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Supporting Information

Total Synthesis of (±)-Phomoidride D

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Experimental Procedures

General Information

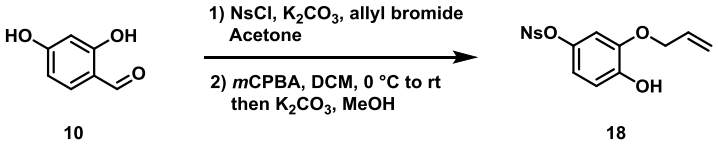
Unless stated otherwise, all reactions were performed using flame or oven-dried glassware and under an atmosphere of nitrogen. DCM, THF, diethyl ether, benzene, and toluene were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Acetonitrile, ethyl acetate, pentanes, hexanes, DMF, DMSO, and DCE were supplied by either Fisher Scientific or Sigma-Aldrich and were used as received. Triethylamine, diisopropylamine, and methanol were stirred over calcium hydride and distilled before use. All other commercially available reagents were used as received. α-Bromoketone **16** was synthesized according to the reported procedure.[1]

Unless stated otherwise, reactions were monitored by thin-layer chromatography using Millipore-Sigma® Glass TLC plates, 60 Å (F-254s indicator, 250 μm thickness). All purifications were performed using Silicyle SiliaFlash® P60 silica (40-63 μm, 230-400 mesh), Millipore Silica Gel 60 (0.040-0.063 mm, 230-400 mesh ASTM), or sigma Aldrich C18-reversed phase silica gel (40-63 μm, 230-400 mesh, fully endcappeed) as the stationary phase as a stationary phase. All melting points were obtained on a Chemglass Life Sciences melting point device (Model: DMP100) and are uncorrected. Infrared spectra were obtained using a Bruker Alpha ATR-IR. High-resolution mass spectroscopy was performed by the central instrument facility at Colorado State University or on a Thermo Orbitrap ESI mass spectrometer at Baylor University. Single-crystal X-ray crystallography was performed by Brian Newell at Colorado State University or Prof. Caleb Martin at Baylor University. ^{1}H and ^{13}C-NMR spectra, were taken on Varian VNMRS 500, Varian Inova 400, Bruker Ascend 400, and Bruker Ascend 600 cryoprobe spectrometers. Infrared spectra were taken on a Nicolet Avatar 320 FTIR or Bruker Alpha Platinum ATR. Chemical Shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz) and are rounded to the nearest 0.1 Hz. The reported chemical shifts are relative to the residual solvent peaks of the indicated deuterated solvents. Multiplicities are defined as s = singlet, br.s = broad singlet, d = doublet, br. d = broad doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, br = broad, app = apparent, par = partial.

High-Performance Liquid Chromatography (HPLC): All HPLC purifications were carried out on a Waters HPLC system (consisting of a Waters 1525 binary HPLC pump with direct injection port and monitored at 254 nm unless otherwise specified with a Waters 2489 UV-Visible detector). All purifications utilized a normal-phase Sunfire, Silica Prep 10 μm, 10 x 250 mm column. Ultra Performance Liquid Chromatography (UPLC)-Mass Spectrometry (MS): All UPLC-MS experiments were carried out on a Waters Acquity H UPLC Class system using the indicated solvent systems as eluents. All separations were performed on a reverse phase Acquity UPLC BEH C18 1.7 μm, 2.1 x 50 mm column.

Experimental Section

Synthesis of Phenol 18



10 **18**

Benzaldehyde Functionlization. To a round bottom flask equipped with a magnetic stir bar was added 2,4-dihydroxybenzaldehyde **10** (40.0 g, 290 mmol), 2-nitrobenzenesulfonyl chloride (NsCl) (64.2 g, 290 mmol), potassium carbonate (K_2CO_3) (96.2 g, 608 mmol), and acetone (965 mL). The flask was capped with a rubber septum containing an 16 gauge needle open to air and stirred vigorously at room temperature. After 24 hours, allyl bromide (36.5 mL, 434 mmol) was added rapidly via syringe and TLC was used to monitor the reaction progress. The TLC plates were developed using a 25% EtOAc/Hex solution and visualized by $KMnO_4$. The reaction was worked up after 48 hours by light concentration and transferring to a separatory funnel containing EtOAc (600 mL). The organic layer was washed with 1 M HCl (750 mL) and brine (250 mL) before drying over $MgSO_4$. Concentration delivered a mixture of regioisomers as a tan solid that was washed with MeOH (~ 500 mL) and filtered by vacuum filtration through a fritted funnel until the filtrate appeared colorless. The resultant white solid contained the functionalized benzaldehyde as a 5:1 (desired:undesired) mixture of regioisomers (56.9 g) which was moved onto the next step without further purification.

Dakin Oxidation. To a round bottom flask equipped with a magnetic stir bar was added the benzaldehyde (56.9 g, 157 mmol) and dichloromethane (DCM) (500 mL). The solution was cooled in an ice/water bath and *m*CPBA (35.1 g, 77%, 157 mmol) was added. The flask was capped with a rubber septum fitted with a 1 gauge needle open to air and the reaction was allowed to slowly warm to room temperature within the bath. After 18 hours, K_2CO_3 (32.5 g, 235 mmol) and MeOH (660 mL) were added all at once. After an additional 48 hours, the reaction was concentrated and dissolved again in H_2O:EtOAc (1:2). The layers were separated and the aqueous layer was extracted with EtOAc (2x) and the combined organics were washed with brine and dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→50% EtOAc/Hex) afforded phenol **18** (53.1 g, 56% yield) as a tan solid.

R_f =0.49 (50% EtOAc/Hex)

m.p.=81-83 °C

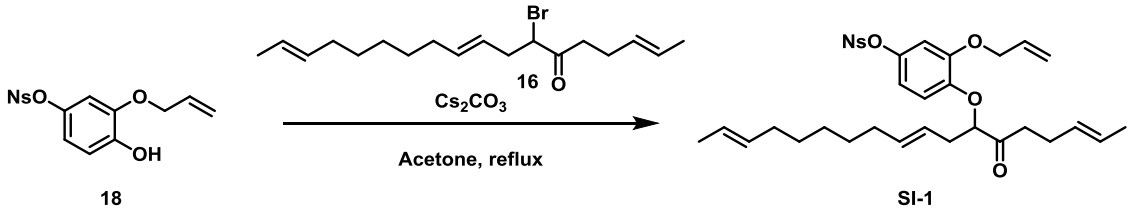
^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.94-7.92 (m, 1H), 7.84-7.79 (m, 2H), 7.67 (ddd, *J* = 7.9, 5.9, 2.9 Hz, 1H), 6.81 (dd, *J* = 5.7 Hz, 2H), 6.65 (dd, *J* = 8.7, 2.6 Hz, 1H), 5.99 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.60 (s, 1H), 5.40-5.30 (m, 2H), 4.55 (d, *J* = 12.0 Hz, 2H)

^{13}C-NMR (150 MHz; $CDCl_3$): δ 145.6, 145.1, 141.6, 135.2, 132.3, 131.8, 131.8, 128.2, 124.7, 119.1, 114.8, 114.4, 107.1, 70.1.

FTIR (thin film/NaCl): 3498, 3098, 2923, 1545, 1504, 1381,11273, 1228, 192, 1120, 854, 832, 589 cm^{-1}.

HRMS (ESI) m/z Calc'd for $C_{15}H_{13}NO_7SNa$ $[M+Na]^+$: 374.0305, found: 374.0305.

Synthesis of α-Phenoxy Ketone SI-1



To a pressure vessel equipped with a magnetic stir bar was added phenol **18** (13.0 g, 37 mmol), α-bromo ketone **16** (8.40 g, 25 mmol), cesium carbonate (Cs_2CO_3) (12.0 g, 37 mmol), and acetone (62.0 mL). The reaction vessel was sealed and placed in an oil bath, it was then heated to 56 °C. The reaction was removed from the heating bath after 2.5 hours. Upon cooling to room temperature, the solution was filtered through a fritted funnel and the solid was washed with EtOAc. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→50% EtOAc/Hex) afforded α-phenoxy ketone **SI-1** (9.90 g, 66% yield) as a brown oil.

R_f = 0.24 (25% EtOAc/Hex)

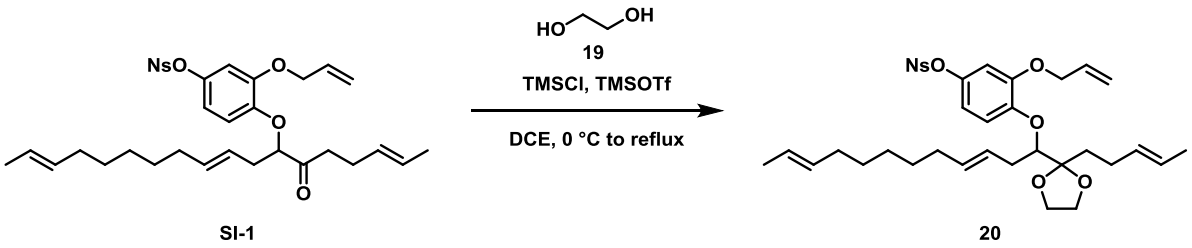
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.96-7.94 (m, 1H), 7.84-7.80 (m, 2H), 7.67 (ddd, *J* = 7.9, 5.8, 3.0 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.70-6.65 (m, 2H), 5.96 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 1H), 5.55-5.50 (m, 1H), 5.45-5.33 (m, 5H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.49 (dt, *J* = 5.3, 1.5 Hz, 2H), 4.42 (t, *J* = 4.0 Hz, 1H), 2.66-2.48 (m, 4H), 2.23-2.15 (m, 2H), 1.98-1.92 (m, 4H), 1.64-1.60 (m, 6H), 1.34-1.22 (m, 7H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 210.3, 149.7, 148.7, 147.0, 135.3, 135.0, 132.3, 132.2, 131.9, 131.5, 129.5, 128.3, 125.9, 124.8, 124.7, 123.3, 118.3, 117.0, 108.9, 85.4, 69.9, 38.0, 35.6, 32.5, 32.5, 29.4, 29.1, 28.7, 25.8, 17.9, 17.9.

FTIR (neat): 2924, 2854, 1717, 1604, 1545, 1502, 1421, 1385, 1264, 1193, 1125, 963, 853, 829, 780, 589 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{33}H_{41}NO_8SNa$ $[M+Na]^+$: 634.2451, found: 634.2442.

Synthesis of Ketal 20



SI-1 20

To a sealed tube under N_2 atmosphere was added α-phenoxy ketone **SI-1** (9.10 g, 15.0 mmol), ethylene glycol **19** (11.0 mL, 194 mmol) and 1,2-dichloroethane (DCE) (149 mL). The reaction vessel was then cooled in an ice water bath and TMSCl (24.6 mL, 194 mmol) and TMSOTf (0.400 mL, 2.20 mmol) were added. After 10 minutes, the cooling bath was removed and the reaction was allowed to warm to room temperature over 10 minutes, then the N_2 inlet was replaced and the reaction vessel was sealed. The reaction was then placed in an 86 °C oil bath and was heated for 6.5 hours, after which the heating bath was removed and the reaction was allowed to cool to room temperature. Upon cooling, the reaction was further cooled in an ice water bath and Et_3N (26.0 mL) was added slowly (vigorous reaction resulting in gas evolution). The solution was transferred to a separatory funnel and washed with H_2O (200 mL). The aqueous was extracted with DCM (3x) and the combined organics were washed with brine, then dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→30% EtOAc/Hex) afforded glycol acetal **20** (9.00 g, 92% yield) as a brown oil.

R_f = 0.66 (50% EtOAc/Hex)

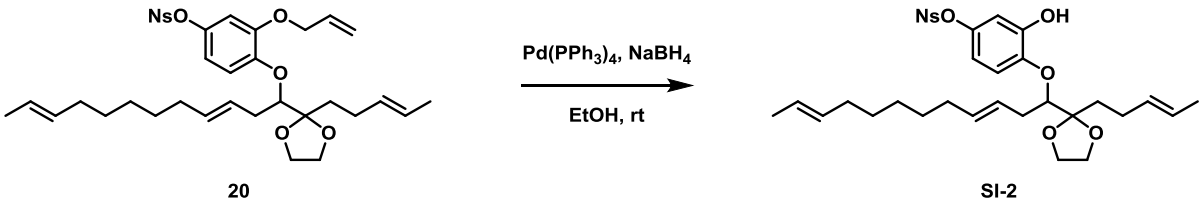
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.96-7.92 (m, 1H), 7.83-7.78 (m, 2H), 7.69-7.63 (m, 1H), 6.85-6.81 (m, 1H), 6.73-6.66 (m, 2H), 6.00-5.91 (m, 1H), 5.51-5.33 (m, 7H), 5.24-5.21 (m, 1H), 4.50-4.42 (m, 2H), 4.14-4.10 (m, 1H), 4.03-3.88 (m, 3H), 2.42-2.40 (m, 1H), 2.06-1.88 (m, 7H), 1.75-1.68 (m, 1H), 1.64-1.61 (m, 5H), 1.32-1.20 (m, 7H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 149.4, 148.8, 142.4, 135.2, 133.2, 132.6, 132.3, 131.8, 131.5, 130.8, 126.0, 124.8, 124.7, 124.6, 117.8, 116.0, 114.0, 111.3, 108.4, 83.7, 70.0, 66.1, 65.8, 60.4, 34.0, 33.9, 32.5, 29.4, 29.2, 28.7, 25.8, 17.9, 17.9.

FTIR (neat): 2923, 2854, 1720, 1595, 1501, 1384, 1365 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{35}H_{45}NO_9SNa$ $[M+Na]^+$: 678.2707, found: 678.2704.

Synthesis of Phenol SI-2



20 **SI-2**

To a flask equipped with a magnetic stir bar was added ketal **20** (4.30 g, 6.56 mmol), $Pd(PPh_3)_4$ (0.379 g, 0.328 mmol), $NaBH_4$ (0.124 g, 3.28 mmol), and the flask was evacuated and backfilled with N_2 three times. EtOH (65.6 mL, degassed by freeze-pump-thaw) was cannulated and the reaction was allowed to stir at room temperature. TLC was used to monitor the reaction progress. The TLC plates were developed using a 50% EtOAc/Hex solution and visualized by $KMnO_4$. After 3 hours, the reaction looked complete, so the reaction was quenched with a saturated aqueous solution of NH_4Cl (20.0 mL). The reaction was diluted with EtOAc (100 mL) and transferred to a separatory funnel, where the organic was washed with H_2O (90.0 mL) and brine. Drying over Na_2SO_4, concentration, and purification via silica gel flash column chromatography (10% gradient, 0% → 60% EtOAc/Hex) afforded phenol **SI-2** (3.15 g, 78% yield) as an orange oil.

R_f = 0.19 (25% EtOAc/Hex)

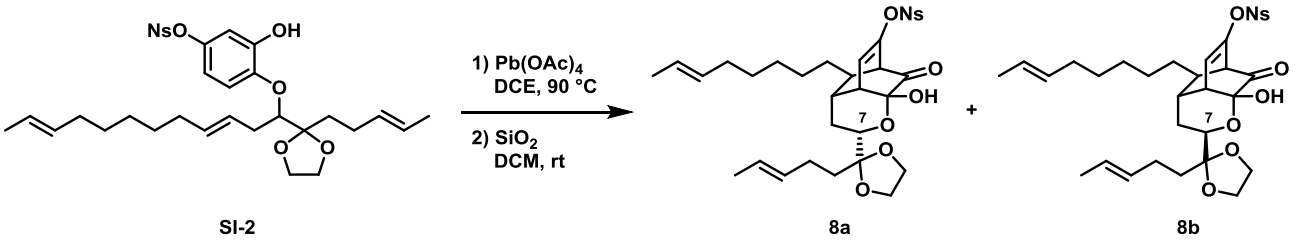
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.83-7.80 (m, 2H), 7.68-7.65 (m, 1H), 7.58 (s, 1H), 6.96 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 2.9 Hz, 1H), 6.62 (dd, *J* = 8.8, 2.9 Hz, 1H), 5.55-5.51 (m, 1H), 5.47-5.32 (m, 5H), 4.05-3.98 (m, 4H), 3.80 (dd, *J* = 7.6, 4.6 Hz, 1H), 2.48-2.44 (m, 2H), 2.13-2.03 (m, 2H), 1.96-1.92 (m, 3H), 1.91-1.86 (m, 1H), 1.761.71 (m, 1H), 1.64-1.59 (m, 6H), 1.33-1.22 (m, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ 149.2, 148.8, 145.8, 144.7, 135.2, 134.1, 132.2, 131.8, 131.5, 130.3, 128.6, 125.5, 125.4, 124.8, 124.7, 120.7, 113.1, 111.5, 110.2, 86.1, 66.1, 66.0, 34.7, 33.9, 32.5, 32.5, 29.4, 29.1, 28.7, 25.7, 17.9, 17.9.

FTIR (neat): 3495, 3257, 3017, 2925, 2854, 1601, 1547, 1495, 1386, 1366, 1193, 1118, 962, 830, 588 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{32}H_{41}NO_9SNa$ $[M+Na]^+$: 638.2400, found: 638.2392.

Synthesis of α-Hydroxy Ketone 8



SI-2 8a 8b

To a pressure vessel equipped with a magnetic stir bar was added the phenol **SI-2** (4.43 g, 7.01 mmol), $Pb(OAc)_4$ (3.13 g, 8.41 mmol), and 1,2-dichloroethane (DCE) (70.1 mL). The reaction vessel was stirred at room temperature for 25 minutes after which it was placed into a 90 °C oil bath. After 18 hours, the reaction was removed from the heating bath and after an additional hour, it was filtered through a fritted funnel using DCM to rinse the flask. After concentration, the crude oil was dissolved in DCM (70.1 mL) and silica gel (19 g) was added. The reaction was stirred at room temperature and the reaction progress was followed by TLC. The TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized by $KMnO_4$. After 24 hours, the silica gel was removed by vacuum filtration and solid was washed with EtOAc (250 mL). Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→70% EtOAc/Hex) afforded α-hydroxy ketone **8** (3.19 g, 72% yield, 1:3 dr α:β, **8a** and **8b** respectively) as a brown sticky foam. (Note: diastereomeric ratio was determined using the crude ^{1}H-NMR)

R_f = 0.28 (50% EtOAc/Hex)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.00-7.98 (m, 1H), 7.5 -7.82 (m, 2H), 7.72-7.66 (m, 1H), 6.13 (dd, *J* = 7.6, 2.3 Hz, 0.26H), 6.05 (dd, *J* = 7.6, 2.5 Hz, 0.73H), 5.44-5.34 (m, 4H), 4.01-3.90 (m, 4H), 3.51-3.44 (m, 1H), 3.29-3.19 (m, 2H), 2.89 (dd, *J* = 7.6, 2.6 Hz, 0.21H), 2.65 (dd, *J* = 7.5, 3.4 Hz, 0.82H), 2.05-1.89 (m, 6H), 1.82-1.72 (m, 2H), 1.721.70 (m, 1H), 1.65-1.59 (m, 5H), 1.48-1.44 (m, 1H), 1.34-1.26 (m, 7H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 206.2, 198.1, 148.5, 144.7, 144.2, 135.7, 133.2, 132.9, 132.1, 132.0, 131.3, 131.2, 130.7, 130.6, 127.6, 125.1, 125.0, 124.9, 124.9, 124.9, 124.8, 119.4, 119.3, 110.2, 110.0, 110.0, 90.7, 90.2, 73.8, 72.8, 66.5, 66.2, 65.9, 65.4, 55.5, 55.1, 43.5, 42.5, 40.6, 38.3, 36.0, 35.7, 35.3, 34.6, 34.0, 32.4, 30.4, 29.3, 29.3, 29.0, 28.9, 28.8, 26.9, 26.7, 25.9, 25.7, 17.9, 17.9, 12.8, 12.7.

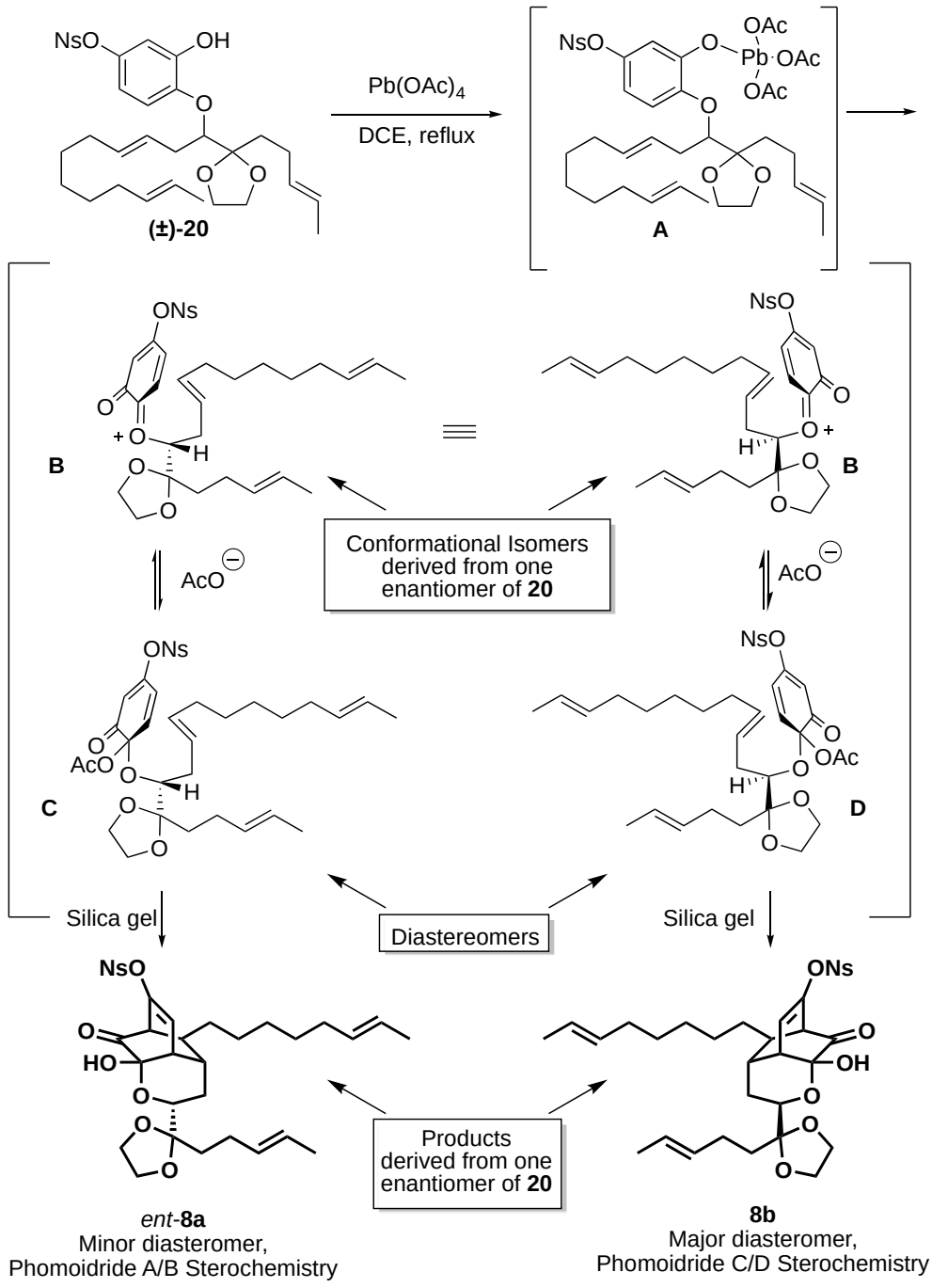
FTIR (neat): 3410, 2926, 2855, 2360, 1746, 1545, 1388, 1192, 1110, 966, 851, 737 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{32}H_{41}NO_{10}SNa$ $[M+Na]^+$: 654.2349, found: 654.2355.

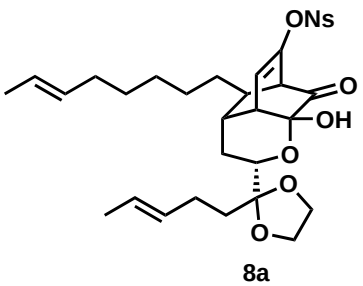
Mechanistic Considerations:

Although the mechanistic details of this Diels-Alder reaction have not been fully delineated, as illustrated in the Scheme below, the diastereoselective outcome can likely be attributed to a combination of two extremes; either diastereoselective attack of acetate during acetal formation (i.e. **D** forms in preference to **C**) is followed by rapid Diels-Alder cycloaddition or the initially formed acetals (**C** and **D**) rapidly equilibrate relative to the differential rates of their diastereomeric Diels-Alder reactions (**C** to *ent*-**8a** and **D** to **8b**). As illustrated,the former scenario would require that **C** and **D** be produced in a 1:3 ratio, respectively, followed by conversion to *ent*-**8**□ and **8**□ prior to any equilibration. The

second extreme would involve rapid interconversion of **C** and **D** relative the differential rates of formation of *ent*-**8** (slow) and **8** (fast).

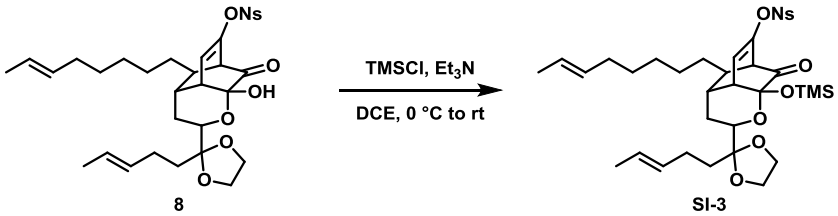


Note: In this Scheme we depict the products derived from a single enantiomer of the racemic starting material (**20**). The products **8a** and **8b**, as drawn in Scheme 3 of the manuscript and the above exerimental, derive from different enantiomers of **20**. We chose to illustrate **8a** rather than **ent-8a** in the manunscript to allow for easier visual comparison of the diastereomeric products.



8a

Synthesis of Silyl Ether SI-3



To a round bottom flask equipped with a magnetic stir bar was added α-hydroxy ketone **8** (1.80 g, 2.85 mmol, 1:3 α:β mixture), and DCM (28.5 mL). The solution was cooled in an ice water bath, at which point chlorotrimethylsilane (TMSCl) (0.550 mL, 4.27 mmol) and triethylamine (Et_3N) (0.600 mL, 4.27 mmol) were added. TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with CAM. After stirring at 0 °C for 4 hours, TMSCl (0.550 mL, 4.27 mmol) and Et_3N (0.600 mL, 4.27 mmol) were added and the reaction was allowed to slowly warm to room temperature, with the bath, overnight. In the morning, the reaction was cooled to 0 °C, TMSCl (0.550 mL, 4.27 mmol) and Et_3N (0.600 mL, 4.27 mmol) were again added. After four additional hours of slowly warming to room temperature with the bath, the reaction was quenched with the addition of $NaHCO_3$ (14.0 mL). The solution was transferred to a separatory funnel, and the aqueous layer was extracted with DCM (2x). The combined organics were dried over Na_2SO_4. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→30% EtOAc/Hex) afforded silyl ether **SI-3** (1.73 g, 86% yield, 1:3 α:β mixture) as a yellow oil.

R_f = 0.42 (20% EtOAc/Hex)

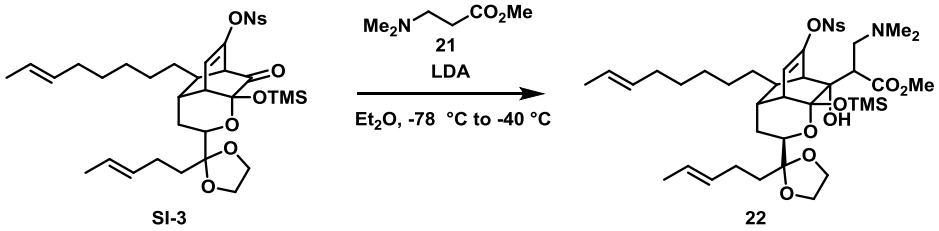
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.01-7.99 (m, 0.24H), 7.98-7.96 (m, 0.75H), 7.86-7.81 (m, 2H), 7.75-7.71 (m, 0.24H), 7.69-7.65 (m, 0.79H), 6.07 (dd, *J* =10.0, 5.0 Hz, 0.25H), 6.04 (dd, *J* = 10.0, 5.0 Hz, 0.75H), 5.45-5.32 (m, 4H), 4.03-3.82 (m, 5H), 3.49-3.43 (m, 1H), 3.15-3.14 (m, 0.24H), 3.08-3.05 (m, 0.80H), 2.73 (dd, *J* = 7.6, 2.7 Hz, 0.25H), 2.55 (dd, *J* = 7.6, 2.7 Hz, 0.80H), 2.07-1.99 (m, 1H), 1.961.89 m, 3H), 1.87-1.80 (m, 2H), 1.76-1.66 (m, 2H), 1.661.61 (m, 6H), 1.58-1.52 m, 2H), 1.44-1.41 (m, 1H), 1.34-1.24 (m, 8H), 0.17 (s, 7H), 0.15 (s, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 204.2, 197.6, 148.5, 144.7, 144.3, 135.5, 135.5, 132.7, 132.6, 132.4, 132.3, 132.2, 131.4, 131.3, 130.6, 130.6, 130.5, 129.8, 128.2, 125.1, 125.0, 124.9, 124.9, 124.8, 124.8, 124.0, 123.9, 119.3, 119.2, 110.5, 110.3, 110.3, 92.7, 92.2, 73.1, 73.1, 72.5, 66.3, 66.0, 659., 64.9, 56.0, 55.9, 45.6, 43.5, 41.9, 41.2, 36.8, 36.7, 36.3, 34.8, 34.5, 34.3, 32.5, 32.4, 30.8, 29.3, 29.1, 29.0, 27.0, 26.7, 26.2, 25.7, 17.9, 1.8, 1.5.

FTIR (neat): 2926, 2855, 1752, 1651, 1546, 1390, 149, 1194, 1088, 1045, 843, 755, 736 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{35}H_{49}NO_{10}SSiNa$ $[M+Na]^+$: 726.2739, found: 726.2734.

Synthesis of Amine 22



Synthesis of Lithium Enolate solution 0.5M in Et_2O. To an oven-dried round bottom flask equipped with a magnetic stir bar was added diisopropylamine (*i*Pr_2NH) (1.35 mL, 9.49 mmol) and Et_2O (17.3 mL). The solution was cooled to 78 °C in a dry ice/acetone bath and *n*-butyllithium (*n*BuLi) (3.62 mL, 2.5 M in hexanes, 9.06 mmol) was added. The reaction was stirred at –78 °C for 1 hour before the addition of methyl 3-(dimethylamino)propionate **21** (1.24 mL, 8.63 mmol). The resultant mixture was stirred for 30 minutes at –78 °C before being placed into and ice/salt water bath for 15 minutes and then warmed to room temperature for additional 20 minutes. The enolate solution was cooled again to –78 °C before use.

Aldol Reaction. To an oven-dried round bottom flask equipped with a magnetic stir bar was added silyl ether **SI-3** (1.21 g, 1.73 mmol) (azeotroped with toluene 3x prior to use) and Et_2O (17.3 mL). The solution was cooled in a dry ice/acetone bath and the enolate solution was added dropwise via cannula over 45-60 minutes. The reaction was stirred at this temperature for an additional 1.5 hours before being placed into a dry ice/acetonitrile bath. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution (10% MeOH/DCM for product) and visualized with CAM. After 3 hours, the solution was cooled again to –78 °C and after 20 minutes, the reaction was quenched with the addition of sat. aq. NH_4Cl (10.0 mL). After warming to room temperature, the solution was transferred to a separatory funnel and diluted with EtOAc. The organic layer was dried over Na_2SO_4. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→100% EtOAc/Hex) afforded amine **22** (0.773 g, 54% yield, 1:2 dr, α:β mixture) as an off-white solid.

R_f = 0.50 (10% MeOH/DCM)

m.p.=104-107 °C

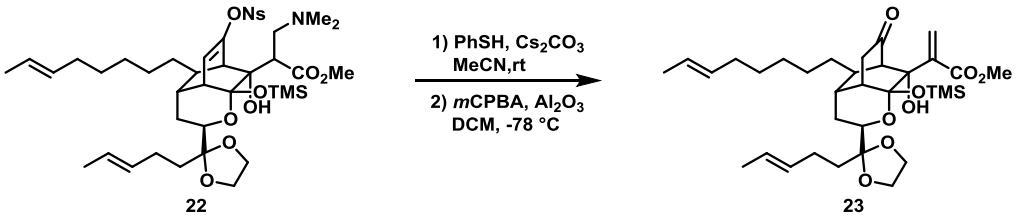
^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.19-8.17 (m, 1H), 7.84-7.79 (m, 2H), 7.76-7.72 (m, 1H), 5.67 (dd, *J* = 7.4, 2.8 Hz, 1H), 5.46-5.34 (m, 4H), 4.80 (dd, *J* = 10.3, 5.6 Hz, 1H), 3.99-3.88 (m, 5H), 3.67 (s, 3H), 3.19 (dd, *J* = 12.8, 8.9 Hz, 1H), 2.92 (dd, *J* = 8.9, 3.1 Hz, 1H), 2.74 (dd, *J* = 12.8, 3.3 Hz), 2.45-2.44 (m, 1H), 2.28-2.22 (m, 8H), 2.10-1.87 (m, 7H), 1.67-1.59 (m, 7H), 1.57-1.55 (m, 2H), 1.40-1.39 (m, 1H), 1.27-1.21 (m, 3H), 1.17-1.06 (m, 5H), 0.17 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 176.3, 148.7, 148.5, 134.9, 132.0, 131.5, 131.4, 131.2, 130.1, 124.9, 124.6, 124.4, 111.3, 111.3, 100.3, 81.1, 73.5, 66.8, 64.7, 59.7, 52.1, 51.5, 48.9, 17.5, 46.3, 37.4, 36.9, 34.7, 34.6, 32.5, 29.4, 29.3, 28.8, 27.1, 26.4, 17.9, 17.9, 2.1.

FTIR (neat): 3419, 2927, 2856, 1704, 1652, 1547, 1391, 1194, 1109, 1051, 907, 842, 720, 583 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{41}H_{63}N_2O_{12}SSi$ $[M+H]^+$:835.3865, found: 835.3866.

Synthesis of Methyl Ester 23



Nosyl Deprotection. To a round bottom flask equipped with a magnetic stir bar was added amine **22** (0.330 g, 0.400 mmol) and acetonitrile (MeCN) (4.00 mL). Thiophenol (0.061 mL, 0.590 mmol) and cesium carbnonate (Cs_2CO_3) (0.190 g, 0.590 mmol) were then added and the reaction was stirred at room temperature. TLC was used to follow the reaction progress and the TLC plates were developed using a 20% EtOAc/Hexanes solution and visualized with CAM. After 3.5 hours, the reaction was quenched with sat. aq. NH_4Cl (2.00 mL) and diluted with EtOAc. The organic layer was separated and dried over Na_2SO_4. Concentration and purification via silica gel flash column chromatography (5% gradient, 5%→20%; then 100% EtOAc/Hex) afforded the ketone.

Cope Elimination. To a round bottom flask equipped with a magnetic stir bar was added the ketone and DCM (3.10 mL). The solution was cooled in a dry ice/acetone bath and stirred at this temperature for 10 minutes before the addition of 3-chloroperbenzoic acid (*m*CPBA) (0.210 g, 0.32 mmol) as a solution in DCM, which was added slowly dropwise (~ 1 drop/second) to keep the solution temperature consistent. Upon completion of addition, basic alumina (Al_2O_3) (0.210 g) was added to the solution and was stirred 20 seconds at this temperature before the solution quickly passed through a plug of basic alumina (12.0 g) (presaturated with DCM) and vacuum filtered using a 10% MeOH/DCM solution (25.0 mL) to wash. Concentration and purification of the filtrate via silica gel flash column chromatography (0%→5% EtOAc/Hex) afforded methyl ester **23** (0.110 g, 36% yield from TMS ether **SI-3**) as a clear oil and as a single diastereomer.

R_f = 0.82 (50% EtOAc/Hex)

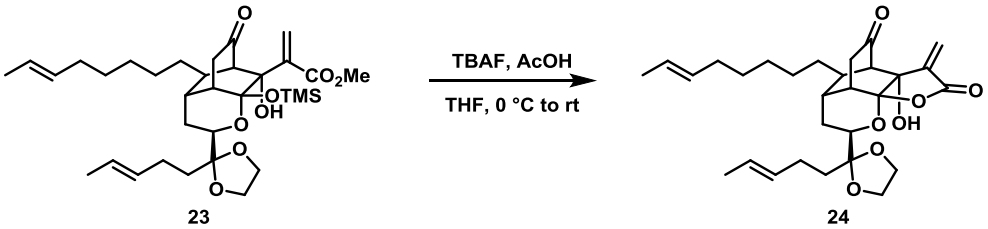
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.84 (s, 1H), 5.75 (s, 1H), 5.70 (s, 1H), 5.53-5.35 (m, 4H), 4.89 (dd, *J* = 11.3, 4.2 Hz, 1H), 4.03-3.90 (m, 4H), 3.79 (s, 3H), 2.68 (d, *J* = 2.4 Hz, 1H), 2.45 (dd, *J* = 19.3, 2.3 Hz, 1H), 2.39-2.34 (m, 1H), 2.21-2.06 (m, 2H), 2.02-1.94 (m, 4H), 1.82-1.76 (m, 2H), 1.66-1.60 (m, 9H), 1.34-1.24 (m, 8H), 0.13 (s, 9H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 213.6, 170.0, 143.5, 131.4, 131.1, 124.7, 124.7, 121.5, 111.2, 100.1, 80.2, 74.5, 66.1, 65.1, 59.1, 51.9, 43.7, 39.3, 36.7, 35.8, 34.8, 33.2, 32.5, 29.9, 29.4, 29.2, 26.9, 26.6, 18.0, 17.9, 2.0.

FTIR (neat): 3437, 2926, 2855, 1724, 1705, 1441, 1322, 1250, 1177, 1100, 951, 916, 732 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{33}H_{52}O_8SiNa$ $[M+Na]^+$: 627.3324, found: 627.3329.

Synthesis of Lactone 24



23 24

To a round bottom flask equipped with a magnetic stir bar was added methyl ester **22** (0.852 g, 1.41 mmol) and THF (14.0 mL). The solution was then cooled in an ice/water bath and acetic acid (AcOH) (0.400 mL, 7.05 mmol) was added, followed by the addition of tetrabutylammonium fluoride (TBAF) (2.82 mL, 1.0 M in THF, 2.82 mmol). TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with CAM. After stirring for 30 min in an ice/water bath, the reaction was warmed to room temperature and continued to stir for an additional 2.5 hours. Then TBAF (1.41 mL, 1.0 M in THF, 1.41 mmol) was again added followed by another TBAF (1.41 mL, 1.0 M in THF, 1.41 mmol) addition after an additional 45 minutes. After a total of 24 hours, the reaction was worked up by pouring into H_2O (50.0 mL), the organic layer was washed with brine, and dried over Na_2SO_4. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→40% EtOAc/Hex) afforded lactone **24** (0.620 g, 89% yield) as a white foam.

R_f = 0.21 (25% EtOAc/Hex)

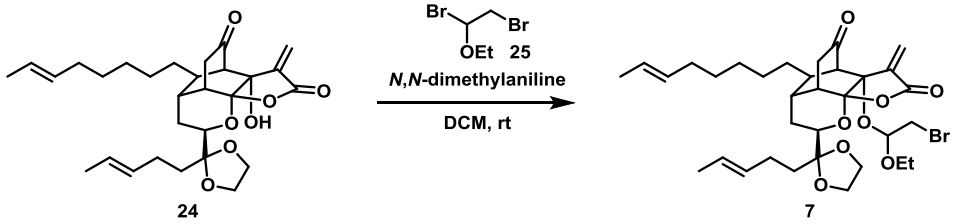
^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.48 (s, 1H), 5.98 (s, 1H), 5.48-5.38 (m, 4H), 4.56 (dd, *J* = 12.2, 4.0 Hz, 1H), 4.34 (s, 1H), 4.18-3.88 (m, 4H), 2.72 (d, *J* = 2.5 Hz, 1H), 2.18-2.11 (m, 4H), 2.08-2.01 (m, 2H), 1.95-1.87 (m, 3H), 1.85-1.75 (m, 2H), 1.67-1.57 (m, 7H), 1.36-1.15 (m, 8H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 208.5, 165.8, 139.7, 131.2, 130.6, 130.1, 125.2, 124.9, 110.7, 105.4, 76.6, 75.2, 66.3, 66.1, 59.6, 39.8, 38.5, 37.0, 36.1, 34.1, 33.7, 32.4, 30.9, 29.3, 29.0, 26.9, 25.7, 17.9.

FTIR (neat): 3373, 2927, 2855, 1777, 1735, 1439, 1406, 1190, 1161, 1098, 1046, 1022, 1046, 967 cm^{-1}.

HRMS (ESI) *m/z* Calc'd.for $C_{29}H_{40}O_7Na$ $[M+Na]^+$: 523.2666, found: 523.2669.

Synthesis of Bromoacetal 7



To a round bottom flask equipped with a magnetic stir bar was added lactone **24** (azeotroped with toluene x3 prior to use) (0.381 g, 0.761 mmol) and DCM (3.81 mL). *N,N*-dimethylaniline (freshly distilled, 150 torr, 155 °C) (0.482 mL, 3.81 mmol) and bromoacetal **25** (freshly distilled, ~ 0.2 mmHg, 52 °C) (0.882 g, 3.81 mmol) were then added. TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with $KMnO_4$. After 24 hours, the reaction was quenched with the addition of sat. aq. $NaHCO_3$ (4.00 mL) and diluted with DCM. The organic layer was washed with brine and dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (5% gradient, 5%→20% EtOAc/Hex) afforded the ethyl acetal **7** (0.449 g, 91% yield, 1:1 dr) as a green oil.

R_f = 0.42 (30% EtOAc/Hex)

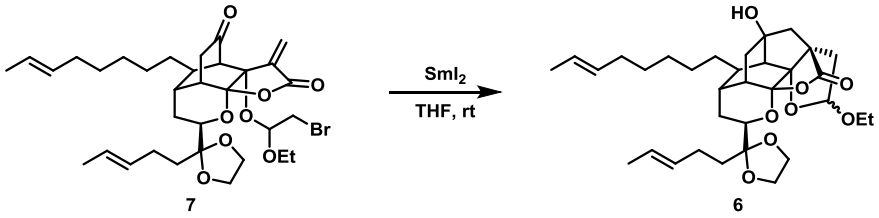
^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.60 (s, 1H), 6.02 (s, 1H), 5.83 (s, 1H), 5.49-5.34 (m, 8H), 4.87-4.85 (m, 1H), 4.76-4.74 (m, 1H), 4.65-4.62 (m, 1H), 4.52-4.49 (m, 1H), 4.16-4.08 (m, 1H), 4.01-3.95 (m, 1H), 3.72-3.68 (m, 1H), 3.64-3.60 (m, 1H), 3.60-3.52 (m, 1H), 3.49-3.32 (m, 5H), 2.94 (s, 1H), 2.85 (s, 1H), 2.31-2.24 (m, 2H), 2.15-2.01 (m, 11H), 1.95-1.92 (m, 4H), 1.87-1.84 (m, 4H), 1.79-1.68 (m, 2H), 1.69-1.58 (m, 16H), 1.32-1.26 (m, 16 H), 1.18 (m, 3H), 1.09 (t, *J* = 6.9 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$): δ 208.5, 208.3, 165.9, 165.9, 135.4, 135.1, 132.5, 131.3, 131.2, 130.8, 130.6, 130.0, 125.2, 125.0, 124.8, 124.8, 110.7, 110.6, 106.5, 105.9, 97.2, 96.7, 79.7, 79.2, 77.1 , 66.7, 66.5, 66.5, 66.3, 61.0, 60.3, 60.2, 59.0, 40.5, 40.4, 38.3, 38.3, 37.4, 37.1, 36.0, 36.0, 34.7, 34.4, 33.5, 33.4, 32.5, 31.9, 31.4, 31.0, 30.6, 29.3, 29.3, 28.9, 26.8, 26.7, 26.7, 25.9, 25.8, 17.9, 14.9, 14.9, 12.8.

FTIR (neat): 2926, 2854, 1778, 1733, 1442, 1405, 1374, 1281, 1191, 1161, 1112, 1072, 1046, 966, 812 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{33}H_{47}O_8BrNa$ $[M+Na]^+$: 673.2347, found: 673.2340.

Synthesis of Isotwistane 6



7 6

SmI_2 Formation. To a schlenk tube equipped with a magnetic stir bar and fitted with a water cooled condenser was added newly filed samarium powder (0.744 g, 4.95 mmol) and THF (25.0 mL). A separate solution of 1,2-diiodoethane[1] (0.775 g, 2.75 mmol) in THF (2.50 mL) was added and the reaction stirred at room temperature until it had turned dark blue in color (25 minutes). The reaction was then placed into a 55 °C bath and heated for 4 hours. The SmI_2 solution (0.10 M in THF) was cooled to room temperature prior to use.

Cascade Cyclization. To a round bottom flask equipped with a magnetic stir bar was added SmI_2 (26.4 mL, 0.10 M in THF, 5.00 mmol). A solution of the bromoacetal **7** (0.506 mg, 0.777 mmol) in THF (5.50 mL) was then added. TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with *p*-anisaldehyde stain. The reaction was quenched after 15 minutes with the addition of sat. aq. NH_4Cl (8.00 mL), and 1.0 M HCl (4.00 mL). The solution was then diluted with EtOAc and washed with brine before drying over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→40% EtOAc/Hex) afforded isotwistane **6** (0.304 g, 68% yield, 1:1 dr) as a green sticky foam. (Isotwistane **6** was carried onto the next step as a 1:1 diastereomeric mixture)

Diastereomer One
R_f = 0.19 (25% EtOAc/Hex)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.37 (m, 4H), 4.19 (dd, *J* = 12.3, 2.8 Hz, 1H), 4.01-3.95 (m, 2H), 3.74 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.48 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.75 (dd, *J* = 14.2, 5.7 Hz, 1H), 2.37 (d, *J* = 2.7 Hz, 1H), 2.29-2.27 (m, 1H), 2.21-2.16 (m, 2H), 2.10-1.88 (m, 7H), 1.86-1.79 (m, 3H), 1.77-1.71 (m, 1H), 1.69-1.58 (m, 10H), 1.53-1.49 (m, 1H), 1.35-1.30 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 177.6, 131.4, 131.1, 124.7, 124.7, 110.5, 109.3, 107.2, 95.5, 77.7, 74.3, 66.1, 65.3, 63.8, 56.8, 51.8, 51.5, 44.0, 39.1, 37.4, 37.3, 36.6, 33.8, 33.8, 33.7, 32.5, 30.9, 29.5, 29.3, 27.9, 25.9, 17.9, 15.1.

FTIR (neat): 3476, 2925, 2855, 1780, 1149, 1299, 1110, 1071, 1044, 967, 920 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{33}H_{48}O_8Na$ $[M+Na]^+$: 595.3241, found: 595.3240.

Diastereomer Two
R_f = 0.46 (50% EtOAc/Hex)

[1] 1,2-diiodoethane was taken up in ether, washed with a 1:1 mixture of sat. aq. $Na_2S_2O_3$, brine, dried over Na_2SO_4, concentrated, and dried under vacuum. All were taken care of in the dark to exclude light.

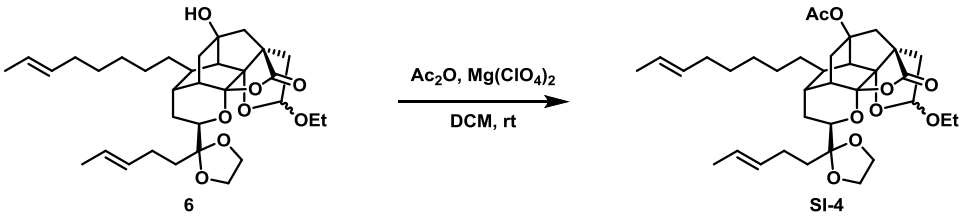
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.46-5.37 (m, 4H), 5.30 (d, *J* = 4.1 Hz, 1H), 4.18-4.10 (m, 2H), 4.07-4.03 (m, 2H), 3.95-3.91 (m, 1H), 3.88-3.85 (m, 1H), 3.35 (dq, *J* = 9.0, 6.9 Hz, 1H), 2.65 (d, *J* = 12.8 Hz, 1H), 2.17 (d, *J* = 13.0 Hz, 1H), 2.08-2.02 (m, 2H), 1.98-1.69 (m, 12H), 1.67-1.55 (m, 10H), 1.51-1.47 (m, 1H), 1.36-1.28 (m, 6H), 1.13 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 177.1, 131.4, 130.9, 124.9, 124.7, 110.5, 107.9, 107.3, 96.1, 79.0, 75.5, 66.4, 66.0, 62.4, 56.4, 52.5, 50.8, 43.8, 39.3, 38.4, 37.4, 35.8, 34.4, 33.6, 32.5, 32.4, 29.5, 29.3, 27.9, 25.8, 17.9, 14.8.

FTIR (neat): 3460, 2923, 2855, 1763, 1443, 1269, 1168, 1130, 1066, 988, 966, 872, 732 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{33}H_{48}O_8Na$ $[M+Na]^+$: 595.3241, found: 595.3240.

Synthesis of Acetate SI-4



To a round bottom flask equipped with a magnetic stir bar was added isotwistane **6** (0.283 g, 0.494 mmol) (azeotroped with toluene x3 prior to use), $Mg(ClO_4)_2$ (0.011 g, 0.049 mmol), DCM (2.60 mL), and acetic anhydride (Ac_2O) (0.140 mL, 1.48 mmol). The reaction was stirred at room temperature for 24 hours. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution and visualized with CAM. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→15% EtOAc/Hex) afforded the acetate **SI-4** (0.238 g, 78% yield, 1:3.3 dr) as a white foam.

R_f = 0.33 (30% EtOAc/Hex)

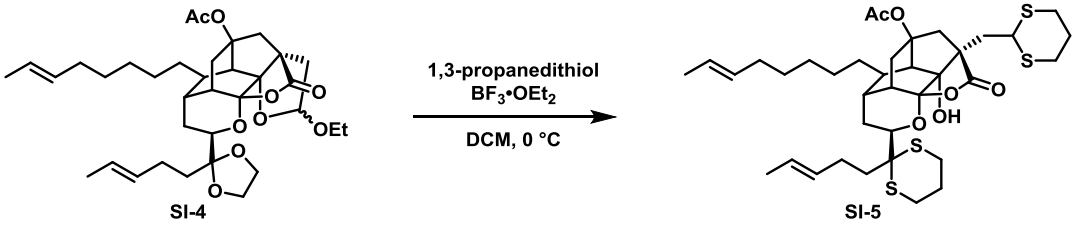
^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.47-5.36 (m, 5 H), 5.33-5.30 (m, 1H), 4.22-4.11 (m, 2H), 4.08-4.03 (m, 2H), 4.00-3.90 (m, 2H), 3.89-3.83 (m, 1H), 3.77-3.71 (m ,0.31H), 3.54-3.46 (m, 0.29H), 3.36 (dq, *J* = 9.1, 7.0 Hz, 1H), 2.99 (d, *J* = 13.1 Hz, 0.30H), 2.82 (d, *J* = 13.1 Hz, 1H), 2.79-7.75 (m, 0.25H), 2.68 (d, *J* = 12.8 Hz, 1H), 2.41-2.33 (m, 2H), 2.20-2.12 (m, 1H), 2.09-2.02 (m, 3H), 1.98-1.97 (m, 5.3H), 1.95-1.90 (m, 1.30H), 1.85-1.69 (m, 7H), 1.65-1.59 (m, 8 H), 1.56-1.42 (m, 5H), 1.37-1.25 (m, 7.6H), 1.22 (t, *J* = 7.1 Hz, 1H), 1.14 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.2, 176.6, 169.4, 169.4, 131.3, 131.1, 130.9, 130.5, 125.0, 124.8, 124.8, 124.7, 123.9, 110.5, 110.5, 109.7, 107.8, 107.7, 107.1, 94.5, 94.0, 84.4, 83.0, 77.2, 75.6, 74.4, 66.4, 66.2, 66.1, 65.4, 63.9, 62.5, 57.5, 57.2, 50.2, 49.5, 47.2, 46.3, 43.9, 43.7, 38.9, 38.8, 37.5, 37.5, 36.9, 36.2, 35.7, 35.7, 34.5, 33.8, 33.5, 33.3, 32.5, 32.5, 32.2, 30.7, 29.6, 29.5, 29.4, 29.4, 27.6, 26.8, 26.0, 25.8, 21.6, 21.5, 17.9, 15.1, 14.8.

FTIR (neat): 2928, 2854, 2019, 1787, 1738, 1440, 1368, 1262, 1236, 1209, 1160, 1090, 1042, 992, 968 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{35}H_{50}O_9Na$ $[M+Na]^+$: 637.3347, found: 637.3342.

Synthesis of Bis-dithiane SI-5



To a round bottom flask equipped with a magnetic stir bar was added the acetate **SI-4** (0.382 g, 0.588 mmol) and DCM (5.88 mL). The solution was cooled in and ice/salt/water bath and 1,3-propanedithiol (0.297 mL, 2.94 mmol). After 5 minutes, $BF_3{\cdot}OEt_2$ (0.373 mL, 2.94 mmol) was added dropwise. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution and visualized with CAM. After 40 minutes at 0 °C, acetone (3.00 mL) was added and the reaction was stirred for an additional 10 minutes before it was quenched with the addition of sat. aq. $NaHCO_3$ (6.00 mL). The organic layer was washed with sat. aq. NH_4Cl, H_2O, and brine before drying over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→30% EtOAc/Hex) afforded the bis-dithiane **SI-5** (0.296 g, 70% yield) as a white foam.

R_f = 0.44 (30% EtOAc/Hex)

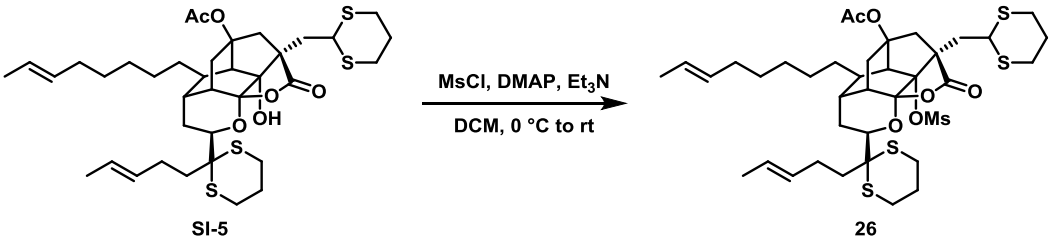
^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.48-5.30 (m, 4H), 4.77 (dd, *J* = 12.1, 3.4 Hz, 1H), 4.50 (dd, *J* = 7.8, 6.6 Hz, 1H), 3.50 (s, 1H), 3.36-3.23 (m, 2H), 2.90-2.80 (m, 5H), 2.60 (dt, *J* = 13.5, 4.2 Hz, 1H), 2.54-2.49 (m, 1H), 2.48-2.29 (m, 4H), 2.27-2.21 (m, 2H), 2.10-2.04 (m, 4H), 1.99-1.89 (m, 6H), 1.86-1.75 (m, 6H), 1.65-1.59 (m, 7H), 1.56-1.46 (m, 2H), 1.39-1.25 (m, 7H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.5, 169.6, 131.3, 130.1, 125.8, 124.8, 106.6, 83.6, 79.8, 53.8, 51.9, 49.9, 49.3, 42.1, 38.9, 38.1, 37.4, 36.9, 35.8, 32.8, 32.5, 32.0, 29.5, 29.5, 29.2, 28.4, 27.6, 27.3, 25.2, 24.8, 21.6, 17.9.

FTIR (neat): 3441, 3103, 2922, 2853, 1772, 1737, 1437, 1366, 1260, 1234, 1164, 1014, 965, 927, 869, 811 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{37}H_{54}O_6S_4Na$ $[M+Na]^+$: 745.2695, found: 745.2704.

Synthesis of Mesylate 26



To a round bottom flask equipped with a magnetic stir bar was added the bis-dithiane **SI-5** (0.14 g, 0.12 mmol), 4-(dimethylamino)pyridine (DMAP) (0.074 g, 0.602 mmol), Et_3N (0.061 mL, 0.602 mmol), and DCM (2.01 mL). The solution was cooled in an ice/salt/water bath and methanesulfonyl chloride (0.047 mL, 0.602 mmol) was added dropwise. The reaction was then allowed to slowly warm to room temperature with the bath. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution and visualized with CAM. After 5.5 hours, the reaction was again cooled to 0 °C and quenched with 1 M HCl (1.00 mL). After warming to room temperature, the solution was diluted to DCM and the organic layer was washed with brine before drying over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→55% EtOAc/Hex) afforded mesylate **26** (0.153 g, 95% yield) as a white solid.

