

Supporting Information

“Stereocontrolled Synthesis of Kalihinol C”

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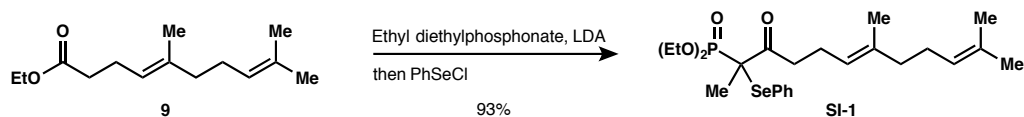
10550 North Torrey Pines Road, La Jolla, CA 92037

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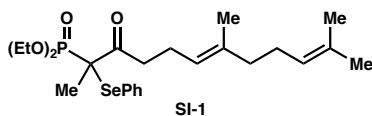
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Materials and methods. All reactions were carried out under positive pressure of argon in a well-ventilated fume hood unless otherwise noted. Hexanes (ACS grade), ethyl acetate (ACS grade), toluene (ACS grade), and diethyl ether (anhydrous ACS grade) were purchased from Sigma-Aldrich and used without further purification. Dichloromethane (ACS grade), acetonitrile (ACS grade), chloroform (ACS grade), and isopropanol (ACS grade) were purchased from Fisher Chemical and used without further purification. Anhydrous tetrahydrofuran was purchased from Sigma-Aldrich. Anhydrous dichloromethane was distilled from calcium hydride (10% w/v) under positive pressure of argon. Anhydrous DMSO was purchased from Acros Organic and further dried by fractional distillation under reduced pressure onto activated 4Å molecular sieves (discarding the first 20%). Anhydrous ethyl acetate was distilled from calcium hydride (10% w/v) under positive pressure of argon. Anhydrous 1,2-dichlorobenzene was distilled from calcium hydride (10% w/v) under positive pressure of argon. Commercially available reagents were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates from EMD Chemicals (TLC Silica gel 60 F₂₅₄). Flash column chromatography was performed over Silica gel 60 (particle size 0.04-0.063 mm) from EMD chemicals. GC/MS analysis was performed on Agilent 7820A/5975 GC/MSD system with helium as the carrier gas. ¹H NMR and ¹³C 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 ¹H NMR, 77.00 ppm ¹³C NMR; C₆D₆ @ 7.16 ppm ¹H NMR, 128.00 ppm ¹³C NMR). Low resolution mass spectra were recorded on an Agilent 6120 Quadrupole LC/MS system with an ESI probe.

Experimental procedures.



Selenide SI-1. A solution of *N,N*-diisopropylamine (11.8 mL, 84.2 mmol) in anhydrous THF (43 mL) was cooled to 0 °C and treated with *n*-BuLi (29.9 mL of a 2.68 M solution in hexanes, 80.1 mmol). In a separate flask, ester **9**¹ (8.86 g, 39.5 mmol) and ethyl diethylphosphonate (6.4 mL, 39.5 mmol) were dissolved in anhydrous THF (66 mL) and cooled to -10 °C. According to Maloney et al.,² this solution was treated drop-wise with the previously prepared solution of LDA. The reaction mixture was then cooled to -78 °C and treated drop-wise with a solution of PhSeCl (15.1 g, 78.8 mmol) in anhydrous THF (158 mL). The reaction mixture was subsequently quenched at the same temperature with saturated aqueous ammonium chloride. The resulting mixture was stirred vigorously as it warmed to room temperature and then diluted with hexanes. The layers were separated, and the aqueous phase was extracted three times with hexanes. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 30% AcOEt in hexanes) afforded 18.3 g (93% yield) of selenide **SI-1** as a yellow oil.



Selenide SI-1

¹H NMR (400 MHz, C₆D₆):

δ 7.58-7.53 (m, 2 H)	4.02-3.88 (m, 2 H)	1.67 (br s, 6 H)
7.02-6.90 (m, 3 H)	3.66 (ddd, <i>J</i> = 17.0, 8.7, 6.8 Hz, 1 H)	1.65 (d, <i>J</i> = 14.9 Hz, 3 H)
5.40 (t, <i>J</i> = 7.0 Hz, 1 H)	3.18 (ddd, <i>J</i> = 17.2, 8.5, 6.0 Hz, 1 H)	1.54 (br s, 3 H)
5.22 (t, <i>J</i> = 6.9 Hz, 1 H)	2.75-2.56 (m, 2 H)	1.06 (t, <i>J</i> = 7.1 Hz, 3 H)
4.17-4.06 (m, 2 H)	2.21-2.03 (m, 4 H)	1.00 (t, <i>J</i> = 7.1 Hz, 3 H)

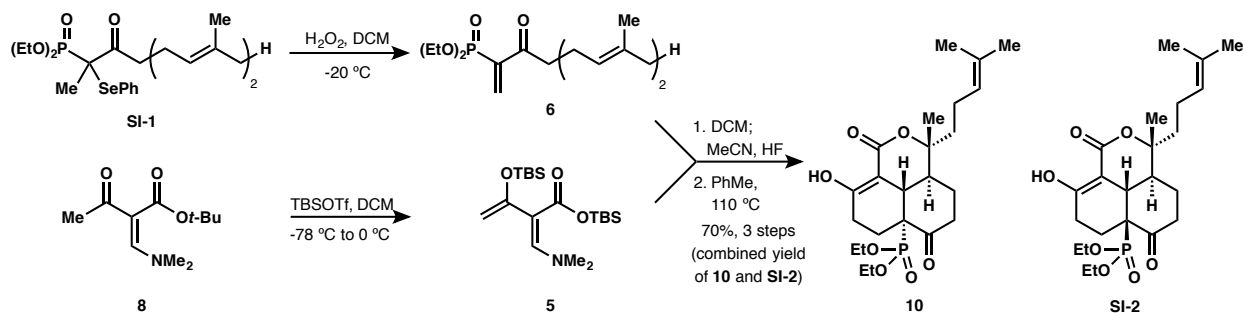
¹³C NMR (150 MHz, C₆D₆):

δ 201.52 (d, ² <i>J</i> _{C-P} = 2.7 Hz)	123.85	24.09
138.21	64.06 (d, ² <i>J</i> _{C-P} = 6.7 Hz)	19.23 (d, ² <i>J</i> _{C-P} = 3.2 Hz)
136.08	63.03 (d, ² <i>J</i> _{C-P} = 7.4 Hz)	17.72
131.12	53.72 (d, ¹ <i>J</i> _{C-P} = 138.4 Hz)	16.49 (d, ³ <i>J</i> _{C-P} = 5.4 Hz)
129.67	40.18	16.32 (d, ³ <i>J</i> _{C-P} = 5.6 Hz)
129.14	40.01	16.17
126.12 (d, ³ <i>J</i> _{C-P} = 6.0 Hz)	27.13	
124.89	25.83	

GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C 0 min, then 30 °C/min to 280 °C, then hold 10 min at 280 °C): due to thermal instability of **SI-1**, two peaks were observed corresponding to (SePh)₂ (*t_R* = 6.844 min) and reductively de-selenated **SI-1** (*t_R* = 7.422 min, see mass data below).

MS (EI, 70 eV): *m/z* (%) 344.2 (0.2, M⁺), 275.1 (3), 235.1 (31), 221.1 (13), 193.1 (28), 165.0 (37), 137.0 (35), 109.0 (28), 81.0 (16), 69.1 (16)

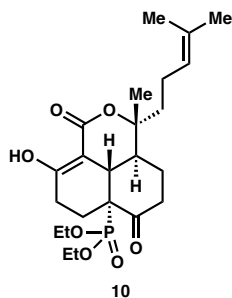
TLC: R_f = 0.46 (40% AcOEt in hexanes)



Phosphonate 10. A solution of vinylogous carbamate **8**³ (9.0 g, 42.2 mmol) and triethylamine (29.3 mL, 210 mmol) in anhydrous dichloromethane (422 mL) was cooled to -78°C and treated drop-wise with TBSOTf (24.1 mL, 105 mmol). The reaction mixture was allowed to warm to 0°C , stirred 10 min, and diluted with hexanes (to approx. 3:1 hexanes/DCM). The reaction mixture was quenched with water, and the resulting biphasic mixture was stirred vigorously 30 min. Layers were separated, and the aqueous phase was extracted three times with hexanes. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure to deliver crude silyl ester **5**.

In a separate flask, a vigorously stirring solution of selenide **SI-1** (18.3 g, 36.7 mmol) in dichloromethane (367 mL) was cooled to -20°C and treated with aqueous H_2O_2 (12.6 mL of a 35% w/w solution, 147 mmol) (*Note 1*). The reaction mixture was stirred 2 h at this temperature and quenched with saturated aqueous NaHCO_3 . The resulting biphasic mixture was stirred vigorously as it warmed to room temperature, and then diluted with hexanes. Layers were separated, and the aqueous phase was extracted twice with hexanes. The combined organic layers were washed with saturated aqueous NaHCO_3 , brine, dried over Na_2SO_4 , concentrated under reduced pressure, and azeotroped with PhMe once. This residue was immediately dissolved in dichloromethane (74 mL) and treated with a solution of previously prepared silyl ester **5** in dichloromethane (84 mL). The resulting solution was allowed to stand 21 h at room temperature. To this solution was added acetonitrile (220 mL), and then aqueous HF (6.39 mL of a 50% w/w solution, 184 mmol). The reaction mixture was stirred 5 min, quenched with water, and diluted with AcOEt. Layers were separated, and the aqueous phase was extracted with AcOEt twice. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was dissolved in PhMe (734 mL) and heated at reflux for 12 h. The solution was allowed to cool to room temperature, and then loaded directly to a silica gel column. Purification by flash column chromatography on silica gel (elution with 50% AcOEt in hexanes) afforded 9.77 g (59% yield, over 3 steps) of phosphonate **10** as an orange solid and 1.86 g (11% yield, over 3 steps) of the C-P bond epimer (**SI-2**) as an orange oil.

Note 1: For the oxidative de-selenation, efforts to exclude air and moisture were not taken.



Phosphonate 10

^1H NMR (600 MHz, C_6D_6):

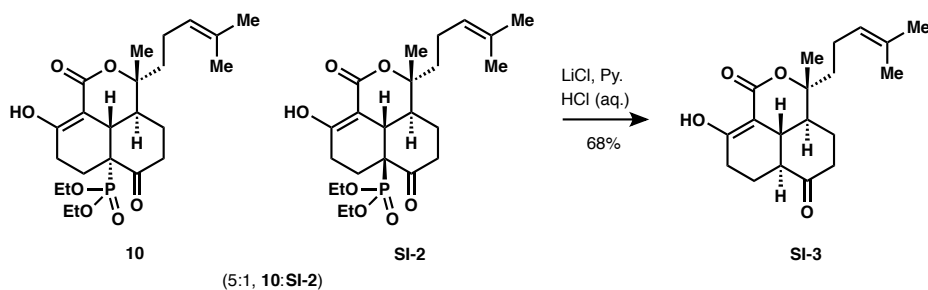
δ 5.09 (t, J = 7.2 Hz, 1 H)	2.49 (m, 1 H)	1.46-1.31 (m, 2 H)
4.02-3.86 (m, 2 H)	2.21-1.98 (m, 4 H)	1.20-1.13 (m, 1 H)
3.86-3.74 (m, 2 H)	1.91 (qd, J = 12.4, 6.4 Hz, 1 H)	1.05 (s, 3 H)
3.50 (dd, J = 22.8, 12.4 Hz, 1 H)	1.67 (s, 3 H)	0.99 (t, J = 7.0 Hz, 3 H)
2.83 (m, 1 H)	1.65-1.48 (m, 2 H)	0.90 (t, J = 7.1 Hz, 3 H)
2.68 (ddd, J = 17.8, 5.8, 1.2 Hz, 1 H)	1.53 (s, 3 H)	

^{13}C NMR (150 MHz, C_6D_6):

δ 207.03 ($^2J_{\text{C-P}}$ = 3.5 Hz)	62.82 ($^2J_{\text{C-P}}$ = 7.5 Hz)	25.62 ($^2J_{\text{C-P}}$ = 6.0 Hz)
176.49	53.85 ($^1J_{\text{C-P}}$ = 28.3 Hz)	22.60
171.47	42.03 ($^2J_{\text{C-P}}$ = 5.8 Hz)	21.85
132.04	40.33	21.35
124.06	38.77	17.65
94.66 ($^3J_{\text{C-P}}$ = 3.3 Hz)	33.75 ($^3J_{\text{C-P}}$ = 0.9 Hz)	16.34
84.68	26.84	16.30
63.42 ($^2J_{\text{C-P}}$ = 7.0 Hz)	25.81	

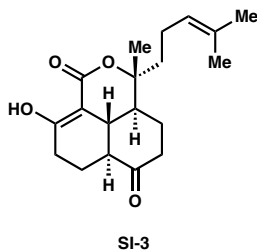
LRMS (ESI) calculated for $\text{C}_{23}\text{H}_{36}\text{O}_7\text{P}$ $[\text{M}+\text{H}]^+$: 455.2, found 455.3

TLC: R_f = 0.20 (50% AcOEt in hexanes)



Tricyclic lactone SI-3. The mixture of phosphonate **10** and its C-P bond epimer (**SI-2**) (3.00 g, 6.60 mmol) was dissolved in pyridine (66 mL) and treated sequentially with LiCl (1.40 g, 33.0 mmol) and 5.56 N aqueous HCl (5.94 mL, 33.0 mmol). The solution was degassed and heated to 90 °C for 13 h (mono-dealkylation). The reaction mixture was then heated to 110 °C for 10 h (dephosphonylation) (*Note 1*). The reaction mixture was diluted with AcOEt and poured into 1 N aqueous HCl. Layers were separated, and the aqueous layer was extracted with AcOEt twice. The combined organic layers were washed with 1 N aqueous HCl, brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 15% AcOEt in hexanes) delivered 1.44 g (68% yield) of tricyclic lactone **SI-3** as a pale yellow powder.

Note 1: Heating first to 90 °C, then to 110 °C is crucial to obtain complete conversion. Heating immediately to 110 °C causes the reaction to stall.



Tricyclic lactone **SI-3**

¹H NMR (600 MHz, C₆D₆):

δ 5.14 (t, <i>J</i> = 7.0 Hz, 1 H)	1.70 (s, 3 H)
2.19-2.08 (m, 4 H)	1.58 (s, 3 H)
2.06-1.99 (m, 1 H)	1.49-1.42 (m, 1 H)
1.99-1.93 (m, 1 H)	1.38-1.21 (m, 6 H)
1.80 (t, <i>J</i> = 11.5 Hz, 1 H)	0.76 (s, 3 H)
1.74 (td, <i>J</i> = 13.9, 6.3 Hz, 1 H)	

¹³C NMR (150 MHz, C₆D₆):

δ 206.95	48.72	25.81
175.04	41.87	21.62
170.85	40.02	21.10
132.16	40.01	20.79
124.00	39.11	17.69

95.31

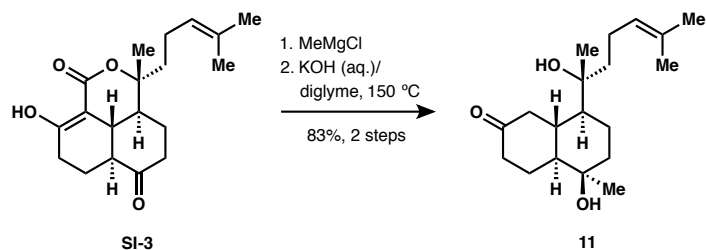
28.21

84.12

26.98

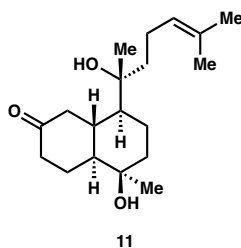
LRMS (ESI) calculated for $C_{19}H_{27}O_4$ $[M+H]^+$: 319.2, found 319.2

TLC: R_f = 0.46 (40% AcOEt in hexanes)



Ketodiol 11. A solution of tricyclic lactone **SI-3** (5.15 g, 16.2 mmol) in THF (162 mL) was cooled to -78°C and treated drop-wise with MeMgCl (20.3 mL of a 3.19 M solution in THF, 64.8 mmol). The resulting solution was allowed to warm to 0°C and stirred for 30 min. The reaction mixture was quenched carefully with saturated aqueous ammonium chloride and diluted with hexanes. The resulting biphasic mixture was stirred vigorously as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to deliver the crude alcohol (5.40 g). A portion of this intermediate (4.90 g, 14.7 mmol) was dissolved in degassed diglyme (74 mL). This solution was evenly divided (7.4 mL each, 1.47 mmol) among ten nitrogen-flushed 25 mL microwave vials containing BHT (3.2 mg, 0.0147 mmol). To each vial was added degassed aqueous potassium hydroxide (7.4 mL of a 0.5 M solution each, 3.70 mmol). These mixtures were heated to 150°C with stirring in an oil bath for 14 h behind a blast shield, then allowed to cool to room temperature (*Note 1*). The contents of each vial were combined, and each vial was rinsed with Et_2O and water. Layers were separated, and the aqueous phase was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 50% AcOEt in hexanes) delivered 3.76 g of ketodiol **11** (83% yield, over 2 steps) as a pale yellow powder.

Note 1: The reaction mixture is sufficiently basic to etch the glassware over the course of the reaction.



Ketodiol 11

^1H NMR (600 MHz, CDCl_3):

δ 5.13 (t, $J = 6.9$ Hz, 1 H)	2.04-1.91 (m, 2H)	1.42 (ddd, $J = 11.9, 10.6, 3.2$ Hz, 1 H)
3.23 (ddd, $J = 14.8, 3.7, 2.6$ Hz, 1 H)	1.76-1.71 (m, 1H)	1.39-1.31 (m, 3 H)
2.40 (ddt, $J = 14.0, 4.8, 2.7$ Hz, 1 H)	1.68 (s, 3 H)	1.29-1.23 (br s, 1H)
2.32 (tdd, $J = 14.0, 6.2, 1.1$ Hz, 1 H)	1.66-1.58 (m, 2H)	1.27 (s, 3 H)
2.19 (ddt, $J = 13.4, 6.1, 3.0$ Hz, 1 H)	1.61 (s, 3 H)	1.20-1.15 (br s, 1 H)
2.14-2.06 (m, 1 H)	1.57-1.49 (m, 2 H)	1.14 (s, 3 H)

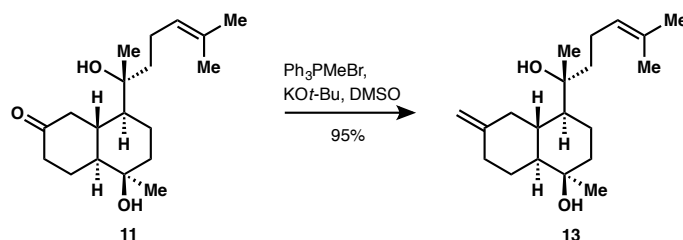
2.10 (ddd, $J = 15.0, 12.8, 1.1$ Hz, 1 H)

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

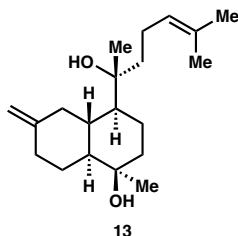
δ 212.40	47.82	25.59
132.07	42.89	23.72
124.18	40.68	23.17
75.63	40.65	21.35
70.17	39.93	17.72
50.85	29.03	
49.11	25.73	

LRMS (ESI) calculated for $\text{C}_{19}\text{H}_{32}\text{NaO}_3$ $[\text{M}+\text{Na}]^+$: 331.2, found 331.0; calculated for $\text{C}_{19}\text{H}_{31}\text{O}_2$ $[\text{M}-\text{OH}]^+$: 291.2, found 291.0; calculated for $\text{C}_{19}\text{H}_{29}\text{O}$ $[\text{M}-\text{H}_2\text{O}-\text{OH}]^+$: 273.2, found 273.0.

TLC: $R_f = 0.28$ (50% AcOEt in hexanes)



Diene 13. Ph_3PMeBr (7.95 g, 22.3 mmol) was dried by carefully melting under vacuum using a propane torch, placed under a nitrogen atmosphere, and allowed to solidify as it cooled to room temperature. The resulting glassy solid was broken up with a spatula with minimal exposure to air, then placed under an atmosphere of argon (balloon). To this solid was added an oven dried stir bar, followed by a solution of ketodiol **11** (3.26 g, 10.6 mmol) in anhydrous DMSO (106 mL). To this solution was added KOt-Bu (20.3 mL of a 1.04 M solution in THF, 21.1 mmol) in a rapid drop-wise fashion. After stirring 1 h, the reaction mixture was quenched with water (100 mL) and diluted with hexanes (200 mL). The resulting biphasic mixture was stirred vigorously 20 min. The layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 , and concentrated partially under reduced pressure. The resulting suspension was treated with minimal dichloromethane to effect complete dissolution, and loaded directly to a silica gel column. Purification by flash column chromatography on silica gel (elution with 20% AcOEt in hexanes) delivered 3.10 g of diene **13** (95% yield) as a pale yellow foam.



Diene 13

^1H NMR (400 MHz, CDCl_3):

δ 5.13 (tt, $J = 7.1, 1.3$ Hz, 1 H)	1.75-1.69 (m, 2 H)	1.29-1.21 (m, 3 H)
4.61 (br s, 1 H)	1.69 (s, 3 H)	1.20 (s, 3 H)
4.58 (br s, 1 H)	1.63 (s, 3 H)	1.19-1.16 (m, 1 H)
3.12 (ddd, $J = 13.4, 3.5, 1.9$ Hz, 1 H)	1.62-1.51 (m, 3 H)	1.17 (s, 3 H)
2.38-2.30 (m, 1 H)	1.46 (td, $J = 13.4, 3.9$ Hz, 1 H)	1.15 (br s, 1 H)
2.15-2.06 (m, 1 H)	1.39 (ddd, $J = 14.1, 10.9, 5.7$ Hz, 1 H)	
2.06-1.95 (m, 3 H)	1.32 (td, $J = 12.7, 3.4$ Hz, 1 H)	

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

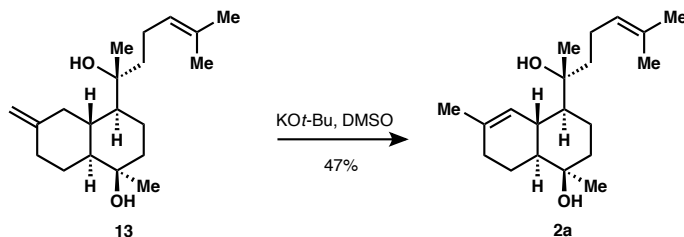
δ 149.44	50.11	27.29
131.93	42.79	25.74
124.41	41.33	23.94

106.79	41.07	23.02
76.00	40.64	21.45
70.41	34.51	17.73
51.03	28.84	

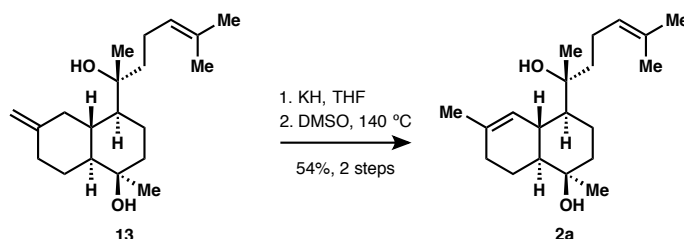
LRMS (ESI) calculated for $C_{20}H_{34}NaO_2$ $[M+Na]^+$: 329.2, found 329.0; calculated for $C_{20}H_{33}O$ $[M-OH]^+$: 289.3, found 289.0; calculated for $C_{20}H_{31}$ $[M-H_2O-OH]^+$: 271.2, found 271.1.

TLC: R_f = 0.43 (20% AcOEt in hexanes)

Isomerization procedures:



a) Protokalihinol (2a). To a flame-dried flask containing a stir bar and KOt-Bu (0.277 g, 2.47 mmol) was added a solution of diene **13** (0.189 g, 0.618 mmol) in anhydrous DMSO (25 mL). The solution was heated to 140 °C for 3 h, cooled to room temperature, quenched with water, and diluted with hexanes. After vigorously stirring 5 min, the layers were separated, and the aqueous phase was extracted with hexanes six times. The combined organic layers were washed with water, brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 0.192 g of crude **2a**. Purification by preparative TLC on silver impregnated silica (see below) afforded 89 mg of protokalihinol (**2a**) (47 % yield) as a pale yellow foam.



b) Protokalihinol (2a). To a flame-dried flask containing a stir bar (*Note 1*) was added a suspension of KH (0.185 g of ca. 35% w/w suspension). The suspension was freed from mineral oil by adding hexanes (ca. 1 mL), stirring vigorously under nitrogen, removing the majority of hexanes by syringe (*Note 2*), concentrating the resulting suspension under reduced pressure (*Note 3*), and replacing the atmosphere with nitrogen (this procedure was repeated five times) (*Note 4*). To the solid KH (69 mg, 1.72 mmol) was added anhydrous THF (3.48 mL), and the stirring suspension was cooled to 0 °C. A solution of diene **13** (0.424 g, 1.39 mmol) in THF (3.48 mL) was introduced drop-wise at this temperature. The effervescing mixture was allowed to warm to room temperature and stirred 1 h. A portion of this solution (6.25 mL, 1.25 mmol) was transferred to a flame-dried flask. This solution was concentrated under a stream of argon, then under reduced pressure without exposure to air. The resulting residue was placed under an atmosphere of argon, dissolved in anhydrous DMSO (25 mL), heated to 140 °C for 3 h, cooled to room temperature, quenched with water, and diluted with hexanes. After vigorously stirring the biphasic mixture 20 min, the layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with water, brine, dried over Na₂SO₄, and concentrated under

reduced pressure. Purification by preparative TLC on silver impregnated silica (see below) afforded 0.207 g of protokalihinol (**2a**) (54% yield, over 2 steps) as a pale yellow foam.

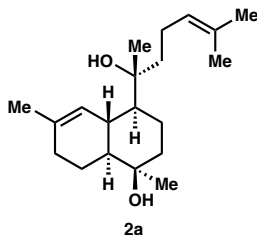
Note 1: The mass of the flask, stir bar, and septum was recorded at this point, prior to addition of KH.

Note 2: The hexanes rinses typically contain a trace of KH and thus were quenched by adding directly to a 1:1 mixture of hexanes and isopropanol.

Note 3: All manipulations must be performed without exposure to air, as KH is extremely pyrophoric.

Note 4: The mass was recorded at this point and compared to the initial tare weight to determine the exact mass of KH that was transferred.

Procedure for purification of 2a: Each TLC plate (20x20 cm plate, 250 micron thickness) was briefly submerged in a 10% w/v solution of AgNO₃ in acetonitrile contained in a large, flat glass dish. The TLC plate was removed, and the excess solution was allowed to drip back into the glass dish. The plate was dried in an oven at 115 °C for 1.5 h, removed, and allowed to cool to room temperature, protected from light. A maximum of 50 mg of crude **2a** in dichloromethane (ca. 100 mg/mL) was loaded to each plate in a straight line about 2 cm above the bottom of the plate and 1.5 cm from each side. The plate was then developed in a preparative TLC chamber (mobile phase 50% AcOEt in hexanes) until the solvent reached approximately 1 to 2 cm from the top of the plate. The plate was removed and allowed to dry in the dark. An approximately 2.5 cm strip was cut from the side of the plate and visualized using acidic anisaldehyde stain and heat. This strip was aligned with the rest of the plate, and the desired band ($R_f \sim 0.5$) was outlined in pencil on the remainder of the plate. This band was scraped off using a razor blade, collected in a vial, sonicated with AcOEt, filtered, and washed several times with AcOEt. The filtrate was concentrated under reduced pressure to deliver pure **2a**. This procedure was repeated as necessary to purify all of the crude from each isomerization.



