Glycomimetic building blocks: a divergent synthesis of epimers of shikimic acid

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Supporting Information:

I. General Procedures and Materials
II. Spectral Data

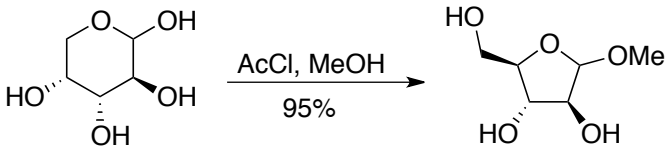
I. General Procedures and Materials:

All compounds were purchased from Sigma Aldrich (Milwaukee, WI) or Fischer Scientific (Pittsburgh, PA). Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Diisopropylethylamine (DIEA) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride.

All reactions were run under nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 F254 (250 μm layer thickness). Analyte visualization was accomplished using a UV lamp and charring with p-anisaldehyde solution. Flash chromatography was performed on Scientific Adsorbents Incorporated silica gel (32-63 μm, 60 Å pore size) using distilled reagent grade hexanes and ACS grade ethyl acetate (EtOAc) or methanol, CH_2Cl_2 and acetic acid. Some compounds were purified on semi-prep-HPLC using a Vydac Protein and Peptide C_{18} column. Gradient elution was performed at 10 mL/min with acetonitrile and water (both containing TFA, 0.1%).

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC-300 or Varian Inova-500 spectrometers, and chemical shifts are reported relative to tetramethylsilane or residual solvent peaks in parts per million ($CHCl_3$: ^1H: ™ 7.26, ^{13}C: ™ 77.0; MeOH: ^1H: ™ 3.31, ^{13}C: 49.15; D_2O: ^1H: ™ 4.80, ^3C: referenced to ^1H. Peak multiplicity is reported as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), etc. High resolution electrospray ionization mass spectra (HRESI-MS) were obtained on a Micromass LCT.

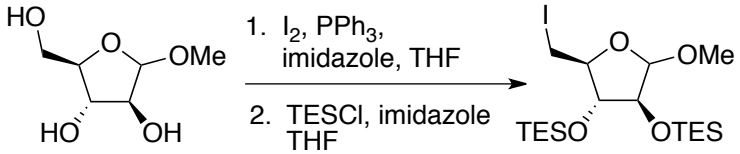
1-*O*-Methyl-D-arabinofuranoside (9)



8 **9**

Acetyl chloride (1.90 mL, 26.6 mmol) was added dropwise to methanol (15 mL) at 0 °C. This solution was transferred to a solution of D-(-)-arabinose (5.03 g, 33.5 mmol) in methanol (120 mL) and stirred for 5 h. The mixture was neutralized with solid NH_4HCO_3, filtered, and the solution was concentrated under reduced pressure to afford a yellow solid. The solid was dissolved in 1:4 MeOH:CH_2Cl_2 solution (100 mL), and the solution was filtered to remove salts. The solution was then concentrated under reduced pressure to afford a yellow oil. The oil was purified by flash chromatography (1:4 MeOH:CH_2Cl_2) to afford **9** as a 3:1 mixture of anomers (A:B) as a colorless oil (5.21 g, 31.7 mmol, 95%). R_f (1:4 MeOH:CH_2Cl_2): 0.36. ^{1}H NMR (300 MHz, CD_3OD): δ 4.75 (d, 1H, anomer A), 4.74 (d, 1H anomer B), 3.9 - 3.6 (br m, 5H), 3.41 (s, 3H, B), 3.36 (s, 3H, A). ^{13}C NMR (150 MHz, CD_3OD) δ 110.74, 104.20, 85.70, 84.61, 83.51, 79.20, 78.91, 77.02, 65.24, 63.22, 55.67, 55.40. MS (EI, *m/z*): 165.1 (M^+) (M^+ calc'd 165.2). HRMS (ESI, *m/z*): 187.0587 (M+Na) (M+Na calc'd 187.0577).

5-Iodo-1-*O*-methy-l-2,3-bis-*O*-triethylsilyl-D-arabinofuranose (10):



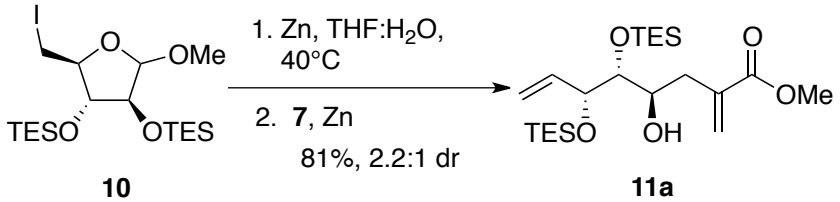
9 **10**

To a 3-neck round-bottom flask equipped with a reflux condenser and addition funnel, imidazole (3.14 g, 46.2 mmol) and triphenylphosphine (3.37 g, 12.8 mmol) were added. Arabinofuranoside **9** (1.29 g, 8.47 mmol) in THF (56 mL) was added to the flask, and the mixture was heated to reflux. A solution of I_2 (3.24 g, 12.8 mmol) in THF (13 mL) was added to the mixture through the addition funnel over a 3 h period. The mixture was heated at reflux for an additional 30 minutes and then cooled to RT and concentrated under reduced pressure to afford a colorless oil. The oil was purified by flash chromatography (100% CH_2Cl_2 → 1:19 MeOH:CH_2Cl_2) to afford 5-iodo-1-*O*-methyl-D-arabinofuranoside as 3:1 mixture of anomers obtained as a colorless syrup. Triphenyl phosphine oxide and imidazole could be detected. R_f (1:19 MeOH:CH_2Cl_2): 0.17. R_f for triphenyl phosphine oxide: 0.15. R_f for imidazole: 0.20.

To a solution of crude 5-iodo-1-*O*-methyl-D-arabinofuranoside (2.40 g, 8.47 mmol) and imidazole (3.14 g, 46.2 mmol) in CH_2Cl_2 (43 mL), triethylsilyl chloride (6.20 mL, 32.3 mmol) was added dropwise. A white precipitate formed during addition. After 2 h, no starting material remained as judged via TLC. The mixture was quenched by addition of water (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic layers were dried with $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to afford a colorless syrup. The syrup was purified by flash chromatography (1:29 EtOAc:hexanes → 1:19 EtOAc:hexanes) to afford **9** as a colorless liquid (3.19 g, 6.34 mmol, 75% over 2 steps). R_f (1:19 EtOAc:hexanes): 0.52. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (d, *J*=2.2, 1H, anomer A), 4.71 (d, *J*=3.9, 1H, anomer B), 4.15 - 4.0 (m, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.40 (s, 3H, B), 3.38 (s,

3H, A), 3.3 - 3.2 (m, 1H), 0.98 (m, 18H), 0.64 (m, 12H). ^{13}C NMR (150 MHz) δ 109.60, 103.50, 84.27, 83.08, 82.34, 81.90, 80.39, 79.90, 55.68, 55.54, 6.99, 6.92, 6.87, 5.22, 5.00, 4.93. HRMS (ESI$^+$ *m/z*): 525.1346 (M+Na) (M+Na calc'd 525.1324).

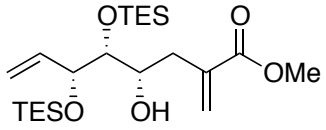
(4*R*,5*R*,6*R*)-Methyl 2-methylene-4,5,6-tris((triethylsilyl)oxy)oct-7-enoate (11a):



10 **11a**

To a 3-neck flask equipped with a reflux condenser, zinc dust (1.35 g, 20.6 mmol) was added. The flask was purged with $Ar_{(g)}$. Deoxygenated THF (12 mL) and deoxygenated Milli-Q water (1.6 mL) was added to the flask and heated to 38°C. A solution of **9** (1.01 g, 2.01 mmol) in deoxygenated THF (2 mL) was added to the flask and agitated by sonication for 1.5 h. Compound **7**, methyl-2-(bromomethyl)acrylate (0.71 mL, 6.0 mmol), was added to the solution dropwise over 1 h with constant sonication. The mixture was agitated by sonication for an additional 15 minutes before it was cooled to RT. The mixture was filtered through a pad of celite and diluted with water (20 mL). The aqueous layer was extracted with diethyl ether (2 x 20 mL) and CH_2Cl_2 (1 x 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried with $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to afford a colorless oil. The oil was purified by flash chromatography (CH_2Cl_2) to afford **15a** (0.709 g, 1.59 mmol, 81%) as a mixture of diastereomers 2.2:1 desired:undesired. R_f (CH_2Cl_2): 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (dd, *J*=1.1, 1H), 6.09 (ddd, *J*=17.8, 15.0, 4.4, 1H), 5.70 (d, *J*=0.8, 1H), 5.35 (dt, *J*=17.2, 1.8, 1H), 5.26 (dt, *J*=10.7, 1.7, 1H), 4.40 (m, 1H), 3.90 (m, 2H), 3.85 (s, 3H), 3.76 (dd, *J*=7.6, 4.4, 1H), 2.78 (d, *J*=13.9, 1H), 2.20 (dd, *J*=14.3, 13.1, 1H), 0.90 (m, 18H), 0.60 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.10, 137.86, 135.91, 126.82, 116.27, 76.77, 76.14, 71.43, 76.77, 76.14, 71.44, 51.95, 36.39, 7.06, 6.94, 5.27, 4.84. HRMS (ESI$^+$ *m/z*): 445.2811 (M+H) (M+H calc'd 445.2801).

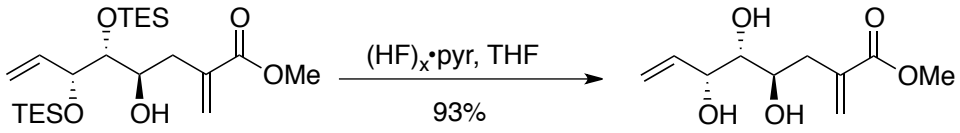
(4*S*,5*R*,6*R*)-Methyl 2-methylene-4,5,6-tris((triethylsilyl)oxy)oct-7-enoate (11b):



11b

Minor diastereomer isolated from the reaction of compound **10** above. R_f (CH_2Cl_2): 0.25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, *J*=1.6, 1H), 6.01 (ddd, *J*=17.2, 10.4, 5.8, 1H), 5.63 (d, *J*=1.3, 1H), 5.23 (dt, *J*=17.2, 1.7, 1H), 5.18 (dt, *J*=10.5, 1.5, 1H), 4.18 (m, 1H), 3.94 (m, 1H), 3.70 (s, 3H), 3.57 (dd, *J*=5.2, 2.7, 1H), 2.57 – 2.37 (m, 2H), 1.05 – 0.90 (m, 18H), 0.71 – 0.55 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.930, 137.837, 137.647, 127.000, 115.771, 77.023, 75.564, 68.547, 51.962, 37.707, 7.085, 6.990, 5.343, 5.093. HRMS (ESI$^+$ *m/z*): 445.2800 (M+H) (M+H calc'd 445.2801).

