Supporting Information

Dynamic Strategic Bond Analysis Yields a 10-step Synthesis of 20-nor-Salvinorin A, a Potent κ-OR Agonist

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Contents:

General Methods and Materials

Synthetic methods. All reactions were carried out under positive pressure of argon in a well-ventilated fume hood unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F_{254}). Flash column chromatography was performed over Silica gel 60 (particle size 0.04-0.063 mm) from EMD chemicals. Mass spectra were recorded on an Agilent 6120 Quadrupole LC/MS system with an ESI probe unless otherwise noted. EI MS analysis was performed on Agilent 7820A/5975 GC/MSD system with helium as the carrier gas. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-400 and Bruker DRX-600 (equipped with cryoprobe) spectrometers using residual solvent peaks as internal standard (CDCl3 @ 7.26 ppm ^{1}H NMR, 77.06 ppm ^{13}C NMR; CD_3CN @ 1.94 ppm ^{1}H NMR).

Cell based signaling assays. The competition binding studies were performed on CHO-K1 cells expressing the human KOR (CHO-hKOR)[41], as described[42]. Briefly, 10 µg membranes were incubated with 1 nM [^{3}H]-U69,593 (PerkinElmer) and increasing concentrations of the test compounds for 1 hour at 25 °C. The assay was terminated via filtration through GF/B glass fiber filters pretreated with 0.1% polyethyleneimine on a Brandel cell harvester. Filters were counted with Microscint on a TopCount NXT microplate scintillation counter (PerkinElmer). Nonspecific binding was determined in the presence of 10 µM U69,593. Total receptor number was determined by [^{3}H]-U69,593 saturation binding (K_D = 1.07 nM, B_{Max} = 708 fmol/mg protein). Binding affinities at the mu and delta opioid receptors were determined by competition binding with [^{3}H]-DAMGO and –Diprenorphine on membranes prepared from CHO cells expressing the human MOR and human DOR, respectively (for [^{3}H]-DAMGO at hMOR: K_D = 1.02 nM, B_{Max} = 1584 fmol/mg protein; for [^{3}H]-Diprenorphine at hDOR: K_D = 0.70 nM, B_{Max} = 1461 fmol/mg protein). Nonspecific binding was determined in the presence of 10 µM naloxone. Inhibition of cAMP was determined by incubating CHO-hKOR cells (4,000 cells/well in low-volume 384-well plates) with the test ligands and 25 µM RO-20-1724 (Sigma Aldrich) and 20 µM forskolin (Sigma Aldrich) for 30 minutes at 25 °C. The CISBIO cAMP HTRF HiRange assay was used to quantify cAMP levels according to the manufacturer's instructions.

Chloroquine phosphate-induced pruritus. Experiments were carried out with 10-14 week male C57BL/6J mice purchased from The Jackson Laboratory. Mice were group housed (3-5 mice/cage) and maintained on a 12-hour light/dark cycle. All mice were cared for in accordance to the guidelines set forth by the National Institutes of Health and with the approval of The Scripps Research Institute Animal Care and Use Committee. The ability of the agnoists' to block chloroquine phosphate (Sigma Aldrich) induced pruritus was evaluated as previously described (*19,40*). Mice were habituated to the testing boxes for 1 hour and then pretreated with either vehicle (1:1:8, DMSO: Tween 80: 0.9% sterile saline) or 3 mg/kg U50,488H or salvinorin A, or 20-nor-SalA (10 µl/g, s.c.-flank) for 10 minutes. Mice were then challenged with 40 mg/kg chloroquine phosphate (5 µl/g, s.c.-neck) and the number of scratching bouts were counted in 5 minute intervals for 1 hour by a blinded investigator.

Data and statistical analysis. Data were analyzed using GraphPad Prism 6.0h software. For each individual cell based assay, compounds were run in duplicate (binding) or triplicate (cAMP) and normalized to the U69,593 response. Dose response curves were generated using three-parameter nonlinear regression analysis. Data are from $n \geq 3$ independent experiments and are presented as mean ± S.E.M.

Docking. The currently available crystal structure of κ-OR (PDB: 4djh) had been co-crystallized with an inverse agonist JDTic and reflects conformation of the binding pocket specific to JDTic (Figure S2). Therefore, it is not readily suitable for agonist docking. For a more accurate model, we have developed a template-based homology model of active state of κ-OR to use in the docking studies of agonists SalA and 20-nor-SalA. Aa a close homology template, we used agonist-bound mu opioid receptor (μ-OR) structure (PDB:5c1m), which shares 69.9% sequence identity with κ-OR. The resulting active state homology model was thoroughly optimized, including full sampling of the receptor side-chains. Soft grid docking approach was used to find possible binding poses of the ligands with docking effort value of 50, and the docking box covering the whole extracellular half of the receptor. The ligand poses found among top three hits in three independent docking runs were retained for further optimization. Optimization was performed in all-atom model by Monte Carlo minimization sampling of the ligand conformation and residue side chains within 4 Å of the ligand. All molecular modeling operations, including homology modeling and ligand dockings, were performed in Molsoft ICM-Pro v3.8-5 molecular modeling software.

Materials. Hexanes (ACS grade), ethyl acetate (ACS grade), toluene (ACS grade), and diethyl ether (anhydrous ACS grade) were purchased from Sigma-Aldrich and used without further purification. Dichloromethane (ACS grade), acetonitrile (ACS grade), and chloroform (ACS grade) were purchased from Fisher Chemical and used without further purification.

Anhydrous tetrahydrofuran was purchased from Sigma-Aldrich and used without further purification. Anhydrous HMPA was distilled from calcium hydride (10% w/v) through a frit of steel wool under reduced pressure. Anhydrous zinc chloride was dried by stirring at 150 °C under reduced pressure for several hours. Acrolein was distilled under reduced pressure and collected at -78 °C. Anhydrous dichloromethane was distilled from calcium hydride (10% w/v) under positive pressure of argon or obtained by passing the previously degassed solvent through an activated alumina column. Anhydrous triethylamine was purchased from Sigma-Aldrich and used without further purification. Anhydrous methanesulfonyl chloride was distilled from phosphorus pentoxide (10% w/v) under reduced pressure. Anhydrous DBU was distilled from calcium hydride (10% w/v) through a frit of steel wool under reduced pressure. Anhydrous dimethylsulfoxide was purchased from Sigma-Aldrich and used without further purification. Anhydrous methanol was obtained by passing the previously degassed solvent through an activated alumina column. Anhydrous potassium carbonate was dried at 200 °C for at least 12 hours. Anhydrous diisopropylamine was distilled from calcium hydride (10% w/v) under positive pressure of Argon. *n*-Butyllithium was titrated with a solution of recrystallized diphenylacetic acid in anhydrous tetrahydrofuran. Acetic anhydride was distilled from potassium carbonate under positive pressure of argon. Anhydrous acetonitrile was distilled from phosphorus pentoxide (10% w/v) under positive pressure of argon. Anhydrous DMF was purchased from Sigma-Aldrich and used without further purification. 3-bromofuran was passed through a 3 cm plug of neutral aluminum oxide. Anhydrous hexafluoroisopropanol was stirred over calcium hydride (10% w/v) for 30 minutes, then distilled under positive pressure of argon. Commercially available reagents were used without further purification unless otherwise noted.

The reference compounds U69,593 was purchased from Sigma Aldrich and was prepared in ethanol as a 10 mM stock. NorBNI (nor-Binaltorphimine dihydrochloride; Sigma Aldrich), U50,488H (Tocris), salvinorin A (Enzo Life Sciences) and the salvinorin A analogs were prepared as 10 mM stocks in DMSO.

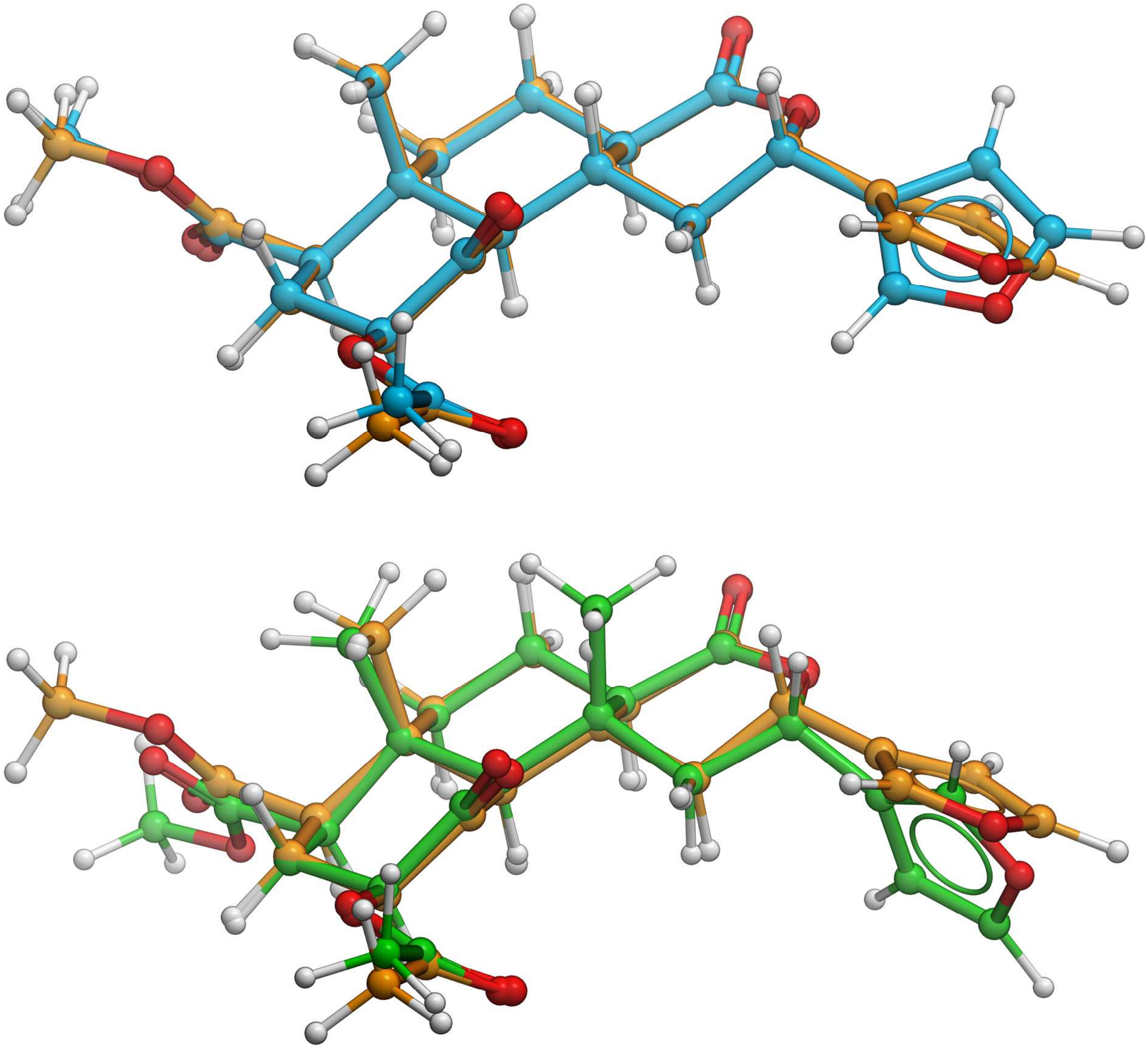


Figure S1. Superimposition of crystalline 20-nor-SalA (orange) and QM geometrically optimized structures for 20-nor-SalA (cyan), and SalA (green) structures represented in balls and sticks. Overall the geometry of the ring system is maintained for both the ligands. However, the removal of the C-20 methyl group of 20-nor-SalA slightly displaces the C-19 methyl and C-12 of the lactone ring, resulting in subtle deviation in the position of the furan ring.

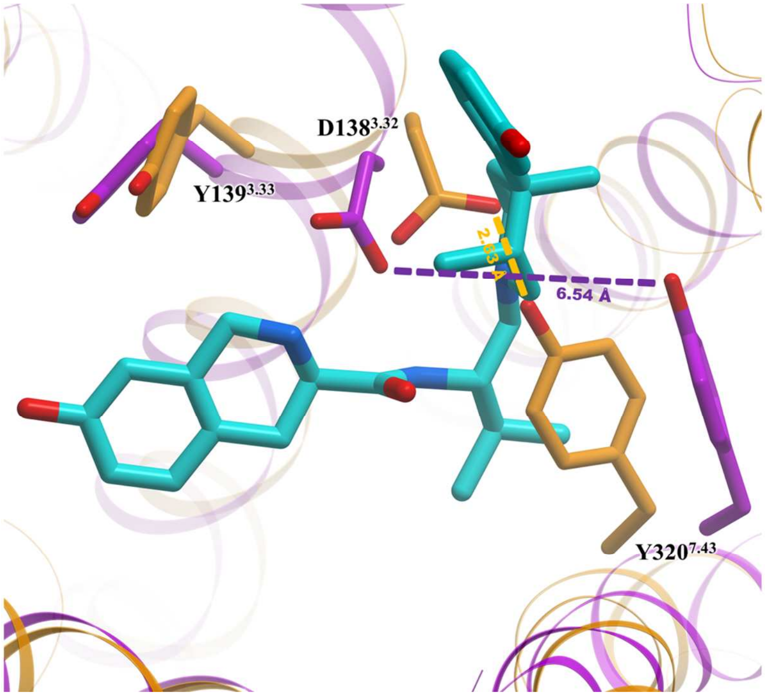
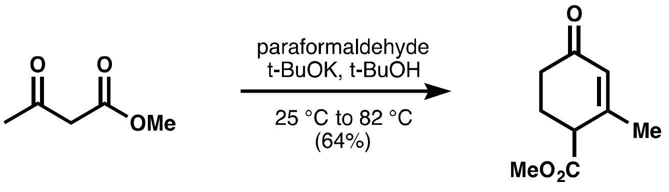


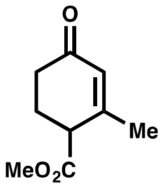
Figure S2. Superimposition of “inactive” form of kappa opioid receptor (PDB ID: 4djh) and homology model of “active” form of kappa opioid receptor, shown in purple and orange colored ribbon representation, respectively. The co-crystallized ligand, JDTic, and amino acid residues are shown in sticks representation. Distances between carboxylate oxygen of D138$^{3.32}$ and Y320$^{7.43}$ are shown in broken lines. The inward movement of D138$^{3.32}$ and Y320$^{7.43}$ in the “active” model drastically reduces the pocket volume and reshapes the pocket.

Synthetic Procedures and Characterization of Intermediates



4

Hagemann Ester 4. Hagemann's ester **4** is commercially available from Sigma-Aldrich (among others). Alternatively, it could be prepared *via* the following procedure: Methyl acetoacetate (85 mL, 788 mmol) was dissolved in *tert*-butanol (450 mL) and stirred with a magnetic stir bar at 25 °C. Paraformaldehyde (11.6 g, 386 mmol) was added to this solution in a single portion. To this colorless, opaque solution was added solid potassium *tert*-butoxide (4.4 g, 39.2 mmol) in portions, over ten minutes. The reaction was stirred at 25 °C for one hour; the reaction became faintly yellow. More solid potassium *tert*-butoxide (11.6 g, 103 mmol) was added in portions, over fifteen minutes. The reaction was heated to reflux for 12–18 hours. The yellow, opaque mixture was cooled to room temperature and concentrated *in vacuo* to less than 150 mL. Dichloromethane (200 mL) and 1 M hydrochloric acid (200 mL) were added, the mixture was shaken well (a gas evolved), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2x100 mL). The organic fractions were combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was fractionally distilled at 4 torr; the fraction boiling from 79 °C to 82 °C was collected and weighed to 41.7 g (248 mmol, 64%).



4

Hagemann Ester 4.

TLC: R_f = 0.20 (25% EtOAc in hexanes). UV active. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Faintly yellow oil

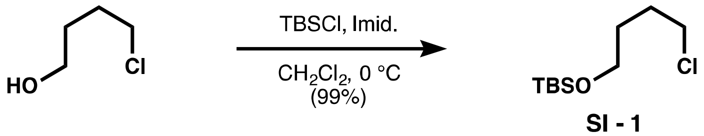
LRMS (ESI) calculated for $C_9H_{13}O_3$ $[M + H]^+$: 169.1, found 169.0

^{1}H NMR (600 MHz, $CDCl_3$):

δ 5.94 (t, J = 1.3 Hz, 1H)
3.73 (s, 3H)
3.26 (t, J = 5 Hz, 1H)
2.56–2.49 (m, 1H)
2.35–2.29 (m, 2H)
2.22–2.16 (m, 1H)
1.99 (s, 3H)

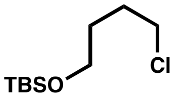
^{13}C NMR (150 MHz, $CDCl_3$):

δ 198.20
172.02
156.81
128.54
52.40
45.87
34.26
26.06
23.49



SI - 1

Silyl ether SI-1. Silyl ether **SI-1** is commercially available from Sigma-Aldrich (among others). Alternatively, it could be prepared *via* the following procedure: Solid *tert*-butyldimethylsilyl chloride (137 g, 909 mmol) was dissolved in dichloromethane (800 mL) and stirred with a magnetic stir bar at 0 °C. 85% 4-chlorobutanol[mass balance THF/HCl] (100 mL, 852 mmol) was added as a solution in dichloromethane (100 mL). The mixture was stirred at 0 °C for 30 minutes, followed by the addition of solid imidazole (71.3 g, 1048 mmol) in a single portion. This mixture was stirred at 0 °C until TLC indicated the alcohol was consumed, typically 1.5 hours. The reaction mixture was filtered through a medium glass frit, and the glassware was rinsed with dichloromethane. The filtrate was concentrated *in vacuo*, and the resulting translucent oil was stored at -20 °C for 12 hours. A colorless precipitate formed at this temperature. Hexanes (300 mL) was added, the suspension was passed through a Celite/$MgSO_4$ plug over a fine frit, and more hexanes (2x200 mL) was passed through the filter. The filtrate was concentrated under reduced pressure to give a colorless, transparent oil which weighed 189 g (848 mmol, 99%).



SI - 1

Silyl ether SI-1.

TLC: R_f = 0.27 (Hexanes). UV inactive. Observed to stain by PMA

Physical Appearance: Colorless oil

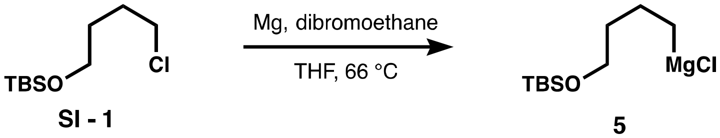
MS (EI, 70 eV): *m/z (relative abundance)* 223.1 (<0.1,), 221.1 (<0.1), 167.0 (3.3), 165.1 (10), 125.0 (38), 123.0 (100), 95.0 (26), 93.0 (67), 75.1 (12), 73.1 (14), 55.1 (22)

^{1}H NMR (400 MHz, $CDCl_3$):

δ 3.64 (t, J = 9.2 Hz, 2H)	3.57 (t, J =10 Hz, 2H)	1.89–1.82 (m, 2H)
1.69–1.62 (m, 2H)	0.89 (s, 9H)	0.05 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$):

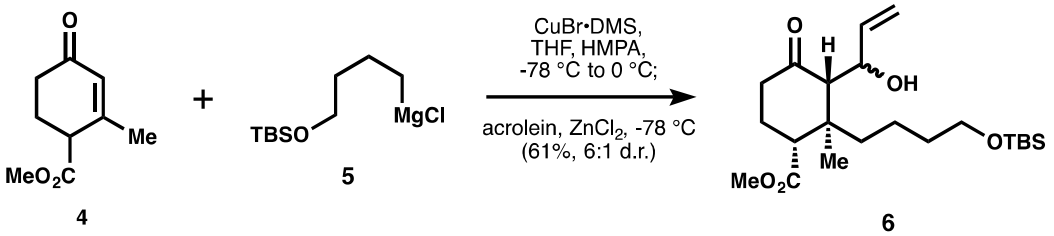
δ 62.34	45.15	30.11
29.37	25.98	18.36
-5.28		



SI - 1

5

Grignard reagent 5. Grignard reagent **5** is commercially available from Sigma-Aldrich, among others. Alternatively, it could be prepared *via* the following procedure: Magnesium turnings (11 g, 452 mmol) were suspended in anhydrous tetrahydrofuran (120 mL) and the mixture was stirred vigorously at 22 °C with a magnetic stir bar. Dibromoethane (2.2 mL, 25.5 mmol) was added in portions over ten minutes and the glassware was rinsed into solution with anhydrous tetrahydrofuran (10 mL). The mixture was stirred vigorously at reflux for 20 minutes, during which time a gas evolved. In a separate flask, alkyl chloride **SI-1** (85.3 g, 383 mmol) was dissolved in anhydrous tetrahydrofuran (120 mL, ca. 230 total mL in solution). This alkyl chloride solution was added to the magnesium suspension portionwise over 30 minutes, and the glassware was rinsed with more anhydrous tetrahydrofuran (20 mL). The reaction was stirred vigorously at reflux for 5 hours, cooled to room temperature, then diluted with anhydrous tetrahydrofuran (120 mL). The remaining solids were allowed to settle, and the supernatant was decanted via cannula to a separate flask. An aliquot was titrated with iodine in anhydrous tetrahydrofuran, typically the reagent is measured between 0.55 and 0.65M.

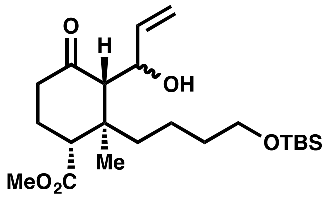


Allylic alcohol 6. Copper(I) Bromide-dimethylsulfide complex (29 g, 141 mmol) was suspended in a mixture of anhydrous tetrahydrofuran (250 mL) and anhydrous HMPA (34.4 mL, 198 mmol). The suspension was cooled to -30 °C and stirred with a magnetic stir bar for 20 minutes. A tetrahydrofuran solution of Grignard reagent **S3** (460 mL, 0.63M, 290 mmol) was added *via* addition funnel, dropwise (at this scale, over 2.5 hours) during which time the temperature was maintained between -25 and -15 °C. Once addition was complete, the reaction was stirred between -30 °C and -20 °C for 30 minutes, then cooled to -78 °C and stirred for 20 additional minutes. A solution of Hagemann's ester **4** (23.2 g, 138 mmol) in anhydrous tetrahydrofuran (460 mL) was prepared in a separate flask, then transferred to a second addition funnel. This solution was added dropwise at -78 °C over 1.5 hours, and the glassware was rinsed with anhydrous tetrahydrofuran (30 mL). The reaction was allowed to warm to 0 °C (this took 4 hours on this scale, but less time on smaller batches). When TLC samples indicated complete consumption of Hagemann's Ester **4**, the reaction mixture was cooled back to -78 °C (typically TLCs indicated consumption at the first timepoint at 0 °C). The reaction was stirred at -78 °C for 15 minutes, during which time another oven-dried addition funnel was installed and charged with a solution of anhydrous zinc chloride (40.8 g, 299 mmol) in anhydrous tetrahydrofuran (450 mL + 50 mL). This solution was added at -78 °C over 30 minutes, and the reaction was stirred at -78 °C for an additional 10 minutes. Acrolein (44 mL, 657 mmol) was added over 5 minutes and the reaction was stirred for 5 additional minutes at -78 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride (2.5 L), and the flask was stirred vigorously while warming to room temperature. Once at room temperature, 1.2 L ethyl acetate was added, followed by an aqueous solution of Na_2EDTA (110 g in 1.6 L of water), these layers were shaken together *(Note 1).* The aqueous layer was separated, while the organic layer and aqueous/organic emulsion were filtered through Celite and a medium frit; this filter was washed with water and ethyl acetate. The (newly separable) layers were separated, the aqueous fractions were combined and extracted with ethyl acetate (3x500 mL). The combined organic fractions were washed with water (2x500 mL) and brine (500 mL). The organic layer was dried with magnesium sulfate, filtered, and stored at 4 °C overnight. The solvent was removed *in vacuo (Note 2)*. The crude mixture was purified by flash column chromatography with 1.2 kg of silica in a 13 cm diameter column, with a gradient of 10% EtOAc/Hexanes –>15% –>20% –> 25% EtOAc/Hexanes. The combined fractions were concentrated *in vacuo* to give a yellow oil (*Note 3)* which weighed 35 g (84.8 mmol, 61%).

Note 1. Addition of disodium EDTA solubilized the otherwise intractable blue-green (presumably copper-related) precipitate, albeit incompletely. Enough precipitate was removed by the EDTA to render filtration possible and the mixture workable.

Note 2. The crude mixture was extremely prone to bumping.

Note 3. The fractions that were collected were typically contaminated with acrolein dimers (<5% by mass); these impurities did not hamper the following reaction.



6

Allylic alcohol 6.

TLC: R$_f$ = 0.29 (25% EtOAc in hexanes). UV inactive. Observed to stain by KMnO$_4$ and anisaldehyde (yellow-green).

Physical Appearance: Faintly yellow oil

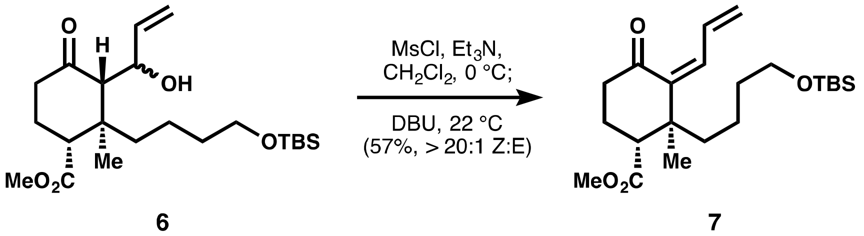
LRMS (ESI) calculated for $C_{22}H_{40}NaO_5Si$ $[M + Na]^+$: 435.3, found 435.2; calculated for $C_{22}H_{39}O_4Si$ $[M - OH]^+$: 395.3, found 395.3; calculated for $C_{19}H_{37}O_4Si$ $[M - CH_2CHCHO + H]^+$ 357.2, found 357.2

^{1}H NMR (600 MHz, CDCl$_3$):

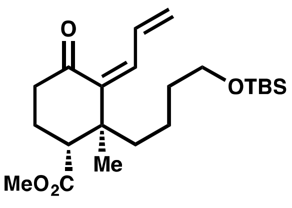
δ 6.07 (ddd, J = 17.3, 10.3, 7.3 Hz, 1H)
5.27 (d, J = 17.1 Hz, 1H)
5.14 (d, 10.3 Hz, 1H)
4.46 (q, J = 6.5 Hz, 1H)
3.71 (s, 3H)
3.58 (t, J = 6.2 Hz, 2H)
3.19 (d, J = 5.0 Hz, 1H)
2.81 (t, J = 5.3 Hz, 1H)
2.72 (ddd, J = 15.7, 8.8, 7.8 Hz, 1H)
2.49 (d, J = 6.6 Hz, 1H)
2.28 (dt, J = 14.9, 6.1 Hz, 1H)
2.08–1.96 (m, 2H)
1.87–1.82 (m, 1H)
1.47–1.42 (m, 2H)
1.35–1.29 (m, 1H)
1.27–1.18 (m, 2H)
1.11 (s, 3H)
0.88 (s, 9H)
0.03 (s, 6H)

^{13}C NMR (150 MHz, CDCl$_3$):

δ 212.82
175.00
139.75
116.39
71.70
62.73
61.97
51.58
46.21
43.09
38.75
36.16
33.18
26.00
24.18
22.76
19.17
18.38
-5.21



Enone 7. Allylic alcohol **6** (35 g, 84.8 mmol) was dissolved in anhydrous dichloromethane (600 mL) and stirred with a magnetic stir bar at 0 °C. Anhydrous triethylamine (30 mL, 215 mmol) was added, followed by the dropwise addition of anhydrous methanesulfonyl chloride (8.5 mL, 109.8 mmol). The reaction was stirred at 0 °C until TLC indicated the allylic alcohol was consumed, typically 2.5 hours. Anhydrous DBU (38 mL, 254 mmol) was added, and the reaction was stirred at 0 °C for an additional 30 minutes. The reaction was warmed to 22 °C and stirred at this temperature for 12 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (300 mL), and the resulting biphasic mixture was stirred vigorously for 30 minutes. The layers were separated, and the aqueous layer was extracted with dichloromethane (3x150 mL). The organic fractions were combined and washed with saturated aqueous ammonium chloride (400 mL), this aqueous layer was re-extracted with dichloromethane (3x100 mL). The organic fractions were combined again and washed with brine (400 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography with 1.2 kg of silica in a 13 cm diameter column, with a gradient of 5% Et_2O/Hexanes –> 10% –> 12.5% –> 15% –> 20 % Et_2O/Hexanes. The combined fractions were concentrated *in vacuo,* and weighed to 18.9 g (47.9 mmol, 57%).



7

Enone 7.

TLC: R_f = 0.34 (20% Et_2O in hexanes). UV active. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Faintly yellow oil

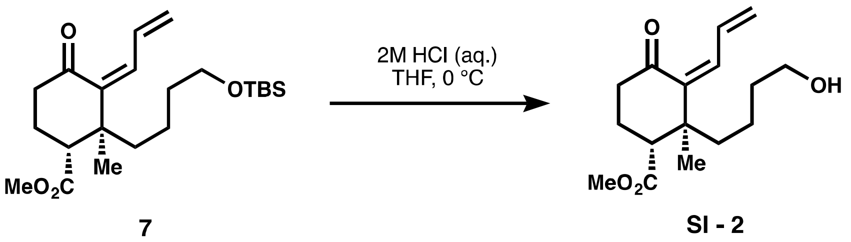
LRMS (ESI) calculated for $C_{22}H_{38}KO_4Si$ $[M + K]^+$: 433.2, found 433.2; calculated for $C_{22}H_{38}NaO_4Si$ $[M + Na]^+$: 417.2, found 417.2; calculated for $C_{22}H_{39}O_4Si$ $[M + H]^+$: 395.3, found 395.2

^{1}H NMR (600 MHz, $CDCl_3$):

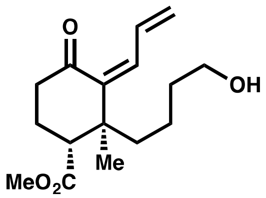
δ 6.88 (dt, J = 16.9, 10.6 Hz, 1H)
6.02 (d, J = 10.9 Hz, 1H)
5.38 (dd, J = 16.9, 1.9 Hz, 1H)
5.28 (dd, J = 10.0, 1.9 Hz, 1H)
3.67 (s, 3H)
3.59–3.55 (m, 2H)
2.86–2.80 (m, 1H)
2.73 (t, J = 4.7 Hz, 1H)
2.42 (ddd, J = 16.0, 5.9, 4.2 Hz, 1H)
2.20–2.14 (m, 1H)
2.07–2.02 (m, 1H)
1.48–1.40 (m, 4H)
1.30–1.25 (m, 2H)
1.15 (s, 3H)
0.88 (s, 9H)
0.03 (s, 6H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 204.22
174.14
144.04
133.65
131.92
122.47
62.83
51.47
48.92
44.09
39.73
39.07
33.14
26.00
22.78
22.09
19.71
18.37
-5.21



Alcohol SI-2. Enone **7** (18.9 g, 47.9 mmol) was dissolved in tetrahydrofuran (750 mL) and stirred with a magnetic stir bar at 0 °C for 20 mintues. Aqueous 2N hydrochloric acid (120 mL) was added over ten minutes, and the reaction was stirred at 0 °C until it was determined by TLC that the starting material was consumed, typically 2 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (500 mL) and the homogeneous mixture was stirred until it reached 22 °C. Ethyl acetate (150 mL) was added, resulting in the aqueous and organic layers separating immediately. The resulting biphasic mixture was stirred vigorously for 20 minutes, and the layers were separated. The aqueous layer extracted with ethyl acetate (2x200 mL) and the organic fractions were combined. The organic layer was washed with water (250 mL), washed with brine (250 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The impurities did not interfere with the subsequent reaction and the crude material was used directly.



SI - 2

Alcohol SI-2.

