Supporting Information

Enantioselective Total Synthesis of Pladienolide B: A Potent Spliceosome Inhibitor

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GENERAL EXPERIMENTAL METHODS:

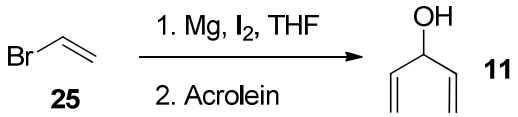
Chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained as follows: pyridine and dichloromethane were distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium wire with benzophenone as an indicator. All other solvents were reagent grade. All moisture sensitive reactions were carried out in oven dried glassware under argon. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance ARX- 400, Bruker DRX-500, or Bruker Avance-III-800 spectrometer. Chemical shifts are given in ppm and are referenced against the diluting solvent. For chloroform-d: ^{13}C triplet = 77.00 $CDCl_3$ and ^{1}H singlet = 7.26 ppm. For methanol-d_4: ^{13}C septuplet = 49.05 and ^{1}H quintuplet = 3.31 ppm. Characteristic splitting patterns due to spin spin coupling are expressed as follows: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quint = quintet, sept = septuplet. All coupling constants are measured in hertz. FTIR spectra were recorded using a NaCl plate on a Perkin Elmer Spectrum RX I spectrometer. Optical rotations were recorded on a Perkin Elmer 341 polarimeter. Low resolution mass spectrum were recorded on a FinniganMAT LCQ or Hewlett-Packard Engine mass spectrometer. High resolution mass spectrum were recorded on a FinniganMAT XL95 mass spectrometer calibrated against PPG. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 3-5 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. Visualization was carried out with short-wave UV or staining with phosphomolybdic acid (PMA). HPLC data was collected using a system composed of an Agilent 1100 series degasser, quaternary pump, thermostatable column compartment, variable wavelength detector, and Agilent 1200 series autosampler and fraction collector controlled by Chemstation software.

EXPERIMENTAL DETAILS

Macrocycle Synthesis

1. Synthesis of C1-C8 Fragment

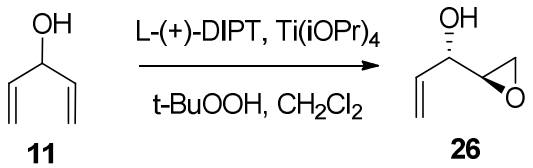
Grignard Acrolein



penta-1,4-dien-3-ol (17): [922-65-6] Prepared in a similar fashion as Shishido et al.[1] Under argon, Mg turning (6.7 g, 275 mmol), which had been previously washed with dilute HCl and dried, and I_2 (catalytic) were suspended in 100 mL THF and warmed to 40 °C. A few ml of a solution of vinyl bromide **25** (28.1 g, 263 mmol) in THF (150 mL) were added. Following initiation, the remaining vinyl bromide solution was added dropwise at such a rate that maintained a gentle reflux. After the addition was complete, the solution was refluxed for an additional hr then cooled to 0 °C. Acrolein was added dropwise and the reaction allowed to warm to 23 °C and stir for 2 h. The reaction was cooled to -20 °C and slowly quenched with 10% HCl until all solids had dissolved. The reaction was diluted with Et_2O (freshly distilled to remove trace EtOH) and the phases separated. The aqueous layer was extracted once with Et_2O. The combined organic layers were dried with brine and $MgSO_4$ and condensed. The crude material was distilled under vacuum (first at 100 torr and 35 °C bath temperature to remove residual THF and then product at 55 °C head, 75 torr) to provide 14 g (67% yield) of alcohol **11** as a clear oil.[2]

TLC 30:70 EtOAc:Hexane, R_f = 0.50 visualized with PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.88 (ddd, *J* = 6, 10.3, 16.6 Hz, 2H), 5.26 (d, *J* = 17.4 Hz, 2H), 5.13 (d, *J* = 10.4 Hz, 2H), 4.60 (t, *J* = 5.6 Hz, 1H), 2.0 (br s, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.2, 115.1, 73.9.

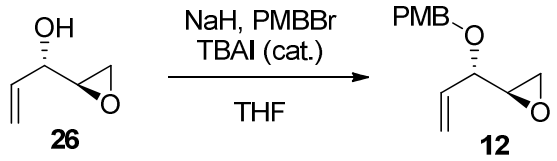
Epoxide Synthesis



(*S*)-1-((*R*)-oxiran-2-yl)prop-2-en-1-ol (26): [100017-22-9] Prepared in a similar fashion as Romero et al.[3] Under argon, dried 4Å sieves (1.5 g) were suspended in CH_2Cl_2 (40 mL) and cooled to -40 °C. Ti(*i*OPr)$_4$ (1.2 mL, 3.9 mmol) and L-DIPT (1.1 mL, 5 mmol) were added and the mixture was allowed to stir for 30 min. Alcohol **11** (3.3 g, 38 mmol) and cumene hydroperoxide (9.7 mL, 66 mmoL) were added and the reaction allowed to stir for 36 hrs. The reaction was quenched with sat. Na_2SO_4 (5 mL) and diluted with Et_2O (50 ml). The mixture was warmed to rt and stirred for 3 h. The mixture was filtered over celite, condensed and purified by silica chromatography (20:80→40:60 EtOAc:Hexane). Solvents were removed under reduced pressure and the product distilled (80 °C at 30 torr, 120 °C bath temperature) to provide 2.0 g (51% yield) of epoxide **26** as a clear oil. [4]

TLC 30:70 EtOAc:Hexane, R_f = 0.25 visualized with anisaldehyde.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (ddd, *J* = 6.2, 10.4, 17.0 Hz, 1H), 5.31 (dt, *J* = 1.2, 17.6 Hz, 1H), 5.18 (dt, *J* = 1.2, 10.2 Hz, 1H), 4.20-4.15 (m, 1H), 3.27 (br s, 1H), 3.00 (q, *J* = 3.4 Hz, 1H), 2.73 (dd, *J* = 2.8, 2.8 Hz, 1H), 2.69 (dt, *J* = 4.1, 8.9 Hz, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.7, 117.2, 70.5, 54.0, 43.8.

PMB Protection

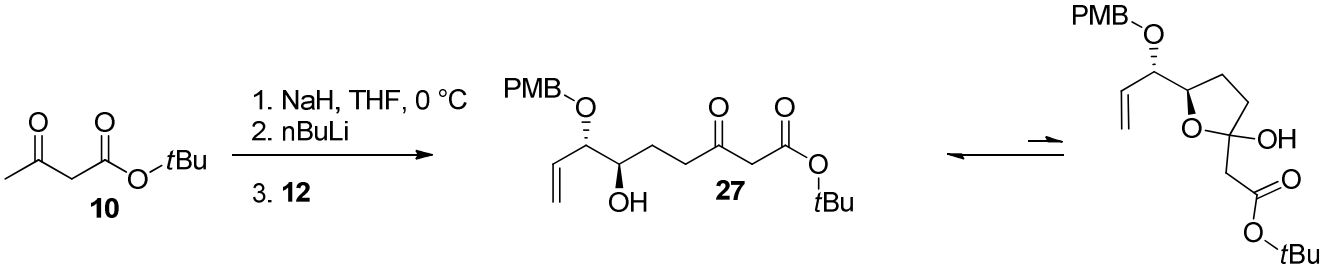


(*R*)-2-((*S*)-1-((4-methoxybenzyl)oxy)allyl)oxirane (12): [118207-36-6] 1-(bromomethyl)-4-methoxybenzene (PMBBr) was prepared in a similar fashion as Maier et al.[5] PMB-OH (12.8 g, 92 mmol) was dissolved into Et_2O (100 mL) and cooled to 0 °C. PBr_3 (4.3 mL, 46 mmol) was added and the reaction allowed to stir for 2 h. The reaction was poured into a mixture of sat. $NaHCO_3$ and ice. The organic layer was separated and washed twice with sat. $NaHCO_3$. The organic layer was dried over brine and $MgSO_4$ then filtered and evaporated to give 18.5 g (quantitative yield) of PMBBr as a clear oil that was used without further purification.[6]

PMB ether **12** was prepared in a similar fashion as Nakatsuka et al and Schreiber et al.[7] Under argon, NaH (3.2 g, 60 wt-% in oil, 79 mmol) and TBAI (catalytic) were suspended in THF (100 mL) and cooled to 0 °C. PMB-Br (above) and epoxide **26** (6.6 g, 66 mmol) were added dropwise. The reaction was allowed to warm to 23 °C and stir overnight. The reaction was quenched with H_2O and diluted with Et_2O. The organic layer was dried with brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (10:90 EtOAc:Hexane) to give 12.3 g (85% yield) of product as a clear oil.

TLC 10:90 EtOAc:Hexane, R_f = 0.36 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27-7.22 (m, 2H), 6.90-6.85 (m, 2H), 5.87-5.77 (m, 1H), 5.37-5.30 (m, 2H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 3.76 (s, 3H), 3.80-3.76 m, 1H), 3.07-3.02 (m, 1H), 2.73 (t, *J* = 4.3 Hz, 1H), 2.64 (dd, *J* = 2.7, 5.4 Hz, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 134.3, 129.9, 129.0, 119.0, 113.4, 78.7, 70.0, 54.8, 52.8, 44.4.

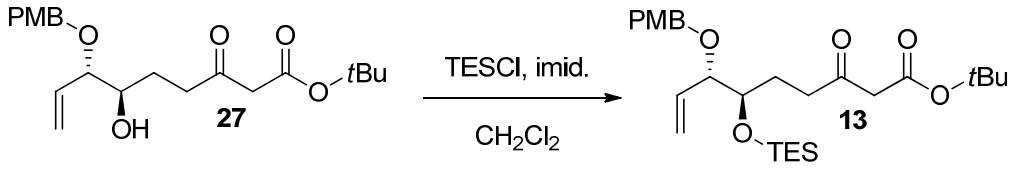
Epoxide Opening



(6*R*,7*S*)-*tert*-butyl 6-hydroxy-7-((4-methoxybenzyl)oxy)-3-oxonon-8-enoate (27): Under argon, NaH (7.9 g, 197 mmol) was suspended in THF (200 mL) and cooled to 0 °C. *t*-butyl acetoacetate **10** (31.6 ml, 191 mmol) was added dropwise causing a light yellow color. After stirring for 15 min, *n*-BuLi (120 mL, 1.6 N in hexane, 191 mmol) was added causing the solution to turn cloudy orange. Epoxide **12** (14 g, 64 mmol) in THF (30 mL) was added dropwise and the reaction allowed to stir overnight. The reaction was quenched with H_2O, diluted with Et_2O (300 mL), and washed with 1% HCl (100 mL x 2). The organic layer was dried over brine and Na_2SO_4 and condensed under low temperature. The crude material was purified by silica chromatography (20:80→50:50 EtOAc:Hexane) to provide 36 g of crude alcohol **27** as a clear yellow oil that was used without further purification.[8]

TLC 30:70 EtOAc:Hexane, R_f = 0.37 visualized with UV and PMA.
FTIR (thin film) $\tilde{\nu}_{max}$: 3461, 2978, 1732, 1715, 1613, 1514, 1368, 1249, 1154, 1036, 822 cm^{-1}.
$[\alpha]_D^{20}$ 28.5 (*c* 2.46, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 401.1 (100%), $[M+H]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{30}O_6$, 401.1940; found, 401.1942.

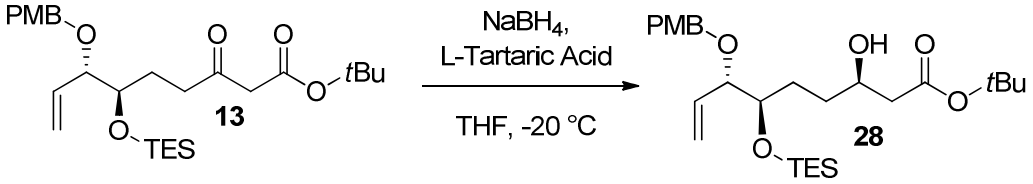
TES Protection



(6*R*,7*S*)-*tert*-butyl 7-((4-methoxybenzyl)oxy)-3-oxo-6-((triethylsilyl)oxy)non-8-enoate (13): Under argon, crude ester **27** (36 g, 64 mmol) was dissolved into CH_2Cl_2 (200 mL) and cooled to 0 °C. Imidazole (11.1 g, 162 mmol) was added followed by TESCl (11.5 mL, 68 mmol). The reaction was allowed to warm to 23 °C and stir 4 h. The reaction was cooled to 0 °C, quenched with H_2O and diluted with Et_2O (300 mL). The organic layer was washed with 1% HCl (2 x 50 mL) and then dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90→20:80 EtOAc:Hexane) to give 39 g of crude silyl ether **13** as a clear oil.[9]

TLC 10:90 EtOAc:Hexane, R_f = 0.35 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.78 (ddd, *J* = 7.7, 10.4, 17.7 Hz, 1H), 5.32 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.25 (dd, *J* = 1.8, 17.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 3H), 3.78-3.74 (m, 1H), 3.57 (dd, *J* = 4.9, 7.7 Hz, 1H), 3.28 (s, 2H), 2.58-2.46 (m, 2H), 1.87-1.72 (m, 2H), 1.45 (s, 9H), 0.91 (t, *J* = 8.2 Hz, 9H), 0.57 (q, *J* = 8.0, 15.9 Hz, 6H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 203.2, 166.4, 159.0, 135.8, 130.4, 129.4, 119.2, 113.6, 82.6, 81.6, 73.3, 69.7, 55.1, 50.5, 38.2, 27.9, 26.9, 6.9, 5.0.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 2876, 1736, 1717, 1613, 1514, 1368, 1302, 1249, 1172, 1149, 1081, 1037, 1009, 821, 742 cm^{-1}.
$[\alpha]_D^{20}$ 17.7 (*c* 2.54, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 515.2 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{44}O_6Si$, 515.2805; found, 515.2800.

$NaBH_4$/Tartaric Acid Reduction

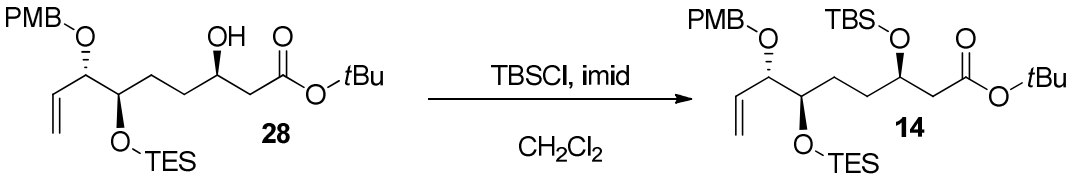


(3*R*,6*R*,7*S*)-*tert*-butyl 3-hydroxy-7-((4-methoxybenzyl)oxy)-6-((triethylsilyl)oxy)non-8-enoate (28): $NaBH_4$ (10.6 g, 280 mmol) and L-tartaric acid (42 g, 280 mmol) were suspended in THF (700 mL) and the solution was heated to reflux for 3 h then cooled to -20 °C. Crude ketone **13** (39 g, 64 mmol) in THF (120 mL) was added dropwise. After stirring for 48 hr, the reaction was quenched with 2 N NaOH (300 mL) and diluted with Et_2O (400 mL). The organic layer was washed with 1 N NaOH and sat. $NaHCO_3$ and then dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90→20:80 EtOAc:Hexane) to give 21 g (66 % yield over 3 steps) of alcohol **28** as a clear oil.[10]

TLC 10:90 EtOAc:Hexane, R_f = 0.18 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (d, *J* = 8.3 Hz, 2H), 8.86 (d, *J* = 8.3 Hz, 2H), 5.81 (ddd, *J* = 7.8, 10.2, 17.7 Hz, 1H), 5.31 (dd, *J* = 1.9, 10 Hz, 1H), 5.24 (dd, *J* = 2.0, 17.2 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.97-3.88 (m, 1H), 3.80 (s, 3H), 3.76 (dd, *J* = 4.2, 7.8 Hz, 1H), 3.61 (dd, *J* = 4.7, 8.0 Hz, 1H), 3.08 (br s, 1H), 2.39 (dd, *J* = 3.4, 16.4 Hz, 1H), 1.73-1.40 (m, 4H), 1.46 (s, 9H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 7.7 Hz, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 158.9, 136.0, 130.6, 129.4, 119.0, 113.6, 83.0, 81.1, 74.3, 69.8, 68.1, 55.2, 42.2, 31.8, 29.2, 28.1, 6.9, 5.1.
FTIR (thin film) $\tilde{\nu}_{max}$: 3488, 2954, 2876, 1728, 1614, 1514, 1458, 1368, 1302, 1248, 1153, 1038, 1009, 929, 820, 743 cm^{-1}.
$[\alpha]_D^{20}$ 11.9 (*c* 1.53, $CHCl_3$).

LR-ESI (+) *m/z* (relative intensity), ion: 461.5 (100%), $[M+Na\text{-}t\text{-butyl}]^+$, 517.6 (50%) $[M+Na]^+$, 533.5 (5%), $[M+K]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{27}H_{46}O_6Si$, 517.2961; found, 517.2969.

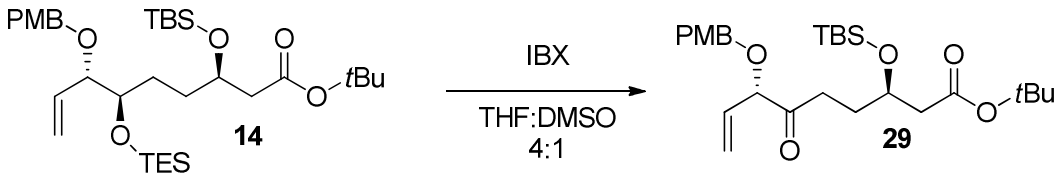
TBS Protection



(3*R*,6*R*,7*S*)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-((triethylsilyl)oxy)non-8-enoate (14): Under argon, alcohol **28** (21 g, 42 mmol) was dissolved into CH_2Cl_2 (90 mL). Imidazole (7.2 g, 106 mmol) was added followed by TBSCl (8.3 g, 55 mmol) and a catalytic amound of DMAP. After stirring overnight, the reaction was quenched with H_2O and diluted with Et_2O. The organic layer washed with 2% HCl (x2) and then dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography to give 24 g (93% yield) of silyl ether **14** as a clear oil.[9]

TLC 10:90 EtOAc:Hexane, R_f = 0.75 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.81 (ddd, *J* = 7.9, 10.5, 17.8 Hz, 1H), 5.31 (dd, *J* = 2, 10.4 Hz, 1H), 5.22 (dd, *J* = 2.0, 17.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 4.10-4.03 (m, 1H), 3.80 (s, 3H), 3.74-3.70 (m, 1H), 3.62-3.57 (m, 1H), 2.37 (dd, *J* = 6.7, 15.0 Hz, 1H), 2.30 (dd, *J* = 5.8, 14.9 Hz, 1H), 1.64-1.55 (m, 1H), 1.50-1.40 (m, 2H), 1.44 (s, 9H), 0.93 (t, *J* = 8.1 Hz, 9H), 0.87 (s, 9H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 6H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.0, 158.9, 135.9, 130.7, 129.3, 119.0, 113.6, 83.3, 80.1, 74.9, 69.8, 69.5, 55.2, 43.9, 33.2, 29.2, 28.1, 26.0, 25.8, 18.0, 7.0, 6.9, 5.1, 5.0, -4.6, -4.7.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 2877, 1732, 1614, 1587, 1514, 1463, 1367, 1302, 1249, 1155, 1085, 1040, 1006, 927, 836, 776, 742 cm^{-1}.
$[\alpha]_D^{20}$ 7.1 (*c* 3.33, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 575.6 (100%), $[M+Na\text{-}t\text{-butyl}]^+$, 631.7 (25%) $[M+Na]^+$, 647.7 (8%), $[M+K]^+$
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{33}H_{60}O_6Si_2$, 631.3826; found, 631.3832.

IBX Silyl Deprotection/Oxidation



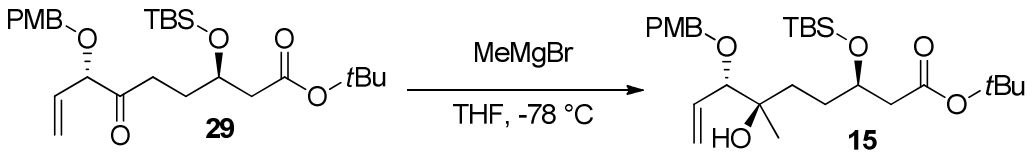
2-iodoxybenzoic acid: [61717-82-6] Prepared in a similar fashion as Frigerio et al.[11] 2-iodobenzoic acid (50 g, 0.2 mol) was added to a solution of Oxone (181 g, 0.29 mol) in deionized water (650 mL, 0.45 M). The reaction mixture was warmed to 70 °C over 20 min and mechanically stirred at this temperature for 3 h. The mixture was cooled to 0 °C for 1.5 hr stirring slowly. The mixture was filtered and the solids washed with water (6 x 100 mL) and acetone (2 x 100 mL). The solid was dried at 23 °C for 24 h providing 48.7 g (87% yield) of IBX as a white solid that was stored at -15 °C between uses.

(3*R*,7*S*)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-oxonon-8-enoate (29): Under argon, silyl ether **14** (15.9 g, 26 mmol) was dissolved into DMSO (25 mL) and THF (75 m). IBX (36 g, 130 mmol) was added and the reaction allowed to stir at 23 °C for 36 h. The reaction was quenched with H_2O and diluted with Et_2O. Solids were removed by filtration. The organic layer was washed with H_2O and dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (5:95→10:90 EtOAc:Hexane) to give 7.7 g (60% yield) of ketone **29** and 6.8 g (43% yield) of starting material **14** (quantitative BRSM).[12]

TLC 10:90 EtOAc:Hexane, R_f = 0.50 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.78 (ddd, *J* = 6.4, 10.5, 17.1 Hz, 1H), 5.45 (dt, *J* = 1.6, 17.2 Hz, 1H), 5.36 (dt, *J* = 1.6, 10.4 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 8.9 Hz, 1H), 4.27 (dt, *J* = 1.6, 6.4 Hz, 1H), 4.11 (quint, *J* = 5.5 Hz, 1H), 3.81 (s, 3H), 2.68 (ddd, *J* = 5.7, 9.8, 18.3 Hz, 1H), 2.59 (ddd, *J* = 5.5, 9.8, 18.3 Hz, 1H), 2.38 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.27 (dd, *J* = 6.3, 15.0 Hz, 1H), 1.82-1.74 (m, 1H), 1.73-1.65 (m, 1H), 1.43 (s, 9H), 0.85 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 209.1, 170.6, 159.3, 133.1, 129.5, 129.4, 119.5, 113.8, 85.4, 80.5, 70.8, 68.2, 55.3, 43.6, 33.3, 30.3, 28.1, 25.8, 18.0, -4.7.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 2929, 2856, 1727, 1612, 1514, 1460, 1368, 1250, 1153, 1082, 836, 776 cm^{-1}.
$[\alpha]_D^{20}$ -18.3 (*c* 0.60, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 459.4 (70%), [M+Na-*t*butyl]$^+$, 515.5 (100%), [M+Na]$^+$, 531.5 (72%), [M+K]$^+$.
HR-ESI (+) *m/z*: [M+Na]$^+$ calcd for $C_{27}H_{44}O_6Si$, 515.2805; found, 515.2799.

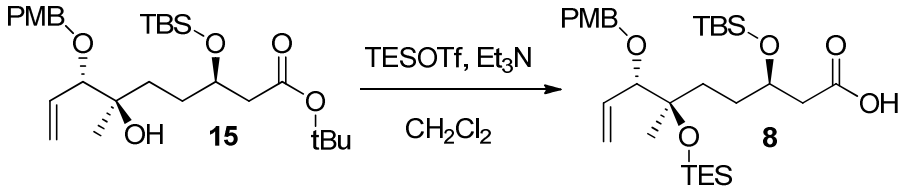
Grignard Addition



(3*R*,6*R*,7*S*)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-7-((4-methoxybenzyl)oxy)-6-methylnon-8-enoate (15): Under argon, ketone **29** (7.7 g, 15.6 mmol) was dissolved into THF (150 mL) and cooled to -78 °C. MeMgBr (6.2 mL, 3M in Et_2O, 18.7 mmol) was added dropwise and the reaction allowed to stir for 2 h. The reaction was warmed to -40 °C, quenched with sat. NH_4Cl, and diluted with Et_2O. The organic layer was washed with 1% HCl, dried with brine and Na_2SO_4, and evaporated. The crude material was purified by silica chromatography (10:90→20:80 EtOAc:Hexane) to give 6.7 g (85% yield, 97% BRSM) of alcohol **15** as a clear oil. 1 g (13% yield) of starting ketone **29** was also recovered.[13]

TLC 20:80 EtOAc:Hexane, R_f = 0.50 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 800 MHz): δ 7.24-7.22 (m, 2H), 6.88-6.86 (m, 2H), 5.79 (ddd, *J* = 8.1, 10.3, 18.4 Hz, 1H), 5.37 (dd, *J* = 1.8, 10.4 Hz, 1H), 5.29 (dd, *J* = 1.9, 17.4 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H) 4.25 (d, *J* = 11.3 Hz, 1H0, 4.06 (quint, *J* = 5.8 Hz, 1H), 3.81 (s, 3H), 3.56 (d, *J* = 8.1 Hz, 1H), 2.38 (dd, *J* = 6.4, 15.0 Hz, 1H), 2.37 (br s, 1H), 2.31 (dd, *J* = 6.0, 14.9 Hz, 1H), 1.68 (dt, *J* = 4.4, 12.7 Hz, 1H), 1.63-1.58 (m, 1H), 1.58-1.52 (m, 1H), 1.43 (s, 9H), 1.35-1.30 (m, 1H), 1.11 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 200 MHz): δ 171.0, 159.2, 134.9, 130.4, 129.4, 120.1, 113.8, 87.2, 80.3, 73.5, 70.3, 69.6, 55.3, 43.8, 32.1, 30.7, 28.2, 25.9, 23.2, 18.0, -4.5, -4.6.
FTIR (thin film) $\tilde{\nu}_{max}$: 3546, 2929, 2856, 1731, 1613, 1515, 1464, 1368, 1250, 1157, 1074, 835, 776 cm^{-1}.
$[\alpha]_D^{20}$ 10.8 (*c* 0.46, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 531.2 (100%), [M+Na]$^+$.
HR-ESI (+) *m/z*: [M+Na]$^+$ calcd for $C_{28}H_{48}O_6Si$, 531.3118; found, 531.3119.

TESOTf Acid Synthesis



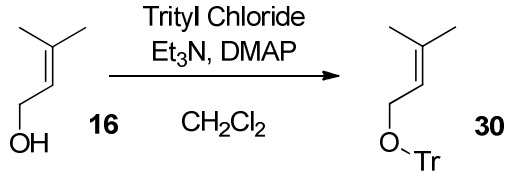
(3*R*,6*R*,7*S*)-3-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-methyl-6-((triethylsilyl)oxy)non-8-enoic acid (8): Under argon, alcohol **15** (4.2 g, 8.3 mmol) was dissolved into CH_2Cl_2 (40 mL) and cooled to 0 °C. Et_3N (3.7 mL, 26 mmol) was added followed by the addition of TESOTf (4.1 mL, 18.2 mmol). After stirring for 2 h, the reaction was quenched with H_2 and diluted with Et_2O. The organic layer was washed with 1% HCl and then dried with brine and Na_2SO_4 and evaporated. The crude material was purified by silica chromatography (10:90→20:80 EtOAc:Hexane) to give 4.5 g (96% yield) of acid **8** as a clear oil.[14]

TLC 20:80 EtOAc:Hexane, R_f = 0.50 visualized with UV and PMA. Same R_f as **15**.
^{1}H NMR ($CDCl_3$, 800 MHz): δ 10.7 (br s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.81 (ddd, *J* = 7.4, 10.4, 17.6 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.22 (d, *J* = 11.3 Hz, 1H), 4.01 (quint., *J* = 5.8 Hz, 1H), 3.80 (s, 3H), 3.52 (d, *J* = 7.4 Hz, 1H), 2.50 (dd, *J* = 5.2, 15.3 Hz, 1H), 2.45 (dd, *J* = 5.8, 15.3 Hz, 1H), 1.79-1.73 (m, 1H), 1.62-1.54 (m, 2H), 1.27-1.22 (m, 1H), 1.17 (s, 3H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.88 (s, 9H), 0.55 (dq, *J* = 3.2, 7.8 Hz, 6H), 0.07 (s, 3H), 0.07 (s, 3H).
^{13}C NMR ($CDCl_3$, 200 MHz): δ 175.2, 158.9, 135.5, 130.1, 129.3, 118.9, 113.6, 85.1, 76.6, 70.1, 70.1, 55.2, 41.9, 36.2, 31.0, 25.7, 23.8, 17.9, 7.2, 6.9, -4.5, -4.9.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 1712, 1614, 1514, 1463, 1302, 1249, 1081, 1006, 836, 776, 742 cm^{-1}.
$[\alpha]_D^{20}$ 11.3 (*c* 0.62, $CHCl_3$).

LR-ESI (+) *m/z* (relative intensity), ion: 589.2 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{30}H_{54}O_6Si2$, 589.3357; found, 589.3361.

2. Synthesis of C_9-C_{14} Fragment

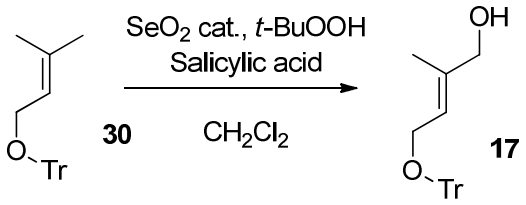
Trityl protection



(((3-methylbut-2-en-1-yl)oxy)methanetriyl)tribenzene (30): [141561-63-9] Prepared in a similar fashion as Jyothi et al.[15] Under argon, 3-methyl-2-buten-1-ol **16** (7.6 g, 88 mmol) and trityl chloride (22 g, 80 mmol) were dissolved into CH_2Cl_2 (160 mL, [0.5 M]) producing a clear olive green solution. After cooling to 0 °C, Et_3N (22 ml, 160 mmol) and DMAP (100 mg, catalytic) were added causing the solution to turn yellow and form a white precipitate. The reaction was allowed to warm to 23 °C and stir overnight. The reaction was diluted with Et_2O (150 mL) and washed with 1% HCl (2 x 10 ml). The organic layer was dried over brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (5:95 → 10:90 EtOAc:Hexane) to give 26 g (quantitative) of the desired trityl ether **30** as a clear oil.