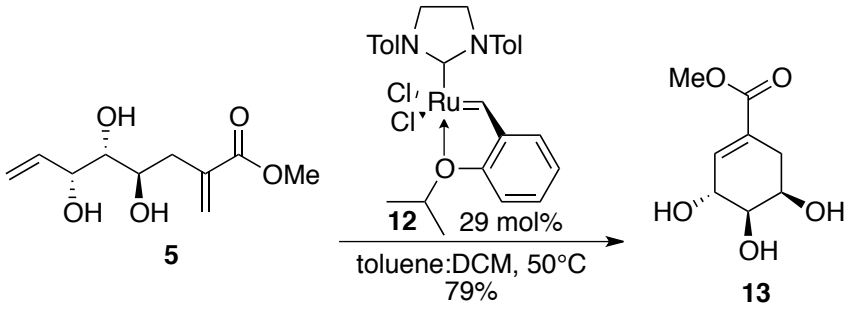
(4*R*,5*R*,6*R*)-Methyl 2-methylene-4,5,6-trihydroxyoct-7-enoate (5):



11a **5**

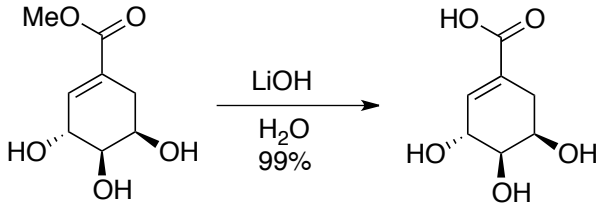
To a solution of **11a** (0.526 g, 1.18 mmol) in anhydrous THF (12 mL), $(HF)_x$·pyridine (0.21 mL, 12 mmol) was added dropwise. The solution was stirred for 10 h under $Ar_{(g)}$. The product was concentrated under reduced pressure and purified by flash chromatography (1:19 MeOH:CH_2Cl_2) to afford **5** as a colorless oil (0.237 g, 1.10 mmol, 93%). R_f (1:19 MeOH:CH_2Cl_2): 0.17. ^{1}H NMR (300 MHz, CD_3OD) δ 6.20 (d, *J*=1.4, 1H), 5.89 (ddd, *J*=17.3, 10.4, 5.8, 1H), 5.69 (d, *J*=0.8, 1H), 5.25 (dt, *J*=17.3, 1.6, 1H), 5.18 (dt, *J*=10.4, 1.4, 1H), 4.29 (m, 1H), 3.77 (ddd, *J*=9.7, 7.2, 2.7, 1H), 3.73 (s, 3H), 3.33 (s, 1H), 2.84 (ddd, *J*=14.2, 2.7, 0.8, 1H), 2.30 (ddd, *J*=14.4, 9.7, 0.7, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 169.587, 140.097, 139.167, 128.158, 116.158, 78.136, 73.467, 71.345, 52.491, 37.062. HRMS (ESI^+ *m/z*): 239.0878 (M+Na) (M+Na calc'd 239.0890).

(-)-Methyl 4-*epi*-shikimate (13):



To a 3-neck round-bottom flask equipped with a reflux condenser, Hoveyda-Grubbs catalyst **12** (0.010 g, 0.017 mmol) was added and purged with $Ar_{(g)}$. Toluene (73 mL) was added and the solution was heated to 50 °C. In a separate flask, diene **16** (0.013 g, 0.060 mmol) was dissolved in CH_2Cl_2 (5 mL). The solution was added dropwise to the reaction flask via cannula over 1 h. After 5 h, the mixture was cooled to room temperature, filtered and the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (100% CH_2Cl_2 → 1:9 MeOH:CH_2Cl_2) to afford **13** as a pale brown solid (9.0 mg, 0.047 mmol, 79%). R_f (1:9 MeOH:CH_2Cl_2): 0.23. ^{1}H NMR (300 MHz, CD_3OD) δ 6.76 (dt, *J*=3.4, 1.9, 1H), 4.30 (m, 1H), 4.05 (td, *J*=4.7, 2.4, 1H), 3.72 (s, 3H), 3.62 (dd, *J*=6.6, 2.4), 2.61 – 2.40 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 168.785, 139.402, 129.813, 75.084, 70.393, 69.111, 52.539, 32.071. HRMS (ESI^+ *m/z*): 211.0587 (M+Na) (M+Na calc'd 211.0577).

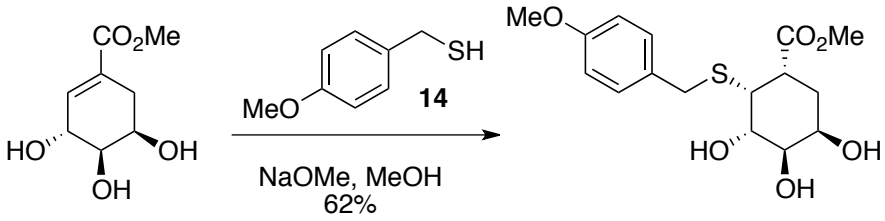
(-)-4-*epi*-Shikimic acid (3):



13 **3**

To a solution of **13** (0.407 g 2.16 mmol) in THF (5.4 mL), 1 M LiOH (5.4 mL, 5.4 mmol) was added and the mixture was stirred for 2 h. The solution was neutralized with acidic resin, filtered and the solution was concentrated under reduced pressure to afford **3** as a pale brown solid (0.370 g, 2.13 mmol, 99%). The purity of the product was verified by ^{1}H NMR. ^{1}H NMR (300 MHz, CD_3OD) δ 6.61 (dt, *J*=3.3, 1.7, 1H), 4.17 (m, 1H), 4.03 (td, *J*=4.9, 2.4, 1H), 3.62 (dd, *J*=6.1, 2.1, 1H), 2.63 – 2.40 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 173.149, 135.872, 133.606, 75.479, 70.843, 69.504, 32.773. HRMS (ESI^- *m/z*): 173.0442 (M-H) (M-H calc'd 173.0445).

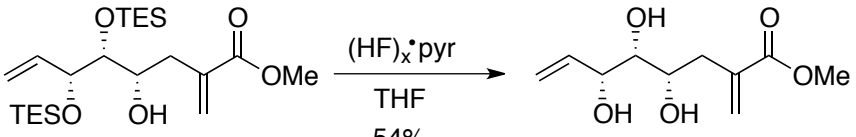
(1*S*,2*R*,3*S*,4*R*,5*R*)-Methyl 3,4,5-trihydroxy-2-((-4-methoxybenzyl)thio) cyclohexanecarboxylate (15):



13 **15**

To a vial containing thiol **13** (0.096 g, 0.57mmol) and 4-methoxy-α-toluenethiol **14** (0.14 mL, 1.0 mmol), anhydrous methanol (5.7 mL) and 25% NaOMe in methanol (0.22 mL, 1.0 mmol) was added. The solution was stirred overnight. The solution was quenched to pH = 6 with acidic resin and filtered. The solution was concentrated under reduced pressure to afford a pale yellow solid. The crude compound was purified by flash chromatography (1:9 MeOH:CH_2Cl_2) to afford **15** (0.107 g, 0.31 mmol, 62%) as a white solid. Rf (1:4 MeOH:CH_2Cl_2): 0.57. ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (d, 2H), 6.85 (d, 2H), 4.0 (dd, *J*=9.4, 3.9, 1H), 3.95 (d, *J*=4.5, 1H), 3.80 (d, *J*=3.2, 2H), 3.74 (s, 3H), 3.61 (dd, *J*=9.7, 3.3, 1H), 3.51 (s, 3H), 3.48 (td, *J*=4.1, 1.8, 1H), 3.14 (dt, 12.5, 3.6, 1H), 1.94 (dddd, *J*=14.6, 7.6, 3.8, 1.8, 1H), 1.75 (ddd, *J*=14.1, 12.6, 2.4, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 174.876, 160.355, 132.042, 131.941, 131.551, 131.345, 114.974, 73.940, 72.839, 69.566, 55.944, 52.486, 42.199, 38.943, 30.674. HRMS (ESI^+ *m/z*): 365.1043 (M+Na) (M+Na calc'd 365.1030).

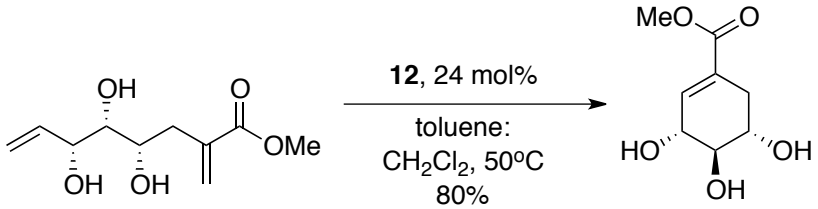
(4*S*,5*R*,6*R*)-Methyl 2-methylene-4,5,6-trihydroxyoct-7-enoate (16):



11b **16**

To a solution of diene **11b** (0.213 g, 0.479 mmol) in anhydrous THF (4.8 mL), $(HF)_x$·pyridine (0.087 mL, 4.79 mmol) was added dropwise. A white precipitate formed, and the mixture was stirred overnight. The mixture was concentrated under reduced pressure and purified by flash chromatography (1:29 MeOH:CH_2Cl_2) to afford **16** as a white solid (0.059g, 0.258 mmol, 58%). Rf (1:19 MeOH:CH_2Cl_2): 0.10. ^{1}H NMR (300 MHz, CD_3OD) δ 6.21 (d, *J*=1.5, 1H), 5.89 (ddd, *J*=17.4, 10.5, 6.6, 1H), 5.72 (d, *J*=1.4, 1H), 5.27 (dt, *J*=17.3, 1.8, 1H), 5.19 (dt, *J*=10.4, 1.1, 1H), 4.18 (t, *J*=6.6, 1H), 3.83 (ddd, *J*=7.8, 5.9, 2.3, 1H), 3.65 (s, 3H), 3.26 (dd, *J*=6.6, 2.3, 1H), 2.64 – 2.48 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD) δ 169.309, 139.326, 138.836, 128.459, 117.180, 76.963, 75.529, 70.990, 52.505, 38.131. HRMS (ESI$^+$ *m/z*): 239.0878 (M+Na) (M+Na calc'd 239.0890).

