

Stereostructural Analysis of Flexible Oxidized Fatty Acids by VCD Spectroscopy

Tohru Taniguchi,^{*a} Naka Ida,^b Takuya Kitahara,^b Davidson Obinna Agbo^b and Kenji Monde^{*a}

^a *Frontier Research Center for Advanced Material and Life Science, Faculty of Advanced Life Science, Hokkaido University, Kita 21 Nishi 11, Sapporo 001-0021, Japan*

^b *Graduate School of Life Science, Hokkaido University, Kita 21 Nishi 11, Sapporo 001-0021, Japan*

Supporting Information

| | |
|-----|--|
| S2 | Supporting Figures and Tables |
| S14 | Experimental and Computational Details |
| S16 | Synthetic Procedures |
| S21 | References |
| S22 | NMR Spectra |
| S39 | Cartesian Coordinates of Selected Conformers |

Supporting Figures and Tables

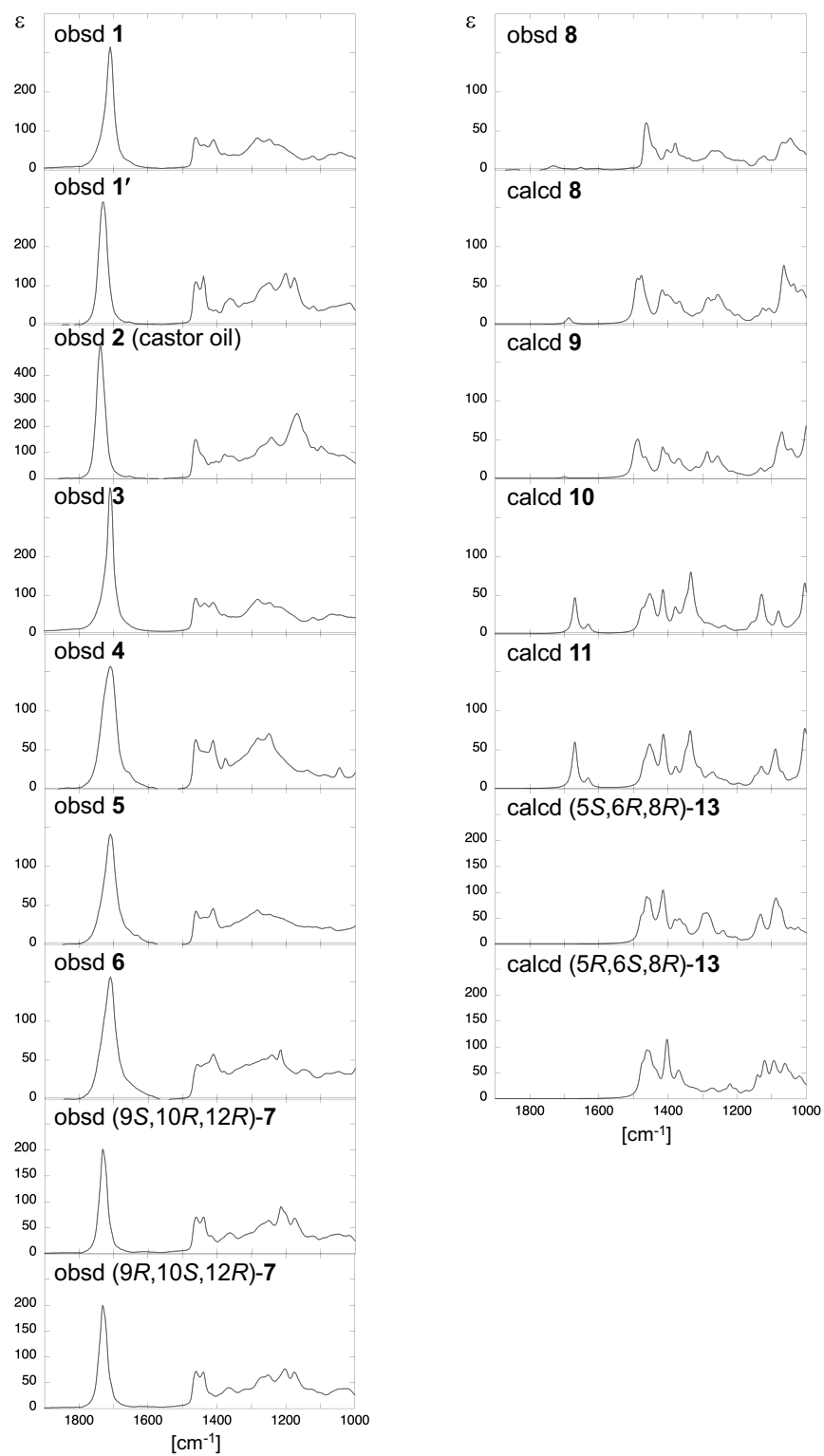


Fig. S1 IR spectra of oxidized lipids **1-7** and their truncated models. See captions of Figures 1, 2, 3, and S4 for the measurement and calculation conditions.

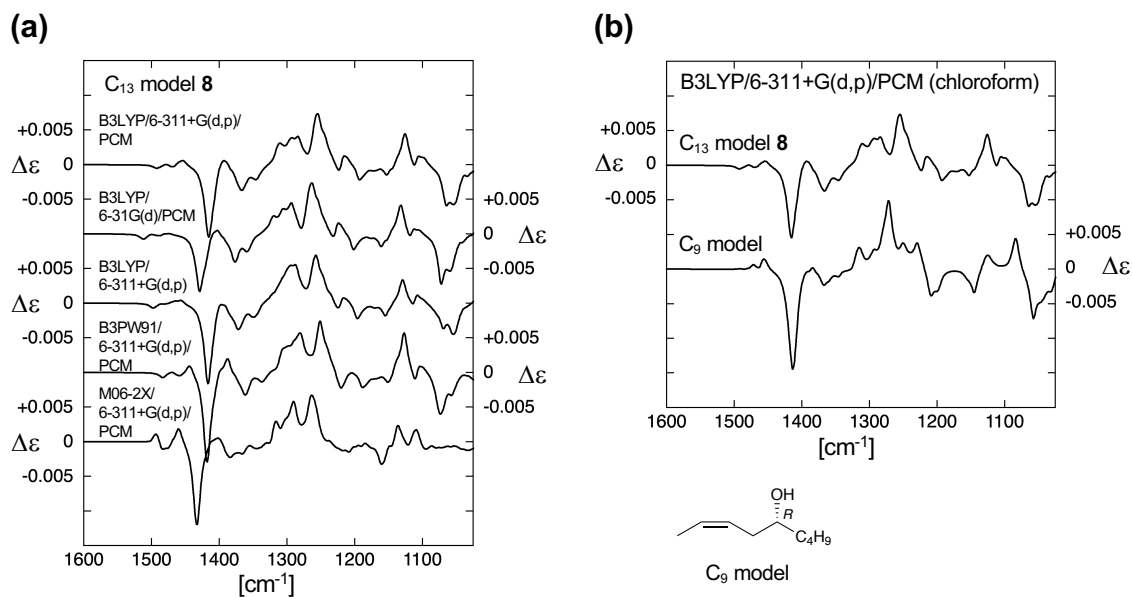


Fig. S2 Theoretical VCD spectra for (a) C_{13} model **8** calculated at several theoretical conditions and for (b) C_9 model calculated at B3LYP/6-311+G(d,p)/PCM (chloroform). All the PCM were applied for chloroform. No solvent effects were considered for the third condition in (a).

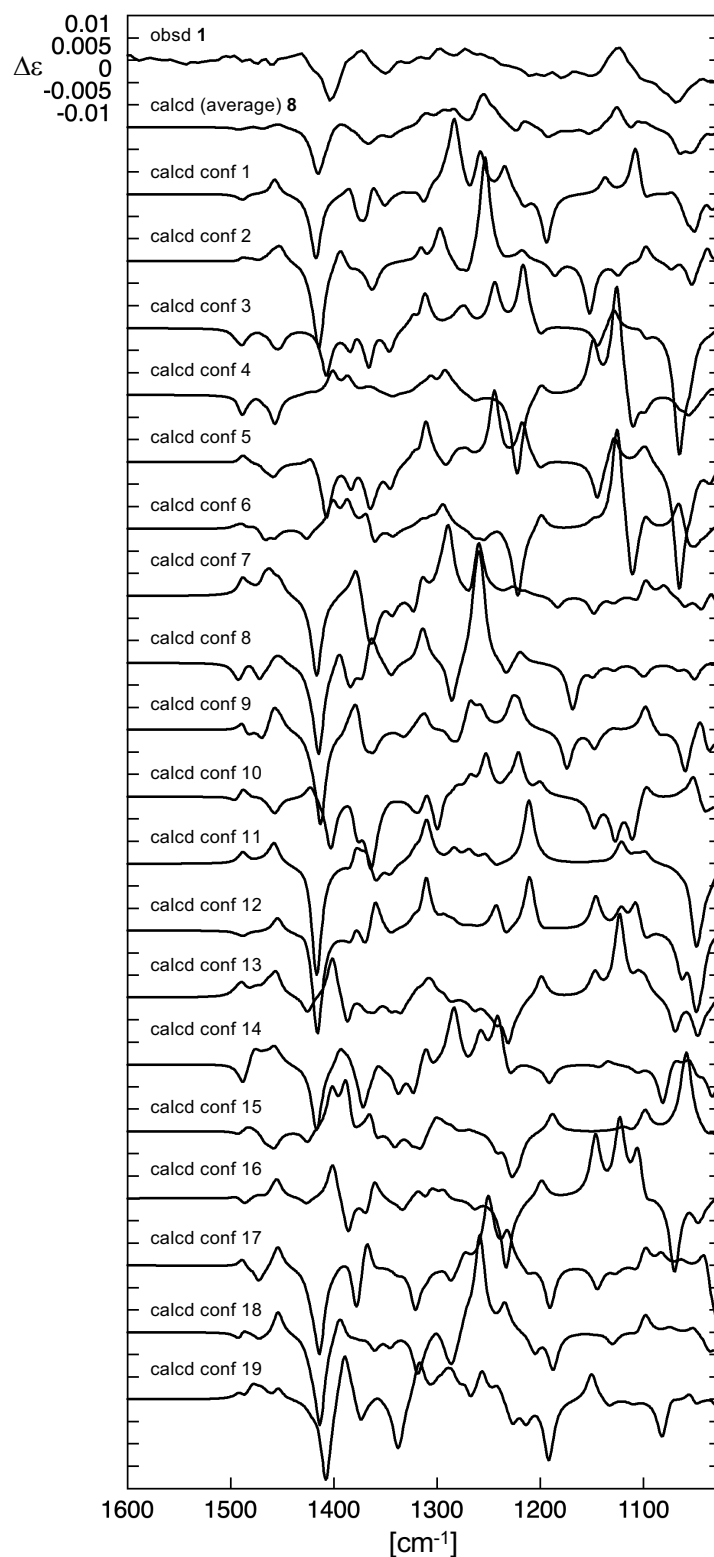


Fig. S3 Conformational studies of hydroxy fatty acid **1** by comparison of the experimental VCD spectrum of **1** and theoretical VCD spectra for each conformer of **8** listed in Table S1a and the Boltzmann-averaged final VCD spectrum. Measurement conditions: 0.6 M in CDCl_3 ; $l = 85 \mu\text{m}$. Calculation conditions: DFT/B3LYP/6-311+G(d,p)/PCM (chloroform). Scaling factor: 0.99.

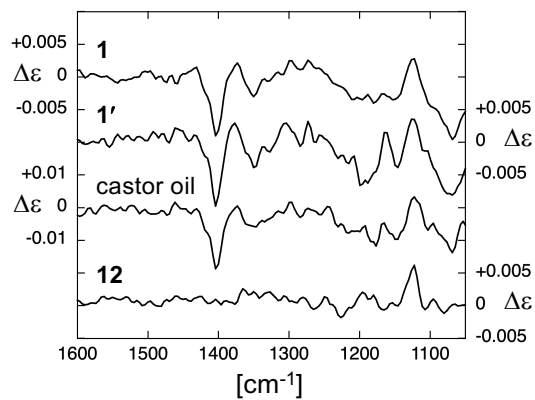


Fig. S4 VCD spectra of **1**, **1'**, castor oil, and **12**. The observed VCD spectrum of castor oil is presented as $\Delta\epsilon$ with assuming its composition as pure **2**. Measurement conditions: c 0.6 M (for **1**, **1'**, and **12**) or 0.2 M (for castor oil) in CDCl_3 ; l 85 μm .

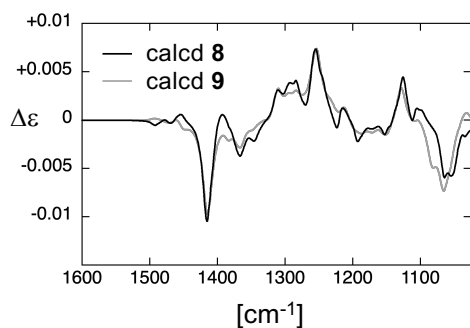


Fig. S5 Direct comparison of the theoretical VCD spectra of **8** and **9**. See the caption of Figure 1 for the calculation conditions.

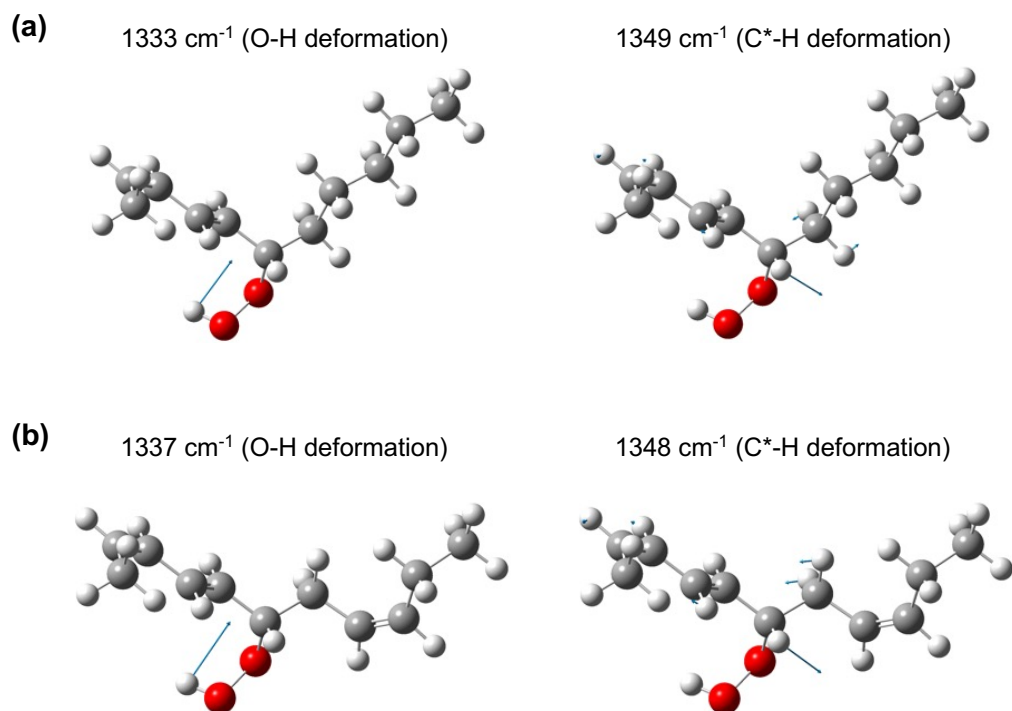


Fig. S6 Vibrational modes of O-H deformation (left) and C^* -H deformation (right) for (a) **10** and (b) **11**, where C^* indicates the asymmetric carbon. Displacement vectors (arbitrary length) of each atom are shown as arrows. Calculation conditions: DFT/B3LYP/6-311+G(d,p)/PCM (chloroform). Scaling factor: 0.98.

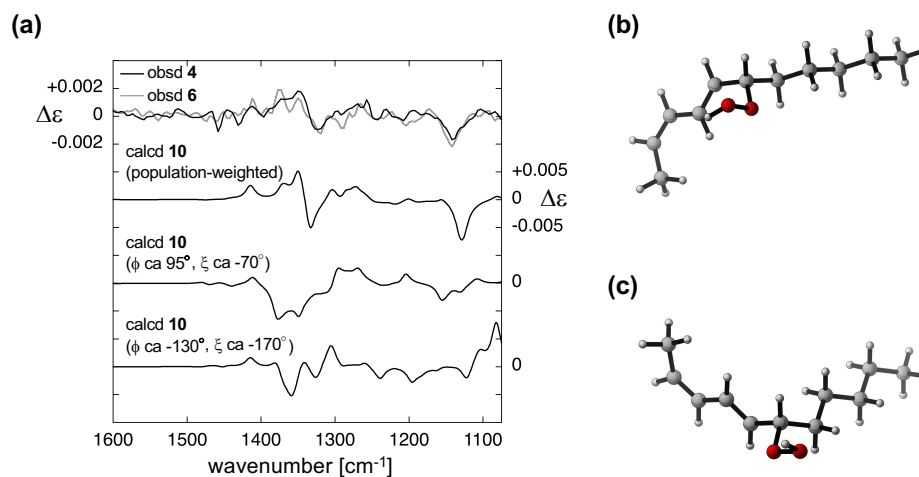


Fig. S7 Conformational studies of lipid hydroperoxides. (a) Comparison of (i) the experimental VCD spectra of **4** and **6**; (ii) theoretical population-weighted VCD spectrum of **10** for the conformers listed in Table S1c, for which those with ϕ (C4-C5-C6-C7) of ca -130° and ξ (C5-C6-O1-O2) of ca -70° are the main species; (iii) theoretical VCD spectrum of **10** for the conformers with ϕ of ca 95° and ξ of ca -70° ; and (iv) theoretical VCD spectrum of **10** for the conformers with ϕ of ca -130° and ξ of ca -170° . (b) The most stable conformer with ϕ of ca 95° and ξ of ca -70° . This conformer corresponds to the conformer 15 in Table S1c. (c) The most stable conformer with ϕ of ca -130° and ξ of ca -170° . This conformer corresponds to the conformer 13 in Table S1c. To obtain the VCD spectra (iii) and (iv), conformers with these dihedral angles were selected from the DFT-optimized conformational set that includes conformers not listed in Table S1c and then their VCD spectra were calculated at B3LYP/6-311+G(d,p)/PCM (chloroform). The resultant VCD spectra for each conformer were averaged based on their Boltzmann population. Measurement conditions: 1.5 M in CDCl_3 ; $l = 85 \mu\text{m}$. Calculation conditions: DFT/B3LYP/6-311+G(d,p)/PCM (chloroform). Scaling factor: 0.98.

