Supporting Information

Title: L-Selectride-Mediated Highly Diastereoselective Asymmetric Reductive Aldol Reaction: Access to an Important Subunit for Bioactive Molecules

Authors: Arun K. Ghosh,* Jorden P. Kass, David D. Anderson, Xiaoming Xu, Christine A. Marian

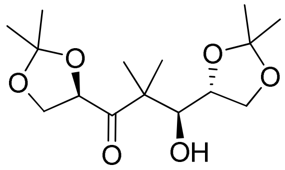
Departments of Chemistry and Med. Chemistry, Purdue University, West Lafayette, IN 47907

Table of Contents:

I. General Experimental Methods:

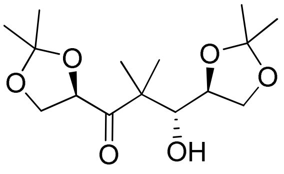
Chemicals and reagents were purchased from commercial suppliers and used without further purification. Anhydrous solvents were obtained as follows: pyridine and dichloromethane were distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium wire with benzophenone as 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, sept = septuplet. All coupling constants are measured in hertz. FTIR spectra were recorded on a Mattson Genesis II FT-IR spectrometer using a NaCl plate or on a Perkin Elmer Spectrum RX I spectrometer using a KBr pellot. 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. All chromatographic reagents used were HPLC grade.

II. Experimental Details



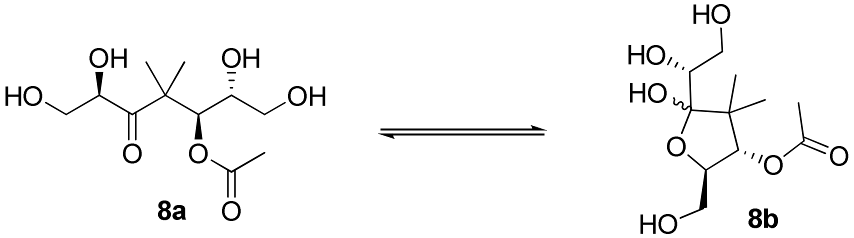
6

(*S*)-1,3-bis((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropan-1-one (6): Enone **5**[1] (100 mg, 0.59 mmol) was dissolved in Et_2O (20 mL) and cooled to -78 °C. L-selectride (0.59 mL, 1.0 M in THF, 0.59 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde **4**[2] (150 mg, 1.18 mmol) was dissolved in Et_2O (20 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine (10 mL) and dried with $MgSO_4$. The crude material was purified by silica chromatography (40:60 EtOAc:Hexane) to give 125 mg (70% yield) of product as a clear oil. TLC 50:50 EtOAc:Hexane R_f = 0.47 visualized with PMA. $[\alpha]_D^{23}$ +14.7 (*c* 0.54, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87 (t, *J* = 6.8 Hz, 1H), 4.15-4.00 (m, 5H), 3.86 (m, 1H), 2.59 (brs, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.0, 110.7, 109.0, 77.2, 76.5, 75.8, 66.8, 66.4, 50.2, 26.1, 25.7, 25.5, 25.2, 21.2, 19.4. FTIR (NaCl) ν_{max} = 3434, 2986, 2936, 1712, 1645, 1455, 1372, 1258, 1214, 1154, 1062, 937, 848 cm^{-1}. CI (+) LRMS *m/z* (relative intensity): 245 (100%), 285 (35%), 301 (3%). CI (+) HRMS (*m/z*): $[M-H_2O+H]^+$ calcd for $C_{15}H_{26}O_6$ 285.1702; found, 285.1706.



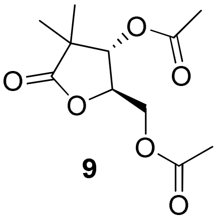
7

(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylpropan-1-one (7): Enone **5**[1] (100 mg, 0.59 mmol) was dissolved in diethyl ether (20 mL) and cooled to -78 °C. L-selectride (0.59 mL, 1.0 M in THF, 0.59 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde ent-**4**[3] (150 mg, 1.18 mmol) was dissolved in diethyl ether (20 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate. The organic layer was then washed with brine (10 mL) and dried with $MgSO_4$. The crude product (67% yield) was purified by silica chromatography (40:60 EtOAc:Hexane) to give 119 mg of product as a clear oil. TLC 50:50 EtOAc:Hexane $R_f = 0.47$ visualized with PMA. $[\alpha]_D^{23}$ +121.3 (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 4.87 (t, *J* = 7.2 Hz, 1H), 4.18 (t, *J* = 8.4 Hz, 1H), 4.03 (m, 2H), 3.96 (m, 2H), 3.88 (m, 1H), 2.49 (d, *J* = 5.6 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.5, 110.9, 109.1, 77.2, 76.5, 75.9, 67.2, 66.6, 50.9, 26.3, 25.7, 25.4, 25.3, 21.2, 19.6. FTIR (NaCl) ν_{max} = 3437, 2985, 2934, 2884, 1711, 1468, 1372, 1258, 1218, 1156, 1062, 937, 851, 773 cm^{-1}. CI (+) LRMS *m/z* (relative intensity): 245 (100%), 285 (27%), 301 (2%). CI (+) HRMS (*m/z*): $[M-H_2O+H]^+$ calcd for $C_{15}H_{26}O_6$ 285.1702; found, 285.1705.



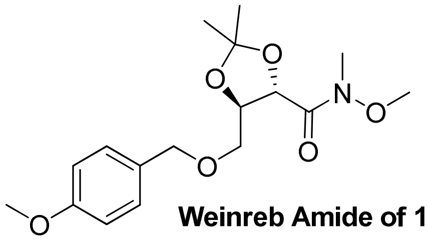
8a **8b**

(2*R*,3*S*,6*R*)-1,2,6,7-tetrahydroxy-4,4-dimethyl-5-oxoheptan-3-yl acetate (8): Aldol product **6** (70 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (1 mL). Acetic anhydride (66 µL, 0.70 mmol), triethyl amine (97 µL, 0.70 mmol), and 4-(dimethylamino)pyridine (3 mg, 0.023 mmol) were added. The mixture was stirred for 1 h. The reaction was diluted with CH_2Cl_2 (10 mL) washed with water (2 x 10 mL) and with brine (10 mL). The organic layer was dried over $MgSO_4$ and solvents removed under reduced pressure. The crude oil was purified by silica chromatography (30:70 EtOAc:Hexane) to give 66 mg (83% yield) of acylated **6**. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.52 (d, 1H), 4.83 (t, 1H), 4.15-3.96 (m, 4H), 2.01 (s, 3H), 1.48(s, 3H), 1.37(s, 3H), 1.31(s, 3H), 1.26(s, 3H), 1.23(s, 3H), 1.09(s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.0, 169.9, 110.6, 109.6, 77.2, 76.7, 74.5, 67.4, 66.0, 49.7, 25.8, 25.6, 25.5, 25.4, 23.2, 20.7, 17.6. Acylated **6** (66 mg) was then dissolved in acetic acid (2 mL, 40% in H_2O) and heated at 80 °C for 2 hr. The solvent was removed under reduced pressure followed by azeotropic removal of excess solvent with toluene and chloroform. This gave product **8** in 91% yield, which was used without further purification. $[\alpha]_D^{20}$ -11.5 (*c* 0.24, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.27 (d, 1H), 5.15 (br, 1H), 4.08-3.65 (m, 7H), 3.46 (br, 1H), 2.29 (br 1H), 2.10 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 107.3, 80.3, 78.0, 70.8, 63.8, 62.7, 48.3, 21.1, 20.9, 17.9. FTIR (NaCl) ν_{max} = 3393, 2976, 2941, 1731, 1643, 1470, 1372, 1245, 1136 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 286.99 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{20}O_7$ 287.1107; found, 287.1109.



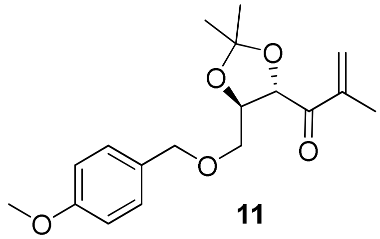
9

((2*R*,3*S*)-3-acetoxy-4,4-dimethyl-5-oxotetrahydrofuran-2-yl)methyl acetate (9): Alcohol **8** (20 mg, 0.075 mmol) was dissolved in pyridine (1 mL) and cooled to 0 °C. Acetic anhydride (14 µL, 0.15 mmol) was then added. This was allowed to warm to rt and stir for 18 h. The crude material was purified by silica chromatography (20:80 EtOAc:Hexane) give 12 mg (45% yield) of selectively acylated **8**. Acylated **8** (12 mg, 0.034 mmol) was dissolved in CH_2Cl_2 (1 mL). $NaIO_4$ (45 mg, 0.21 mmol) was added. The reaction was buffered with sat. $NaHCO_3$ (0.1 mL). The reaction stirred overnight at which time the starting material appeared consumed by TLC. The material was purified by silica chromatography (40:60 EtOAc:Hexane) to give 4 mg (50% yield) of lactone **9**. Alternatively, alcohol **26** (64 mg, 0.23 mmol) was dissolved into dichloromethane (2 mL). $NaIO_4$ (214 mg, 1.00 mmol) was added in one portion. Sat. $NaHCO_3$ (0.25 mL) was added to buffer the reaction. This was stirred overnight until consumption of starting material was seen by TLC. The acid was obtained in 99% yield (63mg) and was used without further purification. The crude acid (63 mg, 0.23 mmol) was then dissolved in acetic acid (2 mL, 40% in H_2O) and heated at 80°C for 2 h. Solvent was removed under reduced pressure followed by azeotropic removal of excess solvent with toluene and chloroform. This gave product **27** in 91% yield, which was used without further purification. Lactone **27** (43 mg, 0.21 mmol) was dissolved in CH_2Cl_2 (0.5 mL). Then acetic anhydride (60 µL, 0.64 mmol), triethyl amine (85 µL, 0.64 mmol), and 4-(dimethylamino)pyridine (2.4 mg, 0.02 mmol) were added. The mixture was stirred for 1 h. The reaction was then diluted with CH_2Cl_2 (10mL), washed with water (2 x 10 mL), and brine (10 mL). The organic layer was then dried on $MgSO_4$ and the solvent removed. The crude oil was purified by silica chromatography (30:70 EtOAc:Hexane) to give 36 mg (70% yield) of **9**. Spectroscopic data was consistent with previously reported results.[4] $[\alpha]_D^{20}$ +53.2 (*c* 0.42, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.10 (d, 1H), 4.0-4.5 (m, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 1.36 (s, 3H), 1.21 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.5, 170.3, 169.9, 77.7, 76.2, 62.8, 43.0, 23.8, 20.6, 20.5, 19.2 ppm. FTIR (NaCl) ν_{max} = 2960, 2925, 2854, 1783, 1733, 1639, 1459, 1372, 1220, 1127, 1149 cm^{-1}.



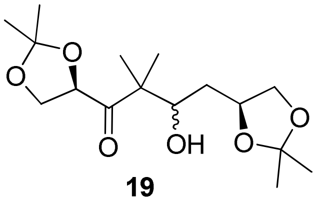
Weinreb Amide of 10

(4*S*,5*R*)-N-methoxy-5-((4-methoxybenzyloxy)methyl)-N,2,2-trimethyl-1,3-dioxolane-4-carboxamide (Weinreb Amide of 10): Under argon, combined **10**[5] (415 mg, 1.4 mmol), *N,O*-dimethylhydroxylamine hydrochloride (167 mg, 1.7 mmol), and triethylamine (250 µL, 1.7 mmol). Dissolved into dichloromethane (15 mL) and cooled to 0 °C. Dicyclohexylcarbodiimide (351 mg, 1.7 mmol) dissolved in dichloromethane (15 mL) was added dropwise. The reaction stirred for 1 h at rt. White solids were observed at the end of the reaction. The reaction was filtered over celite and solvents removed under reduced pressure to give a white solid. This was purified by silica chromatography (25:75 EtOAc:Hexane) to afford 344 mg (72.1% yield) of the Weinreb amide as a mixture of clear oil and white solids. TLC 40:60 EtOAc:Hexane R_f = 0.33 visualized by UV and with PMA. $[\alpha]_D^{23}$ -5.8 (*c* 1.09, MeOH). ^1H NMR (MeOD, 400 MHz) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.77 (br, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.43 (br, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 3.64 (dd, *J* = 2.8, 4 Hz, 2H), 3.19 (brs, 3H), 1.44 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (MeOD, 100 MHz) δ 172.1, 160.8, 131.4, 130.6, 114.8, 112.5, 79.5, 75.6, 74.1, 70.7, 62.2, 55.7, 32.7, 27.6, 26.7. FTIR (KBr) ν_{max} = 3448, 2990, 2936, 2852, 1654, 1628, 1578, 1509, 1459, 1382, 1303, 1249, 1214, 1173, 1088, 1035, 1000, 852, 825 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 362.11 (100%). ESI (+) HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{25}NO_6$ 362.1580; found, 362.1581.



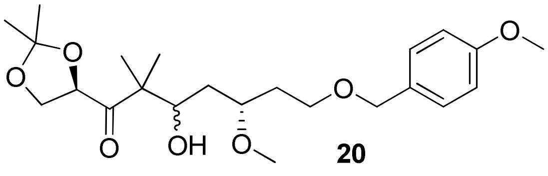
11

1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-one (11): Under argon, the Weinreb amide of **10** (226.2 mg, 0.67 mmol) was dissolved into THF and cooled to 0 °C. Isopropenyl magnesium bromide (6.7 mL, 3.35 mmol) was added dropwise and the reaction was refluxed at 60 °C for 2 h. The reaction was quenched with sat. NH_4Cl (5 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (5 mL) and dried over sodium sulfate. Solvents were removed under reduced pressure and the crude material purified by silica chromatography (15:85 EtOAc:Hexane) to give 191.1 mg (89.1% yield) of **11** as a clear oil. TLC 20:80 EtOAc:Hexane $R_f = 0.3$ visualized by UV or with PMA. $[\alpha]_D^{23}$ -17.1 (*c* 0.94, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 5.91 (q, *J* = 1.2 Hz, 1H), 4.85 (d, *J* = 6.8 Hz, 2H), 4.55 (d, *J* = 12 Hz, 1H), 4.50 (d, *J* = 11.2 Hz, 1H), 4.46 (m, 1H), 3.79 (s, 3H), 3.67 (dd, *J* = 3.6, 10.4 Hz, 1H), 3.59 (dd, *J* = 4.8, 10.8 Hz, 1H), 1.88 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2, 159.1, 142.8, 129.8, 129.3, 128.0, 113.7, 110.8, 77.8, 77.2, 73.1, 69.2, 55.2, 27.0, 26.2, 17.8. FTIR (NaCl) ν_{max} = 2984, 2922, 2859, 1681, 1613, 1513, 1455, 1372, 1302, 1246, 1213, 1171, 1082, 1035, 944, 848, 820 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 343.12 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{24}O_5$ 343.1521; found, 343.1520.



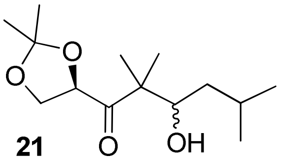
19

1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-dimethylbutan-1-one (19): Enone **5**[1] (45 mg, 0.26 mmol) was dissolved into Et_2O (8 mL) and cooled to -78 °C. L-selectride (0.26 mL, 1.0 M in THF, 0.26 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde **15**[6] (59.1 mg, 0.41 mmol) was dissolved in Et_2O (5 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O and extracted with ethyl acetate. The organic layer was then washed with brine and dried with $MgSO_4$. The crude was purified by silica chromatography (40:60 EtOAc:Hexane) to give 69 mg (83.9% yield) of **19** as a clear oil. Ratio of isomers was 42:58 based on isolated yield. For the minor isomer: TLC 40:60 EtOAc:Hexane $R_f = 0.44$ visualized with PMA. $[\alpha]_D^{23}$ -9.0 (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (t, *J* = 6.8 Hz, 1H), 4.32 (m, 1H), 4.19 (dd, *J* = 7.2, 8.4 Hz, 1H), 4.09 (dd, *J* = 6, 8.4 Hz, 1H), 4.05 (ddd, *J* = 1.6, 5.6, 10.8 Hz, 1H), 3.99 (dd, *J* = 6.8, 8.4 Hz, 1H), 3.60 (t, *J* = 7.2 Hz, 1H), 2.80 (d, *J* = 5.2 Hz, 1H), 1.69 (m, 1H), 1.56 (m, 1H), 1.48 (s, 3H), 1.41 (s, 6H), 1.35 (s, 3H), 1.19 (s, 3H), 1.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.2, 111.1, 108.6, 76.7, 73.9, 72.9, 69.5, 66.6, 51.6, 34.8, 26.9, 25.7, 25.6, 25.5, 21.6, 18.3. FTIR (NaCl) ν_{max} = 3114, 2988, 1652, 1373, 1251, 1216, 1156, 1065 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 339.08 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{28}O_6S$ 339.1784; found, 339.1788. For the major isomer: TLC 50:50 EtOAc:Hexane $R_f = 0.46$ visualized with PMA. $[\alpha]_D^{23}$ +22.3 (*c* 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.95 (t, *J* = 7.2 Hz, 1H), 4.30 (m, 1H), 4.22 (dd, *J* = 6.8 Hz, 8.4 Hz, 1H), 4.12 (m, 2H), 3.96 (dd, *J* = 6.8, 7.2 Hz, 1H), 3.58 (dd, *J* = 7.2, 8 Hz, 1H), 3.50 (d, *J* = 1.6 Hz, 1H), 1.68 (ddd, *J* = 1.2, 3.2, 14 Hz, 1H), 1.53 (m, 1H), 1.45 (s, 3H), 1.41 (brs, 6H), 1.36 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.6, 110.8, 109.7, 76.5, 75.5, 69.7, 67.3, 51.5, 34.9, 26.9, 25.7, 25.7, 20.7, 18.6. FTIR (NaCl) ν_{max} = 3406, 2985, 2958, 2934, 1653, 1374, 1258, 1216, 1155, 1065 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 339.08 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{28}O_6S$ 339.1784; found, 339.1788.



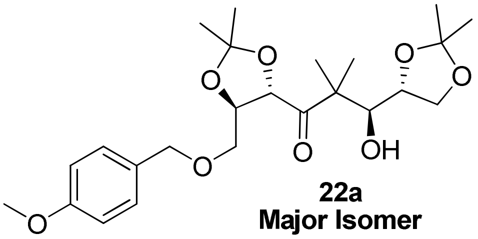
20

(*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-5-methoxy-7-(4-methoxybenzyloxy)-2,2-dimethylheptan-1-one (20): Enone **5**[1] (35 mg, 0.21 mmol) was dissolved into Et$_2$O (5 mL) and cooled to -78 ^{o}C. L-selectride (0.23 mL, 1.0 M in THF, 0.23 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde **16** (75 mg, 0.3 mmol) was dissolved in Et$_2$O (5 mL) and cooled to -78 ^{o}C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH$_4$Cl. The reaction mixture was diluted with H$_2$O and extracted with ethyl acetate. The organic layer was then washed with brine and dried with MgSO$_4$. The crude material was purified by silica chromatography (40:60 EtOAc:Hexane) to give 55 mg (63% yield) of **20** as a clear oil. TLC 50:50 EtOAc:Hexane R$_f$ = 0.52 visualized by UV or with PMA. $[\alpha]_D^{23}$ +13.1 (*c* 0.47, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.23 (d, *J* = 7.5 Hz, 4H), 6.83 (d, *J* = 9 Hz, 4H), 4.76 (t, *J* = 7.5 Hz, 1H), 4.72 (t, *J* = 7.5 Hz, 1H), 4.19 (m, 4H), 3.95 (t, *J* = 8.5 Hz, 2H), 3.87 (m, 1H), 3.72 (m, 2H), 3.65 (m, 1H), 3.56 (m, 1H), 3.52 (s, 6H), 3.38 (m, 1H), 3.30-3.18 (m, 5H), 3.03 (s, 7H), 1.60-1.44 (m, 3H), 1.35 (m, 2H), 1.23 (m, 1H), 1.14 (m, 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.95 (s, 6H), 0.67 (s, 3H), 0.64 (s, 3H), 0.63 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ 212.2, 211.8, 159.1, 130.1, 129.3, 129.2, 113.7, 110.7, 110.7, 80.2, 77.5, 76.9, 76.6, 72.7, 72.5, 67.3, 66.6, 66.2, 66.0, 57.2, 56.5, 55.2, 51.4, 51.1, 35.3, 33.6, 33.3, 33.0, 25.7, 21.3, 20.8, 18.3. FTIR (NaCl) ν_{max} = 3433, 2984, 2936, 2876, 1643, 1513, 1465, 1372, 1302, 1248, 1173, 1154, 1083, 1033, 936 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 447.14 (100%). ESI (+) HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{23}H_{36}O_7$ 447.2359; found, 447.2355. Ratio of isomers was 42:58 by HPLC: Zorbax XDB-C$_{18}$ (150 x 4.6 mm, 5 micron); Flow = 1.5 mL/min; λ = 215 nm; Gradient T = 0-1 min (25:75 MeCN:H$_2$O); T = 15-17 min (90:10 MeCN:H$_2$O), T = 17.1-20 min (25:75 MeCN:H$_2$O); Major Isomer R$_t$ = 8.5 min; Minor Isomer R$_t$ = 8.0; Ref. phenol R$_t$ = 2.7 min; toluene R$_t$ = 9.1 min; BHT R$_t$ = 15.6 min.



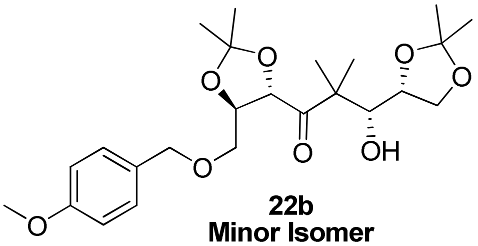
21

(*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2,5-trimethylhexan-1-one (21): Enone **5**[1] (54 mg, 0.32 mmol) was dissolved in Et$_2$O (5 mL) and cooled to -78 ^{o}C. L-selectride (0.32 mL, 1.0 M in THF, 0.32 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Isovaleraldehyde **17** (51 µL, 0.48 mmol) was dissolved in Et$_2$O (5 mL) and cooled to -78 ^{o}C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH$_4$Cl. The reaction mixture was diluted with H$_2$O and extracted with ethyl acetate. The organic layer was then washed with brine and dried with MgSO$_4$. The crude material was purified by silica chromatography (25:75 EtOAc:Hexane) to give 35 mg (42% yield) of **21** as a clear oil. TLC 40:60 EtOAc:Hexane R$_f$ = 0.40 visualized with PMA. $[\alpha]_D^{23}$ +7.3 (*c* 0.50, CHCl$_3$). 50:50 Mix of isomers by NMR. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.89-4.82 (m, 2H), 4.25-4.17 (m, 2H), 4.02-3.98 (m, 1H), 3.95-3.91 (m, 1H), 3.90-3.84 (m, 2H), 2.31 (d, *J* = 2.31, 1H), 2.15 (d, *J* = 2.15, 1H), 1.82 (m, 3H), 1.49 (s, 6H), 1.41 (s, 6H), 1.30 (m, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz) δ 212.9, 212.6, 111.0, 110.9, 74.1, 67.1, 66.5, 51.9, 51.7, 40.6, 40.4, 25.7, 25.6, 25.5, 24.7, 24.7, 24.0, 21.8, 21.3, 21.0, 18.6, 18.4. FTIR (NaCl) ν_{max} = 3108, 1652, 1260, 1217, 1155, 1067 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 281.03 (100%). ESI (+) HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{14}H_{26}O_4$ 281.1729; found, 281.1731.