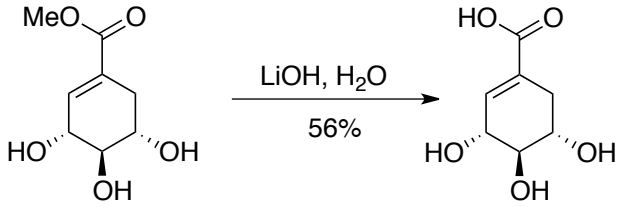
(+)-Methyl 3-*epi*-shikimate (17):



16 **17**

To a 3-neck round-bottom flask equipped with a reflux condenser, Hoveyda-Grubbs catalyst **12** (8.0 mg, 0.014 mmol) was added and purged with $N_{2(g)}$. Toluene (26 mL) was added, and the solution was heated to 50 °C. In a separate flask, a solution of diene **16** (0.012 g, 0.057 mmol) in CH_2Cl_2 (5 mL) was added to the mixture flask dropwise via cannula. After 5 h, the mixture was cooled to room temperature, filtered and the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (100% CH_2Cl_2 → 1:9 MeOH:CH_2Cl_2) to afford **17** (8.0 mg, 0.042 mmol, 80%) as a white solid. Rf (1:9 MeOH:CH_2Cl_2): 0.13. ^{1}H NMR (300 MHz, CD_3OD) δ 6.67 (t, *J*=2.4, 1H), 4.15 (m, 1H), 3.75 (s, 3H), 3.65 (td, *J*=9.6, 5.8, 1H), 3.37 (dd, *J*=10.1, 7.8, 1H), 2.78 (ddd, *J*=17.5, 5.9, 1.2), 2.17 (dddd, *J*=17.4, 9.7, 3.6, 2.6, 1H). ^{13}C NMR (150 MHz, CD_3OD) δ 168.399, 140.876, 129.298, 78.443, 73.191, 70.306, 52.583, 33.626. MS (ESI$^+$ *m/z*): 399.1268 (2M+Na) (2M+Na calc'd 399.1262).

(+)-3-*epi*-Shikimic acid (18)

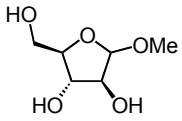


17 **18**

To a flask containing **17** (9.0 mg, 0.050 mmol), 1.0 M LiOH (0.25 mL, 0.25 mmol) was added, and the solution was stirred for 2 h. The solution was neutralized with acidic resin, filtered and the solution concentrated under reduced pressure. The product was purified via semi-prep-HPLC on Vydac Protein and Peptide C18 column #018 with 35% → 95% acetonitrile in water with 0.1% TFA over 21 minutes. Concentration *in vacuo* afforded the acid **18** (5.0 mg, 0.028 mmol, 56%) as a white solid. ^{1}H NMR (300 MHz, D_2O) δ 6.64 (t, *J*=2.5, 1H), 4.29 (m, 1H), 3.80 (td, *J*=9.9, 5.8, 1H), 3.50 (dd, *J*=10.2, 8.1, 1H), 2.81 (dd, *J*=15.9, 5.6, 1H), 2.23 (m, 1H). ^{13}C NMR (250 MHz, D_2O) δ 171.144, 137.827, 129.894, 76.495, 71.650, 68.767, 32.170. HRMS (ESI^- *m/z*): 173.047 (M-H) (M-H calc'd 173.0455)

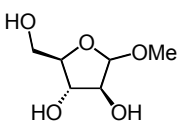
II. Spectral Data

^{1}H NMR of compound **9** (in CD_3OD, 300 MHz)

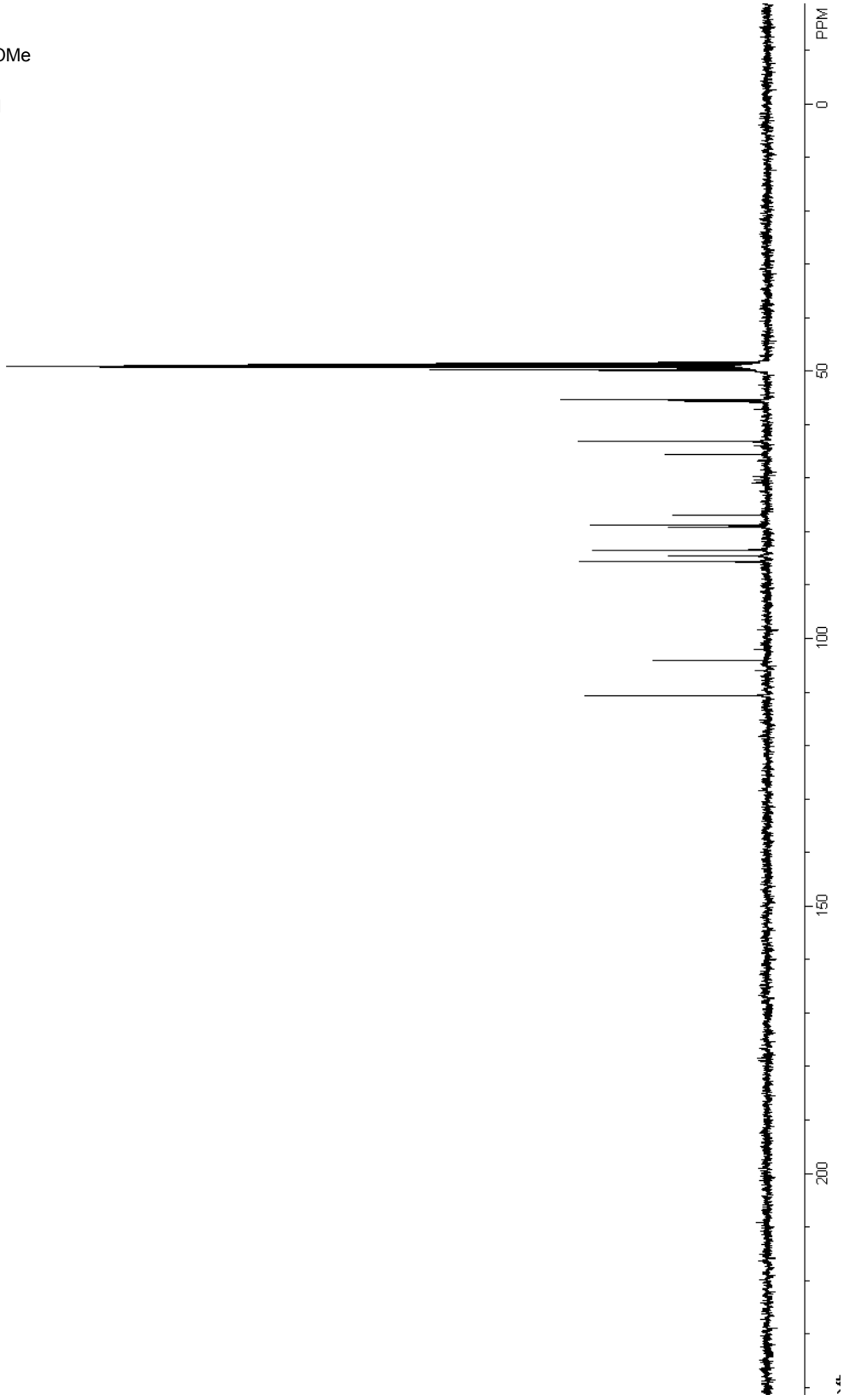


9

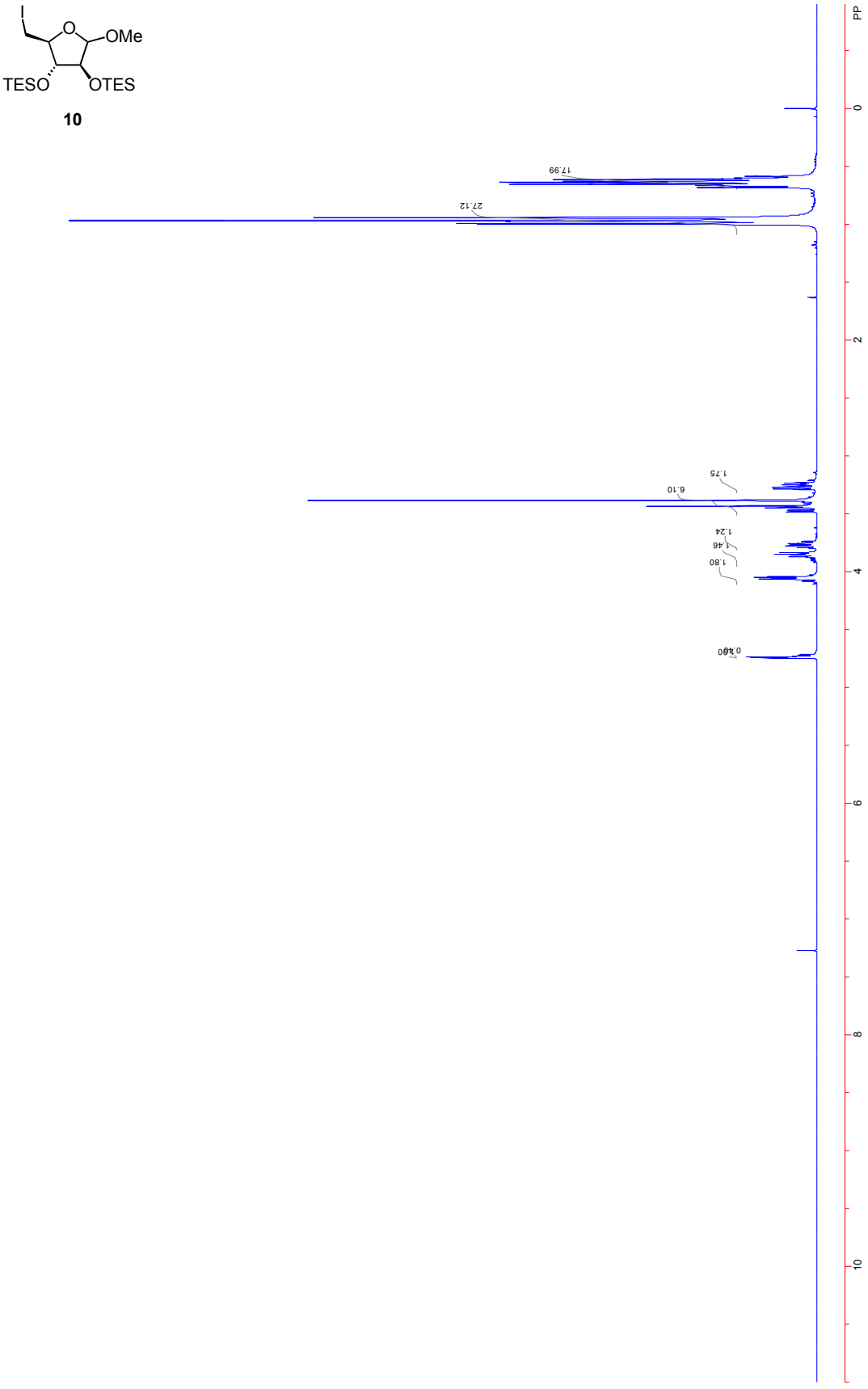
^{13}C NMR of compound **9** (in CD_3OD, 150 MHz)



