SUPPORTING INFORMATION

Stereochemistry of Linoleic Acid Esters of Hydroxy Linoleic Acids.

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SUPPORTING INFORMATION

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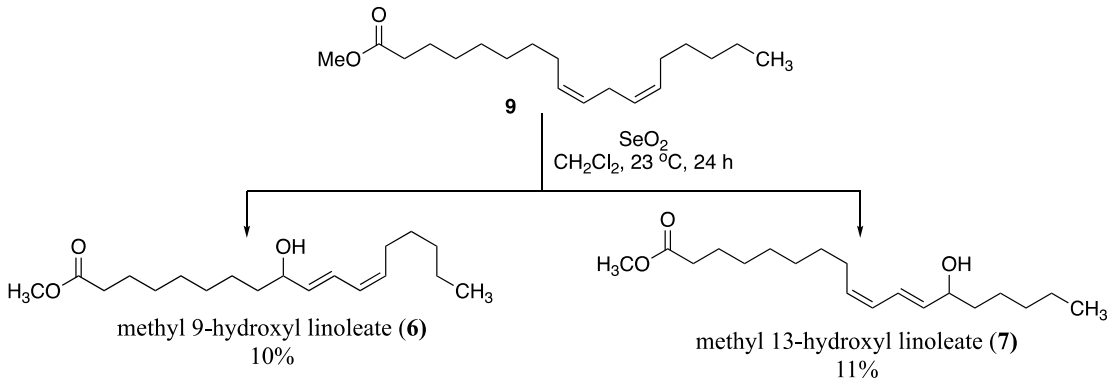
General Information

All reactions were performed in oven-dried glassware sealed with rubber septa and under nitrogen atmosphere, unless otherwise indicated. Air- and/or moisture-sensitive liquids or solutions were transferred by cannula or syringe. Organic solutions were concentrated by rotary evaporator at 30 millibar with the water bath heated to not more than 40 °C, unless specified otherwise. Tetrahydrofuran (THF), dichloromethane (DCM) were purified with a Pure-Solve MD-5 Solvent Purification System (Innovative Technology). 99.8% Extra Dry N, N-dimethlyformaide (DMF) were supplied by Acros Organics. Thin-layer chromatography (TLC) was performed using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD Chemicals) and visualized with a UV lamp (short and long wave) and/or aqueous potassium permanganate ($KMnO_4$) stain. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian 600 MHz (^1H at 600 MHz, ^{13}C at 150 MHz, ^{13}C DEPTQ at 150 MHz). All spectra were taken in $CDCl_3$ with shifts reported in parts per million (ppm) referenced to protium or carbon of the solvent (7.26 or 77.16, respectively). Coupling constants are reported in Hertz (Hz). Data for ^1H-NMR are reported as follows: chemical shift (ppm, reference to protium; s = single, d = doublet, t = triplet, m = multiplet, coupling constant (Hz), and integration). High Resolution Mass Spectra (HRMS) were acquired on an Agilent 6230 High Resolution time-of-flight mass spectrometer and reported as m/z for the molecular ion $[M+Na]^+$, $[M+H]^+$ and $[M-H]^-$.

General Synthetic Procedures

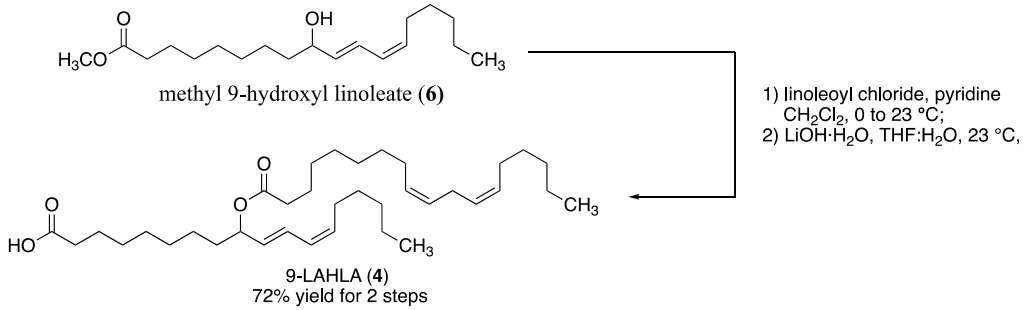
The synthesis of 9- and 13-LAHLA

selenium dioxide oxidation



To a stirred solution of selenium dioxide (1.0 g, 9.3 mmol, 1.0 eq) in CH_2Cl_2 (18 mL) was added neat methyl linoleate (**9**) (2.7 g, 3.0 mL 9.3 mmol, 1.0 eq) under nitrogen atmosphere at 23 °C and stirred for 24 hours. The reaction was diluted with an aqueous solution of NaCl (10% w/w, 25 mL). The resulting mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The crude material was purified via silica gel column chromatography using hexane:EtOAc (90:10 to 89:11) to give methyl 9-hydroxyl linoleate **6** (290 mg, 10%) the methyl 13-hydroxyl linoleate **7** (310 mg, 11%) as oils. Spectra were in agreement with those previously reported[1].

Esterification



To a stirred solution of methyl 9-hydroxyl linoleate **6** (63 mg, 0.2 mmol, 1.0 eq) in dry CH_2Cl_2 (5.0 mL) was added neat pyridine (82 µL, 1.0 mmol, 5.0 eq) dropwise via syringe. The reaction

vessel was placed in an ice water bath and stirred for 5 minutes. Neat linoleoyl chloride (72 µL, 0.22 mmol, 1.1 eq) was added via syringe slowly. The reaction mixture was stirred at 23 °C for 20 h. The reaction was diluted with water (2.5 mL) and stirred for 10 minutes. The organic phase was collected, and the aqueous layer was extracted with CH_2Cl_2 (4.0 mL × 2). The combined CH_2Cl_2 layers were washed with 0.5 M aqueous hydrochloric acid (3.5 mL), saturate aqueous sodium bicarbonate (3.5 mL), and then brine (3.5 mL). The CH_2Cl_2 solution was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (97:3) to give the 9-LAHLA methyl ester **10** (91 mg).

(10E,12*Z*)-1-methoxy-1-oxooctadeca-10,12-dien-9-yl (9*Z*,12*Z*)-octadeca-9,12-dienoate (9-LAHLA methyl ester, 10)

R_f = 0.6 (silica gel, 90:10 hexanes:EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.94 (t, *J* = 11.1 Hz, 1H), 5.55 (dd, *J* = 15.2, 7.5 Hz, 1H), 5.48 – 5.30 (m, 6H), 3.67 (s, 3H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.32 (m, 4H), 2.16 (m, 2H), 2.07 – 2.03 (m, 4H), 1.64 (m, 4H), 1.38 – 1.26 (m, 30H), 0.88 (m, 6H); **^{13}C NMR-DEPTQ** (150 MHz, $CDCl_3$) δ 174.5, 173.3, 133.7, 131.3, 130.4, 130.2, 128.2, 128.0, 127.7, 74.6, 51.6, 34.9, 34.7, 34.2, 31.7, 29.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.9, 27.3, 25.8, 25.2, 25.1, 25.0, 22.7, 14.2; **IR** (film, cm^{-1}): 2927, 2855, 1738, 1458, 1364, 1170; **MS** (ESI) calc. for $C_{37}H_{64}O_4Na$ $[M+Na]^+$: 595.47, obs. 595.41.

Selective hydrolysis of the 9-LAHLA methyl ester 10

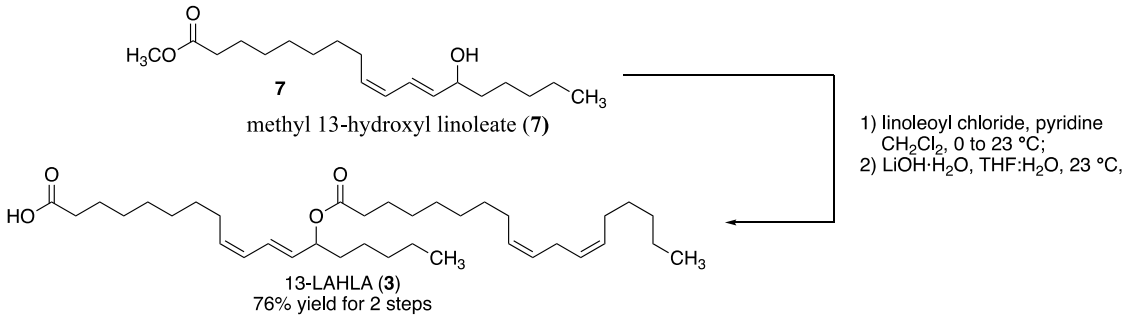
To a stirred solution of 9-LAHLA methyl ester **10** (91 mg, 0.16 mmol, 1.0 eq.) in THF (0.8 mL) at 23 °C was added an aqueous solution of lithium hydroxide (0.32 mL, 1 M, 0.32 mmol, 2.0 eq). The reaction mixture was stirred for 24 h and cooled to 0 °C. The reaction was diluted with 2N aqueous hydrochloric acid (6 mL) and then extracted with ether (18 mL × 3). The combined ether solution was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAC:AcOH (94:5:1) to give the 9-LAHLA **4** (82 mg, 0.146 mmol, 72% for two steps).

(10*E*,12*Z*)-9-(((9*Z*,12*Z*)-octadeca-9,12-dienoyl)oxy)octadeca-10,12-dienoic acid (9-LAHLA, 4)

R_f = 0.4 (silica gel, 80:20 hexanes:EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 15.2, 11.0 Hz, 1H), 5.94 (t, *J* = 11.0 Hz, 1H), 5.55 (dd, *J* = 15.2, 7.4 Hz, 1H), 5.48 – 5.31 (m, 6H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.32 (m, 4H), 2.16 (d, *J* = 7.5 Hz, 2H), 2.04 (m, 4H), 1.66 – 1.61 (m, 4H), 1.37 – 1.26 (m, 31H), 0.89 (t, *J* = 6.7 Hz, 6H); **^{13}C NMR-DEPTQ** (150 MHz, $CDCl_3$) δ 179.2, 173.5, 133.8, 131.2, 130.4, 130.2, 128.2, 128.1, 128.0, 127.7, 74.8, 34.9, 34.7, 34.0, 31.7, 29.8, 29.5, 29.3,

29.2, 29.1, 29.0, 27.8, 27.3, 25.8, 25.2, 25.0, 24.8, 22.7, 14.2; **IR** (film, cm^{-1}): 2925, 2854, 1708, 1734, 1463, 1170; **HRMS** (ESI) calc. for $C_{36}H_{62}O_4Na$ $[M+Na]^+$: 581.4540, obs. 581.4539.

Esterification



To a stirred solution of methyl 13-hydroxyl linoleate **7** (50 mg, 0.16 mmol, 1.0 eq) in dry CH_2Cl_2 (2.0 mL) was added neat pyridine (65 µL, 0.80 mmol, 5.0 eq). The reaction was cooled to 0 °C and stirred for 10 min. Neat linoleoyl chloride (57 µL, 0.18 mmol, 1.1 eq) was added via syringe slowly. The reaction mixture was warmed to 23 °C and stirred overnight. The reaction was diluted with water (2.0 mL) and extracted with CH_2Cl_2 (3.0 mL × 2). The combined CH_2Cl_2 solution was washed with 0.5 M aqueous hydrochloric acid (3.0 mL), saturate aqueous sodium bicarbonate (3.0 mL), and then brine (3.0 mL). The CH_2Cl_2 solution was dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (96:4) to give the 13-LAHLA methyl ester **11** (82 mg).

methyl (9*Z*,11*E*)-13-(((9*Z*,12*Z*)-octadeca-9,12-dienoyl)oxy)octadeca-9,11-dienoate (13-LAHLA methyl ester, 11)

R_f = 0.6 (silica gel, 90:10 hexanes:EtOAc); **1H NMR** (600 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.93 (t, *J* = 11.0 Hz, 1H), 5.55 (m, 1H), 5.47 – 5.27 (m, 6H), 3.66 (s, 3H), 2.76 (t, *J* = 6.9 Hz, 2H), 2.29 (m, 4H), 2.15 (m, 2H), 2.06 – 2.02 (m, 4H), 1.62 (s, 4H), 1.39 – 1.23 (m, 30H), 0.88 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.5, 173.3, 133.7, 131.2, 130.4, 130.2, 128.2, 128.0, 127.7, 74.6, 51.6, 34.8, 34.7, 34.2, 31.7, 29.7, 29.6, 29.5, 29.3, 29.2, 27.9, 27.3, 25.8, 25.2, 25.1, 25.0, 22.7, 14.2; **IR** (film, cm^{-1}): 2926, 2855, 2360, 2341, 1739, 1458, 1171; **MS** (ESI) calc. for $C_{37}H_{64}O_4Na$ $[M+Na]^+$: 595.47, obs. 595.39.

Selective hydrolysis of 13-LAHLA methyl ester 11

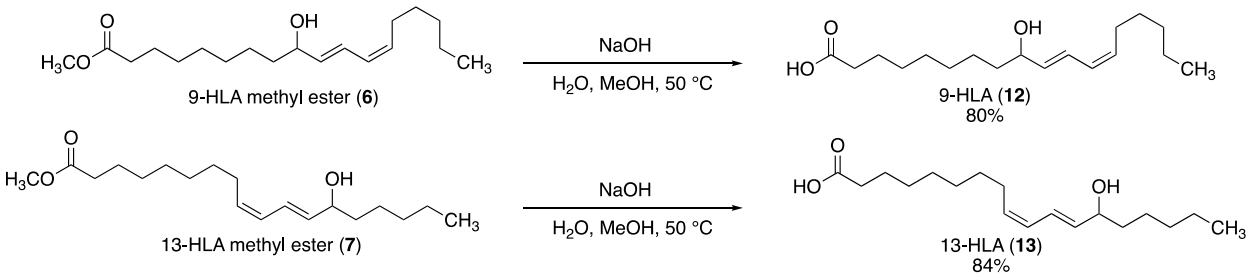
To a stirred solution of 13-LAHLA methyl ester **11** (82 mg, 0.14 mmol, 1.0 eq) in THF (0.7 mL) at 23 °C was added an aqueous solution of lithium hydroxide (0.3 mL, 1 M, 0.30 mmol, 2.0

eq). The reaction mixture was stirred for 24 hours and cooled to 0 °C. The reaction was diluted with 2N aqueous hydrochloric acid (6 mL) and then extracted with ether (15 mL × 3). The combined ether solution was dried over sodium sulfate, filtered and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAC:AcOH (93:6:1) to give the 13-LAHLA **3** (68 mg, 0.12 mmol, 76% for two steps).

(9*Z*,11*E*)-13-(((9*Z*,12*Z*)-octadeca-9,12-dienoyl)oxy)octadeca-9,11-dienoic acid (13-LAHLA, 3)

R_f = 0.4 (silica gel, 80:20 hexanes:EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 15.2, 11.1 Hz, 1H), 5.93 (t, *J* = 11.0 Hz, 1H), 5.55 (dd, *J* = 15.2, 7.5 Hz, 1H), 5.47 – 5.28 (m, 6H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.34 (m, 2H), 2.31 – 2.27 (m, 2H), 2.16 (m, 2H), 2.04 (m, 4H), 1.62 (m, 4H), 1.38 – 1.25 (m, 31H), 0.88 (m, 6H); **^{13}C NMR-DEPTQ** (150 MHz, $CDCl_3$) δ 179.2, 173.5, 133.8, 131.2, 130.4, 130.2, 128.2, 128.1, 128.0, 127.7, 74.8, 34.9, 34.7, 34.0, 31.7, 29.7, 29.5, 29.3, 29.1, 29.0, 27.8, 27.3, 25.8, 25.2, 25.0, 24.8, 22.7, 14.2; **IR** (film, cm^{-1}): 2927, 2854, 2362, 2341, 1735, 1708, 1460, 1174; **HRMS** (ESI) calc. for $C_{36}H_{62}O_4Na$ $[M+Na]^+$: 581.4540, obs. 581.4543.

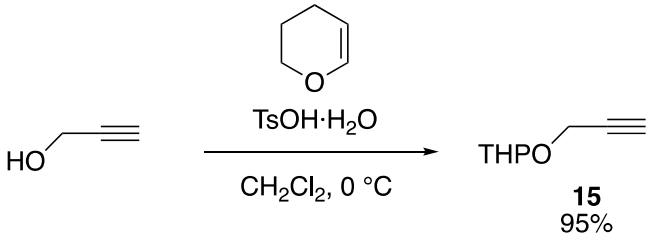
Preparation of 9-HLA (13) and 13-HLA (14)



9-HLA methyl ester **6** (50 mg, 0.16 mmol, 1.0 eq) was dissolved into methanol (5 mL). To the reaction was added 1 M aqueous solution of NaOH (5mL) at 23 °C. The reaction mixture was warmed to 50 °C and stirred for 1 h. The reaction was cooled to 0 °C, diluted with 1N aqueous hydrochloric acid (5 mL), and then extracted with ethyl acetate (10 mL × 3). The combined ethyl acetate solution was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAC:AcOH (50:49:1) to give the 9-HLA **12** (38 mg, 0.13 mmol, 80%). Hydrolysis of 13-HLA methyl ester **7** (50 mg, 0.16 mmol, 1.0 eq) was carried out under same procedure to obtain 13-HLA **13** (40 mg, 0.14 mmol, 84%). Spectra were in agreement with those previously reported.[1]

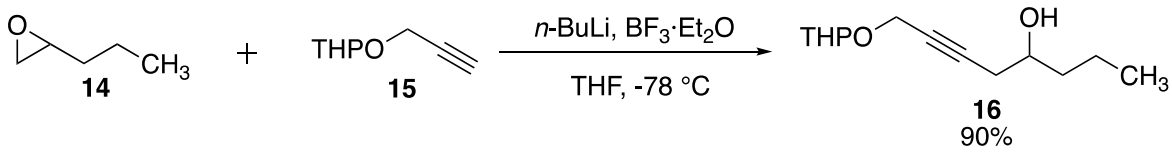
The synthesis of 15-LAHLA and 15-HLA

Preparation of 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (15)



To a solution of 3-butyn-1-ol (4.2 mL, 71.4 mmol, 1.0 eq) in CH_2Cl_2 (100 mL) at 0 °C was added solid $TsOH·H_2O$ (150 mg, 0.7 mmol, 0.01 eq) followed by adding neat 3,4- dihydro-2H-pyran (7.2 mL, 78.5 mmol, 1.1 eq). After stirring at 0 °C for 10 min, the reaction was warmed to 23 °C and stirred for 1 h. The reaction was diluted with saturated sodium bicarbonate (35 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined CH_2Cl_2 solution was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAC (10:1) to give the acetal **15** (9.5 g, 95% yield, R_f = 0.3 in 10:1 hexanes/EtOAc) as an oil. NMR and mass spectrometry were in complete agreement with literature values.[2]

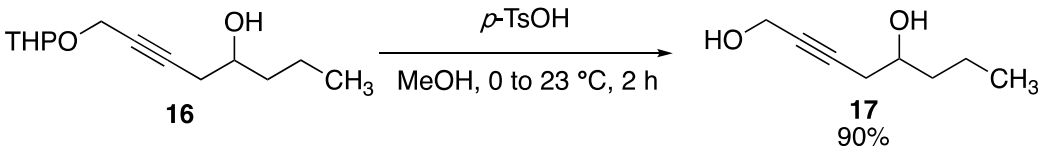
regioselective ring opening of epoxide 14



Under an atmosphere of nitrogen, *n*-BuLi (2.5 M in hexane, 14.4 mL, 36 mmol, 1.0 eq) was added to the solution of **15** (5.0 g, 36 mmol) in anhydrous THF (200 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min. To the reaction was added $BF_3·Et_2O$ (4.5 mL, 36 mmol, 1.0 eq) and stirred at −78 °C for 30 min. Then the reaction mixture was warmed up to 0 °C and stirred for 1 h. After that, the reaction was cooled to −78 °C again and a solution of epoxide **14** (3.0 g, 36 mmol, 1.0 eq) in anhydrous THF (20 mL) was added. The reaction mixture was stirred at −78 °C for another 3 h. The reaction was diluted with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined ethyl acetate solution was washed

with brine (30 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (3:1 to 1:1) to yield **16** (7.3 g, 90%) as an oil. NMR and mass spectrometry were in complete agreement with literature values.[3]

Removal of the THP protecting group

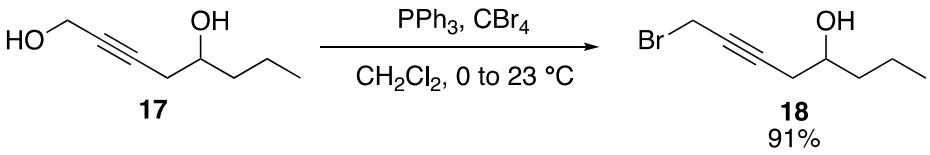


Alcohol **16** (1.3 g, 5.6 mmol, 1.0 eq) was dissolved in methanol (56 mL). Stirring was initiated, giving a clear solution. The reaction was cooled to 0 °C and stirred for 15 min. Solid 4-methylbenzenesulfonic acid (215 mg, 1.1 mmol, 0.2 eq) was added in one portion. The reaction mixture was warmed to 23 °C and stirred for 2 h. The resulting mixture was evaporated under reduced pressure to remove methanol, diluted with ethyl acetate (50 mL). The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL × 2), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (4:1 to 2:1) to yield **17** (724 mg, 90%) as an oil.

oct-2-yne-1,5-diol (17)

R_f = 0.20 (silica gel, 2:1 hexanes:EtOAc, $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 4.24 (t, *J* = 2.3 Hz, 2H), 3.75 (m, 1H), 3.35 (s, OH), 3.00 (s, OH), 2.45 (m, 1H), 2.31 (m, 1H), 1.58 – 1.41 (m, 3H), 1.41 – 1.28 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 82.8, 80.9, 69.9, 51.1, 38.5, 27.6, 19.0, 14.1; **IR** (film, cm^{-1}): 2958, 2872, 1423, 1008; **HRMS** (ESI) calc. for $C_8H_{14}O_2Na$ $[M+Na]^+$: 165.0886, obs. 165.0887.

Selective bromination

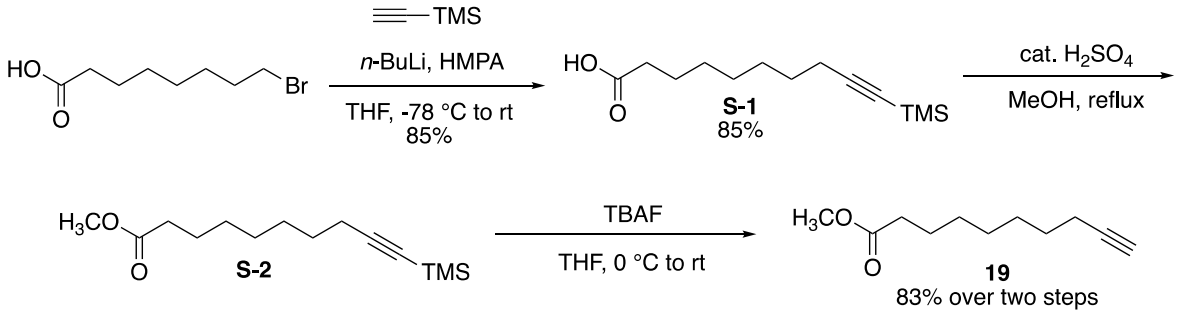


To a solution of oct-2-yne-1,5-diol **17** (724 mg, 5.1 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (51 mL) was added solid triphenylphosphine (1.5 g, 5.6 mmol, 1.1 eq) and carbon tetrabromide (1.8 g, 5.6 mmol, 1.1 eq) at 0 °C. The reaction mixture was warmed to 23 °C and stirred overnight. The solvent was removed under reduced pressure to obtain the crude material, which was purified via flash column chromatography using hexanes:EtOAc (8:1 to 4:1) to yield **18** (946 mg, 91%) as an oil.

8-bromooct-6-yn-4-ol (18)

R_f = 0.80 (silica gel, 2:1 hexanes:EtOAc, $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 3.92 (t, *J* = 2.4 Hz, 2H), 3.75 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.03 (s, OH), 1.55 – 1.46 (m, 2H), 1.46 – 1.40 (m, 1H), 1.40 – 1.28 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 84.5, 77.8, 69.8, 38.5, 28.0, 18.9, 15.4, 14.1. **IR** (film, cm^{-1}): 2958, 2931, 2233, 1424, 1209, 1013. **HRMS** (ESI) calc. for $C_8H_{13}BrONa$ $[M+Na]^+$: 227.0045, obs. 227.0047.

Preparation of known alkyne 19



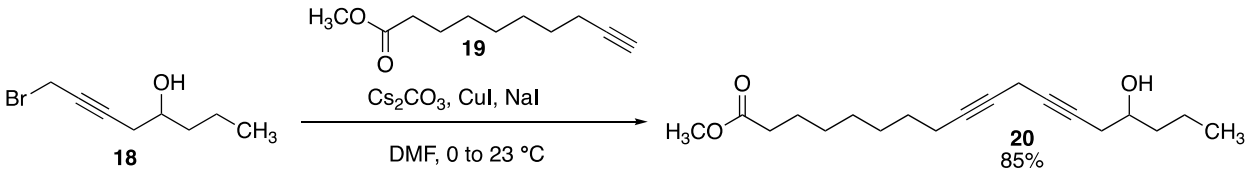
Under an atmosphere of nitrogen, to a solution (trimethylsilyl)acethylene (3.4 mL, 24.0 mmol, 1.8 eq) in anhydrous THF (20 mL) was added *n*-BuLi (2.5M in hexanes, 11.6 mL, 29.0 mmol, 1.2 eq) at –78 °C and stirred for 20 min. To the reaction mixture was added a solution of 8-bromooctanoic acid (3.0 g, 13.5 mmol, 1.0 eq) in anhydrous THF (60 mL) and neat HMPA (40 mL) via syringe at –78 °C, and then stirred for 2 h. The reaction was diluted with saturated aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (50 mL × 3). The combined ethyl acetate solution was washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified via flash silica gel column chromatography using hexane:EtOAc (5:1) to give **S-1** (2.7 g, 85%) as a colorless oil.

A 250 mL round-bottom flask was equipped with stir bar and charged with **S-1** (2.7 g, 11.2 mmol, 1.0 eq) in MeOH (150 mL). Concentrated sulfuric acid (3 mL) was added at 23 °C. The

reaction was warmed to reflux and stirred for 2 h. The solvent was then removed under reduced pressure to obtain the crude material, which was dissolved into ethyl acetate (200 mL). The ethyl acetate was washed with saturated aqueous sodium bicarbonate (30 mL) and brine (30 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product **S-2**, which was then used for the next step without any purification.

