SUPPORTING INFORMATION

Direct Macrolactonization of Seco Acids via Hafnium(IV) Catalysis.

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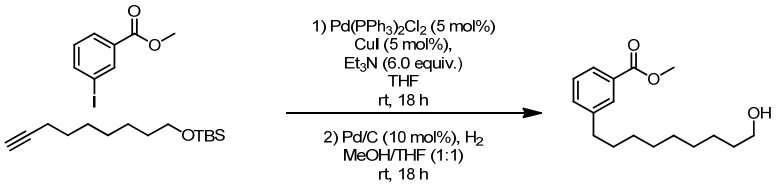
SUPPORTING INFORMATION

TABLE OF CONTENTS:

General:

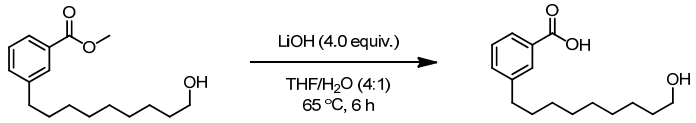
All reactions that were carried out under anhydrous conditions were performed under an inert argon or nitrogen atmosphere in glassware that had previously been dried overnight at 120 ^{o}C or had been flame dried and cooled under a stream of argon or nitrogen.[1] All chemical products were obtained from Sigma-Aldrich Chemical Company or Strem Chemicals and were reagent quality. Technical solvents were obtained from VWR International Co. Methyl 3-iodobenzoate[2], 9-(*tert*-butyldimethylsilyloxy)non-1-yne[3], 11-(*tert*-butyldimethylsilyloxy)undec-1-yne[4], 20-heneicosan-1-ol[5], 8-(triisopropylsilyloxy)octanol[6], 8-(*tert*-butyldimethylsilyloxy)octanol[7], (2,2-dimethyl-1,3-dioxolan-4-yl) methanol[8], 15-(*tert*-butyldimethylsilyloxy)pentadecanoic acid[9], methyl (15-hydroxypentadecyl)-*L*-phenylalanyl-*L*-phenylalaninium trifluoroacetate[10], 8-hydroxyoctan-1-ol acetate[11] and 12-oxooctadecanoic acid[12] were prepared according to literature procedure. Anhydrous solvents (CH_2Cl_2, Et_2O, THF, DMF, toluene, and *n*-hexane) were dried and deoxygenated using a GlassContour system (Irvine, CA). Isolated yields reflect the mass obtained following flash column silica gel chromatography. Organic compounds were purified using the method reported by W. C. Still[13] and using silica gel obtained from Silicycle Chemical division (40-63 nm; 230-240 mesh). Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel 60 coated with a fluorescence indicator (Silicycle Chemical division, 0.25 mm, F_{254}.). Visualization of TLC plate was performed by UV (254 nm), $KMnO_4$ or *p*-anisaldehyde stains. All mixed solvent eluents are reported as v/v solutions. Concentration refers to removal of volatiles at low pressure on a rotary evaporator. All reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR. NMR spectra were taken in deuterated $CDCl_3$ using Bruker AV-300 and AV-400 instruments unless otherwise noted. Signals due to the solvent served as the internal standard ($CHCl_3$: δ 7.27 for ^{1}H, δ 77.0 for ^{13}C). The acquisition parameters are shown on all spectra. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of couplings constants (*J*) corresponds to the order of the multiplicity assignment. High resolution mass spectroscopy (HRMS) was done by the Centre régional de spectrométrie de masse at the Département de Chimie, Université de Montréal from an Agilent LC-MSD TOF system using ESI mode of ionization unless otherwise noted.

SYNTHETIS OF MACROCYCLE PRECURSORS



54 %

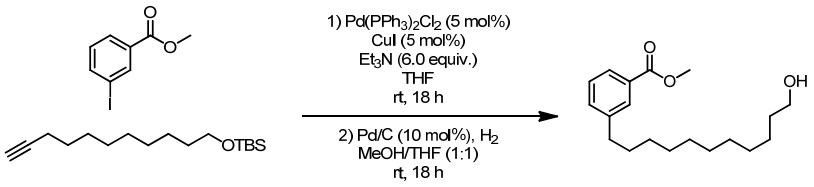
Methyl 3-(9-hydroxynon-1-yl)benzoate (S1): Methyl 3-iodobenzoate (500 mg, 1.91 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (10 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (67 mg, 0.096 mmol, 0.05 equiv.) and CuI (18.3 mg, 0.096 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 minutes. Triethylamine (1.59 mL, 11.46 mmol, 6.0 equiv.) and the alkyne (592 mg, 2.10 mmol, 1.1 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduce pressure and passed through a short pad of silica (20 % EtOAc in hexanes). The crude was dissolved in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL). Pd/C (405 mg, 5% w/w, 0.191 mmol, 0.1 equiv.) was added and the reaction mixture was purged with H_2 for 10 minutes. A balloon filled with H_2 equipped with a syringe was put on the septum and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was passed through a short pad of Celite® and concentrated under reduced pressure. Purification by flash chromatography (10% to 30% EtOAc in hexanes) was performed to afford the desired product as a colorless oil (253 mg, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.36 (m, 2H), 3.92 (s, 3H), 3.64 (t, *J*= 6.8 Hz), 2.65 (t, *J*= 8.0 Hz) 1.65-1.55 (m, 4H), 1.38-1.31 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 143.2, 133.1, 130.0, 129.5, 128.2, 126.9, 63.0, 52.0, 35.7, 32.7, 31.3, 29.4, 29.3, 29.3, 29.1, 25.7 ppm; HRMS (ESI+) for $C_{17}H_{27}O_3$ $[M + H]^+$ calculated: 278.1882 found: 278.1893.



61 %

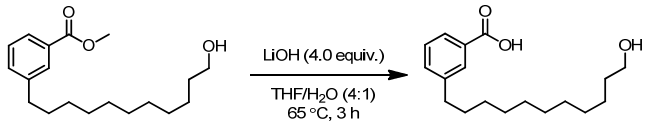
3-(9-Hydroxynon-1-yl)benzoic acid (S2): Methyl 3-(9-hydroxynon-1-yl)benzoate (253 mg, 0.91 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (4.8 mL). LiOH (87 mg, 3.64 mmol, 4.0 equiv.) was added as an aqueous solution (1.2 mL). The reaction mixture was stirred at 65 ^{o}C for 6 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a white solid (145 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.43-7.36 (m, 2H), 6.78 (br s, 1H (OH)), 3.66 (t, *J*= 6.4 Hz, 2H), 2.67 (t, *J*= 7.6 Hz, 2H), 1.66-1.55 (m, 4H), 1.31 (m, 10H) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 171.8, 143.3, 133.8, 130.0, 129.4, 128.4, 127.5, 63.0, 35.6, 32.6, 31.2, 29.4, 29.32, 29.29, 29.1, 25.7 ppm; HRMS (ESI+) for $C_{16}H_{25}O_3$ $[M + H]^+$ calculated: 264.1725 found: 264.1738.



44 %

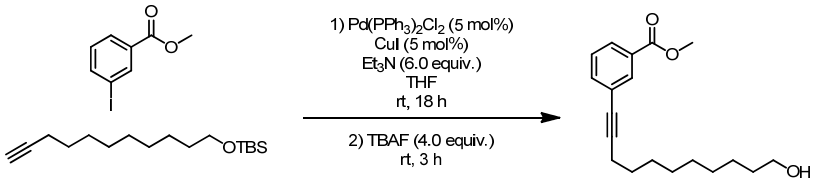
Methyl 3-(11-hydroxyundec-1-yl)benzoate (S3): Methyl 3-iodobenzoate (300 mg, 1.15 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (6 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (40 mg, 0.057 mmol, 0.05 equiv.) and CuI (11 mg, 0.057 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 minutes. Triethylamine (0.95 mL, 6.87 mmol, 6.0 equiv.) and the alkyne (355 mg, 1.26 mmol, 1.1 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduce pressure and passed through a short padof silica (20 % EtOAc in hexanes). The crude was dissolved in a mixture of methanol (5 mL) and tetrahydrofuran (5 mL). Pd/C (244 mg, 5% w/w, 1.15 mmol, 0.1 equiv.) was added and the reaction mixture was purged with H_2 for 10 minutes. A balloon filled with H_2 equipped with a syringe was put on the septum and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was passed through a short pad of Celite® and concentrated under reduced pressure. Purification by flash chromatography (10 % to 30 % EtOAc in hexanes) was performed to the desired product as a colorless oil (154 mg, 44 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.36 (m, 2H), 3.92 (s. 3H), 3.64 (t, *J*= 6.8 Hz, 2H), 2.65 (t, *J*= 7.2 Hz), 1.65-1.55 (m, 4H), 1.31-1.27 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 143.2, 133.1, 130.0, 129.5, 128.2, 126.9 63.1, 52.0, 35.7, 32.8, 31.3, 29.55, 29.51, 29.48, 29.42, 29.38, 29.2, 25.7 ppm; HRMS (ESI+) for $C_{19}H_{31}O_3$ $[M + H]^+$ calculated: 306.2195 found: 306.2207.



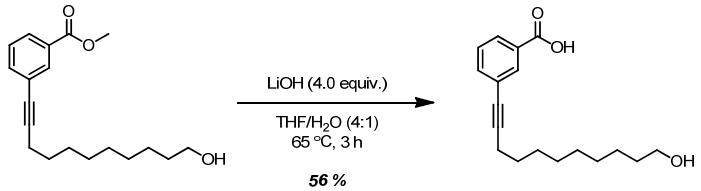
85 %

3-(11-Hydroxyundec-1-yl)benzoic acid (S4): Methyl 3-(11-hydroxyundec-1-yl)benzoate (154 mg, 0.50 mmol, 1.0 eq) was dissolved in tetrahydrofuran (4 mL). LiOH (48 mg, 2.01 mmol, 4.0 eq) was added as an aqueous solution (1 mL). The reaction mixture was stirred at 65 ^{o}C for 3h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford

the desired product acid as a white solid (125 mg, 85 %).[1]H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.44-7.37 (m, 2H), 3.67 (t, *J*= 6.6 Hz, 2H), 2.68 (t, *J*= 7.4 Hz, 2H), 1.67-1.55 (m, 4H), 1.33-1.28 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 143.3, 133.9, 130.1, 129.1, 128.4, 127.5, 63.1, 35.6, 32.7, 31.2, 29.5, 29.44, 29.42, 29.38, 29.3, 29.0, 25.7 ppm; HRMS (ESI+) for $C_{18}H_{29}O_3$ $[M + H]^+$ calculated: 293.2111 found: 293.2110.

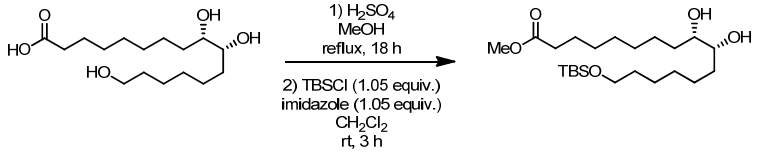


Methyl 3-(11-hydroxyundec-1-yn-1-yl)benzoate (S5): Methyl 3-iodobenzoate (165 mg, 0.629 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (3 mL, 0.2 M). $Pd(PPh_3)Cl_2$ (22 mg, 0.032 mmol, 0.05 equiv.) and CuI (6.1 mg, 0.032 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 minutes. Triethylamine (0.53 mL, 3.77 mmol, 6.0 equiv.) and the alkyne (195 mg, 0.691 mmol, 1.1 equiv.) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 10 mL) was added and the slurry was concentrated under reduce pressure and passed through a short pad of silica (20 % EtOAc in hexanes). The crude was dissolved in THF (12 mL) and TBAF (2.43 mL as 1M solution in THF, 2.43 mmol, 4.0 equiv.) was added to the solution. The reaction mixture was stirred at room temperature for 3 hours and was then quenched by adding NH_4Cl saturated solution (10 mL). Extraction with EtOAc was performed (2 x 10 mL) and the organic phase was washed with water (20 mL) and brine (20 mL). The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product as a colorless oil (74 mg, 39 % over two steps). [1]H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.93 (d, *J*= 7.7 Hz, 1H), 7.56 (d, *J*= 7.4 Hz, 1H), 7.36 (dd, *J*= 7.6 Hz, 7.6 Hz, 1H), 3.92 (s, 3H), 3.65 (t, *J*= 6.6Hz, 2H), 2.42 (t, *J*= 7.0Hz, 2H), 1.65-1.55 (m, 4H), 1.50-1.42 (m, 2H), 1.34 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.7, 132.7, 130.2 128.4, 128.3, 124.5, 91.5, 79.6, 63.0, 52.2, 32.8, 29.4, 29.3, 29.0, 28.8, 28.6, 25.7, 19.3 ppm; HRMS (ESI+) for $C_{19}H_{27}O_3$ $[M + H]^+$ calculated: 303.1955, found: 303.1965.



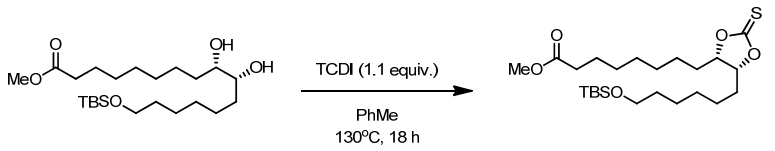
3-(11-Hydroxyundec-1-yn-1-yl)benzoic acid (S6): Methyl 3-(11-hydroxyundec-1-yn-1-yl)benzoate (74 mg, 0.243 mmol, 1.0 eq) was dissolved in tetrahydrofuran (3.2 mL). LiOH

(23 mg, 0.972 mmol, 4.0 eq) was added as an aqueous solution (0.8 mL). The reaction mixture was stirred at 65 ^{o}C for 3 h. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a white solid (39 mg, 56 %) (Note: Seco acid **S6** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^{1}H and ^{13}C spectra). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99 (d, *J*= 7.6 Hz, 1H), 7.61 (d, *J*= 8.0 Hz, 1H), 7.40 (dd, *J*= 8.0 Hz, 8.0 Hz, 1H), 7.49 (br s, 1H (OH)), 3.67 (t, *J*= 6.4Hz, 2H), 2.42 (t, *J*= 6.8 Hz, 2H), 1.64-1.58 (4H), 1.50-1.47 (m, 2H), 1.35 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 136.4, 133.3, 129.0, 128.4, 124.7, 91.8, 79.6, 63.0, 32.6, 29.4, 29.3, 29.0, 28.8, 28.5, 25.7, 19.3 ppm; HRMS (ESI+) for $C_{18}H_{25}O_3$ $[M + H]^+$ calculated: 289.1798, found: 289.1800.



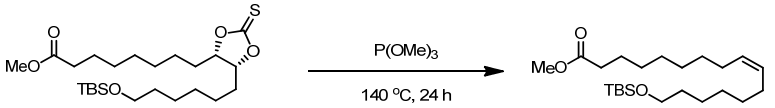
***(±)-erythro*-Methyl 16-*tert*-butyldimethylsilyloxy-9,10-dihydroxyhexadecanoate (S7)**

(±)-*erythro*-aleuritic acid (500 mg, 1.64 mmol, 1.0 equiv.) was dissolved in MeOH (40 mL). Concentrated H_2SO_4 (5-10 drops) was added to the solution. The reaction mixture was heated to reflux for 18 hours and then brought back to room temperature and quenched by the addition of a K_2CO_3 saturated solution (until pH = 7). Extraction was performed by the addition of EtOAc (100 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with H_2O (100 mL) and brine (75 mL), dried over Na_2SO_4 and concentrated under reduce pressure. The crude was the dissolved in CH_2Cl_2 (15 mL). TBSCl (260 mg, 1.72 mmol, 1.05 equiv.) and imidazole (117 mg, 1.72 mmol, 1.05 equiv.) were added to the solution. The reaction mixture was stirred at room temperature for 3 hours and was quenched by the addition of water (10 mL). Extraction was performed with EtOAc (2 x 25 mL) and the combined organic phases were washed with water (20 mL) and brine (20 mL). Silica gel was added (10 mL) and the slurry was concentrated under reduced pressure. Flash chromatography was performed (25 % EtOAc in hexanes) to afford the desired product as a white solid (534 mg, 84 % over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.62 (t, J=6.8Hz, 2H), 3.42-3.40 (m, 2H), 2.32 (t, *J*= 7.2Hz, 2H), 2.08-2.04 (br s, 2H (OH)), 1.65-1.62 (m, 2H), 1.53-1.34 (m, 20H), 0.92 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 74.5, 74.4, 63.2, 51.4, 34.0, 33.6 (2C), 32.8, 29.5, 29.4, 29.1, 29.0, 26.0, 25.8, 25.6, 25.5, 24.9, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{23}H_{49}O_5Si$ $[M + H]^+$ calculated : 433.3344 found: 433.3364.



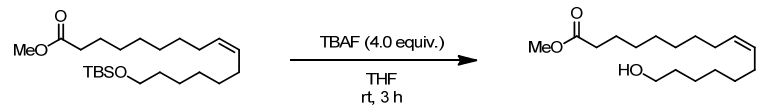
98 %

(±)-*erythro*-Methyl 8-((6-*tert*-butyldimethylsilyloxy)hexyl-2-thioxo-1,3-dioxolan-4-yl)octanoate (S8). The diol **S7** (200 mg, 0.462 mmol, 1.0 equiv.) was dissolved in PhMe (3.0 mL) in a sealed tube. TCDI was added (90.4 mg, 0.508 mmol, 1.1 equiv.) and the reaction vial was sealed and the mixture was stirred at 130°C for 18 hours. The solution was cooled down to room temperature and silica gel (10 mL) was added and the slurry was concentrated under reduced pressure. Flash chromatography was performed (5-10 % EtOAc in hexanes) to afford the desired product (215 mg, 98 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46-4.44 (m, 2H), 3.68 (s, 3H), 3.61 (t, *J*= 6.4Hz, 2H), 2.32 (t, *J*=7.2 Hz, 2H), 1.80-1.60 (m, 6H), 1.53-1.50 (m, 4H), 1.40-1.30 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191,7, 174.2, 86.8 (2C), 63.0, 51.5, 34.0, 33.25, 33.21, 32.6, 29.0, 28.92 (2C), 28.90, 25.9, 25.6, 24.8, 24.64, 24.59, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{24}H_{47}O_5SSi$ $[M + H]^+$ calculated: 475.2908 found: 475.2927.



62 %

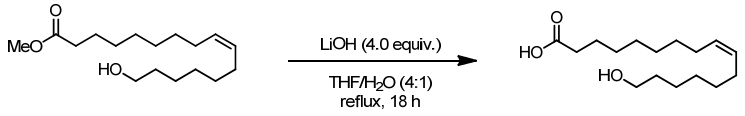
Methyl (*Z*)-16-(*tert*-butyldimethylsilyloxy)hexadec-9-enoate (S9) The thiocarbonate **S8** (200mg, 0.423 mmol, 1.0 equiv.) was dissolved in trimethylphosphite (10 mL) in a sealed tube. The reaction mixture was stirred at 140°C for 24 hours. The solution was cooled to room temperature and concentrated under reduced pressure. Flash chromatrography (3 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (101 mg, 62 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39-5.38 (m, 2H), 3.67 (s, 3H), 3.60 (t, *J*= 6.4Hz, 2H), 2.31 (t, *J*= 6.8Hz, 2H), 1.94 (m, 4H), 1.35-1.30 (m, 4H), 1,30 (m, 14H), 0.90 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 130.3 (2C), 63.3, 51.4, 34.1, 32.8, 32.54, 32.52, 29.6, 29.5, 29.1 (2C), 28.9(2C), 26.0, 25.6, 24.9, 18.4, -5.3 ppm; HRMS (ESI+) for $C_{23}H_{47}O_3Si$ $[M + H]^+$ calculated: 399.3289 found: 399.3301.



58 %

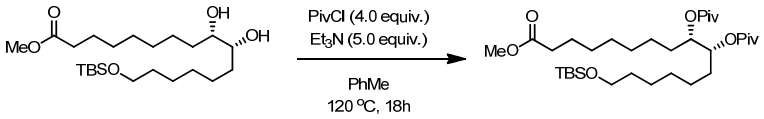
Methyl (*Z*)-16-hydroxyhexadec-9-enoate (S10) Compound **S9** (100 mg, 0.263 mmol, 1.0 equiv.) was dissolved in THF (4 mL). A solution of TBAF (1M in THF) (1.05 mL, 4.0 equiv.) was added and the mixture was stirred at room temperature for 3 hours. The reaction was quenched by the addition of water (5 mL). Extraction with EtOAc (2 x 10

mL) was performed and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic phase was then dried under Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (40 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (41 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38-5.36 (m, 2H), 3.66 (s, 3H), 3.63 (t, *J*= 6.8Hz, 2H), 2.30 (t, *J*=7.2Hz, 2H), 1.96, (m, 4H), 1.62-1.54 (m, 4H), 1.35-1.28 (m, 14H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 130.3, 130.2, 63.0, 51.4, 34.1, 32.7, 32.5, 32.4, 29.50, 29.48, 29.1 (2C), 28.9, 28.8, 25.6, 24.9 ppm; HRMS (ESI+) for $C_{17}H_{33}O_3$ $[M + H]^+$ calculated: 285.2424 found: 285.2436.



96 %

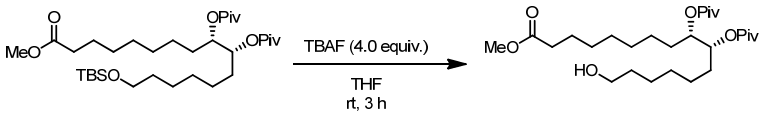
(*Z*)-16-hydroxyhexadec-9-enoic acid (S11) The methyl ester **S10** (41 mg, 0.152 mmol, 1.0 equiv.) was dissolved in THF (1.6 mL). LiOH (15 mg, 0.608 mmol, 4.0 equiv.) was dissolved in water (0.4 mL) and added to the previous mixture. The solution was stirred at reflux for 18 hours. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the product as a white solid (39 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38-5.37 (m, 2H), 3.65 (t, *J*= 6.7 Hz, 2H), 2.34 (t, *J*= 7.4 Hz, 2H), 1.99-1.96 (m, 4H), 1.63-1.57 (m, 4H), 1.40-1.25 (m, 14H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 130.4, 130.3, 63.0, 34.0, 32.6, 32.45, 32.43, 29.5, 29.03, 29.00, 28.8, 28.7, 25.6, 24.7 ppm; HRMS (ESI+) for $C_{16}H_{31}O_3$ $[M + H]^+$ calculated 271.2268 found: 271.2273.



88 %

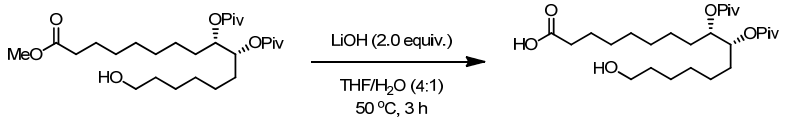
(±)-*erythro*-Methyl 16-(*tert*-butyldimethylsilyloxy)heptadecane-8,9-diyl[bis(2,2-dimethylpropanoate)]oate (S12) The diol **S7** (206 mg, 0.476 mmol, 1.0 equiv.) was dissolved in PhMe (5 mL) in a sealed tube. Et_3N (0.33 mL, 2.30 mmol, 5.0 equiv.) was added followed by PivCl (0.23 mL, 1.90 mmol, 4.0 equiv.). The reaction mixture was stirred at 120 °C for 18 hours. The reaction was quenched by addition of water (5 mL). Extraction with EtOAc was performed (2 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduce pressure. Flash chromatography (10 % EtOAc in hexanes) was performed to afford the desired product (252 mg, 88 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (m, 2H), 3.67 (s, 3H), 3.59 (t, *J*= 6.8Hz, 2H), 2.30 (t, *J*= 7.6Hz, 2H), 1.63-1.48 (m, 8H), 1.30-1.23 (m, 12H), 1.22 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (2C), 174.2, 73.3 (2C),

63.1, 51.4, 38.9 (2C), 34.1, 32.7, 30.8, 29.23, 29.20, 29.02, 29.00, 27.2 (2 x **C**($\underline{\mathbf{C}}$H$_3$)$_3$), 26.0, 25.6, 25.0, 24.9, 18.4, -5.3ppm; HRMS (ESI+) for $C_{33}H_{64}O_7SiNa$ $[M + Na]^+$ calculated 623.4314 found: 623.4310.



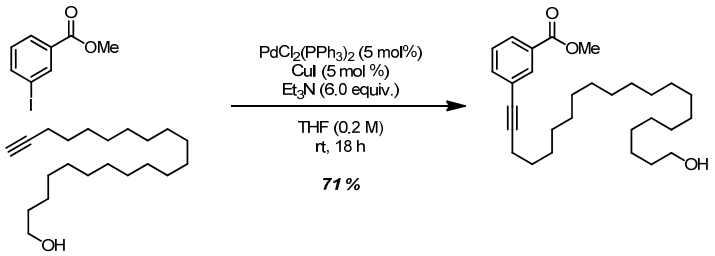
70 %

(±)-*erythro*-Methyl 16-hydroxyheptadecane-9,10-diyl[bis(2,2-dimethylpropanoate)] oate (S13) Compound **S12** (163 mg, 0.272 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL). A solution of TBAF (1M in THF) (1.09 mL, 4.0 equiv.) was added and the mixture was stirred at room temperature for 3 hours. The reaction was quenched by the addition of water (5 mL). Extraction with EtOAc (2 x 10 mL) was performed and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic phase was then dried under Na_2SO_4 and concentrated under reduce pressure. Flash chromatography (40 % EtOAc in hexanes) was performed to afford the desired product as a colorless oil (93 mg, 70 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (m, 2H), 3.67 (s, 3H), 3.63 (t, *J*= 6.6Hz, 2H), 2.29 (t, *J*= 7.8Hz, 2H), 1.65-1.50 (m, 8H), 1.45-1.30 (m, 16H), 1.22 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (2C), 174.3, 73.2 (2C), 62.9, 51.4, 38.9 (2C), 34.0, 32.6, 30.8, 30.7, 29.2, 29.1, 29.01, 29.00, 27.2 (2 x **C**($\underline{\mathbf{C}}$H$_3$)$_3$), 25.5, 25.0, 24.9 ppm; HRMS (ESI+) for $C_{27}H_{51}O_7$ $[M + H]^+$ calculated 487.3629 found: 487.3652

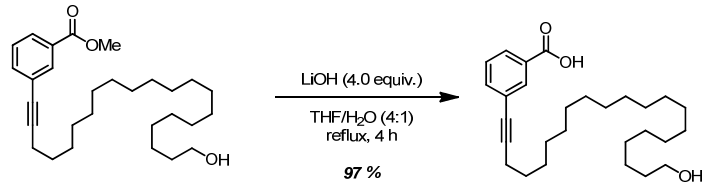


58 %

(±)-*erythro*-16-Hydroxyheptadecane-9,10-diyl[bis(2,2-dimethylpropanoate)]oic acid (S14) Compound **S13** (93 mg, 0.191 mmol, 1.0 equiv.) was dissolved in THF (2.0 mL). LiOH (16 mg, 0.382 mmol, 2.0 equiv.) was dissolved in water (0.5 mL) and added to the THF solution of **S13**. The solution was stirred at 50 °C for 3 hours. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a colorless oil (52 mg, 58 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99-4.96 (m, 2H), 3.63 (t, *J*= 6.5 Hz, 2H), 2.33 (t, *J*= 7.2 Hz, 2H), 1.64-1.23 (m, 24H), 1.21 (s, 18H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 177.9 (2C), 73.2 (2C), 62.8, 38.9 (2C), 33.9, 32.4, 30.7, 30.6, 29.0 (2C), 28.9, 28.8, 27.2 (2 x C($\underline{\mathbf{C}}$H$_3$)$_3$), 25.4, 24.9, 24.6 ppm; HRMS (ESI+) for $C_{26}H_{48}O_7Na$ $[M + Na]^+$ calculated 495.3292 found: 495.3306.

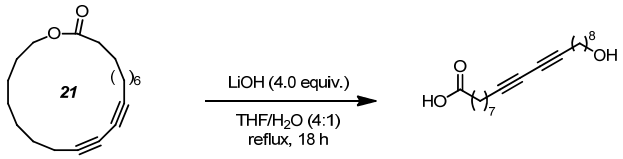


Methyl 3-(21-hydroxyheneicosan-1-yn-1-yl)benzoate (S15) Methyl 3-iodobenzoate (218 mg, 0.832 mmol, 1.0 equiv.) was dissolved in tetrahydrofuran (5 mL, 0.2 M). $Pd(PPh_3)_2Cl_2$ (29 mg, 0.042 mmol, 0.05 equiv.) and CuI (8.0 mg, 0.042 mmol, 0.05 equiv.) were added to the solution and the reaction mixture was purged under N_2 for 5 minutes. Triethylamine (0.69 mL, 4.99 mmol, 6.0 equiv.) and the alkyne (256 mg, 0.832 mmol, 1.0 eq) were added and the reaction mixture was stirred at room temperature for 18 h. Silica (~ 5 mL) was added and the slurry was concentrated under reduce pressure. Flash chromatography (5 to 20 % EtOAc in hexanes) was performed to afford the desired product (261 mg, 71 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J*= 1.6 Hz, 1.6 Hz, 1H), 7.93 (dd, *J*= 7.6 Hz, 7.6Hz, 1.6 Hz, 1H), 7.56 (ddd, *J*= 7.6 Hz, 7.6 Hz, 1.6 Hz, 1H), 7.36 (dd, *J*= 7.6 Hz, 7.6 Hz, 1H), 3.92 (s, 3H), 3.64 (t, *J*= 6.4 Hz, 2H), 2.41 (t, *J*= 6.8 Hz, 2H), 1.65-1.52 (m, 4H), 1.48-1.35 (m, 2H), 1.26 (m, 28H) ppm ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 135.7, 132.7, 130.2, 128.4, 128.3, 124.5, 91.6, 79.6, 63.1, 52.2, 32.8, 29.7 (4C), 29.62, 29.59, 29.58, 29.5, 29.4, 29.1, 28.9, 28.6, 25.7, 19.4 ppm; HRMS (ESI+) for $C_{29}H_{47}O_3$ $[M + H]^+$ calculated: 443.3520 found: 443.3520.

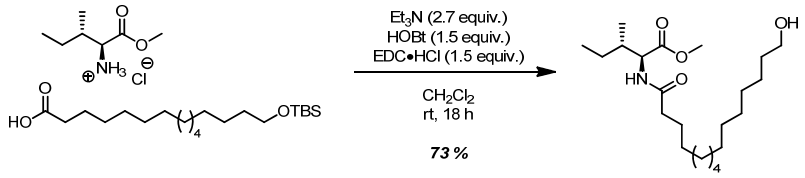


3-(21-Hydroxyheneicosan-1-yn-1-yl)benzoic acid (S16) The methyl ester **S15** (100 mg, 0.226 mmol, 1.0 equiv.) was dissolved in THF (4.0 mL). LiOH (38 mg, 0.903 mmol, 4.0 equiv.) was dissolved in water (1.0 mL) and added to the previous mixture. The solution was stirred at reflux for 4 hours. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 X 5 mL) was performed and the combined organic phases were washed with brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as white solid (94 mg, 97 %).(Note: Seco acid **S16** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^{1}H and ^{13}C spectra). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.98 (d, *J*= 7.7 Hz, 1H), 7.61 (d, *J*= 7.7 Hz, 1H), 7.39 (dd, *J*= 7.7 Hz, 7.7 Hz, 1H), 3.67 (t, *J*= 6.3 Hz, 2H), 2.42 (t, *J*= 7.0 Hz, 2H), 1.64-1.58 (m, 4H), 1.52-1.42 (m, 2H), 1.40-1.22 (m, 26H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.4, 136.3, 133.2, 129.2, 129.0, 128.4, 124.7, 91.8, 79.5, 63.2, 32.7, 29.64, 29.63, 29.62, 29.61, 29.60 (2C), 29.58 (2C) 29.6, 29.55, 29.47, 29.4, 29.1, 28.9, 28.6,

25.7, 19.4 ppm; HRMS (ESI+) for $C_{28}H_{44}O_3Na$ [M + Na]$^+$ calculated: 451.3191 found: 451.3183.

