Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

Efficient, Divergent Synthesis of Cryptophycin Unit A Analogues

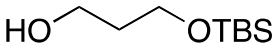
Kyle L. Bolduc, Scott D. Larsen* and David H. Sherman*

Life Sciences Institute and Departments of Medicinal Chemistry, Chemistry, and Microbiology & Immunology, University of Michigan, Ann Arbor, Michigan 48109, United States

Materials and Methods. Unless otherwise stated, all reactions were performed with no extra precautions taken to exclude moisture or air. Anhydrous, inhibitor-free tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were purchased from Sigma-Aldrich, and anhydrous acetonitrile (ACN) was purchased from Acros and used as received. Dichloromethane (DCM) was shaken with sat. aq. $NaHCO_3$, distilled from CaH_2, and degassed with three rounds of a freeze-pump-thaw procedure. All other chemicals were obtained from Sigma-Aldrich, Alfa Aesar, Strem, or TCI and used directly unless otherwise noted.

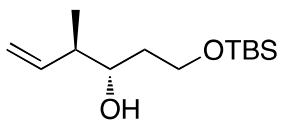
^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Varian 400 and 500 MHz NMRs. Proton chemical shifts are reported in ppm referenced to residual solvent in $CDCl_3$ (7.26 ppm) as the internal standard; carbon chemical shifts are reported in ppm referenced to the centerline of residual solvent in $CDCl_3$ (77.16 ppm) as the internal standard. Proton spectral data are described as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constant (in Hz), and integration. High-resolution mass spectra were obtained on an Agilent Accurate-Mass Q-TOF 6520. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} TLC glass plates with a fluorescent indicator from EMD Chemicals. EMD Silica Gel 60 *Geduran*® (particle size 0.040 – 0.063 mm) silica gel was used for flash chromatography. Visualization was accomplished by UV fluorescence quenching (254 nm) and by *p*-anisaldehyde or potassium permanganate staining with heating.

Experimental Procedures



4

3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (4). To a stirred solution of 1,3-propanediol (5.0 g, 65.71 mmol) in 250 mL anhydrous THF under argon was slowly added solid NaH (2.63 g, 65.71 mmol) at 0 °C. The reaction was stirred for 30 min, then treated with slow addition of TBSCl (9.90 g, 65.71 mmol) dissolved in minimal THF. The reaction was stirred for an additional 1 hour and allowed to warm to room temperature, then quenched with sat. aq. NH_4Cl. Solvent removed by rotary evaporation and residue partitioned between water (100 mL) and ethyl acetate (EtOAc, 100 mL). Aqueous layer extracted with EtOAc (150 mL x 3) and combined organics washed with brine (250 mL) and dried with Na_2SO_4. Evaporation of the solvent and chromatographic purification (SiO_2, 4:1 hexanes:EtOAc [H:E]) afforded the desired product (**4**, 11.56 g, 92%) as a clear, colorless oil. TLC R_f = 0.30 (4:1 H:E). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.81 (m, 4H), 2.65 (s, 1H), 1.76 (q, *J* = 5.5 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 63.01, 62.49, 34.34, 26.01, 18.31, -5.36 ppm; HRMS (ESI+) 191.1462 *m/z* $[M+H]^+$ ($C_9H_{23}O_2Si$ requires 191.1467).

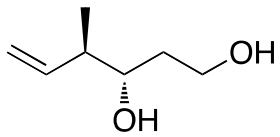


6

(3*S*,4*R*)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylhex-5-en-3-ol (6). To an oven-dried, 100 mL RBF under argon was added **5**[1] (2.45 g, 2.34 mmol), K_3PO_4 (4.96 g, 23.37 mmol), anhydrous THF (25 mL), and water (2.10 mL, 116.85

[1] Flash chromatography of the catalyst did not give significantly higher yield or selectivity, so purification was omitted.

mmol). The 3-buten-2-yl acetate (5.93 mL, 46.74 mmol) and **4** (4.45 g, 23.37 mmol) were then added and reaction stirred at room temp for 30 min. The reaction was then warmed to 70 ^{o}C and stirred under argon for 24 h. Next, the reaction was cooled to room temp and filtered, washing with THF. The filtrate was concentrated *in vacuo* and diluted into pentane (150 mL). Solids removed (or recovered to recycle the catalyst)[2] by filtration and eluent concentrated by rotary evaporation to afford crude **6** as a 6:1 diastereomeric mixture. This residue was used without further purification. TLC R_f = 0.45 (10:1 H:MTBE x2). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.82 (m, 1H), 5.04 (m, 2H), 3.86 (m, 1H), 3.79 (m, 1H), 3.67 (m, 1H), 3.33 (*minor*, d, *J* = 2.5 Hz), 3.17 (*major*, d, *J* = 2.5 Hz, 1H) 2.23 (m, 1H), 1.61 (m, 2H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), -0.05 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.71, 115.10, 75.03, 62.77, 43.94, 35.52, 25.87, 18.15, 15.74, -5.55 ppm; HRMS (ESI+) 245.1931 *m/z* $[M+H]^+$ ($C_{13}H_{29}O_2Si$ requires 245.1937).

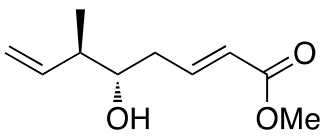


7

(3*S*,4*R*)-4-methylhex-5-ene-1,3-diol (7). The residue from above was dissolved in anhydrous THF (~95 mL) under argon, slowly treated with TBAF (1.0 M in THF, 23.0 mL, 23.37 mmol), and stirred for 1 h at room temperature. Reaction then quenched with sat. aq. NH_4Cl (50 mL) and THF removed by rotary evaporation. Residue partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was washed with EtOAc (100 mL x 3) and combined organics dried with

[2] Recycling the catalyst more than once led to significant erosion of the dr and er in the crotylation.

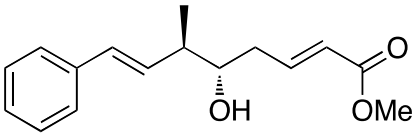
Na_2SO_4 and concentrated. Residue purified by chromatography (50 g Biotage® KP-SIL column, 1:1 H:E, 45 mL/min) on a CombiFlash Retrieve® system to afford the desired product (**7**, 1.60 g, 52% [2 steps]) as a clear, light orange oil. TLC R_f = 0.20 (1:1 H:E). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.73 (m, 1H), 5.09 (m, 2H), 3.84 (m, 2H), 3.63 (m, 1H), 2.98 (bs, 1H), 2.68 (bs, 1H), 2.23 (m, 1H), 1.68 (m, 2H), 1.02 (d, *J* = 5.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.28, 116.53, 75.00, 61.73, 44.68, 35.38, 15.99 ppm; HRMS (ESI+) 153.0885 *m/z* $[M+Na]^+$ ($C_7H_{14}NaO_2$ requires 153.0891).



8

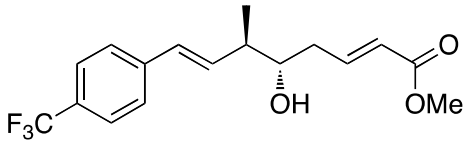
(5*S*,6*R*,*E*)-methyl 5-hydroxy-6-methylocta-2,7-dienoate (8). A solution of **7** (920 mg, 7.07 mmol) and TEMPO (110 mg, 0.707 mmol) in ACN (75 mL) was treated with solid [bis(acetoxy)iodo]benzene (BAIB, 2.62 g, 8.13 mmol) and stirred at room temperature for 2 h. Reaction cooled to 0 °C and treated with solid methyl(triphenylphosphoranylidene) acetate (3.07 g, 9.19 mmol). Reaction stirred for an additional hour, allowing it to warm to room temperature. Reaction then quenched with sat. aq. $Na_2S_2O_3$ and solvent removed *in vacuo*. Recovered material partitioned between water (200 mL) and DCM (200 mL). The aqueous layer was extracted with DCM (100 mL x 2) and combined organics washed with brine and dried with Na_2SO_4. Solvent removed by rotary evaporation and residue flash purified (SiO_2, 4:1 H:E) to afford 937 mg of pure **8** (72%) as a clear, faint yellow oil. TLC R_f = 0.35 (4:1 H:E). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (m, 1H), 5.91 (d, *J* = 15 Hz, 1H), 5.73 (m, 1H), 5.13 (m, 2H), 3.72 (s, 3H), 3.56 (m, 1H),

2.43 (m, 1H), 2.24 (m, 2H), 1.81 (bs, 1H), 1.05 (d, *J* = 5.0 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.92, 145.96, 139.65, 123.32, 117.10, 73.49, 51.61, 44.01, 37.18, 16.32 ppm; HRMS (ESI+) 207.0995 *m/z* $[M+Na]^+$ ($C_{10}H_{16}NaO_3$ requires 207.0997).



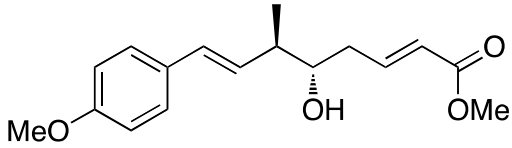
10a

(2*E*,5*S*,6*R*,7*E*)-methyl 5-hydroxy-6-methyl-8-phenylocta-2,7-dienoate (10a). Heck Reaction: $Pd(OAc)_2$ (2 mg, 0.0089 mmol) was added to a flame-dried, screw top vial under argon (solid aryl iodides were also added at this step) and dissolved in a solution of **8** (34 mg, 0.185 mmol) in anhydrous ACN (1.8 mL). The iodobenzene (23 µL, 0.203 mmol) was then added, followed by Et_3N (258 µL, 1.85 mmol). Reaction stirred at 85 ^{o}C for 18 h and then cooled to room temperature. Reaction was concentrated *in vacuo* and residue flash purified (SiO_2, 2:1 H:MTBE) to afford 13 mg of **10a** (31%) as a clear, colorless oil. TLC R_f = 0.60 (1:1 H:MTBE). Compounds **10b**, **10c**, and **10d** prepared through Heck reaction were accessed in an analogous manner. Compound **10a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 2H), 7.31 (m, 2H), 7.24 (m, 1H), 7.05 (m, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.13 (dd, *J* = 8.7, 15.9 Hz, 1H), 5.92 (d, *J* = 15.8 Hz, 1H), 3.74 (s, 3H), 3.66 (m, 1H), 2.41 (m, 3H), 1.74 (d, *J* = 3.9 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.89, 145.81, 137.09, 132.27, 130.99, 128.73, 127.62, 126.29, 123.45, 73.95, 51.64, 43.51, 37.43, 16.96 ppm; HRMS (ESI+) 283.1305 *m/z* $[M+Na]^+$ ($C_{16}H_{20}NaO_3$ requires 283.1310).



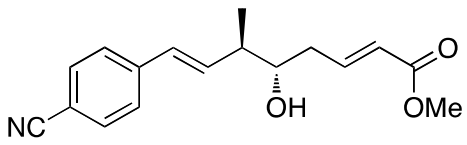
10b

(2*E*,5*S*,6*R*,7*E*)-methyl 5-hydroxy-6-methyl-8-(4-(trifluoromethyl)phenyl) octa-2,7-dienoate (10b): 28%; TLC R_f = 0.60 (1:1 H:MTBE). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.03 (dt, *J* = 7.0, 14.9 Hz, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 8.6, 16.0 Hz, 1H), 5.93 (d, *J* = 15.7 Hz, 1H), 3.73 (s, 3H), 3.70 (m, 1H), 2.45 (m, 3H), 1.71 (d, *J* = 3.9 Hz, 1H), 1.17 (d, *J* = 4.6 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.83, 145.48, 140.62, 133.93, 130.76, 126.48, 126.44, 125.66 (q, *J* = 3.8 Hz), 123.67, 73.89, 51.68, 43.45, 37.63, 16.95 ppm; HRMS (ESI+) 351.1186 *m/z* $[M+Na]^+$ ($C_{17}H_{19}F_3NaO_3$ requires 351.1184).



10c

(2*E*,5*S*,6*R*,7*E*)-methyl 5-hydroxy-8-(4-methoxyphenyl)-6-methylocta-2,7-dienoate (10c): 38%; TLC R_f = 0.55 (1:1 H:MTBE). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, *J* = 6.7 Hz, 2H), 7.06 (m, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.94 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 2.37 (m, 3H), 1.77 (d, *J* = 3.7 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.92, 159.27, 145.93, 131.74, 128.69, 127.49, 123.37, 114.13, 112.94, 73.96, 55.47, 51.64, 43.52, 37.37, 17.03 ppm; HRMS (ESI+) 313.1416 *m/z* $[M+Na]^+$ ($C_{17}H_{22}NaO_4$ requires 313.1416).



10d

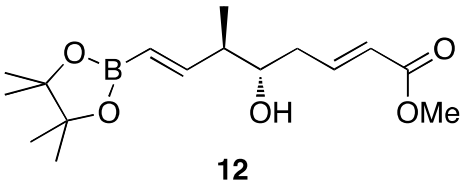
(2*E*,5*S*,6*R*,7*E*)-methyl 8-(4-cyanophenyl)-5-hydroxy-6-methylocta-2,7-dienoate (10d): 30%; TLC R_f = 0.40 (1:1 H:MTBE). ^{1}H

NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.01 (m, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.32 (dd, *J* = 8.6, 16.0 Hz, 1H), 5.92 (d, *J* = 15.7 Hz, 1H), 3.73 (s, 3H), 3.71 (m, 1H), 2.46 (m, 2H), 2.38 (m, 1H), 1.70 (d, *J* = 4.0 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.54, 145.06, 141.40, 135.17, 132.31, 130.15, 126.58, 123.52, 118.86, 110.48, 73.60, 51.46, 43.19, 37.48, 16.71 ppm; HRMS (ESI+) 308.1266 *m/z* $[M+Na]^+$ ($C_{17}H_{19}NNaO_3$ requires 308.1263).

Cross metathesis. Solid Hoveyda-Grubbs II (9 mg, 0.015 mmol) was added to a flame-dried, screw top vial and the atmosphere was exchanged for argon. The catalyst was dissolved in a solution of **8** (54 mg, 0.293 mmol) in anhydrous, degassed DCM (1.17 mL). Styrene (134 µL, 1.17 mmol) was then added via syringe and reaction stirred at reflux temperature for 4 h. Reaction cooled to room temperature, treated with 50 eq. of DMSO, and stirred at room temperature for 12 h. The reaction was then concentrated *in vacuo* and purified by flash chromatography (SiO_2, 2:1 H:MTBE) to afford **10a** (23 mg, 30%) as a clear, colorless oil. Spectra were identical to those collected for **10a** above. Compounds **10b**, **10c**, and **10d** prepared through cross metathesis were accessed in an analogous manner and had spectra identical to those reported above. Compound **10b**: clear, light yellow oil (23%). Compound **10c**: clear, colorless oil (26%). Compound **10d**: clear, light yellow oil (8%).