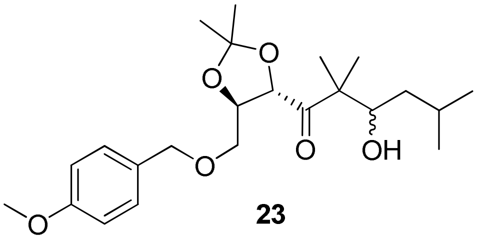
22a
Major Isomer

(*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethylpropan-1-one (22a): Under argon, enone **11** (261 mg, 0.81 mmol) was dissolved into Et_2O (80 mL) and cooled to -78 °C. L-selectride (810 µL, 1 M in THF, 0.81 mmol) was added and the reaction allowed to stir for 10 min at which time TLC indicated all of the enone **11** had been converted to enolate. Aldehyde **4**[2] (377 mg, 2.9 mmol) in Et_2O (20 mL) at -78 °C was added via a cannula. The reaction was allowed to stir for 1 h and was subsequently quenched with several drops of sat. NH_4Cl. The mixture was allowed to warm to rt and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and the solvents were removed under reduced pressure. The crude material was purified by silica chromatography (30:70 EtOAc:Hexane) to give 271 mg (73.9% yield) of **22** as a clear oil. TLC 50:50 EtOAc:Hexane R_f = 0.43 visualized by UV or with PMA. $[\alpha]_D^{23}$ -8.9 (*c* 0.09 $CHCl_3$). ^{1}H NMR ($CDCl_3$, 800 MHz) δ 7.25 (m, 2H), 7.24 (m, 2H), 6.87 (m, 2H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.52 (s, 2H), 4.46 (m, 1H), 4.09 (m, 1H), 4.05 (q, *J* = 6.4 Hz, 1H), 4.00 (dd, *J* = 6.4, 8 Hz, 1H), 3.82 (dd, *J* = 6.4, 8Hz, 1H), 3.80 (s, 3H), 3.64 (dd, *J* = 4, 10.4 Hz, 1H), 3.60 (dd, *J* = 5.6, 10.4 Hz, 1H), 2.61 (br, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.3, 159.1, 129.4, 129.3, 113.6, 110.8, 108.8, 78.0, 76.9, 75.7, 75.4, 73.0, 69.7, 66.9, 54.9, 51.2, 27.0, 26.1, 26.0, 25.0, 20.5, 19.0. FTIR (NaCl) ν_{max} = 3467, 2965, 2935, 2873, 2334, 1706, 1613, 1514, 1463, 1372, 1249, 1214, 1162, 1302, 1068, 1037, 848, 821, 772 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 475.22 (100%). ESI (+) HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{24}H_{36}O_8$ 475.2308; found, 475.2305. Diastereomer (**22b**) content was determined to be 0.9% by HPLC: Zorbax XDB-C_{18} (150 x 4.6 mm, 5 micron); Flow = 1.5 mL/min; λ = 215 nm; Gradient T = 0-1 min (25:75 MeCN:H_2O); T = 15-17 min (90:10 MeCN:H_2O), T = 17.1-20 min (25:75 MeCN:H_2O); **22a** R_t = 9.8 min; **22b** R_t = 10.6 min.



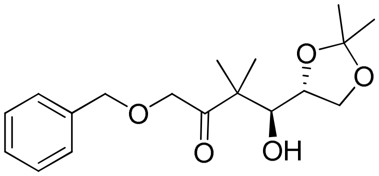
22b
Minor Isomer

(*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethylpropan-1-one (22b): Under argon, enone **11** (41.6 mg, 0.12 mmol) was dissolved into Et_2O (10 mL) and cooled to -78 °C. L-selectride (120 µL, 1 M in THF, 0.12 mmol) was added until HPLC analysis indicated > 98% conversion to the enolate. The reaction was allowed to warm to rt at which time aldehyde **4**[2] (35.8 mg, 0.275 mmol) in Et_2O (8 mL) was added via a cannula. The reaction was complete after 30 min by HPLC and was quenched with several drops of sat. NH_4Cl. HPLC analysis of the crude material showed diastereomer (**22b**) levels were elevated (7.7% by HPLC). Purification of the crude material by silica chromatography (30:70 EtOAc:Hexane) gave 0.9 mg of **22b** as a clear oil. TLC 50:50 EtOAc:Hexane R_f = 0.45 visualized by UV or with PMA. $[\alpha]_D^{23}$ +1.6 (*c* 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 800 MHz) δ 7.26 (m, 2H), 6.87 (dt, *J* = 2.4, 8.8 Hz, 2H), 4.53 (m, 3H), 4.49 (m, 1H), 4.17 (ddd, *J* = 2.4, 6.4, 8 Hz, 1H), 4.00 (dd, *J* = 7.2, 8 Hz, 1H), 3.85 (t, *J* = 8 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, *J* = 2.4, 9.6 Hz, 1H), 3.68 (dd, *J* = 3.2, 10.4 Hz, 1H), 3.57 (dd, *J* = 4.8, 10.4 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 211.9, 159.2, 130.1, 129.3, 113.8, 110.8, 109.5, 78.8, 75.3, 74.5, 73.2, 69.7, 66.8, 55.3, 51.3, 27.1, 26.3, 26.1, 25.7, 22.3, 20.58. FTIR (NaCl) ν_{max} = 1615, 1515, 1457, 1372, 1301, 1249, 1215, 1170, 1066, 1036, 850 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 475.14 (100%). ESI (+) HRMS (*m/z*): [M+Na]$^+$ calcd for $C_{24}H_{36}O_8$ 475.2308; found, 475.2302.



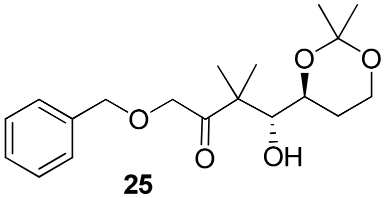
23

3-hydroxy-1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,5-trimethylhexan-1-one (23): Under argon, enone **11** (85 mg, 0.26 mmol) was dissolved into Et_2O (10 mL) and cooled to -78 °C. L-selectride (260 µL, 1 M in THF, 0.26 mmol) was added and the reaction stirred for 10 min allow for the formation of the enolate. Isovaleraldehyde **17** (33.4 mg, 0.39 mmol) in Et_2O (5 mL) was added via a cannula. The reaction was stirred for 1 h, quenched with sat. NH_4Cl, and extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, and solvents removed under reduced pressure. The crude material was purified by silica chromatography (10:90 EtOAc:Hexane) to give 53 mg (50% yield) of **23** as a clear oil. TLC 20:80 EtOAc:Hexane $R_f = 0.4$ visualized by UV. $[\alpha]_D^{23}$ -16.7 (*c* 0.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 800 MHz) δ 7.24 (m, 2H), 6.87 (m, 2H), 4.60 (d, *J* = 7.2 Hz, 1H), 4.54-4.47 (m, 7H), 4.40 (m, 1H), 3.90-3.83 (m, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 3.68-3.59 (m, 4H), 2.44 (br, 1H), 2.40 (br, 1H), 1.80 (m, 1H), 1.75 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.43 (s, 3H), 1.28 (s, 3H), 1.27 (m, 2H), 1.15 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 1.11 (m, 2H), 0.93 (d, *J* = 6.4 Hz, 1H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 212.2, 212.1, 159.3, 159.3, 129.8, 129.5, 129.4, 113.8, 113.7, 111.1, 111.0, 78.0, 77.9, 77.5, 74.0, 73.4, 73.3, 73.2, 69.7, 69.5, 55.2, 53.0, 52.8, 40.5, 40.4, 27.1, 27.0, 26.3, 24.7, 24.7, 24.0, 21.3, 20.8, 18.2, 18.1. FTIR (NaCl) ν_{max} = 3501, 2954, 2935, 2870, 1706, 1613, 1514, 1466, 1382, 1370, 1302, 1249, 1216, 1170, 1076, 1035, 986, 851, 821cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 431.09 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{36}O_6$ 431.2410; found, 431.2409. Ratio of isomers was 38:62 by HPLC; Zorbax XDB-C_{18} (150 x 4.6 mm, 5 micron) coupled to Zorbax Rx-C_{18} (250 x 4.6 mm, 5 micron); Flow = 1.25 mL/min; λ = 215 nm; Isocratic 60:40 MeCN:H_2O; Minor Isomer R_t = 23.4 min; Major Isomer R_t = 24.7 min.



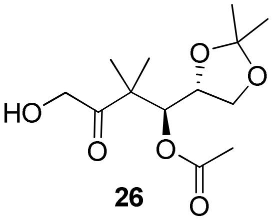
24

(*S*)-1-(benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-3,3-dimethylbutan-2-one (24): Enone **13**[1] (850 mg, 4.47 mmol) was dissolved in Et_2O (50 mL) and cooled to -78 °C. L-selectride (4.47 mL, 1.0 M in Et_2O, 4.47 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde **4**[2] (870 mg, 6.71 mmol) was dissolved in Et_2O (50 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 h and was then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine (10 mL) and dried with $MgSO_4$. The crude was purified by silica chromatography (40:60 EtOAc:Hexane) to give 1.036 g (72%) of **24** as an oil. TLC 60:40 EtOAc:Hexane $R_f = 0.64$ visualized by UV and PMA. $[\alpha]_D^{23}$ +9.0 (*c* 0.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.26 (m, 5H), 4.59 (s, 2H), 4.42 (d, *J* = 17.6 Hz, 1H), 4.32 (d, *J* = 17.6 Hz, 1H), 4.04 (m, 2H), 3.86 (m, 2H), 2.5 (d, *J* 5.2 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.5. 137.3. 128.4. 127.9. 109.0. 77.1. 75.9. 73.1. 72.1. 66.9. 49.5. 26.2. 25.3. 20.7. 20.6. FTIR (NaCl) ν_{max} = 3468, 2984, 2934, 2879, 1714, 1455, 1372, 1257, 1213, 1152, 1062, 850, 739, 699 cm^{-1}. CI (+) LRMS *m/z* (relative intensity): 131.1 (100%), 265.2 (47%), 305.2 (10%), 321.1 (0.9%). CI (+) HRMS (*m/z*): $[M+H-H_2O]^+$ calcd for $C_{18}H_{26}O_5$ 305.1753; found, 305.1756.



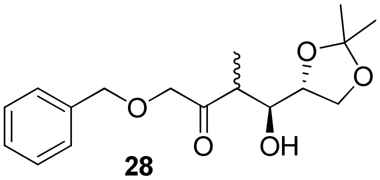
25

(*S*)-1-(benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-4-hydroxy-3,3-dimethylbutan-2-one (25): Enone **13**[1] (42 mg, 0.22 mmol) was dissolved into Et_2O (10 mL) and cooled to -78 °C. L-selectride (0.22 mL, 1.0 M in Et_2O, 0.22 mmol) was then added slowly. This was stirred 10 min to generate the enolate. Aldehyde **18**[7] (70 mg, 0.49 mmol) was dissolved in diethyl ether (10 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. The reaction stirred for 1 hr and was then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate. The organic layer was then washed with brine (10 mL) and dried with $MgSO_4$. The crude material was purified by silica chromatography (20:80→60:40 EtOAc:Hexane) to give 48 mg (65% yield) of **25** as an oil. TLC 60:40 EtOAc:Hexane R_f = 0.35 visualized by UV or with PMA. $[\alpha]_D^{23}$ +2.1 (*c* 0.42, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.27 (m, 5H), 4.61 (d, *J* = 12 Hz, 1H), 4.57 (d, *J* = 12 Hz, 1H), 4.35 (d, *J* = 16.8 Hz, 1H), 4.29 (d, *J* = 16.8 Hz, 1H), 3.96-3.69 (m, 4H), 2.19 (d, *J* = 4.8 Hz, 1H), 1.65 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.2, 137.5, 128.4, 128.0, 127.9, 98.3, 78.4, 73.3, 72.0, 69.8, 59.9, 49.5, 29.5, 28.7, 22.4, 18.8, 18.8. FTIR (NaCl) ν_{max} = 3429, 2923, 2874, 2965, 1712, 1453, 1382, 1372, 1273, 1237, 1200, 1086, 1050, 969, 853, 749, 699 cm^{-1}. HPLC Zorbax XDB-C_{18} (150 x 4.6 mm, 5 micron); Flow = 1.5 mL/min; λ = 215 nm; Gradient T = 0-1 min (25:75 MeCN:H_2O); T = 15-17 min (90:10 MeCN:H_2O), T = 17.1-20 min (25:75 MeCN:H_2O); R_t = 5.6 min; Ref. phenol R_t = 2.3 min; toluene R_t = 8.1 min; BHT R_t = 15.3 min.



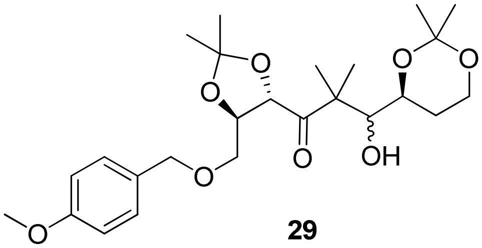
26

(*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-2,2-dimethyl-3-oxobutyl acetate (26): Aldol product **24** (270 mg, 0.83 mmol) was dissolved in dichloromethane (2 mL). Acetic anhydride (236 µL, 2.50 mmol), triethyl amine (348 µL, 2.50 mmol), and 4-(dimethylamino)pyridine (10 mg, 0.083 mmol) were added. The mixture was stirred for 1 hr. The reaction was then diluted with CH_2Cl_2 (10 mL), washed with water (2 x 10 mL), and then with brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude oil was purified by silica chromatography (30:70 EtOAc:Hexane) to give 263 mg of acylated product. Yield = 87%. The acylated product (87 mg, 0.24 mmol) was dissolved in ethyl acetate (5 mL) followed by addition of 10% Pd-C (5 mg). The flask was purged with H_2 and kept at balloon pressure for 24 hrs. The reaction mixture was then filtered through celite and washed with ethyl acetate (15 mL). The solvent was remove under reduced pressure. The crude material was purified by silica chromatography (40:60 EtOAc:Hexane) to give 64 mg (98% yield) of **26**. $[\alpha]_D^{23}$ -10.0 (*c* 0.20, $CHCl_3$), ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (d, 1H), 4.47 (dd, 2H), 4.02 (m, 2H), 3.76 (m, 1H), 3.21 (t, 1H), 2.09 (s, 3H), 1.28 (s, 3H), 1.27 (s, 6H), 1.09 (s, 3H). ^{13}C NMR($CDCl_3$, 125MHz) δ 212.0, 169.8, 110.0, 77.3, 74.5, 67.6, 65.1, 48.3, 25.5, 25.3, 23.5, 20.7, 17.0. FTIR (NaCl) ν_{max} = 3477, 2987, 2936, 1744, 1650, 1372, 1227, 1155 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 296.88 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{22}O_6$ 297.1314; found, 297.1317.



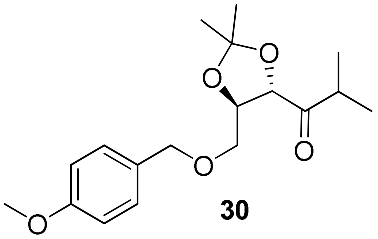
28

(*S*)-1-(benzyloxy)-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxy-3-methylbutan-2-one (28): Enone **14**[8] (53 mg, 0.30 mmol) was dissolved into Et_2O (8 mL) and THF (2 mL) and cooled to -78 °C. L-selectride (0.30 mL, 1.0 M in THF, 0.30 mmol) was added slowly. This was stirred 10 min to generate the enolate. Aldehyde **4**[2] (60 mg, 0.46 mmol) was dissolved into Et_2O (10 mL) and cooled to -78 °C. The aldehyde was added to the enolate via cannula over 5 min. This was stirred for 1 h then quenched with sat. NH_4Cl. The reaction mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine (10 mL) and dried with $MgSO_4$. The crude was purified by silica chromatography (40:60 EtOAc:Hexane). Little product was obtained.



29

3-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-3-hydroxy-1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethylpropan-1-one (29): Under argon, enone **11** (124 mg, 0.39 mmol) was dissolved into Et_2O (20 mL) and cooled to -78 °C. L-selectride (380 µL, 1 M in THF, 0.38 mmol) was added and the reaction was stirred for 10 min at which time TLC indicated all of the enone **11** had been converted to enolate. Aldehyde **18**[7] (110 mg, 0.76 mmol) in Et_2O (10 mL) at -78 °C was added via a cannula. The reaction was stirred for 1 h and subsequently quenched with sat. NH_4Cl. The mixture was allowed to warm to rt and then extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, and solvents removed under reduced pressure. The crude material was purified by silica chromatography (10:90 EtOAc:Hexane) to give two distinct isomers (4:1 by isolated yield) as clear oils. Overall Yield = 64%. Major isomer (92 mg, 0.20 mmol): TLC 50:50 EtOAc:Hexane $R_f = 0.40$ visualized by UV or with PMA. $[\alpha]_D^{23}$ +2.0 (*c* 1.78, $CHCl_3$). ^1H NMR ($CDCl_3$, 800 MHz) δ 7.25 (m, 2H), 6.85 (m, 2H), 4.58 (d, *J* = 8 Hz, 1H), 4.53 (d, *J* = 12 Hz, 1H), 4.51 (d, *J* = 12 Hz, 1H), 4.34 (m, 1H), 4.12 (d, *J* = 8.4 Hz, 1H), 3.94 (dt, *J* = 12, 2.8 Hz, 1H), 3.86 (ddd, *J* = 1.6, 5.6, 12 Hz, 1H), 3.79 (s, 3H), 3.77-3.72 (m, 2H), 3.57 (dd, *J* = 5.6, 10.4 Hz, 1H), 2.10 (brs, 1H), 1.74, (m, 1H), 1.64 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.3, 159.1, 130.1, 129.3, 113.7, 110.4, 98.3, 79.5, 78.0, 76.4, 73.2, 70.2, 69.8, 60.1, 55.2, 51.9, 29.4, 29.3, 26.9, 26.4, 21.0, 18.6, 18.4. FTIR (NaCl) ν_{max} = 3478, 2988, 2925, 2872, 1723, 1710, 1694, 1613, 1586, 1514, 1463, 1381, 1371, 1302, 1248, 1208, 1172, 1085, 1062, 1038, 969, 928, 909, 853, 820, 772 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 489.17 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{38}O_8$ 489.2464; found, 489.2473. Minor isomer (23 mg, 0.05 mmol) TLC 50:50 EtOAc:Hexane $R_f = 0.52$ visualized by UV or with PMA. $[\alpha]_D^{23}$ +2.4 (*c* 0.83, $CHCl_3$). ^1H NMR ($CDCl_3$, 800 MHz) δ 7.26 (m, 2H), 6.87 (m, 2H), 4.55-4.50 (m, 3H), 4.26 (m, 1H), 3.95 (dt, *J* = 2.8, 12.8 Hz, 1H), 3.92 (dd, *J* = 2.4, 12 Hz, 1H), 3.84 (ddd, *J* = 1.6, 5.6, 12 Hz, 1H), 3.80 (s, 3H), 3.72 (dd, *J* = 2.8, 10.8 Hz, 1H), 3.58 (dd, *J* = 5.6, 10.8 Hz, 1H), 3.51 (m, 2H), 2.07 (m, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H), 1.25 (m, 1H), 1.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.4, 159.2, 130.0, 129.3, 113.7, 110.8, 98.4, 79.7, 78.3, 78.1, 73.2, 69.9, 67.3, 59.7, 55.2, 52.3, 29.4, 27.7, 26.9, 26.5, 22.2, 20.9, 18.9. FTIR (NaCl) ν_{max} = 3434, 2923, 2956, 2990, 2853, 1714, 1693, 1644, 1615, 1515, 1463, 1381, 1248, 1171, 1122, 1079, 1171, 1122, 1079, 1035, 971, 852, 819, 753 cm^{-1}. ESI (+) LRMS *m/z* (relative intensity): 489.17 (100%). ESI (+) HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{38}O_8$ 489.2464; found, 489.2463. HPLC Zorbax XDB-C_{18} (150 x 4.6 mm, 5 micron); Flow = 1.5 mL/min; λ = 215 nm; Gradient T = 0-1 min (25:75 MeCN:H_2O); T = 15-17 min (90:10 MeCN:H_2O), T = 17.1-20 min (25:75 MeCN:H_2O); Major R_t = 8.5 min; Minor R_t = 9.9; Ref. phenol R_t = 2.3 min; toluene R_t = 8.1 min; BHT R_t = 15.3 min.



30

1-((4*S*,5*R*)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-one (30): Isolated during HPLC monitoring of the enolate formation of **11** by quenching the enolate with H_2O prior to HPLC analysis. TLC 30:70 EtOAc:Hexane $R_f = 0.57$ visualized by UV or with PMA. $[\alpha]_D^{23}$ +22.2 (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 4.31 (d, *J* = 7.6 Hz, 1H), 4.20 (m, 1H), 3.80 (s, 3H), 3.72 (dd, *J* = 3.2, 10.4 Hz, 1H), 3.59 (d, *J* = 5.6, 10.8 Hz, 1H), 3.11 (sept, *J* = 6.8 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7, 159.2, 130.0, 129.4, 113.7, 110.7, 80.5, 77.5, 73.2, 70.1, 55.2, 36.7, 26.9, 26.2, 18.3, 17.5. FTIR (NaCl) ν_{max} = 2973, 2930, 2873, 1652, 1507, 1457, 1373, 1248, 1172, 1070, 1035 cm^{-1}. CI LRMS *m/z* (relative intensity): 121 (100%), 307 (1%), 322 (1%). CI HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{26}O_5$ 322.1780; found, 322.1788.

