Supporting Information

for

A Homologation Approach to the Synthesis of Difluorinated Cycloalkynes

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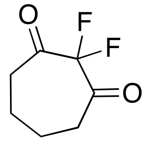
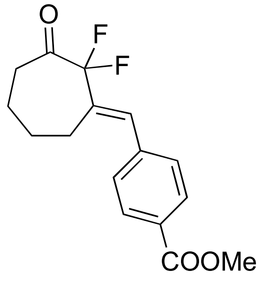
Experimental Procedures

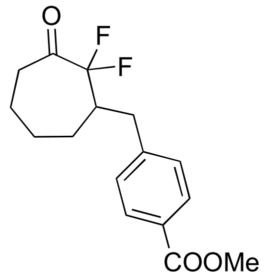
General Experimental Procedure. All chemical reagents were purchased from Sigma-Aldrich, Acros, and TCI and used without purification unless noted otherwise. Anhydrous DMF and MeOH were purchased from Aldrich or Acros in sealed bottles; all other solvents were purified as described by Pangborn *et al.*[i] In all cases, solvent was removed by reduced pressure with a Buchi Rotovapor R-114 equipped with a Welch self-cleaning dry vacuum. Products were further dried by reduced pressure with an Edwards RV5 high vacuum. Thin layer chromatography was performed with EMD 60 Å silica gel plates. Flash chromatography was performed using Silicycle® 60 Å 230-400 mesh silica. All ^{1}H, ^{13}C, and ^{19}F NMR spectra are reported in ppm and referenced to solvent peaks (^{1}H and ^{13}C). Spectra were obtained on Bruker AV-300, AVQ-400, AVB-400, DRX-500, AV-500, or AV-600 instruments. Electron impact (EI) and electrospray ionization (ESI) mass spectra were obtained from the UC Berkeley Mass Spectrometry Facility.



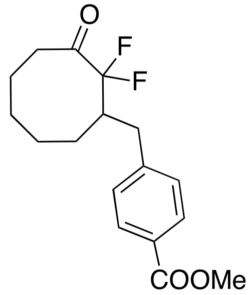
2,2-Difluorocycloheptane-1,3-dione (15). 1,3-cycloheptadione[ii] (**12**, 1.0 g, 7.9 mol, 1.0 equiv.) was dissolved in acetonitrile (44 mL, anhydrous). Cesium carbonate (4.05 g, 12 mmol, 1.6 equiv.) was added and the mixture was stirred at rt for 30 min. It was then cooled to 0 °C and Selectfluor (5.2 g, 15 mmol, 1.8 equiv.) was added. The mixture was warmed to rt and monitored by ^{19}F-NMR for disappearance of Selectfluor. After 1.5 h, the reaction was filtered to remove Cs_2CO_3. The filtrate was evaporated to dryness and pushed through a plug of silica gel eluting with 1:1 hexanes/ethyl acetate. This procedure yielded a mixture of **15** and hydrated **15** (760 mg, 4.5 mmol, 56%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.65 (bs, 2H hydrate), 2.72-2.70 (m, 4H), 2.60 (t, *J* = 6.5 Hz, 2H hydrate), 2.01-1.99 (m, 4H, 2H hydrate), 1.84-1.83 (m, 2H hydrate), 1.68-1.65 (m, 2H hydrate). ^{13}C NMR (150 MHz, $CDCl_3$): δ 198.9 (t, *J* = 23 Hz, hydrate), 197.7 (t, *J* = 25 Hz), 115.3 (t, *J* = 259 Hz, hydrate), 110.1 (t, *J* = 262 Hz), 94.8 (t, *J* = 26 Hz, hydrate), 39.8, 39.3 (hydrate), 37.5 (hydrate), 24.96, 22.6 (hydrate), 22.0 (hydrate). ^{19}F NMR (565 MHz, $CDCl_3$): δ -115.84 (s, 2F), -120.09 (s, 2F, hydrate). HRMS (EI): calcd. for $C_7H_8O_2F_2^+$ $[M]^+$, 162.0492; found, 162.0496.



(*E*)-Methyl 4-((2,2-difluoro-3-oxocycloheptylidene)methyl)benzoate (17). 2,2-Difluorocycloheptane-1,3-dione (**15**, 366 mg, 2.26 mmol, 1.0 equiv.) and (4-(methoxycarbonyl)benzyl) triphenylphosphonium bromide **16** (1.15 g, 2.34 mmol, 1.04 equiv.) were dissolved in THF (32 mL, anhydrous) and cooled to 0 °C. 1,8-Diazabicycloundec-7-ene (410 μL, 2.7 mmol, 1.2 equiv.) was added dropwise and the solution turned yellow in color. The mixture was stirred at 0 °C for 1.5 h, at which point it was quenched with methanol. The mixture was evaporated onto silica gel and further purified by silica gel chromatography using a mixture of 2:1 hexane/toluene with 0,1, or 2% ethyl acetate. The product elutes with 2% ethyl acetate. This procedure yielded 241 mg of product **17** (0.82 mmol, 36%). R$_f$ = 0.7 in 2:1 hexane/ethyl acetate. ^{1}H NMR (600 MHz, CDCl$_3$): δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.10 (s, 1H), 3.92 (s, 3H), 2.70 (dd, *J* = 6.2, 6.2 Hz, 2H), 2.56 (dd, *J* = 5.9, 5.9 Hz, 2H), 1.94-1.92 (m, 2H), 1.84-1.82 (m, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.4 (t, *J* = 29 Hz), 166.6, 139.7, 134. 7 (t, *J* = 20 Hz), 131.1 (t, *J* = 9 Hz), 129.8, 129.6, 128.9, 115.5 (t, *J* = 254 Hz), 52.3, 39.3, 28.11, 27.1, 24.5. ^{19}F NMR (565 MHz, CDCl$_3$): δ -108.11 (s, 2F). HRMS (EI): calcd. for $C_{16}H_{16}O_3F_2^+$ [M]$^+$, 294.1068; found, 294.1064.

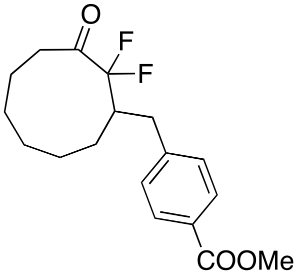


Methyl 4-((2,2-difluoro-3-oxocycloheptyl)methyl)benzoate (11). (*E*)-methyl 4-((2,2-difluoro-3-oxocycloheptylidene)methyl)benzoate (68 mg, 0.23 mmol, 1.0 equiv.) was dissolved in ethanol (1.5 mL) and flushed with nitrogen. Palladium hydroxide on carbon (20%, 7.5 mg) was added and the solution was flushed with hydrogen. The reaction mixture was stirred under a hydrogen atmosphere for 1.5 h, at which point it was filtered through Celite, rinsed with ethanol, and evaporated to dryness to yield pure **11** (70 mg, 0.23 mmol, quant.). R$_f$ = 0.7 in 2:1 hexane/ethyl acetate. ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.87 (s, 3H), 3.18 (dd, *J* = 13.8, 3.5 Hz, 1H), 2.75 (dtd, *J* = 15.2, 6.4, 3.0 Hz, 1H), 2.63-2.58 (m, 1H), 2.46 (dd, *J* = 13.8, 10.9 Hz, 1H), 2.22- 2.13 (m, 1H), 1.92-1.87 (m, 1H), 1.75-1.70 (m, 2H), 1.65-1.62 (m, 1H), 1.36-1.31 (m, 1H), 1.27-1.21 (m, 1H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 201.9 (dd, *J* = 29, 26 Hz), 167.0, 144.4, 130.0, 129.4, 128.7, 119.5 (dd, *J* = 256, 253 Hz), 52.2, 44.5 (dd, *J* = 22, 21 Hz), 38.5, 33.6 (dd, *J* = 6, 4 Hz), 28.3 (dd, *J* = 6, 2 Hz), 25.1, 23.5. ^{19}F NMR (565 MHz, CDCl$_3$): δ -106.63 (d, *J* = 245 Hz, 1F), -120.51 (dd, *J* = 245, 24 Hz, 1F). HRMS (EI): calcd. for $C_{16}H_{18}O_3F_2^+$ [M]$^+$, 296.1224; found, 296.1228.

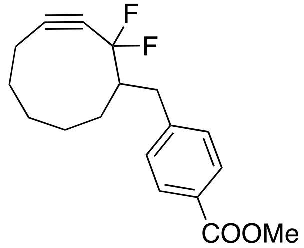


Methyl 4-((2,2-difluoro-3-oxocyclooctyl)methyl)benzoate (9). Difluorocycloheptanone **11** (22 mg, 0.074 mmol, 1.0 equiv.) was dissolved in dichloromethane (1.3 mL, anhydrous) and cooled to -78 ^{o}C. Trimethylaluminum (45 μL of 2 M solution in toluene, 0.090 mmol, 1.2 equiv.) was added followed by trimethylsilyldiazomethane (45 μL of 2 M solution in dichloromethane, 0.090 mmol, 1.2 equiv.) After 10 min, the mixture was quenched with 50 μL methanol and warmed to rt, at which point a saturated solution of aqueous Rochelle's salt (2 mL) was added. The product was extracted into dichloromethane (3 x 3 mL). The organics were combined, dried, decanted, and evaporated to dryness. The crude product was dissolved in a mixture of ethyl acetate (2.5 mL)/methanol (1.5 mL)/3

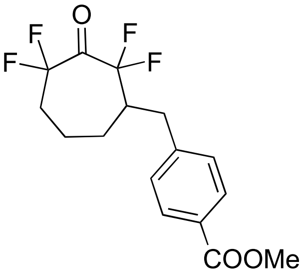
M HCl (1.0 mL) and stirred at rt for 8 h, at which point the mixture was neutralized with sat. sodium bicarbonate. The organics were removed by evaporation and the product was extracted into dichloromethane (3 x 3 mL). The organics were combined, dried, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography using a hexanes/dichloromethane solvent system (2:1, 3:2, 1:1). This procedure resulted in 11 mg of **9** (48%, 0.035 mmol). R_f = 0.3 in 3:1 dichloromethane/hexane. The NMR spectra are consistent with those previously reported.[iii]



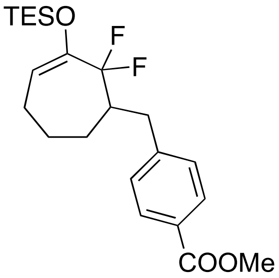
Methyl 4-((2,2-difluoro-3-oxocyclononyl)methyl)benzoate (13). Difluorocyclooctanone **9** (80 mg, 0.26 mmol, 1.0 equiv.) was dissolved in dichloromethane (3.0 mL, anhydrous) and cooled to -78 °C. Trimethylaluminum (150 μL of 2 M solution in toluene, 0.30 mmol, 1.2 equiv.) was added followed by trimethylsilyldiazomethane (150 μL of 2 M solution in dichloromethane, 0.30 mmol, 1.2 equiv.) After 10 min, the mixture was quenched with 0.1 mL methanol and warmed to rt, at which point a saturated solution of aqueous Rochelle's salt (5 mL) was added. The product was extracted into dichloromethane (3 x 5 mL). The organics were combined, dried, decanted, and evaporated to dryness. The crude product was dissolved in a mixture of ethyl acetate (5 mL)/methanol (3 mL)/3 M HCl (2 mL) and stirred at rt for 8 h, at which point the mixture was neutralized with sat. sodium bicarbonate. The organics were removed by evaporation and the product was extracted into dichloromethane (3 x 5 mL). The organics were combined, dried, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography using a hexanes/dichloromethane solvent system (2:1, 3:2, 1:1). This procedure resulted in 41 mg of **13** (50%, 0.13 mmol). R_f = 0.3 in 3:1 dichloromethane/hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.90 (s, 3H), 3.29 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.79 – 2.64 (m, 2H), 2.54 (dd, *J* = 13.5, 11.1 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.00-1.90 (m, 1H), 1.82-1.72 (m, 1H), 1.67 – 1.58 (m, 1H), 1.56 – 1.47 (m, 1H), 1.44 – 1.09 (m, 5H), 0.91-0.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (dd, *J* = 30.5, 26.6 Hz), 167.1, 144.5, 130.0, 129.5, 128.7, 119.4 (dd, *J* = 259.3, 251.8 Hz), 52.3, 43.5 (t, *J* = 21.7 Hz), 37.3, 34.35 (t, *J* = 5.0 Hz), 25.2, 25.1, 24.8, 24.0, 23.6 (d, *J* = 7.6Hz). HRMS (ESI): calcd. for $C_{18}H_{22}O_3F_2$ $[M+H]^+$, 324.1537; found 324.1534.



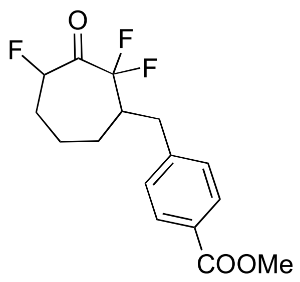
4-((2,2-difluorocyclonon-3-ynyl)methyl)benzoic acid (14).
A 0.5 M solution of KHMDS in toluene (0.36 mL, 0.18 mmol, 1.1 equiv.) was added to THF (4.3 mL, anhydrous) and the solution was cooled to -78 °C. Ketone **13** (56 mg, 0.17 mmol, 1.0 equiv.) in THF (1.7 mL, anhydrous) was added dropwise. The reaction was stirred for 1 h at -78 °C, at which point *N*-phenyltrifluoromethanesulfonimide (65 mg, 0.18 mmol, 1.1 equiv.) in THF (1.7 mL, anhydrous) was added. The solution was allowed to warm to rt overnight, stirred for 21 h then quenched with 1.0 mL methanol and concentrated. The crude material was purified by silica gel chromatography (4:1 hexanes/ toluene with 1% triethylamine with a 0-5% gradient of ethyl acetate to obtain 26 mg of impure vinyl triflate intermediate. The impure vinyl trifate was dissolved in 0.60 mL dry THF and the solution cooled to 0 °C. A 2 M solution of LDA (purchased from Sigma-Aldrich, 0.055 mL, 0.11 mmol, about 2.0 equiv) was then added and the solution allowed to stir at the same temperature for 40 min. The reaction was then quenched with an excess of methanol and concentrated. The crude material was purified by silica gel chromatography (hexanes to 1:20 ethyl acetate/ hexanes) to yield the desired cyclononyne in 9% yield (4.6 mg, 0.015 mmol). ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.97 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 3.91 (s, 3H), 3.19 (dd, J = 13.8, 3.6 Hz, 1H), 2.51(dd, J = 13.2, 11.4 Hz, 1H), 2.35 – 2.20 (m, 3H), 1.79-1.77(m, 1H), 1.70-1.64 (m, 2H), 1.54 – 1.45 (m, 4H), 1.27 – 1.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.0, 145.2, 129.7, 129.2, 128.2, 117.7 (m), 100.8, 80.5, (m) 52.0, 51.4 (m), 34.3, 29.0, 27.0 (d, J = 4.0 Hz), 25.8, 25.4, 19.0. ^{19}F NMR (376 MHz, CDCl$_3$): δ -90.98 (d, J = 263 Hz, 1F), -99.86 (dd, J = 259, 23 Hz, 1F).HRMS (ES): calcd. for $C_{18}H_{20}O_2F_2$ [M]$^+$, 306.1431; found, 306.1430.



Methyl 4-((2,2,4,4-tetrafluoro-3-oxocycloheptyl)methyl)benzoate (20). Difluoroketone **11** (595 mg, 2.1 mmol, 1.0 equiv.) was dissolved in cyclohexane (5 mL) in the presence of molecular sieves, trifluoroacetic acid (1 drop), and hexylamine (0.28 mL, 2.1 mmol, 1.0 equiv.). This mixture was heated to reflux for 10 h, at which point, it was cooled to rt, evaporated to dryness and the residue was dissolved in ether (75 mL). The ether solution was washed with saturated NaHCO$_3$ (50 mL) and brine (50 mL). The organics were dried, decanted, and evaporated to a residue containing the hexylimine of **11**. The residue was dissolved in acetonitrile (20 mL, anhydrous) and sodium sulfate (590 mg, 4.2 mmol, 2.0 equiv.) was added followed by Selectfluor (2.21 g, 6.2 mmol, 3.0 equiv.). The mixture was refluxed overnight. The following morning, 3M HCl (1 mL) was added and the mixture was heated for an additional 10 min. The solution was then cooled to rt and the acetonitrile was removed by evaporation. The residue was dissolved in ether (75 mL) and washed with saturated NaHCO$_3$ (50 mL) and brine (50 mL). The ether was dried, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography with a hexane/ethyl acetate solvent system (6:1 to 2:1). This procedure yielded 288 mg of **20** (0.87 mmol, 43%) as a mixture of ketone and hydrate. R_f = 0.6 in 3:1 toluene/acetone. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H hydrate), 7.29-7.26 (m, 2H, 2H hydrate), 4.02 (bs, 1H hydrate), 3.93 (s, 3H, 4H hydrate), 3.29 (d, *J* = 9.5 Hz, 1H hydrate), 3.25 (dd, *J* = 13.8, 3.5 Hz, 1H), 2.56-2.51 (m, 1H, 2H hydrate), 2.42-2.37 (m, 2H), 2.33-2.25 (m, 1H hydrate), 2.19-2.12 (m, 1H, 1H hydrate), 1.85-1.71 (m, 2H, 2H hydrate), 1.58-1.53 (m, 1H), 1.44-1.38 (m, 1H, 2H hydrate). ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.02 (m), 167.3, 167.1 (hydrate), 145.1 (hydrate), 143.6, 130.2 (hydrate), 130.0, 129.5, 129.4 (hydrate), 129.1 (hydrate), 128.6, 121.7 (apparent t, *J* = 254 Hz), 121.2 (apparent t, *J* = 250 Hz, hydrate),118.4 (apparent t, *J* = 255 Hz, hydrate) 116.8 (t, *J* = 252 Hz) 94.8 (apparent dt, *J* = 53, 27 Hz, hydrate), 52.4 (hydrate), 52.3, 45.7 (t, *J* = 23 Hz, hydrate), 43.7 (t, *J* = 25.1 Hz), 35.0 (dd, *J* = 7, 5 Hz), 34.7 (t, *J* = 24 Hz, hydrate), 33.4 (apparent t, *J* = 4 Hz, hydrate), 32.7 (t, *J* = 24 Hz), 27.5 (d, *J* = 5 Hz, hydrate), 26.0 (d, *J* = 8 Hz), 20.2 (dd, *J* = 8, 3 Hz, hydrate), 19.5 (t, *J* = 6 Hz). ^{19}F NMR (565 MHz, $CDCl_3$): δ -98.01 (dq, *J* = 268, 11 Hz, 1F), -103.08 (dtd, *J* = 259, 20, 10 Hz, 1F hydrate), -104.20 (dm, *J* = 260 Hz, 1F), -105.55 (dddd, *J* = 268, 23, 13, 9 Hz, 1F), -107.64 (ddt, *J* = 260, 23, 10 Hz, 1F hydrate), -108.65 (dm, *J* = 260.0 Hz, 1F hydrate), -119.26 (ddd, *J* = 260, 24, 12 Hz, 1F), -121.66 (ddd, *J* = 260, 26, 20 Hz, 1F hydrate). HRMS (EI): calcd. for $C_{16}H_{16}O_3F_4^+$ $[M]^+$, 332.1036; found, 332.1039.



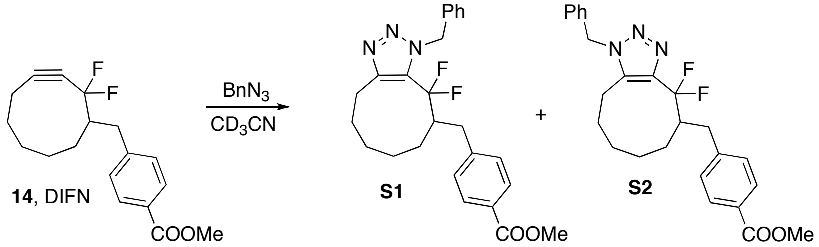
Methyl 4-((2,2-difluoro-3-(triethylsilyloxy)cyclohept-3-enyl)methyl)benzoate (21). Difluoroketone **11** (350 mg, 1.18 mmol, 1.00 equiv.) was dissolved in THF (20 mL, anhydrous) and cooled to -78 °C. Lithium bis(trimethylsilyl)amide (1.45 mL of 1M solution in THF, 1.42 mmol, 1.2 equiv.) was added and the mixture was stirred for 2 h, at which point triethylsilyl chloride (400 μL, 2.4 mmol, 2 equiv.) was added and the reaction mixture was warmed to rt over 3 h. The reaction was quenched with MeOH and evaporated to dryness. The crude product was purified by silica gel chromatography using a hexane/ethyl acetate solvent system (20:1, 15:1). This procedure resulted in 433 mg **21** (1.06 mmol, 89%). R_f = 0.8 in 8:1 hexanes/ethyl acetate. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 5.36 (apparent t, *J* = 7 Hz, 1H), 3.90 (s, 3H), 3.22 (dd, *J* = 13.7, 3.5 Hz, 1H), 2.60 (dd, *J* = 13.7, 10.7 Hz, 1H), 2.39-2.31 (m, 1H), 2.13 – 2.09 (m, 2H), 1.68 – 1.48 (m, 4H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.71 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 147.2 (t, *J* = 25.7 Hz), 145.7, 130.0, 129.5, 128.4, 121.1 (dd, *J* = 243.1, 245.2 Hz), 113.1 (t, *J* = 6.1 Hz), 52.2, 44.3, (dd, *J* = 21.8, 23.9 Hz), 34.4 (dd, *J* = 2.5, 7.7 Hz), 26.5 (dd, *J* = 3.1, 4.1 Hz), 23.8, 23.1, 6.8, 5.1. ^{19}F NMR (564 MHz, $CDCl_3$): δ -95.7 (d, *J* = 264.0 Hz, 1F), -106.5 (dd, *J* = 264.5, 22.7 Hz, 1F). HRMS (EI): calcd. for $C_{22}H_{32}O_3F_2Si^+$ $[M]^+$, 410.2089; found, 410.2074.