Suzuki-Miyaura cross coupling. $[Pd_2(dba)_3]$ (2 mg, 0.0018 mmol), tricyclohexylphosphine (1 mg, 0.0043 mmol), and K_3PO_4 (32 mg, 0.153 mmol) were added to a flame-dried screw top vial under argon and suspended in a

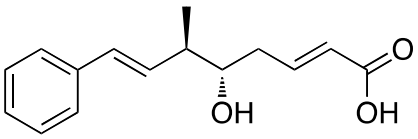
solution of **12** (28 mg, 0.090 mmol) in anhydrous DME (240 µL). Water that had been degassed under vacuum in a sonicator (120 µL) and iodobenzene (12 µL, 0.108 mmol) were then added and reaction stirred at 85 ^{o}C for 2 h. Reaction cooled to room temperature and diluted with water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (5 mL x 3) and combined organics washed with brine (10 mL) and dried with Na_2SO_4. Solvent removed *in vacuo* and residue flash purified (SiO_2, 2:1 H:MTBE) to afford **10a** (10 mg, 42%) as a clear, colorless oil. Spectra were identical to those collected for **10a** above. Compounds **10b**, **10c**, and **10d** prepared through Suzuki-Miyaura coupling were accessed in an analogous manner and had spectra identical to those reported above. Compound **10b**: clear, light yellow oil (55%). Compound **10c**: clear, colorless oil (53%). Compound **10d**: clear, light yellow oil (63%).



12

(2*E*,5*S*,6*R*,7*E*)-methyl 5-hydroxy-6-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-2,7-dienoate (12). Solid Hoveyda-Grubbs II (190 mg, 0.304 mmol) was added to a flame-dried 2-neck flask equipped with a reflux condenser under argon and dissolved in anhydrous, degassed DCM (20 mL). A solution of **8** (1.12 g, 6.08 mmol) in 10 mL DCM was then added to the flask. Vinylboronic acid pinacol ester (2.06 mL, 12.16 mmol) was passed through a plug of activated charcoal immediately prior to use and added via syringe to the stirring reaction mixture. Reaction heated at reflux temperature for 4 h, then cooled to room temperature and treated with 50

eq. of DMSO, stirring overnight, to allow removal of colored ruthenium byproducts upon silica purification.[3] Reaction concentrated and residue purified by flash chromatography (SiO_2, 3:1 pentane:EtOAc) to afford 934 mg of **12** as a clear, light tan oil (50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.01 (m, 1H), 6.52 (dd, *J* = 7.9, 18.1 Hz, 1H), 5.91 (d, *J* = 15.8 Hz, 1H), 5.53 (d, *J* = 18.1 Hz, 1H), 3.73 (s, 3H), 3.62 (m, 1H), 2.37 (m, 3H), 1.66 (d, *J* = 4.2 Hz, 1H), 1.27 (s, 12H), 1.06 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.89, 154.28, 145.89, 123.53, 83.44, 73.45, 51.63, 45.74, 37.13, 24.97, 24.93, 15.78 ppm; HRMS (ESI+) 333.1858 *m/z* $[M+Na]^+$ ($C_{16}H_{27}BNaO_5$ requires 333.1849).

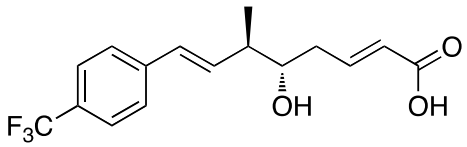


13a

(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-6-methyl-8-phenylocta-2,7-dienoic acid (13a). A solution of **10a** (10 mg, 0.038 mmol) in a 1:1:0.5 mixture of methanol/water/THF (385 µL) was treated with solid LiOH•H_2O (5 mg, 0.115 mmol) and stirred at room temperature for 2 h. Reaction then quenched with 0.1 M HCl and diluted with water (2 mL) and EtOAc (2 mL). Aqueous layer extracted with EtOAc (2 mL x 2) and combined organics washed with brine and dried with Na_2SO_4. Solvent removed *in vacuo* and residue purified by flash chromatography (SiO_2, 5:95 MeOH:DCM + 0.1% HOAc) to afford **13a** as a clear, light yellow oil (8.5 mg, 89%). TLC R_f = 0.50 (5:95 MeOH:DCM + 0.1% HOAc). Compounds **13b**, **13c**, and **13d** were hydrolyzed using an identical procedure. Compound **13a**: ^{1}H and ^{13}C NMR spectra matched

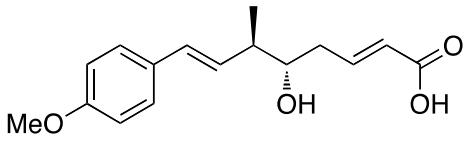
[3] Y. M. Ahn, K. L. Yang, G. I. Georg; *Org. Lett.* **2001**, *3*, 1411-1413.

those previously reported[4]; HRMS (ESI+) 269.1149 *m/z* $[M+Na]^+$ ($C_{15}H_{18}NaO_3$ requires 269.1154).



13b

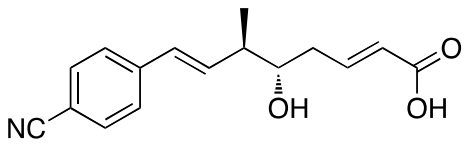
(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-6-methyl-8-(4-(trifluoromethyl)phenyl)octa-2,7-dienoic acid (13b). 90%; TLC R_f = 0.50 (5:95 MeOH:DCM + 0.1% HOAc). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.15 (dt, *J* = 7.4, 15.7 Hz, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.24 (dd, *J* = 8.7, 16.0 Hz, 1H), 5.93 (d, *J* = 15.7 Hz, 1H), 3.72 (m, 1H), 2.48 (m, 3H), 1.17 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.88, 148.57, 140.52, 133.68, 130.98, 126.50, 126.45, 125.70 (q, *J* = 3.8 Hz), 122.96, 73.91, 43.57, 37.60, 16.89 ppm; HRMS (ESI+) 337.1027 *m/z* $[M+Na]^+$ ($C_{16}H_{17}F_3NaO_3$ requires 337.1027).



13c

(2*E*,5*S*,6*R*,7*E*)-5-hydroxy-8-(4-methoxyphenyl)-6-methylocta-2,7-dienoic acid (13c). 84%; TLC R_f = 0.45 (5:95 MeOH:DCM + 0.1% HOAc). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.16 (dt, *J* = 7.3, 15.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 5.95 (m, 2H), 3.81 (s, 3H), 3.65 (m, 1H), 2.51 (m, 1H), 2.38 (m, 2H), 1.13 (d, *J* = 9.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.87, 159.30, 148.70, 131.88, 129.83, 128.54, 127.51, 122.83, 114.15, 73.96, 55.47, 43.62, 37.41, 17.00 ppm; HRMS (ESI+) 299.1260 *m/z* $[M+Na]^+$ ($C_{16}H_{20}NaO_4$ requires 299.1259).

[4] W. Seufert, Z. Q. Beck, and D. H. Sherman; *Angew. Chem. Int. Ed.* **2007**, *46*, 9298-9300.

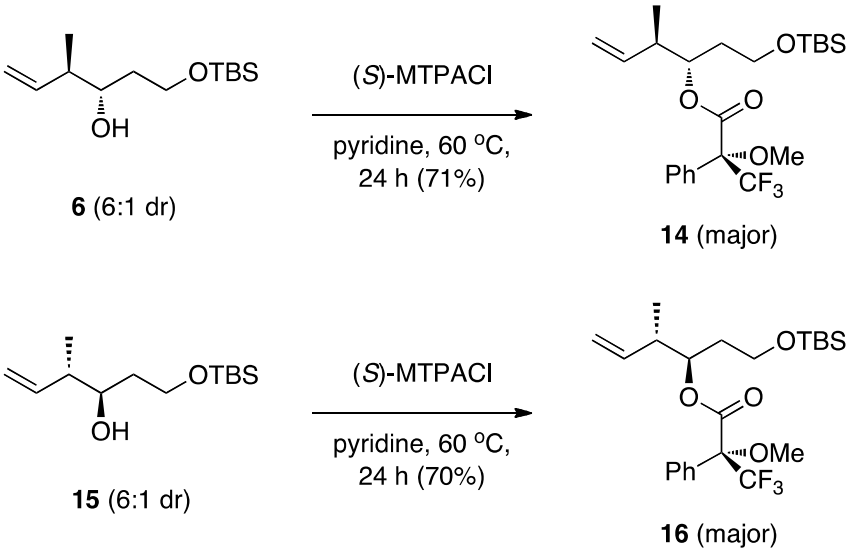


13d

(2*E*,5*S*,6*R*,7*E*)-8-(4-cyanophenyl)-5-hydroxy-6-methylocta-2,7-dienoic acid (13d). 73%; TLC R_f = 0.35 (5:95 MeOH:DCM + 0.1% HOAc). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.16 (dt, *J* = 7.3, 15.6 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.31 (dd, *J* = 8.6, 16.0 Hz, 1H), 5.94 (d, *J* = 15.7 Hz, 1H), 3.75 (m, 1H), 2.47 (m, 3H), 1.18 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.74, 148.84, 141.57, 135.15, 132.60, 130.67, 126.93, 126.85, 122.81, 119.05, 73.88, 43.61, 37.73, 16.90 ppm; HRMS (ESI+) 294.1102 *m/z* $[M+Na]^+$ ($C_{16}H_{17}NNaO_3$ requires 294.1106).

Mosher Ester Analysis

Scheme 1. Synthesis of Mosher Ester Derivatives **14** and **16**.



(*R*)-(3*S*,4*R*)-1-((*tert*-butyldimethylsilyl)oxy)-4-methylhex-5-en-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (14). A solution of **6** (6 mg, 0.025 mmol) in anhydrous pyridine (50 µL) was treated with fresh (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (*S*-MTPACl, 14 µL, 0.074 mmol) and stirred at 60 °C under argon for 24 h. Reaction then cooled to room temperature, concentrated under vacuum, and purified by flash chromatography (SiO_2, 12:1 H:MTBE) to afford 8 mg of **14** (71%). TLC R_f = 0.90 (10:1 H:MTBE). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (m, 2H), 7.40 (m, 3H), 5.67 (m, 1H), 5.24 (m, 1H), 5.05 (m, 2H), 3.61 (m, 2H), 3.54 (s, 3H), 2.54 (m, 1H), 1.80 (m, 2H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.24, 138.60, 132.45, 129.68, 127.60, 124.71, 122.42, 116.42, 77.30, 59.40, 55.53, 41.07, 33.89, 26.01, 18.37, 15.37, -5.28 ppm; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -71.19 (*minor*), -71.23 (*major*) ppm; HRMS (ESI+) 483.2159 *m/z* $[M+Na]^+$

($C_{23}H_{35}F_3NaO_4Si$ requires 483.2154). Compound **15** was prepared from **4** and (*S*)-(-)-**5**, the Mosher ester of which (**16**) was used for ^{19}F NMR comparison purposes.

Compound **15**: 72%; TLC R_f = 0.45 (10:1 H:MTBE x2). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.80 (m, 1H), 5.04 (m, 2H), 3.83 (m, 2H), 3.68 (m, 1H), 3.36 (*minor*, d, *J* = 2.2 Hz), 3.21 (*major*, d, *J* = 2.2 Hz, 1H), 2.23 (m, 1H), 1.63 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.20, 110.32, 75.00, 65.65, 43.95, 35.53, 25.88, 18.16, 15.21, -5.51 ppm; HRMS (ESI+) 245.1935 *m/z* $[M+H]^+$ ($C_{13}H_{29}O_2Si$ requires 245.1937).

Compound **16**: 70%; TLC R_f = 0.90 (10:1 H:MTBE). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.55 (m, 2H), 7.39 (m, 3H), 5.72 (m, 1H), 5.24 (m, 1H), 5.06 (m, 2H), 3.54 (s, 3H), 3.50 (m, 2H), 2.57 (m, 1H), 1.74 (m, 2H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.30, 138.85, 132.40, 129.69, 128.48, 127.63, 124.69, 122.40, 116.40, 77.37, 59.20, 55.57, 41.27, 33.84, 26.00, 18.33, 15.62, -5.29 ppm; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -71.20 (*major*), -71.23 (*minor*) ppm; HRMS (ESI+) 483.2157 *m/z* $[M+Na]^+$ ($C_{23}H_{35}F_3NaO_4Si$ requires 483.2154).

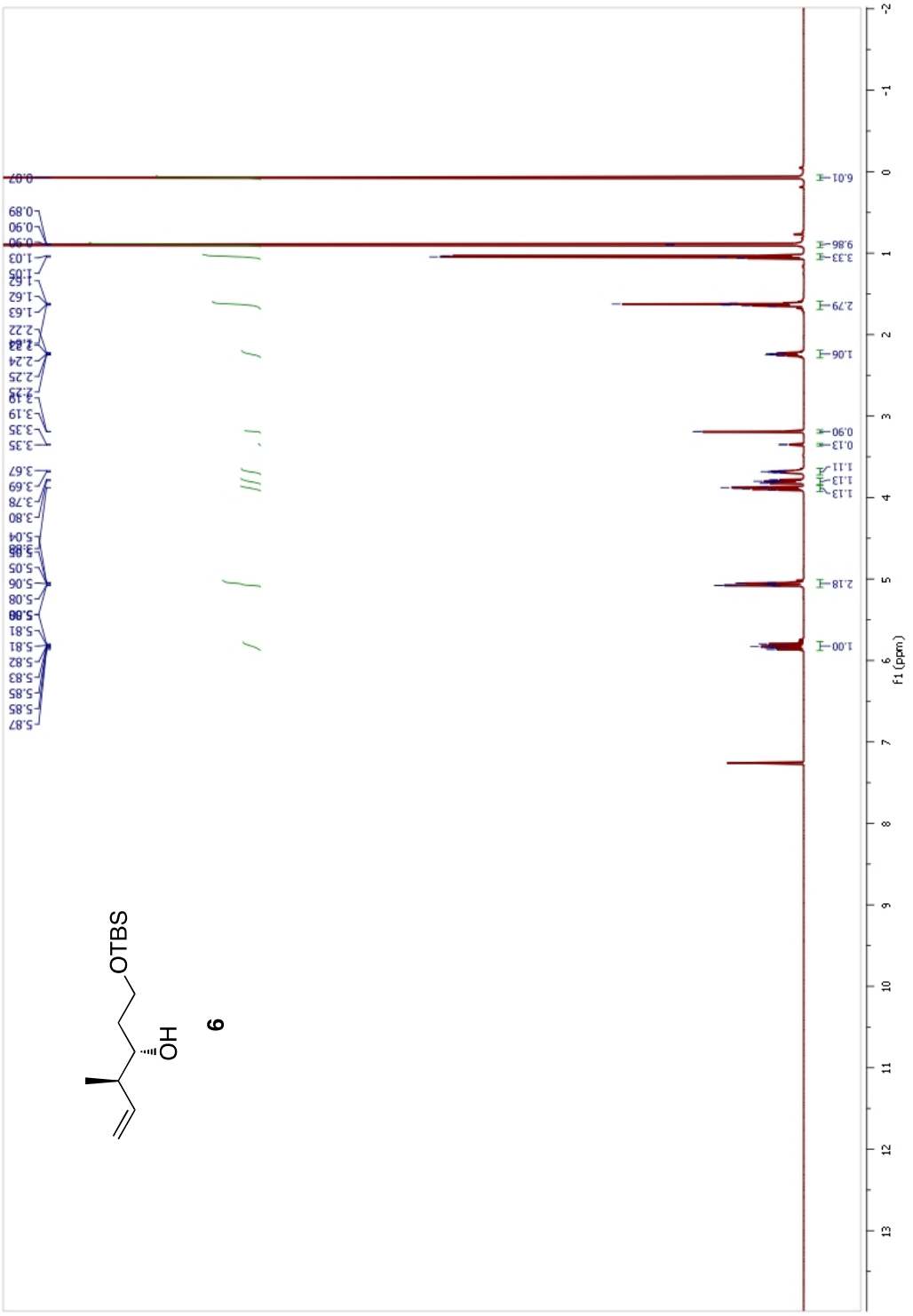


Figure 1: ^{1}H NMR Spectrum of Compound 6.