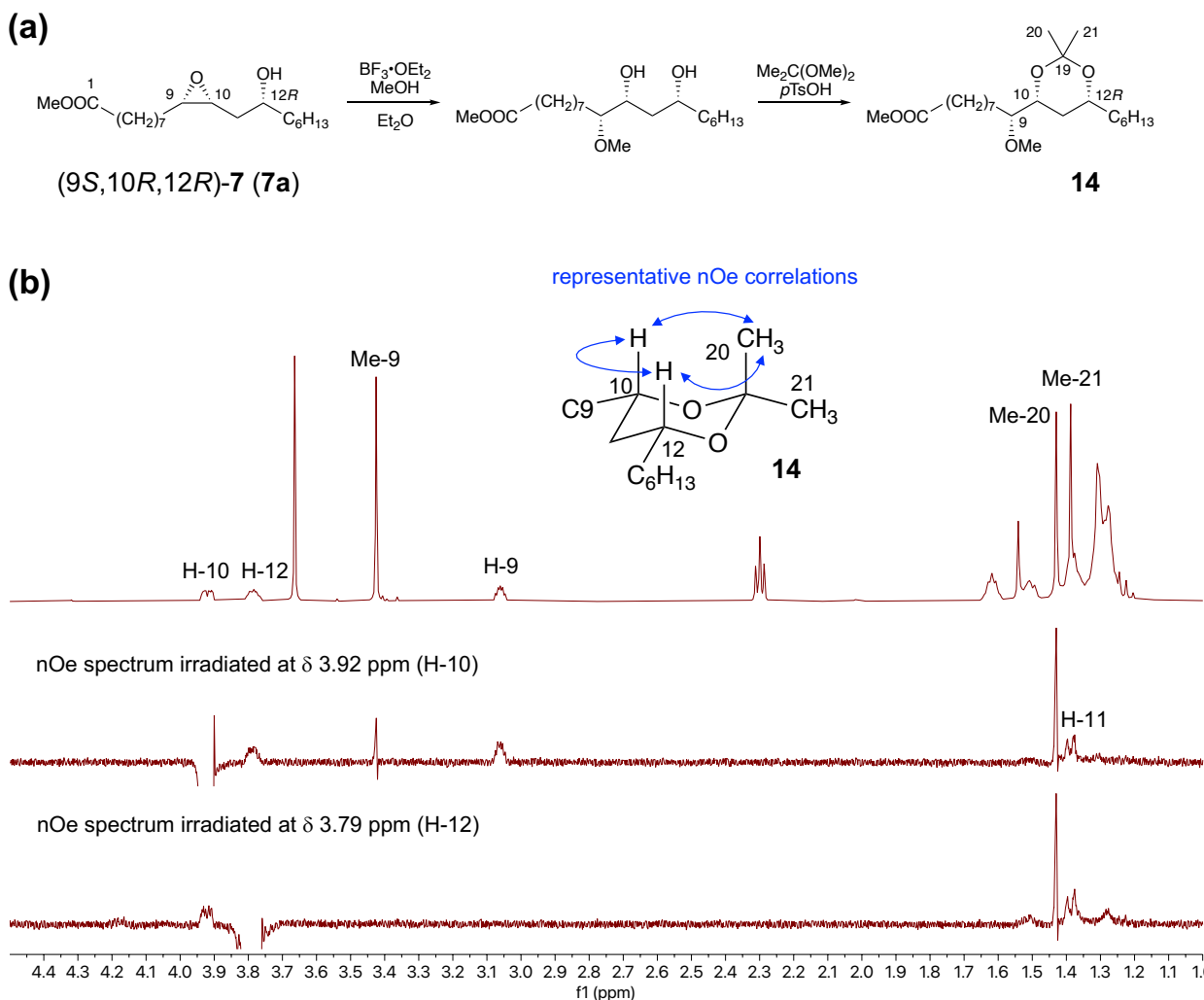
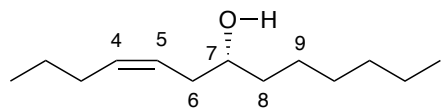


Fig. S8 Verification of the absolute configuration of **7** by nOe measurement. (a) Conversion of **7a** to a 10,12-acetonide (**14**). Note that this conversion does not change the absolute configuration at C10 and C12. (b) ^1H NMR spectrum of **14** measured in CDCl_3 , and two nOe spectra irradiated at its H-10 and H-12. Representative nOe correlations relevant for the absolute configuration determination are shown as blue arrows in the chemical structure. These correlations suggested **14** to be a *syn*-configured 10,12-acetonide. From these results, **7a** was assigned as (9*S*,10*R*,12*R*)-**7** and accordingly **7b** as (9*R*,10*S*,12*R*)-**7**.

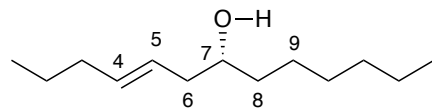
Table S1a Relative energy (ΔE , in kcal/mol), Boltzmann population calculated at 298 K (P), and dihedral angles ϕ , ψ , ω , and ξ of the stable conformers of **8** predicted by DFT/B3LYP/6-311+G(d,p)/PCM (chloroform).



$$\begin{aligned}\phi &= \angle \text{C4-C5-C6-C7} \\ \psi &= \angle \text{C5-C6-C7-C8} \\ \omega &= \angle \text{C6-C7-C8-C9} \\ \xi &= \angle \text{C6-C7-O-H}\end{aligned}$$

| conformer | ΔE [kcal/mol] | P | ϕ [°] | ψ [°] | ω [°] | ξ [°] |
|-----------|-----------------------|-------|------------|------------|--------------|-----------|
| 1 | 0.000 | 0.174 | 115.3 | 178.4 | -178.3 | 49.3 |
| 2 | 0.035 | 0.164 | 111.5 | 178.5 | -175.6 | 48.4 |
| 3 | 0.377 | 0.092 | -103.3 | -176.7 | -173.3 | 65.6 |
| 4 | 0.412 | 0.087 | -106.7 | -63.8 | -171.5 | -53.3 |
| 5 | 0.466 | 0.079 | -105.6 | -176.6 | -173.4 | 66.0 |
| 6 | 0.497 | 0.075 | -110.5 | -63.5 | -171.4 | -53.6 |
| 7 | 0.824 | 0.044 | 111.2 | 178.4 | -179.0 | 49.3 |
| 8 | 0.841 | 0.042 | 115.5 | 178.1 | -175.0 | 48.7 |
| 9 | 0.868 | 0.040 | 111.4 | 178.6 | -175.3 | 48.4 |
| 10 | 1.008 | 0.032 | -104.5 | -175.8 | -65.8 | 63.0 |
| 11 | 1.127 | 0.026 | 127.3 | -59.5 | -172.0 | 62.9 |
| 12 | 1.129 | 0.026 | 131.7 | -59.4 | -172.0 | 62.4 |
| 13 | 1.287 | 0.020 | 115.0 | -65.1 | -172.3 | -71.8 |
| 14 | 1.313 | 0.019 | 111.7 | 178.6 | -178.3 | 49.2 |
| 15 | 1.324 | 0.019 | -110.5 | -63.7 | -171.4 | -53.5 |
| 16 | 1.374 | 0.017 | 119.5 | -64.6 | -171.7 | -72.8 |
| 17 | 1.411 | 0.016 | 112.2 | 179.8 | -64.9 | 48.2 |
| 18 | 1.417 | 0.016 | 111.9 | 179.9 | -65.2 | 48.1 |
| 19 | 1.575 | 0.012 | 112.9 | 174.9 | 60.1 | 47.9 |

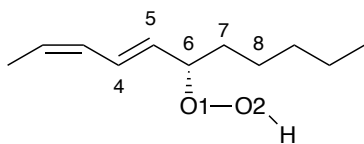
Table S1b Relative energy (ΔE , in kcal/mol), Boltzmann population calculated at 298 K (P), and dihedral angles ϕ , ψ , ω , and ξ of the stable conformers of **9** predicted by DFT/B3LYP/6-311+G(d,p)/PCM (chloroform).



$$\begin{aligned}\phi &= \angle \text{C4-C5-C6-C7} \\ \psi &= \angle \text{C5-C6-C7-C8} \\ \omega &= \angle \text{C6-C7-C8-C9} \\ \xi &= \angle \text{C6-C7-O-H}\end{aligned}$$

| conformer | ΔE [kcal/mol] | P | ϕ [°] | ψ [°] | ω [°] | ξ [°] |
|-----------|-----------------------|-------|------------|------------|--------------|-----------|
| 1 | 0.000 | 0.234 | 113.8 | 178.2 | -176.0 | 46.2 |
| 2 | 0.221 | 0.161 | 110.9 | 178.6 | -176.5 | 45.9 |
| 3 | 0.675 | 0.075 | -112.1 | -178.4 | -173.4 | 68.3 |
| 4 | 0.692 | 0.073 | -112.4 | -178.6 | -173.2 | 68.4 |
| 5 | 0.893 | 0.052 | -122.8 | 174.4 | -174.7 | -65.2 |
| 6 | 0.980 | 0.045 | 111.5 | 178.8 | -179.0 | 45.8 |
| 7 | 0.988 | 0.044 | 111.2 | 178.6 | -175.9 | 45.6 |
| 8 | 0.989 | 0.044 | 110.6 | 178.7 | -176.2 | 46.1 |
| 9 | 1.011 | 0.042 | 110.6 | 178.6 | -178.6 | 46.7 |
| 10 | 1.024 | 0.042 | 110.9 | 178.7 | -178.6 | 46.7 |
| 11 | 1.095 | 0.037 | 111.4 | 178.2 | -175.7 | 46.1 |
| 12 | 1.122 | 0.035 | 111.2 | 178.4 | -175.7 | 45.9 |
| 13 | 1.170 | 0.033 | -110.6 | -63.6 | -171.5 | -49.9 |
| 14 | 1.365 | 0.023 | -108.1 | -64.1 | -171.7 | -48.8 |
| 15 | 1.436 | 0.021 | -107.1 | -63.7 | -171.4 | -50.6 |
| 16 | 1.464 | 0.020 | 111.2 | 179.7 | -67.7 | 44.7 |
| 17 | 1.497 | 0.019 | 111.7 | 179.4 | -68.5 | 43.9 |

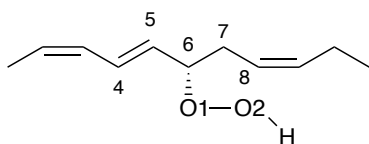
Table S1c Relative energy (ΔE , in kcal/mol), Boltzmann population calculated at 298 K (P), and dihedral angles ϕ , ψ , ξ , and χ of the stable conformers of **10** predicted by DFT/B3LYP/6-311+G(d,p)/PCM (chloroform).



$$\begin{aligned}\phi &= \angle \text{C4-C5-C6-C7} \\ \psi &= \angle \text{C5-C6-C7-C8} \\ \xi &= \angle \text{C5-C6-O1-O2} \\ \chi &= \angle \text{C6-O1-O2-H}\end{aligned}$$

| conformer | ΔE [kcal/mol] | P | ϕ [°] | ψ [°] | ξ [°] | χ [°] |
|-----------|-----------------------|-------|------------|------------|-----------|------------|
| 1 | 0.000 | 0.202 | -130.3 | 67.0 | -70.4 | 88.1 |
| 2 | 0.003 | 0.201 | -128.7 | 173.1 | -72.2 | 89.0 |
| 3 | 0.731 | 0.059 | -128.9 | 176.1 | -72.7 | 89.1 |
| 4 | 0.738 | 0.058 | -121.0 | 173.5 | -67.7 | -110.1 |
| 5 | 0.784 | 0.054 | -131.6 | 63.8 | -71.2 | 88.5 |
| 6 | 0.790 | 0.053 | -122.3 | 67.4 | -65.3 | -109.3 |
| 7 | 0.845 | 0.049 | -128.6 | 173.3 | -72.3 | 88.9 |
| 8 | 0.851 | 0.048 | -130.4 | 67.0 | -70.4 | 88.3 |
| 9 | 0.852 | 0.048 | -130.7 | 66.9 | -70.5 | 88.2 |
| 10 | 0.856 | 0.048 | -128.9 | 173.3 | -72.3 | 89.1 |
| 11 | 0.882 | 0.046 | -130.2 | 67.5 | -70.5 | 89.0 |
| 12 | 0.888 | 0.045 | -129.0 | 173.5 | -72.0 | 88.9 |
| 13 | 1.065 | 0.033 | -126.7 | 69.9 | -173.8 | 109.0 |
| 14 | 1.224 | 0.026 | -128.4 | 68.8 | -171.0 | -112.2 |
| 15 | 1.494 | 0.016 | 95.9 | 169.2 | -74.8 | 88.3 |
| 16 | 1.562 | 0.014 | -128.6 | 177.5 | -72.4 | 88.6 |

Table S1d Relative energy (ΔE , in kcal/mol), Boltzmann population calculated at 298 K (P), and dihedral angles ϕ , ψ , ξ , and χ of the stable conformers of **11** predicted by DFT/B3LYP/6-311+G(d,p)/PCM (chloroform).



$$\begin{aligned}\phi &= \angle \text{C4-C5-C6-C7} \\ \psi &= \angle \text{C5-C6-C7-C8} \\ \xi &= \angle \text{C5-C6-O1-O2} \\ \chi &= \angle \text{C6-O1-O2-H}\end{aligned}$$

| conformer | ΔE [kcal/mol] | P | ϕ [°] | ψ [°] | ξ [°] | χ [°] |
|-----------|-----------------------|-------|------------|------------|-----------|------------|
| 1 | 0.000 | 0.108 | -128.9 | 174.1 | -72.8 | 90.1 |
| 2 | 0.016 | 0.106 | -129.4 | 173.6 | -73.0 | 90.1 |
| 3 | 0.061 | 0.098 | -129.3 | 64.4 | -70.9 | 88.9 |
| 4 | 0.092 | 0.093 | -129.0 | 64.8 | -70.8 | 89.3 |
| 5 | 0.136 | 0.086 | -131.3 | 68.9 | -70.8 | 88.5 |
| 6 | 0.174 | 0.081 | -132.1 | 68.0 | -70.8 | 88.5 |
| 7 | 0.195 | 0.078 | -128.1 | 172.8 | -71.9 | 90.3 |
| 8 | 0.230 | 0.074 | -128.8 | 172.3 | -72.1 | 90.2 |
| 9 | 0.593 | 0.04 | -128.8 | -59.7 | -70.5 | 89.9 |
| 10 | 0.645 | 0.037 | -128.8 | -59.2 | -70.4 | 90.0 |
| 11 | 0.650 | 0.036 | -121.9 | 174.8 | -67.8 | -109.3 |
| 12 | 0.665 | 0.035 | -121.0 | 174.6 | -68.0 | -109.2 |
| 13 | 1.071 | 0.018 | -127.0 | 66.2 | -171.4 | -115.4 |
| 14 | 1.091 | 0.017 | -123.9 | -54.6 | -70.3 | 92.3 |
| 15 | 1.108 | 0.017 | -126.9 | 66.3 | -171.2 | -115.6 |
| 16 | 1.133 | 0.016 | -123.5 | -55.5 | -70.3 | 92.4 |
| 17 | 1.142 | 0.016 | -123.1 | -178.7 | -156.0 | -81.5 |
| 18 | 1.157 | 0.015 | -130.3 | 71.3 | -170.9 | -115.2 |
| 19 | 1.163 | 0.015 | -123.2 | -178.7 | -156.2 | -81.5 |
| 20 | 1.178 | 0.014 | -130.5 | 70.8 | -170.7 | -115.3 |

Table S2 Scaling factor, VCD spectral similarity (S_E), VCD spectral similarity for the opposite enantiomer (S_{-E}), and enantiomer similarity index (ESI, which is calculated by $S_E - S_{-E}$) for the VCD spectra of oxidized lipids and their calculation models obtained by a numerical algorithm implemented in CompareVOA software.

| Experimental spectra | Theoretical spectra | Scaling factor | S_E | S_{-E} | ESI | Confidence level |
|---|--|----------------|-------|----------|-------|------------------|
| 1 | 8 | 0.99 | 69.0 | 6.7 | 62.3 | 99 |
| 8 | 8 | 0.99 | 77.3 | 6.0 | 71.3 | 99 |
| 3 | 9 | 0.99 | 72.3 | 2.4 | 69.9 | 99 |
| 4 | 10 | 0.98 | 83.0 | 8.8 | 74.1 | 99 |
| 5 | 11 | 0.98 | 77.9 | 9.7 | 68.2 | 99 |
| 6 | 10 | 0.98 | 72.3 | 7.2 | 65.1 | 99 |
| (9 <i>S</i> ,10 <i>R</i> ,12 <i>R</i>)- 7 | (5 <i>S</i> ,6 <i>R</i> ,8 <i>R</i>)- 13 | 0.97 | 77.2 | 2.7 | 74.5 | 99 |
| (9 <i>R</i> ,10 <i>S</i> ,12 <i>R</i>)- 7 | (5 <i>R</i> ,6 <i>S</i> ,8 <i>R</i>)- 13 | 0.97 | 72.3 | 15.3 | 57.0 | 97 |
| (9 <i>S</i> ,10 <i>R</i> ,12 <i>R</i>)- 7 | (5 <i>R</i> ,6 <i>S</i> ,8 <i>R</i>)- 13 | 0.97 | 40.6 | 23.1 | 17.5 | 31 |
| (9 <i>R</i> ,10 <i>S</i> ,12 <i>R</i>)- 7 | (5 <i>S</i> ,6 <i>R</i> ,8 <i>R</i>)- 13 | 0.97 | 23.2 | 45.6 | -22.4 | - |

Experimental and Computational Details

General Experimental Details

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Varian Inova instrument at 25 °C, except for the nOe experiments in Figure S8, which was carried out on a Bruker Avance III HD spectrometer (600 MHz). Chemical shift values (δ) are reported in ppm relative to tetramethylsilane, CDCl_3 (^{13}C , δ 77.16), or CD_3OD (^1H , δ 3.31). The following abbreviations were used for signal multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; and br = broad. Electrospray ionization mass spectrometry and electron ionization mass spectrometry were measured on a Thermo Scientific Exactive and JEOL JMS-T100GCv, respectively. For vibrational spectroscopy, each sample was dissolved in CDCl_3 and placed in a BaF_2 cell. VCD and IR spectra were recorded using a BioTools ChiralIR-2X or JASCO FVS-6000 spectrometer with 8 cm^{-1} resolution for 4000 and 16 scans, respectively. All the VCD and IR spectra were corrected by solvent spectra obtained under the identical measurement conditions. Diastereoseparation of (9*S*,10*R*,12*R*)- and (9*R*,10*S*,12*R*)-methyl-12-benzoyloxy-9,10-epoxyoctadecanoate was performed on a Chiralpak[®] IA guard column (1.0 cm ϕ \times 2 cm) and semi-preparative column (1.0 cm ϕ \times 25 cm) using two JASCO PU-2086 intelligent pumps equipped with a JASCO MX-2080-31 solvent mixing module on a PU-2075 intelligent UV/Vis detector. Soybean type I lipoxigenase was purchased from Sigma. Castor oil (reagent grade) was purchased from Fujifilm Wako Pure Chemical Corporation. Methyl ricinelaidate was purchased from Obracht Serdary Research Laboratories (Canada). Purchased chemicals were used without further purification, except for methyl ricinoleate (**1'**), which was used after silica-gel column chromatography (hexane-EtOAc = 10:1) purification.