To a solution of crude **S-2** (2.7g) in THF (100 mL) was added TBAF (1.0 M in THF, 15.5 mL, 15.5 mmol, 1.5 eq) at 23 °C and stirred overnight. The reaction was diluted with brine (30 mL) and extracted with ethyl acetate (50 mL × 3). The combined ethyl acetate solution was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified via flash silica gel column chromatography using hexane/EtOAc (50:1 to 30:1) to give alkyne **19** (1.7 g, 83% over two steps) as an oil. NMR and mass spectrometry were in complete agreement with literature values.[4]

copper-catalyzed cross coupling reaction



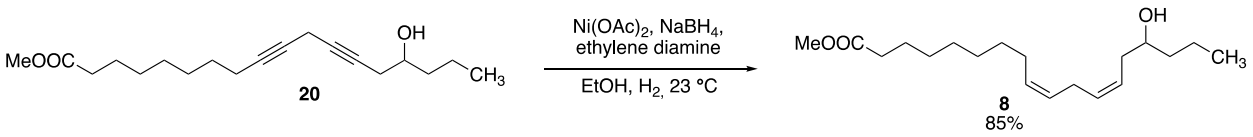
Under an atmosphere of nitrogen, the known alkyne **19** (556 mg, 3 mmol, 1.5 eq) was dissolved in anhydrous N, N-dimethlyformaide (20 mL). Stirring was initiated, giving a clear solution. The reaction was cooled to 0 °C and stirred for 15 min. To the reaction was added NaI (457 mg, 3 mmol, 1.5 eq), CuI (580 mg, 3.0 mmol, 1.5 eq) and Cs_2CO_3 (994 mg, 3.0 mmol, 1.5 eq). The reaction mixture was stirred at 0 °C for 20 minutes and the color changed to green. A solution of 8-bromooct-6-yn-4-ol **18** (415 mg, 2.0 mmol, 1.0 eq) in anhydrous N, N-dimethlyformaide (10 mL) was added by syringe and the reaction was stirred at 0 °C for 10 minutes. The reaction was warmed to 23 °C and stirred overnight. The reaction was diluted with saturated aqueous ammonium chloride (10 mL). The reaction mixture was stirred vigorously until the color changed to blue. The resulting mixture was extracted with ethyl acetate (15 mL × 3). The combined ethyl acetate organics were washed with brine (10 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography

using hexanes:EtOAc (8:1 to 4:1) to yield **20** (530 mg. 85%) as an oil, which was dissolved in ethyl acetate, stored at 0 °C, and used for the next step as soon as possible.

methyl 15-hydroxyoctadeca-9,12-diynoate (20)

R_f = 0.40 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 3.72 (m, 1H), 3.65 (s, 3H), 3.13 (m, 2H), 2.39 (m, 1H), 2.32 – 2.25 (m, 3H), 2.13 (m, 2H), 1.98 (br s, OH), 1.64 – 1.57 (m, 2H), 1.51 – 1.43 (m, 4H), 1.39 – 1.30 (m, 8H), 0.95 – 0.89 (m, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 174.5, 80.8, 77.5, 76.8, 74.2, 69.9, 51.6, 38.5, 34.2, 29.1, 28.9, 28.8, 28.7, 27.9, 25.0, 19.0, 18.9, 14.1, 9.9; **IR** (film, cm^{-1}): 2933, 2858, 1736, 1439, 1172. **HRMS** (ESI) calc. for $C_{19}H_{30}O_3Na$ $[M+Na]^+$: 329.2091, obs. 329.2093.

Semihydrogenation of the skipped diynes



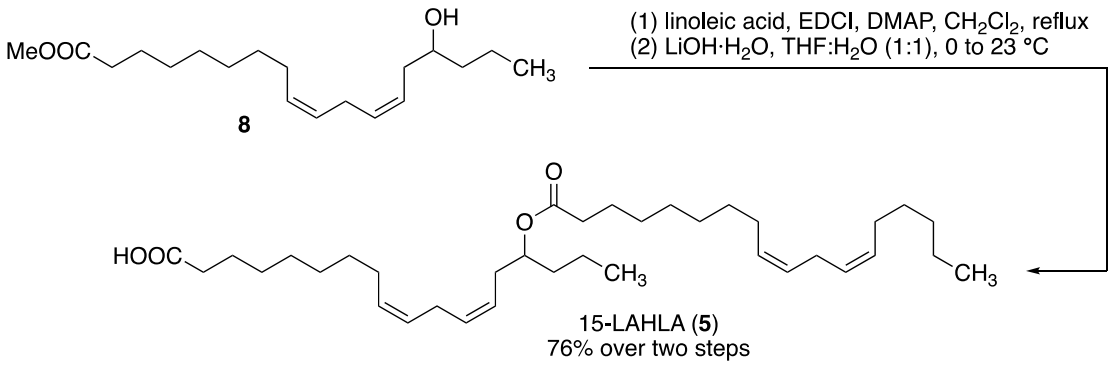
A flask was charged with nickel acetate tetrahydrate (431 mg, 1.7 mmol, 1.0 eq) and ethanol (25 mL). The solution was purged with H_2 gas and a suspension of $NaBH_4$ (65 mg, 1.7 mmol, 1.0 eq) in ethanol (5 mL) was added. The color of reaction mixture immediately turned to black. The reaction was stirred at 23 °C for 20 min. Neat ethylenediamine (0.35 mL, 5.1 mmol, 3.0 eq) was added, followed by adding a solution of the skipped diyne **20** (530 mg, 1.7 mmol, 1.0 eq) in ethanol (5 mL). The reaction was stirred vigorously at 23 °C for 30 min. The reaction was filtered through celite and washed with ethyl acetate (100 mL). The filtrate was concentrated in vacuo. The concentrate was diluted in hexanes:EtOAc (4:1, 50 mL), washed with brine (10 mL × 2), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (12:1 to 8:1) to yield **8** (455 mg, 85%) as an oil.

methyl (9*Z*,12*Z*)-15-hydroxyoctadeca-9,12-dienoate (8)

R_f = 0.50 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.57– 5.51 (m, 1H), 5.47 – 5.29 (m, 3H), 3.66 (s, 3H), 3.64 (s, 1H), 2.84 – 2.76 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.24 (m, 2H), 2.04 (m, 2H), 1.65 – 1.23 (m, 14H), 0.97 – 0.90 (m, 3H). **^{13}C-NMR** (150 MHz, $CDCl_3$): δ 174.5, 131.6, 130.6, 127.6, 125.7, 71.3, 51.6, 39.2, 35.5, 34.2, 29.7, 29.3, 29.2, 27.4,

25.9, 25.1, 19.1, 14.3. **IR** (film, cm^{-1}): 2928, 2856, 1736, 1437, 1172; **HRMS** (ESI) calc. for $C_{19}H_{34}O_3Na$ $[M+Na]^+$: 333.2400, obs. 333.2403.

Esterification and selective hydrolysis of the methyl ester



Under an atmosphere of nitrogen, neat linoleic acid (30 μL, 0.1 mmol, 2.0 eq) was dissolved in anhydrous CH_2Cl_2 (3 mL). Stirring was initiated, giving a clear solution. The reaction was cooled to 0 °C and stirred for 15 min. To the reaction was added solid EDCI (19 mg, 0.1 mmol, 2.0 eq) and DMAP (12 mg, 0.1 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 20 min. A solution of **8** (15 mg, 0.05 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (1 mL) was added. The reaction was warmed to reflux and stirred overnight. The solvent was then removed under reduced pressure and the crude material was purified via flash column chromatography using hexanes:EtOAc (10:1 to 6:1) to get the intermediate (22 mg).

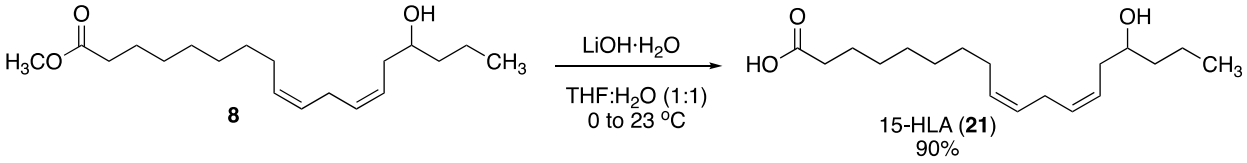
The intermediate (22 mg) was dissolved in THF:H_2O (3 mL : 3 mL), cooled to 0 °C, and stirred for 15 min. To the reaction was added $LiOH·H_2O$ (10 mg, 0.23 mmol, 6.0 eq) in one portion. The reaction was warmed to 23 °C and stirred overnight. The reaction was diluted with 1N aqueous hydrochloric acid (2 mL) and extracted with ethyl acetate (8 mL × 3). The combined ethyl acetate solution was washed with brine (5 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc:acetic acid (75:23:2) to yield **15-LAHLA** (20 mg, 76% over two steps) as an oil.

(9*Z*,12*Z*)-15-(((9*Z*,12*Z*)-octadeca-9,12-dienoyl)oxy)octadeca-9,12-dienoic acid (15-LAHLA, 5)

R_f = 0.20 (silica gel, 3:1 hexanes:EtOAc, $KMnO_4$); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.44 (m, 1H), 5.34 (m, 7H), 4.91 (m, 1H), 2.77 (t, *J* = 6.8 Hz, 4H), 2.37 – 2.24 (m, 6H), 2.04 (m, 6H), 1.62 (m, 4H), 1.52 (m, 2H), 1.32 (m, 24H), 0.89 (m, 6H). **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 179.8, 173.8,

130.8, 130.5, 130.3, 130.2, 128.2, 128.0, 127.6, 124.7, 73.5, 36.0, 34.8, 34.1, 32.2, 31.7, 29.8, 29.7, 29.5, 29.3, 29.2, 27.3, 25.9, 25.8, 25.2, 24.8, 22.7, 18.8, 14.2, 14.1; **IR** (film, cm^{-1}): 3010, 2926, 2855, 1733, 1709, 1464, 1179; **HRMS** (ESI) calc. for $C_{36}H_{61}O_4$ $[M-H]^-$: 557.4577, obs. 557.4575.

Preparation of 15-HLA



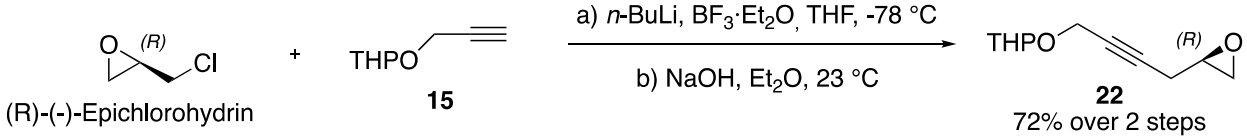
The 15-HLA methyl ester **8** (40 mg, 0.13 mmol, 1.0 eq) was dissolved in THF:H_2O (4 mL : 4 mL), cooled to 0 °C, and stirred for 15 min. To the reaction was added solid LiOH·H_2O (33 mg, 0.77 mmol, 6.0 eq) in one portion. The reaction was warmed to 23 °C and stirred overnight. The reaction was diluted with 1N aqueous hydrochloric acid (3 mL) and extracted with ethyl acetate (10 mL × 3). The combined ethyl acetate solution was washed with brine (5 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc:acetic acid (66:32:2) to yield **15-HLA 21** (34 mg, 90%) as an oil.

(9*Z*,12*Z*)-15-hydroxyoctadeca-9,12-dienoic acid (15-HLA, 21)

$\mathbf{R_f}$ = 0.20 (silica gel, 2:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.52 (m, 1H), 5.45 – 5.28 (m, 3H), 3.65 (m, 1H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.32 (m, 2H), 2.23 (m, 2H), 2.02 (m, 2H), 1.62 (m, 2H), 1.49 – 1.23 (m, 12H), 0.91 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 179.6, 131.4, 130.5, 127.6, 125.5, 71.4, 39.0, 35.3, 34.2, 29.6, 29.2, 29.1, 27.3, 25.9, 24.8, 19.0, 14.2. **IR** (film, cm^{-1}): 3340, 3010, 2856, 1710, 1465. **HRMS** (ESI) calc. for $C_{18}H_{31}O_3$ $[M-H]^-$: 295.2279, obs. 295.2278.

Synthesis of enantiopure S-15-LAHLA (5-*S*) and R-15-LAHLA (5-*R*)

regioselective ring opening and epoxide formation



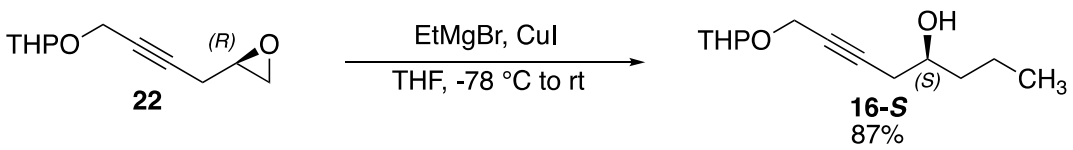
Under an atmosphere of nitrogen, *n*-BuLi (2.5 M in hexane, 8.5 mL, 21 mmol, 1.0 eq) was added to a solution of **15** (3.0 g, 21 mmol, 1.0 eq) in anhydrous THF (120 mL) at −78 °C and then stirred for 15 min. To the reaction was added $BF_3 \cdot Et_2O$ (2.7 mL, 21 mmol, 1.0 eq) and stirred at −78 °C for 30 min. Then the reaction was warmed to 0 °C and stirred for 1 h. After that, the reaction was cooled to −78 °C again and a solution of (R)-(−)-epichlorohydrin (2.0 g, 21 mmol, 1.0 eq) in anhydrous THF (20 mL) was added. The reaction was stirred at −78 °C for another 3 h. The reaction was diluted with saturated aqueous ammonium chloride (40 mL) and extracted with ethyl acetate (40 mL × 3). The combined ethyl acetate solution was washed with brine (30 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via flash silica gel column chromatography to afford the chlorohydrin intermediate (4.4 g), which was used for the next step directly.

Under an atmosphere of nitrogen, the chlorohydrin intermediate (4.4 g, 19.0 mmol, 1.0 eq) was dissolved in anhydrous ether (55 mL). Stirring was initiated, giving a clear solution. Solid sodium hydroxide (4.6 g, 144 mmol, 6.0 eq) was added in one portion at 23 °C and stirred vigorously for 24 h. The reaction mixture was vacuum filtered into a dry flask containing 4Å mole sieves, rinsing the filter cake with anhydrous ether (25 mL × 3). The combined ether solution was then removed under reduced pressure. The crude material was purified via flash column chromatography using hexanes:EtOAc (10:1 to 6:1) to yield epoxide **22** (3.0 g, 72% over two steps) as an oil. Spectra were in agreement with those previously reported.[5]

2-((4-((*R*)-oxiran-2-yl)but-2-yn-1-yl)oxy)tetrahydro-2*H*-pyran (22)

R_f = 0.5 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 4.75 (t, *J* = 3.5 Hz, 1H), 4.21 (m, 2H), 3.79 (m, 1H), 3.49 (m, 1H), 3.07 (m, 1H), 2.75 (t, *J* = 4.4 Hz, 1H), 2.62 (m, 2H), 2.47 (m, 1H), 1.79 (m, 1H), 1.70 (m, 1H), 1.57 (m, 2H), 1.50 (m, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 96.8, 80.6, 78.3, 62.0, 54.5, 49.9, 46.5, 30.3, 25.4, 22.7, 19.1.

regioselective ring opening

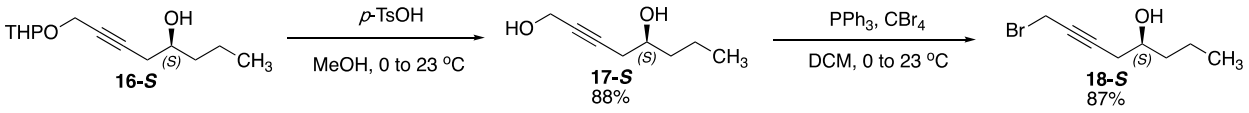


Under an atmosphere of nitrogen, the epoxide **22** (3.0 g, 15.3 mmol, 1.0 eq) and solid copper (I) iodide (292 mg, 1.5 mmol, 0.1 eq) were dissolved in anhydrous THF (100 mL). The reaction mixture was cooled to −78 °C and stirred for 20 min. Ethylmagnesium bromide (1.0 M in THF, 23 mL, 1.5 eq) was added dropwise over 20 min and stirred at −78 °C for 1 h. The reaction mixture was warmed to 23 °C and stirred for 5 h. The reaction was diluted with saturated aqueous ammonium chloride (30 mL). The reaction mixture was stirred vigorously until the color changed to a brilliant, royal blue. The reaction mixture was extracted with ethyl acetate (50 mL x 3). The combined ethyl acetate solution was washed with brine (30 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (3:1 to 1:1) to yield **16-*S*** (3.0 g, 87%) as an oil. Spectra were in complete agreement with literature values.[3]

(4*S*)-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-6-yn-4-ol (16-*S*)

R_f = 0.2 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 4.78 (t, *J* = 3.6 Hz, 1H), 4.31 – 4.16 (m, 2H), 3.82 (m, 1H), 3.72 (m, 1H), 3.50 (m, 1H), 2.47 – 2.39 (m, 1H), 2.32 (m, 1H), 2.20 (s, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.63 – 1.39 (m, 7H), 1.34 (m, 1H), 0.90 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 97.0, 83.1, 78.5, 69.8, 62.1, 54.8, 38.5, 30.4, 27.9, 25.4, 18.9, 14.1. **HRMS** (ESI) calc. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1461, obs. 249.1460.

Removal of the THP protecting group and Selective bromination



The alcohol **16-*S*** (1.0 g, 4.4 mmol, 1.0 eq) was dissolved in methanol (40 mL). Stirring was initiated, giving a clear solution. The reaction was cooled to 0 °C and stirred for 15 min. Solid 4-methylbenzenesulfonic acid (17 mg, 0.9 mmol, 0.2 eq) was added in one portion. The reaction was warmed to 23 °C and stirred for 2 h. The reaction mixture was evaporated under reduced pressure to remove methanol, diluted with ethyl acetate (30 mL). The ethyl acetate solution was washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL × 2), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel

column chromatography using hexanes:EtOAc (4:1 to 2:1) to yield oct-2-yne-1,5-diol **17-*S*** (553 mg, 88%) as an oil.

(*S*)-oct-2-yne-1,5-diol (17-*S*)

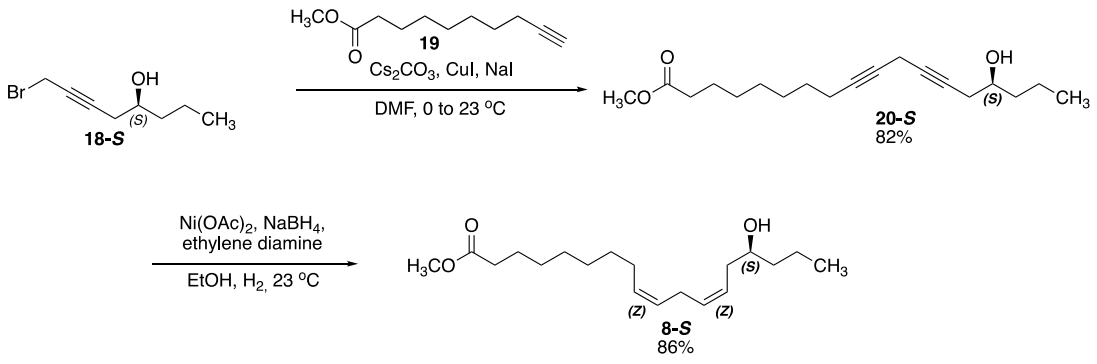
R_f = 0.20 (silica gel, 2:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.20 (t, *J* = 2.4 Hz, 2H), 4.20 (s, OH), 3.72 (m, 1H), 3.67 (brs, OH), 2.41 (m, 1H), 2.27 (m, 1H), 1.54 – 1.36 (m, 3H), 1.31 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 82.7, 80.7, 69.8, 50.8, 38.4, 27.5, 18.9, 14.0. **IR** (film, cm^{-1}): 2958, 2872, 1423, 1008; **HRMS** (ESI) calc. for $C_8H_{14}O_2Na$ $[M+Na]^+$: 165.0886, obs. 165.0887.

To a solution of oct-2-yne-1,5-diol **17-*S*** (553 mg, 3.9 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (35 mL) was added triphenylphosphine (1.1 g, 4.3 mmol, 1.1 eq) and carbon tetrabromide (1.4 g, 4.1 mmol, 1.1 eq) at 0 °C. The reaction was warmed to 23 °C and stirred overnight. The solvent was removed under reduced pressure and the crude material was purified via column chromatography using hexanes:EtOAc (8:1 to 4:1) to yield **18-*S*** (691 mg, 87%) as an oil.

(*S*)-8-bromooct-6-yn-4-ol (18-*S*)

R_f = 0.80 (silica gel, 2:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 3.92 (t, *J* = 2.4 Hz, 2H), 3.76 (m, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 1.93 (d, *J* = 3.8 Hz, OH), 1.54 – 1.40 (m, 3H), 1.40 – 1.31 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 84.5, 77.8, 69.8, 38.6, 28.0, 18.9, 15.3, 14.1. **IR** (film, cm^{-1}): 2960, 2930, 2871, 2232, 1425, 1208, 1011. **HRMS** (ESI) calc. for $C_8H_{13}BrONa$ $[M+Na]^+$: 227.0046, obs. 227.0047.

Copper-catalyzed cross coupling reaction and Semihydrogenation of the skipped diynes



Under an atmosphere of nitrogen, the known alkyne **19** (270 mg, 2 mmol, 1.5 eq) was dissolved in anhydrous N, N-dimethlyformaide (15 mL). Stirring was initiated, giving a clear

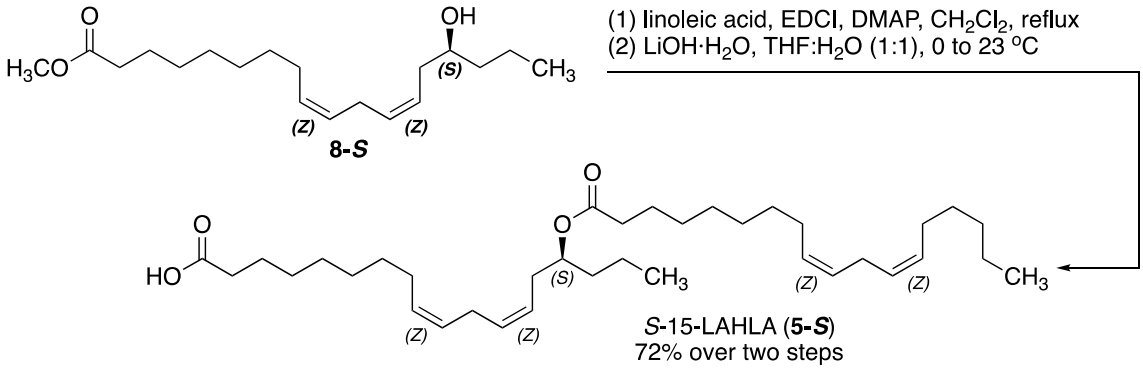
solution. The reaction was cooled to 0 °C and stirred for 15 min. To the reaction was added NaI (305 mg, 2 mmol, 1.5 eq), CuI (387 mg, 2.0 mmol, 1.5 eq) and Cs_2CO_3 (663 mg, 2.0 mmol, 1.5 eq). The reaction mixture was stirred at 0 °C for 20 min, and the color changed to green. A solution of (*S*)-8-bromooct-6-yn-4-ol **(18-*S*)** (277 mg, 1.3 mmol, 1.0 eq) in anhydrous N, N-dimethlyformaide (5 mL) was added into the reaction mixture at 0 °C and stirred for 10 min. The reaction was warmed to 23 °C and stirred overnight. The reaction was diluted with saturated aqueous ammonium chloride (10 mL). The mixture was stirred vigorously until the color changed to blue. The resulting mixture was extracted with ethyl acetate (15 mL × 3). Combined ethyl acetate solution was washed with brine (10 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (8:1 to 4:1) to yield **20-*S*** (326 mg, 82%) as an oil, which was dissolved in ethyl acetate for storage and used for next step as soon as possible.

A flask was charged with nickel acetate tetrahydrate (265 mg, 1.1 mmol, 1.0 eq) and 95% ethanol (20 mL). The reaction mixture was purged with H_2 gas, and then a suspension of $NaBH_4$ (42 mg, 1.7 mmol, 1.0 eq) in ethanol (5 mL) was added at 23 °C. The reaction immediately turned a black color. The reaction was stirred at 23 °C for 20 min. Neat Ethylenediamine (0.22 mL, 3.3 mmol, 3.0 eq) was added, followed by adding a solution of the skipped diyne **20-S** (326 mg, 1.1 mmol, 1.0 eq) in ethanol (5 mL). The reaction was stirred vigorously under H_2 atmosphere at 23 °C. After 30 min, the reaction was filtered through celite and washed with ethyl acetate. The filtrate was concentrated in vacuo. The crude product was diluted in hexanes:EtOAc (4:1, 50 mL) and the organic solution was washed with brine (10 mL × 2), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (12:1 to 8:1) to yield **8-*S*** (293 mg, 86%) as an oil.

methyl (*S*,9*Z*,12*Z*)-15-hydroxyoctadeca-9,12-dienoate (8-S)

R_f = 0.50 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.58 – 5.50 (m, 1H), 5.47 – 5.29 (m, 3H), 3.66 (s, 4H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.24 (m, 2H), 2.04 (m, 2H), 1.66 – 1.56 (m, 2H), 1.46 (m, 2H), 1.39 – 1.32 (m, 2H), 1.29 (m, 8H), 0.93 (t, *J* = 6.8 Hz, 3H).**^{13}C NMR** (150 MHz, $CDCl_3$) δ 174.5, 131.6, 130.6, 127.6, 125.7, 71.3, 51.6, 39.2, 35.5, 34.2, 29.7, 29.3, 29.2, 27.4, 25.9, 25.1, 19.1, 14.3. **IR** (film, cm^{-1}): 2929, 2855, 1735, 1438, 1170; **HRMS** (ESI) calc. for $C_{19}H_{34}O_3Na$ $[M+Na]^+$: 333.2400, obs. 333.2397.

Esterification and selective hydrolysis of the methyl ester



Under an atmosphere of nitrogen, neat linoleic acid (0.2 mL, 0.65 mmol, 2.0 eq) was dissolved into anhydrous CH_2Cl_2 (10 mL). Stirring was initiated, giving a clear solution. The reaction was cooled to 0 °C for 15 min before adding solid EDCI (124 mg, 0.65 mmol, 2.0 eq) and DMAP (79 mg, 0.65 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 20 min. A solution of **8-*S*** (100 mg, 0.32 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (5 mL) was added. The reaction was warmed to reflux and stirred overnight. The solvent was then removed under reduced pressure and the crude material was purified via flash column chromatography using hexanes:EtOAc (10:1 to 6:1) to get the intermediate (165 mg).

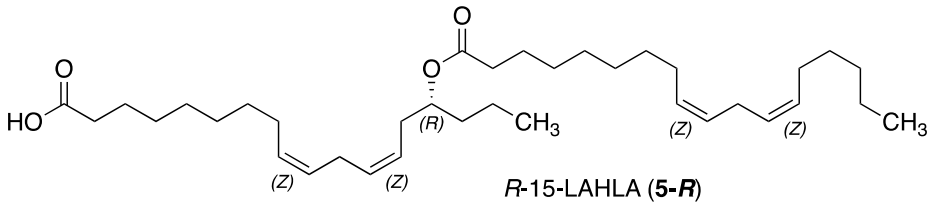
The intermediate (165 mg) was dissolved in THF:H_2O (8 mL : 8 mL) and cooled to 0 °C and stirred for 15 min before adding LiOH·H_2O (73 mg, 1.7 mmol, 6.0 eq) in one portion. The reaction was warmed to 23 °C and stirred overnight. The reaction was diluted with 1N aqueous hydrochloric acid (2 mL) and extracted with ethyl acetate (10 mL × 3). The combined ethyl acetate solution was washed with brine (5 mL), dried over sodium sulfate, filtered, and then concentrated in vacuo. The crude material was purified by silica gel column chromatography using hexanes:EtOAc:acetic acid (75:23:2) to yield **S-15-LAHLA** (**5-*S***, 128 mg, 72% over two steps) as an oil.

(9*Z*,12*Z*)-15-(((9*Z*,12*Z*)-octadeca-9,12-dienoyl)oxy)octadeca-9,12-dienoic acid (*S*-15-LAHLA, 5-*S*)

R_f = 0.20 (silica gel, 3:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 5.44 (m, 1H), 5.34 (m, 7H), 4.91 (m, 1H), 2.77 (t, *J* = 7.0 Hz, 4H), 2.34 (m, 3H), 2.31 (m, 1H), 2.27 (m, 2H), 2.04 (m, 6H), 1.62 (m, 4H), 1.57 – 1.47 (m, 2H), 1.31 (m, 24H), 0.89 (m, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 179.6, 173.8, 130.8, 130.5, 130.4, 130.2, 128.2, 128.0, 127.6, 124.7, 73.5, 36.0, 34.8, 34.1, 32.2, 31.7, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 27.3, 25.9, 25.8, 25.2, 24.8, 22.7,

18.8, 14.2, 14.1. $[\alpha]_D^{23} = -16.9$ (*c* 1.8, $CHCl_3$), **IR** (film, cm^{-1}): 3011, 2925, 2855, 1732, 1710, 1465, 1180; **HRMS** (ESI) calc. for $C_{36}H_{62}O_4Na$ $[M+Na]^+$: 581.4540, obs. 581.4534.