TLC 10:90 EtOAc:Hexane, $R_f = 0.73$ visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54-7.49 (m, 6H), 7.36 (m, 6H), 7.29-7.23 (m, 3H), 5.52-5.47 (m, 1H), 3.63 (d, *J* = 6.4 Hz, 2H), 1.78 (s, 3H), 1.52 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.4, 135.3, 128.7, 127.9, 127.7, 126.8, 121.5, 86.5, 61.2, 25.8, 18.1.

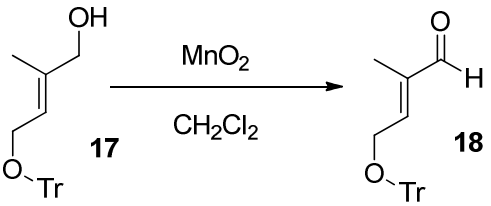
Riley oxidation



(*E*)-2-methyl-4-(trityloxy)but-2-en-1-ol (17): Under argon, SeO_2 (190 mg, 1.7 mmol) and salicylic acid (1.2 g, 8.5 mmol) was dissolved into CH_2Cl_2 (20 mL). *t*-BuOOH (5 N in benzene, 34 mL, 170 mmol) was added. After stirring for 15 min, ether **30** (26 g, 80 mmol) in CH_2Cl_2 (20 mL) was added dropwise and the reaction was allowed to stir for 48 h. The reaction was diluted with Et_2O (100 mL) and washed with 1 N NaOH (3 x 25 mL). The organic layer was dried with brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (5:95→10:90→20:80→30:70 EtOAc:Hexane) to provide 14.2 g (52% yield) of alcohol **17** as a viscous clear oil. 11.8 g (45% yield) of starting material **30** was recovered along with 0.8 g (3%) of crude aldehyde **18**.[16]

TLC 20:80 EtOAc:Hexane, $R_f = 0.21$ visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.50 (m, 6H), 7.38-7.32 (m, 6H), 7.31-7.25 (m, 6H), 5.77-5.72 (m, 1H), 4.06 (d, *J* = 6.2 Hz, 2H), 3.74 (d, *J* = 6.4 Hz, 2H), 1.55 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.1, 137.4, 128.6, 127.8, 126.9, 122.2, 86.7, 68.2, 60.8, 13.9.
FTIR (thin film) $\tilde{\nu}_{max}$: 3338, 3085, 3058, 3032, 2917, 2861, 1596, 1490, 1448, 1381, 1319, 1266, 1221, 1154, 1054, 899, 950, 763, 746, 706, 649, 633 cm^{-1}.
LR-ESI (+) *m/z* (relative intensity), ion: 367.2 (100), $[M+Na]^+$, 383.0 (31), $[M+K]^+$.
LR-APCI (+) *m/z* (relative intensity), ion: 243.1 (100%), $[CPh_3]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{24}O_{24}O_2$, 367.1674; found, 367.1679.

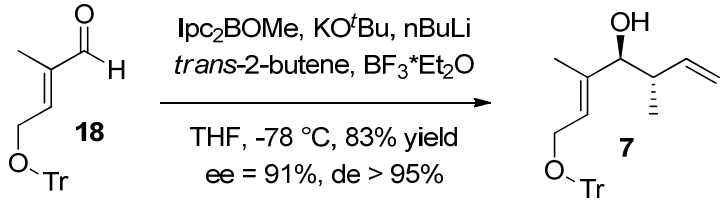
MnO_2 oxidation



(*E*)-2-methyl-4-(trityloxy)but-2-enal (18): [116760-95-3] Allylic alcohol **17** (14.5 g, 42.5 mmol) was dissolved into CH_2Cl_2 (175 mL). MnO_2 (115 g, 1.3 mol) was added portion wise until the starting material was consumed as indicated by TLC. The mixture was filtered over celite, rinsing with CH_2Cl_2. Solvents were removed under reduced pressure to provide 12.6 g (87% yield) of the desired aldehyde **18** as a white solid.[17]

TLC 20:80 EtOAc:Hexane, R_f = 0.78 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.42 (s, 1H), 7.53 (m, 6H), 7.38-7.33 (m, 6H), 7.32-7.26 (m, 3H), 6.65-6.61 (m, 1H), 4.07 (d, *J* = 5.2 Hz, 2H), 1.60 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 194.5, 150.5, 143.6, 138.5, 128.6, 128.0, 127.2, 87.3, 61.5, 9.5.

Brown's Crotylation



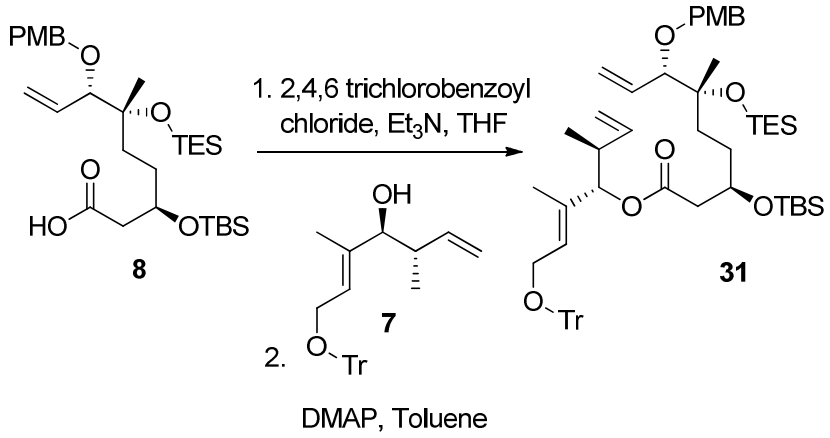
(-)-*B*-Methoxydiisopinocampehylborane: [85134-98-1] (-)-*B*-Methoxydiisopinocampehylborane (IPC_2BOMe) is commercially available or made be prepared fresh from (1*R*)-(+)-α-pinene.[18]

(3*S*,4*S*,*E*)-3,5-dimethyl-7-(trityloxy)hepta-1,5-dien-4-ol (7): Under argon, KO*t*Bu (7 mL, 1 M in THF, 7 mmol) was cooled to -78 °C. *Trans*-2-butene (1.1 mL, 12 mmol) was trapped in a graduated cylinder at -78 °C and transferred by cannula to the KO*t*Bu. *n*BuLi (4.4 mL, 1.6 M in hexane, 7 mmol) was added dropwise over 15 min. The reaction was allowed to warm to -50 °C for 30 min and subsequently cooled to -78 °C. (-)-IPC_2BOMe (2.6 g, 8.2 mmol) in THF (10 mL) was added via cannula over 15 min. After stirring for 30 min, BF_3•OEt_2 (1.3 mL, 10 mmol) was added followed by the aldehyde **18** (2 g, 5.8 mmol) dissolved in THF (15 mL) and precooled to -78 °C. The reaction was allowed to stir overnight at -78 °C. 3 N NaOH (5 mL) was added followed by the slow addition of H_2O_2 (5 ml, 30 wt-% in H_2O) as the mixture warmed to 23 °C. The reaction was heated to 50 °C for 3 hr and subsequently cooled to 23 °C. The mixture was diluted with Et_2O and layers separated. The aqueous layer was extracted with Et_2O. The combined organic layers were dried with brine and Na_2SO_4 and condensed. Pinene alcohol was removed by distillation under full vacuum (80 °C head temperature, 130 °C base). The remaining residue was purified by silica chromatography (10:90→15:85 EtOAc:Hexane) to afford 1.7 g (73 % yield) of homoallylic alcohol **7** as a clear oil in > 82% *ee*.[19]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52-7.46 (m, 6H), 7.35-7.28 (m, 6H), 7.28-7.22 (m, 3H), 5.83-5.73 (m, 1H), 5.72-5.67 (m, 1H), 5.21-5.14 (m, 2H), 3.77-3.65 (m, 3H), 2.32 (sextet, *J* = 7.4 Hz, 1H), 1.78 (d, *J* = 2.4 Hz, 1H), 1.48 (s, 3H), 0.94 (d, *J* = 6.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 140.9, 137.4, 128.6, 127.7, 126.9, 125.6, 116.5, 86.7, 80.7, 60.9, 42.0, 16.7, 11.5.
FTIR (thin film) $\tilde{\nu}_{max}$: 3436, 3059, 2973, 2870, 1490, 1448, 1222, 1054, 1030, 912, 763, 746, 707, 632 cm^{-1}.
$[\alpha]_D^{20}$ -6.2 (*c* 1.27, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 421.1 (100%), $[M+Na]^+$.
HR-ESI (+)*m/z*: $[M+Na]^+$ calcd for $C_{28}H_{30}O_2$, 421.2143; found, 421.2147.
Chiral HPLC: Chiralpak IA 250 x 4.6 mm, 5 micron; 5:95 IPA:Hexane, flow = 1 mL/min, T = 15 °C, UV = 210 nm, R_t minor = 5.0 min, R_t major = 5.4 min.

3. Synthesis of the Macrocyclic Ring

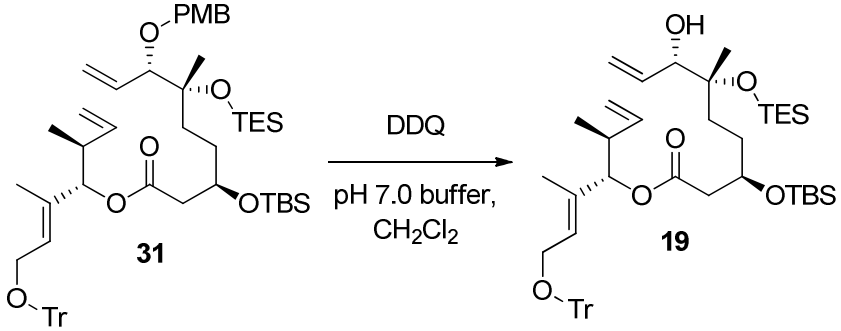
Esterification



(3*R*,6*R*,7*S*)-(3*S*,4*S*,*E*)-3,5-dimethyl-7-(trityloxy)hepta-1,5-dien-4-yl 3-((tert-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-6-methyl-6-((triethylsilyl)oxy)non-8-enoate (31): Under argon, Et_3N (0.8 mL, 5.7 mmol) was dissolved into THF (10 mL) and cooled to 0 °C. 2,4,6 trichlorobenzoyl chloride (0.8 mL, 4.9 mmoL) was added dropwise followed by acid **8** (2.5 g, 4.4 mmol). The reaction was warmed to 23 °C and stirred for 30 min. Solvents were removed under reduced pressure. The reaction was cooled to 0 °C and suspended in toluene (10 mL). Alcohol **7** (2 g, 4.9 mmol) and DMAP (800 mg, 6.6 mmol) in toluene (10 mL) were added dropwise and the reaction allowed to warm to 23 °C and stir overnight. The reaction was quenched with H_2O, diluted with Et_2O, and washed with 2% HCl. The organic layer was dried over Na_2SO_4 and condensed. The crude material was purified by silica chromatography (5:95 → 10:90 EtOAc:Hexane) to give 2.9 g (68 % yield) of ester **31** as a clear oil.[20]

TLC 10:90 EtOAc:Hexane, R_f = 0.75 visualized with UV and PMA.
^{1}H NMR ($CDCl_3$, 800 MHz): δ 7.48-7.22 (m, 17H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.85-5.80 (m, 1H), 5.76-5.70 (m, 2H), 5.30 (dd, *J* = 2.2, 10.2 Hz, 5.20 (dd, *J* = 2.1, 17.4 Hz, 1H), 5.07-4.99 (m, 3H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 4.03 (sept, *J* = 5.9 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 6 Hz, 2H), 3.50 (d, *J* = 7.4 Hz, 1H), 2.46 (sept., *J* = 7.3 Hz, 1H), 2.43 (dd, *J* = 6.3, 15.0 Hz, 1H), 2.36 (dd, *J* = 5.9, 15.2 Hz, 1H), 1.76 (td, *J* = 4.2, 13.0 Hz, 1H), 1.57-1.52 (m, 1H), 1.48-1.43 (m, 1H), 1.45 (s, 3H), 1.25 (td, *J* = 4.1, 13.0 Hz, 1H), 1.15 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.87 (s, 9H), 0.58-0.53 (m, 6H), 0.04 (s, 3H), 0.03 (s, 3H).
^{13}C NMR ($CDCl_3$, 200 MHz): δ 170.5, 158.9, 144.2, 140.2, 135.6, 134.3, 130.9, 129.3, 128.7, 128.3, 128.0, 127.7, 126.9, 126.5, 118.7, 115.2, 113.5, 86.7, 85.2, 81.5, 70.0, 69.7, 60.7, 55.2, 43.2, 40.3, 36.1, 31.4, 25.9, 23.8, 18.0, 16.7, 12.6, 7.2, 6.9, -4.6, -4.6.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 2930, 2875, 1736, 1613, 1514, 1449, 1248, 1078, 835, 706 cm^{-1}.
$[\alpha]_D^{20}$ -2.5 (*c* 1.00, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 969.5 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{58}H_{82}O_7Si_2$, 969.5497; found, 969.5505.

PMB Deprotection

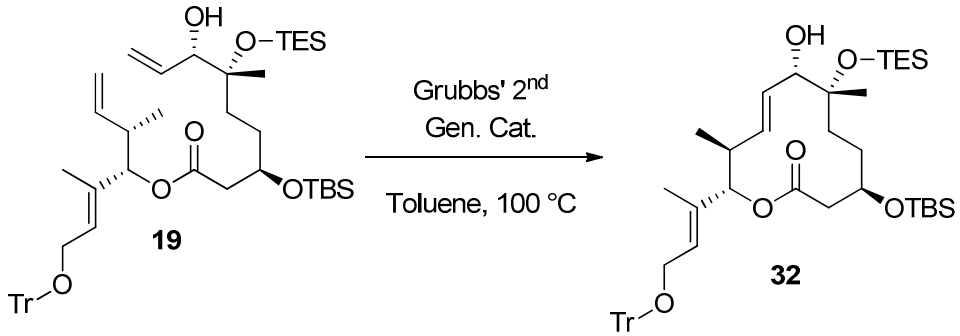


(3*R*,6*R*,7*S*)-(3*S*,4*S*,*E*)-3,5-dimethyl-7-(trityloxy)hepta-1,5-dien-4-yl 3-((tert-butyldimethylsilyl)oxy)-7-hydroxy-6-methyl-6-((triethylsilyl)oxy)non-8-enoate (19): Ester **31** (2.9 g, 3 mmol) was dissolved into CH_2Cl_2 (30 mL). pH 7.0 buffer (3 mL) was added followed DDQ (890 mg, 3.9 mmol) portionwise. After stirring at 23 °C for 1 h, the reaction was quenched with sat. $NaHCO_3$ and diluted with Et_2O. The organic layer was washed with sat. $NaHCO_3$ then dried with brine and Na_2SO_4. Solvents were removed under

reduced pressure and the crude material was purified by silica chromatography (20:80 EtOAc Hexane) to give 1.9 g (75% yield) of alcohol **19** as a clear oil.[21]

TLC 10:90 EtOAc:Hexane, R_f = 0.33 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50-7.20 (m, 15H), 5.84 (ddd, *J* = 6.6, 10.5, 17.2 Hz, 1H), 5.73 (m, 1H), 5.69 (dd, *J* = 7.7, 10.0 Hz, 1H), 5.30 (dt, *J* = 1.7, 17.4 Hz, 1H), 5.18 (dt, *J* = 1.4, 10.6 Hz, 1H), 5.08-4.99 (m, 3H), 4.05 (quint, *J* = 5.8 Hz, 1H), 3.84 (d, *J* = 6.3 Hz, 1H), 3.63 (d, *J* = 6.1 Hz, 2H), 2.64 (br s, 1H), 2.48 (m, 1H), 2.45 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.38 (dd, *J* = 6.4, 15.1 Hz, 1H), 1.77-1.66 (m, 1H), 1.59-1.52 (m, 2H), 1.46 (s, 3H), 1.33-1.27 (m, 1H), 1.20 (s, 3H), 0.96 (d, *J* = 8.1 Hz, 3H), 0.95 (t, *J* = 8.1 Hz, 9H), 0.87 (s, 9H), 0.62 (q, *J* = 8.0 Hz, 6H), 0.06 (s, 3H), 0.04 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 144.1, 140.1, 136.3, 134.1, 128.6, 127.7, 126.9, 126.6, 117.1, 115.2, 86.7, 81.5, 79.6, 77.8, 69.3, 60.7, 42.8, 40.2, 33.0, 31.3, 29.7, 25.8, 24.1, 18.0, 16.7, 12.6, 7.1, 6.7, -4.7, -4.7.
FTIR (thin film) $\tilde{\nu}_{max}$: 3546, 2956, 2928, 2855, 1736, 1449, 1376, 1252, 1176, 1066, 1003, 918, 836, 775, 744, 706 cm^{-1}.
$[\alpha]_D^{20}$ -14.1 (*c* 1.10, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 849.4 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{50}H_{74}O_6Si_2$, 849.4922; found, 849.4917.

Ring Closing Metathesis



(*E*)-4-((tert-butyldimethylsilyl)oxy)-8-hydroxy-7,11-dimethyl-7-((triethylsilyl)oxy)-12-((E)-4-(trityloxy)but-2-en-2-yl)oxacyclododec-9-en-2-one (32): Under argon, allylic alcohol **19** (800 mg, 0.97 mmol) and *p*-benzoquinone (10 mg, 0.1 mmol) was dissolved into toluene (200 ml) and heated to 100 °C.[34] Grubbs' 2nd generation catalyst (170 mg, 0.2 mmol) in toluene (5 mL) was added dropwise over the course of 1 h. After 3 hrs the reaction was cooled and solvents were removed under reduced pressure. Purification by silica chromatography (8:92 EtOAc:Hexane) provided 640 mg (83% yield) of lactone **32** as a single isomer and a clear oil.

TLC 10:90 EtOAc:Hexane, R_f = 0.25 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48-7.43 (m, 6H), 7.33-7.27 (m, 6H), 7.26-7.21 (m, 3H), 5.84-5.78 (m, 1H), 5.57 (dd, *J* = 9.6, 15.2 Hz, 1H), 5.41 (dd, *J* = 9.8, 15. 3 Hz, 1H), 5.04 (d, *J* = 10.7 Hz, 1H), 3.85-3.77 (m, 1H), 3.70-3.56 (m, 3H), 2.69 (d, *J* = 10.7 Hz, 1H), 2.50-2.35 (m, 3H), 1.70-1.25 (m, 4H), 1.45 (s, 3H), 1.33 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.65 (q, *J* = 7.9 Hz, 6H), 0.08 (s, 3H), 0.08 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 144.1, 136.5, 133.5, 130.1, 128.6, 128.4, 127.7, 126.9, 86.7, 82.0, 78.0, 77.7, 71.0, 60.7, 41.4, 40.4, 37.9, 30.7, 25.8, 24.7, 18.1, 17.0, 11.9, 7.1, 6.8, -4.7, -4.8.
FTIR (thin film) $\tilde{\nu}_{max}$: 3546, 2956, 2928, 2875, 2855, 1738, 1492, 1449, 1374, 1250, 1172, 1092, 1018, 979, 836, 774, 745, 707, 632 cm^{-1}.
$[\alpha]_D^{20}$ -12.3 (*c* 1.00, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 821.4 (100), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{48}H_{70}O_6Si_2$, 821.4609; found, 821.4600.

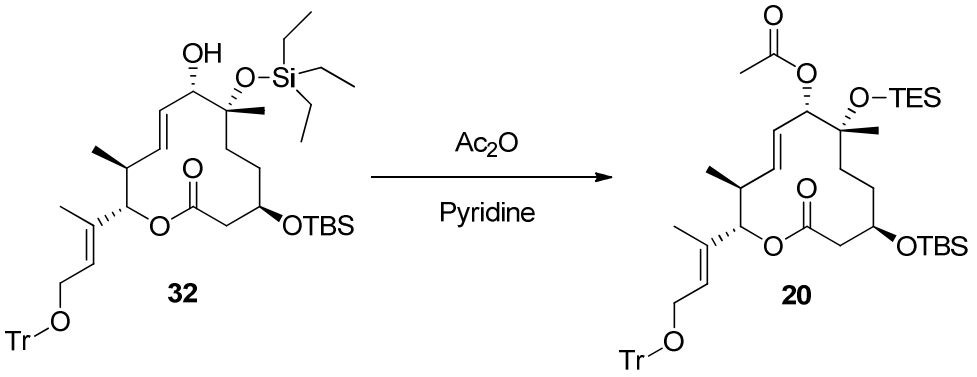
(4*R*,7*R*,8*S*,11*R*,12*R*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-7,11-dimethyl-7-((triethylsilyl)oxy)-12-((*E*)-4-(trityloxy)but-2-en-2-yl)oxacyclododec-9-en-2-one (32b):

The C10/C11 diastereomer was isolated by normal phase HPLC (Zorbax CN, 1.5% IPA in hexane, 220 nm).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.43 (m, 6H), 7.32-7.27 (m, 6H), 7.25-7.22 (m, 3H), 5.79 (t, *J* = 6.2 Hz, 1H), 5.59 (dd, *J* = 9.7, 15.3 Hz, 1H), 5.28 (dd, *J* = 9.9, 15.2 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.35-4.30 (m, 1H), 3.65 (d, *J* = 6.1 Hz, 2H0, 3.52 (t, *J* = 9.7

Hz, 1H), 2.67 (d, *J* = 11.0 Hz, 1H), 2.50-2.40 (m, 3H), 1.90-1.30 (m, 4H), 1.46 (s, 3H), 1.30 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.65 (q, *J* = 8 Hz, 6H), 0.07 (s, 3H), 0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2, 144.1, 135.4, 133.3, 130.9, 128.7, 128.6, 127.8, 126.9, 86.8, 81.5, 78.0, 77.8, 67.8, 60.7, 40.9, 40.5, 31.6, 28.1, 25.8, 25.6, 24.3, 27.8, 16.7, 11.7, 7.1, 6.8, -4.9.

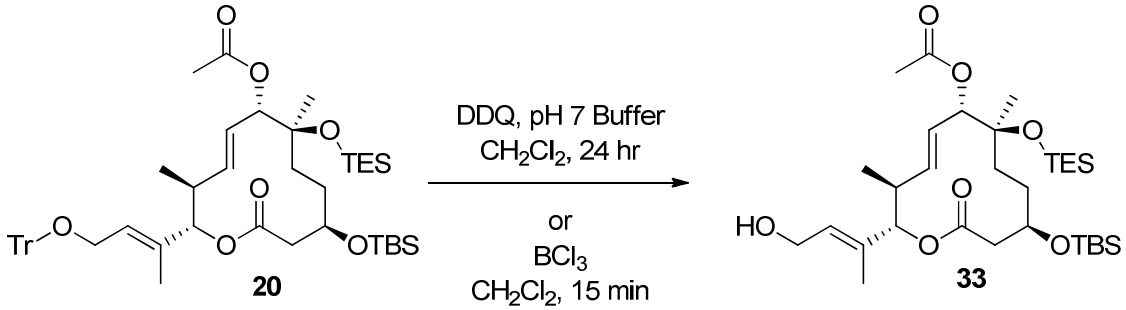
Acetylization



(*E*)-10-((tert-butyldimethylsilyl)oxy)-3,7-dimethyl-12-oxo-7-((triethylsilyl)oxy)-2-((*E*)-4-(trityloxy)but-2-en-2-yl)oxacyclododec-4-en-6-yl acetate (20): Under argon, lactone **32** (20 mg, 0.03 mmol) was dissolve into pyridine (0.6 mL, 8 mmol). Ac_2O (0.3 mL, 3 mmol) was added and the reaction allowed to stir at 23 °C for 24 h. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (5:95→10:90 EtOAc:Hexane) providing 18 mg (87% yield) of acetate **20** as a clear oil.

TLC 10:90 EtOAc:Hexane, R_f = 0.33 visualized with UV and anisaldehyde. Just above SM.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.43 (m, 6H), 7.32-7.27 (m, 6H), 7.25-7.20 (m, 3H), 5.80 (t, *J* = 4.9 Hz, 1H), 5.65-5.60 (m, 2H), 5.03-4.98 (m, 2H), 3.80 (sext, *J* = 4.4 Hz, 1H), 3.64 (d, *J* = 6.2 Hz, 1H), 2.48-2.36 (m, 3H), 2.06 (s, 3H), 1.70-1.25 (m, 4H), 1.45 (s, 3H), 1.21 (s, 3H), 0.99 (t, *J* = 8.1 Hz, 9H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.66-0.59 (m, 6H), 0.07 (s, 3H), 0.06 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.4, 168.6, 144.1, 140.1, 133.6, 128.6, 128.4, 127.8, 126.9, 125.9, 86.7, 81.9, 79.4, 76.1, 70.3, 60.7, 40.7, 40.5, 38.5, 30.7, 29.7, 25.8, 24.3, 21.4, 18.1, 16.7, 12.0, 7.1, 6.9, 4.8.
FTIR (thin film) $\tilde{\nu}_{max}$: 2955, 2929, 1740, 1449, 1368, 1240, 1172, 1110, 1060, 1023, 979, 836, 745, 707 cm^{-1}.
$[\alpha]_D^{20}$ -4.2 (*c* 1.90, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 863.5 (100), $[M+Na]^+$, 879.0 (74), $[M+K]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{50}H_{72}O_7Si_2$, 863.4714; found, 863.4707.

Trityl Deprotection



(*E*)-10-((tert-butyldimethylsilyl)oxy)-2-((E)-4-hydroxybut-2-en-2-yl)-3,7-dimethyl-12-oxo-7-((triethylsilyl)oxy)oxacyclododec-4-en-6-yl acetate (33): Under argon, trityl ether **20** (20 mg, 20 µmol) was dissolved into CH_2Cl_2 (5 mL) and cooled to -78 'C. BCl_3 (25 µL, 1 M in CH_2Cl_2, 25 µmol) was added and the reaction allowed to warm to -40 °C and stirred for 30 min. The reaction was quenched by the addition of MeOH (0.25 mL). The mixture was immediately poured into sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (20:80→30:70 EtOAc:Hexane) providing 9.4 mg (68% yield) of alcohol **33** as a clear oil.[22]

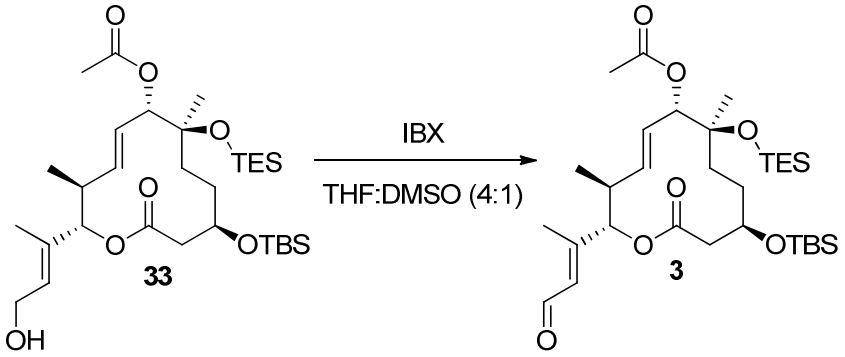
Alternatively:

Trityl ether **20** (100 mg, 0.12 mmol) was dissolved into CH_2Cl_2 (10 mL) and cooled to 0 °C. pH 7.0 phosphate buffer (1 mL) was added followed by the addition of DDQ (80 mg, 0.4 mmol). The reaction was allowed to warm to rt and stir for 24 hr. The reaction

was quenched with sat. $NaHCO_3$ and diluted with Et_2O. The organic layer was dried with brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (20:80→30:70 EtOAc:Hexane) providing 55 mg (77% yield) of alcohol **33** as a clear oil.

TLC 30:70 EtOAc:Hexane, R_f = 0.33 visualized with anisaldehyde.
^{1}H NMR ($CDCl_3$, 800 MHz): δ 5.75 (t, *J* = 6.6 Hz, 1H), 5.64 (dd, *J* = 9.4, 15.3 Hz, 1H), 5.58 (dd, *J* = 9.8, 15.3 Hz, 1H), 4.98 (d, *J* = 9.5 Hz, 1H), 4.94 (d, *J* = 10.6 Hz, 1H), 4.22 (dd, *J* = 6.6, 13.1 Hz, 1H), 4.18 (dd, *J* = 6.3, 13.0 Hz, 1H), 3.82-3.79 (m, 1H), 2.49-2.42 (m, 2H), 2.39 (dd, *J* = 5.0, 13.8 Hz, 1H), 2.05 (s, 3H), 1.65 (s, 3H), 1.65-1.63 (m, 1H), 1.45-1.42 (m, 2H), 1.35-1.29 (m, 2H), 1.21 (s, 3H), 0.99 (t, *J* = 7.8 Hz, 6H), 0.99 (s, 3H), 0.90 (s, 9H), 0.67-0.59 (m, 9H), 0.07 (s, 3H), 0.05 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 168.7, 139.9, 134.4, 130.2, 126.0, 82.1, 79.4, 76.1, 70.3, 59.0, 40.6, 40.3, 38.5, 30.8, 25.8, 24.3, 21.4, 18.1, 16.6, 11.8, 7.1, 6.9, 1.0, -4.8.
FTIR (thin film) ν_{max}: 3468, 2956, 1738, 1463, 1371, 1242, 1174, 1111, 1021, 979, 837, 776, cm^{-1}.
$[\alpha]_D^{20}$ 2.2 (*c* 0.65, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 621.2 (100), $[M+Na]^+$; 1218.7 (45), $[2M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{31}H_{58}O_7Si_2$, 621.3619; found, 621.3626.