Protokalihinol (**2a**)

¹H NMR (600 MHz, CDCl₃):

δ 6.25 (s, 1 H)	1.91 (t, $J = 6.3$ Hz, 1 H)	1.43-1.29 (m, 2 H)
5.12 (t, $J = 6.9$ Hz, 1 H)	1.74 (dt, $J = 13.4, 3.0$ Hz, 1 H)	1.28-1.24 (m, 1 H)
2.27 (t, $J = 9.5$ Hz, 1 H)	1.68 (br s, 3 H)	1.23 (s, 3 H)
2.16-2.07 (m, 1 H)	1.67 (br s, 3 H)	1.21 (s, 3 H)
2.07-1.97 (m, 2 H)	1.61 (br s, 3 H)	1.18 (d, $J = 10.4$ Hz, 1 H)
1.94 (dd, $J = 12.4, 5.2$ Hz, 1 H)	1.58-1.43 (m, 6 H)	

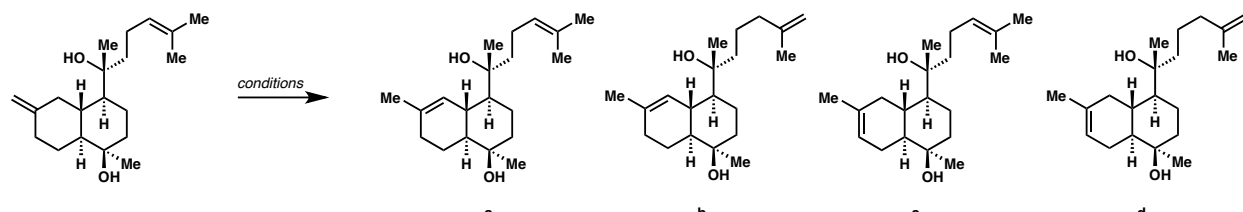
¹³C NMR (150 MHz, CDCl₃):

δ 133.65	48.10	24.89
131.81	43.04	24.14
125.03	40.55	22.99
124.40	38.50	22.63
75.93	30.57	21.34
70.49	28.57	17.69
50.59	25.72	

LRMS (ESI) calculated for $C_{20}H_{34}NaO_2$ $[M+Na]^+$: 329.2, found 329.0; calculated for $C_{20}H_{33}O$ $[M-OH]^+$: 289.3, found 289.1; calculated for $C_{20}H_{31}$ $[M-H_2O-OH]^+$: 271.2, found 271.1.

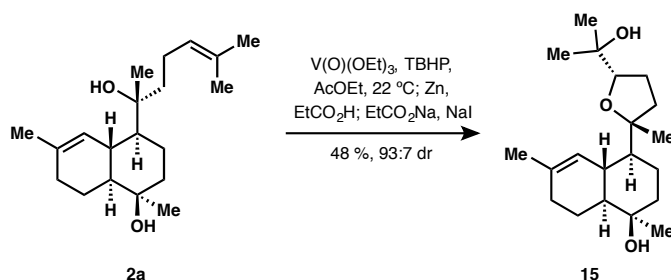
TLC: R_f = 0.33 (20% AcOEt in hexanes)

Optimization Table:

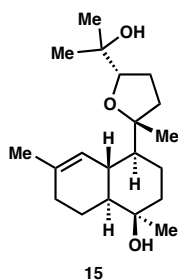


conditions	conversion (%)	(a+b):(c+d)	%a	comments
40 equiv. <i>t</i> -BuOK, DMSO (0.01 M), 140 °C, 3h; then 150 °C 3h	95 ^a	2.7:1 ^a	52 ^a	wet DMSO
16 equiv. <i>t</i> -BuOK, DMSO (0.025 M), 140 °C, 3h	90 ^a	4:1 ^a	52 ^a	wet DMSO
8 equiv. <i>t</i> -BuOK, DMSO (0.05 M), 140 °C, 3h	67 ^a	5:1 ^a	32 ^a	wet DMSO
16 equiv. <i>t</i> -BuOK, DMSO (0.025 M), 140 °C, 3h	86 ^a	1:1 ^a	28 ^a	anhydrous DMSO
0.02 equiv. Co(Sal(<i>t</i> Bu), <i>i</i> Bu)Cl•H ₂ O, 0.04 equiv. PhSiH ₃ , PhH, 22 °C, 1.5h	42 ^a	<1:20 ^a	0 ^a	<5% linear alkene isomerization
0.2 equiv. RhCl ₃ •3H ₂ O, EtOH/H ₂ O (4:1), 70 °C, 18h	56 ^b	1:1 ^b	—	
4 equiv. <i>t</i> -BuOK, DMSO (0.025 M), 140 °C, 3h	82 ^a	5:1 ^a	55 ^a	
4 equiv. <i>t</i> -BuOK, DMSO (0.025 M), 140 °C, 3h (0.19 g S.M.)	—	—	45 ^c	
1.2 equiv. BuLi, DMSO (0.025 M), 140 °C - 175 °C	0	—		no reaction at 175 °C for 1 h
10 equiv. Cs ₂ CO ₃ , DMSO (0.025 M), 140°C - 175 °C	0	—		no reaction at 175 °C for 1 h
4 equiv. LiOt-Bu, DMSO (0.025 M), 140 °C, 1h; 175 °C 1h	2	—	0	2% conversion to bis-terminal alkene
4 equiv. NaOt-Bu, DMSO (0.025 M), 140°C, 1h; 175 °C 1h	40	>20:1	21	18% b + bis-terminal alkene
4 equiv. <i>t</i> -BuOK, HMPA (0.025 M), 140°C, 8h	71	3:1	38	reaction did not progress significantly beyond 4h mark
4 equiv. <i>t</i> -BuOK, diglyme (0.025 M), 140°C, 1h; 180 °C	<5	—	—	very slow
4 equiv. <i>t</i> -BuOK, TMU (0.025 M), 140°C	<5	—	—	very slow, gel-like precipitate formed upon heating
4 equiv. <i>t</i> -BuOK, DMAc (0.025 M), 140°C, 1h	<5	—	0	gel-like precipitate formed upon heating
4 equiv. <i>t</i> -BuOK, DMPU (0.025 M), 140°C, 8h	78	3:1	42	reaction did not progress significantly beyond 4h mark
1.2 equiv. KH, DMPU (0.025 M), 140 °C	~0			effectively no reaction
1.2 equiv. KH, DMSO (0.025 M), 140 °C, 3h	78	7:1	54	

Notes: a) Calculated by ¹H NMR; b) Calculated by GCMS; c) isolated yield



Tetrahydrofuran 15. To anhydrous AcOEt (4.7 mL) over 3Å molecular sieves was added vanadium(V) oxytriethoxide (50 μL , 0.282 mmol, final concentration 0.0534 M) and anhydrous *tert*-butylhydroperoxide (0.53 mL of a 5.81 M solution in decane, 3.08 mmol, final concentration 0.583 M). A portion of this solution (1.7 mL, 0.0908 mmol V(O)(OEt)_3 , 0.992 mmol TBHP) was added to a flask containing protokalinol (**2a**) (61 mg, 0.199 mmol) in AcOEt (1.53 mL). The solution was allowed to stand 8 h at room temperature (double epoxidation), then was cooled to 0 $^\circ\text{C}$. To this solution was added sequentially an oven-dried stir bar, activated zinc powder (0.114 g, 1.74 mmol), and propionic acid (0.298 mL, 4.00 mmol). The mixture was stirred vigorously as it warmed to room temperature, then was heated to 40 $^\circ\text{C}$ for 1.5 h (cycloetherification). The mixture was subsequently cooled to 0 $^\circ\text{C}$, and sodium propionate (0.213 g, 2.22 mmol) and sodium iodide (0.540 g, 3.60 mmol) were added sequentially against a backflow of argon. The reaction mixture was allowed to warm to room temperature, and was stirred vigorously at this temperature 12 h (deoxygenation). The reaction mixture was subsequently quenched with saturated aqueous sodium bicarbonate, and diluted with AcOEt. The mixture was stirred vigorously 30 min, filtered through Celite, and the filter cake was washed with AcOEt. Layers were separated, and the aqueous phase was extracted with AcOEt three times. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 25% AcOEt in hexanes) delivered 31 mg of tetrahydrofuran **15** (48% yield) as a pale yellow foam.



Tetrahydrofuran **15**

^1H NMR (600 MHz, CDCl_3):

δ 6.26 (s, 1 H)	1.91 (tt, J = Hz, 1 H)	1.28-1.24 (m, 1 H)
3.86 (t, J = Hz, 1 H)	1.86-1.76 (m, 2 H)	1.24 (s, 3 H)
2.23 (m, 1 H)	1.74-1.55 (m, 4 H)	1.22 (s, 3 H)
2.11 (br s, 1 H)	1.64 (br s, 3 H)	1.16 (td, J = 10.7, 2.0 Hz, 1 H)

2.07-1.98 (m, 1 H)	1.52-1.42 (m, 3 H)	1.15 (s, 3 H)
1.98-1.92 (m, 1 H)	1.36 (qd, $J = 12.3, 5.7$ Hz, 1 H)	1.10 (s, 3 H)

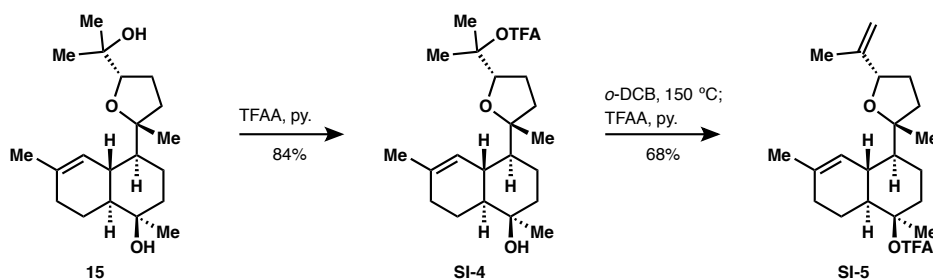
^{13}C NMR (150 MHz, CDCl_3):

δ 132.66	47.80	25.71
125.80	40.54	24.42
86.97	38.61	24.21
84.28	38.42	23.86
71.24	30.61	22.63
70.54	28.53	19.10
52.13	27.55	

GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C 0 min, then 20 °C/min to 280 °C, then hold 2 min at 280 °C): $t_R = 10.666$ min

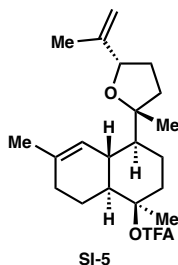
MS (EI, 70 eV): m/z (%) 304.3 (0.1, $\text{M-H}_2\text{O}^+$), 286.2 (0.2, $\text{M-2(H}_2\text{O)}^+$), 187.2 (6), 159 (10), 143.1 (100), 125.1 (30), 119.1 (8), 105.1 (12), 91.1 (11), 85.1 (19), 71.1 (20), 59.1 (12)

TLC: $R_f = 0.23$ (25% AcOEt in hexanes)



Trifluoroacetate SI-5. To tetrahydrofuran **15** (0.167 g, 0.519 mmol) and pyridine (0.419 mL, 5.18 mmol) in anhydrous dichloromethane (3.46 mL) at -78 °C was added trifluoroacetic anhydride (1.09 mL of a 0.5 M solution in dichloromethane, 0.545 mmol) drop-wise. The bath was allowed to warm slowly to 0 °C over 1.5 h, and the reaction mixture was stirred at this temperature for an additional 20 min. The reaction mixture was subsequently quenched with 1 N aqueous HCl, diluted with hexanes, and stirred vigorously as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 15% AcOEt in hexanes) delivered 181 mg of trifluoroacetate **SI-4** (84% yield) as a white foam and 22 mg of recovered **15** (13% yield).

A portion of intermediate **SI-4** (20 mg, 0.0478 mmol) was dissolved in anhydrous 1,2-dichlorobenzene (1.9 mL). The solution was treated with anhydrous triethylamine (33 µL, 0.237 mmol) and heated to 150 °C for 12.7 h. The reaction mixture was cooled to 0 °C and treated with pyridine (39 µL, 0.482 mmol) followed by trifluoroacetic anhydride (0.48 mL of a 0.5 M solution in DCM, 0.240 mmol). The reaction mixture was stirred at this temperature 35 min, then quenched with 1 N aqueous HCl (4.8 mL), and stirred vigorously as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with hexanes twice. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over Na₂SO₄, and decanted. Without concentration, this solution was loaded directly to a silica gel column. Purification by flash column chromatography on silica gel (elution of *o*-DCB with hexanes; then elution of product with 20% DCM in hexanes) delivered 13 mg of trifluoroacetate **SI-5** (68% yield) as a pale yellow solid.



Trifluoroacetate **SI-5**

¹H (600 MHz, CDCl₃):

δ 6.33 (br s, 1 H)	2.12-1.93 (m, 4 H)	1.46 (td, <i>J</i> = 14.3, 4.1 Hz, 1 H)
4.98 (br s, 1 H)	1.70 (br s, 3 H)	1.39 (ddd, <i>J</i> = 12.4, 11.1, 3.4 Hz, 1 H)

4.73 (br s, 1 H)	1.69-1.66 (m, 3 H)	1.22 (ddd, $J = 12.1, 10.4, 2.0$ Hz, 1 H)
4.46 (dd, $J = 8.0, 3.6$ Hz, 1 H)	1.65 (br s, 3 H)	1.19-1.09 (m, 1 H)
2.75 (dt, $J = 14.8, 3.3$ Hz, 1 H)	1.62 (s, 3 H)	1.11 (s, 3 H)
2.35 (tdd, $J = 9.0, 4.1, 2.0$ Hz, 1 H)	1.61-1.50 (m, 2 H)	

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

δ 156.14 (q, $^2J_{\text{C-F}} = 41.0$ Hz)	80.56	28.73
146.82	51.11	24.96
132.24	48.76	23.63
125.50	37.80	23.57
114.53 (q, $^1J_{\text{C-F}} = 287.4$ Hz)	37.77	22.52
109.08	34.78	19.27
88.89	30.49	18.81
86.65		

GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 200 °C; column temperature 50 °C 0 min, then 20 °C/min to 280 °C, then hold 2 min at 280 °C): due to thermal instability of **SI-5**, three peaks were observed corresponding to regioisomeric elimination products: $t_{R,1} = 9.482$ min; $t_{R,2} = 9.545$ min (major, see mass data below); $t_{R,3} = 9.613$ min.

MS (EI, 70 eV): m/z (%) 286.2 (0.4, M-TFA⁺), 185.1 (9), 159 (20), 145 (8), 125 (100), 107 (27), 91 (14), 81 (12), 67 (5), 55 (11)

TLC: $R_f = 0.27$ (20% DCM in hexanes)

80.64

30.49

18.78

GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C 0 min, then 20 °C/min to 280 °C, then hold 2 min at 280 °C): t_R = 10.649 min

MS (EI, 70 eV): m/z (%) 313.2 (0.3, M^+), 286.1 (0.5, $M-HCN^+$), 187.1 (9), 162.1 (27), 143.1 (26), 125.1 (100), 119.1 (18), 105.1 (41), 91.1 (30), 81.1 (31), 67.0 (18), 53.0 (15)

TLC: R_f = 0.34 (5% AcOEt in hexanes)

60.60

37.79

19.21

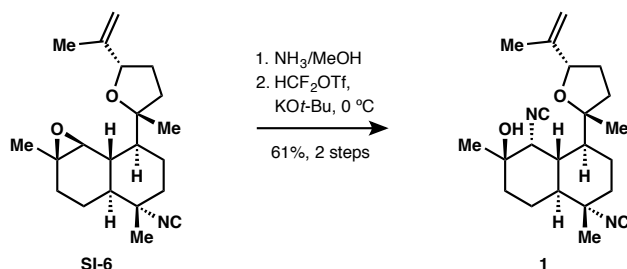
60.42 (t, $^1J_{\text{C-N}} = 5.2$ Hz)

30.46

18.64

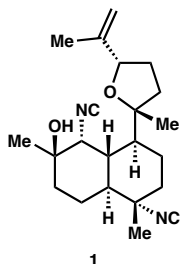
LRMS (ESI) calculated for $\text{C}_{21}\text{H}_{31}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 352.2, found 352.2; calculated for $\text{C}_{21}\text{H}_{32}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 330.2, found 330.2; calculated for $\text{C}_{20}\text{H}_{31}\text{O}_2$ $[\text{M}-\text{NC}]^+$: 303.2, found 303.2.

TLC: $R_f = 0.29$ (10% AcOEt in hexanes)



Kalihinol C (1). To a nitrogen-flushed microwave vial containing epoxide **SI-6** (14 mg, 0.0425 mmol) was added 7 M NH_3/MeOH (0.99 mL, 6.93 mmol). The sealed microwave vial was heated to 80 °C for 48 h, allowed to cool to room temperature, and concentrated under a stream of nitrogen to deliver 15 mg of the corresponding crude amino-alcohol as a white solid.

A portion of this intermediate (4.8 mg, 0.0139 mmol) was dissolved in anhydrous THF (41 μL) and treated with KOt-Bu (67 μL of a 1.04 M solution in THF, 0.0697 mmol), followed by difluoromethyltriflate⁶ (31 μL of a 1 M solution in THF, 0.0310 mmol) drop-wise at 0 °C. The reaction mixture was stirred at this temperature for 1 h, quenched with water, and diluted with Et_2O . The biphasic mixture was stirred vigorously 5 min as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with Et_2O twice. The aqueous phase was basified with aqueous sodium hydroxide (50% w/w), and extracted with Et_2O an additional two times. The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 25% AcOEt in hexanes) afforded 3.0 mg of kalihinol C (**1**) (61% yield, over 2 steps) as a yellow oil.



Kalihinol C (**1**)

^1H NMR (600 MHz, CDCl_3):

δ 5.04 (s, 1 H)	1.72-1.52 (m, 6 H)
4.77 (s, 1 H)	1.43 (s, 3 H)
4.50 (br s, 1 H)	1.34 (t, $J = 1.86$ Hz, 3 H)
4.42 (dd, $J = 9.10, 4.10$ Hz, 1 H)	1.22 (ddd, $J = 13.5, 13.5, 3.6$ Hz, 1 H)
2.14-1.98 (m, 3 H)	1.17 (br s, 1 H)
1.96-1.77 (m, 5 H)	1.05 (s, 3 H)
1.73 (s, 3 H)	

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

δ 157.73 (t, $^1J_{\text{C-N}} = 5.3$ Hz)	59.87 (t, $^1J_{\text{C-N}} = 5.4$ Hz)	28.81
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153.22 (t, $^1J_{C-N} = 4.4$ Hz)	46.30	28.74
146.27	42.16	24.29
109.97	39.91	21.64
86.22	38.18	20.73
80.83	36.07	18.26
70.58	32.65	18.16
63.16 (t, $^1J_{C-N} = 5.5$ Hz)		

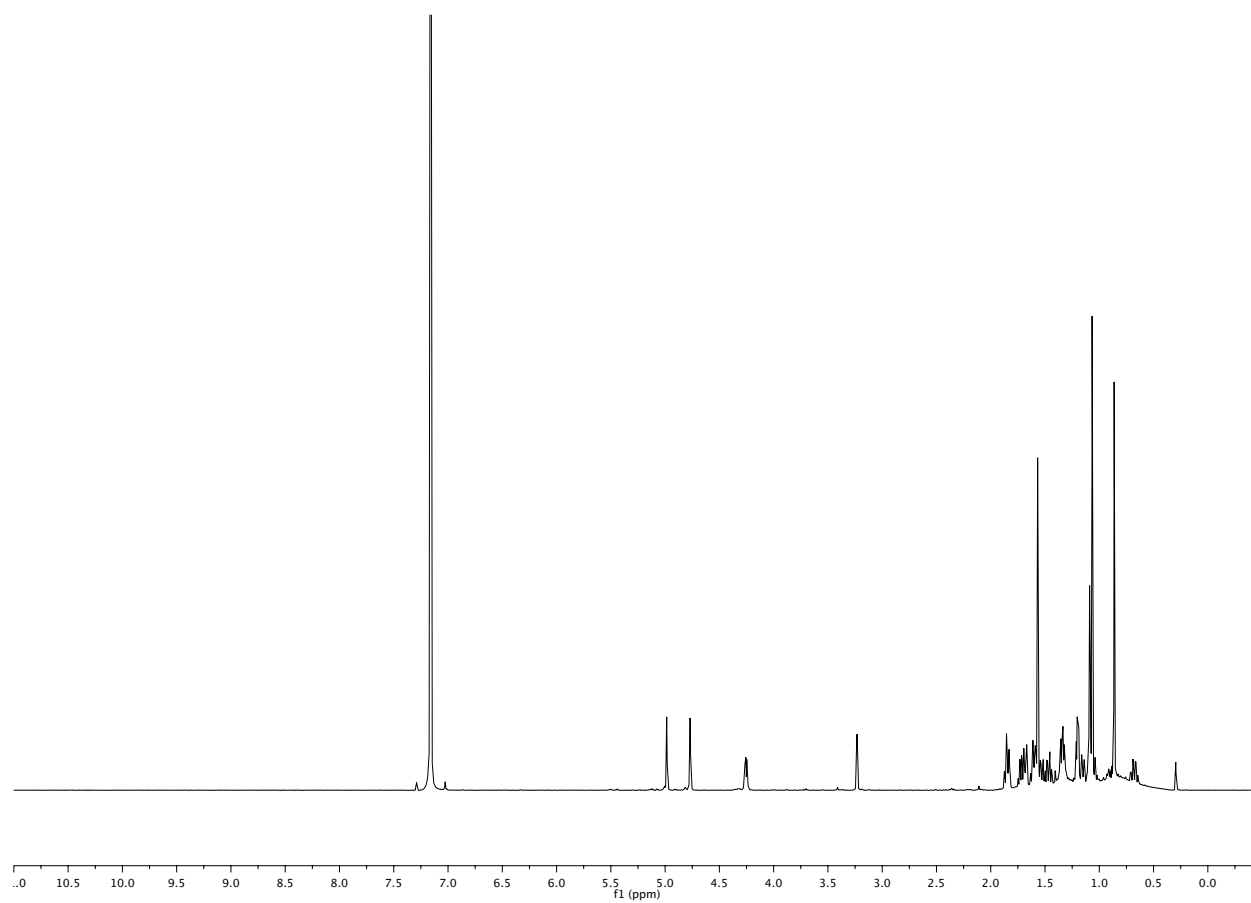
LRMS (ESI) calculated for $C_{22}H_{32}N_2O_2Na$ $[M+Na]^+$: 379.2, found 379.2; calculated for $C_{22}H_{33}N_2O_2$ $[M+H]^+$: 357.3, found 357.3; calculated for $C_{21}H_{32}NO_2$ $[M-CN]^+$: 330.2, found 330.2; calculated for $C_{21}H_{30}NO$ $[M-H_2O-CN]^+$: 312.2, found 312.2; calculated for $C_{20}H_{31}O_2$ $[M-HCN-CN]^+$: 303.2, found 303.2.

TLC: $R_f = 0.28$ (30% AcOEt in hexanes)

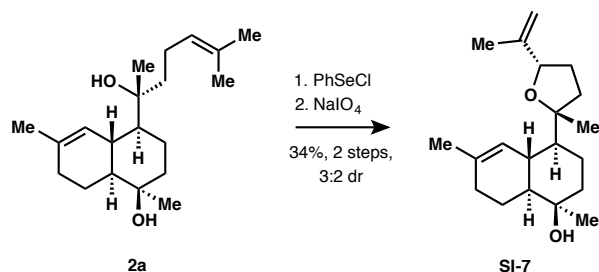
Comparison of ^{13}C NMR data for synthetic kalihinol C (**1**) to literature values ($CDCl_3$; δ , ppm)

Synthetic 1	Synthetic 1 ⁷	Natural 1 ⁸	Δ (Synthetic)	Δ (Natural)
157.7	n.d.	n.d.	—	—
153.2	n.d.	n.d.	—	—
146.3	146.3	146.2	0.0	0.1
110.0	110.0	110.0	0.0	0.0
86.2	86.2	86.2	0.0	0.0
80.8	80.9	80.9	-0.1	-0.1
70.6	70.6	70.5	0.0	0.1
63.2	63.2	63.2	0.0	0.0
59.9	59.9	59.9	0.0	0.0
46.3	46.3	46.3	0.0	0.0
42.2	42.2	42.2	0.0	0.0
39.9	39.9	40.0	0.0	-0.1
38.2	38.2	38.2	0.0	0.0
36.1	36.1	36.1	0.0	0.0
32.7	32.7	32.7	0.0	0.0
28.8	28.8	28.8	0.0	0.0
28.7	28.7	28.7	0.0	0.0
24.3	24.3	24.3	0.0	0.0
21.6	21.7	21.7	-0.1	-0.1
20.7	20.7	20.7	0.0	0.0
18.3	18.3	18.2	0.0	0.1
18.2	18.2	18.2	0.0	0.0

Crude ^1H NMR of aminolysis, C_6D_6 , 600 MHz

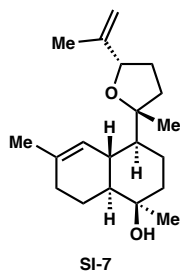


Other approaches: A-ring functionalization



Tetrahydrofuran SI-7. A solution of diene **2a** (0.050 g, 0.163 mmol) and pyridine (0.015 mL, 0.180 mmol) in dichloromethane (1.6 mL) at -78 °C was treated with a solution of PhSeCl (0.0438 g, 0.229 mmol) in dichloromethane (2.1 mL) drop-wise.⁷ The resulting solution was stirred 20 min, quenched with saturated aqueous NaHCO₃, and diluted with hexanes. The resulting biphasic mixture was stirred vigorously as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 15% AcOEt in hexanes) afforded 62 mg of the mixture of selenides (82% yield, 3:2 dr) as a colorless foam.

The mixture of selenides (62 mg, 0.134 mmol) was dissolved in MeCN (2.2 mL) and water (0.54 mL), and treated with NaIO₄ (0.0575 g, 0.269 mmol). The reaction mixture was stirred 0.5 h, quenched with saturated aqueous NaHCO₃, diluted with hexanes, and stirred vigorously 0.5 h. Layers were separated and the aqueous phase was extracted with hexanes five times, then Et₂O twice. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 75% DCM in hexanes) afforded 17 mg of tetrahydrofuran **SI-7** (42% yield, single diastereomer) as a colorless oil.