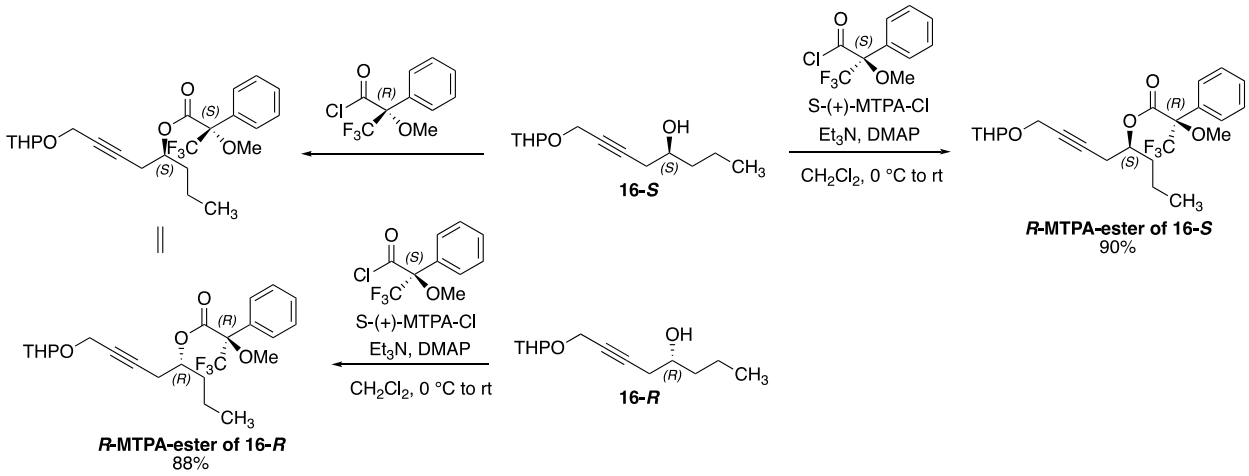
Preparation of R-15-LAHLA (5-R)



R-15-LAHLA (**5-*R***)

R-15-LAHLA (**5-*R***) was obtained through the same ten step sequence with substituting (S)-(+)-epichlorohydrin at the start of the synthesis (in place of (R)-(−)-epichlorohydrin). NMR and mass spectrometry were in complete agreement with S-15-LAHLA (**5-*S***) values. $[\alpha]_D^{23} = +7.3$ (*c* 1.2, $CHCl_3$).

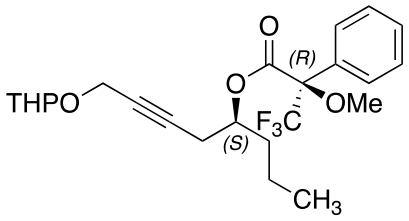
Determination of % ee by the Mosher ester method.



General procedure

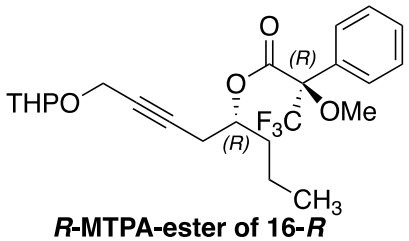
Under an atmosphere of nitrogen, to a stirred solution of alcohol **16-S** (50 mg, 0.22 mmol, 1.0 eq) in dry CH_2Cl_2 (10 mL) was added neat Et_3N (37 μL, 0.27 mmol, 1.2 eq), solid DMAP (3 mg, 0.02 mmol, 0.1 eq) and neat S-(+)-MTPA-Cl (50 μL, 0.27 mmol, 1.2 eq) at 0 °C. The reaction mixture was warmed to 23 °C and stirred overnight. The reaction was diluted with saturate aqueous sodium bicarbonate (2 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined CH_2Cl_2 solution

was washed with brine (8 mL), dried over Na_2SO_4, filtered, and then concentrated in vacuo. The crude material was purified via silica gel column chromatography using hexanes:EtOAc (10:1 to 5:1) to yield **R-MTPA-ester** of **16-S**. **R-MTPA-ester** of **16-R** was obtained under the same procedure starting from **16-R**.



R*-MTPA-ester of 16-*S

R_f = 0.5 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.54 (m, 2H), 7.42 – 7.37 (m, 3H), 5.20 – 5.12 (m, 1H), 4.74 (m, 1H), 4.23 – 4.09 (m, 2H), 3.81 (m, 1H), 3.54 (s, 3H), 3.50 (m, 1H), 2.55 (m, 2H), 1.85 – 1.67 (m, 4H), 1.62 – 1.55 (m, 2H), 1.55 – 1.30 (m, 4H), 0.93 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.3, 132.2, 129.7, 128.5, 127.6, 123.4 (q, *J* = 288.4 Hz), 96.8, 81.1, 78.5, 74.8, 62.2, 55.6, 54.4, 35.2, 30.4, 25.5, 24.1, 19.2, 18.5, 13.9. **IR** (film, cm^{-1}): 2958, 2856, 1738. **HRMS** (ESI) calc. for $C_{23}H_{29}F_3O_5NH_4$ $[M+NH_4]^+$: 460.2305, obs. 460.2298. The % *ee* was determined from the analysis by ^{1}H NMR. The methoxy group of ***R*-MTPA-ester** of **16-*S*** with signals at δ 3.60 and 3.54 in a 1:99 ratio and 98% *ee* for **16-*S***.



R*-MTPA-ester of 16-*R

R_f = 0.5 (silica gel, 4:1 hexanes:EtOAc, $KMnO_4$); **^{1}H NMR** (600 MHz, Chloroform-*d*) δ 7.58 (m, 2H), 7.42 – 7.37 (m, 3H), 5.18 (m, 1H), 4.79 – 4.75 (m, 1H), 4.29 – 4.16 (m, 2H), 3.82 (m, 1H), 3.61 (s, 3H), 3.53 – 3.48 (m, 1H), 2.70 – 2.54 (m, 2H), 1.86 – 1.77 (m, 1H), 1.70 (m, 2H), 1.64 – 1.48 (m, 5H), 1.31 – 1.14 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.3, 132.5, 129.7, 128.5, 127.4, 123.4 (q, *J* = 288.4 Hz), 96.9, 81.4, 78.8, 74.8, 62.2, 55.8, 54.5, 35.1, 30.4, 25.5, 24.3, 19.3, 18.2, 13.8. **IR** (film, cm^{-1}): 2958, 2856, 1738. **HRMS** (ESI) calc. for $C_{23}H_{29}F_3O_5NH_4$ $[M+NH_4]^+$: 460.2305, obs. 460.2300. The % *ee* was determined from the analysis

by ^{1}H NMR. The methoxy group of ***R*-MTPA-ester** of **16-*R*** with signals at δ 3.61 and 3.54 in a 99:1 ratio and 98% *ee* for **16-*R***.

Analytical and Bioactivity Assays

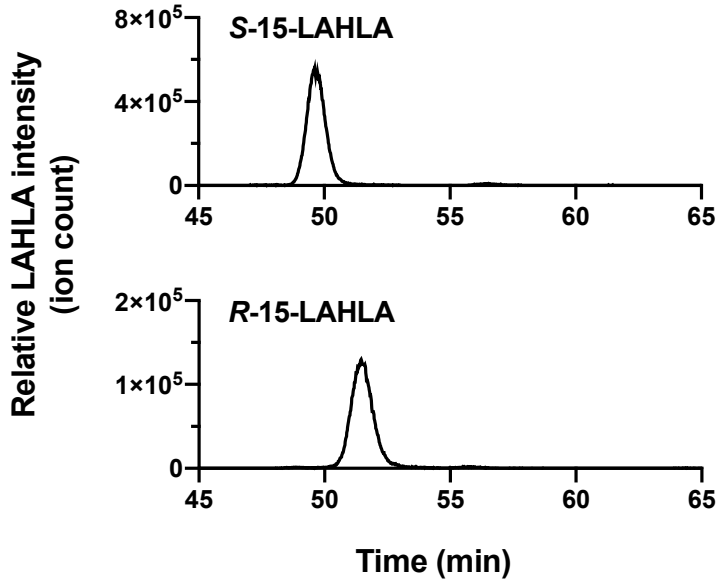


Figure S1. LC-MS chromatograms of *S*-15-LAHLA (top panel) and *R*-15-LAHLA (bottom panel).

Culturing. RAW 264.7 cells were cultured in RPMI 1640 (Gibco), supplemented with L-glutamine (2mM), 10% FBS at 37 °C and 5% CO_2. All experiments were performed on or prior to passage 15.

Quantification of IL-6 upon LPS Stimulation Assay. RAW 264.7 cells were seeded onto 48-well plates (2.5×10^4 cells per well) a day prior to treatment. Once adhered to the wells, cell were treated with DMSO or LPS (100 ng/mL) and compounds of interest individually at 25 μM. Supernantants were collected 20 hours post-treatment and subjected to IL-6 quantification using mouse IL-6 ELISA MAX^{TM} Deluxe Kits (BioLegend). Adherent cells were subjected to MTT cell viability assay to quantify the percentage of viable cells.

Post-Treatment Analysis of Cell Proliferation using MTT Assay. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was dissolved in sterile PBS (5 mg/mL) and filtered through a 0.22 μm Sterile Millex Filter to prepare a 500 μg/mL solution in RPMI. Prepared solution was added to adherent cells and incubated at 37 °C for 4 hours. Sterile DMSO was then

supplied upon removal of MTT solution. Relative cell viabilities were quantified using a plate reader at an absorbance of 570 nm.

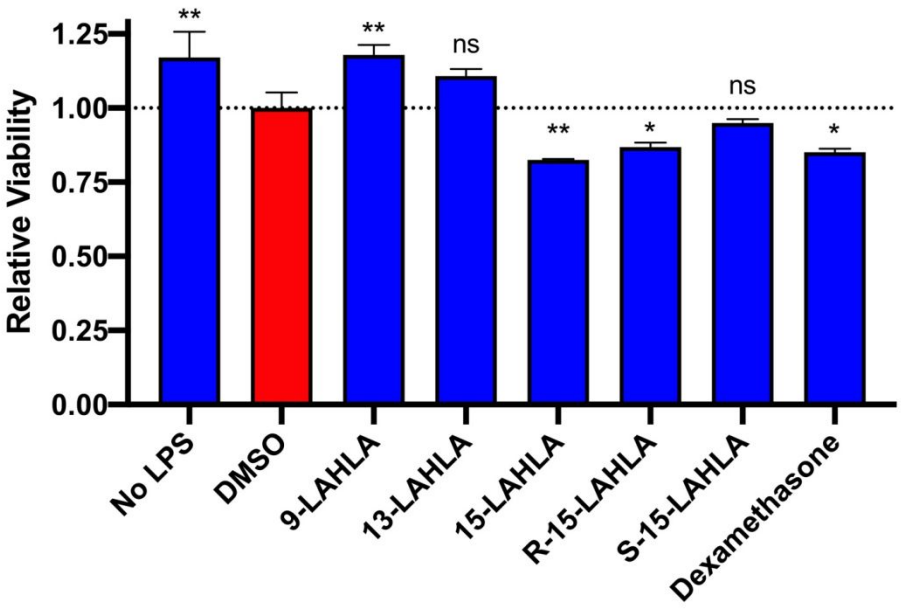


Figure S2. Measuring cell viability of RAW 264.7 cells. Upon removal of media post-treatment, adherent cells were subjected to MTT cell viability assay. Data are means ± S.E.M with n = 3 per treatment. *p, < 0.05; **p, < 0.01 versus DMSO by one-way ANOVA.

Figure S3 need to be changed.

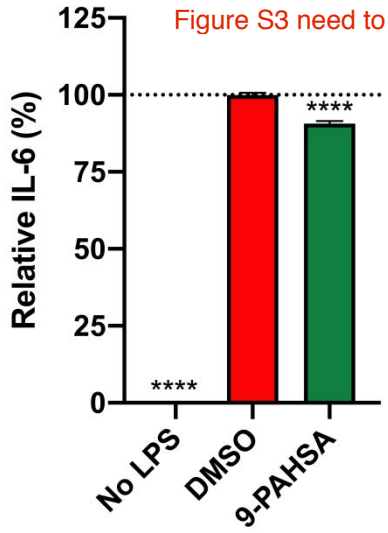


Figure S3. Inhibition of Interleukin-6 (IL-6) by 9-PAHSA. Quantitation of IL-6 following a 20-hour treatment of 9-PAHSA at 25 μM. Data are means ± S.E.M with n = 3 per treatment group. ****p, < 0.0001 versus DMSO by one-way ANOVA.

Change "****p" to "*p".

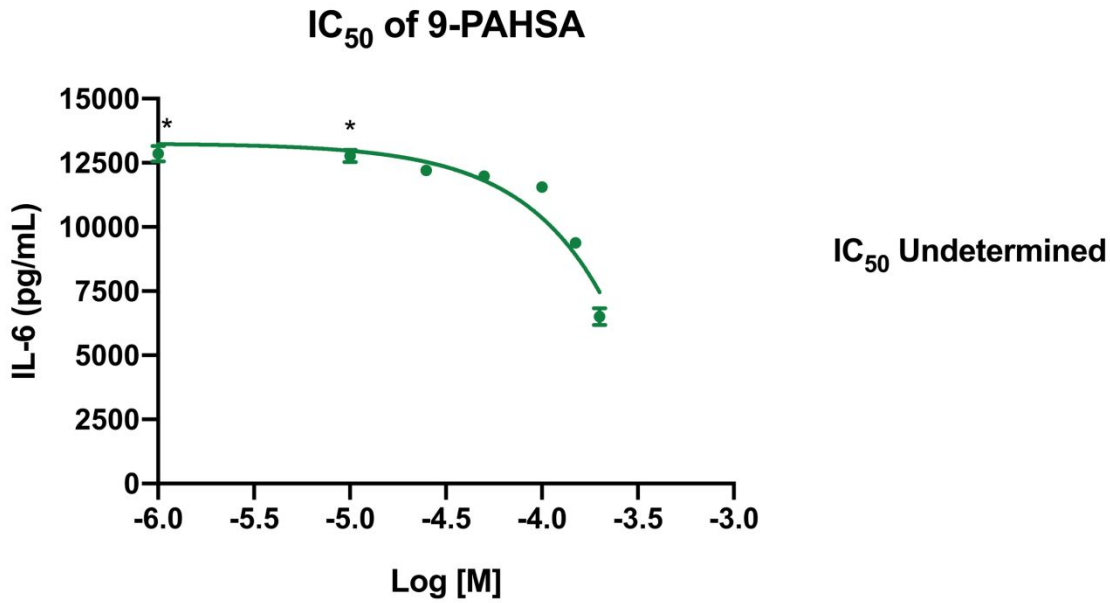
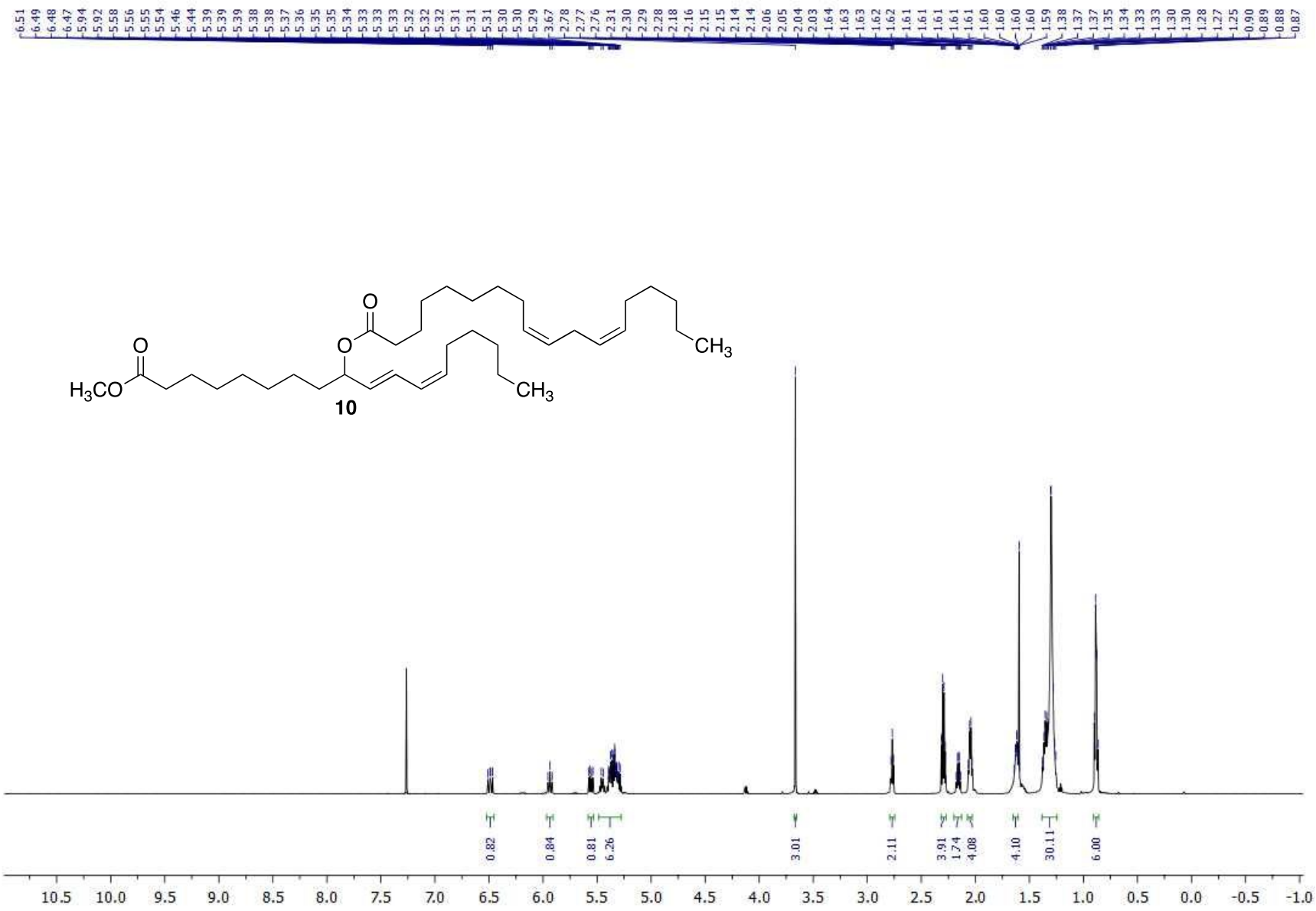
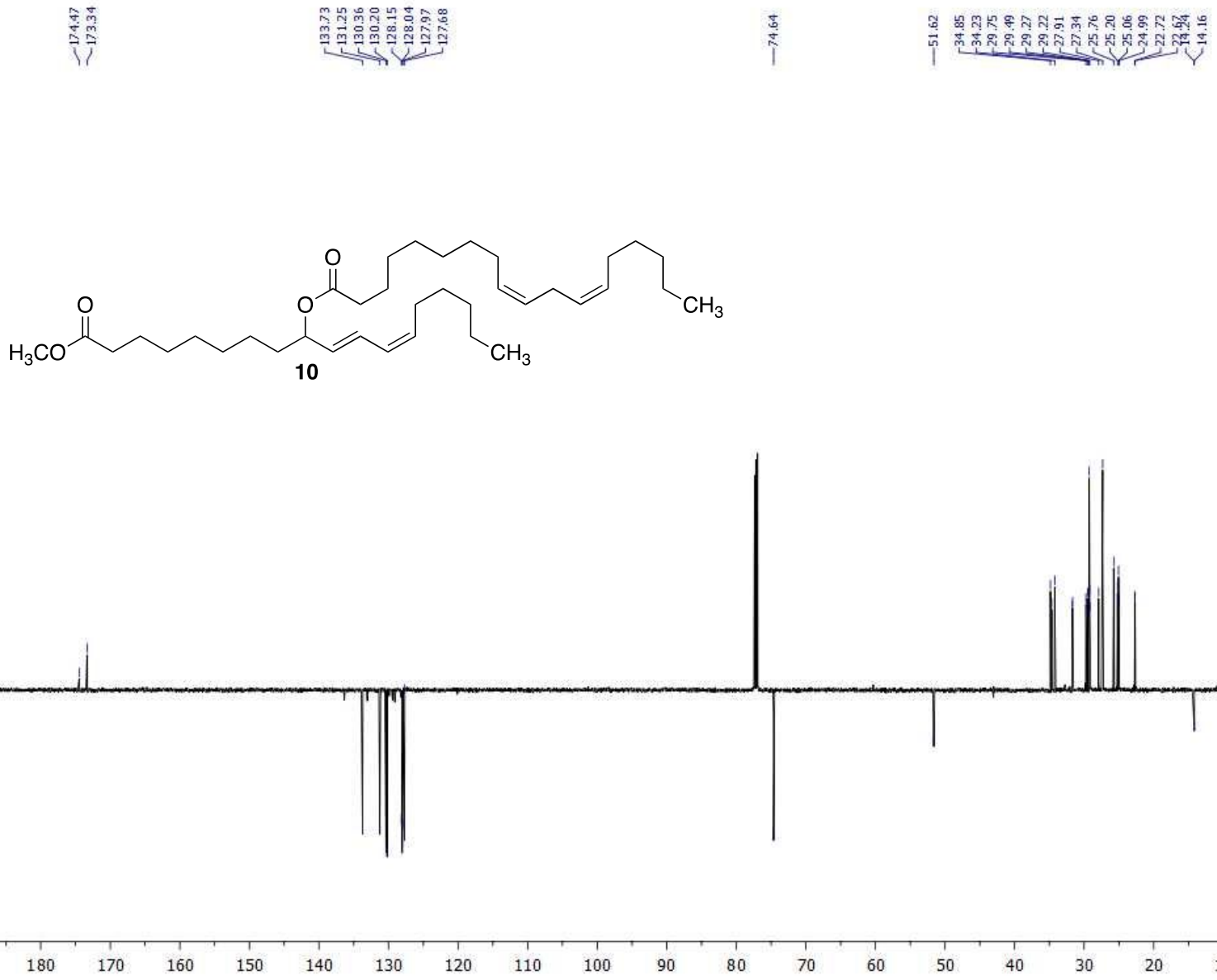


Figure S4. Inhibition of Interleukin-6 (IL-6) by 9-PAHSA. Quantitation of IL-6 following 20-hour treatments of 9-PAHSA. Higher treatment dosages of 9-PAHSA contributed to prominent cell death (data not shown) and failed to abolish IL-6 signaling effectively. Data are means ± S.E.M with n = 3 per treatment dosage group. All p values are ≤ 0.0001 unless indicated otherwise. *p, < 0.05 versus DMSO by one-way ANOVA.

Spectral Data


6.51 6.49 6.48 6.47 5.94 5.92 5.58 5.56 5.55 5.54 5.46 5.44 5.39 5.39 5.39 5.38 5.38 5.37 5.36 5.35 5.35 5.34 5.33 5.33 5.33 5.32 5.32 5.32 5.31 5.31 5.31 5.30 5.30 5.29 3.67 2.78 2.77 2.76 2.31 2.30 2.29 2.28 2.18 2.16 2.15 2.15 2.14 2.14 2.06 2.05 2.04 2.03 1.64 1.63 1.63 1.62 1.62 1.61 1.61 1.61 1.61 1.61 1.61 1.60 1.60 1.60 1.60 1.59 1.38 1.37 1.37 1.35 1.34 1.33 1.33 1.30 1.30 1.28 1.27 1.25 0.90 0.89 0.88 0.87
O
O
O
H3CO
CH3
CH3
10
0.82
0.84
0.81
6.26
3.01
2.11
3.91
1.74
4.08
4.10
30.11
6.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0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133.73
131.25
130.36
130.20
128.15
128.04
127.97
127.68
74.64
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34.85
34.23
29.75
29.49
29.27
29.22
27.91
27.34
25.76
25.20
25.06
24.99
22.72
14.24
14.16
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O
O
H3CO
CH3
CH3
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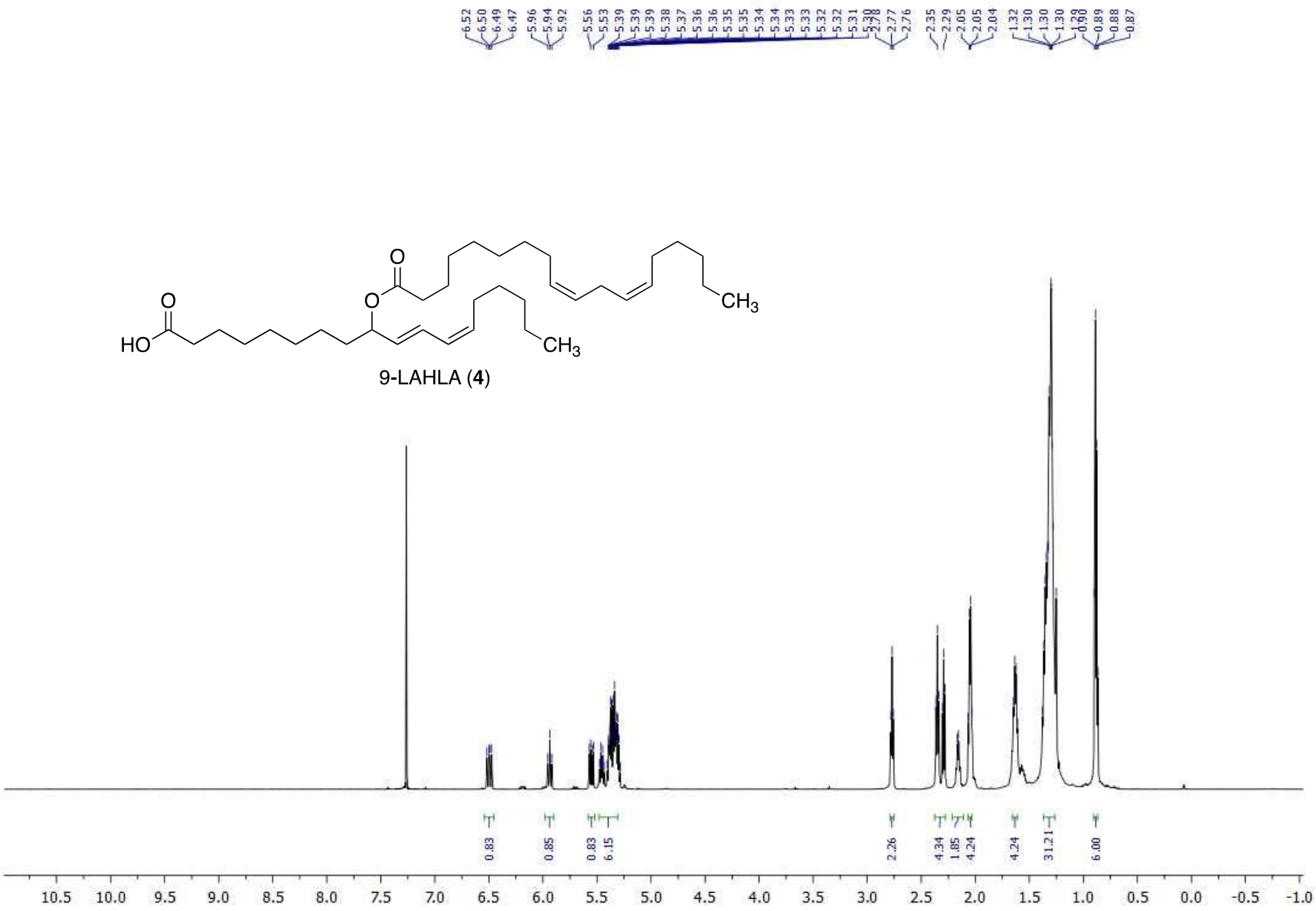
70
60
50
40
30
20
10
0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5.33
5.32
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5.31
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2.29
2.05
2.05
2.04
1.32
1.30
1.30
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0.87
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O
O
HO
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CH3
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0.85
0.83
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4.34
1.85
4.24
4.24
31.21
6.00
10.5
10.0
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9.0
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6.0
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5.0
4.5
4.0
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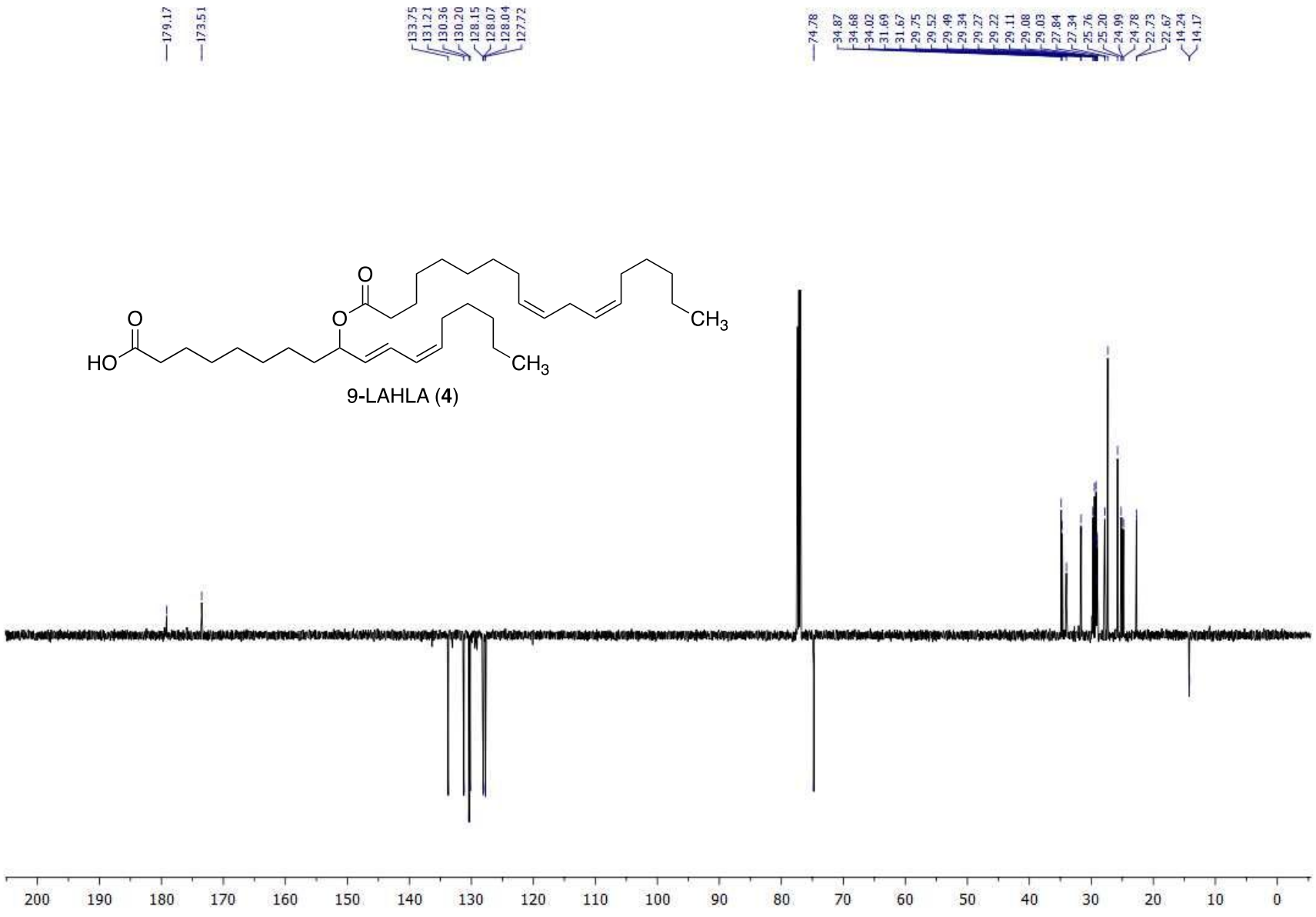
-0.5
-1.0