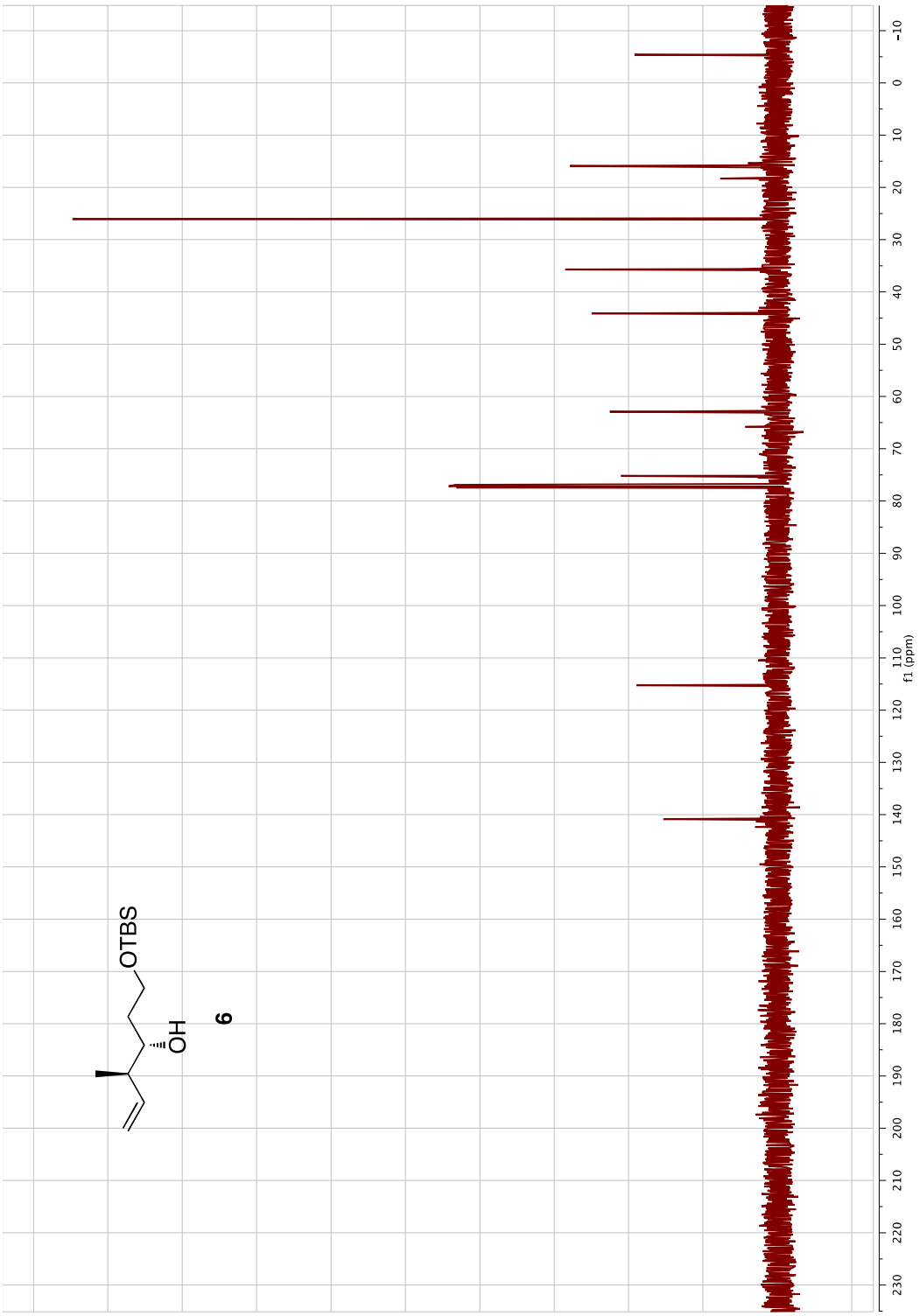


Figure 2: ^{13}C NMR Spectrum of Compound 6.

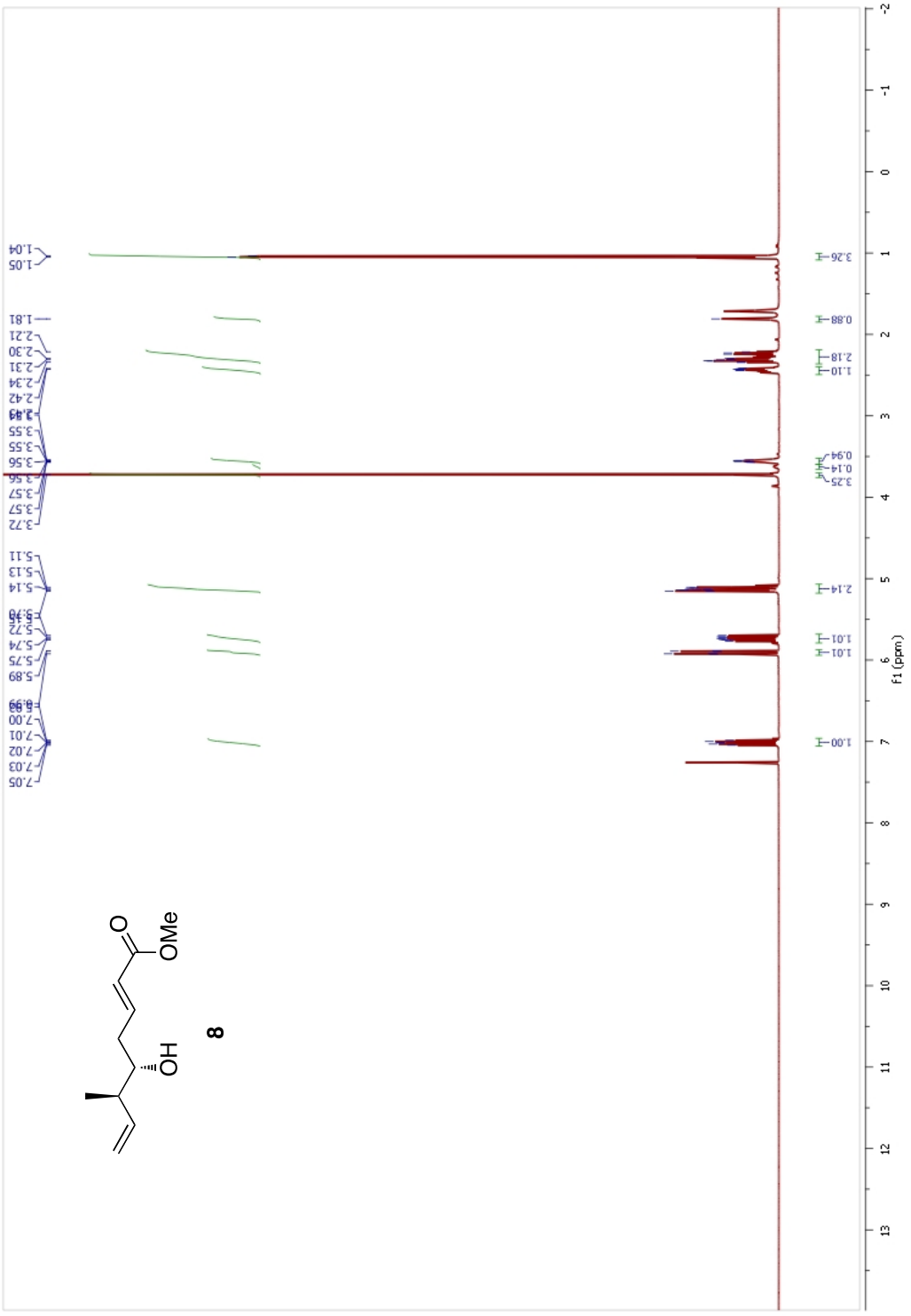


Figure 3: ^{1}H NMR Spectrum of Compound 8.

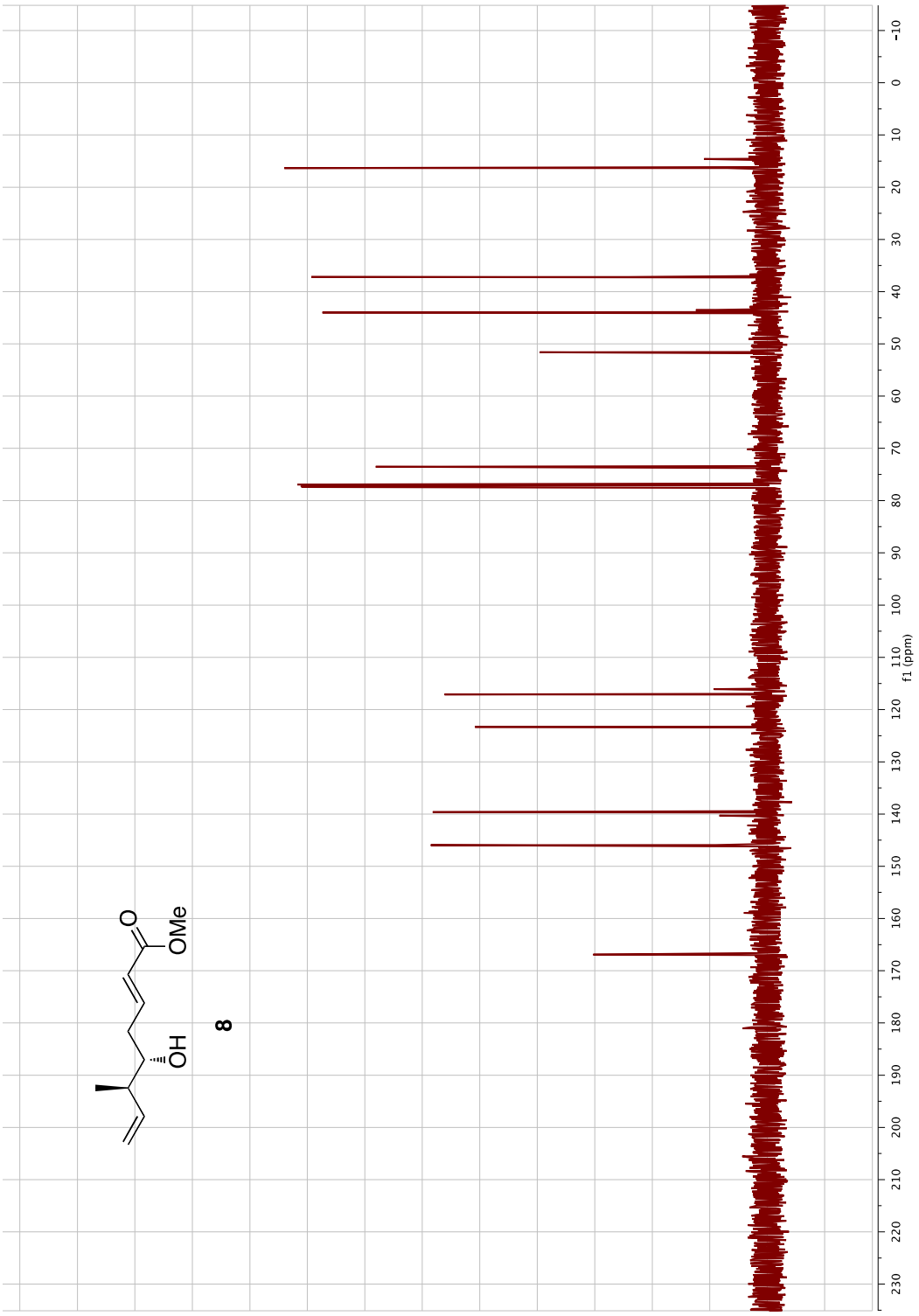


Figure 4: ^{13}C NMR Spectrum of Compound 8.

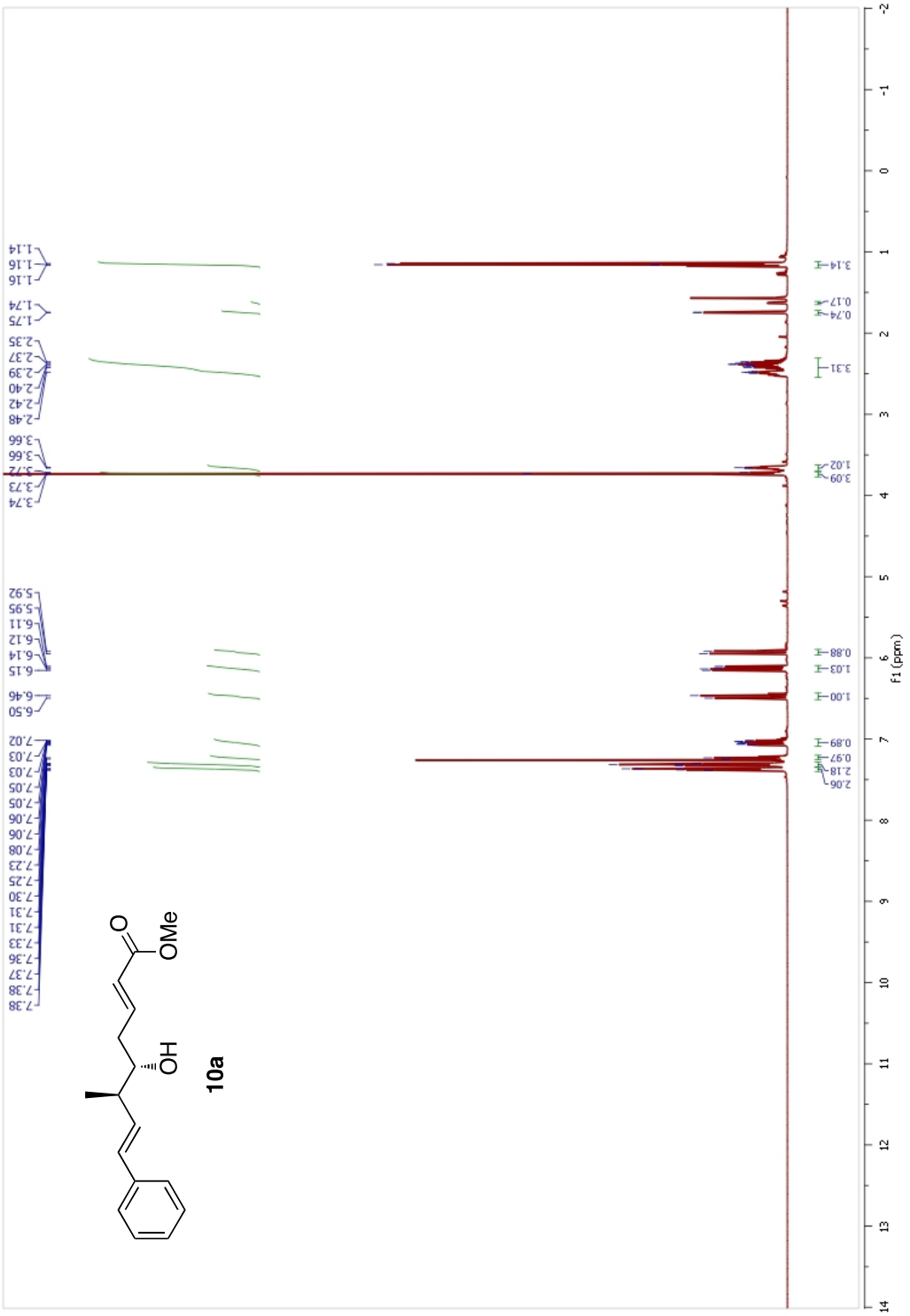


Figure 5: ^{1}H NMR Spectrum of Compound 10a.