Tetrahydrofuran **SI-7**

¹H NMR (CDCl₃, 400 MHz):

δ 6.32 (s, 1 H)	2.10-1.87 (m, 4 H)	1.55-1.27 (m, 5 H)
4.99 (br s, 1 H)	1.76-1.57 (m, 5 H)	1.22 (s, 3 H)
4.72 (br s, 1 H)	1.70 (s, 3 H)	1.16 (td, <i>J</i> = 10.7, 2.0 Hz, 1 H)
4.45 (dd, <i>J</i> = 8.4, 4.9 Hz, 1 H)	1.63 (br s, 3 H)	1.16 (s, 3 H)
2.20 (dddt, <i>J</i> = 10.6, 8.3, 4.1, 2.0 Hz, 1 H)		

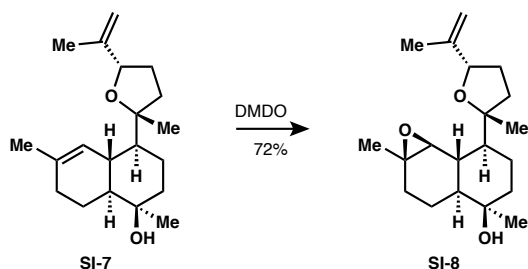
¹³C NMR (CDCl₃, 150 MHz):

δ 146.91	52.02	28.49
131.96	47.57	25.48
126.15	40.47	23.70
109.04	38.43	22.80
86.92	37.88	19.77
80.51	30.74	18.82
70.48	28.84	

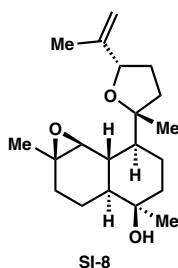
GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C 0 min, then 20 °C/min to 280 °C, then hold 2 min at 280 °C): t_R = 10.168 min

MS (EI, 70 eV): m/z (%) 304.1 (0.04, M^+), 286.2 (0.09), 268.2 (0.5), 185.1 (2), 162.1 (12), 147 (14), 125 (100), 115 (11), 107 (31), 91 (30), 81 (28), 67 (13), 55 (13)

TLC: R_f = 0.23 (DCM)



Epoxide SI-8. To tetrahydrofuran **SI-7** (23.7 mg, 0.0778 mmol) in acetone (0.86 mL) and hexafluoroisopropanol (0.86 mL) at -50 °C was added dimethyldioxirane in 1:1 acetone/hexafluoroisopropanol (1.7 mL of a 0.046 M solution, 0.0782 mmol) drop-wise. The reaction mixture was stirred at this temperature 1 h, then warmed to -30 °C over 0.5 h. The reaction mixture was stirred an additional 3 h at this temperature. The reaction mixture was removed from the cold bath and immediately concentrated under a stream of nitrogen. Purification by flash column chromatography on silica gel (elution with 25% AcOEt in hexanes) delivered 18 mg of epoxide **SI-8** (72% yield) as a colorless oil and 4.5 mg of recovered **SI-7** (18% yield).



Epoxide **SI-8**

¹H NMR (CDCl₃, 600 MHz):

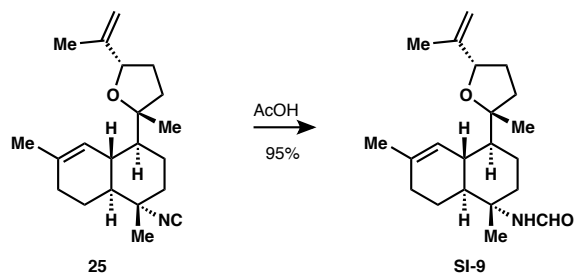
δ 4.91 (br s, 1 H)	1.75-1.60 (m, 5 H)	1.25-1.19 (m, 1 H)
4.72 (br s, 1 H)	1.68 (s, 3 H)	1.23 (s, 3 H)
4.44 (dd, <i>J</i> = 8.9, 4.4 Hz, 1 H)	1.59-1.39 (m, 7 H)	1.17 (s, 3 H)
2.14-2.03 (m, 2 H)	1.27 (s, 3 H)	0.95 (td, <i>J</i> = 11.8, 2.0 Hz, 1 H)
1.91 (t, <i>J</i> = 11.2 Hz, 1 H)		

¹³C NMR (CDCl₃, 150 MHz):

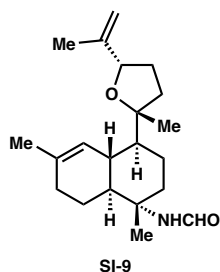
δ 146.89	50.81	28.56
108.87	47.28	25.89
87.00	40.18	23.40
80.35	39.09	19.35
70.33	37.82	19.29
61.58	30.84	18.72
58.48	28.64	

LRMS (ESI) calculated for $C_{20}H_{32}O_3Na$ $[M+Na]^+$: 343.2, found 342.9; calculated for $C_{20}H_{33}O_3$ $[M+H]^+$: 321.2, found 321.0; calculated for $C_{20}H_{31}O_2$ $[M-OH]^+$: 303.2, found 303.0; calculated for $C_{20}H_{29}O$ $[M-H_2O-OH]^+$: 285.2, found 285.0

TLC: R_f = 0.18 (25% AcOEt in hexanes)



Formamide SI-9. Isonitrile **25** (9.5 mg, 0.0304 mmol) was dissolved in AcOH (0.61 mL). After standing 4.3 h at room temperature, the reaction mixture was concentrated under reduced pressure by azeotrope with PhMe, then CHCl₃. Purification by flash column chromatography on silica gel (elution with 30% AcOEt in hexanes) delivered 9.5 mg of formamide **SI-9** (95% yield) as a colorless foam.



Formamide **SI-9**

¹H NMR (major rotamer, 600 MHz, CDCl₃):

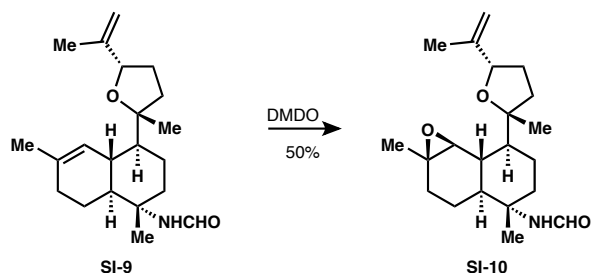
δ 8.29 (d, <i>J</i> = 12.3 Hz, 1 H)	4.46 (dd, <i>J</i> = 10.0, 4.8 Hz, 1 H)	1.70 (s, 3 H)
6.30 (s, 1 H)	2.18-1.90 (m, 5 H)	1.64 (s, 3 H)
5.61 (d, <i>J</i> = 12.1 Hz, 1 H)	1.88 (dt, <i>J</i> = 12.9, 3.3 Hz, 1 H)	1.45-1.16 (m, 3 H)
4.97 (s, 1 H)	1.86-1.76 (m, 1 H)	1.23 (s, 3 H)
4.74 (s, 1 H)	1.71-1.60 (m, 5 H)	1.14 (s, 3 H)

¹³C NMR (major rotamer, 150 MHz, CDCl₃):

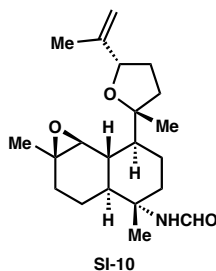
δ 162.74	55.43	28.73
146.64	51.67	26.27
132.81	48.69	23.60
125.25	42.07	23.23
109.20	39.40	19.58
86.46	37.96	19.00
80.61	30.68	18.79

LRMS (ESI) calculated for C₂₁H₃₃NO₂Na [M+Na]⁺: 354.2, found 354.3; calculated for C₂₁H₃₄NO₂ [M+H]⁺: 332.3, found 332.3; calculated for C₂₁H₃₂NO [M-OH]⁺: 314.3, found 314.3; calculated for C₂₀H₃₁O [M-H₂O-NC]⁺: 287.2, found 287.3; calculated for C₂₀H₂₉ [M-2(H₂O)-NC]⁺: 269.2, found 269.3

TLC: R_f = 0.15 (30% AcOEt in hexanes)



Epoxide SI-10. To formamide **SI-9** (9.5 mg, 0.0287 mmol) in acetone (0.32 mL) and hexafluoroisopropanol (0.32 mL) at -50 °C was added dimethyldioxirane in 1:1 acetone/hexafluoroisopropanol (0.63 mL of a 0.046 M solution, 0.0290 mmol) drop-wise. The reaction mixture was stirred at this temperature 1 h, then warmed to -30 °C over 0.5 h. The reaction mixture was stirred an additional 3 h at this temperature. The reaction mixture was removed from the cold bath and immediately concentrated under a stream of nitrogen. Purification by preparative TLC on silica gel (elution with 75% AcOEt in hexanes) afforded 5.0 mg of epoxide **SI-10** (50% yield) as a white foam.



Epoxide **SI-10**

¹H NMR (equal mixture of rotamers, 600 MHz, CDCl₃):

δ 8.25 (d, <i>J</i> = 12.3 Hz, 1 H)	4.18 (s, 1 H)	1.47 (ddt, <i>J</i> = 12.9, 5.2, 2.0 Hz, 1 H)
8.04 (d, <i>J</i> = 2.2 Hz, 1 H)	2.35 (td, <i>J</i> = 13.6, 4.1 Hz, 1 H)	1.42 (ddt, <i>J</i> = 12.9, 5.3, 2.1 Hz, 1 H)
5.53 (d, <i>J</i> = 12.1 Hz, 1 H)	2.16-1.94 (m, 5 H)	1.36-1.12 (m, 3 H)
5.05 (br s, 1 H)	1.86 (dt, <i>J</i> = 13.0, 3.4 Hz, 1 H)	1.27 (s, 3 H)
4.90 (br s, 1 H)	1.84 (dt, <i>J</i> = 13.0, 3.4 Hz, 1 H)	1.26 (s, 3 H)
4.90 (br s, 1 H)	1.77 (t, <i>J</i> = 11.6 Hz, 1 H)	1.21 (s, 3 H)
4.73 (br s, 1 H)	1.75-1.63 (m, 12 H)	1.20 (s, 3 H)
4.72 (br s, 1 H)	1.68 (br s, 3 H)	1.18 (s, 3 H)
4.48-4.39 (m, 2 H)	1.67 (br s, 3 H)	1.13 (s, 3 H)
4.20 (s, 1 H)	1.63-1.55 (m, 4 H)	

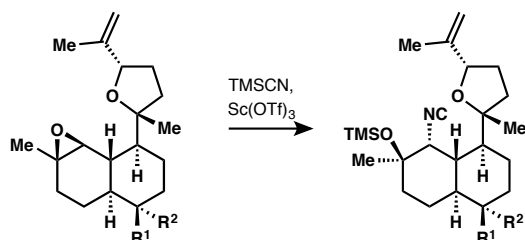
¹³C NMR (equal mixture of rotamers, 150 MHz, CDCl₃):

δ 162.59	50.36	26.72
160.27	50.06	26.52
146.63	48.41	23.29
146.53	43.31	23.23
109.12	41.82	19.90

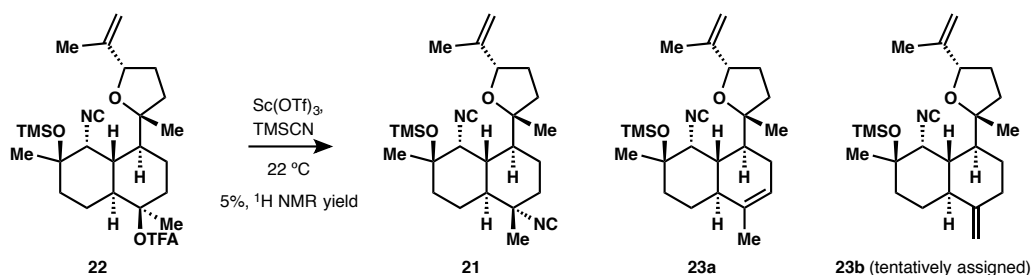
86.70	40.16	19.54
86.46	40.05	19.41
80.49	37.89	19.24
61.52	37.87	19.21
61.02	36.68	18.77
58.76	30.74	18.67
58.70	30.69	18.58
57.40	28.66	
55.49	28.55	

LRMS (ESI) calculated for $C_{21}H_{33}NO_3Na$ $[M+Na]^+$: 370.2, found 370.3; calculated for $C_{21}H_{34}NO_3$ $[M+H]^+$: 348.3, found 348.3; calculated for $C_{21}H_{32}NO_2$ $[M-OH]^+$: 330.2, found 330.3; calculated for $C_{20}H_{31}O_2$ $[M-H_2O-NC]^+$: 303.2, found 303.3; calculated for $C_{20}H_{29}O$ $[M-2(H_2O)-NC]^+$: 285.2, found 285.2

TLC: R_f = 0.21 (50% AcOEt in hexanes)

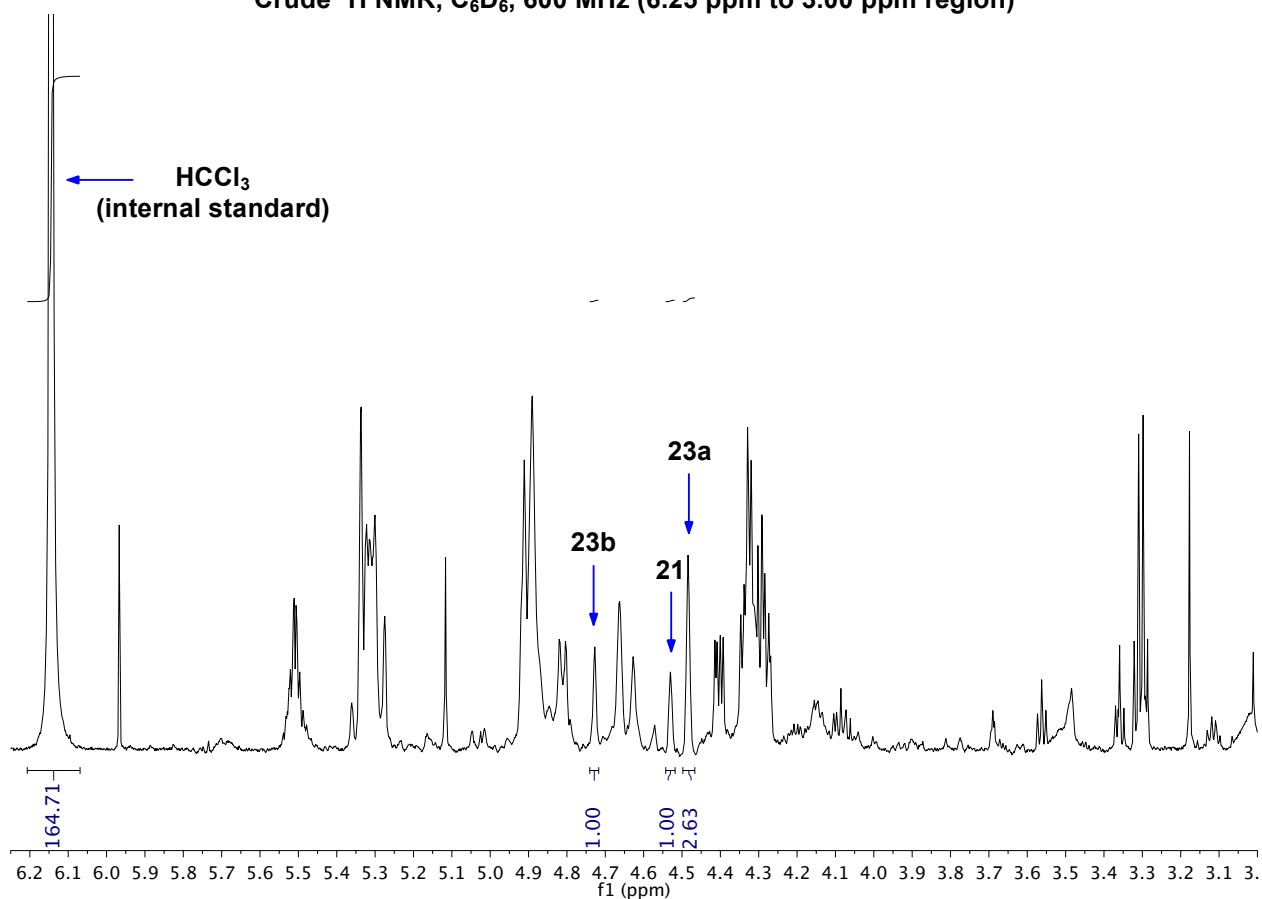


General procedure for epoxide opening with TMSCN. A solution of epoxide in freshly distilled TMSCN (see individual examples for concentration) was treated with an equal volume of a solution of Sc(OTf)₃ (briefly dried under vacuum at ~ 250-300 °C) in freshly distilled TMSCN (0.1 M). The resulting solution was allowed to stand at room temperature (see individual examples for reaction time) and then quenched with TMEDA (15 equiv. with respect to Sc(OTf)₃). The reaction mixture was concentrated under reduced pressure, suspended in hexanes, treated with saturated aqueous NaHCO₃, and mixed thoroughly. Layers were separated, and the aqueous phase was extracted with hexanes twice. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Product ratios and/or yields were determined by ¹H NMR for the crude product mixtures. In certain cases, purification by column chromatography was performed to determine the identity of by-products.



Bis-isonitrile 21. Solvolytic isocyanation of **22** (1.3 mg, 0.00252 mmol, 0.025 M in TMSCN) was performed according to “General procedure for epoxide opening with TMSCN ” over the course of 22 h, delivering bis-isonitrile **21** in 5% yield and diene **23** in 17% yield. Yields were determined by ^1H NMR of the crude product mixture in C_6D_6 (0.6 mL) against an internal standard of HCCl_3 (0.0318 M).

Crude ^1H NMR, C_6D_6 , 600 MHz (6.25 ppm to 3.00 ppm region)

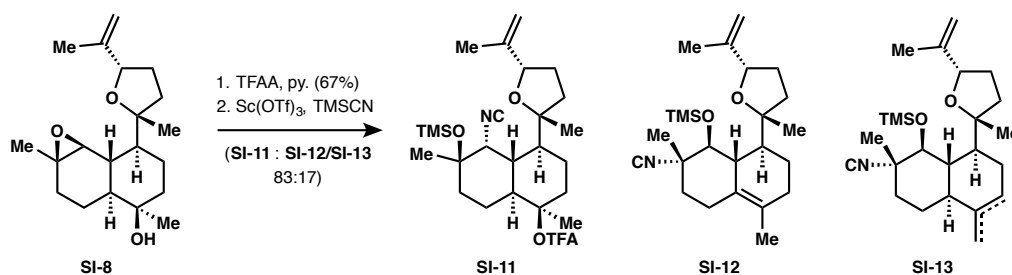


Calculated yield:

$$\% \text{ yield } (\mathbf{21}) = (0.0318 \text{ M} \times (1/164.71) \times 0.6 \text{ mL}) / 0.00252 \text{ mmol} = 4.6\%$$

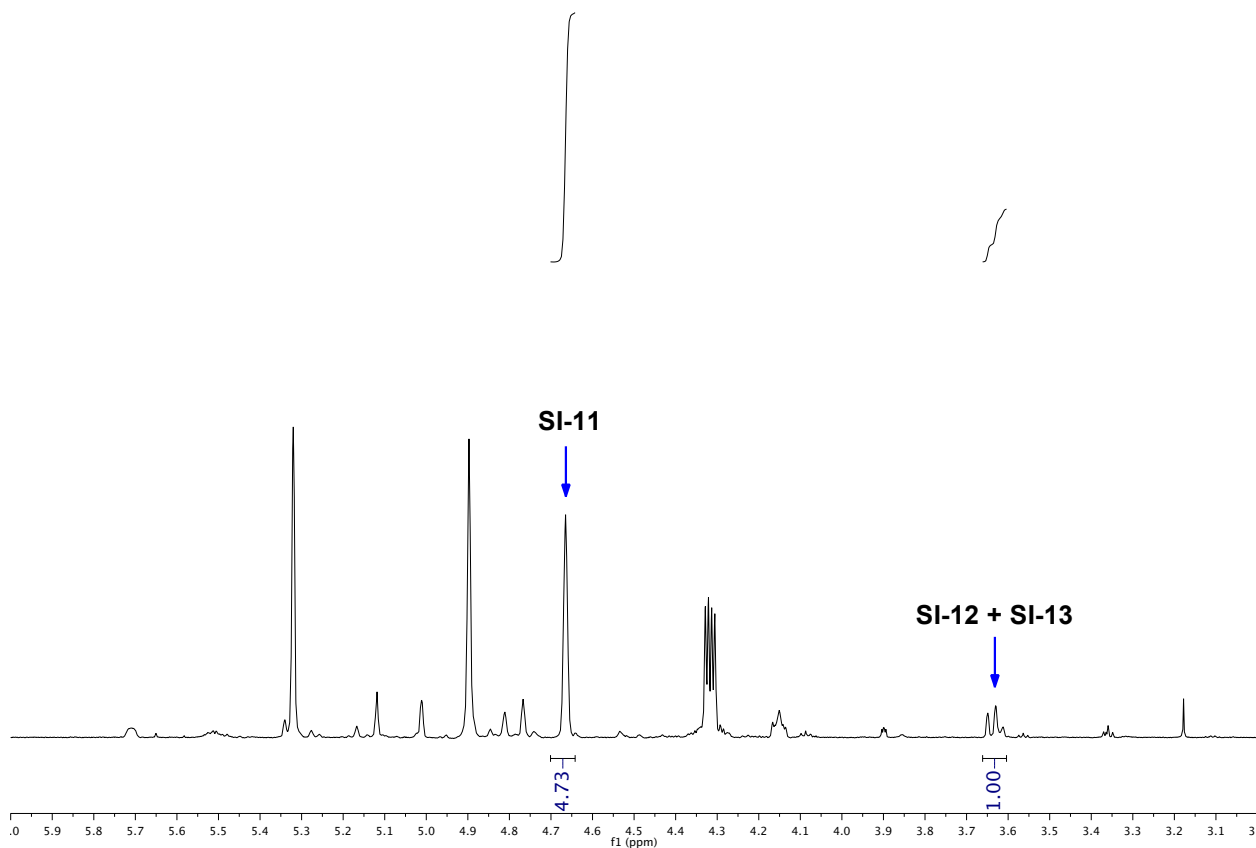
$$\% \text{ yield } (\mathbf{23a}) = (0.0318 \text{ M} \times (2.63/164.71) \times 0.6 \text{ mL}) / 0.00252 \text{ mmol} = 12.1\%$$

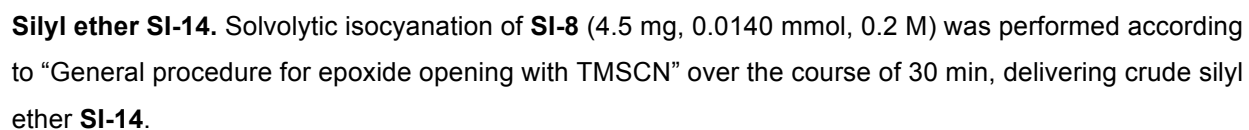
$$\% \text{ yield } (\mathbf{23b}) = (0.0318 \text{ M} \times (1/164.71) \times 0.6 \text{ mL}) / 0.00252 \text{ mmol} = 4.6\%$$



Trifluoroacetate SI-11. A solution of epoxide **SI-8** (4 mg, 0.0125 mmol) and anhydrous pyridine (12 μ L, 0.148 mmol) in DCM (0.25 mL) was treated with trifluoroacetic anhydride (10 μ L, 0.0719 mmol) at 0 $^{\circ}$ C. The reaction mixture was stirred at this temperature 20 min, quenched with 1 N aqueous HCl, diluted with hexanes, and stirred vigorously as it warmed to room temperature. Layers were separated, and the aqueous phase was extracted with hexanes twice. The combined organic layers were washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (elution with 5% AcOEt in hexanes) afforded 3.5 mg of trifluoroacetate **20** (67% yield) as a colorless oil. Then, solvolytic isocyanation of **20** (3.5 mg, 0.00840 mmol, 0.084 M in TMSCN) was performed according to "General procedure for epoxide opening with TMSCN" over the course of 5 min, delivering crude trifluoroacetate **SI-11** and regioisomeric dienes **SI-12** and **SI-13**. The ratio of products was determined by ¹H NMR in C₆D₆.