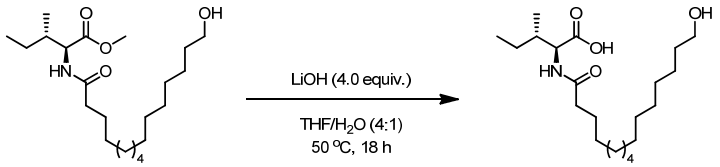


20-Hydroxyicosa-10,12-diynoic acid (S17) The macrolactone[14] (150 mg, 0.47 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (8.0 mL). LiOH (79 mg, 1.88 mmol, 4.0 equiv.) was added as dissolved in water (2.0 mL) and added to the previous mixture. The solution was stirred at reflux for 18 hours. The reaction mixture was cooled down to room temperature and HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 10 mL) was performed and the combined organic phases were washed with brine (25 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a white solid (130 mg, 86 %). (Note: Seco acid **S17** is highly insoluble in $CDCl_3$ which made it difficult to obtain quality ^{1}H and ^{13}C spectra). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (bs, OH), 3.66 (t, *J*= 5.0 Hz, 2H), 2.45-2.32 (m, 2H), 2.25 (t, *J*= 5.6 Hz, 4H), 1.72-1.46 (m, 6H), 1.43-1.22 (m, 16H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 77.42 (2C), 65.3 (2C), 63.0, 33.9, 32.6, 29.7, 29.0 (2C), 28.9, 28.8, 28.7, 28.2 (2C), 25.5, 24.6, 24.5, 19.2 ppm; HRMS (ESI+) for $C_{20}H_{33}O_3$ [M + H]$^+$ calculated: 321.2426 found: 321.2424.

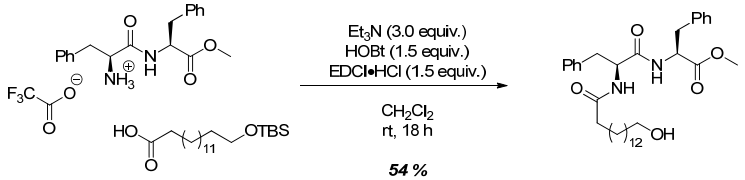


Methyl (15-hydroxypentadecanoyl)-*L*-isoleucinate (S18) The isoleucine salt (500 mg, 2.75 mmol, 1.2 equiv.) and Et_3N (0.86 mL, 6.18 mmol, 2.7 equiv.) were added in CH_2Cl_2 (10 mL) and the mixture was stirred at room temperature upon complete dissolution. 15-(tert-butyldimethylsilyloxy)pentadecanoic acid was added (854 mg, 2.29 mmol, 1.0 equiv.) to the solution followed by HOBt (464 mg, 3.44 mmol, 1.5 equiv.) and EDC●HCl (660 mg, 3.44 mmol, 1.5 equiv.) and the mixture was stirred at room temperature for 18 hours. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a 5 % w/w citric acid aqueous solution (10 mL) and a $NaHCO_3$ saturated aqueous solution (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (10 to 40 % EtOAc in hexanes) was performed to afford the *in-situ* TBS-deprotected product (640 mg, 73 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08

(d, J= 8.4 Hz, 1H (NH)), 4.59 (dd, J= 8.7 Hz, 5.0 Hz, 1H), 3.70 (s, 3H), 3.60 (t, J= 6.6 Hz, 2H), 2.20 (t, J= 7.3 Hz, 2H), 1.90 (br, s, 1H (OH)), 1.89-1.80 (m, 1H), 1.65-1.50 (m, 4H), 1.48-1.35 (m, 1H), 1.34-1.20 (m, 20H), 1.19-1.05 (m, 1H), 0.92-0.86 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.7, 62.8, 56.1, 51.9, 37.9, 36.6, 32.7, 29.5 (2C), 29.4 (3C), 29.35, 29.33, 29.2, 29.1, 25.7, 25.6, 25.1., 15.3, 11.4 ppm; HRMS (ESI+) for $C_{22}H_{44}NO_4$ $[M + H]^+$ calculated 386.3265 found: 386.3282.

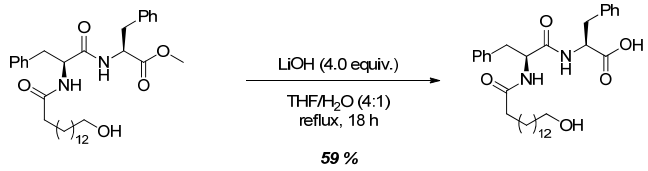


(15-hydroxypentadecanoyl)-*L*-isoleucine (S19) The methyl ester **S18** (527 mg, 1.37 mmol, 1.0 equiv.) was dissolved in THF (20 mL). LiOH (230 mg, 548 mmol, 4.0 equiv.) was dissolved in H_2O (5 mL) and was added to the previous solution. The reaction mixture was stirred at 50 °C for 18 hours and was then cooled down to room temperature. HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 25 mL) was performed and the combined organic phases were washed with brine (100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a white solid (421 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J= 8.5 Hz, 1H (NH)), 5.64 (br s, 1H (OH), 4.61 (dd, J= 8.5 Hz, 4.8 Hz, 1H), 3.66 (t, J= 6.7 Hz, 2H), 2.25 (t, J= 7.4 Hz, 2H), 1.97-1.87 (m, 1H), 1.68-1.45 (m, 5H), 1.40-1.12 (m, 21H), 0.95-0.92 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 173.8, 63.0, 56.4, 37.6, 36.6, 32.6, 29.5, 29.43 (2C), 29.41 (2C), 29.32, 29.30, 29.1, 29.1, 25.6 (2C), 25.1, 15.4, 11.6 ppm; HRMS (ESI+) for $C_{21}H_{40}NO_4$ $[M + H]^+$ calculated 370.2963 found: 370.2962.



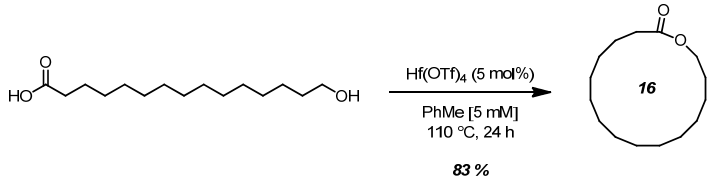
Methyl (15-hydroxypendecyl)-*L*-phenylalanyl-*L*-phenylalaninate (S20) Phe-Phe methyl ester TFA salt (343 mg, 0.780 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (8 mL). 15-(tert-butyldimethylsilyloxy)pentadecanoic acid was added (290 mg, 0.780 mmol, 1.0 equiv.) to the solution followed by HOBt (158 mg, 1.17 mmol, 1.5 equiv.), EDC●HCl (225 mg, 1.17 mmol, 1.5 equiv.) and Et_3N (0.33 mL, 2.34 mmol, 3.0 equiv.) and the

mixture was stirred at room temperature for 18 hours. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with a 5 % w/w citric acid aqueous solution (10 mL) and a $NaHCO_3$ saturated aqueous solution (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (30 % to 100 % EtOAc in hexanes) was performed to afford the desired product (237 mg, 54 %) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.18 (m, 8H), 7.02-7.00 (m, 2H), 6.39 (d, J= 7.4 Hz, 1H), 6.11 (d, J= 7.6 Hz, 1H), 4.74 (ddd, J= 7.4 Hz, 7.4 Hz, 6.3 Hz, 1H), 4.66 (ddd, J= 7.6 Hz, 7.6Hz, 7.1 Hz, 1H), 3.68 (s, 3H), 3.63 (t, J= 6.6 Hz, 2H), 3.10-2.94 (m, 4H), 2.11 (t, J= 7.0 Hz, 2H), 1.60-1.48 (m, 4H), 1.37-1.20 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 171.2, 170.6, 136.4, 135.6, 129.3, 129.1, 128.54, 128.50, 127.1, 126.9, 63.0, 54.0, 53.4, 52.2, 38.0, 37.8, 36.5, 32.8, 29.51 (2C), 29.49 (2C), 29.37, 29.35, 29.2, 29.1, 25.7, 25.5 ppm; HRMS (ESI +) for $C_{34}H_{51}N_2O_5$ ($M + H^+$) calculated mass : 567.3793, found 567.3805.

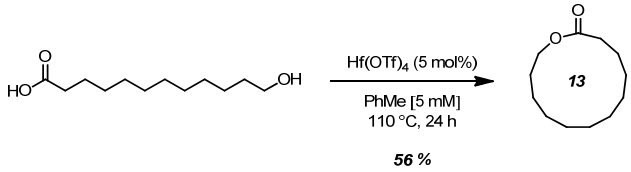


(15-hydroxypentadecyl)-*L*-phenylalanyl-*L*-phenylalanine (S21) The methyl ester **S20** (210 mg, 0.371 mmol, 1.0 equiv.) was dissolved in THF (6 mL). LiOH (62 mg, 1.48 mmol, 4.0 equiv.) was dissolved in H_2O (1.5 mL) and was added to the previous solution. The reaction mixture was stirred at 50 ^{o}C for 18 hours and was then cooled down to room temperature. HCl 1M was added until the mixture was neutralized (pH = 7). Extraction with EtOAc (3 x 10 mL) was performed and the combined organic phases were washed with brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired product as a white solid (120 mg, 59 %). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.71 (br s, 1H), 8.19 (d, J=7.8 Hz, 1H), 7.92 (d, J= 8.7 Hz, 1H), 7.27-7.15 (m, 10H), 4.55 (ddd, J= 7.8 Hz, 5.2 Hz, 4.0 Hz, 1H), 4.44 (ddd, J= 10.4 Hz, 8.7 Hz, 8.4 Hz, 1H), 4.33 (br s, 1H), 3.37 (t, J= 6.6 Hz, 2H), 3.08 (dd, J= 13.9 Hz, 5.2 Hz, 1H), 2.98 (dd, J= 14.0 Hz, 4.0 Hz, 1H), 2.93 (dd, J= 13.6 Hz, 8.4 Hz, 1H), 2.68 (dd, J= 13.9 Hz, 10.4 Hz, 1H), 1.96 (t, J= 6.8 Hz, 2H), 1.41-1.02 (m, 24 H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.7, 171.9, 171.5, 138.0, 137.4, 129.1 (2C), 128.1, 127.8, 126.4, 126.1, 60.7, 53.4, 37.4, 36.6, 35.2, 32.5, 29.11, 29.06 (2C), 29.04 (3C), 28.97, 28.89, 28.8, 28.4, 25.5, 25.2 ppm; HRMS (ESI +) for $C_{33}H_{48}N_2O_5Na$ ($M + Na^+$) calculated mass : 575.3455, found 575.3460.

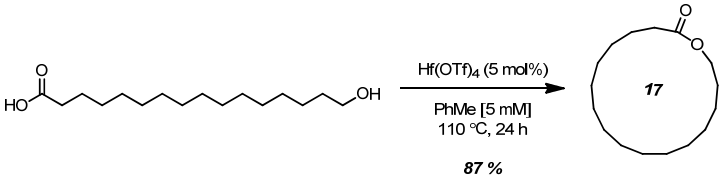
SYNTHESIS OF MACROLACTONES



1-Oxacyclohexadecan-2-one (2) 15-Hydroxypentadecanoic acid (26 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduce pressure and purified by flash chromatography (3 % Et_2O in hexanes) to the desired product as a white solid (20 mg, 83 %). Spectral data were in accordance with those previously reported in the literature.[9]

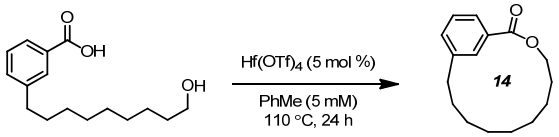


1-Oxacyclotridecan-2-one (4) 12-Hydroxypentadecanoic acid (22 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired product as a colorless oil (11 mg, 56 %). Spectral data were in accordance with those previously reported in the literature.[9]



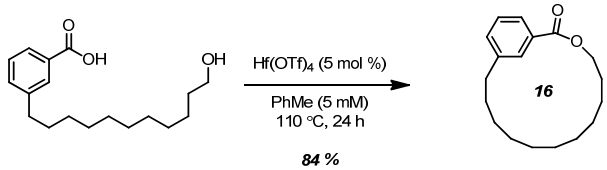
1-Oxacycloheptadecan-2-one (5)16-Hydroxypentadecanoic acid (27 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduce pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired

product as a white solid (22 mg, 87 %). Spectral data were in accordance with those previously reported in the literature.[9]



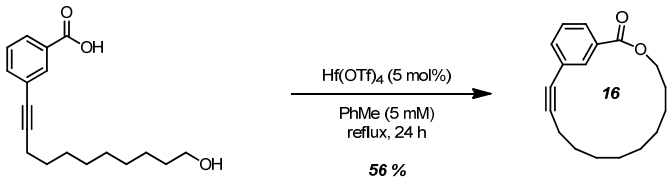
90 %

3-Oxabiclyclo[11.3.1]heptadeca-1(17),13,15-trien-2-one (6): 3-(9-Hydroxynon-1-yl)benzoic acid (26 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduce pressure and purified by flash chromatography (3 % EtOAc in hexanes) to the desired product as a white solid (22 mg, 90 %). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.85 (d, *J*=6.7 Hz, 1H), 7.39-7.35 (m, 2H), 4.38 (t, *J*= 5.0 Hz, 2H), 2.81(t, *J*= 5.5 Hz, 2H), 1.82-1.78 (m, 4H), 1.66-1.62 (m, 2H), 1.52 (m, 6H), 1.38-1.36 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 141.2, 133.8, 130.4, 128.6, 128.4, 126.5, 66.3, 31.8, 28.5, 27.9, 27.5, 26.7, 26.6, 25.1, 24.3 ppm; HRMS (ESI+) for $C_{16}H_{23}O_2$ $[M + H]^+$ calculated: 247.1693 found: 247.1693.

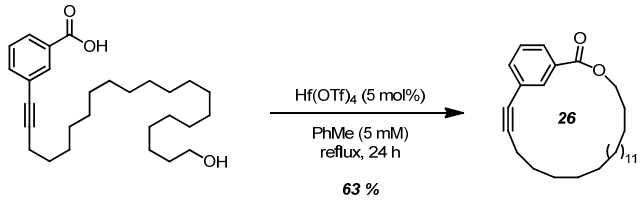


84 %

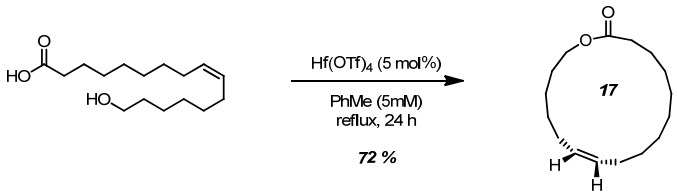
3-Oxabicyclo[13.3.1]nonadeca-1(19),15,17-trien-2-one (7) : 3-(11-Hydroxyundec-1-yl)benzoic acid (29 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product (23 mg, 84 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.90 (m, 2H), 7.39-7.35 (m, 2H), 4.38 (t, *J*= 5.4 Hz, 2H), 2.75 (t, *J*= 6.2Hz, 2H), 1.80-1.68 (m, 4H), 1.58-1.52 (m, 2H), 1.31-1.24 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 142.1, 133.6, 130.3, 129.1, 128.5, 127.2, 65.0, 33.4, 28.5, 27.51, 27.48, 27.45, 27.37, 27.3, 26.9, 25.6, 25.4 ppm; HRMS (ESI+) for $C_{18}H_{27}O_2$ $[M + H]^+$ calculated: 275.2006 found: 275.2005.



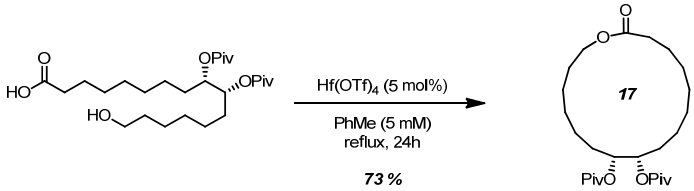
3-Oxobicyclo[13.3.1]nonadeca-1(19)-15,17-trien-13-yn-2-one (8) The hydroxyacid **S6** (29 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05equiv.) was added to the solution and the reaction mixture heated to 110 ^{o}C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product (15 mg, 56 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (dd, *J* = 1.5 Hz, 1.5 Hz 1H), 7.92 (dd, *J* = 7.7 Hz, 7.7 Hz, 1.5 Hz, 1H), 7.42 - 7.49 (m, 1H), 7.34-7.42 (m, 1H), 4.34 - 4.41 (m, 2H), 2.41 - 2.48 (m, 2H), 1.82-1.80 (m, 2H), 1.77 -1.65 (m, 8H), 1.57-1.41 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 136.2, 132.5, 130.6, 128.6, 128.1, 124.5, 93.6, 82.1, 66.4, 30.6, 30.1, 29.9, 28.8, 28.4, 28.2, 27.7, 19.2 ppm; HRMS (ESI) m/z calculated for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.1693; found 271.1693.



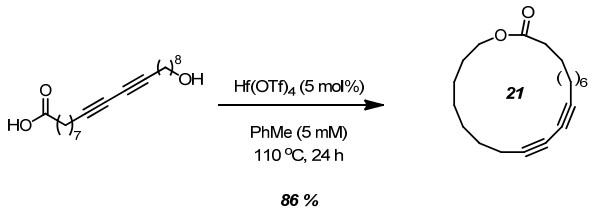
3-Oxobicyclo[23.3.1]nonacosa-1(29)-25,27-trien-23-yn-2-one (9) The hydroxyacid **S16** (43 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^{o}C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to afford the desired product as a white solid (26 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J*= 1.6 Hz, 1.6 Hz, 1H), 7.96 (ddd, *J*= 8.0 Hz, 8.0 Hz, 1.6 Hz, 1H), 7.57 (ddd, *J*= 8.4 Hz, 8.4 Hz, 1.6 Hz, 1H), 7.37 (dd, *J*= 8.0 Hz, 8.0 Hz, 1H), 4.34 (t, *J*= 6.4 Hz, 2H), 2.44 (t, *J*= 7.2 Hz, 2H), 1.82-1.62 (m, 2 H), 1.66-1.60 (m, 2H), 1.51-1.35 (m, 4H), 1.27 (m, 26H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 135.5, 132.5, 130.7, 128.7, 128.3, 124.4, 91.5, 79.9, 65.3, 29.6, 28.96, 28.91, 28.84, 28.82, 28.80, 28.79, 28.77, 28.74, 28.72 (2C), 28.70, 28.65, 28.60, 28.4, 28.3, 26.0, 19.3 ppm; HRMS (ESI+) for $C_{28}H_{42}O_2$ $[M+H]^+$ calculated: 411.3258 found: 411.3249.



(9*Z*)-isoambrettolide (10) (*Z*)-16-Hydroxyhexadec-9-enoic acid (27 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (3 % Et_2O in hexanes) to afford the desired product as a white solid (18 mg, 72 %). Spectral data were in accordance with those previously reported in the literature[15].

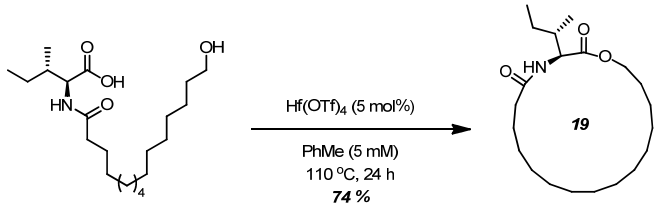


(±)-*erythro*-10,11-Bis[2,2-(dimethyl)propanoate]oxaheptadecan-2-one (11) The hydroxyacid **S14** (47 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 % Et_2O in hexanes) to afford the desired product as a colorless oil (33 mg, 73 %). ^1H NMR (400 MHz, $CDCl_3$) δ 5.10-5.05 (m, 1H), 5.03-4.98 (m, 1H), 4.18-4.10 (m, 2H), 2.34 (t, *J*= 6.4 Hz, 2H), 1.75-1.25 (m, 22H), 1.19 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 177.7, 174.0, 73.2, 72.3, 64.1, 38.8, 34.6, 30.0, 29.2, 28.6, 28.1, 28.0, 27.7, 27.5, 27.22, 27.20, 25.6, 25.0, 23.7, 22.7 ppm; HRMS (ESI+) for $C_{26}H_{46}O_6Na$ $[M+Na]^+$ calculated: 477.3187 found: 477.3166.



Oxacycloicosa-10,12-diyne-2-one (12) The hydroxyacid **S17** (32 mg, 0.10 mmol, 1.0 equiv.) was dissolved in toluene (20 mL, 5 mM). $Hf(OTf)_4$ (3.9 mg, 0.005 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 ^oC. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 1 mL) was added and the slurry was concentrated under reduced pressure and

purified by flash chromatography (10 % EtOAc in hexanes) to afford the macrocycle as a white solid (26 mg, 86 %). Spectral data were in accordance with those previously reported in the literature[14].

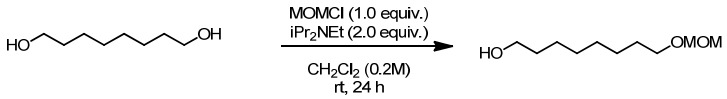


(*S*)-3-((*S*)-*sec*-butyl)-1-oxa-4-azacyclononadecane-2,5-dione (13)The hydroxyacid **S19** (64 mg, 0.173 mmol, 1.0 equiv.) was dissolved in toluene (35 mL, 5 mM). $Hf(OTf)_4$ (6.7 mg, 0.0087 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 to 50 % EtOAc in hexanes) to afford the macrocycle as a white solid (45 mg, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, J= 8.5 Hz, 1H (NH)), 4.61 (dd, J= 8.7 Hz, 5.2 Hz, 1H), 4.40-4.34 (m, 1H), 3.99 (dt, J= 10.7 Hz, 5.7 Hz, 1H), 2.33 (dt, J= 14.6 Hz, 6.4 Hz, 1H), 2.19-2.12 (m, 1H), 1.92-1.86 (m, 1H), 1.80-1.50 (m, 4H), 1.49-1.38 (m, 1H), 1.37-1.20 (m, 20H), 1.20-1.10 (m, 1H), 0.95-0.91 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.8, 64.9, 56.6, 38.0, 36.5, 28.5, 28.09, 28.07, 28.04, 28.01, 27.9, 27.5, 27.1, 27.0, 25.20, 25.19, 25.0, 15.4, 11.5 ppm; HRMS (ESI+) for $C_{21}H_{40}NO_3$ $[M + H]^+$ calculated: 354.3003 found: 354.3008.

(3*S*, 6*S*)-3,6-dibenzyl-1-oxa-4,7-diazacyclodocosane-2,5-dione (14) The hydroxyacid (**S21)** (65 mg, 0.1119 mmol, 1.0 equiv.) was dissolved in toluene (24 mL, 5 mM). $Hf(OTf)_4$ (4.6 mg, 0.0056 mmol, 0.05 equiv.) was added to the solution and the reaction mixture heated to 110 °C. The reaction mixture was stirred at this temperature for 24 h. After cooling down to room temperature, silica gel (~ 2 mL) was added and the slurry was concentrated under reduced pressure and purified by flash chromatography (10 to 60 % EtOAc in hexanes) to afford the macrocycle as a white solid (37 mg, 57 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.19 (m, 8H), 6.92-6.89 (m, 2H), 6.26 (d, J= 6.8 Hz, 1H), 5.83 (d, J= 7.1 Hz, 1H), 4.67-4.58 (m, 2H), 4.23-4.15 (m, 1H), 4.12-4.05 (m, 1H), 3.22-2.90 (m, 4H), 2.20-2.05

(m, 6H), 1.63-1.54 (m, 8 H), 1.28-1.25 (m, 16 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.3, 170.8, 170.2, 136.8, 135.8, 129.5, 129.2, 128.8, 128.4, 127.2, 127.1, 65.4, 54.1, 53.9, 37.6, 37.4, 36.3, 28.09 (3C), 28.05 (2C), 28.01 (3C), 27.96, 27.91, 25.1 (2C) ppm; ; HRMS (ESI +) for $C_{33}H_{47}N_2O_4$ ($M + H^+$) calculated mass : 535.3530, found 535.3529.

SYNTHESIS OF ESTERIFICATION PRECURSORS



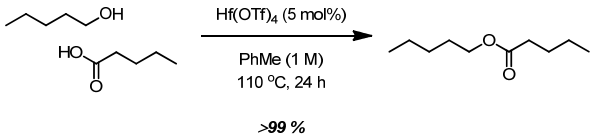
60 %

8-(methoxymethoxy)octanol (S22) 1,8-octanediol (1.00 g, 6.84 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (34 mL). iPr_2NEt (2.38 mL, 13.7 mmol, 2.00 equiv.) was added followed by MOMCl (0.52 mL, 6.8 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature for 24 h and was subsequently quenched by the addition of a saturated solution of NH_4Cl (25 mL). Extraction with CH_2Cl_2 (2 x 30 mL) was performed and the combined organic layers were washed with water (30 mL) and brine (30 mL) and dried over Na_2SO_4. The organic phase was the concentrated under reduced pressure and flash chromatography (20 % EtOAc in hexanes) was performed to afford the product as a colorless oil (775 mg, 60 %). ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 2H), 3.62 (t, J= 6.6 Hz, 2H), 3.51 (t, J= 6.6 Hz, 2H), 3.35 (s, 3H), 1.75 (br s, 1H (OH)), 1.70-1.50 (m, 4H), 1.35-1.25 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.3, 67.8, 62.9, 55.0, 32.7, 29.6, 29.32, 29.30, 26.1, 25.6 ppm; HRMS (ESI+) for $C_{10}H_{22}O_3Na$ $[M + Na]^+$ calculated 213.1461 found: 213.1469.

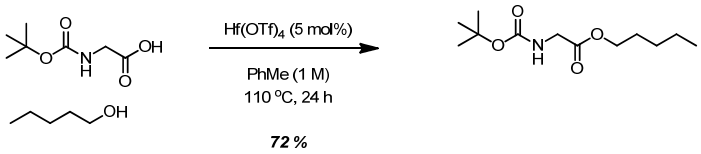
SYNTHESIS OF ESTERS

General procedure A: An open oven-dried sealable tube was charged with the carboxylic acid (1.00 mmol, 1.00 equiv.) and dissolved in toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and the alcohol (1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 ^oC for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography.

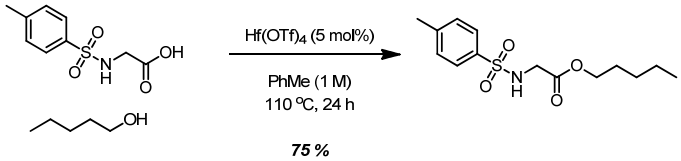
General procedure B: An open oven-dried sealable tube was charged with the carboxylic acid (1.00 mmol, 1.00 equiv.), *i*Pr_2NEt (0.087 mL, 050 mmol, 0.5 equiv.) and dissolved toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and the alcohol (1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 ^oC for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography.



Pentyl pentanoate (15) Following general procedure A, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (171 mg, >99 %). Spectral data were in accordance with those previously reported in the literature.[16]

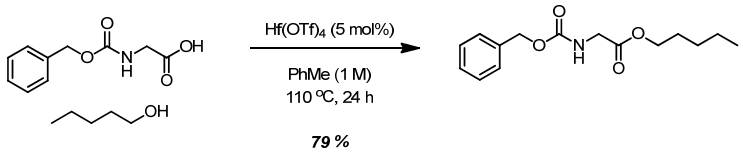


Pentyl ((*tert*-butyloxy)carbonyl)glycinate (16) Following general procedure A, flash chromatography (15 % EtOAc in hexanes) was performed to afford the product as a colorless oil (176 mg, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (br s, 1H (NH)), 4.11 (t, *J*= 6.7 Hz, 2H), 3.87 (d, *J*= 5.4 Hz, 2H), 1.65-1.57 (m, 2H), 1.44-1.40 (m, 11H), 1.35-1.28 (m, 4H), 0.88 (t, *J*= 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.7, 79.8, 65.4, 42.3, 28.2, 28.1, 27.8, 22.2, 13.8 ppm; HRMS (ESI+) for $C_{12}H_{23}NO_4Na$ $[M + Na]^+$ calculated 268.1519 found: 268.1525.

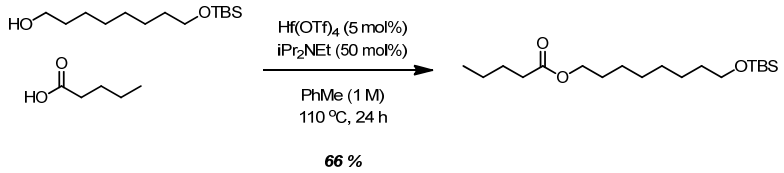


Pentyl *N*-(*p*-tosyl)glycinate (17) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) was performed to afford the product as a white solid (224 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J*= 8.1 Hz, 2H), 7.30 (d, *J*= 8.1 Hz, 2H), 5.23 (br s, 1H (NH)), 4.01 (t, *J*= 6.9 Hz, 2H), 3.77 (d, *J*= 5.5 Hz, 2H), 2.42 (s, 3H), 1.55-1.50 (m, 2H), 1.30-1.22 (m, 4H), 0.88 (t, *J*= 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz,

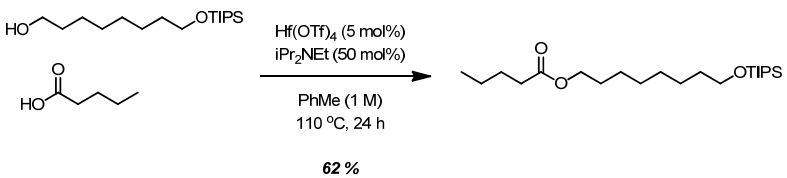
$CDCl_3$) δ 168.8, 143.7, 136.2, 129.7, 127.2, 65.9, 44.1, 28.0, 27.7, 22.1, 21.4, 13.8 ppm; HRMS (ESI+) for $C_{14}H_{22}NO_4S$ $[M + H]^+$ calculated 300.1264 found: 300.1278.



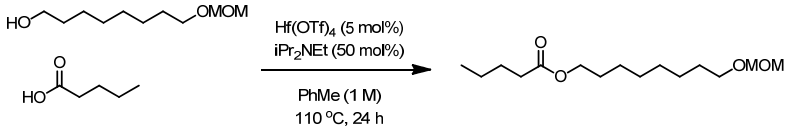
Pentyl ((benzyloxy)carbonyl)glycinate (18) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) was performed to afford the product as a colorless oil (220 mg, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 5.64 (br s, 1H (NH)), 5.10 (s, 2H), 4.11 (t, *J*= 6.8 Hz), 3.92 (d, *J*= 7.0 Hz, 2H), 1.65-1.55 (m, 2H), 1.35-1.25 (m, 4H), 0.90 (t, *J*= 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 156.2, 136.1, 128.2, 127.85, 127.79, 66.7, 65.3, 42.5, 27.9, 27.7, 22.0, 13.7 ppm; $C_{15}H_{22}NO_4$ $[M + H]^+$ calculated 280.1543 found: 280.1551.



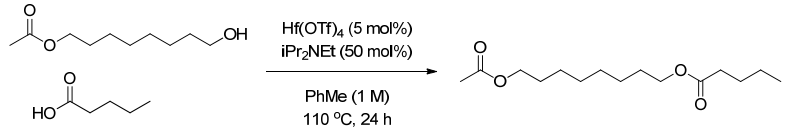
8-(*tert*-Butyldimethylsilyloxy)octyl pentanoate (19) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (178 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.,06 (t, *J*= 6.7Hz, 2H), 3.61 (t, *J*= 6.5Hz, 2H), 2.31 (t, *J*= 7.3 Hz, 2H), 1.64-1.60 (m, 2H), 1.55-1.48 (m, 2H), 1.40-1.30 (m, 8H), 0.94-0.90 (m, 12H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 64.3, 63.2, 34.1, 32.8, 29.3, 29.2, 28.6, 27.1, 26.0, 25.9, 25.7, 22.2, 18.3, 13.7, -5.3 ppm; HRMS (ESI+) for $C_{19}H_{41}O_3Si$ $[M + H]^+$ calculated 345.2820 found: 345.2831.



