.706 1.702 1.694 1.681 1.656 1.644 1.633 1.622 1.583 1.576 1.571 1.565 1.554 1.543 1.470 1.466 1.462 1.456 1.448 1.435 1.339 1.310 1.298 1.290 1.279 1.206 1.194
^{1}H NMR, C_6D_6, 600 MHz
CH3
CH3
OH
CH3
O
O
H
OH
S40
C_6HD_5
0.83 1.88 3.60 0.89 0.85 1.06 0.88 1.16 2.02 1.36 2.01 3.75 3.21 1.43 2.97
f1 (ppm)

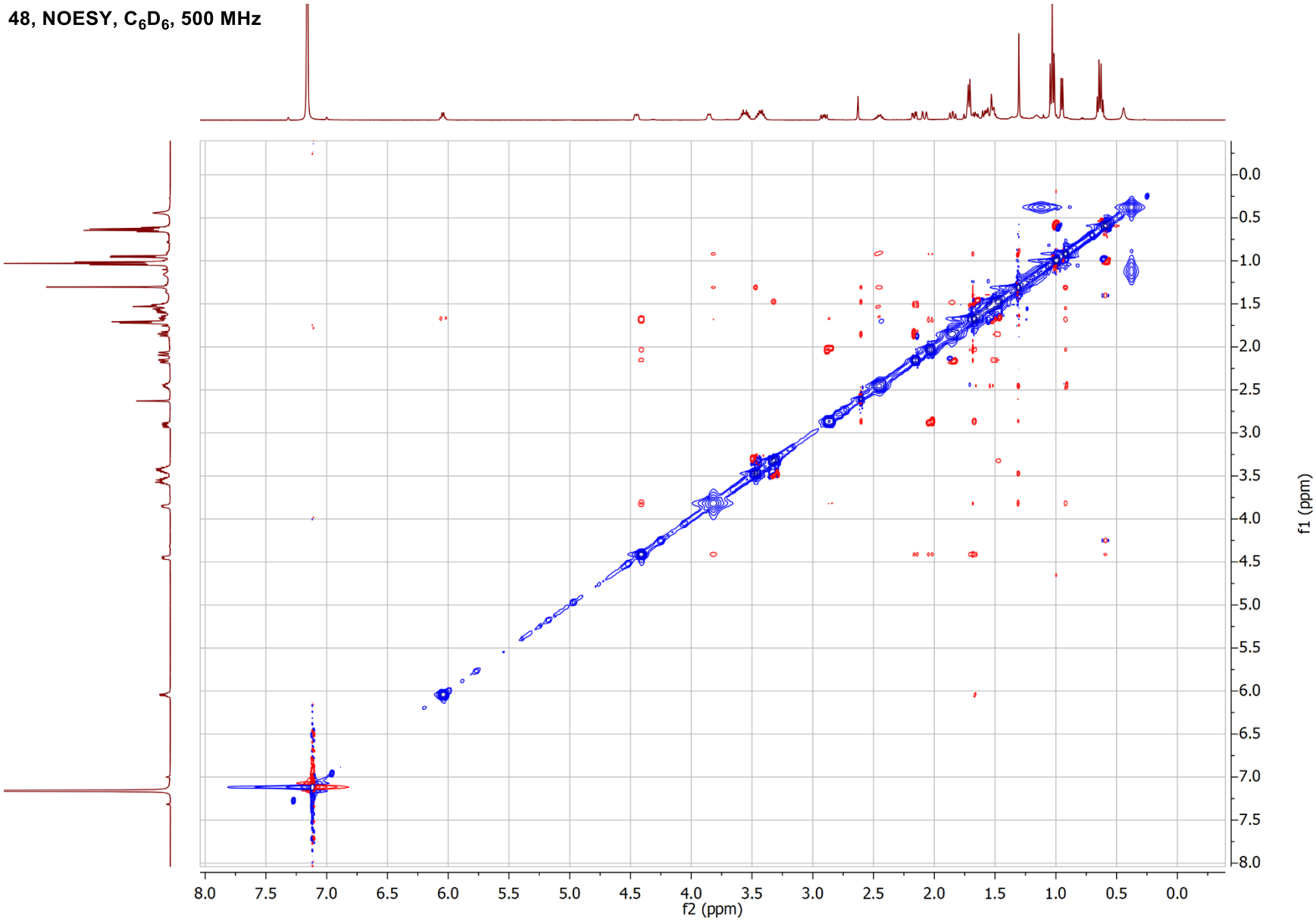

13C{1H} NMR, C6D6, 150 MHz
CH3
CH3
OH
CH3
O
O
H
OH
S40
C6D6
119.4
78.5
77.6
74.3
64.4
62.8
60.7
60.4
50.8
49.7
46.5
46.5
45.7
35.8
35.5
25.1
16.5
16.2
3.3
500
450
400
350
300
250
200
150
100
50
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

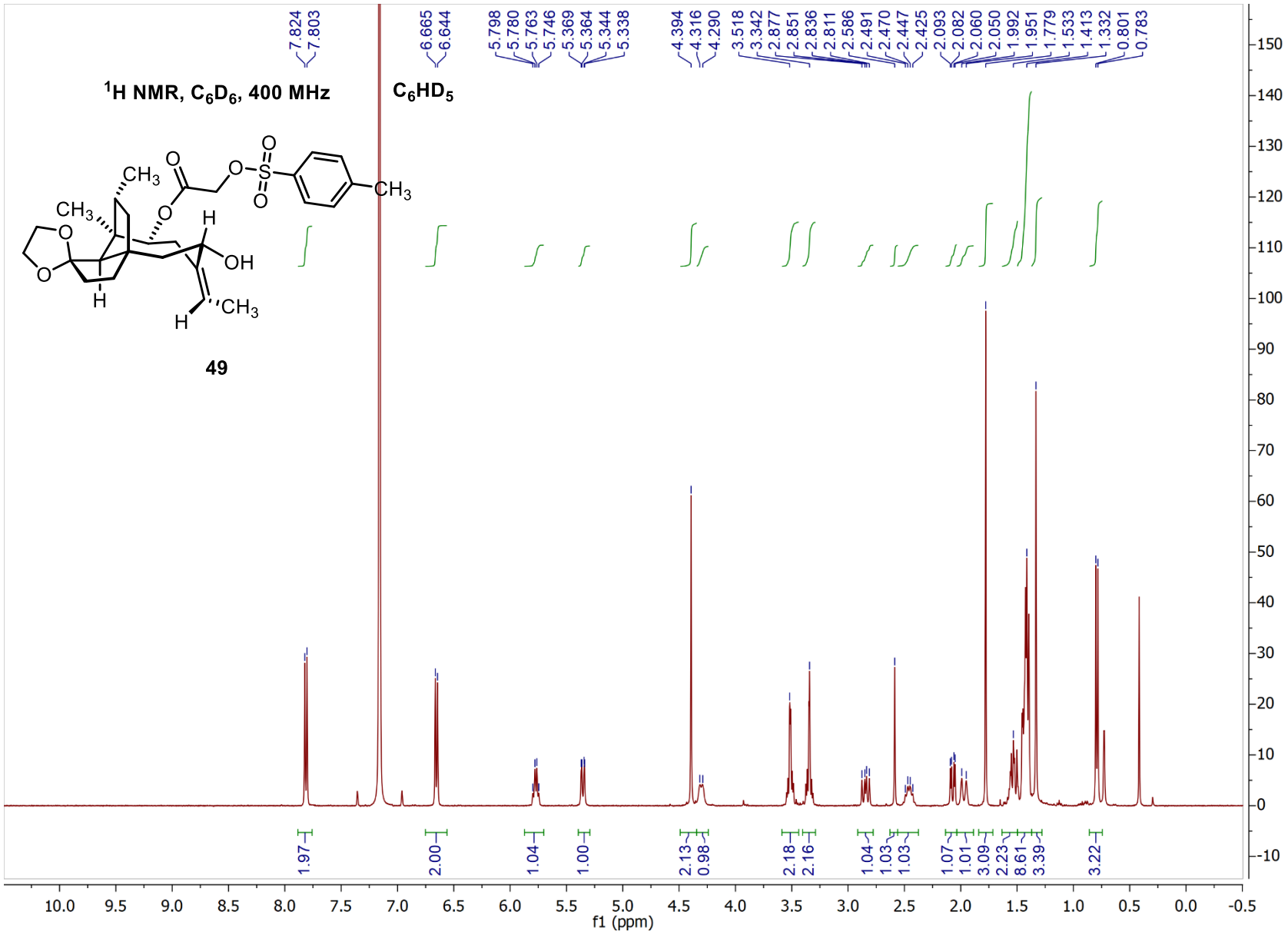

9.504
9.501
^{1}H NMR, C_6D_6, 600 MHz
CH3
CH3
OH
CH3
O
O
H
O
47
C_6HD_5
3.651
3.647
3.634
3.630
3.343
2.548
2.468
2.392
2.263
2.259
2.233
2.118
2.048
2.038
2.026
2.013
2.001
1.866
1.754
1.650
1.472
1.239
1.083
1.071
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0.77
1.00
5.04
1.31
1.22
1.08
1.04
1.25
1.32
1.81
1.91
3.58
7.88
4.38
2.71
10.0
9.5
9.0
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
1.0
0.5
0.0
-0.5
f1 (ppm)

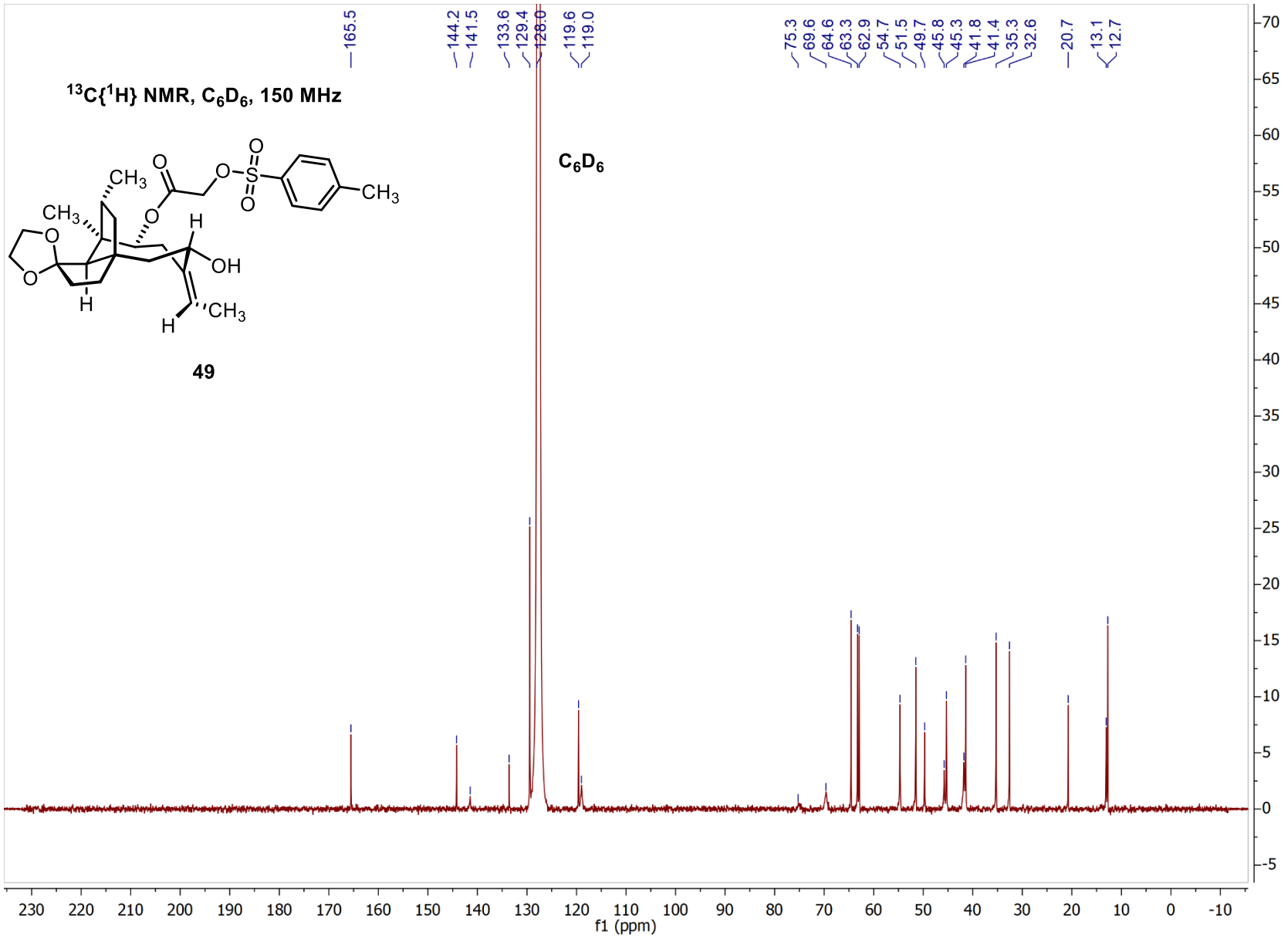

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
47
C_6D_6
201.3
118.9
78.6
77.4
74.5
64.6
62.8
60.8
57.6
50.5
48.5
46.6
45.8
36.5
35.8
25.1
16.6
16.4
3.2
f1 (ppm)

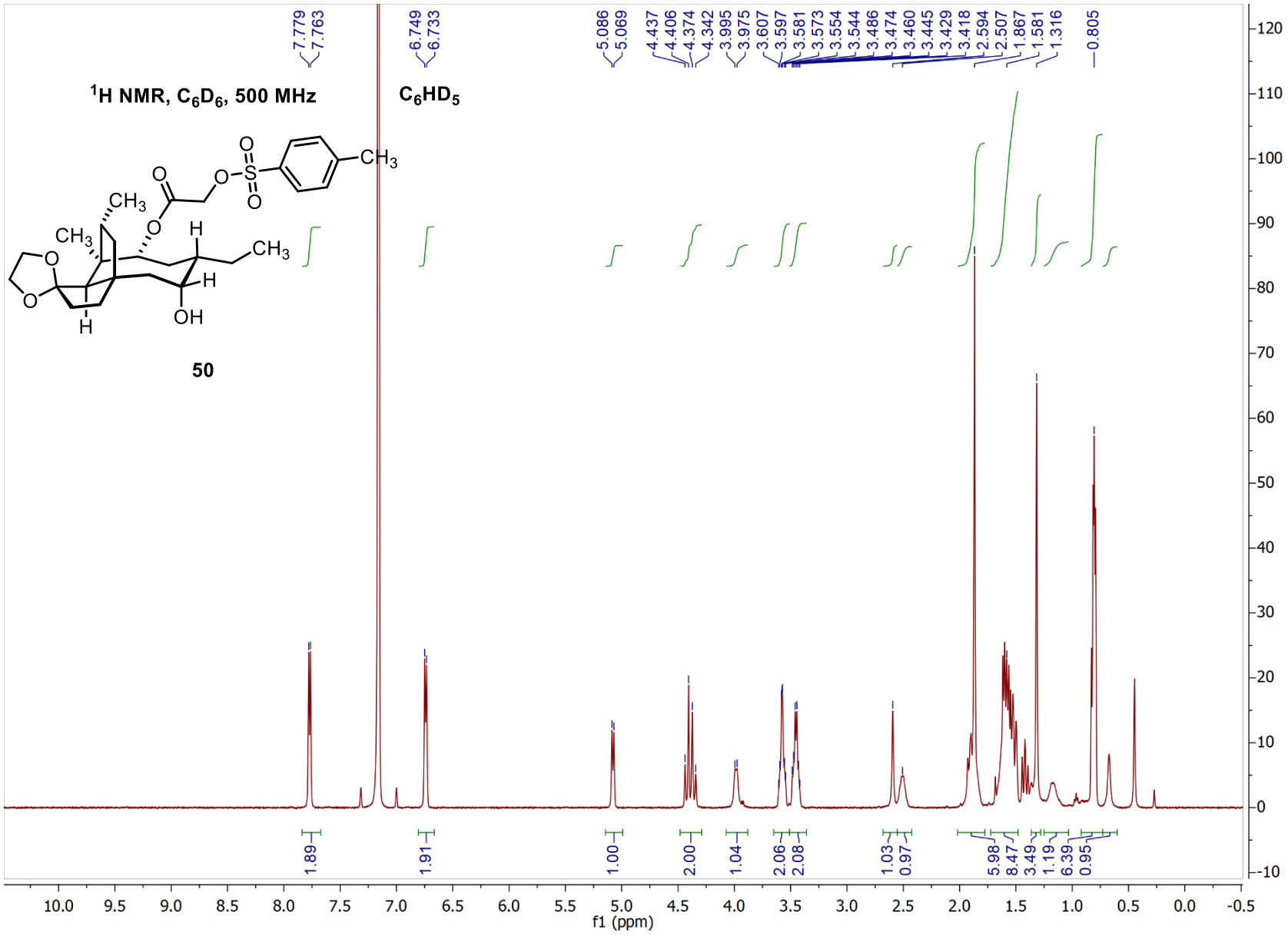

^{1}H NMR, C_6D_6, 500 MHz
C_6HD_5
48
f1 (ppm)

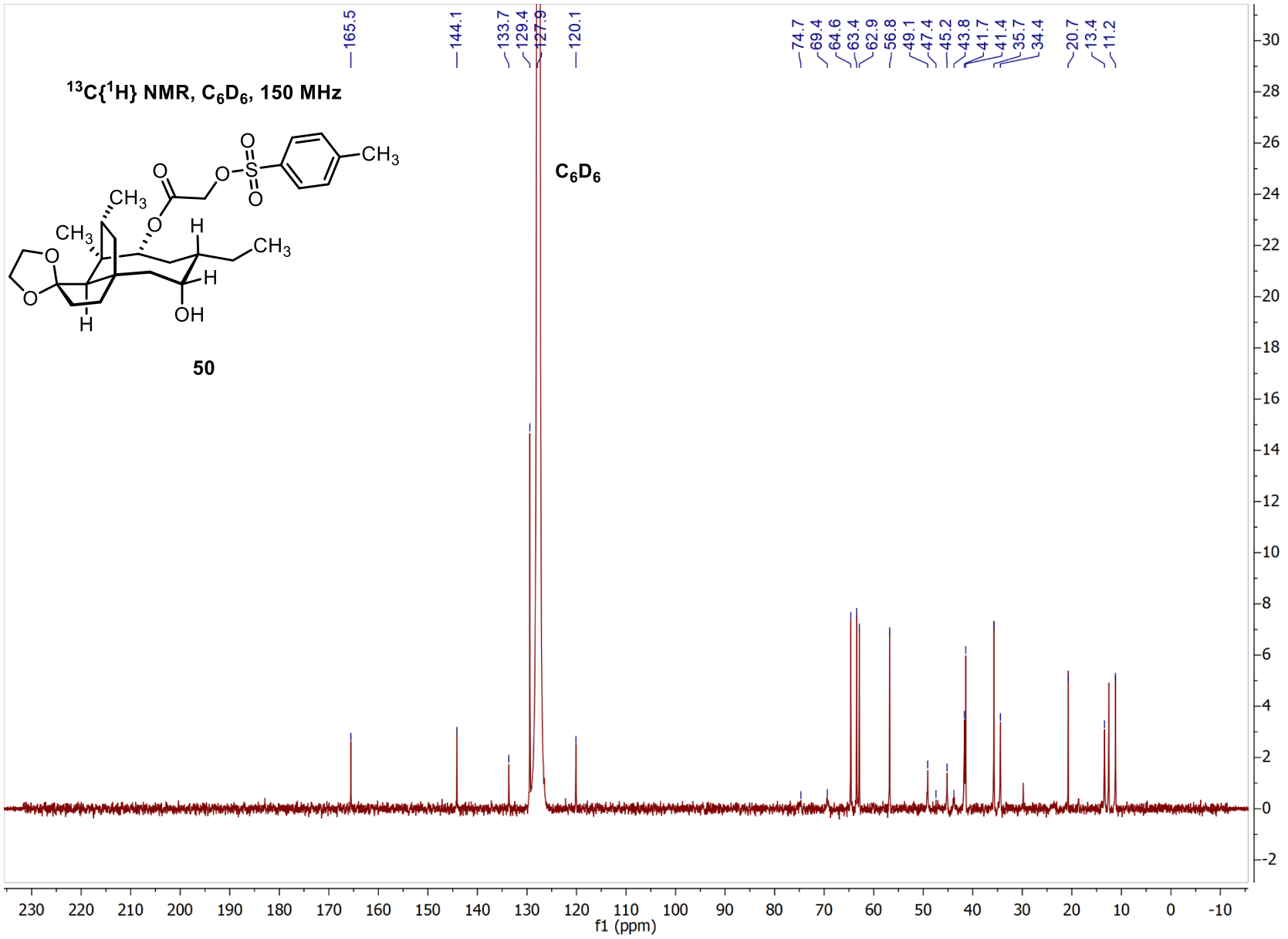

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
48
C_6D_6
120.3
63.6
63.4
55.4
53.9
51.3
47.0
45.6
43.0
42.4
36.1
35.9
14.0
13.5
7.3
5.3
f1 (ppm)

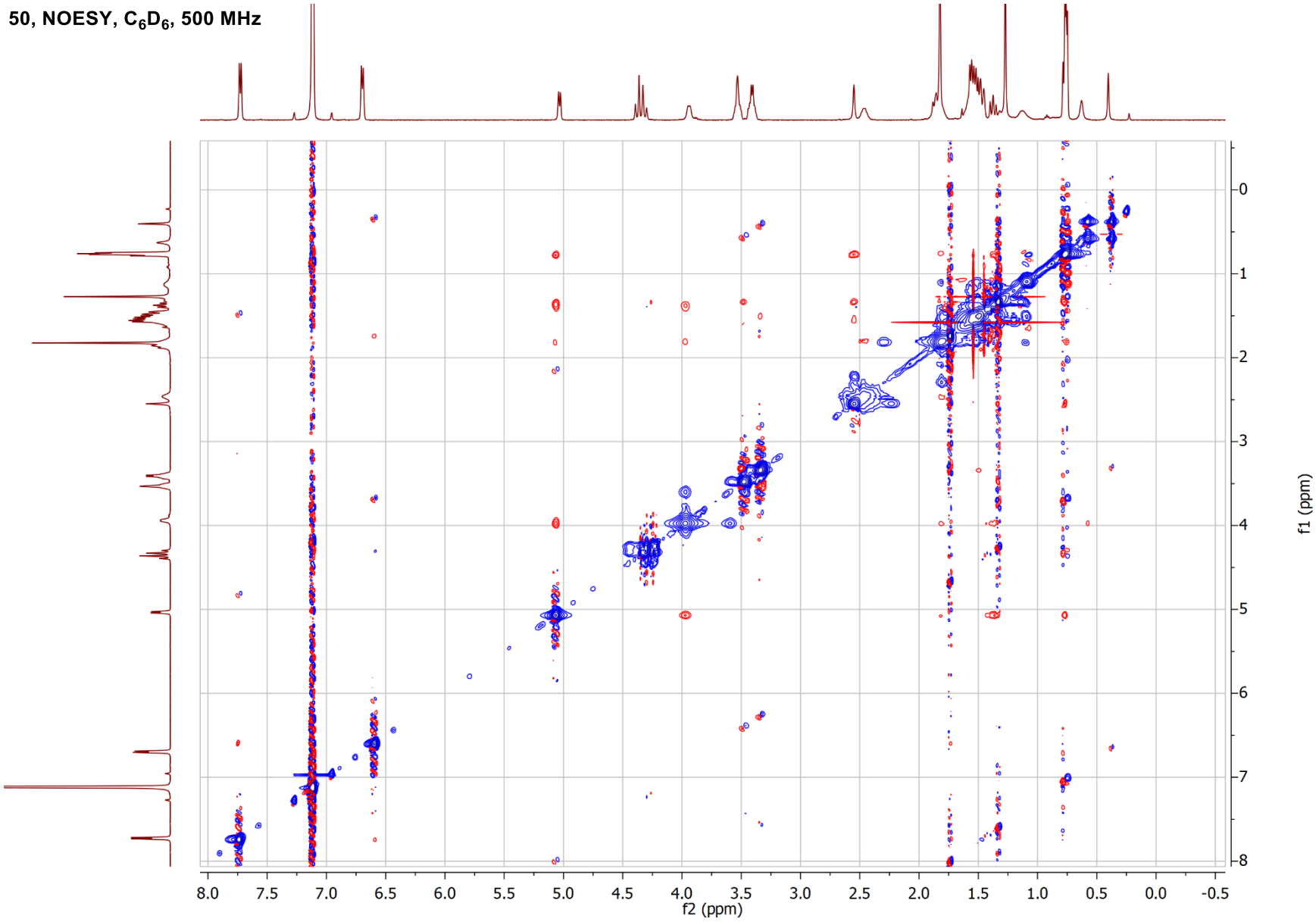

48, NOESY, C6D6, 500 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

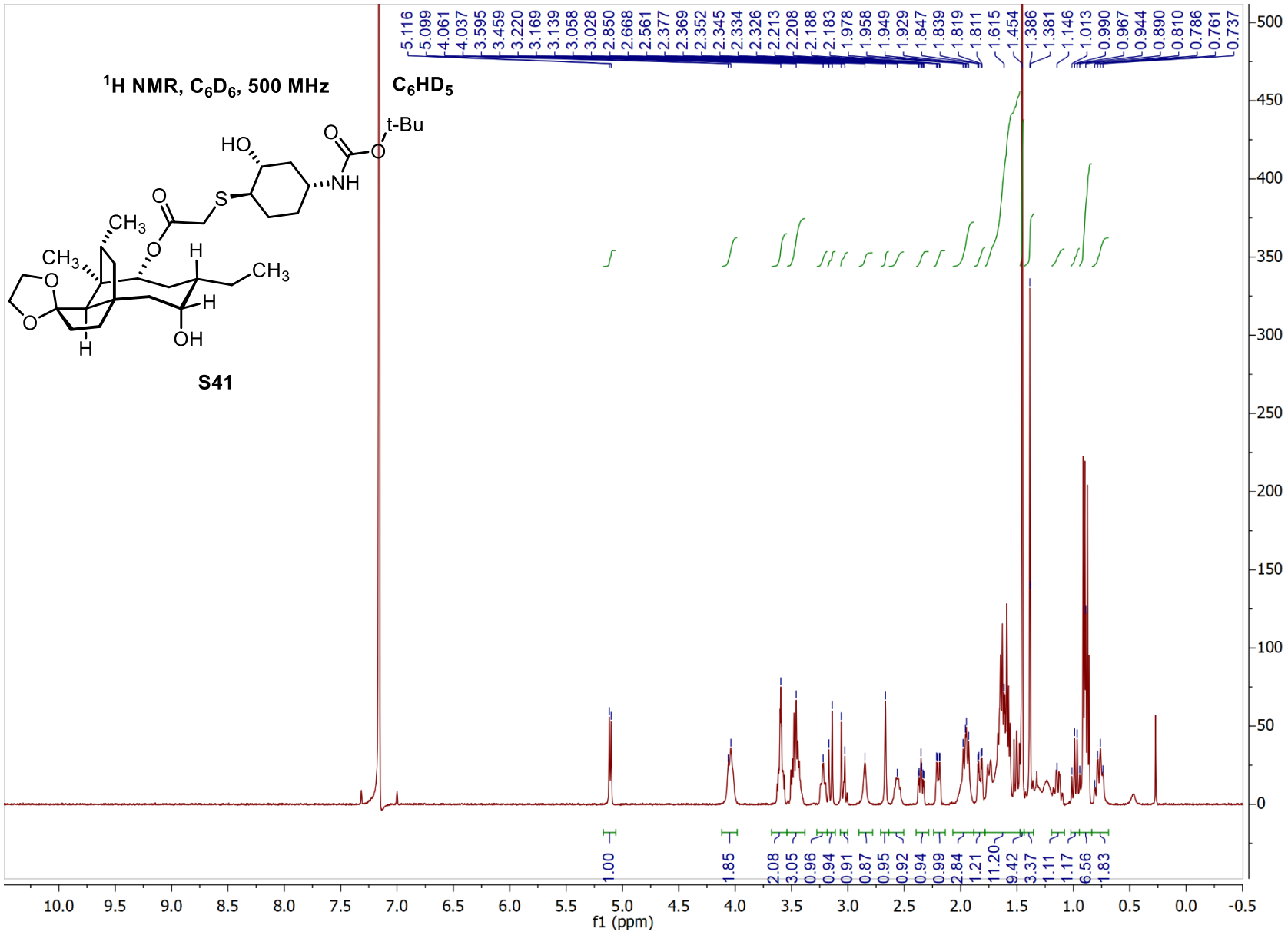

7.824
7.803
6.665
6.644
5.798
5.780
5.763
5.746
5.369
5.364
5.344
5.338
4.394
4.316
4.290
3.518
3.342
2.877
2.851
2.836
2.811
2.586
2.491
2.470
2.447
2.425
2.093
2.082
2.060
2.050
1.992
1.951
1.779
1.533
1.413
1.332
0.801
0.783
^{1}H NMR, C_6D_6, 400 MHz
C_6HD_5
49
1.97
2.00
1.04
1.00
2.13
0.98
2.18
2.16
1.04
1.03
1.03
1.07
1.01
3.09
2.23
8.61
3.39
3.22
f1 (ppm)

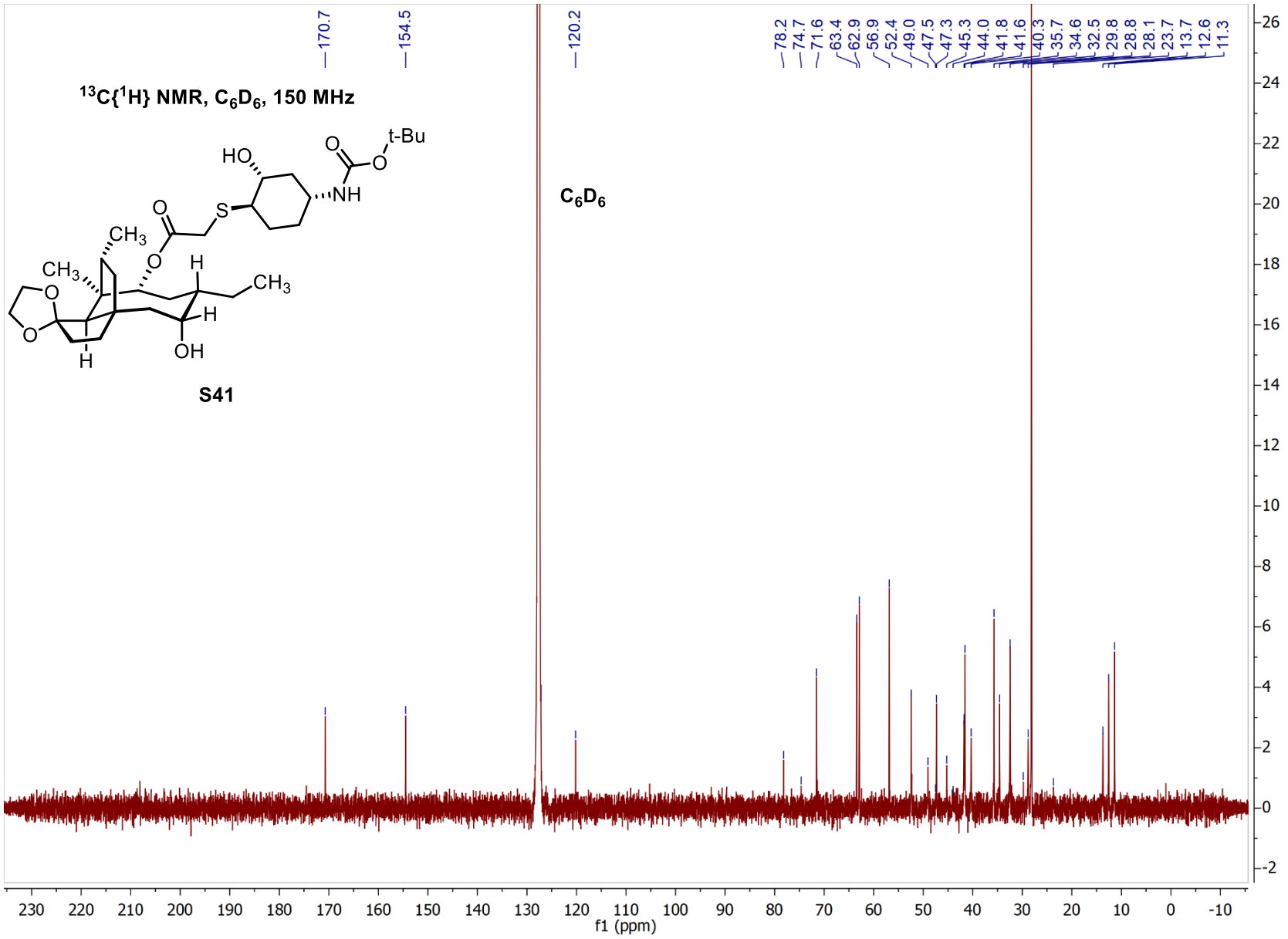

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
49
165.5
144.2
141.5
133.6
129.4
128.0
119.6
119.0
75.3
69.6
64.6
63.3
62.9
54.7
51.5
49.7
45.8
45.3
41.8
41.4
35.3
32.6
20.7
13.1
12.7
f1 (ppm)

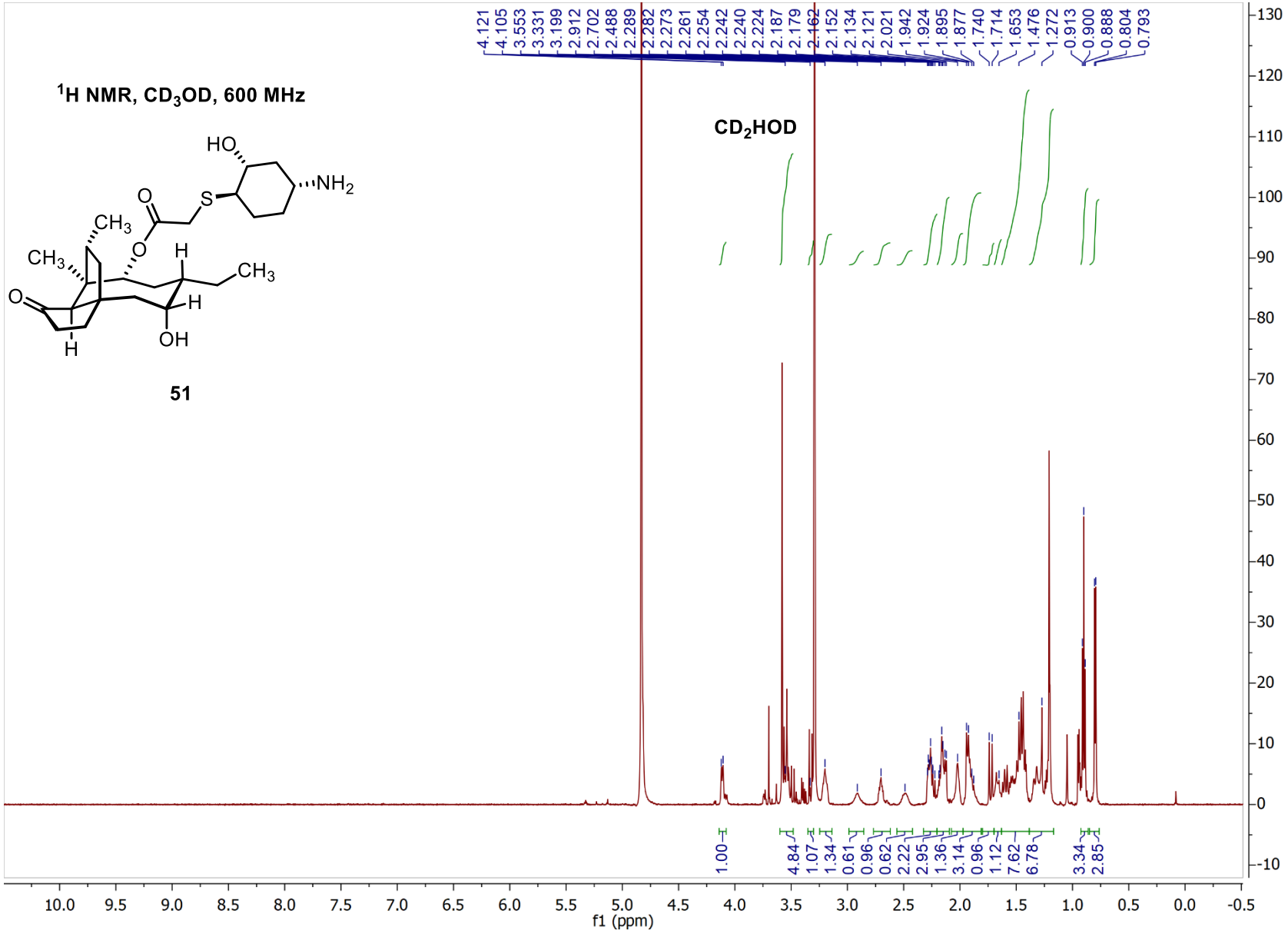

^{1}H NMR, C_6D_6, 500 MHz
C_6HD_5
50
f1 (ppm)

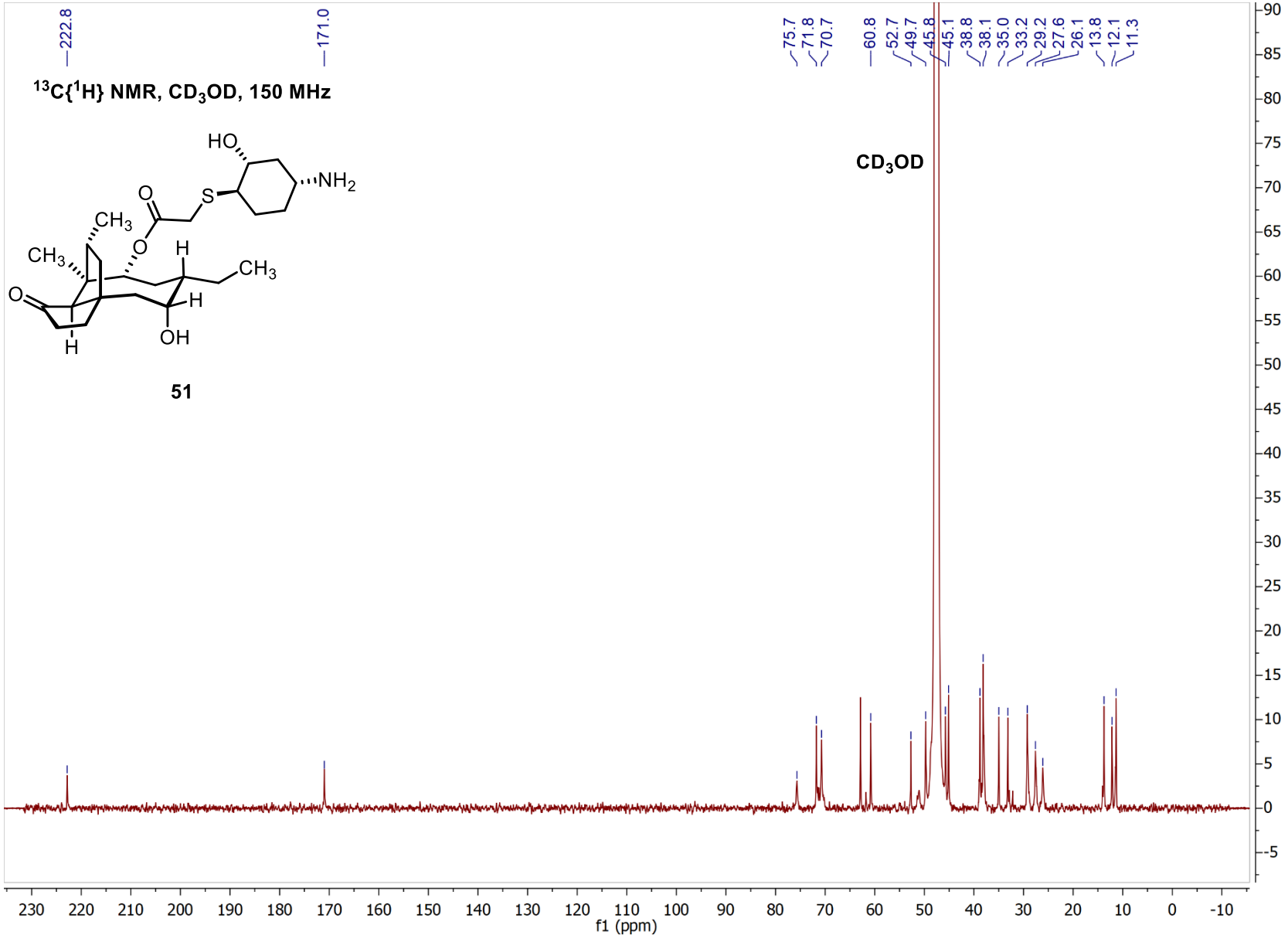

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
50
C_6D_6
165.5
144.1
133.7
129.4
127.9
120.1
74.7
69.4
64.6
63.4
62.9
56.8
49.1
47.4
45.2
43.8
41.7
41.4
35.7
34.4
20.7
13.4
11.2
f1 (ppm)

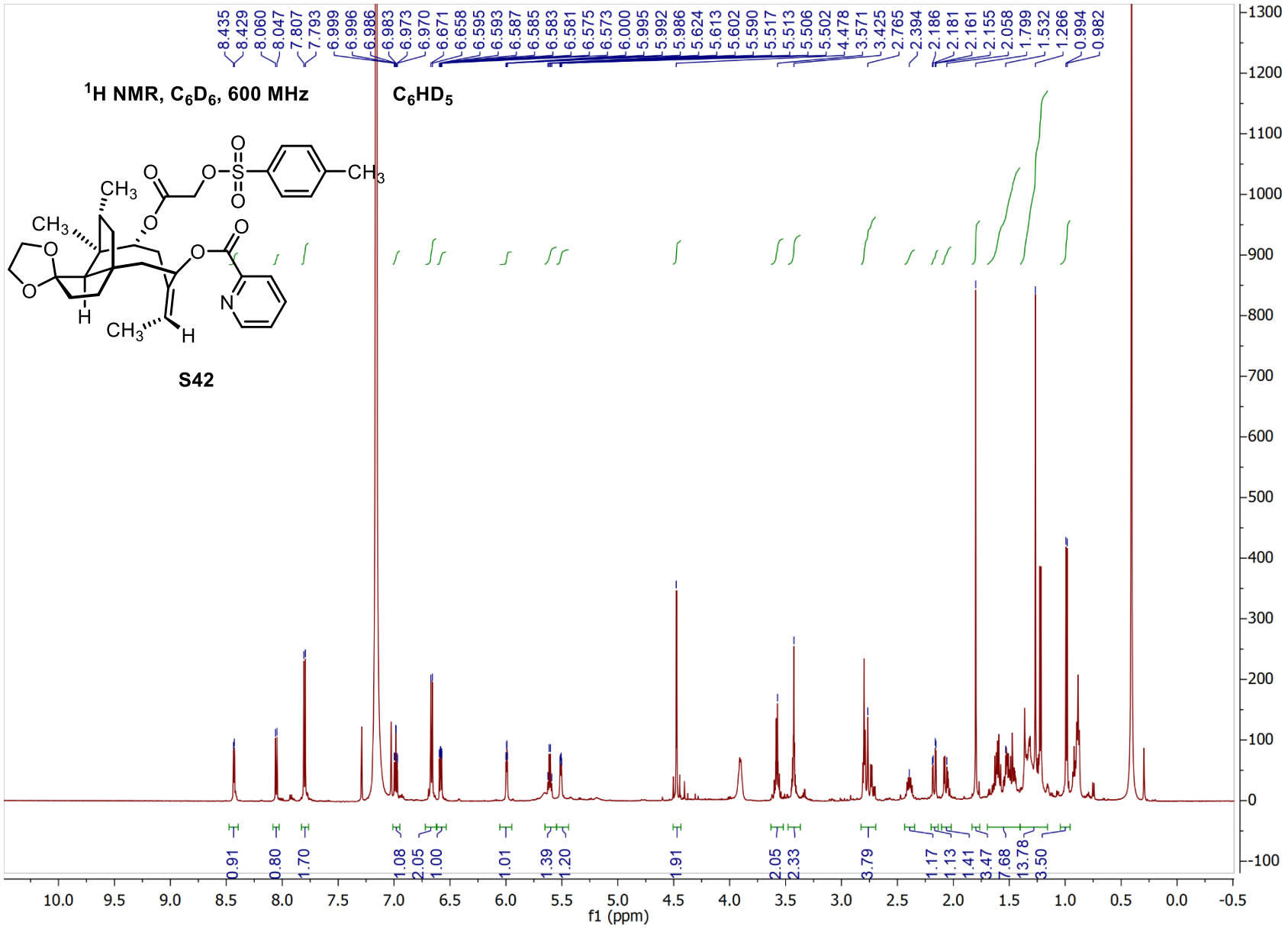

50, NOESY, C6D6, 500 MHz
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

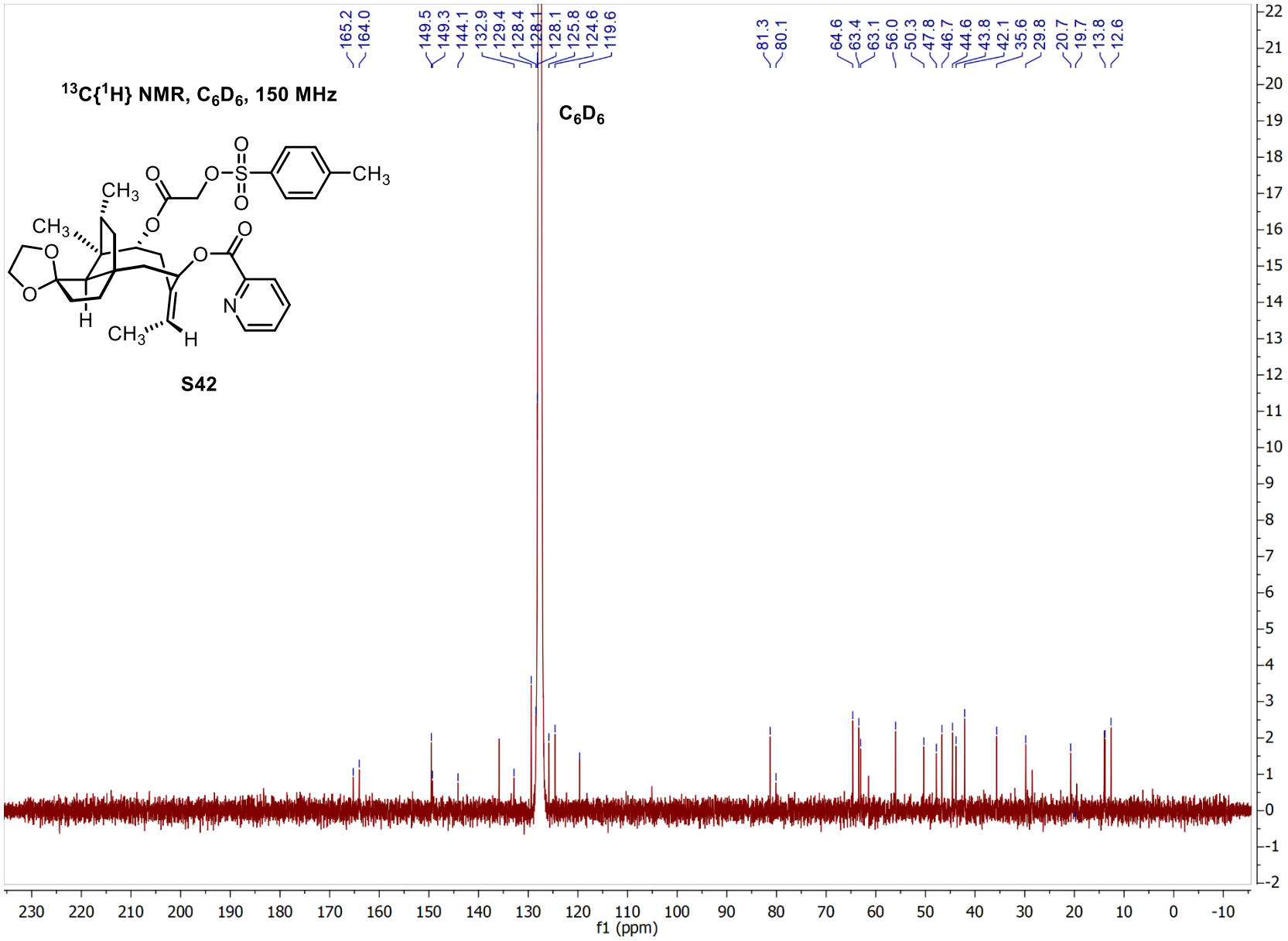

^{1}H NMR, C_6D_6, 500 MHz
C_6HD_5
t-Bu
HO
O
NH
S
CH3
CH3
CH3
O
H
H
H
OH
S41
5.116
5.099
4.061
4.037
3.595
3.459
3.220
3.169
3.139
3.058
3.028
2.850
2.668
2.561
2.377
2.369
2.352
2.345
2.334
2.326
2.213
2.208
2.188
2.183
1.978
1.958
1.949
1.929
1.847
1.839
1.819
1.811
1.615
1.454
1.386
1.381
1.146
1.013
0.990
0.967
0.944
0.890
0.810
0.786
0.761
0.737
1.00
1.85
2.08
3.05
0.96
0.94
0.91
0.87
0.95
0.92
0.94
0.99
2.84
1.21
11.20
9.42
3.37
1.11
1.17
6.56
1.83
f1 (ppm)

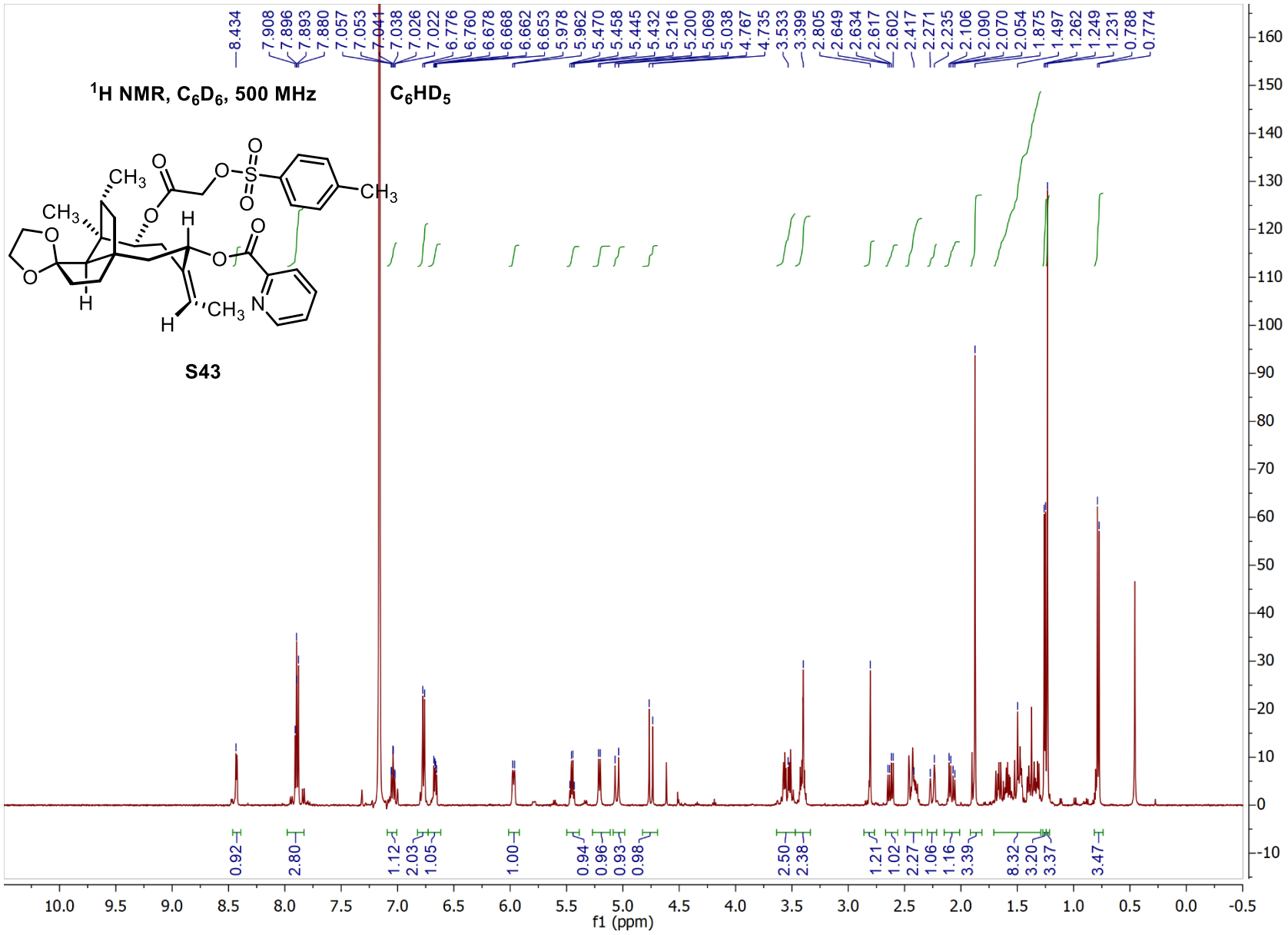

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
S41
C_6D_6
170.7
154.5
120.2
78.2
74.7
71.6
63.4
62.9
56.9
52.4
49.0
47.5
47.3
45.3
44.0
41.8
41.6
40.3
35.7
34.6
32.5
29.8
28.8
28.1
23.7
13.7
12.6
11.3
f1 (ppm)

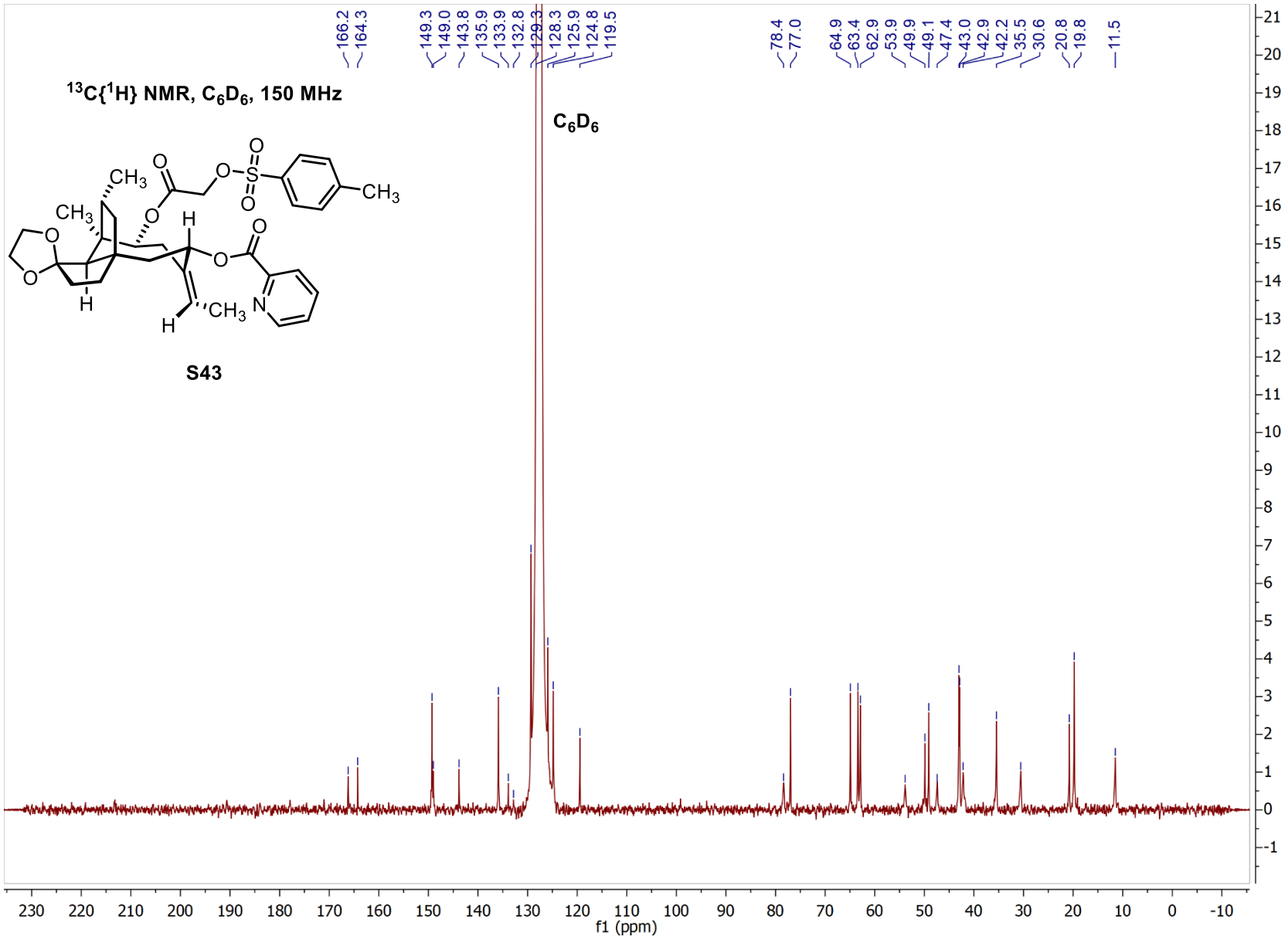

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
51
4.121
4.105
3.553
3.331
3.199
2.912
2.702
2.488
2.289
2.282
2.273
2.261
2.254
2.242
2.240
2.224
2.187
2.179
2.162
2.152
2.134
2.121
2.021
1.942
1.924
1.895
1.877
1.740
1.714
1.653
1.476
1.272
0.913
0.900
0.888
0.804
0.793
1.00
4.84
1.07
1.34
0.61
0.96
0.62
2.22
2.95
1.36
3.14
0.96
1.12
7.62
6.78
3.34
2.85
f1 (ppm)

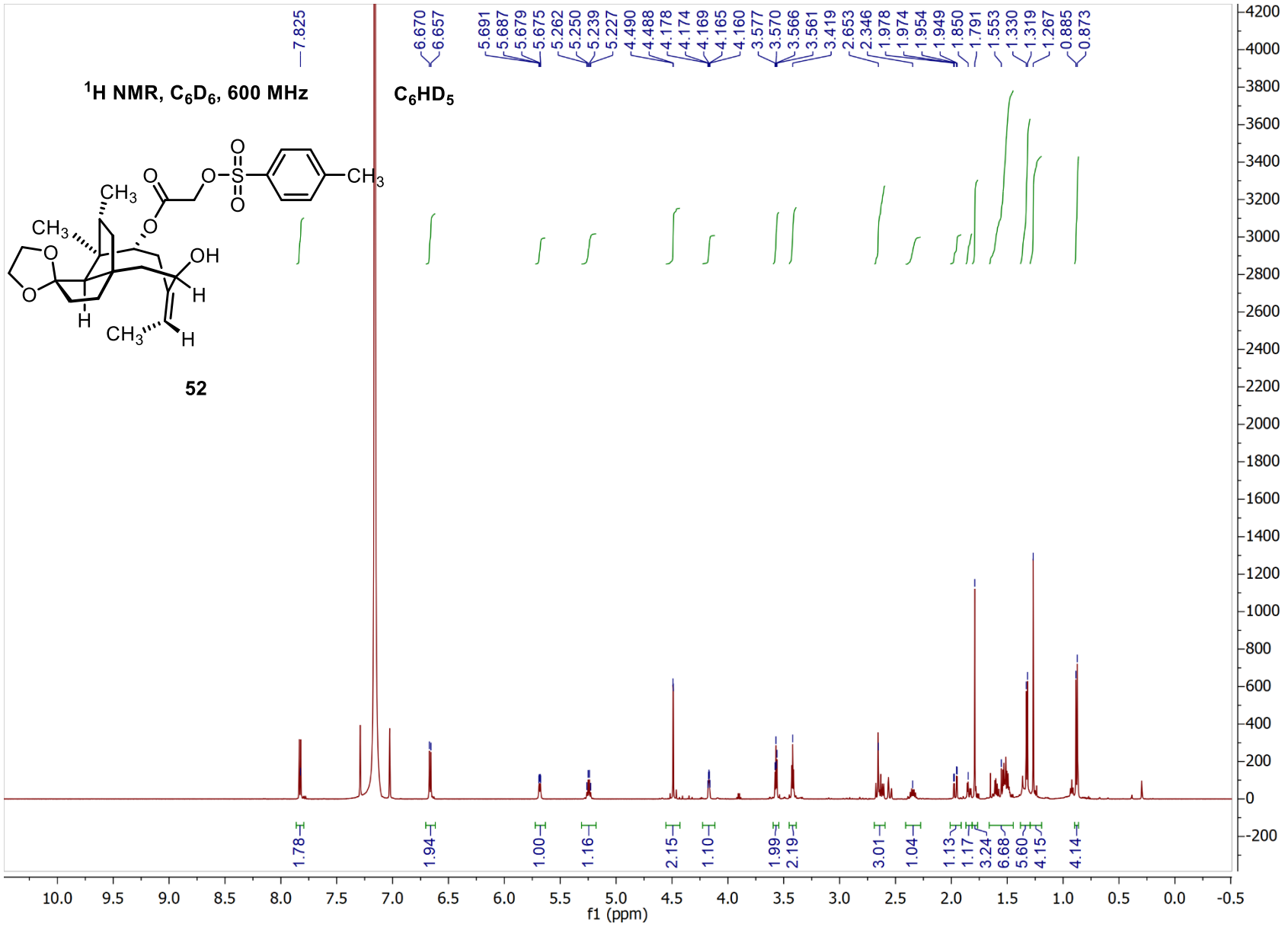

222.8
171.0
75.7
71.8
70.7
60.8
52.7
49.7
45.8
45.1
38.8
38.1
35.0
33.2
29.2
27.6
26.1
13.8
12.1
11.3
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
HO
NH2
O
S
CH3
CH3
O
H
CH3
O
H
OH
H
51
f1 (ppm)