R_f = 0.35 (25% EtOAc/Hex)

m.p.=78-80 ˚C

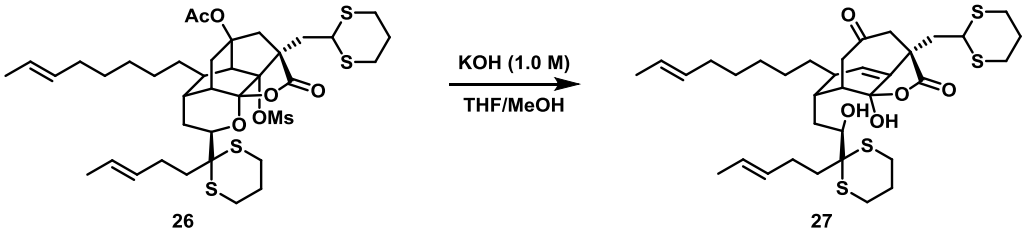
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.47-5.33 (m, 4H), 4.81 (dd, *J* = 12.0, 3.2 Hz, 1H), 4.77-4.74 (m, 1H), 3.49-3.44 (m, 1H), 3.36 (s, 3H), 3.30 (d, *J* = 2.4 Hz, 1H), 3.02-2.91 (m, 3H), 2.83-2.78 (m, 2H), 2.62-2.56 (m, 2H), 2.51-2.45 (m, 2H), 2.42-2.39 (m, 2H), 2.35-2.29 (m, 3H), 2.11-1.95 (m, 9H), 1.88-1.76 (m, 6H), 1.63-1.60 (m, 6H), 1.56-1.44 (m, 3H), 1.41-1.25 (m, 7H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 174.8, 169.3, 131.4, 130.1, 125.7, 124.7, 105.9, 95.8, 83.9, 79.6, 53.2, 52.4, 47.8, 47.7, 42.5, 40.6, 39.6, 38.4, 38.3, 36.9, 35.8, 35.8, 32.7, 32.5, 32.2, 31.0, 30.5, 29.5, 29.1, 28.1, 27.7, 27.2, 26.8, 25.4, 24.8, 21.5, 17.9, 17.9.

FTIR (neat): 2923, 2854, 1777, 1738, 1438, 1340, 1261, 1234, 1160, 1683, 965, 878, 736 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{38}H_{56}O_8S_5Na$ $[M+Na]^+$: 823.2471, found: 823.2465.

Synthesis of Diol 27



26 27

To a round bottom flask equipped with a magnetic stir bar was added mesylate **26** (0.244 g, 0.304 mmol), THF (1.52 mL), and MeOH (1.52 mL). To the stirred solution was added an aqueous solution of KOH (1.52 mL, 1.0 M, 1. 52 mmol) over 30 seconds and the flask was sealed with a glass stopper. After 10 minutes, the reaction was placed into a 40 °C oil bath. TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with CAM. After 5 hours, the reaction was removed from the hot bath and was cooled to room temperature. The reaction was then quenched with the addition of 1 M HCl (1.60 mL) until the solution reached a pH ~ 2 and then diluted with EtOAc. The organic layer was washed with 1 M HCl, H_2O, and brine before being dried over Na_2SO_4. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→60% EtOAc/Hex) afforded diol **27** (0.184 g, 89% yield) as a white foam.

R_f = 0.52 (50% EtOAc/Hex)

m.p.=62-64 ˚C

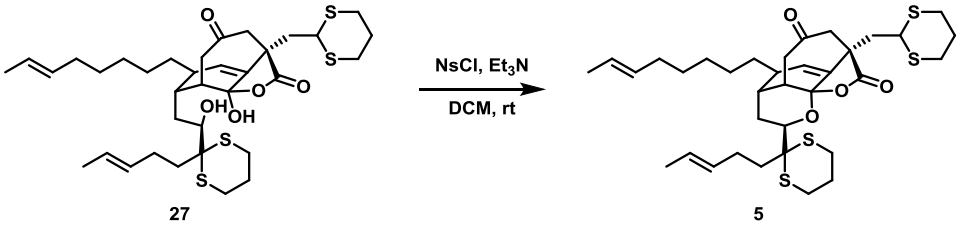
^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.66 (d, *J* = 3.5 Hz, 1H), 5.47-5.34 (m, 4H), 5.08 (s, 1H), 4.17-4.10 (m, 2H), 3.18 (s, 1H), 2.94-2.86 (m, 4H), 2.82-2.59 (m, 8H), 2.56 (d, *J* = 15.5 Hz, 1H), 2.40-2.36 (m, 1H), 2.28-2.15 (m, 5H), 2.07-2.03 (m, 2H), 1.97-1.79 (m, 5H), 1.73-1.57 (m, 10H), 1.50-1.42 (m, 1H), 1.37-1.11 (m, 7H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 205.8, 177.3, 142.1, 132.2, 131.3, 130.3, 125.6, 124.7, 107.3, 68.6, 58.7, 58.6, 48.2, 48.1, 47.0, 40.6, 38.7, 38.3, 34.3, 33.6, 32.7, 32.5, 29.5, 29.3, 27.7, 26.1, 25.3, 24.9, 24.1, 17.9.

FTIR (neat): 3478, 2923, 2853, 1769, 1693, 1438, 1274, 1108, 966, 908, 729, 647 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{35}H_{53}O_5S_4$ $[M+H]^+$: 703.2590, found: 703.2585.

Synthesis of ketone 5



To a vial equipped with a magnetic stir bar was added diol **27** (0.024 g, 0.035 mmol), 4-nitrobenzenesulfonyl chloride (NsCl) (0.016 g, 0.070 mmol), Et_3N (0.015 mL, 0.11 mmol), and DCM (0.400 mL). The vial was capped and the reaction was stirred at room temperature. TLC was used to follow the reaction progress and the TLC plates were developed using a 50% EtOAc/Hexanes solution and visualized with CAM. After 6 hours, the reaction was quenched with the addition of 1M HCl (0.130 mL) and diluted with DCM. The organic layer was washed with 1M HCl, H_2O, and brine before being dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (100% DCM until excess NsCl was eluted, then 5% gradient, 0%→30% EtOAc/Hex) afforded ketone **5** (0.016 g, 67% yield) as a white foam.

R_f = 0.43 (25% EtOAc/Hex)

m.p.=67-68 ˚C

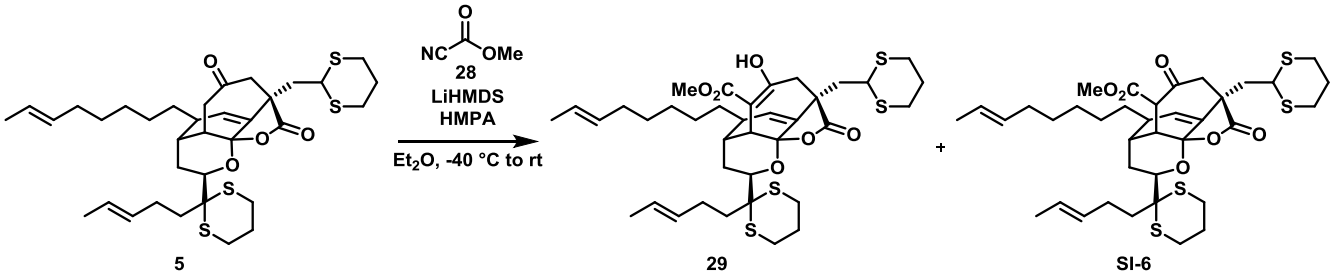
^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.81 (s, 1H), 5.47-5.30 (m, 4H), 4.19-4.12 (m, 2H), 3.50-3.37 (m, 2H), 2.88-2.82 (m, 2H), 2.75-2.64 (m, 5H), 2.55 (d, *J* = 14.4 Hz, 1H), 2.50-2.46 (m, 3H), 2.35-2.17 (m, 4H), 2.15-1.90 (m, 8H), 1.83-1.72 (m, 2H), 1.65-1.58 (m, 8H), 1.43-1.25 (m, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 204.7, 175.8, 138.4, 132.0, 131.2, 130.1, 125.7, 124.9, 105.8, 83.6, 60.8, 52.7, 49.4, 45.1, 43.0, 42.6, 41.7, 38.4, 38.2, 36.9, 36.5, 35.4, 32.5, 29.4, 28.9, 28.9, 28.6, 28.3, 28.2, 27.8, 27.2, 25.5, 24.9, 17.9, 17.9.

FTIR (neat): 3016, 2923, 2853, 1761, 1697, 1437, 1371, 1269, 1152, 966 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{35}H_{50}O_4S_4Na$ $[M+Na]^+$: 685.2484, found: 685.2480.

Synthesis of Enol 29



To an oven-dried vial equipped with a stir bar was added ketone **5** (19.3 mg, 0.029 mmol) (azeotroped with toluene x3 prior to use) in Et_2O (0.291 mL). The solution was cooled to -40 °C in a dry ice/MeCN bath and lithium bis(trimethylsilyl)amide (LiHMDS) (27.7 µL, 0.028 mmol) was added dropwise. The reaction mixture was stirred in dry ice/MeCN bath for 15 minutes and then it was stirred in an ice bath for 1 hour, at which point additional LiHMDS (43.7 µL, 0.044 mmol) was added dropwise. After 20 minutes, the reaction was cooled to -40 °C in a dry ice/MeCN bath, at which point hexamethylphophramide (HMPA) (7.60 µL, 0.044 mmol) and methyl cyanoformate (3.46 µL, 0.044 mmol) were added sequentially. After 10 minutes, dry ice/MeCN bath was removed and the reaction was warmed to room temperature, at which point the reaction mixture turned deep orange in color. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution and visualized with CAM. After an hour, the reaction was cooled to 0 °C and was quenched with sat. aq. NH_4Cl (0.200 mL) and was allowed to warm to room temperature. The solution was then diluted with EtOAc and the organic layer was washed with H_2O and brine. After drying over $MgSO_4$ and concentration, purification via HPLC (0%→18% EtOAc/Hex, λ = 259 nm, flow rate = 10 mL/min) afforded enol **29** (0.0126 g, 60% yield) as a white foam. (Note: Occassionally, trace amount of keto tautomer (**SI-6**) was observed under the reaction conditions.)

Enol Tautomer
R_f = 0.53 (25% EtOAc/Hex)

^{1}H-NMR (600 MHz, $CDCl_3$): δ 13.82 (s, 1H), 5.75 (s, 1H), 5.46-5.33 (m, 4H), 4.18-4.15 (m, 2H), 3.82 (s, 1H), 3.46 (dddd, *J* = 33.0, 14.4, 12.2, 2.8 Hz, 2H), 3.22 (s, 1H), 2.84 (ddd, *J* = 14.2, 7.2, 2.9 Hz, 2H), 2.80 (d, *J* = 17.4 Hz, 1H), 7.74-7.69 (m, 3H), 2.59 (dd, *J* = 17.5, 1.3 Hz, 1H), 2.48 (ddt, *J* = 21.7, 13.4, 4.0 Hz, 2H), 2.43 (d, *J* = 3.2 Hz, 1H), 2.34-2.28 (m, 1H), 2.21 (dd, *J* = 14.4, 8.2 Hz, 1H), 2.16 (td, *J* = 12.4, 3.2 Hz, 1H), 2.11-2.00 (m, 4H), 1.96-1.89 (m, 3H), 1.82-1.75 (m, 2H), 1.65-1.57 (m, 7H), 1.33-1.12 (m, 9H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ 175.6, 174.5, 171.6, 136.4, 131.2, 130.3, 125.7, 125.0, 104.2, 100.0, 83.2, 55.0, 527, 52.6, 49.1, 44.6, 42.6, 42.0, 38.4, 36.6, 36.5, 35.8, 35.3, 32.4, 29.3, 28.9, 28.9, 28.6, 28.3, 27.9, 27.8, 27.2, 25.5, 24.9, 17.9.

FTIR (neat): 2923, 2853, 1786, 1639, 1573, 1438 cm^{-1}.
HRMS (ESI) *m/z* Calc'd. for $C_{37}H_{52}O_6S_4Na$ $[M+Na]^+$: 743.2539, found: 743.2534.

Keto Tautomer
R_f = 0.32 (25% EtOAc/Hex)

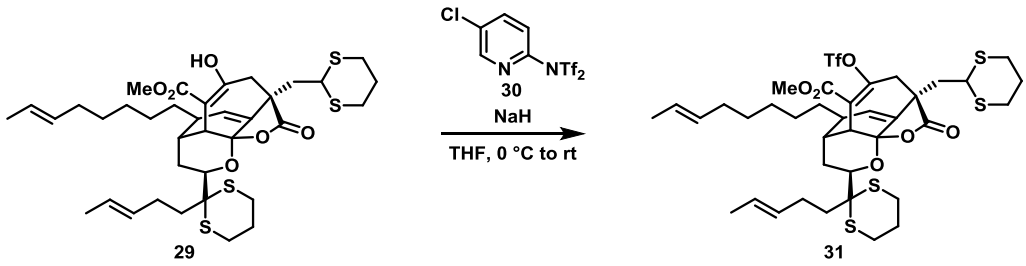
^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.91 (s, 1H), 5.45-5.31 (m, 4H), 4.16 (t, *J* = 8.5 Hz, 1H), 4.12 (dd, *J* = 11.7 Hz, 1H), 3.74 (s, 3H), 3.46-3.40 (m, 2H), 3.21 (d, *J* = 4.6 Hz, 1H), 3.09-3.08 (m, 1H), 2.92 (d, *J* = 13.2 Hz, 1H), 2.87-2.82 (m, 2H), 2.77-2.69 (m, 3H), 2.59 (d, *J* = 13.2 Hz, 1H), 2.48-2.43 (m, 2H), 2.35-2.14 (m, 6H), 2.10-1.89 (m, 8H), 1.78-1.71 (m, 2H), 1.65-1.58 (m, 6H), 1.53-1.50 (m, 1H), 1.38-1.28 (m, 6H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ 200.6, 174.5, 169.0, 138.6, 131.7, 131.1, 130.1, 125.8, 125.0, 104.4, 84.0, 61.3, 61.2, 52.9, 52.4, 49.9, 45.6, 41.7, 39.0, 38.5, 37.4, 35.6, 35.1, 32.5, 29.9, 29.4, 28.9, 28.7, 28.4, 28.2, 27.9, 27.1, 25.4, 24.8, 18.0, 17.9.

FTIR (neat): 2919, 2852, 1792, 1747, 1706, 1435, 1260, 1012, 965, 801, 734 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{37}H_{52}O_6S_4Na$ $[M+Na]^+$: 743.2539, found: 743.2534.

Synthesis of Enol Triflate 31



To an oven-dried vial equipped with a magnetic stir bar was added NaH (2.430 mg, 0.061 mmol) under N_2. The vial was capped and was cooled to 0 °C in an ice/water bath, at which point a solutoin of enol **29** (21.9 mg, 0.030 mmol) in THF (0.608 mL) was added. The resulting suspension was allowed to slowly warm to at room temperature and stir for an hour, then the suspension was recooled to 0 °C, at which point a solution of *N*-(5-Chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (Comins' reagent) **30** (0.179 g, 0.046 mmol) in THF (0.608 mL) was added dropwise. Resulting reaction mixture continued to stir at 0 °C, slowly warm to room temperature with the bath. After an hour, the reaction was recooled to 0 °C and was quenched with the addition of H_2O (0.120 mL) and diluted with EtOAc. The layer was separated and the organic layer was washed with EtOAc three times. Combined organics were washed with brine, then dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (5% gradient, 0%→10% EtOAc/Hex) afforded enol triflate **31** (0.019 g, 73% yield) as a white foam. (Note: Purification can also be performed using HPLC (0%→15% EtOAc/Hex, λ = 259 nm, flow rate = 10 mL/min))

R_f = 0.52 (25% EtOAc/Hex)

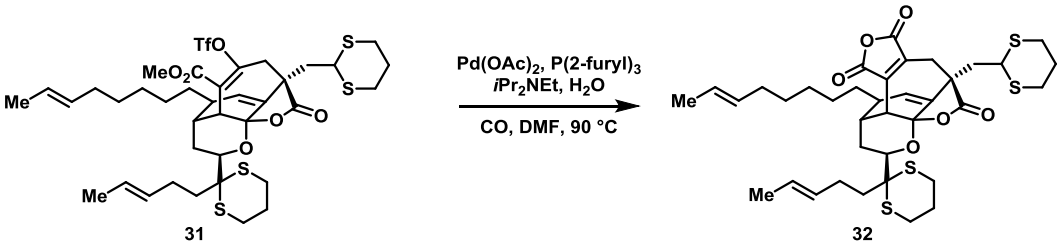
^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 1H) 5.48-5.30 (m, 4H), 4.18-4.11 (m, 2H), 3.82 (s, 3H), 3.47-3.33 (m, 2H), 3.05 (s, 1H), 2.87-2.81 (m, 2H), 2.76-2.68 (m, 5H), 2.50-2.44 (m, 3H), 2.29 (dd, *J* = 14.3, 8.3 Hz, 2H), 2.16-1.92 (m, 8H), 1.81-1.71 (m, 2H), 1.64-1.61 (m, 7H), 1.57-1.54 (m, 1H), 1.52-1.44 (m, 2H), 1.40-1.25 (m, 8H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.6, 165.7 ,145.0 ,134.4 ,132.2, 131.3, 130.0, 129.0, 125.8, 124.8, 103.4, 83.3, 53.1, 52.5, 50.6, 49.9, 47.6, 42.3, 42.1, 38.4, 36.0, 35.4, 35.0, 34.8, 32.4, 29.3, 28.8, 28.7, 28.4, 28.3, 27.9, 27.9, 27.8, 27.2, 25.4, 24.8, 17.9.

FTIR (neat): 2926, 2856, 1789, 1736, 1420, 1263, 1212, 1135, 1022, 967, 907, 868, 733 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{35}H_{51}F_3O_8S_5Na$ $[M+Na]^+$: 875.2032, found: 875.2027.

Synthesis of Maleic Anhydride 32



To a vial equipped with a stir bar was added enol triflate **31** (8.80 mg, 10.3 µmol), palladium(II) acetate (2.32 mg, 10.3 µmol), tri(2-furyl)phosphine (11.97 mg, 0.052 mmol), DMF (737 µL), *i*Pr_2EtN (13.5 µL, 0.077 mmol) and H_2O (13.9 µL, 0.774 mmol) sequentially. Then the reaction mixture was vigorously stirred and was purged with CO for 15 minutes. The reaction was then replaced with a balloon of CO and was heated to 90 °C in an oil bath. The reaction continued to stir at 90 °C for 2 hours and then it was cooled to room temperature in the bath over 30 min, at which point it was quenched with 1 M HCl (1.47 mL). The resulting solution mixture was continued to stir for 10 minutes, and then it was diluted with EtOAc. Aqueous layer was extracted with EtOAc three times. Combined organics were washed with brine and then dried over $MgSO_4$. Concentration and purification via HPLC (0%→10% EtOAc/Hex, λ = 280 nm, flow rate = 10 mL/min) afforded maleic anhydride **32** (0.052 g, 73% yield) as a pale yellow oil.

R_f = 0.44 (25% EtOAc/Hex)

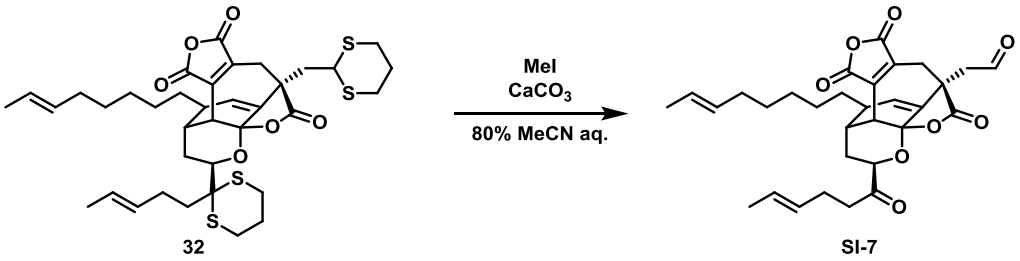
^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.82 (s, 1H), 5.47-5.33 (m, 4H), 4.21 (dd, *J* = 11.8, 2.4 Hz, 1H), 4.15 (t, *J* = 8.3 Hz, 1H), 3.41 (ddd, *J* = 14.1, 11.9, 2.9 Hz, 1H), 3.34-3.28 (m, 2H), 3.08 (dd, *J* = 19.2, 1.4 Hz, 1H), 2.88-2.83 (m, 3H), 2.75-2.71 (m, 2H), 2.64 (d, *J* = 3.4 Hz, 1H), 2.56-2.49 (m, 3H), 3.36-2.29 (m , 3H), 2.20-2.17 (m, 1H), 2.08-2.01 (m, 3H), 1.96-1.92 (m, 3H), 1.84-1.77 (m, 2H), 1.72 (ddd, *J* = 13.2, 4.0, 2.5 Hz, 1H), 1.65-1.61 (m, 6H), 1.60-1.57 (m, 1H), 1.32-1.20 (m, 8H), 1.10 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.02 (ddt, *J* = 9.8, 7.3, 4.2 Hz, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ 174.8, 164.6, 164.3, 142.0, 140.3, 136.2, 132.0, 131.0, 130.0, 125.9, 125.1, 103.6, 83.3, 52.6, 51.3, 45.4, 44.4, 42.3, 41.8, 38.3, 36.7, 36.5, 36.3, 34.4, 32.3, 32.3, 29.2,29.2, 28.8, 28.4, 28.2, 27.7, 27.2, 27.2, 25.4, 24.7, 19.7.

FTIR (neat): 2924, 2853, 1790, 1767, 1440, 1262, 1133, 1025, 967, 917 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{37}H_{48}O_6S_4Na$ $[M+Na]^+$: 739.2226, found: 739.2224.

Synthesis of Aldehyde SI-7



To a vial equipped with a stir bar was added a solution of maleic anhydride **32** (11.1 mg, 0.015 mmol) in 80% MeCN aq. solution (0.010 M) at room temperature. To the stirring mixture was added the iodomethane (77.0 µL, 1.24 mmol) and calcium carbonate (6.97 mg, 0.070 mmol) sequentially at room temperature. The reaction was capped and was stirred for 60 hours. TLC was used to follow the reaction progress and the TLC plates were developed using a 25% EtOAc/Hexanes solution and visualized with CAM. Upon reaction completion, the reaction was quenched with 1 M HCl. Aquesous layer was extracted with EtOAc twice. Combined organic layer were washed with $Na_2S_2O_3$ sat. aq solution, dried over $MgSO_4$. Concentration and purification via silica gel flash column chromatography (10% gradient, 0%→30% EA/Hex+1% AcOH) afforded aldehyde **SI-7** (5.60 mg, 67% yield) as a white foam.

(Note: Occasionally, crude ^{1}H-NMR spectrum indicated the presence of aldehyde with the spiroacetal opened resulting in a diol. The diol can be cyclized upon exposure to 3 quiv of methanesulfonic acid (MSA) in $CDCl_3$.[2] Cyclization conversion could be monitored by ^{1}H-NMR. Upon cnversion completion, the mixture was diluted with H_2O. Aqueous layer was extracted with DCM. Combined organics were dried over $MgSO_4$, and then concentrated in vacuo.)

R_f = 0.67 (50% EtOAc/Hex+1% AcOH)

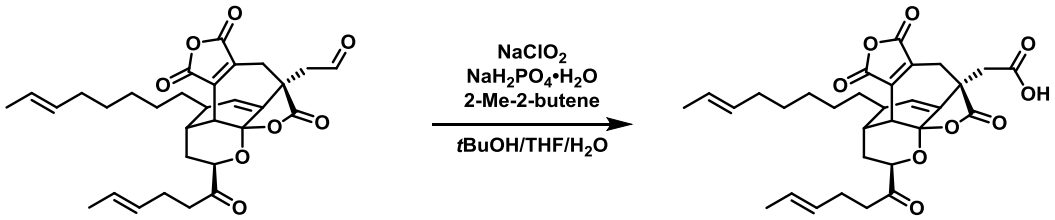
^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.72 (s, 1H), 5.75 (t, *J* = 1.4 Hz, 1H), 5.51-5.34 (m, 4H), 4.19 (dd, *J* = 12.3, 3.2 Hz, 1H), 3.40 (d, *J* = 19.0 Hz, 1H), 3.29 (d, *J* = 2.1 Hz, 1H), 3.18 (d, *J* = 19.0 Hz, 1H), 3.04 (dd, *J* = 19.2, 1.3 Hz, 1H), 2.86-2.76 (m, 2H), 2.68-2.61 (m, 2H), 2.31-2.27 (m, 2H), 2.23-2.20 (m, 1H), 2.05-1.99 (m, 1H), 1.95-1.86 (m, 3H), 1.64-1.63 (m, 6H), 1.59-1.57 (m, 1H), 1.31-1.19 (m, 8H, overlapped with grease), 1.14-1.08 (m, 1H), 1.05-0.98 (m, 1H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ 208.8, 195.7, 174.3, 164.5, 164.1, 142.1, 140.2, 136.3, 131.6, 130.9, 129.4, 126.1, 125.2, 103.3, 76.7, 47.2, 45.7, 44.3, 42.9, 40.8, 38.2, 36.5, 36.3, 34.8, 32.3, 29.2, 28.6, 27.6, 25.9, 17.9, 17.9.

FTIR (neat): 2923, 2854, 2018, 1800, 1769, 1718, 1454, 1263, 1118, 970, 928 cm^{-1}.

HRMS (ESI) *m/z* Calc'd. for $C_{31}H_{36}O_8Na$ $[M+Na]^+$: 559.2302, found: 559.2303.

Synthesis of Phomoidride D (4)



SI-7 Phomoidride D (4)

To a vial equipped with a stir bar was added aldehyde **SI-7** (2.60 mg, 4.85 µmol) *t*BuOH (0.291 mL) and THF (97 µL) was added. Then to the stirring mixture was added 2-methylbut-2-ene (25.7 µL, 0.242 mmol), followed by the addition of a solution of sodium chlorite ($NaClO_2$) (1.32 mg, 0.015 mmol) and sodium dihydrogenphosphate monohydrate ($NaH_2PO_4 \cdot H_2O$) (3.49 mg, 0.029 mmol) in H_2O (97 µL). The resulting reaction mixture was stirred for 1.5 hours and reaction progress was monitored by UPLC. Upon consumption of aldehyde, the reaction was quenched with 1 M HCl and was diluted with EtOAc. Aqueous layer was extracted with EtOAc twice. Combined organics were washed with sat. aq. $Na_2S_2O_3$ solution, dried over $MgSO_4$, and then concentrated in vacuo. The crude mixture was purified by reversed phase flash column chromatography using reversed phase C18 silica (80/20 0.1% HCO_2H aq./MeCN→35/65 0.1% HCO_2H aq./MeCN) to afford 2.60 mg (97% yield) of phomoidride D (**4**).

^{1}H-NMR (600 MHz, acetone-d_6): δ 6.22, (s, 1H), 5.49-5.41 (m, 2H), 5.40-5.37 (m, 2H), 4.30 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.29-3.20 (m, 3H), 3.03-2.91 (m, 2H), 2.76-2.65 (m, 3H), 2.39 (t, *J* = 7.2 Hz, 1H), 2.24-2.20 (m, 2H), 2.04-2.02 (m, 1H), 1.98-1.96 (m, 1H), 1.94-1.90 (m, 2H), 1.60 (m, 3H), 1.60-1.59 (m, 3H), 1.42-1.33 (m, 2H), 1.32-1.18 (m, 8H, overlapped with grease).

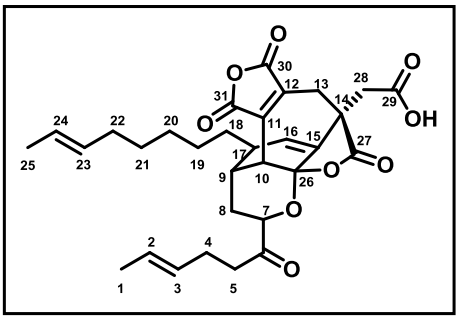
^{13}C-NMR (150 MHz, acetone-d_6): δ 208.2, 175.9, 171.2, 166.0, 165.9, 142.3, 142.0, 137.3, 132.9, 132.1, 130.9, 126.2, 125.4, 104.2, 77.4, 49.8, 45.2, 43.4, 41.7, 38.7, 37.6, 36.9, 35.3, 33.1, 30.1, 29.5, 28.2, 26.8, 18.0.

FTIR (neat): 3447, 2925, 2855, 1796, 1766, 1716, 1437, 1404, 1262, 1154, 1126, 1038, 967, 927, 722 cm^{-1}.

HRMS (ESI) *m*/*z* Calc'd. for $C_{31}H_{36}O_9Na$ $[M+Na]^+$: 575.2257, found: 575.2285; *m*/*z* Calc'd. for $C_{31}H_{35}O_9$ $[M-H]^+$: 551.2287, found: 551.2276.

Table S1 ^{1}H and ^{13}C NMR Data for Phomoidride D in acetone-d_6

C (position)	^{13}C-NMR δ (ppm)	^{1}H-NMR δ (ppm)	(LR) C-H Correlation	H-H Correlation
1	18.0	1.60	-	H4
2	126.2	5.44	H4	H4
3	130.9	5.44	H4, H5	H4
4	26.8	2.21	H5	H5
5	38.7	2.71	-	H4
6	208.2	-	-	-
7	77.4	4.30	-	H8
8	35.3	2.03/1.97	-	H9
9	37.6	2.66	-	H8, H10
10	45.2	3.29	H8	H9
11	142/142.3	-	H10, H13	-
12	142/142.3	-	H10, H13	-
13	43.4	3.02/2.93	H28	H28
14	49.8	-	H13, H16, H28	-
15	137.3	-	H13, H16, H28	-
16	132.9	6.22	H17	H17
17	41.7	2.38	H16, H28	H18/19
18	36.9	1.24	-	-
19	28.2	1.36	-	-
20	29.5	1.25	-	-
21	30.1	1.25	H18, H22	-
22	33.1	1.92	-	-
23	132.1	5.38	H22	H22
24	125.4	5.38	H22	H22
25	18.0	1.59	-	-
26	104.2	-	H16, H28	-
27	175.9	-	H13, H28	-
28	36.4	3.28/3.22	H13	H13
29	171.2	-	H28	-
30	165.9	-	H13	-
31	166.0	-	H13	-



References

[1] G. K. Murphy, T. Shirahta, N. Hama, N., A. Bedermann, P. Dong, T. C. McMahon, B. M. Twenter, D. A. Spiegel, I. M. McDonald, N. Taniguchi, M. Inoue, J. L. Wood, *J. Org. Chem*. **2013**, *78*, 477.

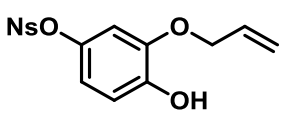
[2] D. Meng, Q. Tan, S. J. Danishefsky, *Angew. Chem.* **1999**, *111*, 1582; *Angew. Chem. Int. Ed.* **1999**, *38*, 3197.

Author Contributions

Contributions are listed employing the following Format:
Author: Nature of Contribution(s), Degree of Contribution

Leung, J. C.: Synthesis Design, Execution, and author of the Original Draft, Equal
Bedermann, A. A.: Synthesis Design and Execution, Equal
Njardarson, J.T.: Synthesis Design and Execution, Lead
Spiegel, D. A.;: Synthesis Design and Execution, Equal
Murphy, G. K.: Synthesis Design and Execution, Equal
Hama, N.: Synthesis Design and Execution, Equal
Twenter, B. M.; Synthesis Design and Execution, Equal
Dong, Ping: Synthesis Design and Execution, Equal
Shirahata, T.: Synthesis Design and Execution, Equal
McDonald, I. M.: Synthesis Design and Execution, Equal
Inoue, M.: Synthesis Design and Execution, Equal
Taniguchi, N.: Synthesis Execution, Supporting
McMahon, T. C.: Synthesis Execution, Supporting
Schneider, C. M.: Synthesis Execution, Supporting
Tao, N.: Synthesis Execution, Supporting
Stoltz, B.: Synthesis Design, Supporting
Wood, J. L.; Synthesis Design, Lead

NMR Spectra



18

Figure 1 ^{1}H-NMR (600 MHz, $CDCl_3$) for phenol **18**

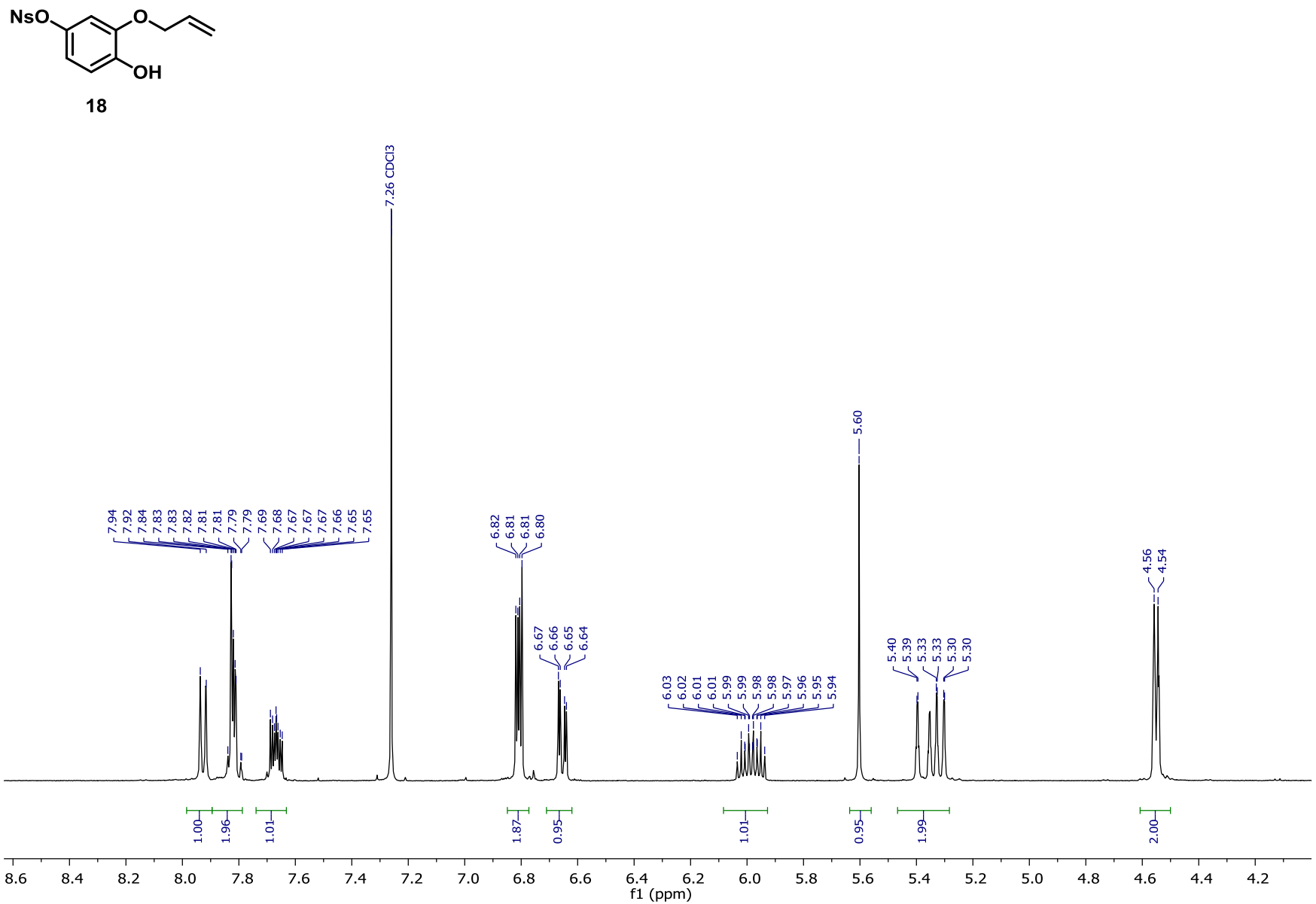


Figure 2 ^{1}H-NMR (600 MHz, $CDCl_3$) for phenol **18** (inset)

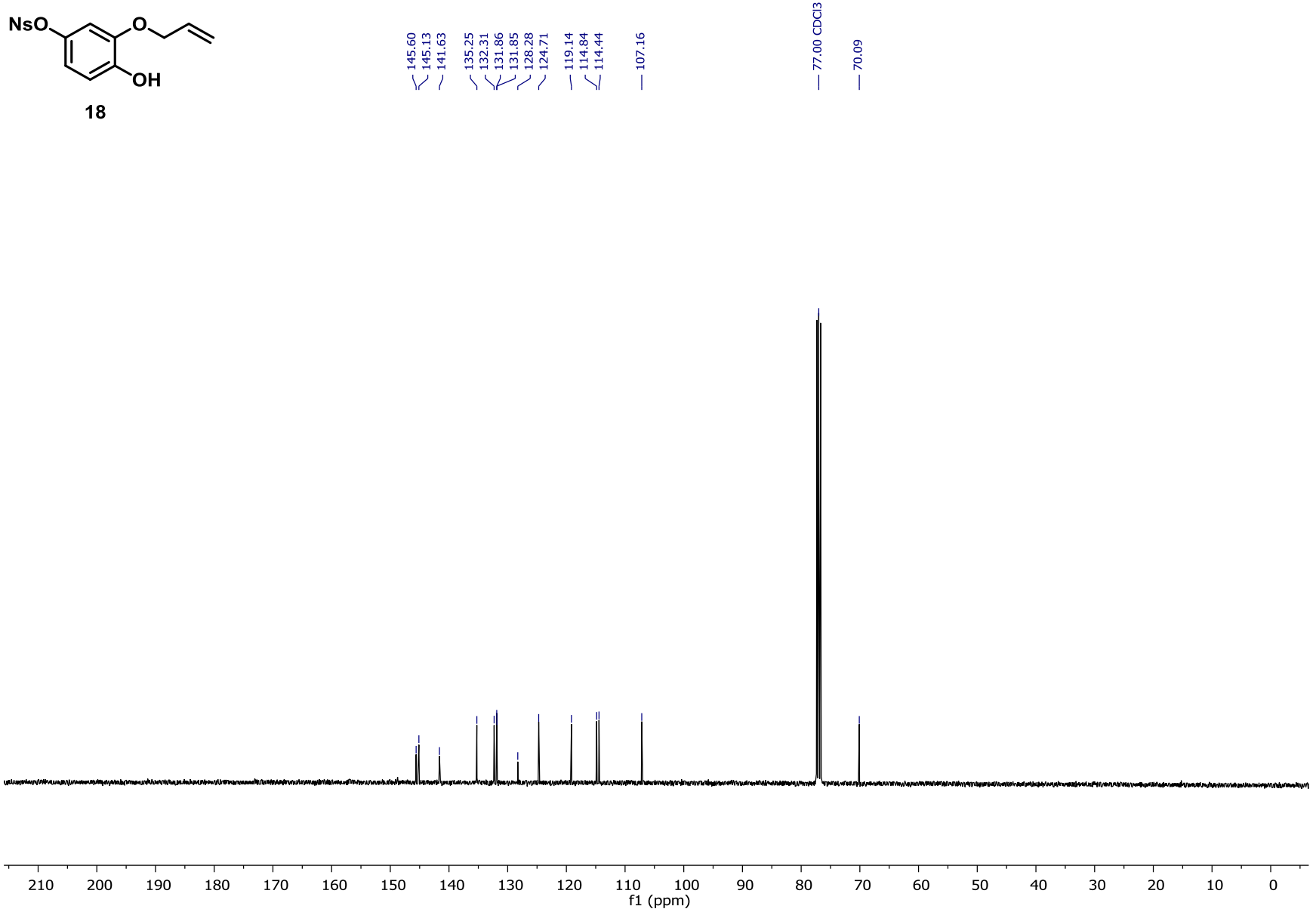


Figure 3 ^{13}C-NMR (150 MHz, $CDCl_3$) for phenol **18**

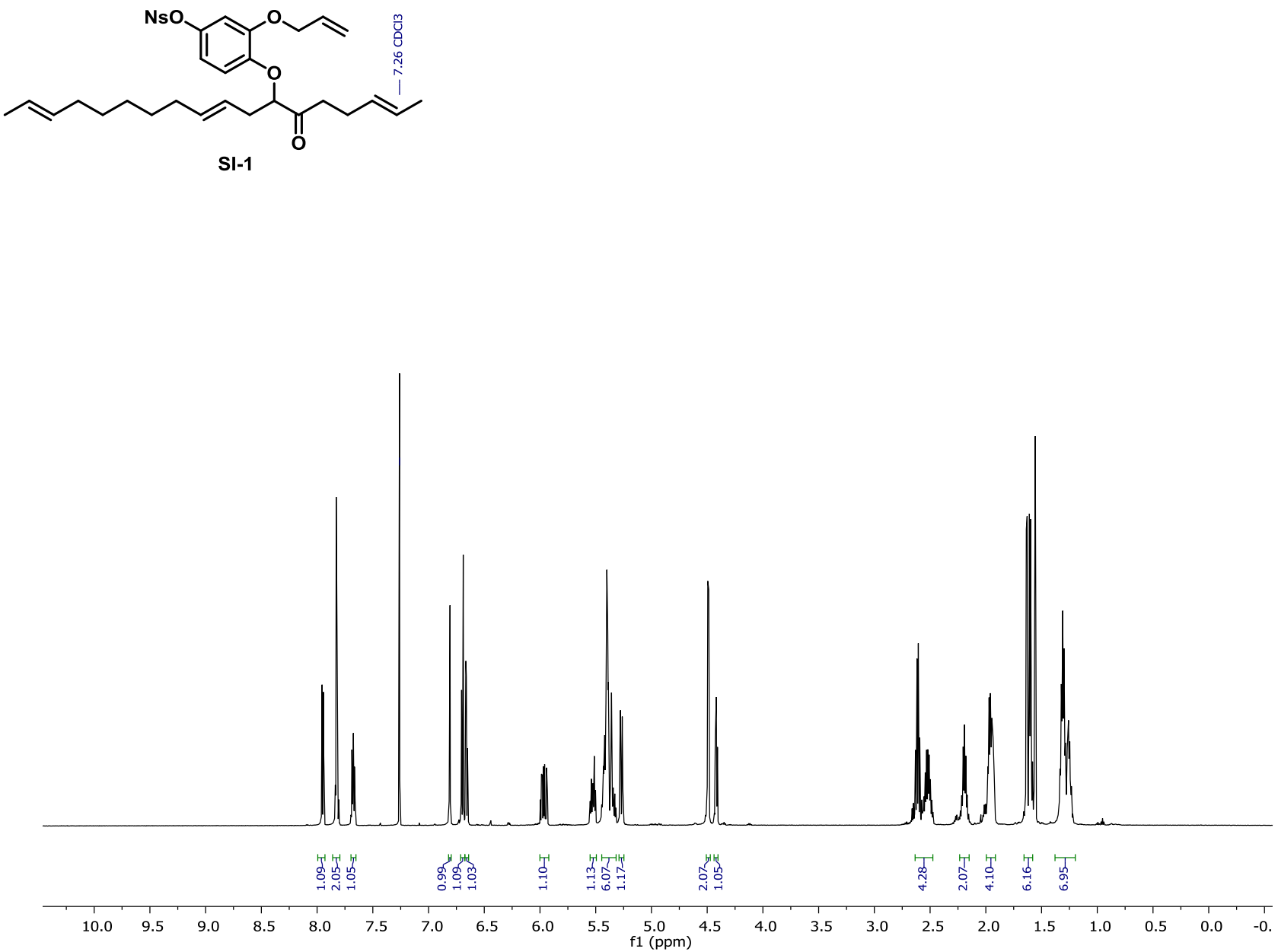


Figure 4 ^{1}H-NMR (600 MHz, $CDCl_3$) for α-phenoxy ketone **SI-1**

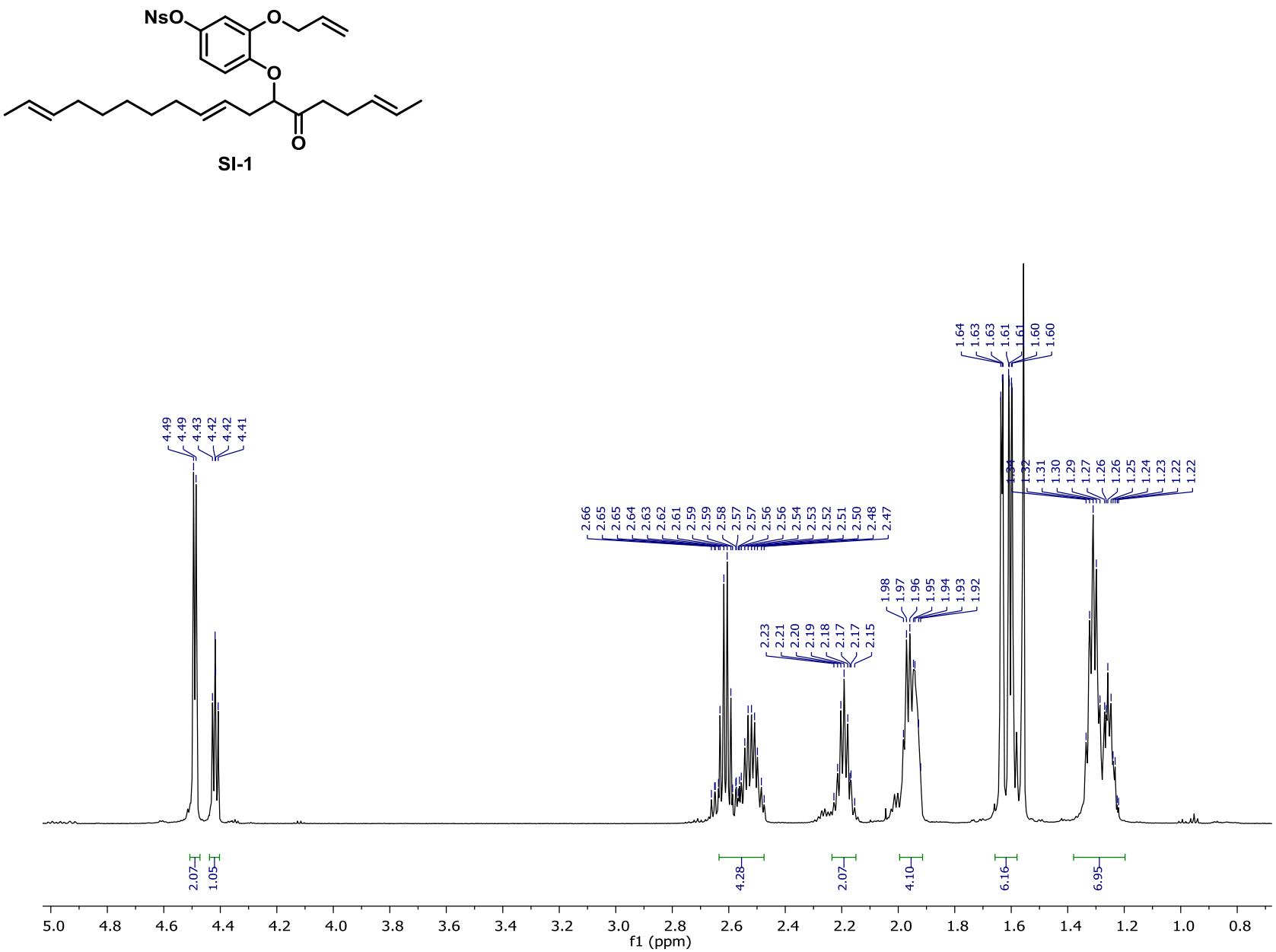


Figure 5 ^{1}H-NMR (600 MHz, $CDCl_3$) for α-phenoxy ketone **SI-1 (**inset)

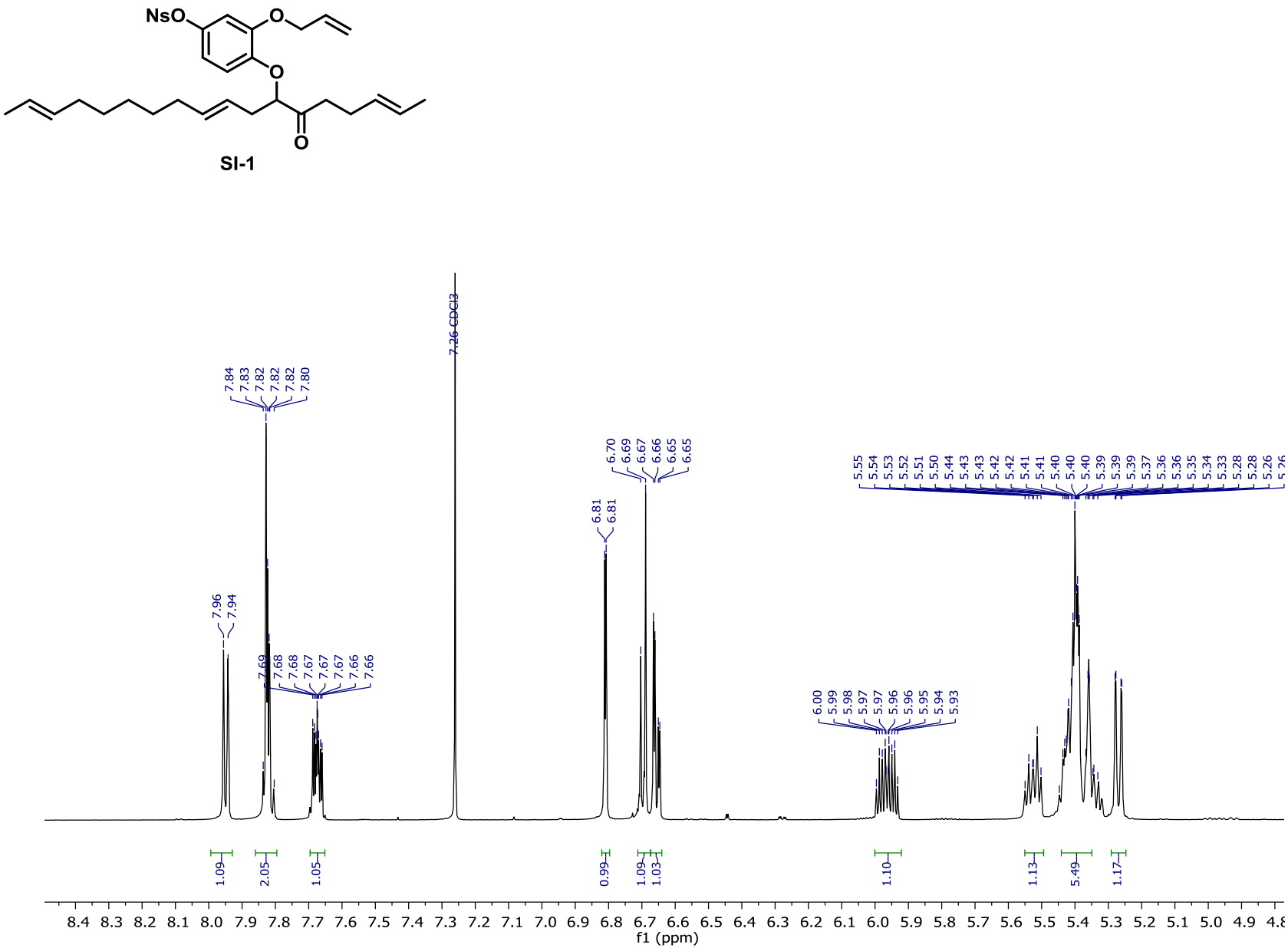


Figure 6 ^{1}H-NMR (600 MHz, $CDCl_3$) for α-phenoxy ketone **SI-1 (**inset)

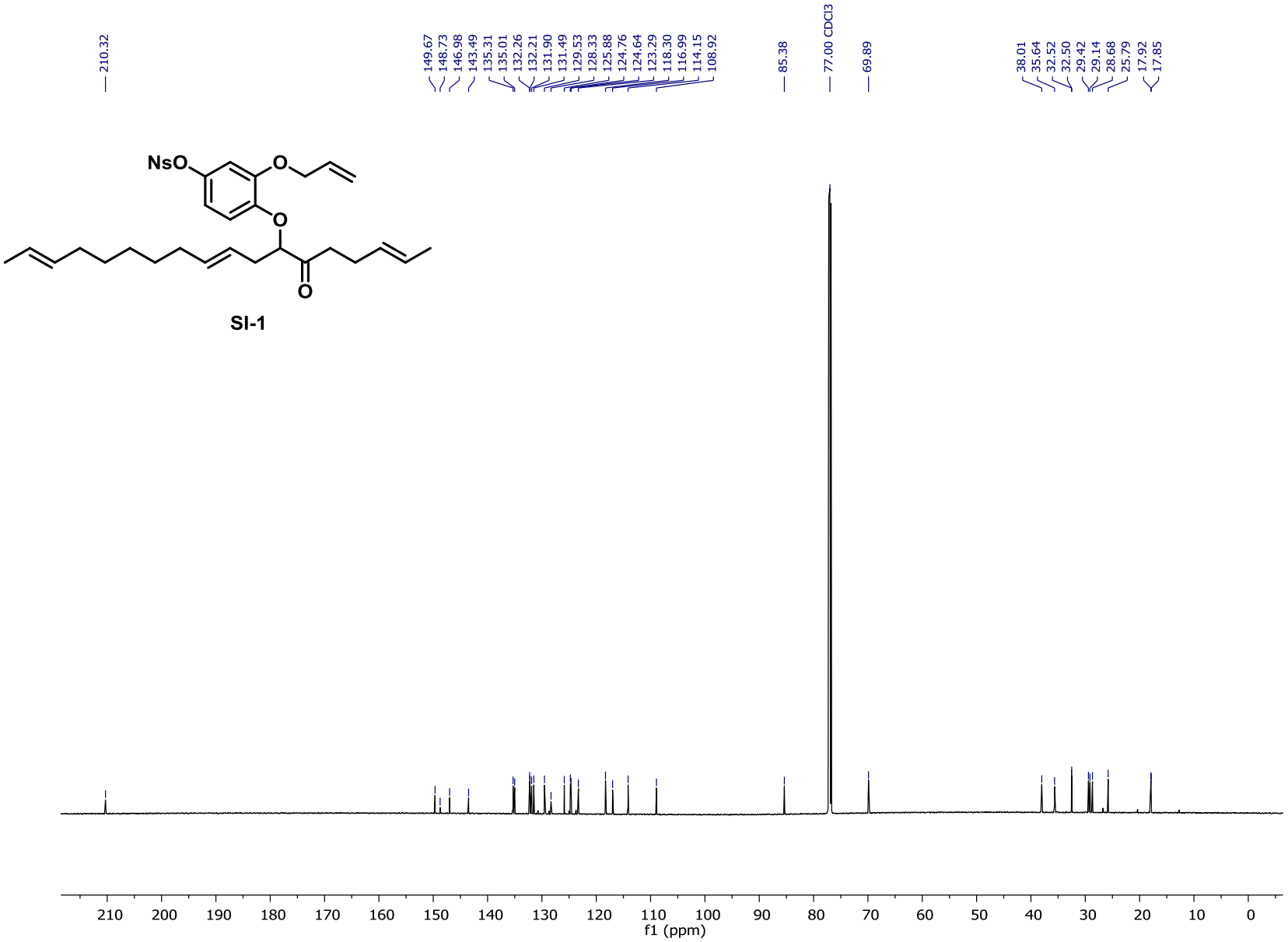
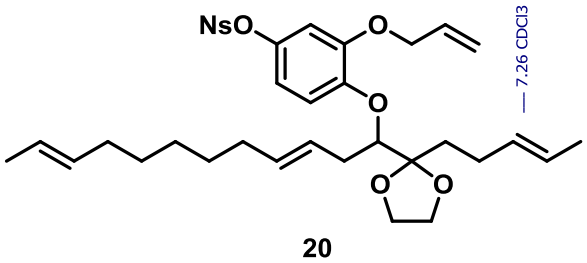


Figure 7 ^{13}C-NMR (150 MHz, $CDCl_3$) for α-phenoxy ketone **SI-1**



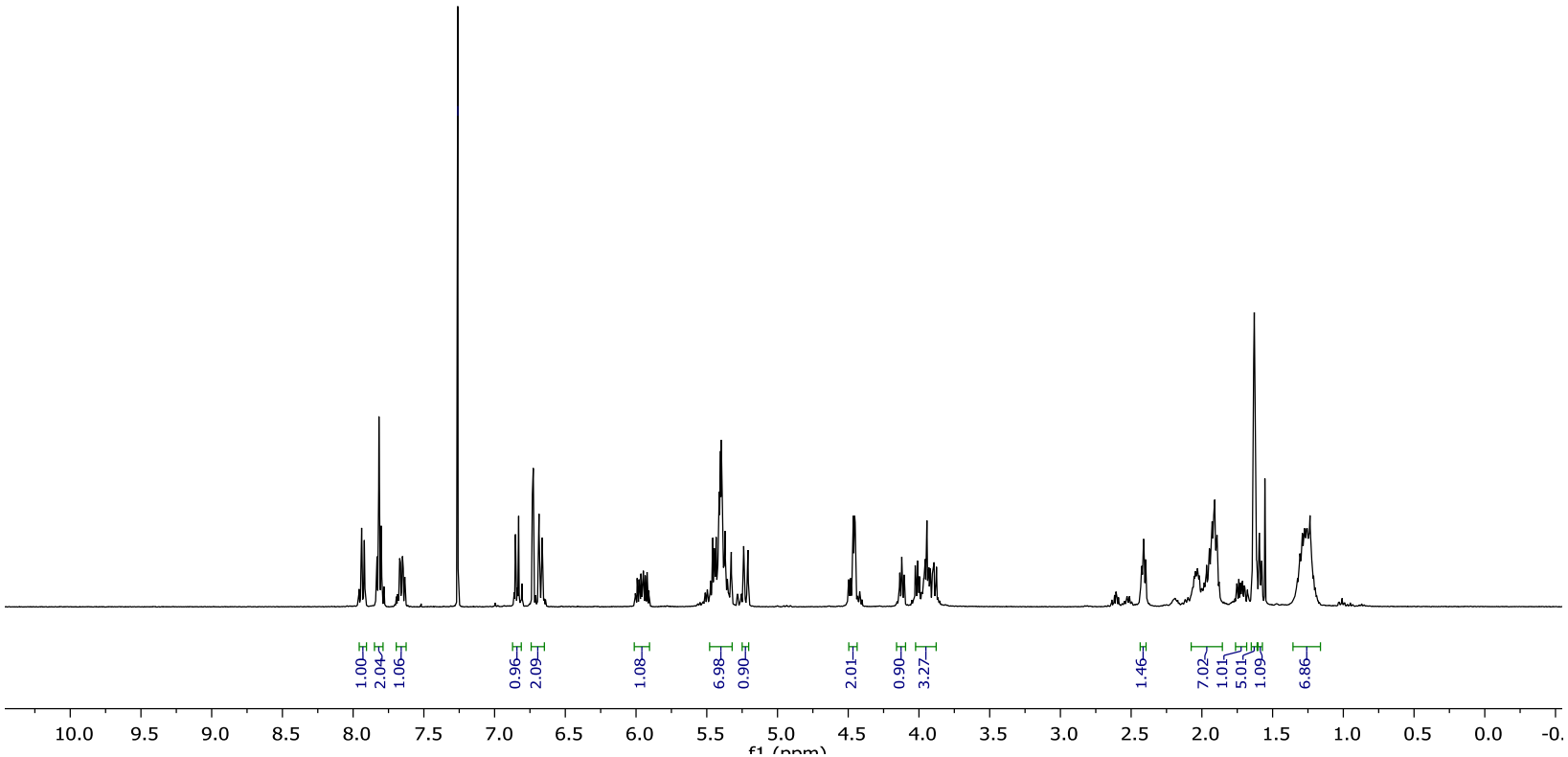
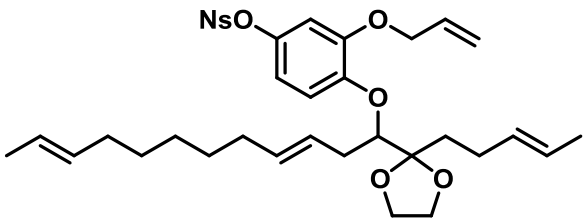


