Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supporting Information

First stereoselective total synthesis of 4(*S*),5(*S*)-oxido-17(*S*)-hydroxy-6(*E*),8(*E*),10(*Z*),13(*Z*),15(*E*),19(*Z*)-docosahexaenoic acid, the biosynthetic precursor of resolvins D3 and D4

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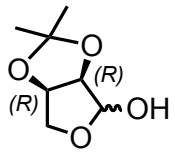
General Information

Unless otherwise indicated, all reactions were carried out in a flame-dried flask with stir bar under argon atmosphere routed through a three-necked valve. Reactions were carried out using DriSolv solvents purchased from VWR or Sigma Aldrich. All reagents were purchased and used without further purification from Sigma Aldrich, Strem Chemicals, Combi-Blocks, Cambridge Isotope Laboratories, and Alfa Aesar. Reaction progress was monitored and recorded using EMD analytical thin-layer chromatography (TLC) plates, Silica Gel 60 F254. TLC plates were visualized through UV absorbance, (254 nm), or staining techniques including vanillin, phosphomolybdic acid, potassium-permanganate, or ninhydrin followed by heating. Unless otherwise noted, purification was carried out by manual flash column chromatography using Silica Gel (100-200 mesh) or with automated platform using the Biotage Isolera One. The percent yield of the final products was measured using a UV-vis spectrophotometer (Thermo Scientific Evolution 201). Characterization was carried out using NMR and UV and HRMS where necessary. All ^{1}H, ^{13}C and gCOSY data were acquired on Varian NMR spectrometers at 400, 500 or 600 MHz, respectively, for ^{1}H NMR and at 101, 126 or 151 MHz, respectively, for ^{13}C NMR. ^{1}H and ^{13}C chemical shifts (δ) are recorded in parts per million (ppm), relative to the residual protium and carbon solvent resonances in ^{1}H NMR (e.g., $CDCl_3$, ^{1}H = 7.26 ppm; and CD_3OD, ^{1}H = 3.31 ppm) and ^{13}C NMR (e.g., $CDCl_3$, ^{13}C = 77.00 ppm; and CD_3OD, ^{13}C = 49.00 ppm), respectively. Splitting patterns are denoted by s, d, t, dd, td, ddd, and m and refer to the respective multiplicities; singlet, doublet, triplet, doublet of doublets, triplet of doublets, doublet of doublet of doublet and multiplet. High-resolution mass spectra were recorded on an Agilent 6545XT QTOF instrument coupled with a 1290 LC system. The QTOF mass spectrometer was equipped with an ESI source. GC-HRMS data were procured on an Agilent 7890 GC system equipped with an Agilent 7250 QTOF mass detector (electron ionization, 70 eV) and an HP-5MS column using He as a carrier gas.

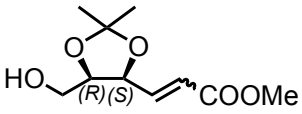
Experimental Procedures



6

(3a*R*,6a*R*)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (6): A mixture of D-erythronolactone (**7**) (3 g, 25 mmol), p-toluenesulfonic acid monohydrate (100 mg), and 2,2-dimethoxypropane (25 mL) in DMF (20 mL) was refluxed for 4h. Then saturated $NaHCO_3$ solution (2 mL) was added, and excess 2,2-dimethoxypropane was evaporated *in vacuo*. Extraction with $CHCl_3$, filtration, anhydrification (Na_2SO_4), and evaporation delivered the crude isopropylidene lactone, which was chromatographed on silica column (35% EtOAc/ hexanes) to afford pure material (3.8 g, 95%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.92 – 4.83 (m, 1H), 4.74 (d, *J* = 5.6 Hz, 1H), 4.45 (t, *J* = 0.6 Hz, 1H), 4.42 (d, *J* = 3.8 Hz, 1H), 1.48 (q, *J* = 0.7 Hz, 3H), 1.40 (q, *J* = 0.7 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.99, 114.04, 75.43, 74.60, 70.18, 26.75, 25.62.

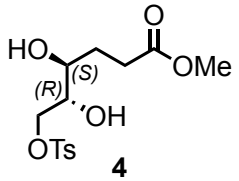
To a solution of the isopropylidene-protected D-erythronolactone (4.6 g, 30 mmol) in dichloromethane (100 mL) was added via a needle/syringe a 1M solution of diisobutylaluminium hydride (DIBAL-H) in dichloromethane (50 mL, 50 mmol) added at -75 °C under an inert atmosphere. The resulting mixture was stirred for 3h at -72 °C, after which methanol (16 mL) was added to it cautiously, to destroy the excess DIBAL-H. After being warmed to room temperature, the reaction mixture was poured into a mixture of ethyl acetate and water (1:1). The mixture was acidified to pH 3 (monitored with a pH-meter) with dilute sulfuric acid and the layers were separated. The aqueous phase was extracted with EtOAc and the extract evaporated to give the corresponding lactol **6** as a yellow solid (4.35 g, 93%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.45 – 5.39 (m, 1H), 4.84 (dd, *J* = 5.9, 3.6 Hz, 1H), 4.59 (d, *J* = 5.9 Hz, 1H), 4.07 (dd, *J* = 3.6, 0.6 Hz, 1H), 4.06 – 4.01 (m, 1H), 2.29 (d, *J* = 2.3 Hz, 1H), 1.47 (d, *J* = 0.7 Hz, 3H), 1.33 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 112.30, 101.86, 85.13, 79.95, 72.07, 26.21, 24.74.



5

Methyl 3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (5): Subsequently, to a solution of (2*R*,3*R*)- 2,3-O-isopropylidene-D-erythrose **6** (3.8 g, 23.6 mmol) in CH_2Cl_2 (100 mL) were added methyl (triphenylphosphoranylidene)acetate (9.5 g, 28.4 mmol) and benzoic acid (0.10 g, 0.82 mmol). The solution was heated under reflux for 18h. The solvent was evaporated and the residue was triturated with 30% ether in hexane (4x 100 mL). The combined extracts were evaporated and the residue was purified by column chromatography on silica gel (40% EtOAc in hexanes) to give an *E*/*Z* isomeric mixture of the unsaturated ester **5** as a colorless oil, predominantly in the *Z*-form. *Z*-isomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.41 (dd, *J* = 11.6, 6.9 Hz, 1H), 5.95 (dd, *J* = 11.6, 1.8 Hz, 1H), 5.59 (ddd, *J* = 7.4, 6.9, 1.8 Hz, 1H), 4.58 (ddd, *J* = 7.4, 5.0, 3.6 Hz, 1H), 3.73 (s, 3H), 3.61 (dd, *J* = 11.8, 3.6 Hz, 1H), 3.46 (dd, *J* = 11.7,

4.9 Hz, 1H), 1.53 (s, 1H), 1.41 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.40, 147.64, 120.51, 108.87, 78.78, 74.83, 61.46, 51.65, 27.33, 24.59.

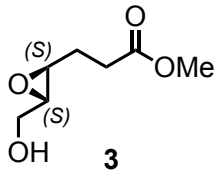


4

Methyl (4*S*,5*R*)-4,5-dihydroxy-6-(tosyloxy)hexanoate (4): To a solution of the unsaturated mixture of ester **5** (3.6 g, 16.6 mmol) in ethyl acetate (50 mL) was added 5% Pd on charcoal (1.0 g). The black mixture was evacuated and back-filled with hydrogen gas 3-5 times and then stirred under H_2 (ca. 1 atm) for 2.5 h. The mixture was diluted with ethyl acetate (100 mL) and filtered through a pad of Celite, and the residue was washed with ethyl acetate (3x 30 mL). The filtrates were evaporated under reduced pressure to give the saturated ester (3.6 g, 100% quant.). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.22 – 4.13 (m, 2H), 3.68 (s, 3H), 3.68 – 3.64 (m, 2H), 2.60 – 2.51 (m, 1H), 2.44 (s, 1H), 1.85 (d, *J* = 8.6 Hz, 2H), 1.80 (d, *J* = 6.1 Hz, 1H), 1.46 (s, 3H), 1.35 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.56, 108.32, 77.69, 75.91, 61.60, 51.64, 30.92, 28.07, 25.41, 24.68. HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{18}NaO_5^+$ ([M+Na]$^+$) 241.1046, found 241.1051.

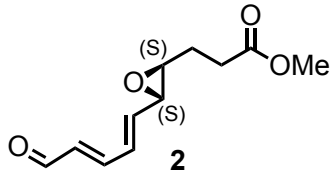
A solution of the saturated ester (900 mg, 4.12 mmol) in dry pyridine (5 mL) was cooled to 0°C and tosyl chloride (1.0 g, 5.25 mmol, 1.3 eq) in dry pyridine (1 mL) was added dropwise within 5 min. The reaction mixture was stirred for 18h, quenched with methanol, concentrated under reduced pressure, and then under high vacuum to remove pyridine. The resulting crude product was purified by flash chromatography (40% EtOAc in hexanes) to give an isopropylidene tosylate intermediate (1.3 g, 85%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.24 (d, *J* = 6.0 Hz, 1H), 4.19 – 4.11 (m, 1H), 4.03 (m, 1H), 3.96 (d, *J* = 6.1 Hz, 1H), 3.68 (s, 3H), 2.49 (d, *J* = 2.7 Hz, 1H), 2.45 (s, 3H), 2.44 – 2.36 (m, 1H), 1.85 – 1.77 (m, 1H), 1.71 (d, *J* = 10.4 Hz, 1H), 1.32 (d, *J* = 0.8 Hz, 3H), 1.29 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.25, 145.02, 132.57, 129.89(2), 128.04(2), 108.85, 75.80, 74.60, 67.66, 51.66, 30.75, 27.87, 25.34, 24.36, 21.63.

Subsequently, to a solution of acetonide above (1.5 g, 4.03 mmol) in dry methanol (10 mL) was added two drops conc. hydrochloric acid and the resulting mixture was stirred at room temperature for 7–10h (with TLC monitoring). After reaction completion, the solvent was removed under vacuum to afford tosylate **4** as yellow oil (1.3 g, 100%, quant.) without further purification. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.74 (m, 2H), 7.44 – 7.32 (m, 2H), 4.45 (td, *J* = 7.1, 6.1 Hz, 1H), 4.18 (dd, *J* = 10.7, 4.0 Hz, 1H), 4.09 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.98 (td, *J* = 6.1, 4.0 Hz, 1H), 3.50 (s, 3H), 2.63 – 2.48 (m, 2H), 2.47 (s, 3H), 2.37 – 2.18 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.48, 145.49, 132.16, 130.09(2), 128.00(2), 78.51, 70.35, 70.14, 50.89, 27.94, 23.12, 21.69. **Note**: Prudent care should be made during this reaction; addition of more than catalytic HCl cleaves the methyl ester.



3

Methyl 3-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)propanoate (3): The tosylate **4** (0.55 g, 1.65 mmol) was dissolved in dry methanol (1 ml) and sodium methoxide (0.45 g, 8.3 mmol, 5 eq) was added along with a scoop of Na_2SO_4. The mixture was stirred at room temperature for 16h. The mixture was then diluted with ether and the solids were filtered out through a pad of silica. The filtrate was concentrated in vacuo and the crude was purified on silica column with EtOAc/ Hexanes (30%) to afford epoxy alcohol **3** as a colorless oil (0.08 mg, 30%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.94 – 3.86 (m, 1H), 3.69 (s, 3H), 3.65 (ddd, *J* = 12.4, 7.3, 4.1 Hz, 1H), 3.03 (ddd, *J* = 6.7, 4.7, 2.3 Hz, 1H), 2.96 (dt, *J* = 4.1, 2.5 Hz, 1H), 2.53 – 2.43 (m, 2H), 2.01 (dtd, *J* = 14.2, 7.6, 4.7 Hz, 1H), 1.83 (dq, *J* = 13.9, 6.8 Hz, 1H), 1.61 (dd, *J* = 7.5, 5.4 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.17, 61.45, 58.34, 54.69, 51.74, 30.17, 26.74. HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{12}NaO_4^+$ ([M+Na]$^+$) 183.0628, found 183.0624.



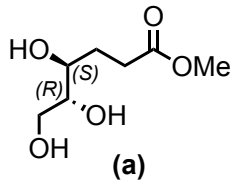
2

Methyl 3-((2*S*,3*S*) -3-((1*E*,3*E*) -5-oxopenta -1,3-dien-1-yl)oxiran-2-yl)propanoate (2): Under open air, to a solution of epoxy alcohol **3** (0.14 g, 0.87 mmol) in 10 mL of DCM was added 600 mg of $NaHCO_3$ and 600mg of Dess-Martin periodinane (DMP) along with a drop of tap water. The slurry mixture was stirred for one hour and monitored by TLC. After the reaction was complete, the reaction was worked up with a 1:1 $NaHCO_3$/$Na_2S_2O_3$ saturated solution and extracted with DCM (3x 30 mL). The organic phase was dried over sodium sulfate and the solvents were evaporated in vacuo. The crude was purified on a silica column with EtOAc/ Hexanes (10%) to afford the one-carbon epoxy aldehyde intermediate as a colorless oil (0.12 g, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.02 (d, *J* = 6.2 Hz, 1H), 3.71 (s, 3H), 3.39 – 3.31 (m, 1H), 3.18 (d, *J* = 6.2 Hz, 1H), 2.56 – 2.45 (m, 2H), 2.19 – 2.02 (m, 1H), 1.91 (dd, *J* = 14.5, 6.6 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.80, 172.62, 59.05, 55.57, 51.91, 29.88, 26.43.

Subsequently, to a 10 mL pear-shaped flame-dried flask, the aldehyde above (0.04 mg, 0.25 mmol) and (triphenylphosphoranylidene) acetaldehyde (0.1 g, 0.33 mmol, 1.3 eq) were added and dissolved in 0.7 mL of toluene and refluxed at 90 ^{o}C for 2 h. Then more (triphenylphosphoranylidene) acetaldehyde was added (0.05g, 0.17 mmol). The reaction continued refluxing for 1h and was closely monitored by TLC (20% EtOAc/ Hexanes). After completion the reaction mixture was concentrated *in vacuo* and directly subjected to purification (without workup) on a Biotage auto-column platform with 10% EtOAc/hexanes to afford the desired homologated four-carbon epoxy aldehyde **2** as a yellow oil (0.015g, 28%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.58 (d, *J* = 7.9 Hz, 1H), 7.07 (ddd, *J* = 15.4, 11.0, 0.7 Hz, 1H), 6.63 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.17 (dd, *J* = 15.4, 7.9 Hz, 1H), 5.96 (dd, *J* = 15.4, 7.4 Hz, 1H), 3.70 (s, 3H), 3.28 – 3.24 (m, 1H), 3.00 (ddd, *J* = 6.6, 4.7, 2.0 Hz, 1H), 2.52 – 2.47 (m, 2H), 2.11 –

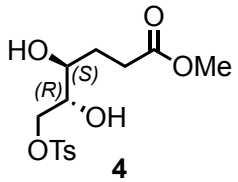
2.00 (m, 1H), 1.90 – 1.81 (m, 1H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 193.46, 172.99, 149.74, 140.65, 132.31, 131.07, 60.23, 57.38, 51.79, 29.97, 27.10.

ALTERNATIVELY: An analogous route was employed to generate epoxy aldehyde **2** intermediate directly from D-Erythose (**23**).



(a)

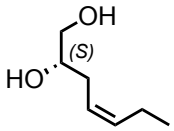
Methyl (4*S*,5*R*)-4,5,6-trihydroxyhex-2-enoate (a): Part 1: To a solution of D-erythrose **(23)** (0.757g, 6.3 mmol) in 10 mL of anhydrous THF was added methyl (triphenylphosphoranylidene) acetate (2.5 g, 7.5 mmol, 1.2 eq). The reaction mixture was refluxed at 65°C for 16h. Without workup the solvent was removed *in vacuo* and the crude mixture was purified on silica gel using MeOH/CH_2Cl_2 (10%) as the eluent to afford an unsaturated triol ester (1.08g, 97%) as a clear colorless oil. ^{1}H NMR (400 MHz, Methanol-*d*4) 7.13 (dd, *J* = 15.7, 4.8 Hz, 1H), 6.19 (ddd, *J* = 5.8, 2.0, 0.4 Hz, 1H), 6.09 (dd, *J* = 15.7, 1.8 Hz, 1H), 4.16 (m, 1H), 3.72 (s, 3H), 3.52 (m, 4H). ^{13}C NMR (101 MHz, Methanol-*d*4) 174.13, 167.20, 148.69, 74.35, 71.25, 62.92, 50.66.
Part 2: To a solution of the unsaturated ester (0.8g, 4.54 mmol) in 12 mL of EtOAc was added one scoop of 5% palladium on charcoal. The reaction was stirred under H_2 gas overnight. The reaction mixture was filtered through Celite and with no workup the solvent evaporated to afford the title hydrogenated oily product (**a**) in quantitative yield. ^{1}H NMR (500 MHz, Methanol-d_4) δ 3.70 (dd, *J* = 3.8, 1.0 Hz, 1H), 3.66 (d, *J* = 1.0 Hz, 3H), 3.60 – 3.52 (m, 1H), 3.52 – 3.45 (m, 1H), 3.43 (dd, *J* = 3.9, 1.0 Hz, 1H), 2.53 (d, *J* = 1.1 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.08 – 1.95 (m, 1H), 1.68 (ddd, *J* = 13.7, 5.3, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 174.74, 74.75, 71.10, 63.34, 50.60, 29.77, 27.98.