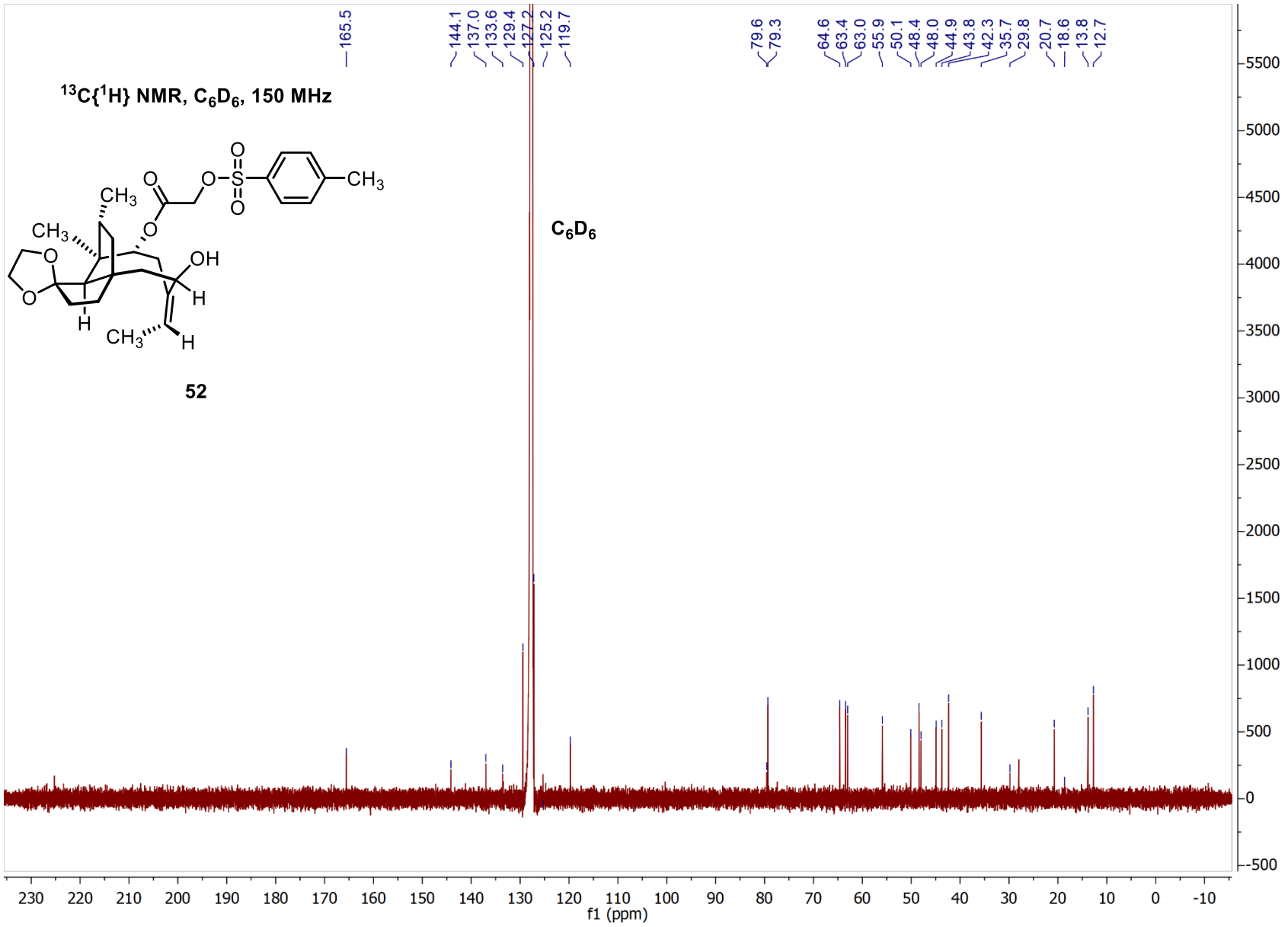

8.435
8.429
8.060
8.047
7.807
7.793
6.999
6.996
6.986
6.983
6.973
6.970
6.671
6.658
6.595
6.593
6.587
6.585
6.583
6.581
6.575
6.573
6.000
5.995
5.992
5.986
5.624
5.613
5.602
5.590
5.517
5.513
5.506
5.502
4.478
3.571
3.425
2.765
2.394
2.186
2.181
2.161
2.155
2.058
1.799
1.532
1.266
0.994
0.982
1H NMR, C6D6, 600 MHz
C6HD5
S42
0.91
0.80
1.70
1.08
2.05
1.00
1.01
1.39
1.20
1.91
2.05
2.33
3.79
1.17
1.13
1.41
3.47
7.68
13.78
3.50
f1 (ppm)

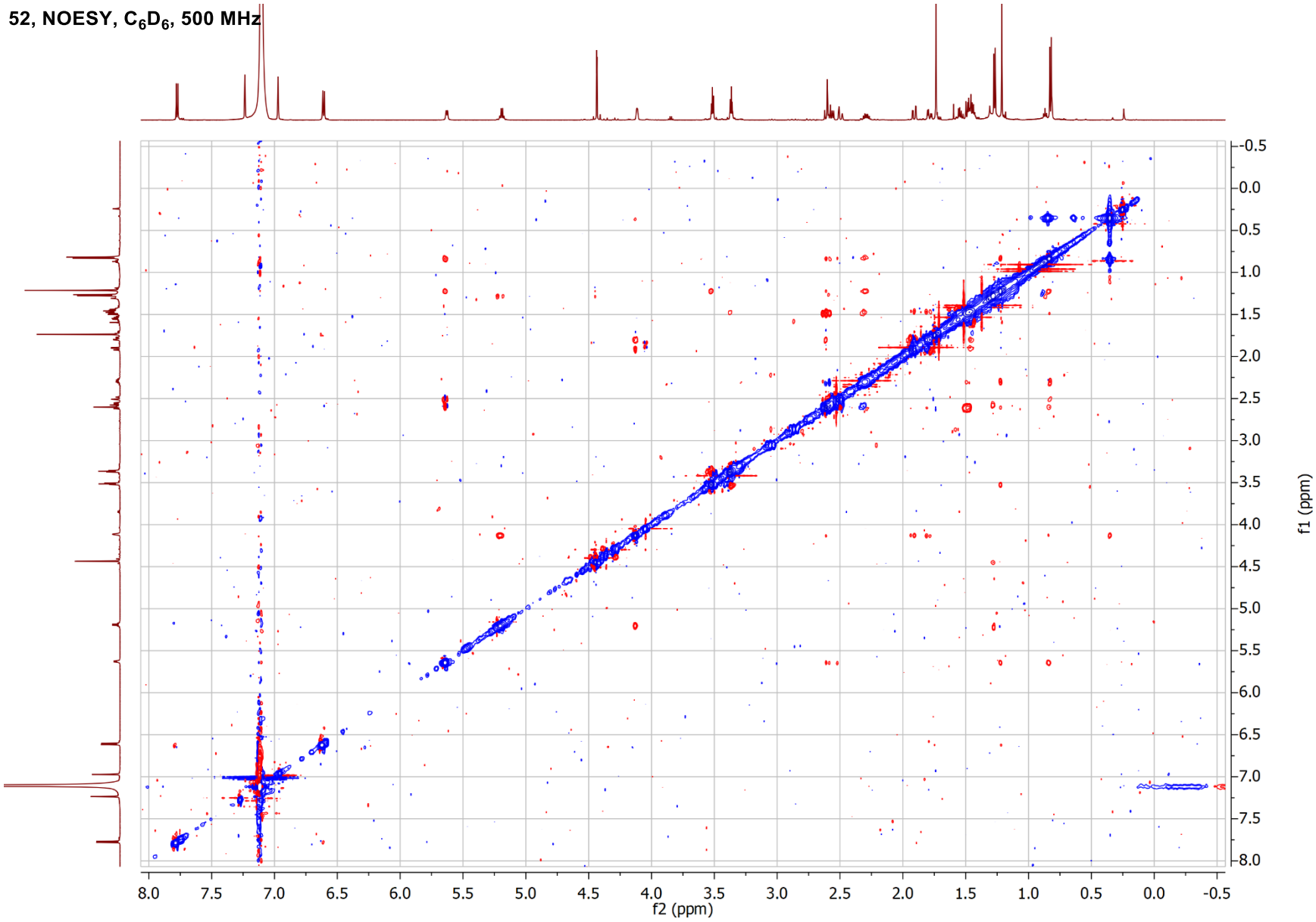

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
S42
165.2
164.0
149.5
149.3
144.1
132.9
129.4
128.4
128.1
128.1
125.8
124.6
119.6
81.3
80.1
64.6
63.4
63.1
56.0
50.3
47.8
46.7
44.6
43.8
42.1
35.6
29.8
20.7
19.7
13.8
12.6
f1 (ppm)

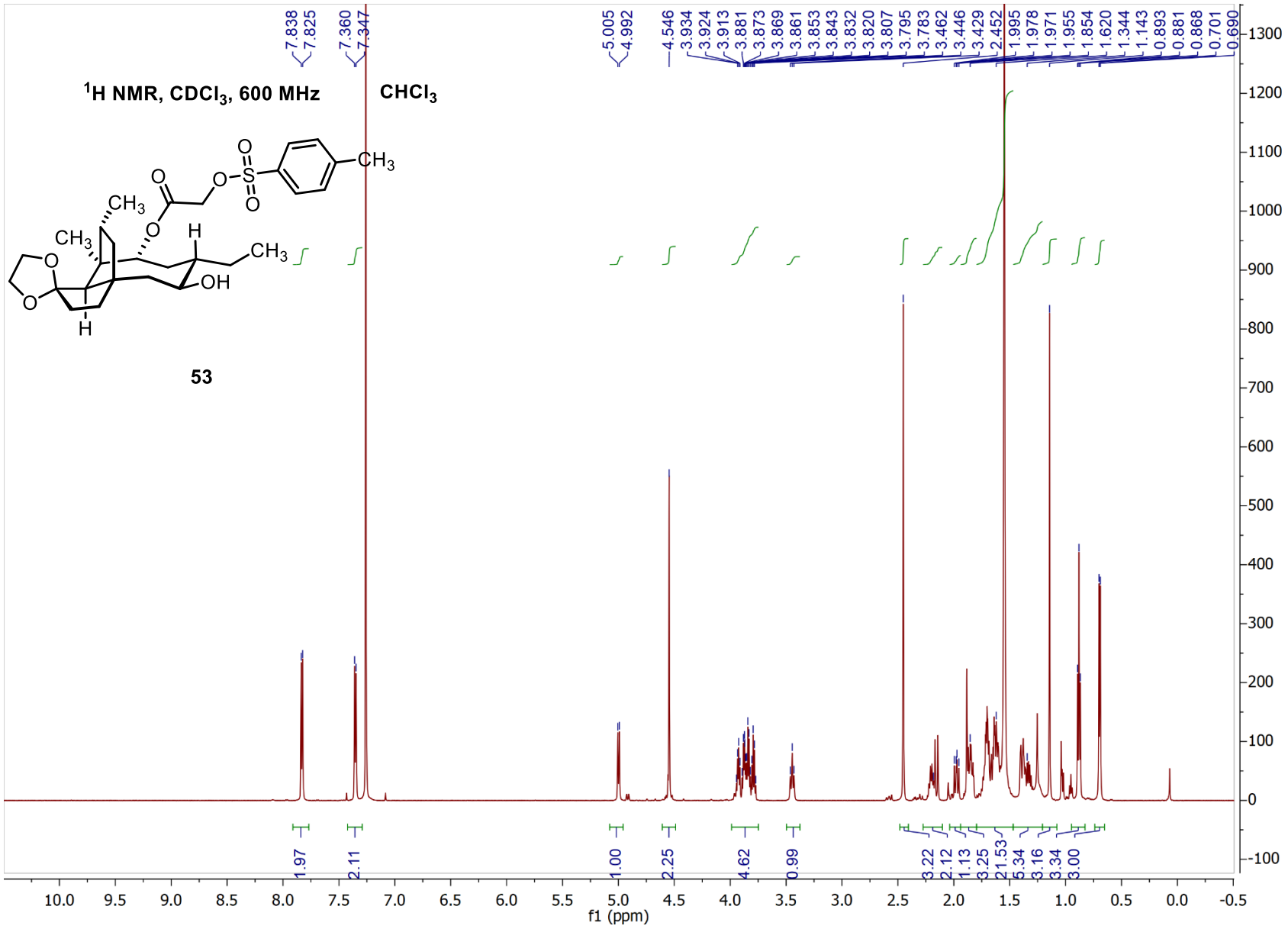

8.434
7.908
7.896
7.893
7.880
7.057
7.053
7.041
7.038
7.026
7.022
6.776
6.760
6.678
6.668
6.662
6.653
5.978
5.962
5.470
5.458
5.445
5.432
5.216
5.200
5.069
5.038
4.767
4.735
3.533
3.399
2.805
2.649
2.634
2.617
2.602
2.417
2.271
2.235
2.106
2.090
2.070
2.054
1.875
1.497
1.262
1.249
1.231
0.788
0.774
^{1}H NMR, C_6D_6, 500 MHz
C_6HD_5
S43
0.92
2.80
1.12
2.03
1.05
1.00
0.94
0.96
0.93
0.98
2.50
2.38
1.21
1.02
2.27
1.06
1.16
3.39
8.32
3.20
3.37
3.47
f1 (ppm)

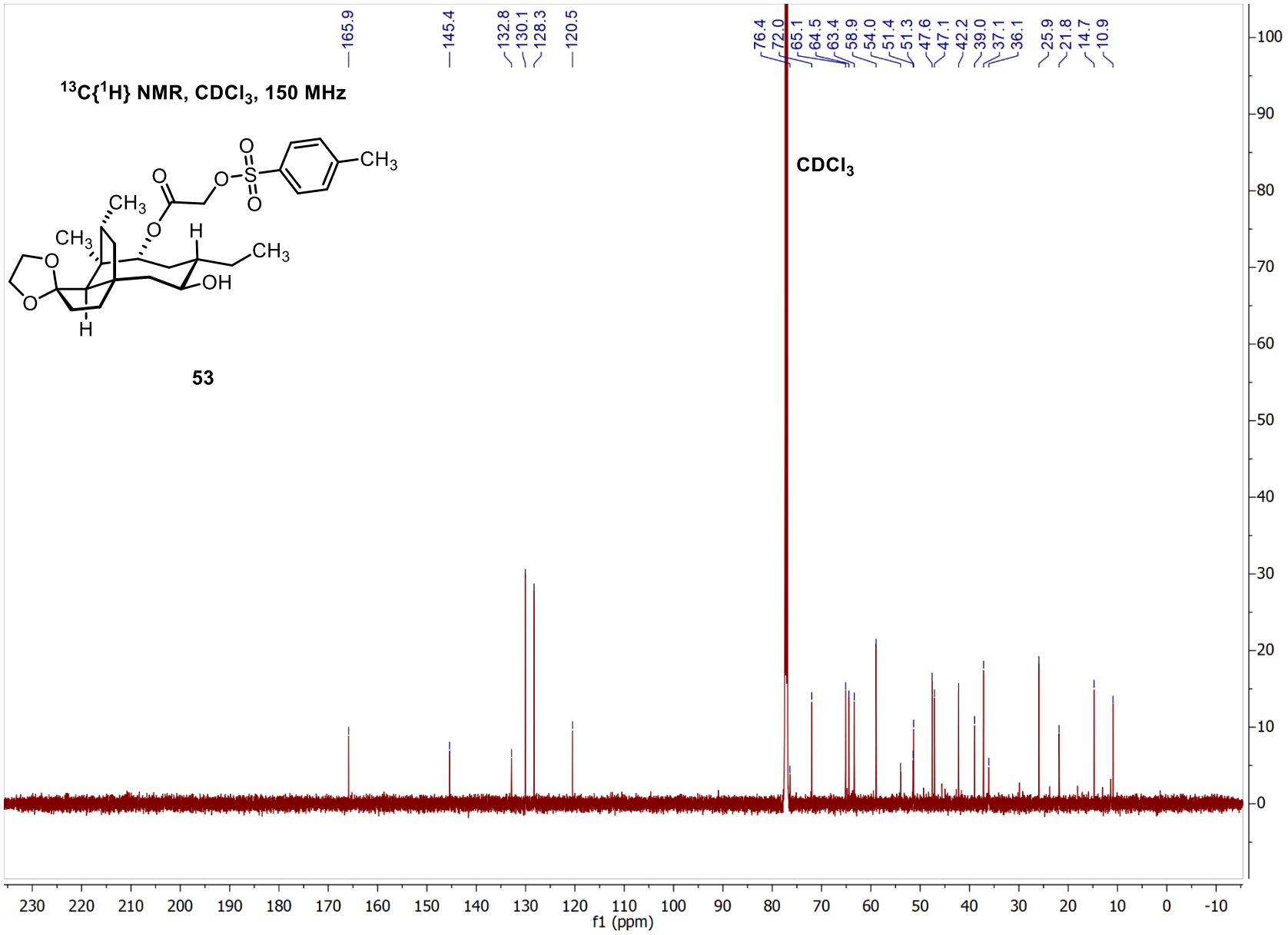

166.2
164.3
149.3
149.0
143.8
135.9
133.9
132.8
129.3
128.3
125.9
124.8
119.5
78.4
77.0
64.9
63.4
62.9
53.9
49.9
49.1
47.4
43.0
42.9
42.2
35.5
30.6
20.8
19.8
11.5
$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
S43
f1 (ppm)

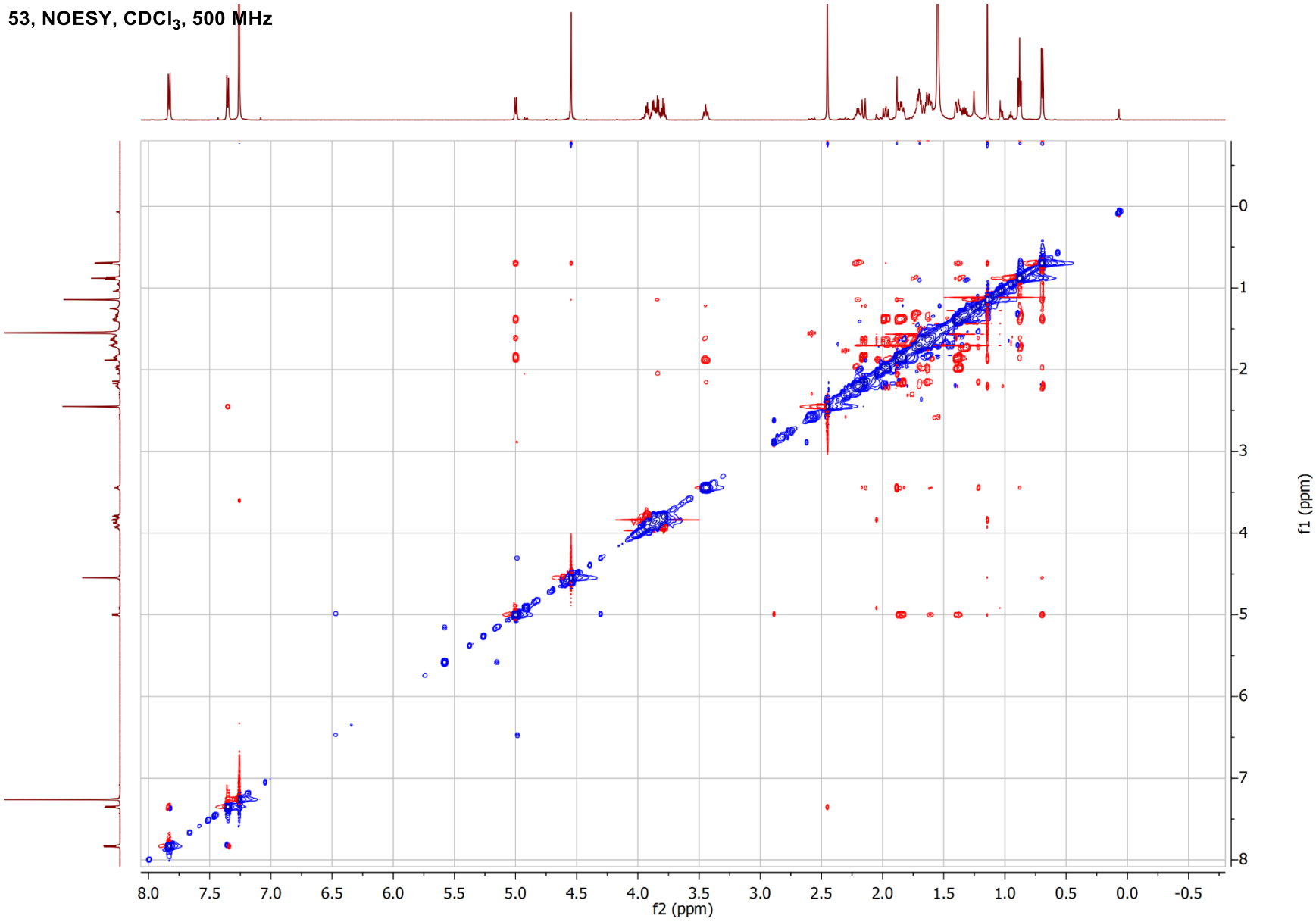

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
52
7.825
6.670
6.657
5.691
5.687
5.679
5.675
5.262
5.250
5.239
5.227
4.490
4.488
4.178
4.174
4.169
4.165
4.160
3.577
3.570
3.566
3.561
3.419
2.653
2.346
1.978
1.974
1.954
1.949
1.850
1.791
1.553
1.330
1.319
1.267
0.885
0.873
1.78
1.94
1.00
1.16
2.15
1.10
1.99
2.19
3.01
1.04
1.13
1.17
3.24
6.68
5.60
4.15
4.14
f1 (ppm)

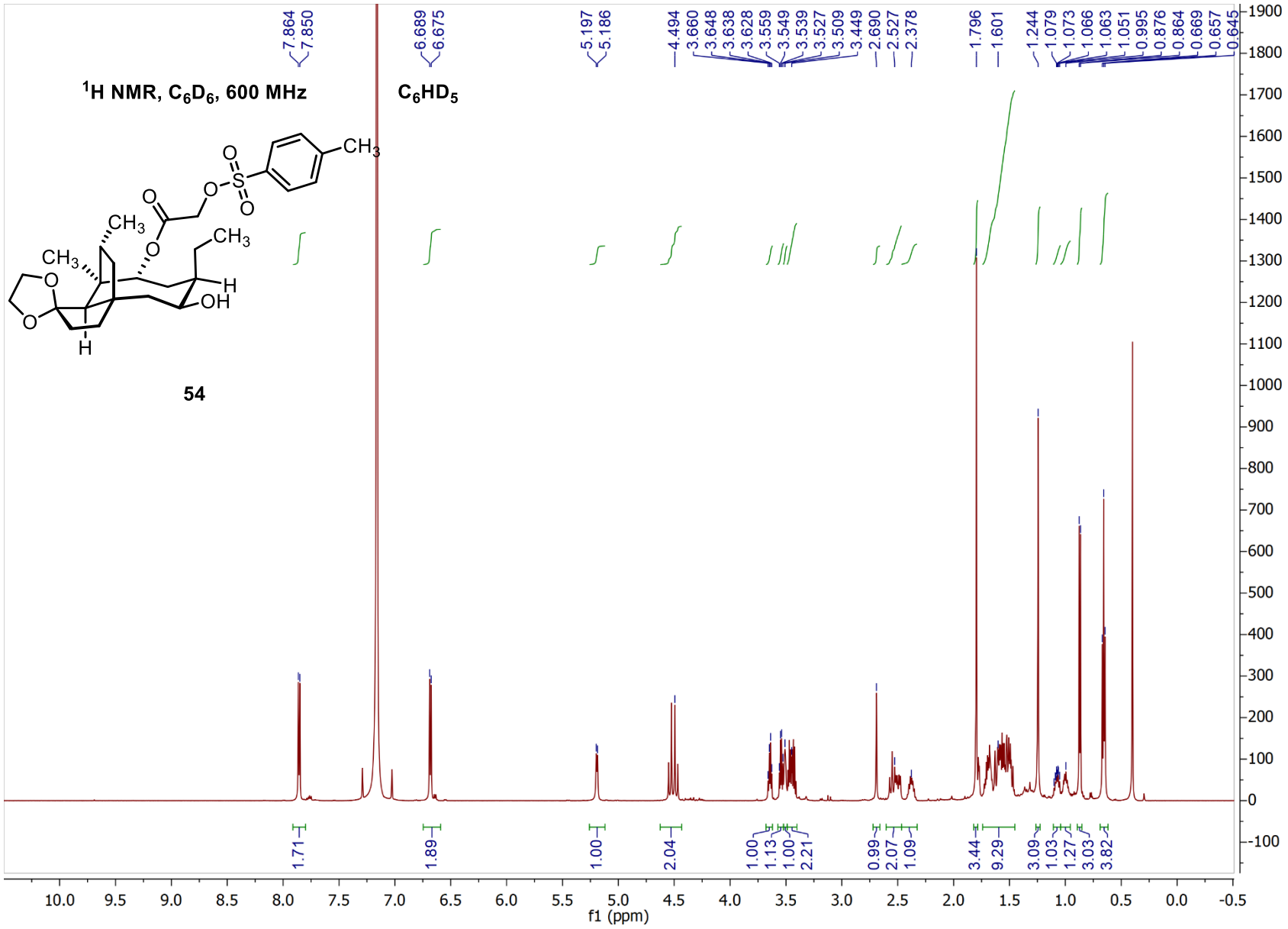

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
52
C_6D_6
165.5
144.1
137.0
133.6
129.4
127.2
125.2
119.7
79.6
79.3
64.6
63.4
63.0
55.9
50.1
48.4
48.0
44.9
43.8
42.3
35.7
29.8
20.7
18.6
13.8
12.7
f1 (ppm)

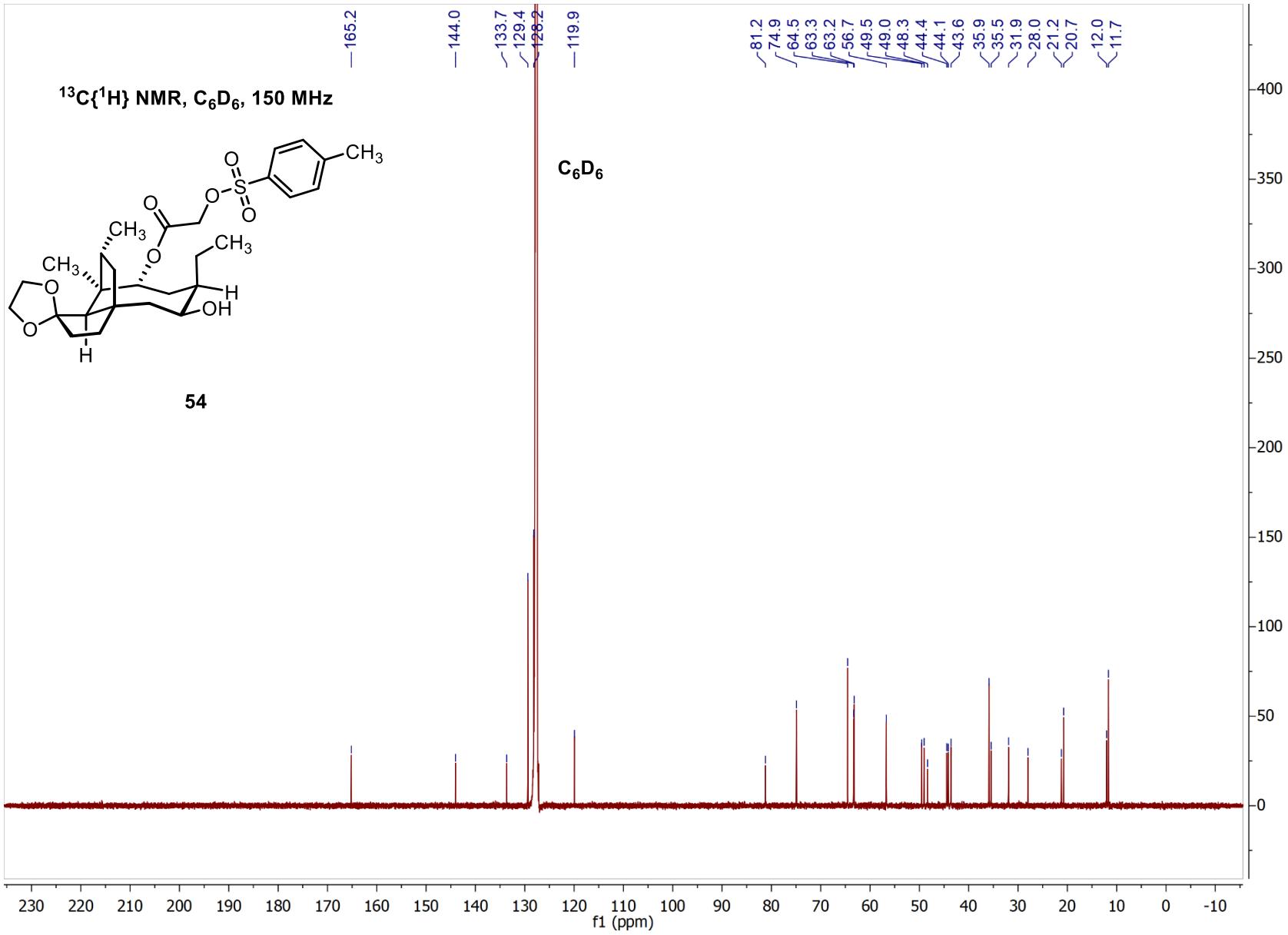

52, NOESY, C6D6, 500 MHz
f2 (ppm)
f1 (ppm)

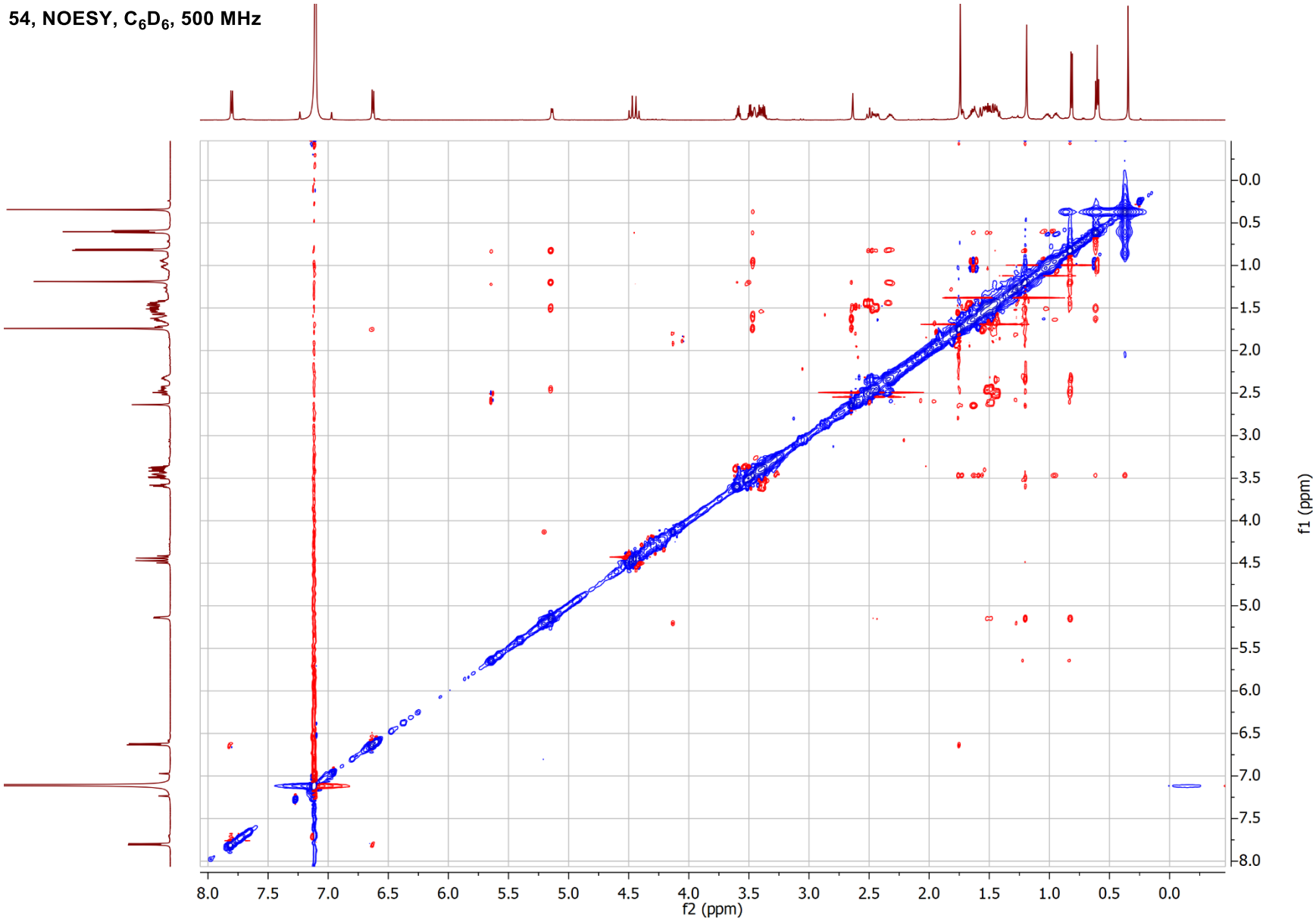

^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
53
f1 (ppm)

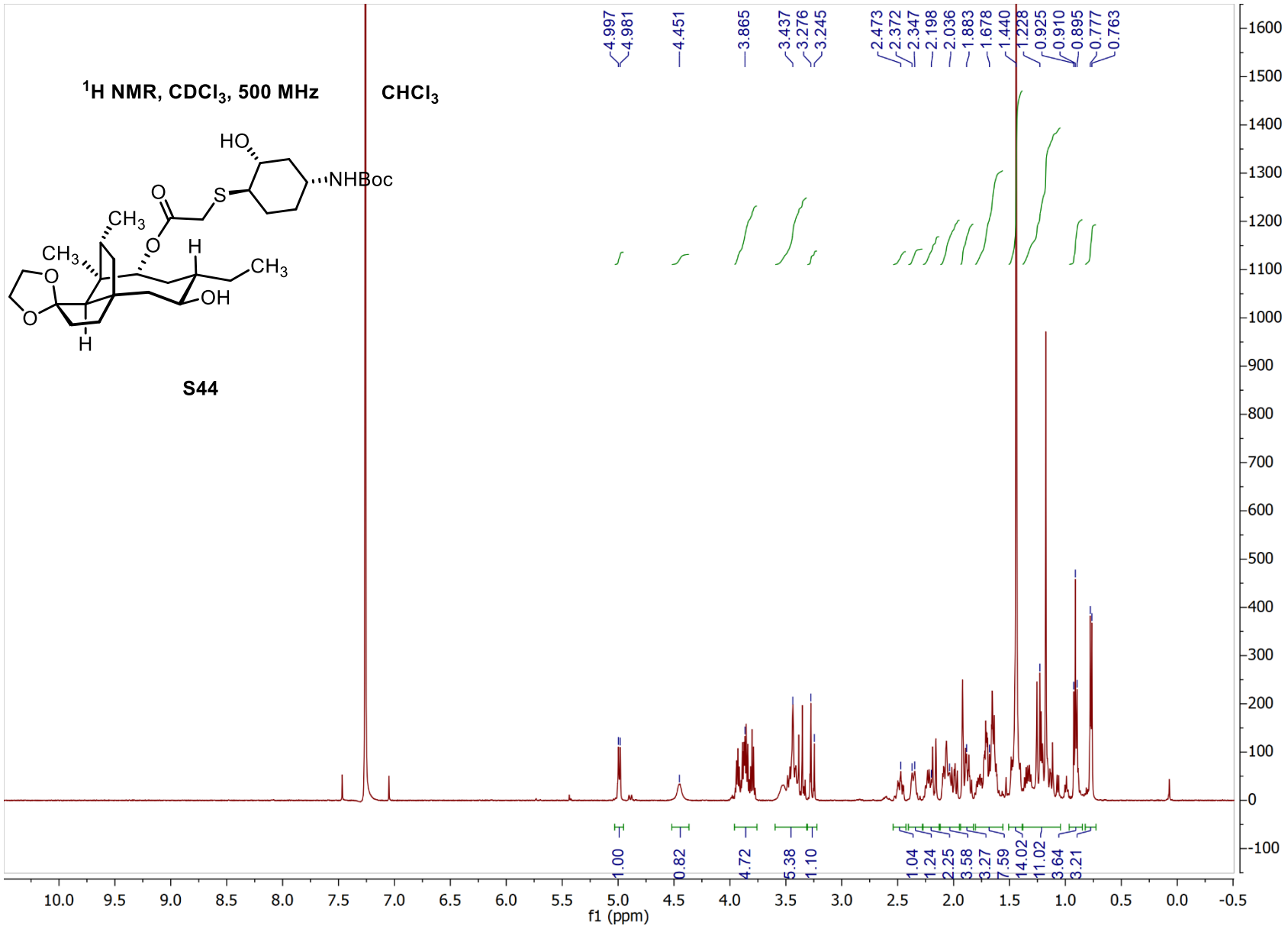

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
53
$CDCl_3$
165.9
145.4
132.8
130.1
128.3
120.5
76.4
72.0
65.1
64.5
63.4
58.9
54.0
51.4
51.3
47.6
47.1
42.2
39.0
37.1
36.1
25.9
21.8
14.7
10.9
f1 (ppm)

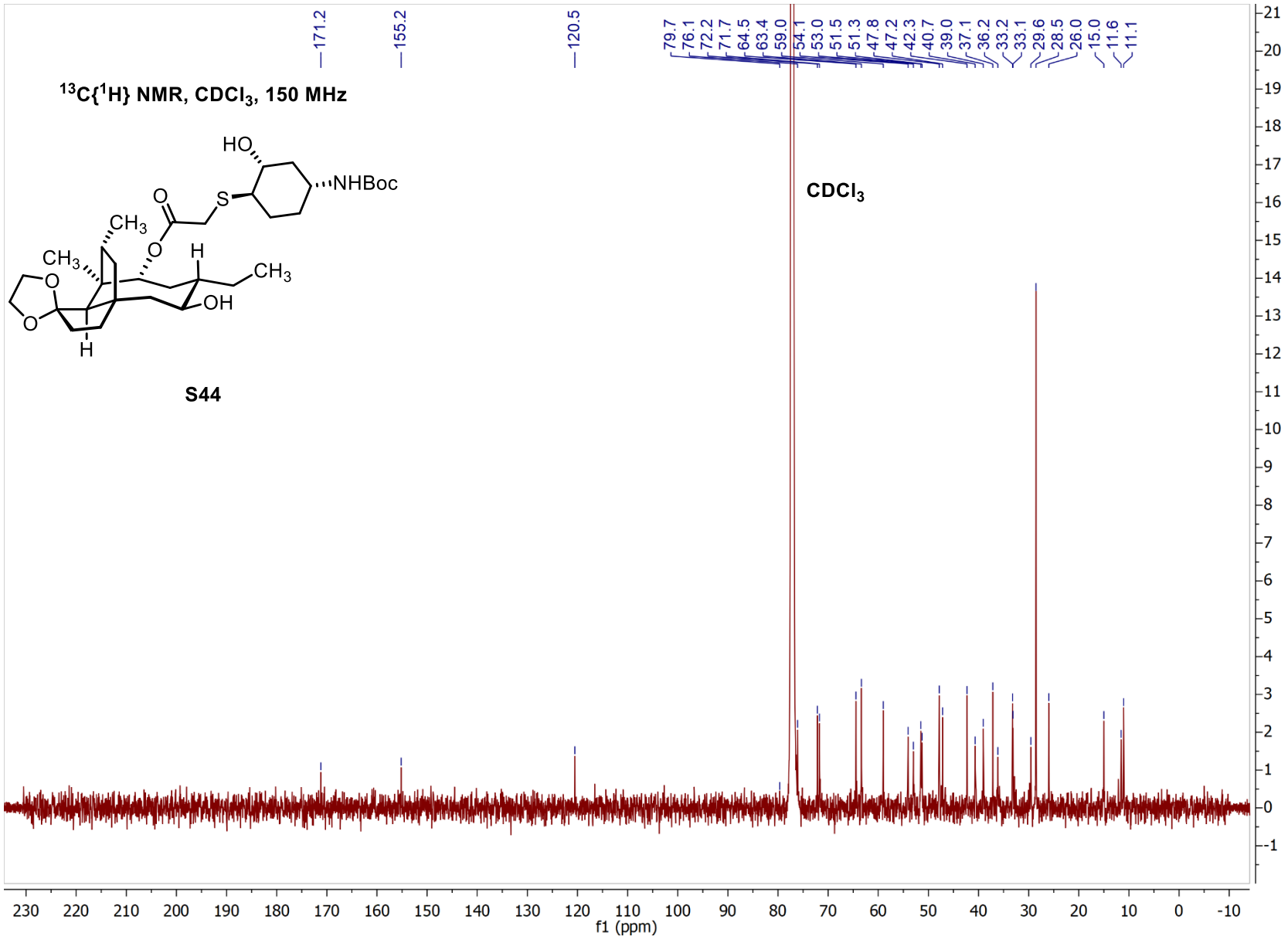

53, NOESY, CDCl3, 500 MHz
f2 (ppm)
f1 (ppm)

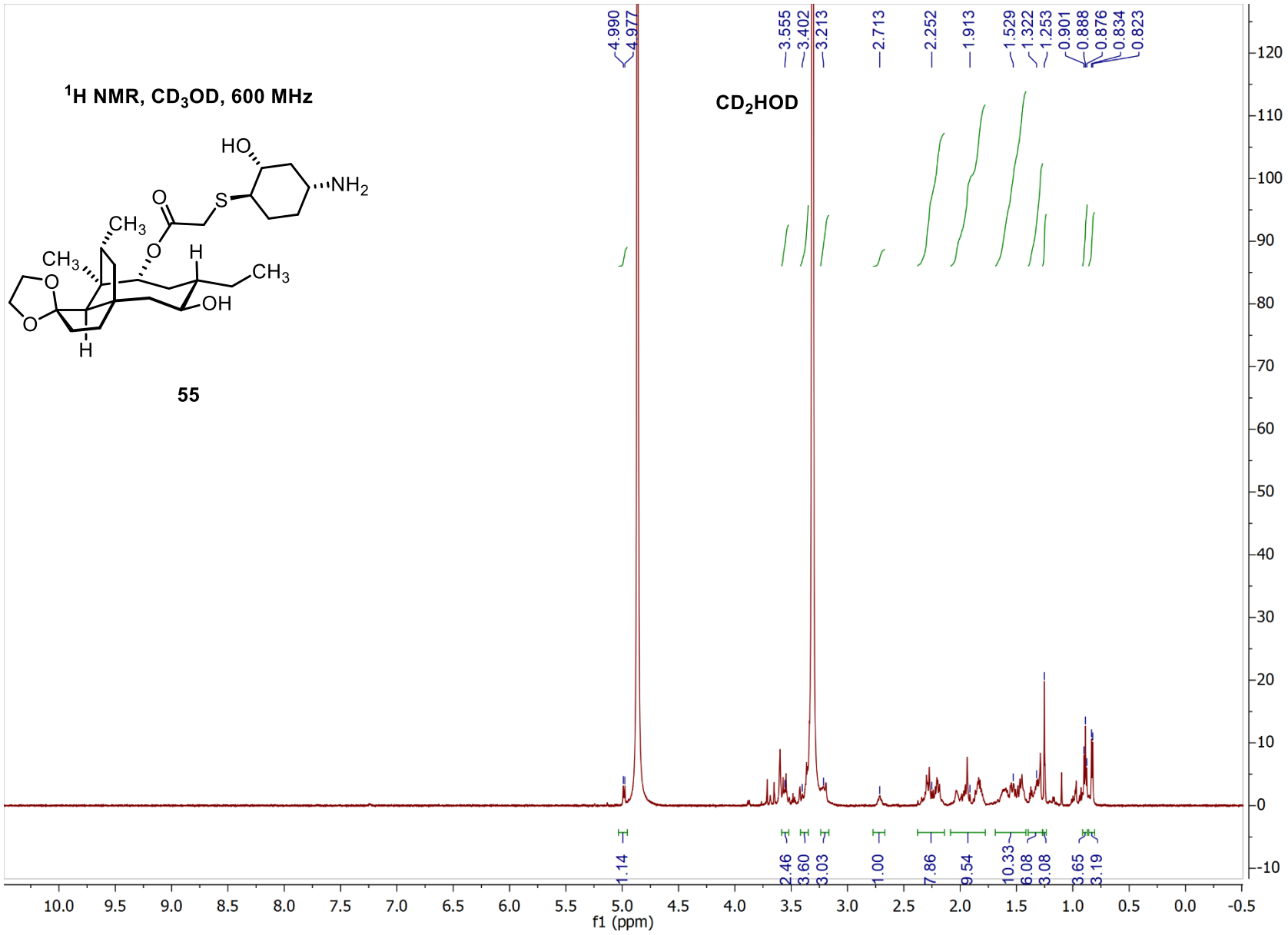

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
54
f1 (ppm)

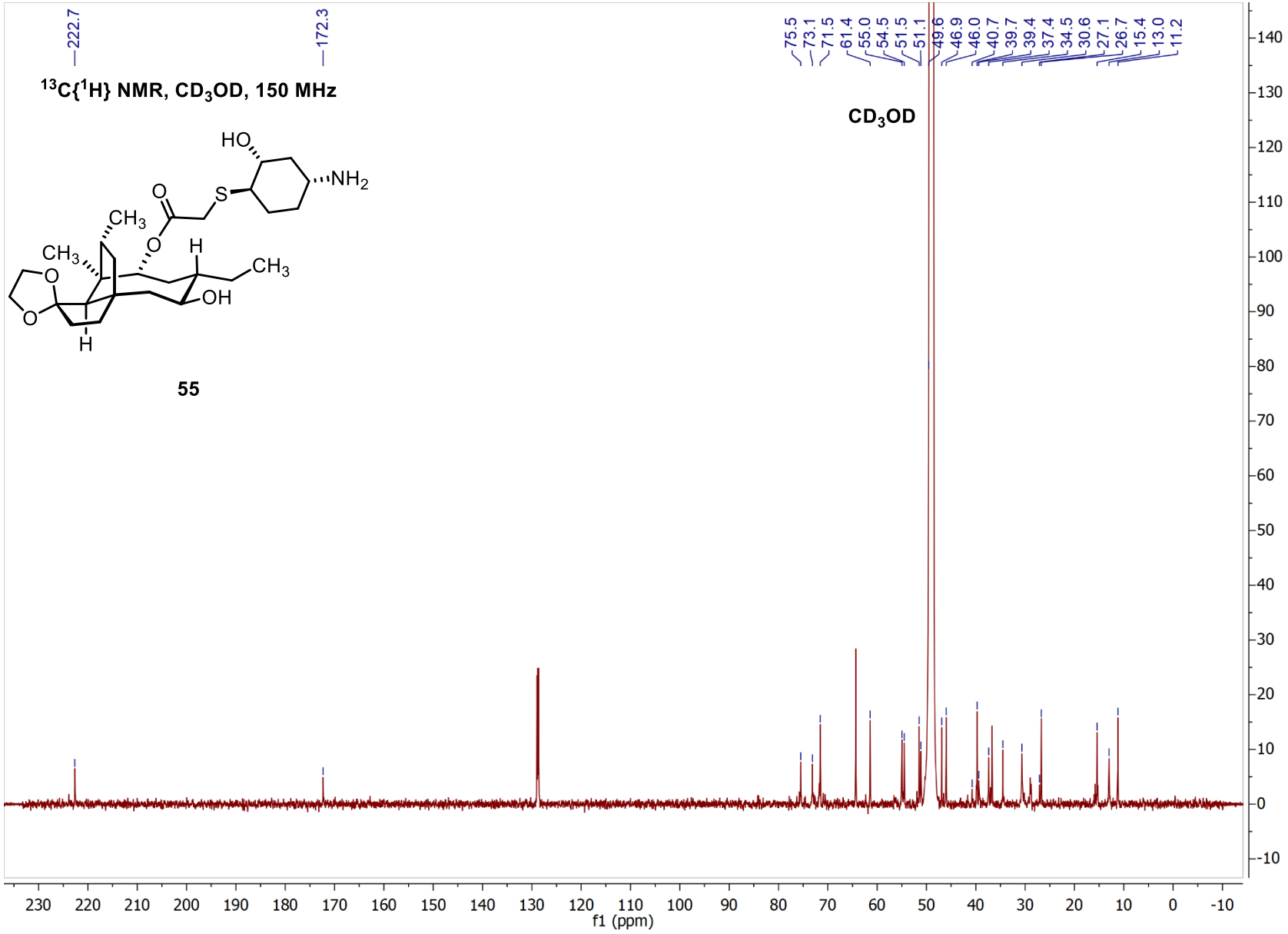

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
54
165.2
144.0
133.7
129.4
128.2
119.9
81.2
74.9
64.5
63.3
63.2
56.7
49.5
49.0
48.3
44.4
44.1
43.6
35.9
35.5
31.9
28.0
21.2
20.7
12.0
11.7
f1 (ppm)

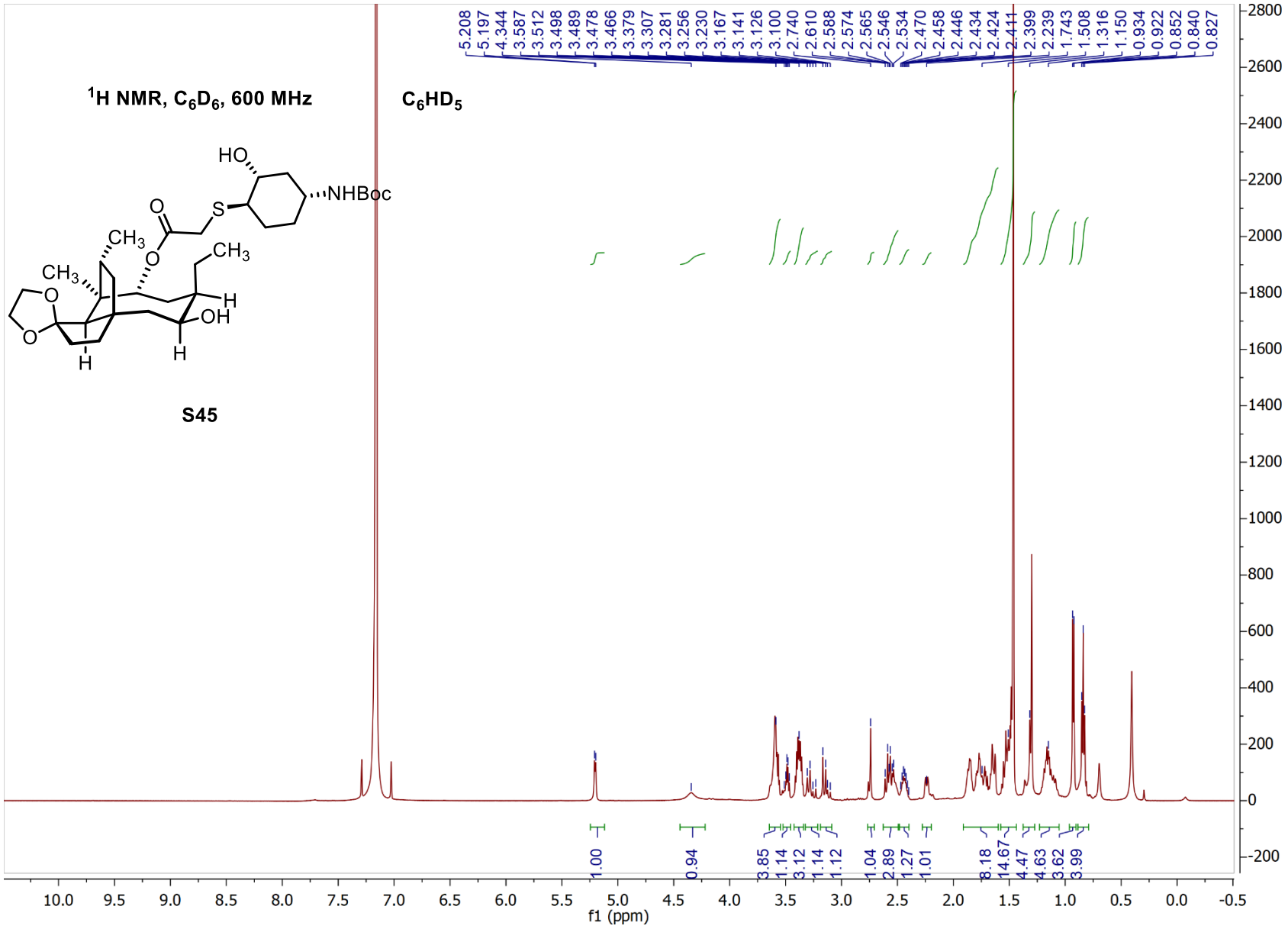

54, NOESY, C6D6, 500 MHz
f2 (ppm)
f1 (ppm)

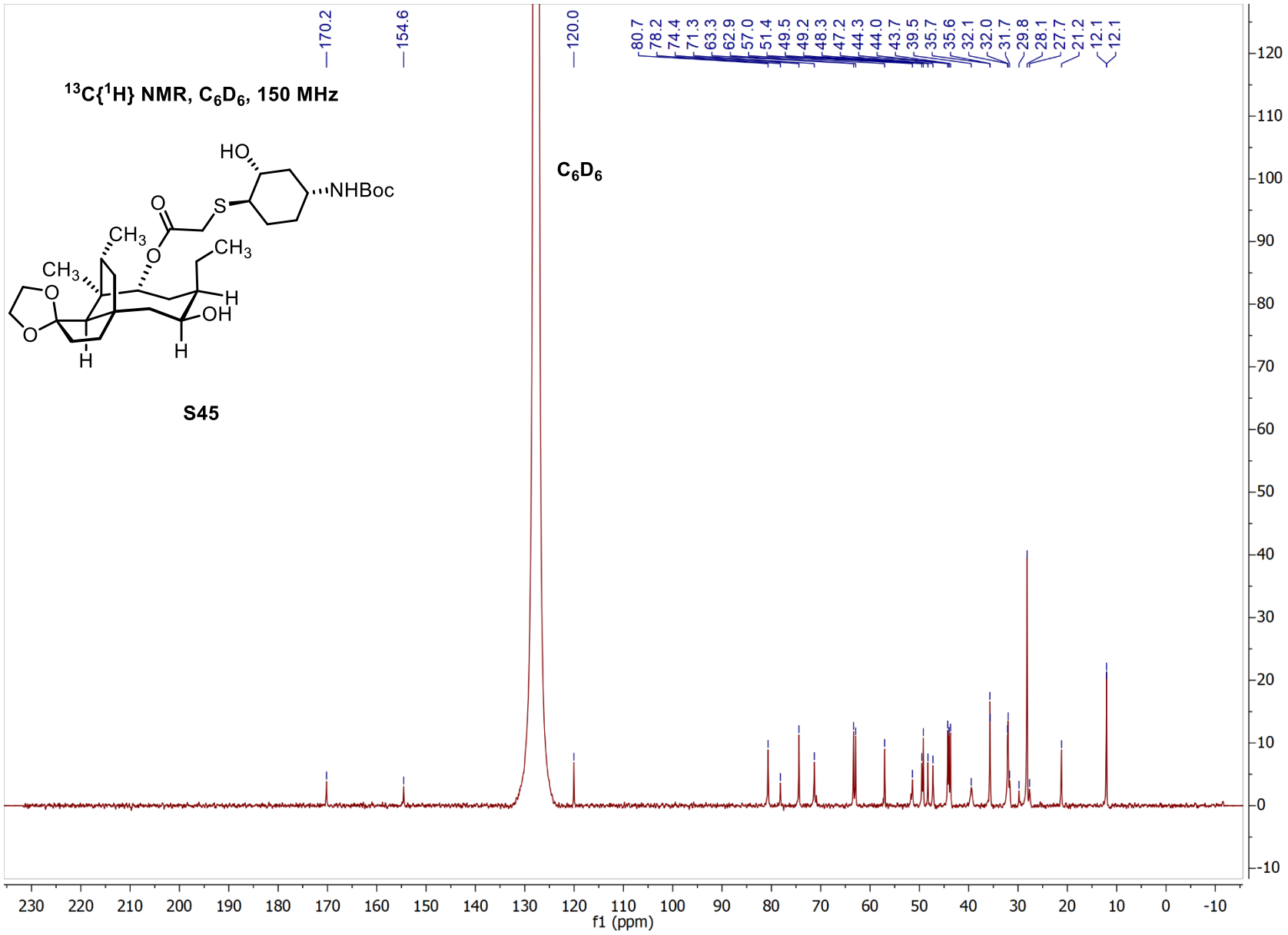

^{1}H NMR, $CDCl_3$, 500 MHz
$CHCl_3$
HO
NHBoc
S
O
CH_3
O
H
CH_3
O
CH_3
OH
O
H
S44
4.997
4.981
4.451
3.865
3.437
3.276
3.245
2.473
2.372
2.347
2.198
2.036
1.883
1.678
1.440
1.228
0.925
0.910
0.895
0.777
0.763
1.00
0.82
4.72
5.38
1.10
1.04
1.24
2.25
3.58
3.27
7.59
14.02
11.02
3.64
3.21
f1 (ppm)