Figure 1. ^{1}H NMR Spectra of **6**

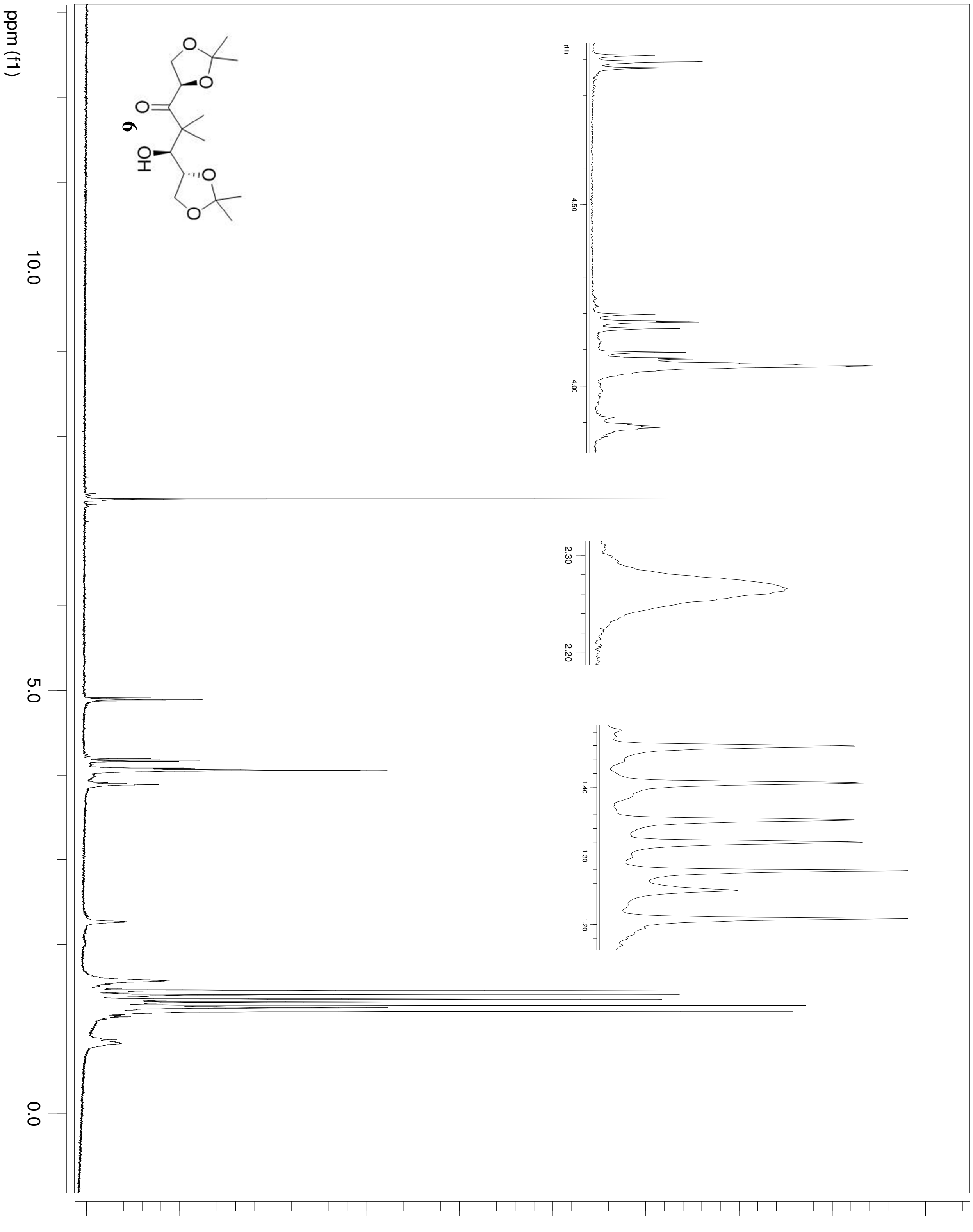


Figure 2. ^{13}C NMR Spectra of **6**

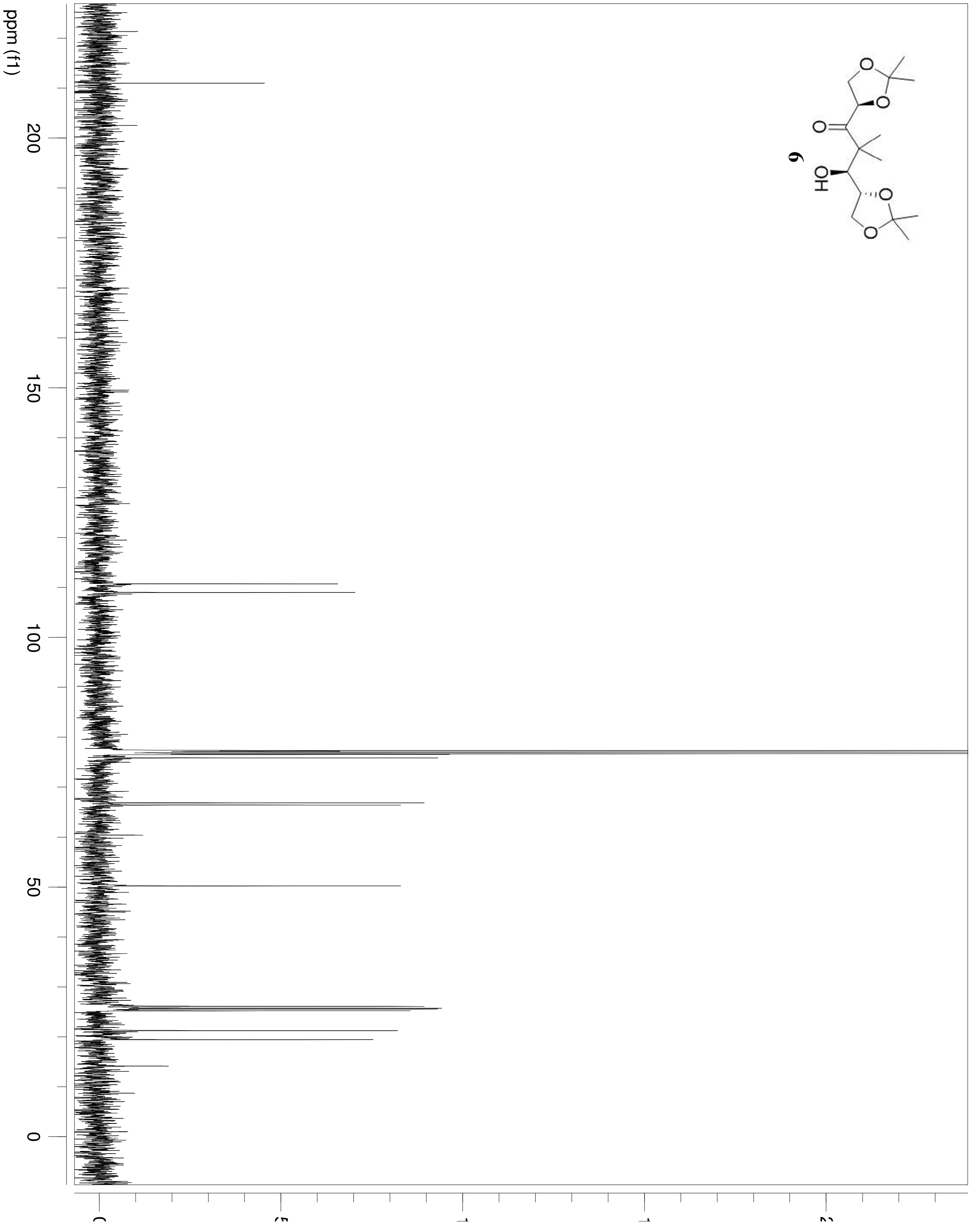


Figure 3. ^{1}H NMR Spectra of **7**

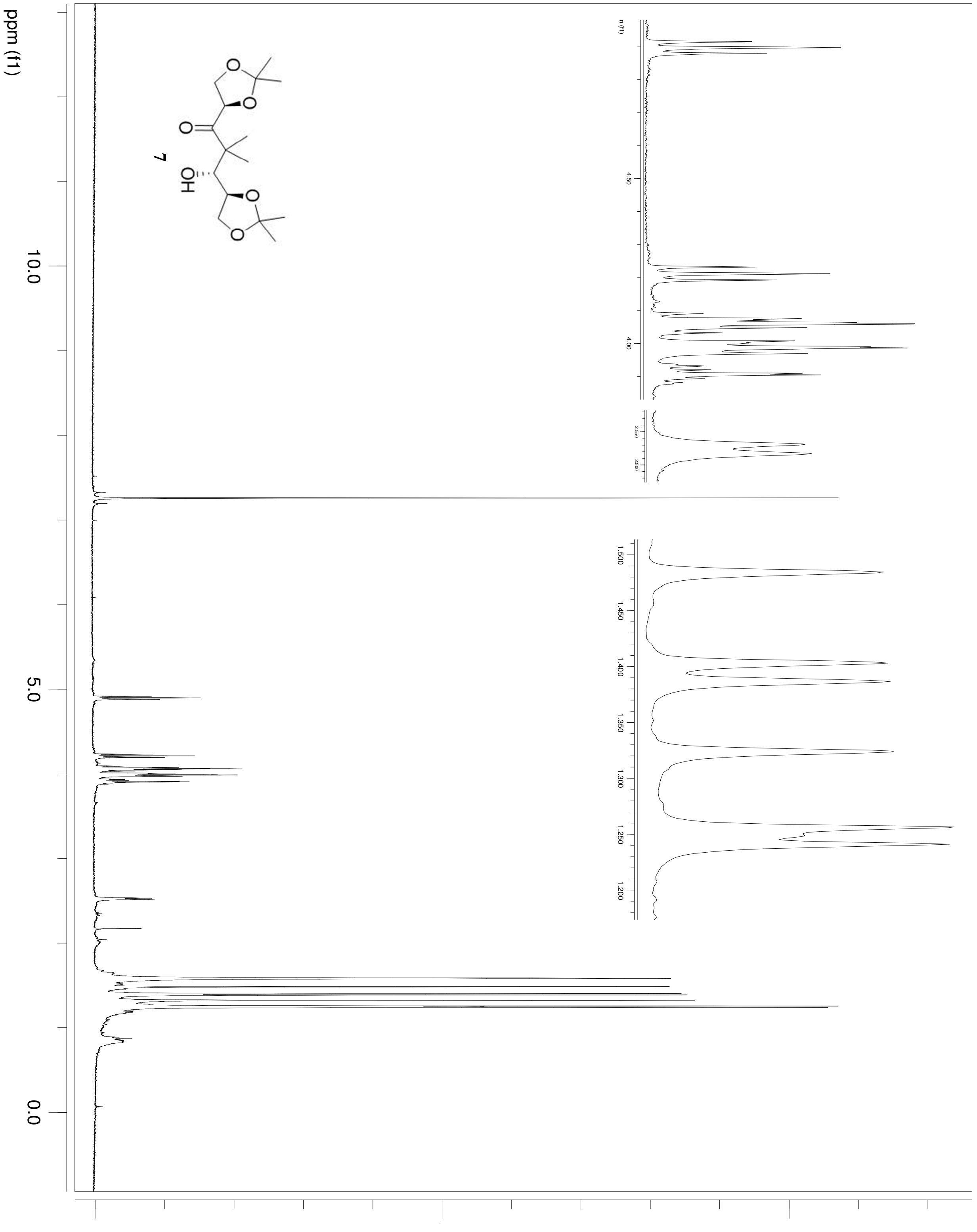


Figure 4. ^{13}C NMR Spectra of **7**

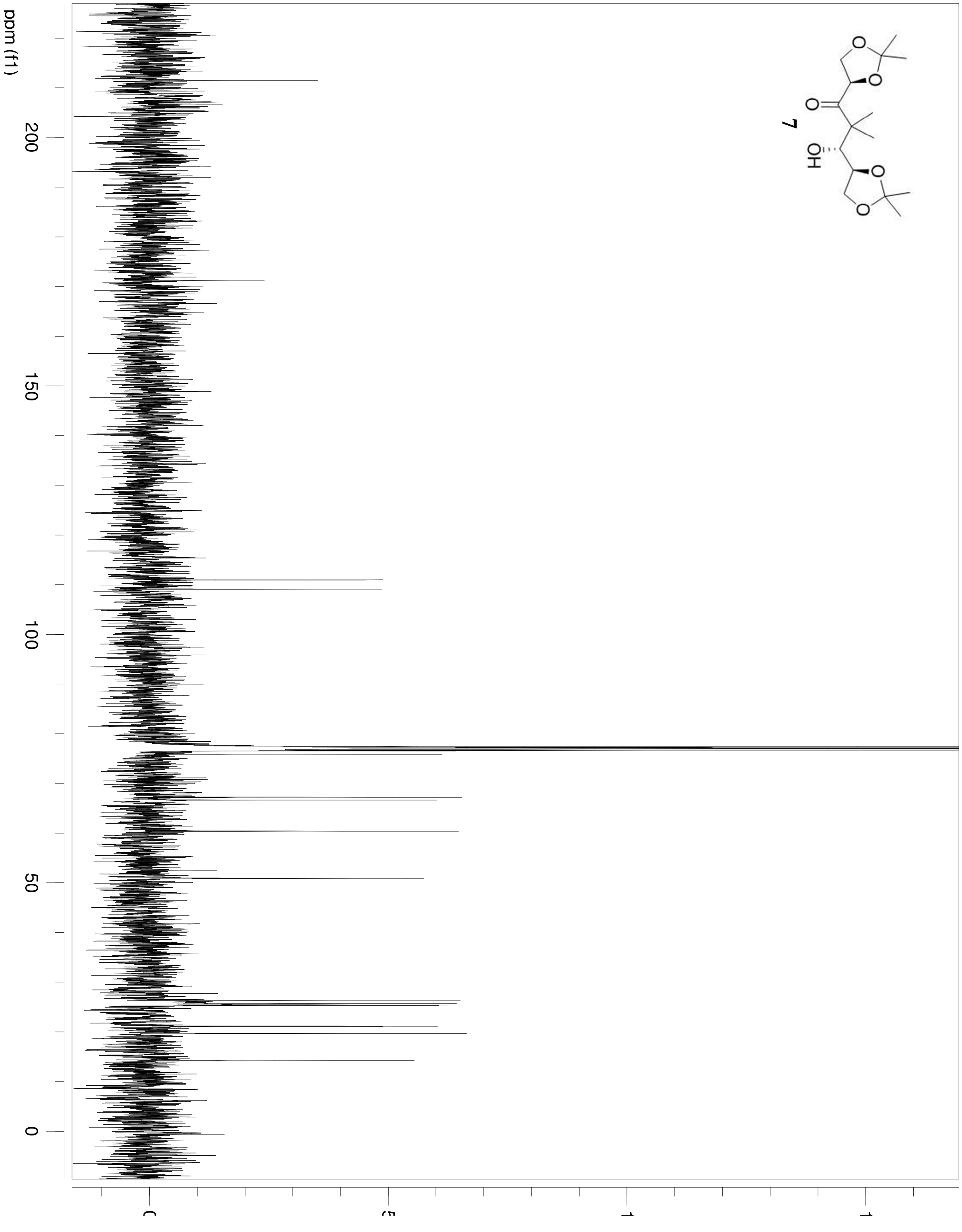


Figure 5. ^{1}H NMR Spectra of Acylated **6**

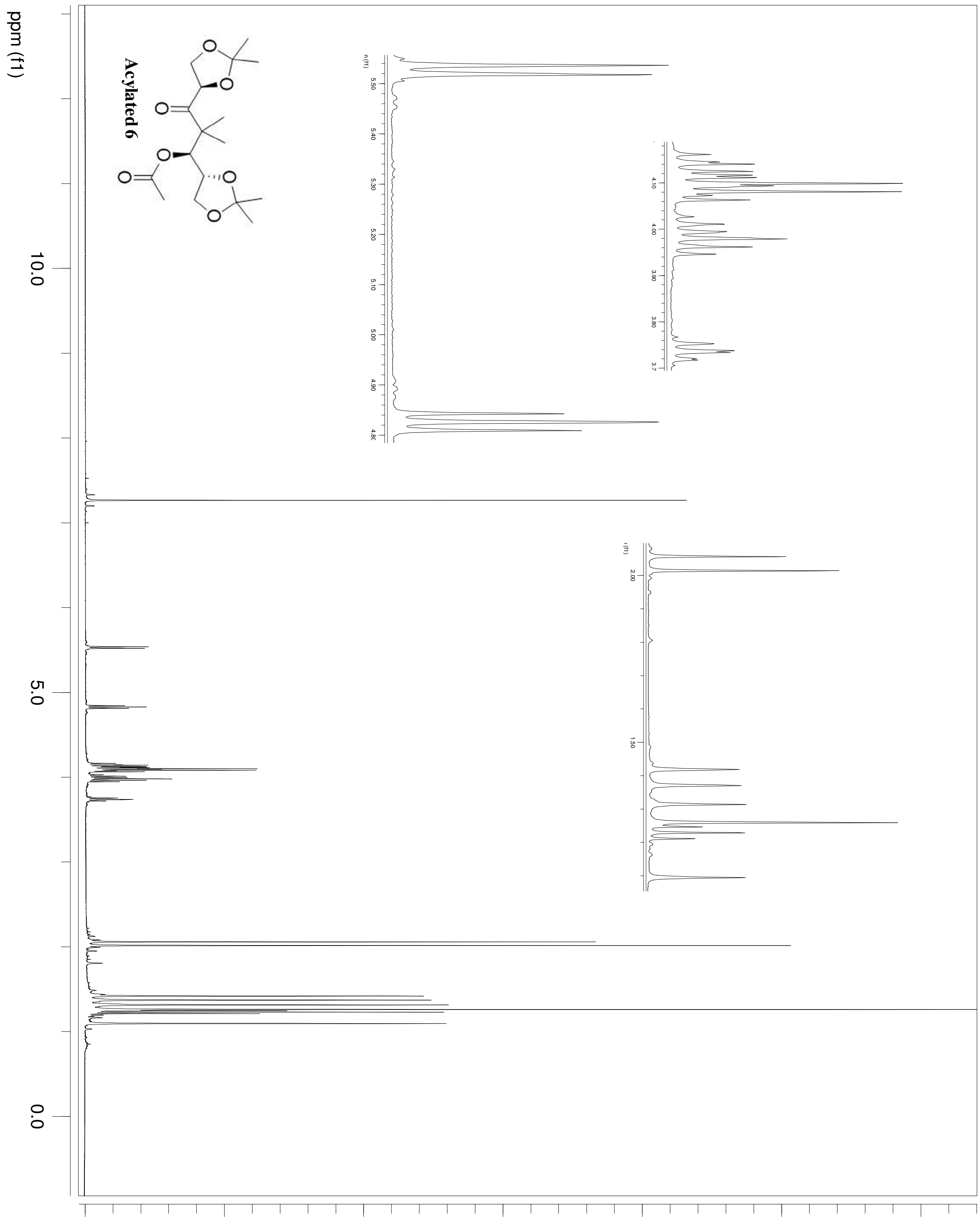


Figure 6. ^{13}C NMR Spectra of Acylated **6**

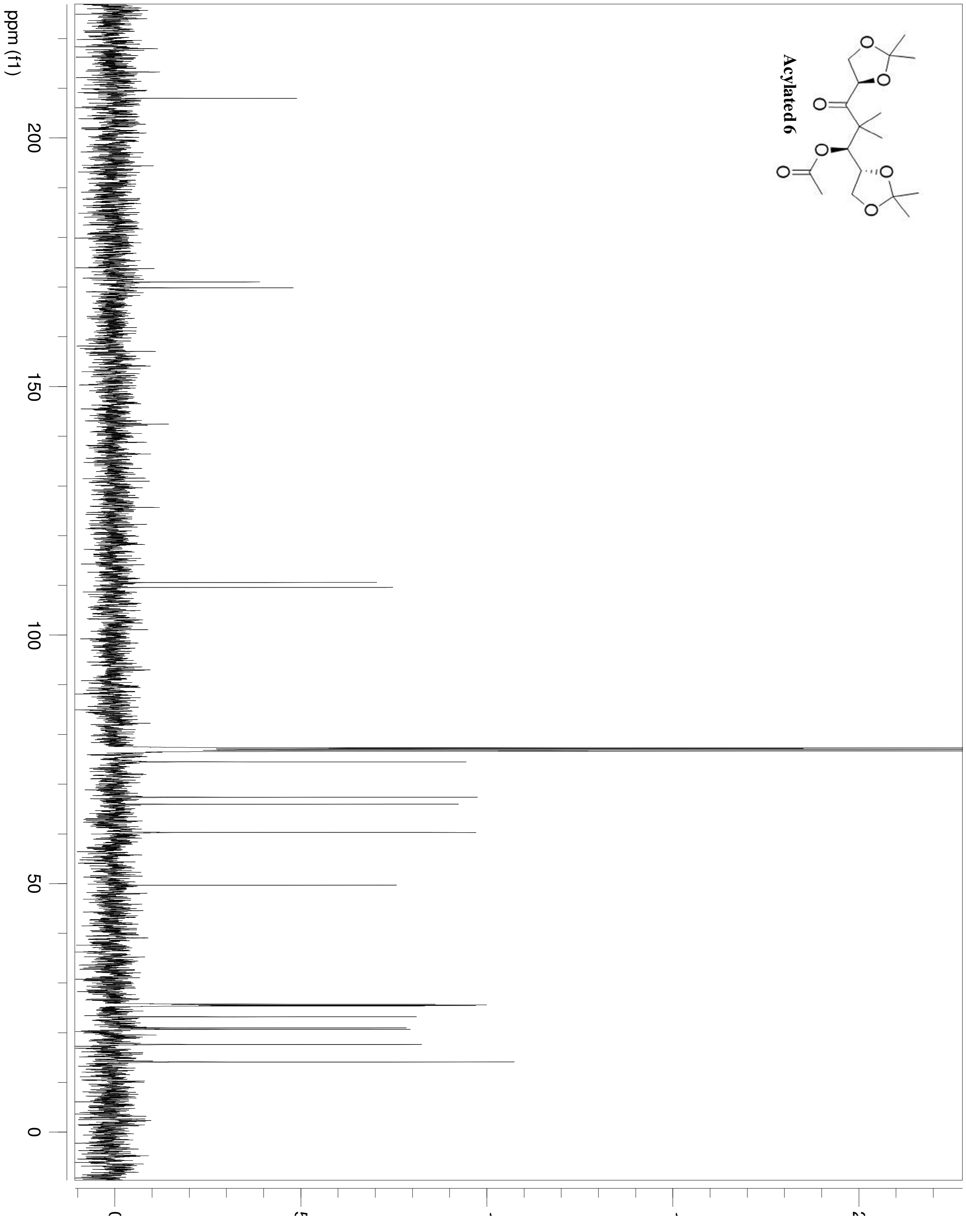


Figure 7. ^1H NMR Spectra of **8**

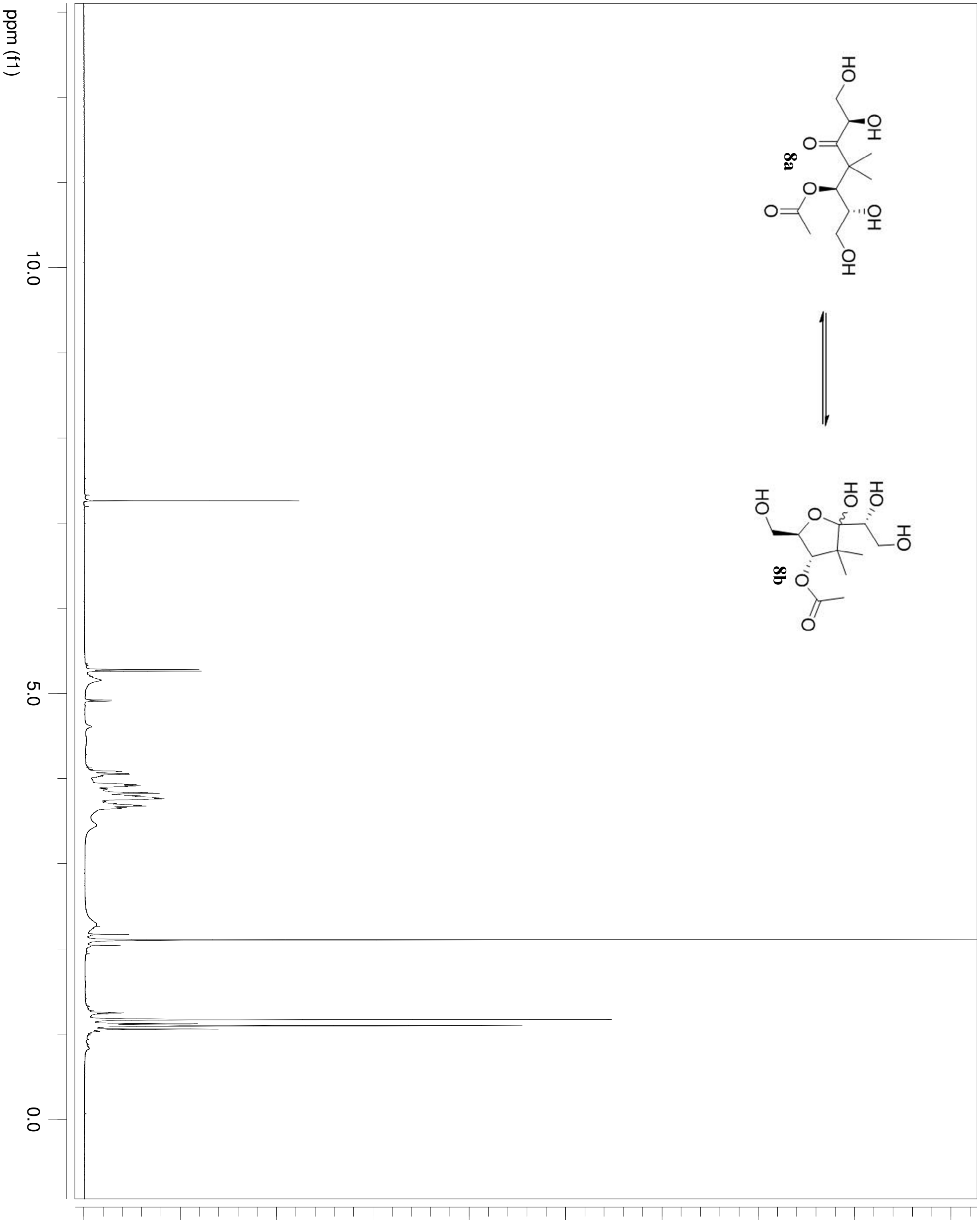