General Computational Details

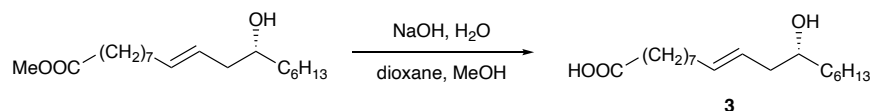
Preliminary MMFF conformational search of each model was performed on Spartan'18 program.^[1] Stable geometries within a 10-20 kJ/mol energy window were optimized using DFT/B3LYP/6-31G(d) on Spartan'18 program without considering solvent effects. Optimized conformers within 2.0-3.0 kcal/mol energy were further optimized on Gaussian16 software package^[2] using DFT/B3LYP/6-311+G(d,p)/PCM (chloroform) or other conditions described in each Figure captions. All the resultant conformers within 1.60 kcal/mol from the most stable were used for the following VCD calculations. Alternatively, a smaller energy window was applied when the Boltzmann population of each higher-energy conformer becomes lower than 1.0%. VCD spectra of each resultant conformer were calculated at the same level of theory as that used for the final optimization. The calculated frequencies, dipole strengths, and rotational strengths were converted to VCD spectra on GaussView6 software using a peak half-width a half height of 6 or 8 cm^{-1} . The

final spectra were obtained upon weighted average of the spectra of each conformer based on its Boltzmann population at 298 K.

Quantitative comparison of the observed and calculated VCD spectra were performed using CompareVOA software (BioTools, Inc.). As all the calculations were performed for model compounds, their IR spectra were not compared and instead identical IR data were selected to run the program. Scaling factors were manually set. The width of the triangular weighting function was set as a default value (20 cm^{-1}).

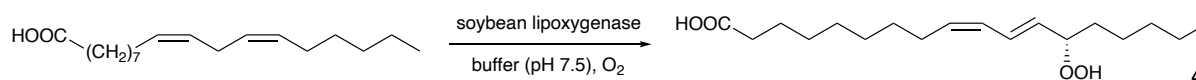
Synthetic Procedures

Preparation of **3**



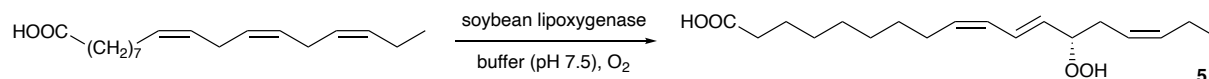
To methyl ricinelaidate (118 mg, 378 μ mol) in dioxane (2 mL) and methanol (1 mL) was added 2 M NaOH aq (1.5 mL) and the mixture was vigorously stirred overnight at 50 °C. The mixture was then diluted with CHCl₃, washed with 2 M HCl aq, and dried over MgSO₄. After removal of the solvent, the mixture was purified by silica-gel column chromatography (chloroform:MeOH = 9:1), which afforded **3** (70 mg, 62%). Its spectroscopic data were virtually identical with those reported.^[3]

Preparation of **4**



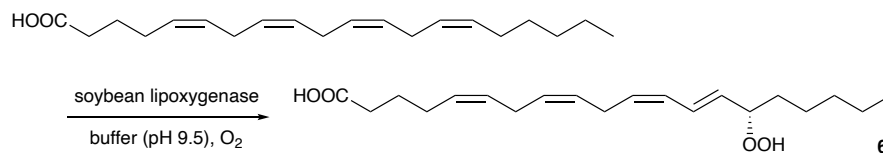
Lipid hydroperoxides were prepared according to a literature procedure^[4] with slight modifications. To a 0 °C solution of pH 7.5 phosphate buffer (50 mL) bubbled with a stream of O₂ was added soybean type I lipoxygenase (10 mg). After 30 min, linoleic acid (250 mg, 891 μ mol) in cold EtOH (2 mL) was added below the surface of the solution using a pipette. After 5 h, the mixture was acidified with 2 M HCl aq and extracted with EtOAc. The organic phase was washed with brine and dried over MgSO₄. Removal of the solvent afforded pure **4**^[5] (200 mg, 72%).

Preparation of **5**



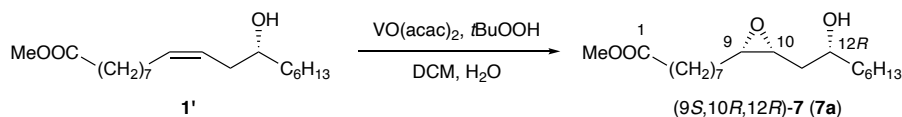
In a similar manner to the preparation of **4**, α -linolenic acid (250 mg, 898 μ mol) was converted to **5**^[6] (157 mg, 56%).

Preparation of **6**



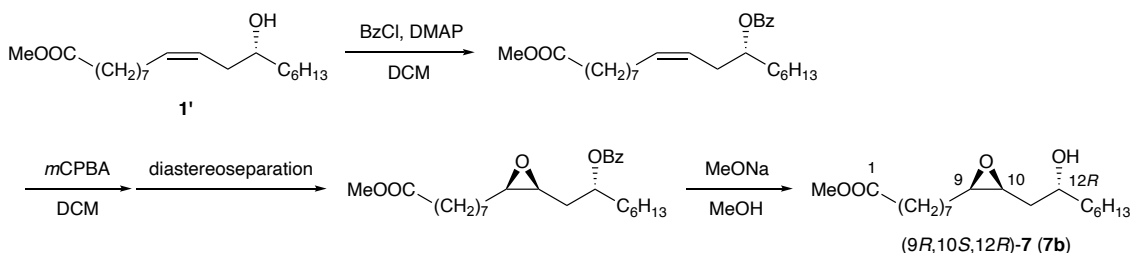
In a similar manner to the preparation of **4**, but with using pH 9.5 phosphate buffer, arachidonic acid (56 mg, 0.18 mmol) was converted to **6**^[7] (55 mg, 89%).

Preparation of (9*S*,10*R*,12*R*)-7 (7a)



To **1'** (100 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was added vanadyl acetylacetonate (19 mg) and the mixture was stirred at 0 °C under nitrogen atmosphere. After 10 minutes, 70% tert-butyl hydroperoxide aq (75 μL) was added and the mixture was stirred at 0 °C for 1 hour, and then at rt for 10 minutes. The mixture was diluted with CH_2Cl_2 , sequentially washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ aq and brine, and then dried over MgSO_4 . After removal of the solvent, the mixture was purified by silica-gel column chromatography (hexane:EtOAc = 3:1), which afforded (9*S*,10*R*,12*R*)-7^[8-10] (53 mg, 47%). (9*S*,10*R*,12*R*)-7; ^1H NMR (CDCl_3) δ 3.90 (m, H-12, 1H), 3.67 (s, Me, 3H), 3.12 (m, H-9, 1H), 2.92 (m, H-10, 1H), 2.36 (br, OH-12, 1H), 2.31 (t, H-2, $J = 7.5$ Hz, 2H), 1.80 (ddd, H-8a, $J = 14.5, 4.0, 4.0$ Hz, 1H), 1.63 (m, H-3, 2H), 1.57-1.25 (m, $\text{CH}_2 \times 10$, H-8b, 21H), 0.89 (t, H-18, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 174.3 (C-1), 71.0 (C-12), 56.4 (C-10), 55.5 (C-9), 51.5 (Me), 37.5 (C-11), 34.8 (C-8), 34.1 (C-2), 31.9, 29.4, 29.3, 29.2, 29.1, 28.0, 26.5, 25.6 ($\text{CH}_2 \times 8$), 25.0 (C-3), 22.7 (CH_2), 14.2 (C-18).

Preparation of (9*R*,10*S*,12*R*)-7 (7b)

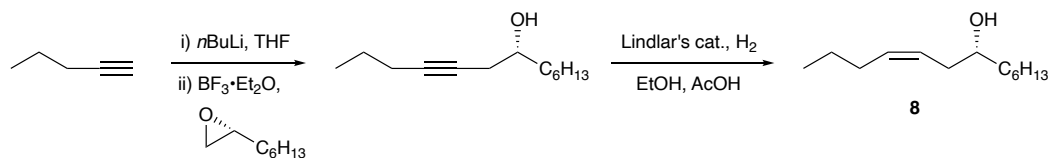


To **1'** (630 mg, 2.02 mmol) in CH_2Cl_2 (6 mL) was added BzCl (350 μL) and DMAP (490 mg) and the mixture was stirred at 45 °C for 1 h. The mixture was diluted with EtOAc, washed sequentially with 2 M HCl aq, 2 M NaOH aq and brine, and then dried over MgSO_4 . After removal of the solvent, the crude methyl (9*Z*,12*R*)-12-benzoyloxyoctadec-9-enoate (960 mg) was used for the next reaction without further purification. Methyl (9*Z*,12*R*)-12-benzoyloxyoctadec-9-enoate; ^1H NMR (CDCl_3) δ 8.04 (m, ArH, 2H), 7.54 (m, ArH, 1H), 7.43 (m, ArH, 2H), 5.47 (m, H-9, 1H), 5.41 (m, H-10, 1H), 5.14 (m, H-12, 1H), 3.66 (s, Me, 3H), 2.50-2.37 (m, H-11, 2H), 2.29 (t, H-2, $J = 7.5$ Hz, 2H), 2.03 (m, H-8, 2H), 1.75-1.60 (m, H-13, 2H), 1.60 (m, H-3, 2H), 1.44-1.22 (m, $\text{CH}_2 \times 8$, 16H), 0.87 (t, H-18, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 174.3 (C-1), 166.3 (OCOPh), 132.8 (C-9), 132.8 (Ar), 130.9 (Ar), 129.6 (Ar), 128.3 (Ar), 124.3 (C-10), 74.7 (C-12), 51.5 (Me), 34.2 (C-2), 33.8 (C-13), 32.1 (C-11), 31.8, 29.6, 29.3, 29.2, 29.2, 29.2 ($\text{CH}_2 \times 6$), 27.4 (C-8), 25.5 (CH_2), 25.0 (C-3), 22.7 (CH_2), 14.1 (C-18); HRMS (ESI) m/z calcd for $\text{C}_{26}\text{H}_{40}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$]⁺ 439.2819, found 439.2815.

To the crude methyl (9*Z*,12*R*)-12-benzoyloxyoctadec-9-enoate (960 mg) in CH₂Cl₂ (20 mL) was added *m*CPBA (440 mg, 70%) at 0 °C and the mixture was stirred for overnight at rt. The reaction mixture was diluted with EtOAc, washed sequentially with 2M NaOH aq and brine, and then dried over MgSO₄. After removal of the solvent, the mixture was subjected to silica-gel column chromatography (hexane:EtOAc = 5:1), which afforded a diastereomeric mixture of methyl 12-benzoyloxy-9,10-epoxyoctadecanoate (450 mg, 52% in 2 steps, dr = 6:5). Diastereoseparation using Chiralpak® IA column (hexane:EtOH = 97:3) afforded methyl (9*R*,10*S*,12*R*)-12-benzoyloxy-9,10-epoxyoctadecanoate (240 mg). Methyl (9*R*,10*S*,12*R*)-12-benzoyloxy-9,10-epoxyoctadecanoate; ¹H NMR (CDCl₃) δ 8.05 (m, ArH, 2H), 7.56 (m, ArH, 1H), 7.45 (m, ArH, 2H), 5.32 (m, H-12, 1H), 3.66 (s, Me, 3H), 3.05 (m, H-10, 1H), 2.88 (m, H-9, 1H), 2.29 (t, H-2, *J* = 7.5 Hz, 2H), 1.97 (ddd, H-11a, *J* = 14.5, 7.7, 5.2 Hz, 1H), 1.84 (ddd, H-11b, *J* = 14.5, 6.8, 5.2 Hz, 1H), 1.80-1.70 (m, H-13, 2H), 1.60 (m, H-3, 2H), 1.47 (m, H-8, 2H), 1.45-1.22 (m, CH₂ × 8, 16H), 0.86 (t, H-18, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 174.4 (C-1), 166.3 (OCOPh), 133.0 (Ar), 130.6 (Ar), 129.7 (Ar), 128.5 (Ar), 73.2 (C-12), 57.0 (C-9), 54.2 (C-10), 51.6 (Me), 34.7 (C-13), 34.2 (C-2), 33.2 (C-11), 31.8, 29.4, 29.3, 29.3, 29.2 (CH₂ × 5), 28.1 (C-8), 26.6, 25.4 (CH₂ × 2), 25.0 (C-3), 22.7 (CH₂), 14.2 (C-18); HRMS (ESI) *m/z* calcd for C₂₆H₄₀O₅Na [M+Na]⁺ 455.2768, found 455.2762.

To methyl (9*R*,10*S*,12*R*)-12-benzoyloxy-9,10-epoxyoctadecanoate (137 mg, 305 μmol) in MeOH (3 mL) was added MeONa (63 μL, ca 5.0 M in MeOH) dropwise and the mixture was stirred overnight at rt. The mixture was diluted with EtOAc, washed with brine, and then dried over MgSO₄. After removal of the solvent, the mixture was purified by silica-gel column chromatography (hexane:EtOAc = 3:1), which afforded (9*R*,10*S*,12*R*)-7^[8-10] (66 mg, 66%). (9*R*,10*S*,12*R*)-7; ¹H NMR (CDCl₃) δ 3.84 (m, H-12, 1H), 3.67 (s, Me, 3H), 3.15 (m, H-9, 1H), 2.96 (m, H-10, 1H), 2.31 (t, H-2, *J* = 7.5 Hz, 2H), 1.99 (br, OH, 1H), 1.74 (ddd, H-8a, *J* = 14.3, 8.3, 4.2 Hz, 1H), 1.62 (m, H-3, 2H), 1.60-1.20 (m, CH₂ × 10, H-8b, 21H), 0.89 (t, H-18, *J* = 6.7 Hz, 3H); ¹³C NMR (CDCl₃) δ 174.4 (C-1), 70.2 (C-12), 57.2 (C-10), 54.6 (C-9), 51.6 (Me), 37.9 (CH₂), 35.3 (C-8), 34.1 (C-2), 31.9, 29.4, 29.4, 29.2, 29.1, 28.1, 26.5, 25.7 (CH₂ × 8), 25.0 (C-3), 22.7 (CH₂), 14.2 (C-18).

Preparation of **8**

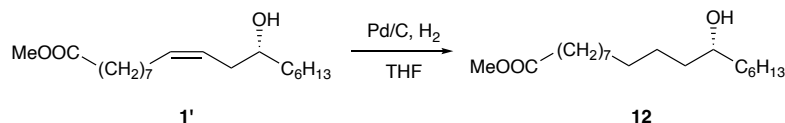


To 1-pentyne (100 mg, 1.47 mmol) in THF (2 mL) was added *n*BuLi (2.5 M hexane solution, 588 μL) at -78 °C and stirred for 10 min. To this solution, (*R*)-1,2-epoxyoctane (112 μL, 0.73 mmol) and BF₃·EtO₂ (185 μL) were added and stirred 30 min at -78 °C and then 3 h at rt. The mixture was

added EtOAc, washed sequentially with sat NaHCO₃ aq and brine, and dried over MgSO₄. After removal of the solvent, the crude mixture was purified by column chromatography (hexane-EtOAc = 10:1), which afforded (*R*)-7-hydroxytridec-4-yne (99 mg, 69%). (*R*)-7-Hydroxytridec-4-yne; ¹H NMR (CDCl₃) δ 3.69 (m, H-7, 1H), 2.40 (ddt, H-6a, *J* = 16.5, 4.6, 2.4 Hz, 1H), 2.27 (ddt, H-6b, *J* = 16.4, 6.9, 2.4 Hz, 1H), 2.15 (tt, H-3, *J* = 7.0, 2.4 Hz, 2H), 1.93 (d, OH, *J* = 4.7 Hz, 1H), 1.56-1.48 (m, H-2, H-8, 4H), 1.42 (m, H-9a, 1H), 1.38-1.24 (m, H-9b, CH₂ × 3, 7H), 0.98 (t, H-1, *J* = 7.4 Hz, 3H), 0.88 (t, H-13, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃) δ 83.3 (C-4), 76.4 (C-5), 70.4 (C-7), 36.4 (C-8), 31.9 (CH₂), 29.4 (CH₂), 27.9 (C-6), 25.8 (C-9), 22.7 (CH₂), 22.6 (C-2), 20.9 (C-3), 14.2 (C-13), 13.6 (C-1); HRMS (EI) *m/z* calcd for C₁₃H₂₄O [M]⁺ 196.1827, found 196.1828.