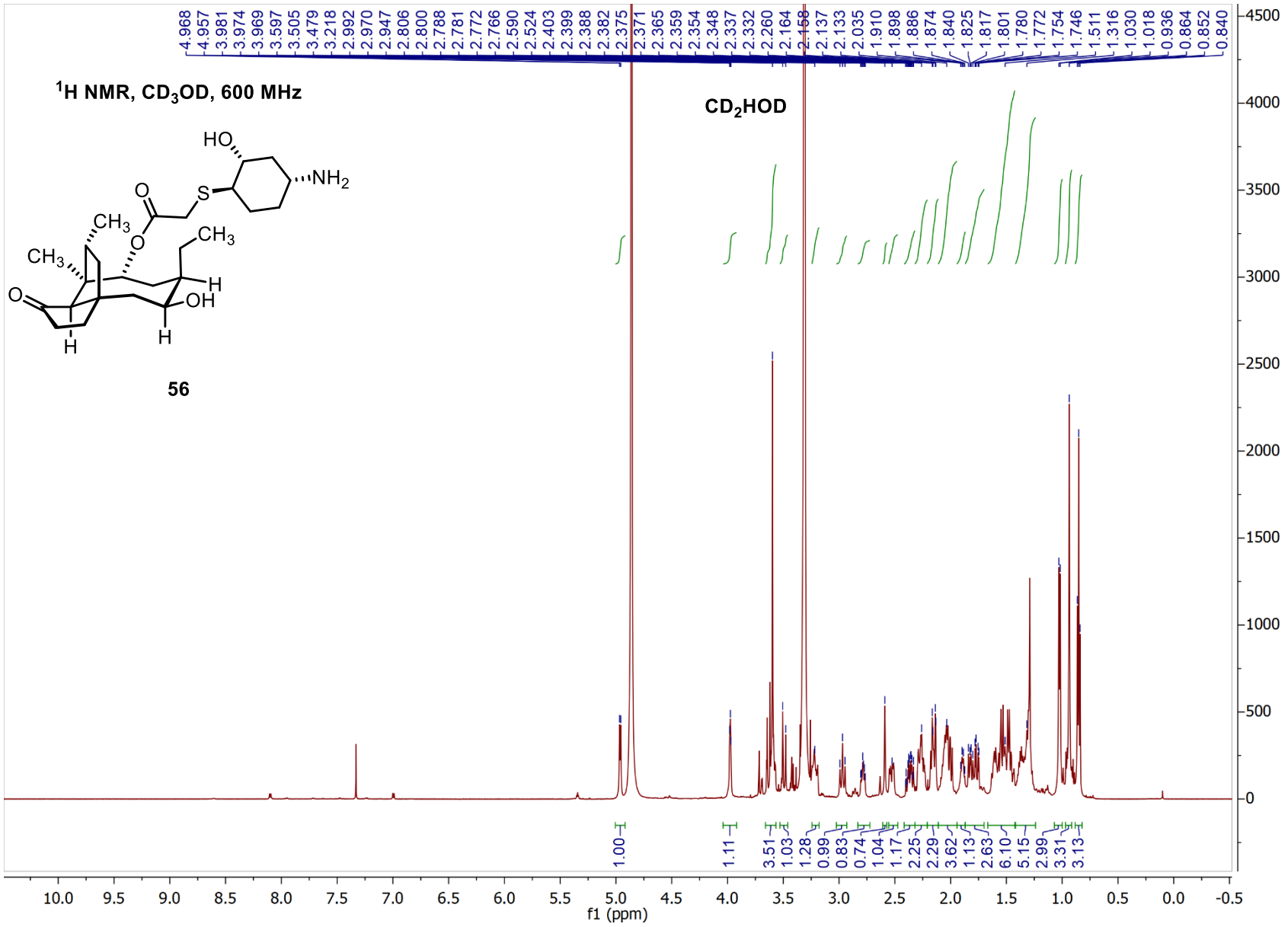

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
171.2
155.2
120.5
79.7
76.1
72.2
71.7
64.5
63.4
59.0
54.1
53.0
51.5
51.3
47.8
47.2
42.3
40.7
39.0
37.1
36.2
33.2
33.1
29.6
28.5
26.0
15.0
11.6
11.1
$CDCl_3$
HO
NHBoc
S
O
CH_3
O
H
CH_3
CH_3
O
O
OH
H
S44
f1 (ppm)

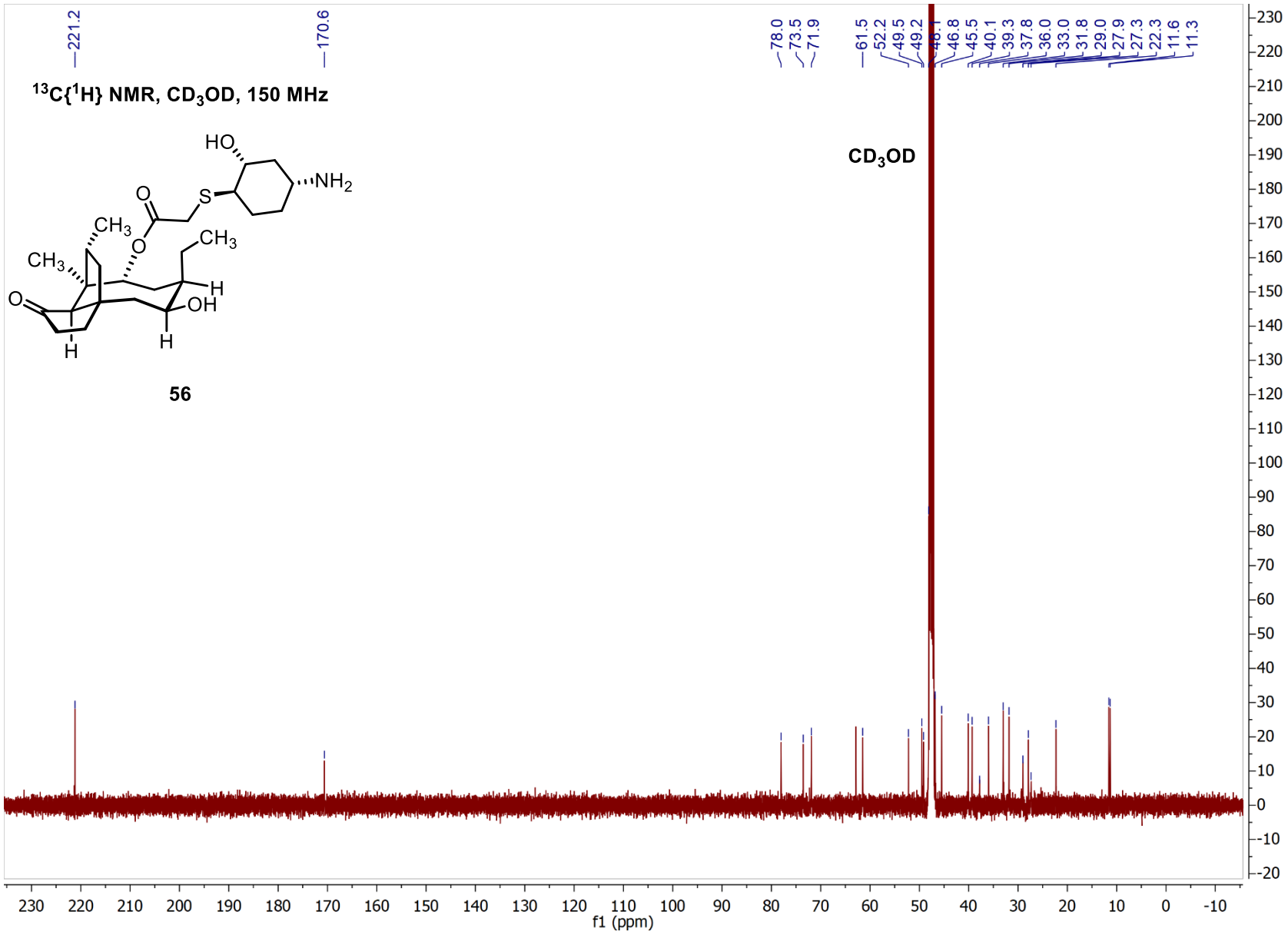

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
55
4.990
4.977
3.555
3.402
3.213
2.713
2.252
1.913
1.529
1.322
1.253
0.901
0.888
0.876
0.834
0.823
1.14
2.46
3.60
3.03
1.00
7.86
9.54
10.33
6.08
3.08
3.65
3.19
f1 (ppm)

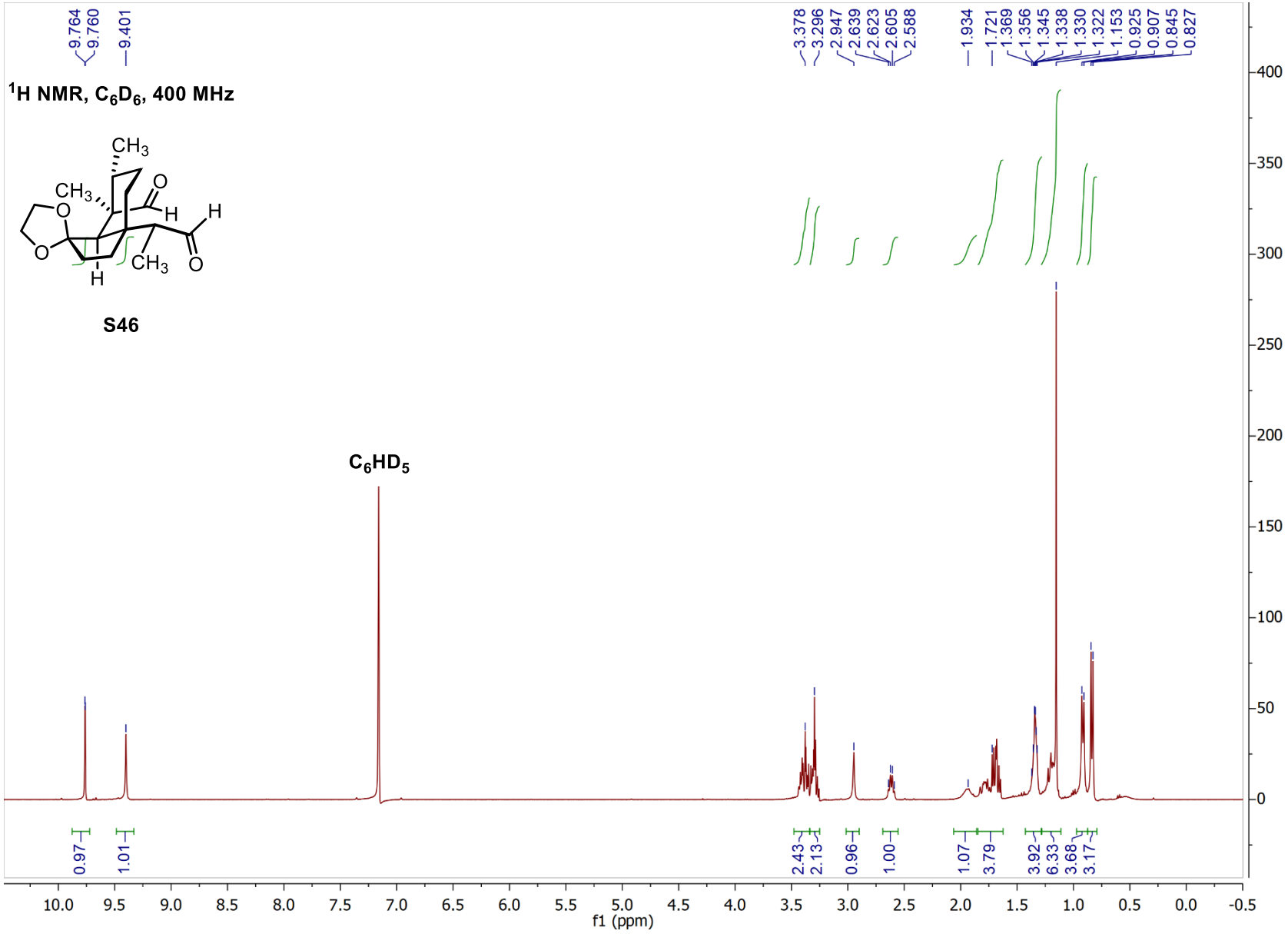

222.7
172.3
75.5
73.1
71.5
61.4
55.0
54.5
51.5
51.1
49.6
46.9
46.0
40.7
39.7
39.4
37.4
34.5
30.6
27.1
26.7
15.4
13.0
11.2
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
HO
NH2
O
S
CH3
CH3
O
H
CH3
O
OH
O
H
55
f1 (ppm)

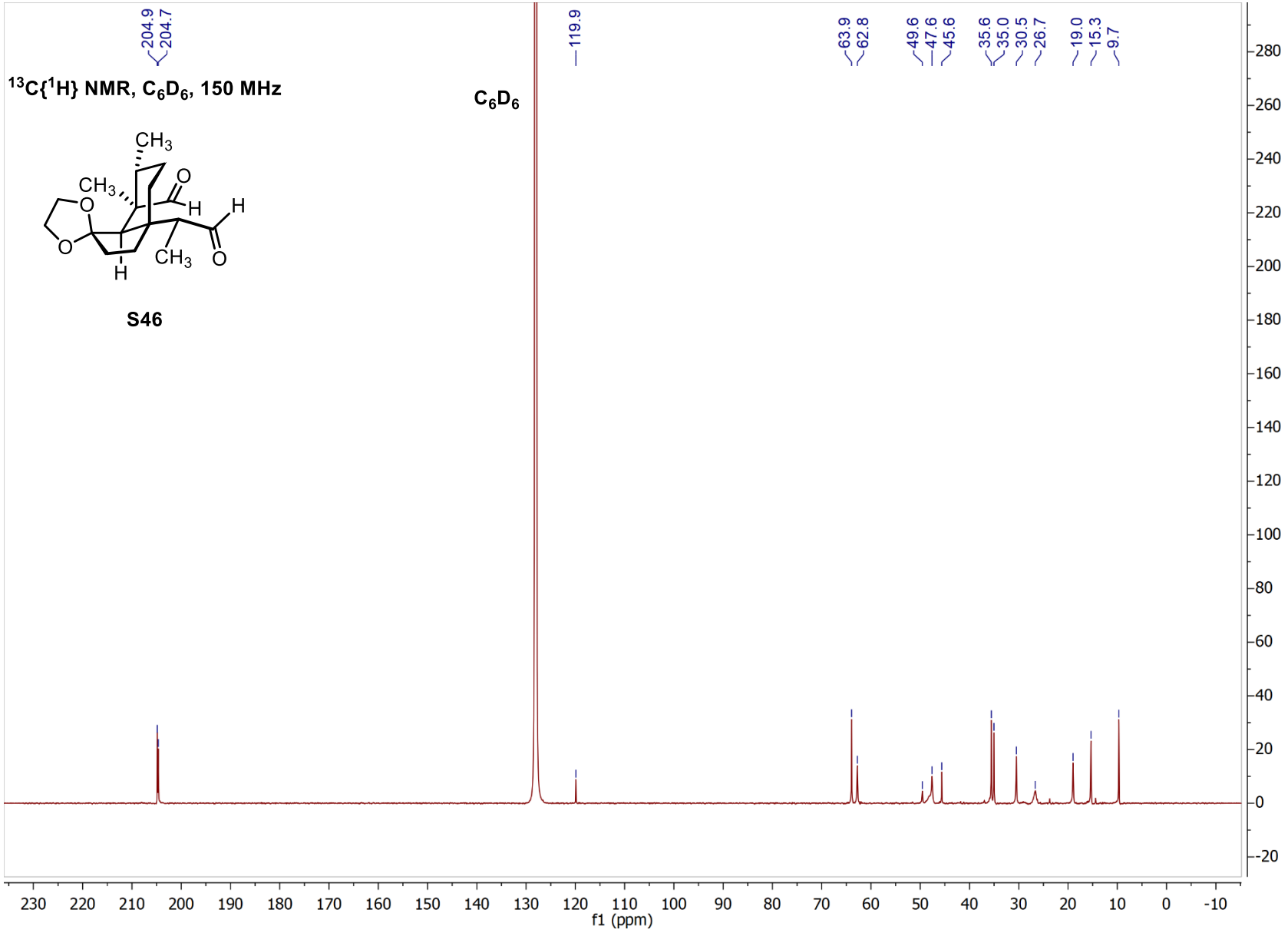

^{1}H NMR, C_6D_6, 600 MHz
C_6HD_5
HO
NHBoc
S
O
CH3
CH3
CH3
O
O
O
H
OH
H
H
S45
5.208
5.197
4.344
3.587
3.512
3.498
3.489
3.478
3.466
3.379
3.307
3.281
3.256
3.230
3.167
3.141
3.126
3.100
2.740
2.610
2.588
2.574
2.565
2.546
2.534
2.470
2.458
2.446
2.434
2.424
2.411
2.399
2.239
1.743
1.508
1.316
1.150
0.934
0.922
0.852
0.840
0.827
1.00
0.94
3.85
1.14
3.12
1.14
1.12
1.04
2.89
1.27
1.01
8.18
14.67
4.47
4.63
3.62
3.99
f1 (ppm)

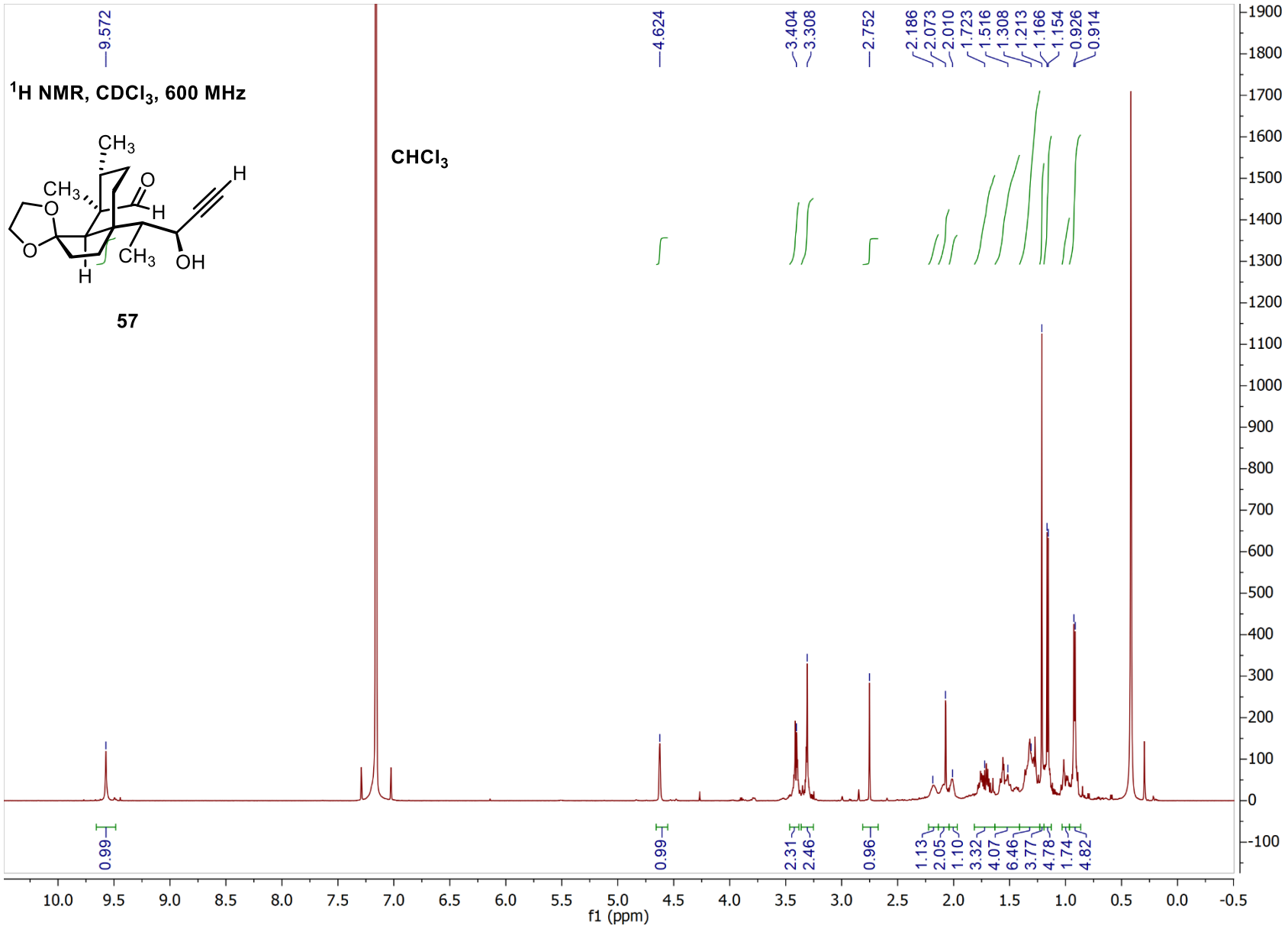

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
S45
C_6D_6
170.2
154.6
120.0
80.7
78.2
74.4
71.3
63.3
62.9
57.0
51.4
49.5
49.2
48.3
47.2
44.3
44.0
43.7
39.5
35.7
35.6
32.1
32.0
31.7
29.8
28.1
27.7
21.2
12.1
12.1
HO
NHBoc
S
O
CH3
CH3
CH3
O
O
O
H
OH
H
H
f1 (ppm)

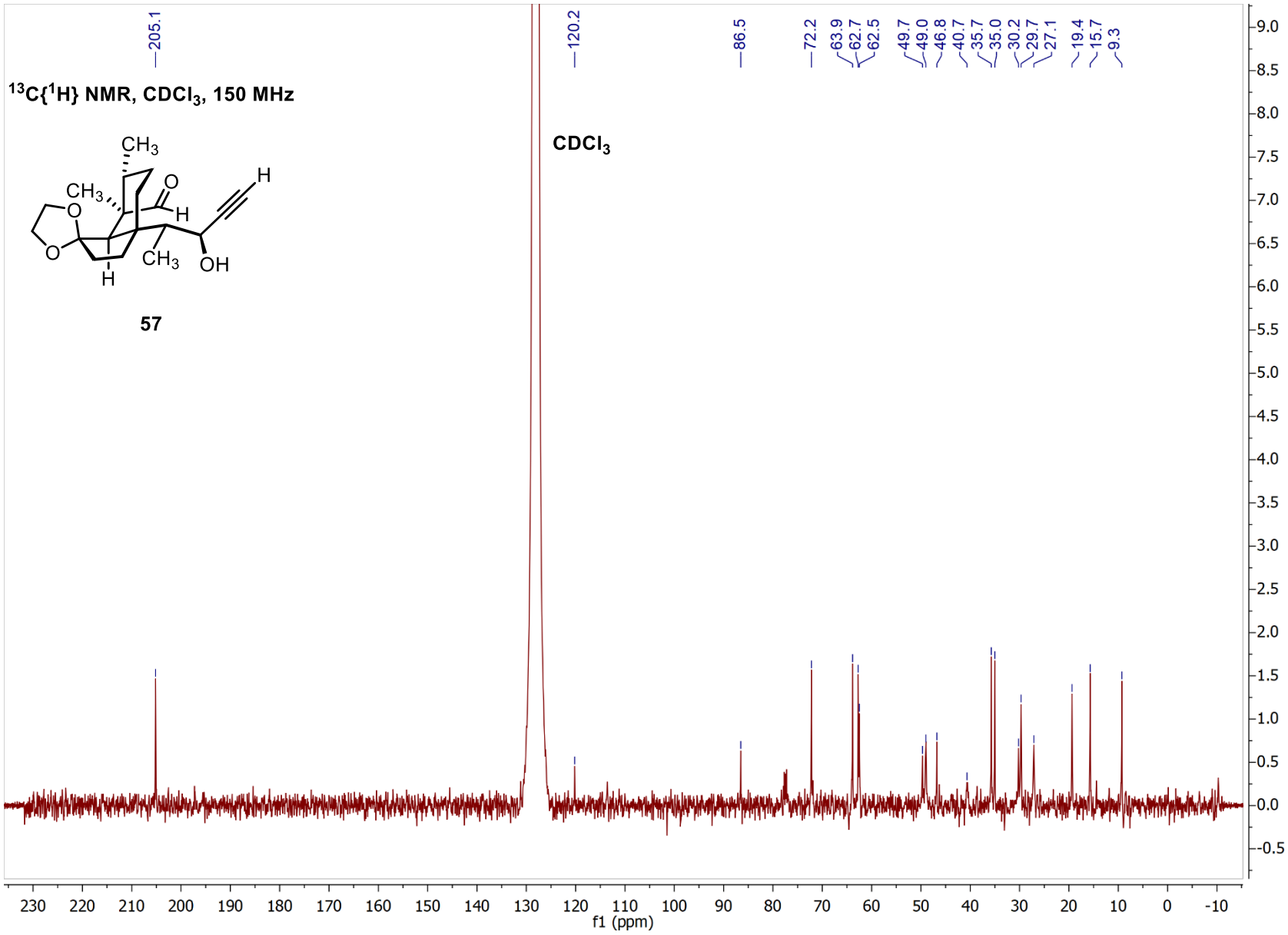

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
56
f1 (ppm)

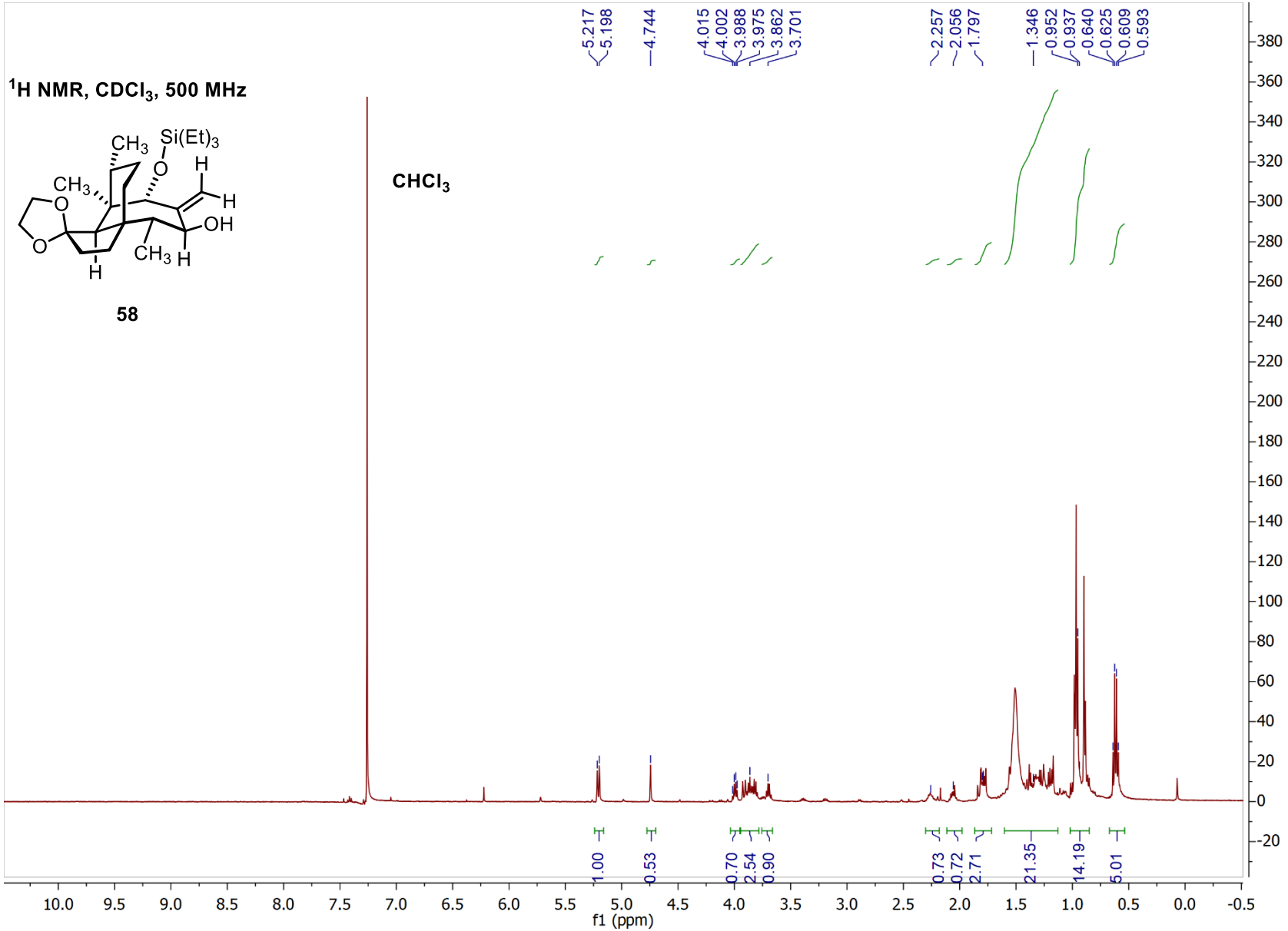

221.2
170.6
78.0
73.5
71.9
61.5
52.2
49.5
49.2
48.1
46.8
45.5
40.1
39.3
37.8
36.0
33.0
31.8
29.0
27.9
27.3
22.3
11.6
11.3
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
HO
NH2
O
S
CH3
CH3
CH3
O
O
H
OH
H
H
56
f1 (ppm)

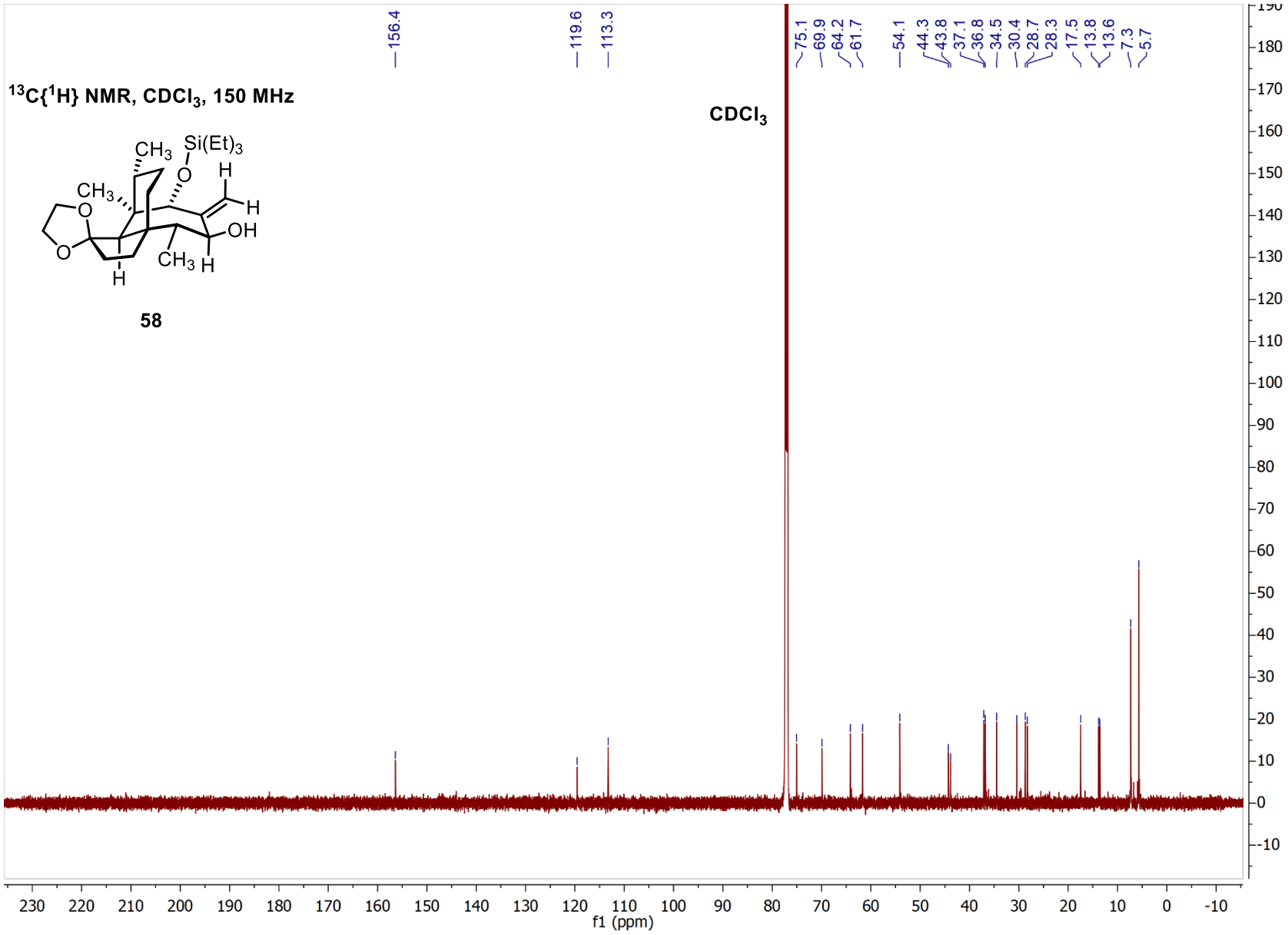

9.764
9.760
9.401
3.378
3.296
2.947
2.639
2.623
2.605
2.588
1.934
1.721
1.369
1.356
1.345
1.338
1.330
1.322
1.153
0.925
0.907
0.845
0.827
^{1}H NMR, C_6D_6, 400 MHz
S46
C_6HD_5
0.97
1.01
2.43
2.13
0.96
1.00
1.07
3.79
3.92
6.33
3.68
3.17
f1 (ppm)


204.9
204.7
119.9
63.9
62.8
49.6
47.6
45.6
35.6
35.0
30.5
26.7
19.0
15.3
9.7
$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
S46
f1 (ppm)

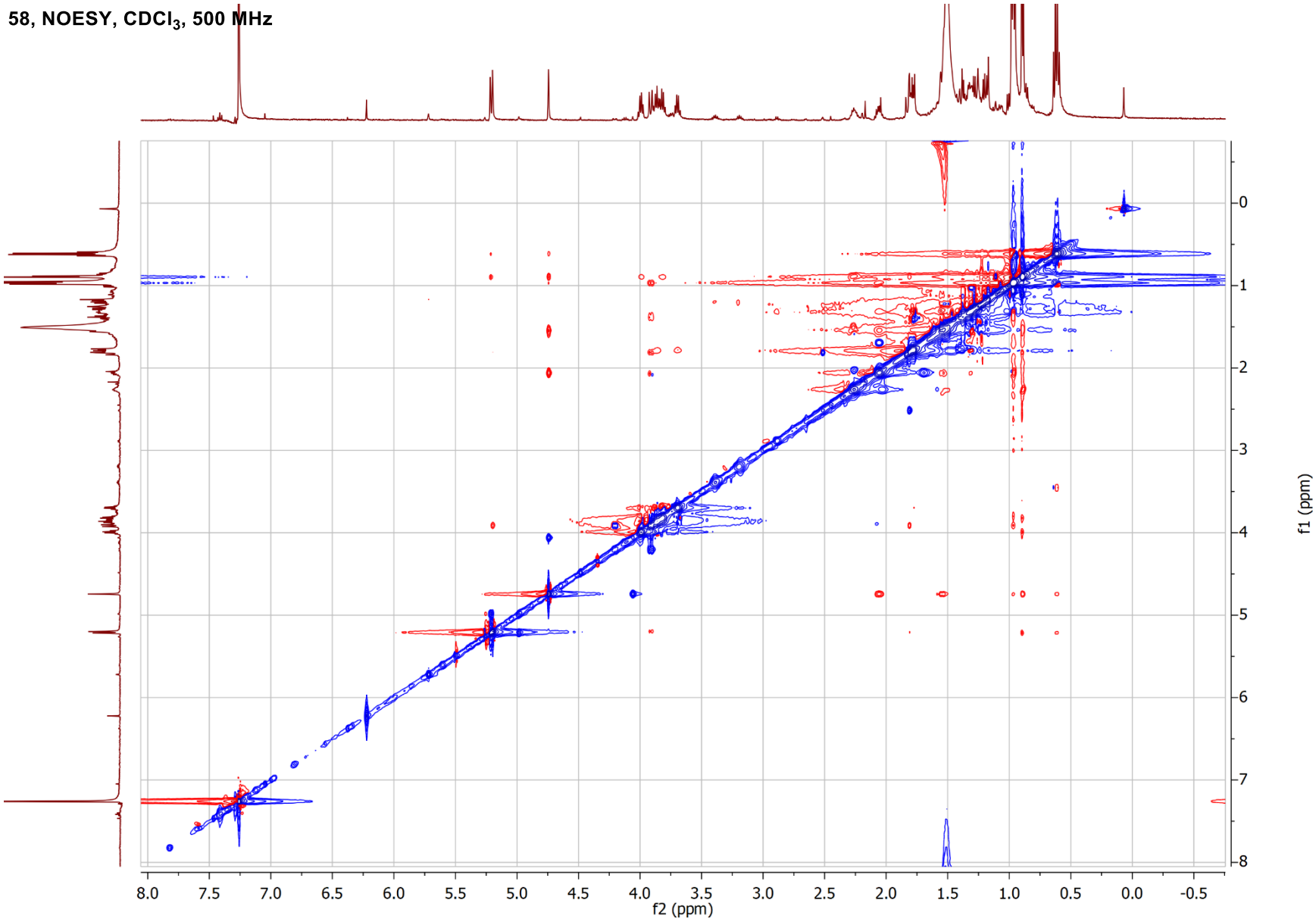

^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
57
9.572
4.624
3.404
3.308
2.752
2.186
2.073
2.010
1.723
1.516
1.308
1.213
1.166
1.154
0.926
0.914
0.99
0.99
2.31
2.46
0.96
1.13
2.05
1.10
3.32
4.07
6.46
3.77
4.78
1.74
4.82
f1 (ppm)

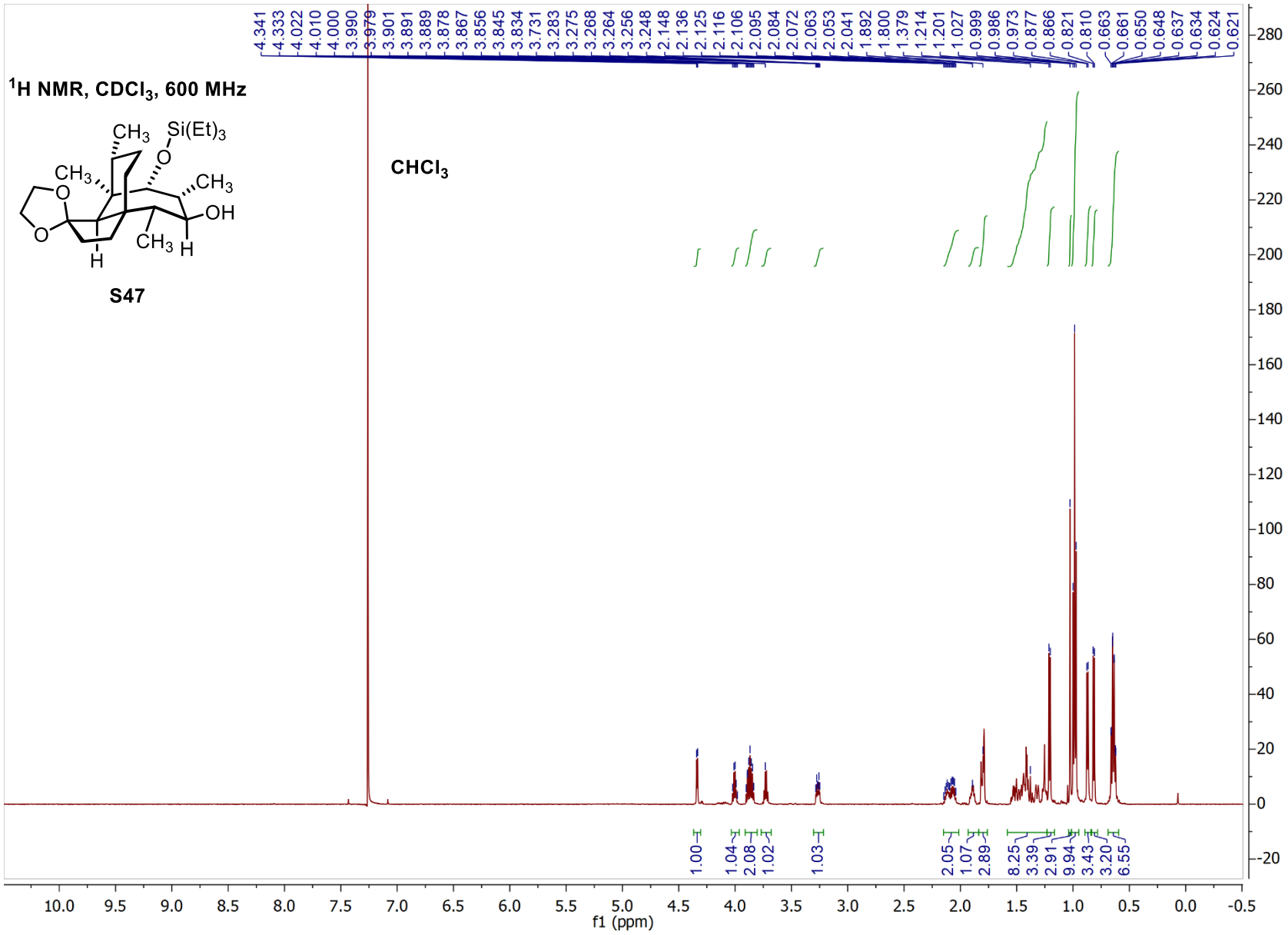

205.1
120.2
86.5
72.2
63.9
62.7
62.5
49.7
49.0
46.8
40.7
35.7
35.0
30.2
29.7
27.1
19.4
15.7
9.3
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
CH3
CH3
O
O
O
H
H
CH3
OH
H
57
f1 (ppm)

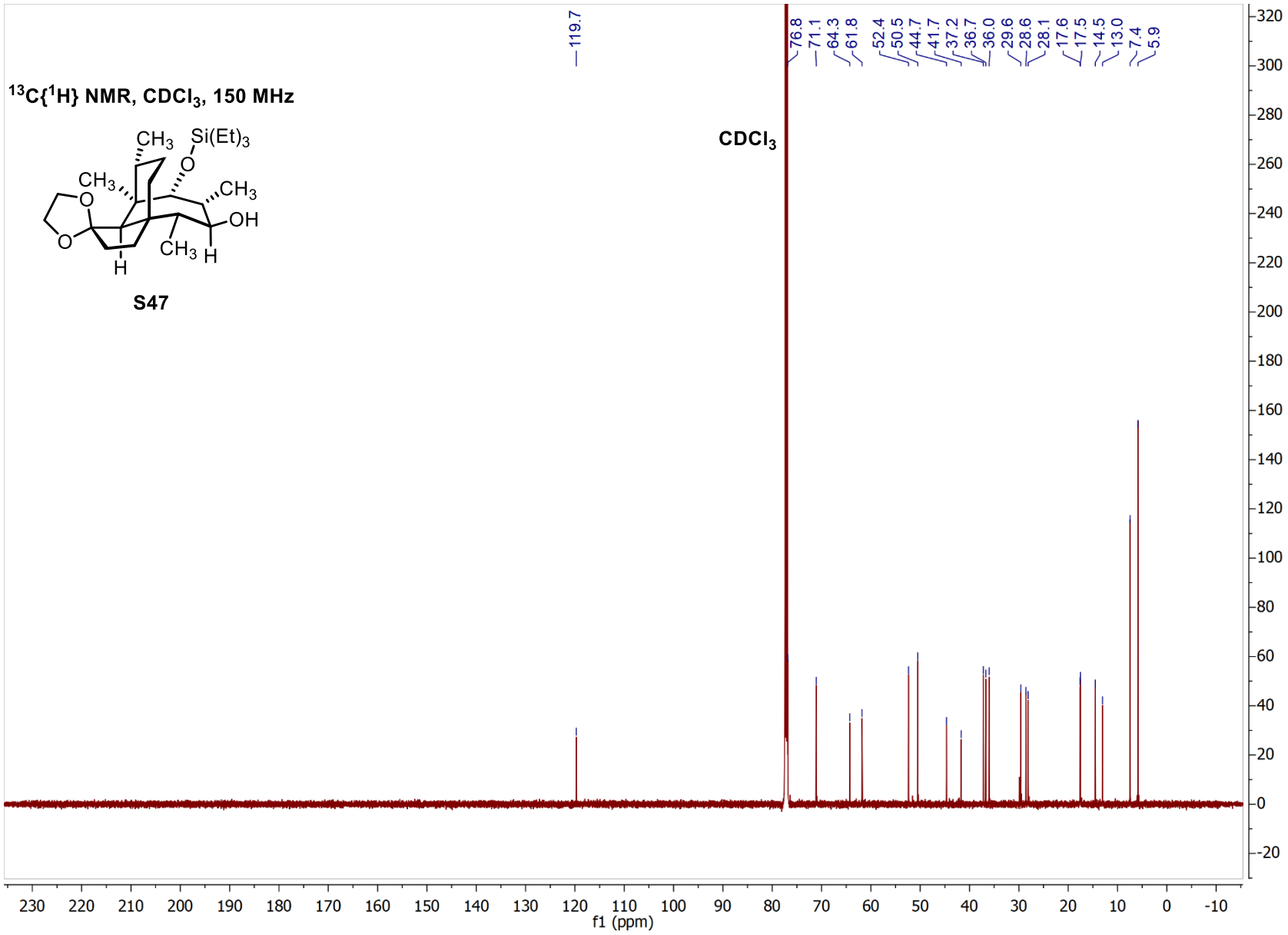

^{1}H NMR, $CDCl_3$, 500 MHz
$CHCl_3$
58
5.217
5.198
4.744
4.015
4.002
3.988
3.975
3.862
3.701
2.257
2.056
1.797
1.346
0.952
0.937
0.640
0.625
0.609
0.593
1.00
0.53
0.70
2.54
0.90
0.73
0.72
2.71
21.35
14.19
5.01
f1 (ppm)

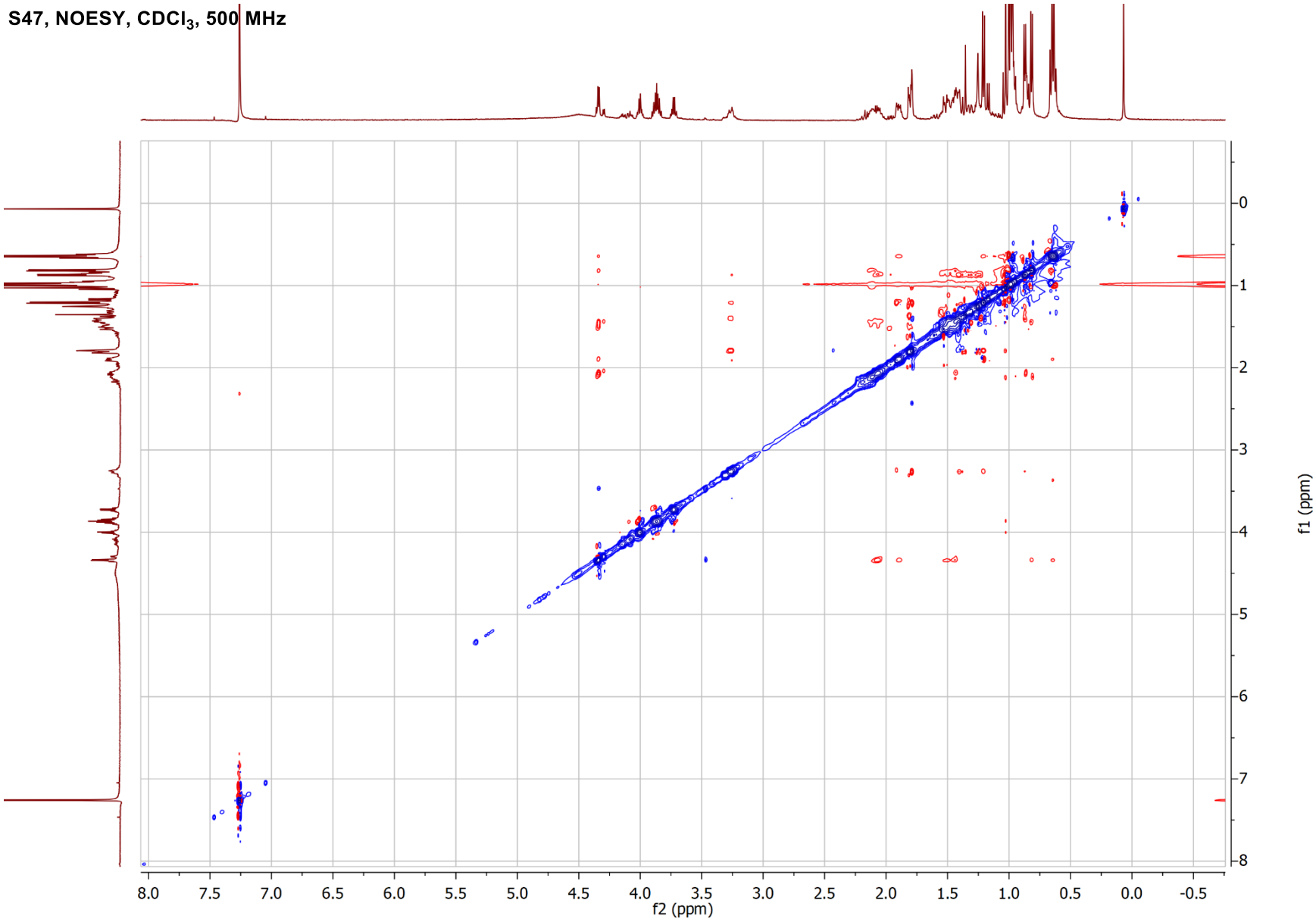

13C{1H} NMR, CDCl3, 150 MHz
CDCl3
156.4
119.6
113.3
75.1
69.9
64.2
61.7
54.1
44.3
43.8
37.1
36.8
34.5
30.4
28.7
28.3
17.5
13.8
13.6
7.3
5.7
CH3
Si(Et)3
O
H
CH3
O
H
OH
O
CH3
H
H
f1 (ppm)

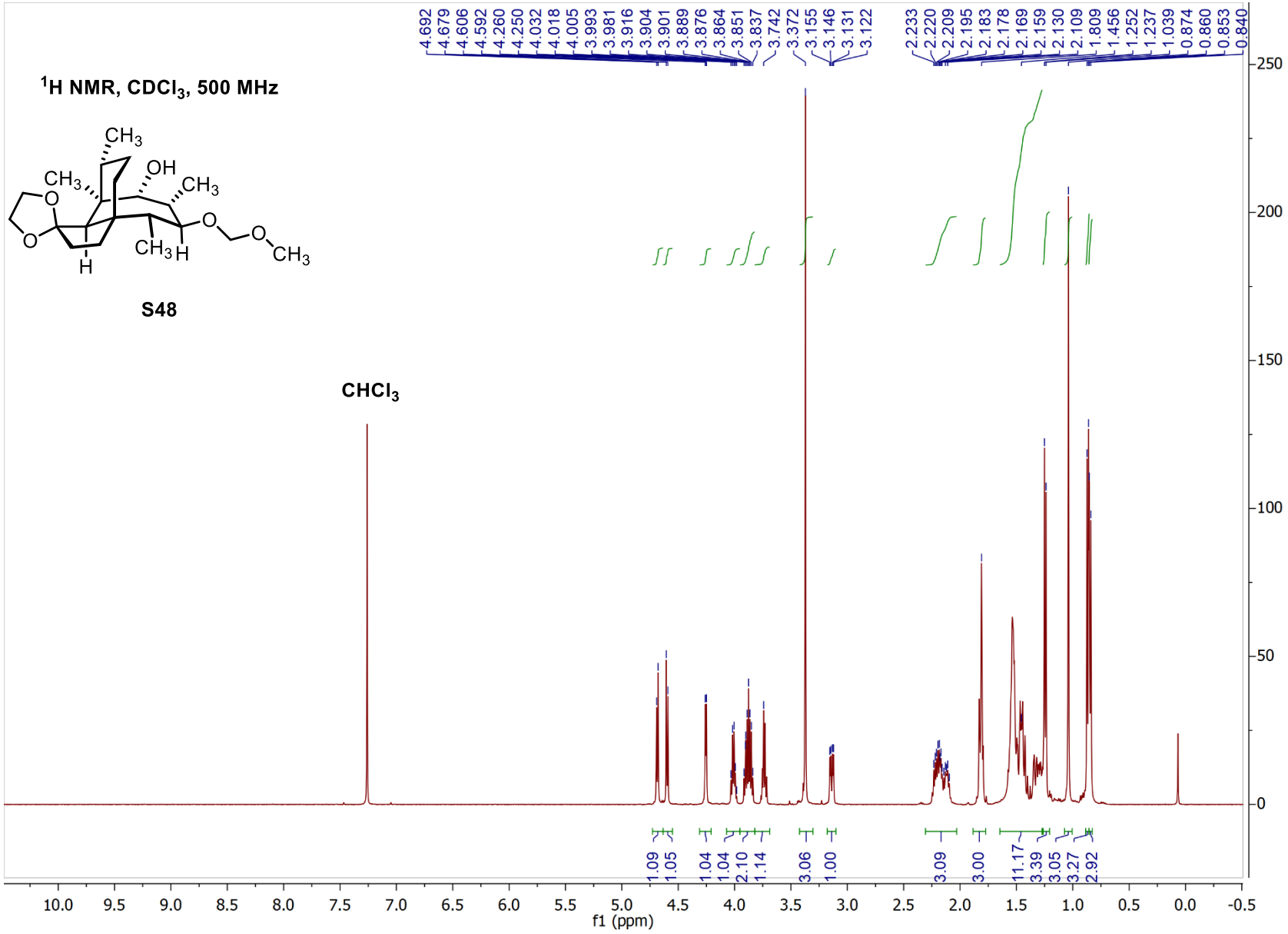
58

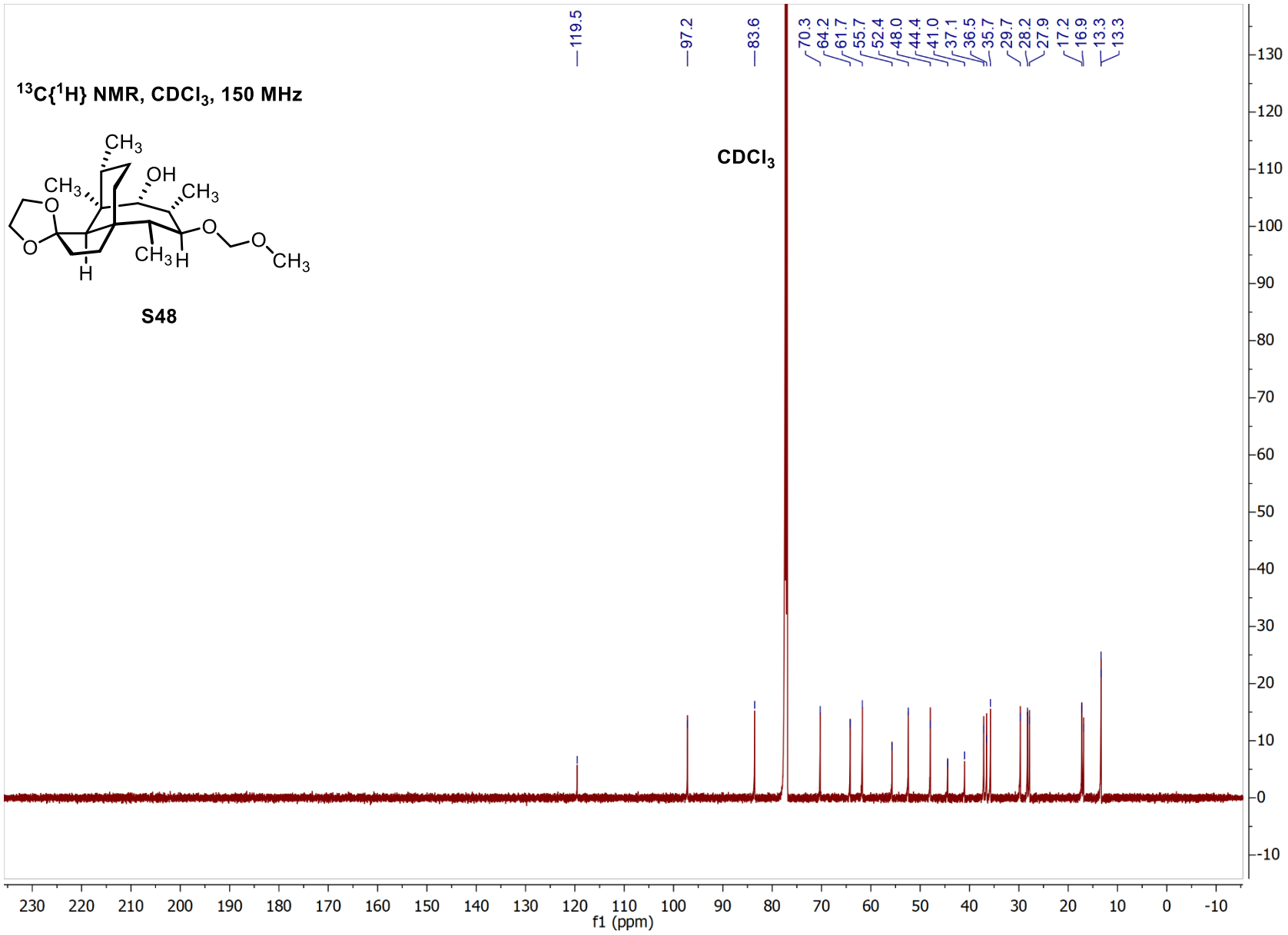

58, NOESY, CDCl3, 500 MHz
f2 (ppm)
f1 (ppm)

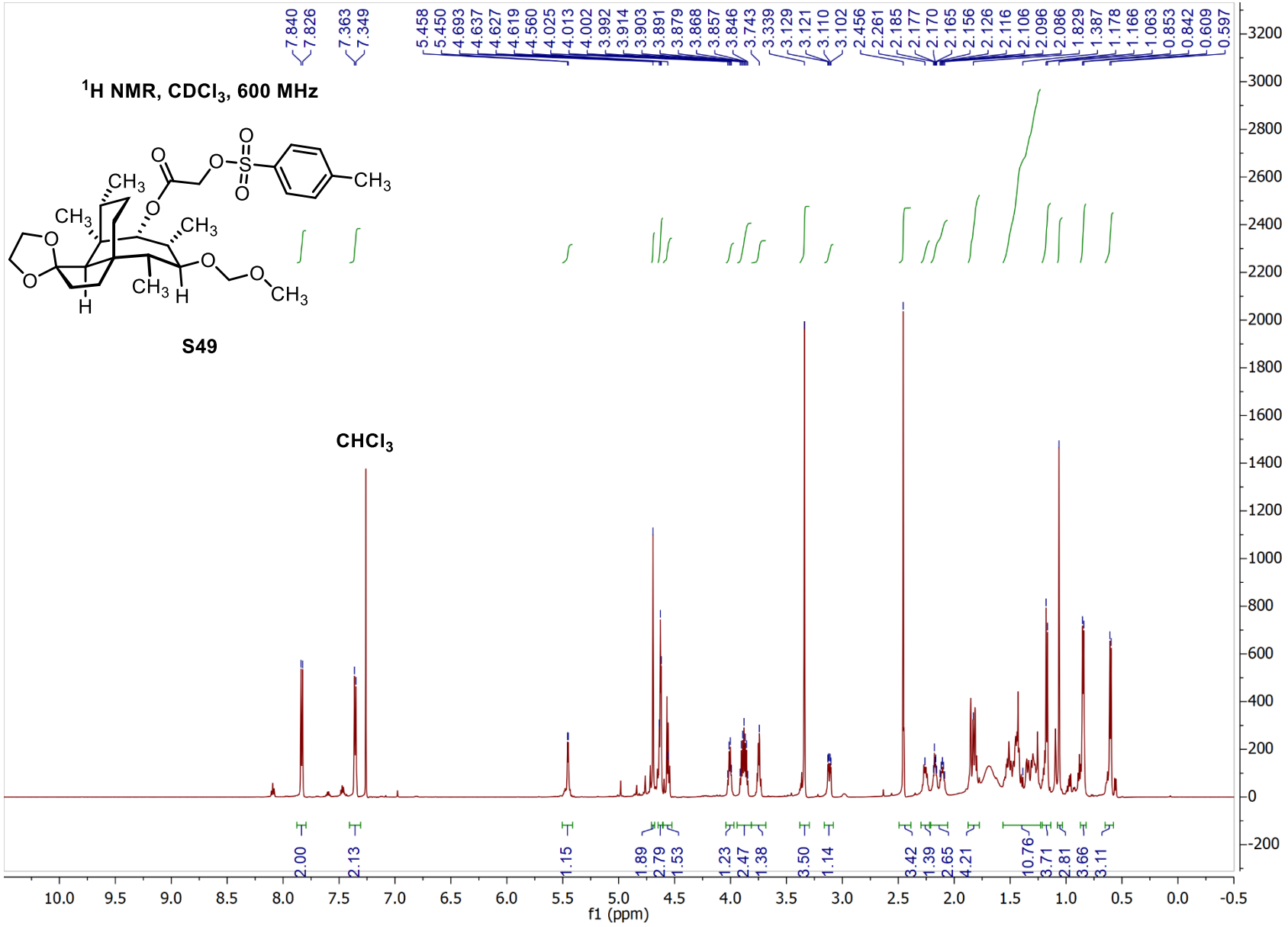

1H NMR, CDCl3, 600 MHz
CHCl3
S47
f1 (ppm)