Crude ¹H NMR, C₆D₆, 600 MHz (6.0 ppm to 3.0 ppm region)





Crude ¹H NMR, CDCl₃, 400 MHz

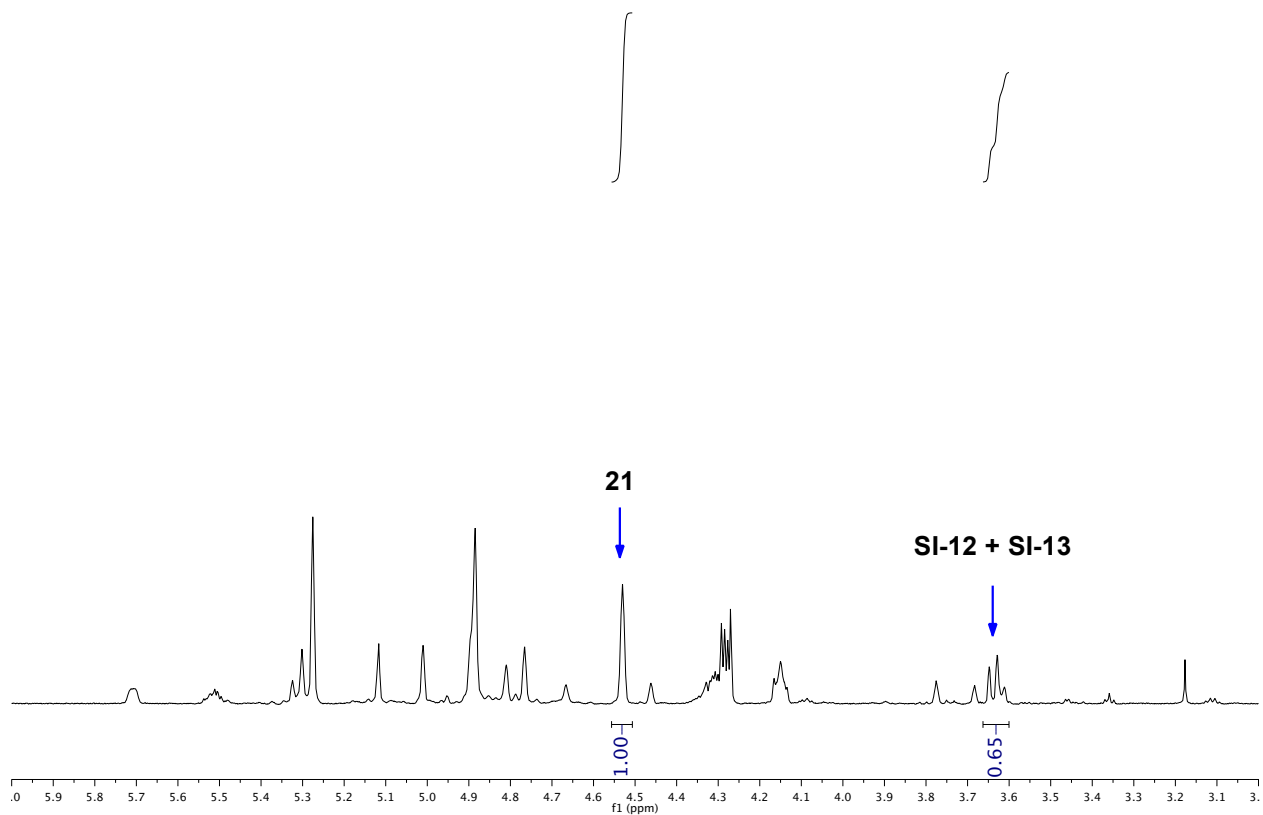


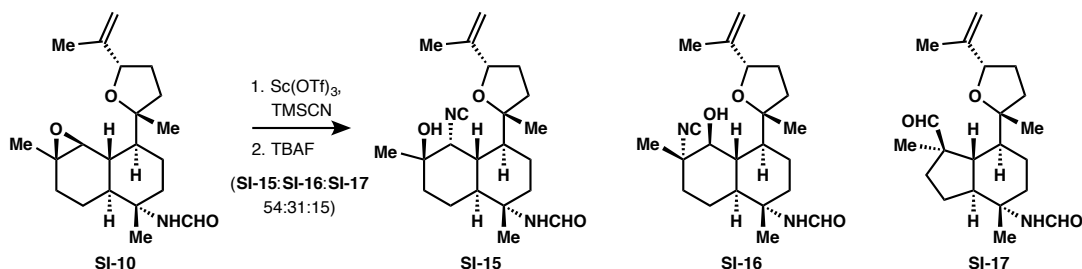
GC (GC/MSD; HP-5MS UI; 139 kPa; flow rate 2 mL/min; inlet temperature 250 °C; column temperature 50 °C 0 min, then 30 °C/min to 280 °C, then hold 10 min at 280 °C): t_R = 7.885 min

MS (EI, 70 eV): m/z (%) 401.3 (0.02, M^+), 386.1 (0.05), 374.1 (0.05), 276.2 (0.5), 249.2 (1), 221.2 (2), 173.1 (5), 160.1 (12), 143.1 (13), 125.1 (100), 107.1 (26), 91.1 (13), 84.0 (22), 73.1 (16), 55.1 (7)

TLC: R_f = 0.57 (10% AcOEt in hexanes)

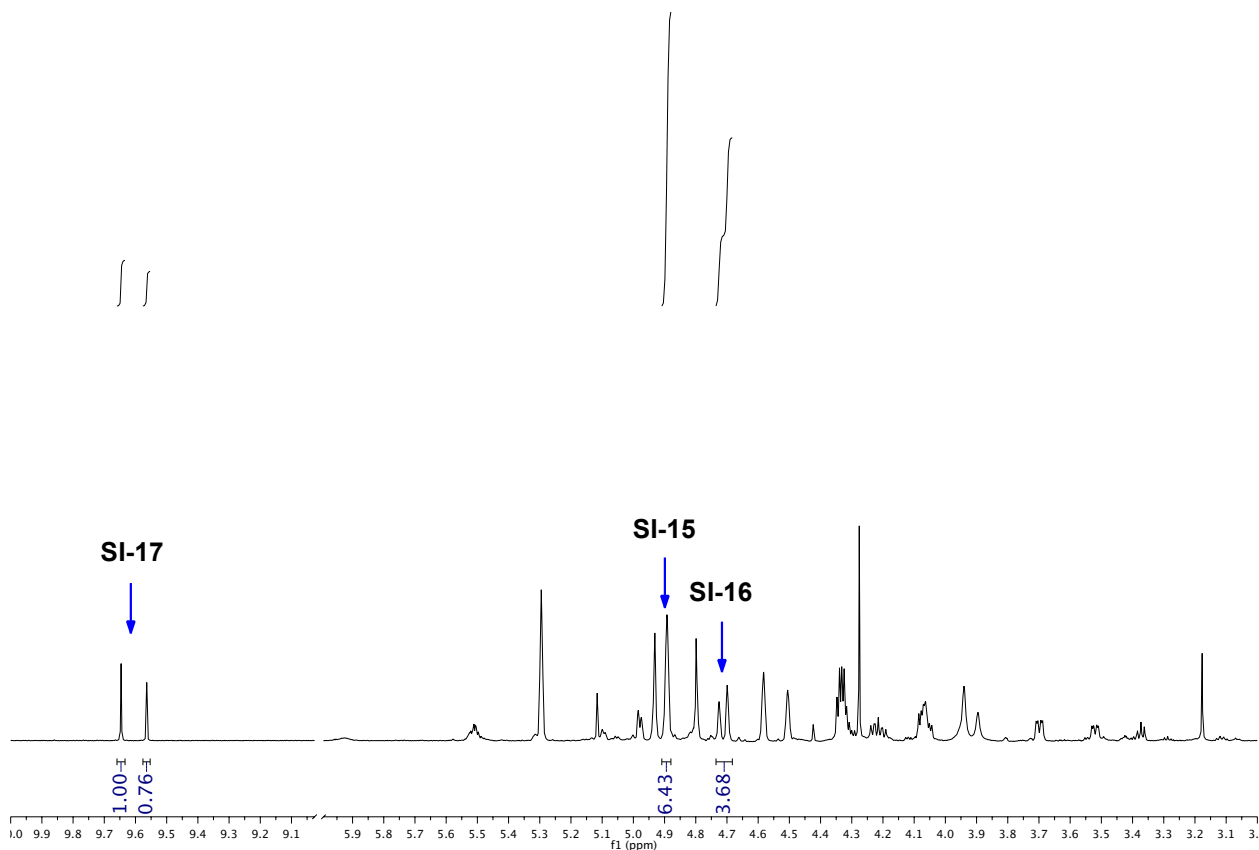
Crude ^1H NMR, C_6D_6 , 600 MHz (6.0 ppm to 3.0 ppm region)





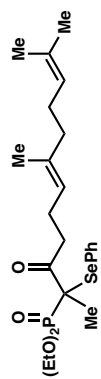
Alcohol SI-15. Solvolytic isocyanation of **SI-10** (5 mg, 0.0144 mmol, 0.144 M) was performed according to “General procedure for epoxide opening with TMSCN ” over the course of 15 min. The crude residue was dissolved in anhydrous THF (0.29 mL), cooled to 0 °C, and treated with TBAF (30 μL of a 0.97 M solution, 0.0291 mmol). After stirring 30 min, the reaction mixture was quenched with pH 7 phosphate buffer and diluted with hexanes. The biphasic mixture was stirred vigorously as it warmed to room temperature. The layers were separated and the aqueous phase was extracted with hexanes three times. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The ratio of products was determined by ^1H NMR in C_6D_6 .

Crude ^1H NMR, C_6D_6 , 600 MHz (10.0 to 9.0 ppm; 6.0 to 3.0 ppm)

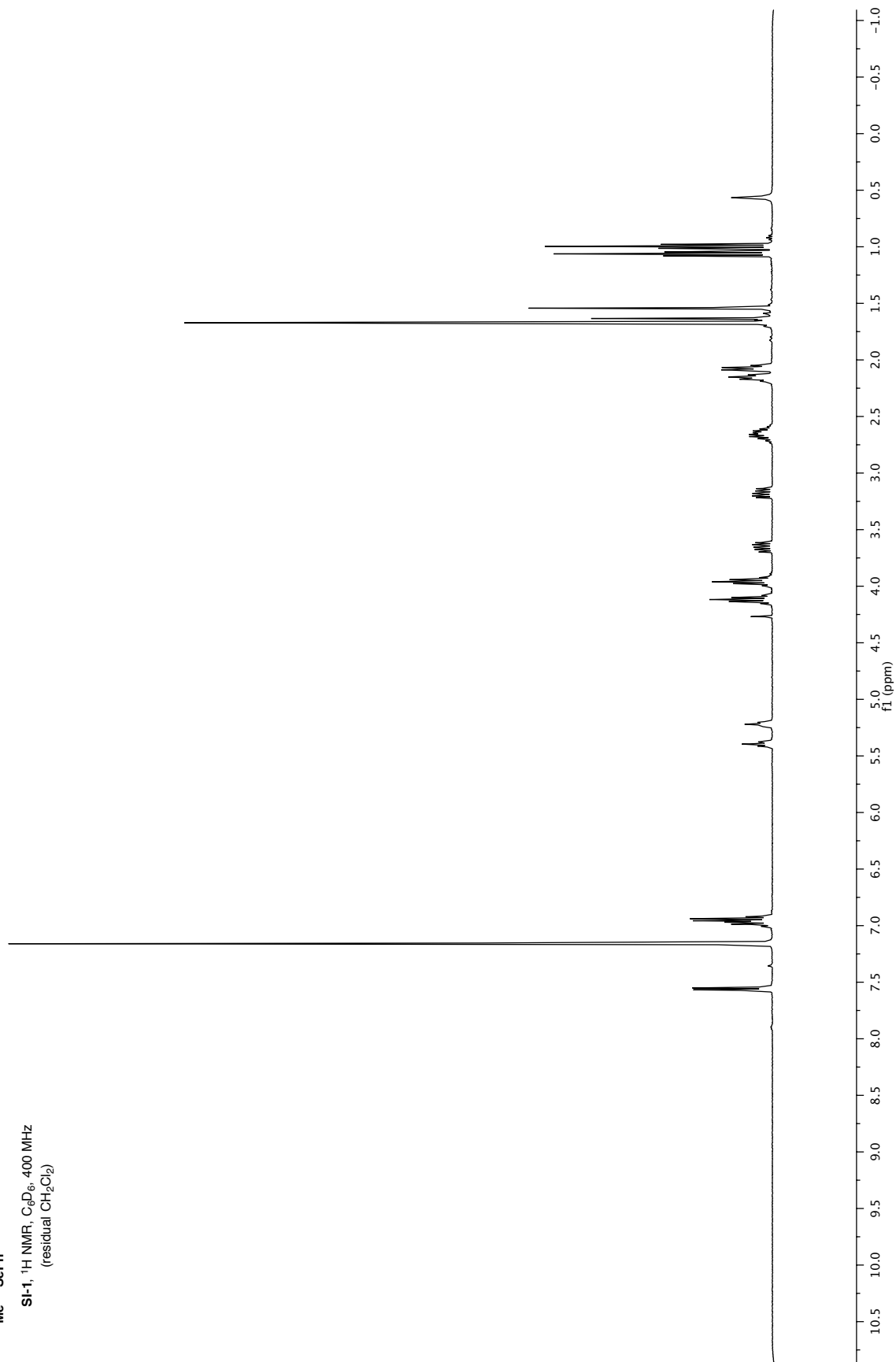


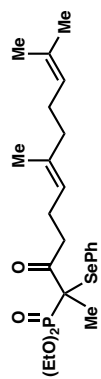
References

- ¹Prepared in quantitative yield according to Kuwajima, I.; and Doi, Y. *Tetrahedron Lett.* **1972**, 12, 1163.
- ²Maloney, K. M.; and Chung, J. Y. L. *J. Org. Chem.* **2009**, 74, 7574.
- ³Prepared in quantitative yield according to Wasserman, H. H.; and Han, W. T. *Tetrahedron Lett.* **1984**, 25, 3743. We found column chromatography to be unnecessary, and thus this step was excluded.
- ⁴See supplementary information of Pronin, S. V.; Reiher, C. A.; and Shenvi, R. A. *Nature* **2013**, 501, 195.
- ⁵Prepared with minor modifications according to Adam, W.; Bialas, J.; and Hadjirapoglou, L. *Chem. Ber.* **1991**, 124, 2377.
- ⁶Prepared according to Levin, V. V.; Dilman, A. D.; Belyakov, P. A.; Struchkova, M. I.; and Tartakovsky, V. A. *J. Fluorine Chem.* **2009**, 130, 667.
- ⁷White, R. D.; Keaney, G. F.; Slown, C. D.; and Wood J. L. *Org. Lett.* **2004**, 6, 1123.
- ⁸Chang, C. W. J.; Patra, A.; Baker, J. A.; and Scheuer, P. J. *J. Am. Chem. Soc.* **1987**, 109, 6119.

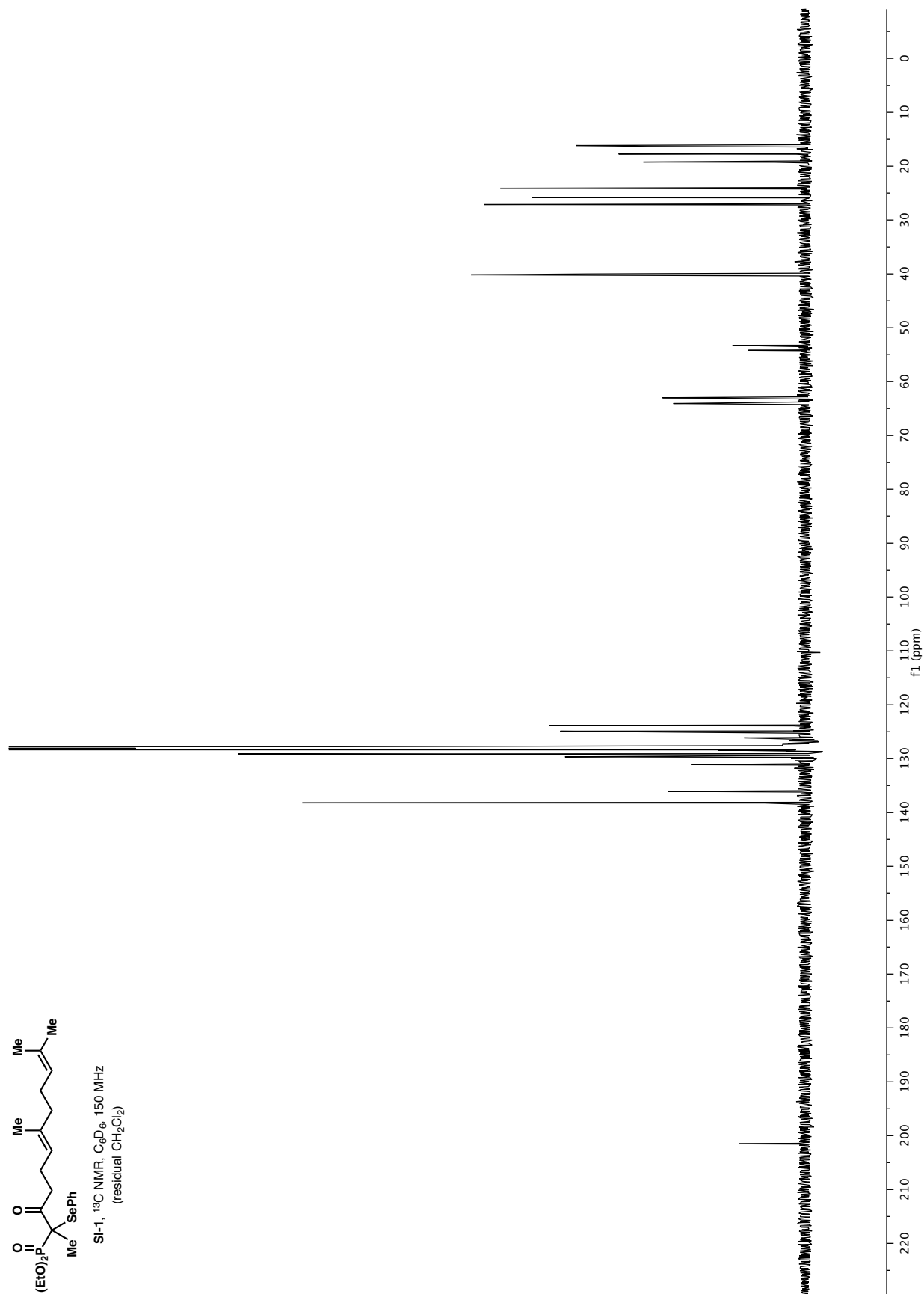


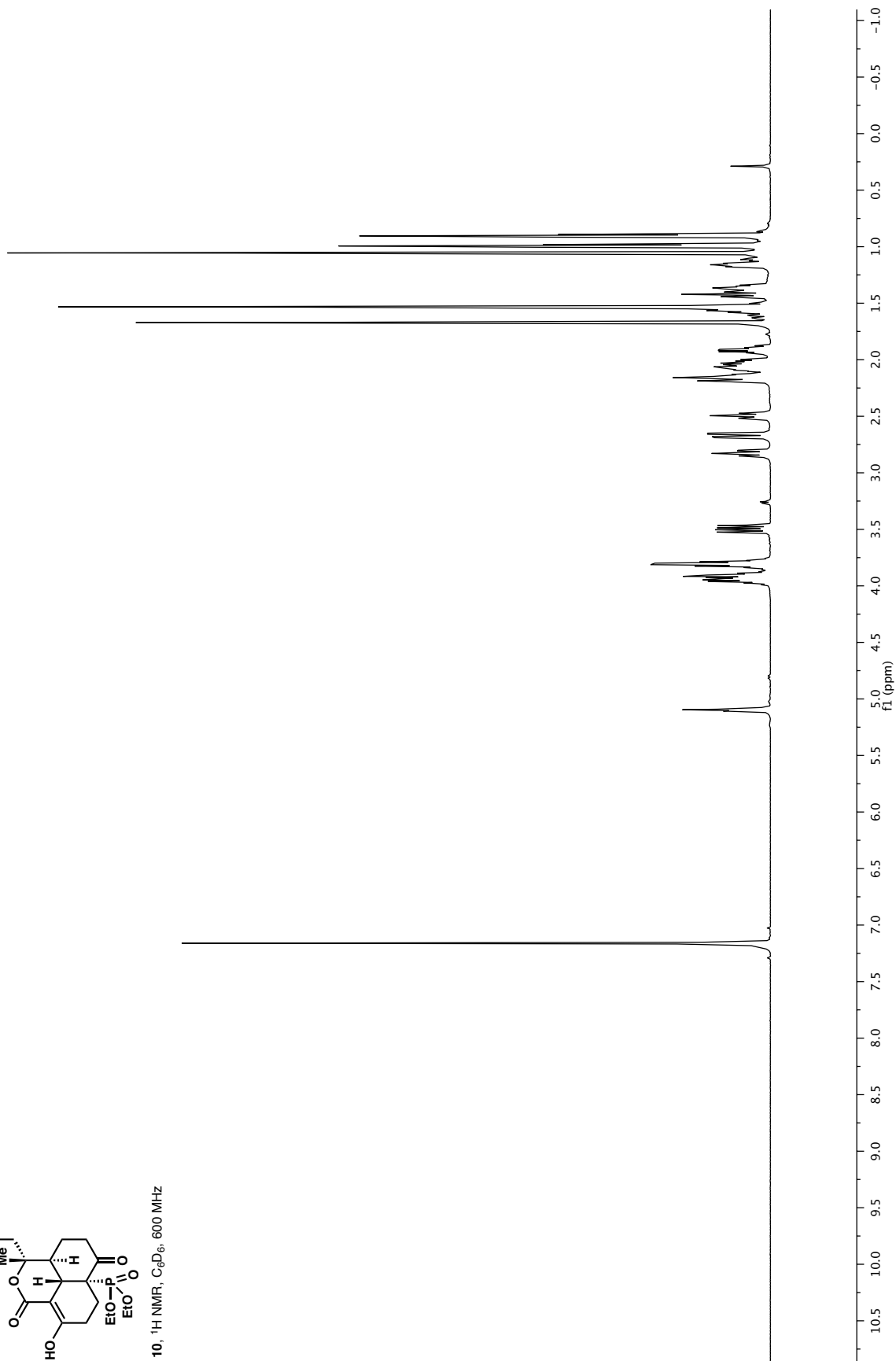
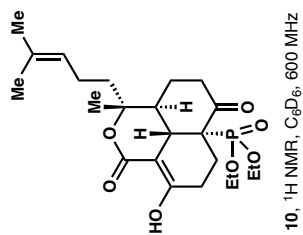
SI-1, ^1H NMR, C_6D_6 , 400 MHz
(residual CH_2Cl_2)

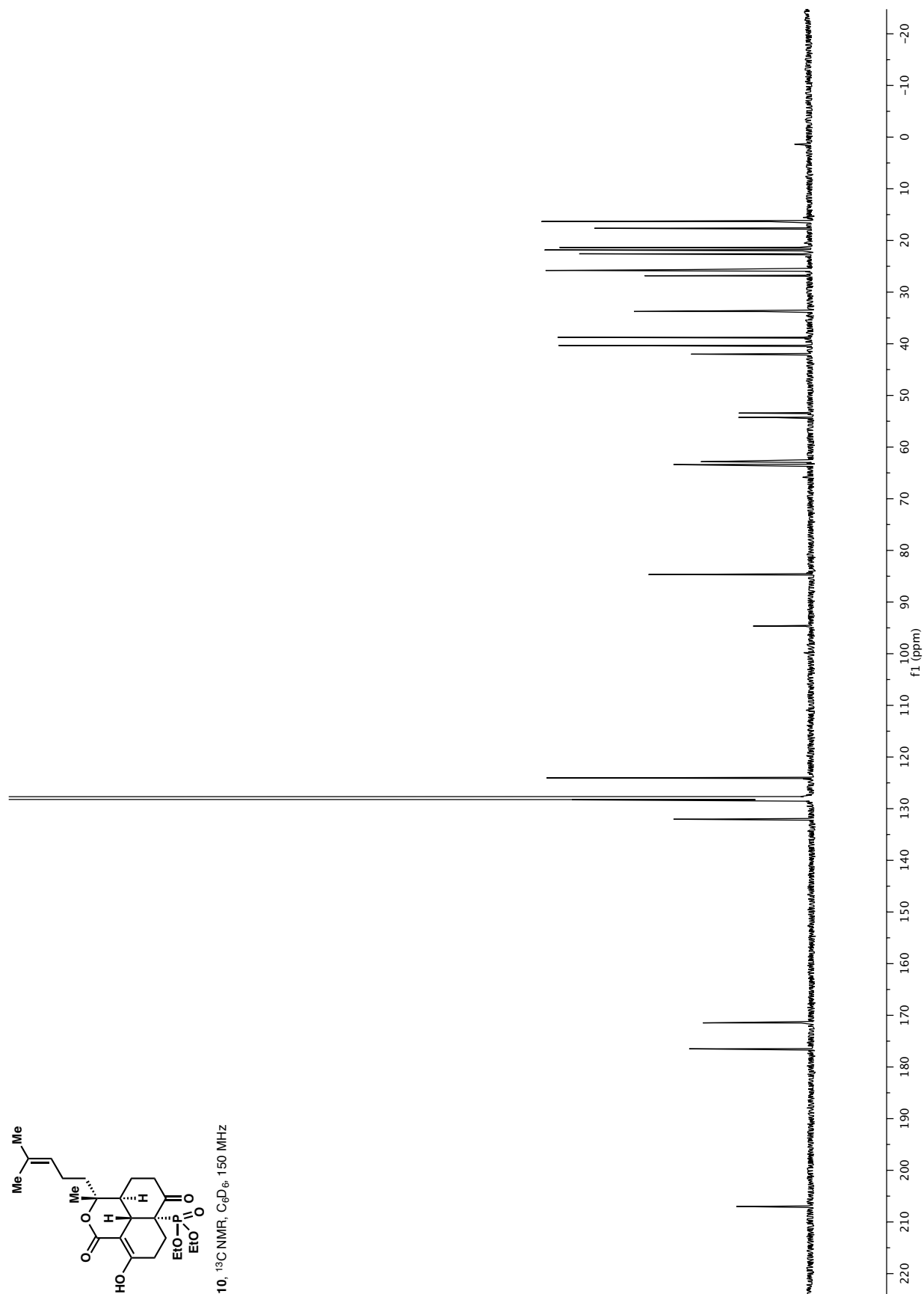
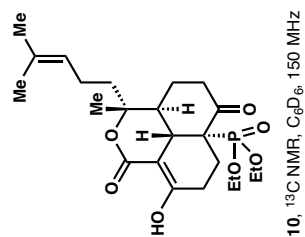


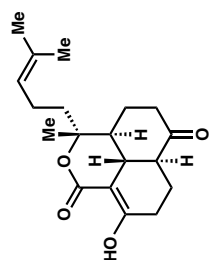


SI-1, ^{13}C NMR, C_6D_6 , 150 MHz
(residual CH_2Cl_2)

