Amide-Directed Photoredox Catalyzed C-C Bond Formation at Unactivated sp^3 C-H Bonds

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General Procedure:

All reactions were carried out under an atmosphere of argon in over-dried glassware. For substrate synthesis, dichloromethane, diethyl ether and toluene were degassed with argon and passed through a column of neutral alumina and a column of Q5 reactant while all other solvents were freshly distilled. Non-distilled solvents were used in the photoredox catalyzed reactions. Unless otherwise stated, flash column chromatography was performed on Silicycle Inc. silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm), Seebach's Magic or potassium permanganate. ^{1}H NMR and ^{13}C NMR spectra were obtained in CDCl3 at ambient temperature and chemical shifts are expressed in parts per million (δ, ppm). Mass spectra were obtained on an Agilent Technologies 6130 Quadropole Mass Spec (LRMS, ESI + APCI). Infrared spectra were collected on a Nicolet iS-50 FT-IR spectrometer. All alkenes are commercially available and were distilled prior to use although control experiments show that non-distilled alkenes give the same results in the photoredox catalyzed reactions. [Ir(dF-CF_3pp)$_2$dtbbp]PF_6 were purchased from Aspira Scientific, Inc. (Milpitas, CA) or Strem Chemicals, Inc. (Newburyport, MA). A Kessil blue LED (34W maximum, 24 VDC) was used as the light source for the photoredox catalyzed reactions.

Synthesis of Substrate

General Procedure A: Synthesis of Amide from Carboxylic Acid

To a solution of the carboxylic acid (1 equiv.) in DCM (0.3 M) was added oxalyl chloride (1.1 equiv.) dropwise. DMF (3 drops) was added. The mixture was stirred at rt until no more gas bubbles were observed (within 3-4h). The solvent was removed under reduced pressure. The crude acid chloride was dissolved in THF (2 mL per mmol of acid chloride). This mixture was added to commercial aq. NH_3 (14.8M, 2 mL per mmol of acid chloride) dropwise at 0 ^{o}C. The mixture was allowed to warm to rt and stir overnight. The mixture was diluted with EtOAc. The organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford the crude amide, which was used without further purification.

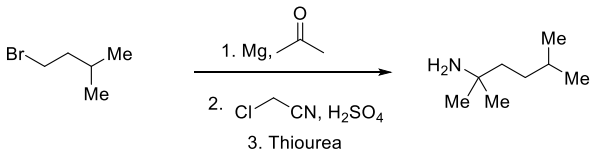
General Procedure B: Synthesis of Amine from Amide

To a solution of the crude amide (1 equiv.) in THF (0.3 M) was added LAH (1.9 equiv.) in portions at 0 ^{o}C. The mixture was allowed to warm to rt and stir overnight. The mixture was cooled to 0 ^{o}C. Water (1 mL per 1 g LAH) was added slowly. 15% NaOH (1 mL per 1 g LAH) was added slowly. Water (3 mL per 1 g) was added. The mixture was allowed to rt and stirred for 15 mins. The mixture was filtered. The solvent in the filtrate was removed under reduced pressure to afford the crude amine, which was used without further purification.

General Procedure C: Trifluoroacetylation of Amine

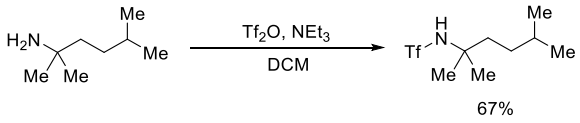
To a solution of the amine (1 equiv.) and NEt_3 (2 equiv.) in DCM (0.25 M) was added trifluoroacetic anhydride (1.02 equiv. or 0.95 equiv. if the amine was not purified in the previous step) at 0 ^{o}C. The mixture was slowly allowed to warm to rt and stir overnight. The reaction was quenched with sat. NH_4Cl. The aqueous layer was extracted with DCM two time. The combined organic layer was washed with sat.

$NaHCO_3$, brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Flash column chromatography afforded the trifluoroacetamide.

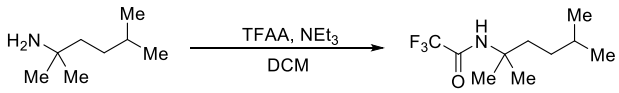


To a solution of acetone (3.20 mL, 43.6 mmol, 1.05 equiv.) in Et_2O (30 mL) was added Grignard reagent in Et_2O (30 mL) freshly prepared from 1-bromo-3-methylbutane(5.0 mL, 41.7 mmol, 1.00 equiv.) and Mg (1.0653 g, 43.8 mmol, 1.05 equiv.) at 0 ^oC. The reaction was allowed to warm to rt and stirred overnight. The reaction was quenched with sat. NH_4Cl solution. The organic and aqueous layer was separated. The organic layer was extracted with Et_2O twice. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to afford 2,5-dimethylhexan-2-ol (3.48 g, 72%). The product was used without further purification.

2,5-dimethylhexan-2-ol (3.44 g, 29.6 mmol, 1 equiv.) and chloroacetonitrile (9.62 mL, 177.6 mmol, 6 equiv.) were dissolved in AcOH (11.3 mL). At 0 ^oC, concentrated sulfuric acid (12.9 mL, 266.4 mmol, 9 equiv.) was added dropwise. The mixture was stirred at rt for 5 h. The mixture was poured into ice-water. The mixture was extracted with DCM three times. The combined organic layer was washed with sat. Na_2CO_3 twice and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. Flash column chromatography (15-20% EtOAc/hexane) afforded 2-chloro-*N*-(2,5-dimethylhexan-2-yl)acetamide as a colorless oil (3.97 g, 73%). A solution of 2-chloro-*N*-(2,5-dimethylhexan-2-yl)acetamide (3.96 g, 19.2 mmol, 1 equiv.), thiourea (1.76 g, 23.1 mmol, 1.20 equiv.) in EtOH/AcOH (39 mL/ 8 mL) was refluxed overnight. The mixture was cooled to rt. Solid NaOH was added until pH is larger than 5. The mixture was extracted with DCM three times. The combined organic layer was extracted with 2M HCl three times. The aqueous layer was basified with NaOH solid and extracted with DCM three times. The combined organic layer was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford crude 2,4-dimethylpentan-2-amine (2.51 g, 100%). It was used without further purification.



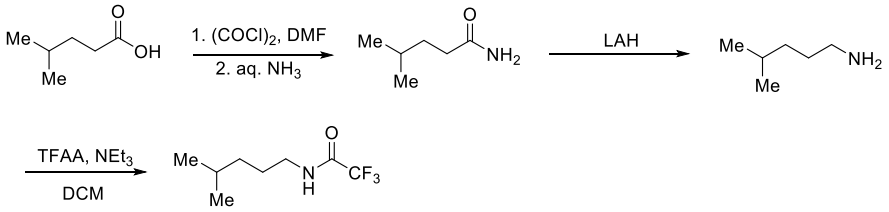
To a solution of 2,4-dimethylpentan-2-amine (1.00 g, 7.74 mmol, 1.0 equiv.) and NEt_3 (1.13 mL, 8.11 mmol, 1.05 equiv.) in DCM (15.5 mL) was added Tf_2O (1.30 mL, 7.74 mmol, 1.0 equiv.) dropwise at –78 ^oC. The mixture was stirred at this temperature for 3 h before quenching with sat. NH_4Cl. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and filtered. Flash column chromatography (3-10% EtOAc/hexane) afforded *N*-(2,5-dimethylhexan-2-yl)-1,1,1-trifluoromethanesulfonamide (1.36 g, 67% as a colorless oil). The spectral data is consistent with the literature.[1]



69%

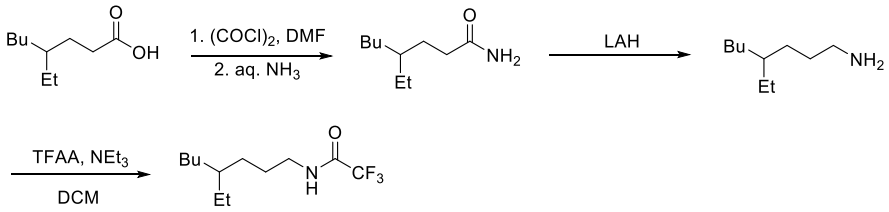
By General Procedure C, N-(2,5-dimethylhexan-2-yl)-2,2,2-trifluoroacetamide (361.9 mg, 69%) was synthesized from 2,4-dimethylpentan-2-amine (303.0 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 6.03 (br, 1H), 1.72-1.68 (m, 2H), 1.49 (septet, *J*= 6.7, 1H), 1.15-1.09 (m, 2H), 0.88-0.86 (d, *J*= 6.7, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.0 (q, *J*= 35.9), 115.6 (q, *J*= 289.4), 55.3, 37.6, 32.8, 28.3, 26.2, 22.5; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.3; Molecular weight [M-H]$^-$: 224.1 (expected), 224.1 (found); IR (cm^{-1}): 3440, 3314 (br), 3091, 2957, 2934, 2873, 1704, 1652.



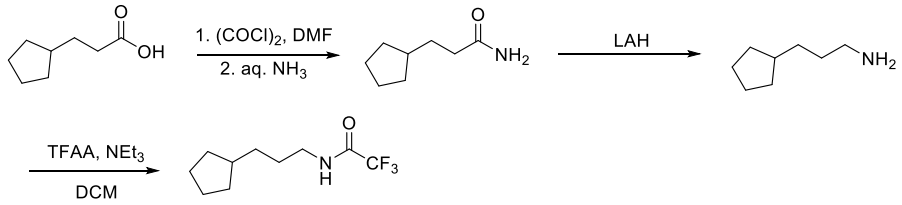
By General Procedure A, 4-methylpentan-1-amine (7.00 g, 90%) was synthesized from 4-methylpentanamide (7.50 g). By General Procedure B, 4-methylpentan-1-amine (4.85 g, 79%) was synthesized from 4-methylpentanamide (7.00 g). By General Procedure C, 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (2.10 g, 45%) was synthesized from 4-methylpentan-1-amine (2.40 g). Flash column chromatography conditions: 10-15% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.77 (br, 1H), 3.31 (q, *J*= 6.9, 2H), 1.60-1.52 (m, 3H), 1.22-1.16 (m, 2H), 0.87 (d, *J*= 6.3, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*= 36.9), 115.9 (q, *J*= 287.6), 40.2, 35.7, 27.6, 26.7, 22.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight [M-H]$^-$: 196.1 (expected), 196.2 (found); IR (cm^{-1}): 3325 (br), 3114, 2959, 2938, 2873, 1703, 1652.



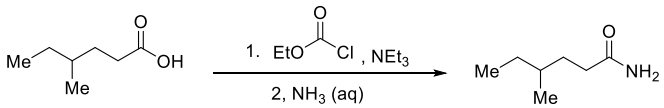
By General Procedure A, 4-ethyloctanamide (1.90 g, 96%) was synthesized from 4-ethyloctanoic acid (2.00 g). By General Procedure B, 4-ethyloctan-1-amine (1.36 g, 92%) was synthesized from 4-ethyloctanamide (1.61 g). By General Procedure C, *N*-(4-ethyloctyl)-2,2,2-trifluoroacetamide (0.946 g, 74%) was synthesized from 4-ethyloctan-1-amine (0.795 g). Flash column chromatography conditions: 7.5-12.5% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.71 (br, 1H), 3.32 (q, *J*= 6.8, 2H), 1.56-1.54 (m, 2H), 1.27-1.21 (m, 11H), 0.87 (t, *J*= 6.9, 3H), 0.82 (t, *J*= 7.2, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 40.4, 38.4, 32.6, 30.0, 28.8, 26.1, 25.7, 23.0, 14.0, 10.7; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight [M-H]$^-$: 252.2 (expected), 252.2 (found); IR (cm^{-1}):3309 (br), 3105, 2959, 2929, 2873, 2860, 1702, 1650.

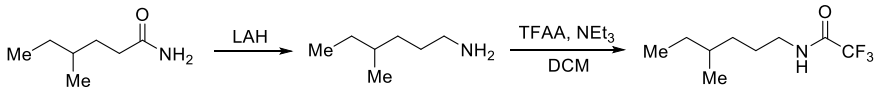


By General Procedure A, 3-cyclopentylpropanamide (2.28 g, 97%) was synthesized from 3-cyclopentylpropanoic acid (2.37 g). By General Procedure B, 3-cyclopentylpropan-1-amine (1.52 g, 74%) was synthesized from 3-cyclopentylpropanamide (2.28 g). By General Procedure C, *N*-(3-cyclopentylpropyl)-2,2,2-trifluoroacetamide (380 mg, 43%) was synthesized from 3-cyclopentylpropanamide (500.0 mg). Flash column chromatography conditions: 15-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.83 (br, 1H), 3.32 (q, *J*= 6.9, 2H), 1.77-1.69 (m, 3H), 1.61-1.46 (m, 6H), 1.34-1.28 (m, 2H), 1.07-1.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*= 36.9), 115.9, (q, *J*= 287.6), 40.2, 39.6, 33.0, 32.5, 28.1, 25.1; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; ; Molecular weight $[M-H]^-$: 222.1 (expected), 222.1 (found); IR (cm^{-1}): 3300 (br), 3105, 2947, 2868, 1701, 1649.

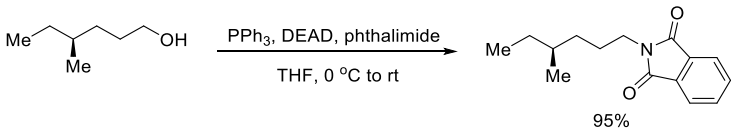


To a solution of 4-methylhexanoic acid (3.04 g, 23.4 mmol, 1 equiv.) and NEt_3 (3.32 mL, 23.8 mmol, 1.02 equiv.) in THF (230 mL) was added ethyl chloroformate (2.27 mL, 23.8 mmol, 1.02 equiv.) dropwise at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 1 h. aq. NH_3 (21.5 mL) was added dropwise. The mixture was allowed to warm to rt and stirred overnight. The mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. Solvent was removed under vacuum to afford 4-methylhexanamide (2.30 g, 76%) as a white solid. It was used without further purification.



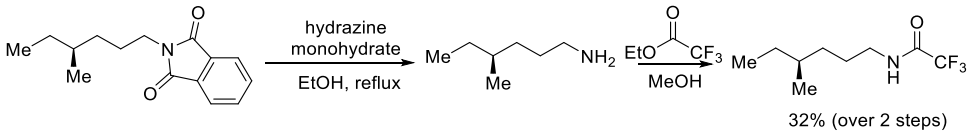
By General Procedure B, 4-methylhexan-1-amine (1.38 g, 76%) was synthesized from 4-methylhexanamide (2.04 g). By General Procedure C, 2,2,2-trifluoro-*N*-(4-methylhexyl)acetamide (0.576 g, 31%) was synthesized from 4-methylhexan-1-amine (1.03 g). Flash column chromatography conditions: 7.5-15% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.72 (br, 1H), 3.32 (q, *J*= 6.8, 2H), 1.62-1.54 (m, 2H), 1.35-1.28 (m, 3H), 1.17-1.08 (m, 2H), 0.86-0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*=36.6), 115.9 (q, *J*= 287.6), 40.3, 34.0, 33.4, 29.2, 26.4, 18.9, 11.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 210.1 (expected), 210.1 (found); IR (cm^{-1}): 3318 (br), 3109, 2961, 2933, 2876, 1702.



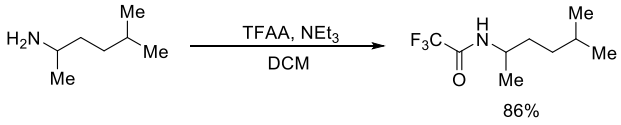
To a solution of commercially available optically active (*S*)-4-methylhexan-1-ol (655.3 mg, 5.64 mmol, 1 equiv.), PPh_3 (1.761 g, 6.77 mmol, 1.2 equiv.) and phthalimide (1.317 g, 6.77 mmol, 1.2 equiv.) in THF (28 mL) was added DEAD (1.05 mL, 6.77 mmol, 1.2 equiv.) at 0 °C dropwise. The mixture was warmed to rt and stirred overnight. Solvent was removed under vacuum. The mixture was filtered through Si gel (50% Et_2O/hex for elution). Flash column chromatography afforded (*S*)-2-(4-methylhexyl)isoindoline-1,3-dione (1.31 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.81-7.79 (m, 2H), 7.69-7,66 (m, 2H), 3.63 (t, *J*= 7.5, 2H), 1.72-1.61 (m, 2H), 1.35-1.28 (m, 3H), 1.14-1.08 (m, 2H), 0.83-0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.4, 133.8, 132.2, 123.1, 38.3, 34.0, 33.5, 29.3, 26.2, 19.0, 11.3; Molecular weight $[M+H]^+$: 246.2 (expected), 246.2 (found); IR (cm^{-1}): 2958, 2934, 2902, 2873, 1775, 1707, 1615.



To a solution of (*S*)-2-(4-methylhexyl)isoindoline-1,3-dione (1.20 g, 4.89 mmol, 1 equiv.) in EtOH (58 mL) was added hydrazine monohydrate (0.835 mL, 17.1 mmol, 3.5 equiv.). The mixture was refluxed overnight. The mixture was cooled to rt. H_2O and 1M NaOH was added to dissolve the solid formed. The mixture was extracted with DCM three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. Solvent was removed under vacuum to afford a 1: 0.63 mixture of (S)-4-methylhexan-1-amine and EtOH (347.4 mg in total). The mixture was dissolved in MeOH (7.2 mL). Ethyl trifluoroacetate (0.190 mL, 1.60 mmol, 1.1 equiv.) was added at 0 °C. The mixture was allowed to warm to rt and stirred overnight. Solvent was removed under vacuum. Flash column chromatography afforded (*S*)-2,2,2-trifluoro-N-(4-methylhexyl)acetamide (325.5 mg, 32% over 2 steps).

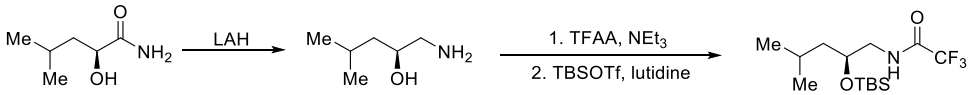
^{1}H NMR ($CDCl_3$, 400 MHz): 6.72 (br, 1H), 3.32 (q, *J*= 6.8, 2H), 1.62-1.54 (m, 2H), 1.35-1.28 (m, 3H), 1.17-1.08 (m, 2H), 0.86-0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*=36.6), 115.9 (q, *J*= 287.6), 40.3, 34.0, 33.4, 29.2, 26.4, 18.9, 11.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 210.1 (expected), 210.1 (found); IR (cm^{-1}): 3318 (br), 3109, 2961, 2933, 2876, 1702.



By General Procedure C, 2,2,2-trifluoro-*N*-(5-methylhexan-2-yl)acetamide (3.14 g, 86%) was synthesized from 5-methylhexan-2-amine (2.00 g). Flash column chromatography conditions: 15% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.54 (br, 1H), 4.00-3.90 (m, 1H), 1.54-1.46 (m, 3H), 1.19-1.14 (m, 5H), 0.86 (d, *J*= 6.7, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.6 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 46.8, 34.9, 34.0, 27.8, 22.3, 20.1; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular Weight $[M-H]^-$: 210.1 (expected), 210.1

(found); IR (cm^{-1}): 3233 (br), 257, 2875, 1738, 1714, 1556, 1460, 1436, 1391, 1363, 1275, 1227, 1185, 1144.



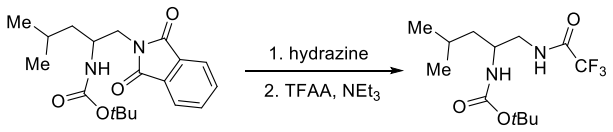
To a solution of the (*S*)-2-hydroxy-4-methylpentanamide[2] (2.54 g, 19.4 mmol, 1 equiv.) in THF (129 mL, 0.15 M) was added LAH (2.20 g, 58.0 mmol, 3 equiv.) in portions at 0 ^{o}C. The mixture was refluxed overnight. The mixture was cooled to 0 ^{o}C. Water (2.2 mL) was added slowly. 15% NaOH (2.2 mL) was added slowly. Water (6.6 mL) was added. The mixture was allowed to rt and stirred for 15 mins. The mixture was filtered. The solvent in the filtrate was removed under reduced pressure to afford crude (*S*)-1-amino-4-methylpentan-2-ol (2.13 g, 94%), which was used without further purification.

To the crude (*S*)-1-amino-4-methylpentan-2-ol (299.0 mg, 2.55 mmol, 1 equiv.) in DCM (10.2 mL, 0.25 M) was added NEt_3 (0.375 mL, 2.68 mmol, 1.05 equiv.) and TFAA (0.34 mL, 2.42 mmol, 0.95 equiv.) at 0 ^{o}C. The mixture was stirred for 30 mins and allowed to warm to rt. The solvent was removed under reduced pressure. The crude product was filtered through Si gel. Flash column chromatography (10-25% EtOAc/hexane) afforded (*S*)-2,2,2-trifluoro-N-(2-hydroxy-4-methylpentyl)acetamide (310.0 mg, 57%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.36 (br, 1H), 3.84-3.78 (m, 1H), 3.50 (ddd, *J*= 13.7, 6.3, 2.7, 1H), 3.15-3.09 (m, 1H), 2.98 (br, 1H), 1.71 (septet, *J*= 6.7, 1H), 1.42-1.35 (m, 1H), 1.25-1.18 (m, 1H), 0.90 (d, *J*= 6.7, 3H), 0.88 (d, *J*= 6.7, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.5 (q, *J*= 37.1), 115.5 (q, *J*= 287.4), 67.9, 45.6, 43.4, 24.0, 22.7, 21.5; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.4; Molecular weight $[M-H]^-$: 212.1 (expected), 212.1 (found); IR (cm^{-1}): 3420, 3311 (br), 3104, 2959, 2937, 2874, 1703.

To (*S*)-2,2,2-trifluoro-N-(2-hydroxy-4-methylpentyl)acetamide (200.5 mg, 0.94 mmol, 1 equiv.) in DCM (19 mL, 0.05 M) was added lutidine (0.326 mL, 2.82 mmol, 3 equiv.) At 0 ^{o}C, TBSOTf (0.431 mL, 0.188 mmol, 2 equiv.) was added. The mixture was slowly warmed to rt. The mixture was stirred at rt for 3.5 h. The reaction was quenched with sat. NH_4Cl. The organic and aqueous layers were separated. The aqueous layer was extracted with DCM twice. The combined organic layer was washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Flash column chromatography (5% EtOAc/hex) afforded (*S*)-N-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)-2,2,2-trifluoroacetamide (285.9 mg, 93%).

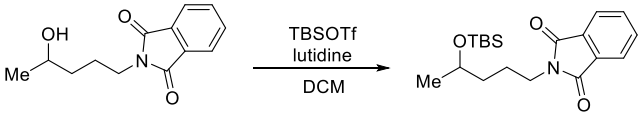
^{1}H NMR ($CDCl_3$, 400 MHz): 6.58 (br, 1H), 3.93-3.93 (m, 1H), 3.51-3.46 (m, 1H), 3.28-3.22(m, 1H), 1.68-1.55 (m, 1H), 1.42-1.25 (m, 2H), 0.87-0.89 (m, 15H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.1 (q, *J*= 36.4), 115.9 (q, *J*= 288.1), 68.6, 45.0, 44.4, 25.7, 24.3, 23.0, 22.6, 17.9, −4.5, −4.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 326.2 (expected), 326.2 (found); IR (cm^{-1}): 3434, 3322 (br), 3106, 2957, 2931, 2885, 2859, 1705.



Anhydrous N_2H_4 (100 µL, 3.29 mmol, 2.0 equiv.) was added to a solution of *tert*-butyl (1-(1,3-dioxoisoindolin-2-yl)-4-methylpentan-2-yl)carbamate[3] (570 mg, 1.65 mmol, 1.0 equiv.) in anhydrous EtOH (17 mL) and anhydrous CH_2Cl_2 (3 mL). The reaction mixture was heated at 60 °C for 12 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with Et_2O. The filtrate was concentrated under reduced pressure. The crude amine was used in the subsequent step without further purification.

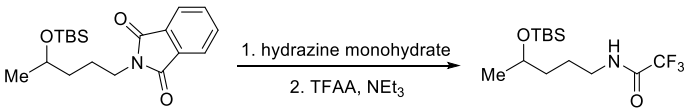
TFAA (0.26 mL, 1.82 mmol, 1.1 equiv.) was added dropwise to a solution of crude and Et_3N (0.46 mL, 3.30 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (5.5 mL) at 0 °C. The reaction mixture was raised to room temperature. The reaction mixture was stirred at this temperature for 5 h and then diluted with H_2O (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (55-65% Et_2O/hexane) to give *tert*-butyl (4-methyl-1-(2,2,2-trifluoroacetamido)pentan-2-yl)carbamate as a white solid (369 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (br, 1H), 7.36 (br, 0.5H, rotamer), 5.30 (br, 0.5H, rotamer), 4.75 (d, *J*= 7.4, 1H), 3.85-3.82 (m, 1H), 3.37-3.23 (m, 2H), 1.67 (septet, *J*= 6.7, 1H), 1.43-1.23 (m, 11H), 0.90-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7 (q, *J*= 37.1), 157.2, 115.9 (q, *J*= 287.7), 80.2, 48.2, 46.5, 41.4, 28.1, 24.7, 22.8, 21.8; Molecular weight $[M+Na]^+$: 335.1558 (expected), 335.1543 (found); IR (cm^{-1}): 3340, 2962, 2935, 1695, 1678, 1527, 1188, 1162, 907, 731.



To a solution of 2-(4-hydroxypentyl)isoindoline-1,3-dione[4] (450.0 mg, 1.93 mmol, 1 equiv.) and lutidine (0.70 mL, 6.01, 3.1 equiv.) in DCM (9.5 mL) was added TBSOTf (0.56 mL, 2.44 mmol, 1.26 equiv.) at 0 ^{o}C. The mixture was stirred at rt for 3h. The reaction was quenched with 1 M HCl. The organic and aqueous layer were separated. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. Flash column chromatography (10-30% Et_2O/hexane) afforded 2-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)isoindoline-1,3-dione (605 mg, 100%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.82-7.80 (m, 2H), 7.68-7.66 (m, 2H), 3.79 (sextet, *J*=6.0, 1H), 3.65 (t, *J*= 7.3, 2H), 1.80-1.71 (m, 2H), 1.46-1.38 (m, 2H), 1.08 (d, *J*=5.9, 3H), 0.83 (s, 9H), 0.00 (6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 168.4, 133.8, 132.2, 123.1, 67.8, 38.1, 36.7, 25.9, 24.8, 23.8, 18.1, –4.41, –4.76; Molecular weight $[M-H]^-$: 348.2 (expected), 348.2 (found); IR (cm^{-1}): 3044, 2954, 2929, 2884, 2856, 1775, 1712.

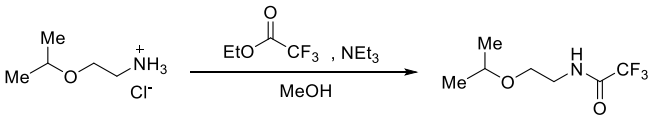


To a solution of 2-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)isoindoline-1,3-dione (589.2 mg, 1.88 mmol., 1 equiv.) in EtOH (23 mL) was added hydrazine monohydrate (0.32 mL, 6.58 mmol, 3.5 equiv.). The mixture was refluxed overnight. The mixture was cooled to rt. Water and 1 M NaOH were added. The mixture was extracted with DCM three times. The combined organic layer was washed with brine, dried

over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford crude 4-((*tert*-butyldimethylsilyl)oxy)pentan-1-amine (343.4 mg, 84%).

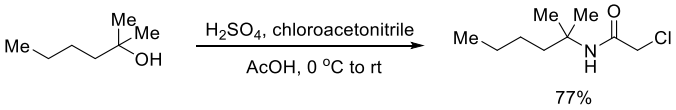
To a solution of the crude 4-((*tert*-butyldimethylsilyl)oxy)pentan-1-amine (300.8 mg, 1.38 mmol, 1 equiv.), NEt_3 (0.196 mL, 1.41 mmol, 1.02 equiv.) in DCM (7 mL) was added TFAA (0.182 mL, 1.31 mmol, 0.95 equiv.) at 0 ^oC dropwise. The mixture was allowed to warm to rt. The mixture was stirred for 3 h. Solvent was removed under vacuum. The mixture was filtered through Si gel. Flash column chromatography (12-22% Et_2O/hexane) afforded N-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)-2,2,2-trifluoroacetamide (396.5 mg, 92%).

^1H NMR ($CDCl_3$, 400 MHz): 6.94 (br, 1H), 3.89-3.82 (m, 1H), 3.46-3.38 (m, 1H), 3.31-3.25 (m, 1H), 1.72-1.54 (m, 2H), 1.48-1.43 (m, 2H), 1.12 (d, *J*=6.3, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.2 (q, *J*= 36.6), 115.9 (q, *J*= 287.6), 67.9, 39.9, 36.3, 25.8, 24.7, 23.3, 18.0, −4.56, −4.90; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 312.2 (expected), 312.2 (found); IR (cm^{-1}): 3313 (br), 2957, 2931, 2860, 1708, 1558, 1463, 1433, 1371, 1255, 1229, 1184, 1148, 1066, 1005.



To a solution of 2-isopropoxyethan-1-aminium chloride (2.50 g, 17.9 mmol, 1.0 equiv.) in MeOH (90 mL) was added NEt_3 (2.75 mL, 19.7 mmol, 1.1 equiv.) and then ethyl trifluoroacetate (2.35 mL, 19.7 mmol, 1.1 equiv.). The mixture was stirred at rt overnight. Solvent was removed under reduced pressure. The crude product was filtered through Si gel. Flash column chromatography (25-35% Et_2O/hexane) afforded 2,2,2-trifluoro-*N*-(2-isopropoxyethyl)acetamide (2.90 g, 81%) as a colorless oil.

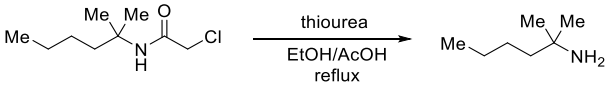
^1H NMR ($CDCl_3$, 400 MHz): 6.94 (br, 1H), 3.55 (septet, *J*= 6.1, 1H), 3.51-3.44 (m, 4H), 1.10 (d, *J*= 6.3, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.2 (q, *J*= 37.1), 115.8 (q, *J*= 287.6), 72.0, 65.2, 39.9, 21.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.3; Molecular weight $[M-H]^-$: 198.1 (expected), 198.1 (found); IR (cm^{-1}): 3317 (br), 3103, 2976, 2937, 2874, 1706, 1553, 1455, 1382, 1371, 1337, 1209, 1151, 1094.



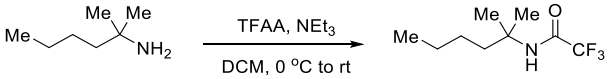
To a solution of 2-methylhexan-2-ol (3.00 g, 25.8 mmol, 1 equiv.) and chloroacetonitrile (9.8 mL, 0.155 mmol, 6.0 equiv.) in AcOH (11.5 mL) was added conc. H_2SO_4 (13.15 mL, 232.2 mmol, 9 equiv.) at 0 ^oC dropwise. The mixture was allowed to warm to rt and stir for 5 h. The mixture was poured into ice/water mixture. The mixture was extracted with DCM three times. The combined organic layer was washed with sat. Na2CO3 twice and brine, dried over Na_2SO_4 and filtered. Solvent was removed under vacuum. Flash column chromatography (20% EtOAc/hexane) afforded 2-chloro-*N*-(2-methylhexan-2-yl)acetamide (3,81 g, 77%).

^1H NMR ($CDCl_3$, 400 MHz): 6.27 (br, 1H), 3.89 (s, 2H), 1.66-1.62 (m, 2H), 1.30 (s, 6H), 1.27-1.17 (m, 4H), 0.86 (t, *J*= 7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 164.7, 54.2, 32.9, 40.0, 26.5, 26.1, 22.9, 14.0;

Molecular weight [M-H]$^-$: 190.1 (expected), 190.1 (found); IR (cm^{-1}): 3413, 3296, 3084, 2957, 2932, 2873, 2862, 1657.

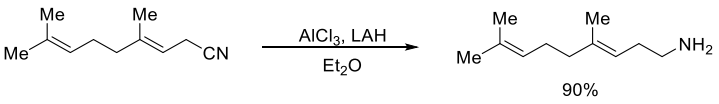


A solution of 2-chloro-*N*-(2-methylhexan-2-yl)acetamide (3.50 g, 18.3 mmol) and thiourea (1.67 g, 21.9 mmol, 1.2 equiv.) in EtOH/AcOH (44 mL, 4.9:1) was refluxed overnight. The mixture was diluted with water. Solid NaOH was added until pH of the solution is less than 5. The mixture was extracted with DCM three times. The combined organic layer was extracted with 2M HCl twice. The combined acidic layer was basified with solid NaOH until pH is higher than 10 and was extracted with DCM three times. The combined organic layer was dried over Na_2SO_4 and filtered. Solvent was removed under vacuum to afford 2-methylhexan-2-amine (705 mg, 34%). It was used without further purification. JC-2322

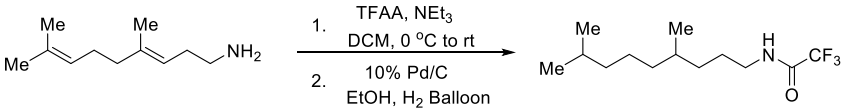


By General Procedure C: 2,2,2-trifluoro-N-(2-methylhexan-2-yl)acetamide (218.7 mg, 48%) was synthesized from 2-methylhexan-2-amine (248.0 mg).

^{1}H NMR ($CDCl_3$, 400 MHz): 6.05 (br, 1H), 1.72-1.68 (m, 2H), 1.35 (s, 6H), 1.31-1.22 (m, 4H), 0.89 (t, *J*= 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz): 156.0 (q, *J*=35.8), 115.6 (q, *J*= 289.3.), 53.5, 39.6, 26.2, 26.0, 22.8, 13.4 ; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.3; Molecular weight [M-H]$^-$: 210.1 (expected), 210.1 (found); IR (cm^{-1}): 3441, 3320, 3095, 2959, 2932, 2865, 1704.



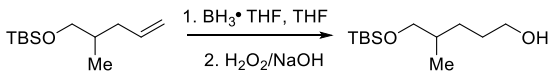
To a solution of LAH (0.226 g, 5.96 mmol, 1 equiv.) in Et_2O (6 mL) was added anhydrous $AlCl_3$ (0.793 g, 5.95 mmol, 1 equiv.) at 0 °C in portions. The mixture was stirred at 10 mins at 0 °C. Homogernanonitrile[5] (0.9711 g, 5.95 mmol, 1 equiv.) in Et_2O (1 mL) was added via cannula. The mixture was stirred at 0 °C for 1 h and was warmed to rt. The mixture was stirred overnight. The reaction was quenched by 1M NaOH. The mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. Crude (*E*)-4,8-dimethylnona-3,7-dien-1-amine (0.900 g, 90%) was used without further purification.



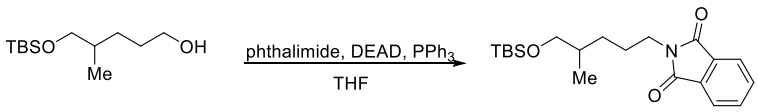
To a solution of (*E*)-4,8-dimethylnona-3,7-dien-1-amine (0.755 g, 4.51 mmol, 1 equiv.) and NEt_3 (0.642 mL, 4.61 mmol, 1.02 equiv.) in DCM (18 mL) was added TFAA (0.595 mL, 4.28 mmol, 0.95 equiv.) dropwise at 0 °C. The mixture was slowly warmed to rt and stirred overnight. The solvent was removed under vacuum. The mixture was filtered through silica gel. Flash column chromatography (4-12%

Et_2O/hex) afforded (*E*)-N-(4,8-dimethylnona-3,7-dien-1-yl)-2,2,2-trifluoroacetamide (0.87 g, 73%). To a solution of (*E*)-N-(4,8-dimethylnona-3,7-dien-1-yl)-2,2,2-trifluoroacetamide (509.4 mg, 1.935 mmol, 1 equiv.) in EtOH (17 mL) was added 10% Pd/C (600 mg). The mixture was stirred under a H_2 atmosphere (H_2 balloon) overnight. The mixture was filtered through celite. Flash column chromatography (10-15% Et_2O/hex) afforded *N*-(4,8-dimethylnonyl)-2,2,2-trifluoroacetamide (473.3 mg, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz): 6.62 (br, 1H), 3.32 (q, *J*= 6.9, 2H), 1.66-1.47 (m, 3H), 1.39-1.06 (m, 9H), 0.86-0.84 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.2 (q, *J*= 36.9), 115.9 (q, *J*= 287.9), 40.3, 39.2, 37.0, 33.8, 32.4, 27.9, 26.5, 24.7, 22.6, 22.5, 19.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 266.2 (expected), 266.2 (found); IR (cm^{-1}): 3306 (br), 3107, 2954, 2927, 2870, 1701.

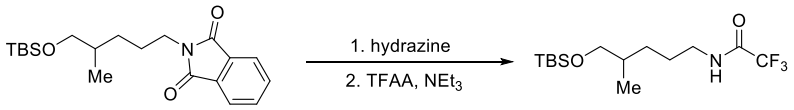


BH_3 (1.0 M in THF, 8.6 mL, 8.61 mmol, 1.0 equiv.) was added dropwise to a solution of *tert*-butyldimethyl((2-methylpent-4-en-1-yl)oxy)silane[6] (1845 mg, 8.61 mmol, 1.0 equiv.) in anhydrous THF (22 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. A premixed solution of NaOH (2.0 M, 20 mL) and H_2O_2 (30%, 10 mL) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction was diluted with H_2O (20 mL) and Et_2O (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20mL). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20-30% EtOAc/hexane) to give 5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-1-ol as a colorless oil (1067 mg, 53%). The Spectral data are in accordance with the published values.[7]



DEAD (0.83 mL, 5.29 mmol, 1.2 equiv.) was added dropwise to a solution of 5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-1-ol (1024 mg, 4.41 mmol, 1.0 equiv.), phthalimide (778 mg, 5.29 mmol, 1.2 equiv.) and Ph_3P (1472 mg, 5.29 mmol, 1.2 equiv.) in anhydrous THF (22 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The reaction solvent was removed under reduced pressure. The crude reaction mixture was suspended in hexane, filtered and concentrated. The crude product was purified by flash column chromatography (3-6% EtOAc/hexane) to give 2-(5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)isoindoline-1,3-dione as a colorless oil (1504 mg, 94%).

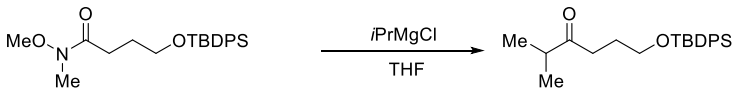
^{1}H NMR (400 MHz, $CDCl_3$): 7.86 - 7.78 (m, 2H), 7.73 - 7.67 (m, 2H), 3.67 (t, *J*= 7.3, 2H), 3.41 (dd, J= 9.8, 5.8, 1H), 3.36 (dd, *J*=9.8, 6.2, 1H), 1.79 - 1.54 (m, 3H), 1.17 - 1.06 (m, 1H), 0.86 (d, *J*= 6.7, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.4, 133.8, 132.2, 123.1, 68.0, 38.3, 35.4, 30.2, 26.1, 25.9, 18.3, 16.6, −5.4; Molecular weight $[M+H]^+$: 362.2152 (expected), 362.2143 (found); IR (cm^{-1}): 2961, 2930, 2857, 1711, 1427, 1110, 700.



Anhydrous N_2H_4 (90 µL, 2.76 mmol, 2.0 equiv.) was added to a solution of 2-(5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)isoindoline-1,3-dione (500 mg, 1.38 mmol, 1.0 equiv.) in anhydrous EtOH (13 mL). The reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with Et_2O. The filtrate was concentrated under reduced pressure. The crude product was suspended in Et_2O and filtered. The crude amine was used in the subsequent step without further purification.

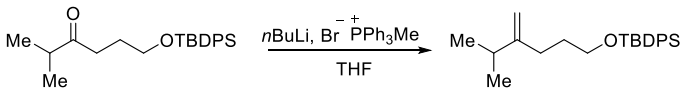
TFAA (0.21 mL, 1.52 mmol, 1.1 equiv.) was added dropwise to a solution of crude amine and Et_3N (0.38 mL, 2.76 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (4.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred at this temperature for 5 h and then diluted with H_2O (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/hexane) to give N-(5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)-2,2,2-trifluoroacetamide as a colorless oil (405 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): 6.66 (br, 1H), 3.42-3.38 (m, 2H), 3.36-3.31 (m, 2H), 1.67-1.53 (m, 3H), 1.50-1.43 (m, 1H), 1.13-1.09 (m, 1H), 0.87-0.85 (m, 12H), 0.86 (d, J = 6.9, 3H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.2 (q, *J* = 36.7), 115.8 (q, *J* = 287.3), 68.0, 40.3, 35.3, 30.2, 26.4, 25.9, 18.3, 16.5, −5.5, −5.5; ; Molecular weight $[M+H]^+$: 328.1920 (expected), 328.1901 (found); IR (cm^{-1}): 3304, 2955, 2930, 2858, 1701, 1560, 1161, 1093, 834.



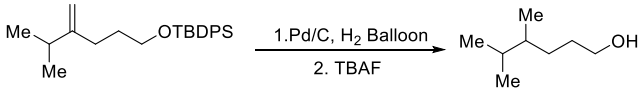
*i*PrMgCl (2.0 M in Et_2O, 12.4 mL, 24.7 mmol, 2.0 equiv.) was added dropwise to a solution of 4-((*tert*-butyldiphenylsilyl)oxy)-N-methoxy-N-methylbutanamide[8] in anhydrous THF (25 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 5 min before being warmed to room temperature. The reaction mixture was stirred at rt for 4 h before being diluted with NH_4Cl (sat. aq., 10 mL) and H_2O (10 ml). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5-10% EtOAc/hexane) to give 6-((*tert*-butyldiphenylsilyl)oxy)-2-methylhexan-3-one as a colorless oil (2323 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.69-7.61 (m, 4H), 7.47-7.34 (m, 6H), 3.68 (t, *J*= 6.1, 2H), 2.59 (septet, *J*= 6.1, 1H), 2.58 (t, *J*= 7.2, 2H), 1.87-1.78 (m, 2H), 1.09 (d, *J*= 6H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 214.6, 135.5, 133.8, 129.6, 127.6, 63.0, 40.9, 36.5, 26.9, 19.2, 18.3; Molecular weight $[M+H]^+$: 369.2250(expected), 369.2238 (found); IR (cm^{-1}): 2961, 2930, 2857, 1711, 1428, 1111, 581.



*n*BuLi (1.6 M in hexanes, 12.0 mL, 19.2 mmol, 4.0 equiv.) was added dropwise to a solution of Ph_3MePBr (7186 mg, 20.1 mmol, 4.2 equiv.) in anhydrous THF (40 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred at this temperature for 1 h. 6-((*tert*-butyldiphenylsilyl)oxy)-2-methylhexan-3-onein anhydrous THF (8 mL) was added dropwise to the reaction mixture. The reaction mixture was heated to 70 °C and stirred at this temperature for 12 h. The reaction mixture was cooled to room temperature and diluted with H_2O (40 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 20 ml). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (2% Et_2O/hexane) to give *tert*-butyl((5-methyl-4-methylenehexyl)oxy)diphenylsilane as a colorless oil (1764 mg, 100%).

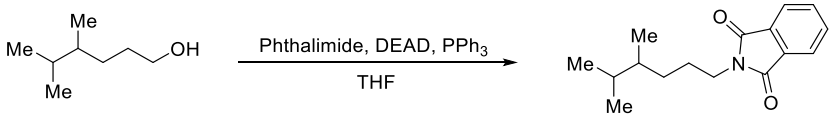
^{1}H NMR (400 MHz, $CDCl_3$): 7.74-7.64 (m, 4H), 7.47-7.33 (m, 6H), 4.74 (s, 1H), 4.66 (s, 1H), 3.69 (t, *J*= 6.4, 2H), 2.22 (septet, *J*= 6.8, 1H), 2.11 (t, *J*= 7.8, 2H), 1.77-1.66 (m, 2H), 1.07 (s, 9H), 1.02 (d, *J*= 6.0, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 155.7, 135.6, 134.1, 129.5, 127.6, 106.2, 63.7, 33.8, 31.2, 30.5, 26.9, 21.8, 19.2; Molecular weight $[M+H]^+$: 367.2457 (expected), 367.2457 (found); IR (cm^{-1}): 2959, 2931, 2858, 1428, 1107, 690.



Pd/C (10%, 250 mg) was added to a solution of give *tert*-butyl((5-methyl-4-methylenehexyl)oxy)diphenylsilane (1620 mg, 4.40 mmol, 1.0 equiv.) in EtOH (22 mL). The atmosphere was removed under reduced pressure and replaced with an atmosphere of H_2 (balloon of H_2 with needle running into the reaction mixture); this process was repeated three times. A balloon of H_2 was connected to the reaction flask and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a plug of Celite. The Celite was washed with Et_2O (100 mL) and the filtrate was concentrated under reduced pressure to give the crude TBDPS protected alcohol which was used in the following step without purification.

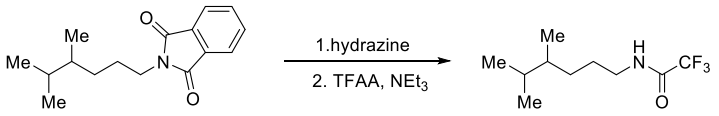
TBAF (1.0 M in THF, 8.8 mL, 8.80 mmol, 2.0 equiv.) was added dropwise to a solution of crude TBDPS protected alcohol in anhydrous THF (20 mL) at room temperature. The reaction mixture was stirred at this temperature for 3 h before being diluted with NH_4Cl (sat. aq., 10 mL) and H_20 (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layer was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20-50% Et_2O/hexane) to give 4,5-dimethylhexan-1-ol as a colorless oil (559 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): 3.62 (t, *J*= 6.8, 2H), 1.67-1.27 (m, 6H), 1.18-1.07 (m, 1H), 0.86 (d, *J*= 6.9, 3H), 0.81 (d, *J*= 6.8, 3H), 0.80 (d, *J*= 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 63.4, 38.4, 32.0, 30.8, 30.1, 20.2, 17.9, 15.3; IR (cm^{-1}): 3317, 2956, 2933, 2871, 1462, 1377, 1058. The molecular weight cannot be observed with MS (EI).



DEAD (0.81 mL, 5.15 mmol, 1.2 equiv.) was added dropwise to a solution of 4,5-dimethylhexan-1-ol (559 mg, 4.29 mmol, 1.0 equiv.), phthalimide (758 mg, 5.15 mmol, 1.2 equiv.) and Ph_3P (1433 mg, 5.15 mmol, 1.2 equiv.) in anhydrous THF (14 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at this temperature for 12 h. The reaction solvent was removed under reduced pressure. The crude reaction mixture was suspended in hexane, filtered and concentrated. The crude product was purified by flash column chromatography (2-10% EtOAc/hexane) to give 2-(4,5-dimethylhexyl)isoindoline-1,3-dione as a colorless oil (1100 mg, 99%).

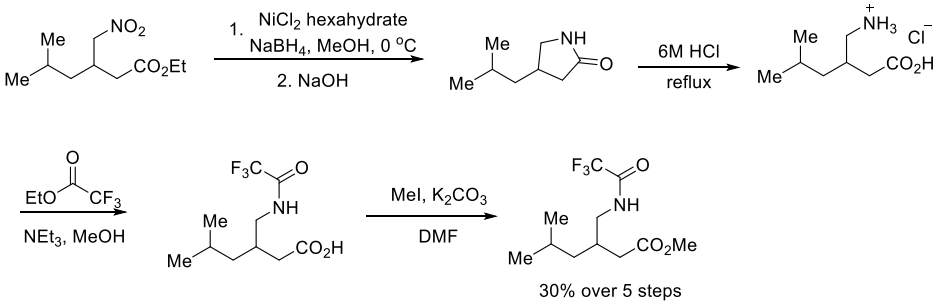
^{1}H NMR (400 MHz, $CDCl_3$): 7.88-7.76 (m, 2H), 7.74-7.65 (m, 2H), 3.65 (t, *J*= 7.4, 2H), 1.74-1.51 (m, 3H), 1.40-1.28 (m, 2H), 1.19-1.08 (m, 1H), 0.84 (d, *J*= 6.8, 3H), 0.79 (d, *J*= 6.7, 3H), 0.78 (d, *J*= 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 168.4, 133.8, 132.2, 123.1, 38.4, 38.2, 31.9, 31.2, 26.6, 20.2, 17.9, 15.2; Molecular weight $[M+H]^+$: 260.1651 (expected), 260.1630 (found); IR (cm^{-1}): 2956, 2871, 1707, 1394, 1361, 717.



Anhydrous N_2H_4 (0.26 mL, 8.33 mmol, 2.0 equiv.) was added to a solution of 2-(4,5-dimethylhexyl)isoindoline-1,3-dione (1080 mg, 4.17 mmol, 1.0 equiv.) in anhydrous EtOH (20 mL). The reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature, filtered. The solid was washed with Et_2O. The filtrate was concentrated under reduced pressure. The crude amine was used in the subsequent step without further purification.

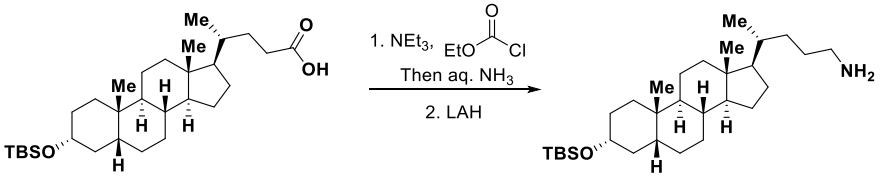
TFAA (0.65 mL, 4.59 mmol, 1.1 equiv.) was added dropwise to a solution of crude amine and Et_3N (1.10 mL, 8.34 mmol, 2.0 equiv.) in anhydrous CH_2Cl_2 (13 mL) at 0 °C. The reaction mixture was raised to room temperature. The reaction mixture was stirred at this temperature for 5 h and then diluted with H_2O (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10-15% Et_2O/hexane) to give *N*-(4,5-dimethylhexyl)-2,2,2-trifluoroacetamide as a colorless oil (412.5 mg, 44%).

^{1}H NMR ($CDCl_3$, 400 MHz): 6.93 (br, 1H), 3.31 (q, *J*= 6.9, 2H), 1.63-1.46 (m, 3H), 1.38-1.23 (m, 2H), 1.14-1.05 (m, 1H), 0.83 (d, *J*= 7.0, 3H), 0.79 (d, *J*= 2.4, 3H), 0.77 (d, *J*= 2.3, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3 (q, *J*= 36.4), 115.9 (q, *J*= 287.6), 40.3, 38.1, 31.8, 31.0, 26.8, 20.0, 17.8, 15.1; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.2 ; Molecular weight $[M-H]^-$: 224.1 (expected), 224.1 (found); IR (cm^{-1}): 3300 (br), 3107, 2959, 2874, 1700.



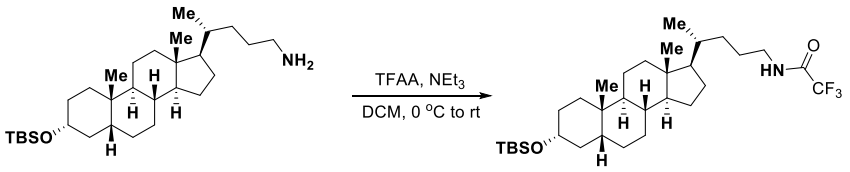
To a solution of ethyl 6-methyl-4-(nitromethyl)heptanoate[9] (1.60 g, 7.3 mmol, 1 equiv.) in MeOH (38.5 mL) was added $NiCl_2$ hexahydrate (1.7282 g,7.3 mmol, 1 equiv.) at 0 °C. $NaBH_4$ (3.0256 g, 80.3 mmol, 11 equiv.) was added in portions and VERY SLOWLY. The mixture was kept at 0 °C for 1 h. 6 M NaOH (9 mL) was added. The mixture was warmed to rt and stirred for 2 h. The mixture was acidified with 2 M HCl. The mixture was extracted with DCM four times. The combined organic layer was dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford 4-isobutylpyrrolidin-2-one. The crude lactam was dissolved in 6 M HCl (35 mL). The mixture was refluxed overnight. The solvent was removed under vacuum to afford 2-(2-carboxyethyl)-4-methylpentan-1-aminium chloride. The crude hydrochloride salt was dissolved in MeOH (28 mL). NEt_3 (2.44 mL, 17.5 mmol, 2.4 equiv.) and ethyl trifluoroacetate (1.06 mL, 10.5 mmol, 1.44 equiv.) was added. The mixture was stirred at rt overnight. Solvent was removed under vacuum. The mixture was dissolved in EtOAc. The mixture was washed with 1 M HCl, dried over Na_2SO_4 and filtered. Solvent was removed under vacuum to afford 6-methyl-4-((2,2,2-trifluoroacetamido)methyl)heptanoic acid. The crude carboxylic acid was dissolved in DMF (23 mL). K_2CO_3 (4.837 g, 35.0 mmol, 4.8 equiv.). MeI (2.18 mL, 35.0 mmol, 4.8 equiv.) was added dropwise. The mixture was stirred for 7 h. The mixture was diluted with Et_2O, washed with H_2O four times and brine twice. It was dried over Na_2SO_4 and filtered. Solvent was removed under vacuum. Flash column chromatography afforded methyl 6-methyl-4-((2,2,2-trifluoroacetamido)methyl)heptanoate (572.9 mg, 30% over 5 steps) as a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.38 (br, 1H), 3.62 (s, 3H), 3.42-3.36 (m, 1H), 3.25-3.18 (m, 1H), 2.37 (dd, *J*= 15.7, 4.7, 1H), 2.26 (dd, *J*= 15.7, 7.8, 1H), 1.64-1.56 (m, 1H), 1.20-1.08 (m, 2H), 0.87 (d, *J*= 6.6, 3H), 0.85 (d, *J*= 6.7, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.9, 157.5 (q, *J*= 36.6), 115.9 (q, *J*= 287.6), 51.77, 44.0, 41.6, 37.4, 32.5, 25.1, 22.5, 22.3; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 268.1 (expected), 268.1 (found); IR (cm^{-1}): 3318 (br), 3104, 2957, 2873, 2851, 1705.



To a solution of TBS-protected lithocholic acid[10] (1.20 g, 2.44 mmol, 1 equiv.) in THF (0.1 M) was added NEt_3 (0.347 mL, 2.49 mmol, 1.02 equiv.) at 0 °C. Ethyl chloroformate (0.238 mL, 2.49 mmol, 1.02 equiv.) was added dropwise. The mixture was stirred at 0 °C for 1 h. aq. NH_3 (2.25 mL, 14.8 M) was added. The mixture was allowed to warm to rt and stir overnight. H_2O was added. The organic and aqueous layers were separated. The aqueous layer was extracted with EtOAc twice. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. The Solvent was removed under reduced pressure to yield the amide (1.20 g, 100%) as a white solid. It was used without further purification.

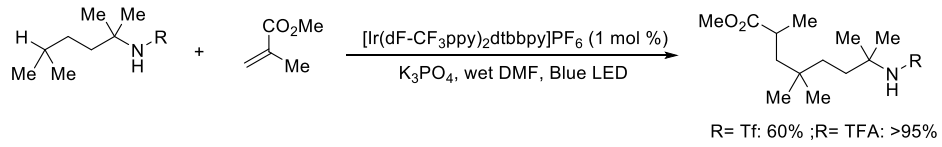
To a solution of the crude amide (1.20 g, 2.44 mmol, 1 equiv.) in THF (16 mL, 0.15 M) was added LAH (0.186 g, 4.88 mmol, 2 equiv.)in portions at 0 ^{o}C. The mixture was allowed to warm to rt and stir overnight. The mixture was cooled to 0 ^{o}C. Water (0.185 mL) was added slowly. 15% NaOH (0.185 mL) was added slowly. Water (0.555 mL) was added. The mixture was allowed to rt and stirred for 15 mins. The mixture was filtered. The solvent in the filtrate was removed under reduced pressure to afford the crude amine (1.14 g, 98%), which was used without further purification.

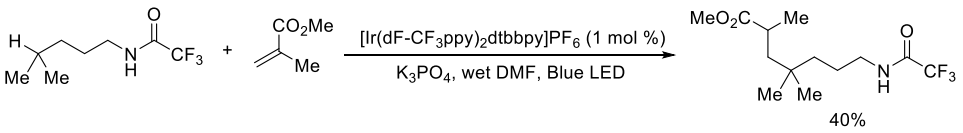


By General Procedure C, the trifluoroacetamide (304.4 mg, 50%) was synthesized from the crude amine (502.4 mg). Conditions for flash column chromatography: 10-15% Et_2O/hexane.

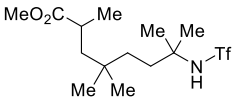
^{1}H NMR ($CDCl_3$, 400 MHz): 6.42 (br, 1H), 3.60-3.54 (m, 1H), 3.35-3.27 (m, 2H), 1.94-0.88 (m, 43H), 0.62 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 157.1 (q, *J*=36.9), 115.1 (q, *J*= 288.0.), 72.8, 56.4, 56.0, 42.7, 42.3, 40.4, 40.2, 40.1, 36.9, 35.8, 35.6, 35.4, 34.6, 32.8, 31.0, 28.2, 27.3, 26.4, 26.0, 25.6, 24.2, 23.4, 20.8, 18.5, 18.3, 12.0, -4.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 570.4 (expected), 570.4 (found); IR (cm^{-1}): 3299, 3103, 2935, 2916, 2883, 2861, 1724, 1700.

Reaction Discovery

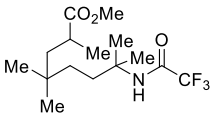




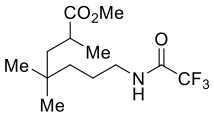
To a mixture of the amine (0.1 mmol, 1 equiv.), alkene (0.15 mmol, 1.5 equiv.) and K_3PO_4 (0.2 mmol, 2 equiv.) in a vial was added 3 drops of deionized water (~40 mg), followed by DMF (1.0 mL). Argon was bubbled through the solution for 5 mins. [Ir(dF-CF_3pp)$_2$dtbbp]PF_6 (0.9 mg, 1 mol %) was added. Argon was bubbled through the solution for another 10 mins. The vial was then capped and illuminated with a Blue LED for 16h (The distance between the Blue LED and the vial is around 1.5 cm). The mixture was filtered through silica gel. The yield was determined by NMR with 1,3,5-trimethoxybenzene as the standard.



^{1}H NMR ($CDCl_3$, 400 MHz): 5.21 (br, 1H), 3.68 (s, 3H), 2.54-2.46 (m, 1H), 1.90 (dd, *J*= 14.5, 9.4), 1.68-1.58 (m, 1H), 1.52-1.46 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.25-1.18 (m, 2H), 1.16 (d, *J*= 7.1, 3H), 1.11 (dd, *J*= 14.0, 9.8), 0.86 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 178.8, 119.3 (q, *J*= 321.2), 60.3, 51.9, 44.5, 37.8, 35.5, 34.9, 32.8, 28.9, 27.5, 27.2, 26.6, 20.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −77.8; Molecular weight $[M-H]^-$: 360.2 (expected), 360.1 (found); IR (cm^{-1}): 3232, 2956, 2876, 1738, 1715, 1460, 1435, 1391, 1362, 1275, 1227, 1185, 1143.

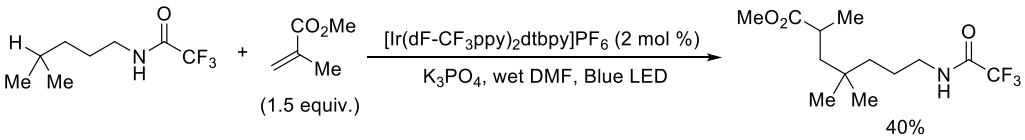


^{1}H NMR ($CDCl_3$, 400 MHz): 6.05 (br, 1H), 3.65 (s, 3H), 2.52-2.45 (m, 1H), 1.85 (dd, *J*= 14.1, 9.4, 1H), 1.68-1.64 (m, 2H), 1.37 (s, 3H), 1.36 (s,3H), 1.18-1.10 (m, 6H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): ; 178.3, 156.0 (q, *J*= 35.9), 115.6 (q, *J*= 289.4), 55.2, 51.6, 45.4, 35.6, 35.6, 34.1, 32.8, 27.0, 26.7, 26.5, 26.1, 20.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 324.2 (expected), 324.2 (found); IR (cm^{-1}): 3332 (br), 3086, 2955, 2875, 1712.



^{1}H NMR ($CDCl_3$, 400 MHz): 6.49 (br, 1H), 3.63 (s, 3H), 3.34-3.24 (m,2H), 2.50-2.43 (m,1H), 1.85 (dd, *J*= 14.4, 9.4), 1.18-1.09 (m, 6H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz):178.3, 157.2 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 51.7, 45.2, 40.6, 38.8, 35.6, 33.0, 27.1, 26.9, 23.6, 20.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 296.2 (expected), 296.2 (found); IR (cm^{-1}): 3317 (br), 3099, 2955, 2876, 1706.

Optimization

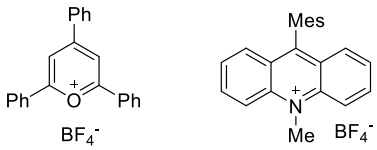


Solvent Effects
DMF: 40%
$CHCl_3$: 56%
DCE: 54%
Dioxane, THF, DME: messy
DMSO: 40%
DMA: 45%
Acetone: 48%
t-Amyl Alchol: 35%
HFIP: 0%
t-Amyl Alchol/$PhCF_3$: 70%
MeCN: 65%, 55% with $[Ir(ppy)_2(dtbpy)]PF_6$
PhMe, PhH, PhCl: 0%
$PhCF_3$: 71%

Base
K_2CO_3: 0%
K_2HPO_4: 0%
K_2HPO_4: 0%
KOAc: 0%
Cs_2CO_3: 54%
Na_3PO_4: 65%
K_3PO_4: 71%
NaOH: 0%

Concentration
0.4 M: >90% (75%)
0.2 M: >90% (71%)
0.13 M: 78%
0.10 M: 71%
0.05 M: 22%
0.03 M: 0%

No product was observed with other photocatalysts:



$Ir(ppy)_3$, $Ru(bpz)_3(PF_6)_2$, $Ru(bpy)_3Cl_2$

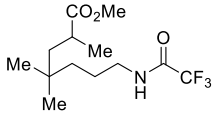
Yields were determined by NMR using 1,3,5-trimethoxybenzene as a standard. Yields in brackets refer to isolated yield after column chromatography.

Photocatalytic C-C Bond Formation at sp^3 C-H Bonds (Alkene and Amide Scope)

General Procedure D: Photocatalytic C-C Bond Formation

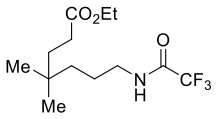
To a mixture of the amine (0.1 mmol, 1 equiv.), alkene and finely ground K_3PO_4 (0.2 mmol, 2 equiv.) in a vial was added 3 drops of deionized water (~40 mg), followed by the solvent. Argon was bubbled through the solution for 5 mins. $[Ir(dF\text{-}CF_3pp)_2dtbbp]PF_6$ (2-5 mol %) was added. Argon was bubbled through the solution for another 10 mins. The vial was then capped and illuminated with a Blue LED for 16-20 h (The distance between the Blue LED and the vial is around 1.5 cm). The mixture was filtered through silica gel. The product was purified by column chromatography.

Alkene Scope



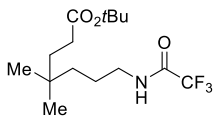
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), methyl 2,4,4-trimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (21.5 mg, 75%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (18.9 mg). Flash column chromatography conditions: 15-35% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.49 (br, 1H), 3.63 (s, 3H), 3.34-3.24 (m,2H), 2.50-2.43 (m,1H), 1.85 (dd, *J*= 14.4, 9.4), 1.18-1.09 (m, 6H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz):178.3, 157.2 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 51.7, 45.2, 40.6, 38.8, 35.6, 33.0, 27.1, 26.9, 23.6, 20.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M\text{-}H]^-$: 296.2 (expected), 296.2 (found); IR (cm^{-1}): 3317 (br), 3099, 2955, 2876, 1706.



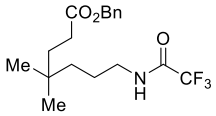
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), ethyl 4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (19.9 mg, 68%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.4 mg). Flash column chromatography conditions: 5-50% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.34 (br, 1H), 4.12 (q, *J*= 7.2, 2H), 3.34 (q, *J*= 6.8, 2H), 2.26-2.22 (m, 2H), 1.57-1.53 (m,4H), 1.25 (t, *J*= 7.2, 3H), 1.23-1.19 (m, 2H), 0.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.2, 157.2 (q, *J*= 37.4), 115.9 (q, *J*= 287.7), 60.4, 40.6, 38.5, 36.1, 32.2, 29.5, 26.6, 23.8, 14.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M\text{-}H]^-$: 296.2 (expected), 296.2 (found); IR (cm^{-1}): 3327 (br), 3104, 2959, 2873, 1706.



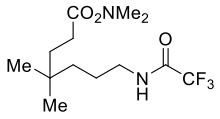
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), *tert*-butyl 4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (21.4 mg, 67%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.3 mg). Flash column chromatography conditions: 20-30% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.35 (br, 1H), 3.33 (q, *J*= 6.8, 2H), 2.27-2.13 (m, 2H), 1.58-1.48 (m,4H), 1.44 (s, 9H), 1.22-1.18 (m, 2H), 0.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.6, 157.1 (q, *J*= 36.6), 115.8 (q, *J*= 288.0), 80.2, 40.6, 38.6, 36.2, 32.3, 30.7, 28.1, 26.6, 23.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 324.2 (expected), 324.2 (found); IR (cm^{-1}): 3319 (br), 3105, 2960, 2936, 2872, 1727, 1704, 1648, 1557, 1504, 1472, 1457.



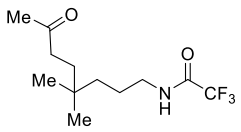
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), benzyl 4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (21.4 mg, 67%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.3 mg). Flash column chromatography conditions: 20-30% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz):7.39-7.32 (m, 5H), 6.36 (br, 1H), 5.11 (s, 2H), 3.31 (q, *J*= 6.8, 2H), 2.32-2.28 (m, 2H), 1.59-1.49 (m, 2H), 1.22-1.19 (m, 2H), 0.86 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.0, 157.1 (q, *J*= 36.6), 135.9, 128.6, 128.3, 128.3, 115.8 (q, *J*= 287.7), 66.3, 40.6, 28.5, 36.1, 32.3, 29.5, 26.6, 23.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular weight $[M-H]^-$: 358.2 (expected), 358.1 (found); IR (cm^{-1}): 3321 (br), 3091, 3035, 2957, 2871, 1704.



By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), *N*-(7-((dimethylamino)oxy)-4,4-dimethyl-7-oxoheptyl)-2,2,2-trifluoroacetamide (14.8 mg, 52%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.0 mg). Flash column chromatography conditions: 50% Et_2O/hexane – Pure EtOAc.

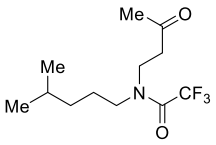
^1H NMR ($CDCl_3$, 400 MHz): 6.79 (br, 1H), 3.33 (q, *J*= 6.6 Hz, 2H), 3.01 (s, 3H), 2.94 (s, 3H), 2.27 (m, 2H), 1.61-1.52 (m, 4H), 1.25-1.20 (m, 2H), 0.88 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.6, 157.3 (q, *J*= 33.6), 115.9 (q, *J*= 288.2), 40.6, 38.2, 36.0, 32.4, 28.2, 27.0, 23.5; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.8; Molecular weight $[M-H]^-$: 311.2 (expected), 311.2 (found); IR (cm^{-1}): 3254 (br), 3086, 2955, 2871, 1718, 1634.



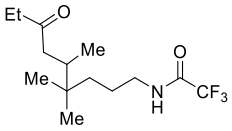
By General Procedure D (1.2 equiv. of alkene, 5 mol % Ir photocatalyst, 0.5 mL $PhCF_3$), *N*-(4,4-dimethyl-7-oxooctyl)-2,2,2-trifluoroacetamide (16.3 mg, 63%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.1 mg). Flash column chromatography conditions: 40-60% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.44 (br, 1H), 3.33 (q, *J*= 6.6, 2H), 2.38-2.34 (m, 2H), 2.15 (s, 3H), 1.58-1.45 (m, 4H), 1.20-1.16 (m, 2H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 209.3, 157.2 (q, *J*= 36.6), 115.9 (q, *J*= 288.1), 40.6, 38.7, 28.6, 34.8, 32.1, 30.0, 26.7, 23.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 266.1 (expected), 266.2 (found); IR (cm^{-1}): 3313 (br), 3097, 2958, 2872, 1706.

When the reaction was carried out with 1.5equiv. of alkene, 2 mol % Ir photocatalyst,0.25 mL $PhCF_3$, the desired product was only isolated in low yield (27%). A significant of aza-Michael addition product (44%) was also obtained. The aza-Michael addition product exists as two rotamers (~1:2), as observed in NMR. Some of the peaks of the two rotamers cannot be distinguished in ^{13}C NMR.

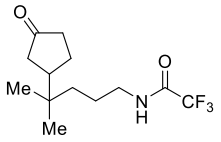


^1H NMR ($CDCl_3$, 400 MHz): 3.67 (t, *J*= 7.6, 1H, minor rotamer), 3.59 (t, *J*= 6.9, 2H, major rotamer), 3.36 (t, *J*= 8.0, 2H, major rotamer), 3.30 (t, *J*= 7.9, 1H, minor rotamer), 2.82 (t, *J*= 6.9, 2H, major rotamer), 2.77 (t, *J*= 7.5, 1H, minor rotamer), 2.19 (s, 1.5 H, minor rotamer), 2.17 (s, 3H, major rotamer), 1.64-1.50 (m, 4.5H, both rotamers), 1.19-1.13 (m, 3H, both rotamers), 0.90-0.87 (m, 9H, both rotamers); ^{13}C NMR ($CDCl_3$, 100 MHz): 206.5 (major rotamer), 205.4 (minor rotamer), 156.9 (q, *J*= 35.9), 116.4 (q, *J*= 287.4), 49.0 (q, *J*= 3.0, major rotamer)), 47.6, 42.7, 42.6, 41.8 (q, *J*=3.3, minor rotamer), 40.8, 35.7, 35.5, 30.2, 30.2, 27.8, 27.6, 26,7, 24.7, 22.4, 22.4 ; ^{19}F NMR ($CDCl_3$, 376 MHz): −69.21 (major rotamer), −60.29 (minor rotamer); IR (cm^{-1}): 2955, 2933, 2872, 1718, 1685, 1464, 1436; Molecular weight $[M+H]^+$: 268.2 (expected); 268.2 (found).



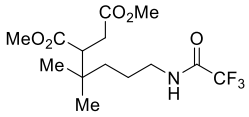
By General Procedure D (3 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), 2,2,2-trifluoro-*N*-(4,4,5-trimethyl-7-oxononyl)acetamide (17.4 mg, 59%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.7 mg). Flash column chromatography conditions: 30-45% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.34 (br, 1H), 3.33 (q, *J*= 6.8, 2H), 2.49-2.32 (m, 3H), 2.14 (dd, *J*= 16.0, 10.2, 1H), 1.97-1,91 (m, 1H), 1.61-1.51 (m, 2H), 1.30-1.17 (m, 2H), 1.05 (t, *J*= 7.3, 3H), 0.82 (s, 6H), 0.79 (d, *J*= 6.6, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 212.0, 157.2 (q, *J*= 33.8), 115.8 (q, *J*= 287.9),44.9, 40.7, 37.1, 36.7, 36.1, 34.7, 24.2, 23.5, 14.9, 7.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 294.2 (expected), 294.2 (found); IR (cm^{-1}): 3326 (br), 3104, 2965, 2942, 2879, 1703.



By General Procedure D (3 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), 2,2,2-trifluoro-*N*-(4-methyl-4-(3-oxocyclopentyl)pentyl)acetamide (13.5 mg, 51%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (18.7 mg). Flash column chromatography conditions: 30-70% Et_2O/hexane.

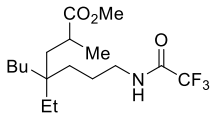
^{1}H NMR ($CDCl_3$, 400 MHz): 6.30 (br, 1H), 3.33 (q, *J*= 6.9, 2H), 2.32 (dd, *J*= 18.4, 8.2, 1H), 2.18-1.91 (m, 5H), 1.63-1.52 (m, 3H), 1.26-1.22 (m, 2H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 219.1, 157.2 (q, *J*= 36.6), 115.8 (q, *J*= 287.9), 46.6, 40.1, 40.0, 39.1, 37.8, 34.0, 24.0, 23.9, 23.7, 23.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 278.1 (expected), 278.1 (found); IR (cm^{-1}): 3313 (br), 3097, 2961, 2874, 1706.



By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), methyl 3-acetoxy-4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (13.7 mg, 40%) was obtained from 2,2,2-trifluoro-*N*-(4-methylpentyl)acetamide (19.8 mg). Flash column chromatography conditions: 45-60% Et_2O/hexane.

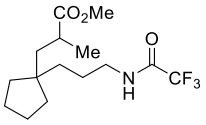
^{1}H NMR ($CDCl_3$, 400 MHz): 6.53 (br, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.40-3.27 (m, 2H), 2.84-2.74 (m, 2H), 2.43 (m, 1H), 1.74-1.66 (m, 1H), 1.69-1.54 (m, 1H), 1.36-1.21 (m, 2H), 0.94 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.3, 172.9, 157.3 (q, *J*= 36.9), 115.8 (q, *J*= 287.9), 51.8, 51.6, 49.1, 40.4, 37.8, 34.9, 32.1, 25.1, 25.0, 23.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular weight $[M-H]^-$: 340.1 (expected), 340.2 (found); IR (cm^{-1}): 3335 (br), 3097, 2954, 2915, 2848, 1708.

Amide Scope



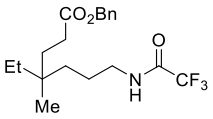
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$methyl 4-ethyl-2-methyl-4-(3-(2,2,2-trifluoroacetamido)propyl)octanoate (28.3 mg, 81%) was obtained from *N*-(4-ethyloctyl)-2,2,2-trifluoroacetamidetrifluoroacetamide (25.2 mg). Flash column chromatography conditions: 15-30% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.56 (br, 1H), 3.65 (s, 3H), 3.35-3.21 (m, 2H), 2.48-2.41 (m,1H), 1.82 (dd, *J*= 14.9, 9.4, 1H), 1.53-1.37 (m, 2H), 1.27-1.08 (m, 13H), 0.89 (t, *J*= 7.3, 3H), 0.72 (two overlapped triplet from each diastereomer, *J*= 7.4, 3H);); ^{13}C NMR ($CDCl_3$, 100 MHz): 178.5, 157.2 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 51.7, 40.7, 39.8, 39.7, 37.7, 35.5, 34.9, 34.9, 33.1, 32.9, 28.3, 28.3, 25.1, 25.0, 23.5, 22.5, 22.4, 20.4, 14.1, 7.4, 7.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular weight $[M-H]^-$: 352.2 (expected), 352.2 (found); IR (cm^{-1}): 3322 (br), 3102, 2957, 2932, 2873, 1704.



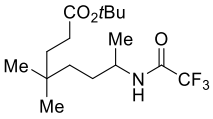
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), methyl 2-methyl-3-(1-(3-(2,2,2-trifluoroacetamido)propyl)cyclopentyl)propanoate (19.1 mg, 61%) was obtained from *N*-(3-cyclopentylpropyl)-2,2,2-trifluoroacetamide (21.7 mg). Flash column chromatography conditions: 30-35% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.58 (br, 1H), 3.66 (s, 3H), 3.39-3.23 (m, 2H), 2.50-2.42 (m, 1H), 1.93 (dd, *J*= 14.5, 9.0, 1H), 1.58-1.23 (m, 13H), 1.16 (d, *J*= 7.0, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 178.4, 157.3 (q, *J*= 36.6), 115.9 (q, *J*= 287.6), 51.7, 45.0, 41.7, 40.6, 37.7, 37.6, 36.3, 34.7, 24.1, 24.0, 23.9, 20.2; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.8; Molecular weight $[M-H]^-$: 322.2 (expected), 322.2 (found); IR (cm^{-1}): 3326 (br), 3105, 2951, 2873, 1705.



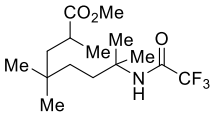
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), benzyl 4-ethyl-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (25.6 mg, 68%) was obtained from enantiomerically enriched (*S*)-2,2,2-trifluoro-*N*-(4-methylhexyl)acetamide (21.3 mg). Flash column chromatography conditions: 25-35% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.39-7.31 (m, 5H), 6.31 (br, 1H), 5.11 (s, 2H), 3.31 (q, *J*=6.8, 2H), 2.29-2.24 (m, 2H), 1.58-1.46 (m, 4H), 1.23-1.16 (m,4H), 0.81-0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.1, 157.1, 135.9, 128.6, 128.2, 115.8, 66.3, 40.6, 35.4, 34.6, 33.3, 31.0, 29.1, 23.9, 23.3, 7.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.6; Molecular weight $[M-H]^-$: 372.2 (expected), 372.1 (found); IR (cm^{-1}): 3335 (br), 3091, 3035, 2961, 2877, 1704.



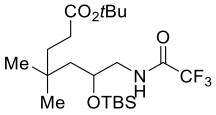
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL DMF), *tert*-butyl 4,4-dimethyl-7-(2,2,2-trifluoroacetamido)octanoate (25.6 mg, 77%) was obtained from 2,2,2-trifluoro-*N*-(5-methylhexan-2-yl)acetamide (20.8 mg). Flash column chromatography conditions: 13-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.03 (br, 1H), 3.93 (quintet, *J*= 7.0, 1H), 2.14-2.10 (m, 2H), 1.49-1.42 (m,12H), 1.20-1.15 (m, 6H), 0.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.6, 156.5 (q, *J*= 36.6), 115.9 (q, *J*= 288.2), 80.2, 47.1, 37.6, 36.1, 32.2, 30.8, 30.7, 28.1, 26.7, 20.5; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.8; Molecular weight $[M-H]^-$: 338.2 (expected), 338.2 (found); IR (cm^{-1}): 3311 (br), 3095, 2960, 2935, 2871, 1726, 1699, 1554, 1456, 1391, 1367, 1207, 1157.