4

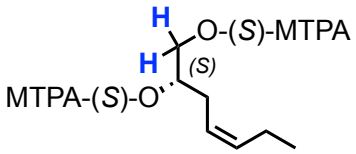
Methyl (4*S*,5*R*)-4,5-dihydroxy-6-(tosyloxy)hexanoate (4): Subsequently, a solution of triol (**a**) (1 g, 5.6 mmol) and dry pyridine (10 mL) was cooled to -10 °C and tosyl chloride (1.3 g, 6.8 mmol, 1.2 eq) in dry pyridine (2 mL) was added dropwise within 15 min. The reaction mixture was stirred for 18h, quenched with methanol, concentrated *in vacuo* and worked up with diethyl ether/half-saturated brine. The organic phase was dried and the solvents were evaporated. Purification by flash Chromatography MeOH/ CH_2Cl_2 (2%) or EtOAc/ Hexanes (40%) gave tosylate **4** (0.5 g, 27%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.31 (m, 2H), 4.50 – 4.41 (m, 1H), 4.23 – 4.15 (m, 1H), 4.10 (d, *J* = 6.1 Hz, 1H), 3.98 (d, *J* = 3.9 Hz, 1H), 3.50 (s, 3H), 2.65 – 2.49 (m, 2H), 2.47 (s, 3H), 2.31 (d, *J* = 9.6 Hz, 1H), 2.28 – 2.18 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.48, 145.49, 132.16, 130.09 (2), 128.00 (2), 78.51, 70.35, 70.14, 50.89, 27.94, 23.12, 21.69.

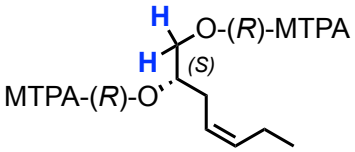
From this point forward, the procedures leading up to building block **2** were carried out similarly as shown above in the route involving D-erythronolactone (**7**).



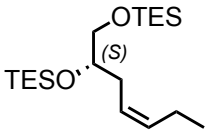
14

(*S*,*Z*)-hept-4-ene-1,2-diol (14). To a solution of nitrosobenzene (4.850 g, 45.281 mmol) and D-proline (0.521 g, 4.528 mmol) in wet $CHCl_3$ (23 mL) was added *cis*-4-heptenal (15.2 g, 136 mmol) dropwise at 0°C and then stirred for 2 h. The reaction mixture is transferred to a solution of $NaBH_4$ (5.14 g, 136 mmol) in EtOH (270 mL) at 0 °C and stirred at 0 °C for 35 min. The reaction is quenched by addition of $NaHCO_3$ (aq). The layers were separated, and the aqueous phase was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The crude product was redissolved in EtOH (190 mL) and AcOH (63 mL), and zinc dust (29.6 g, 453 mmol) was added at rt and the reaction was stirred for 16 h at rt. The mixture was filtered through Celite, concentrated and purified by column chromatography (50% EtOAc:Hexanes) to yield **14** as a colorless liquid (4375 mg, 74% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.64 – 5.51 (m, 1H), 5.46 – 5.28 (m, 1H), 3.76 (dtd, *J* = 7.2, 5.4, 4.8, 2.7 Hz, 1H), 3.69 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.50 (dd, *J* = 11.2, 7.1 Hz, 1H), 2.38 – 2.15 (m, 6H), 2.13 – 2.01 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 135.35, 123.39, 71.82, 66.30, 31.20, 20.67, 14.16. HRMS (GC-TOF) *m*/*z* calcd for $C_7H_{14}O_2^{\bullet+}$ ([M]$^{\bullet+}$) 130.0988, found 130.0991.



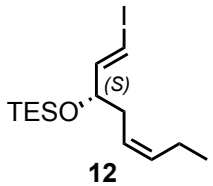


Mosher ester analysis of 14. To a solution of diol **14** or its enantiomer (20 mg, 0.15 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (36 mg, 0.35 mmol), DMAP (1.9 mg, 0.015 mmol), and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride [(*S*)-(+)-MTPA-Cl] or the [(*R*)-(–)-MTPA-Cl] (78 mg, 0.31 mmol) at room temperature and stirred for 1 h. The crude residue was directly subjected to purification by column chromatography (15% EtOAc/ Hexanes), followed by ^{1}H NMR analysis of the diastereomeric (*S* or *R*)-MTPA Mosher esters to confirm purity of the stereogenic configuration of the carbinol center. ^{1}H NMR spectral data of the diastereomer display different chemical shifts of resonances for analogous pairs of protons, e.g., shown in blue (*vide infra*). The (*S*)-MTPA ester shows a δ 4.57 and δ 4.25 chemical shifts, with no observable sets of proton peaks arising from the diastereomer thus confirming a > 99% enantiopurity of **14**.



13

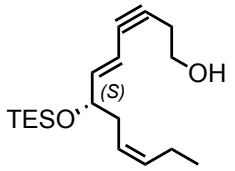
(*S*,*Z*)-3,3,8,8-tetraethyl-5-(pent-2-en-1-yl)-4,7-dioxa-3,8-disiladecane (13). To a mixture of imidazole (2.07 g, 30.4 mmol) and DMAP (169 mg, 1.383 mmol) in dry CH_2Cl_2 (36 mL) was added TESCl at 0 °C, and a solution of **14** (1.80 g, 13.826 mmol) in CH_2Cl_2 (5 mL) was added by cannula under argon. The reaction was stirred for 16 h at room temperature, and quenched with NH_4Cl (aq). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (3% EtOAc/Hexanes) to afford **13** as an oil (4.00 g, 81%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.43 (qt, *J* = 11.0, 6.9 Hz, 2H), 3.70 (p, *J* = 5.8 Hz, 1H), 3.51 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.45 (dd, *J* = 10.0, 6.1 Hz, 1H), 2.33 (dt, *J* = 13.5, 6.0 Hz, 1H), 2.17 (dt, *J* = 13.7, 6.5 Hz, 1H), 2.06 (p, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.9 Hz, 21H), 0.61 (qd, *J* = 8.0, 4.6 Hz, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 133.40, 124.96, 73.27, 66.67, 32.18, 20.67, 14.19, 6.87 (3), 6.76 (3), 4.97 (3), 4.38 (3). HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{42}NaO_2Si_2^+$ ([M+Na]$^+$) 381.2616, found 381.2621.



12

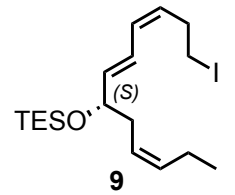
Triethyl(((*S*,1*E*,5*Z*)-1-iodoocta-1,5-dien-3-yl)oxy)silane (12). To a solution of DMSO (1.40 g, 1.27 mL, 17.9 mmol) in CH_2Cl_2 (18 mL) was added a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (4.48 mL, 8.95 mmol) dropwise at -72 °C and stirred for 15 min. Then a solution of compound **13** (730 mg, 2.04 mmol) in CH_2Cl_2 (2 mL) was added to the reaction by cannula and stirred for 20 min at -72 °C and 1h at -40 °C. The reaction is cooled to -72 °C again followed by the dropwise addition of DIPEA (3.95 g, 5.3 mL, 30.5 mmol), and allowed to warm to room temperature slowly for 1 h. NH_4Cl (aq) was added to quench the reaction. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude aldehyde residue was used directly without purification in the next step.

To a suspension of $CrCl_2$ (2.50 g, 20.3 mmol) in THF (35 mL) at 0°C was added a solution of the crude aldehyde (493 mg, 2.03 mmol) and iodoform (1.60 g, 4.07 mmol) in THF by cannula, changing the reaction color from pale green to brown. The reaction was stirred for 3 h at 0 °C and 1h at rt, before quenching by the addition of brine. The layers were separated, and the aqueous phase was extracted with Et_2O. Combined organic layers were washed with $Na_2S_2O_3$ (aq) and dried over $MgSO_4$. The solution was filtered through a pad of silica to remove residual chromium, and concentrated under reduced pressure. The crude product was purified by column chromatography (2% EtOAc/Hexanes) to afford alkenyl iodide **12** as an oil (370 mg, 53% over 2 steps) and used without further purification. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.54 (dd, *J* = 14.4, 6.0 Hz, 1H), 6.23 (dd, *J* = 14.3, 1.2 Hz, 1H), 5.53 – 5.45 (m, 1H), 5.37 – 5.26 (m, 1H), 4.11 – 4.06 (m, 1H), 2.28 – 2.22 (m, 2H), 2.06 – 2.00 (m, 2H), 0.99 – 0.94 (m, 12H), 0.64 – 0.57 (m, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 148.70, 134.29, 123.48, 75.90, 74.93, 35.57, 20.72, 14.17, 6.74(3), 4.79(3).



10

(*S*,5*E*,9*Z*)-7-((triethylsilyl)oxy)dodeca-5,9-dien-3-yn-1-ol (10). To a solution of iodide **12** (325 mg, 887 µmol) in piperidine (5 mL) was added $Pd(OAc)_2(PPh_3)_2$ (66.5 mg, 88.7 µmol) and but-3-yn-1-ol (622 mg, 671 µL, 8.87 mmol) . The reaction was quenched after 3 h with NH_4Cl, and Et_2O was added. The layers were separated, and the aqueous phase was extracted with Et_2O. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified on silica gel (30% EtOAc/Hexanes) to afford title compound **10** as an oil (269 mg, 98.3 %). ^{1}H NMR (600 MHz, Benzene-d_6) δ 6.22 (dd, *J* = 15.8, 5.7 Hz, 1H), 5.89 – 5.83 (m, 1H), 5.52 – 5.39 (m, 2H), 4.14 – 4.09 (m, 1H), 3.36 (q, *J* = 6.4 Hz, 2H), 2.35 – 2.29 (m, 1H), 2.28 – 2.22 (m, 3H), 2.01 – 1.94 (m, 2H), 1.06 – 1.03 (m, 1H), 1.00 – 0.96 (m, 9H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.62 – 0.55 (m, 6H). ^{13}C NMR (151 MHz, Benzene-d_6) δ 145.13, 133.63, 124.15, 109.40, 87.37, 80.34, 72.47, 60.81, 36.03, 23.69, 20.72, 13.94, 6.71 (3), 4.91 (3). HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{32}NaO_2Si^+$ ([M+Na]$^+$) 331.2064, found 331.2080.

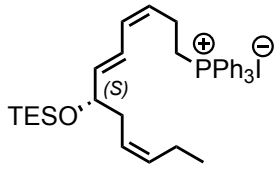


9

Triethyl(((*S*,3*Z*,7*E*,9*Z*)-12-iododododeca-3,7,9-trien-6-yl)oxy)silane (9). To a solution of alcohol **10** (102 mg, 331 µmol) in Et_2O (8 mL) was added Lindlar's catalyst (306 mg) and quinoline (53.4 mg, 49.0 µL, 413 µmol). The reaction mixture was placed under hydrogen atmosphere and stirred for 20 min. TLC analysis (vanillin) showed color change from magenta to black after reaction. After reaction complete, the mixture was filtered through a syringe filter with Et_2O and concentrated. In the case of where the reaction was incomplete (monitored by TLC), the catalyst was removed by filtration and replaced. The crude hydrogenated residue was then employed in the next step without further purification. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{34}NaO_2Si^+$ ([M+Na]$^+$) 333.2220, found 333.2220.

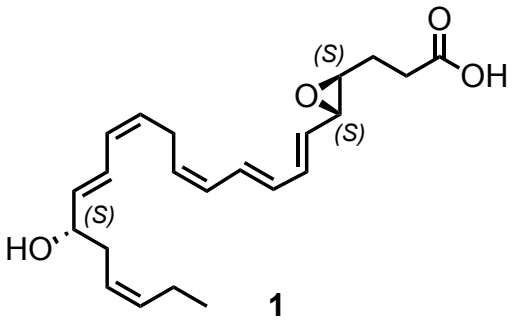
Next, to a solution of triphenylphosphine (92.9 mg, 354 µmol) in THF (10 mL) at 0 °C were added imidazole (30.7 mg, 451 µmol), iodine (98.1 mg, 386 µmol) and a solution of the crude alkene above (100 mg, 322 µmol) in THF. The reaction was stirred at 0 °C for 2h, and then quenched by addition of saturated $Na_2S_2O_3$ (aq). Et_2O was added to separate the layers, and the aqueous phase was extracted 3 x with Et_2O (10 mL). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified on silica gel (3% EtOAc/ Hexanes, dry-loaded on celite) to afford title iodide **9** as an oil (94 mg, 69.0 % over 2 steps). ^{1}H NMR (400 MHz, Benzene-d_6) δ 6.50 (ddt, *J* = 15.1, 11.1, 1.2 Hz, 1H), 6.04 (t, *J* = 11.0 Hz, 1H), 5.74 (dd, *J* = 15.1, 6.0 Hz, 1H), 5.59 – 5.42 (m, 2H), 5.08 (dt, *J* = 10.9, 7.5 Hz, 1H), 4.22 (dt, *J* = 7.1, 5.7 Hz, 1H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.54 – 2.37 (m, 3H), 2.37 – 2.23 (m, 1H), 2.12 – 1.92 (m, 2H), 1.05 (t, *J* = 7.9 Hz, 9H), 0.99 – 0.84 (m, 3H), 0.66 (q, *J* = 7.9 Hz,

6H). ^{13}C NMR (101 MHz, Benzene-d_6) δ 138.36, 133.80, 130.37, 129.52, 125.03, 124.46, 73.21, 36.81, 32.09, 21.18, 14.39, 7.27, 5.48(3), 4.51(3).



8

Triphenyl((*S*,3*Z*,5*E*,9*Z*)-7-((triethylsilyl)oxy)dodeca-3,5,9-trien-1-yl)phosphonium iodide (8). To a solution of iodide **9** (85.0 mg, 202 µmol) in anhydrous acetonitrile (4 mL) was added triphenylphosphine (159 mg, 606 µmol, 3 eq) and DIPEA (131 mg, 0.18 mL, 1.01 mmol). The reaction was refluxed at 80 °C for 16 h. The reaction was cooled to rt and concentrated. The crude product was triturated with pentane (5 mL x 9) at 0 °C until no triphenylphosphine was detectable by TLC/ UV to afford phosphonium salt **8** (117 mg, 84.8 %). ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.93 – 7.84 (m, 3H), 7.77 – 7.67 (m, 12H), 6.20 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.04 (t, *J* = 10.9 Hz, 1H), 5.74 (dd, *J* = 14.9, 6.0 Hz, 1H), 5.49 – 5.28 (m, 3H), 4.17 (q, *J* = 6.2 Hz, 1H), 3.26 (ddd, *J* = 12.8, 9.2, 7.0 Hz, 2H), 2.53 (p, *J* = 7.5 Hz, 2H), 2.28 – 2.17 (m, 2H), 2.07 – 1.95 (m, 2H), 0.97 – 0.88 (m, 12H), 0.58 – 0.47 (m, 6H). ^{13}C NMR (151 MHz, Acetonitrile-d_3) δ 138.84, 135.24 (2), 135.22(2), 133.73(3), 133.66(3), 133.42, 130.38(3), 130.30(3), 129.97, 124.41, 123.34, 118.35, 117.78, 72.41, 42.86, 35.76, 21.98, 20.42, 13.52, 6.22(3), 4.55(3). ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ 23.18. HRMS (ESI-TOF) *m*/*z* calcd for $C_{36}H_{48}OPSi^+$ ([M-I]$^+$) 555.3207, found 555.3230.



1

3-((2*S*,3*S*)-3-((*S*,1*E*,3*E*,5*Z*,8*Z*,10*E*,14*Z*)-12-hydroxyheptadeca-1,3,5,8,10,14-hexaen-1-yl)oxiran-2-yl)propanoic acid (1). Part 1: The phosphonium iodide **8** (88mg, 0.128 mmols) was dried under high vacuum and P_2O_5 in the reaction flask overnight. Still dried THF (1 mL) was added, and the mixture was then cooled to -78 °C. To the reaction mixture a 1M KHMDS solution (27 mg, 0.140 mmol) was added slowly via syringe and the reaction mixture was stirred at this temperature for 20 min. Then the mixture was warmed up to 0 °C and stirred at this temperature for 10 min until the color became red-orange-brown. The reaction mixture was then cooled down to -78 °C and aldehyde **2** (15 mg, 0.073 mmol) was added slowly via syringe, and the mixture was slowly allowed to warm up to 0 °C and stirred for 20 min, while closely watching the color turn dark to black or thick-dark-blue. The reaction mixture was rapidly subjected to a coarse purification without workup or removal of solvent (to avoid destroying the highly labile epoxide) using NEt_3-EtOAc-hexanes (5% - 5% - 90%) as the eluent to afford a

crude residue (presumably containing noticeable ^{1}H NMR signals arising from the triphenylphosphine oxide, a side product of the Wittig reaction) of the silyl ether and methyl ester of epoxide **1** [12 mg, 21%, UV yield ($\varepsilon_{282} \approx 40{,}000\ M^{-1}\ cm^{-1}$)] as yellow oil, which was stored in cyclohexane/ triethylamine (trace amount). ^{1}H NMR (600 MHz, Benzene-d_6) δ 6.73 – 6.66 (m, 1H), 6.50 (dd, *J* = 14.6, 11.8 Hz, 1H), 6.34 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.11 – 5.95 (m, 3H), 5.77 (dd, *J* = 15.1, 6.2 Hz, 1H), 5.58 – 5.49 (m, 2H), 5.46 – 5.32 (m, 2H), 5.28 (dd, *J* = 15.3, 7.8 Hz, 1H), 4.31 – 4.25 (m, 1H), 3.32 (s, 3H), 3.09 – 3.02 (m, 2H), 2.96 (dd, *J* = 7.6, 2.1 Hz, 1H), 2.68 (ddd, *J* = 6.5, 4.7, 2.0 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.36 (dd, *J* = 12.8, 6.9 Hz, 1H), 2.18 – 2.14 (m, 2H), 2.06 – 2.00 (m, 2H), 1.82 – 1.74 (m, 1H), 1.61 – 1.53 (m, 1H), 1.06 (t, *J* = 8.1 Hz, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.70 – 0.66 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.18, 137.26, 137.19, 133.63, 131.58, 130.90, 129.45, 128.78, 128.70, 128.65, 128.40, 127.67, 124.46, 124.10, 72.89, 59.68, 51.74, 36.31, 30.12, 29.69, 27.27, 20.75, 14.17, 6.86 (2), 4.93 (4). **Note**: Due to limited amount of this compound dedicated and available for data acquisition, the ^{13}C NMR proved to have a high S/ N ratio but was nonetheless useful (see, spectra). HRMS (ESI-TOF) *m*/*z* calcd for $C_{29}H_{46}NaO_4Si^+$ ($[M+Na]^+$) 509.3058, found 509.3051.