Oxidation



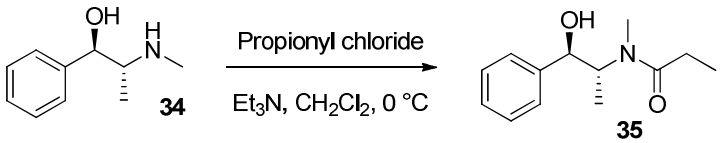
(*E*)-10-((tert-butyldimethylsilyl)oxy)-3,7-dimethyl-12-oxo-2-((*E*)-4-oxobut-2-en-2-yl)-7-((triethylsilyl)oxy)oxacyclododec-4-en-6-yl acetate (3): Alcohol **33** (50 mg, 0.08 mmol) was dissolved into THF (2 mL). DMSO (0.5 mL) was added followed by the addition of IBX (60 mg, 0.2 mmol). After stirring for 4 h, solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90→20:80 EtOAc:Hexane) to give 48 mg (96% yield) of aldehyde **3** as a clear oil.[12a]

TLC 20:80 EtOAc:Hexane, R_f = 0.60 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.03 (d, *J* = 7.7 Hz, 1H), 6.08 (d, *J* = 7.7 Hz, 1H), 5.70 (dd, *J* = 9.5, 15.4 Hz, 1H), 5.58 (dd, *J* = 9.7, 15.3 Hz, 1H), 4.97 (d, *J* = 9.5 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 3.86-3.79 (m, 1H), 2.52-2.46 (m, 1H), 2.45 (d, *J* = 3 Hz, 1H), 2.40 (dd, *J* = 4.8, 13.5 Hz, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.75-1.20 (m, 4H), 1.22 (s, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.67-0.60 (m, 6H), 0.07 (d, *J* = 8.3 Hz, 6H).
FTIR (thin film) ν_{max}: 2956, 2876, 1738, 1682, 1462, 1371, 1243, 1174, 1111, 1063, 1021, 981, 836, 776, 744 cm^{-1}.
$[\alpha]_D^{20}$ 0.7 (*c* 1.2, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 619.3 (100), $[M+Na]^+$; 635.2 (15), $[M+K]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{31}H_{56}O_7Si_2$, 619.3462; found, 619.3454.

Side Chain Synthesis

1. Synthesis of C_{15}-C_{18} Fragment

Pseudoephedrine Alkylation

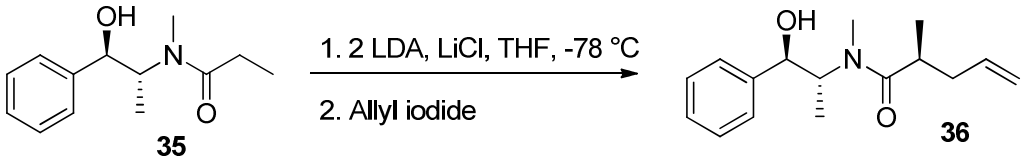


***N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide (35)**: [192060-67-6] Prepared in a similar fashion as Bode et al.[23] Under argon, (*R*, *R*)-(-)-pseudoephedrine **34** (6.2 g, 37.5 mmol) was dissolved into CH_2Cl_2 (75 mL) and cooled to 0 °C. Et_3N (6.3 ml, 45 mmol) was added followed by propionyl chloride (3.4 ml, 39.4 mmol). The reaction was warmed to 23 °C and stirred for 1 h. The reaction was quenched with H_2O (6 ml), diluted with Et_2O (75 ml), and washed with sat. $NaHCO_3$ (x2) and 1 N HCl. The

organic layer was dried with brine and Na_2SO_4 and condensed. The crude material was purified by silica chromatography (5:95→15:85 MeOH:CH_2Cl_2). The resulting clear oil was dissolved into toluene and condensed providing 8.6 g (quantitative) of amide **35** as a white solid.[24]

TLC 70:30 EtOAc:Hexane, R_f = 0.33 visualized with UV and ninhydrin.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.20 (m, 7.1 H), 4.60-4.40 (m, 3.8 H), 3.95 (quint, *J* = 7.5 Hz, 0.4 H), 3.47 (br s, 0.4 H), 2.87 (s, 1.3 H), 2.77 (s, 3H), 2.53-2.17 (m, 2.8 H), 1.12 (m, 8.5 H).
^{13}C NMR ($CDCl_3$, 400 MHz): δ 175.9, 174.9 (minor), 142.3, 141.4 (minor), 128.5, 128.2, 128.0 (minor) 127.5 (minor), 126.8 (minor), 126.3, 76.3, 75.2 (minor), 58.2, 58.0 (minor), 32.3, 27.4, 26.7 (minor), 15.2 (minor), 14.3, 9.5 (minor), 9.1.
FTIR (thin film) $\tilde{\nu}_{max}$: 3392, 2980, 2938, 1622, 1453, 1406, 1377, 1300, 1200, 1122, 1054, 1026, 770, 751, 702 cm^{-1}.
$[\alpha]_D^{20}$ -116.0 (*c* 2.65, $CHCl_3$).

Myer's Asymmetric Alkylation

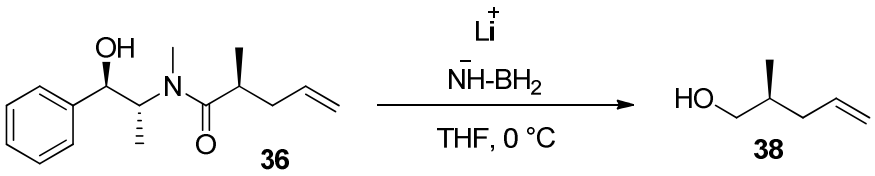


35 **36**

(*S*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide (36): [192060-67-6] Prepared in a similar fashion as Fettes et al.[25] Flame dried LiCl (9.5 g, 225 mmol) was suspended in THF (42 mL) under argon. DIPA (11.8 ml, 84 mmol) was added and the solution cooled to -78 °C. nBuLi (50 mL, 1.6 N in hexane, 81 mmol) was added dropwise. Following the addition, the reaction was warmed to 0 °C and stirred for 15 min then re-cooled to -78 °C. Amide **35** (8.3 g, 37.5 mmol) in THF (100 ml) was added over the course of 10 min. After stirring for 1 hr, the reaction was warmed to 0 °C for 15 min, then 23 °C for 15 min and subsequently cooled to -78 °C. Allyl iodide (5.1 mL, 56 mmol) was added and the reaction stirred for 1 hr. The reaction was warmed to 0 °C, stirred for 1 h, then quenched with sat. NH_4Cl and sat. sodium dithiosulfite (10:1). The organic layer was removed and the aqueous layer extracted with EtOAc (x2). The combined organic layers were dried over brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (70:30 EtOAc:Hexane) to give 10.8 g of olefin **36**.[24]

TLC 70:30 EtOAc:Hexane, R_f = 0.50 visualized with UV and I_2.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.20 (m, 6.3H), 5.80-5.60 (m, 1.3H), 5.12-4.90 (m, 2.7H), 4.60-4.35 (m, 2.7H), 2.87 (s, 0.7H), 2.83 (s, 3H), 2.73-2.65 (m, 1.3H), 2.50-2.25 (m, 1.3H), 2.15-2.00 (m, 1.3H), 1.10-0.97 (m, 7.5H).
^{13}C NMR ($CDCl_3$, 400 MHz): δ 178.1, 177.0 (minor), 142.3, 141.2 (minor), 136.6 (minor), 135.9, 128.5 (minor), 128.2, 127.4, 126.8 (minor), 126.3, 116.4, 116.3 (minor), 76.2, 75.3, 57.9, 37.9, 36.4, 35.6 (minor), 17.4 (minor), 16.9, 15.5 (minor), 14.4.
FTIR (thin film) $\tilde{\nu}_{max}$: 3381, 2976, 2934, 1621, 1453, 1410, 1375, 1112, 1084, 1051, 915, 757, 702 cm^{-1}.
$[\alpha]_D^{20}$ -76.2 (*c* 2.30, $CHCl_3$).

Tertiary Amide Cleavage



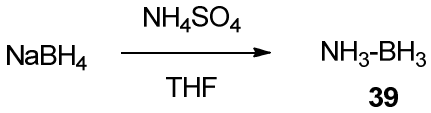
36 **38**

(*S*)-2-methylpent-4-en-1-ol (38): [63501-26-8] Prepared in a similar fashion as Fettes et al.[25] Under argon, ammonia-borane (**5**) (4.9 g, 157.5 mmol) was suspended in THF (300 mL) and cooled to 0 °C. nBuLi (94 mL, 1.6 N in hexane, 150 mmol) was added dropwise. The reaction was allowed to stir for 5 min at 23 °C and was then cooled to 0 °C producing lithium amidotrihydroborate (**39**). Crude olefin **36** (10.8 g, 37.5 mmol) in THF (50 mL) was added dropwise. The reaction was allowed to warm to 23 °C and stir for 10 hr. The reaction was cooled to 0 °C and quenched with 2N HCl (200 mL). After stirring for 90 min, the mixture was diluted with brine (150 mL) and extracted with Et_2O (x3). The combined organic layers were washed with 2N HCl/brine (200 mL) and condensed and then stirred with 1 N NaOH (200 mL) for 3 hr. The mixture was extracted with Et_2O and the combined organic layers were dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (20:80 EtOAc:Hexane) to give 3 g (79% yield over 3 steps) of alcohol **38** as a clear liquid.[26]

TLC 20:80 EtOAc:Hexane, R_f = 0.30 visualized with $KMnO_4$ and I_2.

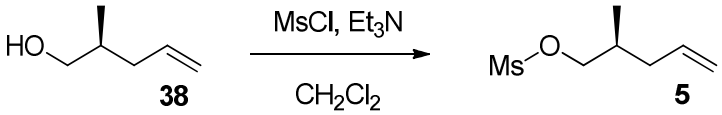
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.82-5.68 (m, 1H), 5.02-4.90 (m, 2H), 3.44 (dd, *J* = 6.2, 10.5 Hz, 1H), 3.38 (dd, *J* = 6.1, 10.6 Hz, 1H), 2.37 (br s, 1H), 2.17-2.07 (m, 1H), 1.90-1.82 (m, 1H), 1.72-1.62 (m, 1H), 1.20 (t, *J* = 6.9 Hz, 2H), 0.86 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 400 MHz): δ 136.9, 115.9, 67.5, 37.7, 35.5, 16.2.
FTIR (thin film) $\tilde{\nu}_{max}$: 3339, 3876, 1457, 1045, 993, 912 cm^{-1}.
$[\alpha]_D^{20}$ -4.6 (*c* 0.88, $CHCl_3$).

Ammonia Borane



Ammonia Borane (39): [13774-81-7] Under argon, $NaBH_4$ (6.3 g, 167 mmol) and $(NH_4)_2SO_4$ (22 g, 167 mmol) were suspended in THF (1 L). The mixture was heated to 40 °C and stirred vigorously overnight. The solution was filtered and condensed providing 2.7 g (52.4% yield) of borane **39** as a white solid.[27]

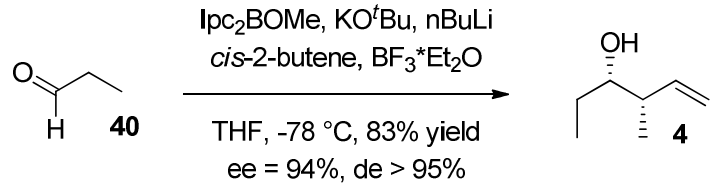
Mesylate



(*S*)-2-methylpent-4-en-1-yl methanesulfonate (5): [226410-08-8] Prepared in a similar fashion as Sjoholm et al.[28] Under argon, alcohol **40** (2.3 g, 23 mmol) was dissolved into CH_2Cl_2 (50 mL) and cooled to 0 °C. Et_3N (4.2 mL, 30 mmol) was added followed by the slow addition of MsCl (2.2 mL, 28 mmol) and a catalytic amount of DMAP. After stirring for 4 hrs the reaction was quenched with water and diluted with Et_2O. The organic layer was separated, washed with 1% HCl, dried with brine and Na_2SO_4 and condensed. Purification by silica chromatography (20:80 EtOAc:Hexane) provided 3.9 g (79% yield) of mesylate **5** as a clear oil.

TLC 20:80 EtOAc:Hexane, R_f = 0.30 visualized with $KMnO_4$ and PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78-5.67 (m, 1H), 5.08-5.00 (m, 2H), 4.07 (dd, *J* = 5.3, 9.8 Hz, 1H), 4.00 (dd, *J* = 6.0, 9.6 Hz, 1H), 2.97 (s, 3H), 2.20-2.12 (m, 1H), 2.00-1.90 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.2, 117.2, 73.8, 37.1, 37.0, 32.7, 16.1.
FTIR (thin film) $\tilde{\nu}_{max}$: 2974, 1466, 1356, 1176, 966, 828 cm^{-1}.
$[\alpha]_D^{20}$ 0.5 (*c* 1.16, $CHCl_3$).

2. Synthesis of C_{19}-C_{23} Fragment



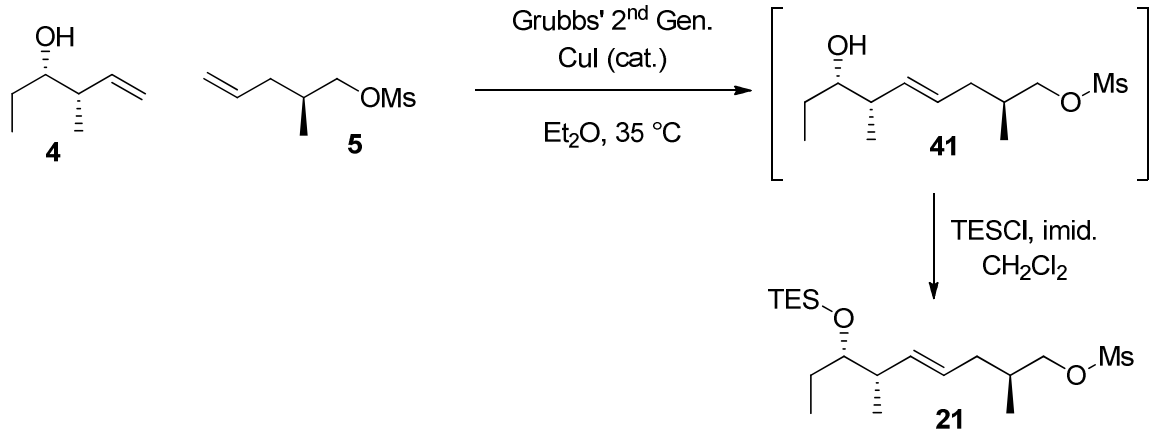
Asymmetric Crotylation

(3*S*,4*S*)-4-methylhex-5-en-3-ol (4): [95273-27-1] Prepared in a similar manner as Roush et al. (70% *ee*) or Brown et al. (90%*ee*).[19a, 29] Under argon, a flask is charged with KO*t*Bu (85 mL, 1.0 M in THF, 85 mmol) and cooled to -78 °C. *Cis*-2-butene (8.4 ml, 90.4 mmol) was added by cannula followed by the slow addition (over 1 h) of nBuLi (53 mL, 1.6 M in hexane, 85 mmol) causing an orange slurry to form. The reaction was warmed to -20 °C for 30 min and then cooled to -78 °C. B(O*i*Pr)$_3$ (19.6 ml, 85 mmol) was added slowly over 1 h creating a clear yellow solution. Following the addition, the reaction was stirred for 10 min and then poured into 10% HCl (160 mL) saturated with NaCl. The pH of the solution was acidic. D-DIPT (20 g, 85 mmol) in Et_2O (40 mL) was added and the layers subsequently separated. The aq. layer was extracted with Et_2O (4 x 40 mL). The combined organic layers were dried over $MgSO_4$ for 2 h, filtered, and condensed. The crude boronic ester (70% estimated yield) was stirred on high vacuum to remove trace solvents. The ester was dissolved into toluene (60 mL). 4A molecular sieves (4g) were added and the solution cooled to -78 °C. Propionaldehyde (5 mL, 70 mmol) was added dropwise and the reaction stirred for 3 h. 2 N NaOH (80 mL) was added and the mixture allowed to warm to 23 °C and stir overnight. The mixture was filtered over celite and the layers subsequently separated. The aq. layer was extracted with Et_2O (2 x 30 mL) and the combined organic layers were dried over Na_2SO_4. Solvents were removed by distillation (toluene removed at 80 torr, 80 °C basebath, 50 °C bp). The crude material was purified by vacuum distillation (bp = 85 °C at 80 torr, 150 °C final base bath) providing 4.6 grams (67% yield) of product **4** as a clear oil.

TLC 20:80 EtOAc:Hexane, R_f = 0.50 visualized with PMA.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87-5.77 (m, 1H), 5.13-5.07 (m, 2H), 3.45-3.39 (m, 1H), 2.33-2.26 (m, 1H), 1.61 (br s, 1H), 1.60-1.52 (m, 1H), 1.46-1.34 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ141.1, 115.0, 76.1, 43.0, 26.8, 14.0, 10.3.
$[\alpha]_D^{20}$ -29.4 (*c* 1.06, $CHCl_3$).
The 4-nitrobenzoate derivatives were analyzed by Chiral HPLC: Chiralpak IC 250 x 4.6 mm, 5 micron; 1:99 IPA:Hexane, flow = 1 mL/min, T = 10 °C, UV = 210 nm, R_t minor = 9.0 min , R_t major = 9.3 min.

3. Synthesis of C15-C23 Fragment

Cross Metathesis / TES Protection



(3*S*,4*S*,8*S*,*E*)-4,8-dimethyl-9-((1-phenyl-1*H*-tetrazol-5-yl)thio)non-5-en-3-ol (41): Under argon, homoallyic alcohol **4** (320 mg, 2.8 mmol) and mesylate **5** (1.0 g, 5.6 mmol) were dissolved into Et_2O (25 mL). CuI (50 mg, 0.28 mmol) was added followed by Grubbs' 2nd generation catalyst (120 mg, 0.14 mmol). The reaction was warmed to 35 °C and stirred 3 h. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (20:80→50:50 EtOAc:Hexane) providing a 1.1 g mixture of olefin **41** and the other cross metathesis products that were purified out in the subsequent step.[30]

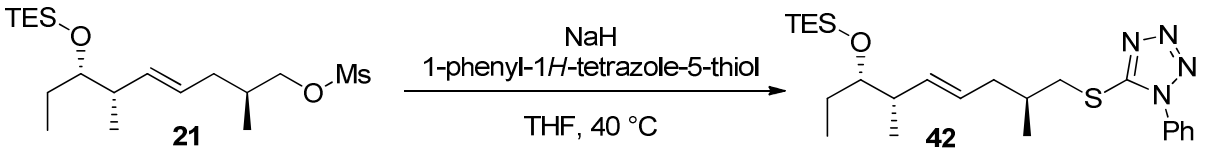
TLC 40:60 EtOAc:Hexane, R_f = 0.35 visualized with PMA and anisaldehyde.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46-5.41 (m, 2H), 4.11-4.00 (m, 2H), 3.37 (quint., *J* = 10.6 Hz, 1H), 3.00 (s, 3H), 2.28-2.21 (m, 1H), 2.21-2.10 (m, 1H), 2.03-1.91 (m, 2H), 1.60-1.50 (m, 1H), 1.42-1.30 (m, 1H), 1.02-0.92 (m, 9H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.8, 127.1, 76.5, 73.7, 42.2, 37.2, 35.9, 33.1, 26.9, 16.2, 14.8, 10.4.
FTIR (thin film) $\tilde{\nu}_{max}$: 3548, 2965, 1460, 1353, 1175, 965, 834, 750 cm^{-1}.
$[\alpha]_D^{20}$ -13.0 (*c* 1.30, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 287.1 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{24}O_4S$, 287.1293; found, 287.1291.
A portion of **21** was deprotected using HCl/THF to provide **41** for analytical characterization.

(2*S*,6*S*,7*S*,*E*)-2,6-dimethyl-7-((triethylsilyl)oxy)non-4-en-1-yl methanesulfonate (21): Under argon, crude olefin **41** (1.1 g, 2.8 mmol theoretical) was dissolved into CH_2Cl_2 (15 mL). Imidazole (480 mg, 7 mmol) and DMAP (17 mg, 0.14 mmol) were added followed by the dropwise addition of TESCl (0.7 mL, 4.2 mmol). The reaction was allowed to stir at 23 °C for 4 h. The reaction was diluted with Et_2O and washed with 1% HCl. The organic layer was dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90 EtOAc:Hexane) providing 497 mg (47% yield two steps) of silyl ether **21** as a clear oil.

TLC 20:80 EtOAc:Hexane, R_f = 0.65 visualized with anisaldehyde.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.50-5.42 (m, 1H), 5.37-5.28 (m, 1H), 4.12-4.06 (m, 1H), 4.03-3.97 (m, 1H), 3.47-3.40 (m, 1H), 2.99 (s, 3H), 2.27-2.21 (m, 1H), 2.17-2.06 (m, 1H), 1.97-1.87 (m, 2H), 1.50-1.30 (m, 2H), 1.00-0.83 (m, 18H), 0.62-0.57 (m, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.1, 125.9, 77.3, 74.1, 41.8, 37.2, 36.0, 33.3, 26.7, 16.2, 16.0, 9.5, 7.0, 5.2.
FTIR (thin film) $\tilde{\nu}_{max}$: 2961, 2877, 1460, 1360, 1239, 1179, 1103, 1010, 963, 826, 742 cm^{-1}.
$[\alpha]_D^{20}$ -9.8 (*c* 2.15, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 401.1 (100%), $[M+Na]^+$.

HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{38}O_4SSi$, 401.2158; found, 401.2163.

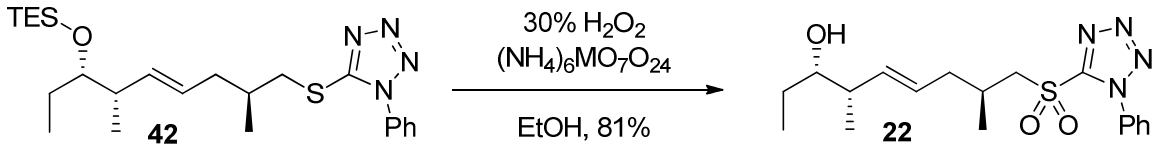
Mesylate Displacement



5-(((2*S*,6*S*,7*S*,*E*)-2,6-dimethyl-7-((triethylsilyl)oxy)non-4-en-1-yl)thio)-1-phenyl-1*H*-tetrazole (42): [934497-73-1] Under argon, 1-phenyl-1*H*-tetrazole-5-thiol (143 mg, 0.8 mmol) and mesylate **21** (230 mg, 0.6 mmol) were dissolved into THF (10 mL). NaH (32 mg, 0.8 mmol) was added and the reaction warmed to 60 °C and stirred overnight. After cooling to 0 °C, the reaction was quenched with H_2O and diluted with Et_2O. The organic layer was washed with 1% HCl and dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90 EtOAc:Hexane) to give 247 mg (88% yield) of sulfide **42** as a clear oil.

TLC 10:90 EtOAc:Hexane, R_f = 0.50 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60-7.50 (m, 5H), 5.50-5.29 (m, 2H), 3.47-3.37 (m, 2H), 3.26 (dd, *J* = 6.6, 12.7 Hz, 1H), 2.30-2.12 (m, 2H), 2.05-1.95 (m, 2H), 1.49-1.33 (m, 2H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 8.1 Hz, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.58 (q, *J* = 7.9 Hz, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.5, 136.0, 133.7, 129.9, 129.7, 126.2, 123.8, 77.3, 41.7, 39.7, 38.9, 33.1, 26.7, 18.8, 15.9, 9.4, 6.9, 5.1.

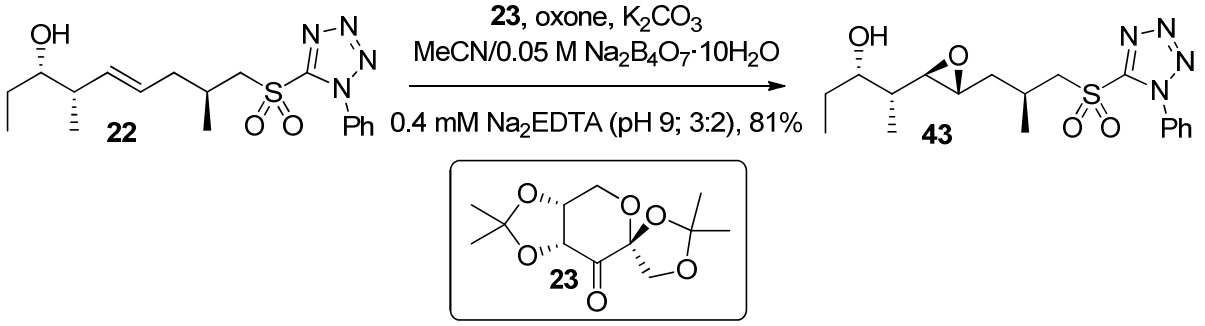
H_2O_2 Oxidation



(3*S*,4*S*,8*S*,*E*)-4,8-dimethyl-9-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)non-5-en-3-ol (22): [934497-74-2] Prepared in a similar fashion as Kanada et al.[31] 30% H_2O_2 (1.2 mL) was added to hexaammonium heptamolybdate tetrahydrate (120 mg, 0.1 mmol) and stirred for 10 min. This was added to sulfide **42** (460 mg, 1 mmol) in EtOH (12 mL) and the reaction was allowed to stir overnight. The mixture was diluted with EtOAc and layers separated. The organic layer was washed with H_2O (x3) then dried with brine and $MgSO_4$. Solvents were removed under reduced pressure to give 307 mg (81% yield) of sulfone as a clear oil.

TLC 20:80 EtOAc:Hexane, R_f = 0.30 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68-7.61 (m, 2H), 7.61 (m, 3H), 5.52-5.35 (m, 2H), 3.89-3.82 (m, 1H), 3.54-3.48 (m, 1H), 3.39-3.33 (m, 1H), 2.43-2.35 (m, 1H), 2.28-2.21 (m, 1H), 2.21-2.14 (m, 2H), 1.66 (br s, 1H), 1.56-1.47 (m, 1H), 1.38-1.31 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.9, 137.0, 133.0, 131.4, 129.6, 126.1, 125.1, 76.4, 60.8, 42.2, 39.4, 28.3, 27.0, 19.6, 14.8, 10.3.

Shi Epoxidation

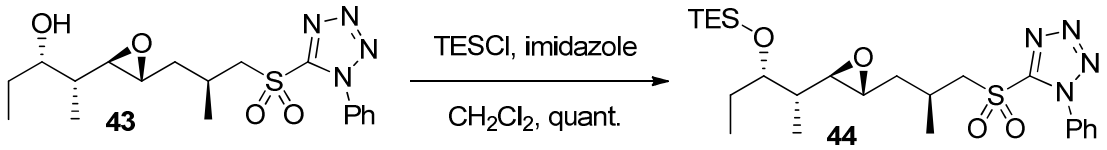


(2*R*,3*S*)-2-((2*R*,3*R*)-3-((*S*)-2-methyl-3-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)propyl)oxiran-2-yl)pentan-3-ol (43): [934497-75-3] Prepared in a similar manner as Kanada et al.[31] Sulfone **22** (307 mg, 0.8 mmol) was dissolved into MeCN (15 mL) and 0.05 M $Na_2B_4O_7{\cdot}10H_2O$ / 0.4 mM Na_2EDTA pH 9 buffer (10 mL) and cooled to 0 °C. Shi's ketal **7** (630 mg, 2.4 mmol) was added followed

by the slow addition (less than 1 h) of a mixture of oxone (2 g, 3.2 mmol) and K_2CO_3 (1.3 g, 9.6 mmol). The reaction was diluted with Et_2O and washed with H_2O. The organic layer was dried with brine and Na_2SO_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (40:60→60:40 EtOAc:Hexane) to provide 256 mg (81% yield) of epoxide **43** as a single isomer.[32]

TLC 40:60 EtOAc:Hexane, R_f = 0.20 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68-7.54 (m, 5H), 3.91 (d, *J* = 7.8 Hz, 1H), 3.63 (d, *J* = 7.5 Hz, 1H), 3.60 (d, *J* = 7.1 Hz, 1H), 2.85-2.80 (m, 1H), 2.70-2.65 (m, 1H), 2.60-2.50 (m, 1H), 1.93-1.85 (m, 1H), 1.32-1.63 (m, 4H), 1.26 (d, *J* = 7.1 Hz, 3H), 0.95-0.87 (m, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 132.9, 131.4, 129.6, 125.1, 74.2, 60.6, 60.0, 55.1, 39.9, 38.2, 27.3, 26.4, 20.0, 10.4, 9.9.