Methyl 4-((2,2,4-trifluoro-3-oxocycloheptyl)methyl) benzoate (22). Silyl enol ether **21** (350 mg, 0.85 mmol, 1.0 equiv.) was dissolved in DMF (25 mL, anhydrous) and cooled to 0 °C. Selectfluor (1.04 g, 2.94 mmol, 3.45 equiv.) was added and the mixture was warmed to rt overnight. The following morning the reaction mixture was quenched with water and extracted with ether (3 x 50 mL). The ether was combined, dried, decanted, and evaporated to dryness. The crude product was purified by silica gel chromatography using a hexane/ethyl acetate solvent system (10:1 to 4:1 gradient). This procedure resulted in **22** as a mixture of diastereomers (195 mg, 0.62 mmol, 73%). R$_f$ = 0.5 in 2:1 hexanes/ethyl acetate. ^{1}H NMR (600 MHz, CDCl$_3$, minor diastereomer designated as H'): δ 7.96 (d, *J* = 8.3 Hz, 2H'), 7.96 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H'), 5.47 (dm, *J* = 48.4, 1H), 5.36 (dtd, *J* = 47.4, 5.8, 2.2 Hz, 1H'), 3.88 (s, 3H, 3H'), 3.29 (dd, *J* = 13.8, 3.6 Hz, 1H), 3.10 (d, *J* = 10.4 Hz, 1H'), 2.51 (dd, *J* = 13.8, 10.5 Hz, 1H), 2.43 – 2.38 (m, 2H'), 2.30 – 2.01 (m, 3H, 2H'), 1.79 – 1.74 (m, 2H'), 1.68 – 1.63 (m, 2H), 1.59 – 1.54 (m, 1H'), 1.44-1.40 (m, 1H'), 1.29 – 1.21 (m, 2H). ^{13}C NMR (150 MHz, CDCl$_3$): δ 197.4 (ddd, *J* = 41.9, 22.9, 18.3 Hz, major), 196.0 (ddd, *J* = 41.9, 24.0, 17.3 Hz, minor), 166.98 (major), 166.95 (minor), 143.9 (major), 143.8 (minor), 130.12 (minor), 130.07 (major), 129.4 (major), 129.3 (minor), 128.93 (minor), 128.87 (major), 119.5 (ddd, *J* = 257.7, 253.7, 2.4 Hz, major), 119.0 (ddd, *J* = 260.1, 248.8, 3.9 Hz, minor), 92.5 (dd, *J* = 186.6, 1.8 Hz, major), 91.9 (dd, *J* = 187.2, 4.2 Hz, minor), 52.22 (minor), 52.20 (major), 44.8 (dd, *J* = 21.8, 20.1 Hz, major), 44.4 (t, *J* = 21.2 Hz, minor), 33.8 (dd, *J* = 4.9, 3.0 Hz, major), 32.9 (dd, *J* = 5.7, 4.4 Hz, minor), 32.3 (dd, *J* = 22.1, 1.0 Hz, minor), 31.5 (dd, 22.8, 1.8 Hz, major), 29.3 (d, *J* = 7.5 Hz, major), 27.0 (dd, *J* = 4.8, 2.4 Hz, minor), 21.7 (major), 19.90 (d, *J* = 4.6 Hz, minor). ^{19}F NMR (565 MHz, CDCl$_3$, minor diastereomer designated as F'): δ -105.54 (dm, *J* = 250.5 Hz, 1F), -107.92 (d, *J* = 260.1 Hz, 1F'), -111.67 (dt, *J* = 258.9, 10.6 Hz, 1F'), -127.35 (ddt, *J* = 250.3, 29.8, 4.0 Hz, 1F), -187.38 (dddd, *J* = 47.7, 28.7, 20.1, 9.3 Hz, 1F'), -190.02 – -192.04 (m, 1F). HRMS (EI): calcd. for $C_{16}H_{17}O_3F_3^+$ [M]$^+$, 314.1130; found, 314.1136.

Reactivity of difluorocyclononyne (DIFN) with benzyl azide

Scheme S1. Reaction between DIFN (**14**) and benzyl azide.



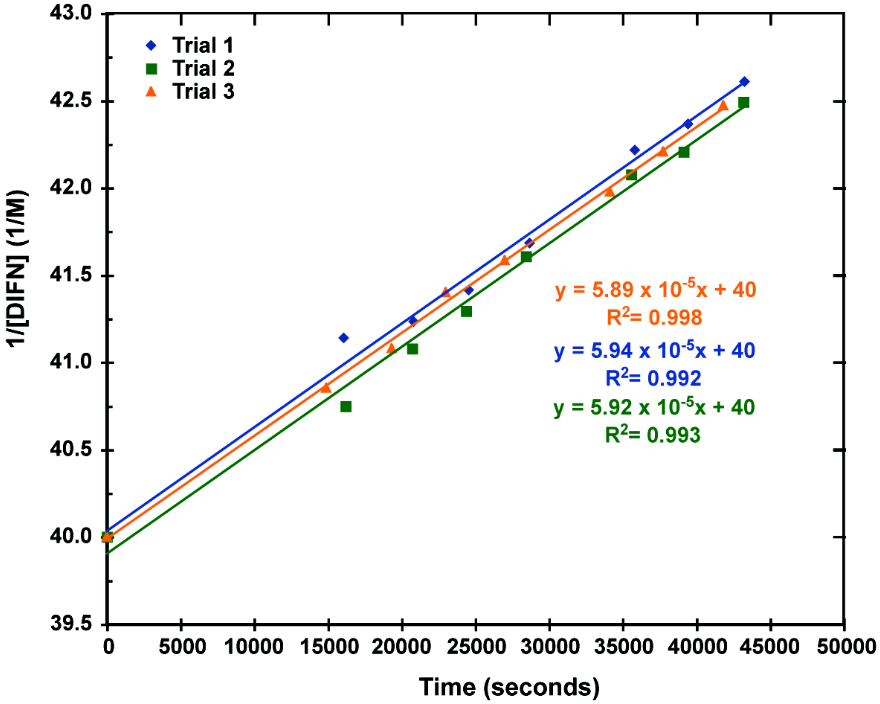


Figure S1. The reaction in Scheme S1 was monitored by ^{1}H NMR for 12.5 h at room temperature. DIFN and benzyl azide were separately dissolved in CD$_3$CN and mixed together in a 1:1 ratio at a concentration of 25 mM. The percent conversion was calculated by the disappearance of DIFN relative to the appearance of triazole products. No products other than **S1** and **S2** were apparent by ^{1}H NMR. The triazole isomers were produced in a ~ 1:1.4 ratio. The second-order rate constant was determined by plotting 1/[**DIFN**] versus time. The plot was fit to a linear regression and the slope corresponds to the second-order rate constant. Shown are data from three replicate experiments.

Further Discussion of Homologation of 20 and 22

The reaction of tetrafluorinated ketone **20** with trimethylsilyl diazomethane in the presence of a variety of Lewis acids favored oxirane formation (**23**) over homologation (Scheme S2, Table 7.1, entries 2-5),[iv] the exception being when trimethylaluminum was employed as a Lewis acid. Instead of facilitating oxirane formation, $AlMe_3$ resulted in methyl addition to yield tertiary alcohol **S3** (entry 1). Ethyldiazoacetate ($N_2CHCOOEt$), a diazo species commonly employed for homologation reactions when oxirane products are competing with the desired transformation,[v] proved unreactive under standard homologation conditions. Upon forcing conditions where **20** was combined with ethyldiazoacetate, unidentifiable products were produced. Further attempts at homologation with the more nucleophilic species $TMSCLiN_2$ (entry 10)[vi] and $N_2CLiCOOEt$ (entry 11)[vii] or $TMSCHN_2$ at elevated temperatures (entries 12-13) did not yield desired product. Lastly, diazomethane yielded epoxide **23** (entry 14-15;17-18) in all cases, save some methyl addition product (**S3**) observed when $AlMe_3$ was the Lewis acid (entry 14). Additionally, with diazomethane and $BF_3{\cdot}OEt_2$, no reaction was observed after overnight at room temperature (entry 16).

Scheme S2. Attempted homologation of ketone **20**.

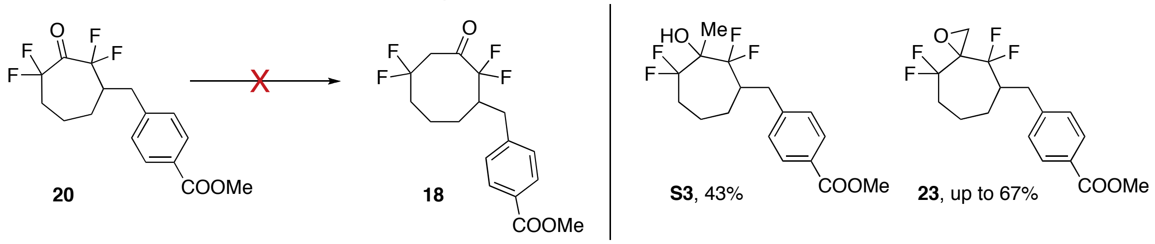


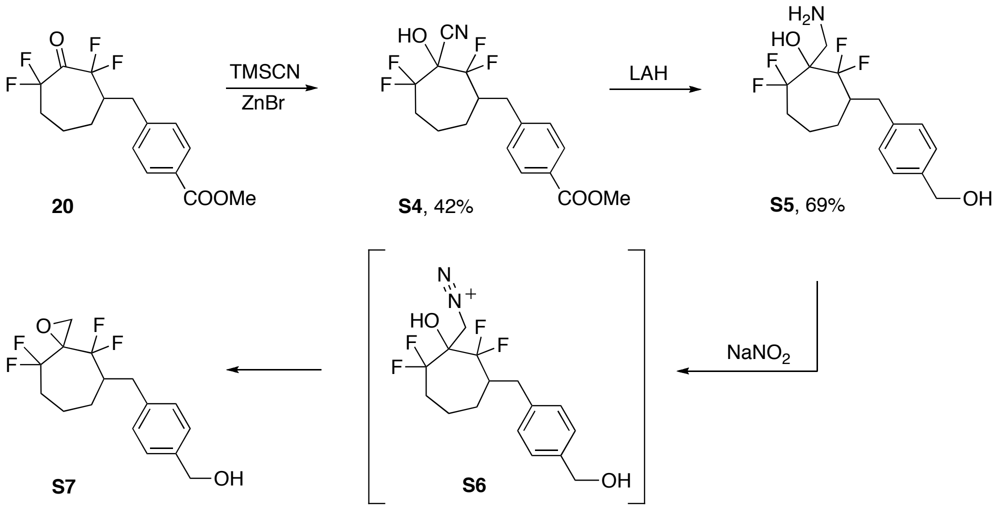
Table S1. Selected homologation attempts.

Entry	Diazo species	Lewis acid	Reaction conditions	Result
1	$TMSCHN_2$	$AlMe_3$	-78 ^{o}C, 3 min	Compound **S3**
2	$TMSCHN_2$	$BF_3{\cdot}OEt_2$	-78 ^{o}C, 2 h	Oxirane **23**
3	$TMSCHN_2$	MAD	0 ^{o}C, 2 h	Oxirane **23**
4	$TMSCHN_2$	TMSOTf	0 ^{o}C, 15 min	Oxirane **23**
5	$TMSCHN_2$	$Sc(OTf)_3$	0 ^{o}C, 30 min	Oxirane **23**
6	$N_2CHCOOEt$	$AlMe_3$	Rt, overnight	No reaction
7	$N_2CHCOOEt$	$BF_3{\cdot}OEt_2$	Rt, overnight	No reaction
8	$N_2CHCOOEt$	$Sc(OTf)_3$	Rt, overnight	No reaction
9	$N_2CHCOOEt$	$BF_3{\cdot}OEt_2$	60 ^{o}C, 1 week	Unknown
10	$TMSCLiN_2$	N/A	40 ^{o}C, overnight	Oxirane **23**
11	$N_2CLiCOOEt$	N/A	40 ^{o}C, 2 h	Decomposition

12	$TMSCHN_2$	None	40 ^{o}C, overnight	Diazocompound (large IR stretch at 2090 nm)
13	$TMSCHN_2$	None	Microwave, 10 min	Diazocompound
14	CH_2N_2	$AlMe_3$	-20 ^{o}C to rt, 1 h	Oxirane **23** (major) compound **S3** (minor)
15	CH_2N_2	BaO	-20 ^{o}C to rt, 1 h	Oxirane **23**
16	CH_2N_2	$BF_3{\cdot}OEt_2$	-20 ^{o}C to rt, overnight	No reaction
17	CH_2N_2	TMSOTf	-20 ^{o}C to rt, 1 h	Oxirane **23**
18	CH_2N_2	$Sc(OTf)_3$	-20 ^{o}C to rt, 1 h	Oxirane **23**

After many unsuccessful attempts to ring-expand **20** to **18**, we looked toward other ways to effect the same transformation (Scheme S3). The desired diazo intermediate (**S6**) could also be formed from amino-alcohol **S5** by treatment with sodium nitrite, as observed in the Tiffeneau- Demjanov rearrangement.[viii] The requisite amino-alcohol **S5** was prepared by cyanohydrin formation (**S4**) followed by reduction with lithium aluminum hydride. However, upon treatment of **S5** with $NaNO_2$, only oxirane formation was observed, suggesting that the initial nucleophilic attack (which is often the rate-determining step in homologation reactions) proceeds as desired and the 1,2-migration is disfavored. At this point, we directed our attention to the homologation of trifluorinated ketone **22**, as we thought that the removal of one electron-withdrawing fluorine atom would be sufficient to promote ring-expansion.

Scheme S3. Tiffeneau-Demjanov rearrangement of tetrafluorinated ketone **20**.



Scheme S4. Attempted homologation of ketone **22**.

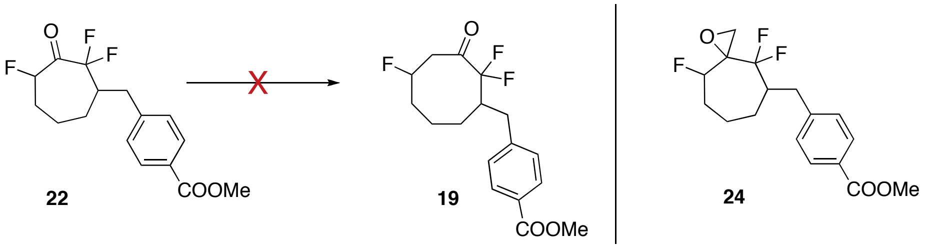
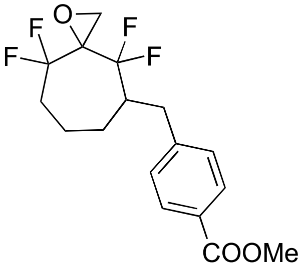


Table S2. Selected homologation attempts.

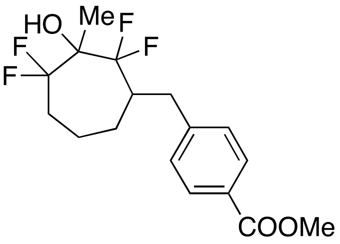
Entry	**Diazo species**	**Lewis acid**	**Reaction conditions**	**Result**
1	TMSCHN$_2$	AlMe$_3$	-78 °C, 30 min	Oxirane **24**
2	TMSCHN$_2$	BF$_3$·OEt$_2$	-78 °C, 2 h	Oxirane **24**
3	CH$_2$N$_2$	BaO	-20 °C to rt, 1 h	Oxirane **24**
4	CH$_2$N$_2$	TMSOTf	-20 °C to rt, 1 h	No reaction

While ketone **22** and **20** did exhibit some differences in reactivity, most notably no methyl addition was observed with AlMe$_3$ as the Lewis acid, we did not observe any desired ring-expanded product. In all trials (Scheme S4, Table S2), the major product observed was oxirane formation. Oxirane **24** has three stereocenters which complicated the product analysis. Additionally, we found that the TMS group, which readily underwent protodesilylation in the case of **20**, was not as labile in the reaction with **22** and a hydrolysis step was necessary before characterization. At this point, we abandoned the homologation approach as a means to synthesize tri- and tetrafluorinated cyclooctynes.

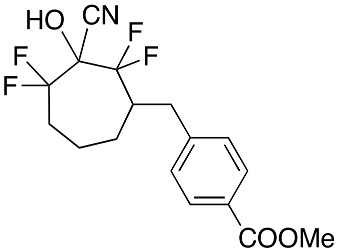
Characterization of Homologation Products



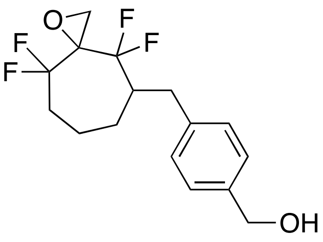
Methyl 4-((4,4,9,9-tetrafluoro-1-oxaspiro[2.6]nonan-5-yl)methyl)benzoate (23). A solution of 0.09 M $\mathrm{TMSCLiN_2}$ was generated by combining trimethylsilyldiazomethane (0.05 mL of a 2.0 M solution in $\mathrm{CH_2Cl_2}$) with *n*-butyllithium (0.06 mL of a 1.6 M solution in hexane) in THF (1.0 mL, anhydrous) at -78 ^{o}C. Tetrafluorinated ketone **20** (20 mg, 0.060 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL, anhydrous) and cooled to 0 ^{o}C. The $\mathrm{TMSCLiN_2}$ (0.67 mL, 0.060 mmol, 1.0 equiv.) was added and the mixture was warmed to rt. No significant reaction was observed at rt and the mixture was heated to 40 ^{o}C overnight. The following morning the mixture was quenched with methanol and evaporated to dryness. The crude product was purified by silica gel chromatography with a hexanes/ether solvent system (40:1 to 10:1) to yield 14 mg of **23** (0.04 mmol, 67%). R_f = 0.7 in 3:1 hexane/ethyl acetate. ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$): δ 8.0-7.96 (m, 2H major, 2H minor) 7.28-7.23 (m, 2H major, 2H minor), 3.91 (s, 3H minor), 3.91 (s, 3H major), 3.30-3.17 (m, 2H major, 2H minor), 3.14-3.10 (m, 1H major, 1H minor), 2.56-2.36 (m, 3H major, 3H minor), 2.18-2.04 (m, 1H major, 1H minor), 1.80-1.65 (m, 2H major, 2H minor), 1.62-1.46 (m, 1H major, 1H minor), 1.41-1.26 (m, 1H major, 1H minor). ^{1}H NMR (600 MHz, $\mathrm{CDCl_3}$, major only): δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 3.91 (d, *J* = 3.1 Hz, 3H), 3.29 (t, *J* = 5.6 Hz, 1H), 3.23 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.11 (t, *J* = 5.9 Hz, 1H), 2.55-2.38 (m, 3H), 2.17-2.04 (m, 1H), 1.75-1.69 (m, 2H), 1.52 (q, *J* = 13.0 Hz, 1H), 1.36 q, *J* = 11.9 Hz, 1H). ^{13}C NMR (150 MHz, $\mathrm{CDCl_3}$, major only): δ 167.1, 144.9, 130.1, 129.4, 128.7, 120.9 (ddd, *J* = 254, 249, 4 Hz), 120.0 (apparent td, *J* = 246, 8 Hz), 60.2-59.6 (m), 52.3, 46.8 (ddd, *J* = 13, 5, 2 Hz), 45.0 (t, *J* = 23 Hz), 36.8 (t, *J* = 25 Hz), 34.6 (dd, *J* = 7, 6 Hz), 29.4 (d, *J* = 4 Hz), 19.45 (d, *J* = 9 Hz). ^{19}F NMR (376 MHz, $\mathrm{CDCl_3}$): δ -88.41 (d, *J* = 261 Hz, 1F major), -92.89 (dq, *J* = 262, 5 Hz, 1F minor), -97.46 (d, *J* = 261 Hz, 1F minor), -103.49 (d, *J* = 261 Hz, 1F major), -105.35 (dddd, *J* = 30, 25, 19, 6 Hz, 1F major), -107.00 (dm, *J* = 214 Hz, 1F minor), -118.04 (ddd, *J* = 260, 28, 14 Hz, 1F major), -120.62 (ddd, *J* = 262, 24, 7 Hz, 1F minor). HRMS (EI): calcd. for $\mathrm{C_{17}H_{18}O_3F_4^+}$ $[M]^+$, 346.1192; found, 346.1195.



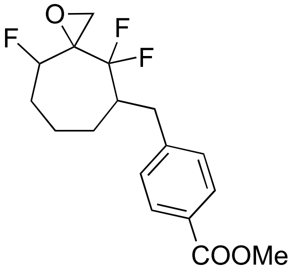
Methyl 4-((2,2,4,4-tetrafluoro-3-hydroxy-3-methylcycloheptyl)methyl)benzoate (S3). Tetrafluorinated ketone **20** (19 mg, 0.057 mmol, 1.0 equiv.) was dissolved in $\mathrm{CH_2Cl_2}$ (0.5 mL) and cooled to 0 ^{o}C. Trimethylaluminum (35 μL of a 2M solution in toluene, 0.070 mmol, 1.2 equiv.) was added and the mixture was stirred for 20 min, at which point trimethylsilyl diazomethane (35 μL of a 2M solution in $\mathrm{CH_2Cl_2}$, 0.070 mmol, 1.2 equiv.) was added. After 5 min, TLC indicated the reaction was complete. The mixture was quenched with sat. aqueous Rochelle's salt and stirred until all aluminum was complexed. This solution was extracted with CH_2Cl_2 (3 x 5 mL). The organics were dried, decanted, evaporated to dryness and the crude product was purified by silica gel chromatography using a hexanes/ether solvent system (20:1 to 2:1). This procedure yielded 9 mg of **S3** (0.026 mmol, 45%) as a mixture of diastereomers (~1:0.3). R_f = 0.7 in 3:1 hexane/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$, major diastereomer only): δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 2H), 3.91 (s, 3H), 3.26 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.80-2.70 (m, 1H), 2.50 (dd, *J* = 13.8, 10.5 Hz, 1H), 2.45-2.34 (m, 1H), 2.20 (s, 1H), 2.04-1.98 (m, 1H), 1.74-1.64 (m, 1H), 1.56-1.51 (m, 6H). ^{19}F NMR (565 MHz, $CDCl_3$): δ -99.07 (ddt, *J* = 264, 21, 7 Hz, 1F), -103.09 (ddd, *J* = 255, 35, 15 Hz, 1F), -105.93 (d, *J* = 265 Hz, 1F), -118.57 (ddd, *J* = 264, 29, 22 Hz, 1F). HRMS (EI): calcd. for $C_{17}H_{20}O_3F_4^+$ [M]$^+$, 348.1349; found, 348.1358.



Methyl 4-((3-cyano-2,2,4,4-tetrafluoro-3-hydroxycycloheptyl)methyl)benzoate (S4). Tetrafluorinated ketone **20** (11 mg, 0.033 mmol, 1.0 equiv.) was dissolved in ether (0.25 mL, anhydrous). Zinc bromine (1 grain) and trimethylsilyl cyanide (~15 μL, 0.1 mmol, 3 equiv.) was added and the reaction mixture was stirred overnight at rt. The following morning the reaction was incomplete and more trimethylsilyl cyanide (~15 μL) was added and the mixture was stirred at rt for an additional 24 h, at which point it was evaporated to dryness. The crude product was purified by silica gel chromatography using a hexanes/ethyl acetate solvent system (**S4** elutes at 4:1). This procedure resulted in 5 mg of **S4** as a 1:0.3 mixture of diastereomers (0.014 mmol, 42%). R_f **=** 0.4 in 3:1 hexane/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 2H minor), 7.98 (d, *J* = 8.3 Hz, 2H major), 7.27-7.25 (m, 2H major, 2H minor), 4.66 (bs, 1H major), 4.39 (bs, 1H minor), 3.92 (s, 3H major, 3H minor), 3.27 (dd, *J* = 13.7, 3.4 Hz, 1H major, 1H minor), 2.73-2.64 (m, 1H major), 2.59-2.53 (m, 1H minor), 2.55 (dd, *J* = 11.0, 13.9 Hz, 1H major), 2.46-2.34 (m, 1H major, 2H minor), 2.24-2.09 (m, 1H major, 1H minor), 1.75-1.68 (m, 1H major, 1H minor), 1.58-1.50 (m, 3H major, 2H minor), 1.42-1.40 (m, 1H minor).