9-LAHLA (**4**)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128.07
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127.72
74.78
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29.75
29.52
29.49
29.34
29.27
29.22
29.11
29.08
29.03
27.84
27.34
25.76
25.20
24.99
24.78
22.73
22.67
14.24
14.17
HO
O
O
O
CH3
CH3
9-LAHLA (4)
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150
140
130
120
110
100
90
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70
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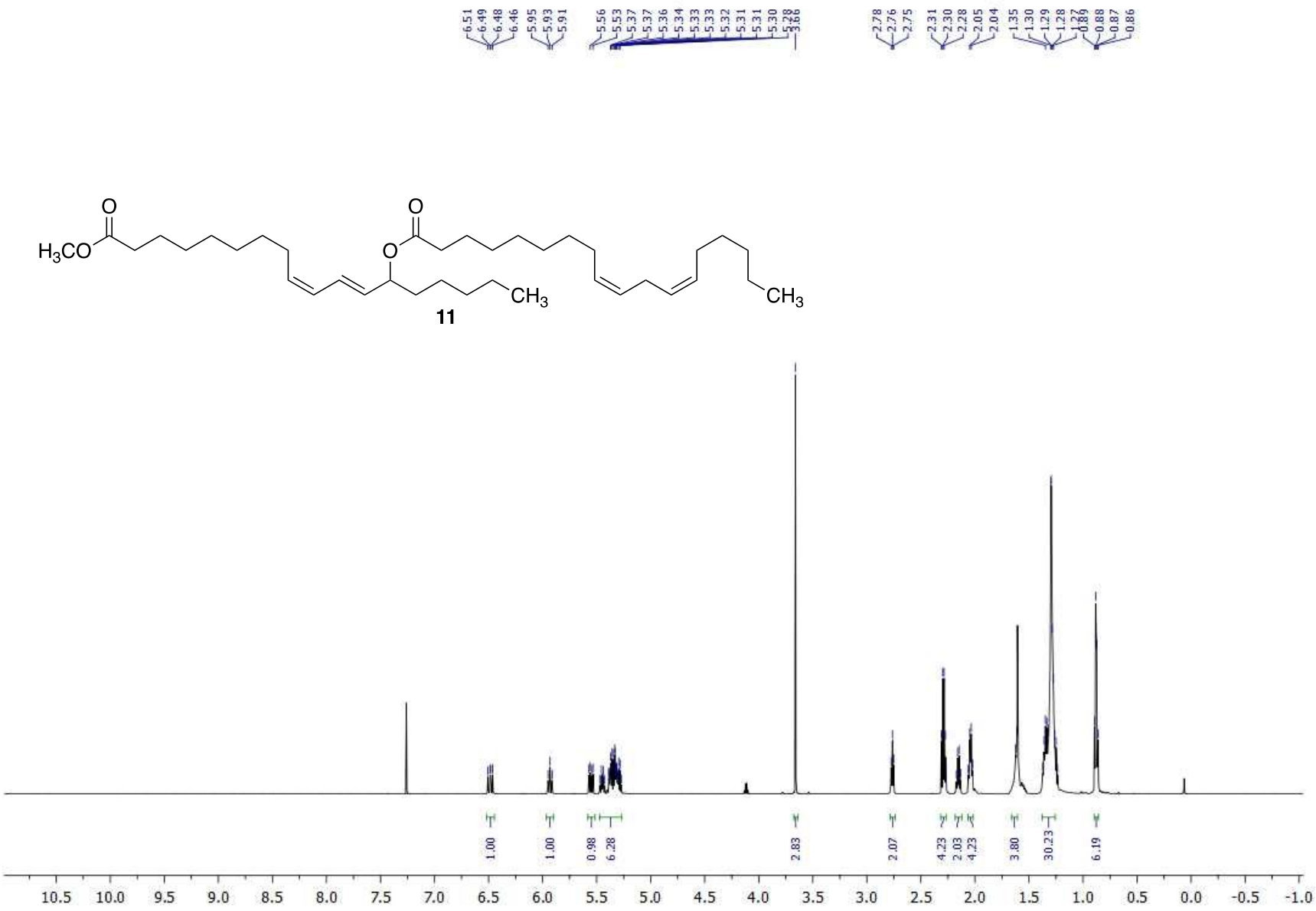
50
40
30
20
10
0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6.46
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5.93
5.91
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5.37
5.37
5.36
5.34
5.33
5.33
5.32
5.31
5.31
5.30
5.28
3.68
2.78
2.76
2.75
2.31
2.30
2.28
2.05
2.04
1.35
1.30
1.29
1.28
1.27
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0.87
0.86
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O
O
H3CO
CH3
CH3
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1.00
0.98
6.28
2.83
2.07
4.23
2.03
4.23
3.80
30.23
6.19
10.5
10.0
9.5
9.0
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8.0
7.5
7.0
6.5
6.0
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5.0
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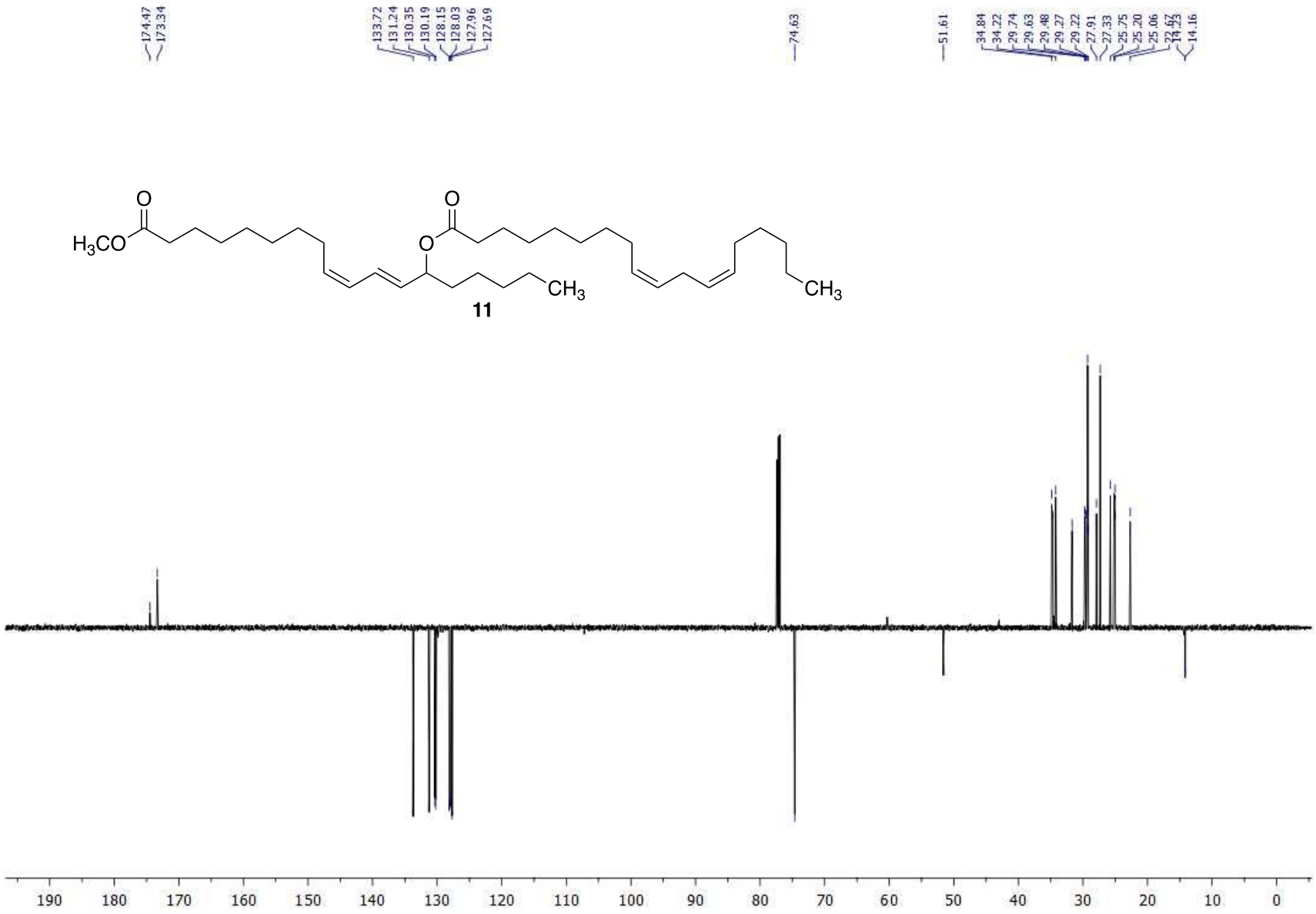
-1.0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128.03
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127.69
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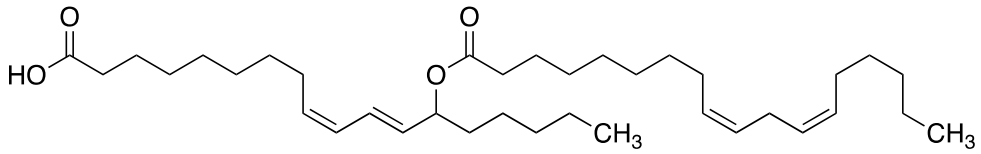
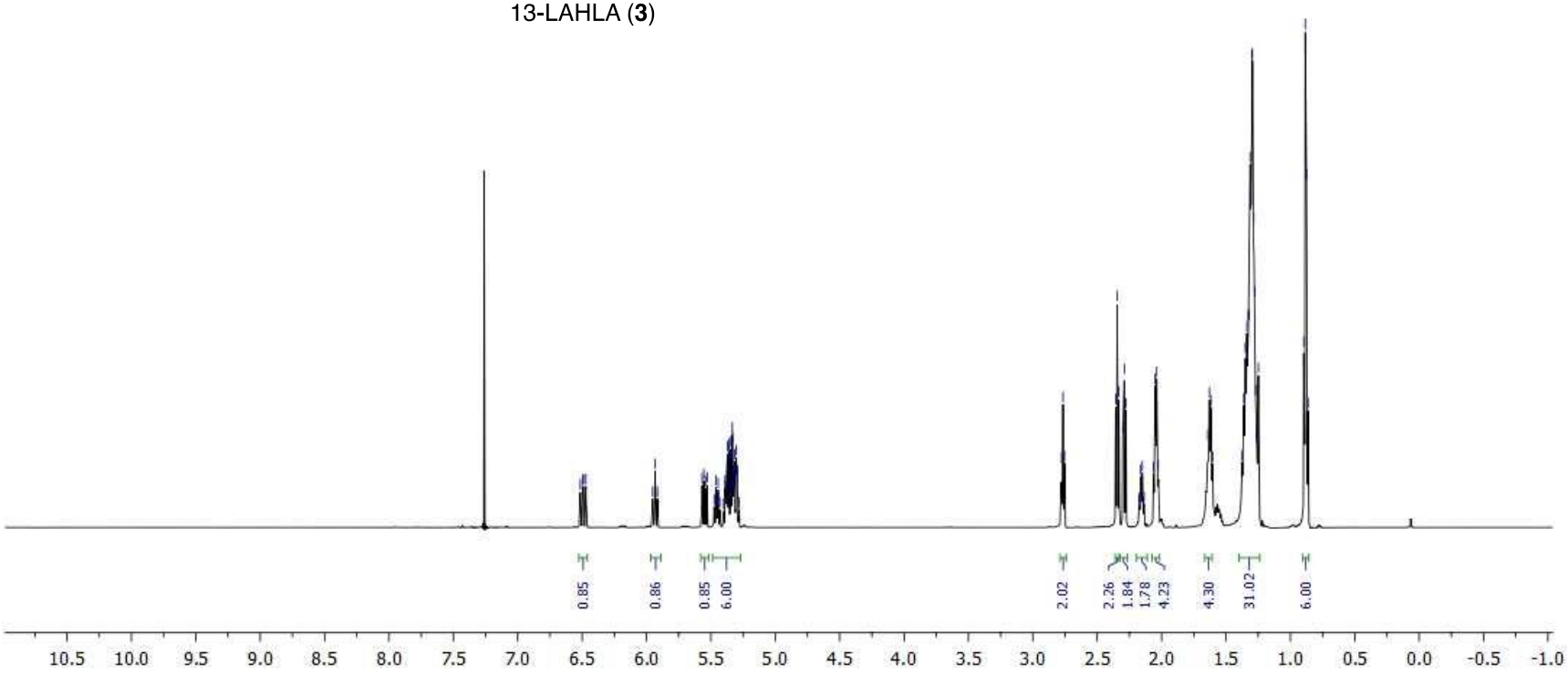
51.61
34.84
34.22
29.74
29.63
29.48
29.27
29.22
27.91
27.33
25.75
25.20
25.06
22.67
14.23
14.16
O
H3CO
O
O
CH3
CH3
11
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


6.51 6.50 6.49 6.47 5.95 5.93 5.92 5.57 5.56 5.54 5.53 5.47 5.46 5.46 5.45 5.44 5.39 5.39 5.38 5.38 5.37 5.37 5.37 5.36 5.36 5.35 5.35 5.35 5.34 5.33 5.33 5.32 5.32 5.32 5.31 5.30 5.29
2.78 2.77 2.75 2.36 2.34 2.33 2.30 2.29 2.28 2.17 2.16 2.15 2.14 2.06 2.05 2.05 2.04 2.03 1.64 1.63 1.62 1.60 1.37 1.36 1.35 1.34 1.33 1.33 1.32 1.31 1.31 1.30 1.29 1.28 1.27 1.27 1.26 1.26 1.25 0.90 0.88 0.87 0.86


O
HO
O
O
CH3
CH3

13-LAHLA (**3**)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0.86
0.85
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2.26
1.84
1.78
4.23
4.30
31.02
6.00
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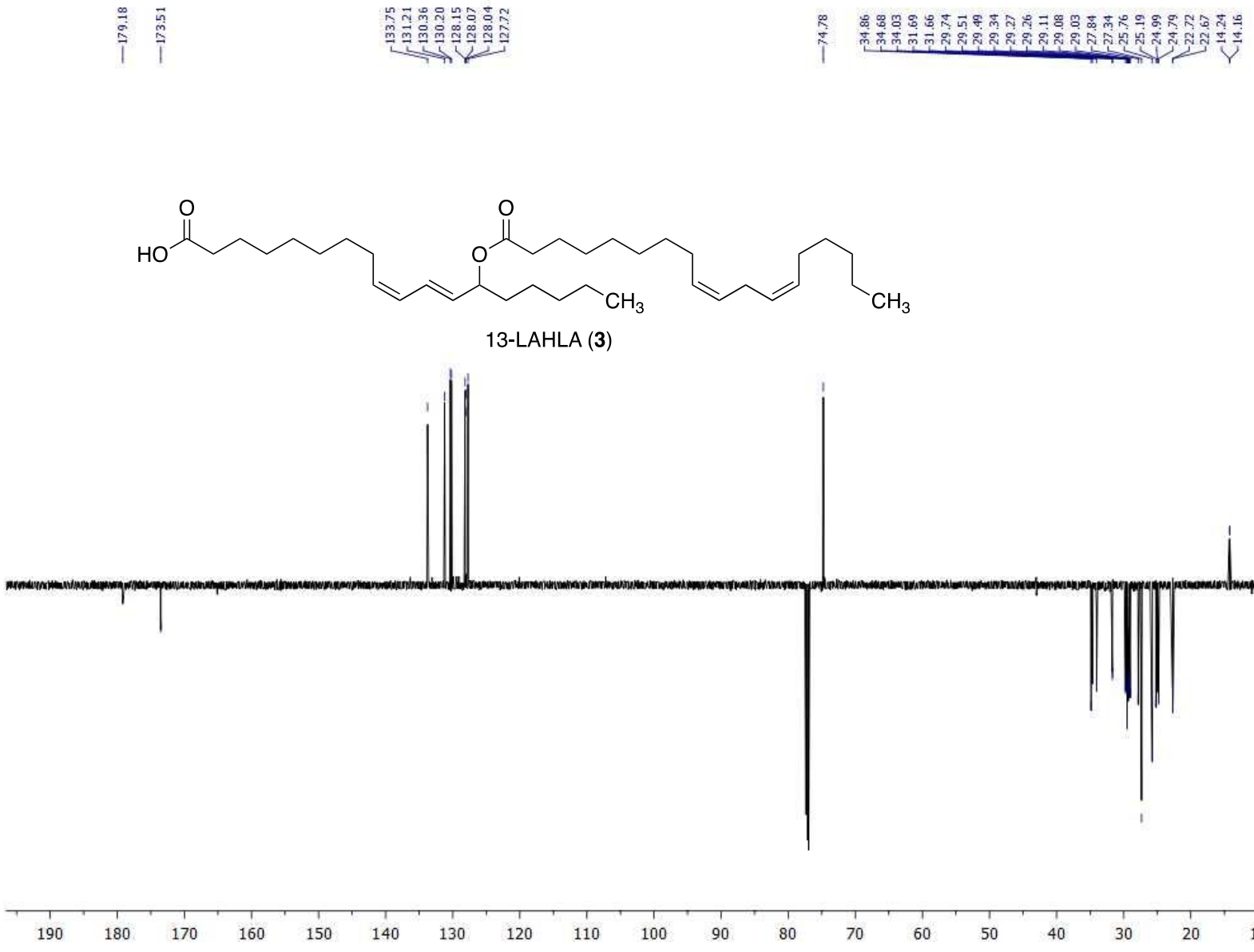
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130.20
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128.07
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127.72
74.78
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34.03
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29.27
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29.03
27.84
27.34
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25.19
24.99
24.79
22.72
22.67
14.24
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O
CH3
CH3
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180
170
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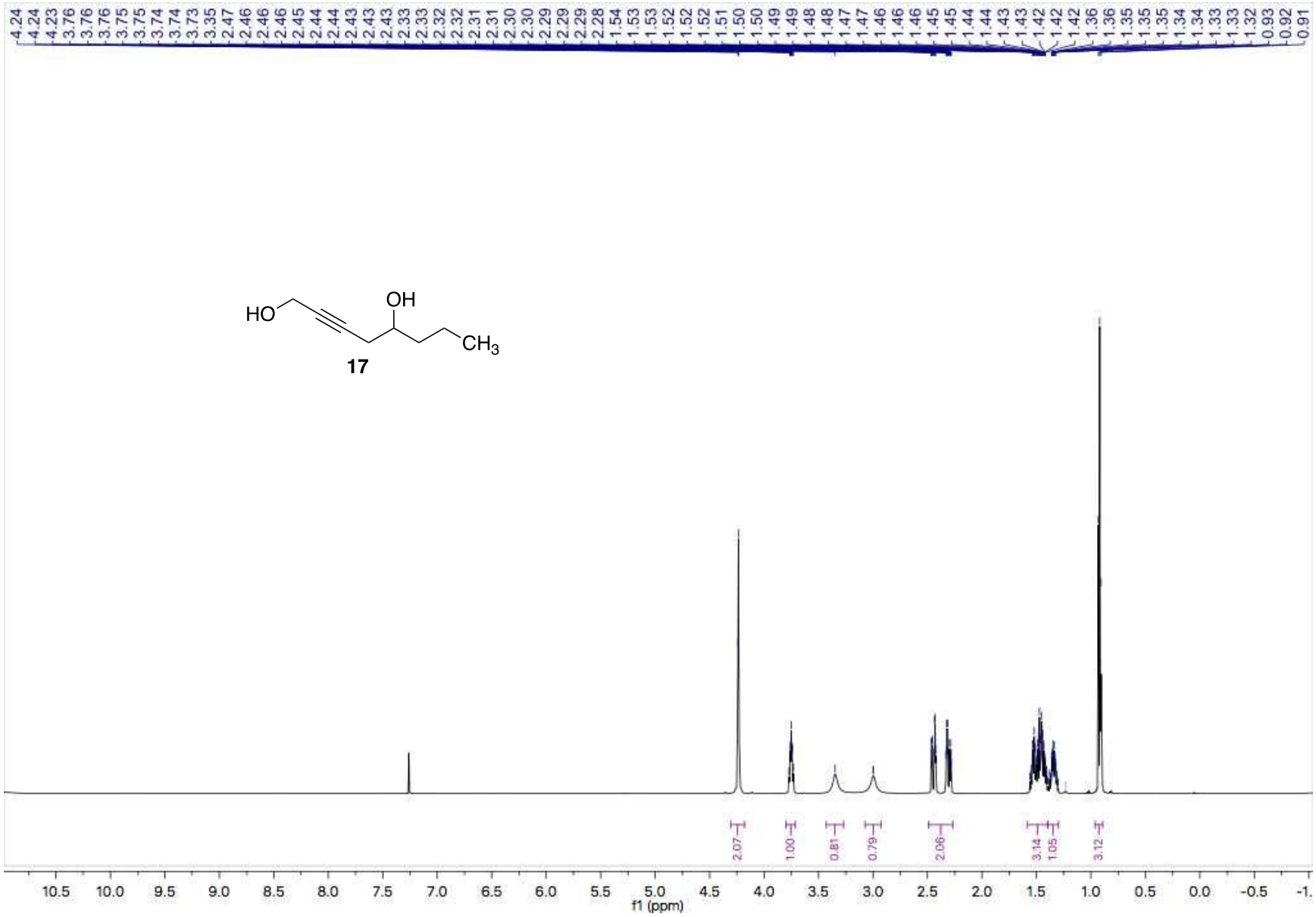
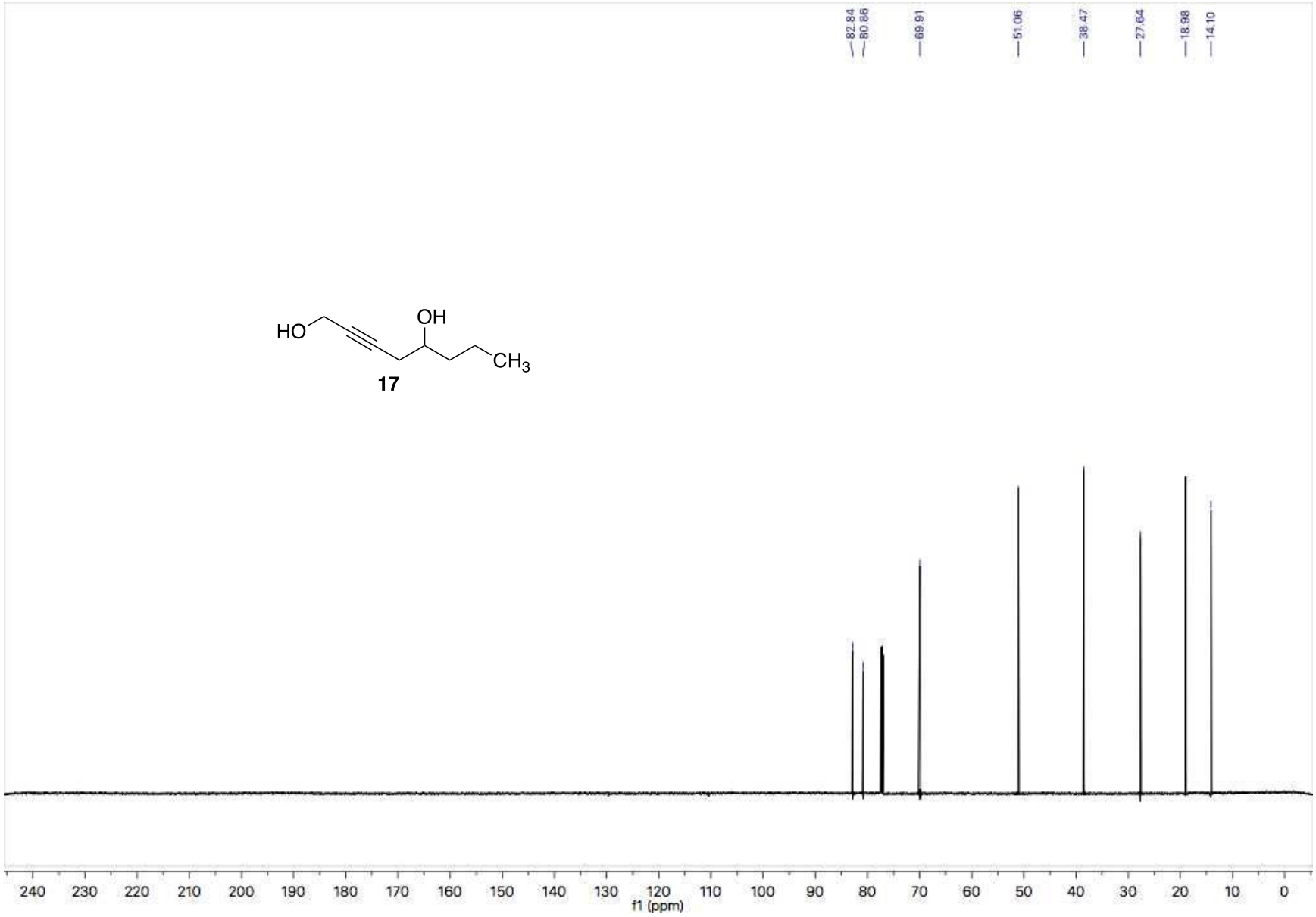
100
90
80
70
60
50
40
30
20
10
0