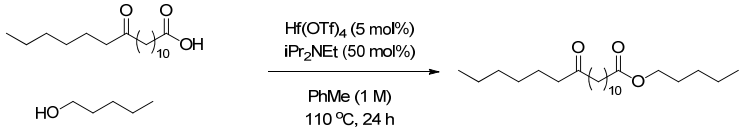
8-(Triisopropylsilyloxy)octyl pentanoate (20) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (217 mg, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (t, *J*= 6.8 Hz, 2H), 3.68 (t, *J*= 6.7 Hz, 2H), 2.30 (t, *J*= 7.4 Hz, 2H), 1.65-1.50 (m, 6H), 1.35-1.25 (m, 10H), 1.09-1.06 (m, 21 H), 0.92 (t, *J*= 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 64.3, 63.4, 34.1, 33.0, 29.3, 29.2, 28.6, 27.1, 25.9, 25.7, 22.2, 17.9, 13.6, 12.0 ppm; HRMS (ESI+) for $C_{22}H_{46}O_3SiNa$ $[M + Na]^+$ calculated 409.3108 found: 409.3128.



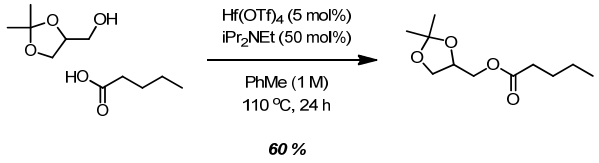
8-(Methoxymethoxy)octyl pentanoate (21) Following general procedure B, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (210 mg, 77 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 2H), 4.02 (t, *J*= 6.8Hz, 2H), 3.48 (t, *J*= 6.6Hz, 2H), 3.32 (s, 3H), 2.26 (t, *J*= 7.5 Hz, 2H), 1.60-1.50 (m, 6H), 1.35-1.25 (m, 10H), 0.88 (t, *J*= 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 96.3, 67.7, 64.2, 54.9, 34.0, 29.6, 29.2, 29.1, 28.5, 27.0, 26.0, 25.8, 22.2, 13.6 ppm; HRMS (ESI+) for $C_{15}H_{30}O_4Na$ $[M + Na]^+$ calculated 297.2036 found: 297.2047.



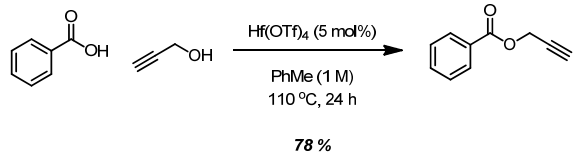
8-acetoxyoctyl pentanoate (22) Following general procedure B, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (129 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.035 (t, J= 6.7 Hz, 2H), 4.030 (t, J= 6.8 Hz, 2H), 2.28 (t, J= 7.4 Hz, 2H), 2.02 (s, 3H), 1.63-1.55 (m, 6H), 1.35-1.25 (m, 10H), 0.89 (t, J= 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 171.1, 64.5, 64.2, 34.0, 29.03, 29.02, 28.53, 28,49, 27.0, 25.8, 25.7, 22.2, 20.9, 13.6 ppm; HRMS (ESI+) for $C_{15}H_{29}O_4$ (M + H^+) calculated mass: 273.2060, found 273.2059.



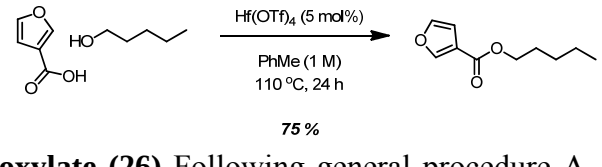
Pentyl 12-oxooctadecanoate (23) Following general procedure A, flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless solid (170 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (t, J= 6.6 Hz, 2H), 2.38-2.34 (m, 4H), 2.27 (t, J= 7.3 Hz, 2H), 1.70-1.50 (m, 8 H), 1.45-1.20 (m, 22H), 0.90-0.84 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 173.9, 64.3, 42.7, 34.3, 31.6, 29.3 (3C), 29.2 (2C), 29.1, 28.9, 28.3, 28.0, 24.9, 23.81, 28.78, 22.4, 22.3, 13.95, 13.89 ppm; HRMS (ESI+) for $C_{23}H_{45}O_3$ ($M + H^+$) calculated mass: 369.3363, found 369.3369.



(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl pentanoate (24) Following general procedure B, flash chromatography (15 % EtOAc in hexanes) afforded the product as a colorless oil (130 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35-4.27 (m, 1H), 4.19-4.05 (m, 3H), 3.74 (dd, *J*= 8.4 Hz, 6.2 Hz, 1H), 2.35 (t, *J*= 7.4 Hz, 2H), 1.66-1.58 (m, 2H), 1.43 (s, 3H), 1.40-1.30 (m, 5H), 0.91 (t, *J*= 7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 109.8, 73.6, 66.3, 64.5, 33.8, 26.9, 29.6, 25.4, 22.2, 13.6 ppm; HRMS (ESI+) for $C_{11}H_{20}O_4Na$ $[M + Na]^+$ calculated 239.1254 found: 239.1255.

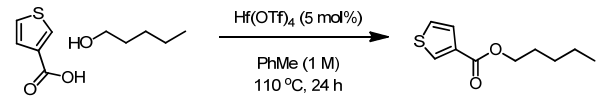


2-propargyl benzoate (25) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (124 mg, 78 %). Spectral data were in accordance with those previously reported in the literature.[17]

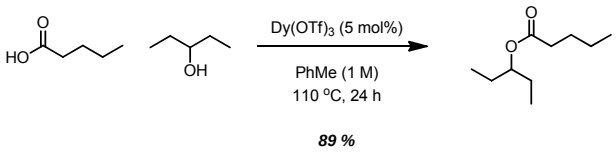


Pentyl furan-3-carboxylate (26) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (144 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.40 (d, *J*= 1.2 Hz, 1H), 6.73 (d, *J*= 1.2 Hz, 1H), 4.23 (t,

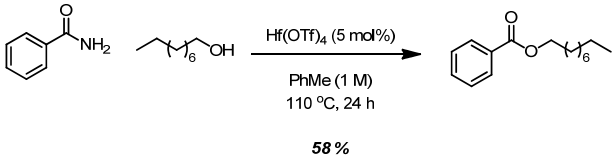
J= 6.8 Hz, 2H), 1.70-1.65 (m, 2H), 1.40-1.30 (m, 4H), 0.90 (t, *J*= 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 147.5, 143.6, 119.6, 109.8, 64.5, 28.3, 28.1, 22.3, 13.9 ppm; HRMS (ESI+) for $C_{10}H_{15}O_3[M + H]^+$ calculated 183.1016 found: 183.1015.



Pentyl thiophen-3-carboxylate (27) Following general procedure A, flash chromatography (10 % EtOAc in hexanes) afforded the product as a colorless oil (177 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J*= 3.1, 1.2 Hz, 1H), 7.53 (dd, *J*= 5.0, 1.2 Hz, 1H), 7.29 (dd, *J*= 5.0, 3.1 Hz, 1H), 4.27 (t, *J*= 6.7 Hz, 2H), 1.77-1.73 (m, 2H), 1.45-1.30 (m, 4H), 0.93 (t, *J*= 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 134.0, 132.4, 127.9, 125.8, 64.8, 28.4, 28.1, 22.3, 13.9 ppm; HRMS (ESI+) for $C_{10}H_{15}O_2S$ [M + H]$^+$ calculated 199.0787 found: 199.0790.



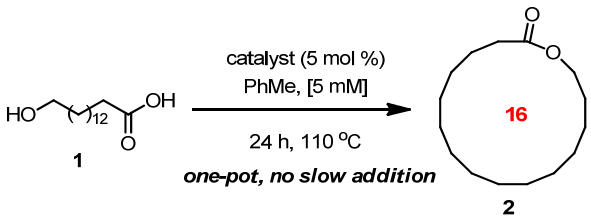
Pentan-3-yl pentanoate (36) Following general procedure A using $Dy(OTf)_3$ (30.5 mg, 0.050 mmol, 0.05 equiv.), flash chromatography (5 % EtOAc in hexanes) afforded the product as a colorless oil (103 mg, 60 %). Spectral data were in accordance with those previously reported in the literature.[18]



Nonyl benzoate (37) An open oven-dried sealable tube was charged with the benzamide acid (121 mg mL, 1.00 mmol, 1.00 equiv.) and dissolved in toluene (1 mL, 1M). $Hf(OTf)_4$ (38 mg, 0.050 mmol, 0.050 equiv.) and nonanol (0.174 mL, 1.0 mmol, 1.0 equiv.) were then added to the mixture and the tube was sealed. The reaction mixture was stirred at 110 ^{o}C for 24 h and then cooled down to room temperature. The tube was opened and silica gel (~ 5 mL) was added. The slurry was concentrated under reduced pressure and purified by flash chromatography (5% EtOAc in hexanes) to afford the product as a colorless oil (145 mg, 58 %). Spectral data were in accordance with those previously reported in the literature.[19]

TABULAR DATA

Table S1: Optimization of a Lewis acid catalyzed macrolactonization process.

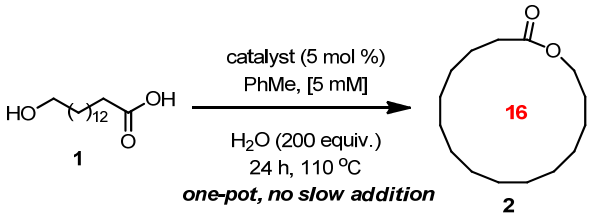


Catalyst	Yield **2** (%)	Catalyst	Yield **2** (%)

1	$AlCl_3$	0	16	$ZrCl_4(THF)_2$	13
2	$MgBr_2 \cdot OEt_2$	0	17	$Zr(tfacac)_3$	0
3	$BF_3 \cdot OEt_2$	36	18	$CuBr_2$	0
4	$B(OH)_3$	0	19	$CuCl_2$	0
5	$TiCp_2Cl_2$	0	20	$Cu(OAc)_2$	25
6	$TiCl_4$	0	21	$Cu(OTf)_2$	54
7	$Fe(acac)_3$	0	22	$Sc(OTf)_3$	45
8	$FeCl_3$	0	23	$Sm(OTf)_3$	21
9	$Fe(OTf)_2$	0	24	$Dy(OTf)_3$	13
10	$Fe(OTf)_3$	0	25	$Yb(OTf)_3$	38
11	$Pd(TFA)_3$	0	26	$Hf(OTf)_4$	83
12	$Ni(acac)_2$	0	26	$HfCl_4(THF)_2$	17
13	AgOTf	22	27	$Hf(On\text{-}Bu)_4$	12
14	$Zn(OTf)_2$	0			
15	$Co(OAc)_2$	0			

[a] Isolated yields following silica gel chromatography. Remaining mass balance is unreacted **1** unless otherwise noted. [b] No trace of **1** was isolated. [c] Polymerization of **1** is observed. [d] Lower catalyst loadings provided lower yields. When 2.5 mol % $Hf(OTf)_4$ was used 72 % of **2** and 27 % re-isolated **1** were obtained.

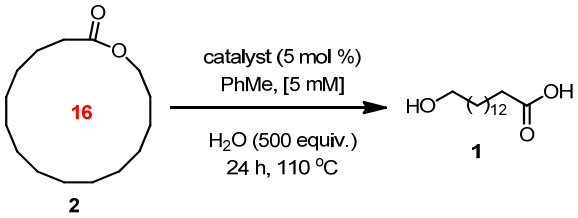
Table S2: Macrolactonization in the presence of excess water.



	Catalyst	Yield **2** (%)[a]		Catalyst	Yield **2** (%)[a]
1	$BF_3{\cdot}OEt_2$	17	7	$Sm(OTf)_3$	0
2	AgOTf	4	8	$Yb(OTf)_3$	0
3	$Cu(OAc)_2$	0	9	$HfCl_4(THF)_2$	0
4	$ZrCl_4(THF)_2$	13	10	$Hf(On\text{-}Bu)_4$	0
5	$Cu(OTf)_2$	<5	11	$Hf(OTf)_4$	83[b]
6	$Sc(OTf)_3$	0	12	$Dy(OTf)_3$	0

[a] Isolated yields following silica gel chromatography. [b] Increasing the water content to 400 equiv. resulted in a decrease in yield to 23 % of **2**.

Table S3: Ring-opening (hydrolysis) of macrolactone **2** under Lewis acid conditions.

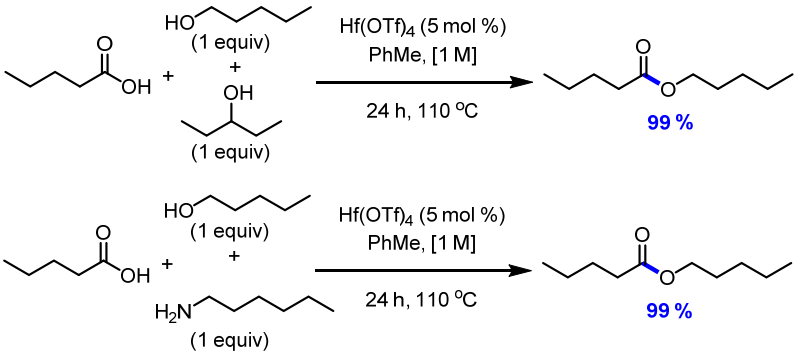


	Catalyst	**2** (%)[a]		Catalyst	**2** (%)[a]
1	$BF_3{\cdot}OEt_2$	99	7	$Sm(OTf)_3$	96
2	AgOTf	83	8	$Yb(OTf)_3$	83
3	$Cu(OAc)_2$	67	9	$HfCl_4(THF)_2$	50
4	$ZrCl_4(THF)_2$	99	10	$Hf(On\text{-}Bu)_4$	99
5	$Cu(OTf)_2$	67	11	$Hf(OTf)_4$	88[b]
6	$Sc(OTf)_3$	58	12	$Dy(OTf)_3$	99

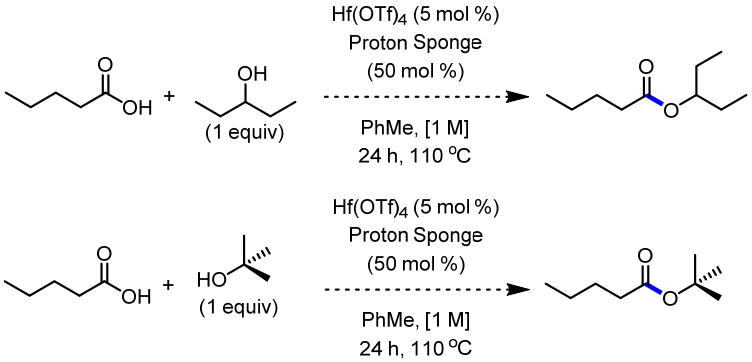
[a] Yields of recovered **2** following silica gel chromatography. [b] The re-isolated yield of **2** remained high (>80 %) even when using 1000 equiv. of added H_2O.

COMPETITION EXPERIMENTS

Competition experiments confirmed selectivity for primary alcohols over secondary alcohols and amines.

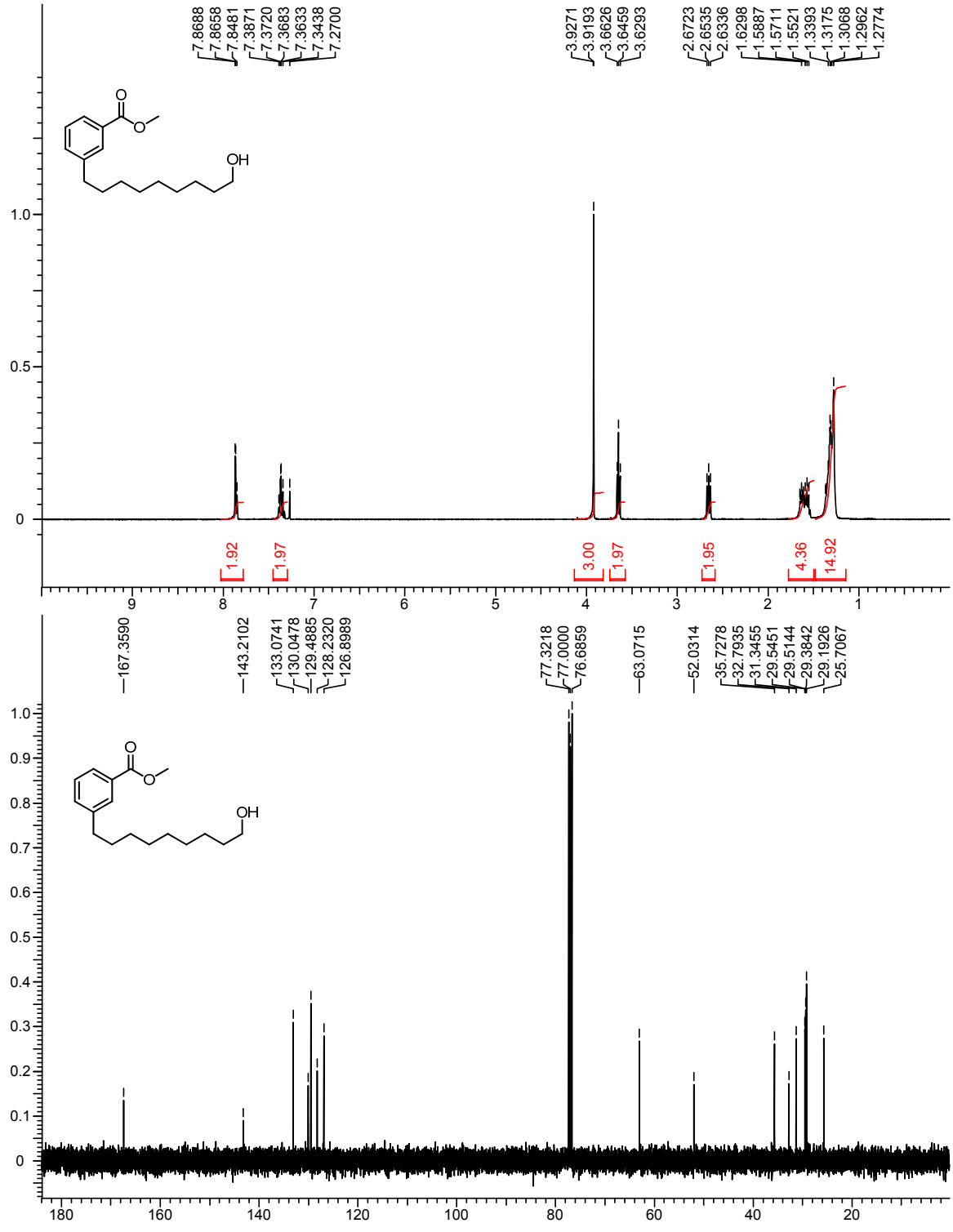


Forcing conditions with secondary or tertiary alcohols did not afford the desired esters.

