

Nickel-Catalyzed Carbonylation of Difluoroalkyl Bromides with Arylboronic Acids

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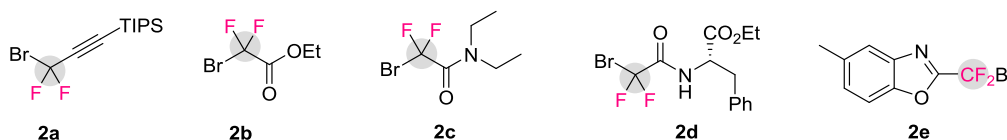
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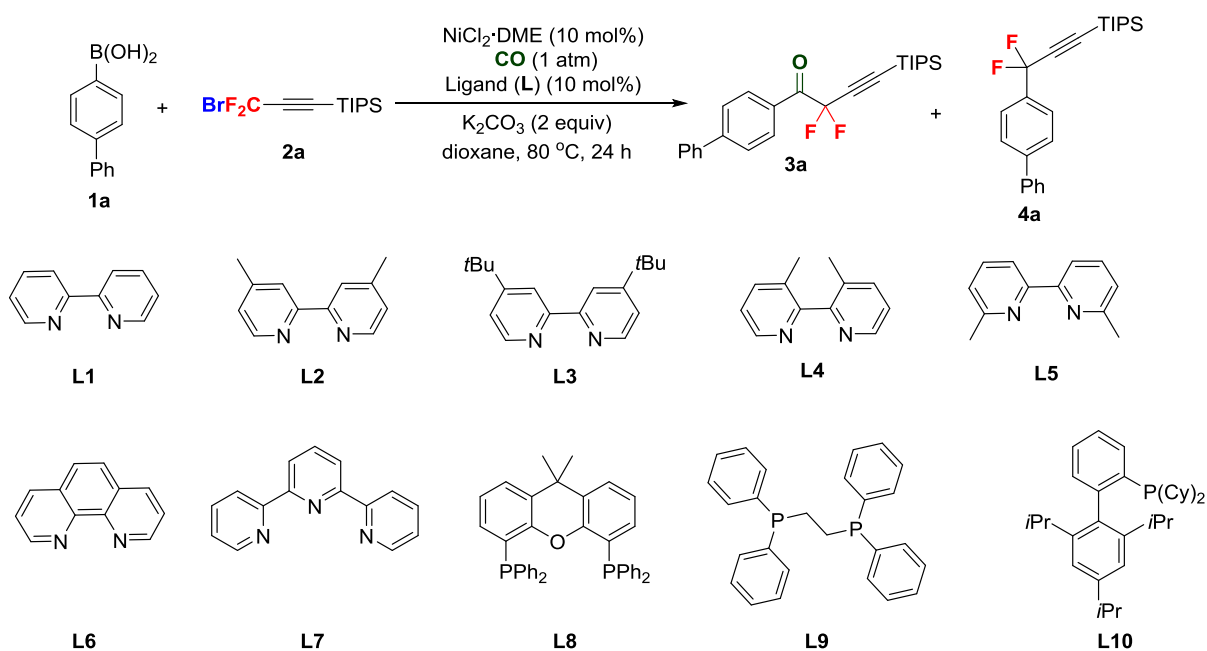
General information: ^1H NMR and ^{13}C NMR spectra were recorded on an Agilent MR 400 and Agilent MR 500 spectrometer. ^{19}F NMR was recorded on an Agilent MR 400 spectrometer (CFCl_3 as an external standard and low field is positive). Chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction.

Materials: All reagents were used as received from commercial sources or prepared as described in the literature. All reagents were weighed and handled under air, and refilled with an inert atmosphere of Ar at room temperature. Dioxane was distilled from sodium immediately before use. Compounds **2a**,¹ **2c**,² **2d**,³ and **2e**,⁴ were prepared according to the literature.



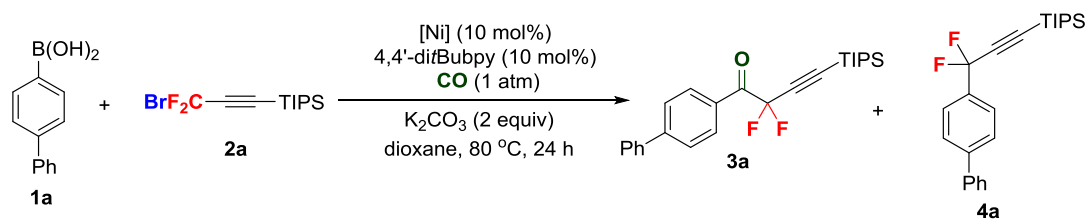
Screening for Ni-Catalyzed Carbonylation of Aryl Boronic Acid **1a with *gem*-Difluoropropargyl Bromide **2a** (Tables S1-S4).** To a 25 mL of Schlenk tube were added 4-biphenylboronic acid **1a** (0.3-0.6 mmol, 1.0-2.0 equiv), $\text{NiCl}_2\cdot\text{DME}$ (5-10 mol %) and ligand (**L**) (5-10 mol %) under air, followed by K_2CO_3 (0.6-1.2 mmol, 2.0-3.0 equiv). The mixture was then evacuated and backfilled with Ar (3 times). The mixture was evacuated again and backfilled with carbon monoxide CO (1 atm, balloon). Compound **2a** (0.3-0.6 mmol, 1.0-2.0 equiv) and dioxane (2 mL) were added subsequently. The Schlenk tube was screw capped and put into a preheated oil bath (50-80 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The yield was determined by ^{19}F NMR before working up. If necessary, the reaction mixture was diluted with ethyl acetate and H_2O . The resulting mixture was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 15:1) to give the product **3a**.