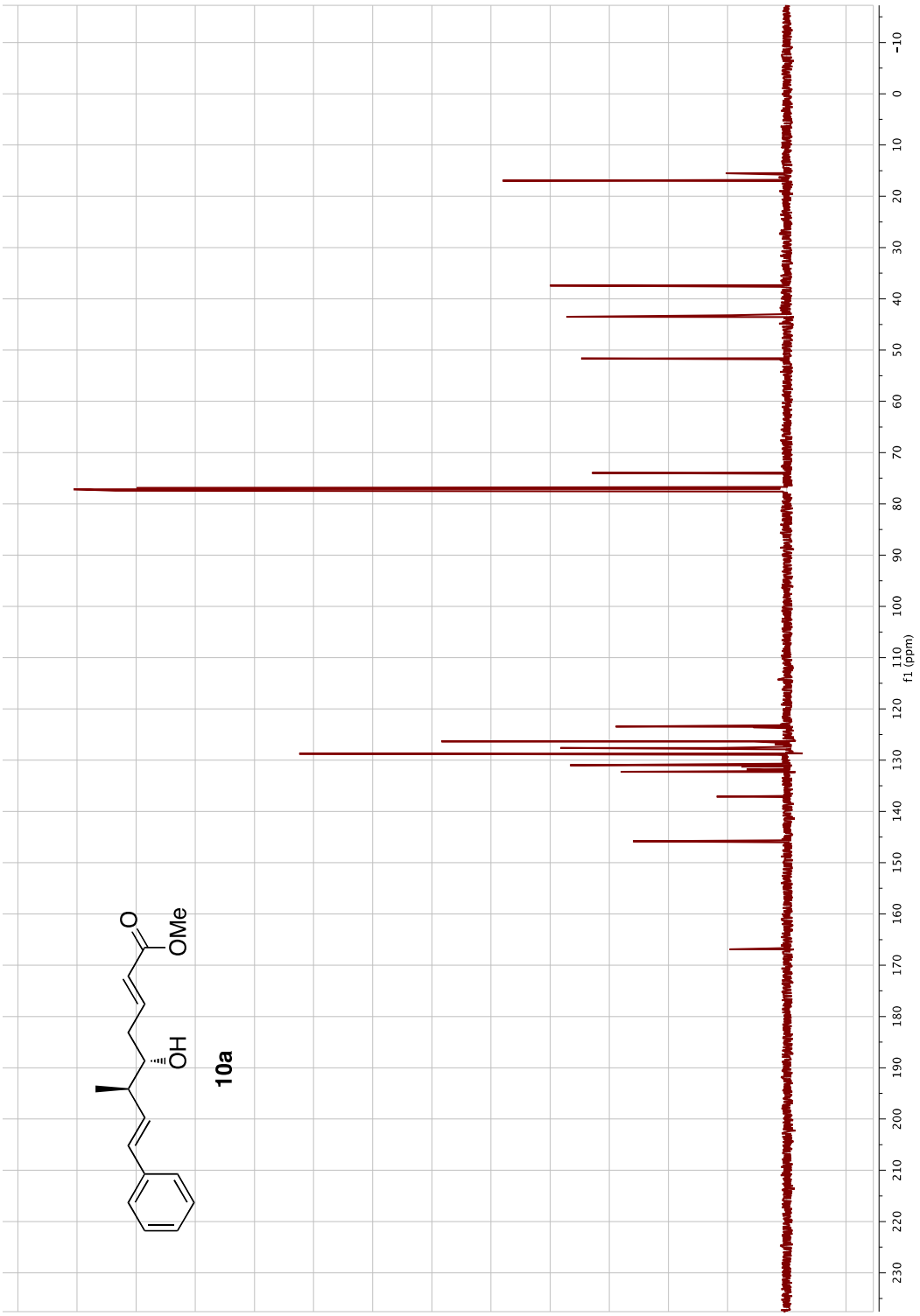


Figure 6: ^{13}C NMR Spectrum of Compound 10a.

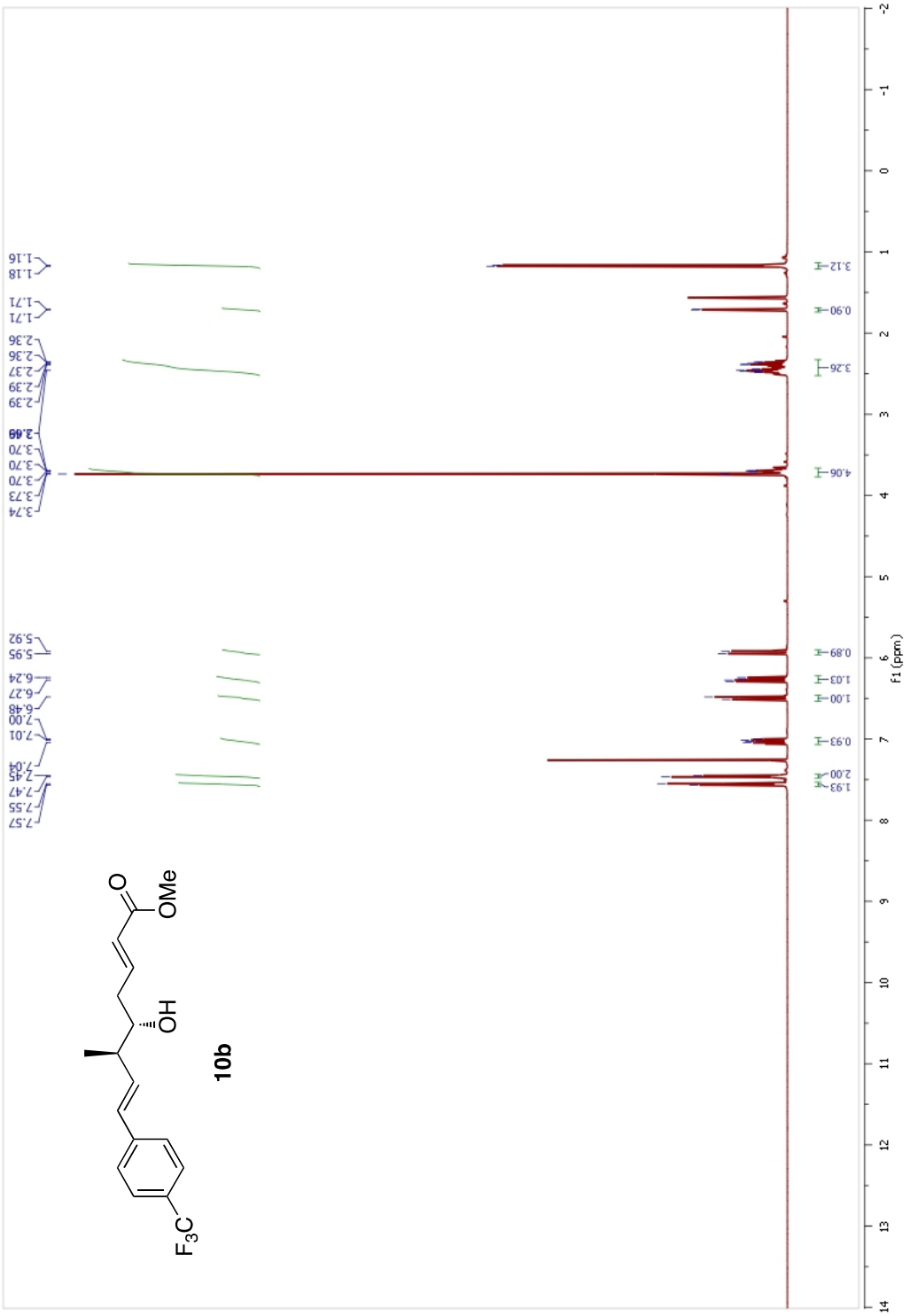


Figure 7: ^{1}H NMR Spectrum of Compound 10b.

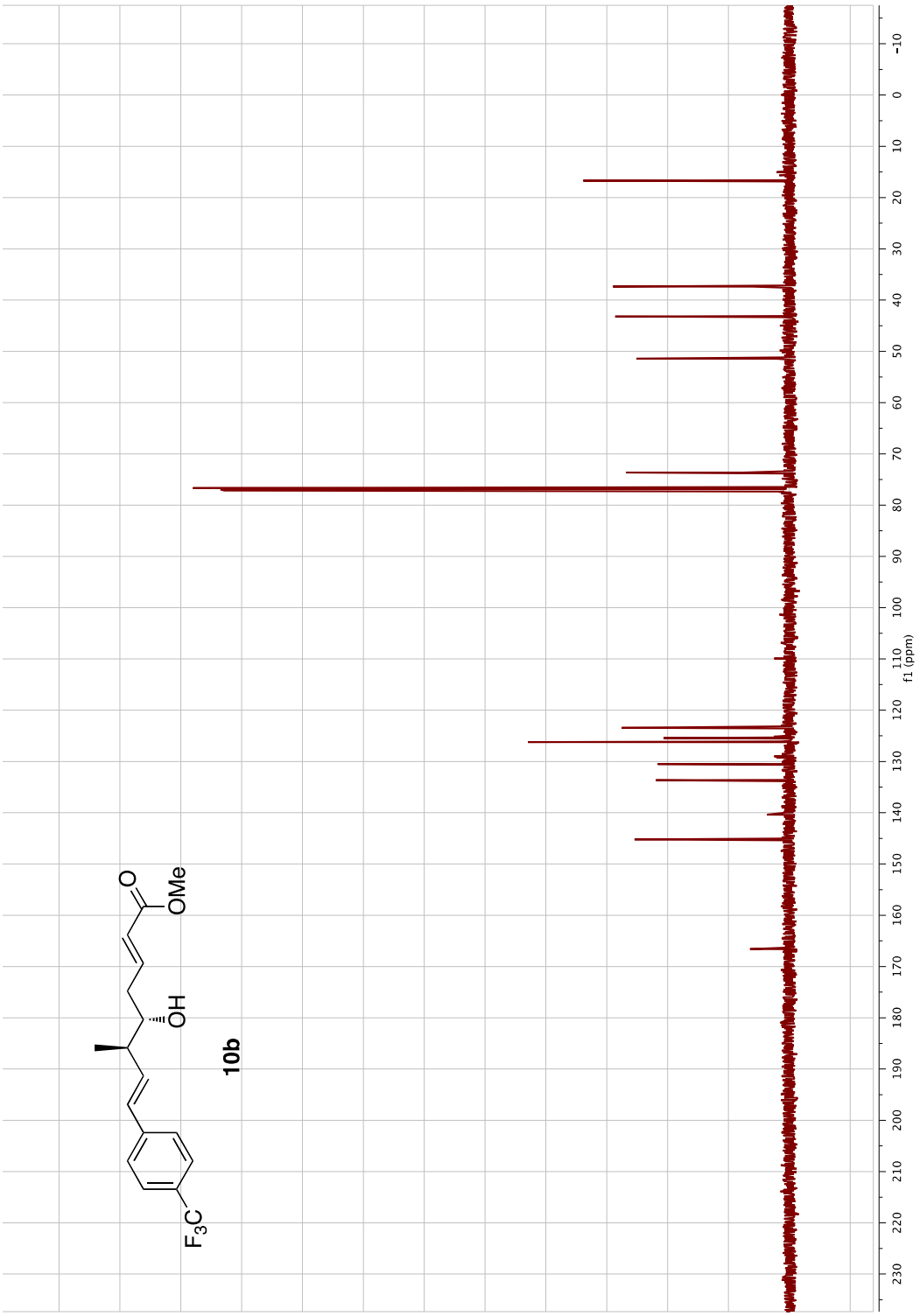


Figure 8: ^{13}C NMR Spectrum of Compound 10b.

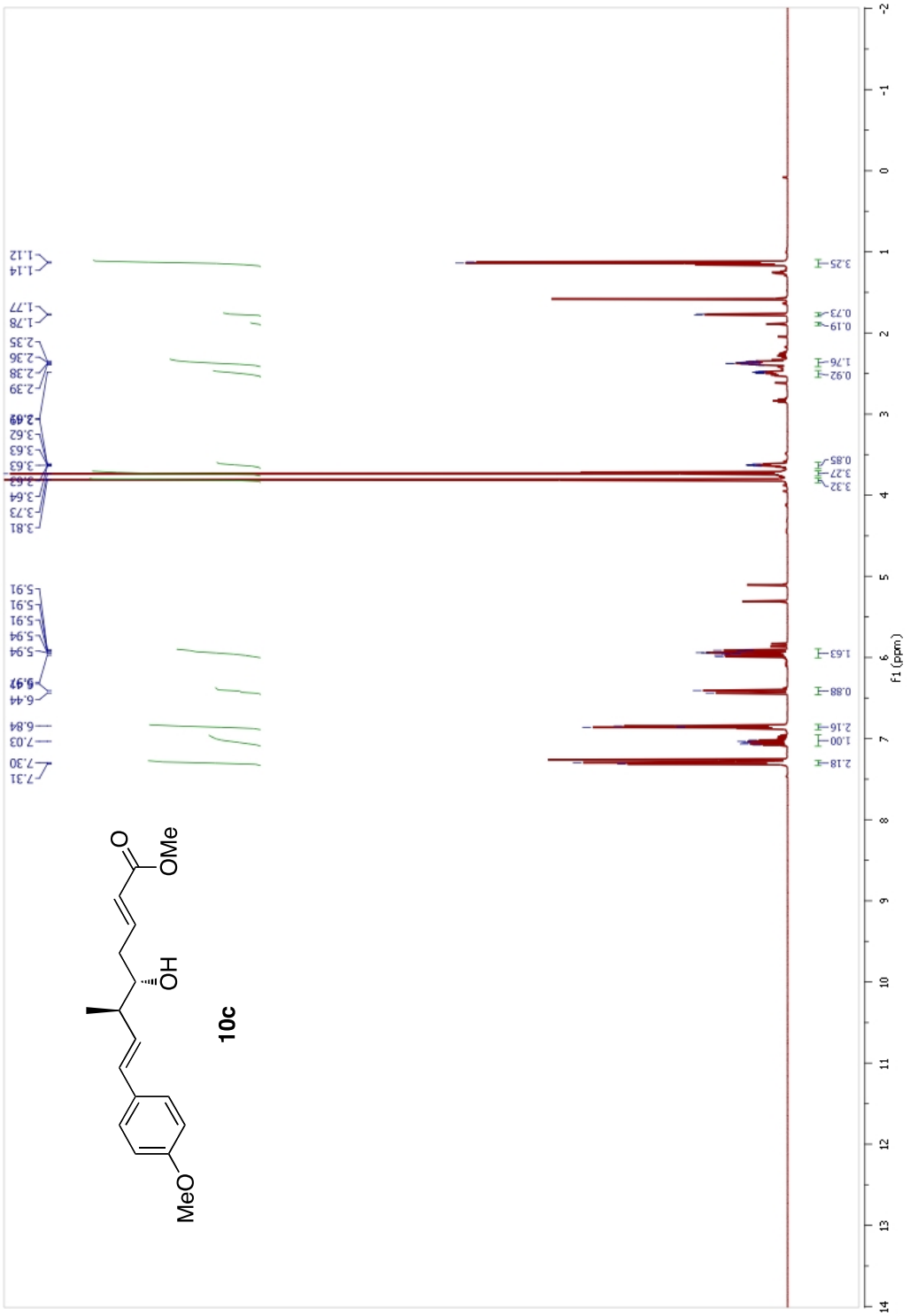


Figure 9: ^{1}H NMR Spectrum of Compound 10c.