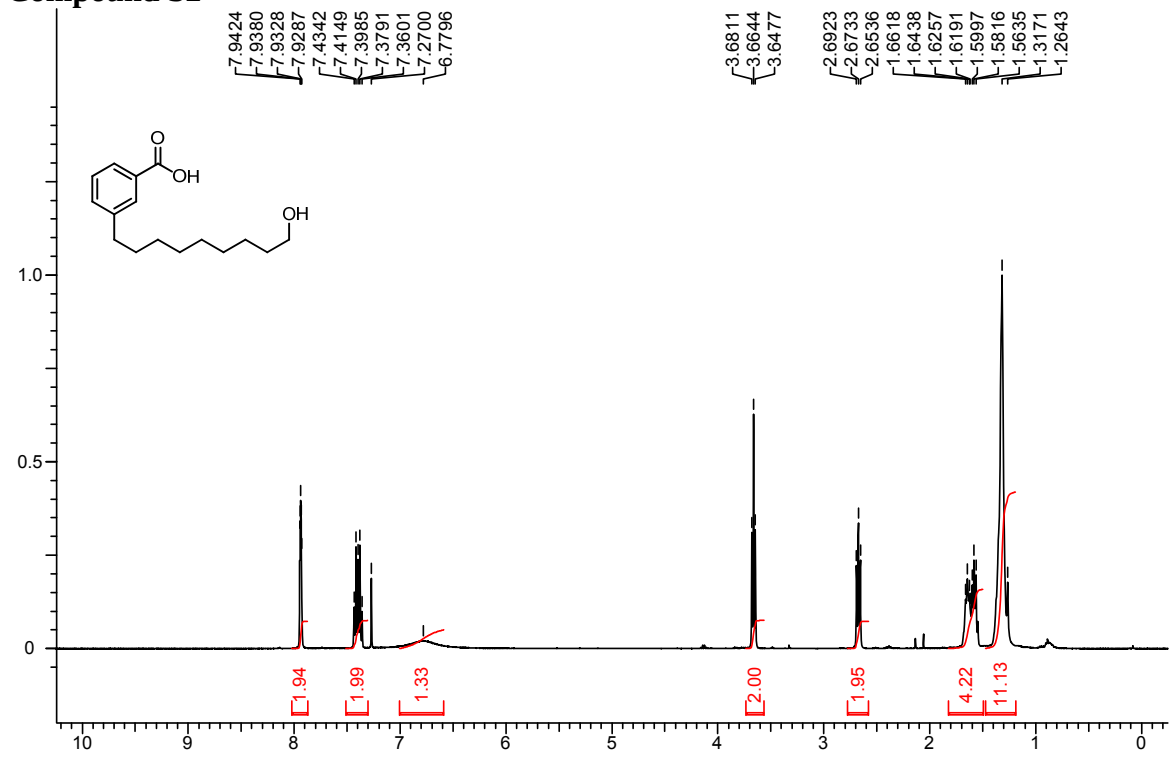


SPECTRAL DATA

Compound S1



Compound S2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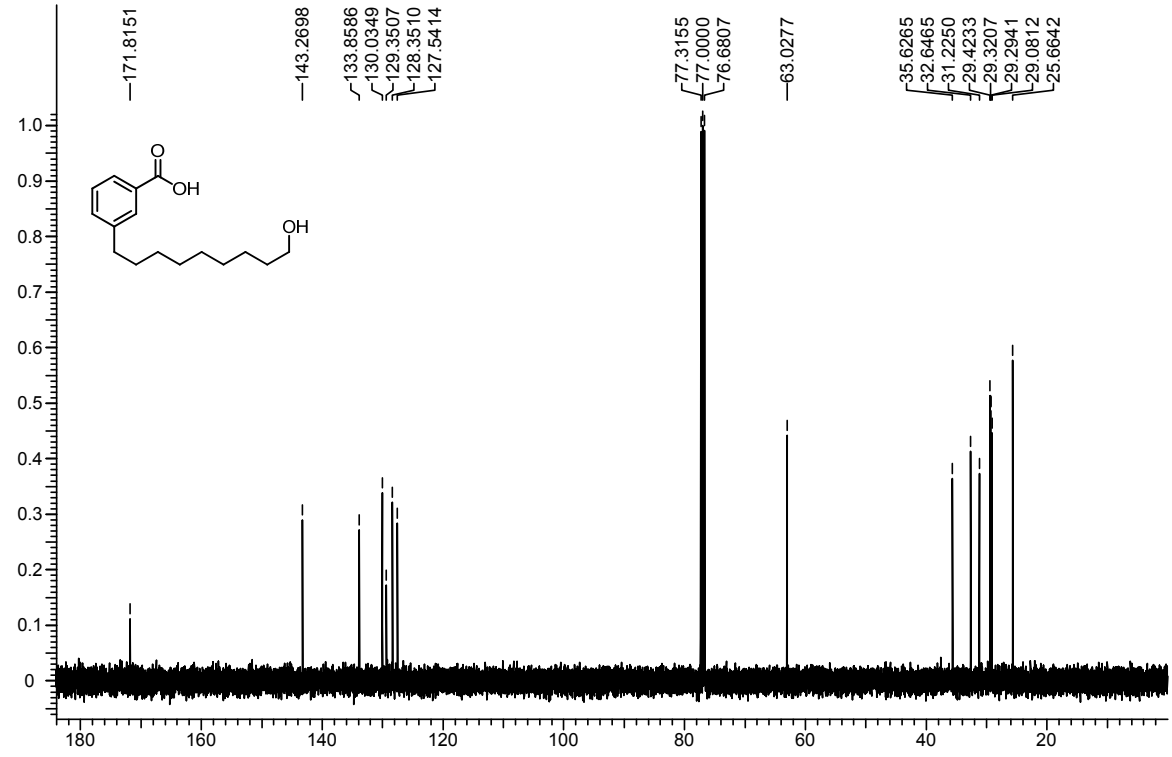
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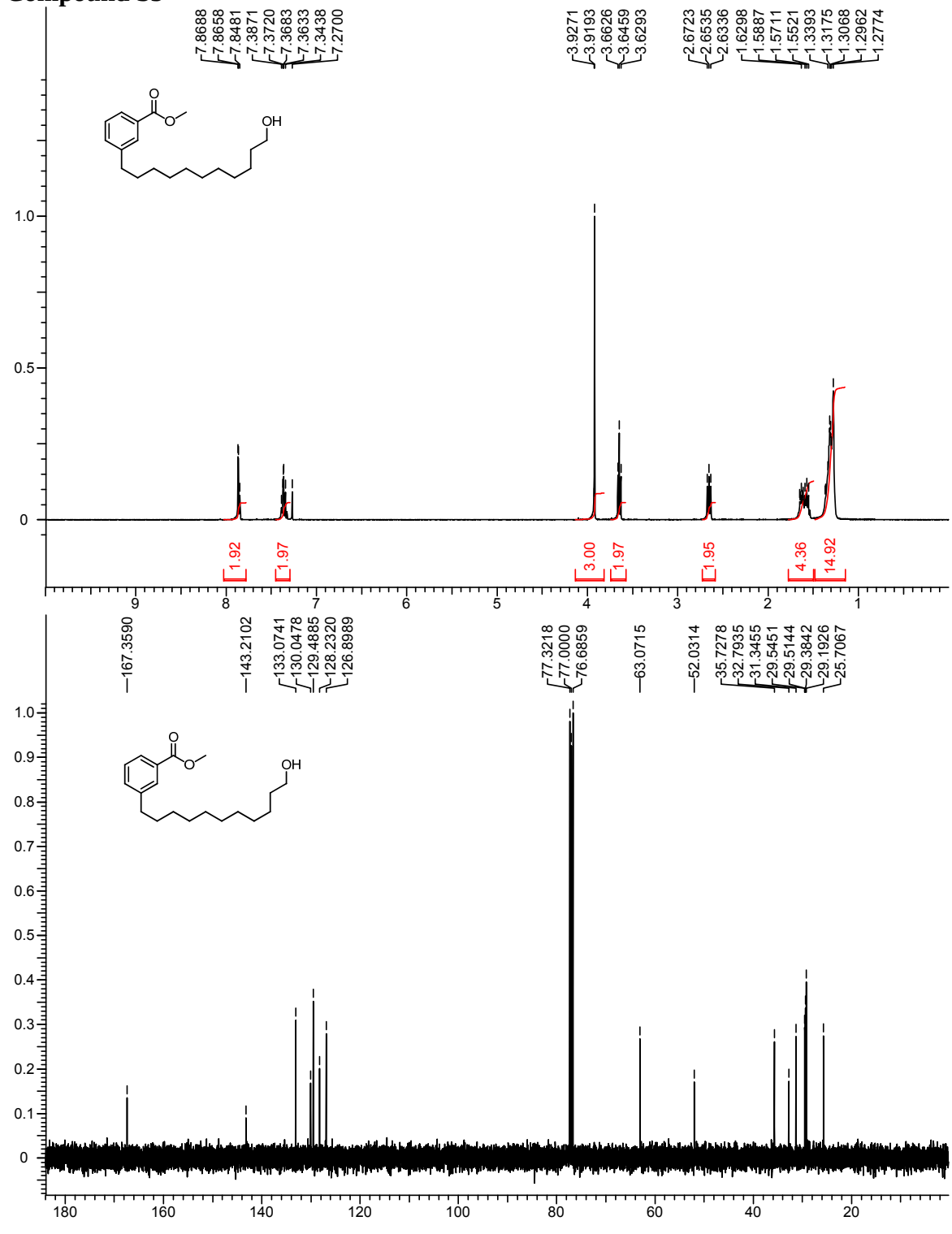
Compound S3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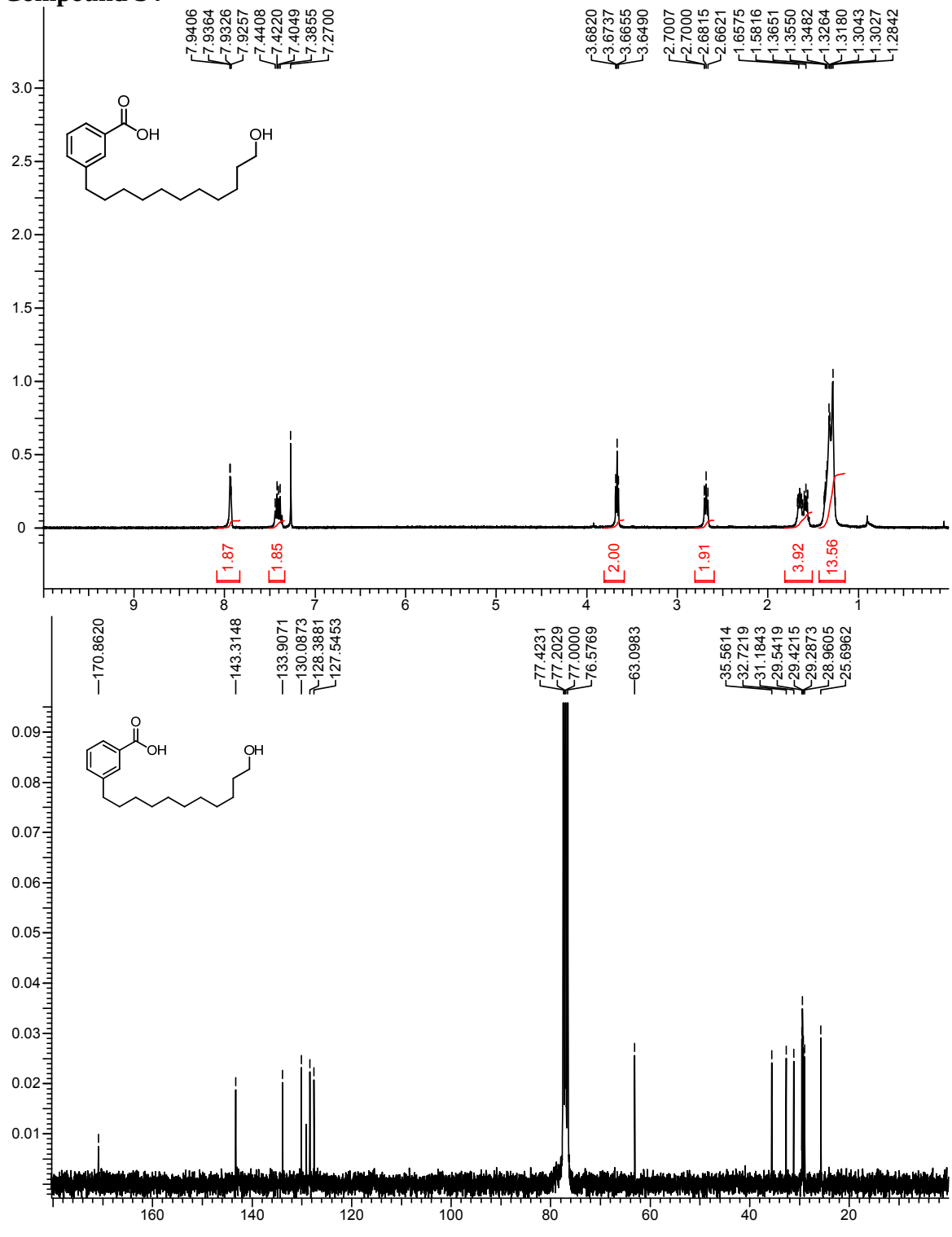
Compound S4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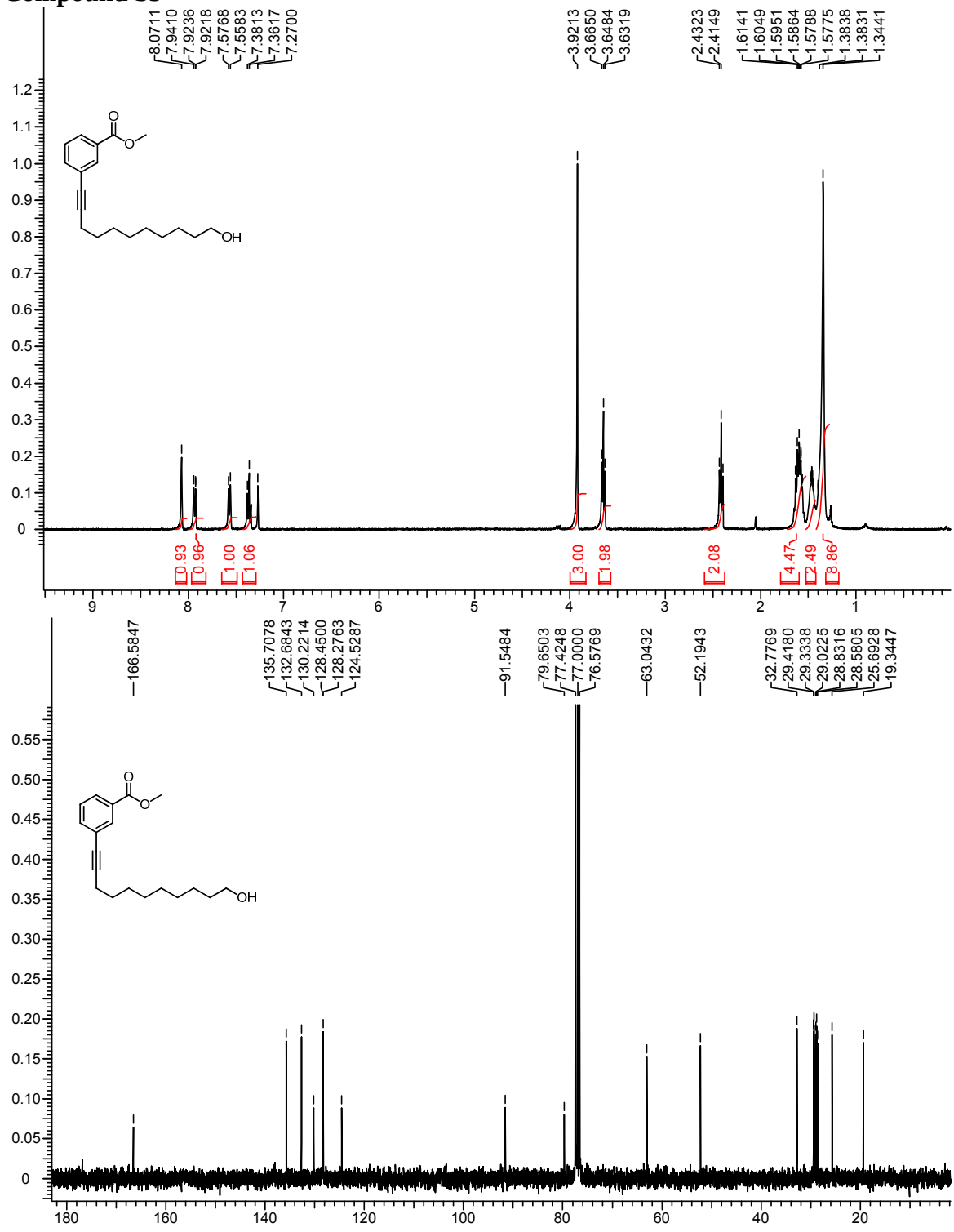
Compound S5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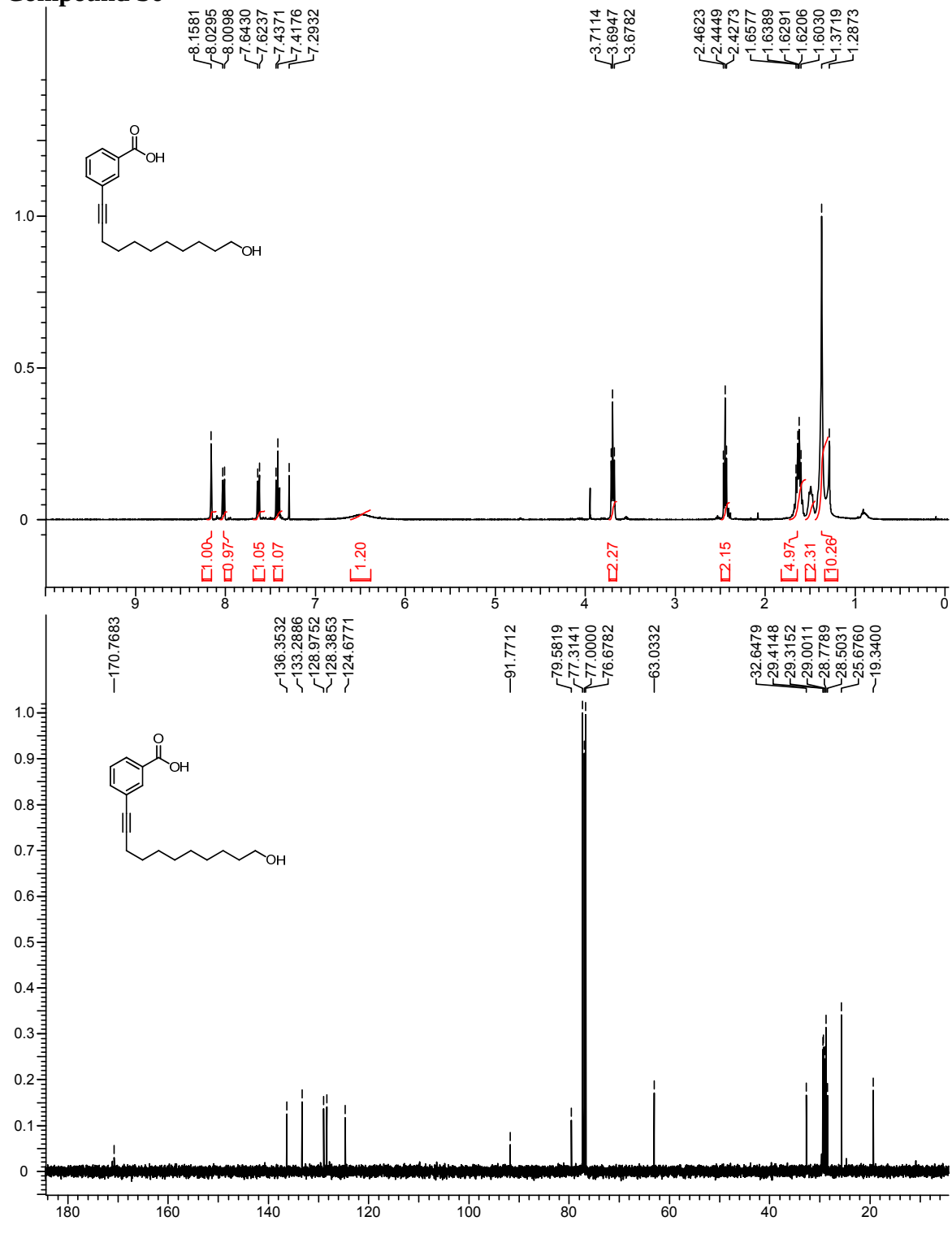
Compound S6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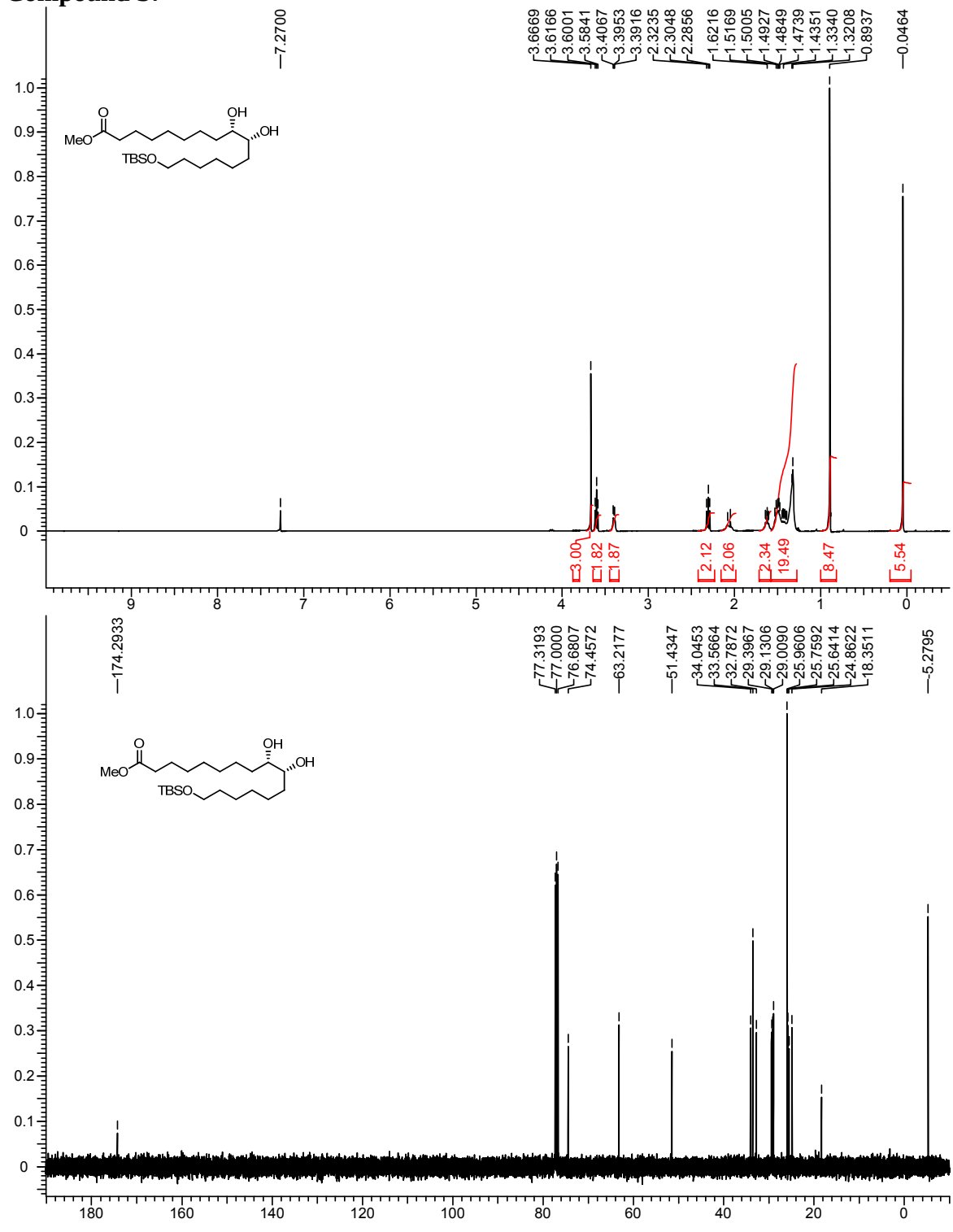
Compound S7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O
OH
OH
TBSO
3.00
1.82
1.87
2.12
2.06
2.34
19.49
8.47
5.54
174.2933
77.3193
77.0000
76.6807
74.4572
63.2177
51.4347
34.0453
33.5664
32.7872
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29.0090
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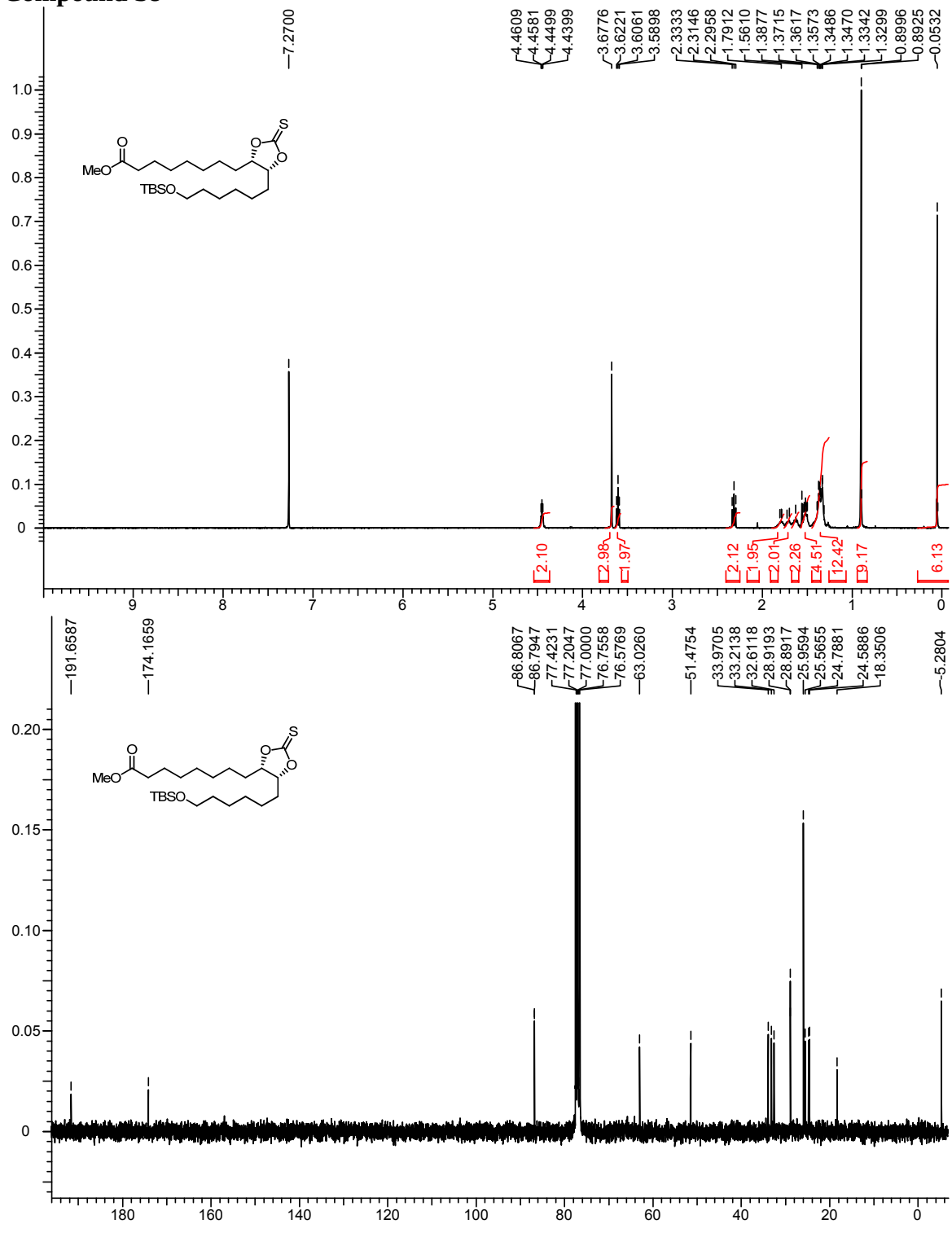
25.7592
25.6414
24.8622
18.3511
5.2795

Compound S8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3.6221
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3.5898
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2.3146
2.2958
1.7912
1.5610
1.3877
1.3715
1.3617
1.3573
1.3486
1.3470
1.3342
1.3299
0.8996
0.8925
0.0532
2.10
2.98
1.97
2.12
1.95
2.01
2.26
4.51
12.42
9.17
6.13
MeO
TBSO
191.6587
174.1659
86.8067
86.7947
77.4231
77.2047
77.0000
76.7558
76.5769
63.0260
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33.2138
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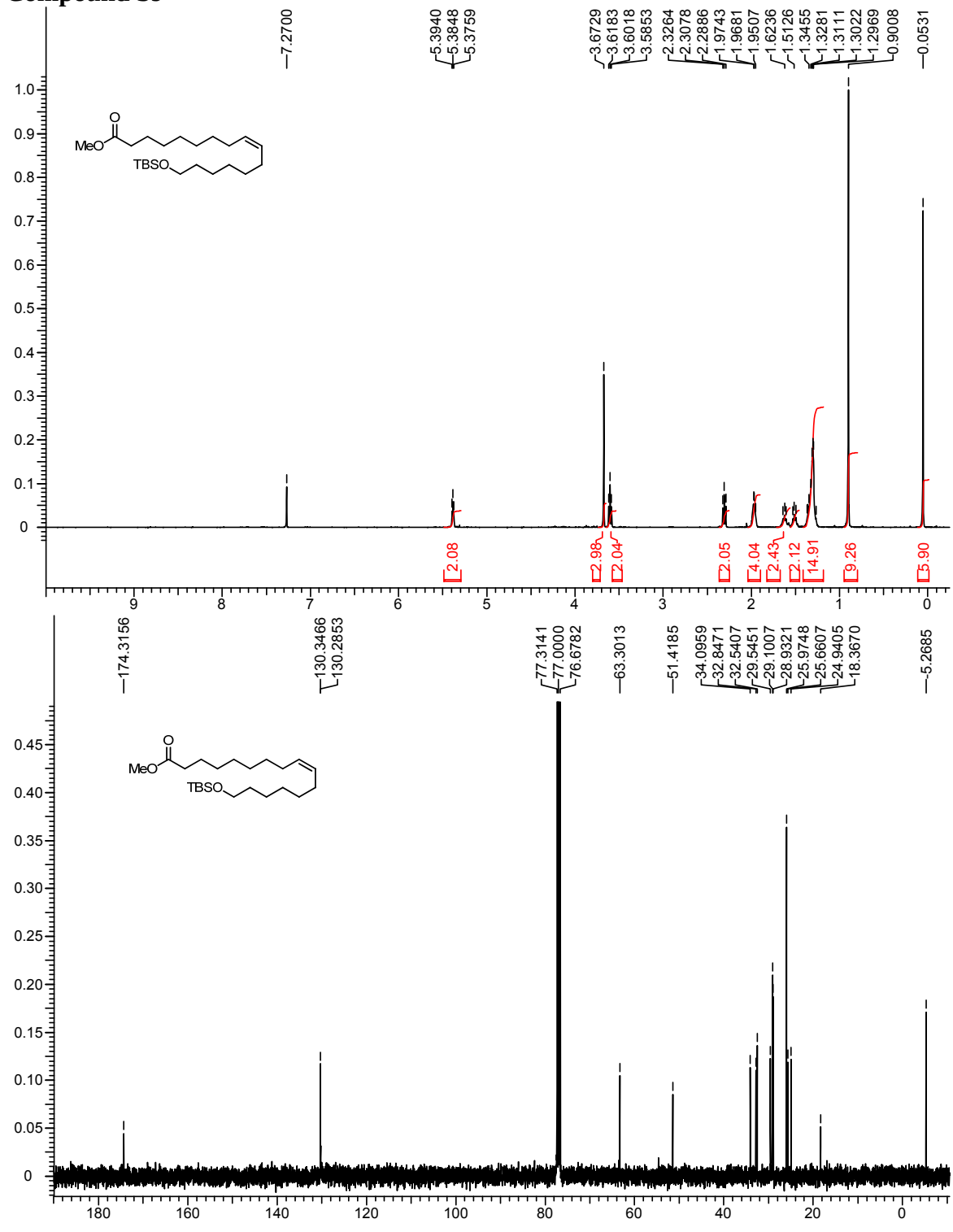
Compound S9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3.6729
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3.6018
3.5853
2.3264
2.3078
2.2886
1.9743
1.9681
1.9507
1.6236
1.5126
1.3455
1.3281
1.3111
1.3022
1.2969
0.9008
0.0531
MeO
TBSO
2.08
2.98
2.04
2.05
4.04
2.43
2.12
14.91
9.26
5.90
174.3156
130.3466
130.2853
77.3141
77.0000
76.6782
63.3013
51.4185
34.0959
32.8471
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24.9405
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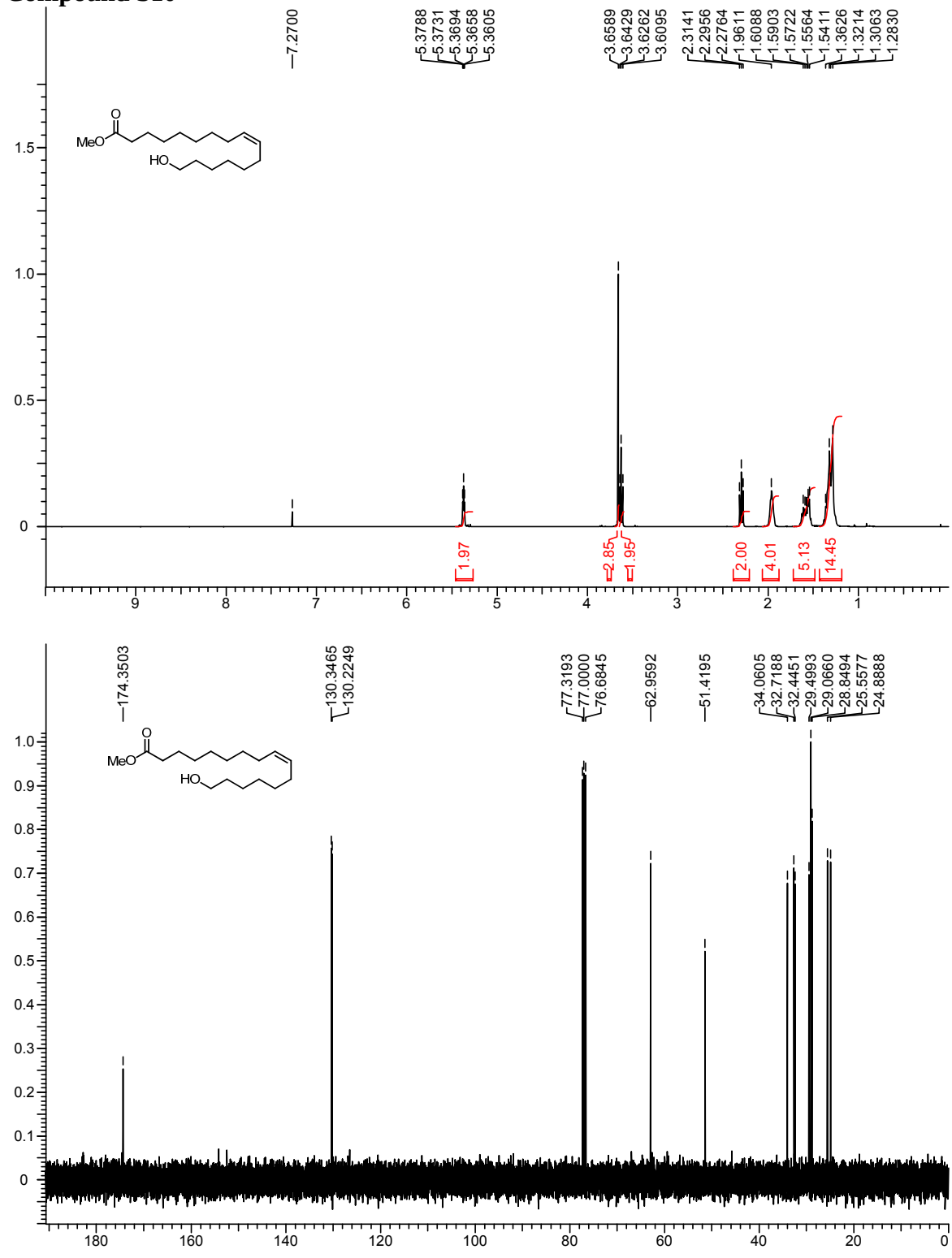
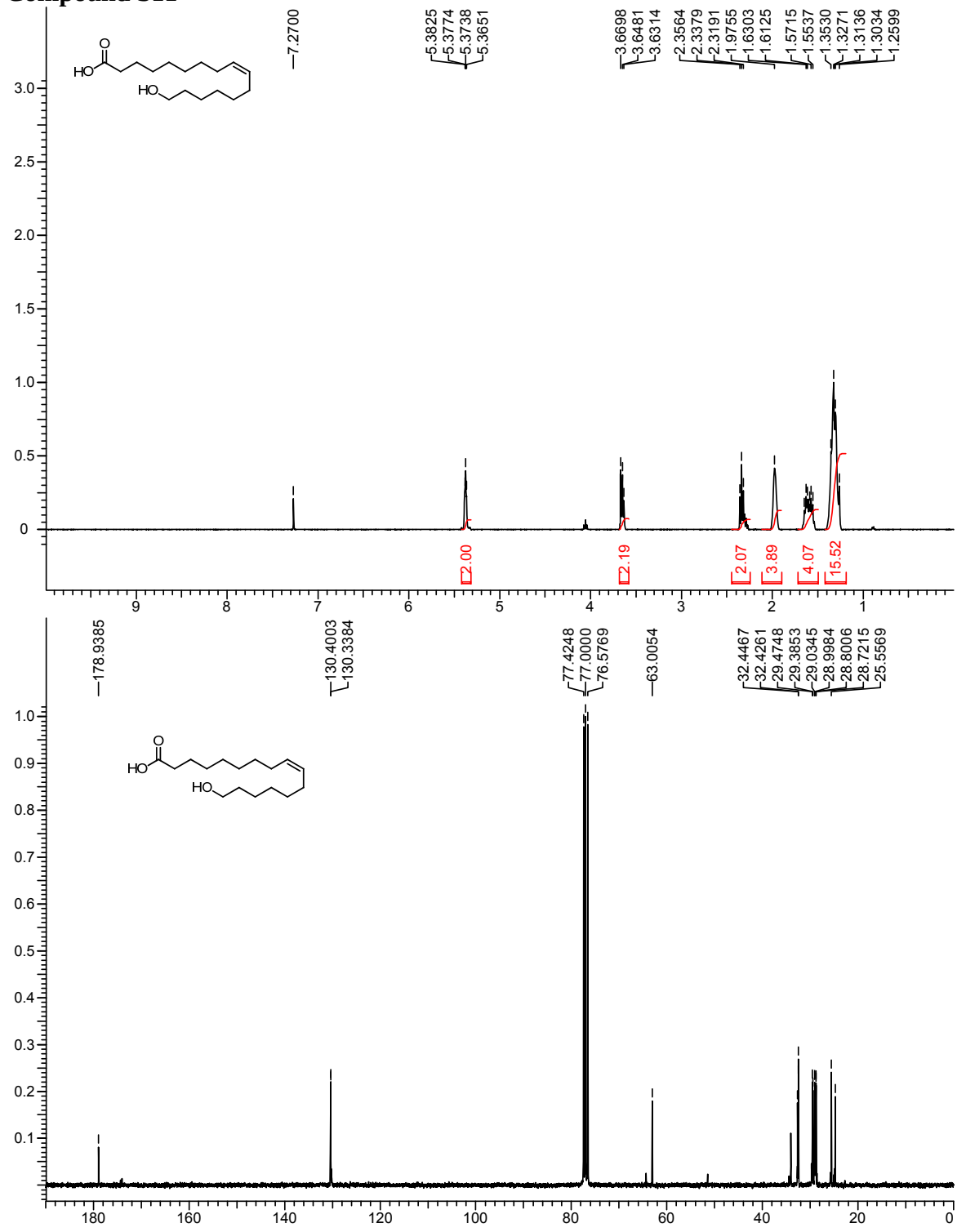
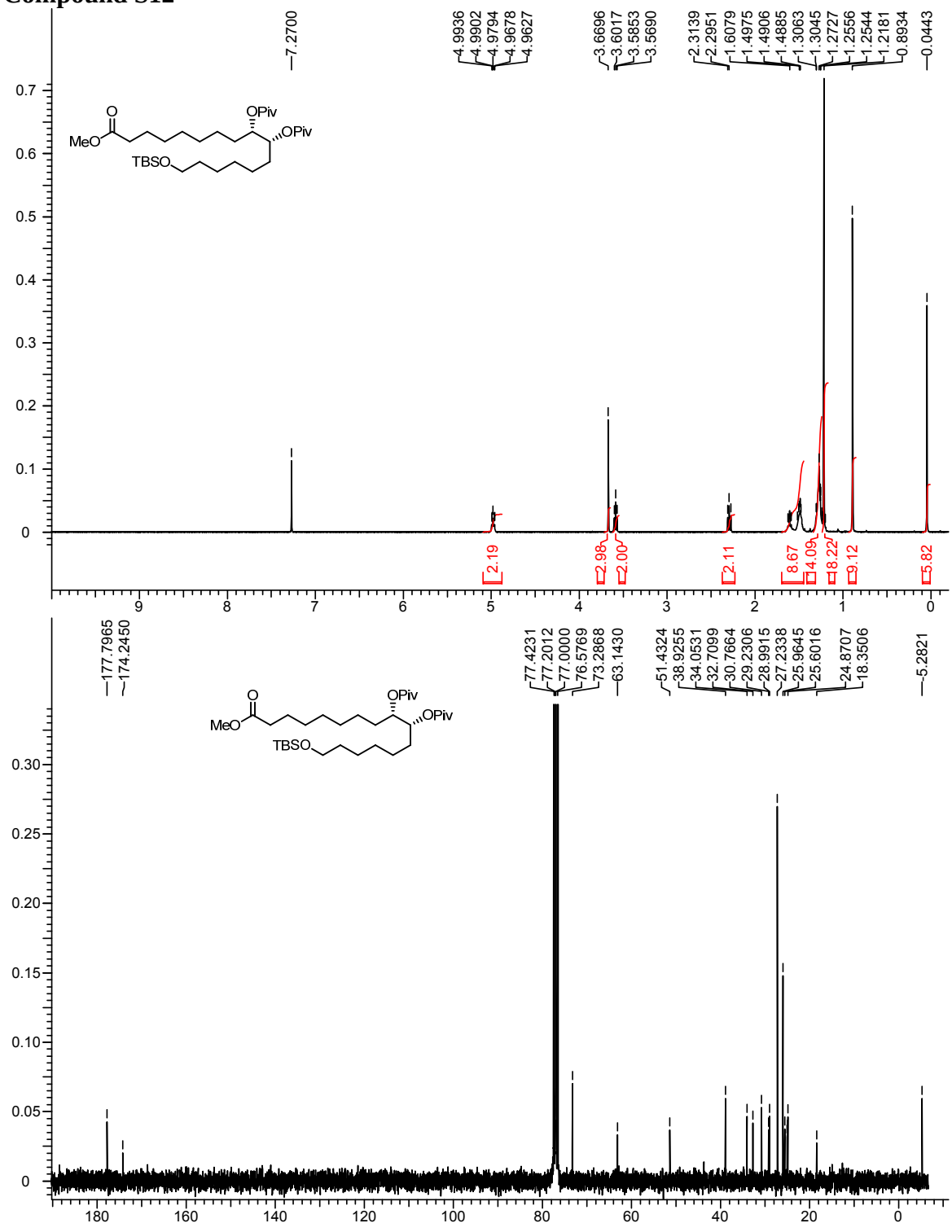
Compound S10