Table S1. Ligand Effect on Ni-Catalyzed Carbonylation of **1a with **2a**.^a**



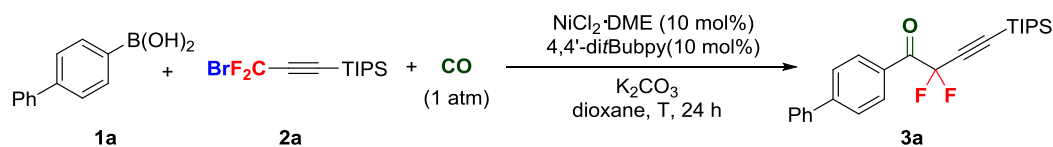
Entry	L (10 mol %)	3a / 4a Yield (%) ^b
1	L1	38 / ND
2	L2	31 / ND
3	L3	52 / ND
4	L4	ND / ND
5	L5	4 / ND
6	L6	41 / ND
7	L7	3 / 41
8	L8	ND / ND
9	L9	ND / ND
10	L10	ND / ND

^aReaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2a** (1.0 equiv), dioxane (2 mL). ^bDetermined by ¹⁹F NMR using fluorobenzene as an internal standard.

Table S2. Screening of Ni Sources for Ni-Catalyzed Carbonylation of 1a with 2a.^a

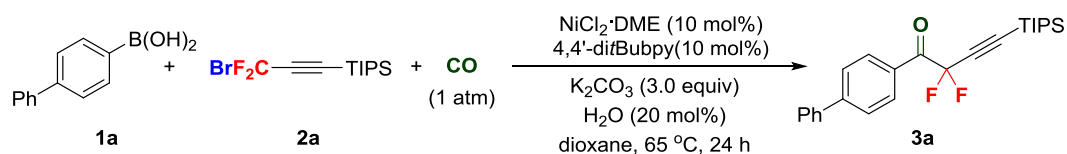
Entry	[Ni] (10 mol%)	3a / 4a Yield (%) ^b
1	NiCl ₂ ·DME	52 / ND
2	NiCl ₂	11 / ND
3	NiI ₂	35 / ND
4	NiCl ₂ (dppe)	34 / ND
5	Ni(NO ₃) ₂ ·6H ₂ O	22 / ND
6	Ni(COD) ₂	49 / ND

^aReaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv), **2a** (1.0 equiv), dioxane (2 mL). ^bDetermined by ¹⁹F NMR using fluorobenzene as an internal standard.

Table S3. Screening of Ni-Catalyzed Carbonylation of 1a with 2a.^a

Entry	1a / (mmol)	2a / (mmol)	K ₂ CO ₃ / (mmol)	T / °C	3a Yield (%) ^b
1	0.3	0.3	0.6	80 °C	52
2	0.3	0.3	0.6	60 °C	53
3	0.3	0.45	0.6	60 °C	56
4	0.45	0.3	0.9	60 °C	62
5	0.45	0.3	0.9	65 °C	70
6 ^c	0.45	0.3	0.9	65 °C	88

^aReaction conditions : dioxane (2 mL), 60 °C, 24 h. ^bDetermined by ¹⁹F NMR using fluorobenzene as internal standard. ^cH₂O (20 mol%) was added.

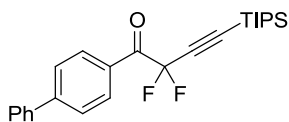
Table S4. Control Experiments of Ni-Catalyzed Carbonylation of 1a with 2a.^a

Entry	[Ni]	L	Base	H ₂ O (20 mol%)	[CO]	3a Yield (%) ^b
1	NiCl ₂ ·DME	4,4'-di- <i>t</i> Bubpy	K ₂ CO ₃	H ₂ O	CO	88
2	none	4,4'-di- <i>t</i> Bubpy	K ₂ CO ₃	H ₂ O	CO	ND
3	NiCl ₂ ·DME	none	K ₂ CO ₃	H ₂ O	CO	ND
4	NiCl ₂ ·DME	4,4'-di- <i>t</i> Bubpy	none	H ₂ O	CO	ND
5	NiCl ₂ ·DME	4,4'-di- <i>t</i> Bubpy	K ₂ CO ₃	none	CO	70
6	NiCl ₂ ·DME	4,4'-di- <i>t</i> Bubpy	K ₂ CO ₃	H ₂ O	none	ND

^aReaction conditions (unless otherwise specified): **1a** (0.45 mmol, 1.5 equiv), **2a** (0.3 mmol, 1.0 equiv), NiCl₂·DME (10 mol%), 4,4'-di-*t*Bubpy (10 mol%), K₂CO₃ (3.0 equiv), H₂O (20 mol%), dioxane (2 mL). ^bDetermined by ¹⁹F NMR using fluorobenzene as an internal standard.