Silyl Protection

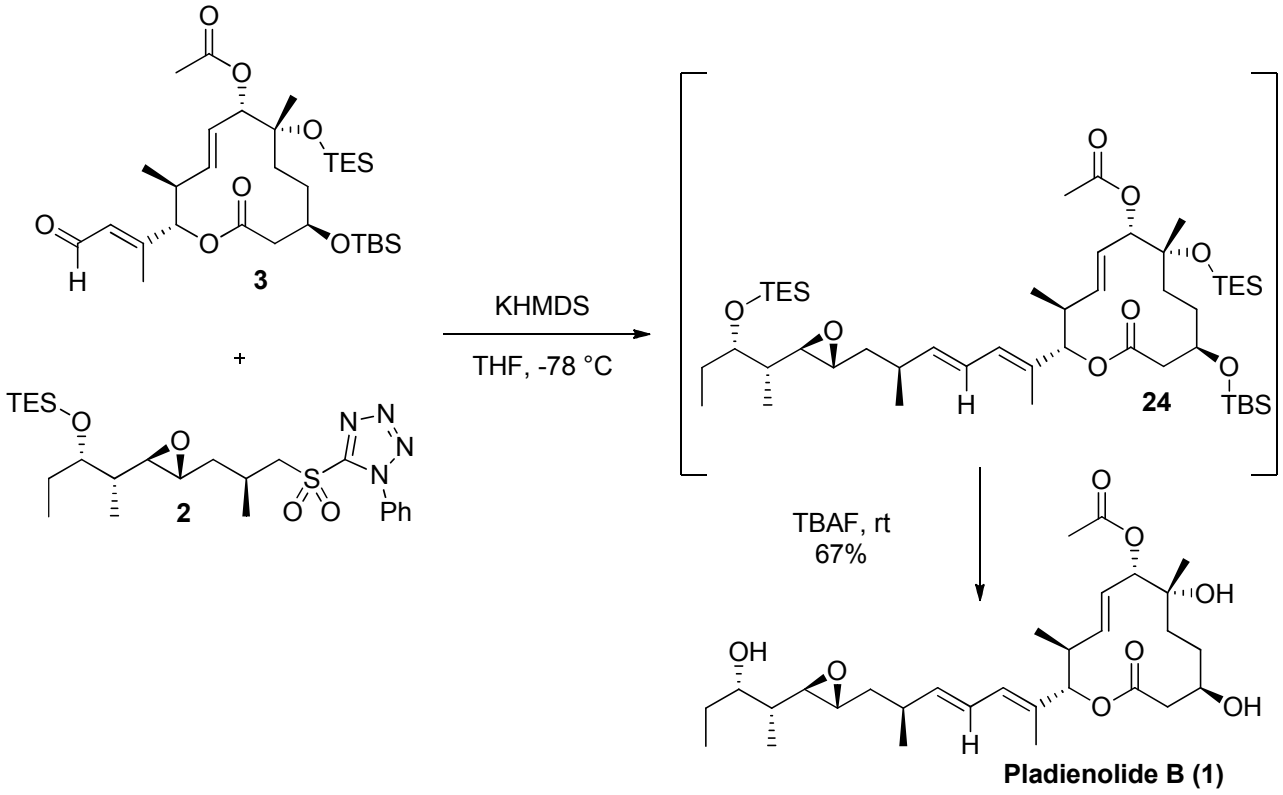


5-(((*S*)-2-methyl-3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-((triethylsilyl)oxy)pentan-2-yl)oxiran-2-yl)propyl)sulfonyl)-1-phenyl-1*H*-tetrazole (44): Under argon, epoxide **43** (250 mg, 0.6 mmol) was dissolved into CH_2Cl_2 (5 mL). Imidazole (110 mg, 1.6 mmol) was added followed by the addition of TESCl (0.14 mL, 1.3 mmol). After stirring for 4 h, the reaction was diluted with Et_2O and washed with 1% HCl. The organic layer was dried with brine and Na_2O_4. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (10:90 EtOAc:Hexane) to provide 324 mg (quant.) of silyl ether **44** as a clear oil.[9]

TLC 10:90 EtOAc:Hexane, R_f = 0.50 visualized with UV and anisaldehyde.
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.56 (m, 5H), 3.92 (dd, *J* = 5.4, 14.5 Hz, 1H), 3.76-3.70 (m, 1H), 3.68 (dd, *J* = 7.5, 14.9 Hz, 1H), 2.79-2.73 (m, 1H), 2.64 (dd, *J* = 2.3 Hz, 7.9 Hz, 1H), 2.64-2.55 (m, 1H), 1.97 (ddd, *J* = 3.8, 5.6, 14.4 Hz, 1H), 1.57-1.46 (m, 3H), 1.38-1.32 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H), 0.61 (q, *J* = 7.7 Hz, 6H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.9, 133.0, 131.4, 129.6, 125.1, 74.3, 61.3, 60.1, 55.5, 39.7, 38.5, 27.5, 27.4, 19.9, 9.8, 9.8, 6.9, 5.1.
FTIR (thin film) $\tilde{\nu}_{max}$: 2961, 2913, 2877, 1498, 1460, 1340, 1154, 1015, 825, 763, 743, 688, 632 cm^{-1}.
$[\alpha]_D^{20}$ 2.8 (*c* 2.85, $CHCl_3$).
LR-ESI (+) *m/z* (relative intensity), ion: 531.6 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{40}N_4O_4SSi$, 531.2437; found, 531.2446.

Final Step

1. Julia Coupling, Silyl Deprotection



Pladienolide B (1): [445493-51-6] Under argon, sulfone **2** (80 mg, 0.16 mmol) was dissolved into THF (5 mL) and cooled to -78 °C. KHMDS (0.4 mL, 0.5 M in Toluene, 0.2 mmol) was added dropwise causing a yellow color to appear. After stirring for 15 min, aldehyde **3** (100 mg, 0.17 mmol) in THF (1 mL) was added. The reaction was allowed to stir for 1 hr during which time the solution turned clear. The solution was passed through a plug of silica and condensed. After dissolving the crude material in THF (5 mL), TBAF (0.3 mL, 1M in THF, 300 μmol) was added and the reaction allowed to warm to 23 °C and stir overnight. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (50:50→70:30 EtOAc:Hexane) to give 57 mg (67% yield) of pladienolide B as a clear oil.[9, 33]

Silyl protected pladienolide B (**24**)
TLC 10:90 EtOAc:Hexane, R_f = 0.50 visualized with UV, CAM and anisaldehyde.
LR-ESI (+) *m/z* (relative intensity), ion: 901.5 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{48}H_{90}O_8Si_3$, 901.5841; found, 901.5850.

Pladienolide B:

TLC 70:30 EtOAc:Hexane, R_f = 0.25 visualized with UV and CAM.
^{1}H NMR (CD_3OD, 800 MHz): δ 6.34 (dd, *J* = 10.7, 15.0 Hz, 1H), 6.11 (d, *J* = 10.7 Hz, 1H), 5.71 (dd, *J* = 9.8, 15.1 Hz, 1H), 5.67 (dd, *J* = 8.4, 15.0 Hz, 1H), 5.58 (dd, *J* = 9.8, 15.1 Hz, 1H), 5.06 (d, *J* = 9.6 Hz, 2H), 3.80 (m, 1H), 3.53 (dt, *J* = 4.3, 8.6 Hz, 1H), 2.74 (dt, *J* = 2.2, 5.9 Hz, 1H), 2.67 (dd, *J* = 2.2, 7.3 hz, 1H), 2.60-2.55 (m, 1h), 2.55-2.53 (m, 2H), 2.52-2.46 (m, 1H), 2.07 (s, 3H), 1.76 (s, 3H), 1.67-1.63 (m, 2H), 1.61-1.56 (m, 1H), 1.55-1.51 (m, 1H), 1.50-1.45 (m, 2H), 1.43-1.34 (m, 2H), 1.23-1.21 (m, 1H), 1.20 (s, 3H), 1.10 (d. *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (CD_3OD, 125 MHz): δ 172.2, 171.7, 142.3, 141.7, 132.4, 132.2, 127.0, 125.9, 84.3, 80.3, 75.3, 74.1, 70.4, 63.0, 58.5, 42.8, 41.7, 40.7, 40.1, 37.5, 36.8, 30.4, 28.6, 24.2, 21.7, 21.1, 16.9, 11.9, 10.9.
FTIR (thin film) $\tilde{\nu}_{max}$: 3436, 2925, 2854, 1730, 1556, 1460, 1377, 1237, 1143, 1101, 1020, 975, 910 cm^{-1}.
$[\alpha]_D^{20}$ 7.3 (*c* 0.26, MeOH).
LR-ESI (+) *m/z* (relative intensity), ion: 559.5 (100%), $[M+Na]^+$.
HR-ESI (+) *m/z*: $[M+Na]^+$ calcd for $C_{30}H_{48}O_8$, 559.3247; found, 559.3238.
Purified on Zorbax-CN column (7:93 IPA:Hexane) prior to analytical characterization.