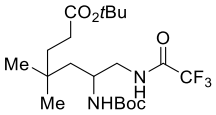
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL DMF), methyl 2,4,4,7-tetramethyl-7-(2,2,2-trifluoroacetamido)octanoate (26.2 mg, 83%) was obtained from *N*-(2,5-dimethylhexan-2-yl)-2,2,2-trifluoroacetamide (21.8 mg). Flash column chromatography conditions: 10-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.05 (br, 1H), 3.65 (s, 3H), 2.52-2.45 (m, 1H), 1.85 (dd, *J*= 14.1, 9.4, 1H), 1.68-1.64 (m, 2H), 1.37 (s, 3H), 1.36 (s,3H), 1.18-1.10 (m, 6H), 0.83 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): ; 178.3, 156.0 (q, *J*= 35.9), 115.6 (q, *J*= 289.4), 55.2, 51.6, 45.4, 35.6, 35.6, 34.1, 32.8, 27.0, 26.7, 26.5, 26.1, 20.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M-H]^-$: 324.2 (expected), 324.2 (found); IR (cm^{-1}): 3332 (br), 3086, 2955, 2875, 1712.



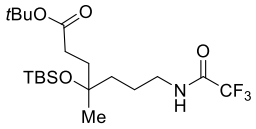
By General Procedure D (3 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL 1:1 $PhCF_3$/*t*-amyl alcohol), *tert*-butyl 6-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (25.5 mg, 60%) was obtained from *N*-(2-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)-2,2,2-trifluoroacetamide (30.6 mg). Flash column chromatography conditions: 5-15% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.59 (br, 1H), 3.97 (quintet, *J*= 5.0, 1H), 3.50 (dt, *J*= 13.3, 4.6, 1H), 3.32-3.26 (m, 1H), 2.23-2..11 (m, 2H), 1.59-1.52 (m, 2H), 1.50-1.36 (m, 11H), 0.92-0.89 (m, 15H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.3, 157.2 (q, *J*= 36.6), 115.6 (q, *J*= 287.6), 80.2, 67.6, 47.2, 46.8, 37.6, 32.0, 30.7, 28.1, 27.2, 26.9, 25.7, 17.8, −4.2, −4.5; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular weight $[M-H]^-$: 454.3 (expected), 454.3 (found); IR (cm^{-1}): 3323 (br), 3096, 2956, 2930, 2858, 1728, 1705.



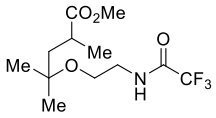
By General Procedure D (3 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL 1:1 $PhCF_3$/*t*-amyl alcohol), *tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-4,4-dimethyl-7-(2,2,2-trifluoroacetamido)heptanoate (28.7 mg, 67%) was obtained from *tert*-butyl (4-methyl-1-(2,2,2-trifluoroacetamido)pentan-2-yl)carbamate (30.2 mg). Flash column chromatography conditions: 30-50% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.61 (br, 1H), 4.61 (d, *J*= 8.2, 1H), 3.95-3.94 (m, 1H), 3.40-3.22 (m, 2H), 2.17 (t, *J*= 8.3, 2H), 1.63-1.50 (m, 2H), 1.44 (s, 9H), 1.42 (s, 9H), 1.33 (d, *J*= 5.8, 2H), 0.91 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.3, 157.7 (q, *J*= 40), 156.9, 115.8 (q, *J*= 286), 80.5, 80.3, 47.9, 46.6, 44.1, 36.9, 32.7, 30.6, 28.2, 26.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.1; Molecular weight $[M+H]^+$: 285.1 (expected for MW-2BOC+2H), 285.1 (found); IR (cm^{-1}): 3676, 3330 (br), 3109, 2977, 2934, 1707, 1638.



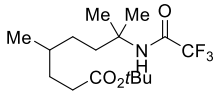
By General Procedure D (3 equiv. of alkene, 5 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), *tert*-butyl 4-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (33.4 mg, 76%) was obtained from *N*-(4-((*tert*-butyldimethylsilyl)oxy)pentyl)-2,2,2-trifluoroacetamide (31.0 mg). Flash column chromatography conditions: 7-20% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.35 (br, 1H), 3.37-3.32 (m, 2H), 2.25 (t, *J*= 8.0, 2H), 1.74-1.70 (m,2H), 1.66-1.59 (m, 2H), 1.44-1.42 (m, 11H), 1.19 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.4, 157.2 (q, *J*= 36.6), 115.8 (q, *J*= 287.9), 80.2, 74.5, 40.3, 39.1, 36.9, 30.6, 28.1, 27.3, 25.8, 23.8, 18.2, –2.01; ^{19}F NMR ($CDCl_3$, 376 MHz): –76.0; Molecular Weight $[M-H]^-$: 440.2 (expected), 440.3 (found); IR (cm^{-1}): 3330 (br), 3096, 2955, 2930, 2886, 2857, 1727, 1703, 1555, 1473, 1463, 1392, 1367, 1311, 1253, 1207, 1152, 1122, 1039.



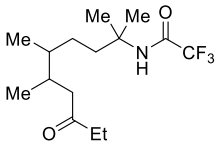
By General Procedure D (3.0 equiv. of alkene, 5 mol% Ir photocatalst, 0.25 mL $PhCF_3$), methyl 2,4-dimethyl-4-(2-(2,2,2-trifluoroacetamido)ethoxy)-pentanoate (25.3 mg, 79%) was obtained from 2,2,2-trifluoro-*N*-(2-isopropoxyethyl)acetamide (19.5 mg). First Chromatography: 25-35% Et_2O/hexane, Si gel; Second chromatography: 25-40% Et_2O/hexane, florisil (200 mesh, fine powder, activated magnesium silicate).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.30 (br, 1H), 3.64-3.58 (m, 4H), 3.44-3.34 (m, 2H), 3.30-3.24 (m, 1H), 2.68-2.59 (m, 1H), 2.12 (dd, *J*= 14.1, 11.0, 1H), 1.41 (dd, *J*= 14.0, 2.3, 1H), 1.17-1.14 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): 178.6, 156.9 (q, *J*= 36.9), 116.0 (q, *J*= 287.6), 74.6, 59.5, 51.5, 46.5, 40.1, 36.0, 26.0, 23.5, 19.2; ^{19}F NMR ($CDCl_3$, 376 MHz): –76.0; Molecular weight $[M-H]^-$: 298.1 (expected), 298.1 (found); IR (cm^{-1}): 3321 (br), 3094, 2975, 2953, 2937, 2879, 1713, 1552, 1462, 1437, 1378, 1367, 1276, 1206, 1148, 1092.



By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL DMF), *tert*-butyl 4,7-dimethyl-7-(2,2,2-trifluoroacetamido)octanoate (12.5 mg, 38%) was obtained from 2,2,2-trifluoro-*N*-(2-methylhexan-2-yl)acetamide (20.4 mg). Flash column chromatography conditions: 10-20% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.91 (br, 1H), 2.28-2.13 (m, 2H), 1.81-1.60 (m, 3H), 1.44 (s, 9H), 1.41-1.39 (m, 1H), 1.37 (s, 6H), 1.31-1.21 (m,2H), 1.13-1.04 (m,1H), 0.88 (d, *J*=6.3); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.2, 156.0 (q, *J*= 35.9), 115.6 (q, *J*= 289.4), 80.1, 55.3, 37.1, 33.2, 32.6, 31.8, 30.7, 28.1, 26.3, 19.2 ; ^{19}F NMR ($CDCl_3$, 376 MHz): –76.2; Molecular weight $[M-H]^-$: 338.2 (expected), 338.1 (found); IR (cm^{-1}): 3436, 3314 (br), 3084, 2975, 2931, 2872, 1706.



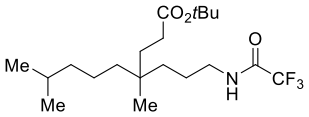
By General Procedure D (3.0 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 DMF), 2,2,2-trifluoro-N-(2,5,6-trimethyl-8-oxodecan-2-yl)acetamide (15.8 mg, 53%) was obtained as a 1:1 inseperable mixture of diastereomers from 2,2,2-trifluoro-*N*-(2-methylhexan-2-yl)acetamide (20.4 mg). Flash column chromatography conditions: 15-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.01 (br, 1H), 5.94 (br, 1H), 2.44-2.32 (m, 6H), 2.27-2.04 (m, 5H), 1.80-1.63 (m, 5H), 1.37 (s, 12H), 1.35-1.20 (m, 4H), 1.04 (t, *J*= 7.5, 6H), 0.85-0.82 (m, 6H), 0.80-0.76 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 211.9, 211.6, 156.03 (q, *J*= 35.9), 155.98 (q, *J*= 35.8), 115.6 (q, *J*= 289.4), 55.4, 47.7, 45.7, 37.8, 37.71, 37.66, 37.3, 36.53, 36.51, 33.2, 32.5, 28.6, 27.5, 26.6, 26.40, 26.37, 26.3, 17.3, 16.1, 14.7, 14.4, 7.8; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.13, −76.16; Molecular weight $[M-H]^-$: 308.2 (expected), 308.2 (found); IR (cm^{-1}): 3326 (br), 3086, 2968, 2938, 2878, 1707.

Photocatalytic C-C Bond Formation at sp^3 C-H Bonds **(Multiple Reactive C-H Bonds)**

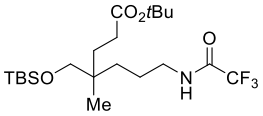
General Procedure D: Photocatalytic C-C Bond Formation

To a mixture of the amine (0.1 mmol, 1 equiv.), alkene and finely ground K_3PO_4 (0.2 mmol, 2 equiv.) in a vial was added 3 drops of deionized water (~40 mg), followed by the solvent. Argon was bubbled through the solution for 5 mins. [Ir(dF-CF_3pp)$_2$dtbbp]PF_6 2-5 mol %) was added. Argon was bubbled through the solution for another 10 mins. The vial was then capped and illuminated with a Blue LED for 16-20 h (The distance between the Blue LED and the vial is around 1.5 cm). The mixture was filtered through silica gel. The product was purified by column chromatography.



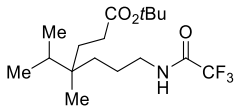
By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$), *tert*-butyl 4,8-dimethyl-4-(3-(2,2,2-trifluoroacetamido)propyl)nonanoate (22.9 mg, 64%) was obtained from *N*-(4,8-dimethylnonyl)-2,2,2-trifluoroacetamide (24.3 mg). Flash column chromatography conditions: 15-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 6.35 (br, 1H), 3.33 (q, *J*= 6.8 Hz, 2H),2.13-2.09 (m, 2H), 1.54-1.48 (m, 5H), 1.44(s, 9H), 1.21=1.11 (m, 7H), 0.86 (d, *J*= 6.6, 6H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.7, 157.1 (q, *J*= 37.1), 115.8 (q, *J*= 287.6), 80.2, 40.6, 39.8, 39.3, 36.0, 34.6, 33.9, 30.3, 28.1, 27.9, 24.5, 23.4, 22.6, 21.1; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.8; Molecular weight [M-H]$^-$: 394.3 (expected), 394.2 (found); IR (cm^{-1}): 3324 (br), 3100, 2956, 2933, 2870, 1728, 1703.



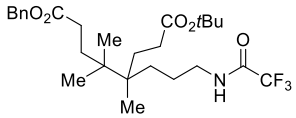
By General Procedure D (3.0 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL $PhCF_3$) *tert*-butyl 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (22.8 mg, 54) was obtained from *N*-(5-((*tert*-butyldimethylsilyl)oxy)-4-methylpentyl)-2,2,2-trifluoroacetamide (30.2 mg). Some starting material (7.8 mg, 20%) was also covered. First chromatography: 10-25% Et_2O/hexane. Second chromatography: 10-45% Et_2O/hexane, florisil (200 mesh, fine powder, activated magnesium silicate)

^{1}H NMR ($CDCl_3$, 400 MHz): 6.29 (br, 1H), 3.34 (q, *J*= 6.5, 2H), 3.25 (s, 2H), 2.17-2.13 (m, 2H), 1.55-1.52 (m, 4H), 1.44 (s, 9H), 1.27-1.24 (m, 2H), 0.88 (s, 9H), 0.79 (s, 3H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.6, 80.1, 68.9, 40.7, 37.0, 33.4, 31.5, 30.3, 28.1, 25.8, 23.3, 21.5, 18.2, −5.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.8; Molecular weight [M-H]$^-$: 454.3 (expected), 454.3 (found); IR (cm^{-1}): 3312 (br), 2955, 2931, 2858, 1728, 1704. The carbons in the trifluoroacetyl group cannot be observed in ^{13}C NMR even after extended NMR time but their presence is supported by ^{19}F NMR.



By General Procedure D (1.5 equiv. of alkene, 2 mol % Ir photocatalyst, 0.25 mL $PhCF_3$) *tert*-butyl 4-isopropyl-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (15.2 mg, 46%) was obtained from *N*-(4,5-dimethylhexyl)-2,2,2-trifluoroacetamide (21.1 mg). Some starting material (9.1 mg, 43%) was also covered. Flash column chromatography conditions: 20-30% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 6.46 (br, 1H), 3.32 (q, *J*= 6.8, 2H), 2.10 (t, *J*= 8.4, 2H), 1.61-1.51 (m, 5H), 1.44 (s, 9H), 1.29-1.18 (m, 2H), 0.83-0.81 (m, 6H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.8, 157.1 (q, *J*= 36.6), 115.9 (q, *J*= 287.9), 80.2, 40.7, 36.6, 33.5, 33.3, 31.3, 30.2, 28.1, 23.2, 20.6, 17.0; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M-H]^-$: 352.2 (expected), 352.2 (found); IR (cm^{-1}): 3318 (br), 3096, 2966, 2878, 1727, 1703.



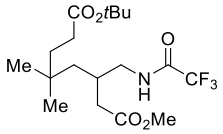
By General Procedure D (3.0 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL $PhCF_3$) 1-benzyl 8-(*tert*-butyl) 4,4,5-trimethyl-5-(3-(2,2,2-trifluoroacetamido)propyl)octanedioate (19.3 mg, 39%) was obtained from *tert*-butyl 4-isopropyl-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (33.9 mg). Flash column chromatography conditions: 25-45% Et_2O/hexane.

^1H NMR ($CDCl_3$, 400 MHz): 7.37-7.29 (m, 5H), 6.40 (br, 1H), 5.11 (s, 2H), 3.31 (q, *J*= 6.8, 2H), 2.34-2.30 (m, 2H), 2.19-2.15 (m, 2H), 1.67-1.55 (m, 6H), 1.44 (s, 9H), 1.35-1.29 (m, 2H), 0.80 (s, 6H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.3, 173.6, 157.2 (q, *J*= 36.9), 136.0, 128.6, 128.3, 128.2, 115.8 (q, *J*= 287.9), 80.4, 66.3, 40.9, 40.1, 38.9, 32.3, 32.0, 31.5, 30.0, 29.8, 28.1, 25.3, 21.7, 21.6, 19.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular Weight $[M-H]^-$: 514.3 (expected), 514.3 (found); IR (cm^{-1}): 3313 (br), 3095, 3074, 2035, 2974, 2881, 1727.

Application to Biologically Interesting Molecules

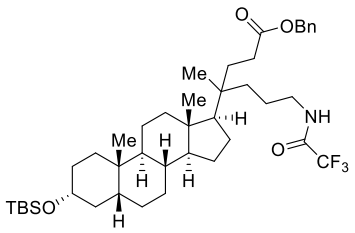
General Procedure D: Photocatalytic C-C Bond Formation

To a mixture of the amine (0.1 mmol, 1 equiv.), alkene and finely ground K_3PO_4 (0.2 mmol, 2 equiv.) in a vial was added 3 drops of deionized water (~40 mg), followed by the solvent. Argon was bubbled through the solution for 5 mins. $[Ir(dF\text{-}CF_3pp)_2dtbbp]PF_6$ (2-5 mol %) was added. Argon was bubbled through the solution for another 10 mins. The vial was then capped and illuminated with a Blue LED for 16-20 h (The distance between the Blue LED and the vial is around 1.5 cm). The mixture was filtered through silica gel. The product was purified by column chromatography.



By General Procedure D (3.0 equiv. of alkene, 4 mol % Ir photocatalyst, 0.25 mL 1:1 $PhCF_3$/*t*-amyl alcohol) 8-(*tert*-butyl) 1-methyl 5,5-dimethyl-3-((2,2,2-trifluoroacetamido)methyl)octanedioate (27.2 mg, 70%) was obtained from methyl 5-methyl-3-((2,2,2-trifluoroacetamido)methyl)hexanoate (26.6 mg). The product was purified by flash column chromatography twice. First Chromatography: 30-40% Et_2O/hexane, Si gel; Second chromatography: 25-100% Et_2O/hexane, florisil (200 mesh, fine powder, activated magnesium silicate)

^1H NMR ($CDCl_3$, 400 MHz): 7.09 (br, 1H), 3.69 (s, 3H), 3.44-3.38 (m, 1H), 3.30-3.23 (m, 1H), 2.46 (dd, *J*= 16.0, 4.3, 1H), 2.35 (dd, *J*= 16.0, 7.8, 1H), 2.23-2.14 (m, 3H), 1.55-1.51 (m, 2H), 1.44 (s, 9H), 1.22 (d, *J*= 5.1, 2H), 0.91-0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.7, 173.3, 157.5 (q, *J*= 37.4), 115.9 (q, *J*= 287.6), 80.3, 51.9, 45.5, 44.0, 39.5, 37.0, 33.2, 30.7, 30.6, 28.1, 26.5, 26.4; ^{19}F NMR ($CDCl_3$, 376 MHz): −76.0; Molecular weight $[M\text{-}H]^-$: 396.2 (expected), 396.2 (found); IR (cm^{-1}): 3327 (br), 309, 2956, 2933, 2874, 2853, 1707.



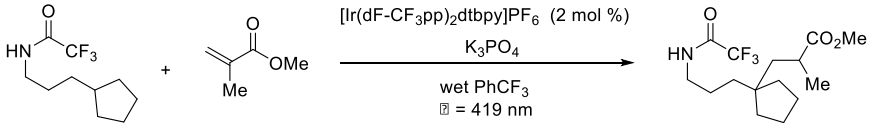
By General Procedure D (1.5 equiv. of alkene, 6 mol % Ir photocatalyst, 0.30 mL 1:1 $PhCF_3$/*t*-amyl alcohol) benzyl 4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*S*,14*S*,17*R*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[*a*]phenanthren-17-yl)-4-methyl-7-(2,2,2-trifluoroacetamido)heptanoate (30.9 mg, 44%) was obtained as a pair of diastereomeric mixture (~2:1) from *N*-((*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[*a*]phenanthren-17-yl)pentyl)-2,2,2-trifluoroacetamide (21.1 mg). Some starting material (25.0 mg, 47%) was also covered. Flash column chromatography conditions: 5-25% Et_2O/hexane.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.39-7.30 (m, 5H), 6.31 (br, 1H), 5.11 (s, 2H), 3.61-3.53 (m, 1H), 3.37-3.24 (m, 2H), 2.29-2.25 (m, 2H), 1.81-1.59 (m, 5), 1.53-0.89 (m, 39H), 0.73 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): 174.1, 157.1 (q, *J*=36.6), 136.0, 135.9, 128.55, 128.54, 128.23, 128.21, 128.19, 72.7, 66.3, 66.3, 56.7, 56.6, 56.5, 43.8, 43.8, 42.2, 40.1, 40.9, 40.6, 40.6, 40.2, 43.8, 43.8, 42.2, 41.0, 40.9, 40.6, 40.6, 40.2, 38.5, 38.5, 36.9, 35.7, 35.6, 35.5, 35.3, 35.3, 34.5, 33.5, 33.2, 31.0, 29.3, 29.0, 27.2, 26.2, 26.0, 23.6, 23.5, 23.3, 23.1, 22.9, 22.8, 22.8, 22.7, 20.6, 18.3, 15.0, 14.9, -4.6; ^{19}F NMR ($CDCl_3$, 376 MHz): −75.9; Molecular weight $[M-H]^-$: 732.5 (expected), 732.5 (found); IR (cm^{-1}): 3326 (br), 3091, 3067, 3034, 2927, 2884, 2857, 1705.

Mechanistic Studies

1. Quantum Yield and On/Off Studies

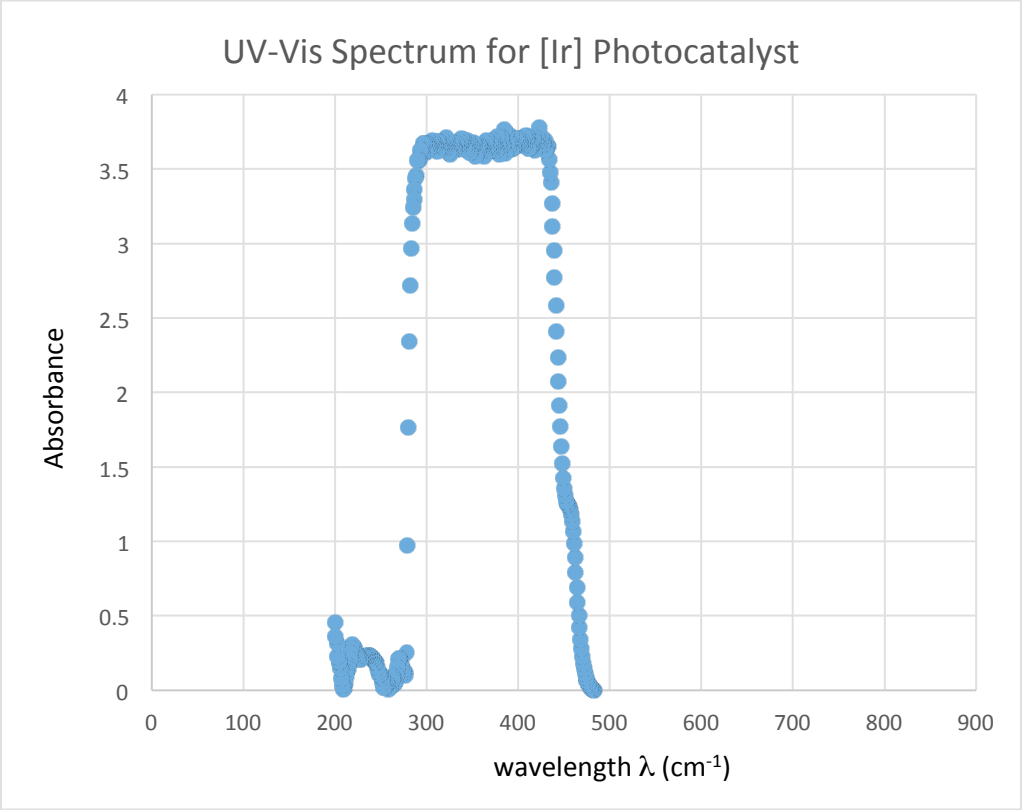
1a. Determination of Quantum Yield



The above reaction was set up in a glove box (44.1 mg starting material, 2 mol % [Ir] photocatalyst, 1.5 equiv. alkene, 2 equiv. K_3PO_4, 0.5 mL $PhCF_3$, 6 drops of H_2O). It was then taken from the glove box and irradiated (λ =419nm) for 2 h (t= 7200 s). After irradiation, the sample was filtered through silica gel. After flash column chromatography (20-40% Et_2O/hexane), 1.2 mg of the alkylated product (1.9%) was isolated.

The above experiment was repeated with 44.3 mg starting material. 1.3 mg of the alkylated product (2.0%) was isolated. The average yield of the two experiments is 1.3 mg.

By UV-Vis, all incident light is absorbed by the [Ir] photocatalyst under the reaction conditions (Absorbance > 3 in $PhCF_3$). Therefore, fraction of light absorbed is ~ 1 (f =1).



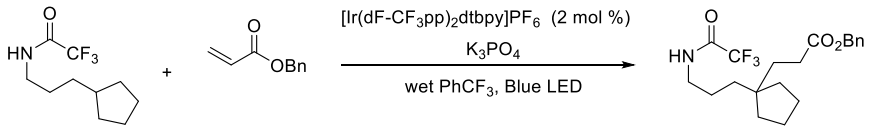
The photon flux of the spectrophotometer was measured by literature procedures (ferrioxalate actinometry).[11] At 419 nm, it was determined to be 5.2 x 10^{-9} einstein s^{-1}.

$$\text{Quantum Yield} = \frac{\text{number of moles of product}}{\text{flux x t x f}}$$

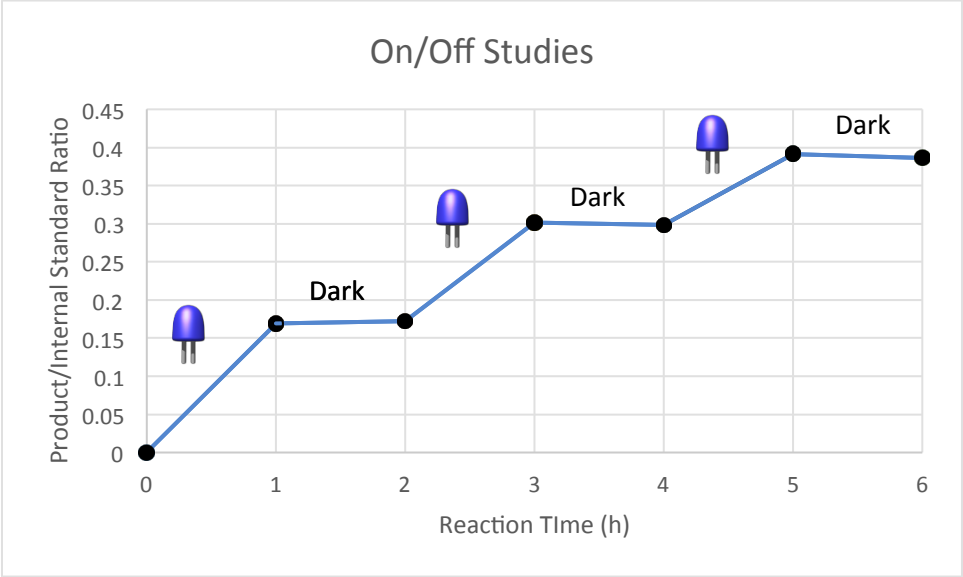
$$= \frac{1.3 / 323 / 1000}{5.2 \times 10^{-9} \times 7200 \times 1}$$

$$= 0.11$$

1b. On/Off Studies



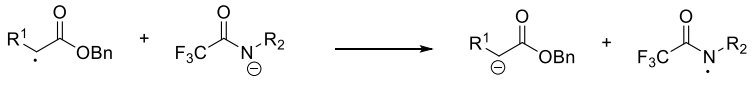
The above reaction was set up (43.8 mg starting material, 2 mol % [Ir] photocatalyst, 1.5 equiv. alkene, 2 equiv. K_3PO_4, 0.5 mL $PhCF_3$, 6 drops of H_2O) according to General Procedure D. Mesitylene was added as an internal standard. The reaction mixture was irradiated with a Blue LED for an hour. An aliquot (20 µL) was taken from the reaction mixture and filtered through a short plug of silica gel. The amount of product was determined by HPLC. The reaction mixture was degassed by bubbling argon through for 10 mins. The reaction mixture was covered by aluminum foil and re-subject to the Blue LED. The amount of the product was determined in the same way as before. After degassing, the reaction mixture was unwrapped and irradiated with the Blue LED. The reaction was monitored for 6 hours in total.



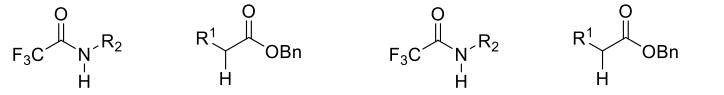
It was observed that the photoredox catalyzed reaction demonstrates an On/Off behavior. The quantum yield (<1) and the On/Off behavior are consistent with a closed catalytic cycle. We believe that chain propagation mechanism is very unlikely by considering the pKa's[12] and bond strength [13,14,15] of the reaction intermediates involved:

Potential Chain Propagation Steps and Counter Evidence:

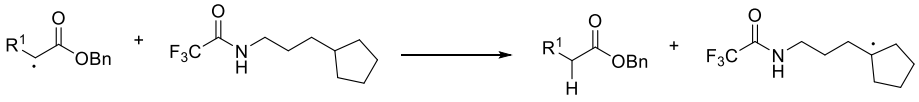
1.



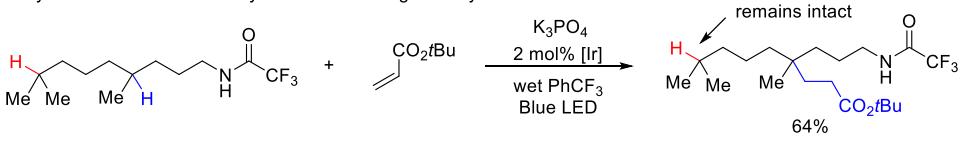
Both negative charge and radical are much less stable on the product side



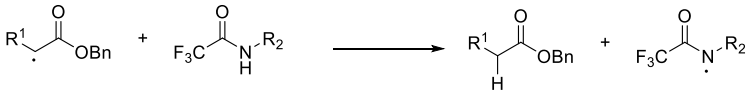
2.



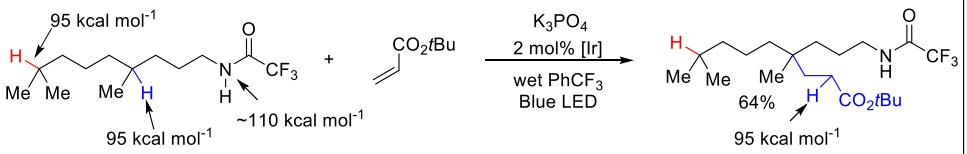
Only the C-H bond directed by the amide undergoes alkylation



3.



3° C-H bond is much weaker than N-H bond and should be preferentially broken
C-H bond α to ester is much weaker than N-H bond

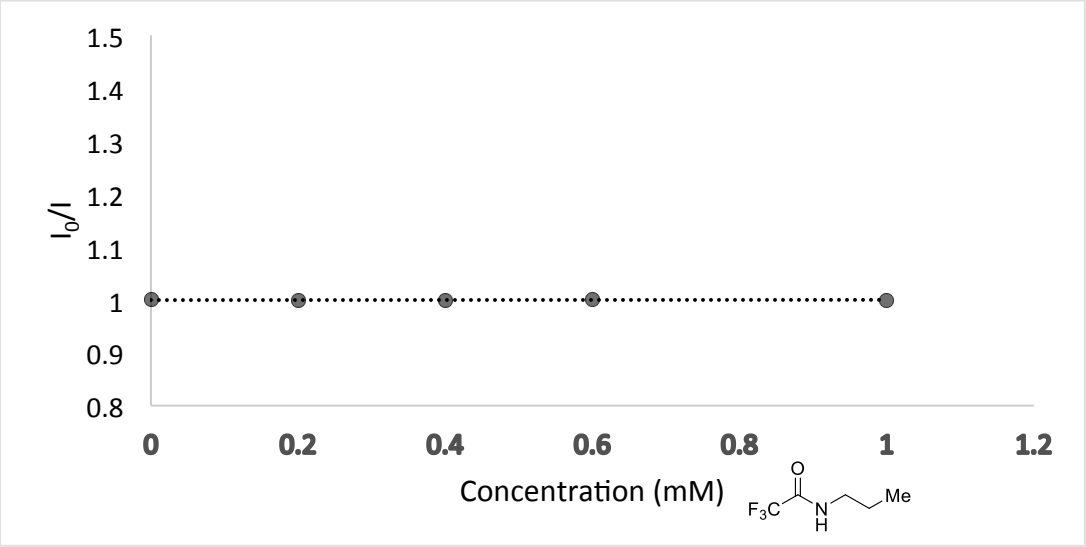


2. Potential Pathway(s) for the Generation of Nitrogen Radical

2a. Possibility of Oxidation/Deprotonation Stepwise Mechanism

Stern-Volmer studies were carried out with Horiba Fluorolog 3(model number: FL3-11). The standard solutions were prepared in DMF, a competent solvent for the reaction. The solutions (0.01 mM Ir photocatalyst and varying concentrations of trifluoroacetamide) were irradiated at 380 nm and luminescence was measured at 470 nm.

[trifluroacetamide] (mM)	0	0.2	0.4	0.6	1.0
I_0/I	1	0.99879	0.99963	1.00021	0.99988



The result shows that the Ir photocatalyst is not quenched by the neutral amide in the absence of a base. This is consistent with CV studies which were obtained with a CH instrument (electrochemical analyzer, CHI1232B, serial number: A3268). A glassy electrode, a Pt mesh counter electron and an Ag/AgCl reference electrode were used and measurement was taken in a 2 mM solution of the amide in MeCN containing 0.1 M NBu_4PF_6. No oxidation was observed even at voltage >2V vs Ag/AgCl (or >1.955 V vs SCE). This suggests that the excited Ir photocatalyst (1.2V vs SCE) cannot oxidize the neutral form of trifluoroacetamide and is consistent with the quenching studies. Thus oxidation/deprotonation stepwise event is unlikely to be responsible for the generation of the nitrogen radical.

2b. Discussion about Deprotonation/Oxidation Stepwise and PCET Mechanism

Stern-Volmer studies were also conducted with the potassium salt of trifluoroacetamide. Standard solutions of potassium propyl(2,2,2-trifluoroacetyl)amide and $[Ir(dF\text{-}CF_3pp)_2dtbbp]PF_6$ in anhydrous DMF were prepared by mixing equal amount of potassium hydride and 2,2,2-trifluoro-*N*-propylacetamide in the glove box to make sure there was no water present. The solutions (0.01 mM Ir photocatalyst and varying concentrations of potassium propyl(2,2,2-trifluoroacetyl)amide) were irradiated at 380 nm and luminescence was measured at 470 nm. The plot was obtained by two independent runs (i.e. new standard solutions were prepared for each run):

Run 1

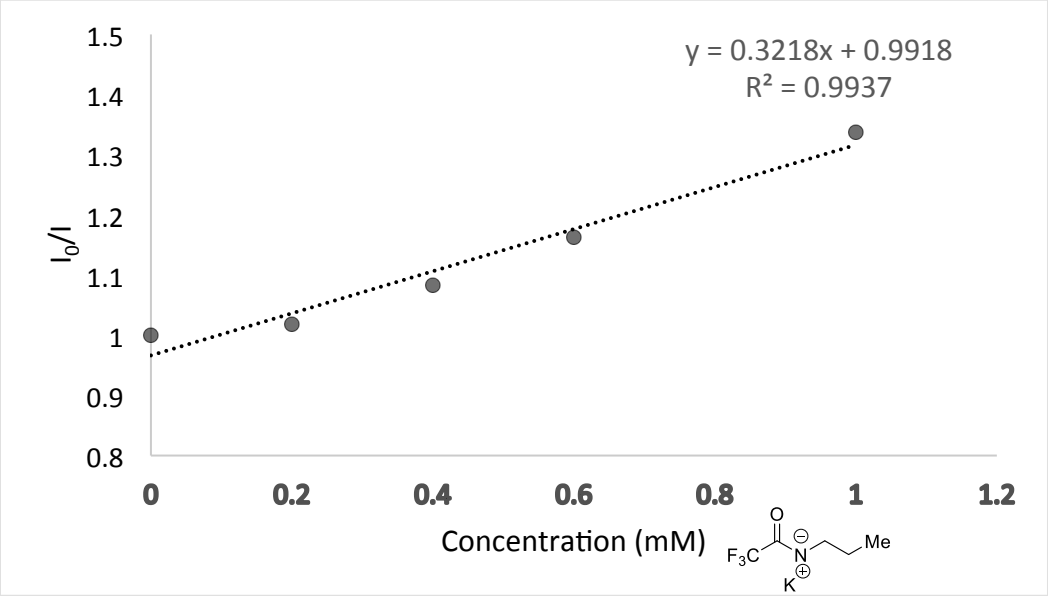
[potassium salt of trifluroacetamide] (mM)	0	0.2	0.4	0.6	1.0
I_0/I	1	1.04686	1.11111	1.19689	1.31199

Run 2

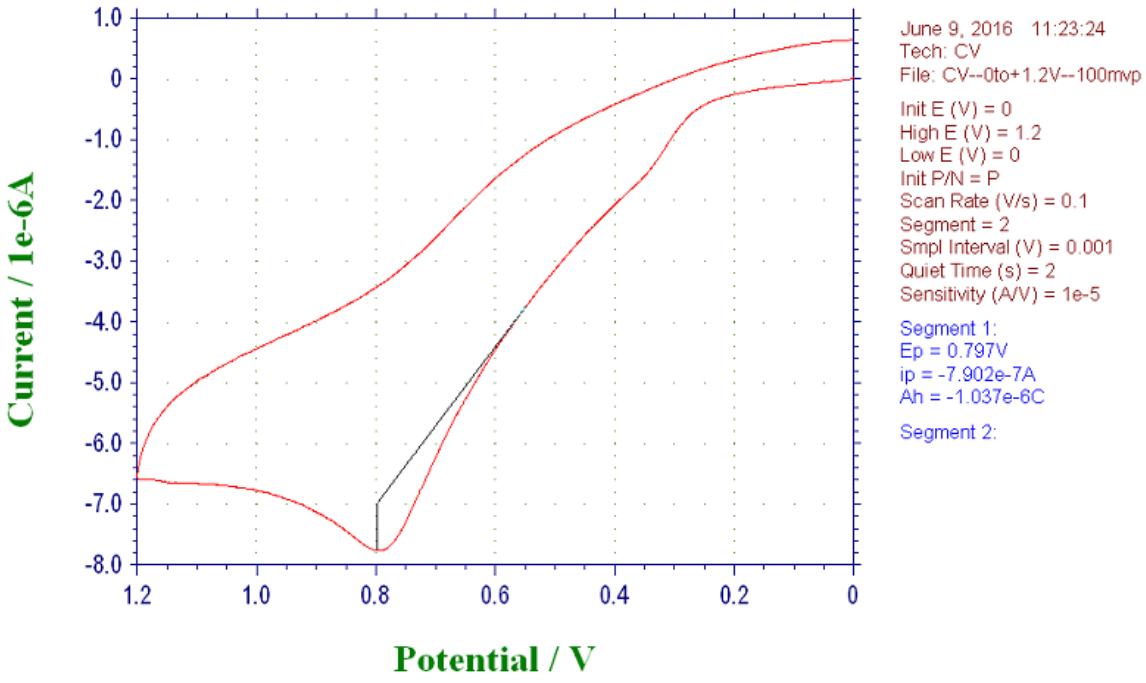
[potassium salt of trifluroacetamide] (mM)	0	0.2	0.4	0.6	1.0
I_0/I	1	0.99000	1.05505	1.14000	1.36214

Average

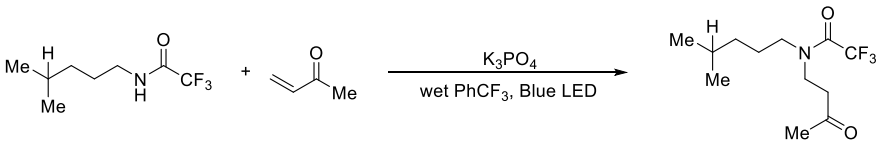
[potassium salt of trifluroacetamide] (mM)	0	0.2	0.4	0.6	1.0
I_0/I	1	1.108434	1.083081	1.163444	1.33707



The result shows that the Ir photocatalyst is quenched by the potassium salt of the trifluoroacetamide. This is consistent with CV studies which indicate that the redox potential of the potassium salt of the trifluoroacetamide is 0.80V vs Ag/AgCl (or 0.77 V vs SCE). The potential suggests that the excited state of the photocatalyst (1.2 V vs SCE) can oxidize the potassium salt of trifluoroacetamide.



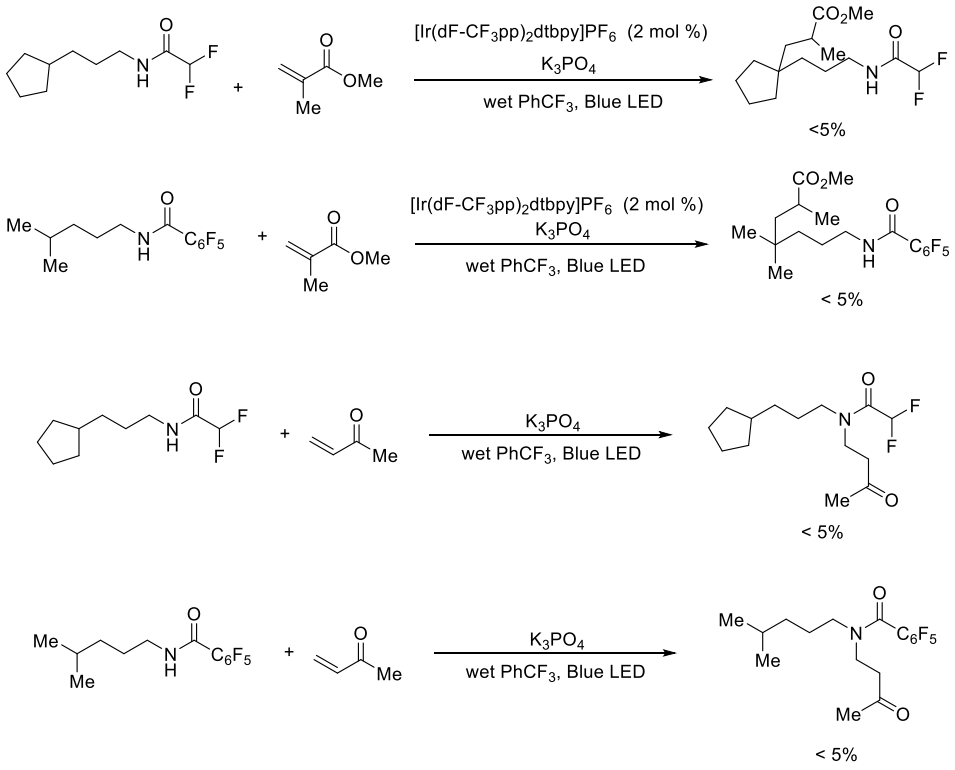
In addition, the presence of negatively charged nitrogen is evidenced by the formation of aza-Michael addition product with K_3PO_4 in $PhCF_3$ (>50% conversion, see below). No aza-Michael adduct is formed, as determined by ^1H NMR, in the absence of K_3PO_4. Substrates bearing weaker electron-withdrawing groups on nitrogen, pentafluorobenzoyl and difluoroacetyl groups (pKa of trifluoroacetic acid[16] =0.2, difluoroacetic acid[17] =1.1, pentafluorobenzoic acid[18] =1.7) do not yield the C-H functionalized product under the photocatalyzed conditions nor do they form the aza-Michael addition product with K_3PO_4 in wet $PhCF_3$ (see below). There appears a correlation between the presence of negatively charged nitrogen and the generation of nitrogen radical. Also, the reaction is biphasic and a three-component (Amide, [Ir] photocatalyst and K_3PO_4) transition state is unlikely. This leads us to believe that deprotonation then oxidation stepwise event is at least partly responsible for the generation of nitrogen radical. It is also noted that the use of a weaker base Cs_2CO_3 (pKa= 10.33) also gives the desired C-H functionalized product in diminished yield, it is therefore possible that the proton-coupled electron transfer (PCET) pathway can operate in tandem with the stepwise mechanism.



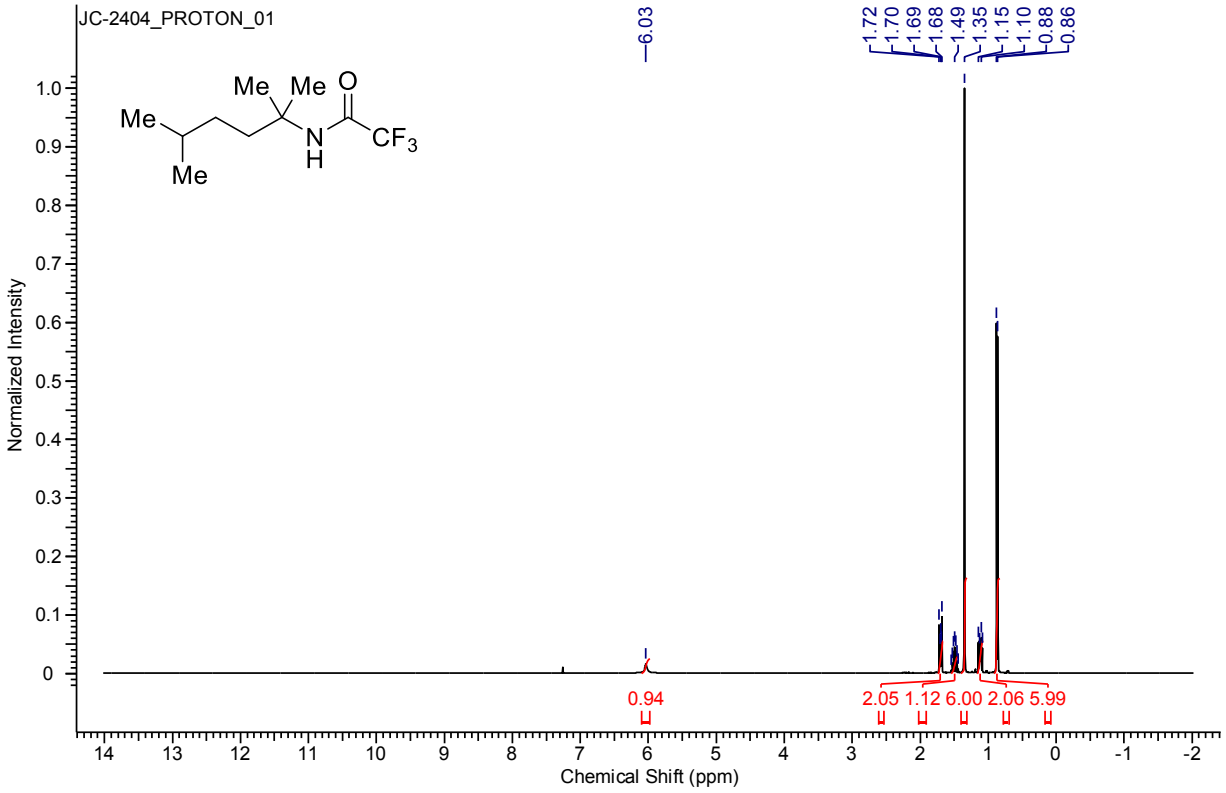
> 50% conversion
Without K_3PO_4: < 5%

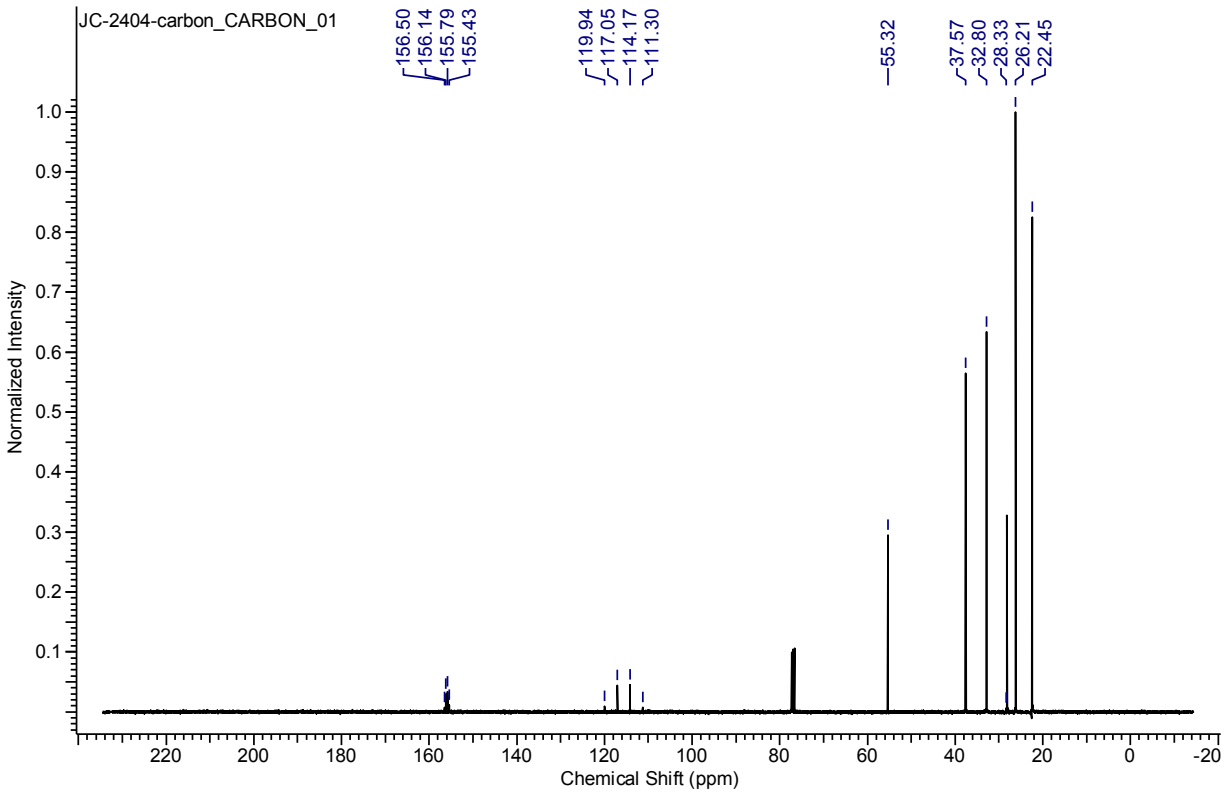
To a mixture of the amine (0.1 mmol, 1 equiv.), methyl vinyl ketone (0.15 mmol, 1.5 equiv.) and K_3PO_4 (0.2 mmol, 2 equiv.) in a vial was added 3 drops of deionized water (~40 mg), followed by $PhCF_3$ (0.25 mL). The vial was then capped and illuminated with a Blue LED for 20 h (The distance between the Blue LED and the vial is around 1.5 cm). The mixture was filtered through silica gel. The conversion was determined by ^1H NMR spectroscopy. The product can be purified by column chromatography (35-60% Et_2O/hexane). The product exists as two rotamers (~1:2), as observed in NMR. Some of the peaks of the two rotamers cannot be distinguished in ^{13}C NMR.

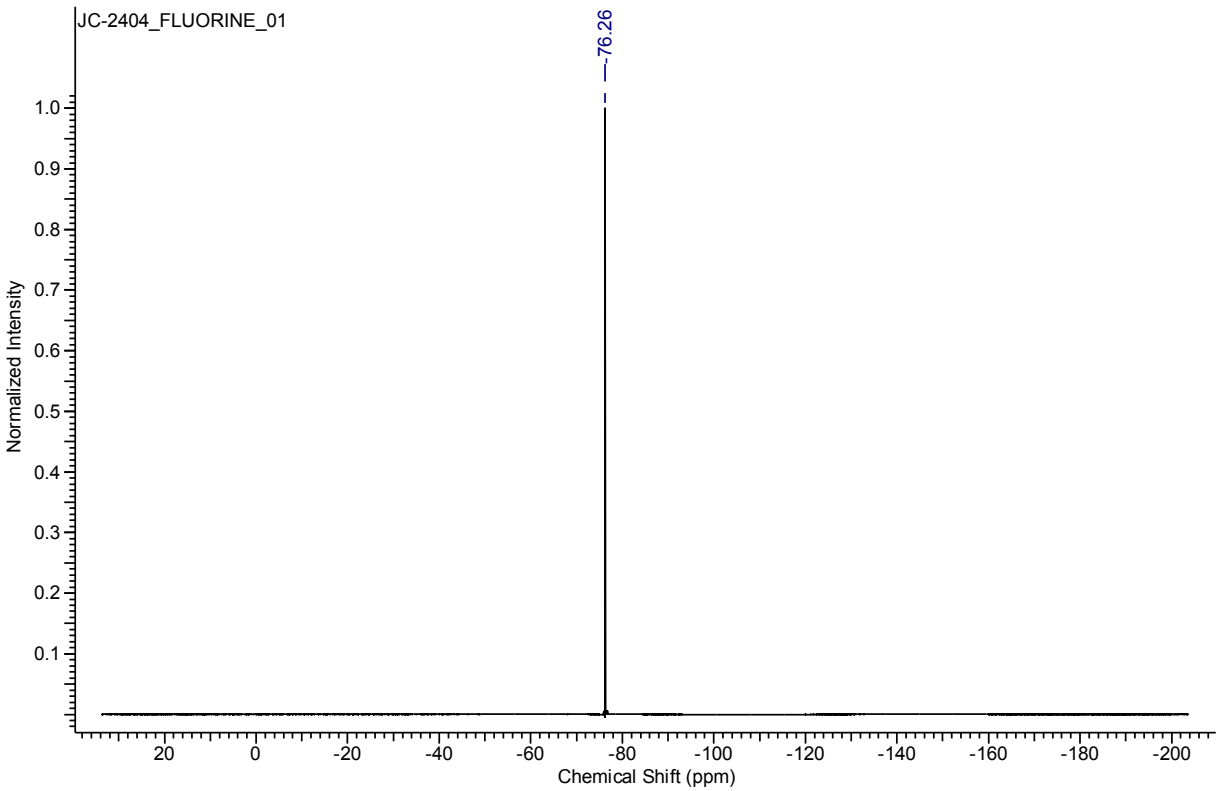
^{1}H NMR ($CDCl_3$, 400 MHz): 3.67 (t, *J*= 7.6, 1H, minor rotamer), 3.59 (t, *J*= 6.9, 2H, major rotamer), 3.36 (t, *J*= 8.0, 2H, major rotamer), 3.30 (t, *J*= 7.9, 1H, minor rotamer), 2.82 (t, *J*= 6.9, 2H, major rotamer), 2.77 (t, *J*= 7.5, 1H, minor rotamer), 2.19 (s, 1.5 H, minor rotamer), 2.17 (s, 3H, major rotamer), 1.64-1.50 (m, 4.5H, both rotamers), 1.19-1.13 (m, 3H, both rotamers), 0.90-0.87 (m, 9H, both rotamers); ^{13}C NMR ($CDCl_3$, 100 MHz): 206.5 (major rotamer), 205.4 (minor rotamer), 156.9 (q, *J*= 35.9), 116.4 (q, *J*= 287.4), 49.0 (q, *J*= 3.0, major rotamer)), 47.6, 42.7, 42.6, 41.8 (q, *J*=3.3, minor rotamer), 40.8, 35.7, 35.5, 30.2, 30.2, 27.8, 27.6, 26,7, 24.7, 22.4, 22.4 ; ^{19}F NMR ($CDCl_3$, 376 MHz): −69.21 (major rotamer), −60.29 (minor rotamer); IR (cm^{-1}): 2955, 2933, 2872, 1718, 1685, 1464, 1436; Molecular weight $[M+H]^+$: 268.2 (expected); 268.2 (found).



NMR Spectra


JC-2404_PROTON_01
Me
Me
Me
Me
O
N
H
CF3
6.03
1.72
1.70
1.69
1.68
1.49
1.35
1.15
1.10
0.88
0.86
0.94
2.05 1.12 6.00 2.06 5.99
Normalized Intensity
Chemical Shift (ppm)


JC-2404-carbon_CARBON_01
156.50
156.14
155.79
155.43
119.94
117.05
114.17
111.30
55.32
37.57
32.80
28.33
26.21
22.45
Normalized Intensity
Chemical Shift (ppm)


JC-2404_FLUORINE_01
-76.26
Normalized Intensity
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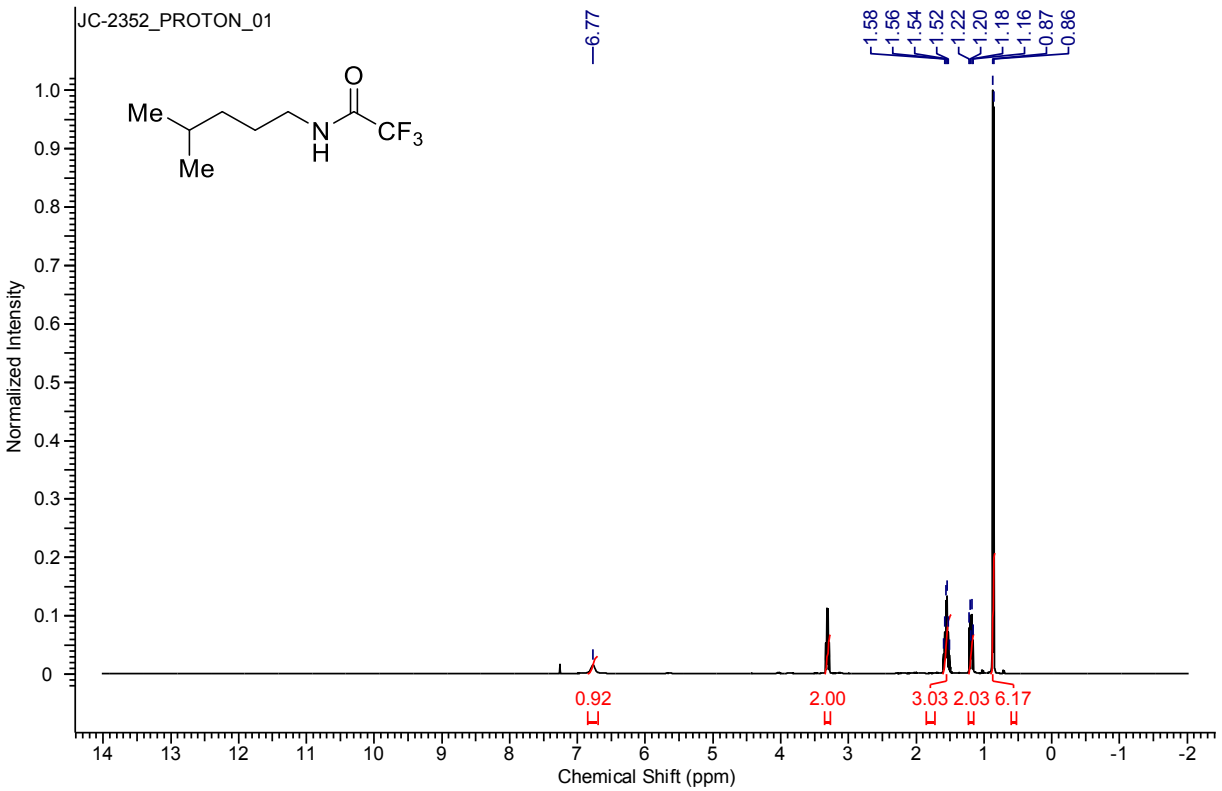
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)


JC-2352_PROTON_01
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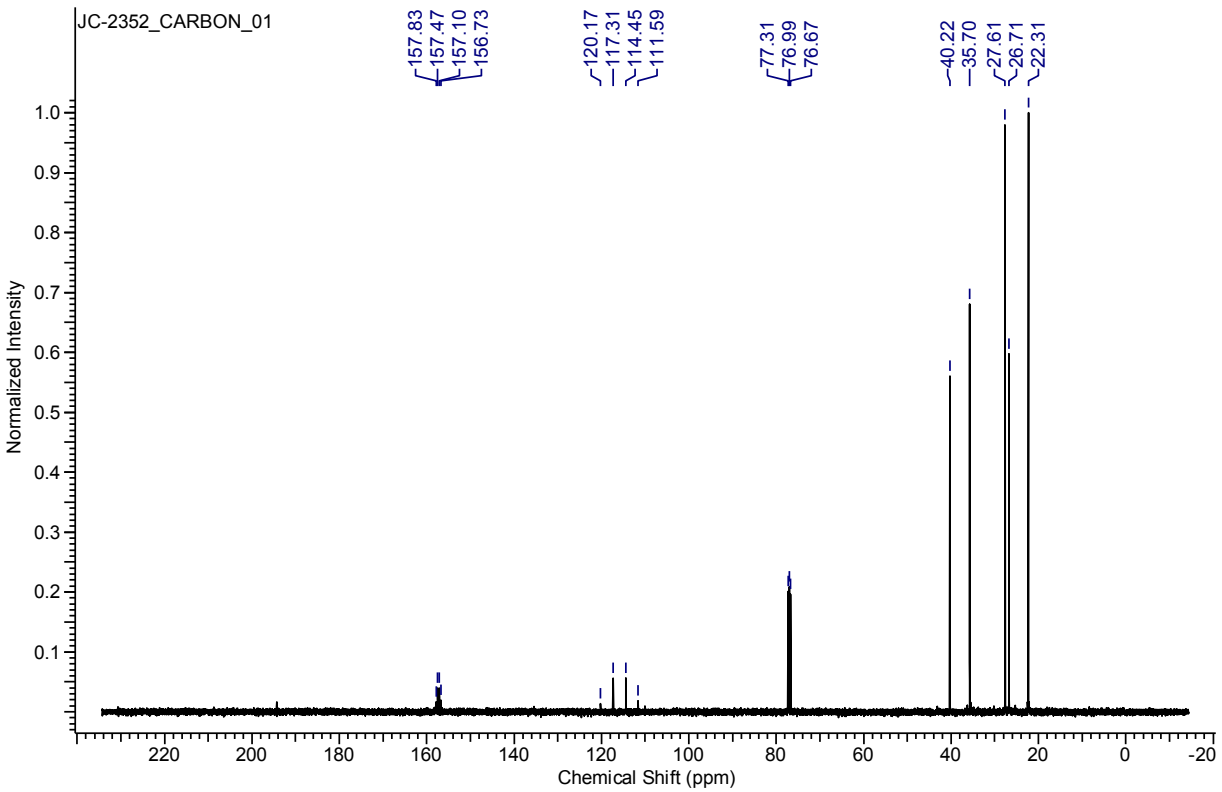
Me
N
H
O
CF3
6.77
1.58
1.56
1.54
1.52
1.22
1.20
1.18
1.16
0.87
0.86
0.92
2.00
3.03
2.03
6.17
Normalized Intensity
Chemical Shift (ppm)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117.31
114.45
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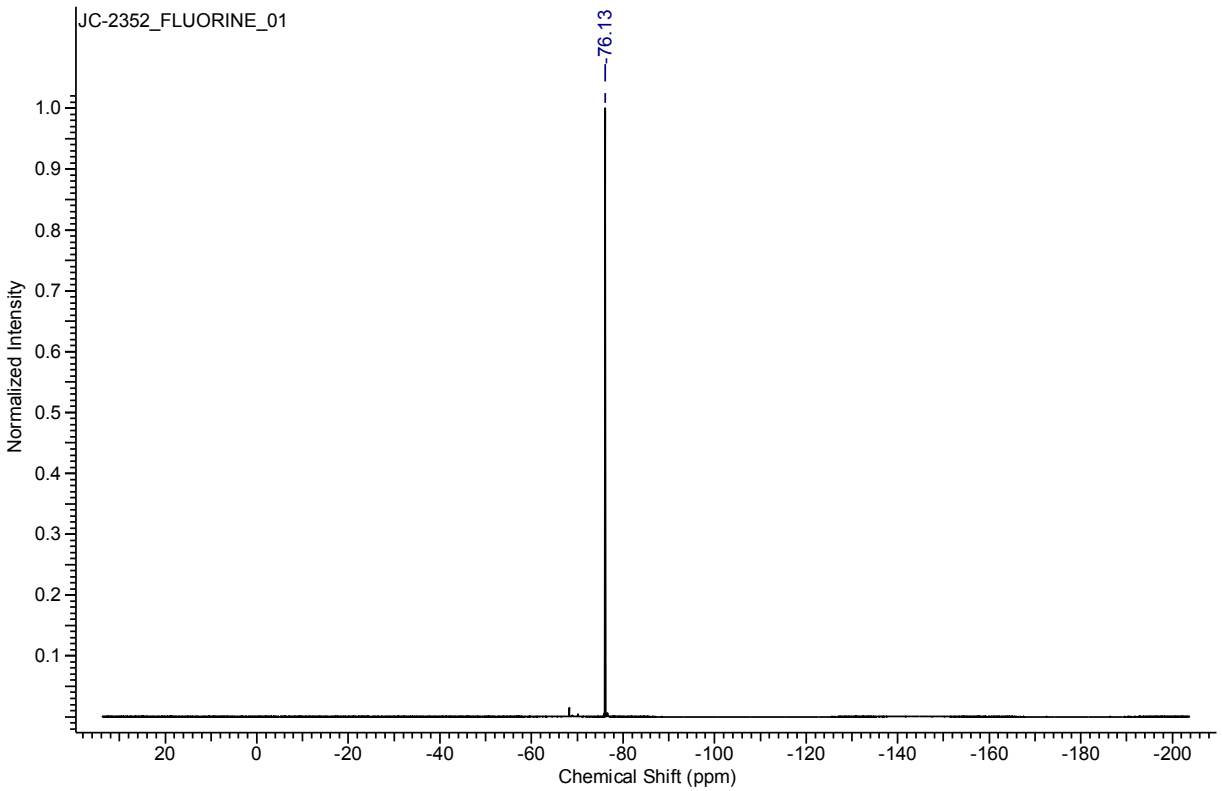
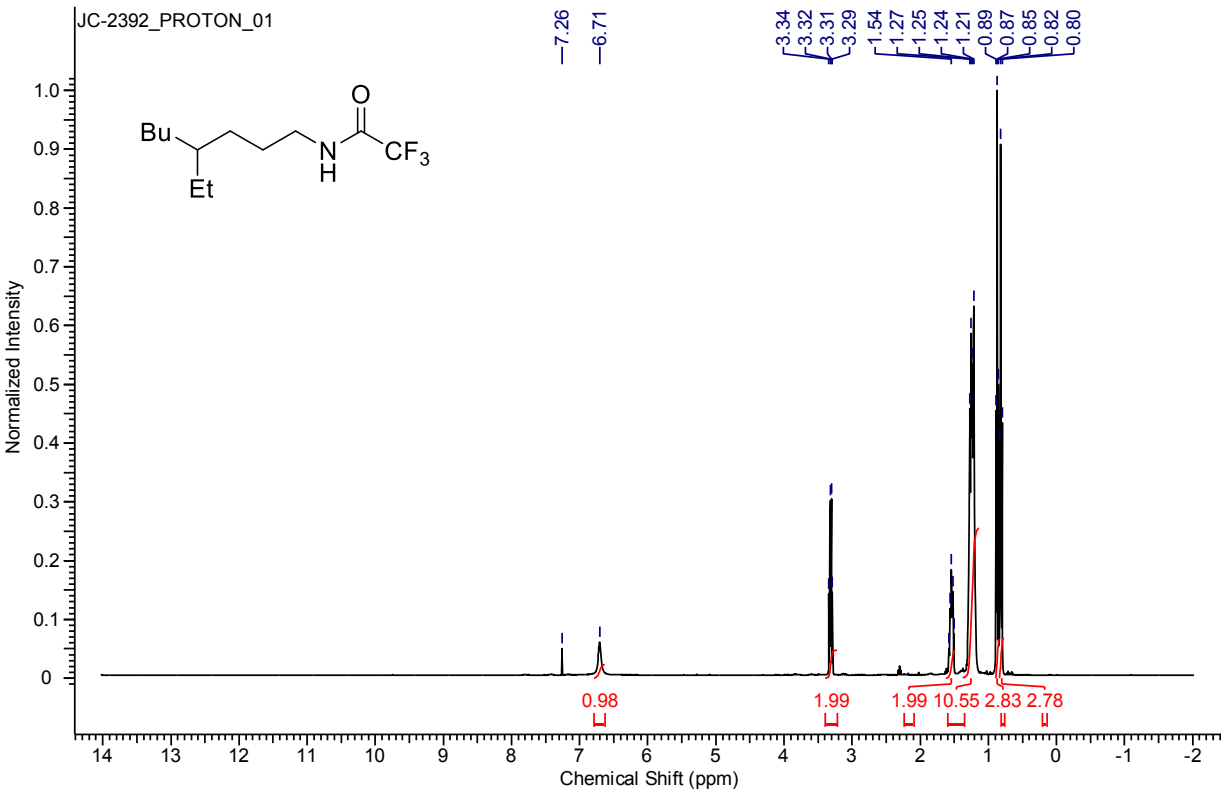
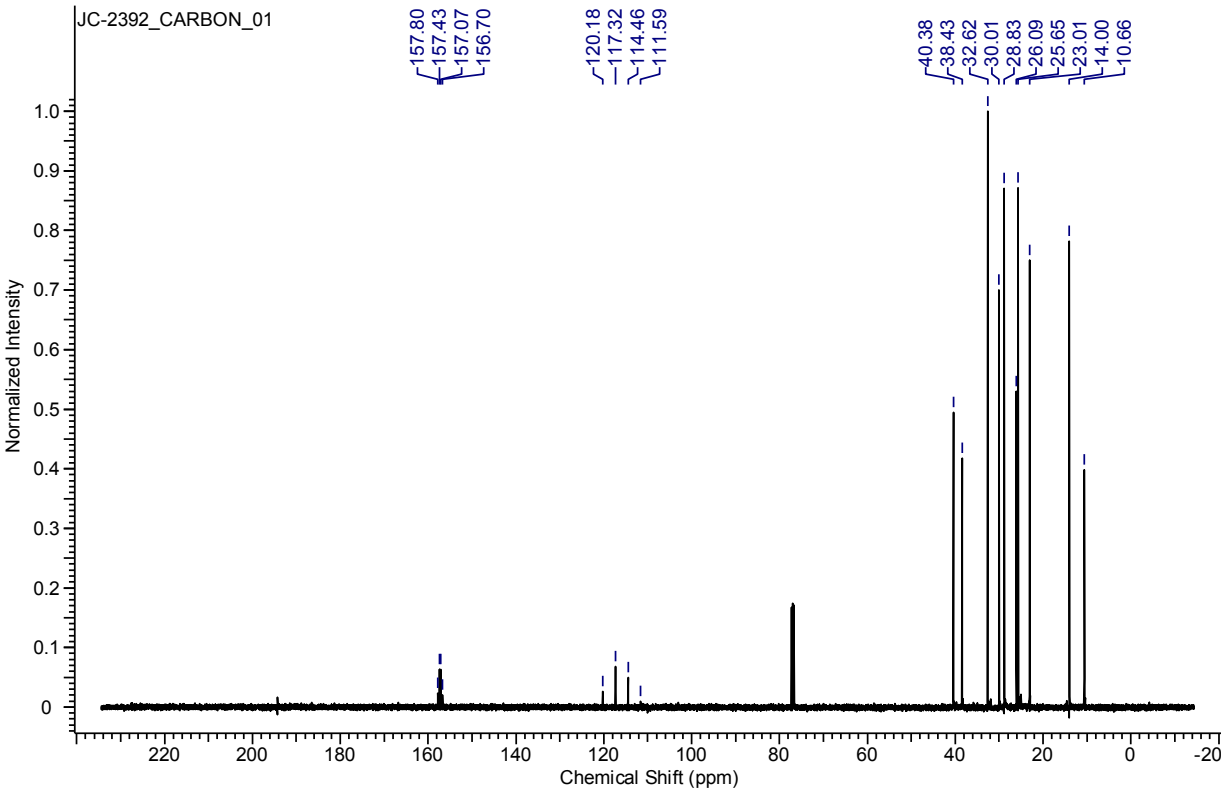
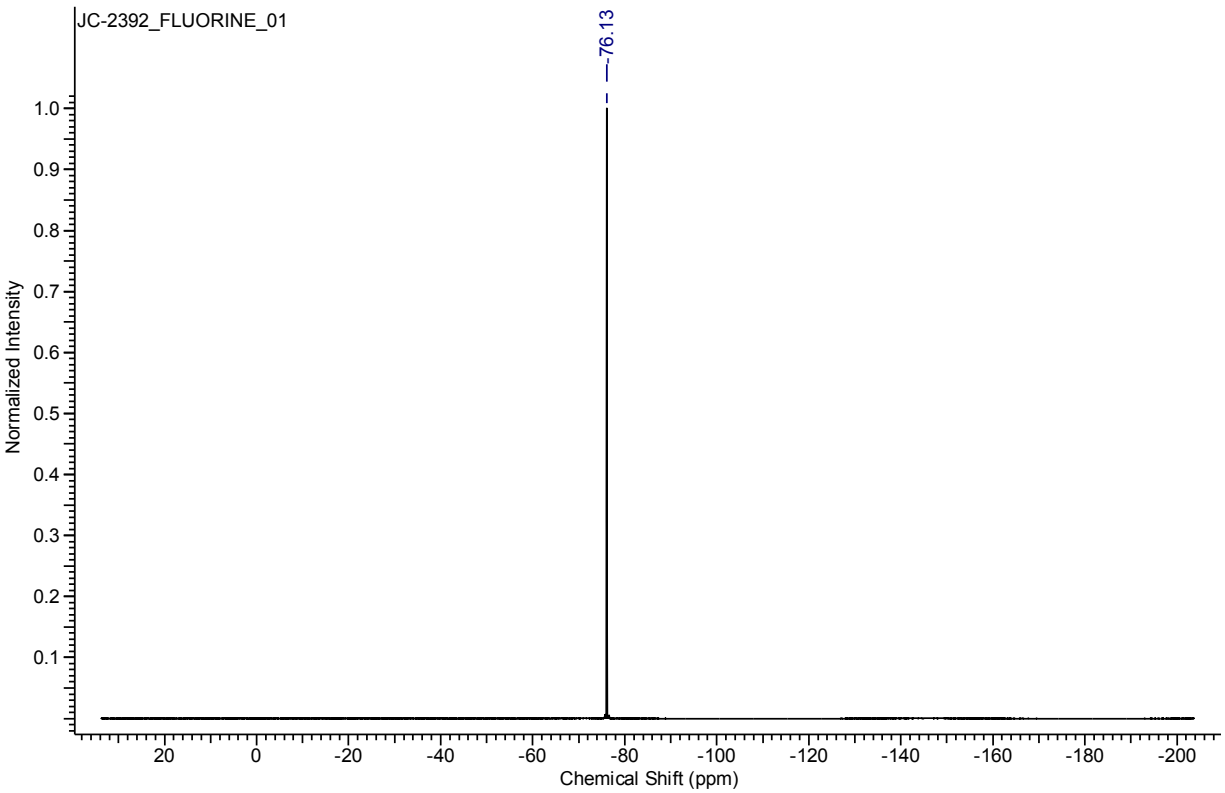
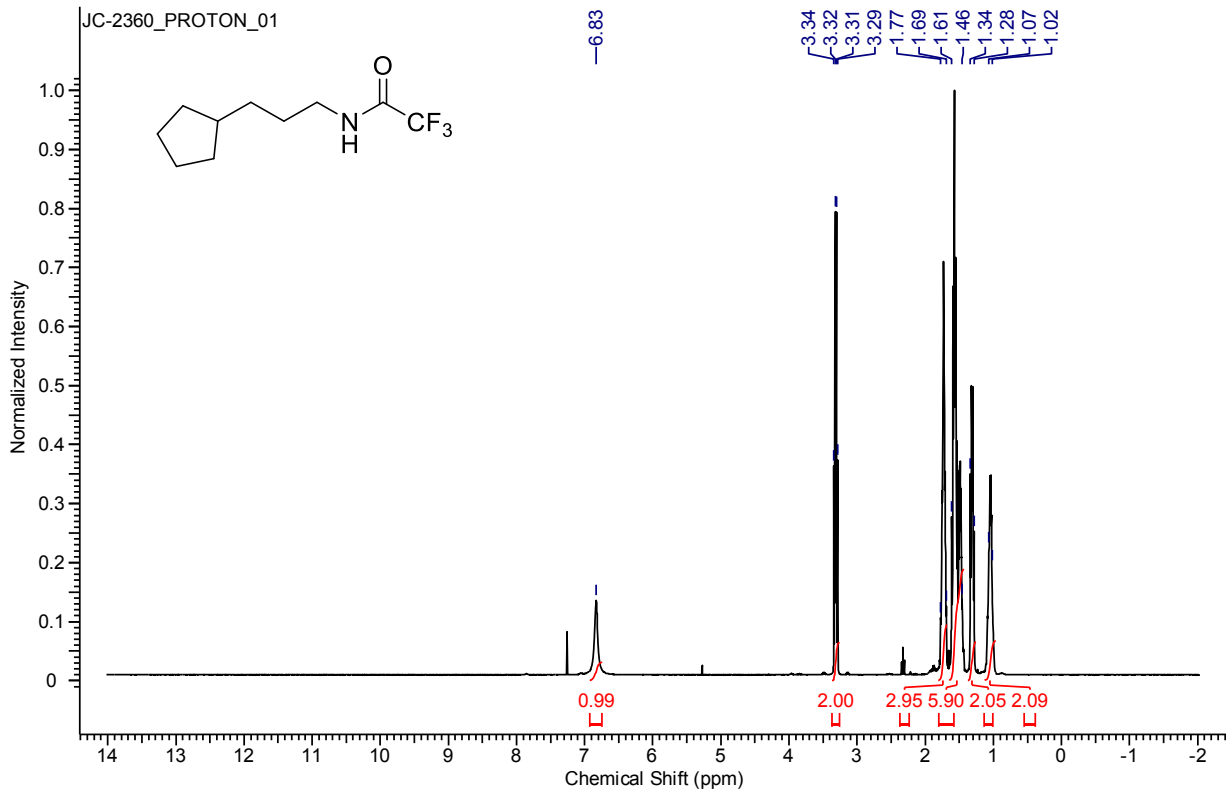
76.99
76.67
40.22
35.70
27.61
26.71
22.31
Normalized Intensity
Chemical Shift (ppm)


JC-2352_FLUORINE_01
-76.13
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)


JC-2392_PROTON_01
7.26
6.71
3.34
3.32
3.31
3.29
1.54
1.27
1.25
1.24
1.21
0.89
0.87
0.85
0.82
0.80
Bu
Et
N
H
O
CF3
0.98
1.99
1.99
10.55
2.83
2.78
Normalized Intensity
Chemical Shift (ppm)


JC-2392_CARBON_01
157.80
157.43
157.07
156.70
120.18
117.32
114.46
111.59
40.38
38.43
32.62
30.01
28.83
26.09
25.65
23.01
14.00
10.66
Normalized Intensity
Chemical Shift (ppm)


JC-2392_FLUORINE_01
-76.13
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)