Prudent care MUST be made for handling and storage of this compound and its deprotected derivatives given their high sensitivity to water, light, acid, heat, etc., conditions which can induce olefin isomerization or epoxide opening.

Part 2: Next, to a solution of the TES ether of **1** (0.25 mg, 1 eq, 0.51 µmol) in THF (0.25 mL) was added a mixture of TBAF (3.0 mg, 11 µL, 22.0 eq, 11 µmol) and acetic acid (0.62 mg, 0.59 µL, 20 eq, 10 µmol) at 0 °C. The reaction was stirred at 0 °C for 7 h, and then the reaction mixture was diluted with 10/ 85/ 5 EtOAc/ cyclohexane/ NEt_3 (1 mL) as the eluent and directly subjected to a very coarse chromatography with a silica cartridge (Sep-Pak Silica Plus Light) to yield the methyl ester of **1** as a colorless oil in moderate 40 - 50% UV yields ($\varepsilon_{282} \approx 40{,}000\ M^{-1}\ cm^{-1}$), again without further purification which would destroy the epoxide moiety. ^{1}H NMR (600 MHz, Benzene-d_6) δ 6.65 (dd, *J* = 15.2, 11.1 Hz, 1H), 6.49 (dd, *J* = 15.0, 11.2 Hz, 1H), 6.32 (dd, *J* = 15.3, 10.8 Hz, 1H), 6.10 – 5.98 (m, 3H), 5.64 (dd, *J* = 15.2, 5.8 Hz, 1H), 5.54 – 5.45 (m, 2H), 5.44 – 5.34 (m, 2H), 5.28 (dd, *J* = 15.3, 7.7 Hz, 1H), 4.08 – 3.99 (m, 1H), 3.32 (s, 3H), 3.02 (t, *J* = 7.6 Hz, 2H), 2.98 – 2.91 (m, 1H), 2.72 – 2.63 (m, 1H), 2.29 – 2.23 (m, 2H), 2.15 (q, *J* = 6.5 Hz, 2H), 2.10 (dt, *J* = 13.4, 6.7 Hz, 2H), 1.99 – 1.92 (m, 2H), 1.26 – 1.16 (m, 3H). At this stage, no appreciable and comprehensive ^{13}C NMR scan was taken due to minuscule amounts available for data acquisition, thus leading to a very noisy spectrum (data not shown). The ^{1}H NMR spectrum was also obtained using a wet1D pulse sequence experiment to attenuate the tall deuterated benzene and water proton resonances (see spectra). HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{32}NaO_4^+$ ($[M+Na]^+$) 395.2193, found 395.2189.

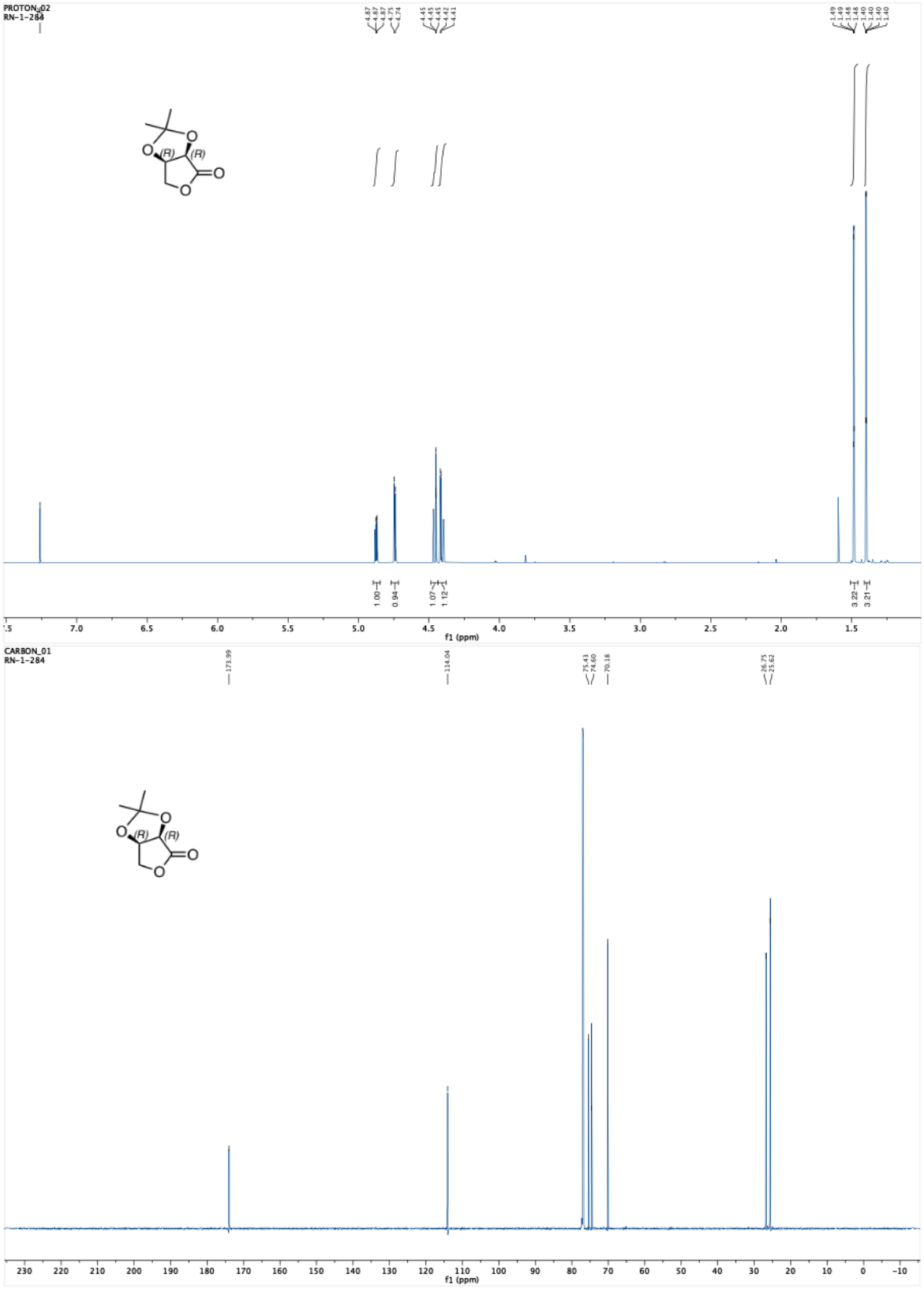
Because the free acid of this epoxydocosanoid is highly unstable, the target compound was stored as the methyl ester and was readily hydrolyzed to the carboxylic acid as needed (part 3).

Part 3: A small amount of the methyl ester was delicately hydrolyzed under basic conditions with NaOH or LiOH in order to obtain high-resolution mass spectrometry and UV data of the final compound, **1**. A ^{1}H NMR experiment was not performed due to the minuscule amount

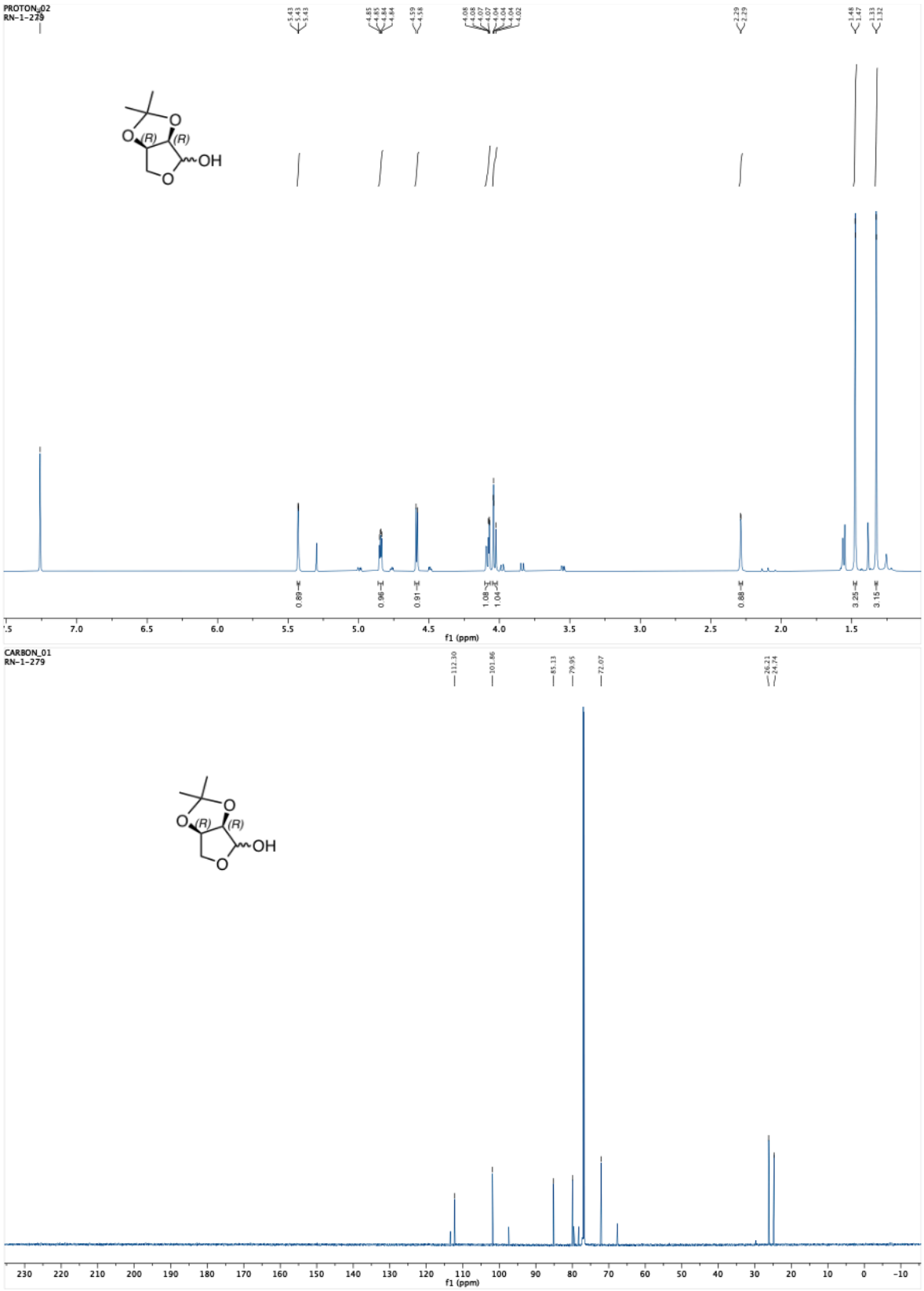
hydrolyzed, as well as the presence of water in this mixture. Harsh conditions, i.e., extended drying time under high vacuum and NMR scans over several hours, were required in order to acquire readable NMR spectra—and all these conditions were unfavorable for the epoxide to remain intact. Therefore only HRMS and UV information were procured for target compound **1**. HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{30}NaO_4^+$ ($[M+Na]^+$) 381.2036, found 381.2049.

Furthermore, this compound gave a UV spectrum with a triplet band of absorption, λ_{max}^{MeOH}, around 282 nm and shoulders at 273 nm and 295 nm, for the conjugated triene system, and a single broad band around 229 nm, indicating the presence of the conjugated diene moiety (*vide infra*).

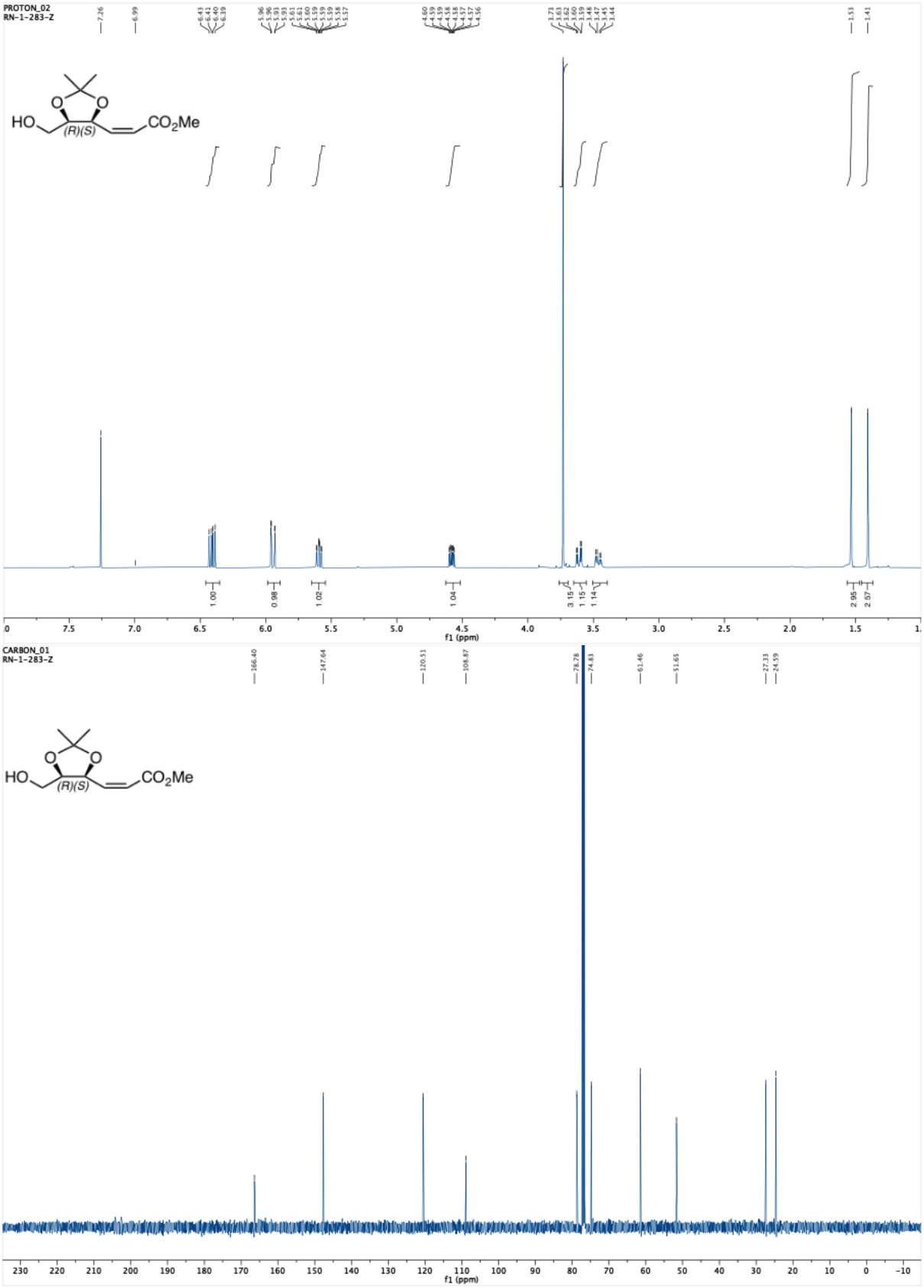
Selected Spectral Data



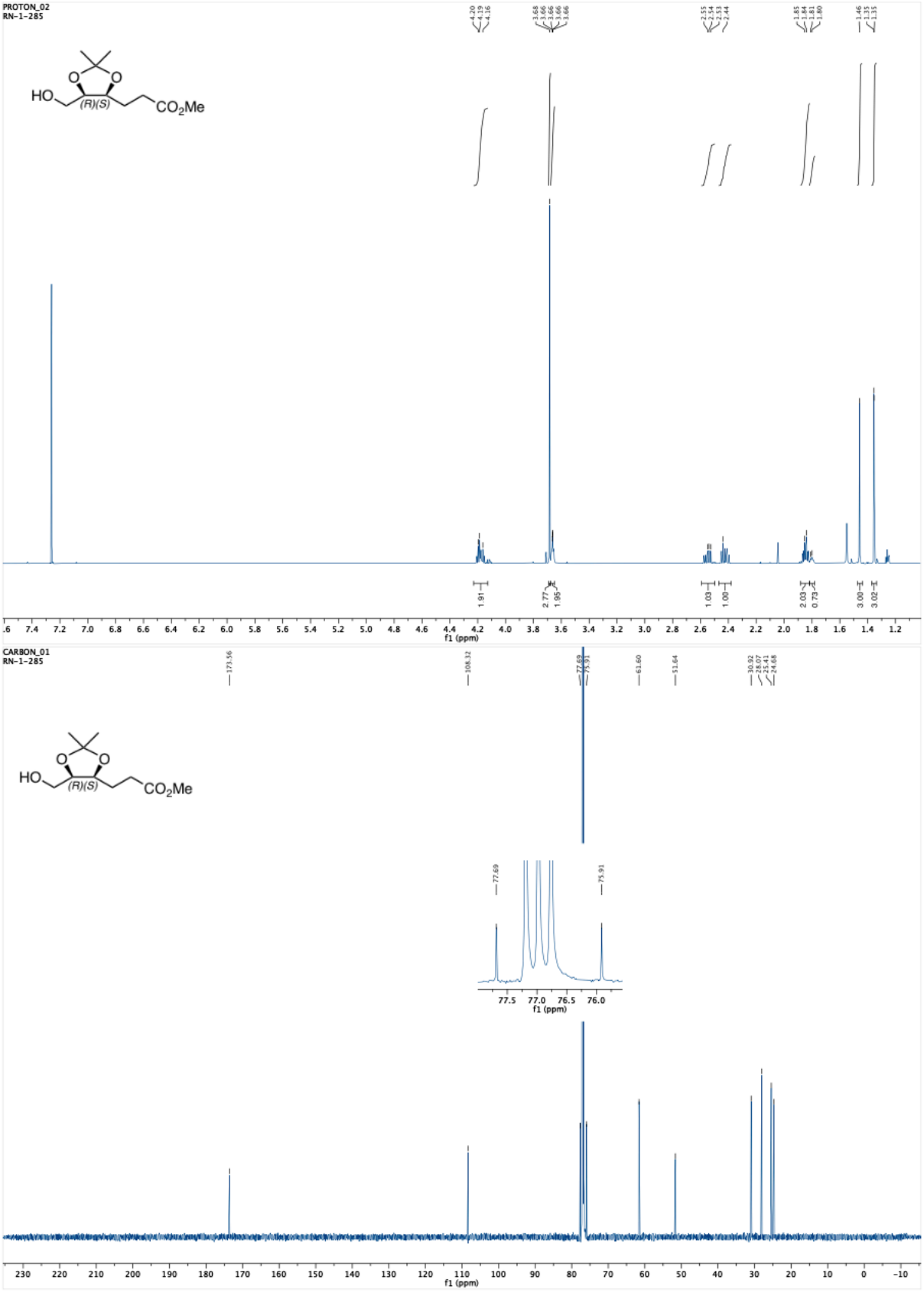
^{1}H and ^{13}C NMR spectra of isopropylidene lactone precursor of compound **6**.