(4-((4,4,9,9-Tetrafluoro-1-oxaspiro[2.6]nonan-5-yl)methyl)phenyl)methanol (S7). Cyanohydrin **S4** (5 mg, 0.014 mmol, 1.0 equiv.) was dissolved in ether (0.2 mL, anhydrous). This solution was added dropwise to a solution of lithium aluminum hydride (0.25 mL, 1M solution in THF, 0.25 mmol, 18 equiv.). The mixture was warmed to 50 °C and allowed to react overnight. The following morning it was quenched with sat. aqueous Rochelle's salt and extracted with ethyl acetate (3 x 15 mL). The organics were combined, dried, decanted, and evaporated to dryness to yield **S5** (3 mg, 0.009 mmol, 69%; HRMS (ESI): calcd. for $C_{16}H_{22}O_2NF_4^+$ $[M+H]^+$, 336.1581; found, 336.1586). This crude product was dissolved in a mixture of water (80 μL) and acetic acid (80 μL). A separate solution of sodium nitrite (8 mg, 0.12 mmol, 13 equiv.) in water (160 μL) was prepared and added to the solution containing amino-alcohol **S5**. The mixture was stirred at rt overnight. The following morning, additional water (2 mL) was added and the product was extracted with ether (3 x 5 mL). The organics were combined, dried, decanted, and evaporated to dryness to yield **S7** as a mixture of diastereomers. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.3 Hz, 2H minor), 7.31 (d, *J* = 8.3 Hz, 2H major), 7.20 (d, *J* = 7.9 Hz, 2H minor), 7.17 (d, *J* = 7.9 Hz, 2H major), 4.69 (s, 2H minor), 4.68 (s, 2H major), 3.29 (dd, *J* = 14.7, 5.7 Hz, 1H major, 1H minor), 3.18-3.10 (m, 2H major, 2H minor), 2.49-2.40 (m, 3H major, 3H minor), 2.15-2.03 (m, 3H major, 3H minor), 1.86-1.22 (m, 3H major, 3H minor). ^{19}F NMR (565 MHz, $CDCl_3$): δ -89.51 (dm, *J* = 259 Hz), -94.15 (dq, *J* = 256, 9 Hz), -98.45 (apparent d, *J* = 257 Hz), -104.71 (d, *J* = 259 Hz), -106.29 (ddddd, *J* = 260, 30, 25, 18, 6 Hz), -107.96 (dm, *J* = 290 Hz), -118.96 (ddd, *J* = 261, 29, 14 Hz), -121.73 (ddd, *J* = 262, 24, 7 Hz). HRMS (EI): calcd. for $C_{16}H_{18}O_2F_4^+$ $[M]^+$, 318.1243; found, 318.1252.



Methyl 4-((4,4,9-trifluoro-1-oxaspiro[2.6]nonan-5-yl)methyl)benzoate (24). Ketone **22** (5.0 mg, 0.016 mmol, 1.0 equiv.) was dissolved in dry DCM (0.25 mL) and cooled to -78 °C. A 2.0 M solution of $AlMe_3$ in toluene (0.010 mL, 0.020 mmol, 1.3 equiv.) was then added and the reaction stirred for 5 min at which point 0.010 mL (0.020 mmol, 1.3 equiv.) of a 2.0M solution of $TMSCHN_2$ in hexanes were added. The reaction was allowed to stir for 1 hr then quenched with an excess of methanol and concentrated. The crude material was taken up in 1N HCl and stirred until a single major product was indicated by TLC. The reaction was then concentrated and purified by preparative TLC (18:82 ethyl acetate/ hexanes) to obtain the epoxide in 51% yield (2.7 mg, 0.0082 mmol). Characterization for major diastereomer only. R_f = 0.7 in 2:1 hexanes/ethyl acetate. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 4.96 (ddt, *J* = 46.2, 7.8, 3.8 Hz, 1H), 3.91 (s, 3H), 3.28 (t, *J* = 5.2 Hz, 1H), 3.21 (dd, *J* = 13.9, 3.1 Hz, 1H), 2.98 (t, *J* = 5.7 Hz, 1H), 2.48 (dd, *J* = 13.8, 10.9 Hz, 1H), 2.43- 2.33 (m, 1H), 2.06-1.91 (m, 2H), 1.73-1.51 (s, 3H), 1.37-1.27 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -102.58 (d, *J* = 256 Hz, 2F), -115.23 (dd, *J* = 252, 22.56 Hz, 1F). HRMS (EI): calcd. for $C_{17}H_{19}O_3F_3^+$ $[M]^+$, 328.1286; found, 328.1294.

References

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[i] Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518-1520.

[ii] Ragan, J.A.; Makowski, T.W.; am Ende, D.J.; Clifford, P.J.; Young, G.R.; Conrad, A.K.; Eisenbeis, S.A. *Org. Proc. Res. Dev.* **1998**, *2*, 379-381.

[iii] Codelli, J.A.; Baskin, J.M.; Agard, N.J.; Bertozzi, C.R. *J. Am. Chem. Soc.* **2008**, *130*, 11486-11493.

[iv] (a) Moebius, D.C.; Kingsbury, J.S. *J. Am. Chem. Sci.* **2009**, *131*, 878-879. (b) Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *Synlett* **1994**, 1283-1290. (c) Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *Synthesis* **1994**, 1283-1290. (d) Norio, H.; Toyohiko, A.; Takayuki, S. *Chem. Pharm. Bull.* **1982**, *30*, 119-124. (e) Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725-4726.

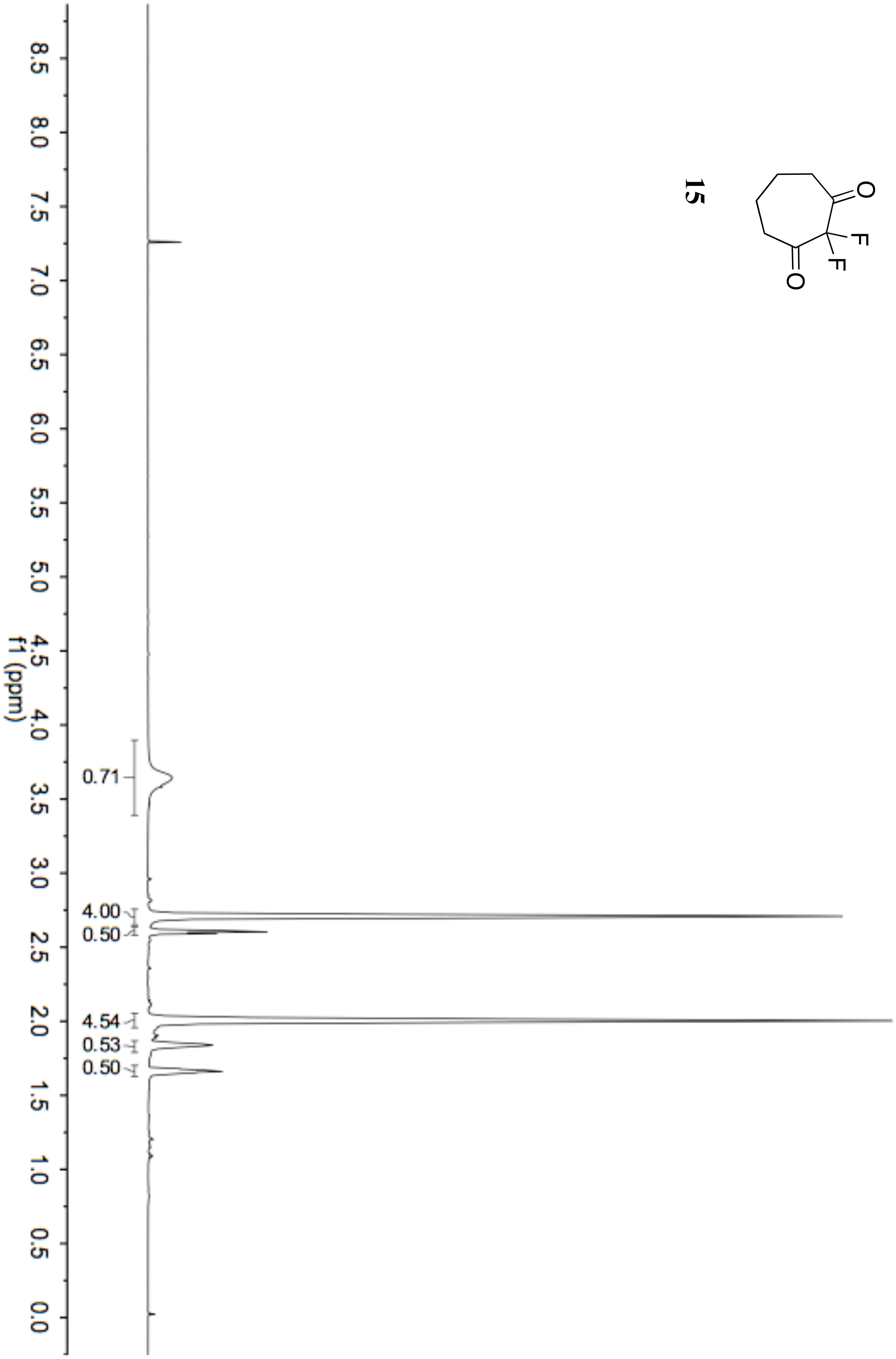
[v] (a) Mock, W.L.; Hartman, M.E. *J. Org. Chem.* **1977**, *42*, 466-472. (b) Mock, W.L.; Hartman, M.E. *J. Org. Chem.* **1977**, *42*, 459-465. (c) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055-5058.

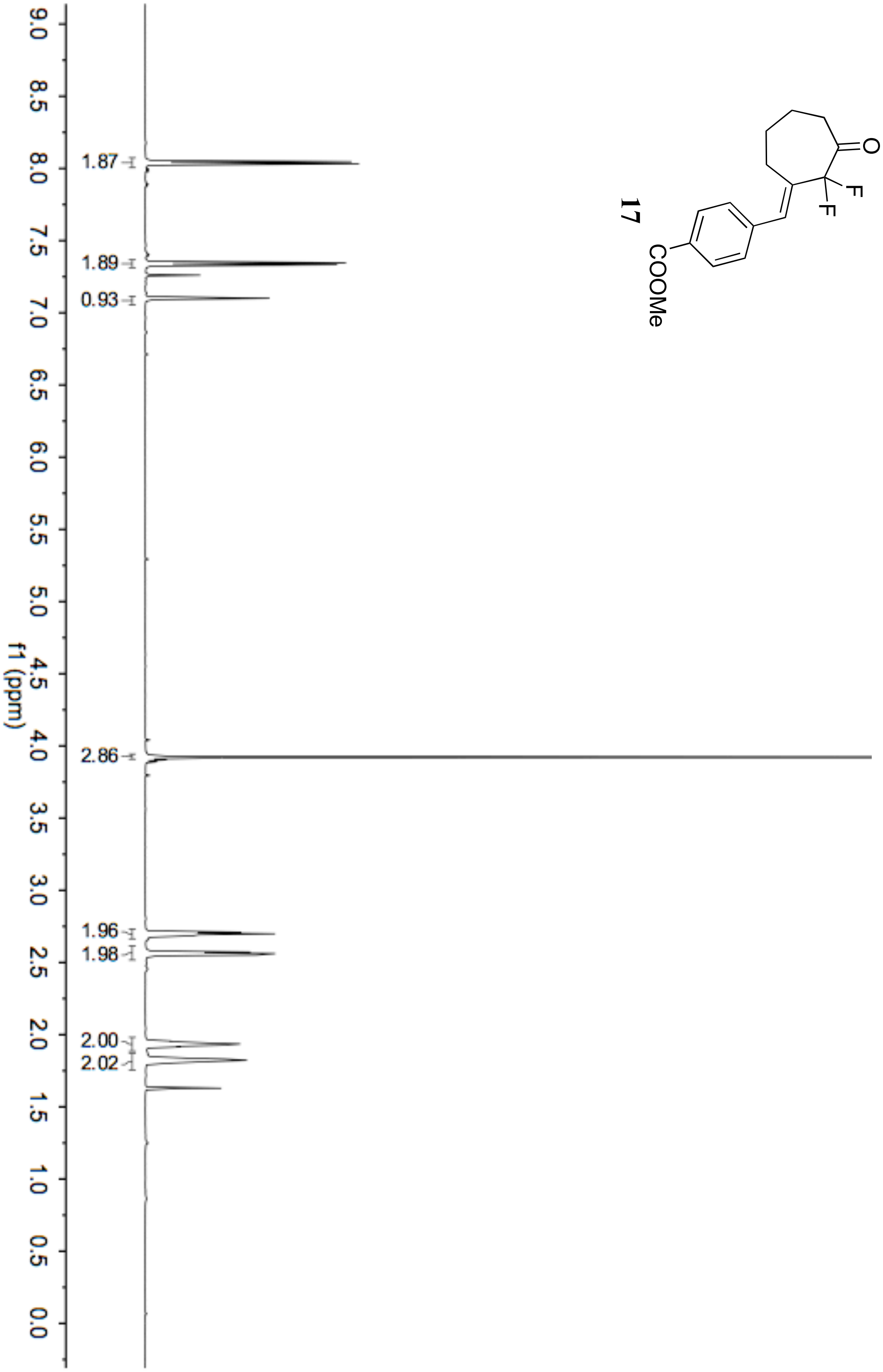
[vi] Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett*, **1994**, 107-108.

[vii] (a) Nagao, K.; Chiba, M.; Kim, S.W. *Synthesis* **1983**, 197-199. (b) Pellicciari, R.; Natalini, B. *J. Chem., Perkin Trans. 1* **1977**, 1822-1824.

[viii] (a) McKinney, M.A.; Patel, P.P. *J. Org. Chem.* **1973**, *38*, 4059-4064. (b) McKinney, M.A.; Patel, P.P *J. Org. Chem.* **1973**, *38*, 4064-4067. (c) Stern, A.G.; Nickon, A. *J. Org. Chem.* **1992**, *57*, 5342-5352.

^{1}H-NMR Spectra:





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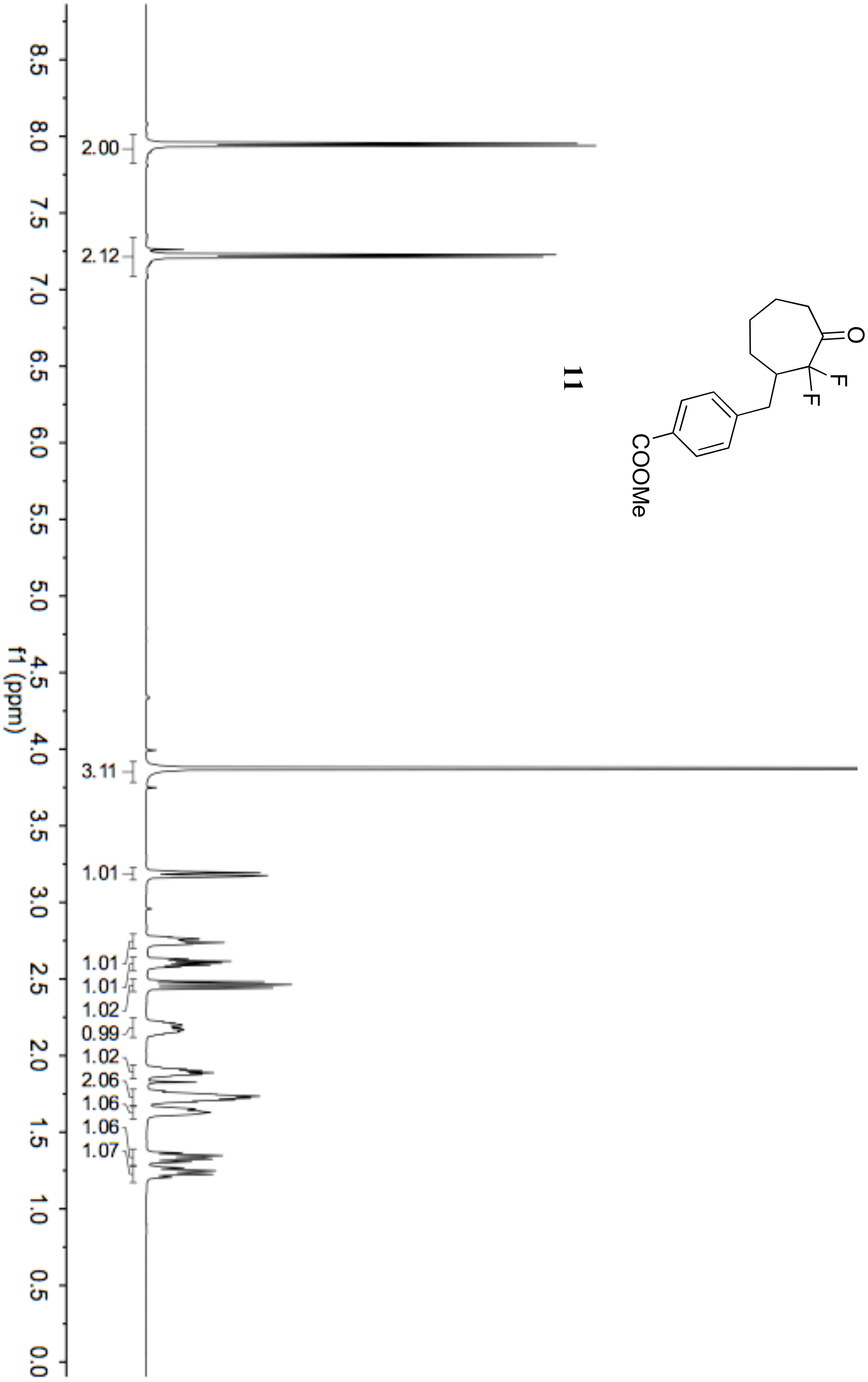
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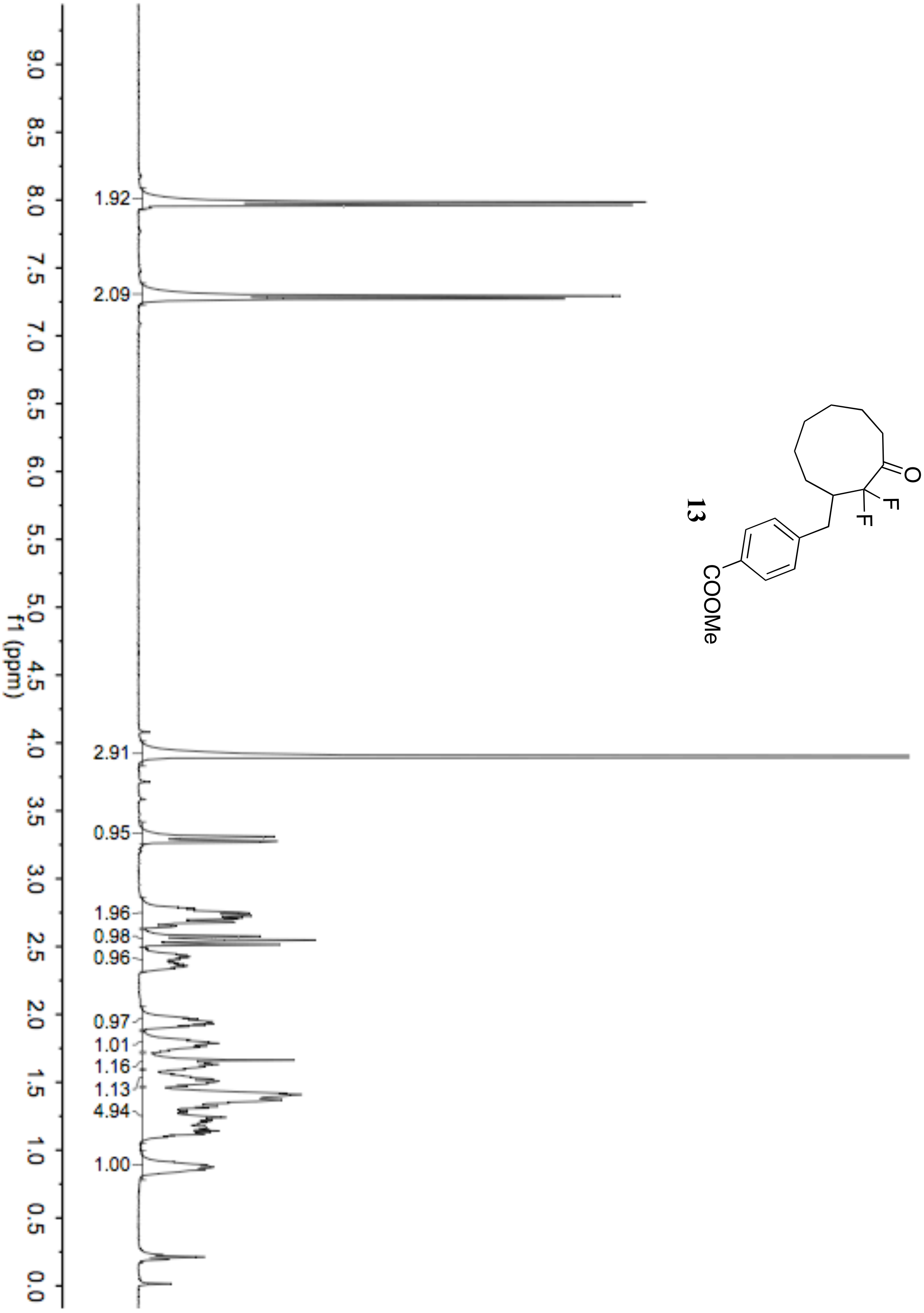
11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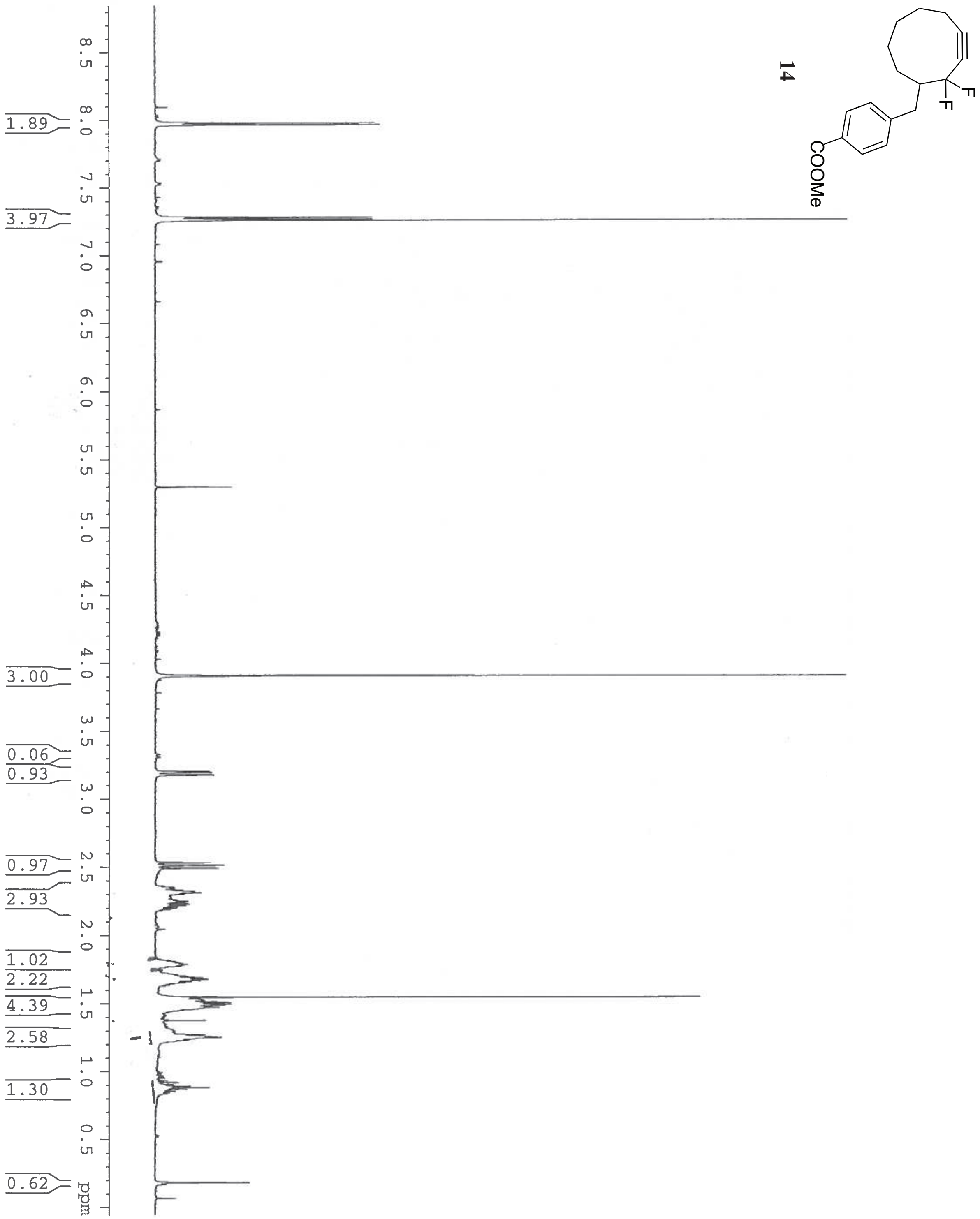
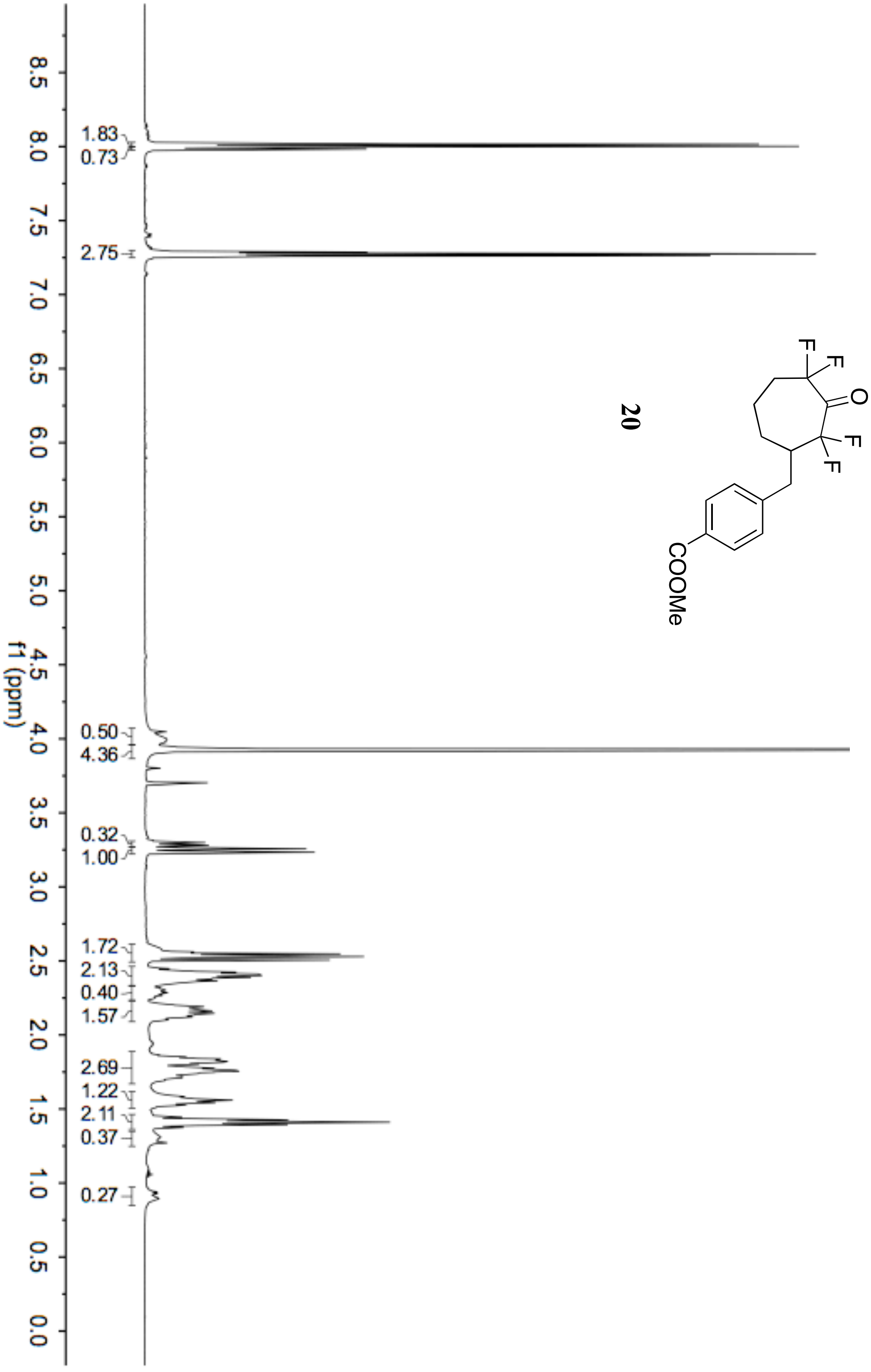
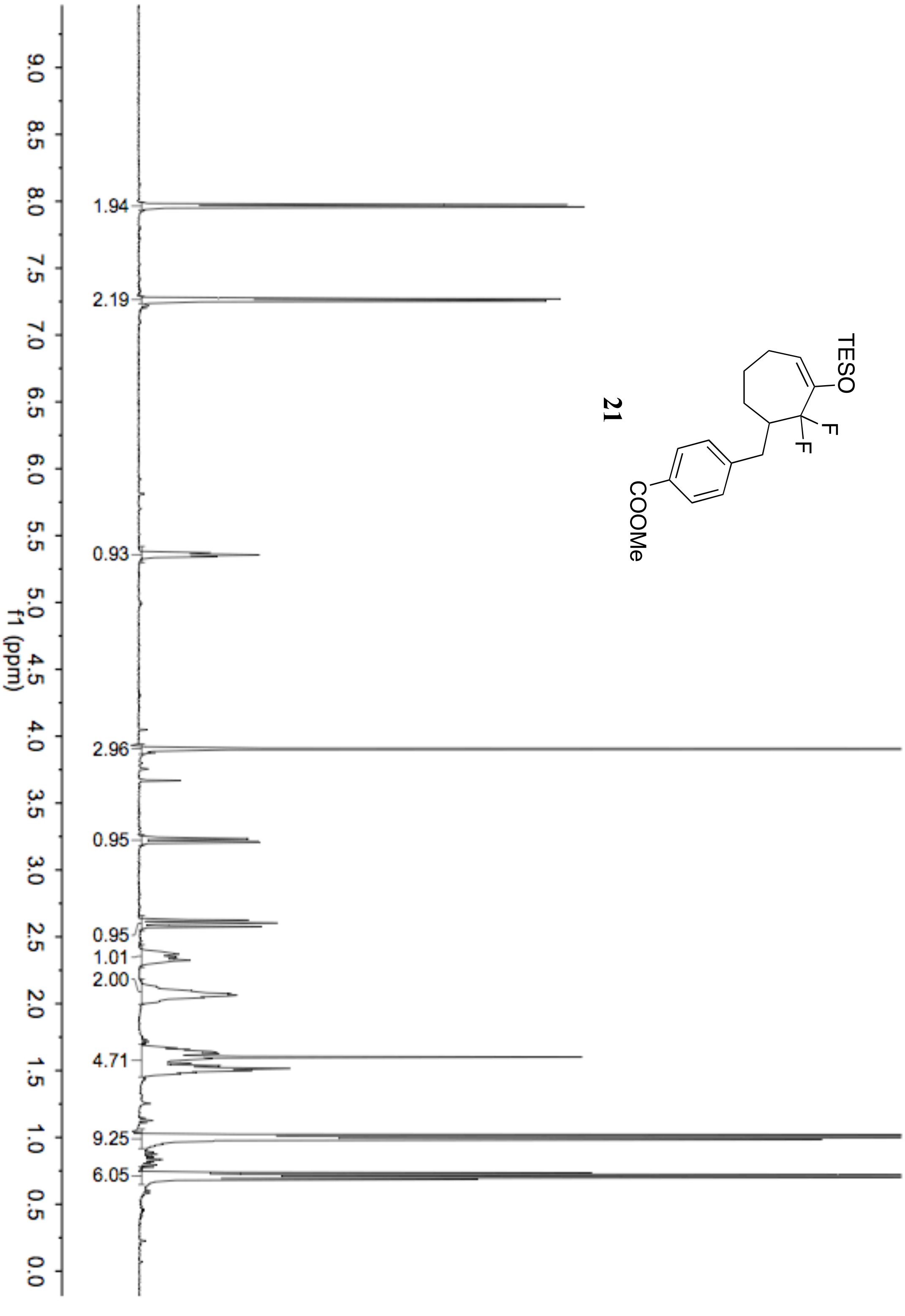
O
F
F
COOMe