Figure 8 ^{1}H-NMR (500 MHz, $CDCl_3$) for ketal **20**



20

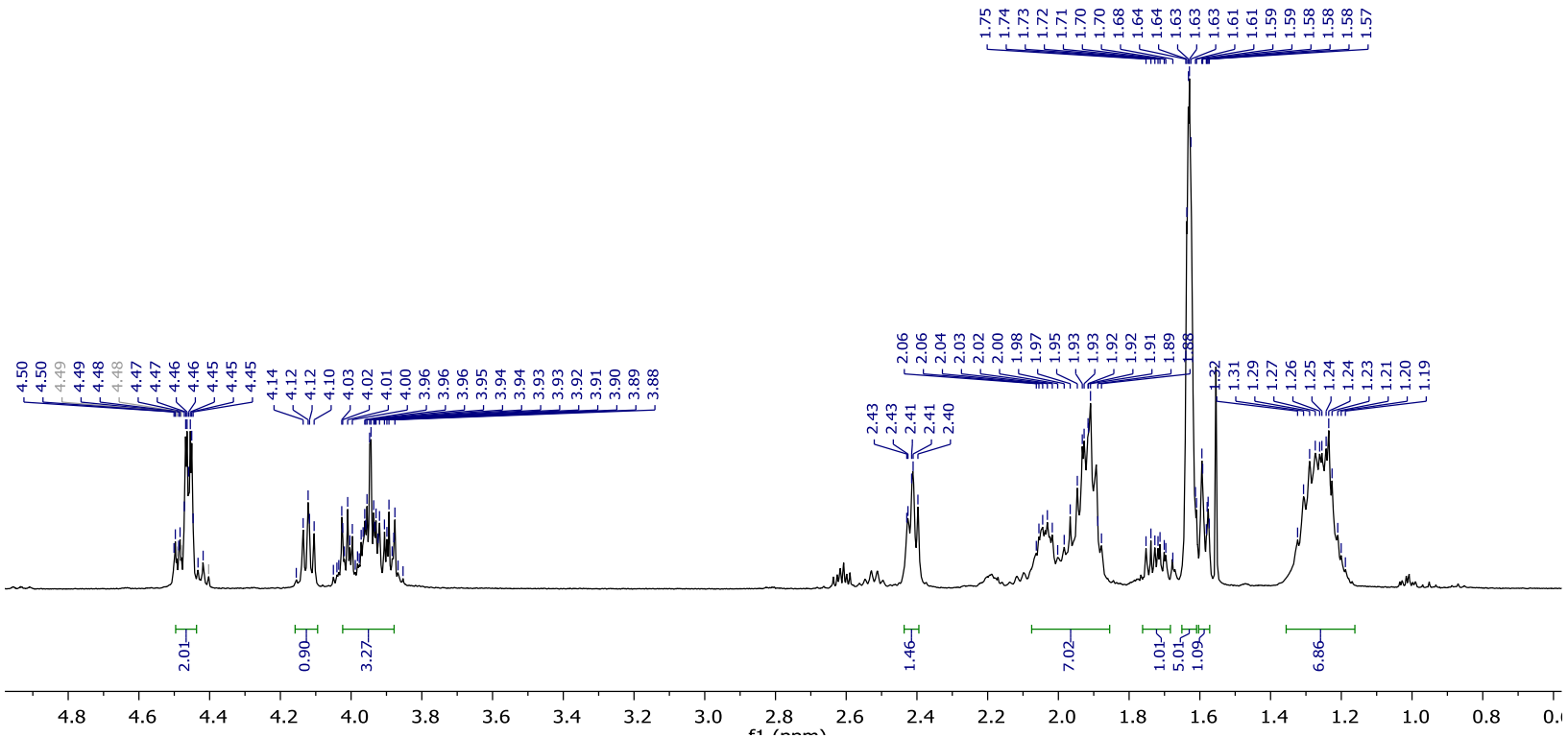
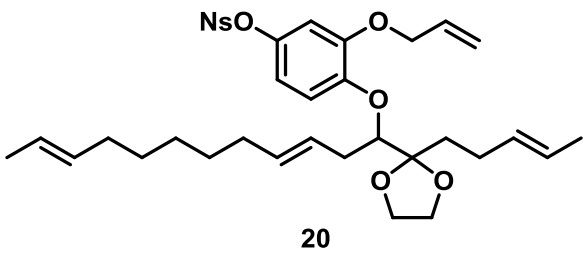


Figure 9 ^{1}H-NMR (500 MHz, $CDCl_3$) for ketal **20** (inset)



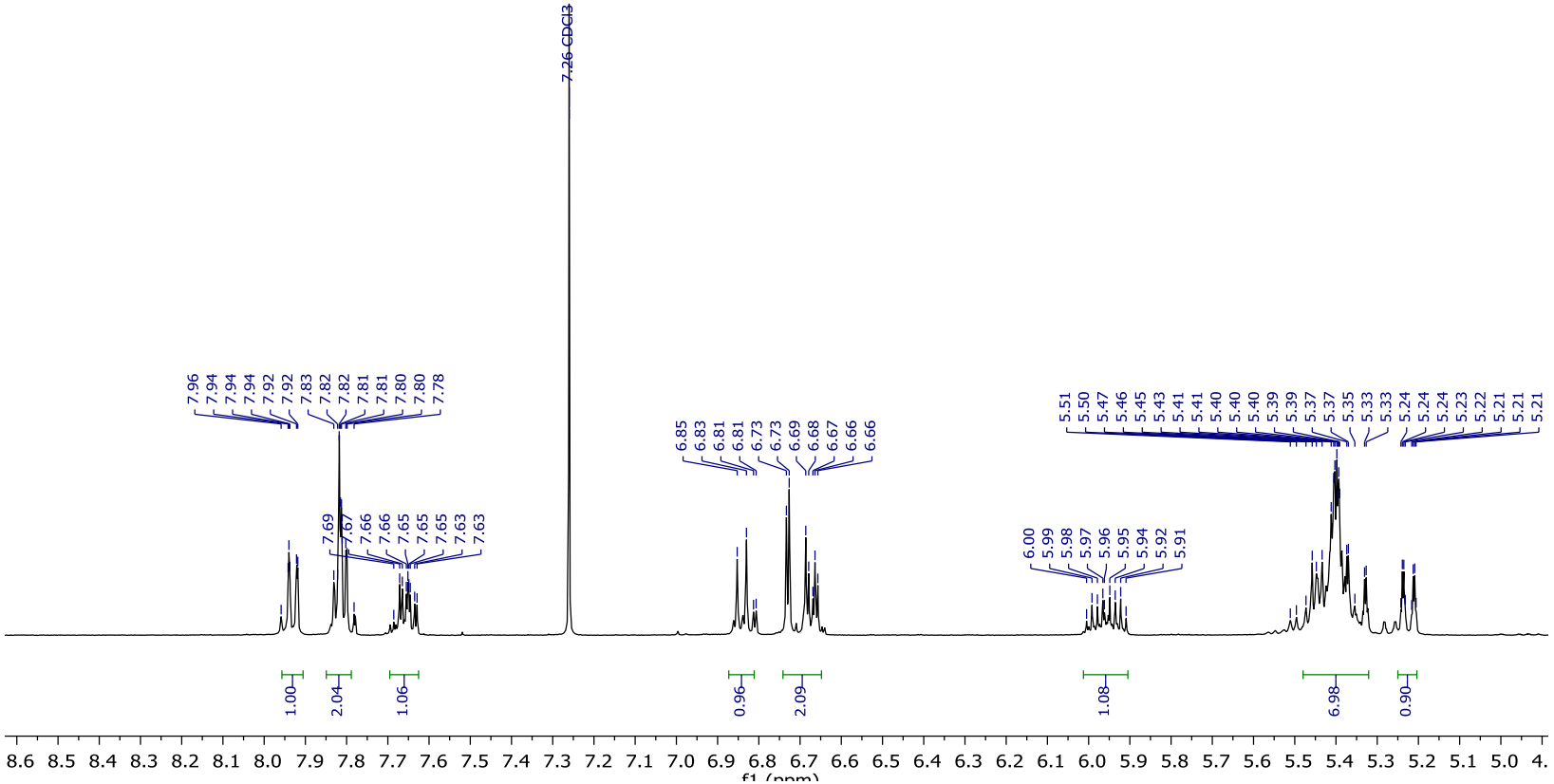


Figure 10 ^{1}H-NMR (500 MHz, $CDCl_3$) for ketal **20** (inset)

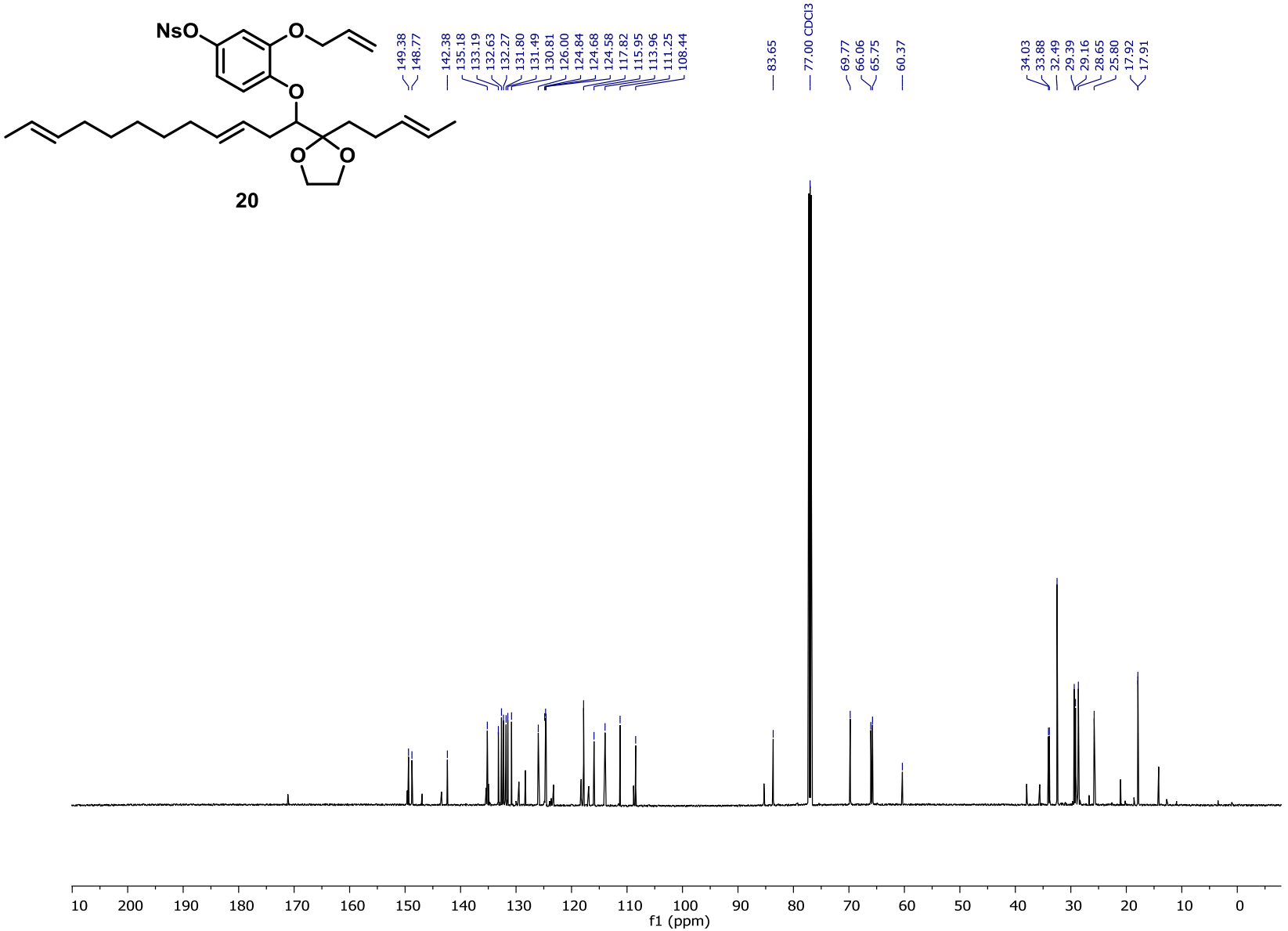


Figure 11 ^{13}C-NMR (125 MHz, $CDCl_3$) for ketal **20**

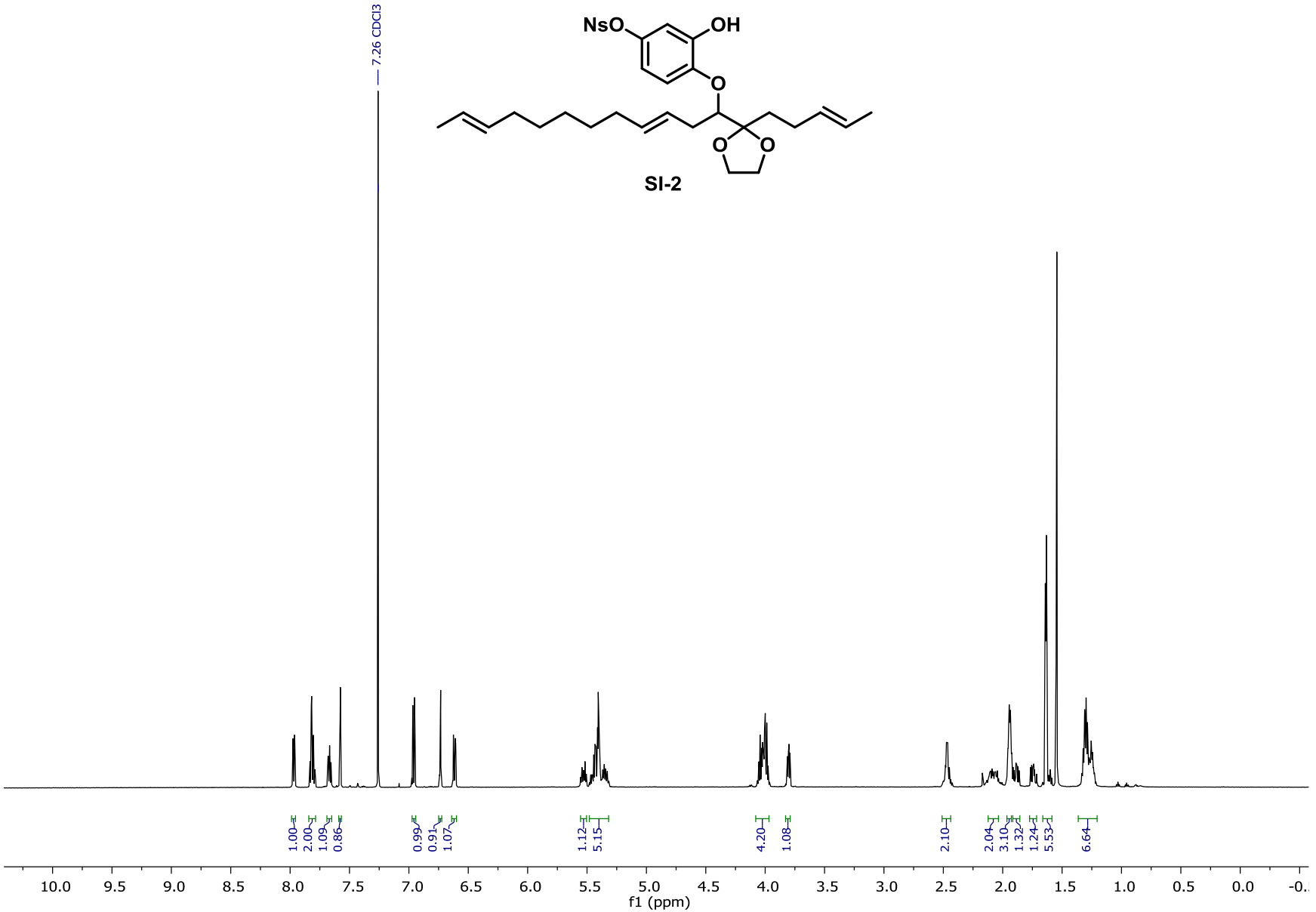


Figure 12 ^{1}H-NMR (600 MHz, $CDCl_3$) for phenol **SI-2**

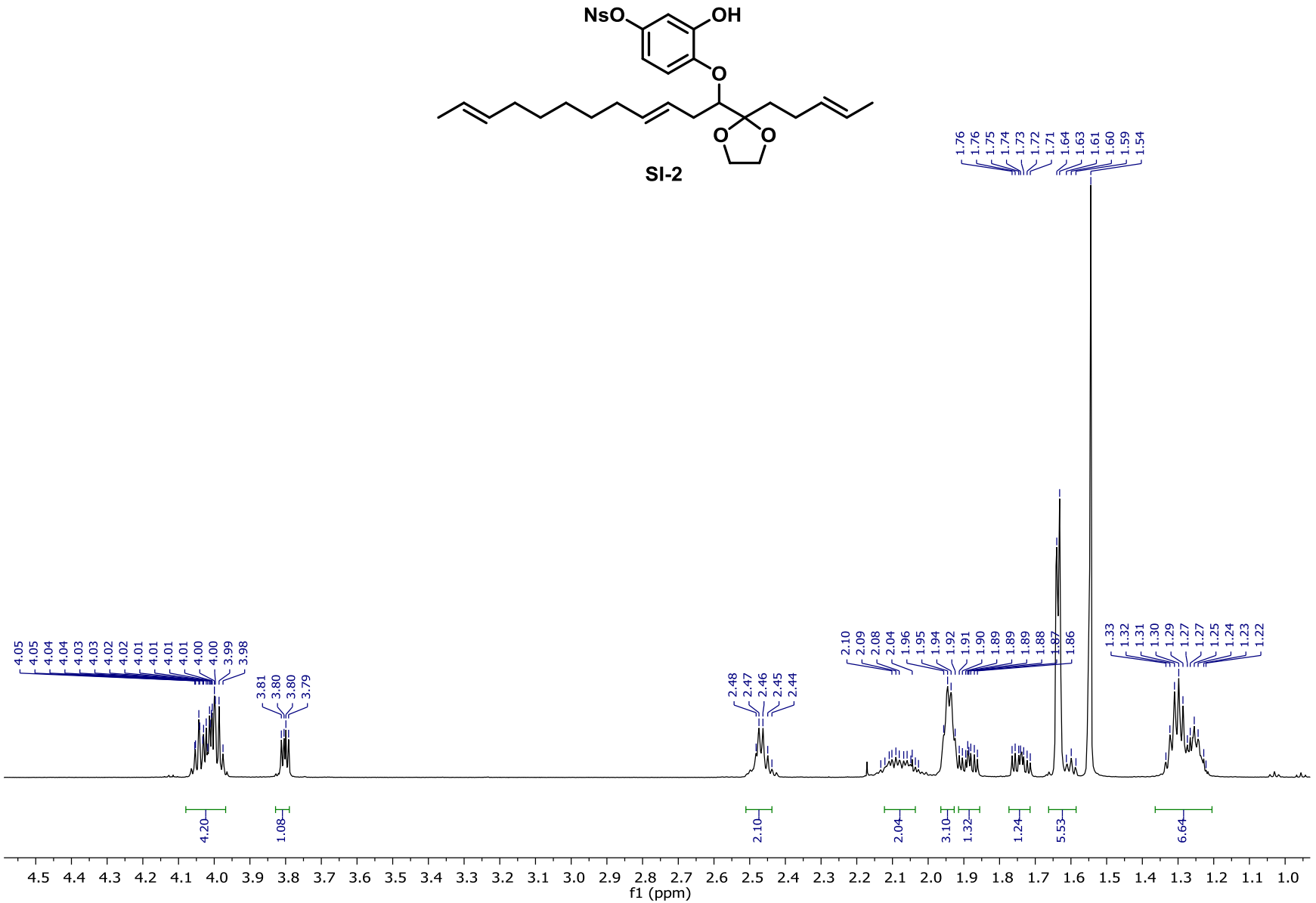


Figure 13 ^{1}H-NMR (600 MHz, $CDCl_3$) for phenol **SI-2** (inset)

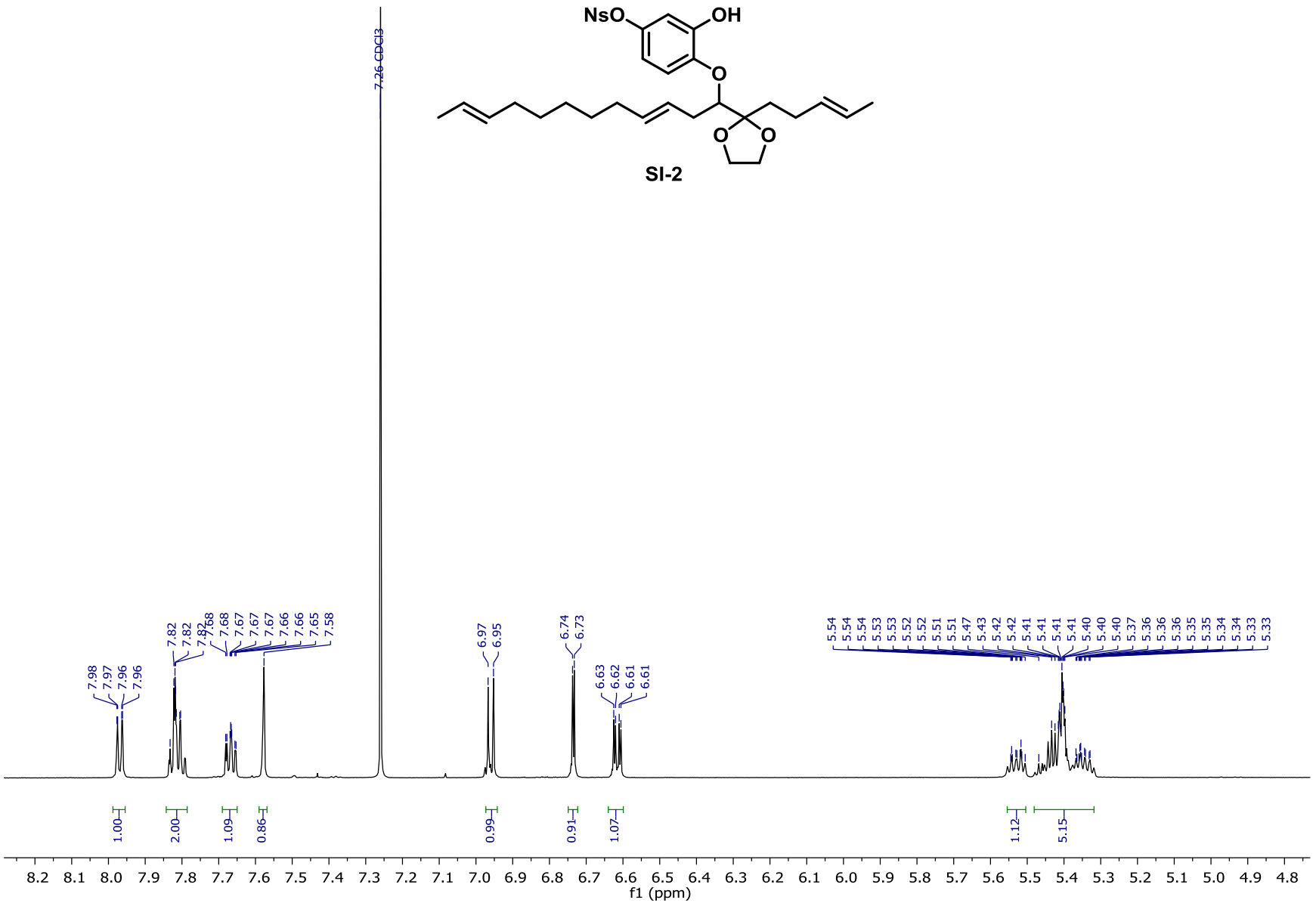


Figure 14 ^{1}H-NMR (600 MHz, $CDCl_3$) for phenol **SI-2** (inset)

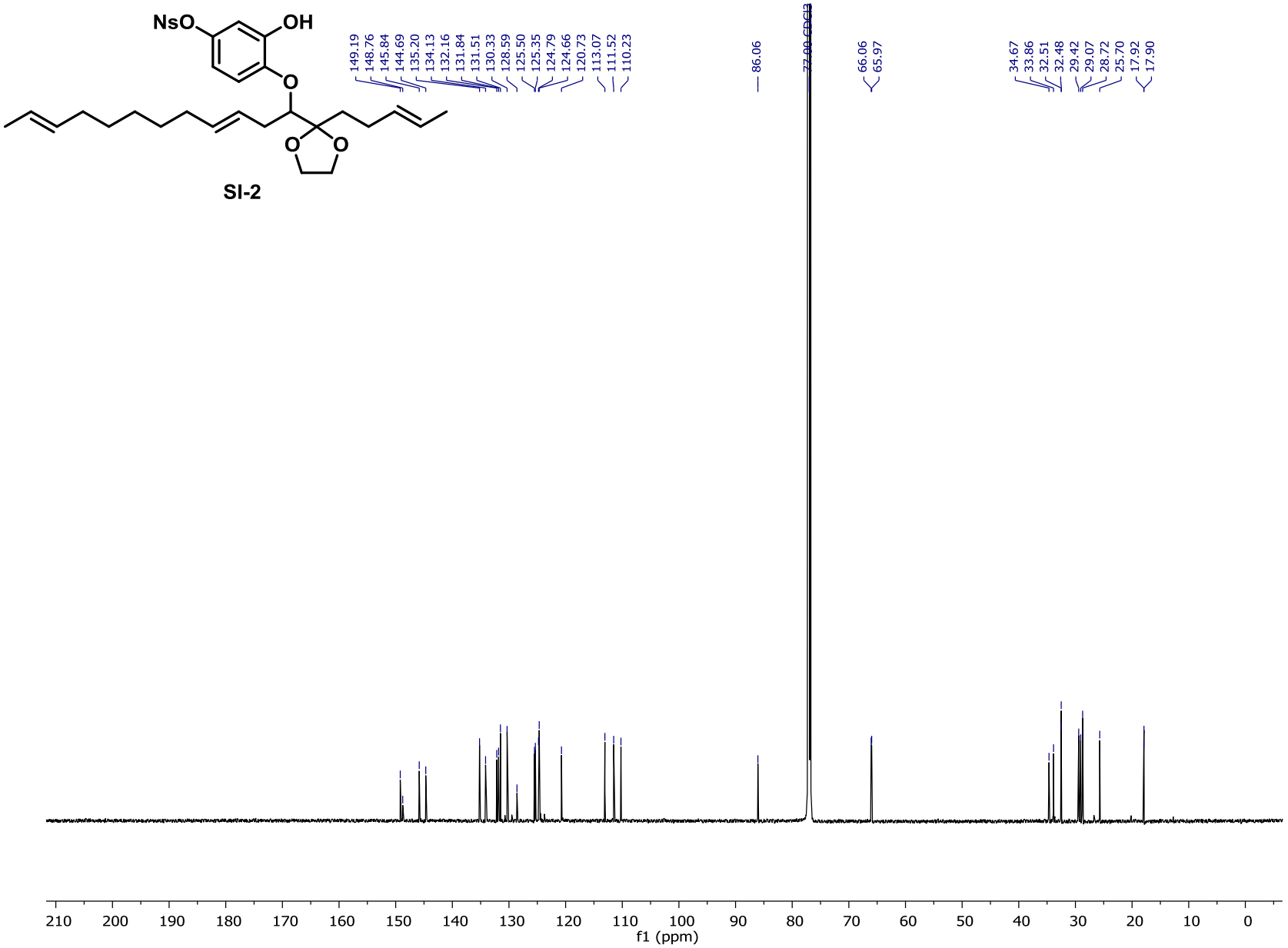


Figure 15 ^{13}C-NMR (150 MHz, $CDCl_3$) for phenol **SI-2**

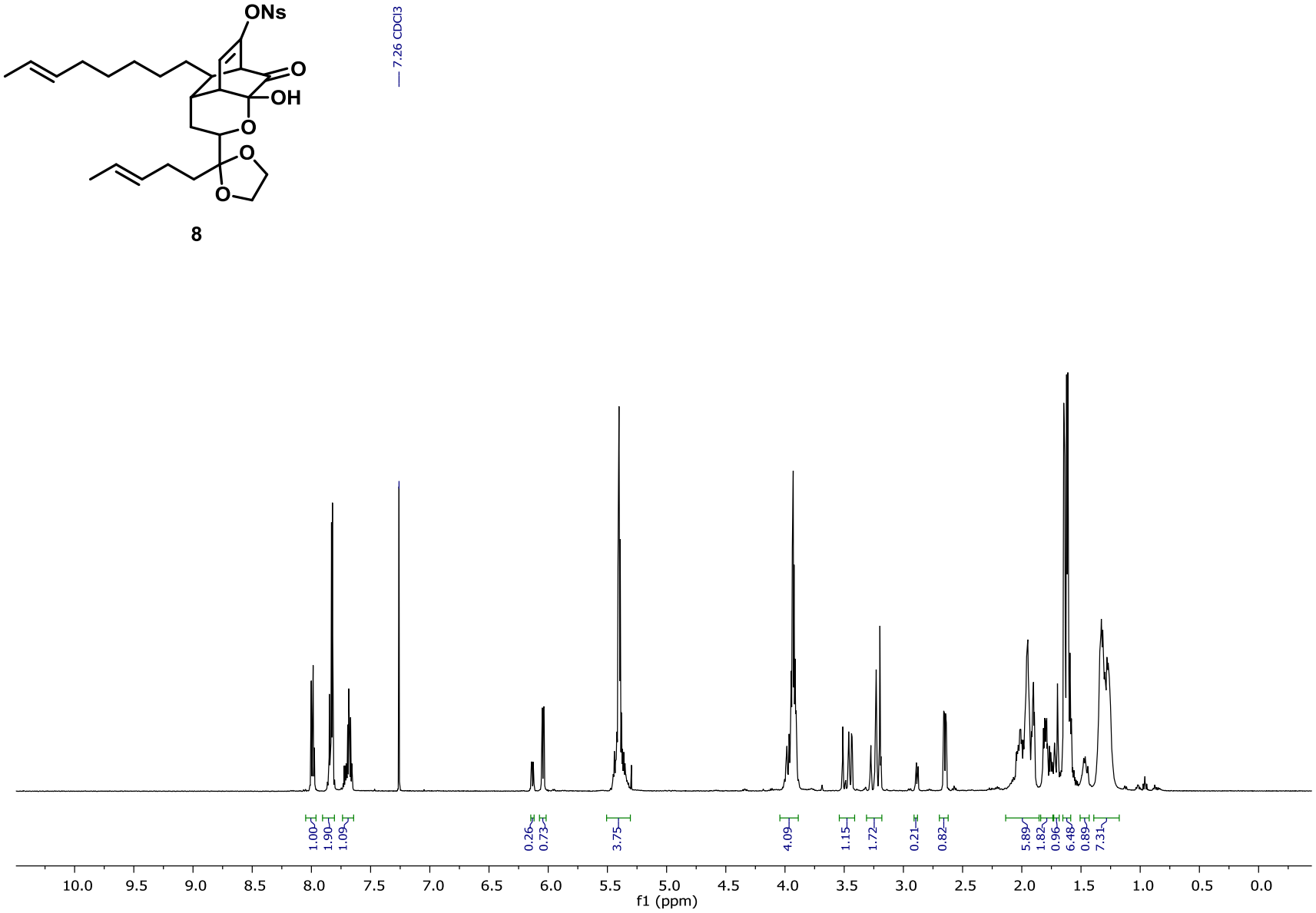


Figure 16 ^{1}H-NMR (500 MHz, $CDCl_3$) for α-hydroxy ketone **8**

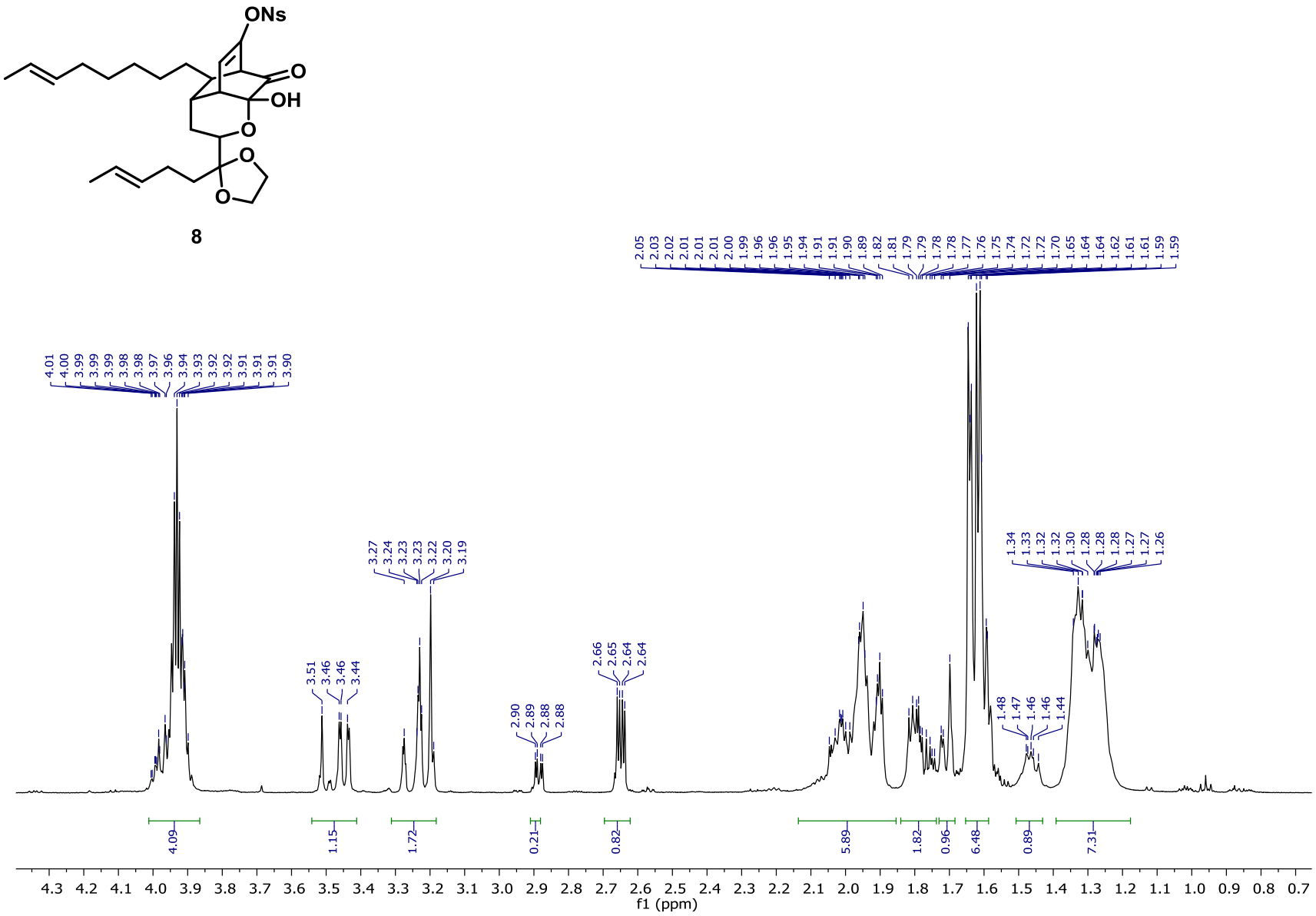


Figure 17 ^{1}H-NMR (500 MHz, $CDCl_3$) for α-hydroxy ketone **8** (inset)

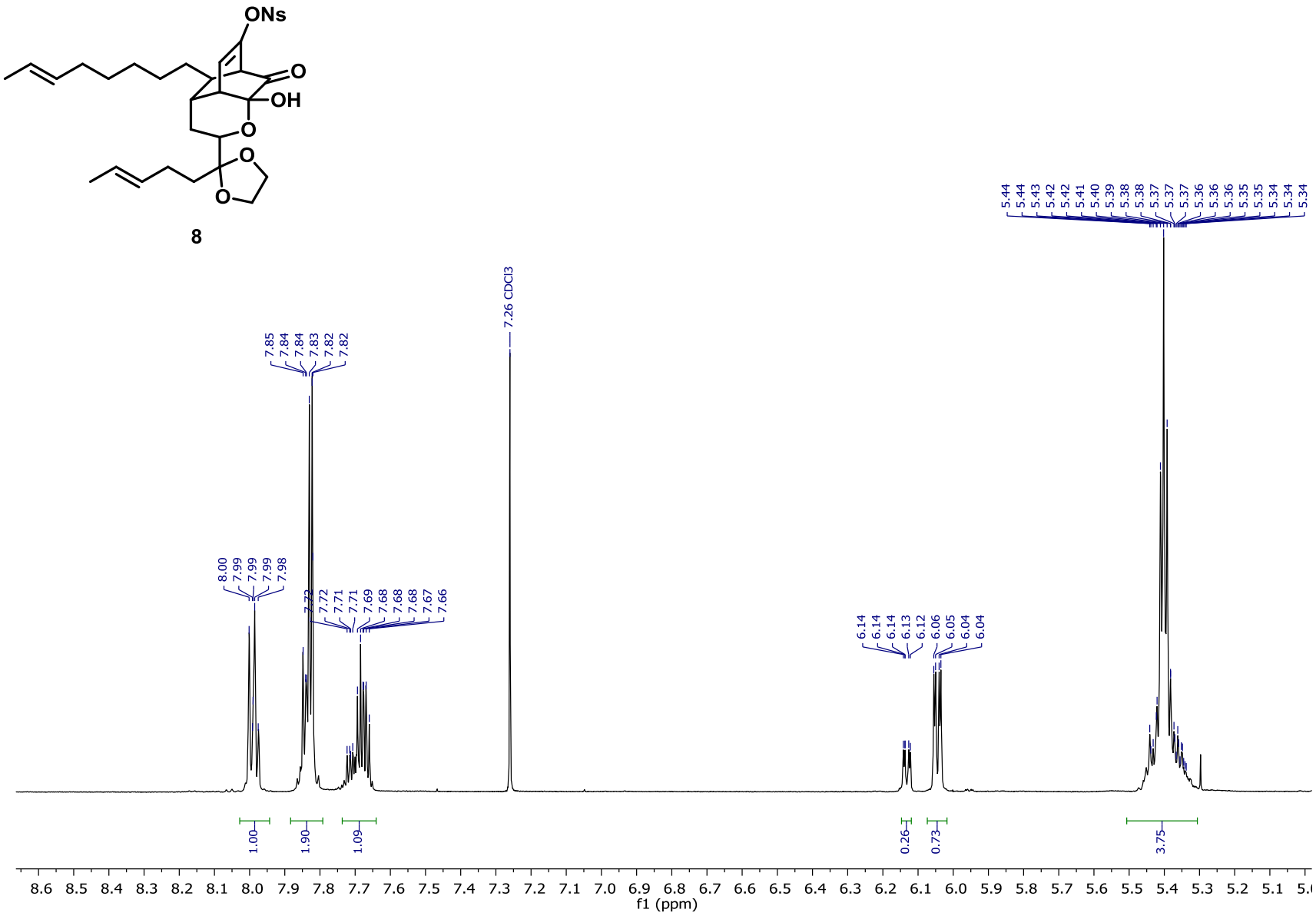


Figure 18 ^{1}H-NMR (500 MHz, $CDCl_3$) for α-hydroxy ketone **8** (inset)

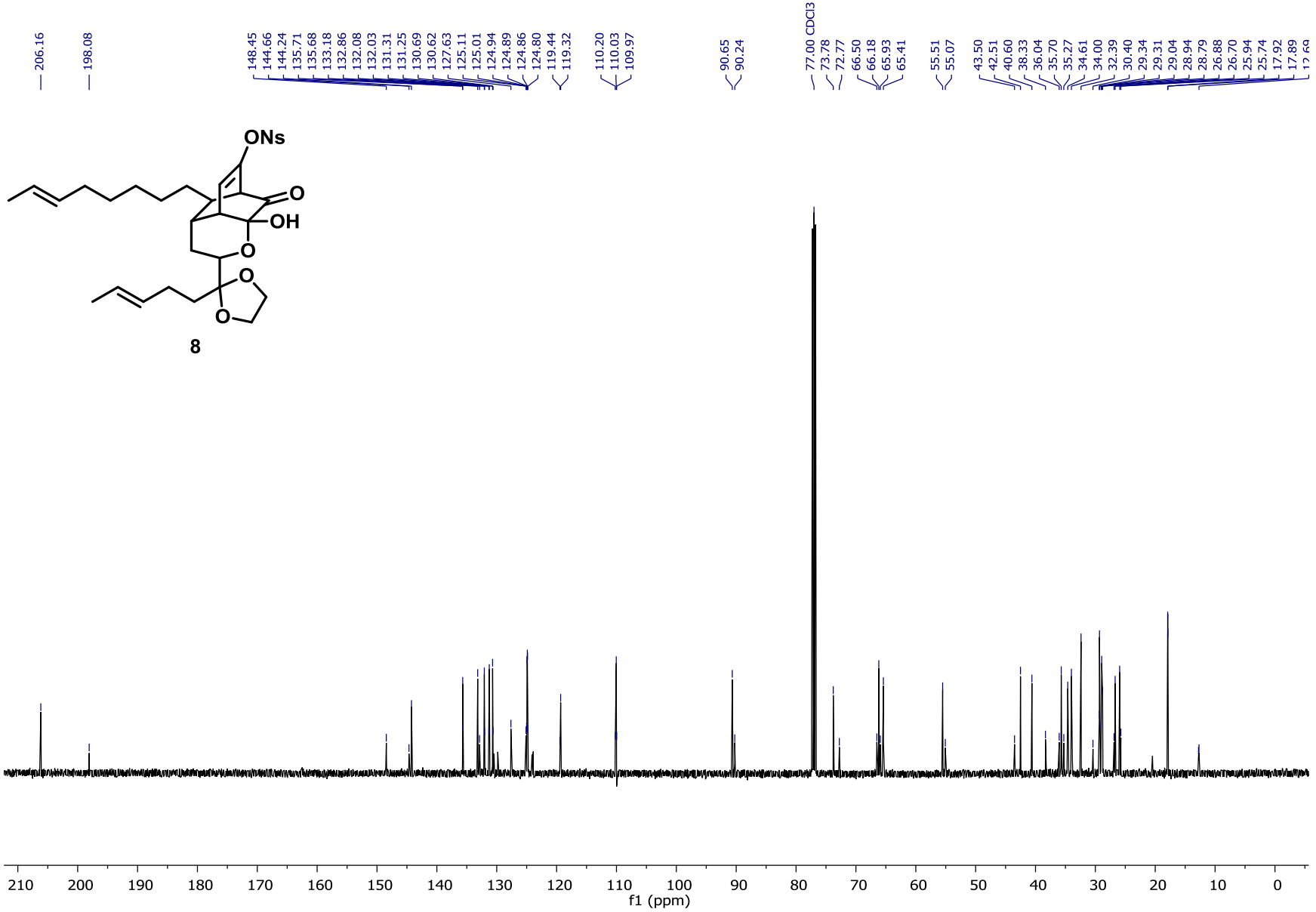


Figure 19 ^{13}C-NMR (125 MHz, $CDCl_3$) for α-hydroxy ketone **8**

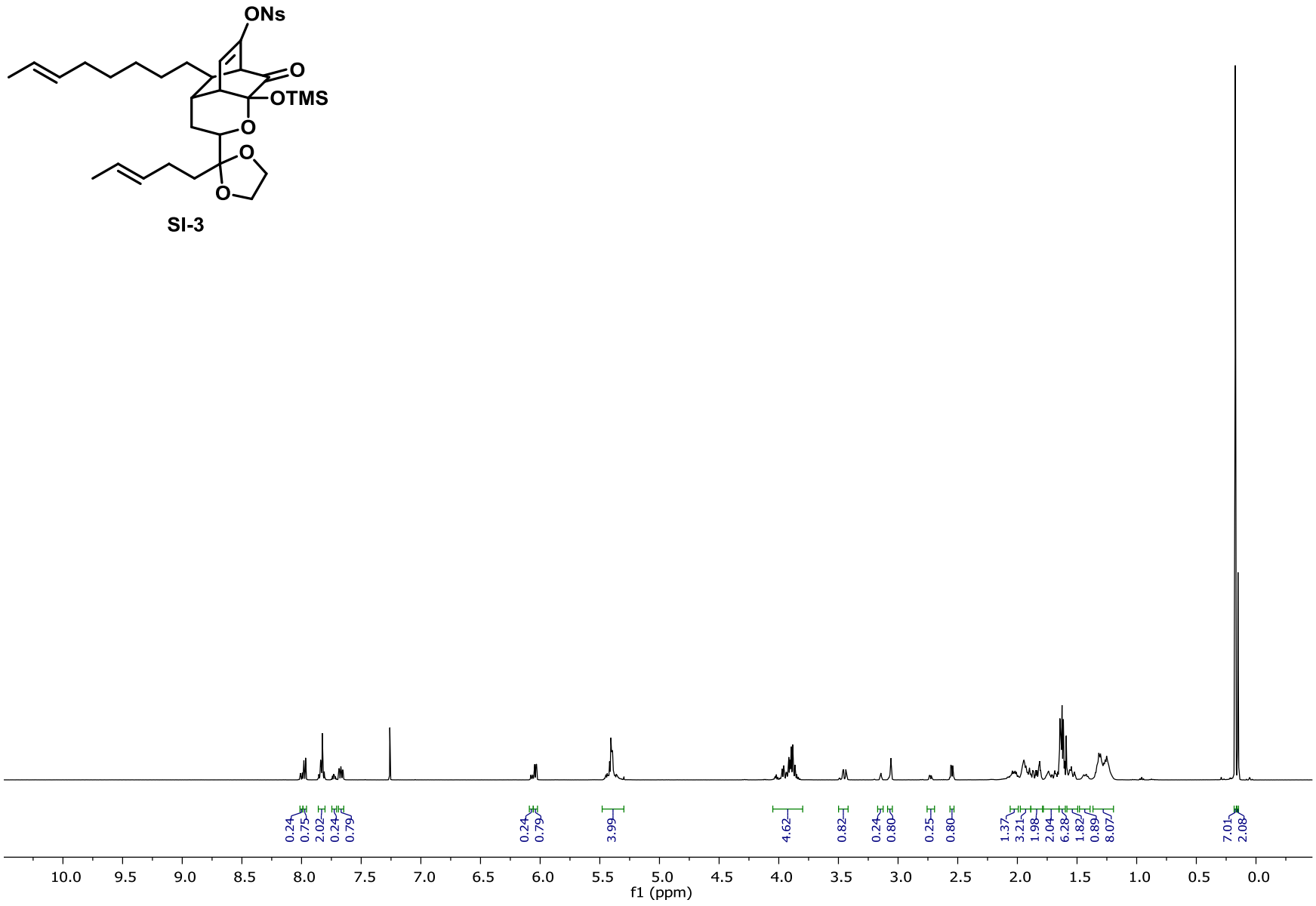


Figure 20 ^{1}H-NMR (500 MHz, $CDCl_3$) for silyl ether **SI-3**

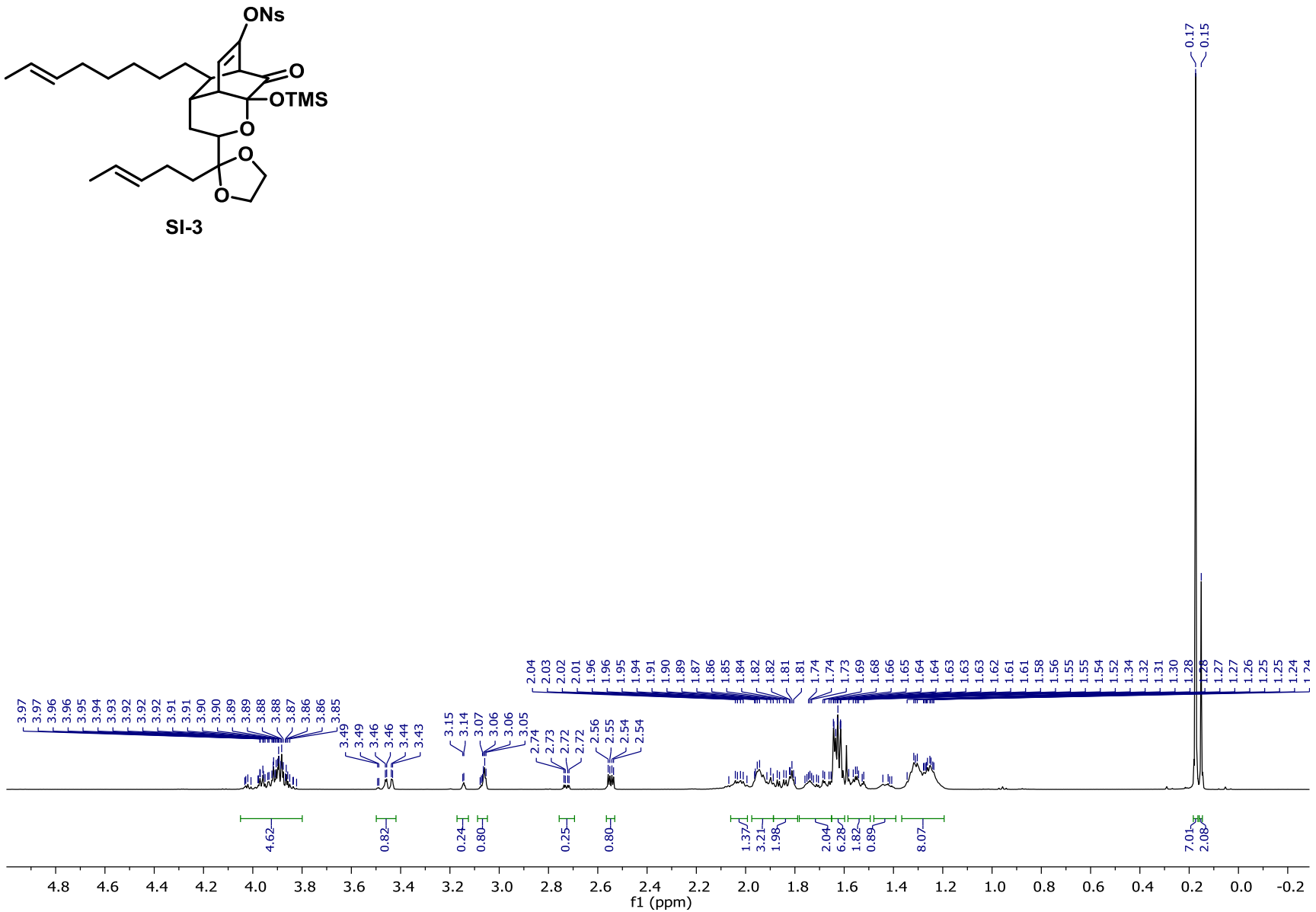
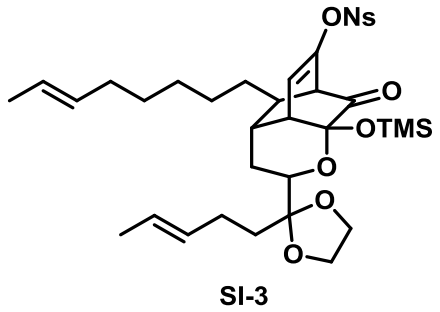


Figure 21 ^{1}H-NMR (500 MHz, $CDCl_3$) for silyl ether **SI-3** (inset)



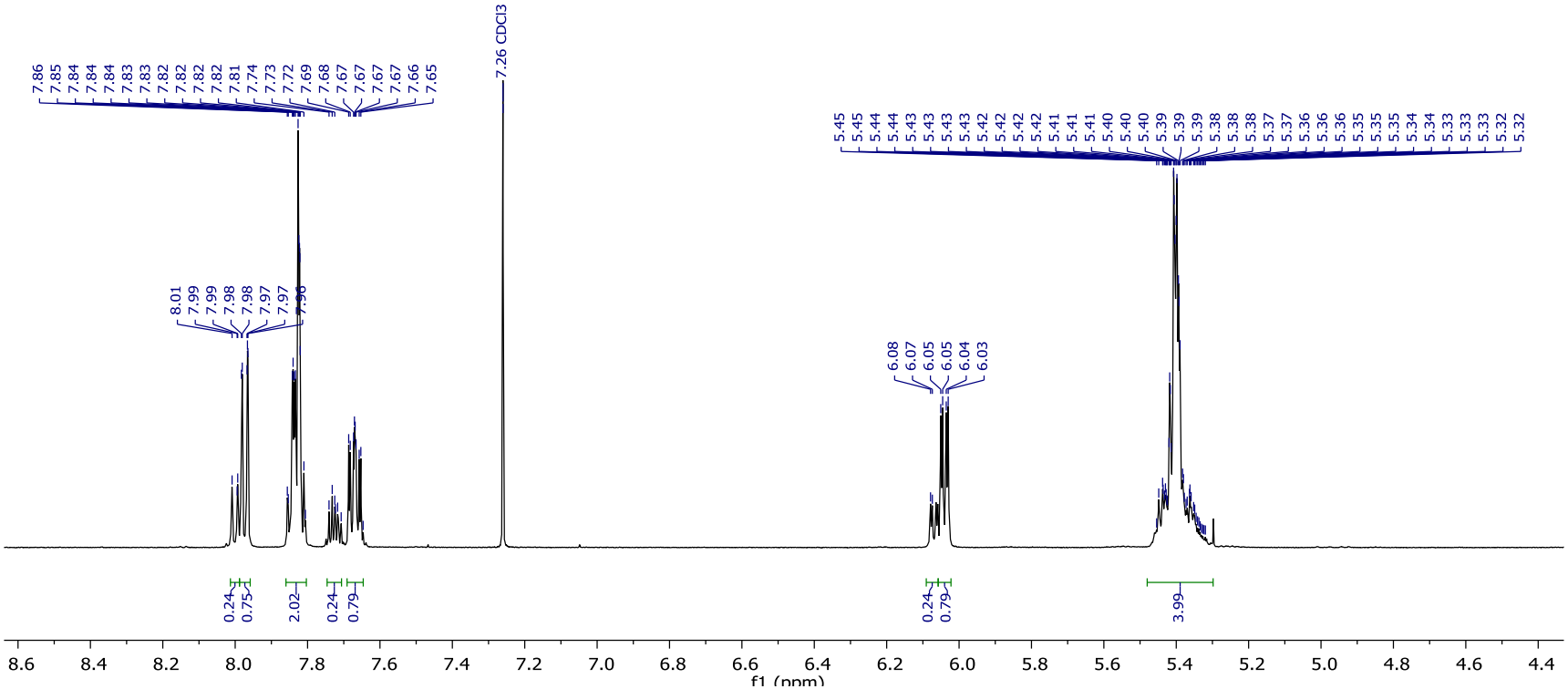


Figure 22 ^{1}H-NMR (500 MHz, $CDCl_3$) for silyl ether **SI-3** (inset)