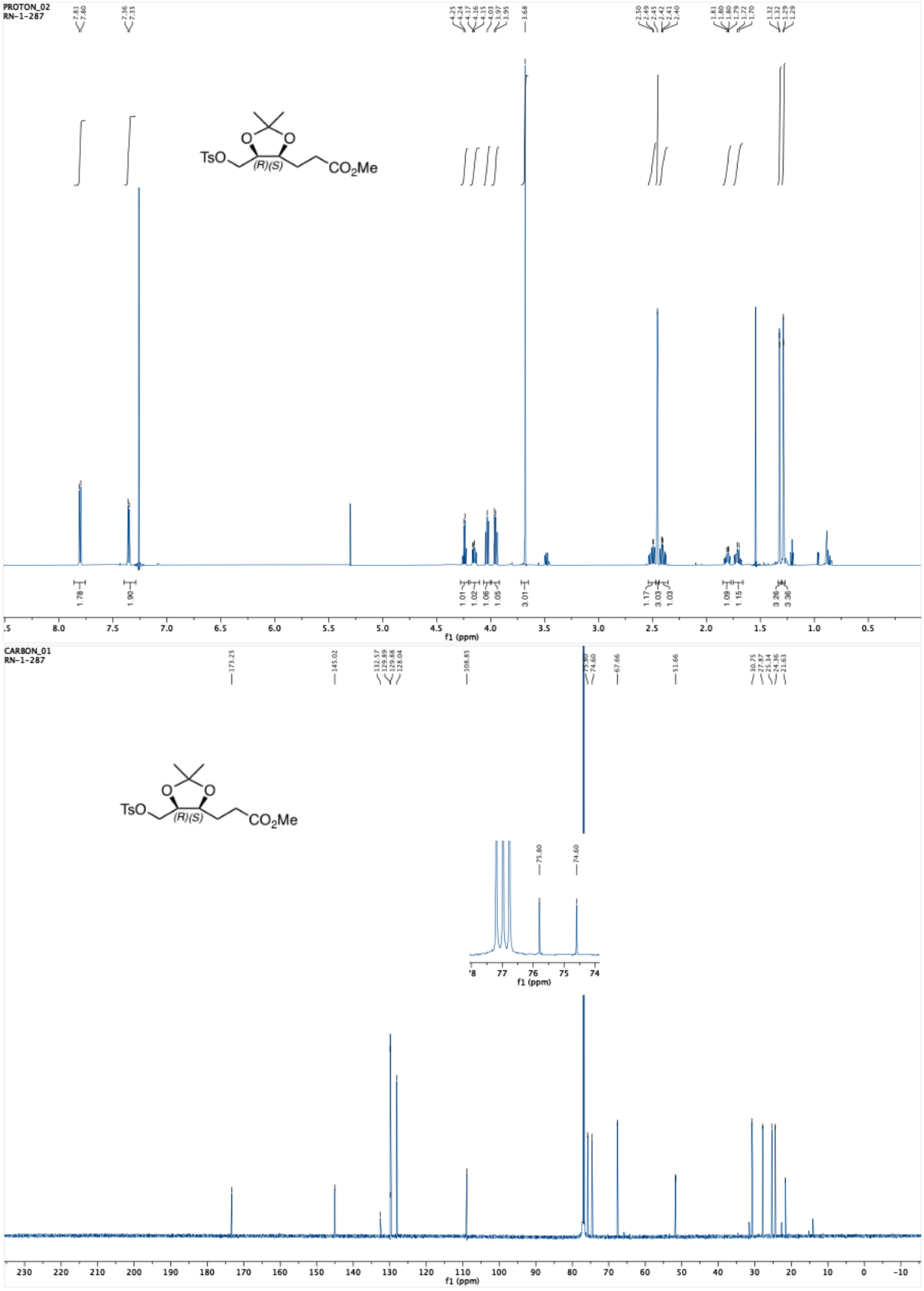
^{1}H and ^{13}C NMR spectra of compound **6**.



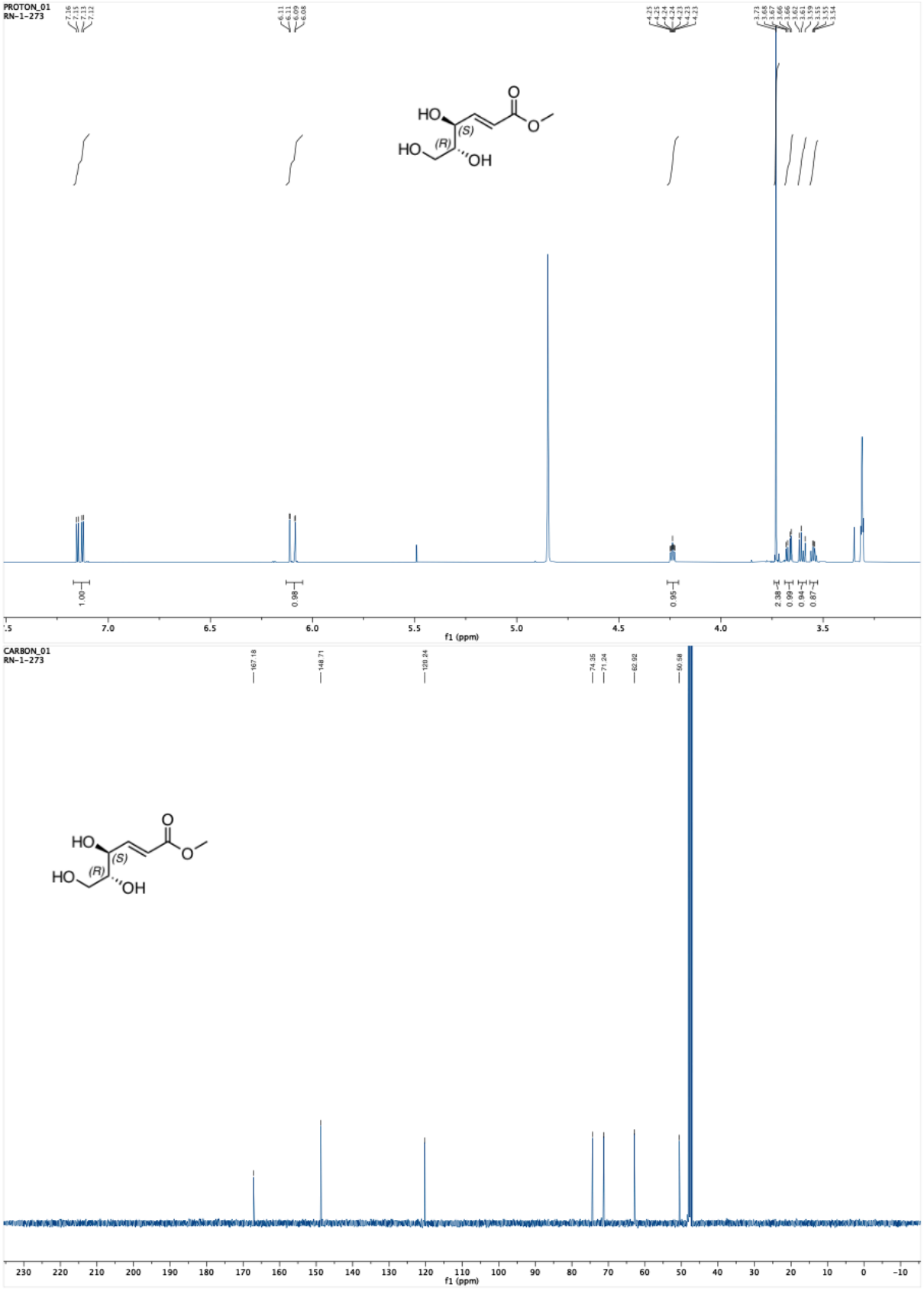
^{1}H and ^{13}C NMR spectra of compound **5** (*Z*-isomer).



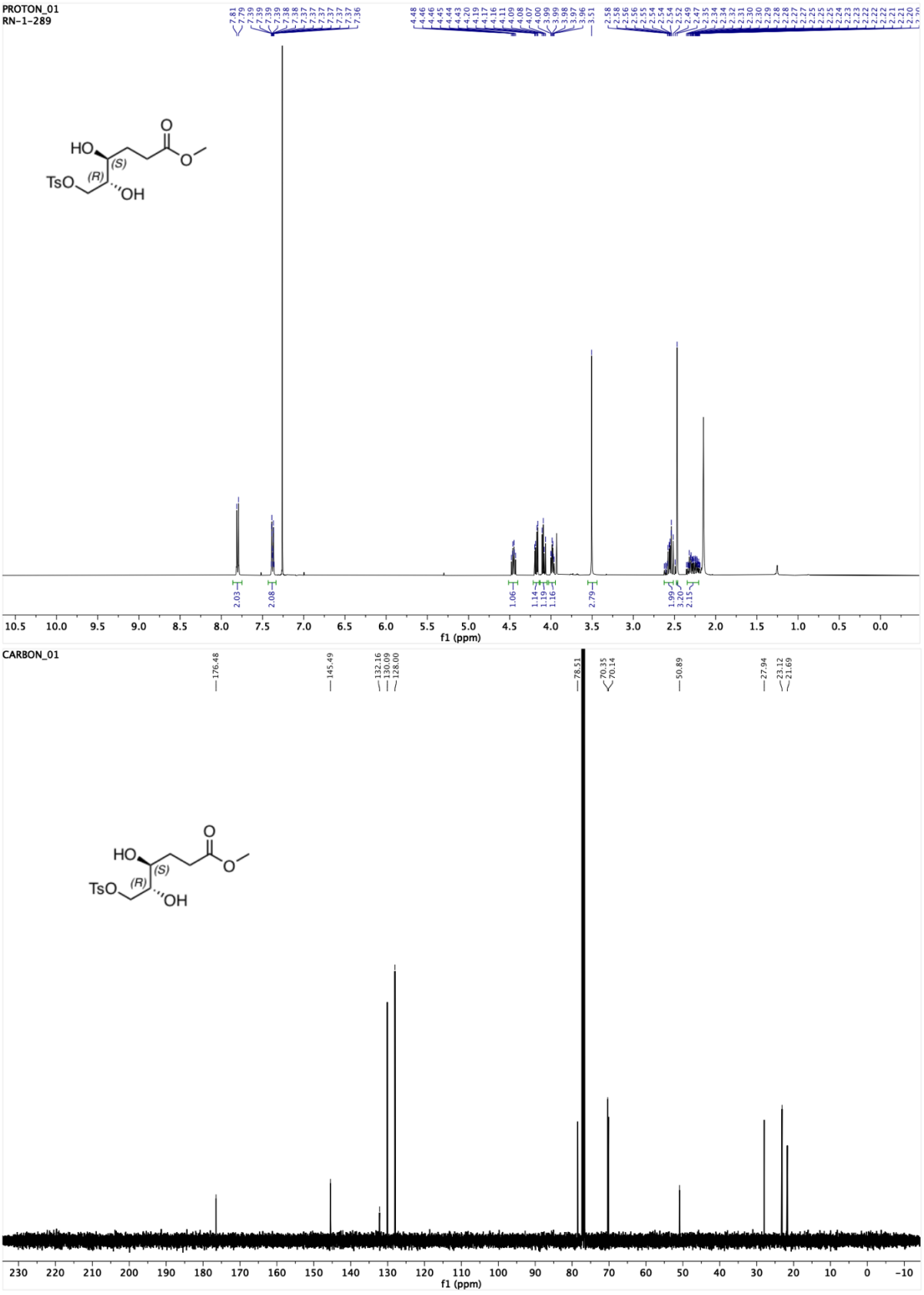
^{1}H and ^{13}C NMR spectra of isopropylidene-hydroxy methyl ester precursor of **4**.



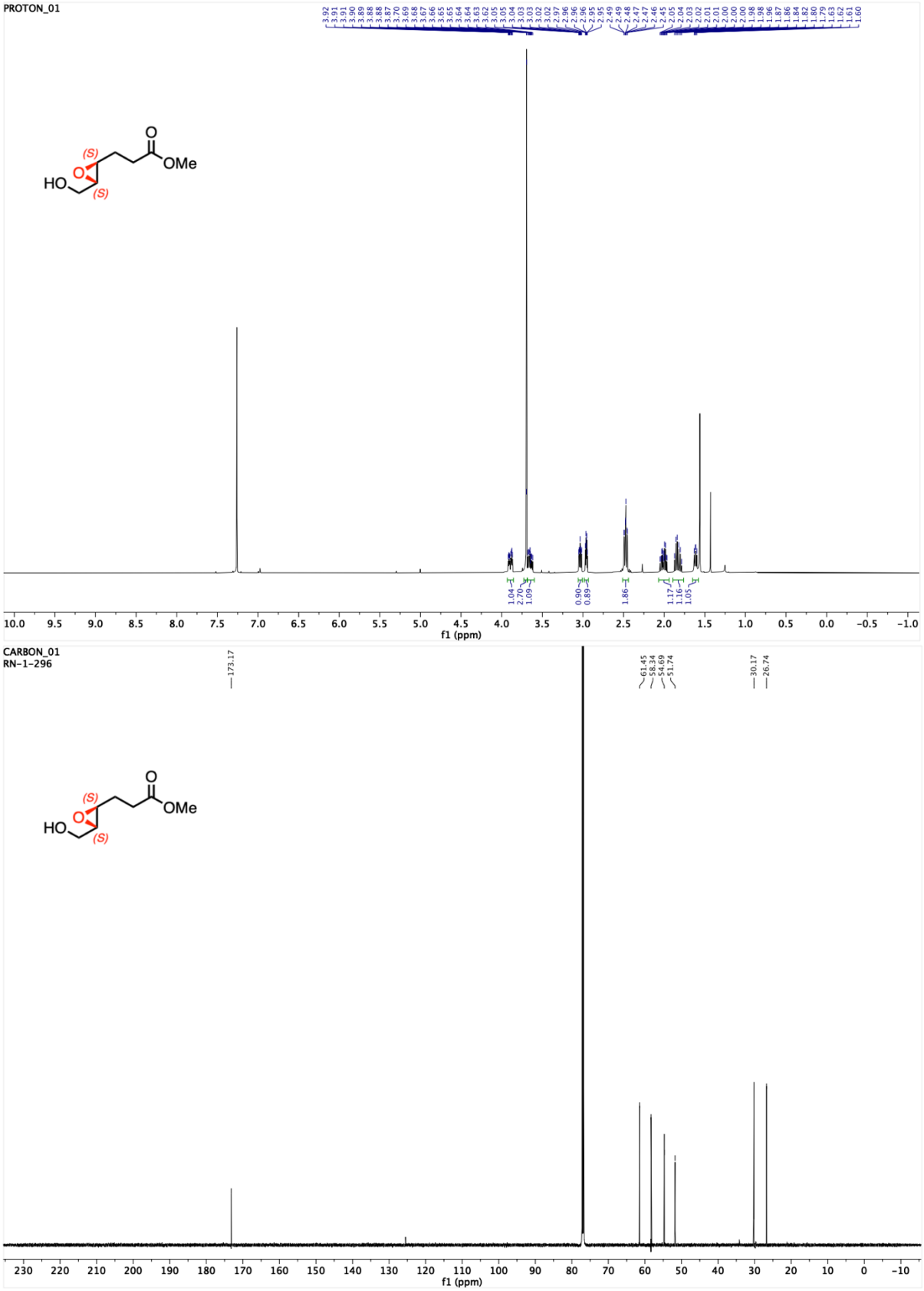
^{1}H and ^{13}C NMR spectra of isopropylidene-tosylate precursor of compound **4**.



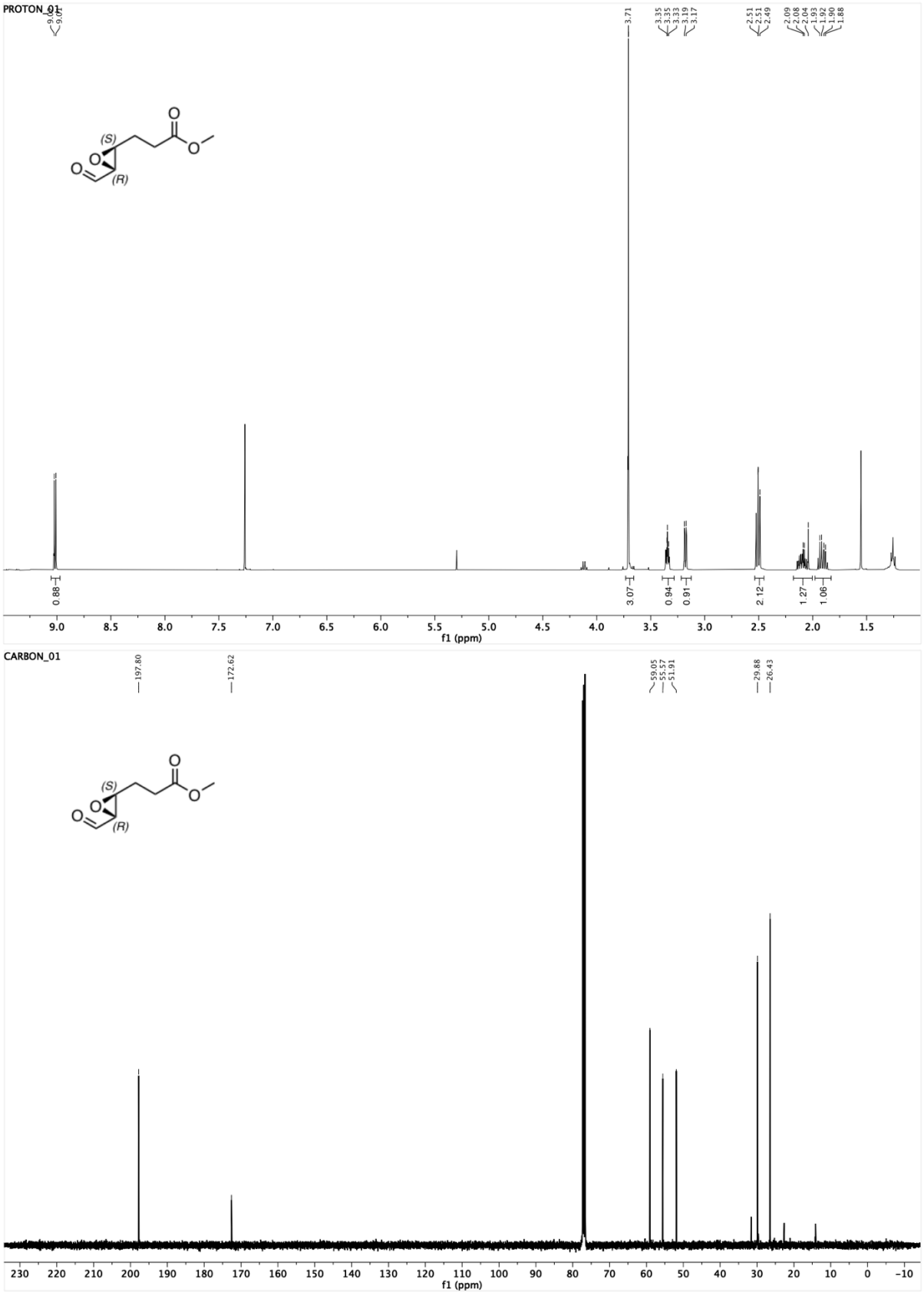
^{1}H and ^{13}C NMR spectra of the *α*,*β*-unsaturated triol produced from D-Erythrose (**23**).