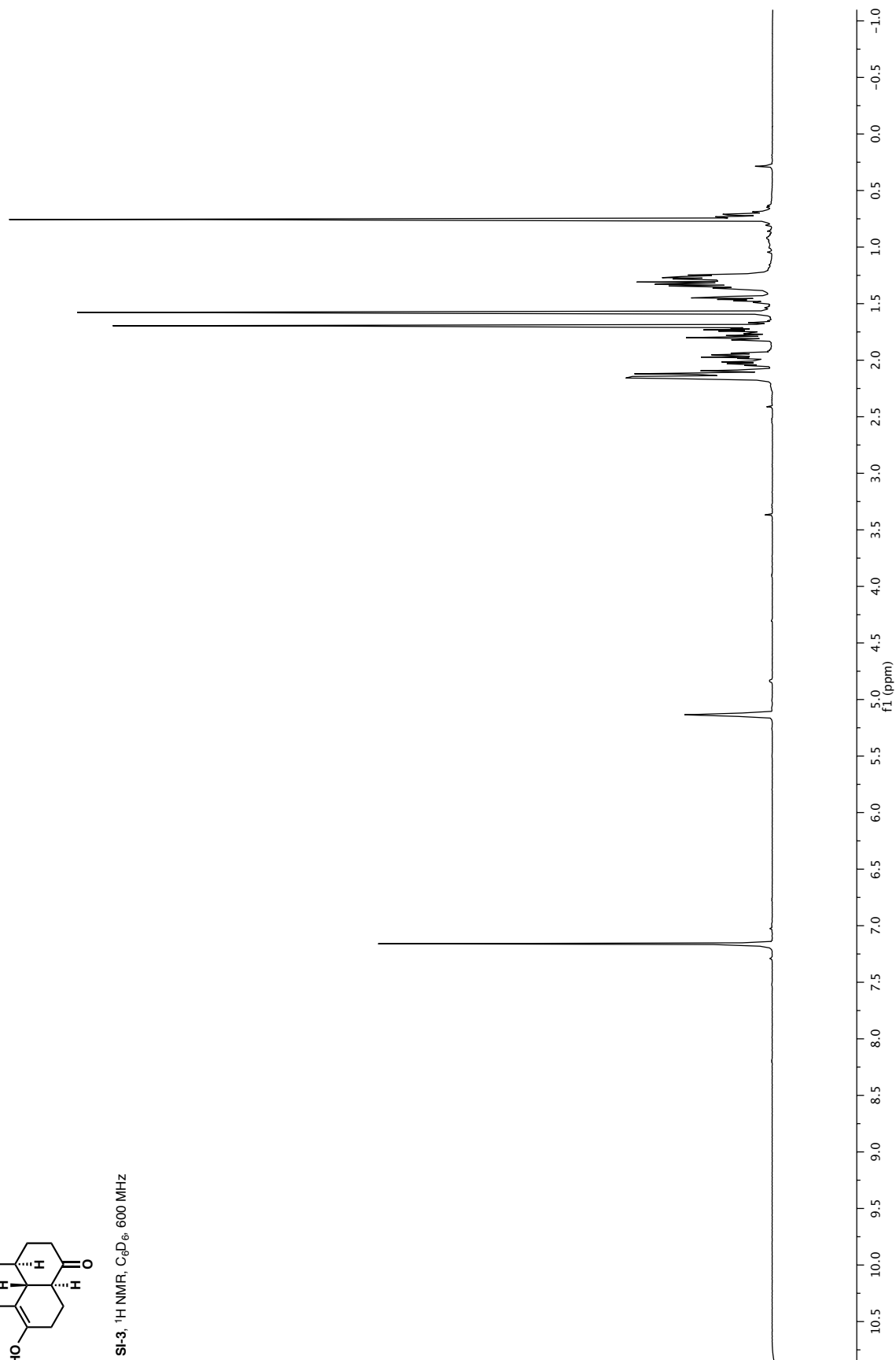


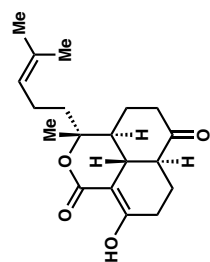




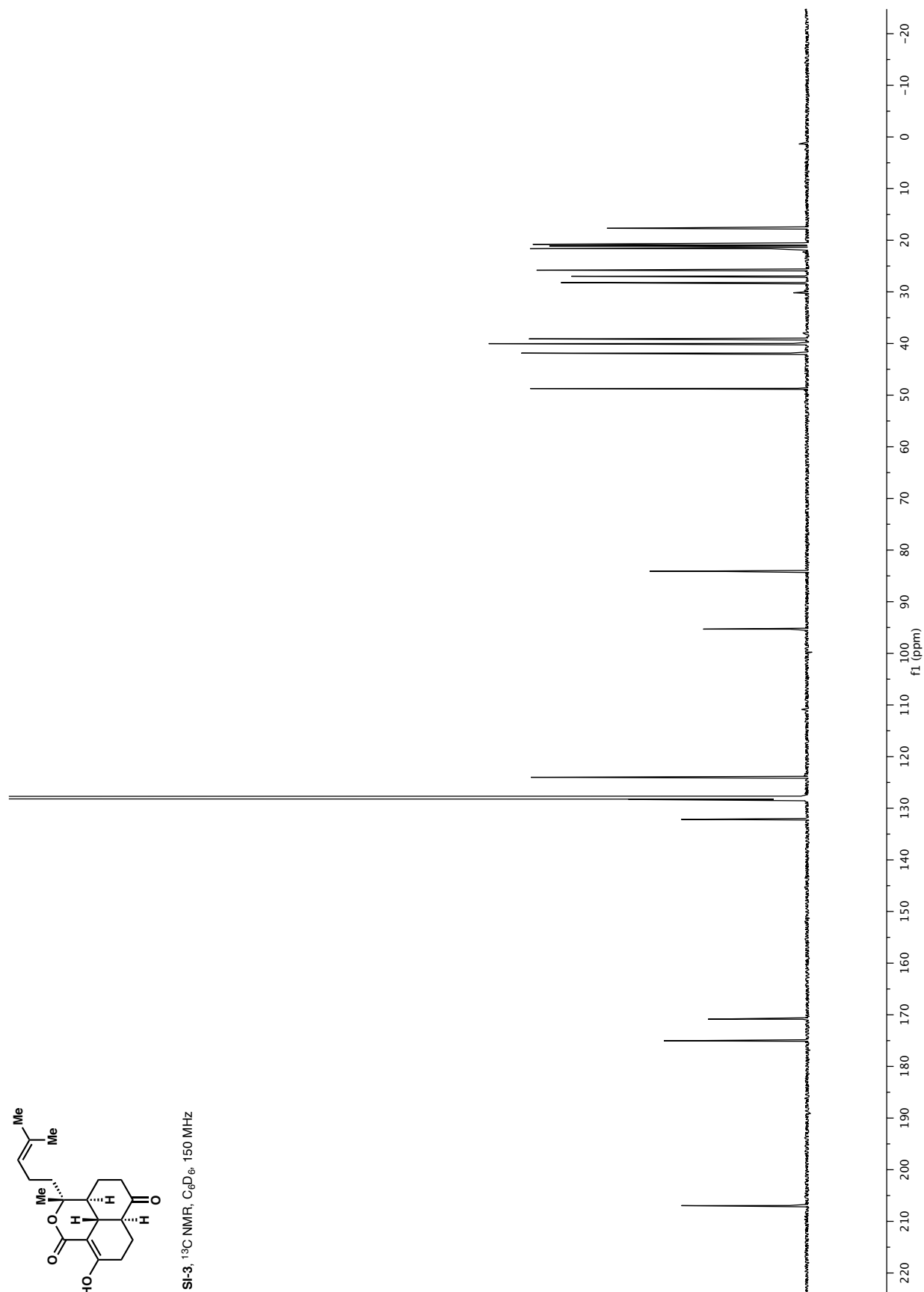


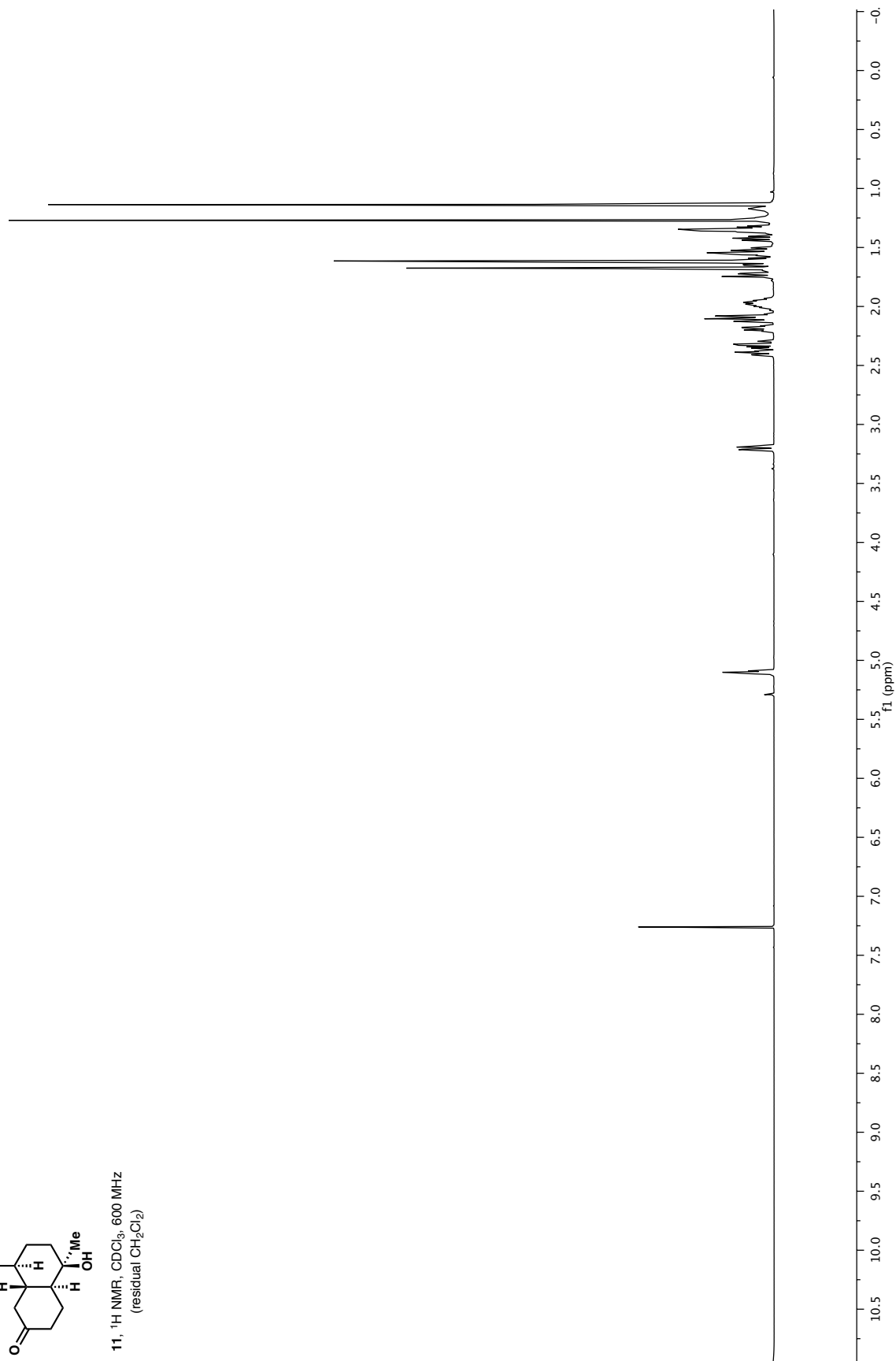
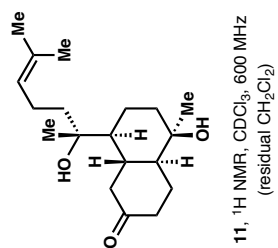
SI-3, ^1H NMR, C_6D_6 , 600 MHz

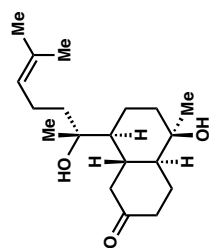




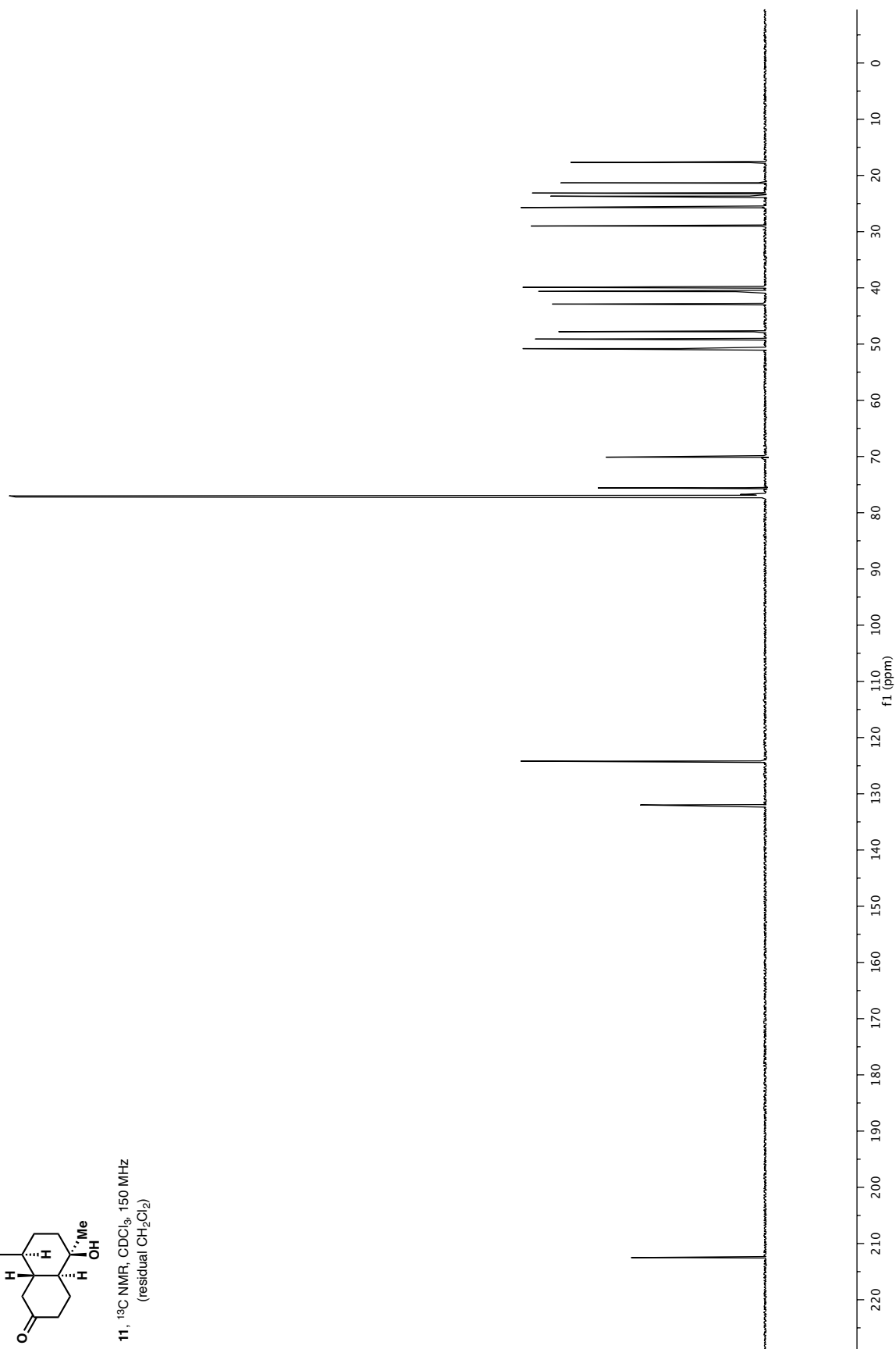
SI-3, ¹³C NMR, C₆D₆, 150 MHz

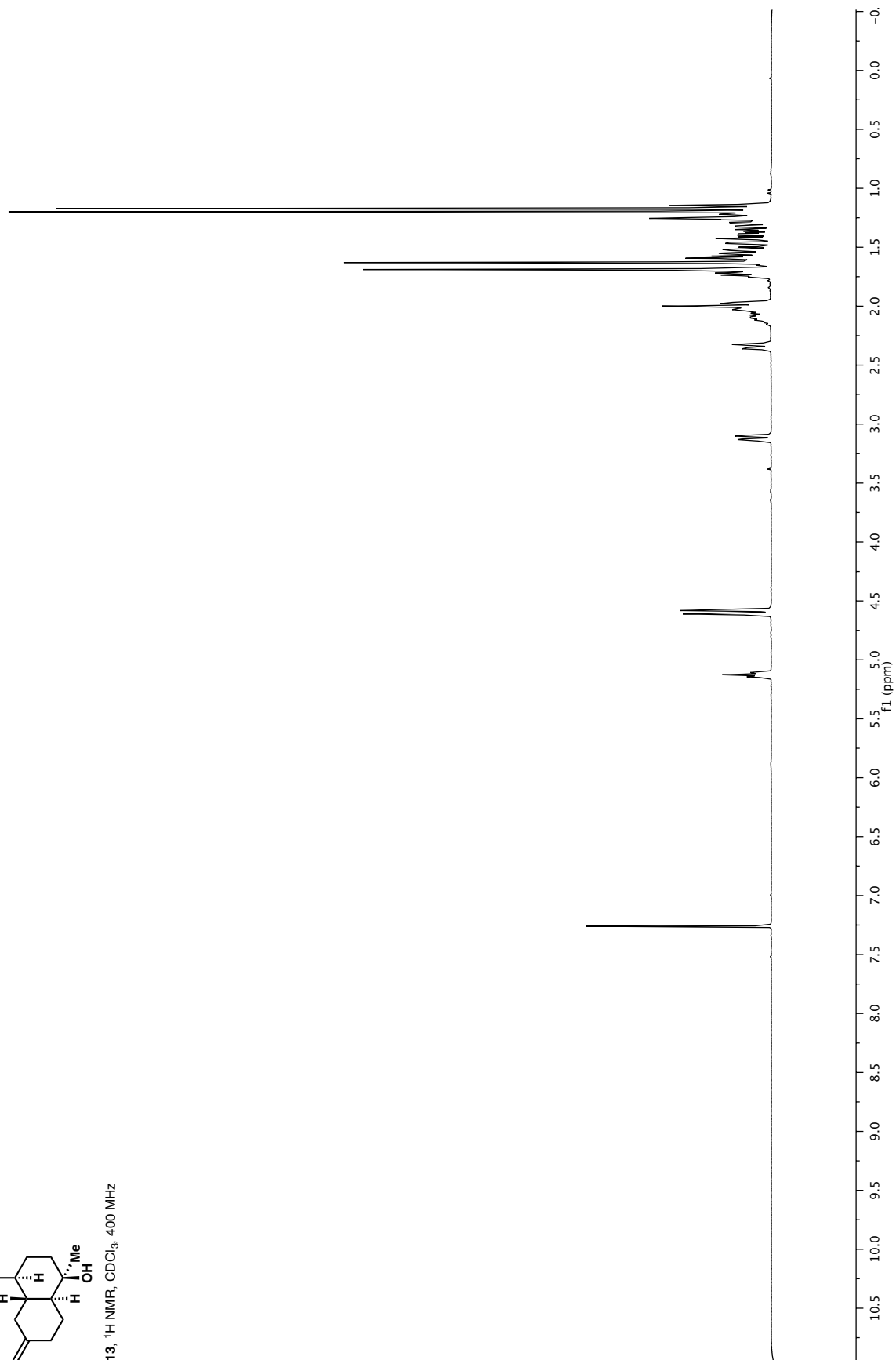
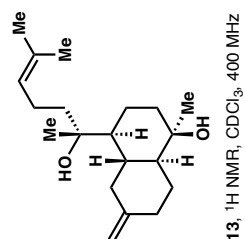


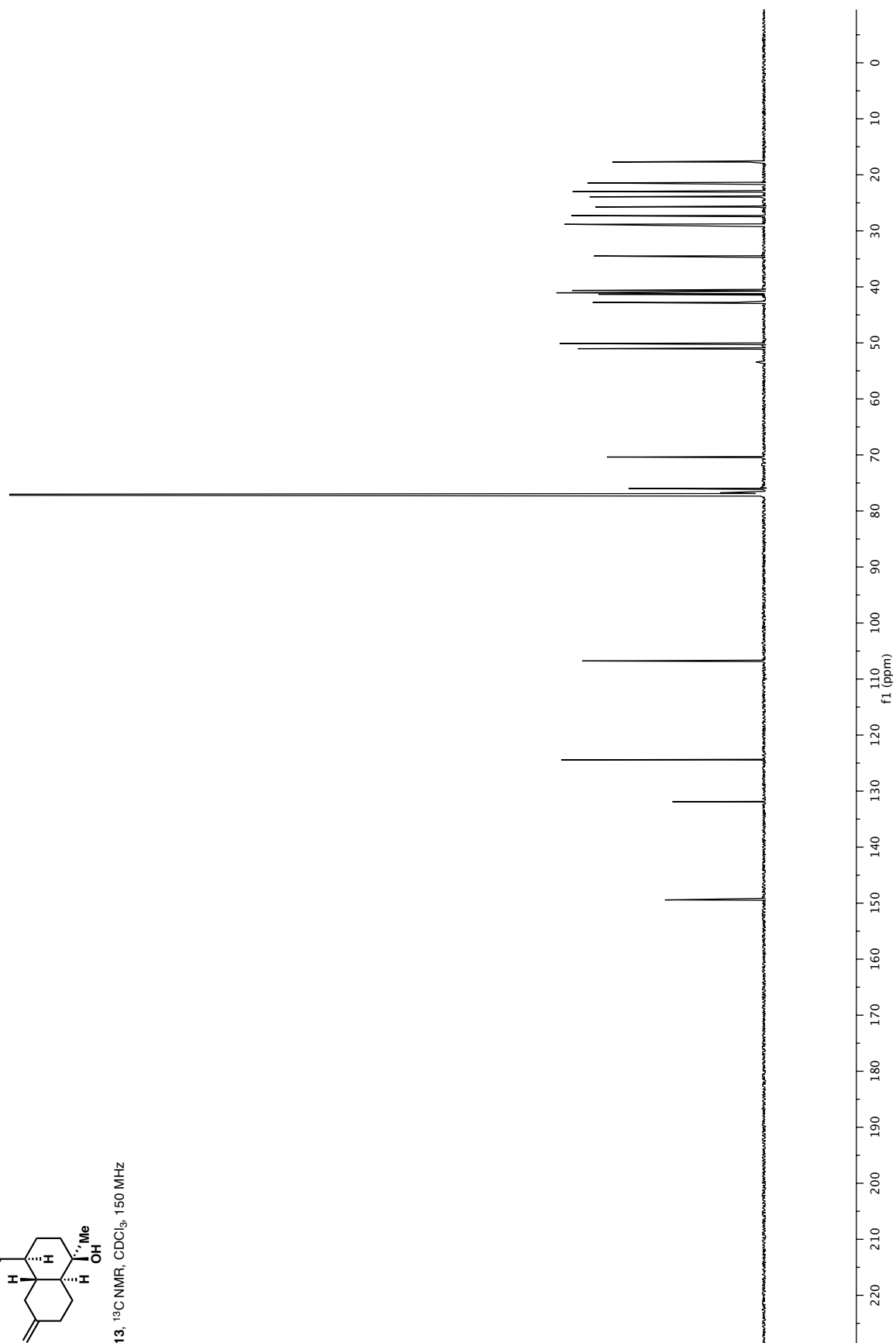
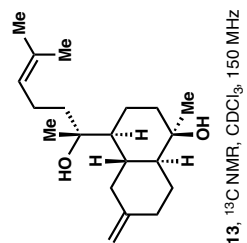


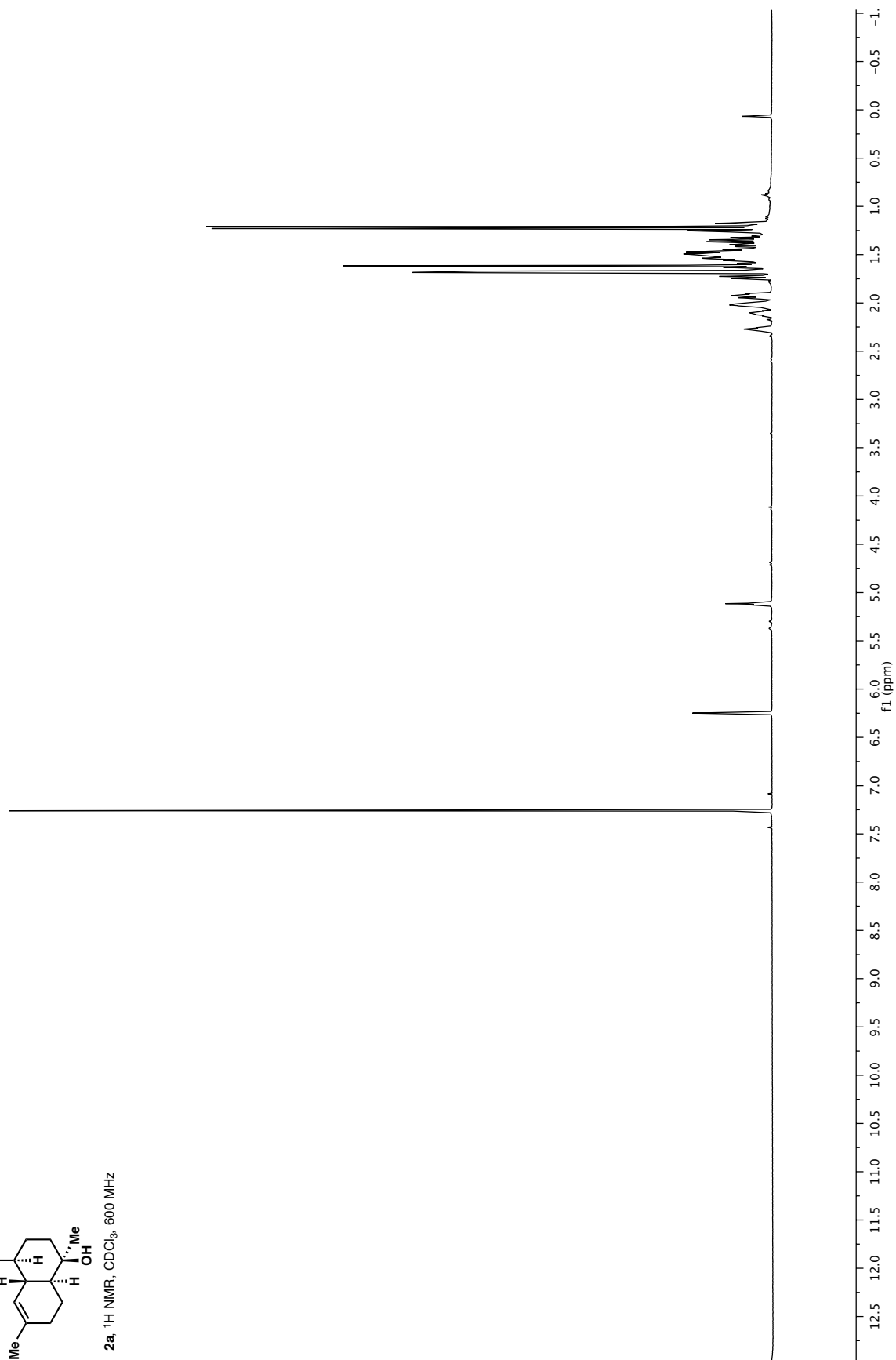
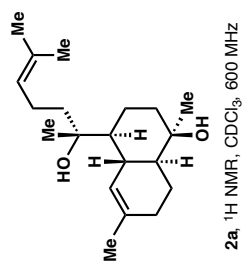


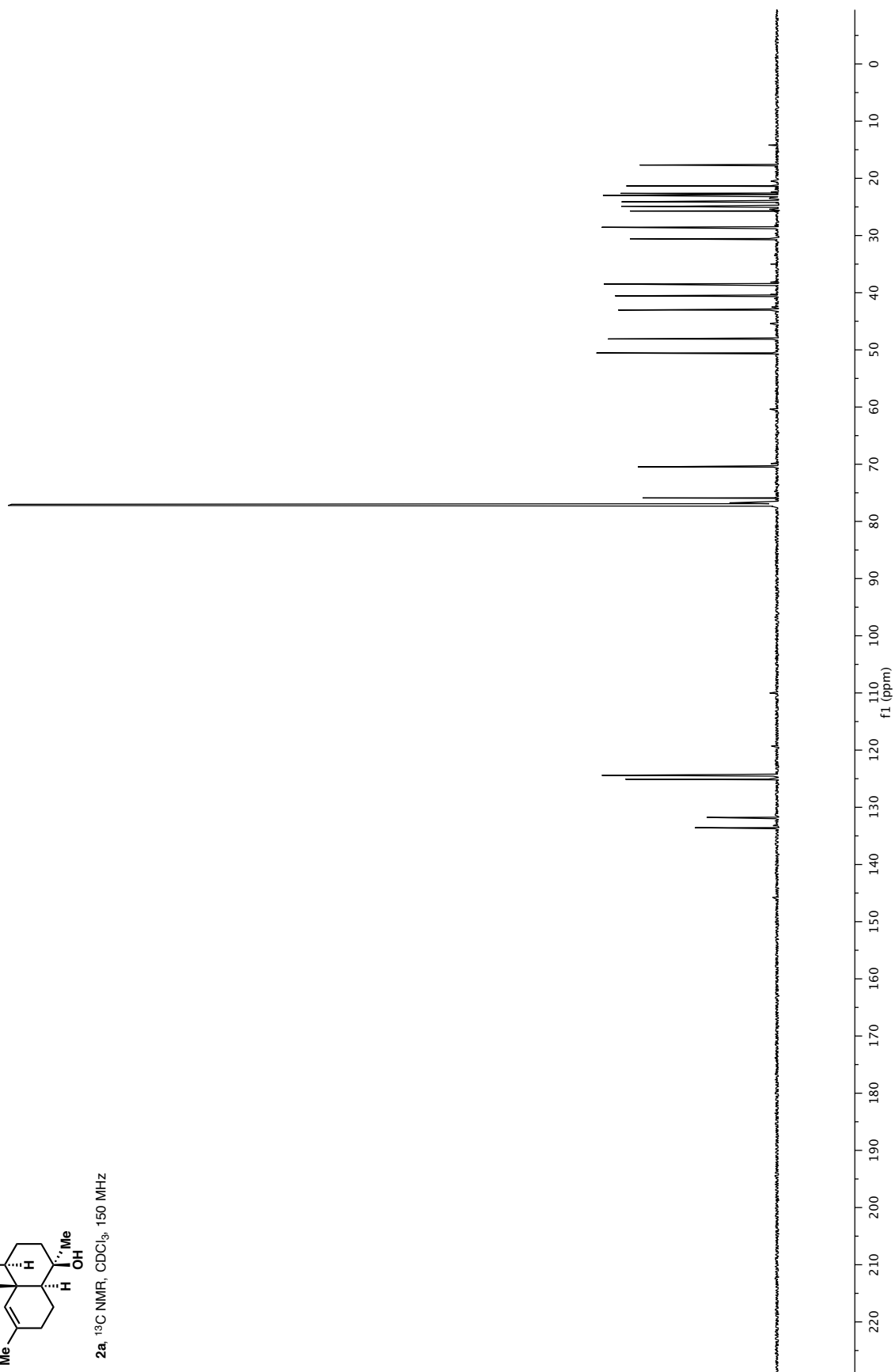
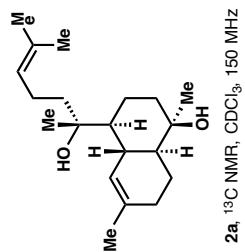
11, ^{13}C NMR, CDCl_3 , 150 MHz
(residual CH_2Cl_2)