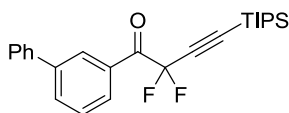
General Procedure for Ni-Catalyzed Carbonylation of Arylboronic Acids **1** with Difluoroalkyl Bromides **2**.

To a 25 mL of Schlenk tube were added aryl boronic acid **1** (0.45 mmol, 1.50 equiv), NiCl₂·DME (10 mol%) and 4,4'-di-*t*Bubpy (10 mol%), K₂CO₃ (3.0 equiv). The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). To the Schlenk tube were added difluoroalkyl bromide **2** (0.3 mmol, 1.0 equiv), H₂O (20 mol%) and dioxane (2 mL). The tube was screw capped and put into a preheated oil bath (65 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The yield was determined by ¹⁹F NMR using fluorobenzene as an internal standard. The reaction mixture was diluted with ethyl acetate and H₂O. The resulting mixture was then extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified with silica gel chromatography to give product **3** or **5**.



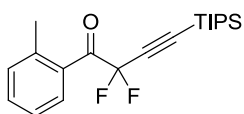
1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3a). The product (101 mg, 82% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 – 7.63 (m, 2H), 7.53 – 7.47 (m, 2H), 7.47 – 7.41 (m, 1H), 1.38 – 0.68 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.4 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.2 (t, J = 29.8 Hz), 147.3, 139.5, 131.1 (t, J = 1.9 Hz), 129.6, 129.1, 128.7, 127.4, 127.2, 106.7 (t, J = 245.0 Hz), 98.5 (t, J = 5.5 Hz), 96.4 (t, J = 36.8 Hz), 18.3, 10.9. IR (thin film) max 3060.6, 3032.8, 2945.6, 1712.8, 1604.5 cm^{-1} . MS (EI): m/z (%) 369 ($[\text{M}-i\text{Pr}]^+$), 181 (100). HRMS calcd. for $\text{C}_{22}\text{H}_{23}\text{OF}_2\text{Si}([\text{M}-i\text{Pr}]^+)$: 369.1486; Found: 369.1483.

Gram-Scale Synthesis: To a 500 mL of Schlenck tube were added arylboronic acid **1a** (4.84 mmol, 0.958 g, 1.5 equiv), $\text{NiCl}_2(\text{DME})$ (10 mol %), and 4,4'-di*t*Bubpy (10 mol%), K_2CO_3 (3.0 equiv). The mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon), **2a** (3.23 mmol, 1.0 g, 1.0 equiv), H_2O (20 mol%) and dioxane (22 mL) were added subsequently. The Schlenck tube was screw capped quickly and put into a preheated oil bath (65 $^\circ\text{C}$). After stirring for 24 h, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and H_2O . The resulting mixture was then extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 20:1) to give product **3a** (931.5 mg, 70% yield).

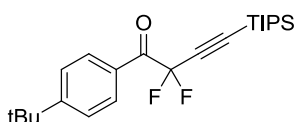


1-([1,1'-Biphenyl]-3-yl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3b). The product (105 mg, 85% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.43 (s, 1 H), 8.19 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.6

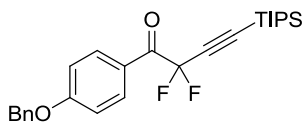
Hz, 1 H), 7.65 – 7.55 (m, 3H), 7.48 (t, $J = 7.4$ Hz, 2 H), 7.41 (t, $J = 7.3$ Hz, 1 H), 1.10 – 0.97 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.4 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.6 (t, $J = 29.7$ Hz), 141.8, 139.7, 133.1, 131.4, 129.07 (t, $J = 1.9$ Hz), 129.03, 129.02, 128.9, 128.0, 127.1, 106.6 (t, $J = 244.7$ Hz), 98.6 (t, $J = 5.3$ Hz), 96.4 (t, $J = 36.8$ Hz), 18.3, 10.8. IR (thin film) max 2945.5, 2892.3, 1716.3, 1599.7, 1463.4 cm^{-1} . MS (EI): m/z (%) 412 (M^+), 181 (100). HRMS calcd. for $\text{C}_{25}\text{H}_{30}\text{OF}_2\text{Si}$: 412.2034; Found: 412.2029.



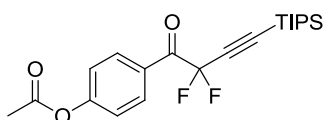
2,2-Difluoro-1-(*o*-tolyl)-4-(triisopropylsilyl)but-3-yn-1-one (3c). The product (72 mg, 68% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 1H), 7.31 (d, $J = 7.7$ Hz, 1H), 7.27 (t, $J = 7.9$ Hz, 1H), 2.54 (s, 3H), 1.08 – 0.98 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.3 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 187.1 (t, $J = 29.2$ Hz), 141.0, 132.9, 132.1, 131.0, 130.4 (t, $J = 3.5$ Hz), 125.3, 106.6 (t, $J = 244.9$ Hz), 97.8 (t, $J = 5.4$ Hz), 96.5 (t, $J = 36.8$ Hz), 21.5, 18.3, 10.8. IR (thin film) max 2946.0, 2867.7, 1718.9, 1602.6 cm^{-1} . MS (EI): m/z (%) 307 ($[\text{M}-i\text{Pr}]^+$), 119 (100). HRMS calcd. for $\text{C}_{17}\text{H}_{21}\text{OF}_2\text{Si}$ ($[\text{M}-i\text{Pr}]^+$): 307.1330; Found: 307.1334.