Figure 8. ^{13}C NMR Spectra of **8**

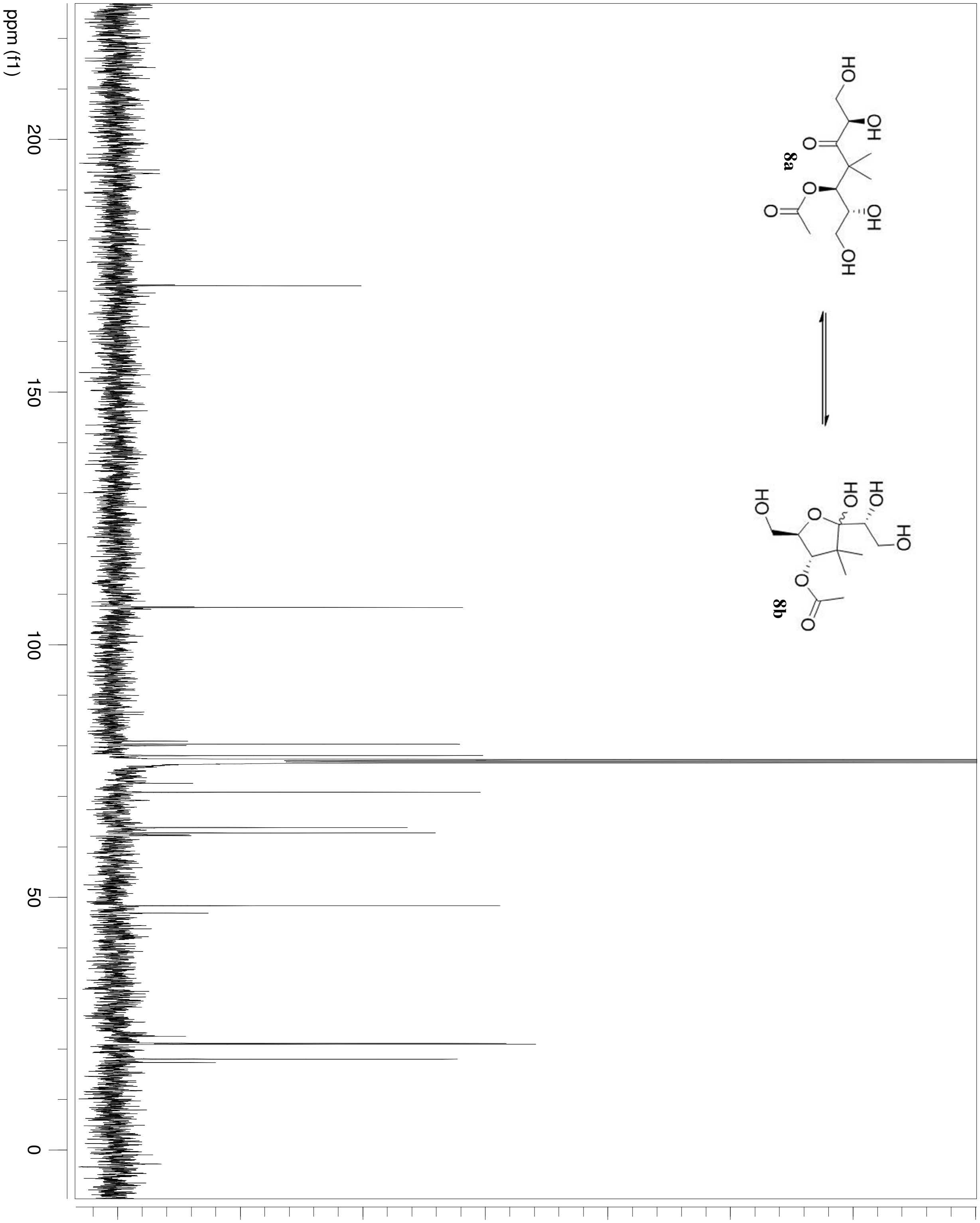


Figure 9. ¹H NMR Spectra of **11**

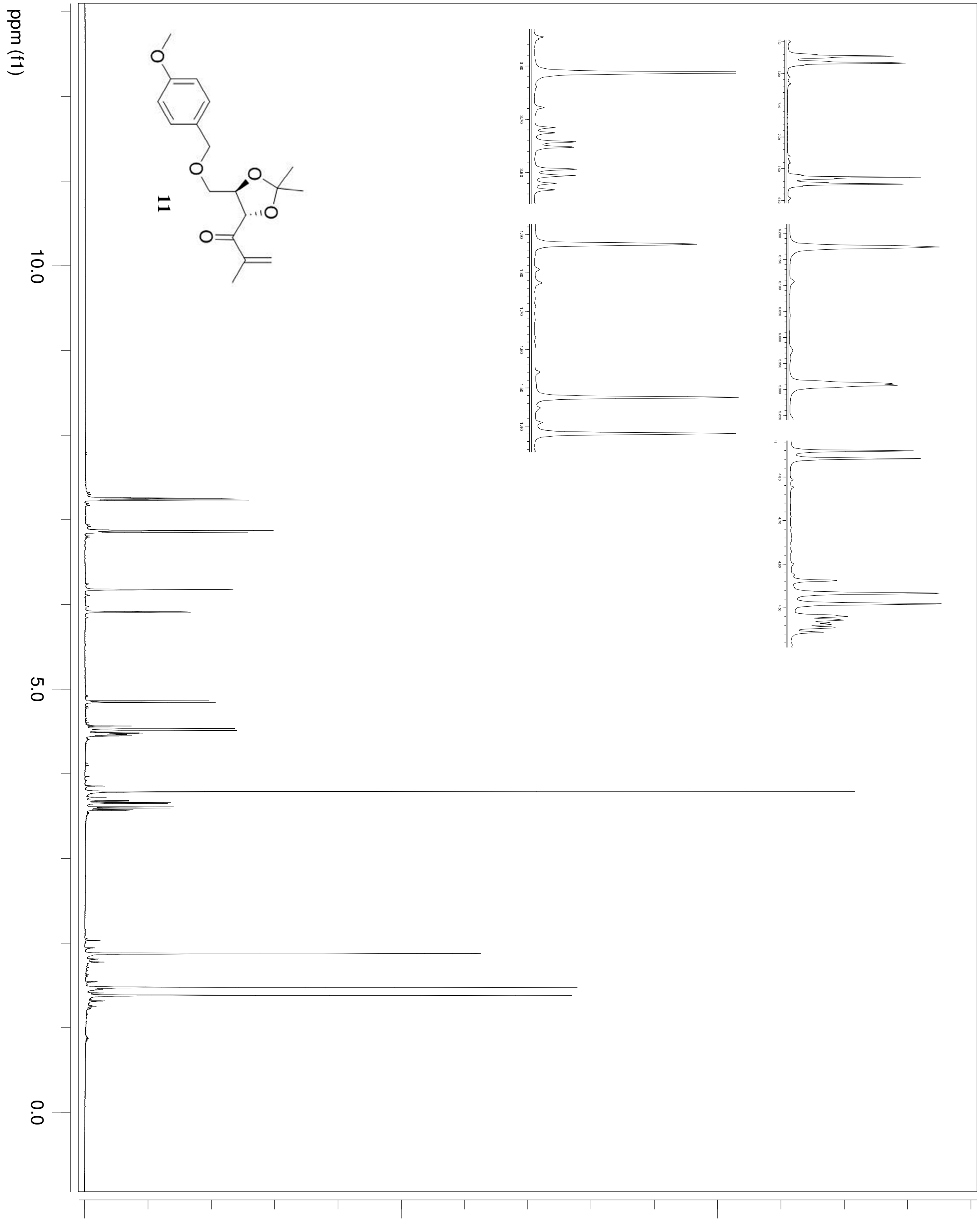

11

Figure 10. ^{13}C NMR Spectra of **11**

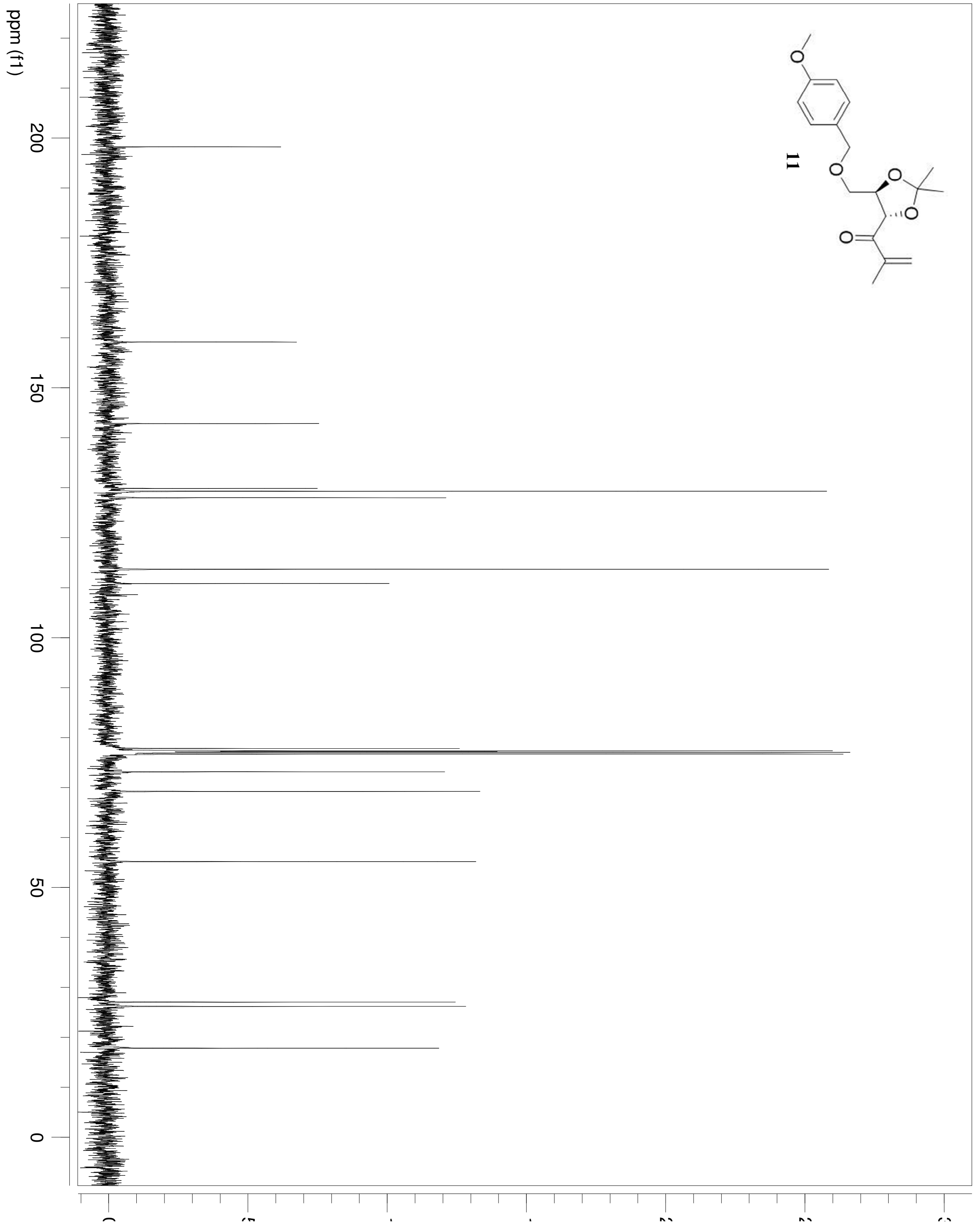


Figure 11. ^{1}H NMR Spectra of **19** Major Isomer

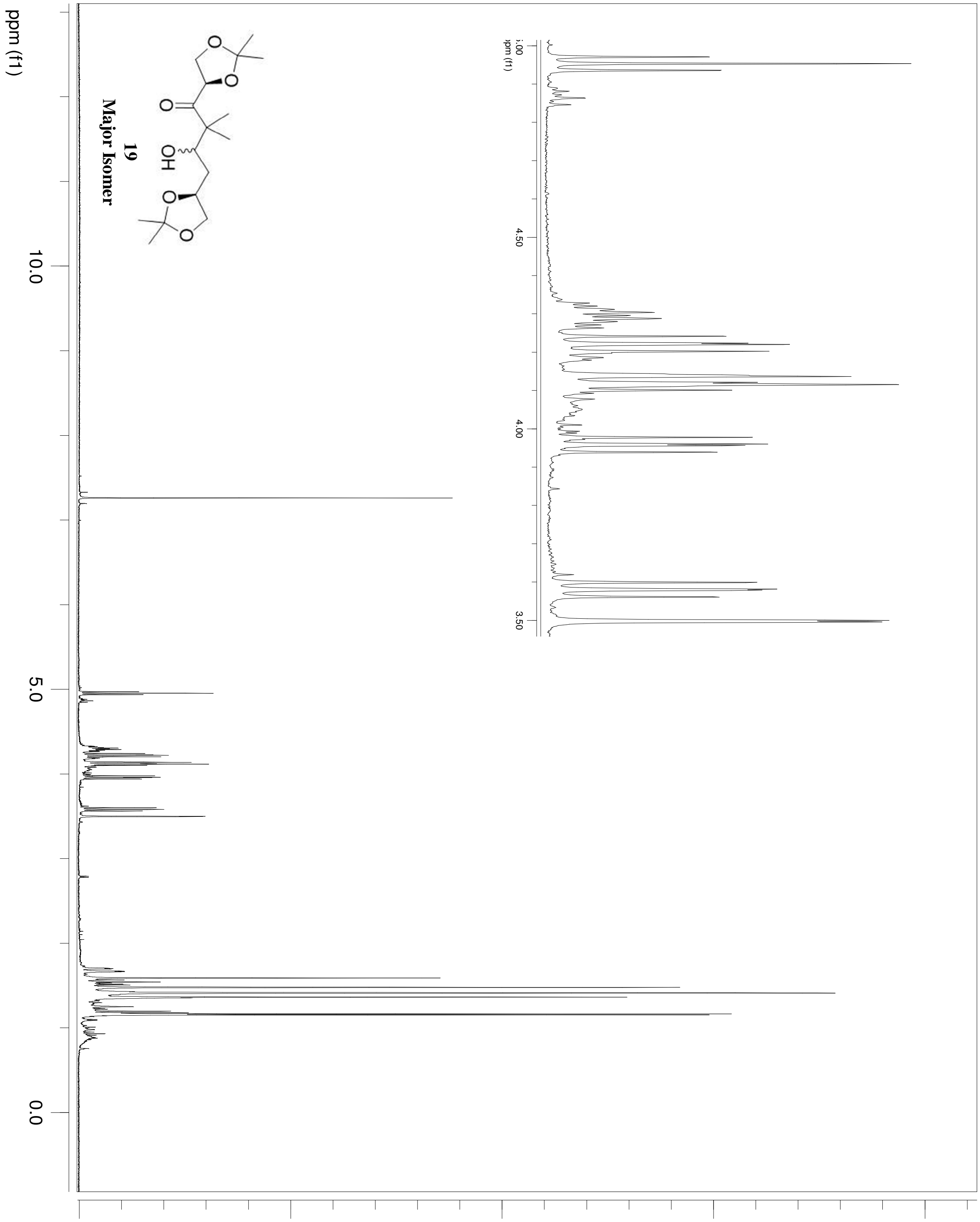


Figure 12. ^{13}C NMR Spectra of **19** Major Isomer

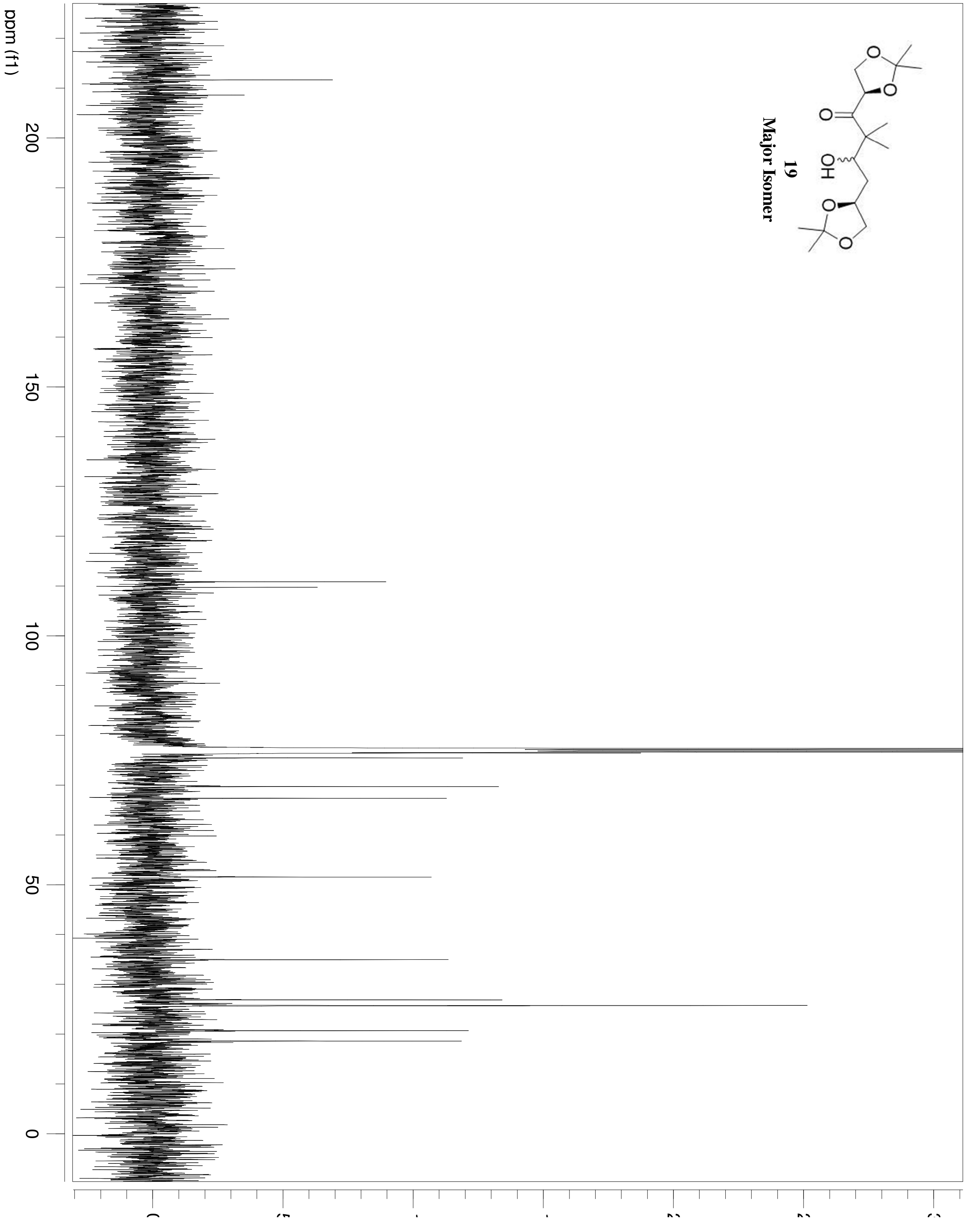


Figure 13. ^{1}H NMR Spectra of **19** Minor Isomer

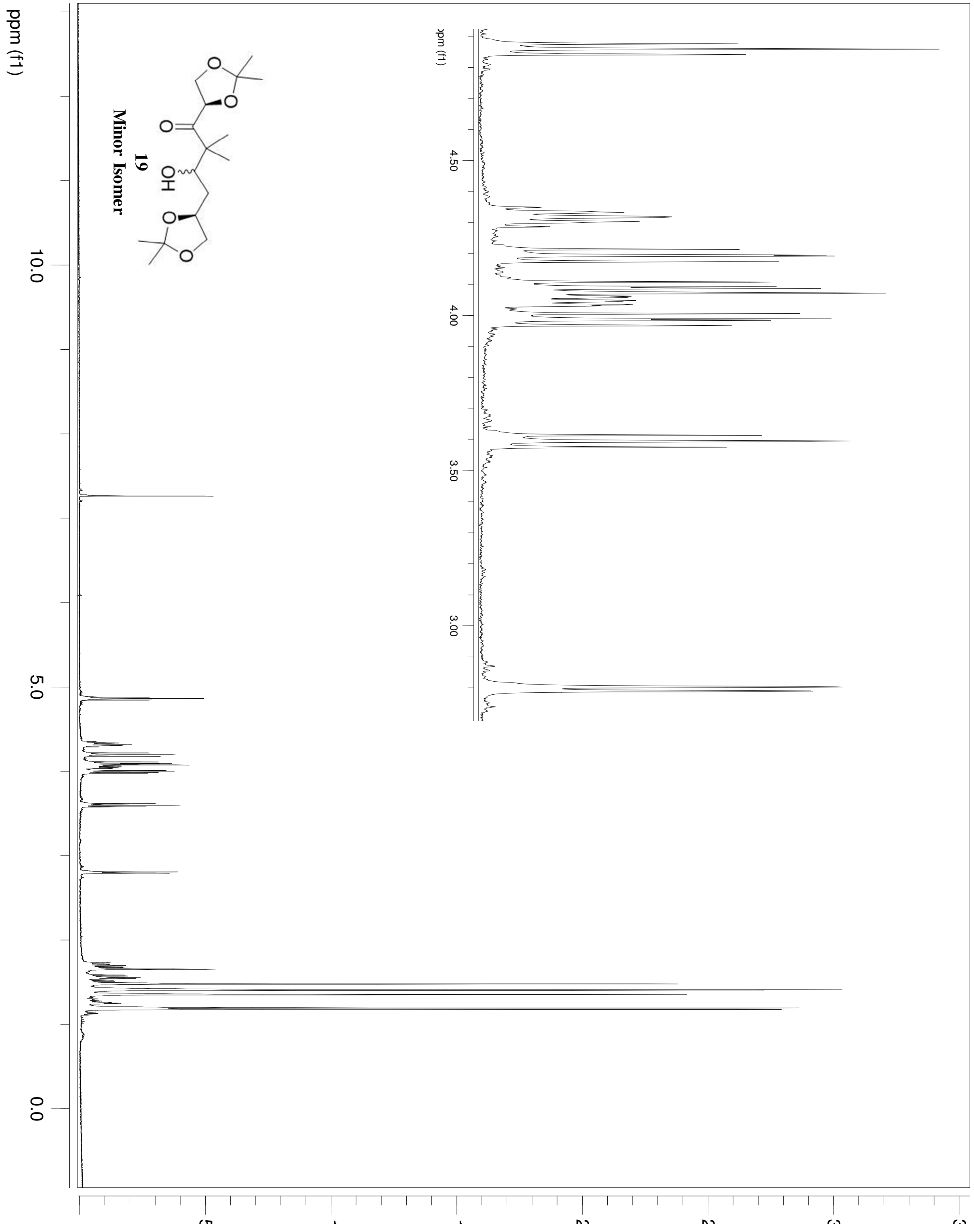
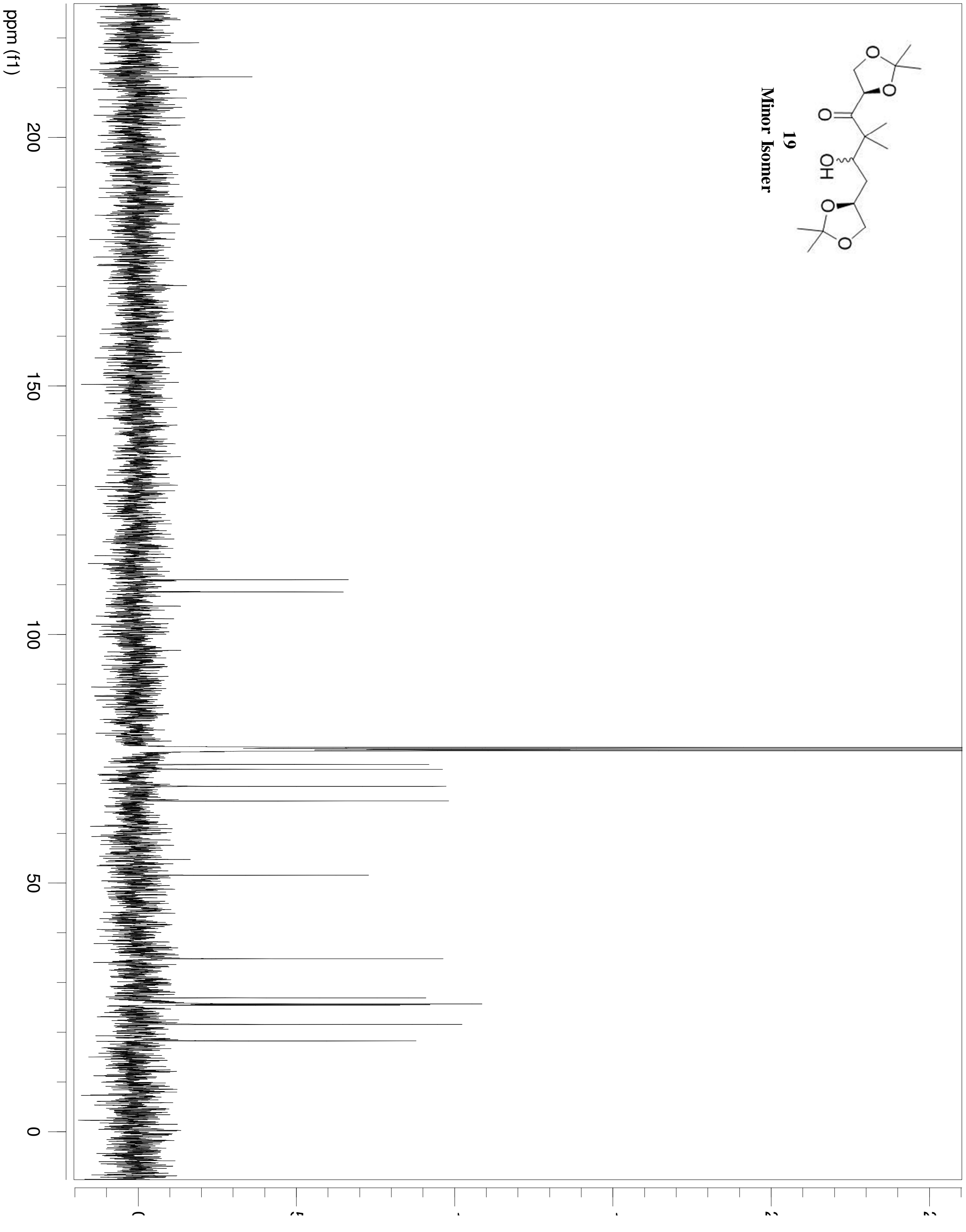