TLC: $R_f = 0.26$ (25% EtOAc in dichloromethane). UV active. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Yellow oil

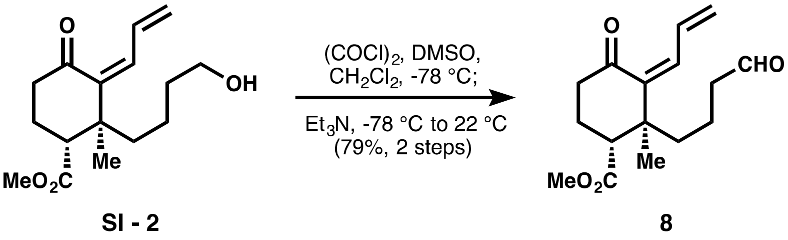
LRMS (ESI) calculated for $C_{16}H_{24}NaO_4$ $[M + Na]^+$: 303.2, found 303.1; calculated for $C_{16}H_{25}O_4$ $[M + H]^+$: 281.2, found 281.1; calculated for $C_{16}H_{23}O_3$ $[M - OH]^+$: 263.2, found 263.1; calculated for $C_{15}H_{21}O_3$ $[M - OCH_3]^+$: 249.1, found 249.1

^{1}H NMR (600 MHz, $CDCl_3$):

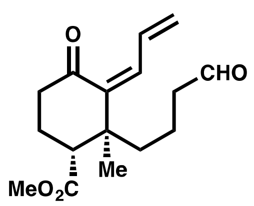
δ 6.87 (ddd, J = 16.9, 10.9, 10.2 Hz, 1H)
6.03 (d, J = 11.0 Hz, 1H)
5.39 (dd, J = 16.9, 1.9 Hz, 1H)
5.29 (dd, J = 10.0, 1.8 Hz, 1H)
3.68 (s, 3H)
3.62 (q, J = 6.2 Hz, 2H)
2.84 (ddd, J = 16.0, 10.6, 7.4 Hz, 1H)
2.73 (t, J = 4.6 Hz, 1H)
2.43 (ddd, J = 16.0, 5.9, 4.2 Hz, 1H)
2.21–2.15 (m, 1H)
2.09–2.04 (m, 1H)
1.54–1.42 (m, 4H)
1.34–1.28 (m, 3H)
1.16 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 204.58
174.06
143.93
133.54
131.99
122.59
62.48
51.52
49.16
44.18
39.50
39.12
32.86
22.86
22.11
19.53



Aldehyde 8. Oxalyl chloride (10 mL, 115 mmol) was dissolved in anhydrous dichloromethane (300 mL) and stirred with a magnetic stir bar at -78 °C for 10 minutes. In a separate flask, a solution of anhydrous dimethylsulfoxide (17 mL, 239 mmol) in anhydrous dichloromethane (150 mL) was prepared; this solution was added to the oxalyl chloride solution dropwise over 20 minutes. Periodically, the reaction vessel's argon balloon was vented to release built up carbon monoxide pressure. The solution was stirred at -78 °C for 20 minutes. In a separate flask, crude alcohol **SI-2** (< 47.9 mmol) was dissolved in anhydrous dichloromethane (300 mL); this solution was added to the reaction mixture dropwise over 20 minutes. The solution was stirred at -78 °C for 30 minutes, after which time anhydrous triethylamine (50 mL, 359 mmol) was added dropwise over 15 minutes. The solution was stirred at -78 °C for 30 minutes, then stirred at 22 °C for one hour. The reaction mixture was quenched with water (700 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (2x250 mL). The organic fractions were combined, washed with brine (400 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography with 750 g of silica in an 8 cm diameter column, with a gradient of 20% EtOAc/Hexanes –> 25% –> 30% EtOAc/Hexanes. The combined fractions were concentrated *in vacuo* to give a faintly yellow oil which weighed 10.5 g (37.7 mmol, 78% over two steps).



8

Aldehyde 8.

TLC: R_f = 0.22 (30% EtOAc in hexanes). UV active. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Faintly yellow oil

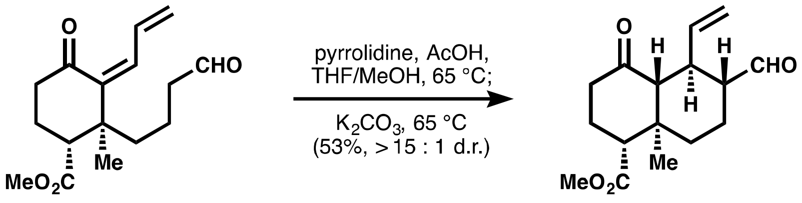
LRMS (ESI) calculated for $C_{16}H_{22}NaO_4$ $[M + Na]^+$: 301.1, found 301.1; calculated for $C_{16}H_{23}O_4$ $[M + H]^+$: 279.2, found 279.1; calculated for $C_{16}H_{21}O_3$ $[M - OH]^+$: 261.1, found 261.1; calculated for $C_{15}H_{21}O_3$ $[M - OCH_3]^+$: 247.1, found 247.1

^{1}H NMR (600 MHz, $CDCl_3$):

δ 9.73 (t, J = 1.3 Hz, 1H)
6.87 (ddd, J = 16.9, 10.9, 10.0 Hz, 1H)
6.06 (d, J = 10.9 Hz, 1H)
5.41 (dd, J = 16.9, 1.9 Hz, 1H)
5.31 (dd, J = 10.0, 1.8 Hz, 1H)
3.68 (s, 3H)
2.84 (ddd, J = 16.0, 10.6, 7.4 Hz, 1H)
2.74 (t, J = 4.7 Hz, 1H)
2.47–2.35 (m, 3H)
2.21–2.15 (m, 1H)
2.10–2.05 (m, 1H)
1.62–1.51 (m, 2H)
1.48–1.38 (m, 2H)
1.17 (s, 3H)

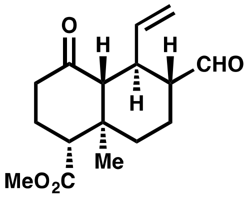
^{13}C NMR (150 MHz, $CDCl_3$):

δ 204.24
201.85
173.89
143.49
133.48
132.29
122.89
51.57
49.02
44.16
43.93
39.16
39.10
22.81
22.07
16.08



8 **9**

Bicycle 9. Aldehyde **8** (10.5 g, 37.7 mmol) was dissolved in a mixture of anhydrous tetrahydrofuran (250 mL) and anhydrous methanol (300 mL) and stirred with a magnetic stir bar at 22 °C. To this solution was added pyrrolidine (6.2 mL, 75.0 mmol), then glacial acetic acid (4.5 mL, 78.6 mmol). The solution was stirred at reflux until TLC indicated the consumption of the enone, typically 2.5 hours. Anhydrous potassium carbonate (26 g, 188 mmol) was added, and the heterogeneous mixture was stirred vigorously at reflux until TLC indicated the complete equilibration of diastereomers, typically 3 hours. At this point, the reaction was cooled to room temperature, and quenched with aqueous 1N hydrochloric acid (500 mL). Ethyl acetate (500 mL) and additional water (400 mL) were added to induce separation. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x175 mL). The organic fractions were combined, and washed with saturated aqueous sodium bicarbonate (2x200 mL), then with brine (200 mL). The solution was dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography with 600 g of silica in an 8 cm diameter column, with a gradient of 15% EtOAc/Hexanes –> 20% –> 25% –> 30% EtOAc/Hexanes. The combined fractions were concentrated *in vacuo* to give a colorless solid which weighed 5.5 g (19.8 mmol, 53%).



9

Bicycle 9.

TLC: R_f = 0.26 (30% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Colorless solid

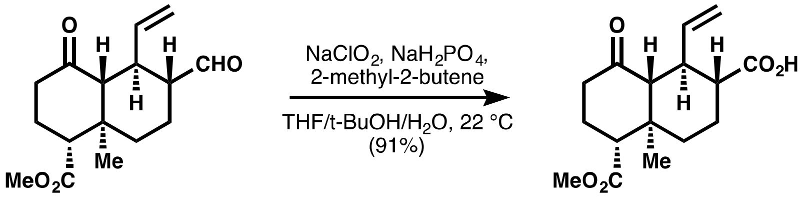
LRMS (ESI) calculated for $C_{16}H_{22}NaO_4$ $[M + Na]^+$: 301.1, found 301.1; calculated for $C_{16}H_{23}O_4$ $[M + H]^+$: 279.2, found 279.1

^{1}H NMR (600 MHz, $CDCl_3$):

δ 9.58 (d, J = 3.1 Hz, 1H)
5.69 (ddd, J = 17.7, 10.3, 7.7 Hz, 1H)
5.10 (dt, J = 17.5, 1.0 Hz, 1H)
5.08 (d, J = 10.5 Hz, 1H)
3.69 (s, 3H)
2.80 (dt, J = 7.7, 11.4 Hz, 1H)
2.72 (dd, J = 12.9, 4.1 Hz, 1H)
2.40–2.37 (m, 2H)
2.34 (d, J = 11.1 Hz, 1H)
2.28–2.19 (m, 2H)
2.15–2.10 (m, 1H)
1.73–1.68 (m, 2H)
1.58–1.49 (m, 2H)
0.92 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 207.99
203.84
173.04
138.94
117.18
61.13
54.03
53.10
51.67
42.10
41.37
37.11
35.12
26.43
20.71
13.59

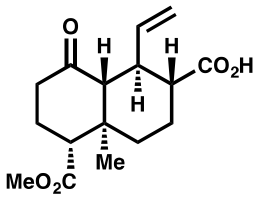


9

10

Carboxylic acid 10. Bicycle **9** (5.5 g, 19.8 mmol) was dissolved in a mixture of *tert*-butanol (300 mL) and tetrahydrofuran (300 mL) and stirred with a magnetic stir bar at 22 °C. 2-methyl-2-butene (85 mL, 802 mmol) was added, followed by monobasic sodium phosphate (9.5 g, 79.2 mmol) as a solution in water (75 mL). Solid sodium chlorite (6.2 g, 68.6 mmol) was added to the mixture in one portion; the reaction was then stirred at 22 °C until TLC indicated consumption of the aldehyde, typically 2.5 hours. The reaction mixture was quenched with water (500 mL) and diluted with ethyl acetate (500 mL). The layers were separated *(Note 4)* and the aqueous layer was extracted with ethyl acetate (3x150 mL). The organic fractions were combined, washed with brine (200 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude solid was purified by azeotropic removal of volatile contaminants with toluene to give a colorless solid which weighed 5.3 g (18.0 mmol, 91%).

Note 4: Further acidification of the aqueous layer beyond what the sodium phosphate naturally causes resulted in marginally improved mass recovery, but an unidentified oxidant was carried into the organic phase. This contaminant interfered with subsequent reactions.



10

Carboxylic acid 10.

TLC: R_f = 0.37 (2% acetic acid, 50% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (yellow).

Physical Appearance: Colorless solid

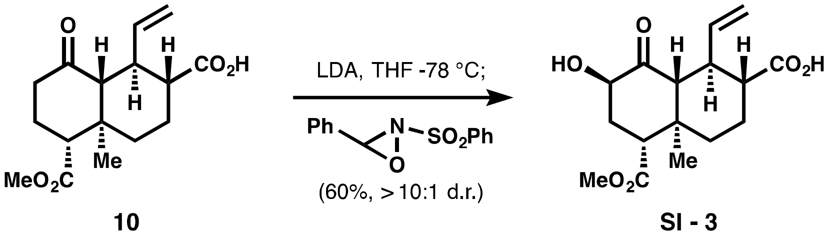
LRMS (ESI) calculated for $C_{16}H_{22}NaO_5$ $[M + Na]^+$: 317.1, found 317.1; calculated for $C_{16}H_{23}O_5$ $[M + H]^+$: 295.2, found 295.1

^{1}H NMR (600 MHz, $CDCl_3$):

δ 5.66 (ddd, J = 17.8, 10.6, 7.7 Hz, 1H)
5.10 (d, J = 17.4 Hz, 1H)
5.01 (d, J = 10.6 Hz, 1H)
3.68 (s, 3H)
2.80 (dt, J = 7.7, 11.5 Hz, 1H)
2.71 (dd, J = 12.9, 4.1 Hz, 1H)
2.38–2.36 (m, 2H)
2.30 (d, J = 11.3 Hz, 1 H)
2.27–2.20 (m, 2H)
2.13–2.08 (m, 1H)
1.88–1.84 (m, 1H)
1.73–1.66 (m, 2H)
1.53 (dt, J = 4.3, 13.9 Hz, 1H)
0.94 (s, 3H)

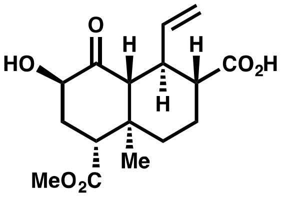
^{13}C NMR (150 MHz, $CDCl_3$):

δ 207.96
180.32
173.12
139.05
116.29
60.93
53.99
51.65
48.40
42.13
41.32
37.58
36.47
26.38
24.12
13.67



10 **SI - 3**

Alcohol SI-3. Anhydrous diisopropylamine (1.5 mL, 10.7 mmol) was dissolved in anhydrous tetrahydrofuran (24 mL), cooled to -78 °C, and stirred with a magnetic stir bar. Freshly titrated *n*-butyllithium as a solution in hexanes (4.65 mL, 2.31 M, 10.7 mmol) was added dropwise over 5 minutes. The solution was stirred at -78 °C for 5 minutes, then 0 °C for 10 minutes, then -78 °C for 10 minutes. In a separate flask, a solution of carboxylic acid **10** (1.5 g, 5.10 mmol) in anhydrous tetrahydrofuran (50 mL) was prepared; this solution was then added dropwise to the LDA solution over 10 minutes *via* cannula. The transfer flask was rinsed with additional anhydrous tetrahydrofuran (10 mL) and added *via* the same cannula. The reaction was stirred at -78 °C for 1 hour. In a separate flask, Davis oxaziridine (1.56 g, 5.97 mmol) was dissolved in anhydrous tetrahydrofuran (25 mL), then added dropwise over 5 minutes *via* cannula. The transfer flask was rinsed with additional anhydrous tetrahydrofuran (10 mL) and added *via* the same cannula. The reaction was stirred at -78 °C for 30 minutes, then warmed to 0 °C for 30 minutes. The reaction was quenched with aqueous 1N hydrochloric acid (75 mL) and diluted with ethyl acetate (75 mL). The layers were separated, the aqueous layer was verified to be pH 2 or lower, and the aqueous layer was then extracted with ethyl acetate (2x50 mL). The organic fractions were combined, washed with a mixture of aqueous 1N hydrochloric acid (50 mL) and brine (50 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography in a 5.5 cm diameter column, with a gradient of 3% AcOH/5% Et_2O/DCM –> 3% AcOH/10% Et_2O/DCM –> 5% AcOH/15%Et_2O/DCM (Caution: these solvent mixtures cause an exotherm when added to silica and rapidly degrade nitrile gloves). The combined fractions were concentrated *in vacuo* to give a colorless solid which weighed 950 mg (3.06 mmol, 60%).



SI - 3

Alcohol SI-3.

TLC: R_f = 0.27 (2% acetic acid, 50% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Colorless solid

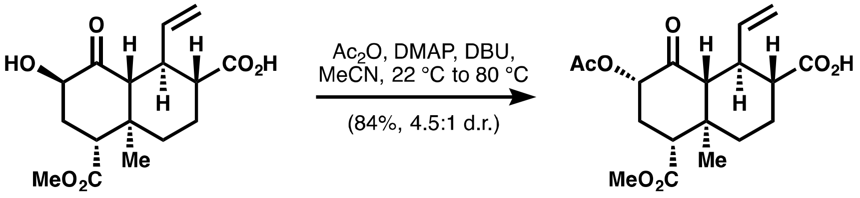
LRMS (ESI) calculated for $C_{16}H_{22}NaO_6$ $[M + Na]^+$: 333.1, found 333.1; calculated for $C_{16}H_{23}O_6$ $[M + H]^+$: 311.1, found 311.1

^{1}H NMR (600 MHz, 5% CD_3OD in CDCl3):

δ 5.60 (ddd, J = 17.8, 10.5, 7.7 Hz, 1H)
5.10 (d, J = 17.3 Hz, 1H)
4.97 (d, J = 10.5 Hz, 1H)
3.93 (t, J = 3 Hz, 1H)
3.65 (s, 3H)
3.08 (d, J = 11.5 Hz, 1H)
3.05 (dd, J = 13.3, 3.8 Hz, 1H)
2.76 (dt, J = 7.8, 11.5 Hz, 1H)
2.29–2.24 (m, 1H)
2.21 (dt, J = 4.1, 11.8 Hz, 1H)
2.07 (dt, J = 14.6, 3.6 Hz, 1H)
1.84–1.80 (m, 1H)
1.68–1.63 (m, 2H)
1.57 (dt, J = 3.7, 14.0 Hz, 1H)
0.87 (s, 3H)

^{13}C NMR (150 MHz, 5% CD_3OD in $CDCl_3$):

δ 210.12
177.17
173.35
138.89
116.15
73.71
54.65
51.58
48.68
48.53
43.11
37.71
36.29
33.96
24.21
13.16

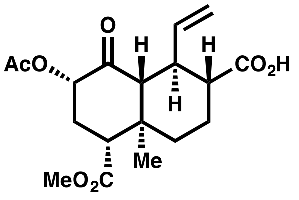


SI - 3 **11**

Acetate 11. Alcohol **SI-3** (791 mg, 2.55 mmol) was dissolved in anhydrous acetonitrile (50 mL). To this solution was added solid 4-(dimethylamino)pyridine (38 mg, 0.31 mmol), followed by acetic anhydride (0.49 mL, 5.19 mmol). The solution was stirred at 22 °C until LCMS indicated complete conversion to the acetate (*Note 5*). After acetylation was deemed complete, anhydrous DBU (2.0 mL, 13.4 mmol) was added, the flask was fitted with an oven-dried reflux condenser and then heated to 80 °C. The epimerization was monitored by NMR (*Note 6*). When an NMR of an aliquot indicated 4.5:1 dr, the flask was cooled to 22 °C and saturated aqueous sodium bicarbonate (50 mL) was added. The mixture was stirred at 22 °C for 1 hour. The mixture was diluted with ethyl acetate (50 mL) and acidified with aqueous 1N hydrochloric acid (75 mL). The layers were separated, the aqueous layer was verified to be pH 2 or lower, and the aqueous layer was then extracted with ethyl acetate (2x50 mL). The organic fractions were combined, washed with a mixture of aqueous 1N hydrochloric acid (25 mL) and brine (25 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography in a 5.5 cm diameter column, with a gradient of 2% AcOH/55% Et$_2$O/Hexanes –> 2% AcOH/65% Et$_2$O/Hexanes–>3% AcOH/75% Et$_2$O/Hexanes. The combined fractions were concentrated *in vacuo* to give a colorless solid which weighed 755 mg (2.14 mmol, 84%).

Note 5: LCMS samples prepared in methanol typically indicate a mixture of the acetate/carboxylic acid and the acetate/acid anhydride.

Note 6: While optimized TLC conditions (3% acetic acid & 70% diethyl ether in hexanes) were able to separate the diastereomers, these conditions were suboptimal for monitoring reaction progress.



11

Acetate 11.

TLC: $R_f = 0.31$ (2% acetic acid, 50% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (brown).

Physical Appearance: Colorless solid

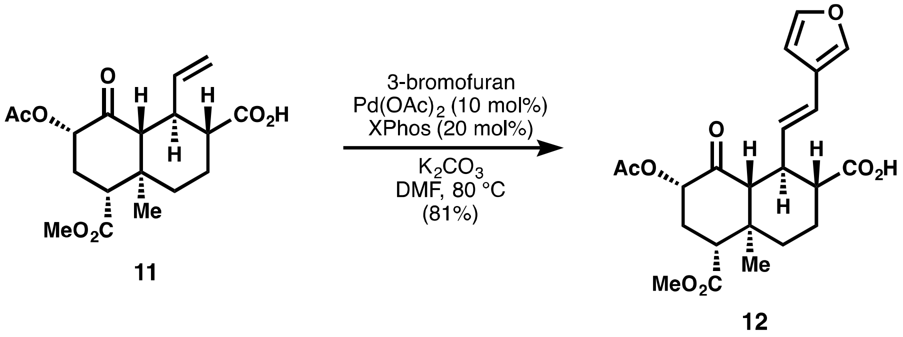
LRMS (ESI) calculated for $C_{18}H_{24}NaO_7$ $[M + Na]^+$: 375.1, found 375.1; calculated for $C_{18}H_{28}NO_7$ $[M + NH_4]^+$: 370.2, found 370.2; calculated for $C_{18}H_{25}O_7$ $[M + H]^+$: 353.2, found 353.1; calculated for $C_{16}H_{21}O_5$ $[M - CH_3CO_2]^+$: 293.1, found 293.1

^1H NMR (600 MHz, $CDCl_3$):

δ 5.62 (ddd, J = 17.6, 10.5, 7.6 Hz, 1H)
5.16 (dd, J = 12.2, 7.6 Hz, 1H)
5.12 (d, J = 17.4 Hz, 1H)
5.05 (d, J = 10.6 Hz, 1H)
3.71 (s, 3H)
2.87 (dt, J = 7.7, 11.3 Hz, 1H)
2.79 (dd, J = 13.2, 4.0 Hz, 1H)
2.39–2.35 (m, 1H)
2.32–2.24 (m, 3H)
2.14 (s, 3H)
1.91–1.88 (m, 1H)
1.78–1.67 (m, 2H)
1.54 (dt, J = 4.0, 13.3 Hz, 1H)
0.93 (s, 3H)

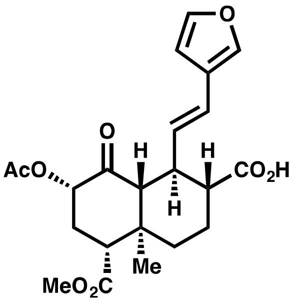
^{13}C NMR (150 MHz, $CDCl_3$):

δ 201.15
179.14
171.73
169.90
137.82
117.17
75.02
58.94
52.07
51.93
48.07
42.23
37.48
36.53
31.65
24.20
20.70
13.79



Furan 12. A solution of acetate **11** (357 mg, 1.01 mmol) in anhydrous DMF (13 mL) was degassed by bubbling with Argon while sonicating for 10 minutes. 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, or 'XPhos' (100 mg, 0.21 mmol) was added, followed by anhydrous potassium carbonate (554 mg, 4.01 mmol). Palladium(II) acetate (25 mg, 0.11 mmol) was added and the solution was stirred at 22 °C for 10 minutes. 3-bromofuran (0.22 mL, 2.45 mmol) was added, and the solution was heated to 80 °C *(Note 7)* and stirred with a magnetic stir bar until LCMS indicated consumption of the starting material, typically 2.5 hours. When the reaction was deemed complete, the reaction was cooled to 22 °C, quenched with aqueous 1N hydrochloric acid (25 mL) and diluted with ethyl acetate (20 mL). The layers were separated, the aqueous layer was verified to be pH 2 or lower, and the aqueous layer was then extracted with ethyl acetate (2x25 mL). The organic fractions were combined, washed with aqueous 1N hydrochloric acid (4x15 mL), then washed with a mixture of aqueous 1N hydrochloric acid (15 mL) and brine (15 mL). It was then dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography in a 4.5 cm diameter column, with a gradient of 3% AcOH/25% EtOAc/Hexanes –> 3% AcOH/35% EtOAc/Hexanes –> 5% AcOH/40% EtOAc/Hexanes. The combined fractions were concentrated *in vacuo* to give a colorless solid which weighed 344 mg (0.822 mmol, 81%).

Note 7. A sufficiently long reflux condenser is important: hot DMF vapor can leech sulfur-containing compounds from the rubber septum used to seal the reaction vessel. These compounds can cause catalyst death.



12

Furan 12.

TLC: R_f = 0.29 (2% acetic acid, 50% EtOAc in hexanes). UV active. Observed to stain by $KMnO_4$ and anisaldehyde (dark violet).

Physical Appearance: Colorless solid

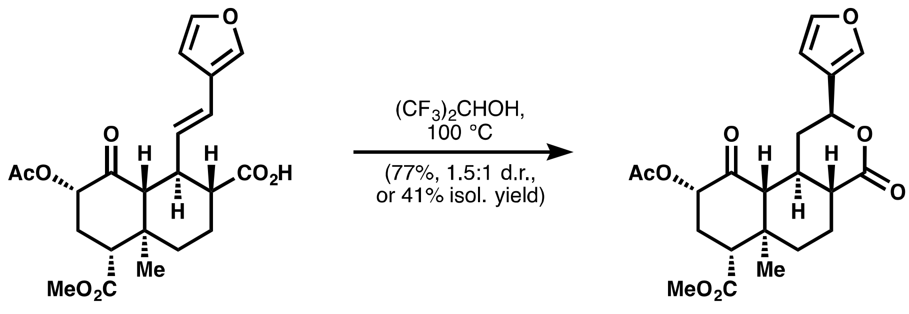
LRMS (ESI) calculated for $C_{22}H_{26}NaO_8$ $[M + Na]^+$: 441.2, found 441.1; calculated for $C_{22}H_{27}O_8$ $[M + H]^+$: 419.2, found 419.1; calculated for $C_{20}H_{23}O_6$ $[M – CH_3CO_2]^+$: 359.1, found 359.1

^{1}H NMR (600 MHz, $CDCl_3$):

δ 7.32 (s, 1H)
7.28 (t, J = 1.4 Hz, 1H)
6.40 (d, 1.7 Hz, 1H)
6.33 (d, J = 16.0 Hz, 1H)
5.61 (dd, J = 15.9, 7.9 Hz, 1H)
5.19 (dd, J = 12.2, 7.6 Hz, 1H)
3.71 (s, 3H)
2.98 (dt, J = 7.9, 11.3 Hz, 1H)
2.79 (dd, J = 13.3, 4.0 Hz, 1H)
2.39 (ddd, J = 13.4, 7.5, 4.0 Hz, 1H)
2.33–2.27 (m, 3H)
2.12 (s, 3H)
1.91 (dq, J = 13.6, 3.4 Hz, 1H)
1.79–1.70 (m, 2H)
1.59–1.53 (dt, J = 4.0, 13.3 Hz, 1H)
0.96 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

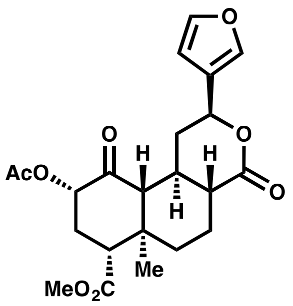
δ 201.02
178.16
171.71
169.78
143.22
140.36
128.67
123.93
122.05
107.65
74.91
59.15
52.10
51.94
48.10
42.29
37.50
36.06
31.80
24.25
20.73
13.83



12 **20-nor-salvinorin A**

20-nor-salvinorin A. An oven-dried 100 mL pressure tube equipped with a magnetic stir bar was charged with furan **12** (344 mg, 0.822 mmol) as a solution in anhydrous hexafluoroisopropanol (12 mL). The reaction vessel was sealed and heated to 100 °C for 18 hours. An aliquot was taken and analyzed by NMR; it indicated a mixture of 49% 20-nor-salvinorin A, 30% of the C-12 epimer, and 21% of the uncyclized alkene (*Note 8*). The reaction was cooled to 22 °C, diluted with ethyl acetate (30 mL), and washed with aqueous 1N hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2x20 mL). The organic fractions were combined, washed with a mixture of aqueous 1N hydrochloric acid (15 mL) and brine (15 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo.* The crude mixture was purified by flash column chromatography in a 4.5 cm diameter column, with a gradient of 35% EtOAc/Hexanes –> 45% EtOAc/Hexanes. The combined fractions were concentrated *in vacuo* to give a colorless solid weighing 140 mg (.335 mmol, 41%). The fractions contaminated with the C-12 epimer and unreacted alkene could be concentrated to 200 mg and resubjected to the reaction conditions.

Note 8: The equilibrium ratio is around 45% 20-nor-salA : 41% 12-epi-20-nor-salA : 9% alkene **12**. The reaction was typically halted before reaching full equilibration as the amount of desired product would not increase.



20-nor-salvinorin A

20-nor-salvinorin A.

TLC: R_f = 0.28 (45% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (violet).

Physical Appearance: Colorless solid

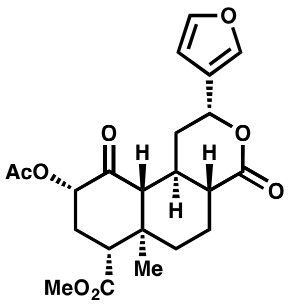
LRMS (ESI) calculated for $C_{22}H_{26}NaO_8$ $[M + Na]^+$: 441.2, found 440.9; calculated for $C_{22}H_{27}O_8$ $[M + H]^+$: 419.2, found 418.9; calculated for $C_{20}H_{23}O_6$ $[M - CH_3CO_2]^+$: 359.1, found 358.9

^{1}H NMR (600 MHz, $CDCl_3$):

δ 7.41 (s, 1H)
7.37 (s, 1H)
6.37 (s, 1H)
5.40 (dd, J = 11.8, 3.5 Hz, 1H)
5.16 (dd, J = 12.2, 7.6 Hz, 1H)
3.71 (s, 3H)
2.79 (dd, J = 13.0, 4.0 Hz, 1H)
2.44 (d, J = 13.3 Hz, 1H)
2.39–2.34 (m, 1H)
2.32–2.21 (m, 4H)
2.15 (s, 3H)
2.04–1.99 (m, 1H)
1.82–1.80 (m, 1H)
1.59–1.43 (m, 3H)
0.90 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 202.14
171.54
171.36
169.95
143.59
139.60
124.95
108.39
75.17
74.98
59.65
51.98
51.89
45.07
42.38
37.90
34.73
31.39
30.89
21.63
20.59
13.57



12-epi-20-nor-salvinorin A

12-epi-20-nor-salvinorin A.

TLC: $R_f = 0.17$ (45% EtOAc in hexanes). UV inactive. Observed to stain by $KMnO_4$ and anisaldehyde (violet).

Physical Appearance: Colorless solid

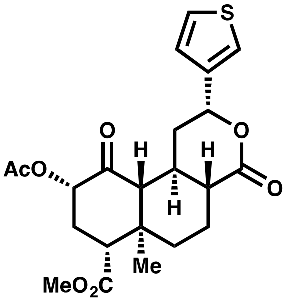
LRMS (ESI) calculated for $C_{22}H_{26}NaO_8$ $[M + Na]^+$: 441.2, found 440.9; calculated for $C_{22}H_{27}O_8$ $[M + H]^+$: 419.2, found 418.9; calculated for $C_{20}H_{23}O_6$ $[M - CH_3CO_2]^+$: 359.1, found 358.9

^1H NMR (600 MHz, $CDCl_3$):

δ 7.55 (q, J = 1.0 Hz, 1H)
7.41 (t, J = 1.7 Hz, 1H)
6.47 (dd, J = 1.8, 0.8 Hz, 1H)
5.39 (dd, J = 7.0, 5.8 Hz, 1H)
5.19 (dd, J = 12.4, 7.6 Hz, 1H)
3.72 (s, 3H)
2.81 (dd, J = 13.1, 4.1 Hz, 1H)
2.55 (ddd, J = 14.3, 7.4, 6.7 Hz, 1H)
2.40–2.31 (m, 3H)
2.29–2.20 (m, 2H)
2.17 (s, 3H)
2.13–2.10 (m, 1H)
1.81–1.79 (m, 1H)
1.64–1.54 (m, 3H)
0.87 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 202.01
172.90
171.55
170.03
143.75
139.99
124.44
108.99
74.97
71.94
61.61
52.01
52.00
42.88
42.58
37.53
33.00
31.32
28.29
21.46
20.65
13.60



13

Thiophene analog 13. Prepared from intermediate **11** by procedures analogous to those reported above.

TLC: R_f = 0.21 (45% EtOAc in hexanes). UV inactive. Observed to stain by anisaldehyde (violet).

Physical appearance: Colorless solid

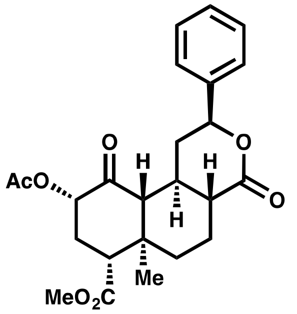
LRMS (ESI) calculated for $C_{22}H_{26}NaO_7S$ $[M + Na]^+$: 457.1, found 456.9; calculated for $C_{20}H_{23}O_5S$ $[M - CH_3CO_2]^+$: 375.1, found 374.9

^{1}H NMR (600 MHz, CDCl$_3$):

δ 7.37 (dt, J = 2.7, 1.3 Hz, 1H)
7.32 (dd, J = 5.0, 2.9 Hz, 1H)
7.12 (dd, J = 5.1, 1.3 Hz, 1H)
5.46 (dd, J = 8.2, 5.5 Hz, 1H)
5.20 (dd, J = 12.5, 7.6 Hz, 1H)
3.73 (s, 3H)
2.82 (dd, J = 13.1, 4.1 Hz, 1H)
2.63 (ddd, J = 15.1, 8.5, 7.2 Hz, 1H)
2.40–2.29 (m, 3H)
2.25–2.23 (m, 2H)
2.16 (s, 3H)
2.14–2.11 (m, 1H)
1.81–1.79 (m, 1H)
1.68–1.63 (m, 1H)
1.60–1.57 (m, 2H)
0.86 (s, 3H)

^{13}C NMR (150 MHz, CDCl$_3$):

δ 202.00
173.09
171.56
170.04
140.04
126.62
126.02
122.40
74.98
74.68
61.84
52.02 (2C)
42.71
42.63
37.53
33.70
31.32
28.36
21.48
20.64
13.61



14

Benzene analog 14. Prepared from intermediate **11** by procedures analogous to those reported above.