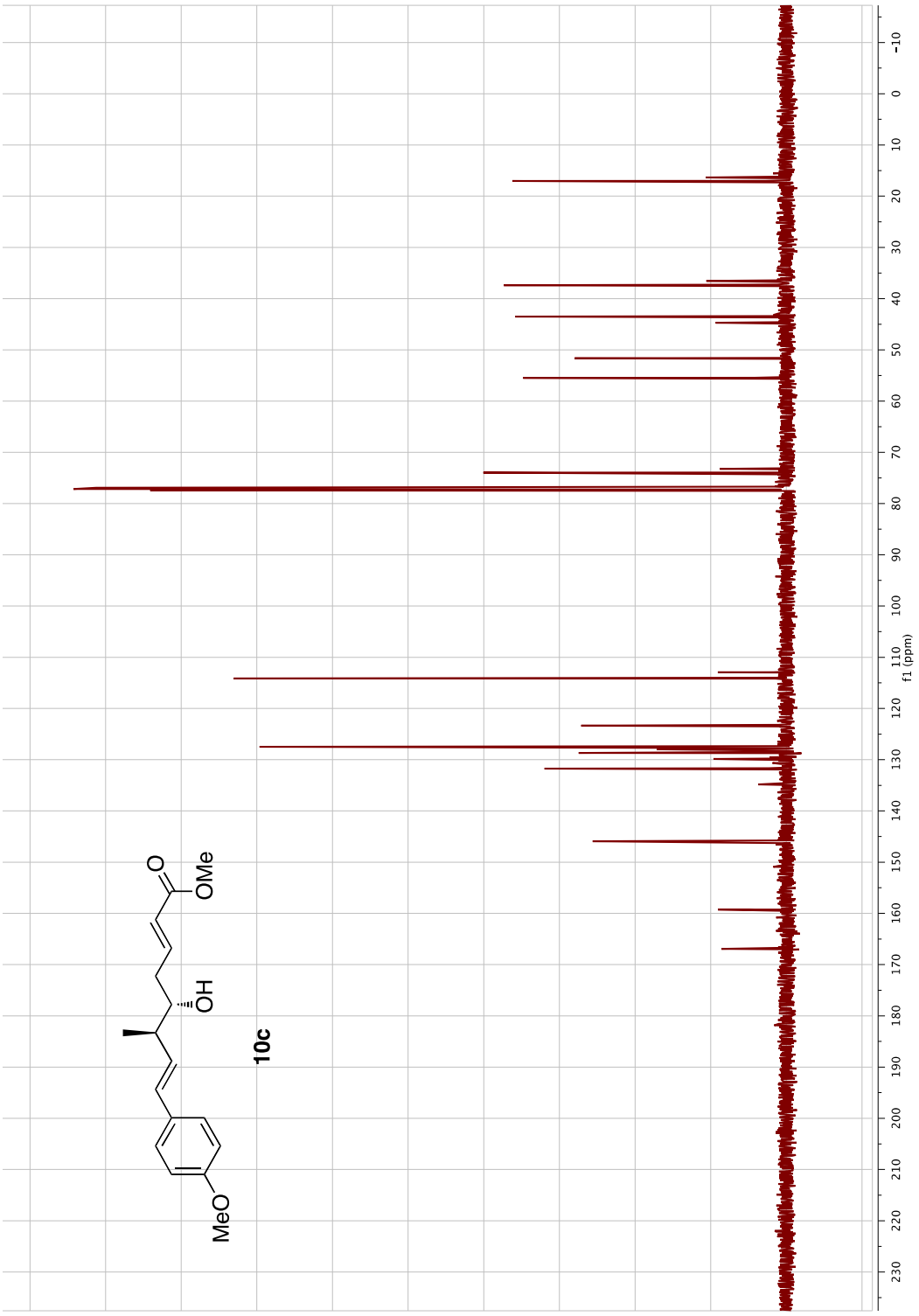


Figure 10: ^{13}C NMR Spectrum of Compound 10c.

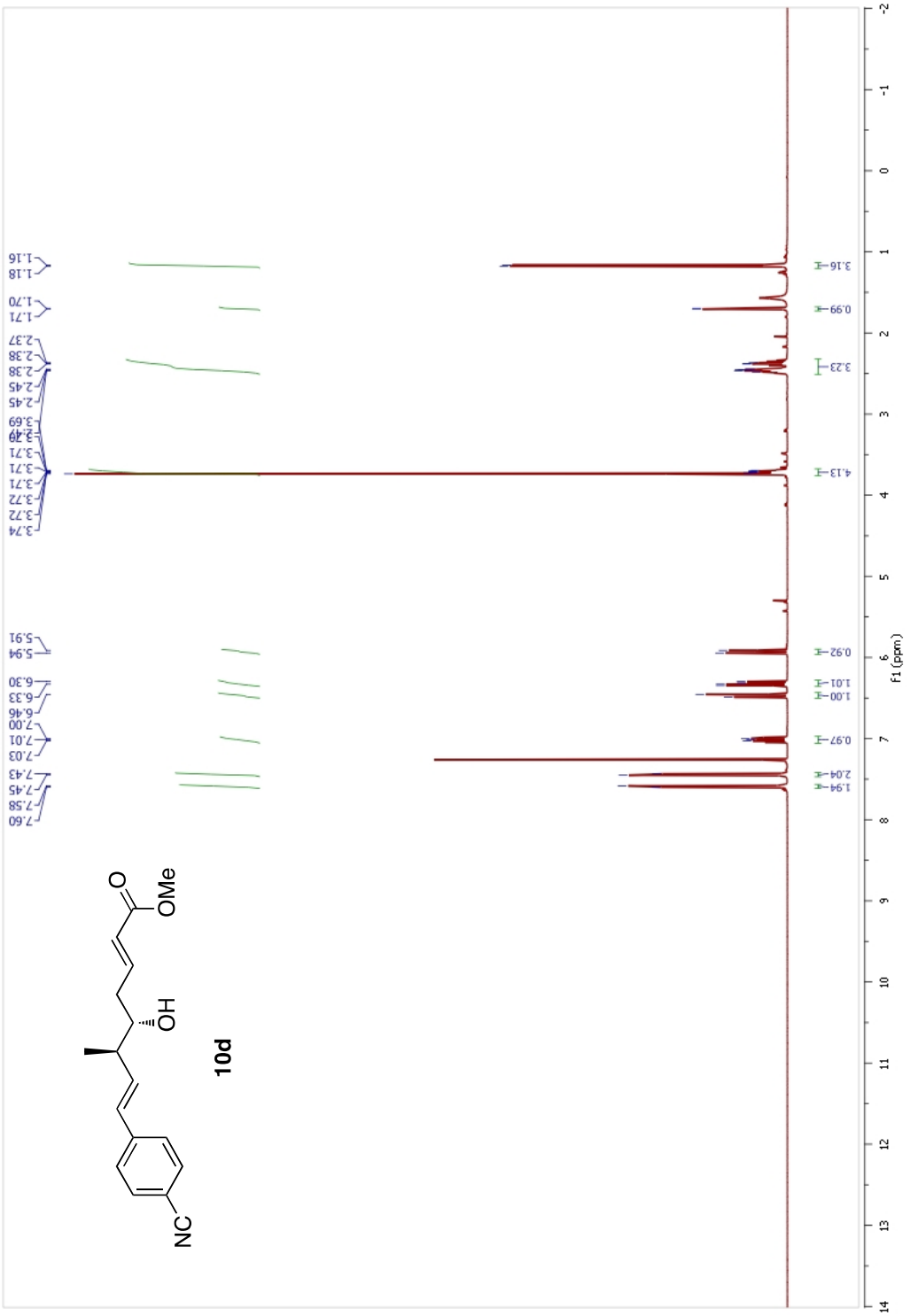


Figure 11: ^{1}H NMR Spectrum of Compound 10d.

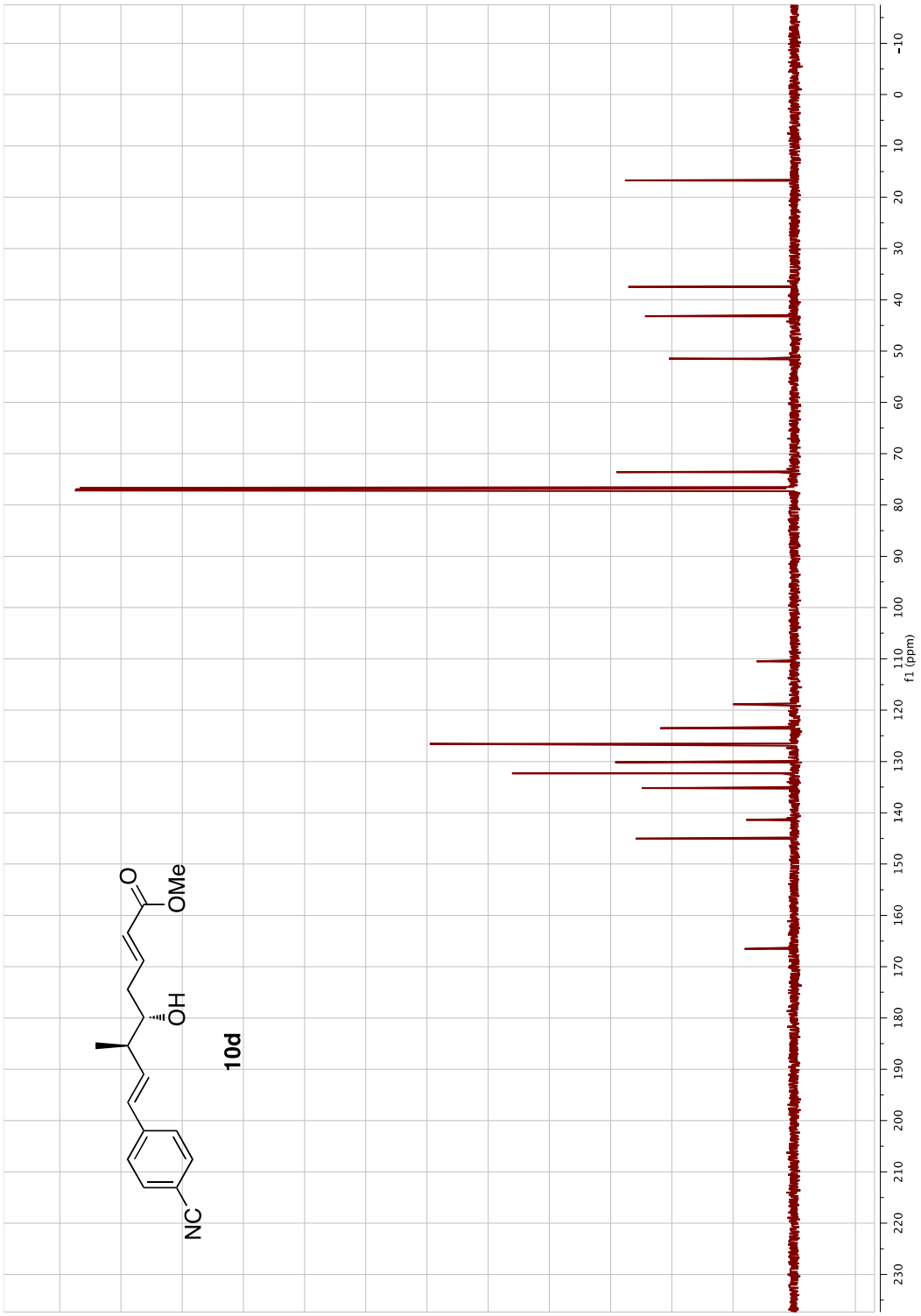


Figure 12: ^{13}C NMR Spectrum of Compound 10d.

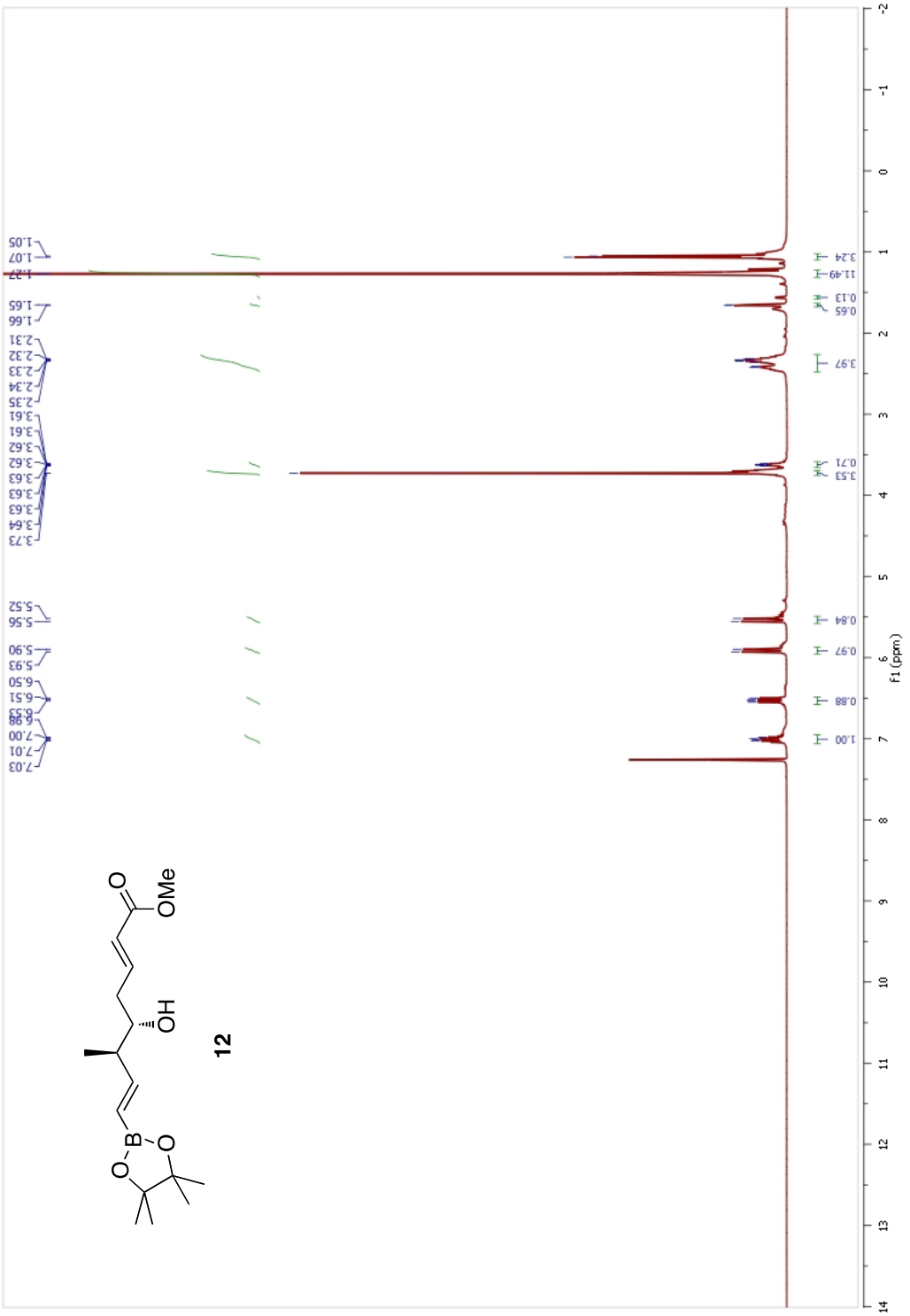


Figure 13: ^{1}H NMR Spectrum of Compound 12.