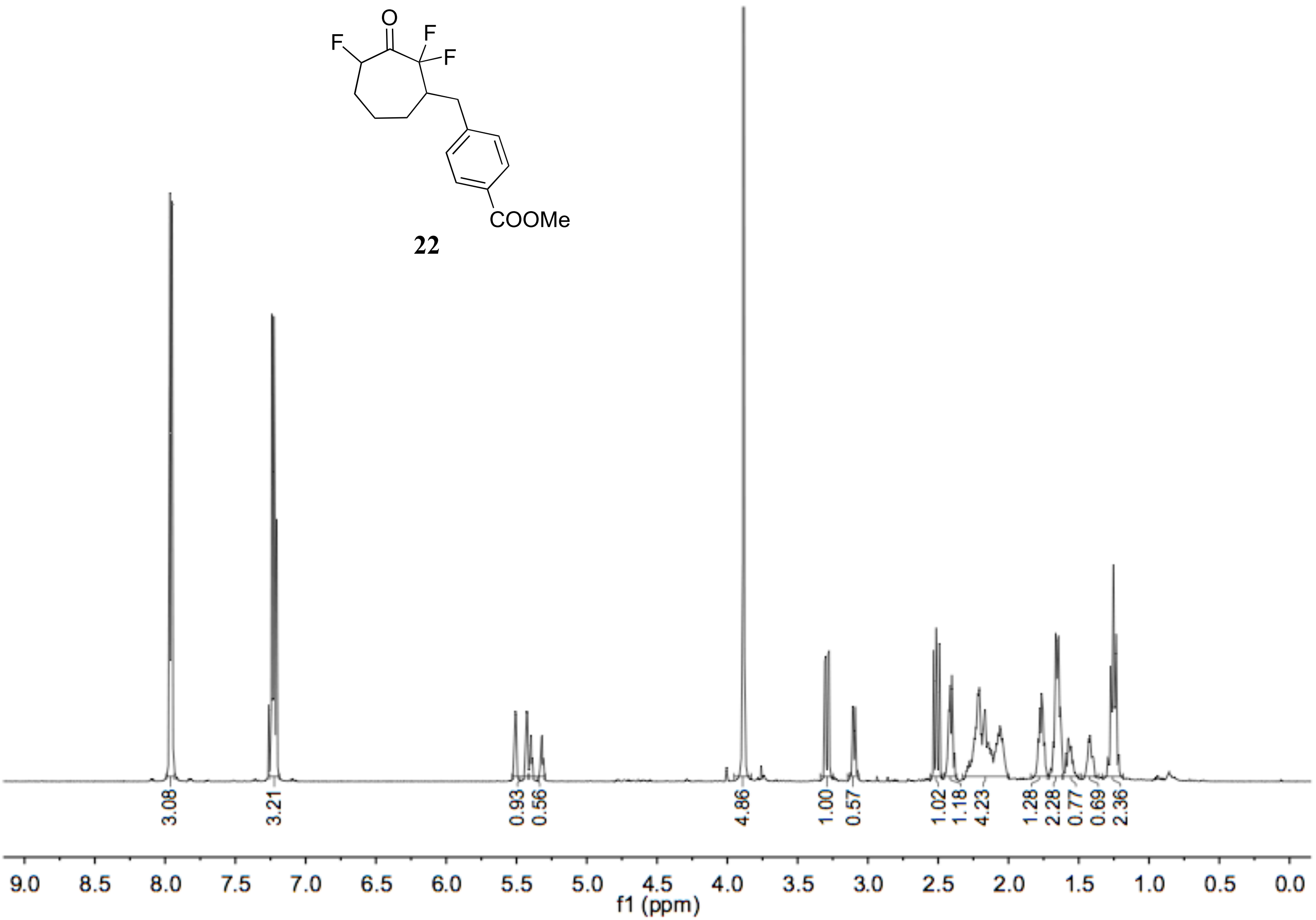

F
F
COOMe
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.89
3.97
3.00
0.06
0.93
0.97
2.93
1.02
2.22
4.39
2.58
1.30
0.62

14

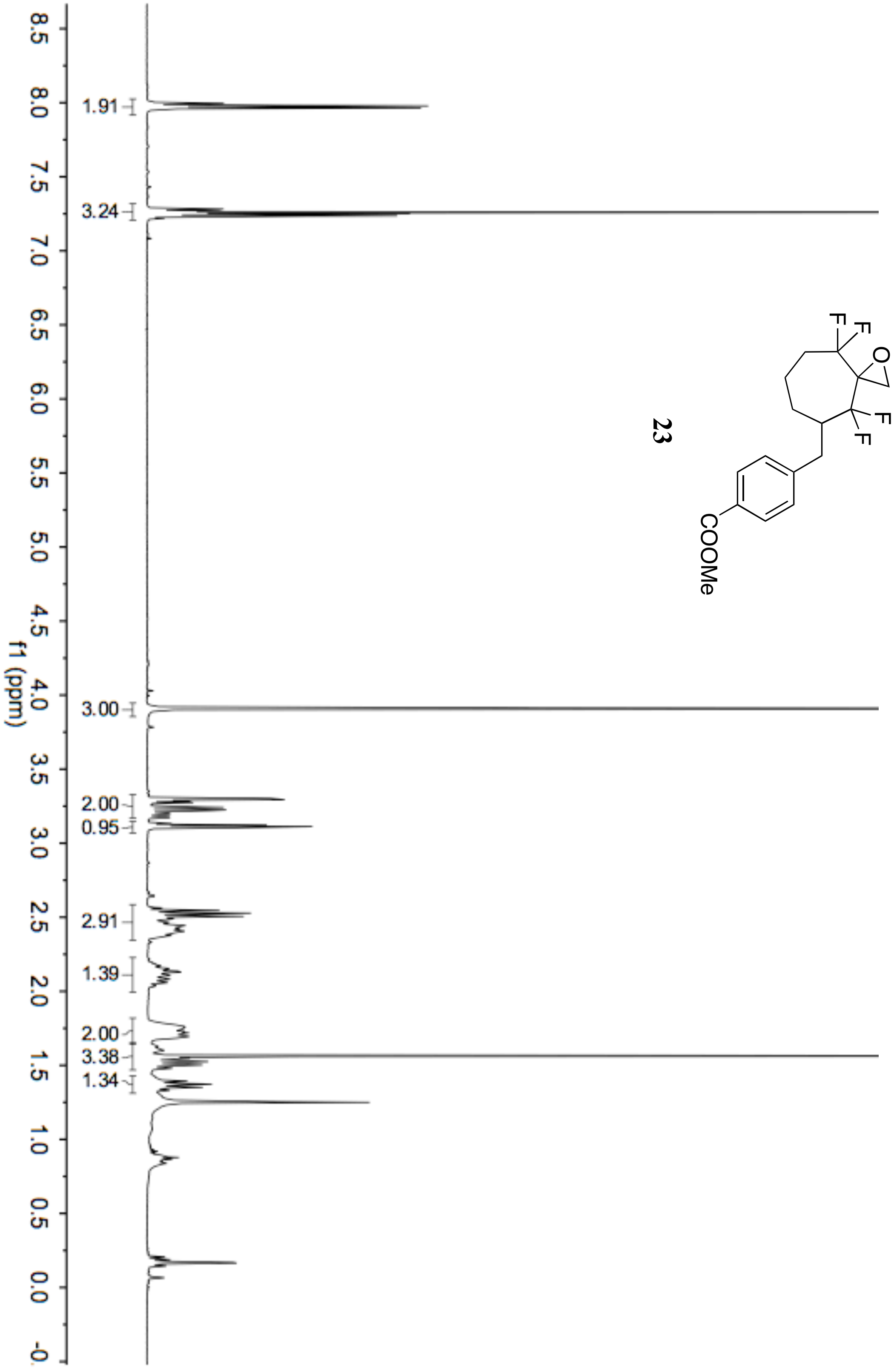

20

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
f1 (ppm)
1.83
0.73
2.75
0.50
4.36
0.32
1.00
1.72
2.13
0.40
1.57
2.69
1.22
2.11
0.37
0.27
F
F
O
F
F
COOMe

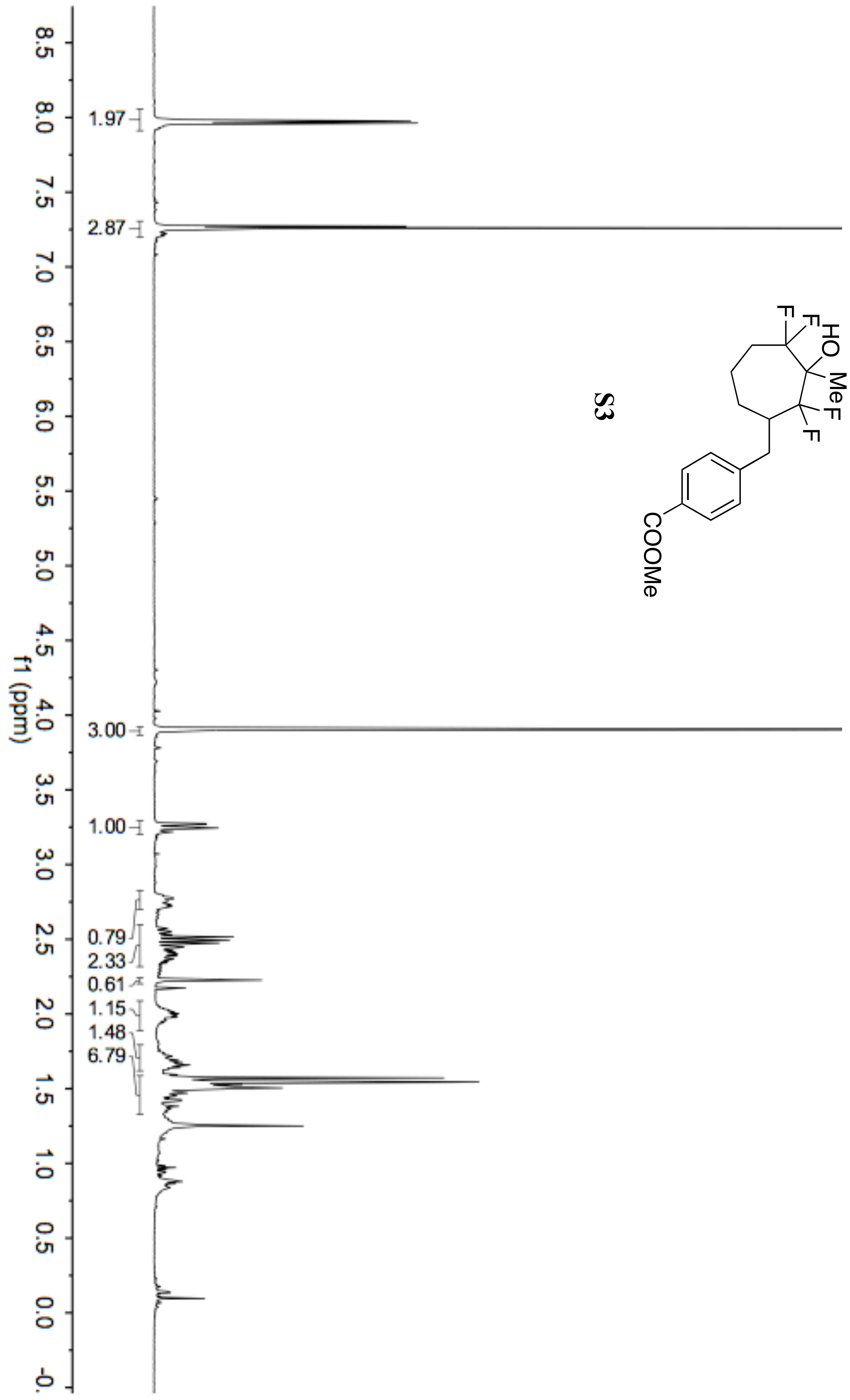

TESO
F
F
COOMe
21
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.94
2.19
0.93
2.96
0.95
0.95
1.01
2.00
4.71
9.25
6.05


22

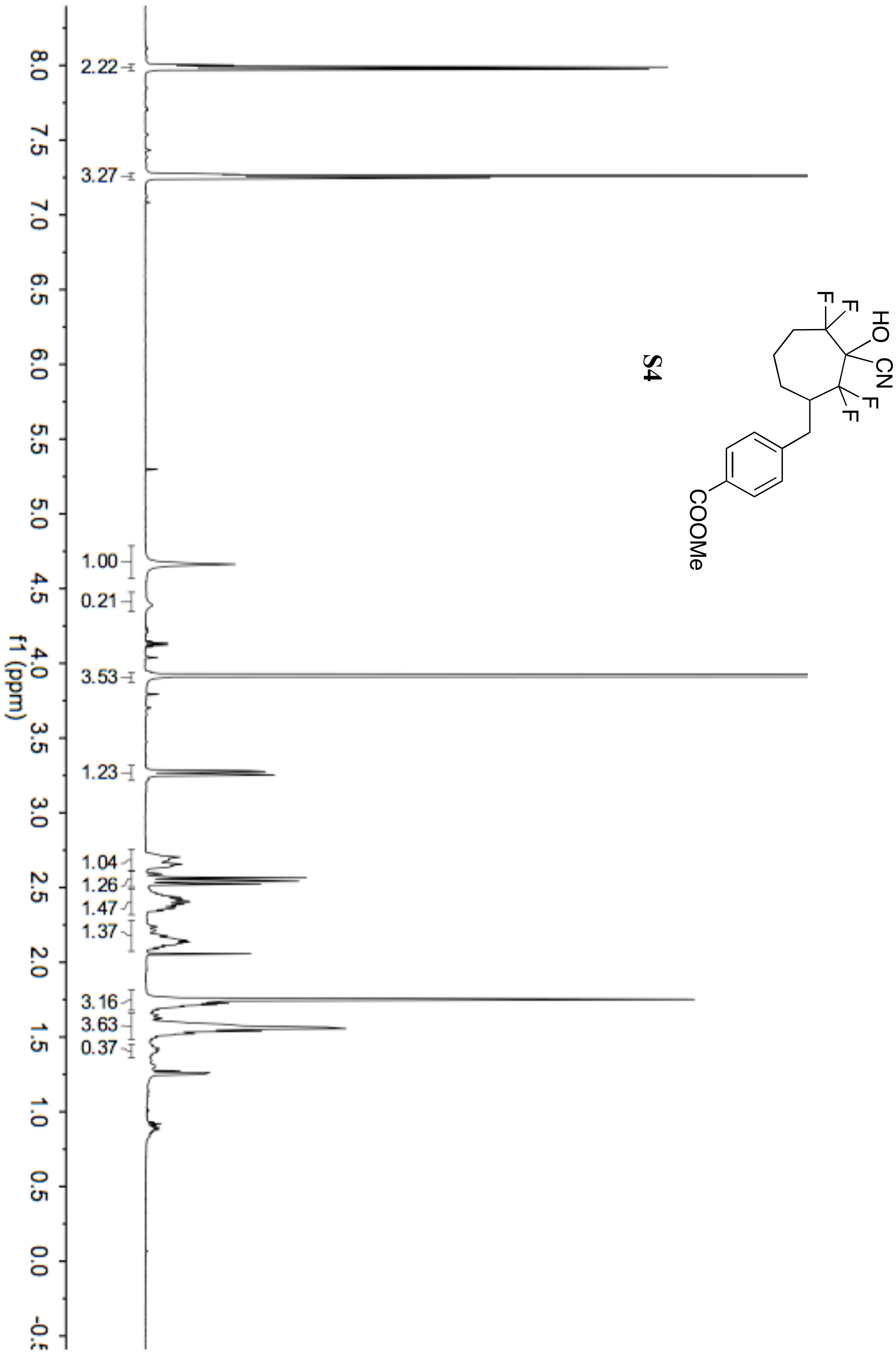
O
F
F
F
COOMe
3.08
3.21
0.93
0.56
4.86
1.00
0.57
1.02
1.18
4.23
1.28
2.28
0.77
0.69
2.36
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