Figure 14. ^{13}C NMR Spectra of **19** Minor Isomer



19
Minor Isomer

Figure 15. ^{1}H NMR Spectra **20**

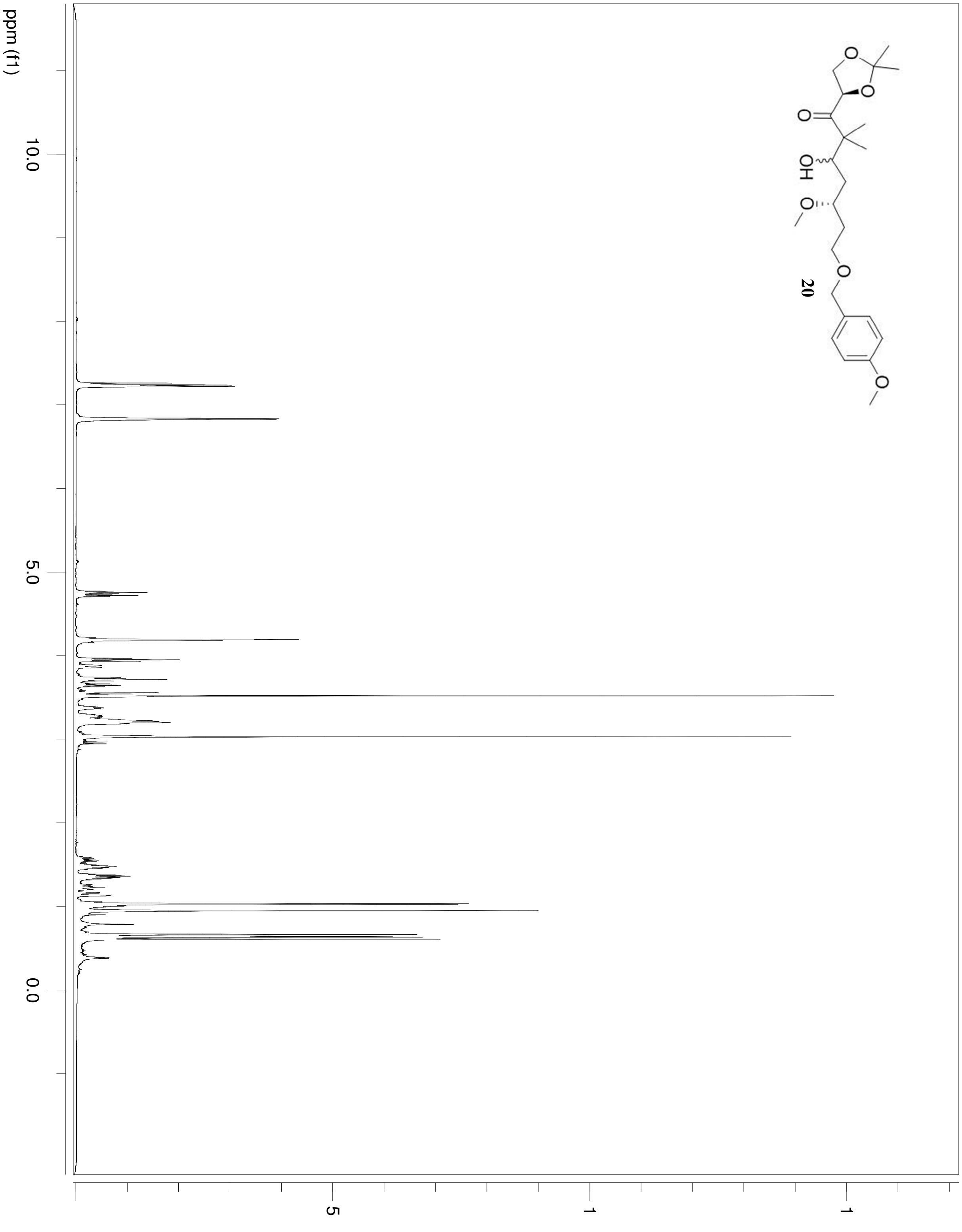


Figure 16. ^{13}C NMR Spectra of **20**

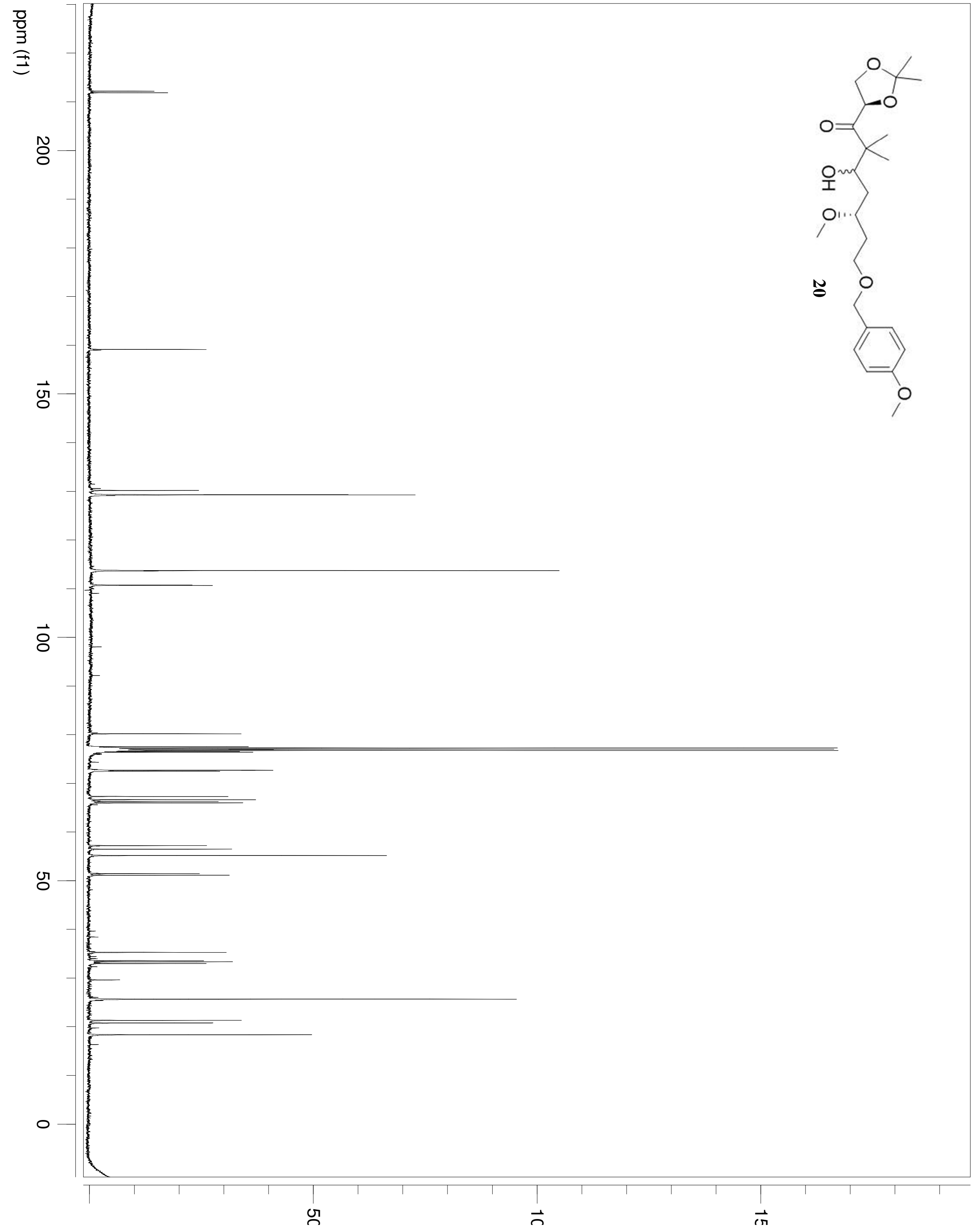


Figure 17. HPLC Chromatogram of Crude **20**

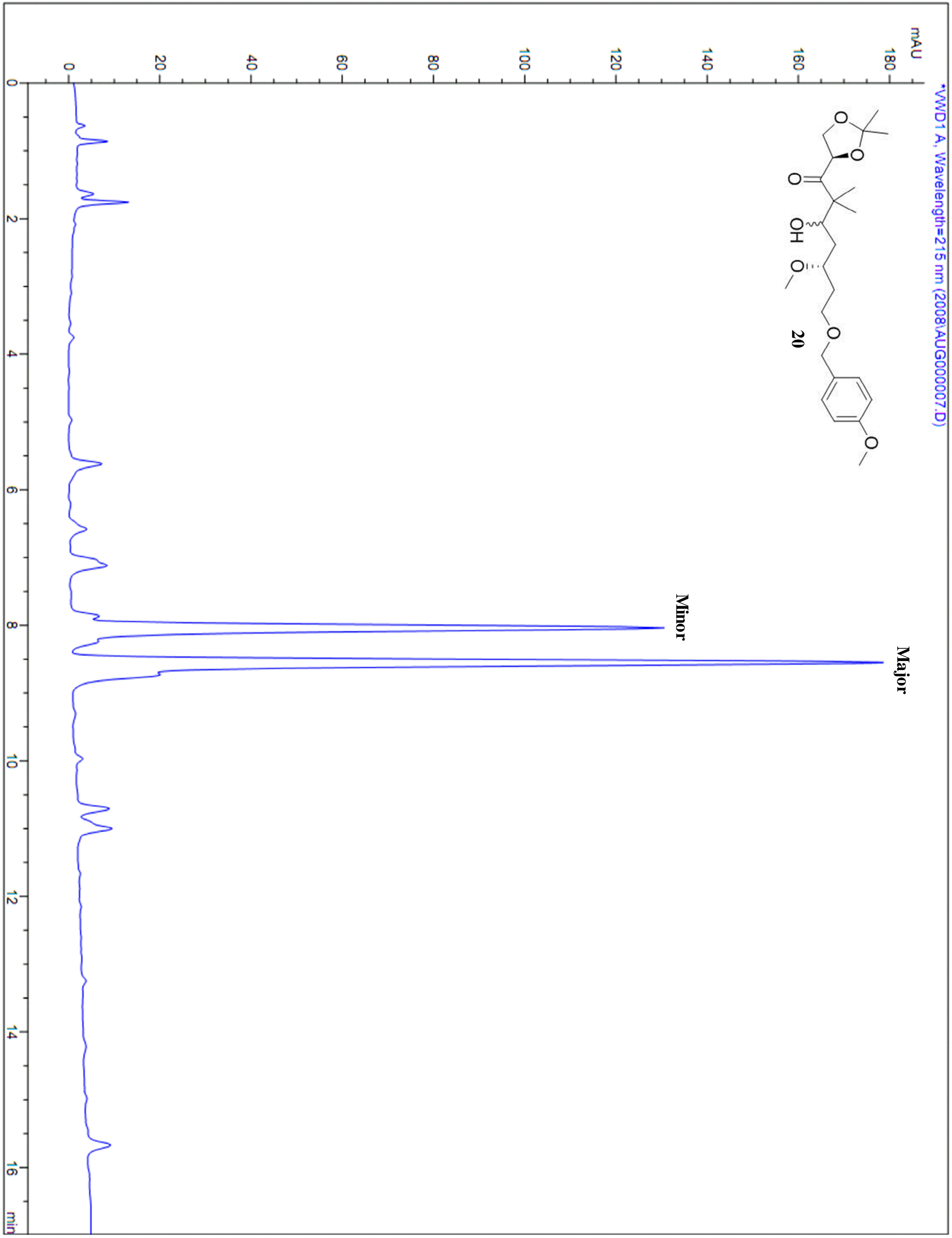


Figure 18. ^{1}H NMR Spectra of **21**

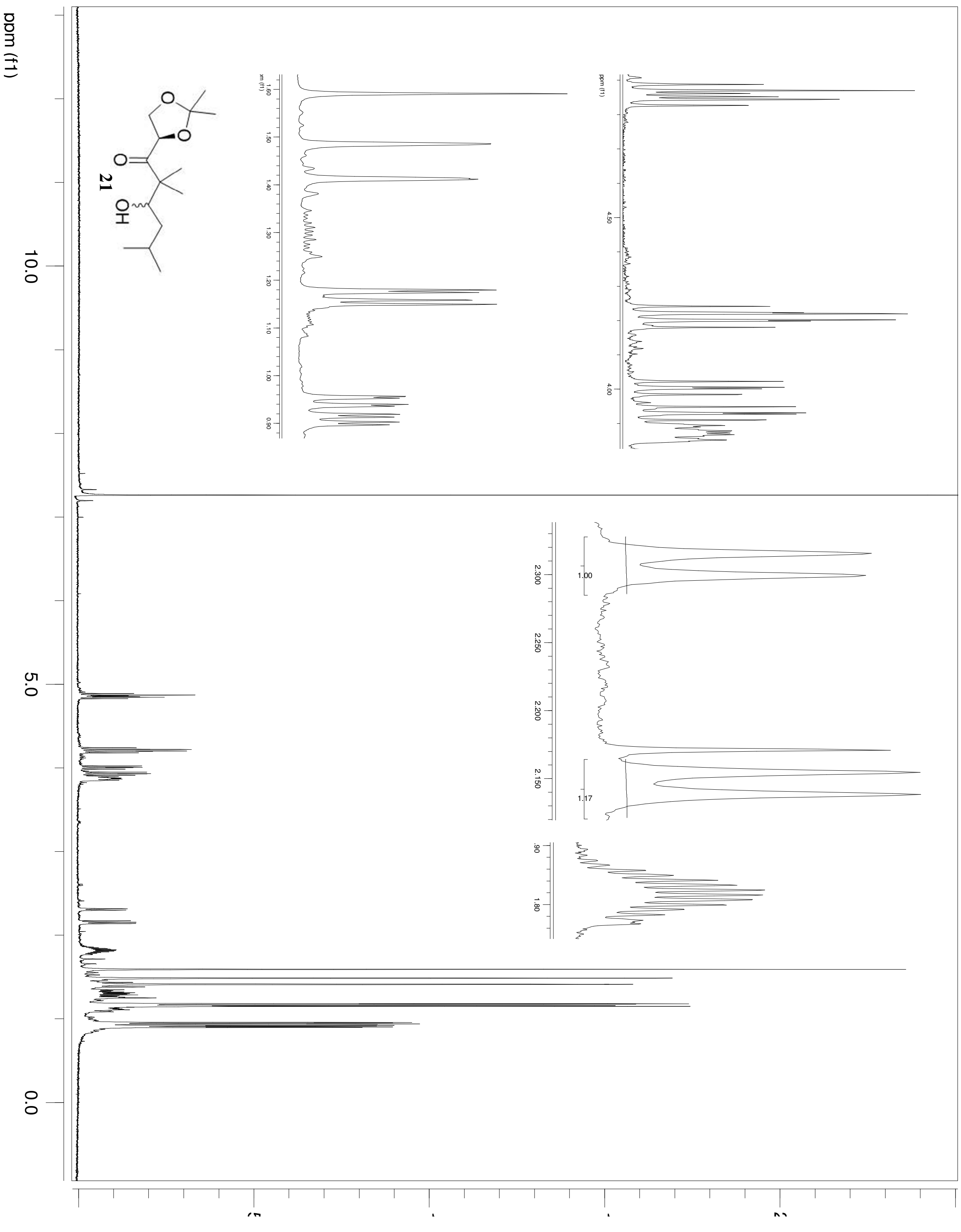


Figure 19. ^{13}C NMR Spectra of **21**

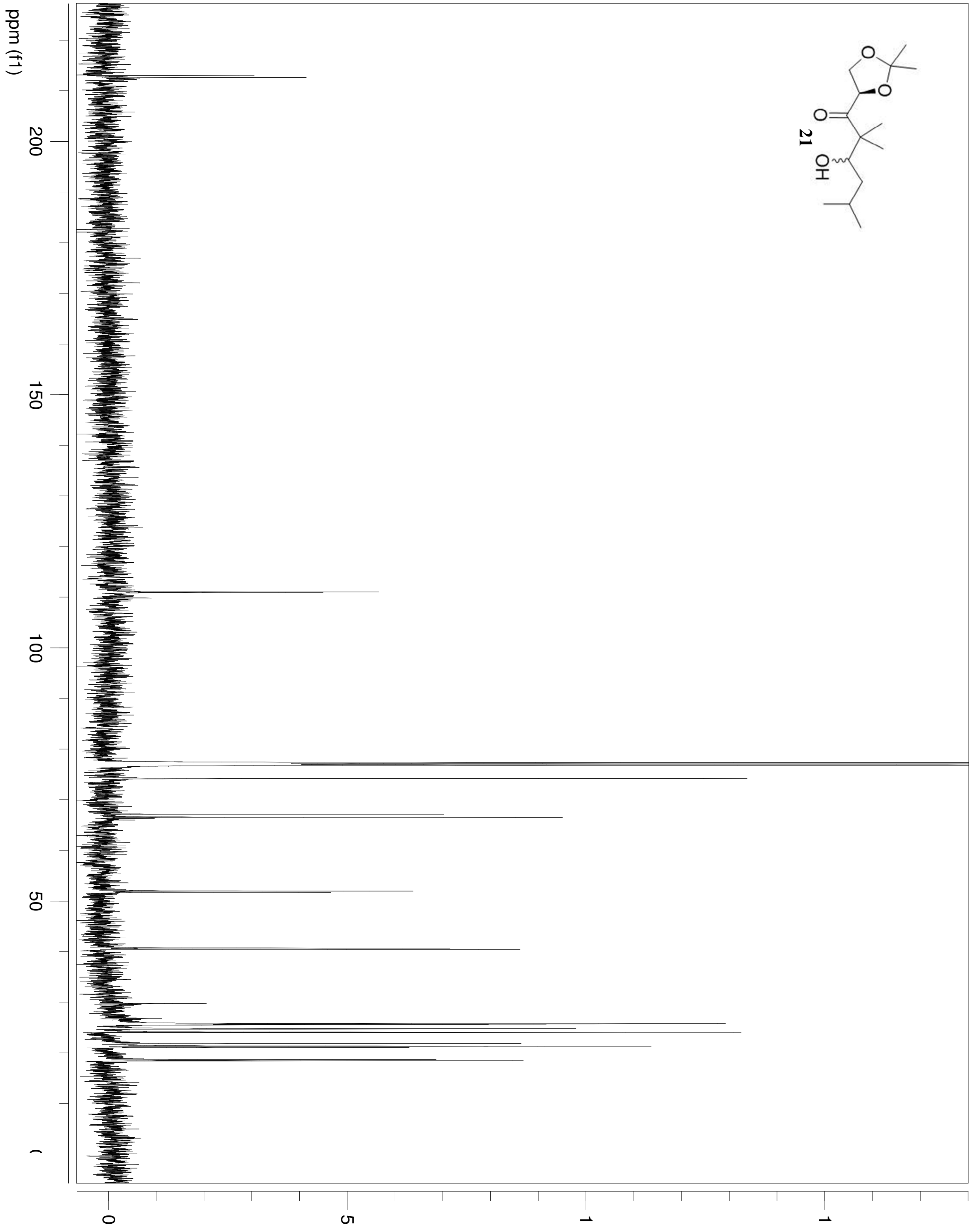