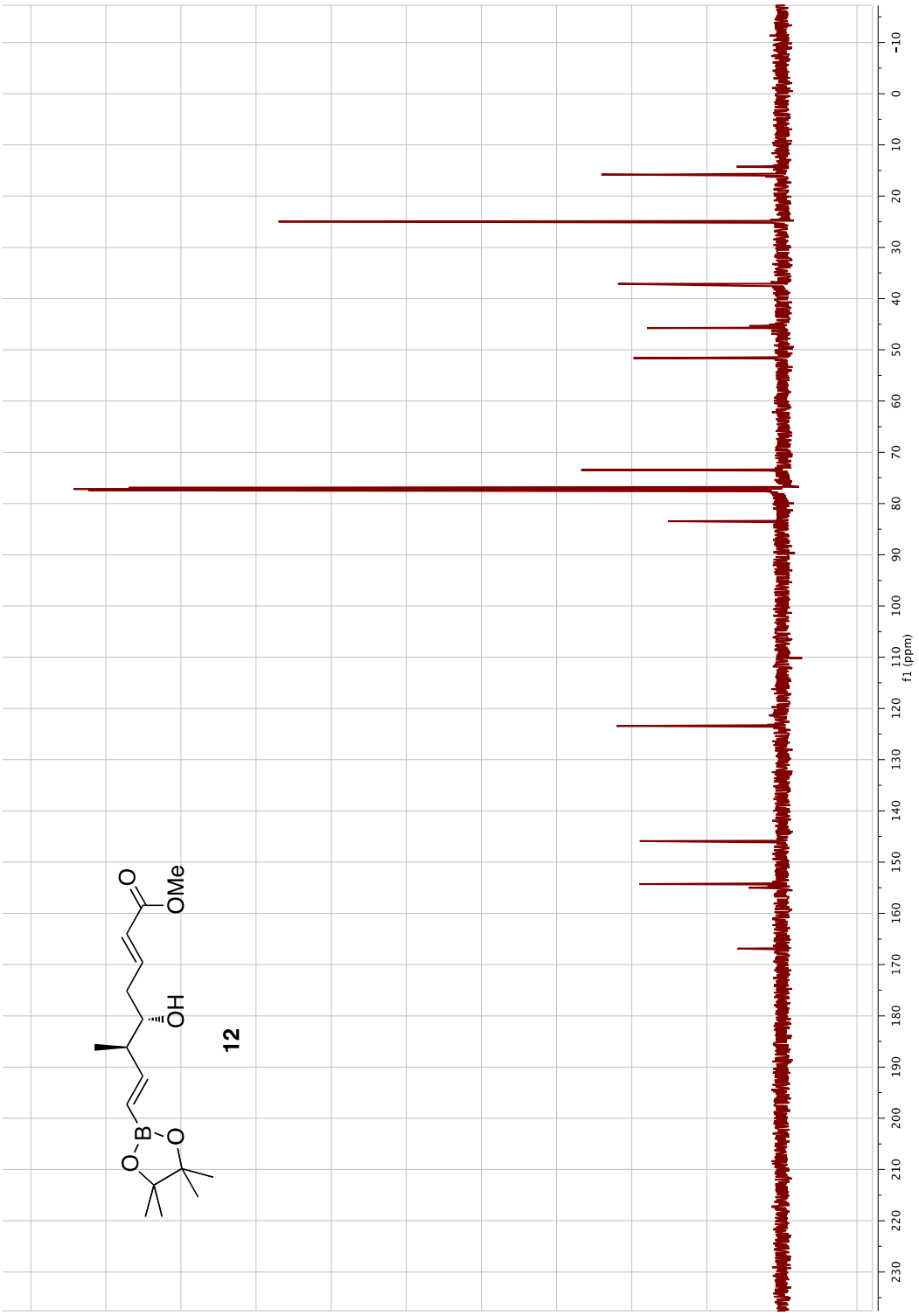


Figure 14: ^{13}C NMR Spectrum of Compound 12.

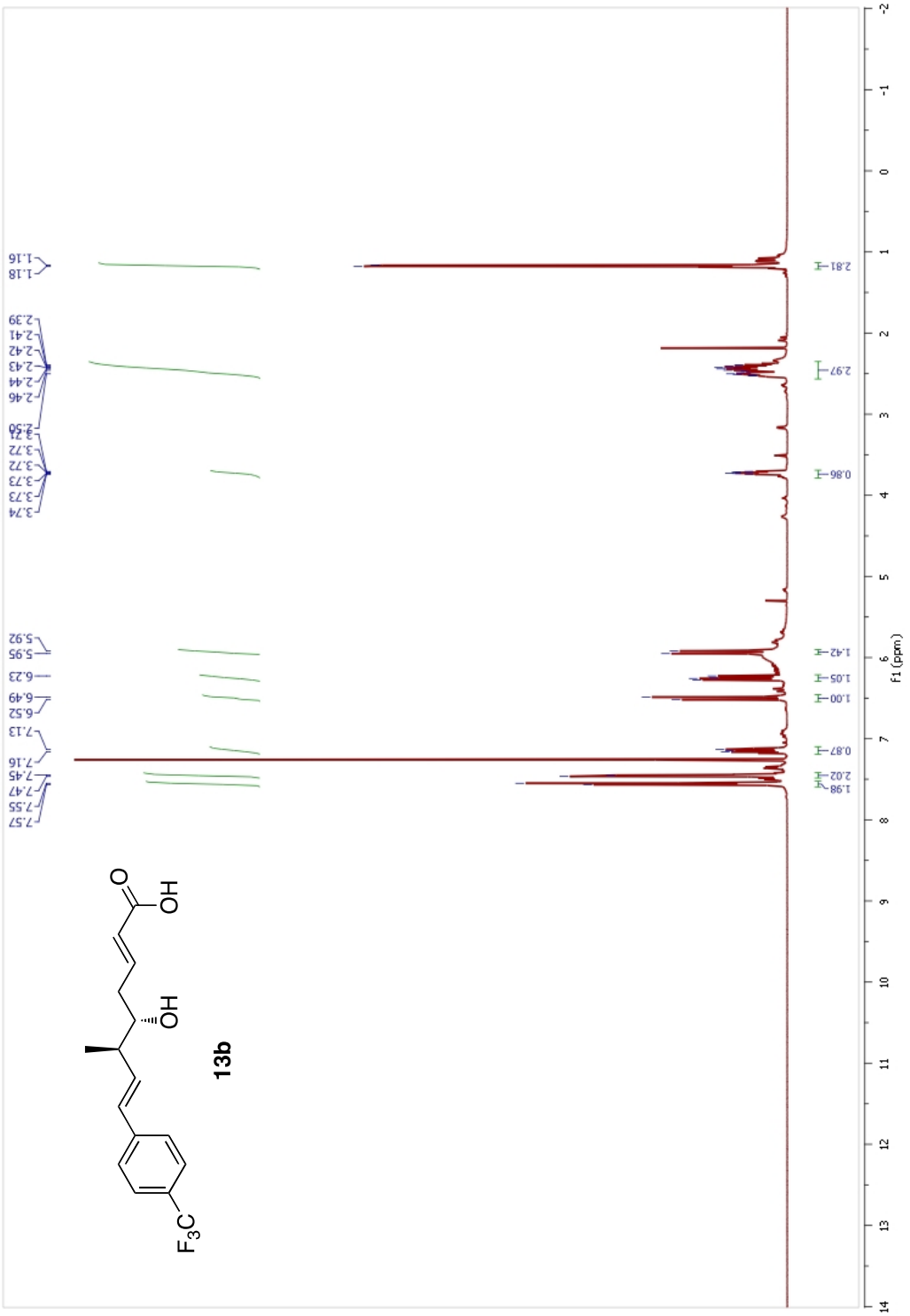


Figure 15: ^{1}H NMR Spectrum of Compound 13b.

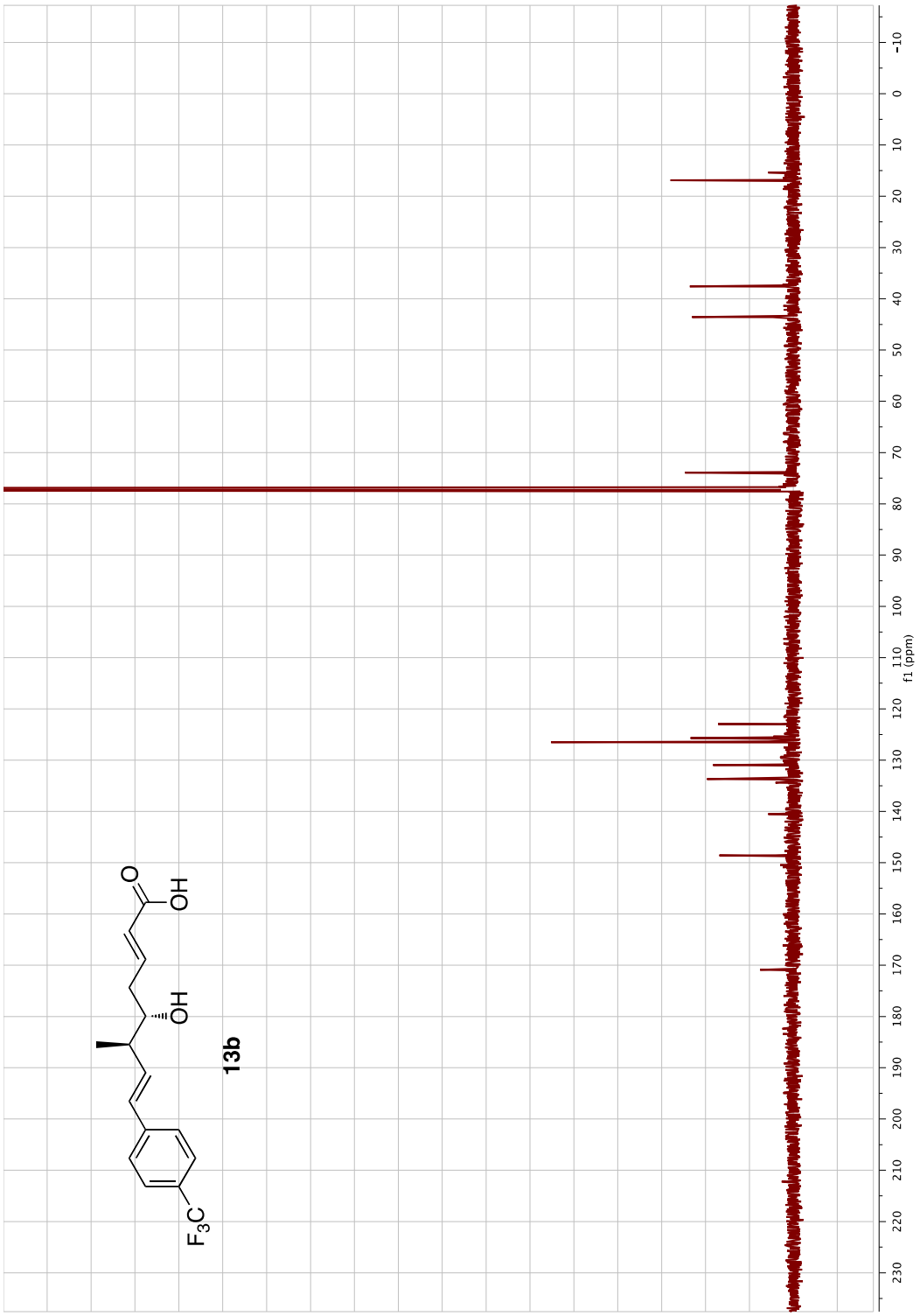


Figure 16: ^{13}C NMR Spectrum of Compound 13b.

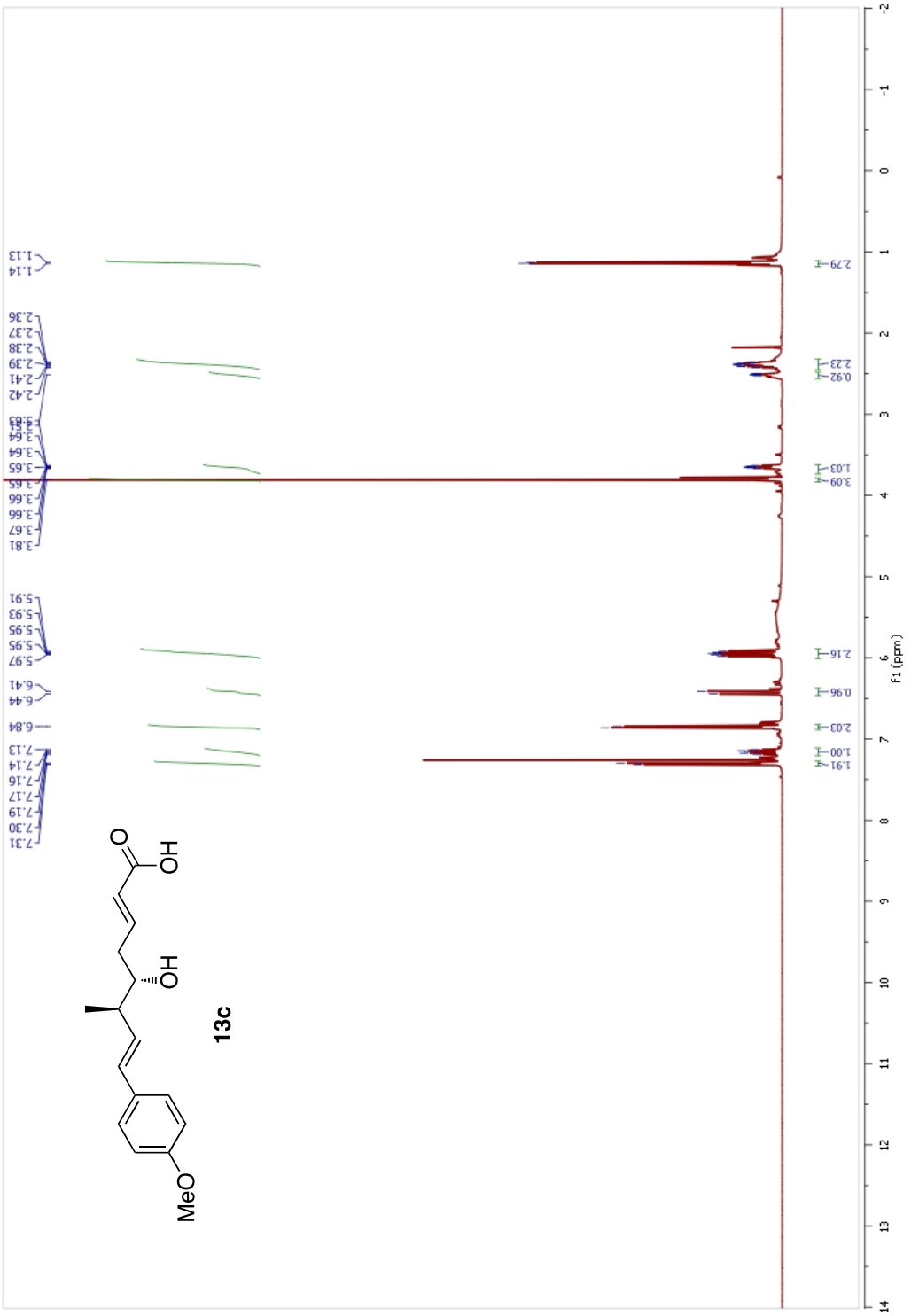


Figure 17: ^{1}H NMR Spectrum of Compound 13c.