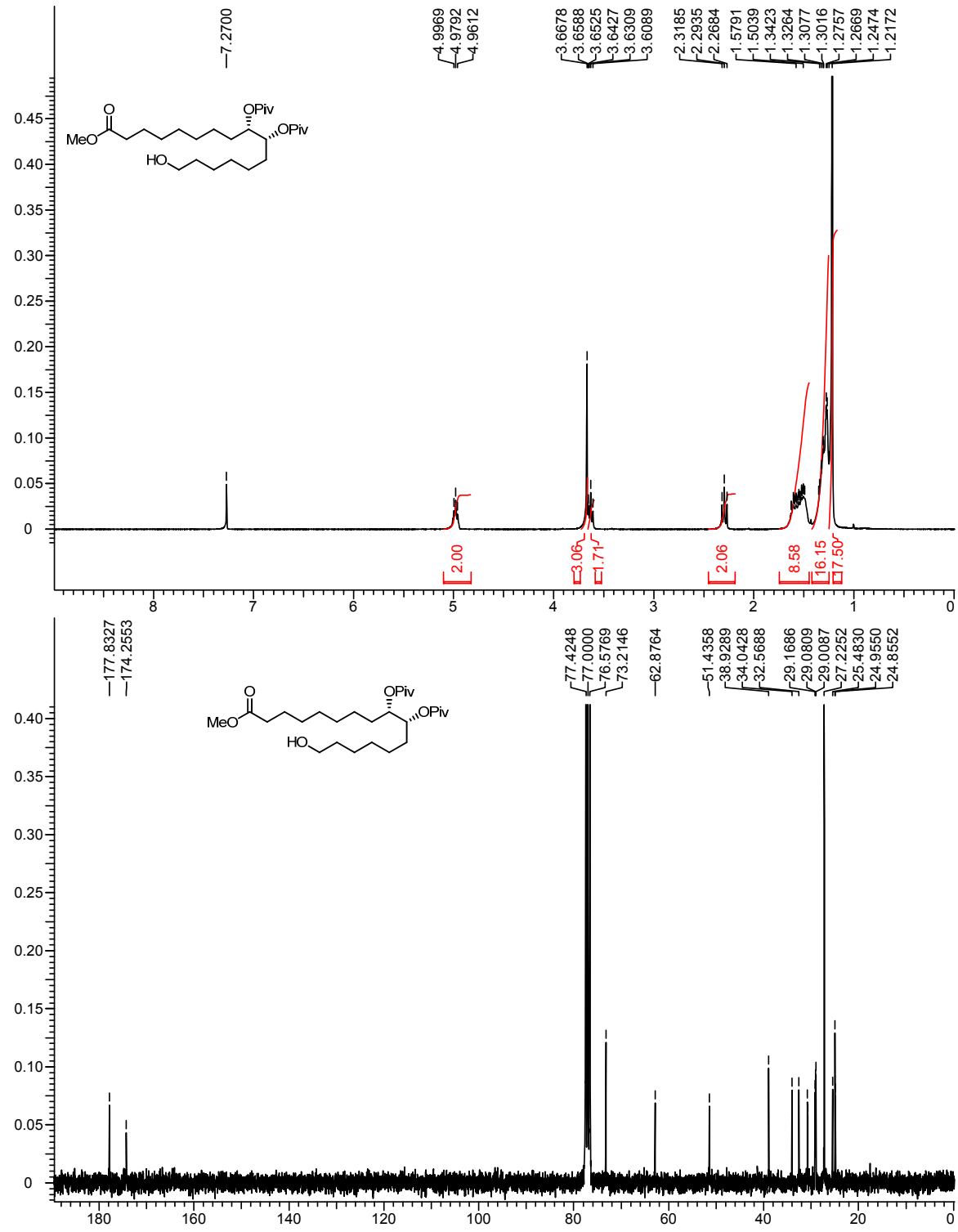
Compound S11



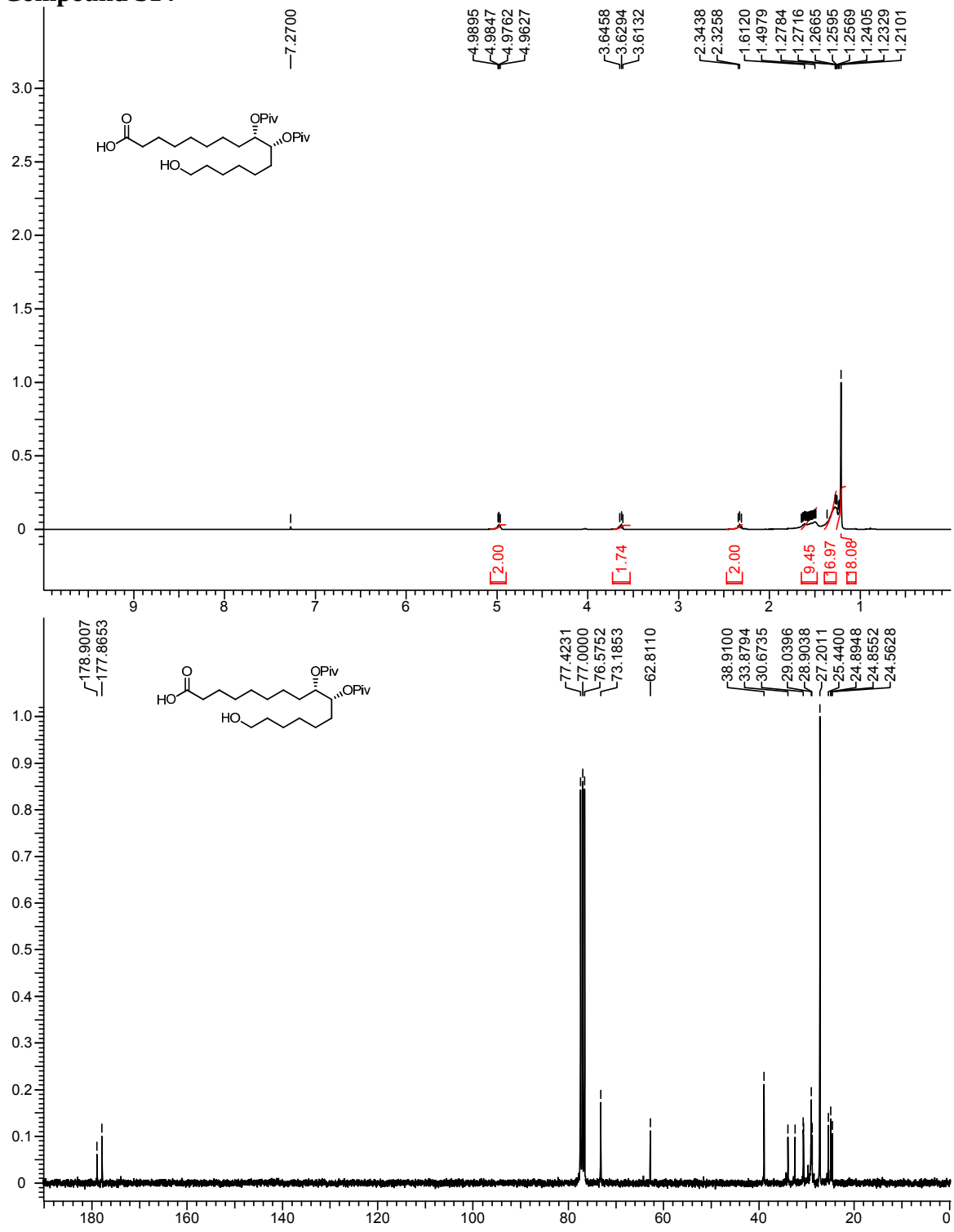
Compound S12



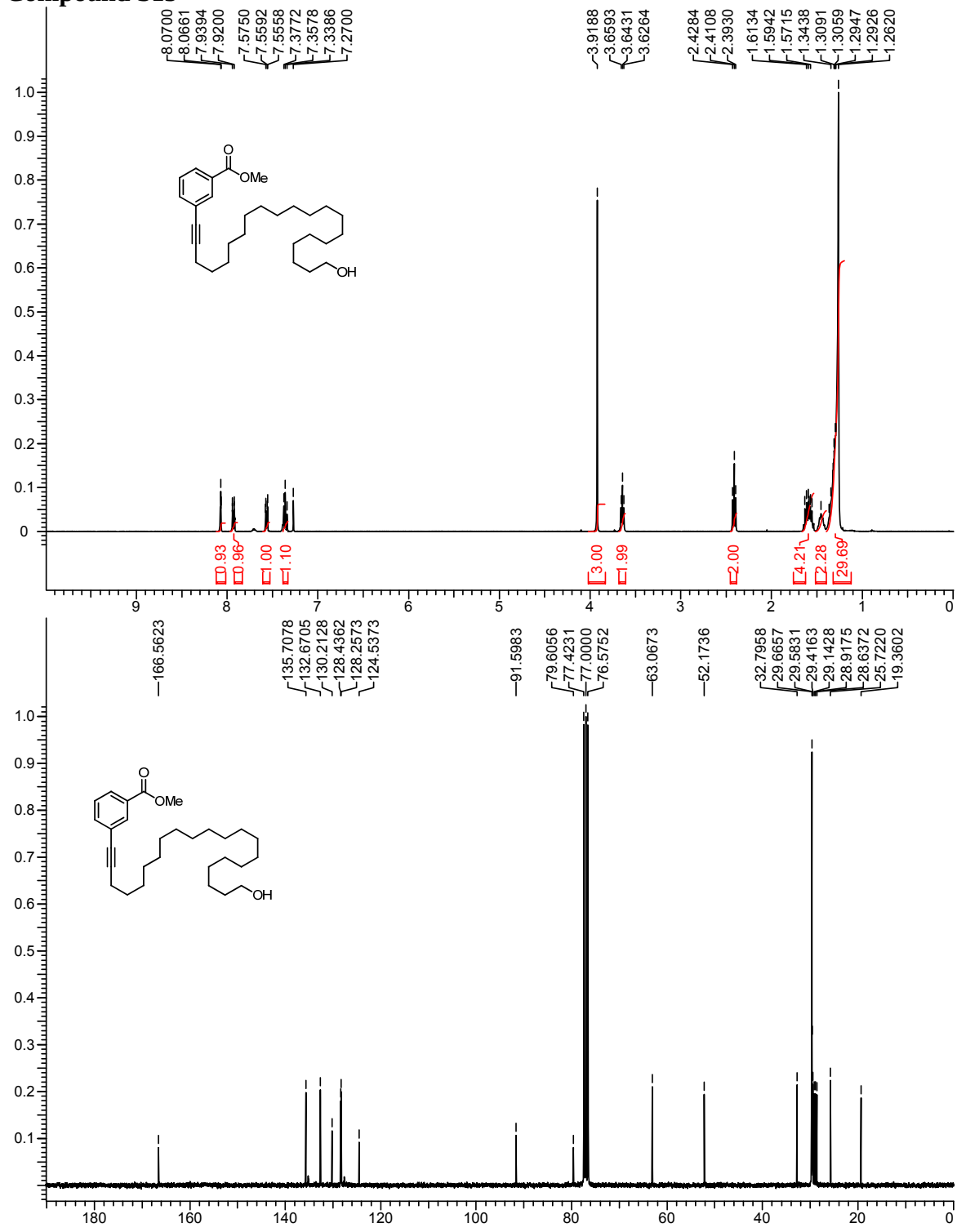
Compound S13



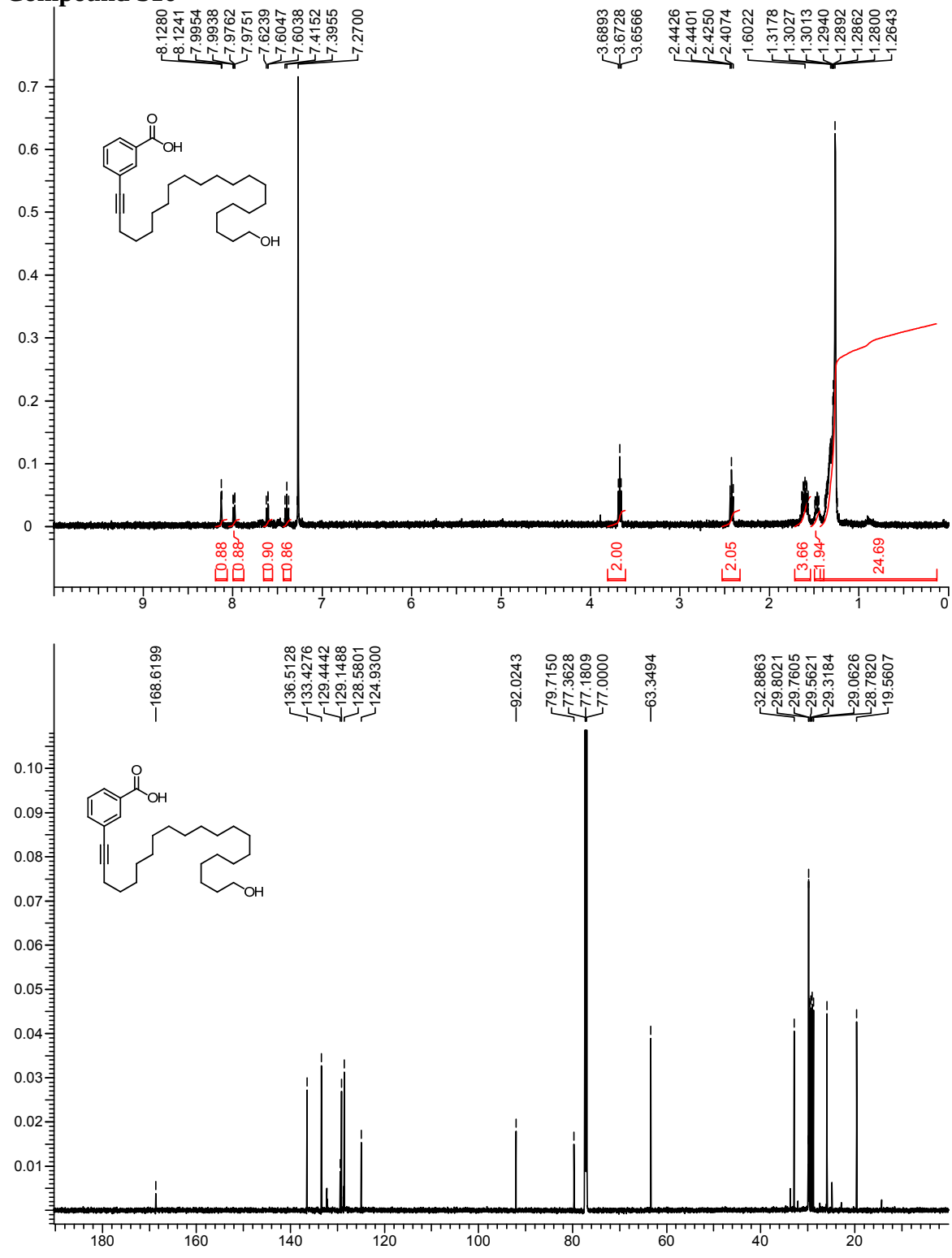
Compound S14



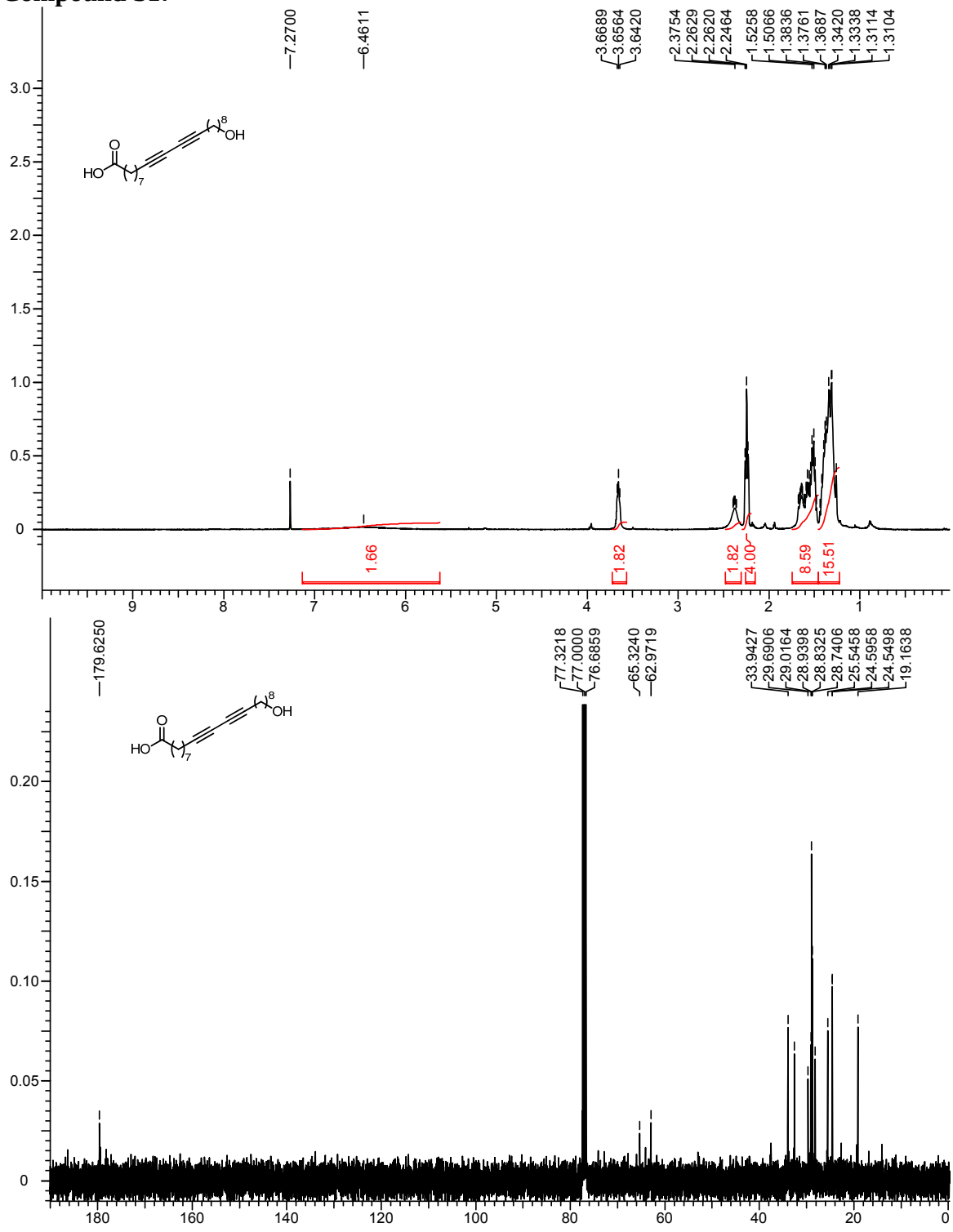
Compound S15



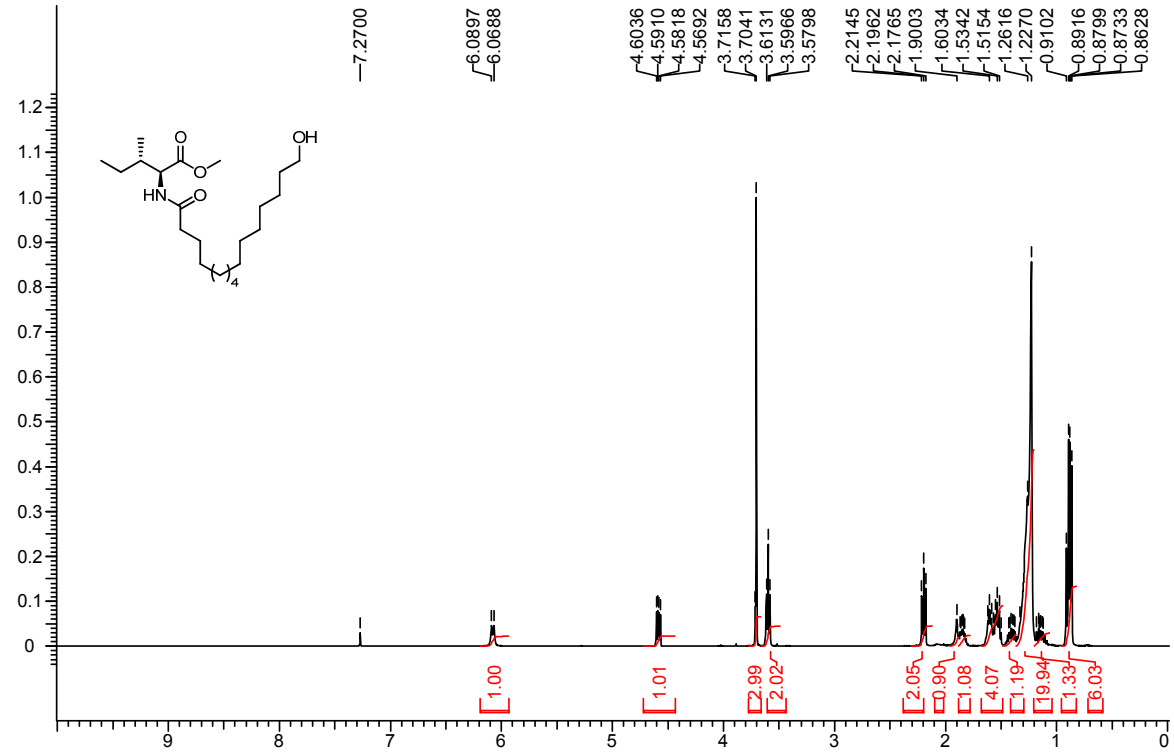
Compound S16

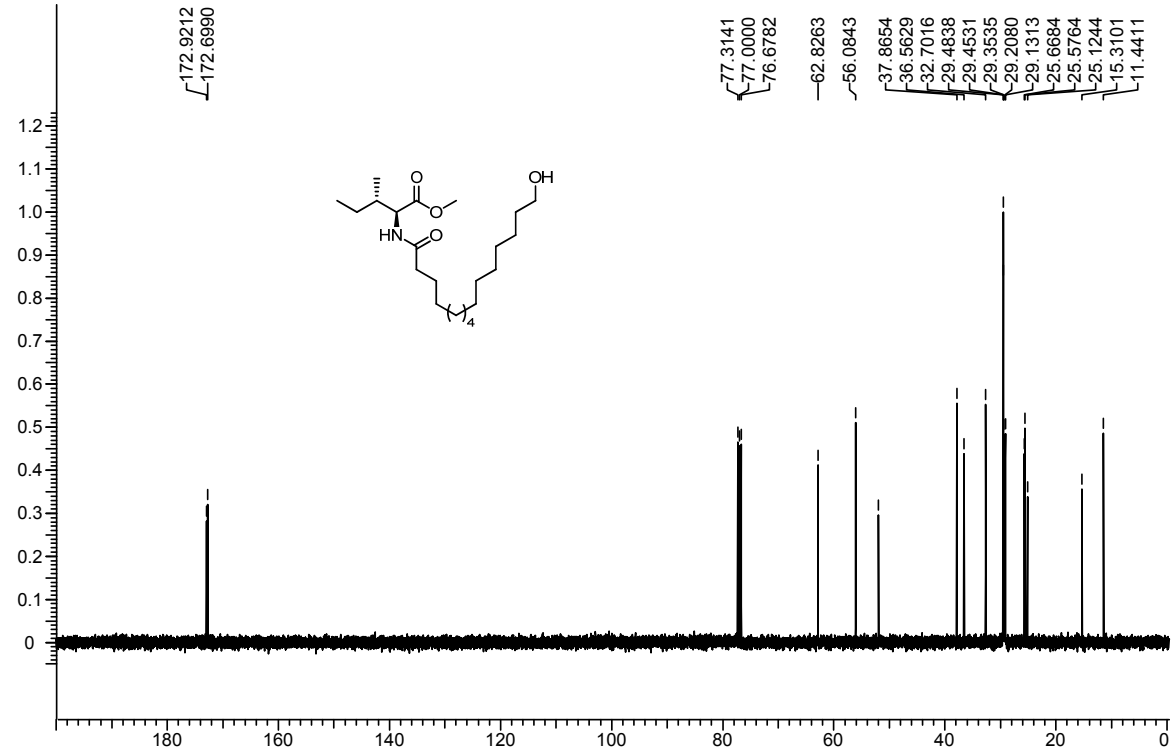


Compound S17

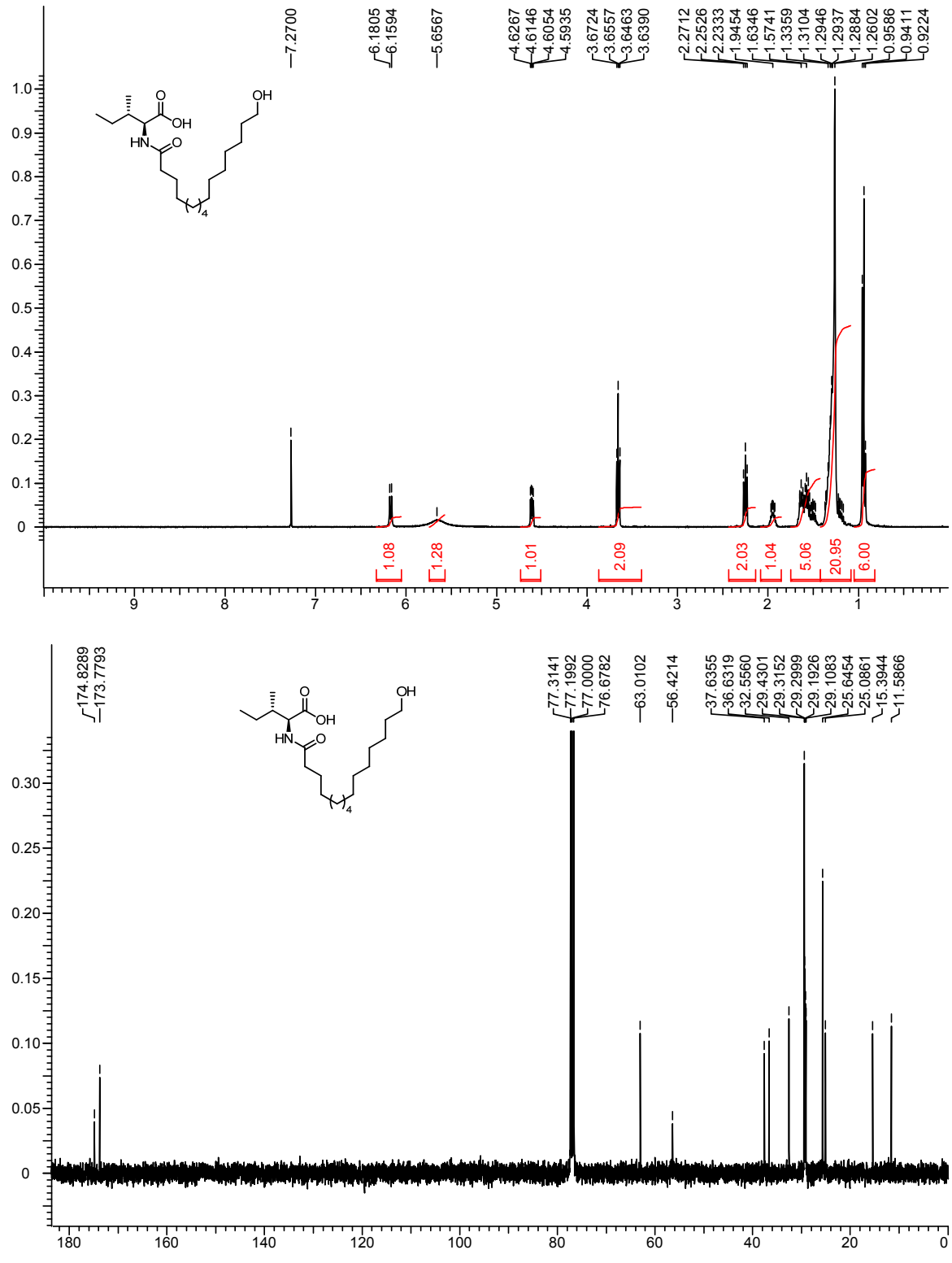


Compound S18

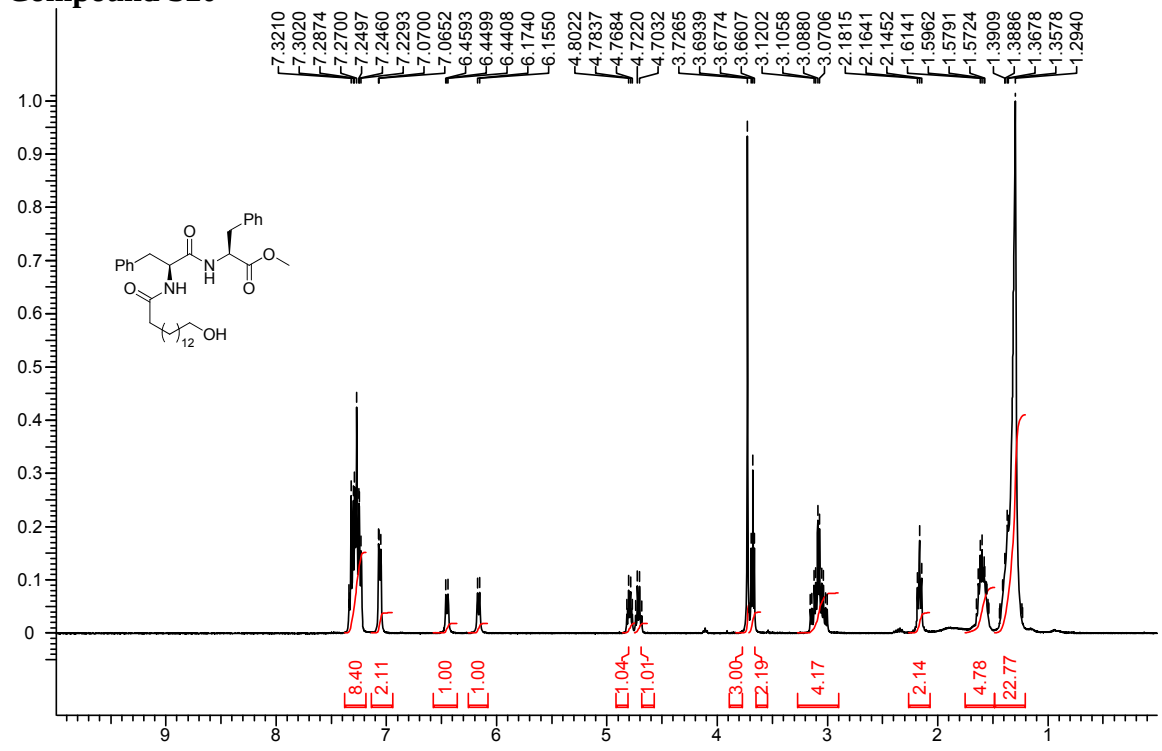


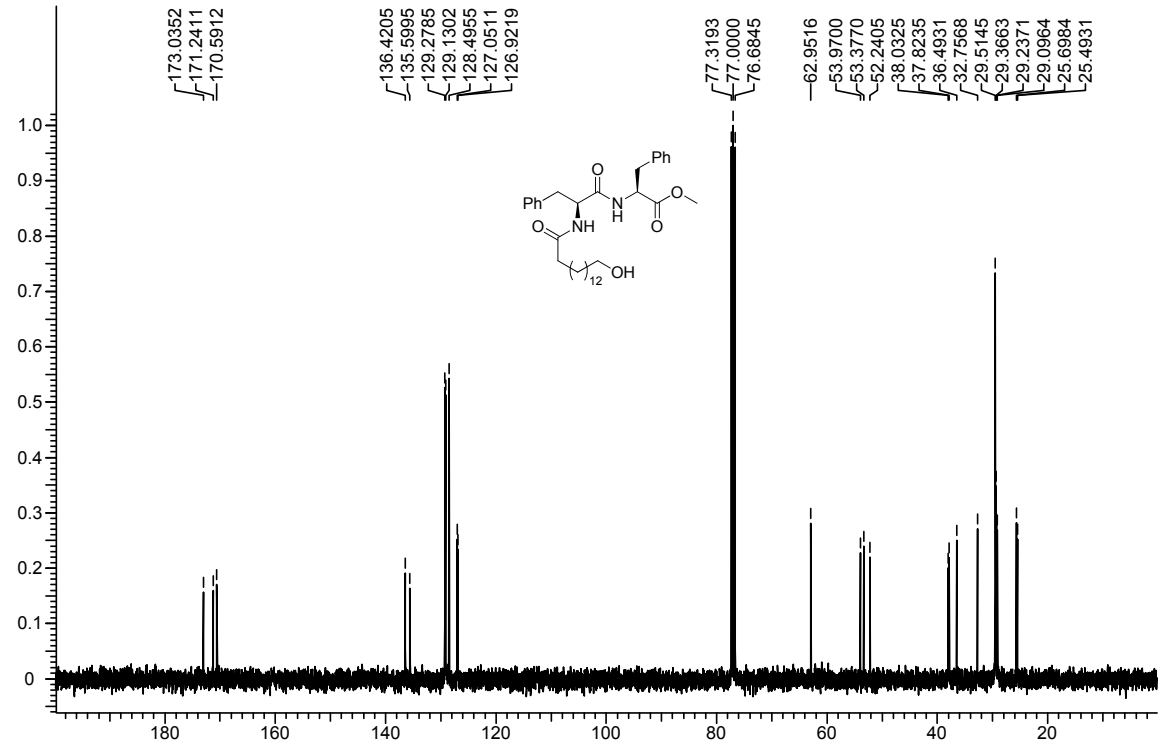


Compound S19

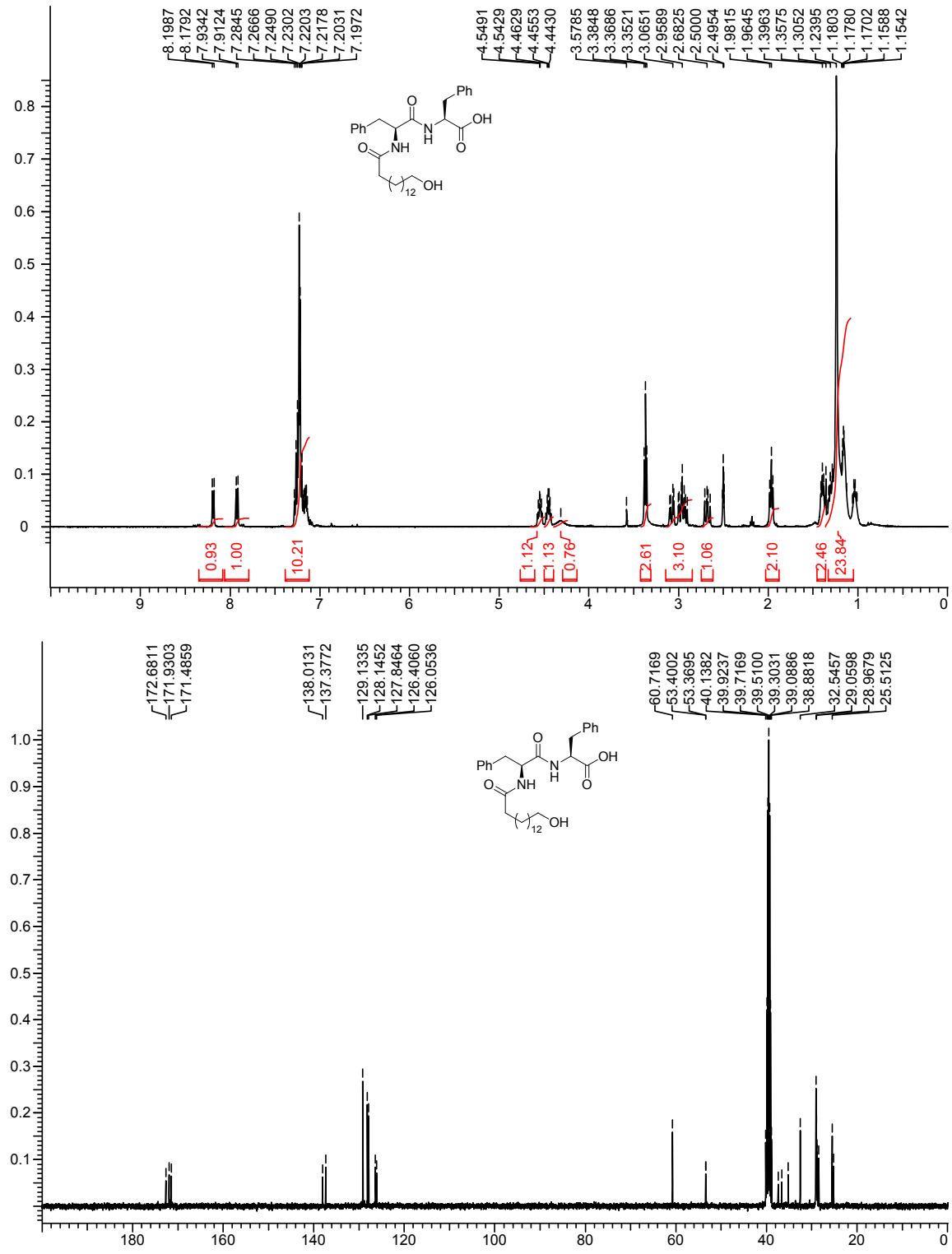


Compound S20

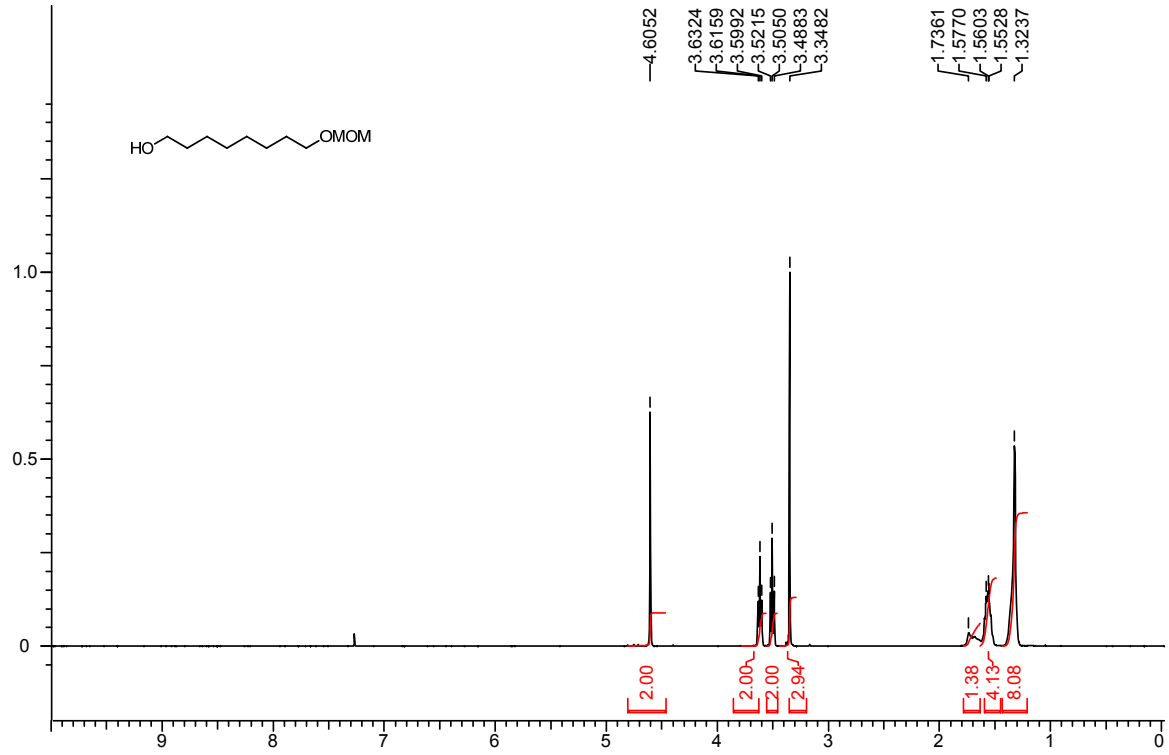


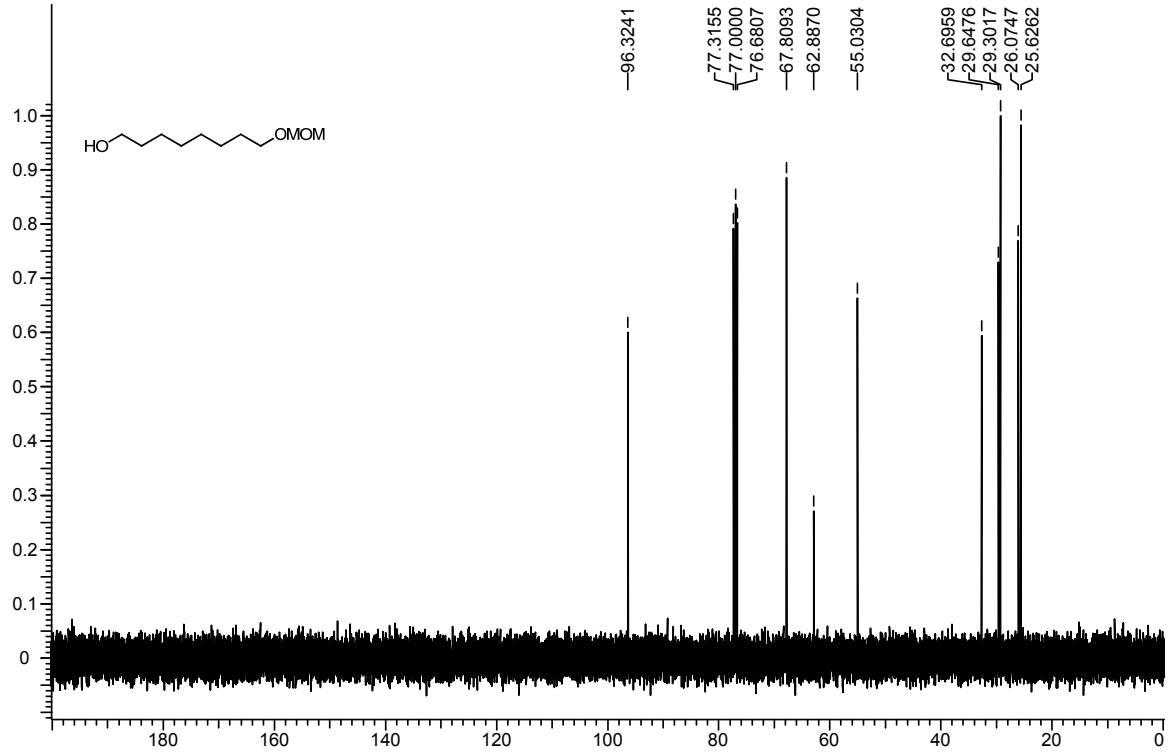


Compound S21

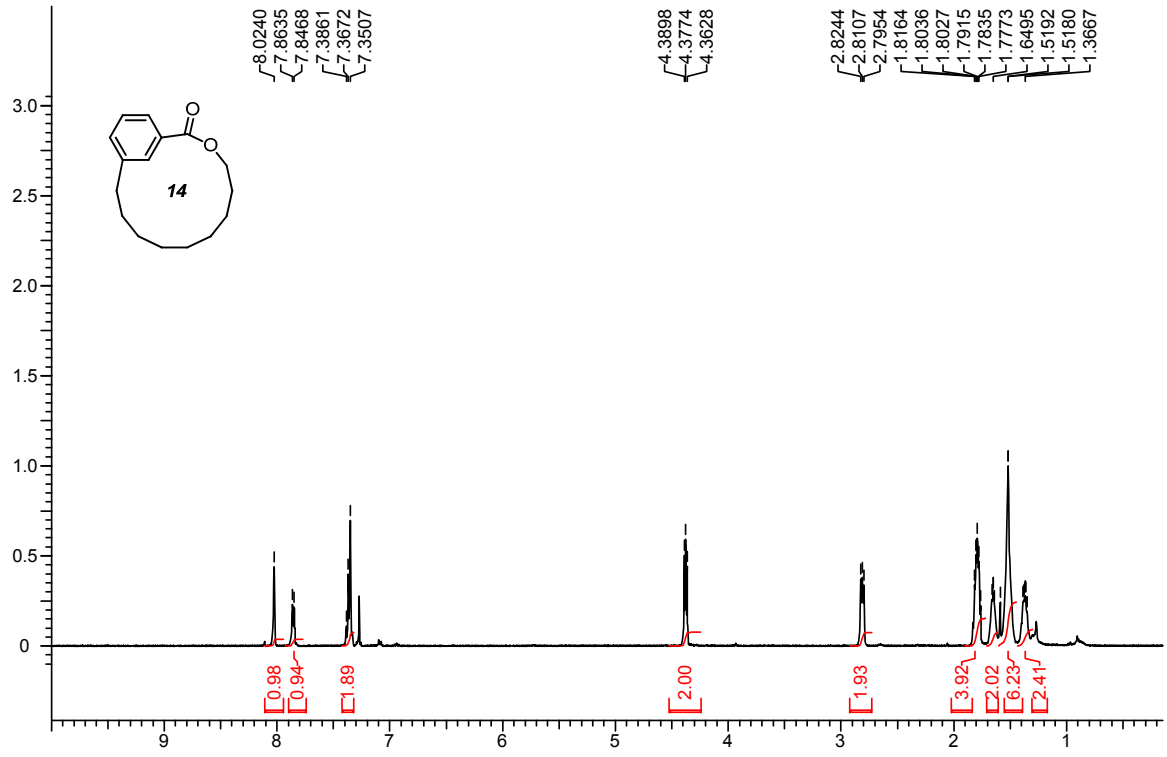


Compound S22





Compound 6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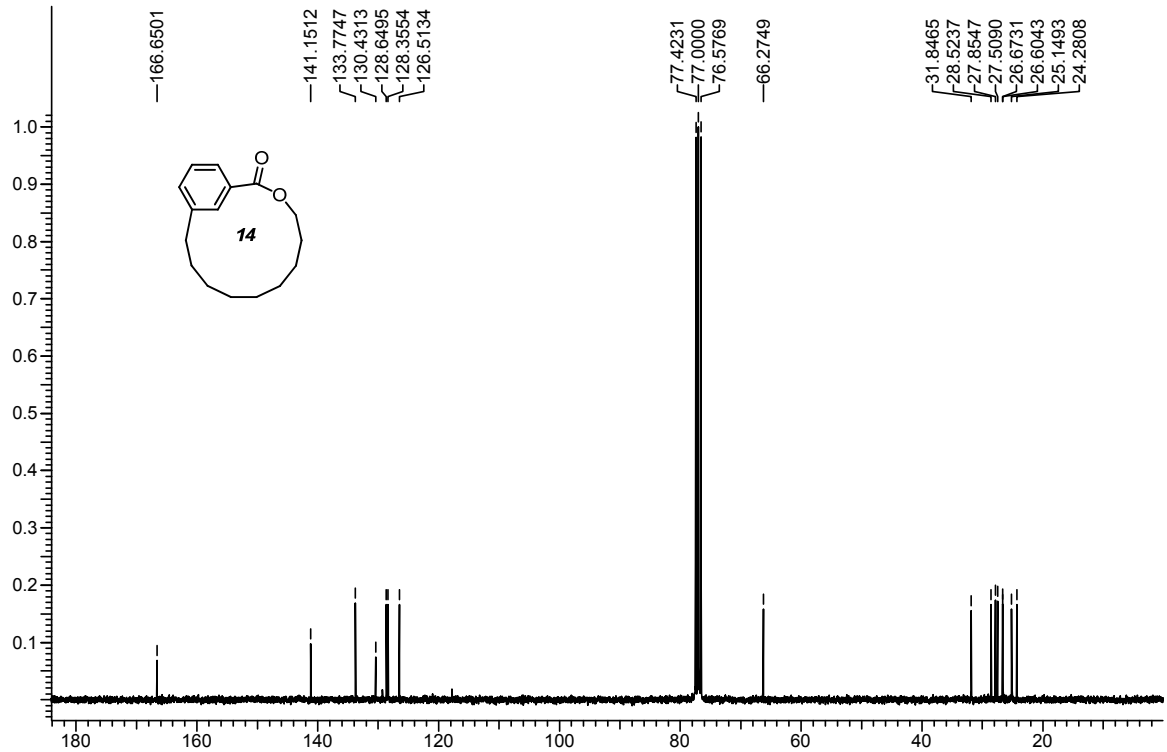
7.3861
7.3672
7.3507
4.3898
4.3774
4.3628
2.8244
2.8107
2.7954
1.8164
1.8036
1.8027
1.7915
1.7835
1.7773
1.6495
1.5192
1.5180
1.3667
14
0.98
0.94
1.89
2.00
1.93
3.92
2.02
6.23
2.41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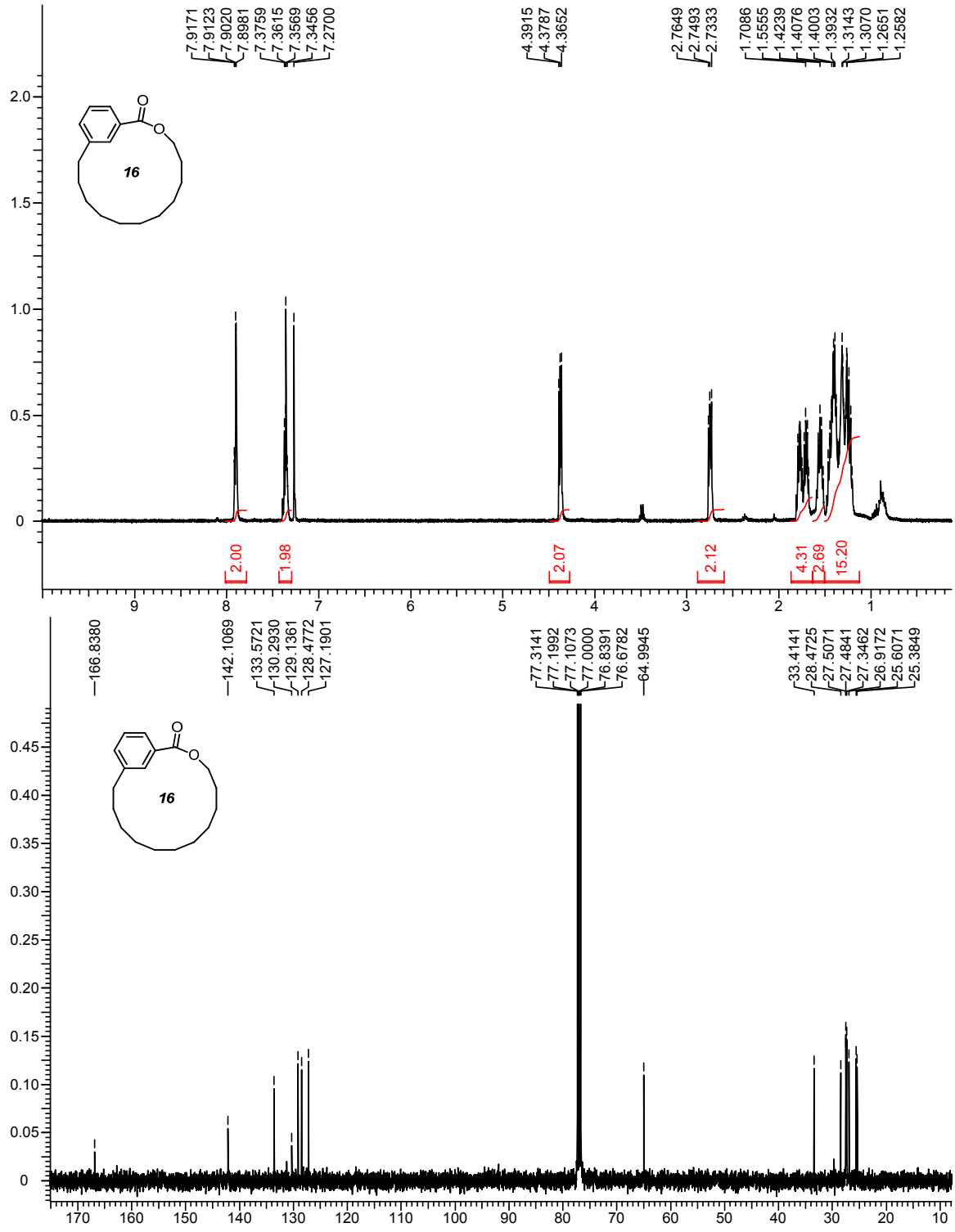
141.1512
133.7747
130.4313
128.6495
128.3554
126.5134
77.4231