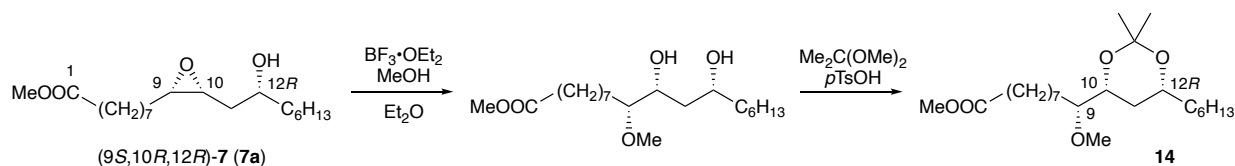
To (*R*)-7-hydroxytridec-4-yne (20 mg, 0.10 mmol) in EtOH (2 mL) was added Lindlar's cat. (5 mg) and AcOH (1 mL) and the mixture was stirred overnight at rt under H₂. The mixture was filtered through Celite[®]. Removal of the solvent yielded **8** (20 mg, qy). **8**; ¹H NMR (CDCl₃) δ 5.57 (m, H-4, 1H), 5.42 (m, H-5, 1H), 3.62 (m, H-7, 1H), 2.22 (m, H-6, 2H), 2.04 (m, H-3, 2H), 1.54 (br, OH, 1H), 1.50-1.42 (m, H-8, 2H), 1.39 (m, H-2, 2H), 1.36-1.25 (m, CH₂ × 4, 8H), 0.91 (t, H-1, *J* = 7.4 Hz, 3H), 0.89 (t, H-13, *J* = 6.9 Hz, 3H); ¹³C NMR (CDCl₃) δ 133.4 (C-4), 125.5 (C-5), 71.7 (C-7), 37.0 (C-8), 35.5 (C-6), 32.0 (CH₂), 29.6 (C-3), 29.5 (CH₂), 25.7 (CH₂), 23.0 (C-2), 22.8 (CH₂), 14.2 (C-13), 13.9 (C-1); HRMS (EI) *m/z* calcd for C₁₃H₂₆O [M]⁺ 198.1984, found 198.1992.

Preparation of **12** (methyl (*R*)-12-hydroxyoctadecanoate)



To **1'** (180 mg, 576 μmol) in THF (2 mL) was added 10% Pd/C (20 mg) and the mixture was stirred overnight at rt under H₂. The mixture was filtered through Celite[®]. Removal of the solvent yielded **12** (180 mg, 99%). Its spectroscopic data were virtually identical with those reported.^[11]

Verification of the absolute configuration of (*9S,10R,12R*)-**7** by nOe measurement



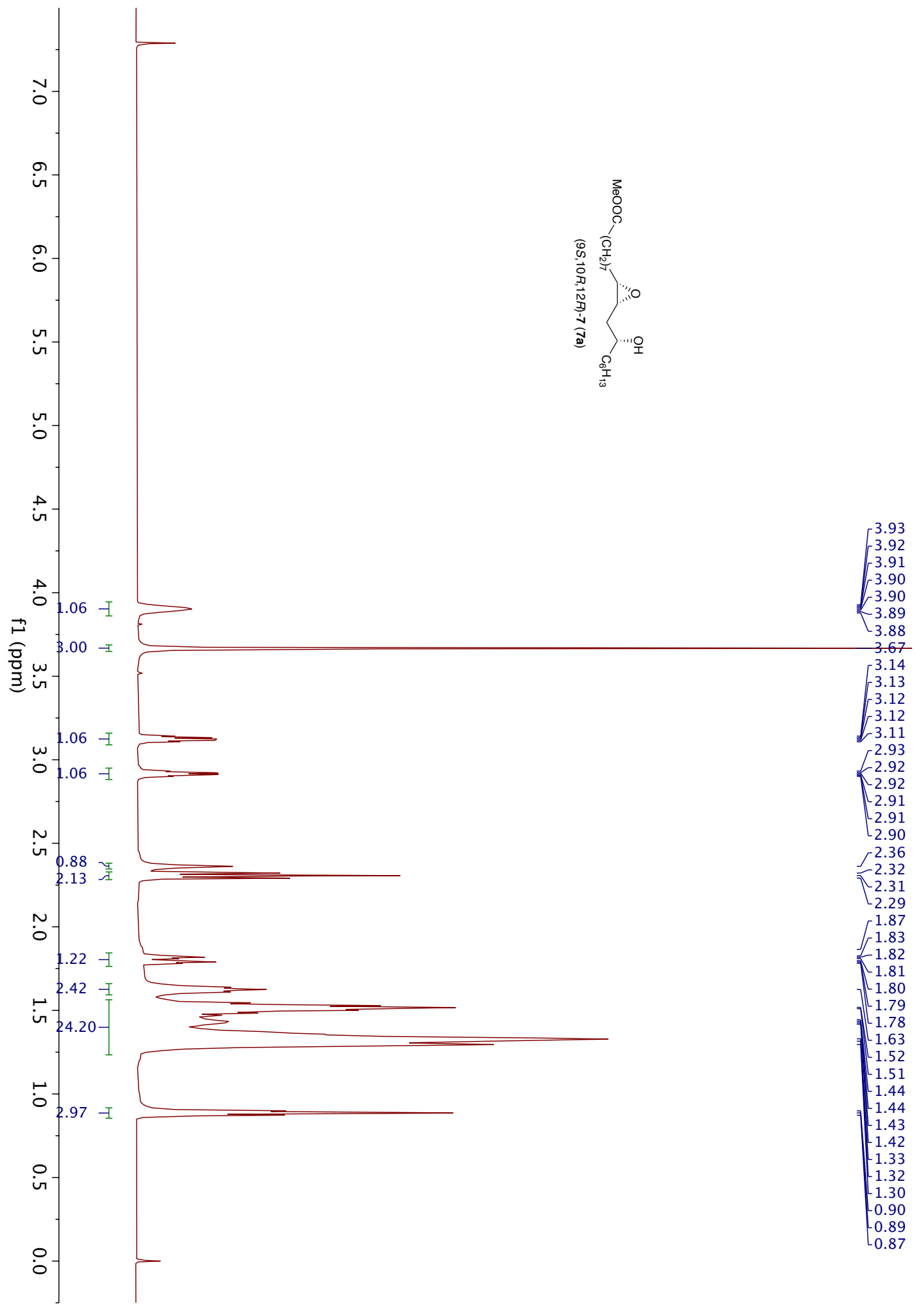
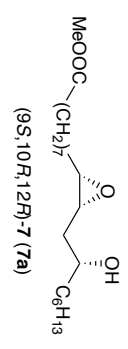
To (*9S,10R,12R*)-**7** (300 mg, 913 μmol) in Et₂O (6 mL) and MeOH (12 mL) was added BF₃•OEt₂ (1.1 mL) and the mixture was stirred overnight at rt. The mixture was diluted with EtOAc, washed sequentially with sat NaHCO₃ aq and brine, and then dried over MgSO₄. After removal of the solvent, the mixture was purified by silica-gel column chromatography (hexane:EtOAc = 2:1), which provided methyl (*9R,10R,12R*)-10,12-dihydroxy-9-methoxyoctadecanoate (79 mg, 24%). Methyl (*9R,10R,12R*)-10,12-dihydroxy-9-methoxyoctadecanoate; ¹H NMR (CDCl₃) δ 3.85 (m, H-

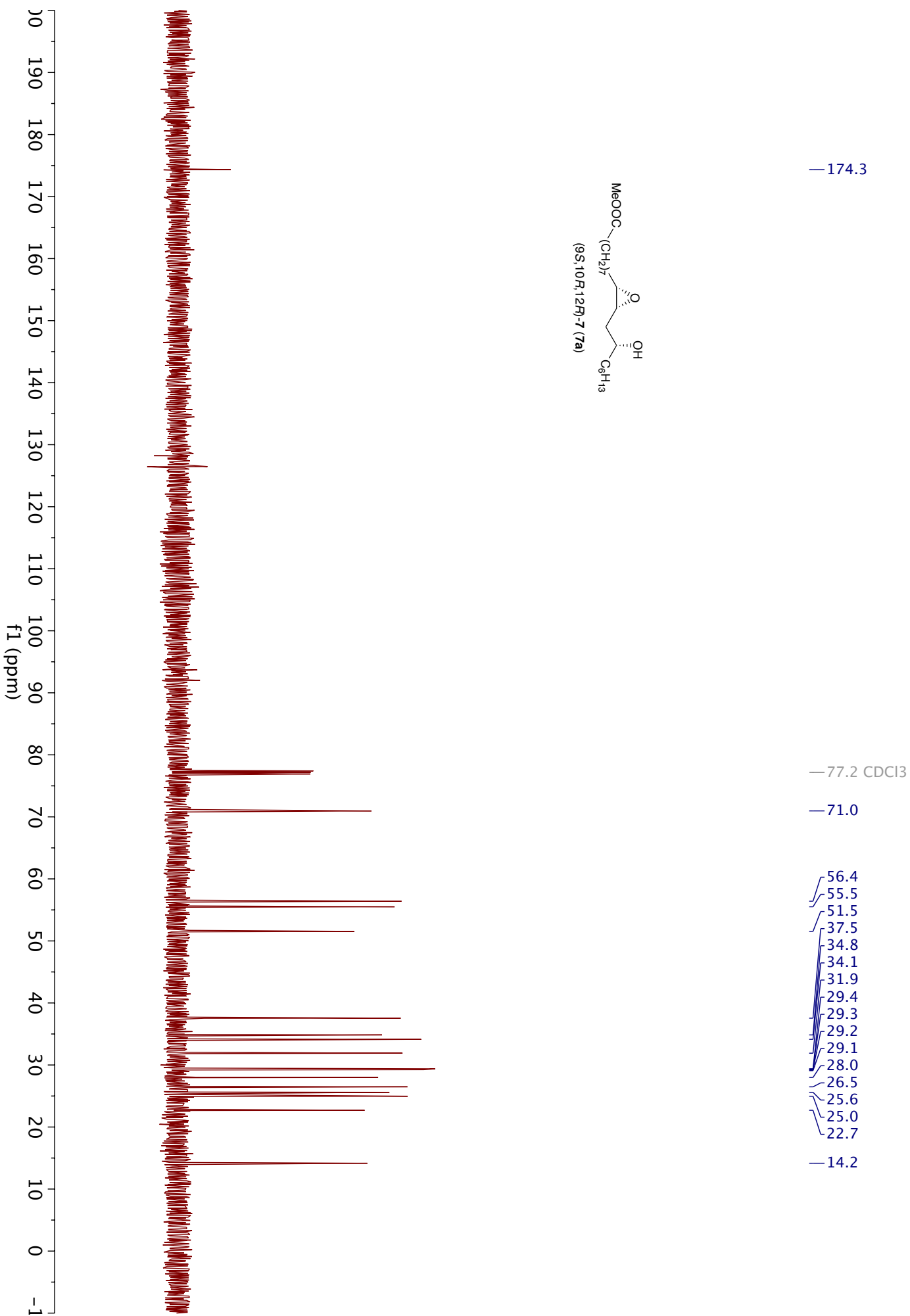
12, 1H), 3.79 (m, H-10, 1H), 3.67 (s, Me, 3H), 3.59 (br, OH-12, 1H), 3.41 (s, Me-9, 3H), 3.22 (br, OH-10, 1H), 3.01 (m, H-9, 1H), 2.30 (t, H-2, $J = 7.5$ Hz, 2H), 1.67-1.21 (m, $\text{CH}_2 \times 12$, 24H), 0.88 (t, H-18, $J = 6.8$ Hz, 3H). Its ^1H NMR chemical shifts in CDCl_3 varied depending on the measurement conditions such as concentrations and perhaps water contents. The ^1H NMR spectrum in CD_3OD seemed more reproducible. ^1H NMR (CD_3OD) δ 3.83-3.75 (m, H-12, H-10, 2H), 3.65 (s, Me, 3H), 3.41 (s, Me-9, 3H), 3.08 (m, H-9, 1H), 2.32 (t, H-2, $J = 7.4$ Hz, 2H), 1.68-1.27 (m, $\text{CH}_2 \times 12$, 24H), 0.90 (t, H-18, $J = 6.9$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 174.4 (C-1), 84.5 (C-9), 73.9 (C-10), 72.4 (C-12), 58.3 (Me-9), 51.5 (Me), 39.1, 38.1 ($\text{CH}_2 \times 2$), 34.1 (C-2), 31.9, 29.8, 29.7, 29.5, 29.3, 29.2, 25.5, 25.2, 25.0, 22.7 ($\text{CH}_2 \times 10$), 14.2 (C-18); HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{40}\text{O}_5\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 383.2768, found 383.2760.

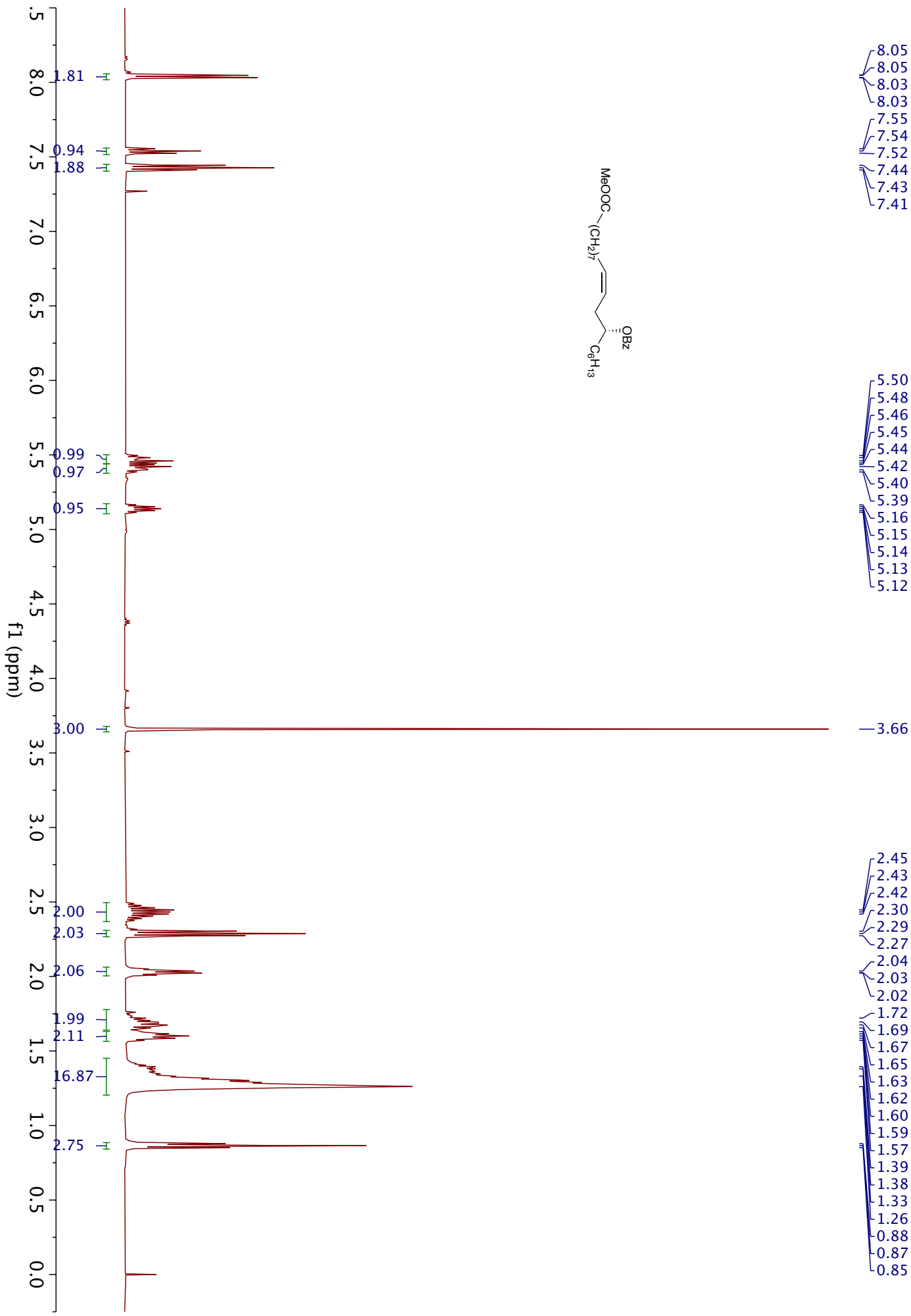
To methyl (9*R*,10*R*,12*R*)-10,12-dihydroxy-9-methoxyoctadecanoate (43.8 mg, 121 μmol) in 2,2-dimethoxypropane (500 μL) was added a catalytic amount of *p*-TsOH and the mixture was stirred at rt for 1 h. The mixture was diluted with EtOAc, washed sequentially with sat NaHCO_3 aq and water, and then dried over MgSO_4 . After removal of the solvent, the mixture was purified by silica gel chromatography (toluene:EtOAc = 20:1) affording **14** (11.6 mg, 24%). **14**; ^1H NMR (CDCl_3) δ 3.92 (ddd, H-10, $J = 11.8, 5.2, 2.5$ Hz, 1H), 3.79 (m, H-12, 1H), 3.67 (s, Me, 3H), 3.43 (s, Me-9, 3H), 3.06 (m, H-9, 1H), 2.30 (t, H-2, $J = 7.5$ Hz, 2H), 1.62 (m, H-3, 2H), 1.56-1.47 (m, H-8a, H-13a, 2H), 1.43, 1.39 (s $\times 2$, $\text{C}(\text{Me})_2$, 3H $\times 2$), 1.45-1.19 (m, $\text{CH}_2 \times 9$, H-8b, H-13b, 20H), 0.88 (t, H-18, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 174.5 (C-1), 98.5 ($\text{C}(\text{Me})_2$), 83.5 (C-9), 70.8 (C-10), 69.1 (C-12), 59.0 (Me-9), 51.6 (Me-12), 36.8 (C-13), 34.2 (C-2), 32.2, 31.9 ($\text{CH}_2 \times 2$), 30.4 ($\text{C}(\text{Me})_2$), 29.8 (CH_2), 29.6 (C-8), 29.4, 29.4, 29.2, 25.8, 25.1 ($\text{CH}_2 \times 5$), 25.1 (C-3), 22.7 (CH_2), 19.9 ($\text{C}(\text{Me})_2$), 14.2 (C-18); HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{44}\text{O}_5\text{Na}$ [$\text{M}+\text{Na}$] $^+$ 423.3081, found 423.3074.