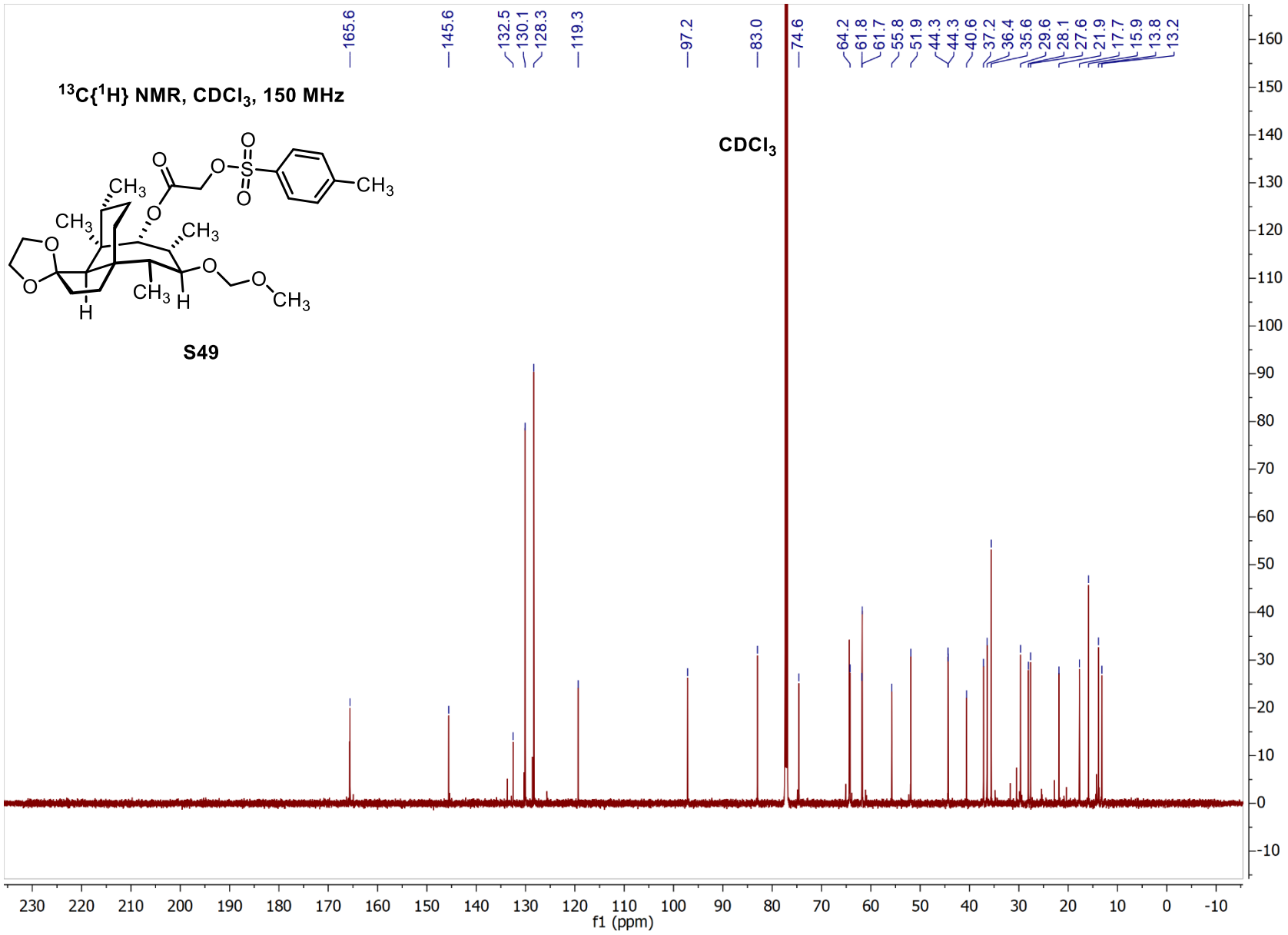

13C{1H} NMR, CDCl3, 150 MHz
CH3
Si(Et)3
O
CH3
CH3
O
OH
O
CH3
H
H
S47
CDCl3
119.7
76.8
71.1
64.3
61.8
52.4
50.5
44.7
41.7
37.2
36.7
36.0
29.6
28.6
28.1
17.6
17.5
14.5
13.0
7.4
5.9
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

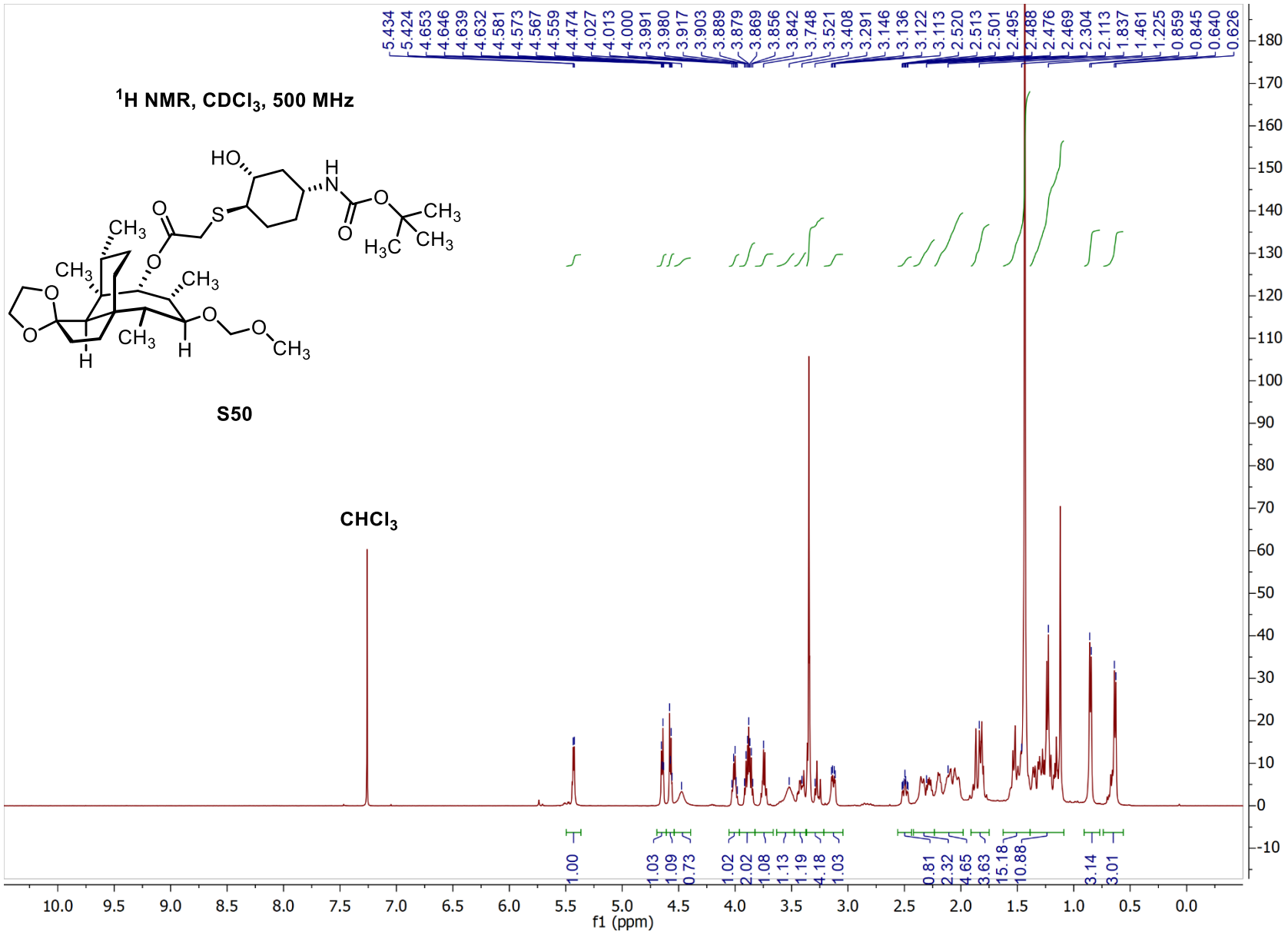

S47, NOESY, CDCl3, 500 MHz
f2 (ppm)
f1 (ppm)

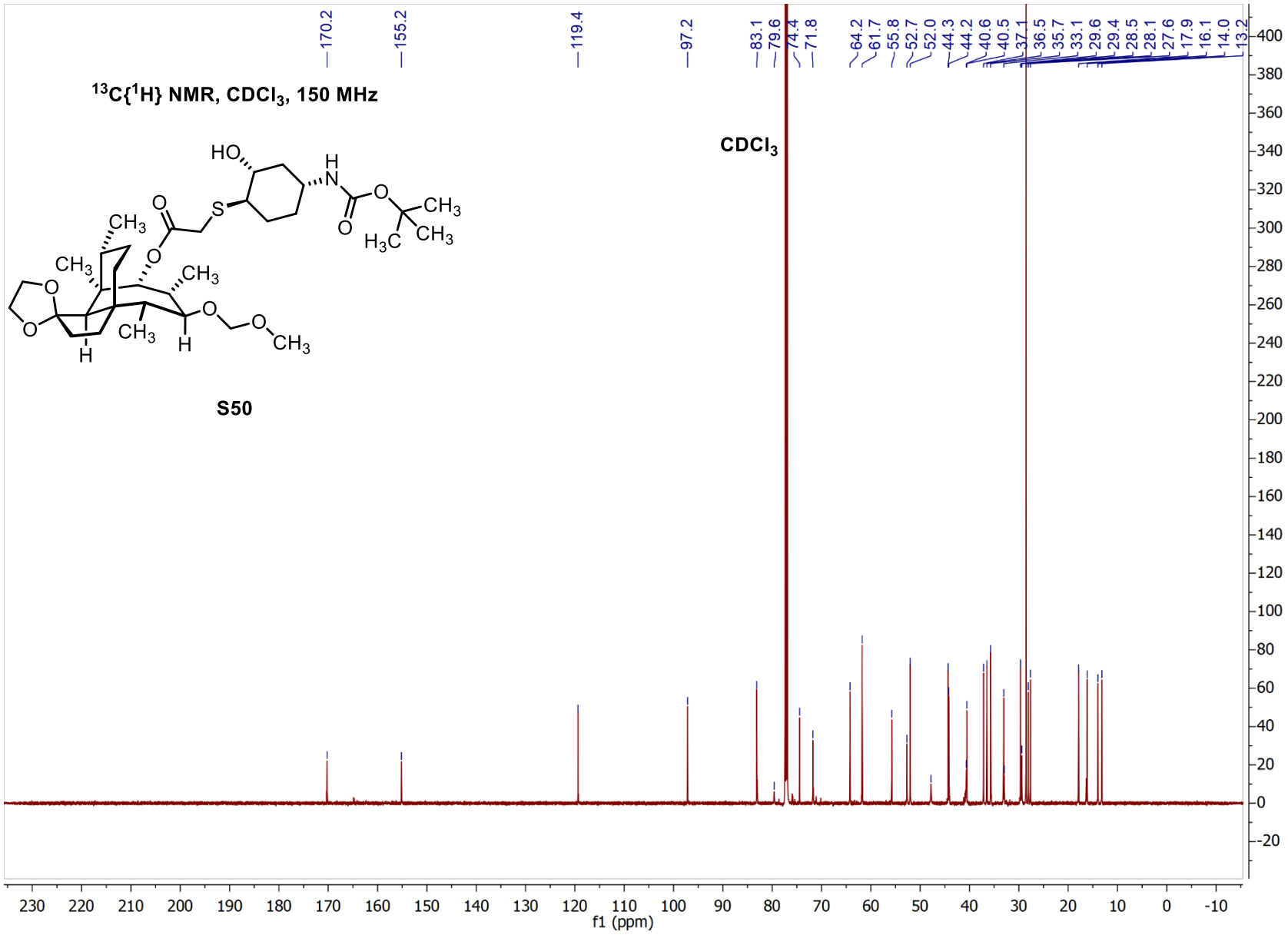

^{1}H NMR, $CDCl_3$, 500 MHz
S48
$CHCl_3$
f1 (ppm)

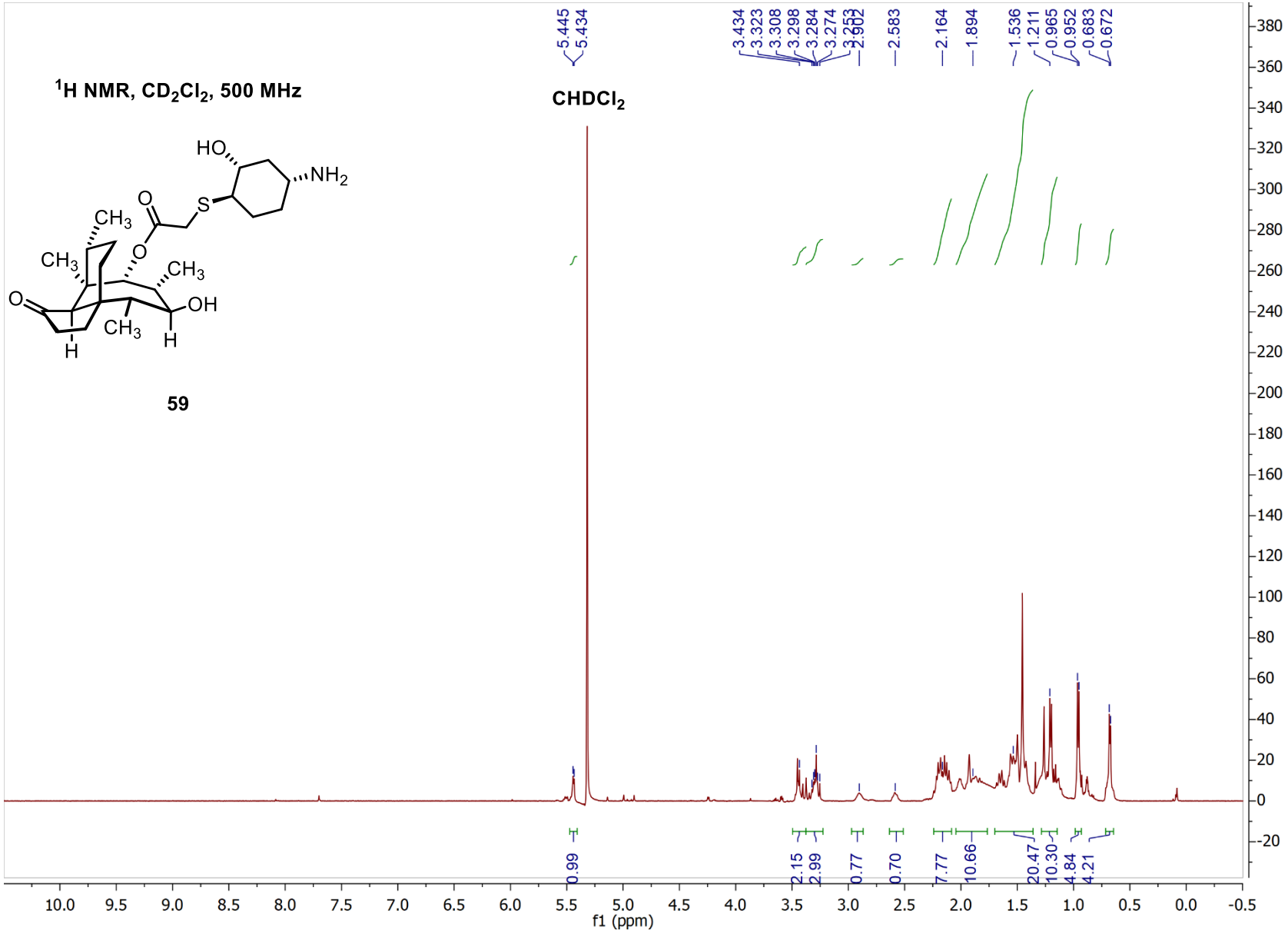

13C{1H} NMR, CDCl3, 150 MHz
CH3
OH
CH3
CH3
O
O
CH3 H
O
O
CH3
H
S48
CDCl3
119.5
97.2
83.6
70.3
64.2
61.7
55.7
52.4
48.0
44.4
41.0
37.1
36.5
35.7
29.7
28.2
27.9
17.2
16.9
13.3
13.3
f1 (ppm)

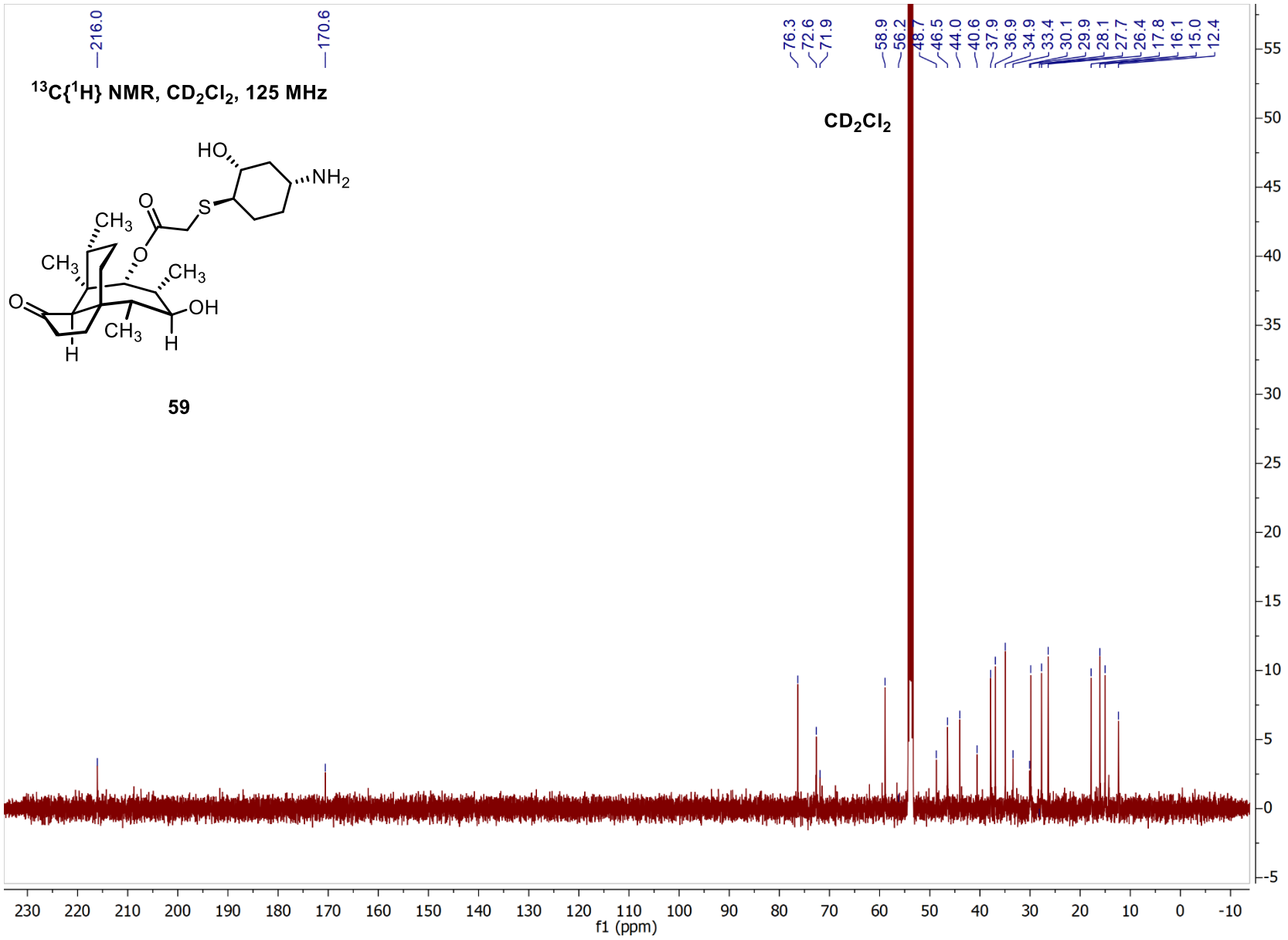

1H NMR, CDCl3, 600 MHz
S49
CHCl3
f1 (ppm)

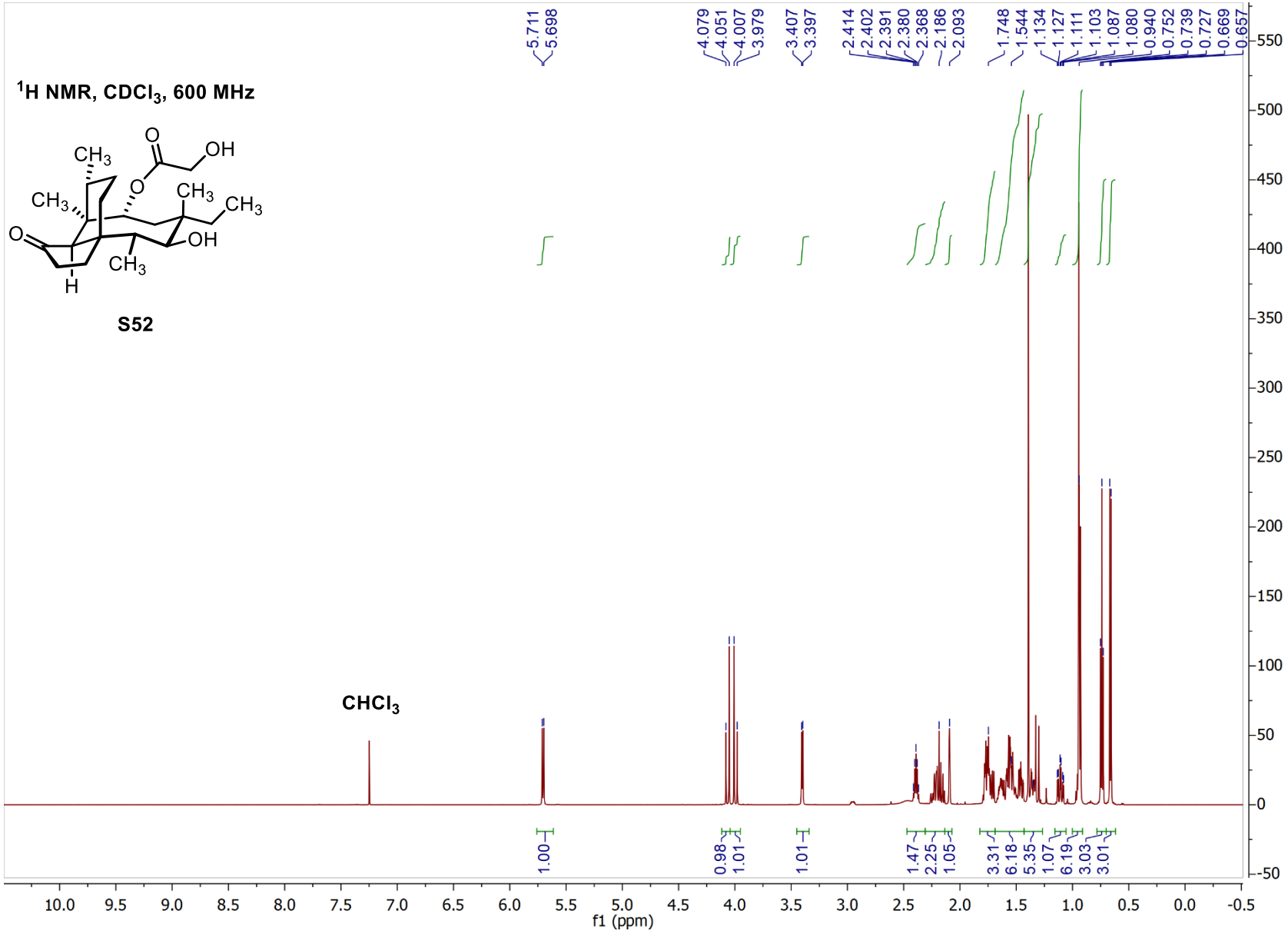

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S49
$CDCl_3$
165.6
145.6
132.5
130.1
128.3
119.3
97.2
83.0
74.6
64.2
61.8
61.7
55.8
51.9
44.3
44.3
40.6
37.2
36.4
35.6
29.6
28.1
27.6
21.9
17.7
15.9
13.8
13.2
f1 (ppm)

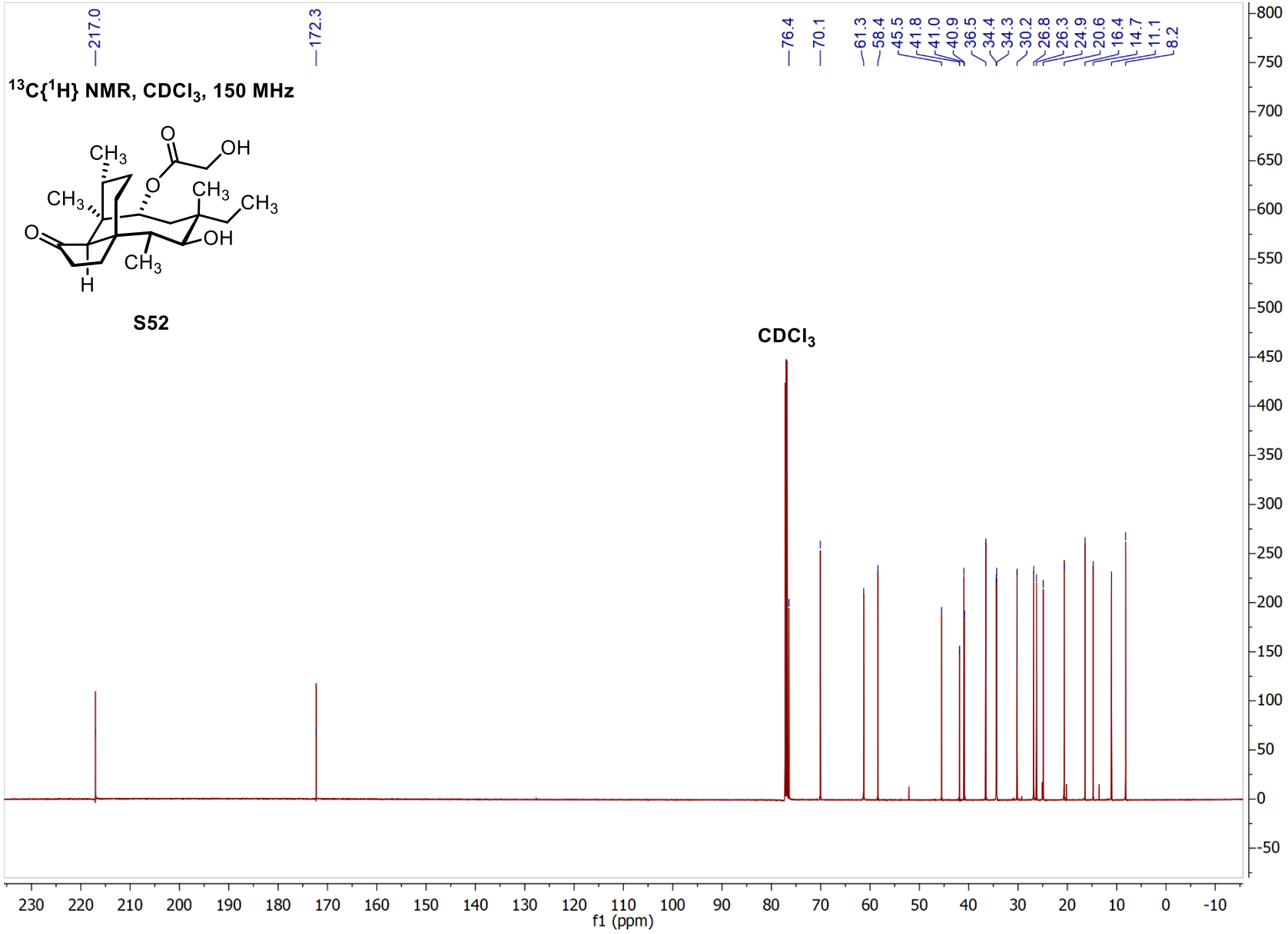

^{1}H NMR, $CDCl_3$, 500 MHz
S50
$CHCl_3$
f1 (ppm)

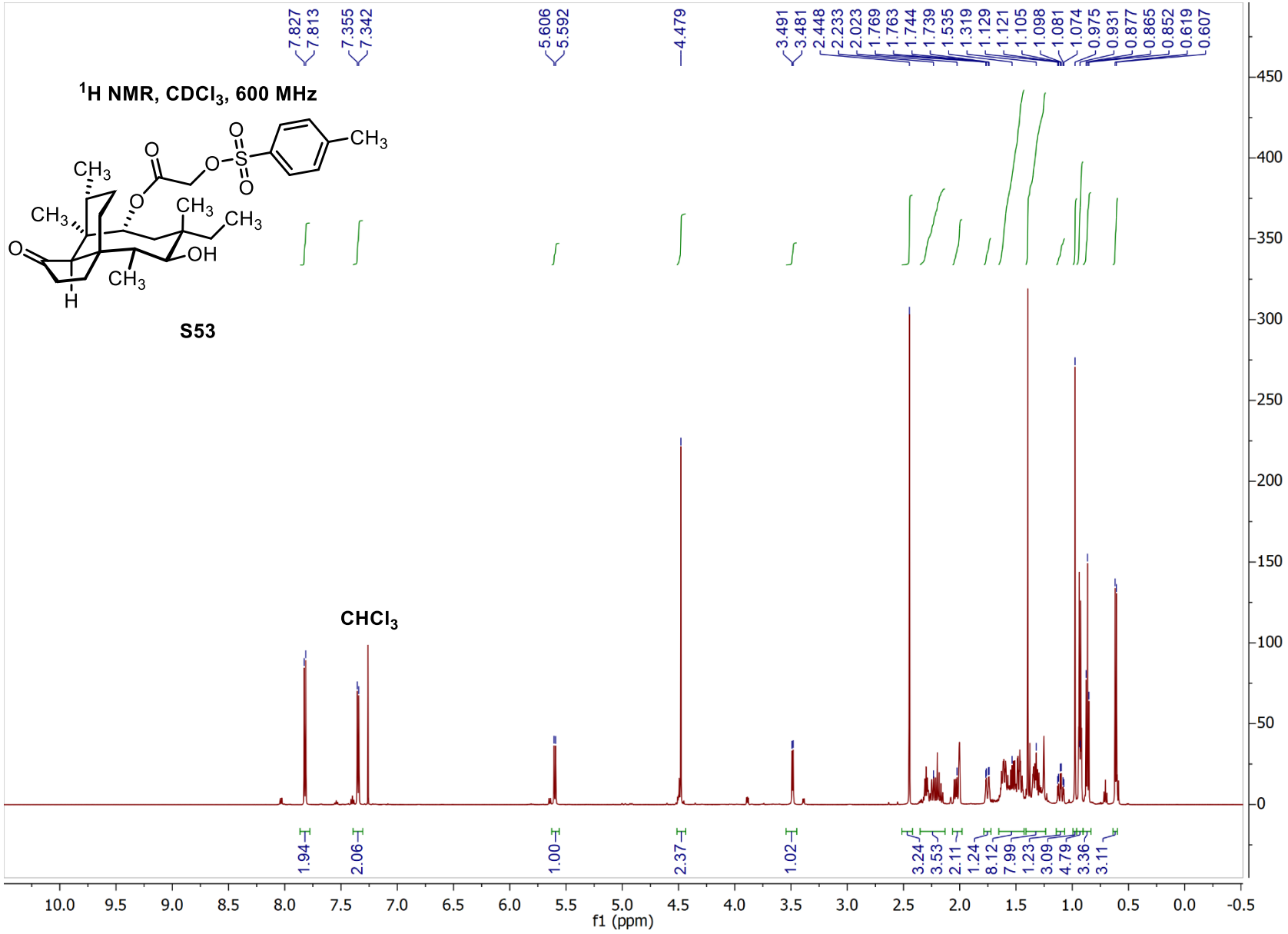

13C{1H} NMR, CDCl3, 150 MHz
CDCl3
S50
170.2
155.2
119.4
97.2
83.1
79.6
74.4
71.8
64.2
61.7
55.8
52.7
52.0
44.3
44.2
40.6
40.5
37.1
36.5
35.7
33.1
29.6
29.4
28.5
28.1
27.6
17.9
16.1
14.0
13.2
f1 (ppm)

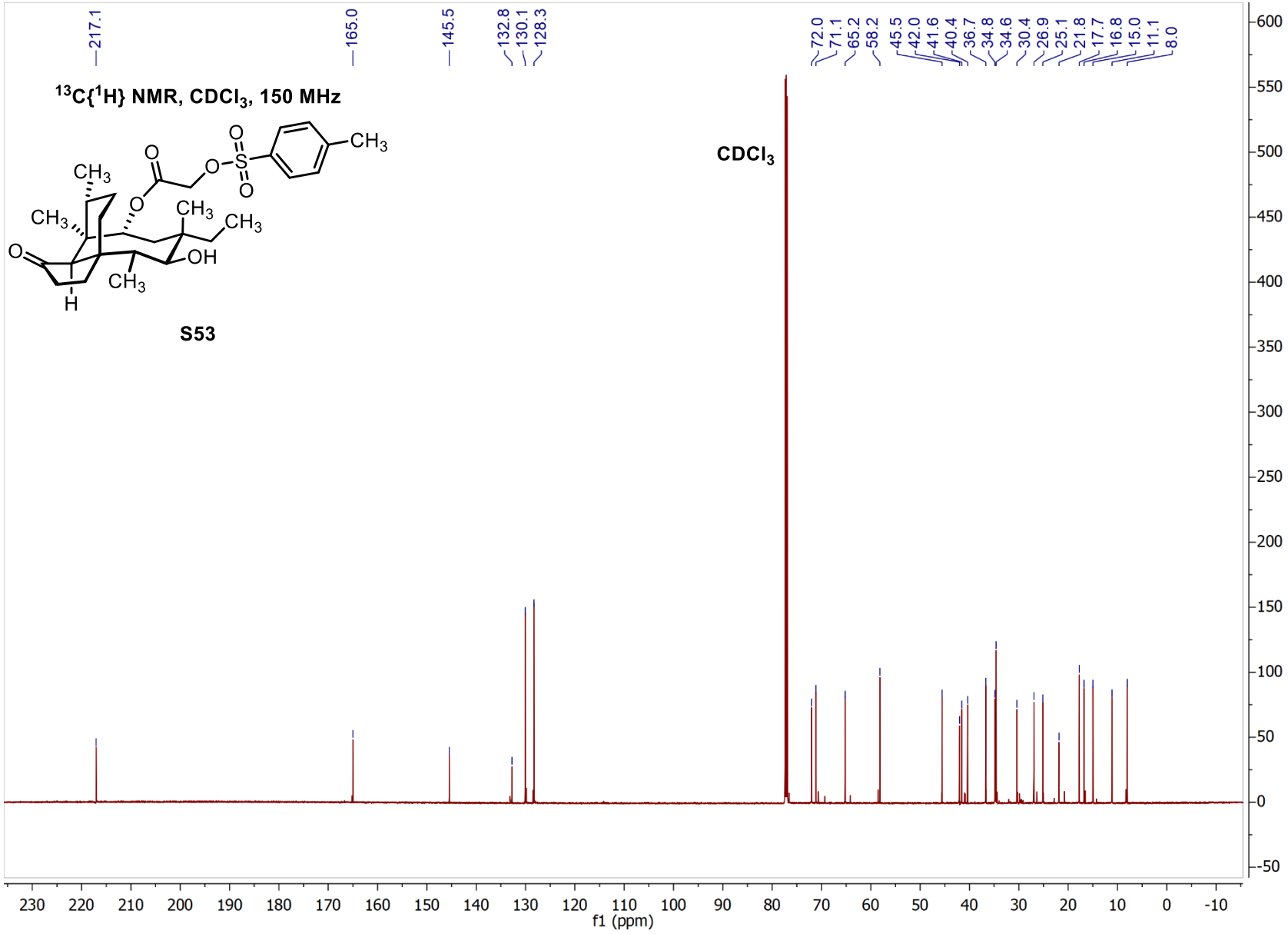

^{1}H NMR, CD_2Cl_2, 500 MHz
$CHDCl_2$
59
5.445
5.434
3.434
3.323
3.308
3.298
3.284
3.274
2.583
2.164
1.894
1.536
1.211
0.965
0.952
0.683
0.672
0.99
2.15
2.99
0.77
0.70
7.77
10.66
20.47
10.30
4.84
4.21
f1 (ppm)

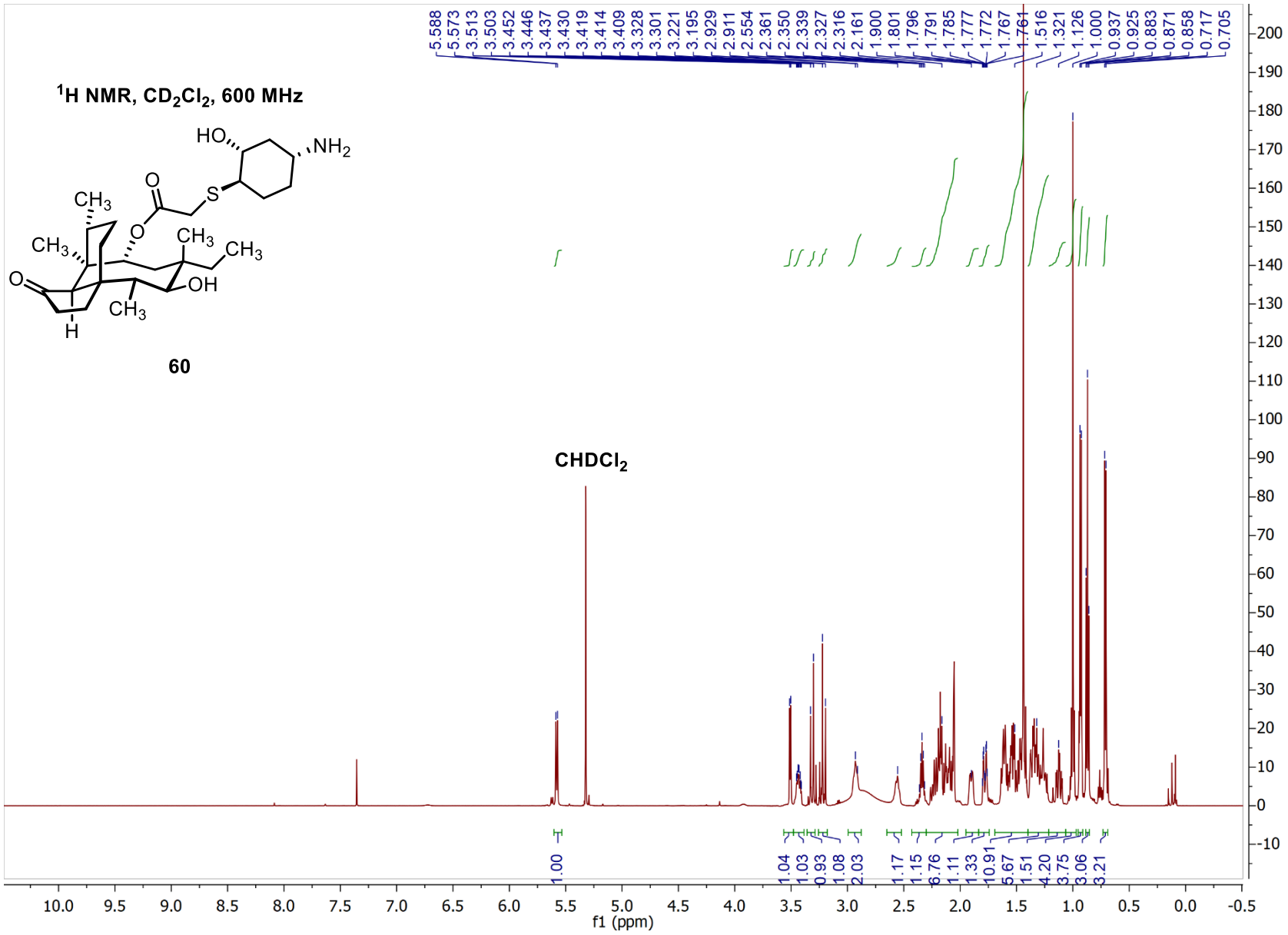

216.0
170.6
76.3
72.6
71.9
58.9
56.2
48.7
46.5
44.0
40.6
37.9
36.9
34.9
33.4
30.1
29.9
28.1
27.7
26.4
17.8
16.1
15.0
12.4
13C{1H} NMR, CD2Cl2, 125 MHz
CD2Cl2
HO
NH2
O
S
CH3
O
CH3
CH3
O
OH
CH3
H
H
59
f1 (ppm)

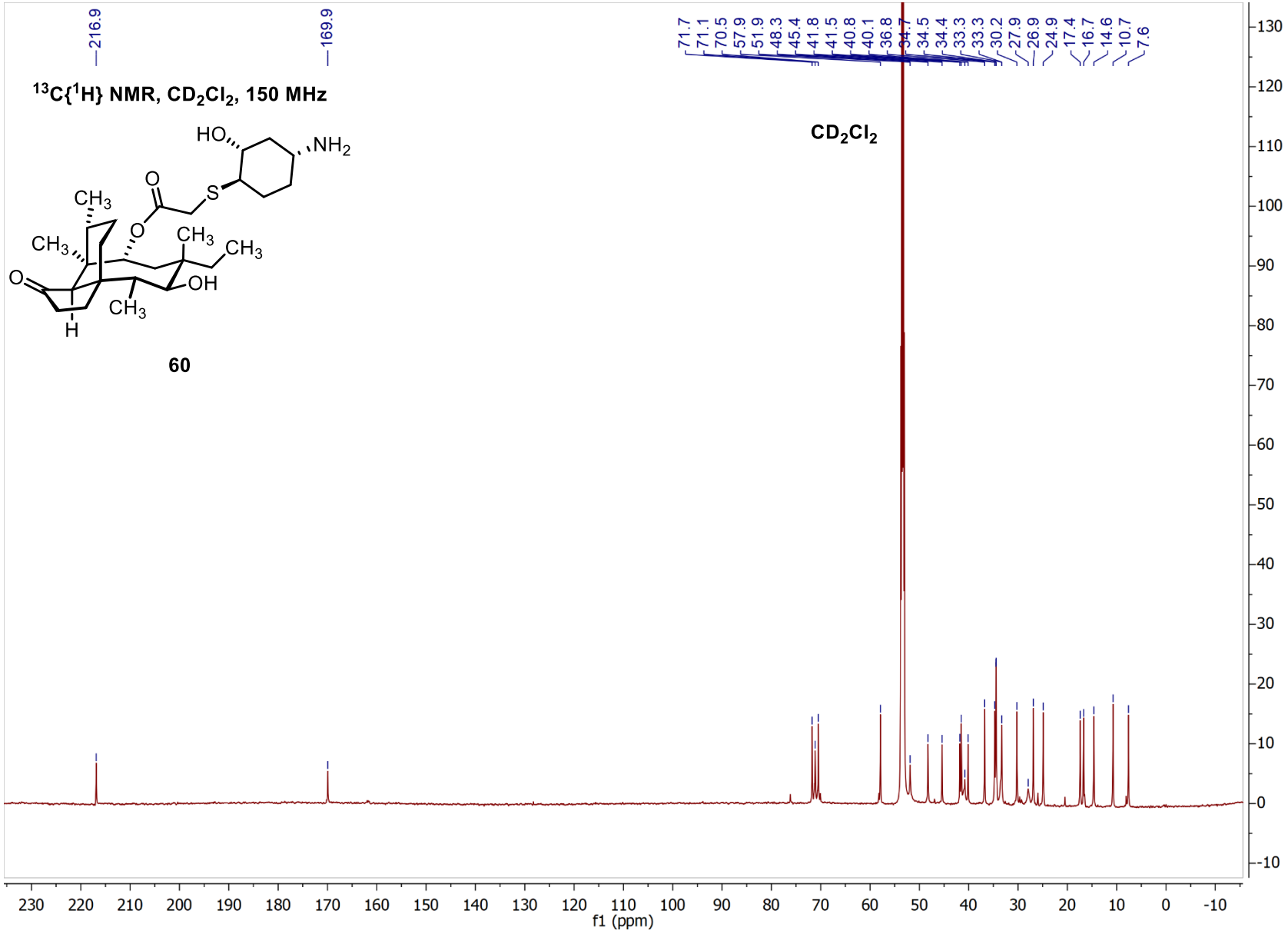

^{1}H NMR, $CDCl_3$, 600 MHz
S52
$CHCl_3$
f1 (ppm)

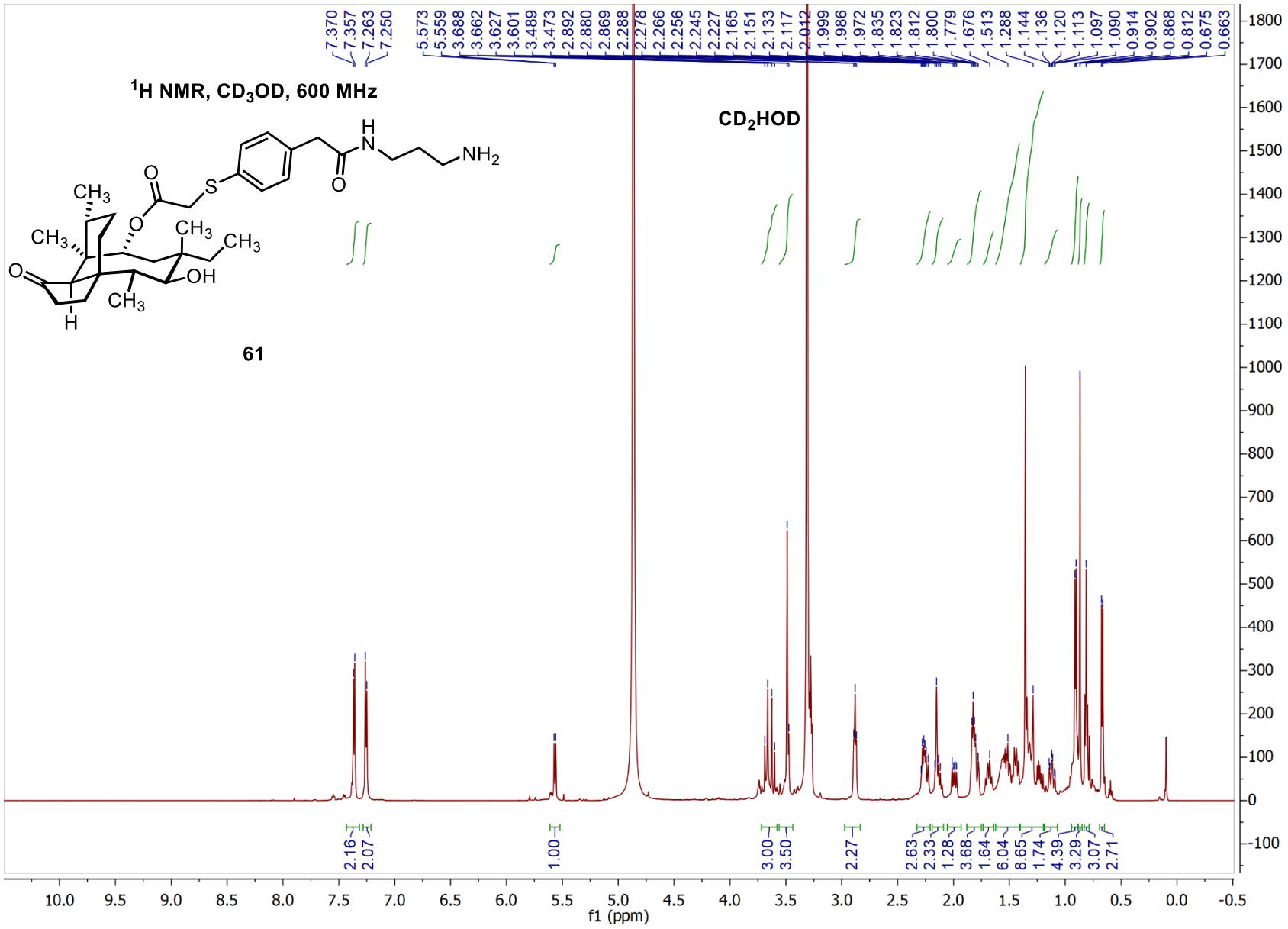

217.0
172.3
76.4
70.1
61.3
58.4
45.5
41.8
41.0
40.9
36.5
34.4
34.3
30.2
26.8
26.3
24.9
20.6
16.4
14.7
11.1
8.2
13C{1H} NMR, CDCl3, 150 MHz
S52
CDCl3
f1 (ppm)

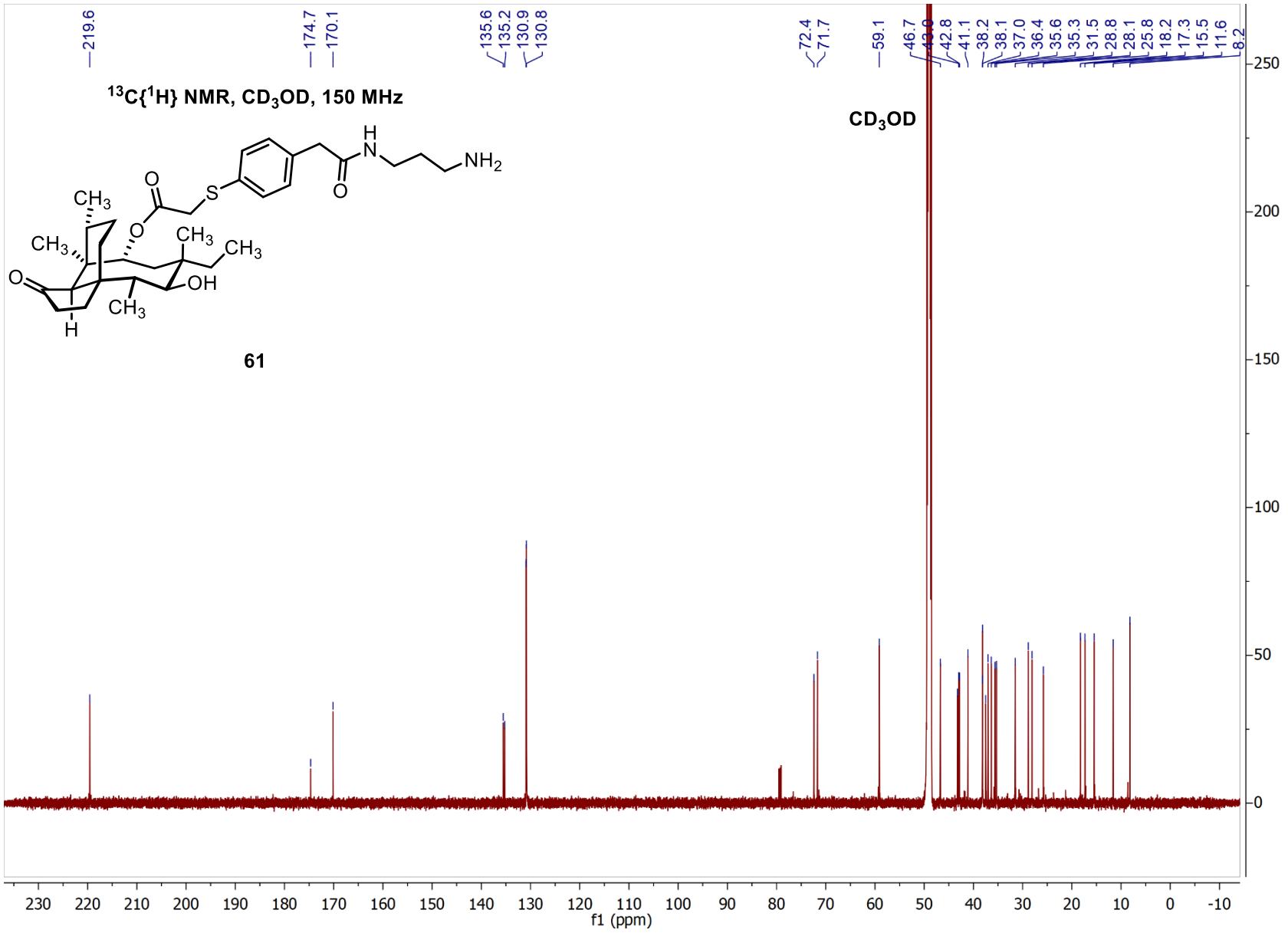

1H NMR, CDCl3, 600 MHz
S53
CHCl3
f1 (ppm)

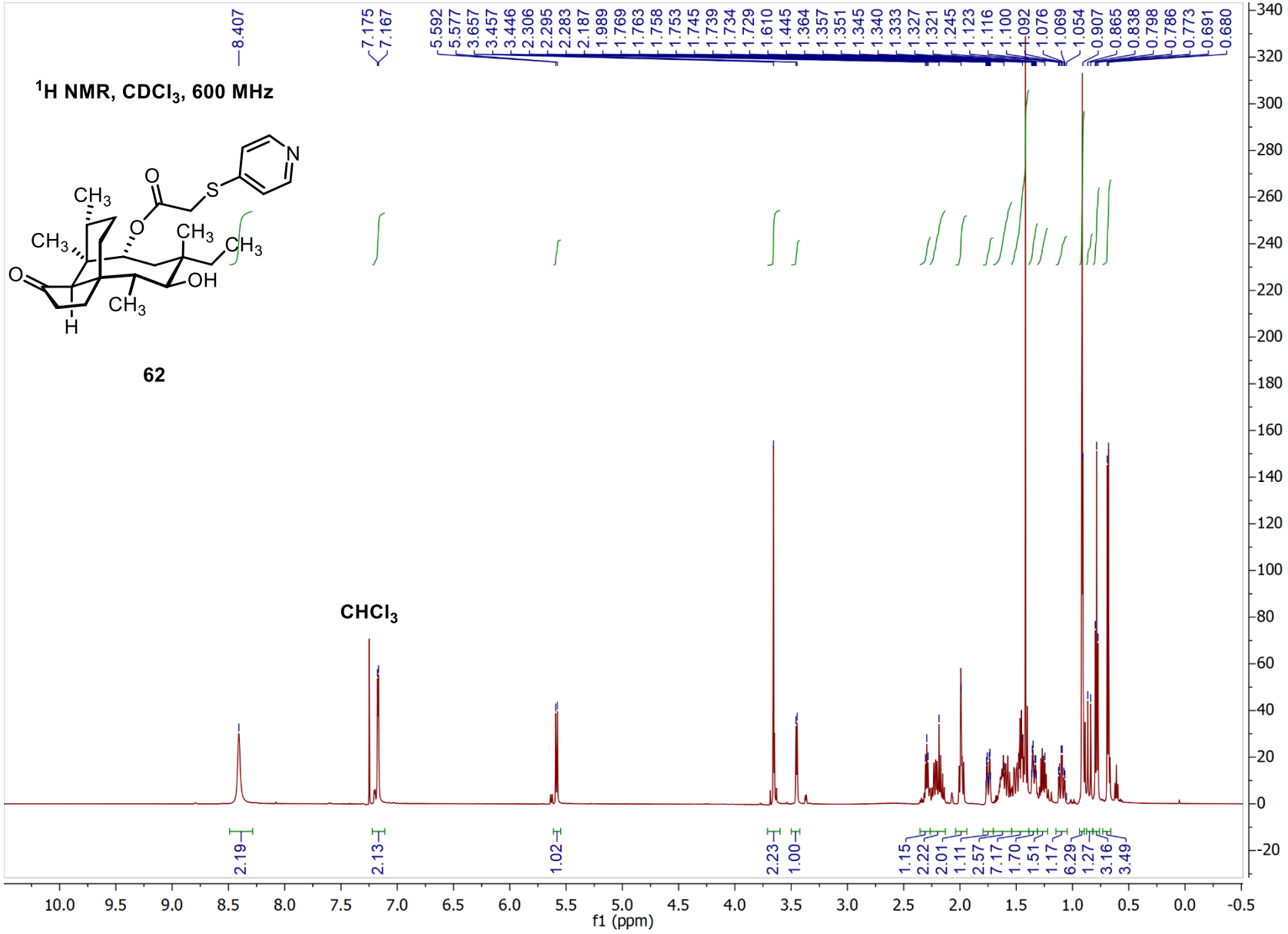

217.1
165.0
145.5
132.8
130.1
128.3
72.0
71.1
65.2
58.2
45.5
42.0
41.6
40.4
36.7
34.8
34.6
30.4
26.9
25.1
21.8
17.7
16.8
15.0
11.1
8.0
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
S53
f1 (ppm)

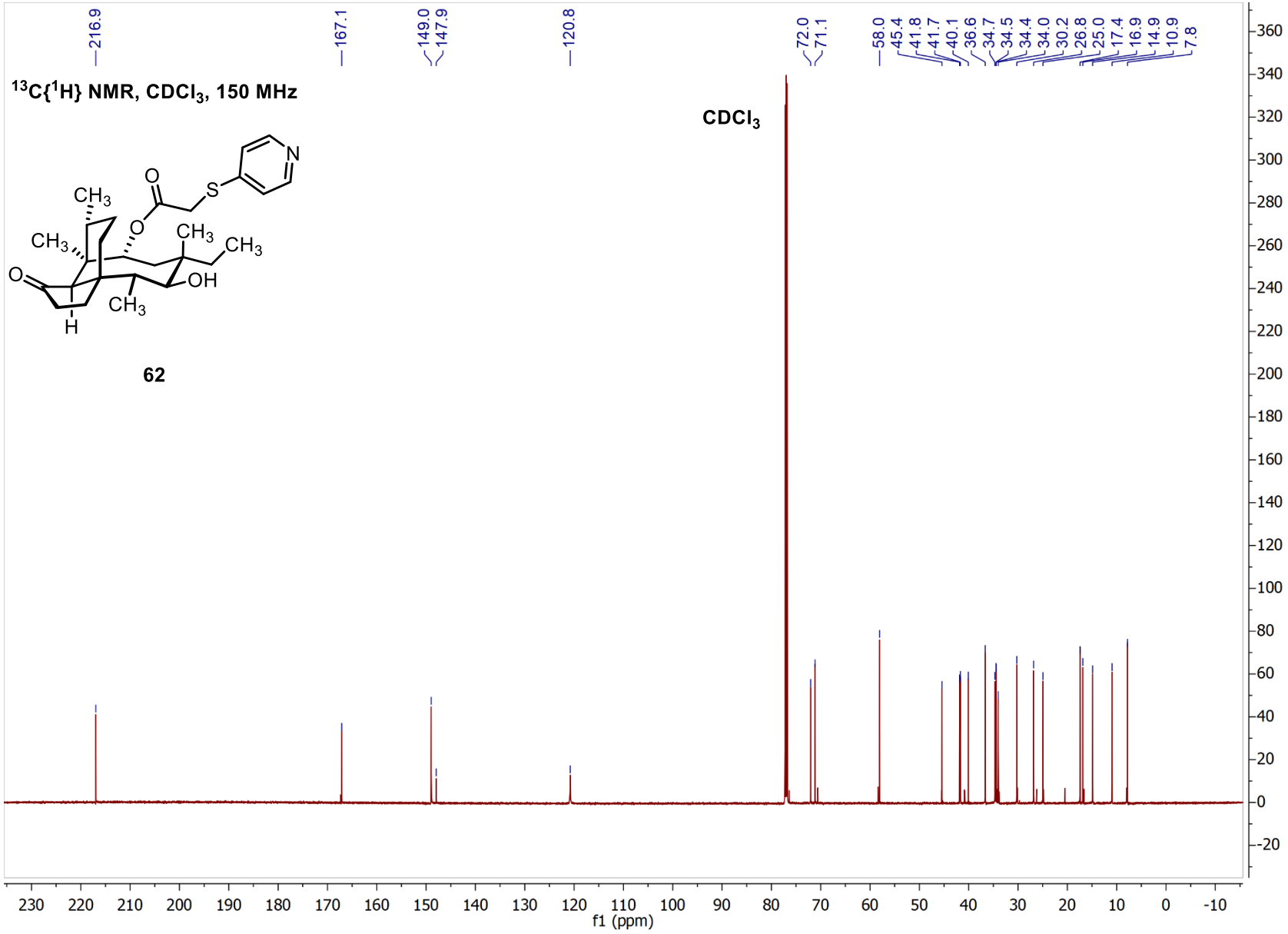

^{1}H NMR, CD_2Cl_2, 600 MHz
HO
NH$_2$
O
S
CH$_3$
O
CH$_3$
CH$_3$
CH$_3$
O
OH
CH$_3$
H
60
CHDCl$_2$
5.588 5.573 3.513 3.503 3.452 3.446 3.437 3.430 3.419 3.414 3.409 3.328 3.301 3.221 3.195 2.929 2.911 2.554 2.361 2.350 2.339 2.327 2.316 2.161 1.900 1.801 1.796 1.791 1.785 1.777 1.772 1.767 1.761 1.516 1.321 1.126 1.000 0.937 0.925 0.883 0.871 0.858 0.717 0.705
1.00 1.04 1.03 0.93 1.08 2.03 1.17 1.15 6.76 1.11 1.33 10.91 5.67 1.51 4.20 3.75 3.06 3.21
f1 (ppm)