13-LAHLA (**3**)


HO
OH
CH3
17
f1 (ppm)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80.86
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51.06
38.47
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14.10
HO
OH
CH3
17
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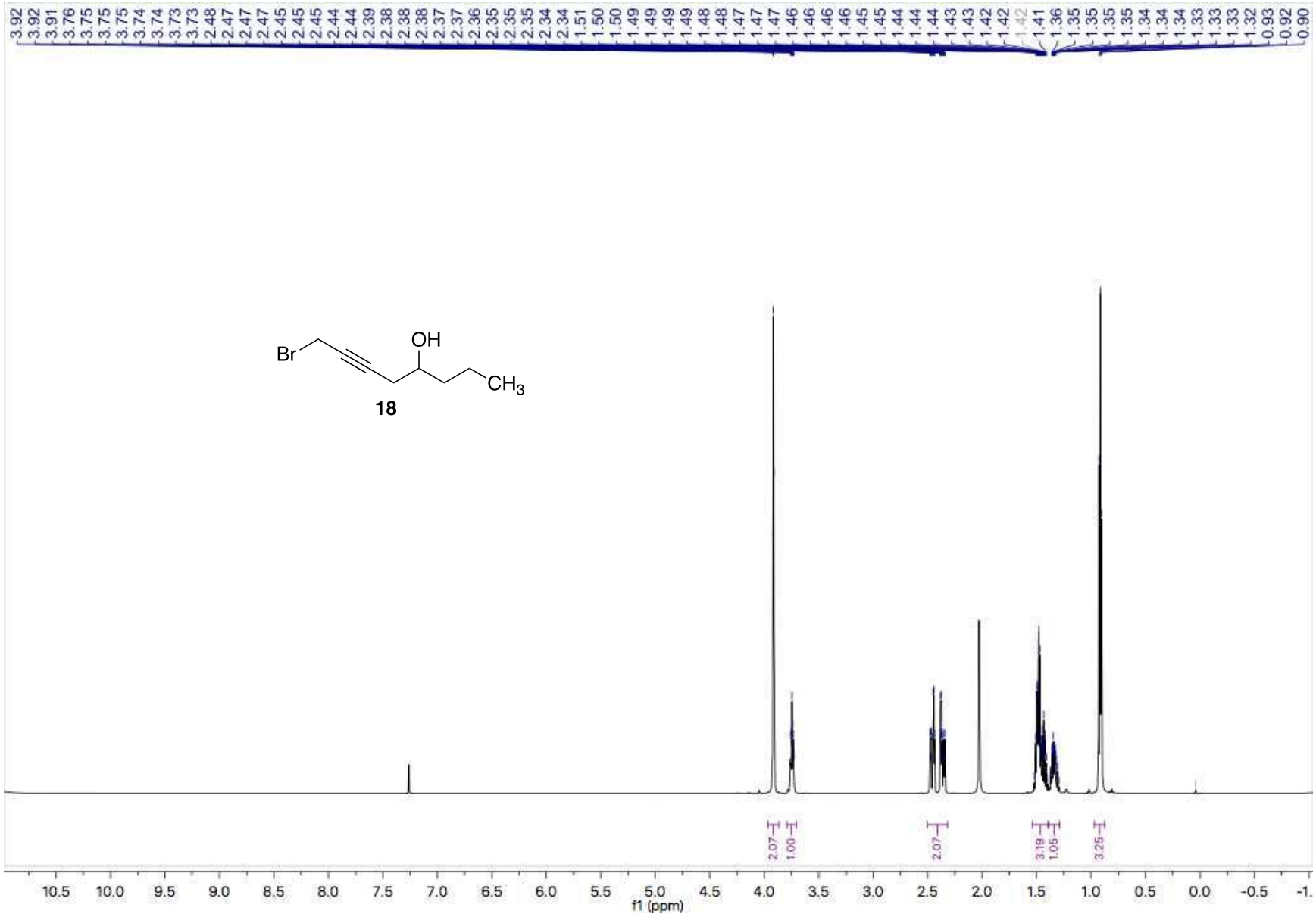
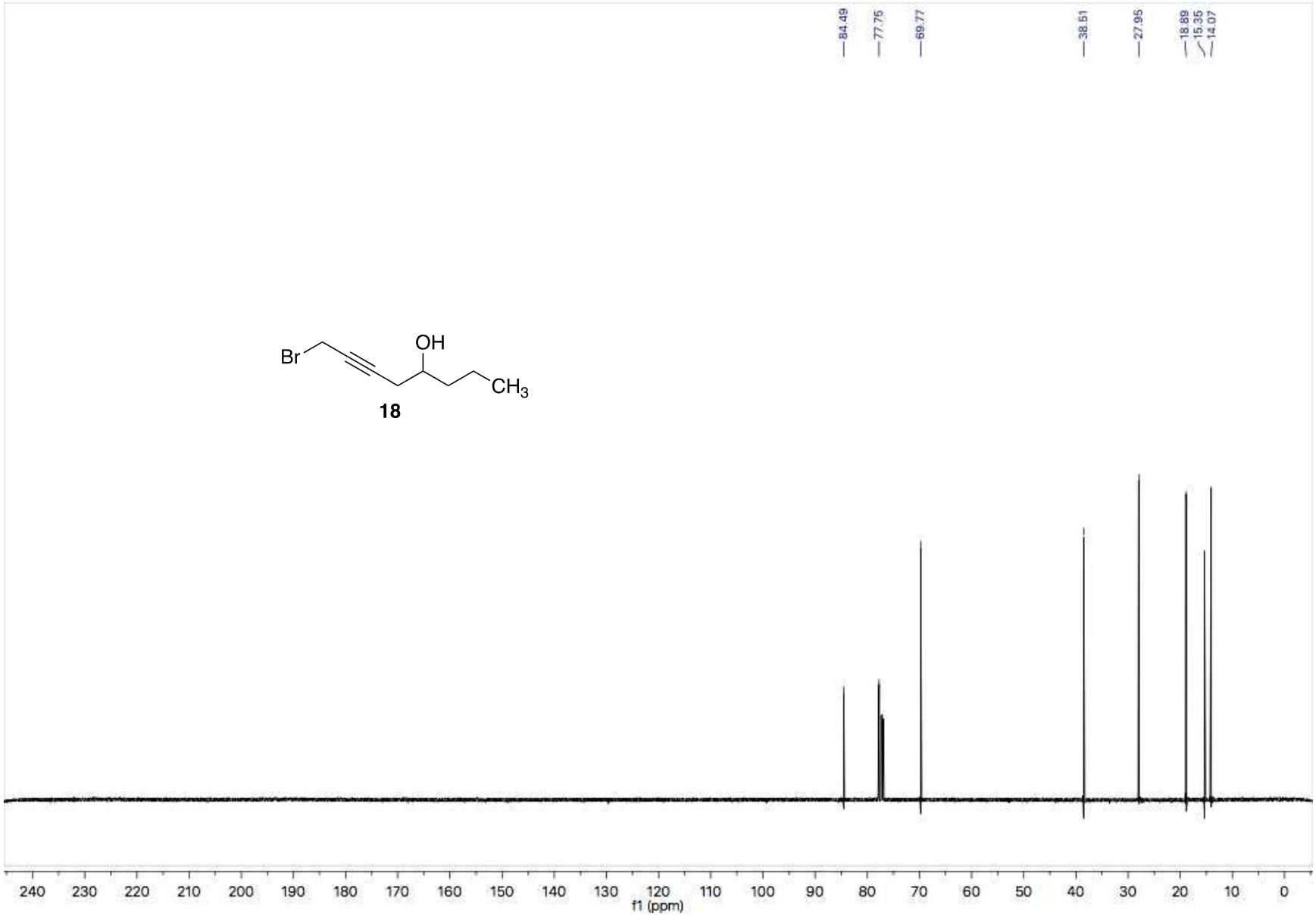
f1 (ppm)


Br
OH
CH3
18
f1 (ppm)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27.95
18.89
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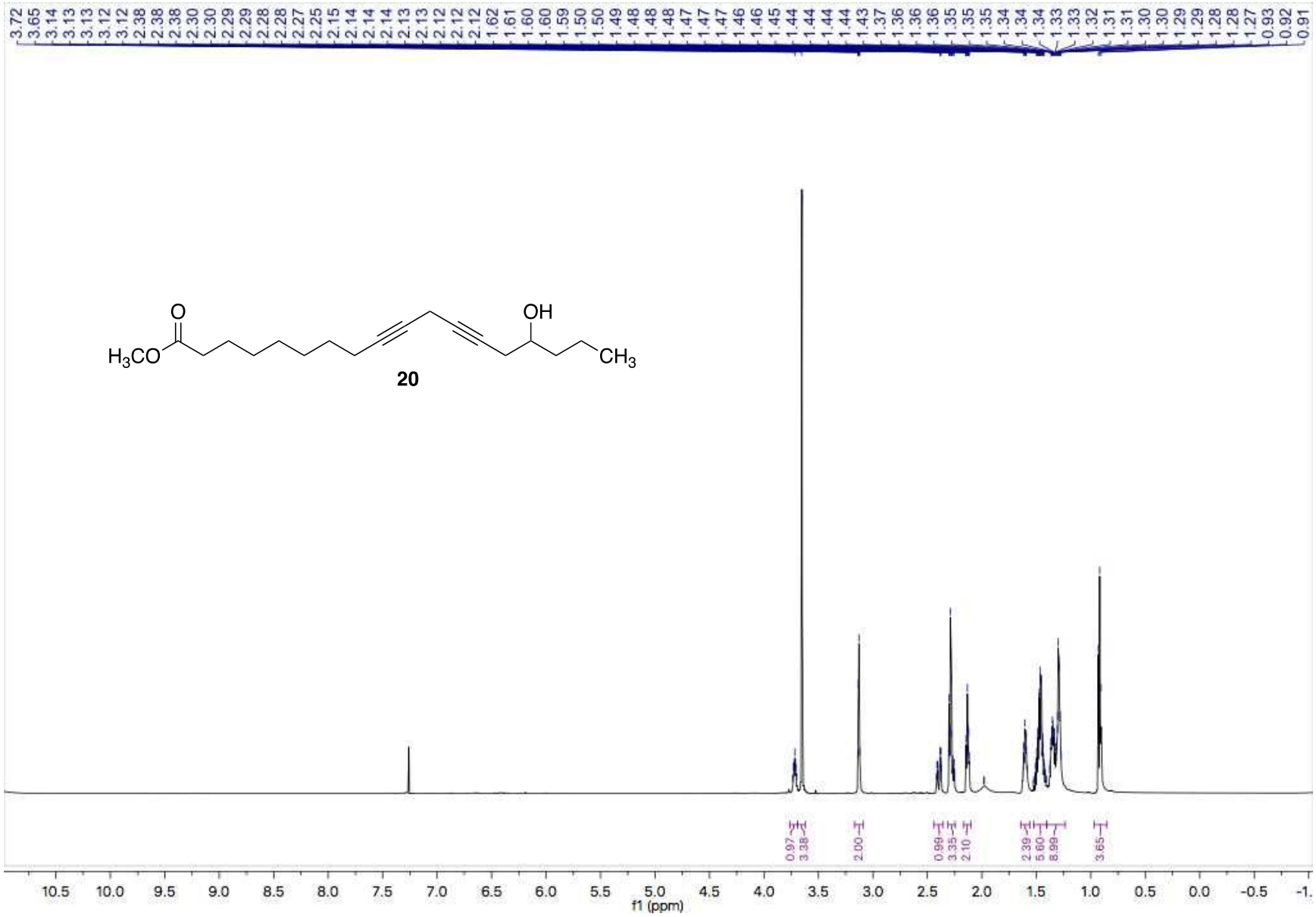
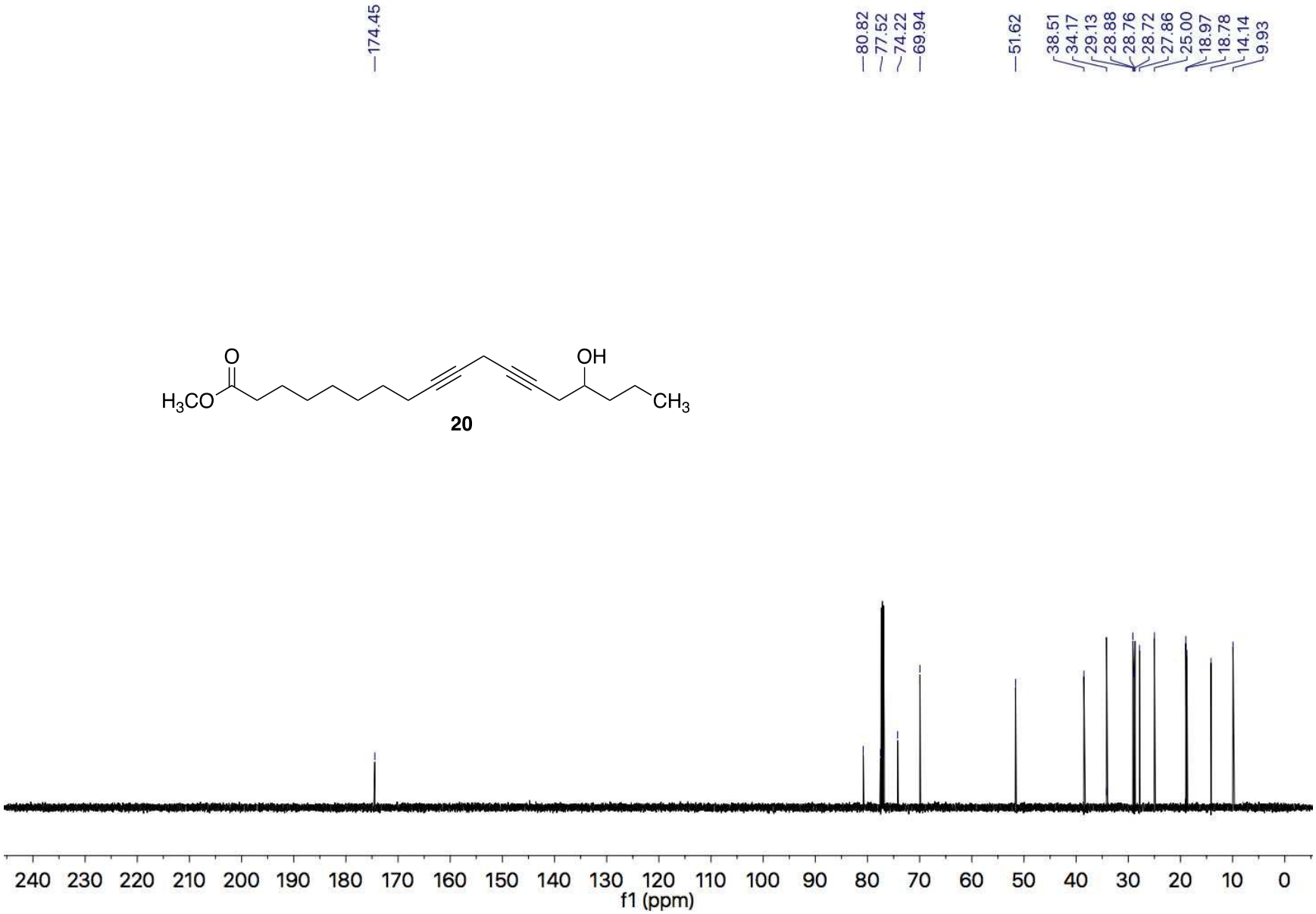
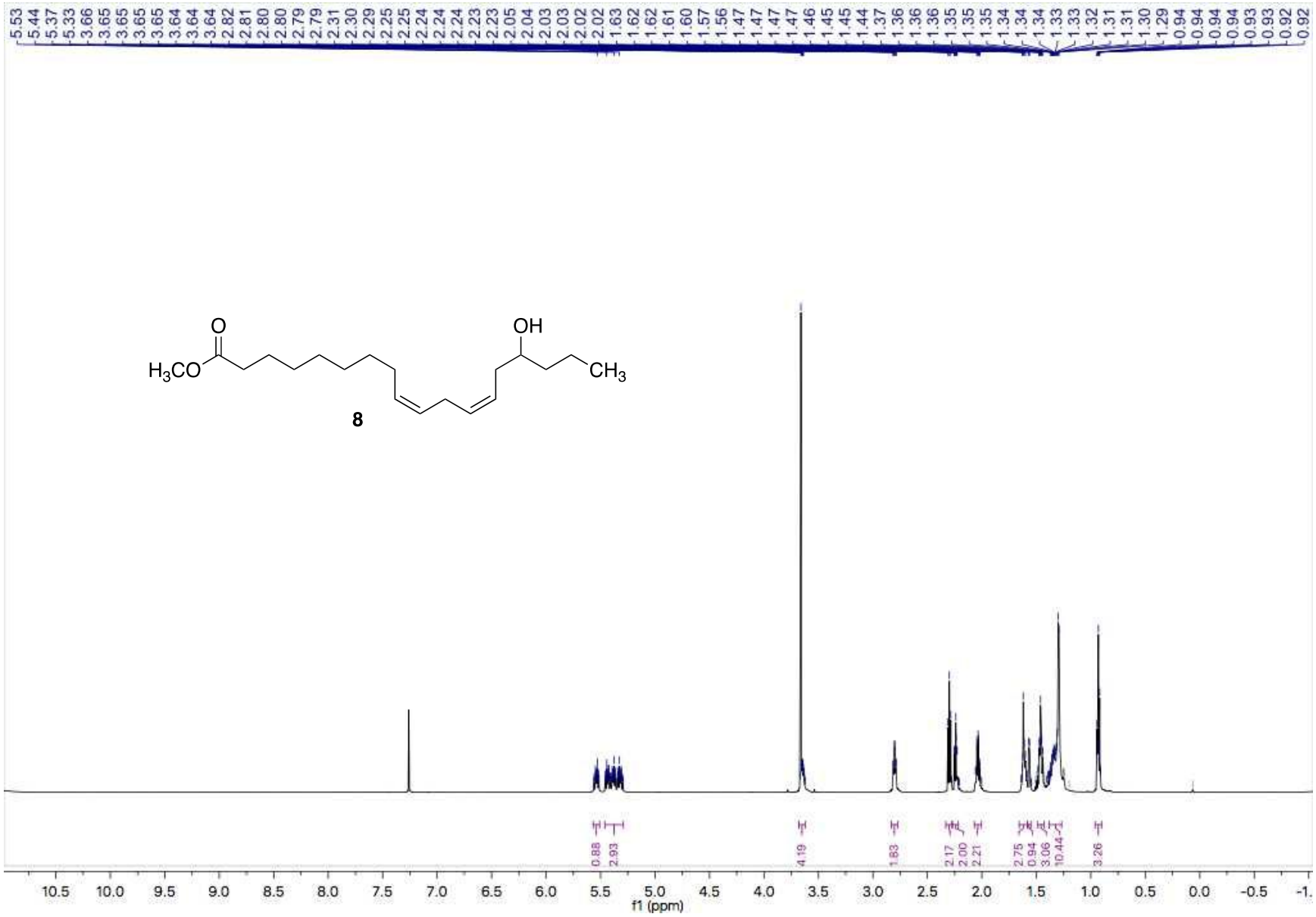
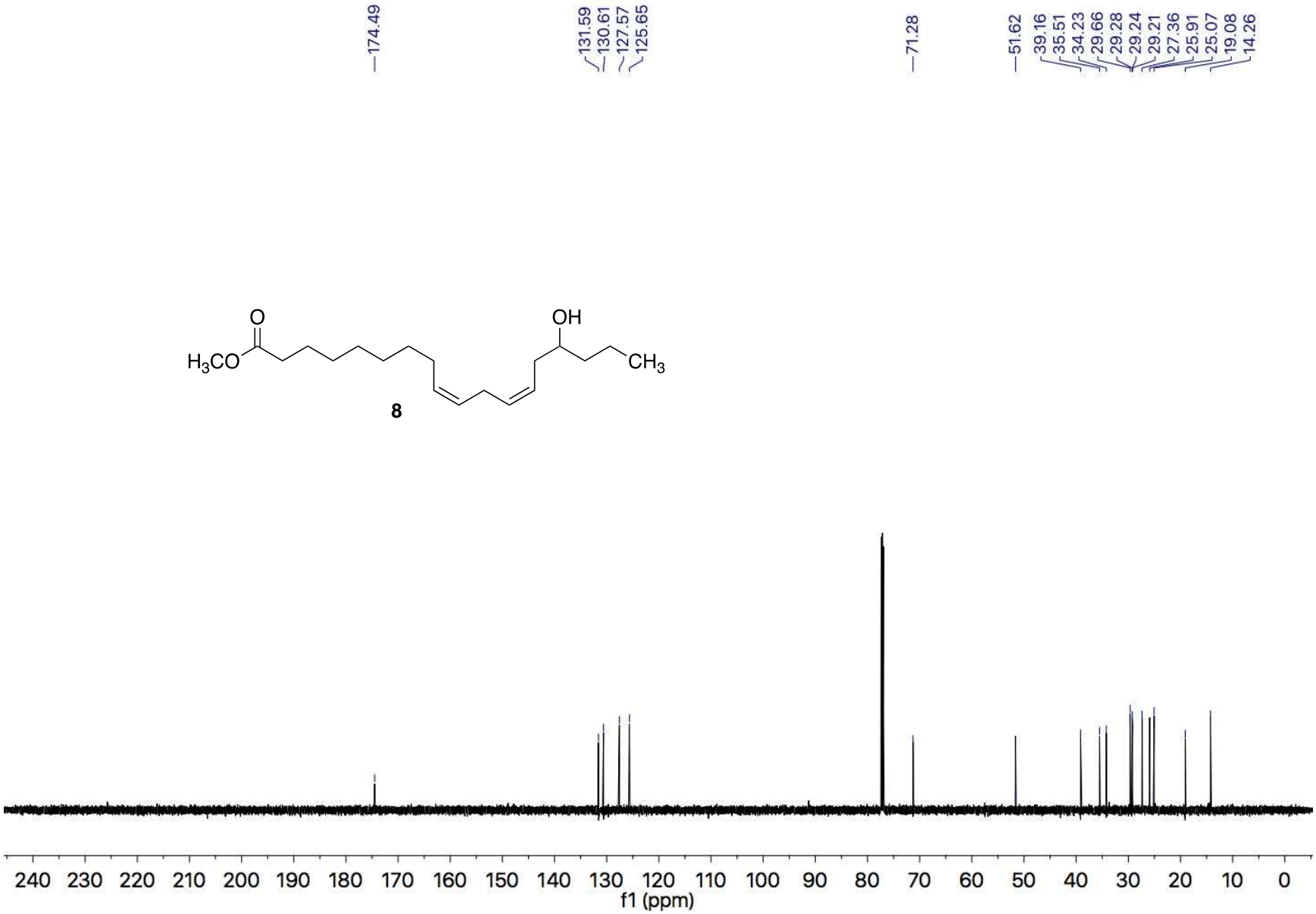
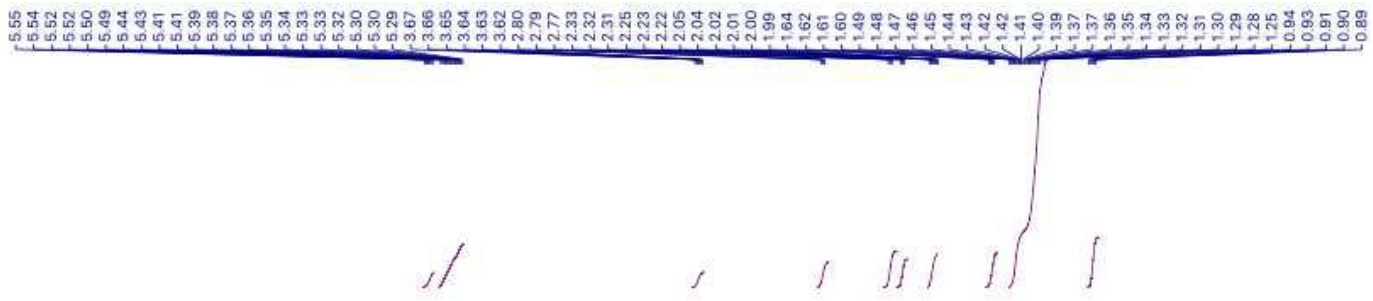
Br
OH
CH3
18
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

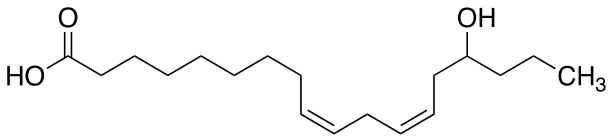

3.72 3.65 3.14 3.13 3.13 3.12 3.12 2.38 2.38 2.30 2.30 2.29 2.29 2.28 2.28 2.27 2.25 2.15 2.14 2.14 2.14 2.13 2.13 2.12 2.12 2.12 1.62 1.61 1.60 1.60 1.59 1.50 1.50 1.49 1.48 1.48 1.48 1.47 1.47 1.47 1.46 1.46 1.45 1.44 1.44 1.44 1.44 1.43 1.37 1.36 1.36 1.36 1.35 1.35 1.35 1.34 1.34 1.34 1.33 1.33 1.32 1.31 1.31 1.30 1.30 1.29 1.29 1.28 1.28 1.27 0.93 0.92 0.91
O
H3CO
OH
CH3
20
0.97
3.38
2.00
0.99
3.35
2.10
2.39
5.60
8.99
3.65
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


174.45
80.82
77.52
74.22
69.94
51.62
38.51
34.17
29.13
28.88
28.76
28.72
27.86
25.00
18.97
18.78
14.14
9.93
O
OH
H3CO
CH3
20
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

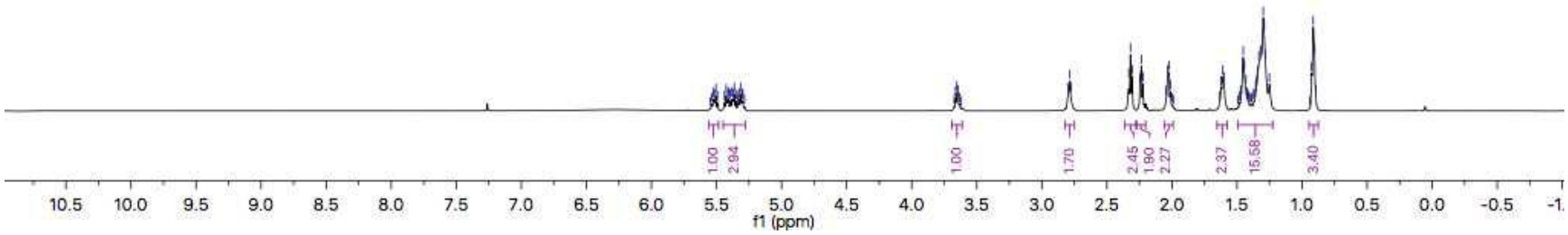

O
H3CO
OH
CH3
8
f1 (ppm)