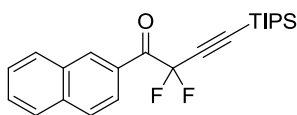
1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3d). The product (94 mg, 80% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 1.35 (s, 9H), 1.10 – 0.96 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.7 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.2 (t, $J = 29.7$ Hz), 158.6, 130.4, 128.2, 125.5, 106.7 (t, $J = 244.0$ Hz), 98.2 (t, $J = 5.6$ Hz), 96.6 (t, $J = 36.9$ Hz), 35.3, 30.9, 18.3, 10.8. IR (thin film) max 2960.9, 2867.9, 1714.9, 1588.9, 1605.3 cm^{-1} . MS (EI): m/z (%) 392 (M^+), 161 (100). HRMS calcd. for $\text{C}_{23}\text{H}_{34}\text{OF}_2\text{Si}$: 392.2347; Found: 392.2350.



1-(4-(Benzyloxy)phenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3e). The product (105 mg, 79% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, J = 8.8 Hz, 2H), 7.49-7.31 (m, 5H), 7.03 (d, J = 8.8 Hz, 2H), 5.16 (s, 2H), 1.17 – 0.97 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.2 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.1 (t, J = 29.4 Hz), 163.7, 135.8, 133.0 (t, J = 2.1 Hz), 128.7, 128.4, 127.4, 123.8, 114.7, 106.8 (t, J = 244.3 Hz), 97.9 (t, J = 5.3 Hz), 96.7 (t, J = 37.0 Hz), 70.3, 18.3, 10.8. IR (thin film) max 2945.4, 2892.1, 1704.5, 1600.8, 1509.8 cm^{-1} . MS (EI): m/z (%) 399 ($[\text{M}-i\text{Pr}]^+$), 91 (100). HRMS calcd. for $\text{C}_{23}\text{H}_{25}\text{O}_2\text{F}_2\text{Si}$ ($[\text{M}-i\text{Pr}]^+$): 399.1592; Found: 399.1593.

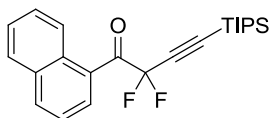


4-(2,2-Difluoro-4-(triisopropylsilyl)but-3-ynoyl)phenyl acetate (3f). The product (91 mg, 77% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 2.33 (s, 3H), 1.09 – 0.99 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.5 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.4 (t, J = 30.1 Hz), 168.4, 155.5, 132.1 (t, J = 2.3 Hz), 128.2, 121.8, 106.6 (t, J = 244.7 Hz), 98.7 (t, J = 5.3 Hz), 96.1 (t, J = 36.8 Hz), 21.1, 18.3, 10.8. IR (thin film) max 2946.4, 2867.9, 1777.2, 1715.8, 1600.8 cm^{-1} . MS (EI): m/z (%) 394 (M^+), 309 (100). HRMS calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3\text{F}_2\text{Si}$: 394.1776; Found: 394.1779.

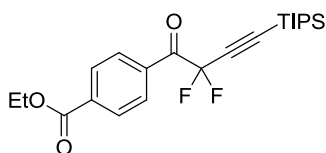


2,2-Difluoro-1-(naphthalen-2-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3g). The product (64 mg, 55% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.80 (s, 1H), 8.16 (dd, J = 8.7 Hz, 1.3 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.61 – 7.55 (m, 1H), 1.13 – 0.96 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -87.9 (s, 2F). ^{13}C NMR (126

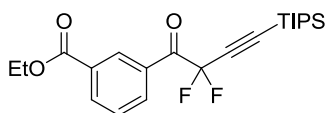
MHz, CDCl₃) δ 184.5 (t, J = 29.7 Hz), 136.1, 133.2 (t, J = 2.5 Hz), 132.1, 130.0, 129.5, 128.5, 128.1, 127.8, 127.1, 124.9 (t, J = 1.5 Hz) 106.7 (t, J = 244.0 Hz), 98.5 (t, J = 5.4 Hz), 96.6 (t, J = 36.7 Hz), 18.3, 10.8. IR (thin film) max 2945.4, 1718.0, 1627.9 cm⁻¹. MS (EI): m/z (%) 386 (M⁺), 155 (100). HRMS calcd. for C₂₃H₂₈OF₂Si: 386.1878; Found: 386.1873.



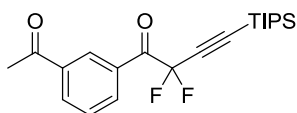
2,2-Difluoro-1-(naphthalen-1-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3h). The product (52 mg, 45% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, J = 8.6 Hz, 1H), 8.38 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 1.04 – 0.94 (m, 21H). ¹⁹F NMR (376 MHz, CDCl₃) δ -87.5 (s, 2F). ¹³C NMR (126 MHz, CDCl₃) δ 187.2 (t, J = 29.5 Hz), 134.6, 133.9, 131.2, 130.7 (t, J = 3.7 Hz), 128.8, 128.7, 128.4, 126.8, 125.4, 123.9, 106.7 (t, J = 246.0 Hz), 97.9 (t, J = 5.4 Hz), 96.7 (t, J = 37.0 Hz), 18.3, 10.8. IR (thin film) max 2945.5, 2892.5, 1706.2, 1594.4, 1509.0 cm⁻¹. MS (EI): m/z (%) 386 (M⁺), 155(100). HRMS calcd. for C₂₃H₂₈OF₂Si: 386.1878; Found: 386.1873.