Figure 20. ^{1}H NMR Spectra of **22a**

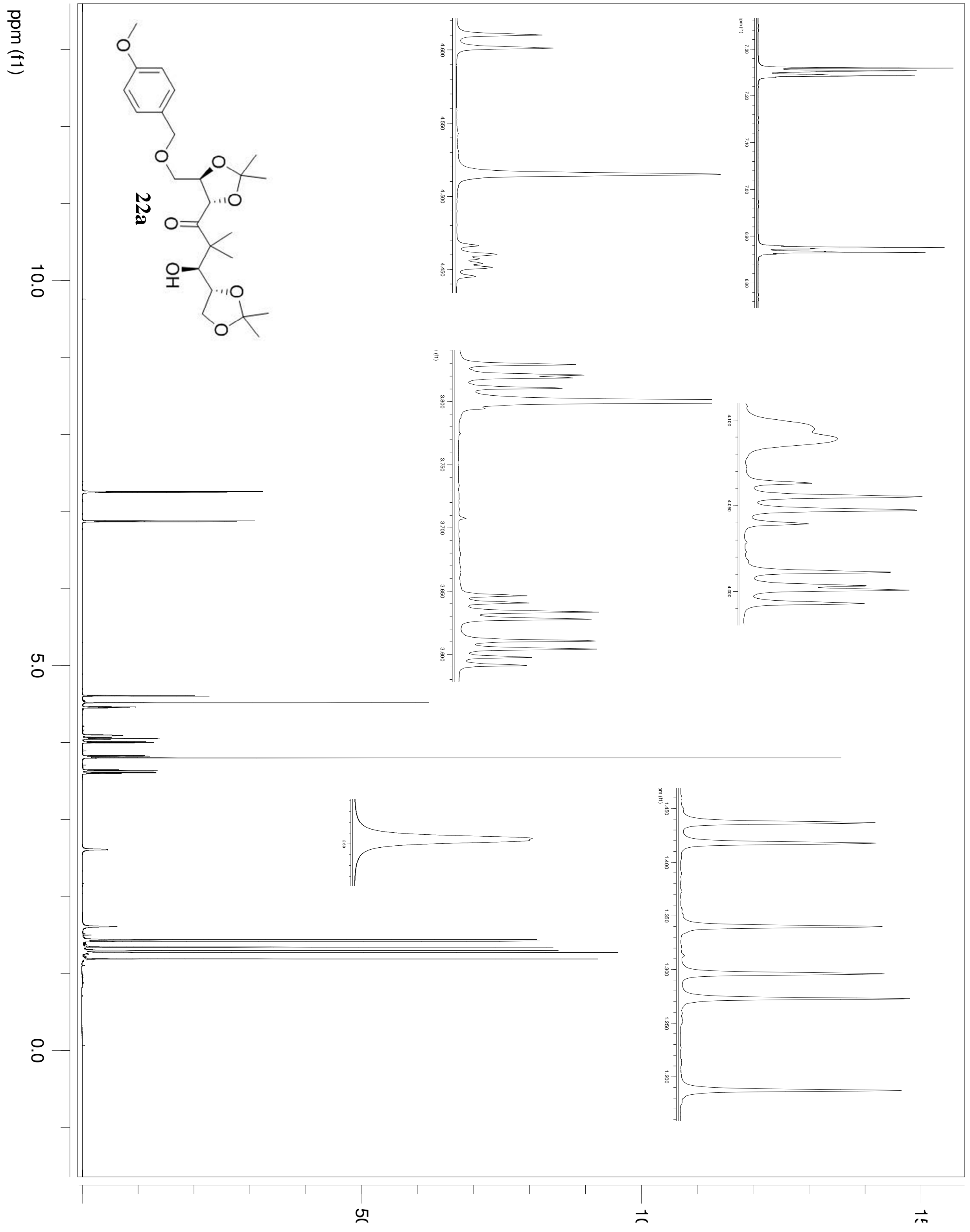


Figure 21. ^{13}C NMR Spectra of **22a**

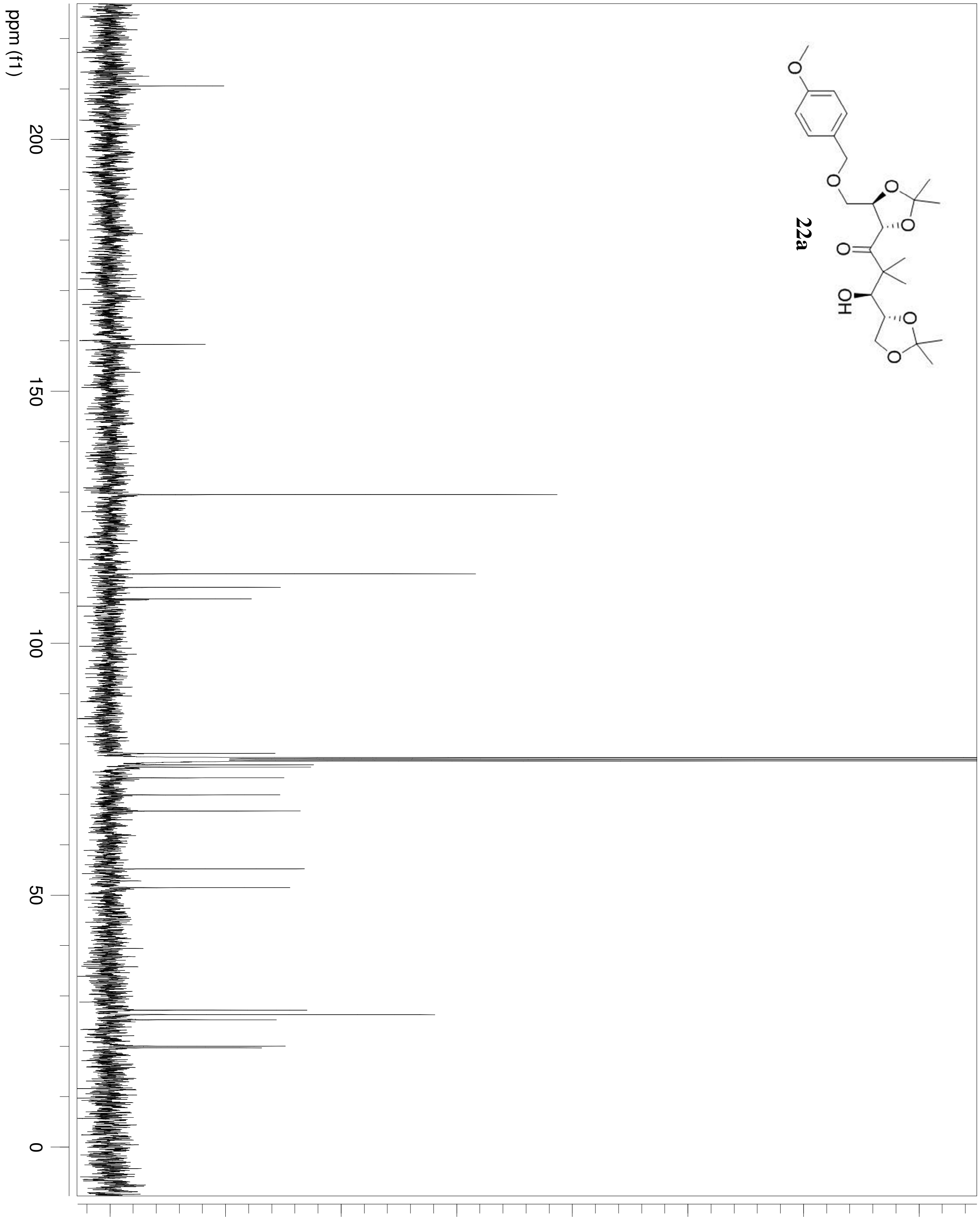


Figure 22. ^{1}H NMR Spectra of **22b**

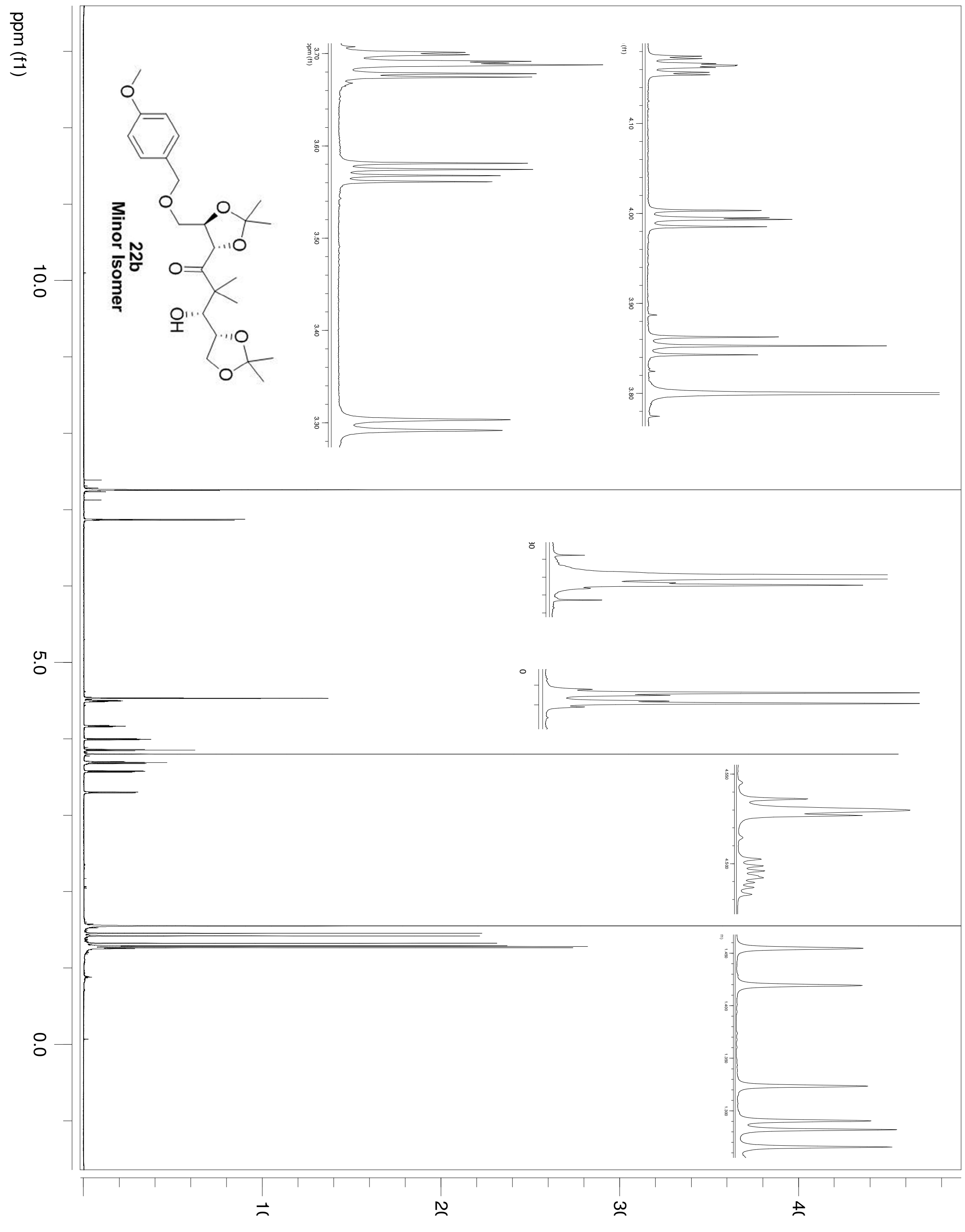


Figure 23. ^{13}C NMR Spectra of **22b**

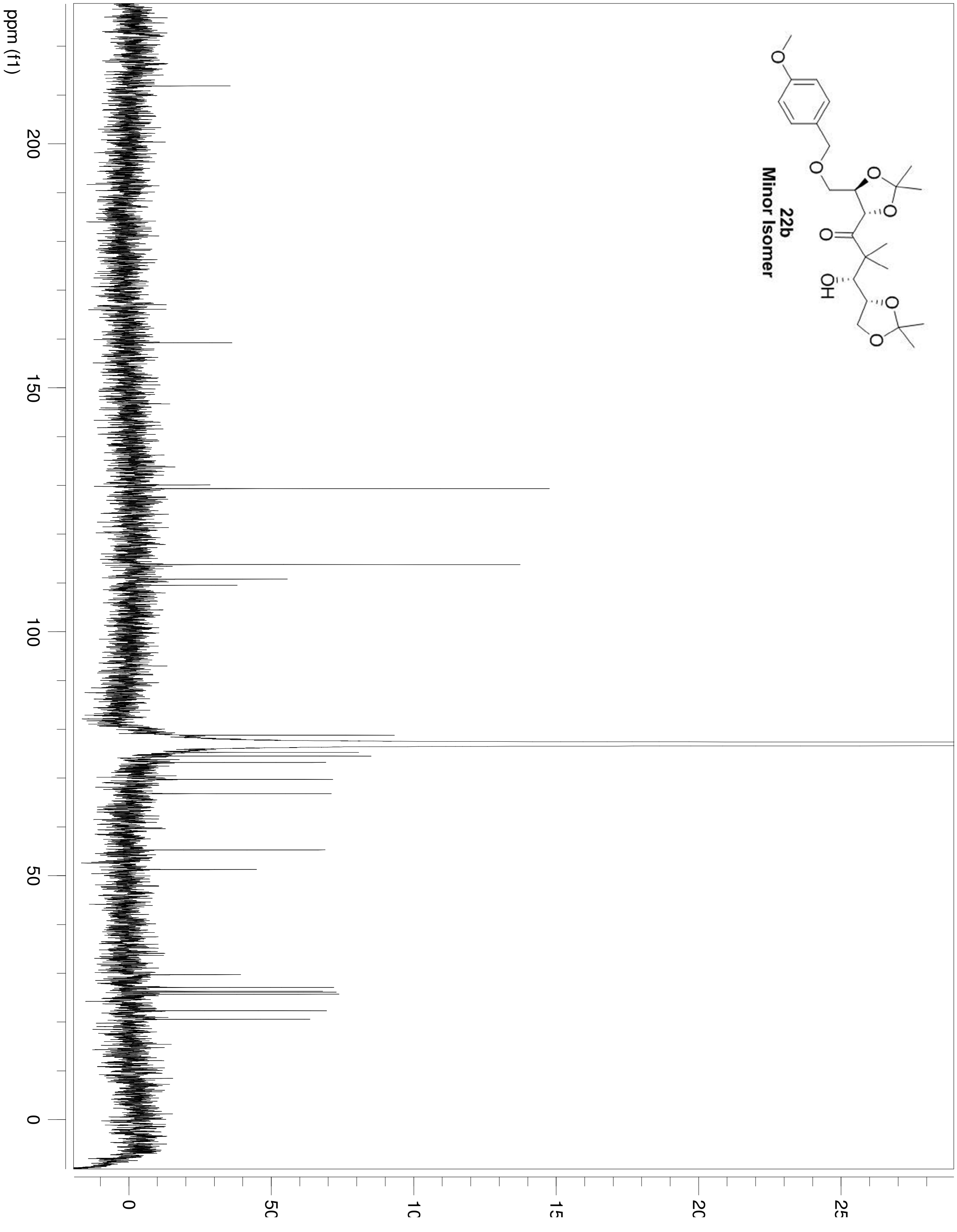


Figure 24. HPLC Chromatogram of the Reaction Profile from the Synthesis of **22**

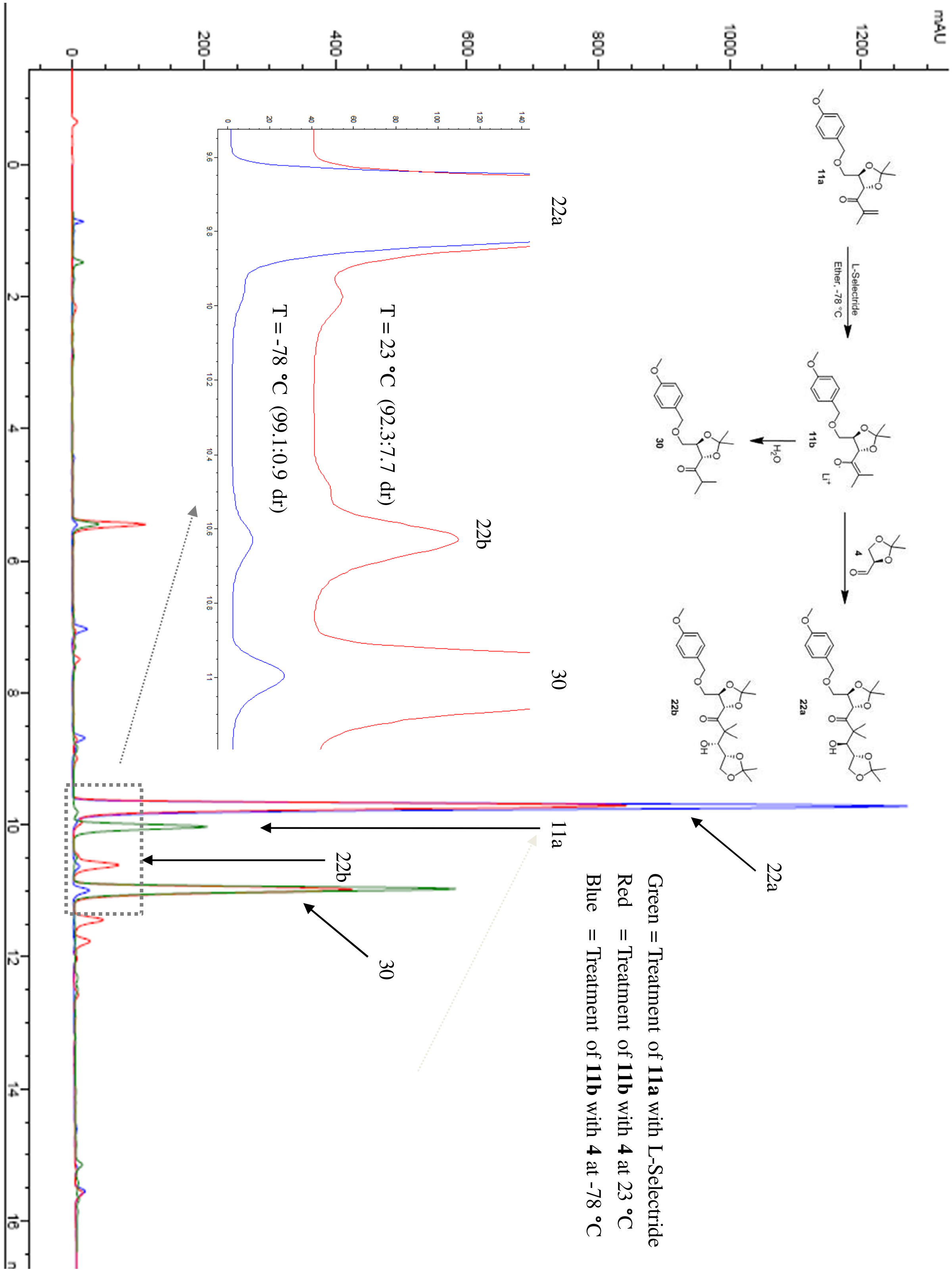
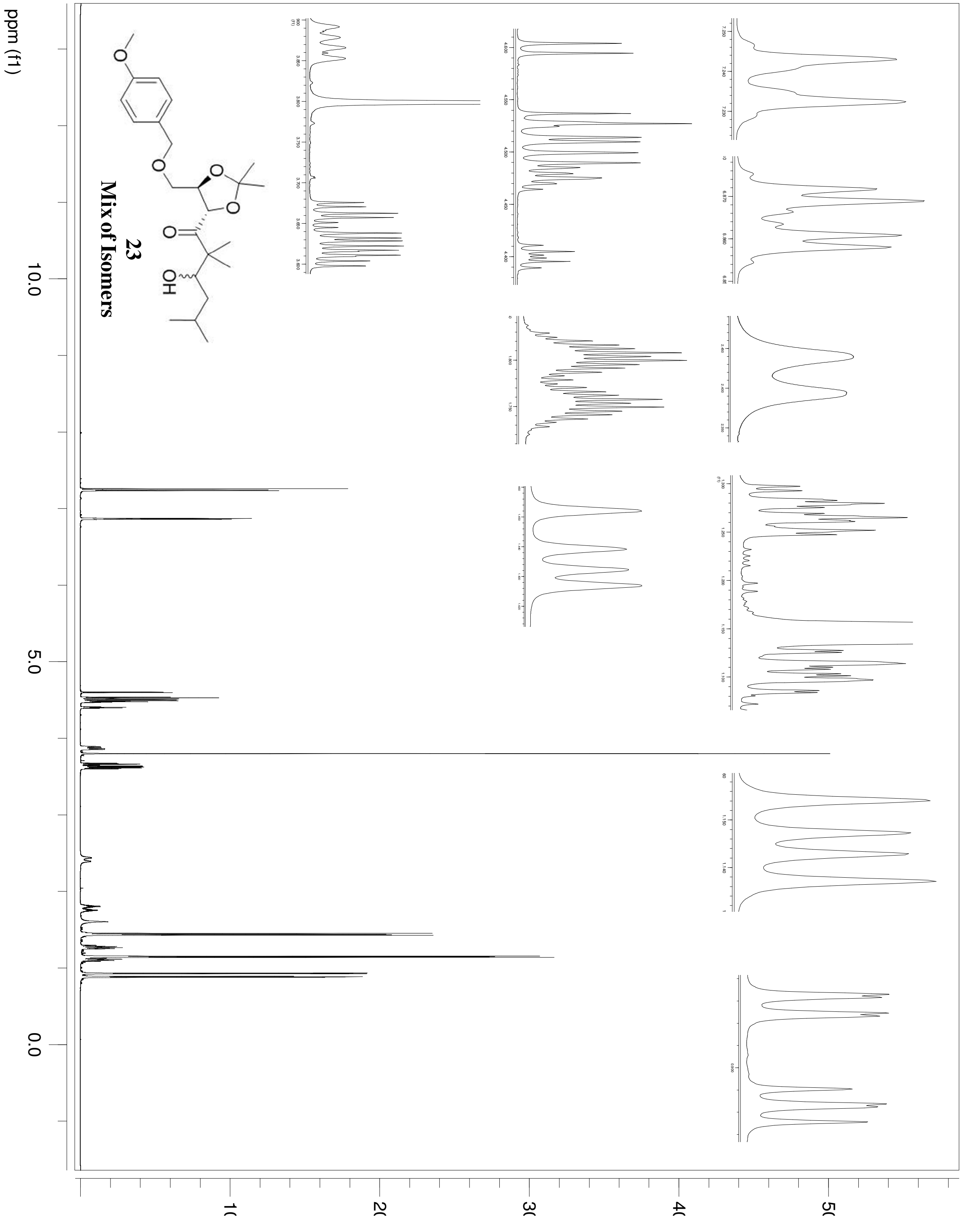