APPENDIX
Macrocycle Synthesis

1. C_1-C_8 Fragment

Figure 1. ^{1}H NMR Spectra of β-keto Ester 27

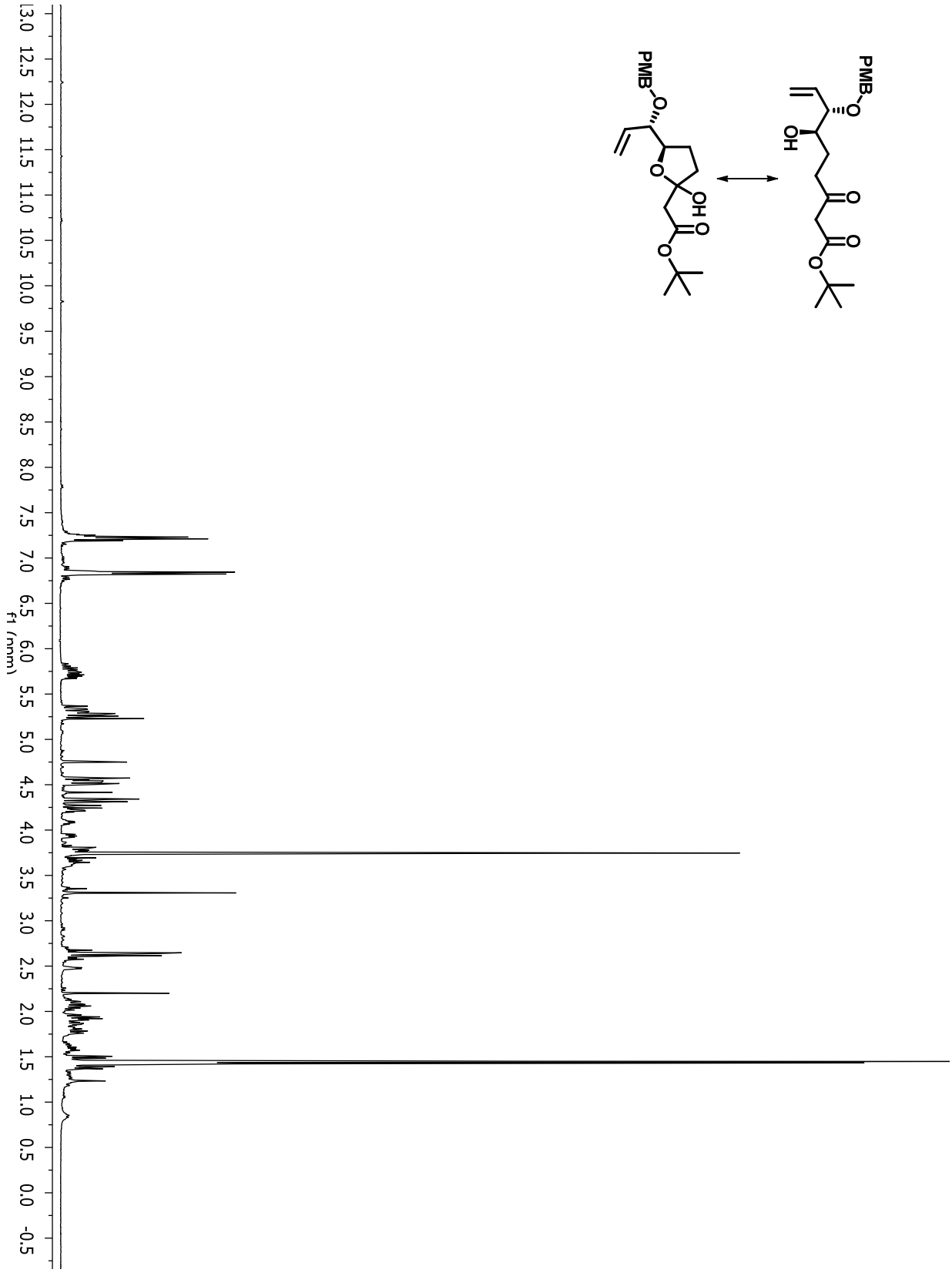


Figure 2. ^{13}**C NMR Spectra of β-keto Ester 27**

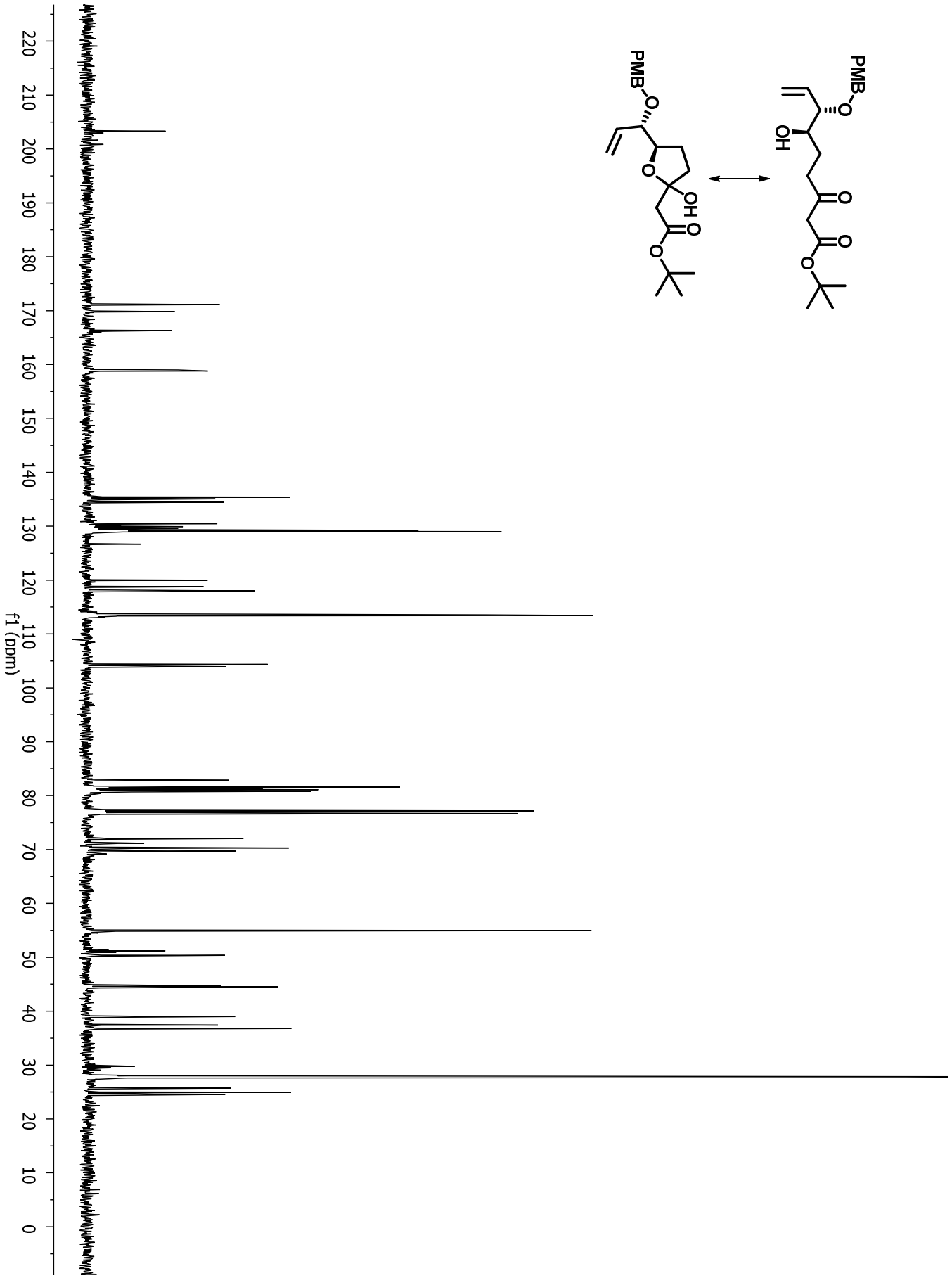


Figure 3. ^{1}**H NMR Spectra of TES Ether 13**

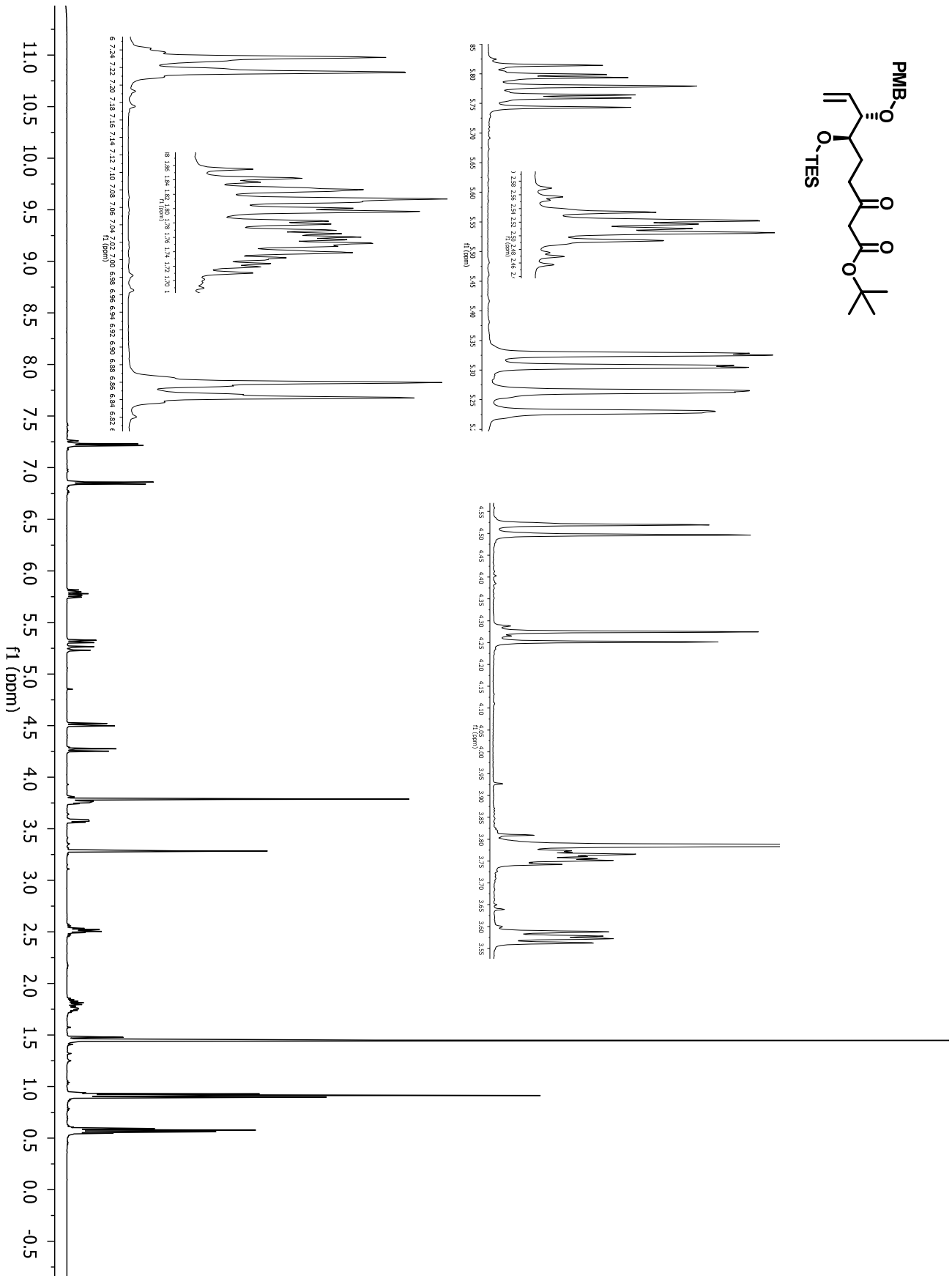


Figure 4. ^{13}**C NMR Spectra of TES Ether 13**

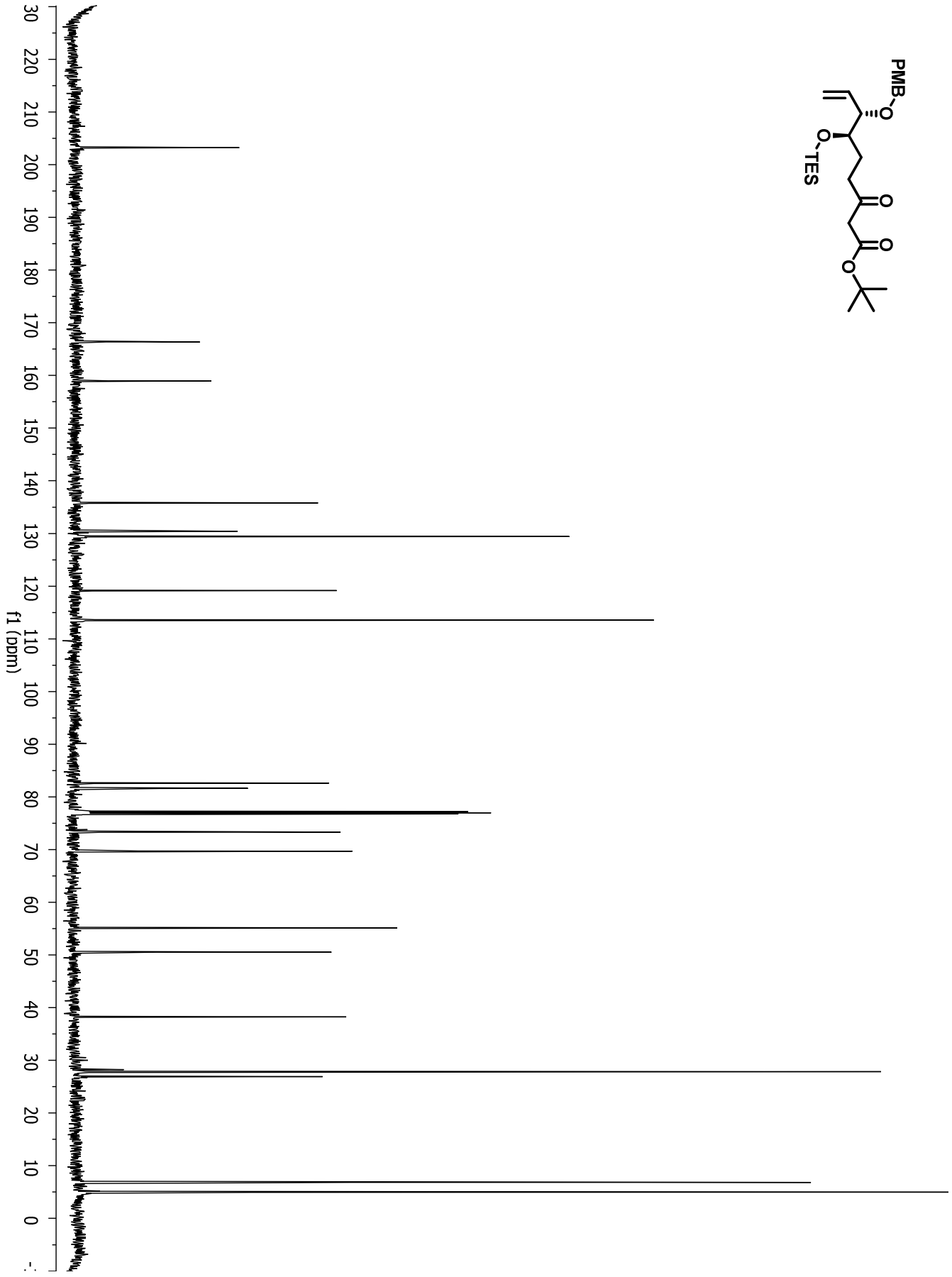


Figure 5. ^{1}H NMR Spectra of β-hydroxy Ester 28

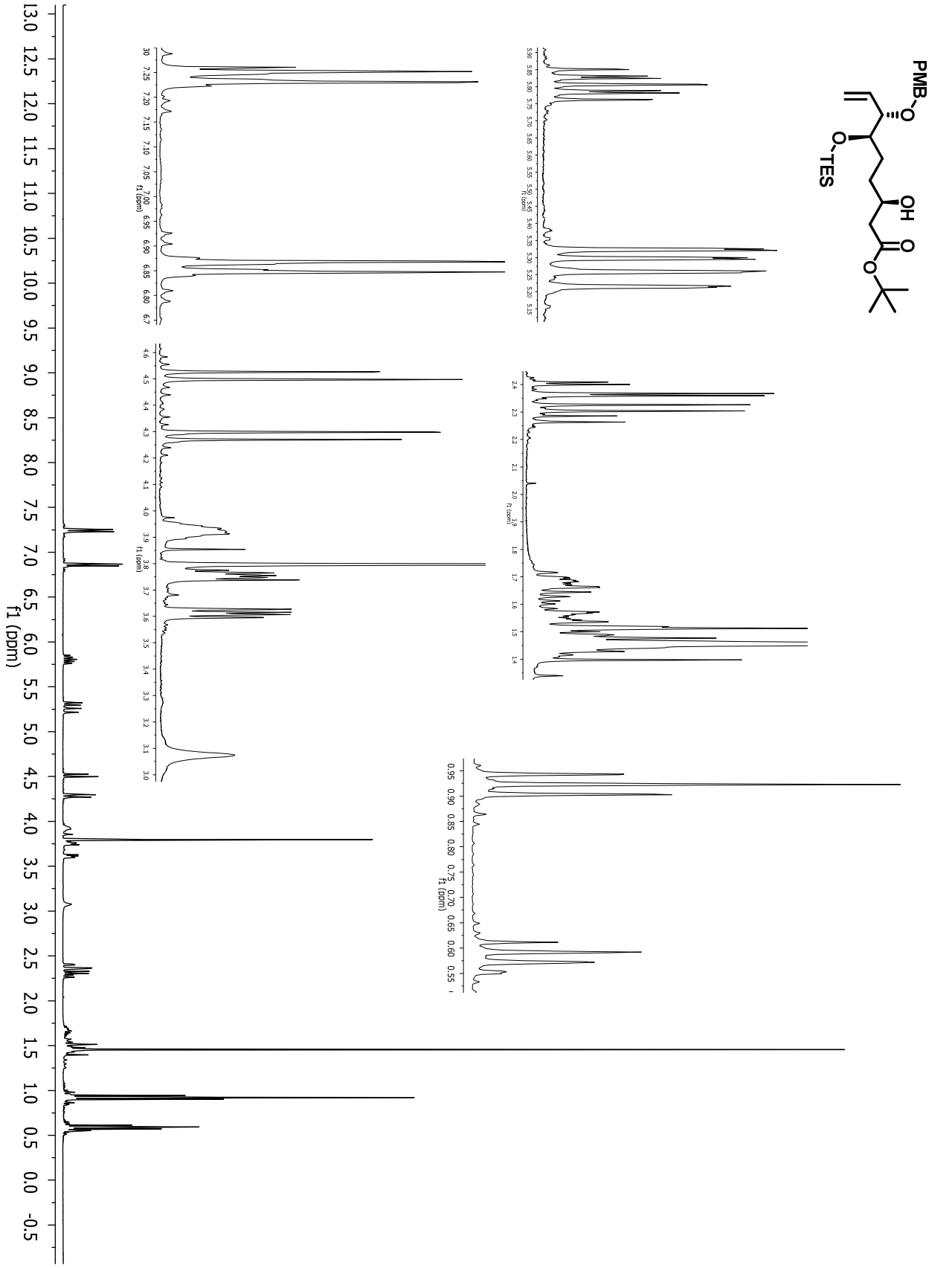


Figure 6. ^{13}C NMR Spectra of β-hydroxy Ester 28

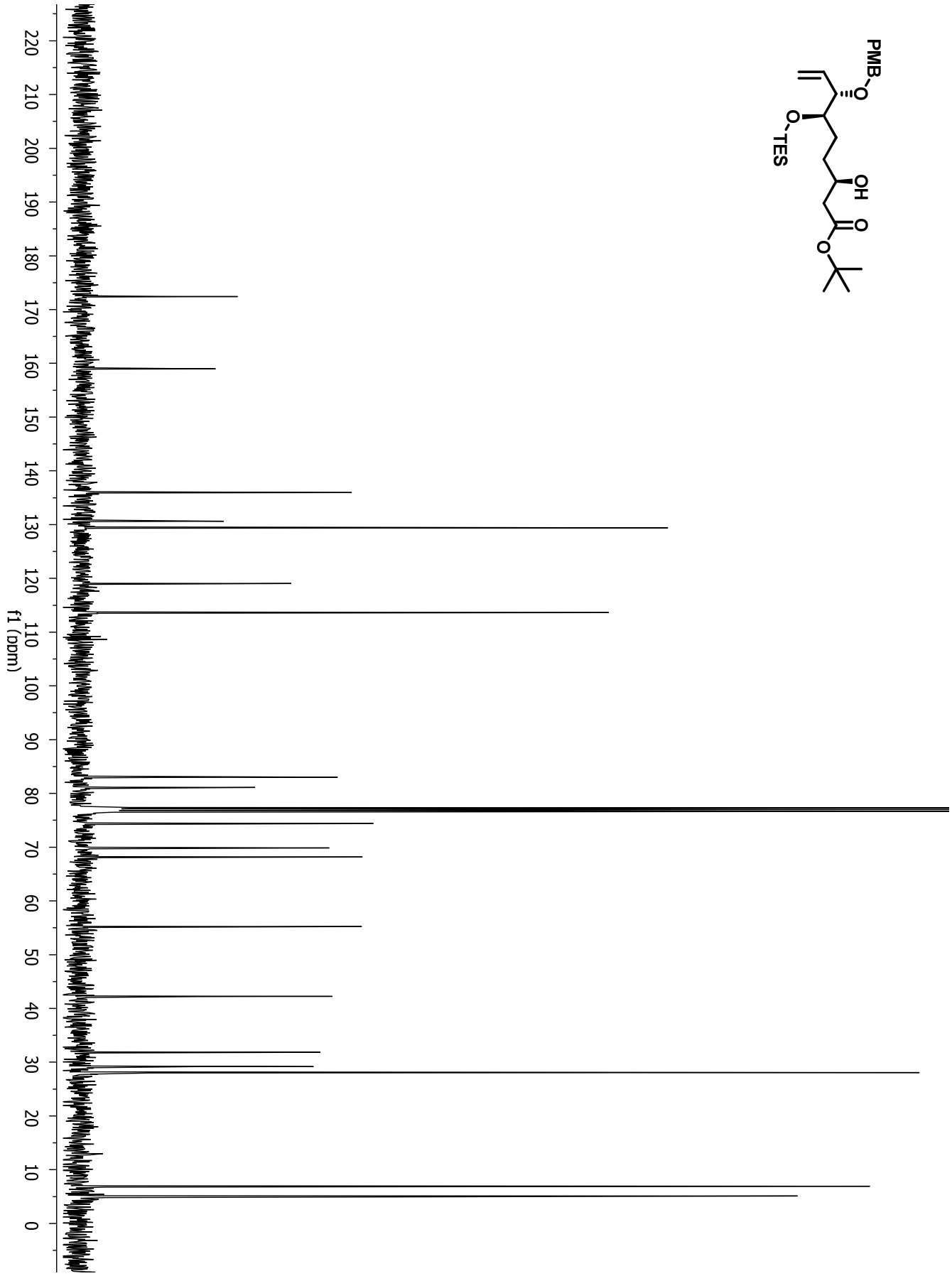


Figure 7. ^{1}H NMR Spectra of TBS Ether 14

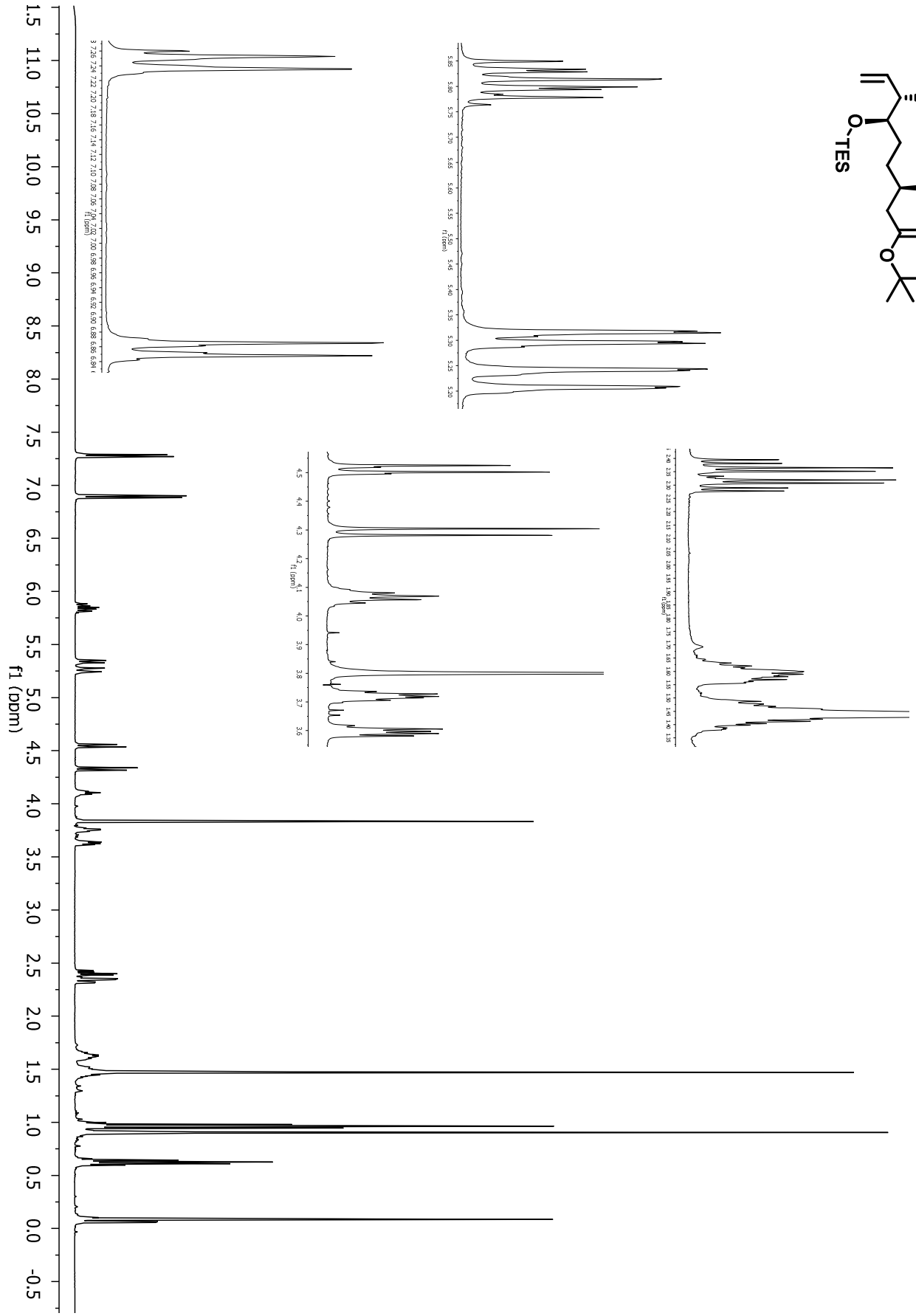


Figure 8. ^{13}C NMR Spectra of TBS Ether 14

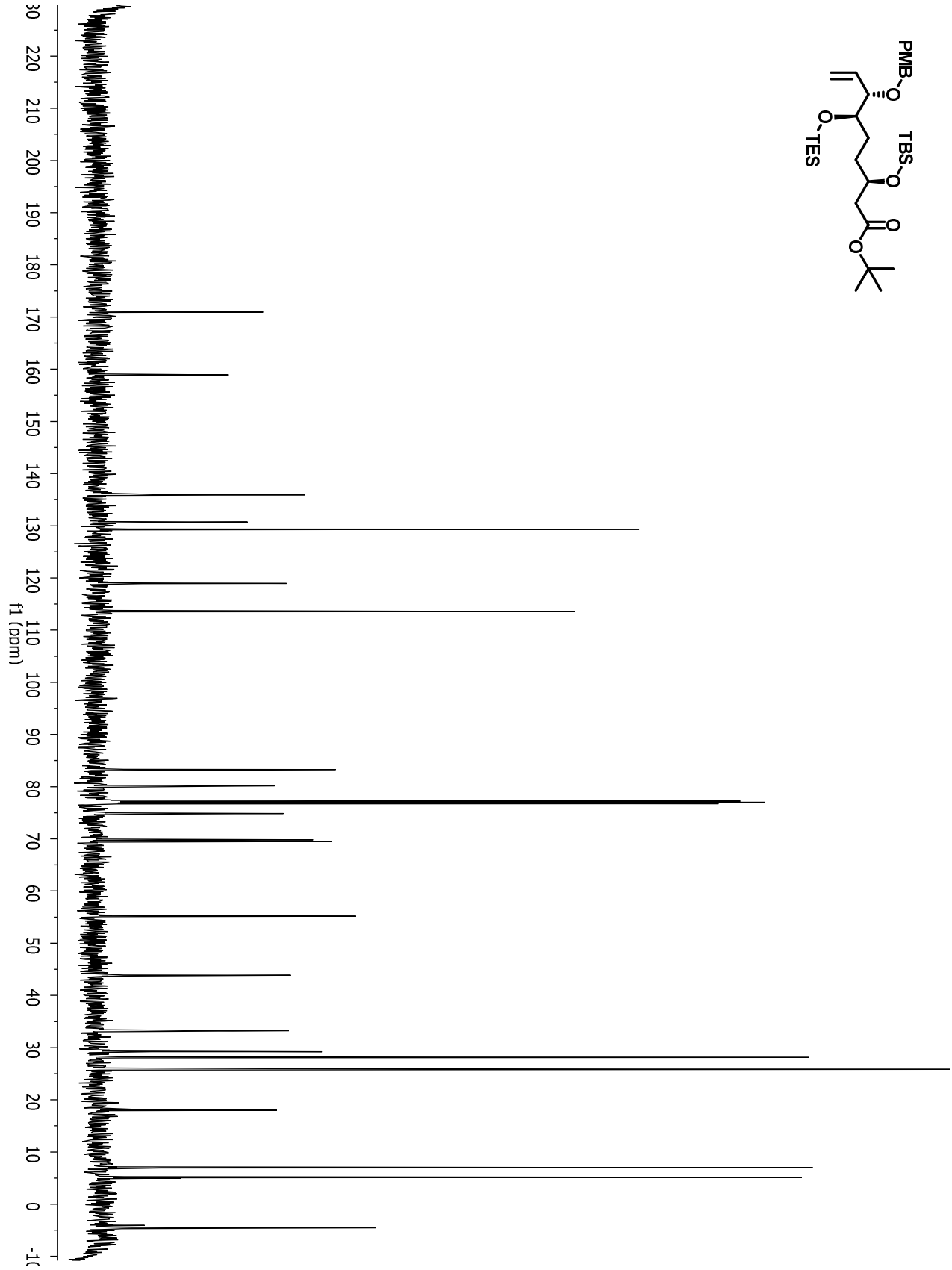


Figure 9. ^{1}H NMR Spectra of Ketone 29

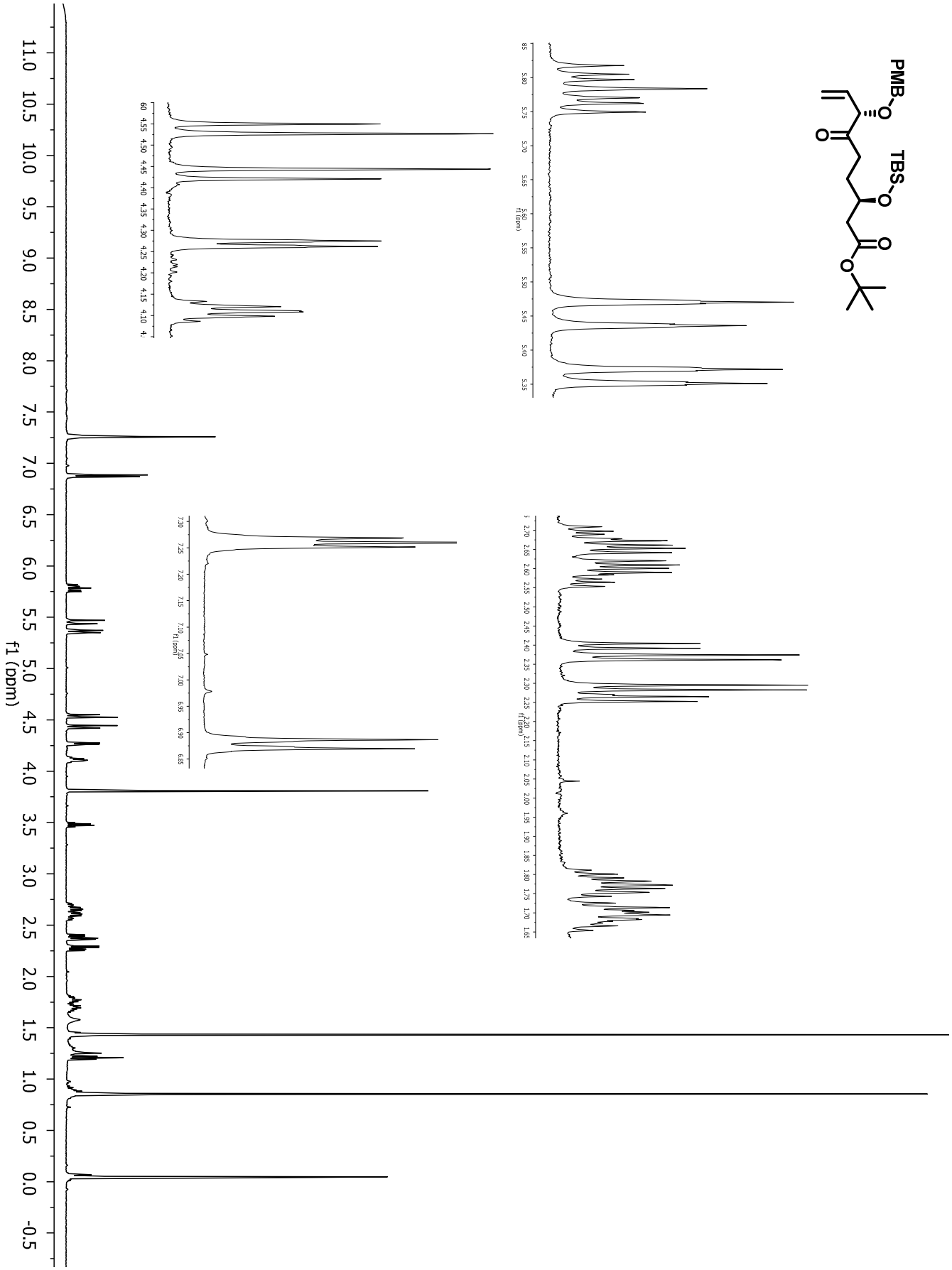


Figure 10. ^{13}C NMR Spectra of Ketone 29

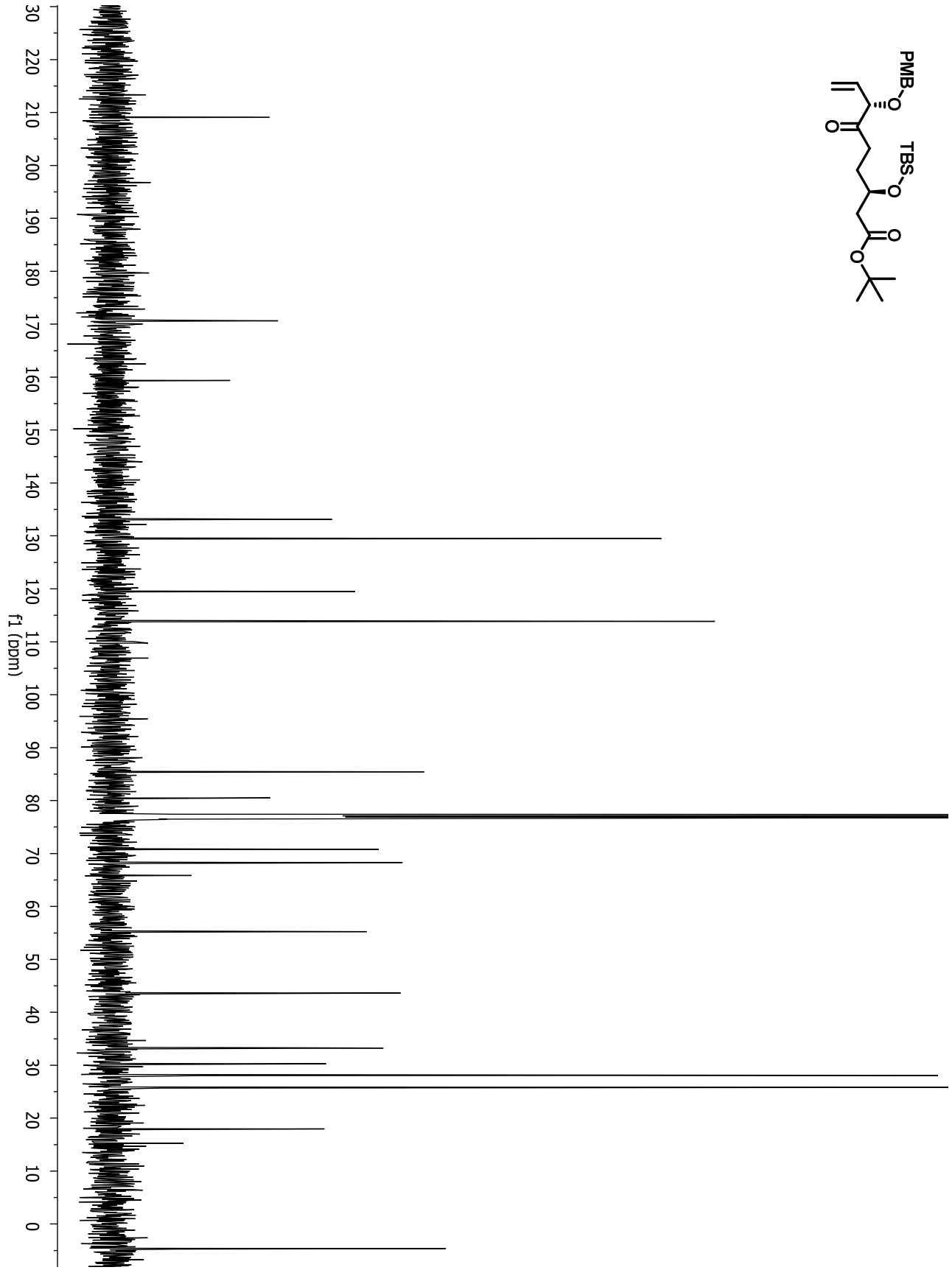


Figure 11. ^{1}H NMR Spectra of Tertiary Alcohol 15

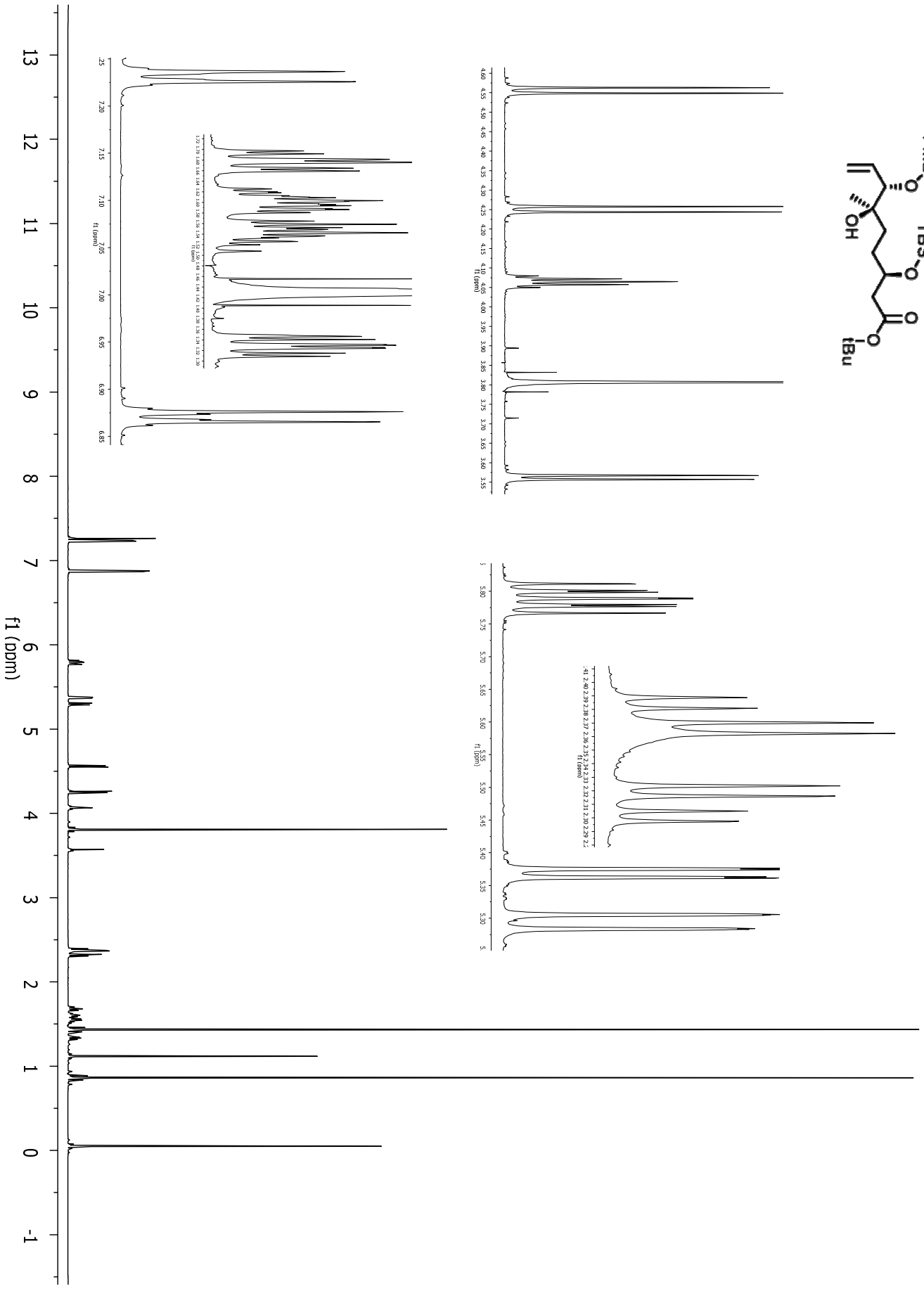


Figure 12. ^{13}C NMR Spectra of Tertiary Alcohol 15

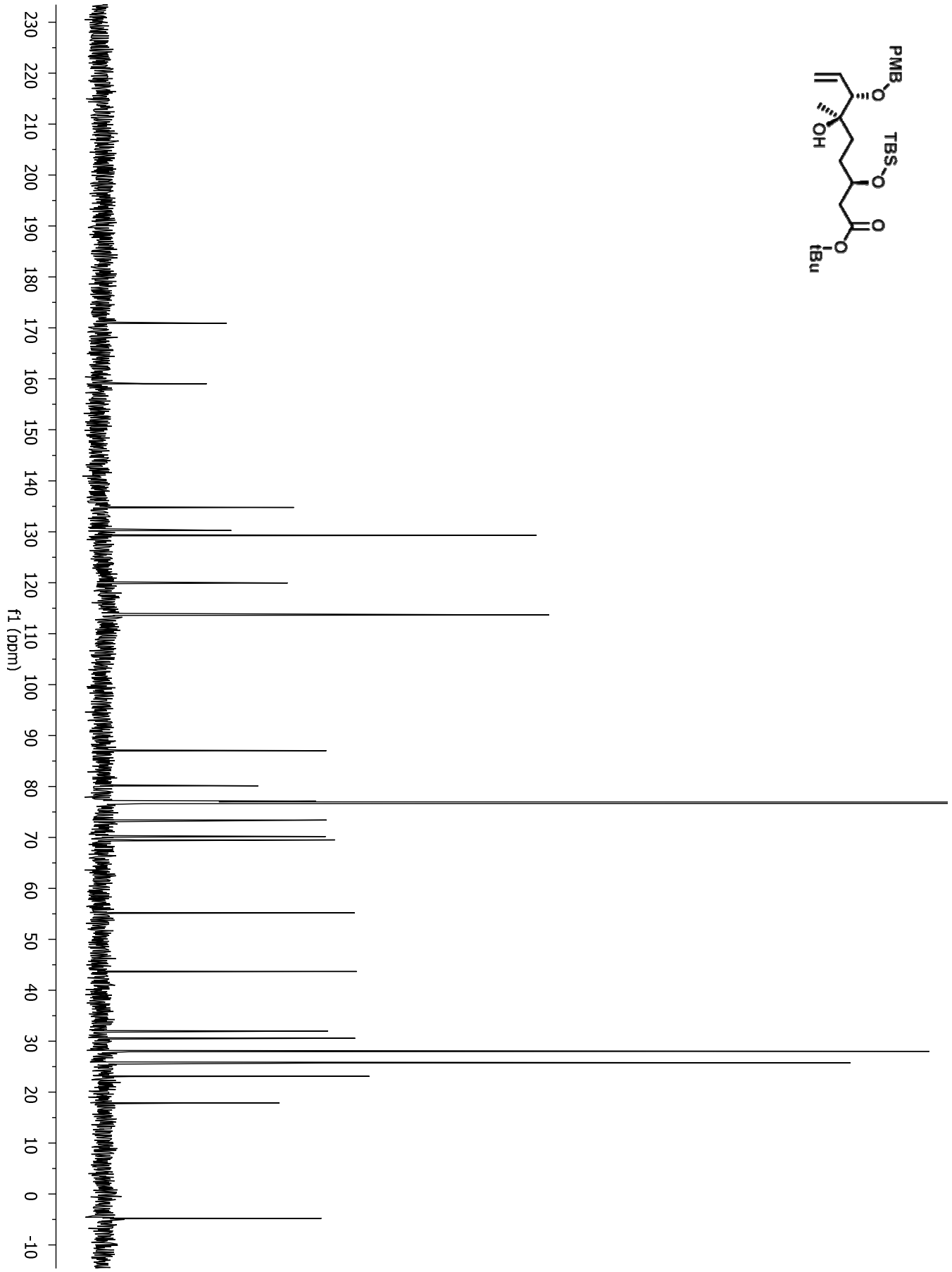


Figure 13. ^{1}H NMR Spectra of Carboxylic Acid 8

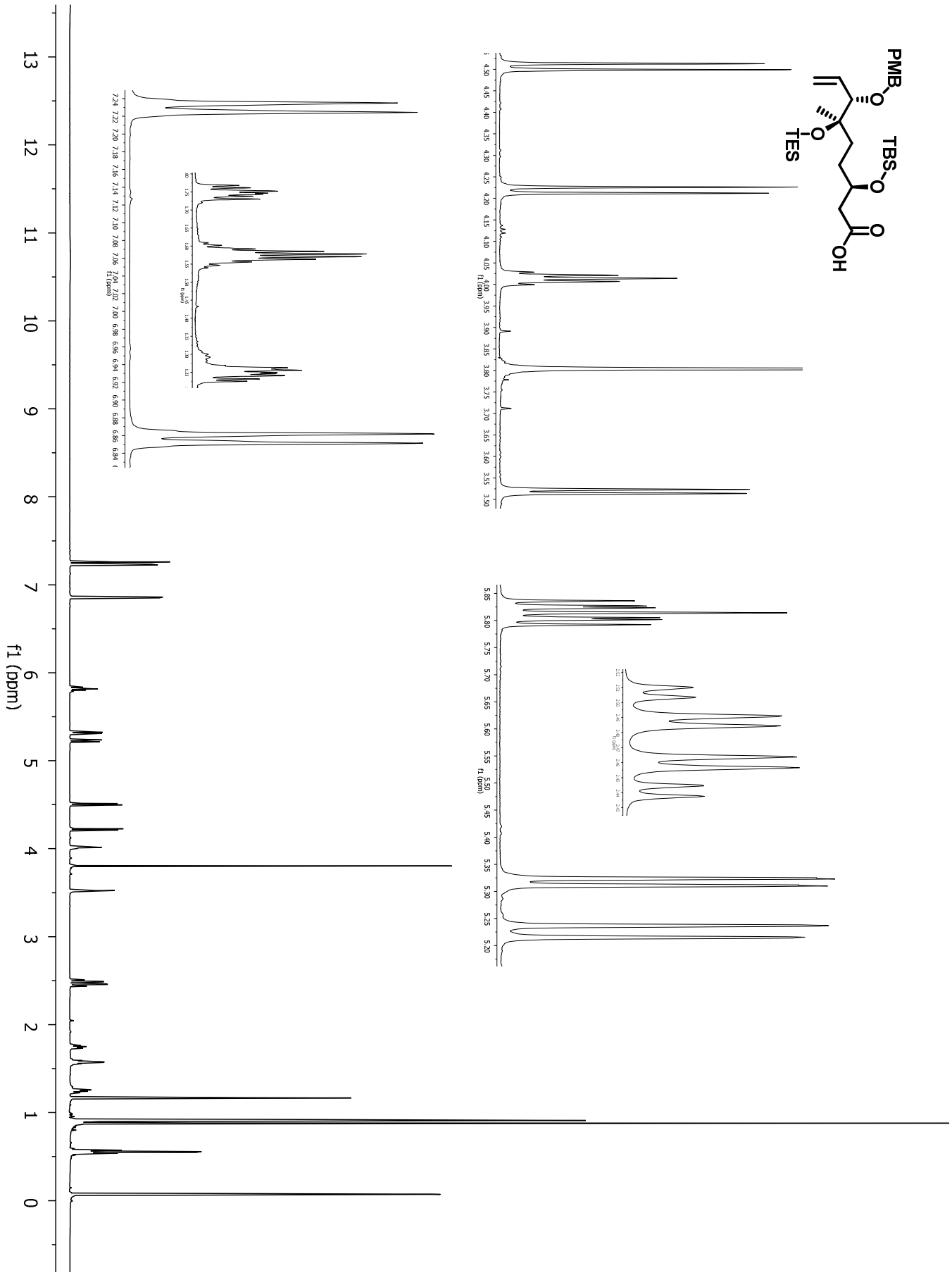
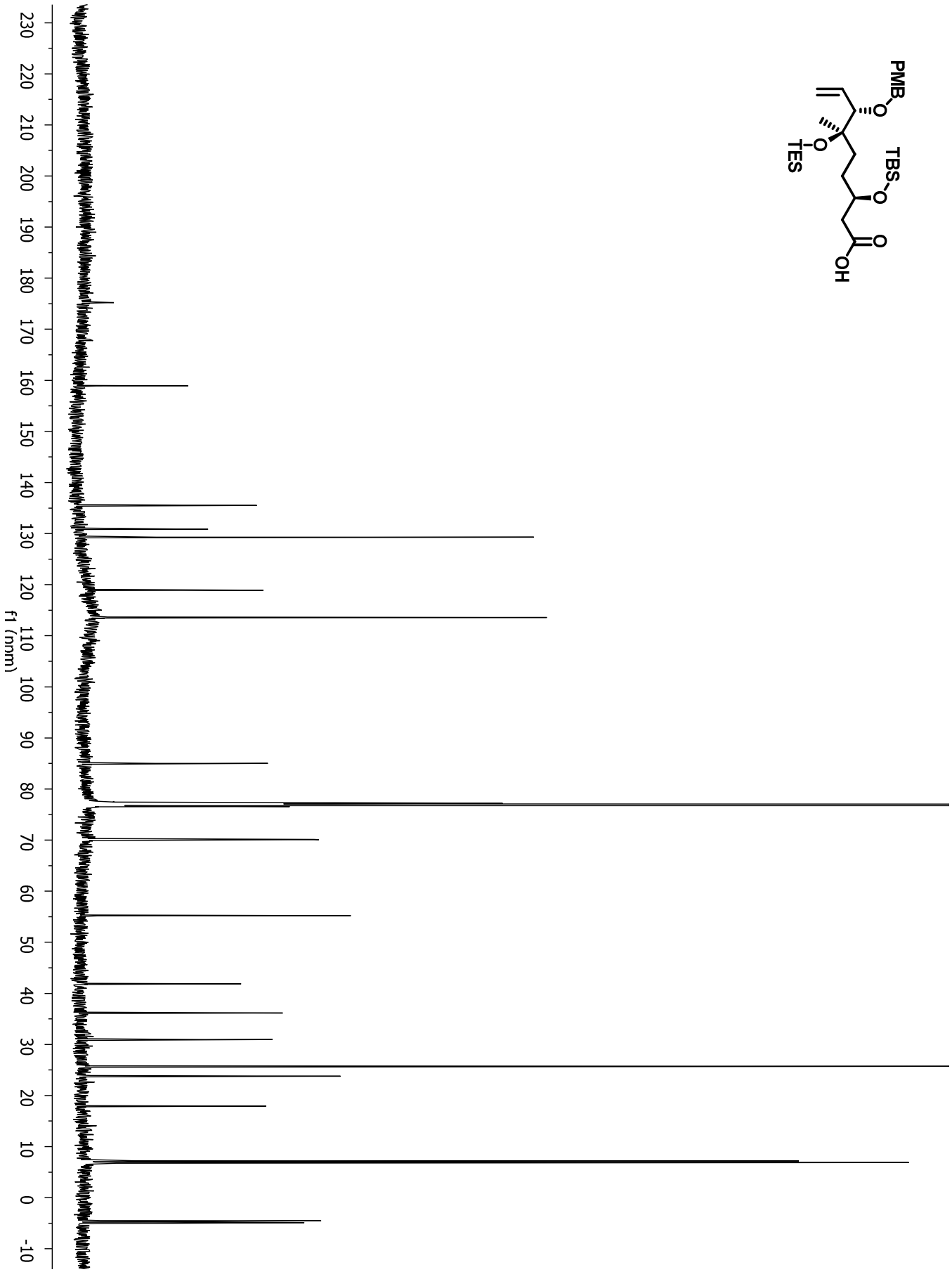