JC-2360_PROTON_01
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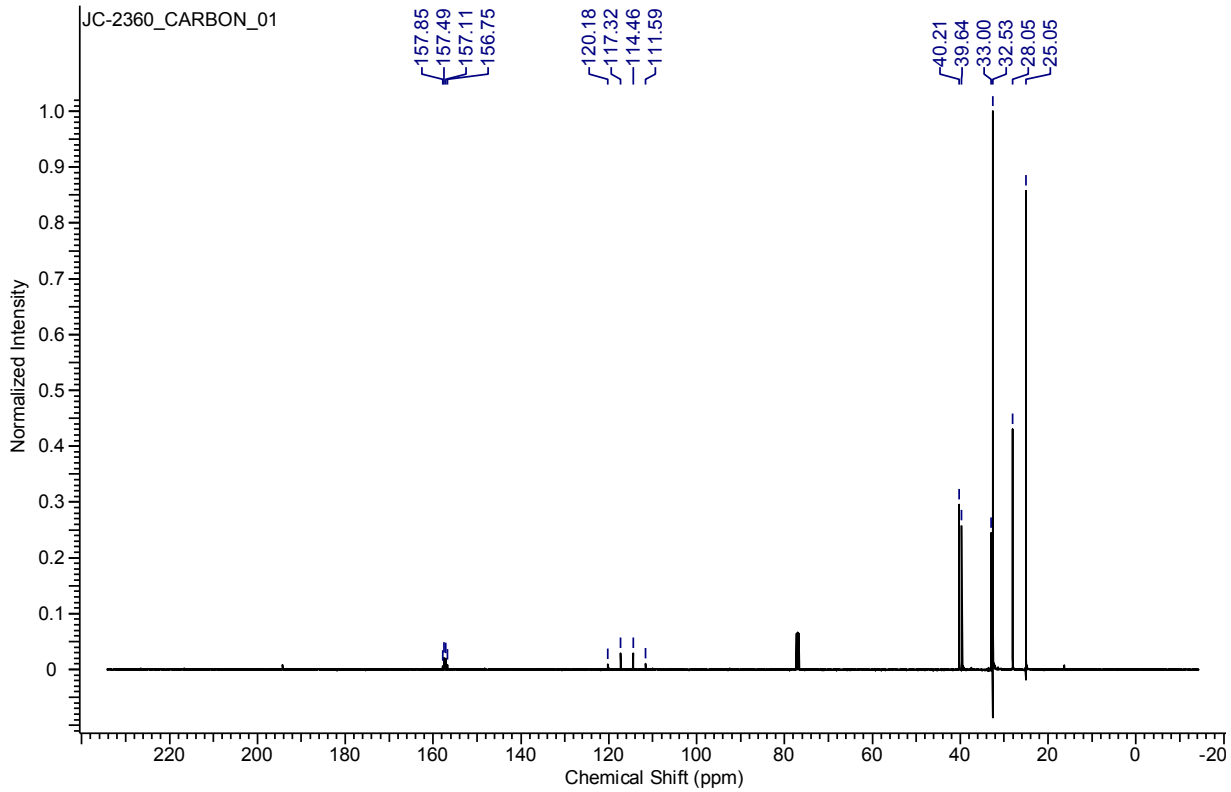
3.32
3.31
3.29
1.77
1.69
1.61
1.46
1.34
1.28
1.07
1.02
O
N
H
CF3
0.99
2.00
2.95
5.90
2.05
2.09
Normalized Intensity
Chemical Shift (ppm)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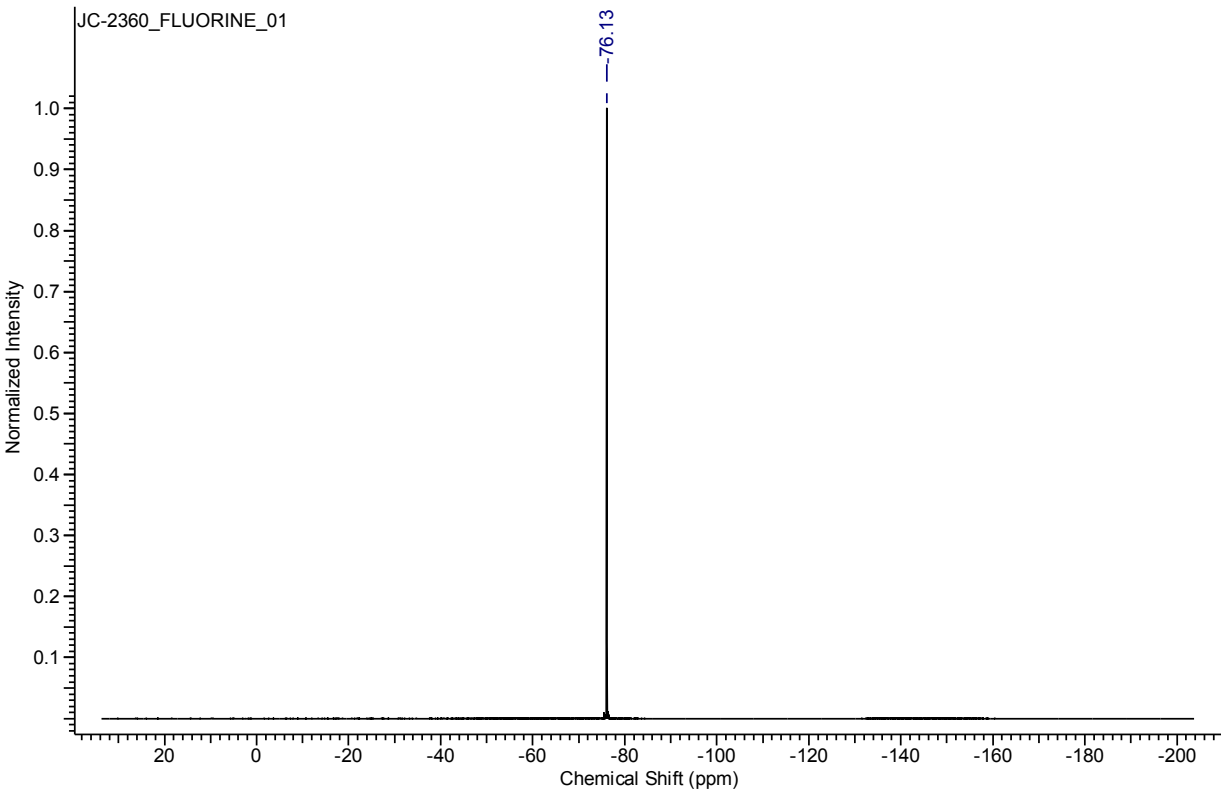
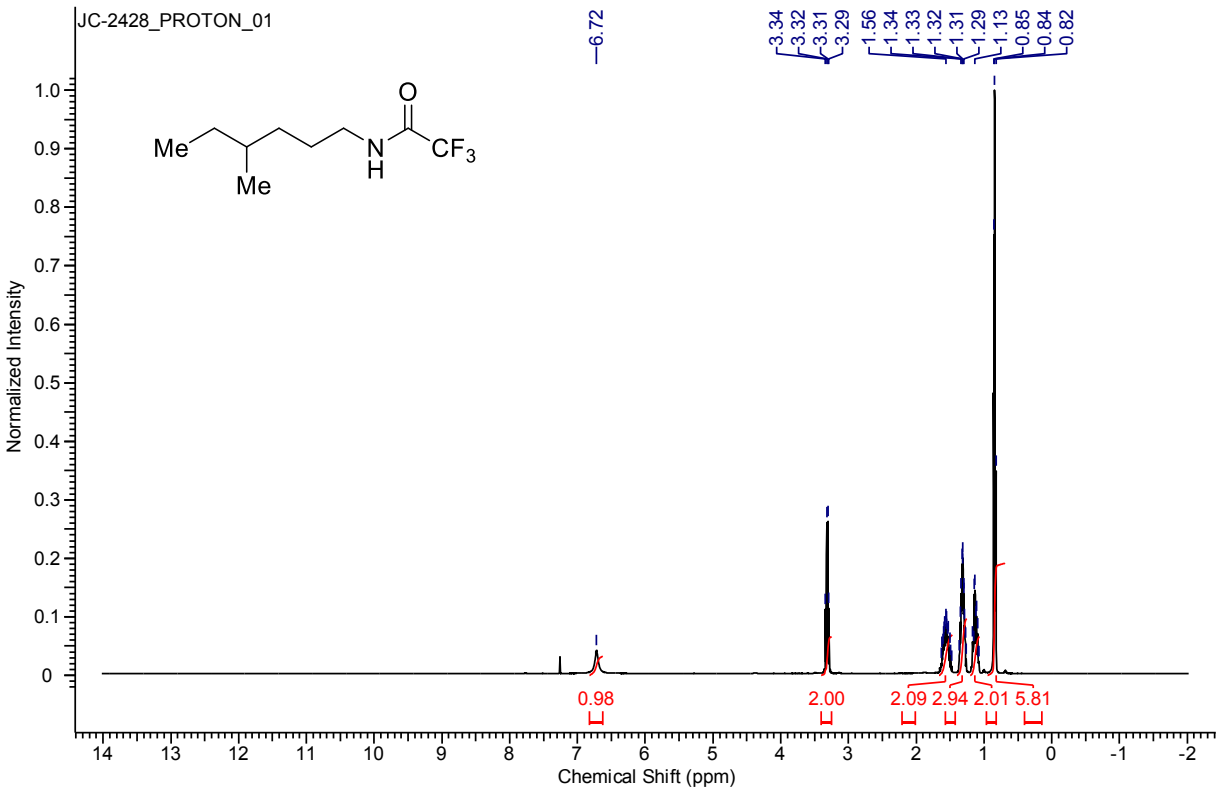
157.11
156.75
120.18
117.32
114.46
111.59
40.21
39.64
33.00
32.53
28.05
25.05
Normalized Intensity
Chemical Shift (ppm)


JC-2360_FLUORINE_01
-76.13
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)


JC-2428_PROTON_01
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3.32
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1.33
1.32
1.31
1.29
1.13
0.85
0.84
0.82
Me
Me
N
H
O
CF3
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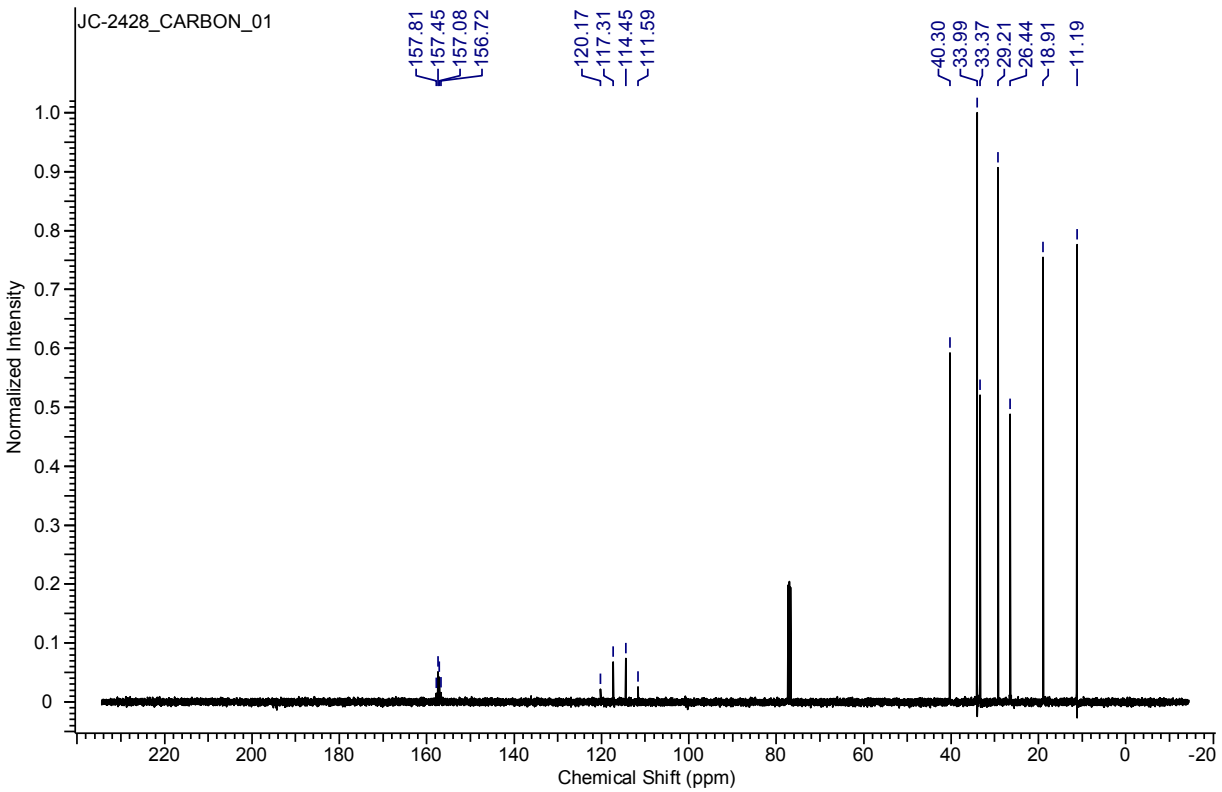
2.09
2.94
2.01
5.81
Normalized Intensity
Chemical Shift (ppm)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157.45
157.08
156.72
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117.31
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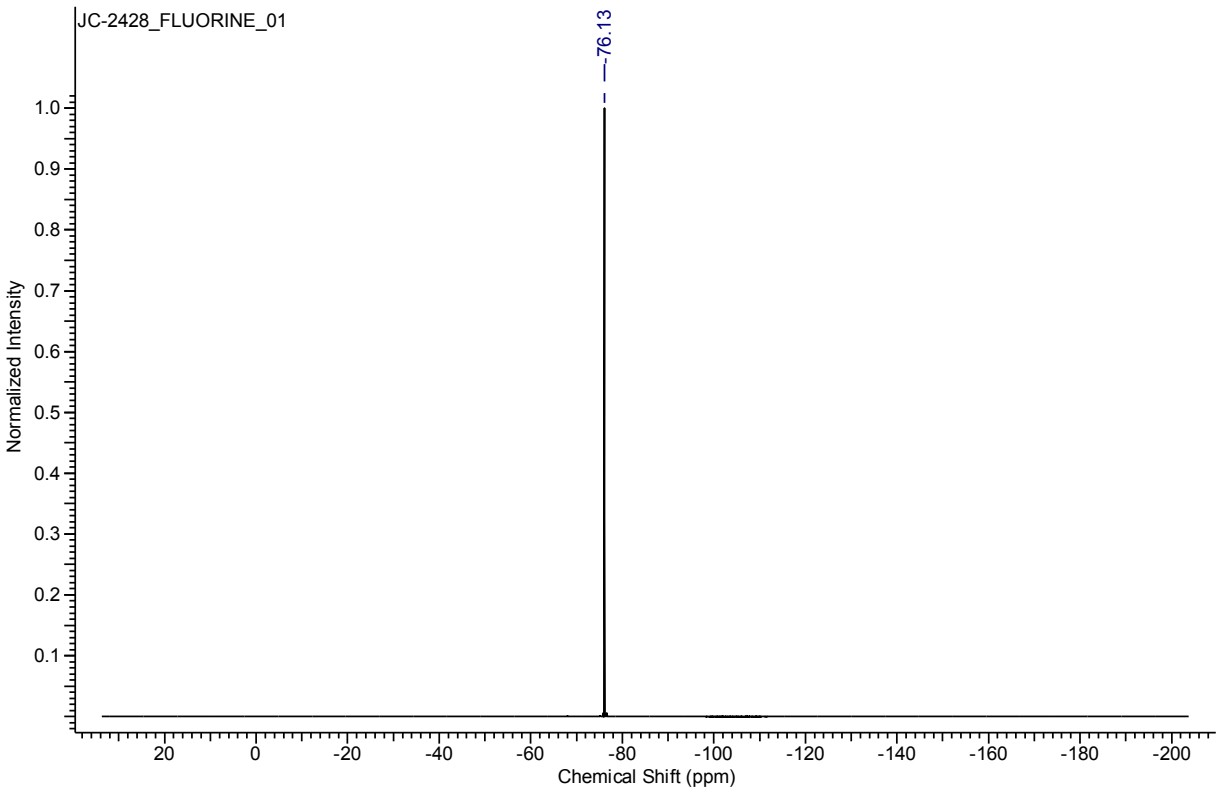
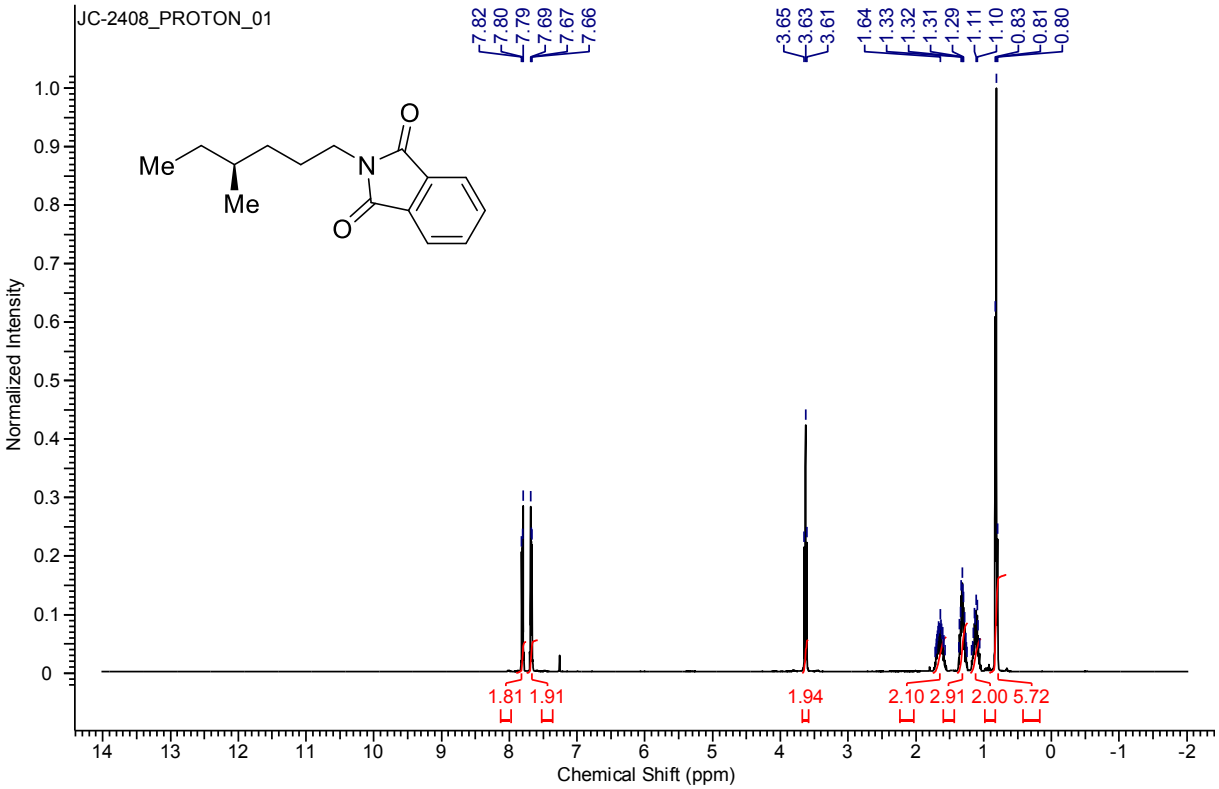
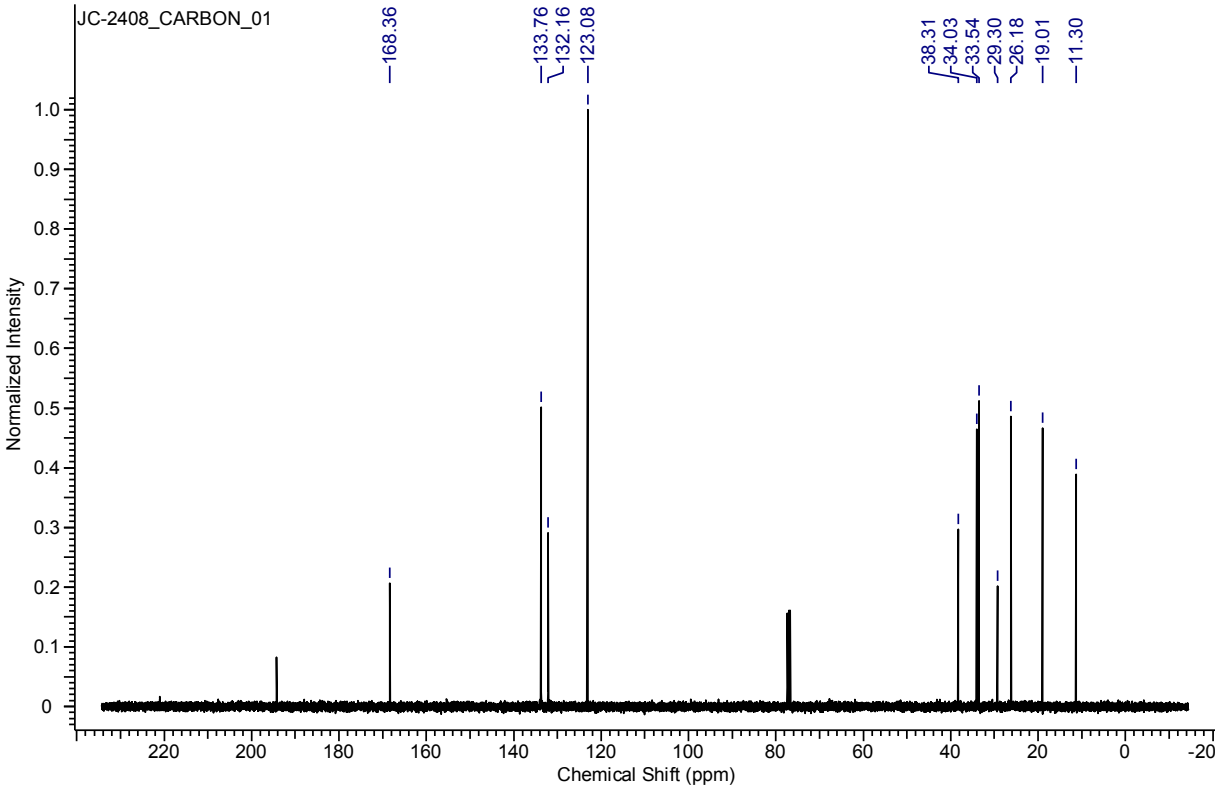
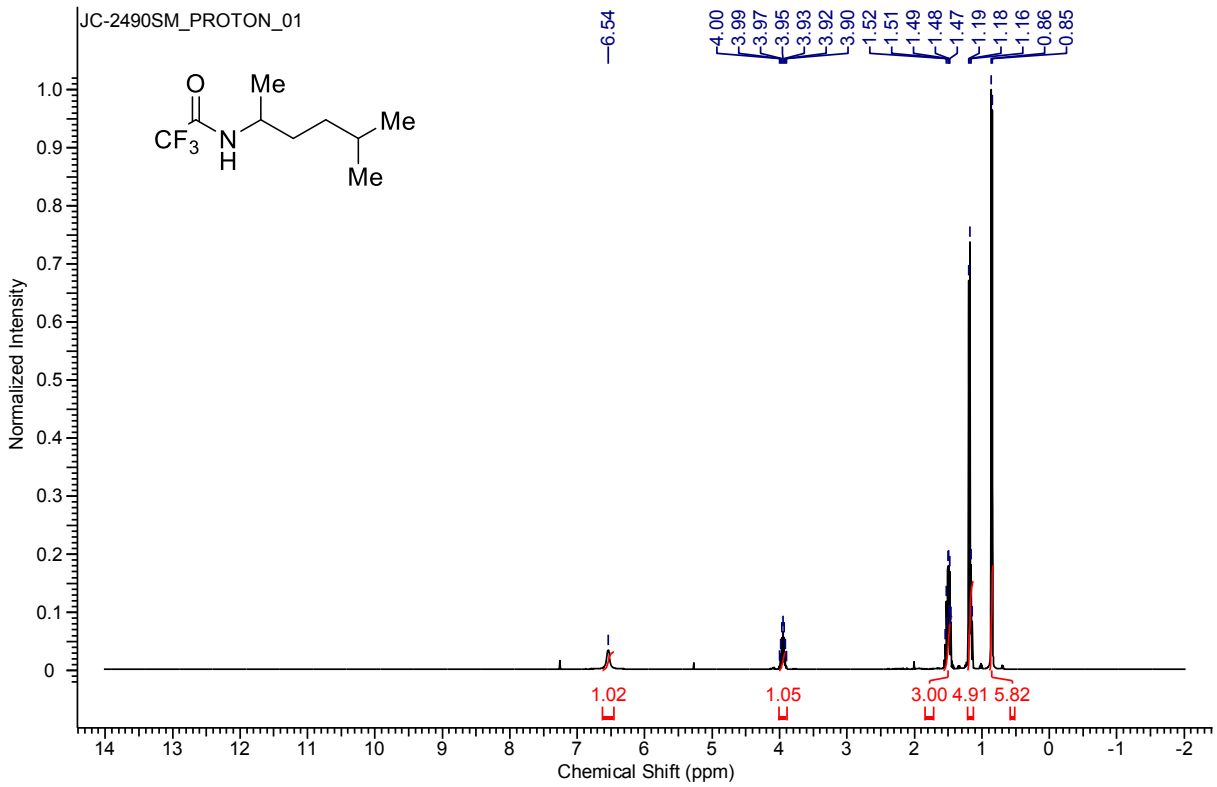
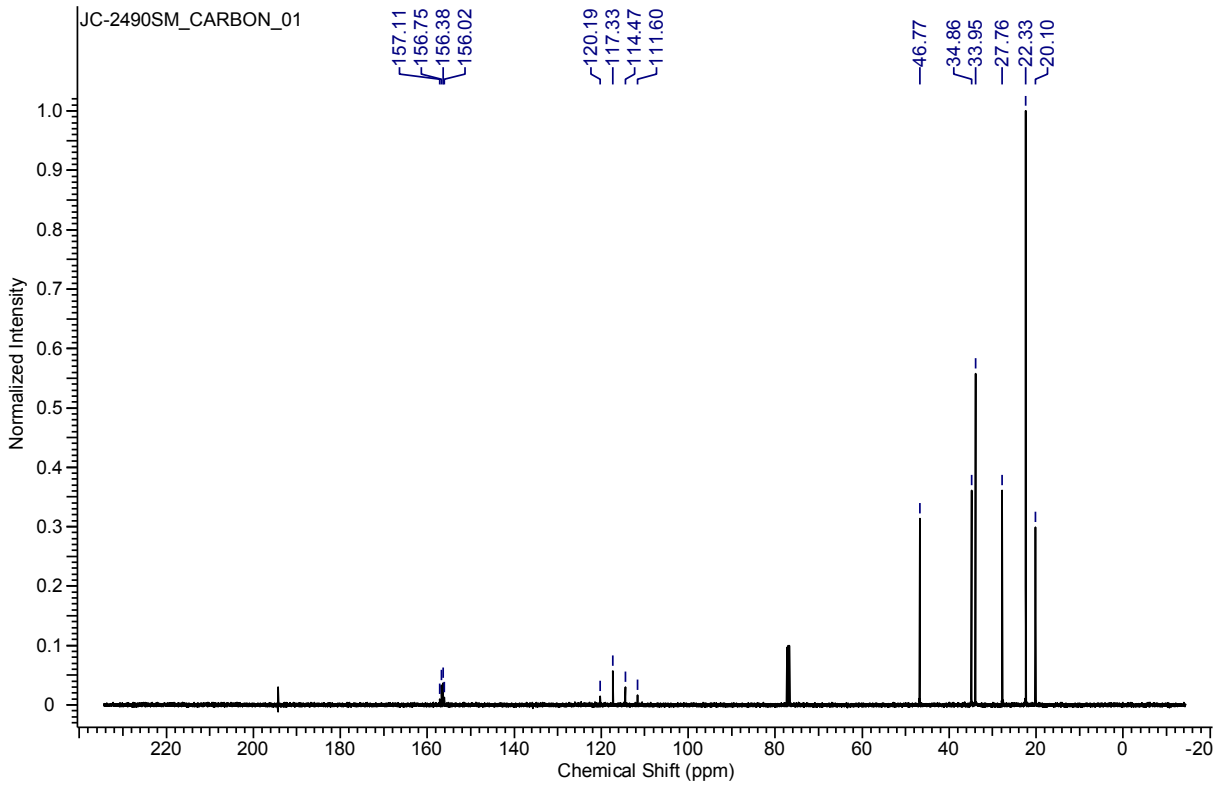
33.37
29.21
26.44
18.91
11.19
Normalized Intensity
Chemical Shift (ppm)

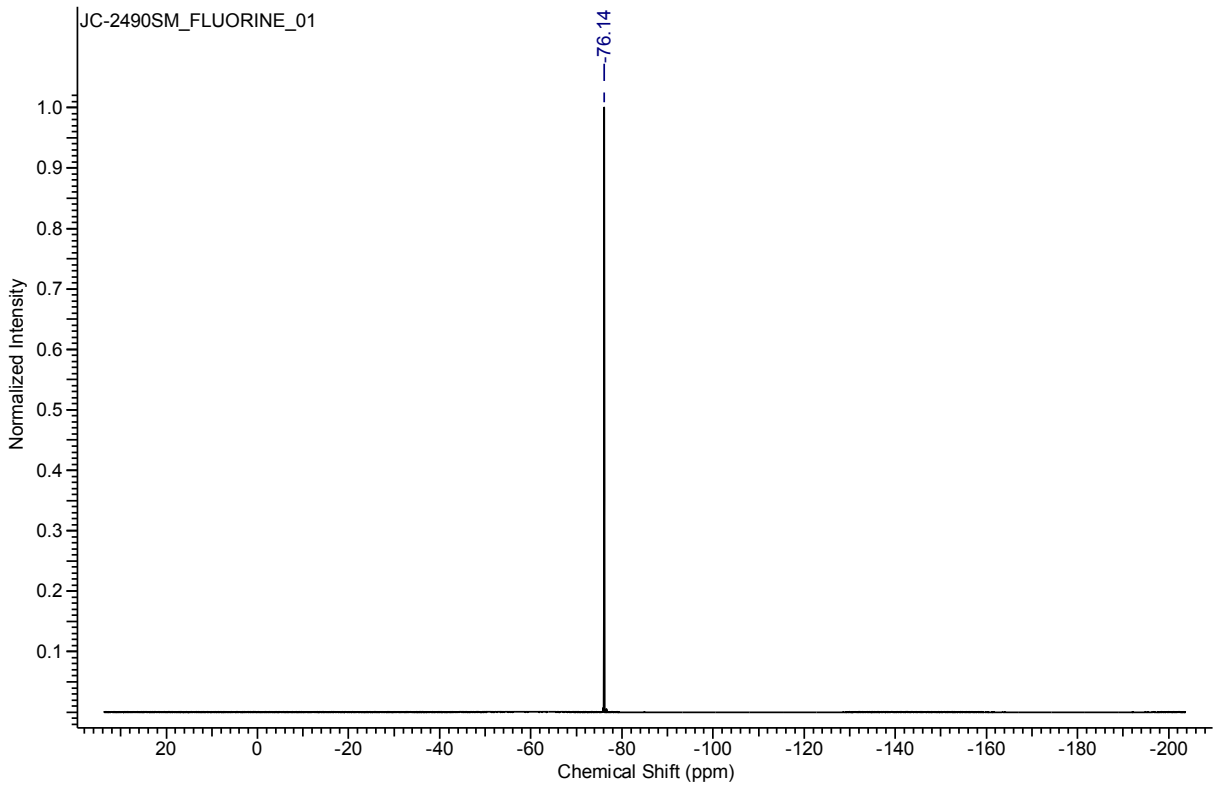

JC-2428_FLUORINE_01
-76.13
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

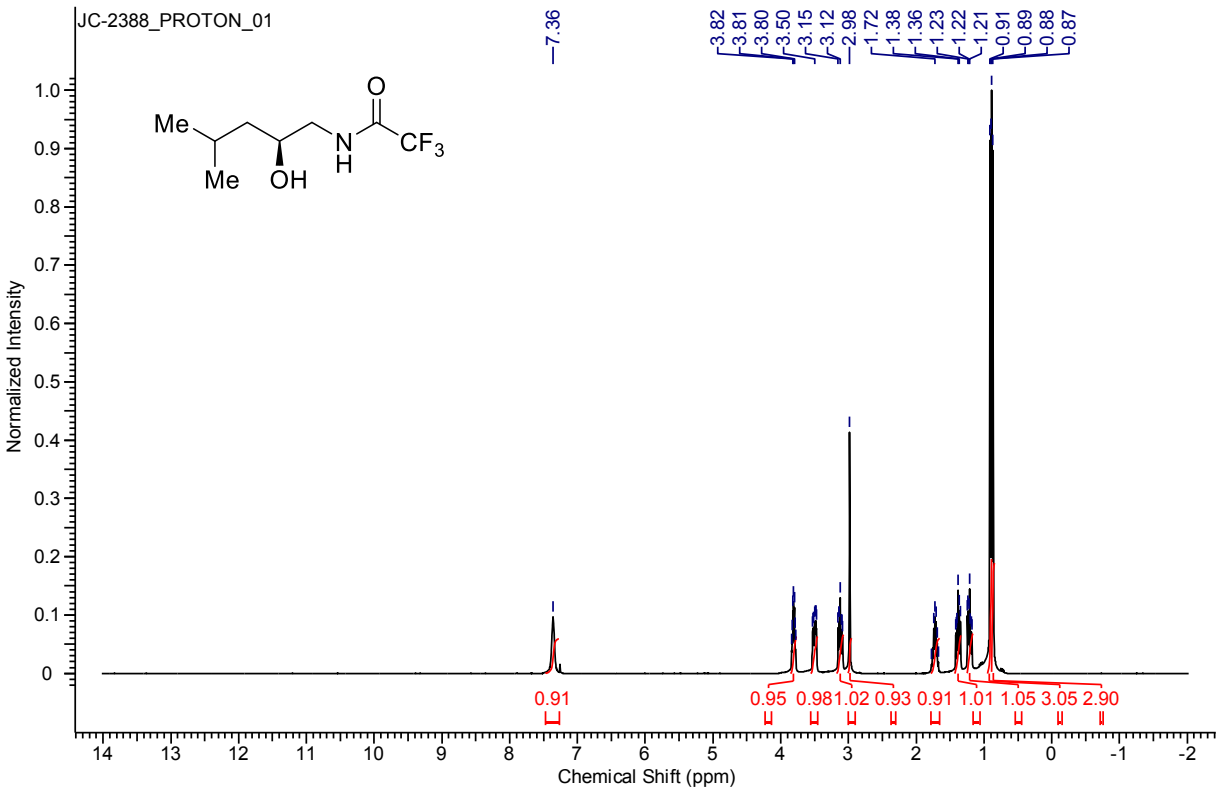

JC-2408_PROTON_01
7.82
7.80
7.79
7.69
7.67
7.66
3.65
3.63
3.61
1.64
1.33
1.32
1.31
1.29
1.11
1.10
0.83
0.81
0.80
Me
Me
N
O
O
Normalized Intensity
1.81
1.91
1.94
2.10
2.91
2.00
5.72
Chemical Shift (ppm)

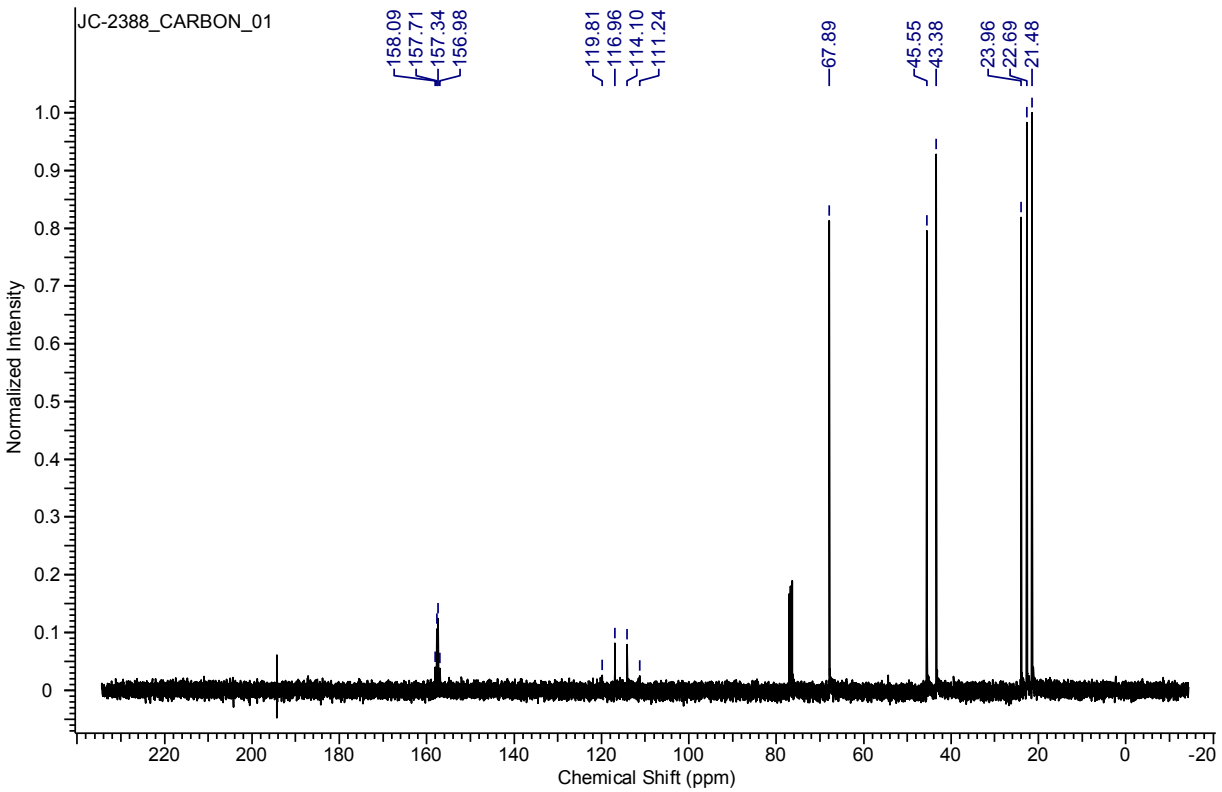

JC-2408_CARBON_01
168.36
133.76
132.16
123.08
38.31
34.03
33.54
29.30
26.18
19.01
11.30
Normalized Intensity
Chemical Shift (ppm)

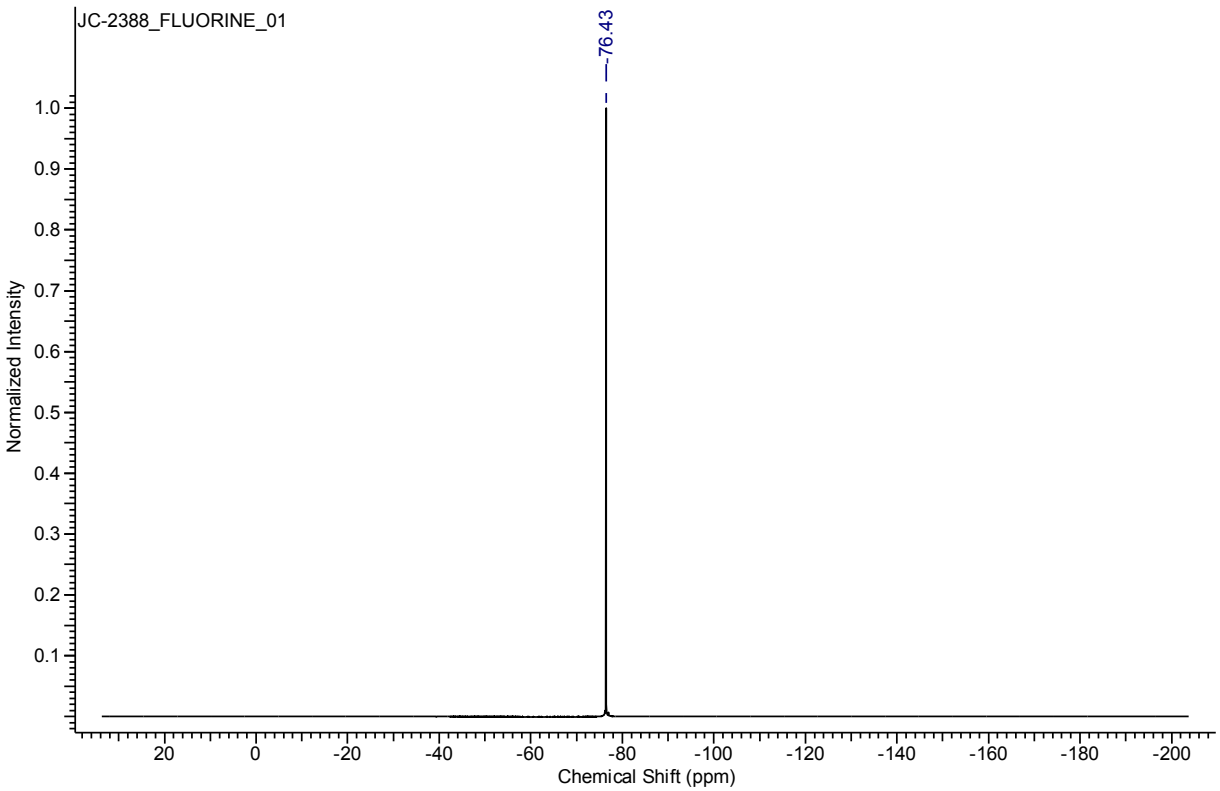

JC-2490SM_PROTON_01
6.54
4.00
3.99
3.97
3.95
3.93
3.92
3.90
1.52
1.51
1.49
1.48
1.47
1.19
1.18
1.16
0.86
0.85
O
Me
CF3
N
H
Me
Me
Normalized Intensity
1.02
1.05
3.00
4.91
5.82
Chemical Shift (ppm)

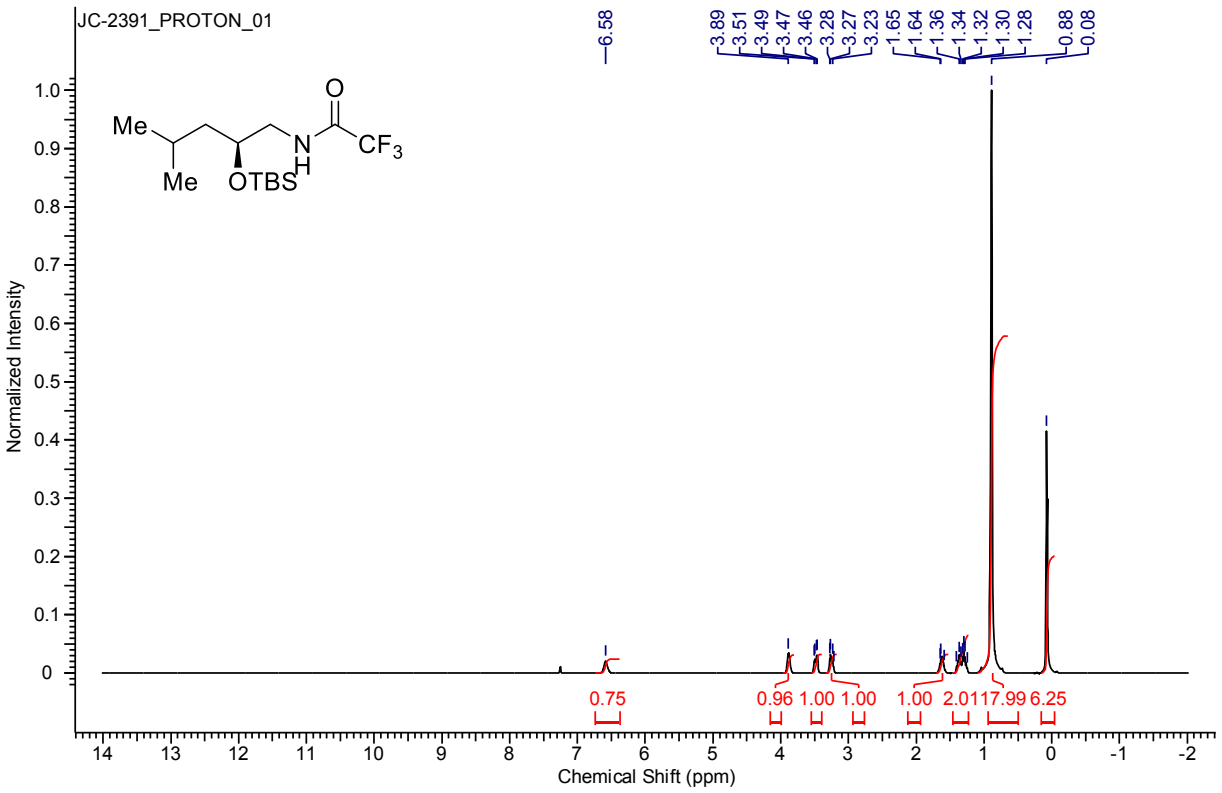

JC-2490SM_CARBON_01
157.11
156.75
156.38
156.02
120.19
117.33
114.47
111.60
46.77
34.86
33.95
27.76
22.33
20.10
Normalized Intensity
Chemical Shift (ppm)

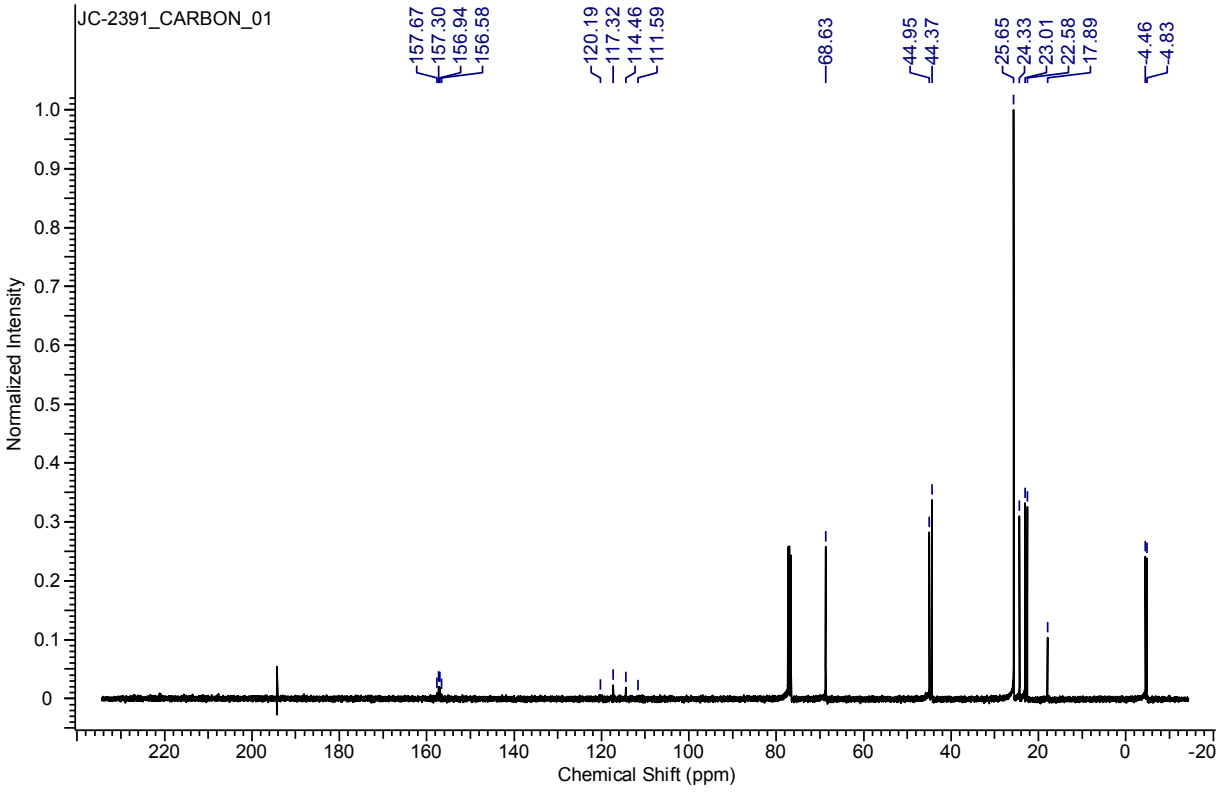

JC-2490SM_FLUORINE_01
-76.14
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

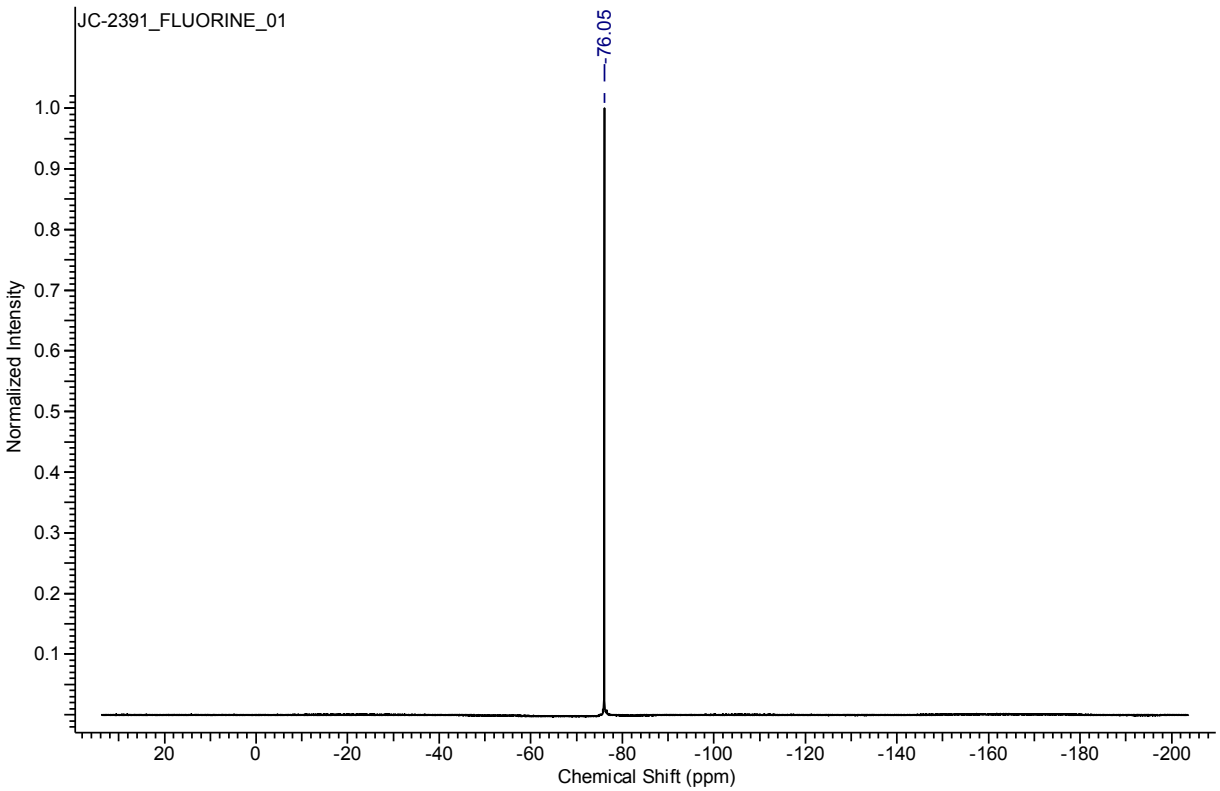

JC-2388_PROTON_01
7.36
3.82
3.81
3.80
3.50
3.15
3.12
2.98
1.72
1.38
1.36
1.23
1.22
1.21
0.91
0.89
0.88
0.87
Me
Me
OH
N
H
O
CF3
Normalized Intensity
Chemical Shift (ppm)
0.91
0.95
0.98
1.02
0.93
0.91
1.01
1.05
3.05
2.90

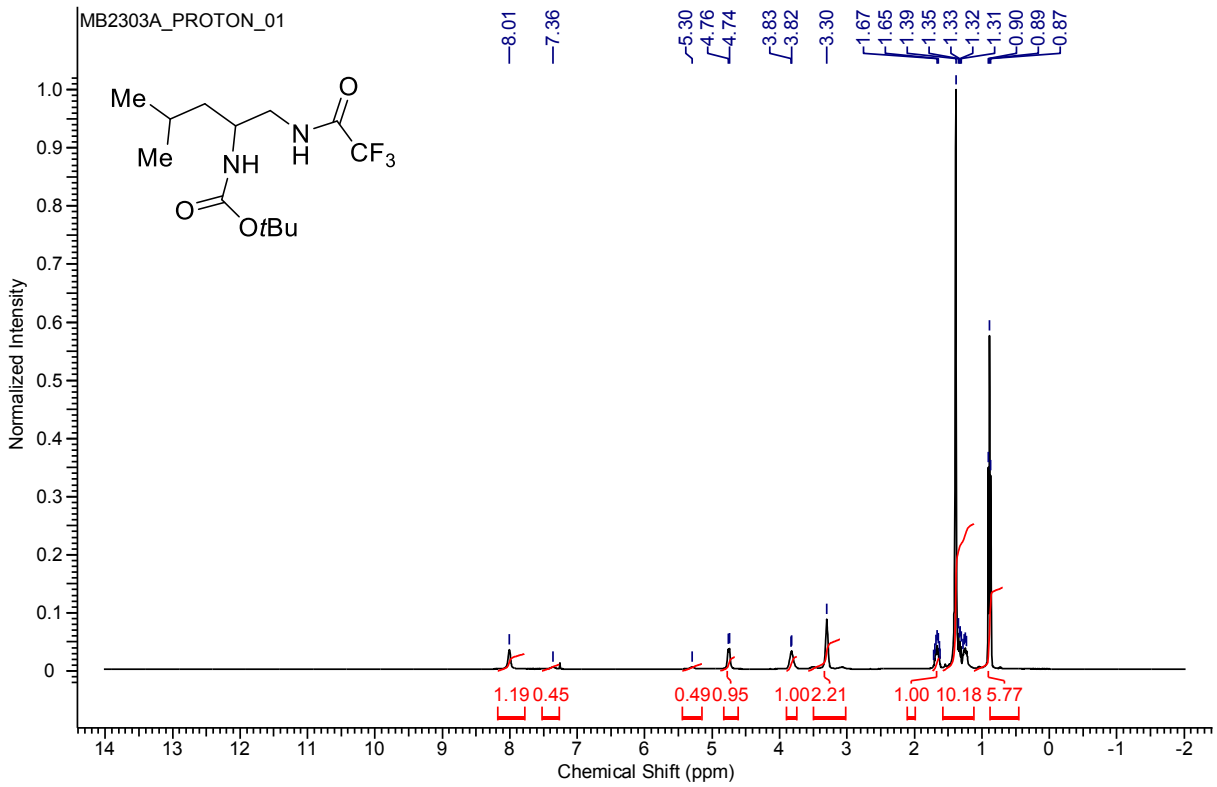

JC-2388_CARBON_01
158.09
157.71
157.34
156.98
119.81
116.96
114.10
111.24
67.89
45.55
43.38
23.96
22.69
21.48
Normalized Intensity
Chemical Shift (ppm)

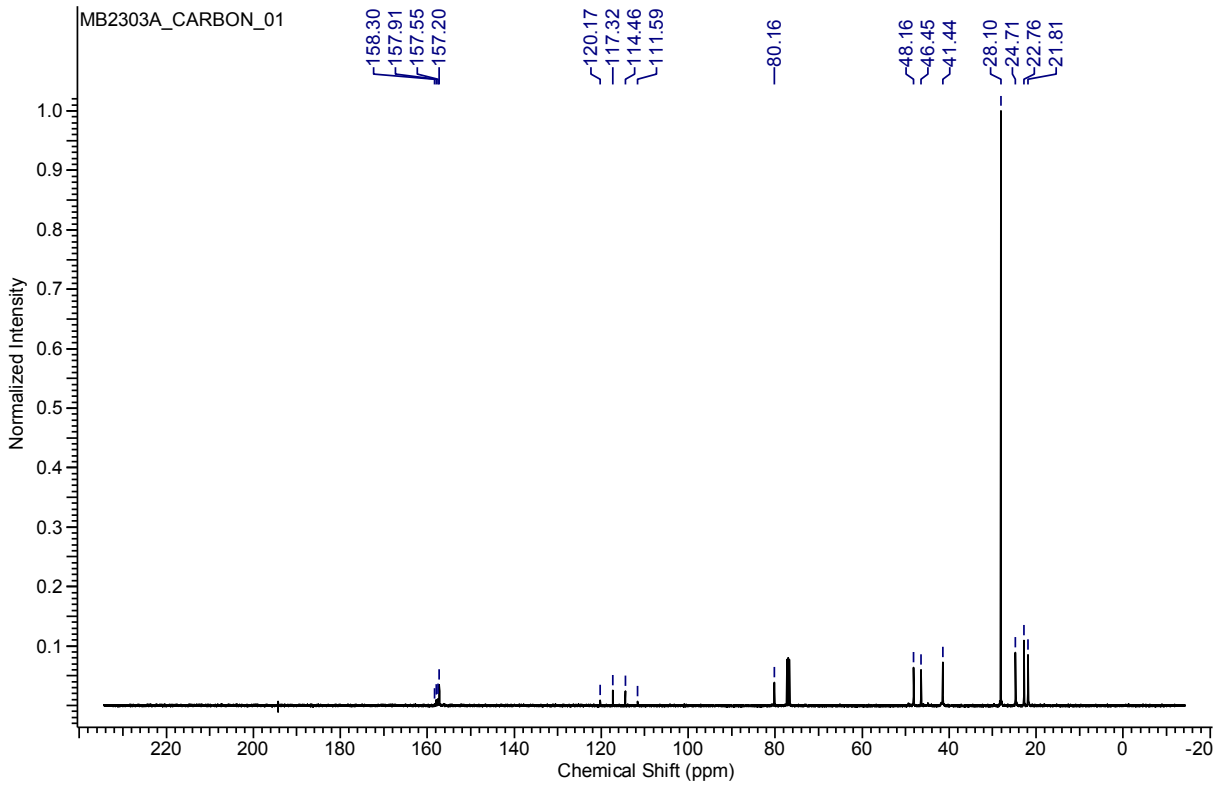

JC-2388_FLUORINE_01
-76.43
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

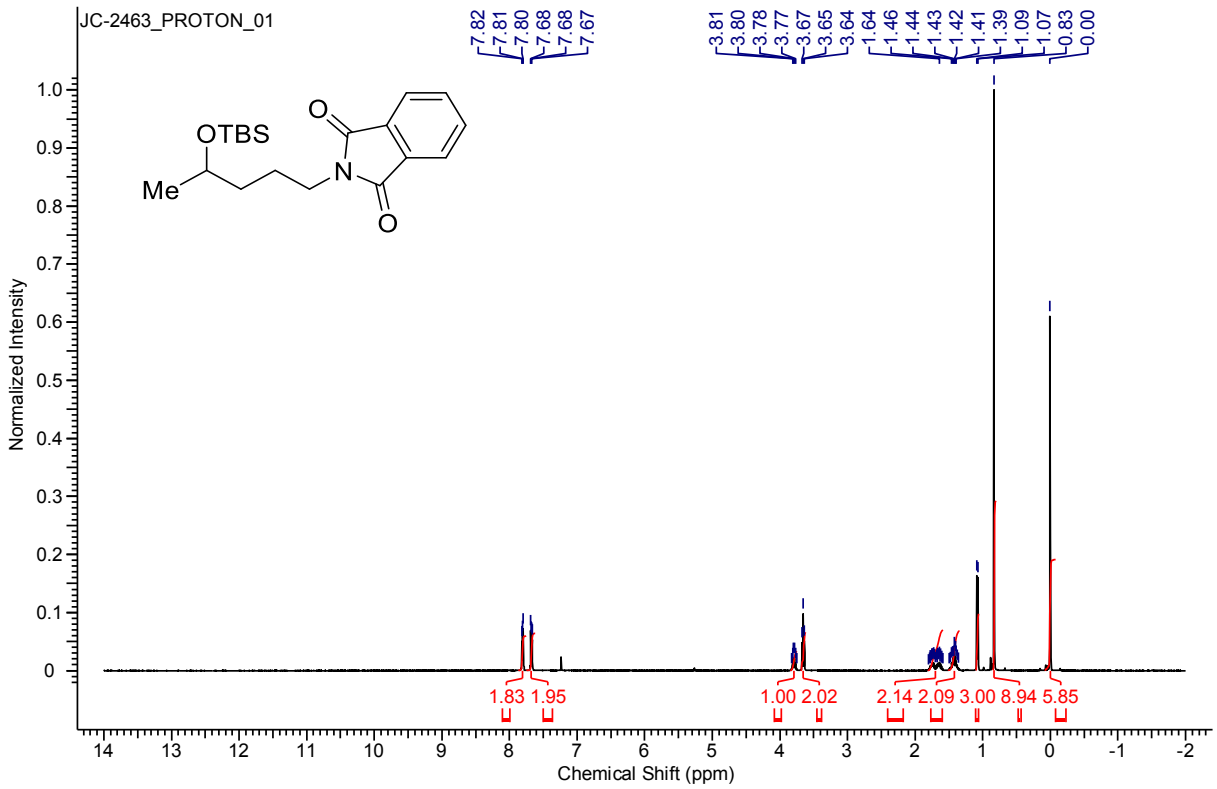

JC-2391_PROTON_01
Me
Me
OTBS
N
H
O
CF3
6.58
3.89
3.51
3.49
3.47
3.46
3.28
3.27
3.23
1.65
1.64
1.36
1.34
1.32
1.30
1.28
0.88
0.08
0.75
0.96
1.00
1.00
1.00
2.01
17.99
6.25
Normalized Intensity
Chemical Shift (ppm)

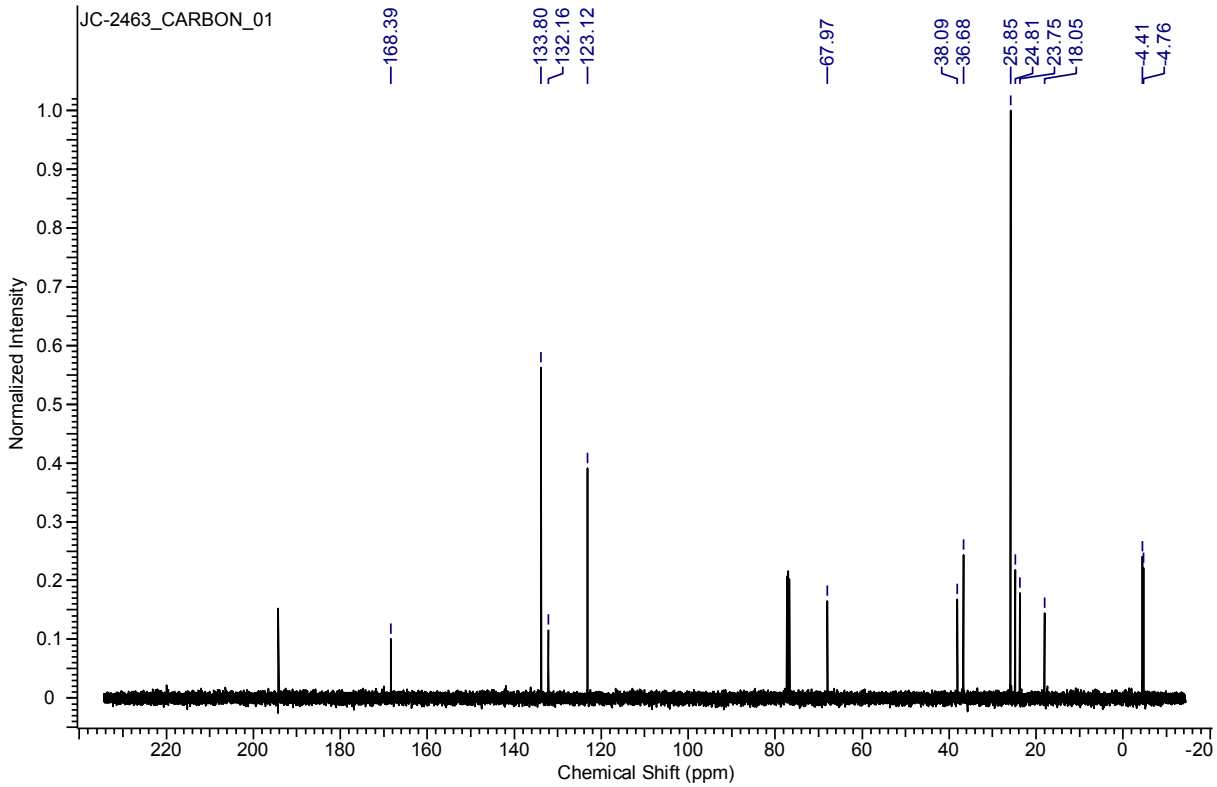

JC-2391_CARBON_01
157.67
157.30
156.94
156.58
120.19
117.32
114.46
111.59
68.63
44.95
44.37
25.65
24.33
23.01
22.58
17.89
-4.46
-4.83
Normalized Intensity
Chemical Shift (ppm)

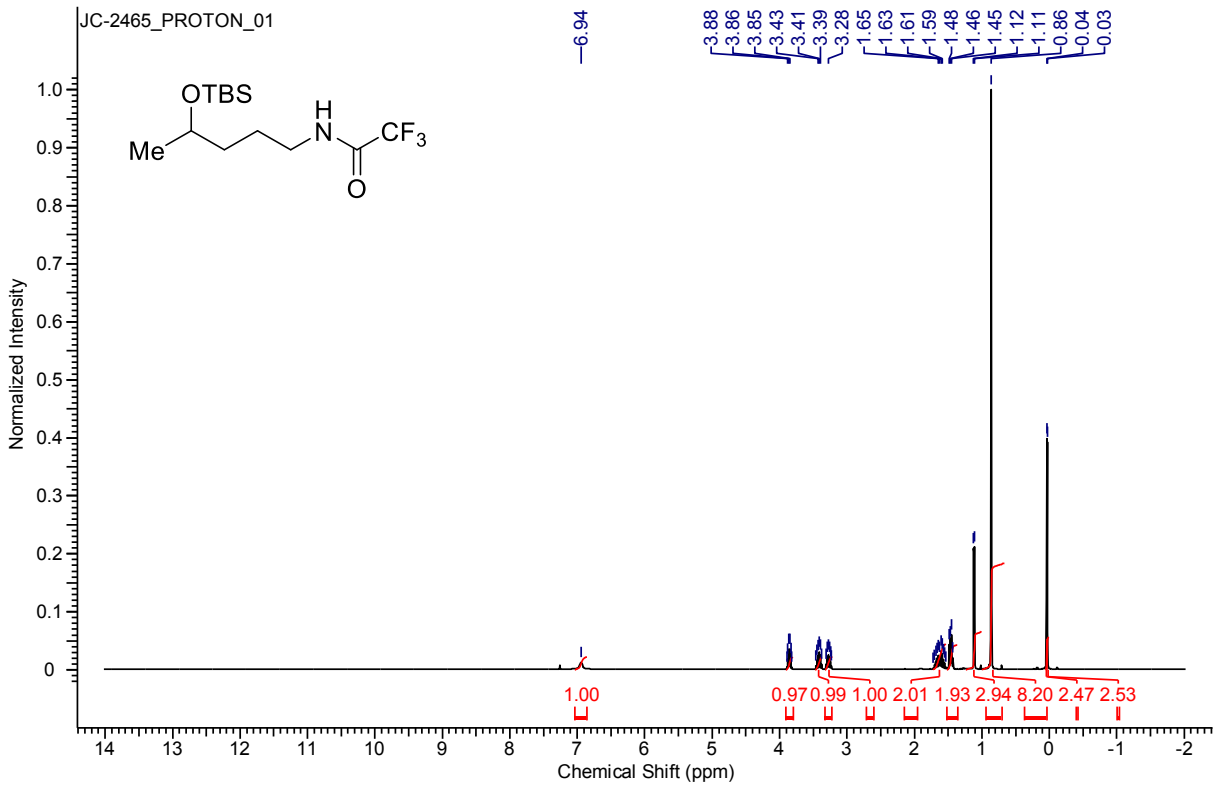

JC-2391_FLUORINE_01
-76.05
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

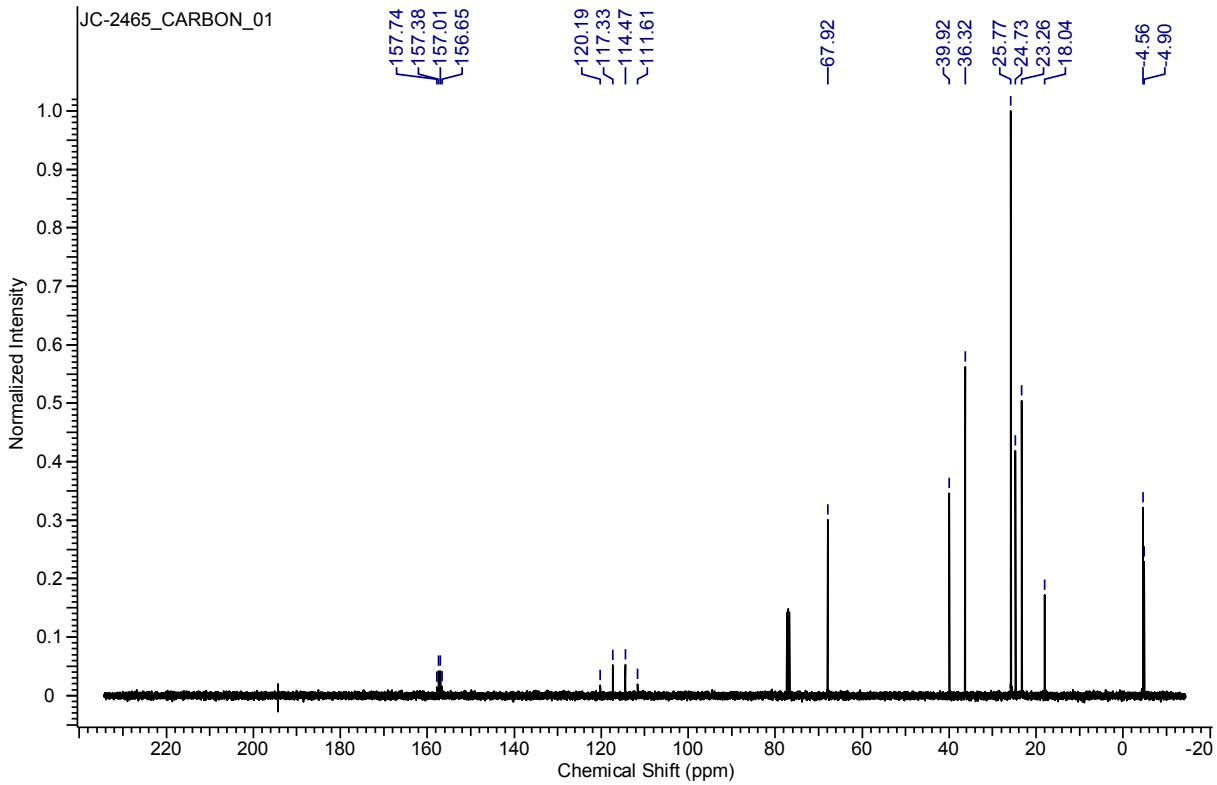

MB2303A_PROTON_01
8.01
7.36
5.30
4.76
4.74
3.83
3.82
3.30
1.67
1.65
1.39
1.35
1.33
1.32
1.31
0.90
0.89
0.87
Me
Me
NH
N
H
O
CF3
O
OtBu
1.19 0.45 0.49 0.95 1.00 2.21 1.00 10.18 5.77
Normalized Intensity
Chemical Shift (ppm)

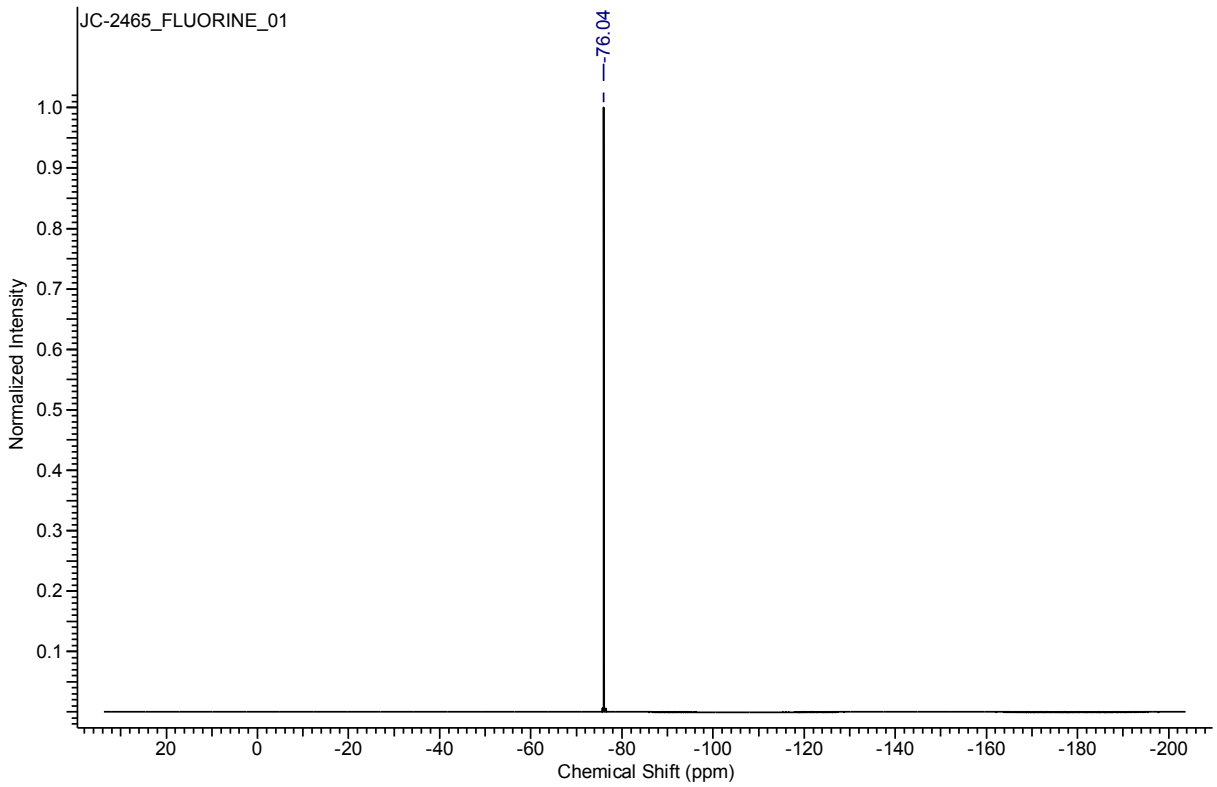

MB2303A_CARBON_01
158.30
157.91
157.55
157.20
120.17
117.32
114.46
111.59
80.16
48.16
46.45
41.44
28.10
24.71
22.76
21.81
Normalized Intensity
Chemical Shift (ppm)

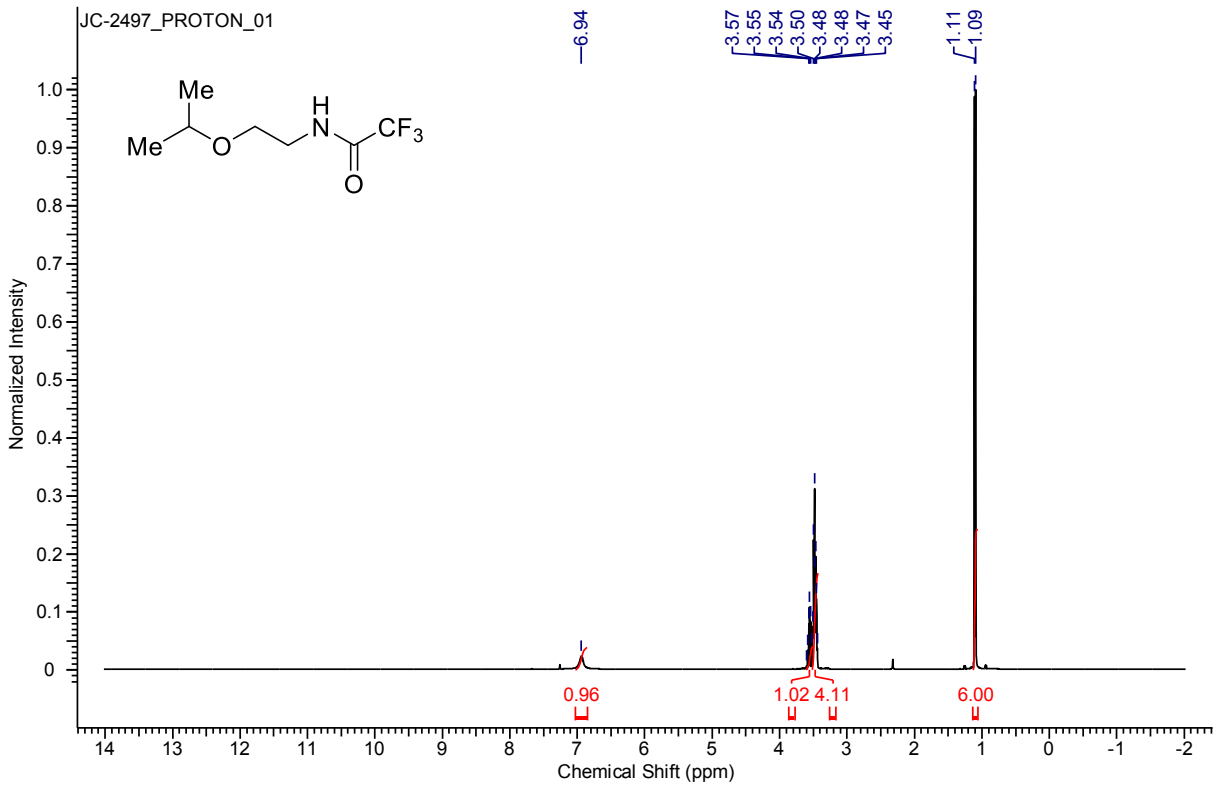

JC-2463_PROTON_01
7.82
7.81
7.80
7.68
7.68
7.67
3.81
3.80
3.78
3.77
3.67
3.65
3.64
1.64
1.46
1.44
1.43
1.42
1.41
1.39
1.09
1.07
0.83
0.00
OTBS
Me
N
O
O
Normalized Intensity
1.83 1.95
1.00 2.02
2.14 2.09 3.00 8.94 5.85
Chemical Shift (ppm)