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.
f1 (ppm)
1.91
3.24
3.00
2.00
0.95
2.91
1.39
2.00
3.38
1.34
F
F
O
F
F
COOMe

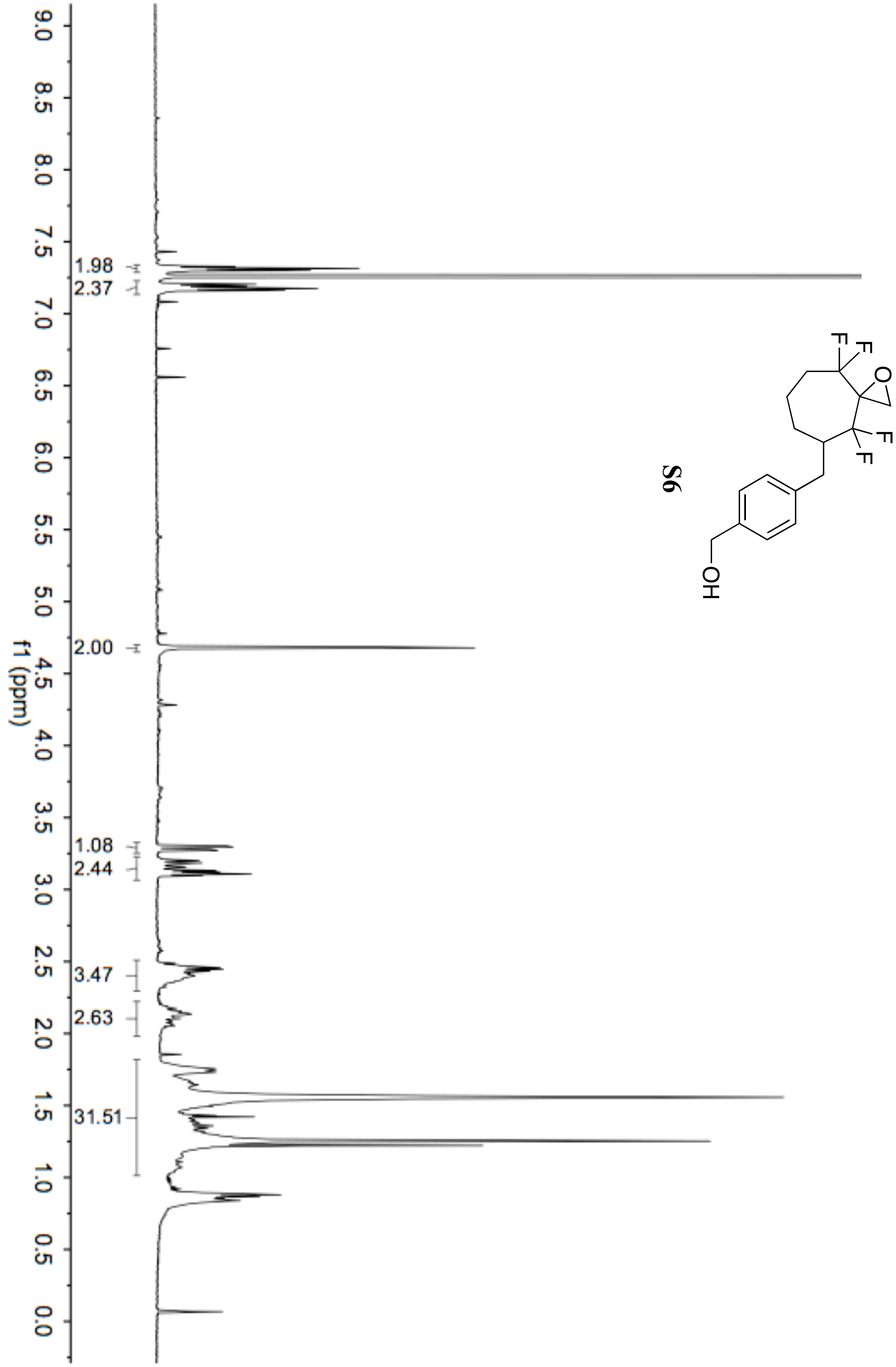
23


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.
f1 (ppm)
1.97
2.87
3.00
1.00
0.79
2.33
0.61
1.15
1.48
6.79
HO
Me
F
F
F
F
COOMe

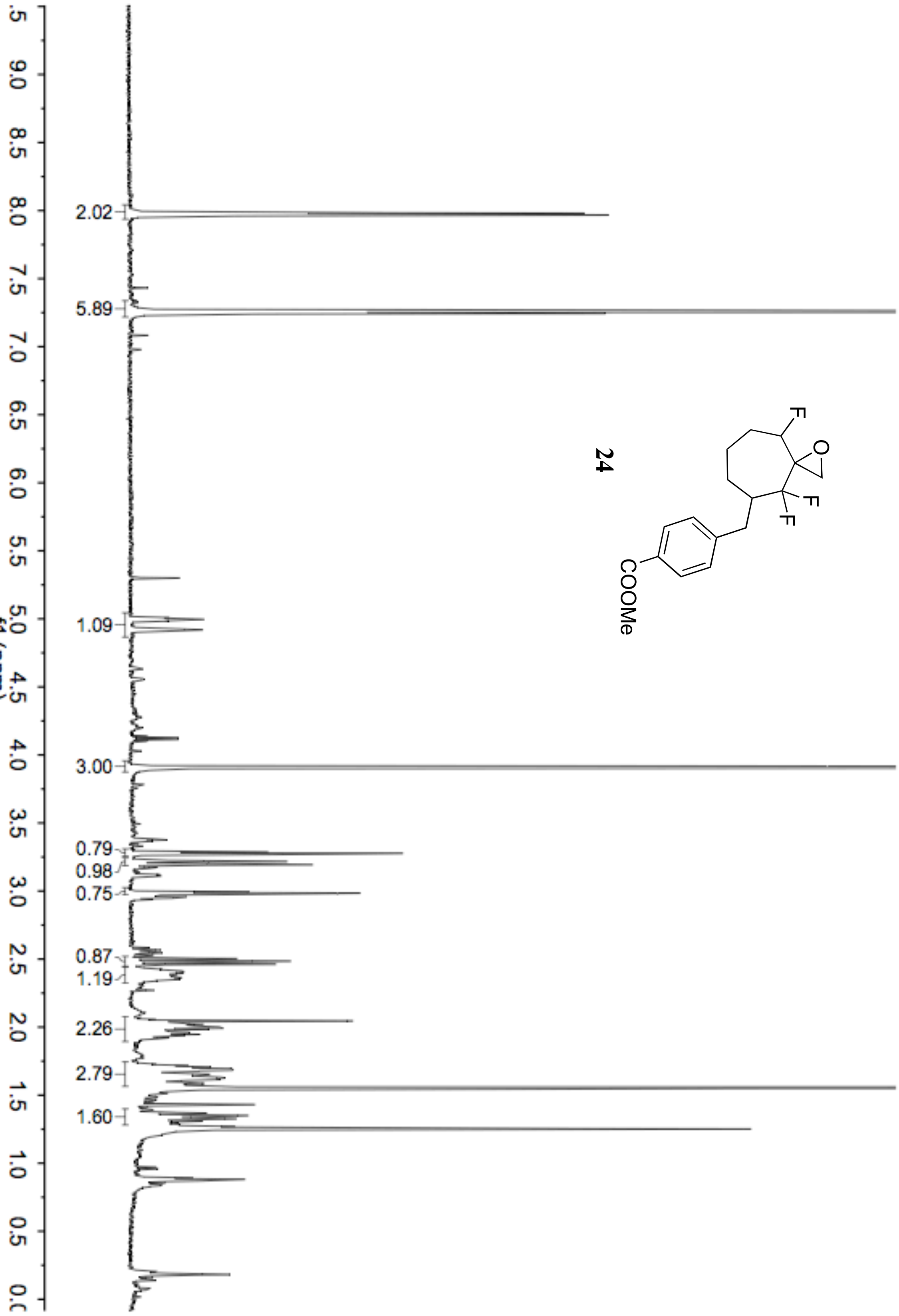
S3


HO
CN
F
F
F
F
COOMe
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)
2.22
3.27
1.00
0.21
3.53
1.23
1.04
1.26
1.47
1.37
3.16
3.63
0.37

S4

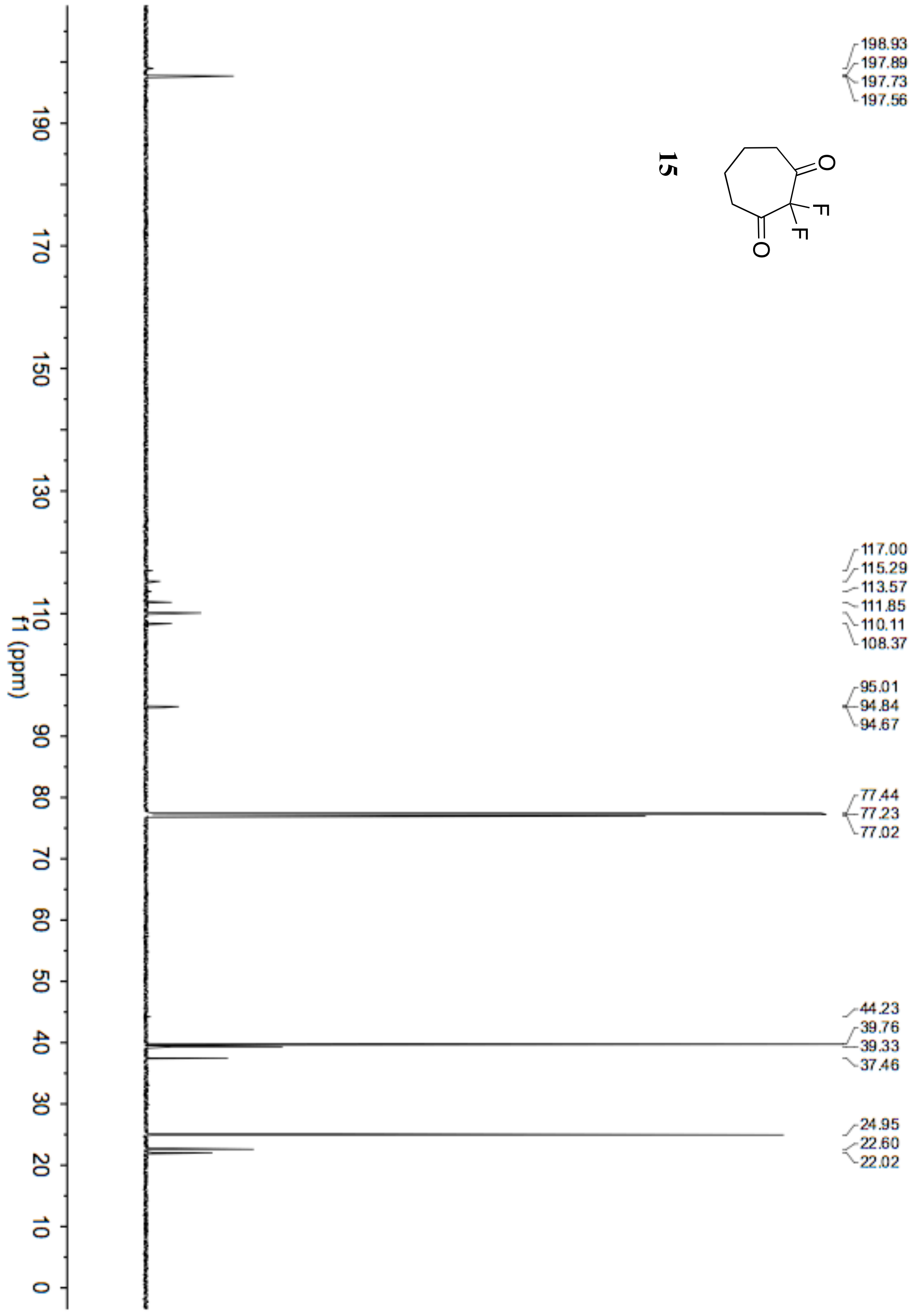

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
1.98
2.37
2.00
1.08
2.44
3.47
2.63
31.51
F
F
O
F
F
OH

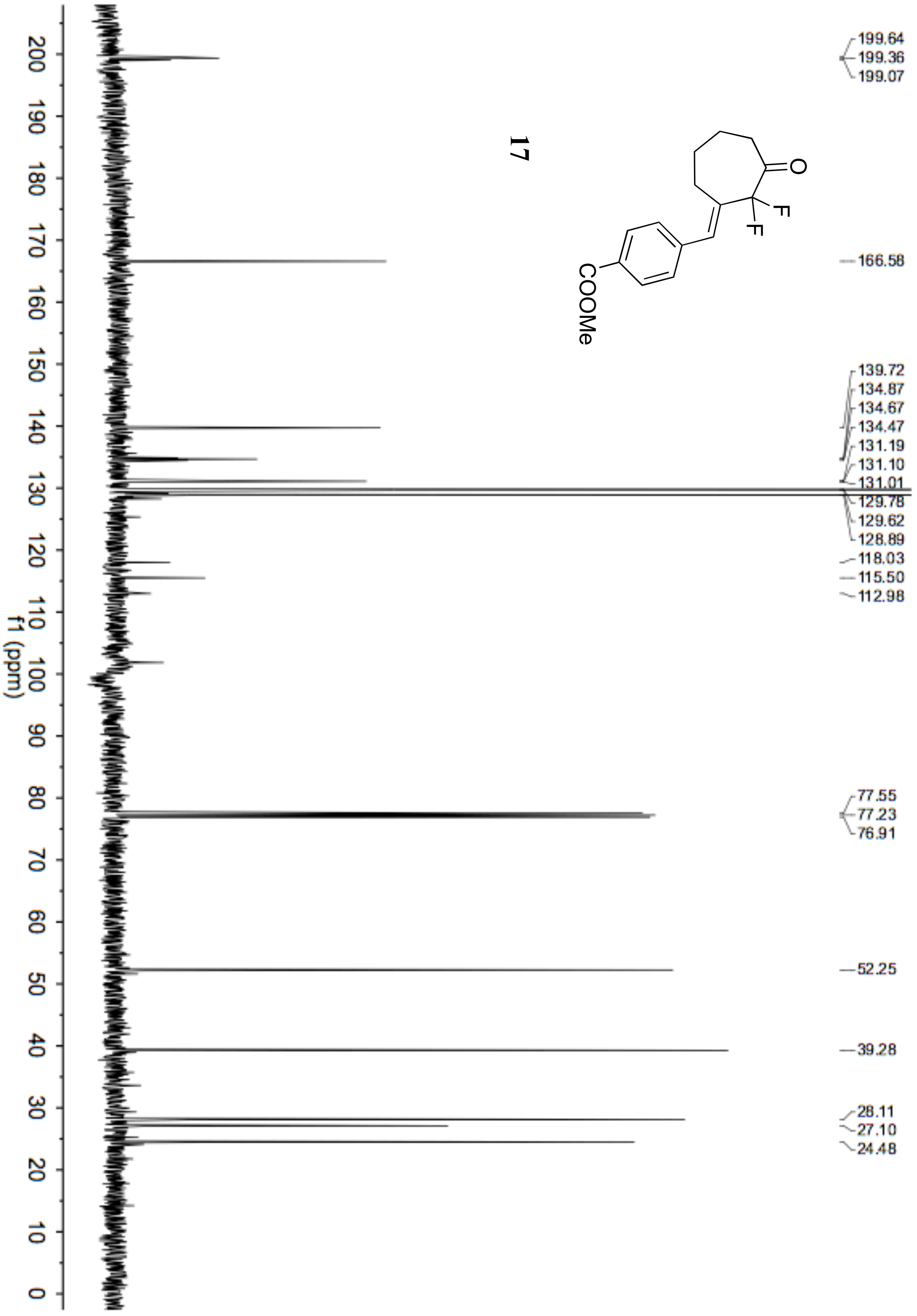
S6


24

.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.C
f1 (ppm)
2.02
5.89
1.09
3.00
0.79
0.98
0.75
0.87
1.19
2.26
2.79
1.60
F
O
F
F
COOMe

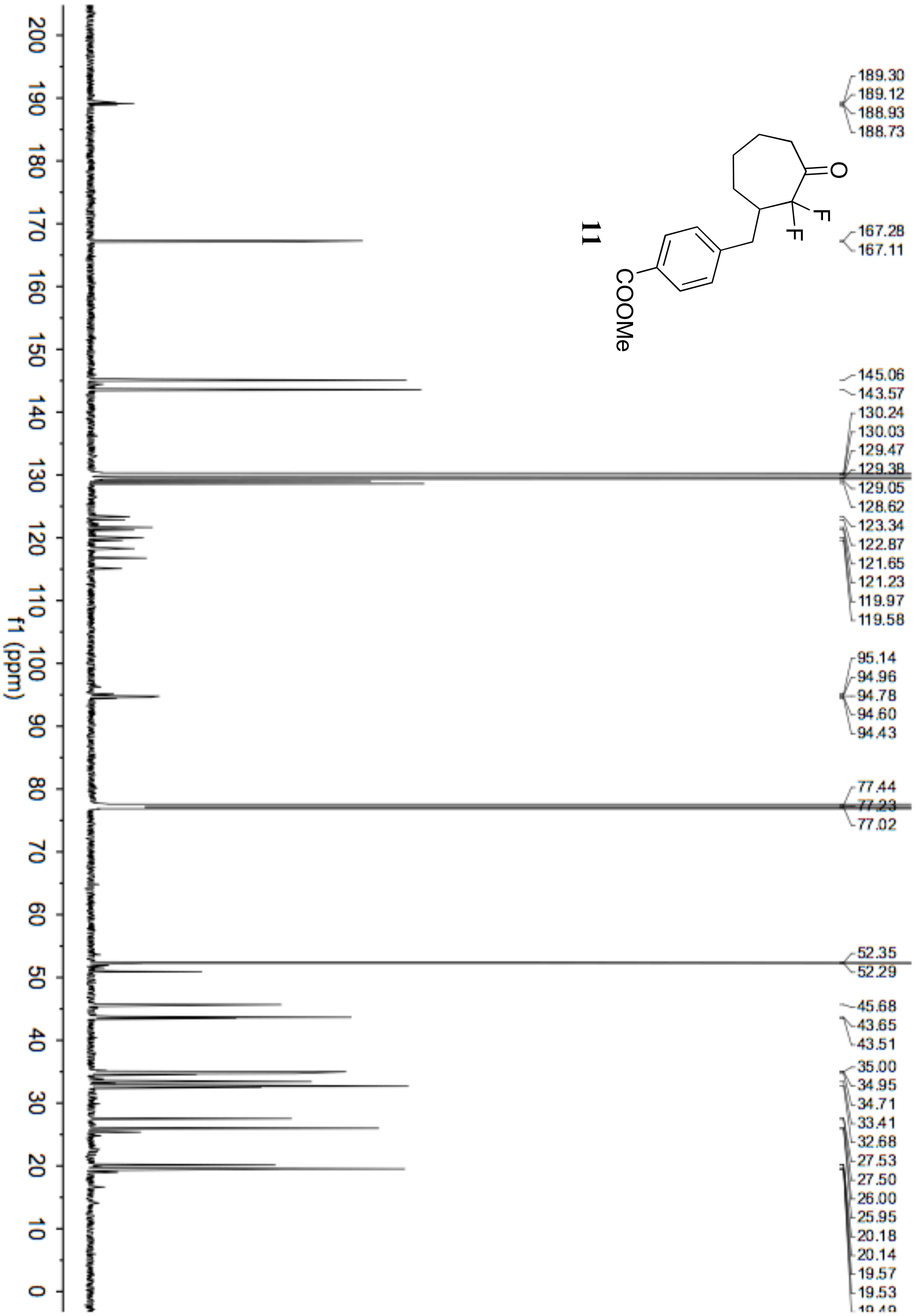
^{13}C NMR Spectra:





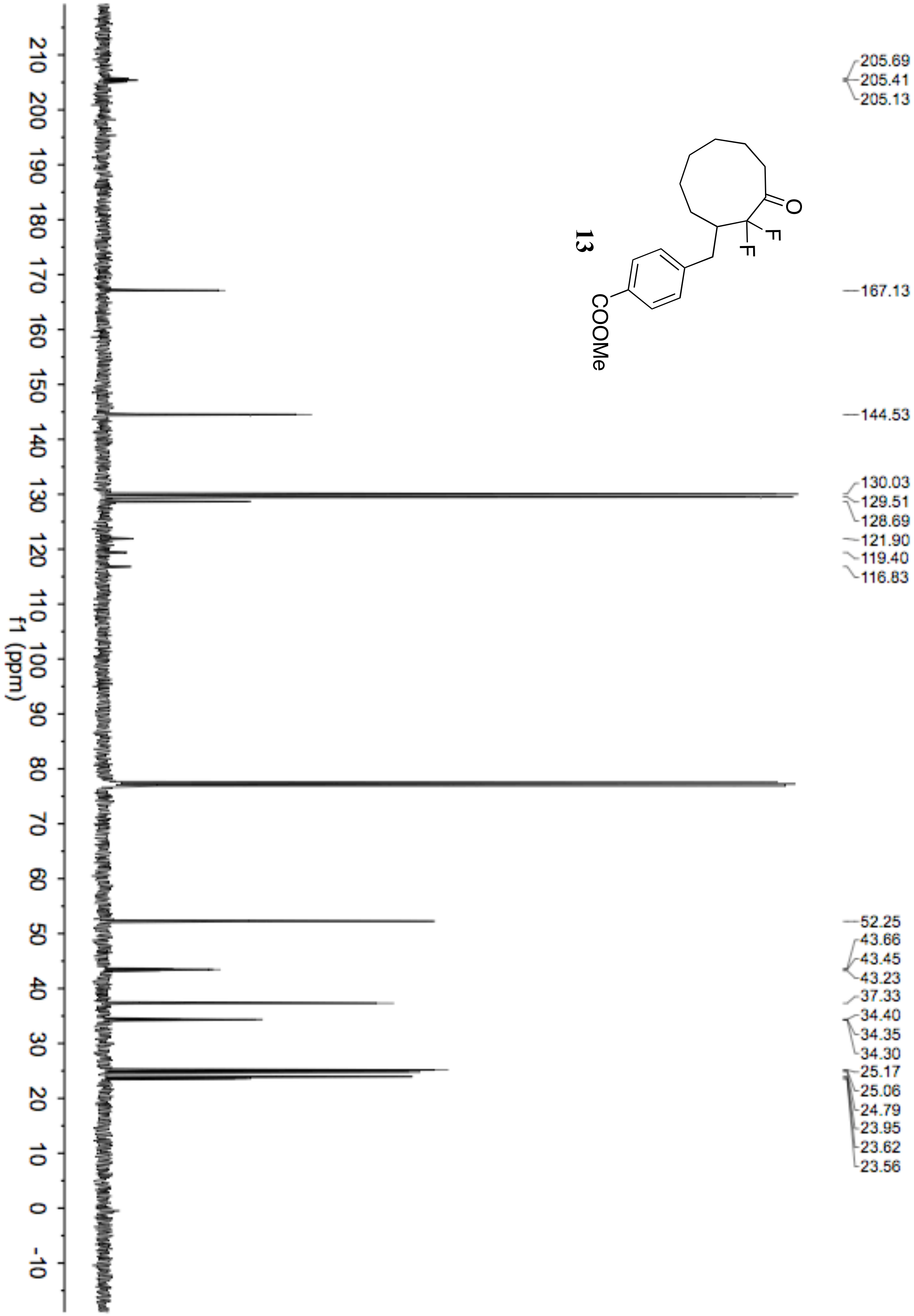
17

O
F
F
COOMe
199.64
199.36
199.07
166.58
139.72
134.87
134.67
134.47
131.19
131.10
131.01
129.78
129.62
128.89
118.03
115.50
112.98
77.55
77.23
76.91
52.25
39.28
28.11
27.10
24.48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

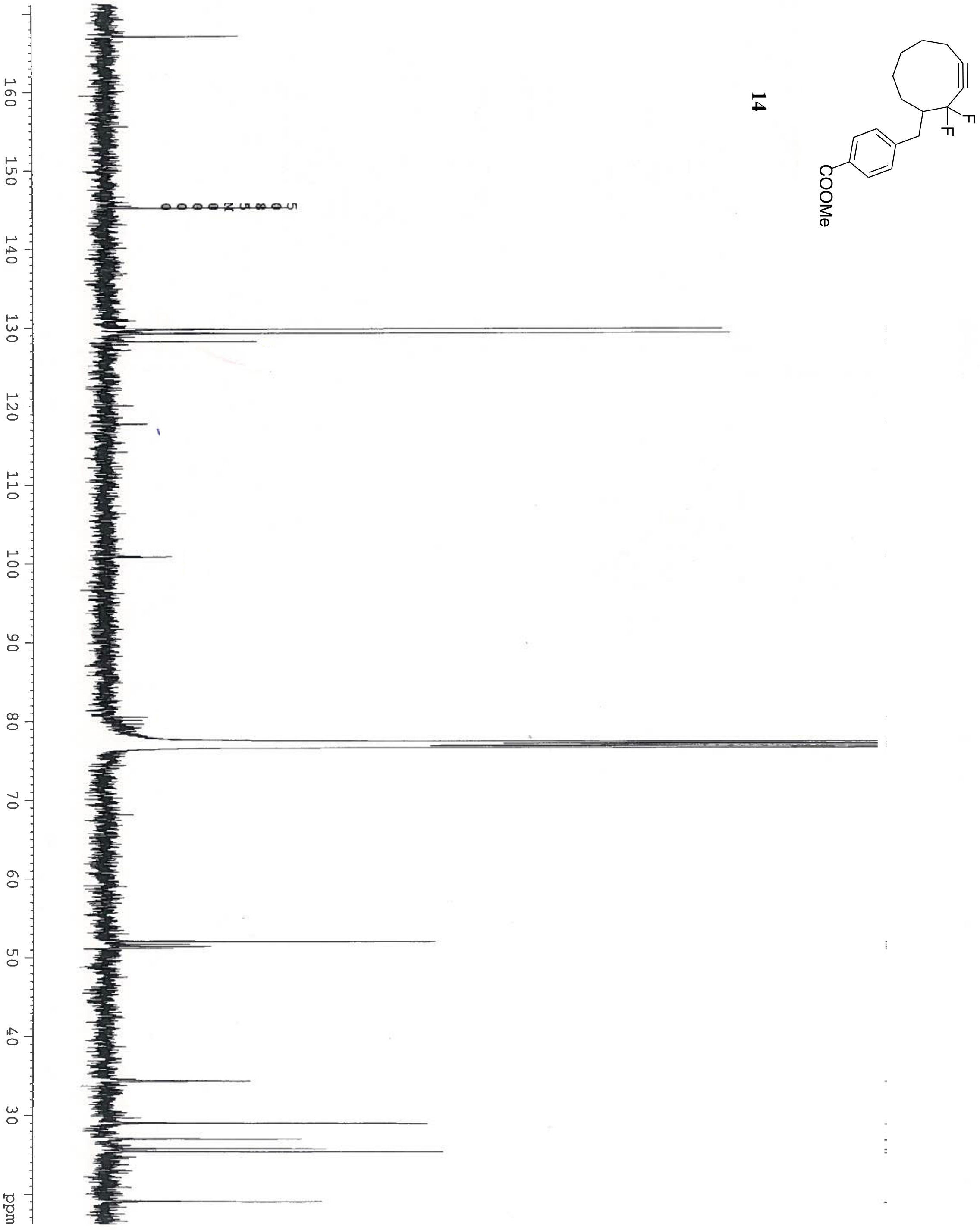


11

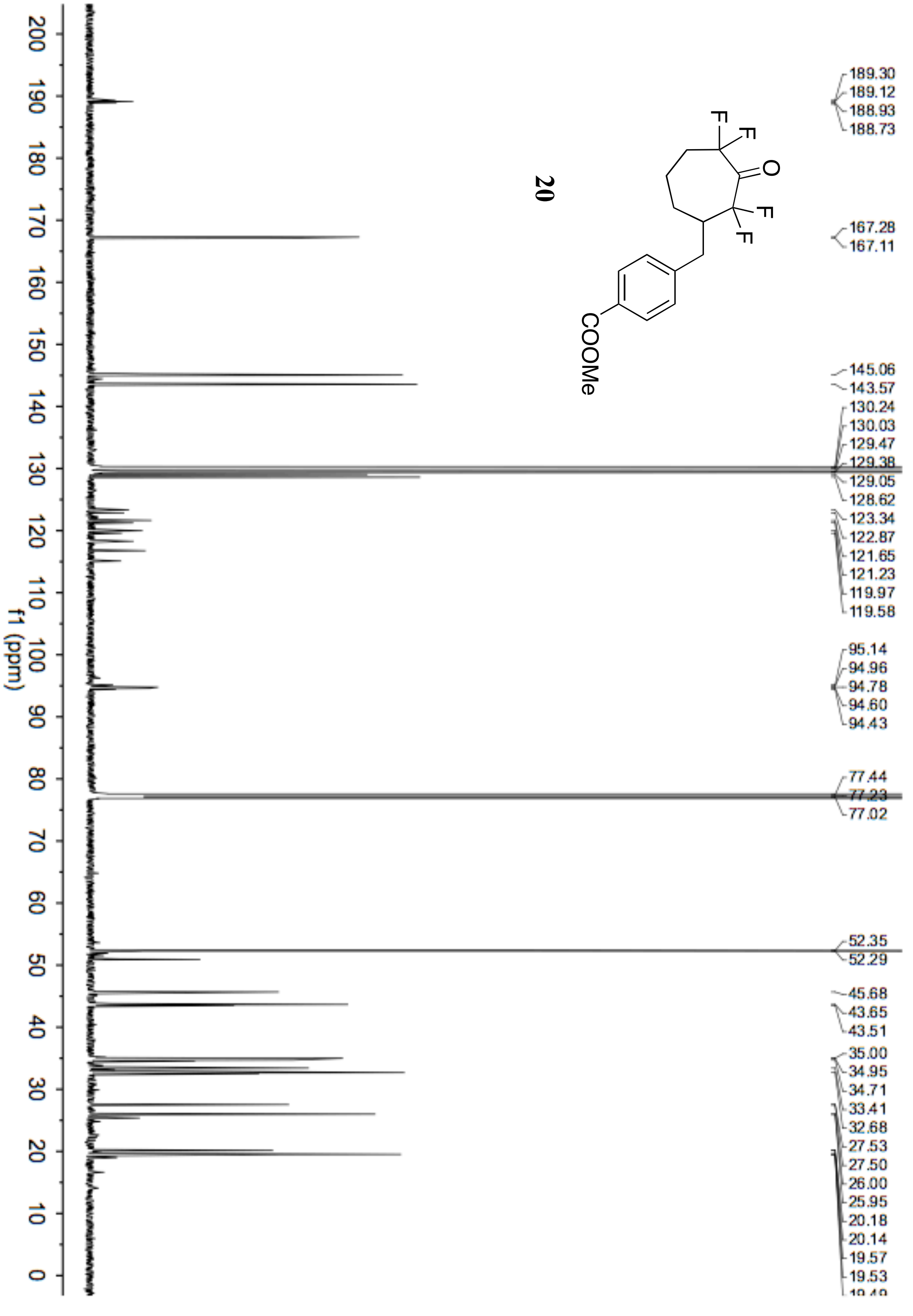
189.30
189.12
188.93
188.73
167.28
167.11
145.06
143.57
130.24
130.03
129.47
129.38
129.05
128.62
123.34
122.87
121.65
121.23
119.97
119.58
95.14
94.96
94.78
94.60
94.43
77.44
77.23
77.02
52.35
52.29
45.68
43.65
43.51
35.00
34.95
34.71
33.41
32.68
27.53
27.50
26.00
25.95
20.18
20.14
19.57
19.53
O
F
F
COOMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
F
F
COOMe
205.69
205.41
205.13
167.13
144.53
130.03
129.51
128.69
121.90
119.40
116.83
52.25
43.66
43.45
43.23
37.33
34.40
34.35
34.30
25.17
25.06
24.79
23.95
23.62
23.56
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

13

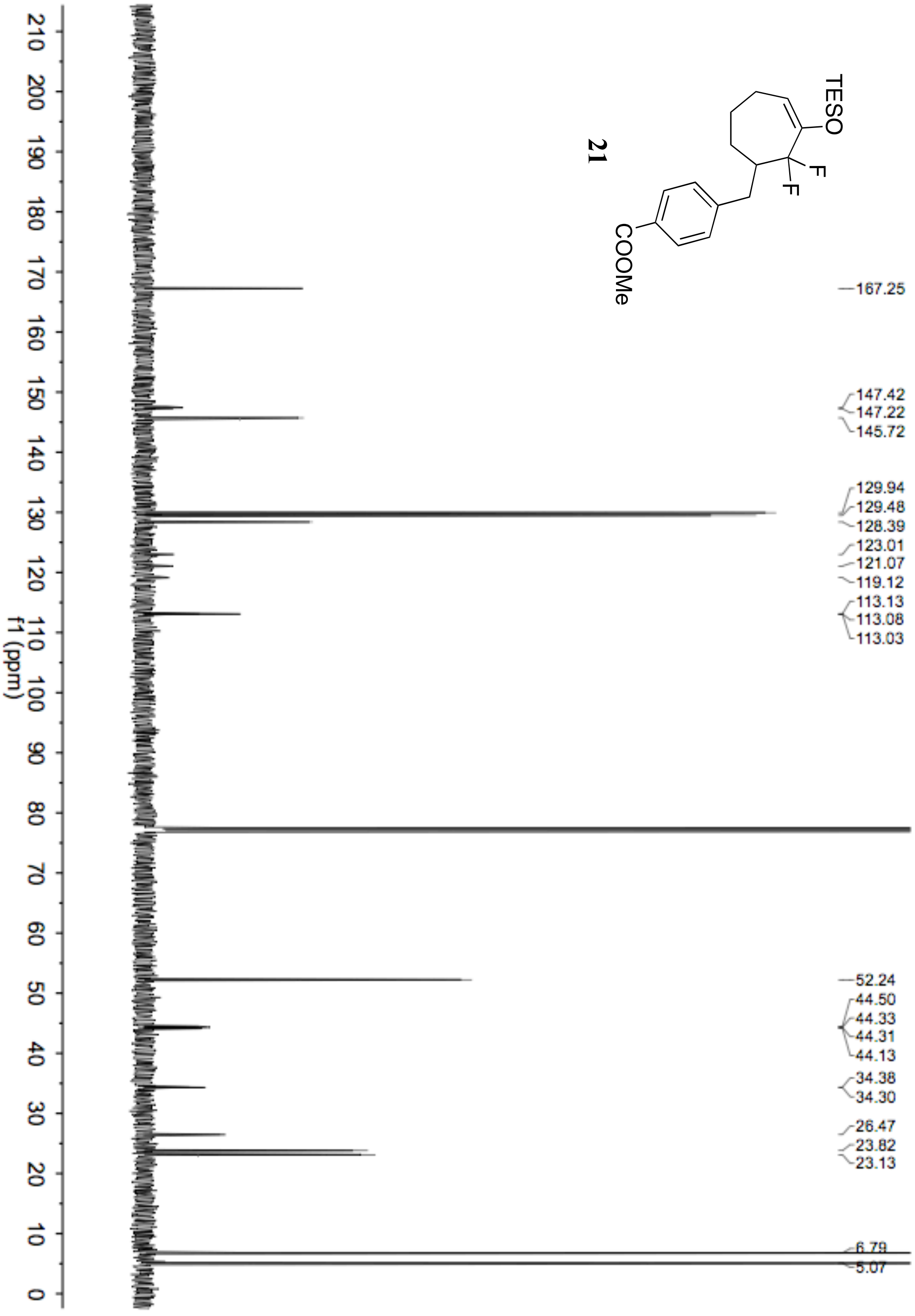


14

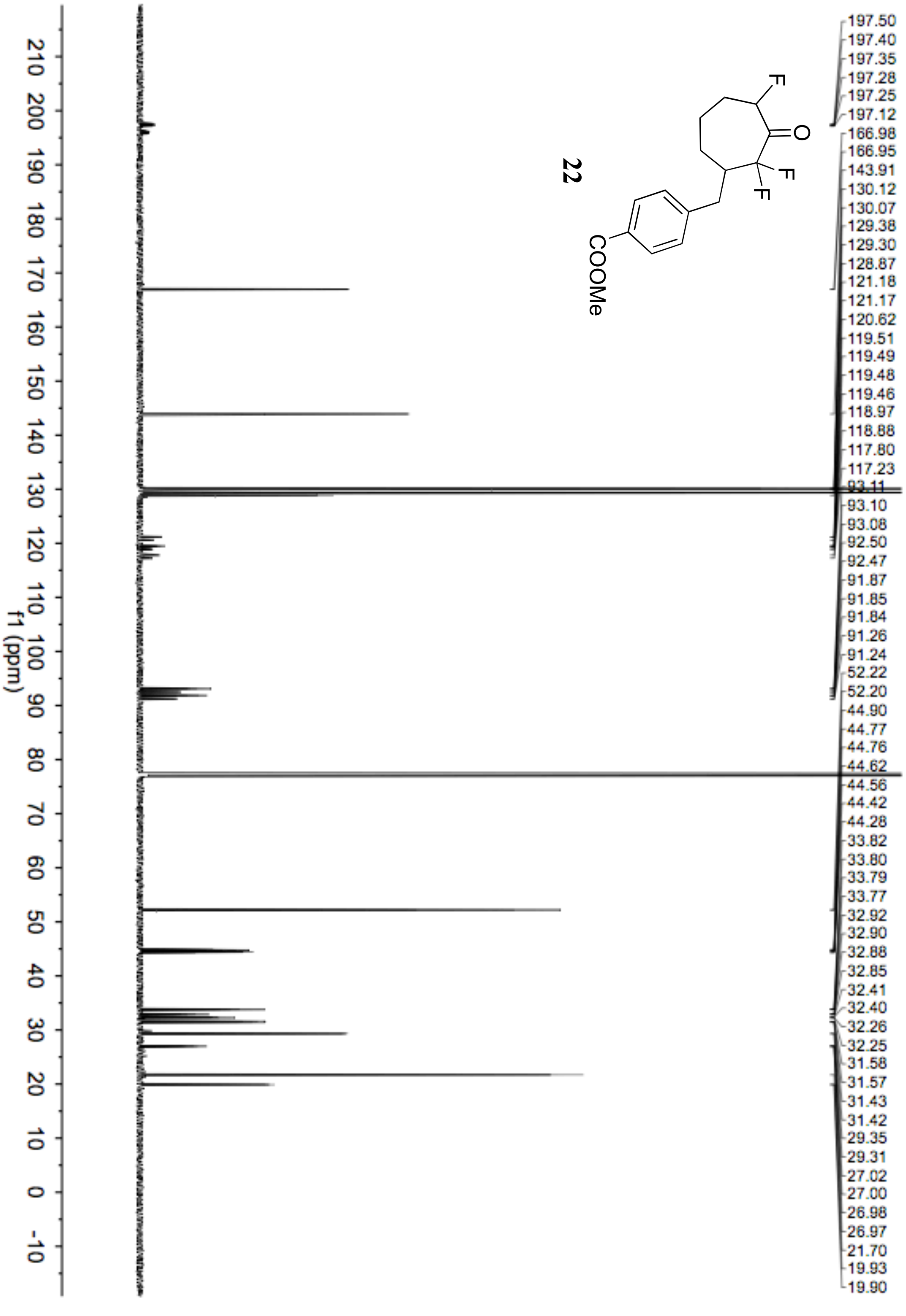


189.30
189.12
188.93
188.73
167.28
167.11
145.06
143.57
130.24
130.03
129.47
129.38
129.05
128.62
123.34
122.87
121.65
121.23
119.97
119.58
95.14
94.96
94.78
94.60
94.43
77.44
77.23
77.02
52.35
52.29
45.68
43.65
43.51
35.00
34.95
34.71
33.41
32.68
27.53
27.50
26.00
25.95
20.18
20.14
19.57
19.53
F
F
O
F
F
COOMe
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

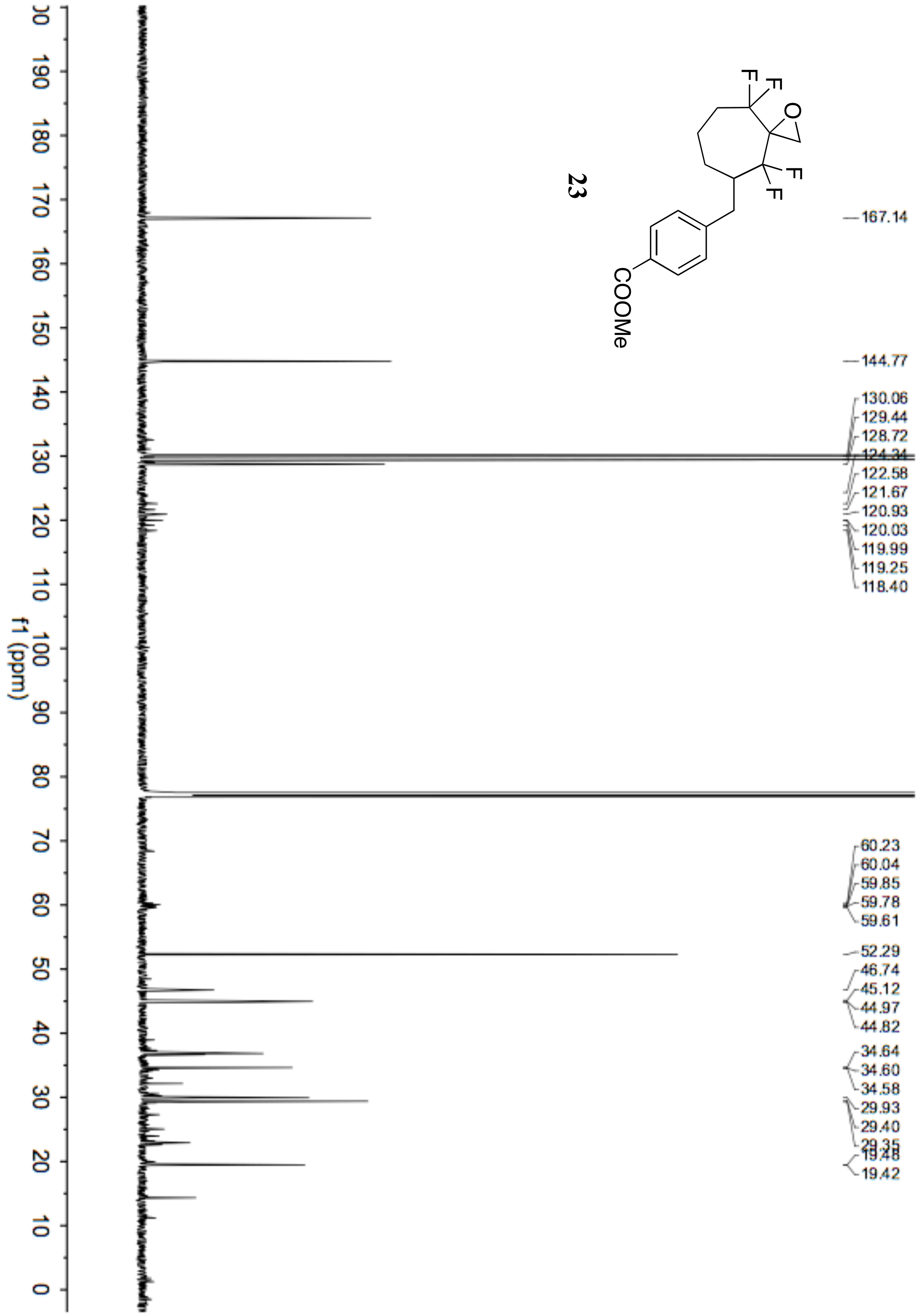
20


21

TESO
F
F
COOMe
167.25
147.42
147.22
145.72
129.94
129.48
128.39
123.01
121.07
119.12
113.13
113.08
113.03
52.24
44.50
44.33
44.31
44.13
34.38
34.30
26.47
23.82
23.13
6.79
5.07
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


197.50
197.40
197.35
197.28
197.25
197.12
166.98
166.95
143.91
130.12
130.07
129.38
129.30
128.87
121.18
121.17
120.62
119.51
119.49
119.48
119.46
118.97
118.88
117.80
117.23
93.11
93.10
93.08
92.50
92.47
91.87
91.85
91.84
91.26
91.24
52.22
52.20
44.90
44.77
44.76
44.62
44.56
44.42
44.28
33.82
33.80
33.79
33.77
32.92
32.90
32.88
32.85
32.41
32.40
32.26
32.25
31.58
31.57
31.43
31.42
29.35
29.31
27.02
27.00
26.98
26.97
21.70
19.93
19.90
F
O
F
F
COOMe
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