Figure 18: ^{13}C NMR Spectrum of Compound 13c.

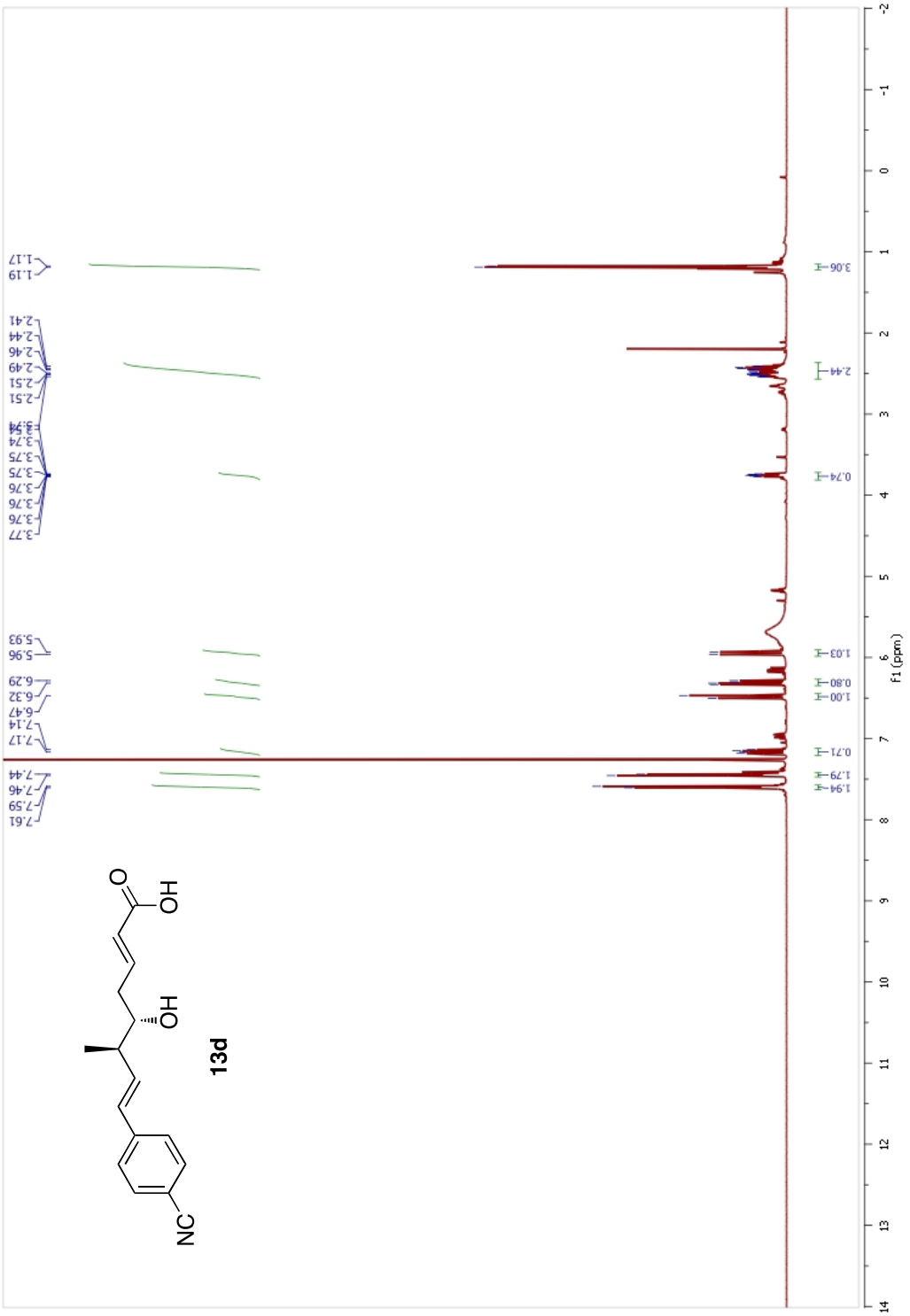


Figure 19: ^{1}H NMR Spectrum of Compound 13d.

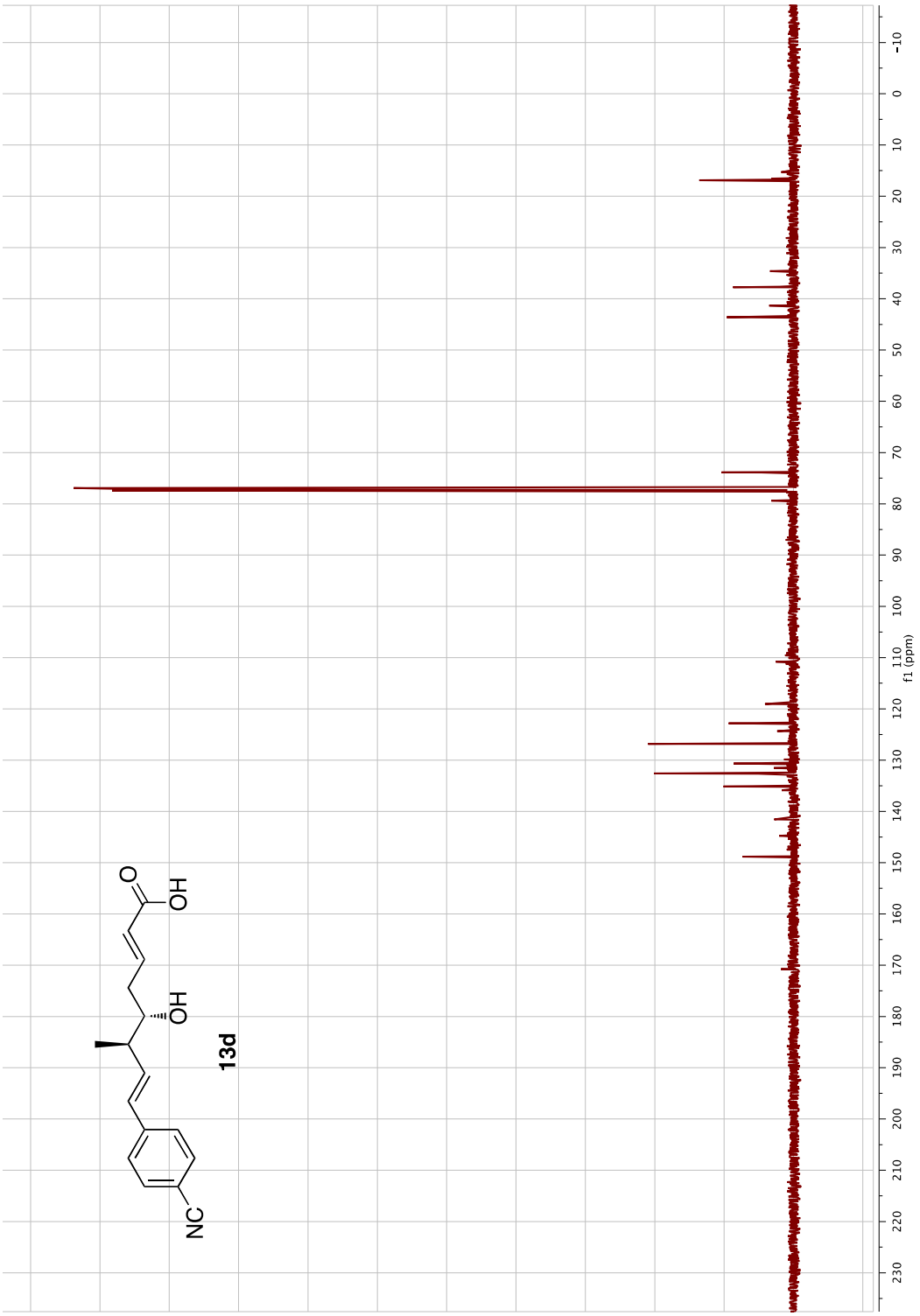


Figure 20: ^{13}C NMR Spectrum of Compound 13d.

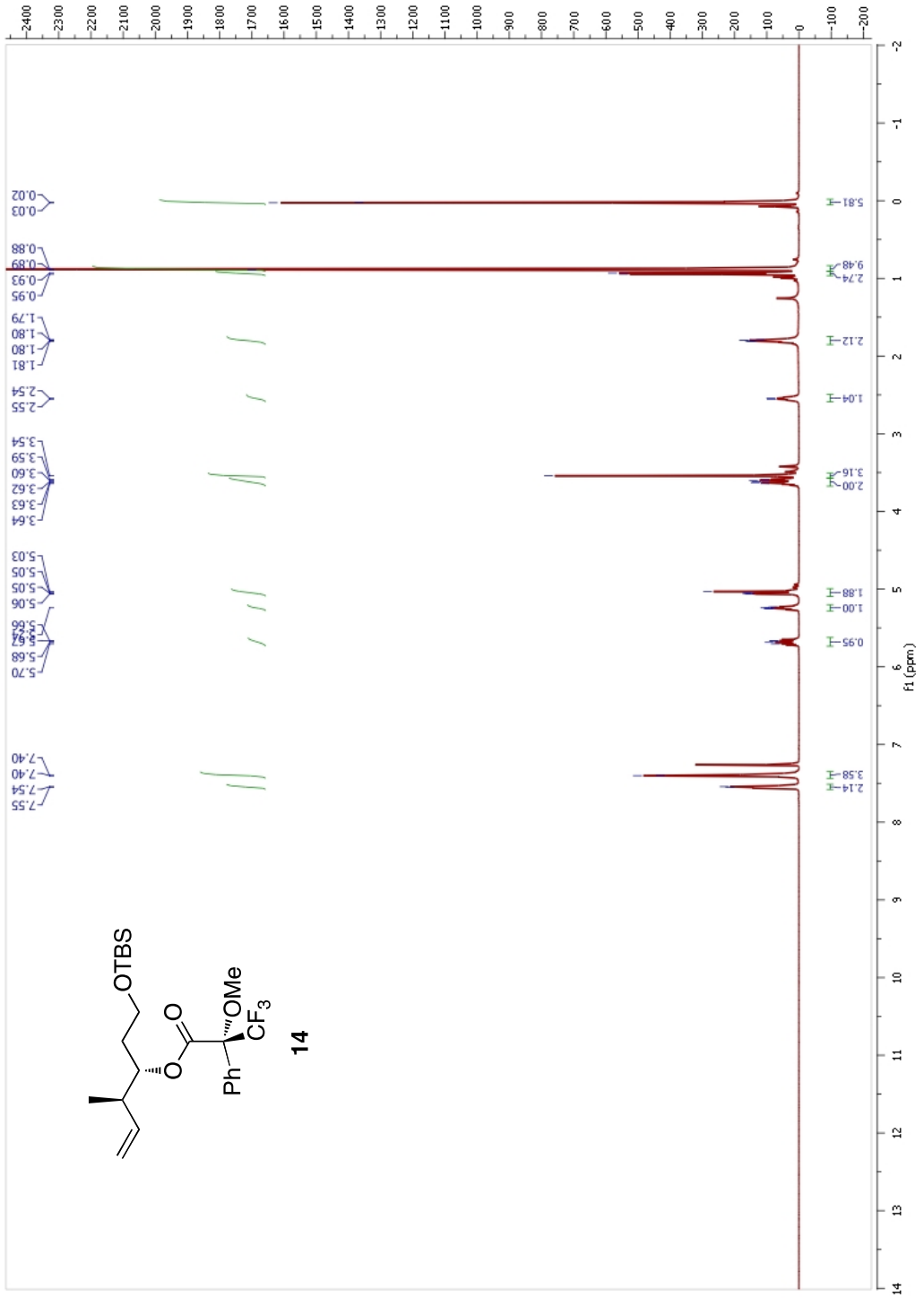


Figure 21: ^{1}H NMR Spectrum of Compound 14.

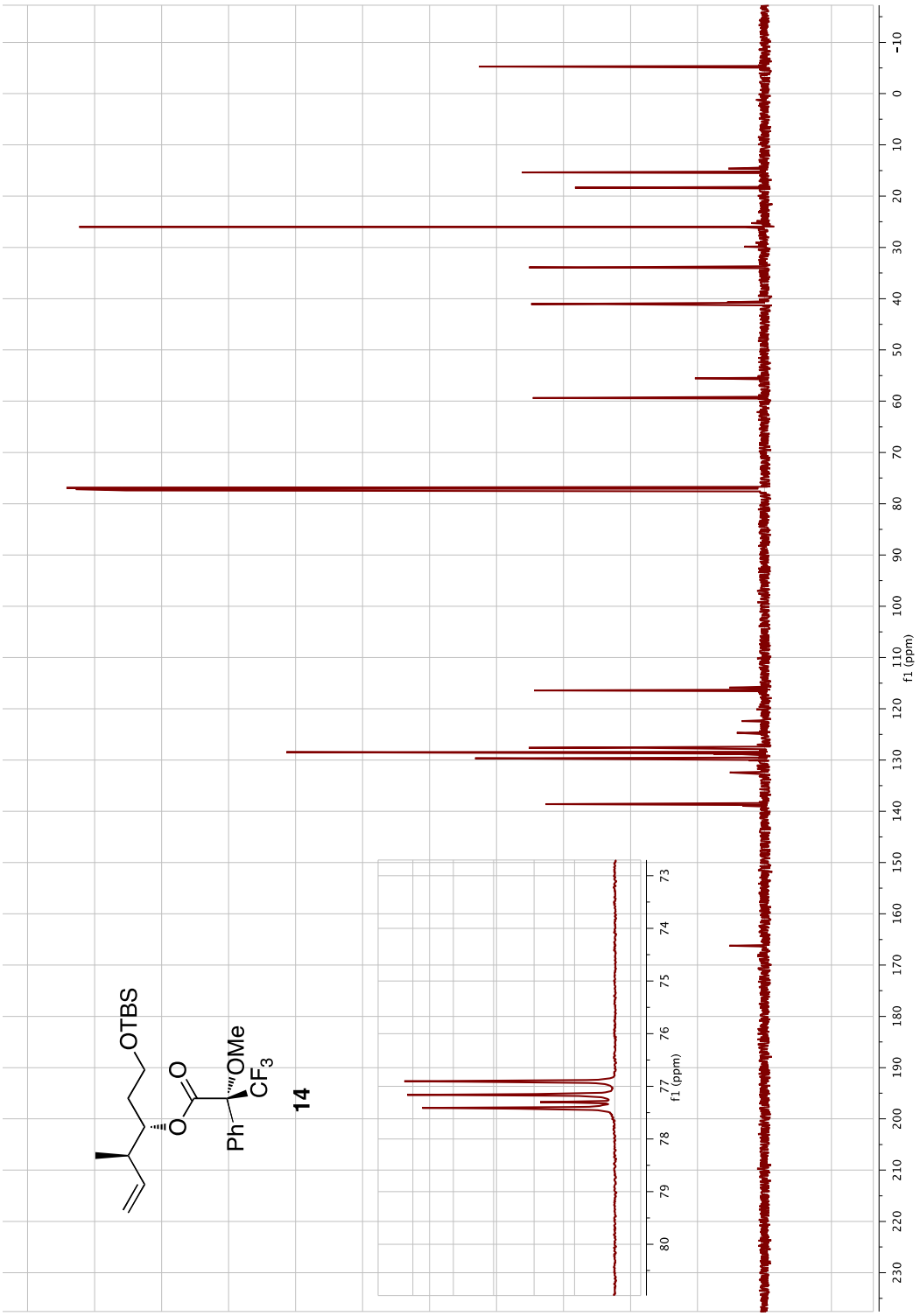


Figure 22: ^{13}C NMR Spectrum of Compound 14.