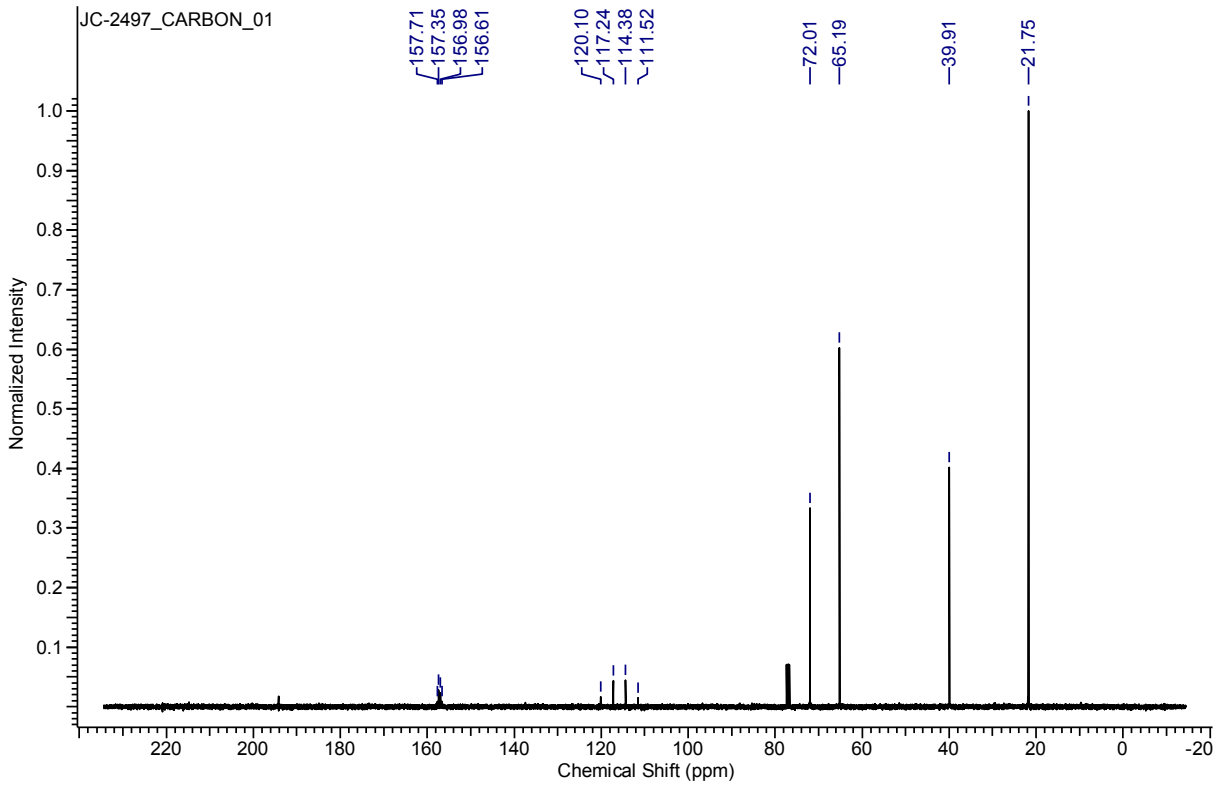

JC-2463_CARBON_01
168.39
133.80
132.16
123.12
67.97
38.09
36.68
25.85
24.81
23.75
18.05
-4.41
-4.76
Normalized Intensity
Chemical Shift (ppm)

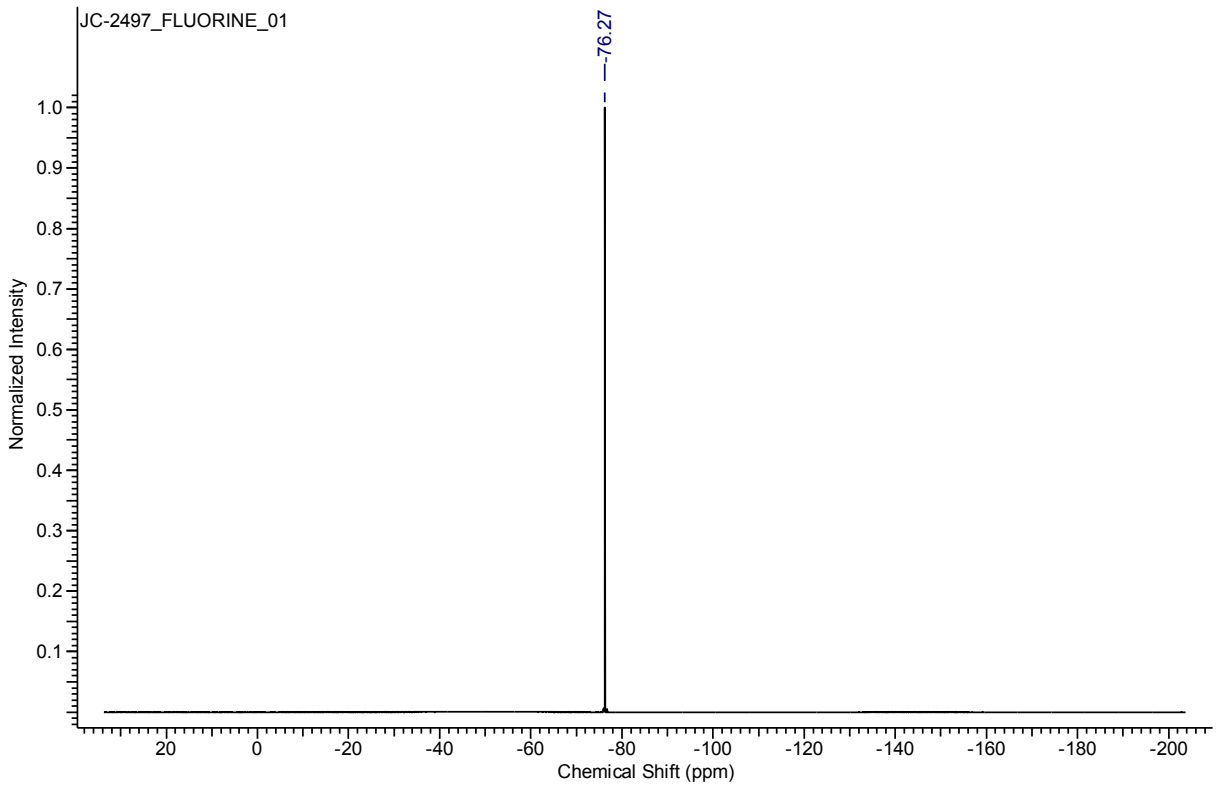

JC-2465_PROTON_01
OTBS
Me
H
N
CF3
O
6.94
3.88
3.86
3.85
3.43
3.41
3.39
3.28
1.65
1.63
1.61
1.59
1.48
1.46
1.45
1.12
1.11
0.86
0.04
0.03
1.00
0.97 0.99 1.00 2.01 1.93 2.94 8.20 2.47 2.53
Normalized Intensity
Chemical Shift (ppm)

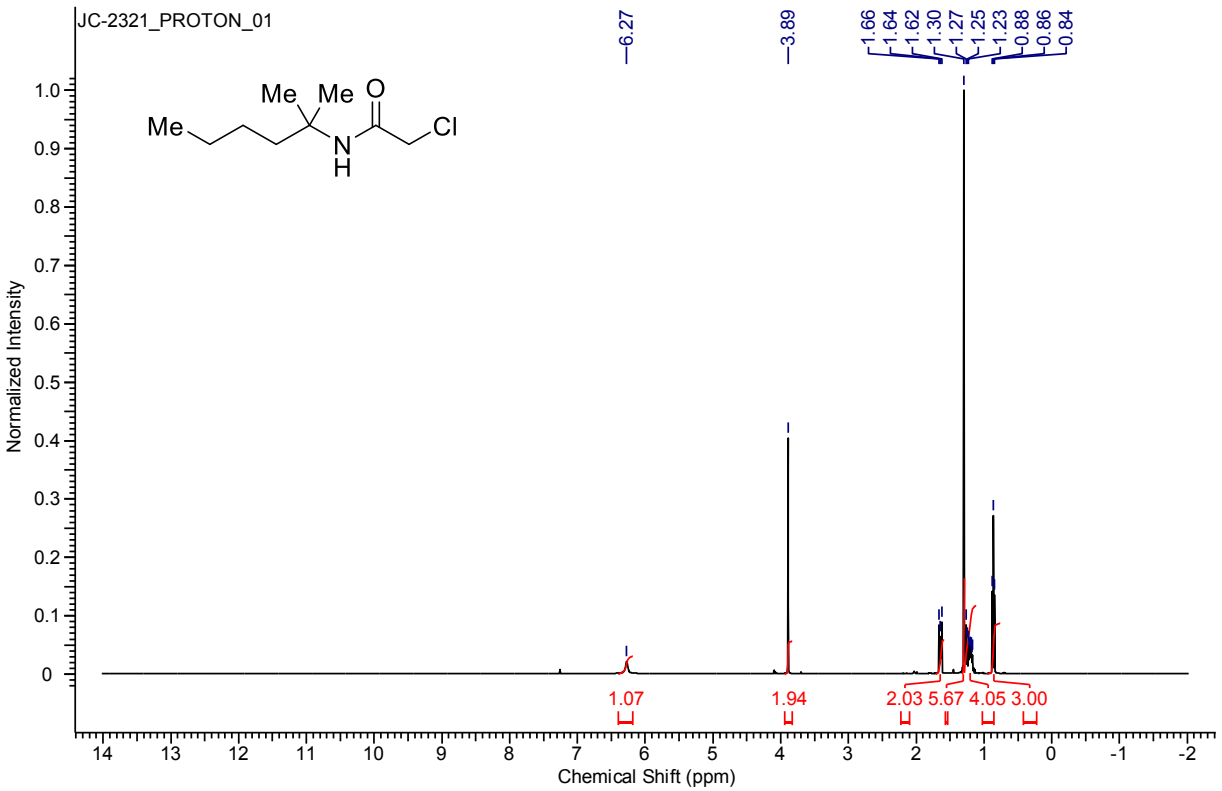

JC-2465_CARBON_01
157.74
157.38
157.01
156.65
120.19
117.33
114.47
111.61
67.92
39.92
36.32
25.77
24.73
23.26
18.04
4.56
4.90
Normalized Intensity
Chemical Shift (ppm)

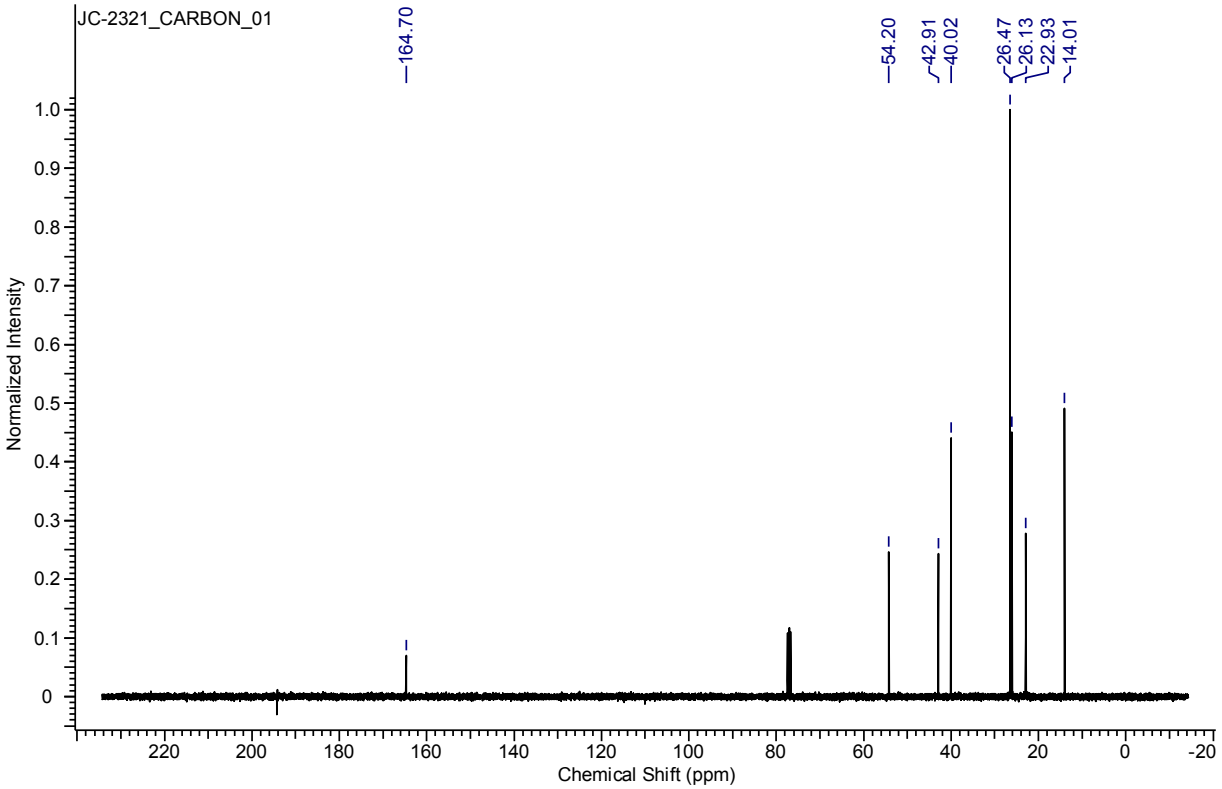

JC-2465_FLUORINE_01
-76.04
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

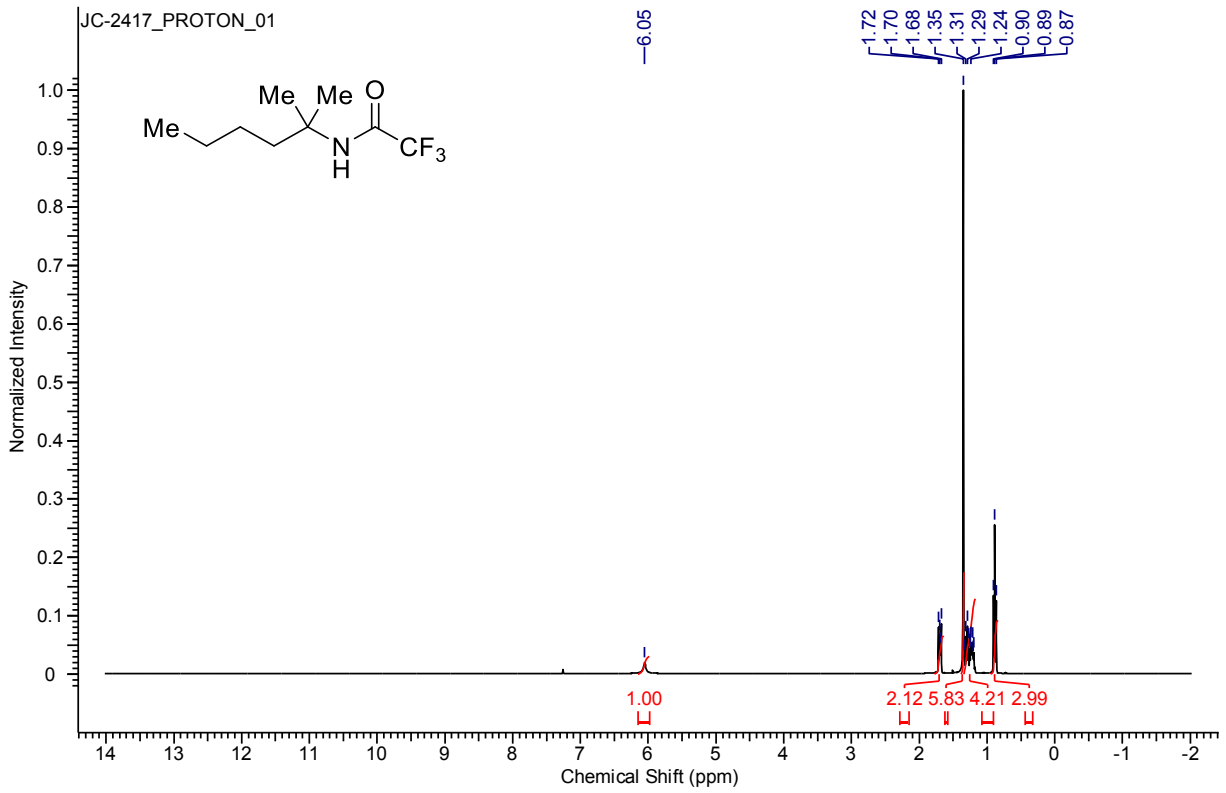

JC-2497_PROTON_01
6.94
3.57
3.55
3.54
3.50
3.48
3.48
3.47
3.45
1.11
1.09
Me
Me
O
H
N
CF3
O
Normalized Intensity
0.96
1.02
4.11
6.00
Chemical Shift (ppm)

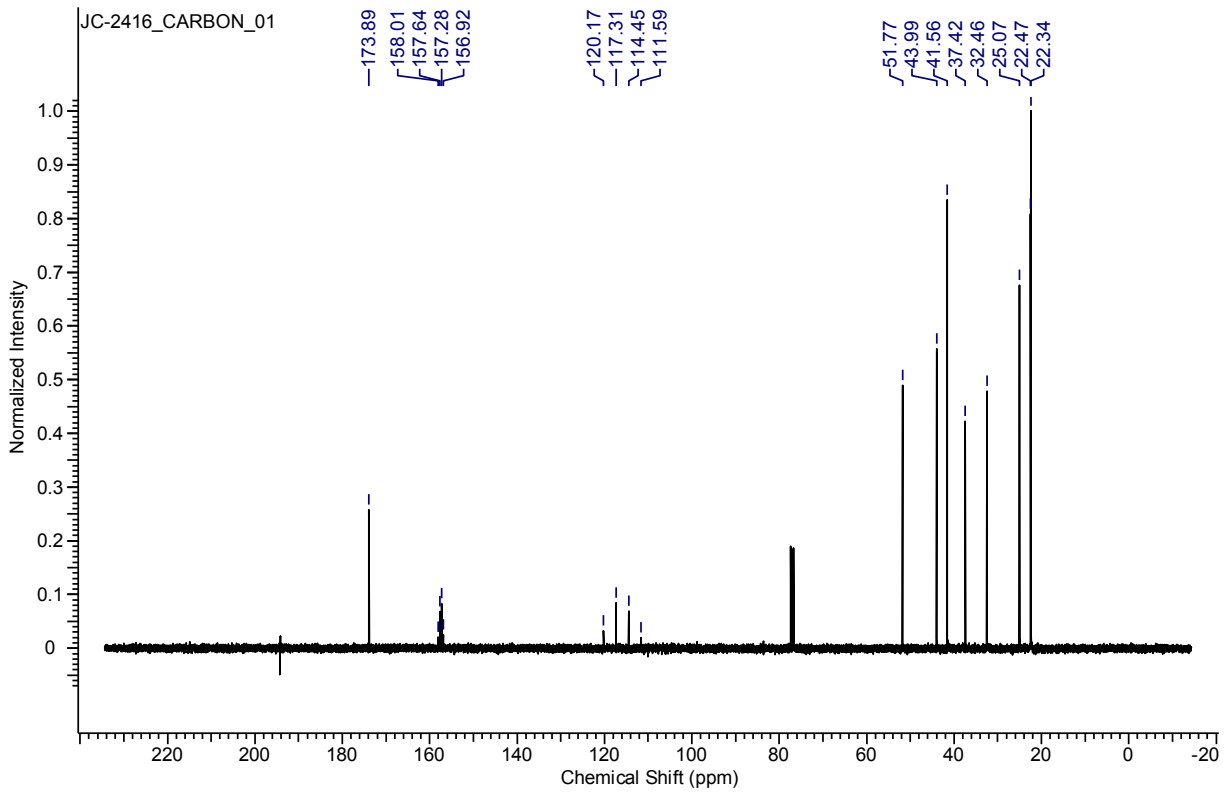

JC-2497_CARBON_01
157.71
157.35
156.98
156.61
120.10
117.24
114.38
111.52
72.01
65.19
39.91
21.75
Normalized Intensity
Chemical Shift (ppm)

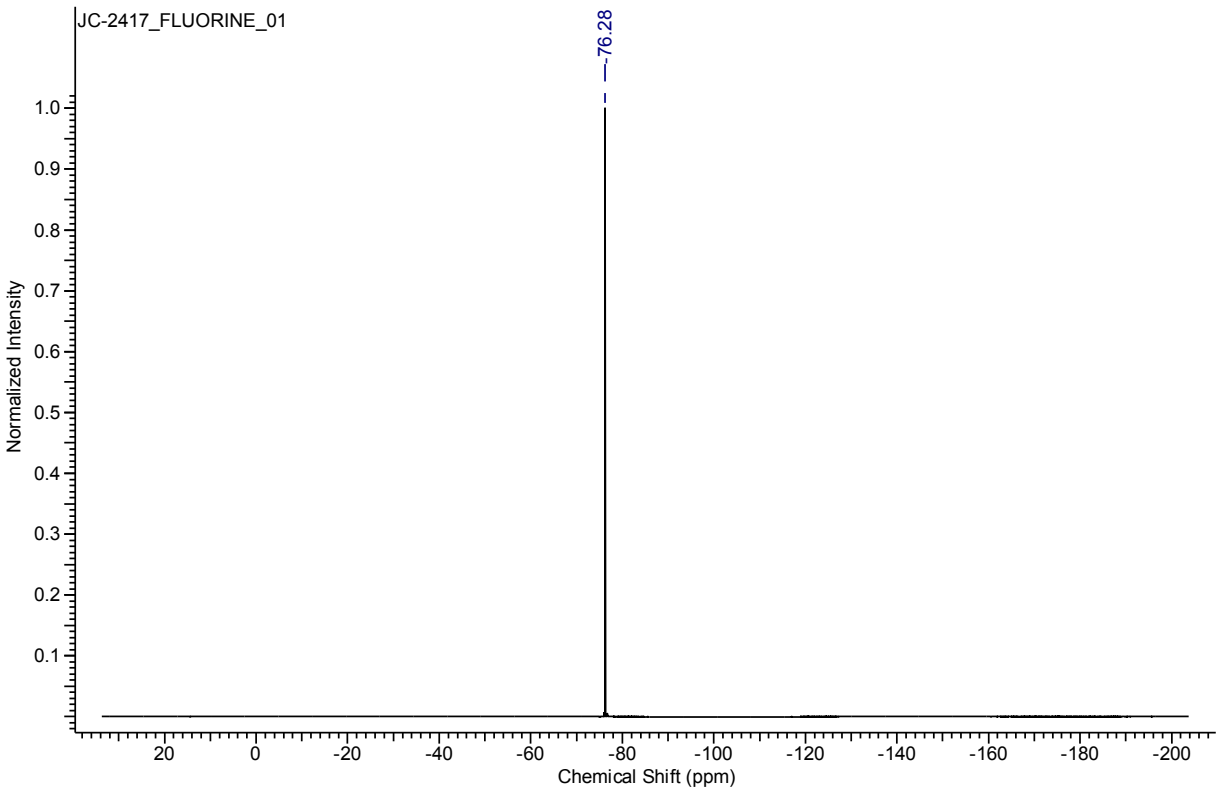

JC-2497_FLUORINE_01
-76.27
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

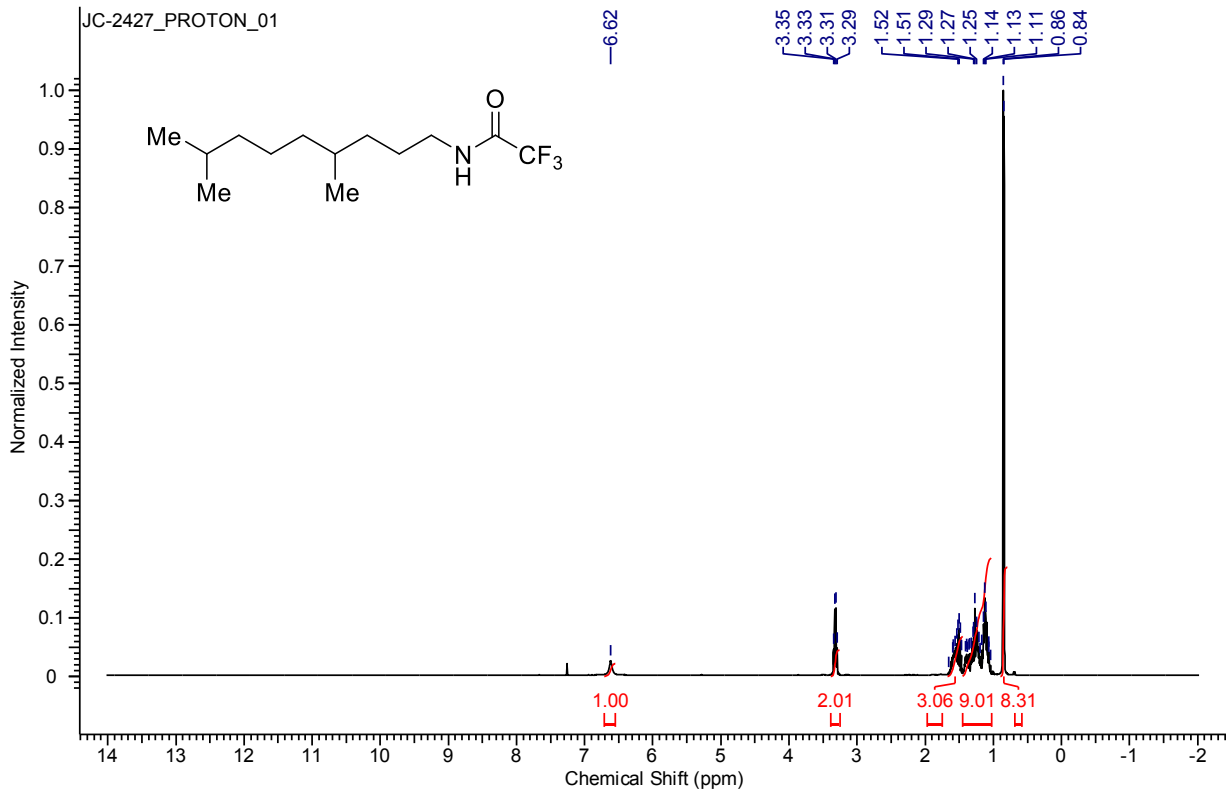

JC-2321_PROTON_01
6.27
3.89
1.66
1.64
1.62
1.30
1.27
1.25
1.23
0.88
0.86
0.84
Me
Me
Me
O
N
H
Cl
1.07
1.94
2.03
5.67
4.05
3.00
Normalized Intensity
Chemical Shift (ppm)

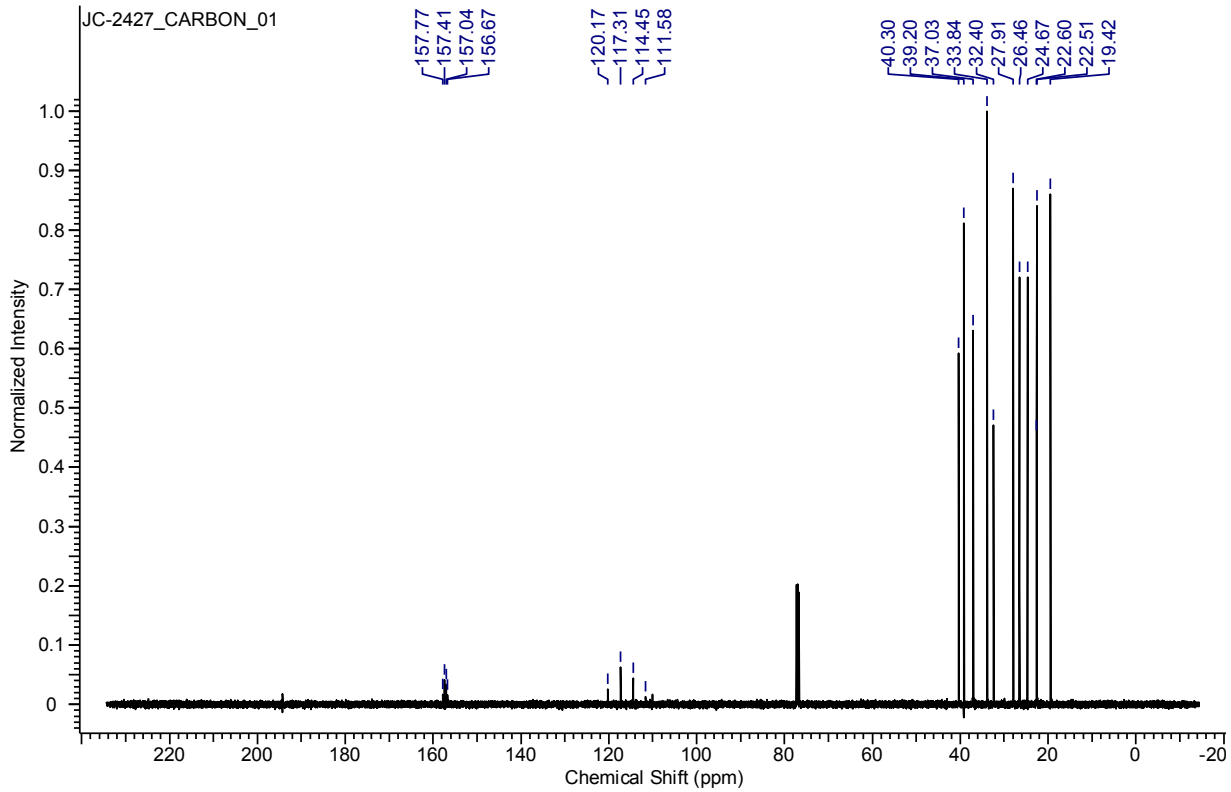

JC-2321_CARBON_01
164.70
54.20
42.91
40.02
26.47
26.13
22.93
14.01
Normalized Intensity
Chemical Shift (ppm)

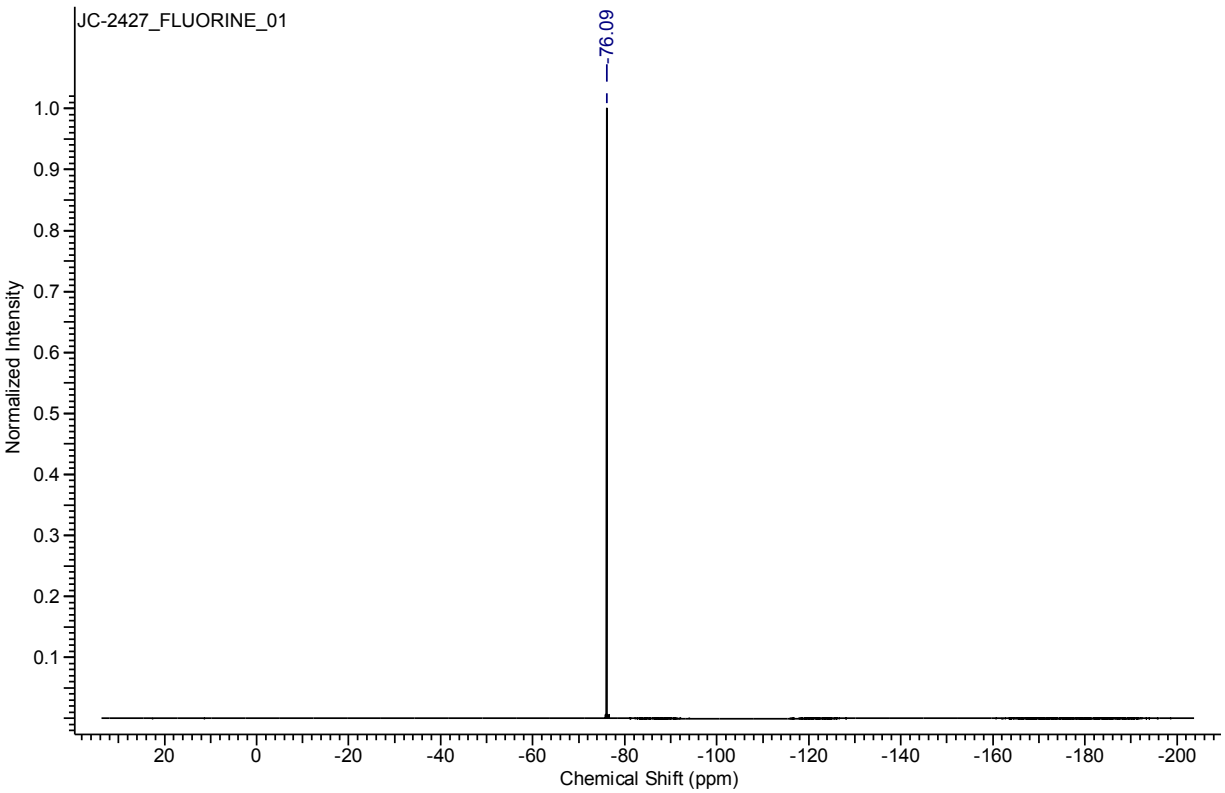

JC-2417_PROTON_01
6.05
1.72
1.70
1.68
1.35
1.31
1.29
1.24
0.90
0.89
0.87
Me
Me
Me
O
N
H
CF3
1.00
2.12
5.83
4.21
2.99
Normalized Intensity
Chemical Shift (ppm)

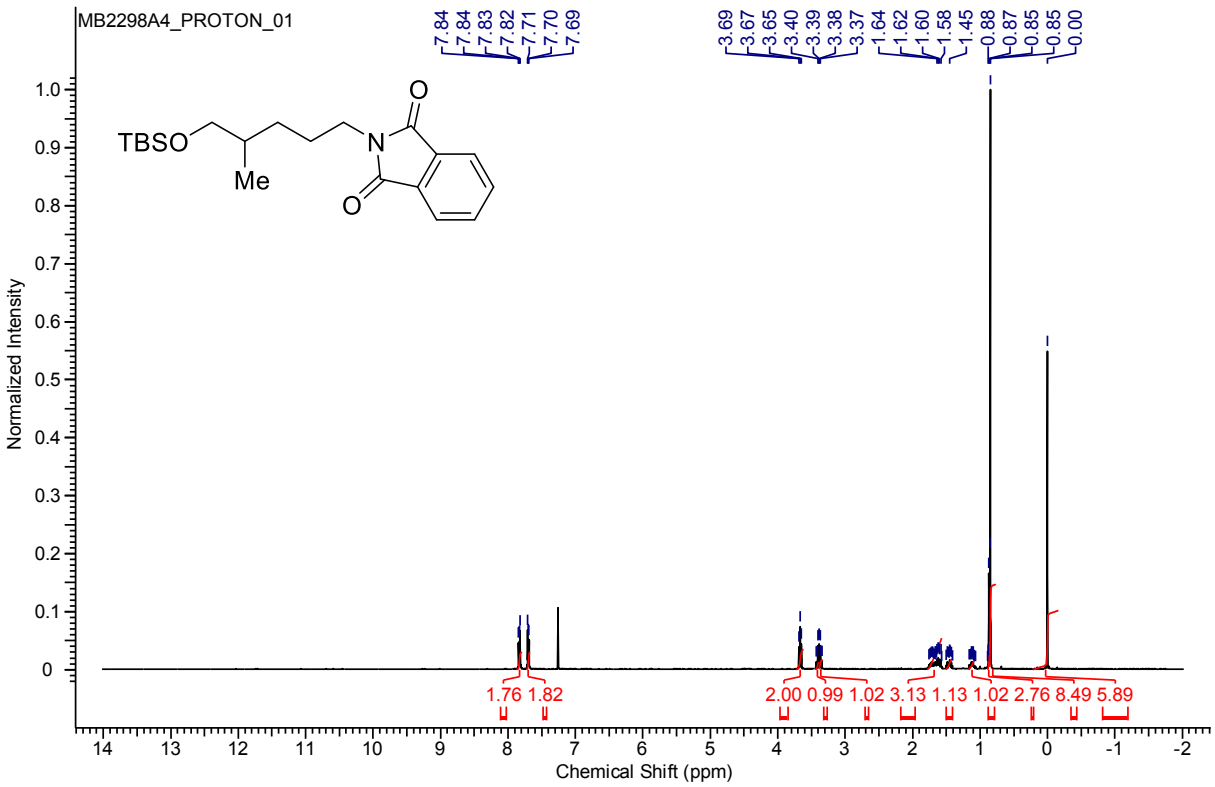

JC-2416_CARBON_01
173.89
158.01
157.64
157.28
156.92
120.17
117.31
114.45
111.59
51.77
43.99
41.56
37.42
32.46
25.07
22.47
22.34
Normalized Intensity
Chemical Shift (ppm)

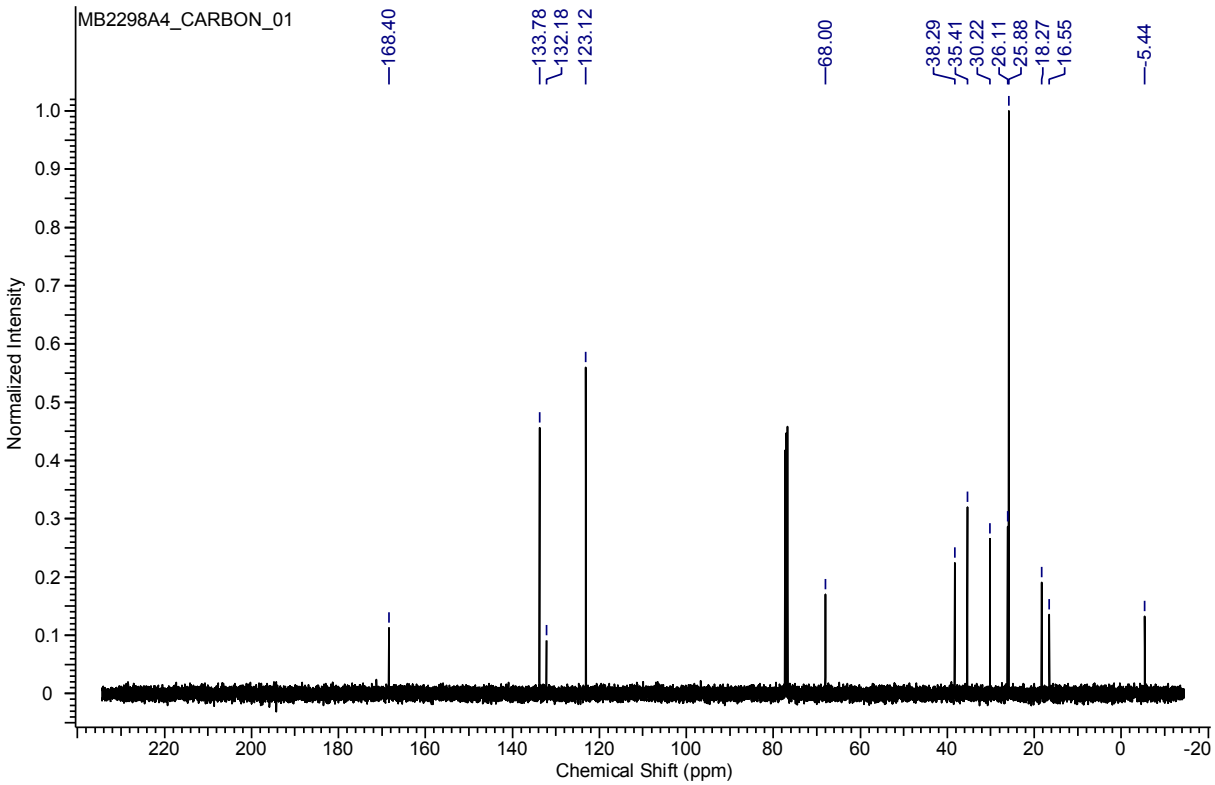

JC-2417_FLUORINE_01
-76.28
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

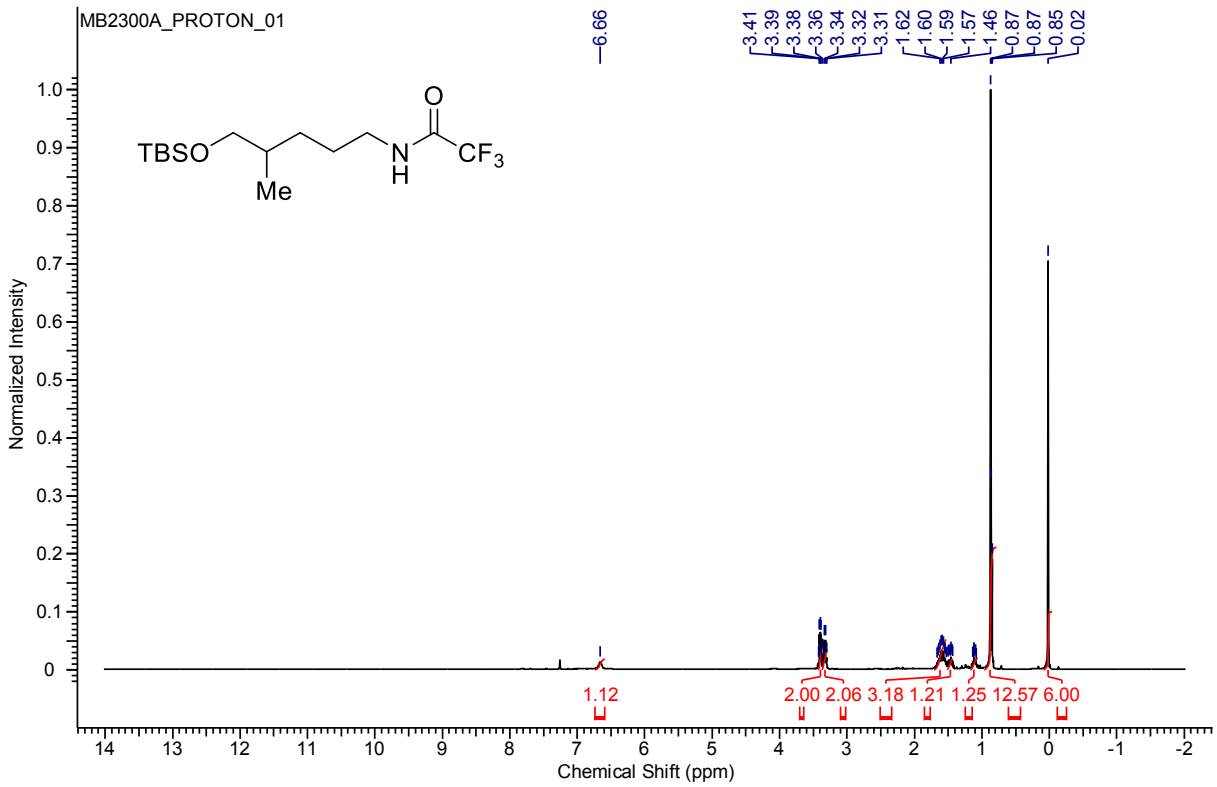

JC-2427_PROTON_01
6.62
3.35
3.33
3.31
3.29
1.52
1.51
1.29
1.27
1.25
1.14
1.13
1.11
0.86
0.84
Me
Me
Me
N
H
O
CF3
1.00
2.01
3.06
9.01
8.31
Normalized Intensity
Chemical Shift (ppm)

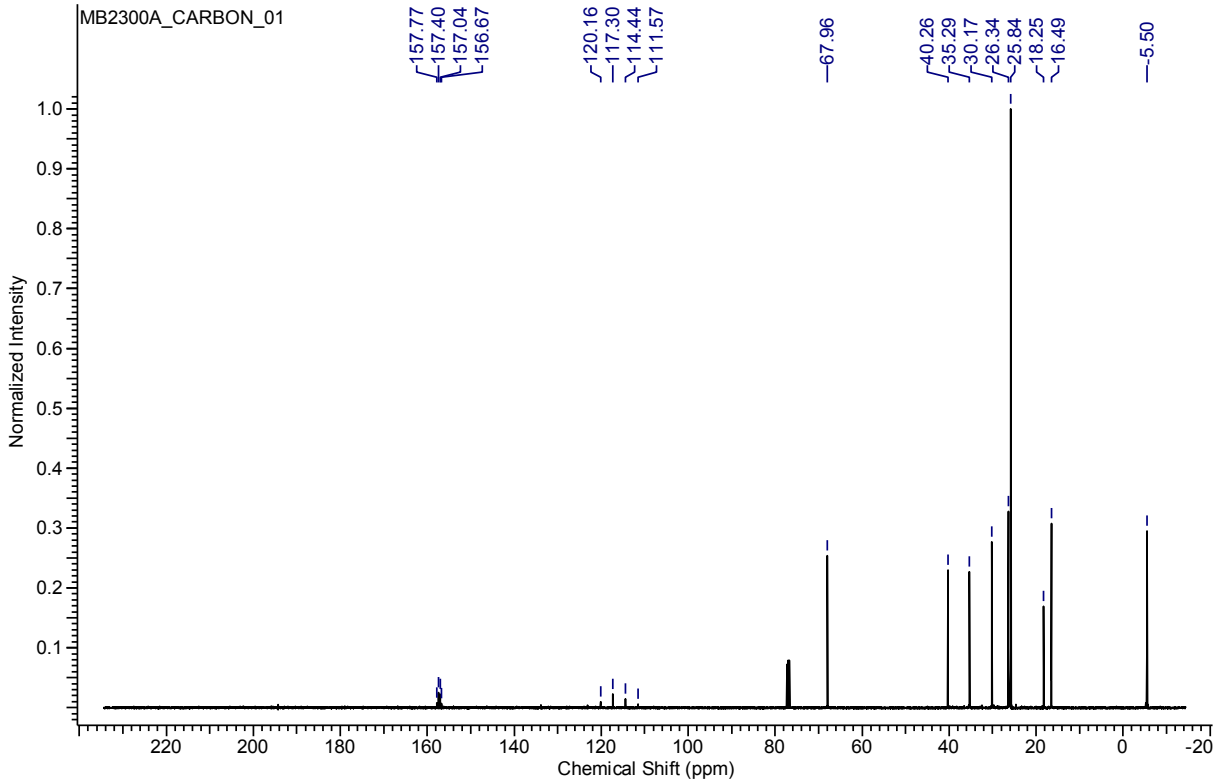

JC-2427_CARBON_01
157.77
157.41
157.04
156.67
120.17
117.31
114.45
111.58
40.30
39.20
37.03
33.84
32.40
27.91
26.46
24.67
22.60
22.51
19.42
Normalized Intensity
Chemical Shift (ppm)

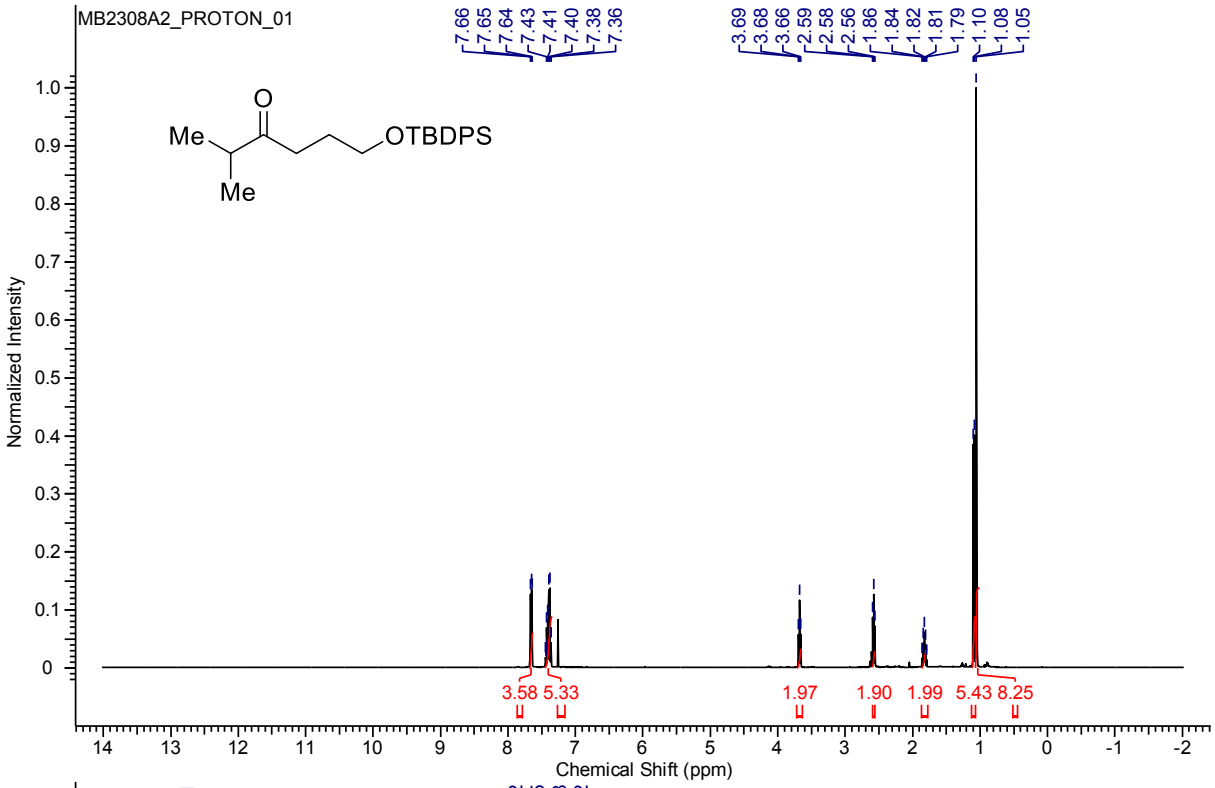

JC-2427_FLUORINE_01
-76.09
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

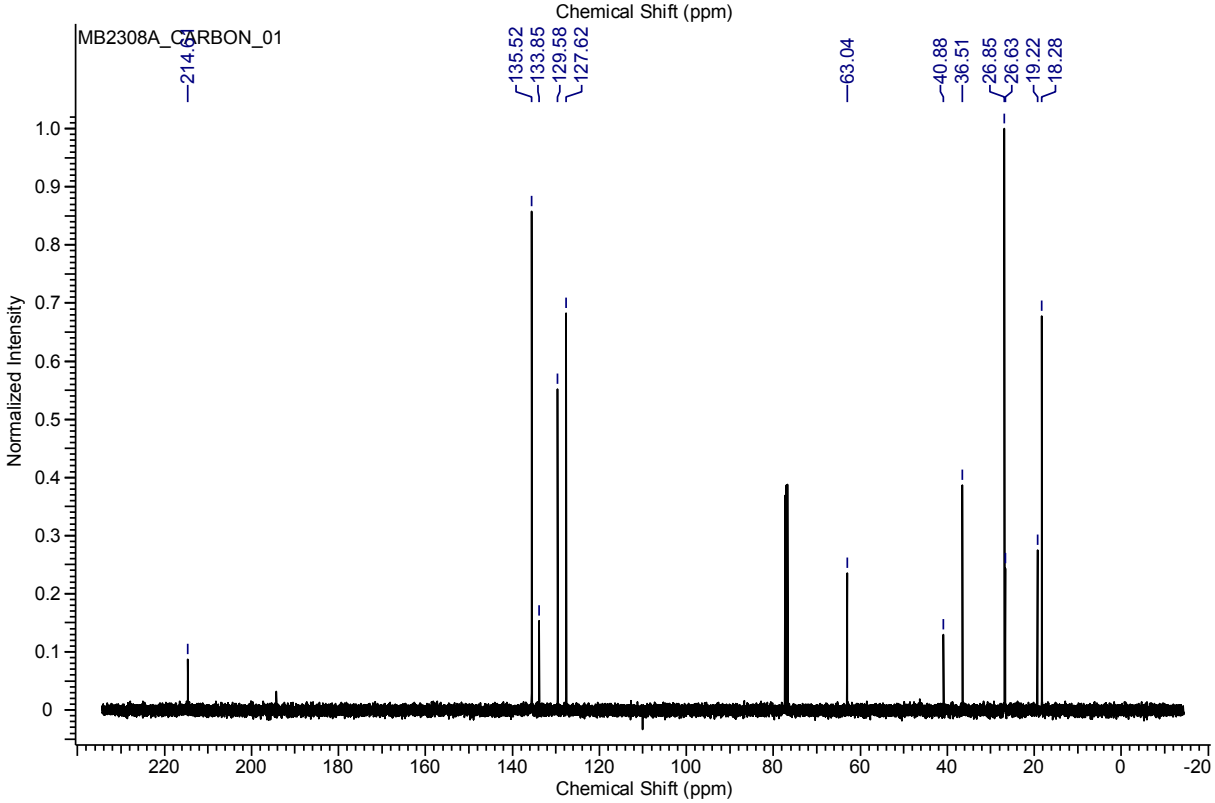

MB2298A4_PROTON_01
7.84
7.84
7.83
7.82
7.71
7.70
7.69
3.69
3.67
3.65
3.40
3.39
3.38
3.37
1.64
1.62
1.60
1.58
1.45
0.88
0.87
0.85
0.85
0.00
TBSO
Me
N
O
O
Normalized Intensity
1.76 1.82
2.00 0.99 1.02 3.13 1.13 1.02 2.76 8.49 5.89
Chemical Shift (ppm)

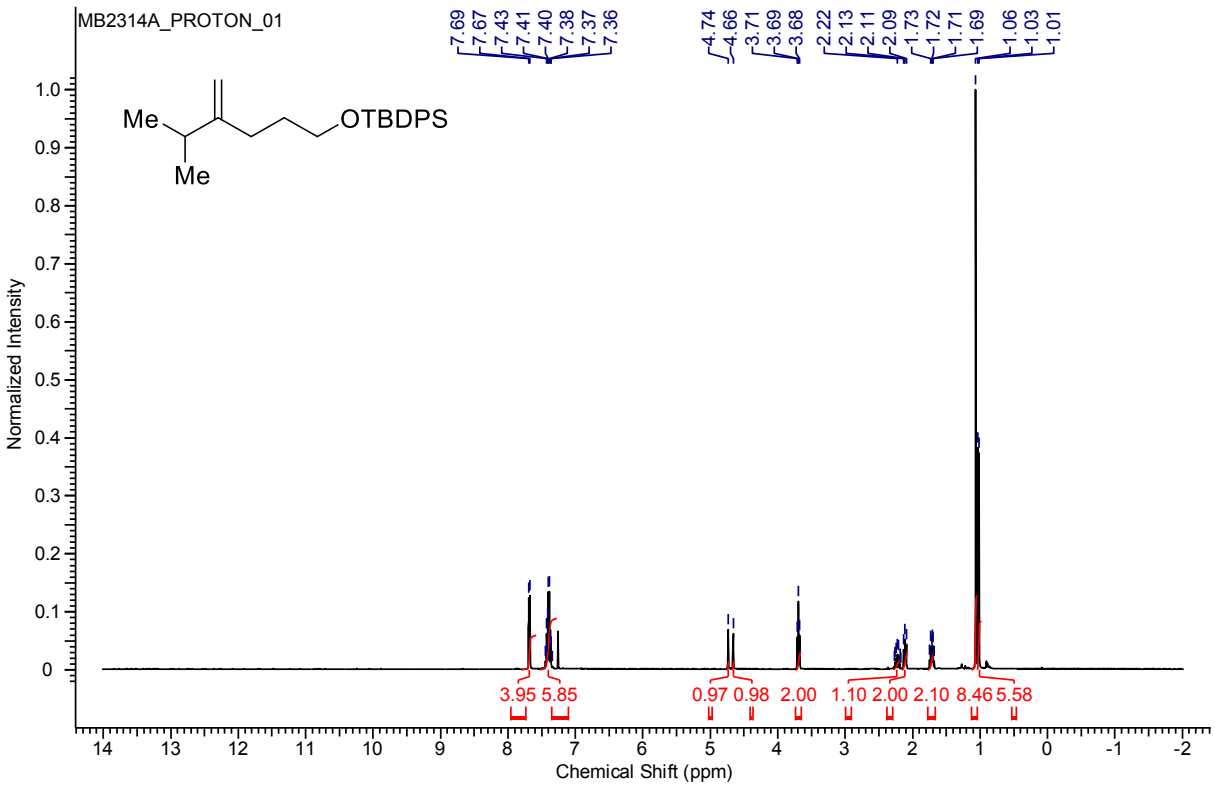

MB2298A4_CARBON_01
168.40
133.78
132.18
123.12
68.00
38.29
35.41
30.22
26.11
25.88
18.27
16.55
5.44
Normalized Intensity
Chemical Shift (ppm)

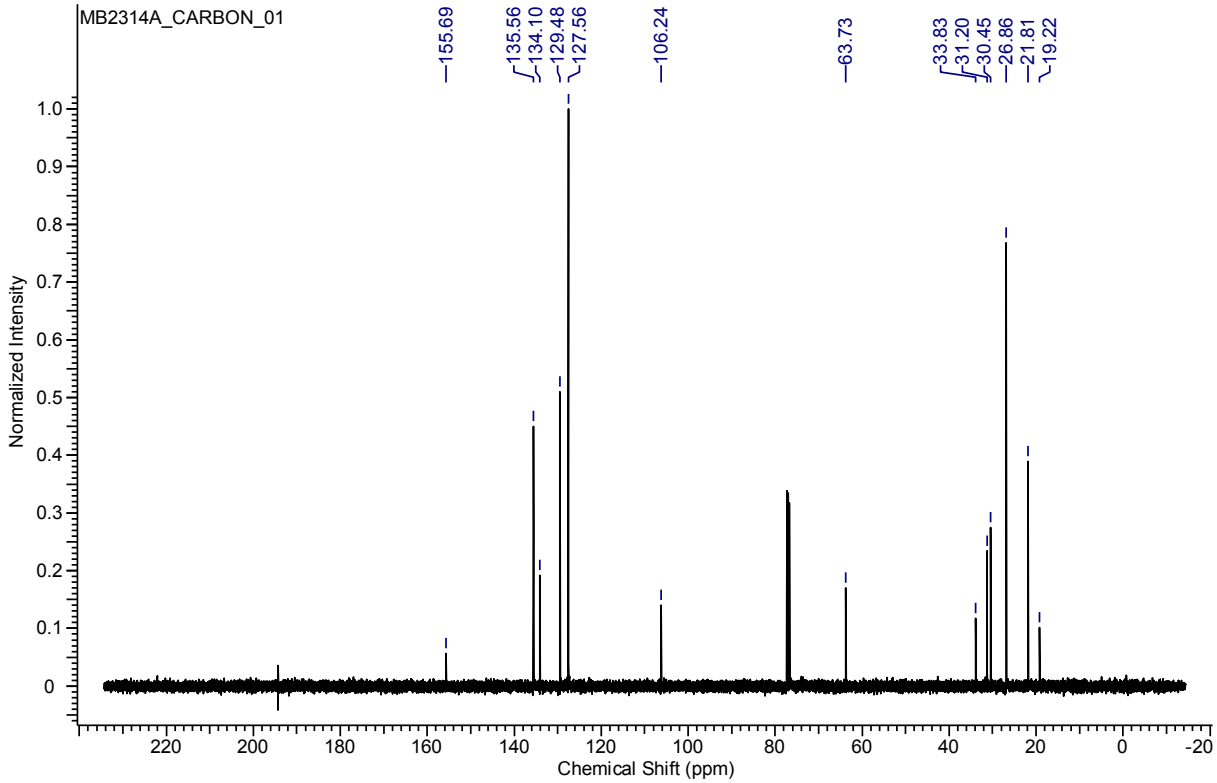

MB2300A_PROTON_01
6.66
3.41
3.39
3.38
3.36
3.34
3.32
3.31
1.62
1.60
1.59
1.57
1.46
0.87
0.87
0.85
0.02
TBSO
Me
N
H
O
CF3
Normalized Intensity
1.12
2.00 2.06 3.18 1.21 1.25 12.57 6.00
Chemical Shift (ppm)

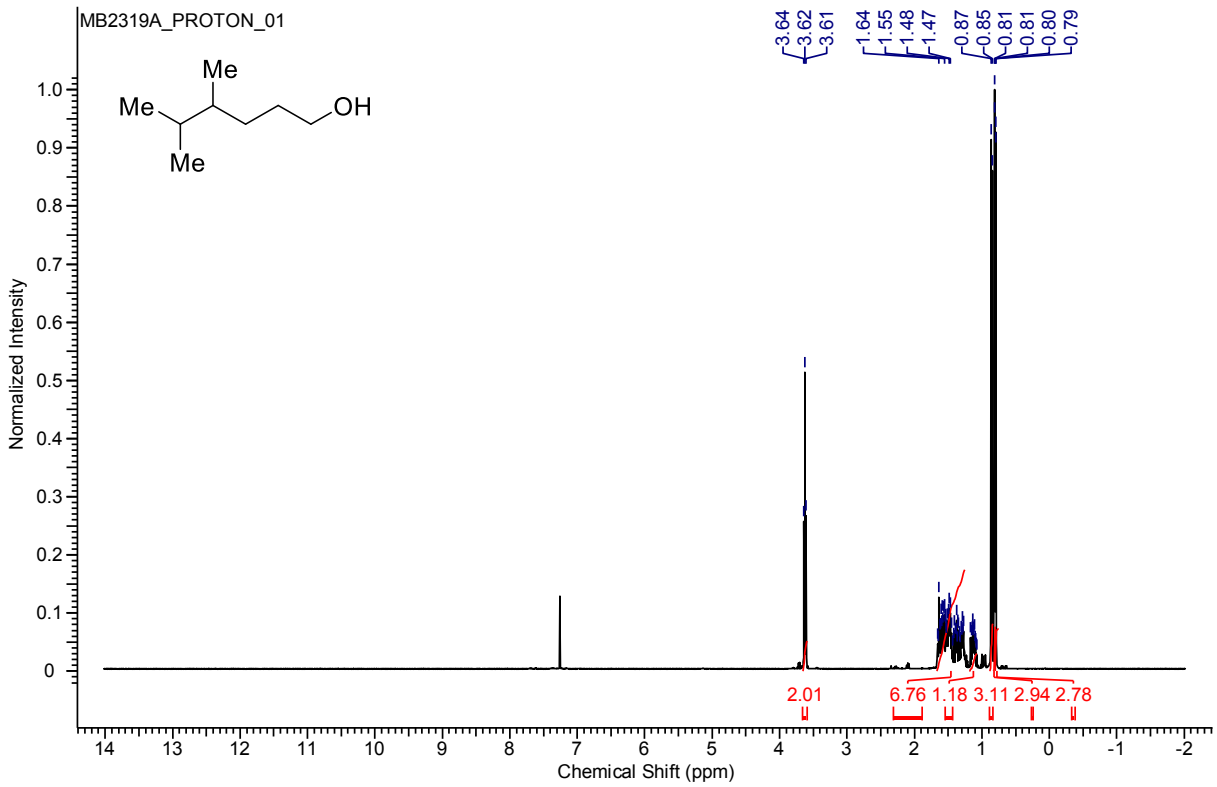

MB2300A_CARBON_01
157.77
157.40
157.04
156.67
120.16
117.30
114.44
111.57
67.96
40.26
35.29
30.17
26.34
25.84
18.25
16.49
5.50
Normalized Intensity
Chemical Shift (ppm)

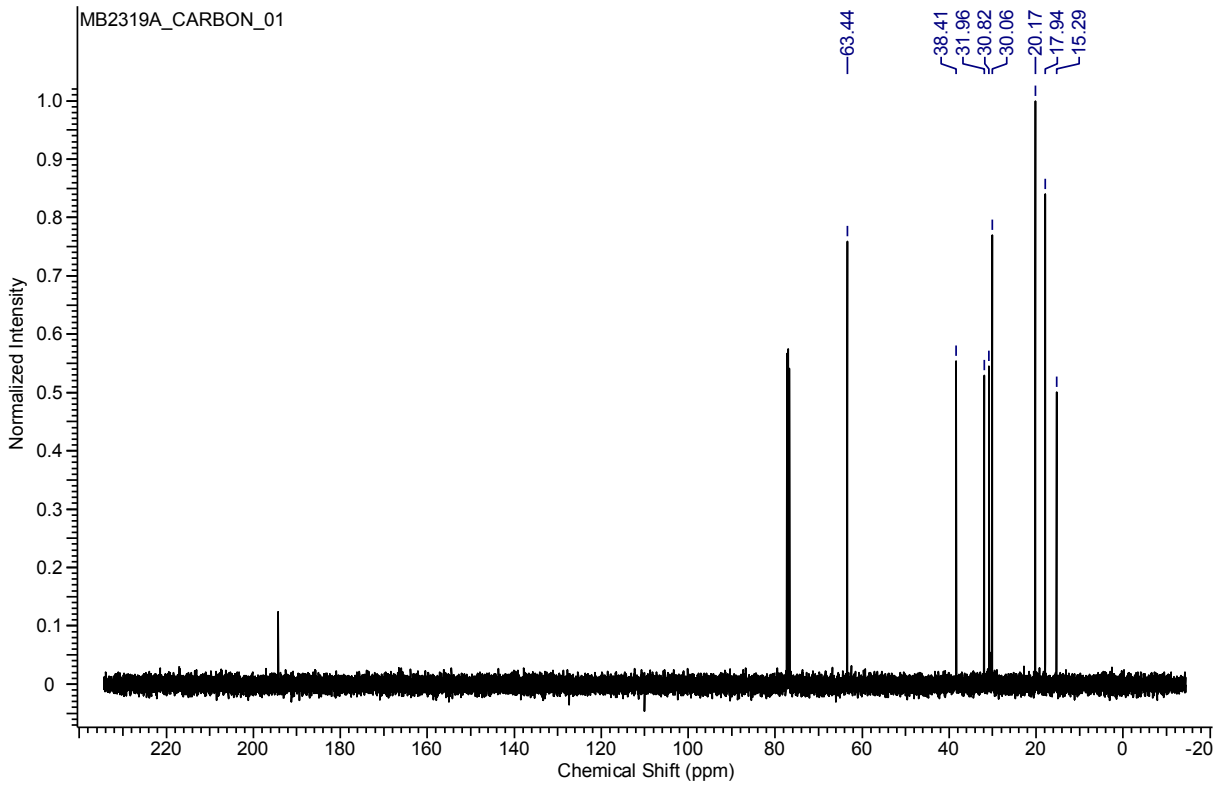

MB2308A2_PROTON_01
7.66
7.65
7.64
7.43
7.41
7.40
7.38
7.36
3.69
3.68
3.66
2.59
2.58
2.56
1.86
1.84
1.82
1.81
1.79
1.10
1.08
1.05
O
Me
OTBDPS
Me
Normalized Intensity
3.58
5.33
1.97
1.90
1.99
5.43
8.25
Chemical Shift (ppm)

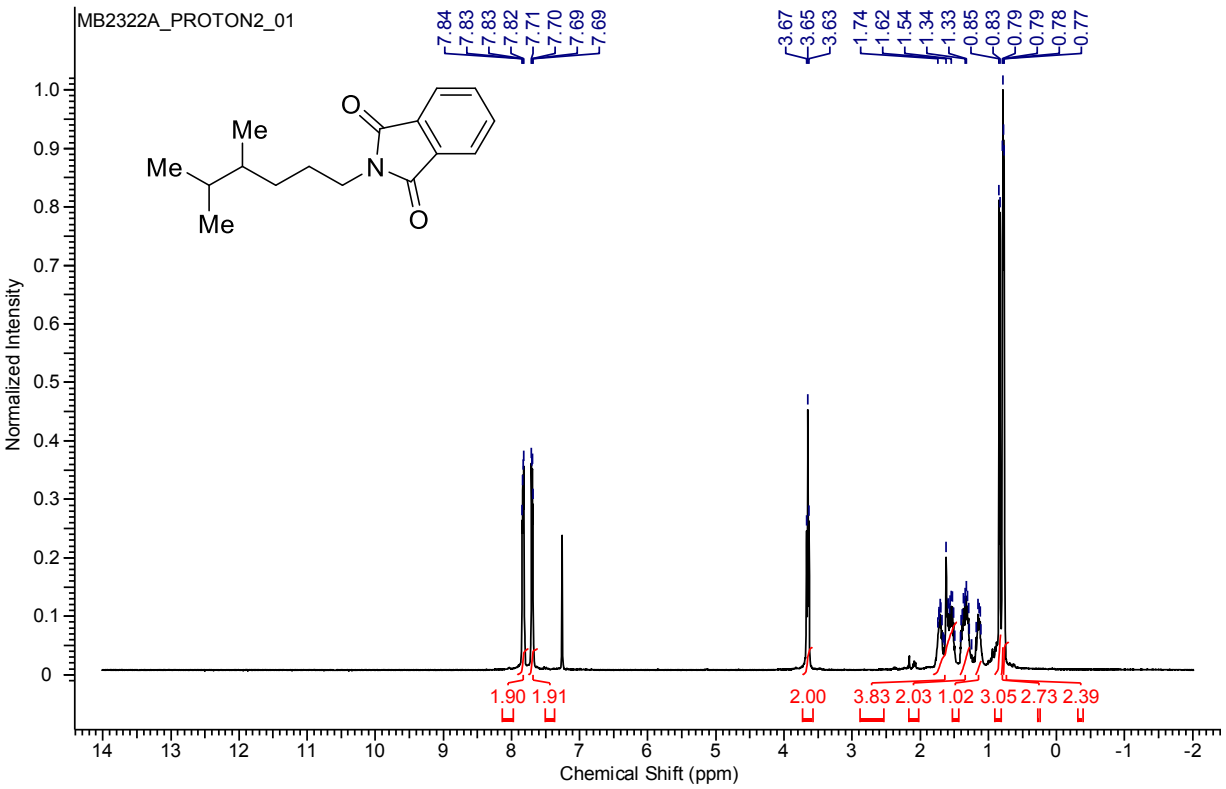

MB2308A_CARBON_01
214.6
135.52
133.85
129.58
127.62
63.04
40.88
36.51
26.85
26.63
19.22
18.28
Normalized Intensity
Chemical Shift (ppm)

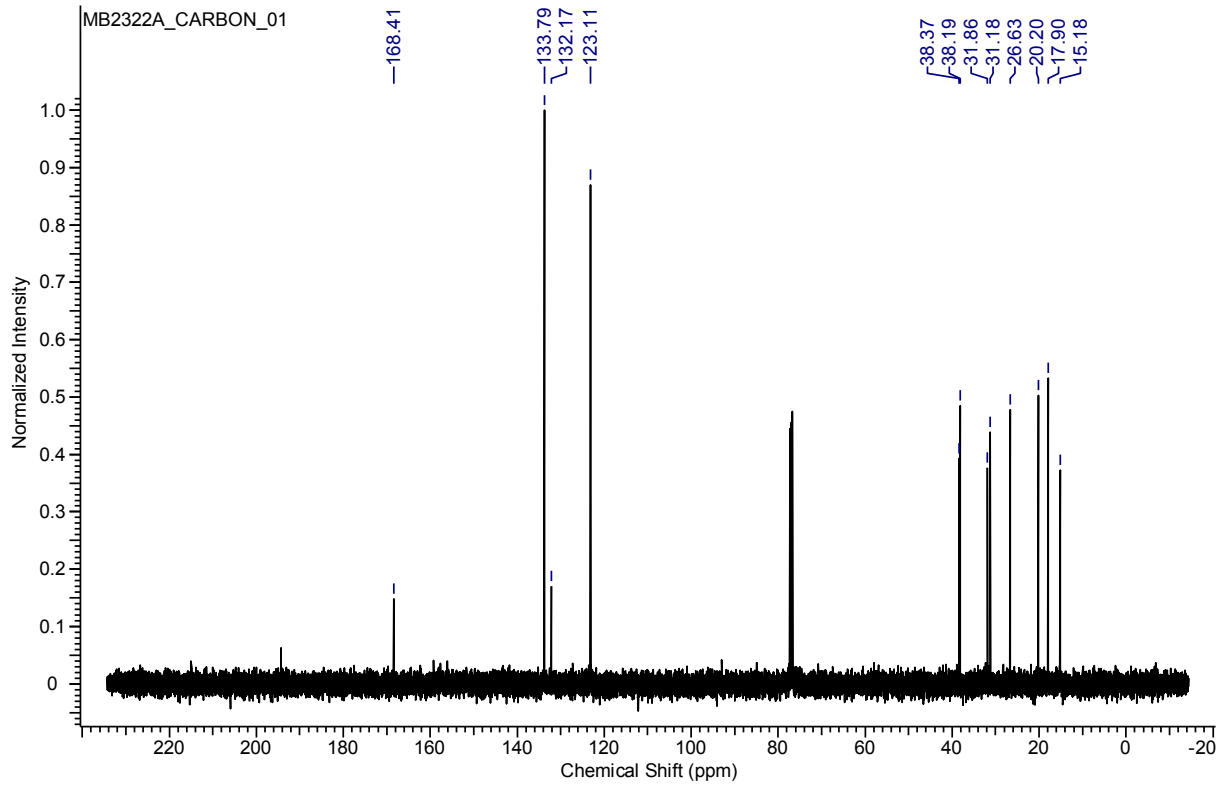

MB2314A_PROTON_01
7.69
7.67
7.43
7.41
7.40
7.38
7.37
7.36
4.74
4.66
3.71
3.69
3.68
2.22
2.13
2.11
2.09
1.73
1.72
1.71
1.69
1.06
1.03
1.01
Me
Me
OTBDPS
Normalized Intensity
3.95 5.85
0.97 0.98 2.00 1.10 2.00 2.10 8.46 5.58
Chemical Shift (ppm)

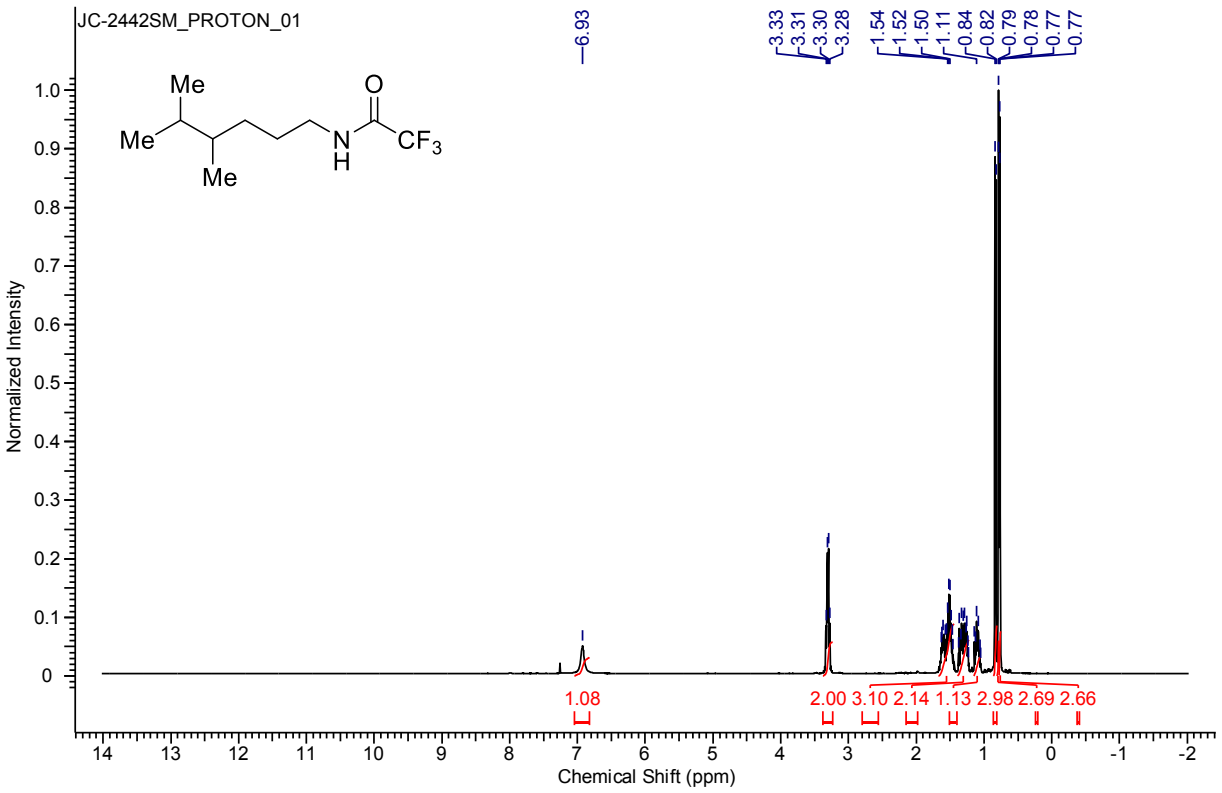

MB2314A_CARBON_01
155.69
135.56
134.10
129.48
127.56
106.24
63.73
33.83
31.20
30.45
26.86
21.81
19.22
Normalized Intensity
Chemical Shift (ppm)

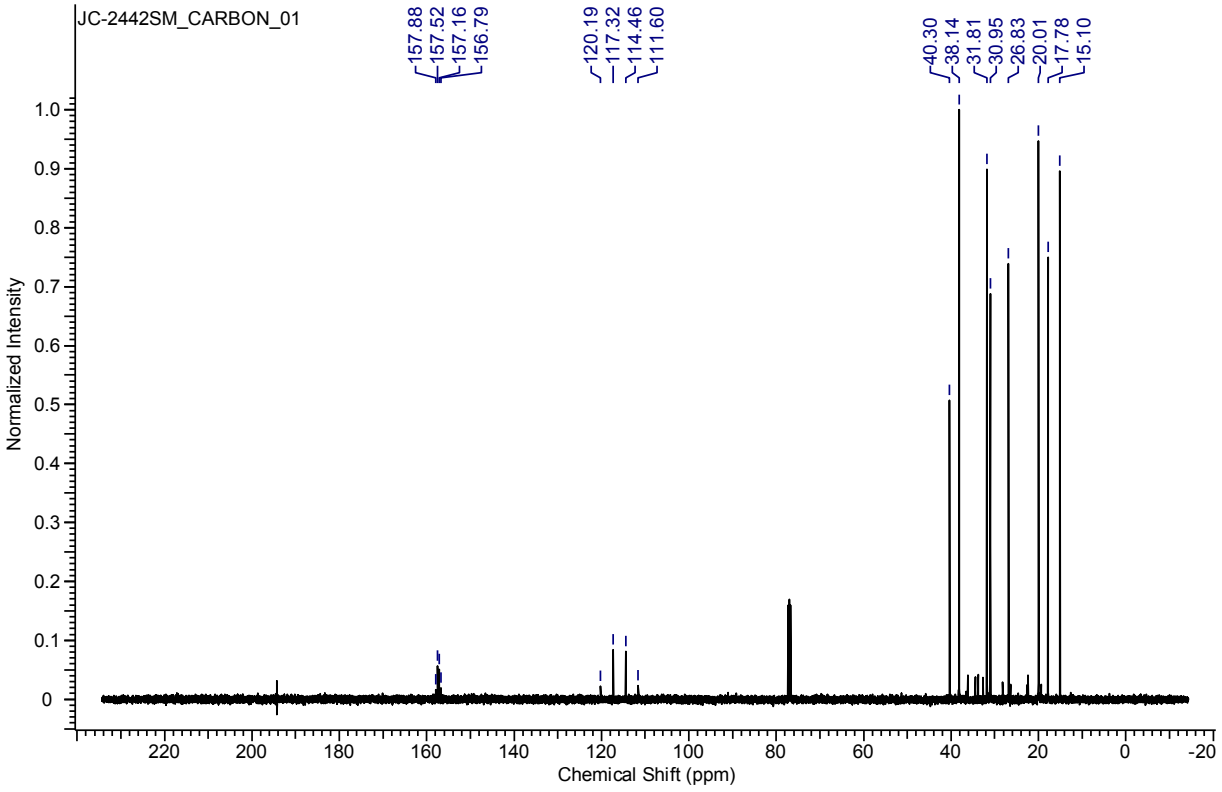

MB2319A_PROTON_01
Me
Me
Me
OH
3.64
3.62
3.61
1.64
1.55
1.48
1.47
0.87
0.85
0.81
0.81
0.80
0.79
2.01
6.76
1.18
3.11
2.94
2.78
Normalized Intensity
Chemical Shift (ppm)