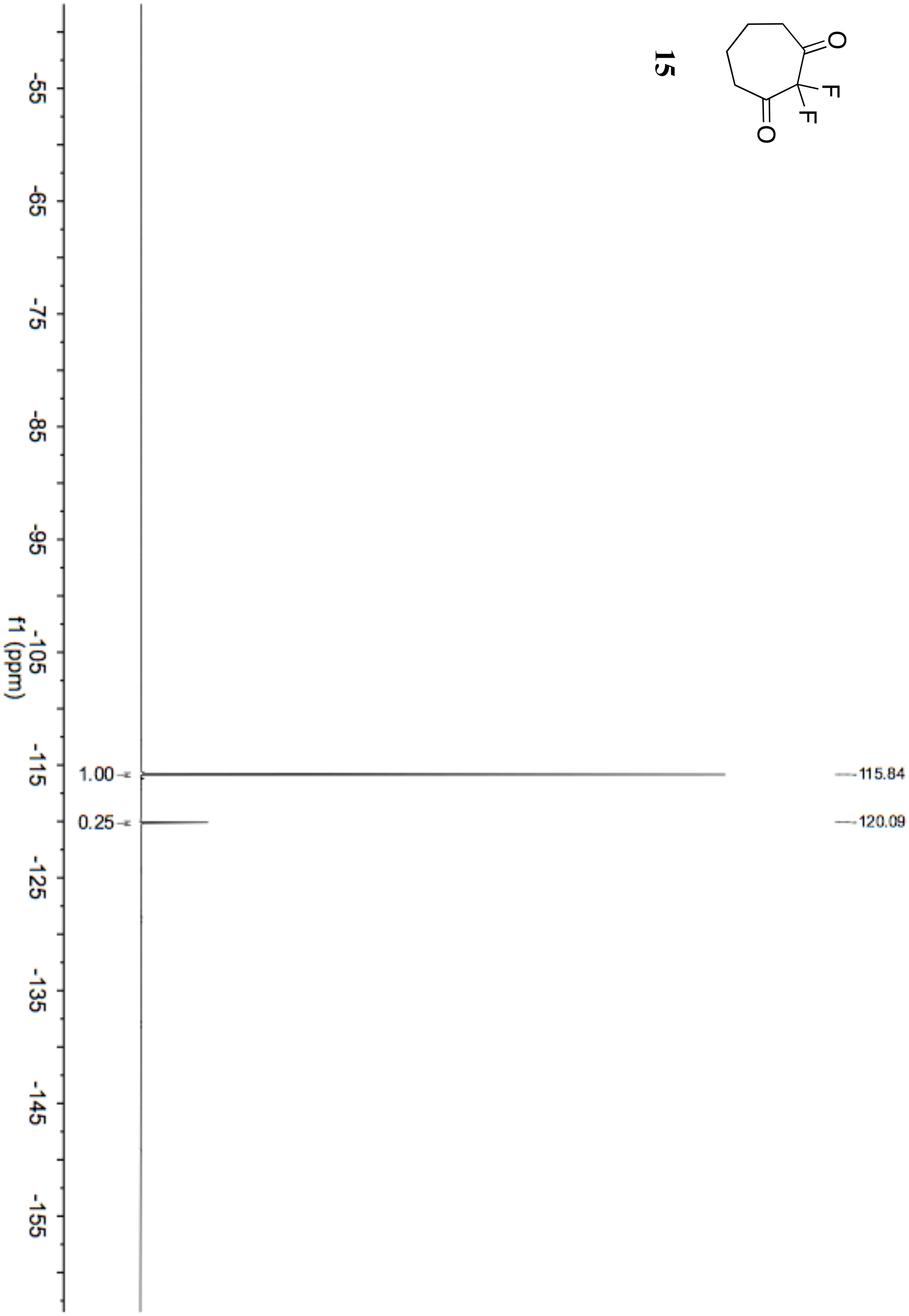
22



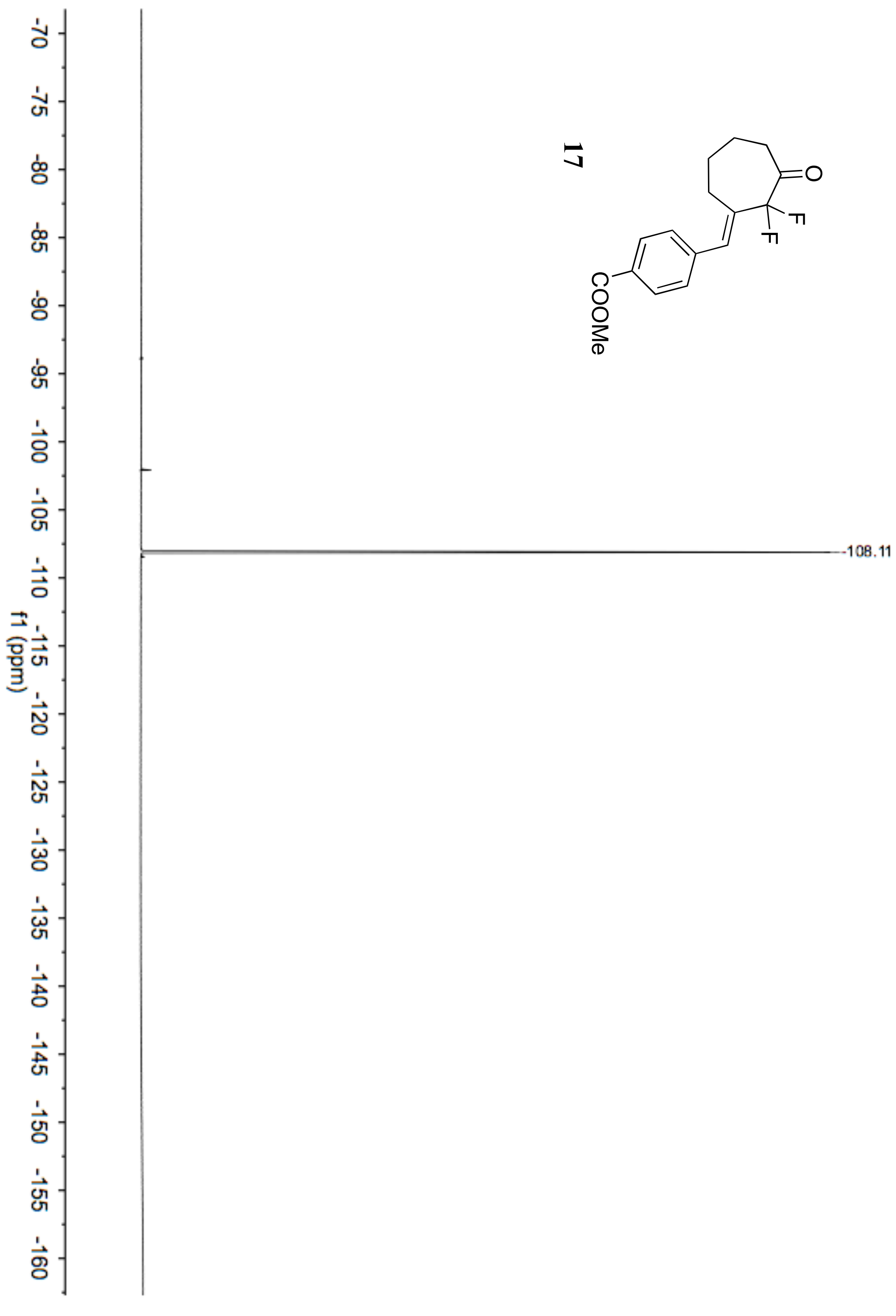
F
F
O
F
F
COOMe
167.14
144.77
130.06
129.44
128.72
124.34
122.58
121.67
120.93
120.03
119.99
119.25
118.40
60.23
60.04
59.85
59.78
59.61
52.29
46.74
45.12
44.97
44.82
34.64
34.60
34.58
29.93
29.40
29.35
19.48
19.42
f1 (ppm)
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

23

^{19}F-NMR Spectra:

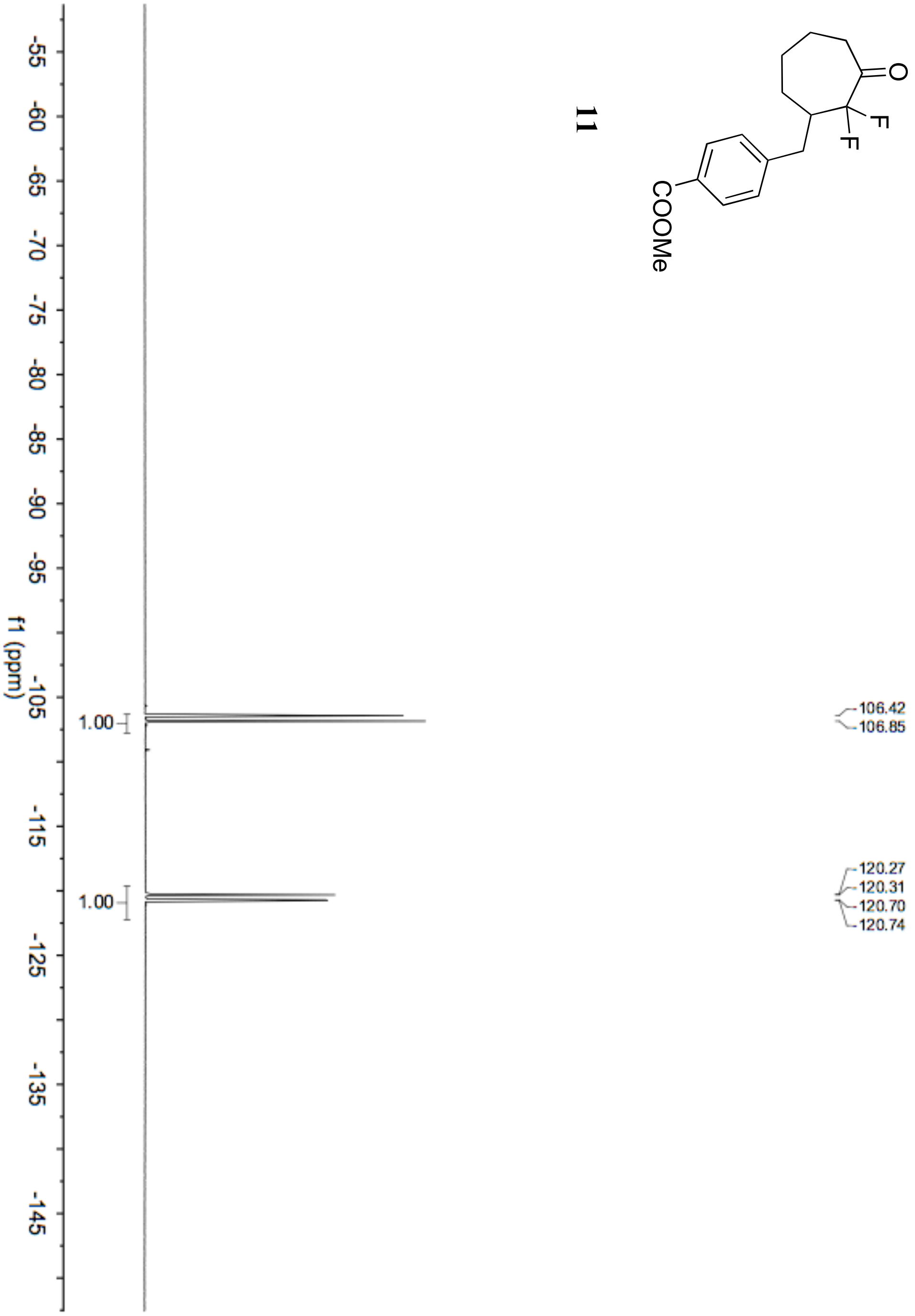


15



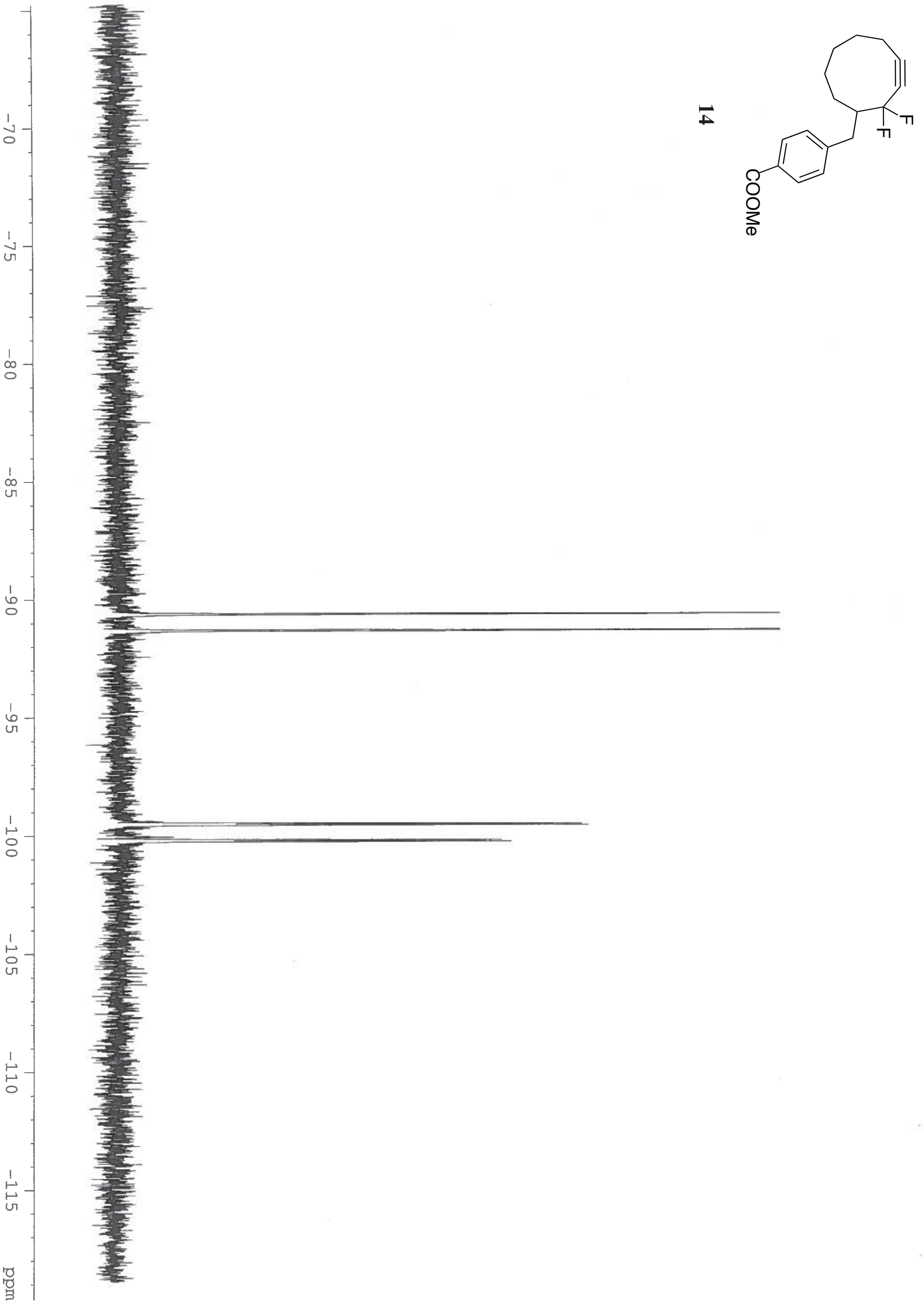
17

O
F
F
COOMe
-108.11
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
f1 (ppm)

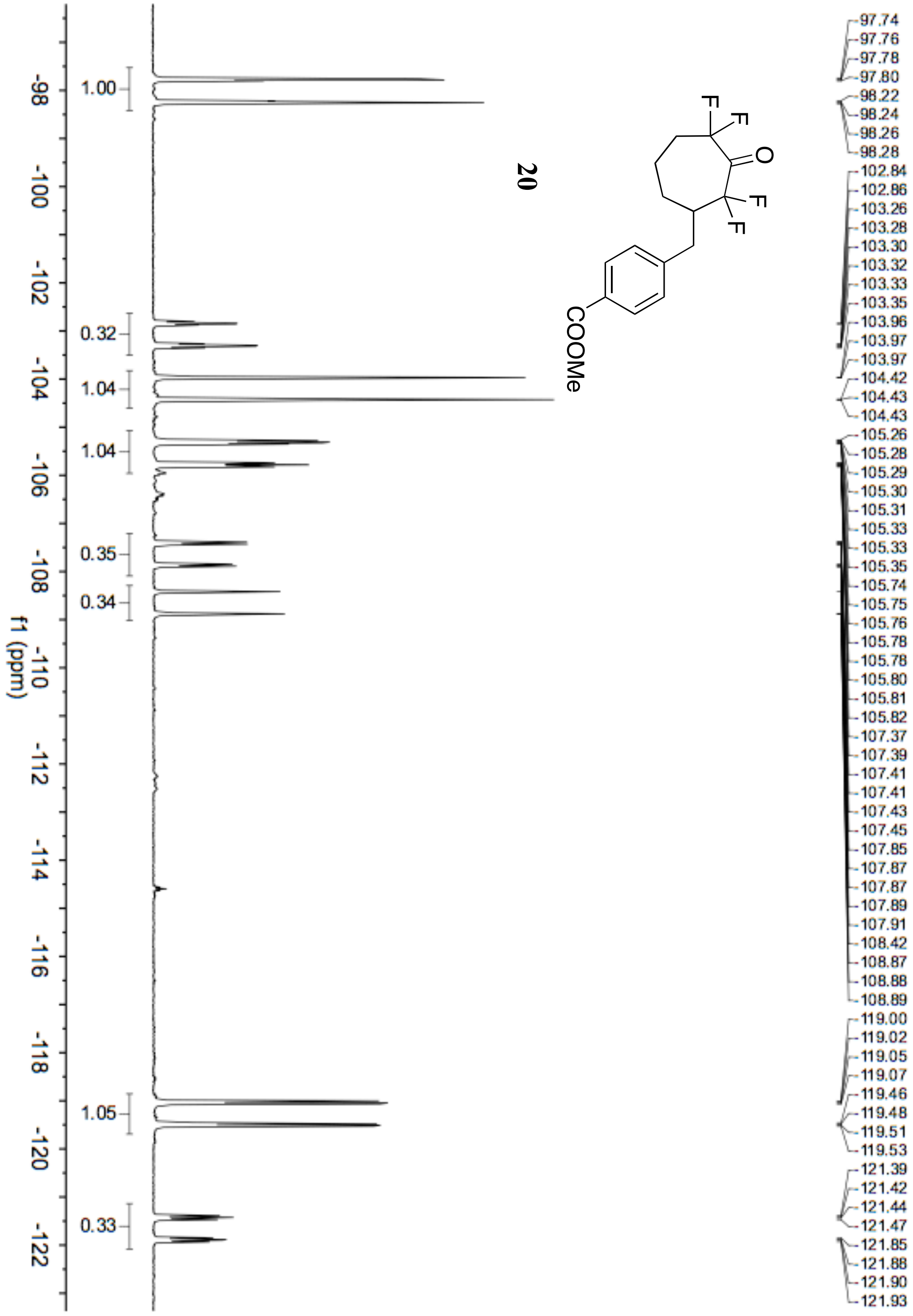


11

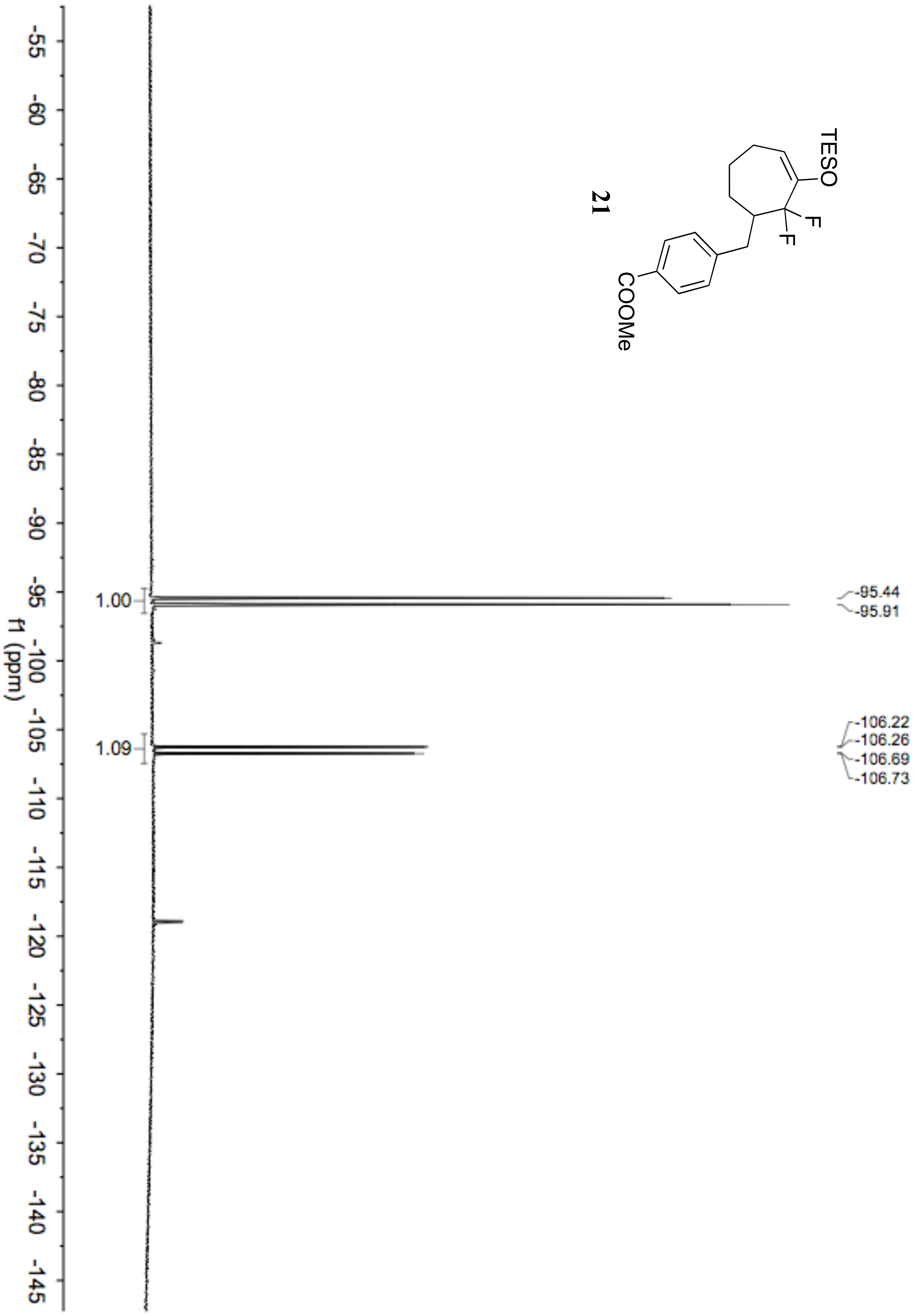
O
F
F
COOMe
-106.42
-106.85
-120.27
-120.31
-120.70
-120.74
1.00
1.00
-55
-60
-65
-70
-75
-80
-85
-90
-95
-105
-115
-125
-135
-145
f1 (ppm)