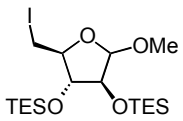
9



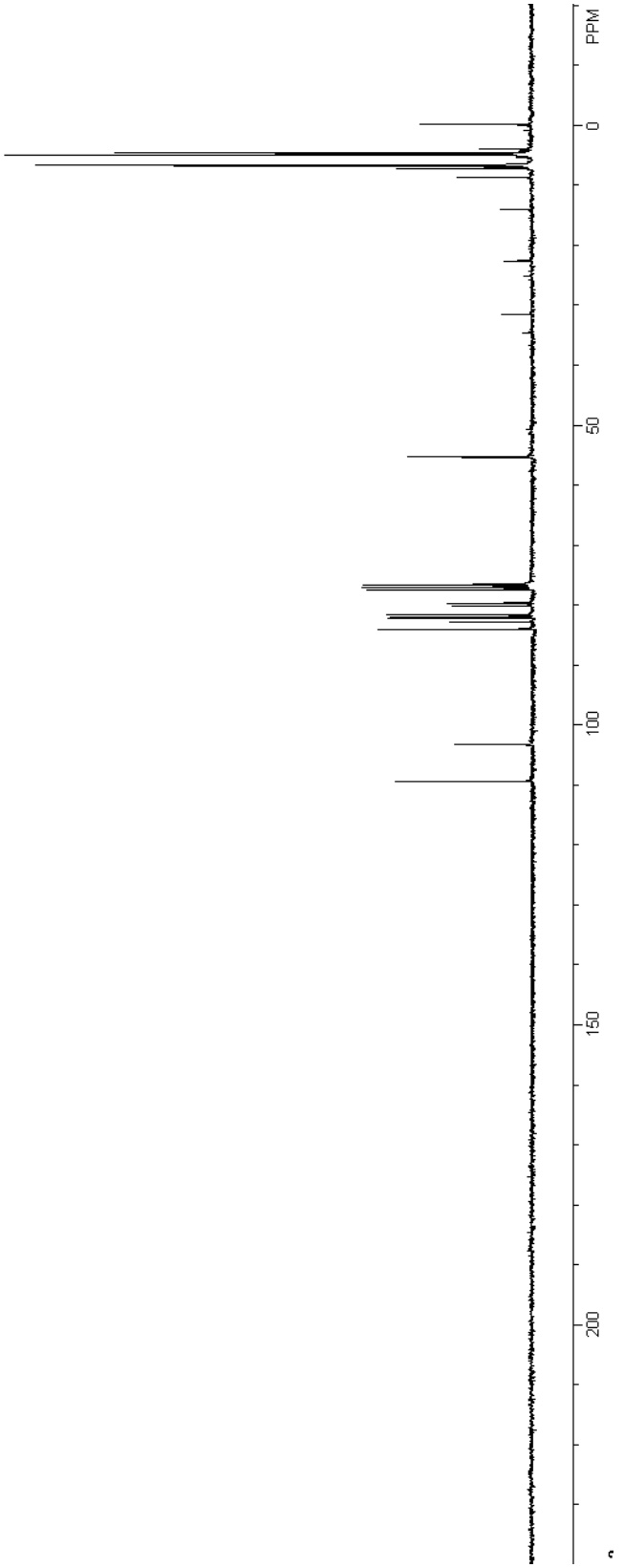
^{1}H NMR of compound **10** (in $CDCl_3$, 300 MHz)



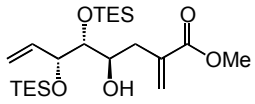
^{13}C NMR of compound **10** (in $CDCl_3$, 150 MHz)



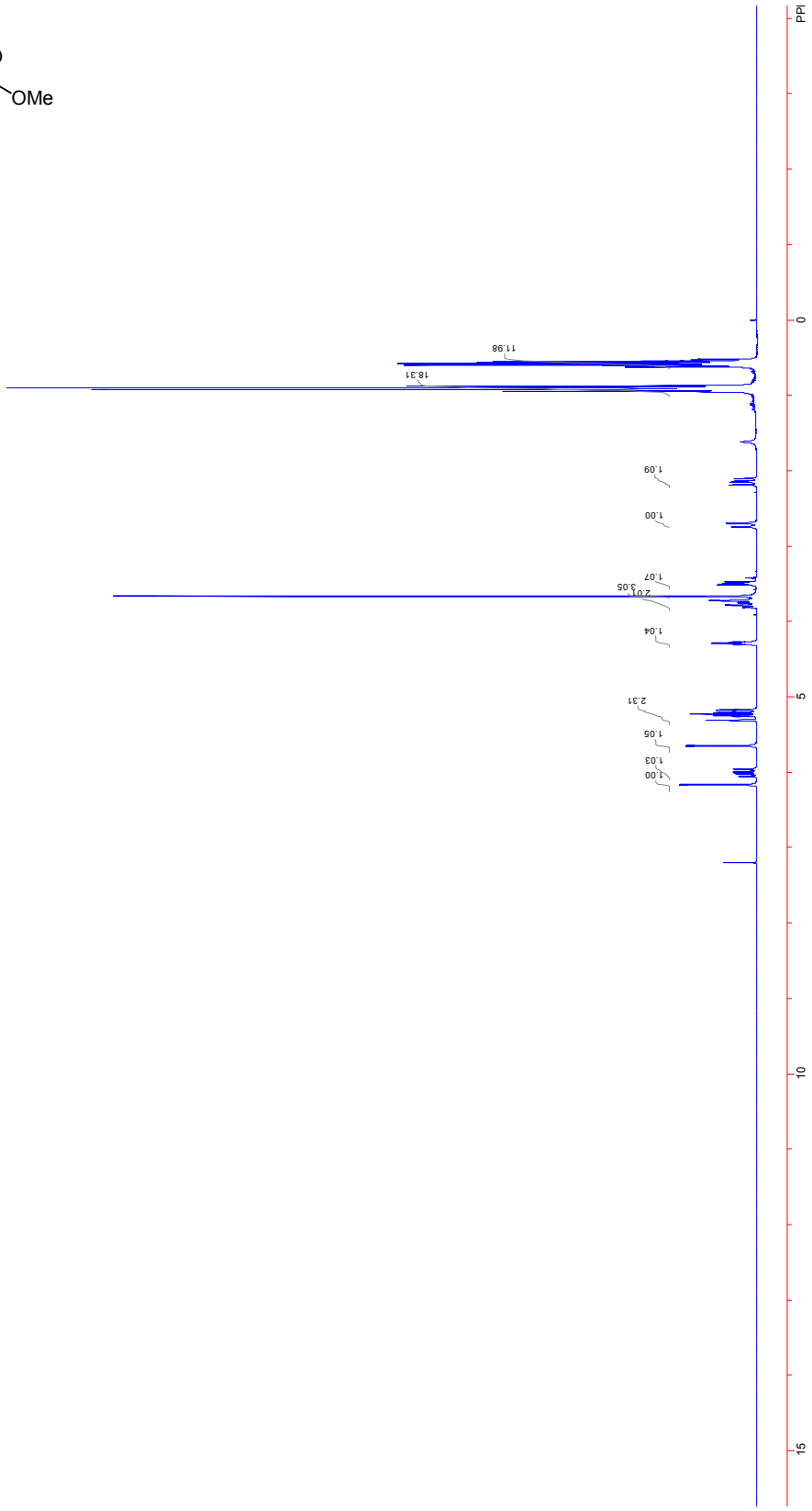
10



^{1}H NMR of compound **11a** (in $CDCl_3$, 300 MHz)

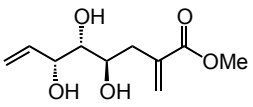


11a



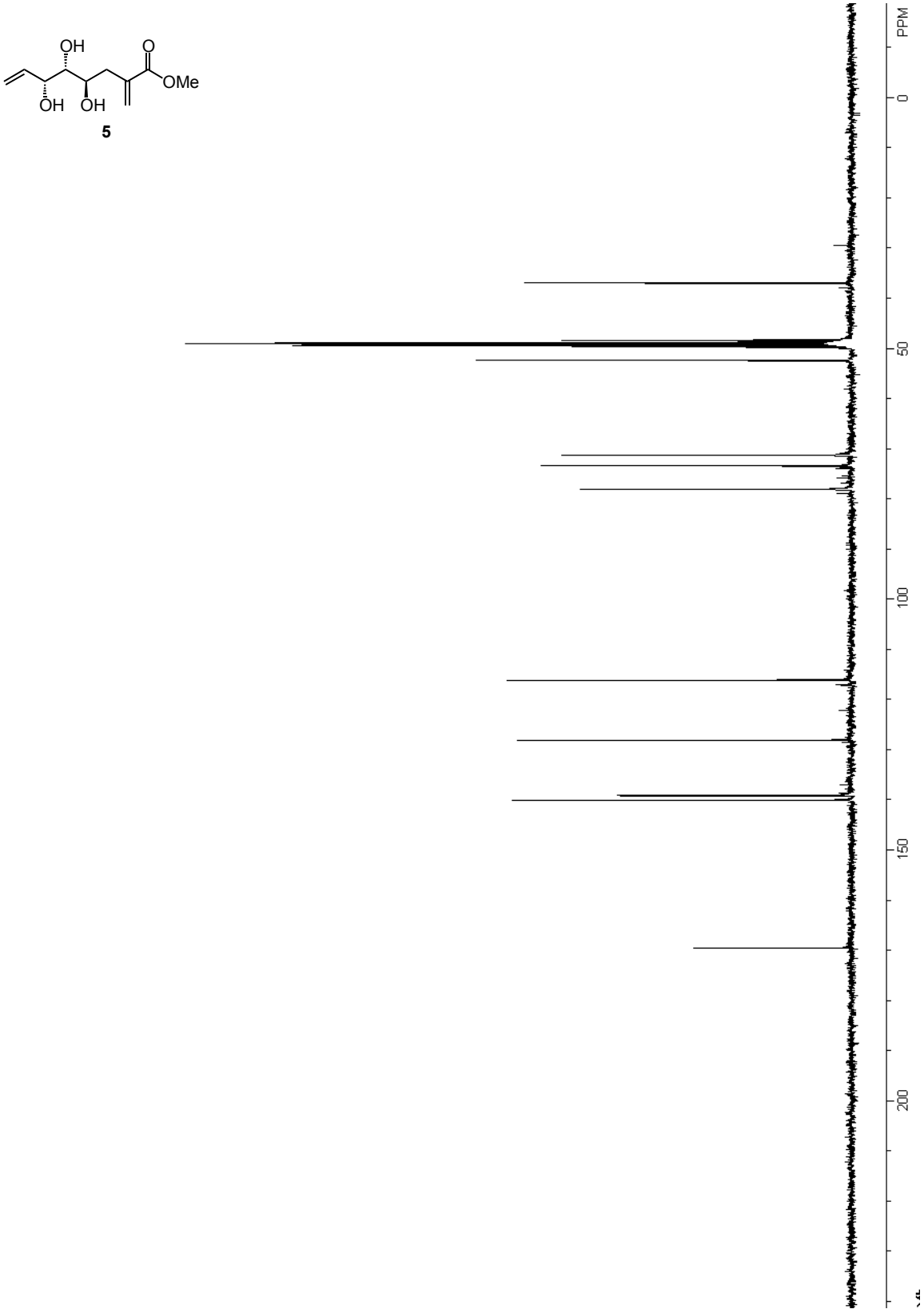
^{13}C NMR of compound **11a** (in $CDCl_3$, 150 MHz)