77.0000
76.5769
66.2749
31.8465
28.5237
27.8547
27.5090
26.6731
26.6043
25.1493
24.2808
14

Compound 7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7.9123
7.9020
7.8981
7.3759
7.3615
7.3569
7.3456
7.2700
4.3915
4.3787
4.3652
2.7649
2.7493
2.7333
1.7086
1.5555
1.4239
1.4076
1.4003
1.3932
1.3143
1.3070
1.2651
1.2582
16
2.00
1.98
2.07
2.12
4.31
2.69
15.20
166.8380
142.1069
133.5721
130.2930
129.1361
128.4772
127.1901
77.3141
77.1992
77.1073
77.0000
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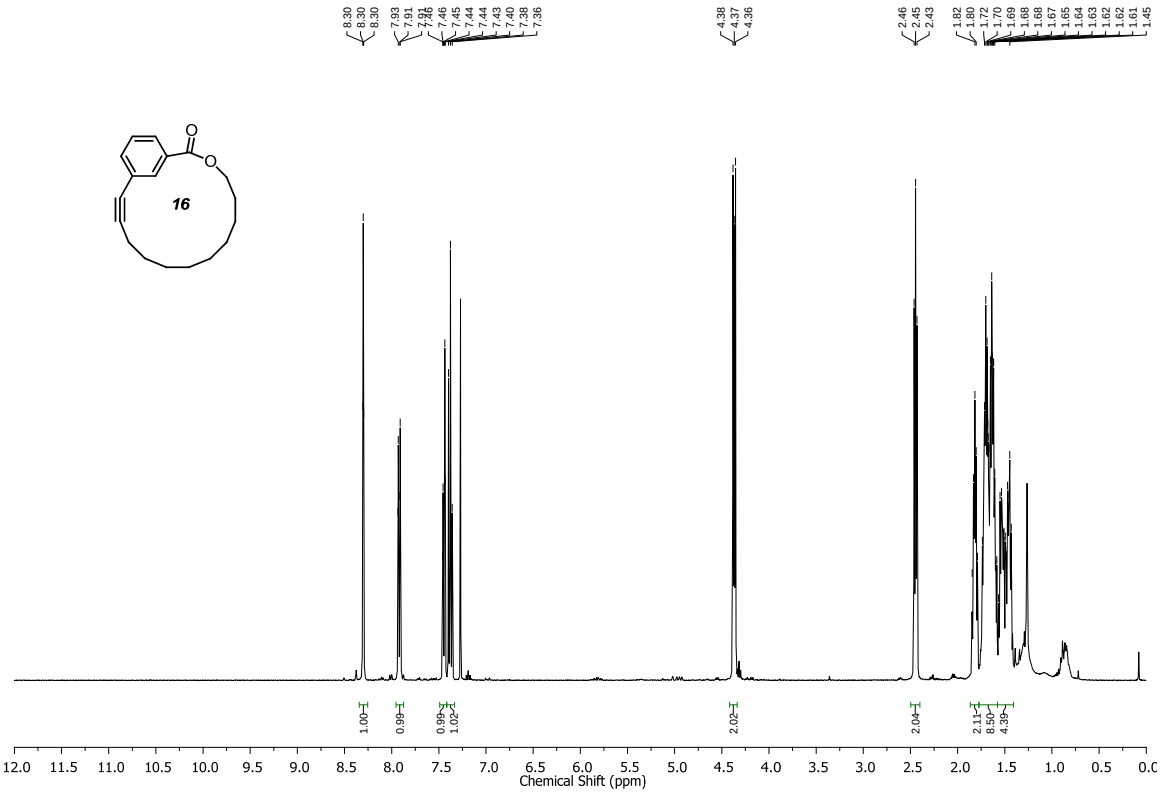
76.6782
64.9945
33.4141
28.4725
27.5071
27.4841
27.3462
26.9172
25.6071
25.3849
16

Compound 8


8.30
8.30
8.30
7.93
7.91
7.91
7.46
7.45
7.44
7.44
7.43
7.40
7.38
7.36
4.38
4.37
4.36
2.46
2.45
2.43
1.82
1.80
1.72
1.70
1.69
1.68
1.68
1.67
1.65
1.64
1.63
1.62
1.61
1.45
16
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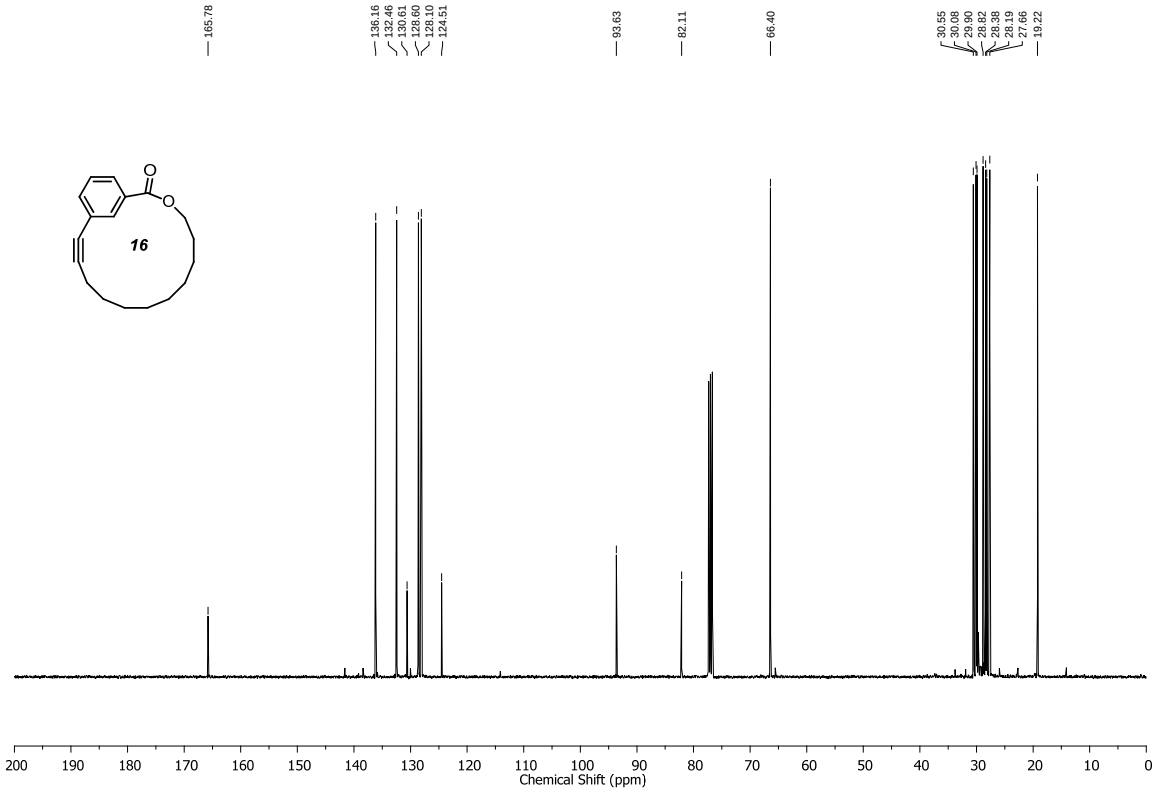
0.99
0.99
1.02
2.02
2.04
2.11
8.50
4.39
Chemical Shift (ppm)


165.78
136.16
132.46
130.61
128.60
128.10
124.51
93.63
82.11
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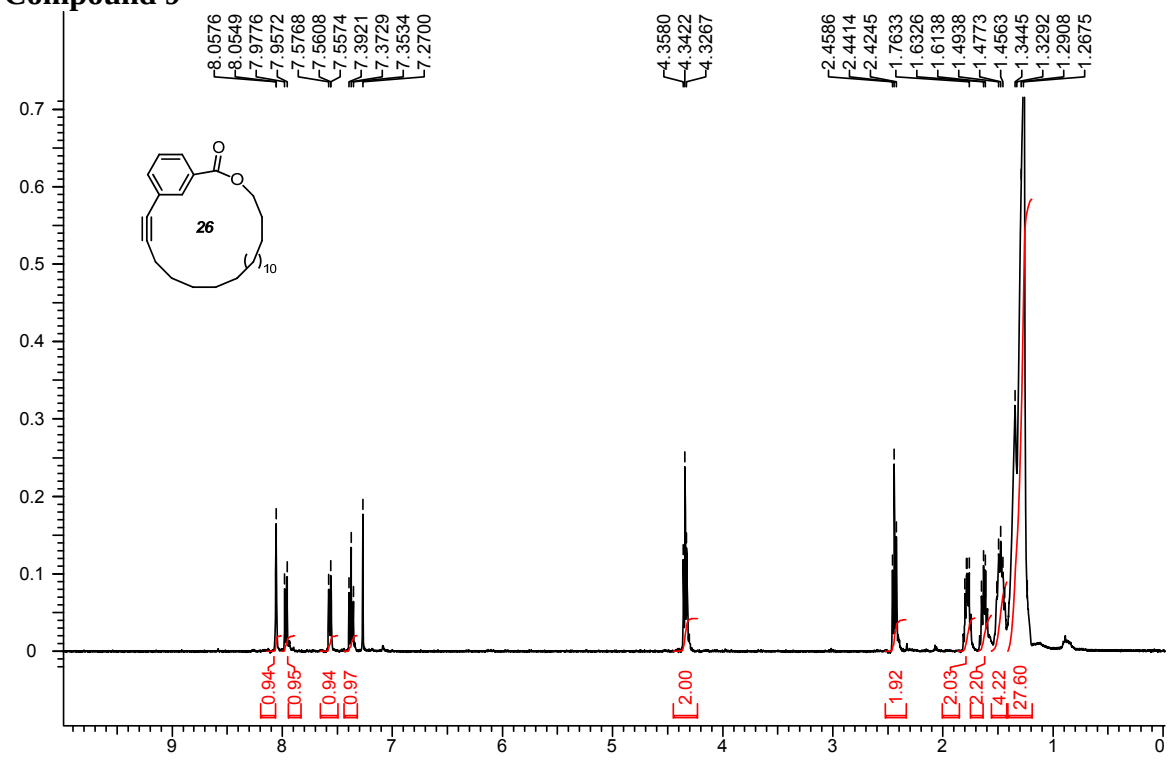
30.55
30.08
29.90
28.82
28.38
28.19
27.66
19.22
16
Chemical Shift (ppm)