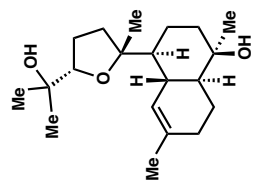




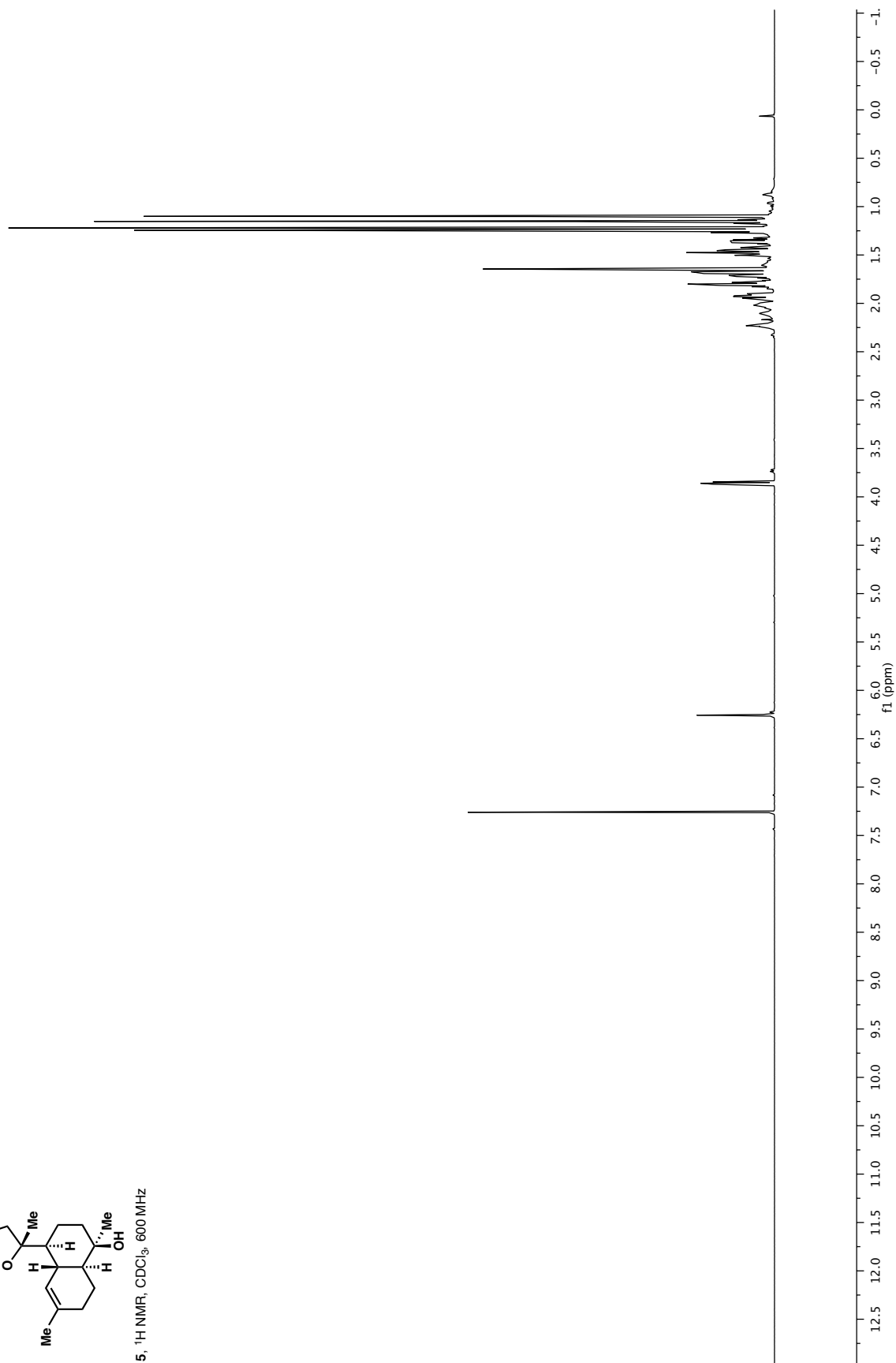


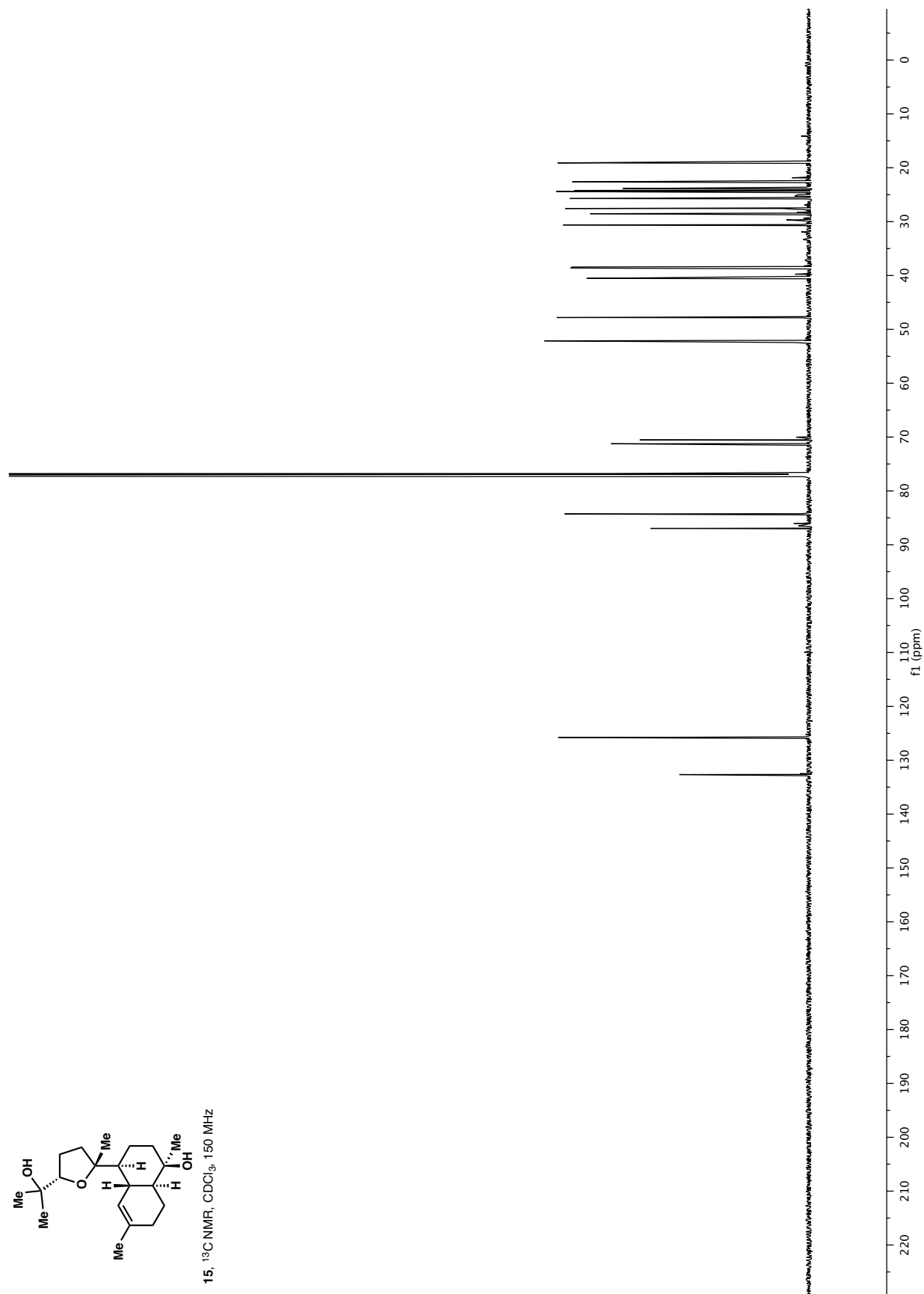
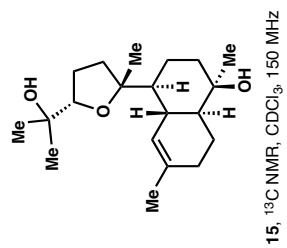


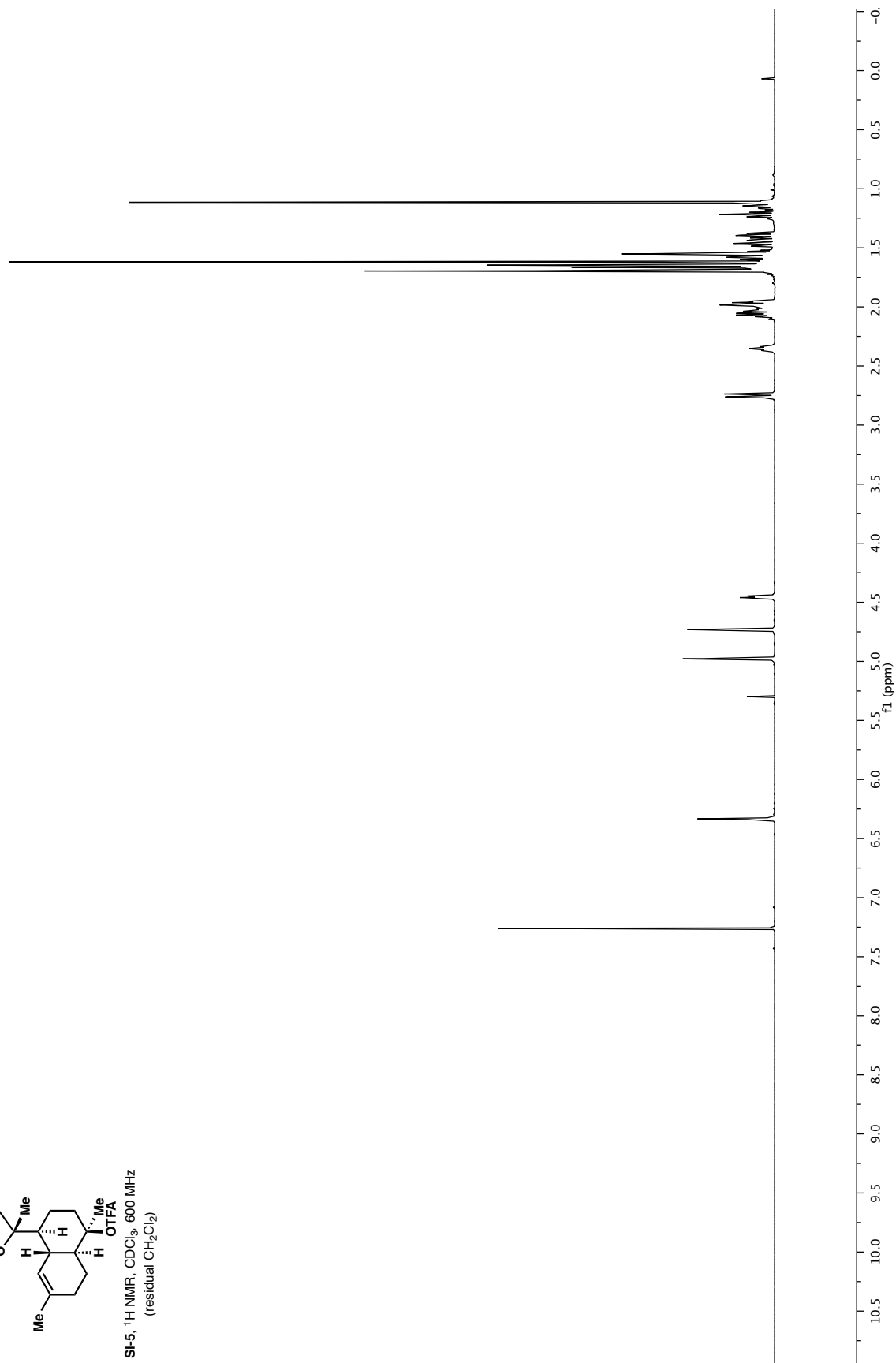
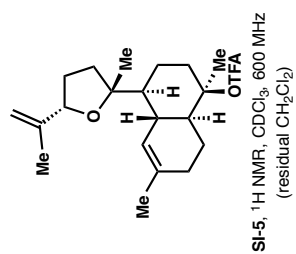


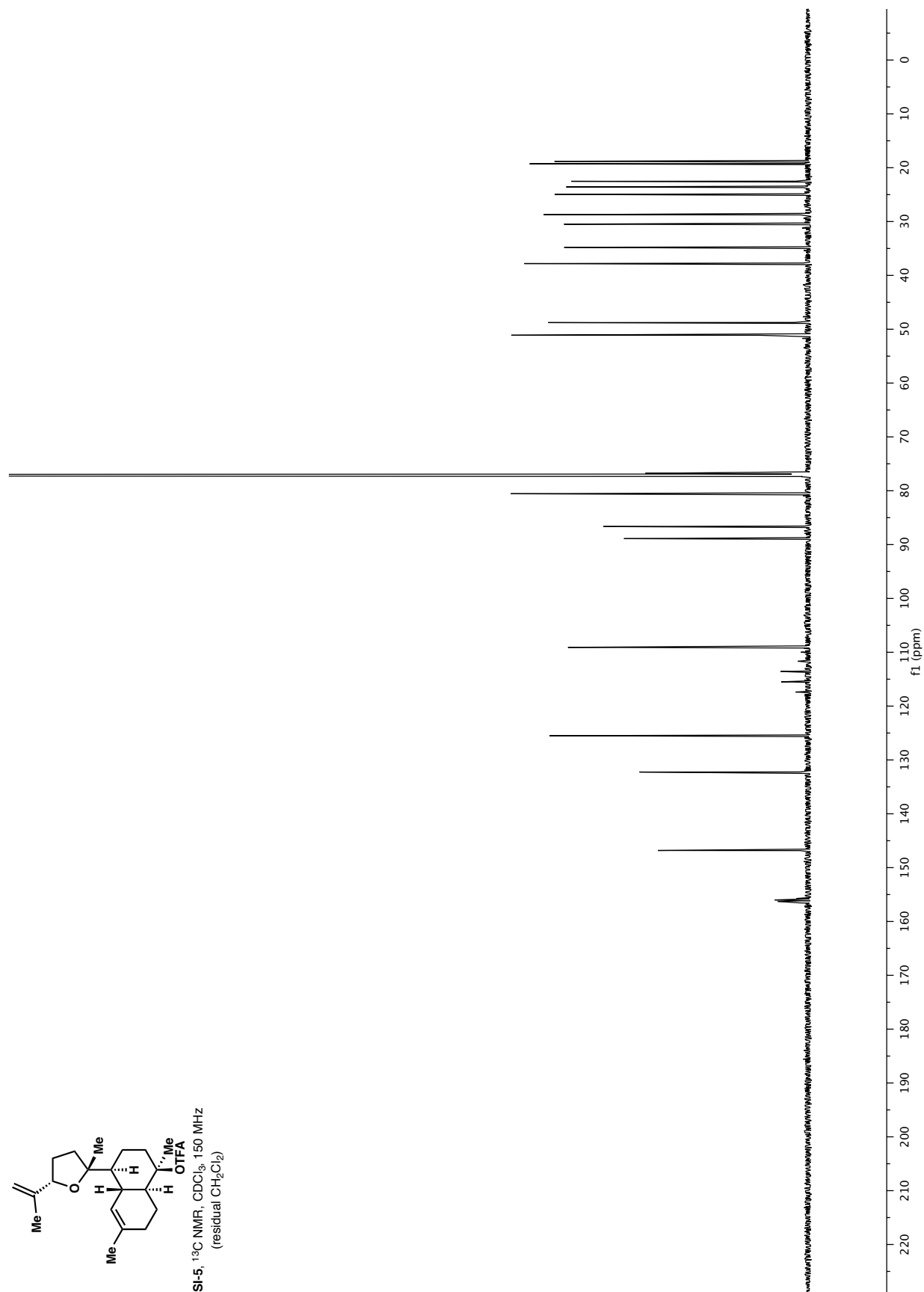
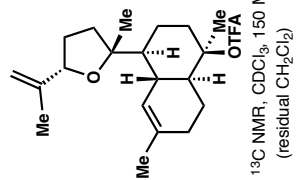


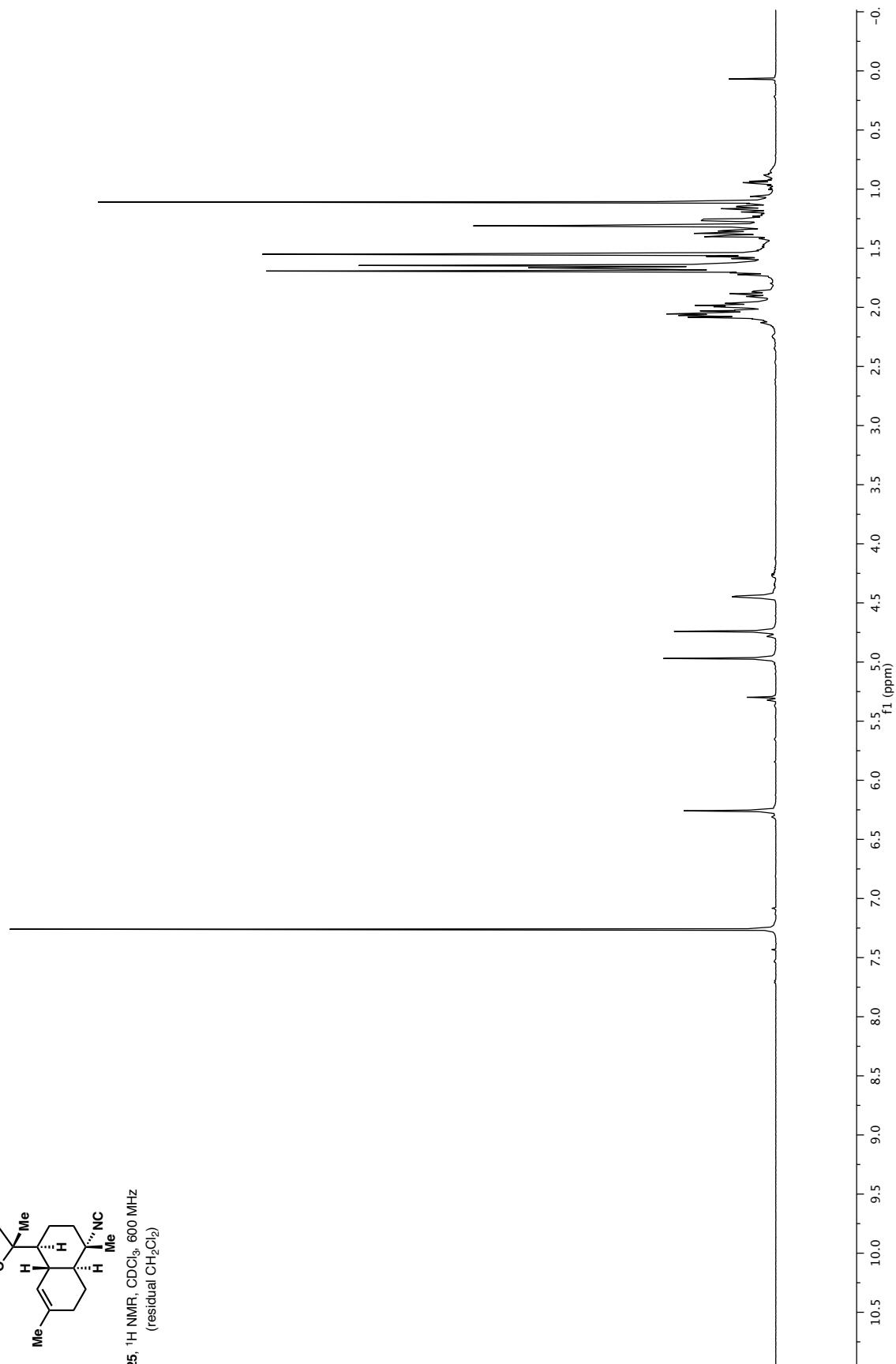
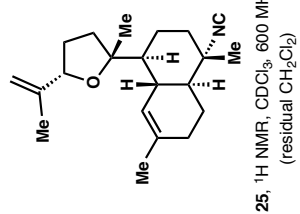
15, ^1H NMR, CDCl_3 , 600 MHz

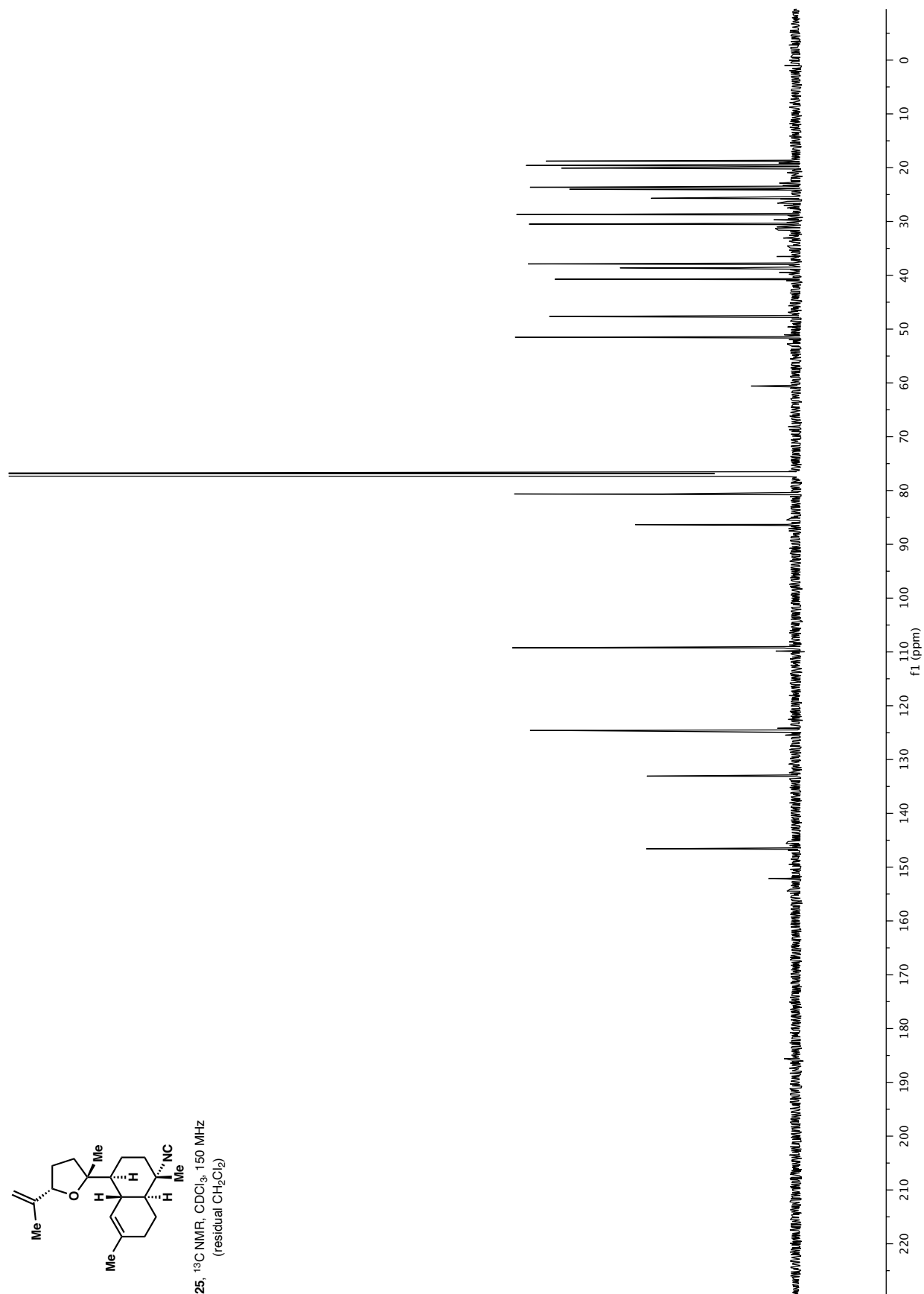
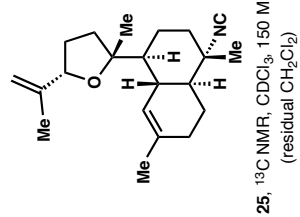