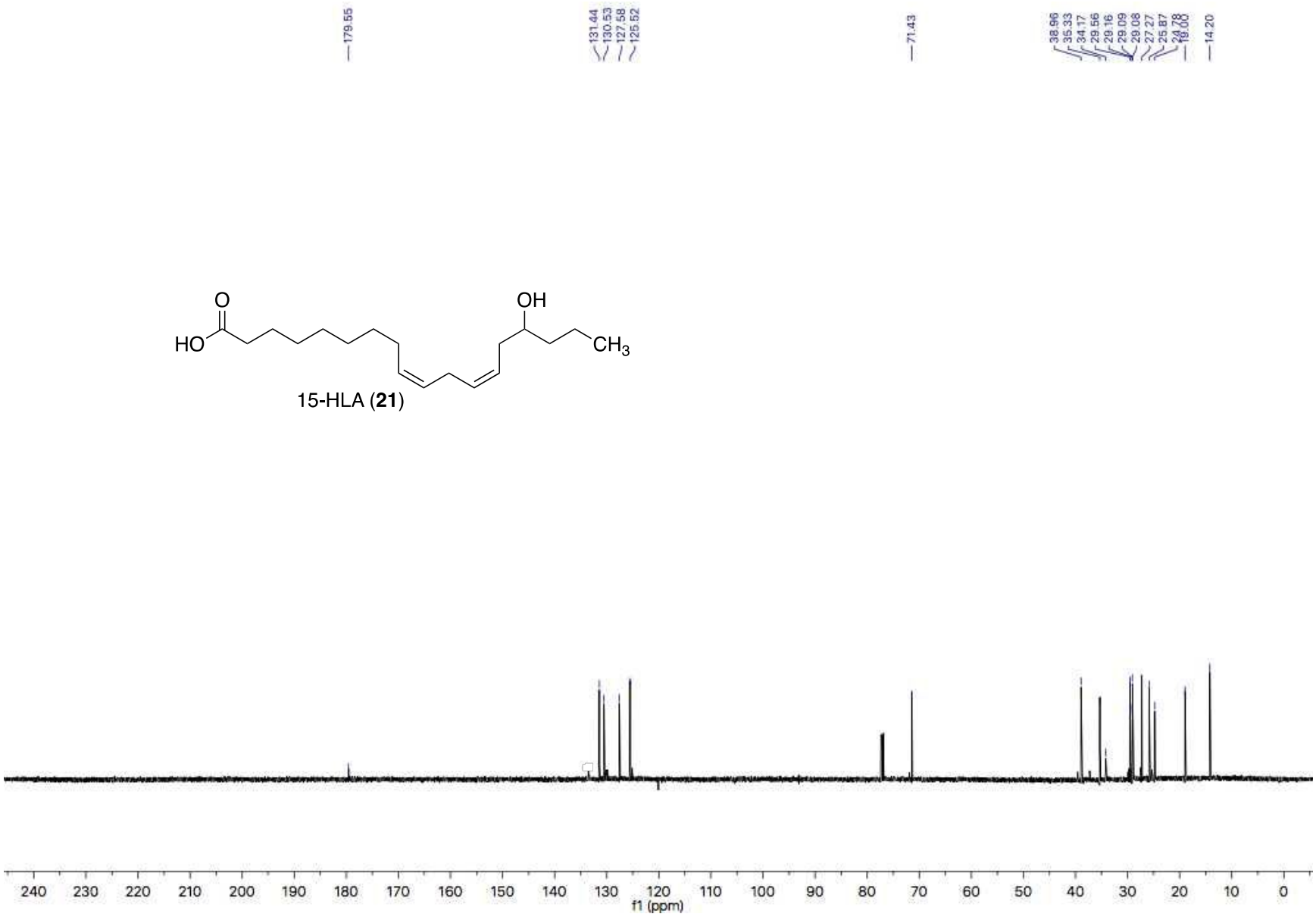

174.49
131.59
130.61
127.57
125.65
71.28
51.62
39.16
35.51
34.23
29.66
29.28
29.24
29.21
27.36
25.91
25.07
19.08
14.26
O
H3CO
OH
CH3
8
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

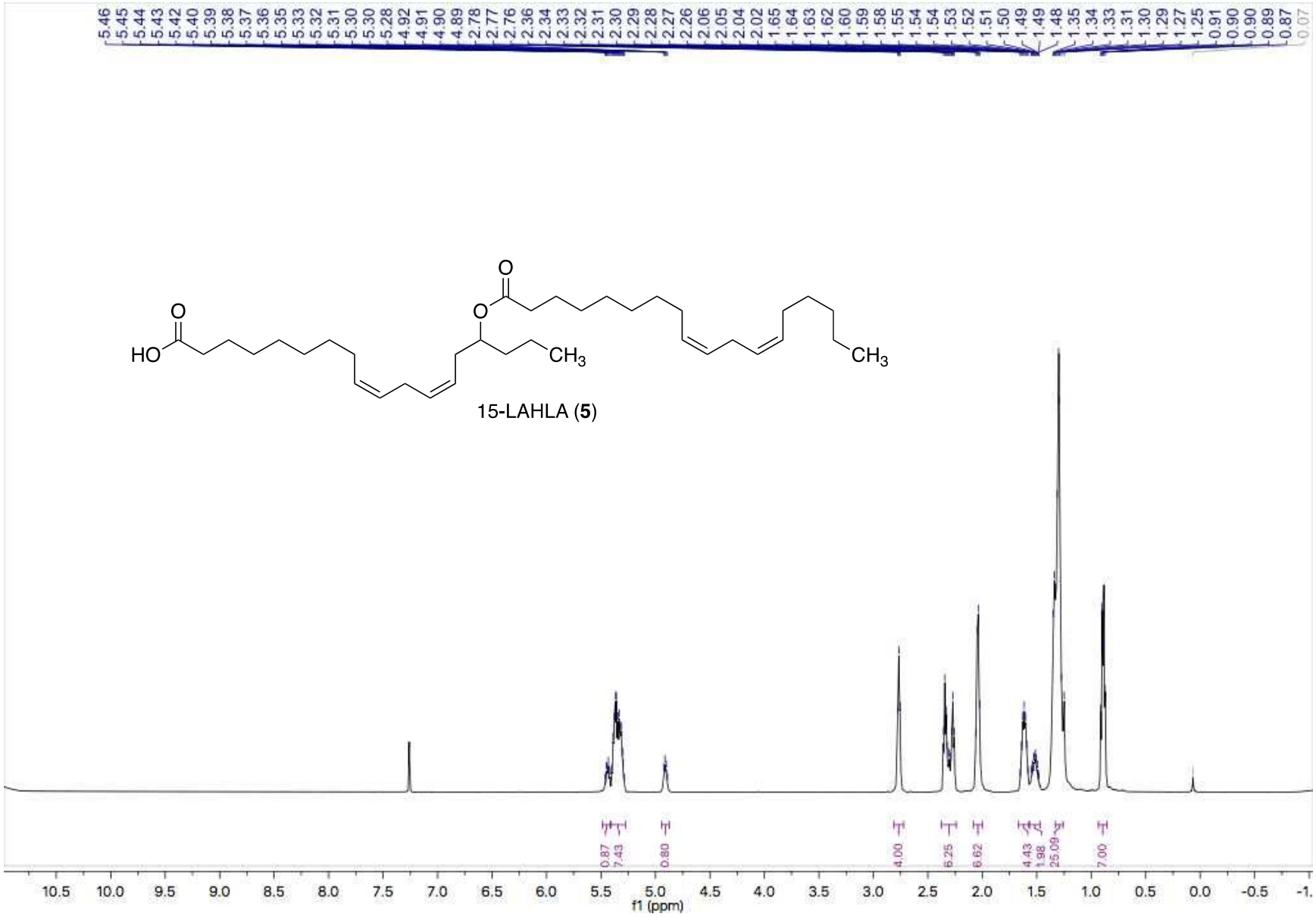

5.55
5.54
5.52
5.52
5.50
5.49
5.44
5.43
5.41
5.41
5.39
5.38
5.37
5.36
5.35
5.34
5.33
5.33
5.32
5.30
5.30
5.29
3.67
3.66
3.65
3.64
3.63
3.62
2.80
2.79
2.77
2.33
2.32
2.31
2.25
2.23
2.22
2.05
2.04
2.02
2.01
2.00
1.99
1.64
1.62
1.61
1.60
1.49
1.48
1.47
1.46
1.45
1.44
1.43
1.42
1.42
1.41
1.40
1.39
1.37
1.37
1.36
1.35
1.34
1.33
1.32
1.31
1.30
1.29
1.28
1.25
0.94
0.93
0.91
0.90
0.89

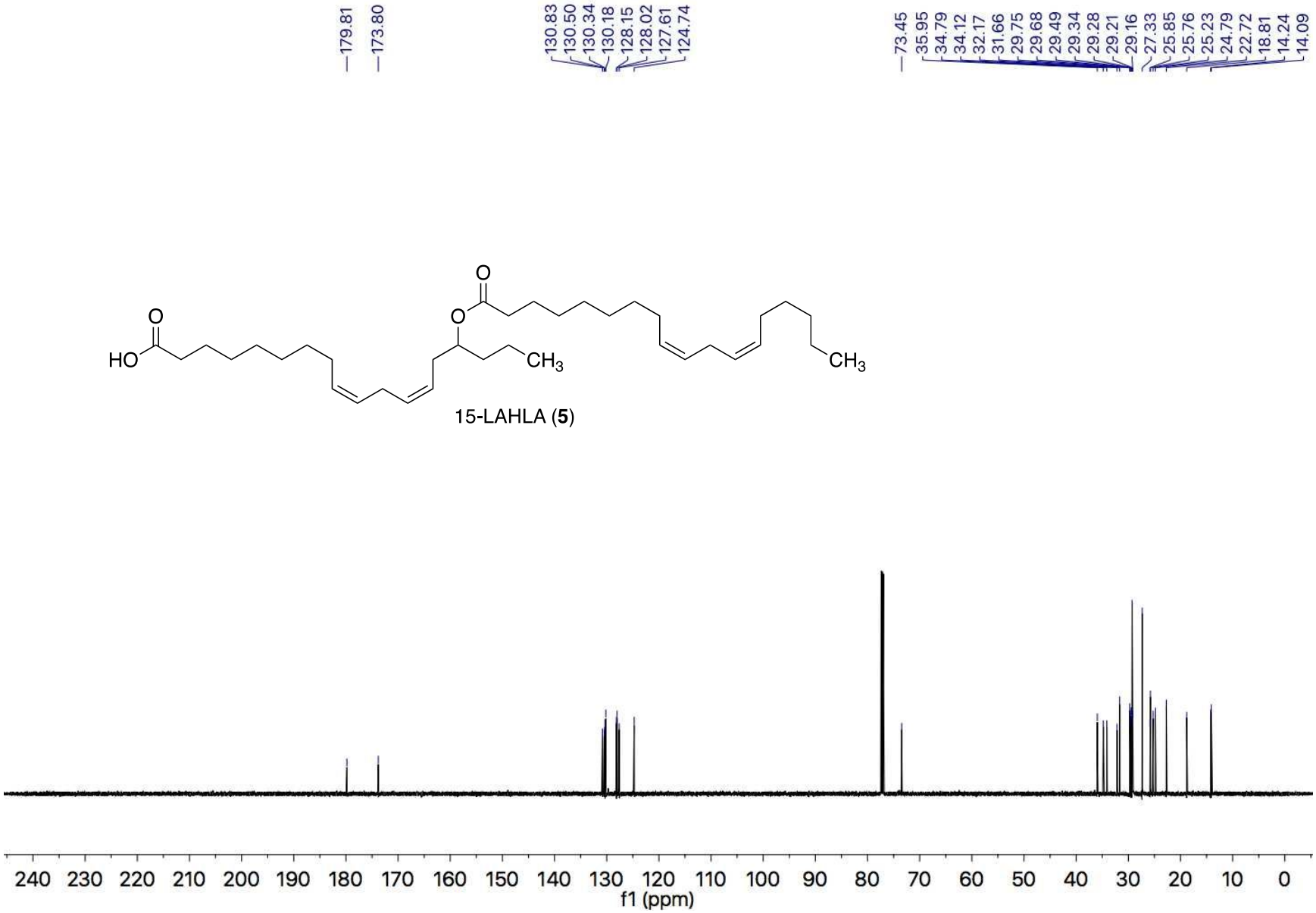

O
HO
OH
CH3

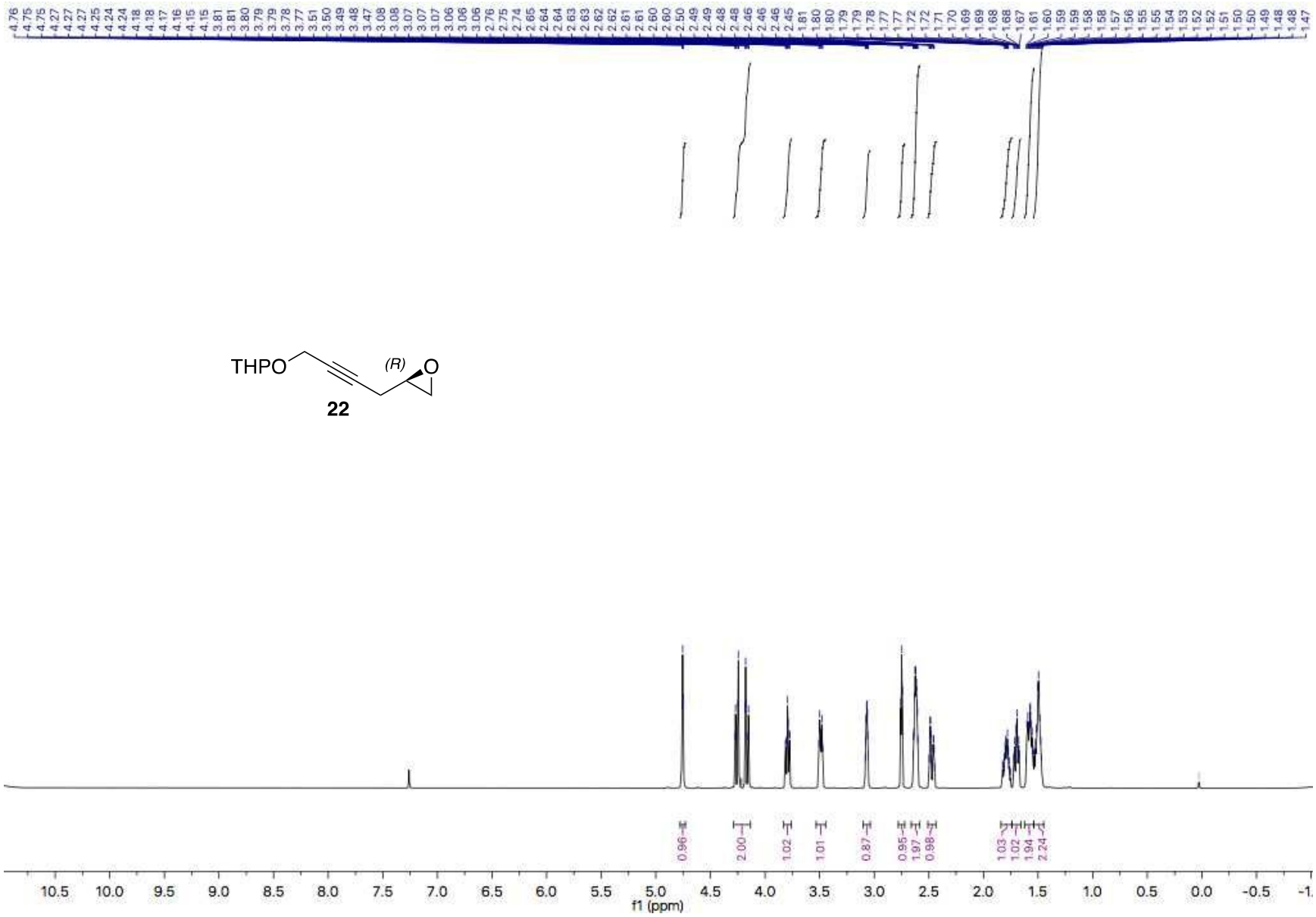
15-HLA (**21**)

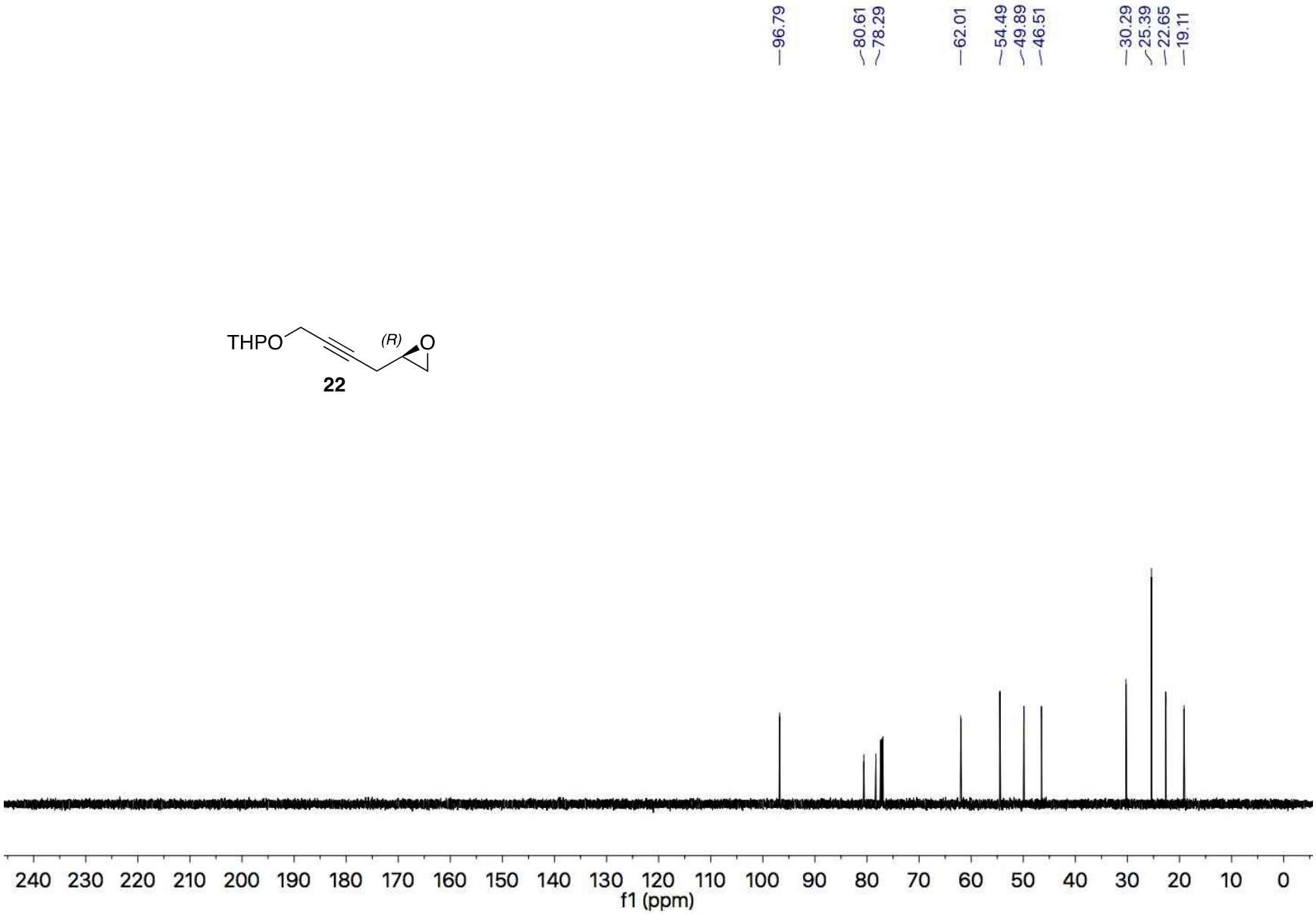

1.00
2.84
1.00
1.70
2.45
1.90
2.27
2.37
15.58
3.40
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

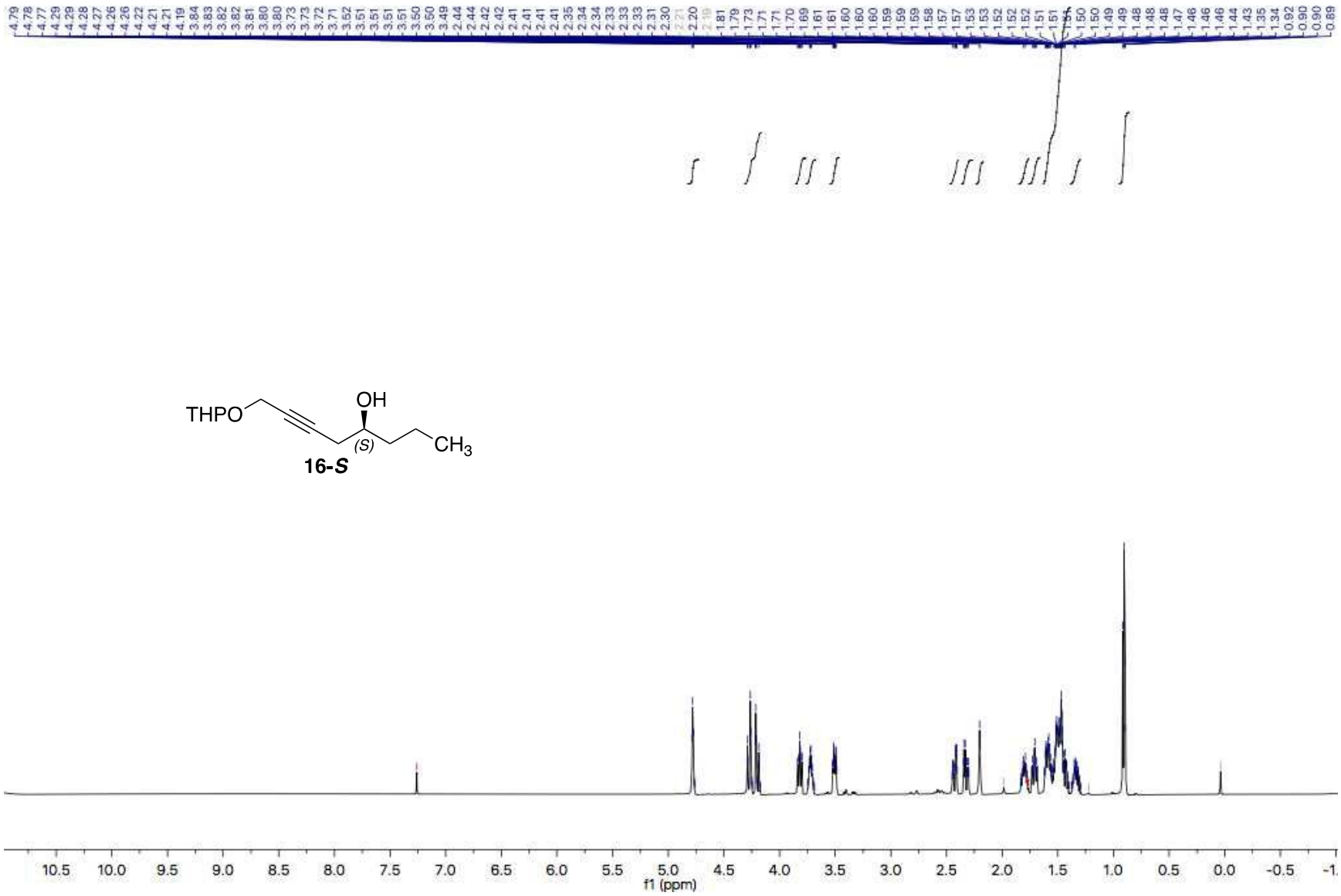

179.55
131.44
130.53
127.58
125.52
71.43
38.96
35.33
34.17
29.56
29.16
29.09
29.08
27.27
25.87
24.78
19.00
14.20
O
HO
OH
CH3
15-HLA (21)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

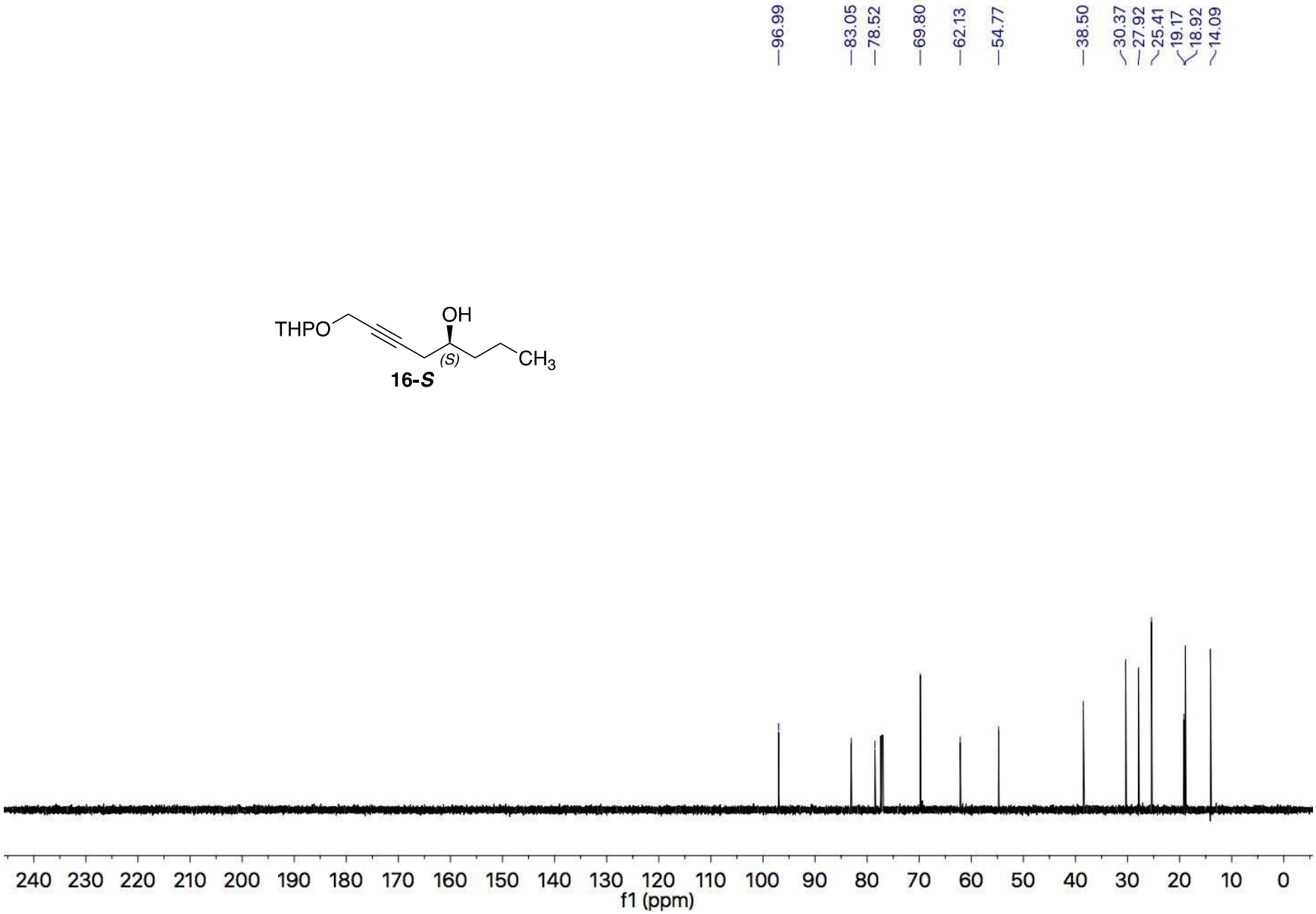

5.46 5.45 5.44 5.43 5.42 5.40 5.39 5.38 5.37 5.36 5.35 5.33 5.32 5.31 5.30 5.30 5.28 4.92 4.91 4.90 4.89 2.78 2.77 2.76 2.36 2.34 2.33 2.32 2.31 2.30 2.29 2.28 2.27 2.26 2.06 2.05 2.04 2.02 1.65 1.64 1.63 1.62 1.60 1.59 1.58 1.55 1.54 1.54 1.53 1.52 1.51 1.50 1.49 1.49 1.48 1.35 1.34 1.33 1.31 1.30 1.29 1.27 1.25 0.91 0.90 0.90 0.89 0.87 0.07
HO
O
O
O
CH3
CH3
15-LAHLA (5)
0.87 7.43 0.80 4.00 6.25 6.62 4.43 1.98 25.09 7.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