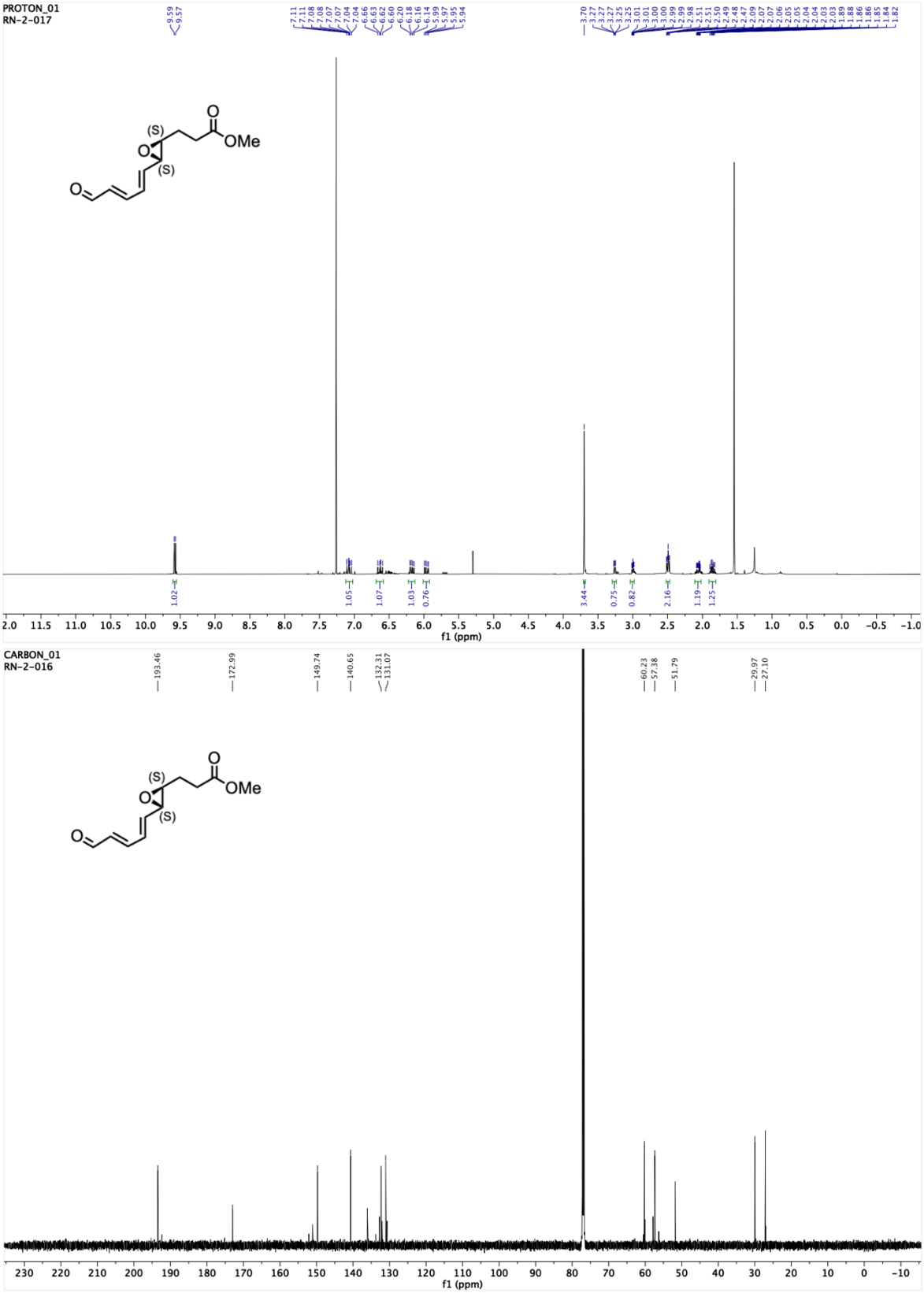
^{1}H and ^{13}C NMR spectra of compound **4**.



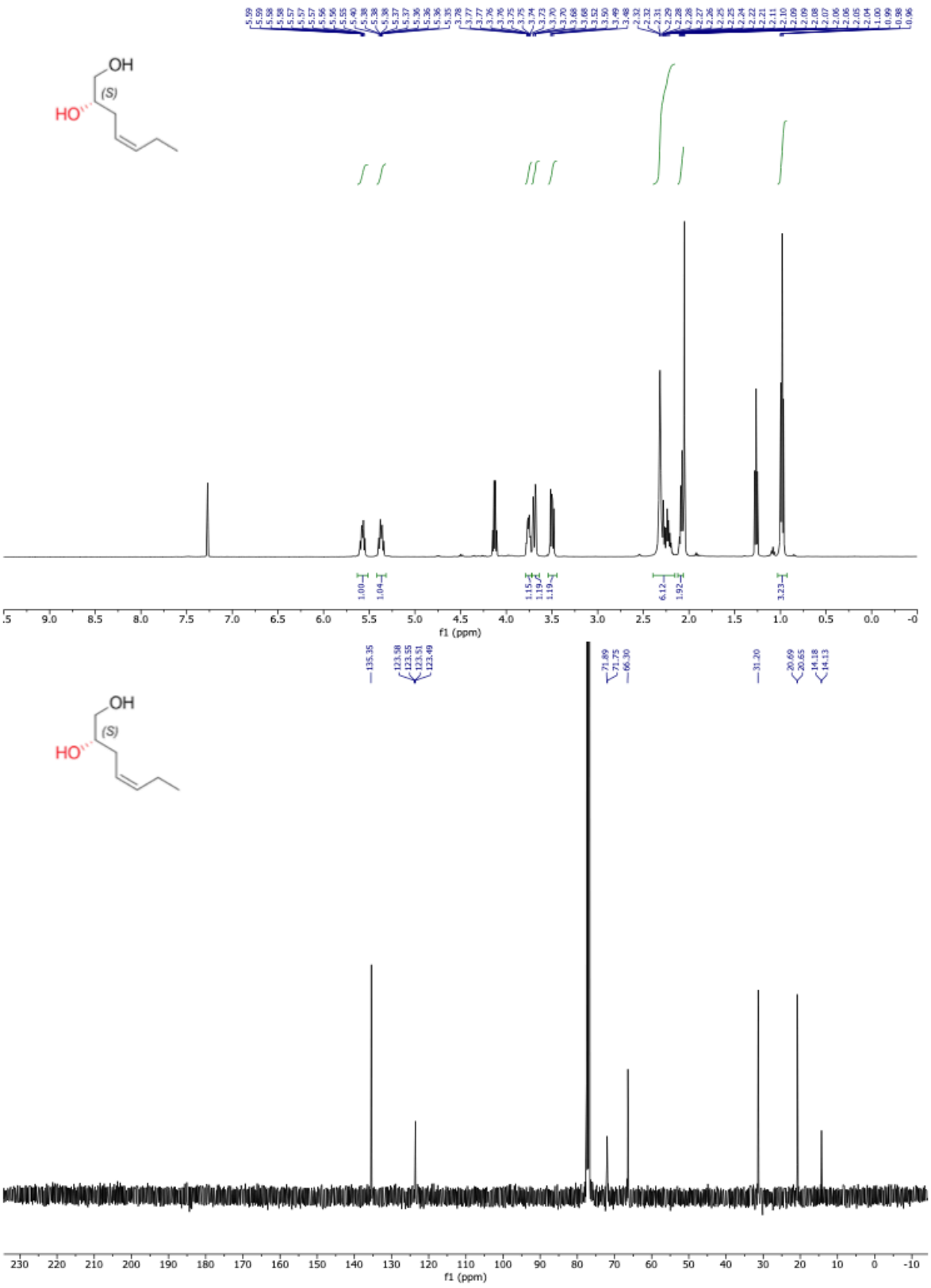
^{1}H and ^{13}C NMR spectra of compound **3**.



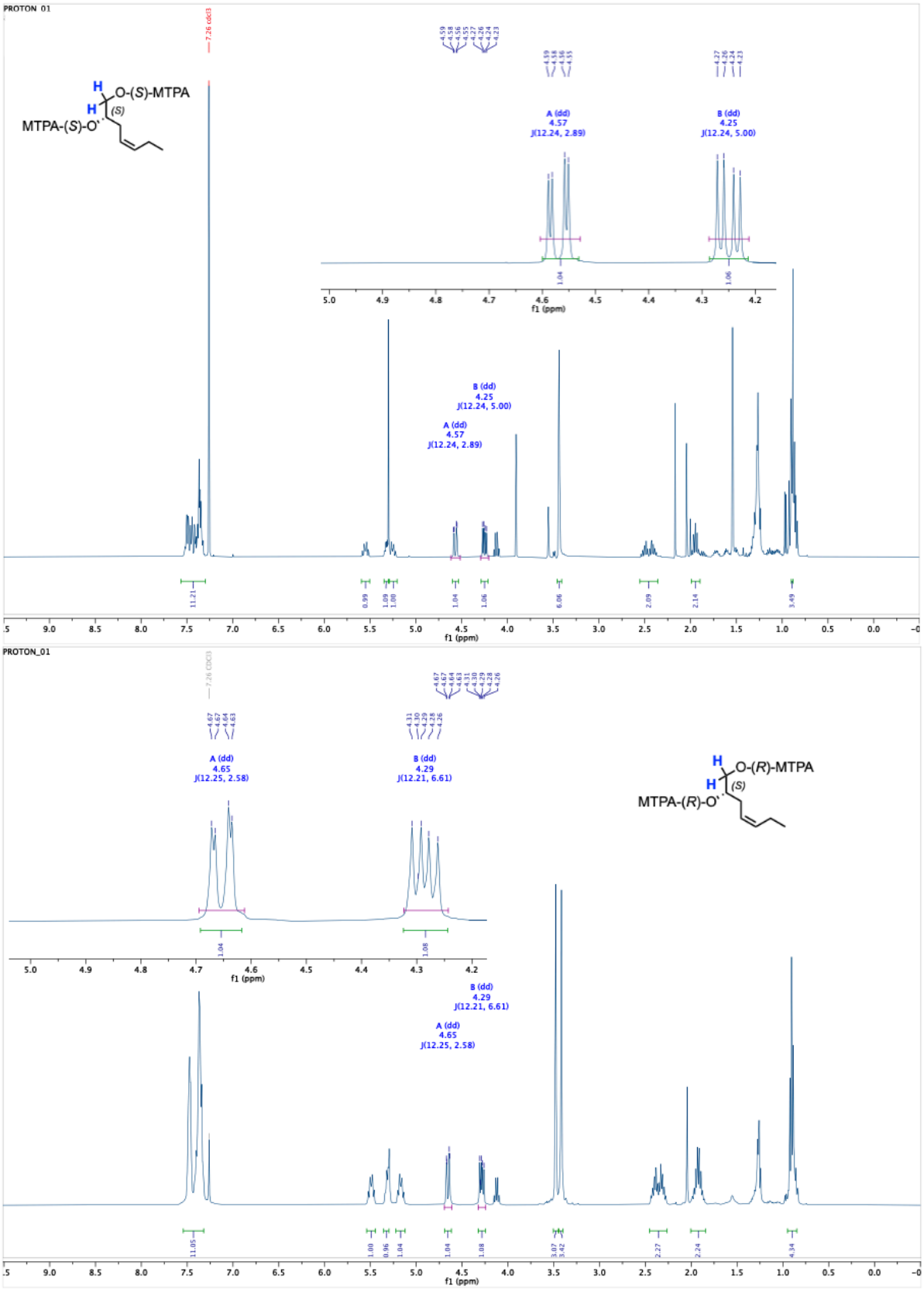
^{1}H and ^{13}C NMR spectra of the direct precursor of compound **2**.



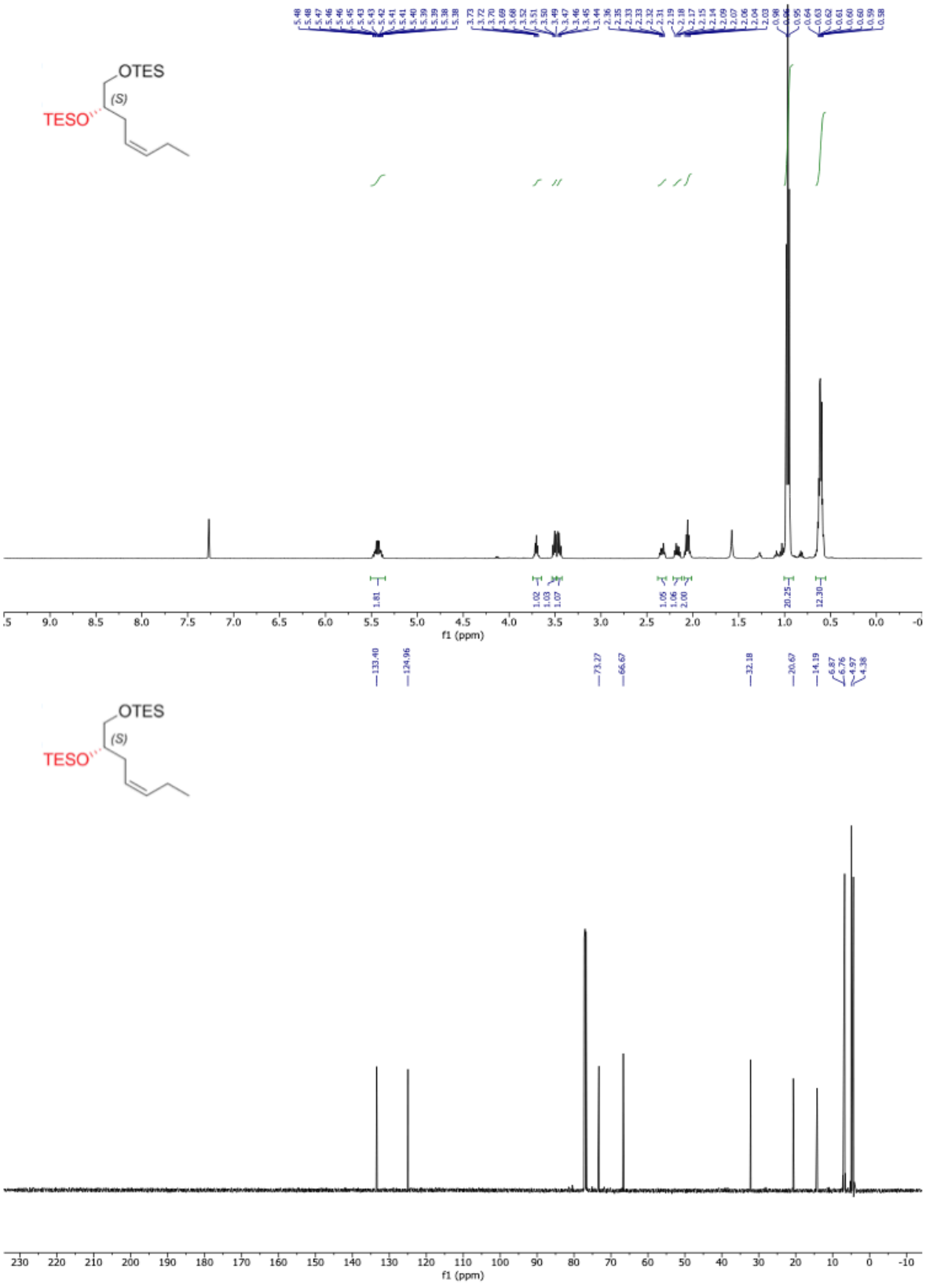
^{1}H and ^{13}C NMR spectra of compound **2**.