TLC: $R_f = 0.37$ (45% EtOAc in hexanes). UV inactive. Observed to stain by anisaldehyde (blue) and faintly by $KMnO_4$.

Physical appearance: Colorless solid

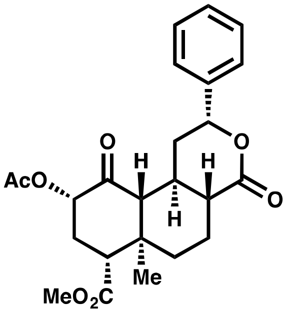
LRMS (ESI) calculated for $C_{24}H_{28}NaO_7$ $[M + Na]^+$: 451.2, found 450.9; calculated for $C_{22}H_{25}O_5$ $[M - CH_3CO_2]^+$: 369.2, found 368.9

^{1}H NMR (600 MHz, $CDCl_3$):

δ 7.35–7.28 (m, 5H)
5.44 (dd, J = 11.9, 3.7 Hz, 1H)
5.13 (dd, J = 12.1, 8.2 Hz, 1H)
3.73 (s, 3H)
2.79 (dd, J = 12.9, 4.3 Hz, 1H)
2.46 (ddd, J = 13.6, 3.9, 2.5 Hz, 1H)
2.40–2.29 (m, 4H)
2.20 (d, J = 10.7 Hz, 1H)
2.15 (s, 3H)
2.09–2.05 (m, 1H)
1.85–1.83 (m, 1H)
1.59–1.56 (m, 2H)
1.44 (dt, J = 13.5, 11.8 Hz, 1H)
0.93 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

δ 202.10
171.61
171.59
169.94
139.69
128.61
128.40
125.69
82.13
75.01
59.76
52.02
51.98
45.30
42.45
38.02
36.64
31.42
31.17
21.73
20.61
13.64



12-*epi*-**14**

Benzene analog 12-*epi*-14. Prepared from intermediate **11** by procedures analogous to those reported above.

TLC: $R_f = 0.24$ (45% EtOAc in hexanes). UV inactive. Observed to stain by anisaldehyde (blue).

Physical appearance: Colorless solid

LRMS (ESI) calculated for $C_{24}H_{28}NaO_7$ $[M + Na]^+$: 451.2, found 450.9; calculated for $C_{22}H_{25}O_5$ $[M – CH_3CO_2]^+$: 369.2, found 368.9

^{1}H NMR (600 MHz, $CDCl_3$):

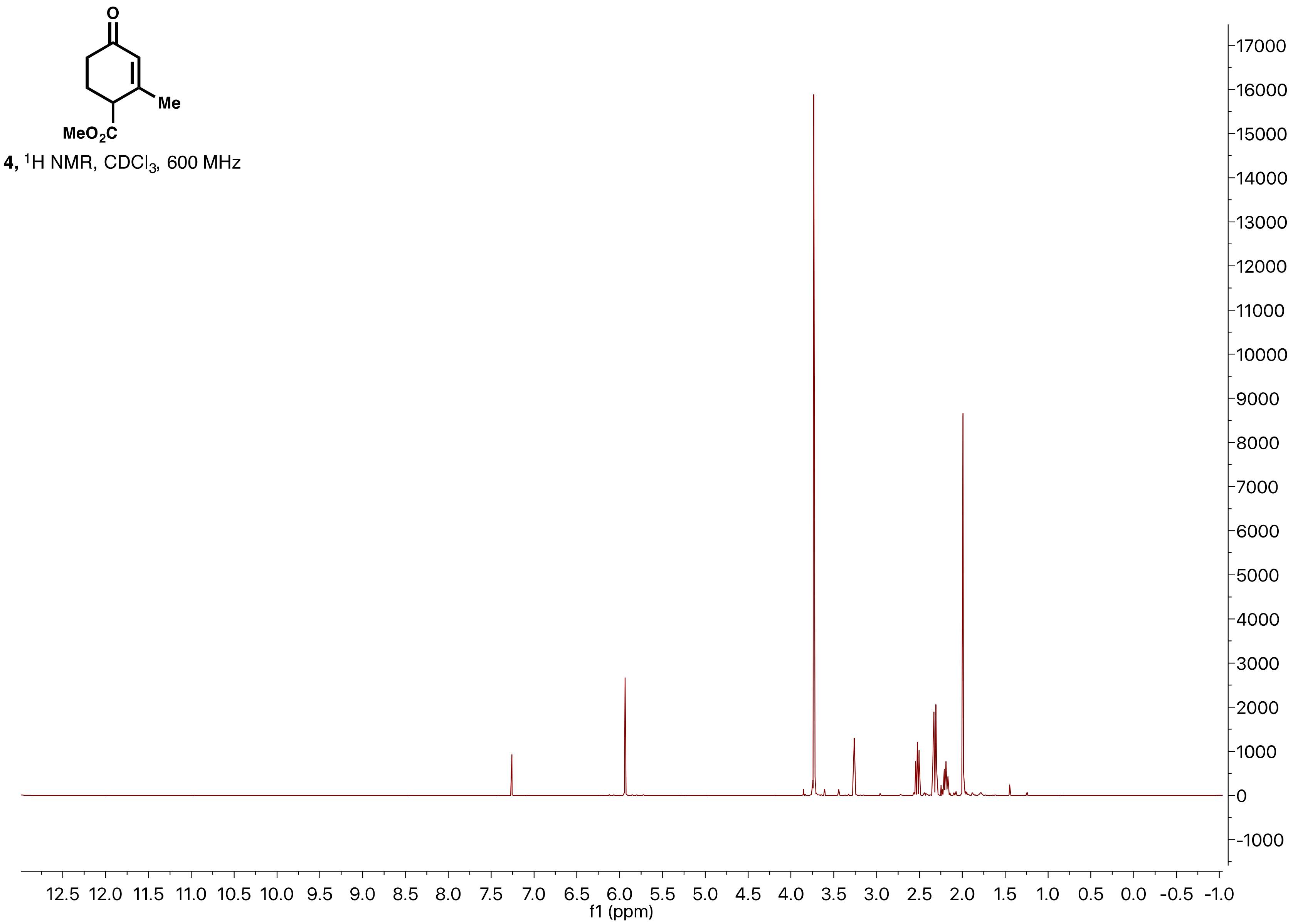
δ 7.37 (m, 5H)
5.30 (dd, J = 10.3, 5.2 Hz, 1H)
5.19 (dd, J = 12.1, 7.6 Hz, 1H)
3.73 (s, 3H)
2.83 (dd, J = 13.1, 4.1 Hz, 1H)
2.55 (ddd, J = 14.9, 10.3, 8.9 Hz, 1H)
2.44 (d, J = 10.9 Hz, 1H)
2.40–2.31 (m, 3H)
2.25–2.20 (m, 1H)
2.13 (s, 3H)
2.13–2.09 (m, 1H)
1.83–1.80 (m, 1H)
1.70–1.58 (m, 3H)
0.88 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$):

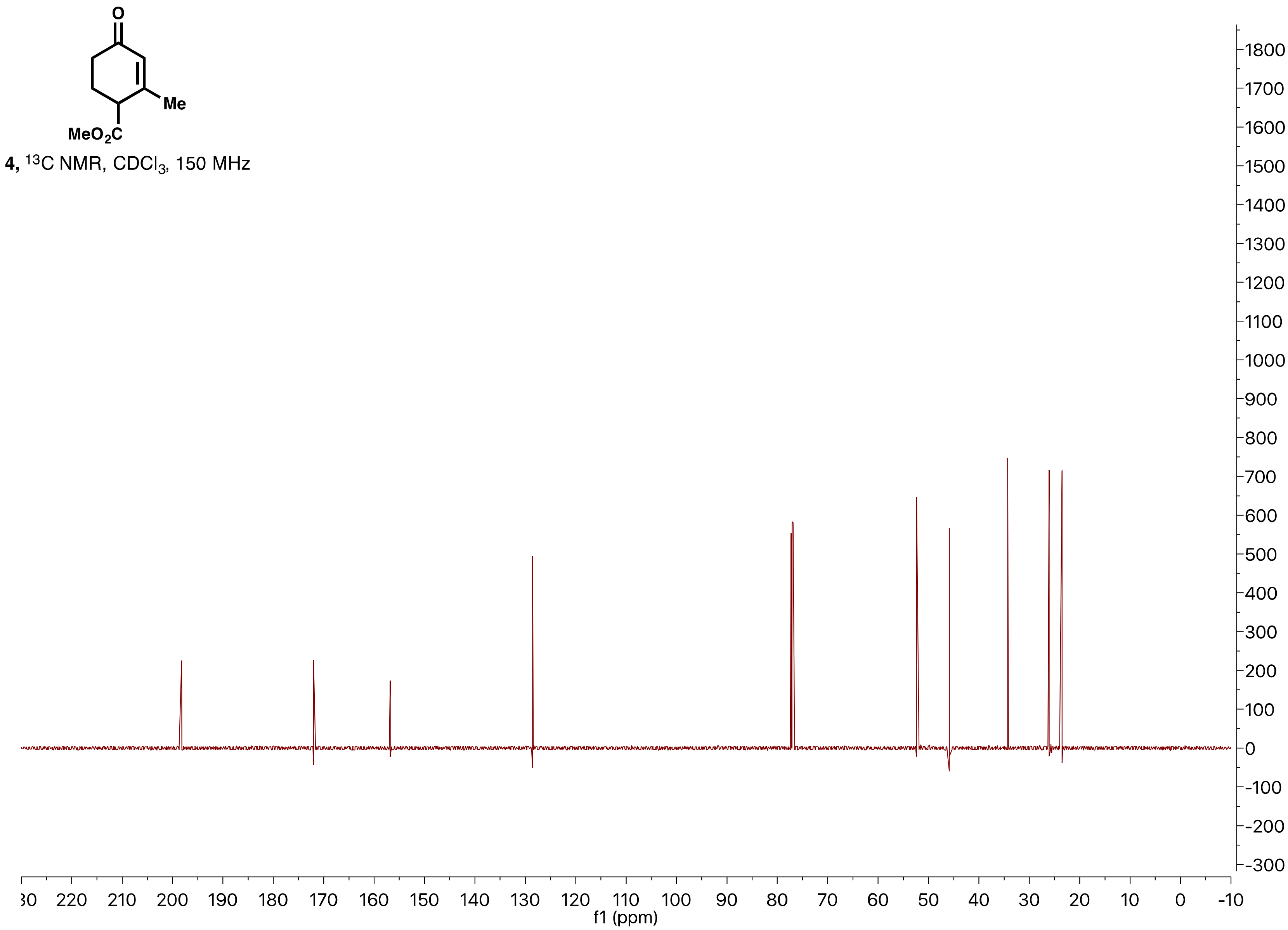
δ 201.78
173.78
171.57
170.05
138.78
128.66
128.42
126.11
77.63
74.98
62.41
52.04
52.03
42.71
41.87
37.41
35.35
31.28
28.53
21.50
20.61
13.61

Table S1. Summary of recorded binding affinities, selectivity ratios, and measured effective concentrations for inhibition of cAMP for known κ-OR agonists and novel analogs (see Methods section)

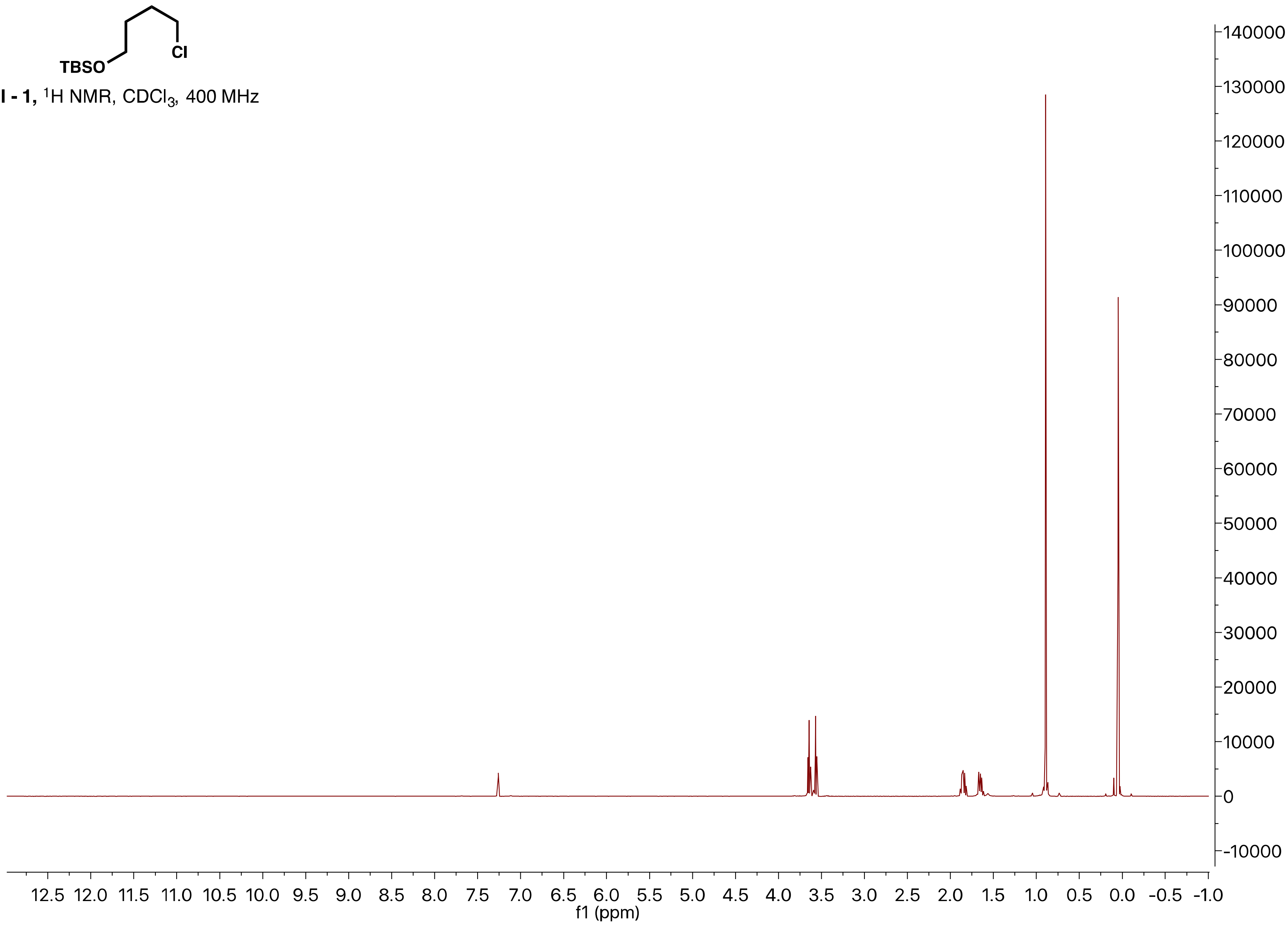
Compound	Binding Affinities (K_i, nM)			K_i ratios		Inhibition of cAMP	
	KOR	MOR	DOR	MOR/ KOR	DOR/ KOR	EC_{50} (nM)	E_{MAX} (%)
U69,593	1.17 ± 0.36	5176 ± 345	>10,000	4424	>153,177	5.7 ± 0.9	100
SalA	0.13± 0.07	616 ± 251	3417 ± 882	4741	26,285	0.95 ± 0.31	99 ± 1
20-nor-**1**	1.08 ± 0.36	7994 ± 2247	>10,000	7402	>10,933	6.1 ± 1.7	99 ± 2
12-epi-20-nor-**1**	2.13 ± 1.20	5113 ± 1547	3628 ± 913	2400	1703	84 ± 13	102 ± 1
13	0.76 ± 0.25	2841 ± 422	2367 ± 748	3738	3114	23 ± 5.9	100 ± 0.3
14	0.53 ± 0.20	4546 ± 516	>10,000	8577	>23,206	15 ± 5.8	95 ± 3
12-epi-**14**	0.79 ± 0.22	5683 ± 1543	5171 ± 633	7194	6546	15 ± 3.4	101 ± 1