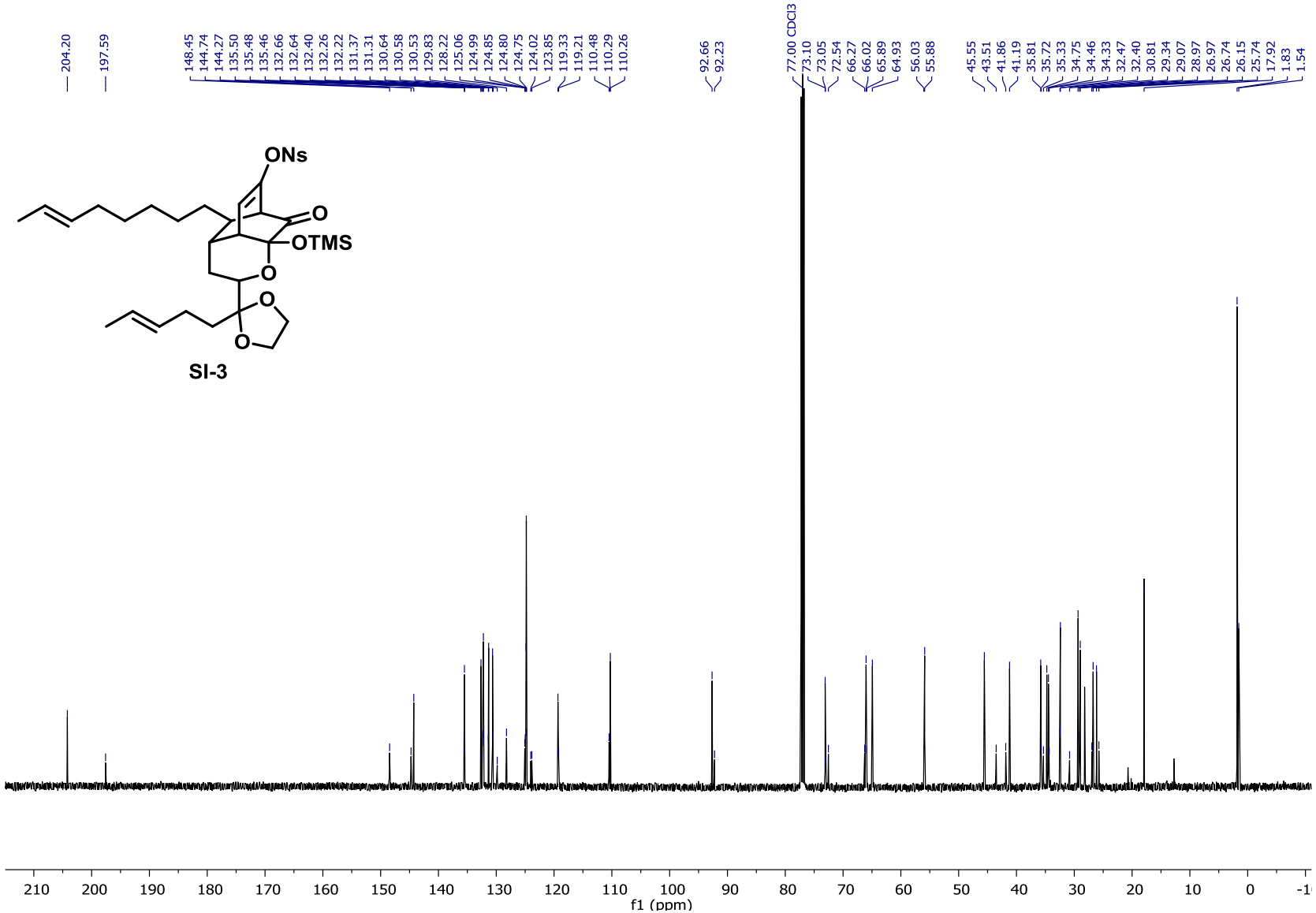


Figure 23 ^{13}C-NMR (125 MHz, $CDCl_3$) for silyl ether **SI-3**

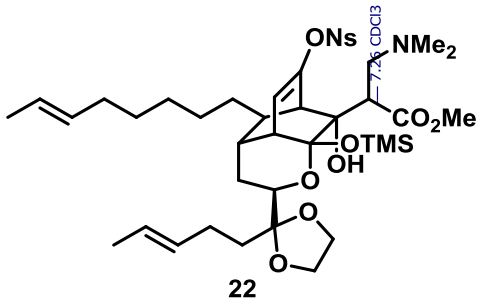


Figure 24 ^{1}H-NMR (500 MHz, $CDCl_3$) for amine **22**

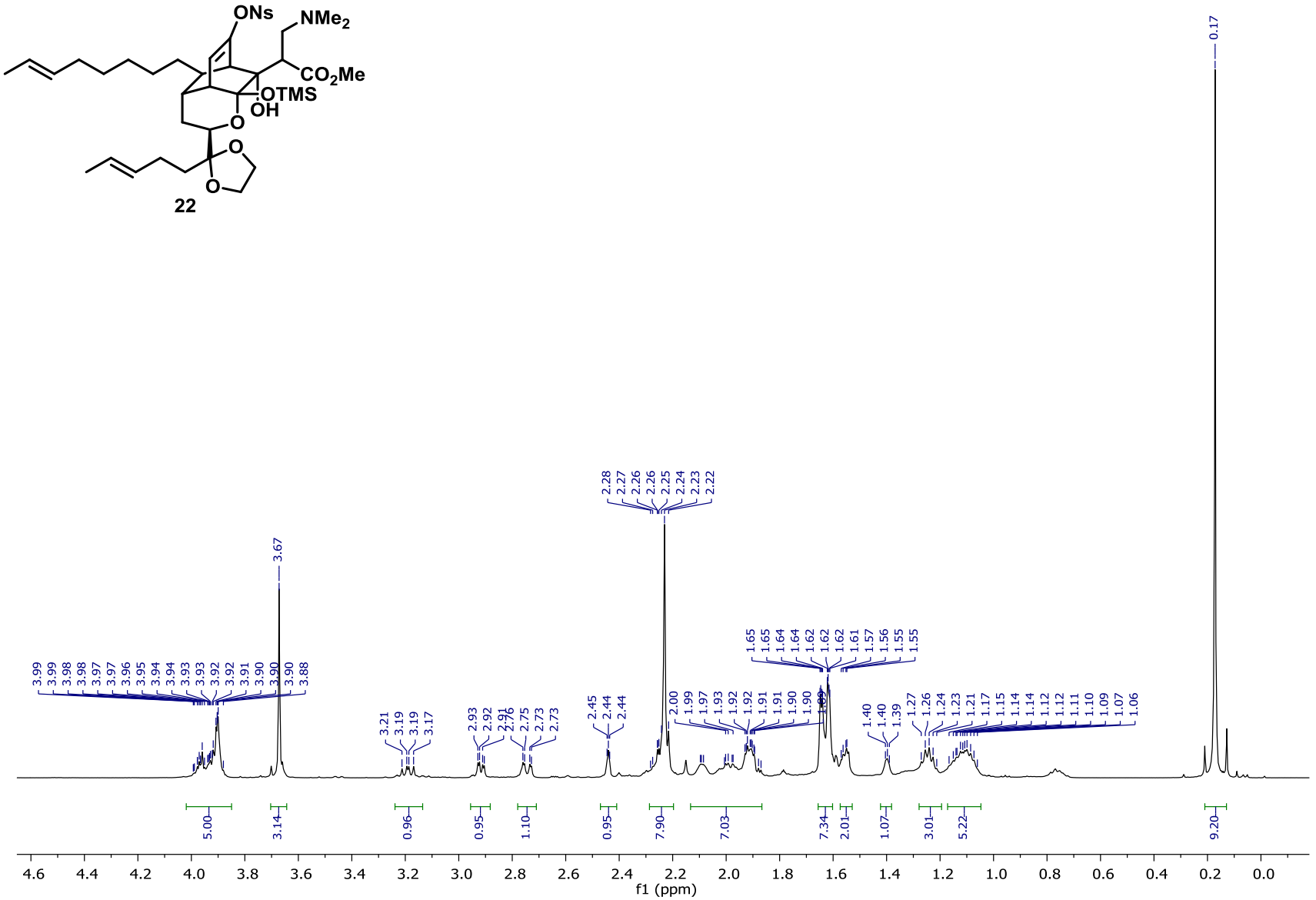
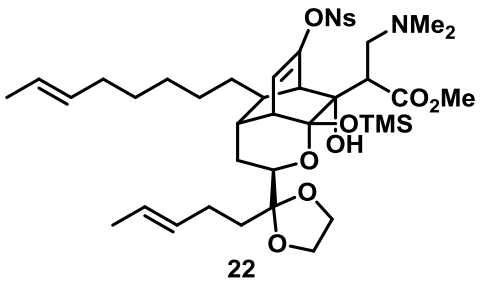


Figure 25 ^{1}H-NMR (500 MHz, $CDCl_3$) for amine **22** (inset)



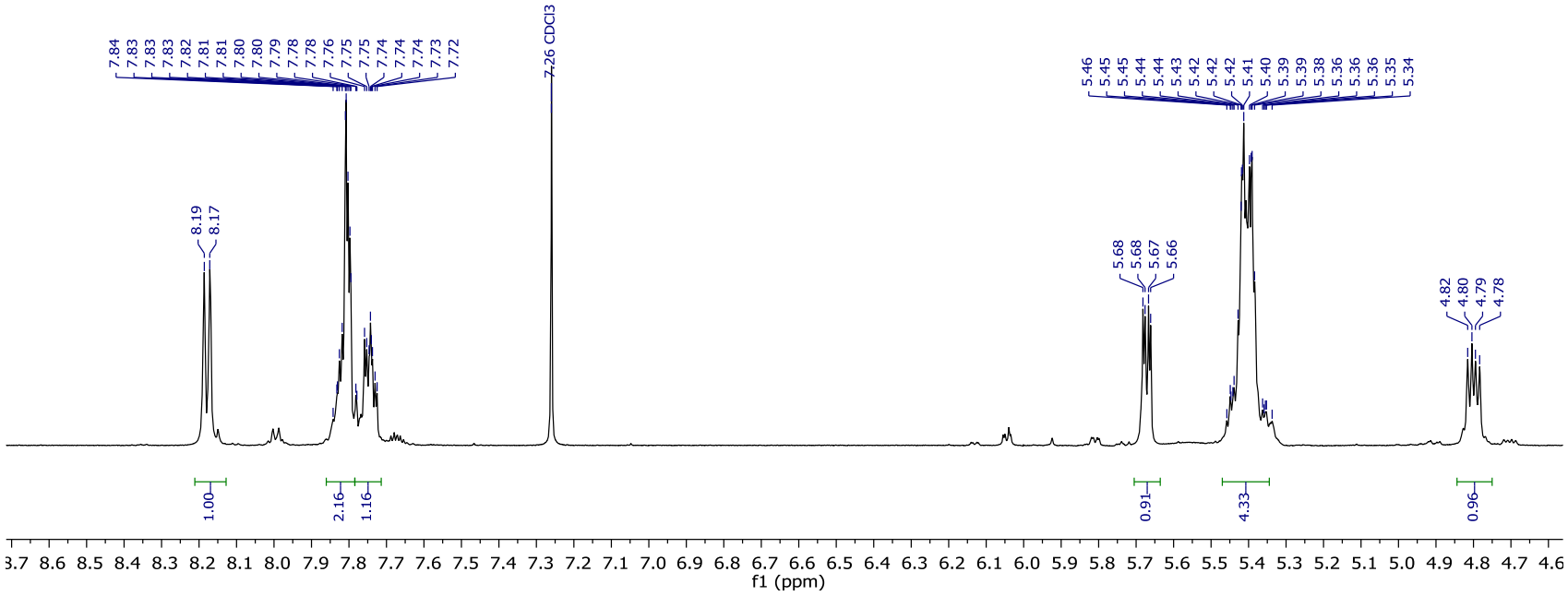


Figure 26 ^{1}H-NMR (500 MHz, $CDCl_3$) for amine **22** (inset)

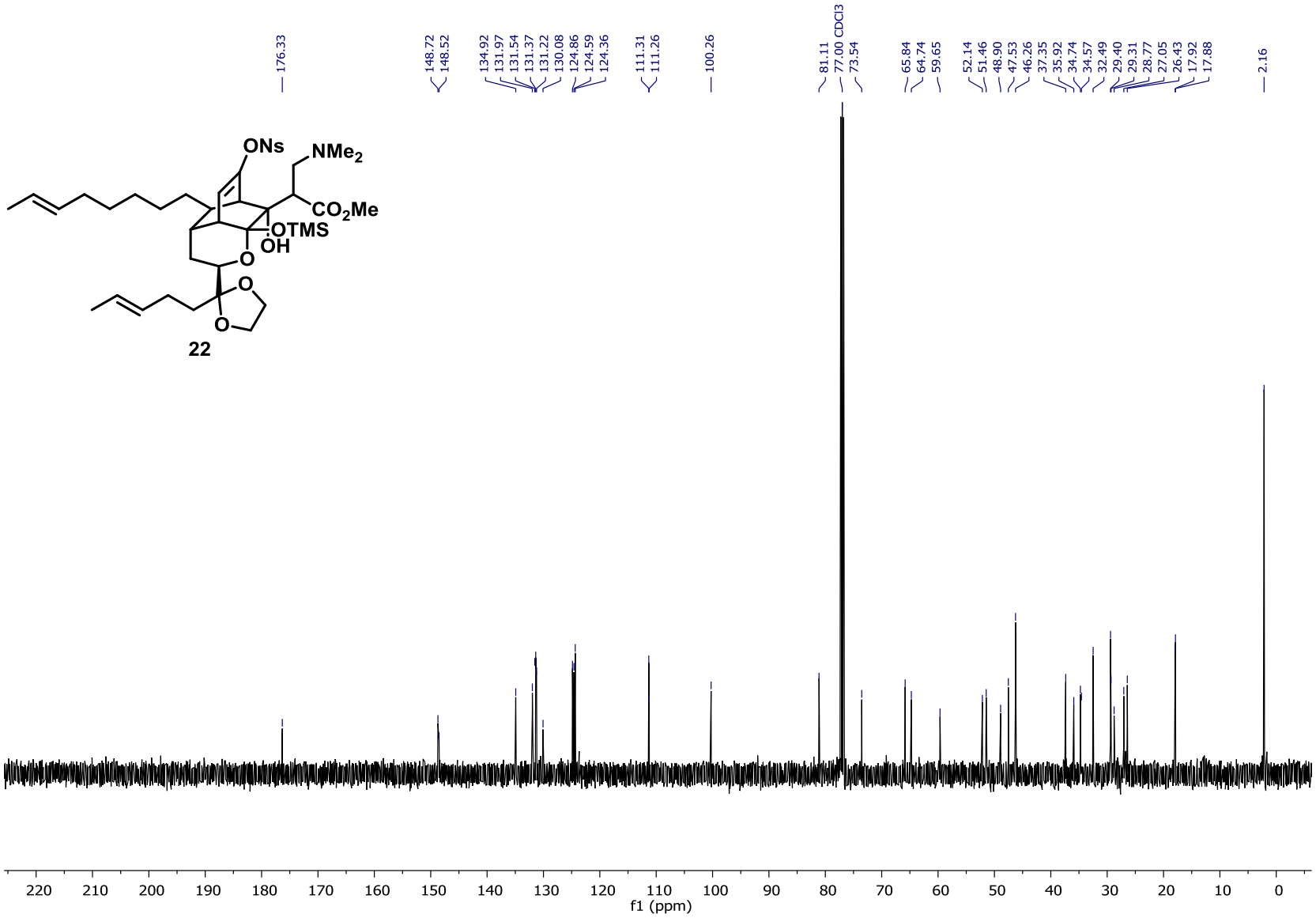


Figure 27 ^{13}C-NMR (125 MHz, $CDCl_3$) for amine **22**

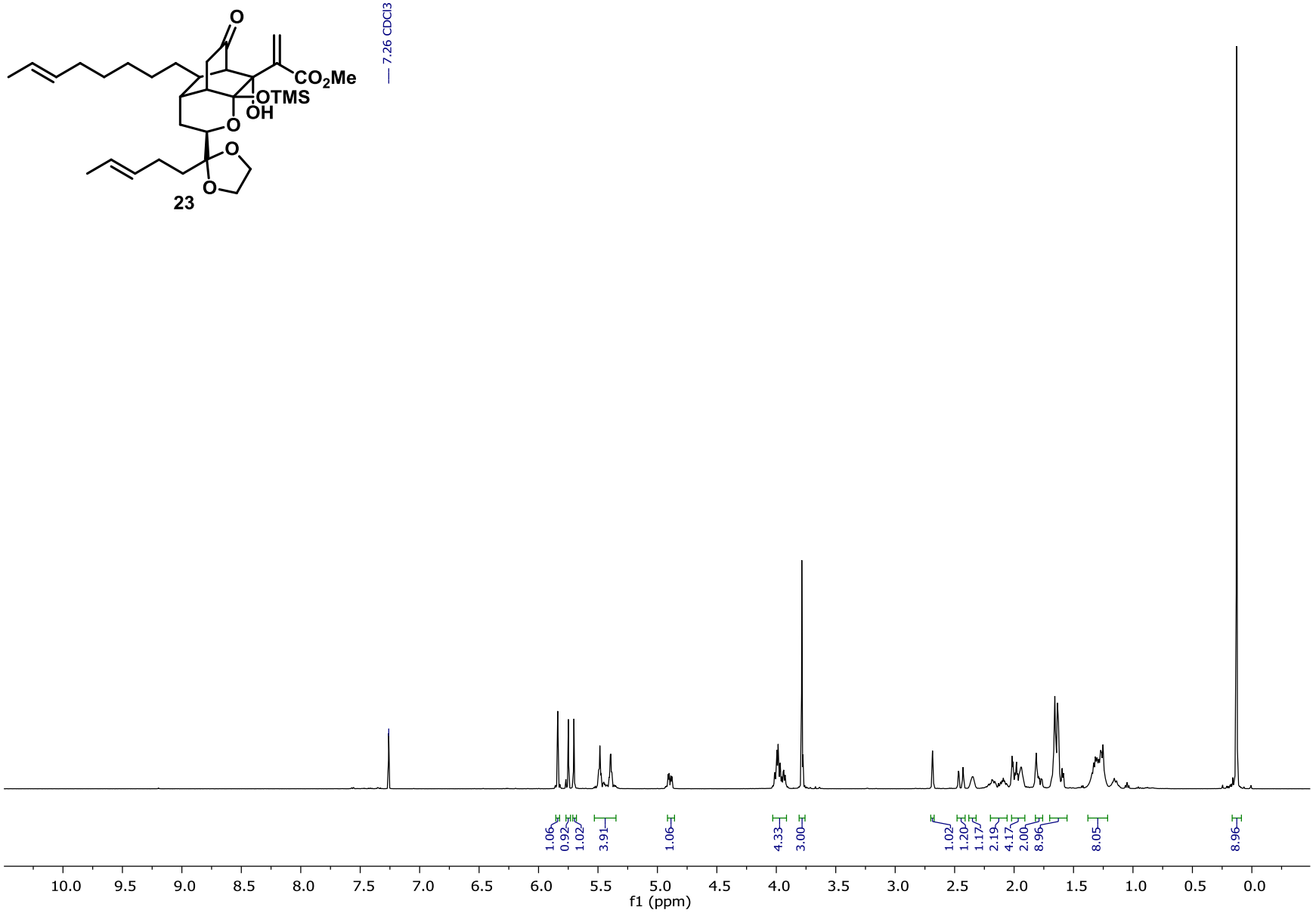


Figure 28 ^{1}H-NMR (500 MHz, $CDCl_3$) for methyl ester **23**

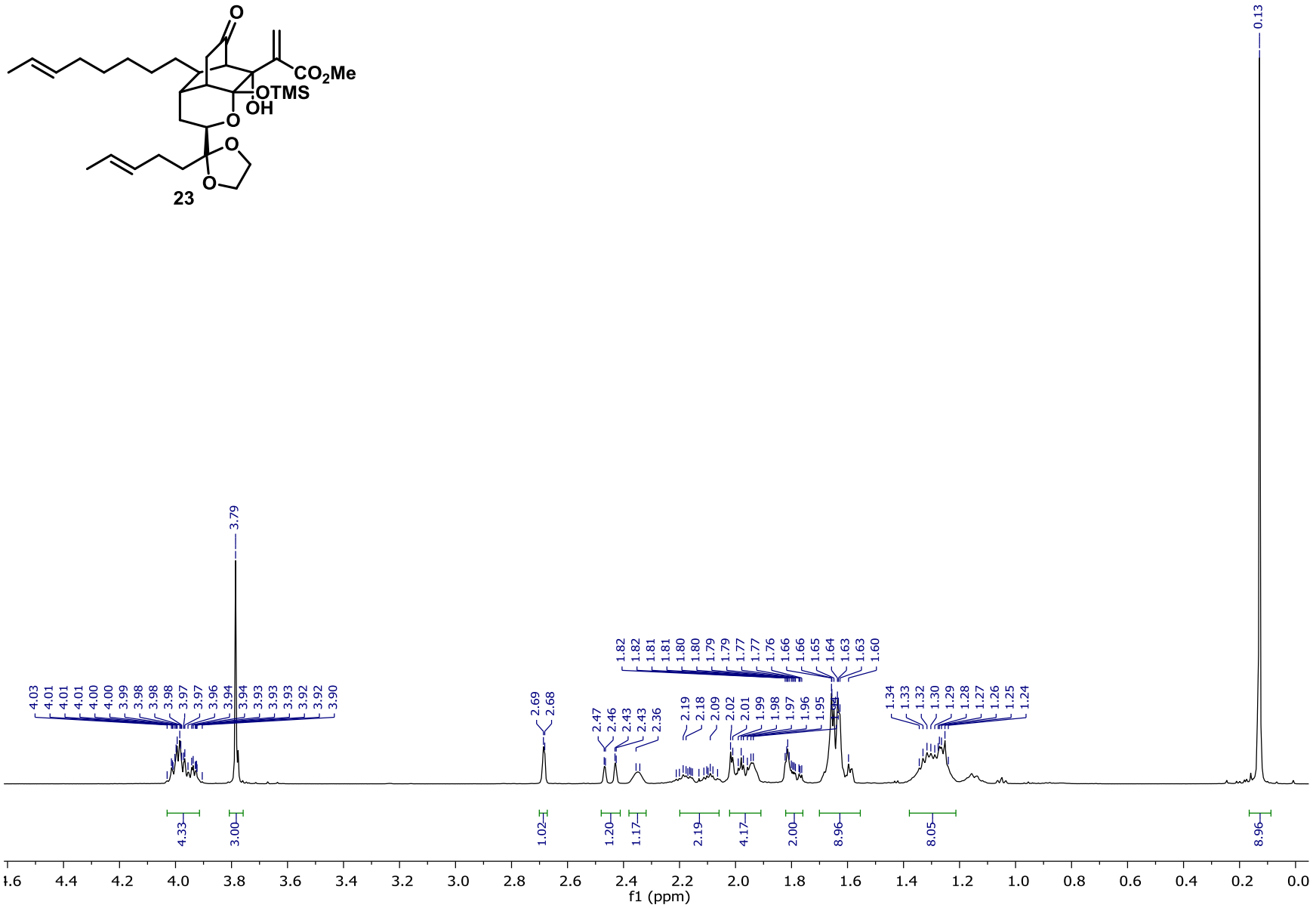


Figure 29 ^{1}H-NMR (500 MHz, $CDCl_3$) for methyl ester **23** (inset)

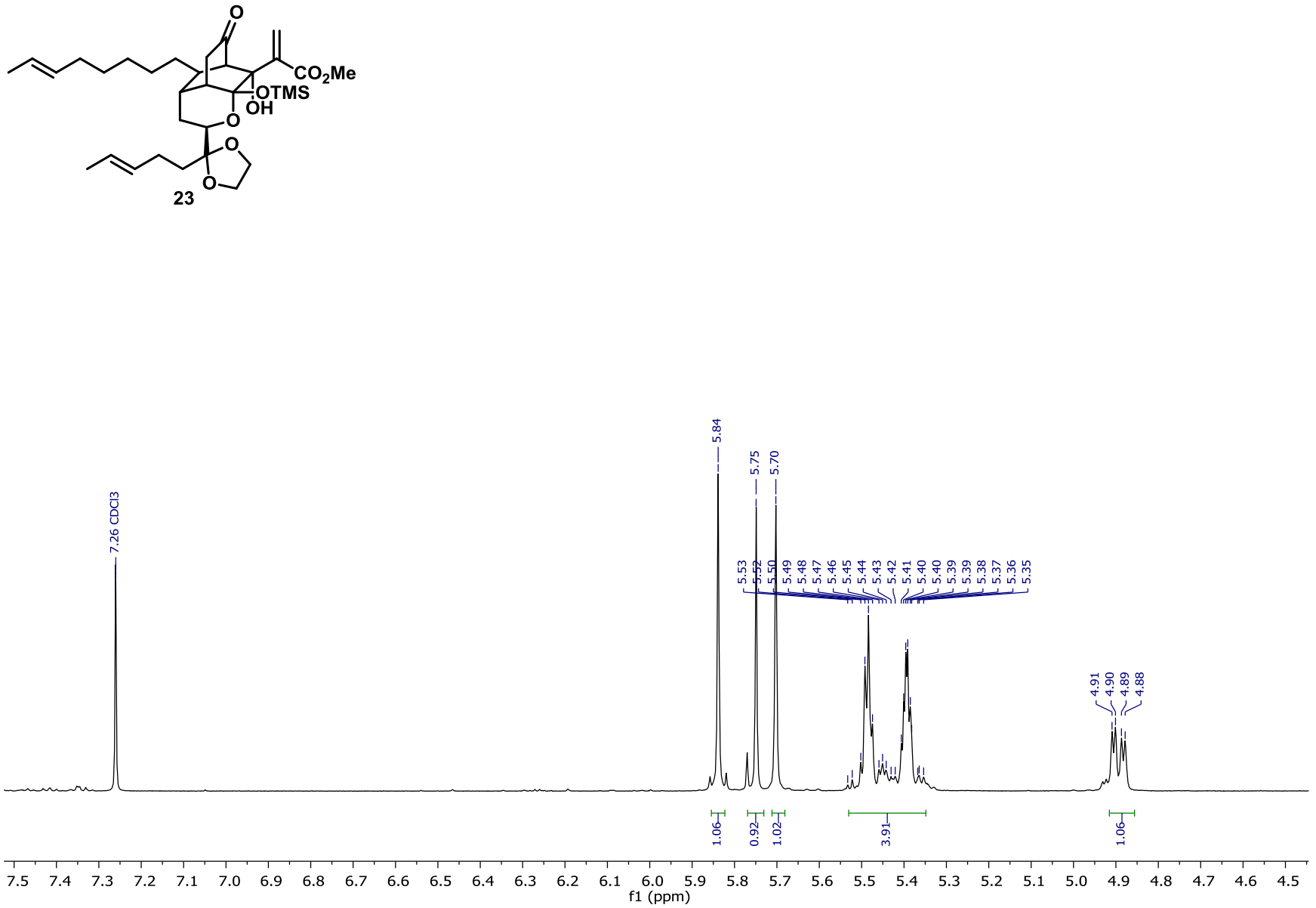
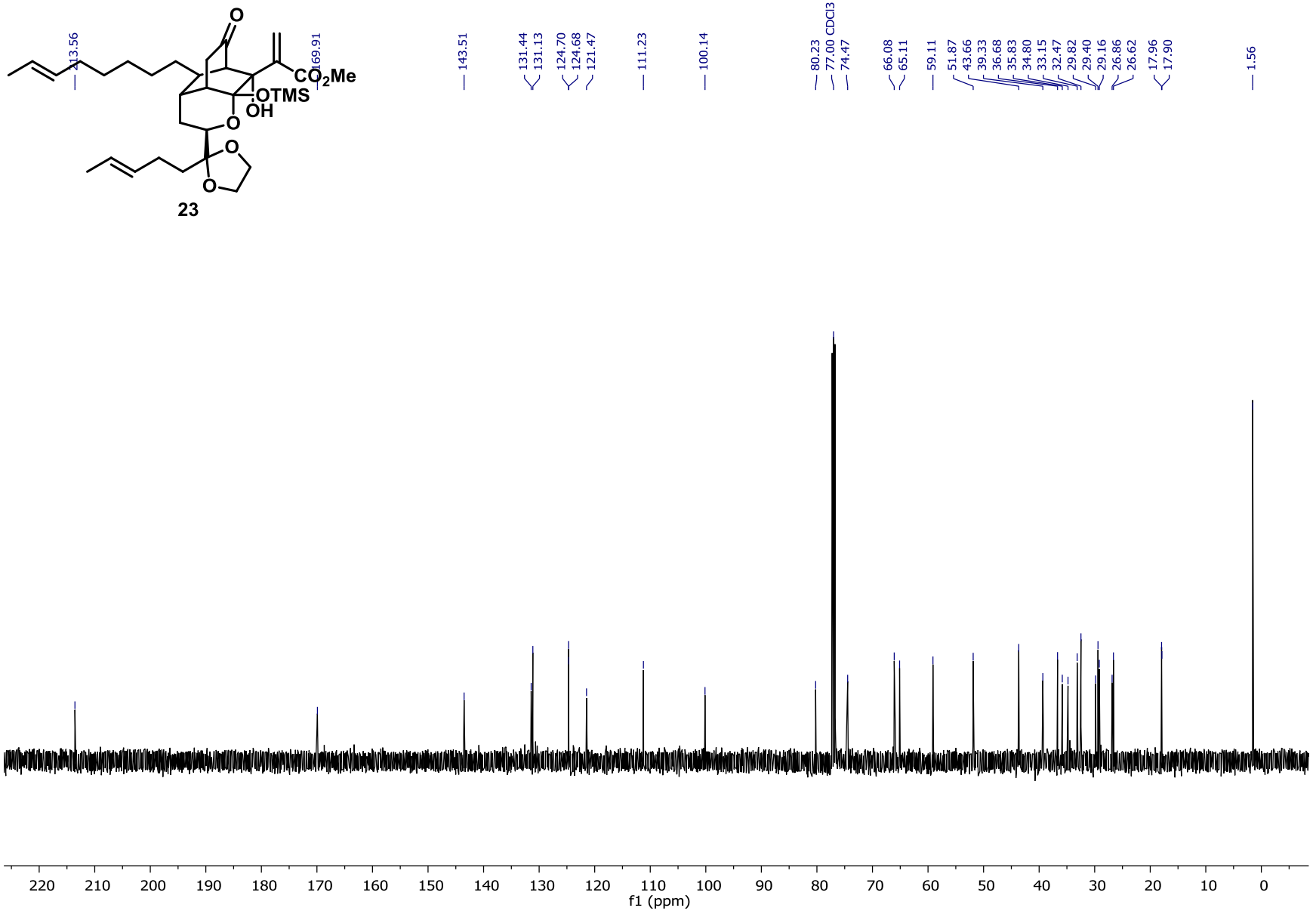


Figure 30 ^{1}H-NMR (500 MHz, $CDCl_3$) for methyl ester **23** (inset)


O
CO2Me
OTMS
OH
O
O
O
23
213.56
169.91
143.51
131.44
131.13
124.70
124.68
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111.23
100.14
80.23
77.00 CDCl3
74.47
66.08
65.11
59.11
51.87
43.66
39.33
36.68
35.83
34.80
33.15
32.47
29.82
29.40
29.16
26.86
26.62
17.96
17.90
1.56
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Figure 31 ^{13}C-NMR (125 MHz, $CDCl_3$) for methyl ester **23**

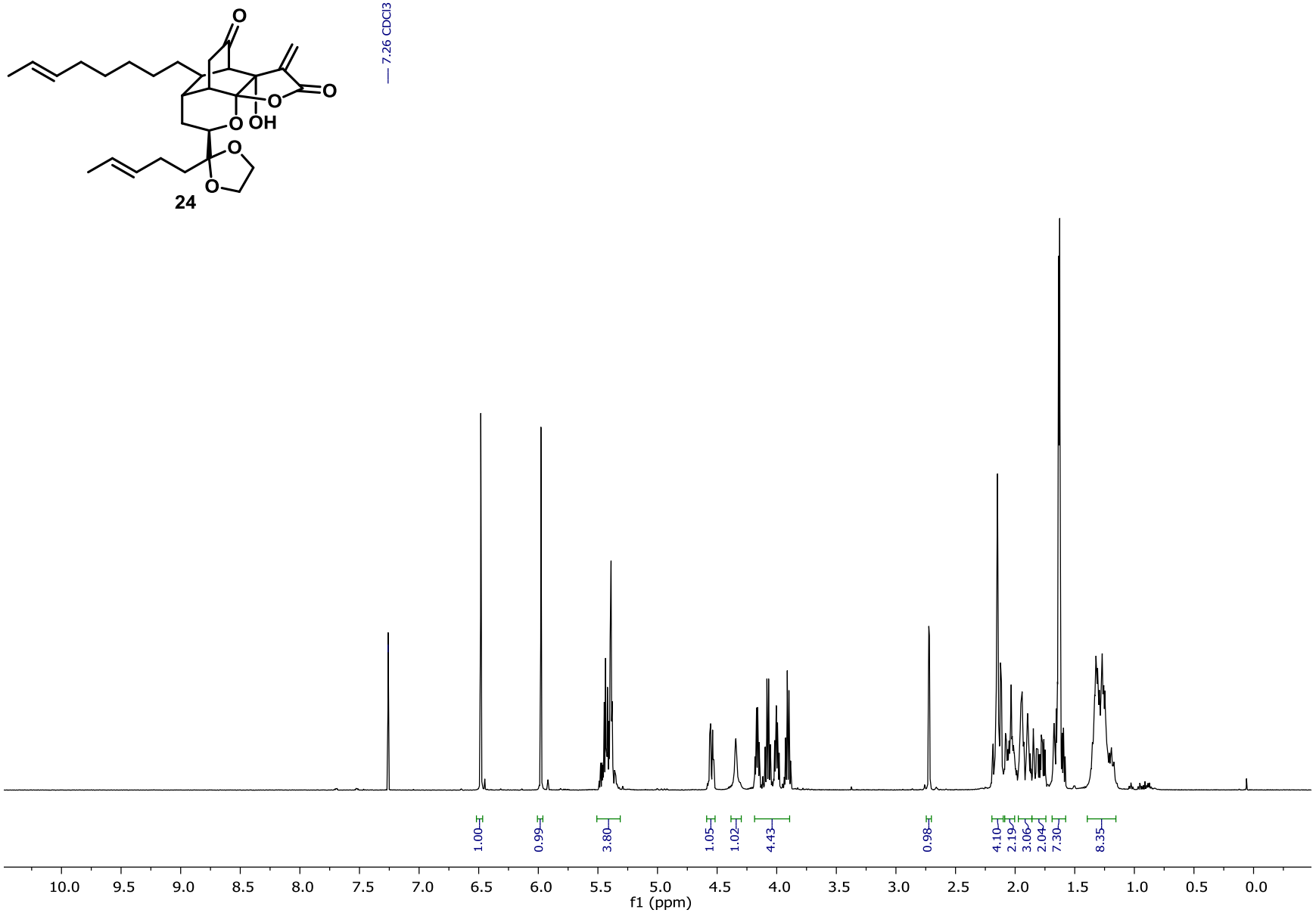


Figure 32 ^{1}H-NMR (500 MHz, $CDCl_3$) for lactone **24**

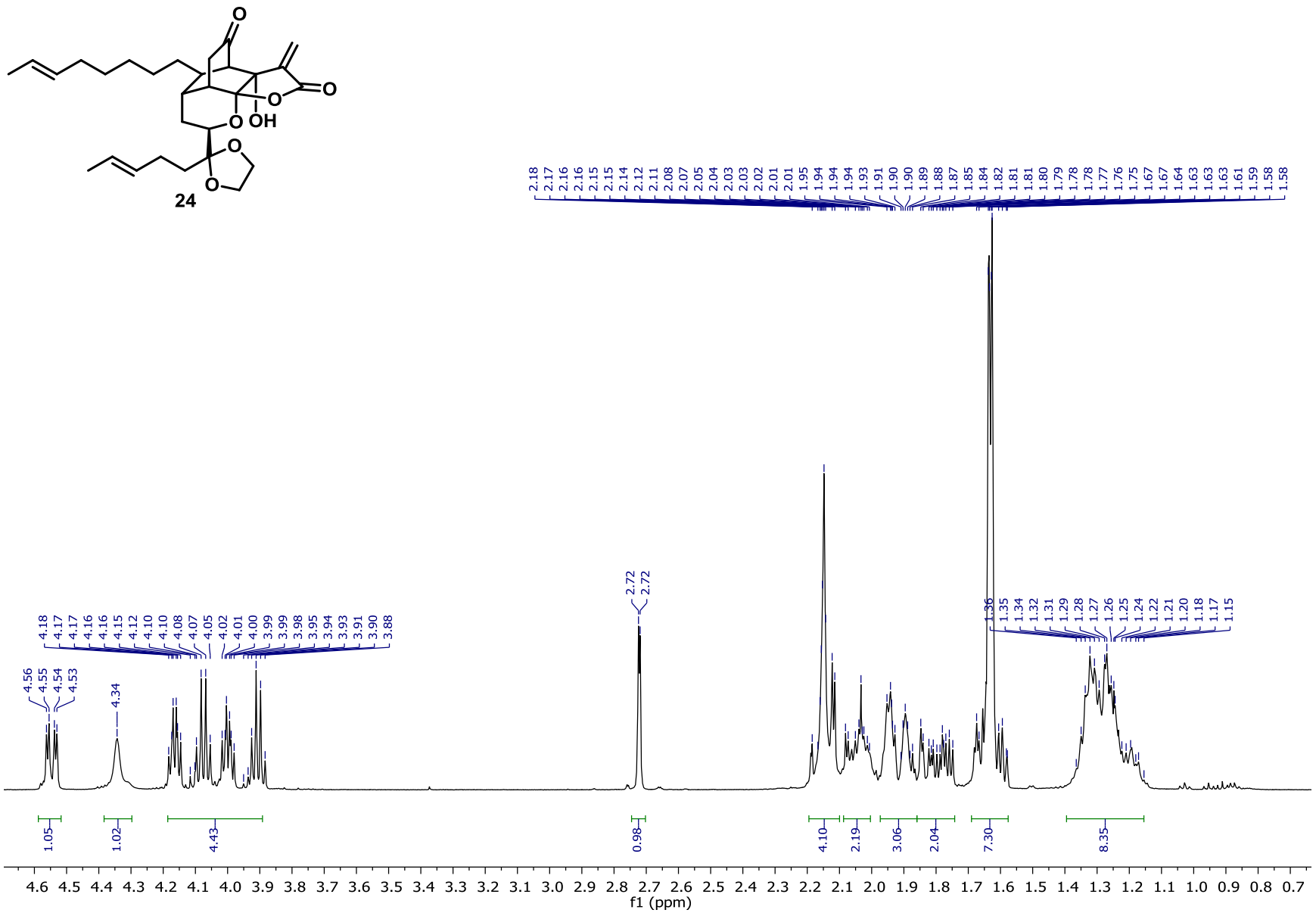
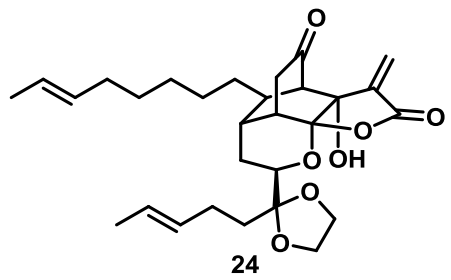


Figure 33 ^{1}H-NMR (500 MHz, $CDCl_3$) for lactone **24** (inset)


O
O
O
O OH
O
O

24

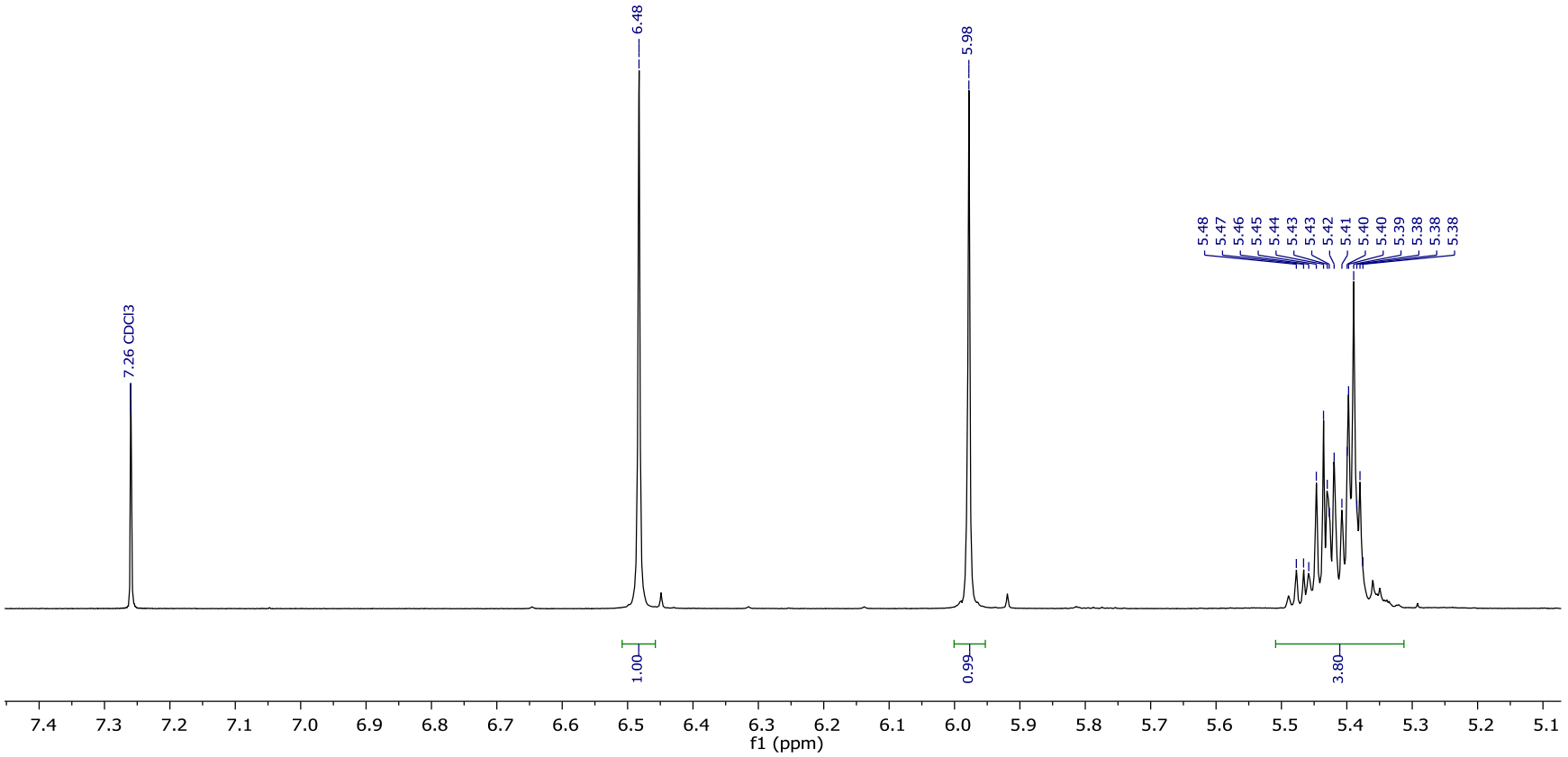

6.48
5.98
5.48
5.47
5.46
5.45
5.44
5.43
5.43
5.42
5.41
5.40
5.40
5.39
5.38
5.38
5.38
7.26 CDCl3
1.00
0.99
3.80
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
f1 (ppm)

Figure 34 ^{1}H-NMR (500 MHz, $CDCl_3$) for lactone **24** (inset)

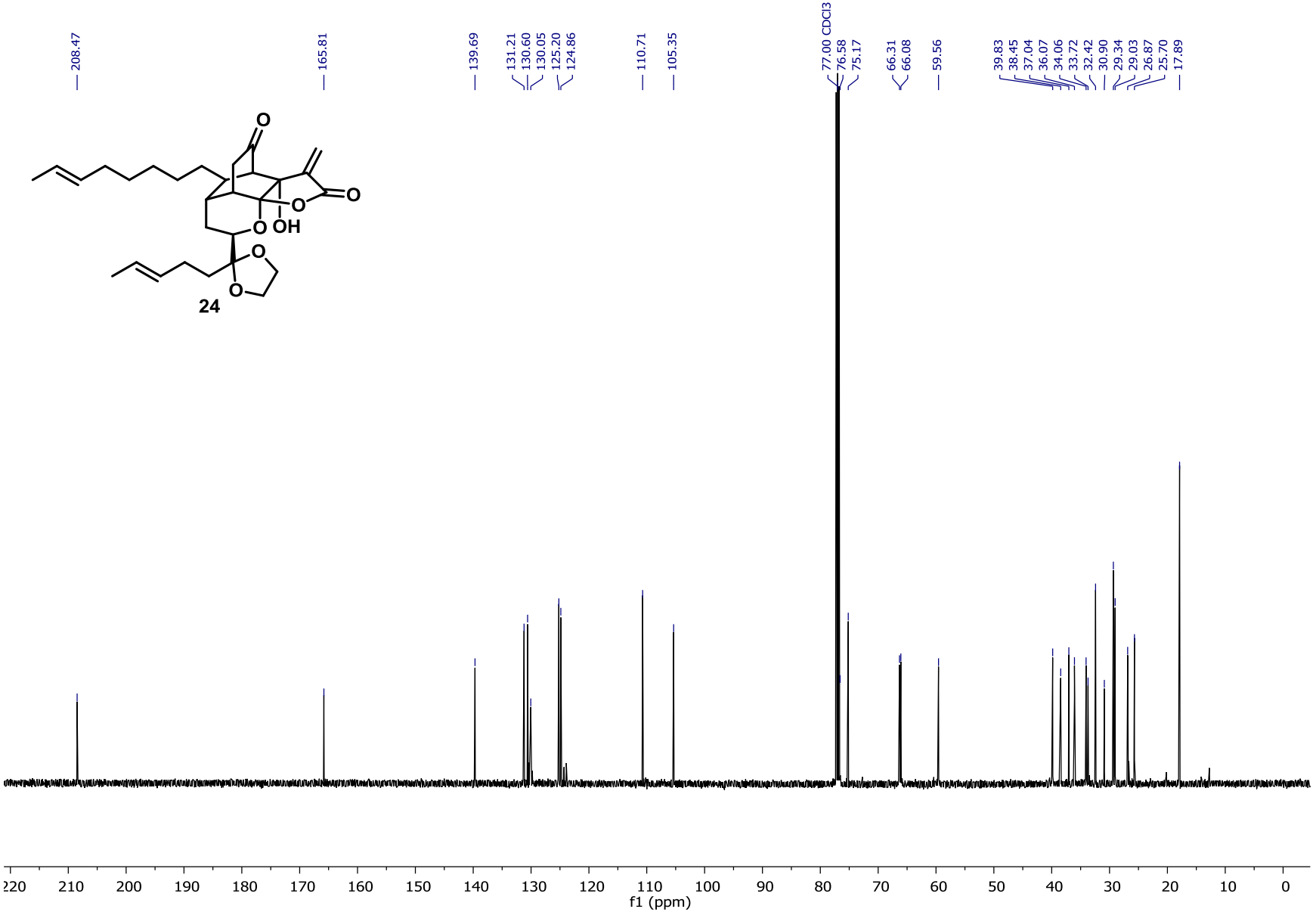


Figure 35 ^{13}C-NMR (125 MHz, $CDCl_3$) for lactone **24**

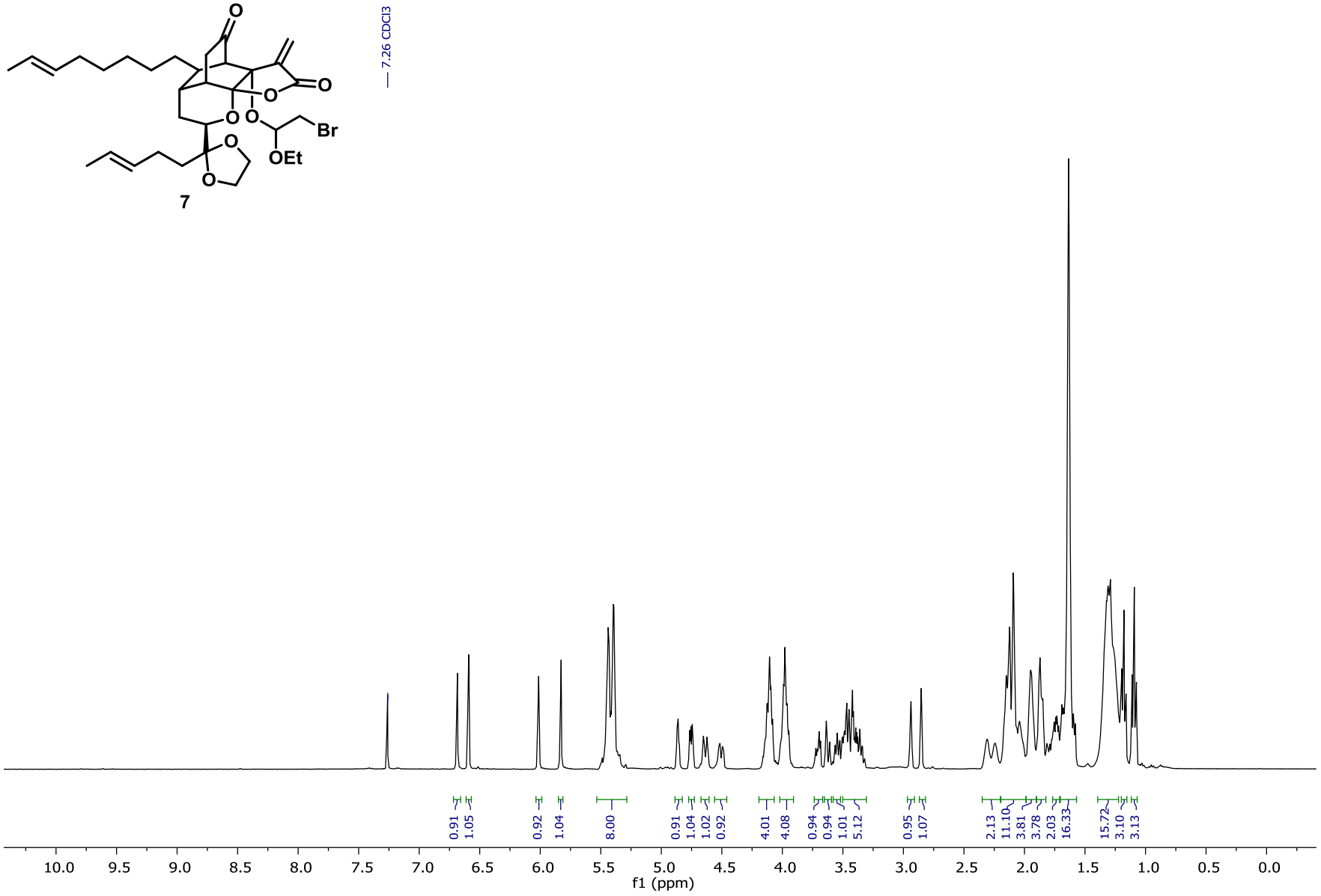


Figure 36 ^{1}H-NMR (400 MHz, $CDCl_3$) for bromoacetal **7**

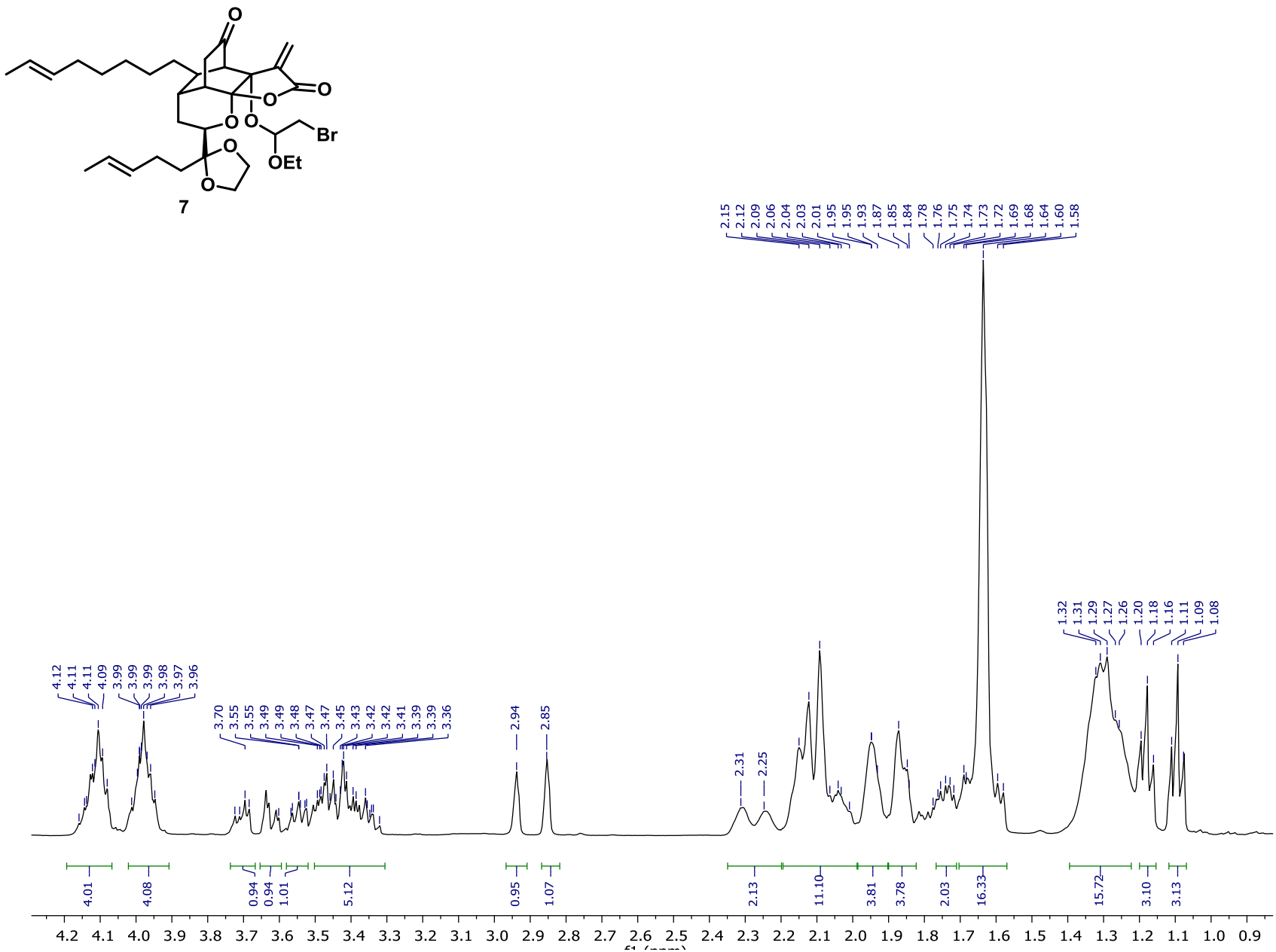
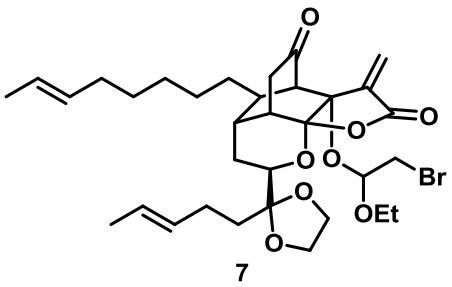


Figure 37 ^{1}H-NMR (400 MHz, $CDCl_3$) for bromoacetal **7** (inset)



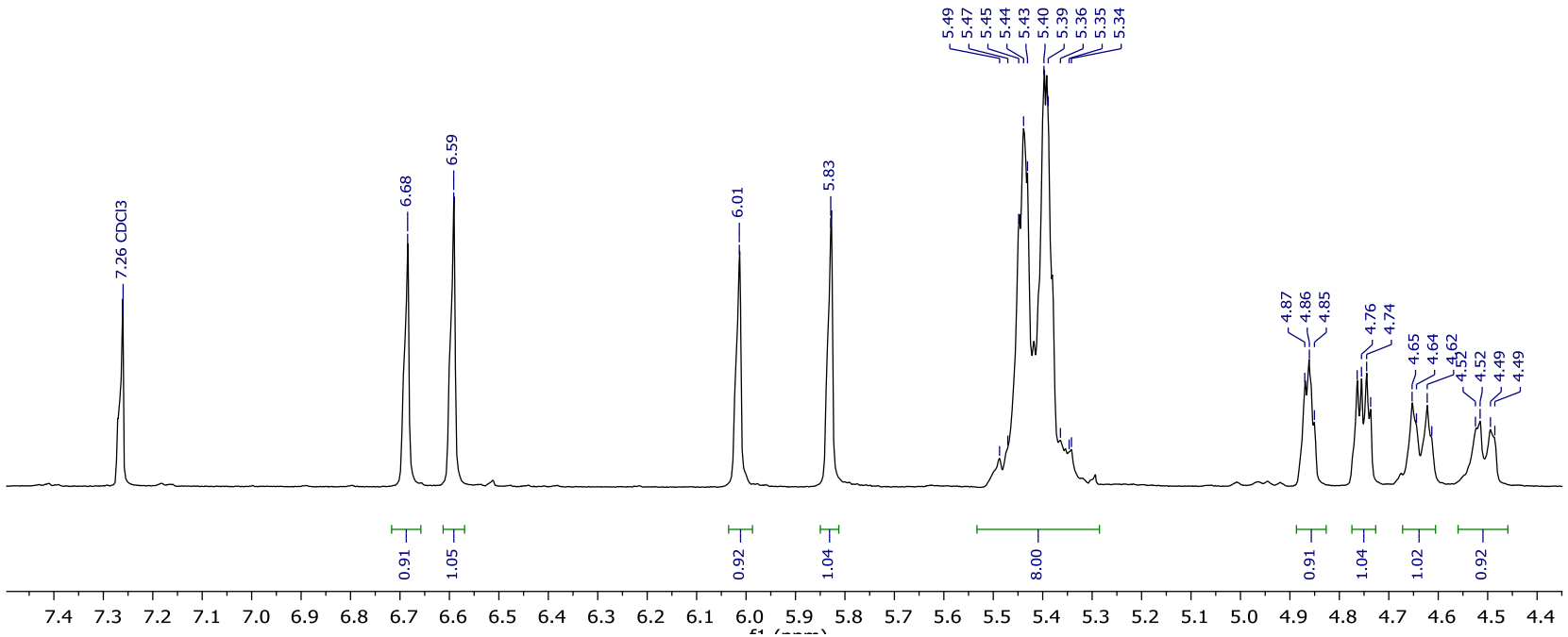


Figure 38 ^{1}H-NMR (400 MHz, $CDCl_3$) for bromoacetal **7** (inset)