Figure 14. ^{13}C NMR Spectra of Carboxylic Acid 8



2. C_9-C_{14} Fragment

Figure 15. ^{1}H NMR Spectra of Allylic Alcohol 17

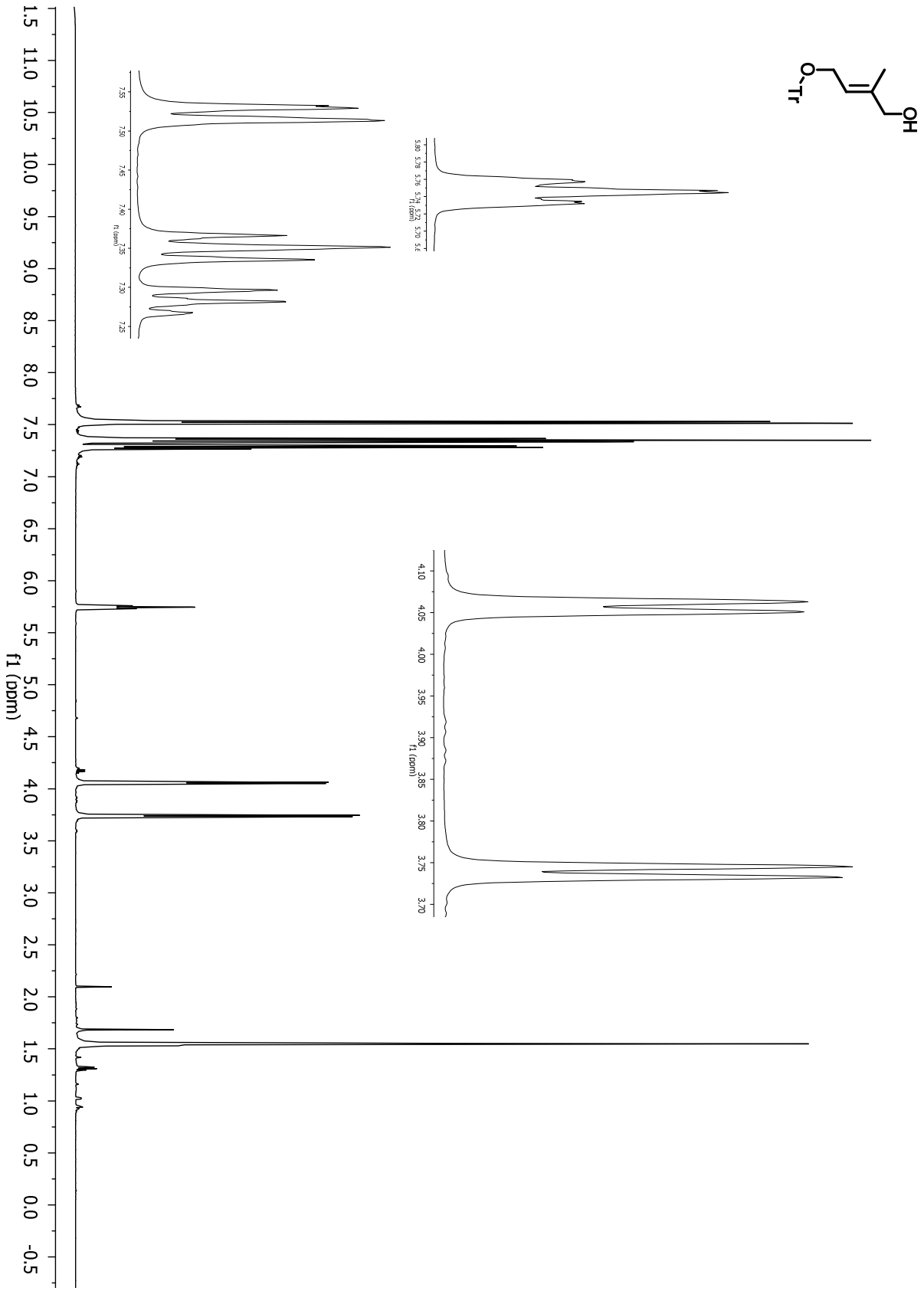


Figure 16. ^{13}C NMR Spectra of Allylic Alcohol 17

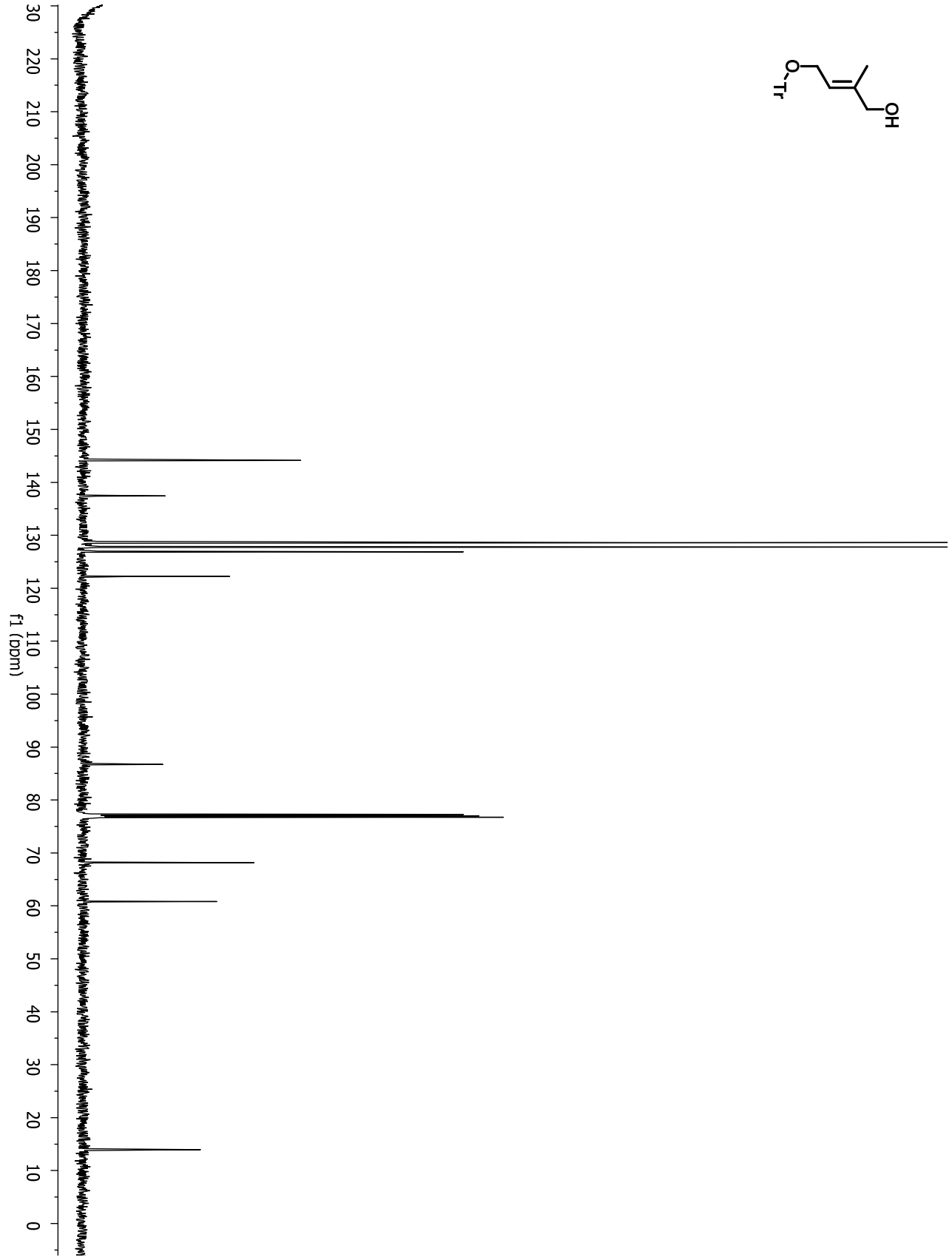


Figure 17. ^{1}H NMR Spectra of Homoallylic Alcohol 7

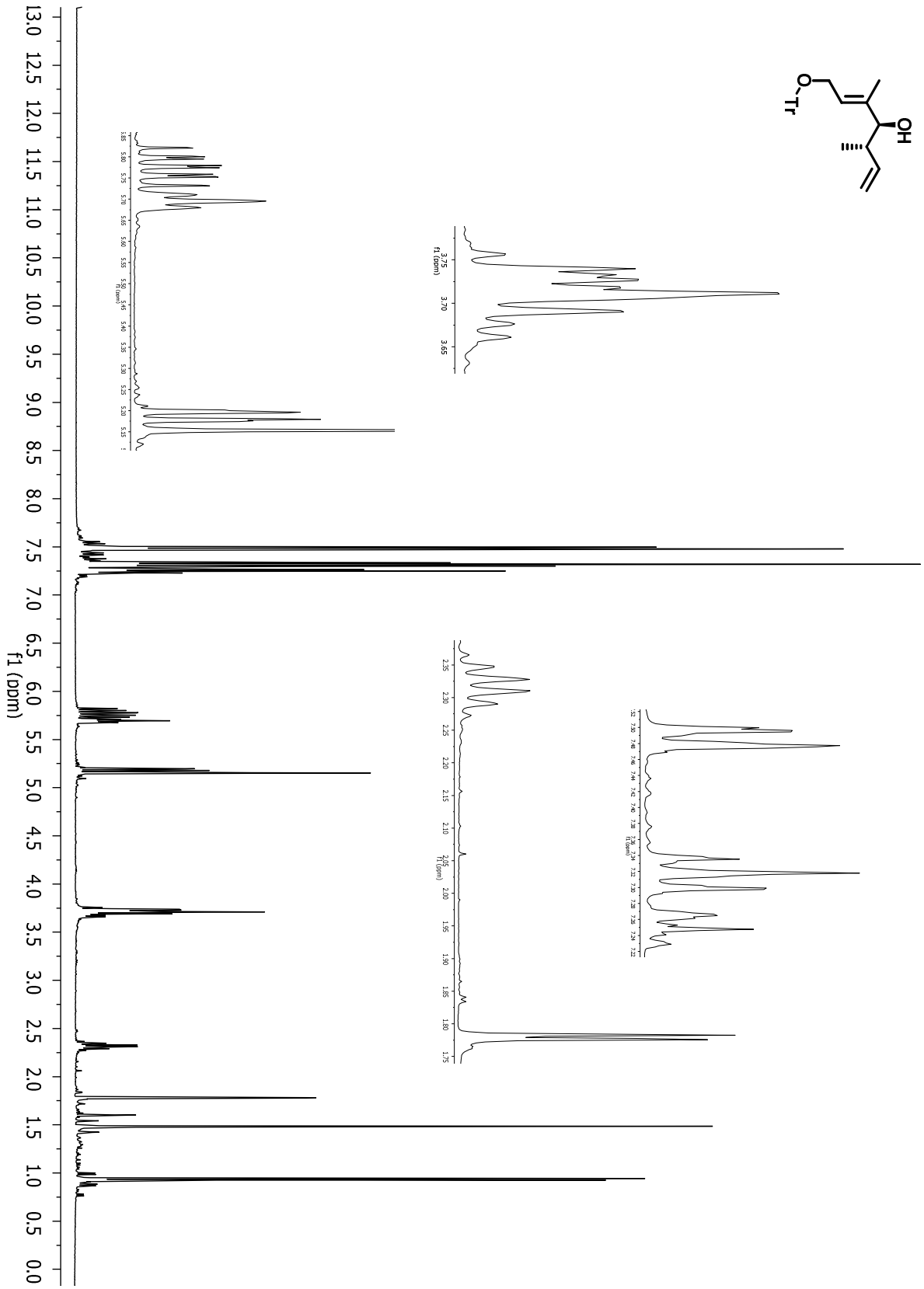
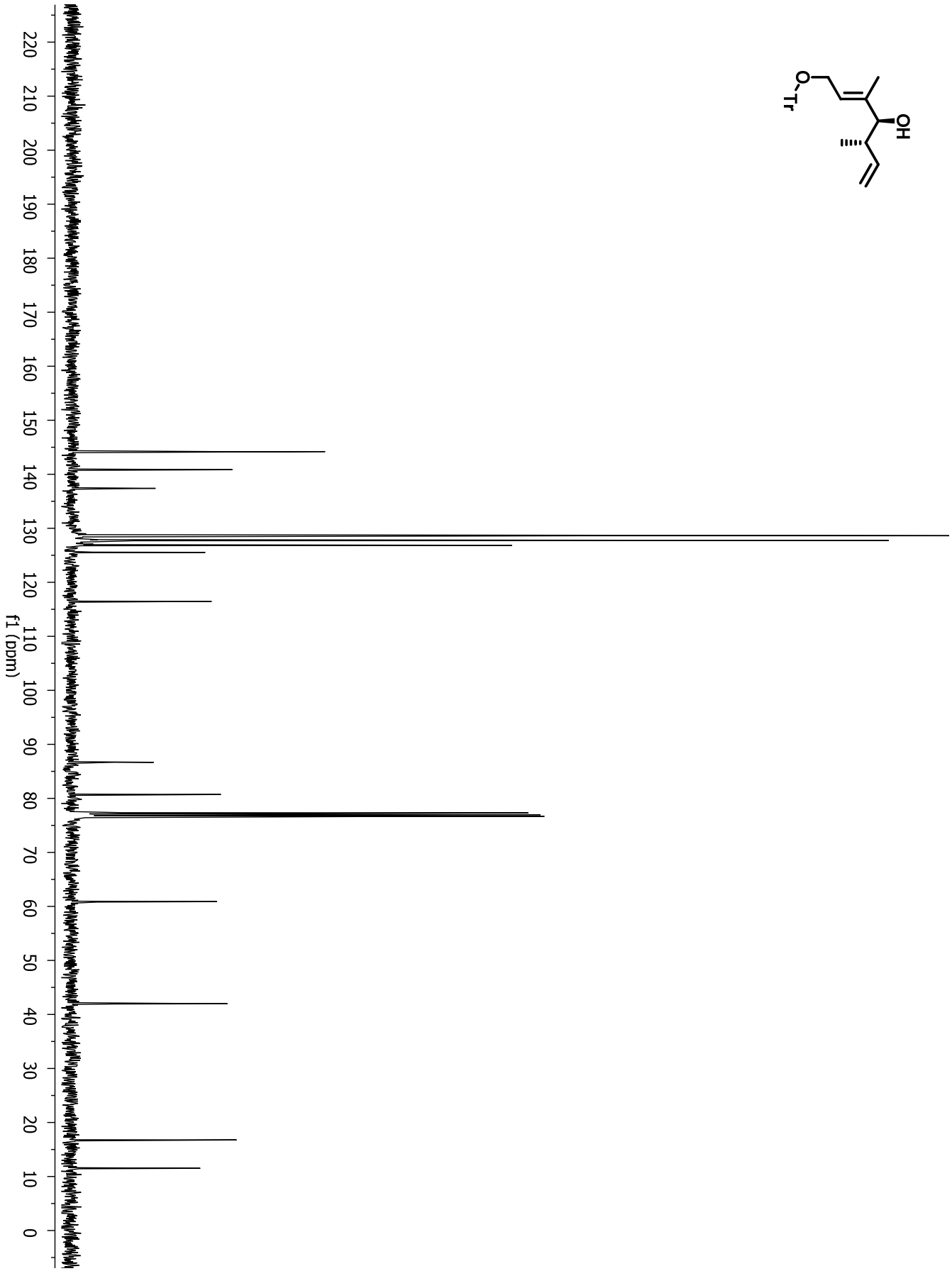