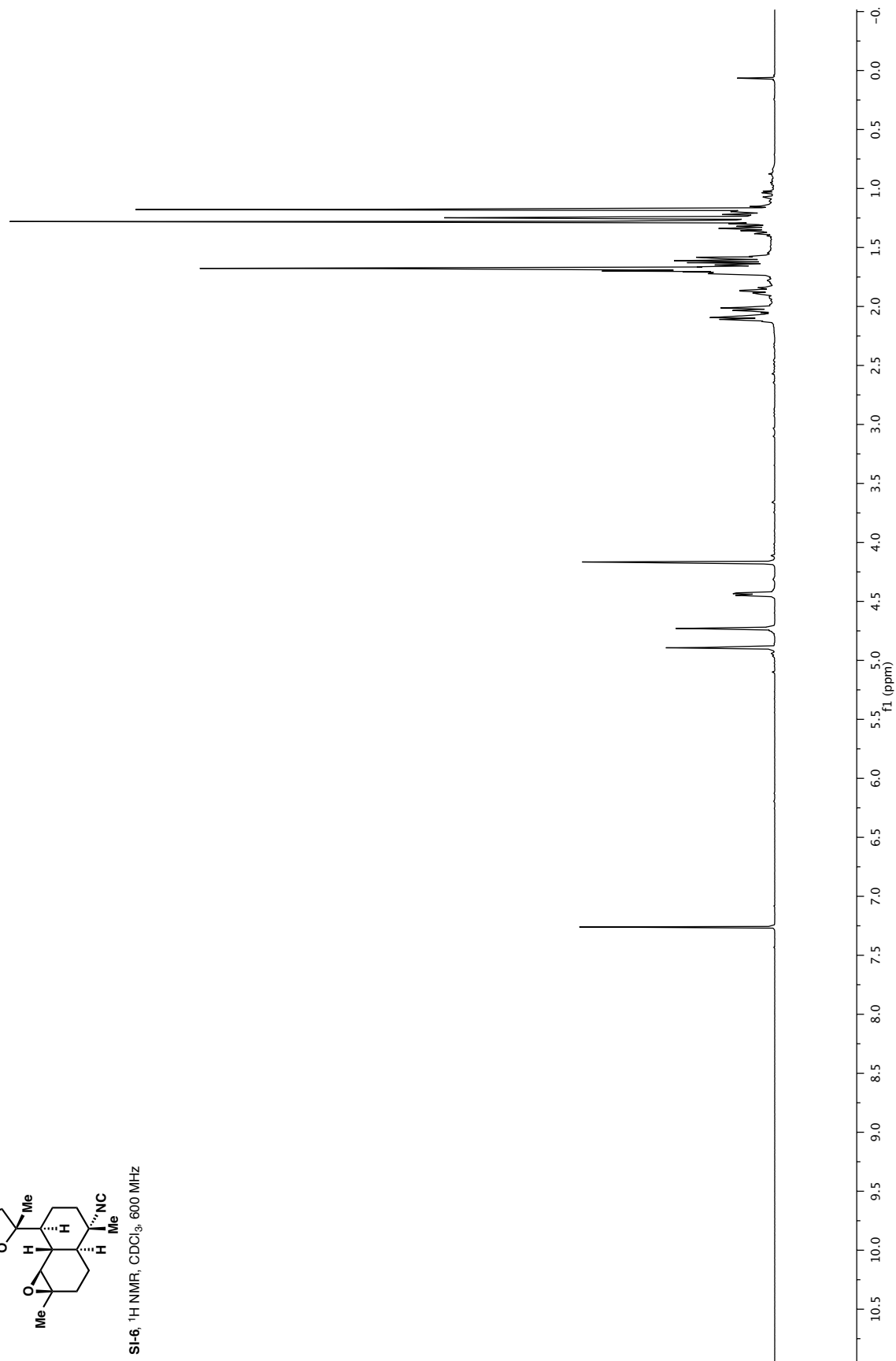
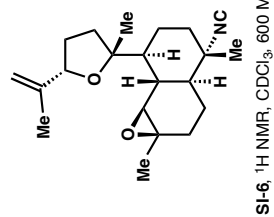


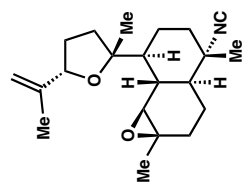




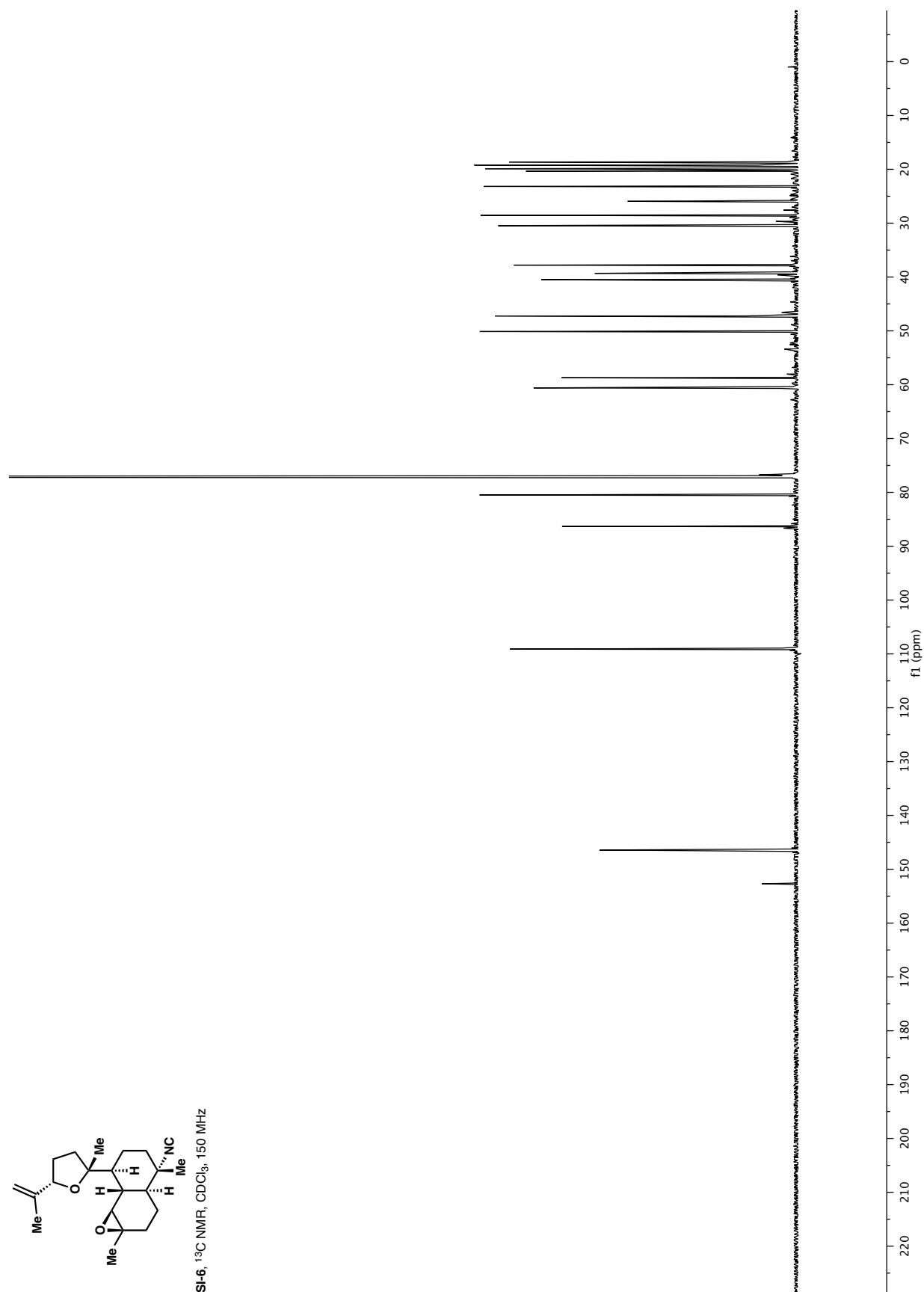


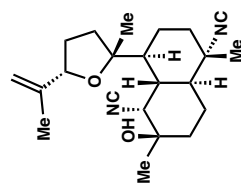




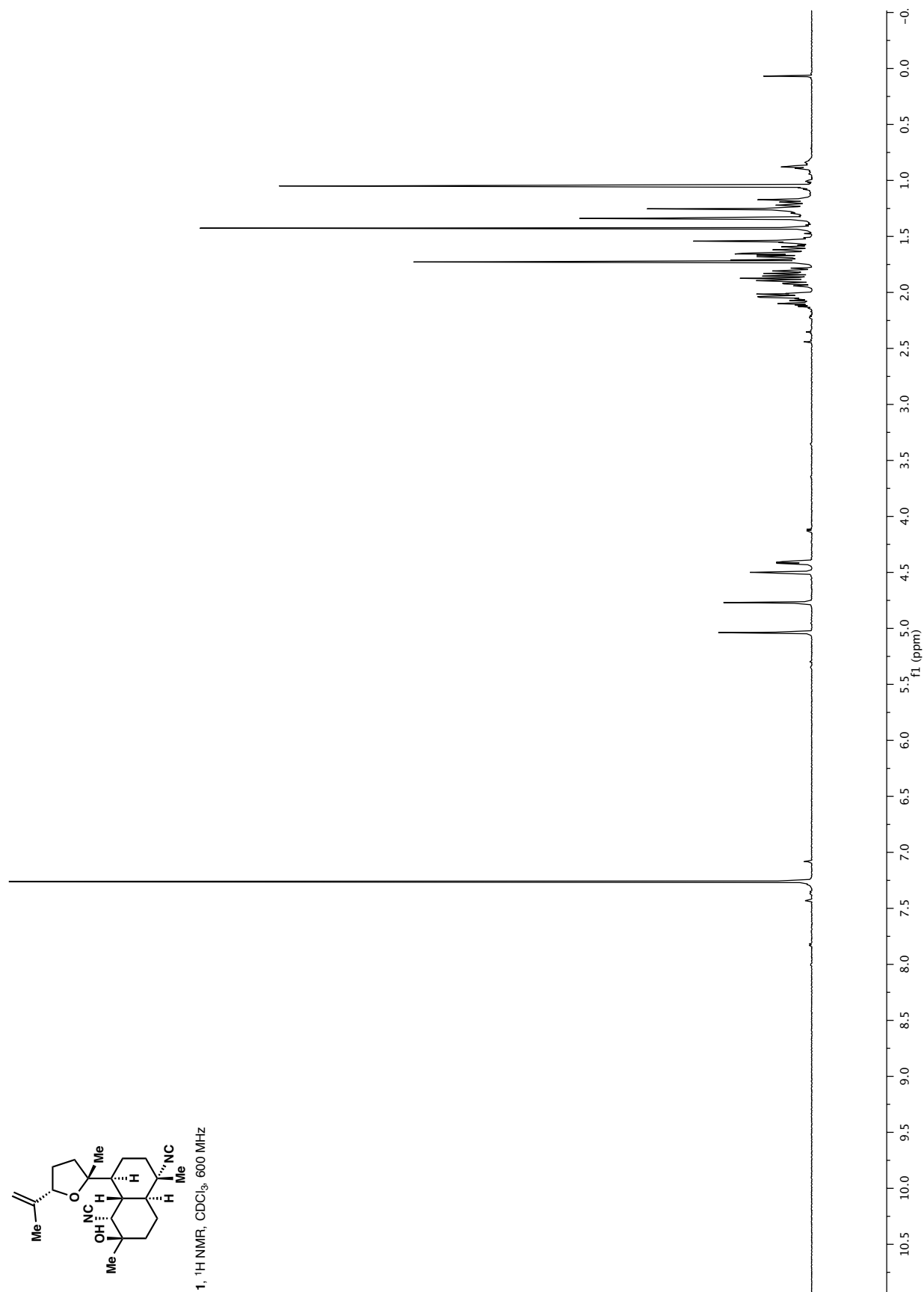


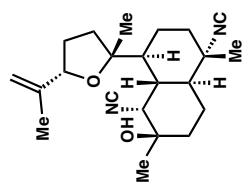
SI-6, ^{13}C NMR, CDCl_3 , 150 MHz



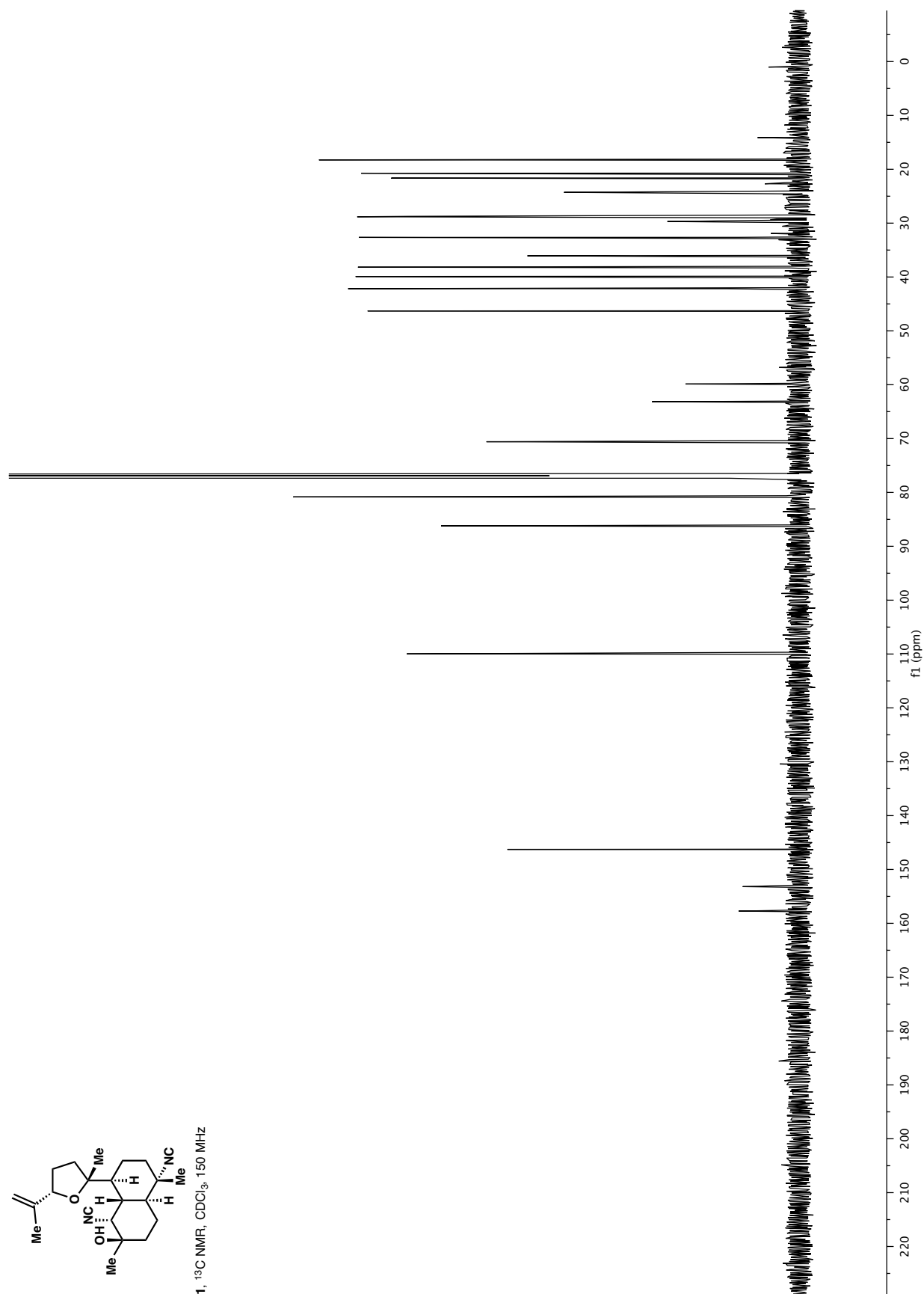


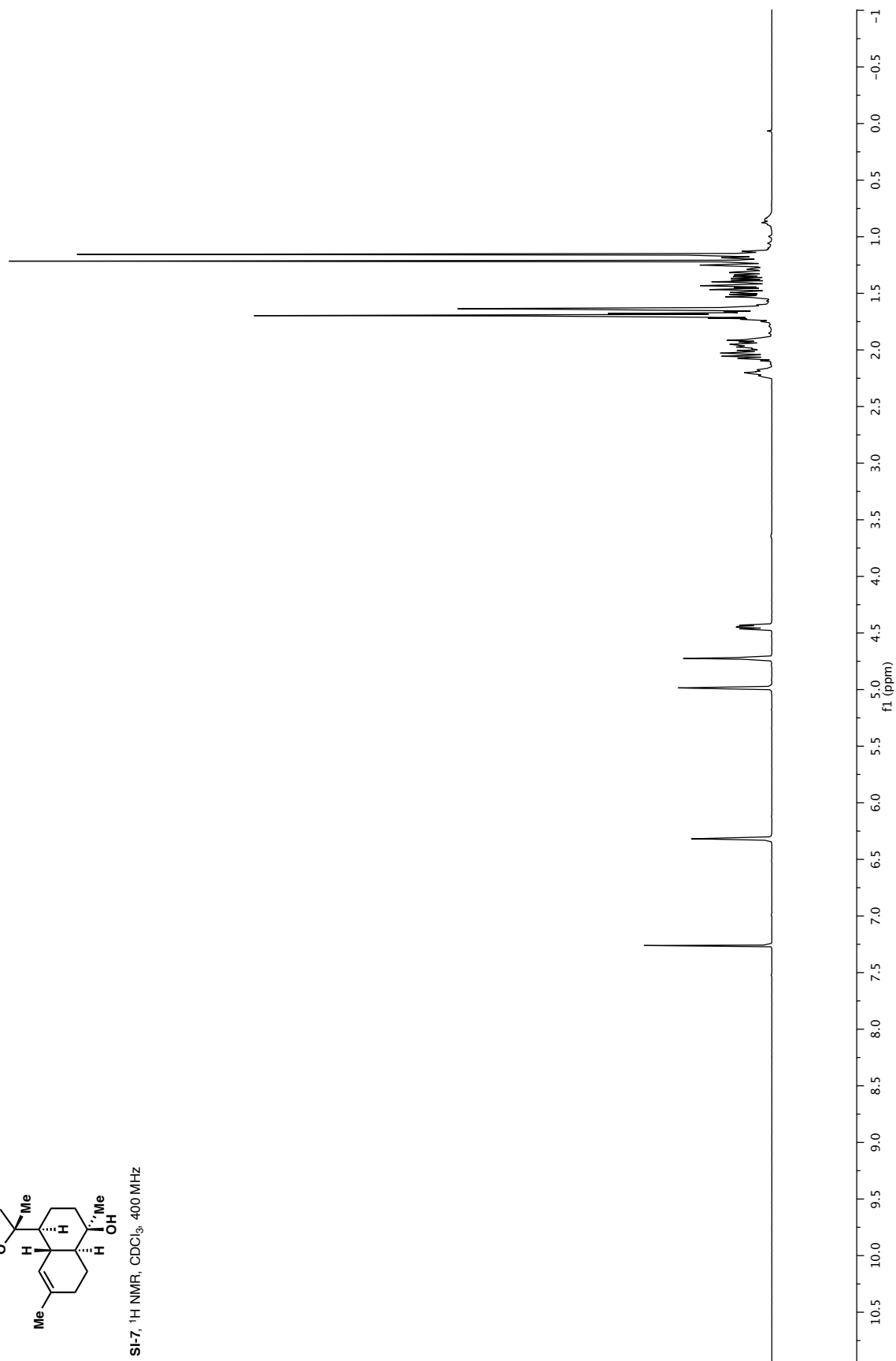
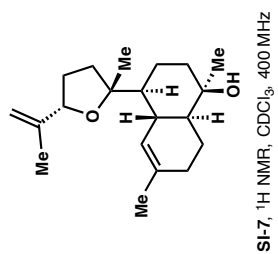
1, ^1H NMR, CDCl_3 , 600 MHz

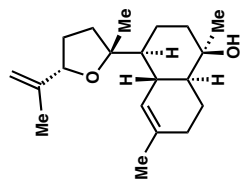




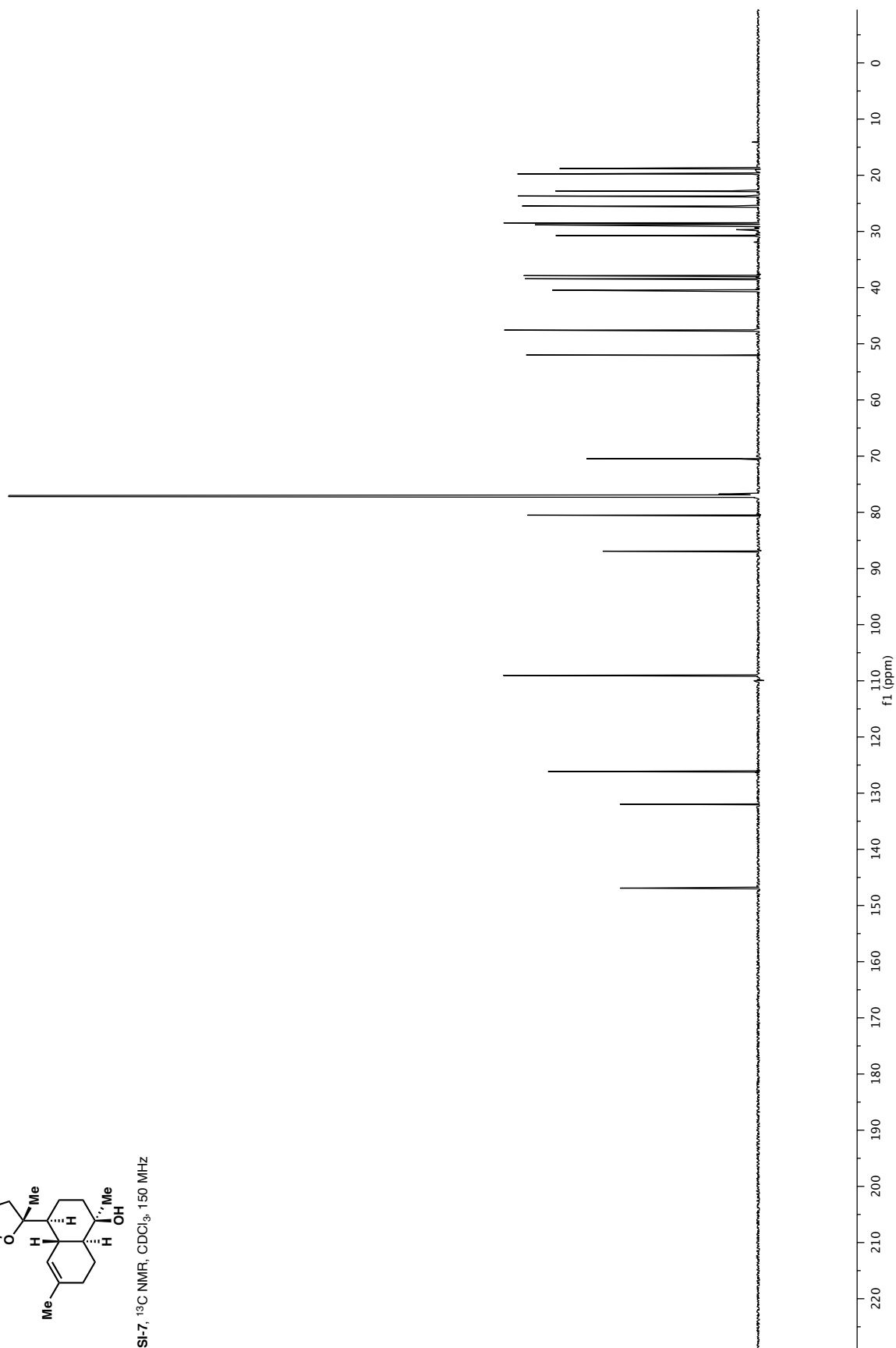
1, ^{13}C NMR, CDCl_3 , 150 MHz

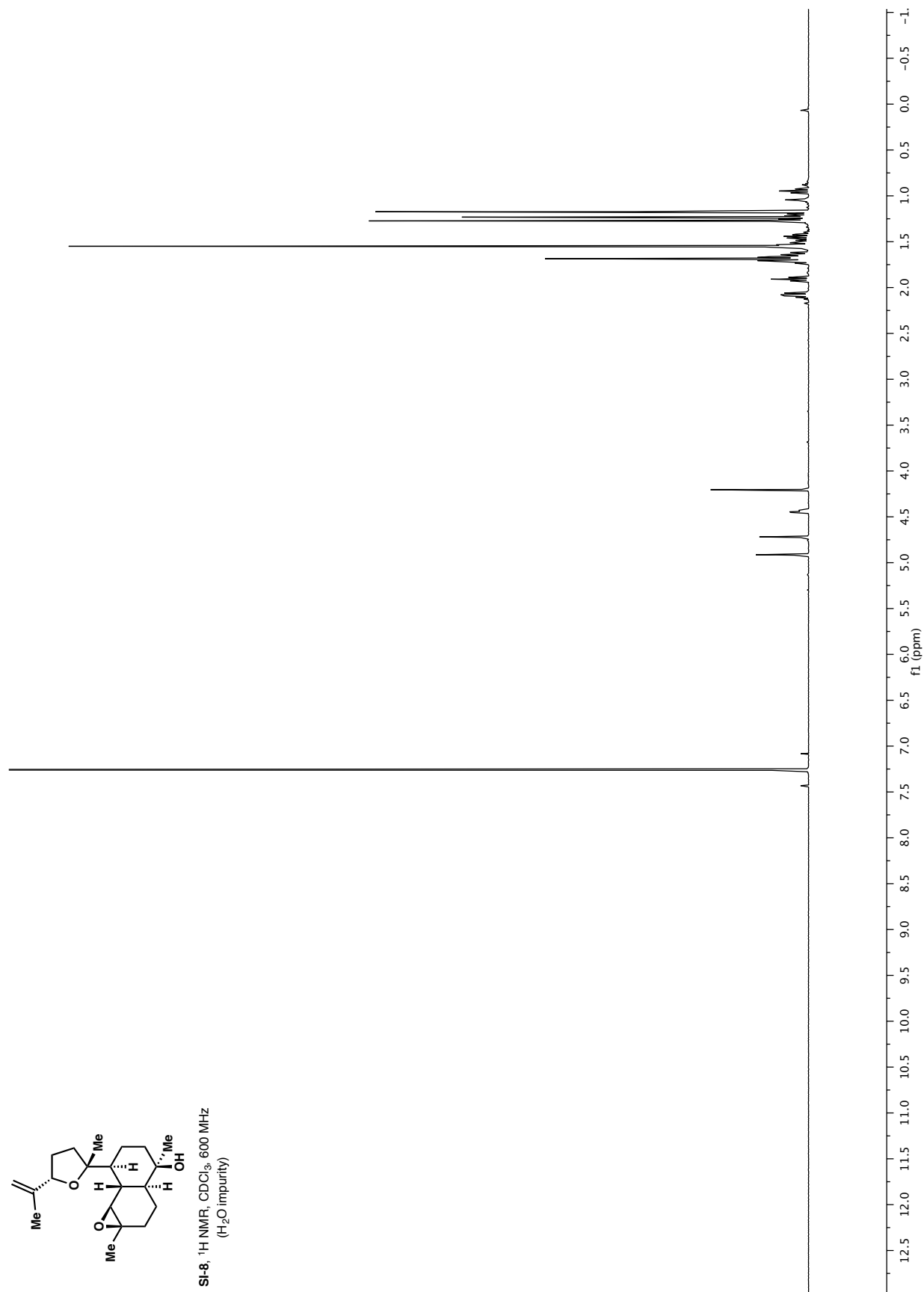
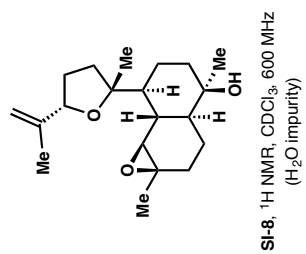