Compound 9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7.9776
7.9572
7.5768
7.5608
7.5574
7.3921
7.3729
7.3534
7.2700
4.3580
4.3422
4.3267
2.4586
2.4414
2.4245
1.7633
1.6326
1.6138
1.4938
1.4773
1.4563
1.3445
1.3292
1.2908
1.2675
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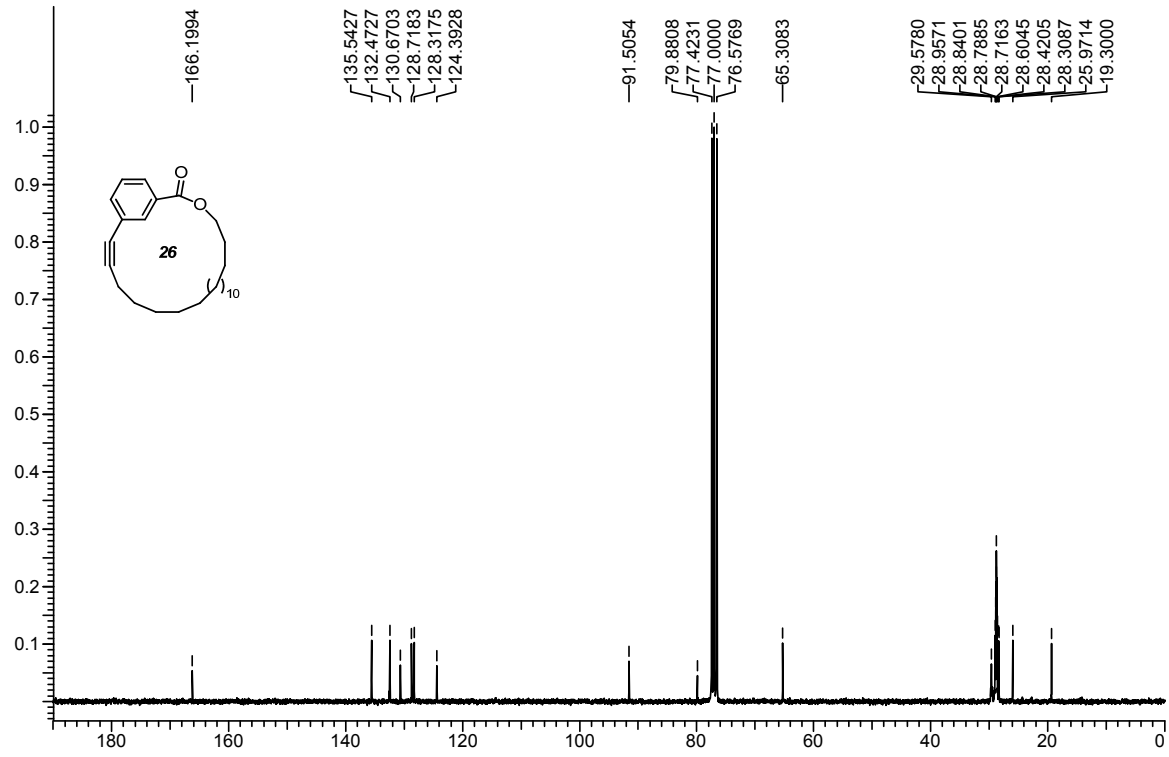
0.95
0.94
0.97
2.00
1.92
2.03
2.20
4.22
27.60
26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128.3175
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79.8808
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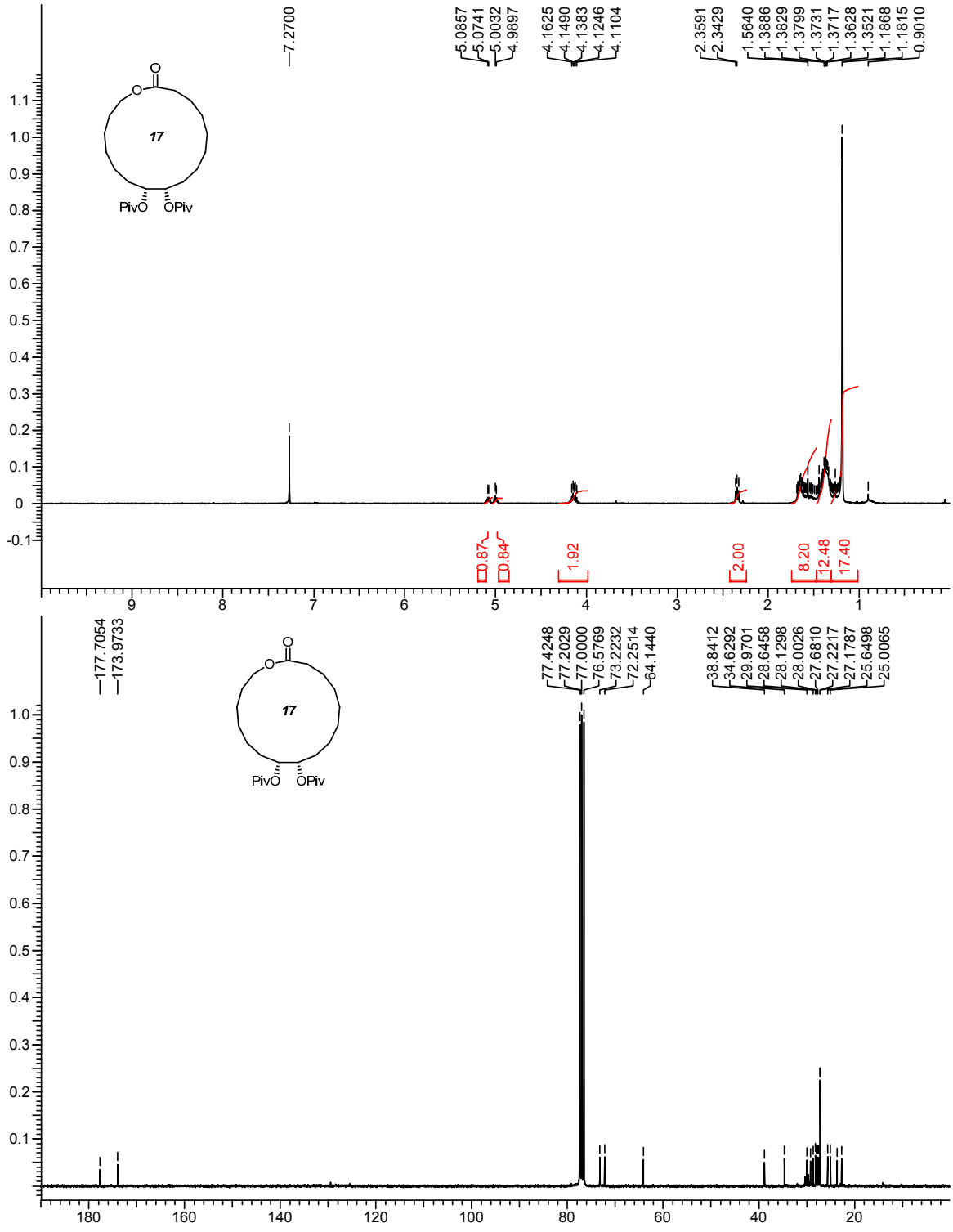
65.3083
29.5780
28.9571
28.8401
28.7885
28.7163
28.6045
28.4205
28.3087
25.9714
19.3000
26

Compound 11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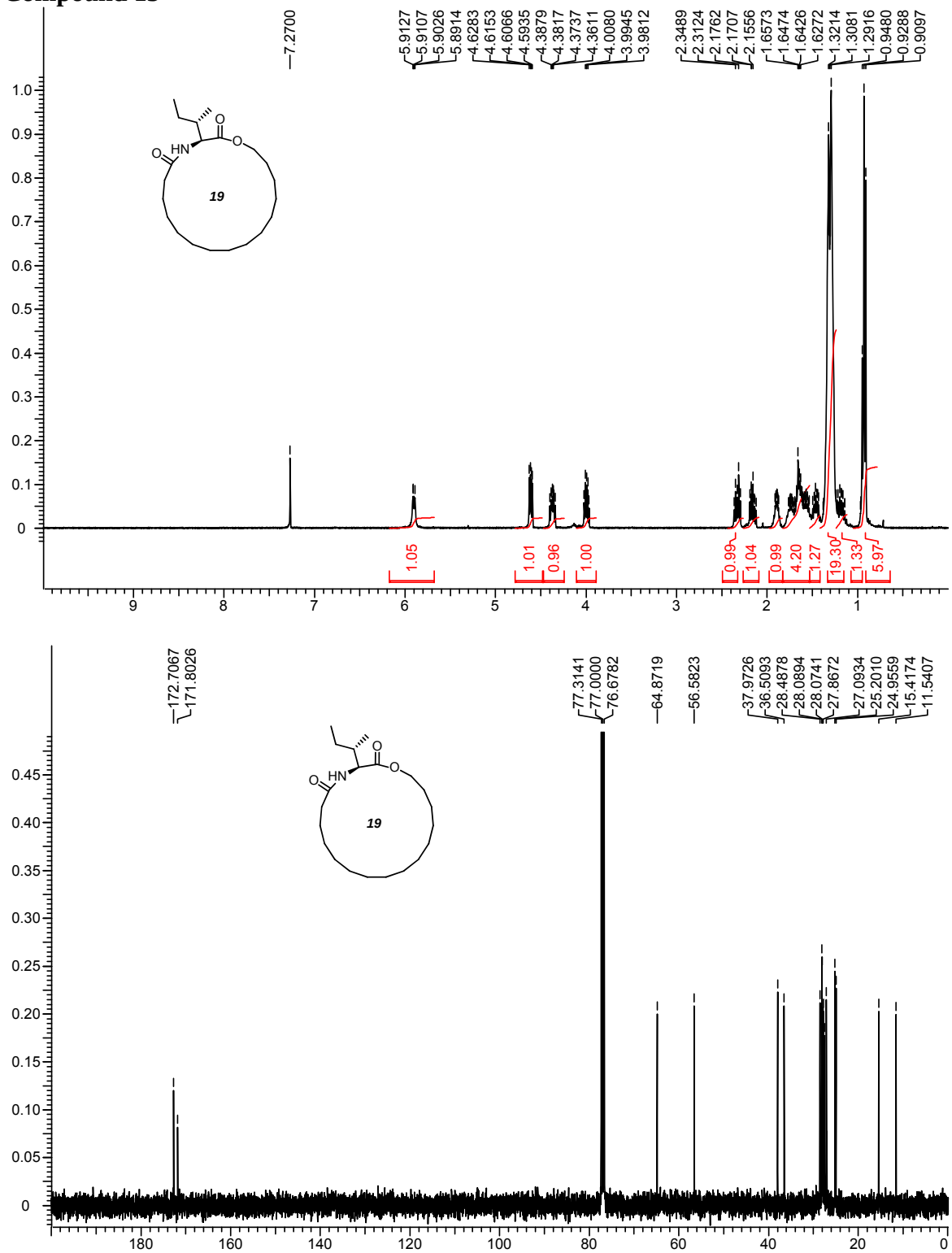
4.1490
4.1383
4.1246
4.1104
2.3591
2.3429
1.5640
1.3886
1.3829
1.3799
1.3731
1.3717
1.3628
1.3521
1.1868
1.1815
0.9010
17
PivO
OPiv
0.87
0.84
1.92
2.00
8.20
2.48
17.40
177.7054
173.9733
77.4248
77.2029
77.0000
76.5769
73.2232
72.2514
64.1440
38.8412
34.6292
29.9701
28.6458
28.1298
28.0026
27.6810
27.2217
27.1787
25.6498
25.0065

Compound 13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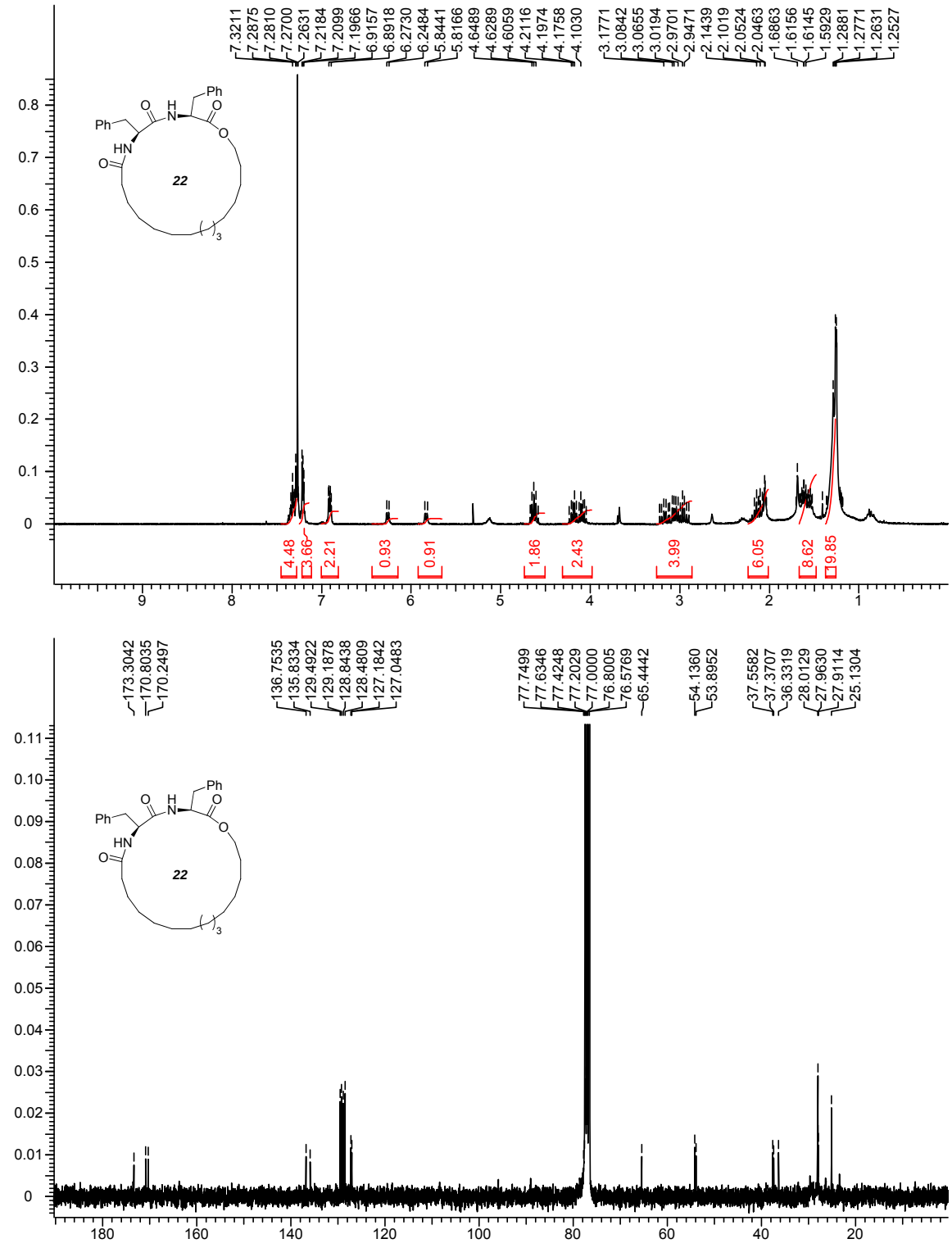
5.9107
5.9026
5.8914
4.6283
4.6153
4.6066
4.5935
4.3879
4.3817
4.3737
4.3611
4.0080
3.9945
3.9812
2.3489
2.3124
2.1762
2.1707
2.1556
1.6573
1.6474
1.6426
1.6272
1.3214
1.3081
1.2916
0.9480
0.9288
0.9097
1.05
1.01
0.96
1.00
0.99
1.04
0.99
4.20
1.27
19.30
1.33
5.97
19
172.7067
171.8026
77.3141
77.0000
76.6782
64.8719
56.5823
37.9726
36.5093
28.4878
28.0894
28.0741
27.8672
27.0934
25.2010
24.9559
15.4174
11.5407
19

Compound 14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7.2631
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6.2730
6.2484
5.8441
5.8166
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4.6289
4.6059
4.2116
4.1974
4.1758
4.1030
3.1771
3.0842
3.0655
3.0194
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2.9471
2.1439
2.1019
2.0524
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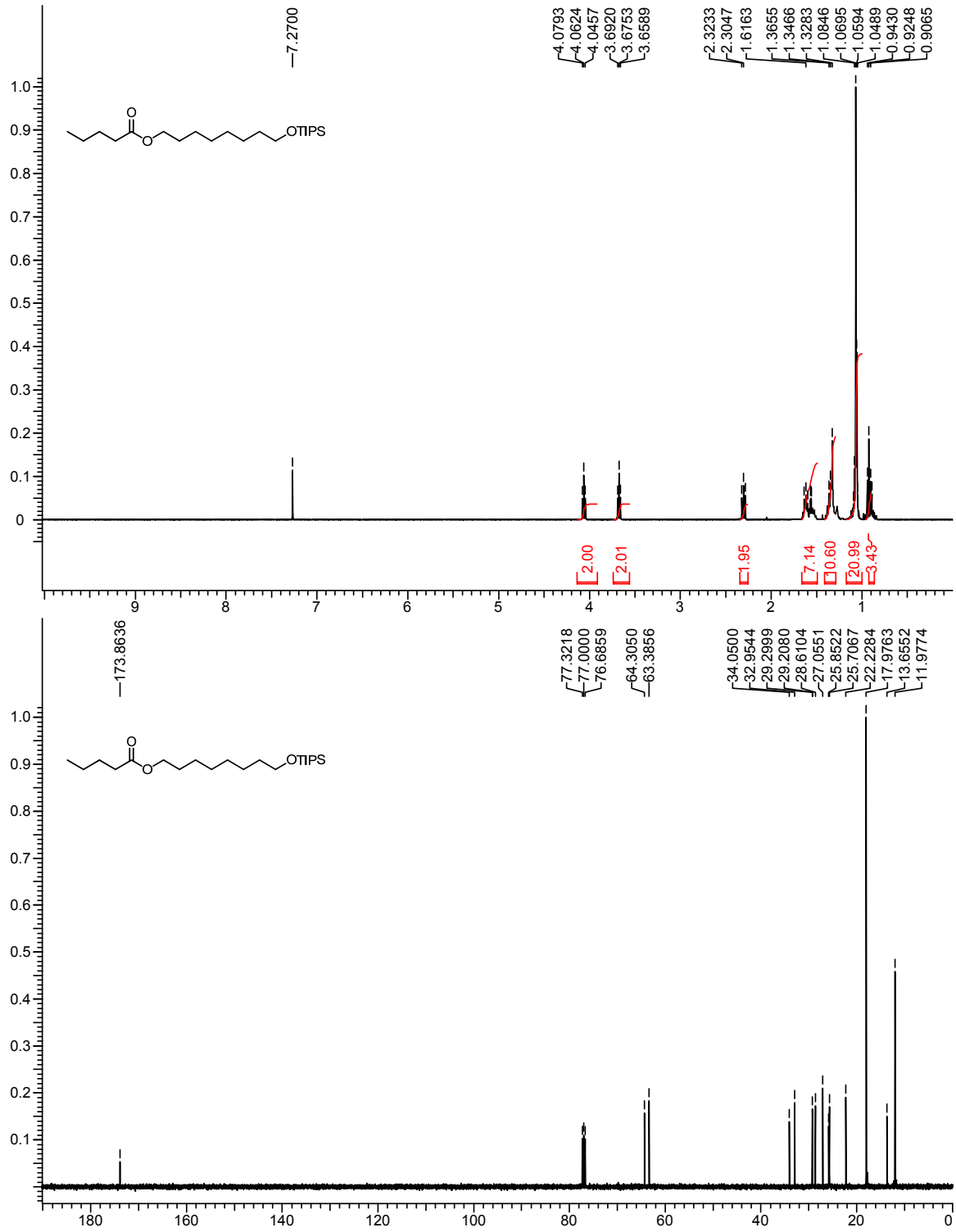
1.6156
1.6145
1.5929
1.2881
1.2771
1.2631
1.2527
22
4.48
3.66
2.21
0.93
0.91
1.86
2.43
3.99
6.05
8.62
9.85
173.3042
170.8035
170.2497
136.7535
135.8334
129.4922
129.1878
128.8438
128.4809
127.1842
127.0483
77.7499
77.6346
77.4248
77.2029
77.0000
76.8005
76.5769
65.4442
54.1360
53.8952
37.5582
37.3707
36.3319
28.0129
27.9630
27.9114
25.1304
22

Compound 20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2.3047
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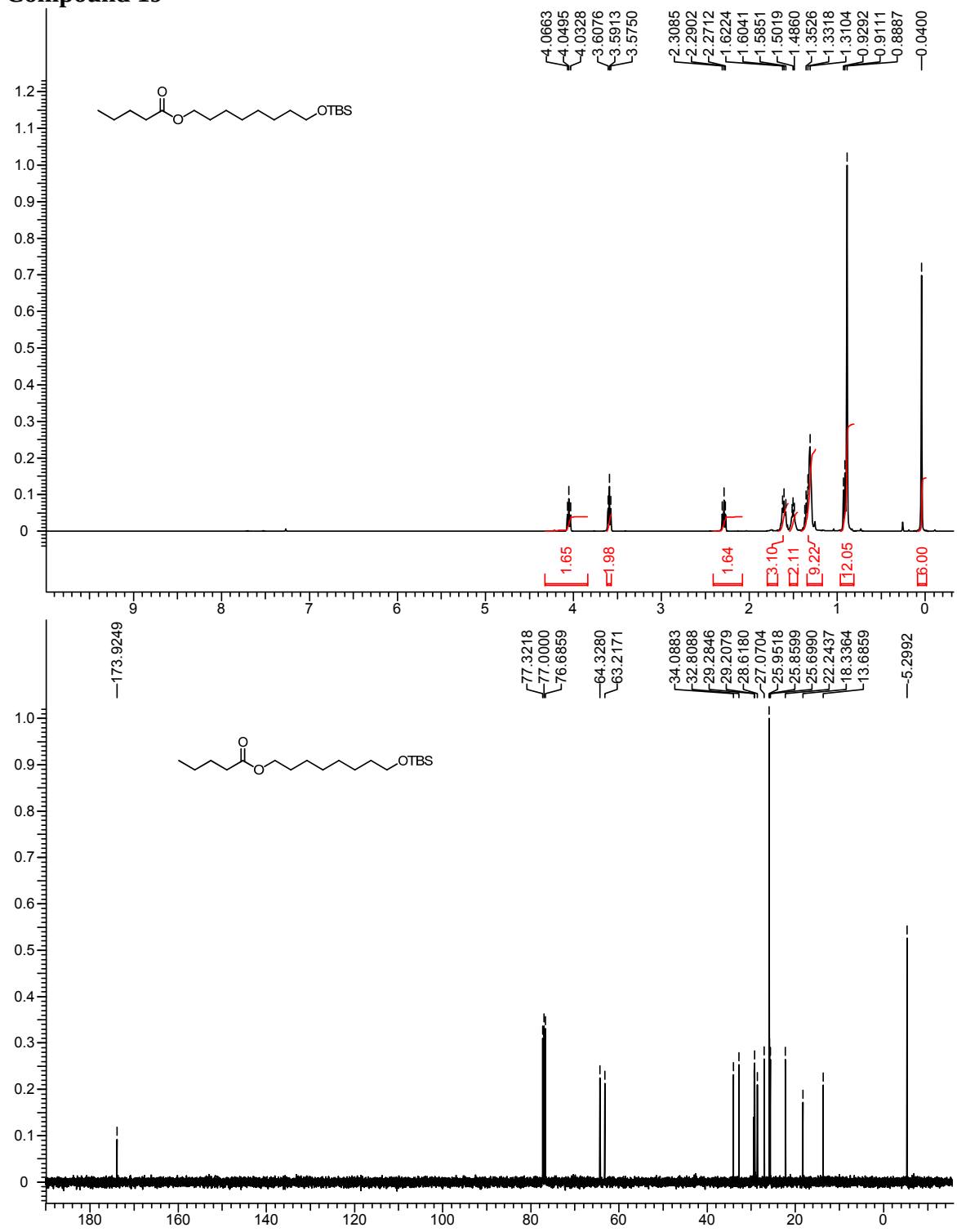
1.3655
1.3466
1.3283
1.0846
1.0695
1.0594
1.0489
0.9430
0.9248
0.9065
OTIPS
2.00
2.01
1.95
7.14
10.60
20.99
3.43
173.8636
77.3218
77.0000
76.6859
64.3050
63.3856
34.0500
32.9544
29.2999
29.2080
28.6104
27.0551
25.8522
25.7067
22.2284
17.9763
13.6552
11.9774
OTIPS

Compound 19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4.0328
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3.5913
3.5750
2.3085
2.2902
2.2712
1.6224
1.6041
1.5851
1.5019
1.4860
1.3526
1.3318
1.3104
0.9292
0.9111
0.8887
0.0400
OTBS
1.65
1.98
1.64
3.10
2.11
9.22
12.05
6.00
173.9249
77.3218
77.0000
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63.2171
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29.2846
29.2079
28.6180
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25.8599
25.6990
22.2437
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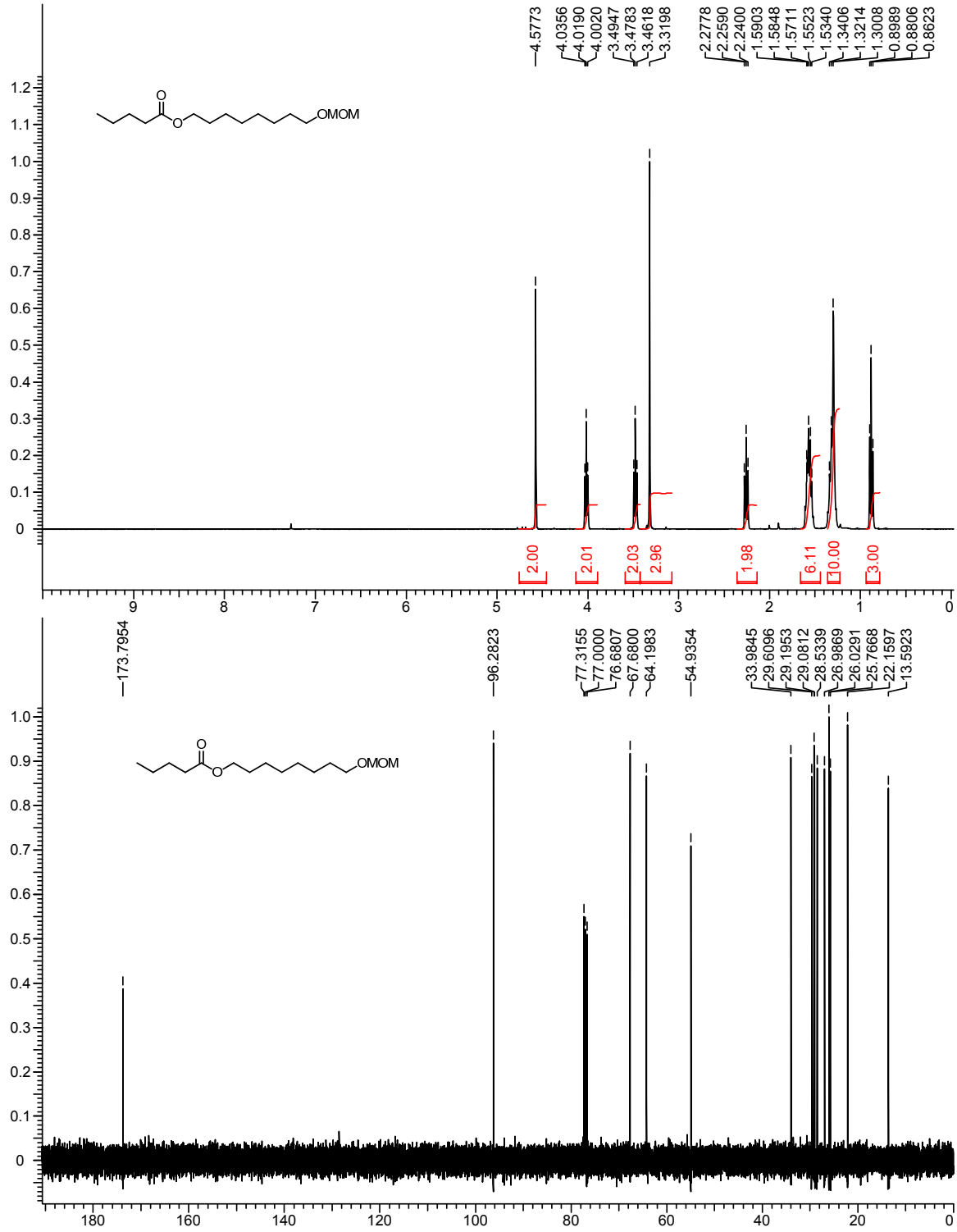
5.2992
OTBS

Compound 21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3.4947
3.4783
3.4618
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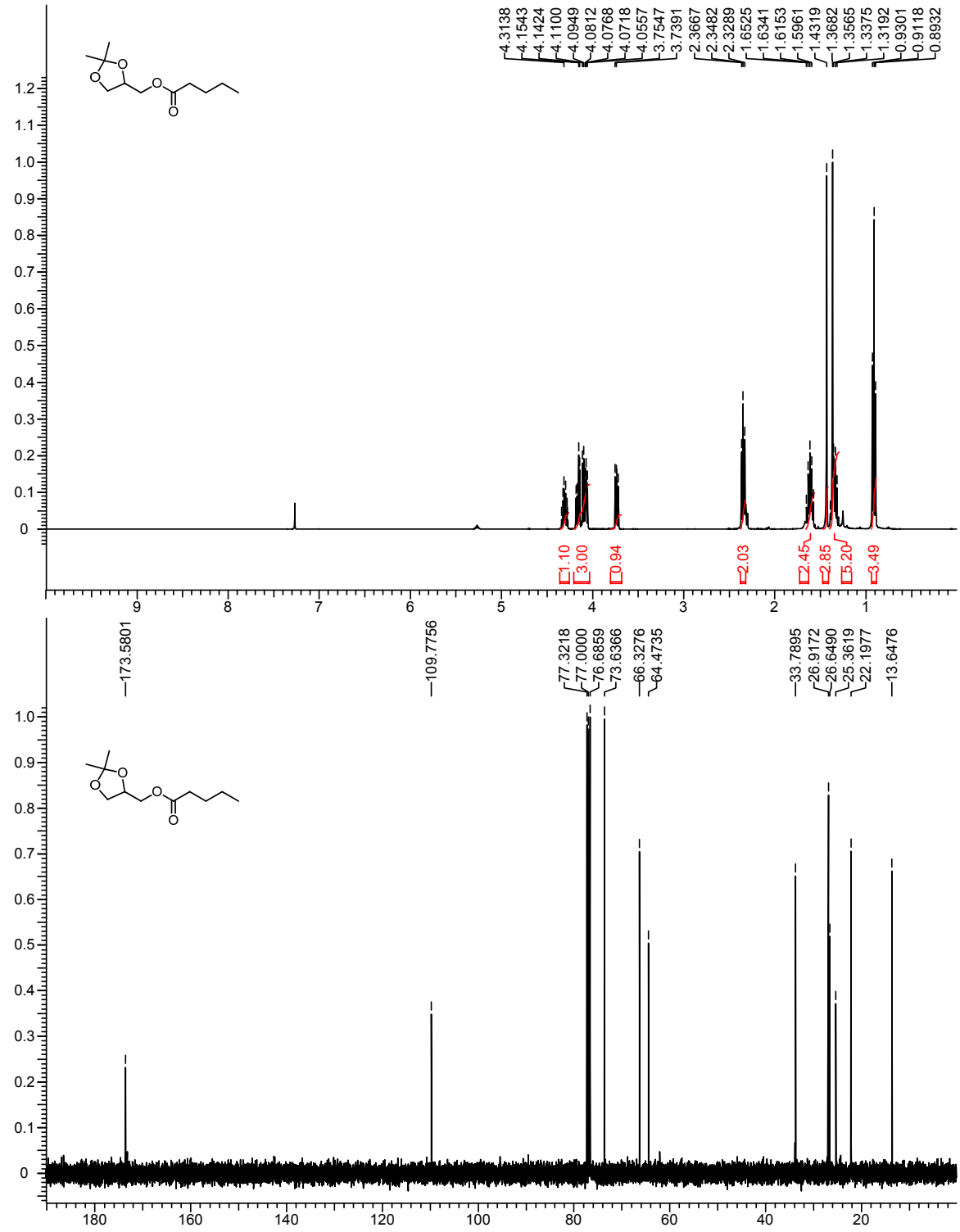
2.2778
2.2590
2.2400
1.5903
1.5848
1.5711
1.5523
1.5340
1.3406
1.3214
1.3008
0.8989
0.8806
0.8623
OMOM
2.00
2.01
2.03
2.96
1.98
6.11
10.00
3.00
173.7954
96.2823
77.3155
77.0000
76.6807
67.6800
64.1983
54.9354
33.9845
29.6096
29.1953
29.0812
28.5339
26.9869
26.0291
25.7668
22.1597
13.5923
OMOM

Compound 24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4.0768
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4.0557
3.7547
3.7391
2.3667
2.3482
2.3289
1.6525
1.6341
1.6153
1.5961
1.4319
1.3682
1.3565
1.3375
1.3192
0.9301
0.9118
0.8932
1.10
3.00
0.94
2.03
2.45
2.85
5.20
3.49
173.5801
109.7756
77.3218
77.0000
76.6859
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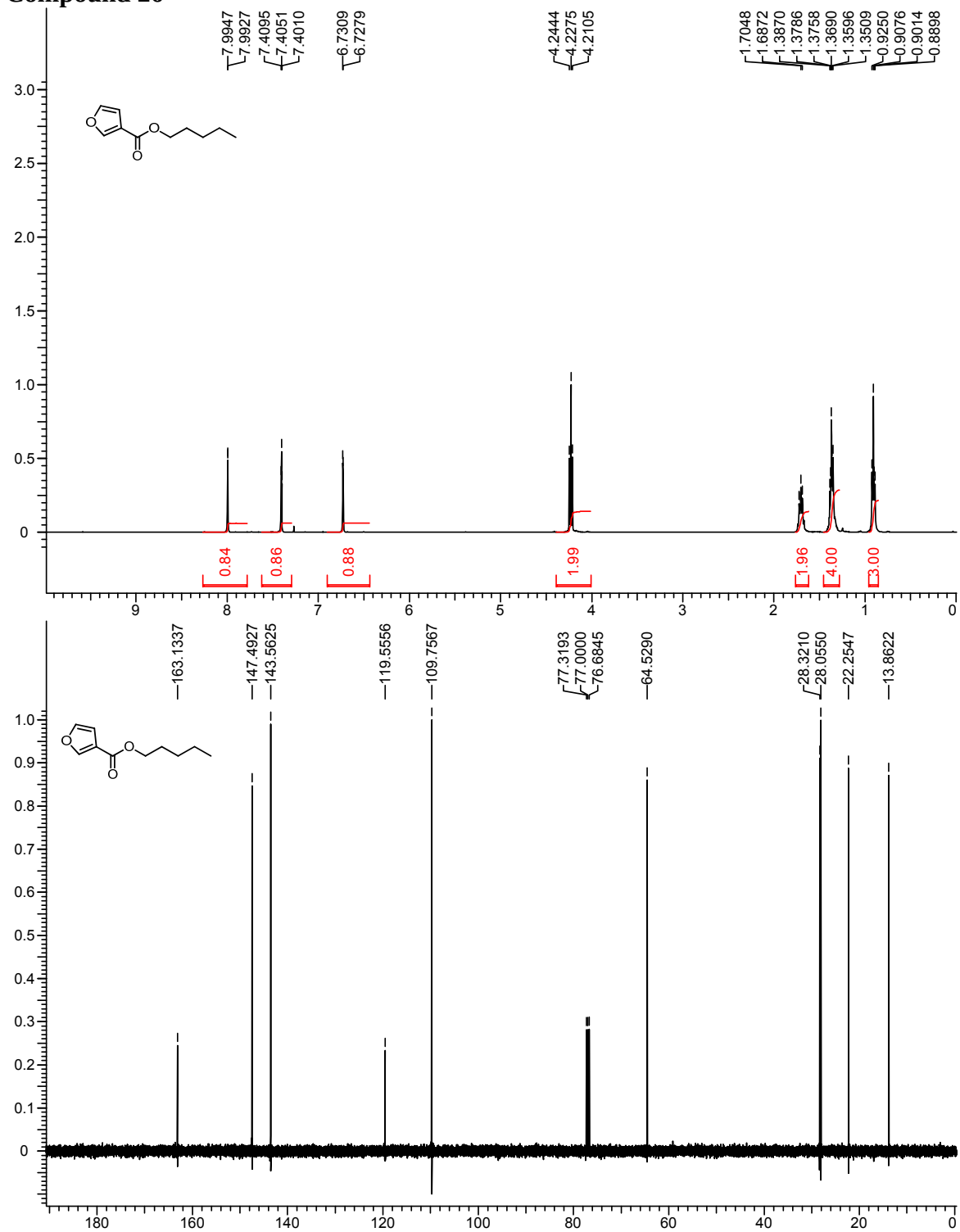
33.7895
26.9172
26.6490
25.3619
22.1977
13.6476