^{1}H NMR of compound **5** (in CD_3OD, 300 MHz)

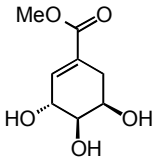


5

^{13}C NMR of compound **5** (in CD_3OD, 150 MHz)

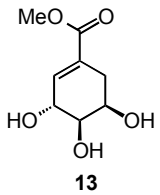


^{1}H NMR of compound **13** (in CD_3OD, 300 MHz)

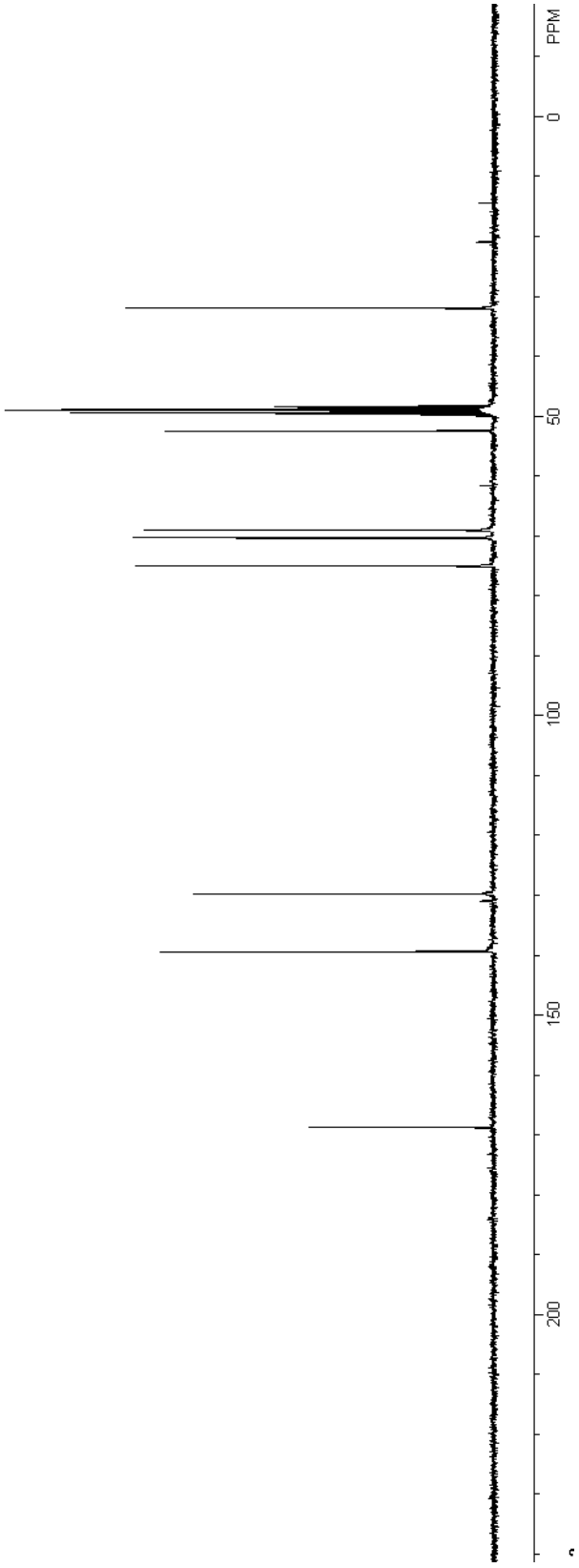


13

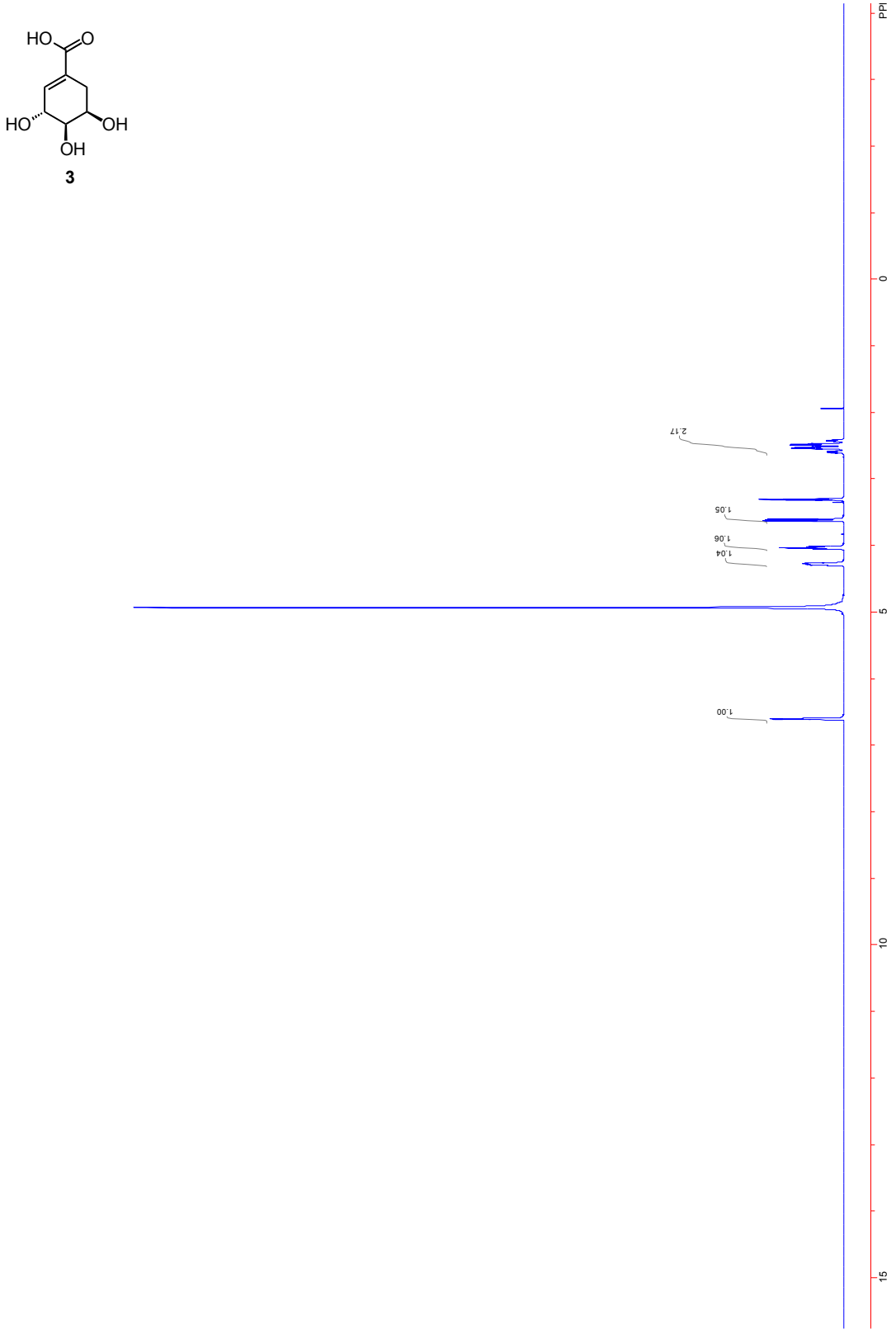
^{13}C NMR of compound **13** (in CD_3OD, 150 MHz)