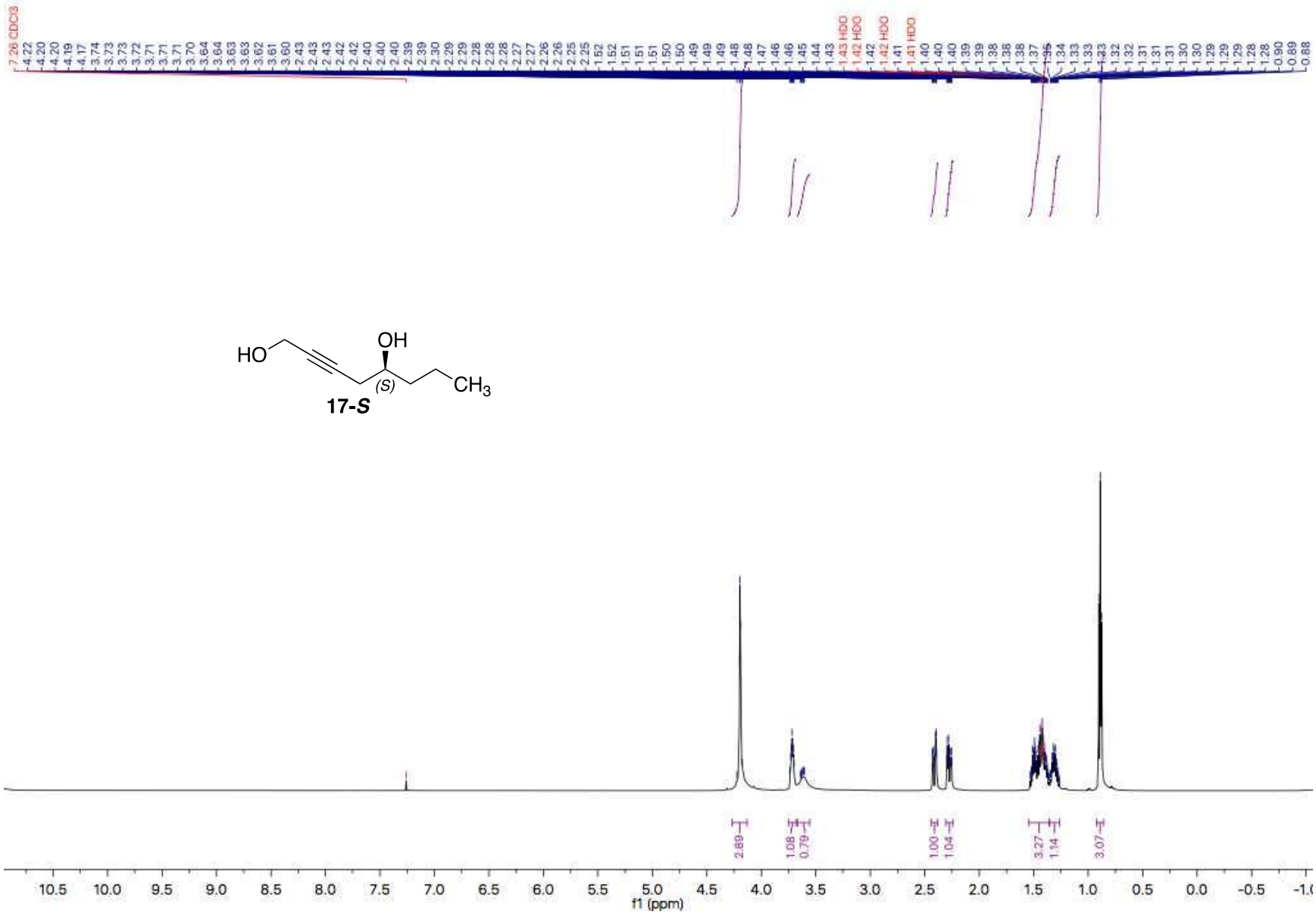

179.81
173.80
130.83
130.50
130.34
130.18
128.15
128.02
127.61
124.74
73.45
35.95
34.79
34.12
32.17
31.66
29.75
29.68
29.49
29.34
29.28
29.21
29.16
27.33
25.85
25.76
25.23
24.79
22.72
18.81
14.24
14.09
HO
O
O
O
CH3
CH3
15-LAHLA (5)
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

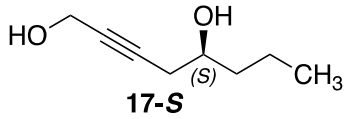

THPO
(R)
O
22
0.96
2.00
1.02
1.01
0.87
0.95
1.97
0.98
1.03
1.02
1.94
2.24
f1 (ppm)


96.79
80.61
78.29
62.01
54.49
49.89
46.51
30.29
25.39
22.65
19.11
THPO
(R)
O
22
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


THPO
OH
(S)
CH3
16-S
f1 (ppm)

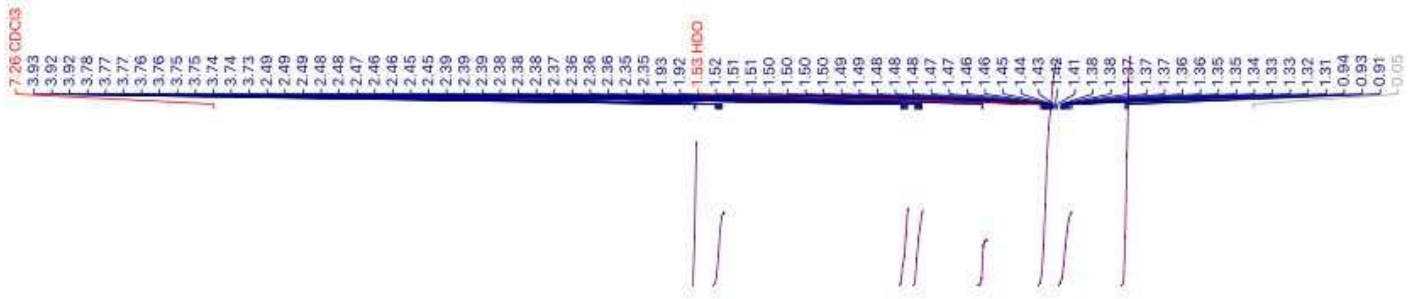

96.99
83.05
78.52
69.80
62.13
54.77
38.50
30.37
27.92
25.41
19.17
18.92
14.09
THPO
OH
(S)
CH3
16-S
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

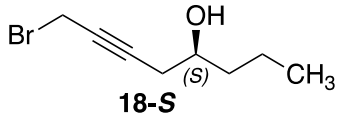

HO
OH
(S)
CH3
17-S
f1 (ppm)


HO
OH
(S)
CH3

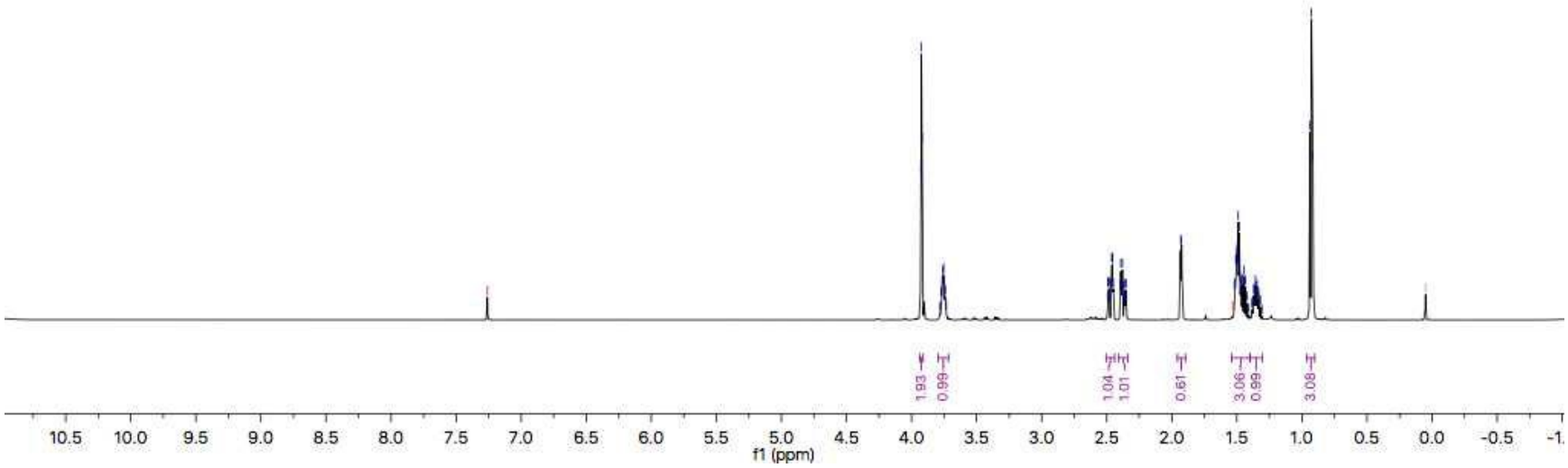
17-*S*

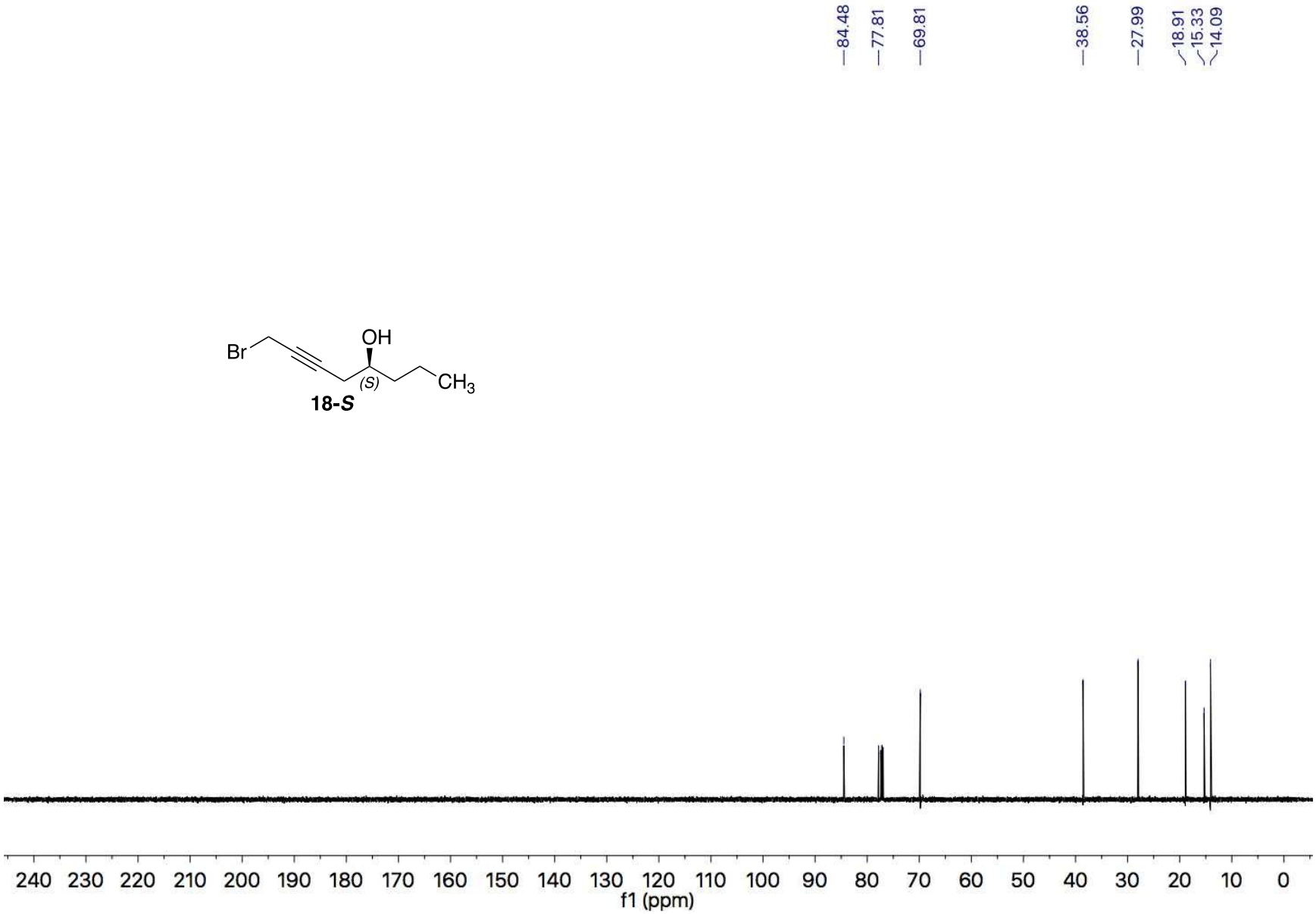
82.74
80.69
69.82
50.76
38.36
27.49
18.94
14.04
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

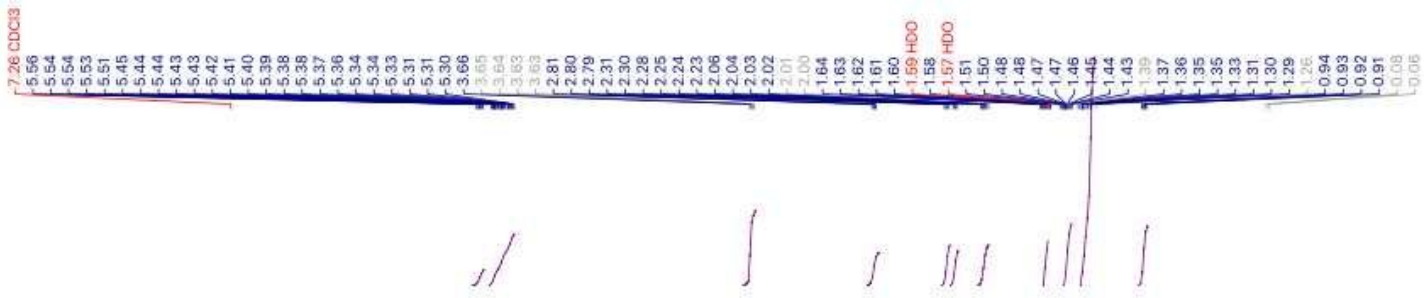

7.26 CDCl3
1.53 HDO

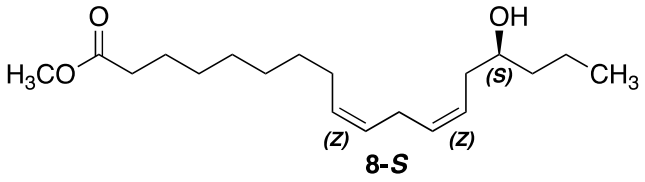

Br
OH
(S)
CH3

18-*S*

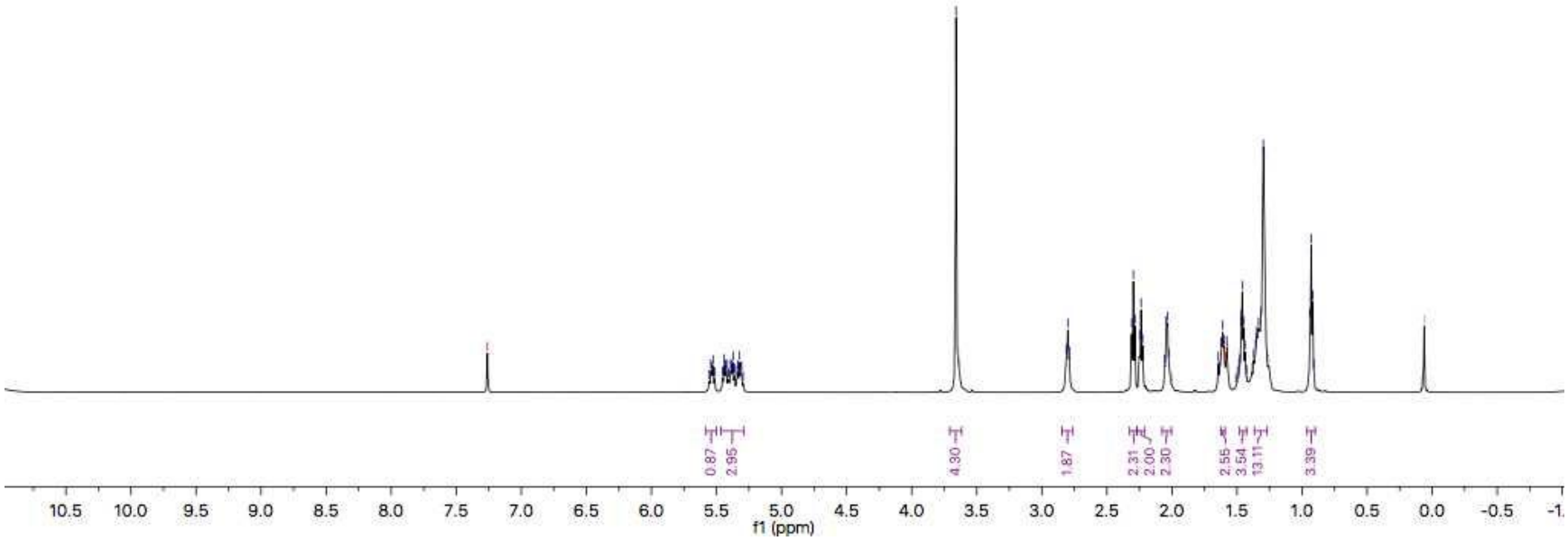

1.93
0.99
1.04
1.01
0.61
3.06
0.99
3.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

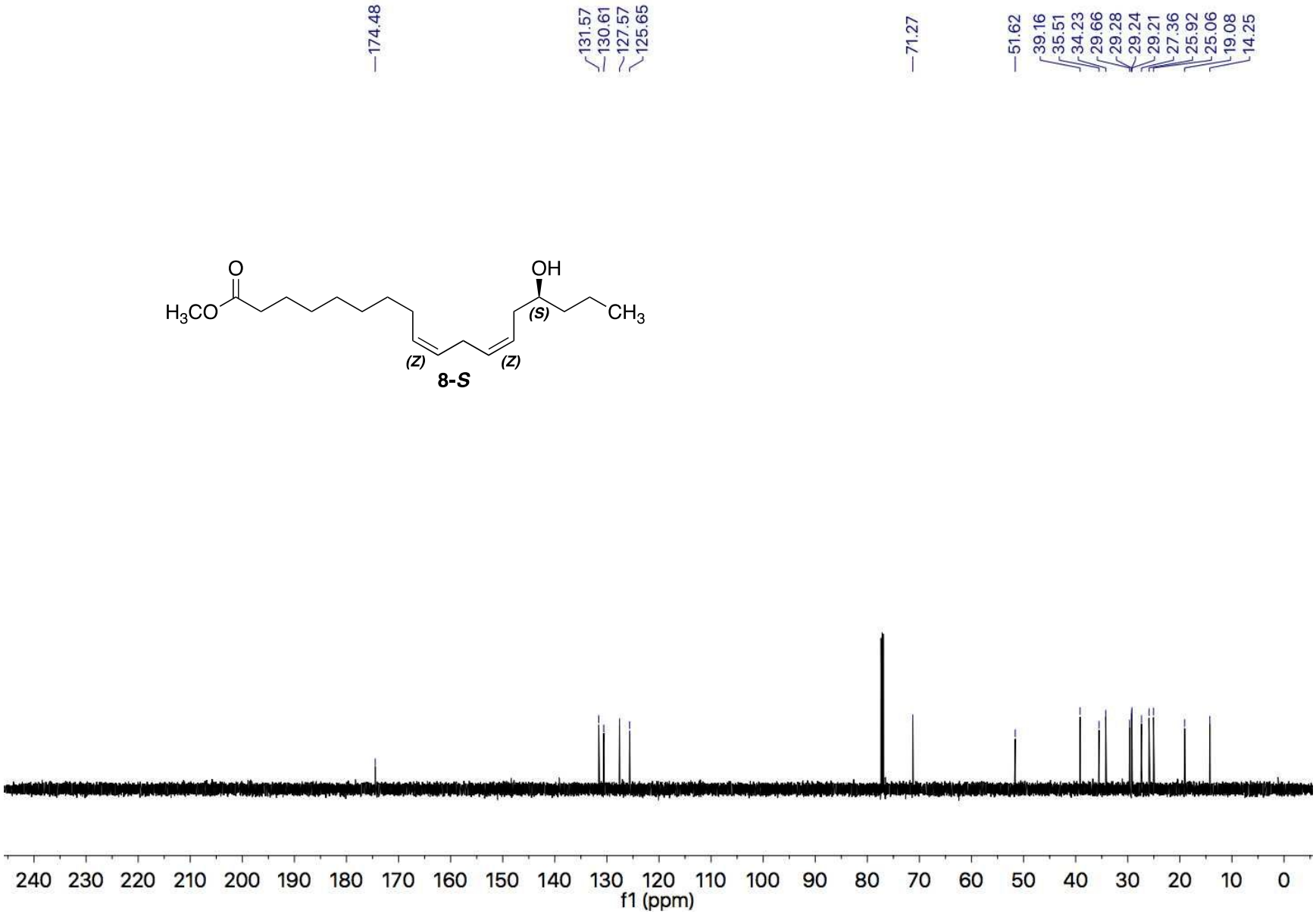

84.48
77.81
69.81
38.56
27.99
18.91
15.33
14.09
Br
OH
(S)
CH3
18-S
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

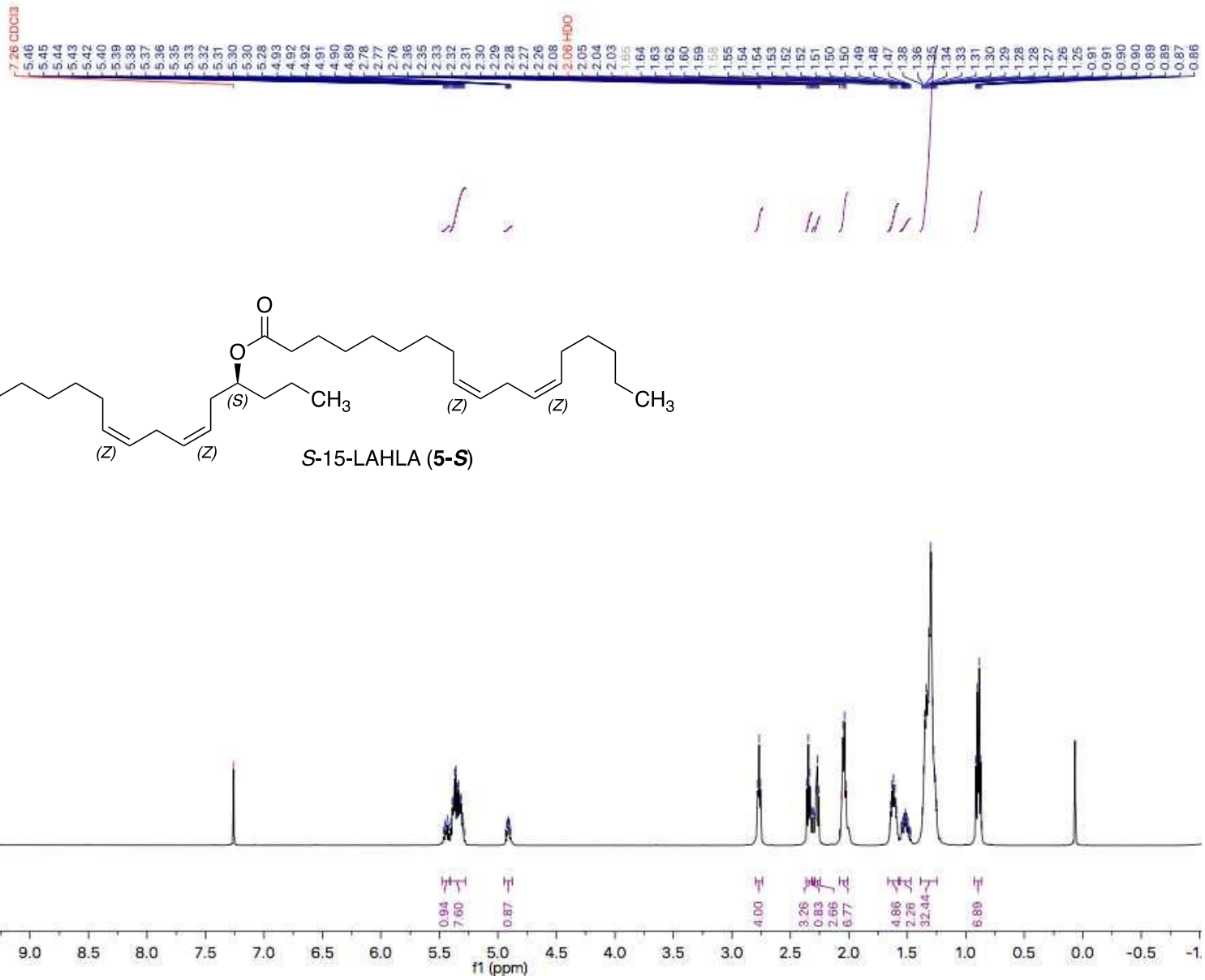

7.26 CDCl3
5.56
5.54
5.54
5.53
5.51
5.45
5.44
5.44
5.43
5.43
5.42
5.41
5.40
5.39
5.38
5.38
5.37
5.36
5.34
5.34
5.33
5.31
5.31
5.30
3.66
3.65
3.64
3.63
2.81
2.80
2.79
2.31
2.30
2.28
2.25
2.24
2.23
2.06
2.04
2.03
2.02
2.01
2.00
1.64
1.63
1.62
1.61
1.60
1.59 HDO
1.58
1.57 HDO
1.51
1.50
1.48
1.48
1.47
1.47
1.46
1.45
1.44
1.43
1.39
1.37
1.36
1.35
1.35
1.33
1.31
1.30
1.29
1.26
0.94
0.93
0.92
0.91
0.08
0.06


O
H3CO
OH
(S)
CH3
(Z)
(Z)