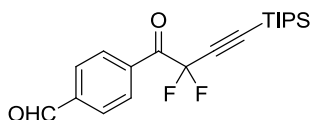
Ethyl 4-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzoate (3i). The product (63 mg, 51% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 15:1). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 8.4 Hz, 2H), 8.14 (d, J = 8.4 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.10 – 0.97 (m, 21H). ¹⁹F NMR (376 MHz, CDCl₃) δ -88.7 (s, 2F). ¹³C NMR (126 MHz, CDCl₃) δ 184.2 (t, J = 30.4 Hz), 165.4, 135.4, 134.0, 130.2 (t, J = 2.1 Hz), 129.6 106.5 (t, J = 244.6 Hz), 99.1 (t, J = 5.5 Hz), 95.8 (t, J = 36.8 Hz), 61.7, 18.3, 14.2, 10.8. IR (thin film) max 2946.1, 2868.0, 1720.3, 1610.7, 1575.0 cm⁻¹. MS (EI): m/z (%) 408 (M⁺), 177 (100). HRMS calcd. for C₂₂H₃₀O₃F₂Si: 408.1932; Found: 408.1935.



Ethyl 3-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzoate (3j). The product (54 mg, 52% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 15:1). ^1H NMR (400 MHz, CDCl_3) δ 8.82 (s, 1H), 8.35 (d, $J = 7.9$ Hz, 1H), 8.31 (dd, $J = 7.8$ Hz, 1.4 Hz, 1H), 7.58 (t, $J = 7.8$ Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.08 – 0.95 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.8 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.8 (t, $J = 30.1$ Hz), 165.2, 135.2, 134.2, 131.3 (t, $J = 2.1$ Hz), 131.2, 131.0, 128.8, 106.5 (t, $J = 244.9$ Hz), 99.0 (t, $J = 5.5$ Hz), 95.9 (t, $J = 36.8$ Hz), 61.5, 18.2, 14.2, 10.8. IR (thin film) max 2946.4, 2868.1, 1723.0, 1604.3 cm^{-1} . MS (EI): m/z (%) 365 ($[\text{M}-i\text{Pr}]^+$), 365 (100). HRMS calcd. for $\text{C}_{19}\text{H}_{23}\text{O}_3\text{F}_2\text{Si}$ ($[\text{M}-i\text{Pr}]^+$): 365.1385; Found: 365.1381.

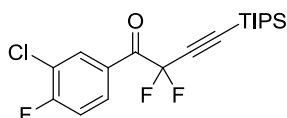


1-(3-Acetylphenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3k). The product (97 mg, 85% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 8.0$ Hz, 1H), 8.06 (s, 1H), 7.93 (d, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 2.21 (s, 3H), 1.07 – 0.98 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.4 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.4 (t, $J = 30.3$ Hz), 168.9, 138.7, 131.2, 129.3, 126.3, 126.2, 120.8, 106.6 (t, $J = 244.7$ Hz), 98.9 (t, $J = 5.5$ Hz), 96.1 (t, $J = 36.8$ Hz), 24.4, 18.3, 10.8. IR (thin film) max 3304.8 (br), 2946.0, 1717.3, 1671.9, 1552.9 cm^{-1} . MS (EI): m/z (%) 378 (M^+), 350 (100). HRMS calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_2\text{F}_2\text{Si}$: 378.1827; Found: 378.1838.

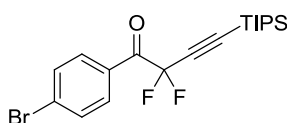


4-(2,2-Difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzaldehyde (3l). The product (56 mg, 51% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 6:1). ^1H NMR (400 MHz, CDCl_3) δ 10.12 (s, 1H), 8.32 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 8.4$ Hz, 2H),

0.98 – 1.04 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.8 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 191.2, 184.0 (t, $J = 30.5$ Hz), 139.8, 135.1, 130.9 (t, $J = 2.1$ Hz), 129.4, 106.4 (t, $J = 244.9$ Hz), 99.5 (t, $J = 5.4$ Hz), 95.7 (t, $J = 36.7$ Hz), 18.3, 10.8. IR (thin film) max 2920.1, 1733.0, 1675.1, 1625.5 cm^{-1} . MS (EI): m/z (%) 364 (M^+), 133 (100). HRMS calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{F}_2\text{Si}$: 364.1670; Found: 364.1680.