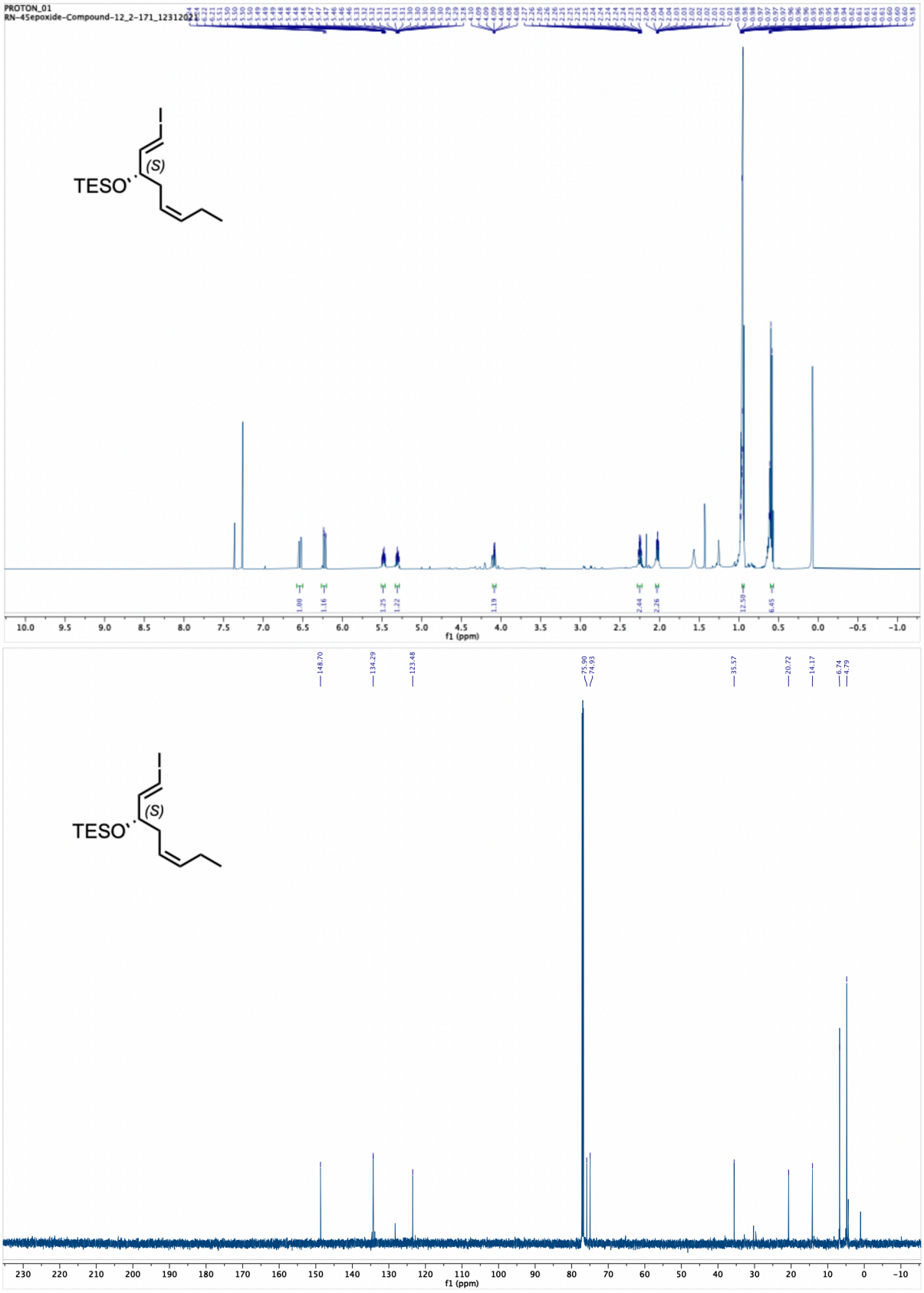
^{1}H and ^{13}C NMR spectra of compound **14**.



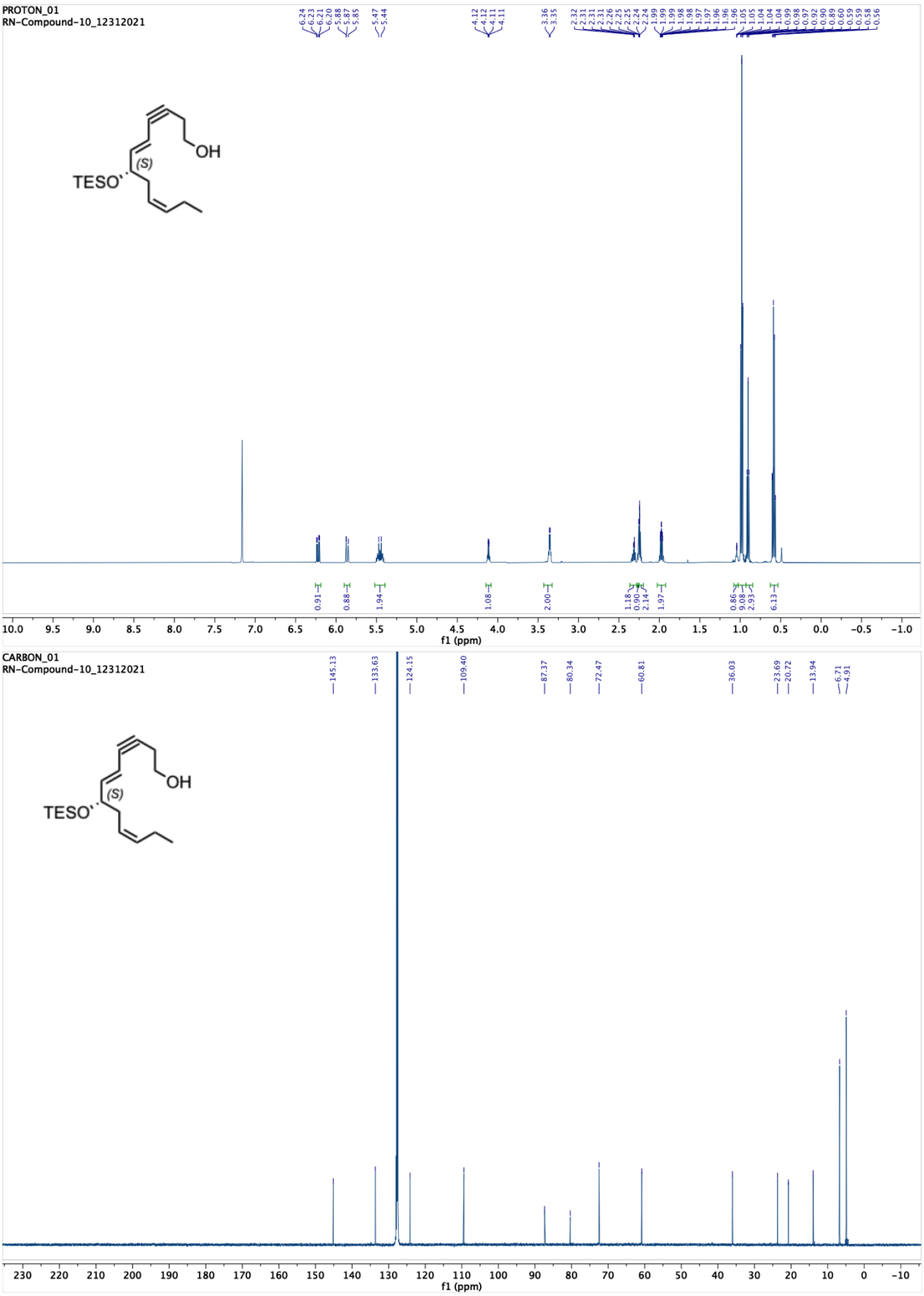
^{1}H NMR (400 MHz, Chloroform-*d*) of crude (*S*)- and (*R*)-MTPA esters of diol **14**.



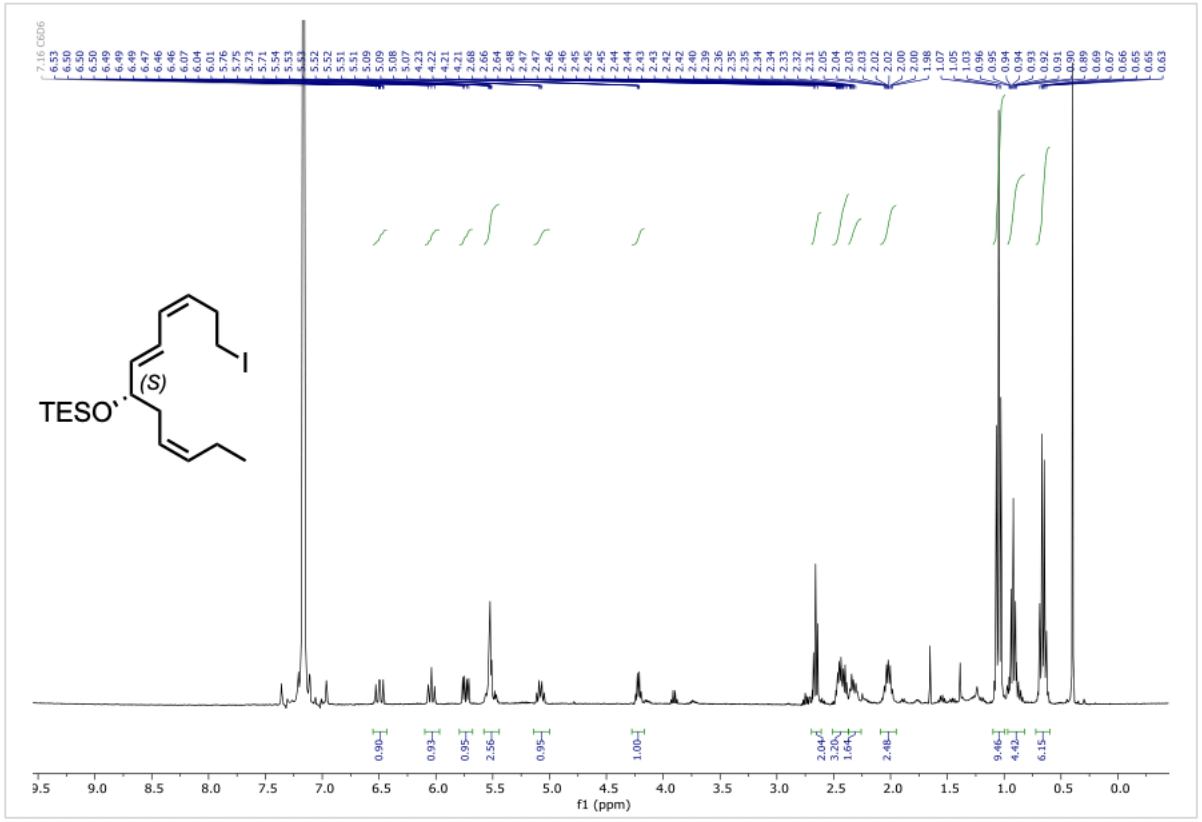
^{1}H and ^{13}C NMR spectra of bis-silyl compound **13**.

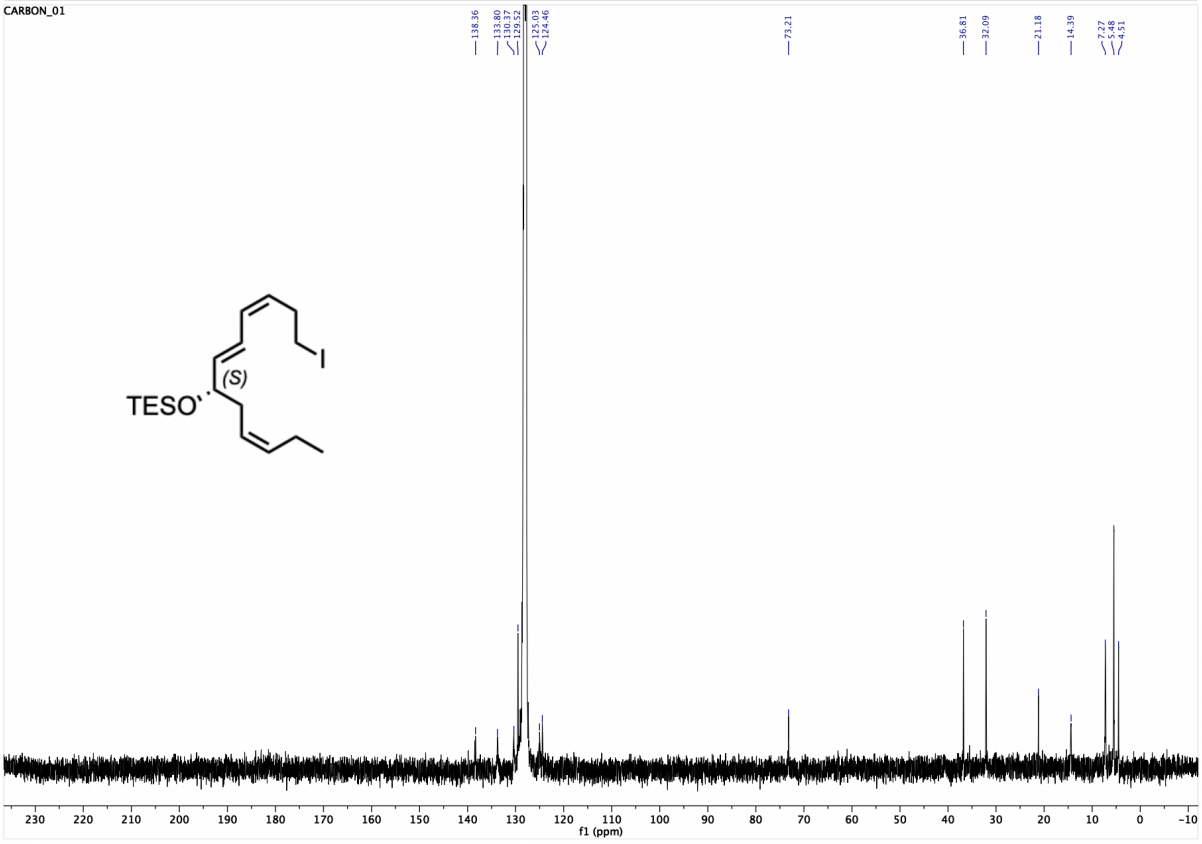


^{1}H and ^{13}C NMR spectra of compound **12**.

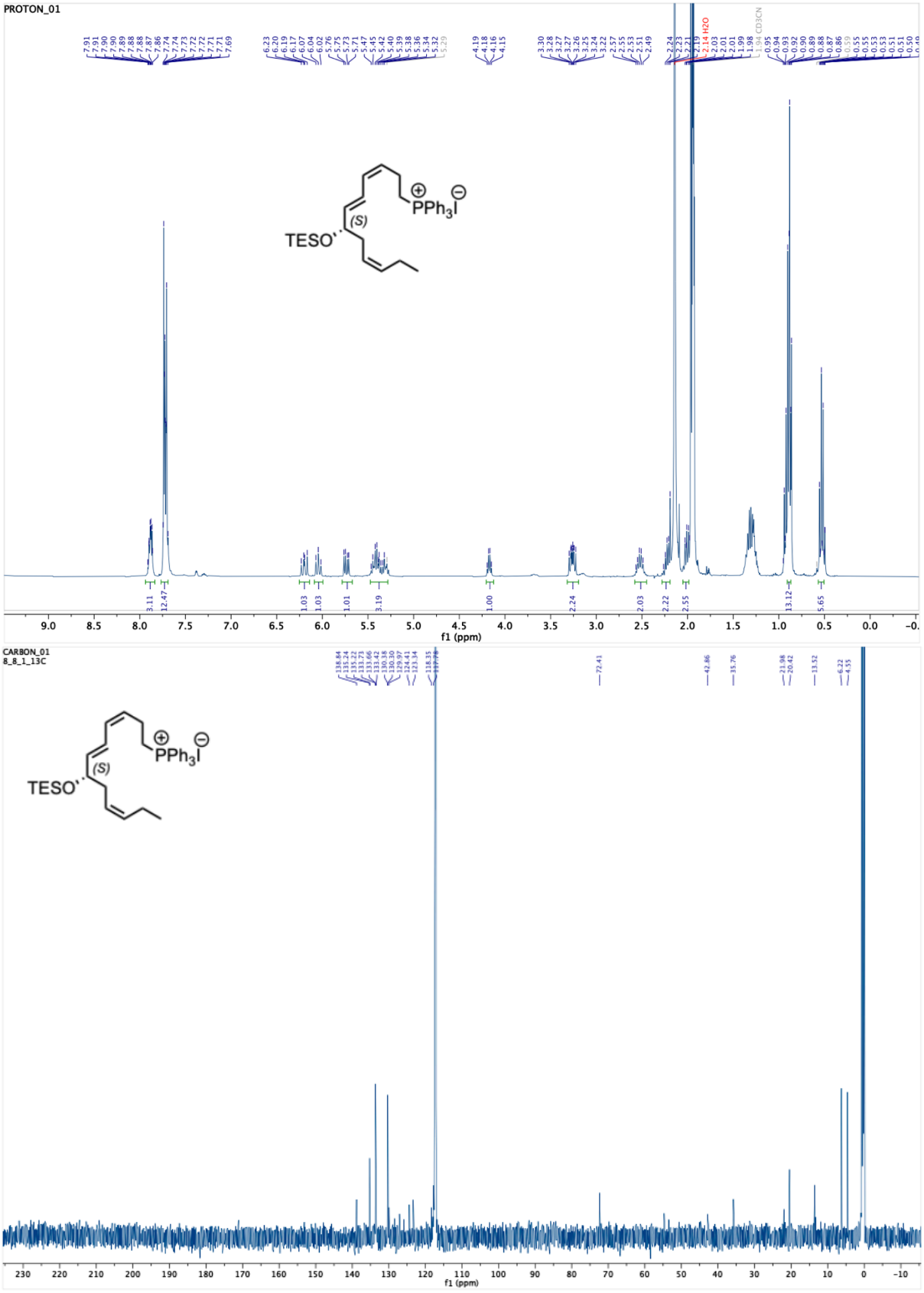


^{1}H and ^{13}C NMR spectra of compound **10**.