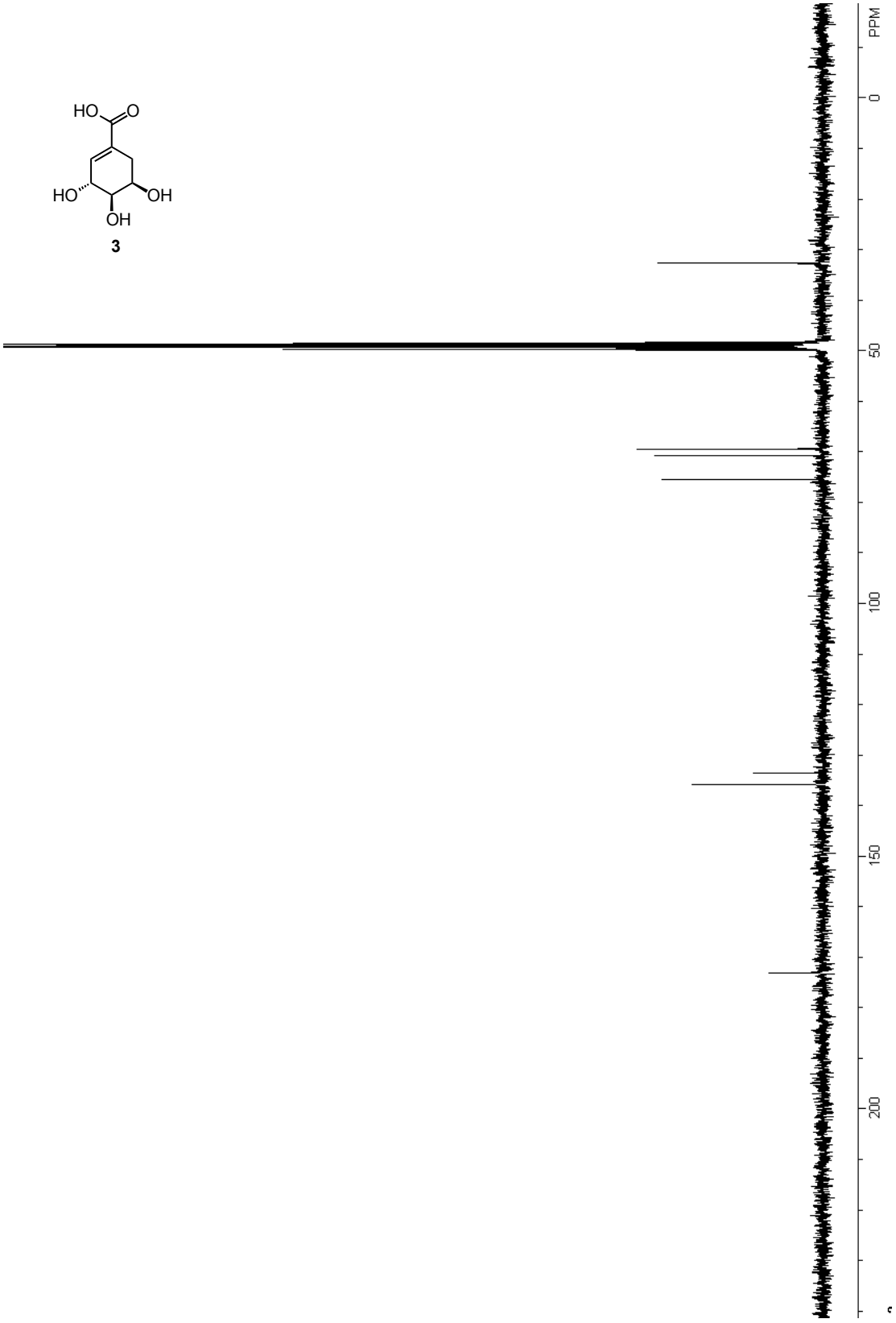
13



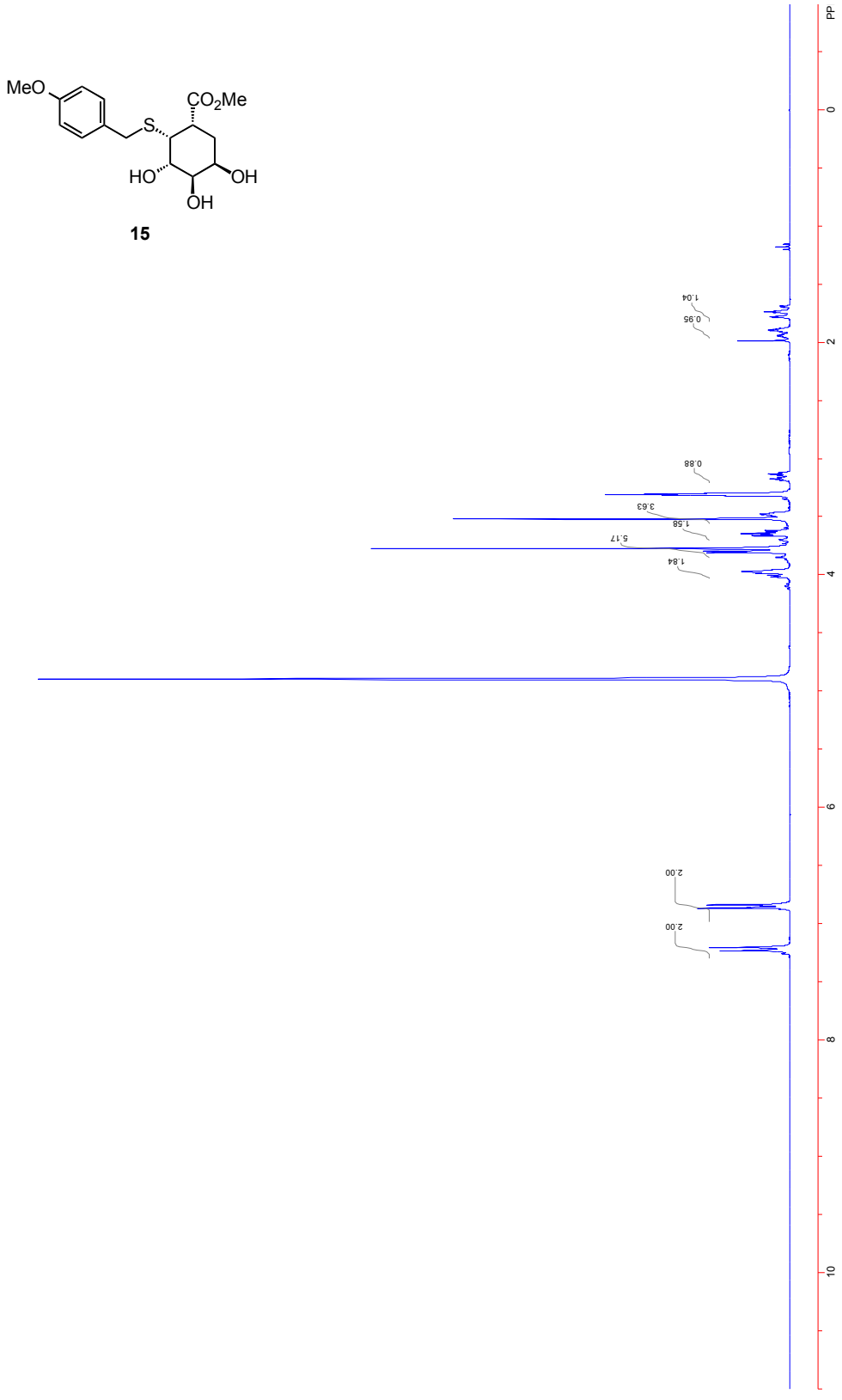
^{1}H NMR of compound **3** (in CD_3OD, 300 MHz)



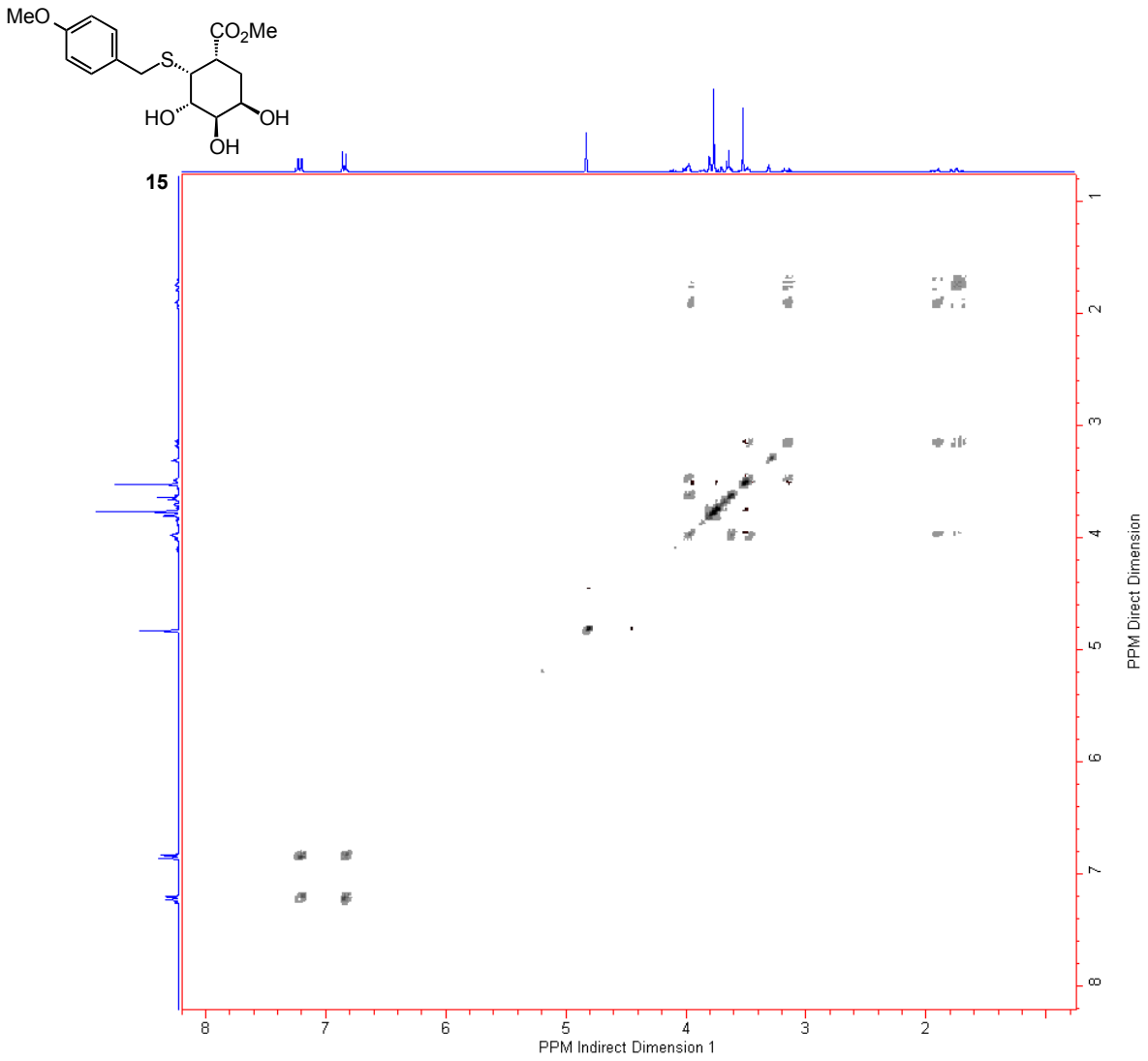
^{13}C NMR of compound **3** (in CD_3OD, 150 MHz)



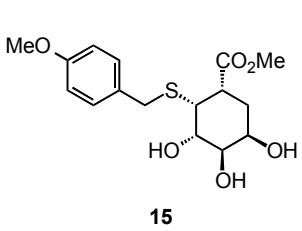
^{1}H NMR of compound **15** (in CD_3OD, 300 MHz)



GCOSY of compound **15** (in CD_3OD, 300 MHz)

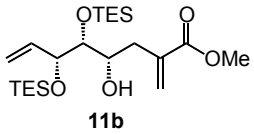


^{13}C NMR of compound **15** (in CD_3OD, 150 MHz)