Figure 25. ^{1}H NMR Spectra of **23**



23
Mix of Isomers

Figure 26. ^{13}C NMR Spectra of **23**

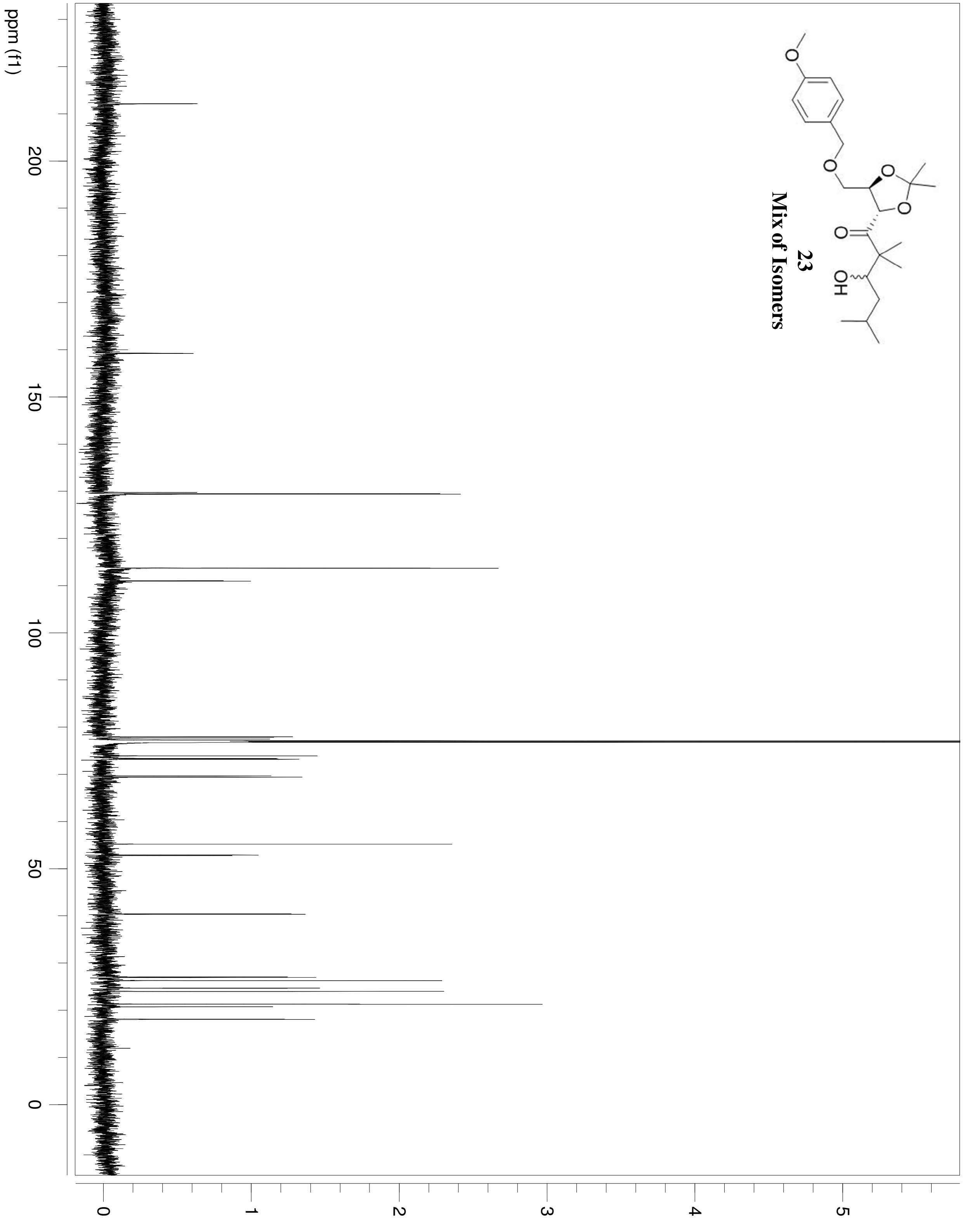


Figure 27. HPLC Chromatogram of Crude **23**

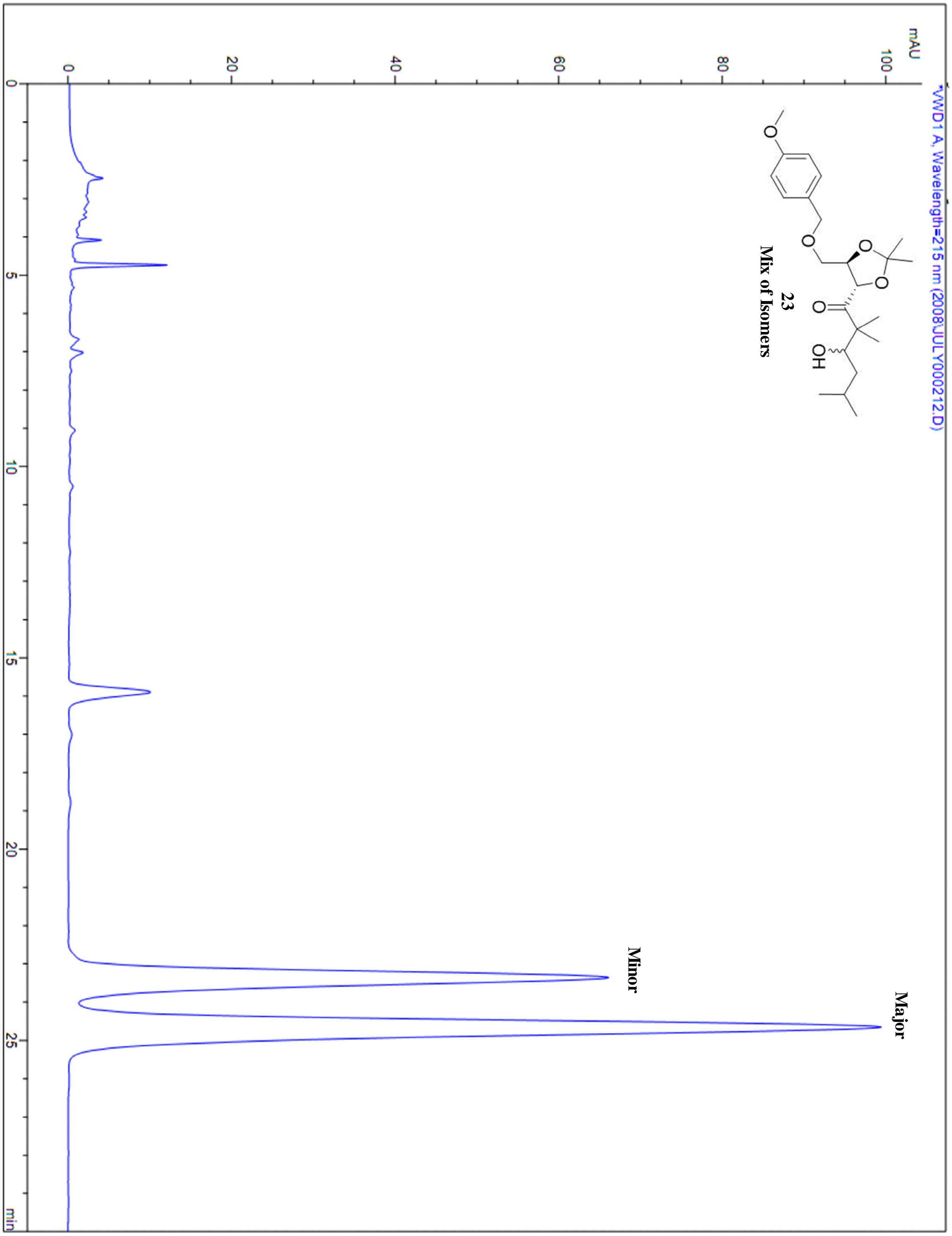


Figure 28. ^{1}H NMR Spectra of **24**

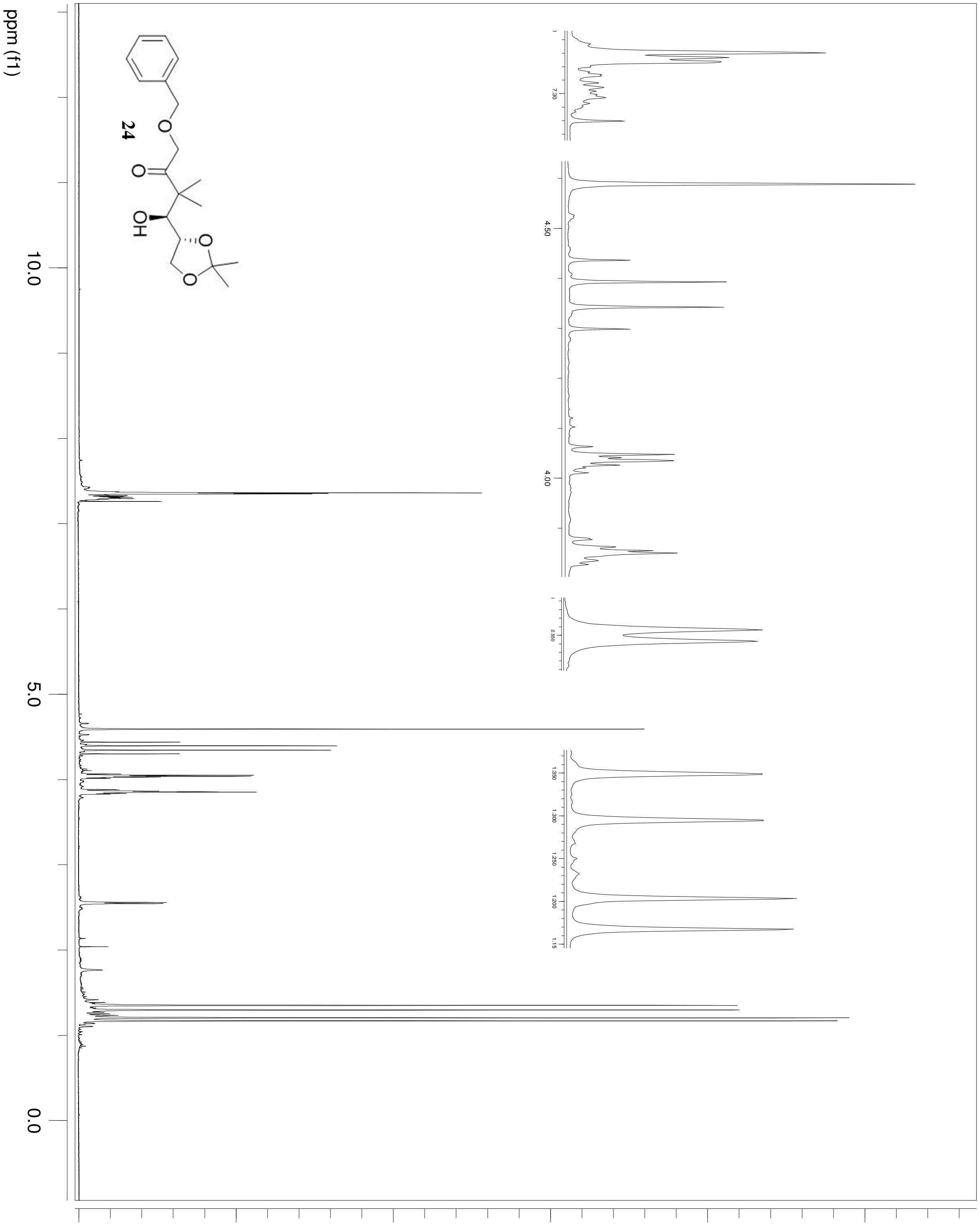


Figure 29. ^{13}C NMR Spectra of **24**

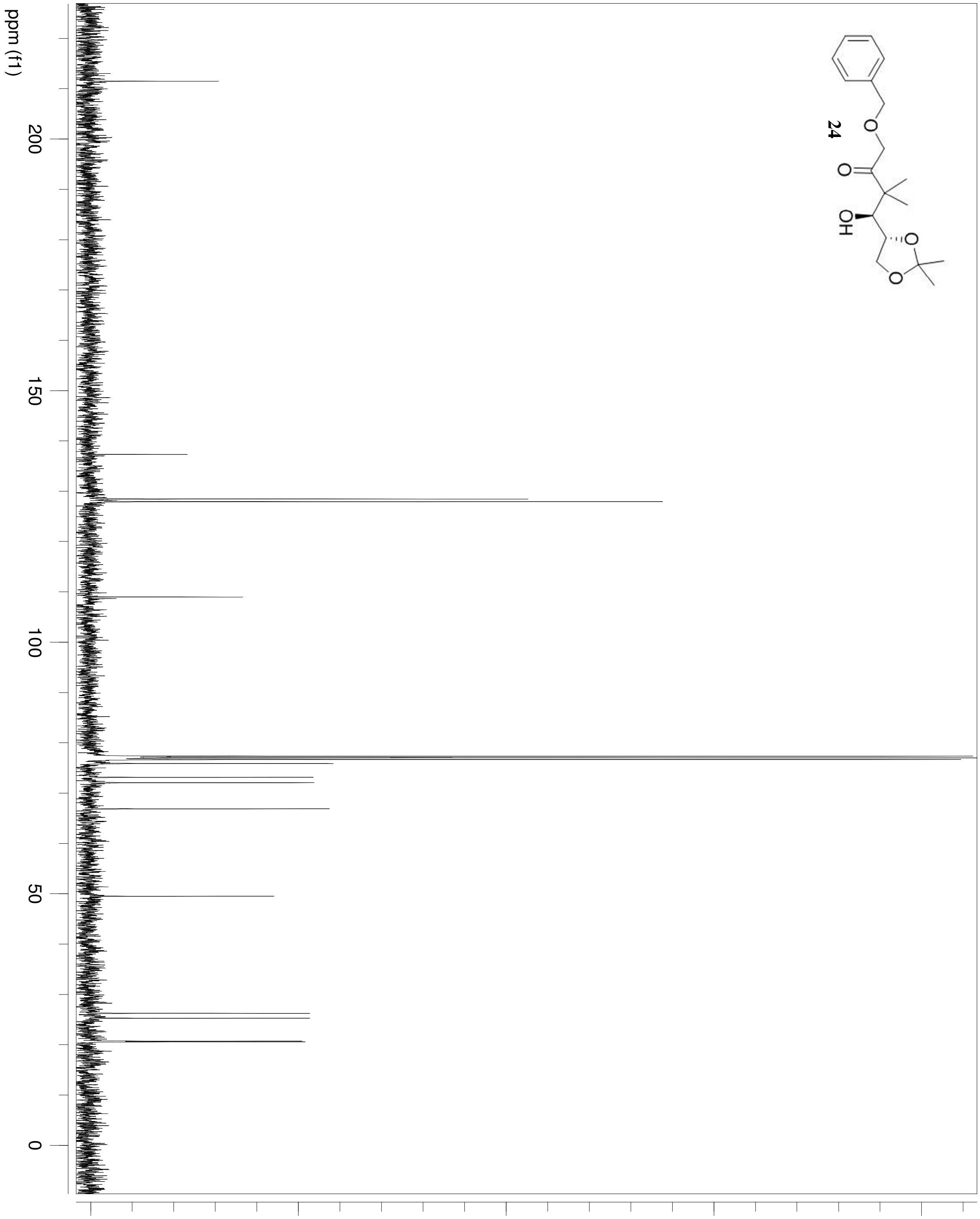


Figure 30. ^{1}H NMR Spectra of **25**

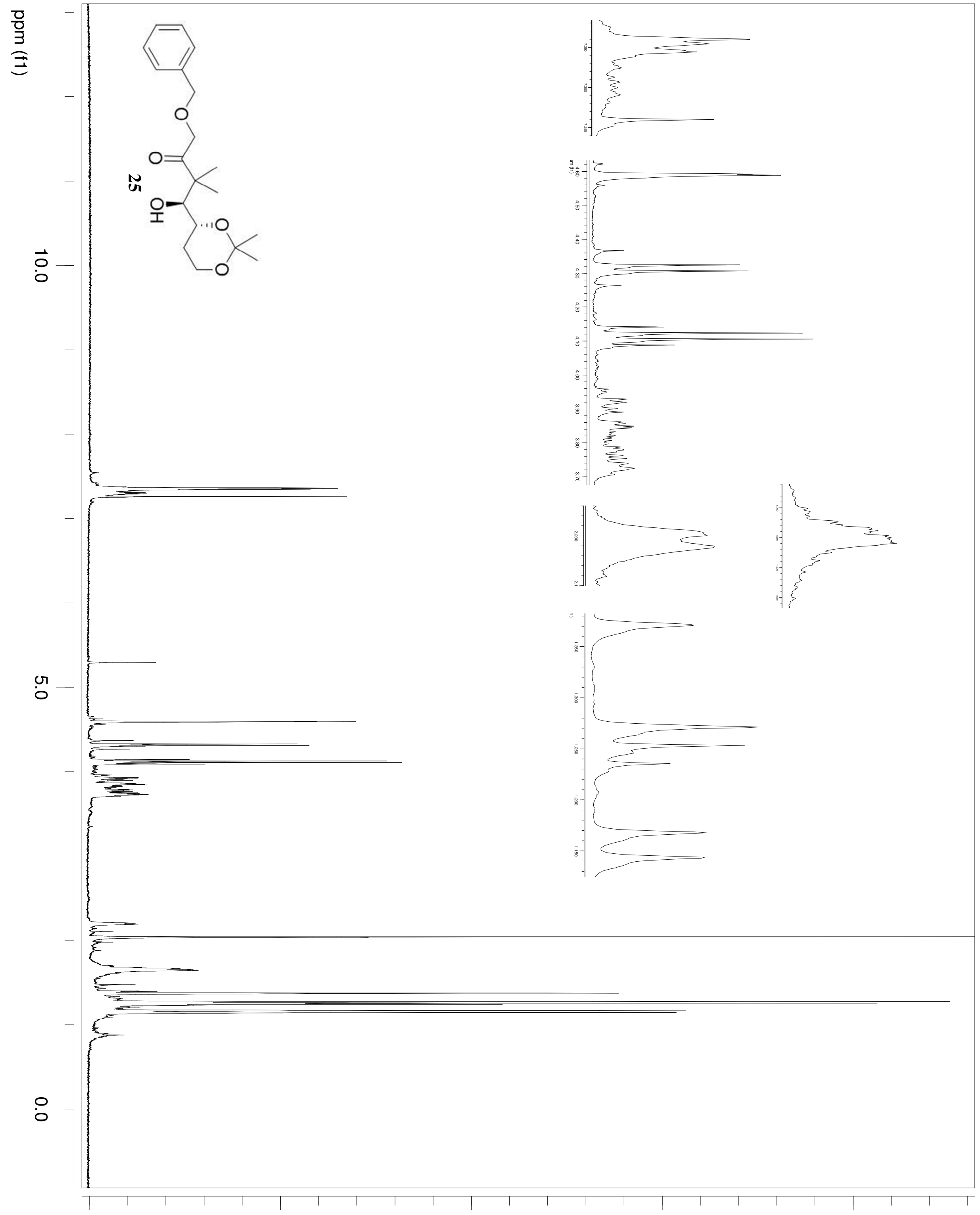


Figure 31. ^{13}C NMR Spectra of **25**

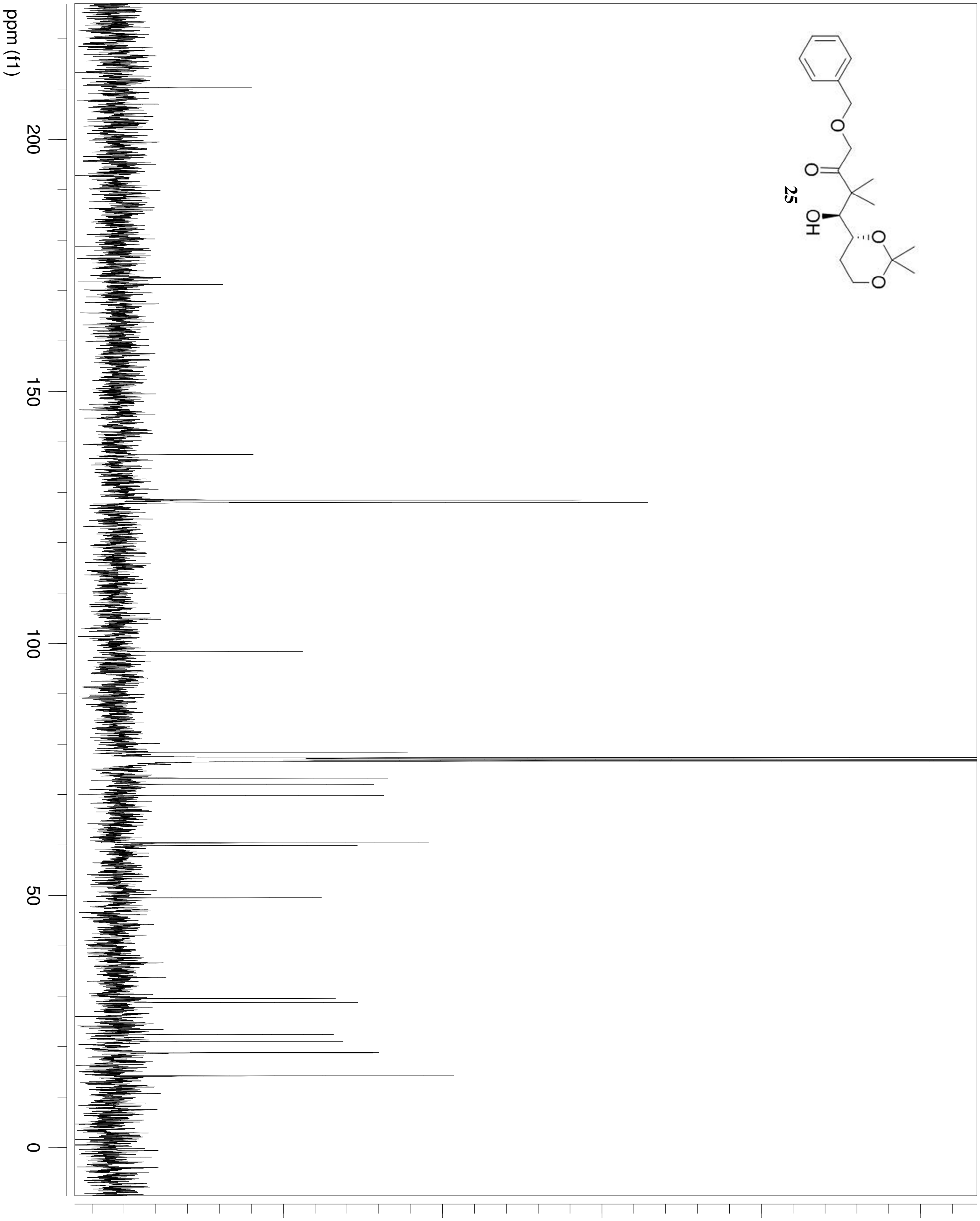


Figure 32. ^{1}H NMR Spectra of **26**

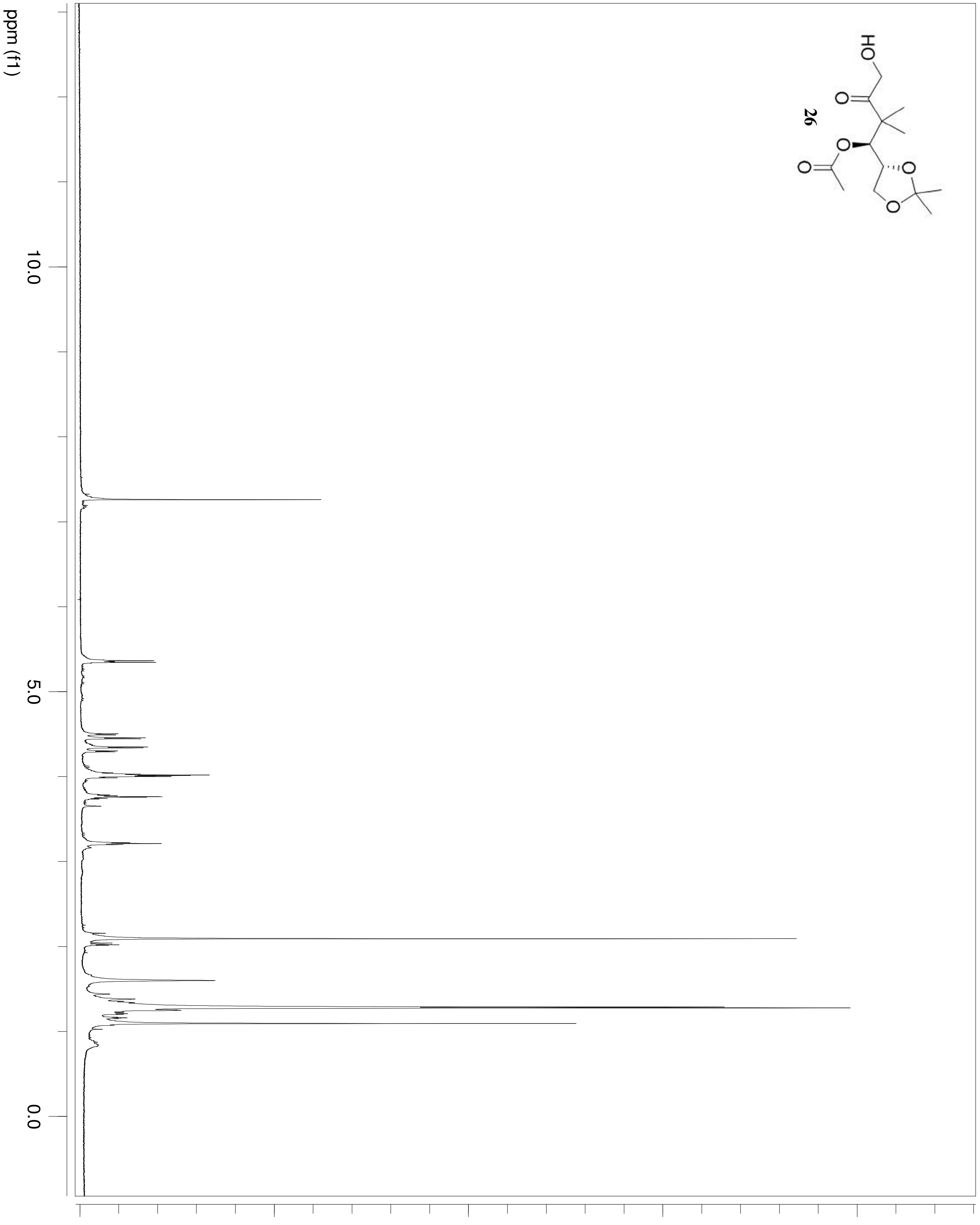


Figure 33. ^{13}C NMR Spectra of **26**

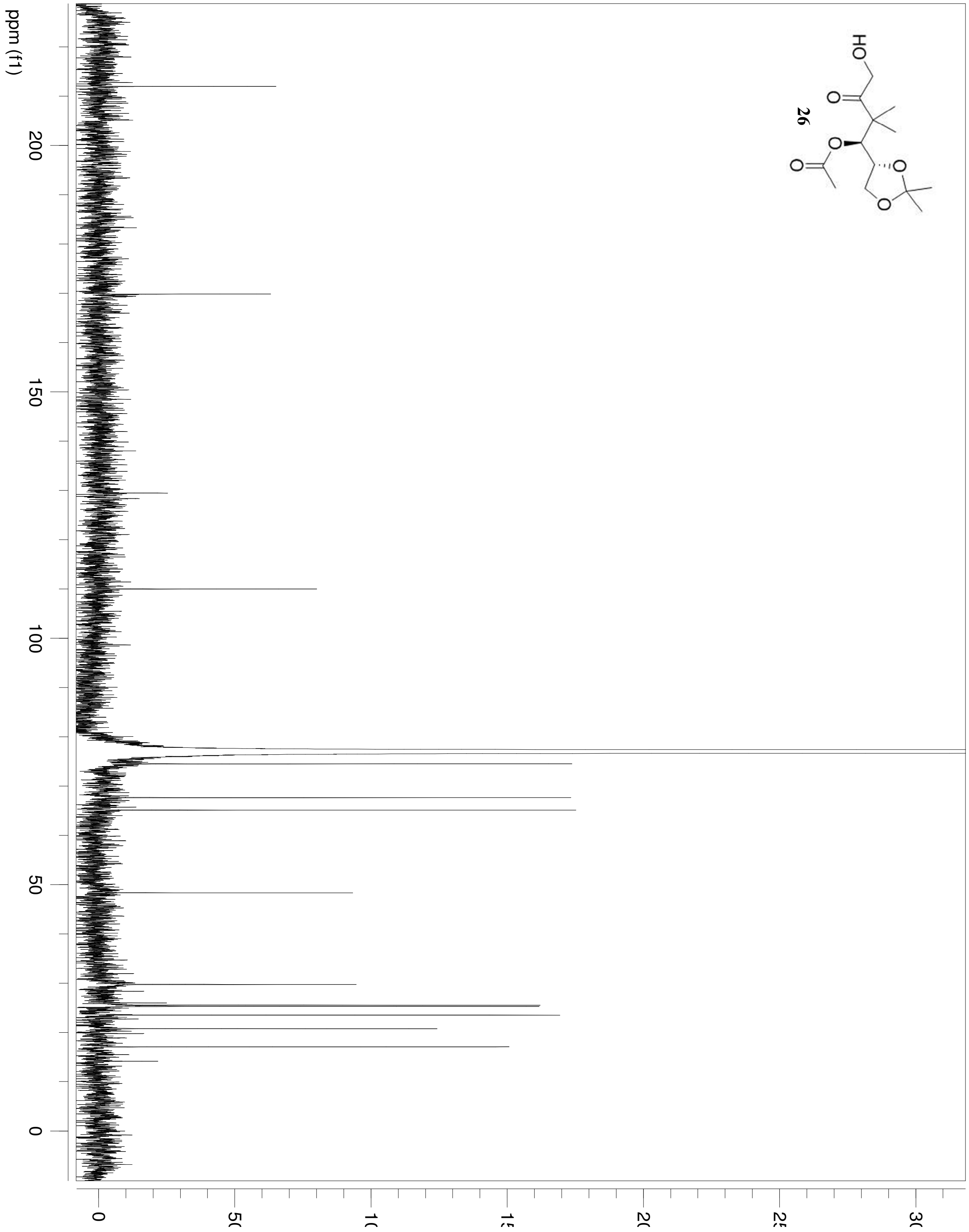


Figure 34. ^{1}H NMR Spectra of **29** Major Isomer

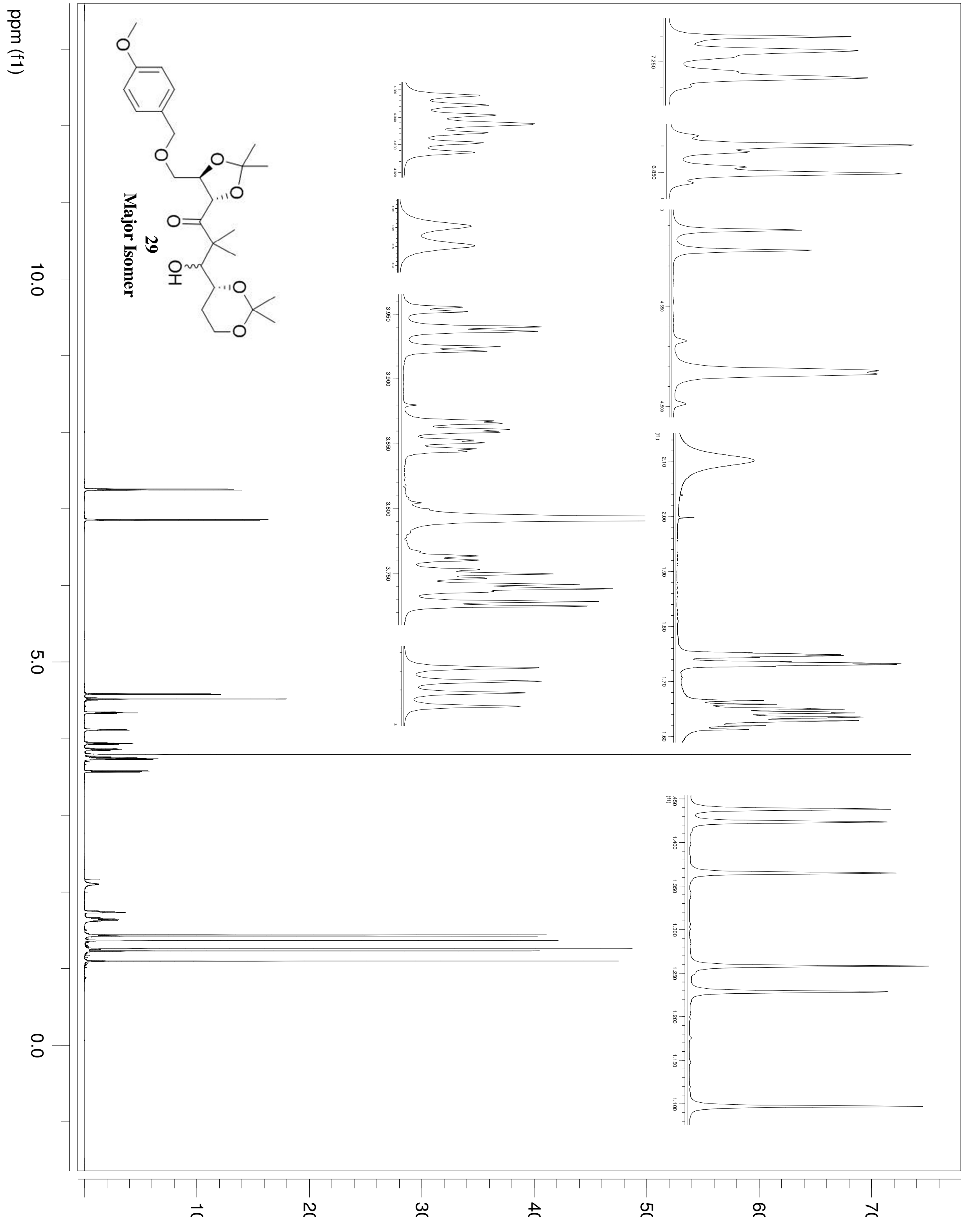


Figure 35. ^{13}C NMR Spectra of **29** Major Isomer

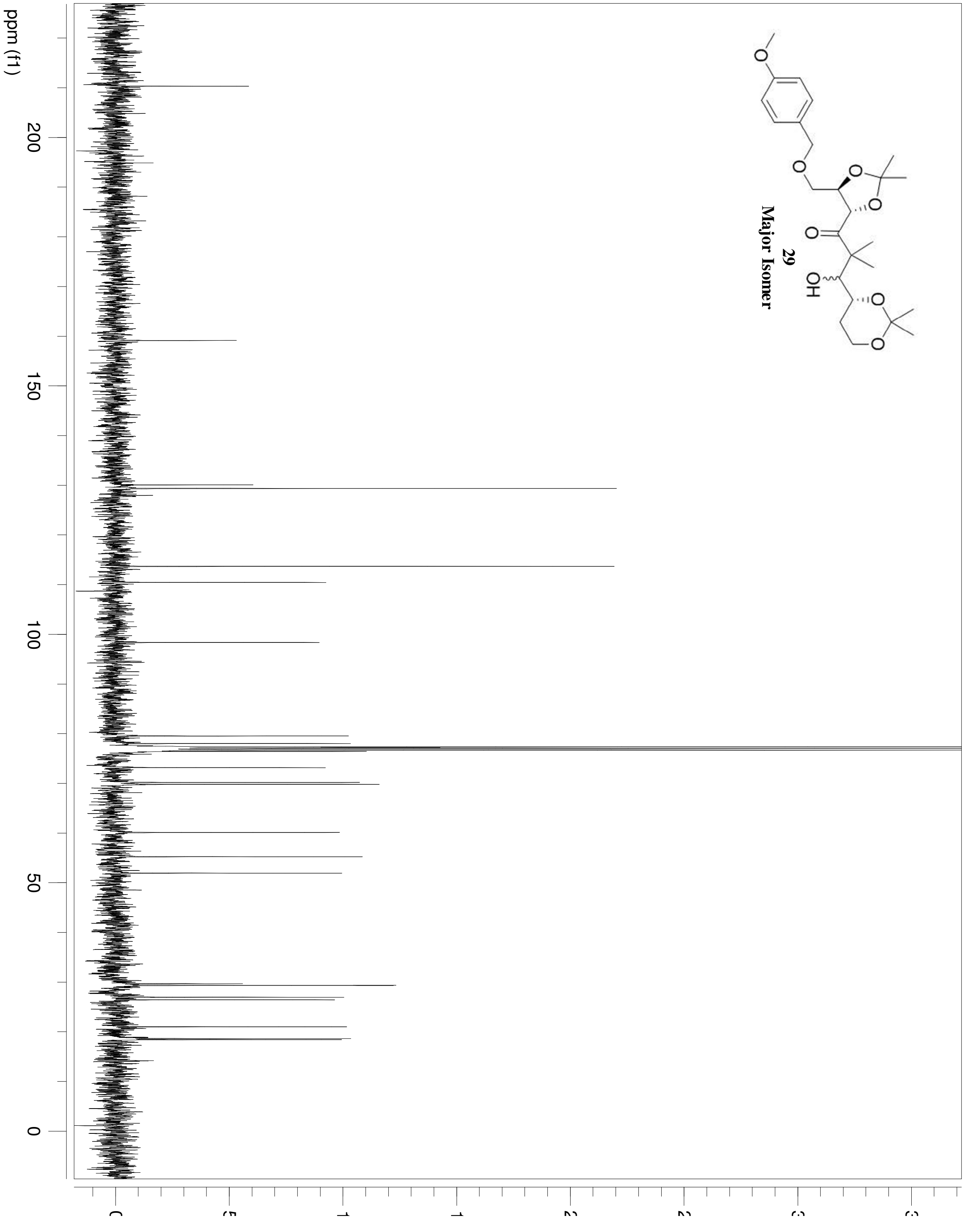


Figure 36. ^{1}H NMR Spectra of **29** Minor Isomer

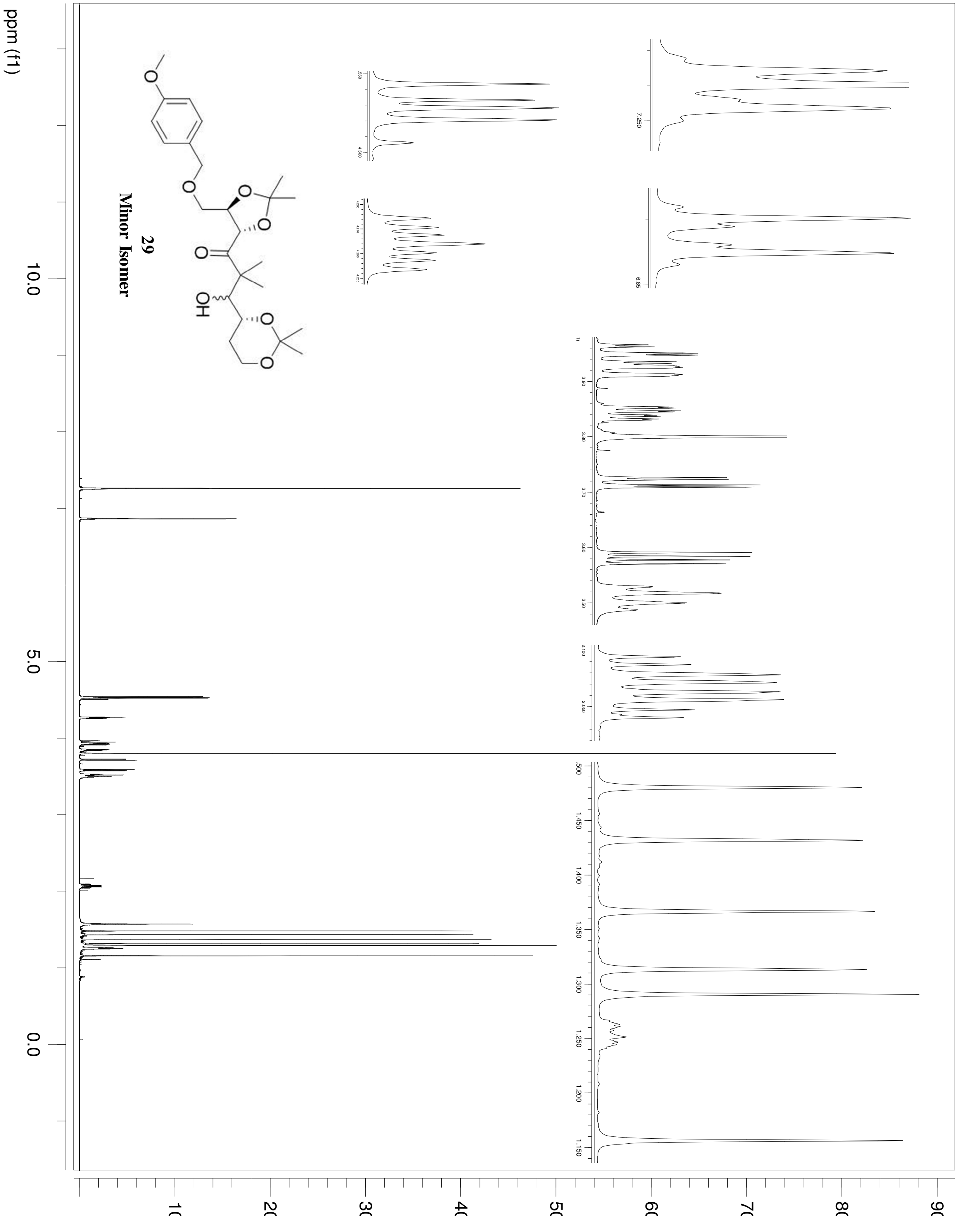


Figure 37. ^{13}C NMR Spectra of **29** Minor Isomer

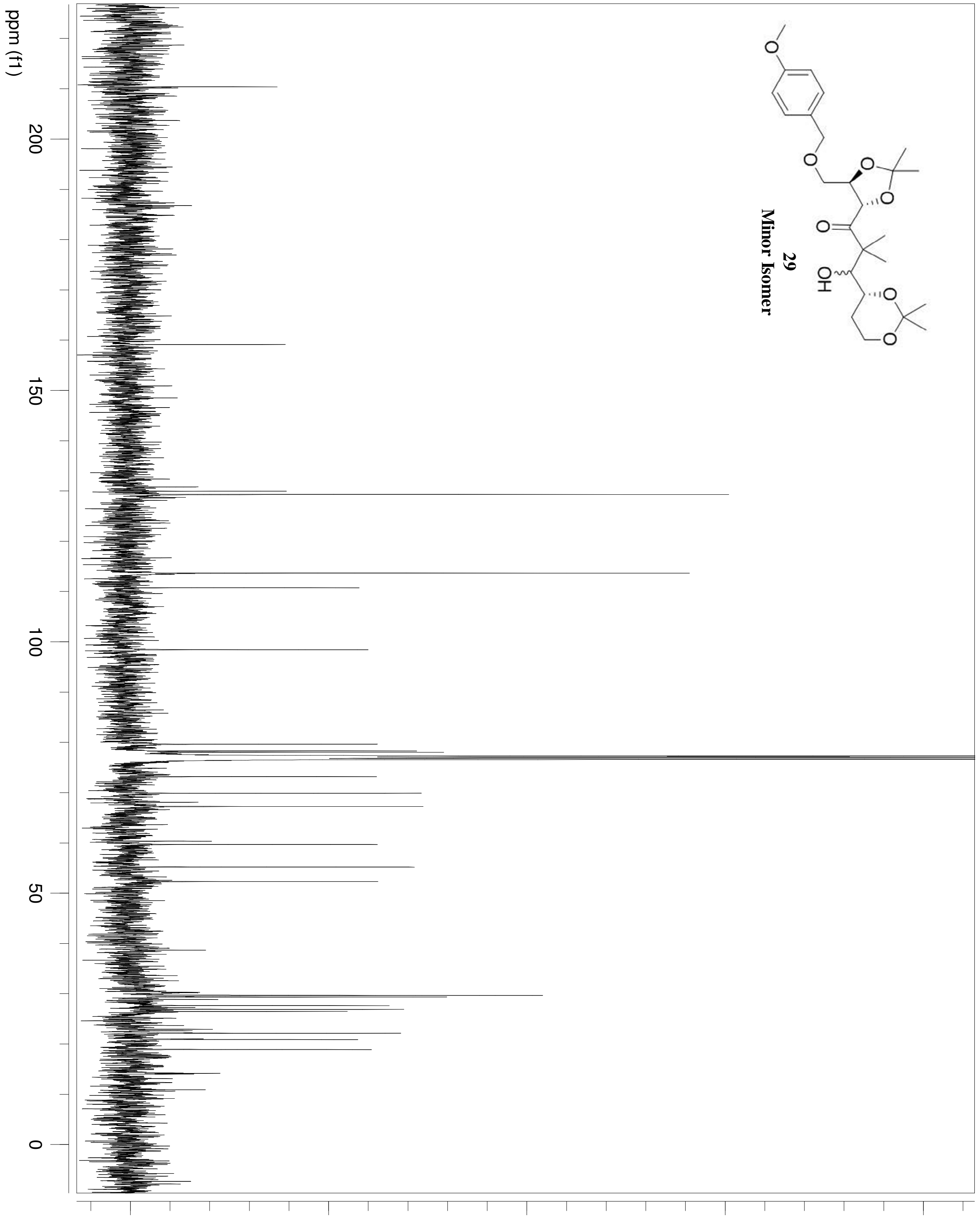


Figure 38. ^{1}H NMR Spectra of **30**

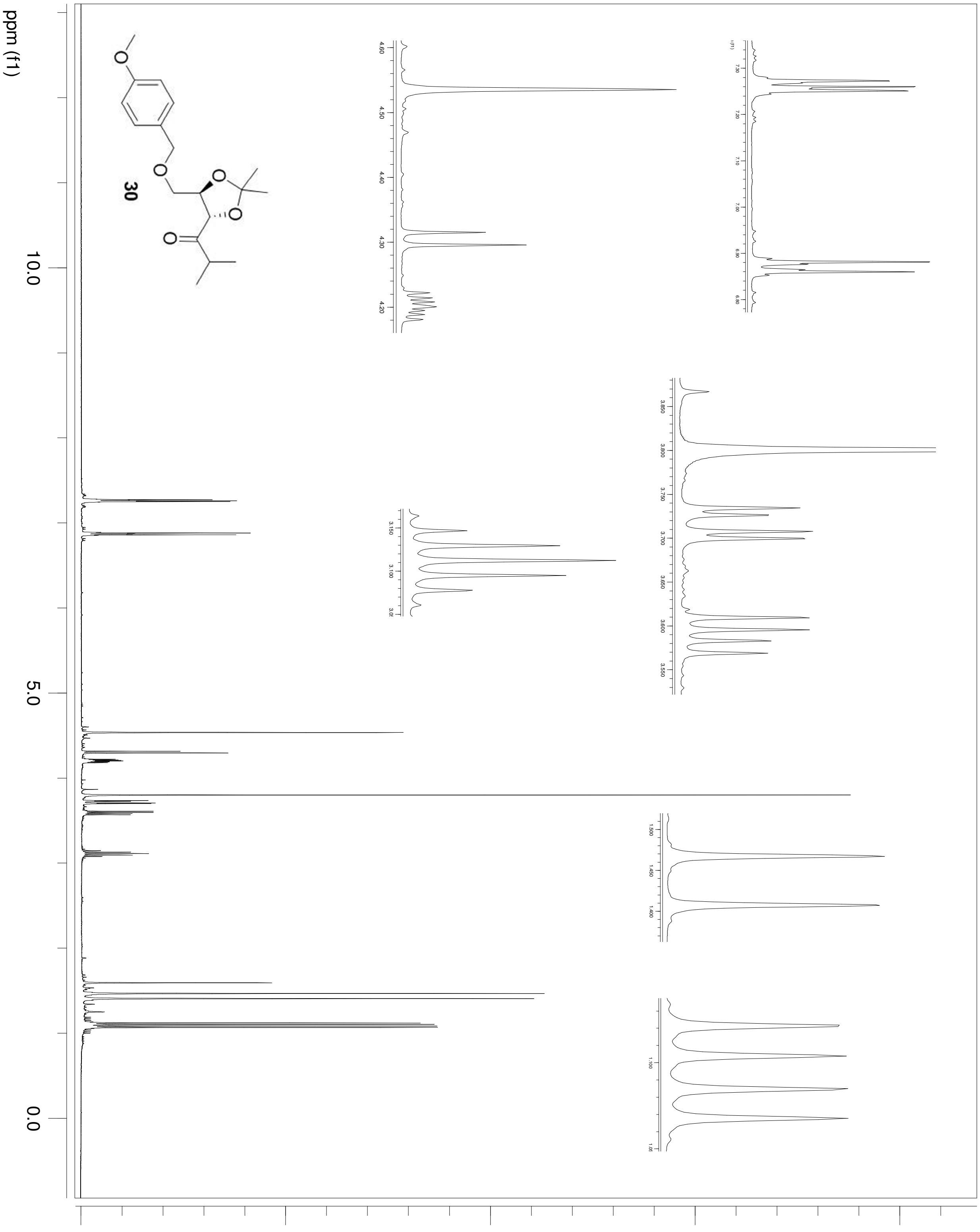
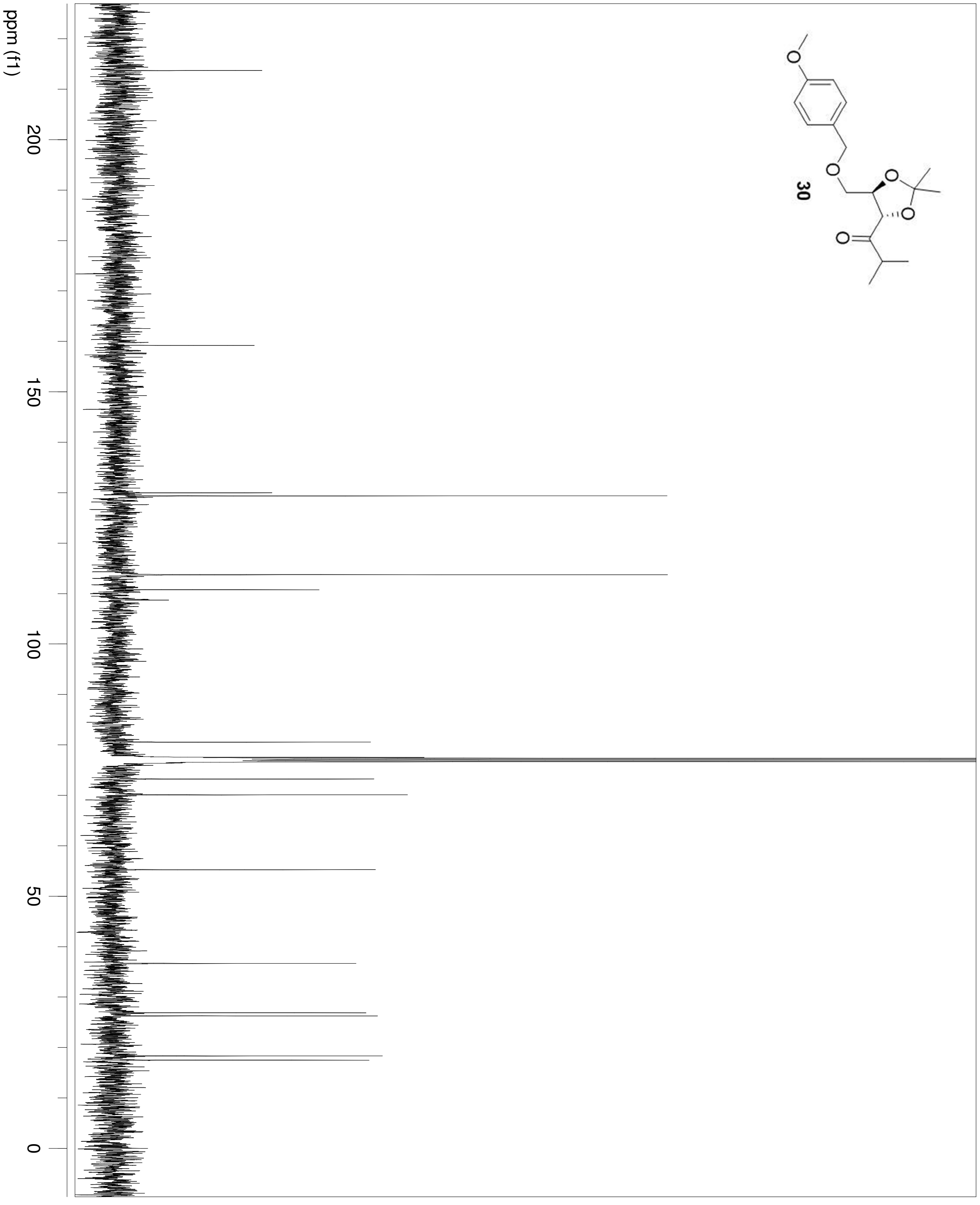