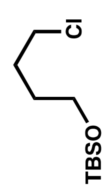
4, ^{1}H NMR, $CDCl_3$, 600 MHz



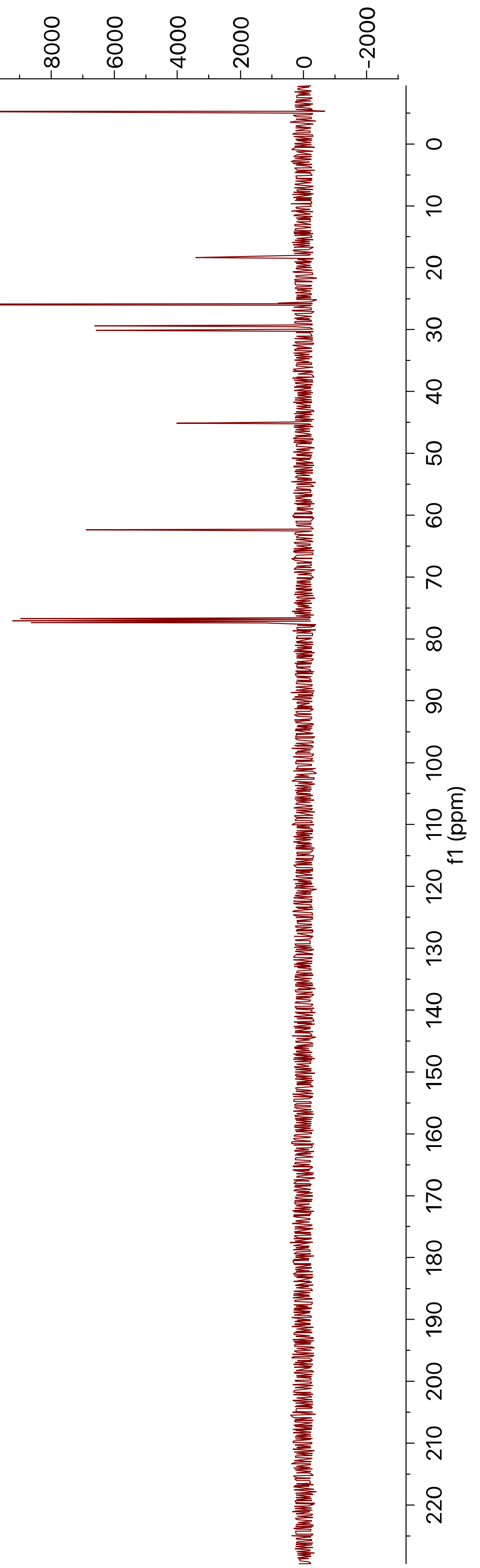
4, ^{13}C NMR, CDCl$_3$, 150 MHz

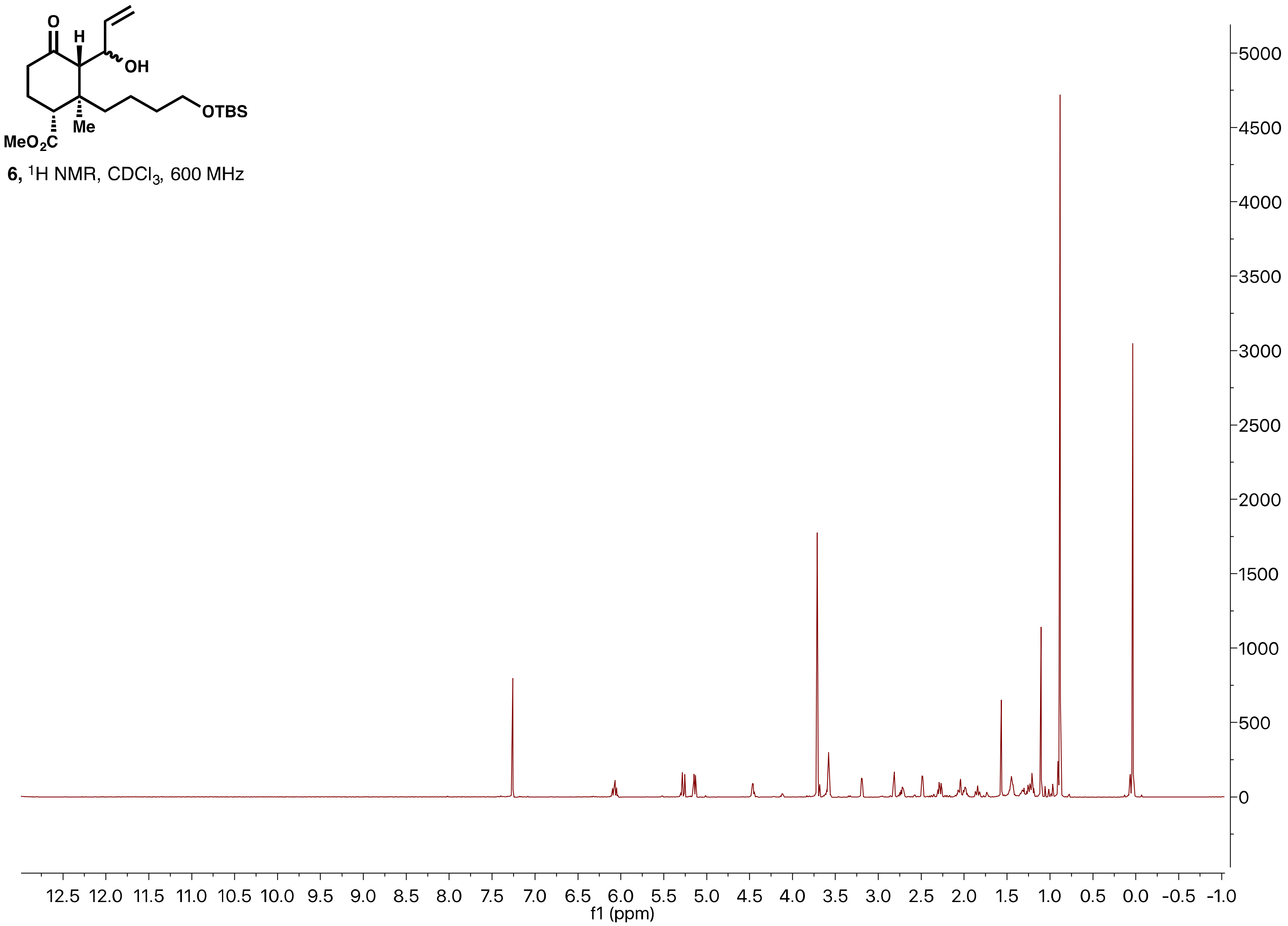


SI - 1, ^{1}H NMR, $CDCl_3$, 400 MHz

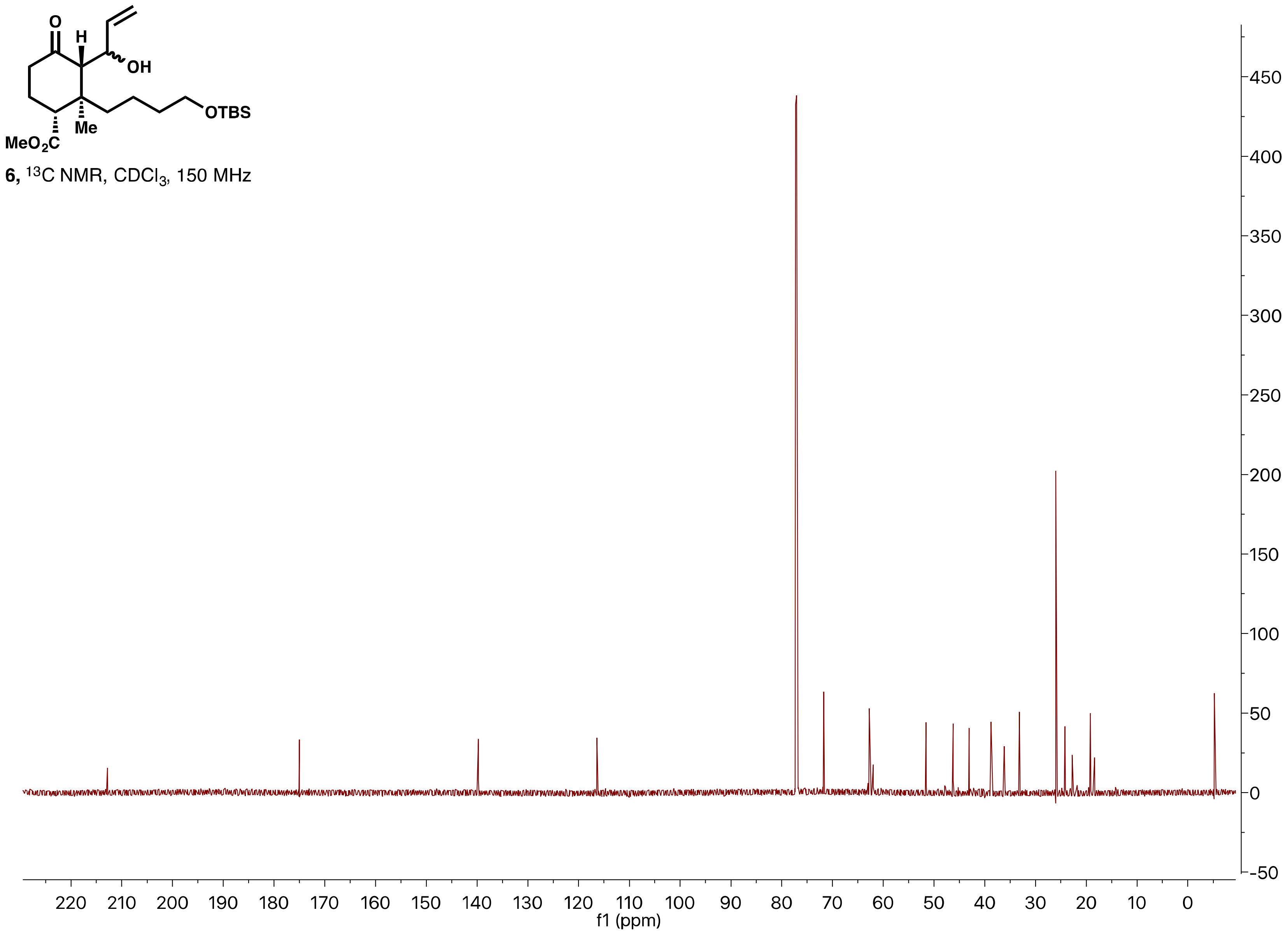


SI - 1, ^{13}C NMR, CDCl$_3$, 100 MHz

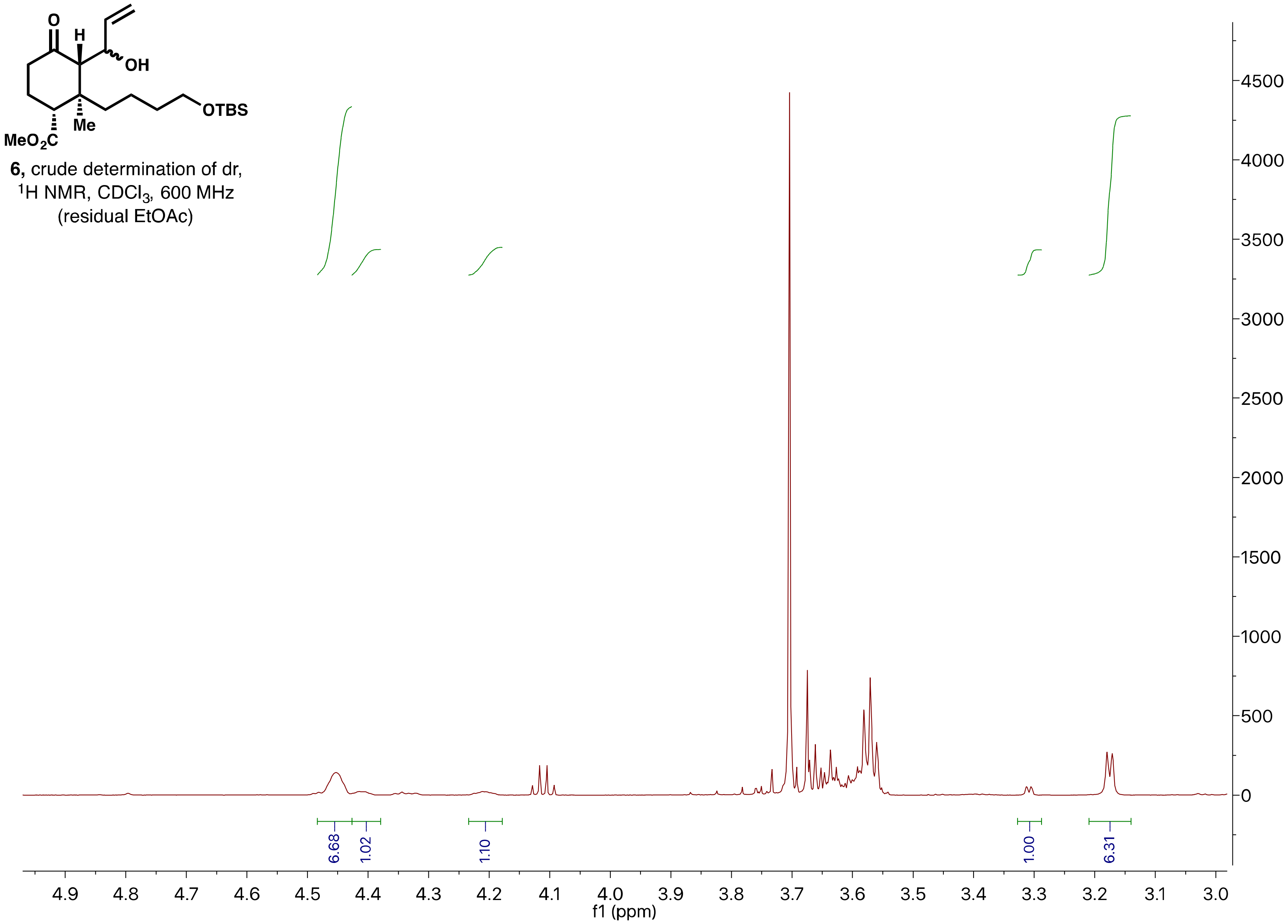




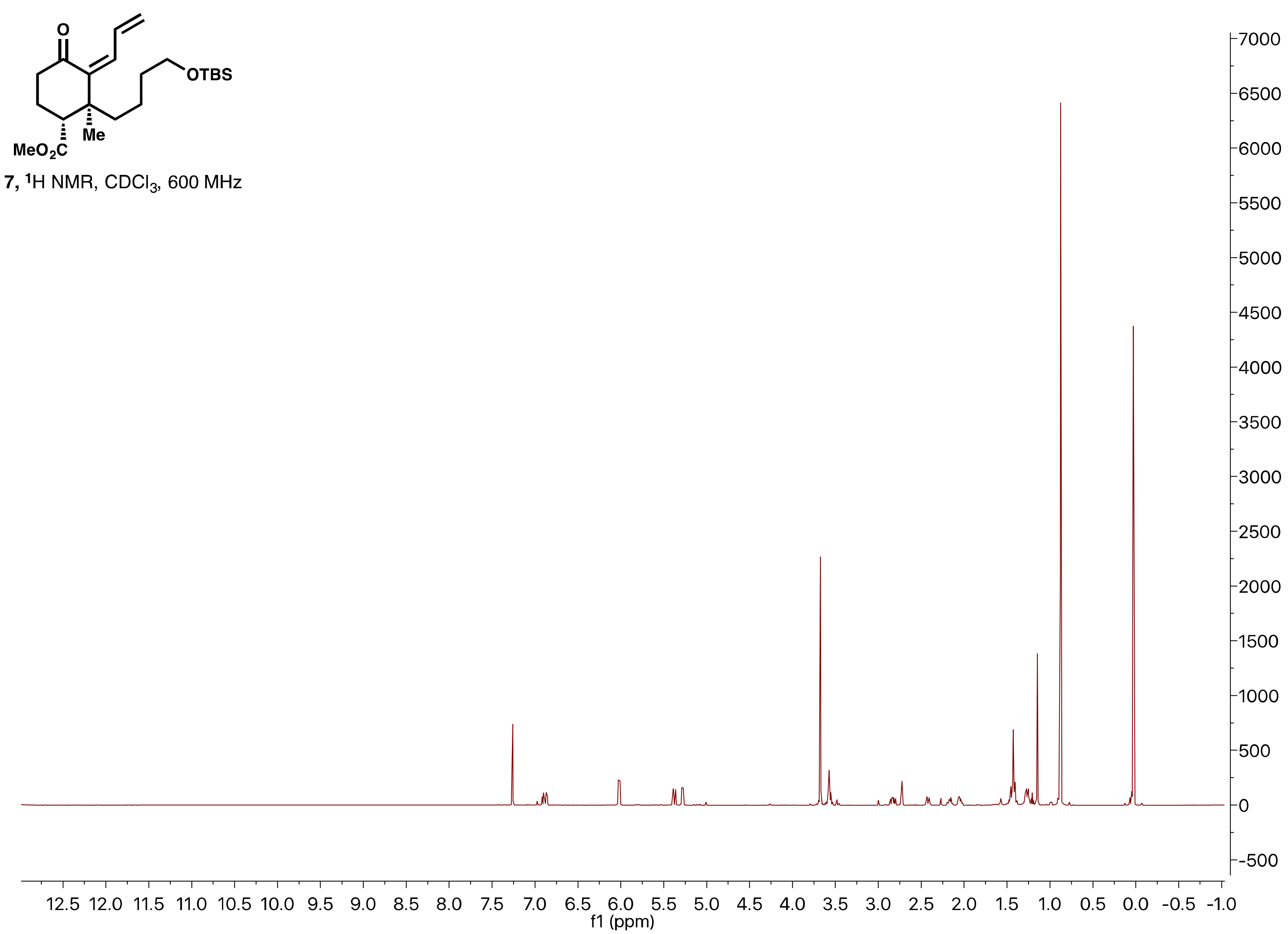
6, ^{1}H NMR, $CDCl_3$, 600 MHz



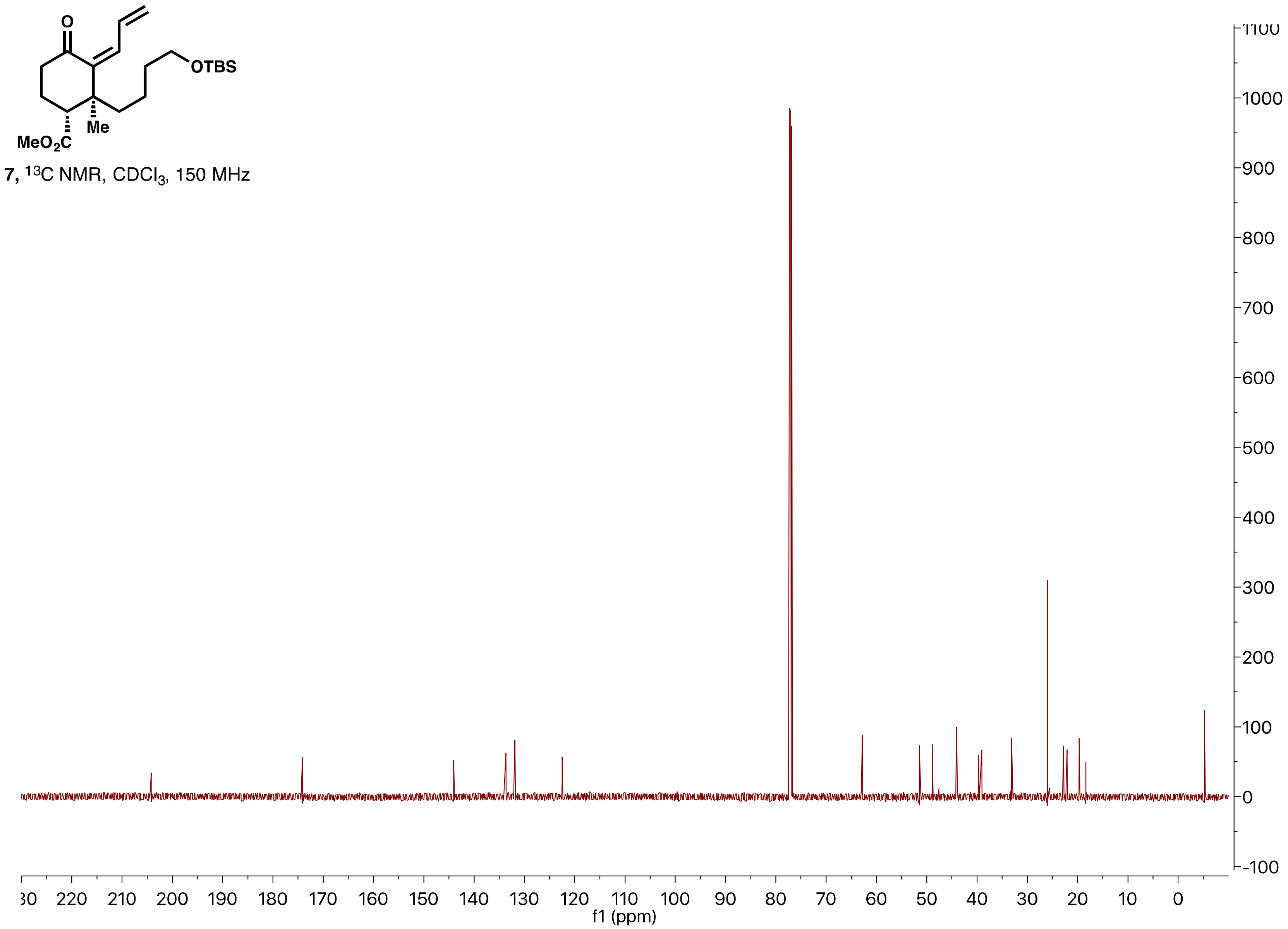
6, ^{13}C NMR, $CDCl_3$, 150 MHz



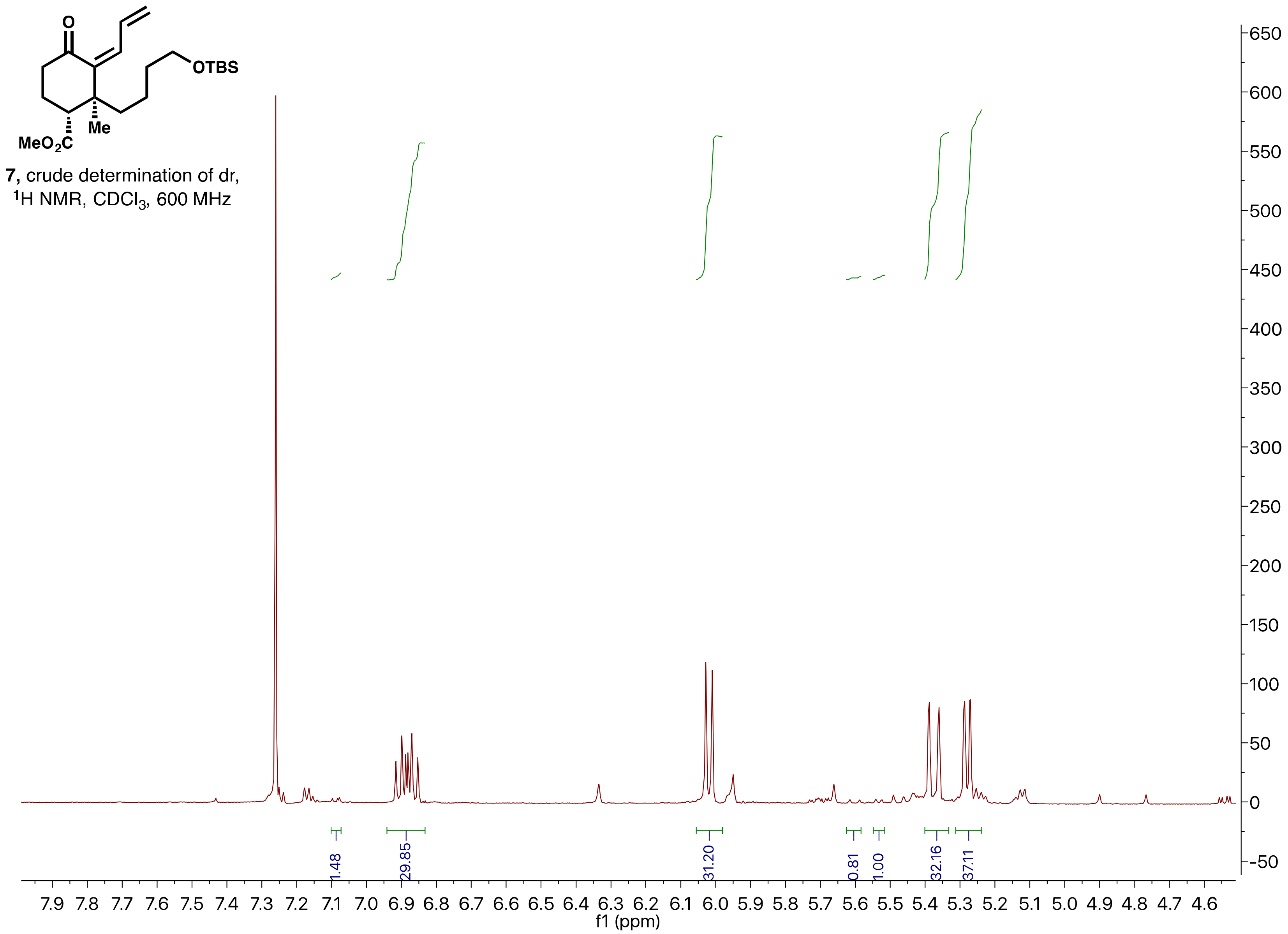
6, crude determination of dr,
^{1}H NMR, $CDCl_3$, 600 MHz
(residual EtOAc)



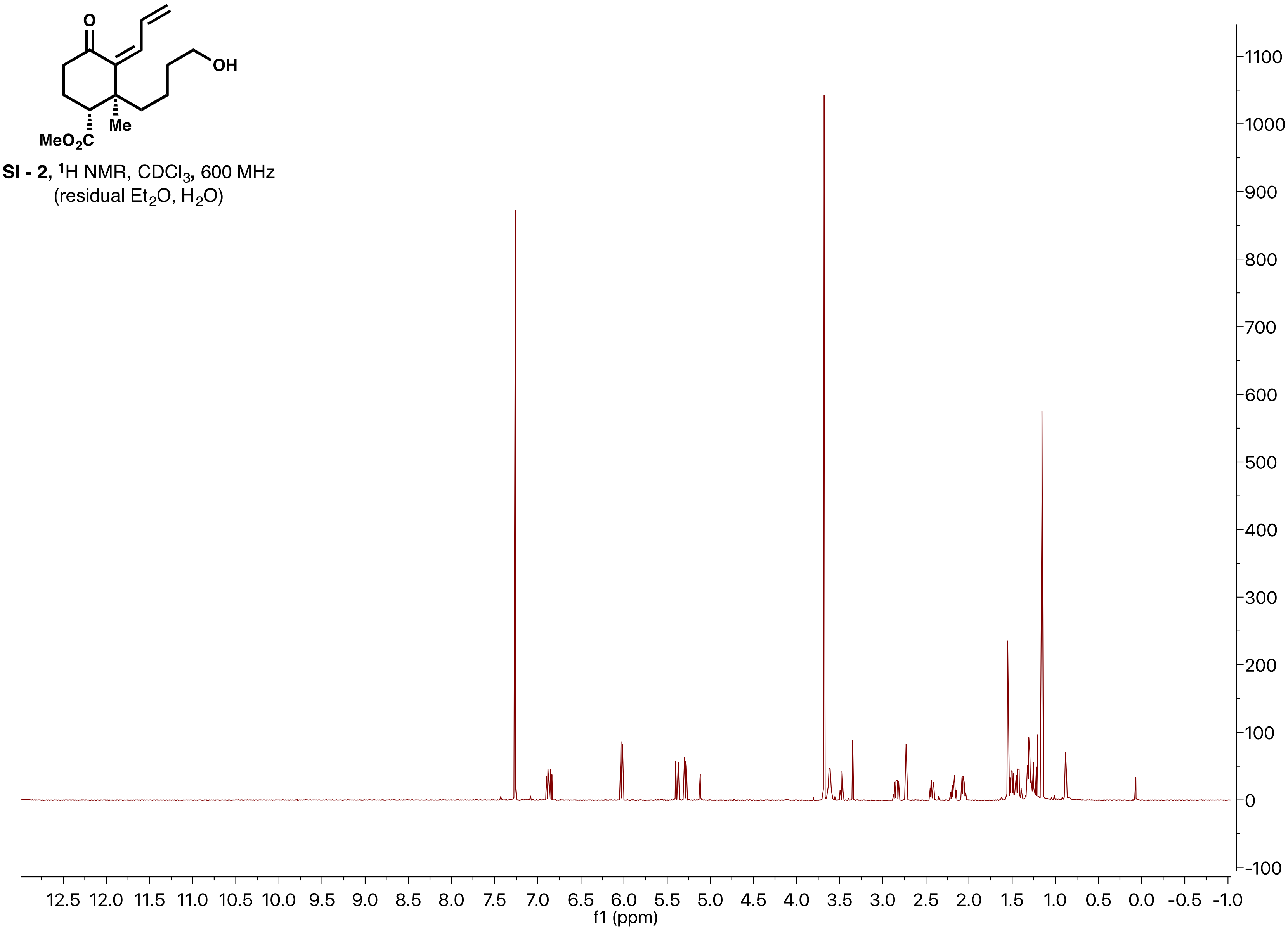
7, ^{1}H NMR, $CDCl_3$, 600 MHz



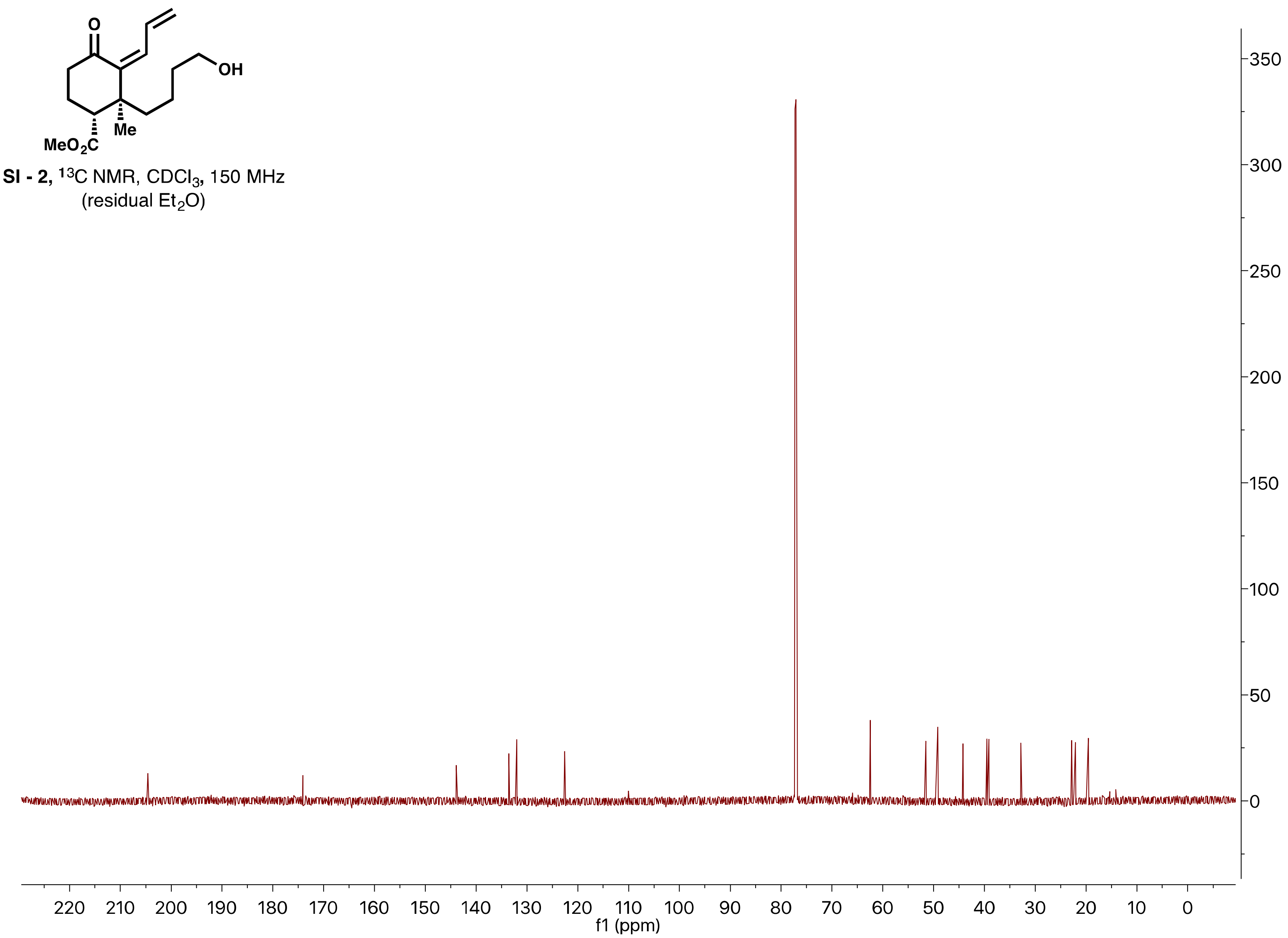
7, ^{13}C NMR, CDCl$_3$, 150 MHz



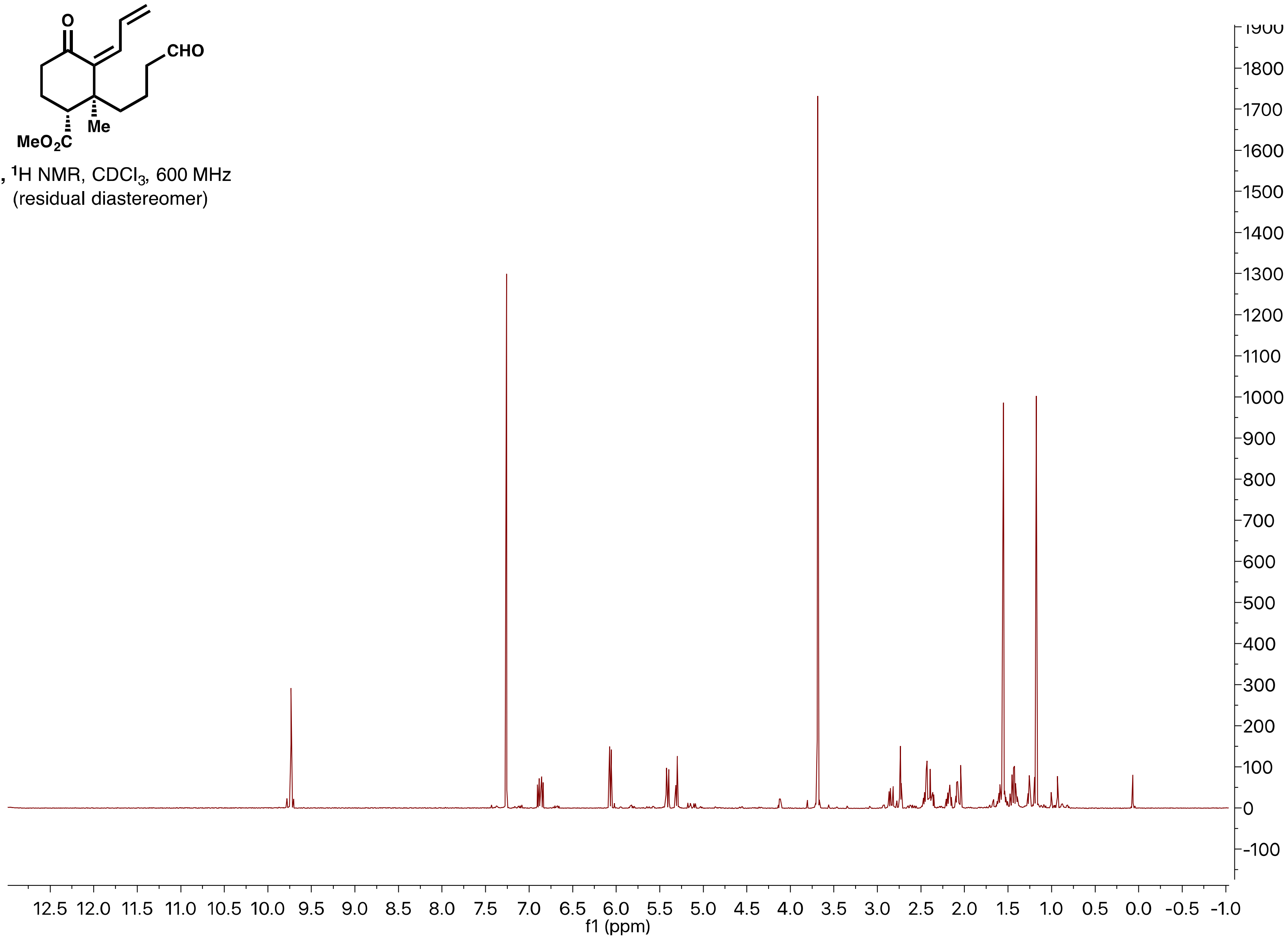
7, crude determination of dr,
^{1}H NMR, $CDCl_3$, 600 MHz



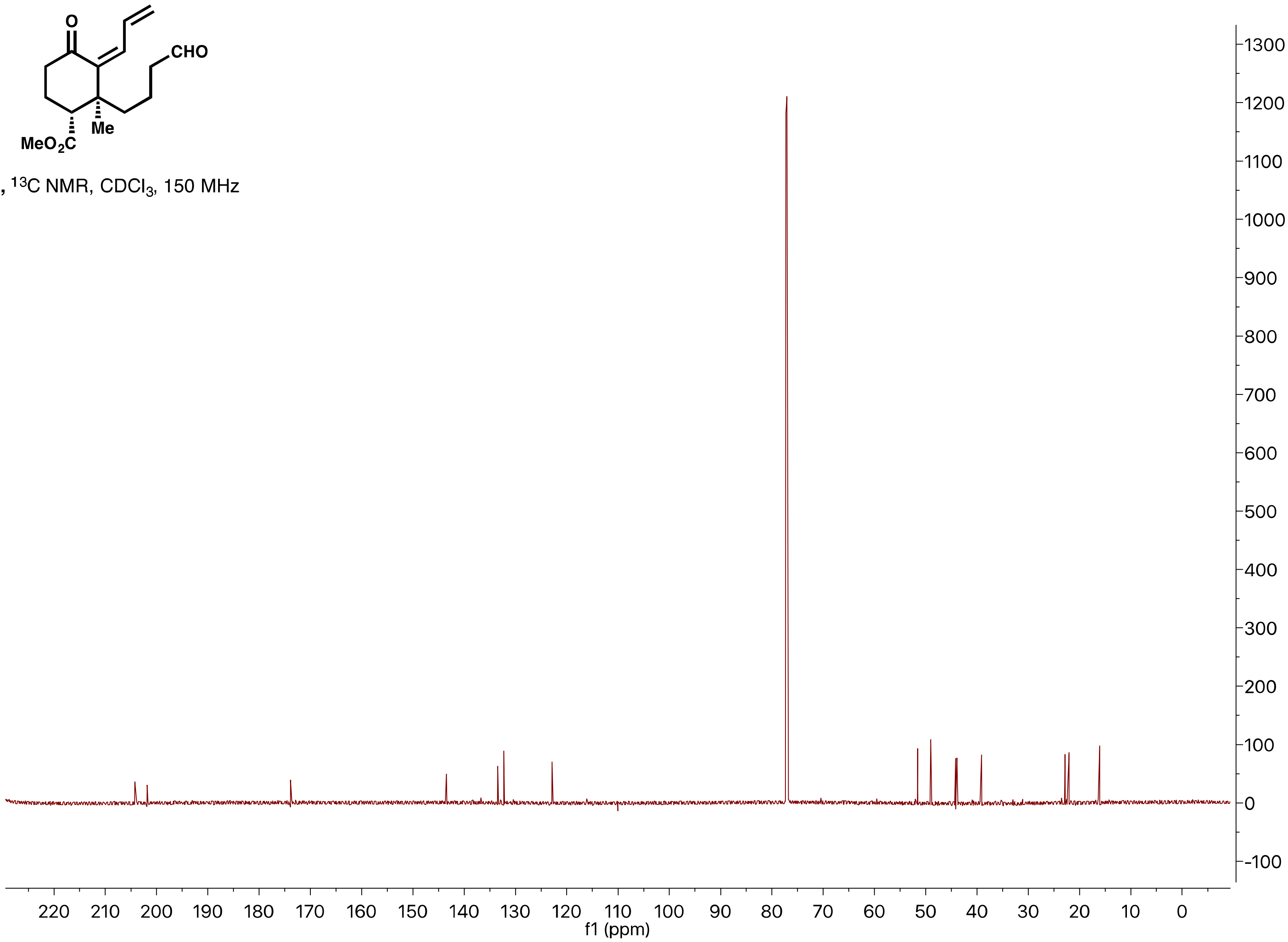
SI - 2, ^{1}H NMR, $CDCl_3$, 600 MHz
(residual Et_2O, H_2O)



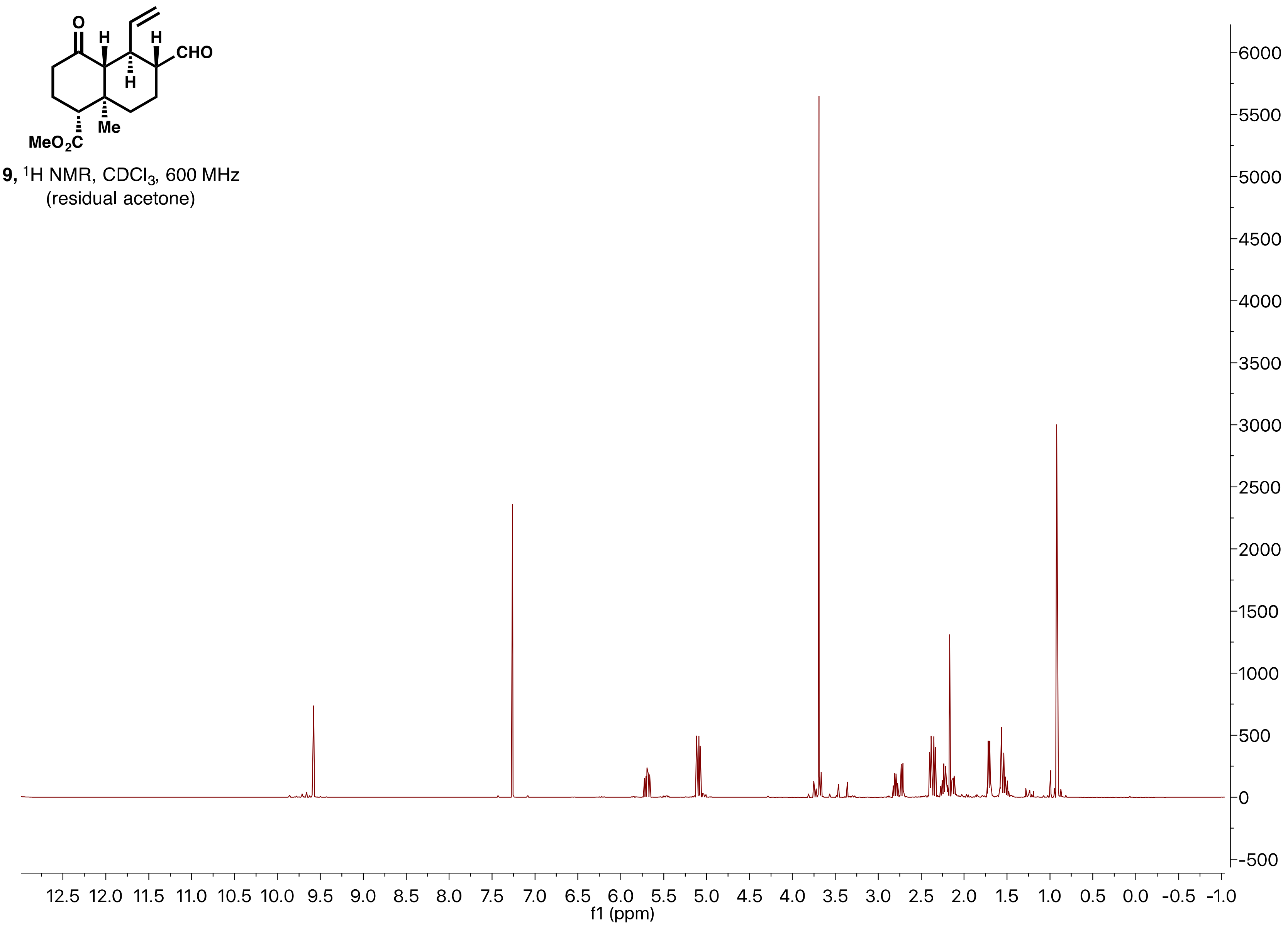
SI - 2, ^{13}C NMR, CDCl$_3$, 150 MHz
(residual Et$_2$O)



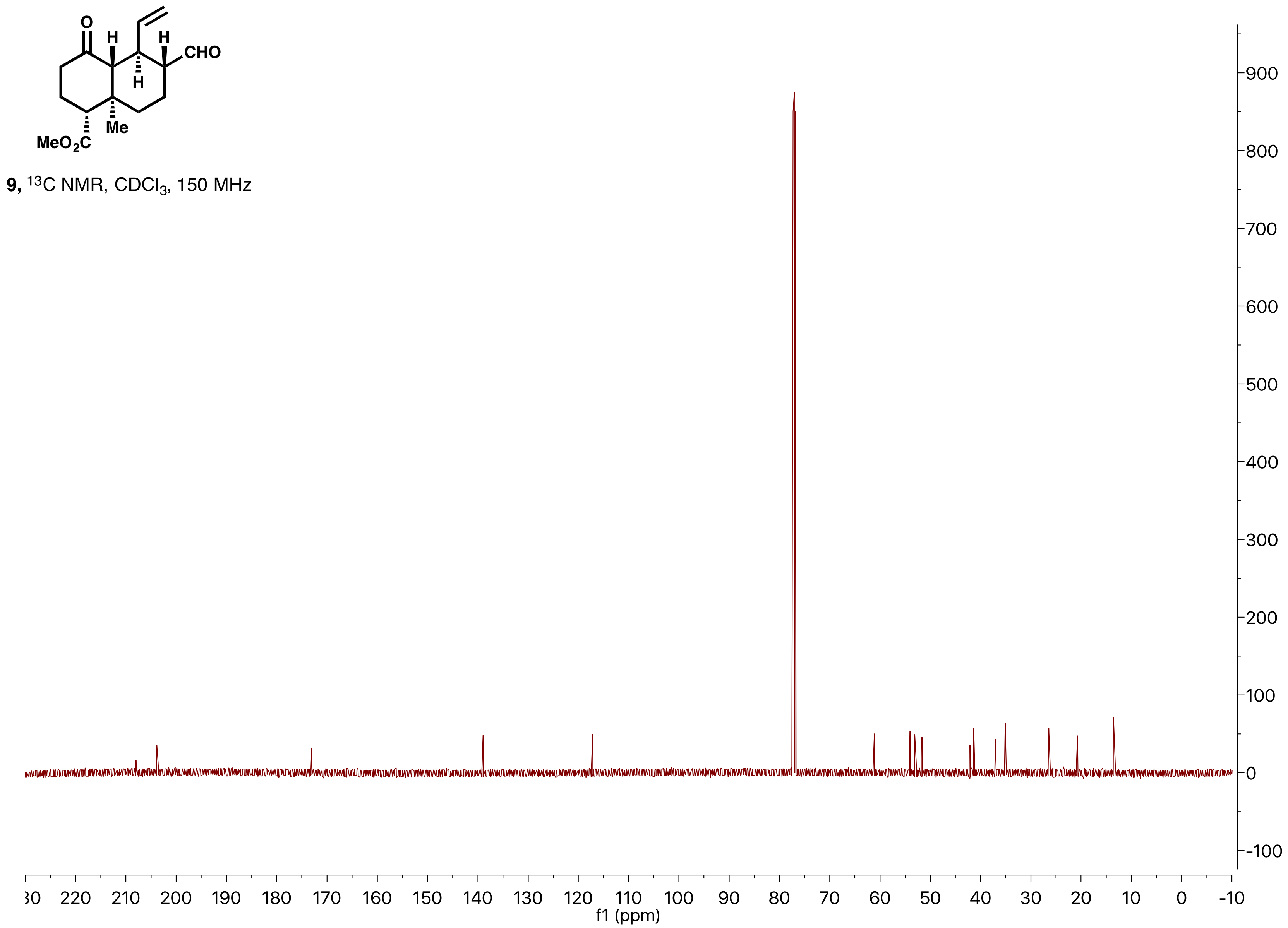
8, ^{1}H NMR, CDCl$_3$, 600 MHz
(residual diastereomer)