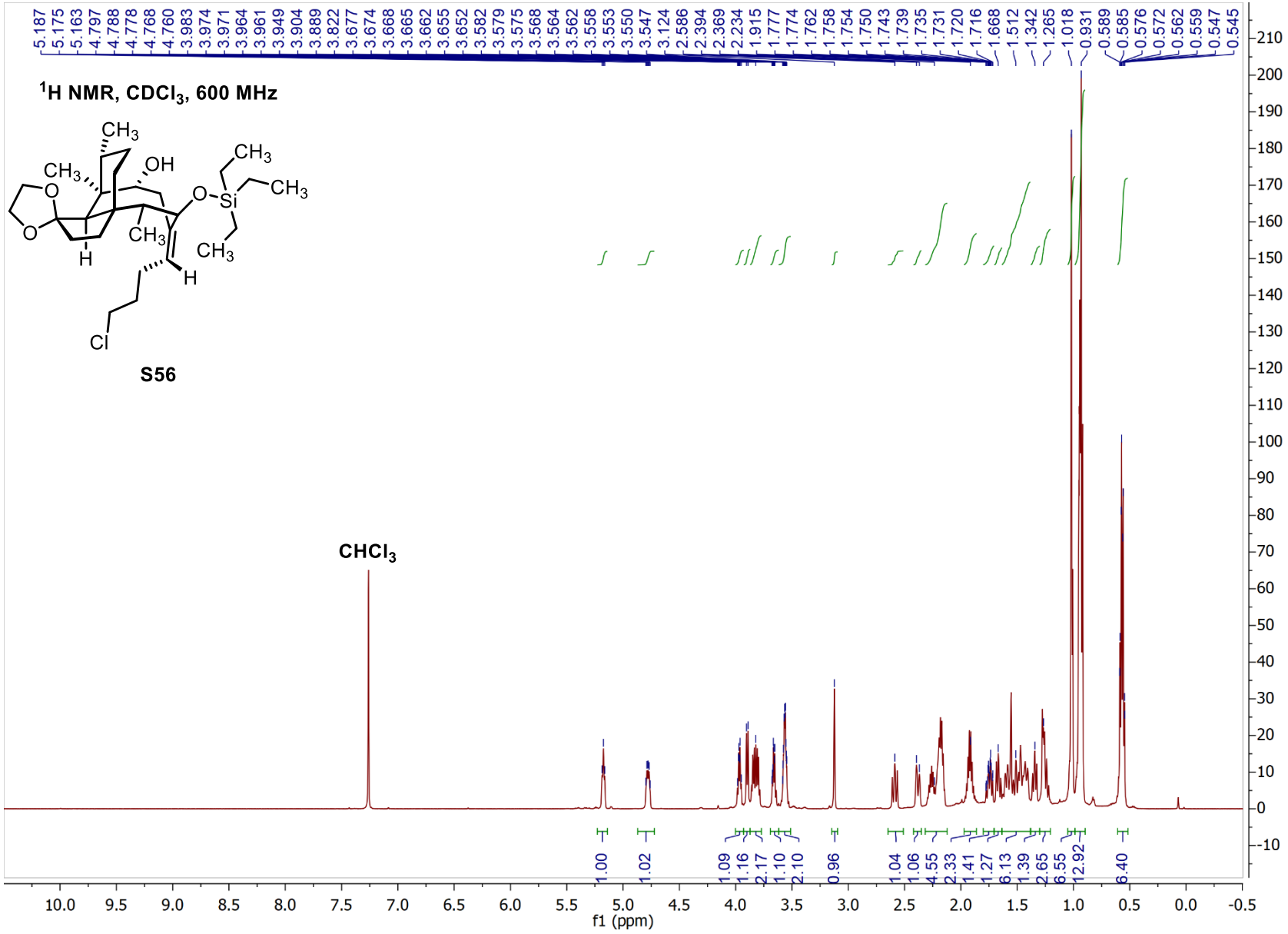

216.9
169.9
71.7
71.1
70.5
57.9
51.9
48.3
45.4
41.8
41.5
40.8
40.1
36.8
34.7
34.5
34.4
33.3
33.3
30.2
27.9
26.9
24.9
17.4
16.7
14.6
10.7
7.6
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
HO
NH2
O
S
CH3
O
CH3
CH3
CH3
O
OH
CH3
H
60
f1 (ppm)

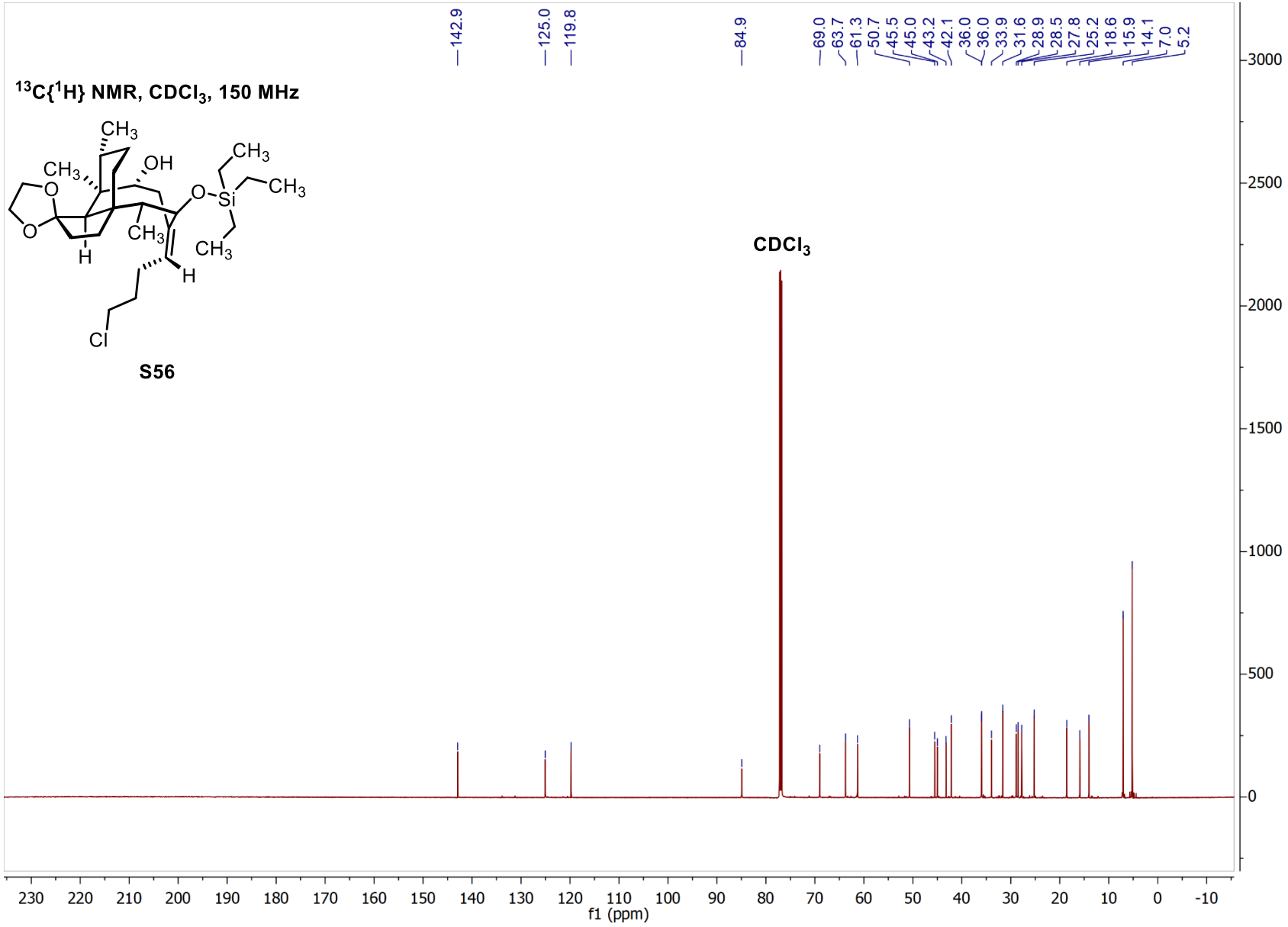

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
61

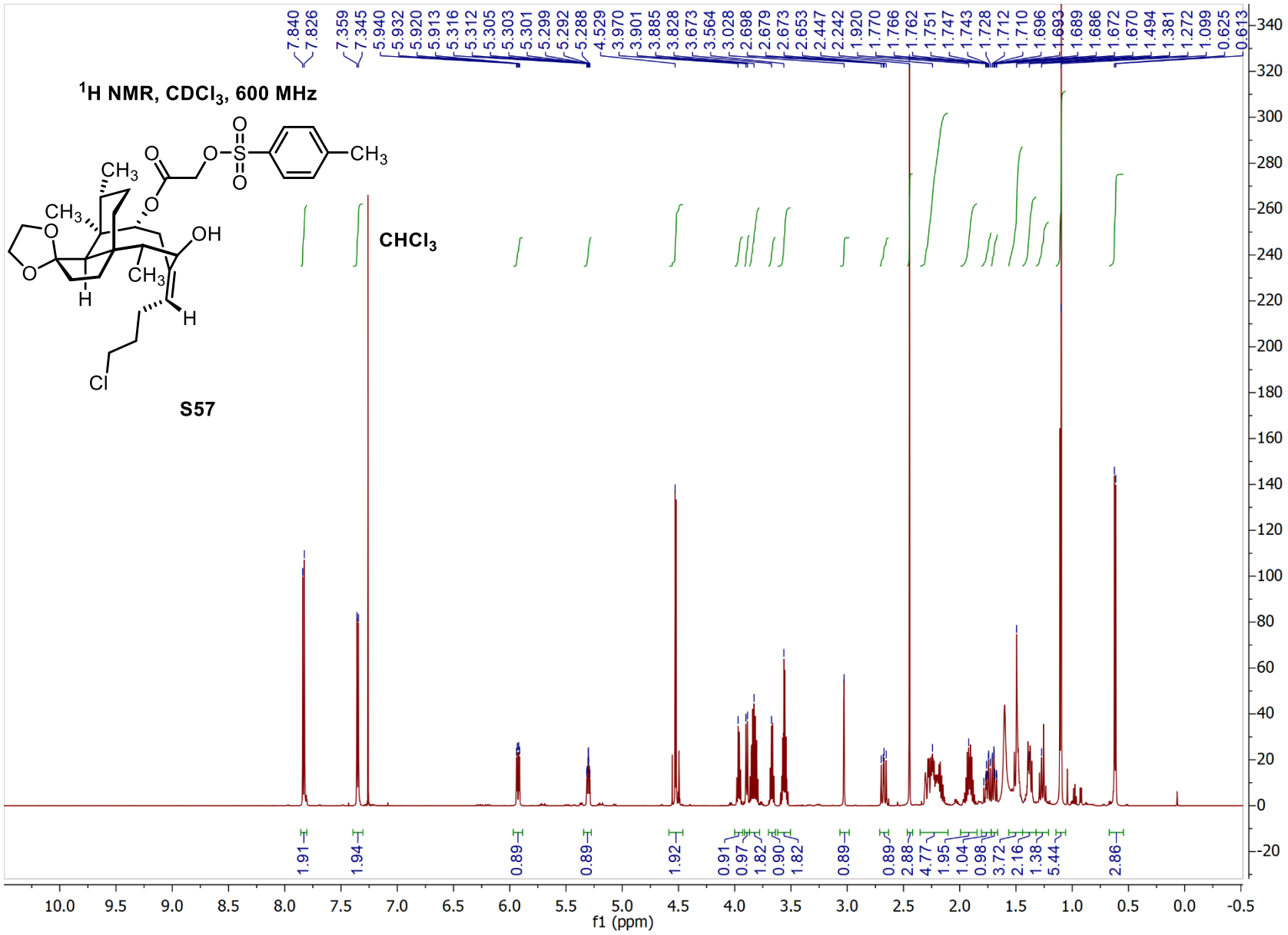

219.6
174.7
170.1
135.6
135.2
130.9
130.8
72.4
71.7
59.1
46.7
43.0
42.8
41.1
38.2
38.1
37.0
36.4
35.6
35.3
31.5
28.8
28.1
25.8
18.2
17.3
15.5
11.6
8.2
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
61
f1 (ppm)

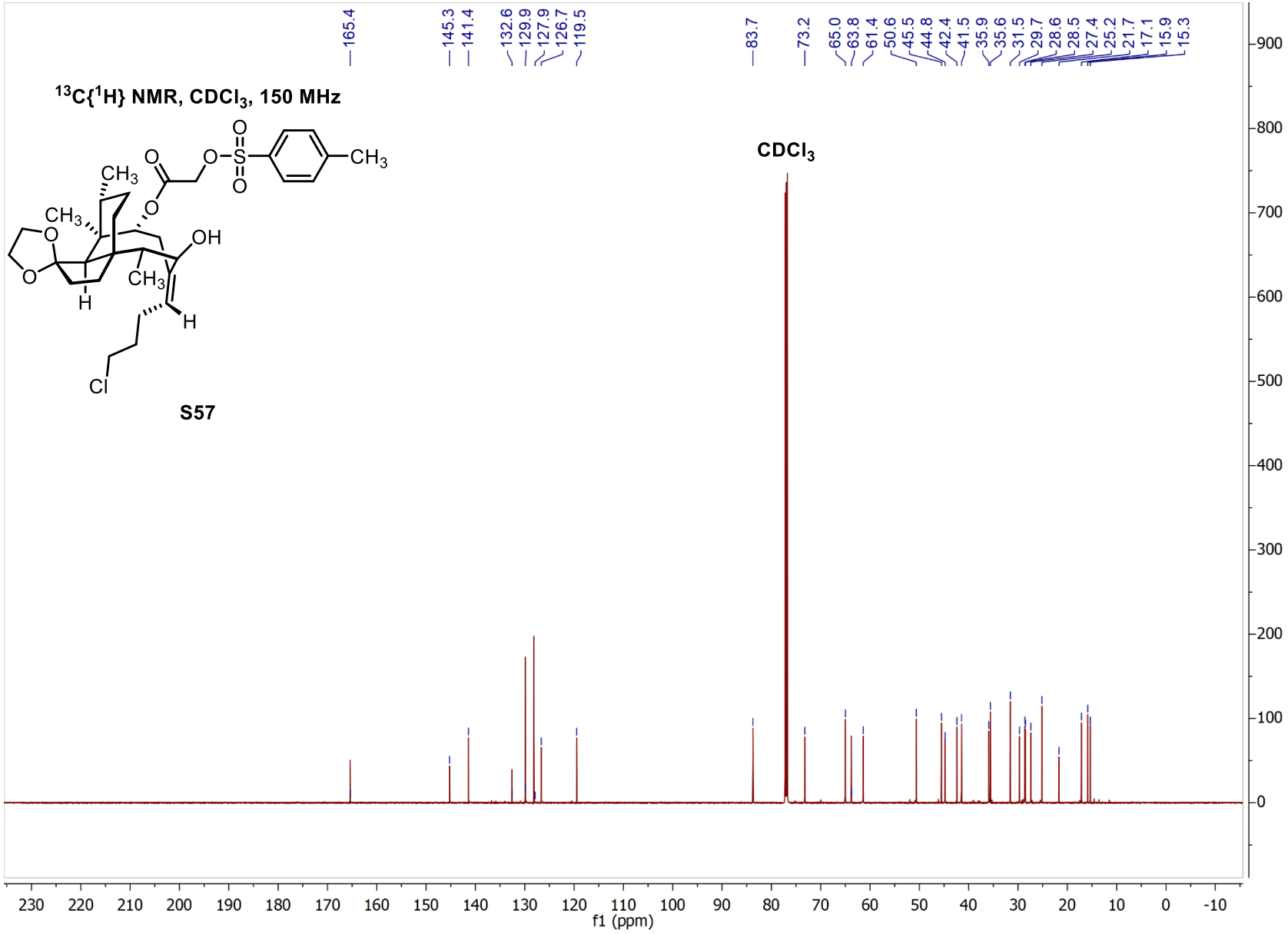

1H NMR, CDCl3, 600 MHz
62
CHCl3
f1 (ppm)

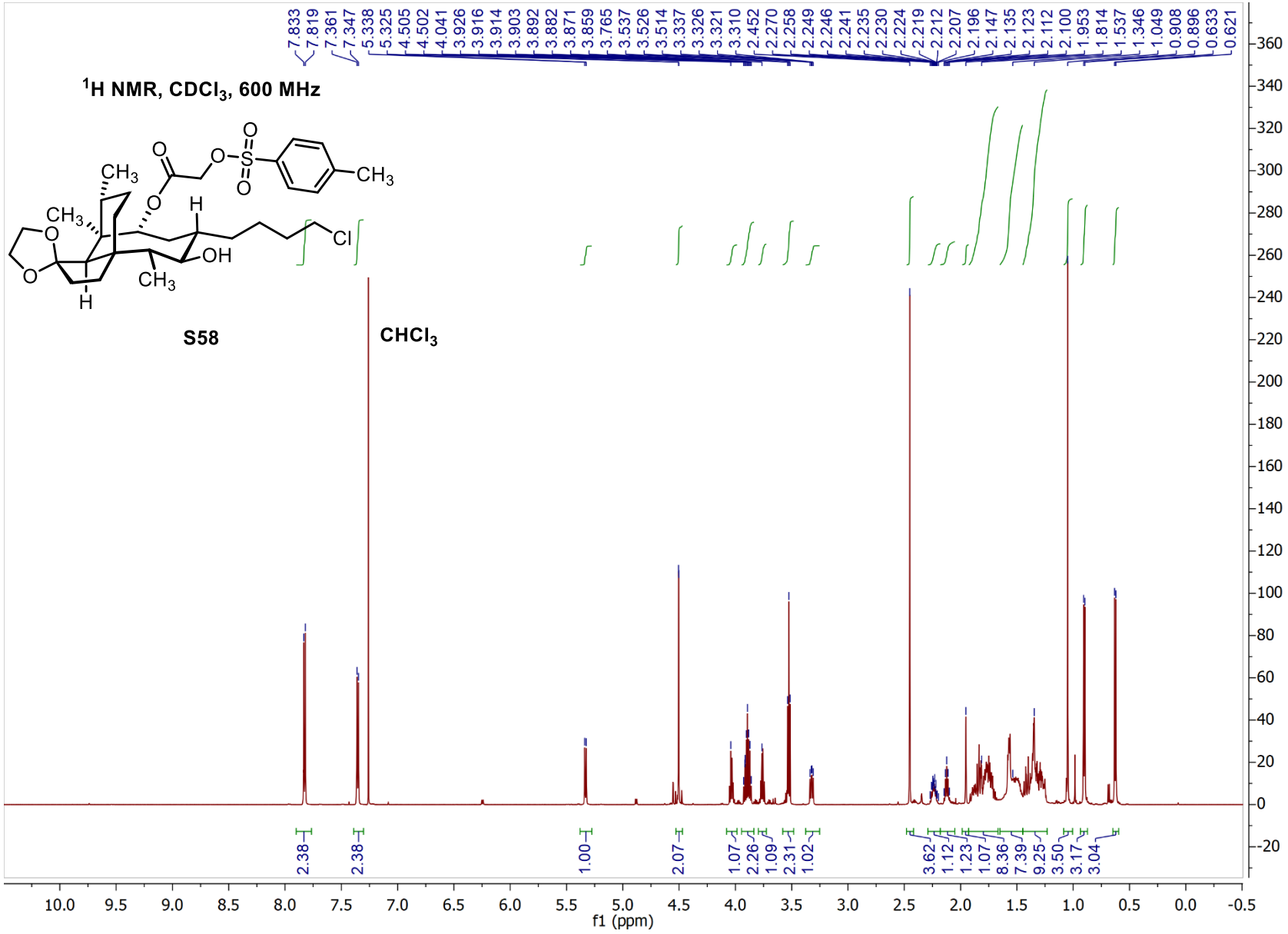

216.9
167.1
149.0
147.9
120.8
72.0
71.1
58.0
45.4
41.8
41.7
40.1
36.6
34.7
34.5
34.4
34.0
30.2
26.8
25.0
17.4
16.9
14.9
10.9
7.8
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
62
f1 (ppm)

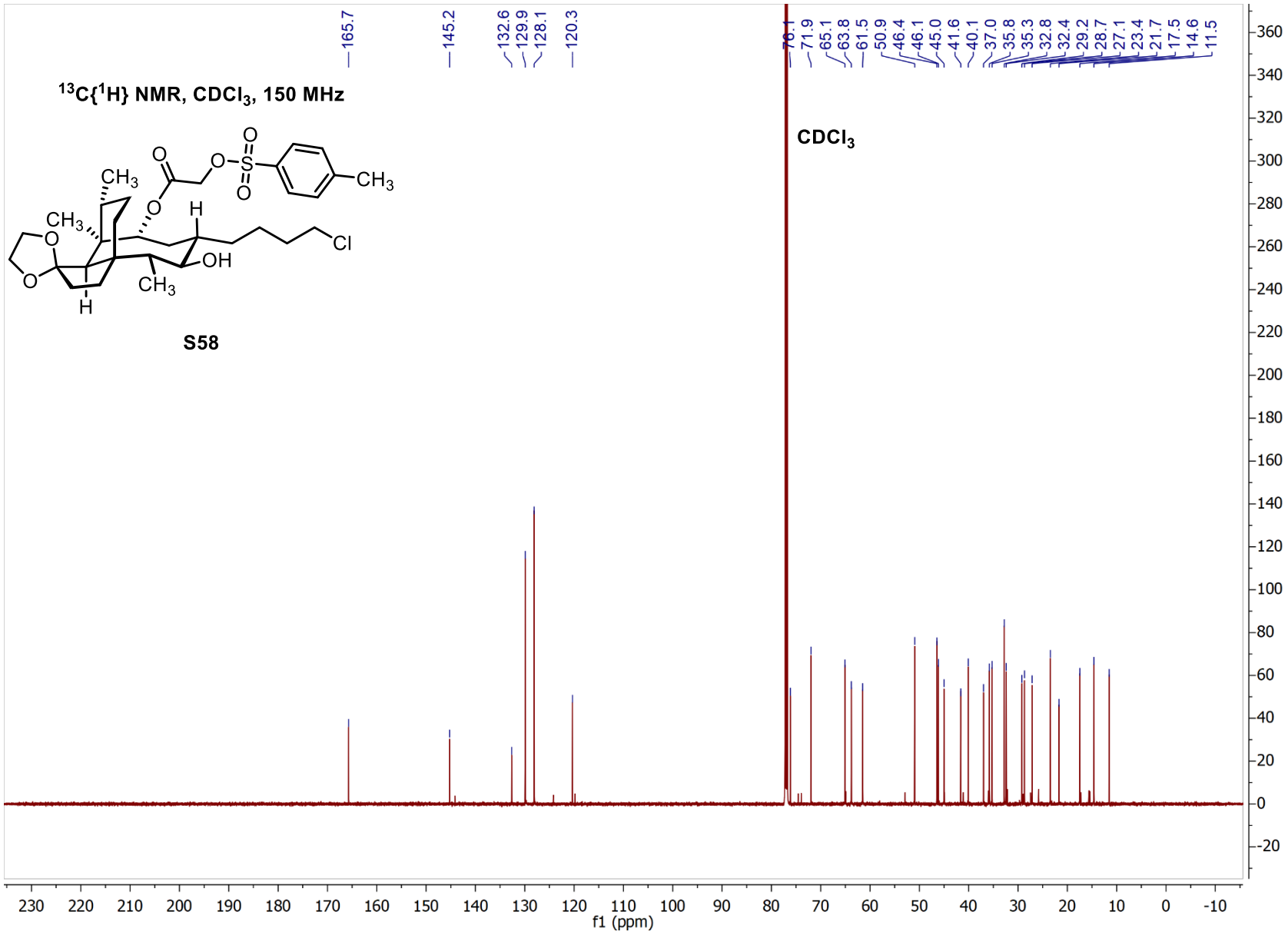

5.187 5.175 5.163 4.797 4.788 4.778 4.768 4.760 3.983 3.974 3.971 3.964 3.961 3.949 3.904 3.889 3.822 3.677 3.674 3.668 3.665 3.662 3.655 3.652 3.582 3.579 3.575 3.568 3.564 3.562 3.558 3.553 3.550 3.547 3.124 2.586 2.394 2.369 2.234 1.915 1.777 1.774 1.762 1.758 1.754 1.750 1.743 1.739 1.735 1.731 1.720 1.716 1.668 1.512 1.342 1.265 1.018 0.931 0.589 0.585 0.576 0.572 0.562 0.559 0.547 0.545
^{1}H NMR, $CDCl_3$, 600 MHz
CH3
CH3
OH
O
O
Si
CH3
CH3
CH3
CH3
H
H
Cl
S56
$CHCl_3$
1.00 1.02 1.09 1.16 2.17 1.10 2.10 0.96 1.04 1.06 4.55 2.33 1.41 1.27 6.13 1.39 2.65 6.55 12.92 6.40
f1 (ppm)

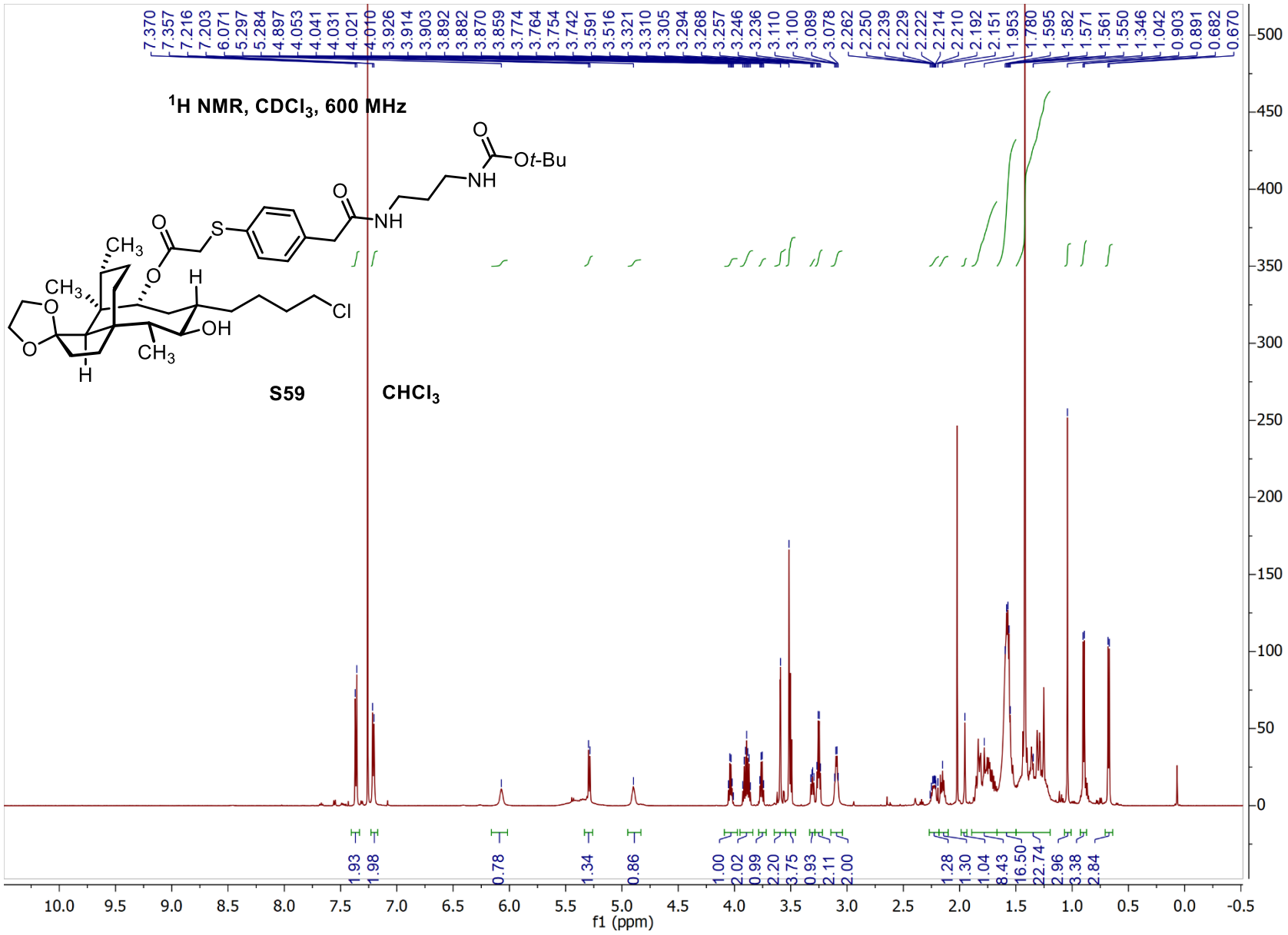

13C{1H} NMR, CDCl3, 150 MHz
S56
CDCl3
142.9
125.0
119.8
84.9
69.0
63.7
61.3
50.7
45.5
45.0
43.2
42.1
36.0
36.0
33.9
31.6
28.9
28.5
27.8
25.2
18.6
15.9
14.1
7.0
5.2
f1 (ppm)

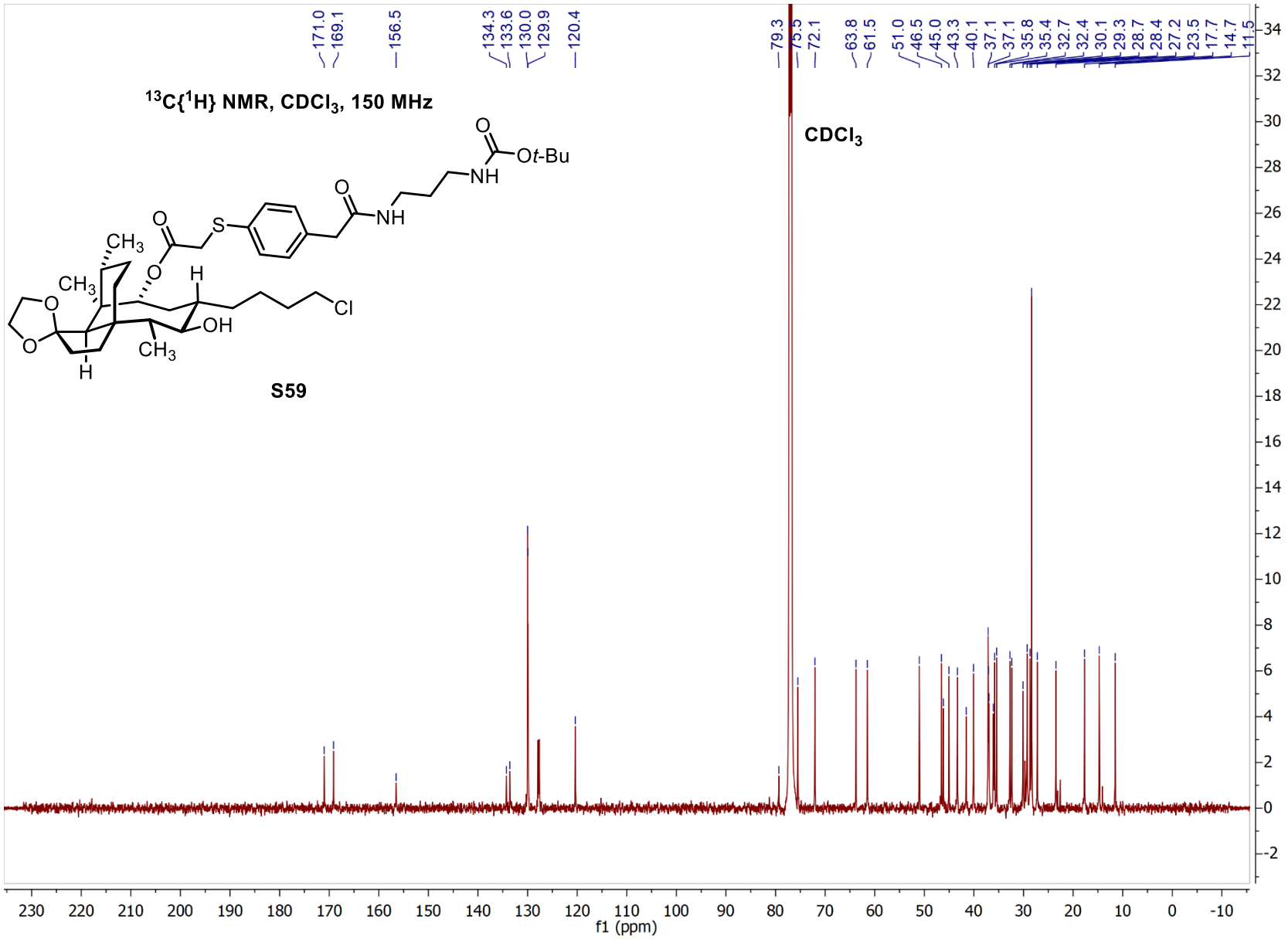

^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
S57
f1 (ppm)

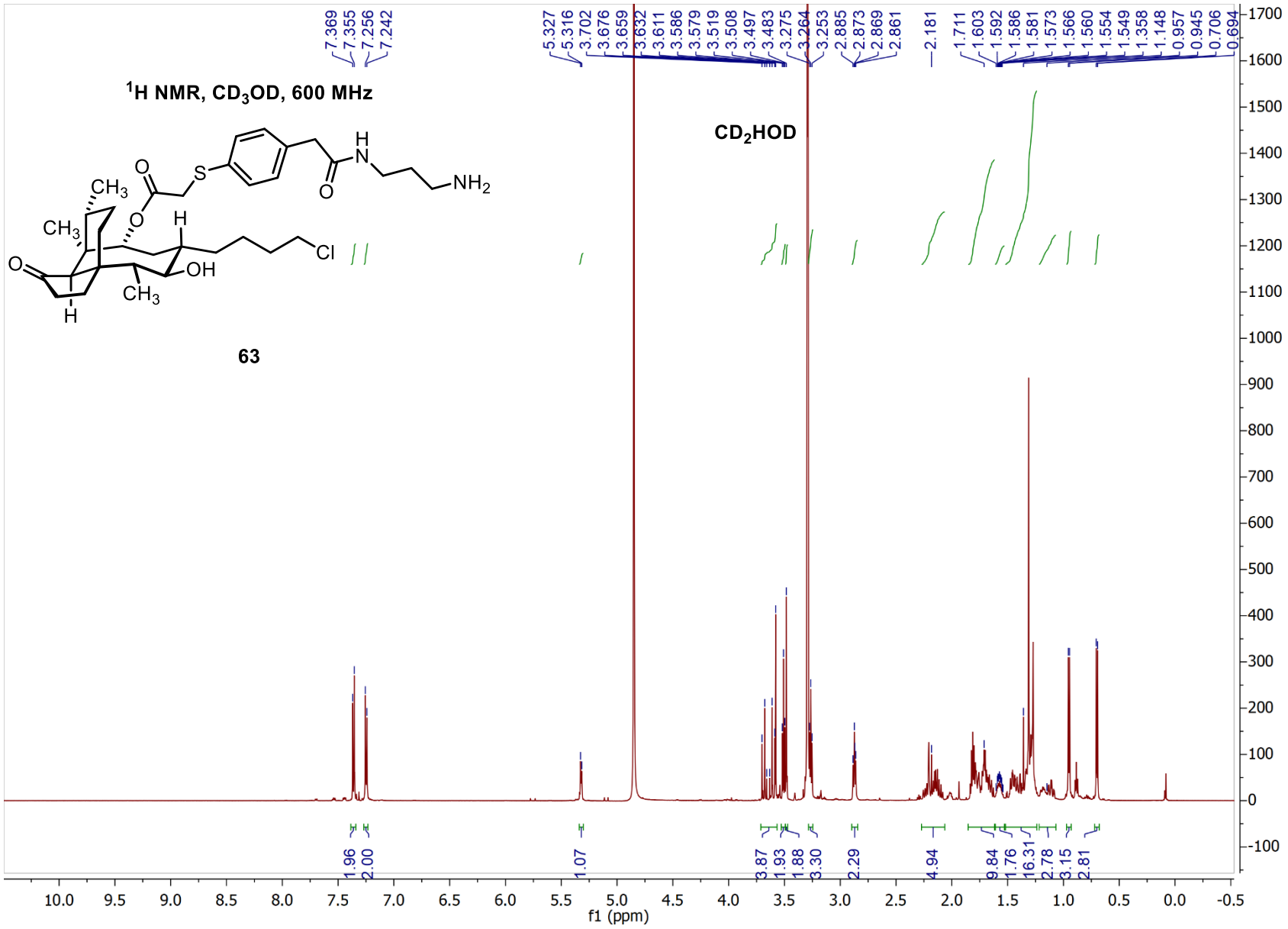

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S57
$CDCl_3$
165.4
145.3
141.4
132.6
129.9
127.9
126.7
119.5
83.7
73.2
65.0
63.8
61.4
50.6
45.5
44.8
42.4
41.5
35.9
35.6
31.5
29.7
28.6
28.5
27.4
25.2
21.7
17.1
15.9
15.3
f1 (ppm)

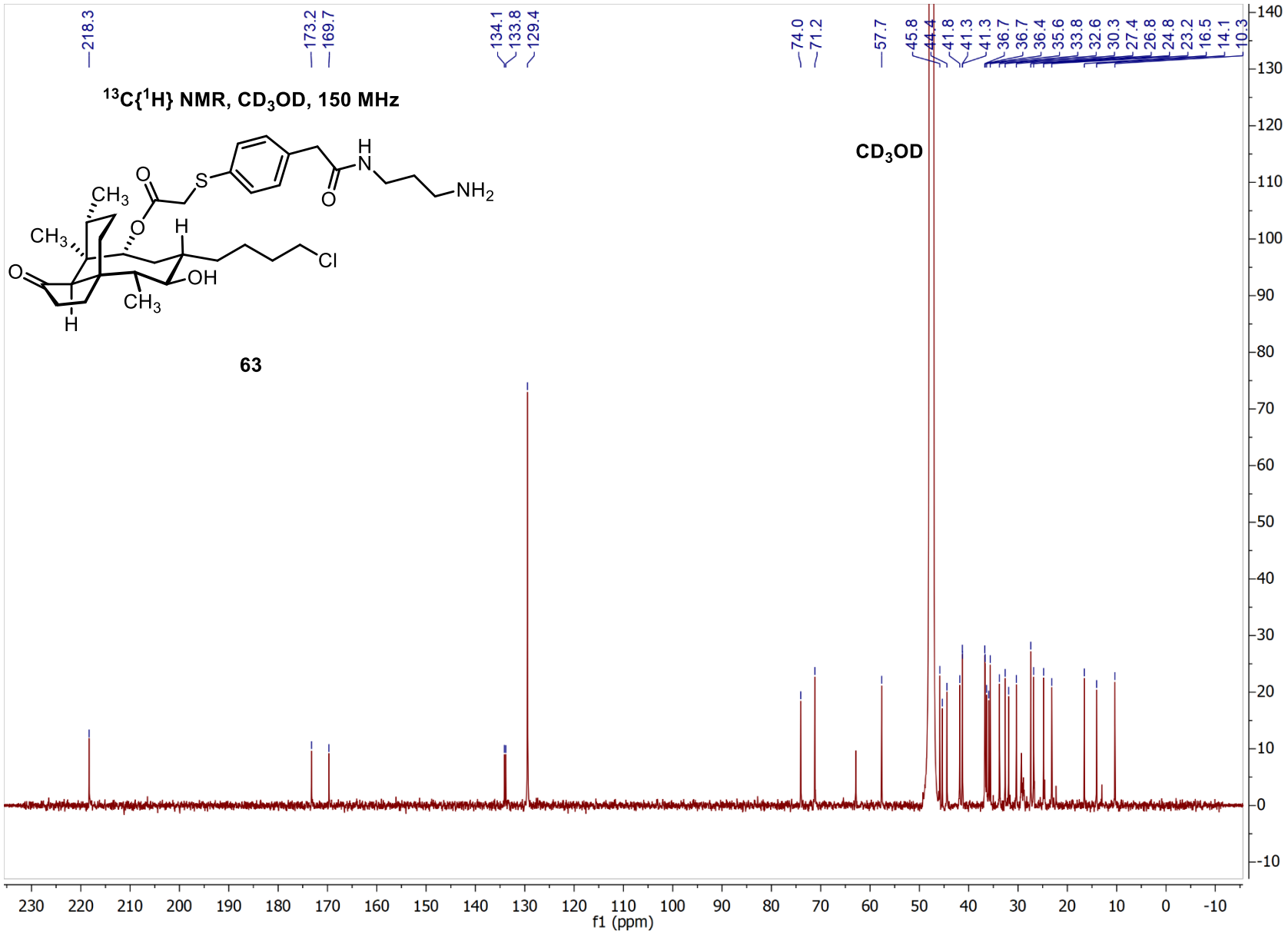

^{1}H NMR, $CDCl_3$, 600 MHz
S58
$CHCl_3$
f1 (ppm)

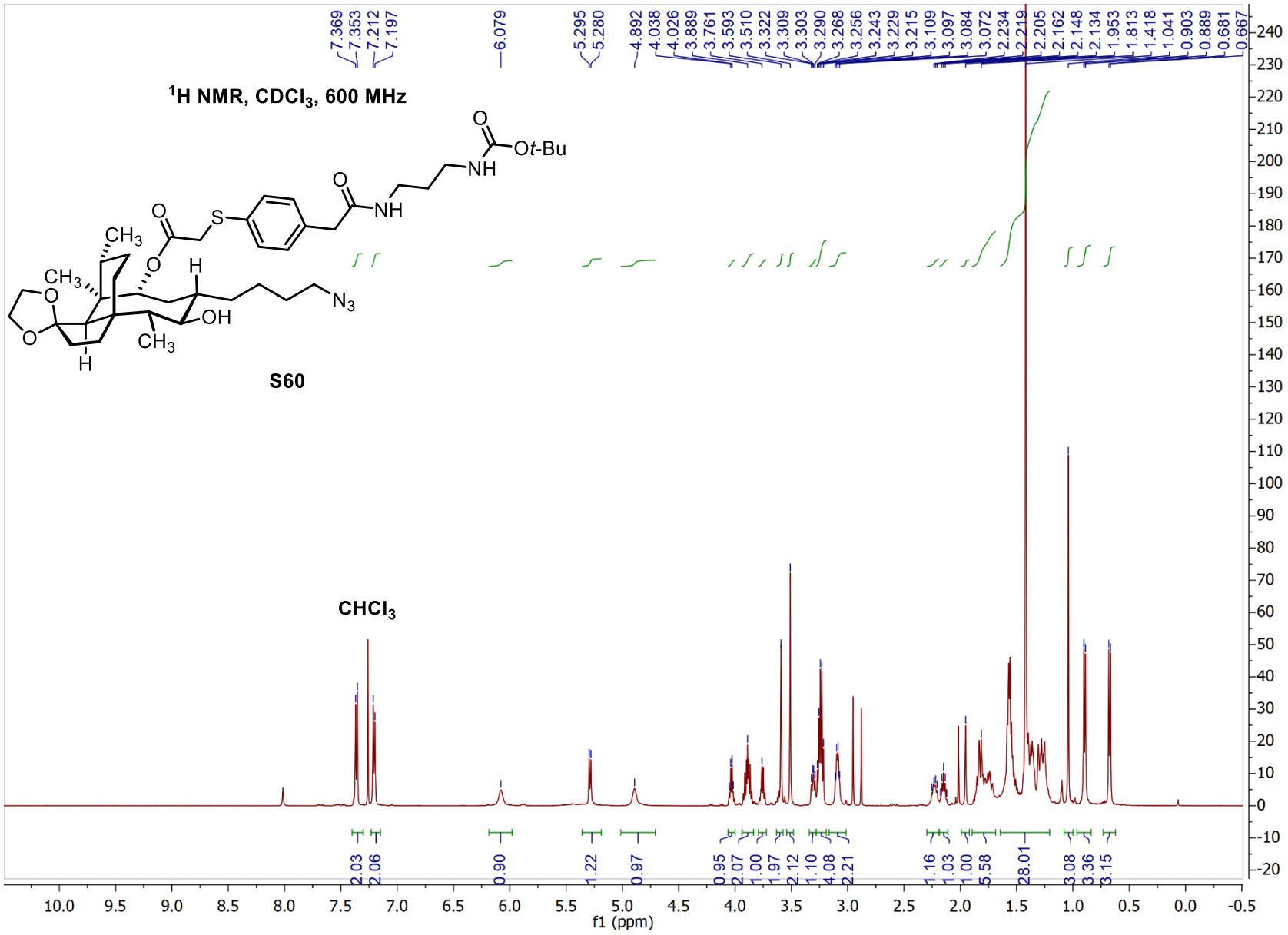

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S58
$CDCl_3$
165.7
145.2
132.6
129.9
128.1
120.3
76.1
71.9
65.1
63.8
61.5
50.9
46.4
46.1
45.0
41.6
40.1
37.0
35.8
35.3
32.8
32.4
29.2
28.7
27.1
23.4
21.7
17.5
14.6
11.5
f1 (ppm)

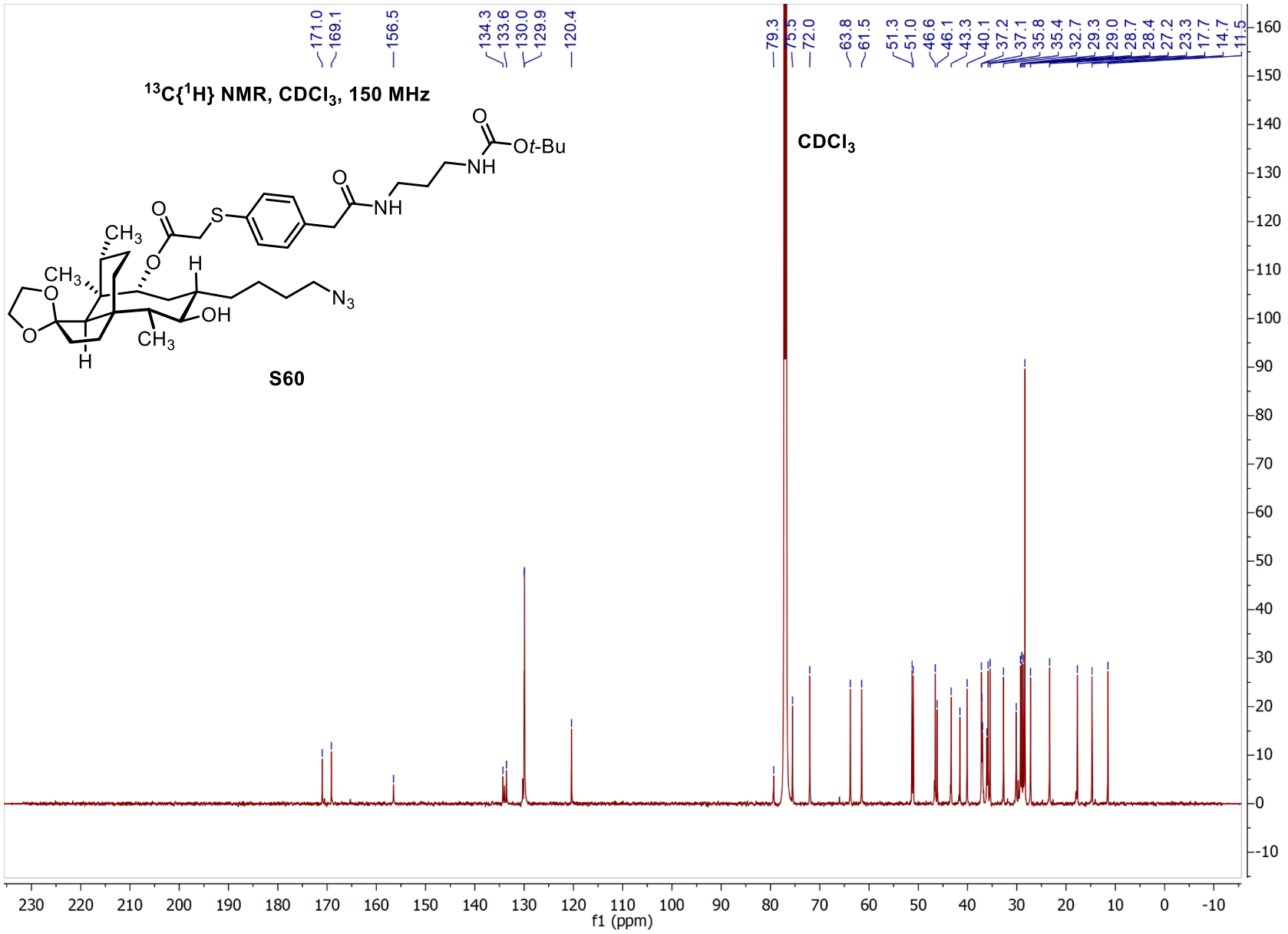

1H NMR, CDCl3, 600 MHz
S59
CHCl3
f1 (ppm)

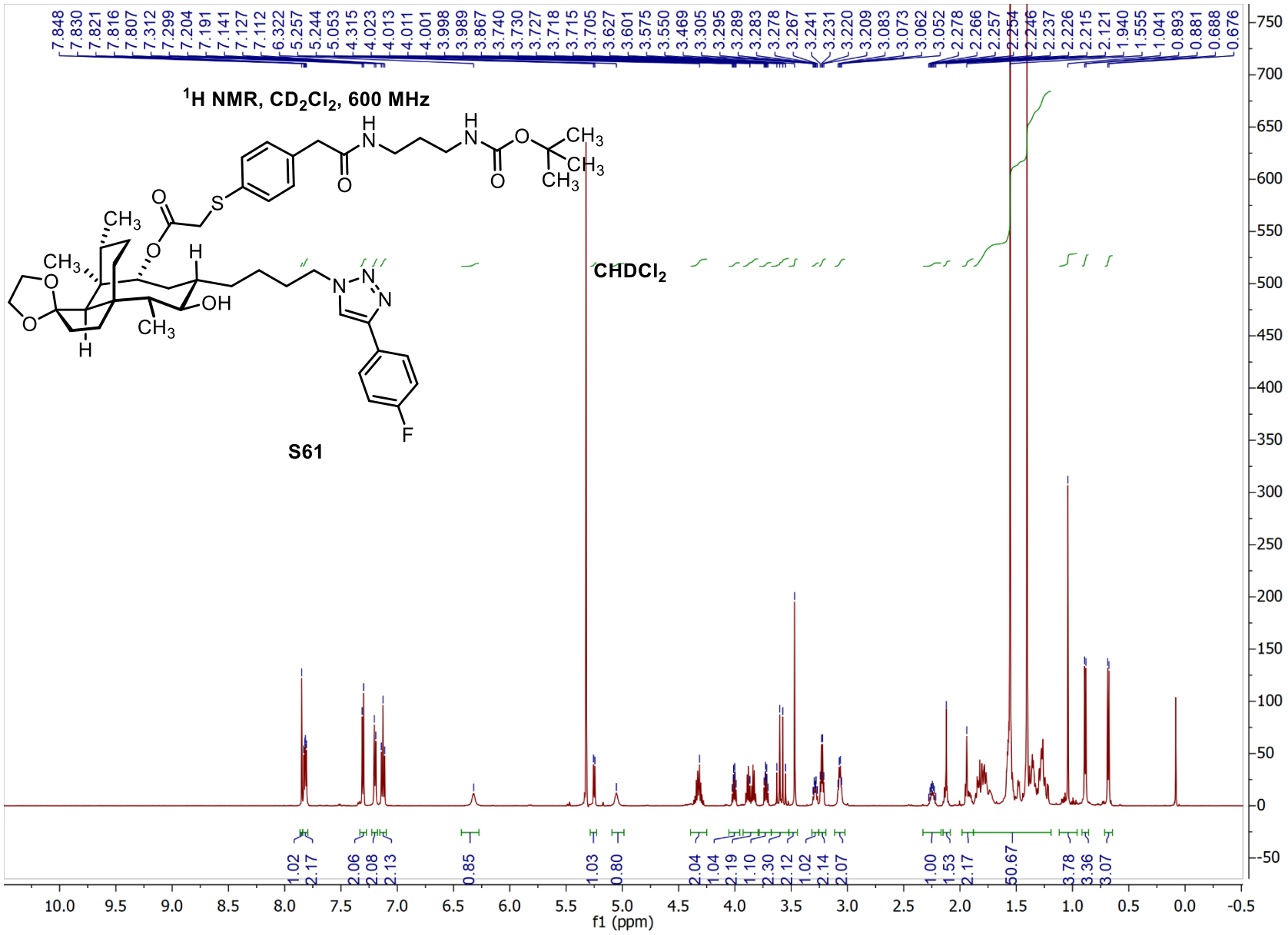

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
$CDCl_3$
S59
171.0
169.1
156.5
134.3
133.6
130.0
129.9
120.4
79.3
75.5
72.1
63.8
61.5
51.0
46.5
45.0
43.3
40.1
37.1
37.1
35.8
35.4
32.7
32.4
30.1
29.3
28.7
28.4
27.2
23.5
17.7
14.7
11.5
f1 (ppm)

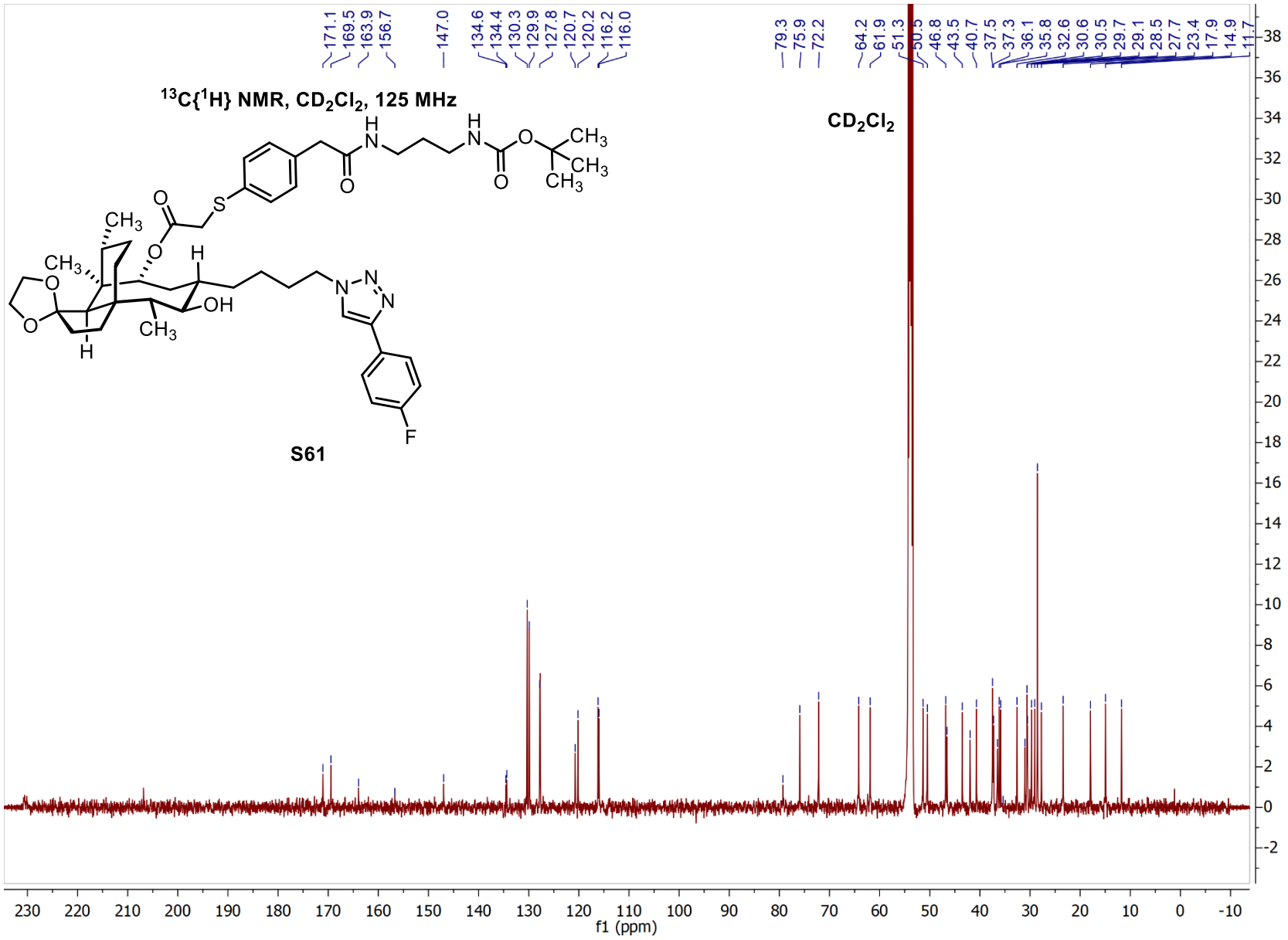

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
63
7.369
7.355
7.256
7.242
5.327
5.316
3.702
3.676
3.659
3.632
3.611
3.586
3.579
3.519
3.508
3.497
3.483
3.275
3.264
3.253
2.885
2.873
2.869
2.861
2.181
1.711
1.603
1.592
1.586
1.581
1.573
1.566
1.560
1.554
1.549
1.358
1.148
0.957
0.945
0.706
0.694
1.96
2.00
1.07
3.87
1.93
1.88
3.30
2.29
4.94
9.84
1.76
16.31
2.78
3.15
2.81
f1 (ppm)

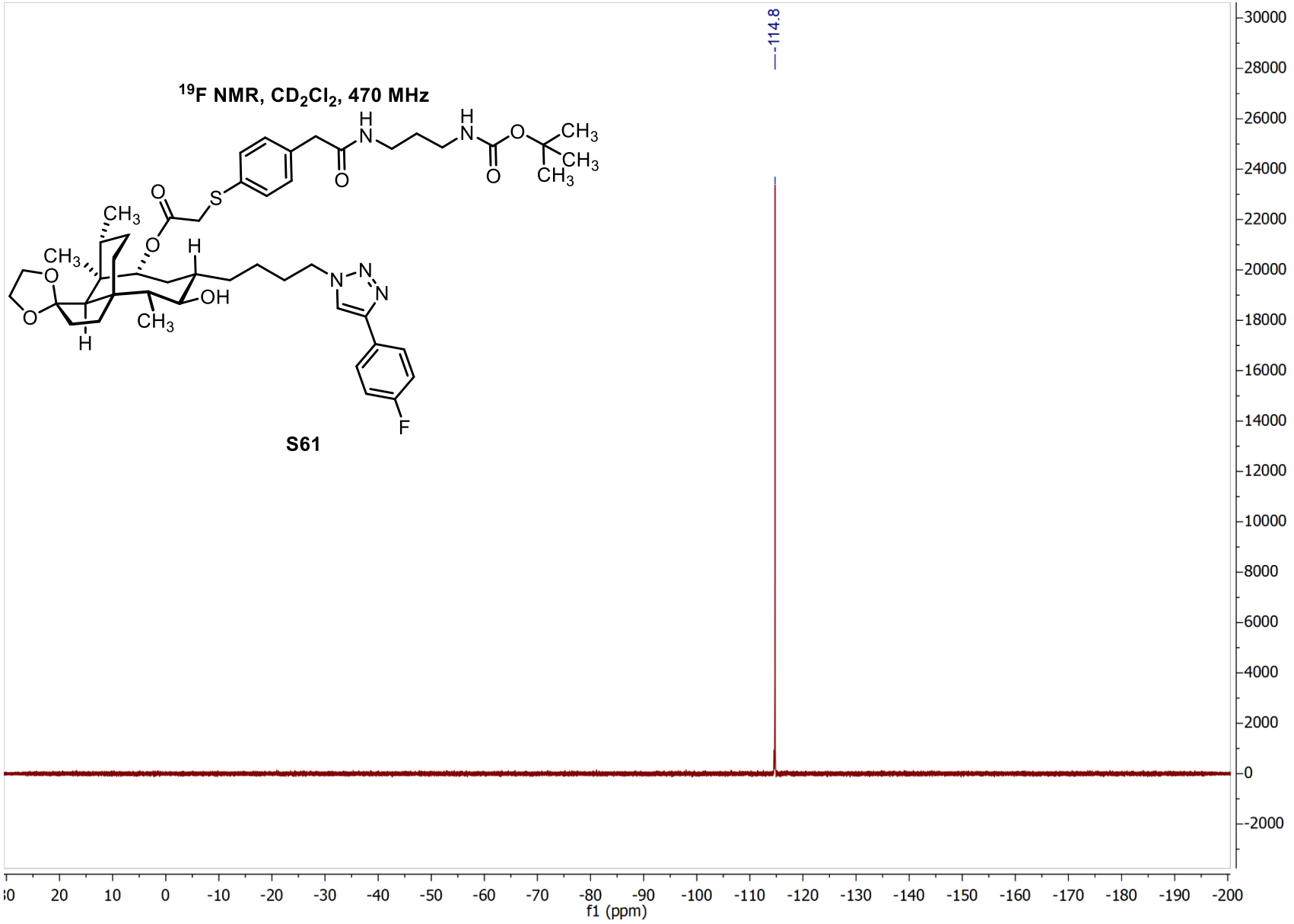

218.3
173.2
169.7
134.1
133.8
129.4
74.0
71.2
57.7
45.8
44.4
41.8
41.3
41.3
36.7
36.7
36.4
35.6
33.8
32.6
30.3
27.4
26.8
24.8
23.2
16.5
14.1
10.3
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
63
f1 (ppm)