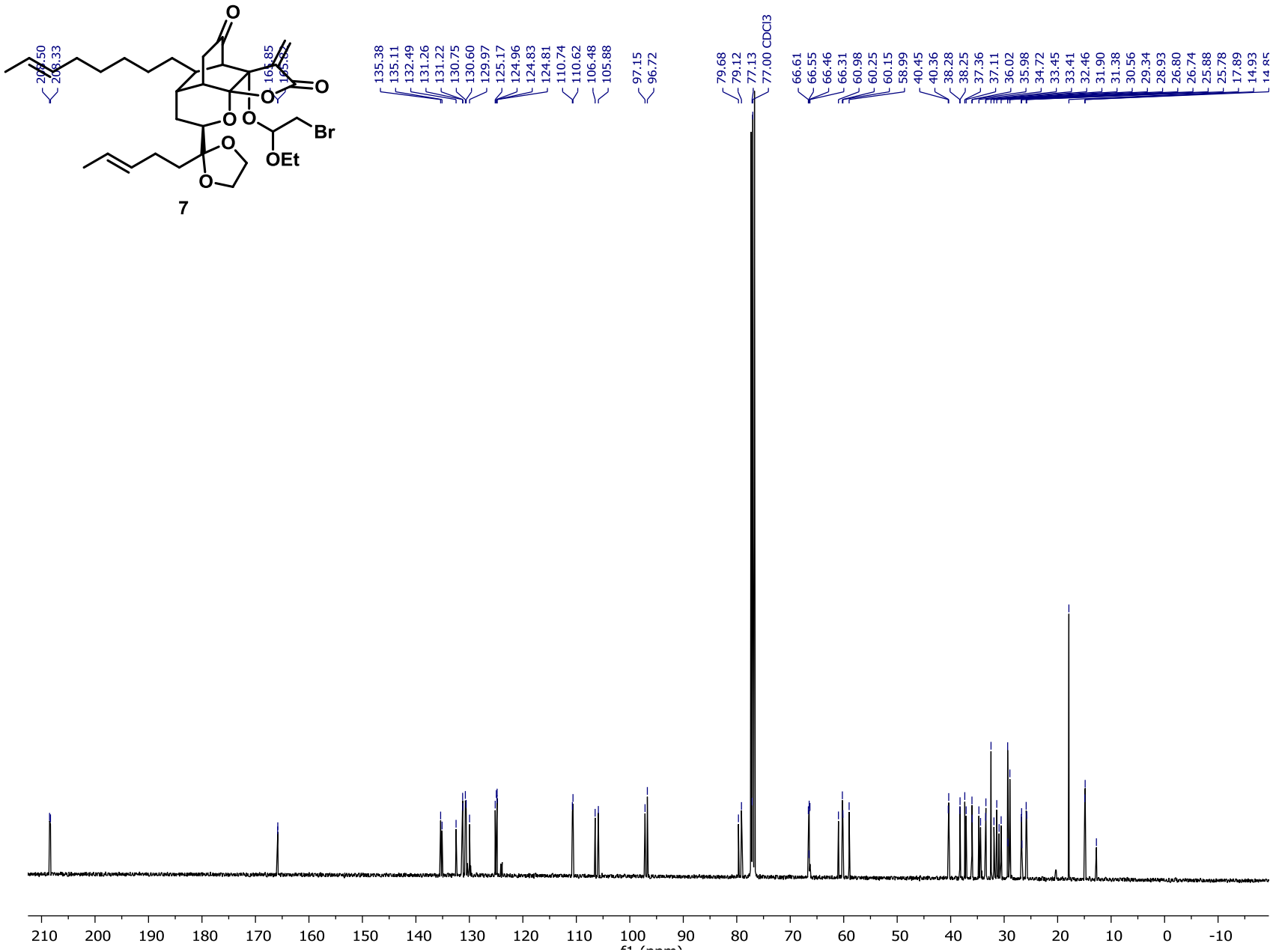
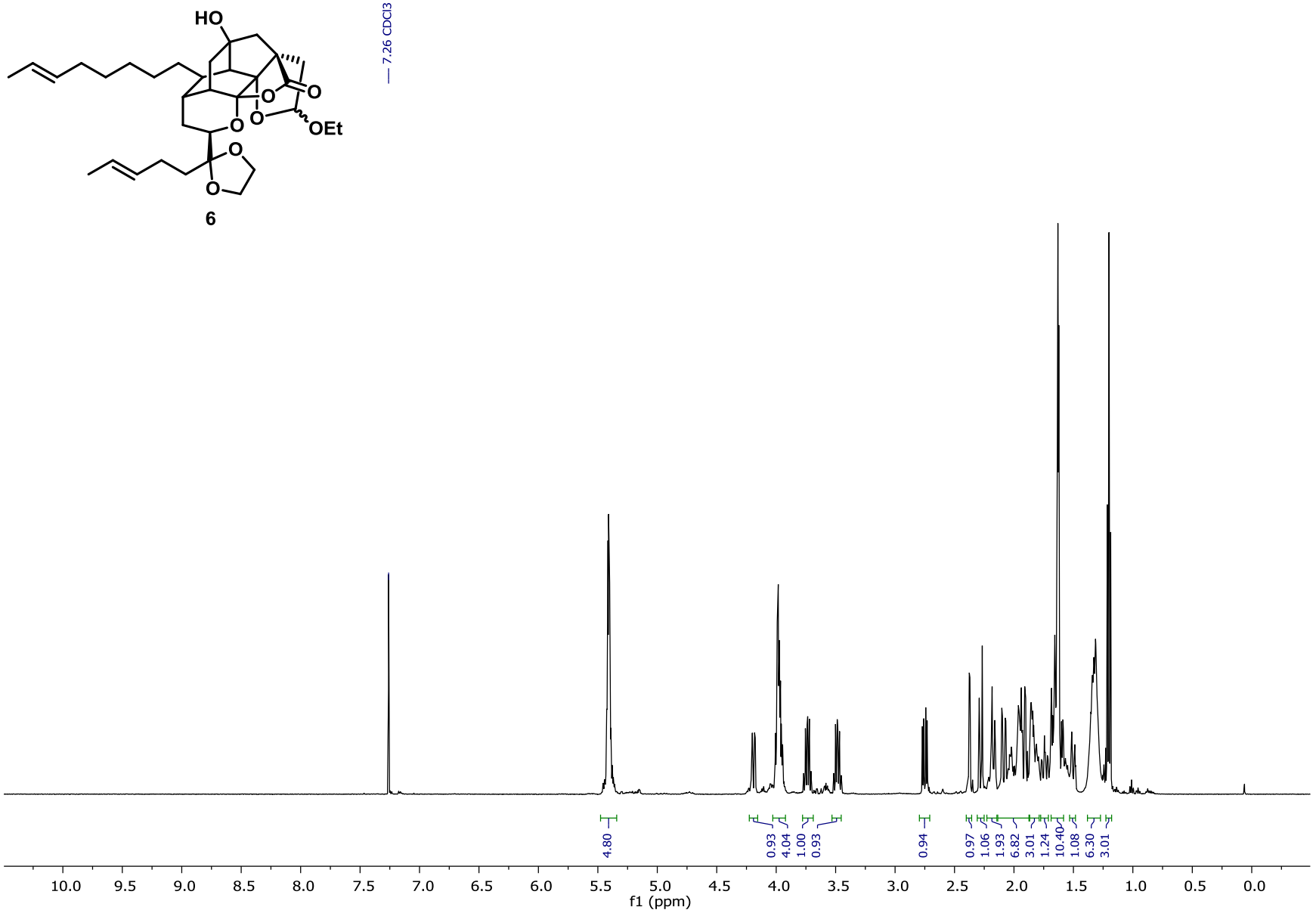


Figure 39 ^{13}C-NMR (100 MHz, $CDCl_3$) for bromoacetal **7**


HO
O
O
O
O
O
OEt
O
O
6
7.26 CDCl3
4.80
0.93
4.04
1.00
0.93
0.94
0.97
1.06
1.93
6.82
3.01
1.24
10.40
1.08
6.30
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

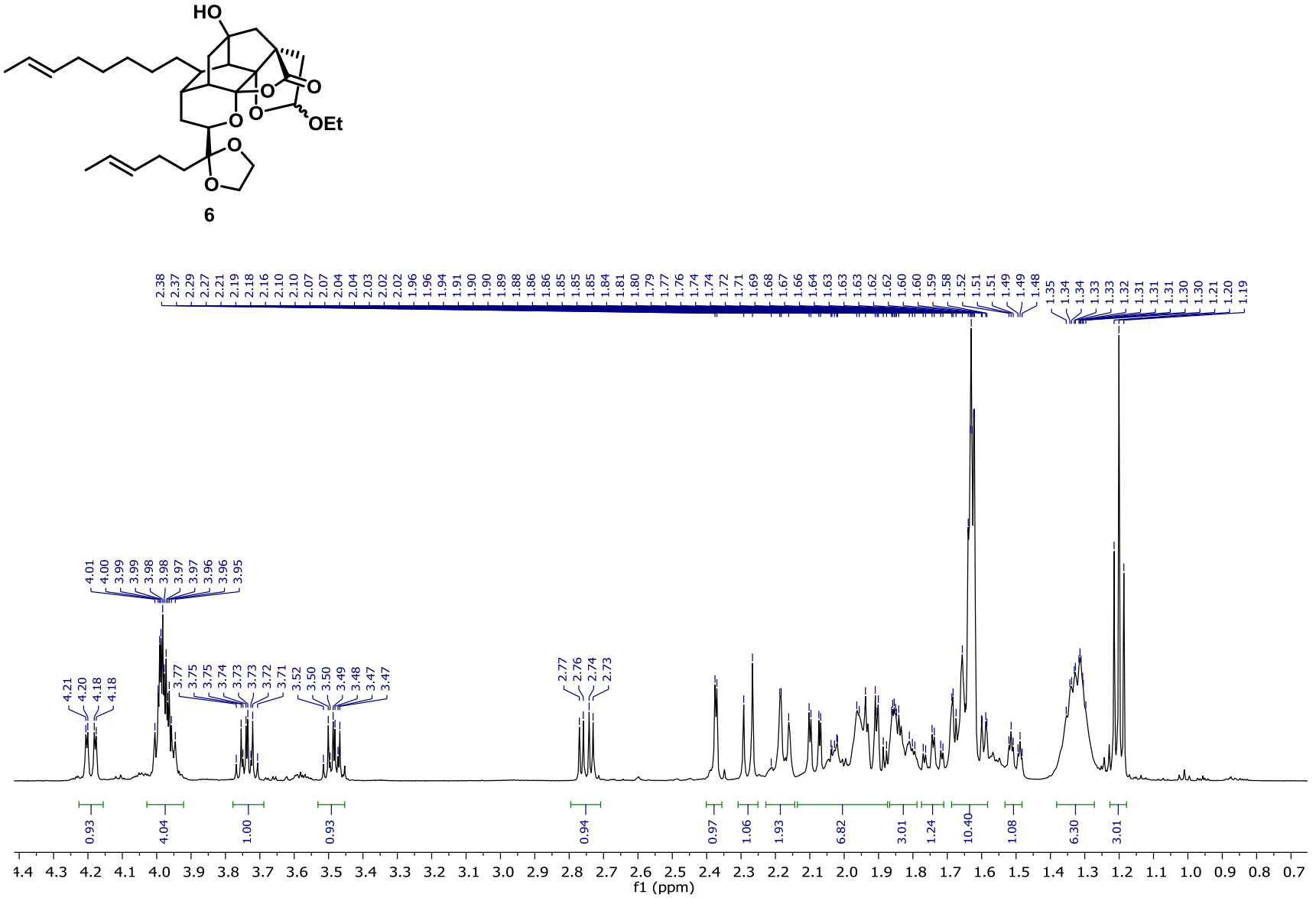
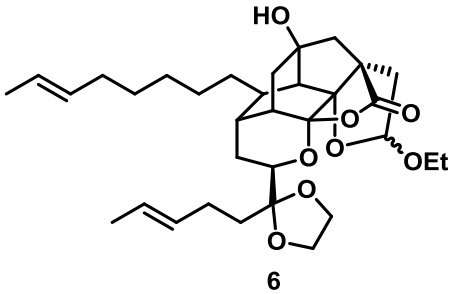


Figure 40 ^{1}H-NMR (500 MHz, $CDCl_3$) for isotwistane **6 (diastereomer one)**



6

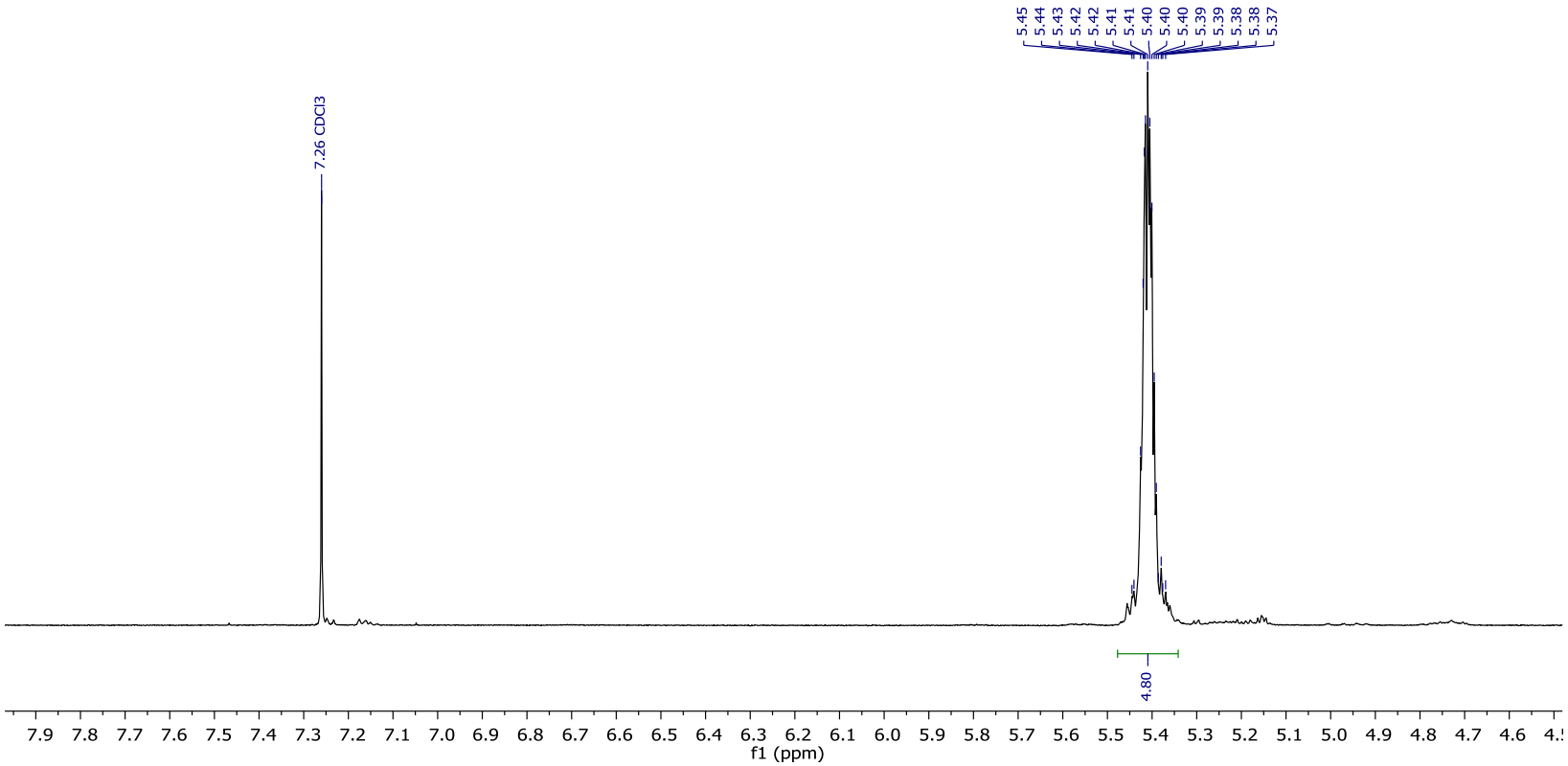


Figure 42 ^{1}H-NMR (500 MHz, $CDCl_3$) for isotwistane **6 (diastereomer one)** (inset)

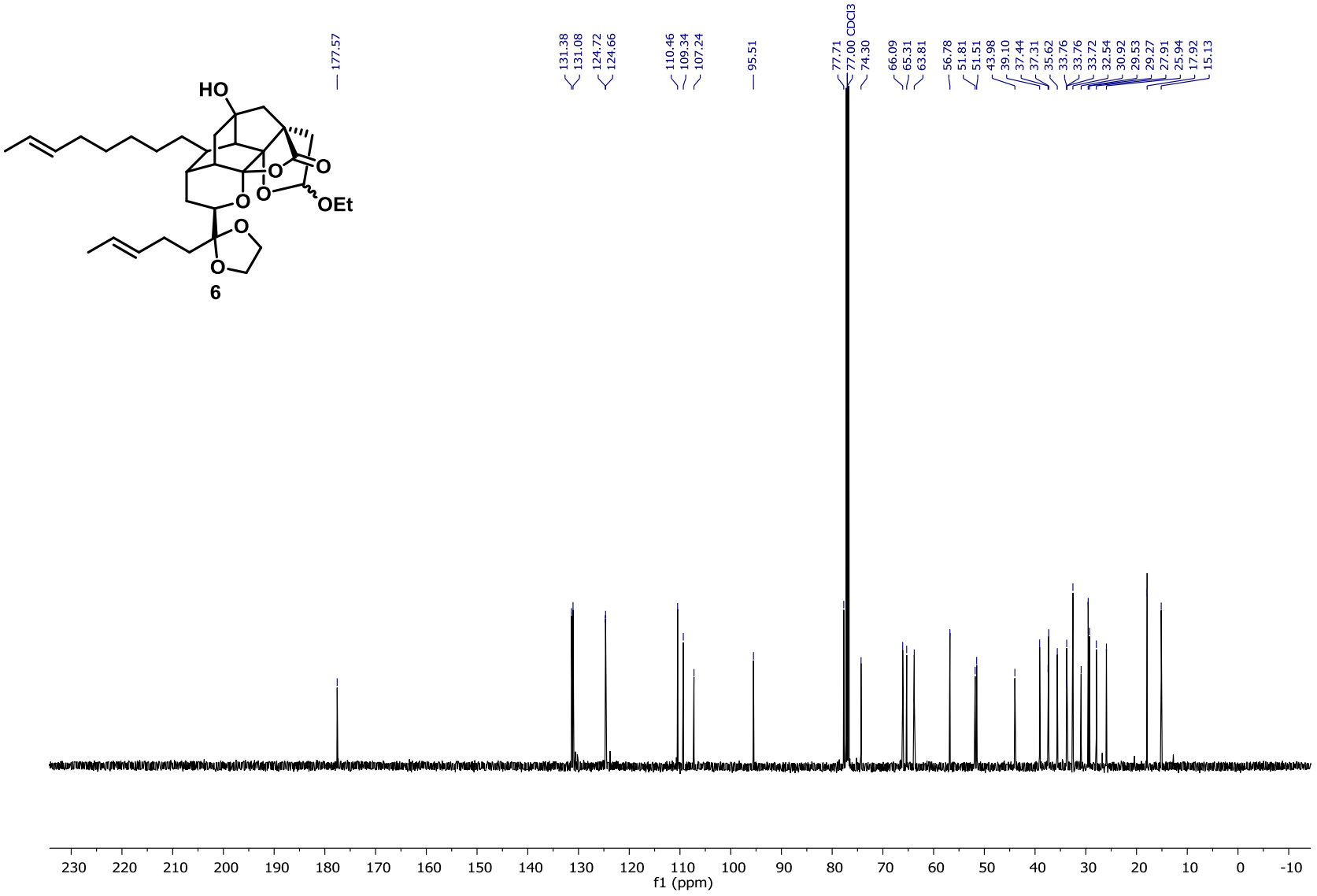


Figure 43 ^{13}C-NMR (125 MHz, $CDCl_3$) for isotwistane **6 (diastereomer one)**

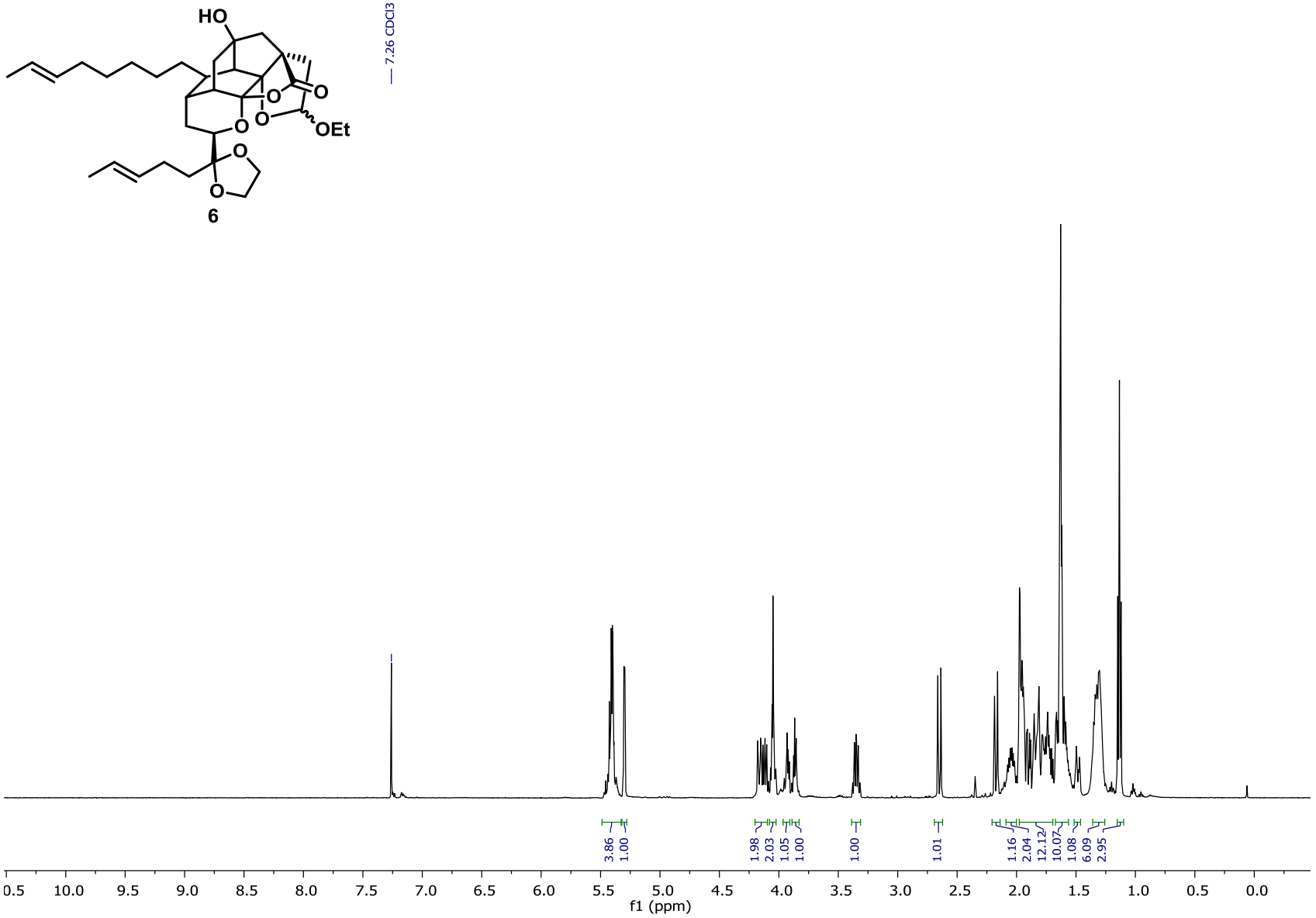


Figure 44 ^{1}H-NMR (500 MHz, $CDCl_3$) for isotwistane **6 (diastereomer two)**

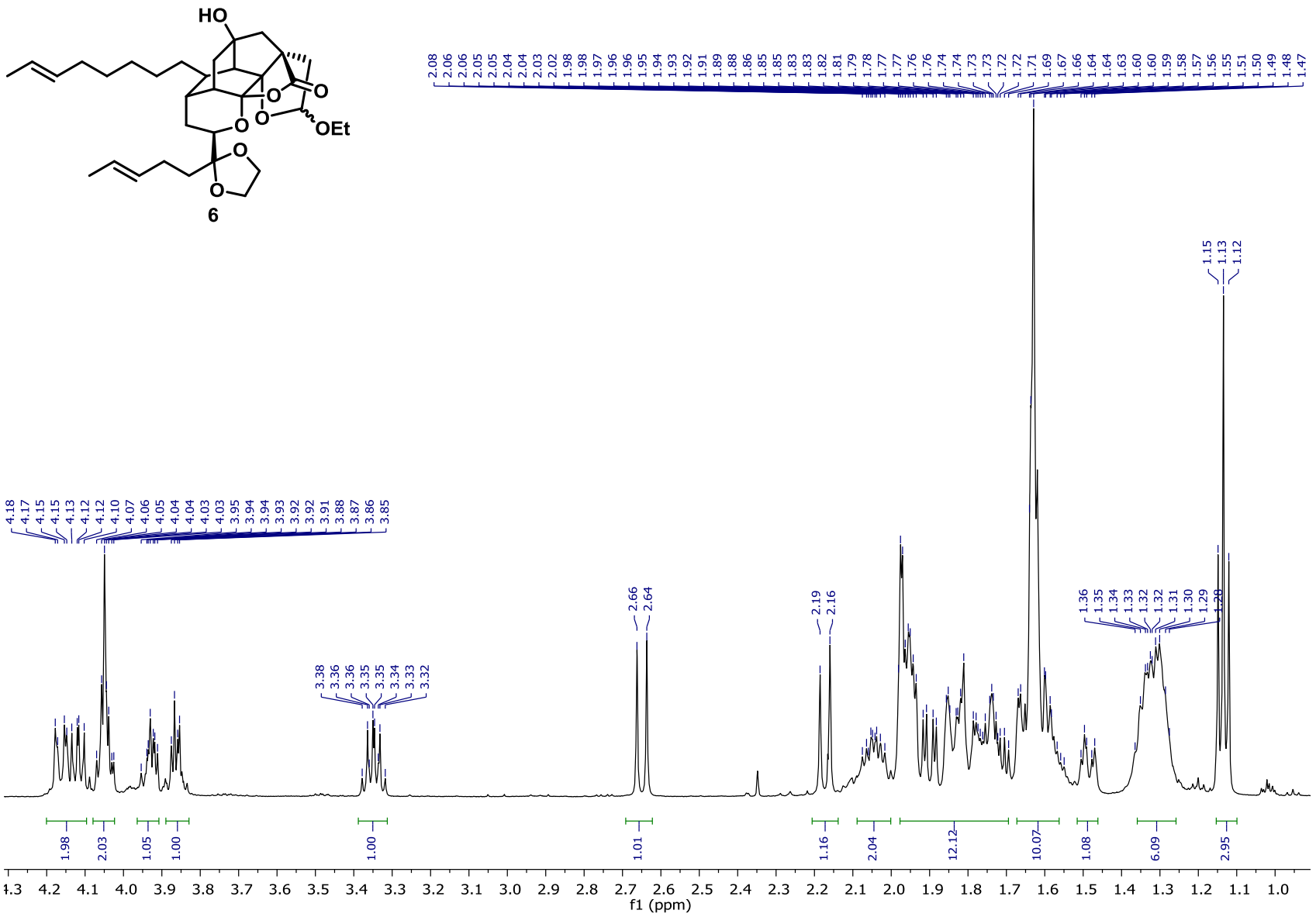
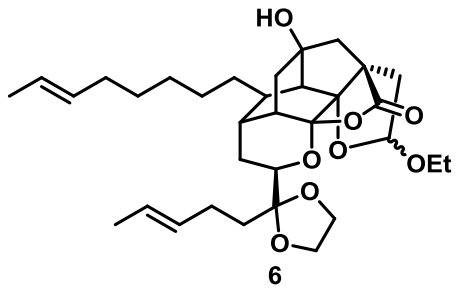


Figure 45 ^{1}H-NMR (500 MHz, $CDCl_3$) for isotwistane **6 (diastereomer two)** (inset)



6

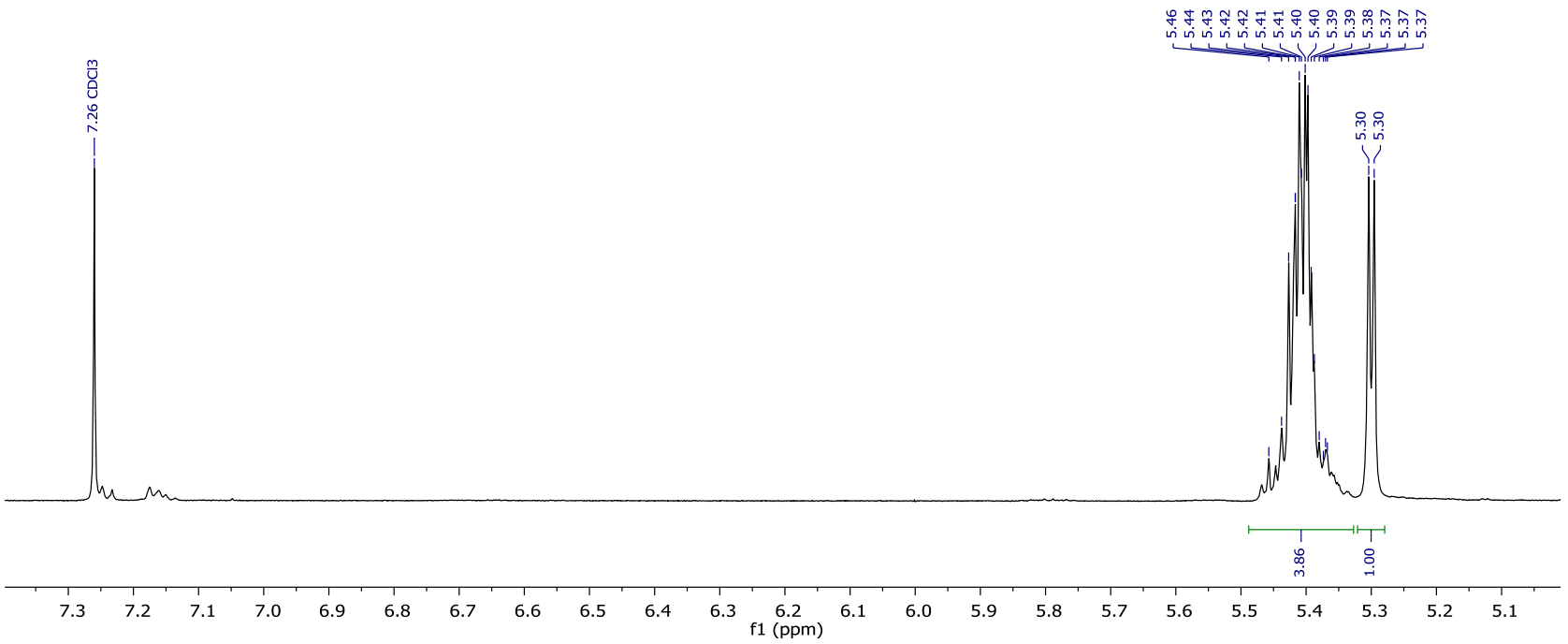


Figure 46 ^{1}H-NMR (500 MHz, $CDCl_3$) for isotwistane **6 (diastereomer two)** (inset)

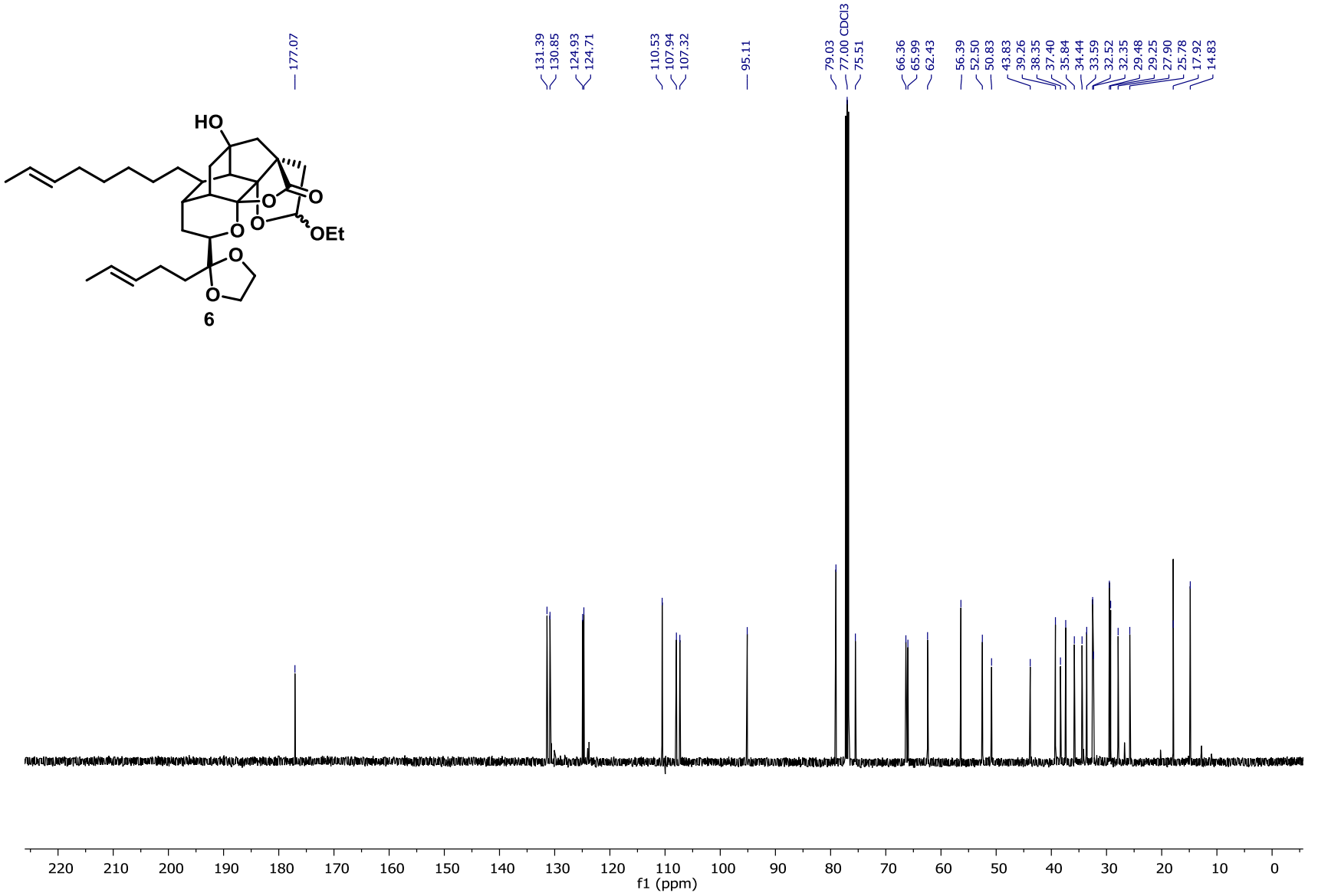


Figure 47 ^{13}C-NMR (125 MHz, $CDCl_3$) for isotwistane **6 (diastereomer two)**

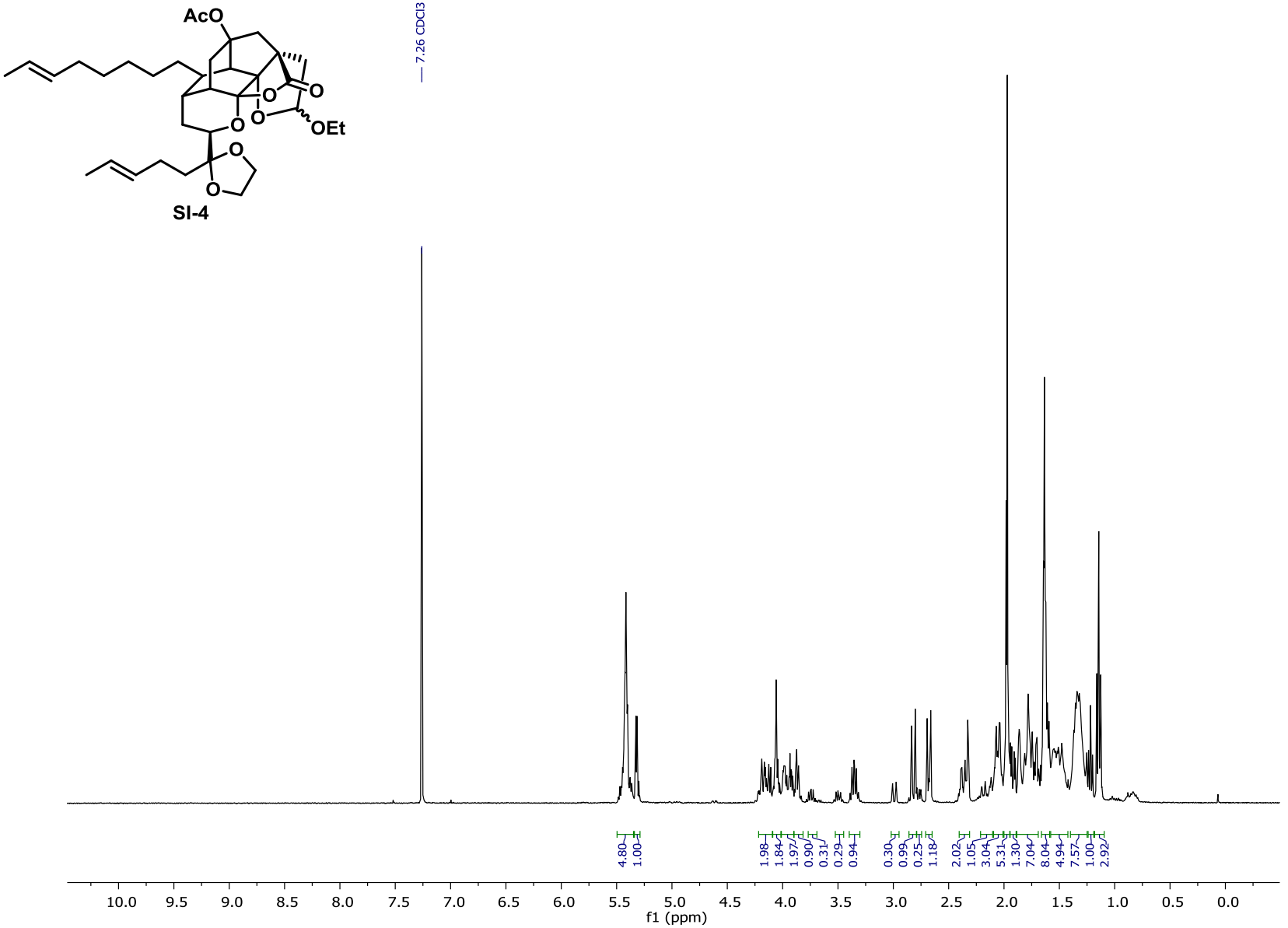


Figure 48 ^{1}H-NMR (400 MHz, $CDCl_3$) for acetate **SI-4**

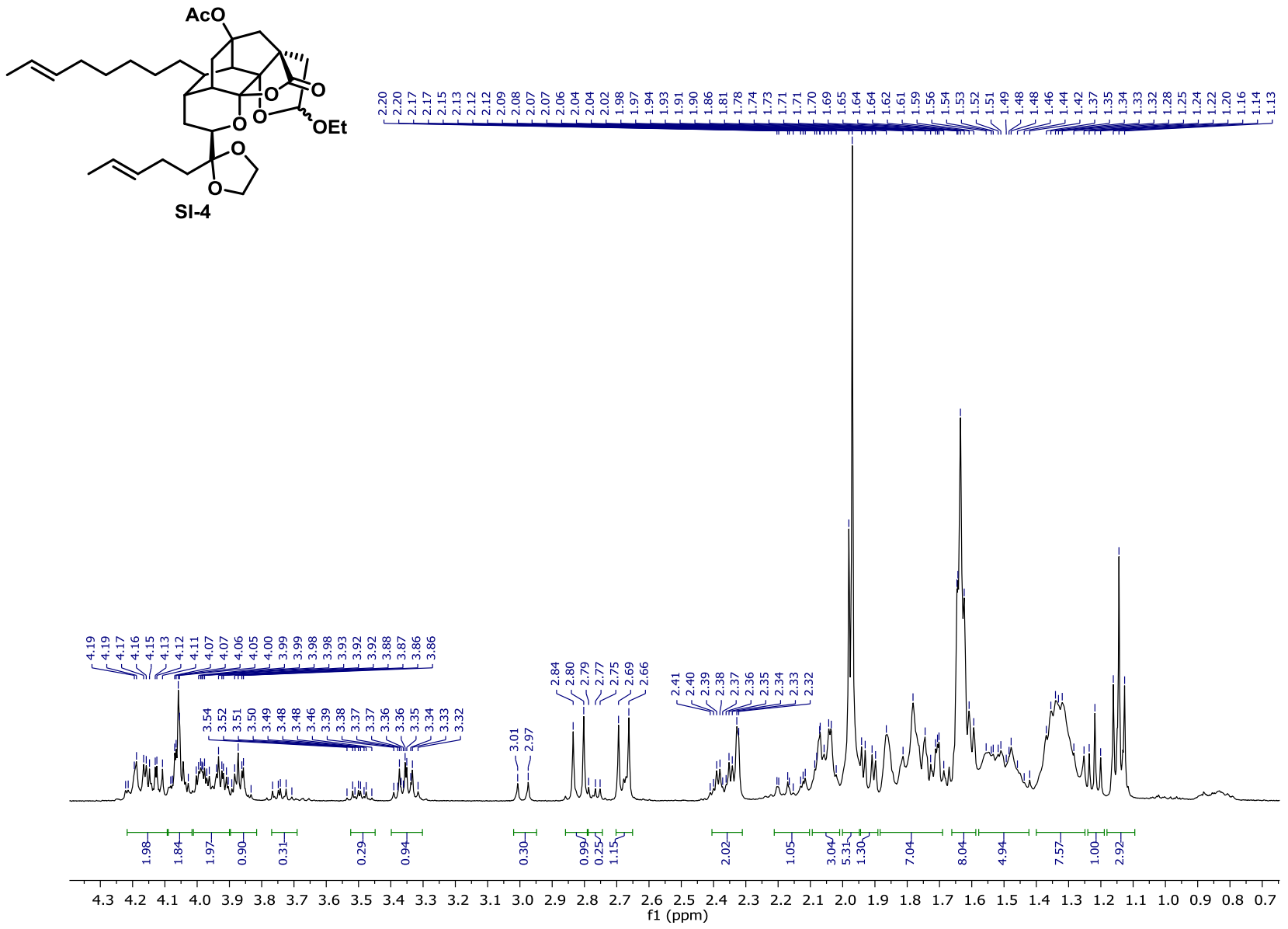


Figure 49 ^{1}H-NMR (400 MHz, $CDCl_3$) for acetate **SI-4** (inset)

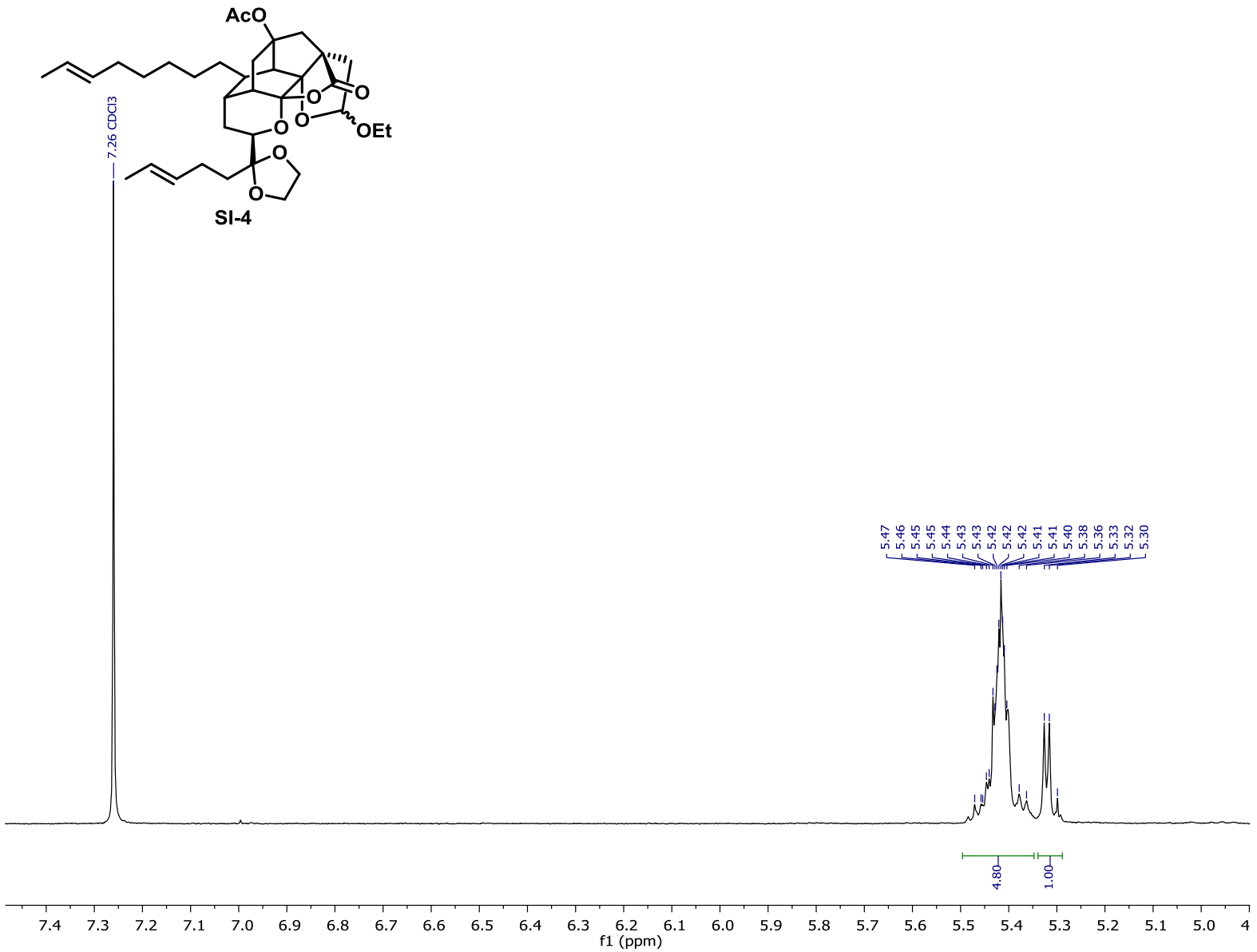


Figure 50 ^{1}H-NMR (400 MHz, $CDCl_3$) for acetate **SI-4** (inset)

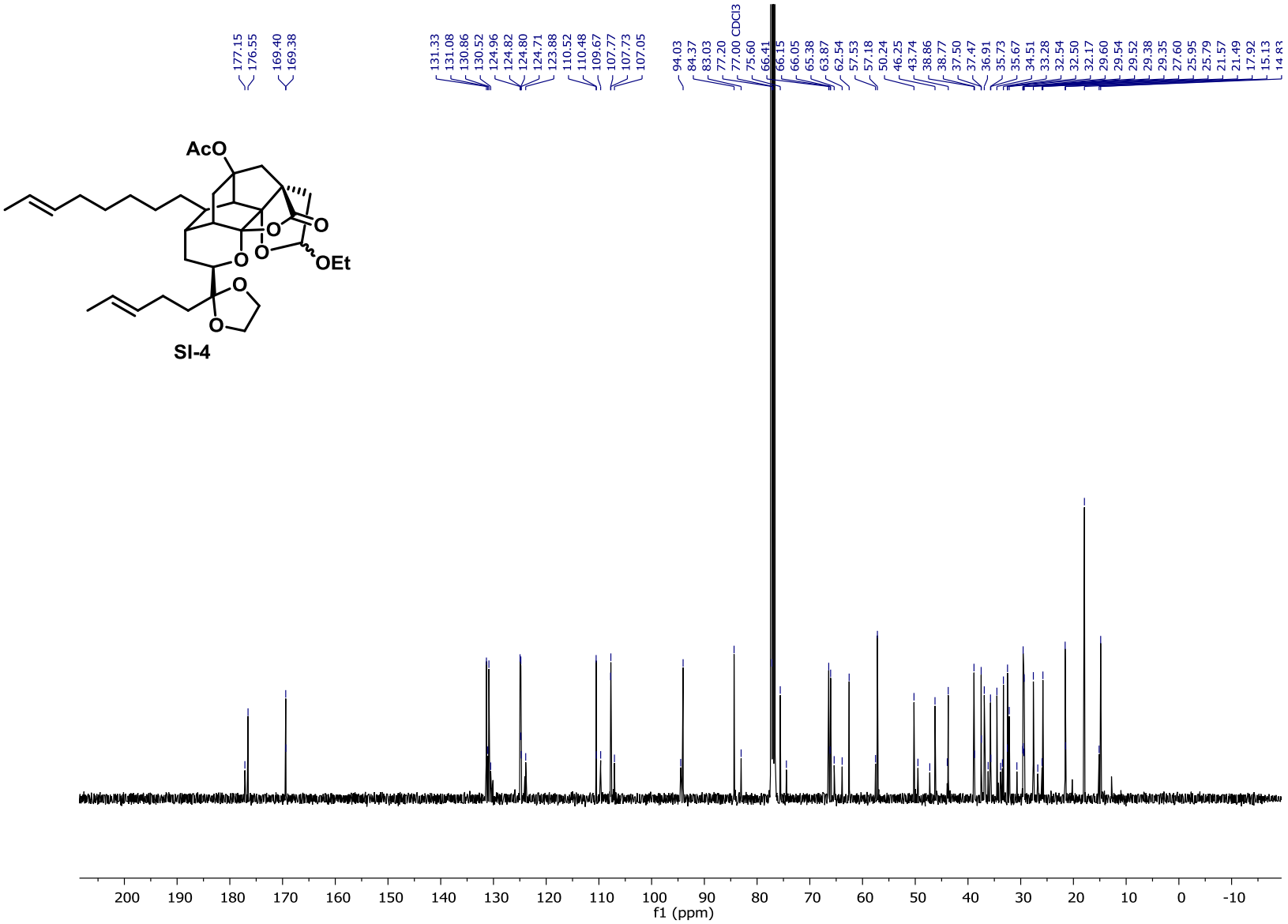


Figure 51 ^{13}C-NMR (100 MHz, $CDCl_3$) for acetate **SI-4**

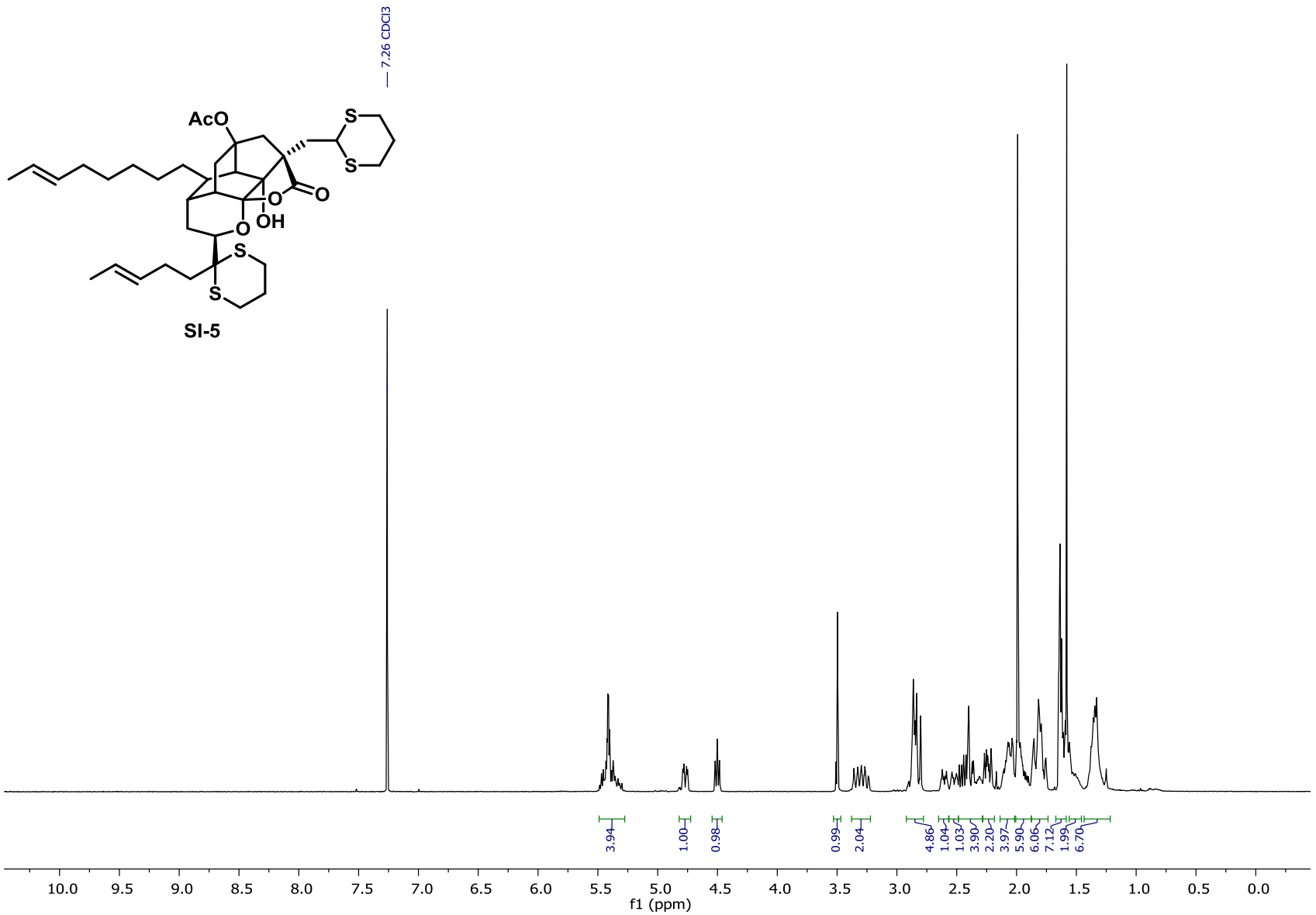


Figure 52 ^{1}H-NMR (400 MHz, $CDCl_3$) for bis-dithiane **SI-5**

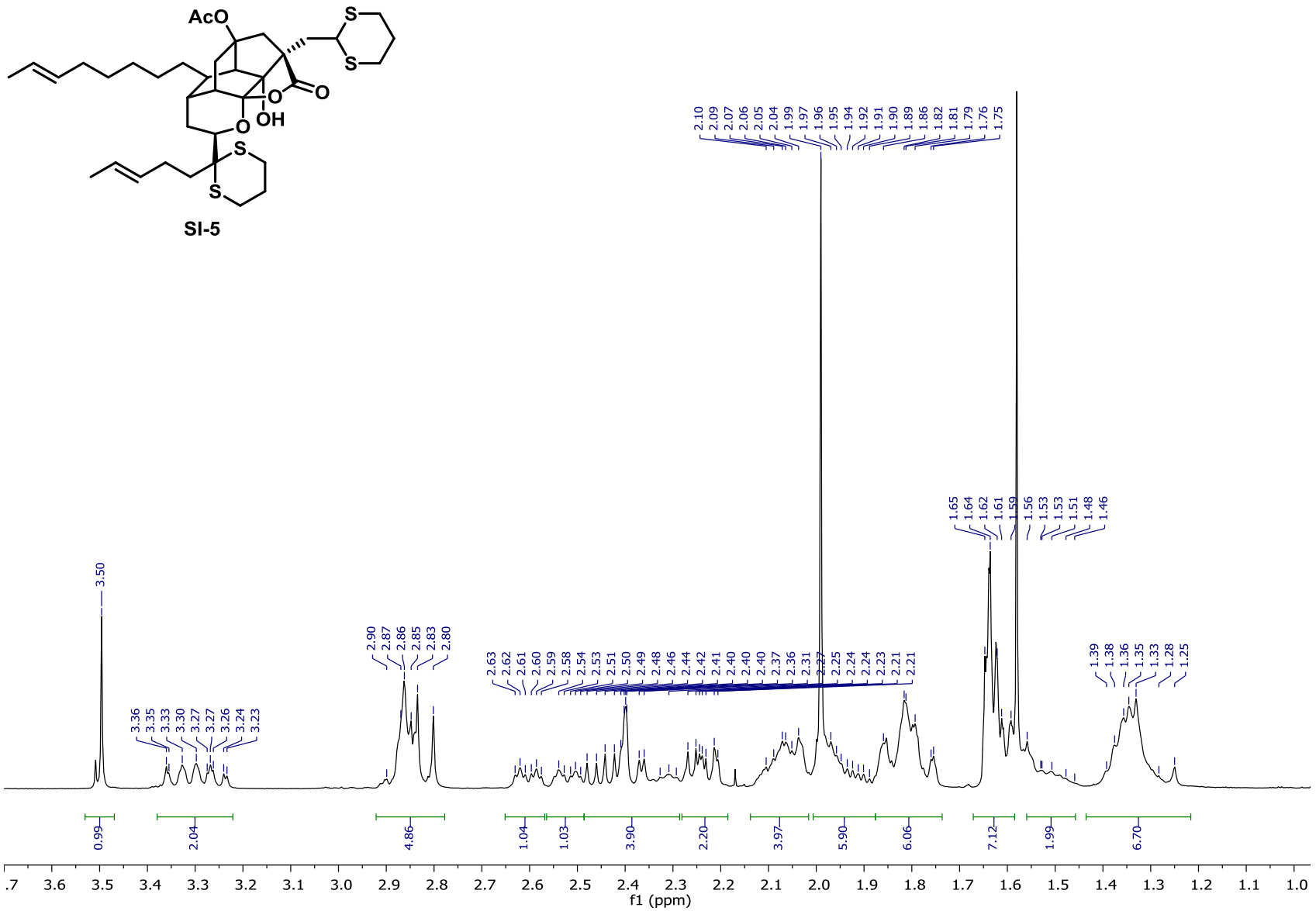


Figure 53 ^{1}H-NMR (400 MHz, $CDCl_3$) for bis-dithiane **SI-5** (inset)