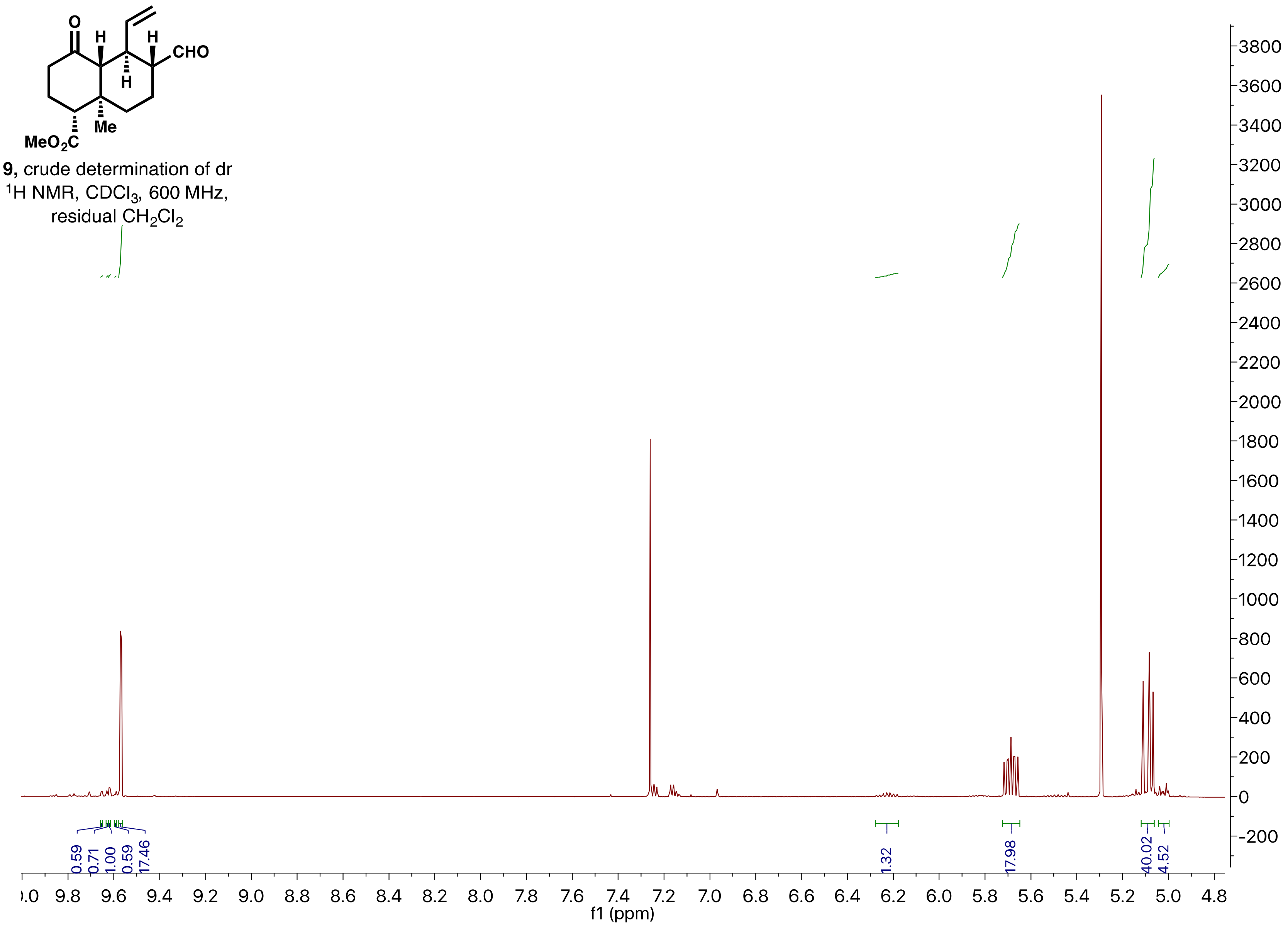
8, ^{13}C NMR, CDCl$_3$, 150 MHz



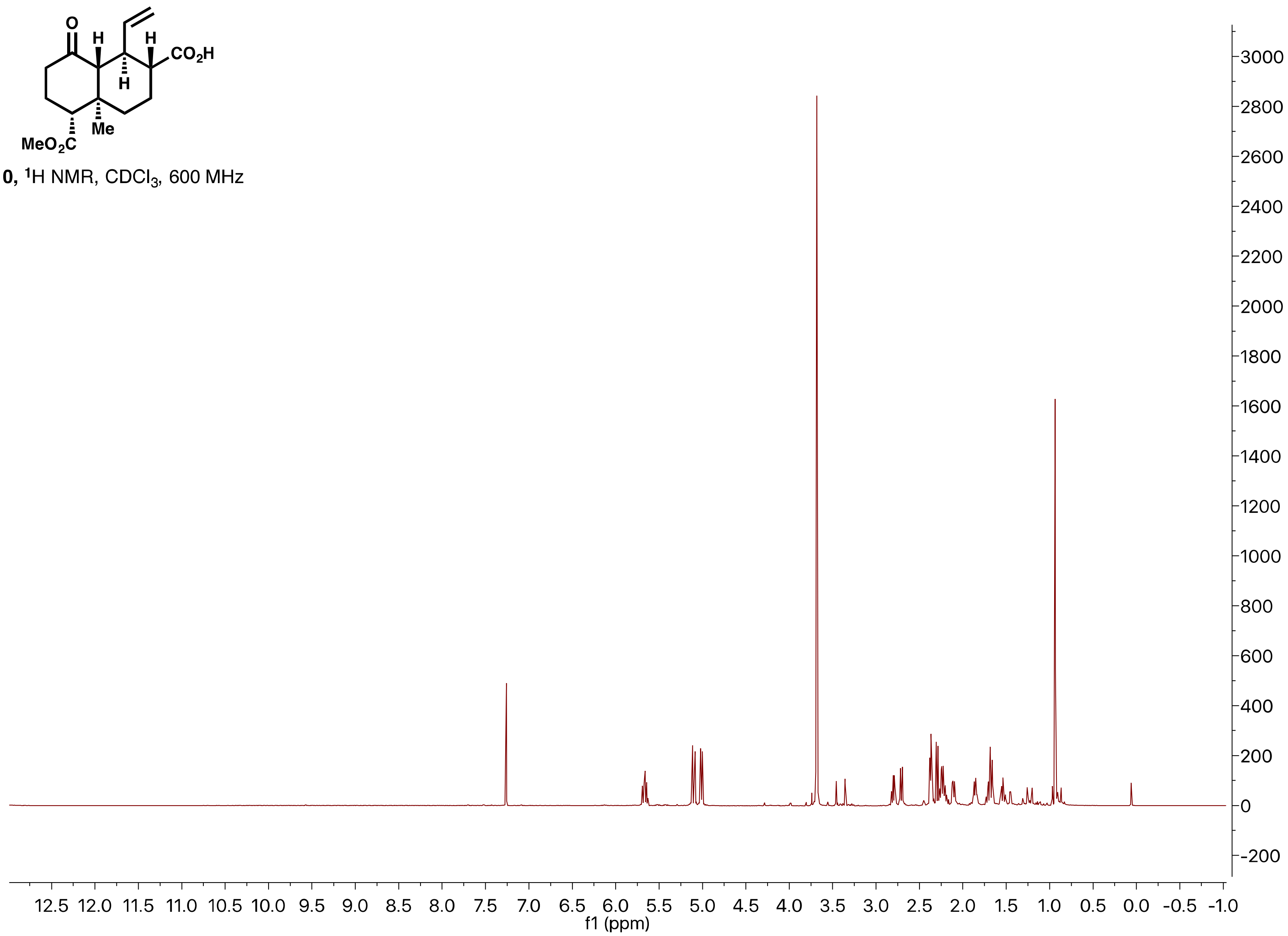
9, ^{1}H NMR, $CDCl_3$, 600 MHz
(residual acetone)

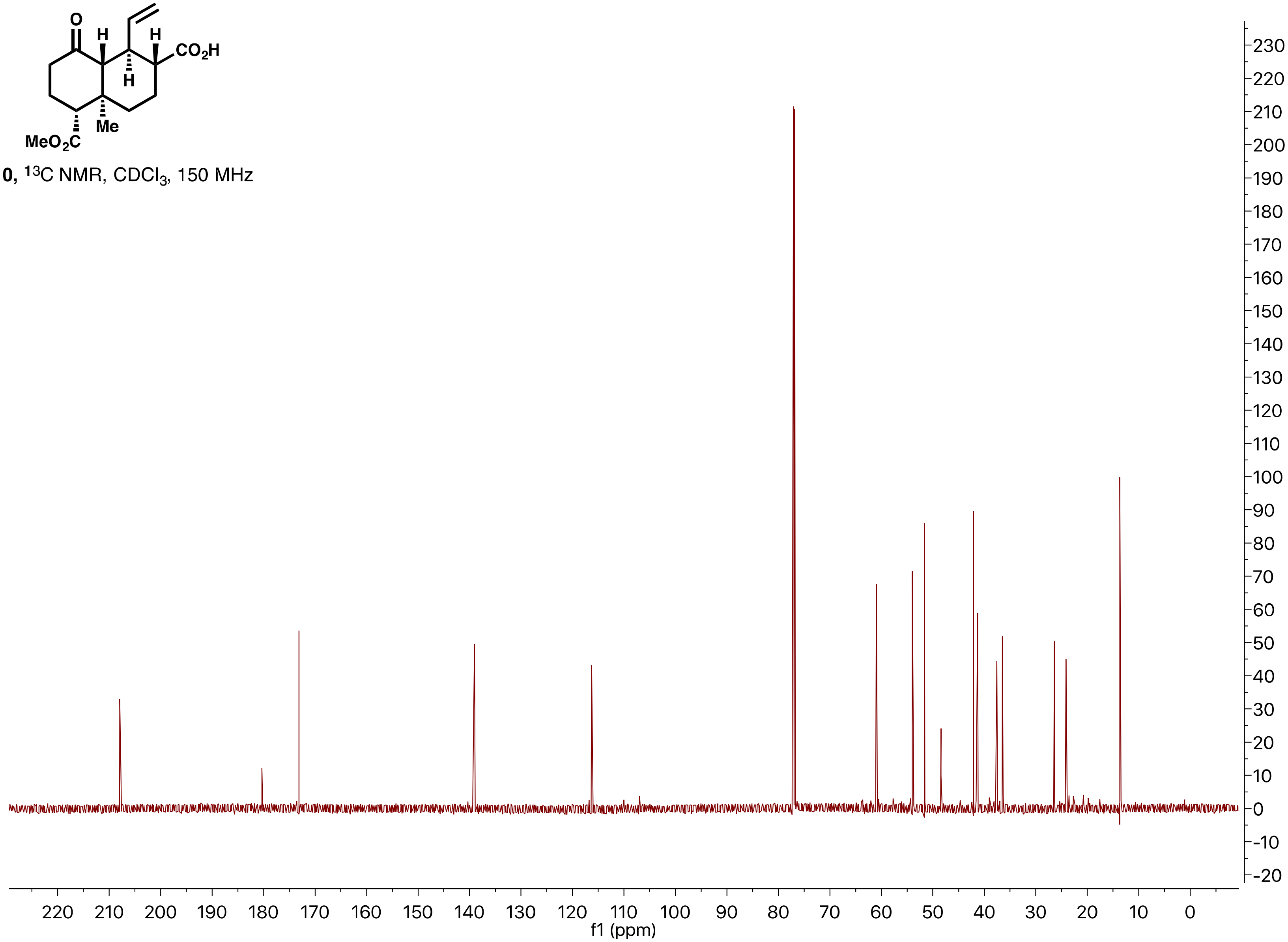


9, ^{13}C NMR, CDCl$_3$, 150 MHz

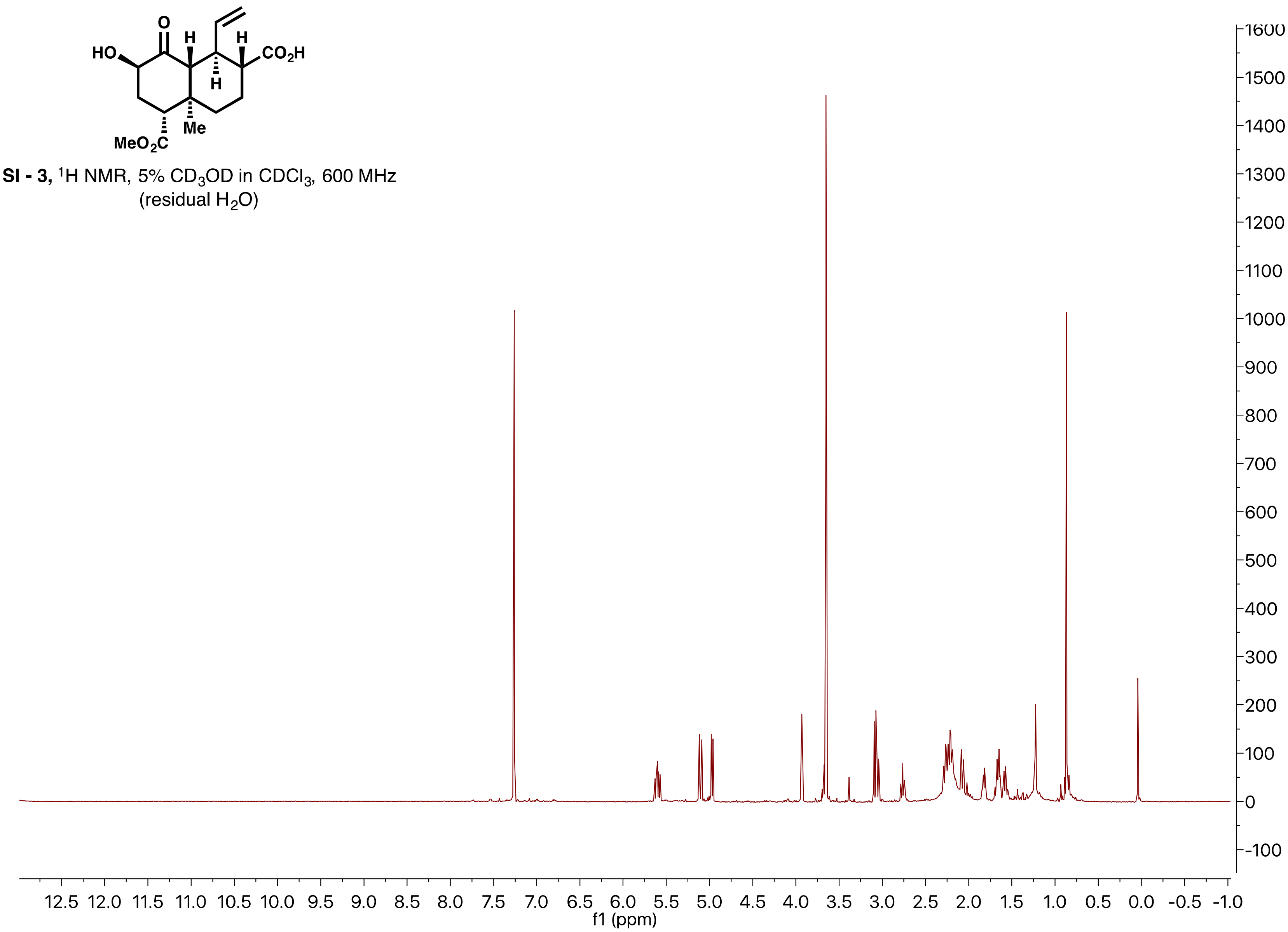


9, crude determination of dr
^{1}H NMR, $CDCl_3$, 600 MHz,
residual CH_2Cl_2

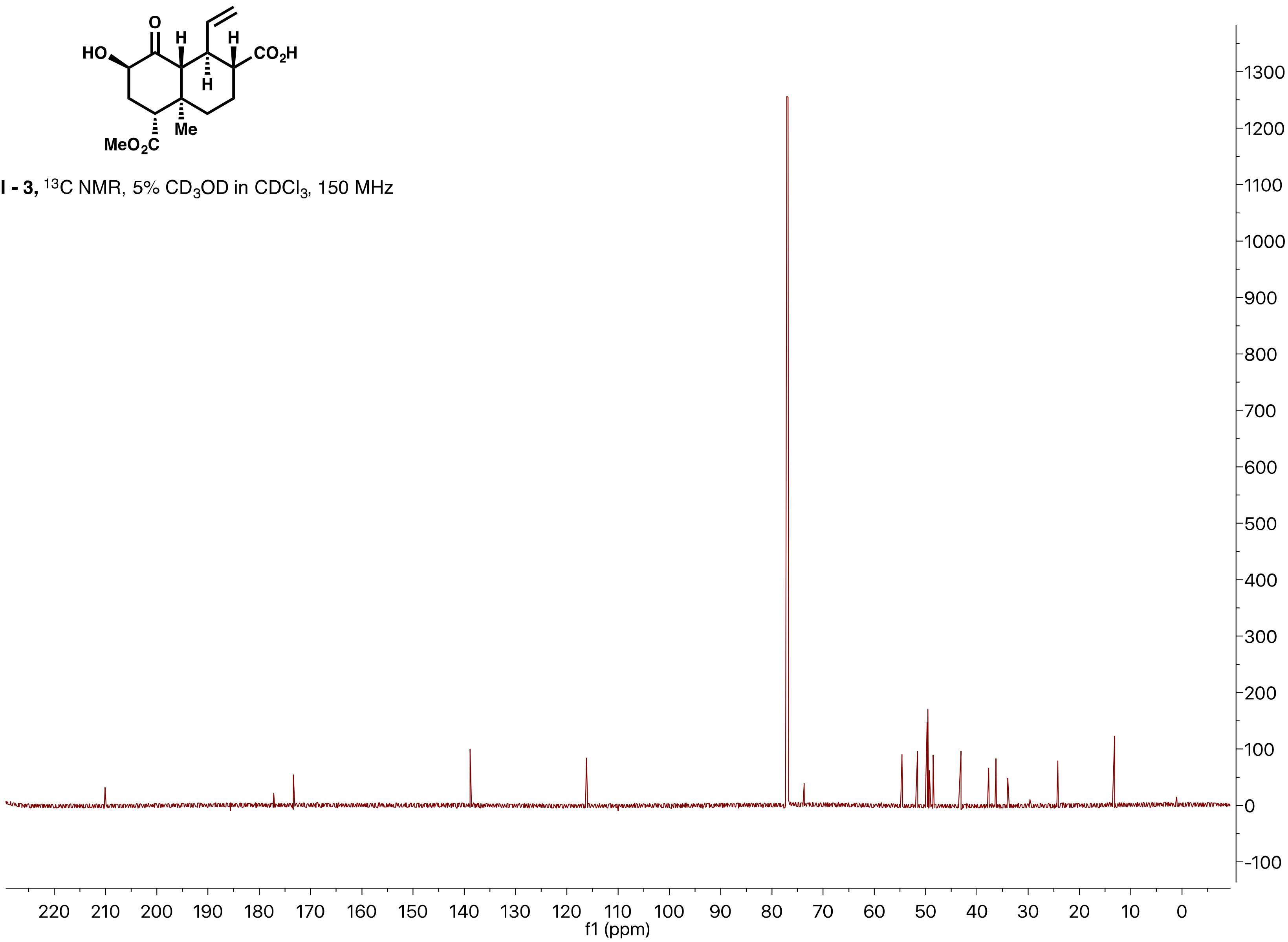

10, ^{1}H NMR, CDCl$_3$, 600 MHz



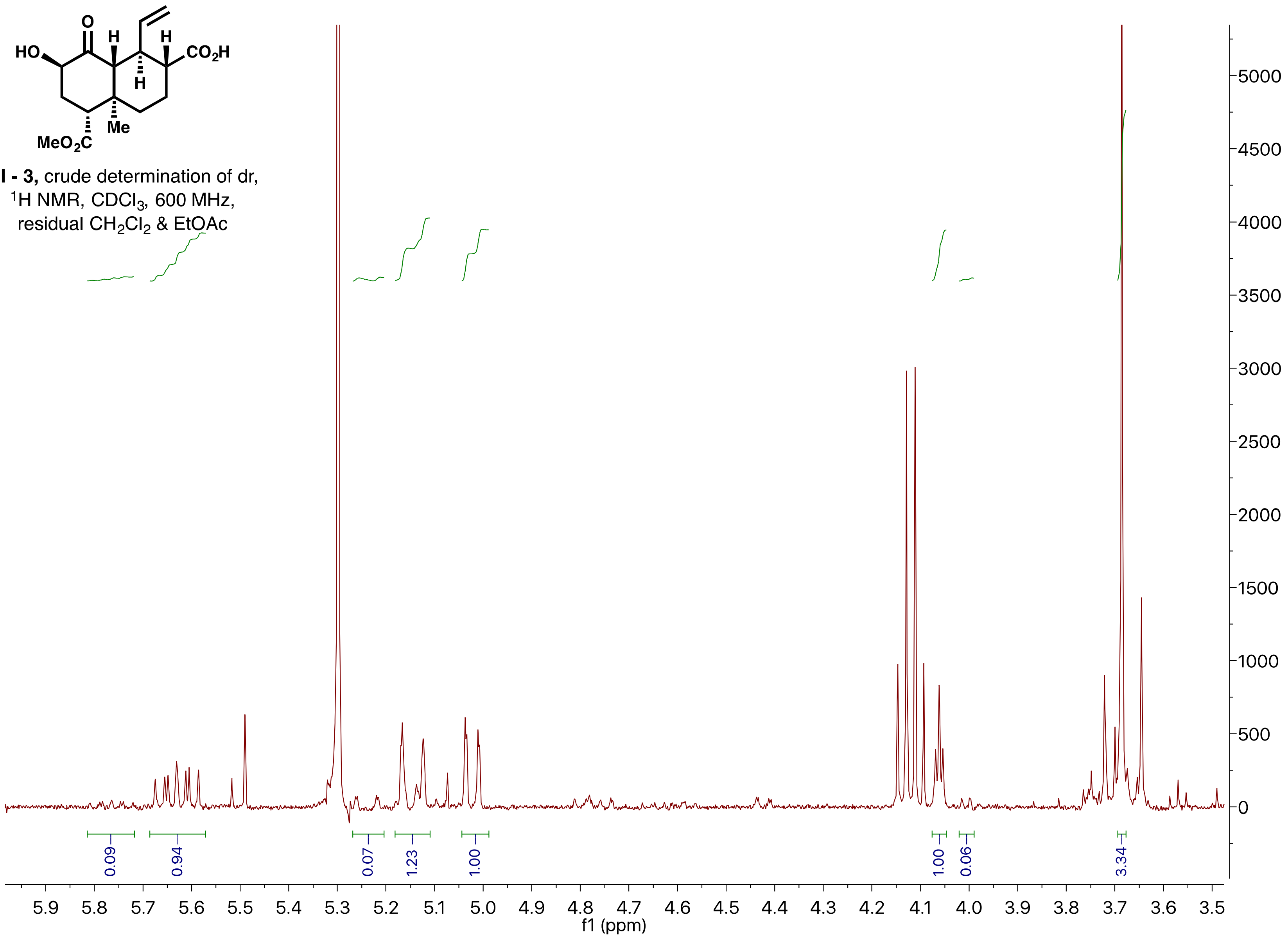
10, ^{13}C NMR, CDCl$_3$, 150 MHz



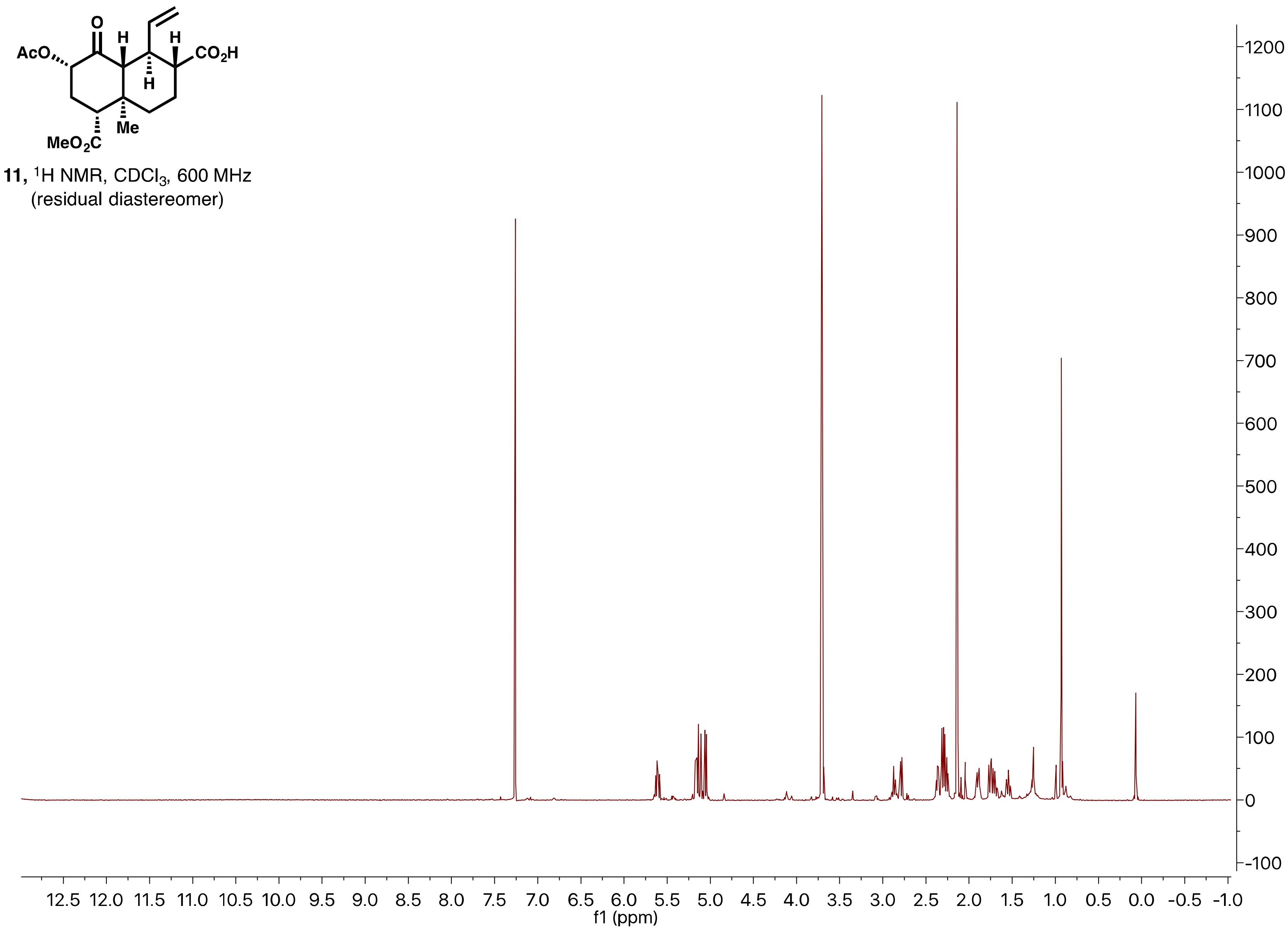
SI - 3, ^{1}H NMR, 5% CD_3OD in $CDCl_3$, 600 MHz
(residual H_2O)



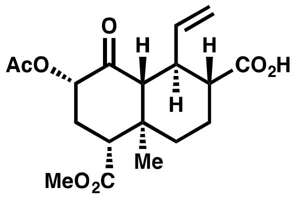
SI - 3, ^{13}C NMR, 5% CD_3OD in $CDCl_3$, 150 MHz



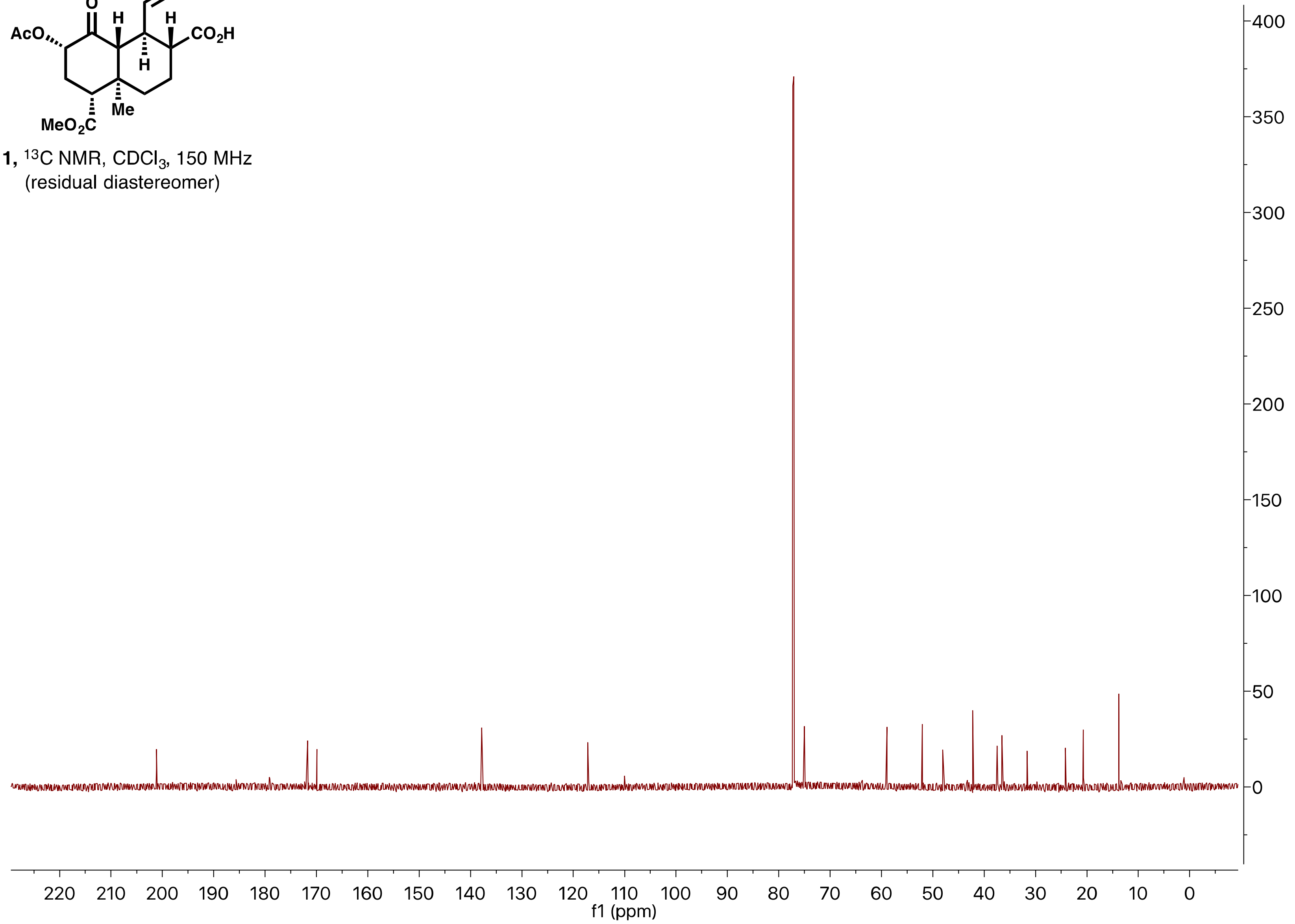
SI - 3, crude determination of dr,
^{1}H NMR, CDCl$_3$, 600 MHz,
residual CH$_2$Cl$_2$ & EtOAc

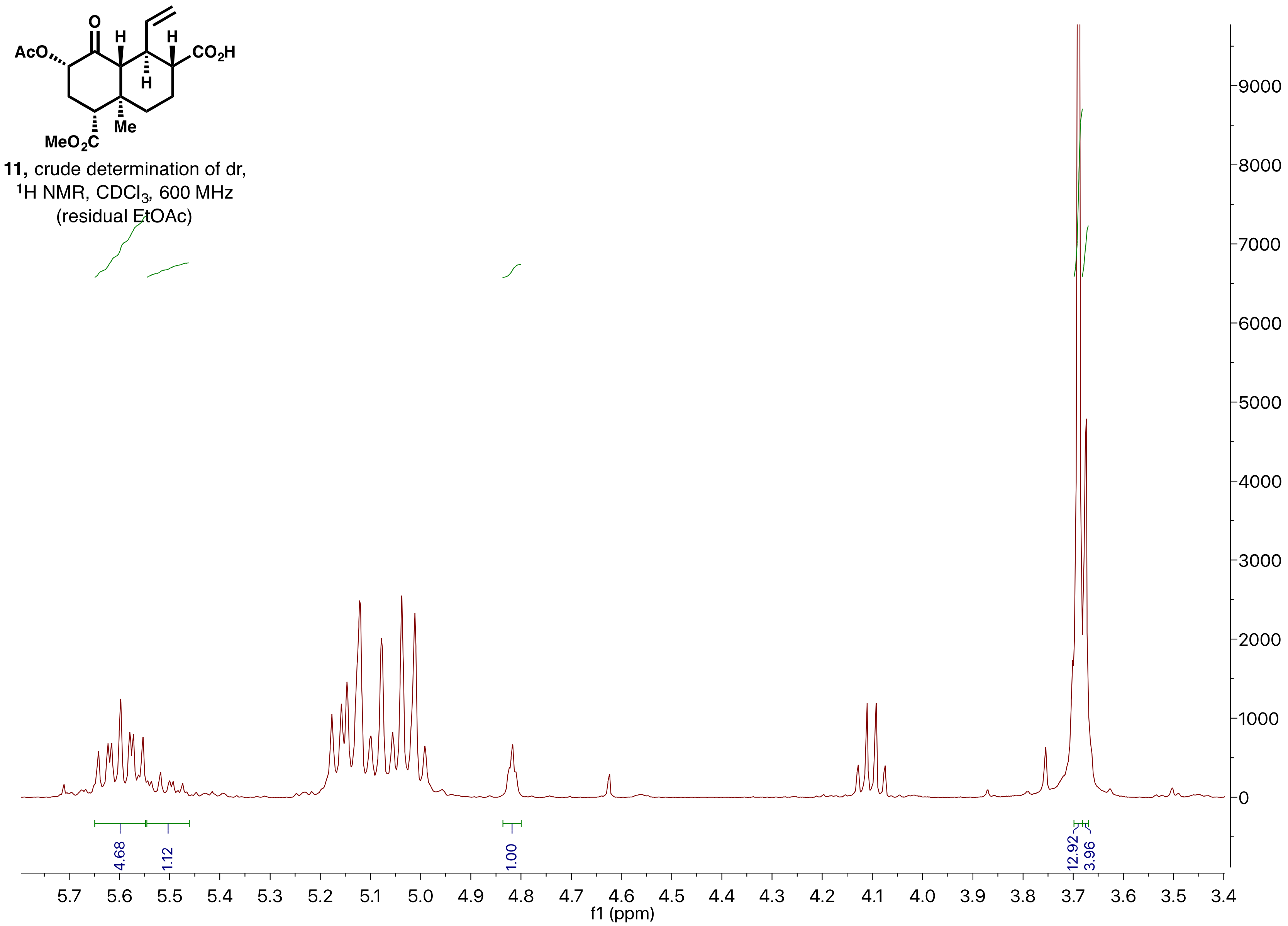


11, ^{1}H NMR, $CDCl_3$, 600 MHz
(residual diastereomer)