Figure 18. ^{13}C NMR Spectra of Homoallylic Alcohol 7



3. Synthesis of the Macrocyclic Ring

Figure 19. ^{1}H NMR Spectra of Ester 31

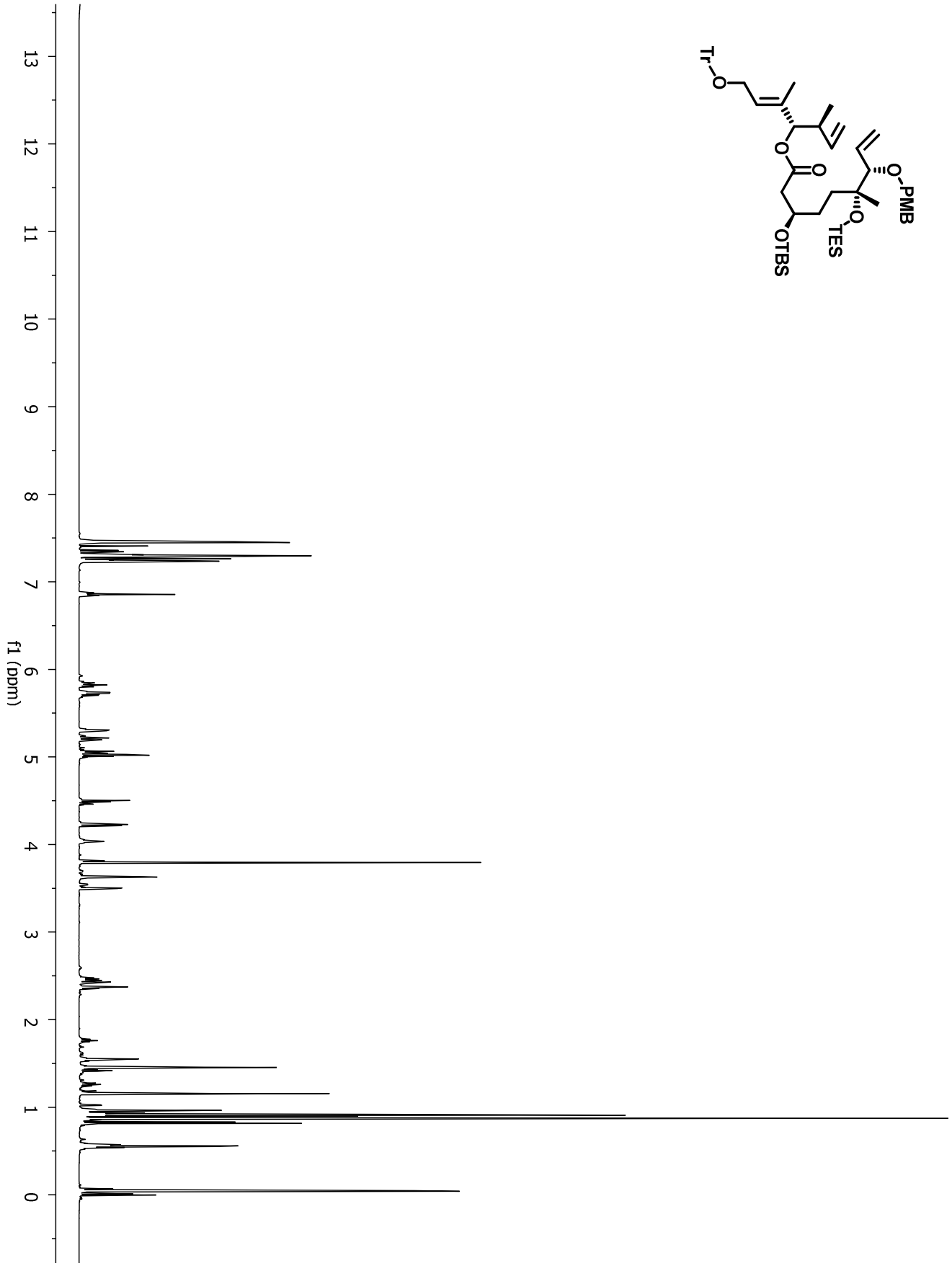


Figure 20. ^{13}C NMR Spectra of Ester 31

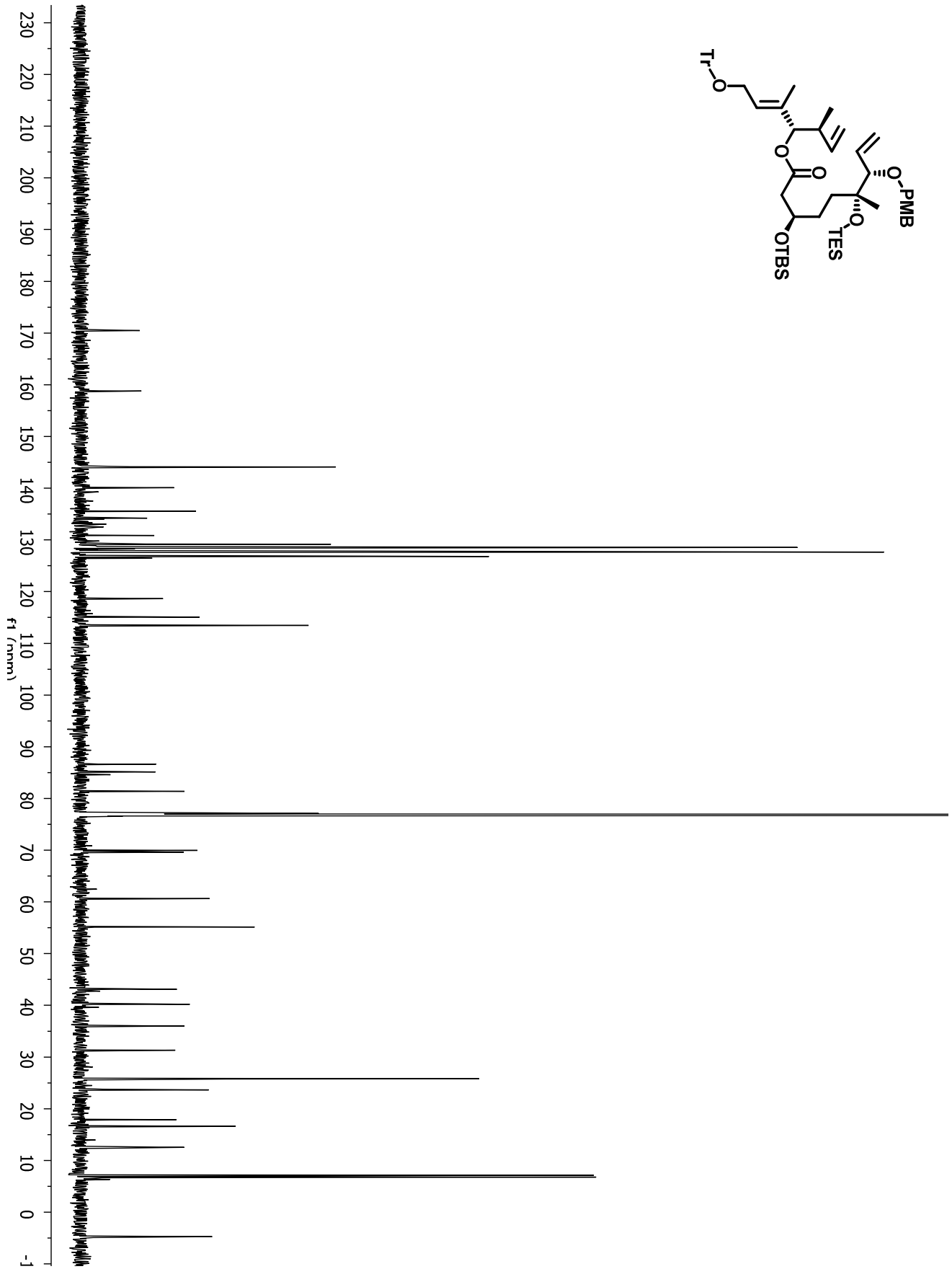


Figure 21. ^{1}H NMR Spectra of Allylic Alcohol 19

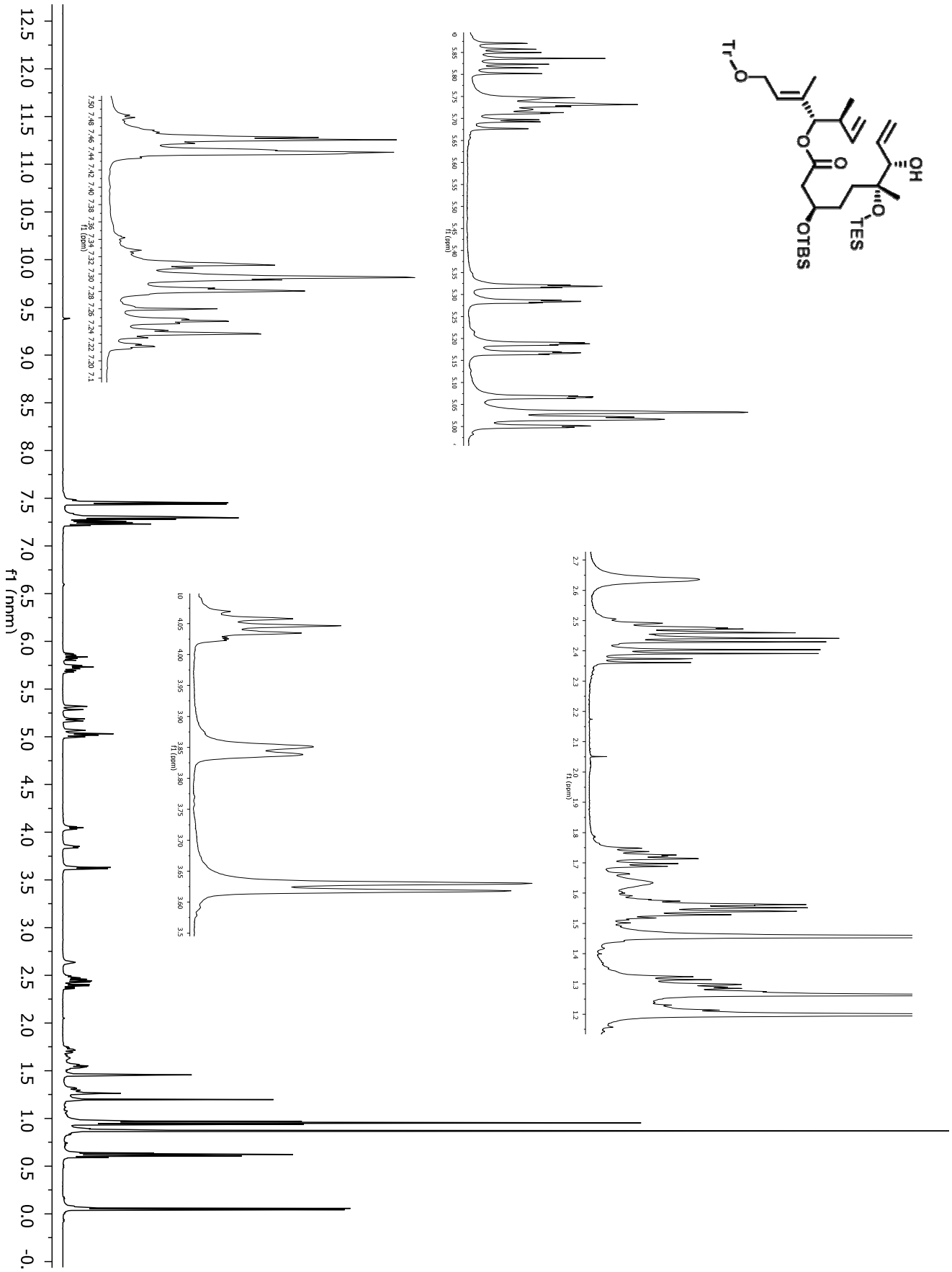


Figure 22. ^{13}**C NMR Spectra of Allylic Alcohol 19**

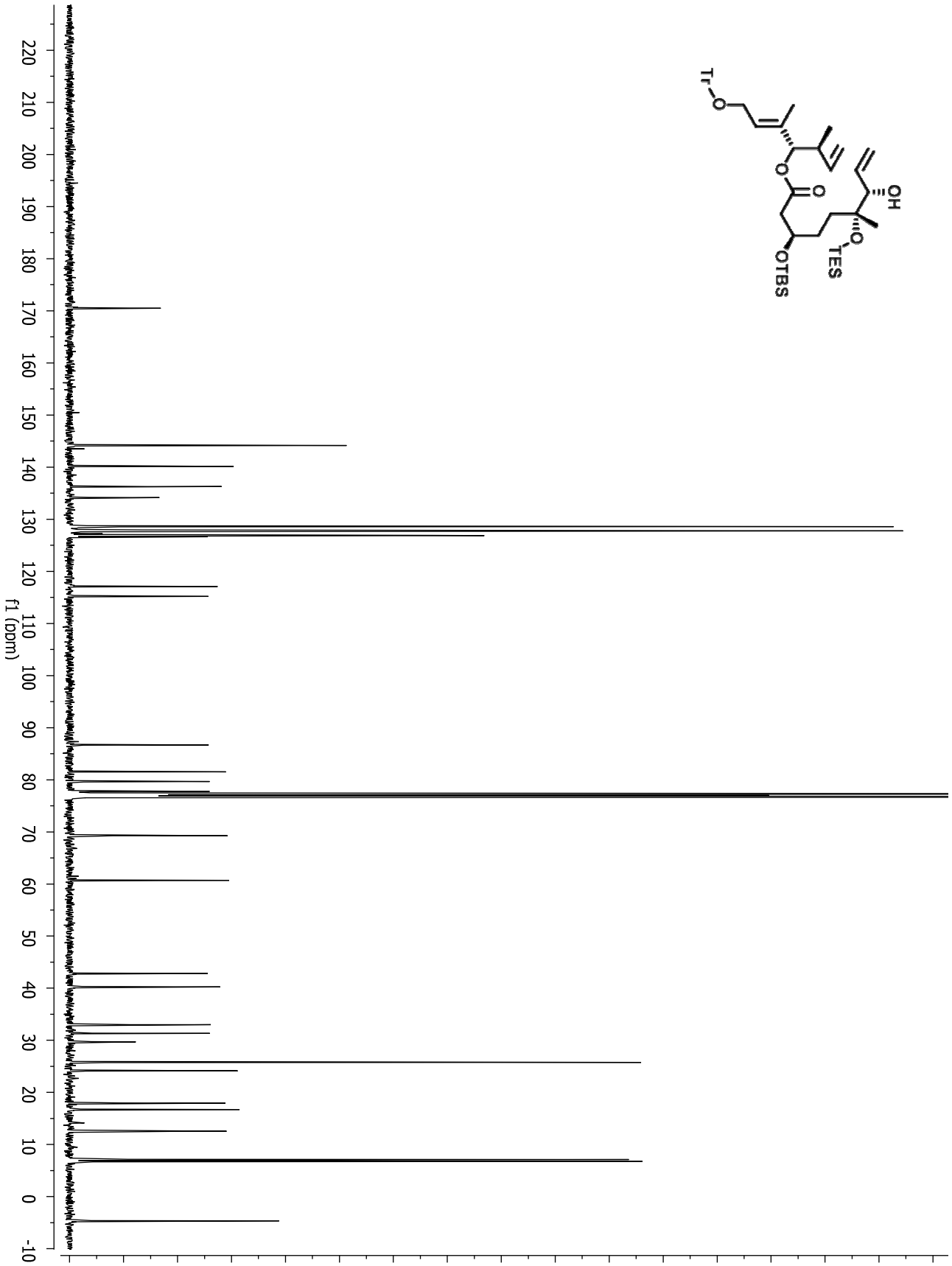


Figure 23. ^{1}**H NMR Spectra of Lactone 32**

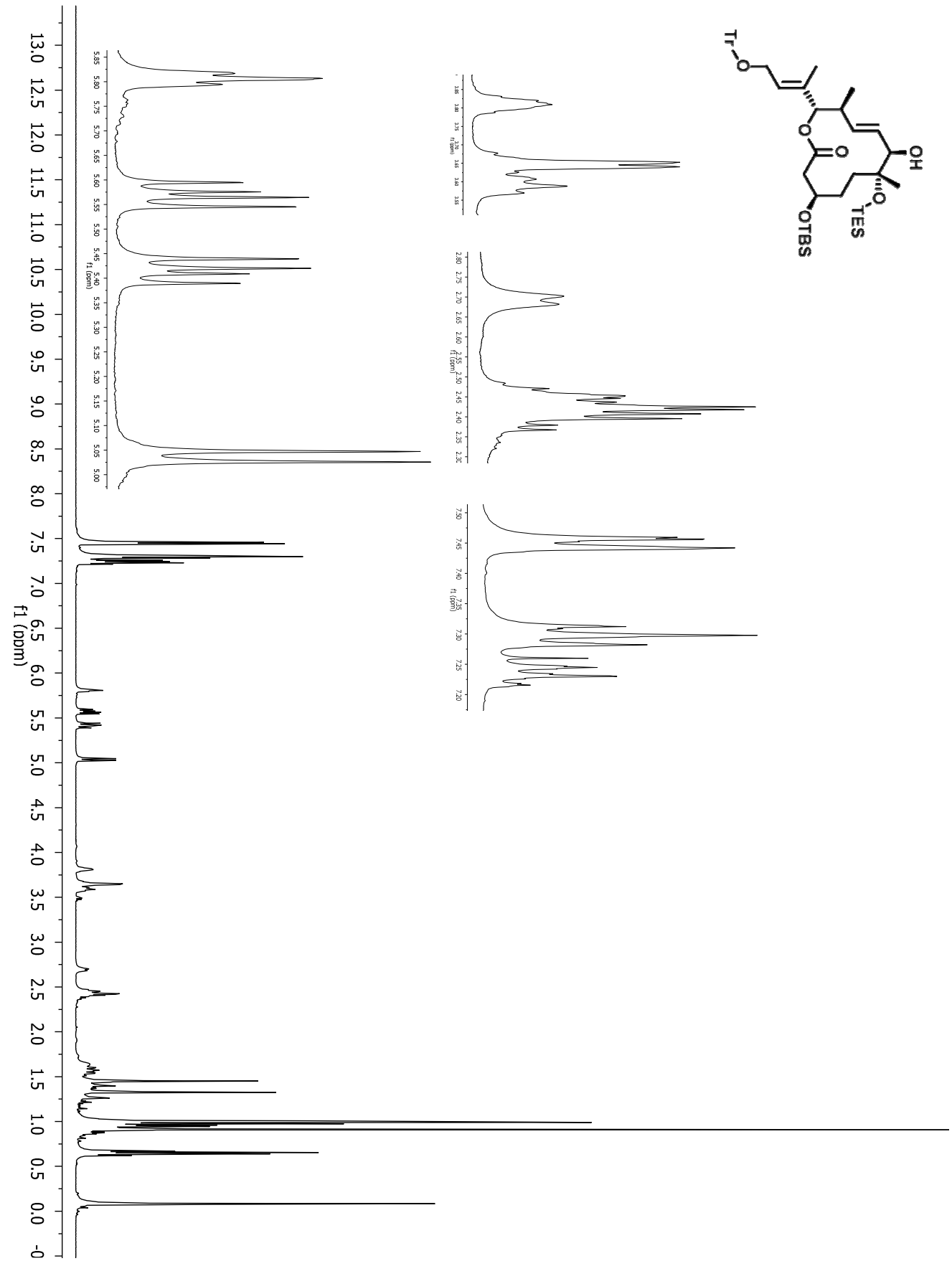


Figure 24. ^{13}C NMR Spectra of Lactone 32

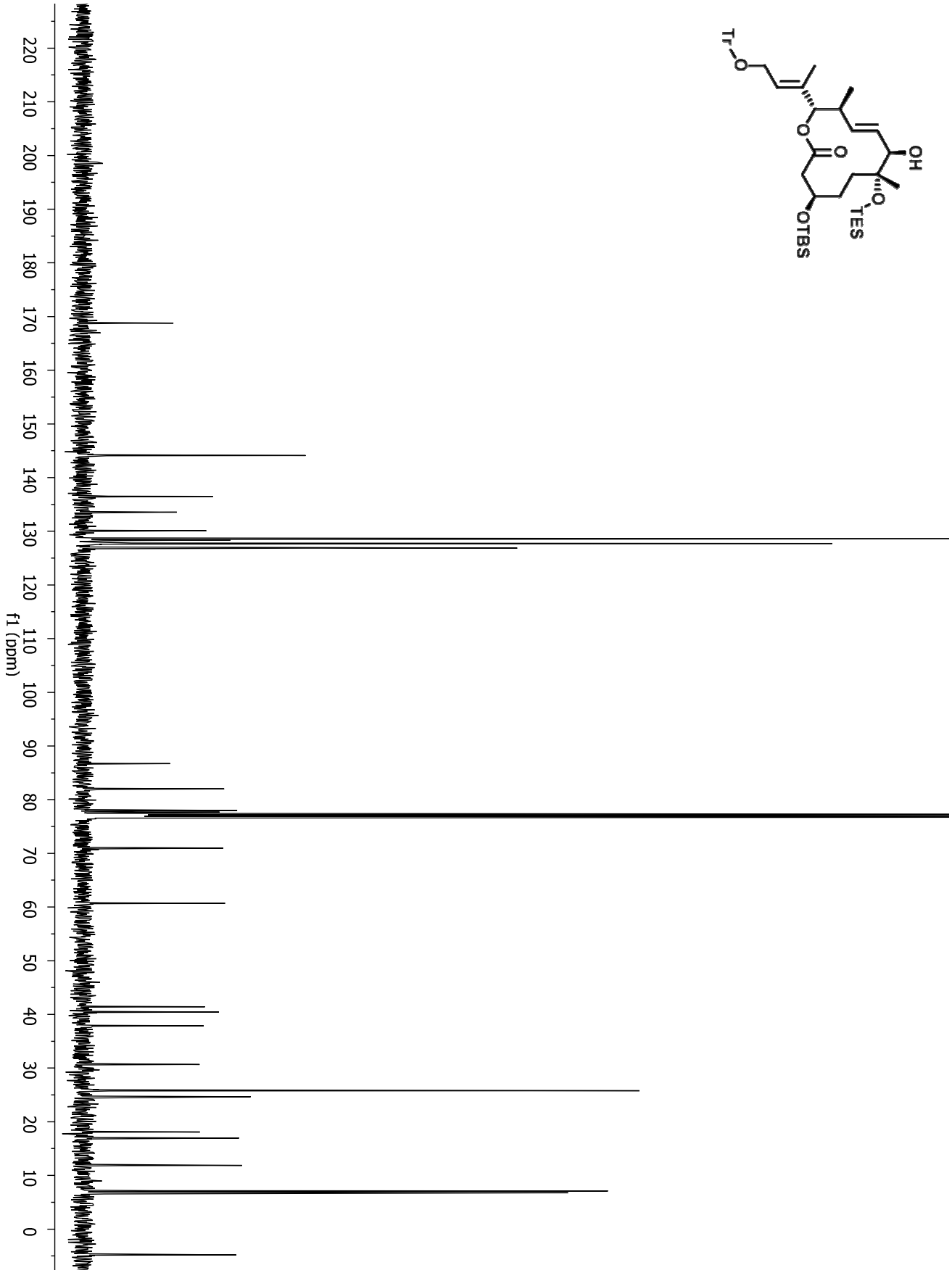


Figure 25. ^{1}H NMR Spectra of Acetate 20

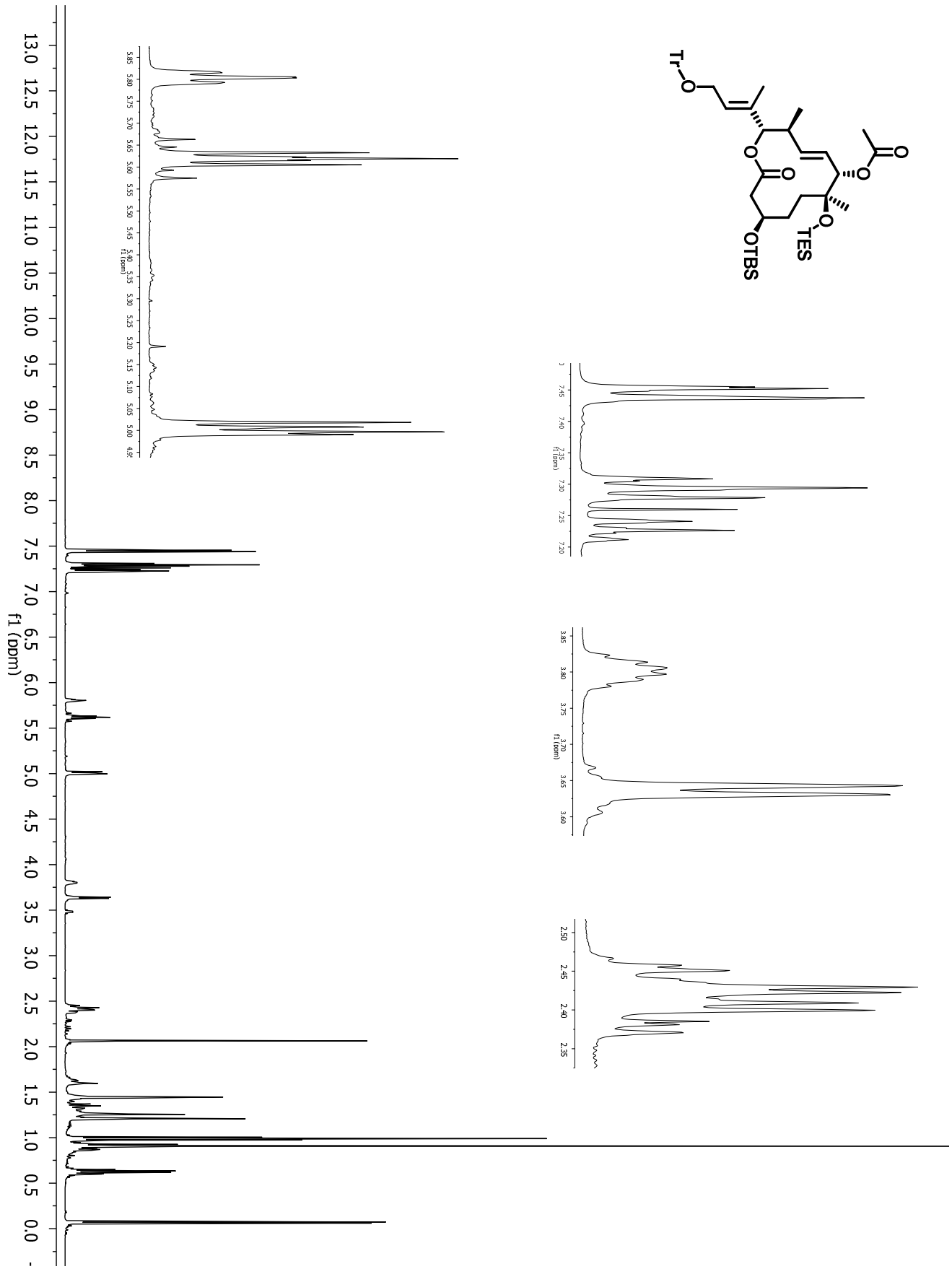


Figure 26. ^{13}C NMR Spectra of Acetate 20

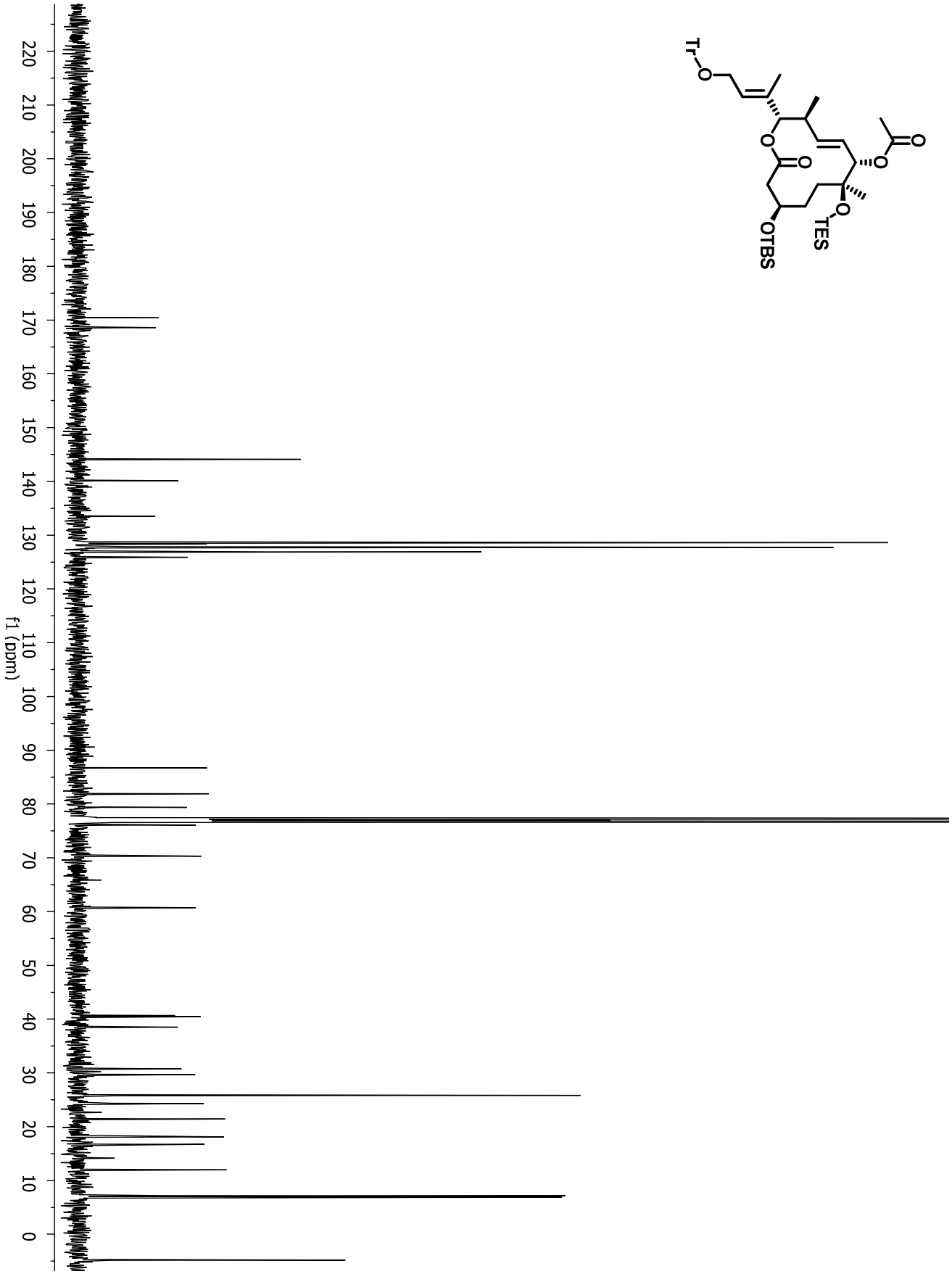


Figure 27. ^{1}H NMR Spectra of Alcohol 33

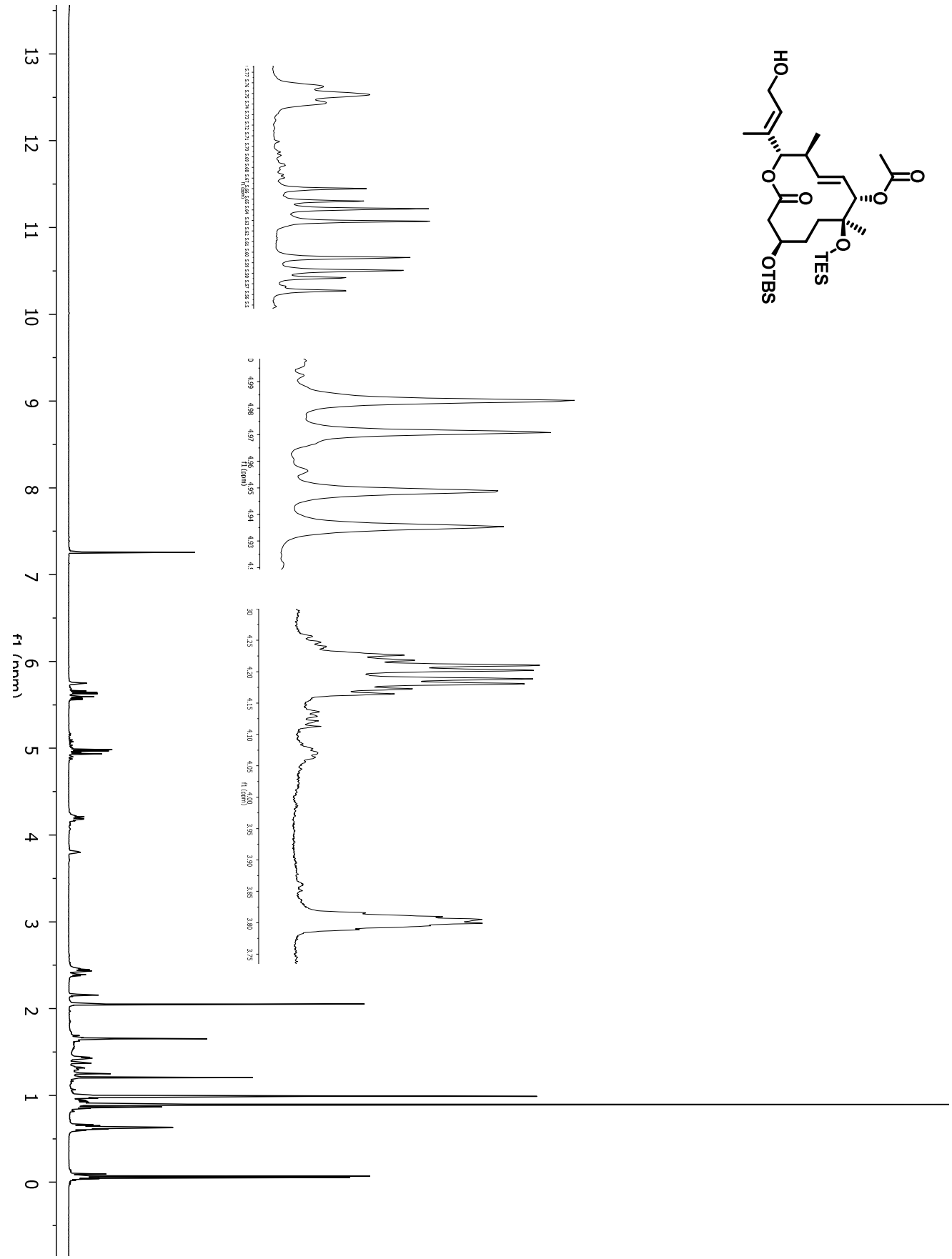


Figure 28. ^{13}**C NMR Spectra of Alcohol 33**

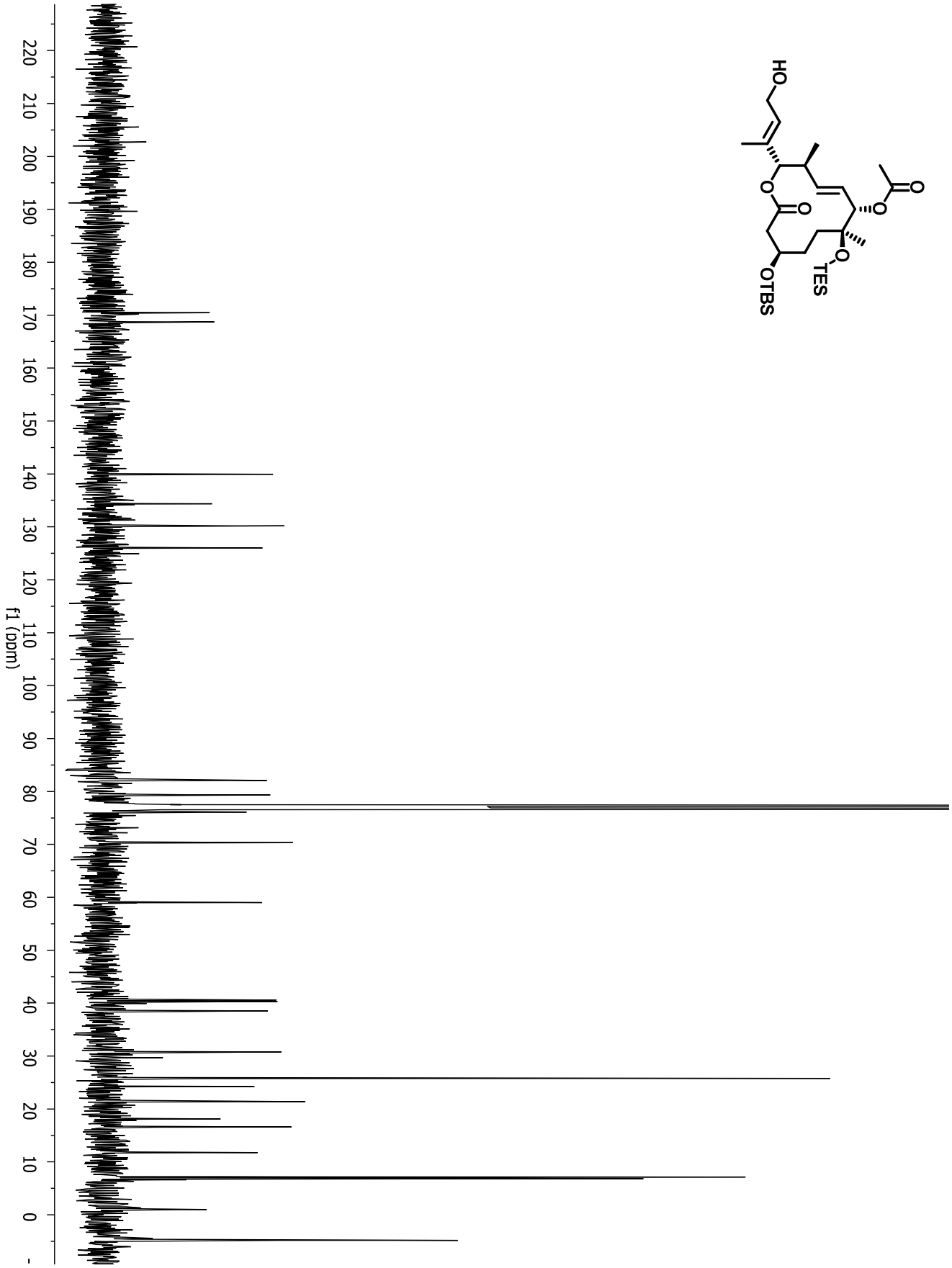
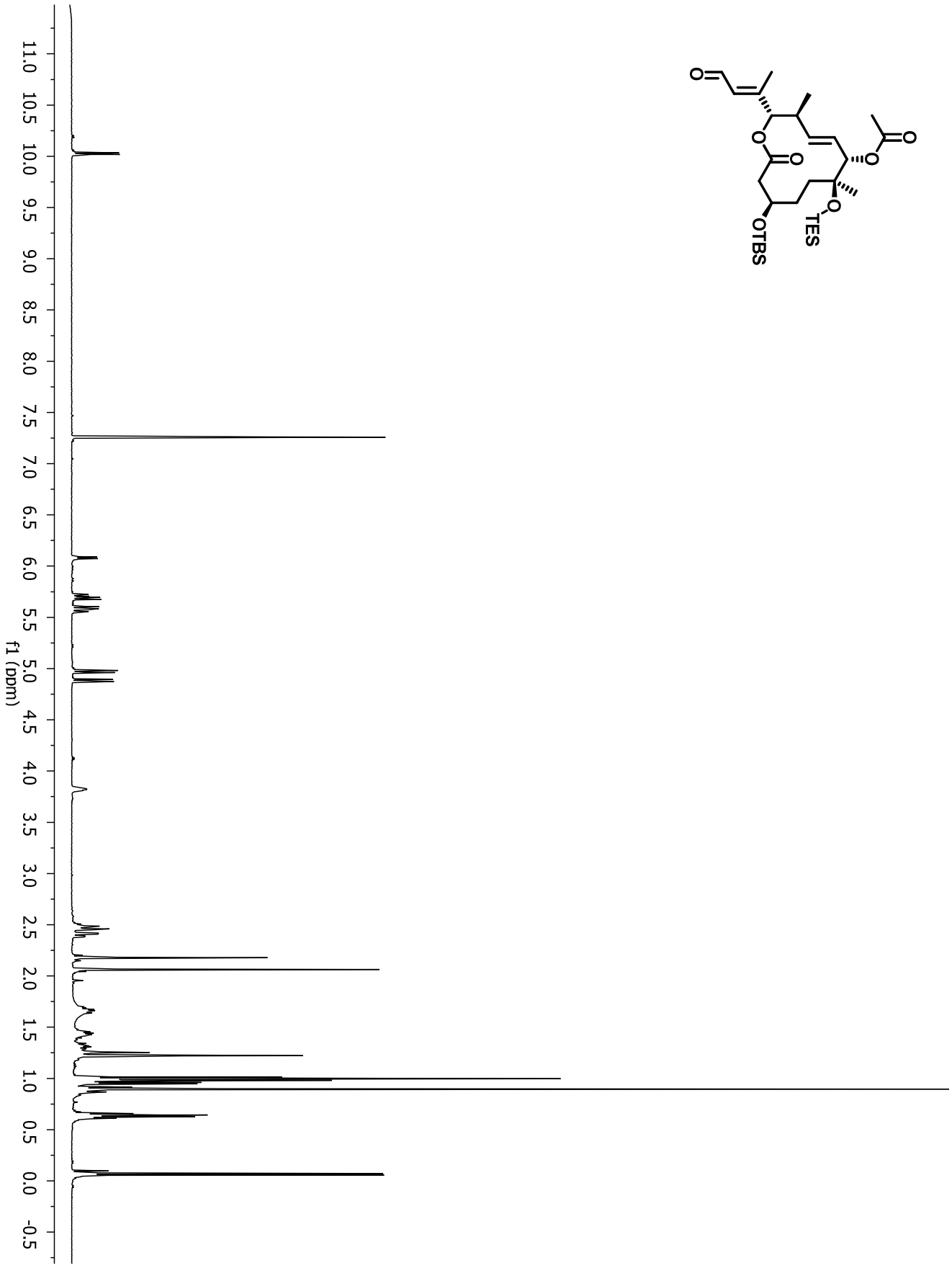