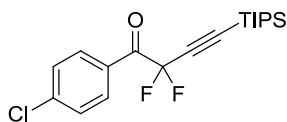


1-(3-Chloro-4-fluorophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3m). The product (47 mg, 40% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 6.9$ Hz, 1.7 Hz, 1H), 8.14 – 8.08 (m, 1H), 7.27 (t, $J = 8.5$ Hz, 1H), 1.08 – 0.98 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.5 (s, 2F), -103.9 – -104.0 (m, 1F). ^{13}C NMR (126 MHz, CDCl_3) δ 182.2 (t, $J = 30.6$ Hz), 161.9 (d, $J = 260.2$ Hz), 133.4 – 133.3 (m), 131.0 (dt, $J = 8.8$ Hz, 2.5 Hz), 127.9 (d, $J = 3.8$ Hz), 122.1 (d, $J = 18.3$ Hz), 117.0 (d, $J = 21.9$ Hz), 106.3 (t, $J = 244.3$ Hz), 99.4 (t, $J = 5.5$ Hz), 95.7 (t, $J = 36.7$ Hz), 18.3, 10.8. IR (thin film) max 2946.8, 2868.1, 1721.6, 1594.7, 1498.9 cm^{-1} . MS (EI): m/z (%) 345 ($[\text{M}-i\text{Pr}]^+$), 191 (100). HRMS calcd. for $\text{C}_{16}\text{H}_{17}\text{OF}_3\text{ClSi}$ ($[\text{M}-i\text{Pr}]^+$): 345.0689; Found: 345.0680.

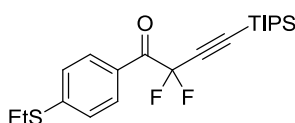


1-(4-Bromophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3n). The product (81 mg, 65% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 1.17 – 0.83 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.6 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.7 (t, $J = 30.4$ Hz), 132.0, 131.7 (t, $J = 2.1$ Hz), 130.2, 129.6, 106.5 (t, $J = 244.8$ Hz), 98.9 (t, $J = 5.5$ Hz), 96.0 (t, $J = 36.8$ Hz), 18.3, 10.8. IR (thin film) max 2945.8, 2892.9, 1718.6, 1585.2 cm^{-1} .

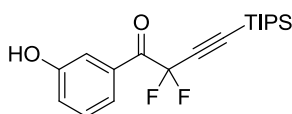
MS (EI): m/z (%) 371 ($[M-iPr]^+$), 183 (100). HRMS calcd. for $C_{16}H_{18}OF_2SiBr$ ($[M-iPr]^+$): 371.0278; Found: 371.0280.



1-(4-Chlorophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3o). The product (78 mg, 70% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). 1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 1.10 – 0.98 (m, 21H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.6 (s, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5 (t, J = 30.4 Hz), 141.3, 131.7 (t, J = 2.3 Hz), 129.2, 129.0, 106.5 (t, J = 244.8 Hz), 98.9 (t, J = 5.4 Hz), 96.0 (t, J = 36.7 Hz), 18.3, 10.8. IR (thin film) max 2946.2, 2893.3, 1718.3, 1590.1, 1463.8 cm^{-1} . MS (EI): m/z (%) 327 ($[M-iPr]^+$), 139 (100). HRMS calcd. for $C_{16}H_{18}OF_2ClSi$ ($[M-iPr]^+$): 327.0784; Found: 327.0787.

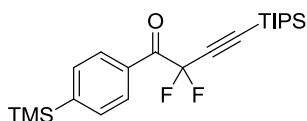


1-(4-(Ethylthio)phenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3p). The product (97 mg, 81% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). 1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 3.03 (q, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.12-0.94 (m, 21H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.4 (s, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5 (t, J = 29.5 Hz), 147.4, 130.7, 127.0, 125.6, 106.6 (t, J = 245.2 Hz), 98.2 (t, J = 5.5 Hz), 96.4 (t, J = 37.2 Hz), 25.7, 18.3, 13.7, 10.8. IR (thin film) max 2945.2, 2892.7, 1706.6, 1588.9, 1490.6 cm^{-1} . MS (EI): m/z (%) 396 (M^+), 165 (100). HRMS calcd. for $C_{21}H_{30}OF_2SiS$: 396.1755; Found: 396.1745.

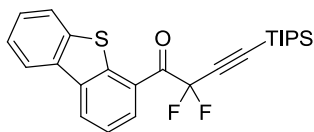


2,2-Difluoro-1-(3-hydroxyphenyl)-4-(triisopropylsilyl)but-3-yn-1-one (3q). The product (69 mg, 65% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether /

EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, J = 7.8 Hz, 1H), 7.63 (s, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.14 (ddd, J = 8.1 Hz, 2.6 Hz, 0.8 Hz, 1H), 5.51 (br, 1 H), 1.62 – 0.59 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.3 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.5 (t, J = 29.8 Hz), 155.8, 132.1, 129.9, 123.2 (t, J = 2.4 Hz), 122.1, 116.6 (t, J = 1.7 Hz), 106.6 (t, J = 244.9 Hz), 98.7 (t, J = 5.5 Hz), 96.2 (t, J = 36.9 Hz), 18.3, 10.8. IR (thin film) max 3446.6 (br), 2946.2, 1702.1, 1598.9, 1459.5 cm^{-1} . MS (EI): m/z (%) 352 (M^+), 121 (100). HRMS calcd. for $\text{C}_{19}\text{H}_{26}\text{O}_2\text{F}_2\text{Si}$: 352.1670; Found: 352.1678.