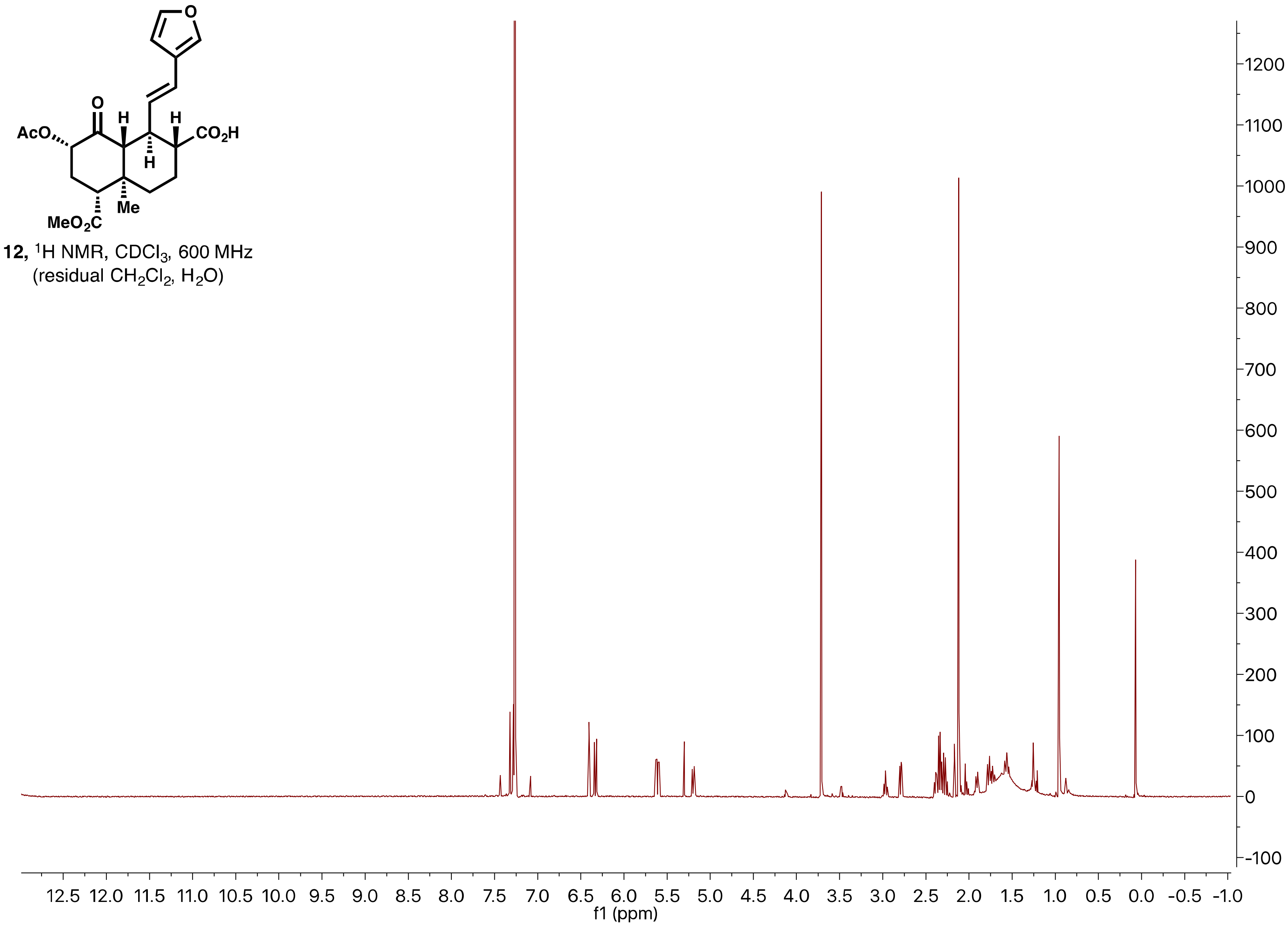


11, ^{13}C NMR, CDCl$_3$, 150 MHz
(residual diastereomer)

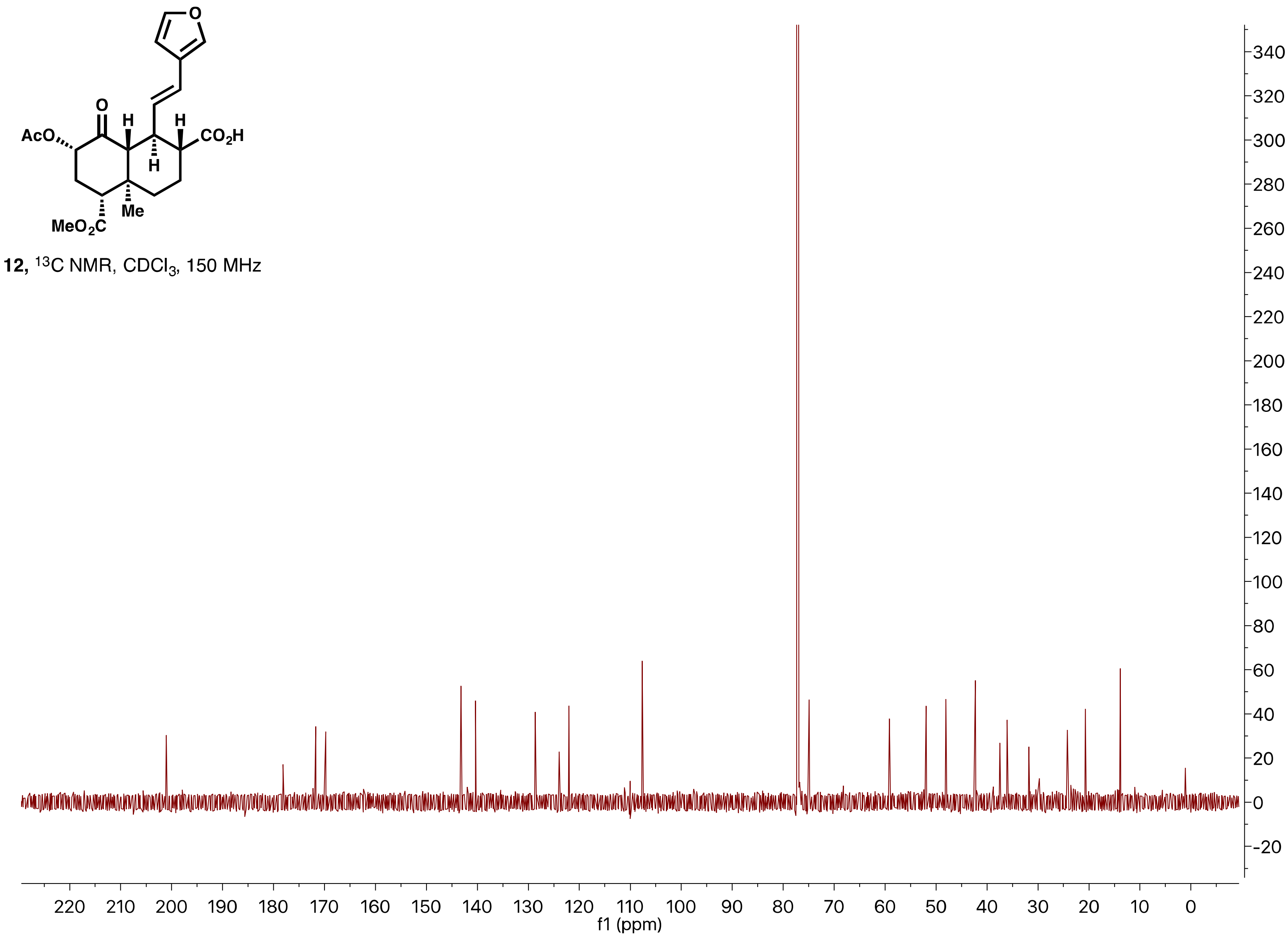




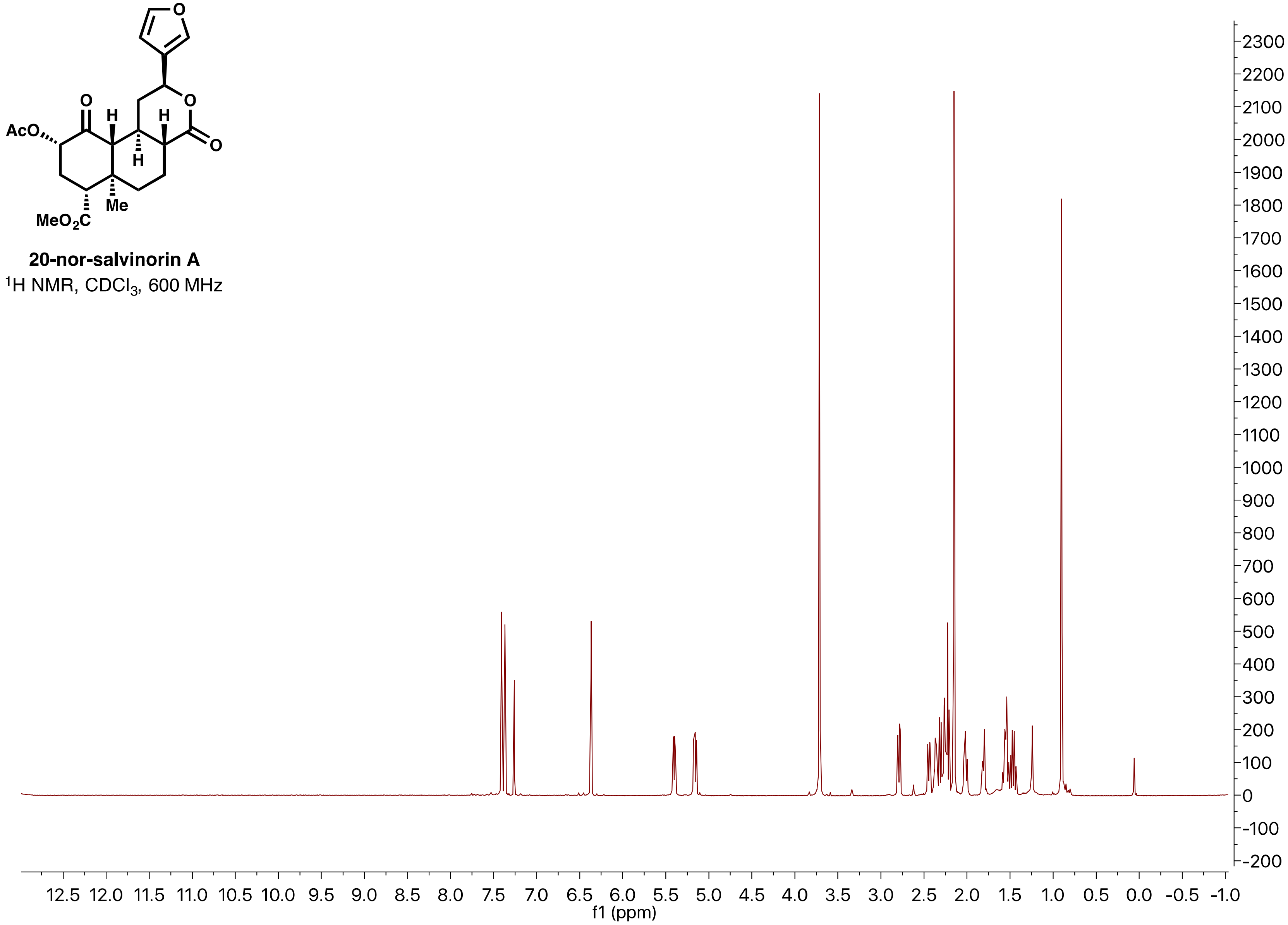
11, crude determination of dr,
^{1}H NMR, $CDCl_3$, 600 MHz
(residual EtOAc)



12, ^{1}H NMR, CDCl$_3$, 600 MHz
(residual CH$_2$Cl$_2$, H$_2$O)

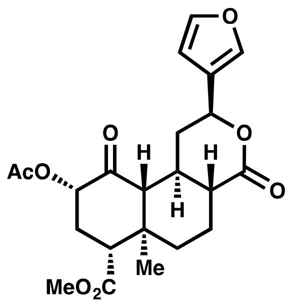


12, ^{13}C NMR, $CDCl_3$, 150 MHz



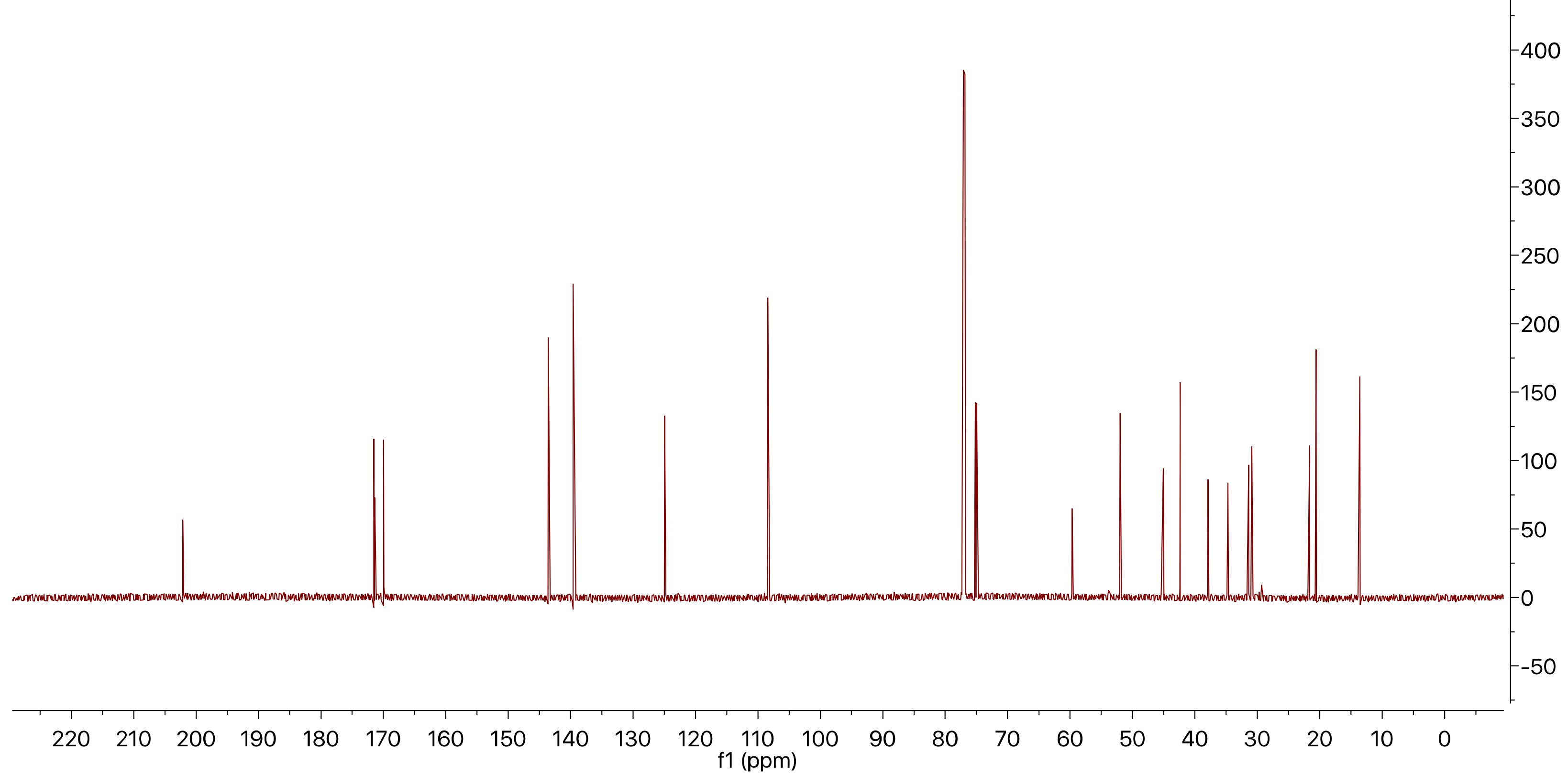
20-nor-salvinorin A

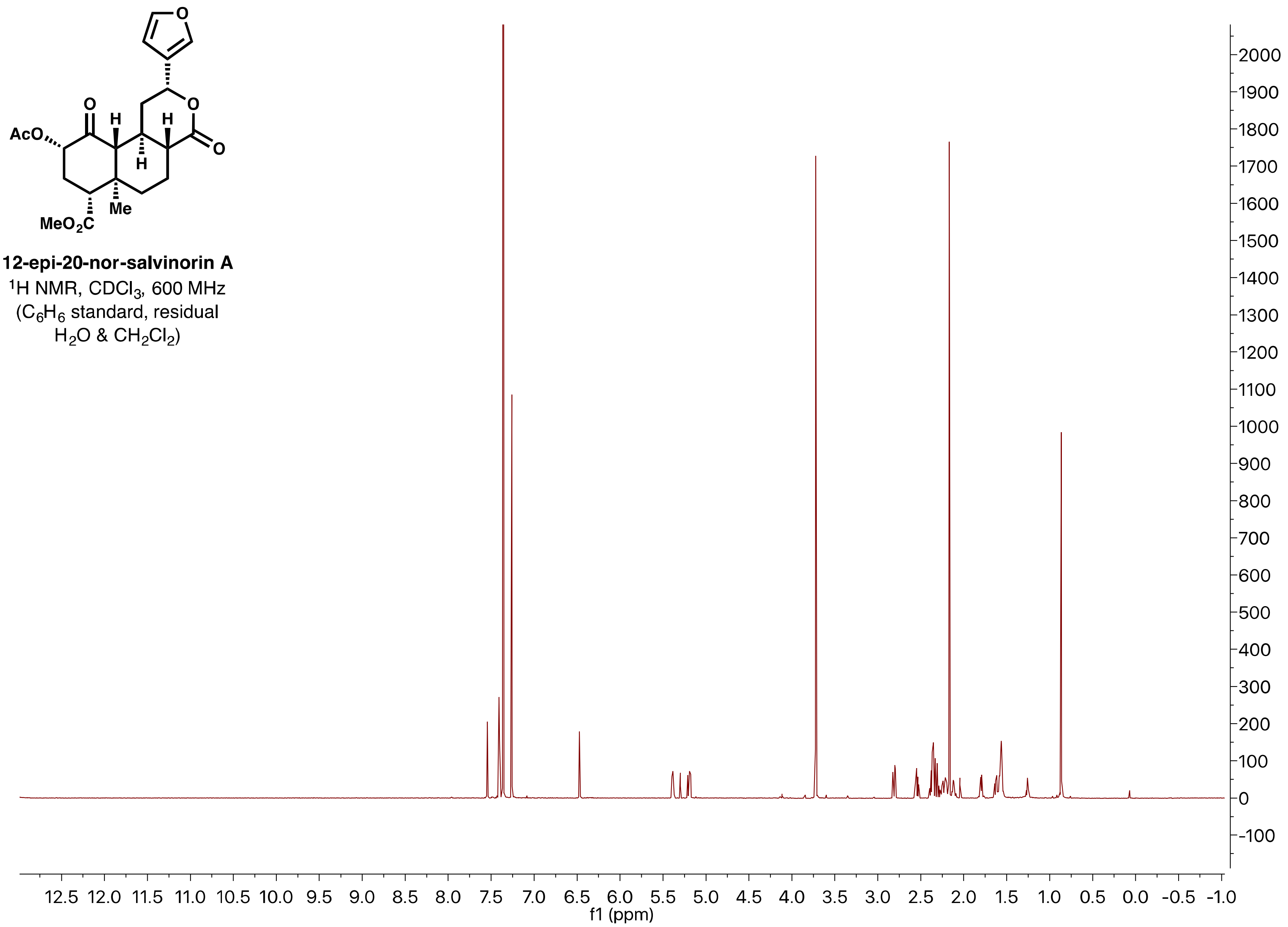
^{1}H NMR, $CDCl_3$, 600 MHz



20-nor-salvinorin A

^{13}C NMR, CDCl$_3$, 150 MHz



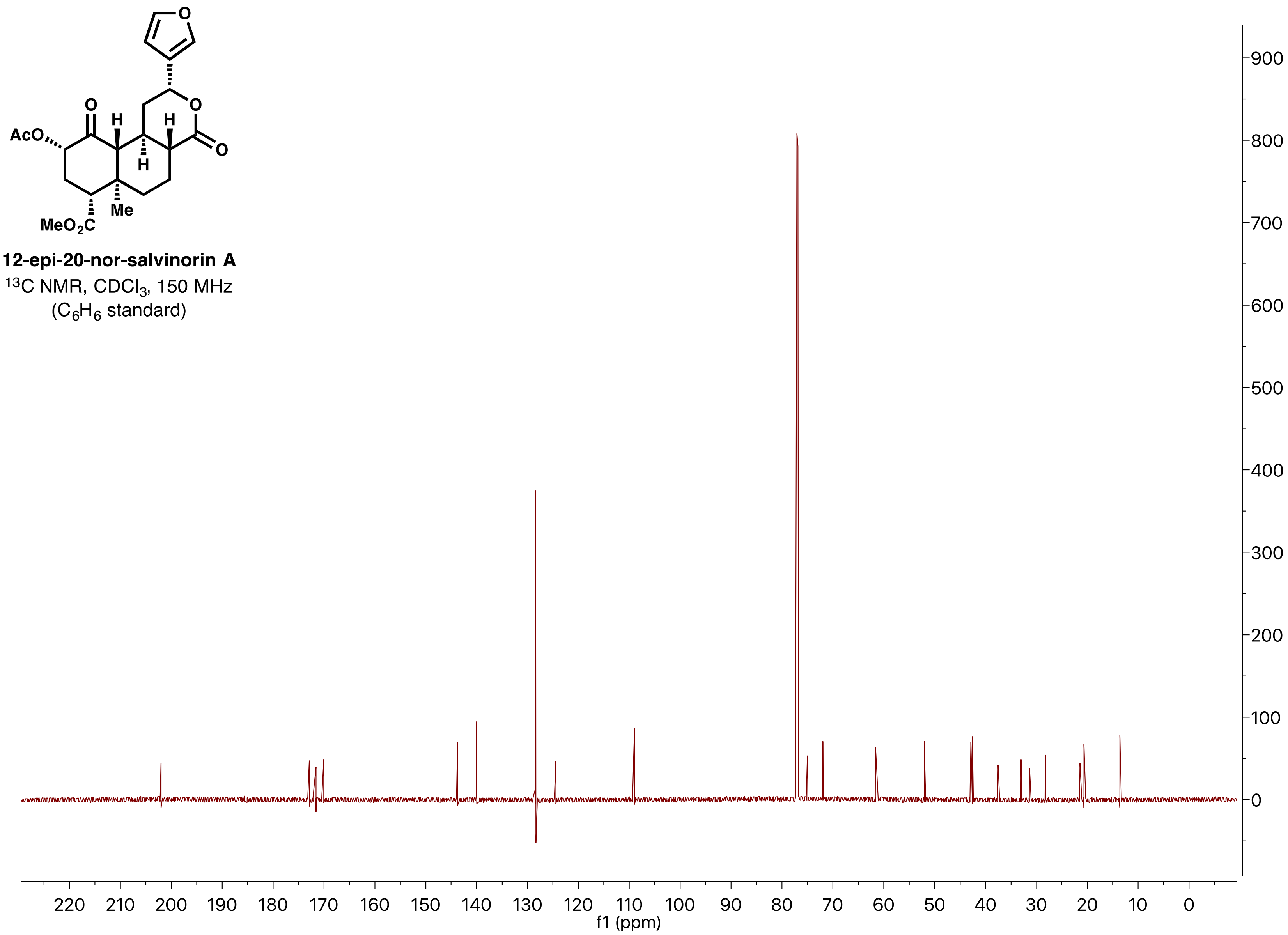


12-epi-20-nor-salvinorin A

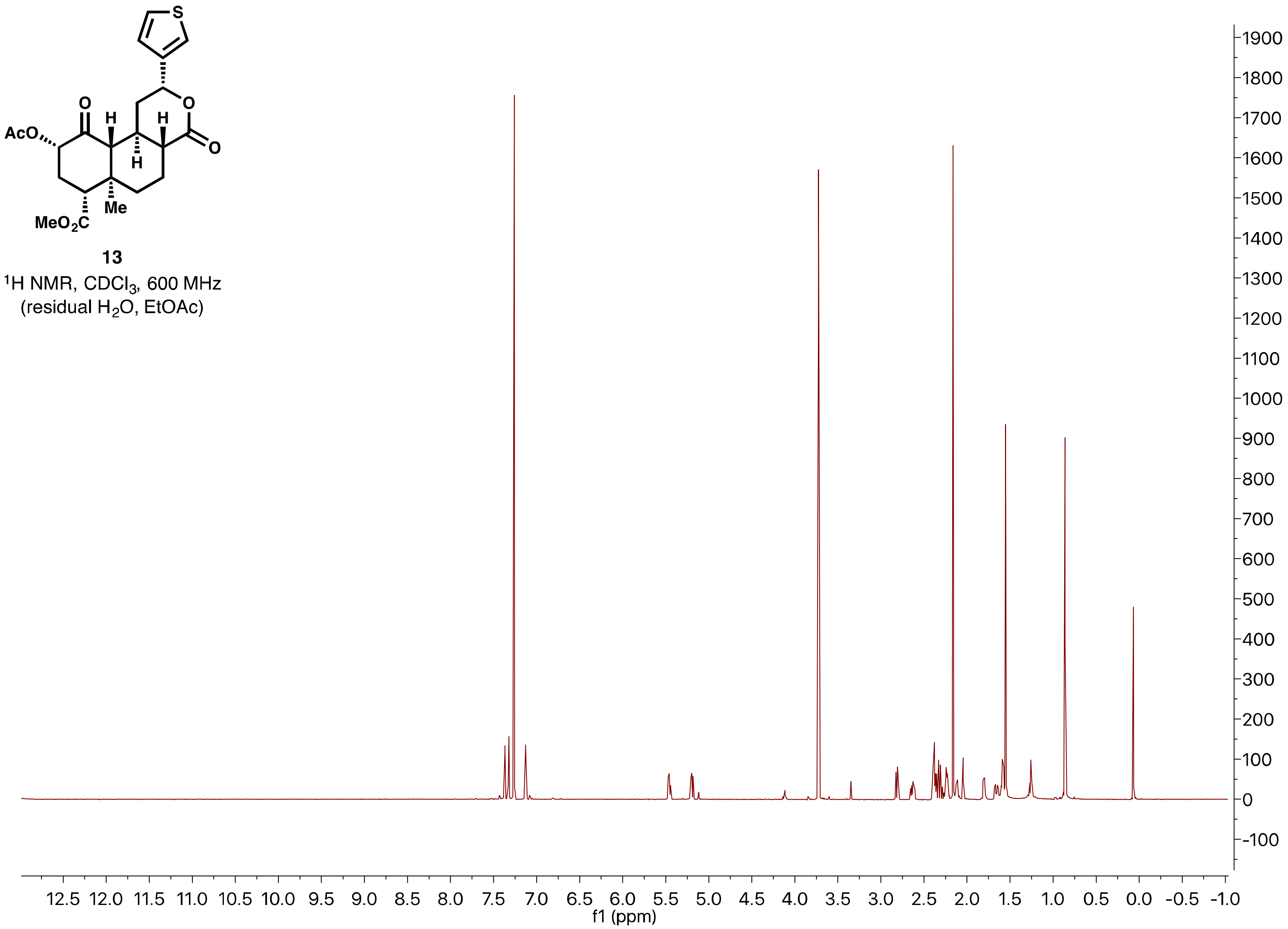
^{1}H NMR, $CDCl_3$, 600 MHz

(C_6H_6 standard, residual

H_2O & CH_2Cl_2)

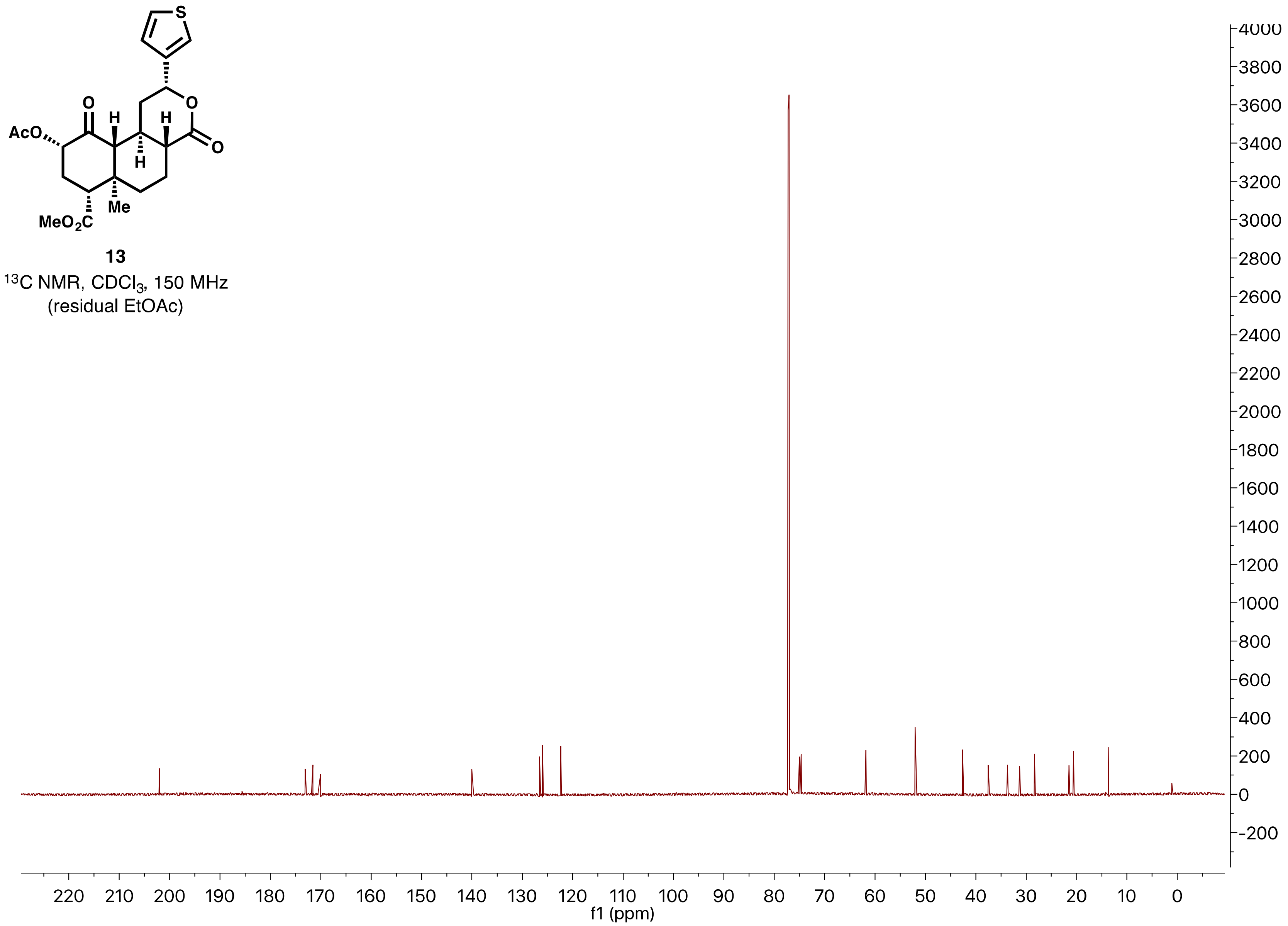


12-epi-20-nor-salvinorin A
^{13}C NMR, $CDCl_3$, 150 MHz
(C_6H_6 standard)