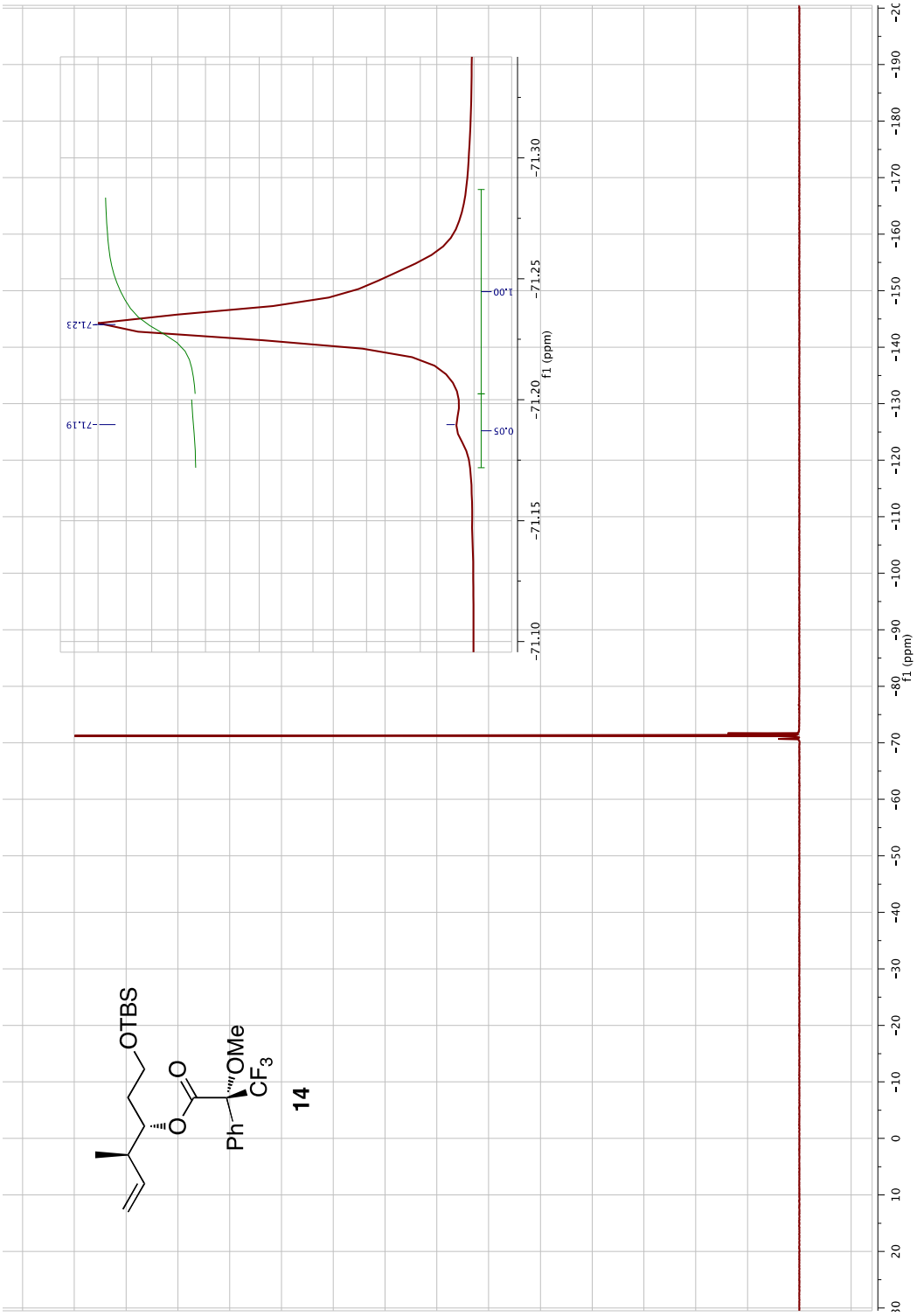


Figure 23: ^{19}F NMR Spectrum of Compound 14.

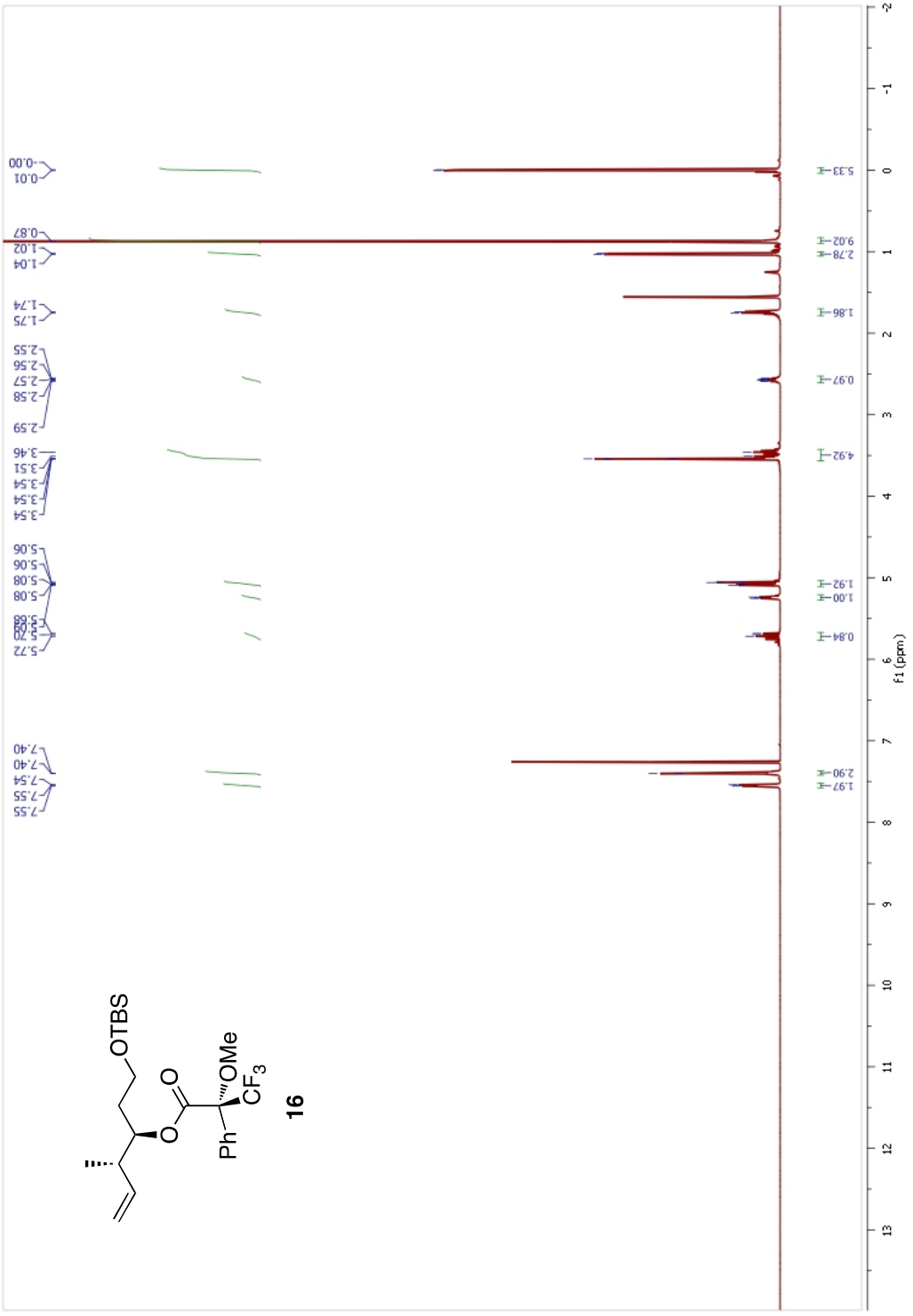


Figure 24: ^{1}H NMR Spectrum of Compound 16.

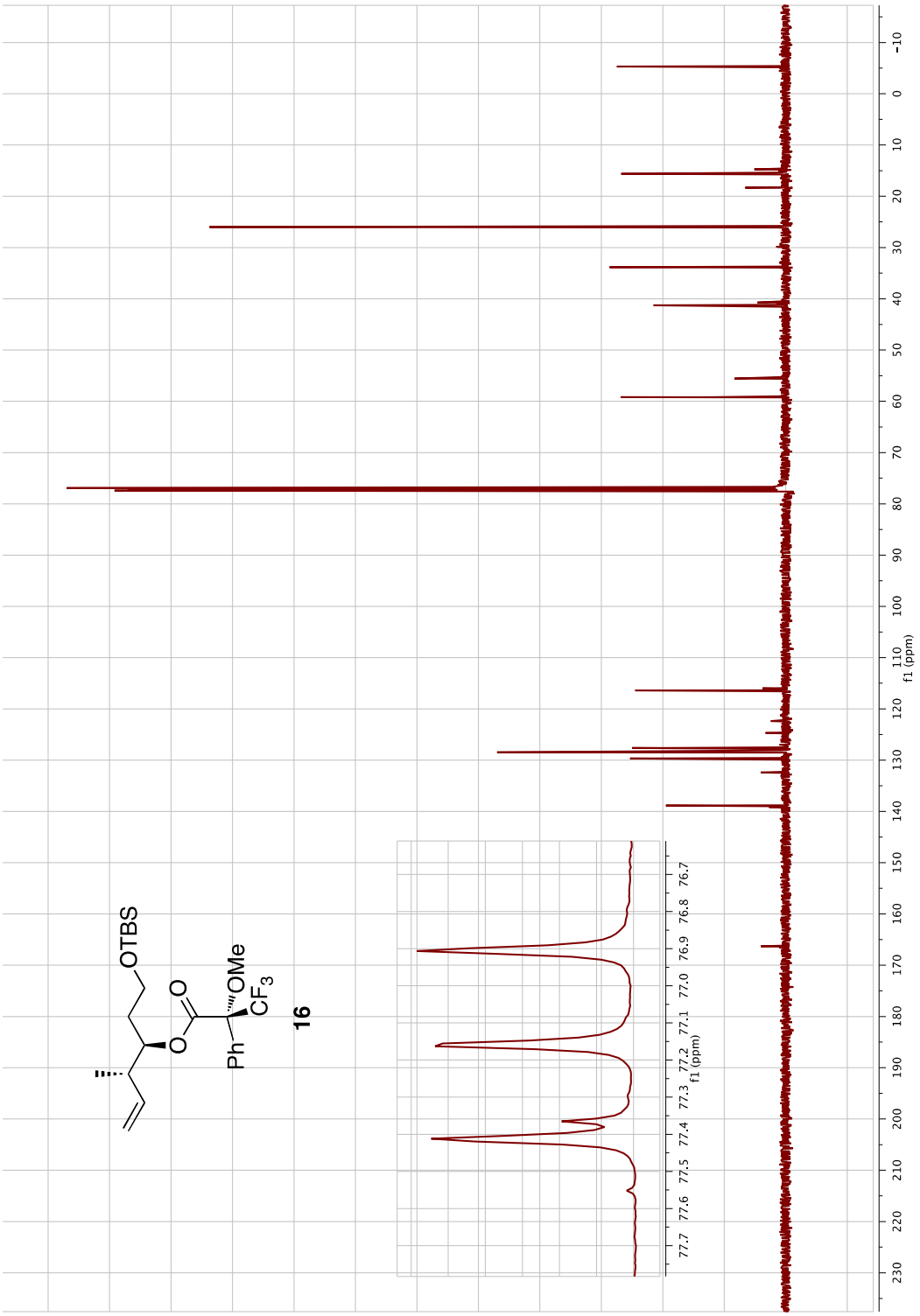


Figure 25: ^{13}C NMR Spectrum of Compound 16.

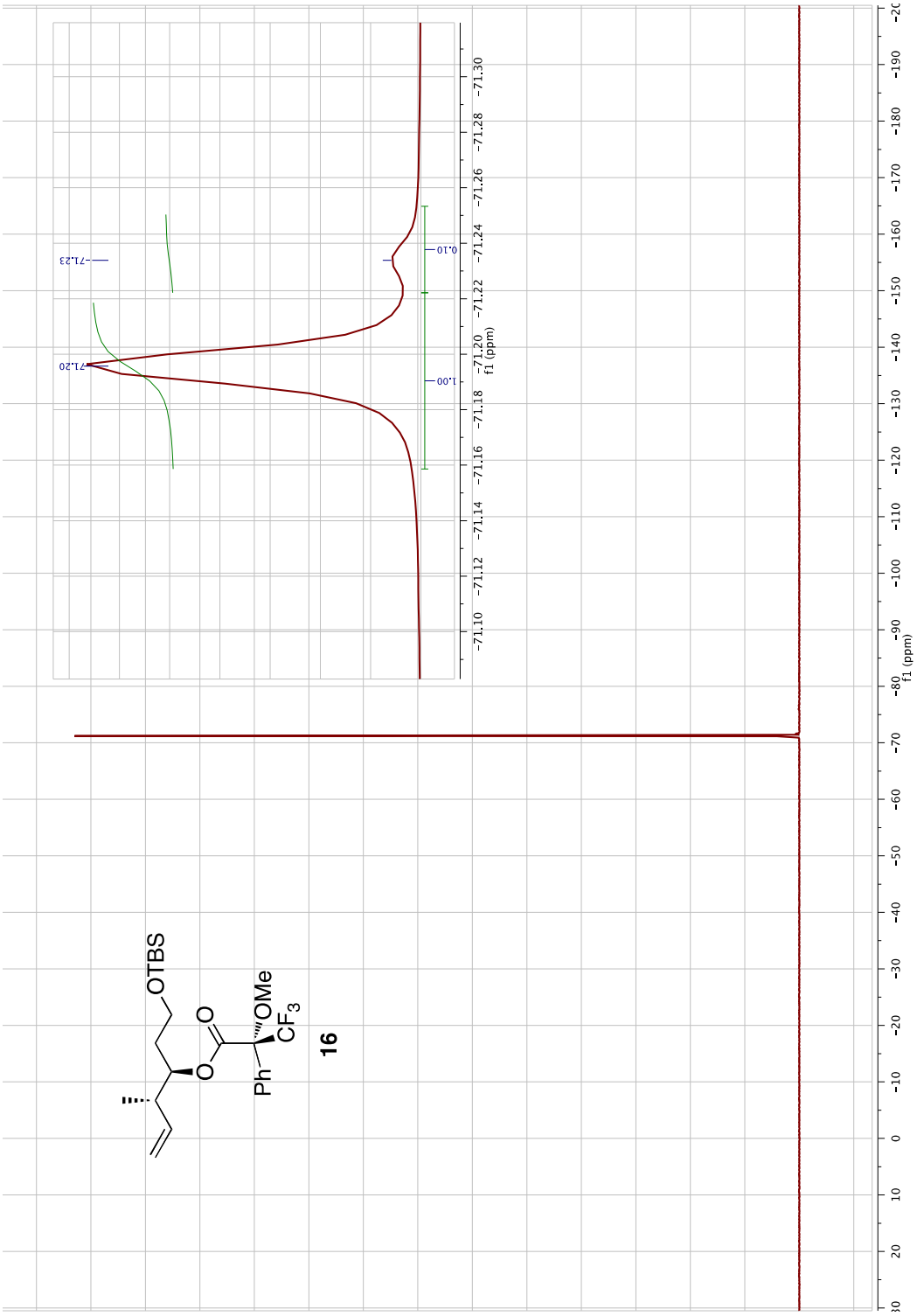


Figure 26: ^{19}F NMR Spectrum of Compound 16.