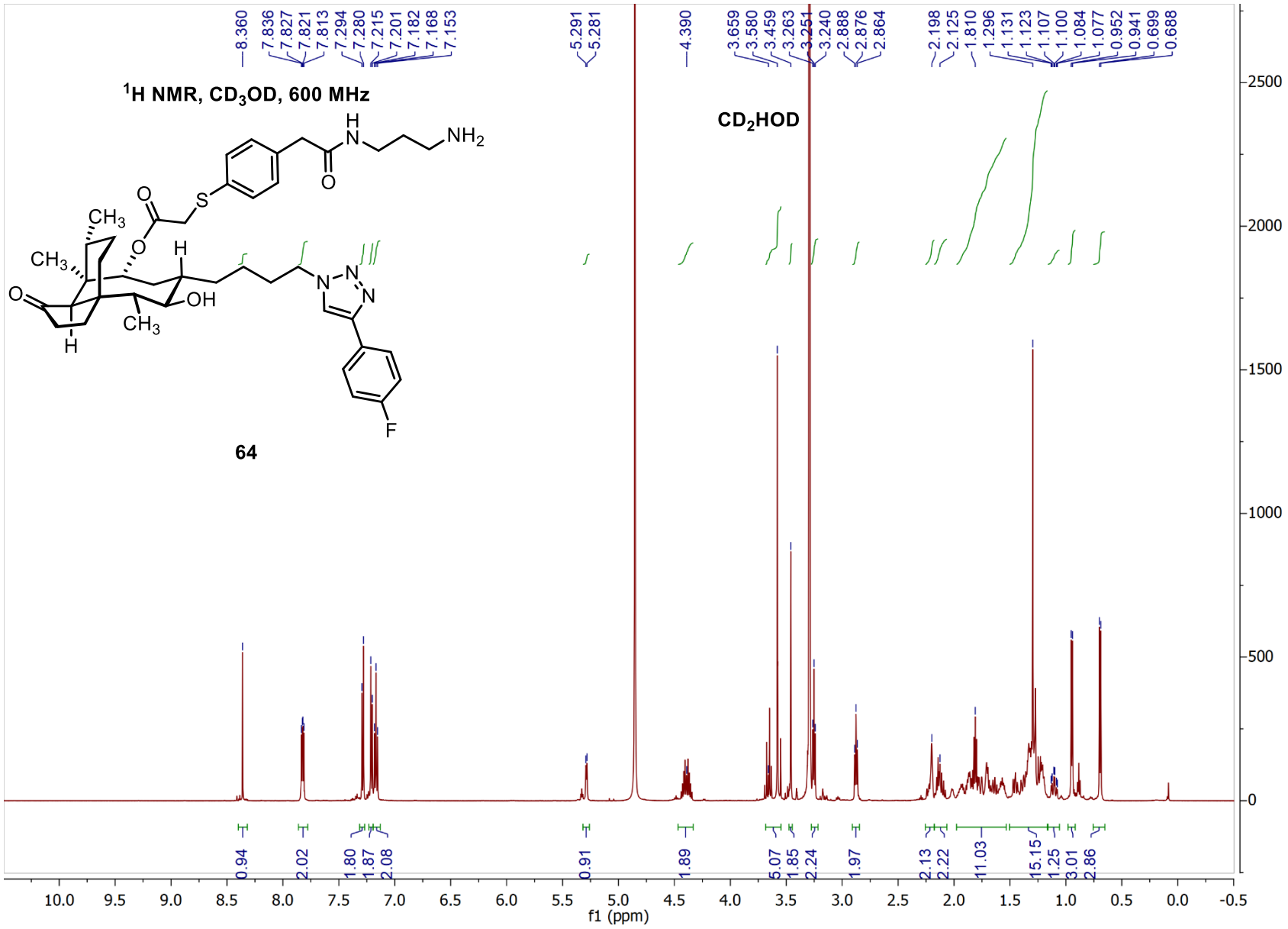

^{1}H NMR, $CDCl_3$, 600 MHz
S60
$CHCl_3$
f1 (ppm)

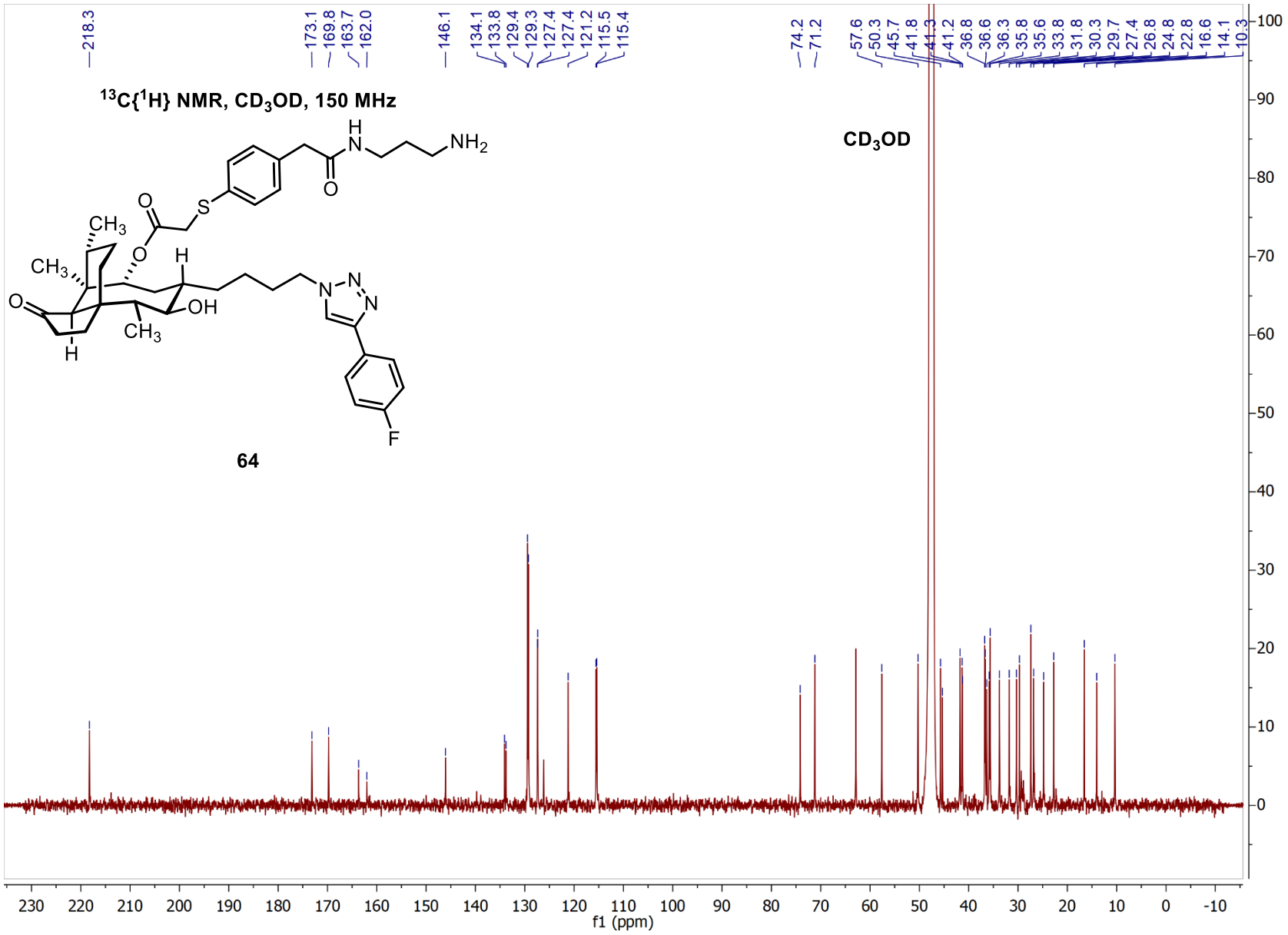

171.0
169.1
156.5
134.3
133.6
130.0
129.9
120.4
79.3
75.5
72.0
63.8
61.5
51.3
51.0
46.6
46.1
43.3
40.1
37.2
37.1
35.8
35.4
32.7
29.3
29.0
28.7
28.4
27.2
23.3
17.7
14.7
11.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
S60
f1 (ppm)

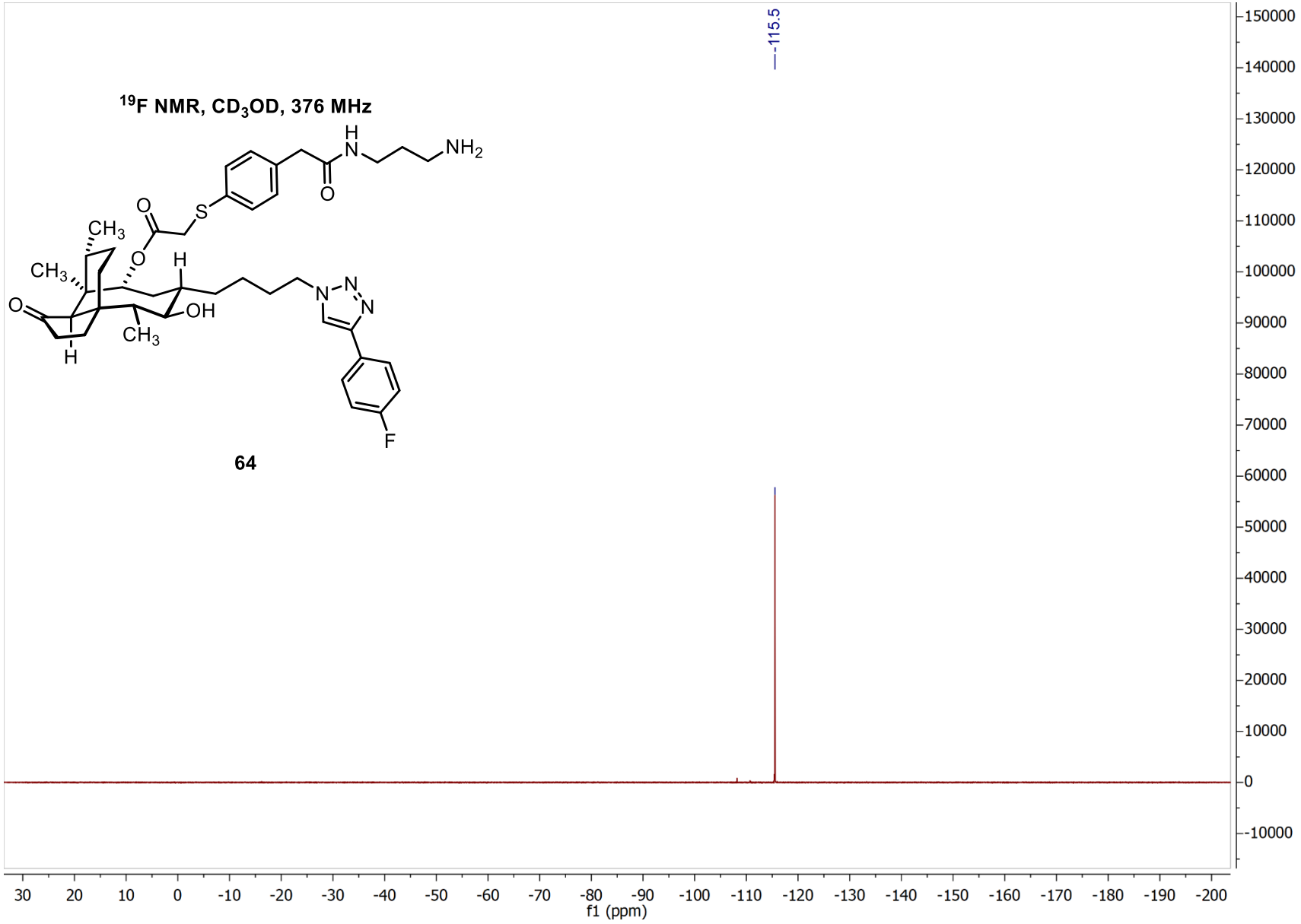

7.848 7.830 7.821 7.816 7.807 7.312 7.299 7.204 7.191 7.141 7.127 7.112 6.322 5.257 5.244 5.053 4.315 4.023 4.013 4.011 4.001 3.998 3.989 3.867 3.740 3.730 3.727 3.718 3.715 3.705 3.627 3.601 3.575 3.550 3.469 3.305 3.295 3.289 3.283 3.278 3.267 3.241 3.231 3.220 3.209 3.083 3.073 3.062 3.052 2.278 2.266 2.257 2.254 2.246 2.237 2.226 2.215 2.121 1.940 1.555 1.041 0.893 0.881 0.688 0.676
^{1}H NMR, CD_2Cl_2, 600 MHz
$CHDCl_2$
S61
1.02 2.17 2.06 2.08 2.13 0.85 1.03 0.80 2.04 1.04 2.19 1.10 2.30 2.12 1.02 2.14 2.07 1.00 1.53 2.17 50.67 3.78 3.36 3.07
f1 (ppm)

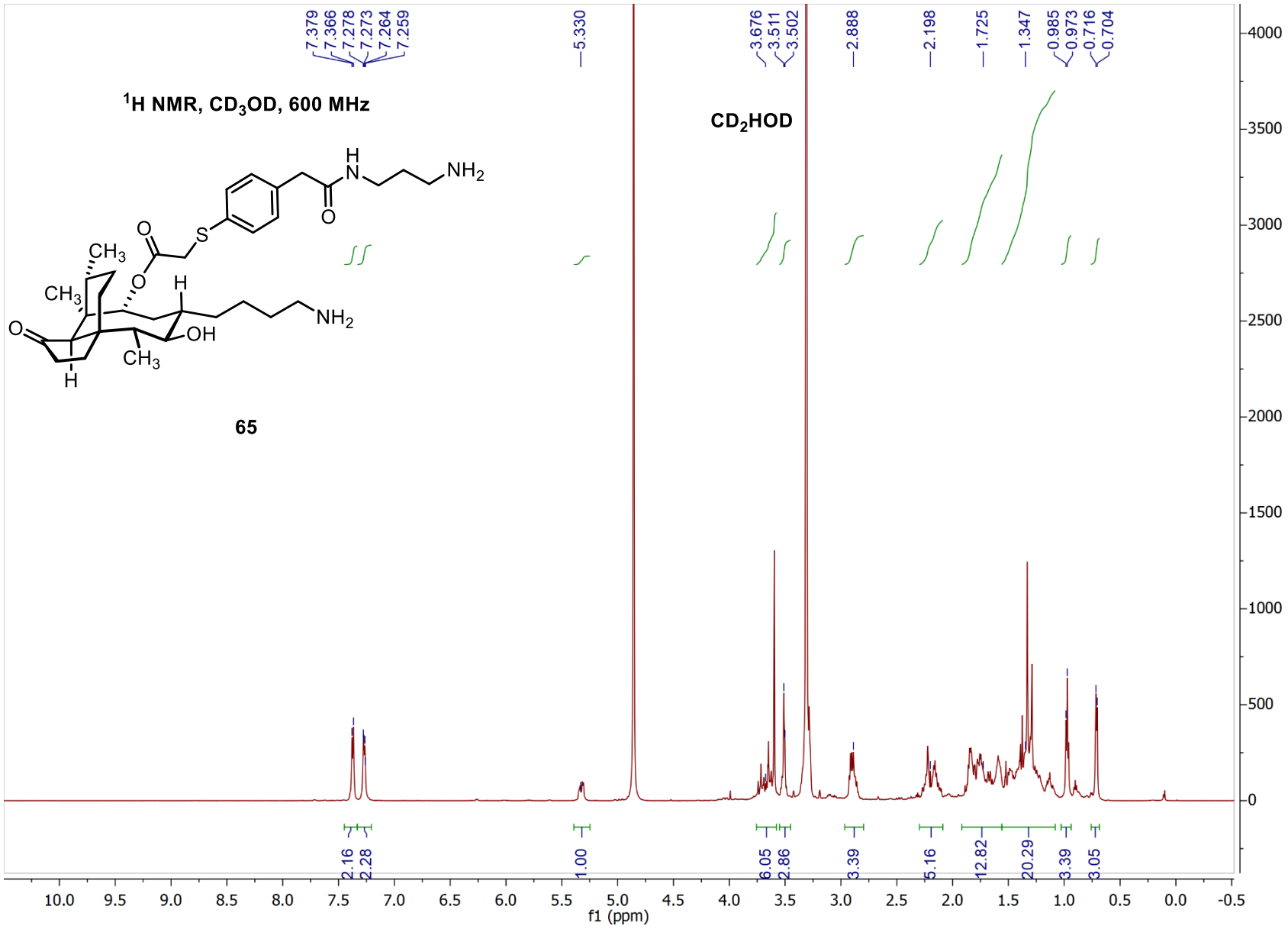

171.1
169.5
163.9
156.7
147.0
134.6
134.4
130.3
129.9
127.8
120.7
120.2
116.2
116.0
79.3
75.9
72.2
64.2
61.9
51.3
50.5
46.8
43.5
40.7
37.5
37.3
36.1
35.8
32.6
30.6
30.5
29.7
29.1
28.5
27.7
23.4
17.9
14.9
11.7
13C{1H} NMR, CD2Cl2, 125 MHz
CD2Cl2
S61
f1 (ppm)

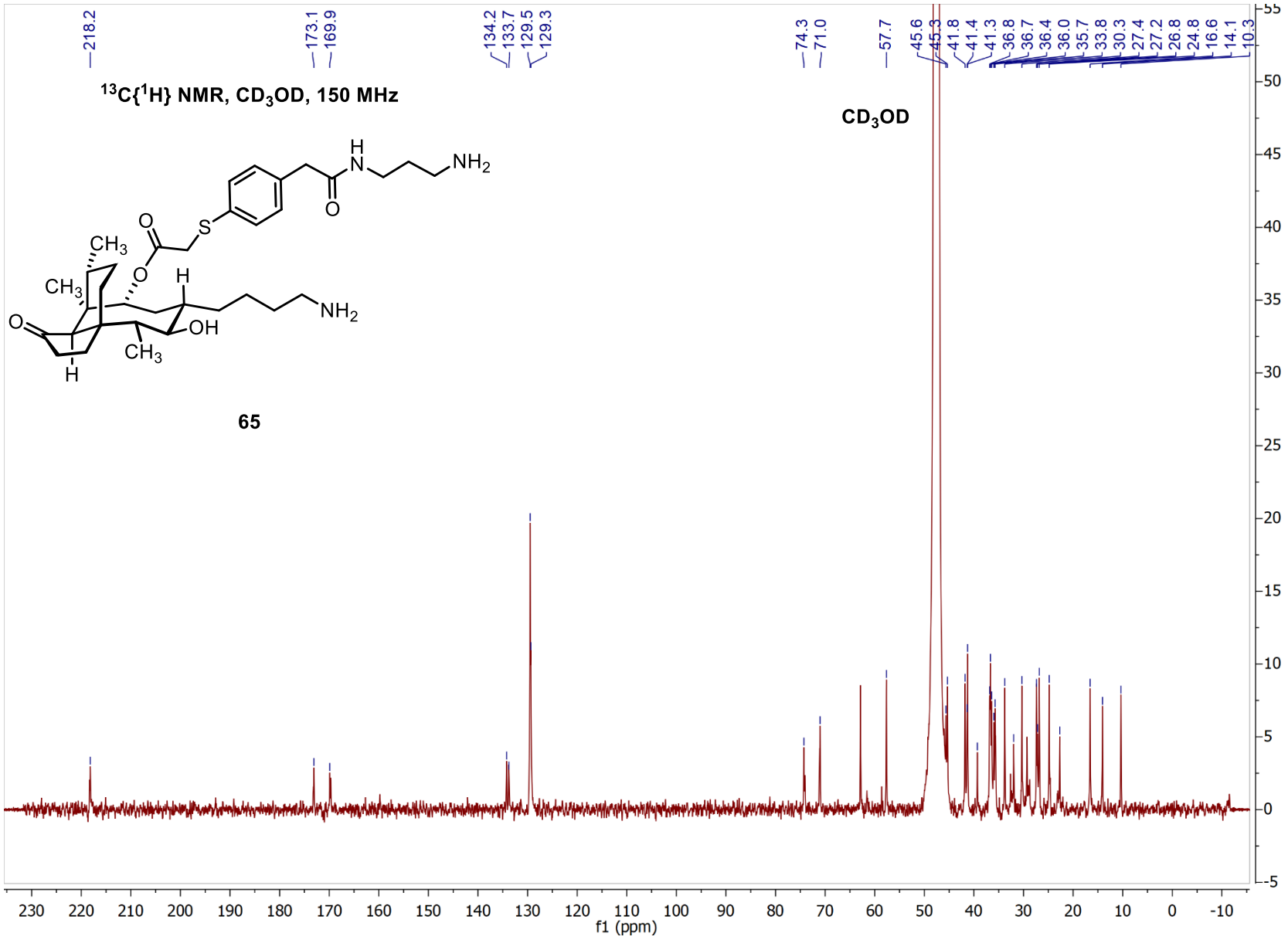

19F NMR, CD2Cl2, 470 MHz
S61
-114.8
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

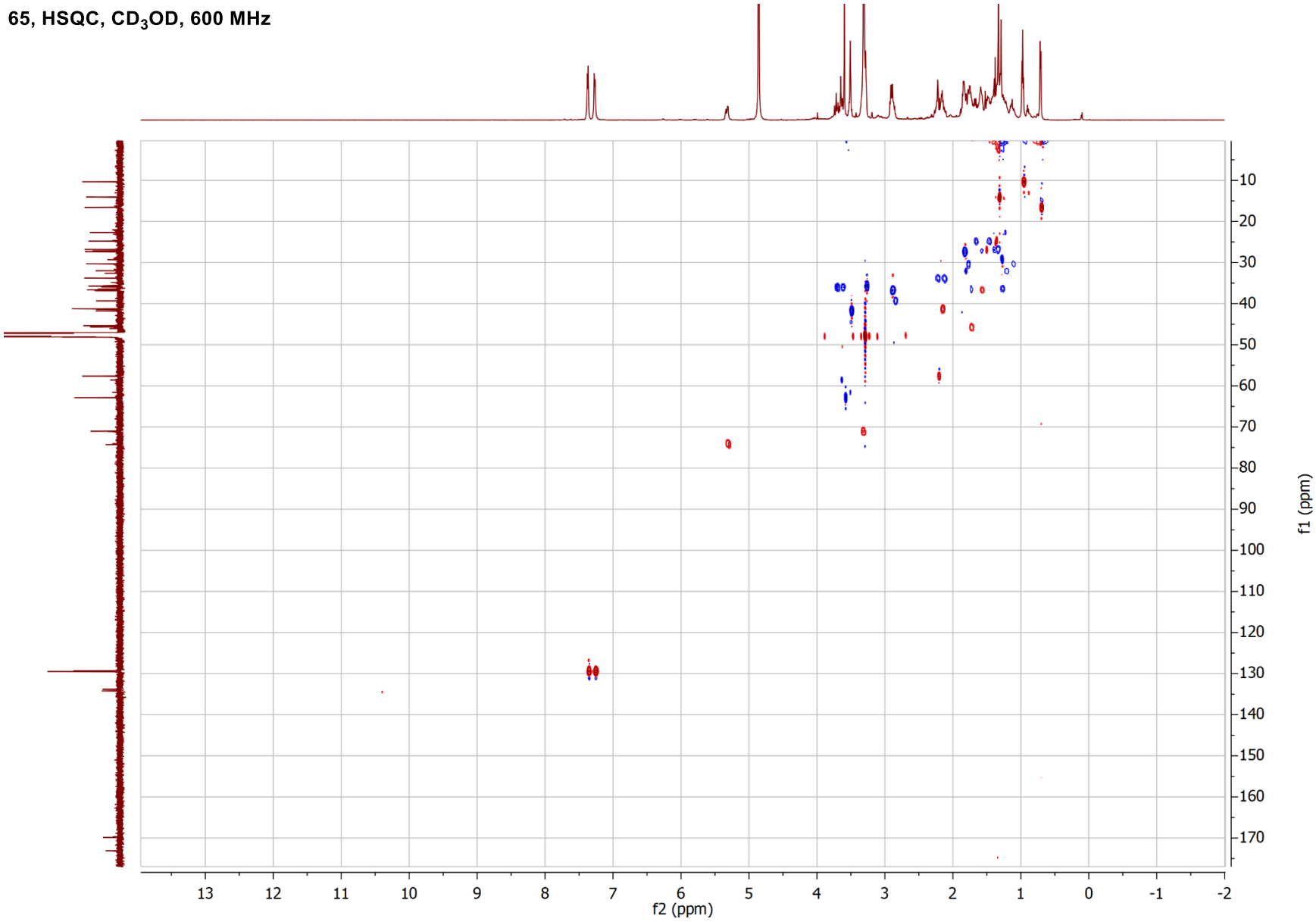

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
64
8.360
7.836
7.827
7.821
7.813
7.294
7.280
7.215
7.201
7.182
7.168
7.153
5.291
5.281
4.390
3.659
3.580
3.459
3.263
3.251
3.240
2.888
2.876
2.864
2.198
2.125
1.810
1.296
1.131
1.123
1.107
1.100
1.084
1.077
0.952
0.941
0.699
0.688
0.94
2.02
1.80
1.87
2.08
0.91
1.89
5.07
1.85
2.24
1.97
2.13
2.22
11.03
15.15
1.25
3.01
2.86
f1 (ppm)

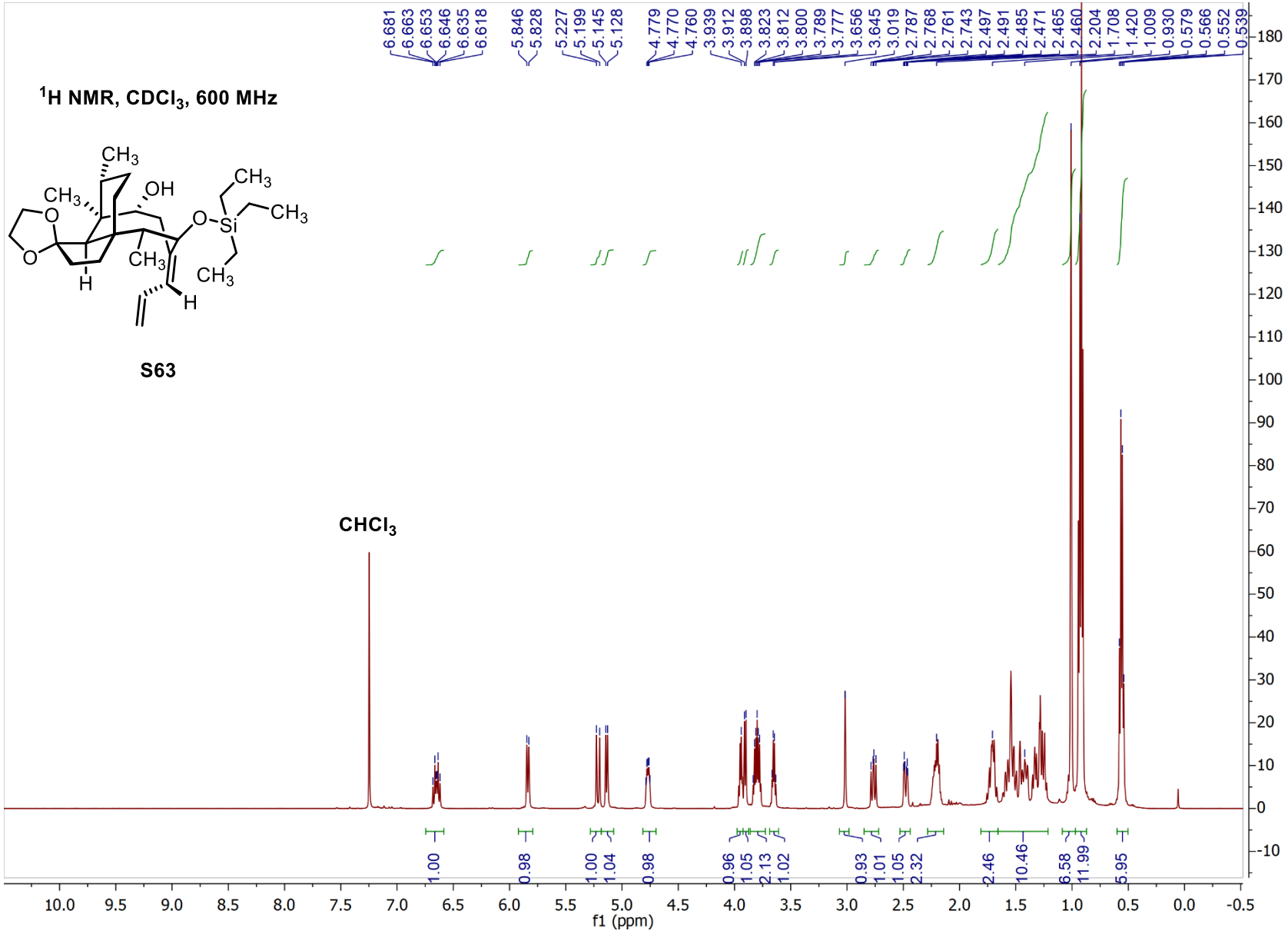

218.3
173.1
169.8
163.7
162.0
146.1
134.1
133.8
129.4
129.3
127.4
127.4
121.2
115.5
115.4
74.2
71.2
57.6
50.3
45.7
41.8
41.3
41.2
36.8
36.6
36.3
35.8
35.6
33.8
31.8
30.3
29.7
27.4
26.8
24.8
22.8
16.6
14.1
10.3
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
64
f1 (ppm)

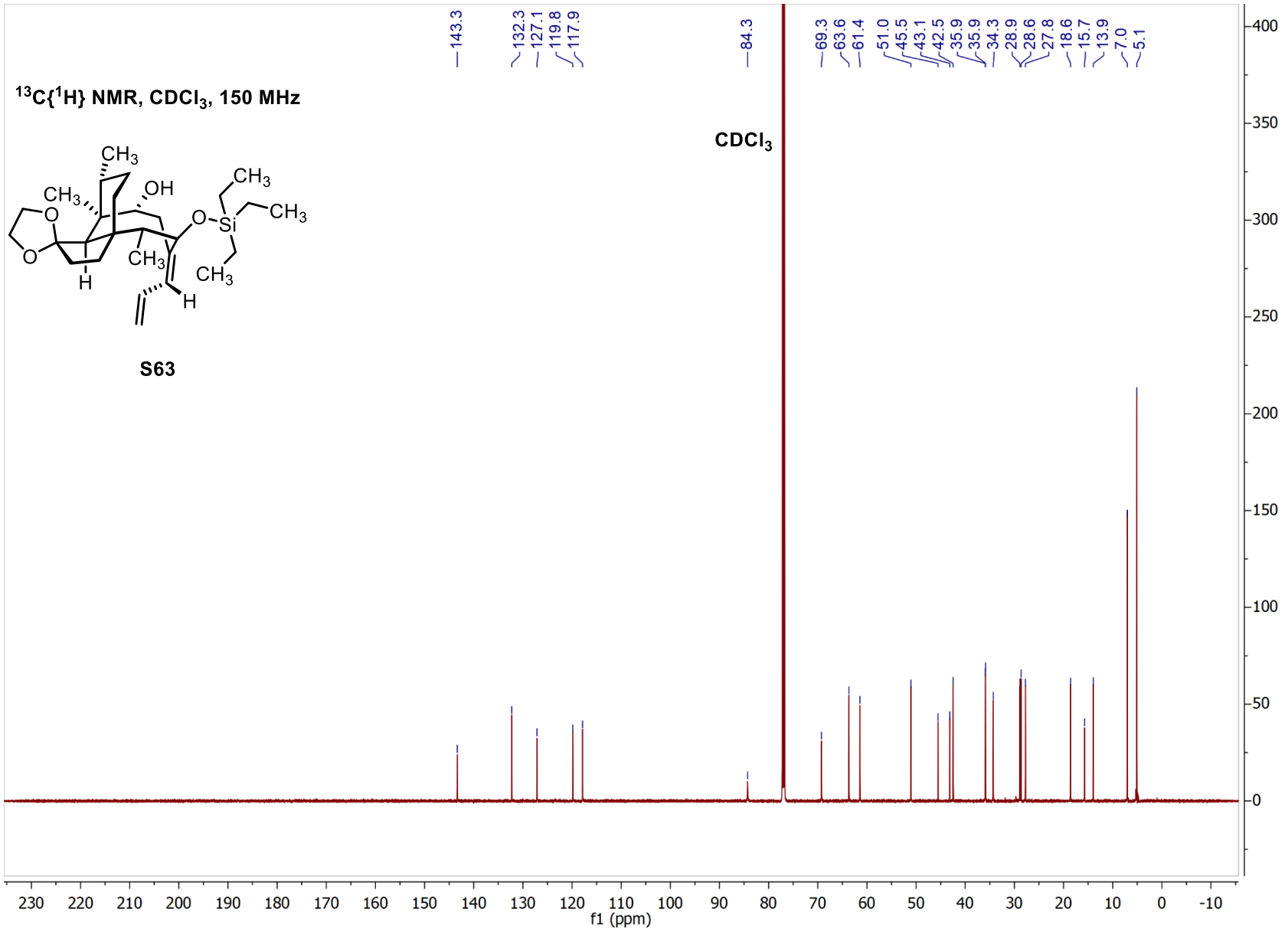

19F NMR, CD3OD, 376 MHz
-115.5
64
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

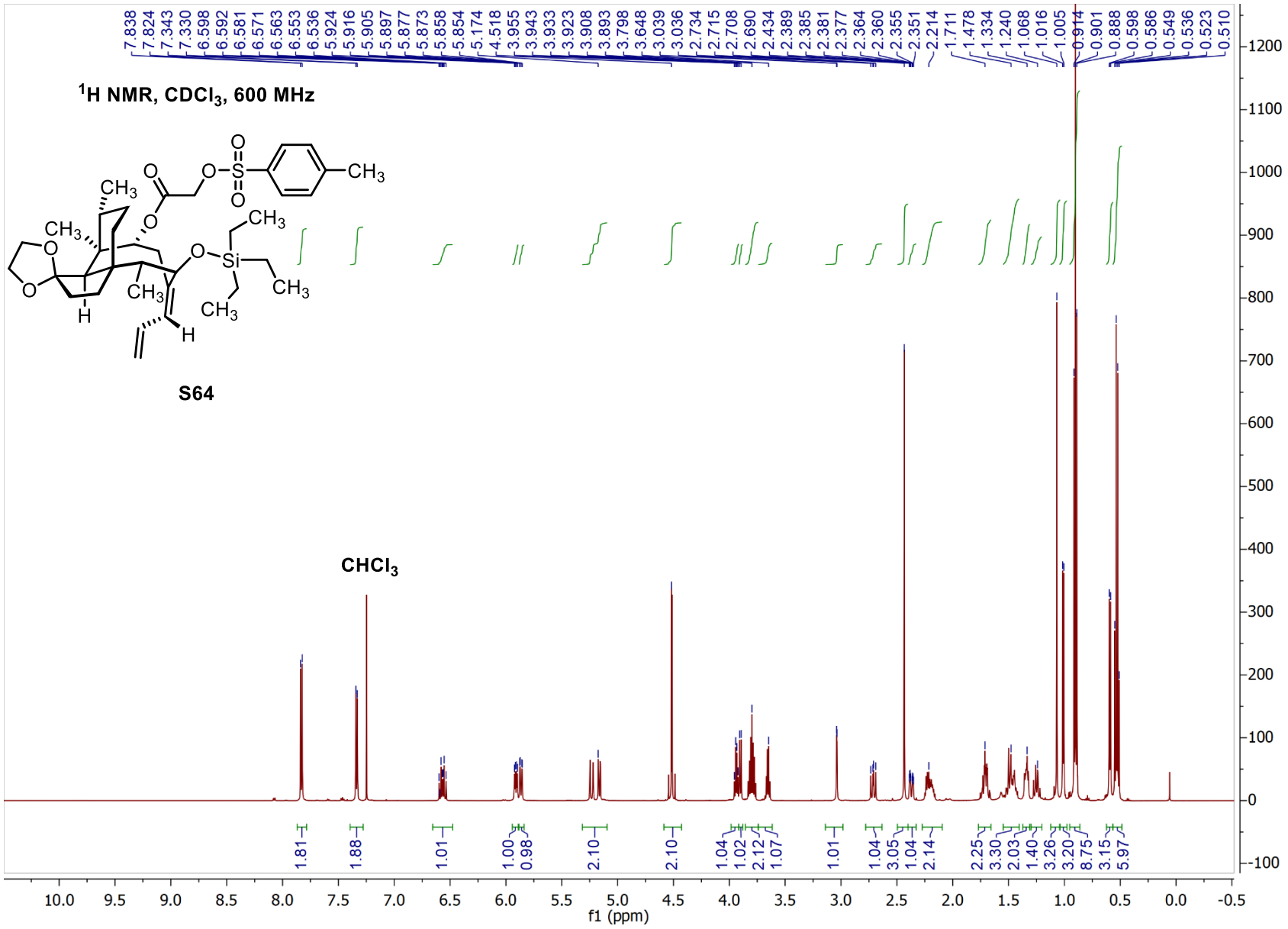

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
65
7.379
7.366
7.278
7.273
7.264
7.259
5.330
3.676
3.511
3.502
2.888
2.198
1.725
1.347
0.985
0.973
0.716
0.704
2.16
2.28
1.00
6.05
2.86
3.39
5.16
12.82
20.29
3.39
3.05
f1 (ppm)

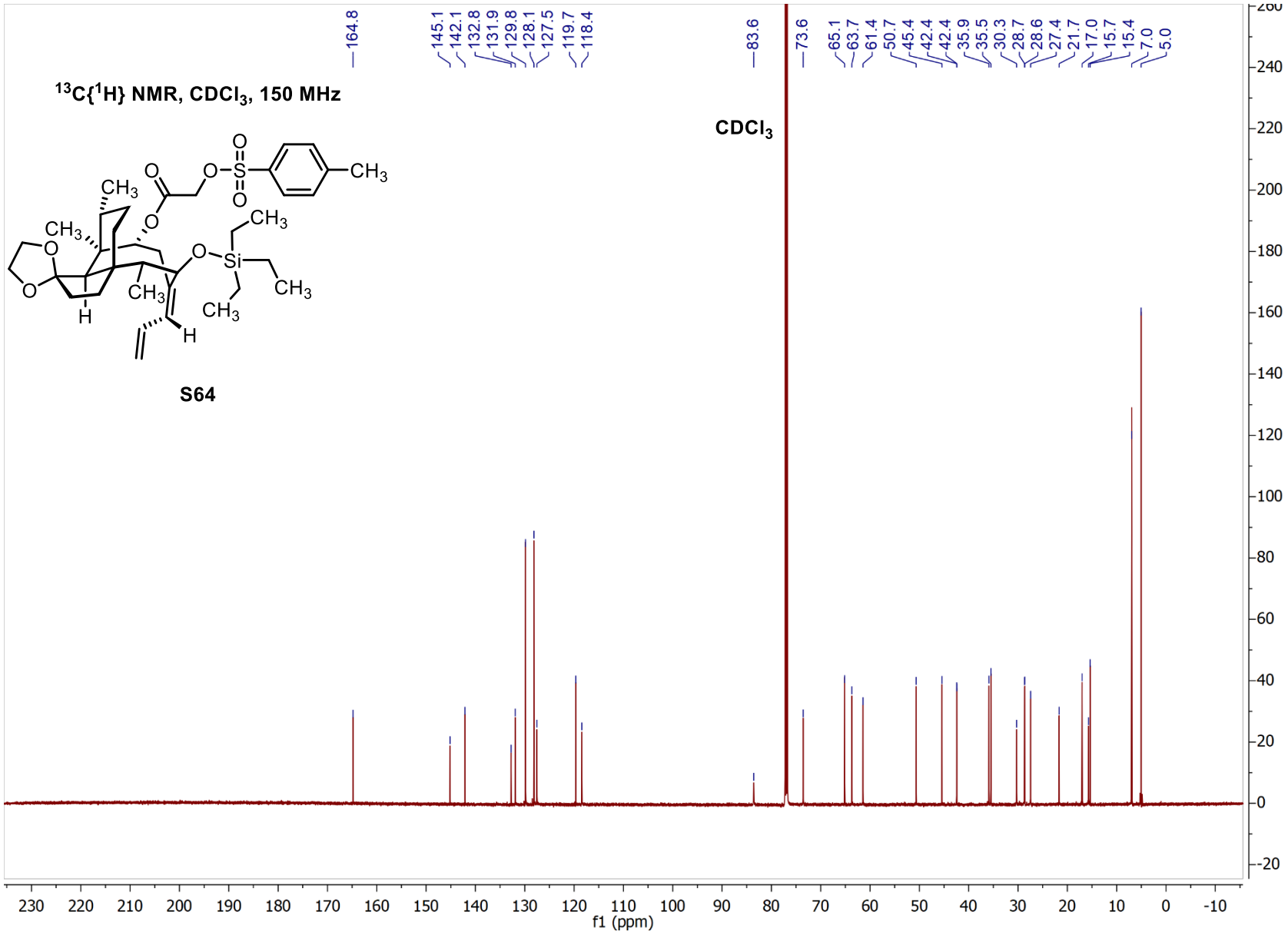

218.2
173.1
169.9
134.2
133.7
129.5
129.3
74.3
71.0
57.7
45.6
45.3
41.8
41.4
41.3
36.8
36.7
36.4
36.0
35.7
33.8
30.3
27.4
27.2
26.8
24.8
16.6
14.1
10.3
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
65
f1 (ppm)

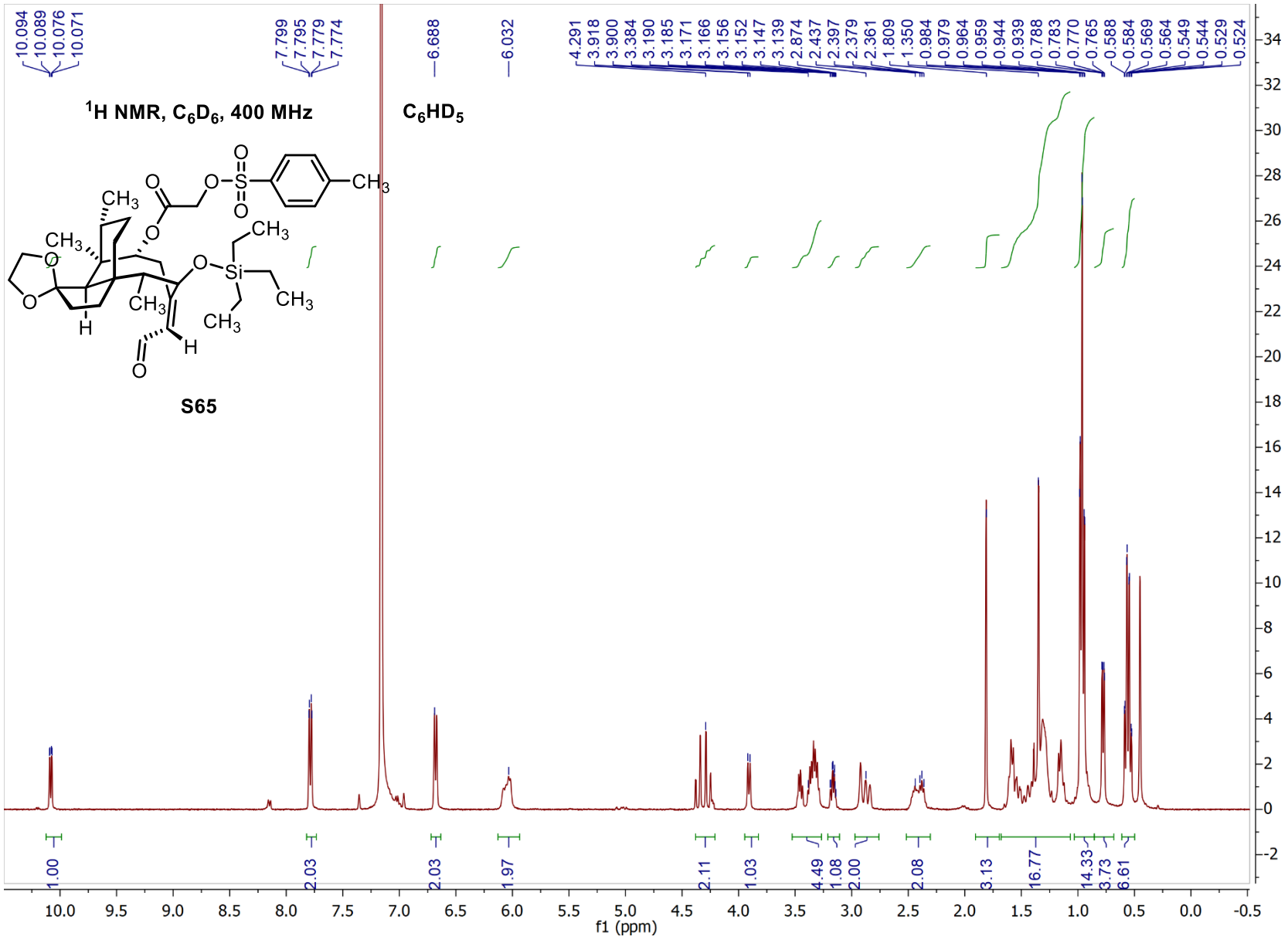

65, HSQC, CD3OD, 600 MHz
f2 (ppm)
f1 (ppm)

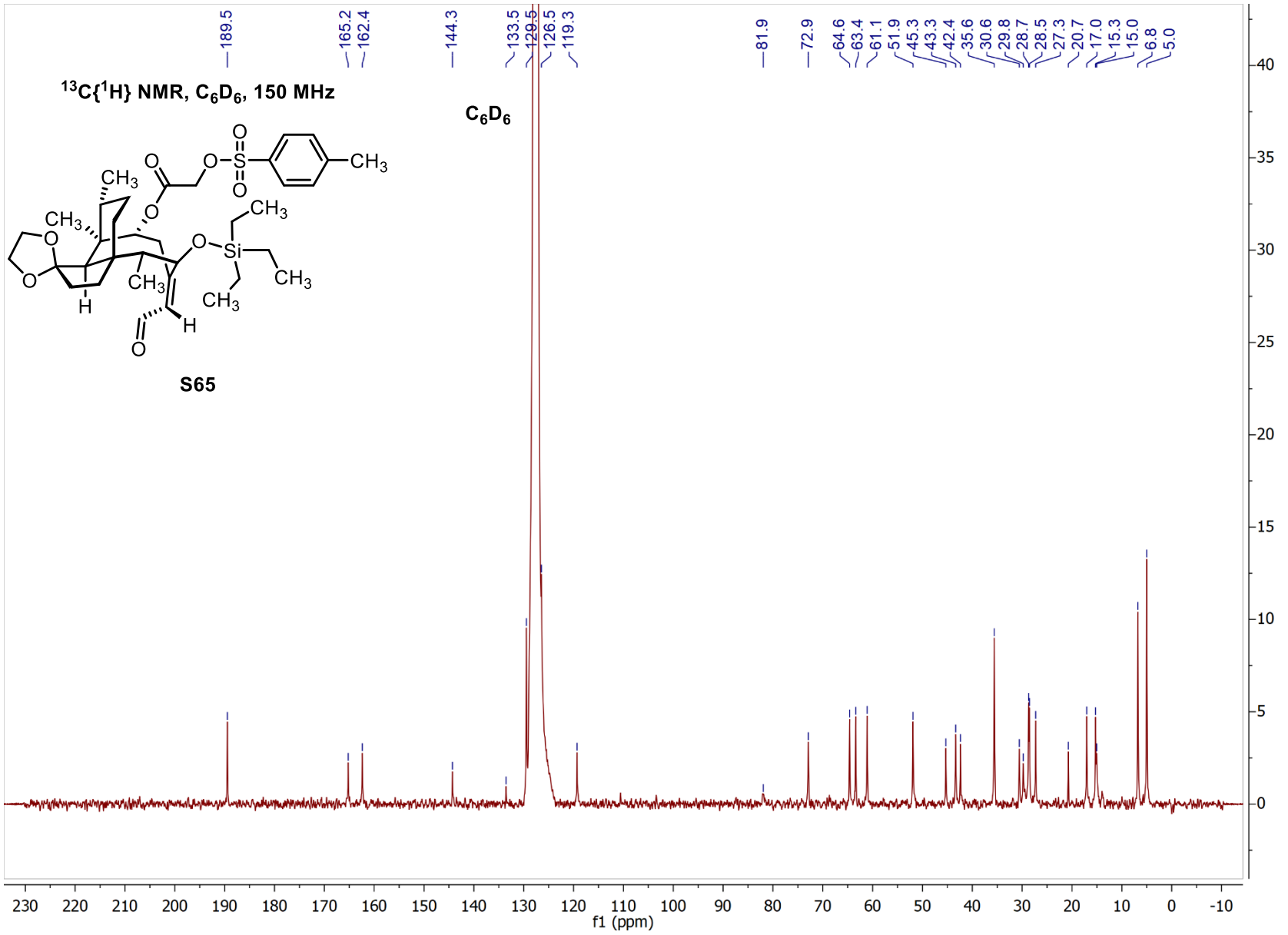

^{1}H NMR, $CDCl_3$, 600 MHz
S63
$CHCl_3$
f1 (ppm)

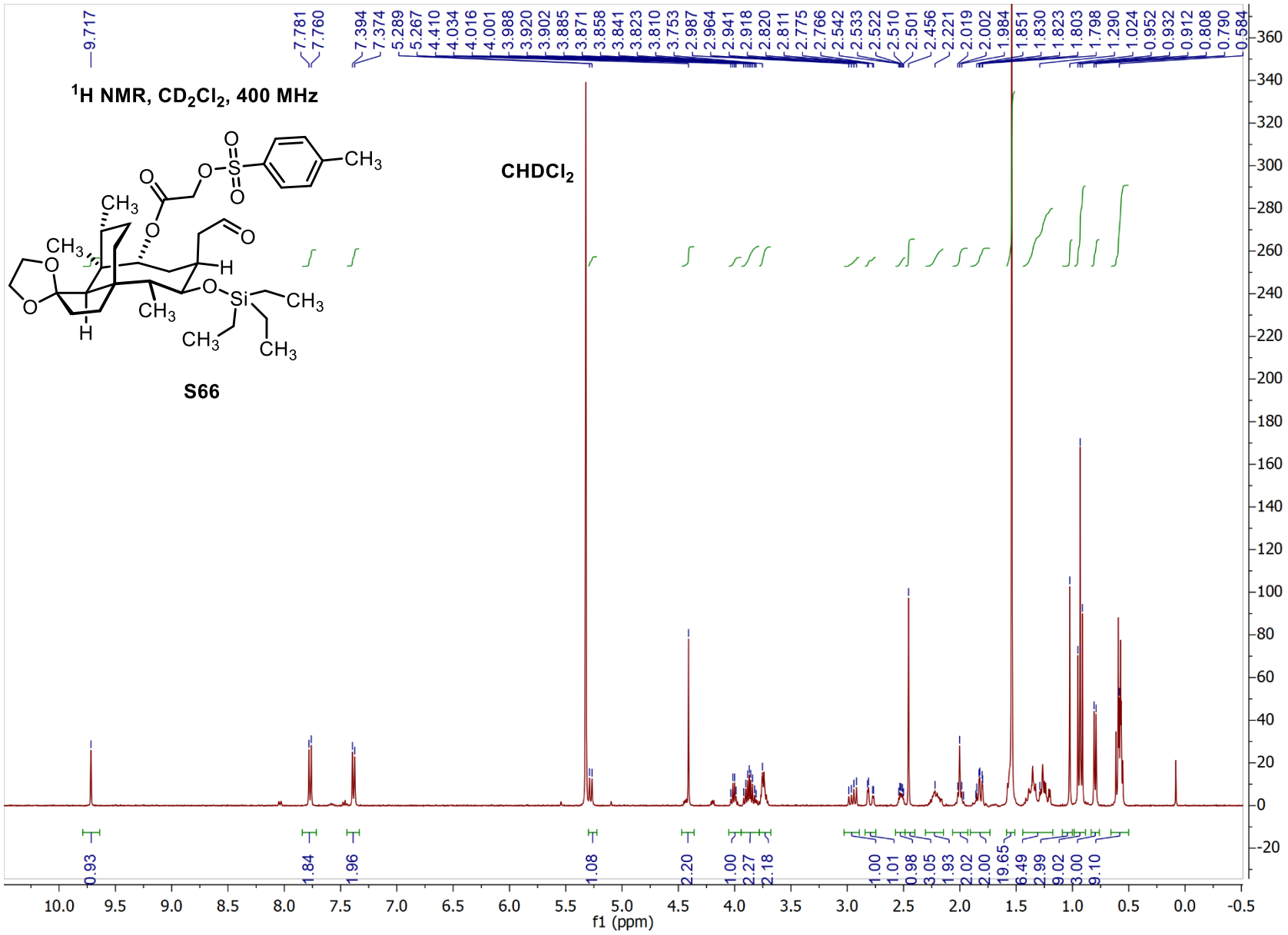

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S63
$CDCl_3$
143.3
132.3
127.1
119.8
117.9
84.3
69.3
63.6
61.4
51.0
45.5
43.1
42.5
35.9
35.9
34.3
28.9
28.6
27.8
18.6
15.7
13.9
7.0
5.1
f1 (ppm)

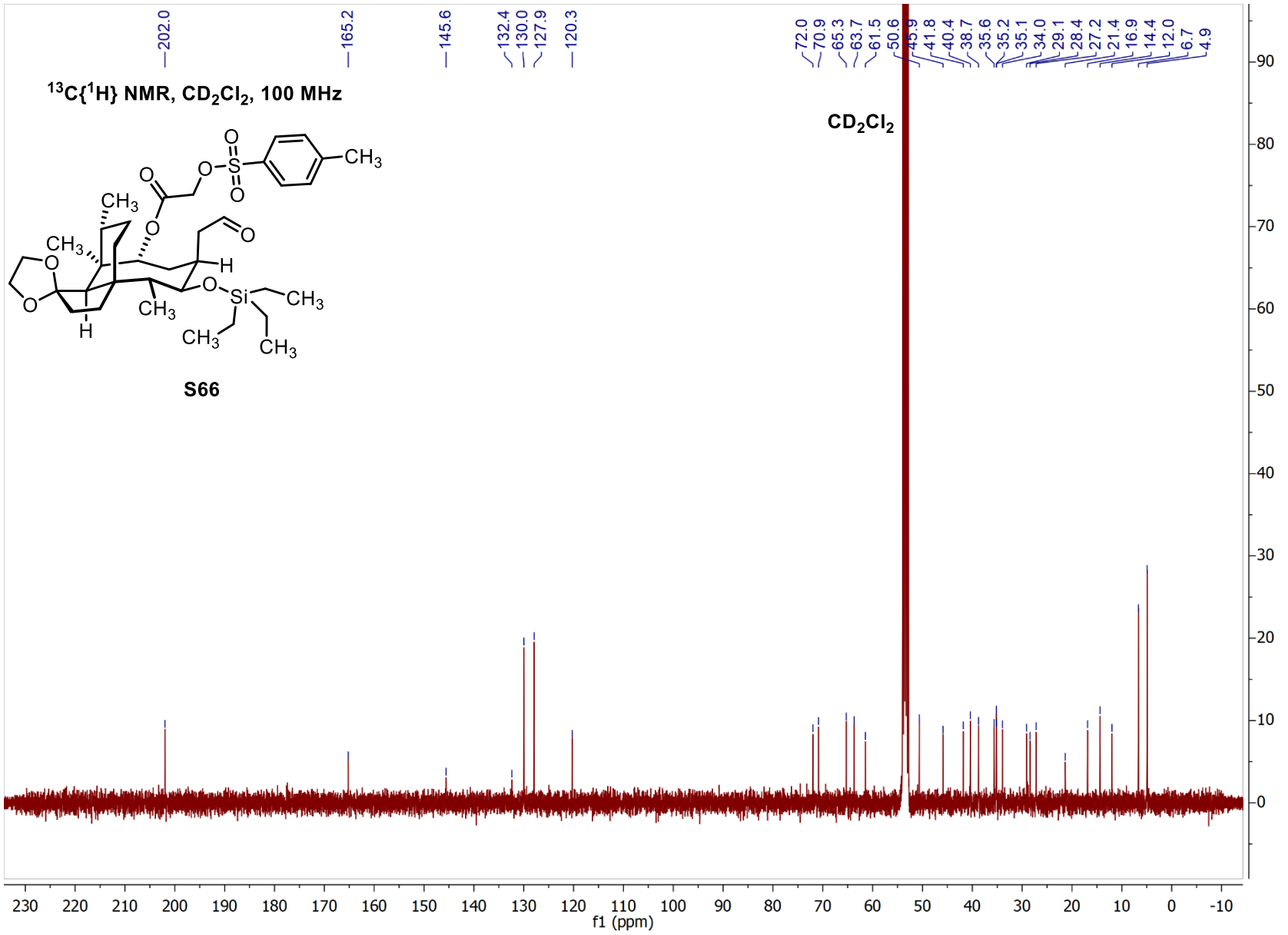

^{1}H NMR, $CDCl_3$, 600 MHz
S64
$CHCl_3$
f1 (ppm)

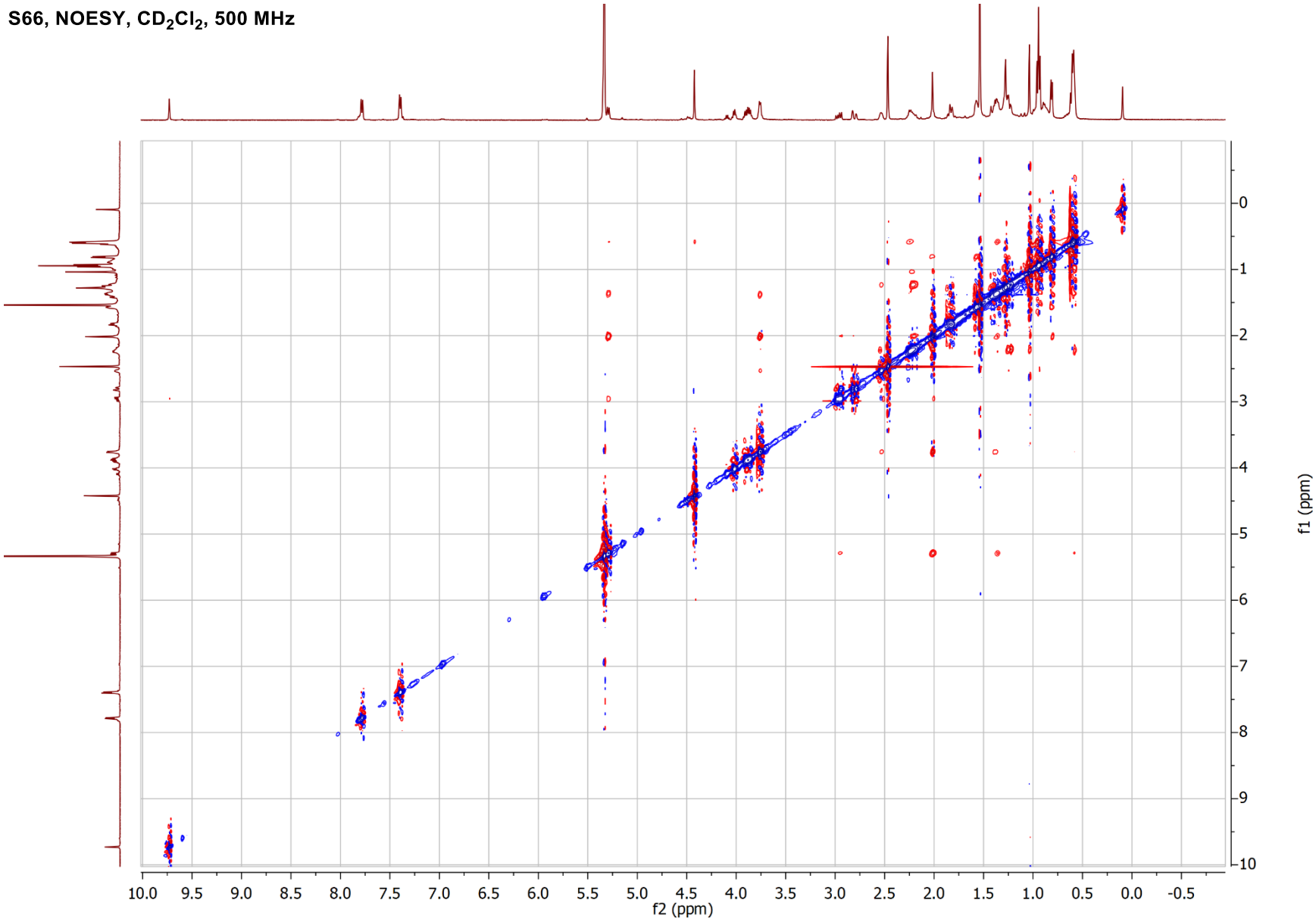

$^{13}C\{^{1}H\}$ NMR, $CDCl_3$, 150 MHz
S64
$CDCl_3$
164.8
145.1
142.1
132.8
131.9
129.8
128.1
127.5
119.7
118.4
83.6
73.6
65.1
63.7
61.4
50.7
45.4
42.4
42.4
35.9
35.5
30.3
28.7
28.6
27.4
21.7
17.0
15.7
15.4
7.0
5.0
f1 (ppm)