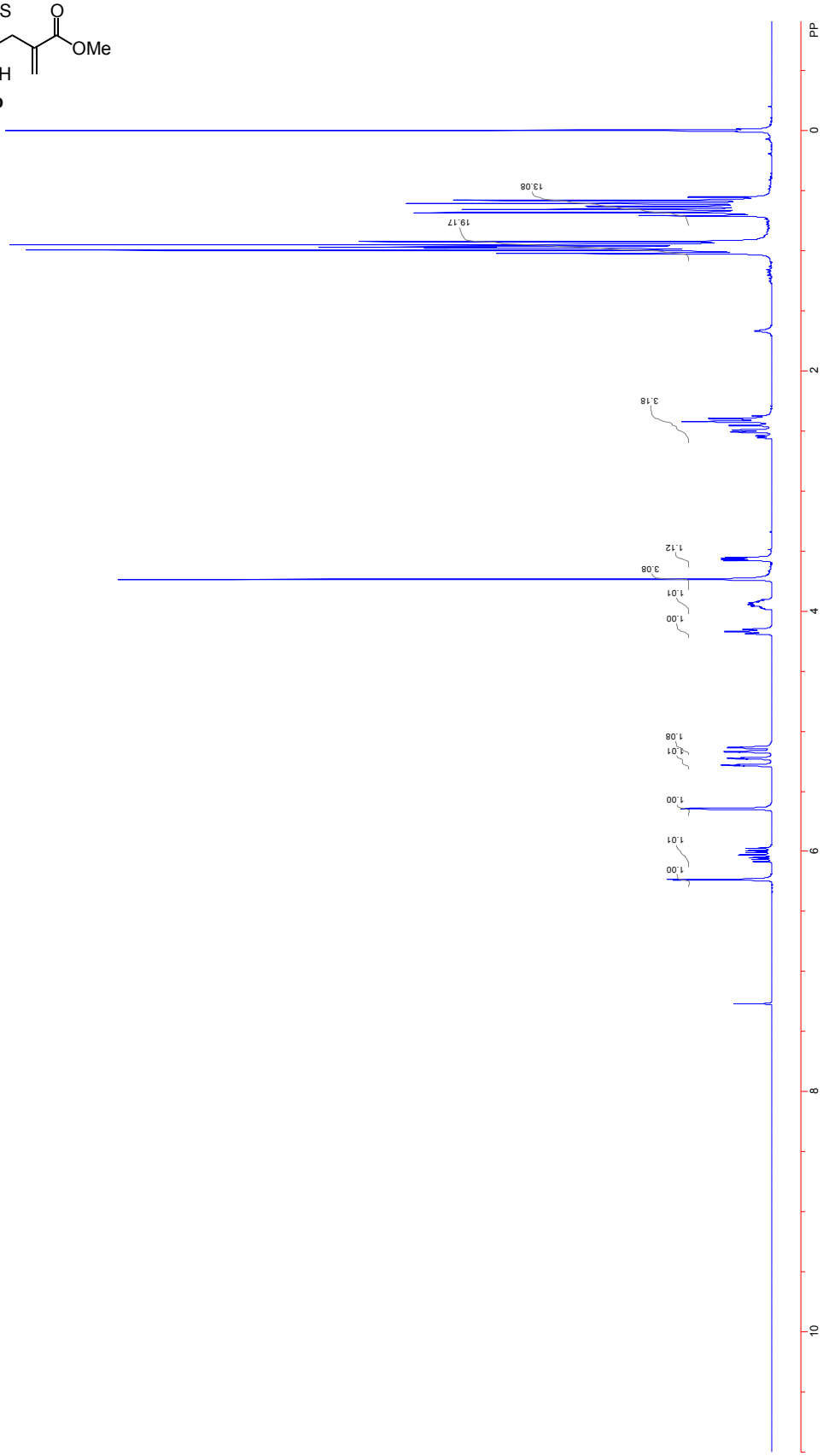


15

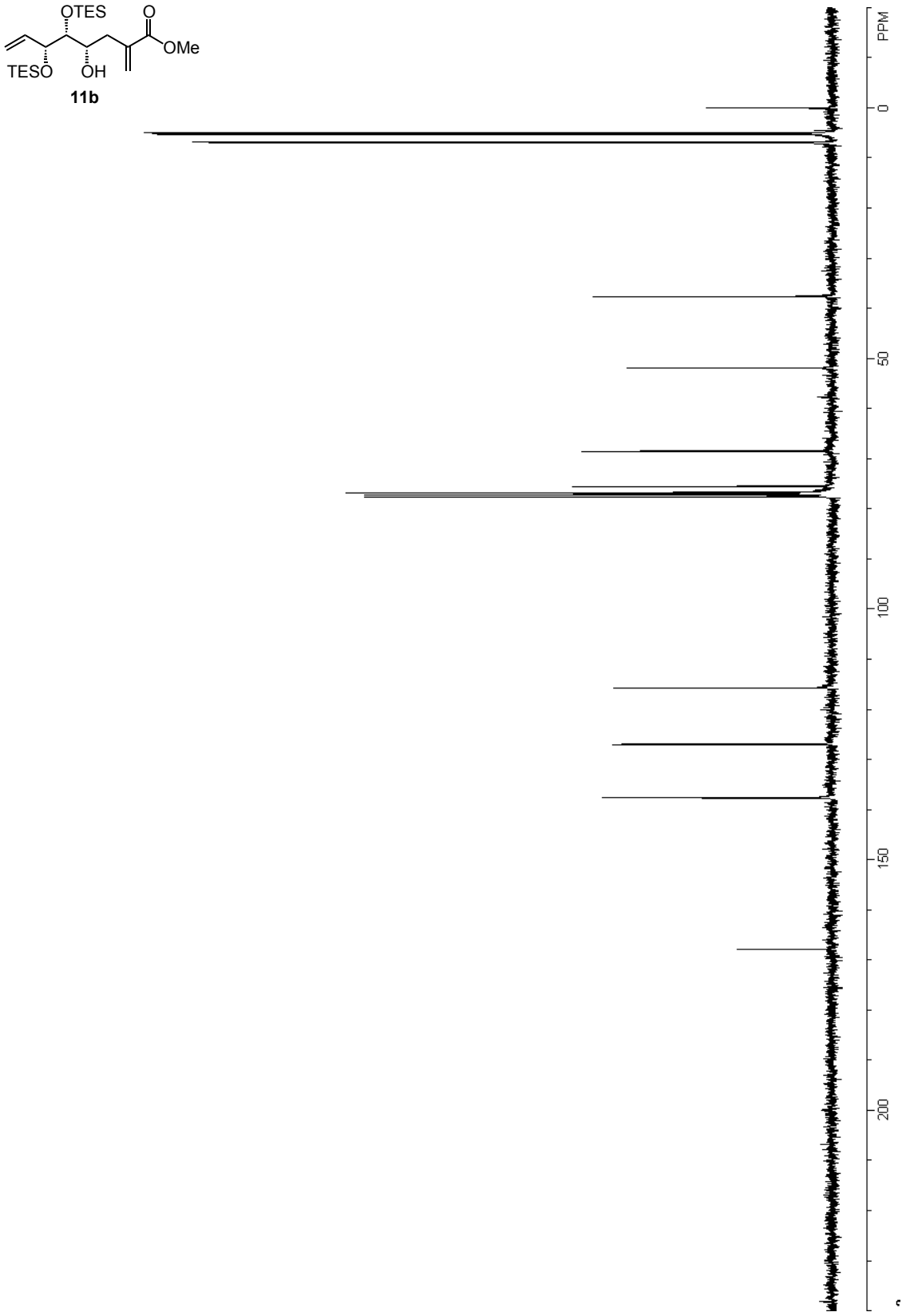
^{1}H NMR of compound **11b** (in $CDCl_3$, 300 MHz)



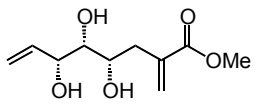
11b



^{13}C NMR of compound **11b** (in $CDCl_3$, 150 MHz)

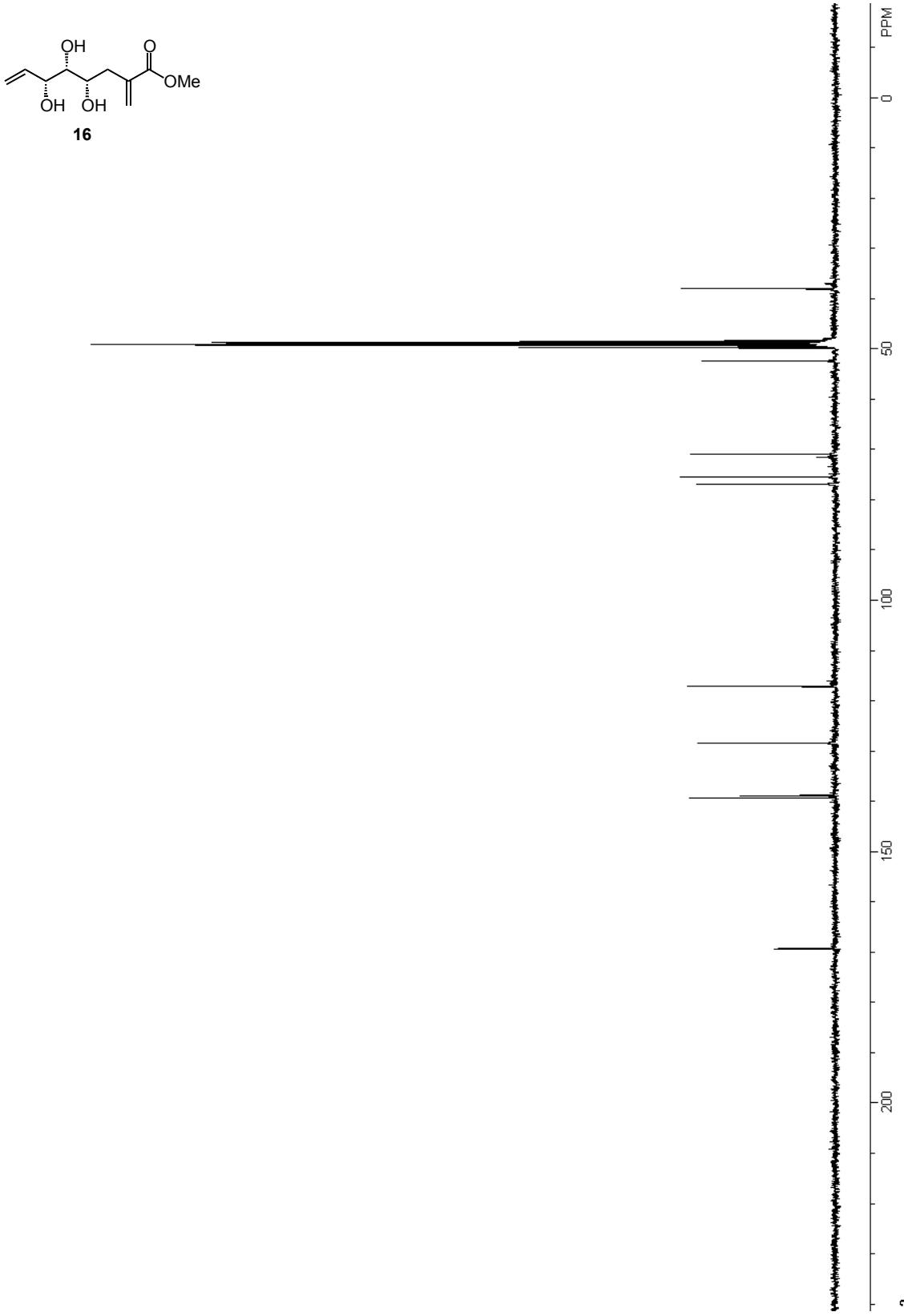


^{1}H NMR of compound **16** (in CD_3OD, 300 MHz)