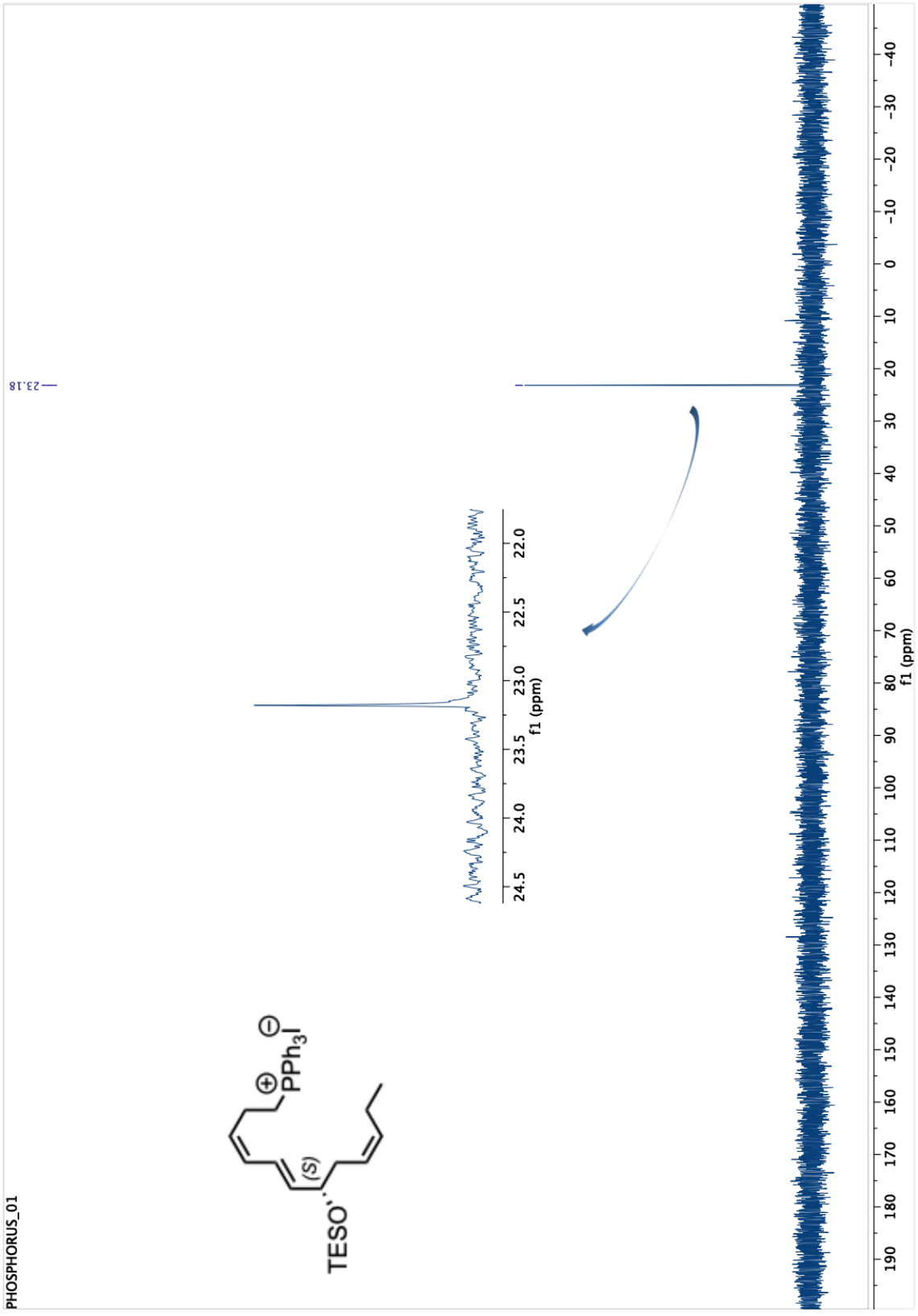




^{1}H and ^{13}C NMR spectra of compound **9**.



^{1}H and ^{13}C NMR spectra of compound **8**.



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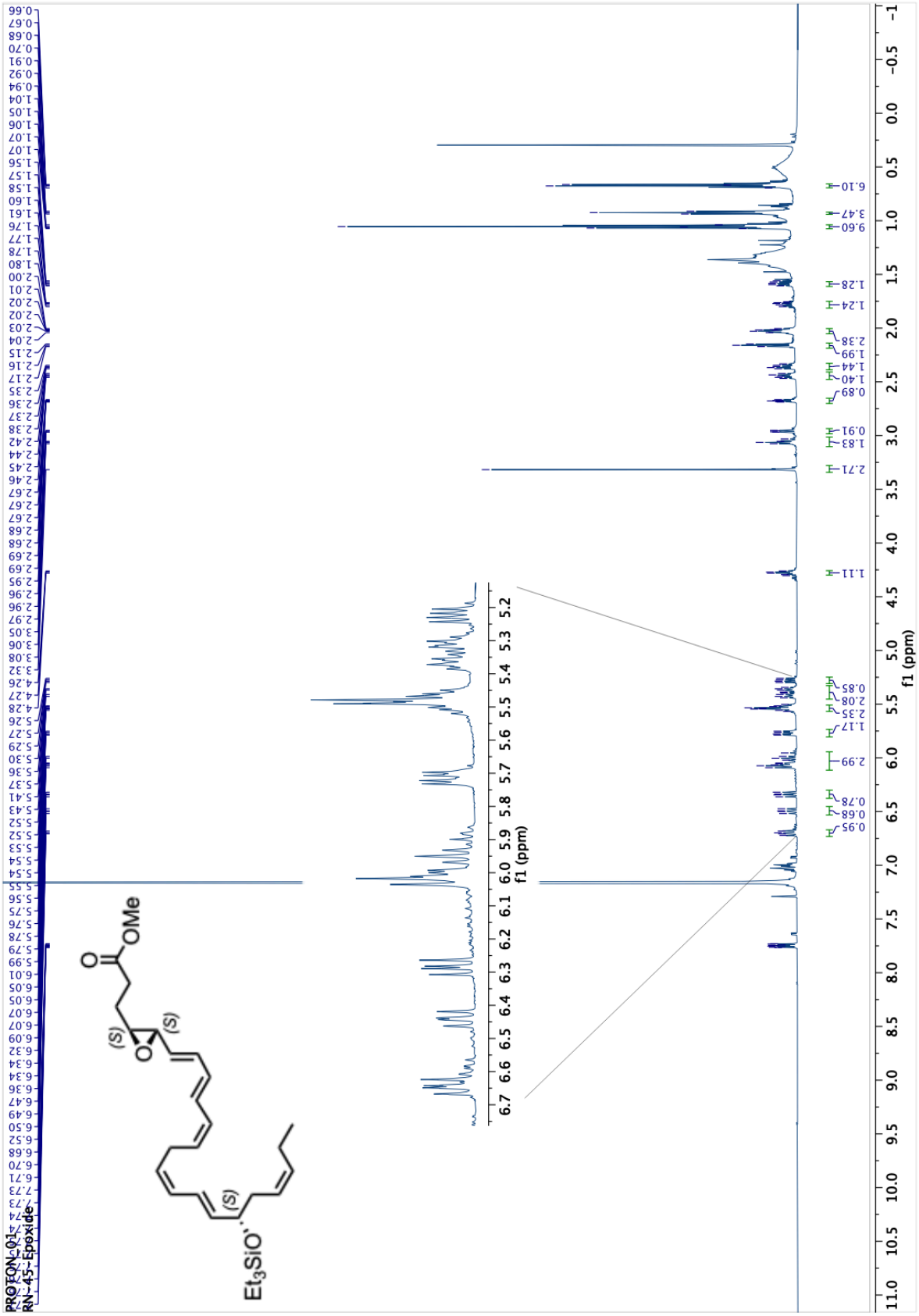
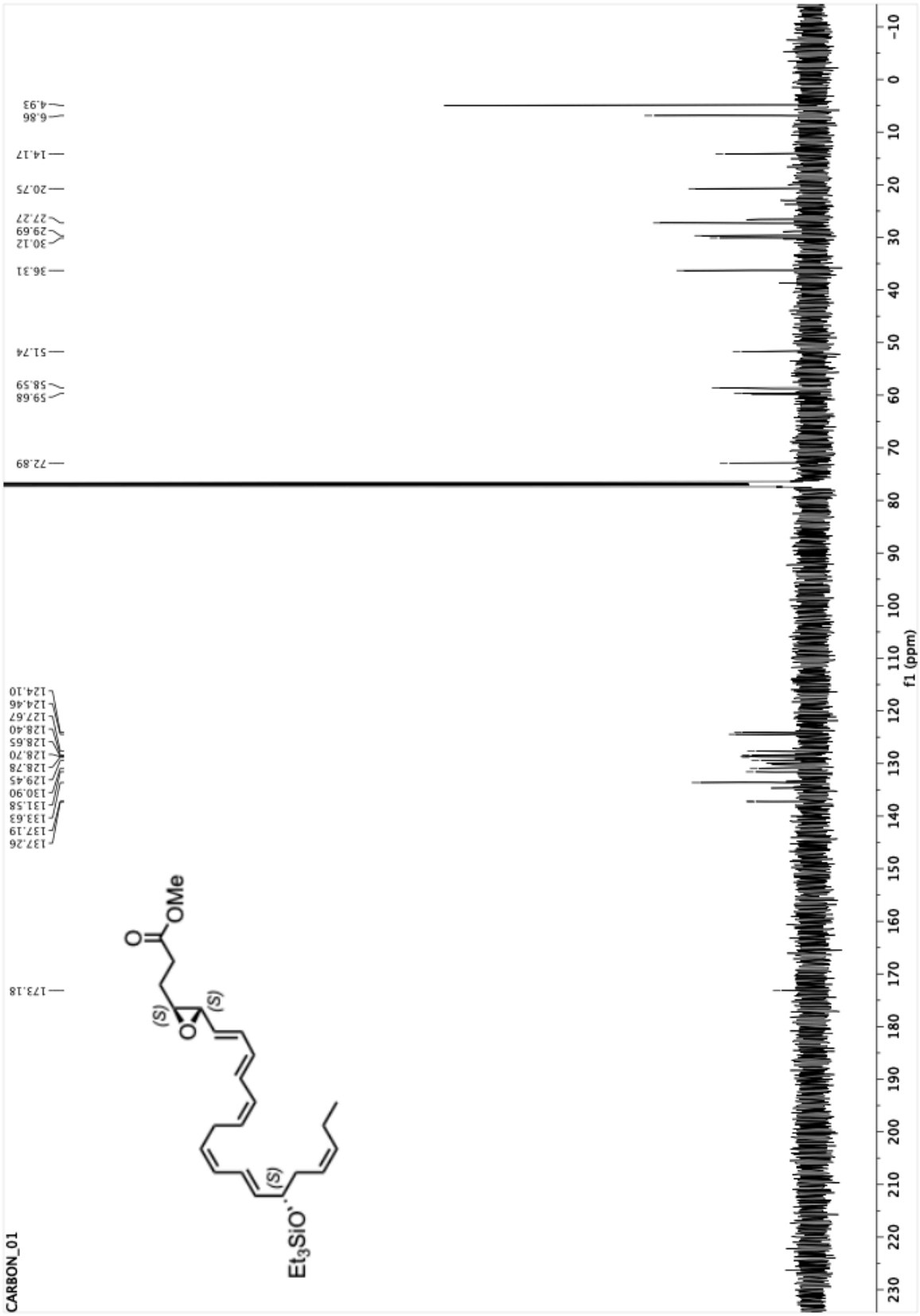
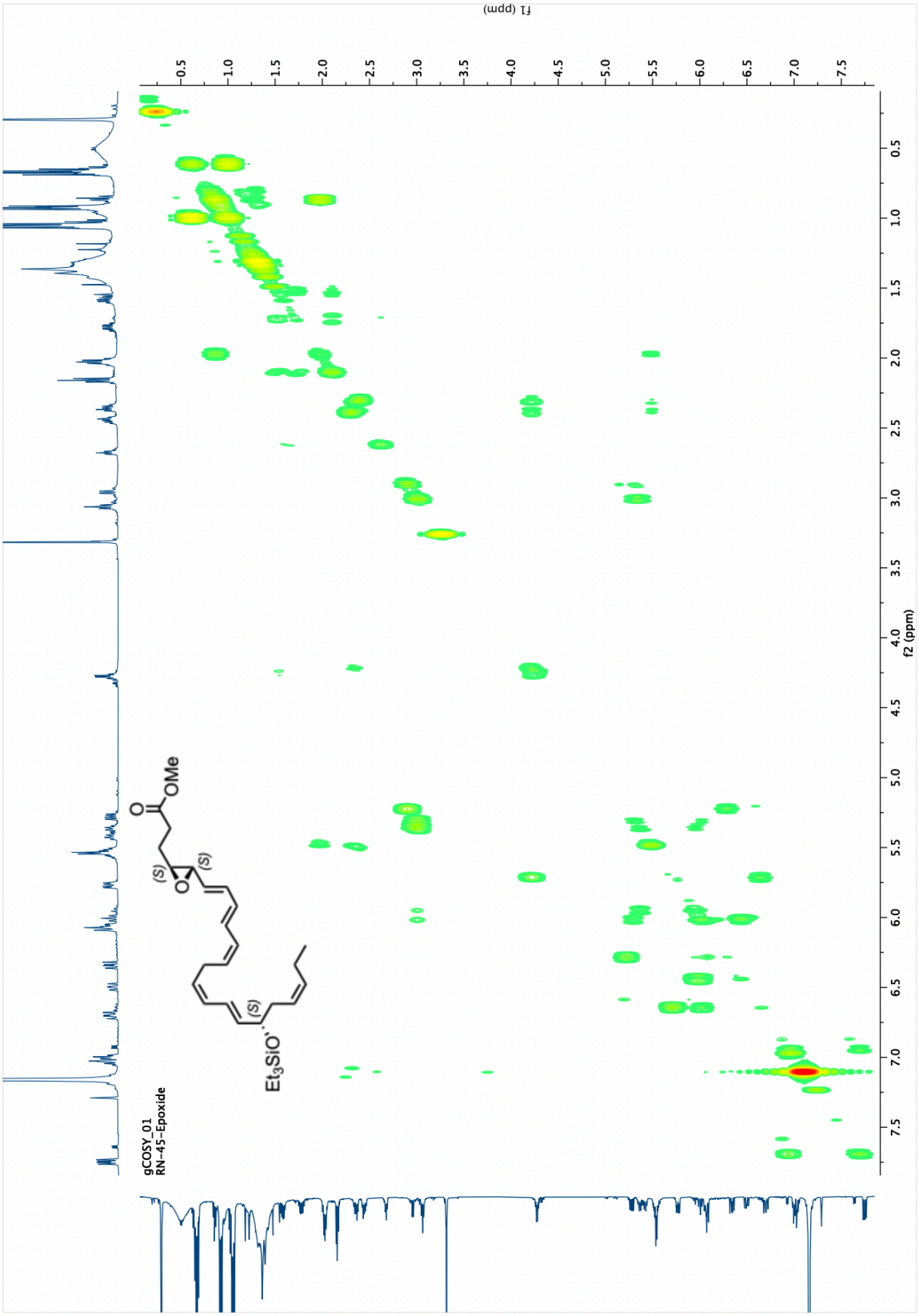
^{31}P NMR spectrum of compound **8**.



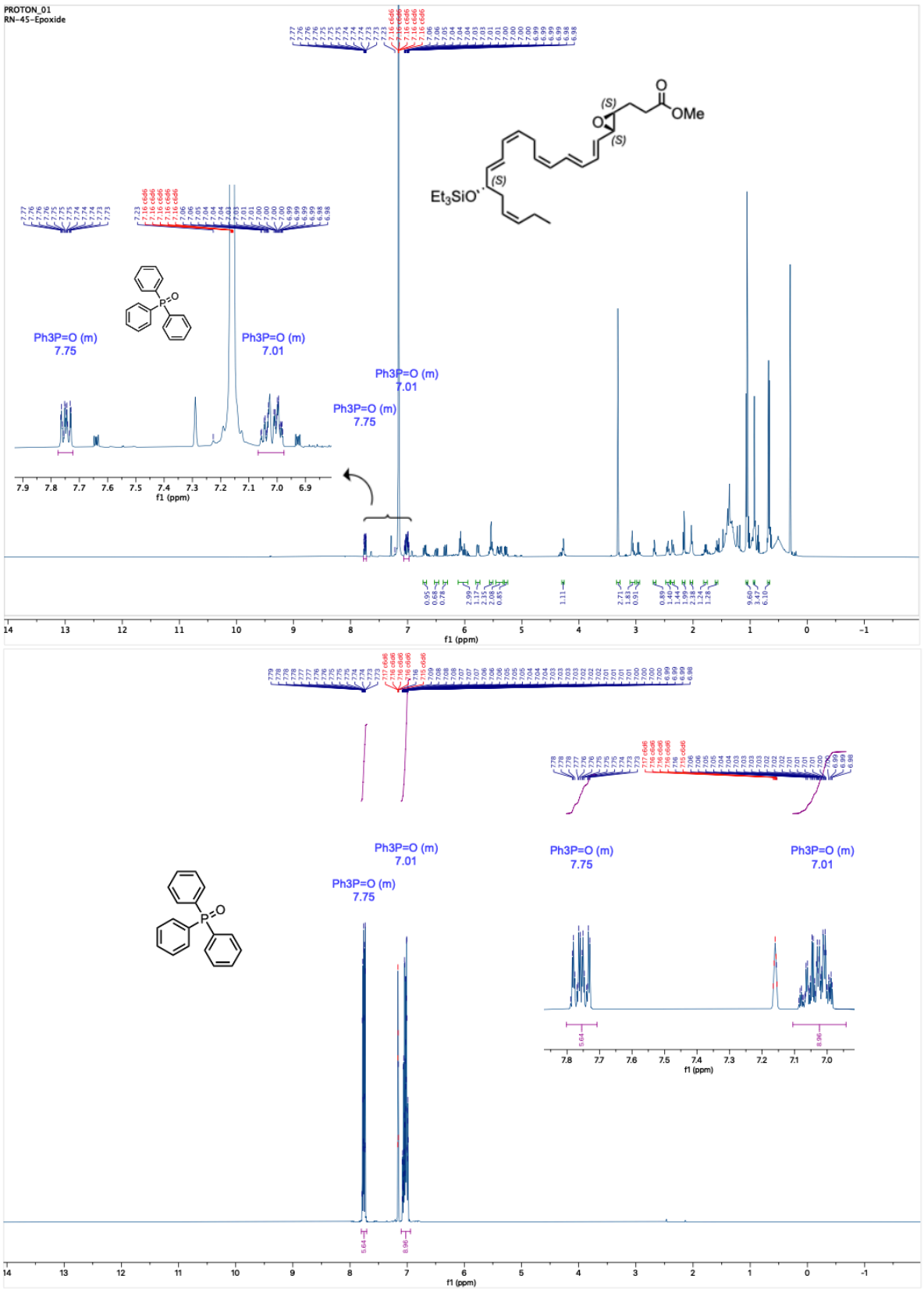
^{1}H NMR of the TES ether of **1**.