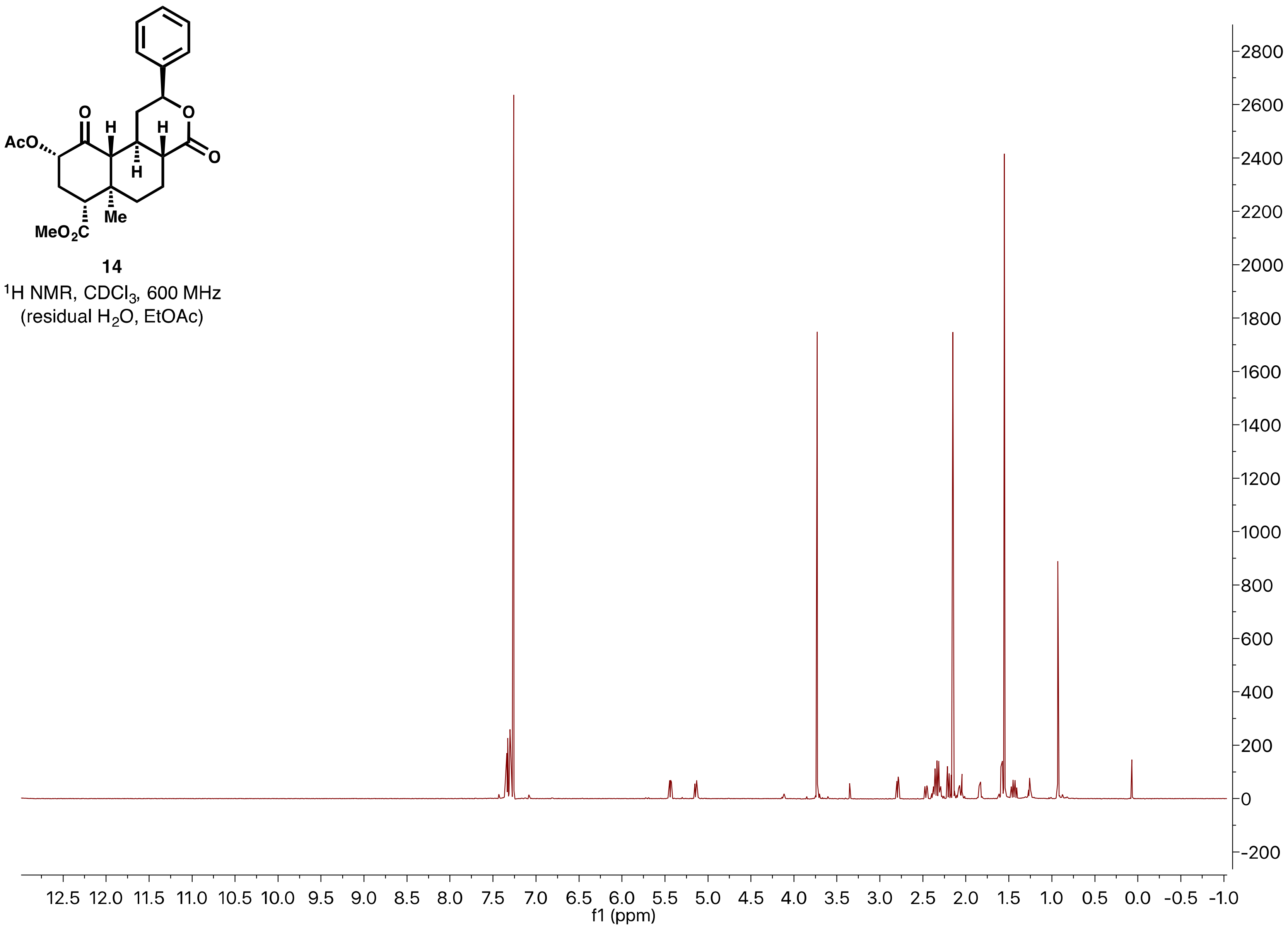
13

^{1}H NMR, $CDCl_3$, 600 MHz
(residual H_2O, EtOAc)



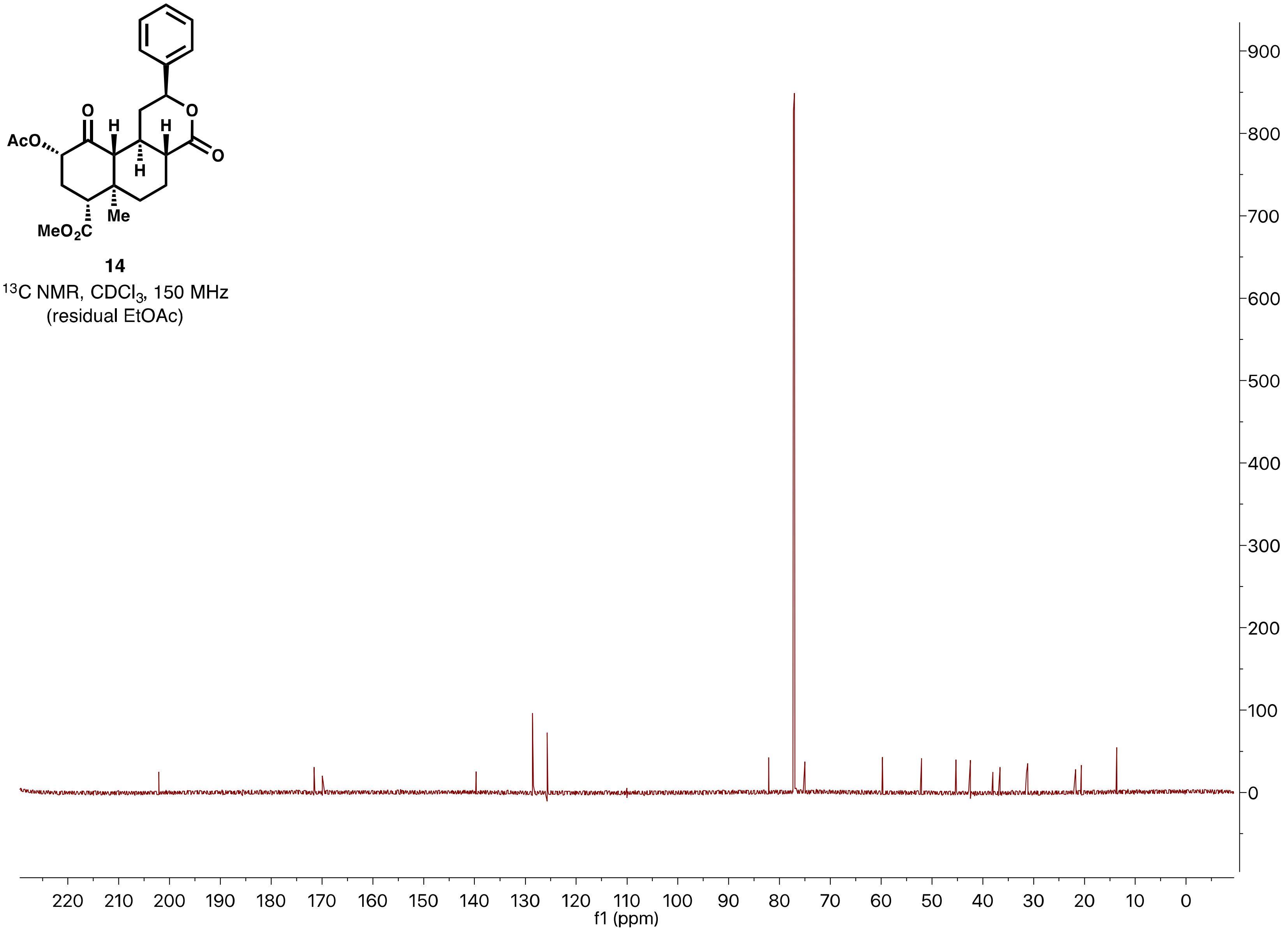
13

^{13}C NMR, $CDCl_3$, 150 MHz
(residual EtOAc)



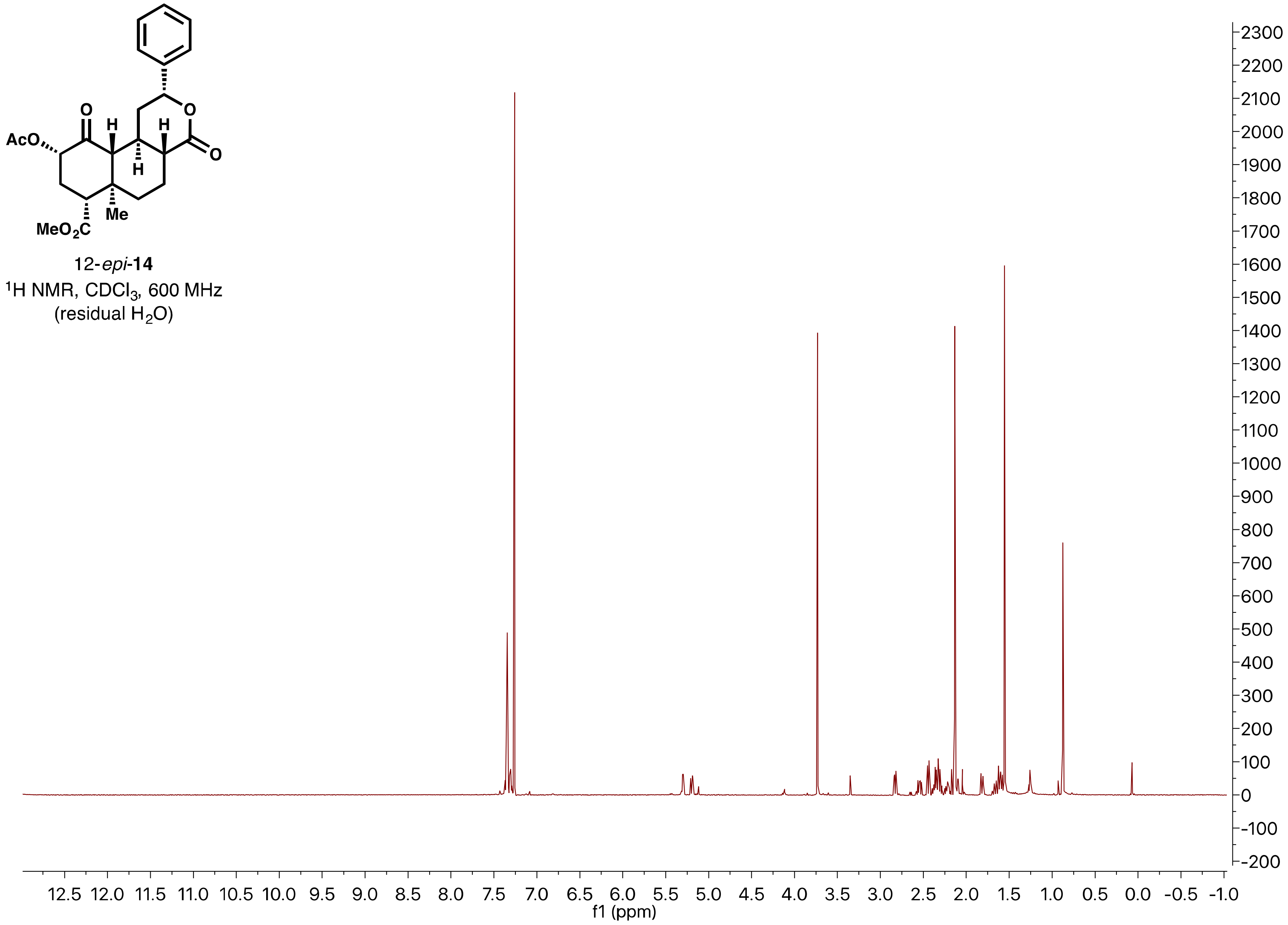
14

^{1}H NMR, CDCl$_3$, 600 MHz
(residual H$_2$O, EtOAc)



14

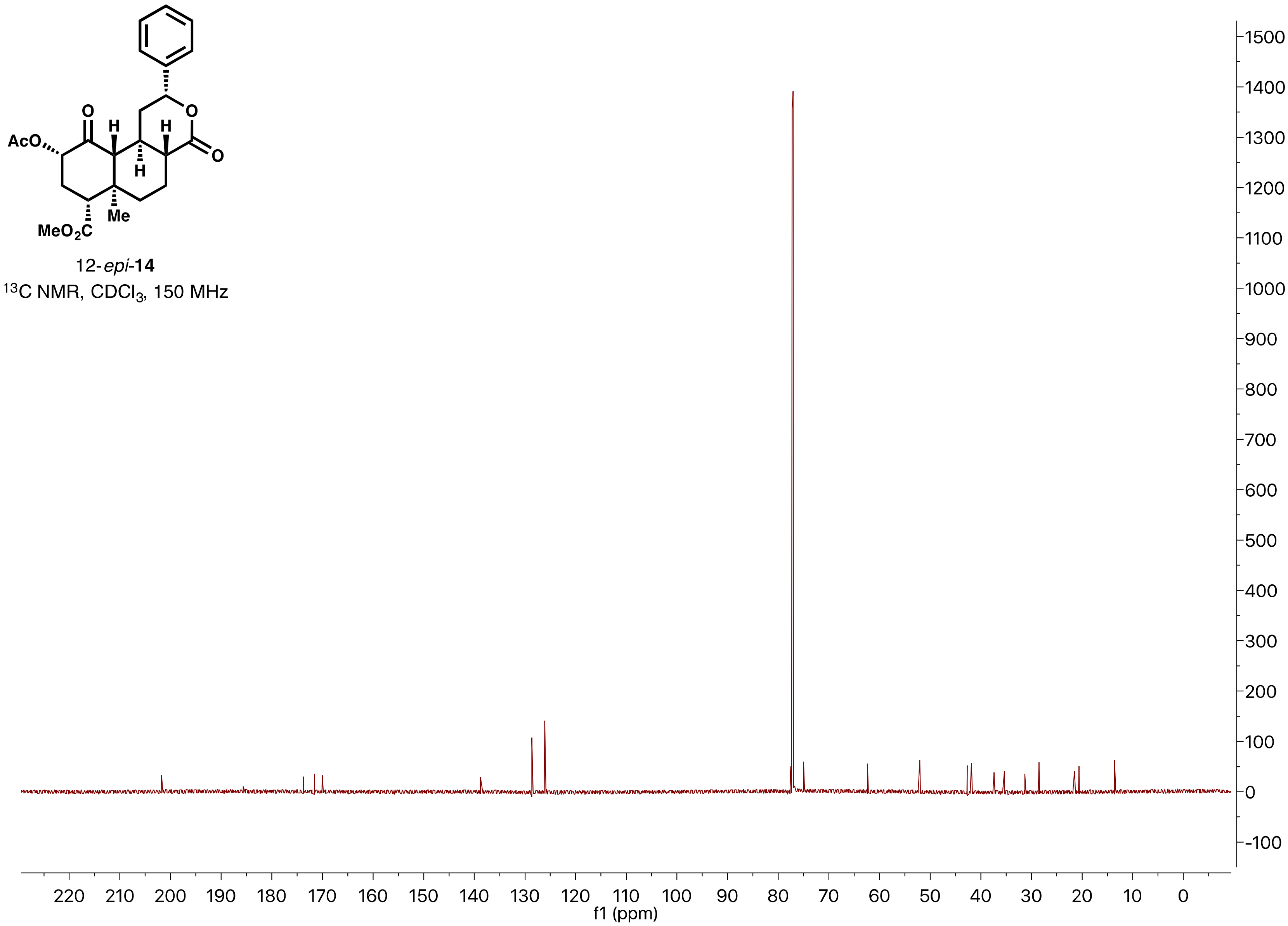
^{13}C NMR, $CDCl_3$, 150 MHz
(residual EtOAc)



12-*epi*-**14**

^{1}H NMR, $CDCl_3$, 600 MHz

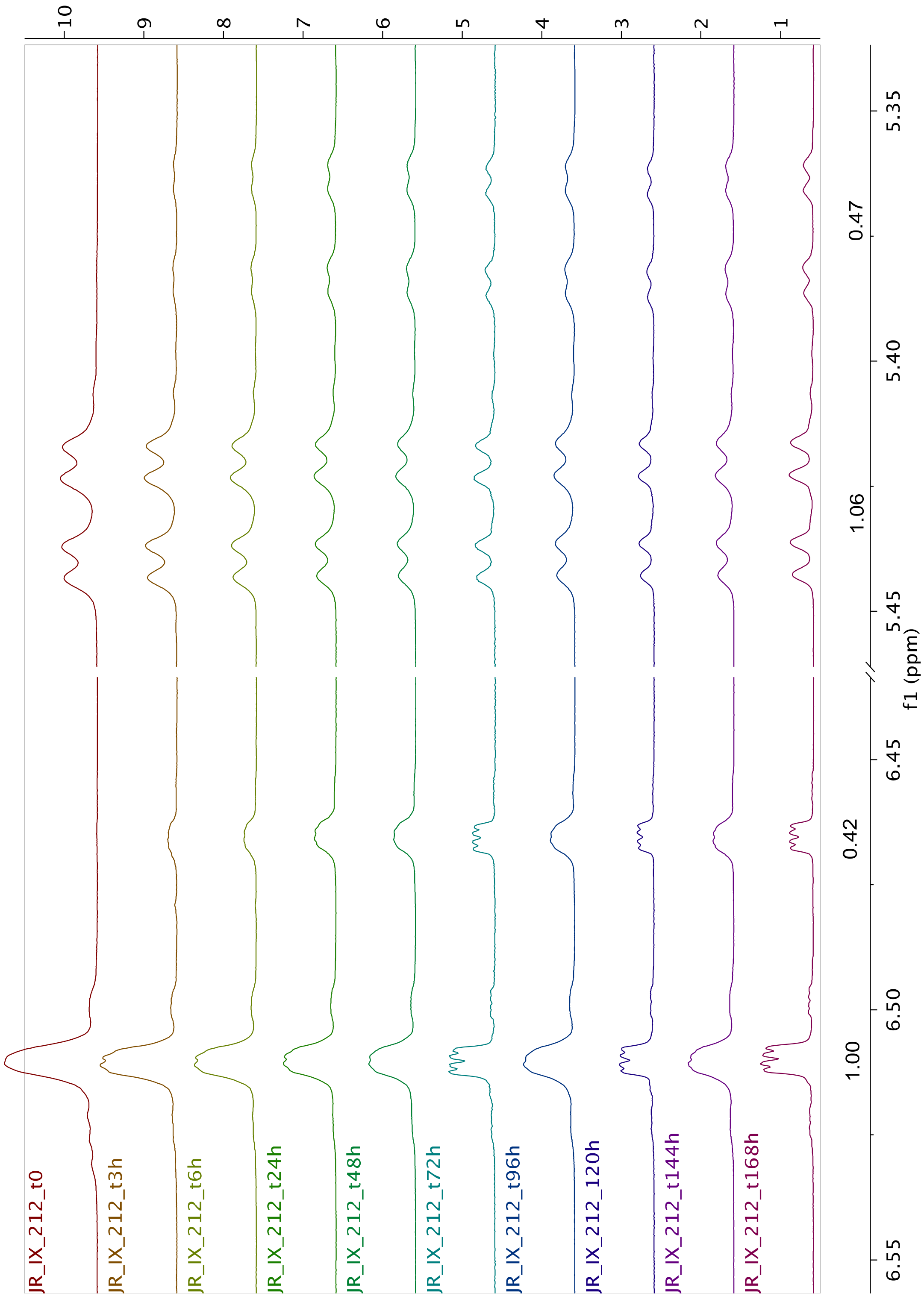
(residual H_2O)



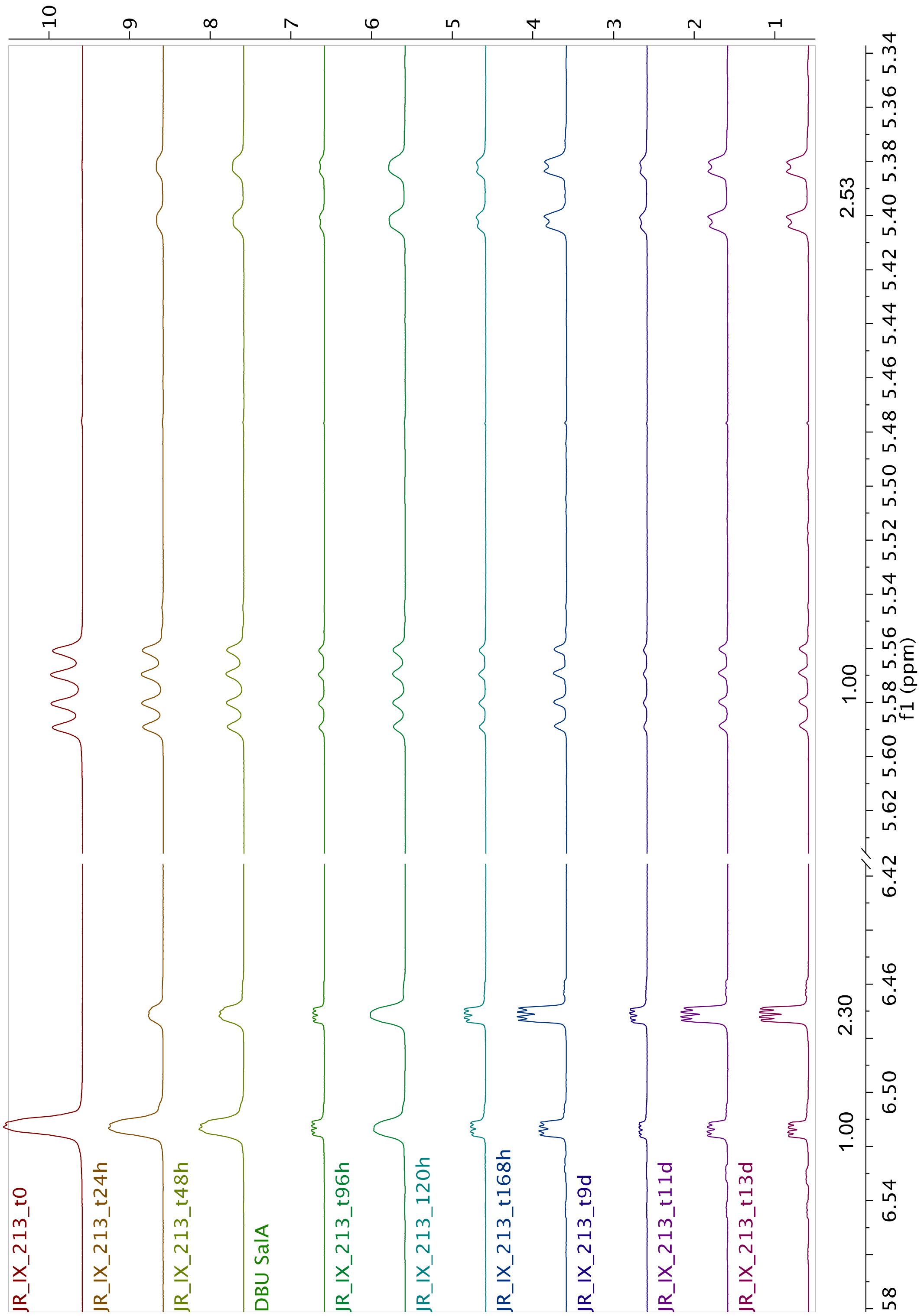
12-*epi*-**14**

^{13}C NMR, CDCl$_3$, 150 MHz

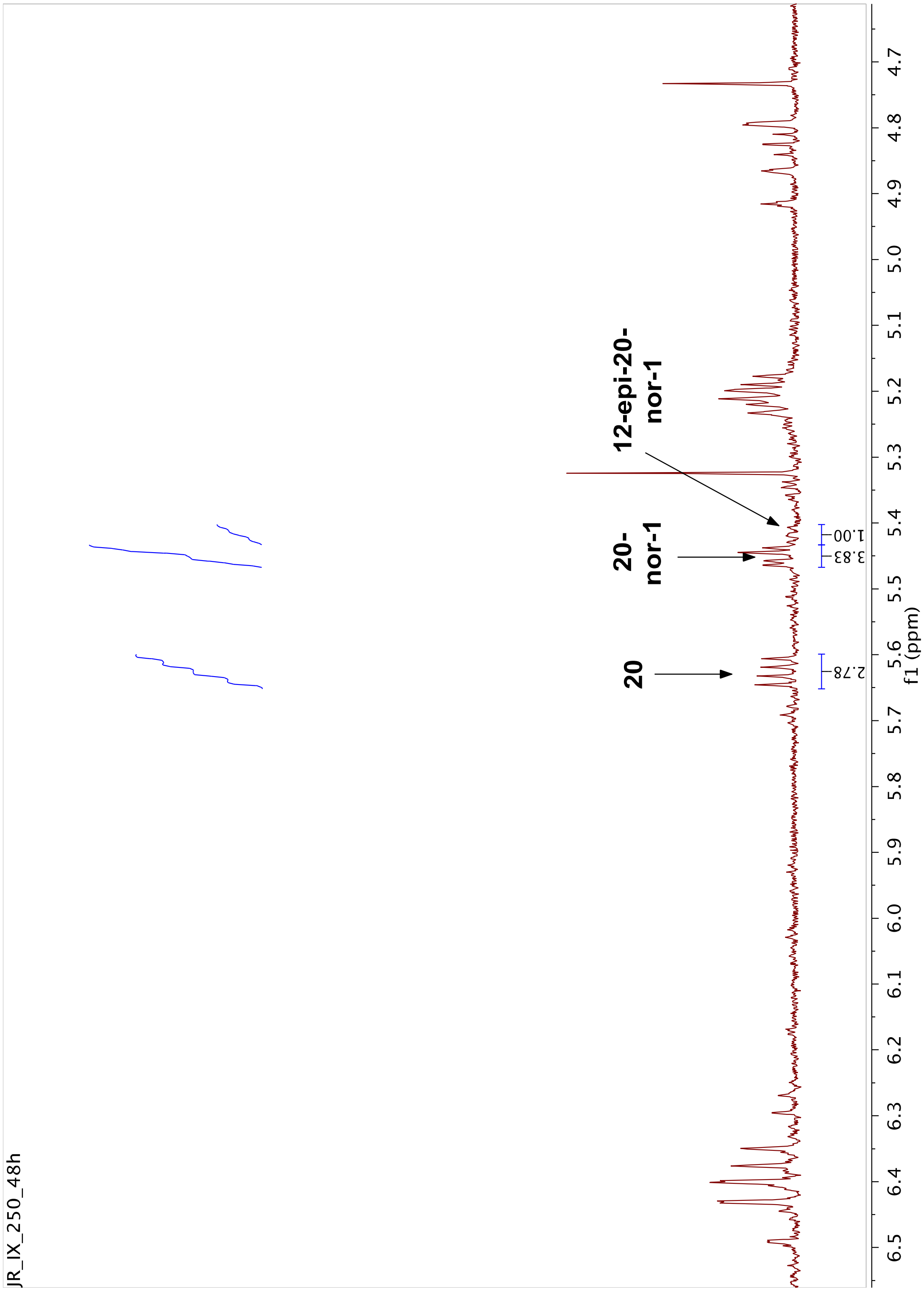
DBU (50 mol %) epimerization of 20-nor-SalA
(0.04 M in CD_3CN, 50 °C)



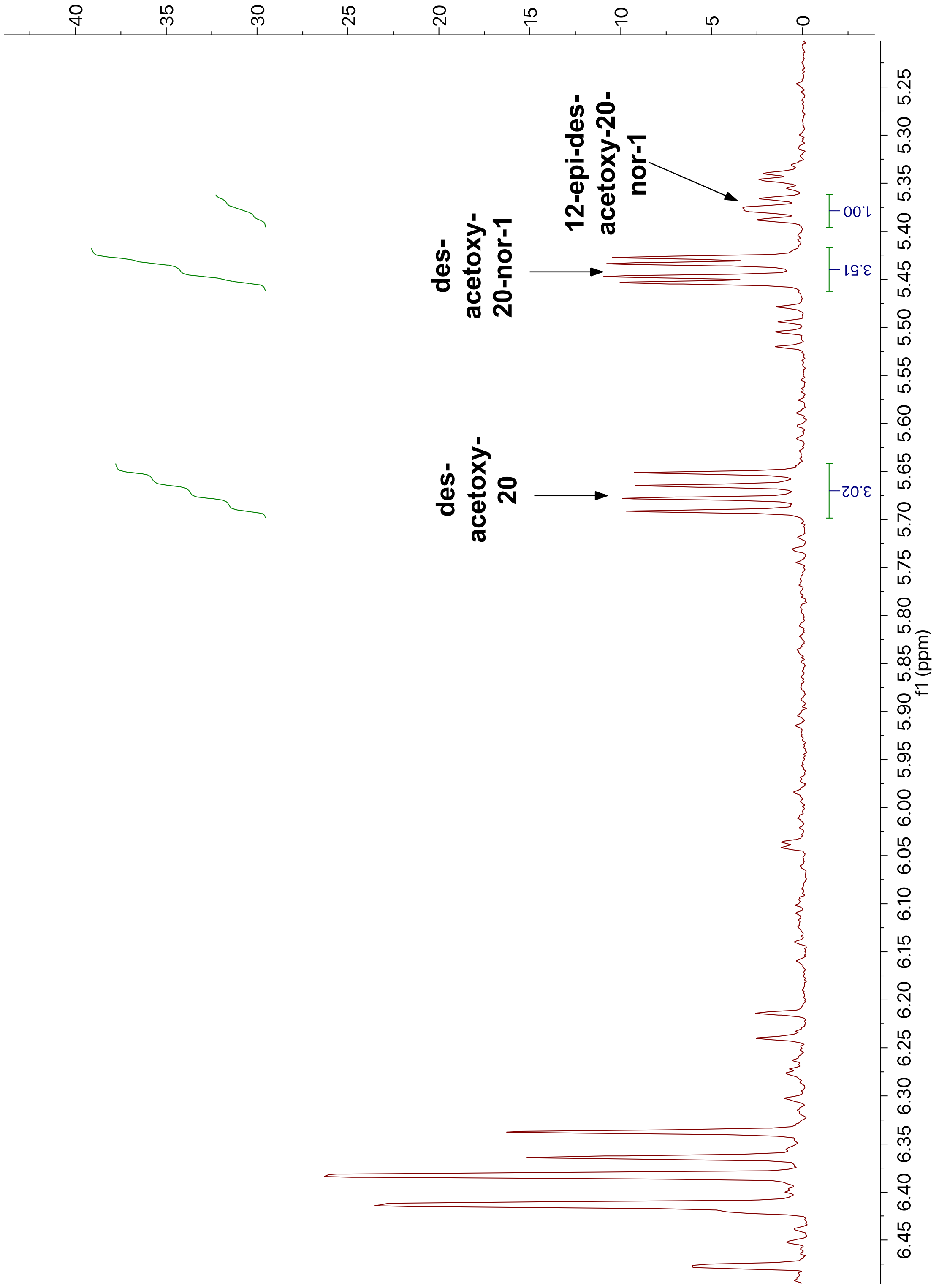
DBU (50 mol %) epimerization of SalA
(0.04 M in CD_3CN, 50 °C)



Evaluation of low-conversion, high-dr HFIP lactonization
3.8:1 dr at 63% conversion, 50 °C, 48h
(^{1}H NMR, $CDCl_3$, 600 MHz, residual CH_2Cl_2, peaks shifted by residual HFIP)

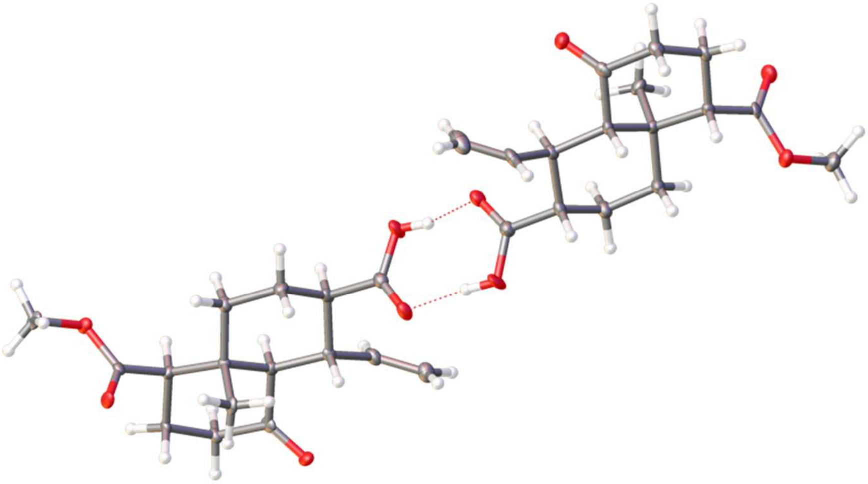


Evaluation of low-conversion, high-dr HFIP lactonization,
des-acetoxy substrate, 3.5:1 dr at 60% conversion, 40 °C, 96h
(^{1}H NMR, CDCl$_3$, 600 MHz, peaks shifted by residual HFIP)



X-Ray Structure Determination for (±)-10

Crystals of **10** were grown by slow evaporation from a ca. 1:1 mixture of (distilled) CH_2Cl_2 and (distilled) *n*-hexane and found to be suitable for X-ray diffraction.