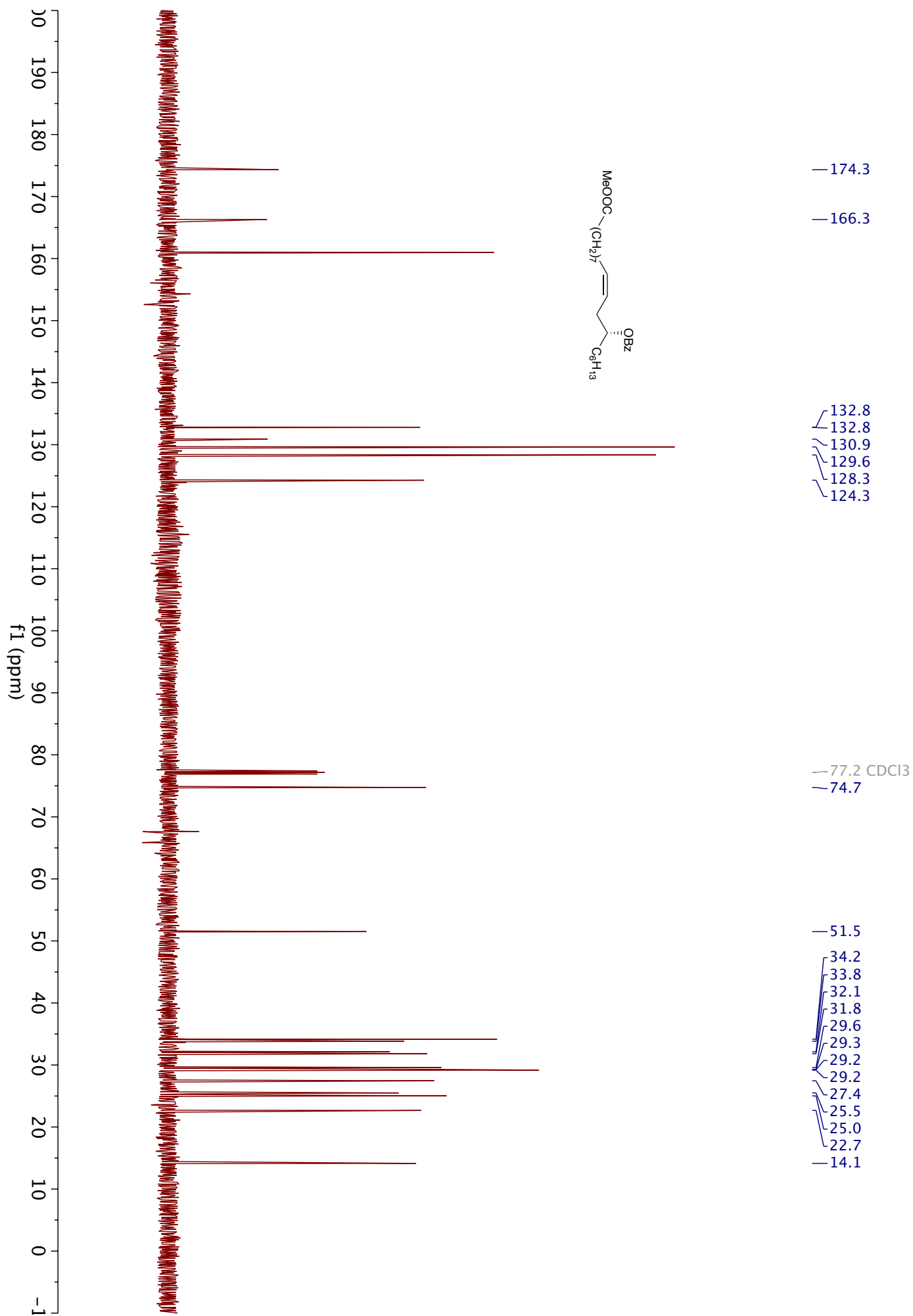
References

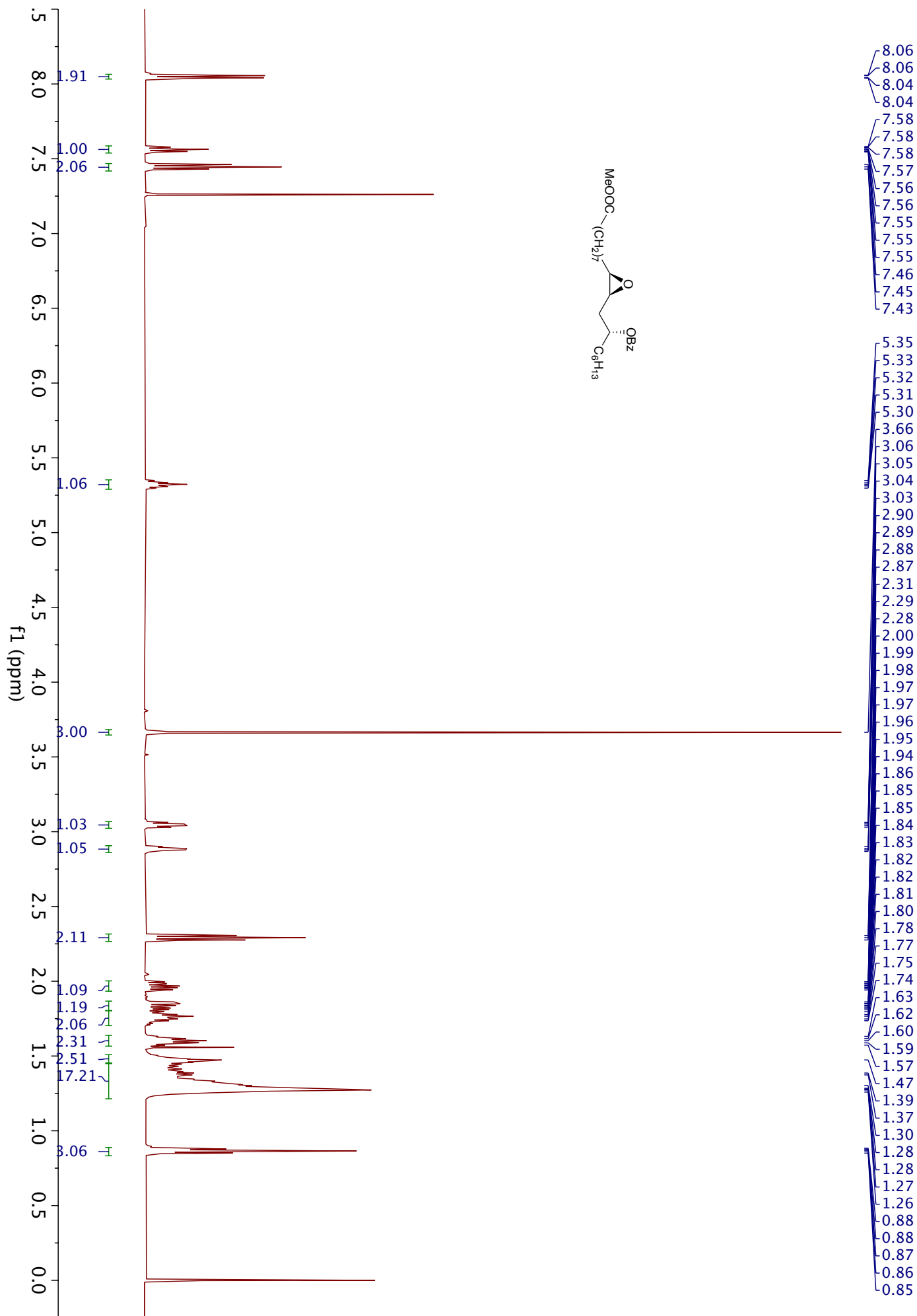
- [1] SPARTAN'18, Wavefunction, Inc., Irvine, CA.
- [2] Gaussian 16, Revision A.03, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.
- [3] Moriello, A. S.; Chinarro, S. L.; Fernández, O. N.; Eras, J.; Amodeo, P.; Canela-Garayoa, R.; Vitale, R. M.; Di Marzo, V.; De Petrocellis, L. *J. Med. Chem.* **2018**, *61*, 8255.
- [4] Dussault, P.; Sahli, A.; Westermeyer, T. *J. Org. Chem.* **1993**, *58*, 5469.
- [5] Watanabe, T.; Katayama, S.; Enoki, M.; Honda, Y.; Kuwahara, M. *Eur. J. Biochem.* **2000**, *267*, 4222.
- [6] Zerbe, P.; Weiler, E. W.; Schaller, F. *Phytochemistry* **2007**, *68*, 229.
- [7] Dussault, P.; Lee, I. Q. *J. Org. Chem.* **1995**, *60*, 218.
- [8] Foglia, T. A.; Sonnet, P. E.; Nunez, A.; Dudley, R. L. *J. Am. Oil Chem. Soc.* **1998**, *75*, 601.
- [9] Omar, M. N. B.; Hamilton, R. J.; Moynihan, H. A. *ARKIVOC* **2003**, *7*, 190.
- [10] Funken, N.; Mühlhaus, F.; Gansäuer, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 12030.
- [11] Pews-Davtyan, A.; Scharnagl, F. K.; Hertrich, M. F.; Kreyenschulte, C.; Bartling, S.; Lund, H.; Jackstell, R.; Beller, M. *Green Chem.* **2019**, *21*, 5104.