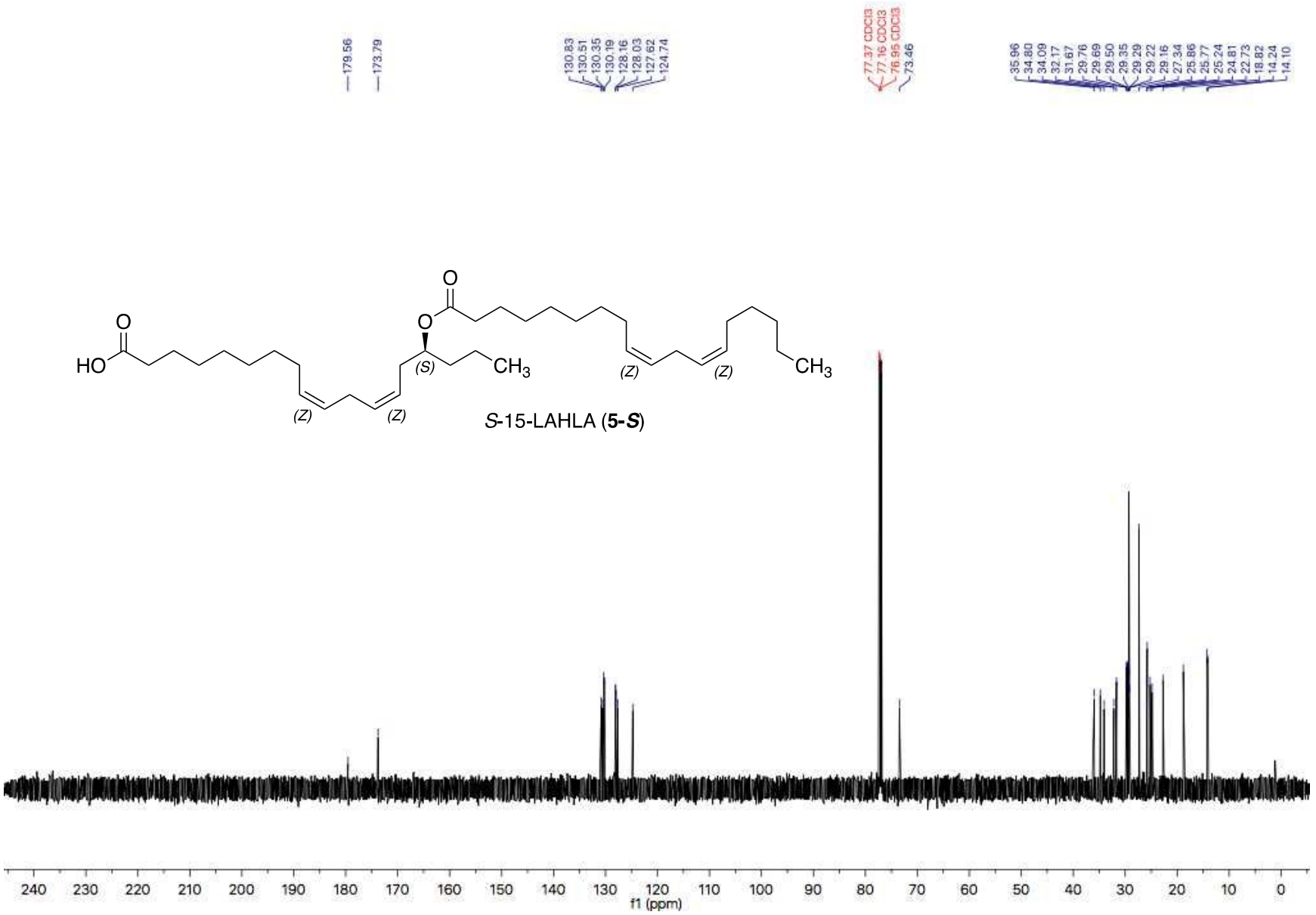
8-*S*

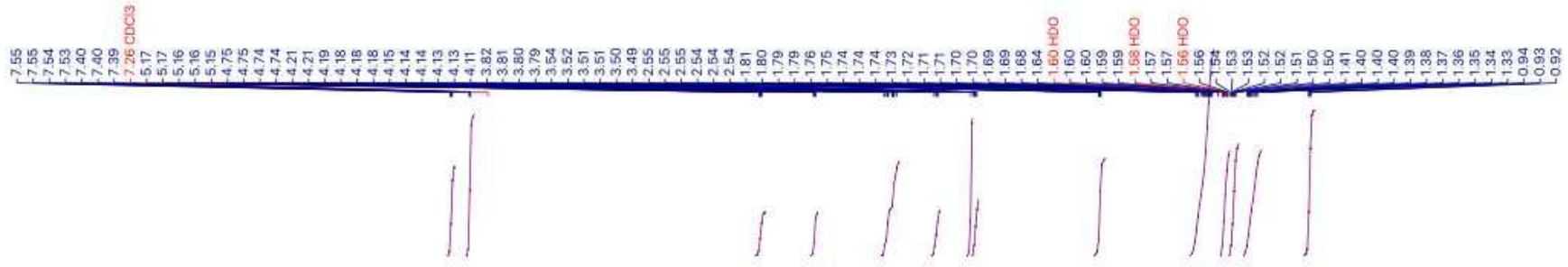

0.87
2.95
4.30
1.87
2.31
2.00
2.30
2.55
3.54
13.11
3.39
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

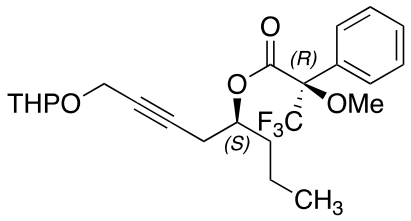

174.48
131.57
130.61
127.57
125.65
71.27
51.62
39.16
35.51
34.23
29.66
29.28
29.24
29.21
27.36
25.92
25.06
19.08
14.25
O
H3CO
OH
(S)
CH3
(Z)
(Z)
8-S
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.26 CDCl3
2.08 HDO
HO
O
O
O
(S)
CH3
(Z)
(Z)
(Z)
(Z)
CH3
0.94
7.60
0.87
4.00
3.26
0.83
2.66
6.77
4.86
2.26
32.44
6.89
f1 (ppm)

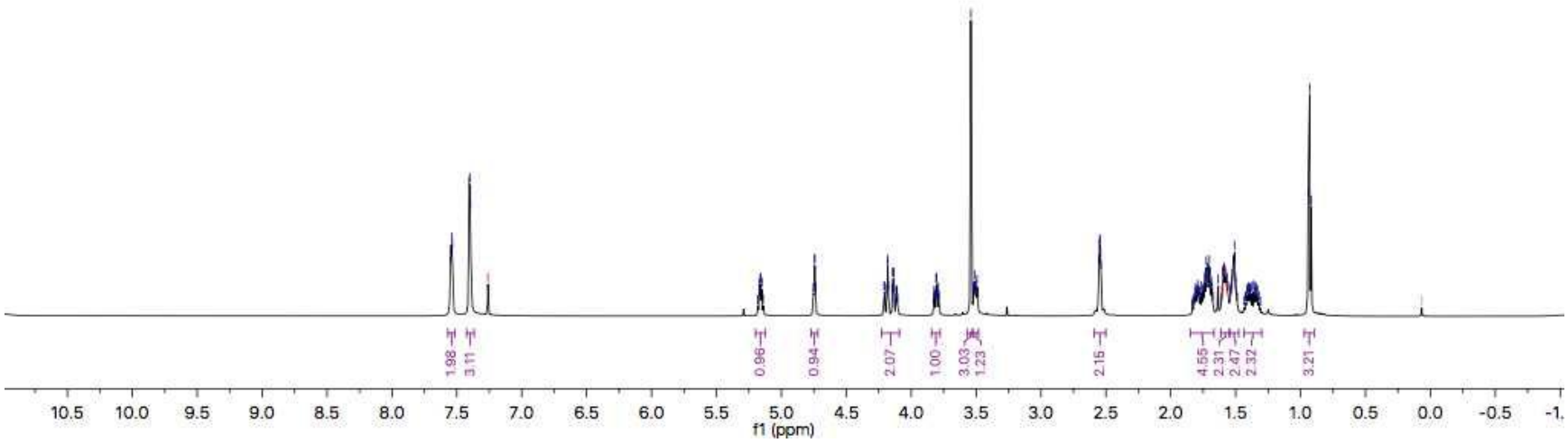
S-15-LAHLA (**5-*S***)

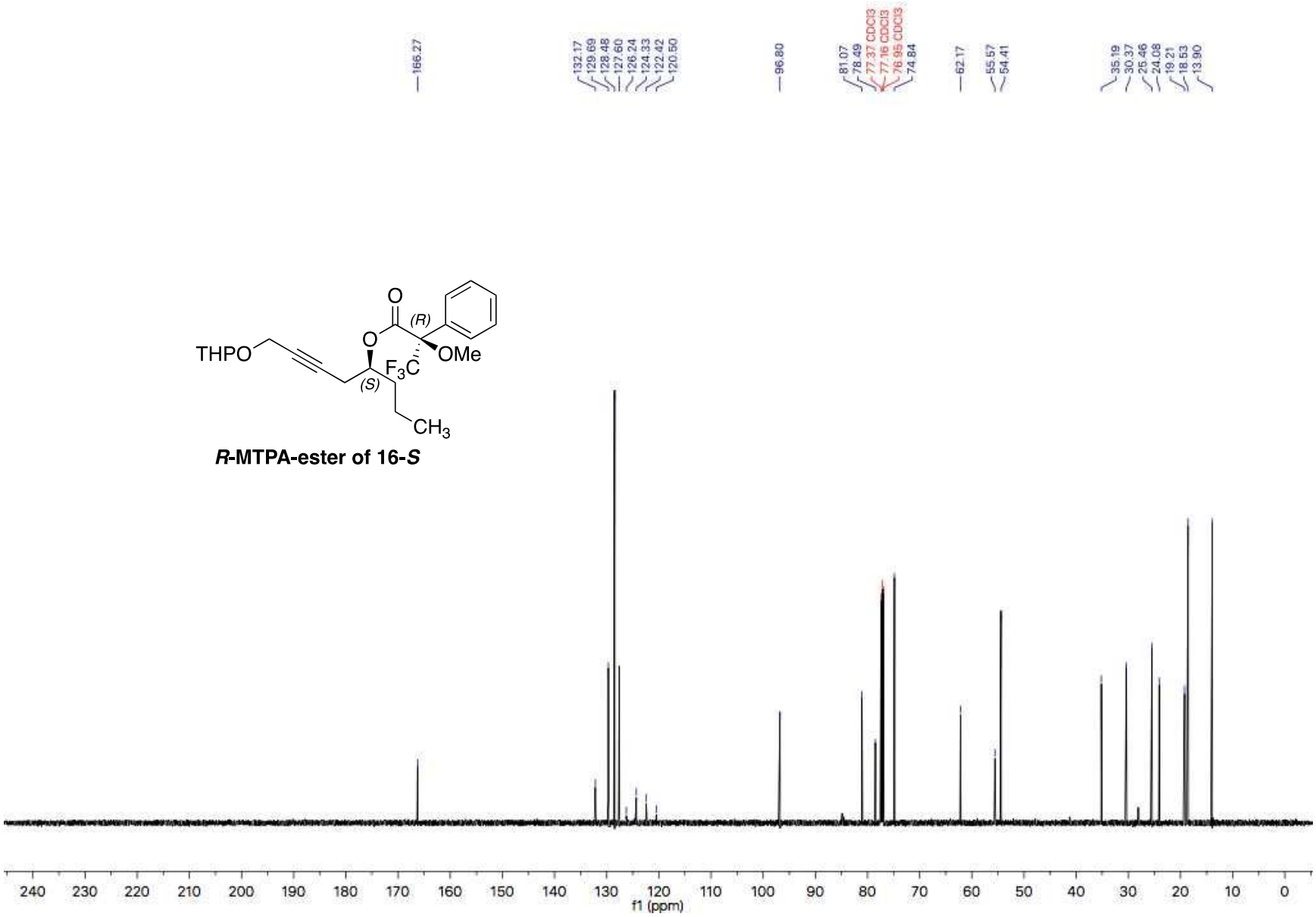

179.56
173.79
130.83
130.51
130.35
130.19
128.16
128.03
127.62
124.74
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
73.46
35.96
34.80
34.09
32.17
31.67
29.76
29.69
29.50
29.35
29.29
29.22
29.16
27.34
25.86
25.77
25.24
24.81
22.73
18.82
14.24
14.10
HO
O
O
O
(S)
CH3
(Z)
(Z)
(Z)
(Z)
CH3
S-15-LAHLA (5-S)
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



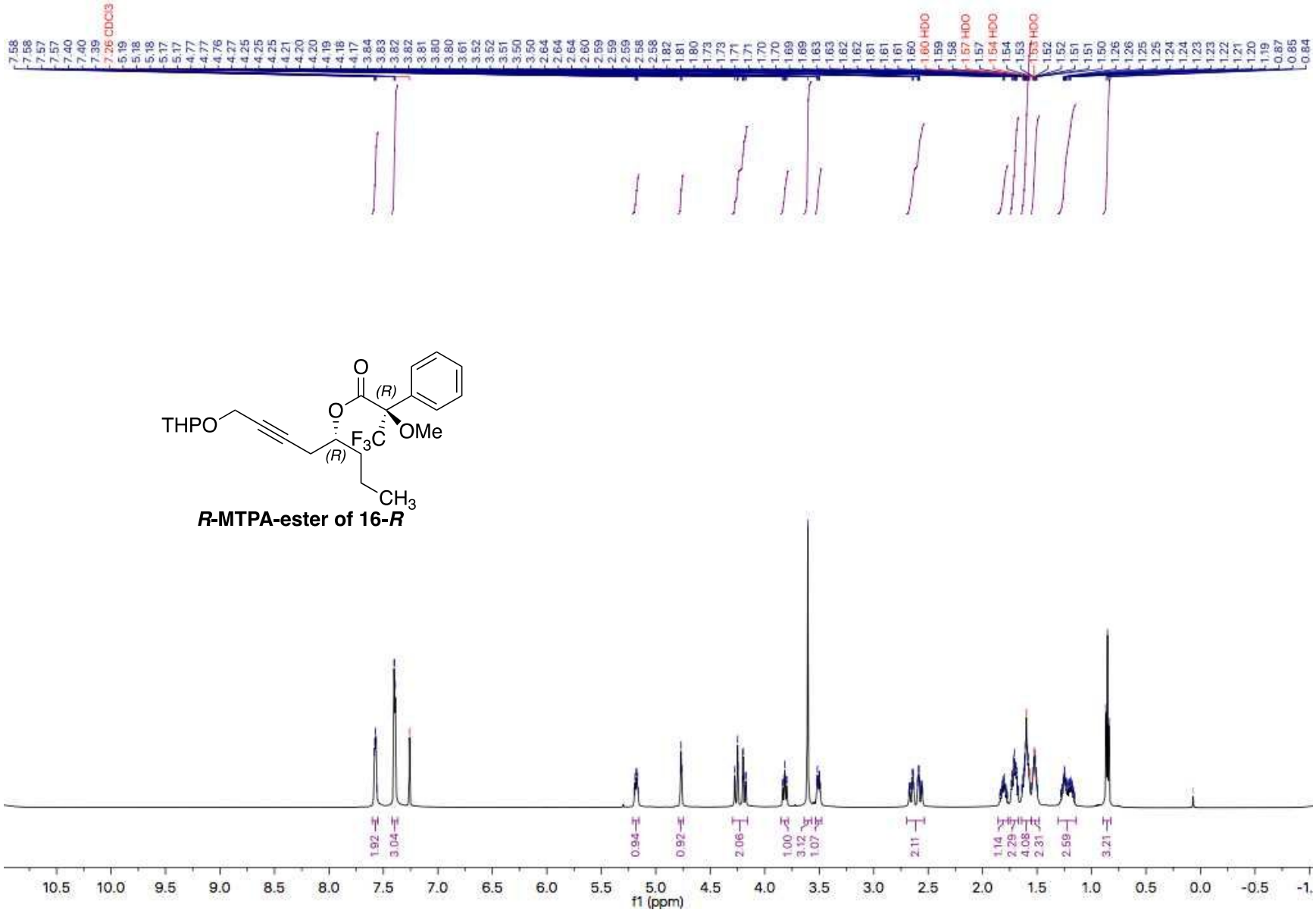


R*-MTPA-ester of 16-*S

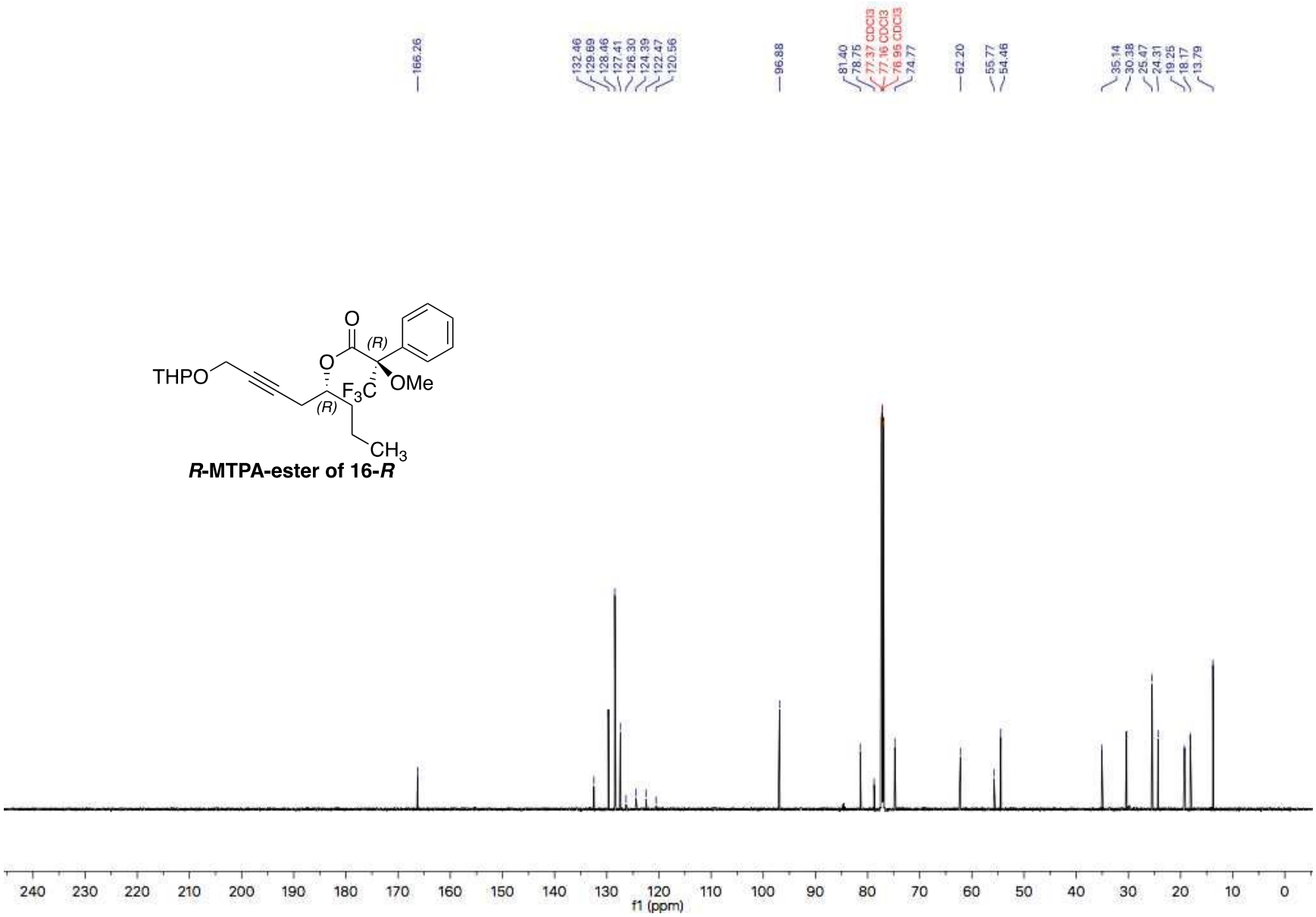




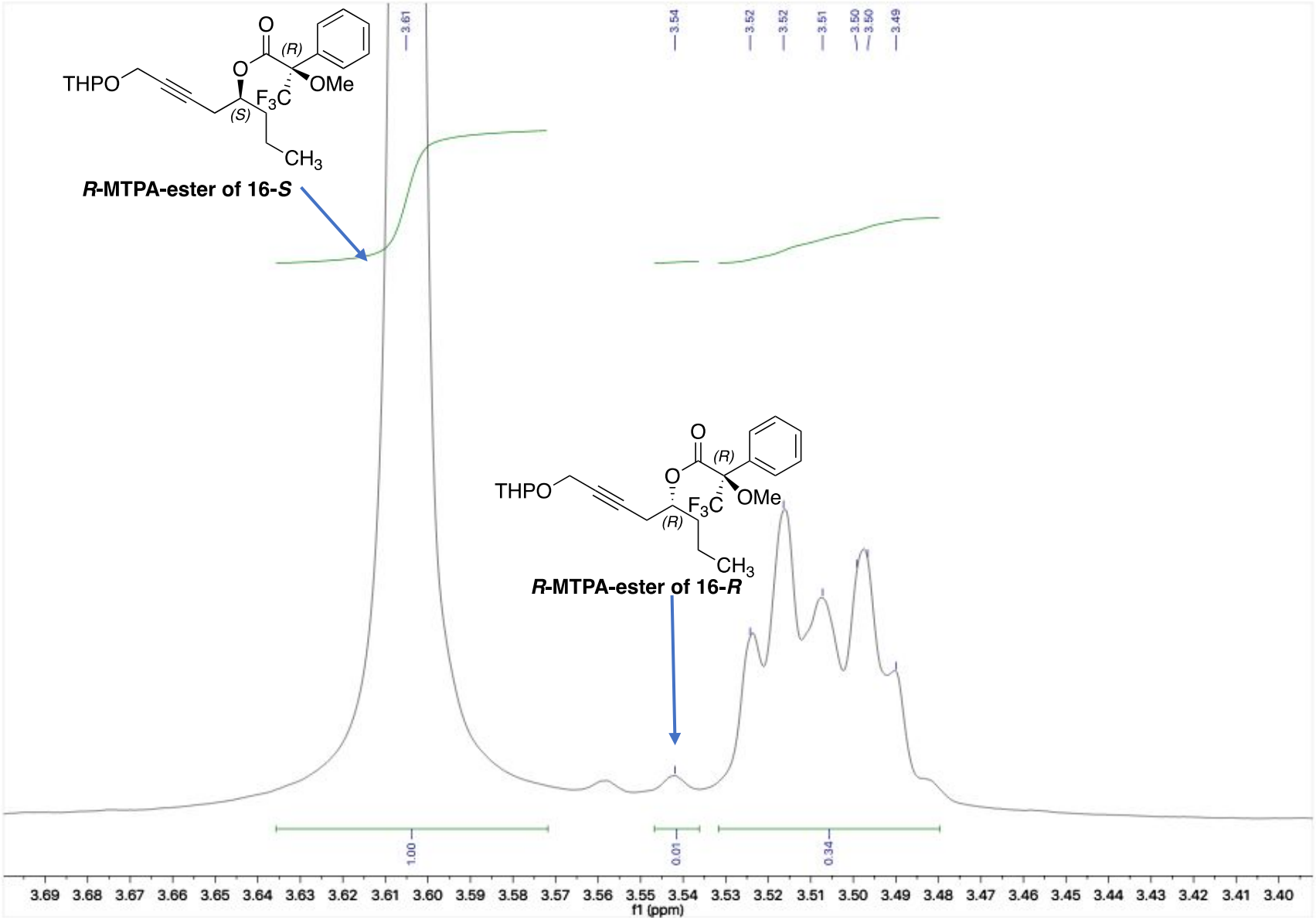
R*-MTPA-ester of 16-*S

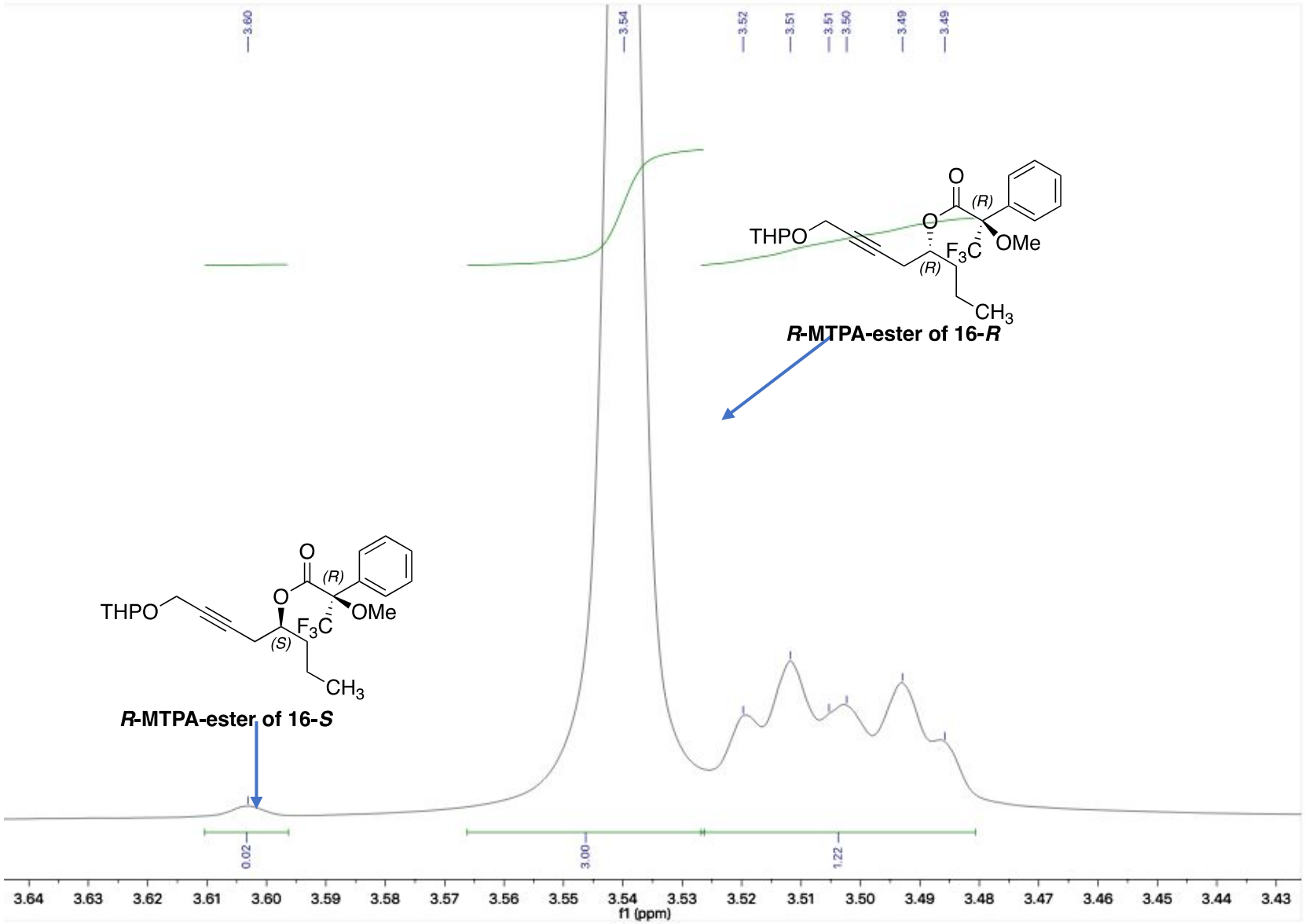


R*-MTPA-ester of 16-*R



R*-MTPA-ester of 16-*R


THPO
O
(R)
O
OMe
F3C
(S)
CH3
R-MTPA-ester of 16-S
THPO
O
(R)
O
OMe
F3C
(R)
CH3
R-MTPA-ester of 16-R
3.61
3.54
3.52
3.52
3.51
3.50
3.50
3.49
1.00
0.01
0.34
3.69 3.68 3.67 3.66 3.65 3.64 3.63 3.62 3.61 3.60 3.59 3.58 3.57 3.56 3.55 3.54 3.53 3.52 3.51 3.50 3.49 3.48 3.47 3.46 3.45 3.44 3.43 3.42 3.41 3.40
f1 (ppm)


3.60
3.54
3.52
3.51
3.51
3.50
3.49
3.49
THPO
O
(R)
O
OMe
F3C
(R)
CH3
R-MTPA-ester of 16-R
THPO
O
(R)
O
OMe
F3C
(S)
CH3
R-MTPA-ester of 16-S
0.02
3.00
1.22
3.64 3.63 3.62 3.61 3.60 3.59 3.58 3.57 3.56 3.55 3.54 3.53 3.52 3.51 3.50 3.49 3.48 3.47 3.46 3.45 3.44 3.43
f1 (ppm)

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