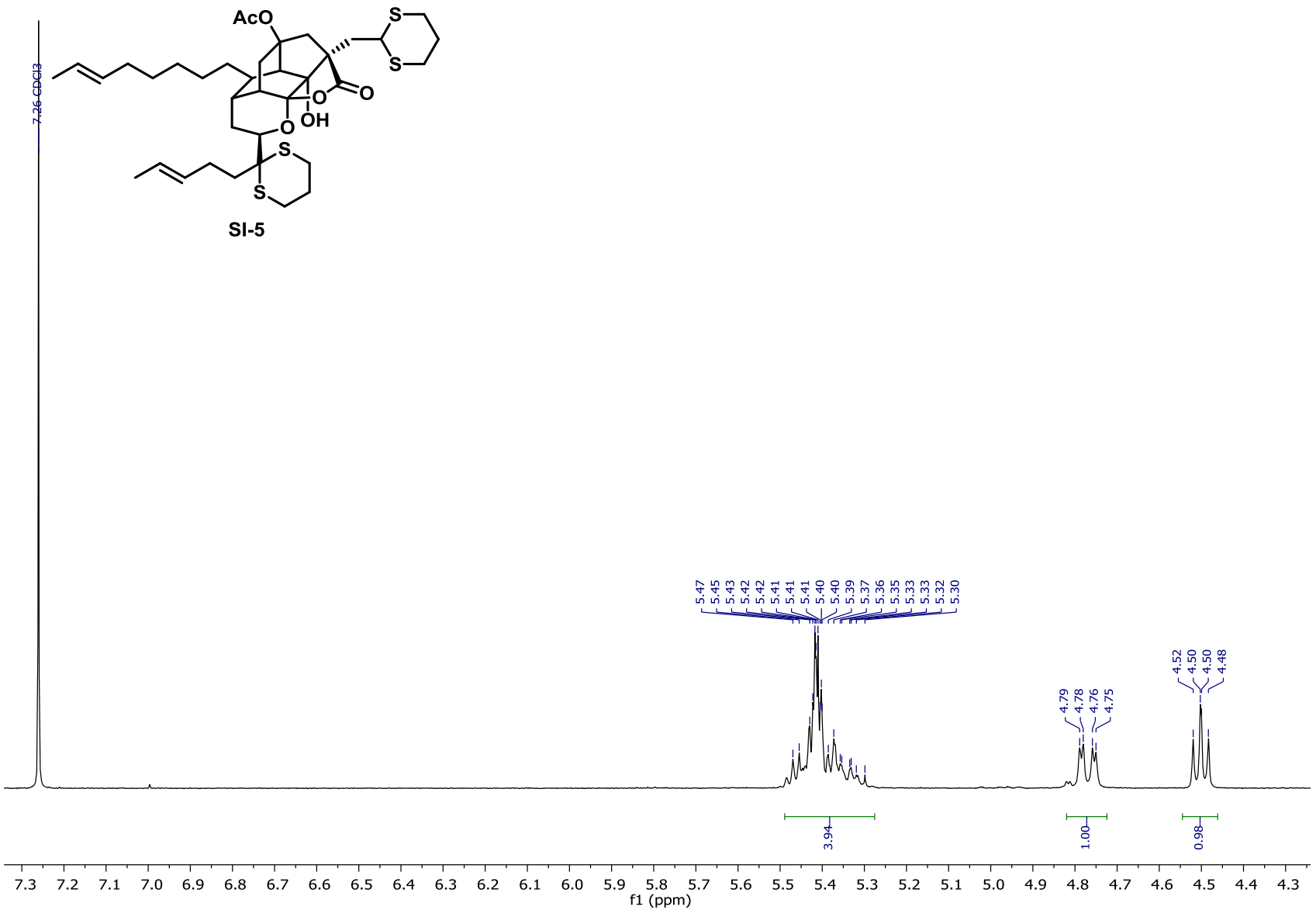


Figure 54 ^{1}H-NMR (400 MHz, $CDCl_3$) for bis-dithiane **SI-5** (inset)

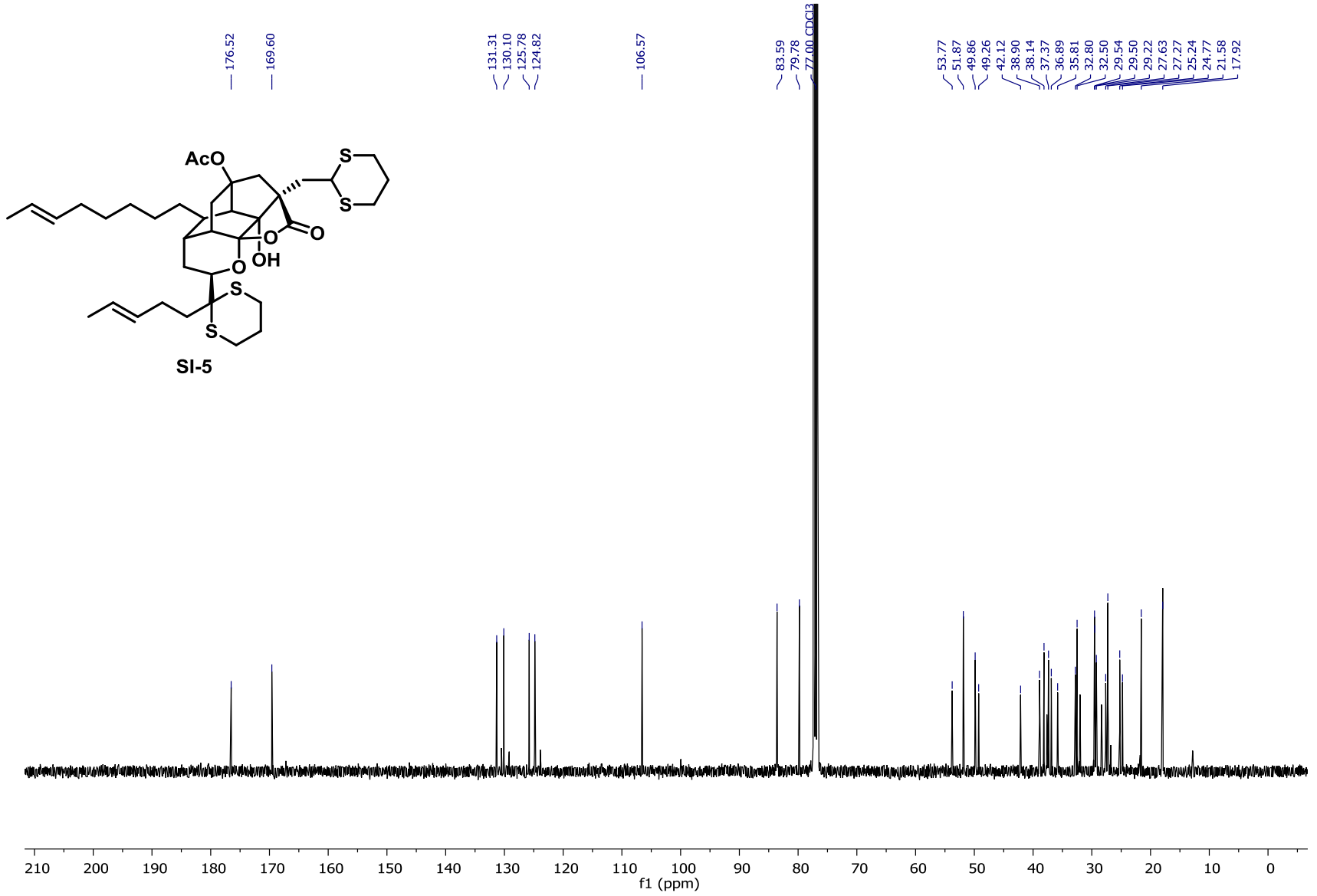


Figure 55 ^{13}C-NMR (100 MHz, $CDCl_3$) for bis-dithiane **SI-5**

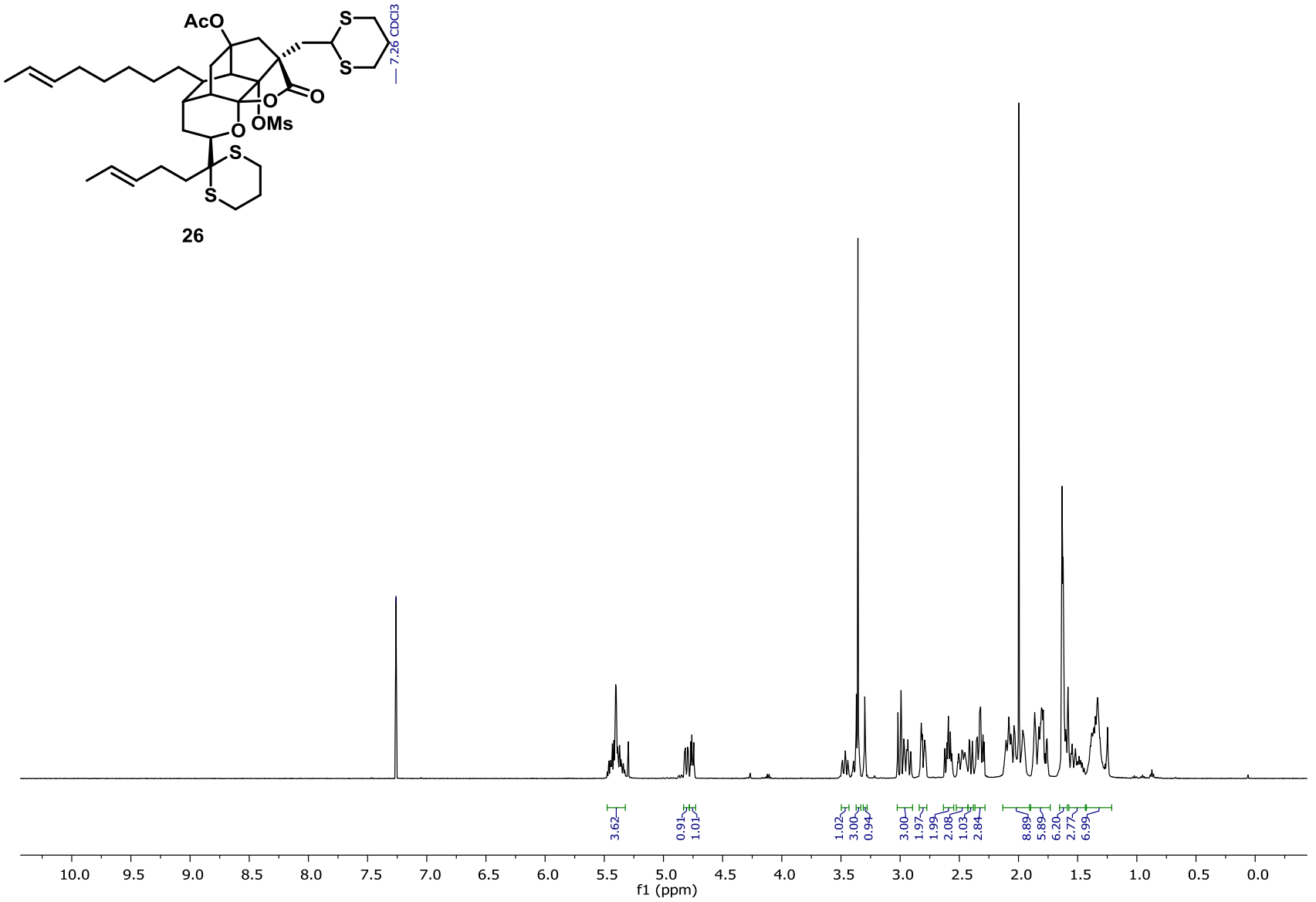


Figure 56 ^{1}H-NMR (500 MHz, $CDCl_3$) for mesylate **26**

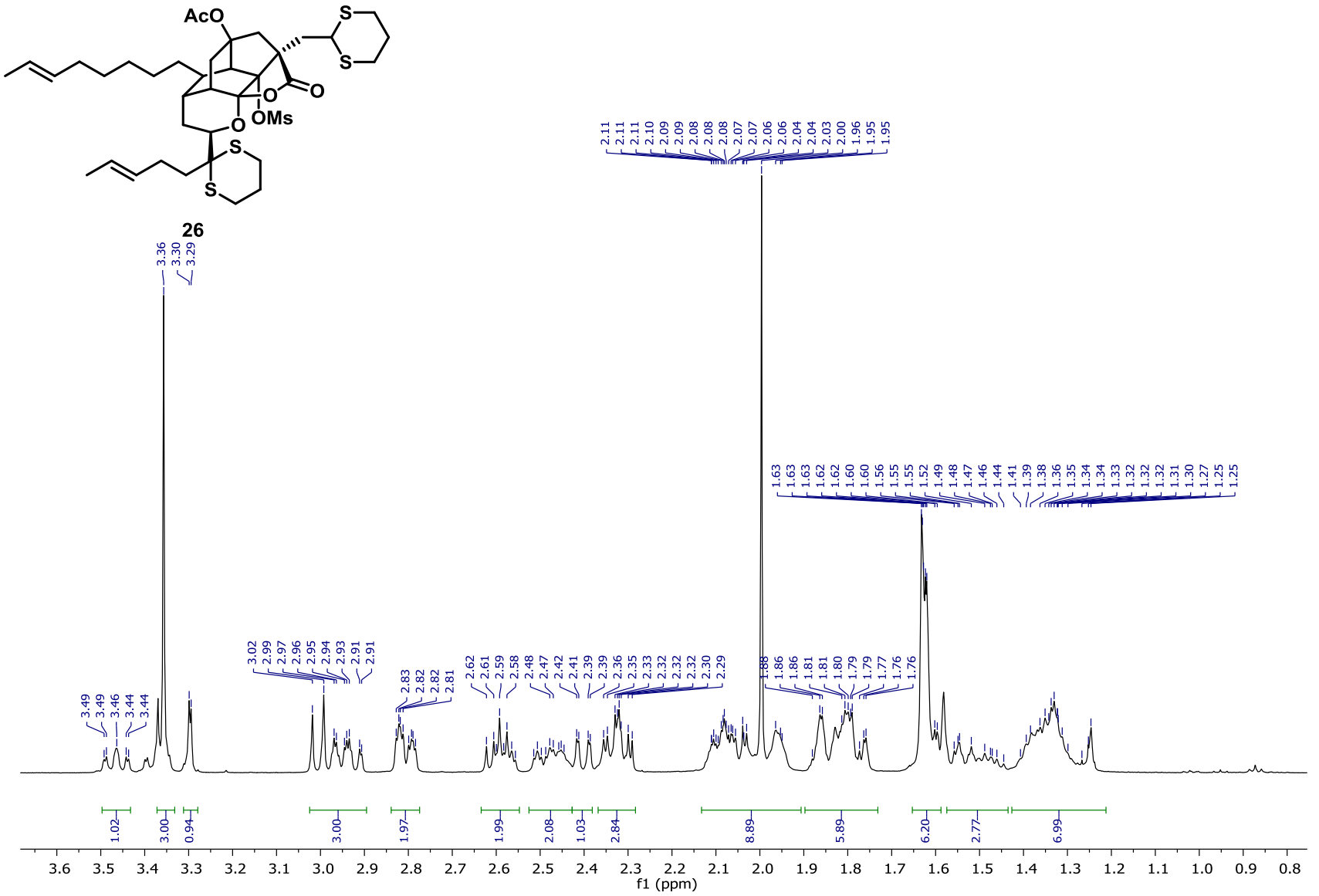


Figure 57 ^{1}H-NMR (500 MHz, $CDCl_3$) for mesylate **26 (**inset)

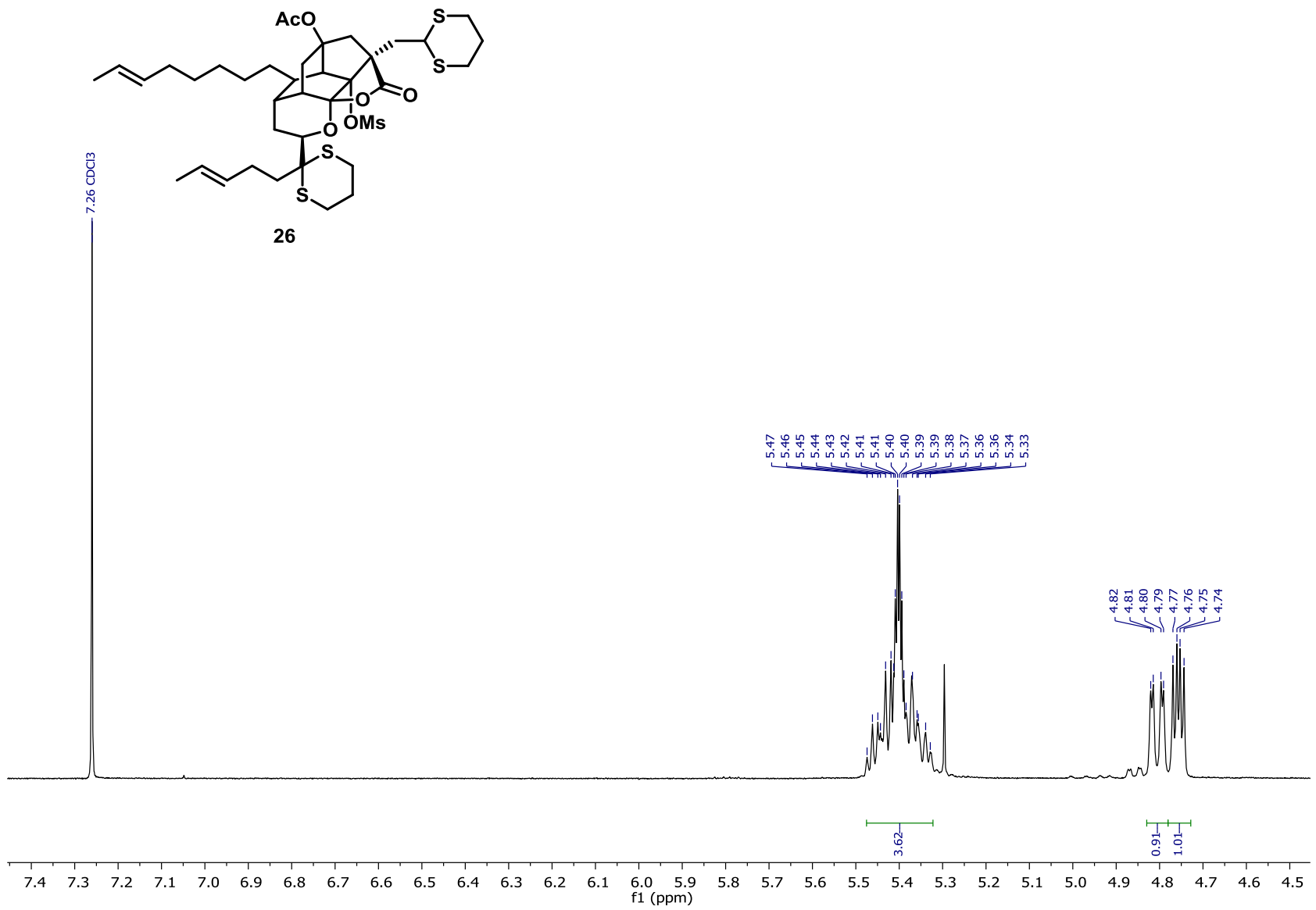


Figure 58 ^{1}H-NMR (500 MHz, $CDCl_3$) for mesylate **26 (**inset)

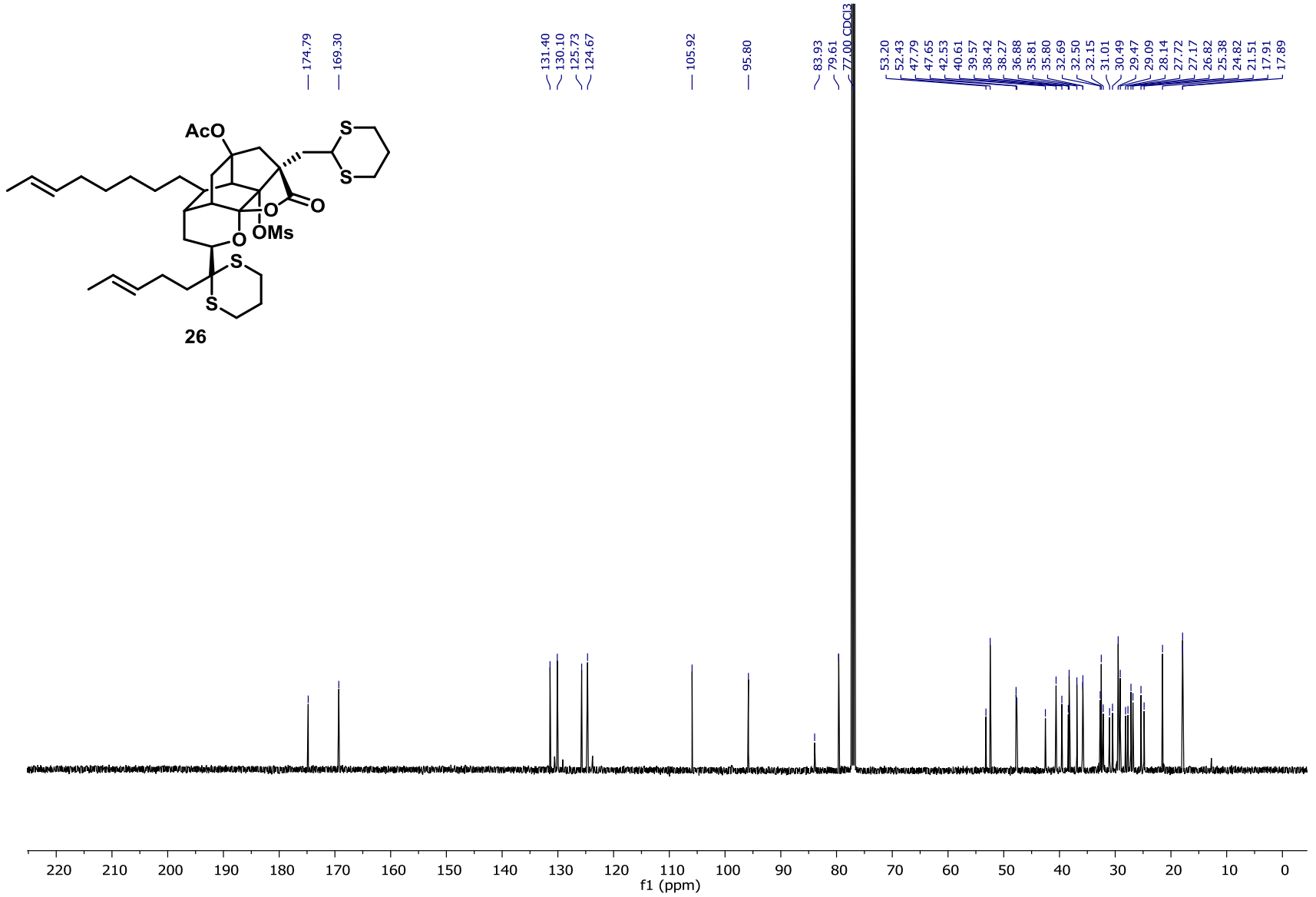


Figure 59 ^{13}C-NMR (125 MHz, $CDCl_3$) for mesylate **26**

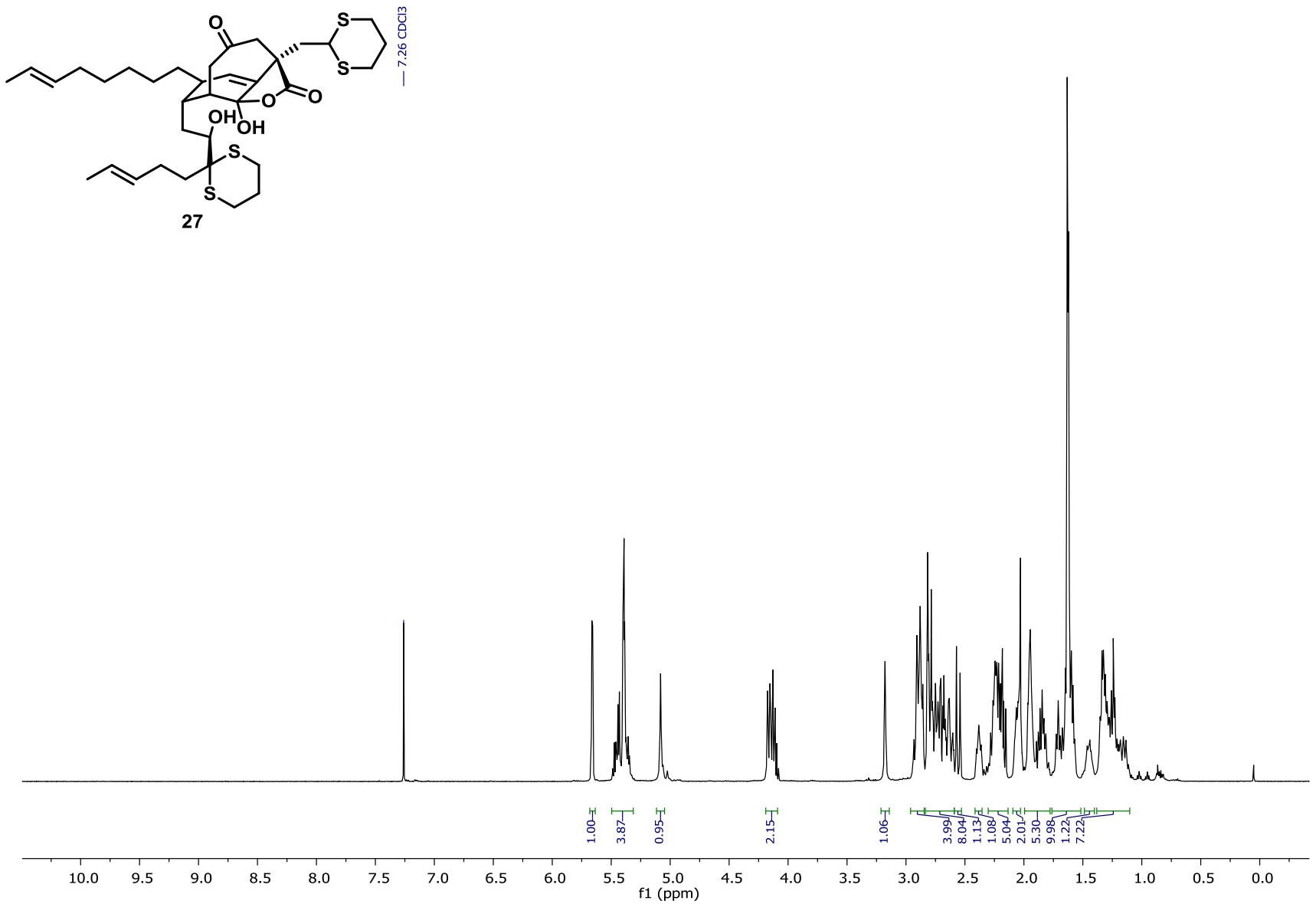


Figure 60 ^{1}H-NMR (500 MHz, $CDCl_3$) for diol **27**

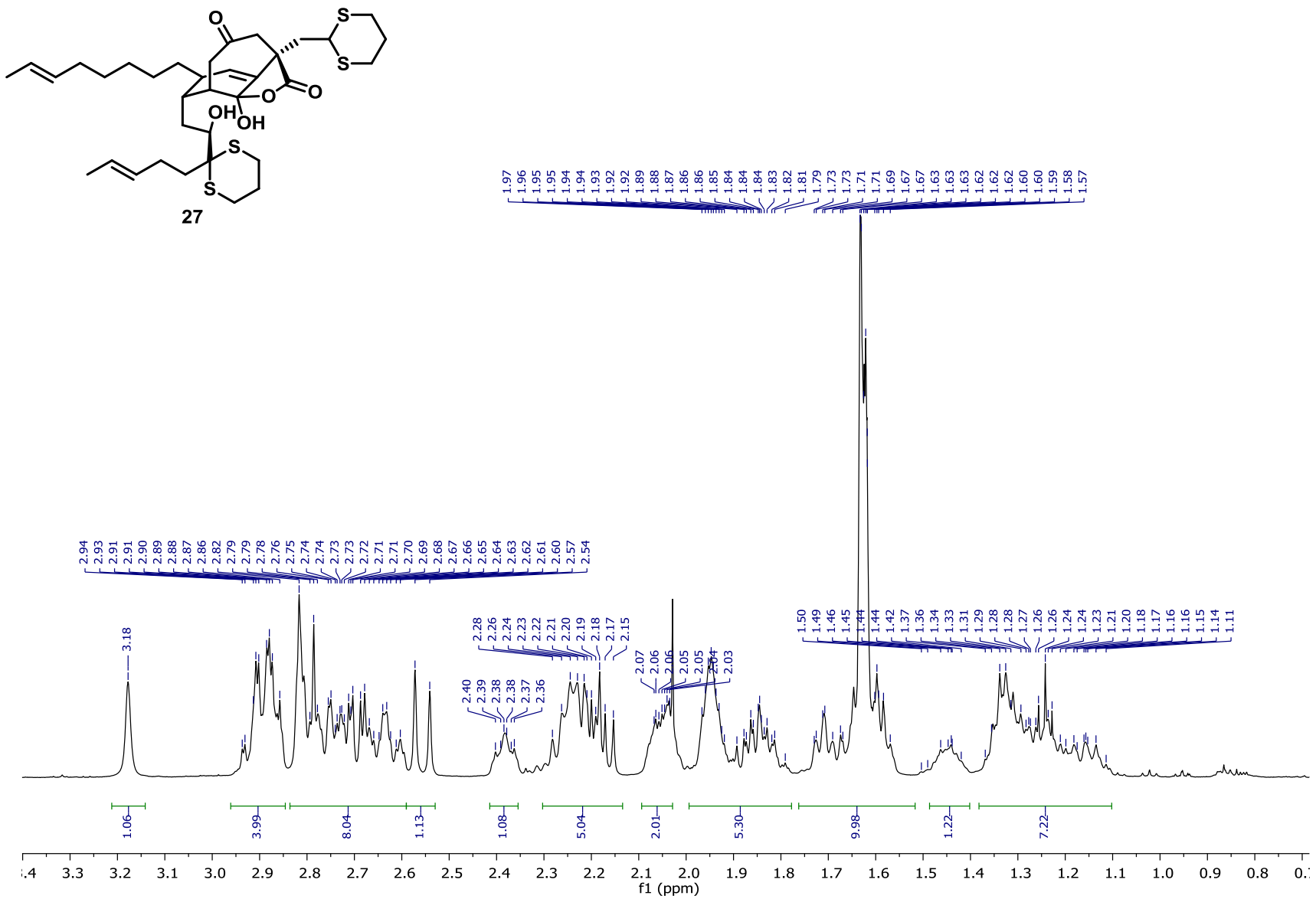


Figure 61 ^{1}H-NMR (500 MHz, $CDCl_3$) for diol **27** (inset)

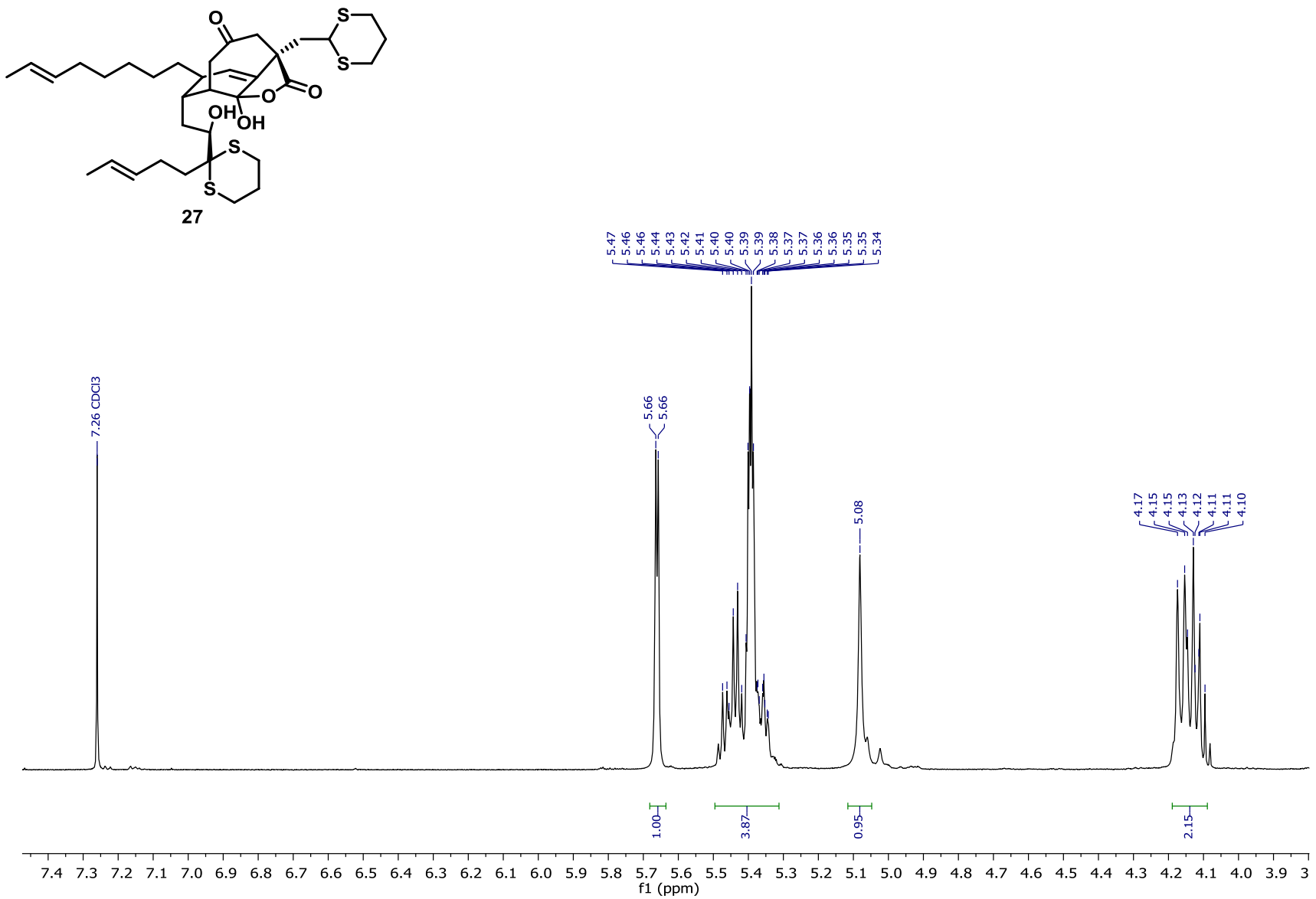


Figure 62 ^{1}H-NMR (500 MHz, $CDCl_3$) for diol **27** (inset)

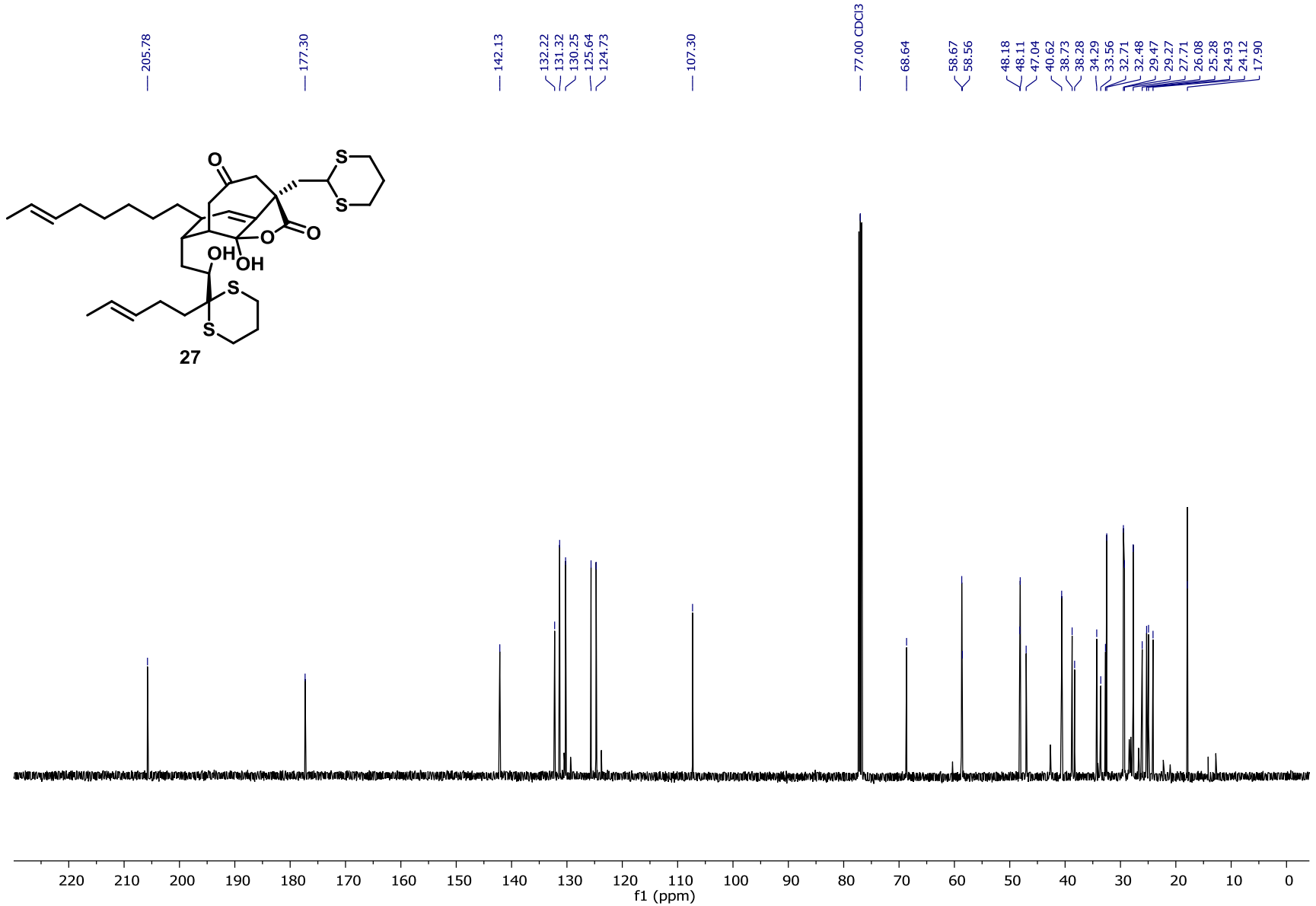


Figure 63 ^{13}C-NMR (125 MHz, $CDCl_3$) for diol **27**

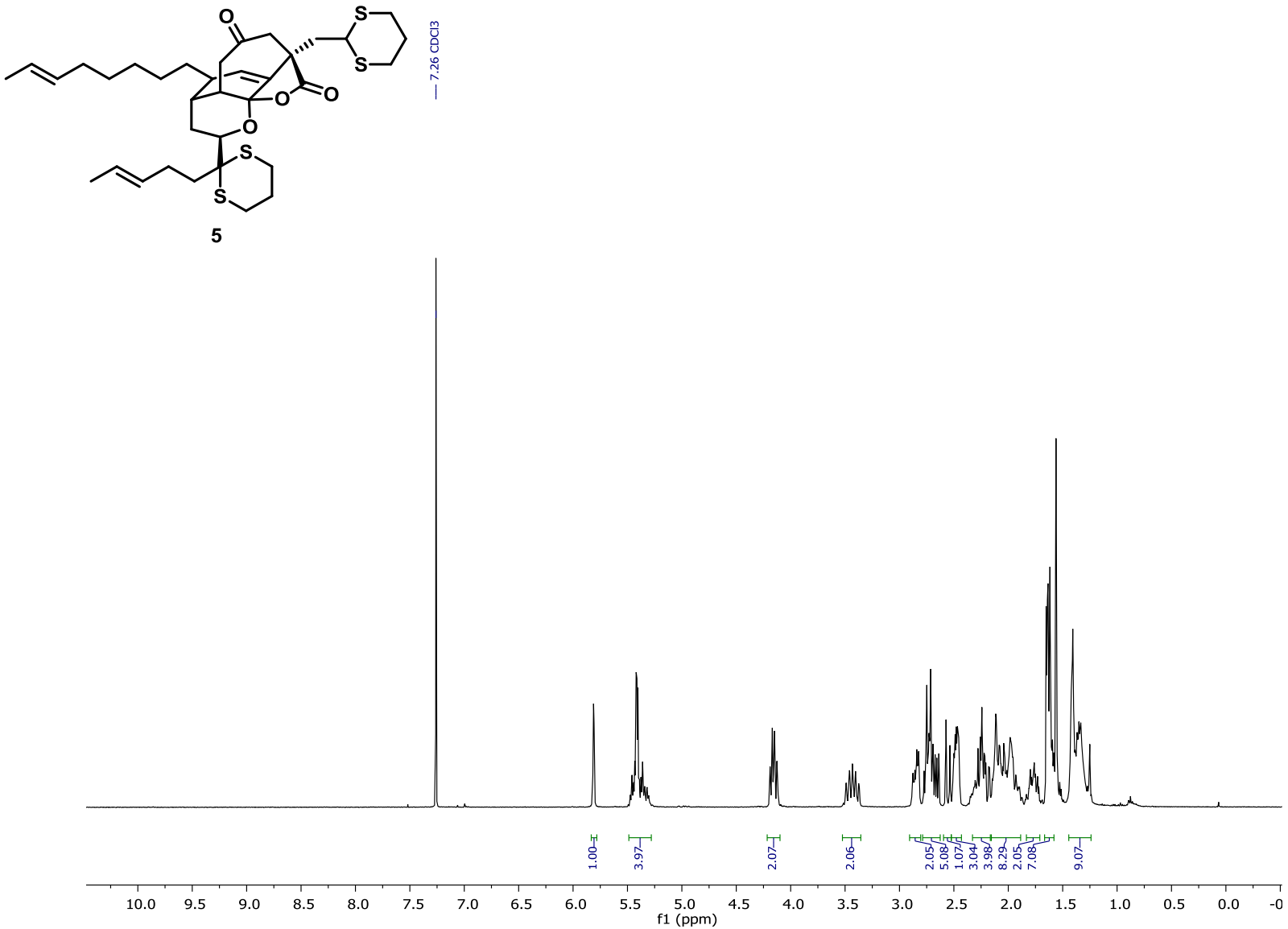
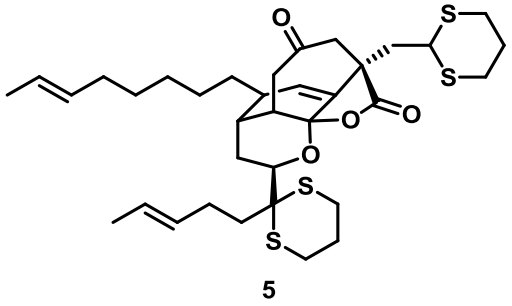


Figure 64 ^{1}H-NMR (400 MHz, $CDCl_3$) for ketone **5**



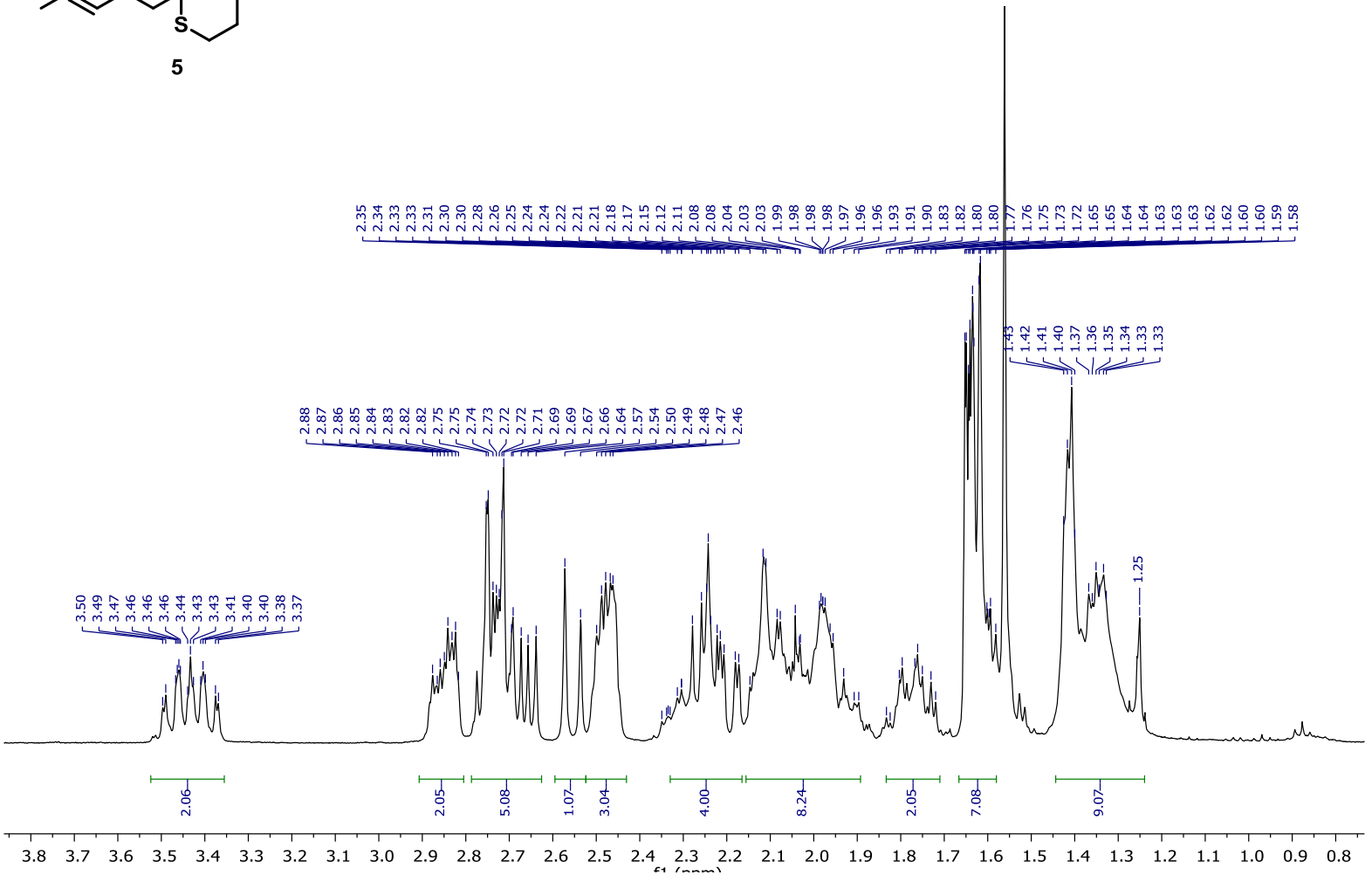


Figure 65 ^{1}H-NMR (400 MHz, $CDCl_3$) for ketone **5** (inset)

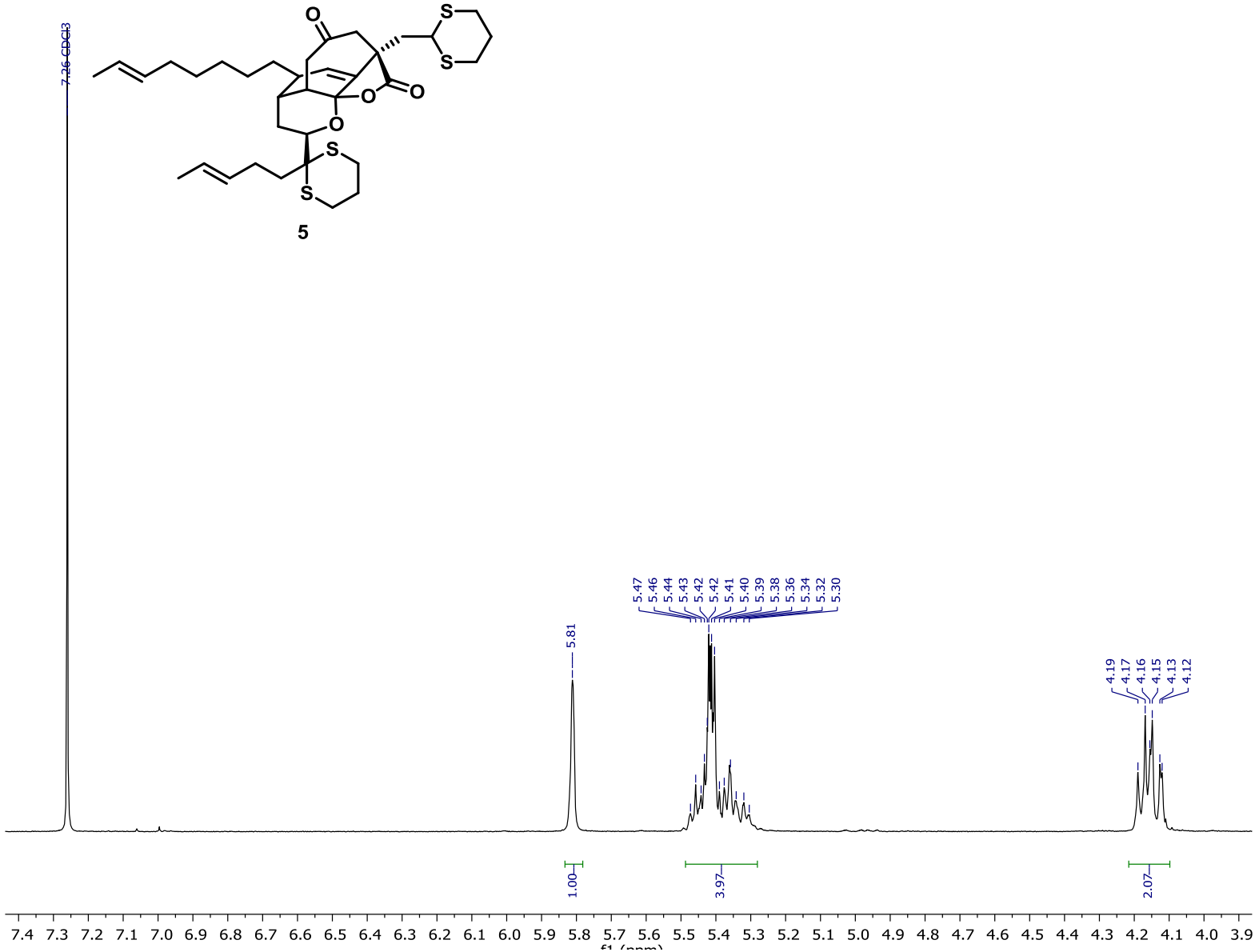


Figure 66 ^{1}H-NMR (400 MHz, $CDCl_3$) for ketone **5** (inset)

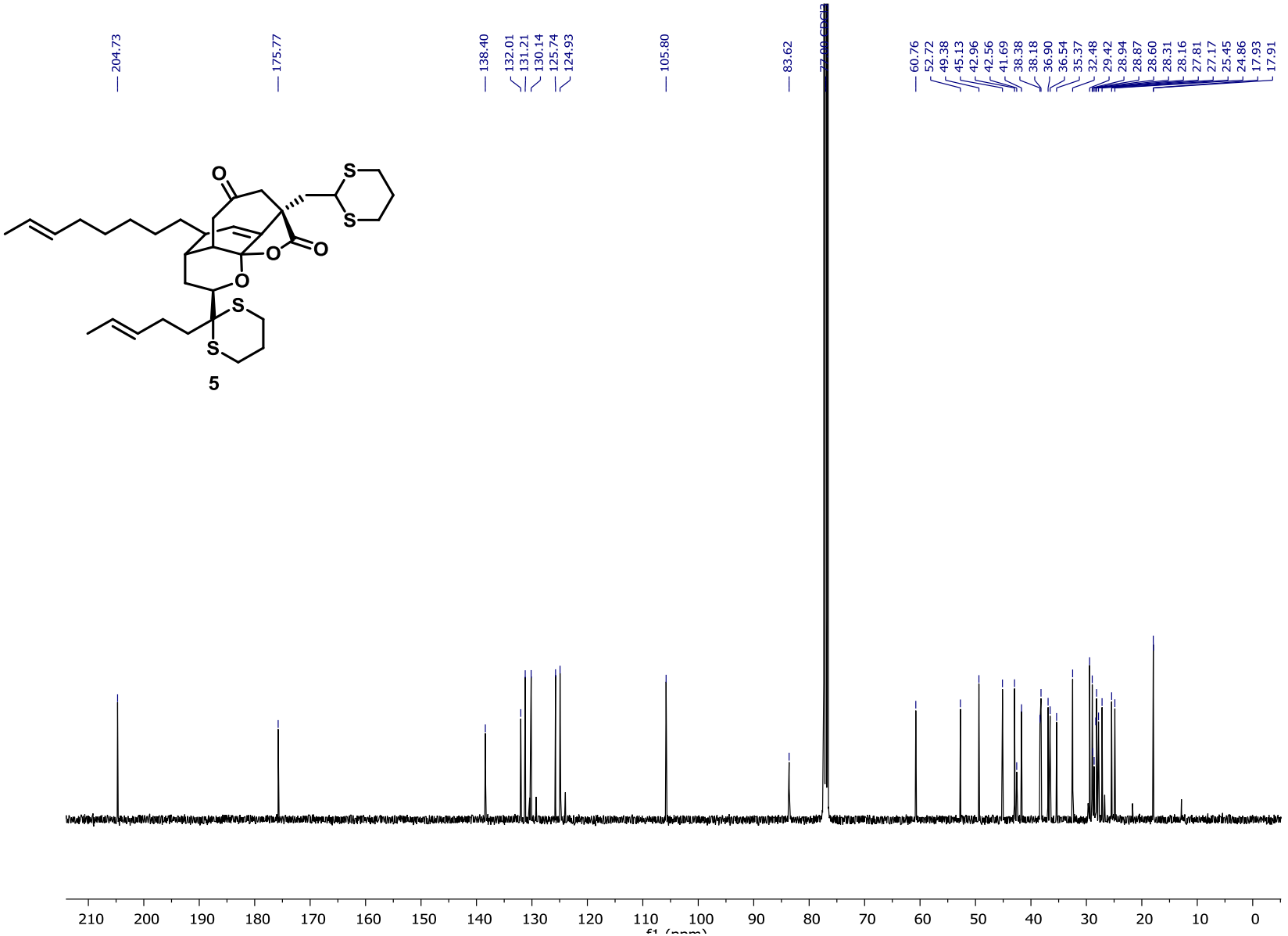


Figure 67 ^{13}C-NMR (100 MHz, $CDCl_3$) for ketone **5**

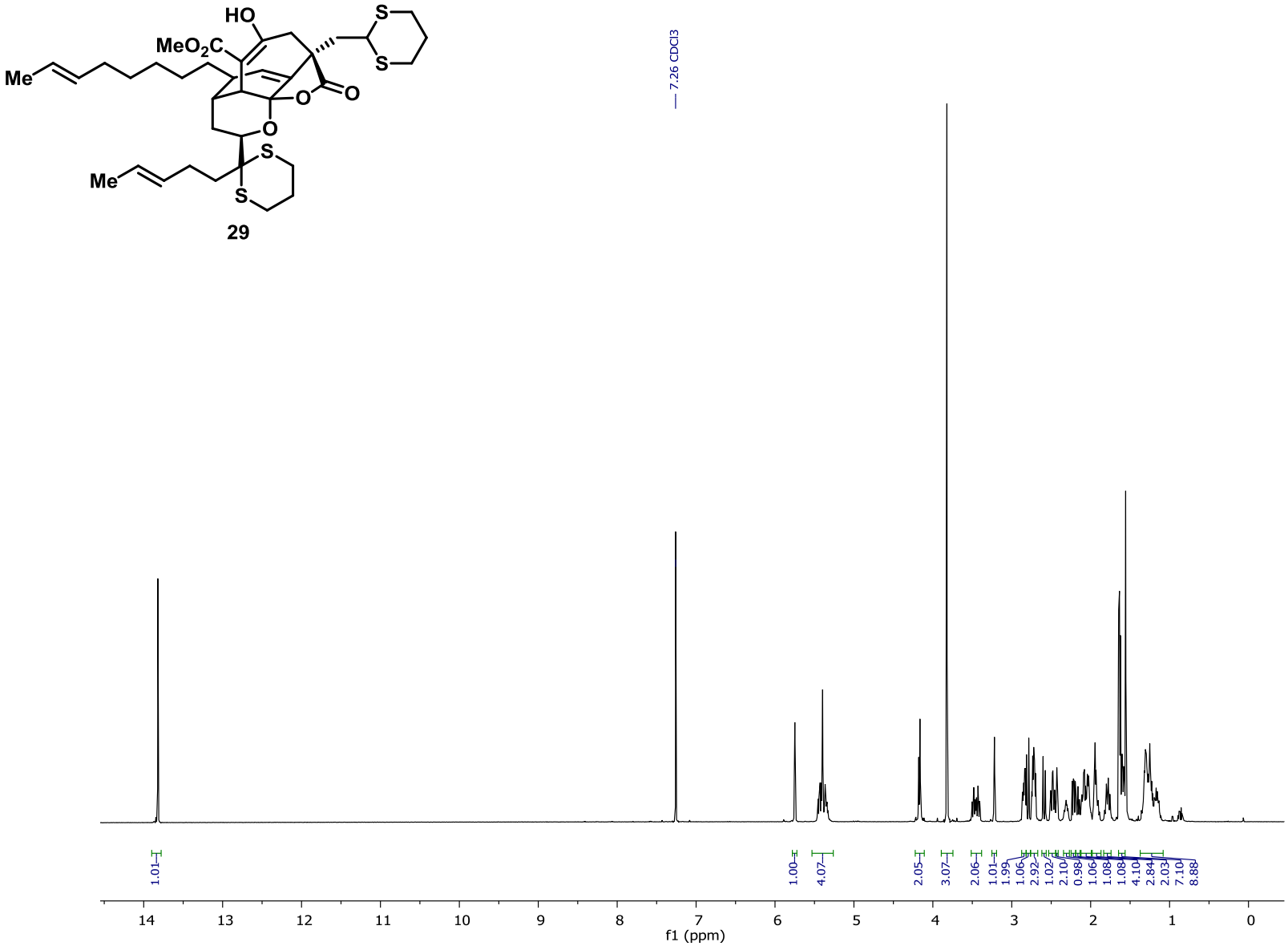
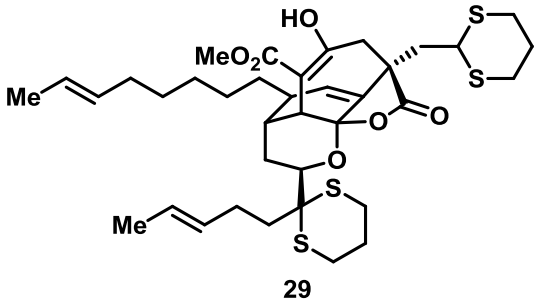