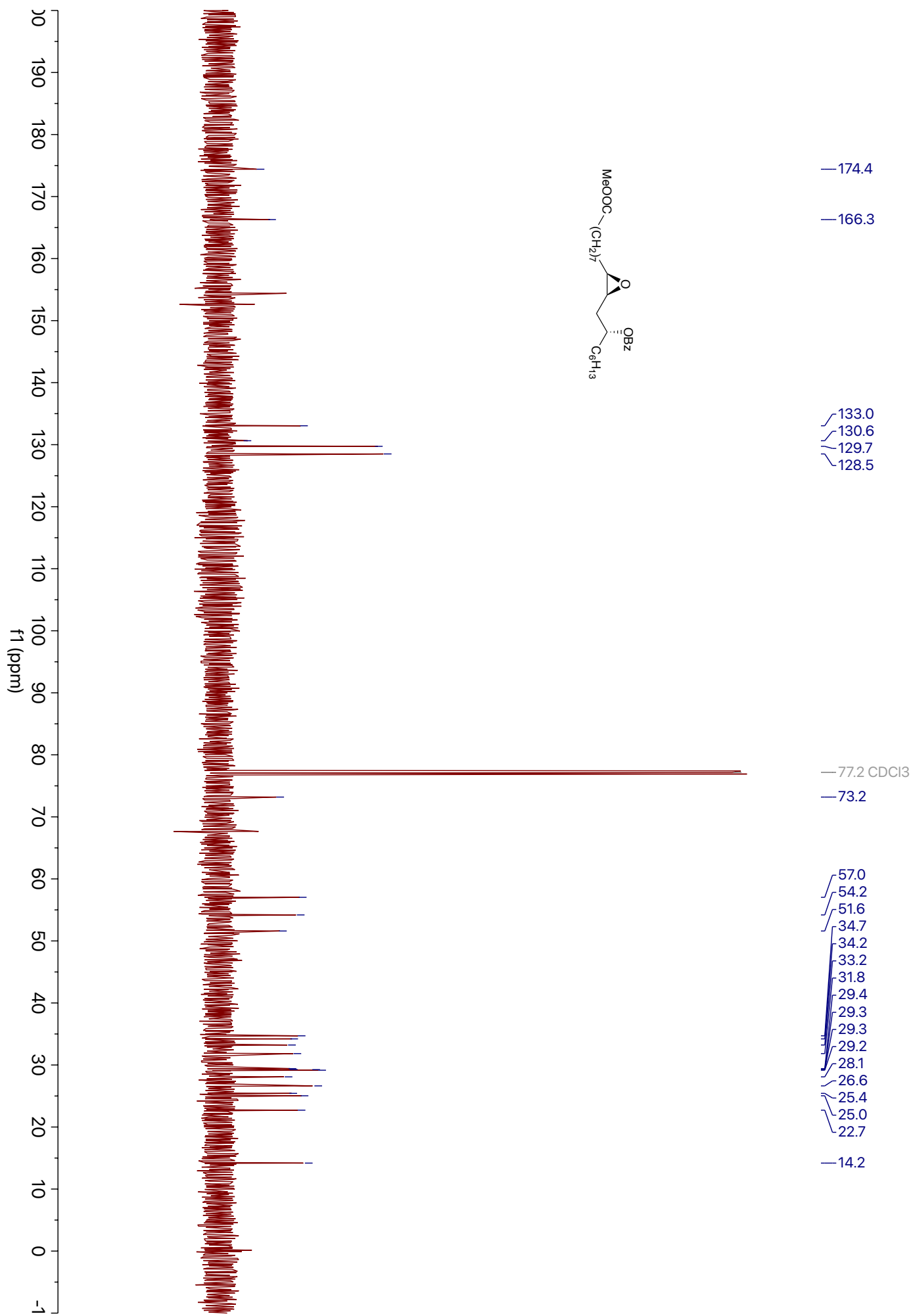


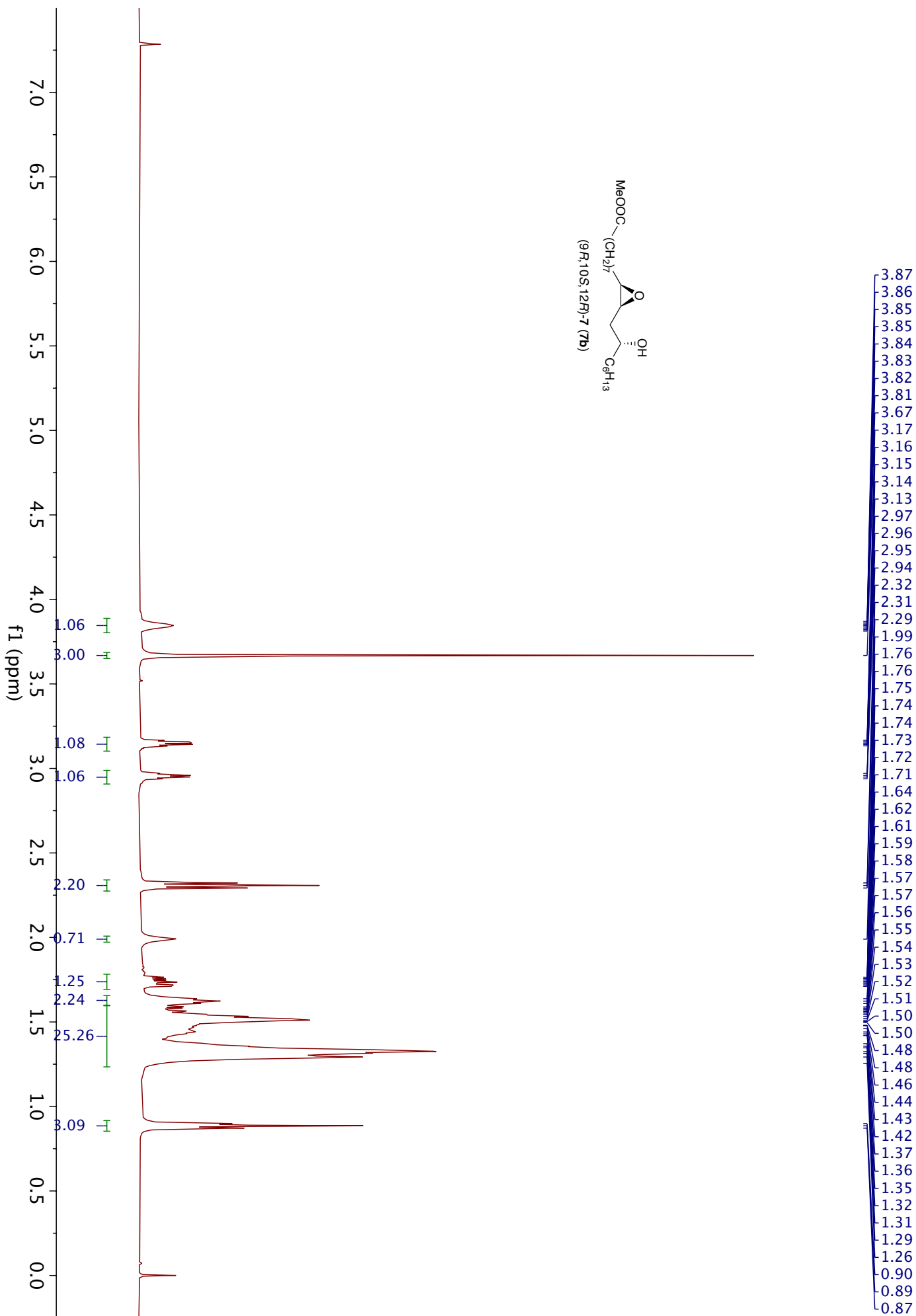


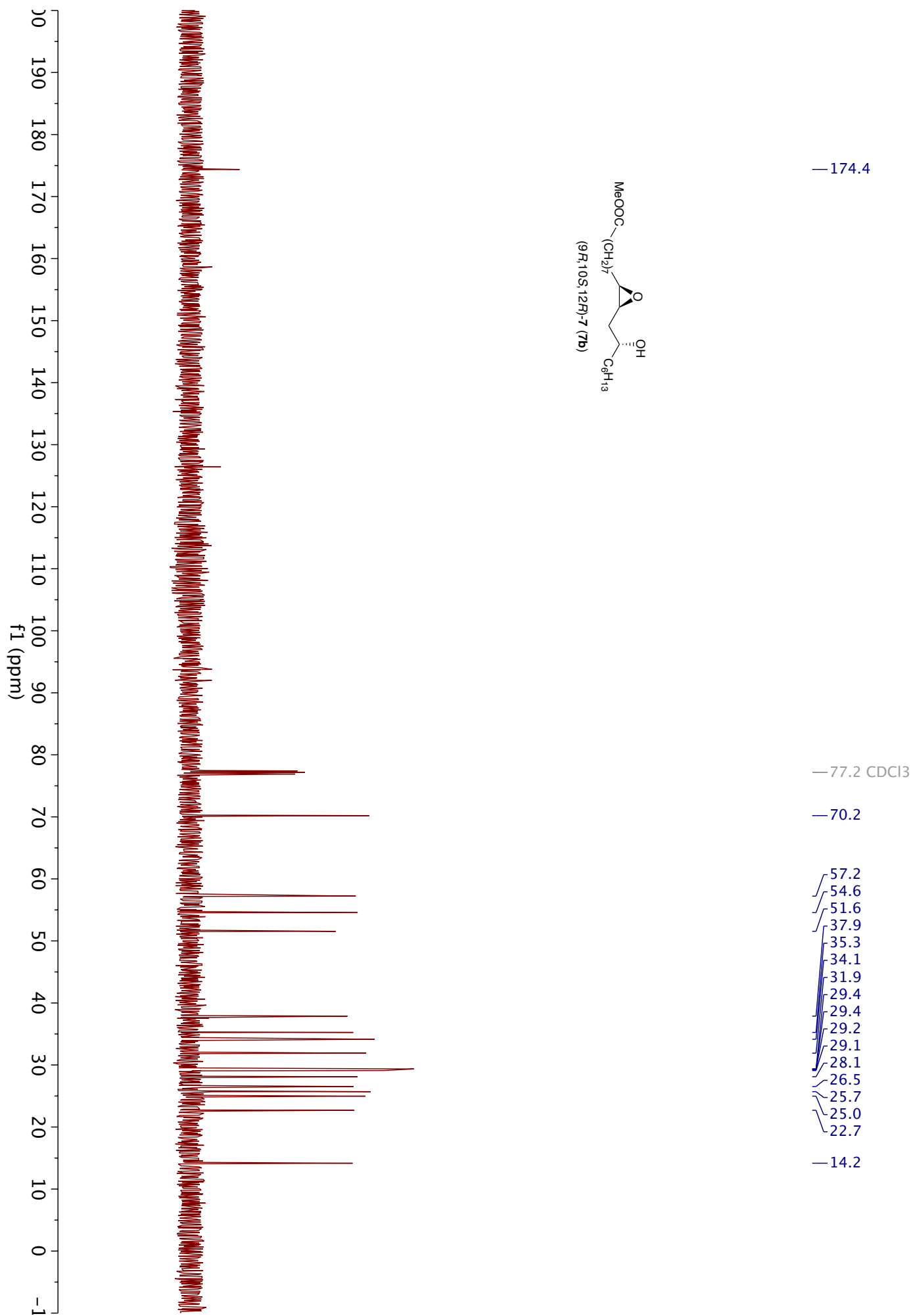


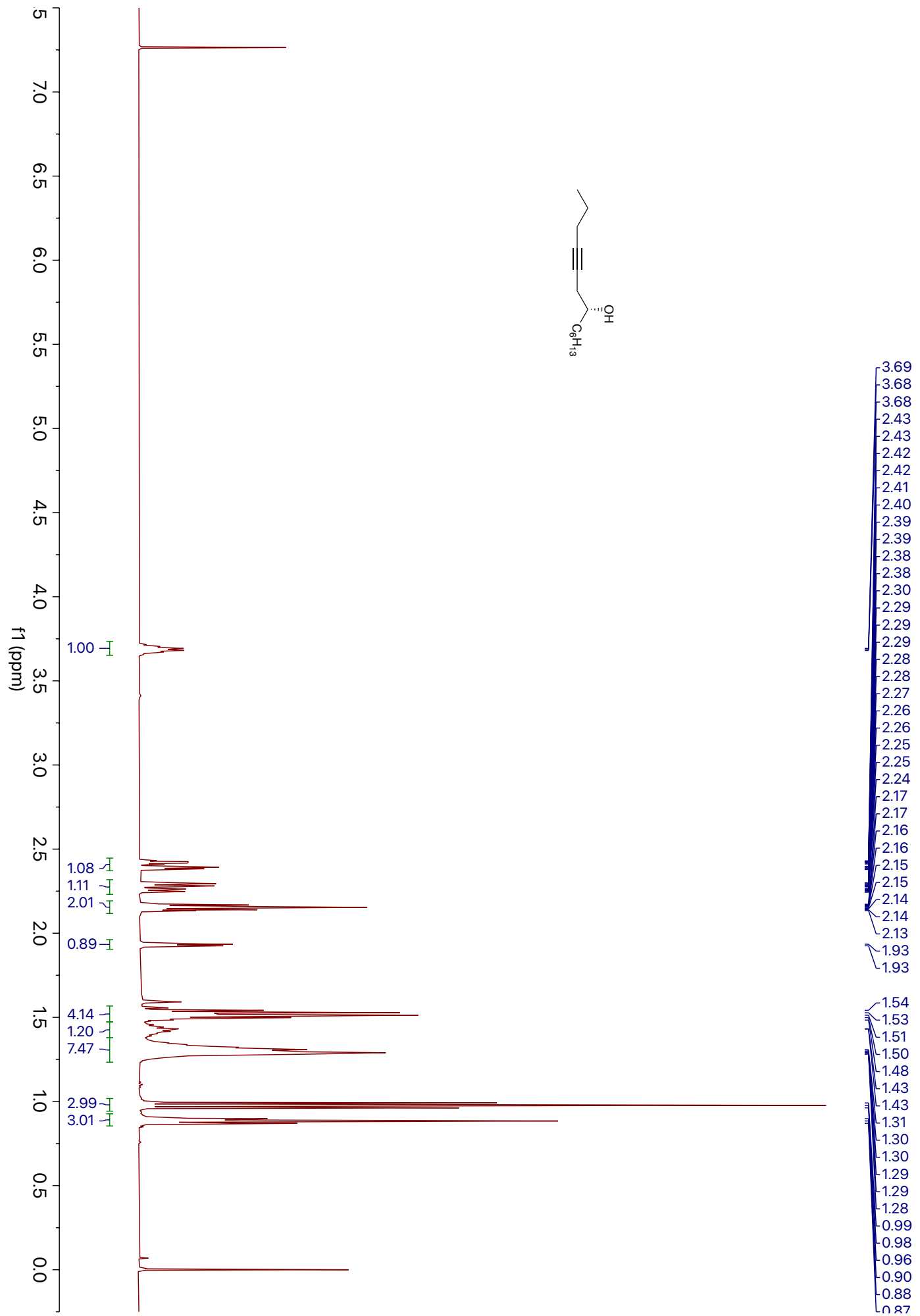
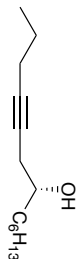