The single crystal X-ray diffraction studies were carried out on a Bruker APEX II Ultra diffractometer equipped with Mo K_{α} radiation ($\lambda = 0.71073$). Crystals of the subject compound were used as received. A 0.150 x 0.05 x 0.06 mm colorless needle was mounted on a Cryoloop with Paratone oil.

Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 45 mm using exposure time 20.0 seconds with a scan width of 0.70°. Data collection was 100.0% complete to 25.242° in θ. A total of 24496 reflections were collected. 6136 reflections were found to be symmetry independent, with a R_{int} of 0.0420. Indexing and unit cell refinement indicated a **Primitive Monoclinic** lattice. The space group was found to be ***P*2₁/n.** The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table S2.

Notes: Centrosymmetric space group, “racemate” crystal

Two independent molecules per asymmetric unit

Proposed structure in agreement with model derived from X-ray.

Solvent have been removed using SQUEEZE procedure, approx. 4 molecules per unit cell ie. 0.5 per $C_{16}H_{22}O_5$

Table S2.1. Crystal data and structure refinement for shenvi_JR-VII-43

Identification code	shenvi_JR-VII-43	
Empirical formula	C16 H22 O5	
Formula weight	294.33	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 15.1830(5) Å	α = 90°
	b = 6.0100(2) Å	β = 95.228(2)°
	c = 36.8552(13) Å	γ = 90°
Volume	3349.0(2) Å^3	
Z	8	
Density (calculated)	1.168 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	1264	
Crystal size	0.15 x 0.06 x 0.05 mm^3	
Theta range for data collection	1.503 to 25.350°.	
Index ranges	-18<=h<=18, -7<=k<=4, -27<=l<=44	
Reflections collected	24496	
Independent reflections	6136 [R(int) = 0.0420]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4908 and 0.4619	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6136 / 0 / 385	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(**I**)]	R1 = 0.0544, wR2 = 0.1105	
R indices (all data)	R1 = 0.0772, wR2 = 0.1197	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.442 and -0.341 e.Å^{-3}	

Table S2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for shenvi_JR-VII-43. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
O(1)	6688(1)	12602(3)	7269(1)	20(1)
O(2)	4302(1)	4142(3)	7574(1)	21(1)
O(3)	3636(1)	7432(3)	7459(1)	23(1)
O(4)	6995(1)	6541(3)	5868(1)	30(1)
O(5)	6274(1)	9789(3)	5872(1)	26(1)
C(1)	7833(2)	11792(4)	6468(1)	24(1)
C(2)	7526(2)	10256(4)	6678(1)	20(1)
C(3)	6568(2)	9557(4)	6672(1)	17(1)
C(4)	6402(2)	7555(4)	6417(1)	18(1)
C(5)	6561(2)	8104(4)	6028(1)	20(1)
C(6)	5452(2)	6649(4)	6409(1)	21(1)
C(7)	5221(2)	6082(4)	6792(1)	19(1)
C(8)	5341(1)	8047(4)	7056(1)	14(1)
C(9)	4692(2)	9931(4)	6940(1)	19(1)
C(10)	5226(2)	7206(4)	7449(1)	16(1)
C(11)	5427(2)	8974(4)	7743(1)	18(1)
C(12)	6352(2)	9983(4)	7723(1)	19(1)
C(13)	6485(1)	10703(4)	7340(1)	18(1)
C(14)	6320(1)	8897(4)	7054(1)	16(1)
C(15)	4302(2)	6321(4)	7488(1)	16(1)
C(16)	3442(2)	3192(4)	7627(1)	24(1)
O(1')	6690(1)	3733(3)	3880(1)	24(1)
O(2')	9309(1)	11626(3)	3574(1)	24(1)
O(3')	9847(1)	8152(3)	3565(1)	26(1)
O(4')	6469(1)	10703(3)	5168(1)	32(1)
O(5')	6989(1)	7224(3)	5169(1)	26(1)
C(1')	5336(2)	5528(5)	4535(1)	34(1)
C(2')	5767(2)	7056(5)	4361(1)	28(1)
C(3')	6762(2)	7302(4)	4388(1)	18(1)
C(4')	7013(2)	9372(4)	4623(1)	22(1)
C(5')	6808(2)	8970(5)	5010(1)	22(1)
C(6')	7997(2)	9962(5)	4632(1)	25(1)

C(7')	8281(2)	10228(4)	4249(1)	23(1)
C(8')	8104(2)	8146(4)	4013(1)	18(1)
C(9')	8685(2)	6207(4)	4165(1)	22(1)
C(10')	8278(2)	8675(4)	3611(1)	19(1)
C(11')	8071(2)	6703(4)	3355(1)	21(1)
C(12')	7124(2)	5849(4)	3376(1)	22(1)
C(13')	6926(2)	5522(4)	3767(1)	20(1)
C(14')	7097(2)	7551(4)	4008(1)	17(1)
C(15')	9226(2)	9397(4)	3583(1)	19(1)
C(16')	10200(2)	12427(5)	3550(1)	28(1)

Table S2.3. Bond lengths [Å] and angles [°] for shenvi_JR-VII-43

O(1)-C(13)	1.217(3)	C(6')-C(7')	1.522(3)
O(2)-C(15)	1.347(3)	C(7')-C(8')	1.533(3)
O(2)-C(16)	1.456(3)	C(8')-C(9')	1.536(3)
O(3)-C(15)	1.209(3)	C(8')-C(10')	1.562(3)
O(4)-C(5)	1.316(3)	C(8')-C(14')	1.569(3)
O(5)-C(5)	1.224(3)	C(10')-C(11')	1.531(3)
C(1)-C(2)	1.319(3)	C(10')-C(15')	1.516(3)
C(2)-C(3)	1.512(3)	C(11')-C(12')	1.535(3)
C(3)-C(4)	1.534(3)	C(12')-C(13')	1.510(3)
C(3)-C(14)	1.543(3)	C(13')-C(14')	1.518(3)
C(4)-C(5)	1.512(3)		
C(4)-C(6)	1.540(3)	C(15)-O(2)-C(16)	115.57(19)
C(6)-C(7)	1.525(3)	C(1)-C(2)-C(3)	125.3(2)
C(7)-C(8)	1.531(3)	C(2)-C(3)-C(4)	109.31(19)
C(8)-C(9)	1.536(3)	C(2)-C(3)-C(14)	111.87(19)
C(8)-C(10)	1.557(3)	C(4)-C(3)-C(14)	108.57(19)
C(8)-C(14)	1.573(3)	C(3)-C(4)-C(6)	112.97(19)
C(10)-C(11)	1.528(3)	C(5)-C(4)-C(3)	112.3(2)
C(10)-C(15)	1.520(3)	C(5)-C(4)-C(6)	106.76(19)
C(11)-C(12)	1.538(3)	O(4)-C(5)-C(4)	113.3(2)
C(12)-C(13)	1.508(3)	O(5)-C(5)-O(4)	123.6(2)
C(13)-C(14)	1.516(3)	O(5)-C(5)-C(4)	123.0(2)
O(1')-C(13')	1.219(3)	C(7)-C(6)-C(4)	110.78(19)
O(2')-C(15')	1.346(3)	C(6)-C(7)-C(8)	113.1(2)
O(2')-C(16')	1.446(3)	C(7)-C(8)-C(9)	110.80(19)
O(3')-C(15')	1.210(3)	C(7)-C(8)-C(10)	108.87(19)
O(4')-C(5')	1.320(3)	C(7)-C(8)-C(14)	107.78(18)
O(5')-C(5')	1.221(3)	C(9)-C(8)-C(10)	112.09(18)
C(1')-C(2')	1.325(4)	C(9)-C(8)-C(14)	110.00(19)
C(2')-C(3')	1.511(3)	C(10)-C(8)-C(14)	107.14(17)
C(3')-C(4')	1.544(4)	C(11)-C(10)-C(8)	113.63(19)
C(3')-C(14')	1.539(3)	C(15)-C(10)-C(8)	112.60(18)
C(4')-C(5')	1.508(3)	C(15)-C(10)-C(11)	107.55(18)
C(4')-C(6')	1.533(3)	C(10)-C(11)-C(12)	111.37(19)
C(13)-C(12)-C(11)	111.00(19)	C(6')-C(7')-C(8')	113.0(2)

O(1)-C(13)-C(12)	121.9(2)	C(7')-C(8')-C(9')	110.4(2)
O(1)-C(13)-C(14)	123.5(2)	C(7')-C(8')-C(10')	109.61(19)
C(12)-C(13)-C(14)	114.6(2)	C(7')-C(8')-C(14')	108.21(19)
C(3)-C(14)-C(8)	113.38(18)	C(9')-C(8')-C(10')	111.09(19)
C(13)-C(14)-C(3)	114.2(2)	C(9')-C(8')-C(14')	111.0(2)
C(13)-C(14)-C(8)	109.01(18)	C(10')-C(8')-C(14')	106.46(18)
O(2)-C(15)-C(10)	112.5(2)	C(11')-C(10')-C(8')	112.7(2)
O(3)-C(15)-O(2)	122.7(2)	C(15')-C(10')-C(8')	111.55(19)
O(3)-C(15)-C(10)	124.8(2)	C(15')-C(10')-C(11')	108.78(19)
C(15')-O(2')-C(16')	115.0(2)	C(10')-C(11')-C(12')	111.59(19)
C(1')-C(2')-C(3')	124.9(3)	C(13')-C(12')-C(11')	111.2(2)
C(2')-C(3')-C(4')	108.0(2)	O(1')-C(13')-C(12')	122.1(2)
C(2')-C(3')-C(14')	111.28(19)	O(1')-C(13')-C(14')	123.2(2)
C(14')-C(3')-C(4')	110.3(2)	C(12')-C(13')-C(14')	114.6(2)
C(5')-C(4')-C(3')	109.9(2)	C(3')-C(14')-C(8')	114.47(19)
C(5')-C(4')-C(6')	107.5(2)	C(13')-C(14')-C(3')	113.7(2)
C(6')-C(4')-C(3')	112.9(2)	C(13')-C(14')-C(8')	107.77(19)
O(4')-C(5')-C(4')	114.4(2)	O(2')-C(15')-C(10')	112.2(2)
O(5')-C(5')-O(4')	123.2(2)	O(3')-C(15')-O(2')	122.6(2)
O(5')-C(5')-C(4')	122.3(2)	O(3')-C(15')-C(10')	125.2(2)
C(7')-C(6')-C(4')	111.1(2)		

Table S2.4. Anisotropic displacement parameters ($Å^2$x 10^3) for shenvi_JR-VII-43. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 $a^{*2}U^{11}$ + … + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	19(1)	16(1)	27(1)	-2(1)	6(1)	-3(1)
O(2)	16(1)	18(1)	29(1)	2(1)	6(1)	-2(1)
O(3)	15(1)	21(1)	33(1)	5(1)	6(1)	2(1)
O(4)	40(1)	31(1)	19(1)	1(1)	11(1)	10(1)
O(5)	31(1)	29(1)	19(1)	2(1)	6(1)	6(1)
C(1)	21(1)	30(2)	22(1)	1(1)	4(1)	-2(1)
C(2)	16(1)	27(2)	18(1)	0(1)	1(1)	2(1)
C(3)	15(1)	20(1)	16(1)	2(1)	2(1)	2(1)
C(4)	19(1)	19(1)	16(1)	0(1)	4(1)	2(1)
C(5)	19(1)	24(2)	19(1)	-2(1)	4(1)	0(1)
C(6)	26(1)	21(1)	17(1)	-6(1)	4(1)	-4(1)
C(7)	18(1)	21(1)	19(1)	0(1)	3(1)	-3(1)
C(8)	13(1)	17(1)	13(1)	-1(1)	2(1)	-1(1)
C(9)	16(1)	22(1)	19(1)	3(1)	4(1)	1(1)
C(10)	14(1)	16(1)	17(1)	1(1)	2(1)	-1(1)
C(11)	19(1)	18(1)	16(1)	1(1)	5(1)	-1(1)
C(12)	16(1)	24(1)	17(1)	-4(1)	1(1)	-3(1)
C(13)	7(1)	22(1)	24(1)	-1(1)	1(1)	1(1)
C(14)	13(1)	17(1)	17(1)	1(1)	1(1)	1(1)
C(15)	20(1)	17(1)	12(1)	0(1)	4(1)	-1(1)
C(16)	17(1)	22(1)	34(2)	0(1)	8(1)	-6(1)
O(1')	24(1)	23(1)	26(1)	1(1)	4(1)	-4(1)
O(2')	22(1)	24(1)	28(1)	3(1)	7(1)	-2(1)
O(3')	22(1)	23(1)	34(1)	-2(1)	8(1)	1(1)
O(4')	51(1)	28(1)	20(1)	0(1)	14(1)	10(1)
O(5')	35(1)	26(1)	18(1)	2(1)	8(1)	3(1)
C(1')	28(2)	48(2)	28(2)	-7(1)	10(1)	-10(1)
C(2')	24(1)	44(2)	16(1)	-5(1)	6(1)	0(1)
C(3')	19(1)	22(1)	16(1)	1(1)	4(1)	0(1)
C(4')	25(1)	24(1)	19(1)	2(1)	6(1)	2(1)
C(5')	23(1)	26(2)	18(1)	-3(1)	4(1)	-1(1)
C(6')	30(1)	25(2)	19(1)	-3(1)	4(1)	-6(1)
C(7')	26(1)	21(1)	22(1)	0(1)	6(1)	-3(1)

C(8')	20(1)	17(1)	17(1)	1(1)	5(1)	0(1)
C(9')	22(1)	22(1)	22(1)	2(1)	4(1)	-1(1)
C(10')	20(1)	17(1)	20(1)	2(1)	5(1)	2(1)
C(11')	19(1)	26(1)	17(1)	-1(1)	4(1)	0(1)
C(12')	21(1)	24(1)	19(1)	-5(1)	3(1)	1(1)
C(13')	12(1)	27(2)	21(1)	0(1)	2(1)	3(1)
C(14')	17(1)	19(1)	16(1)	2(1)	2(1)	1(1)
C(15')	24(1)	19(1)	13(1)	2(1)	3(1)	-1(1)
C(16')	25(1)	25(2)	36(2)	6(1)	7(1)	-5(1)

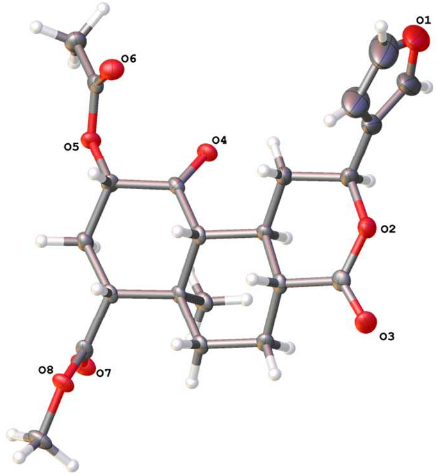
Table S2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for shenvi_JR-VII-43

	x	y	z	U(eq)
H(4)	7003	6841	5646	44
H(1A)	7441	12557	6295	29
H(1B)	8447	12133	6489	29
H(2)	7940	9530	6848	24
H(3)	6183	10820	6579	21
H(4A)	6819	6340	6504	21
H(6A)	5032	7778	6300	25
H(6B)	5395	5299	6254	25
H(7A)	5600	4836	6888	23
H(7B)	4599	5574	6780	23
H(9A)	4085	9364	6928	28
H(9B)	4815	10487	6700	28
H(9C)	4762	11143	7118	28
H(10)	5651	5951	7502	19
H(11A)	5391	8296	7986	21
H(11B)	4977	10168	7712	21
H(12A)	6425	11281	7888	23
H(12B)	6807	8867	7805	23
H(14)	6711	7619	7136	19
H(16A)	3013	3635	7425	36
H(16B)	3245	3737	7857	36
H(16C)	3487	1566	7635	36
H(4')	6389	10382	5384	49
H(1'A)	5654	4483	4689	41
H(1'B)	4708	5479	4504	41
H(2')	5426	8072	4209	33
H(3')	7039	5956	4510	22
H(4'A)	6656	10668	4523	27
H(6'A)	8110	11367	4769	30
H(6'B)	8353	8774	4761	30
H(7'A)	8921	10574	4265	27
H(7'B)	7959	11502	4129	27
H(9'A)	8505	5769	4404	32

H(9'B)	9306	6675	4191	32
H(9'C)	8615	4941	3998	32
H(10')	7883	9936	3525	22
H(11C)	8494	5483	3420	25
H(11D)	8146	7163	3101	25
H(12C)	6700	6931	3256	26
H(12D)	7048	4418	3244	26
H(14')	6761	8813	3885	21
H(16D)	10412	11923	3320	43
H(16E)	10587	11844	3755	43
H(16F)	10203	14057	3558	43

X-Ray Structure Determination for (±)-20-nor-salvinorin A

Crystals of **20-nor-1** were grown by slow evaporation from a ca. 1:1 mixture of (distilled) EtOAc and (distilled) cyclohexane and found to be suitable for X-ray diffraction.



The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_{α} radiation ($\lambda = 0.71073$ Å). A 0.400 x 0.230 x 0.220 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using φ and ϖ scans. Crystal-to-detector distance was 50 mm and exposure time was 3 seconds per frame using a scan width of 1.0°. Data collection was 100% complete to 25.00° in θ. A total of 12045 reflections were collected covering the indices, -27 <=h<=29, -6<=k<=7, -34<=l<=21. 3560 reflections were found to be symmetry independent, with a R_{int} of 0.0924. Indexing and unit cell refinement indicated a *C*-centered, monoclinic lattice. The space group was found to be *C*2/c. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table S3.

Table S3.1. Crystal data and structure refinement for shenvi114_0m_a

Identification code	shenvi114_0m_a	
Empirical formula	C22 H26 O8	
Formula weight	418.43	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c [racemic]	
Unit cell dimensions	a = 25.102(2) Å	α = 90°
	b = 6.0323(6) Å	β = 111.423(5)°
	c = 28.707(3) Å	γ = 90°
Volume	4046.6(7) $Å^3$	
Z	8	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	1776	
Crystal size	0.4 x 0.23 x 0.22 mm^3	
Theta range for data collection	1.743 to 24.994°.	
Index ranges	-27<=h<=29, -6<=k<=7, -34<=l<=21	
Reflections collected	12045	
Independent reflections	3560 [R(int) = 0.0924]	
Completeness to theta = 24.994°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.2590 and 0.0901	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3560 / 0 / 274	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(**I**)]	R1 = 0.0592, wR2 = 0.1322	
R indices (all data)	R1 = 0.0966, wR2 = 0.1539	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.260 and -0.281 e.$Å^{-3}$	

Table S3.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for shenvi114_0m_a. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
O(8)	5289(1)	2140(3)	3433(1)	21(1)
O(5)	6358(1)	10025(3)	4592(1)	21(1)
O(4)	6979(1)	10406(3)	4000(1)	22(1)
O(7)	4920(1)	5489(3)	3157(1)	26(1)
O(2)	8271(1)	5925(3)	3217(1)	25(1)
O(6)	7268(1)	9853(3)	5137(1)	28(1)
O(3)	7800(1)	3437(3)	2665(1)	28(1)
C(13)	6857(1)	6577(4)	3724(1)	16(1)
C(21)	5320(1)	4365(4)	3402(1)	18(1)
C(15)	6794(1)	8558(5)	4023(1)	17(1)
C(8)	7313(1)	4763(5)	3190(1)	19(1)
C(12)	6247(1)	5885(4)	3359(1)	16(1)
C(7)	7277(1)	6931(4)	3456(1)	18(1)
C(17)	5871(1)	7105(5)	4044(1)	20(1)
C(19)	6812(1)	10775(5)	4978(1)	21(1)
C(11)	6301(1)	3857(4)	3058(1)	18(1)
C(18)	5913(1)	5194(4)	3704(1)	17(1)
C(16)	6457(1)	8042(4)	4352(1)	18(1)
C(10)	6734(1)	4111(5)	2803(1)	20(1)
C(9)	7795(1)	4701(5)	2989(1)	21(1)
C(14)	5953(1)	7792(5)	3003(1)	21(1)
C(6)	7873(1)	7548(5)	3806(1)	24(1)
C(22)	4745(1)	1159(4)	3137(1)	25(1)
C(5)	8251(1)	7905(5)	3505(1)	27(1)
C(20)	6671(1)	12851(5)	5194(1)	27(1)
O(1)	9655(1)	10346(9)	4194(1)	103(2)
C(4)	8848(1)	8440(6)	3825(1)	41(1)
C(3)	9235(1)	7130(9)	4214(1)	68(1)
C(1)	9126(2)	10367(8)	3828(2)	65(1)
C(2)	9711(2)	8343(13)	4420(2)	102(2)

Table S3.3. Bond lengths [Å] and angles [°] for shenvi114_0m_a

O(8)-C(21)	1.349(3)	C(10)-H(10A)	0.9900
O(8)-C(22)	1.447(3)	C(10)-H(10B)	0.9900
O(5)-C(19)	1.345(3)	C(14)-H(14A)	0.9800
O(5)-C(16)	1.446(3)	C(14)-H(14B)	0.9800
O(4)-C(15)	1.218(3)	C(14)-H(14C)	0.9800
O(7)-C(21)	1.203(3)	C(6)-H(6A)	0.9900
O(2)-C(9)	1.354(3)	C(6)-H(6B)	0.9900
O(2)-C(5)	1.464(3)	C(6)-C(5)	1.513(4)
O(6)-C(19)	1.203(3)	C(22)-H(22A)	0.9800
O(3)-C(9)	1.205(3)	C(22)-H(22B)	0.9800
C(13)-H(13)	1.0000	C(22)-H(22C)	0.9800
C(13)-C(15)	1.511(4)	C(5)-H(5)	1.0000
C(13)-C(12)	1.565(3)	C(5)-C(4)	1.481(4)
C(13)-C(7)	1.531(3)	C(20)-H(20A)	0.9800
C(21)-C(18)	1.508(4)	C(20)-H(20B)	0.9800
C(15)-C(16)	1.513(4)	C(20)-H(20C)	0.9800
C(8)-H(8)	1.0000	O(1)-C(1)	1.359(5)
C(8)-C(7)	1.533(4)	O(1)-C(2)	1.355(7)
C(8)-C(10)	1.523(4)	C(4)-C(3)	1.421(5)
C(8)-C(9)	1.520(4)	C(4)-C(1)	1.354(5)
C(12)-C(11)	1.533(4)	C(3)-H(3)	0.9500
C(12)-C(18)	1.570(4)	C(3)-C(2)	1.341(6)
C(12)-C(14)	1.536(4)	C(1)-H(1)	0.9500
C(7)-H(7)	1.0000	C(2)-H(2)	0.9500
C(7)-C(6)	1.513(4)	C(21)-O(8)-C(22)	115.6(2)
C(17)-H(17A)	0.9900	C(19)-O(5)-C(16)	115.5(2)
C(17)-H(17B)	0.9900	C(9)-O(2)-C(5)	120.7(2)
C(17)-C(18)	1.538(4)	C(15)-C(13)-H(13)	107.2
C(17)-C(16)	1.521(3)	C(15)-C(13)-C(12)	108.1(2)
C(19)-C(20)	1.498(4)	C(15)-C(13)-C(7)	114.2(2)
C(11)-H(11A)	0.9900	C(12)-C(13)-H(13)	107.2
C(11)-H(11B)	0.9900	C(7)-C(13)-H(13)	107.2
C(11)-C(10)	1.524(4)	C(7)-C(13)-C(12)	112.7(2)
C(18)-H(18)	1.0000	O(8)-C(21)-C(18)	111.1(2)
C(16)-H(16)	1.0000	O(7)-C(21)-O(8)	122.9(2)

O(7)-C(21)-C(18)	126.0(2)	C(10)-C(11)-H(11A)	108.6
O(4)-C(15)-C(13)	124.9(2)	C(10)-C(11)-H(11B)	108.6
O(4)-C(15)-C(16)	122.1(2)	C(21)-C(18)-C(12)	111.5(2)
C(13)-C(15)-C(16)	112.9(2)	C(21)-C(18)-C(17)	109.4(2)
C(7)-C(8)-H(8)	105.6	C(21)-C(18)-H(18)	107.9
C(10)-C(8)-H(8)	105.6	C(12)-C(18)-H(18)	107.9
C(10)-C(8)-C(7)	111.6(2)	C(17)-C(18)-C(12)	112.1(2)
C(9)-C(8)-H(8)	105.6	C(17)-C(18)-H(18)	107.9
C(9)-C(8)-C(7)	114.2(2)	O(5)-C(16)-C(15)	111.1(2)
C(9)-C(8)-C(10)	113.3(2)	O(5)-C(16)-C(17)	106.7(2)
C(13)-C(12)-C(18)	105.5(2)	O(5)-C(16)-H(16)	109.4
C(11)-C(12)-C(13)	108.9(2)	C(15)-C(16)-C(17)	110.9(2)
C(11)-C(12)-C(18)	108.8(2)	C(15)-C(16)-H(16)	109.4
C(11)-C(12)-C(14)	110.0(2)	C(17)-C(16)-H(16)	109.4
C(14)-C(12)-C(13)	111.1(2)	C(8)-C(10)-C(11)	109.5(2)
C(14)-C(12)-C(18)	112.5(2)	C(8)-C(10)-H(10A)	109.8
C(13)-C(7)-C(8)	107.9(2)	C(8)-C(10)-H(10B)	109.8
C(13)-C(7)-H(7)	109.1	C(11)-C(10)-H(10A)	109.8
C(8)-C(7)-H(7)	109.1	C(11)-C(10)-H(10B)	109.8
C(6)-C(7)-C(13)	113.3(2)	H(10A)-C(10)-H(10B)	108.2
C(6)-C(7)-C(8)	108.4(2)	O(2)-C(9)-C(8)	119.2(2)
C(6)-C(7)-H(7)	109.1	O(3)-C(9)-O(2)	117.5(2)
H(17A)-C(17)-H(17B)	107.9	O(3)-C(9)-C(8)	122.9(3)
C(18)-C(17)-H(17A)	109.3	C(12)-C(14)-H(14A)	109.5
C(18)-C(17)-H(17B)	109.3	C(12)-C(14)-H(14B)	109.5
C(16)-C(17)-H(17A)	109.3	C(12)-C(14)-H(14C)	109.5
C(16)-C(17)-H(17B)	109.3	H(14A)-C(14)-H(14B)	109.5
C(16)-C(17)-C(18)	111.8(2)	H(14A)-C(14)-H(14C)	109.5
O(5)-C(19)-C(20)	111.4(2)	H(14B)-C(14)-H(14C)	109.5
O(6)-C(19)-O(5)	124.0(3)	C(7)-C(6)-H(6A)	109.8
O(6)-C(19)-C(20)	124.5(3)	C(7)-C(6)-H(6B)	109.8
C(12)-C(11)-H(11A)	108.6	H(6A)-C(6)-H(6B)	108.3
C(12)-C(11)-H(11B)	108.6	C(5)-C(6)-C(7)	109.3(2)
H(11A)-C(11)-H(11B)	107.6	C(5)-C(6)-H(6A)	109.8
C(10)-C(11)-C(12)	114.6(2)	C(5)-C(6)-H(6B)	109.8
O(8)-C(22)-H(22A)	109.5	H(20A)-C(20)-H(20C)	109.5
O(8)-C(22)-H(22B)	109.5	H(20B)-C(20)-H(20C)	109.5

O(8)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
O(2)-C(5)-C(6)	111.4(2)
O(2)-C(5)-H(5)	108.7
O(2)-C(5)-C(4)	107.0(2)
C(6)-C(5)-H(5)	108.7
C(4)-C(5)-C(6)	112.3(3)
C(4)-C(5)-H(5)	108.7
C(19)-C(20)-H(20A)	109.5
C(19)-C(20)-H(20B)	109.5
C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20B)	109.5
C(2)-O(1)-C(1)	106.2(4)
C(3)-C(4)-C(5)	127.8(3)
C(1)-C(4)-C(5)	126.4(4)
C(1)-C(4)-C(3)	105.7(3)
C(4)-C(3)-H(3)	126.7
C(2)-C(3)-C(4)	106.6(5)
C(2)-C(3)-H(3)	126.7
O(1)-C(1)-H(1)	124.7
C(4)-C(1)-O(1)	110.6(5)
C(4)-C(1)-H(1)	124.7
O(1)-C(2)-H(2)	124.6
C(3)-C(2)-O(1)	110.8(5)
C(3)-C(2)-H(2)	124.6

Table S3.4. Anisotropic displacement parameters ($Å^2$x 10^3) for shenvi114_0m_a. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 $a^{*2}U^{11}$ + … + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(8)	20(1)	11(1)	31(1)	-1(1)	8(1)	-2(1)
O(5)	21(1)	15(1)	27(1)	-7(1)	11(1)	-2(1)
O(4)	26(1)	13(1)	27(1)	-2(1)	10(1)	-3(1)
O(7)	21(1)	14(1)	37(1)	2(1)	6(1)	1(1)
O(2)	24(1)	28(1)	29(1)	-5(1)	15(1)	-3(1)
O(6)	28(1)	24(1)	28(1)	-2(1)	7(1)	2(1)
O(3)	34(1)	19(1)	38(1)	-8(1)	21(1)	0(1)
C(13)	20(1)	11(2)	20(1)	5(1)	10(1)	0(1)
C(21)	25(2)	7(2)	26(2)	-2(1)	15(1)	-1(1)
C(15)	16(1)	15(2)	21(2)	2(1)	6(1)	-2(1)
C(8)	24(1)	12(2)	24(2)	3(1)	14(1)	-1(1)
C(12)	20(1)	9(1)	22(2)	1(1)	11(1)	-2(1)
C(7)	23(1)	11(2)	21(2)	-3(1)	11(1)	-4(1)
C(17)	21(1)	15(2)	26(2)	-1(1)	13(1)	-1(1)
C(19)	25(2)	17(2)	23(2)	3(1)	12(1)	-5(1)
C(11)	22(1)	11(2)	24(2)	3(1)	11(1)	-2(1)
C(18)	19(1)	9(1)	24(2)	3(1)	10(1)	0(1)
C(16)	26(2)	10(2)	24(2)	-4(1)	14(1)	0(1)
C(10)	29(2)	12(2)	25(2)	-4(1)	15(1)	-3(1)
C(9)	28(2)	13(2)	26(2)	3(1)	12(1)	1(1)
C(14)	24(1)	15(2)	25(2)	5(1)	9(1)	-2(1)
C(6)	27(2)	26(2)	25(2)	-6(2)	15(1)	-9(1)
C(22)	20(1)	13(2)	38(2)	-1(1)	6(1)	-5(1)
C(5)	34(2)	24(2)	32(2)	-11(2)	21(2)	-10(1)
C(20)	34(2)	21(2)	31(2)	-7(2)	16(2)	-2(1)
O(1)	61(2)	193(4)	69(2)	-58(3)	39(2)	-82(3)
C(4)	30(2)	63(3)	38(2)	-24(2)	22(2)	-21(2)
C(3)	26(2)	128(4)	48(2)	-12(3)	11(2)	-16(2)
C(1)	50(2)	98(4)	61(3)	-41(3)	37(2)	-47(2)
C(2)	37(3)	216(8)	53(3)	-17(4)	14(2)	-40(4)

Table S3.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for shenvi114_0m_a.

	x	y	z	U(eq)
H(13)	7009	5328	3966	20
H(8)	7408	3590	3454	22
H(7)	7126	8128	3200	21
H(17A)	5629	8299	3835	23
H(17B)	5684	6562	4272	23
H(11A)	6411	2562	3285	22
H(11B)	5921	3539	2799	22
H(18)	6128	3954	3924	20
H(16)	6672	6940	4613	22
H(10A)	6770	2695	2643	24
H(10B)	6603	5263	2540	24
H(14A)	5905	9059	3198	32
H(14B)	5578	7301	2772	32
H(14C)	6190	8232	2813	32
H(6A)	7858	8920	3990	29
H(6B)	8033	6347	4052	29
H(22A)	4687	1266	2781	38
H(22B)	4437	1950	3200	38
H(22C)	4742	-403	3230	38
H(5)	8092	9161	3267	33
H(20A)	6317	13494	4956	41
H(20B)	6984	13918	5260	41
H(20C)	6617	12501	5508	41
H(3)	9168	5678	4309	81
H(1)	8972	11567	3605	78
H(2)	10042	7864	4689	123