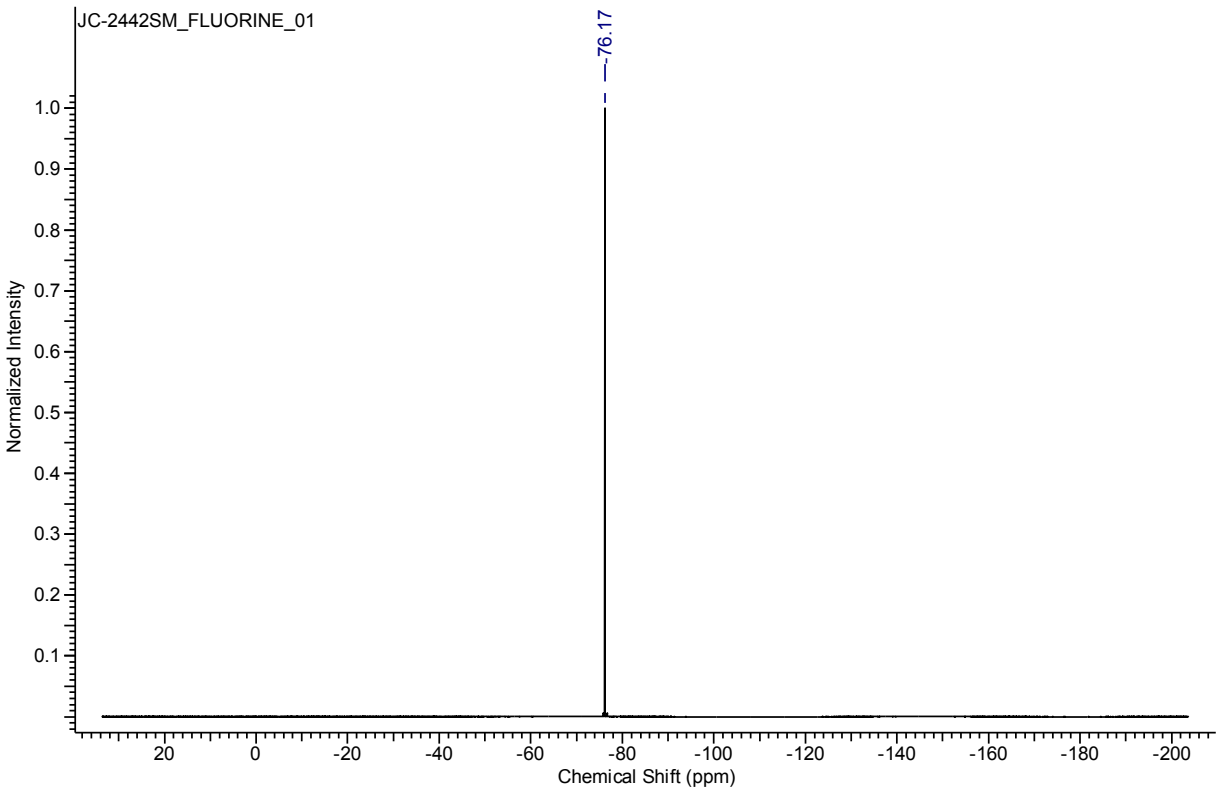

MB2319A_CARBON_01
63.44
38.41
31.96
30.82
30.06
20.17
17.94
15.29
Normalized Intensity
Chemical Shift (ppm)

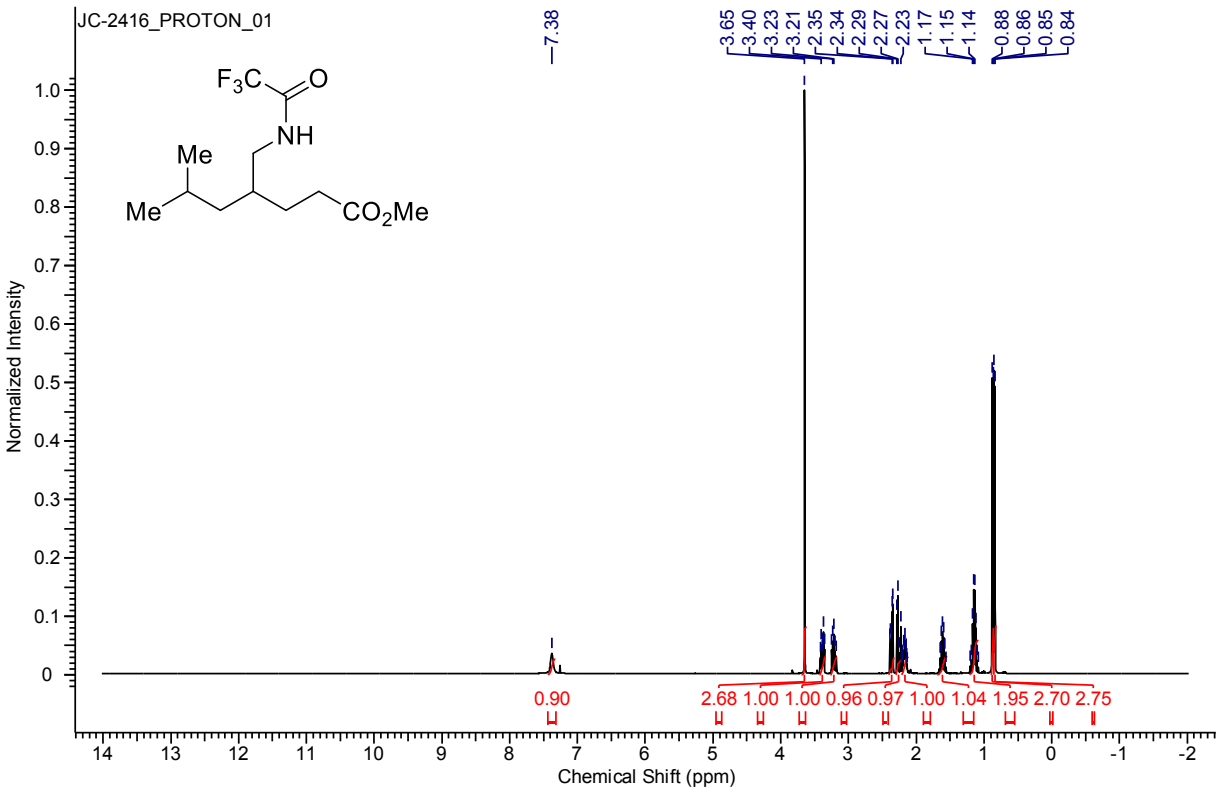

MB2322A_PROTON2_01
7.84
7.83
7.83
7.82
7.71
7.70
7.69
7.69
3.67
3.65
3.63
1.74
1.62
1.54
1.34
1.33
0.85
0.83
0.79
0.79
0.78
0.77
Me
Me
Me
N
O
O
Normalized Intensity
1.90 1.91
2.00
3.83 2.03 1.02 3.05 2.73 2.39
Chemical Shift (ppm)

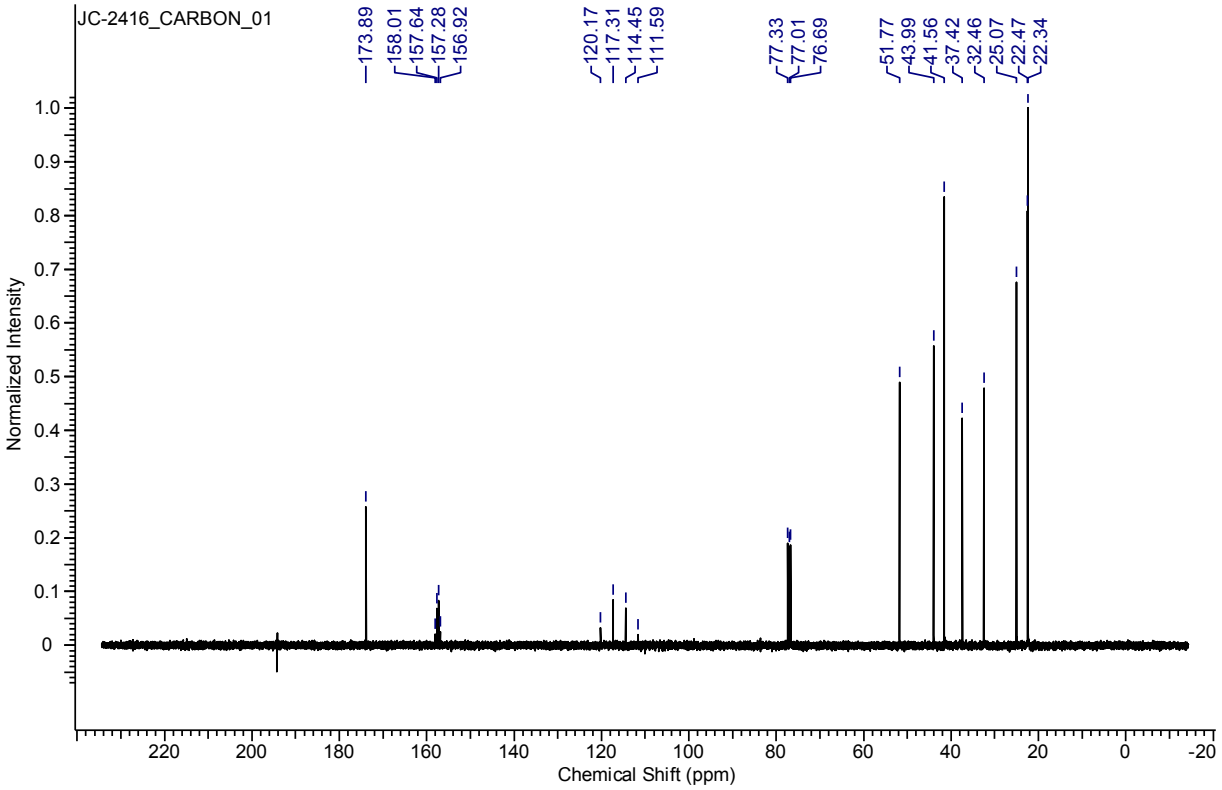

MB2322A_CARBON_01
168.41
133.79
132.17
123.11
38.37
38.19
31.86
31.18
26.63
20.20
17.90
15.18
Normalized Intensity
Chemical Shift (ppm)

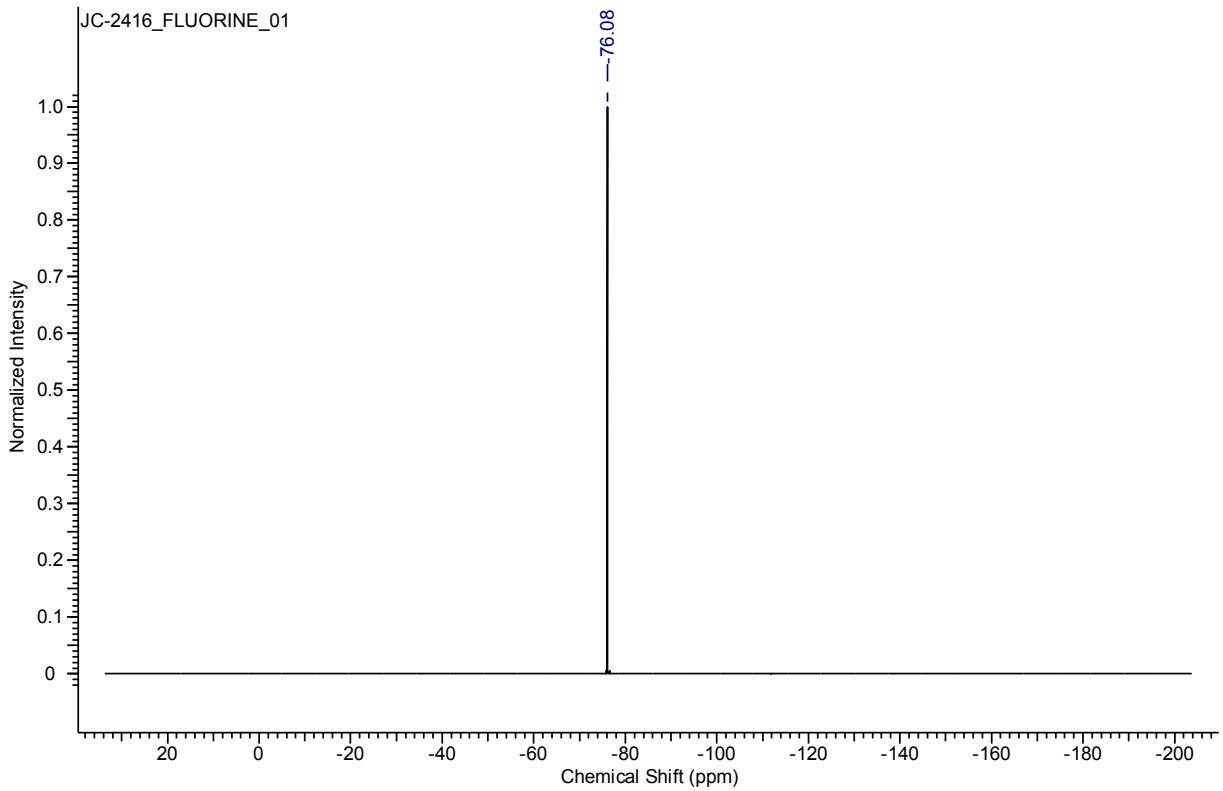

JC-2442SM_PROTON_01
6.93
3.33
3.31
3.30
3.28
1.54
1.52
1.50
1.11
0.84
0.82
0.79
0.78
0.77
0.77
Me
Me
Me
O
N
H
CF3
1.08
2.00 3.10 2.14 1.13 2.98 2.69 2.66
Normalized Intensity
Chemical Shift (ppm)

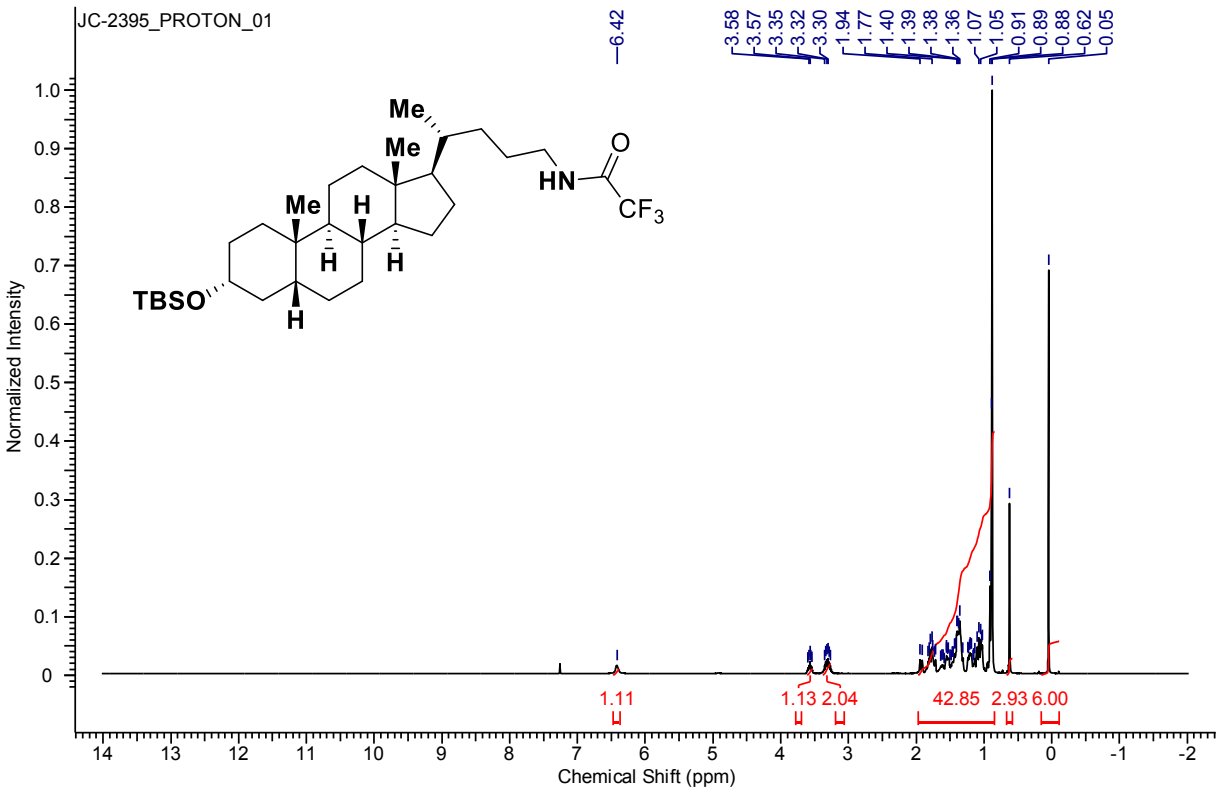

JC-2442SM_CARBON_01
157.88
157.52
157.16
156.79
120.19
117.32
114.46
111.60
40.30
38.14
31.81
30.95
26.83
20.01
17.78
15.10
Normalized Intensity
Chemical Shift (ppm)

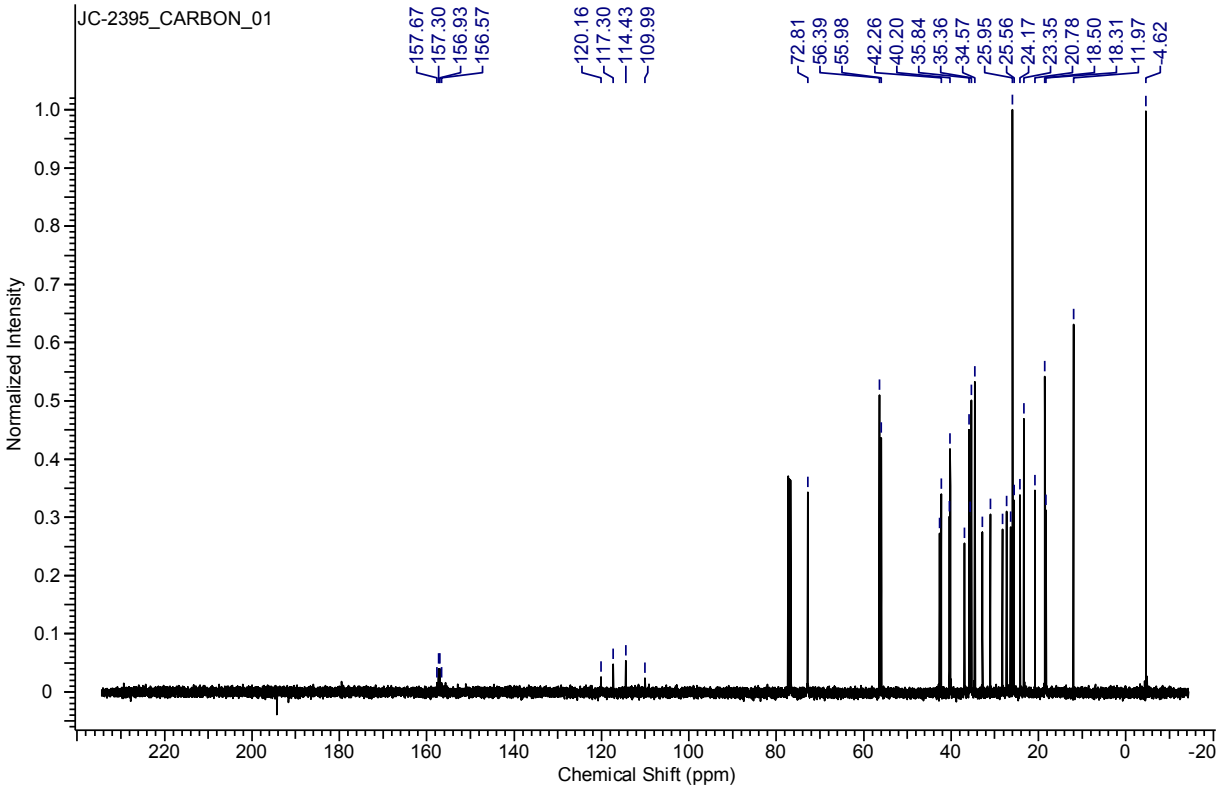

JC-2442SM_FLUORINE_01
-76.17
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

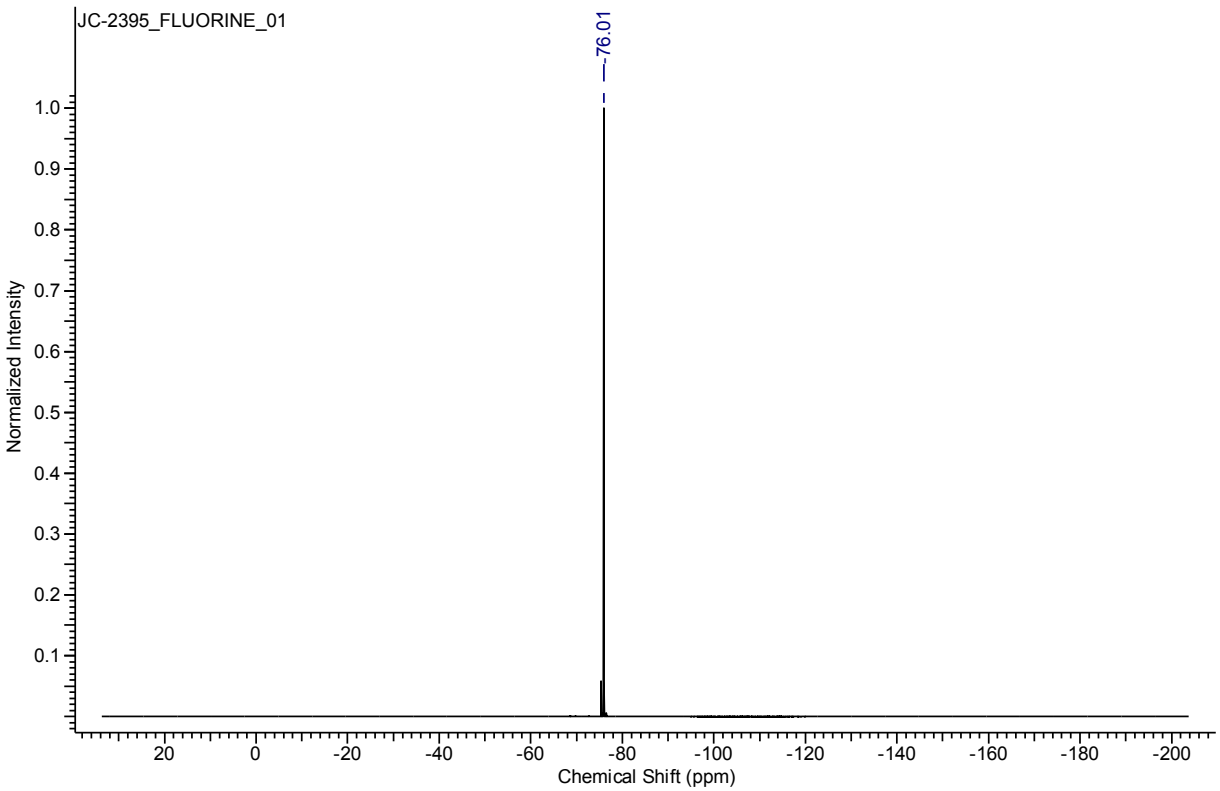

JC-2416_PROTON_01
7.38
3.65
3.40
3.23
3.21
2.35
2.34
2.29
2.27
2.23
1.17
1.15
1.14
0.88
0.86
0.85
0.84
F3C
O
NH
Me
Me
CO2Me
Normalized Intensity
Chemical Shift (ppm)
0.90
2.68 1.00 1.00 0.96 0.97 1.00 1.04 1.95 2.70 2.75

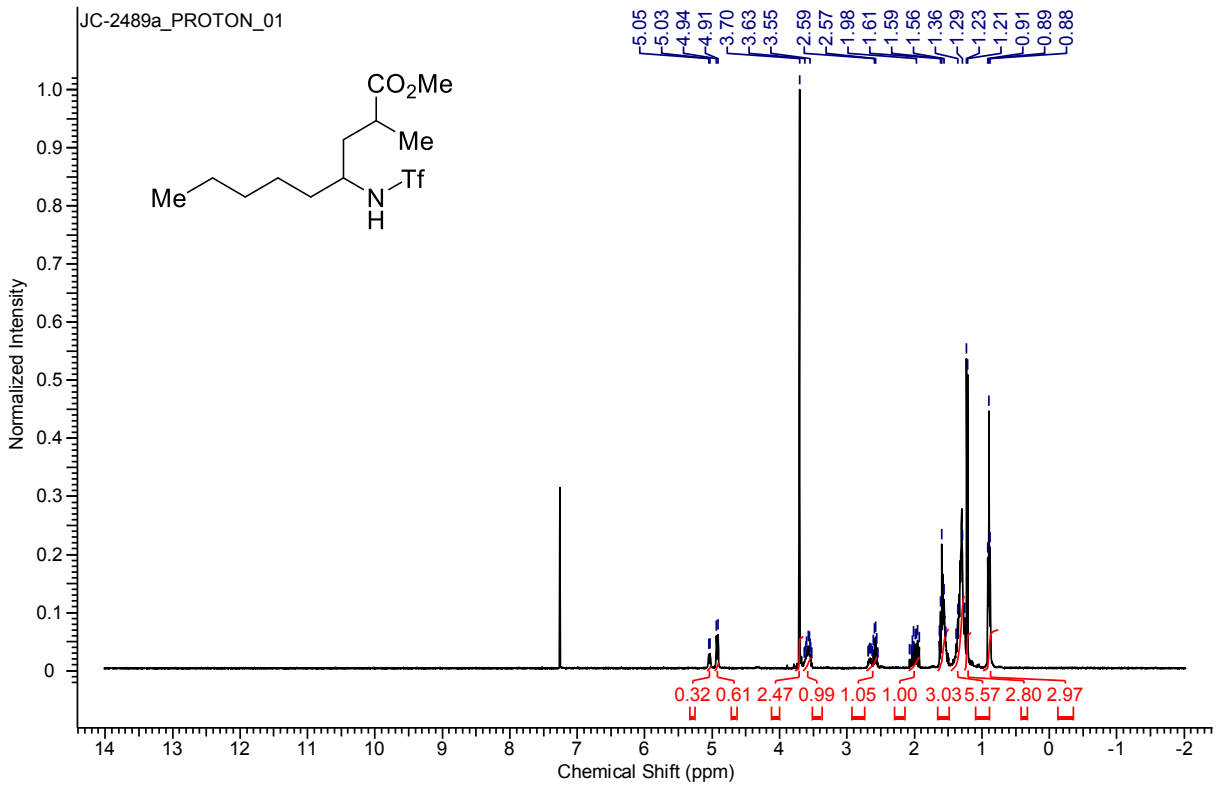

JC-2416_CARBON_01
173.89
158.01
157.64
157.28
156.92
120.17
117.31
114.45
111.59
77.33
77.01
76.69
51.77
43.99
41.56
37.42
32.46
25.07
22.47
22.34
Normalized Intensity
Chemical Shift (ppm)

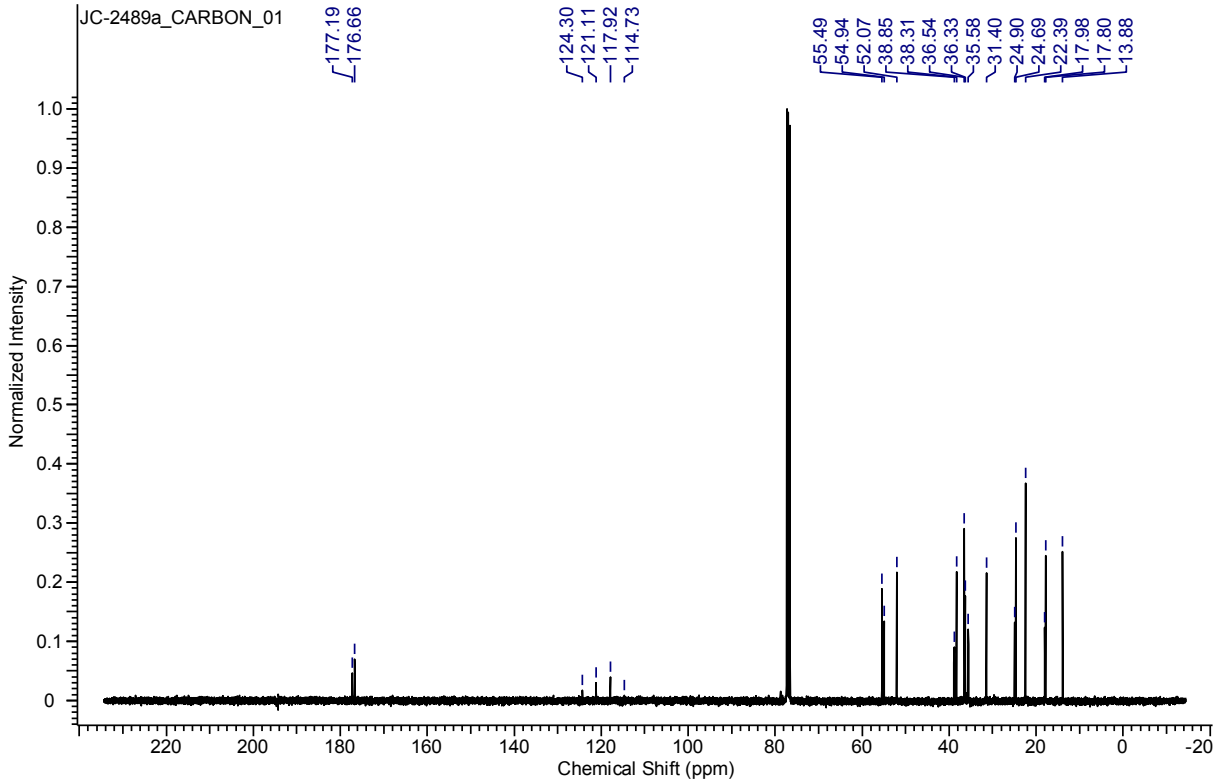

JC-2416_FLUORINE_01
-76.08
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

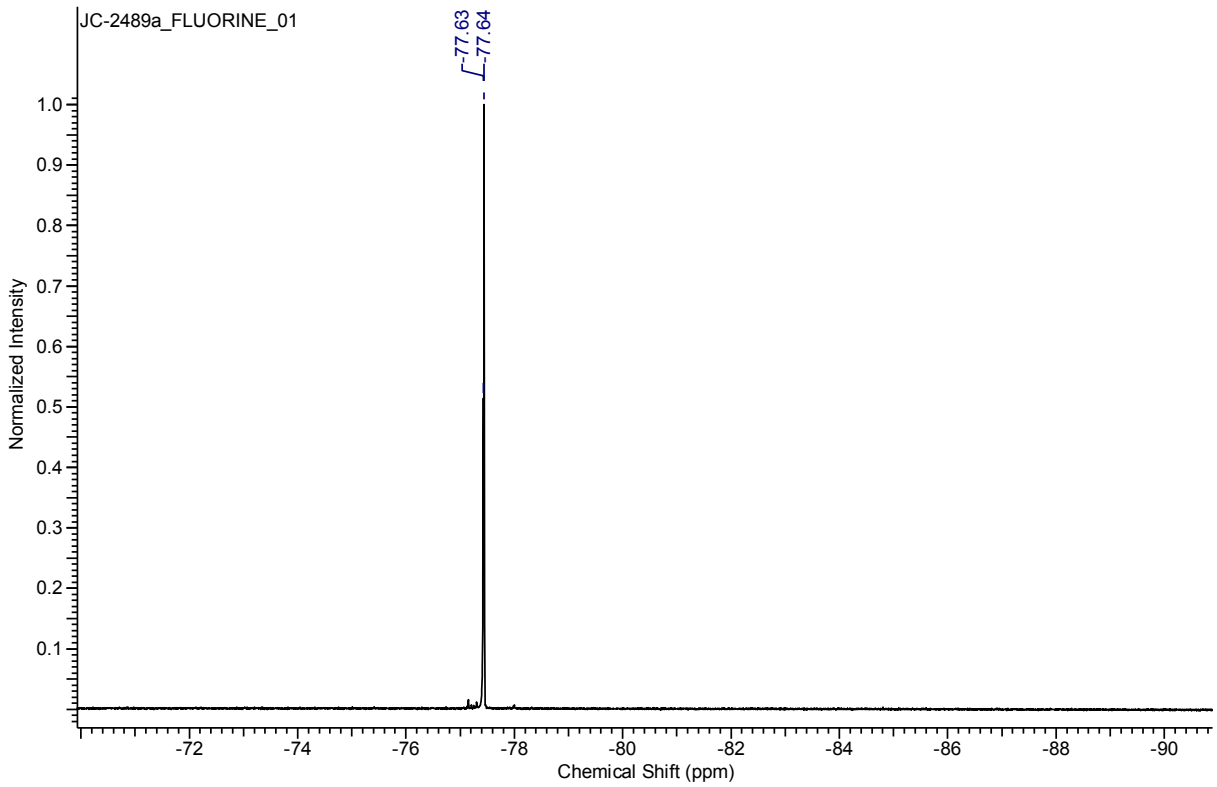

JC-2395_PROTON_01
6.42
3.58
3.57
3.35
3.32
3.30
1.94
1.77
1.40
1.39
1.38
1.36
1.07
1.05
0.91
0.89
0.88
0.62
0.05
Me
Me
Me
H
H
H
H
TBSO
HN
O
CF3
1.11
1.13
2.04
42.85
2.93
6.00
Normalized Intensity
Chemical Shift (ppm)

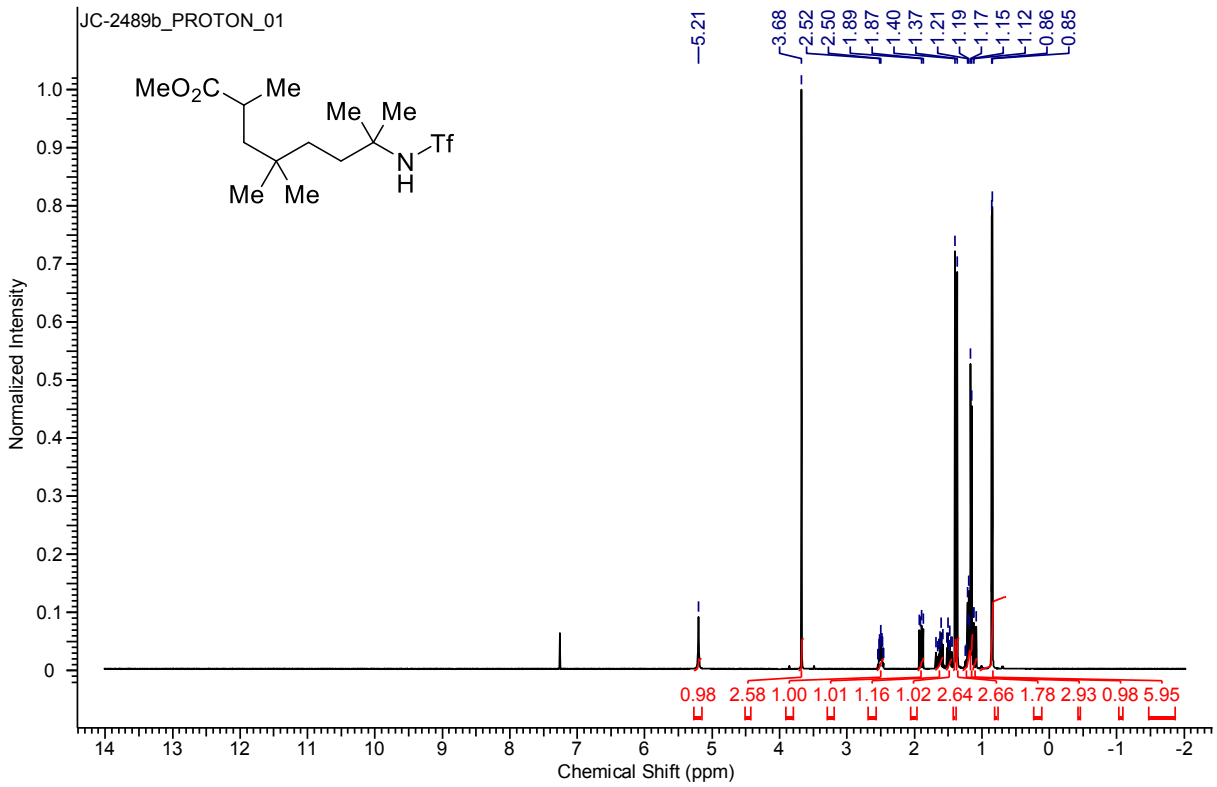

JC-2395_CARBON_01
157.67
157.30
156.93
156.57
120.16
117.30
114.43
109.99
72.81
56.39
55.98
42.26
40.20
35.84
35.36
34.57
25.95
25.56
24.17
23.35
20.78
18.50
18.31
11.97
4.62
Normalized Intensity
Chemical Shift (ppm)

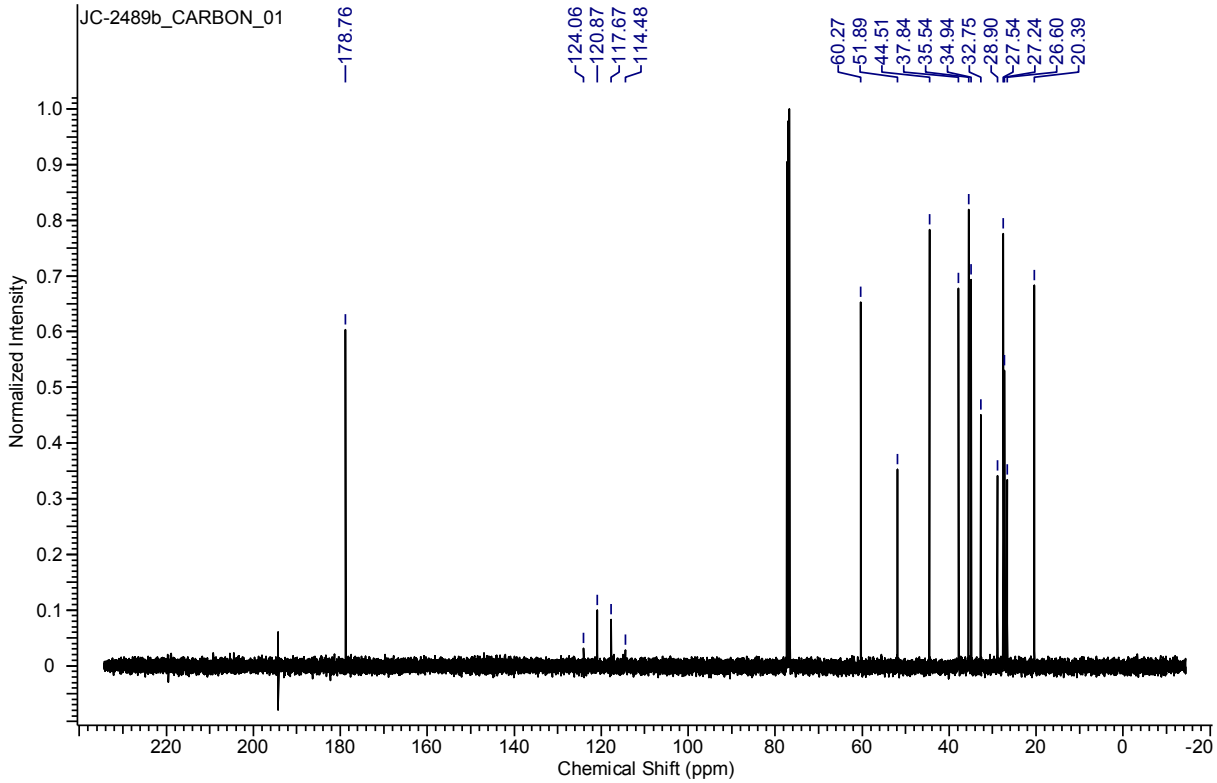

JC-2395_FLUORINE_01
-76.01
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

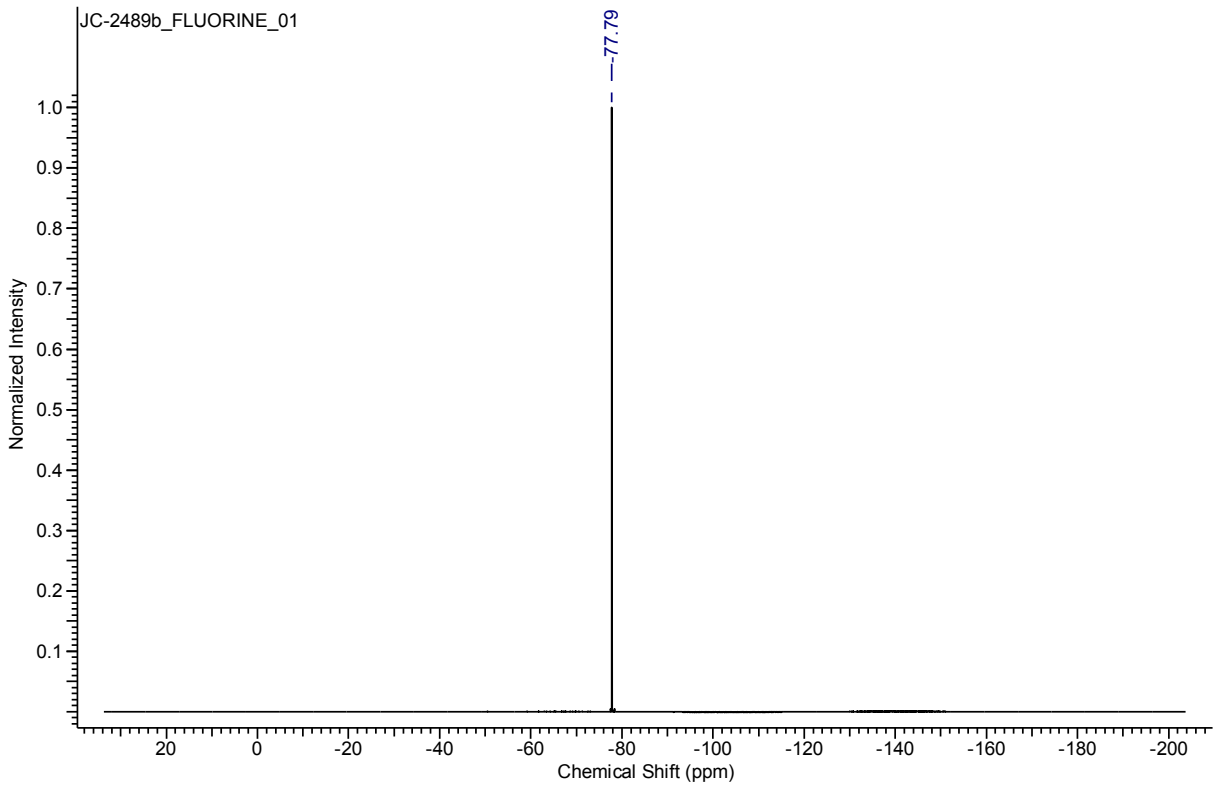

JC-2489a_PROTON_01
5.05
5.03
4.94
4.91
3.70
3.63
3.55
2.59
2.57
1.98
1.61
1.59
1.56
1.36
1.29
1.23
1.21
0.91
0.89
0.88
CO2Me
Me
Tf
N
H
Me
0.32 0.61 2.47 0.99 1.05 1.00 3.03 5.57 2.80 2.97
Normalized Intensity
Chemical Shift (ppm)

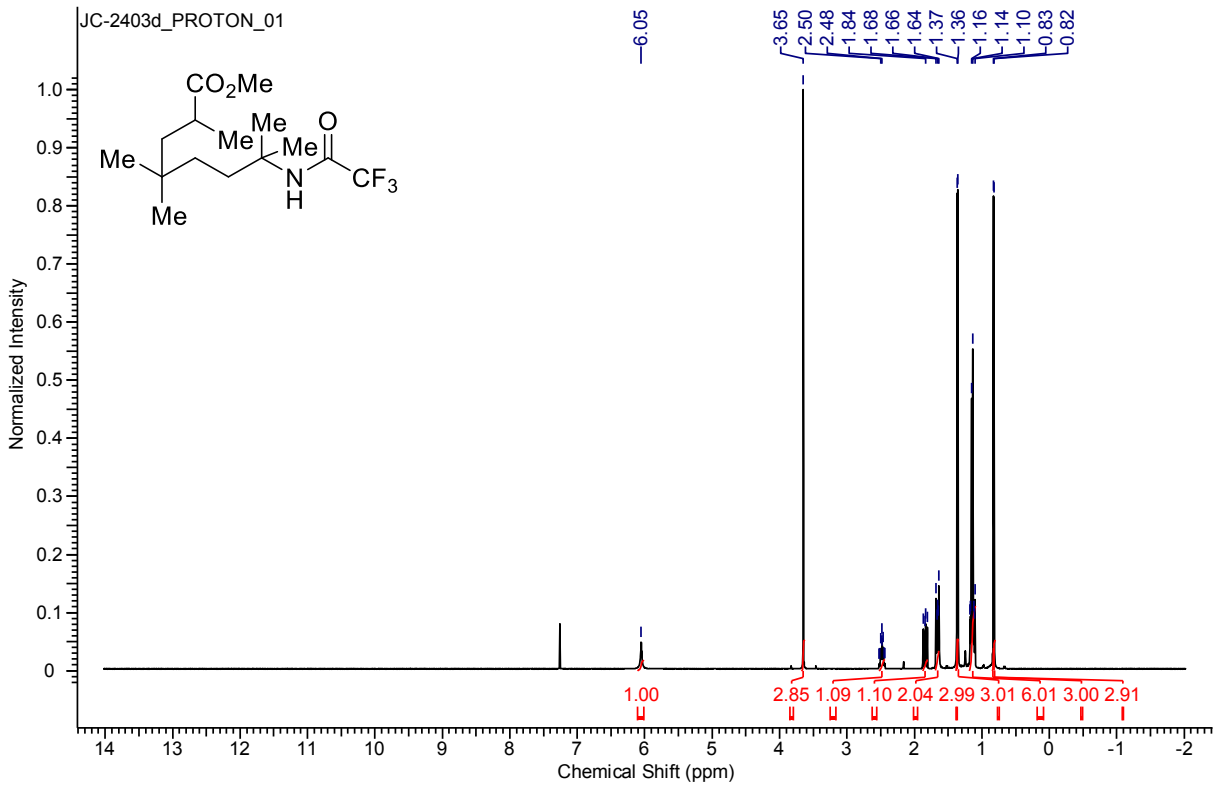

JC-2489a_CARBON_01
177.19
176.66
124.30
121.11
117.92
114.73
55.49
54.94
52.07
38.85
38.31
36.54
36.33
35.58
31.40
24.90
24.69
22.39
17.98
17.80
13.88
Normalized Intensity
Chemical Shift (ppm)

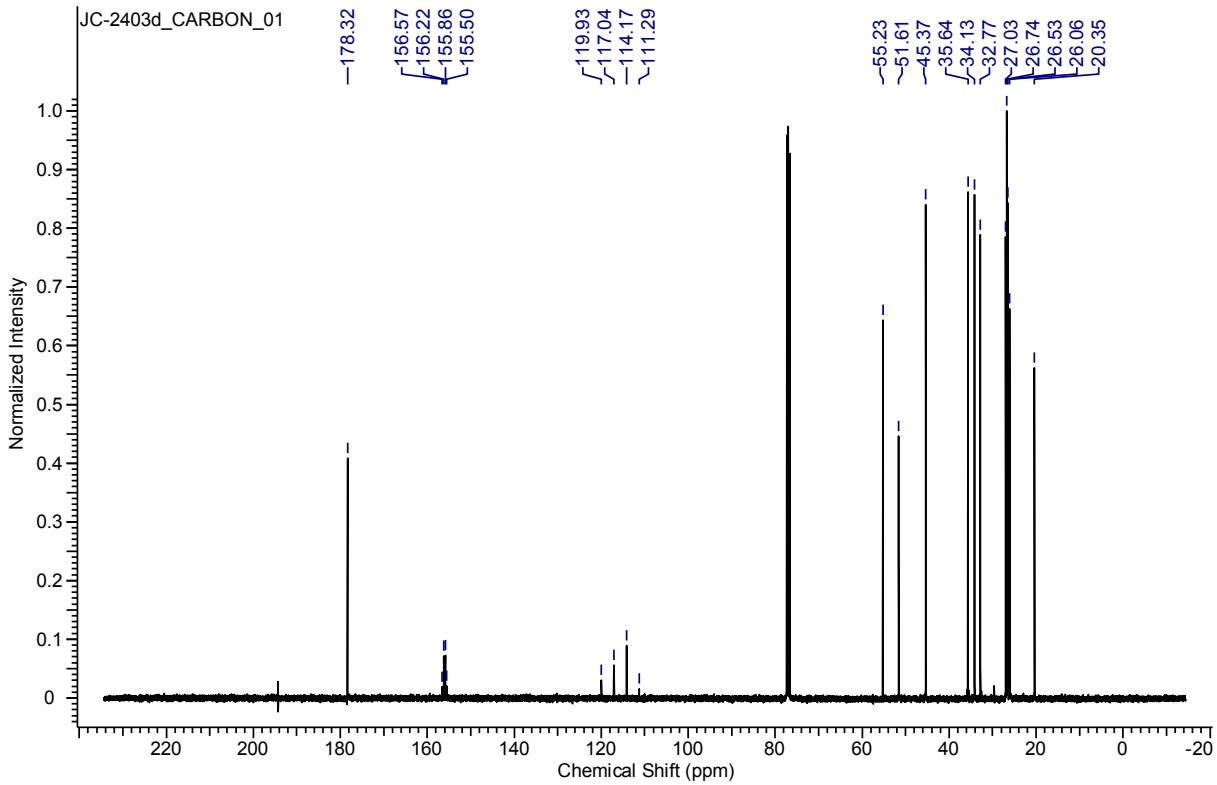

JC-2489a_FLUORINE_01
-77.63
-77.64
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
-72
-74
-76
-78
-80
-82
-84
-86
-88
-90
Chemical Shift (ppm)

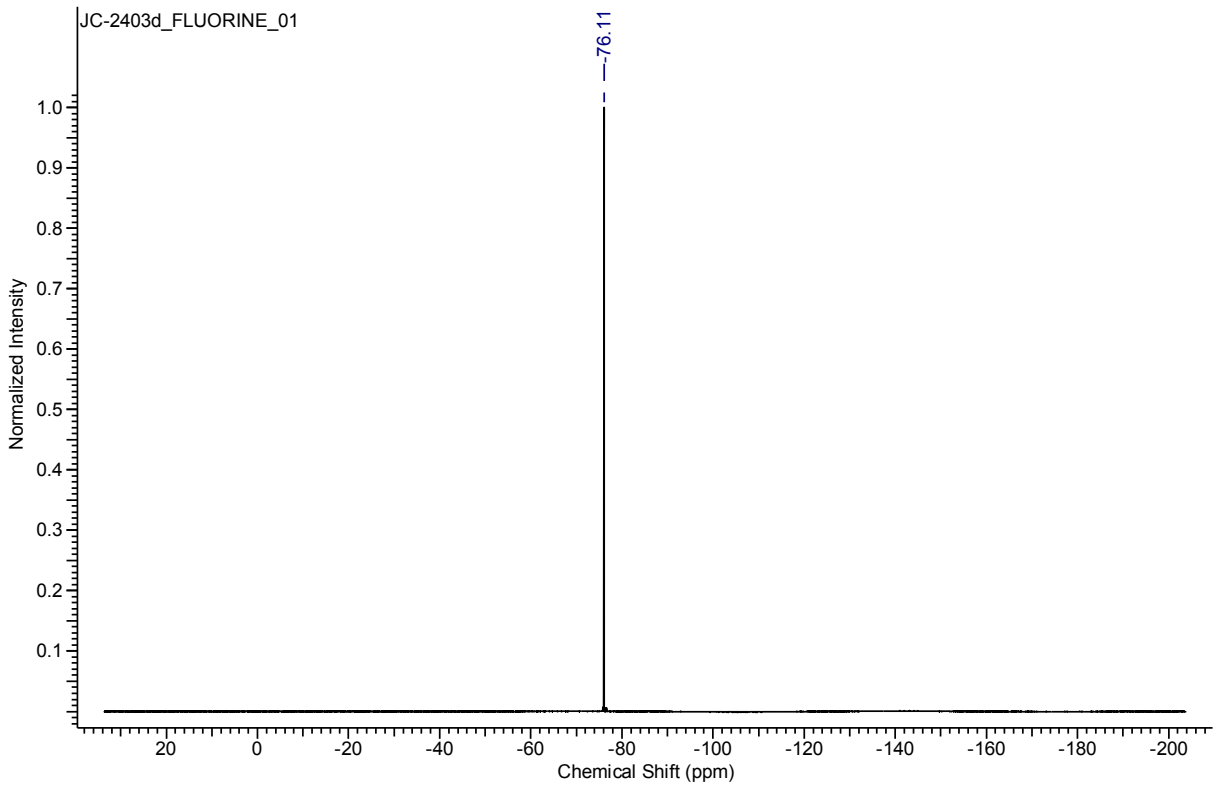

JC-2489b_PROTON_01
MeO2C
Me
Me
Me
Me
Me
N
H
Tf
5.21
3.68
2.52
2.50
1.89
1.87
1.40
1.37
1.21
1.19
1.17
1.15
1.12
0.86
0.85
0.98 2.58 1.00 1.01 1.16 1.02 2.64 2.66 1.78 2.93 0.98 5.95
Normalized Intensity
Chemical Shift (ppm)

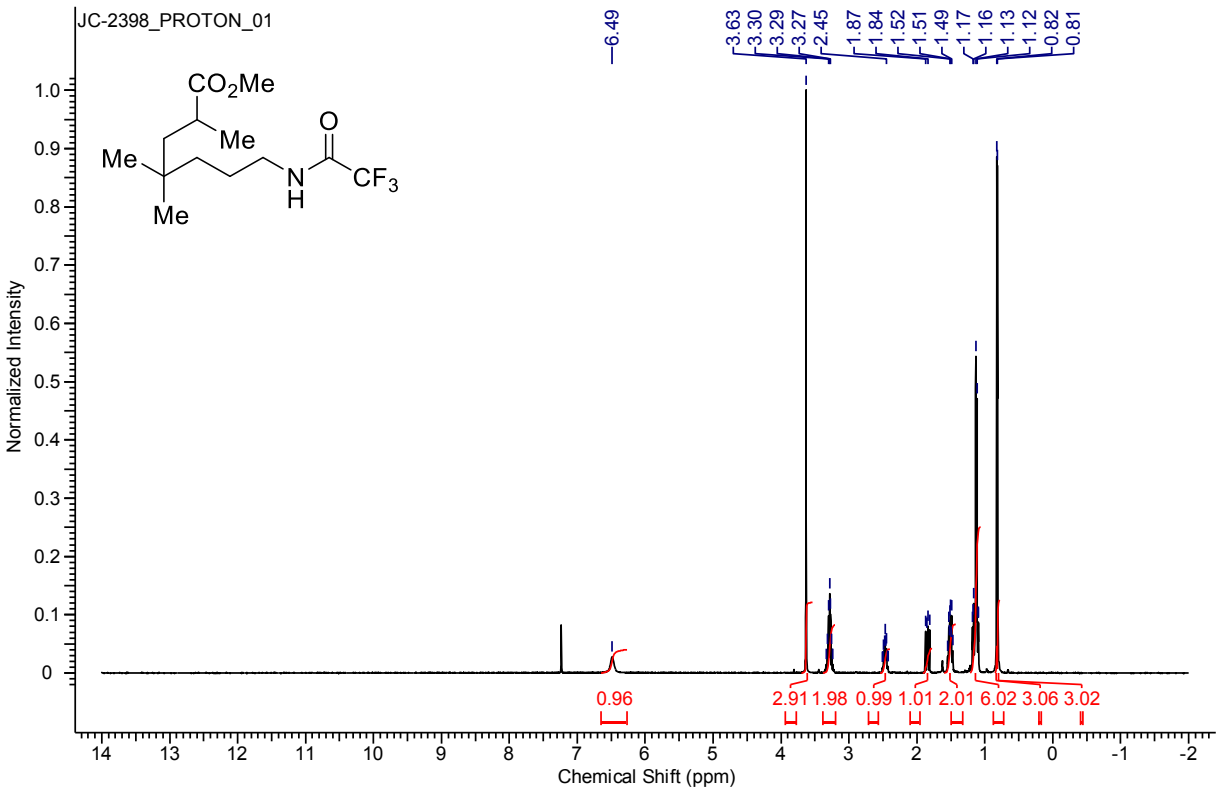

JC-2489b_CARBON_01
178.76
124.06
120.87
117.67
114.48
60.27
51.89
44.51
37.84
35.54
34.94
32.75
28.90
27.54
27.24
26.60
20.39
Normalized Intensity
Chemical Shift (ppm)

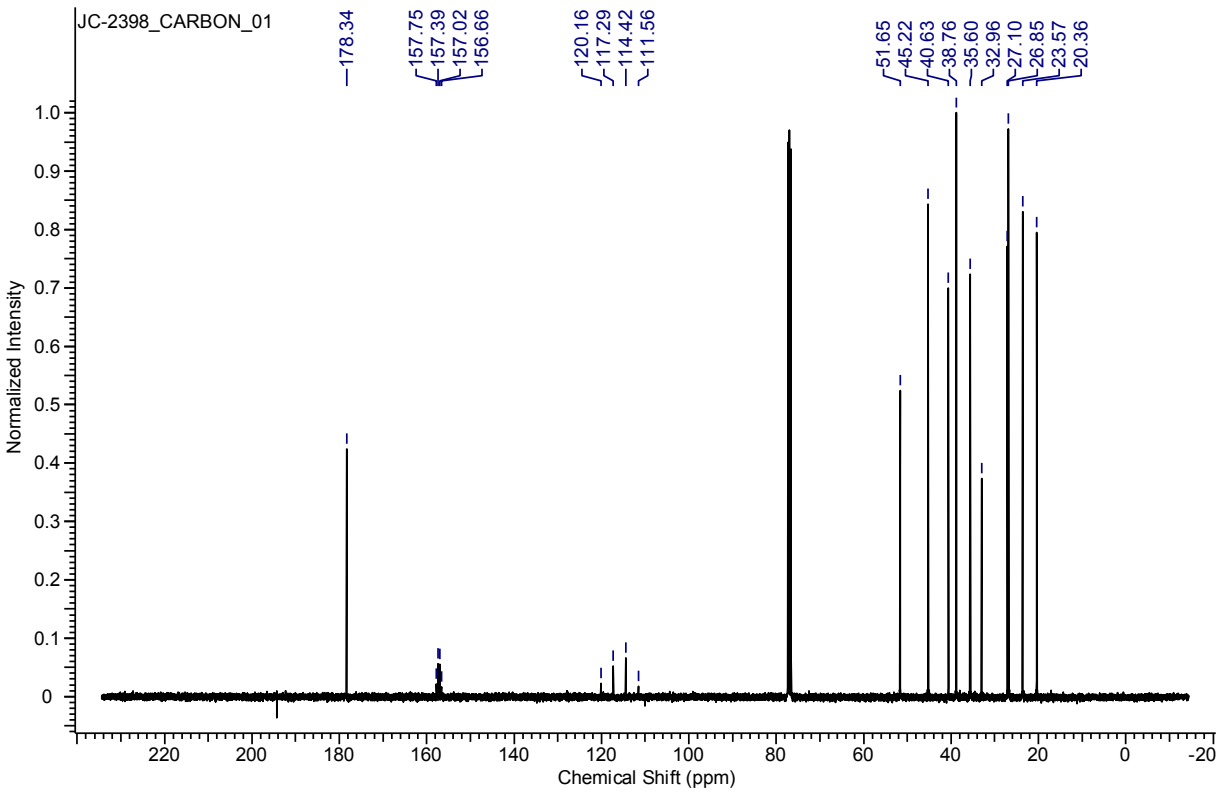

JC-2489b_FLUORINE_01
-77.79
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

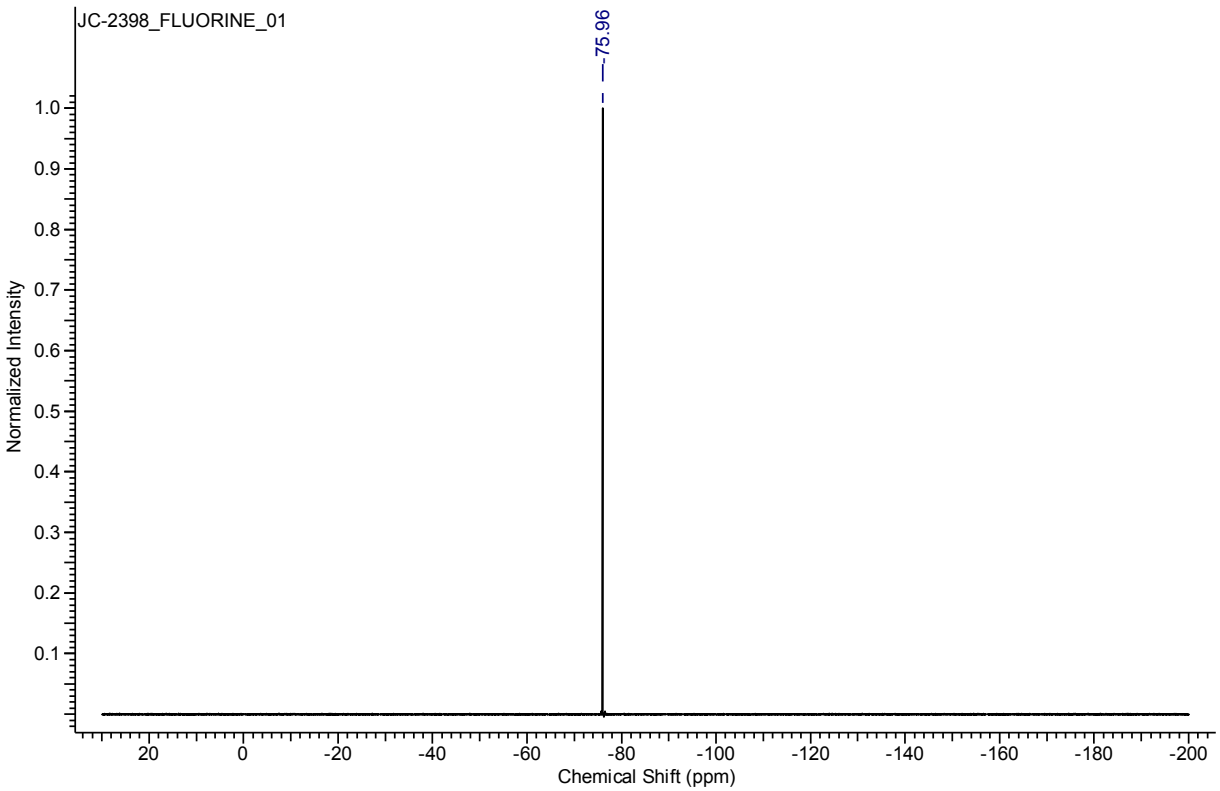

JC-2403d_PROTON_01
6.05
3.65
2.50
2.48
1.84
1.68
1.66
1.64
1.37
1.36
1.16
1.14
1.10
0.83
0.82
CO2Me
Me
Me
Me
O
N
H
CF3
Me
1.00
2.85 1.09 1.10 2.04 2.99 3.01 6.01 3.00 2.91
Normalized Intensity
Chemical Shift (ppm)

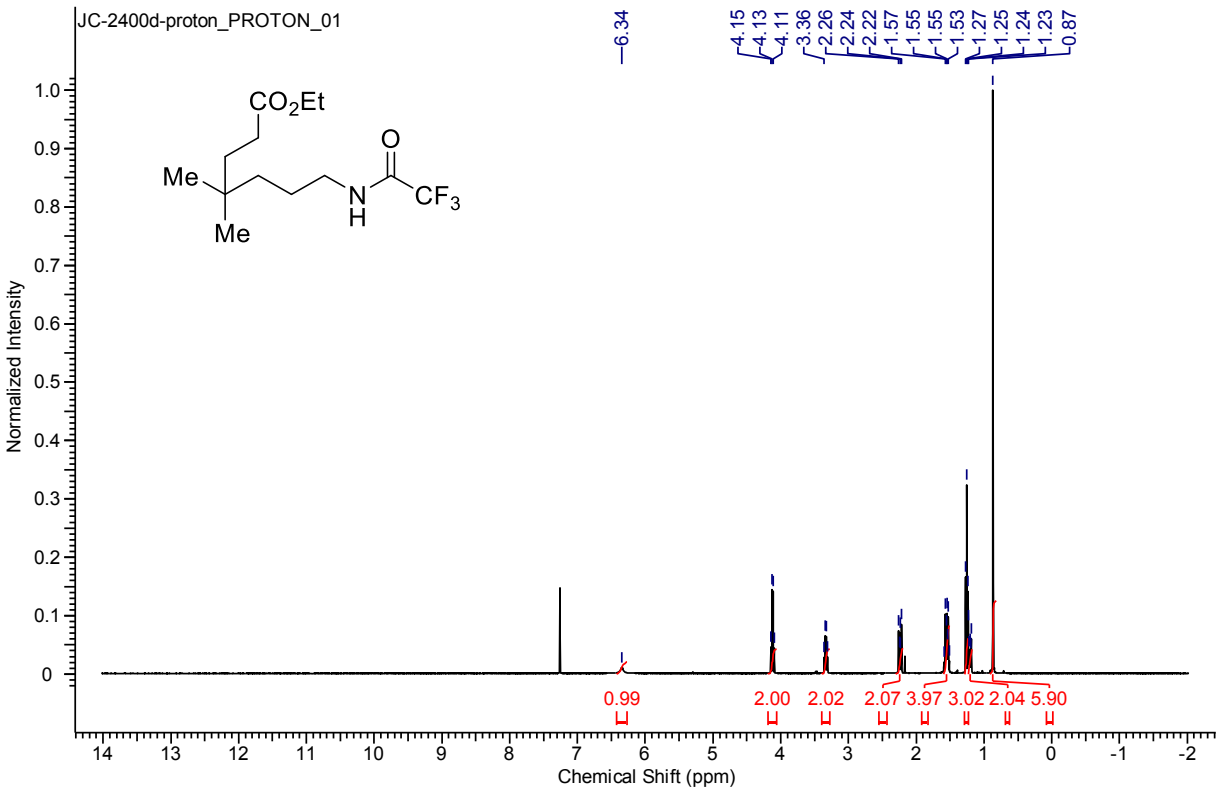

JC-2403d_CARBON_01
178.32
156.57
156.22
155.86
155.50
119.93
117.04
114.17
111.29
55.23
51.61
45.37
35.64
34.13
32.77
27.03
26.74
26.53
26.06
20.35
Normalized Intensity
Chemical Shift (ppm)

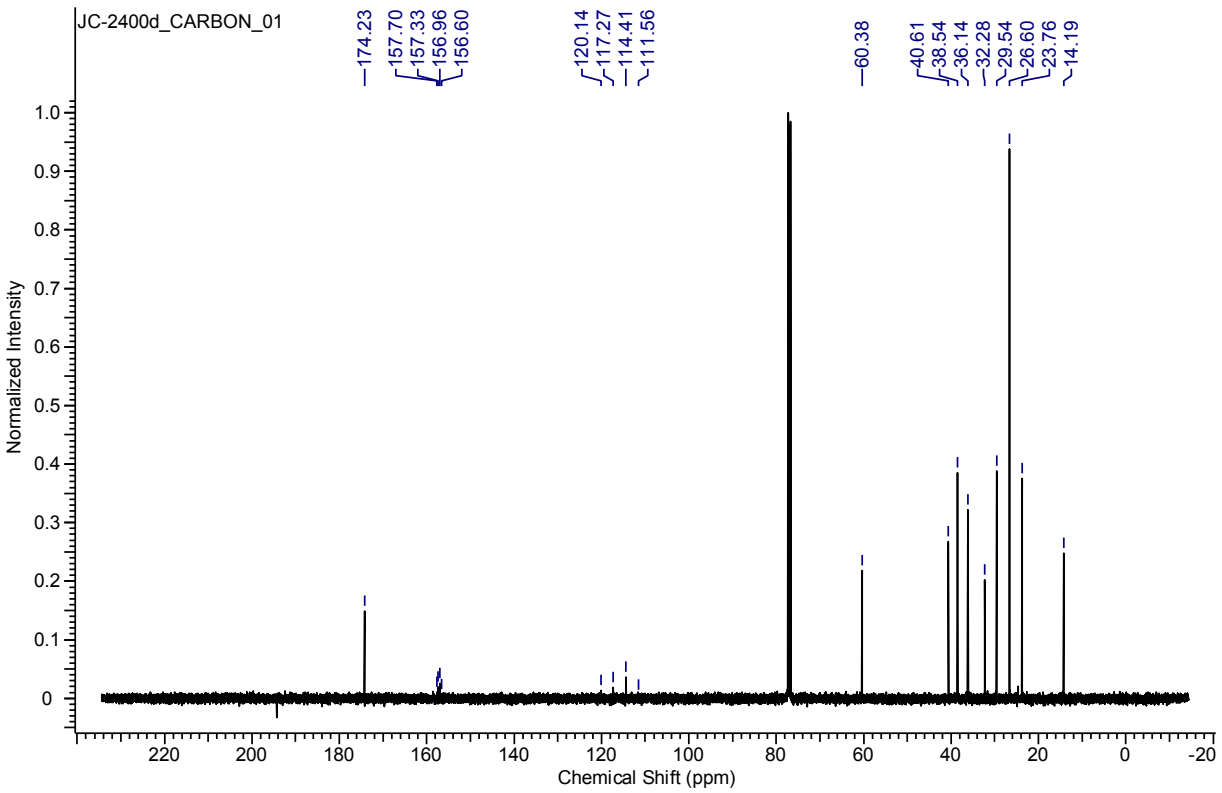

JC-2403d_FLUORINE_01
-76.11
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

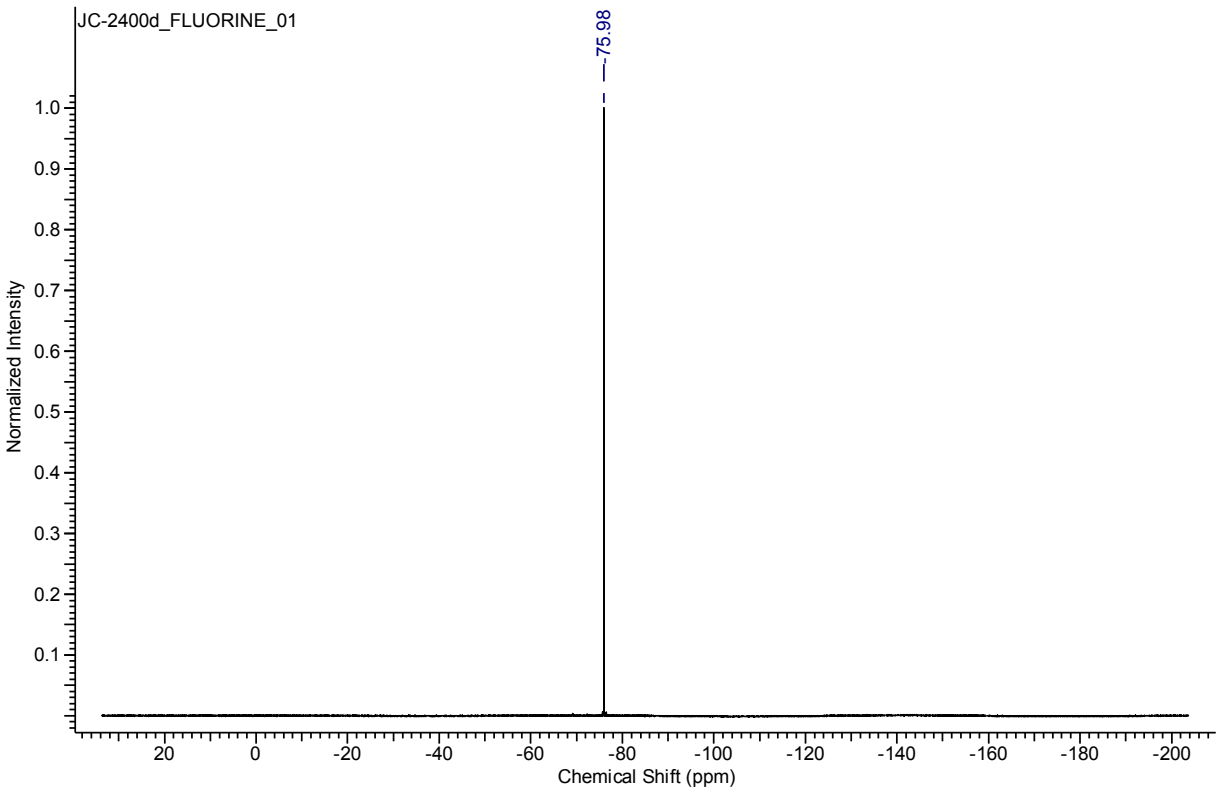

JC-2398_PROTON_01
6.49
3.63
3.30
3.29
3.27
2.45
1.87
1.84
1.52
1.51
1.49
1.17
1.16
1.13
1.12
0.82
0.81
CO2Me
Me
Me
Me
N
H
O
CF3
0.96
2.91
1.98
0.99
1.01
2.01
6.02
3.06
3.02
Normalized Intensity
Chemical Shift (ppm)

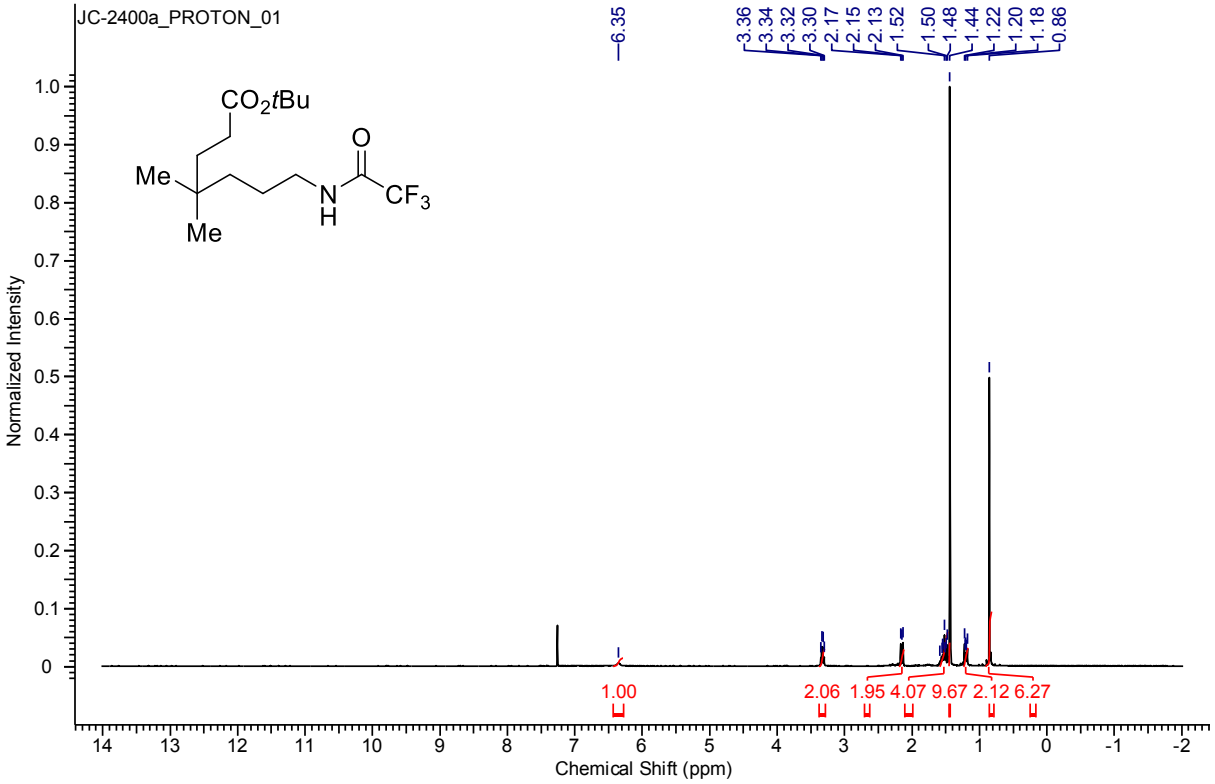

JC-2398_CARBON_01
178.34
157.75
157.39
157.02
156.66
120.16
117.29
114.42
111.56
51.65
45.22
40.63
38.76
35.60
32.96
27.10
26.85
23.57
20.36
Normalized Intensity
Chemical Shift (ppm)