14

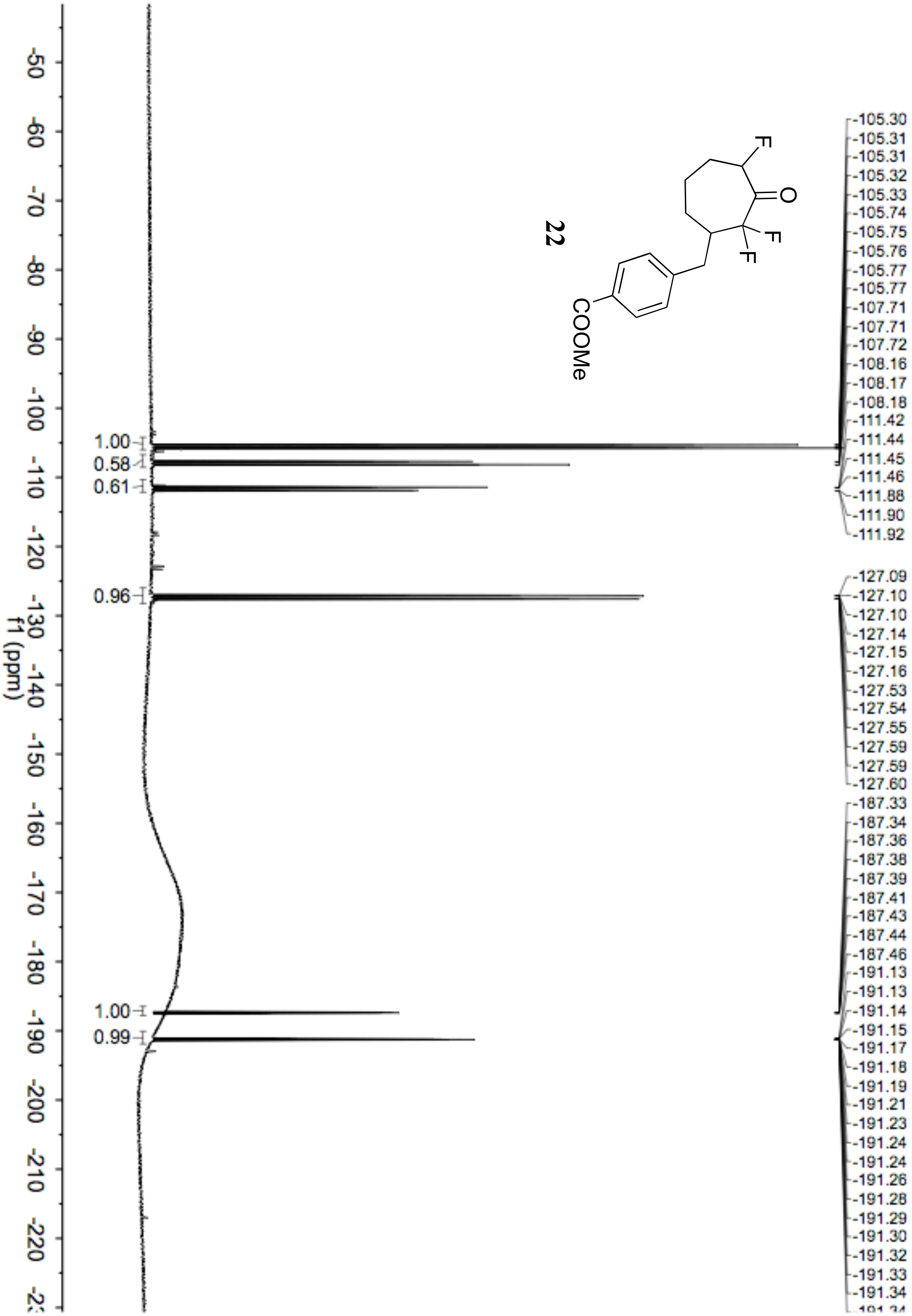

-98
-100
-102
-104
-106
-108
-110
f1 (ppm)
-112
-114
-116
-118
-120
-122
1.00
0.32
1.04
1.04
0.35
0.34
1.05
0.33
F
F
O
F
F
COOMe
97.74
97.76
97.78
97.80
98.22
98.24
98.26
98.28
102.84
102.86
103.26
103.28
103.30
103.32
103.33
103.35
103.96
103.97
103.97
104.42
104.43
104.43
105.26
105.28
105.29
105.30
105.31
105.33
105.33
105.35
105.74
105.75
105.76
105.78
105.78
105.80
105.81
105.82
107.37
107.39
107.41
107.41
107.43
107.45
107.85
107.87
107.87
107.89
107.91
108.42
108.87
108.88
108.89
119.00
119.02
119.05
119.07
119.46
119.48
119.51
119.53
121.39
121.42
121.44
121.47
121.85
121.88
121.90
121.93

20

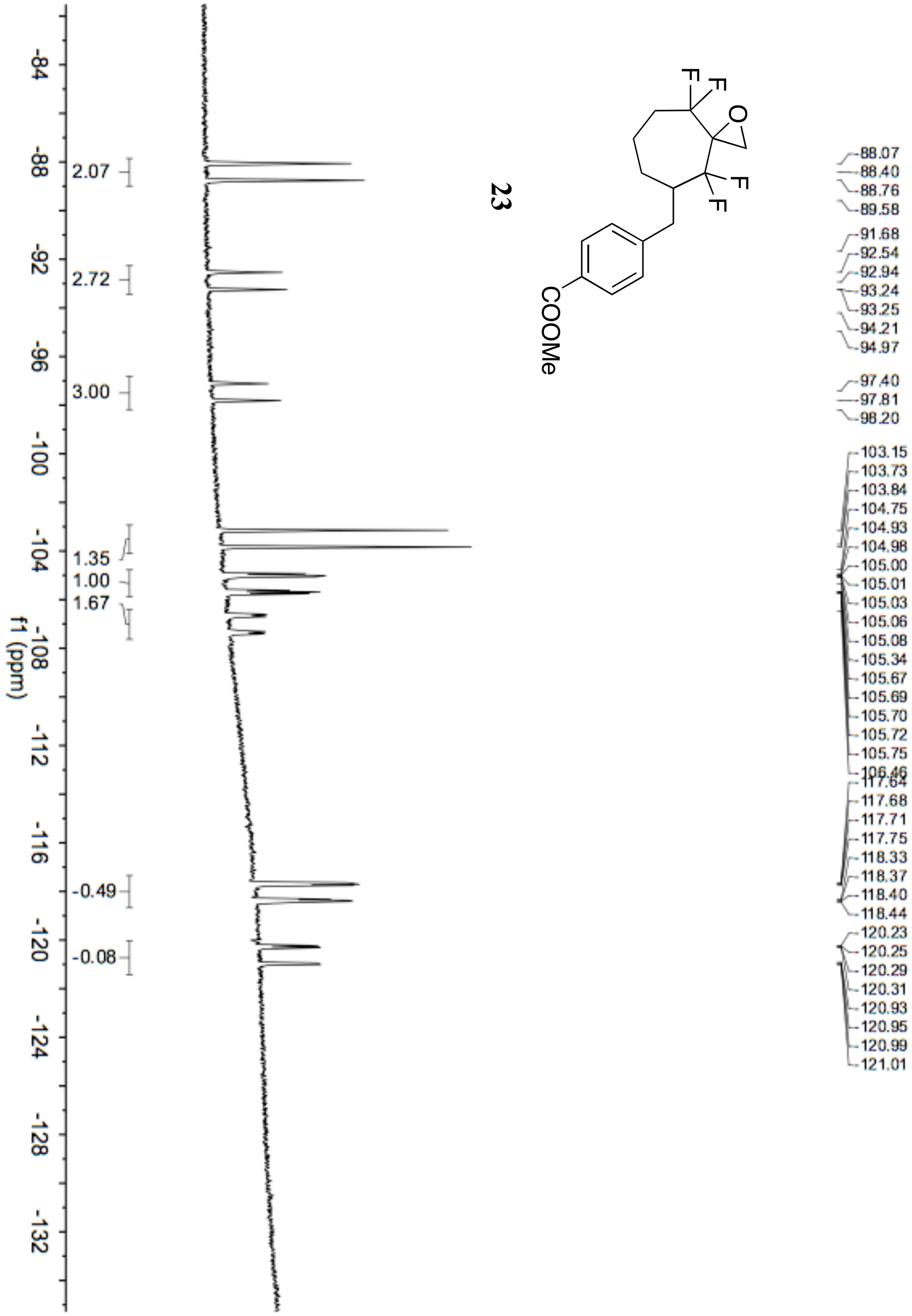


21

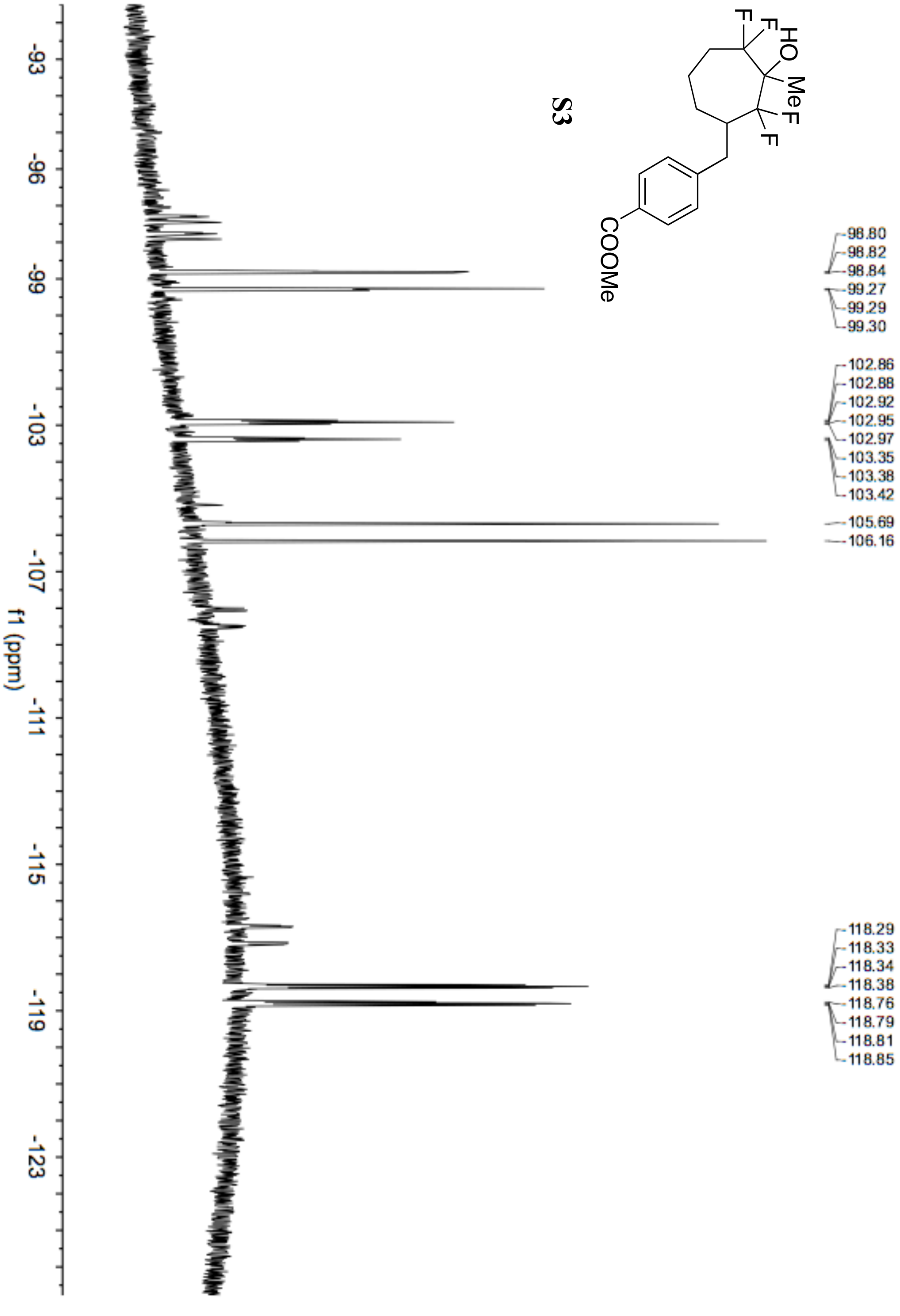
TESO
F
F
COOMe
-95.44
-95.91
-106.22
-106.26
-106.69
-106.73
1.00
1.09
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)


-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)
1.00
0.58
0.61
0.96
1.00
0.99
-105.30
-105.31
-105.31
-105.32
-105.33
-105.74
-105.75
-105.76
-105.77
-105.77
-107.71
-107.71
-107.72
-108.16
-108.17
-108.18
-111.42
-111.44
-111.45
-111.46
-111.88
-111.90
-111.92
-127.09
-127.10
-127.10
-127.14
-127.15
-127.16
-127.53
-127.54
-127.55
-127.59
-127.59
-127.60
-187.33
-187.34
-187.36
-187.38
-187.39
-187.41
-187.43
-187.44
-187.46
-191.13
-191.13
-191.14
-191.15
-191.17
-191.18
-191.19
-191.21
-191.23
-191.24
-191.24
-191.26
-191.28
-191.29
-191.30
-191.32
-191.33
-191.34
F
O
F
F
COOMe

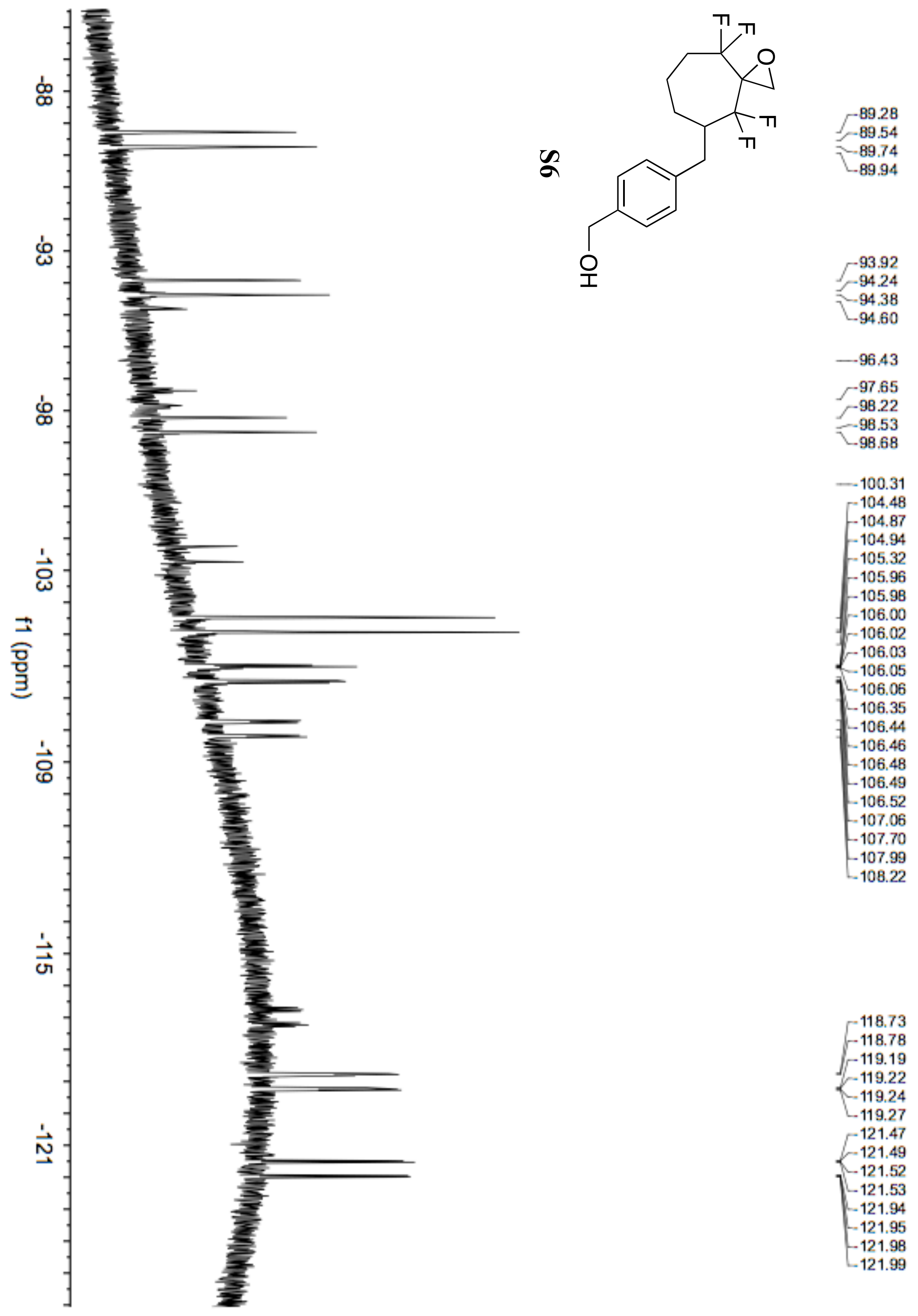
22


O
F
F
F
F
COOMe
-88.07
-88.40
-88.76
-89.58
-91.68
-92.54
-92.94
-93.24
-93.25
-94.21
-94.97
-97.40
-97.81
-98.20
-103.15
-103.73
-103.84
-104.75
-104.93
-104.98
-105.00
-105.01
-105.03
-105.06
-105.08
-105.34
-105.67
-105.69
-105.70
-105.72
-105.75
-106.46
-117.64
-117.68
-117.71
-117.75
-118.33
-118.37
-118.40
-118.44
-120.23
-120.25
-120.29
-120.31
-120.93
-120.95
-120.99
-121.01
2.07
2.72
3.00
1.35
1.00
1.67
-0.49
-0.08
-84
-88
-92
-96
-100
-104
-108
-112
-116
-120
-124
-128
-132
f1 (ppm)

23

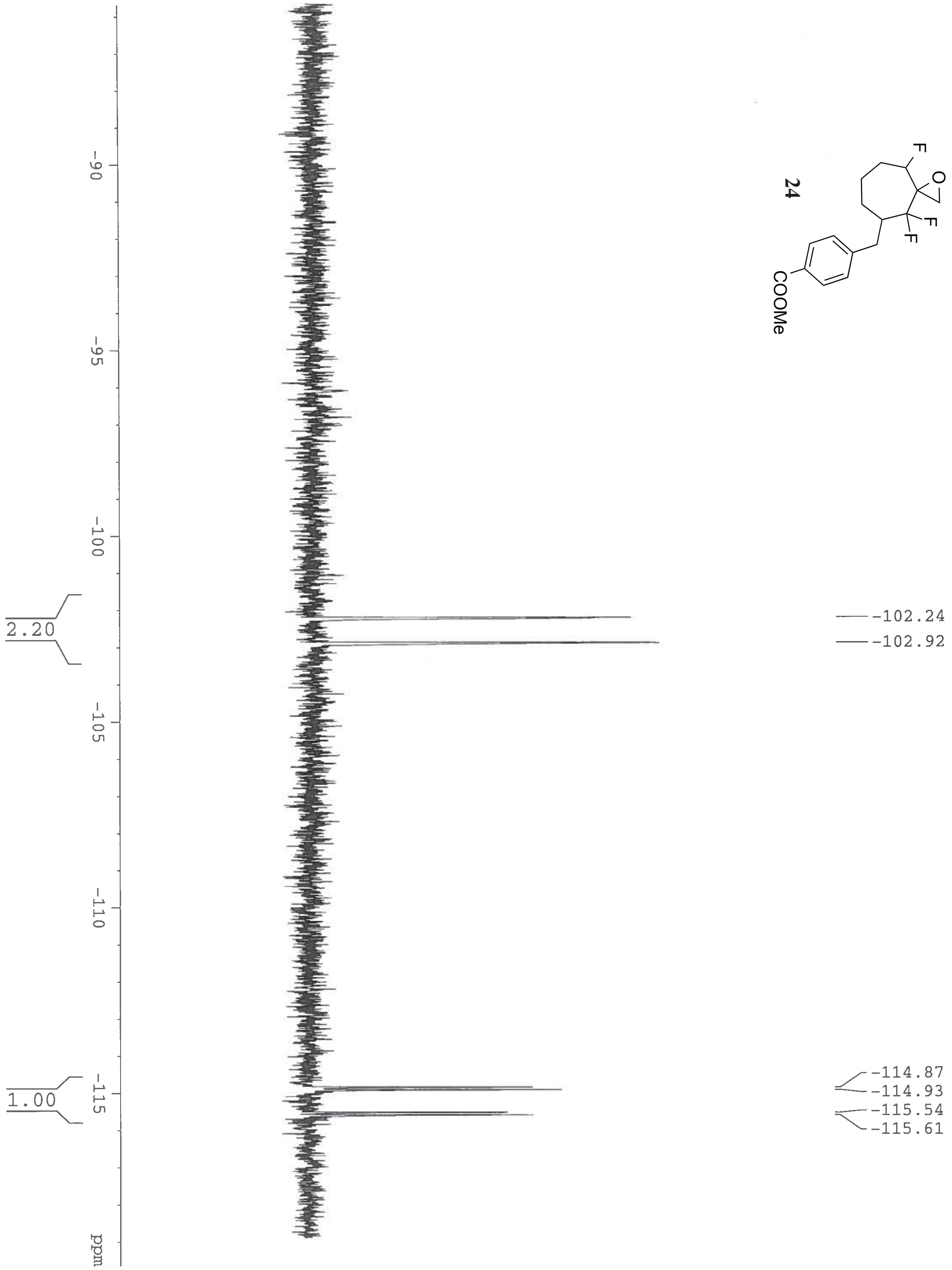

S3

HO
Me
F
F
F
F
COOMe
-98.80
-98.82
-98.84
-99.27
-99.29
-99.30
-102.86
-102.88
-102.92
-102.95
-102.97
-103.35
-103.38
-103.42
-105.69
-106.16
-118.29
-118.33
-118.34
-118.38
-118.76
-118.79
-118.81
-118.85
-93
-96
-99
-103
-107
-111
-115
-119
-123
f1 (ppm)



S6

f1 (ppm)
-88
-93
-98
-103
-109
-115
-121
F
F
O
F
F
OH
-89.28
-89.54
-89.74
-89.94
-93.92
-94.24
-94.38
-94.60
-96.43
-97.65
-98.22
-98.53
-98.68
-100.31
-104.48
-104.87
-104.94
-105.32
-105.96
-105.98
-106.00
-106.02
-106.03
-106.05
-106.06
-106.35
-106.44
-106.46
-106.48
-106.49
-106.52
-107.06
-107.70
-107.99
-108.22
-118.73
-118.78
-119.19
-119.22
-119.24
-119.27
-121.47
-121.49
-121.52
-121.53
-121.94
-121.95
-121.98
-121.99



24

F
O
F
F
COOMe
-90
-95
-100
-105
-110
-115
ppm
2.20
1.00
-102.24
-102.92
-114.87
-114.93
-115.54
-115.61