Figure 68 ^{1}H-NMR (600 MHz, $CDCl_3$) for enol **29**



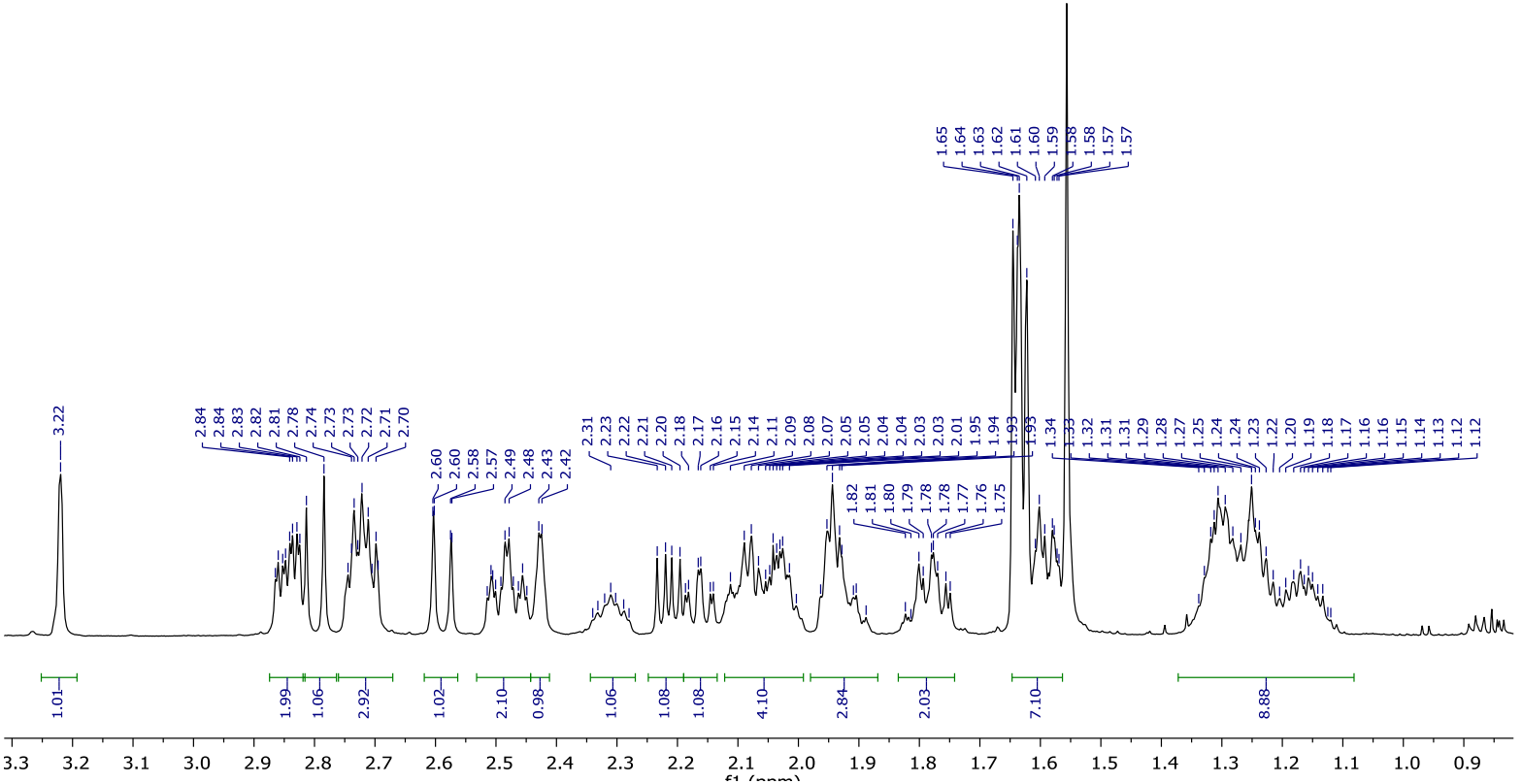


Figure 69 ^{1}H-NMR (600 MHz, $CDCl_3$) for enol **29** (inset)

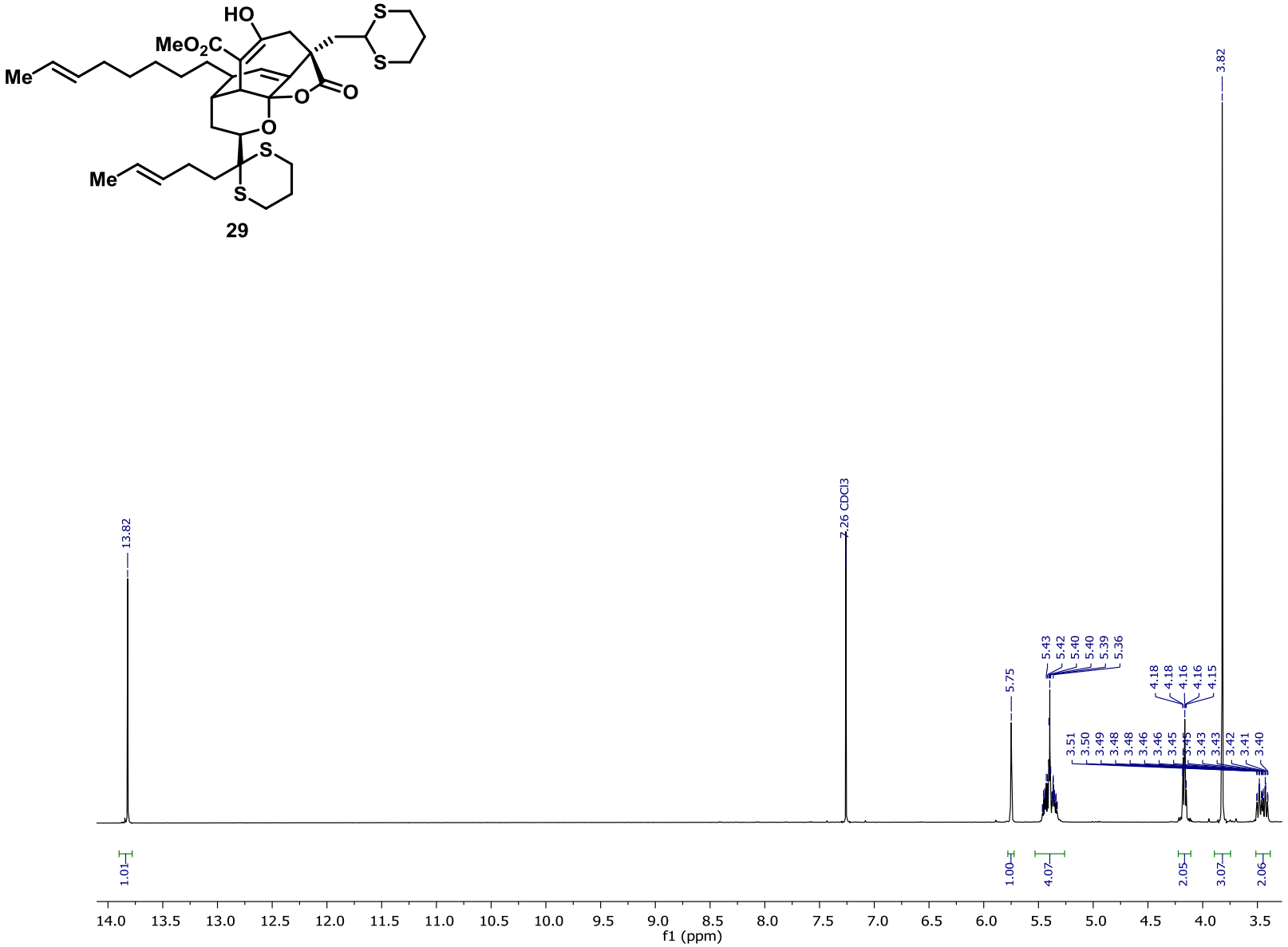


Figure 70 ^{1}H-NMR (600 MHz, $CDCl_3$) for enol **29** (inset)

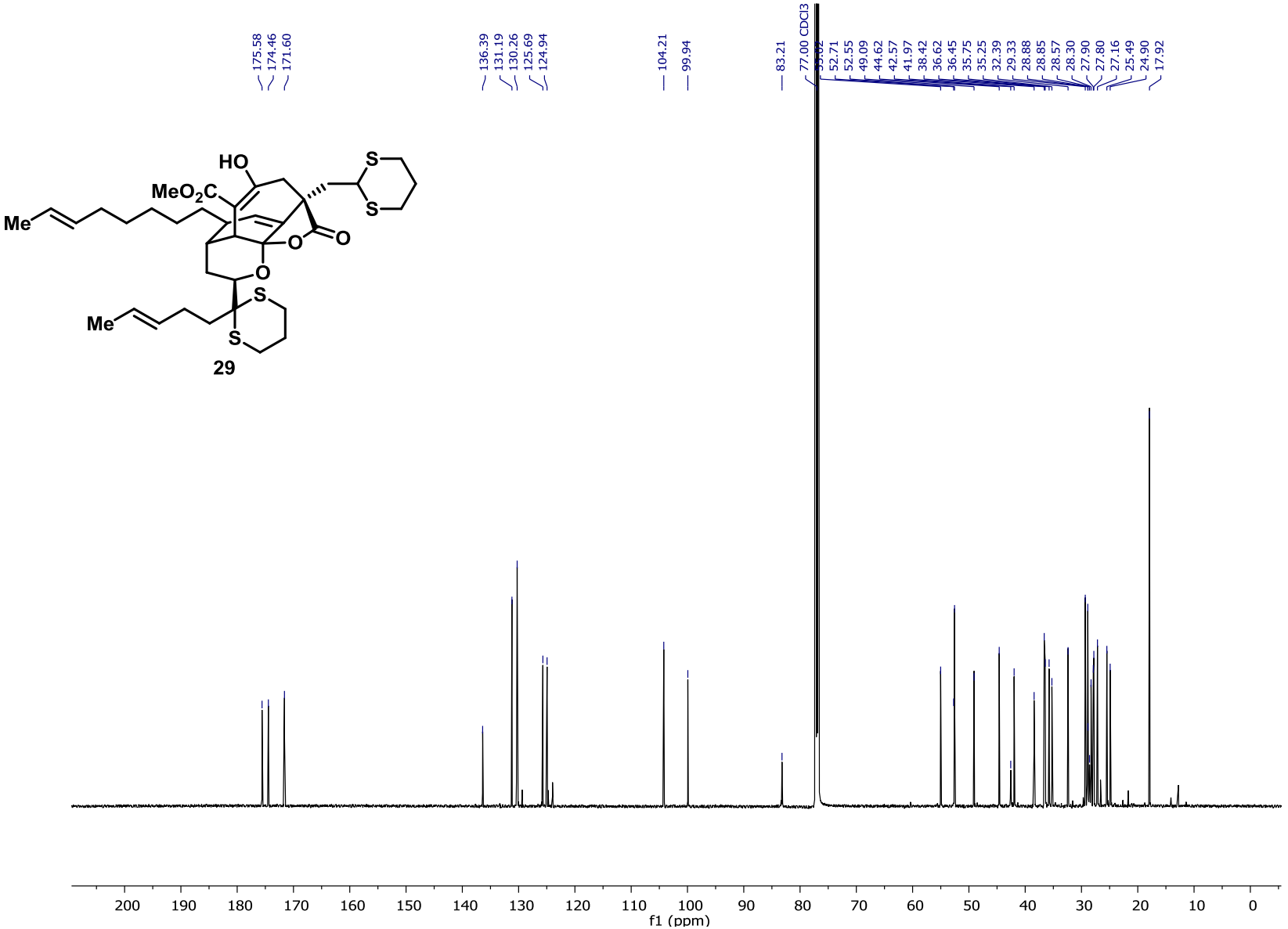


Figure 71 ^{13}C-NMR (150 MHz, $CDCl_3$) for enol **29**

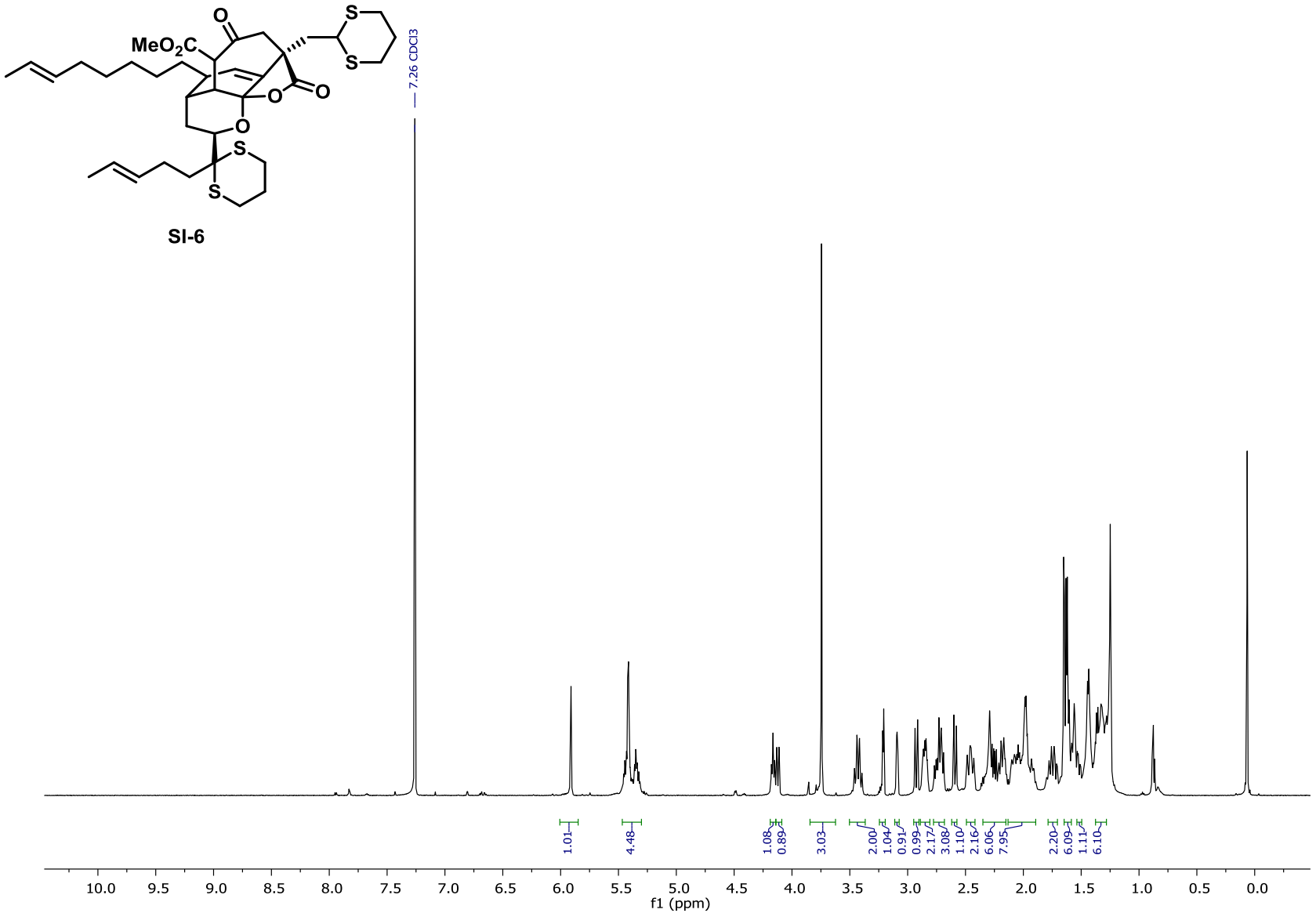


Figure 72 ^{1}H-NMR (600 MHz, $CDCl_3$) for β-keto ester **SI-6**

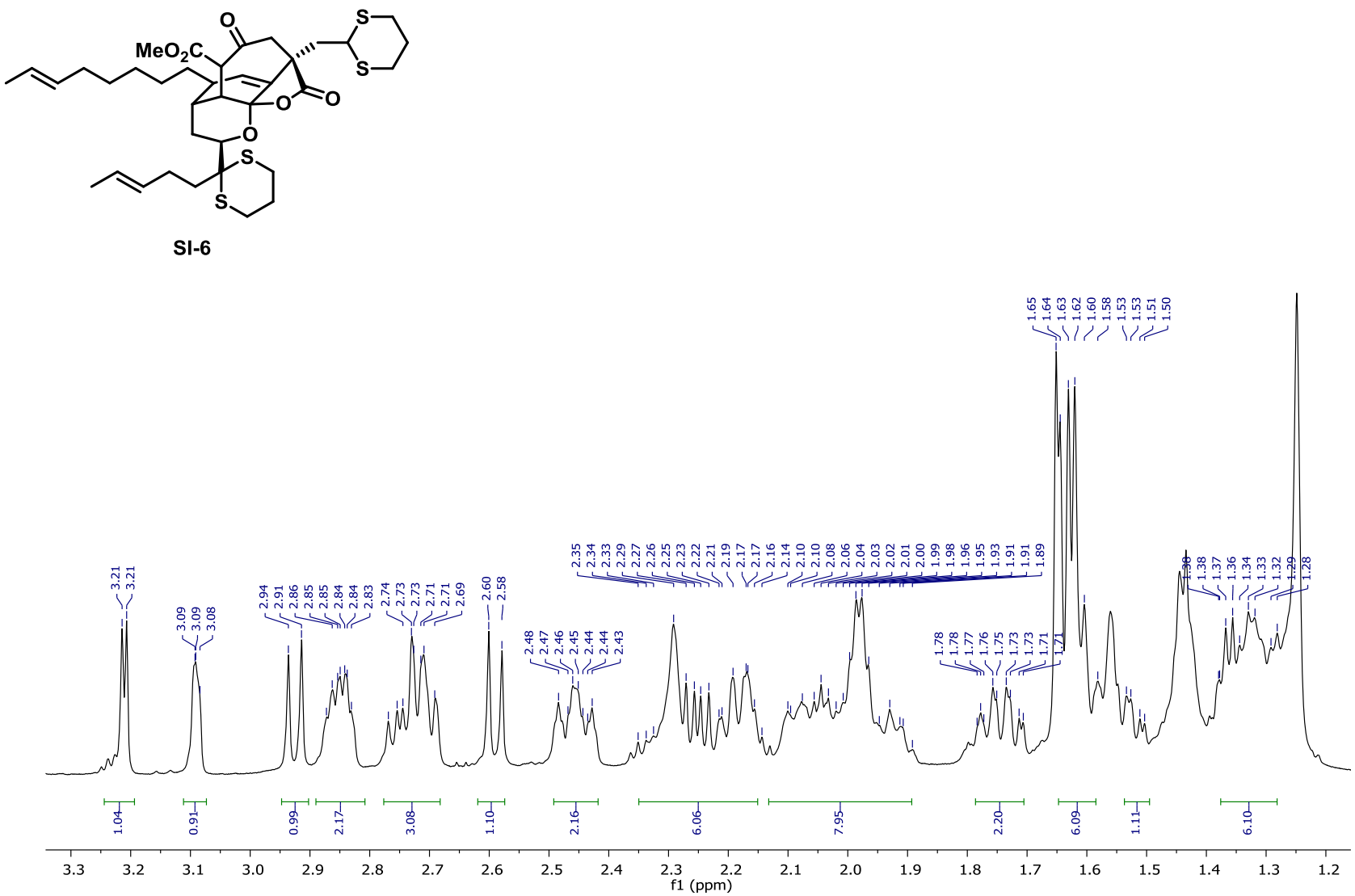


Figure 73 ^{1}H-NMR (600 MHz, $CDCl_3$) for β-keto ester **SI-6** (inset)

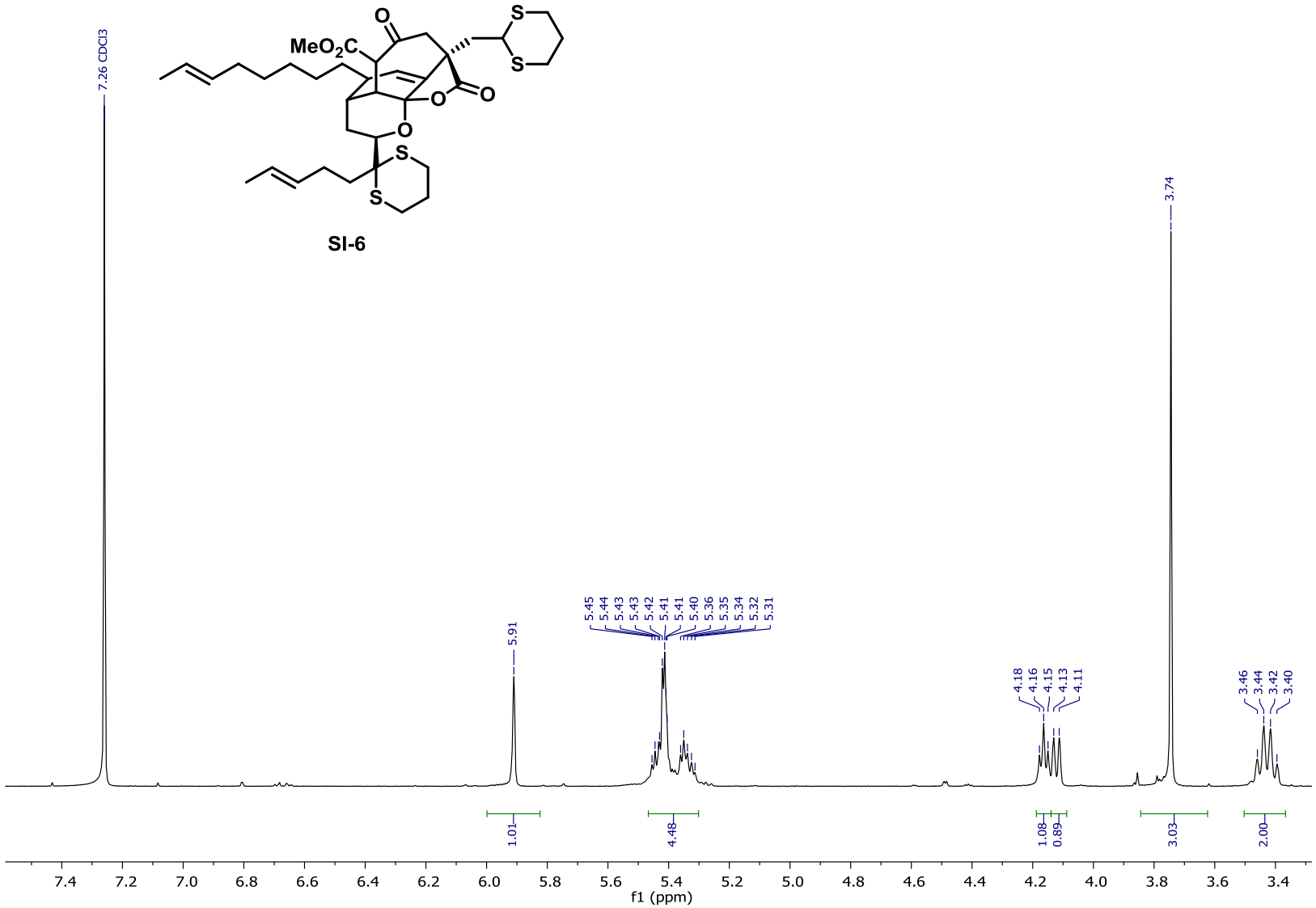


Figure 74 ^{1}H-NMR (600 MHz, $CDCl_3$) for β-keto ester **SI-6** (inset)

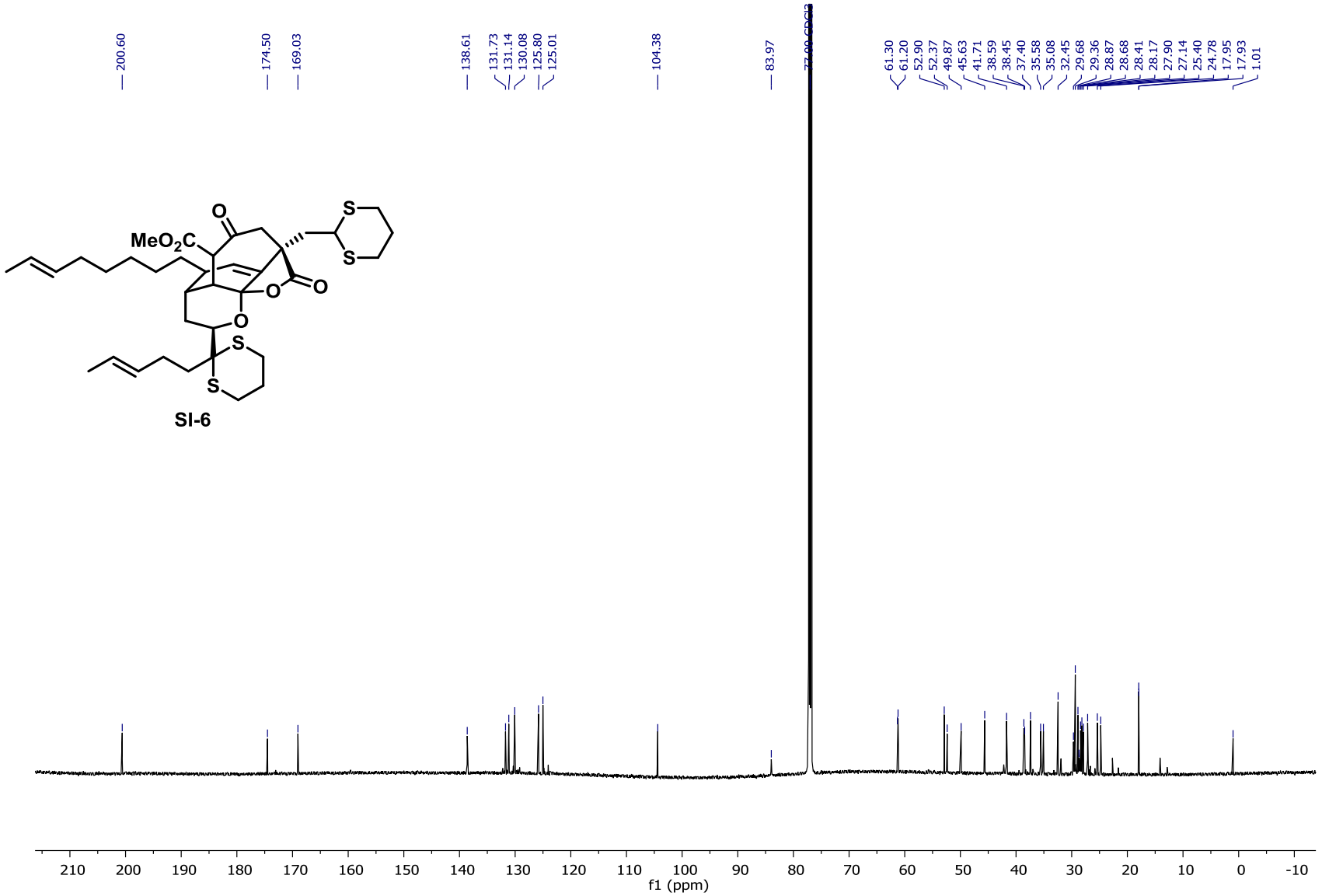


Figure 75 ^{13}C-NMR (150 MHz, $CDCl_3$) for β-keto ester **SI-6**

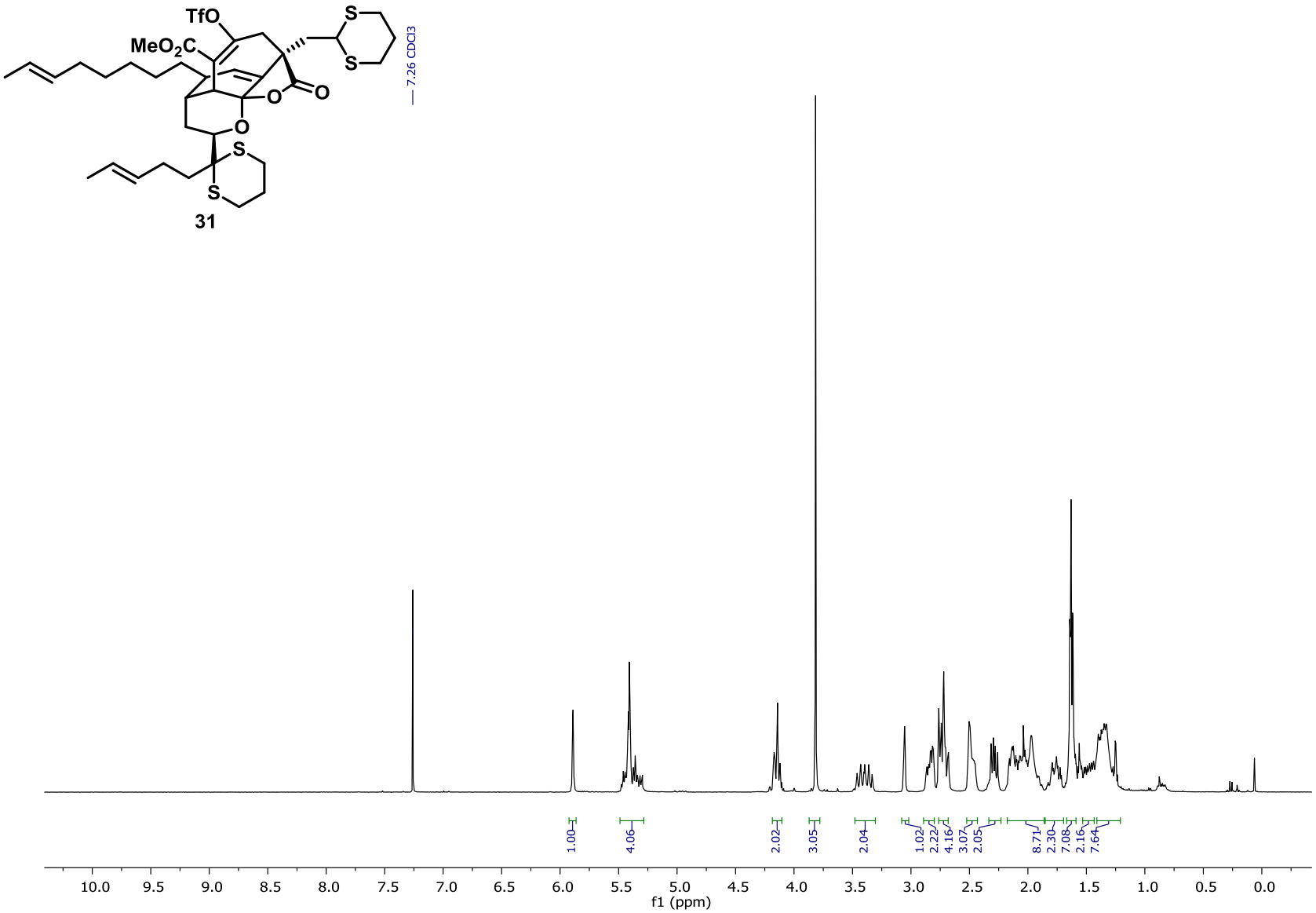


Figure 76 ^{1}H-NMR (400 MHz, $CDCl_3$) for enol triflate **31**

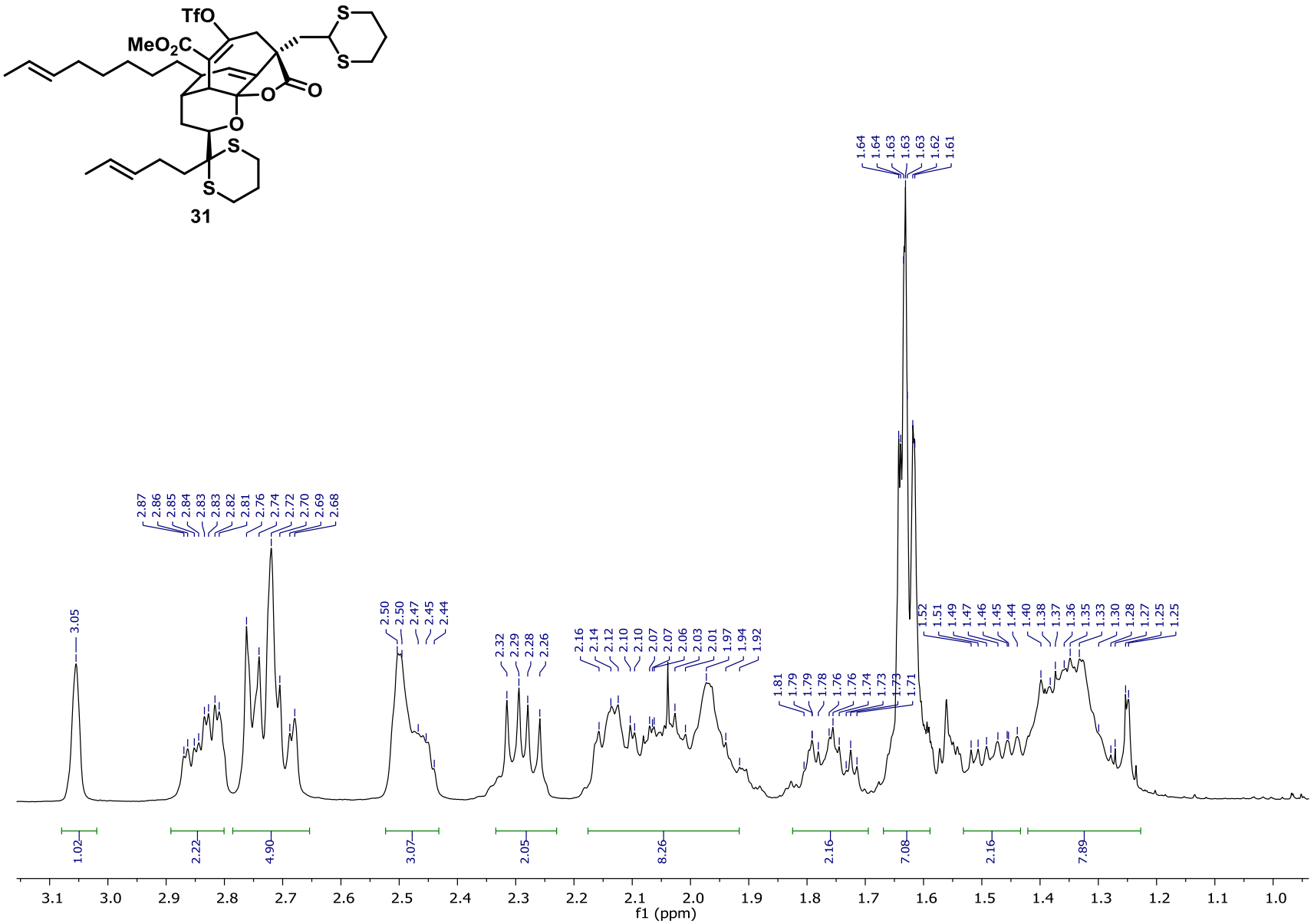


Figure 77 ^{1}H-NMR (400 MHz, $CDCl_3$) for enol triflate **31** (inset)

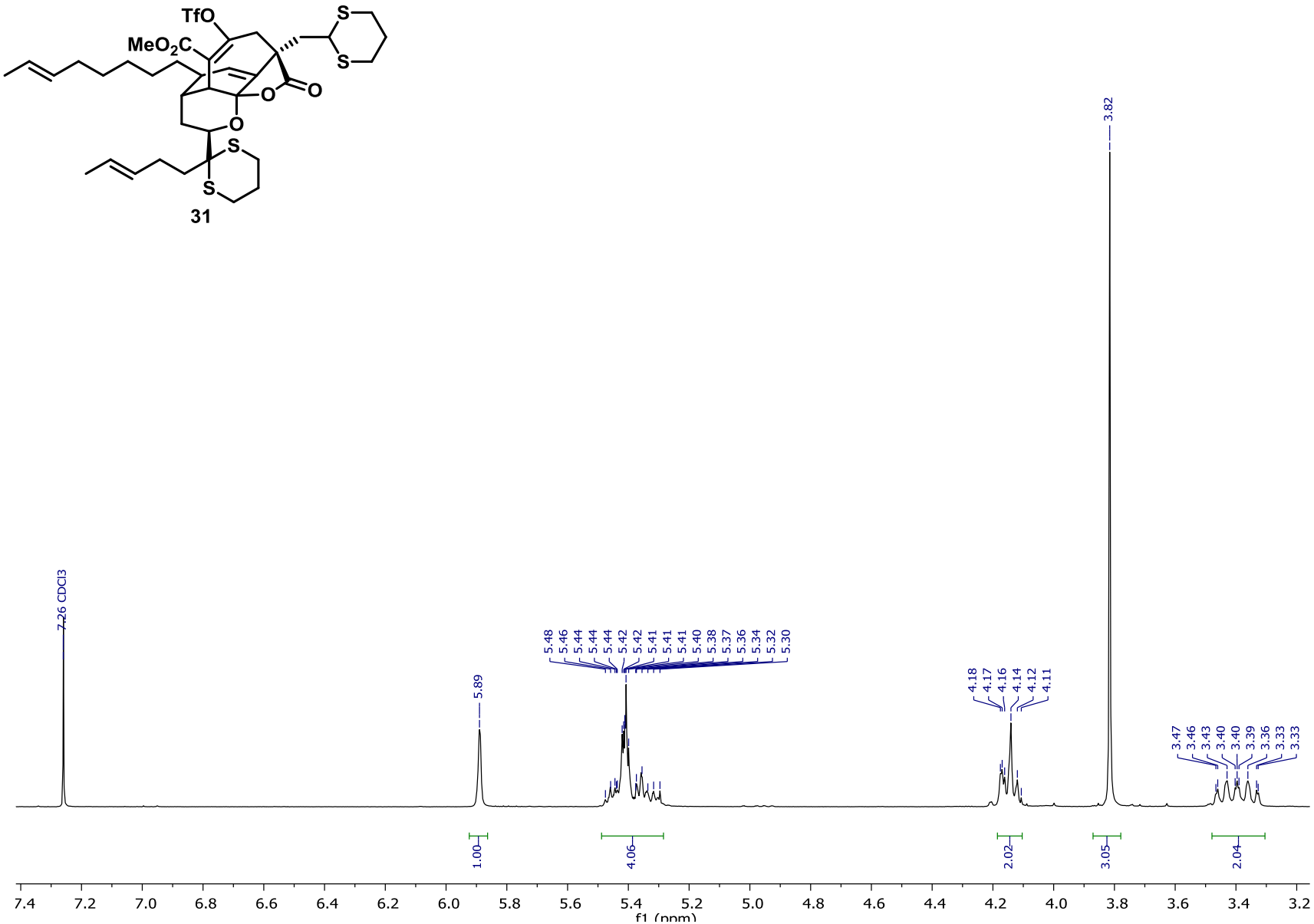


Figure 78 ^{1}H-NMR (400 MHz, $CDCl_3$) for enol triflate **31** (inset)

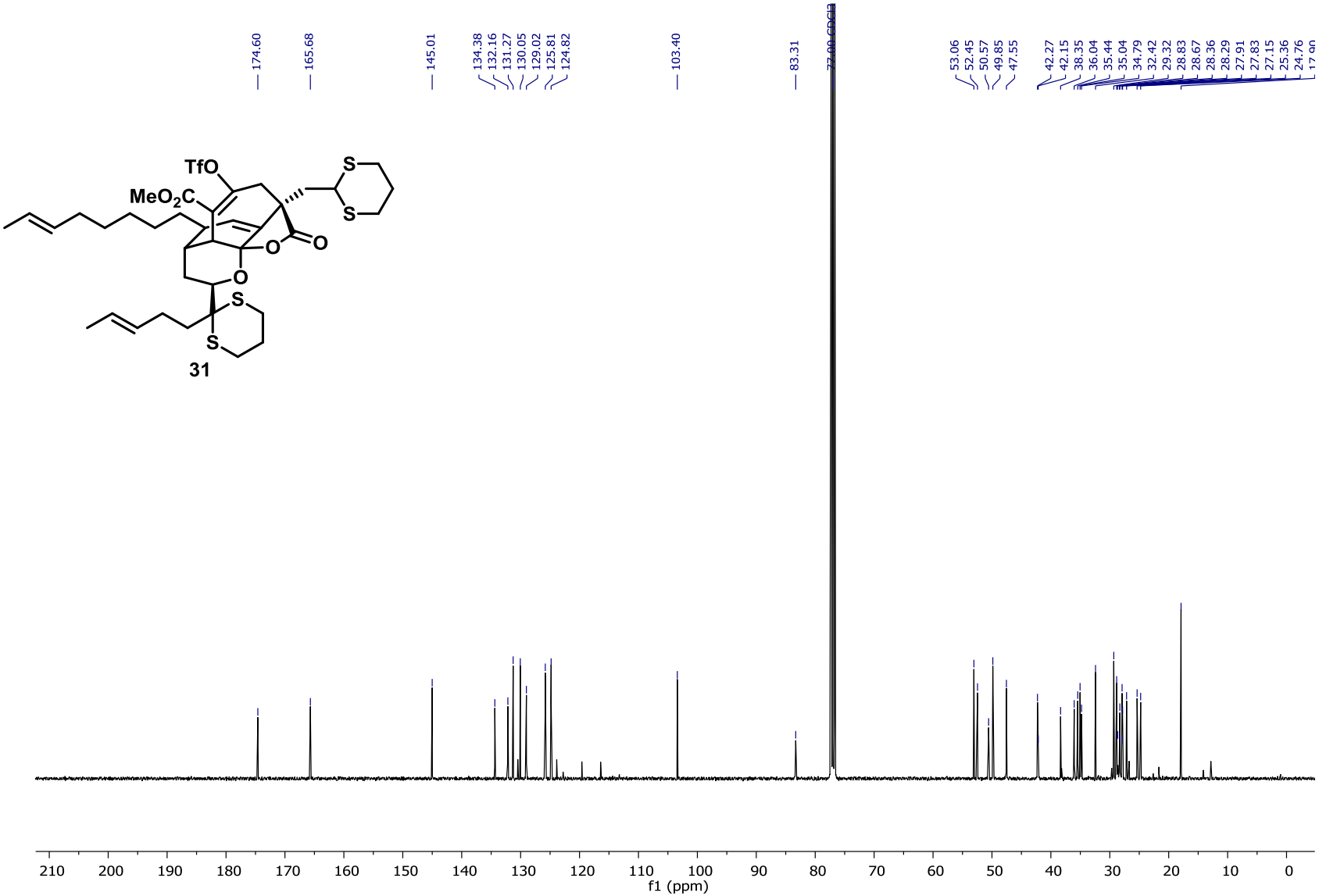


Figure 79 ^{13}C-NMR (100 MHz, $CDCl_3$) for enol triflate **31**

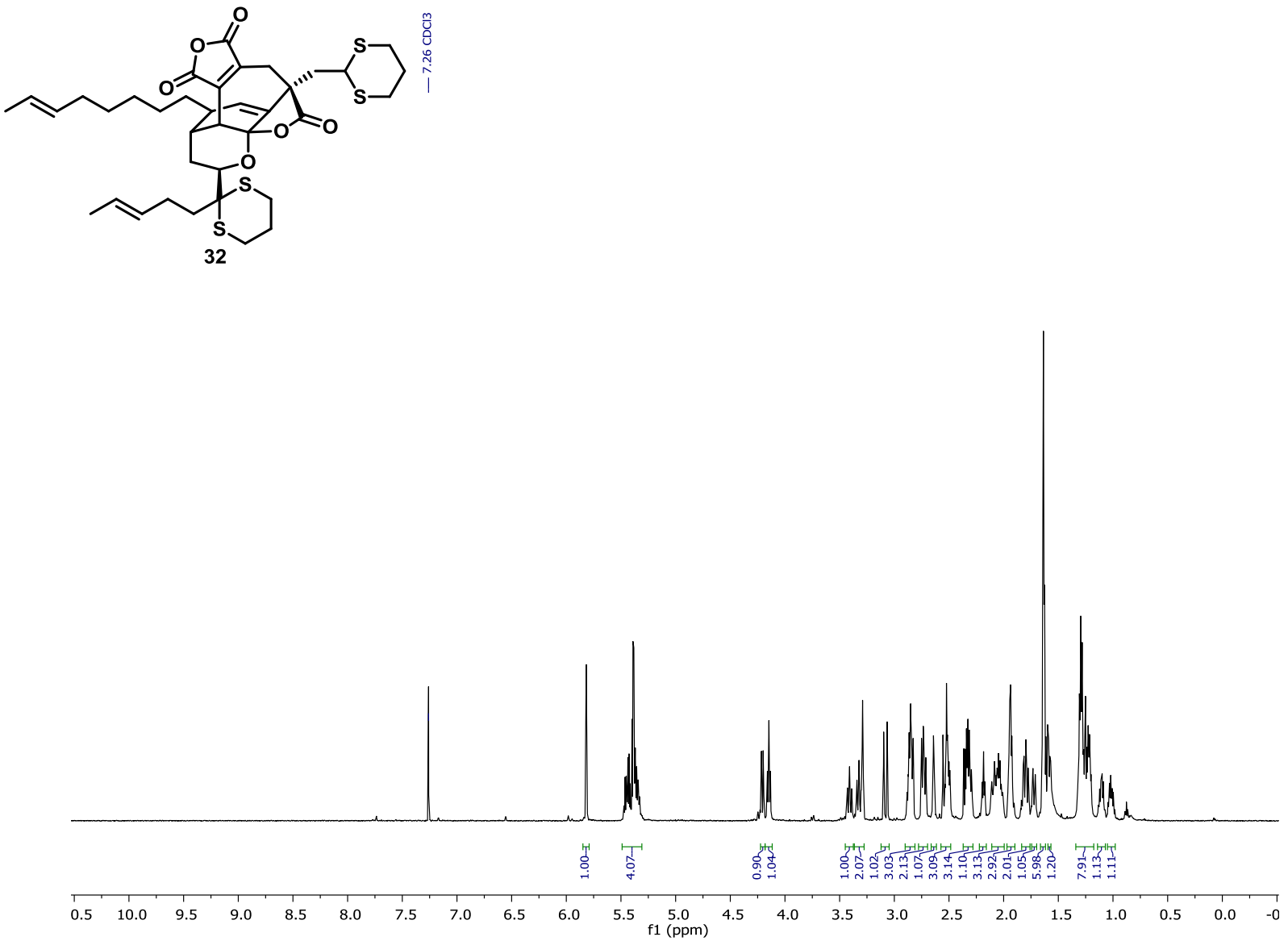


Figure 80 ^{1}H-NMR (600 MHz, $CDCl_3$) for maleic anhydride **32**

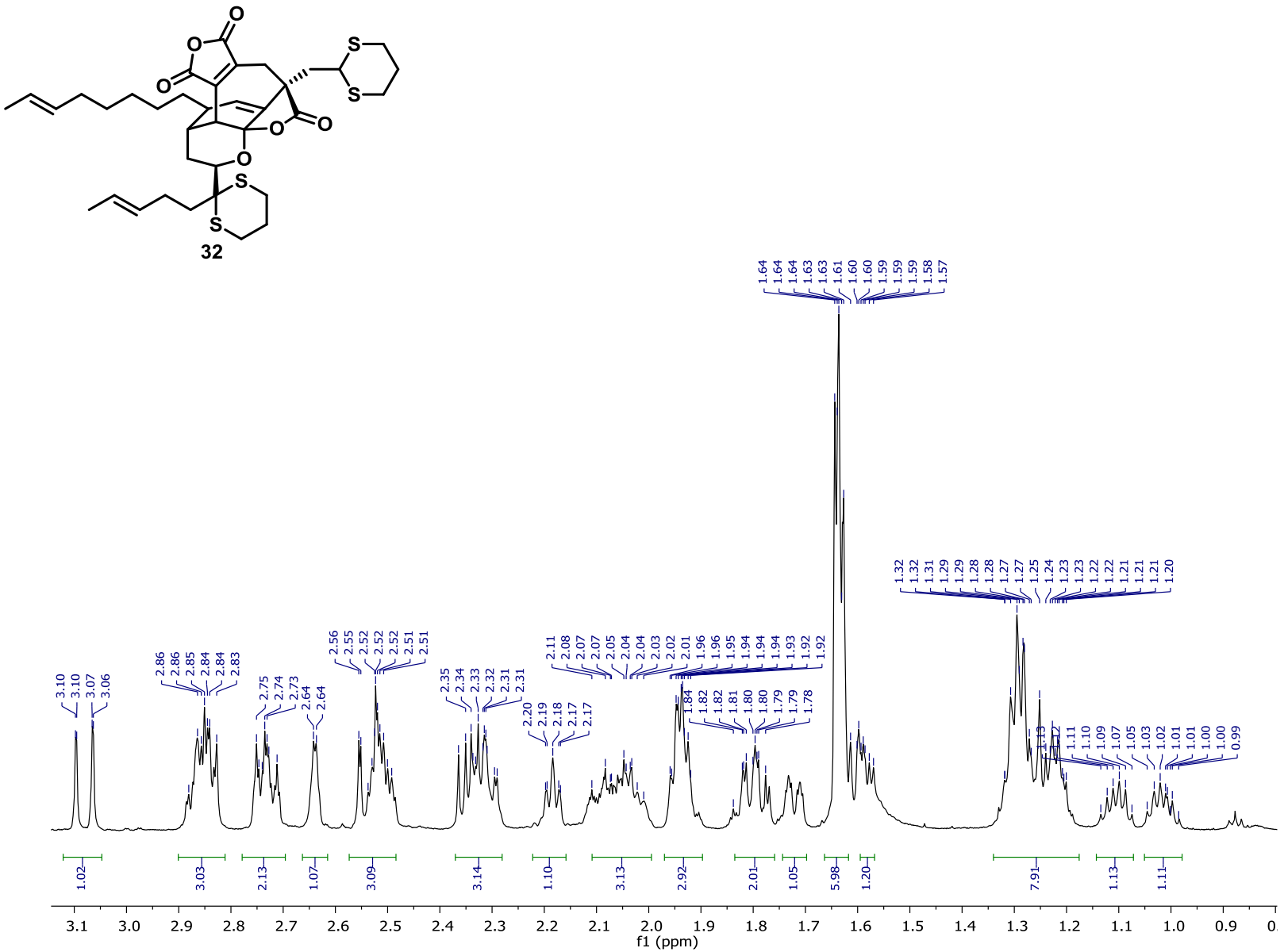
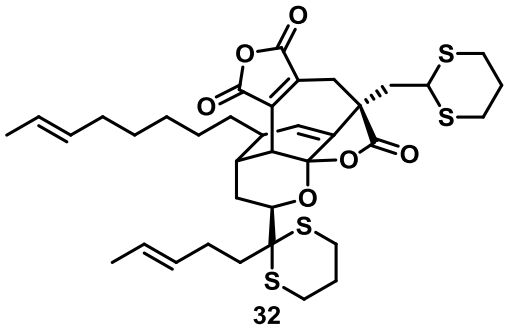


Figure 81 ^{1}H-NMR (600 MHz, $CDCl_3$) for maleic anhydride **32** (inset)



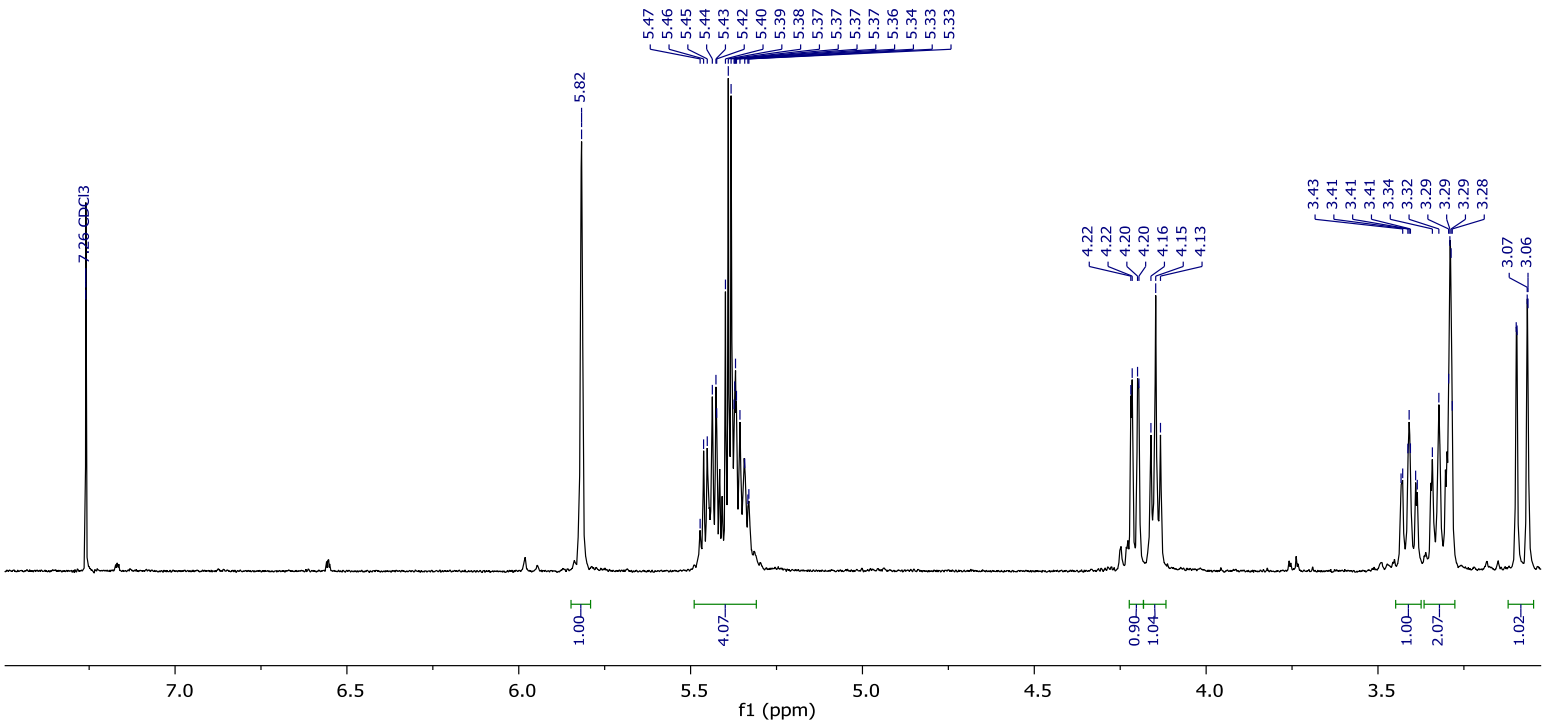


Figure 82 ^{1}H-NMR (600 MHz, $CDCl_3$) for maleic anhydride **32** (inset)