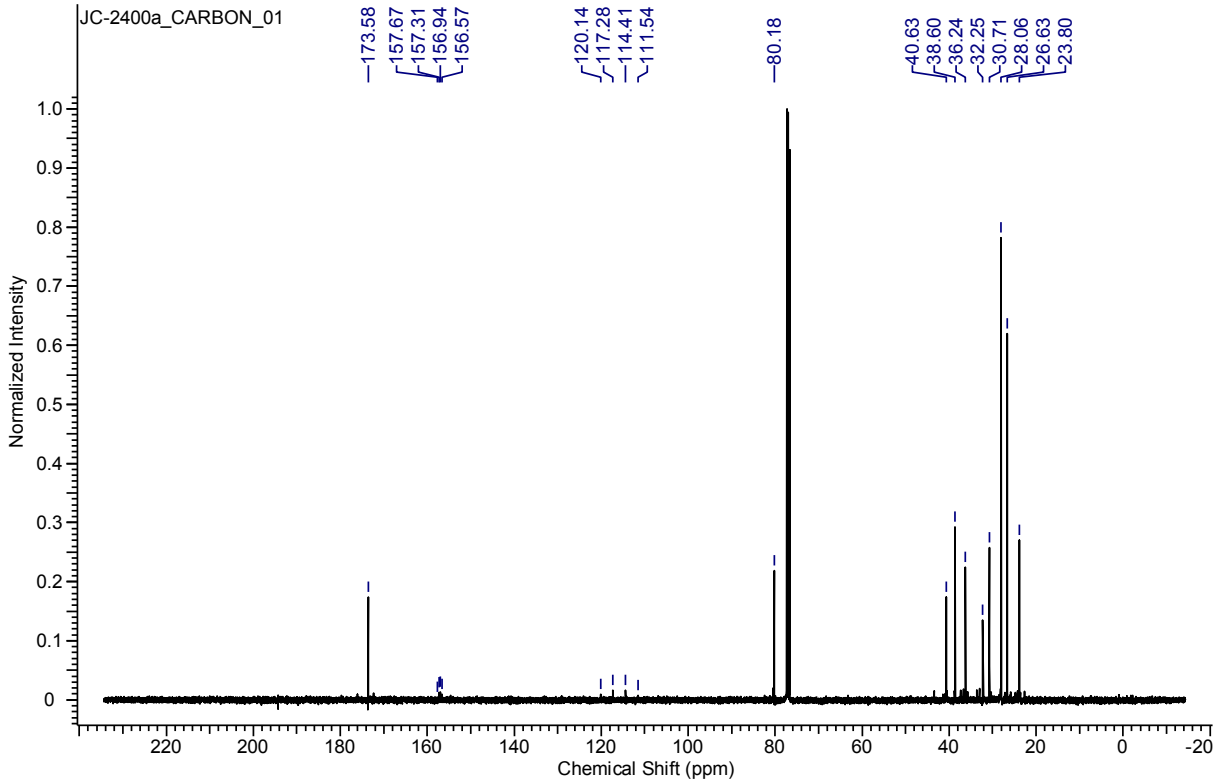

JC-2398_FLUORINE_01
-75.96
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

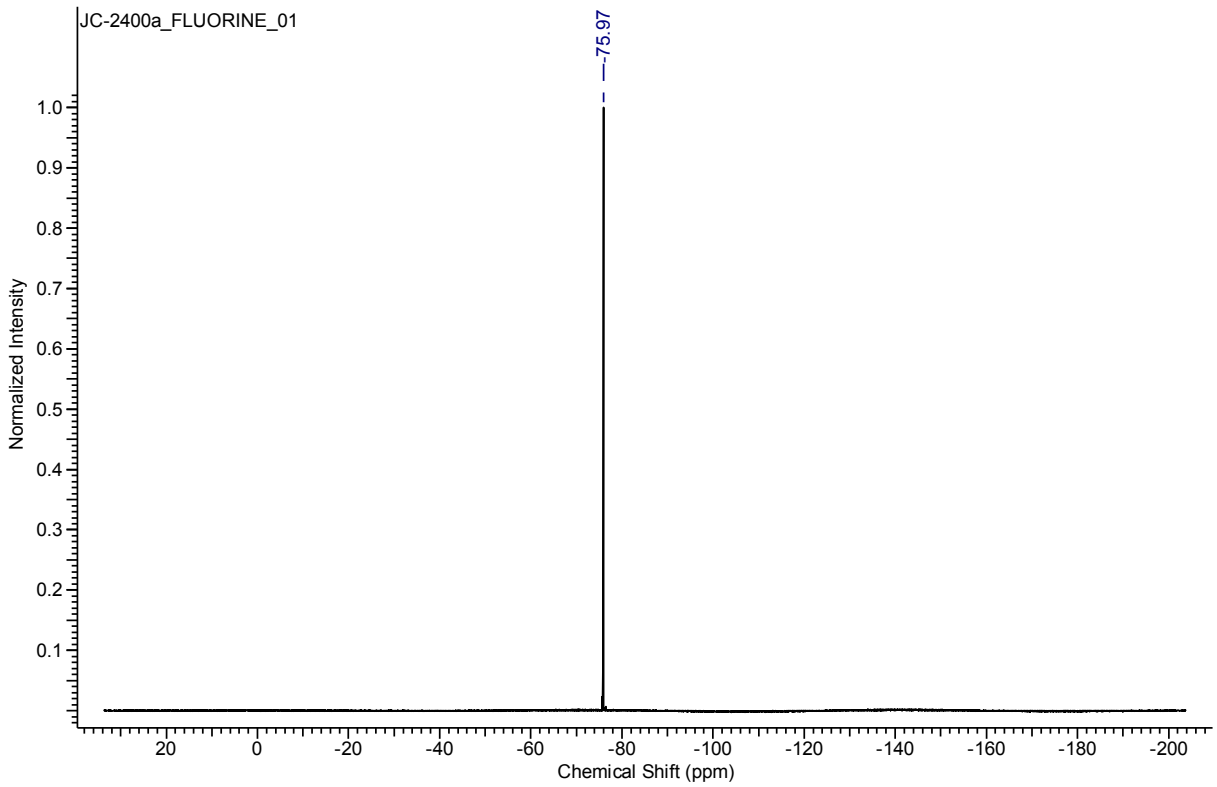

JC-2400d-proton_PROTON_01
6.34
4.15
4.13
4.11
3.36
2.26
2.24
2.22
1.57
1.55
1.55
1.53
1.27
1.25
1.24
1.23
0.87
CO2Et
Me
Me
N
H
O
CF3
0.99
2.00
2.02
2.07
3.97
3.02
2.04
5.90
Normalized Intensity
Chemical Shift (ppm)

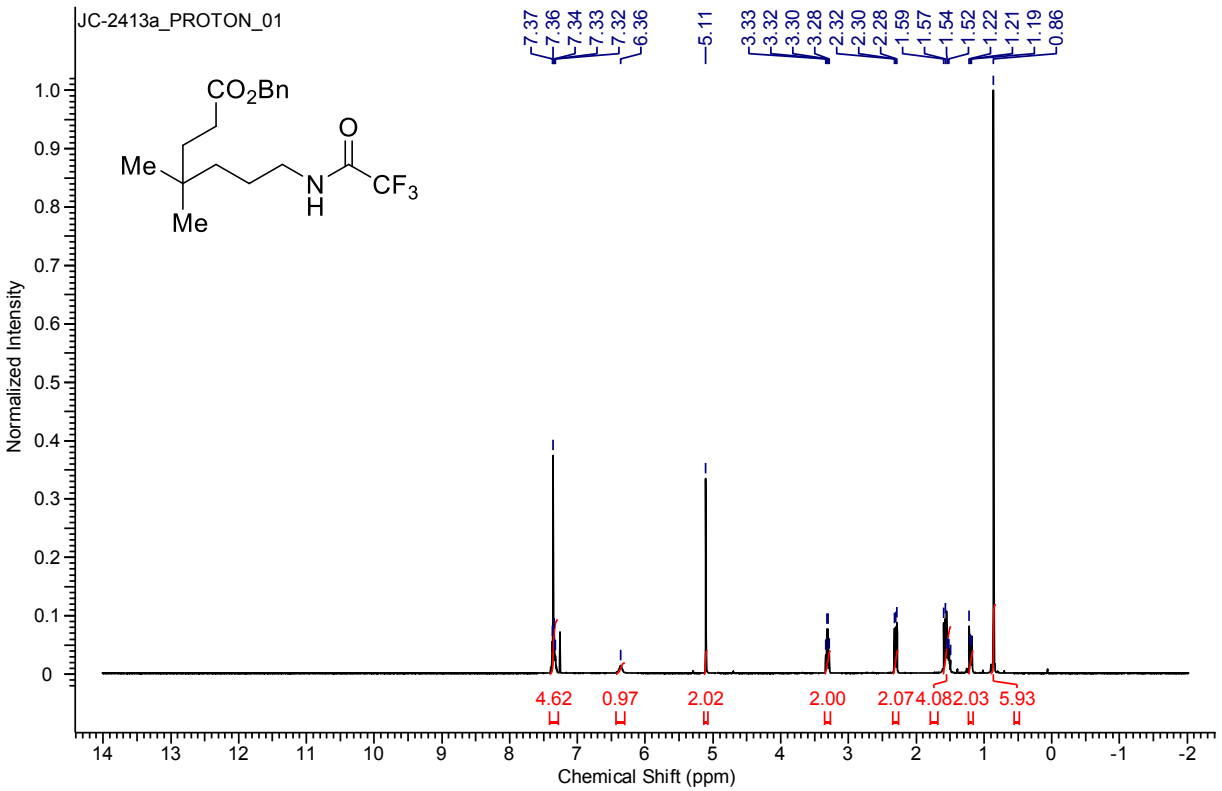

JC-2400d_CARBON_01
174.23
157.70
157.33
156.96
156.60
120.14
117.27
114.41
111.56
60.38
40.61
38.54
36.14
32.28
29.54
26.60
23.76
14.19
Normalized Intensity
Chemical Shift (ppm)

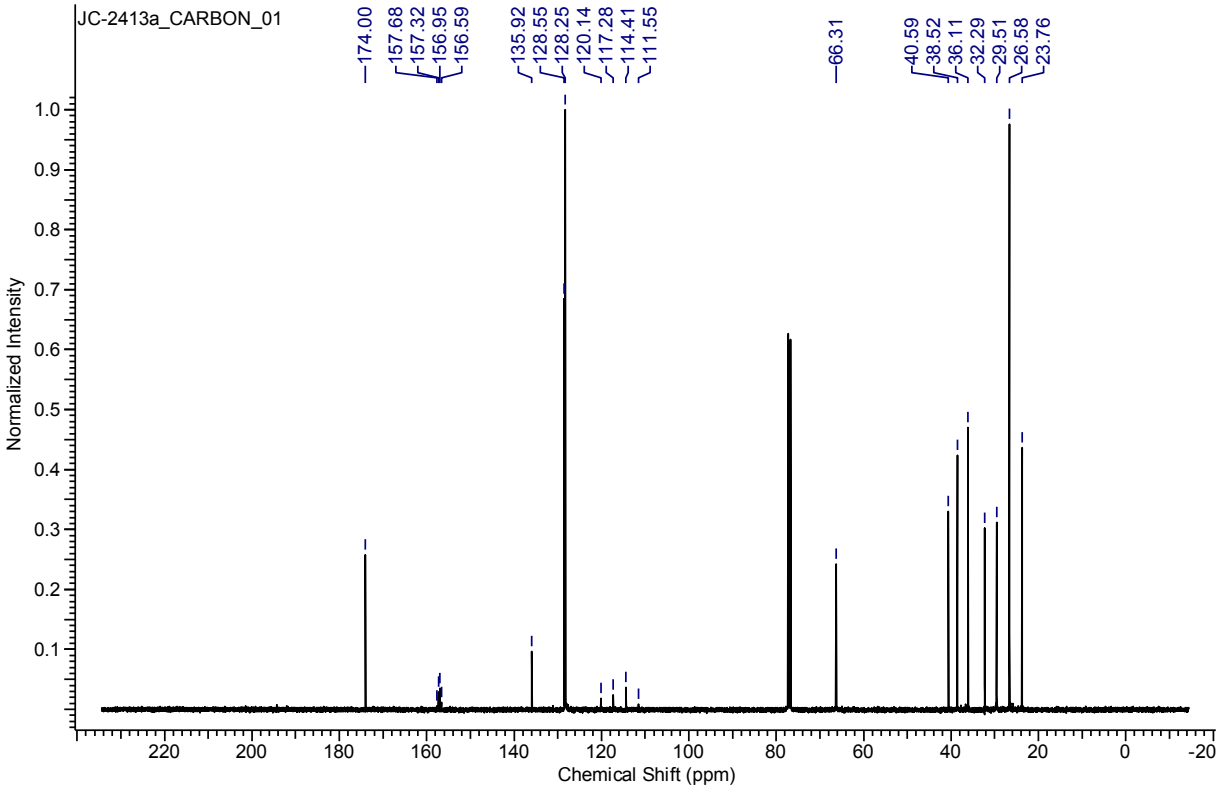

JC-2400d_FLUORINE_01
-75.98
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

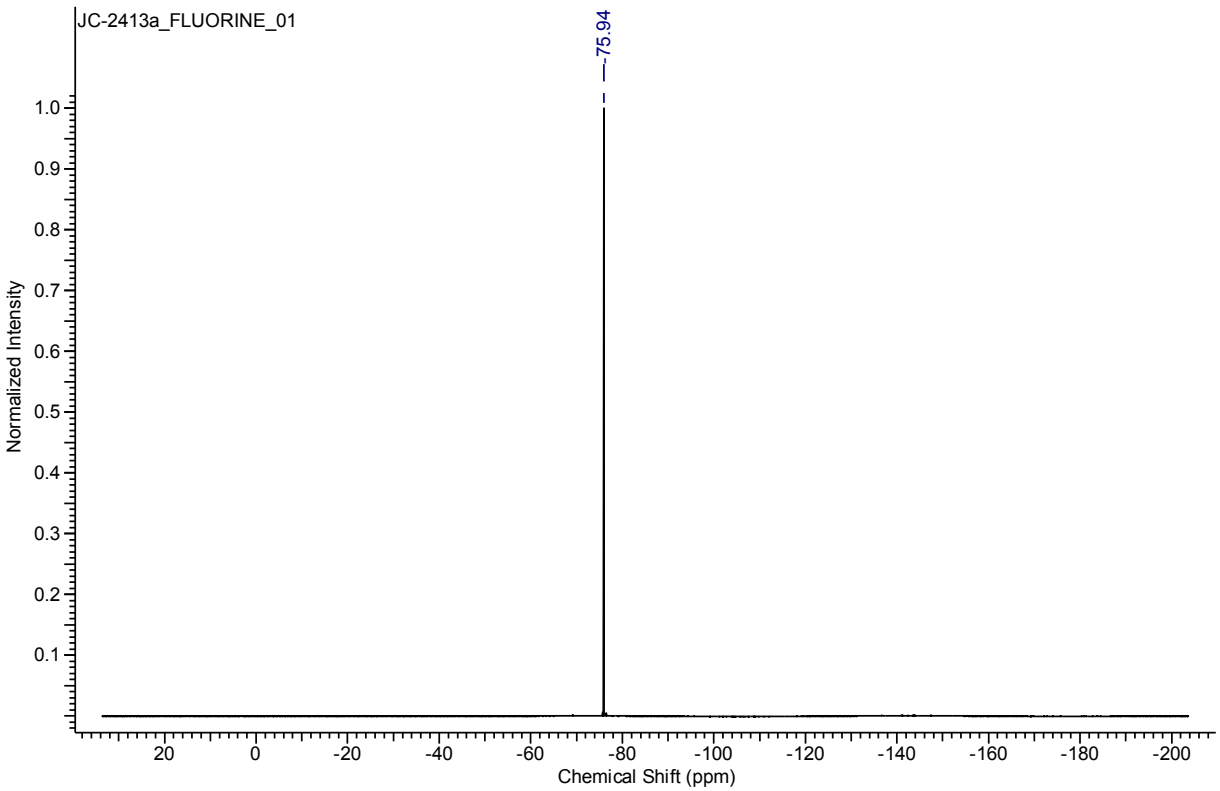

JC-2400a_PROTON_01
6.35
3.36
3.34
3.32
3.30
2.17
2.15
2.13
1.52
1.50
1.48
1.44
1.22
1.20
1.18
0.86
CO2tBu
Me
Me
N
H
O
CF3
Normalized Intensity
1.00
2.06
1.95
4.07
9.67
2.12
6.27
Chemical Shift (ppm)

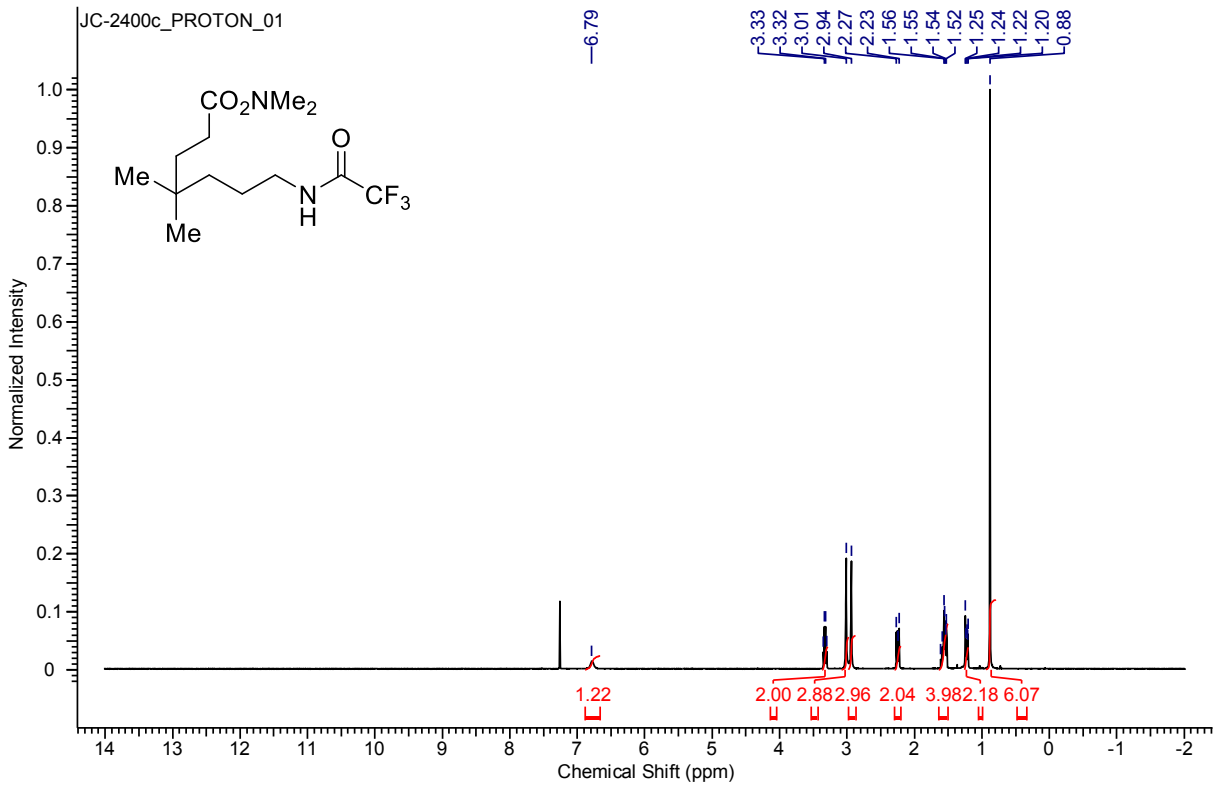

JC-2400a_CARBON_01
173.58
157.67
157.31
156.94
156.57
120.14
117.28
114.41
111.54
80.18
40.63
38.60
36.24
32.25
30.71
28.06
26.63
23.80
Normalized Intensity
Chemical Shift (ppm)

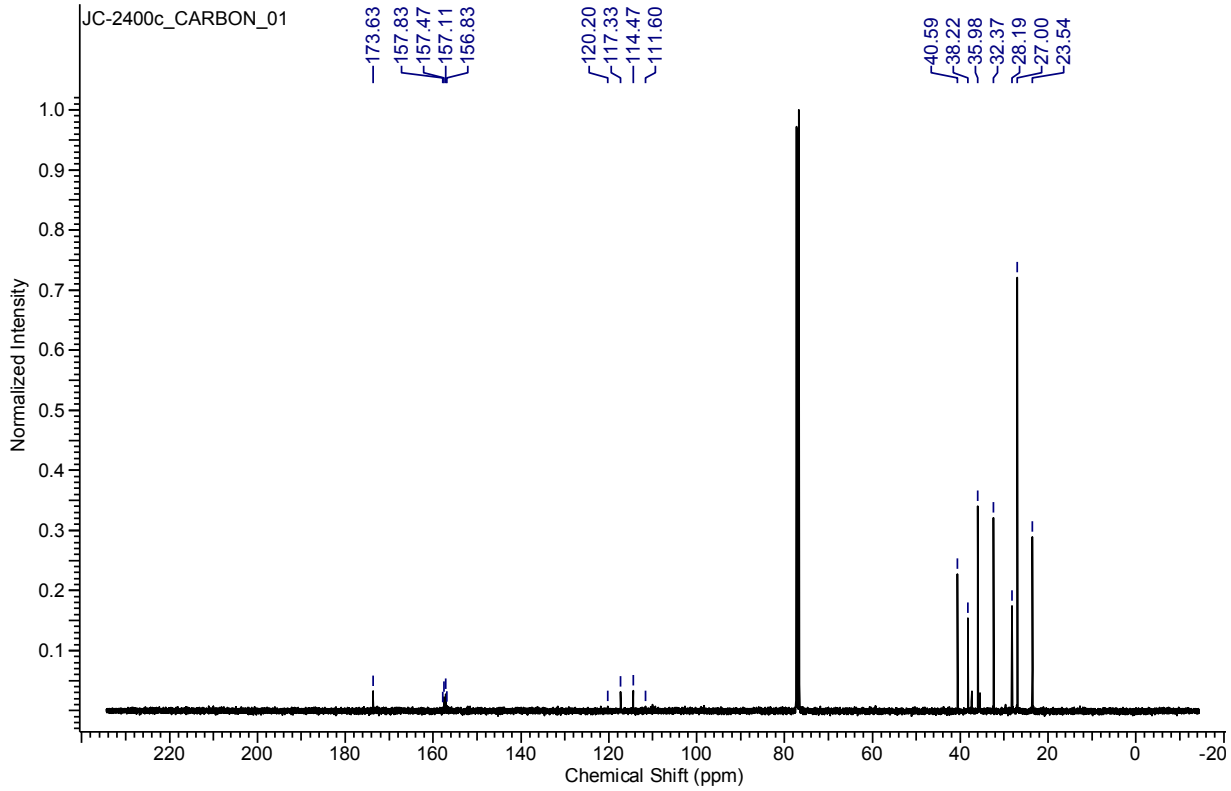

JC-2400a_FLUORINE_01
-75.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

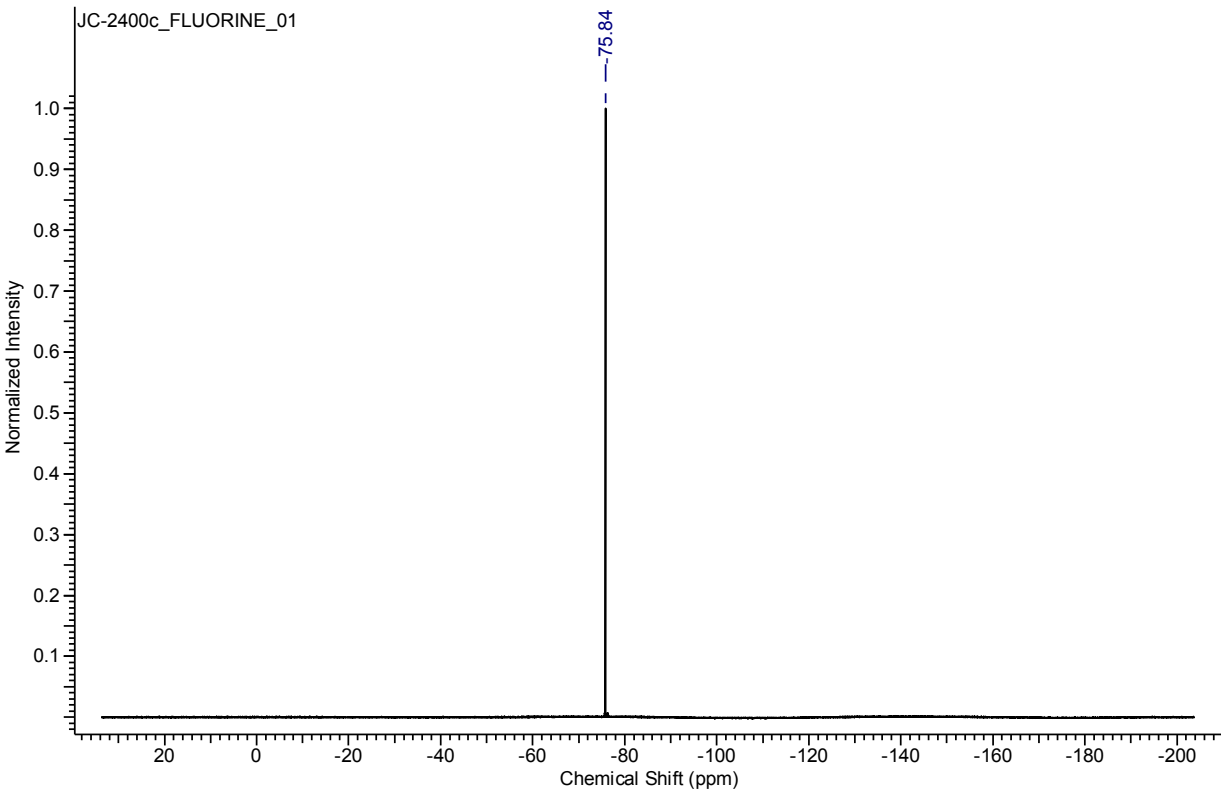

JC-2413a_PROTON_01
7.37
7.36
7.34
7.33
7.32
6.36
5.11
3.33
3.32
3.30
3.28
2.32
2.30
2.28
1.59
1.57
1.54
1.52
1.22
1.21
1.19
0.86
CO2Bn
Me
Me
N
H
O
CF3
4.62
0.97
2.02
2.00
2.07
4.08
2.03
5.93
Normalized Intensity
Chemical Shift (ppm)

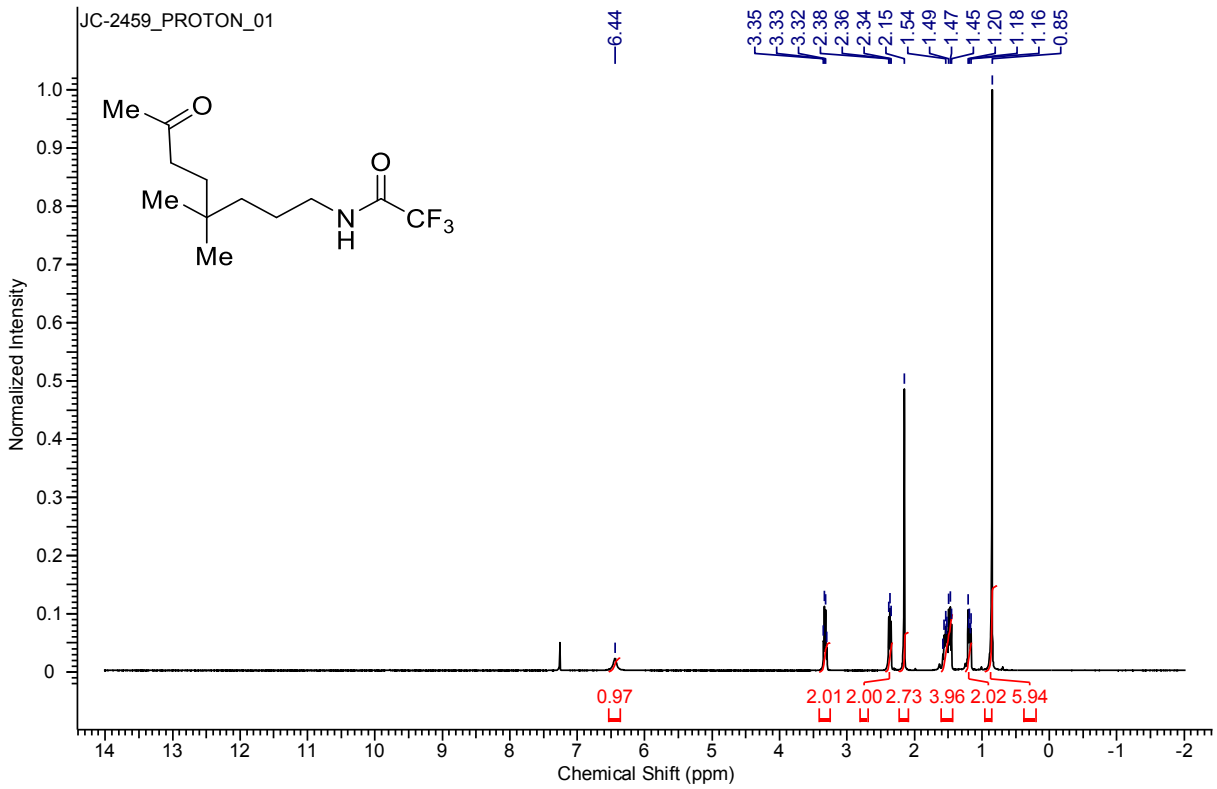

JC-2413a_CARBON_01
174.00
157.68
157.32
156.95
156.59
135.92
128.55
128.25
120.14
117.28
114.41
111.55
66.31
40.59
38.52
36.11
32.29
29.51
26.58
23.76
Normalized Intensity
Chemical Shift (ppm)

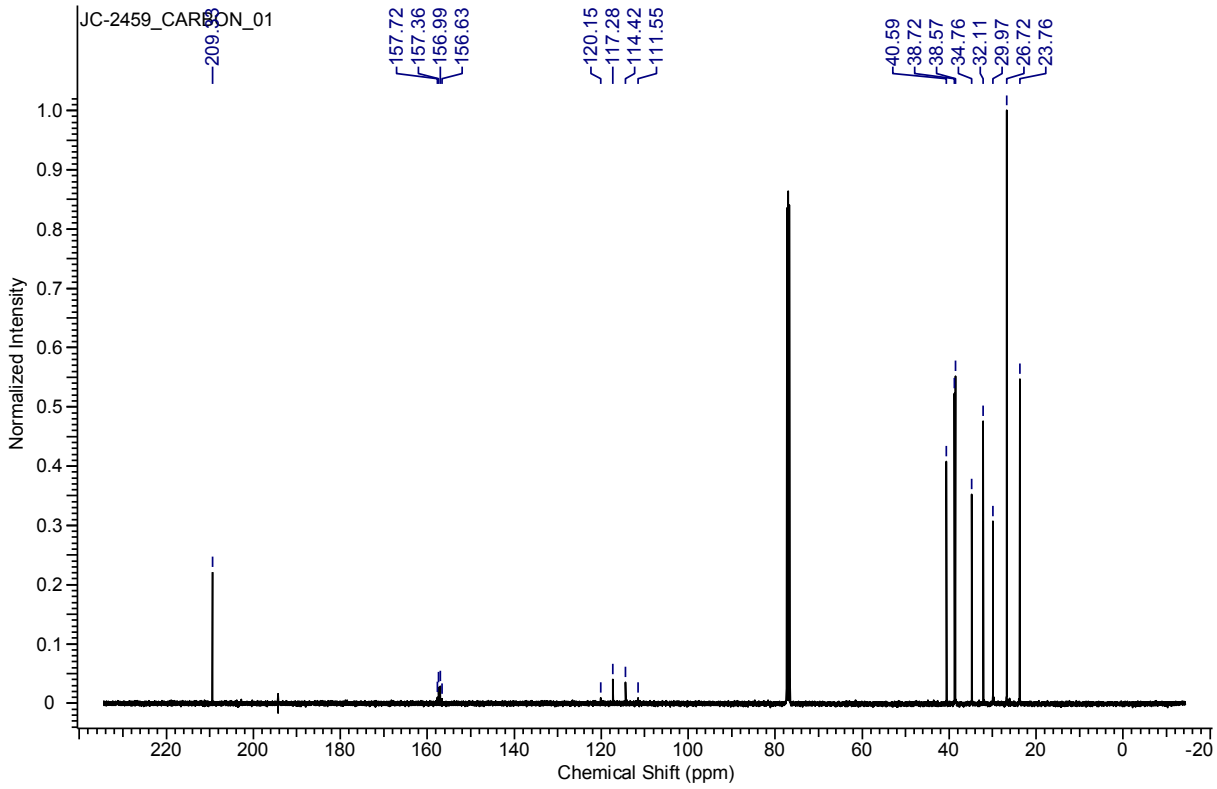

JC-2413a_FLUORINE_01
-75.94
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

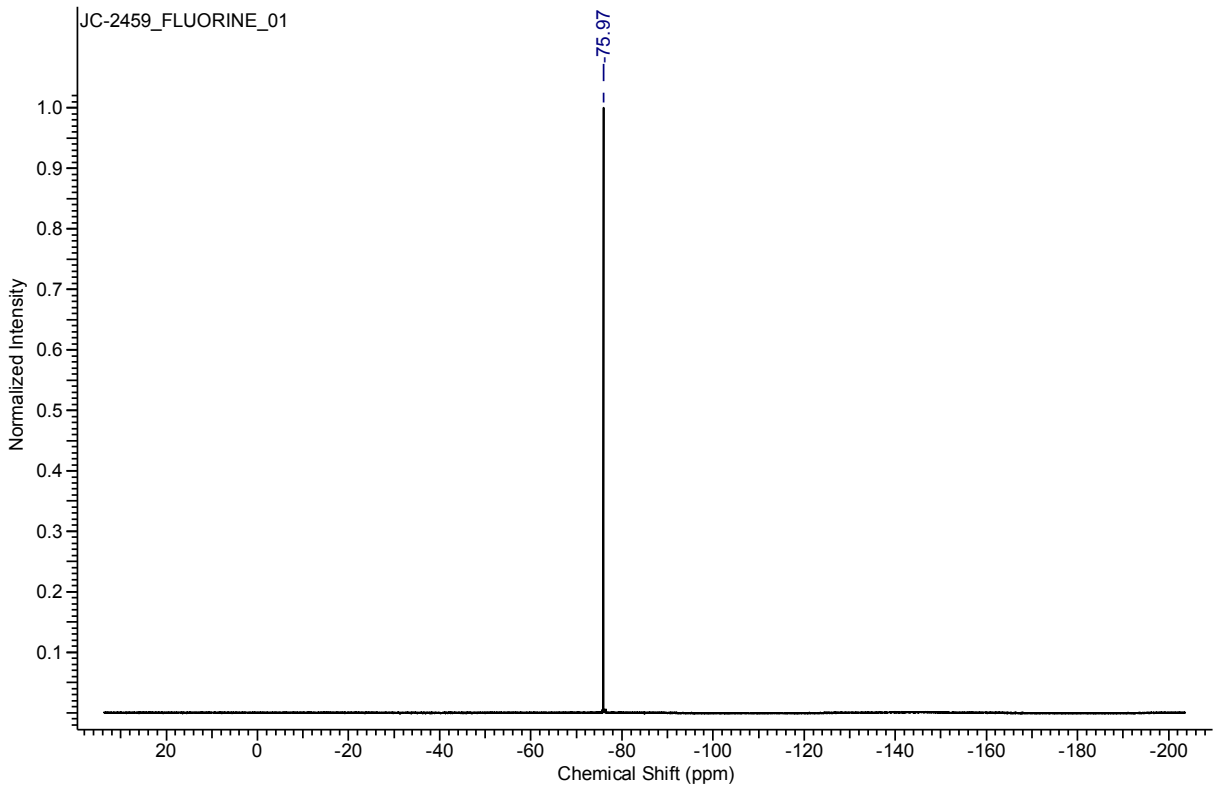

JC-2400c_PROTON_01
6.79
3.33
3.32
3.01
2.94
2.27
2.23
1.56
1.55
1.54
1.52
1.25
1.24
1.22
1.20
0.88
CO2NMe2
Me
Me
N
H
O
CF3
Normalized Intensity
1.22
2.00
2.88
2.96
2.04
3.98
2.18
6.07
Chemical Shift (ppm)

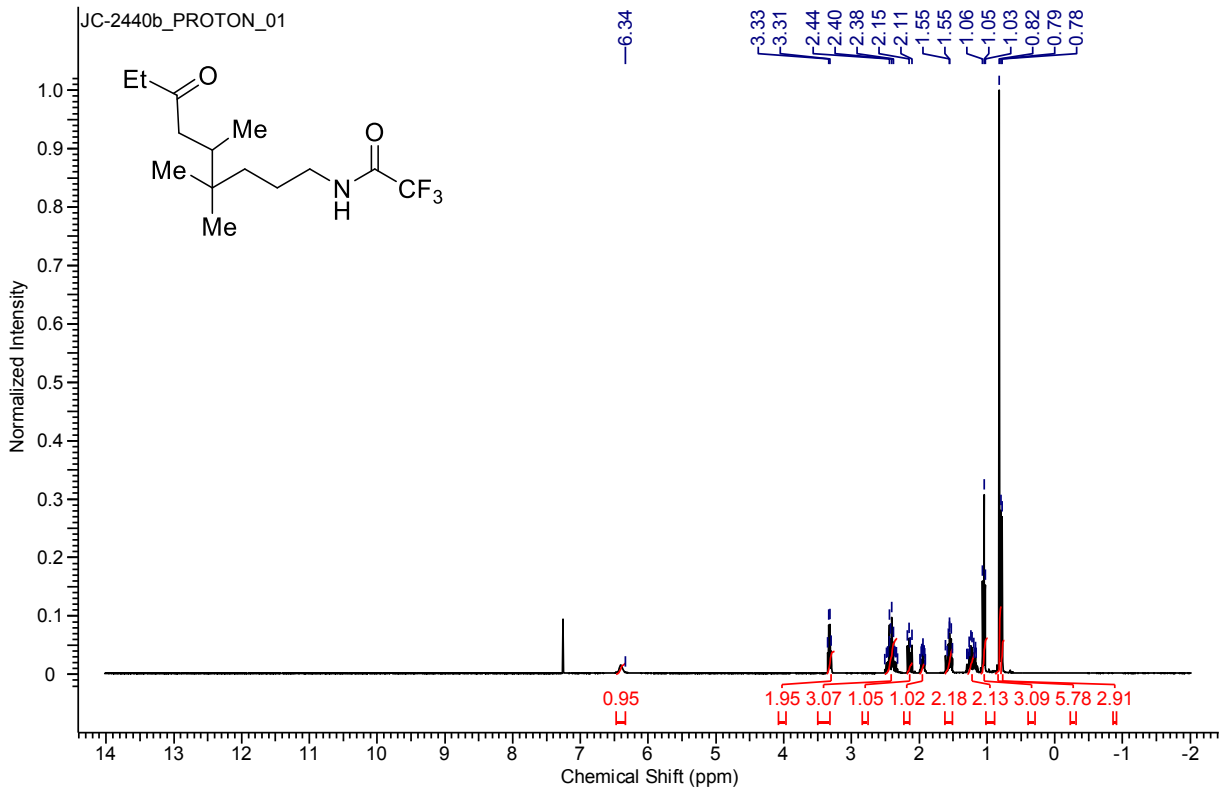

JC-2400c_CARBON_01
173.63
157.83
157.47
157.11
156.83
120.20
117.33
114.47
111.60
40.59
38.22
35.98
32.37
28.19
27.00
23.54
Normalized Intensity
Chemical Shift (ppm)

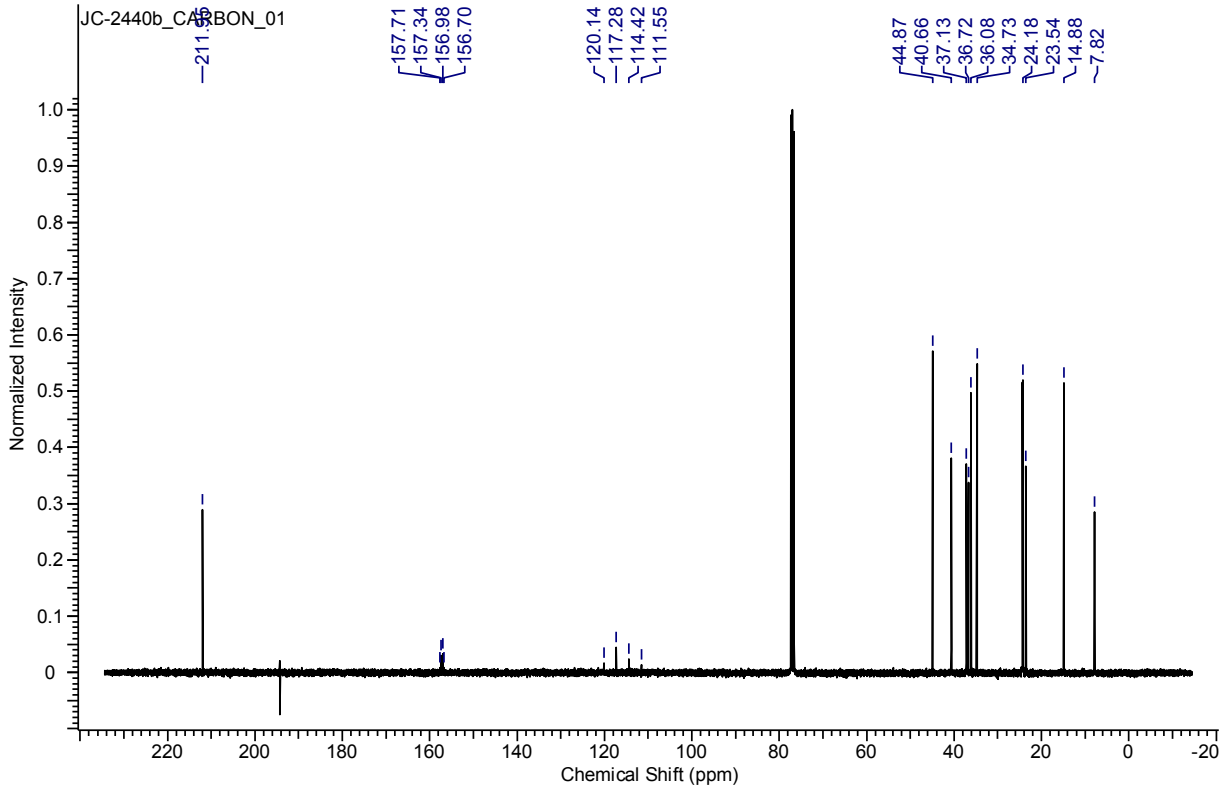

JC-2400c_FLUORINE_01
-75.84
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

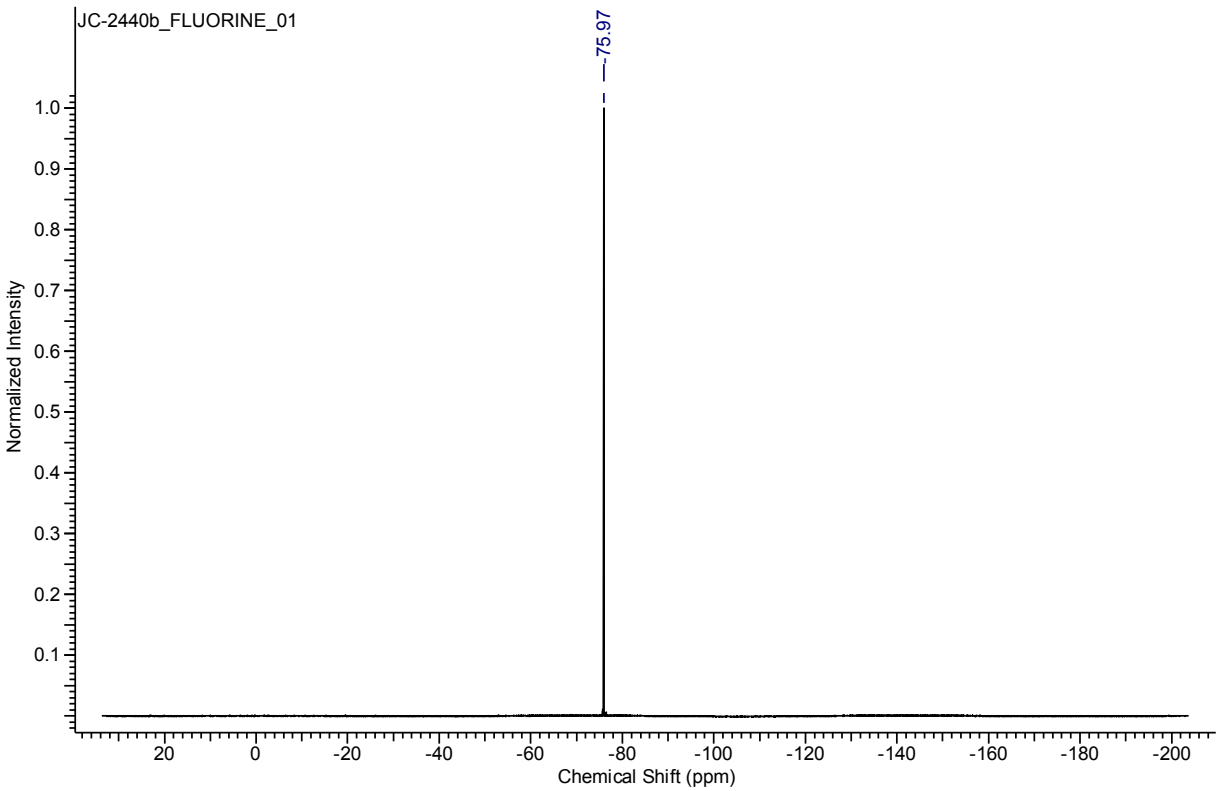

JC-2459_PROTON_01
Me
O
Me
N
H
O
CF3
Me
6.44
3.35
3.33
3.32
2.38
2.36
2.34
2.15
1.54
1.49
1.47
1.45
1.20
1.18
1.16
0.85
0.97
2.01
2.00
2.73
3.96
2.02
5.94
Normalized Intensity
Chemical Shift (ppm)

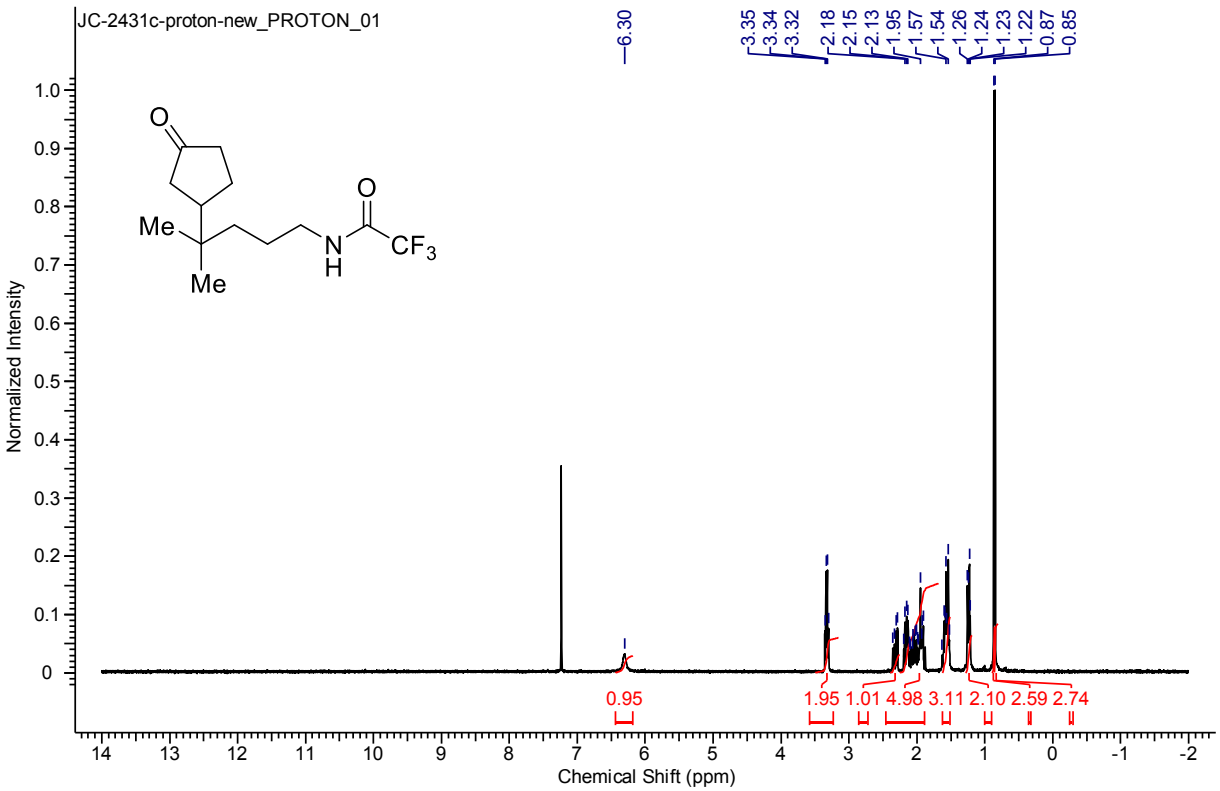

JC-2459_CARBON_01
209.83
157.72
157.36
156.99
156.63
120.15
117.28
114.42
111.55
40.59
38.72
38.57
34.76
32.11
29.97
26.72
23.76
Normalized Intensity
Chemical Shift (ppm)

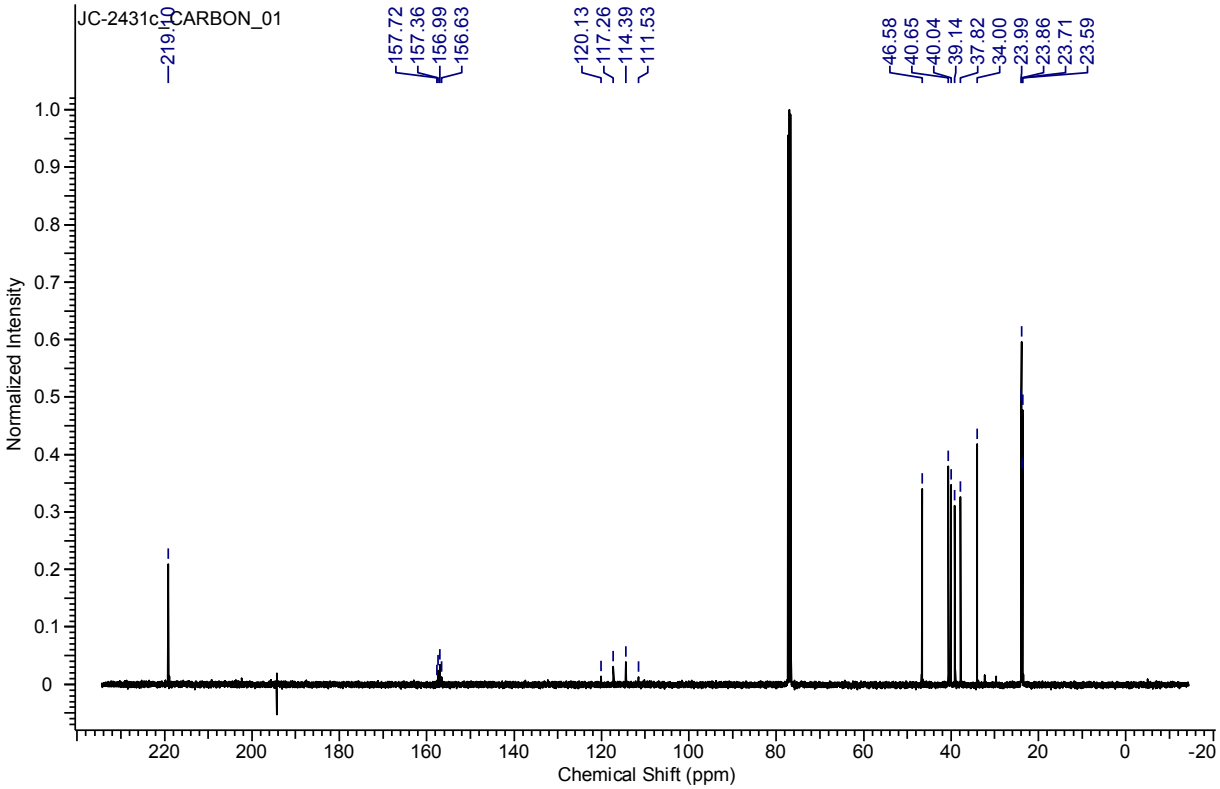

JC-2459_FLUORINE_01
-75.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

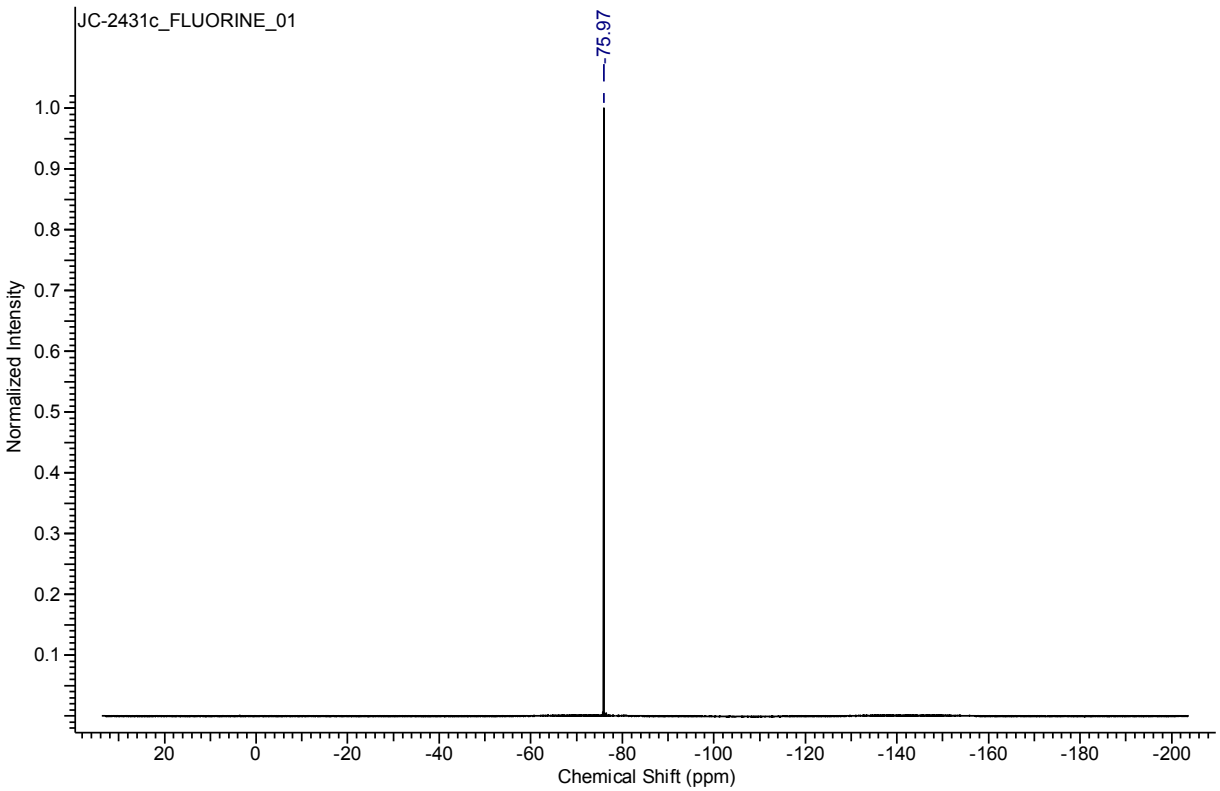

JC-2440b_PROTON_01
Et
O
Me
Me
Me
O
N
H
CF3
6.34
3.33
3.31
2.44
2.40
2.38
2.15
2.11
1.55
1.55
1.06
1.05
1.03
0.82
0.79
0.78
0.95
1.95 3.07 1.05 1.02 2.18 2.13 3.09 5.78 2.91
Normalized Intensity
Chemical Shift (ppm)

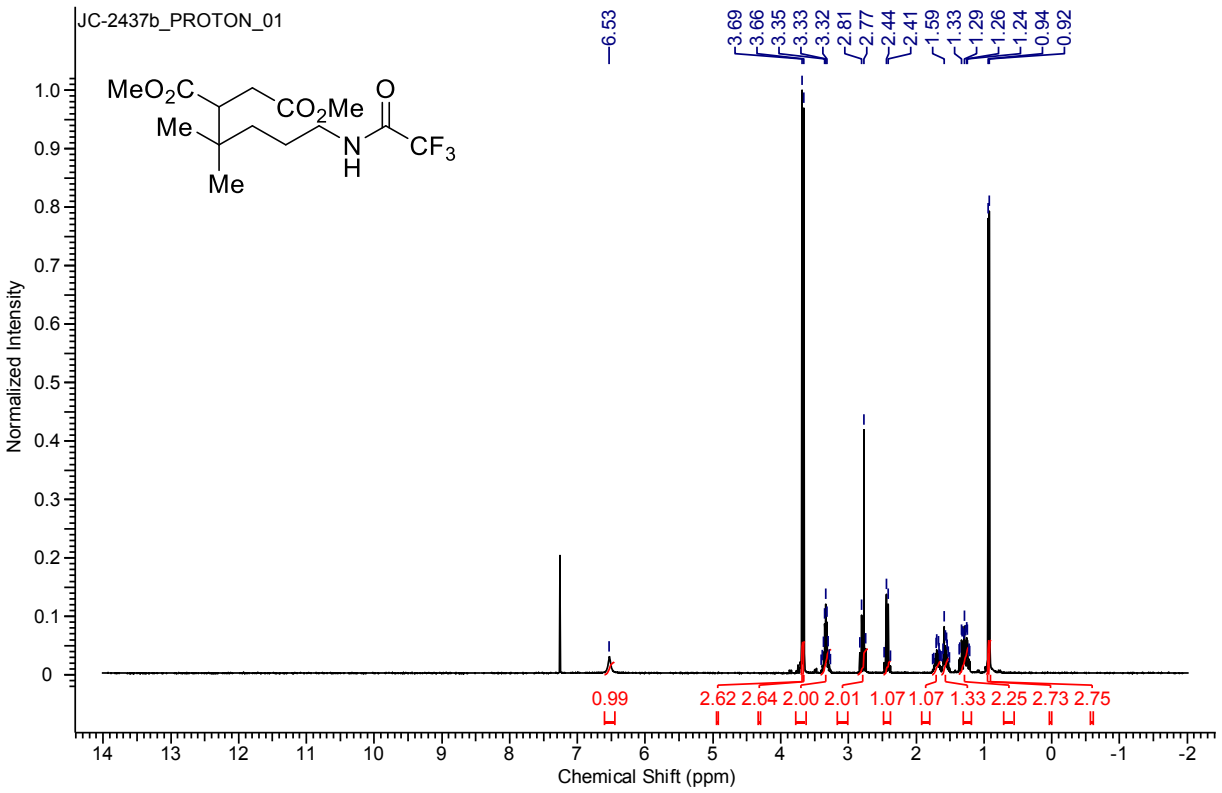

JC-2440b_CARBON_01
211.95
157.71
157.34
156.98
156.70
120.14
117.28
114.42
111.55
44.87
40.66
37.13
36.72
36.08
34.73
24.18
23.54
14.88
7.82
Normalized Intensity
Chemical Shift (ppm)

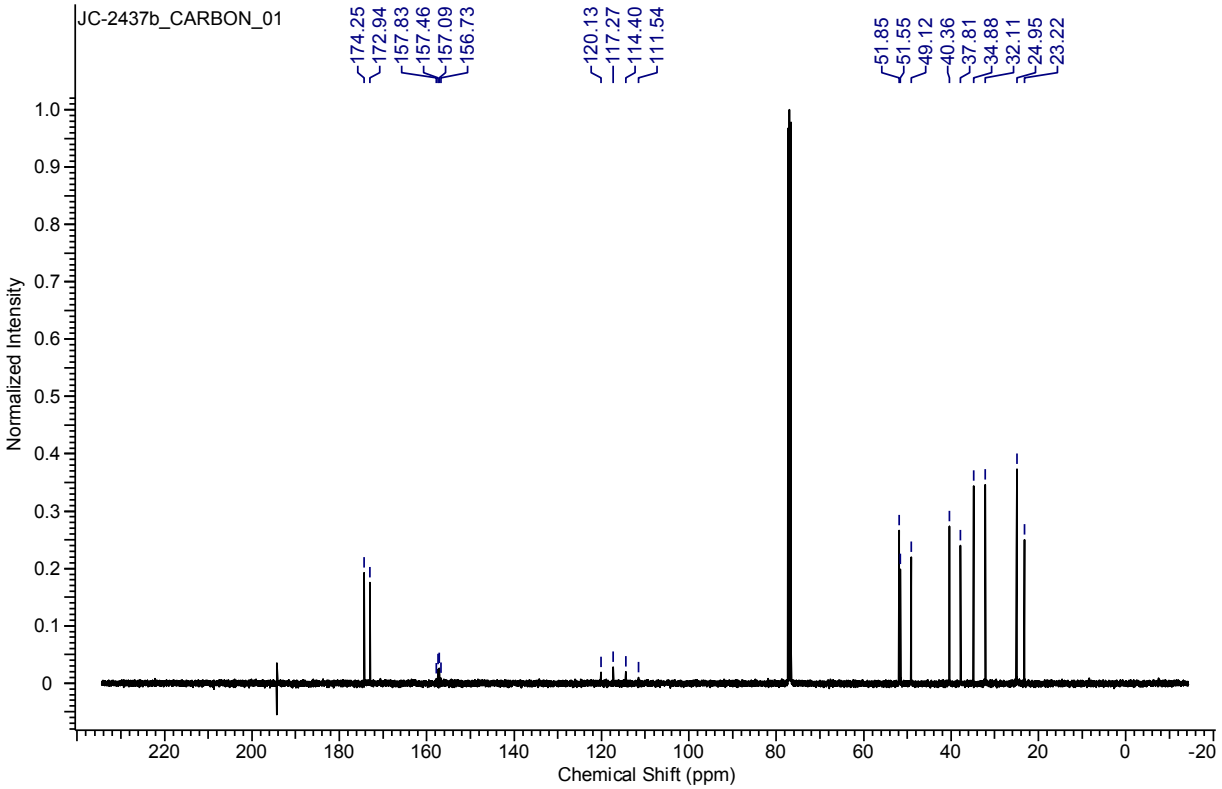

JC-2440b_FLUORINE_01
-75.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

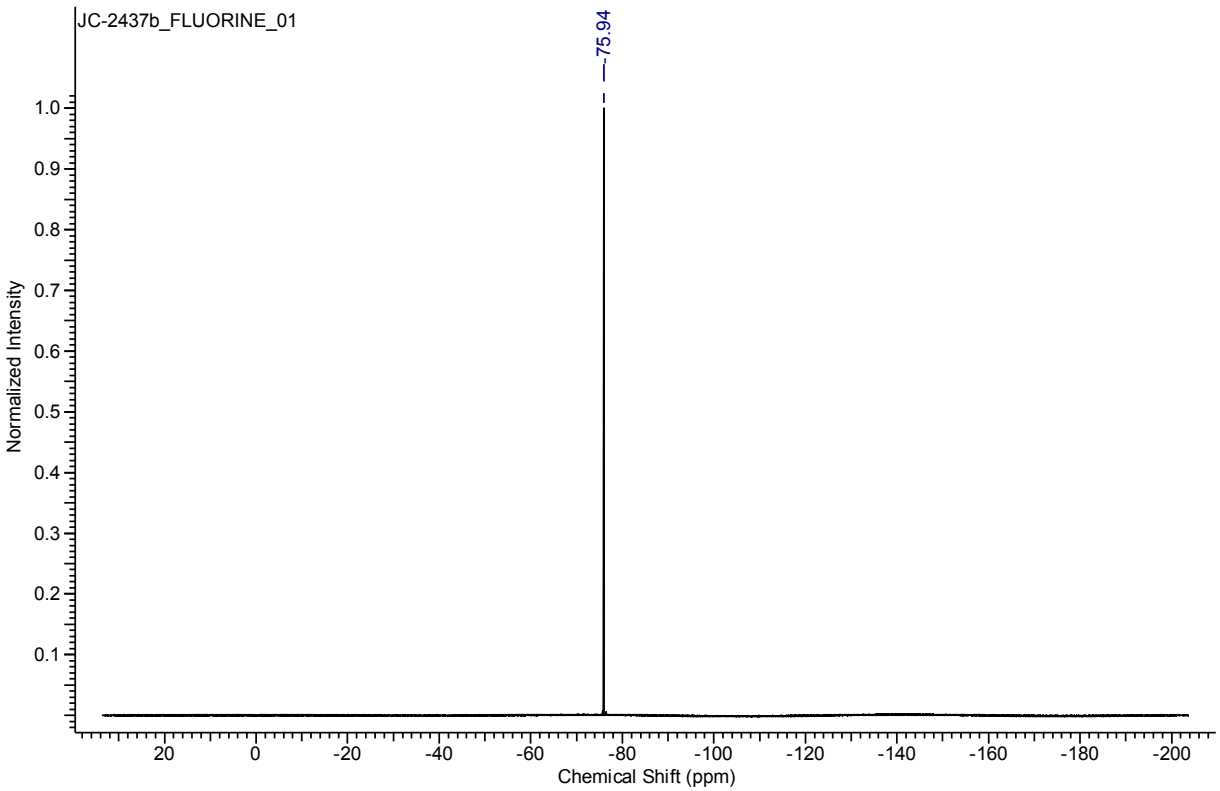

JC-2431c-proton-new_PROTON_01
6.30
3.35
3.34
3.32
2.18
2.15
2.13
1.95
1.57
1.54
1.26
1.24
1.23
1.22
0.87
0.85
O
Me
Me
N
H
O
CF3
Normalized Intensity
Chemical Shift (ppm)
0.95
1.95
1.01
4.98
3.11
2.10
2.59
2.74

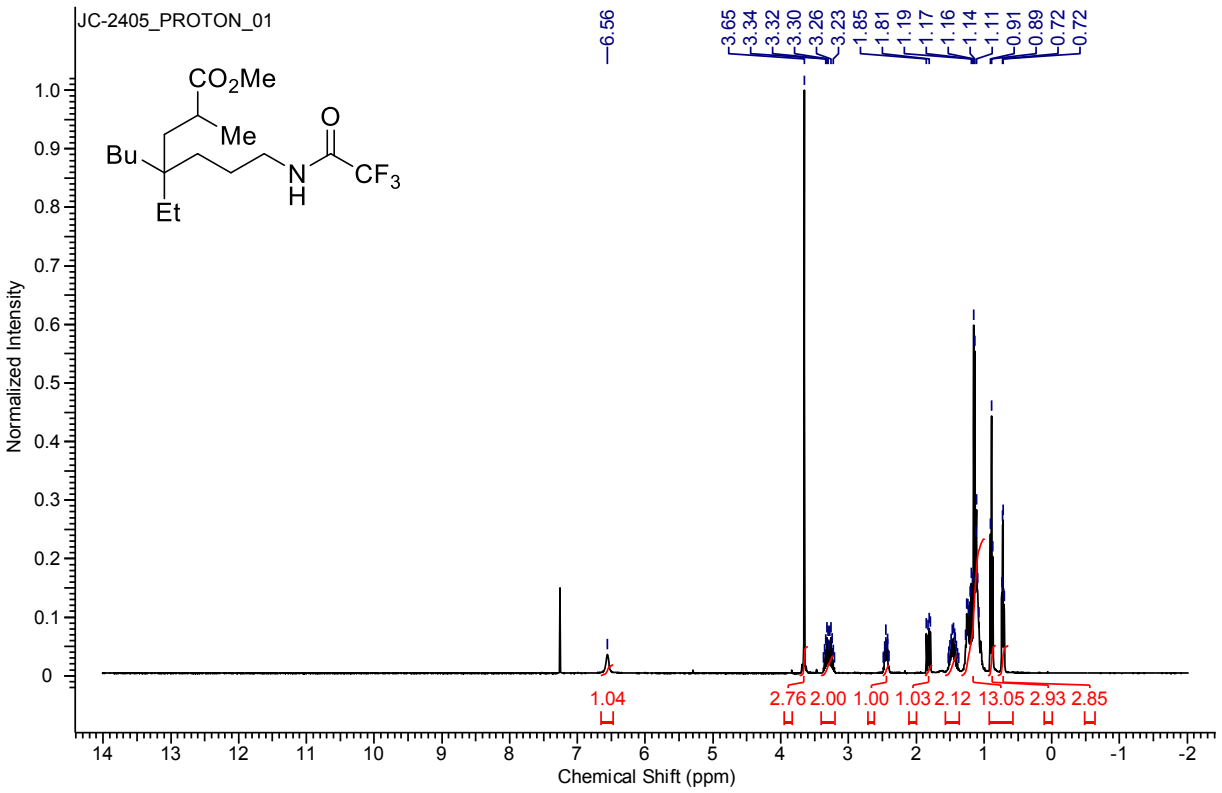

JC-2431c_CARBON_01
219.10
157.72
157.36
156.99
156.63
120.13
117.26
114.39
111.53
46.58
40.65
40.04
39.14
37.82
34.00
23.99
23.86
23.71
23.59
Normalized Intensity
Chemical Shift (ppm)

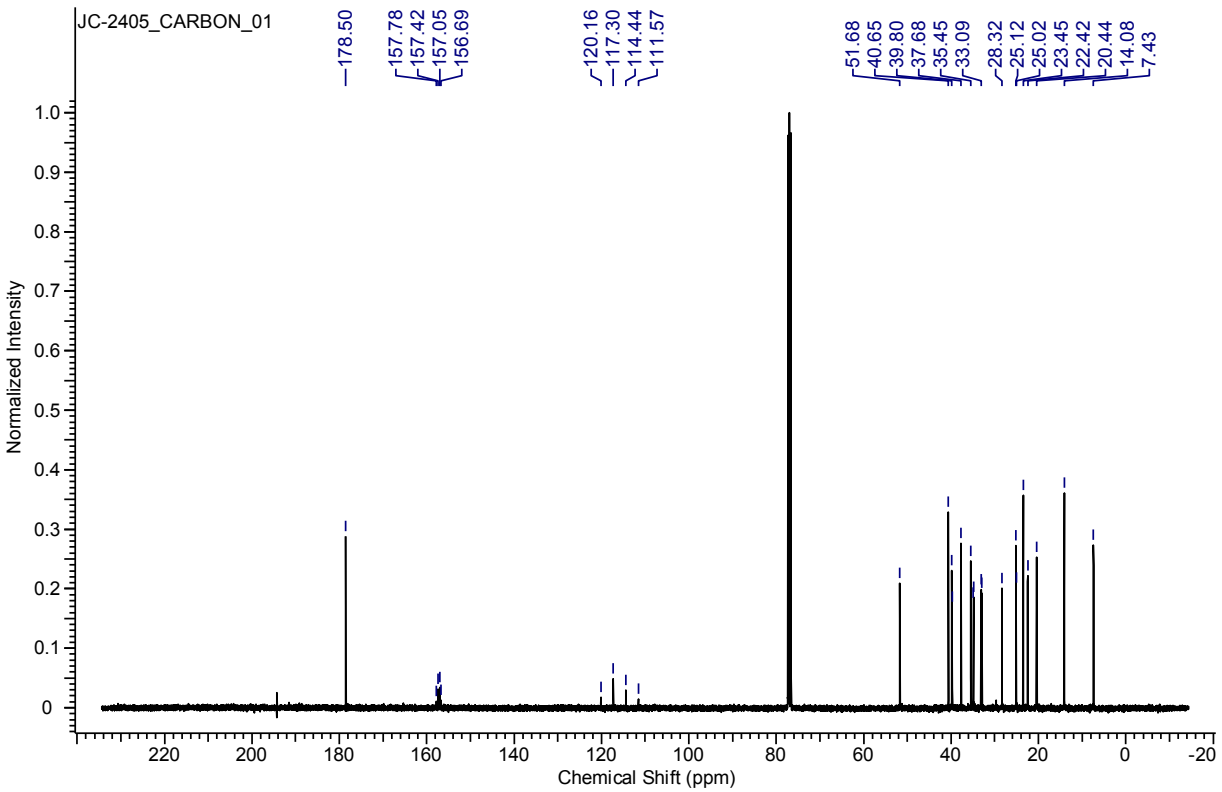

JC-2431c_FLUORINE_01
-75.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

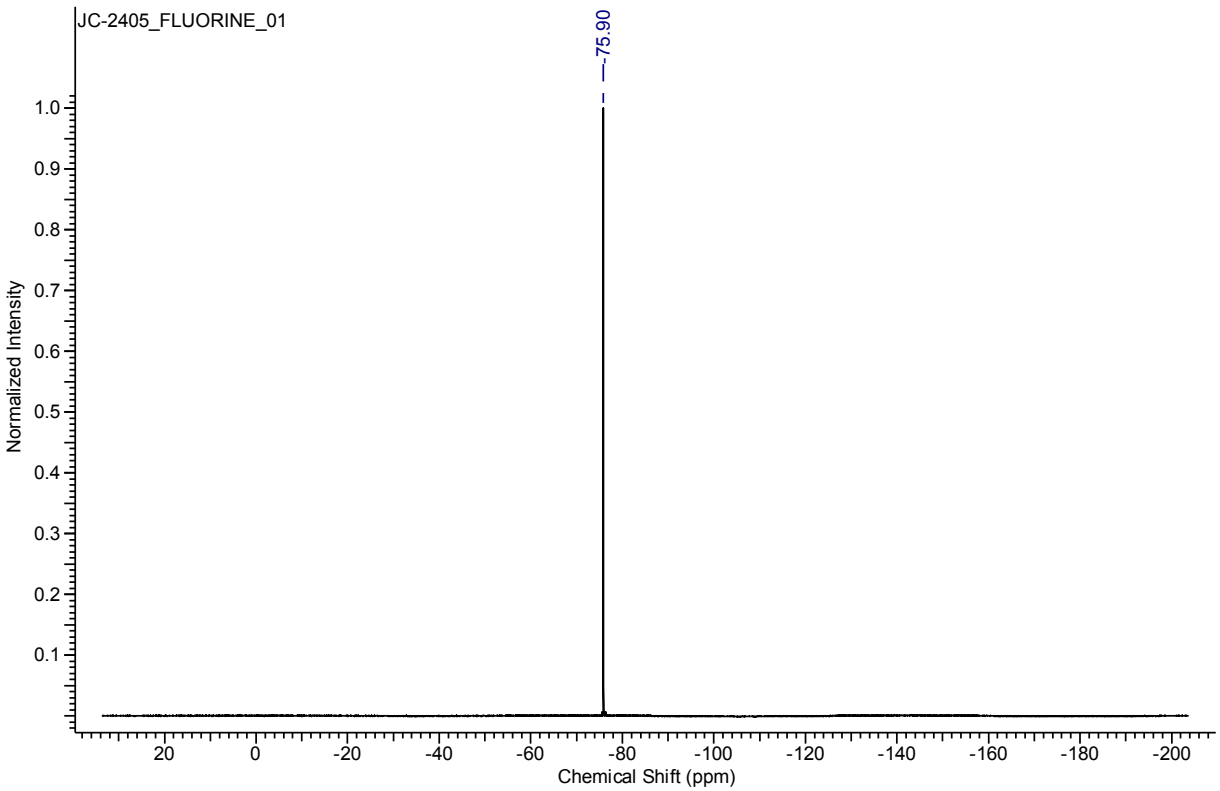

JC-2437b_PROTON_01
MeO2C
CO2Me
Me
Me
N
H
O
CF3
6.53
3.69
3.66
3.35
3.33
3.32
2.81
2.77
2.44
2.41
1.59
1.33
1.29
1.26
1.24
0.94
0.92
0.99
2.62 2.64 2.00 2.01 1.07 1.07 1.33 2.25 2.73 2.75
Normalized Intensity
Chemical Shift (ppm)

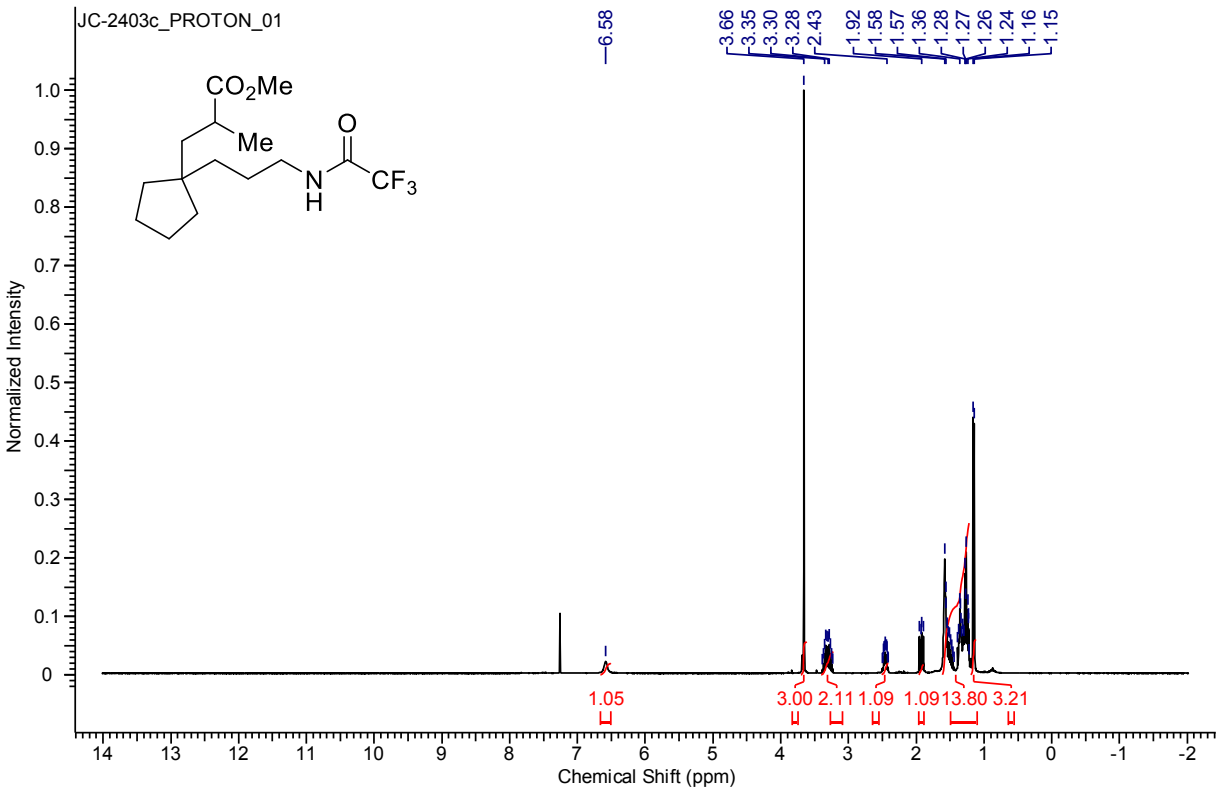

JC-2437b_CARBON_01
174.25
172.94
157.83
157.46
157.09
156.73
120.13
117.27
114.40
111.54
51.85
51.55
49.12
40.36
37.81
34.88
32.11
24.95
23.22
Normalized Intensity
Chemical Shift (ppm)