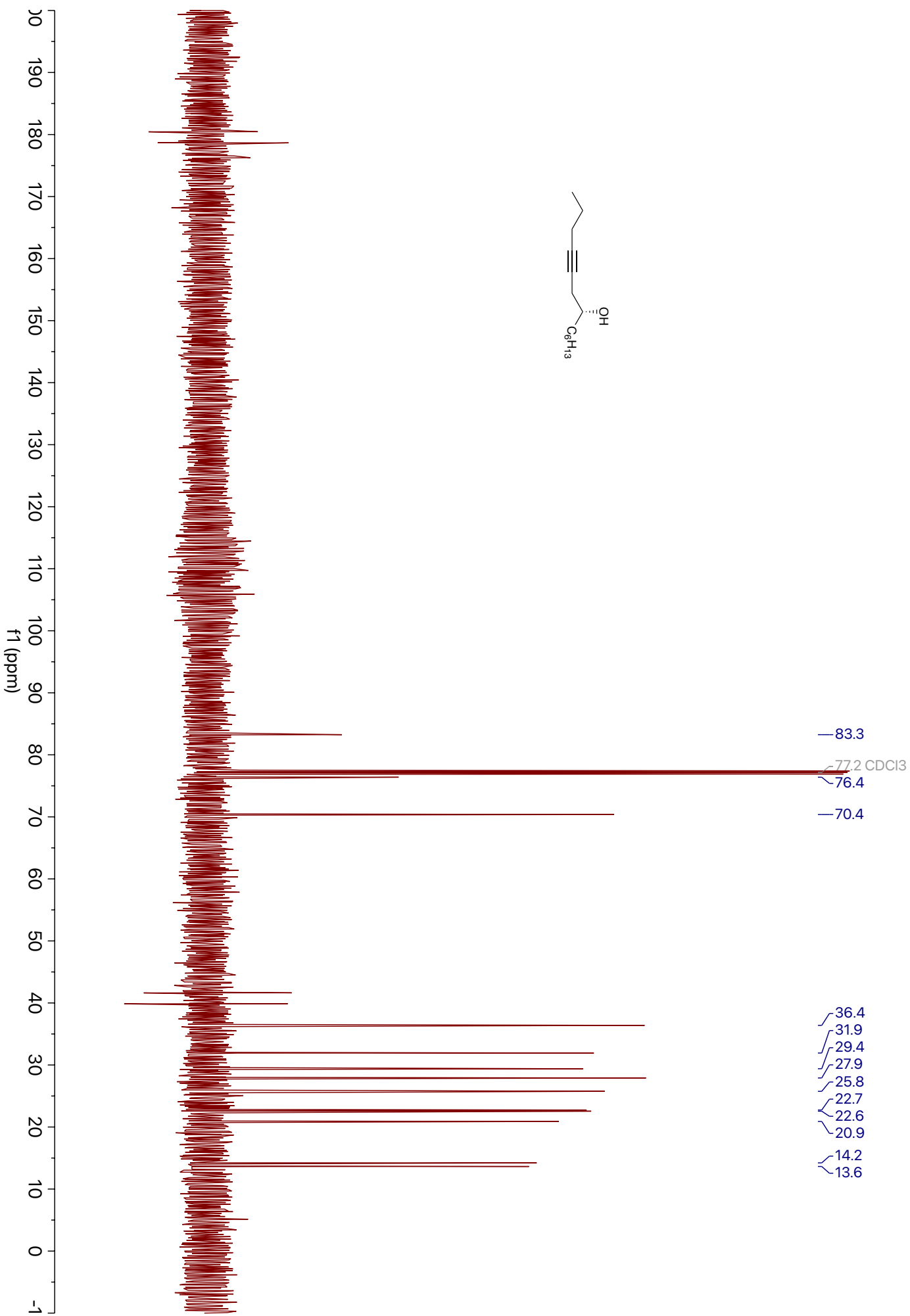


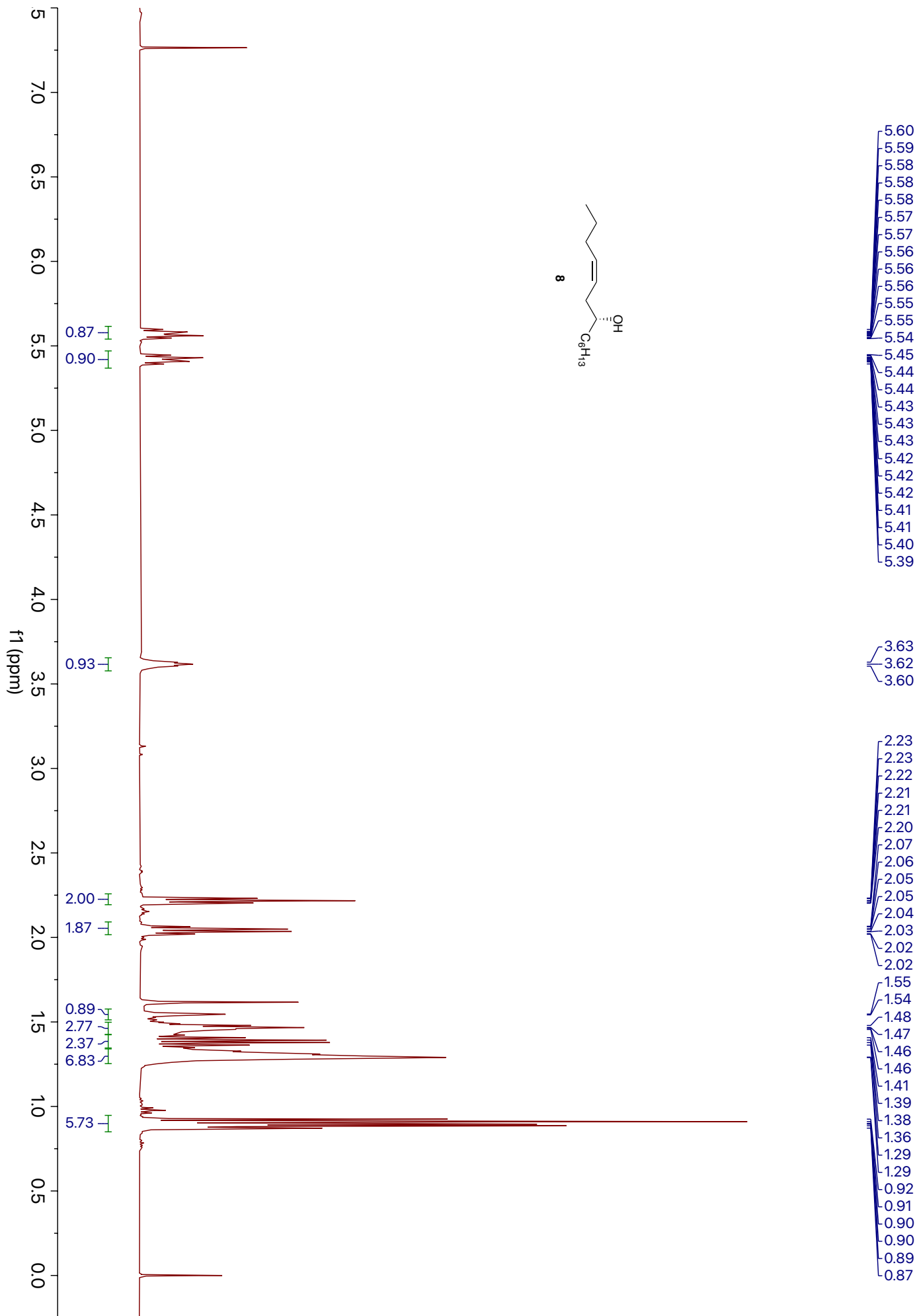


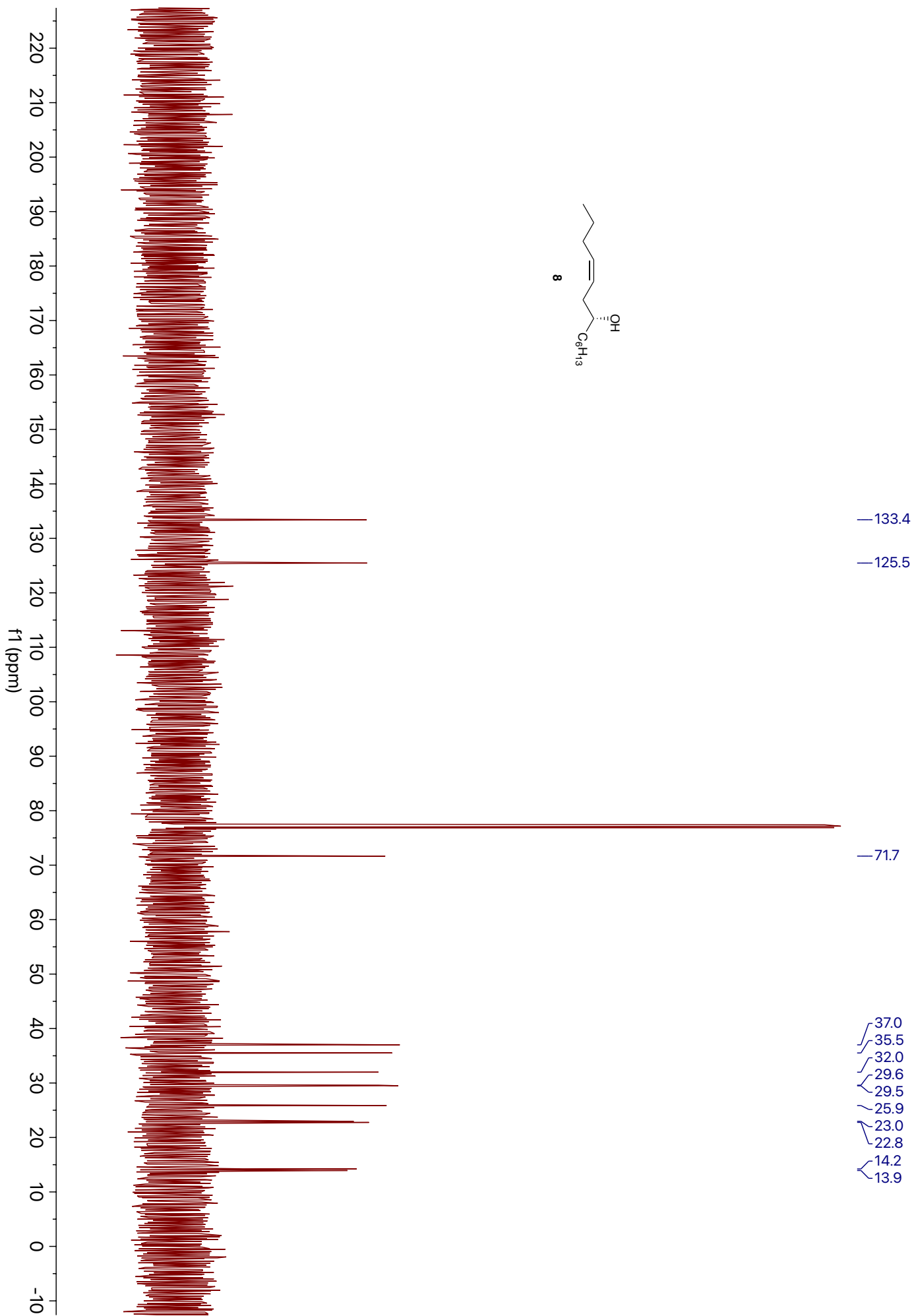


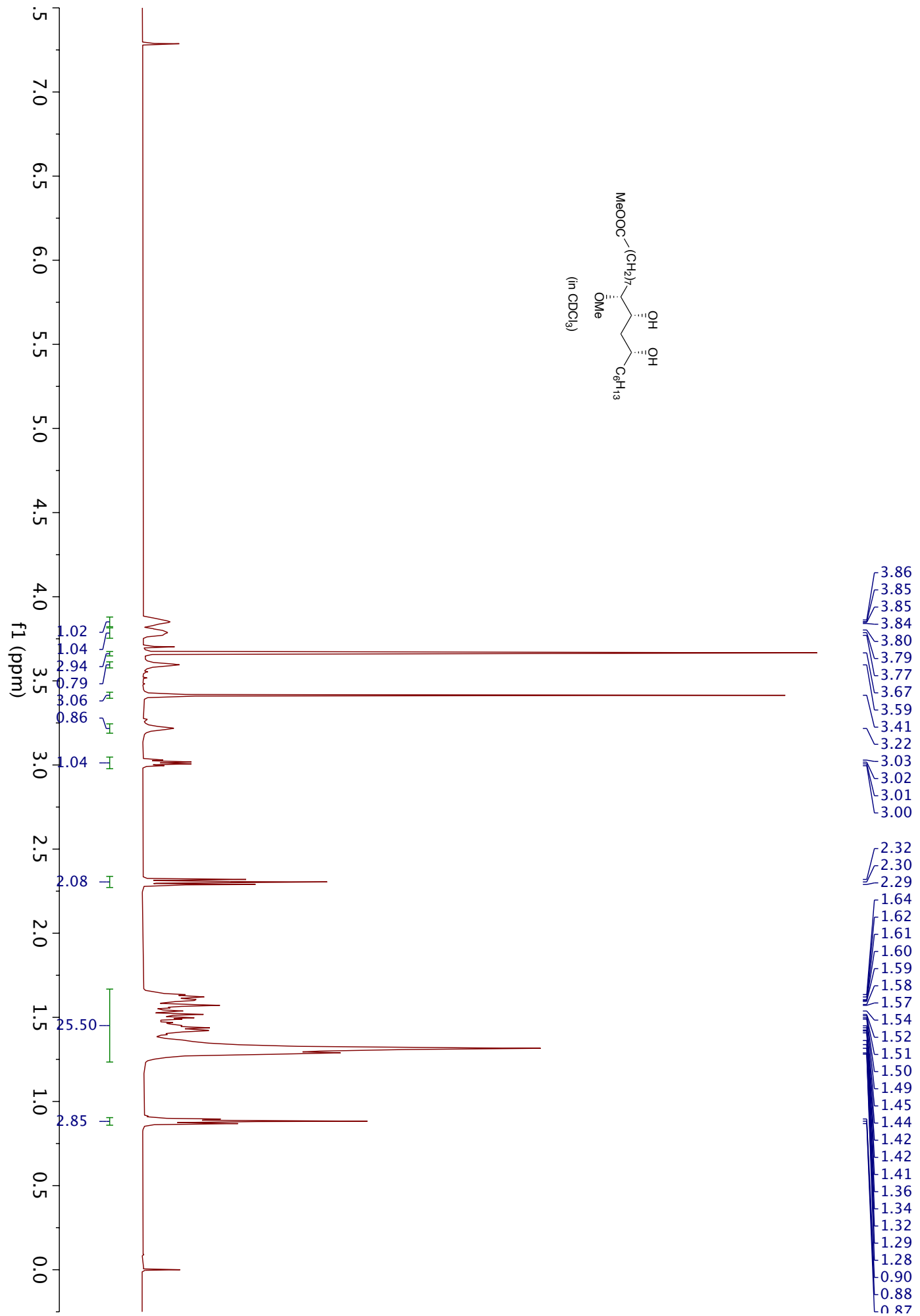
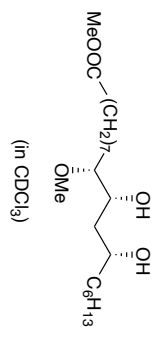