Figure 29. ^{1}H NMR Spectra of Aldehyde 3



4. Cross Metathesis, Epoxidation, Silyl Protection

Figure 30. ^{1}H NMR Spectra of Olefin 41

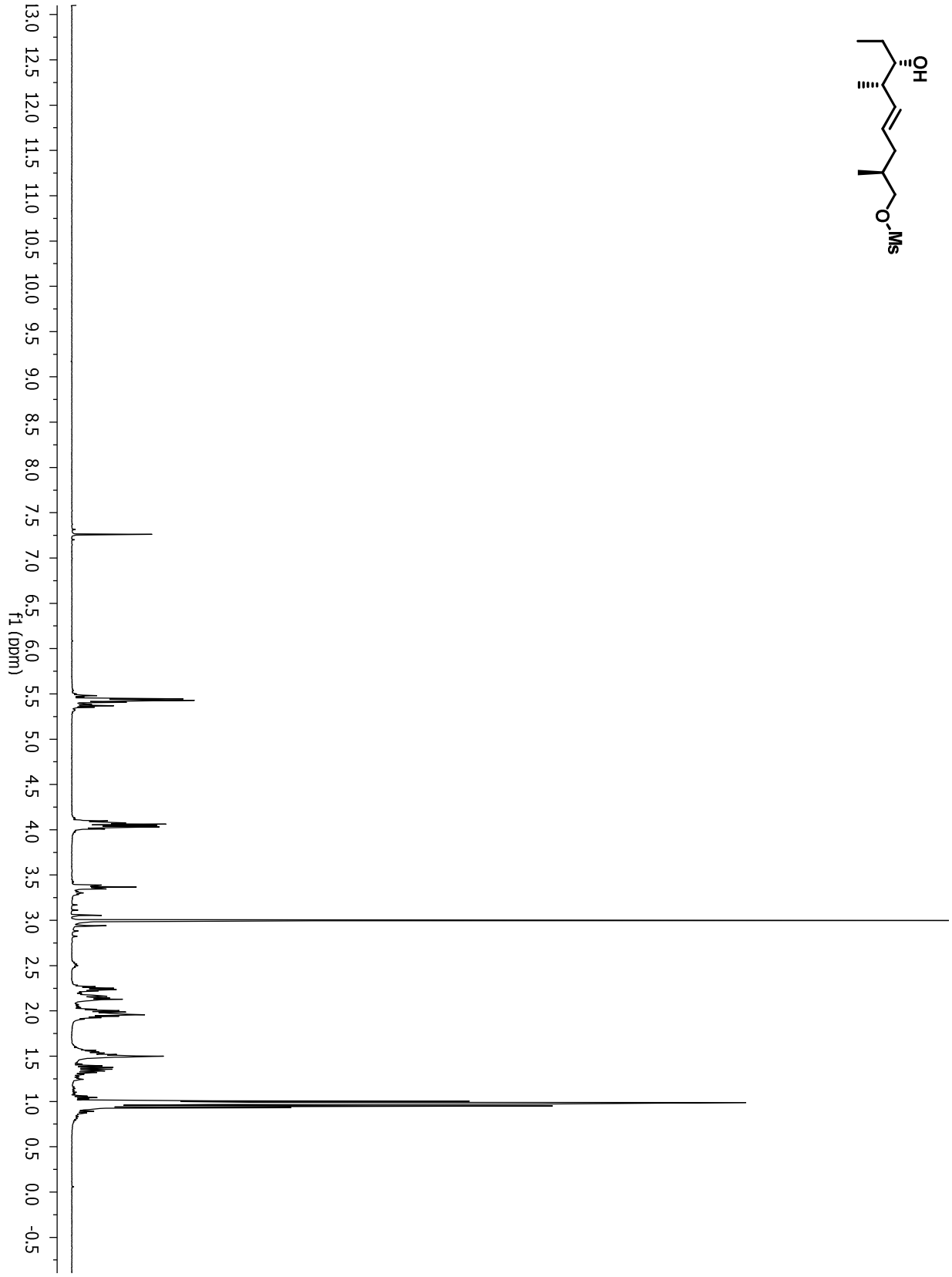


Figure 31. ^{13}C NMR Spectra of Olefin 41

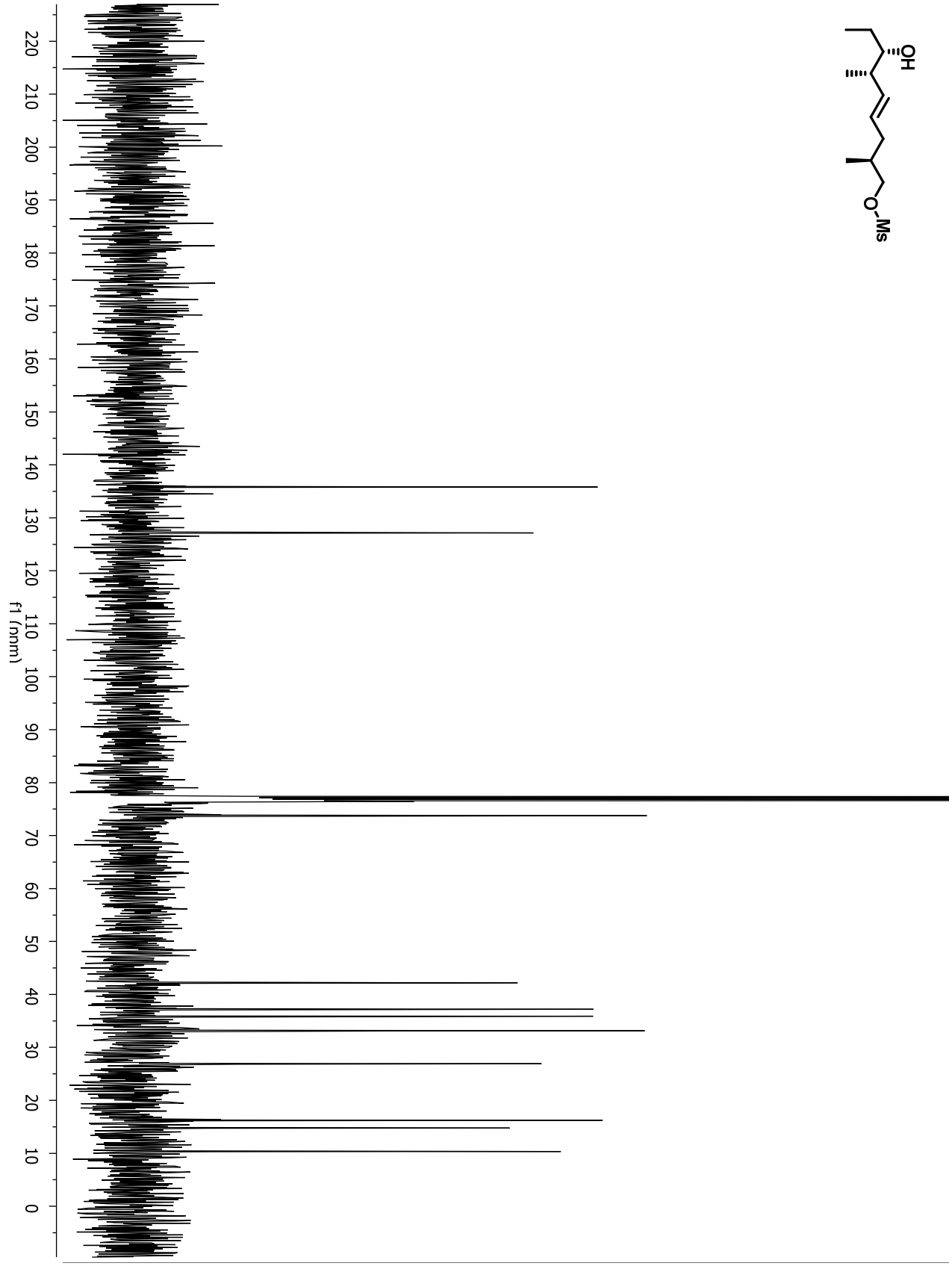


Figure 32. ^{1}**H NMR Spectra of TES Ether 21**

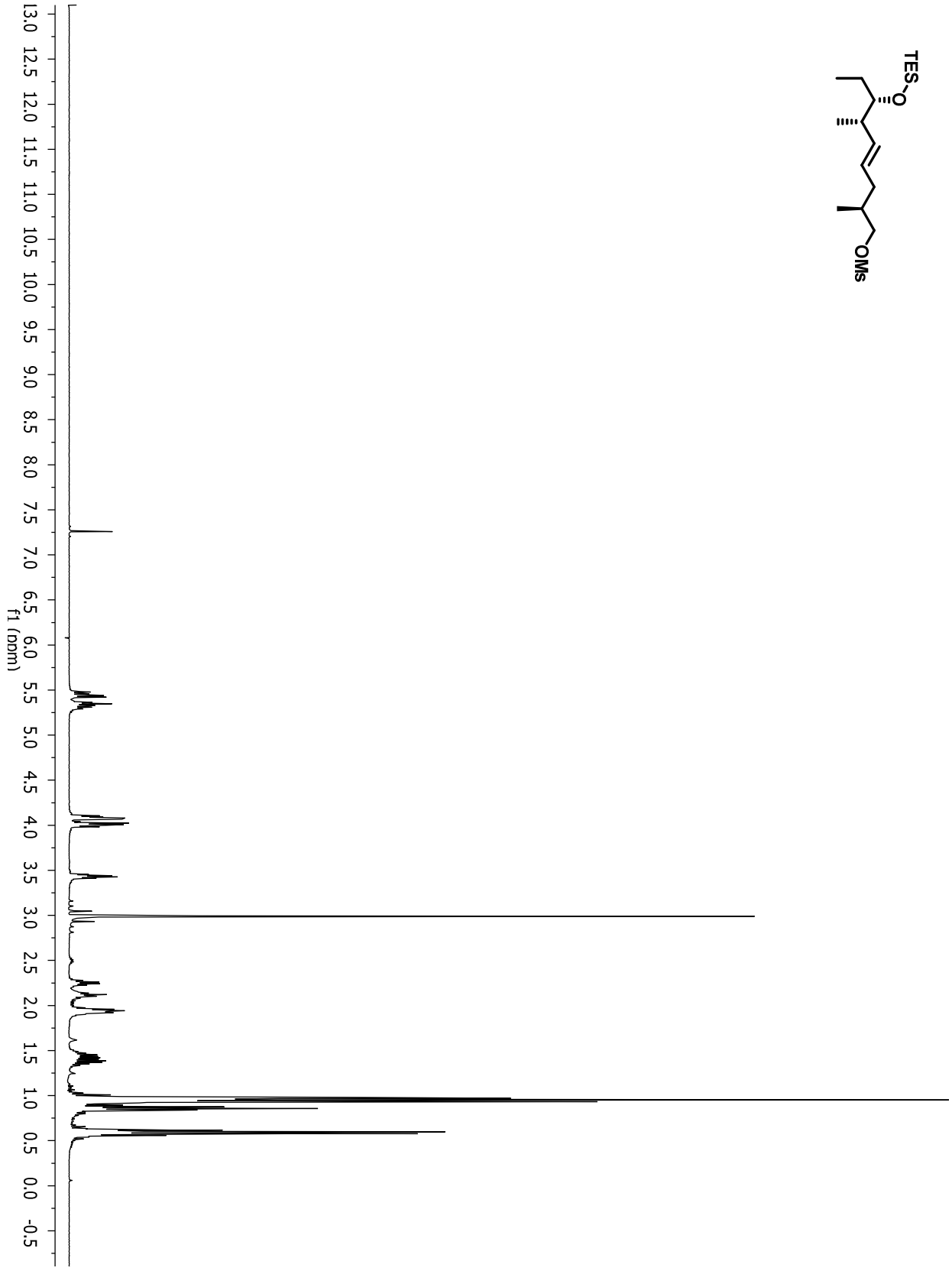


Figure 33. ^{13}C NMR Spectra of TES Ether 21

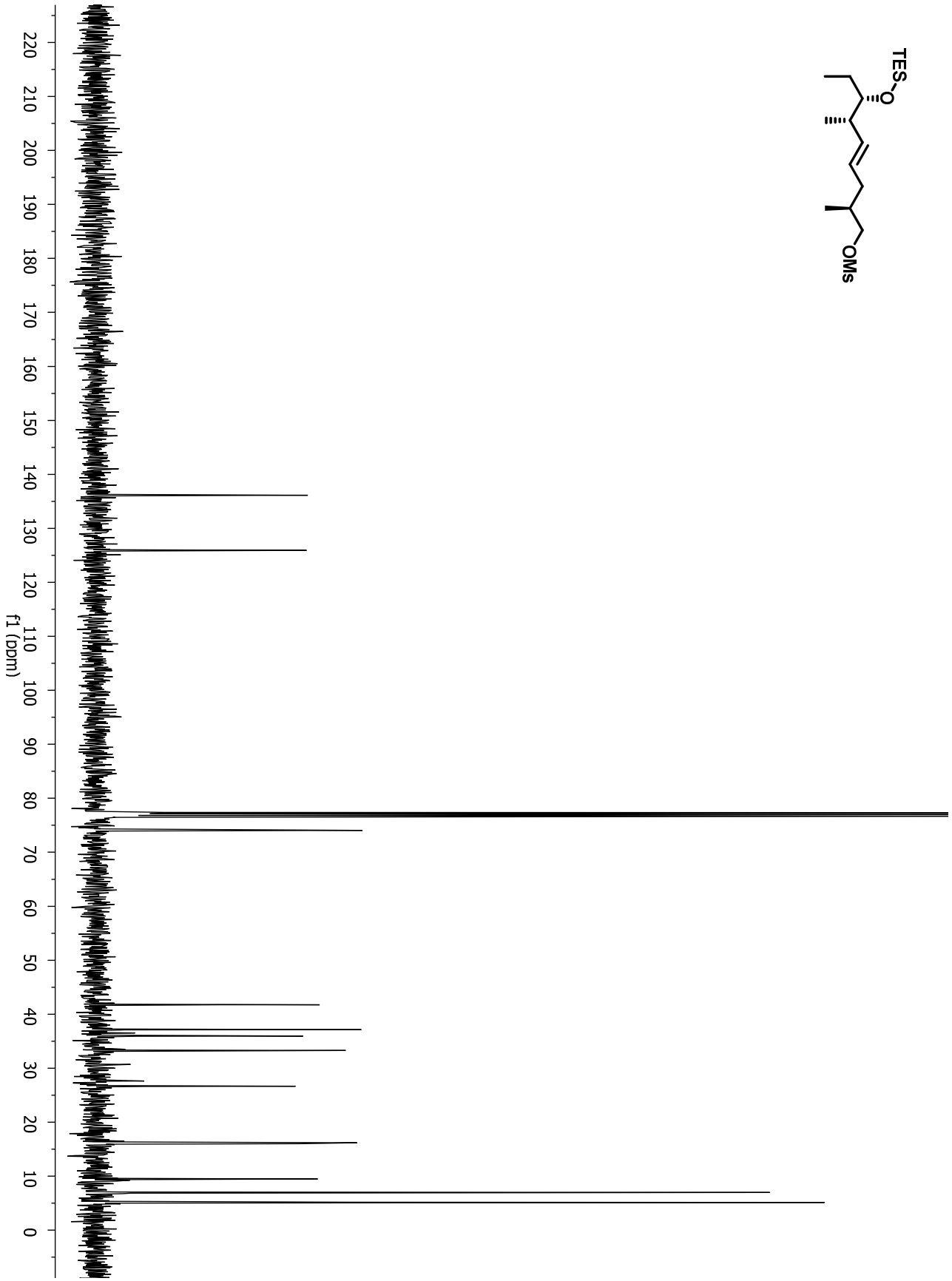


Figure 34. ^{1}H NMR Spectra of TES Ether 44

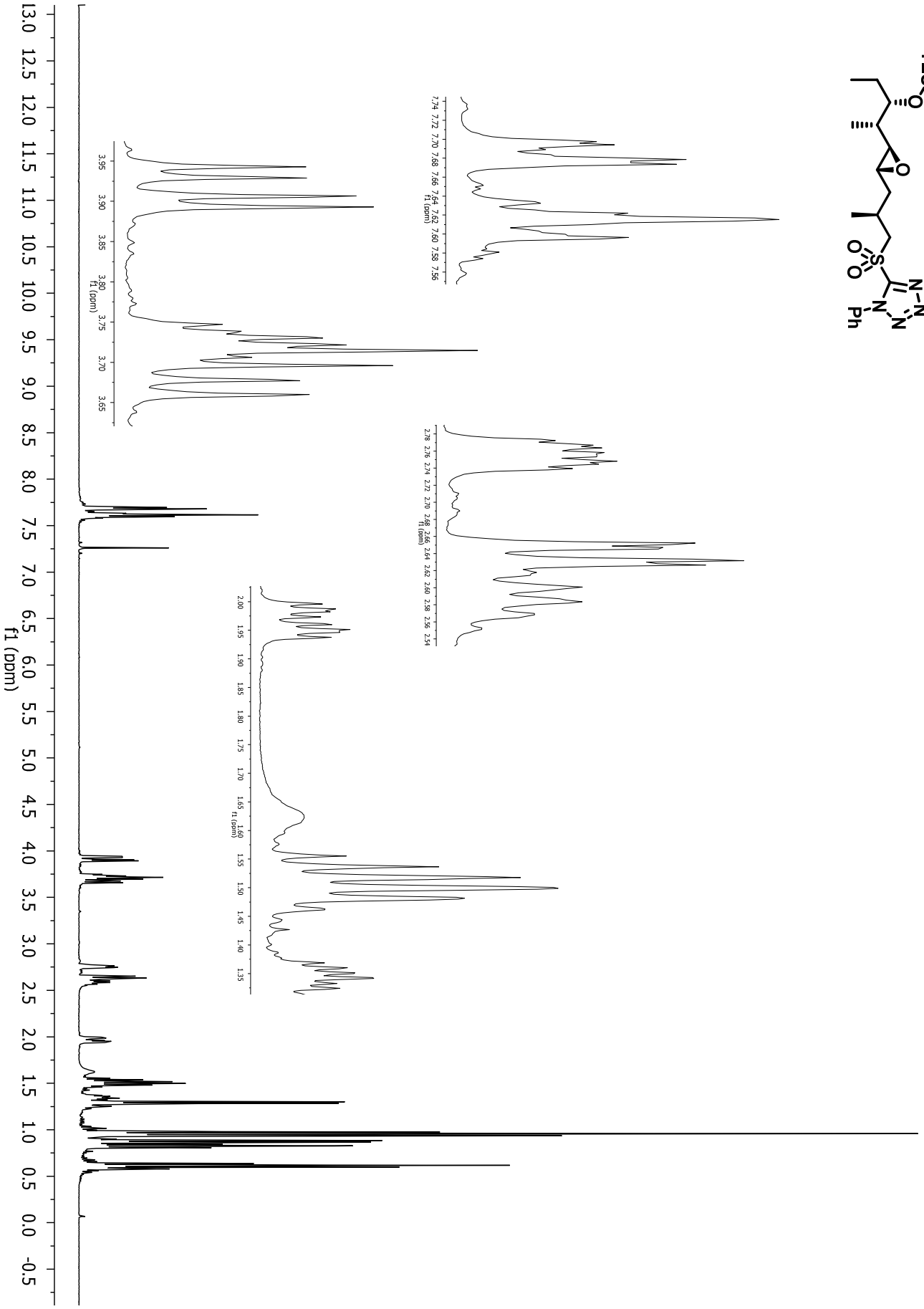
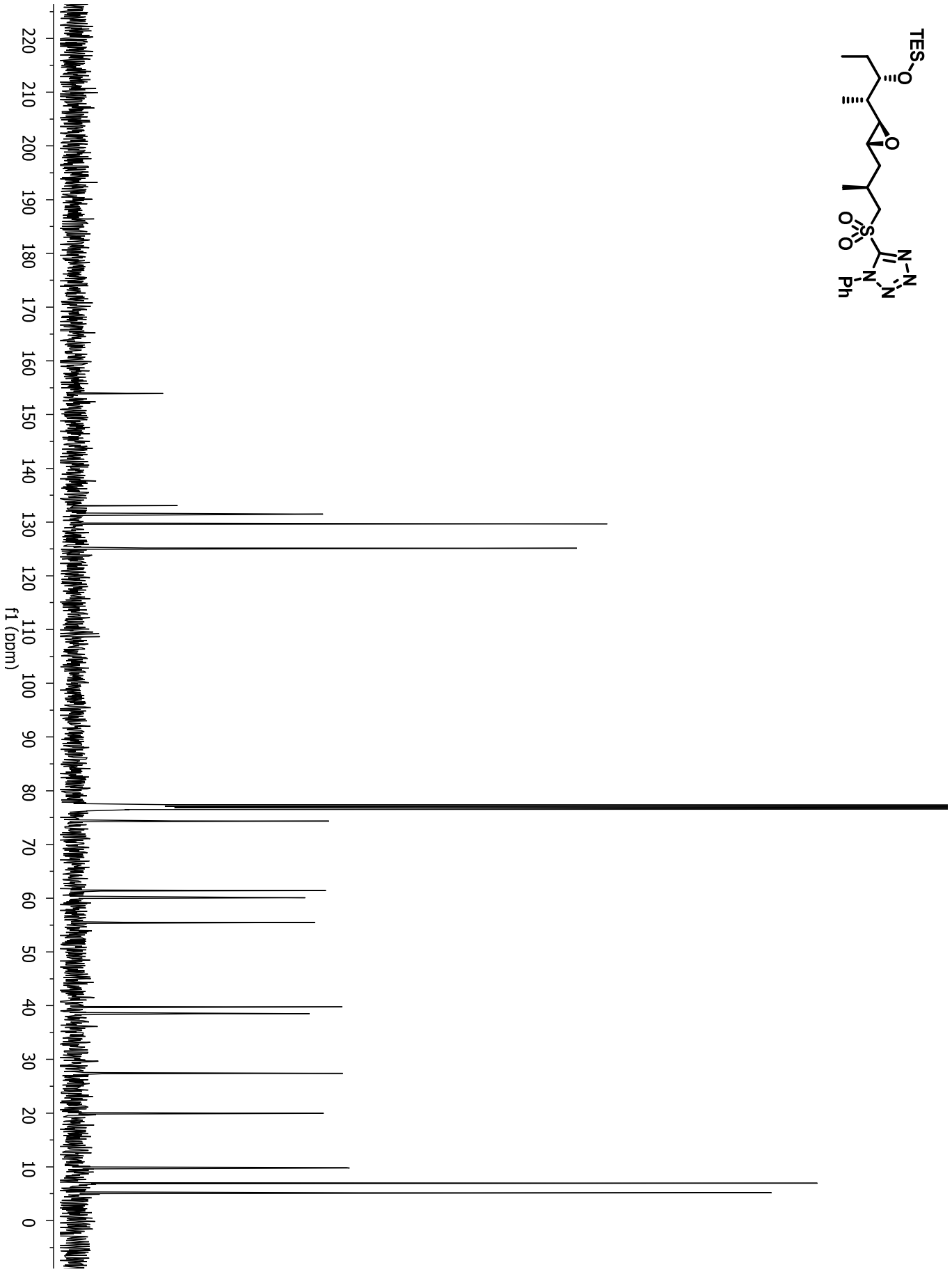


Figure 35. ^{13}C NMR Spectra of TES Ether 44



Final Steps

Figure 36. Comparison of ^{1}H NMR of Natural vs Synthetic Pladienolide B

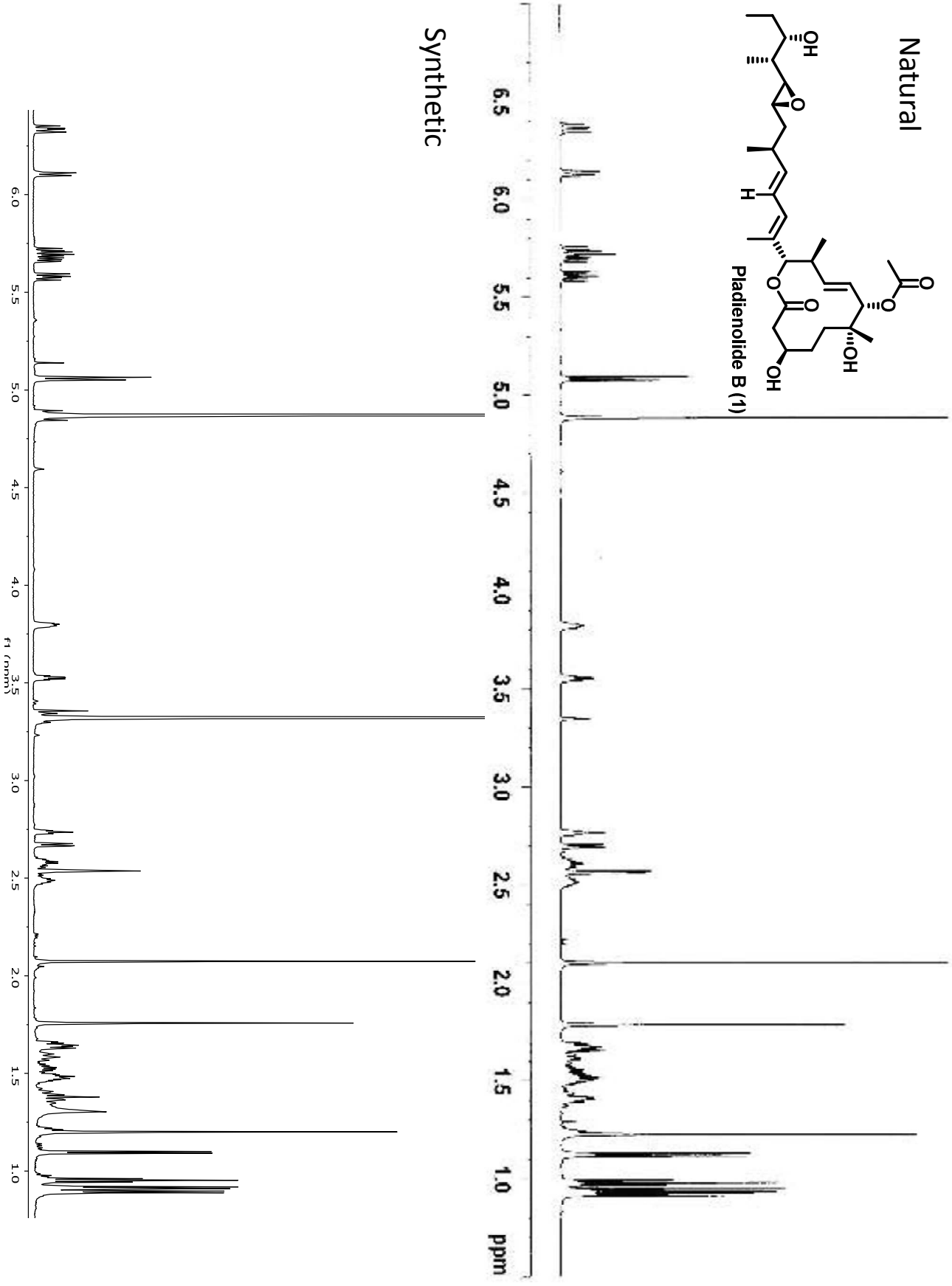
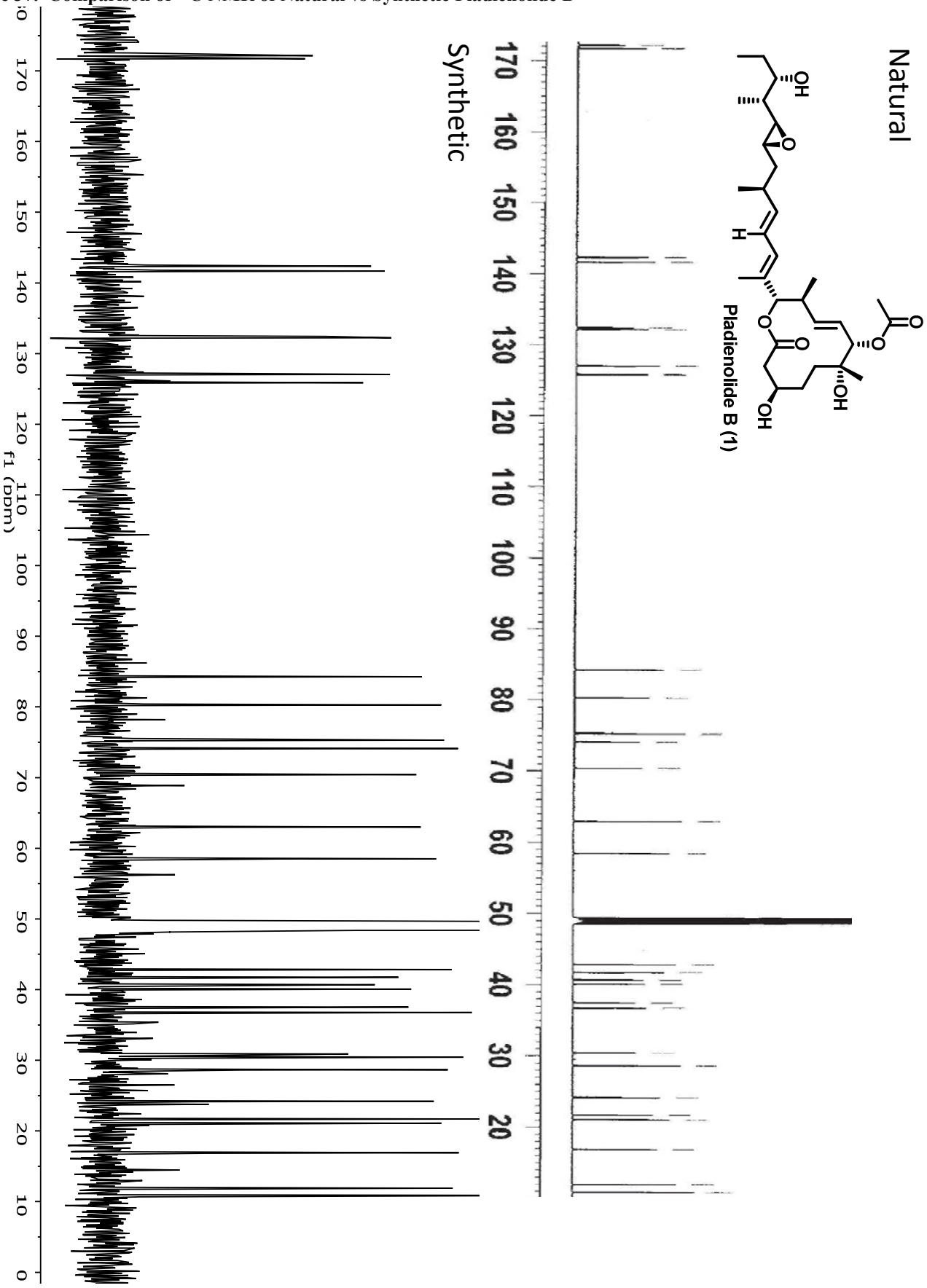


Figure 37. Comparison of ^{13}C NMR of Natural vs Synthetic Pladienolide B



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