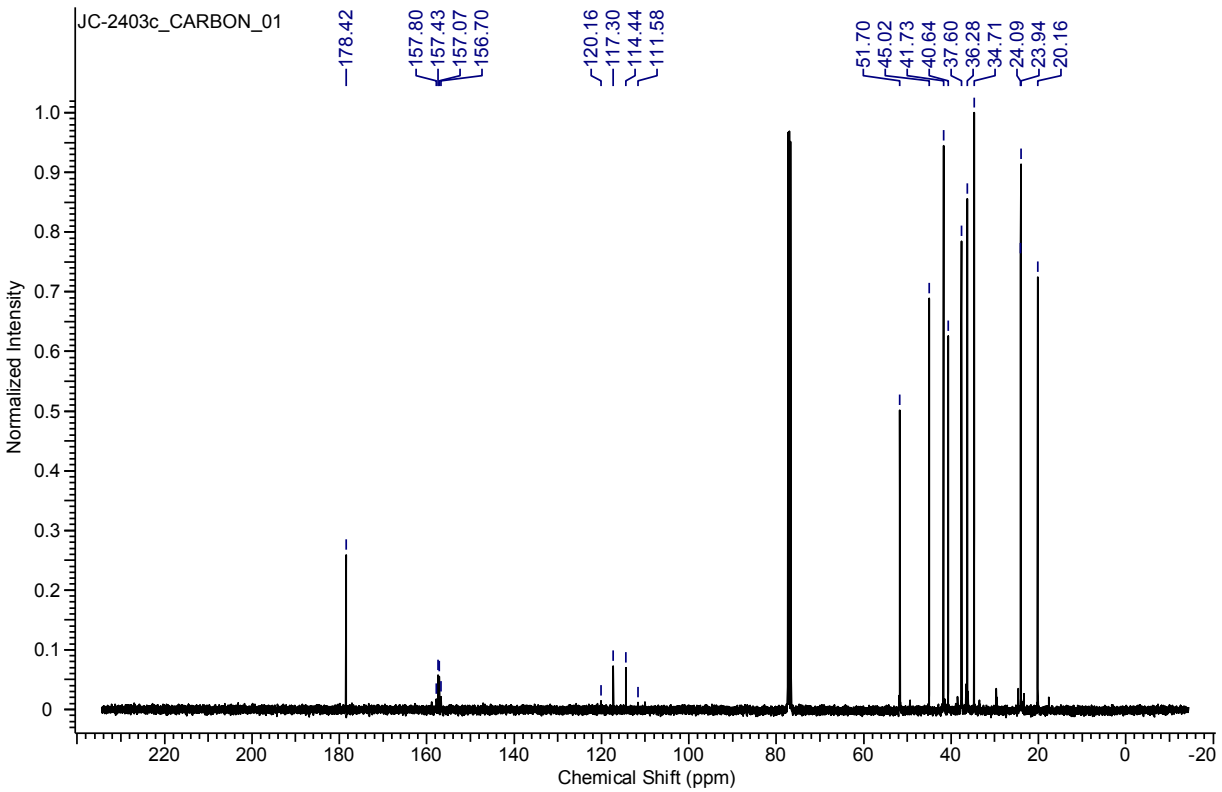

JC-2437b_FLUORINE_01
-75.94
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

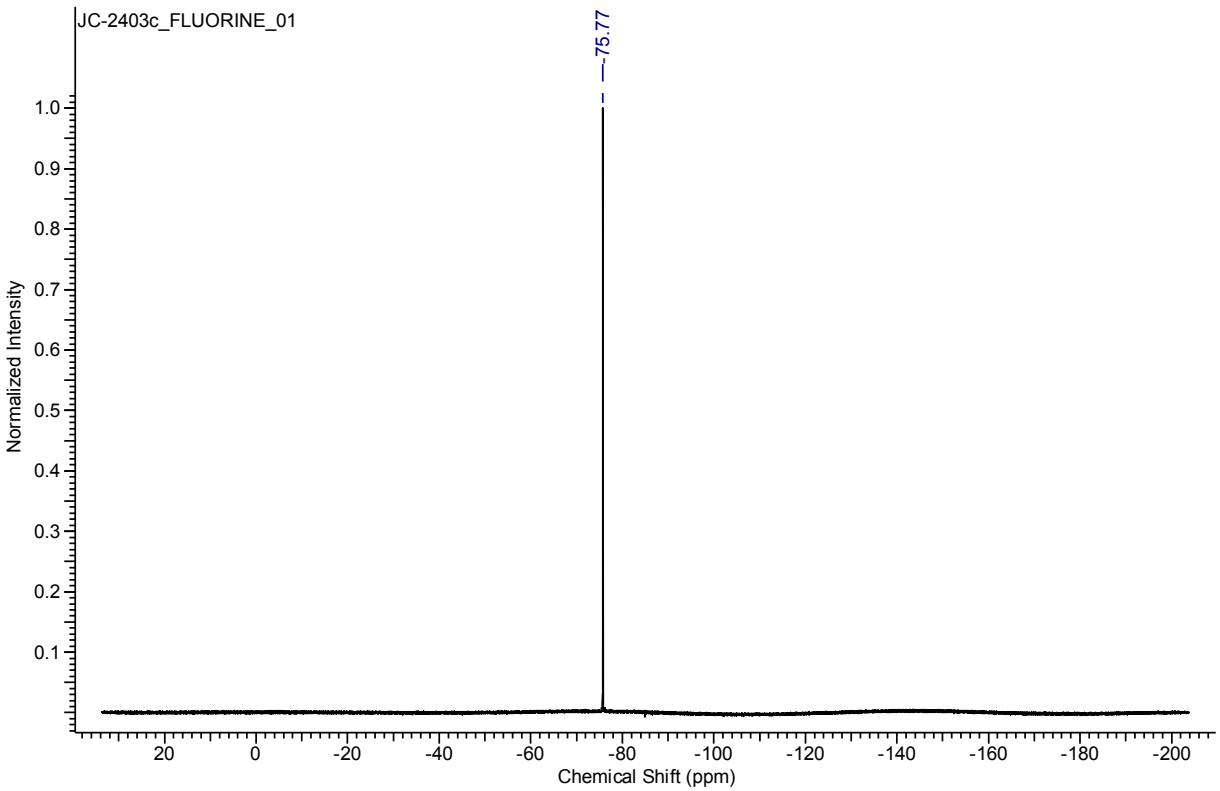

JC-2405_PROTON_01
CO2Me
Me
Bu
Et
N
H
O
CF3
6.56
3.65
3.34
3.32
3.30
3.26
3.23
1.85
1.81
1.19
1.17
1.16
1.14
1.11
0.91
0.89
0.72
0.72
1.04
2.76
2.00
1.00
1.03
2.12
13.05
2.93
2.85
Normalized Intensity
Chemical Shift (ppm)

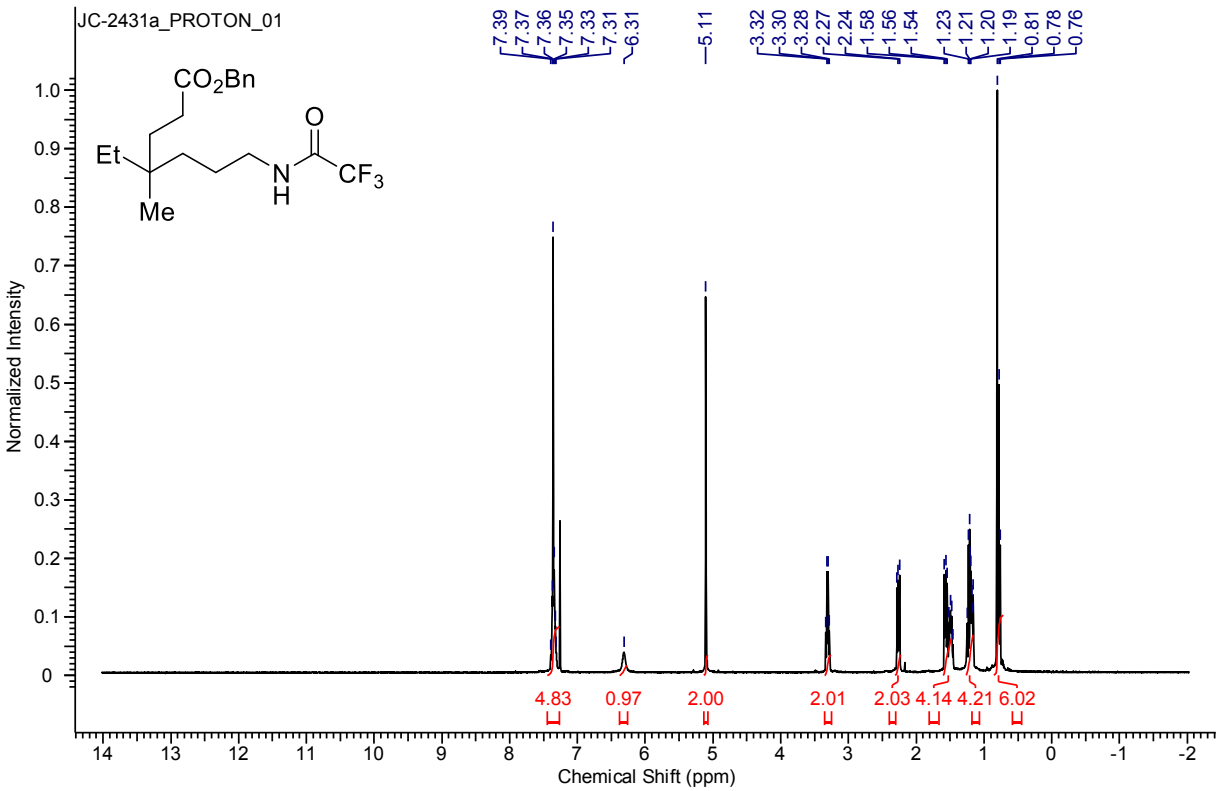

JC-2405_CARBON_01
178.50
157.78
157.42
157.05
156.69
120.16
117.30
114.44
111.57
51.68
40.65
39.80
37.68
35.45
33.09
28.32
25.12
25.02
23.45
22.42
20.44
14.08
7.43
Normalized Intensity
Chemical Shift (ppm)

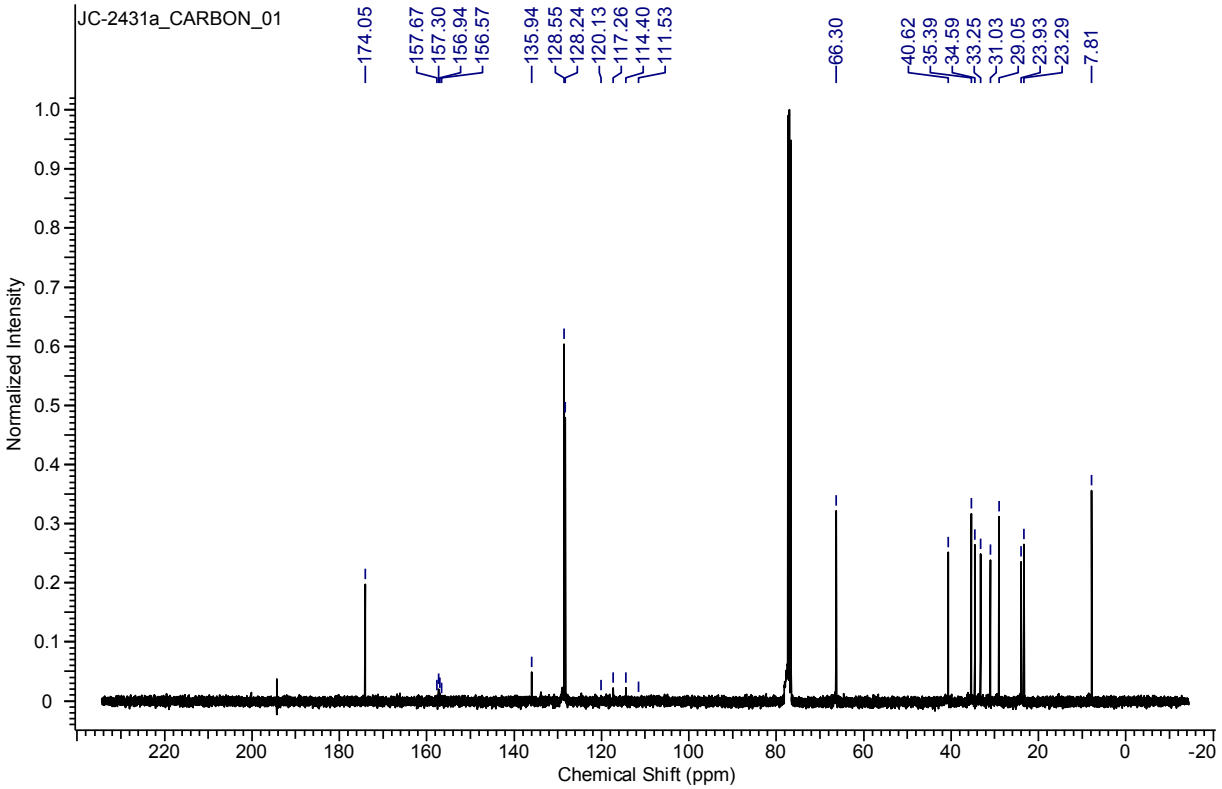

JC-2405_FLUORINE_01
-75.90
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

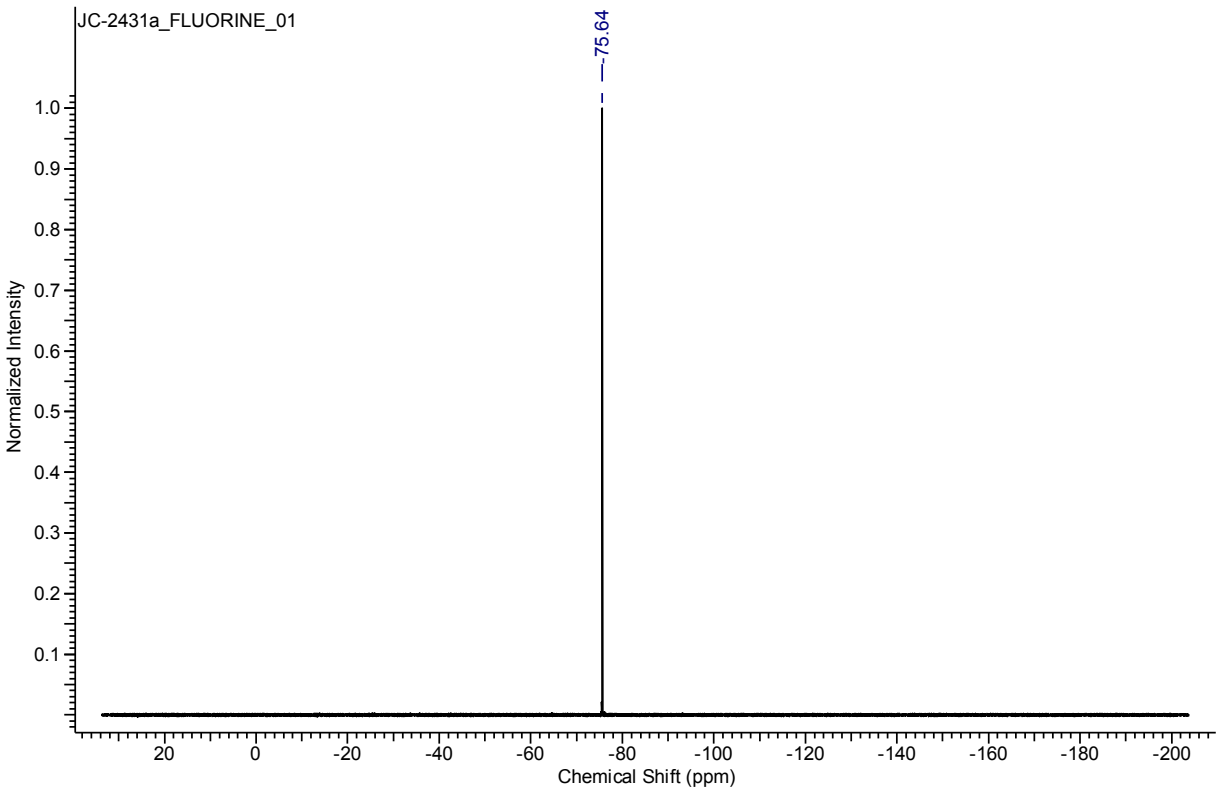

JC-2403c_PROTON_01
6.58
3.66
3.35
3.30
3.28
2.43
1.92
1.58
1.57
1.36
1.28
1.27
1.26
1.24
1.16
1.15
CO2Me
Me
N
H
O
CF3
Normalized Intensity
1.05
3.00
2.11
1.09
1.09
13.80
3.21
Chemical Shift (ppm)

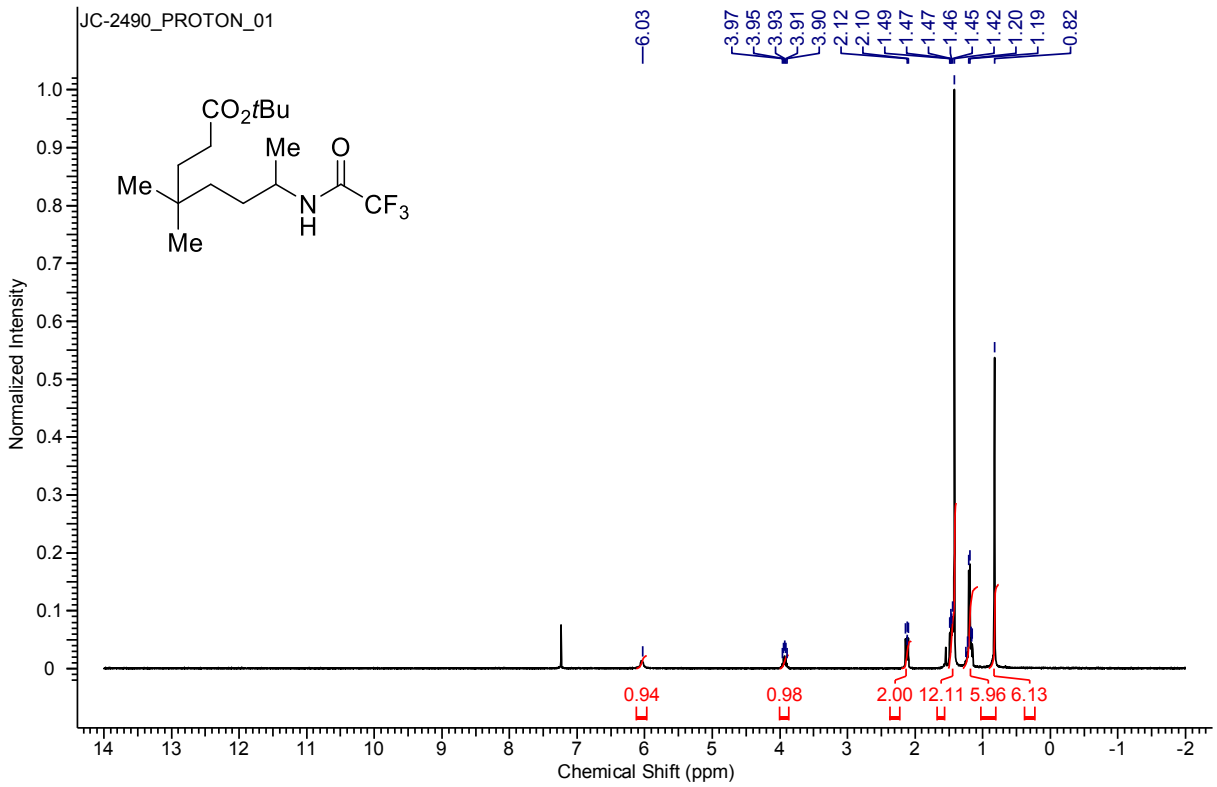

JC-2403c_CARBON_01
178.42
157.80
157.43
157.07
156.70
120.16
117.30
114.44
111.58
51.70
45.02
41.73
40.64
37.60
36.28
34.71
24.09
23.94
20.16
Normalized Intensity
Chemical Shift (ppm)

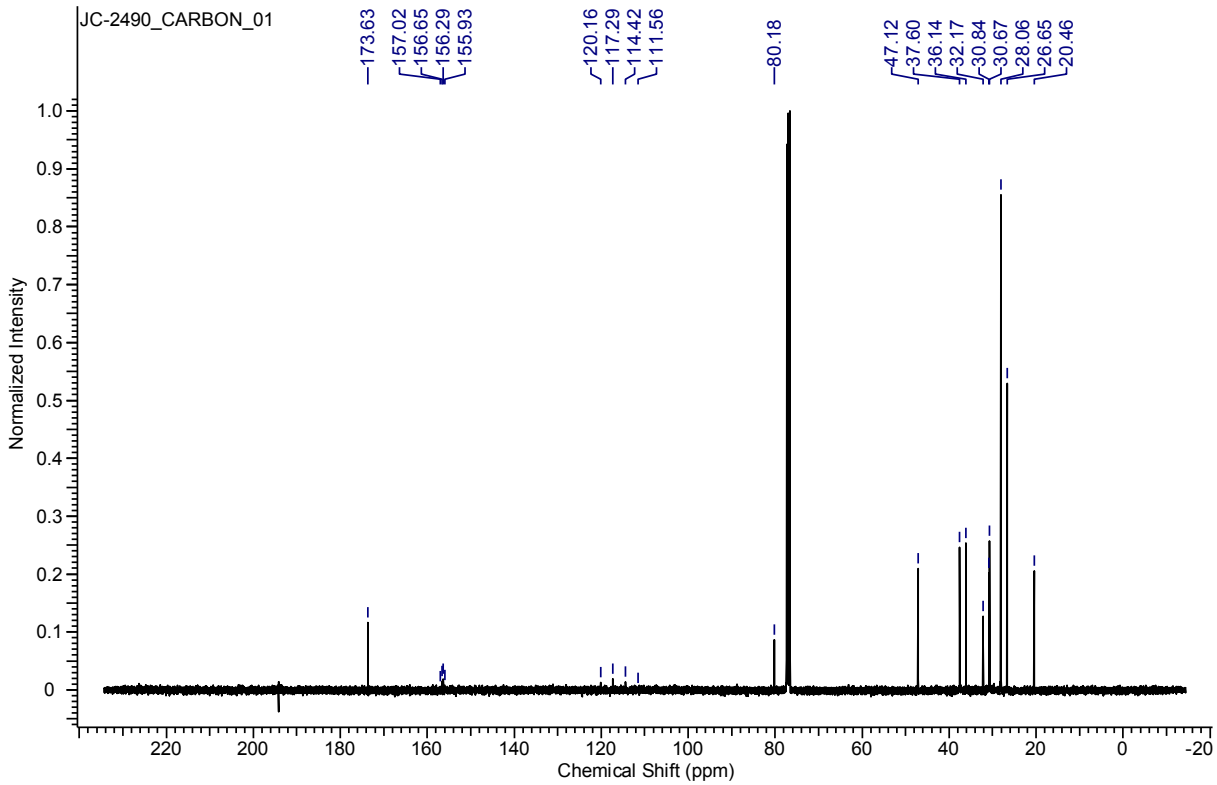

JC-2403c_FLUORINE_01
-75.77
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

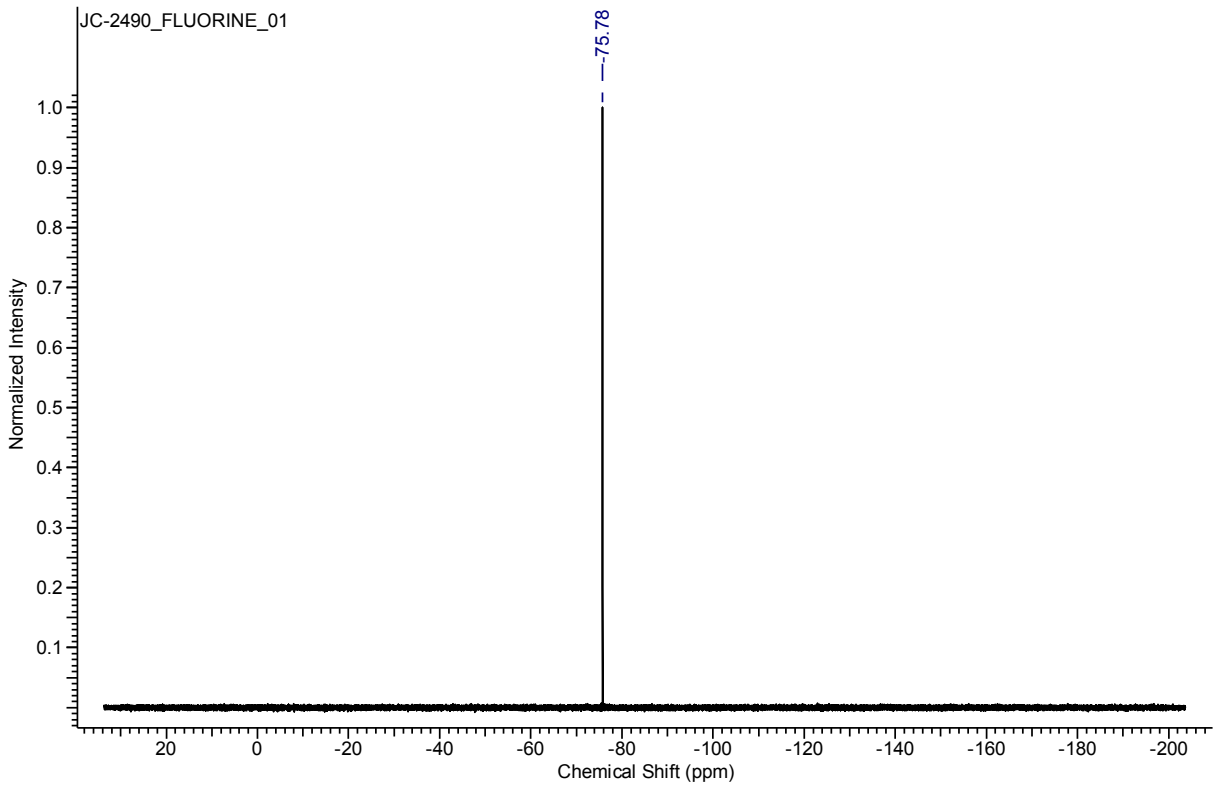

JC-2431a_PROTON_01
7.39
7.37
7.36
7.35
7.33
7.31
6.31
5.11
3.32
3.30
3.28
2.27
2.24
1.58
1.56
1.54
1.23
1.21
1.20
1.19
0.81
0.78
0.76
CO2Bn
Et
Me
N
H
O
CF3
4.83
0.97
2.00
2.01
2.03
4.14
4.21
6.02
Normalized Intensity
Chemical Shift (ppm)

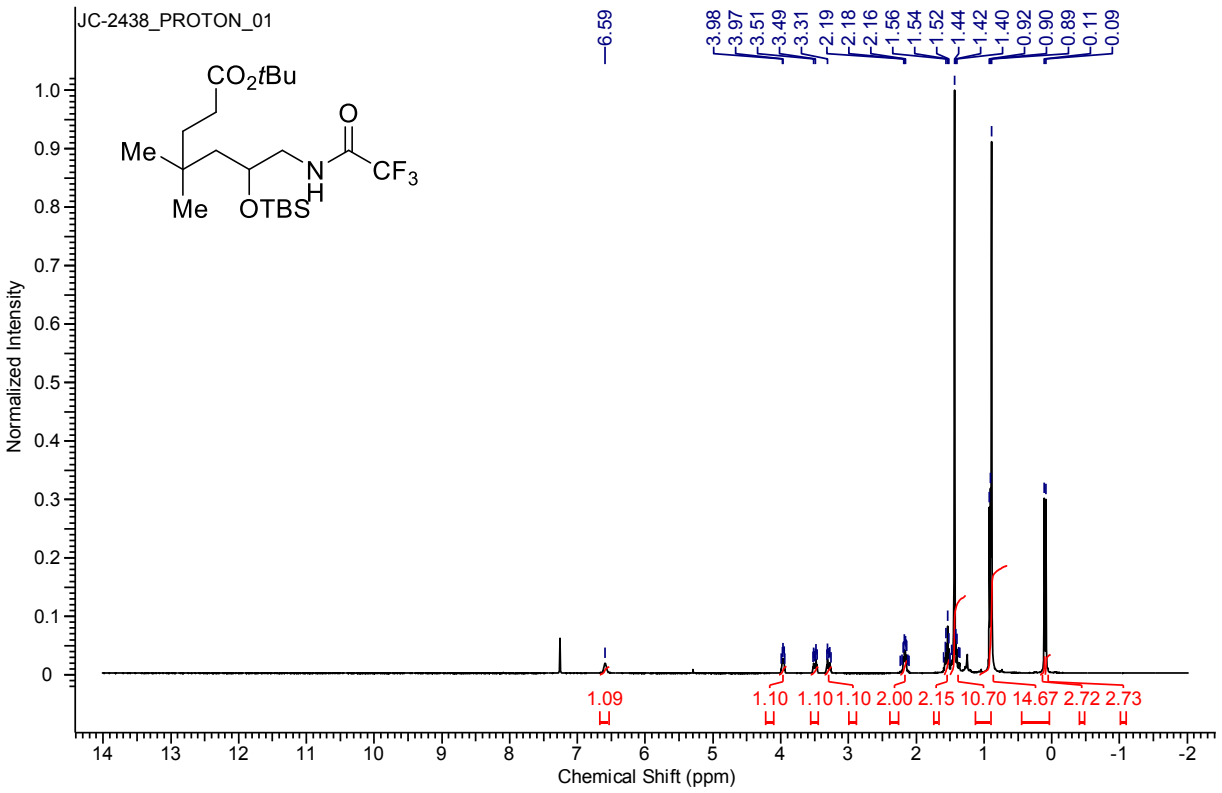

JC-2431a_CARBON_01
174.05
157.67
157.30
156.94
156.57
135.94
128.55
128.24
120.13
117.26
114.40
111.53
66.30
40.62
35.39
34.59
33.25
31.03
29.05
23.93
23.29
7.81
Normalized Intensity
Chemical Shift (ppm)

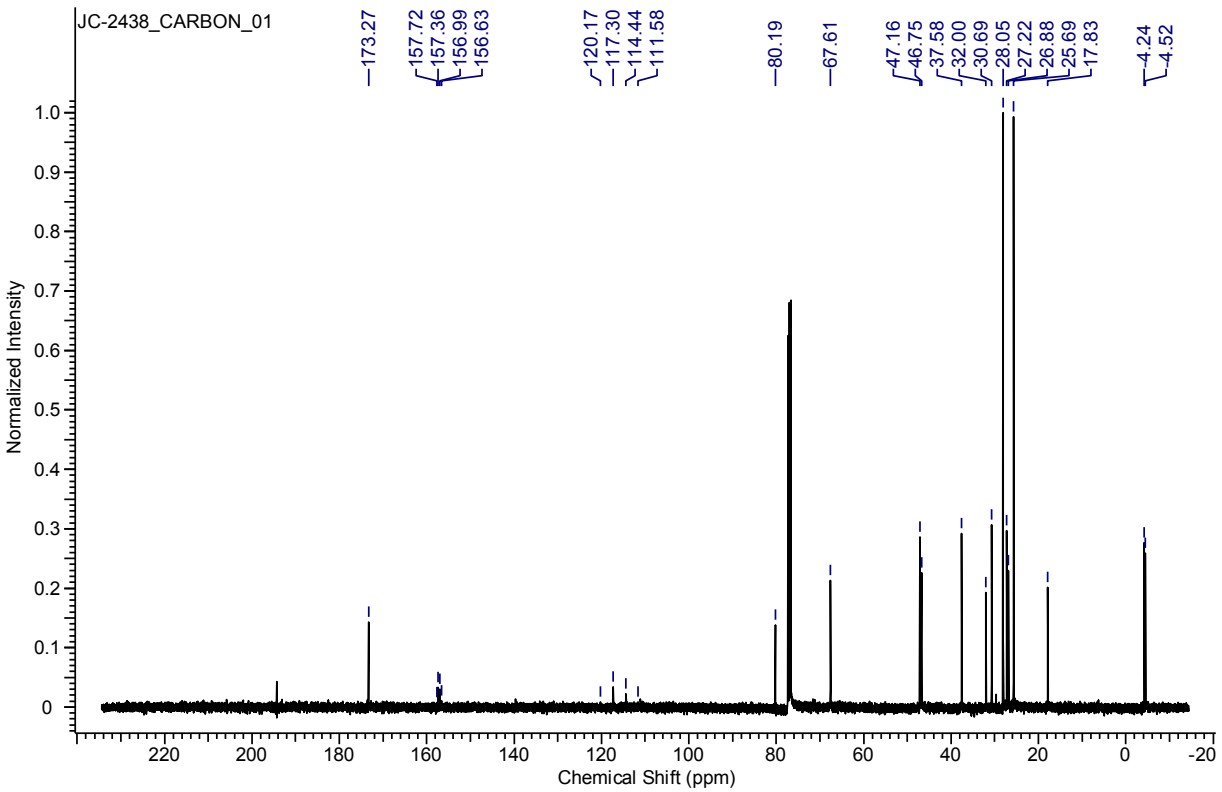

JC-2431a_FLUORINE_01
-75.64
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

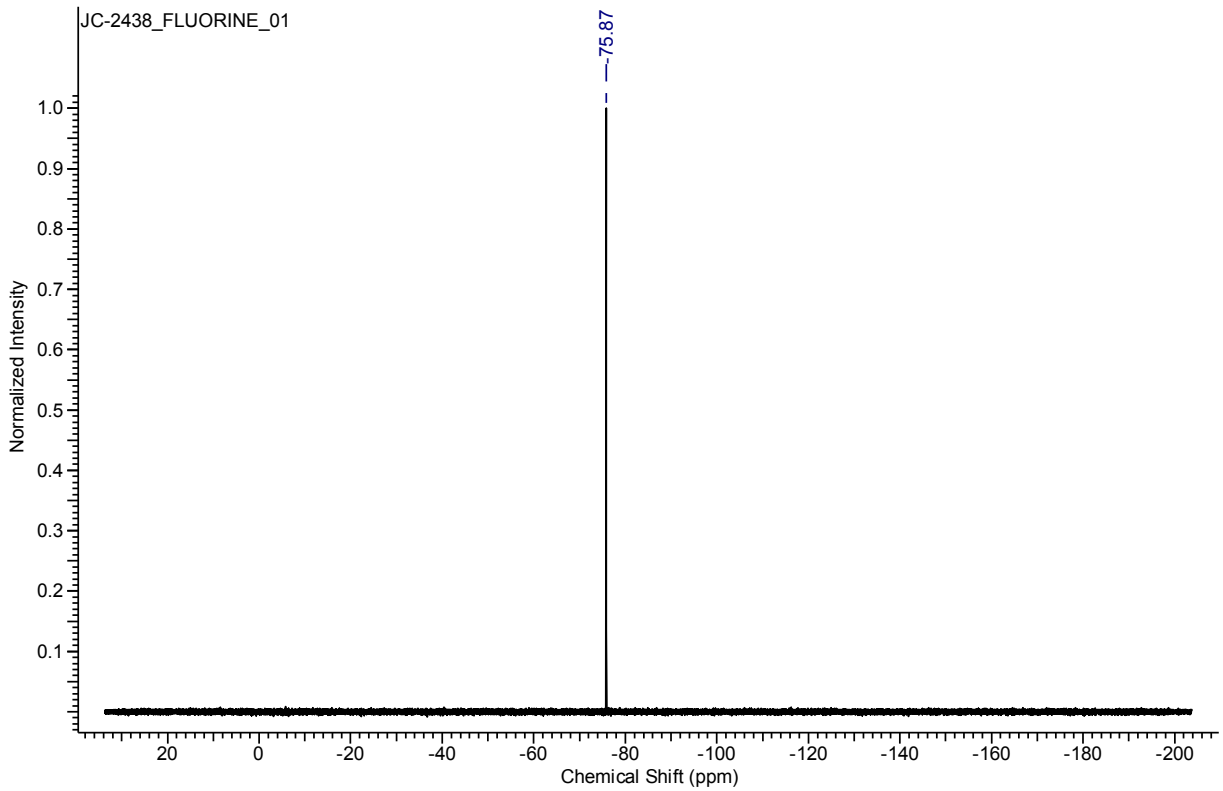

JC-2490_PROTON_01
6.03
3.97
3.95
3.93
3.91
3.90
2.12
2.10
1.49
1.47
1.47
1.46
1.45
1.42
1.20
1.19
0.82
CO2tBu
Me
O
Me
N
H
CF3
Me
Normalized Intensity
0.94
0.98
2.00
12.11
5.96
6.13
Chemical Shift (ppm)

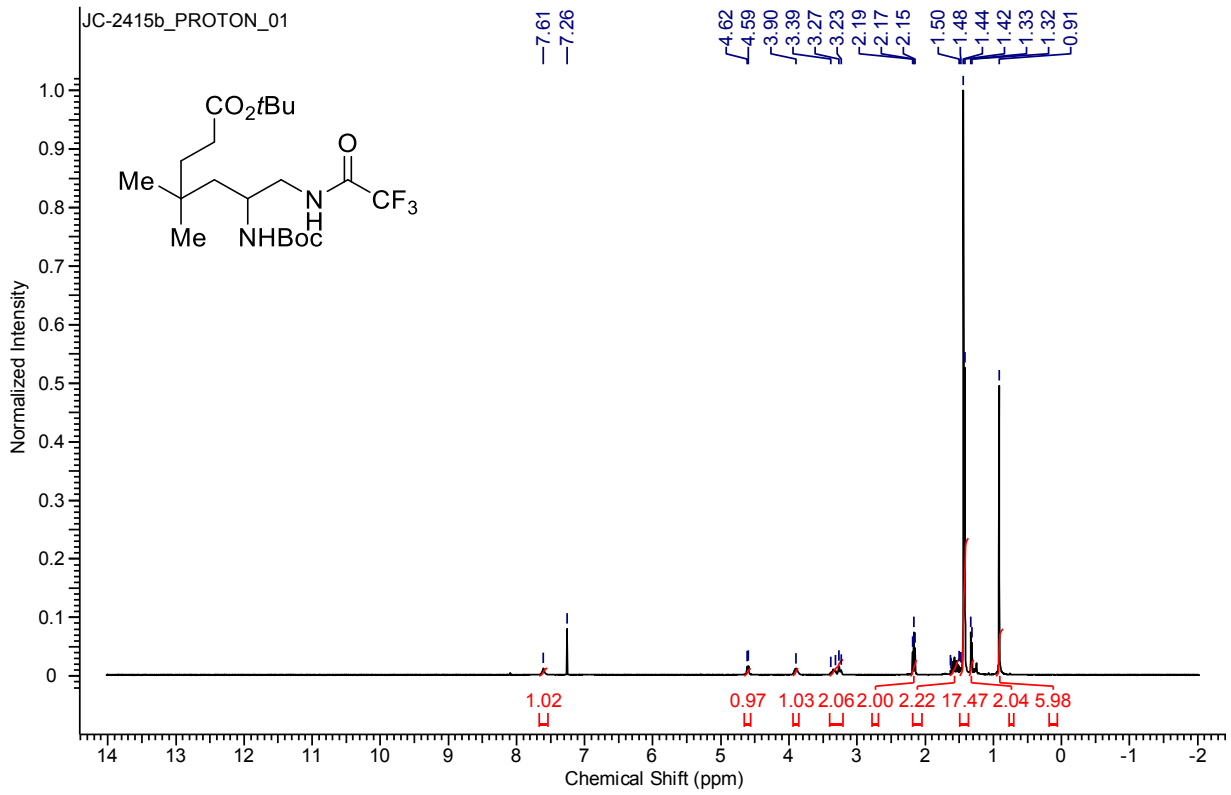

JC-2490_CARBON_01
173.63
157.02
156.65
156.29
155.93
120.16
117.29
114.42
111.56
80.18
47.12
37.60
36.14
32.17
30.84
30.67
28.06
26.65
20.46
Normalized Intensity
Chemical Shift (ppm)

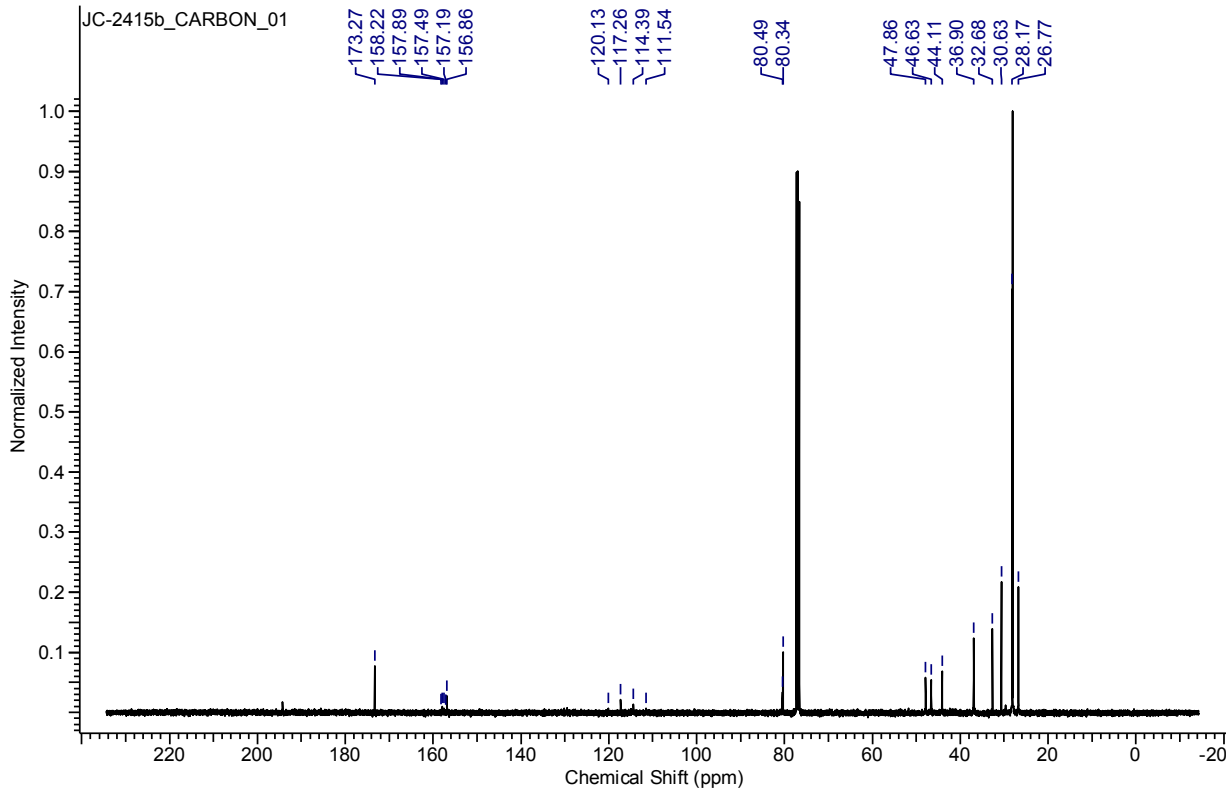

JC-2490_FLUORINE_01
-75.78
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

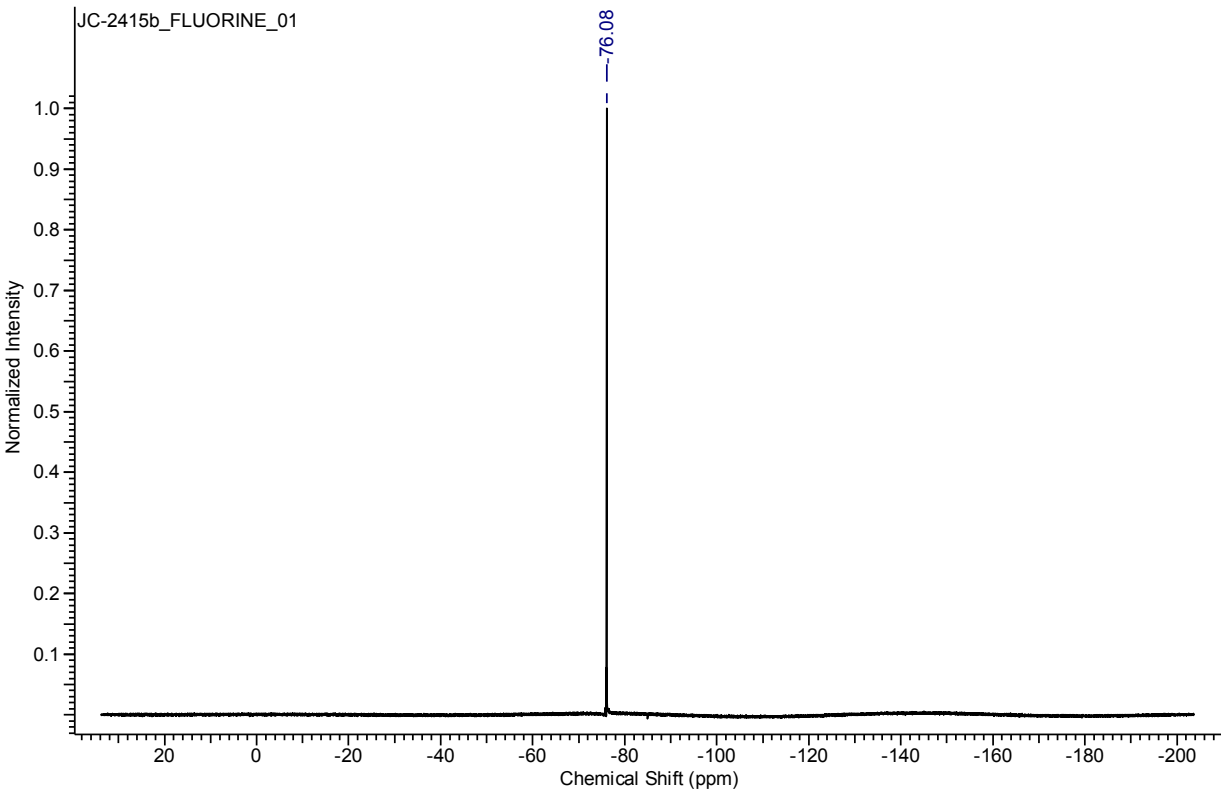

JC-2438_PROTON_01
CO2tBu
Me
Me
OTBS
N
H
O
CF3
6.59
3.98
3.97
3.51
3.49
3.31
2.19
2.18
2.16
1.56
1.54
1.52
1.44
1.42
1.40
0.92
0.90
0.89
0.11
0.09
1.09
1.10
1.10
1.10
2.00
2.15
10.70
14.67
2.72
2.73
Normalized Intensity
Chemical Shift (ppm)

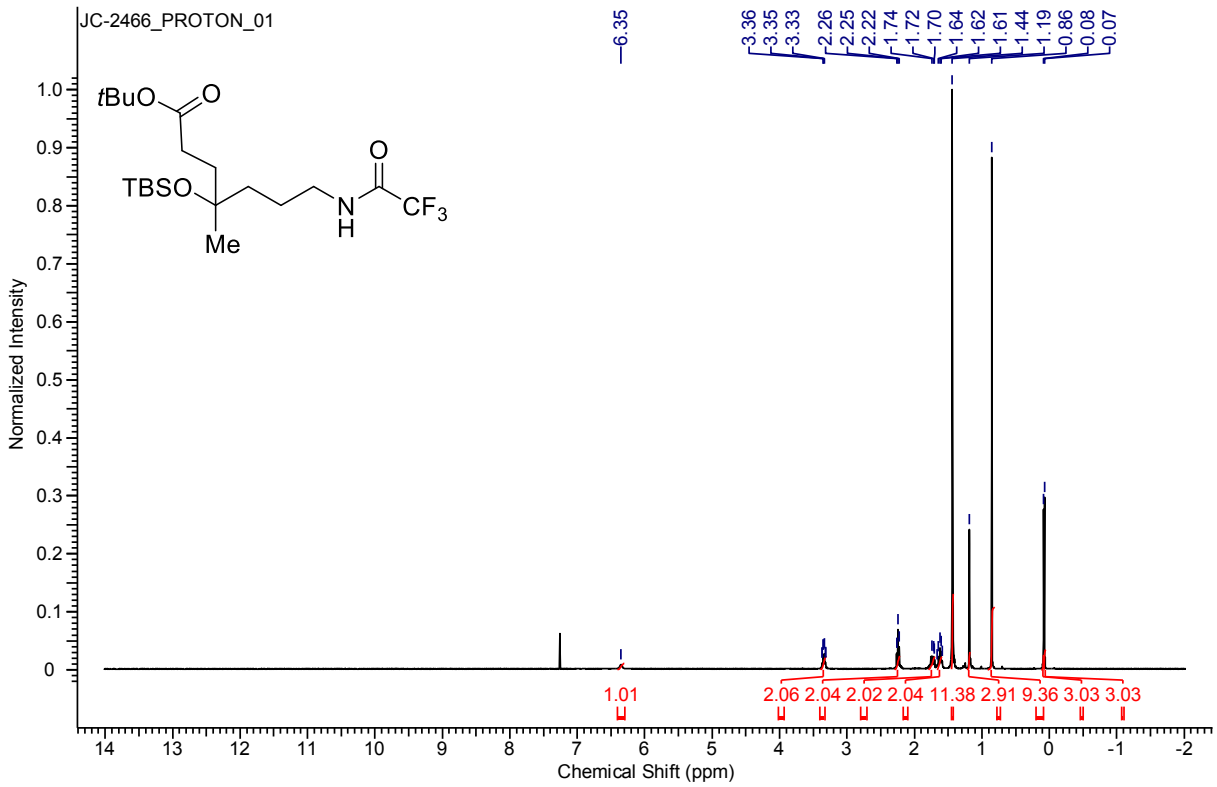

JC-2438_CARBON_01
173.27
157.72
157.36
156.99
156.63
120.17
117.30
114.44
111.58
80.19
67.61
47.16
46.75
37.58
32.00
30.69
28.05
27.22
26.88
25.69
17.83
-4.24
-4.52
Normalized Intensity
Chemical Shift (ppm)

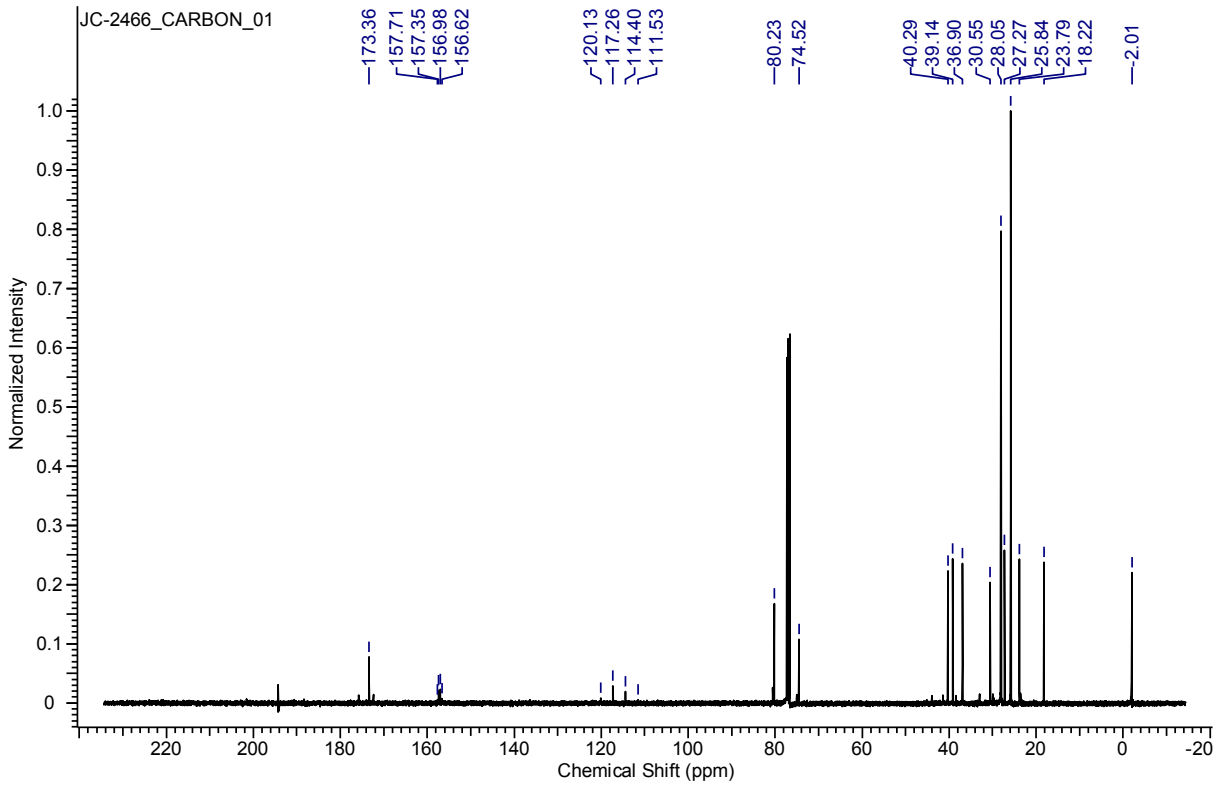

JC-2438_FLUORINE_01
-75.87
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

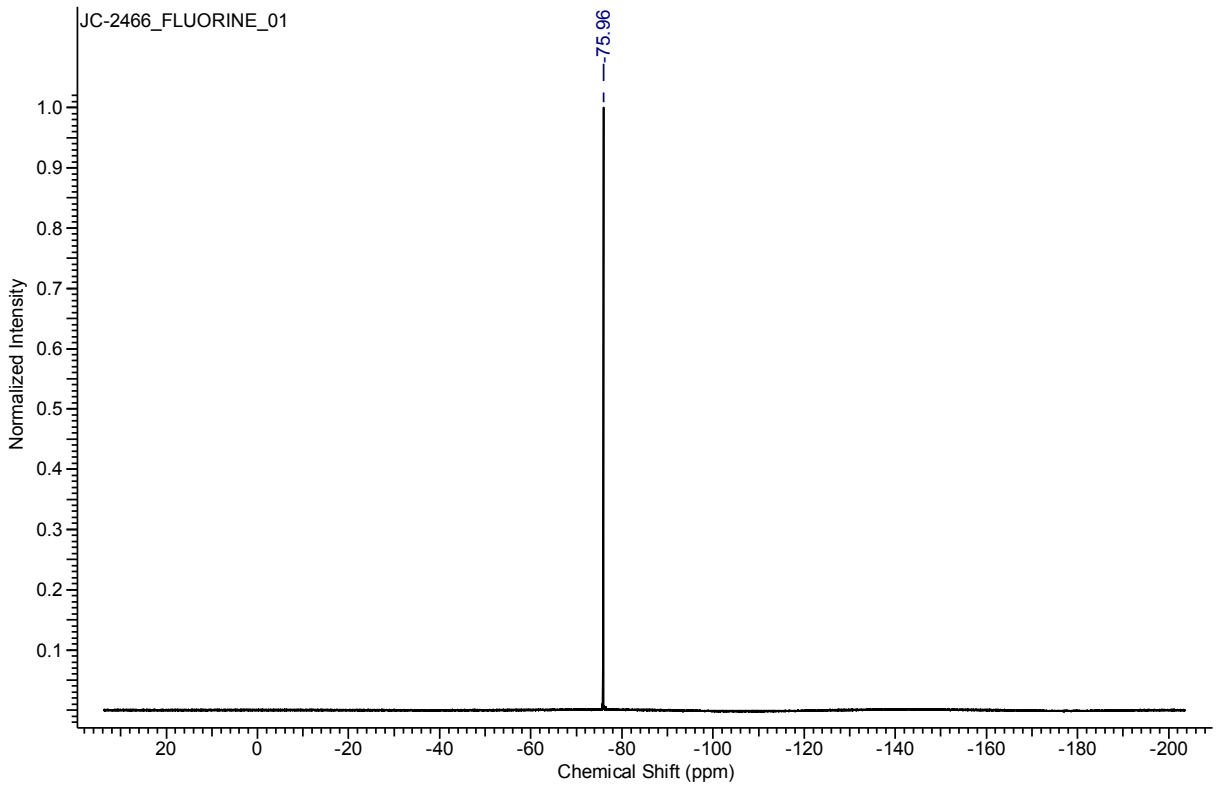

JC-2415b_PROTON_01
7.61
7.26
4.62
4.59
3.90
3.39
3.27
3.23
2.19
2.17
2.15
1.50
1.48
1.44
1.42
1.33
1.32
0.91
CO2tBu
O
Me
N
H
CF3
Me
NHBoc
1.02
0.97
1.03
2.06
2.00
2.22
17.47
2.04
5.98
Normalized Intensity
Chemical Shift (ppm)

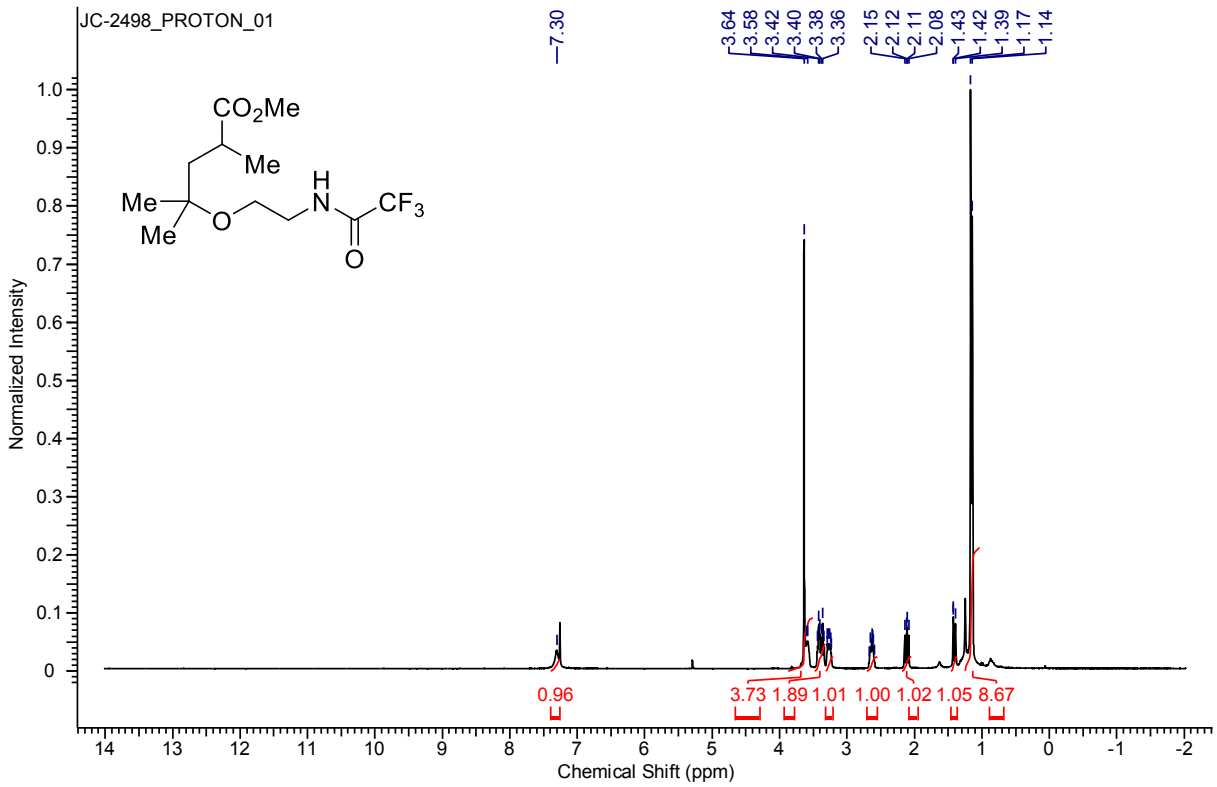

JC-2415b_CARBON_01
173.27
158.22
157.89
157.49
157.19
156.86
120.13
117.26
114.39
111.54
80.49
80.34
47.86
46.63
44.11
36.90
32.68
30.63
28.17
26.77
Normalized Intensity
Chemical Shift (ppm)

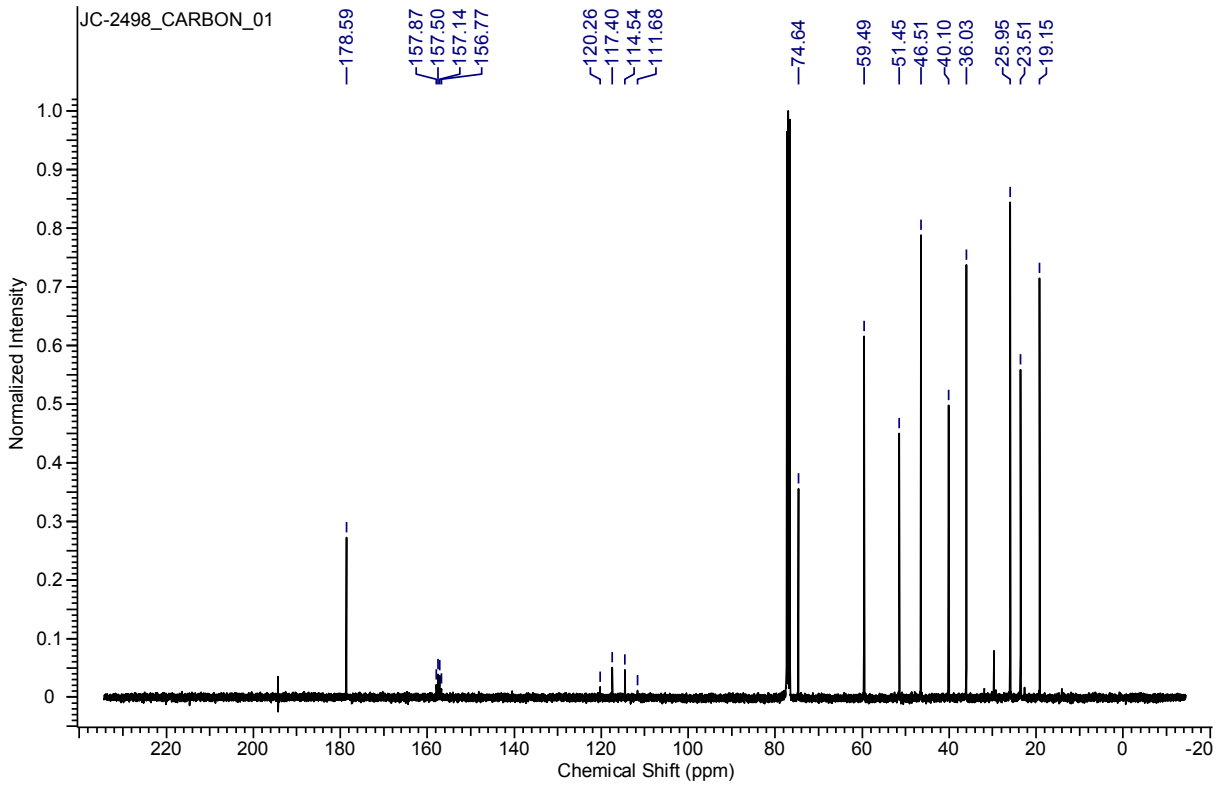

JC-2415b_FLUORINE_01
-76.08
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

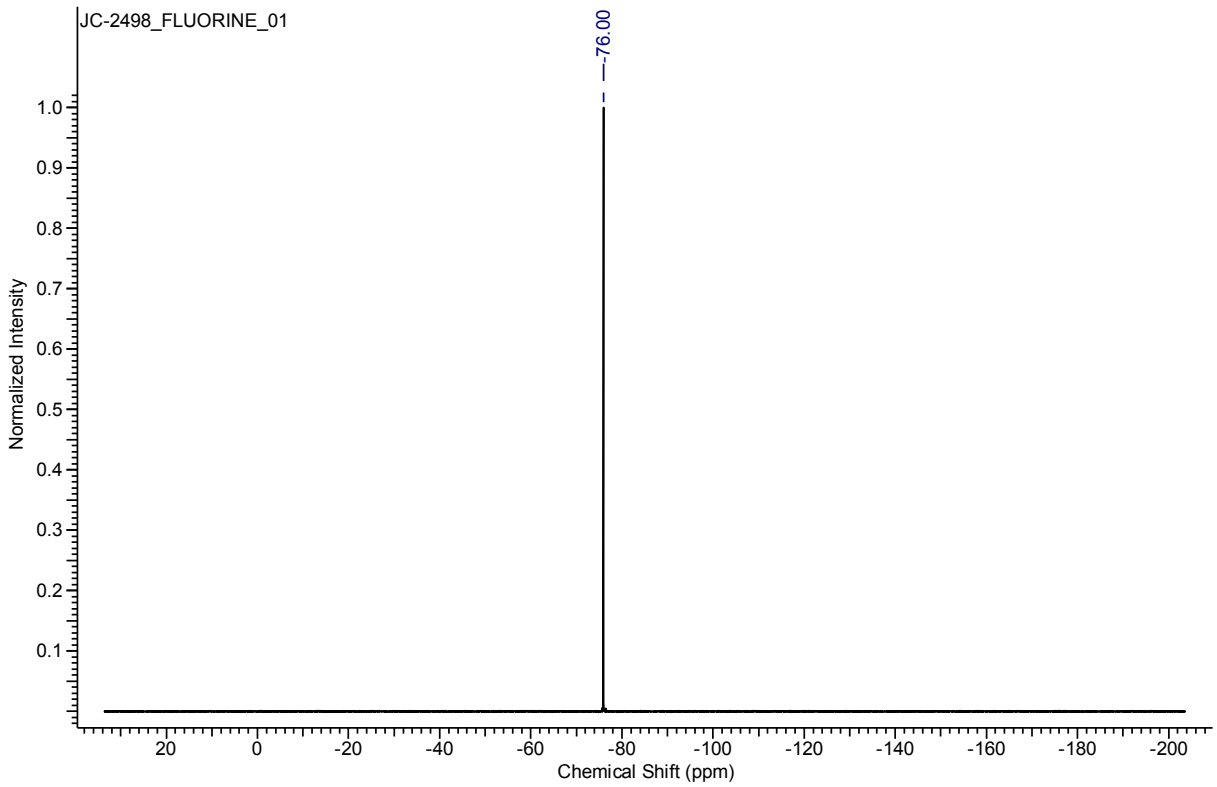

JC-2466_PROTON_01
tBuO
O
TBSO
Me
N
H
O
CF3
6.35
3.36
3.35
3.33
2.26
2.25
2.22
1.74
1.72
1.70
1.64
1.62
1.61
1.44
1.19
0.86
0.08
0.07
1.01
2.06 2.04 2.02 2.04 11.38 2.91 9.36 3.03 3.03
Normalized Intensity
Chemical Shift (ppm)

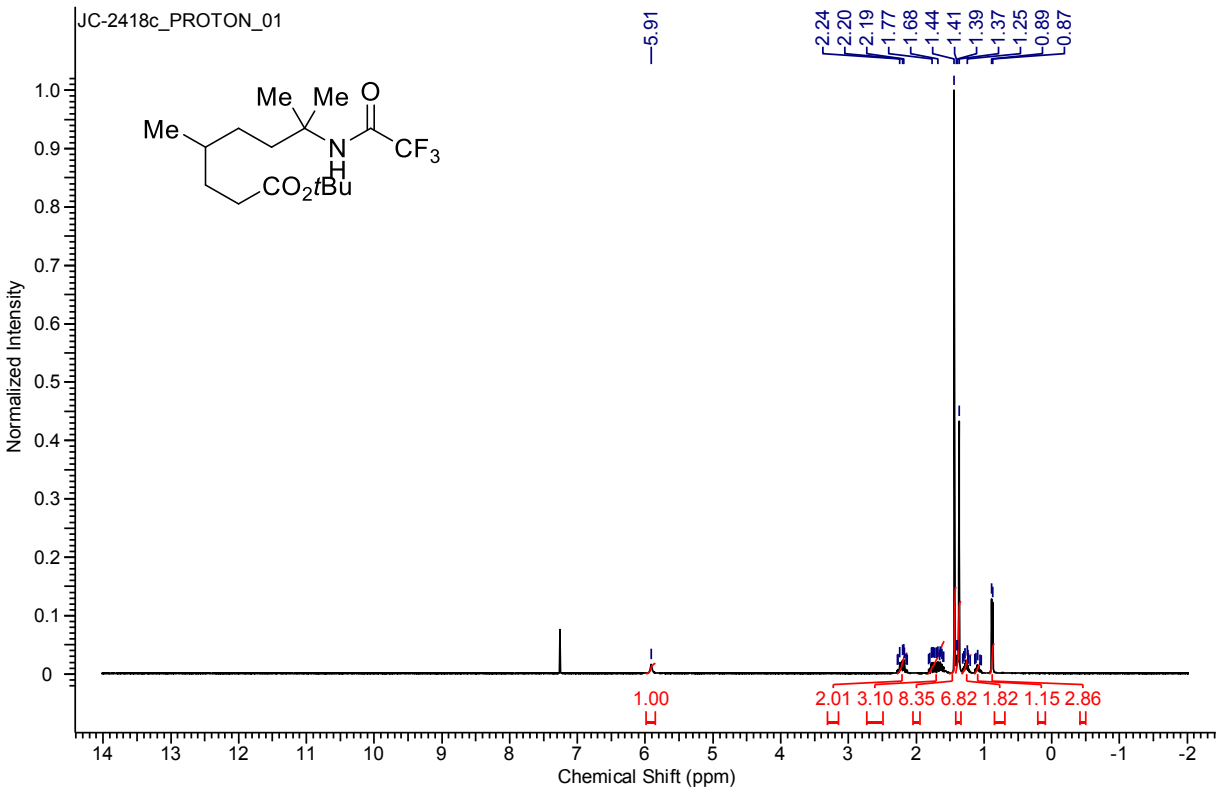

JC-2466_CARBON_01
173.36
157.71
157.35
156.98
156.62
120.13
117.26
114.40
111.53
80.23
74.52
40.29
39.14
36.90
30.55
28.05
27.27
25.84
23.79
18.22
2.01
Normalized Intensity
Chemical Shift (ppm)

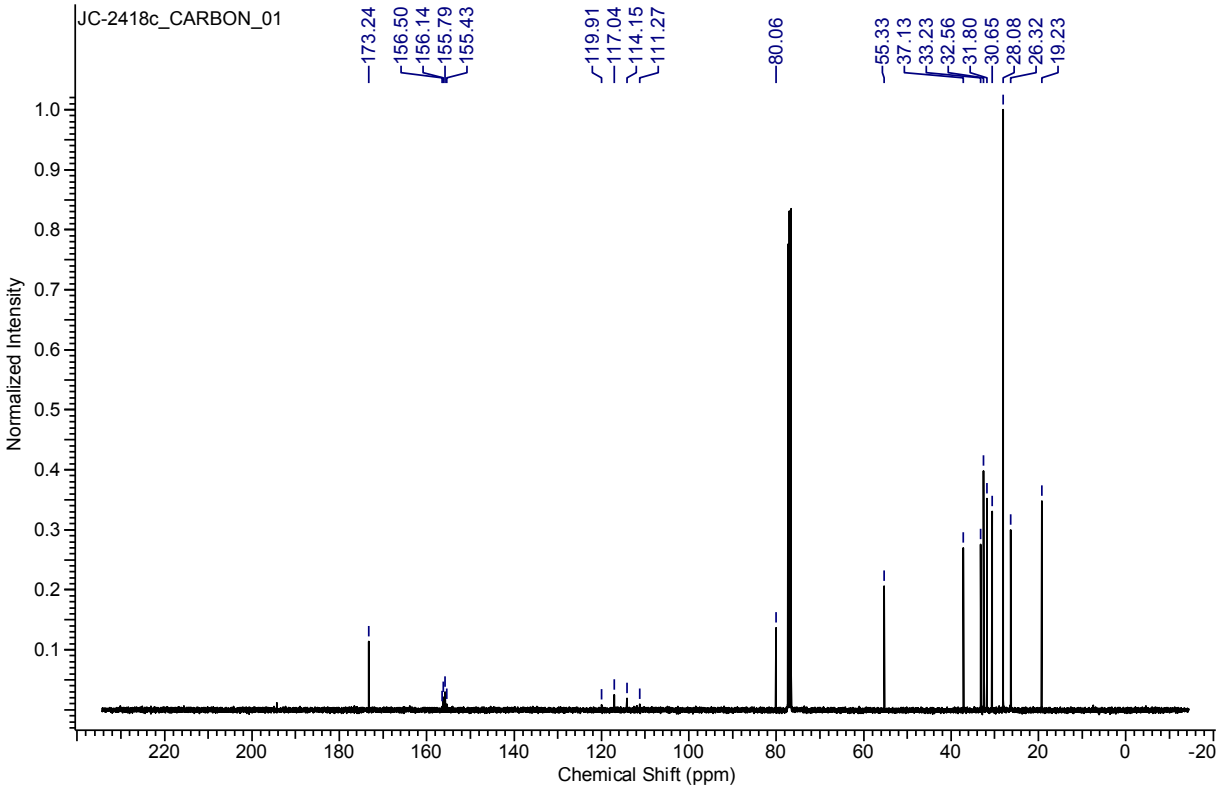

JC-2466_FLUORINE_01
-75.96
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

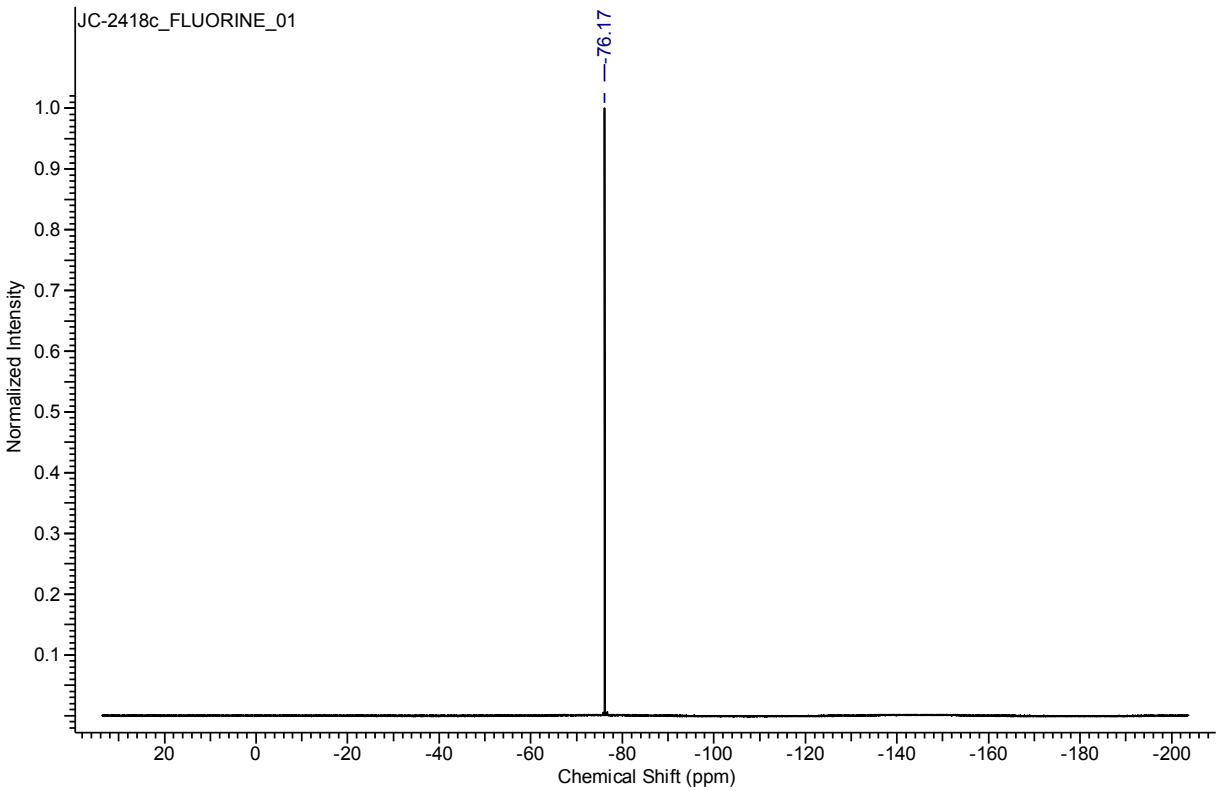

JC-2498_PROTON_01
7.30
3.64
3.58
3.42
3.40
3.38
3.36
2.15
2.12
2.11
2.08
1.43
1.42
1.39
1.17
1.14
CO2Me
Me
Me
Me
H
N
O
CF3
O
Normalized Intensity
Chemical Shift (ppm)
0.96
3.73
1.89
1.01
1.00
1.02
1.05
8.67

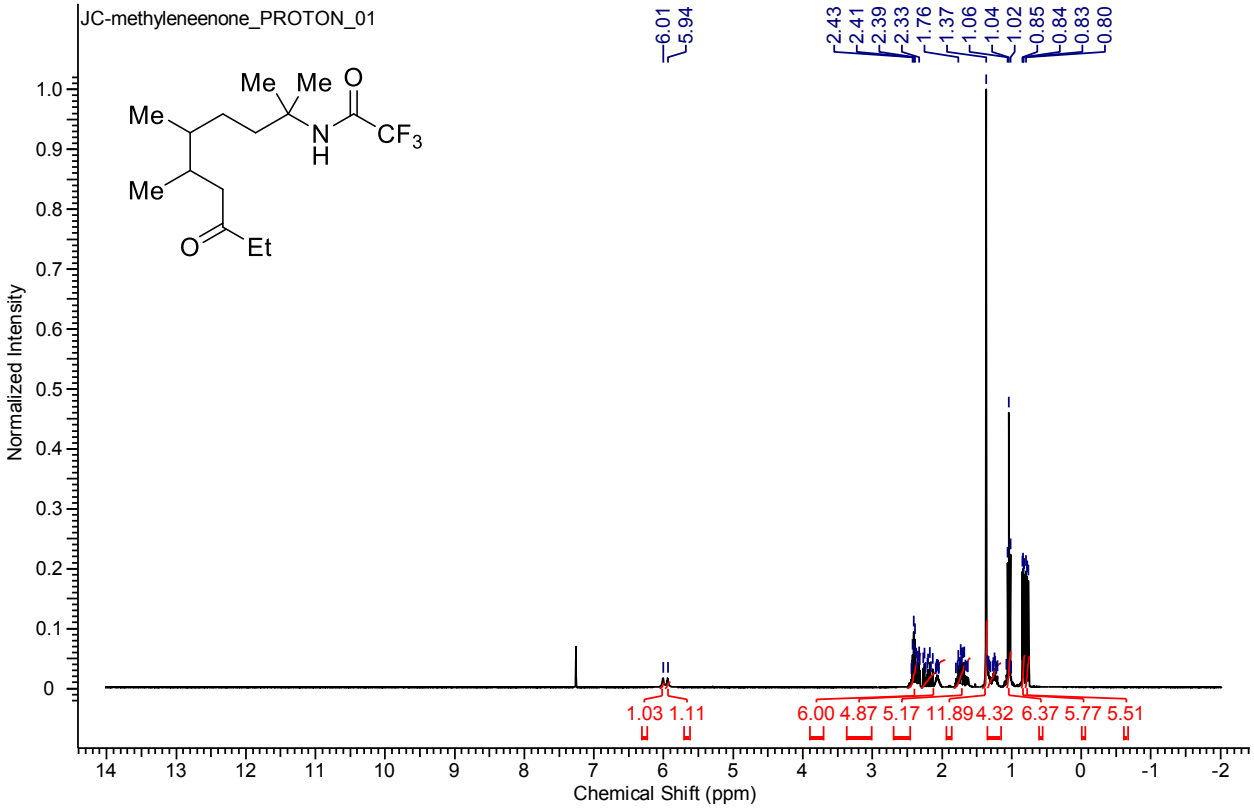

JC-2498_CARBON_01
178.59
157.87
157.50
157.14
156.77
120.26
117.40
114.54
111.68
74.64
59.49
51.45
46.51
40.10
36.03
25.95
23.51
19.15
Normalized Intensity
Chemical Shift (ppm)