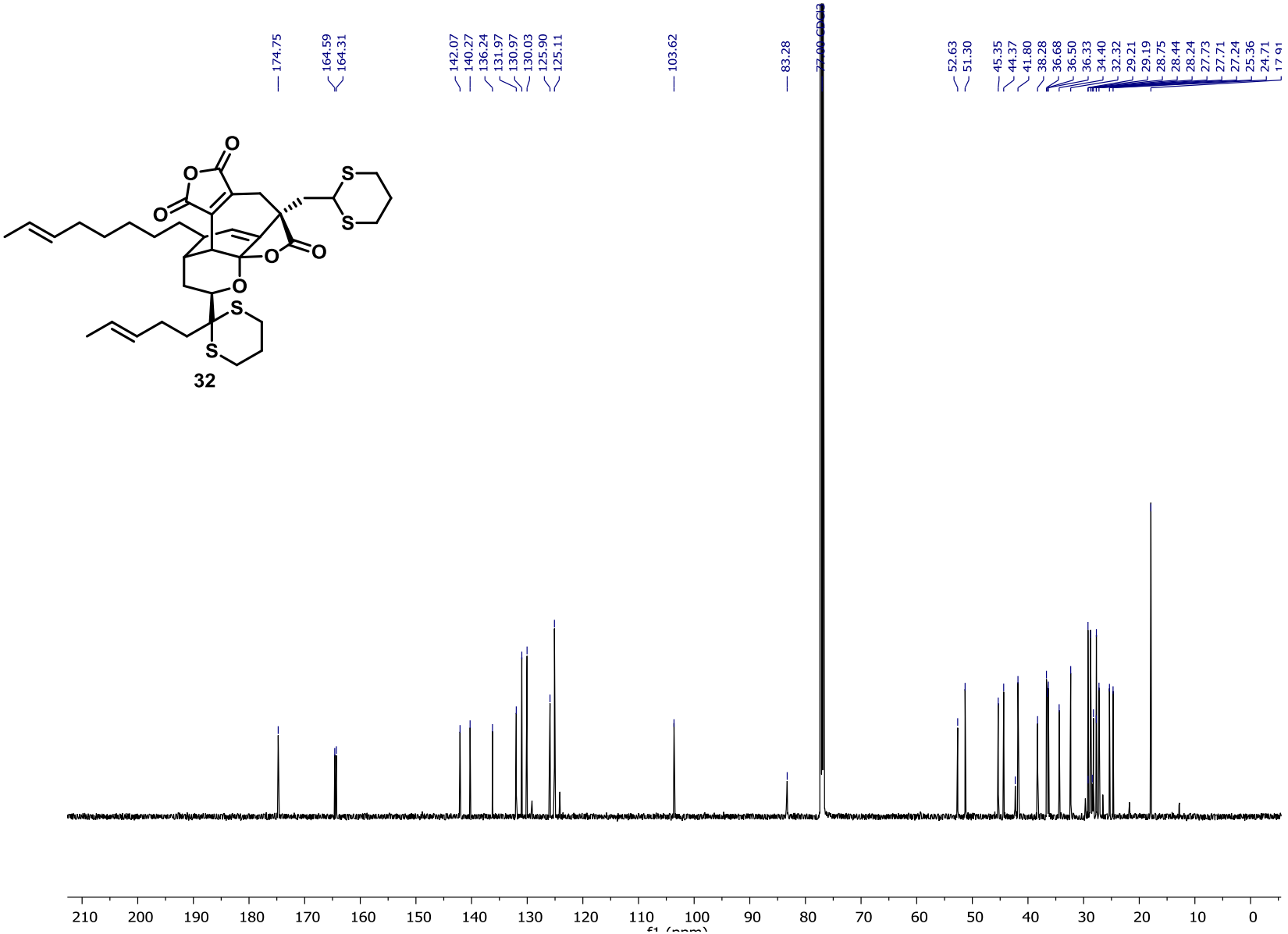


Figure 83 ^{13}C-NMR (150 MHz, $CDCl_3$) for maleic anhydride **32**

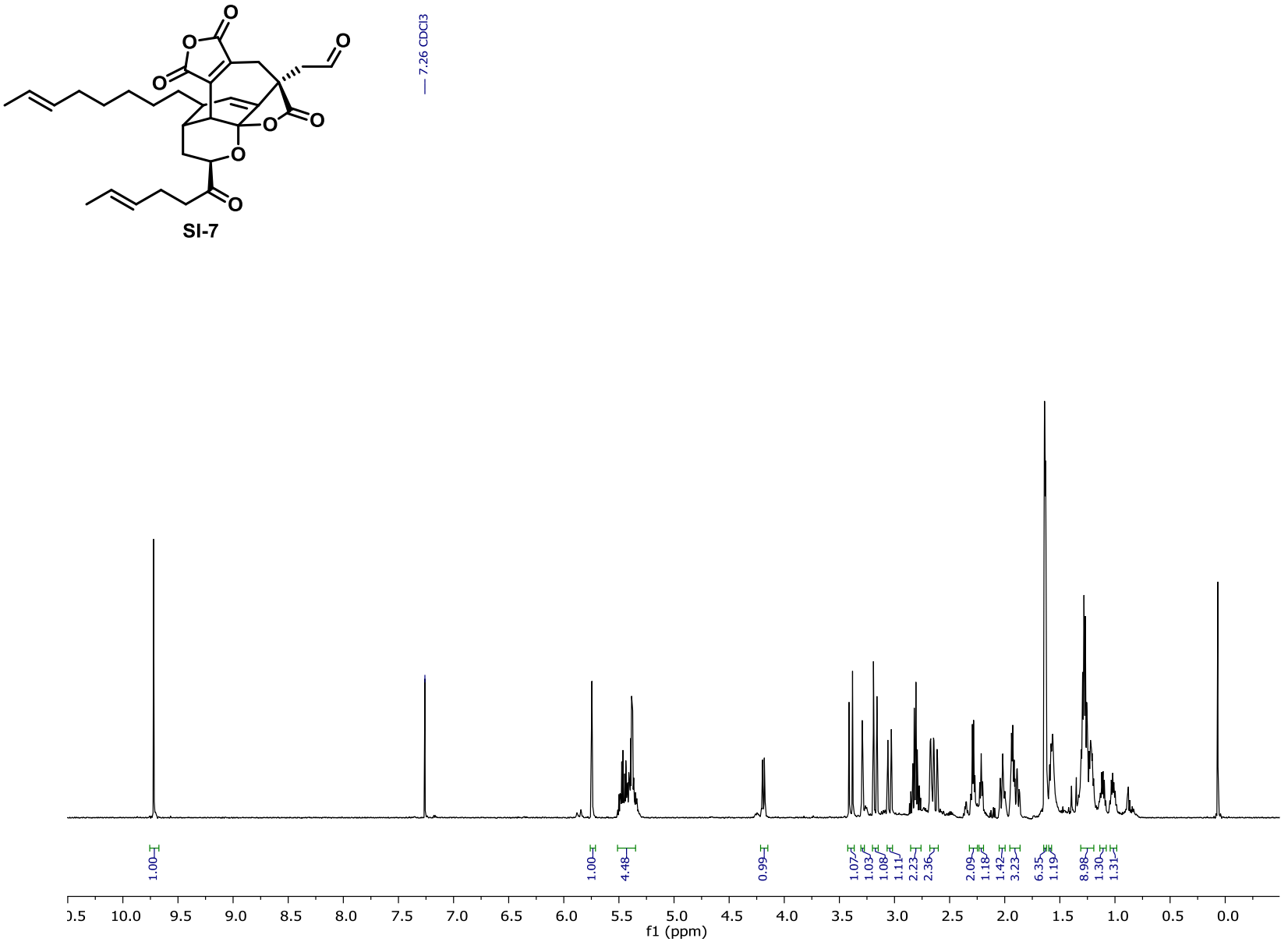


Figure 84 ^{1}H-NMR (600 MHz, $CDCl_3$) for aldehyde **SI-7**

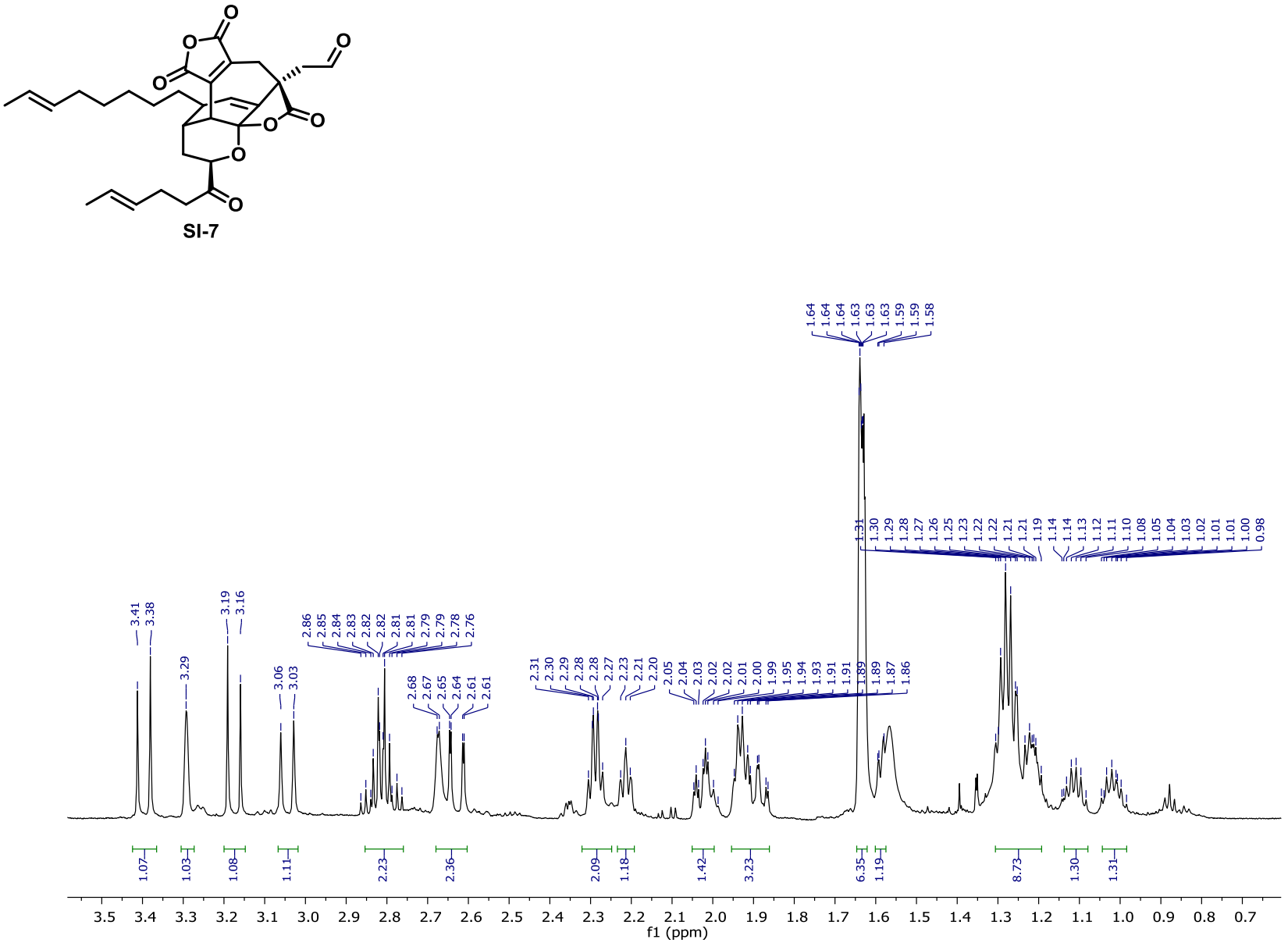


Figure 85 ^{1}H-NMR (600 MHz, $CDCl_3$) for aldehyde **SI-7** (inset)

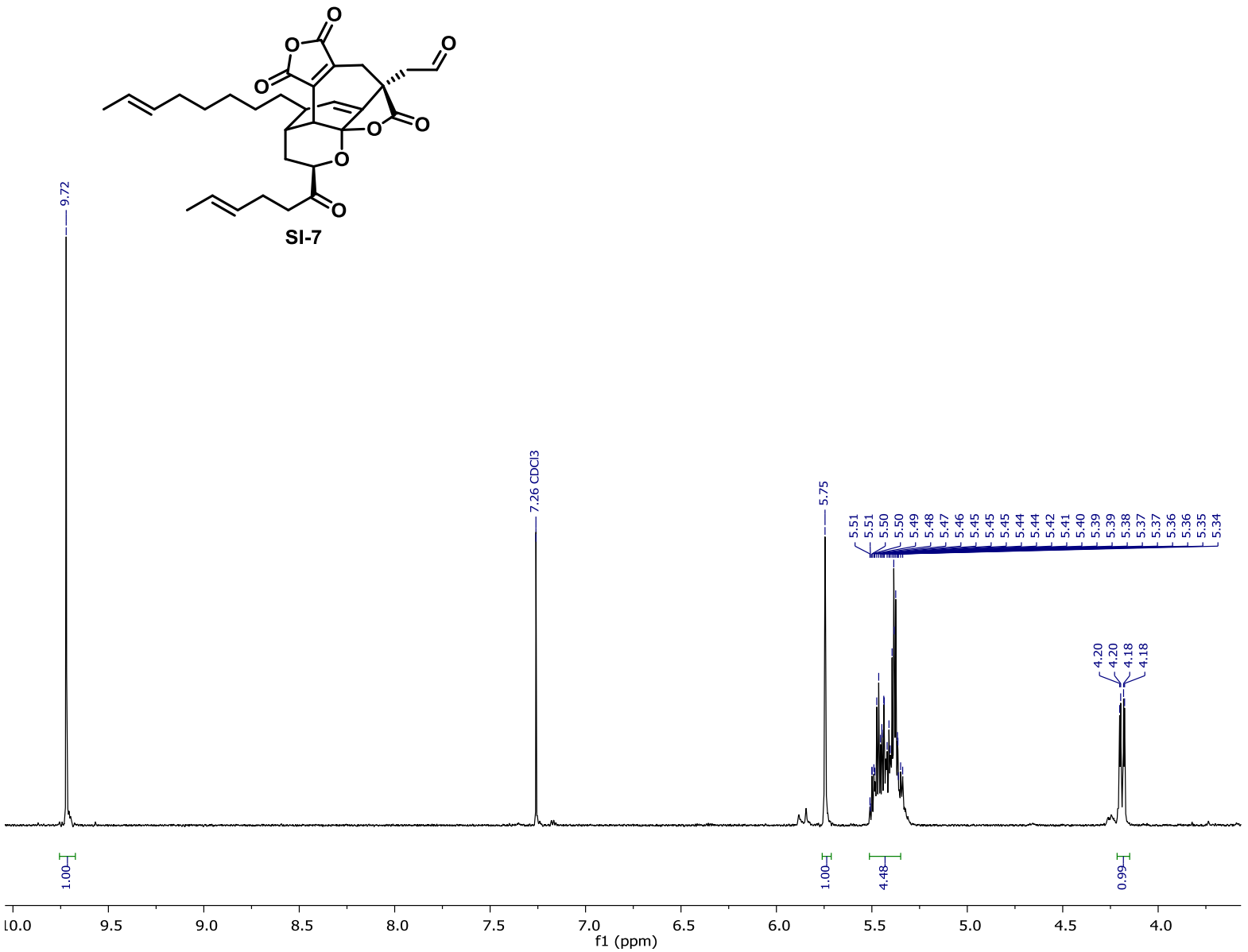


Figure 86 ^{1}H-NMR (600 MHz, $CDCl_3$) for aldehyde **SI-7** (inset)

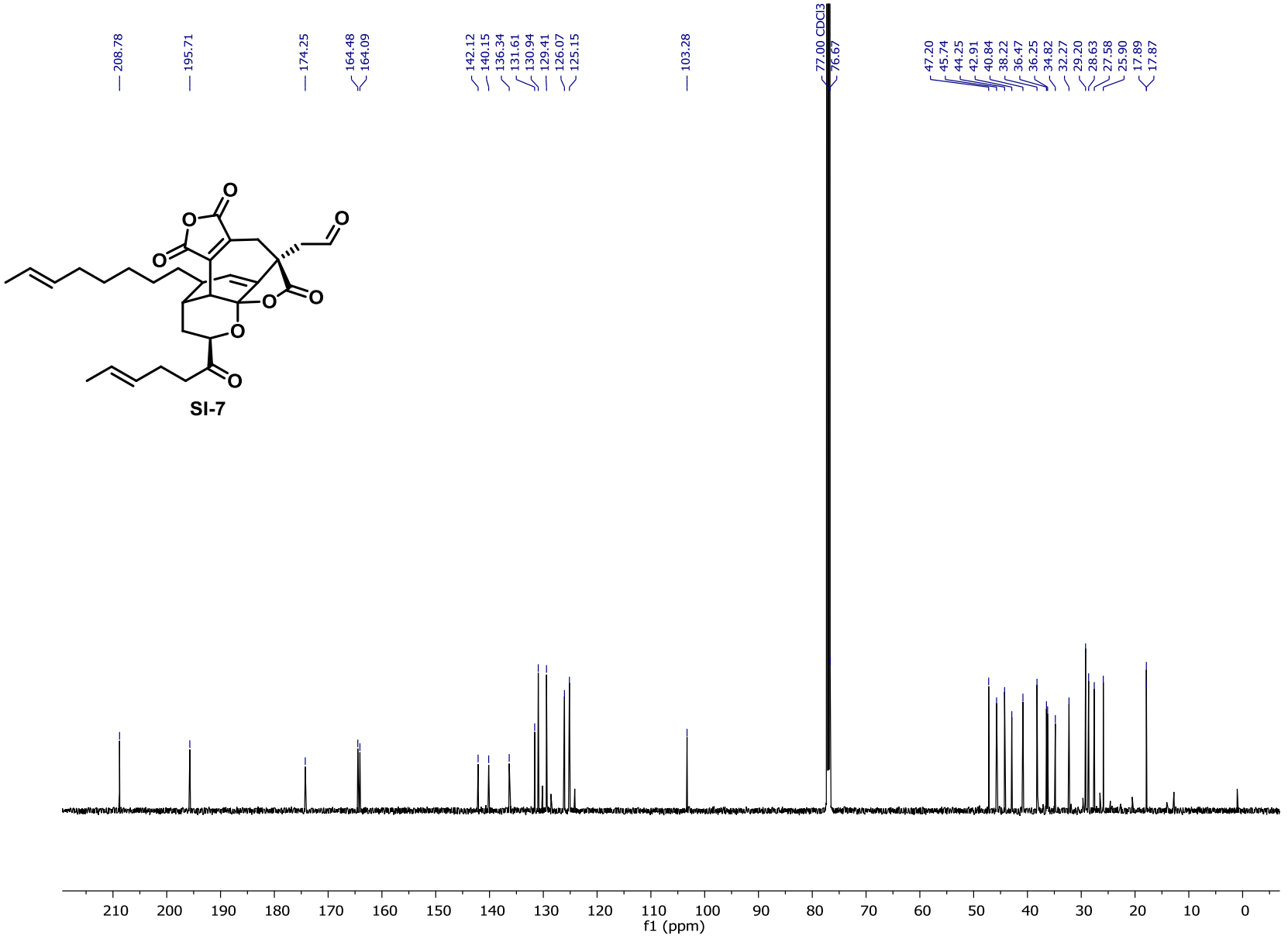


Figure 87 ^{13}C-NMR (150 MHz, $CDCl_3$) for aldehyde **SI-7**

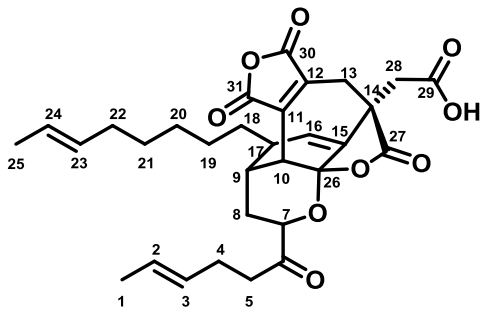


Figure 88 ^{1}H-NMR (600 MHz, acetone-d_6) for phomoidride D **(4)**

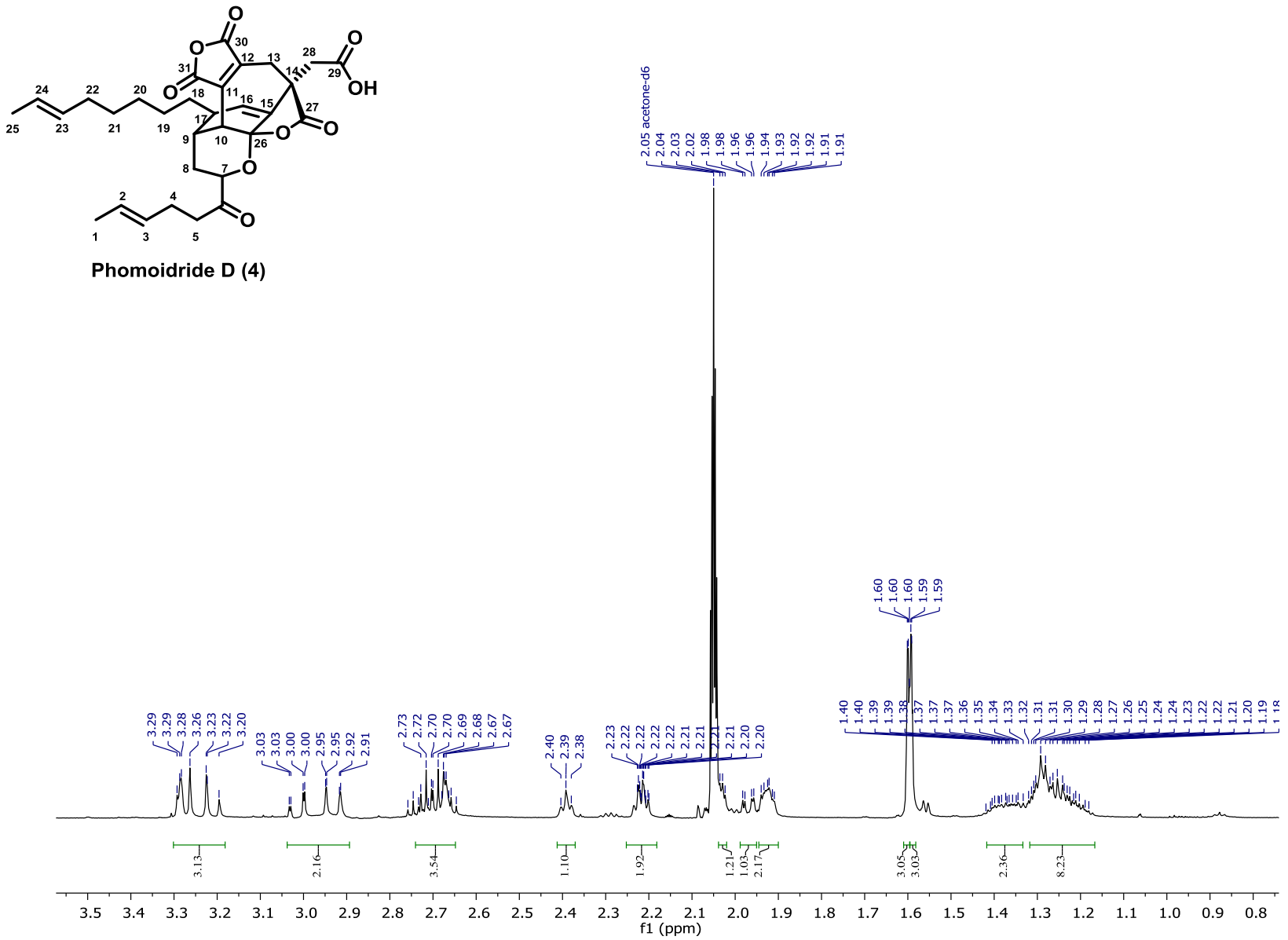
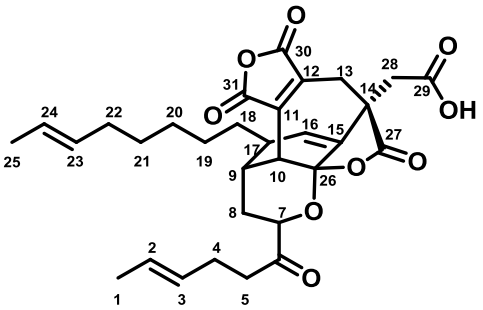


Figure 89 ^{1}H-NMR (600 MHz, acetone-d_6) for phomoidride D **(4)** (inset)



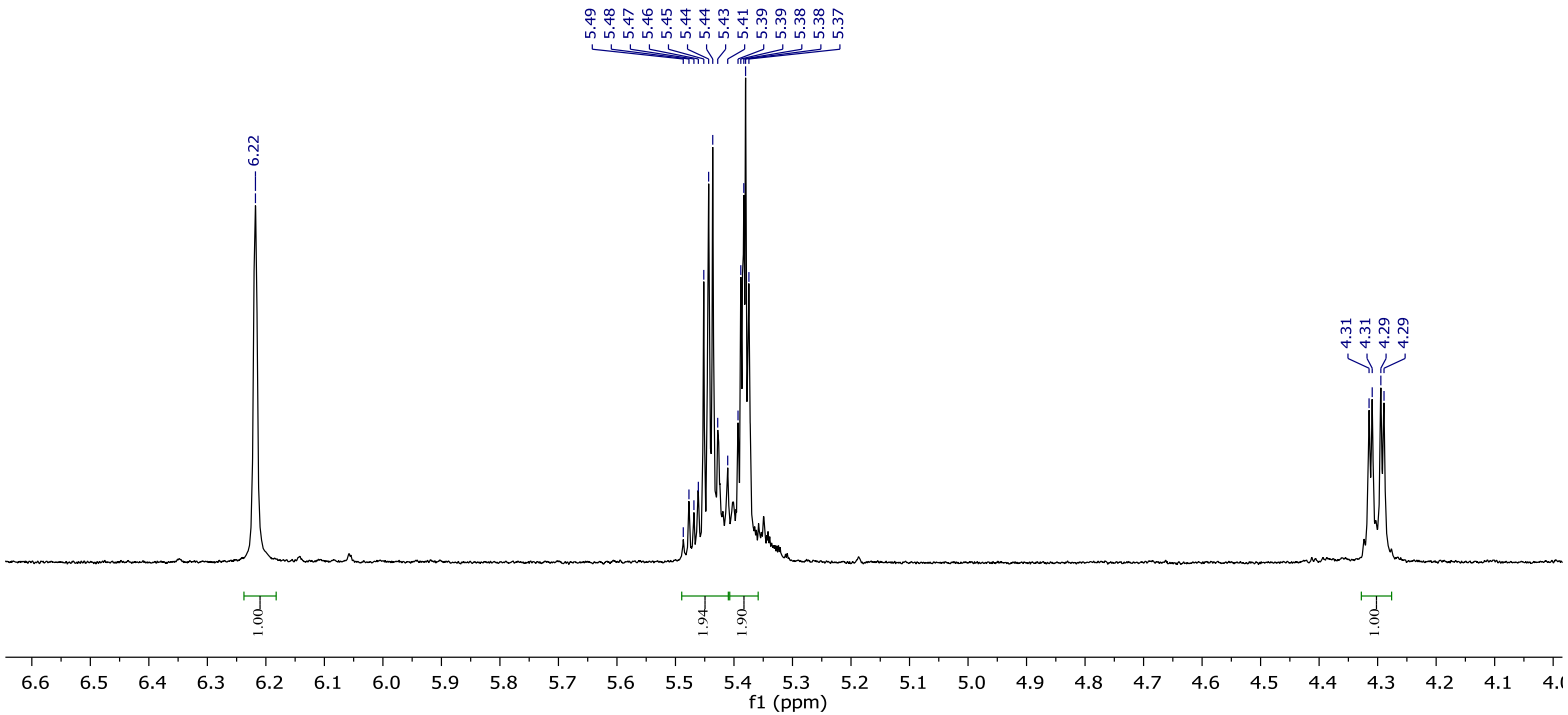


Figure 90 ^{1}H-NMR (600 MHz, acetone-d_6) for phomoidride D **(4)** (inset)

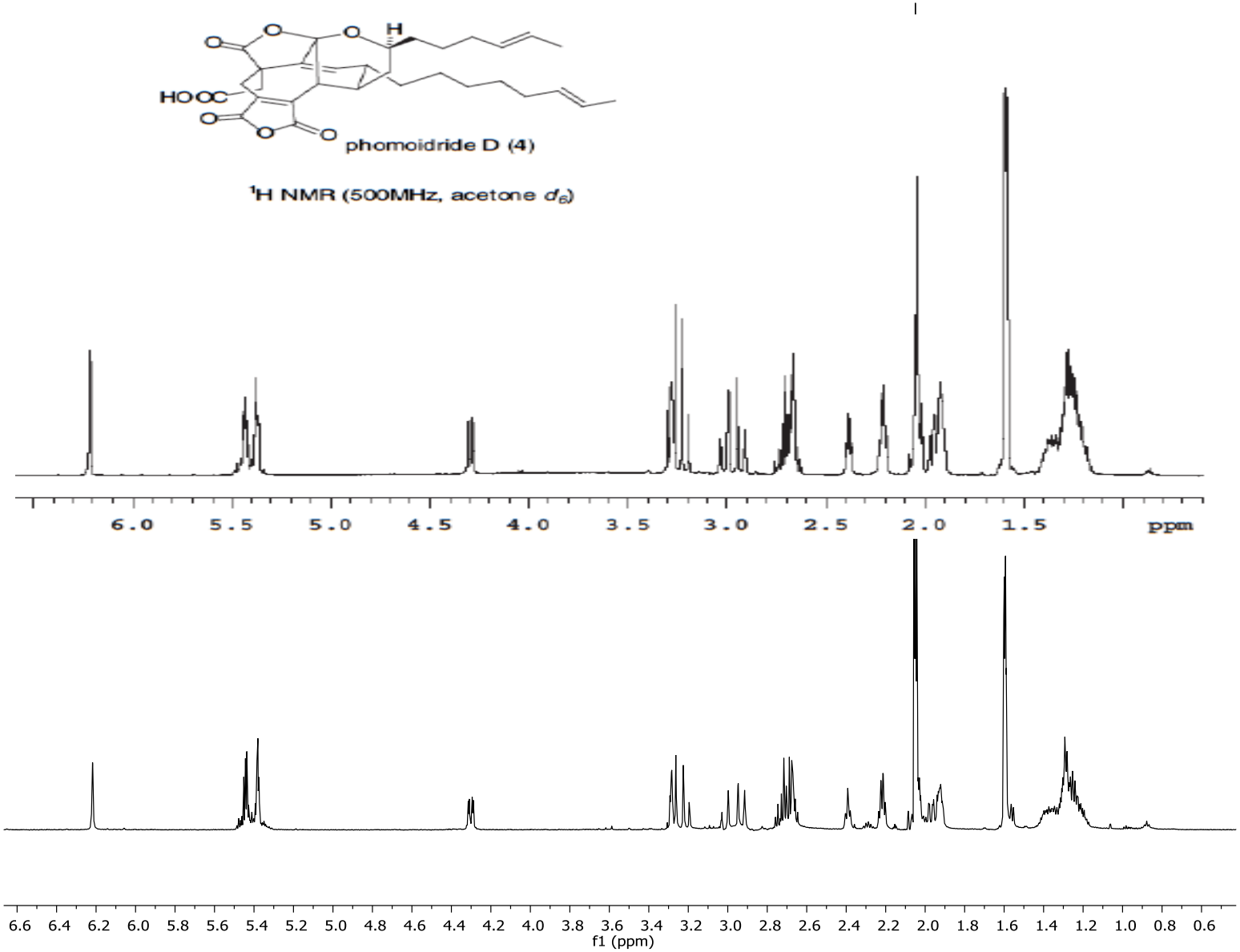


Figure 91 ^{1}H-NMR (acetone-d_6) comparison for phomoidride D (top, Sulikowski (500 MHz); bottom, Wood (600 MHz))

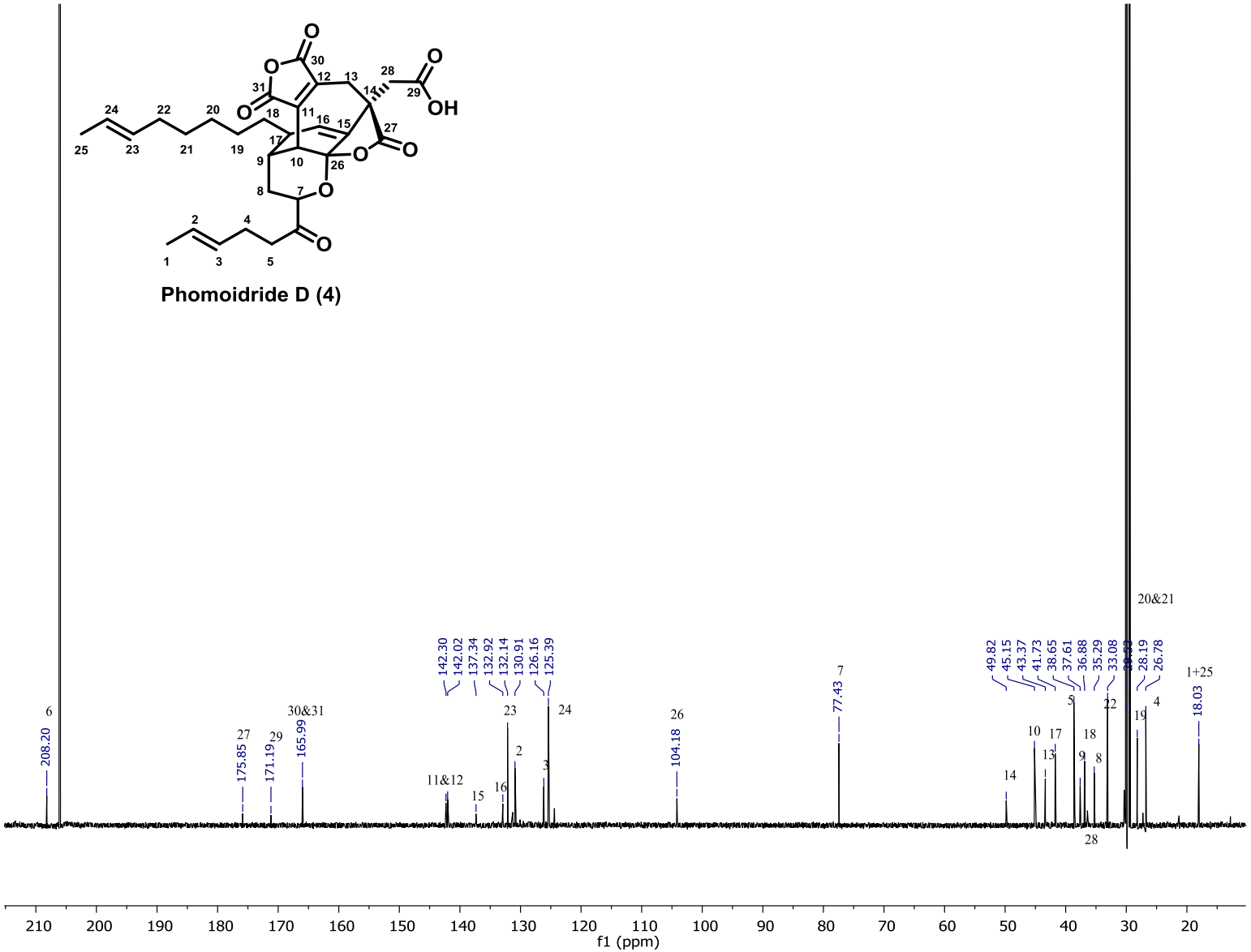


Figure 92 ^{13}C-NMR (150 MHz, acetone-d_6) for phomoidride D **(4)**

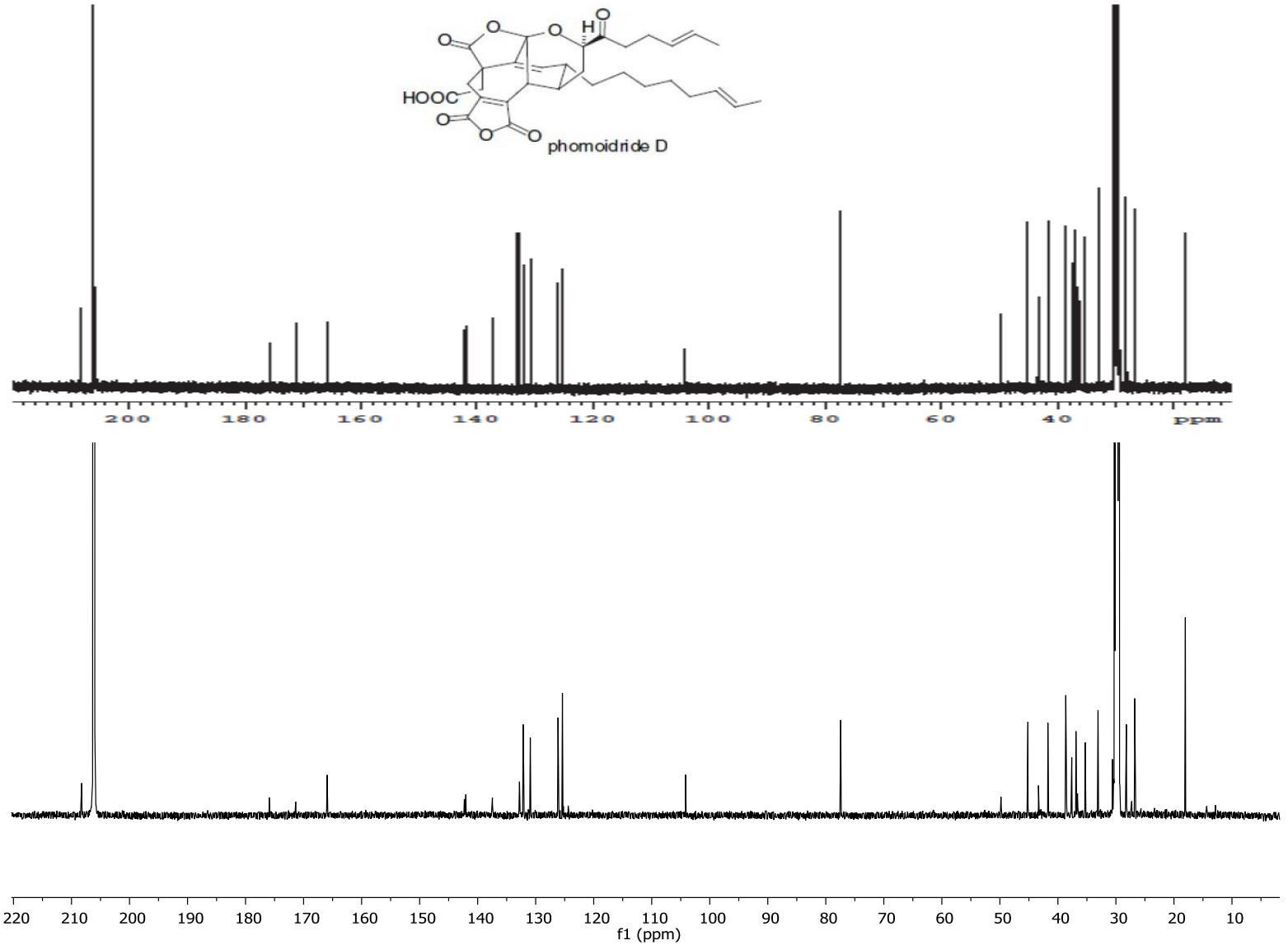


Figure 93 ^{13}C-NMR (acetone-d_6) comparison for phomoidride D (top, Sulikowski (125 MHz); bottom, Wood (150 MHz))

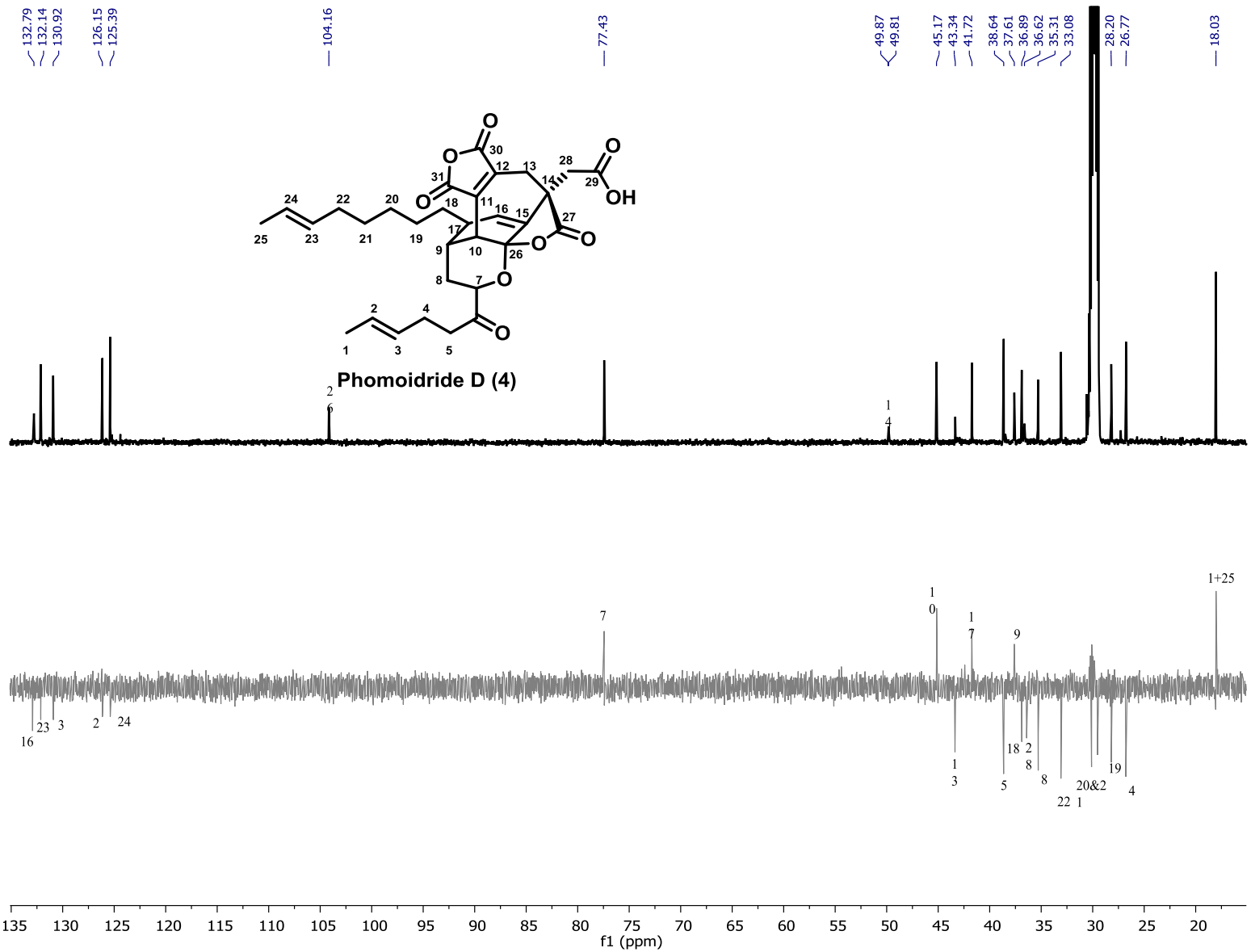


Figure 94 DEPT-135 (150 MHz, acetone-d_6) for phomoidride D **(4)**

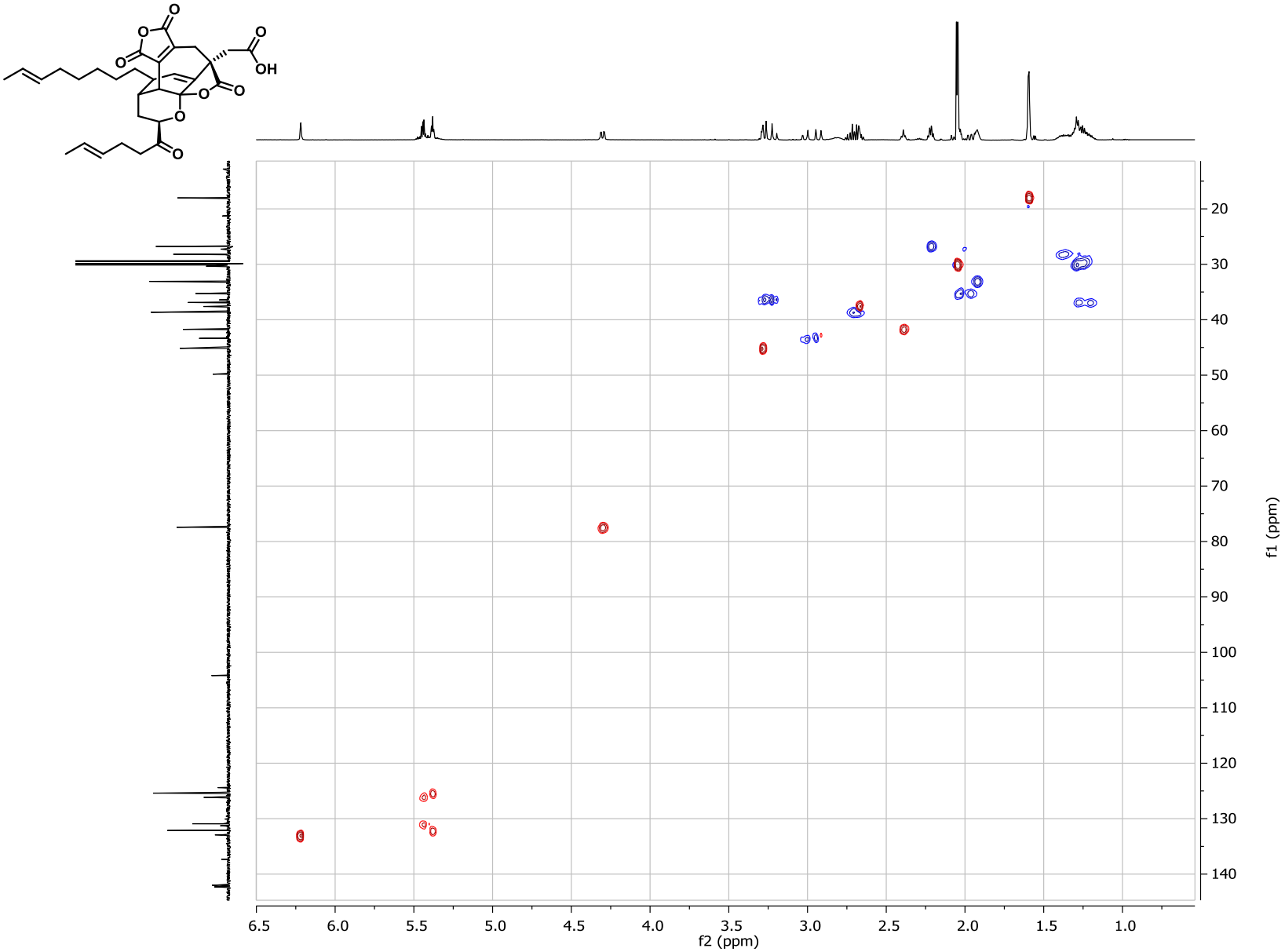


Figure 95 HSQC (acetone-d_6) for phomoidride D **(4)**

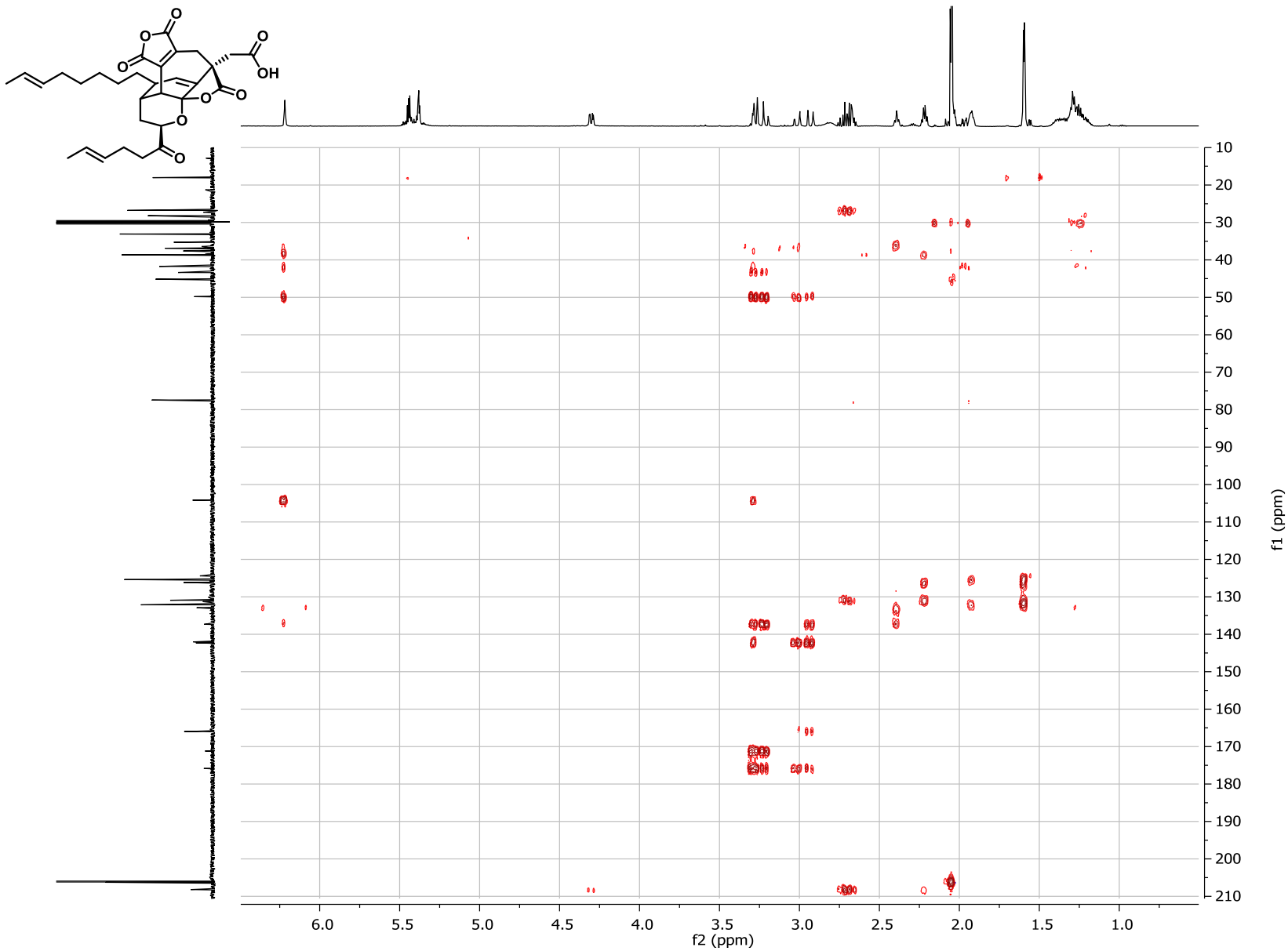


Figure 96 HMBC (acetone-d_6) for phomoidride D **(4)**

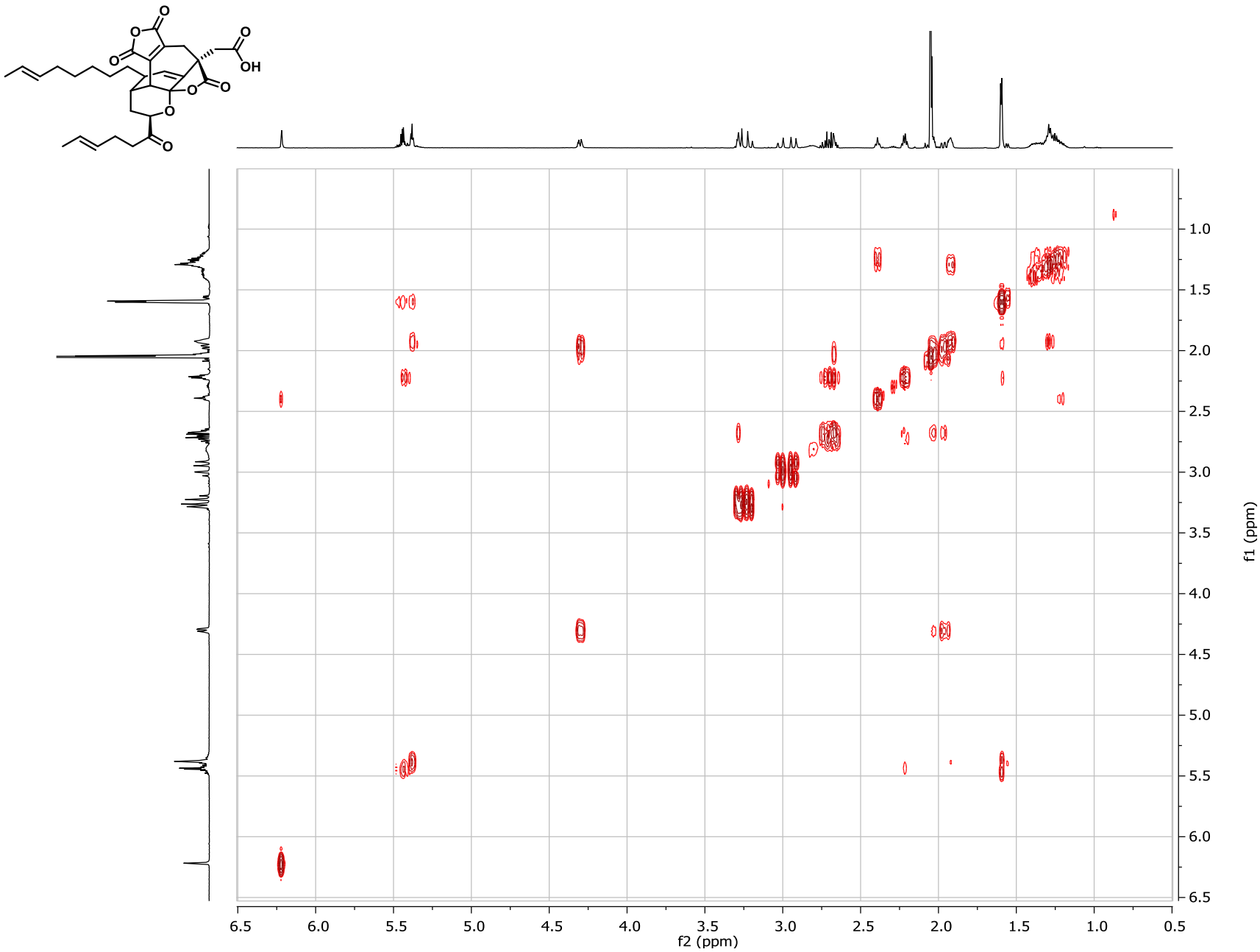


Figure 97 COSY (acetone-d_6) for phomoidride D **(4)**

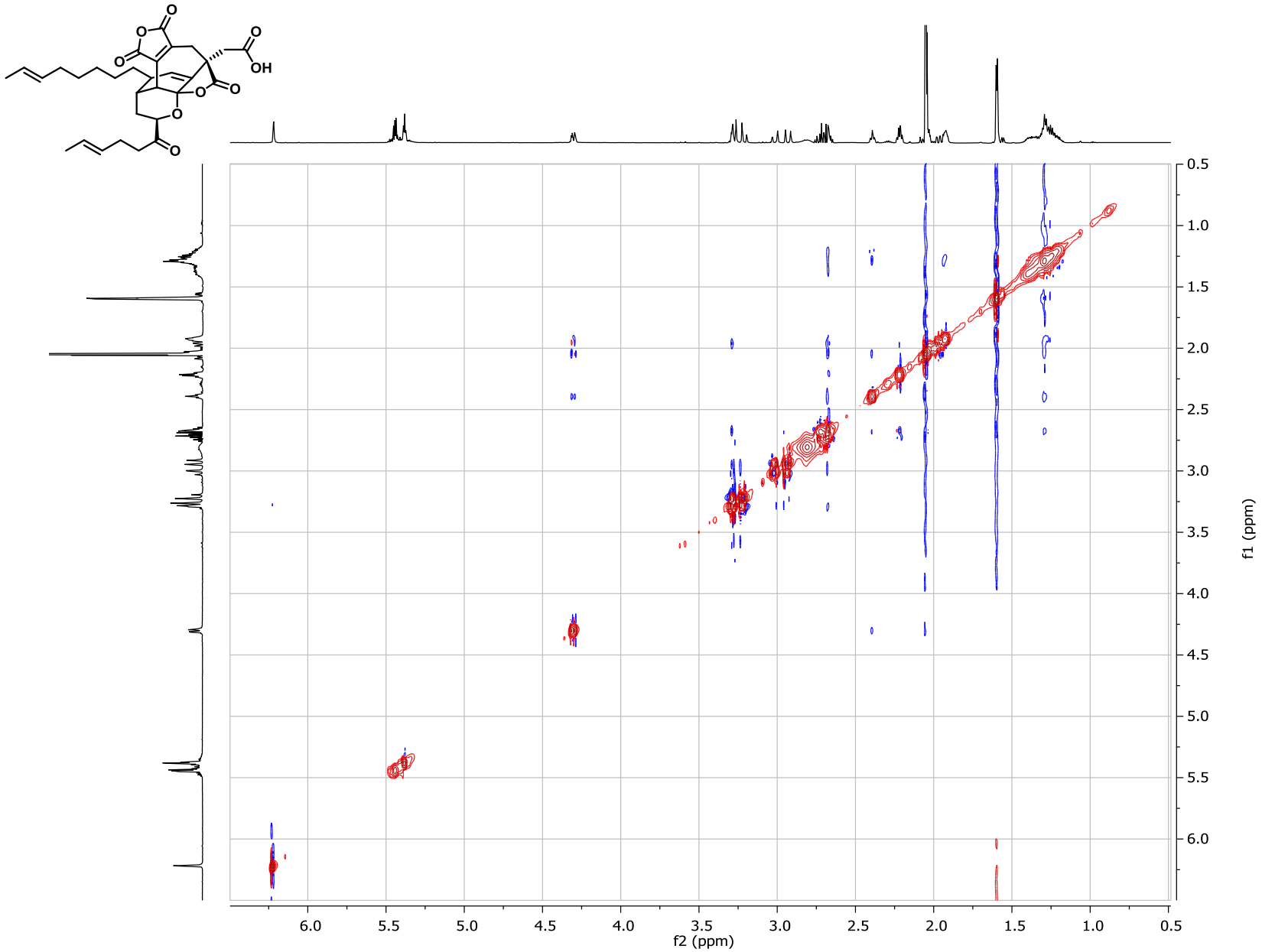


Figure 98 NOESY (acetone-d_6) for phomoidride D **(4)**