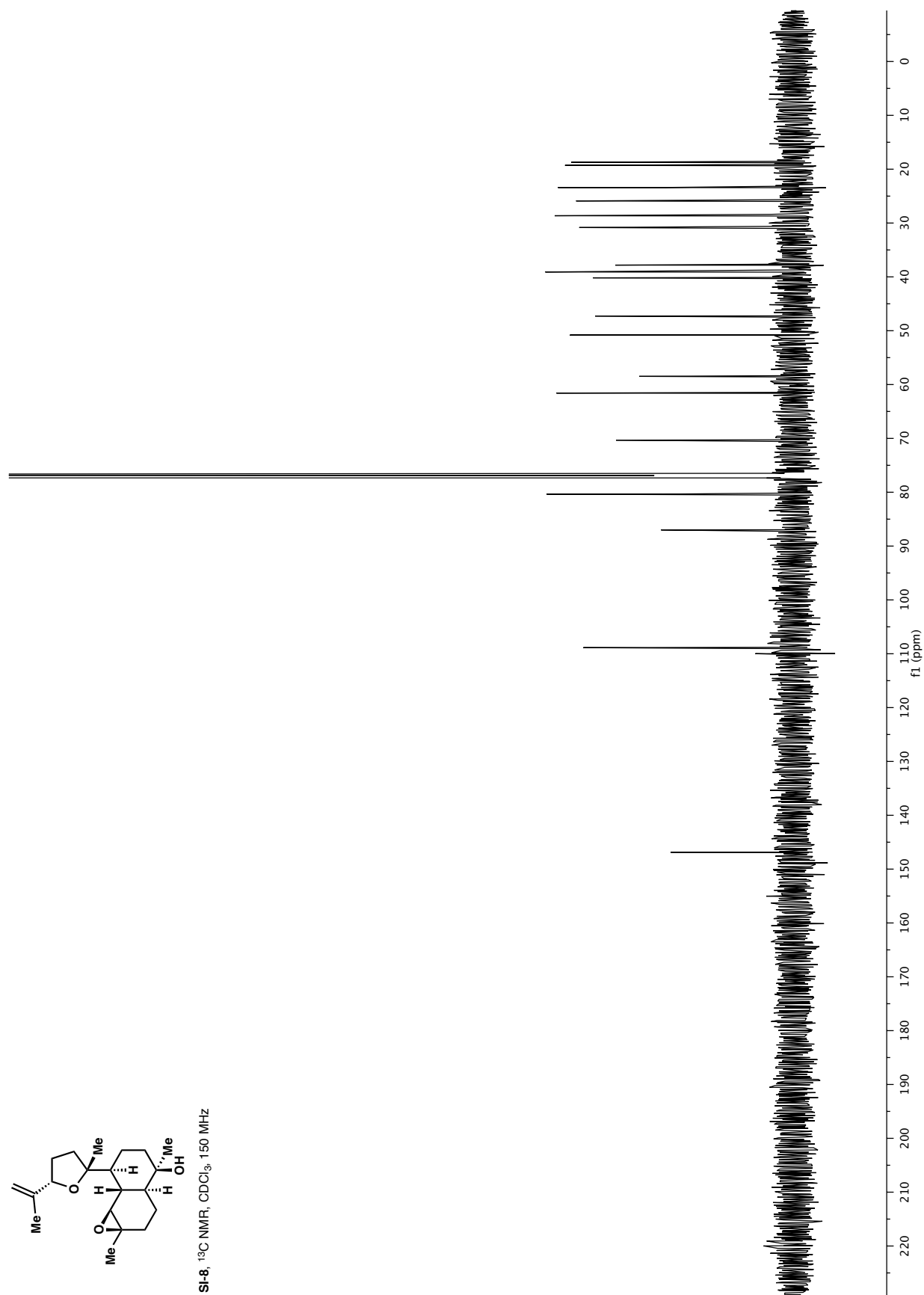
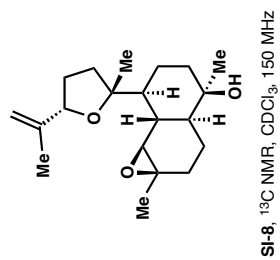


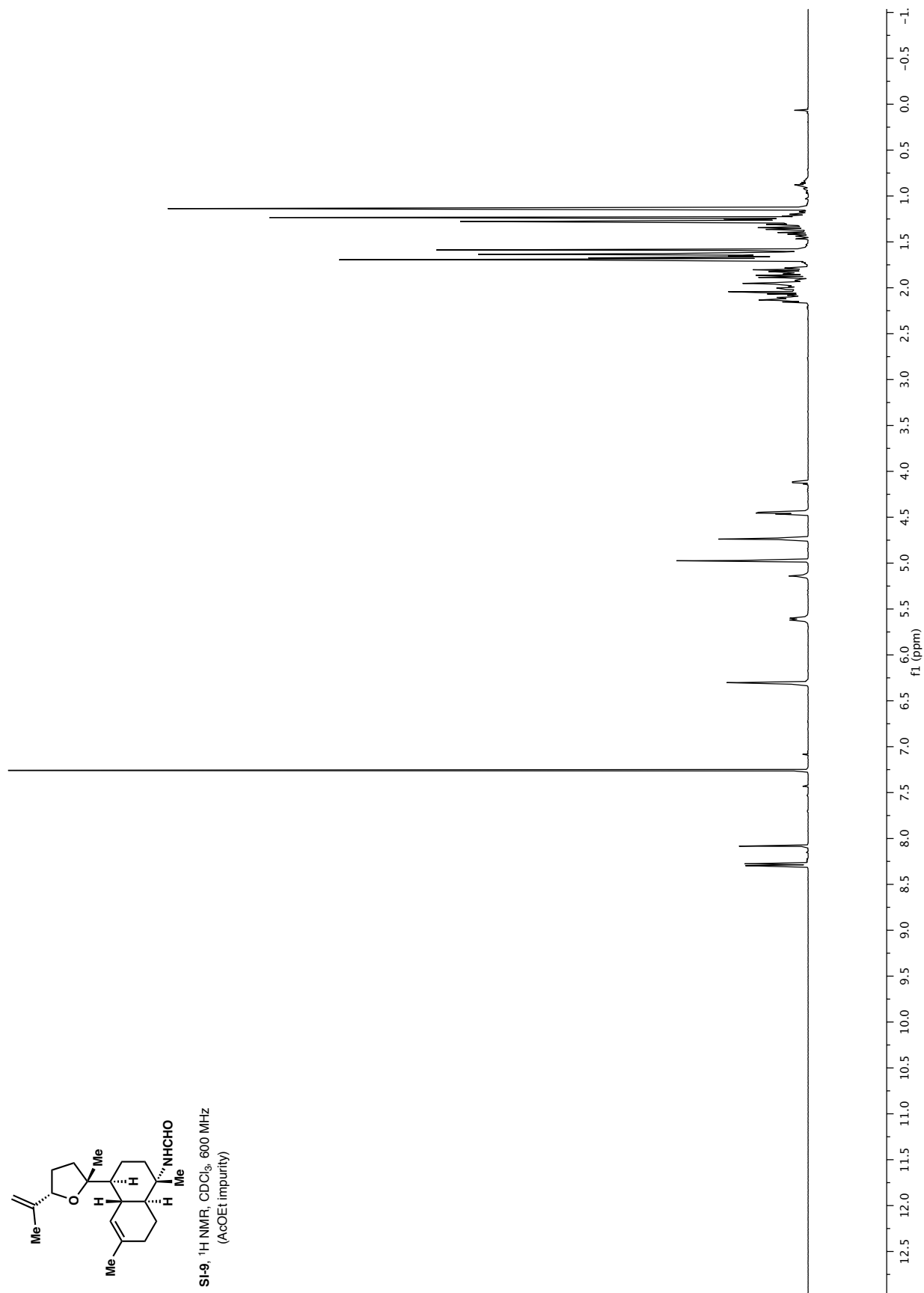
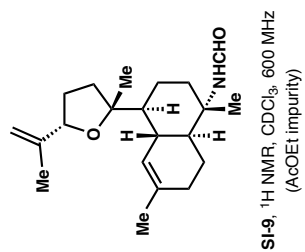


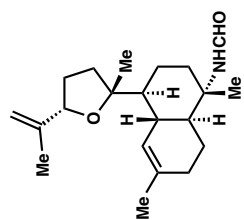
SI-7, ^{13}C NMR, CDCl_3 , 150 MHz



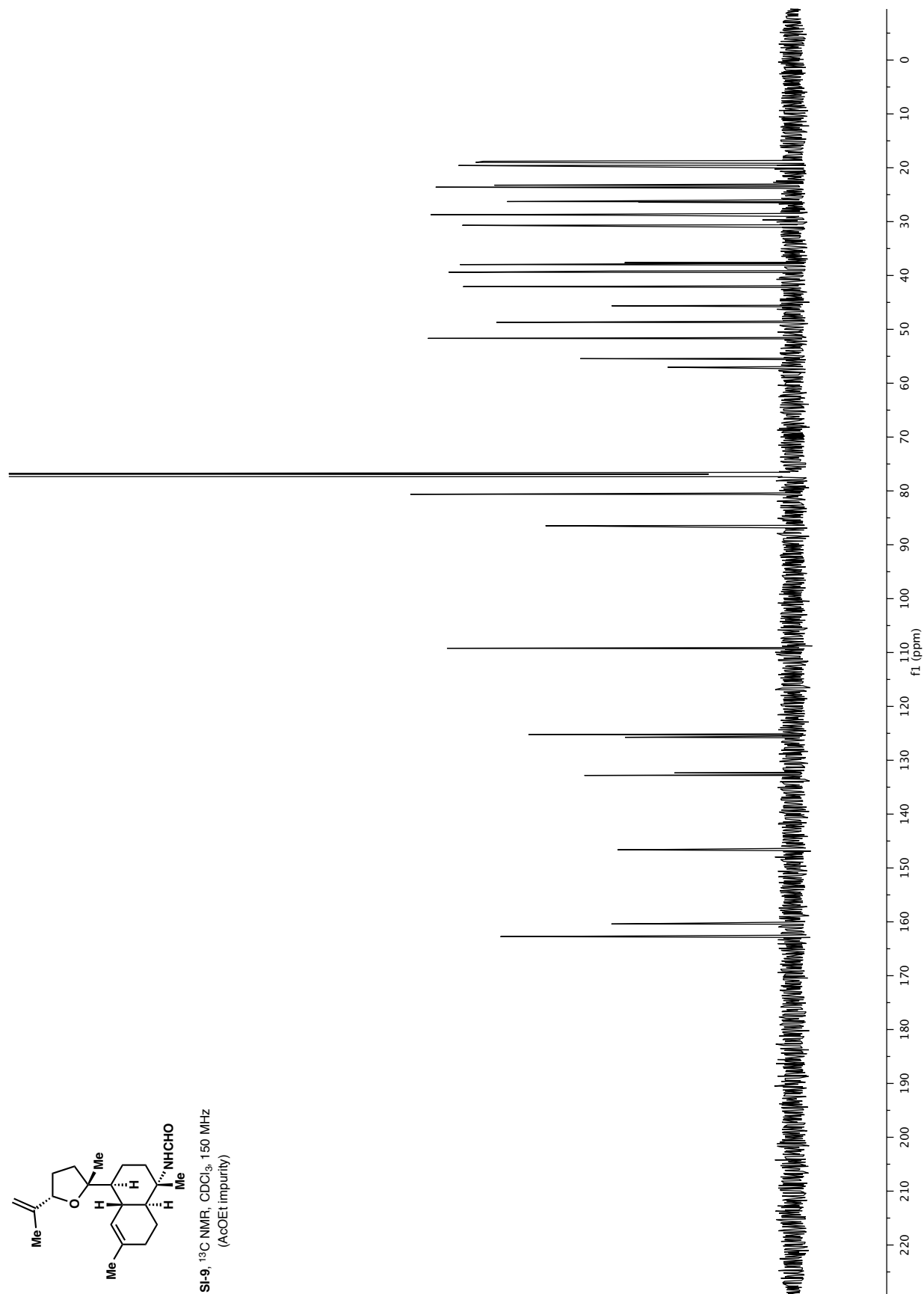


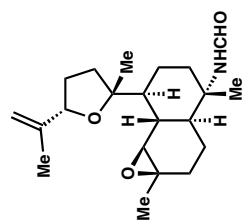




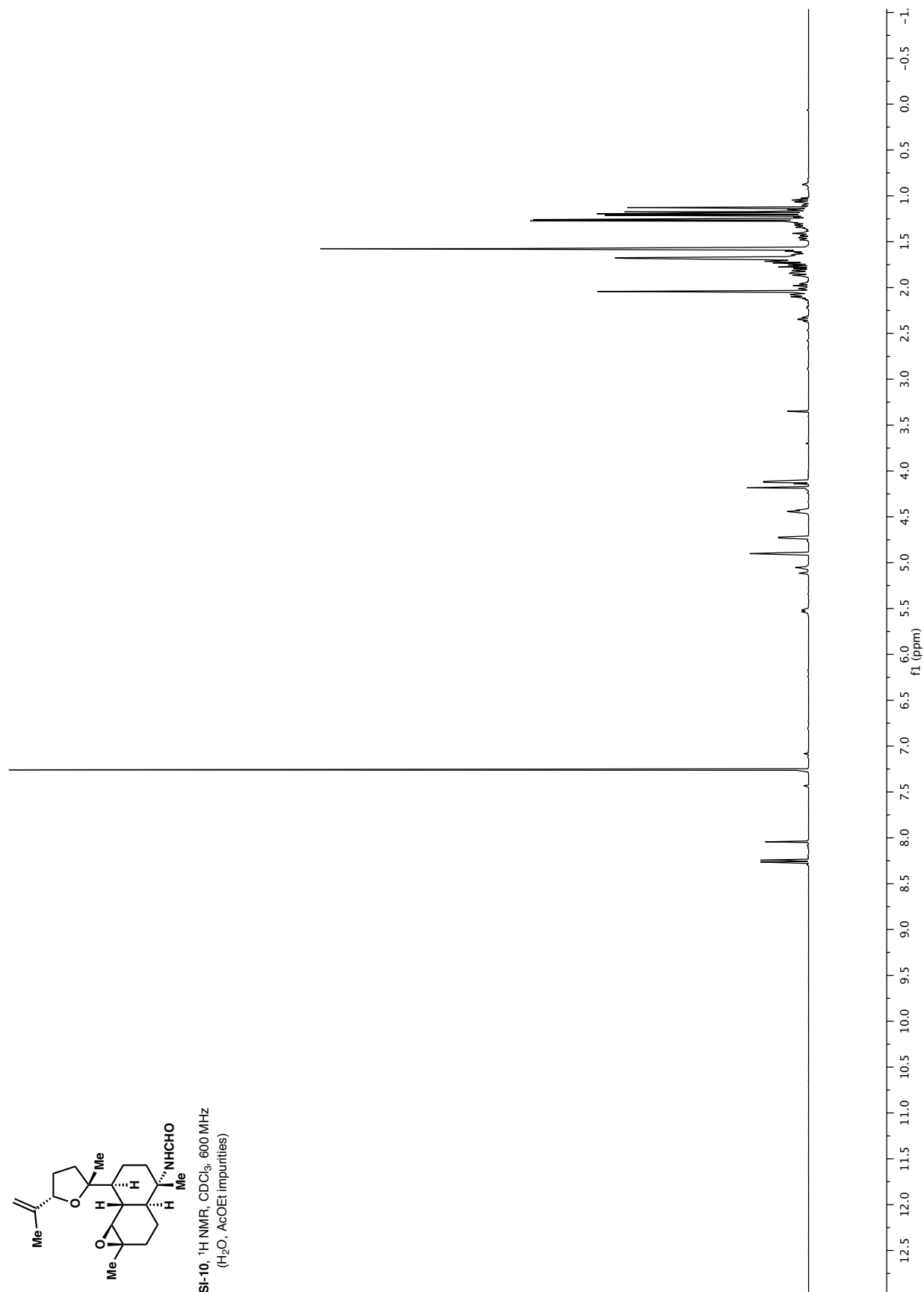


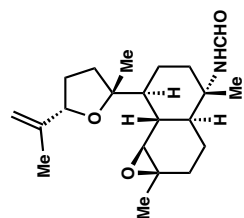
SI-9, ^{13}C NMR, CDCl_3 , 150 MHz
(AcOEt impurity)



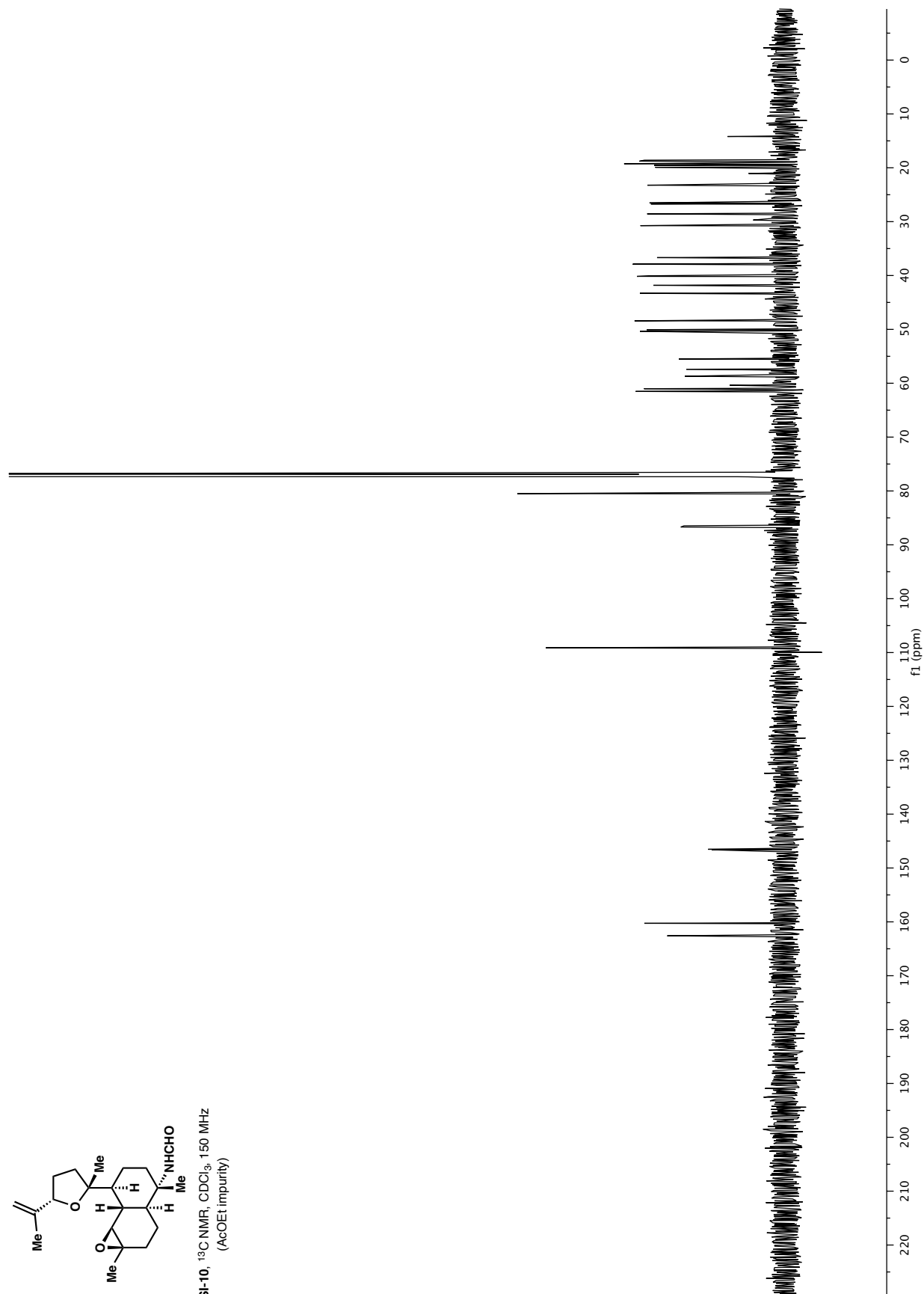


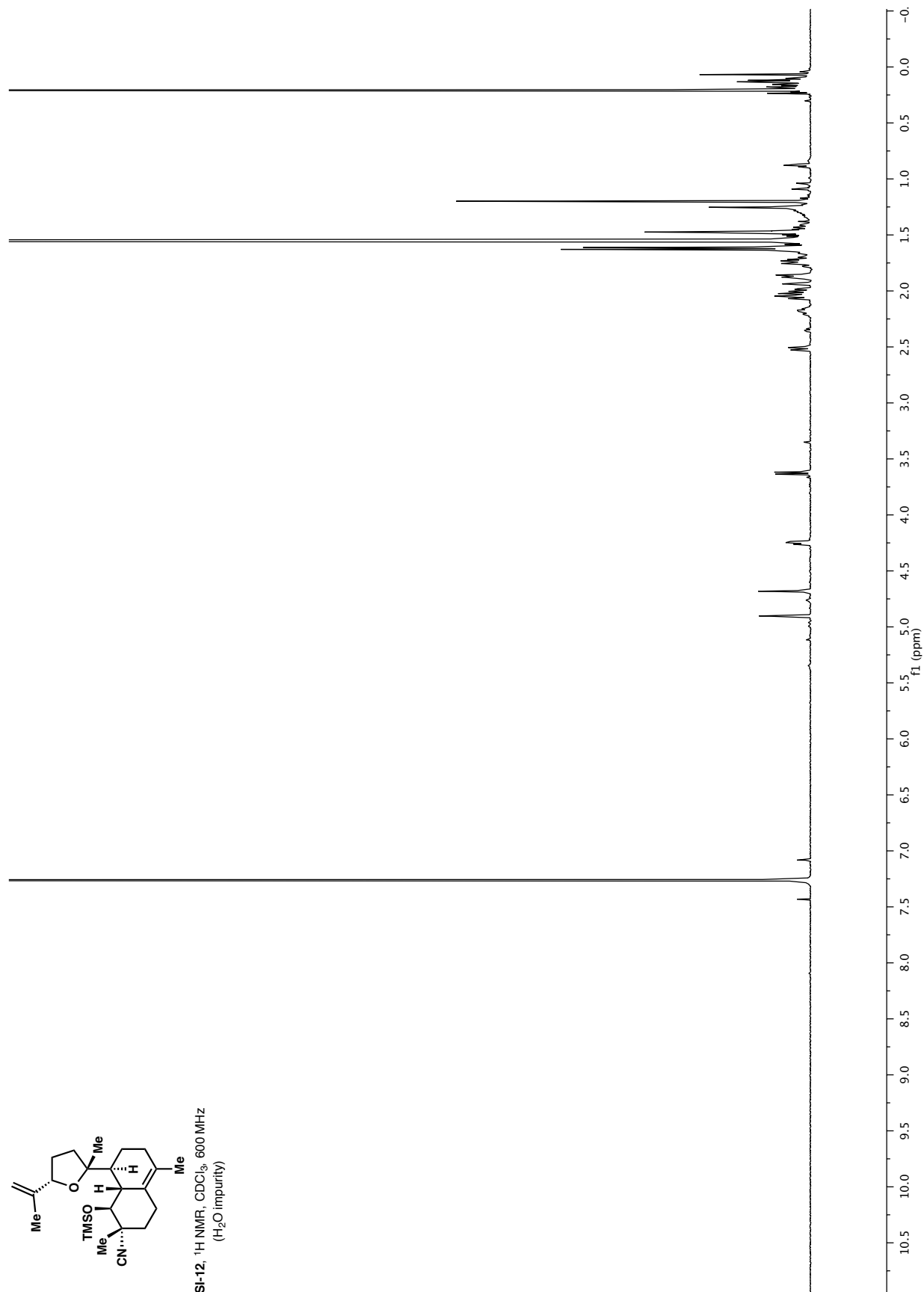
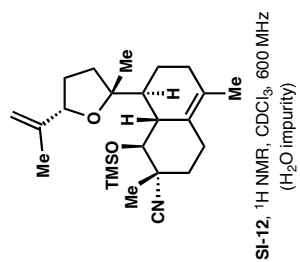
SI-10, ^1H NMR, CDCl_3 , 600 MHz
(H_2O , AcOEt impurities)

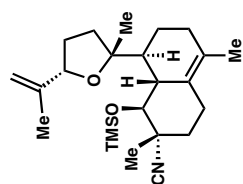




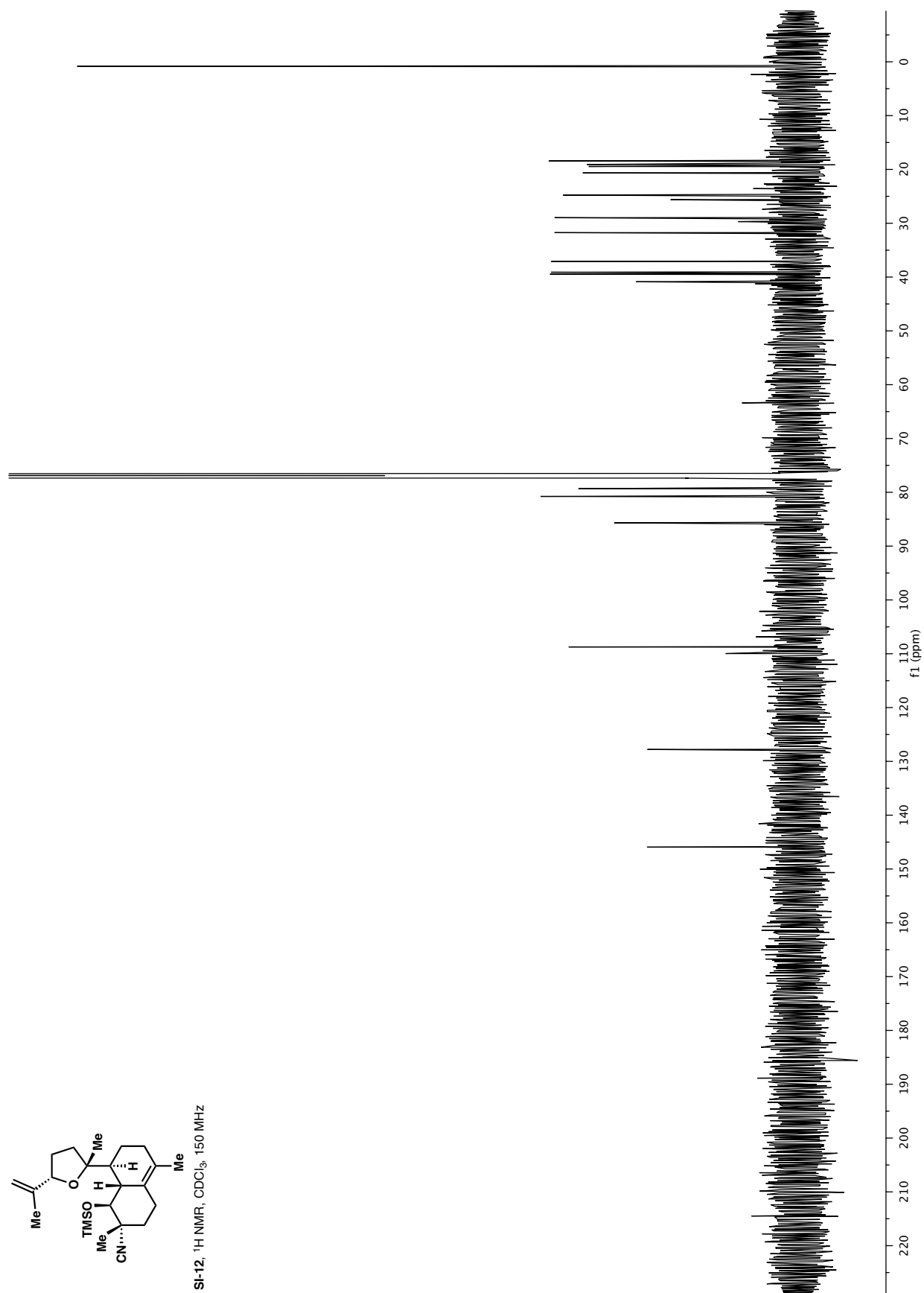
SI-10, ^{13}C NMR, CDCl_3 , 150 MHz
(AcOEt impurity)







SI-12, ^1H NMR, CDCl_3 , 150 MHz



Crystal structure of tricyclic lactone SI-3