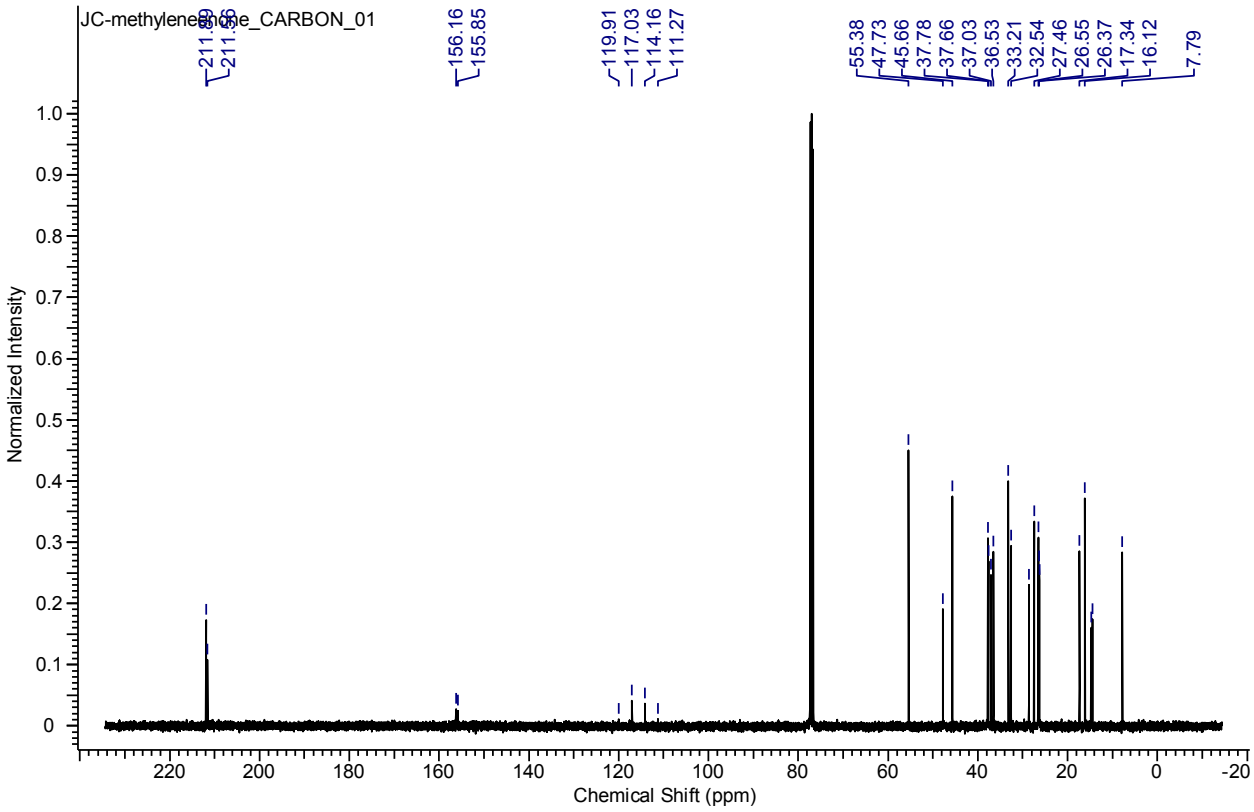

JC-2498_FLUORINE_01
-76.00
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

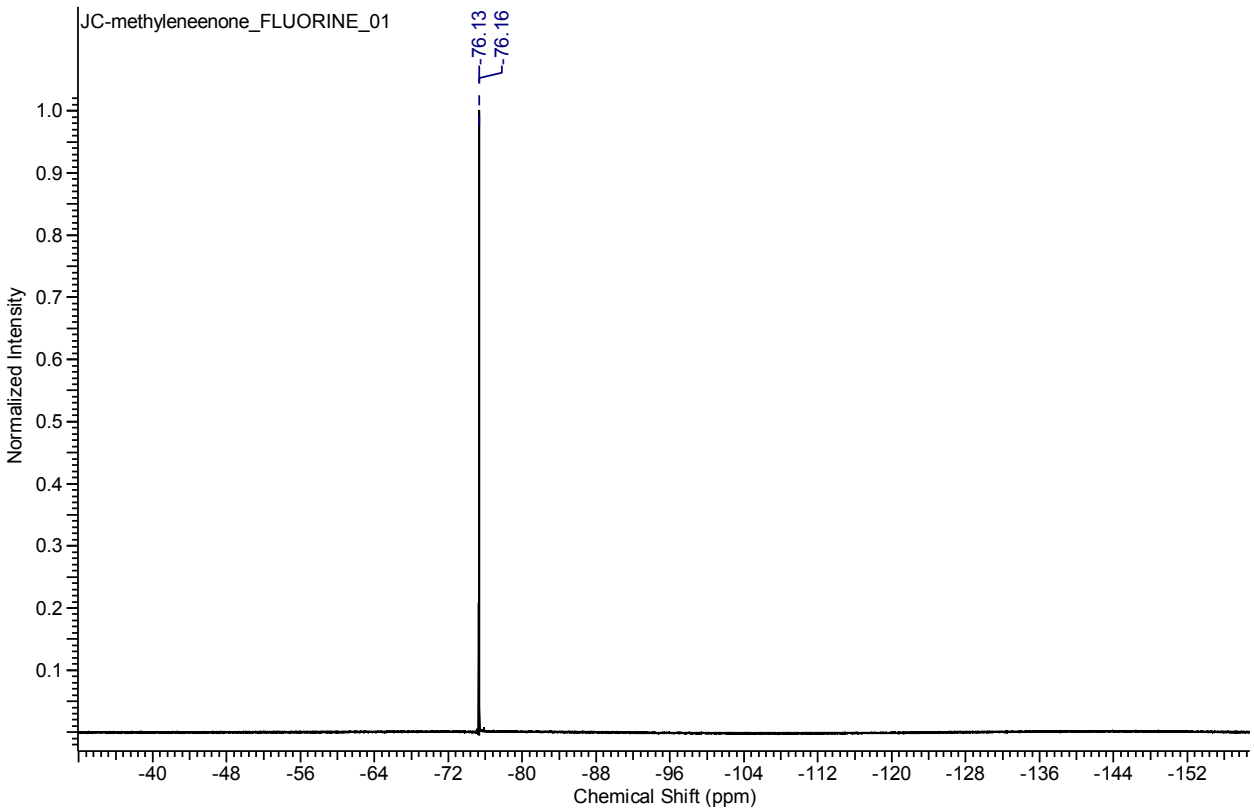

JC-2418c_PROTON_01
5.91
2.24
2.20
2.19
1.77
1.68
1.44
1.41
1.39
1.37
1.25
0.89
0.87
Me
Me
Me
O
N
H
CF3
CO2tBu
1.00
2.01
3.10
8.35
6.82
1.82
1.15
2.86
Normalized Intensity
Chemical Shift (ppm)

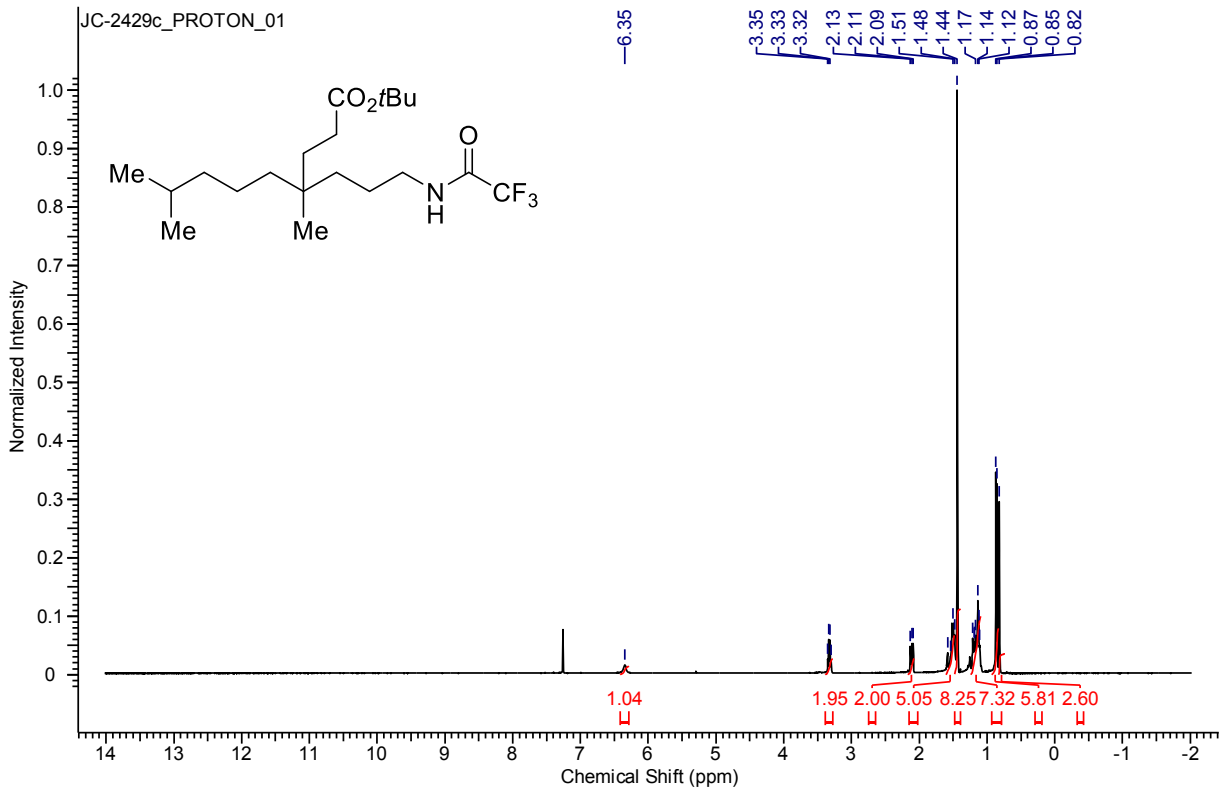

JC-2418c_CARBON_01
173.24
156.50
156.14
155.79
155.43
119.91
117.04
114.15
111.27
80.06
55.33
37.13
33.23
32.56
31.80
30.65
28.08
26.32
19.23
Normalized Intensity
Chemical Shift (ppm)

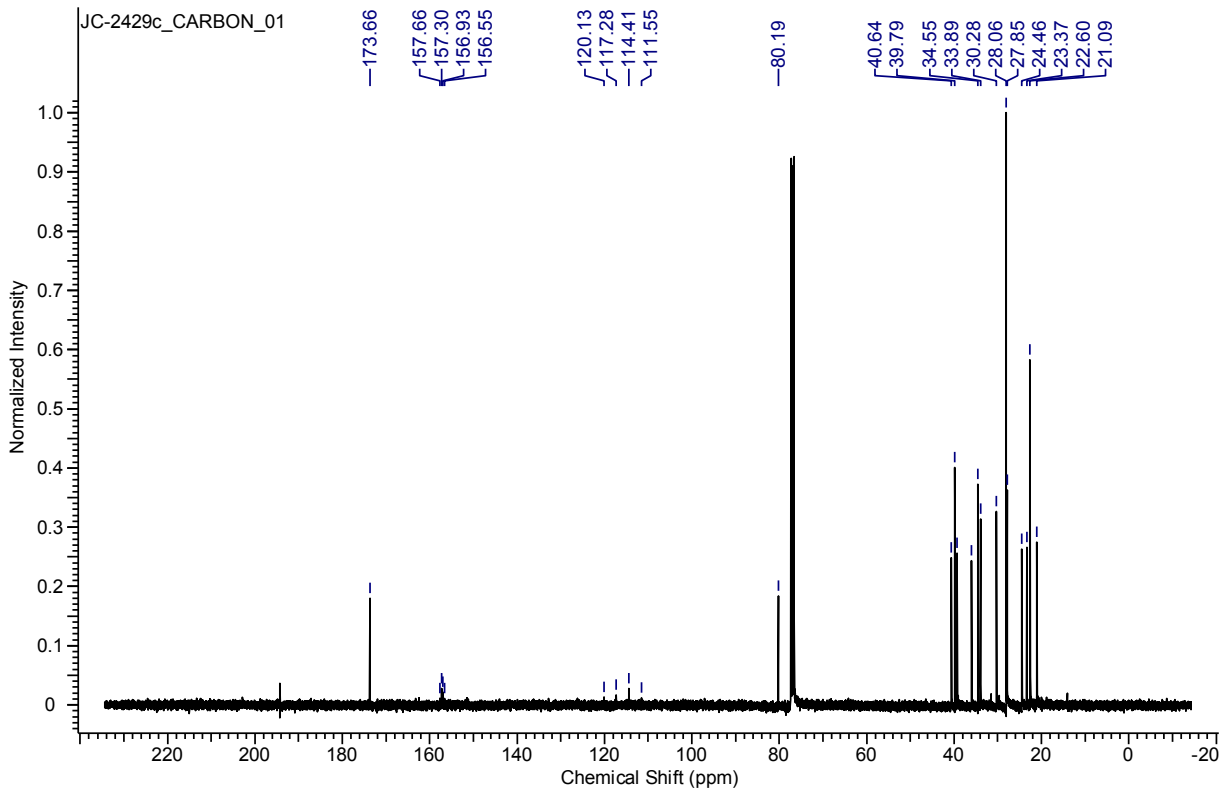

JC-2418c_FLUORINE_01
-76.17
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

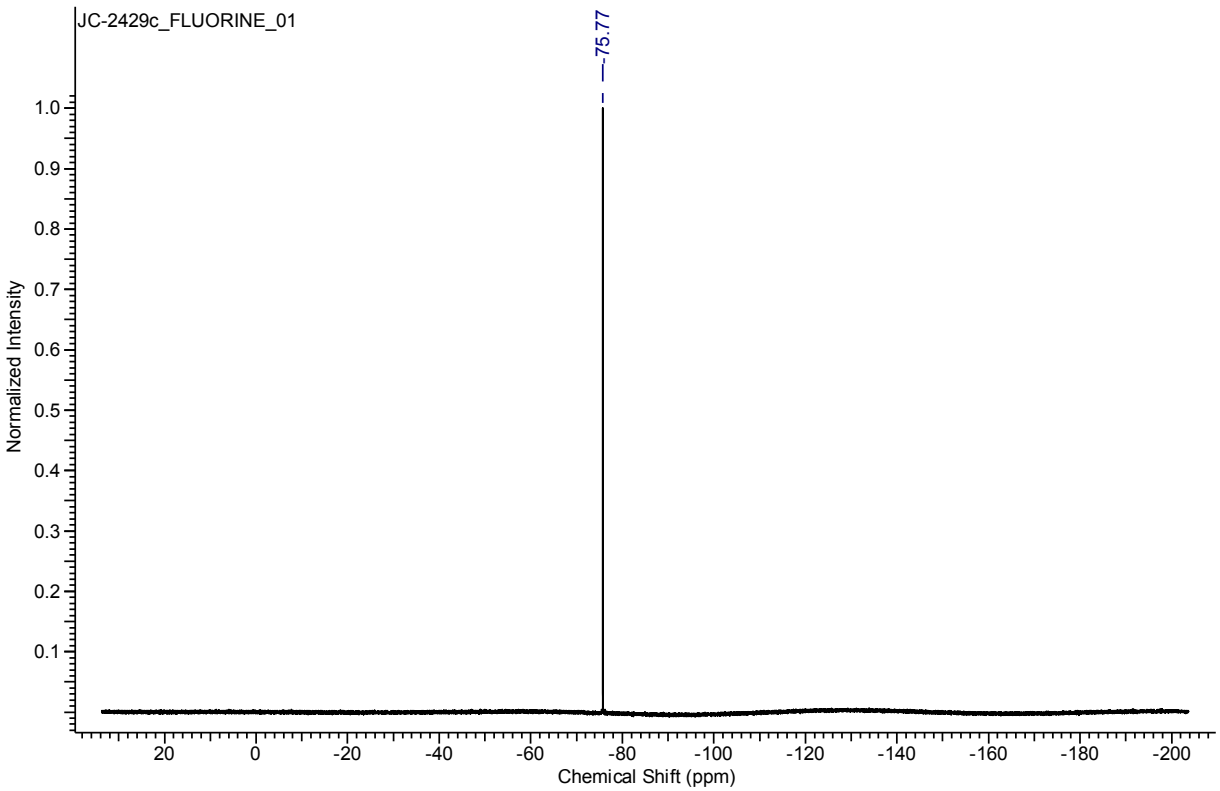

JC-methyleneenone_PROTON_01
Me
Me
Me
Me
O
N
H
CF3
O
Et
6.01
5.94
2.43
2.41
2.39
2.33
1.76
1.37
1.06
1.04
1.02
0.85
0.84
0.83
0.80
1.03 1.11
6.00 4.87 5.17 11.89 4.32 6.37 5.77 5.51
Normalized Intensity
Chemical Shift (ppm)

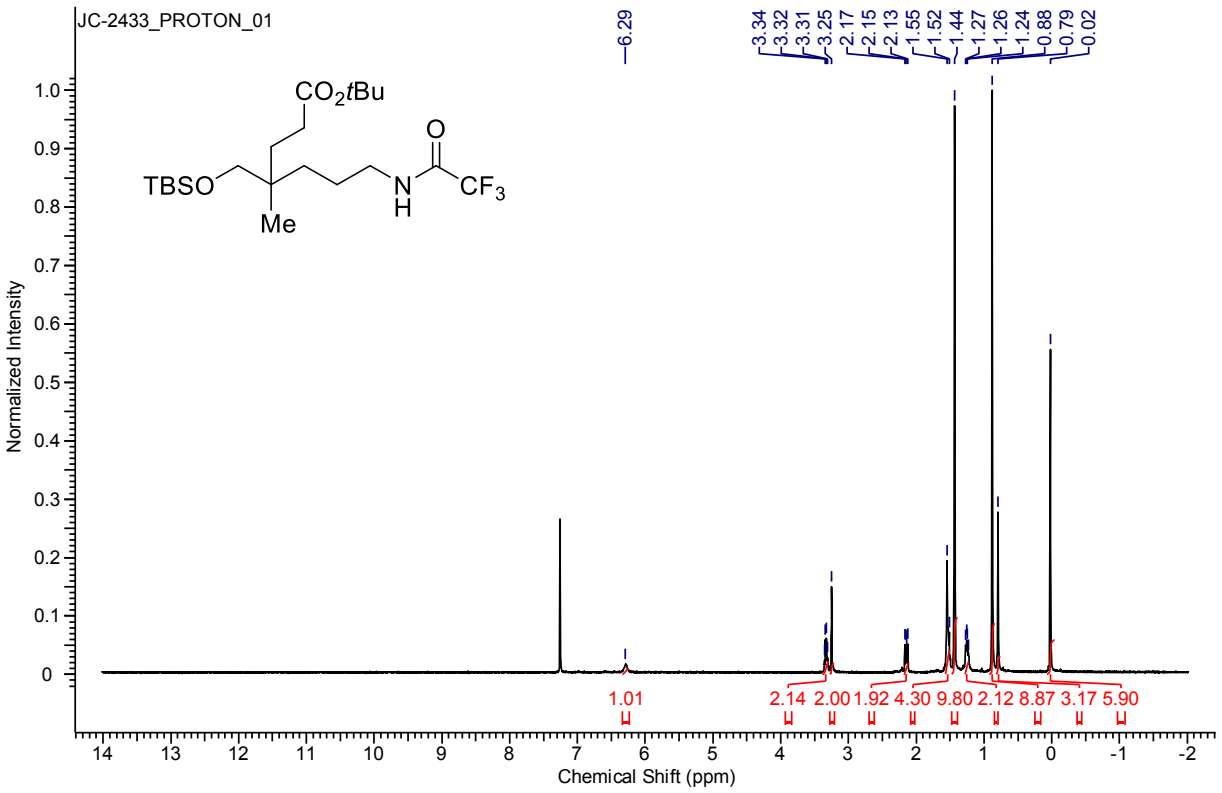

JC-methyleneenone_CARBON_01
211.68
211.08
156.16
155.85
119.91
117.03
114.16
111.27
55.38
47.73
45.66
37.78
37.66
37.03
36.53
33.21
32.54
27.46
26.55
26.37
17.34
16.12
7.79
Normalized Intensity
Chemical Shift (ppm)

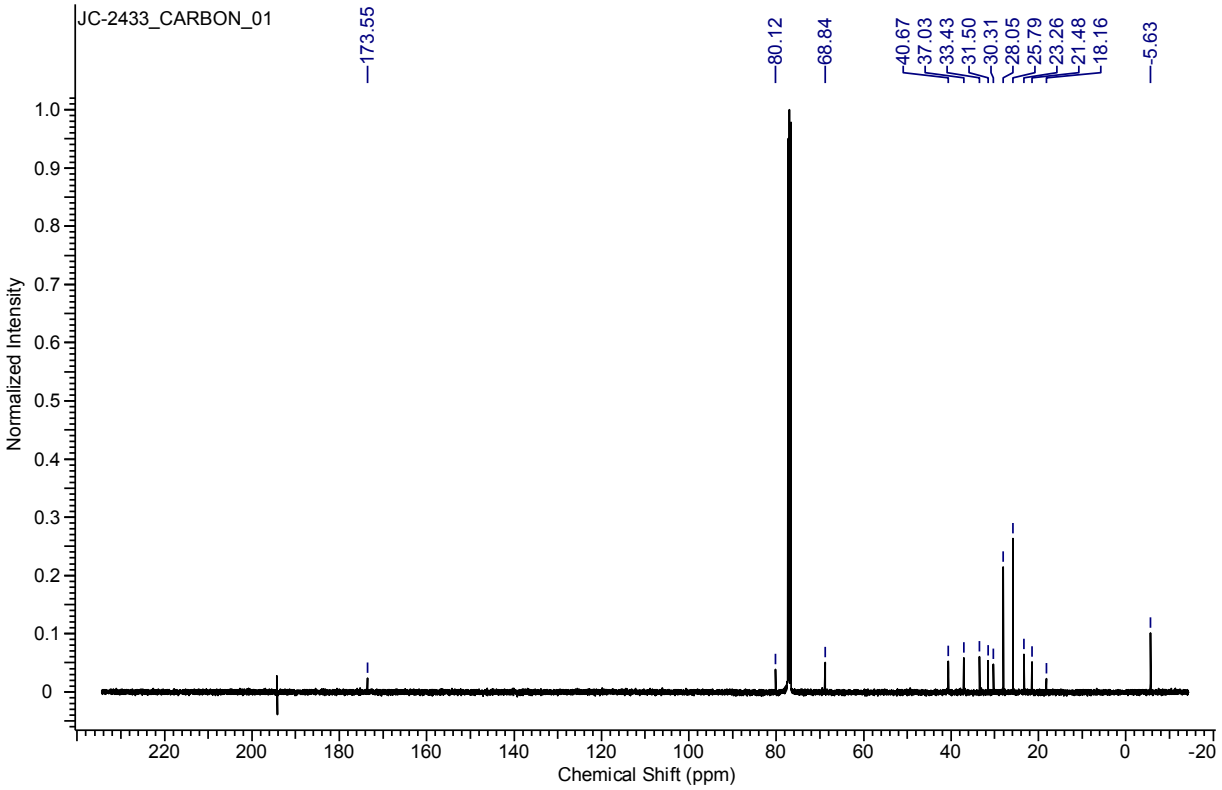

JC-methyleneenone_FLUORINE_01
-76.13
-76.16
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
-40
-48
-56
-64
-72
-80
-88
-96
-104
-112
-120
-128
-136
-144
-152
Chemical Shift (ppm)

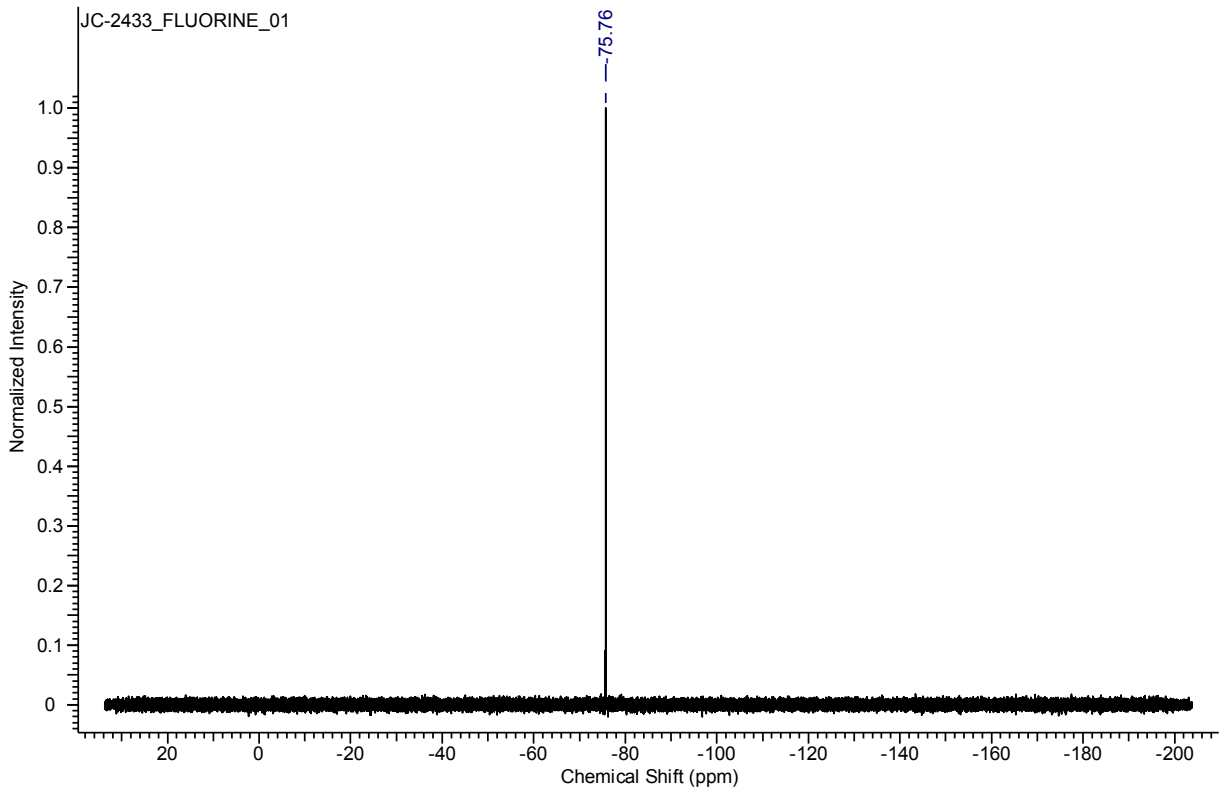

JC-2429c_PROTON_01
6.35
3.35
3.33
3.32
2.13
2.11
2.09
1.51
1.48
1.44
1.17
1.14
1.12
0.87
0.85
0.82
CO2tBu
O
Me
N
H
CF3
Me
Me
Normalized Intensity
1.04
1.95 2.00 5.05 8.25 7.32 5.81 2.60
Chemical Shift (ppm)

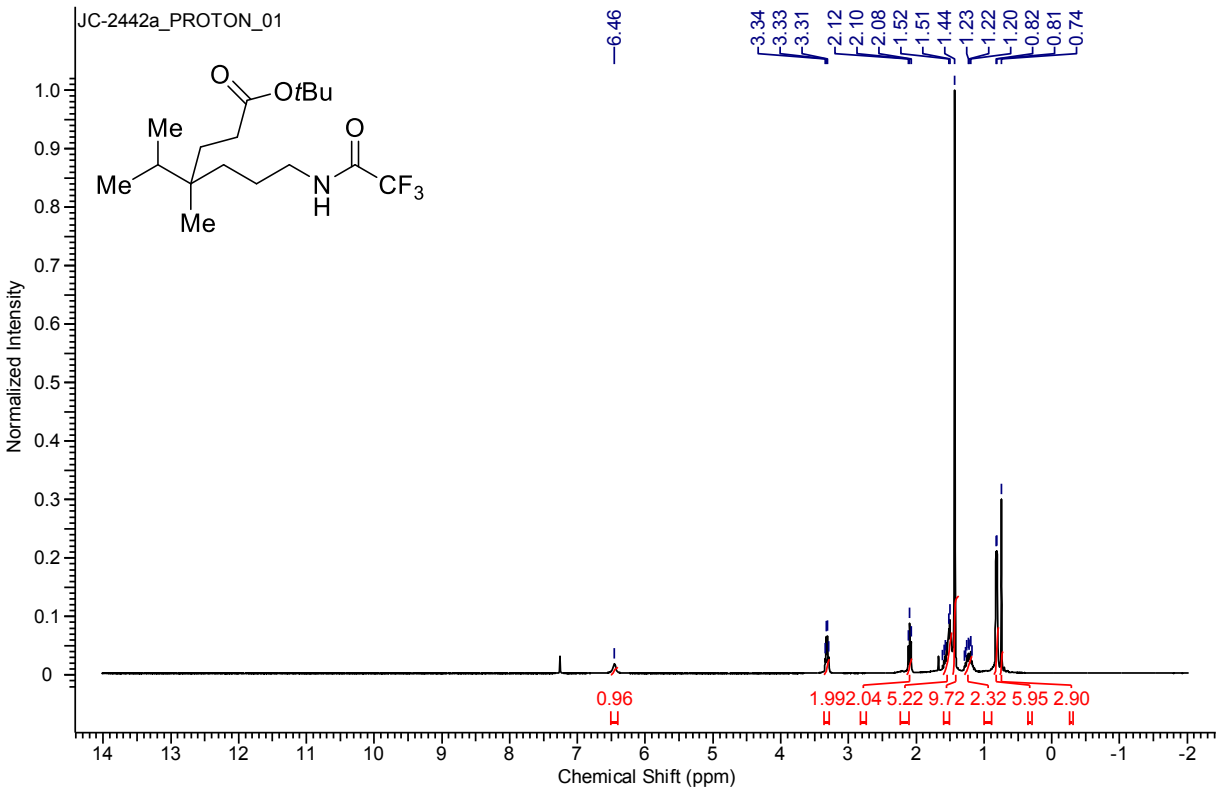

JC-2429c_CARBON_01
173.66
157.66
157.30
156.93
156.55
120.13
117.28
114.41
111.55
80.19
40.64
39.79
34.55
33.89
30.28
28.06
27.85
24.46
23.37
22.60
21.09
Normalized Intensity
Chemical Shift (ppm)

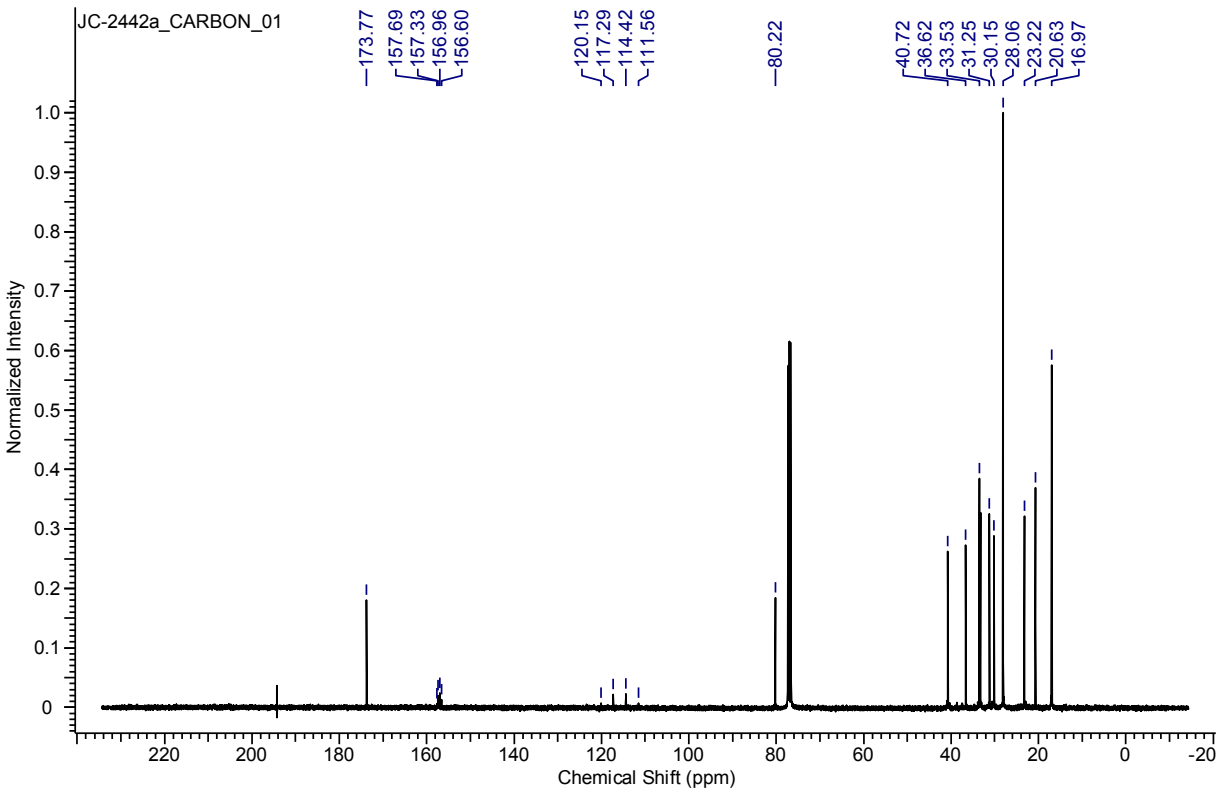

JC-2429c_FLUORINE_01
-75.77
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

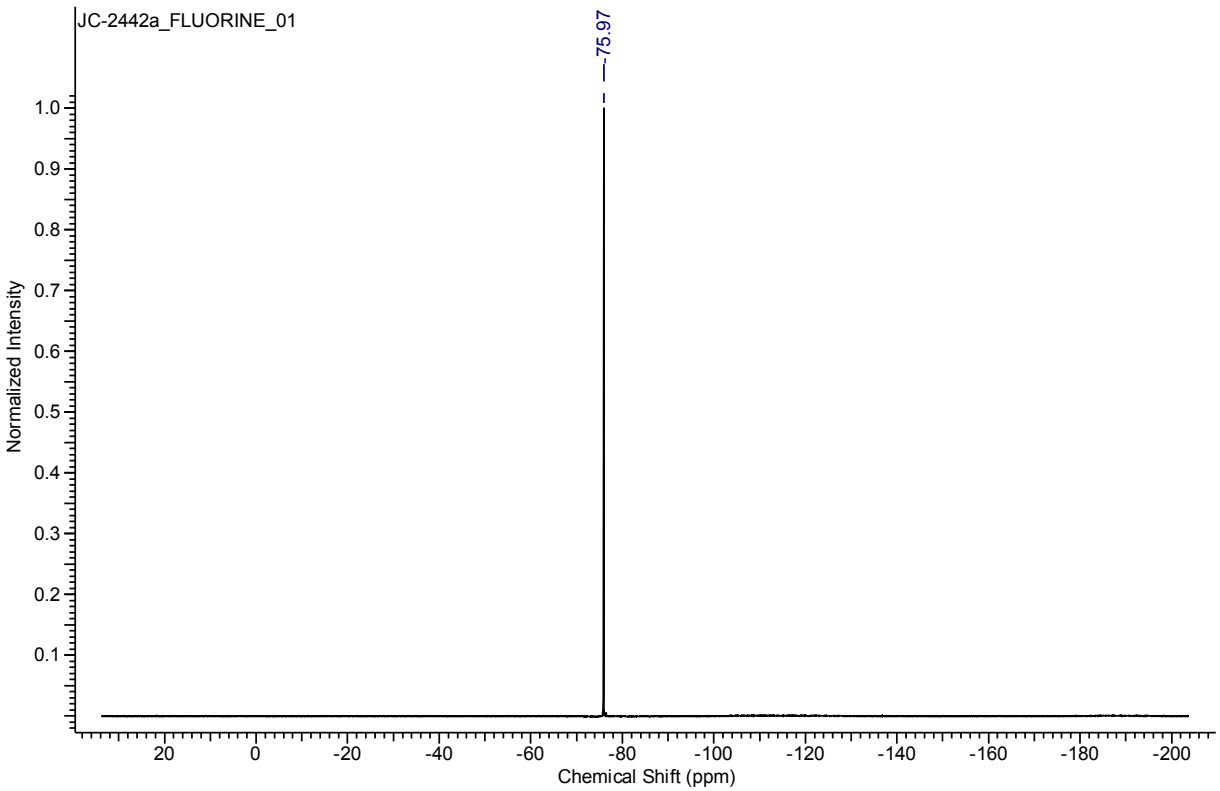

JC-2433_PROTON_01
CO2tBu
TBSO
Me
N
H
O
CF3
6.29
3.34
3.32
3.31
3.25
2.17
2.15
2.13
1.55
1.52
1.44
1.27
1.26
1.24
0.88
0.79
0.02
1.01
2.14
2.00
1.92
4.30
9.80
2.12
8.87
3.17
5.90
Normalized Intensity
Chemical Shift (ppm)

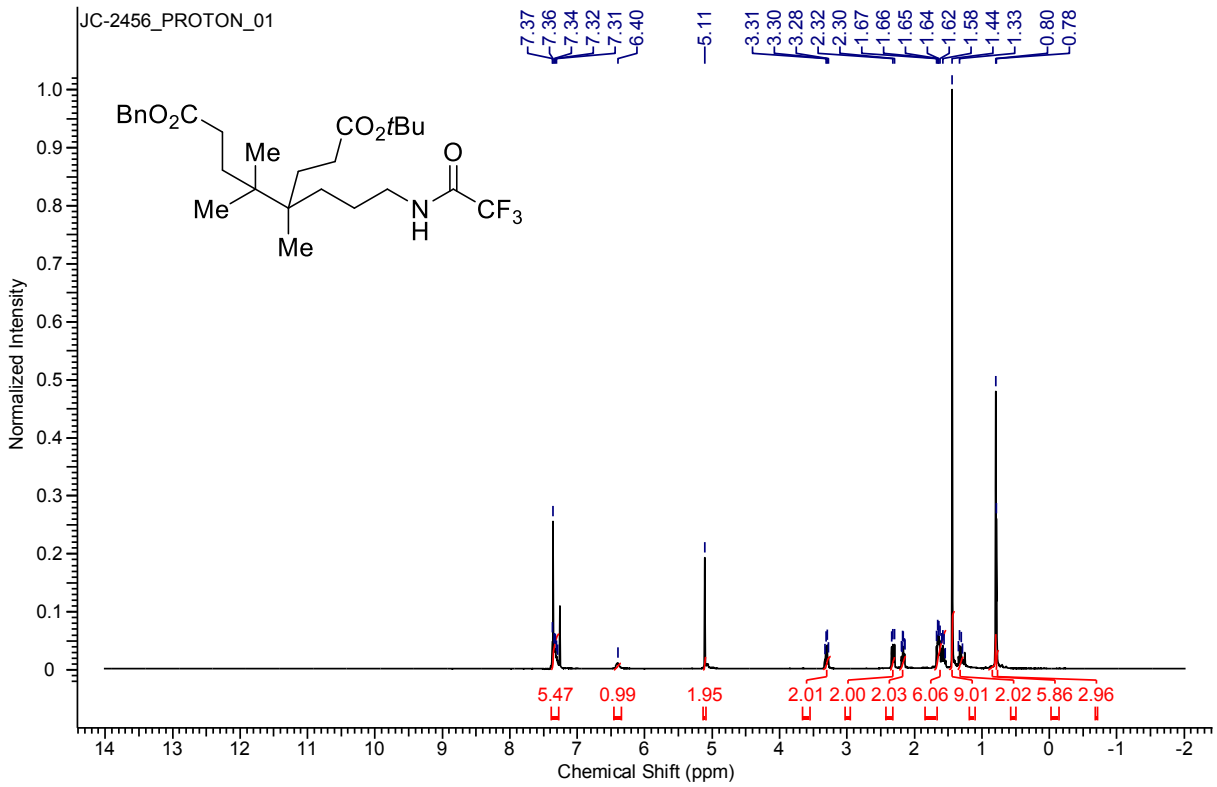

JC-2433_CARBON_01
173.55
80.12
68.84
40.67
37.03
33.43
31.50
30.31
28.05
25.79
23.26
21.48
18.16
-5.63
Normalized Intensity
Chemical Shift (ppm)

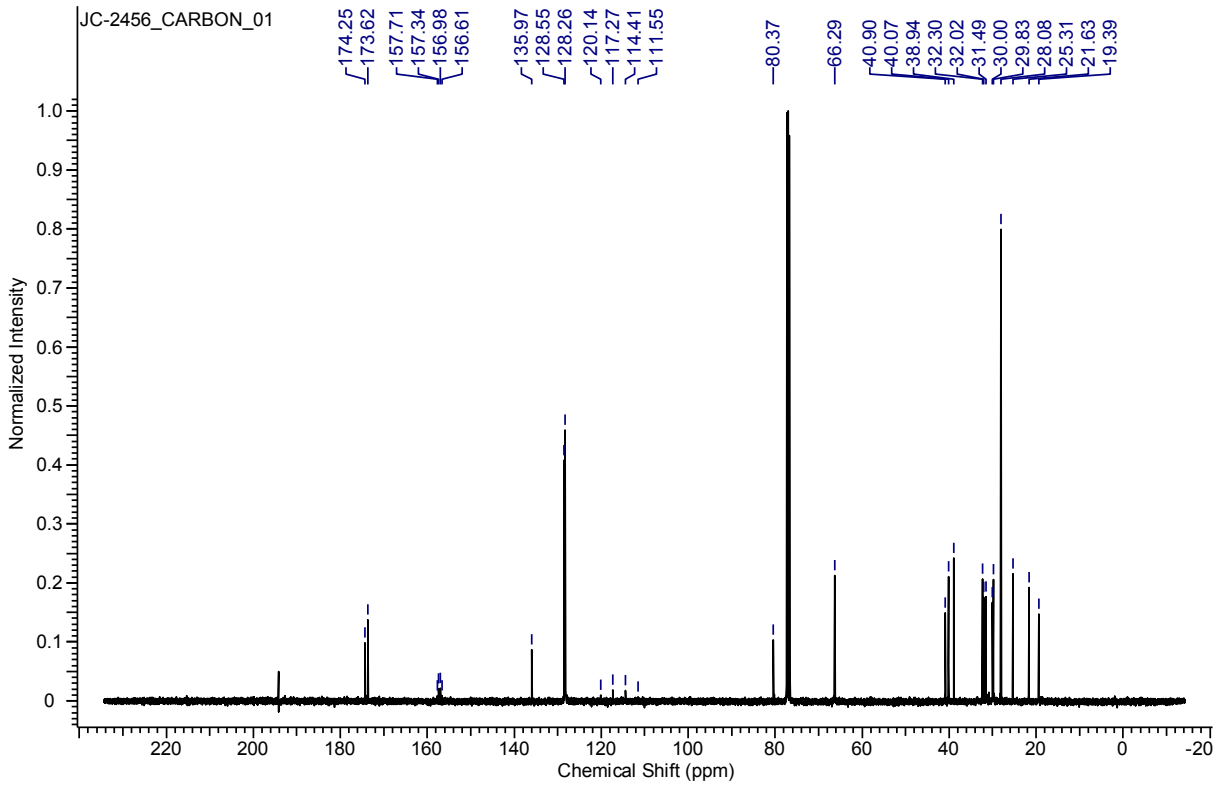

JC-2433_FLUORINE_01
-75.76
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

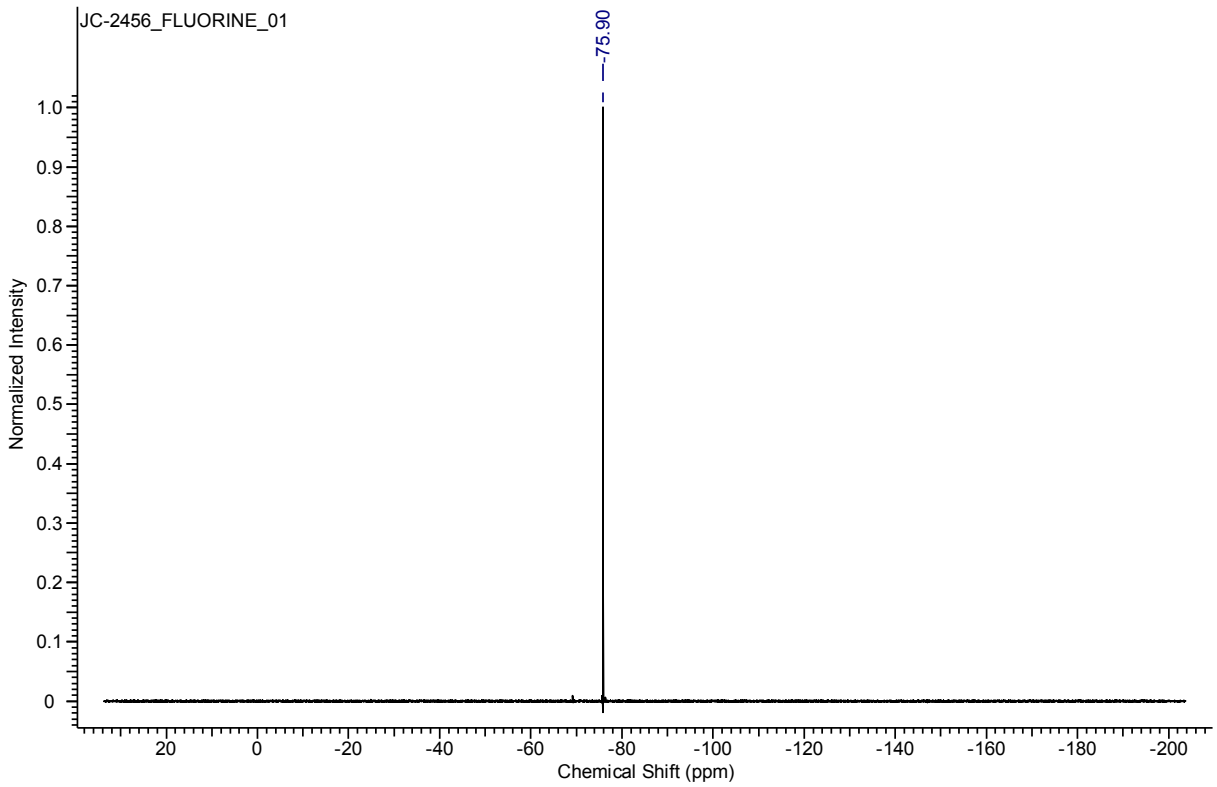

JC-2442a_PROTON_01
6.46
3.34
3.33
3.31
2.12
2.10
2.08
1.52
1.51
1.44
1.23
1.22
1.20
0.82
0.81
0.74
O
OtBu
Me
O
Me
N
H
CF3
Me
0.96
1.99
2.04
5.22
9.72
2.32
5.95
2.90
Normalized Intensity
Chemical Shift (ppm)

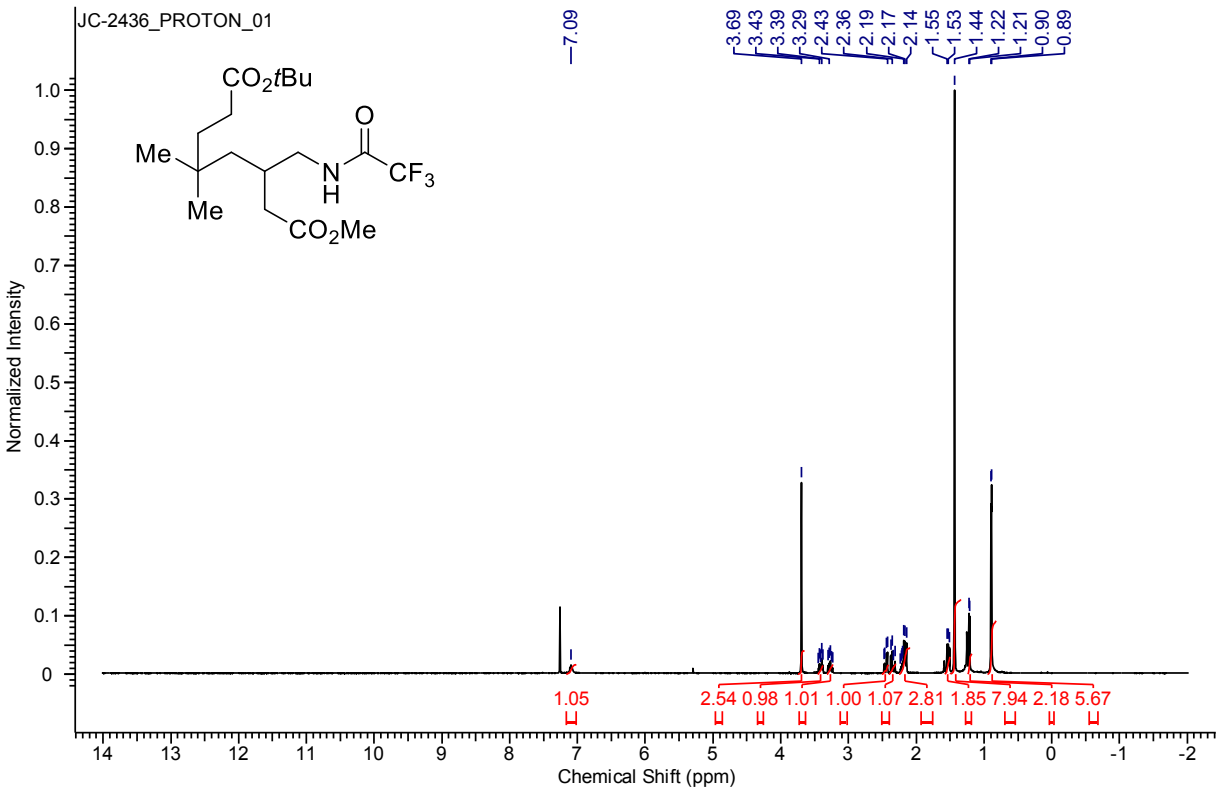

JC-2442a_CARBON_01
173.77
157.69
157.33
156.96
156.60
120.15
117.29
114.42
111.56
80.22
40.72
36.62
33.53
31.25
30.15
28.06
23.22
20.63
16.97
Normalized Intensity
Chemical Shift (ppm)

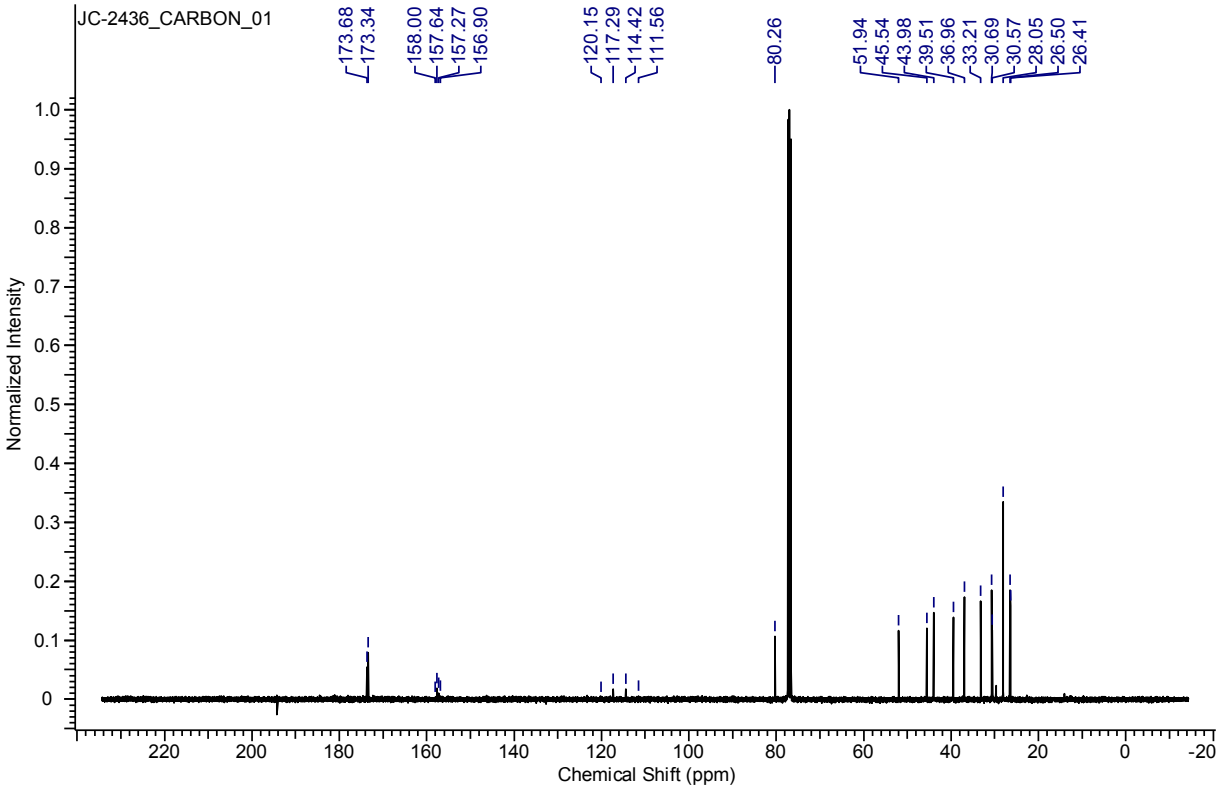

JC-2442a_FLUORINE_01
-75.97
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

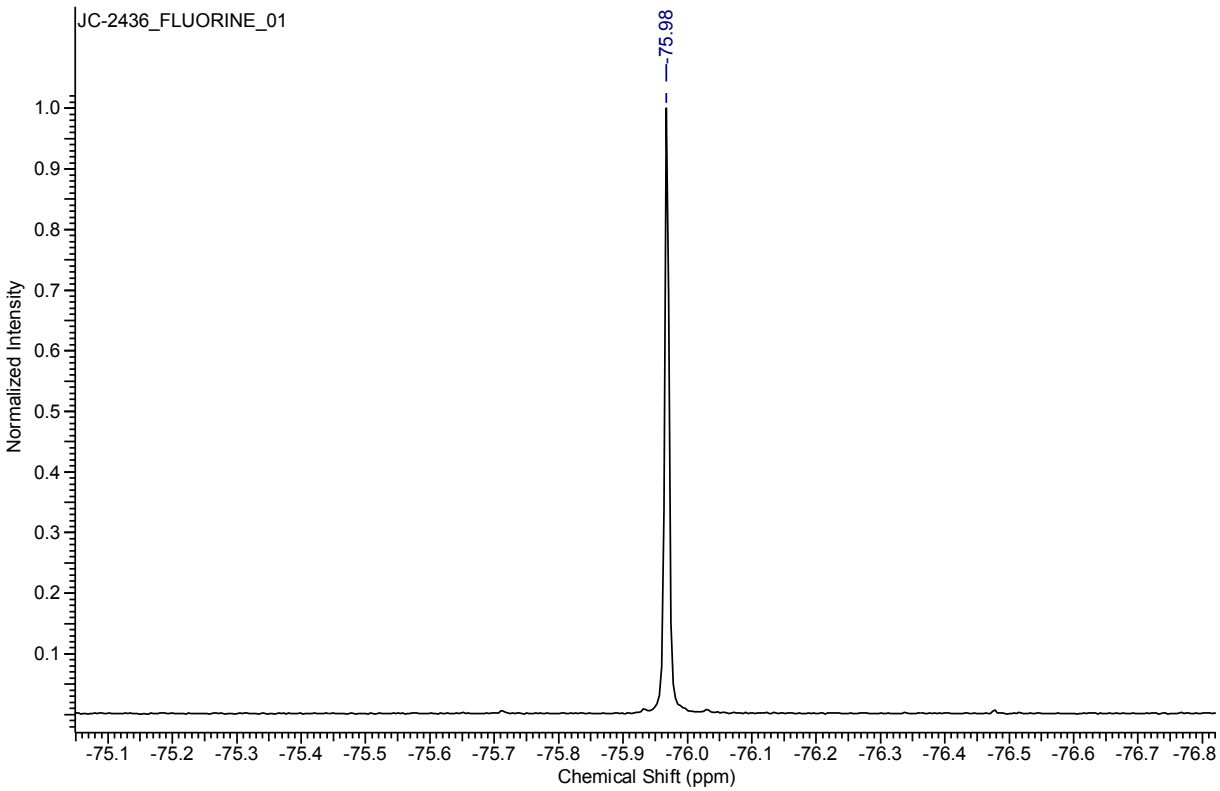

JC-2456_PROTON_01
7.37
7.36
7.34
7.32
7.31
6.40
5.11
3.31
3.30
3.28
2.32
2.30
1.67
1.66
1.65
1.64
1.62
1.58
1.44
1.33
0.80
0.78
BnO2C
CO2tBu
Me
Me
Me
O
N
H
CF3
Normalized Intensity
Chemical Shift (ppm)
5.47
0.99
1.95
2.01
2.00
2.03
6.06
9.01
2.02
5.86
2.96

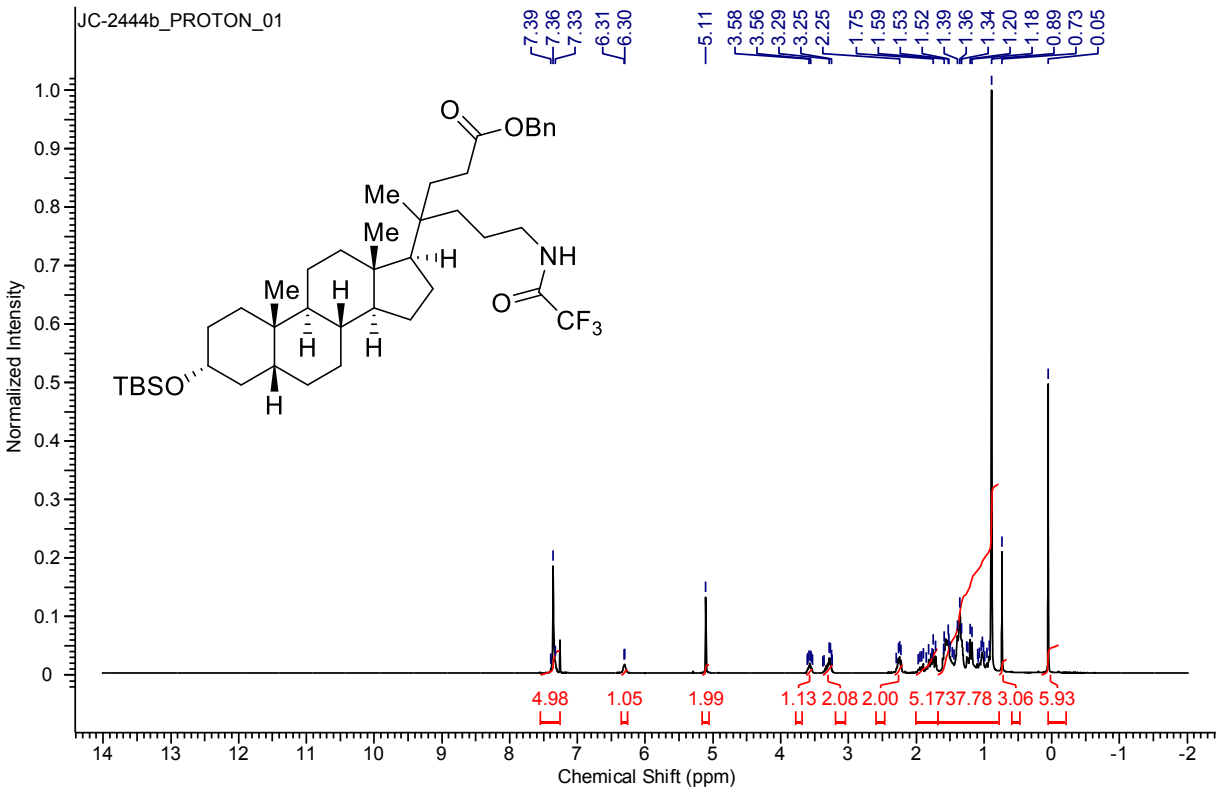

JC-2456_CARBON_01
174.25
173.62
157.71
157.34
156.98
156.61
135.97
128.55
128.26
120.14
117.27
114.41
111.55
80.37
66.29
40.90
40.07
38.94
32.30
32.02
31.49
30.00
29.83
28.08
25.31
21.63
19.39
Normalized Intensity
Chemical Shift (ppm)

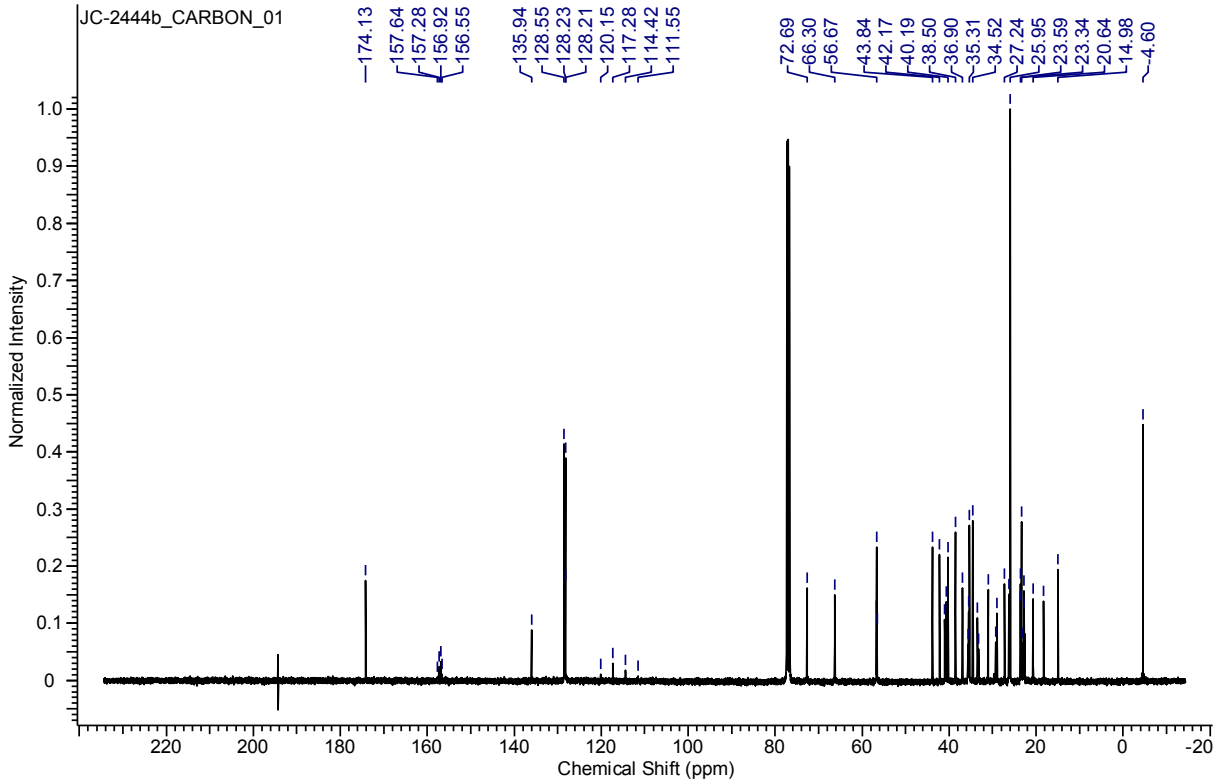

JC-2456_FLUORINE_01
-75.90
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)

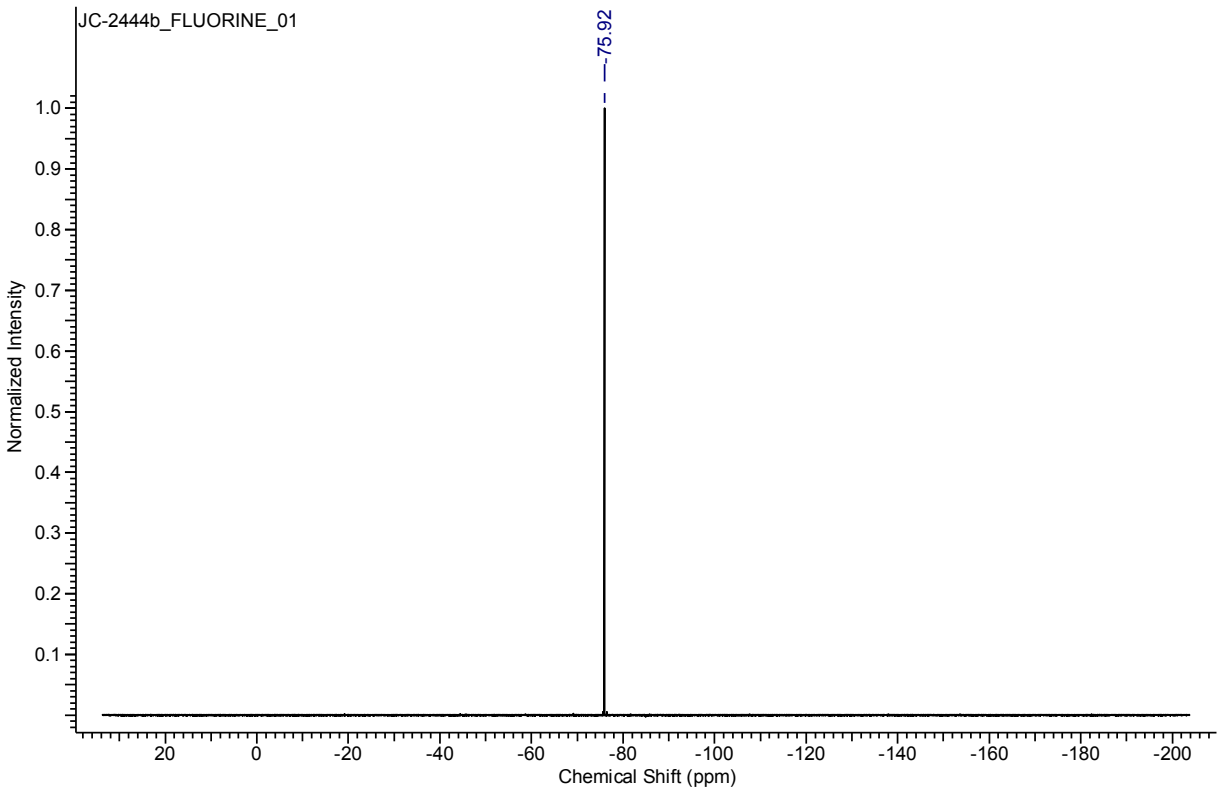

JC-2436_PROTON_01
CO2tBu
Me
Me
N
H
O
CF3
CO2Me
7.09
3.69
3.43
3.39
3.29
2.43
2.36
2.19
2.17
2.14
1.55
1.53
1.44
1.22
1.21
0.90
0.89
1.05
2.54 0.98 1.01 1.00 1.07 2.81 1.85 7.94 2.18 5.67
Normalized Intensity
Chemical Shift (ppm)

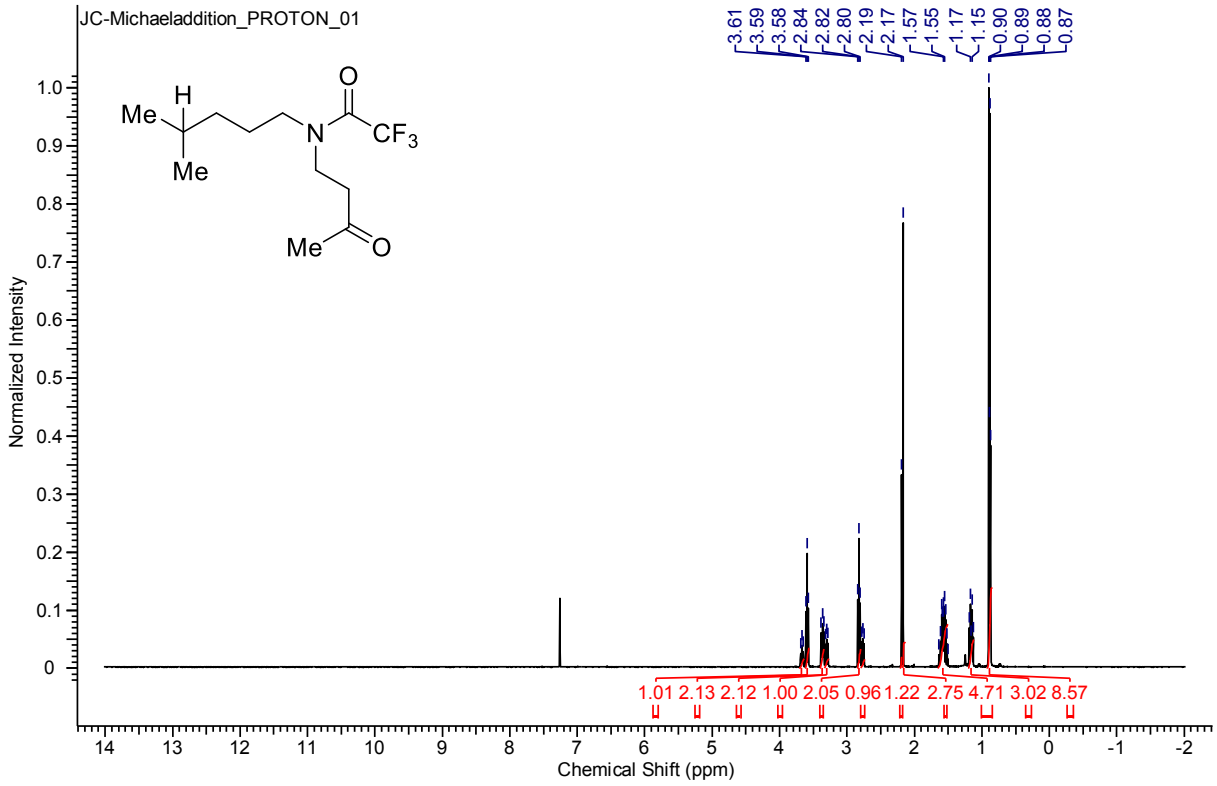

JC-2436_CARBON_01
173.68
173.34
158.00
157.64
157.27
156.90
120.15
117.29
114.42
111.56
80.26
51.94
45.54
43.98
39.51
36.96
33.21
30.69
30.57
28.05
26.50
26.41
Normalized Intensity
Chemical Shift (ppm)

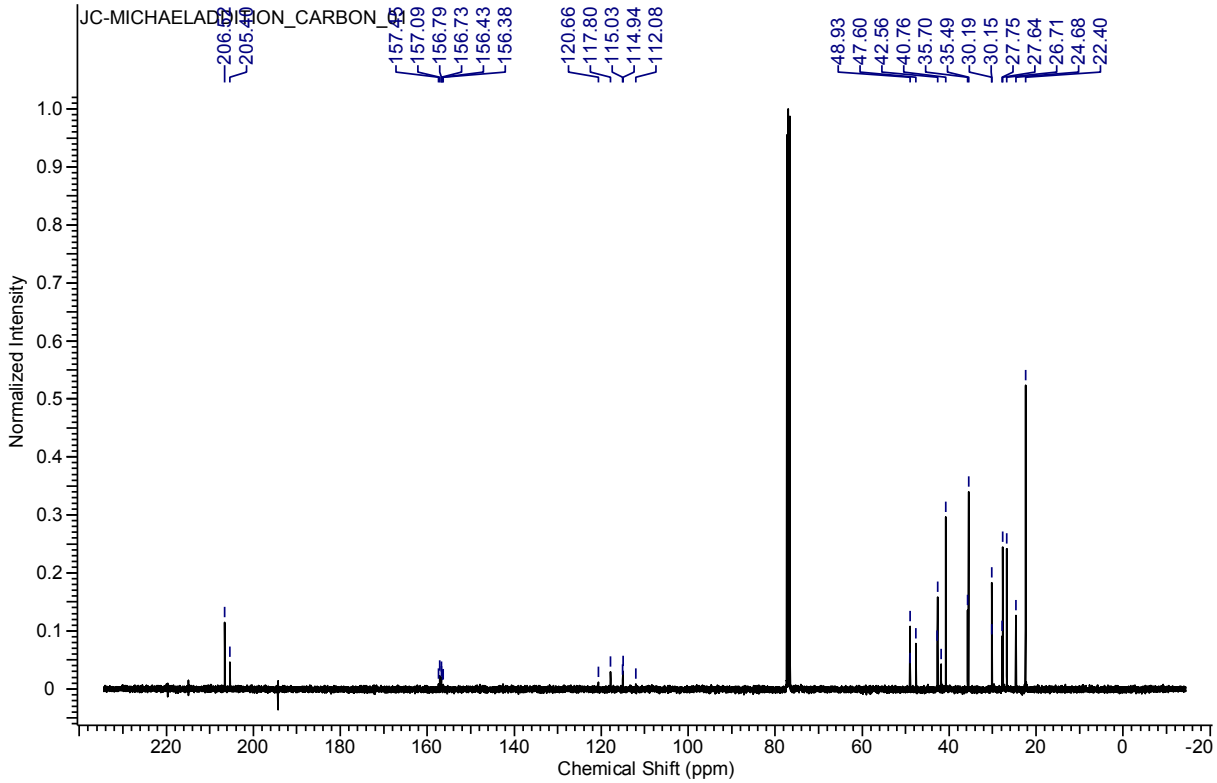

JC-2436_FLUORINE_01
-75.98
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
-75.1 -75.2 -75.3 -75.4 -75.5 -75.6 -75.7 -75.8 -75.9 -76.0 -76.1 -76.2 -76.3 -76.4 -76.5 -76.6 -76.7 -76.8
Chemical Shift (ppm)

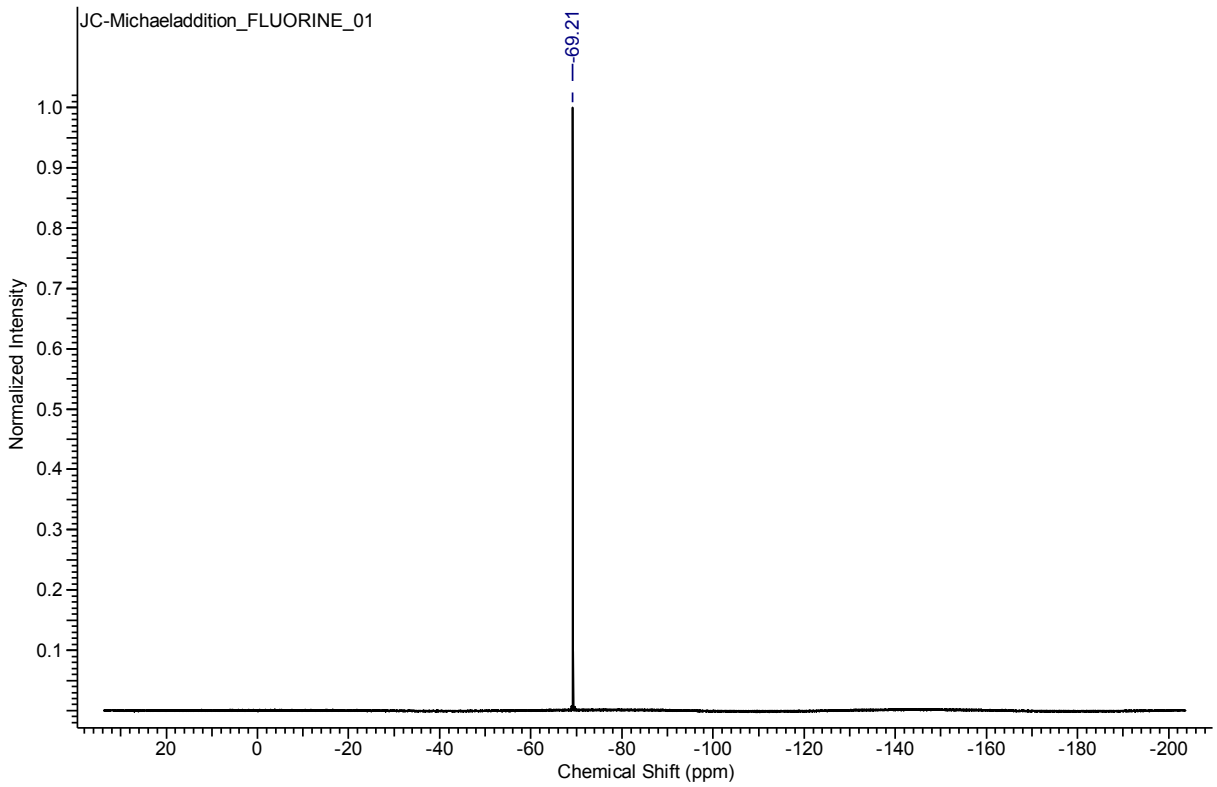

JC-2444b_PROTON_01
7.39
7.36
7.33
6.31
6.30
5.11
3.58
3.56
3.29
3.25
2.25
1.75
1.59
1.53
1.52
1.39
1.36
1.34
1.20
1.18
0.89
0.73
0.05
O
OBn
Me
Me
H
NH
O
CF3
Me
H
H
H
TBSO
H
4.98
1.05
1.99
1.13
2.08
2.00
5.17
37.78
3.06
5.93
Normalized Intensity
Chemical Shift (ppm)


JC-2444b_CARBON_01
174.13
157.64
157.28
156.92
156.55
135.94
128.55
128.23
128.21
120.15
117.28
114.42
111.55
72.69
66.30
56.67
43.84
42.17
40.19
38.50
36.90
35.31
34.52
27.24
25.95
23.59
23.34
20.64
14.98
4.60
Normalized Intensity
Chemical Shift (ppm)


JC-2444b_FLUORINE_01
-75.92
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
Chemical Shift (ppm)


JC-Michaeladdition_PROTON_01
3.61 3.59 3.58 2.84 2.82 2.80 2.19 2.17 1.57 1.55 1.17 1.15 0.90 0.89 0.88 0.87
1.01 2.13 2.12 1.00 2.05 0.96 1.22 2.75 4.71 3.02 8.57
Normalized Intensity
Chemical Shift (ppm)


JC-MICHAELADDITION_CARBON_01
206.49 205.40
157.45 157.09 156.79 156.73 156.43 156.38
120.66 117.80 115.03 114.94 112.08
48.93 47.60 42.56 40.76 35.70 35.49 30.19 30.15 27.75 27.64 26.71 24.68 22.40
Normalized Intensity
Chemical Shift (ppm)



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