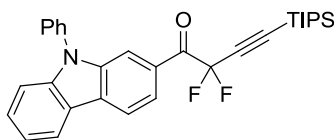


2,2-Difluoro-4-(triisopropylsilyl)-1-(4-(trimethylsilyl)phenyl)but-3-yn-1-one (3r). The product (101 mg, 82% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 1.14-0.82 (m, 21H), 0.30 (s, 9H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.7 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.8 (t, J = 29.7 Hz), 149.4, 133.3, 130.9, 129.1, 106.7 (t, J = 245.4 Hz), 98.4 (t, J = 5.5 Hz), 96.4 (t, J = 37.0 Hz), 18.3, 10.8, -1.5. IR (thin film) max 2947.2, 2867.9, 1716.7, 1596.4, 1544.2 cm^{-1} . MS (EI): m/z (%) 393 ($[\text{M-Me}]^+$), 177 (100). HRMS calcd. for $\text{C}_{21}\text{H}_{31}\text{OF}_2\text{Si}_2$ ($[\text{M-Me}]^+$): 393.1882; Found: 393.1878.

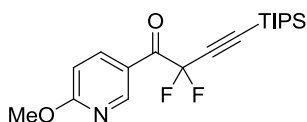


1-(Dibenzo[*b,d*]thiophen-2-yl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3s). The product (88 mg, 66% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.55 (dd, J = 7.8 Hz, 1.0 Hz, 1H), 8.46 (dd, J = 7.8 Hz, 0.9 Hz, 1H), 8.26 – 8.16 (m, 1H), 7.99 – 7.95 (m, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.57 – 7.51 (m, 2H), 1.10 – 0.99 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -86.6 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 183.6 (t, J = 30.1 Hz), 142.0, 141.7, 137.6, 133.7, 131.1 (t, J = 3.6 Hz), 127.6, 127.5, 124.9, 124.7, 123.7, 122.9, 121.4, 106.5 (t, J = 245.0 Hz), 98.9 (t, J = 5.3 Hz), 96.5 (t, J = 36.9 Hz), 18.4,

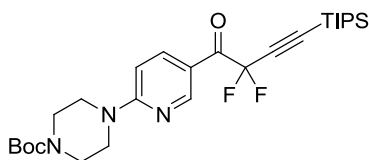
10.9. IR (thin film) max 2945.9, 2867.2, 1718.6, 1691.1, 1585.1 cm^{-1} . MS (EI): m/z (%) 442 (M^+), 183 (100). HRMS calcd. for $\text{C}_{25}\text{H}_{28}\text{OF}_2\text{SiS}$: 442.1598; Found: 442.1601.



2,2-Difluoro-1-(9-phenyl-9H-carbazol-2-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3t). The product (77 mg, 51% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 9.05 (s, 1H), 8.27 (dd, $J = 8.8$ Hz, 1.2 Hz, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.69 – 7.62 (m, 2H), 7.58 – 7.51 (m, 3H), 7.51 – 7.44 (m, 1H), 7.44 – 7.34 (m, 3H), 1.12 – 0.96 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -87.2 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.0 (t, $J = 29.2$ Hz), 144.3, 141.9, 136.6, 130.2, 128.6, 128.4, 127.1, 127.0, 124.4 (t, $J = 2.1$ Hz), 123.3, 123.1, 122.9, 121.3, 120.7, 110.4, 109.7, 107.1 (t, $J = 244.4$ Hz), 97.9 (t, $J = 5.3$ Hz), 97.1 (t, $J = 36.9$ Hz), 18.4, 10.9. IR (thin film) max 2944.9, 2866.3, 1698.5, 1595.0, 1503.3 cm^{-1} . MS (EI): m/z (%) 501 (M^+), 270 (100). HRMS calcd. for $\text{C}_{31}\text{H}_{33}\text{NOF}_2\text{Si}$: 501.2299; Found: 501.2306.

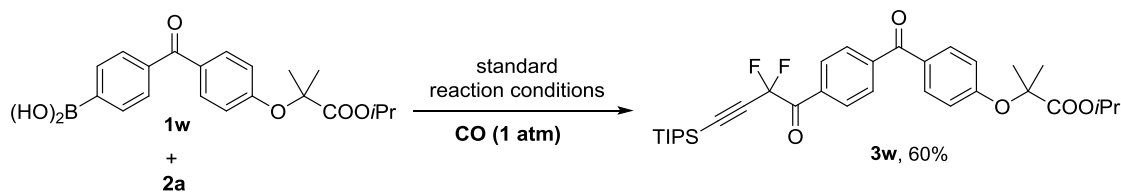


2,2-Difluoro-1-(6-methoxypyridin-3-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3u). The product (88 mg, 80% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 9.03 (d, $J = 2.3$ Hz, 1H), 8.28 (dd, $J = 8.8$ Hz, 2.3 Hz, 1H), 6.81 (d, $J = 8.8$ Hz, 1H), 4.02 (s, 3H), 1.18 – 0.92 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.8 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 182.7 (t, $J = 30.7$ Hz), 167.4, 151.8 (t, $J = 3.4$ Hz), 139.8 (t, $J = 1.8$ Hz), 120.8, 111.2, 106.5 (t, $J = 244.6$ Hz), 98.5 (t, $J = 5.4$ Hz), 96.0 (t, $J = 36.9$ Hz), 54.3, 18.3, 10.8. IR (thin film) max 2947.2, 2868.0, 1711.6, 1601.4, 1498.1 cm^{-1} . MS (EI): m/z (%) 367 (M^+), 136 (100). HRMS calcd. for $\text{C}_{19}\text{H}_{27}\text{NO}_2\text{F}_2\text{Si}$: 367.1779; Found: 367.1781.