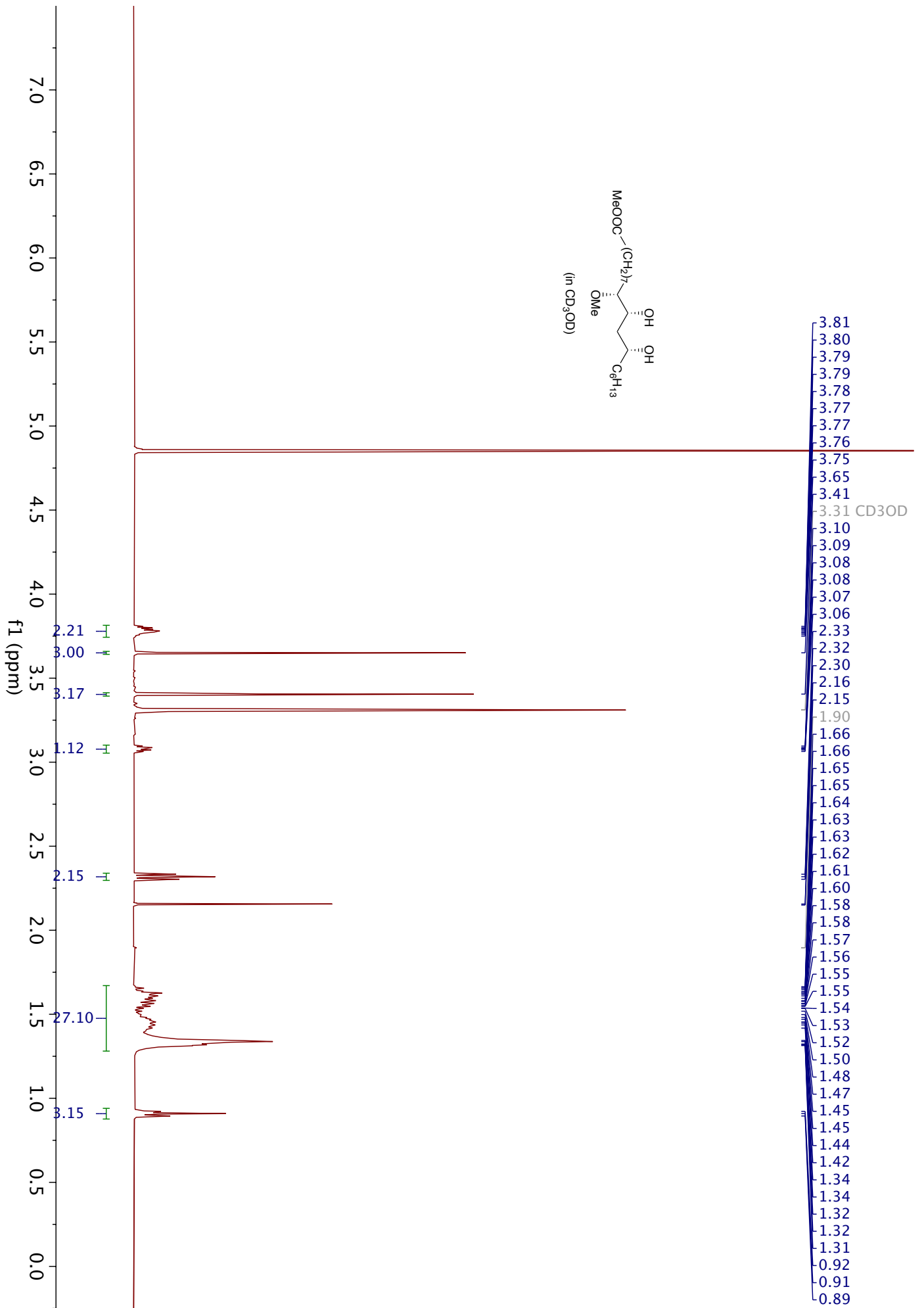


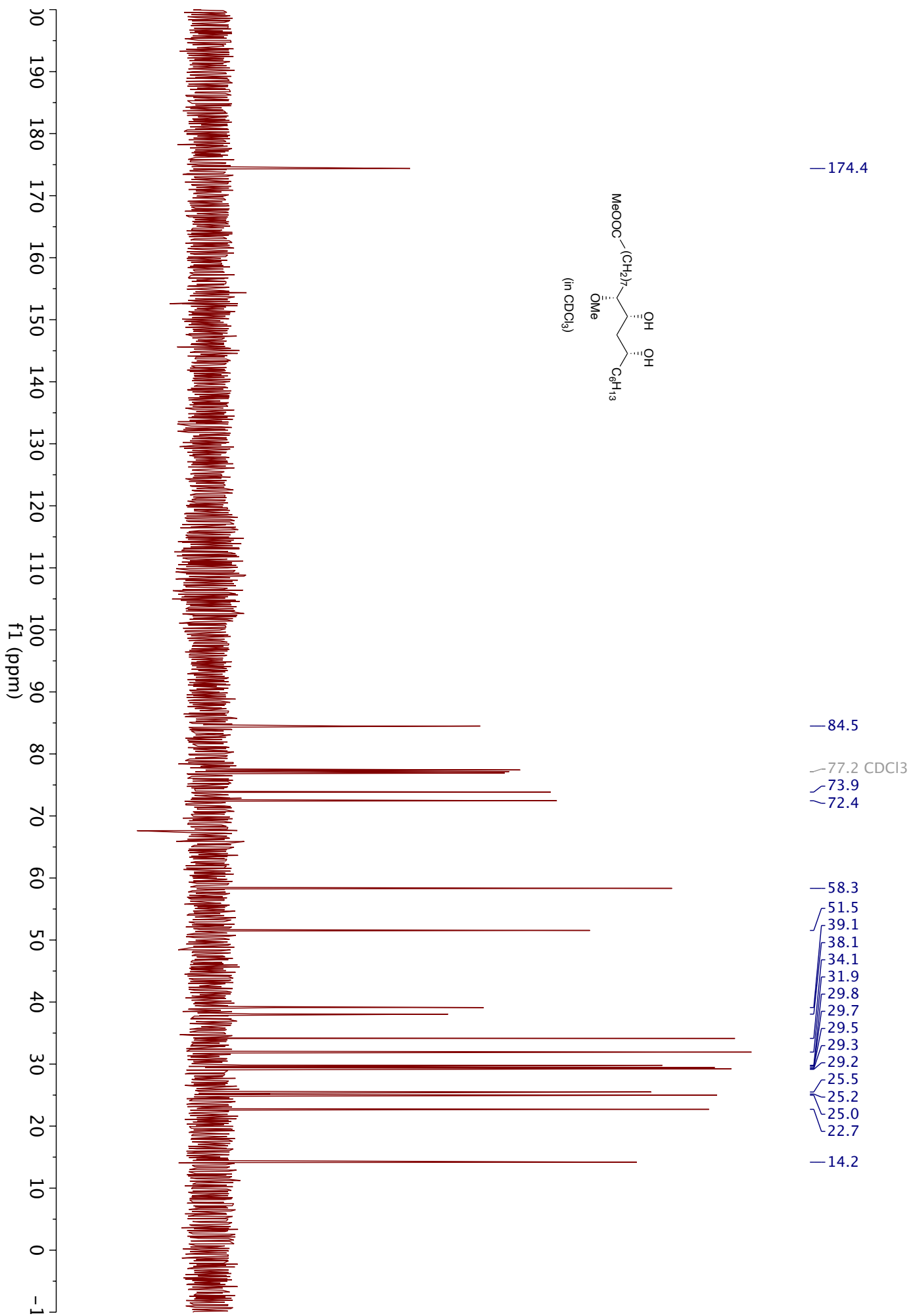


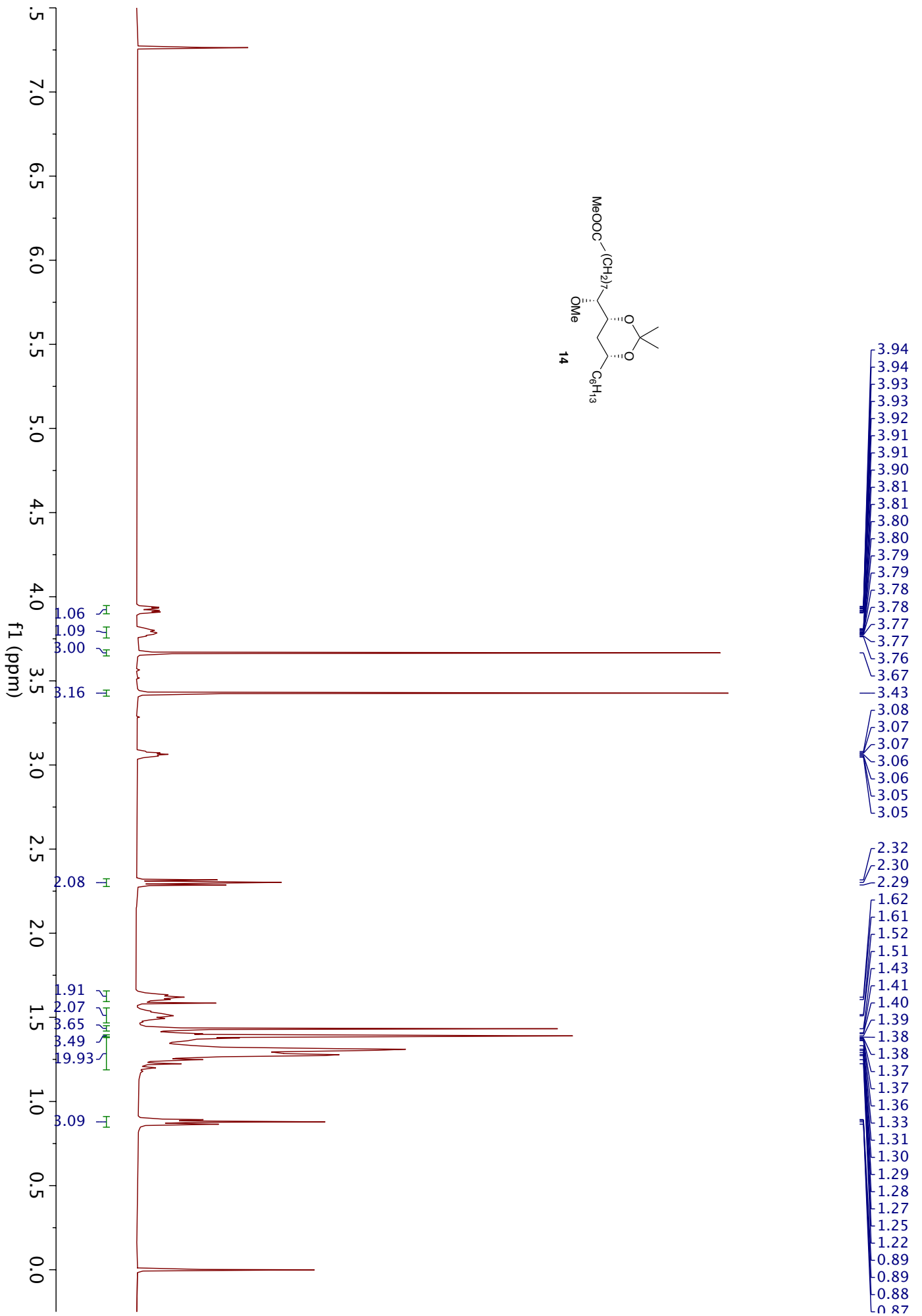


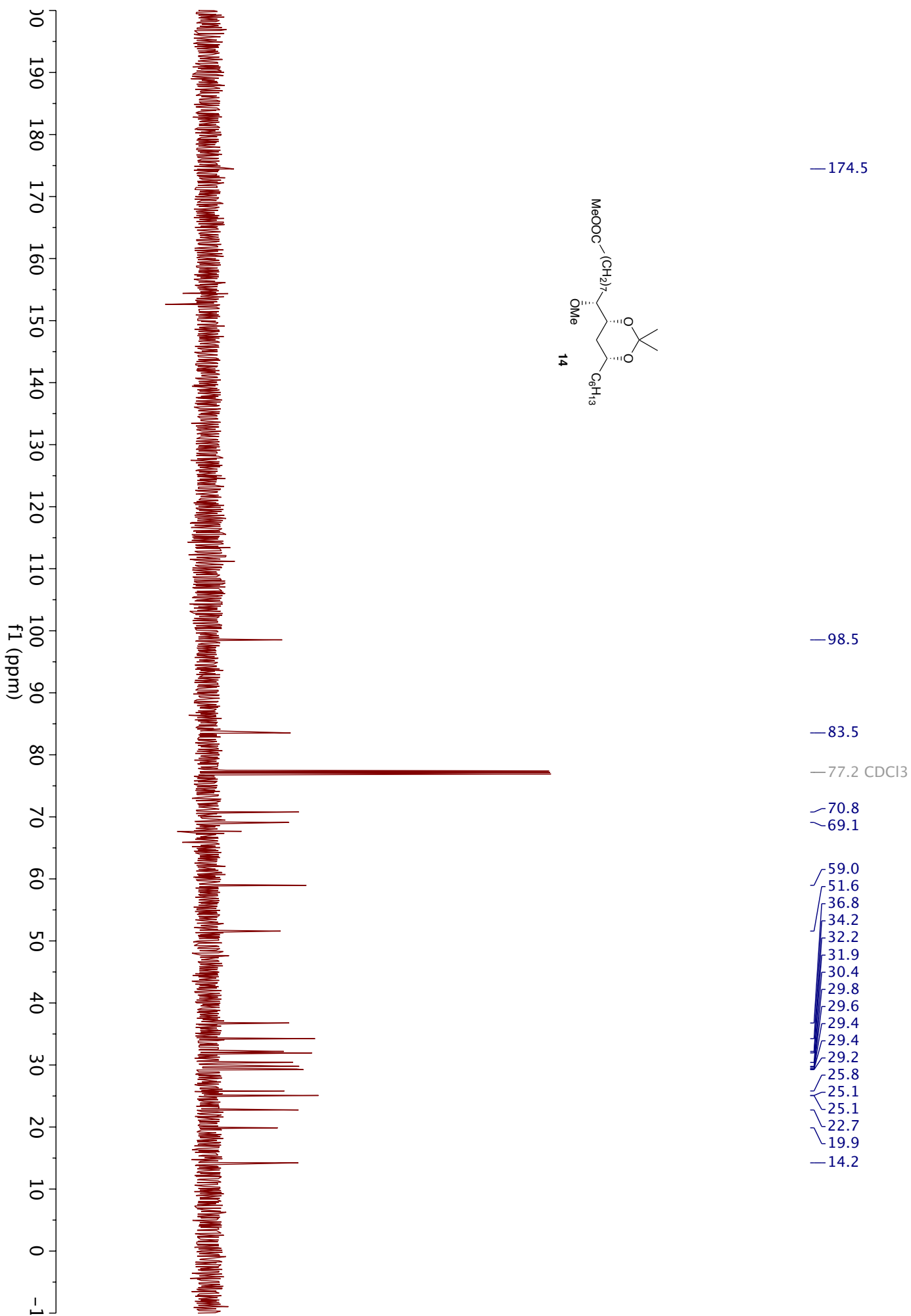












Cartesian Coordinates of Selected Conformers

The most stable conformer of **8** optimized at B3LYP/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| H | 7.176852 | -0.78262 | 0.031125 |
| C | 6.698134 | -0.555939 | -0.927021 |
| H | 7.410775 | 0.017167 | -1.52708 |
| H | 6.519875 | -1.506375 | -1.440258 |
| C | 5.390386 | 0.214817 | -0.722473 |
| H | 4.953514 | 0.45708 | -1.699028 |
| H | 5.605203 | 1.175285 | -0.237963 |
| C | 4.359446 | -0.551691 | 0.113918 |
| H | 4.798324 | -0.797118 | 1.090026 |
| H | 4.143055 | -1.511788 | -0.372495 |
| C | 3.04765 | 0.212544 | 0.327388 |
| H | 2.619434 | 0.460698 | -0.65096 |
| H | 3.263981 | 1.170215 | 0.819762 |
| C | 2.025019 | -0.567083 | 1.163819 |
| H | 2.491251 | -0.847792 | 2.115993 |
| H | 1.775501 | -1.504188 | 0.655751 |
| C | 0.729716 | 0.197966 | 1.47634 |
| H | 0.975995 | 1.146318 | 1.9689 |
| H | 0.131754 | -0.381806 | 2.189114 |
| C | -0.153337 | 0.510181 | 0.269945 |
| H | 0.417757 | 1.100994 | -0.460357 |
| O | -0.520181 | -0.740436 | -0.335121 |
| H | -1.176767 | -0.554048 | -1.017943 |
| C | -1.407231 | 1.313907 | 0.664146 |
| H | -1.072695 | 2.241805 | 1.144483 |
| H | -1.966691 | 0.746104 | 1.411826 |
| C | -2.260065 | 1.655668 | -0.527745 |
| H | -1.783304 | 2.311008 | -1.256161 |
| C | -3.504916 | 1.242873 | -0.797661 |
| H | -3.953246 | 1.596224 | -1.725972 |

| | | | |
|---|-----------|-----------|-----------|
| C | -4.393069 | 0.351457 | 0.025492 |
| H | -5.270656 | 0.932077 | 0.342539 |
| H | -3.890031 | 0.027604 | 0.940363 |
| C | -4.888249 | -0.883402 | -0.750147 |
| H | -4.024785 | -1.485907 | -1.053552 |
| H | -5.375201 | -0.555144 | -1.675943 |
| C | -5.857641 | -1.745956 | 0.062299 |
| H | -6.746223 | -1.175751 | 0.351453 |
| H | -6.191266 | -2.614955 | -0.511438 |
| H | -5.386021 | -2.113658 | 0.978981 |

The most stable conformer of **9** optimized at B3LYP/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| H | 8.120725 | 0.587808 | -0.223583 |
| C | 7.149819 | 0.947857 | 0.12868 |
| H | 6.998735 | 1.951699 | -0.281208 |
| H | 7.204977 | 1.040767 | 1.218156 |
| C | 6.017413 | 0.004721 | -0.288703 |
| H | 6.214065 | -0.999011 | 0.107794 |
| H | 6.010188 | -0.095333 | -1.381012 |
| C | 4.635262 | 0.470766 | 0.183025 |
| H | 4.643647 | 0.573202 | 1.276204 |
| H | 4.438356 | 1.474746 | -0.215054 |
| C | 3.495318 | -0.467847 | -0.227929 |
| H | 3.692384 | -1.471551 | 0.171495 |
| H | 3.488988 | -0.570756 | -1.320877 |
| C | 2.114547 | 0.004141 | 0.242029 |
| H | 2.120026 | 0.107222 | 1.335062 |
| H | 1.912536 | 1.00139 | -0.1614 |
| C | 0.983218 | -0.94567 | -0.167146 |
| H | 1.182249 | -1.945231 | 0.237554 |
| H | 0.957912 | -1.045221 | -1.259313 |
| C | -0.400114 | -0.512614 | 0.309108 |
| H | -0.375393 | -0.385902 | 1.402591 |

| | | | |
|---|-----------|-----------|-----------|
| O | -0.693683 | 0.757394 | -0.295347 |
| H | -1.625504 | 0.949706 | -0.131315 |
| C | -1.490759 | -1.542564 | -0.038592 |
| H | -1.201659 | -2.502152 | 0.407317 |
| H | -1.513955 | -1.67815 | -1.12521 |
| C | -2.850023 | -1.140955 | 0.465505 |
| H | -2.966294 | -1.102917 | 1.549381 |
| C | -3.896356 | -0.825695 | -0.30286 |
| H | -3.777828 | -0.866894 | -1.386778 |
| C | -5.26504 | -0.445723 | 0.191033 |
| H | -5.972536 | -1.228716 | -0.112137 |
| H | -5.270758 | -0.427088 | 1.286895 |
| C | -5.78289 | 0.900189 | -0.355013 |
| H | -6.834608 | 1.005593 | -0.067955 |
| H | -5.766926 | 0.872397 | -1.451091 |
| C | -4.999601 | 2.118493 | 0.140601 |
| H | -5.013795 | 2.177931 | 1.23374 |
| H | -5.427501 | 3.046157 | -0.249299 |
| H | -3.953333 | 2.080567 | -0.175612 |

The most stable conformer of **10** optimized at B3LYP/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| C | -0.291379 | 1.399991 | -0.187264 |
| C | 1.201051 | 1.324499 | 0.152575 |
| H | 1.332152 | 1.516898 | 1.223508 |
| H | 1.709294 | 2.13308 | -0.38253 |
| C | 1.837205 | -0.021044 | -0.218786 |
| H | 1.680824 | -0.212406 | -1.28772 |
| H | 1.328207 | -0.830649 | 0.316042 |
| C | 3.337666 | -0.072446 | 0.090483 |
| H | 3.494363 | 0.123046 | 1.159167 |
| H | 3.847304 | 0.738085 | -0.446138 |
| C | 3.990098 | -1.409676 | -0.278216 |
| H | 3.83291 | -1.604876 | -1.345994 |

| | | | |
|---|-----------|-----------|-----------|
| H | 3.48051 | -2.219319 | 0.258191 |
| C | 5.48896 | -1.456188 | 0.033122 |
| H | 5.923736 | -2.421559 | -0.240941 |
| H | 5.675725 | -1.298134 | 1.100155 |
| H | 6.0307 | -0.679448 | -0.516042 |
| C | -1.14727 | 0.480084 | 0.630108 |
| H | -1.001345 | 0.528945 | 1.708918 |
| C | -2.061032 | -0.359314 | 0.116795 |
| H | -2.184935 | -0.384603 | -0.962848 |
| C | -2.89229 | -1.244776 | 0.91795 |
| H | -2.73634 | -1.19026 | 1.993167 |
| C | -3.817792 | -2.108415 | 0.463046 |
| H | -4.351845 | -2.697167 | 1.20554 |
| C | -4.214982 | -2.369228 | -0.958569 |
| H | -4.059307 | -3.424079 | -1.211123 |
| H | -3.664372 | -1.765066 | -1.679949 |
| H | -0.445469 | 1.219856 | -1.256496 |
| O | -0.638667 | 2.788578 | 0.075665 |
| O | -1.942408 | 3.06628 | -0.492424 |
| H | -2.541069 | 2.820669 | 0.230275 |
| H | -5.283862 | -2.172807 | -1.098576 |

The most stable conformer of **11** optimized at B3LYP/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| C | -2.167266 | -0.230679 | 0.181002 |
| H | -2.100017 | -0.405381 | -0.889826 |
| C | -1.153718 | 0.412696 | 0.78267 |
| H | -1.19221 | 0.606558 | 1.854049 |
| C | -3.349393 | -0.715784 | 0.876663 |
| H | -3.375752 | -0.525323 | 1.947341 |
| C | -4.392934 | -1.365545 | 0.330612 |
| H | -5.198417 | -1.658176 | 1.000451 |
| C | -4.592606 | -1.744946 | -1.105631 |
| H | -4.71222 | -2.829983 | -1.201008 |

| | | | |
|---|-----------|-----------|-----------|
| H | -3.7707 | -1.438024 | -1.752797 |
| H | -5.514339 | -1.297487 | -1.49406 |
| C | 0.067683 | 0.906839 | 0.068591 |
| H | 0.055999 | 0.595719 | -0.980356 |
| C | 1.377369 | 0.45489 | 0.742271 |
| H | 1.304188 | -0.623022 | 0.897326 |
| H | 1.414608 | 0.913665 | 1.738505 |
| C | 2.613461 | 0.819413 | -0.035122 |
| H | 2.762516 | 1.88466 | -0.188618 |
| C | 3.52265 | -0.017355 | -0.547111 |
| H | 4.361676 | 0.430075 | -1.079354 |
| C | 3.560668 | -1.519499 | -0.475992 |
| H | 3.53947 | -1.917322 | -1.498738 |
| H | 2.673856 | -1.914982 | 0.025093 |
| C | 4.825519 | -2.042824 | 0.226078 |
| H | 4.861376 | -1.711266 | 1.2675 |
| H | 5.730094 | -1.679664 | -0.270889 |
| H | 4.853797 | -3.135883 | 0.216049 |
| O | 0.130377 | 2.357391 | 0.098362 |
| O | -0.870331 | 2.89039 | -0.80238 |
| H | -1.642907 | 2.98035 | -0.222716 |

The most stable conformer of (5*S*,6*R*,8*R*)-**13** optimized at M06-2X/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| C | 0.142193 | -0.76804 | -0.447249 |
| C | -1.234515 | -0.102231 | -0.523287 |
| H | -1.208576 | 0.712167 | -1.253804 |
| H | -1.455018 | 0.334224 | 0.453544 |
| C | -2.300349 | -1.078491 | -0.953215 |
| C | -3.55904 | -1.331372 | -0.231292 |
| H | -2.292938 | -1.314799 | -2.015405 |
| H | -4.383747 | -1.714982 | -0.830558 |
| O | -2.470453 | -2.252142 | -0.1394 |
| C | -3.983846 | -0.636054 | 1.034733 |

| | | | |
|---|-----------|-----------|-----------|
| H | -4.495062 | -1.373263 | 1.661382 |
| H | -3.10598 | -0.303819 | 1.594372 |
| C | -4.920204 | 0.541729 | 0.752024 |
| H | -5.302517 | 0.925702 | 1.702884 |
| H | -5.792575 | 0.186433 | 0.190357 |
| C | -4.255276 | 1.683355 | -0.017438 |
| H | -3.377934 | 2.028641 | 0.540496 |
| H | -3.885396 | 1.314329 | -0.979877 |
| C | -5.21007 | 2.851441 | -0.250733 |
| H | -6.082375 | 2.530135 | -0.826043 |
| H | -4.725898 | 3.661905 | -0.798847 |
| C | 1.256111 | 0.250299 | -0.262444 |
| H | 1.221866 | 0.955725 | -1.100185 |
| H | 1.054527 | 0.82165 | 0.651742 |
| C | 2.643098 | -0.38191 | -0.182105 |
| H | 2.67584 | -1.072467 | 0.6655 |
| H | 2.818217 | -0.98252 | -1.083257 |
| C | 3.754193 | 0.656092 | -0.042365 |
| H | 3.574785 | 1.259864 | 0.8556 |
| H | 3.716618 | 1.348079 | -0.892809 |
| C | 5.146066 | 0.034168 | 0.039183 |
| H | 5.1854 | -0.655241 | 0.891293 |
| H | 5.325517 | -0.572626 | -0.856875 |
| H | -5.568796 | 3.254983 | 0.699772 |
| C | 6.260696 | 1.068988 | 0.177018 |
| H | 6.079952 | 1.674314 | 1.071935 |
| H | 6.220241 | 1.756369 | -0.67503 |
| C | 7.645933 | 0.431851 | 0.258268 |
| H | 7.714345 | -0.238844 | 1.118904 |
| H | 8.430353 | 1.185094 | 0.35635 |
| H | 7.855474 | -0.156839 | -0.638856 |
| H | 0.322268 | -1.324673 | -1.38005 |
| O | 0.194974 | -1.670209 | 0.653528 |

| | | | |
|---|-----------|-----------|----------|
| H | -0.624694 | -2.179674 | 0.657853 |
|---|-----------|-----------|----------|

The most stable conformer of (5*R*,6*S*,8*R*)-**13** optimized at M06-2X/6-311+G(d,p)/PCM (chloroform)

| | | | |
|---|-----------|-----------|-----------|
| H | 0.273106 | 2.05258 | 1.656229 |
| C | -0.079605 | 1.415011 | 0.840034 |
| C | -0.631094 | 0.118917 | 1.450834 |
| H | -1.496777 | 0.377834 | 2.062705 |
| H | 0.114991 | -0.322226 | 2.117093 |
| C | -0.986176 | -0.90644 | 0.397464 |
| H | -0.17028 | -1.554593 | 0.085884 |
| C | -2.35031 | -1.407838 | 0.160048 |
| H | -2.431833 | -2.394857 | -0.293291 |
| O | -1.128199 | 2.150253 | 0.215492 |
| H | -1.55021 | 1.551519 | -0.414426 |
| O | -1.761822 | -0.446733 | -0.723796 |
| C | -3.557503 | -0.968449 | 0.944954 |
| H | -3.585104 | -1.533607 | 1.882498 |
| H | -3.453898 | 0.08689 | 1.207363 |
| C | -4.858557 | -1.19915 | 0.167796 |
| H | -5.701655 | -0.884597 | 0.791652 |
| H | -4.98075 | -2.273711 | -0.004981 |
| C | 1.072511 | 1.186417 | -0.137187 |
| H | 1.376919 | 2.166081 | -0.518876 |
| H | 0.703821 | 0.615473 | -0.998327 |
| C | 2.279317 | 0.480397 | 0.478872 |
| H | 2.567665 | 0.991882 | 1.405889 |
| H | 2.014475 | -0.545206 | 0.761348 |
| C | 3.478002 | 0.437867 | -0.466839 |
| H | 3.762184 | 1.462284 | -0.734831 |
| H | 3.183746 | -0.055842 | -1.400907 |
| C | 4.685417 | -0.282427 | 0.12779 |
| H | 4.975036 | 0.207887 | 1.065362 |
| H | 4.403634 | -1.309534 | 0.390523 |

| | | | |
|---|-----------|-----------|-----------|
| C | 5.887456 | -0.316437 | -0.813669 |
| H | 6.167713 | 0.709744 | -1.074804 |
| H | 5.596696 | -0.805606 | -1.749643 |
| C | 7.087687 | -1.038867 | -0.206424 |
| H | 7.408818 | -0.549141 | 0.71677 |
| H | 7.937444 | -1.053163 | -0.891894 |
| H | 6.835097 | -2.074315 | 0.037191 |
| C | -4.918895 | -0.461032 | -1.17313 |
| H | -5.852705 | -0.730741 | -1.675118 |
| H | -4.106852 | -0.8081 | -1.820221 |
| C | -4.841668 | 1.058058 | -1.030146 |
| H | -4.970882 | 1.5505 | -1.995854 |
| H | -3.877392 | 1.37267 | -0.625701 |
| H | -5.622328 | 1.425572 | -0.357589 |