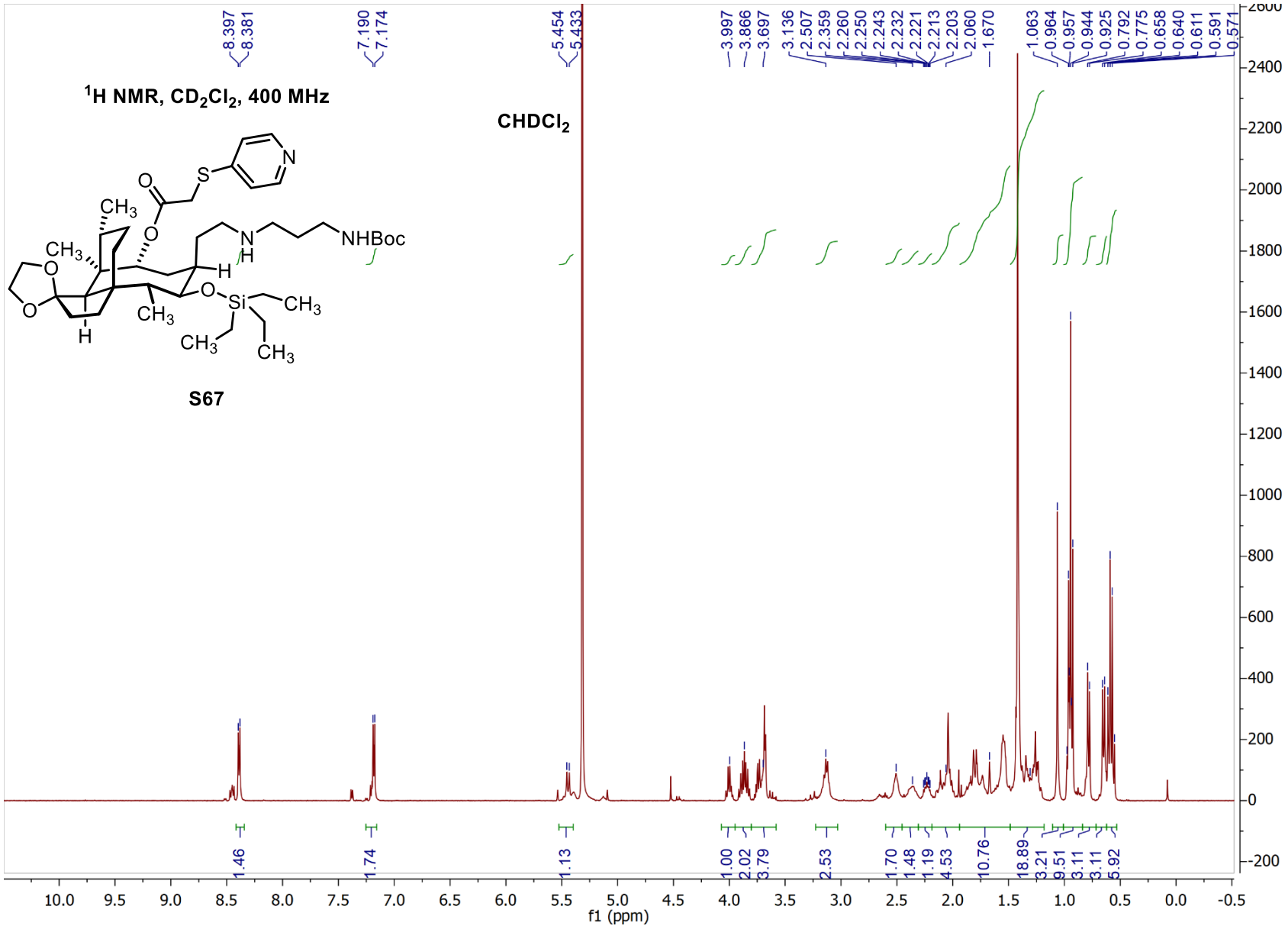

10.094
10.089
10.076
10.071
7.799
7.795
7.779
7.774
6.688
6.032
4.291
3.918
3.900
3.384
3.190
3.185
3.171
3.166
3.156
3.152
3.147
3.139
2.874
2.437
2.397
2.379
2.361
1.809
1.350
0.984
0.979
0.964
0.959
0.944
0.939
0.788
0.783
0.770
0.765
0.588
0.584
0.569
0.564
0.549
0.544
0.529
0.524
^{1}H NMR, C_6D_6, 400 MHz
C_6HD_5
S65
1.00
2.03
2.03
1.97
2.11
1.03
4.49
1.08
2.00
2.08
3.13
16.77
14.33
3.73
6.61
f1 (ppm)

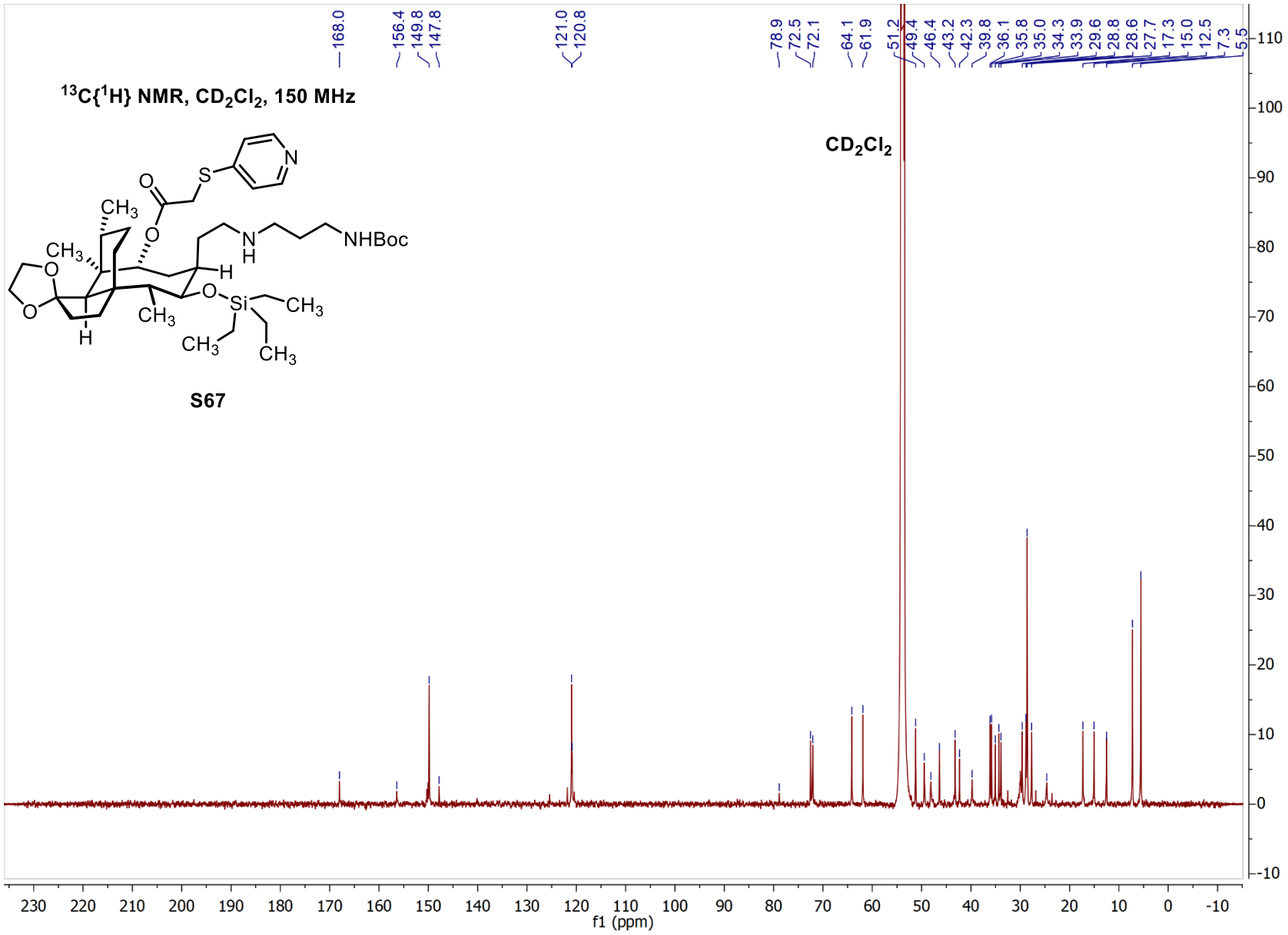

$^{13}C\{^{1}H\}$ NMR, C_6D_6, 150 MHz
C_6D_6
S65
189.5
165.2
162.4
144.3
133.5
129.5
126.5
119.3
81.9
72.9
64.6
63.4
61.1
51.9
45.3
43.3
42.4
35.6
30.6
29.8
28.7
28.5
27.3
20.7
17.0
15.3
15.0
6.8
5.0
f1 (ppm)

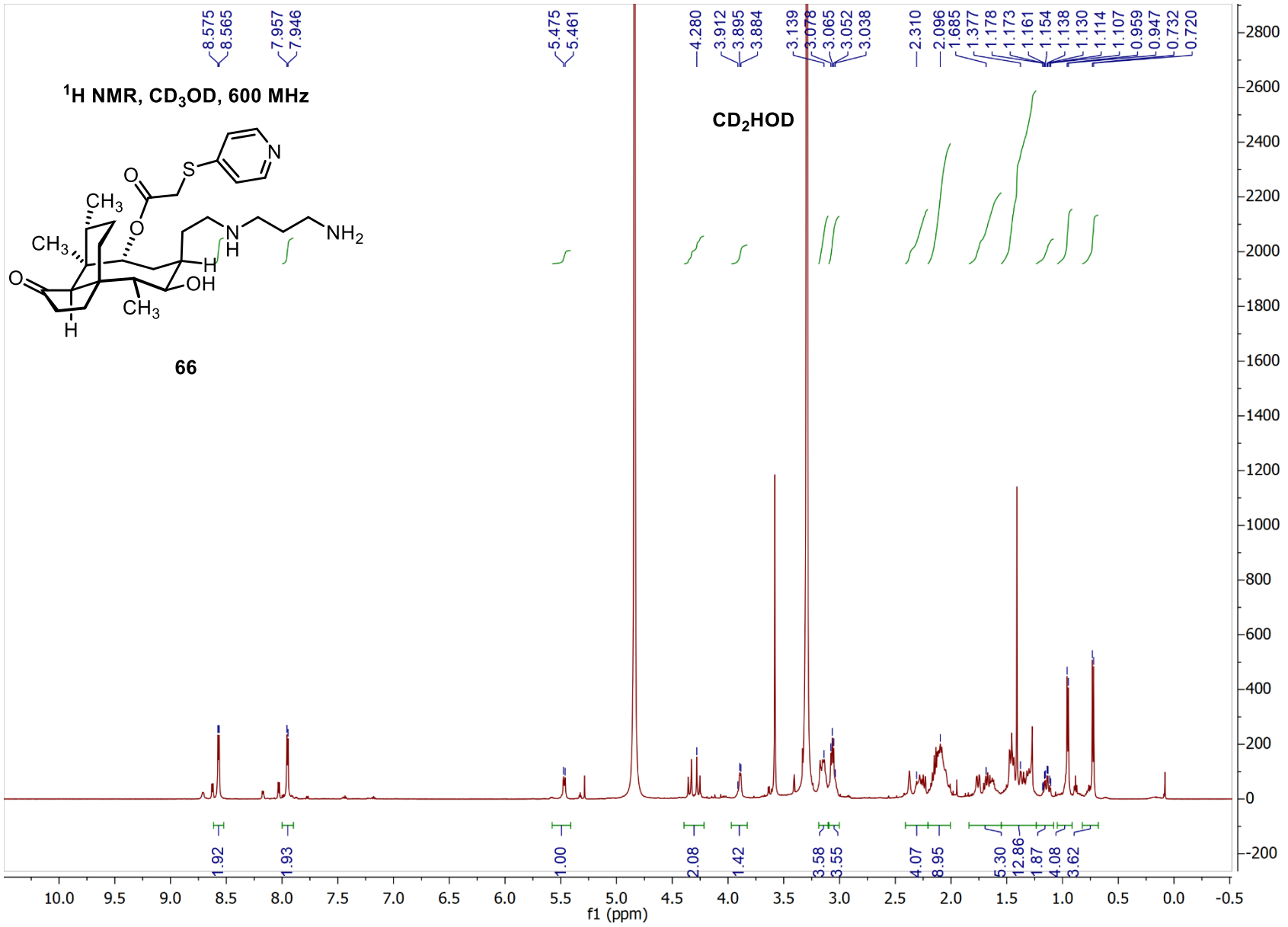

^{1}H NMR, CD_2Cl_2, 400 MHz
CHDCl$_2$
S66
f1 (ppm)

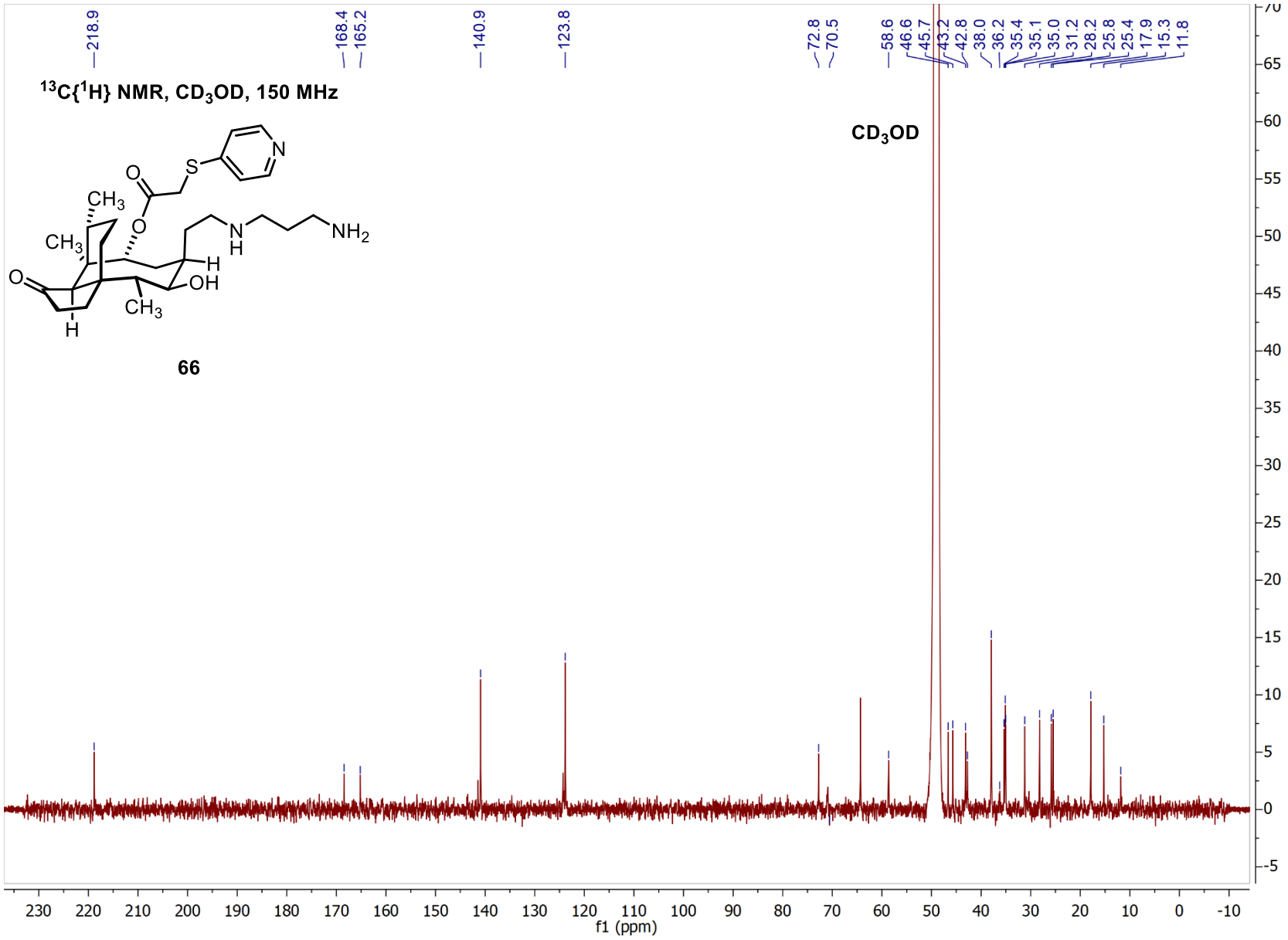

202.0
165.2
145.6
132.4
130.0
127.9
120.3
72.0
70.9
65.3
63.7
61.5
50.6
45.9
41.8
40.4
38.7
35.6
35.2
35.1
34.0
29.1
28.4
27.2
21.4
16.9
14.4
12.0
6.7
4.9
13C{1H} NMR, CD2Cl2, 100 MHz
CD2Cl2
S66
f1 (ppm)

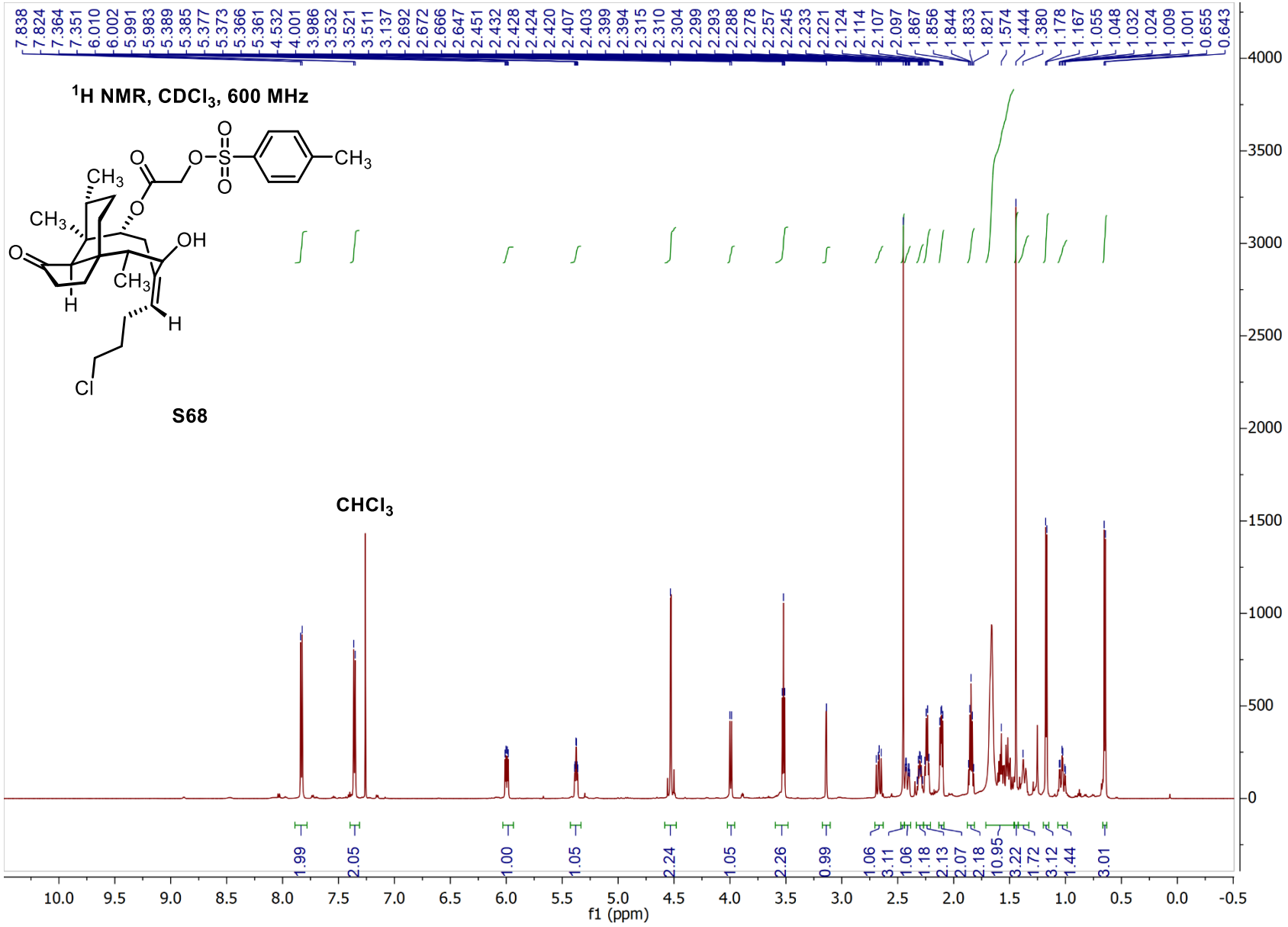

S66, NOESY, CD_2Cl_2, 500 MHz
f2 (ppm)
f1 (ppm)

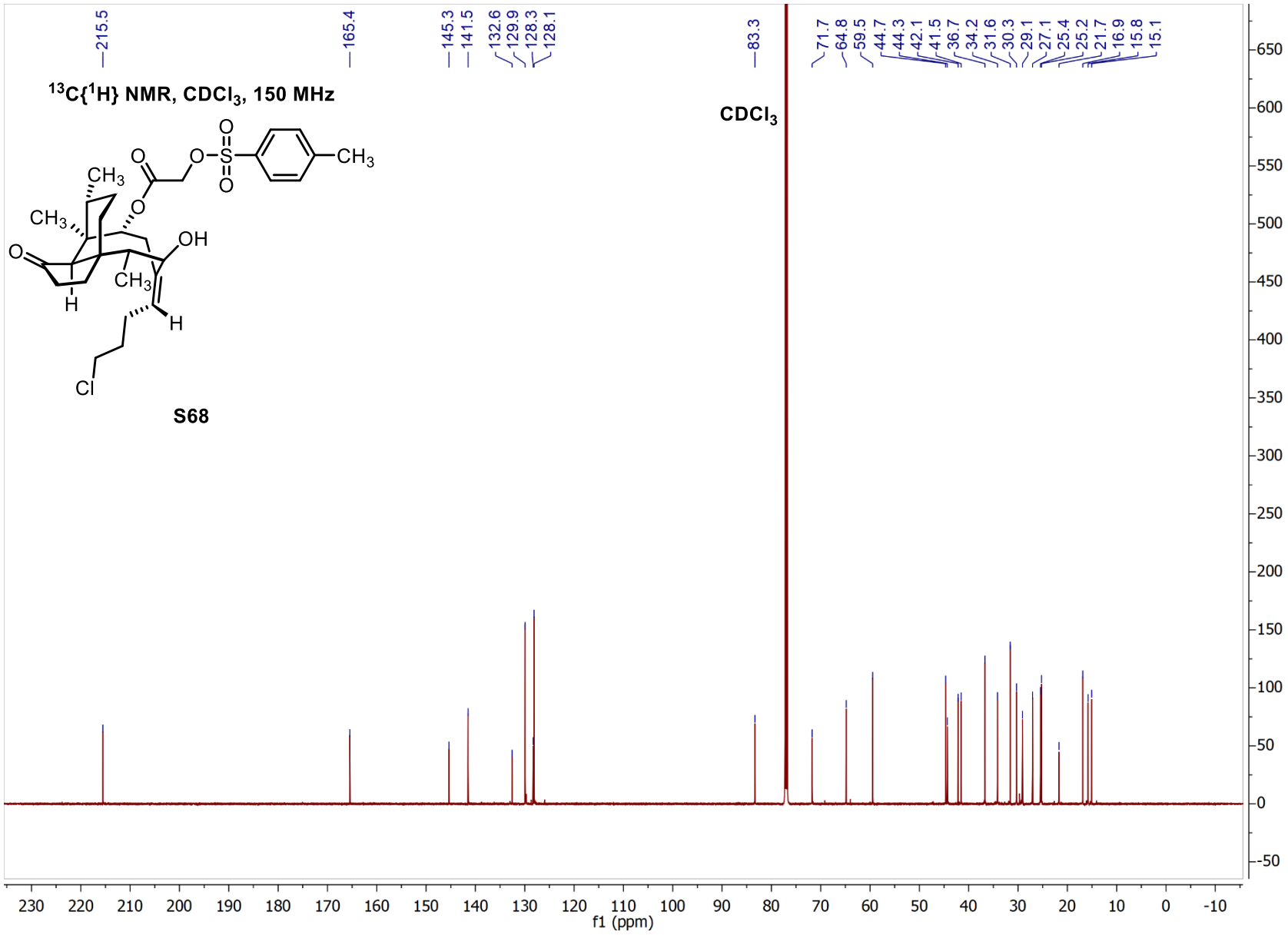

^{1}H NMR, CD_2Cl_2, 400 MHz
$CHDCl_2$
S67
f1 (ppm)

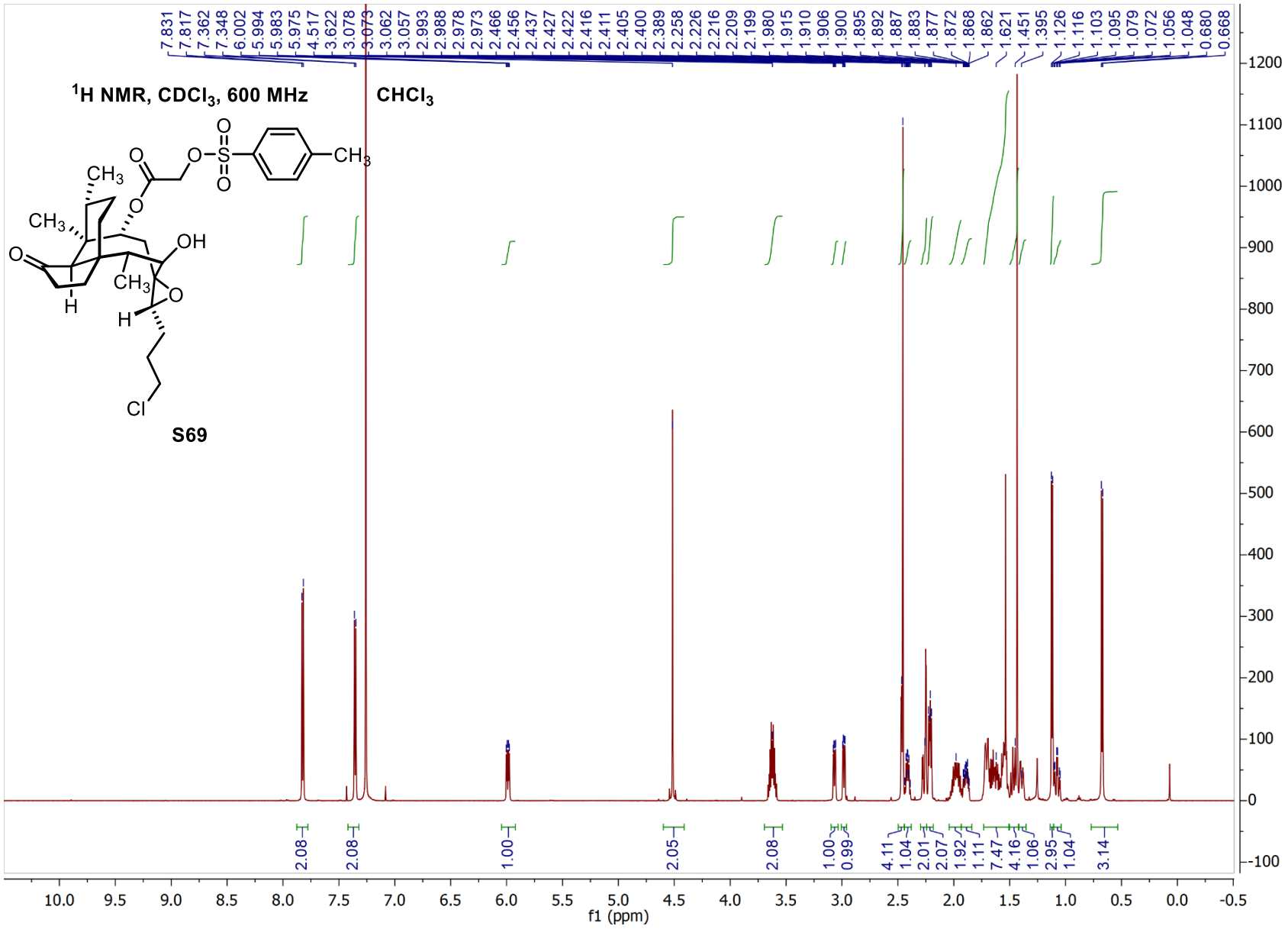

$^{13}C\{^{1}H\}$ NMR, CD_2Cl_2, 150 MHz
S67
CD_2Cl_2
168.0
156.4
149.8
147.8
121.0
120.8
78.9
72.5
72.1
64.1
61.9
51.2
49.4
46.4
43.2
42.3
39.8
36.1
35.8
35.0
34.3
33.9
29.6
28.8
28.6
27.7
17.3
15.0
12.5
7.3
5.5
f1 (ppm)

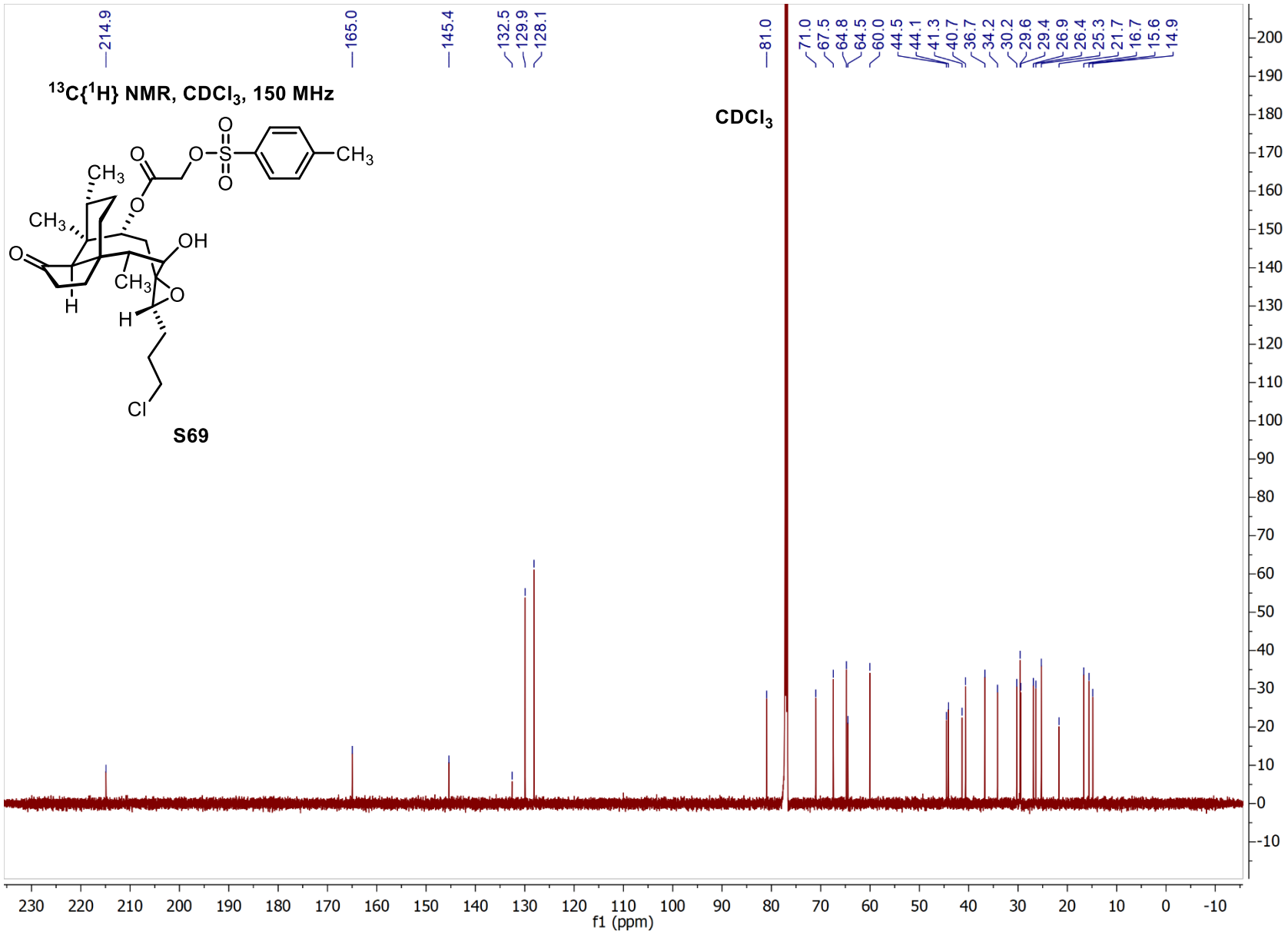

^{1}H NMR, CD_3OD, 600 MHz
CD_2HOD
66
8.575
8.565
7.957
7.946
5.475
5.461
4.280
3.912
3.895
3.884
3.139
3.078
3.065
3.052
3.038
2.310
2.096
1.685
1.377
1.178
1.173
1.161
1.154
1.138
1.130
1.114
1.107
0.959
0.947
0.732
0.720
1.92
1.93
1.00
2.08
1.42
3.58
3.55
4.07
8.95
5.30
12.86
1.87
4.08
3.62
f1 (ppm)

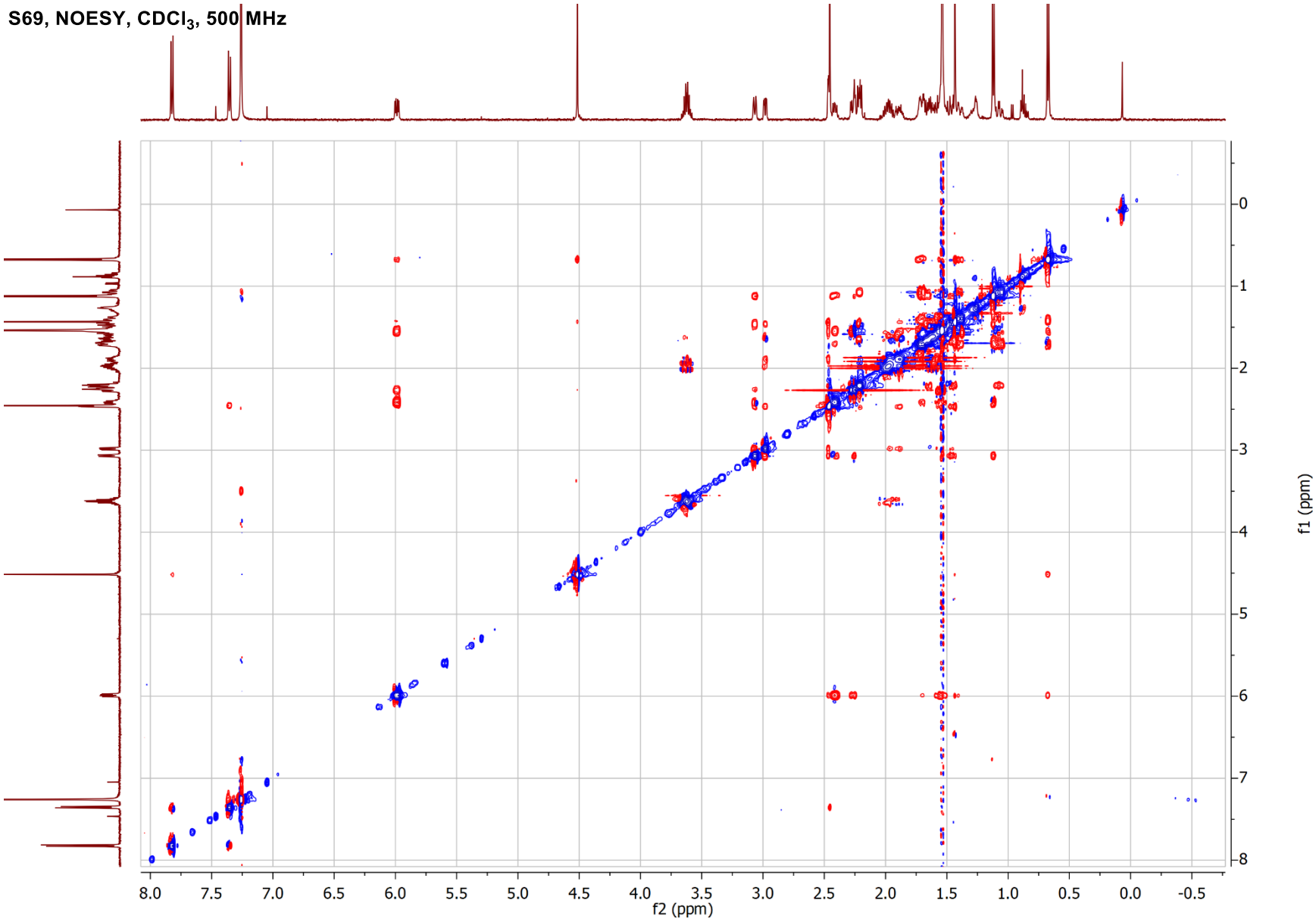

218.9
168.4
165.2
140.9
123.8
72.8
70.5
58.6
46.6
45.7
43.2
42.8
38.0
36.2
35.4
35.1
35.0
31.2
28.2
25.8
25.4
17.9
15.3
11.8
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
66
f1 (ppm)

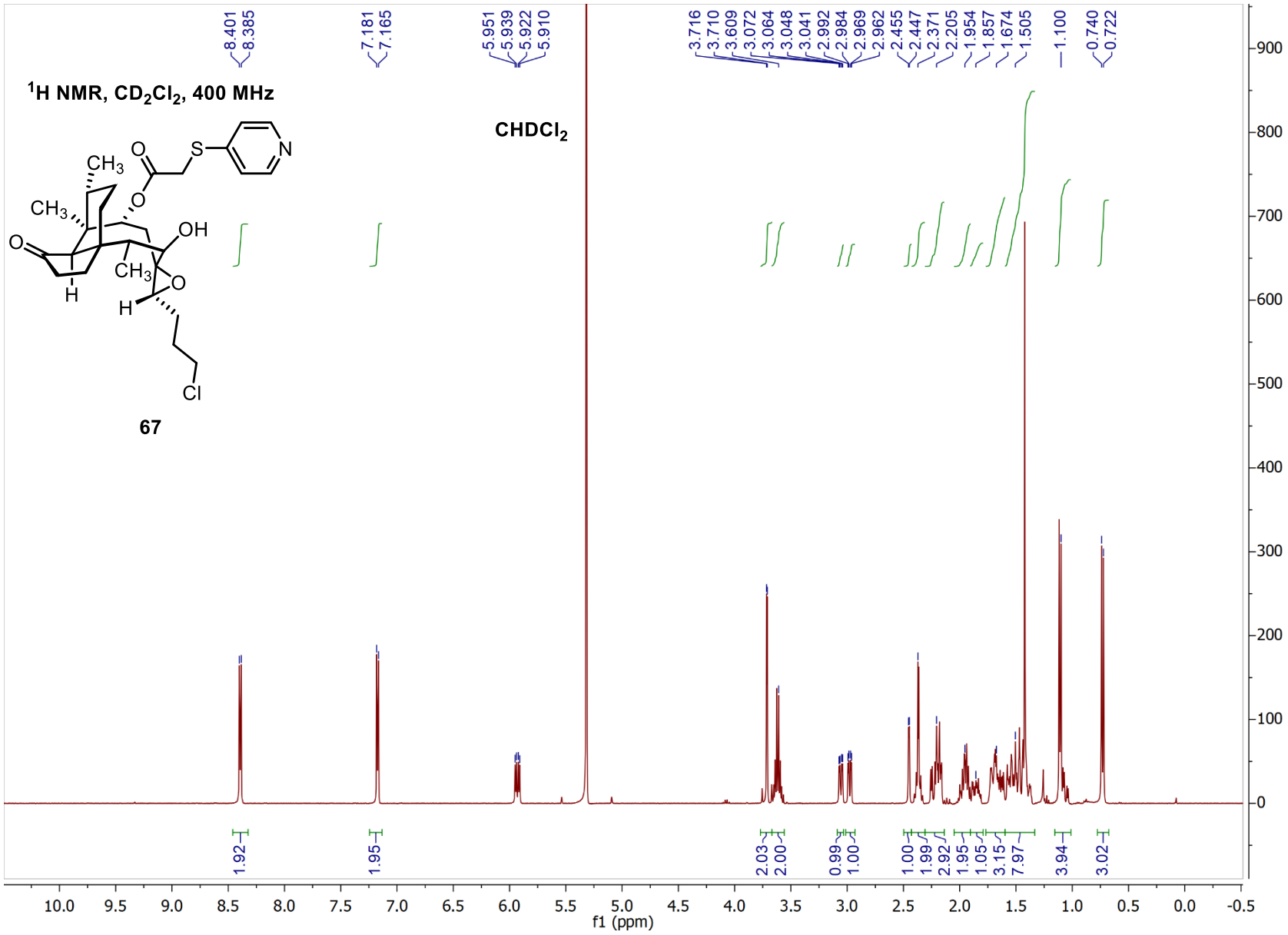

7.838 7.824 7.364 7.351 6.010 6.002 5.991 5.983 5.389 5.385 5.377 5.373 5.366 5.361 4.532 4.001 3.986 3.532 3.521 3.511 3.137 2.692 2.672 2.666 2.647 2.451 2.432 2.428 2.424 2.420 2.407 2.403 2.399 2.394 2.315 2.310 2.304 2.299 2.293 2.288 2.278 2.257 2.245 2.233 2.221 2.124 2.114 2.107 2.097 1.867 1.856 1.844 1.833 1.821 1.574 1.444 1.380 1.178 1.167 1.055 1.048 1.032 1.024 1.009 1.001 0.655 0.643
^{1}H NMR, CDCl$_3$, 600 MHz
S68
CHCl$_3$
1.99 2.05 1.00 1.05 2.24 1.05 2.26 0.99 1.06 3.11 1.06 1.18 2.13 2.07 2.18 10.95 3.22 1.72 3.12 1.44 3.01
f1 (ppm)

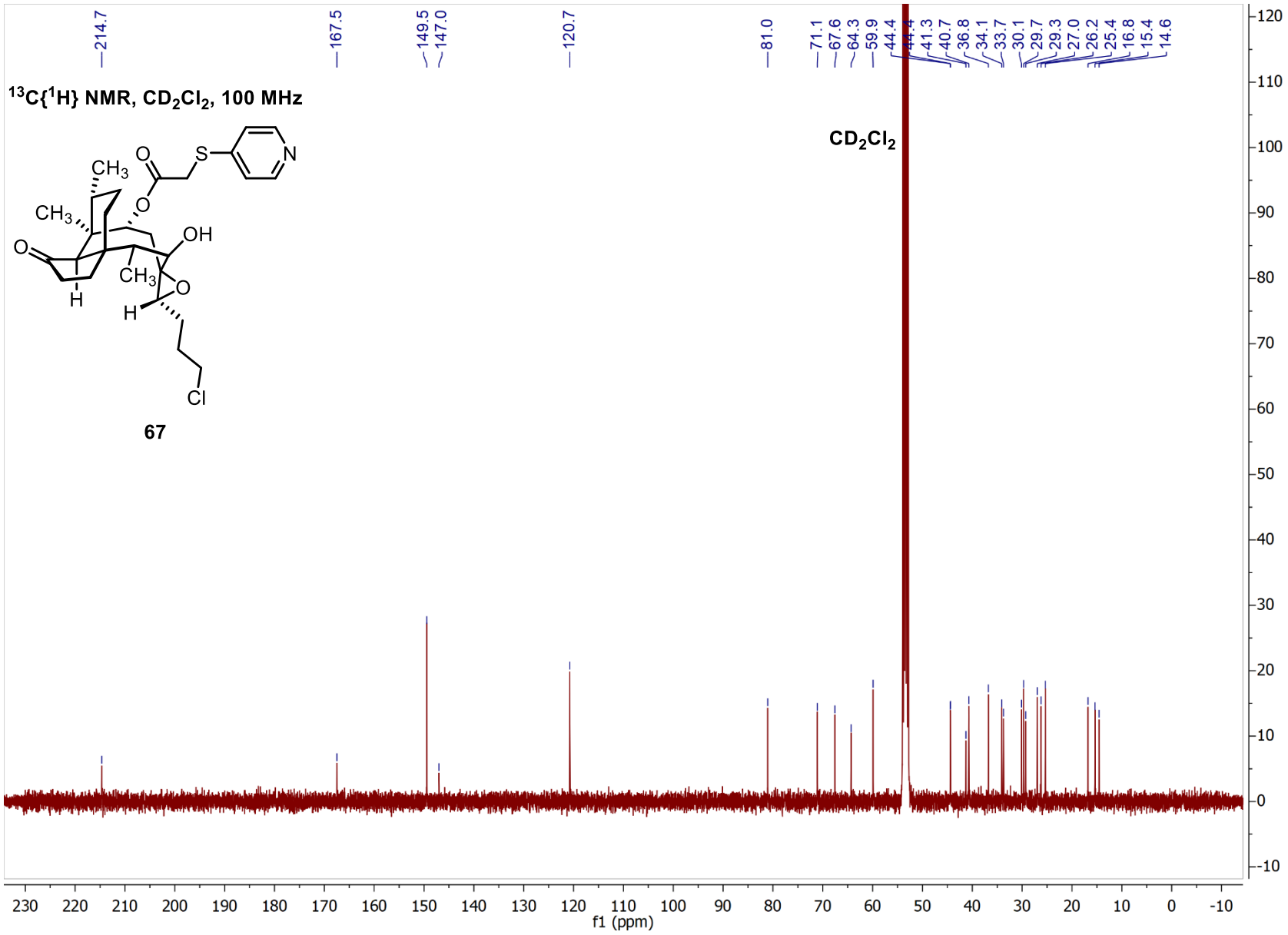

215.5
165.4
145.3
141.5
132.6
129.9
128.3
128.1
83.3
71.7
64.8
59.5
44.7
44.3
42.1
41.5
36.7
34.2
31.6
30.3
29.1
27.1
25.4
25.2
21.7
16.9
15.8
15.1
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
S68
f1 (ppm)

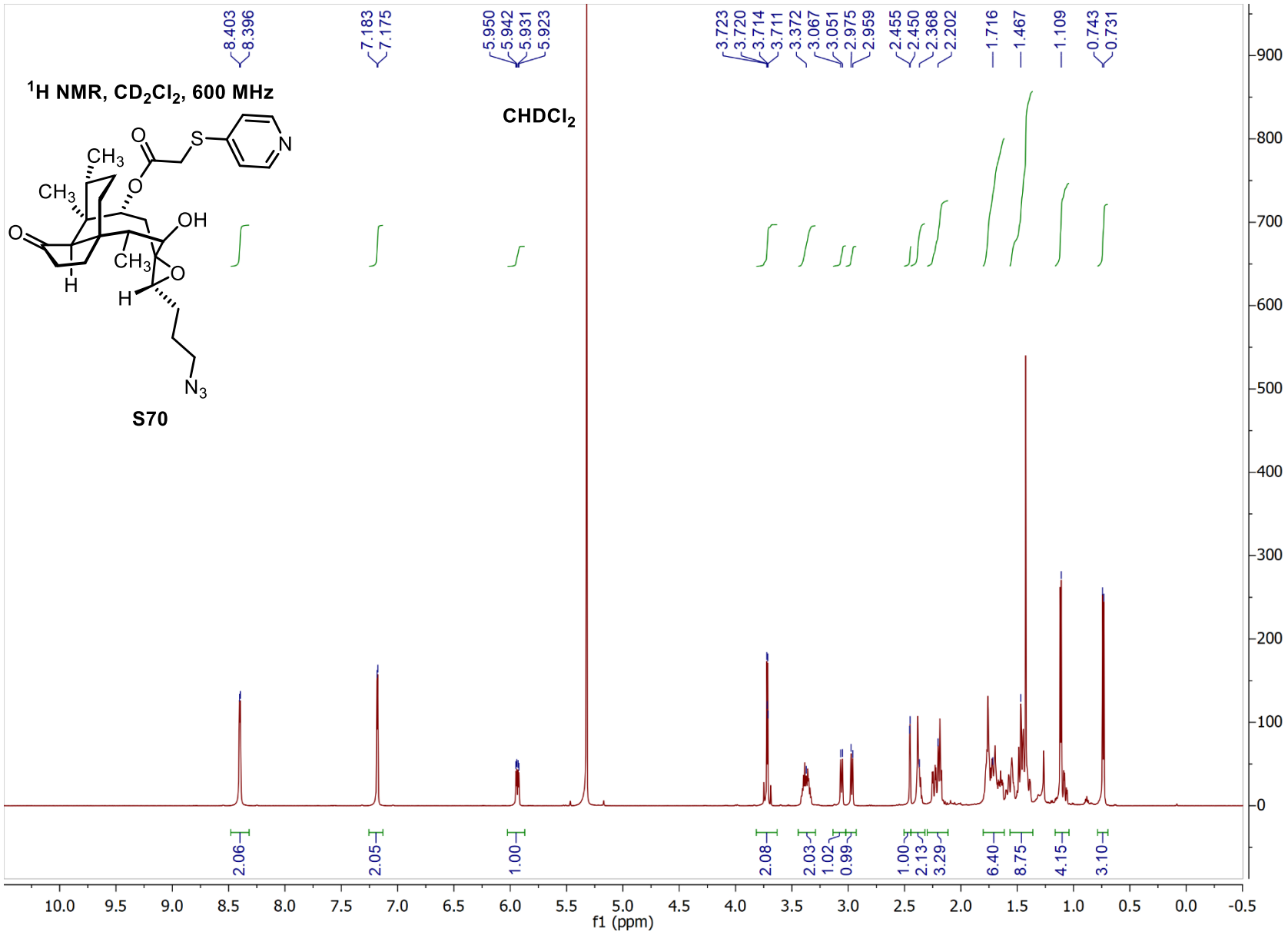

7.831 7.817 7.362 7.348 6.002 5.994 5.983 5.975 4.517 3.622 3.078 3.073 3.062 3.057 2.993 2.988 2.978 2.973 2.466 2.456 2.437 2.427 2.422 2.416 2.411 2.405 2.400 2.389 2.258 2.226 2.216 2.209 2.199 1.980 1.915 1.910 1.906 1.900 1.895 1.892 1.887 1.883 1.877 1.872 1.868 1.862 1.621 1.451 1.395 1.126 1.116 1.103 1.095 1.079 1.072 1.056 1.048 0.680 0.668
^{1}H NMR, $CDCl_3$, 600 MHz
$CHCl_3$
S69
2.08 2.08 1.00 2.05 2.08 1.00 0.99 4.11 1.04 2.01 2.07 1.92 1.11 7.47 4.16 1.06 2.95 1.04 3.14
f1 (ppm)

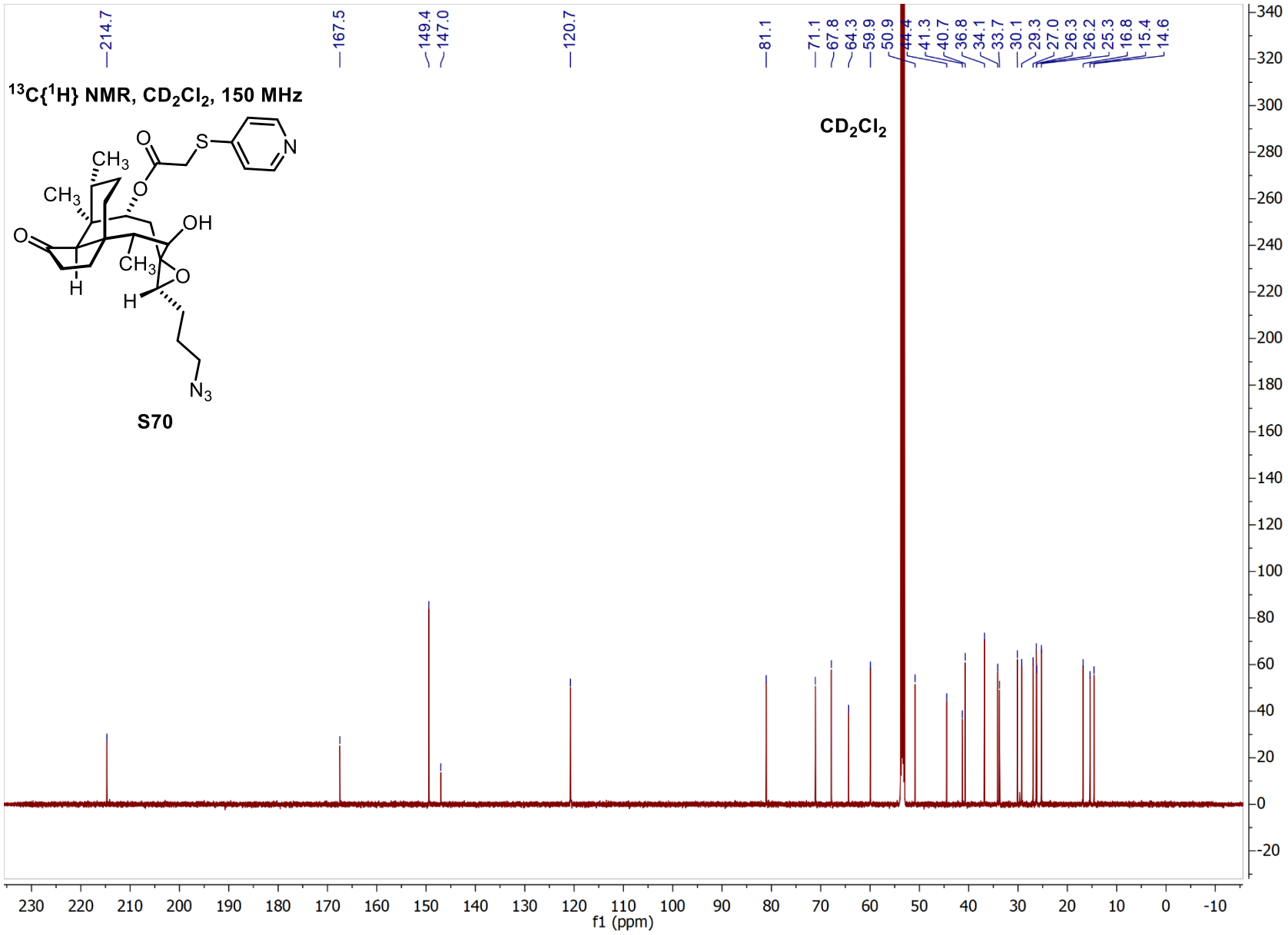

214.9
165.0
145.4
132.5
129.9
128.1
81.0
71.0
67.5
64.8
64.5
60.0
44.5
44.1
41.3
40.7
36.7
34.2
30.2
29.6
29.4
26.9
26.4
25.3
21.7
16.7
15.6
14.9
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
S69
f1 (ppm)

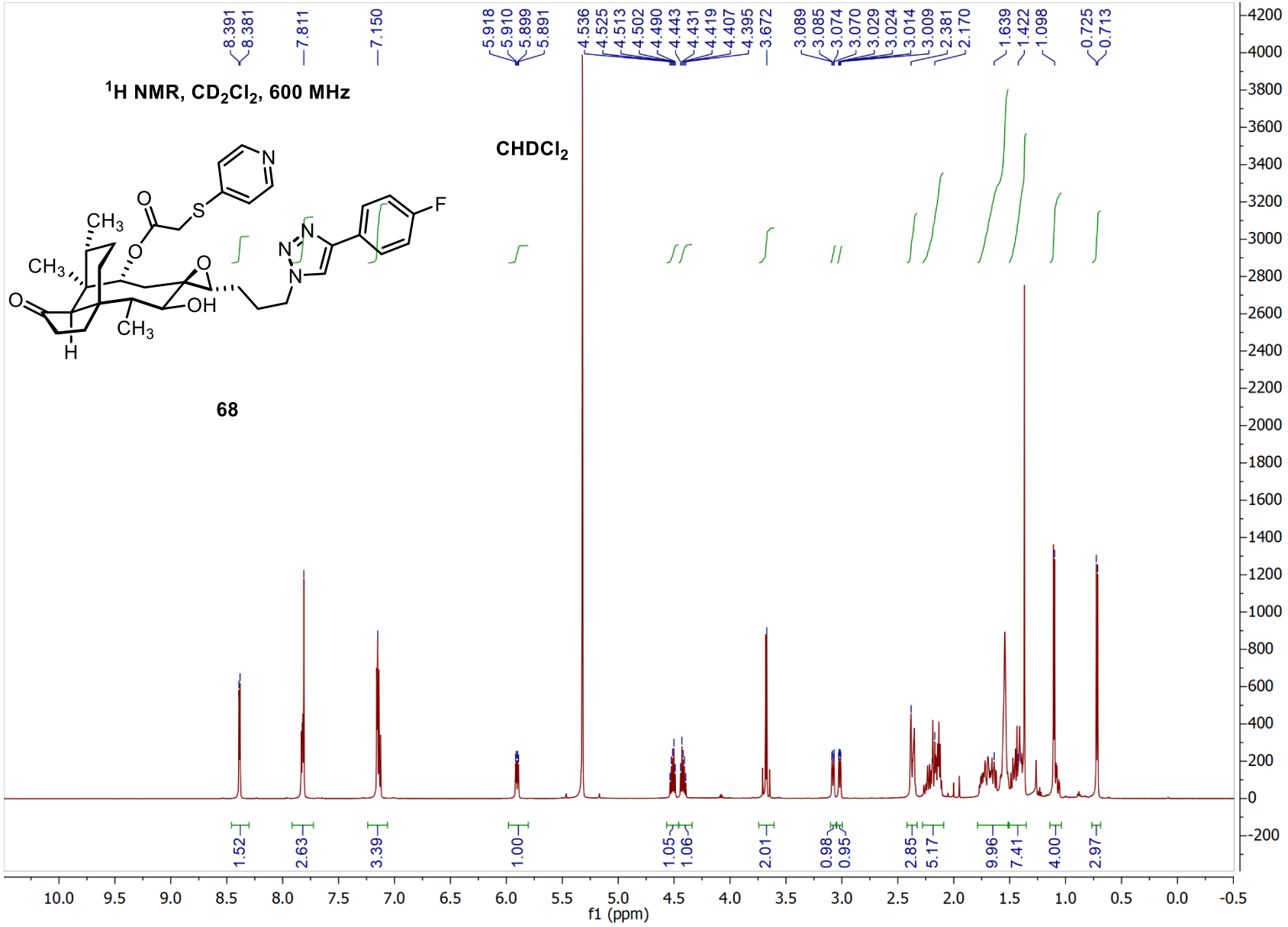

S69, NOESY, CDCl3, 500 MHz
f2 (ppm)
f1 (ppm)


^{1}H NMR, CD_2Cl_2, 400 MHz
$CHDCl_2$
67
f1 (ppm)


214.7
167.5
149.5
147.0
120.7
81.0
71.1
67.6
64.3
59.9
44.4
44.4
41.3
40.7
36.8
34.1
33.7
30.1
29.7
29.3
27.0
26.2
25.4
16.8
15.4
14.6
13C{1H} NMR, CD2Cl2, 100 MHz
CD2Cl2
67
f1 (ppm)


8.403
8.396
7.183
7.175
5.950
5.942
5.931
5.923
3.723
3.720
3.714
3.711
3.372
3.067
3.051
2.975
2.959
2.455
2.450
2.368
2.202
1.716
1.467
1.109
0.743
0.731
^{1}H NMR, CD_2Cl_2, 600 MHz
$CHDCl_2$
S70
2.06
2.05
1.00
2.08
2.03
1.02
0.99
1.00
2.13
3.29
6.40
8.75
4.15
3.10
f1 (ppm)