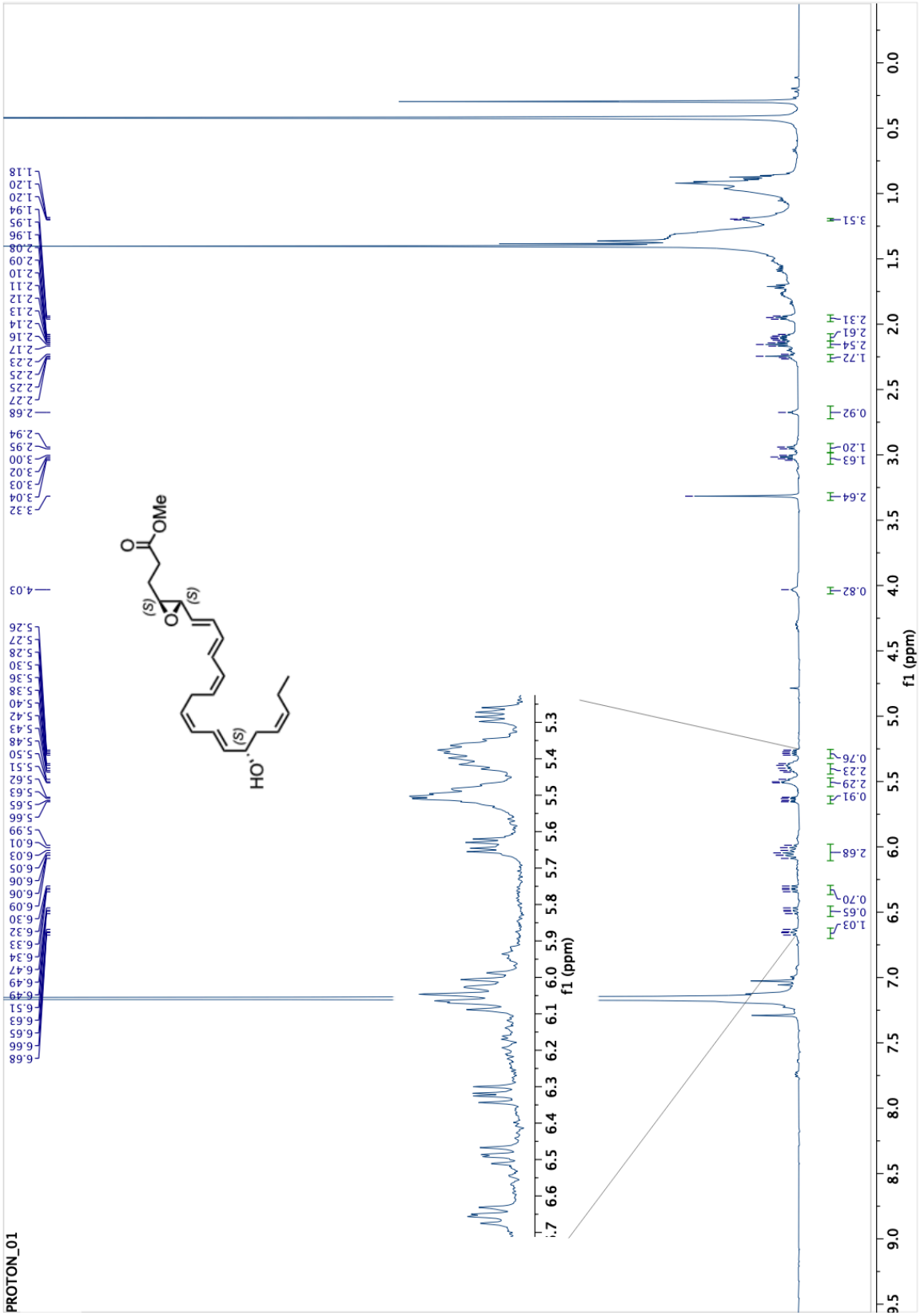
^{13}C NMR of the TES ether of **1**.



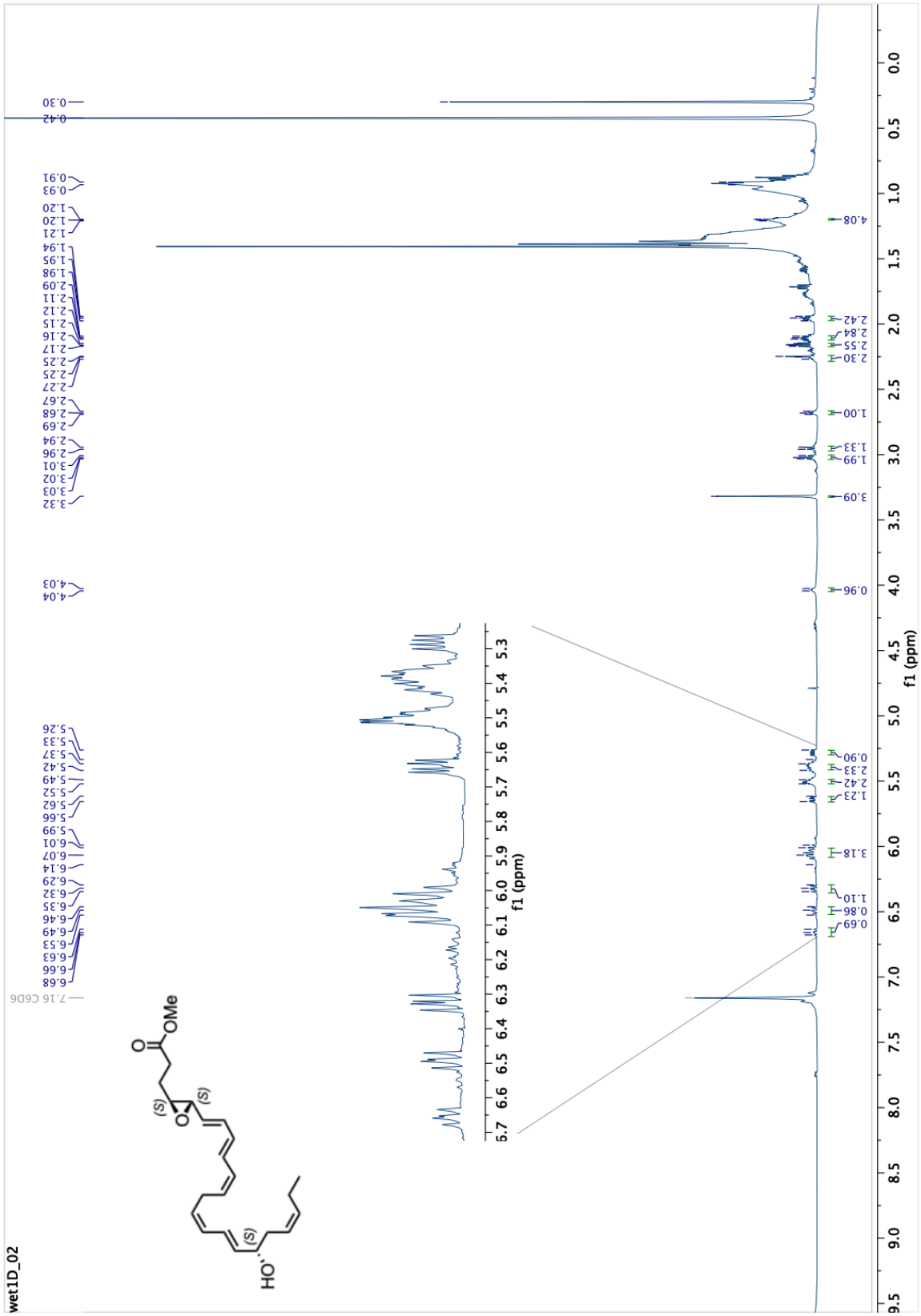
2D COSY NMR of the TES ether of **1**.



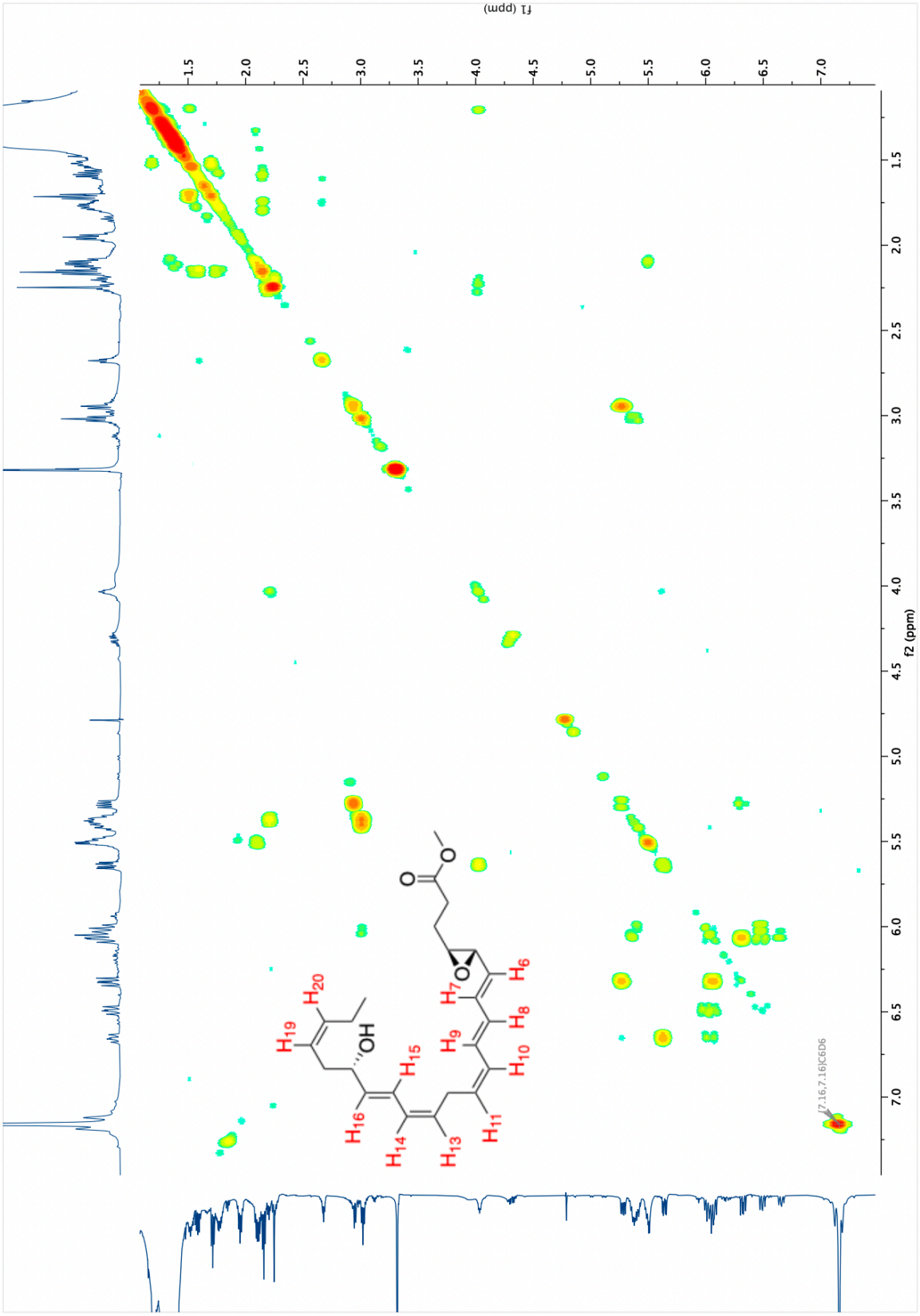
^{1}H NMR confirmation of $Ph_3P=O$ Wittig reaction byproduct in TES ether of **1**.



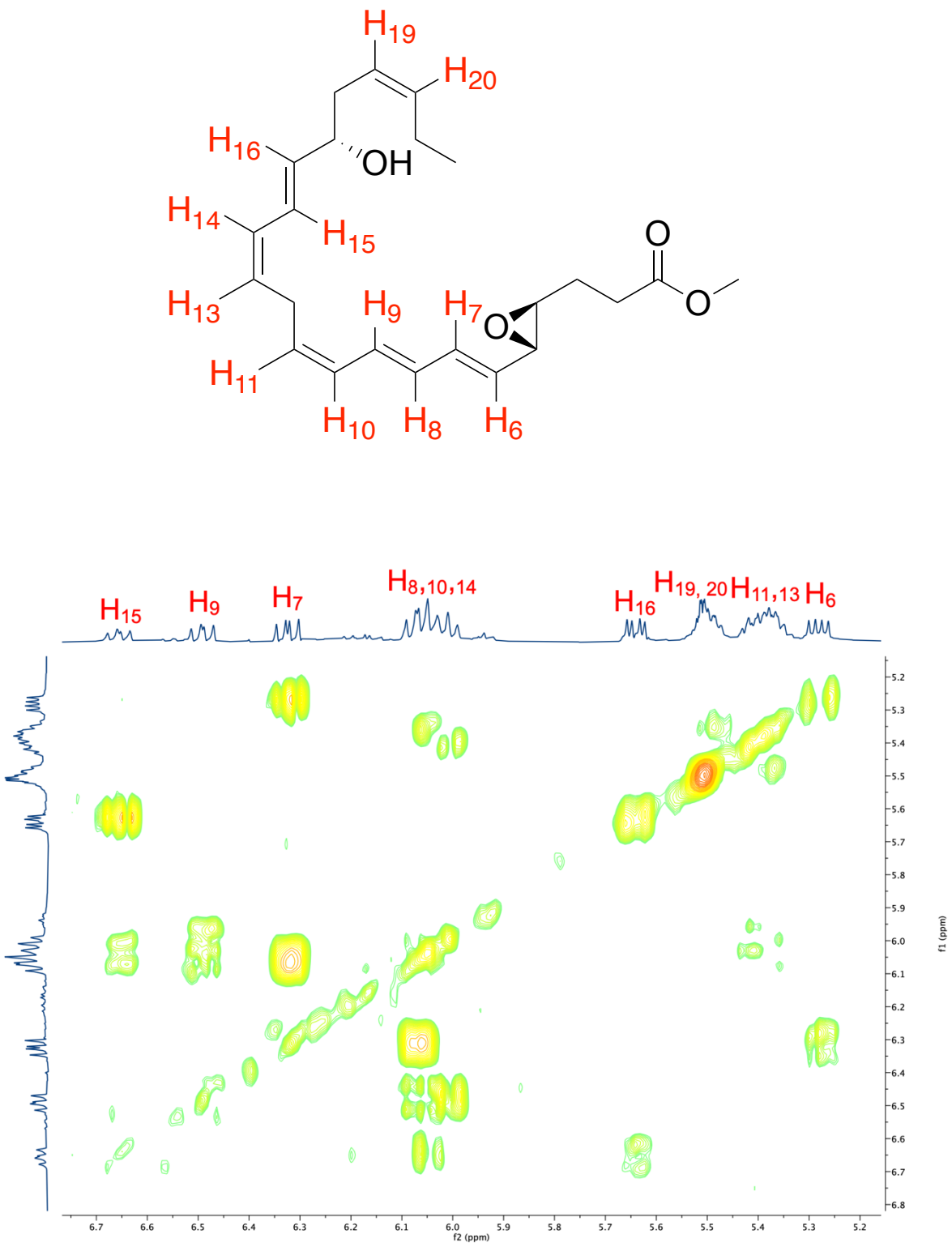
^{1}H NMR of the methyl ester of **1**.



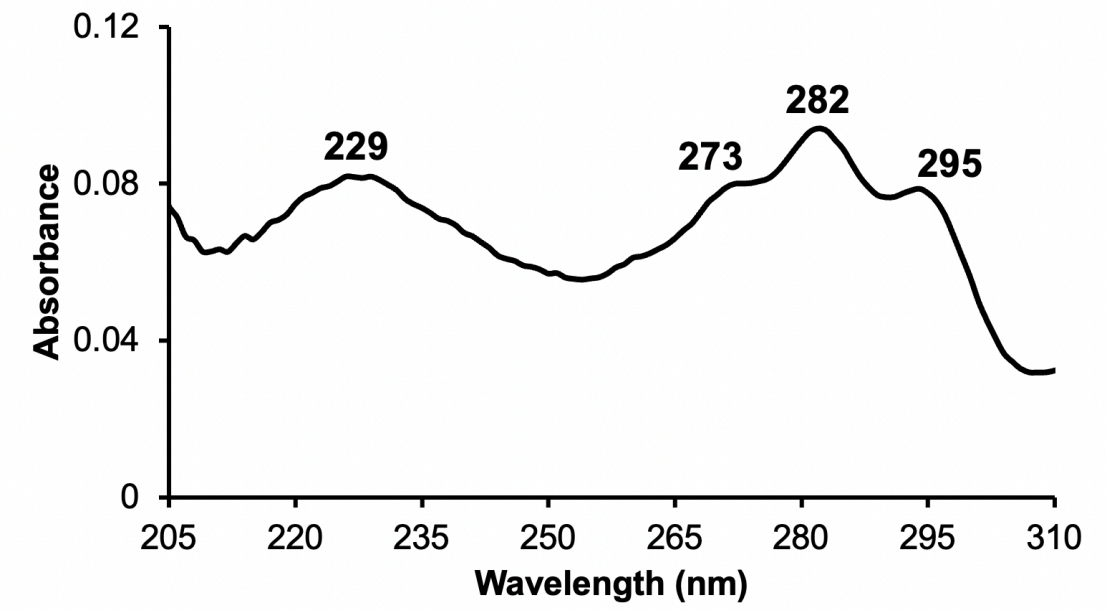
^{1}H NMR (wet1D) of the methyl ester of **1**.



2D COSY NMR of the methyl ester of **1**.



2D COSY NMR (vinylic region) of the methyl ester of **1**.



UV of compound **1** procured in methanol.