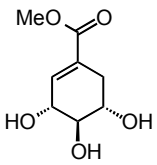


16

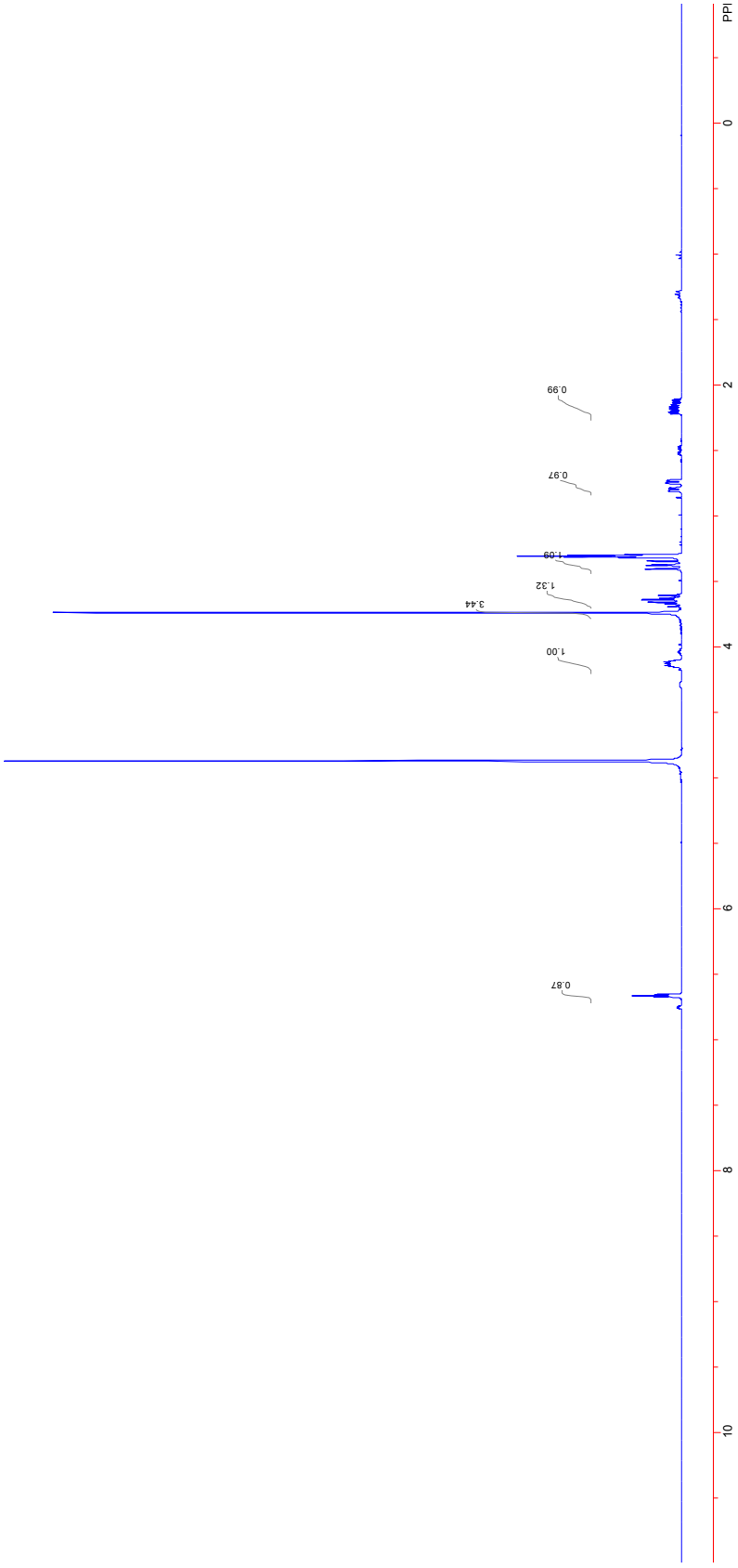
^{13}C NMR of compound **16** (in CD_3OD, 150 MHz)



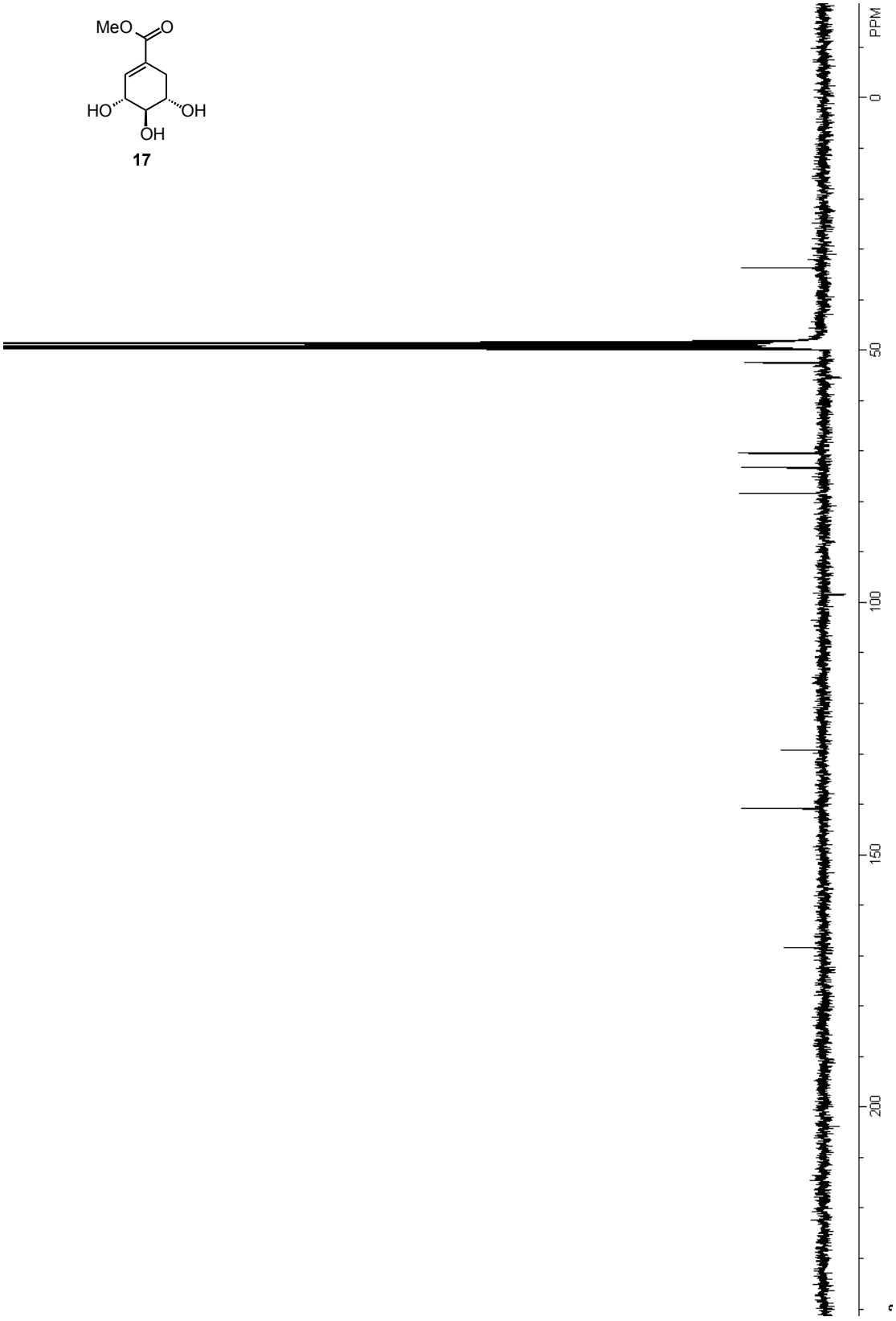
^{1}H NMR of compound **17** (in CD_3OD, 300 MHz)



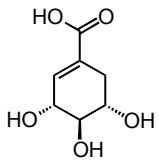
17



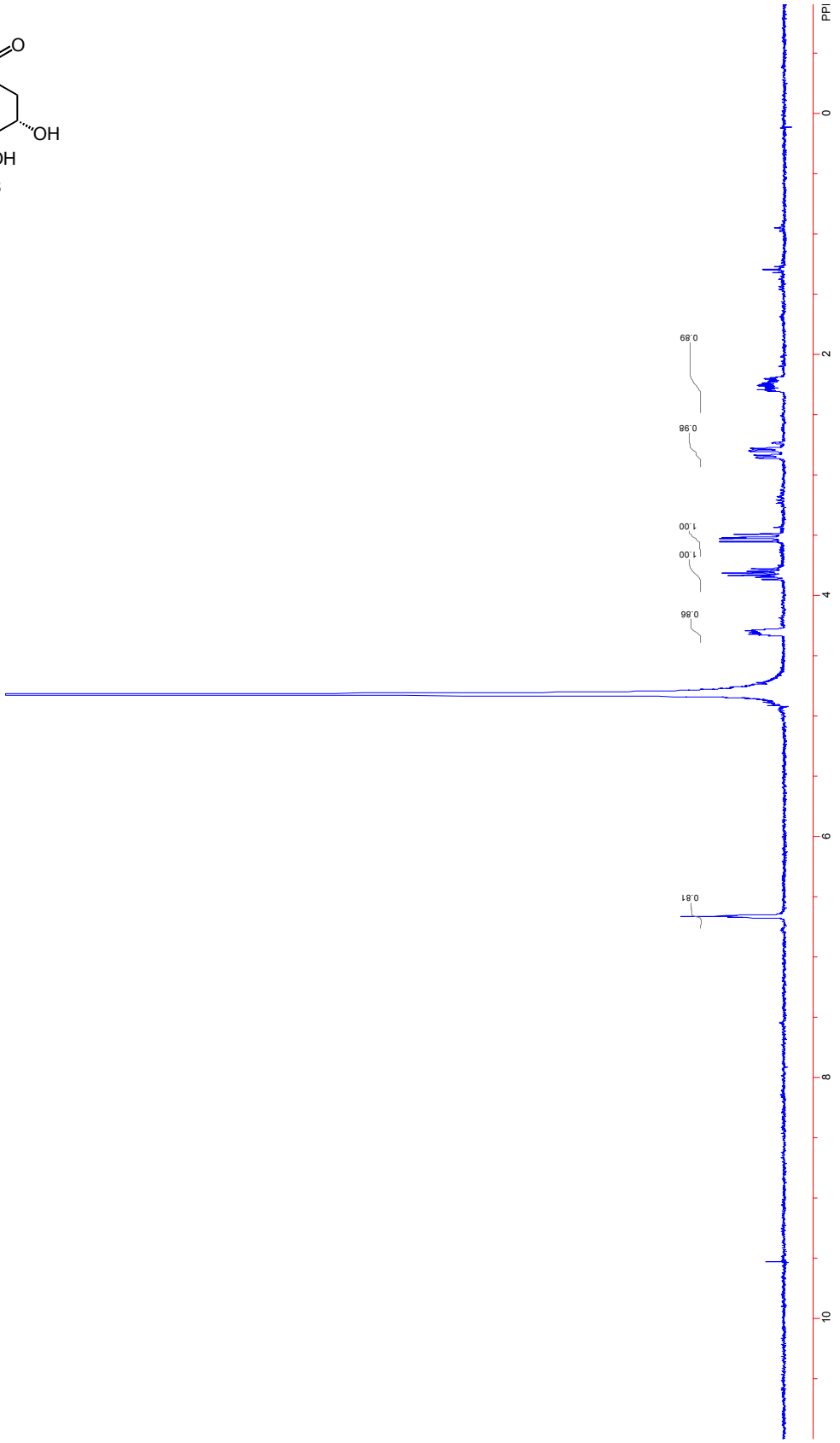
^{13}C NMR of compound **17** (in CD_3OD, 150 MHz)



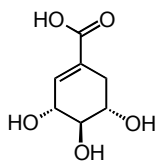
^{1}H NMR of compound **18** (in D_2O, 300 MHz)



18



^{13}C NMR of compound **18** (in D_2O, 250 MHz)



18