214.7
167.5
149.4
147.0
120.7
81.1
71.1
67.8
64.3
59.9
50.9
44.4
41.3
40.7
36.8
34.1
33.7
30.1
29.3
27.0
26.3
26.2
25.3
16.8
15.4
14.6
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
S70
f1 (ppm)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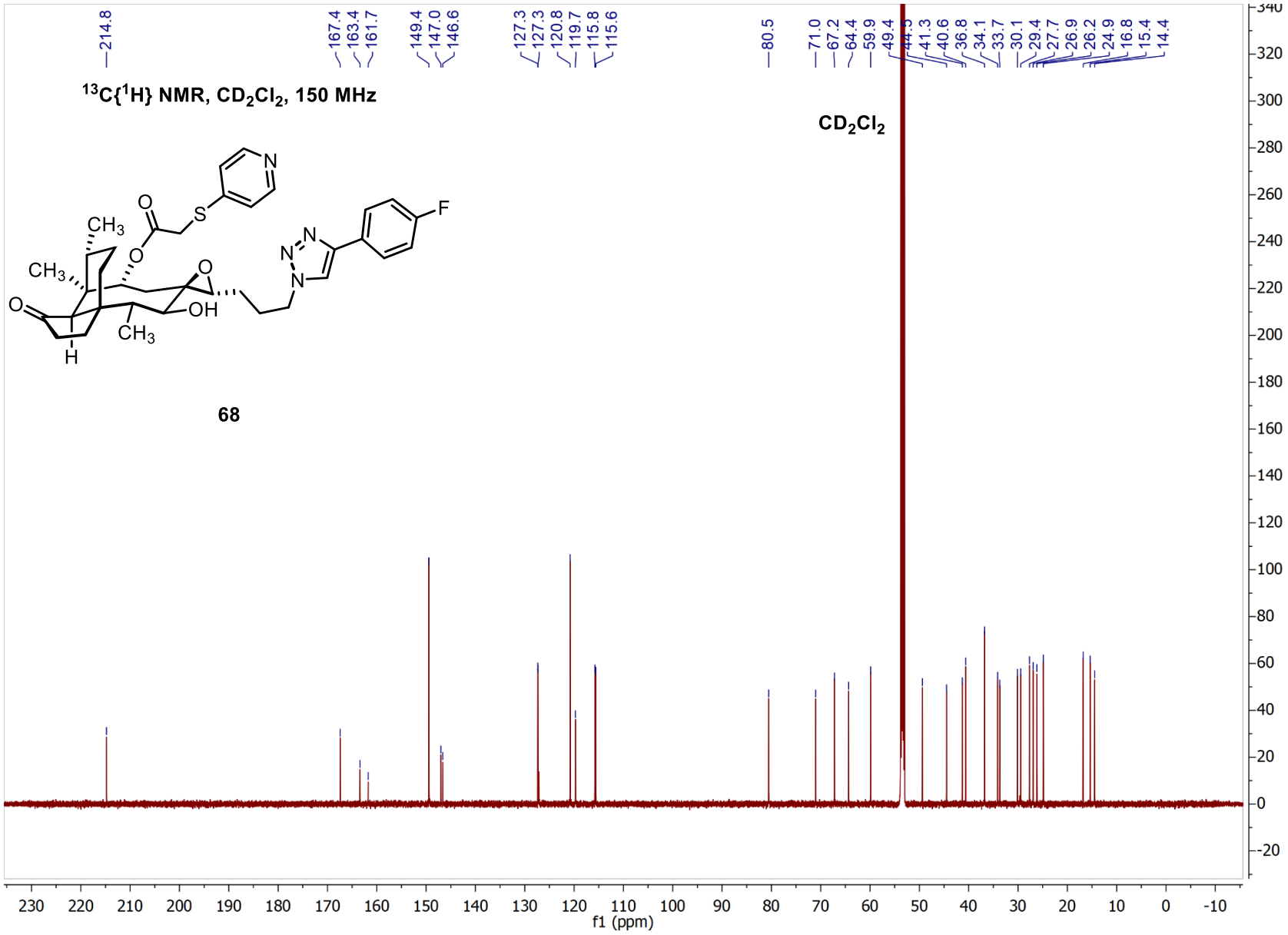
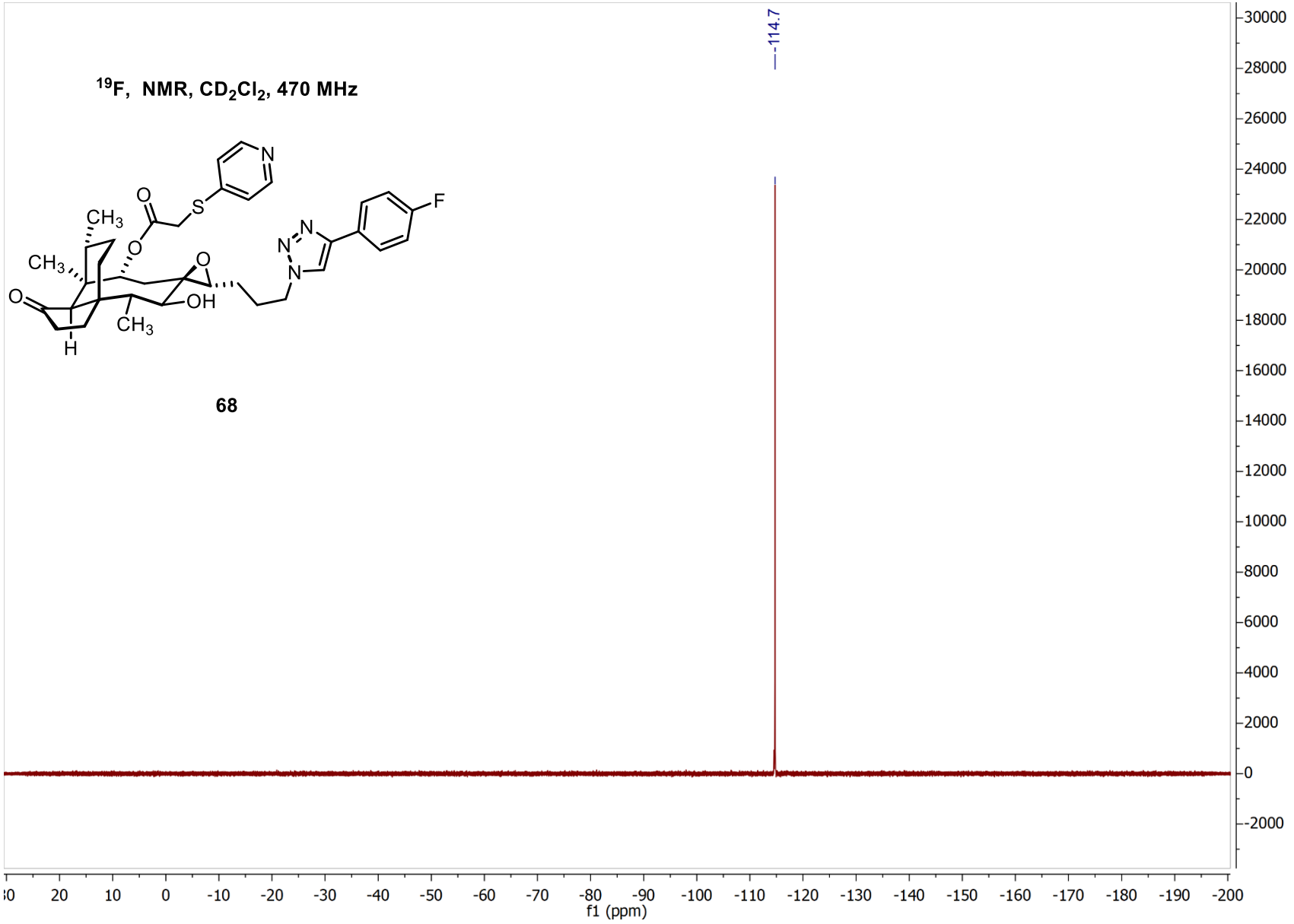
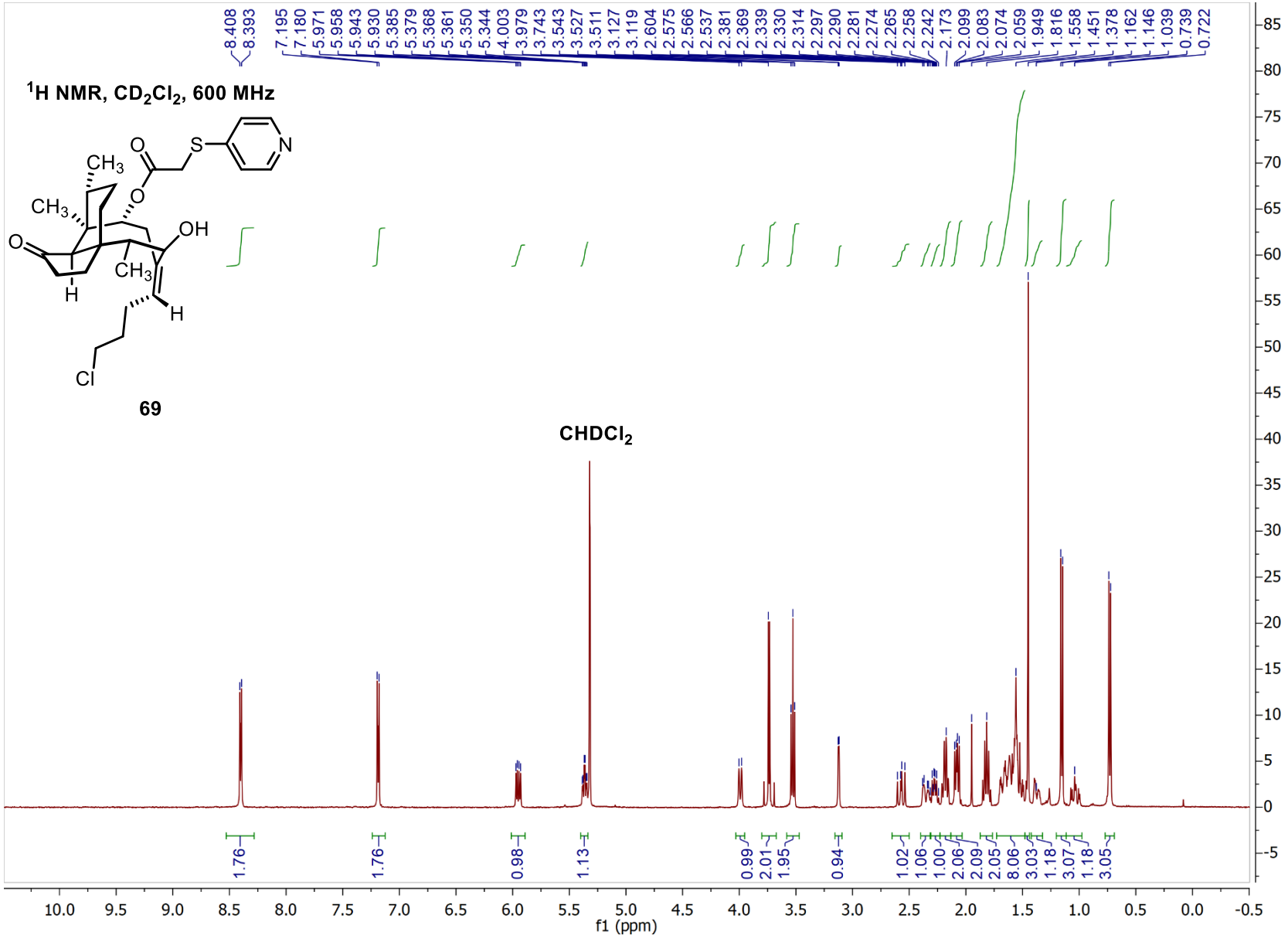
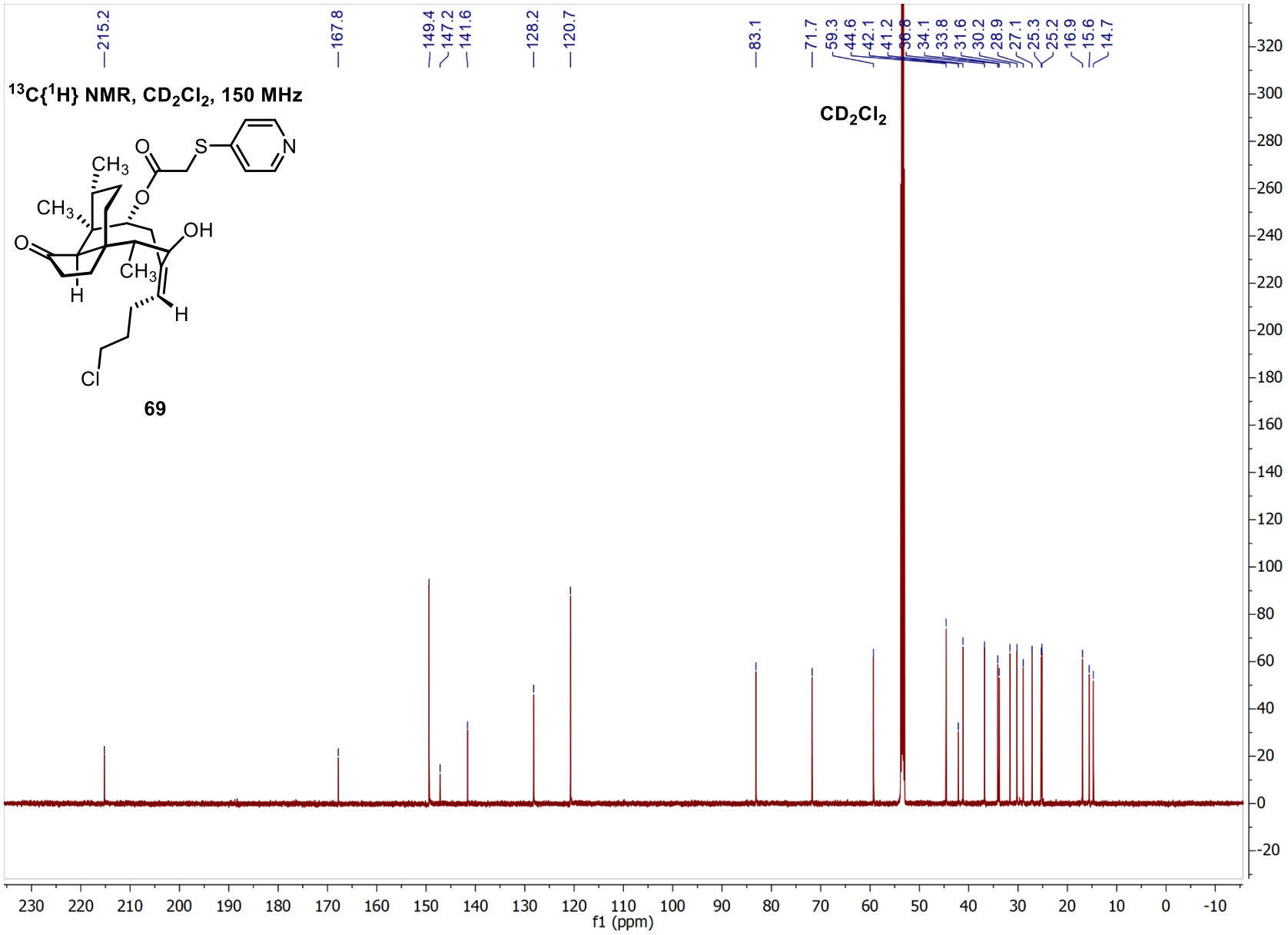
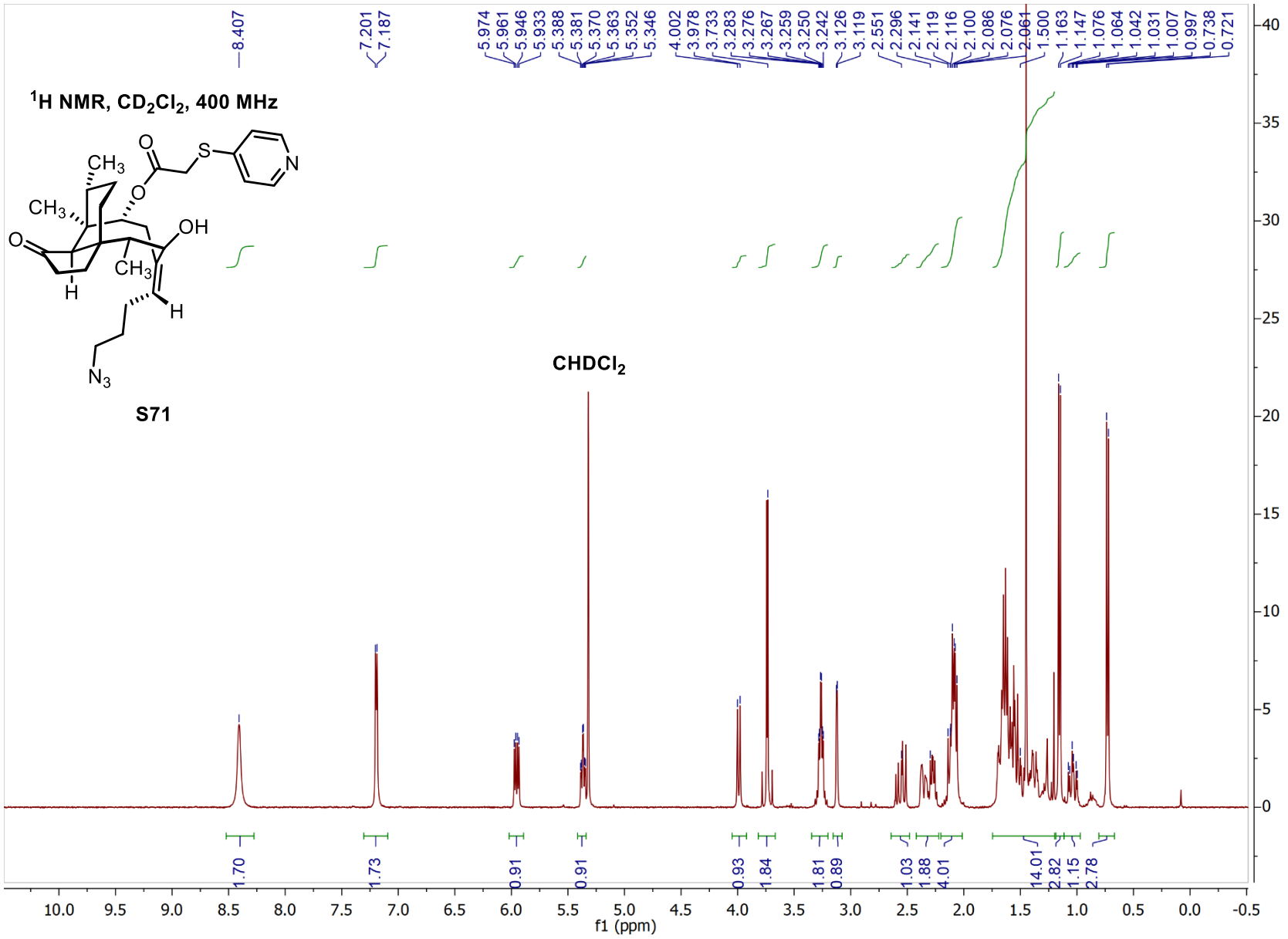
8.381
7.811
7.150
5.918
5.910
5.899
5.891
4.536
4.525
4.513
4.502
4.490
4.443
4.431
4.419
4.407
4.395
3.672
3.089
3.085
3.074
3.070
3.029
3.024
3.014
3.009
2.381
2.170
1.639
1.422
1.098
0.725
0.713
1H NMR, CD2Cl2, 600 MHz
CHDCl2
68
1.52
2.63
3.39
1.00
1.05
1.06
2.01
0.98
0.95
2.85
5.17
9.96
7.41
4.00
2.97
f1 (ppm)

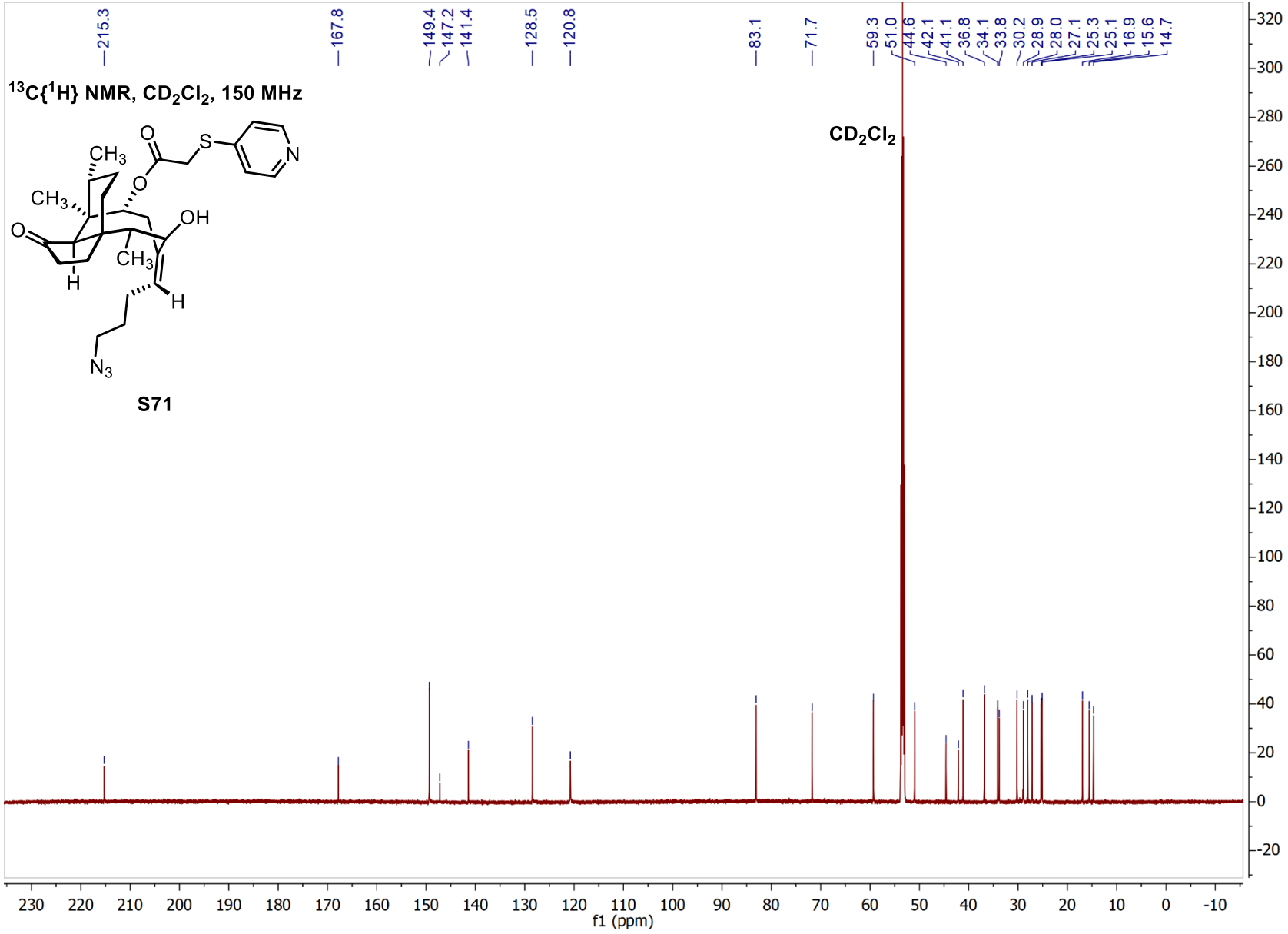

214.8
167.4
163.4
161.7
149.4
147.0
146.6
127.3
127.3
120.8
119.7
115.8
115.6
80.5
71.0
67.2
64.4
59.9
49.4
44.5
41.3
40.6
36.8
34.1
33.7
30.1
29.4
27.7
26.9
26.2
24.9
16.8
15.4
14.4
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
68
f1 (ppm)

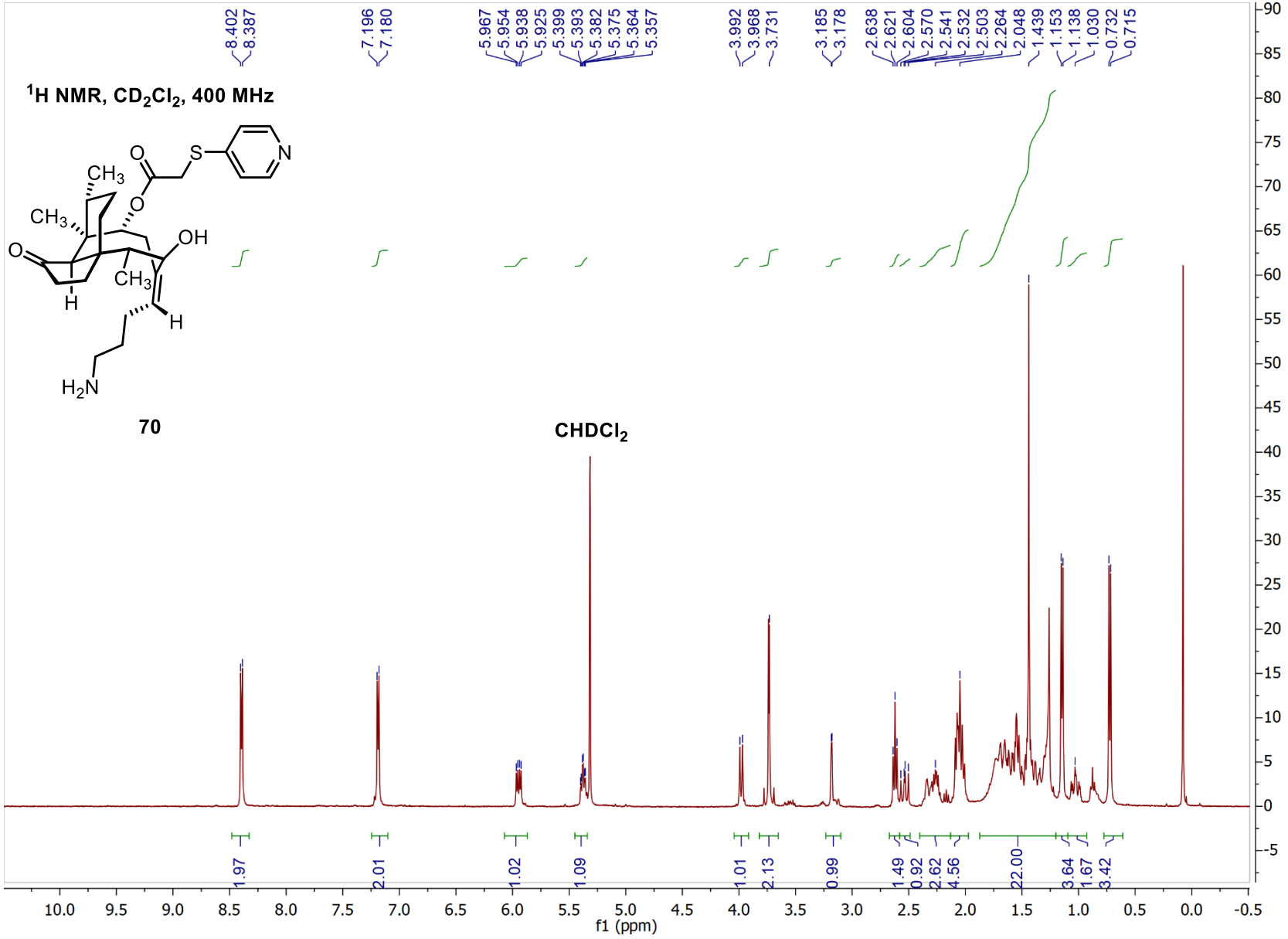

19F, NMR, CD2Cl2, 470 MHz
-114.7
68
f1 (ppm)

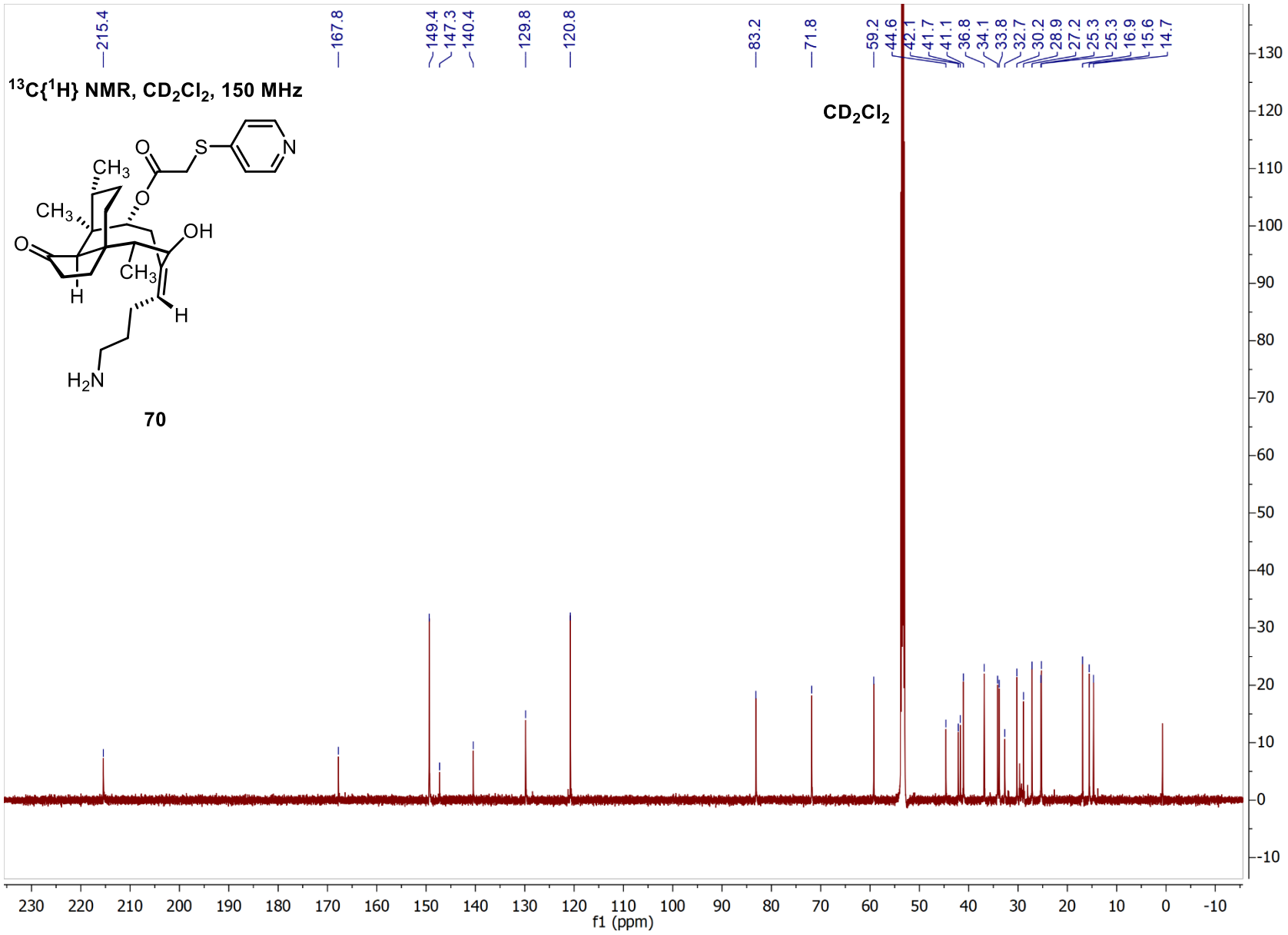

8.408
8.393
7.195
7.180
5.971
5.958
5.943
5.930
5.385
5.379
5.368
5.361
5.350
5.344
4.003
3.979
3.743
3.543
3.527
3.511
3.127
3.119
2.604
2.575
2.566
2.537
2.381
2.369
2.339
2.330
2.314
2.297
2.290
2.281
2.274
2.265
2.258
2.242
2.173
2.099
2.083
2.074
2.059
1.949
1.816
1.558
1.451
1.378
1.162
1.146
1.039
0.739
0.722
^{1}H NMR, CD_2Cl_2, 600 MHz
CH3
CH3
CH3
O
O
O
S
N
OH
H
H
Cl
69
$CHDCl_2$
1.76
1.76
0.98
1.13
0.99
2.01
1.95
0.94
1.02
1.06
1.00
2.06
2.09
2.05
8.06
3.03
1.18
3.07
1.18
3.05
f1 (ppm)

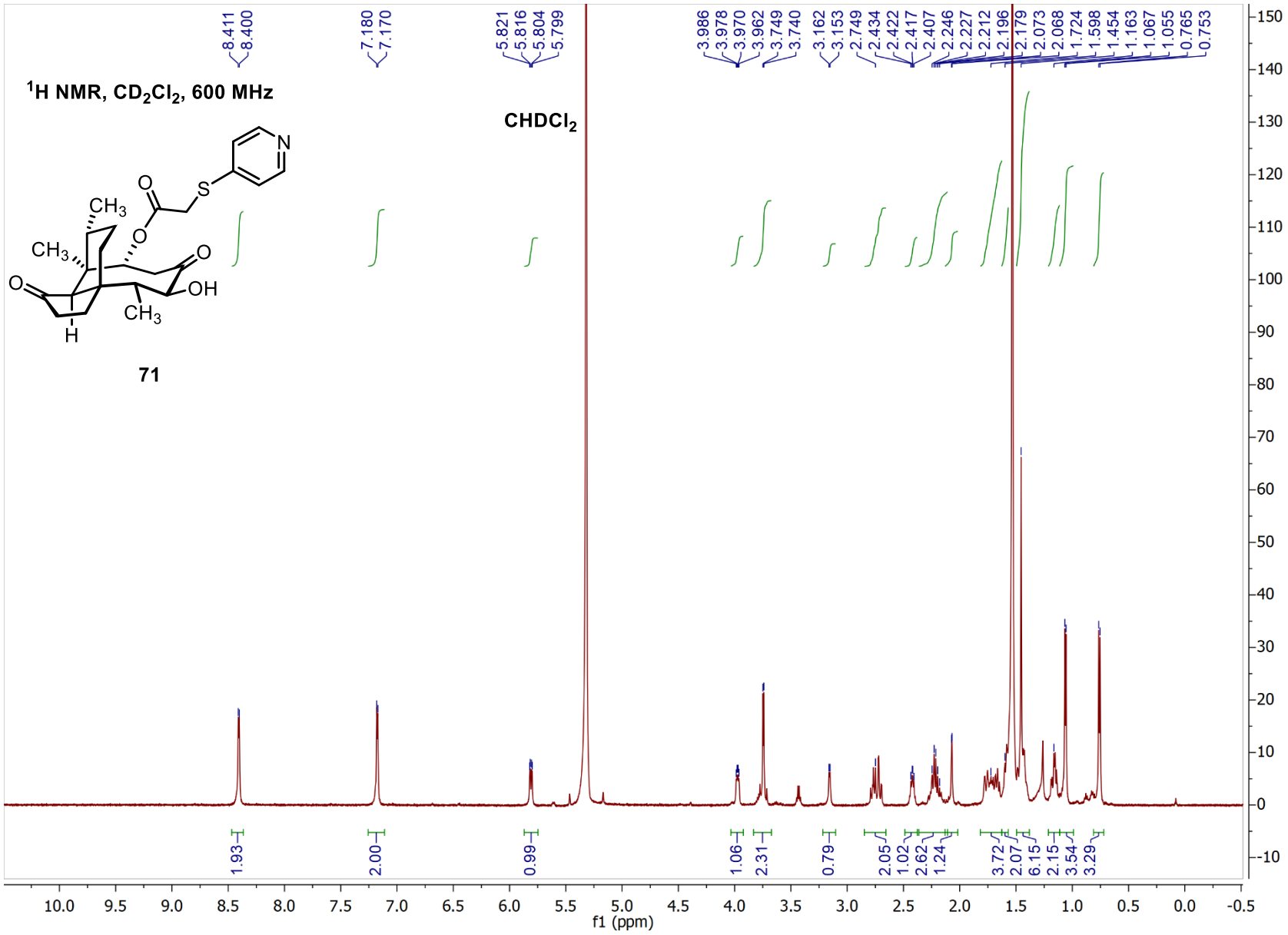

215.2
167.8
149.4
147.2
141.6
128.2
120.7
83.1
71.7
59.3
44.6
42.1
41.2
38.8
34.1
33.8
31.6
30.2
28.9
27.1
25.3
25.2
16.9
15.6
14.7
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
69
f1 (ppm)

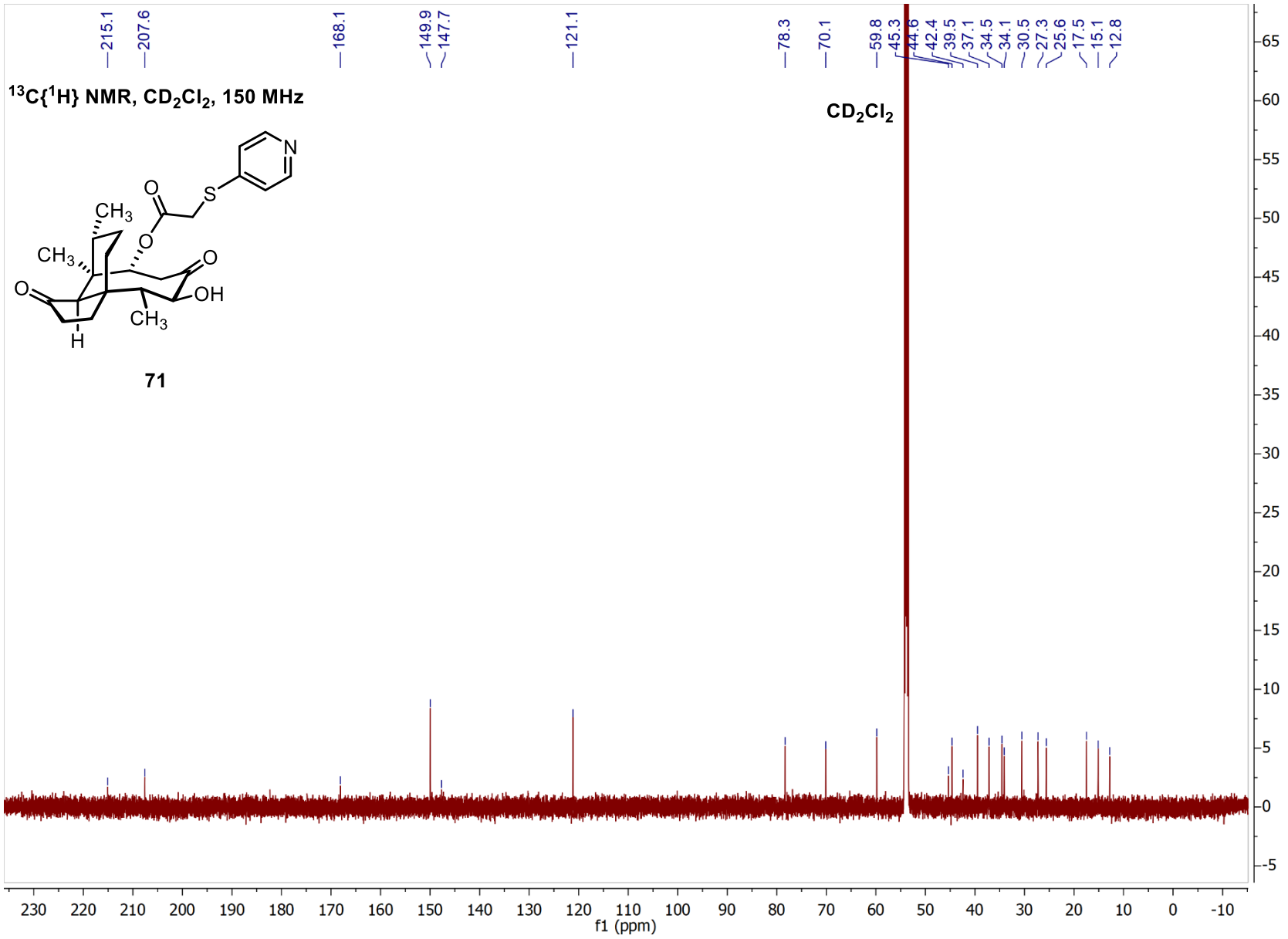

8.407
7.201
7.187
5.974
5.961
5.946
5.933
5.388
5.381
5.370
5.363
5.352
5.346
4.002
3.978
3.733
3.283
3.276
3.267
3.259
3.250
3.242
3.126
3.119
2.551
2.296
2.141
2.119
2.116
2.100
2.086
2.076
2.061
1.500
1.163
1.147
1.076
1.064
1.042
1.031
1.007
0.997
0.738
0.721
^{1}H NMR, CD_2Cl_2, 400 MHz
$CHDCl_2$
S71
1.70
1.73
0.91
0.91
0.93
1.84
1.81
0.89
1.03
1.88
4.01
14.01
2.82
1.15
2.78
f1 (ppm)

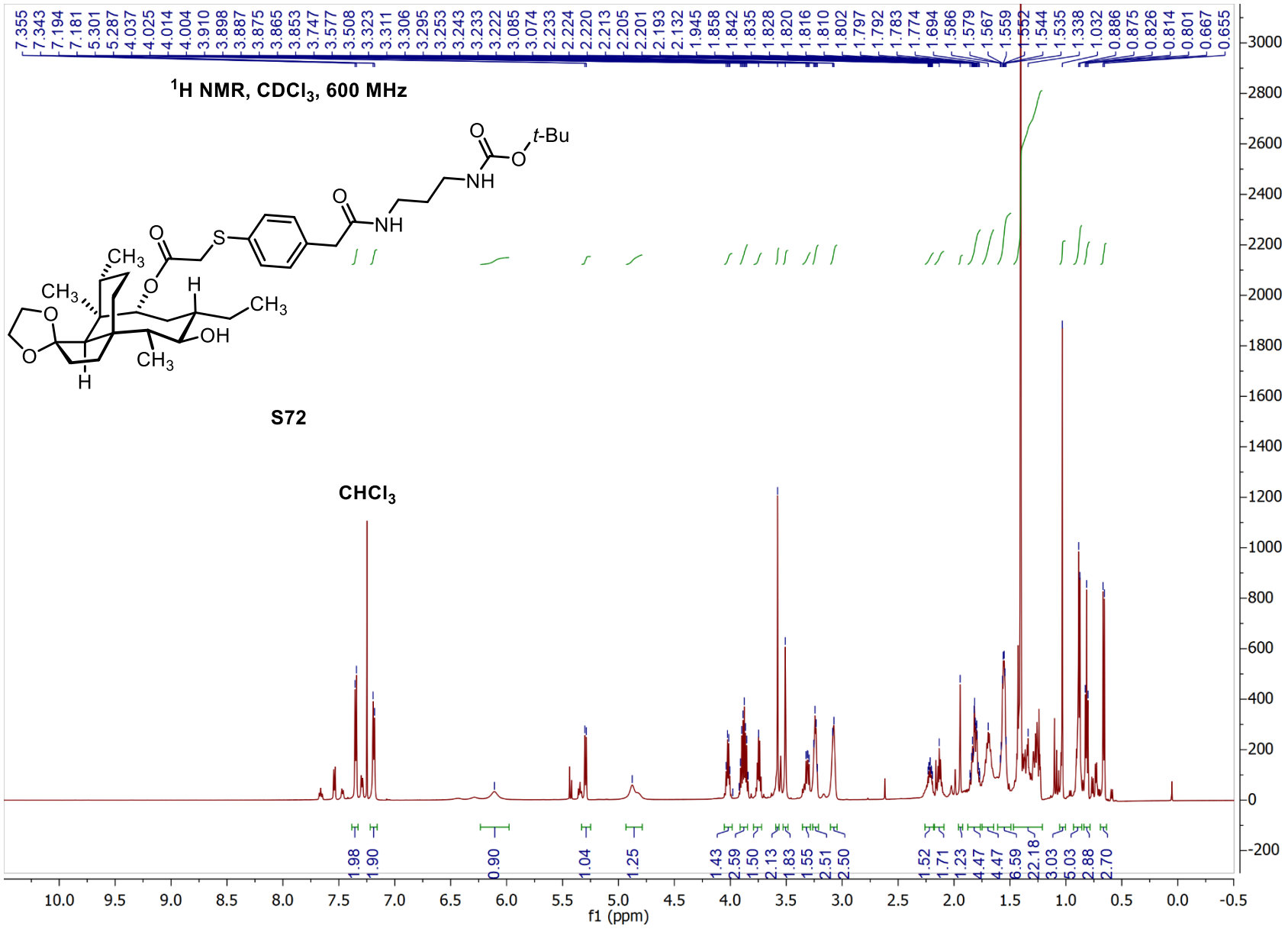

215.3
167.8
149.4
147.2
141.4
128.5
120.8
83.1
71.7
59.3
51.0
44.6
42.1
41.1
36.8
34.1
33.8
30.2
28.9
28.0
27.1
25.3
25.1
16.9
15.6
14.7
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
S71
f1 (ppm)

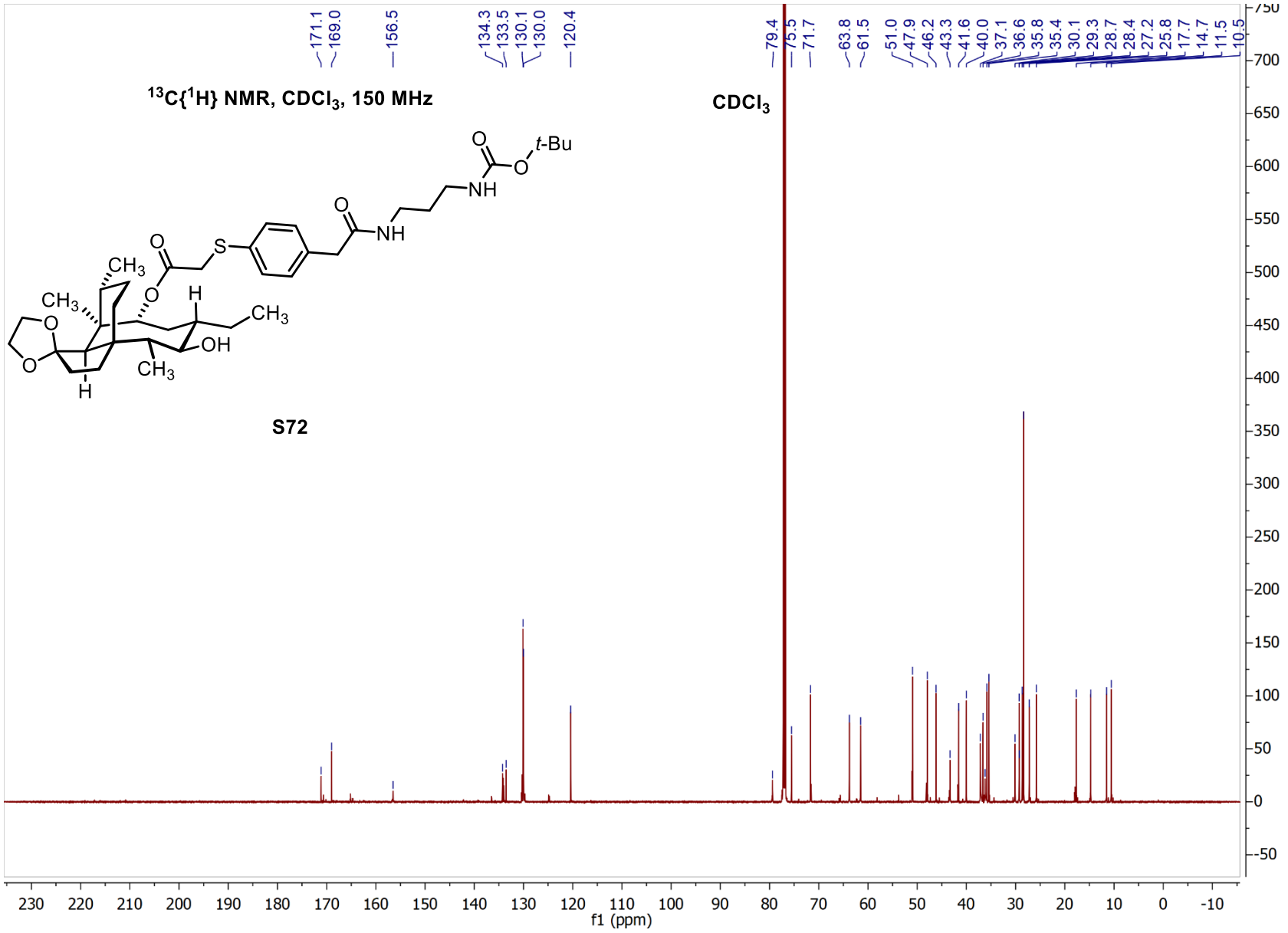

8.402
8.387
7.196
7.180
5.967
5.954
5.938
5.925
5.399
5.393
5.382
5.375
5.364
5.357
3.992
3.968
3.731
3.185
3.178
2.638
2.621
2.604
2.570
2.541
2.532
2.503
2.264
2.048
1.439
1.153
1.138
1.030
0.732
0.715
1H NMR, CD2Cl2, 400 MHz
CH3
CH3
O
S
N
O
O
OH
CH3
O
H
H
H2N
70
CHDCl2
1.97
2.01
1.02
1.09
1.01
2.13
0.99
1.49
0.92
2.62
4.56
22.00
3.64
1.67
3.42
f1 (ppm)

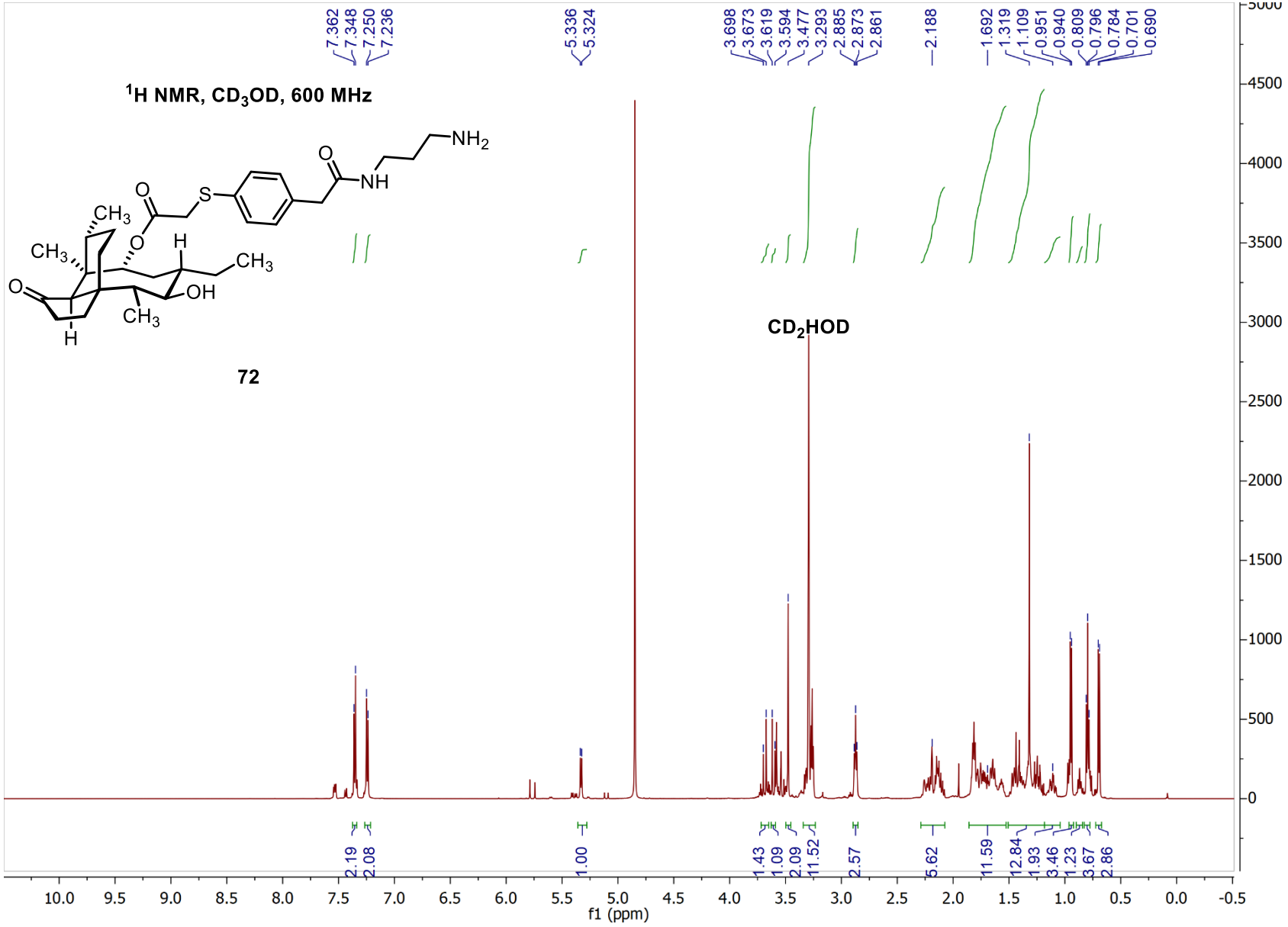

215.4
167.8
149.4
147.3
140.4
129.8
120.8
83.2
71.8
59.2
44.6
42.1
41.7
41.1
36.8
34.1
33.8
32.7
30.2
28.9
27.2
25.3
25.3
16.9
15.6
14.7
13C{1H} NMR, CD2Cl2, 150 MHz
CD2Cl2
70
f1 (ppm)

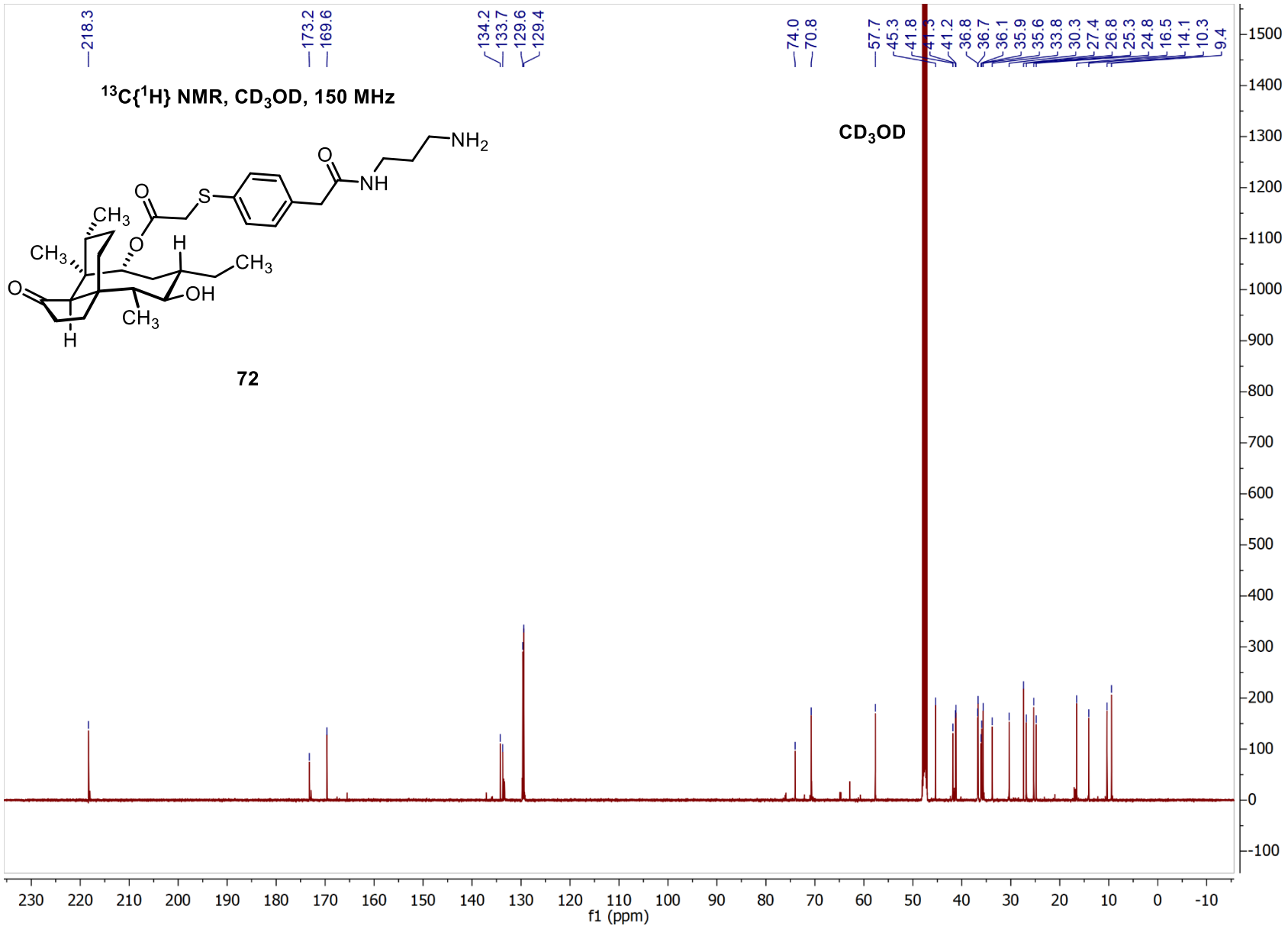

8.411
8.400
7.180
7.170
5.821
5.816
5.804
5.799
3.986
3.978
3.970
3.962
3.749
3.740
3.162
3.153
2.749
2.434
2.422
2.417
2.407
2.246
2.227
2.212
2.196
2.179
2.073
2.068
1.724
1.598
1.454
1.163
1.067
1.055
0.765
0.753
1H NMR, CD2Cl2, 600 MHz
CHDCl2
71
1.93
2.00
0.99
1.06
2.31
0.79
2.05
1.02
2.62
1.24
3.72
2.07
6.15
2.15
3.54
3.29
f1 (ppm)


215.1
207.6
168.1
149.9
147.7
121.1
78.3
70.1
59.8
45.3
44.6
42.4
39.5
37.1
34.5
34.1
30.5
27.3
25.6
17.5
15.1
12.8
$^{13}C\{^{1}H\}$ NMR, CD_2Cl_2, 150 MHz
CD_2Cl_2
71
f1 (ppm)


7.355 7.343 7.194 7.181 5.301 5.287 4.037 4.025 4.014 4.004 3.910 3.898 3.887 3.875 3.865 3.853 3.747 3.577 3.508 3.323 3.311 3.306 3.295 3.253 3.243 3.233 3.222 3.085 3.074 2.233 2.224 2.220 2.213 2.205 2.201 2.193 2.132 1.945 1.858 1.842 1.835 1.828 1.820 1.816 1.810 1.802 1.797 1.792 1.783 1.774 1.694 1.586 1.579 1.567 1.559 1.552 1.544 1.535 1.338 1.032 0.886 0.875 0.826 0.814 0.801 0.667 0.655
^{1}H NMR, $CDCl_3$, 600 MHz
t-Bu
NH
NH
S
O
O
O
O
O
O
H
H
CH3
CH3
CH3
CH3
OH
S72
$CHCl_3$
1.98 1.90 0.90 1.04 1.25 1.43 2.59 1.50 2.13 1.83 1.55 2.51 2.50 1.52 1.71 1.23 4.47 4.47 6.59 22.18 3.03 5.03 2.88 2.70
10.0 9.5 9.0 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 1.0 0.5 0.0 -0.5
f1 (ppm)
3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0 -200


171.1
169.0
156.5
134.3
133.5
130.1
130.0
120.4
79.4
75.5
71.7
63.8
61.5
51.0
47.9
46.2
43.3
41.6
40.0
37.1
36.6
35.8
35.4
30.1
29.3
28.7
28.4
27.2
25.8
17.7
14.7
11.5
10.5
13C{1H} NMR, CDCl3, 150 MHz
CDCl3
t-Bu
NH
NH
S
O
CH3
CH3
CH3
OH
H
H
S72
f1 (ppm)


7.362
7.348
7.250
7.236
5.336
5.324
3.698
3.673
3.619
3.594
3.477
3.293
2.885
2.873
2.861
2.188
1.692
1.319
1.109
0.951
0.940
0.809
0.796
0.784
0.701
0.690
¹H NMR, CD3OD, 600 MHz
NH2
O
NH
O
S
O
CH3
CH3
O
H
CH3
O
OH
CH3
H
72
CD2HOD
2.19
2.08
1.00
1.43
1.09
2.09
11.52
2.57
5.62
11.59
12.84
1.93
3.46
1.23
3.67
2.86
f1 (ppm)


218.3
173.2
169.6
134.2
133.7
129.6
129.4
74.0
70.8
57.7
45.3
41.8
41.3
41.2
36.8
36.7
36.1
35.9
35.6
33.8
30.3
27.4
26.8
25.3
24.8
16.5
14.1
10.3
9.4
13C{1H} NMR, CD3OD, 150 MHz
CD3OD
72
f1 (ppm)

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