Compound 26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7.4010
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6.7279
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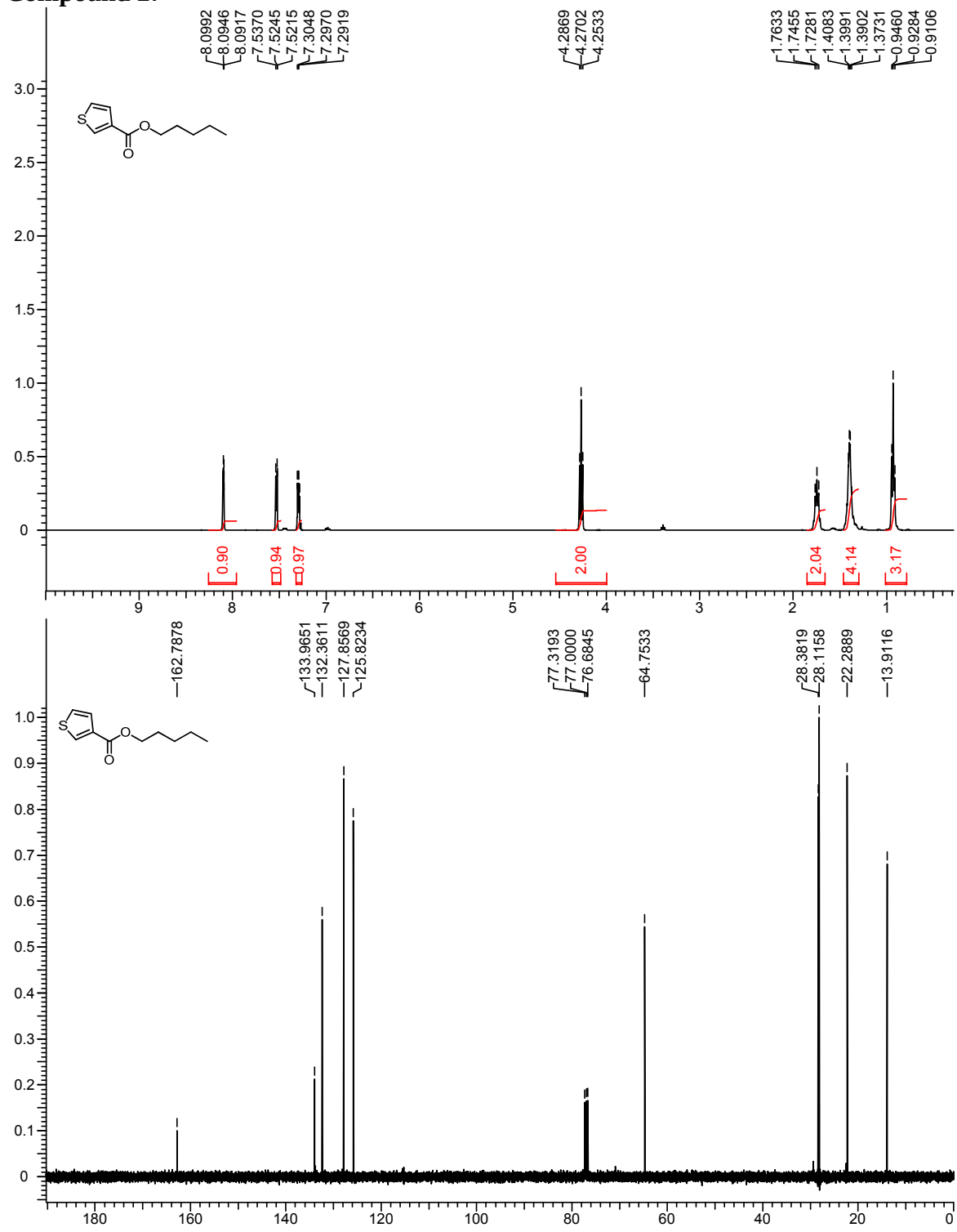
4.2275
4.2105
1.7048
1.6872
1.3870
1.3786
1.3758
1.3690
1.3596
1.3509
0.9250
0.9076
0.9014
0.8898
0.84
0.86
0.88
1.99
1.96
4.00
3.00
163.1337
147.4927
143.5625
119.5556
109.7567
77.3193
77.0000
76.6845
64.5290
28.3210
28.0550
22.2547
13.8622

Compound 27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7.5245
7.5215
7.3048
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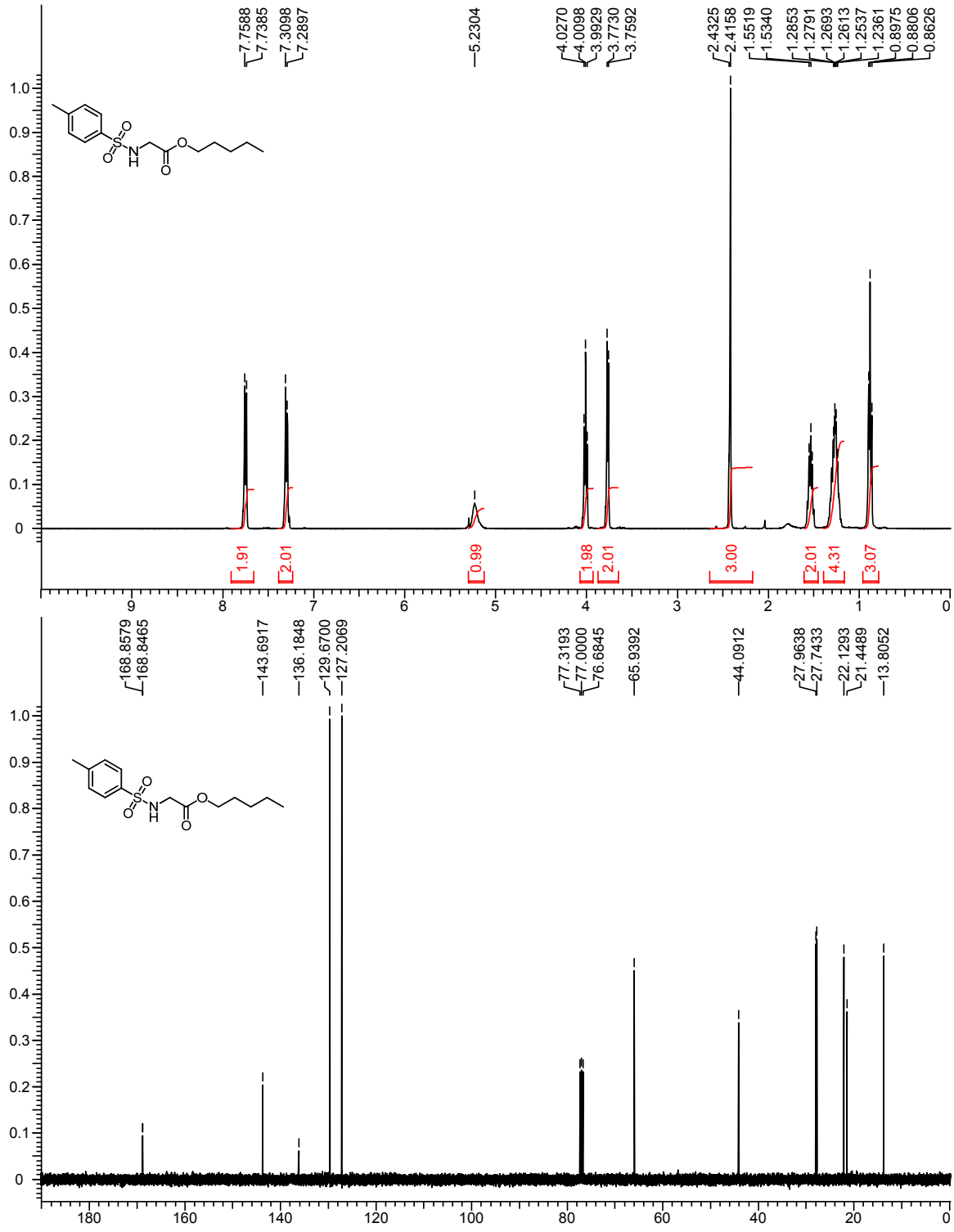
7.2919
4.2869
4.2702
4.2533
1.7633
1.7455
1.7281
1.4083
1.3991
1.3902
1.3731
0.9460
0.9284
0.9106
0.90
0.94
0.97
2.00
2.04
4.14
3.17
162.7878
133.9651
132.3611
127.8569
125.8234
77.3193
77.0000
76.6845
64.7533
28.3819
28.1158
22.2889
13.9116

Compound 17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5.2304
4.0270
4.0098
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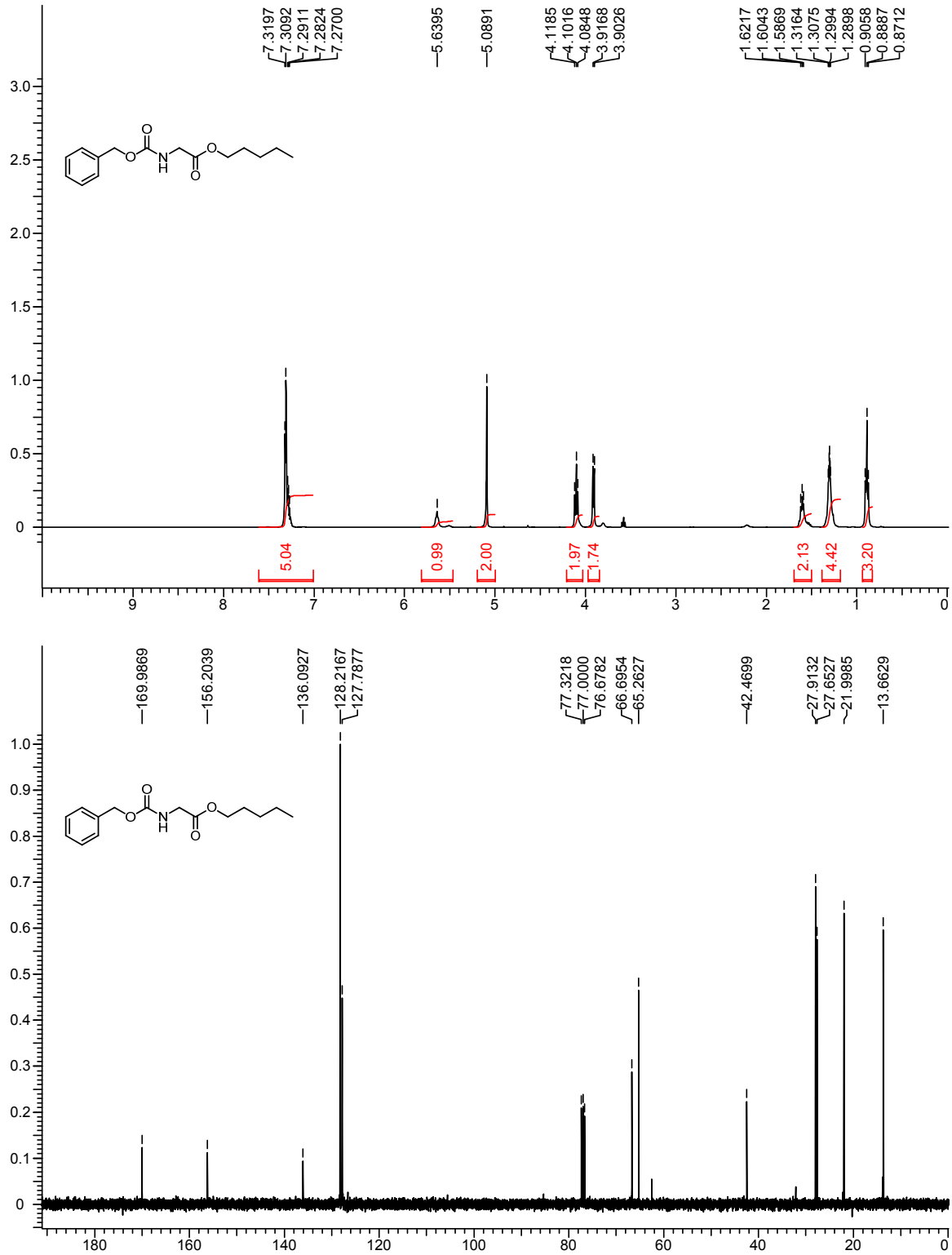
3.7730
3.7592
2.4325
2.4158
1.5519
1.5340
1.2853
1.2791
1.2693
1.2613
1.2537
1.2361
0.8975
0.8806
0.8626
1.91
2.01
0.99
1.98
2.01
3.00
2.01
4.31
3.07
168.8579
168.8465
143.6917
136.1848
129.6700
127.2069
77.3193
77.0000
76.6845
65.9392
44.0912
27.9638
27.7433
22.1293
21.4489
13.8052

Compound 18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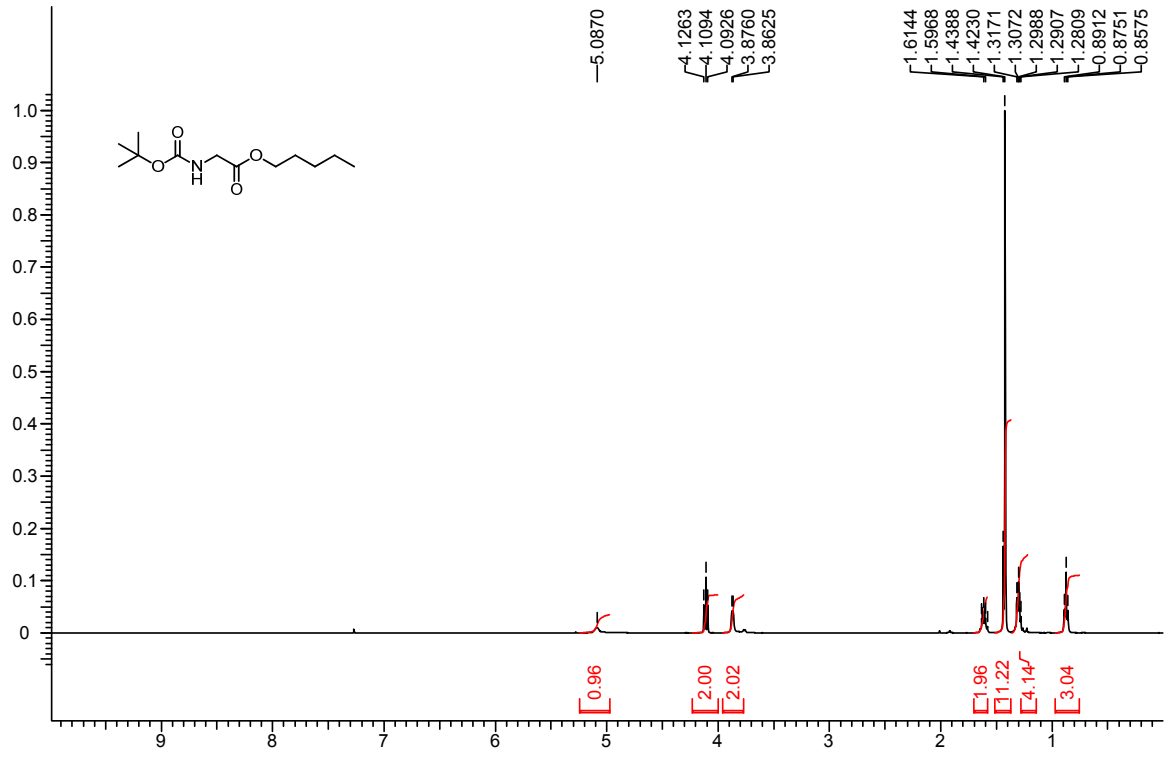
7.2911
7.2824
7.2700
5.6395
5.0891
4.1185
4.1016
4.0848
3.9168
3.9026
1.6217
1.6043
1.5869
1.3164
1.3075
1.2994
1.2898
0.9058
0.8887
0.8712
5.04
0.99
2.00
1.97
1.74
2.13
4.42
3.20
169.9869
156.2039
136.0927
128.2167
127.7877
77.3218
77.0000
76.6782
66.6954
65.2627
42.4699
27.9132
27.6527
21.9985
13.6629

Compound 16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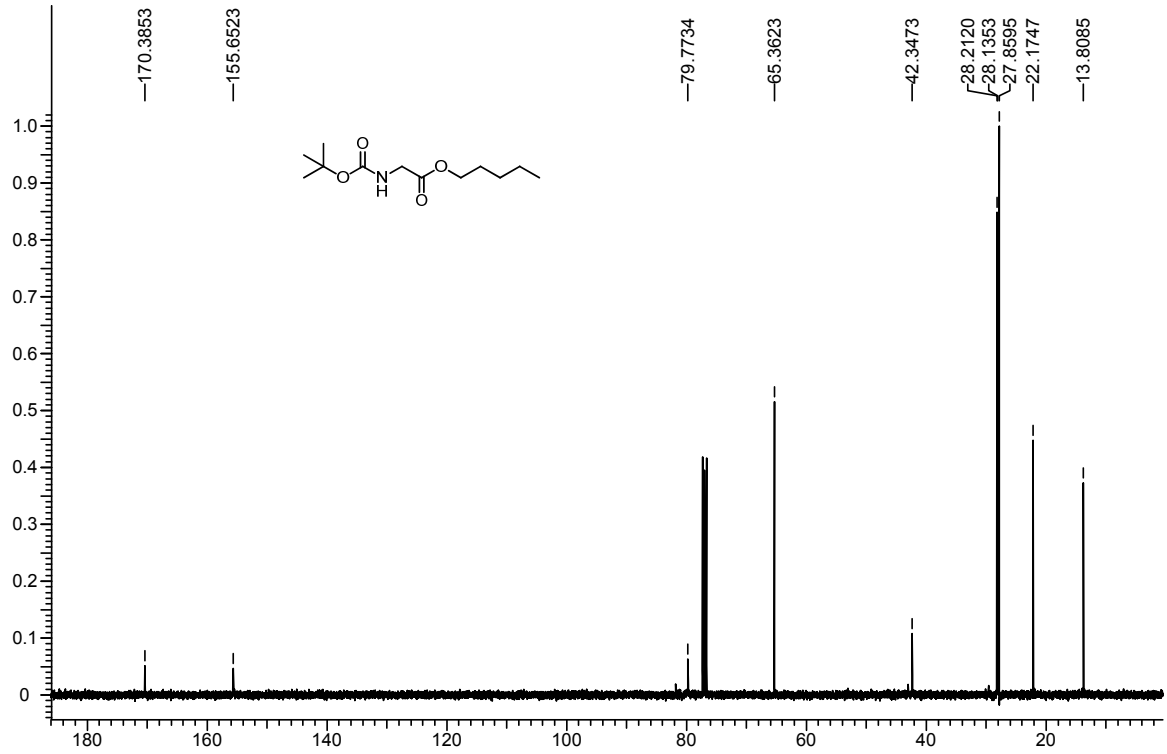
4.1263
4.1094
4.0926
3.8760
3.8625
1.6144
1.5968
1.4388
1.4230
1.3171
1.3072
1.2988
1.2907
1.2809
0.8912
0.8751
0.8575
0.96
2.00
2.02
1.96
1.22
4.14
3.04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65.3623
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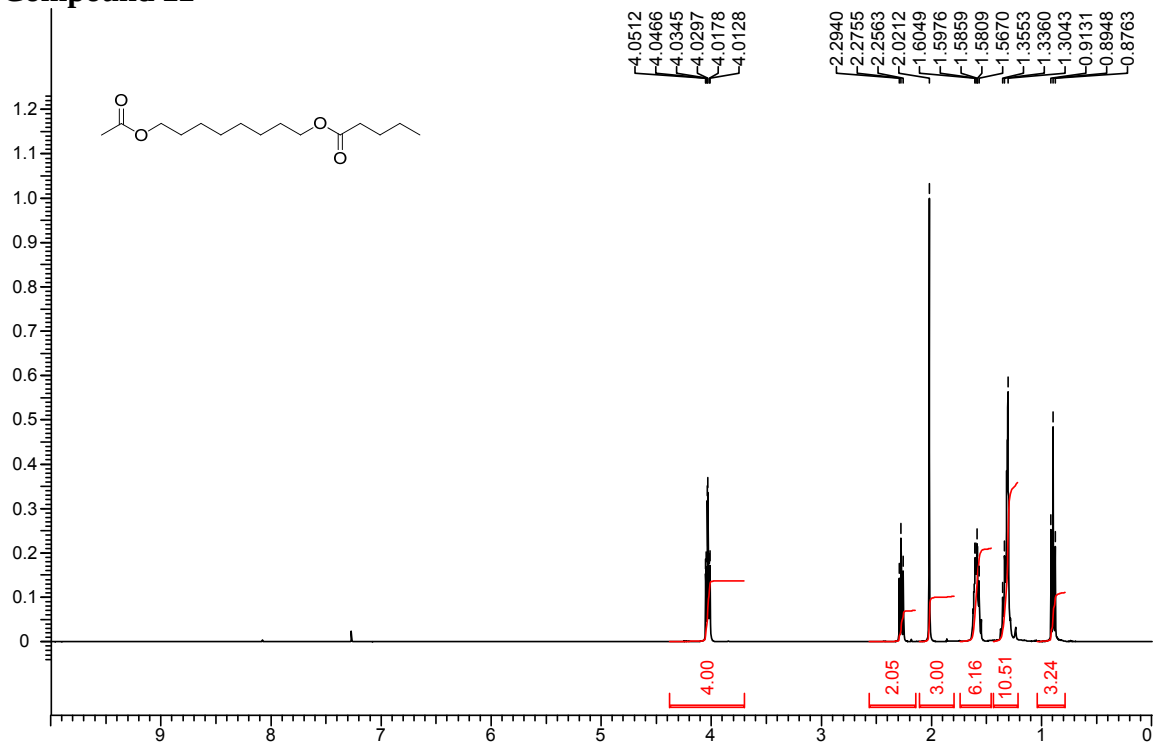
28.1353
27.8595
22.1747
13.8085

Compound 22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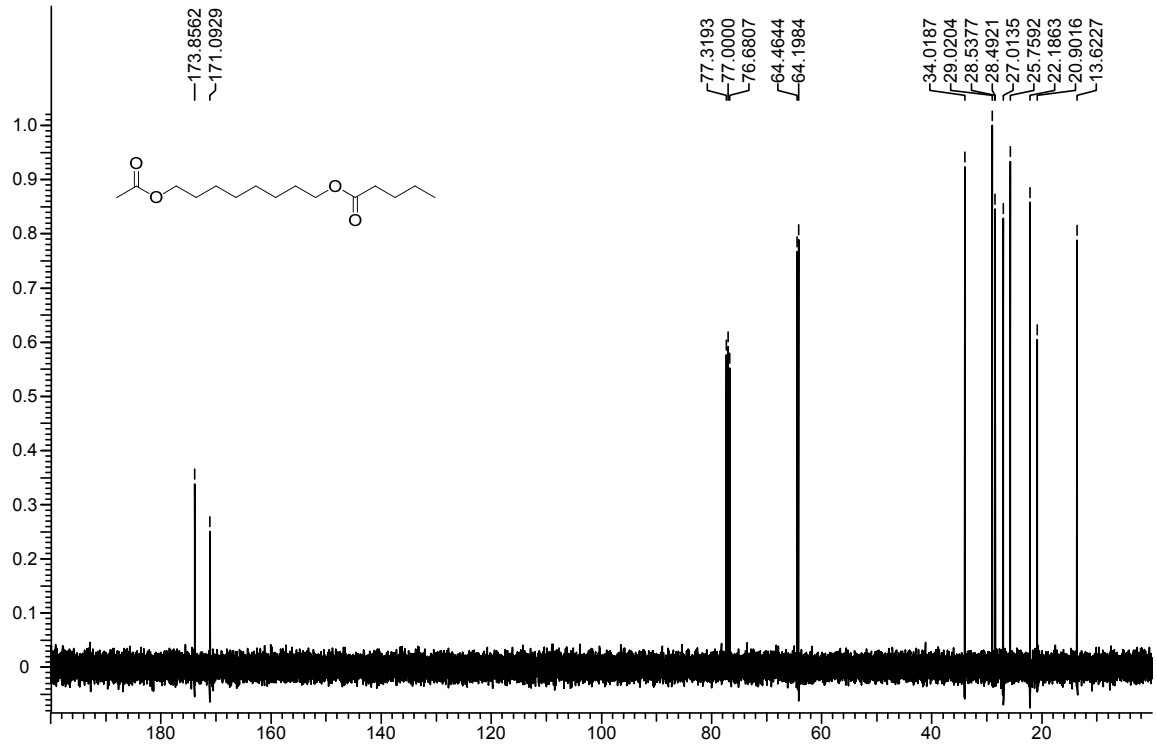
4.0466
4.0345
4.0297
4.0178
4.0128
2.2940
2.2755
2.2563
2.0212
1.6049
1.5976
1.5859
1.5809
1.5670
1.3553
1.3360
1.3043
0.9131
0.8948
0.8763
4.00
2.05
3.00
6.16
10.51
3.24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64.1984
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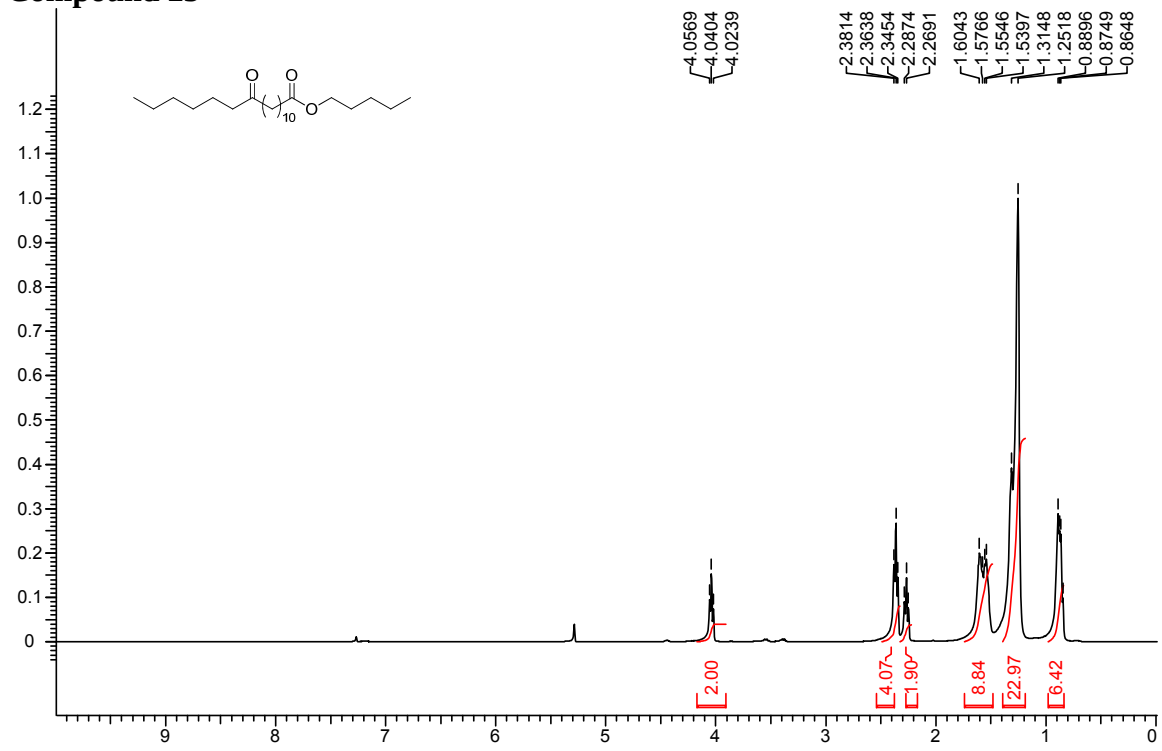
25.7592
22.1863
20.9016
13.6227

Compound 23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4.0239
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2.3638
2.3454
2.2874
2.2691
1.6043
1.5766
1.5546
1.5397
1.3148
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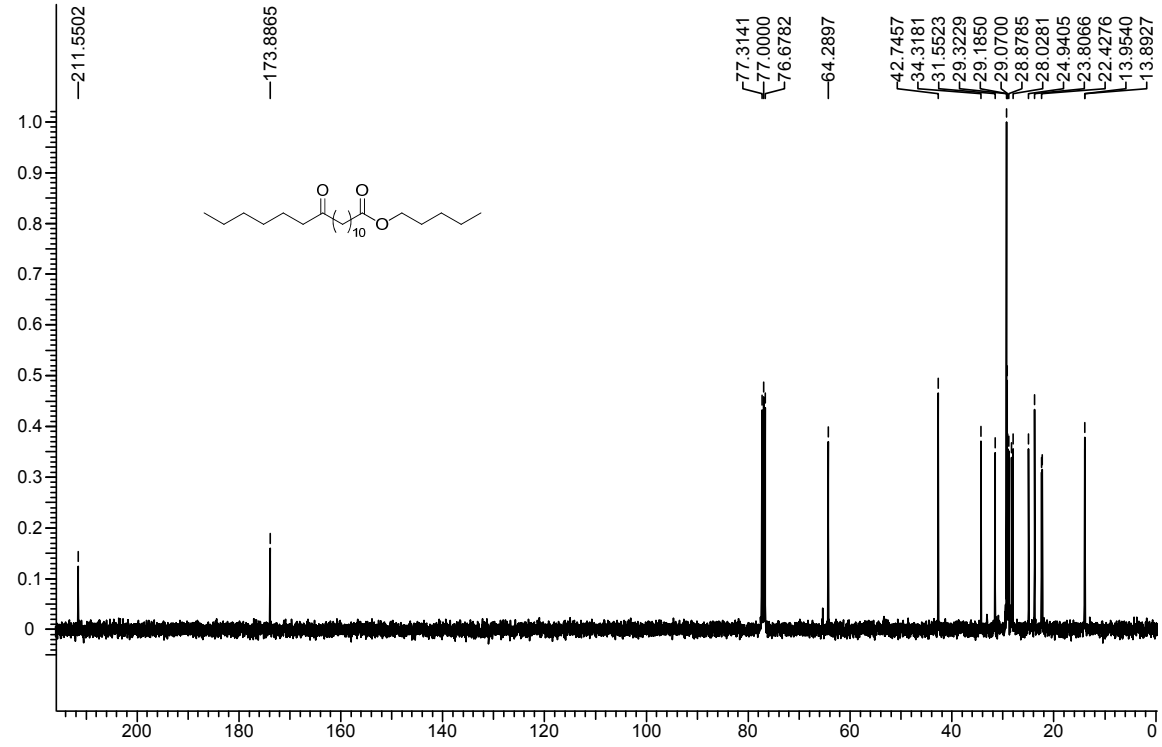
0.8896
0.8749
0.8648
2.00
4.07
1.90
8.84
22.97
6.42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77.0000
76.6782
64.2897
42.7457
34.3181
31.5523
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28.8785
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13.8927

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