Figure 39. ^{13}C NMR Spectra of **30**



III. References

---

[1] Suzuki, S.; Onishi, T.; Fujita, Y.; Otera, J. Regio- and stereoselective oxidation of ene-type chlorinated olefins, *Synthetic Communications*, **1985**, *15*, 1123-9.

[2] Baer, E.; Fischer, H. *J. Biol. Chem.*, **1939**, *128*, 463.

[3] Baker. S. *J. Am. Chem. Soc.*, **1952**, *74*, 827.

[4] Kita, Y.; Yasuda, H.; Tamura, O.; Itoh, F.; Ke, Y. Y.; Tamura, Y. The chemistry of O-silylated ketene acetals; diastereoselective aldol reaction of 2,3-O-isopropylidene-D-(and L)-glyceraldehydes leading to 2-deoxy-D-(and L)-riboses. *Tetrahedron Letters*, **1985**, *26* 5777-80.

[5] Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.*, **1994**, *59*, 4375.

[6] Corey, E.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. Stereospecific total synthesis of prostaglandins E3 and F3, *Journal of the American Chemical Society*, **1971**, *93*, 1490-1.

[7] Molander, G.; Mautner, K. Oxiranyl anions. Improved synthesis of trimethylsilyl-substituted oxiranyl anions and their addition to aldehydes and ketones. *Journal of Organic Chemistry*, **1989**, *54*, 4042-50.

[8] Muller, R.; Plieninger, H. Synthesis of derivatives of α-acetoxy-2-oxobutyraldehyde. *Chemische Berichte*, **1959**, *92*, 3009-15.