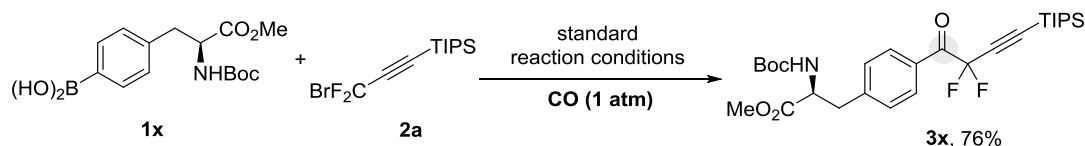
tert-Butyl 4-(5-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)pyridin-2-yl)piperazine-1-carboxylate (3v). The product (53 mg, 61% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.98 (d, J = 1.2 Hz, 1H), 8.16 (dd, J = 9.2 Hz, 2.1 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 3.81 – 3.70 (m, 4H), 3.62 – 3.48 (m, 4H), 1.48 (s, 9H), 1.07 – 1.00 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.3 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 182.1 (t, J = 30.2 Hz), 160.2, 154.6, 153.1 (t, J = 3.1 Hz), 139.1, 116.4, 106.8 (t, J = 244.2 Hz), 105.1, 97.5 (t, J = 5.4 Hz), 96.6 (t, J = 37.2 Hz), 80.3, 28.4, 18.3, 10.8. IR (thin film) max 2944.9, 2866.9, 1695.3, 1596.8 cm^{-1} . MS (EI): m/z (%) 521 (M^+), 190 (100). HRMS calcd. for $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_3\text{F}_2\text{Si}$: 521.2885; Found: 521.2878.

Late-Stage Difluoroalkylation of Biological Active Molecules

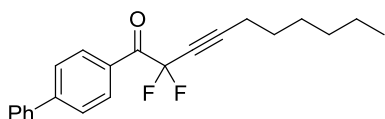


Isopropyl 2-(4-(4-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)-benzoyl)phenoxy)-2-methylpropanoate (3w). To a 25 mL of Schlenk tube were added arylboronic acid **1w**⁵ (0.45 mmol, 1.50 equiv), $\text{NiCl}_2\cdot\text{DME}$ (10 mol %) and 4,4'-di*t*Bubpy (10 mol %) under air, followed by K_2CO_3 (0.9 mmol, 3.0 equiv). The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). **2a** (0.3 mmol, 1.0 equiv), H_2O (20 mol %) and dioxane (2 mL) were added subsequently. The tube was screw capped and put into a preheated oil bath (65 $^\circ\text{C}$). After stirring for 24 h, the reaction mixture was cooled to room temperature. The product **3w** (105 mg, 60% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 5:1). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.08 (hept, J = 6.3 Hz, 1H), 1.66 (s, 6H), 1.20 (d, J = 6.3 Hz, 6H), 1.10 – 0.96 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.8 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 194.2, 184.0 (t, J = 30.2 Hz), 172.9, 160.2,

143.3, 132.9, 132.1, 130.2 (t, $J = 2.0$ Hz), 129.6, 129.4, 117.3, 106.5 (t, $J = 244.2$ Hz), 99.1 (t, $J = 5.4$ Hz), 96.0 (t, $J = 36.9$ Hz), 79.5, 69.4, 25.3, 21.5, 18.3, 10.8. IR (thin film) max 2945.3, 2893.1, 2177.0, 1719.9, 1660.1, 1598.4 cm^{-1} . MS (DRAT): m/z (%) 585 ($[\text{M}+\text{H}]^+$). HRMS(DRAT): calcd for $\text{C}_{33}\text{H}_{42}\text{O}_5\text{F}_2\text{Si}$: 584.2770 ; Found: 585.2838 ($[\text{M}+\text{H}]^+$).

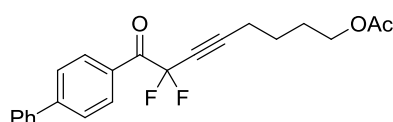


(S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-(4-(2,2-difluoro-4-(triisopropylsilyl)-but-3-ynoyl)phenyl)propanoate (3x). To a 25 mL of Schlenck tube were added arylboronic acid **1x** (0.3 mmol, 1.50 equiv), $\text{NiCl}_2 \cdot \text{DME}$ (10 mol %) and 4,4'-di-*t*-Bubpy (10 mol %) under air, followed by K_2CO_3 (0.6 mmol, 3.0 equiv); The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). **2a** (0.2 mmol, 1.0 equiv), H_2O (20 mol %) and dioxane (2 mL) were added subsequently. The tube was screw capped and put into a preheated oil bath (65 $^\circ\text{C}$). After stirring for 24 h, the reaction mixture was cooled to room temperature. The product **3x** (81.6 mg, 76% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 5:1). ^1H NMR (400 MHz, CDCl_3) δ 8.07 (d, $J = 7.6$ Hz, 2H), 7.22 (d, $J = 7.6$ Hz, 2H), 5.03 (d, $J = 7.2$ Hz, 1H), 4.59 (m, 1H), 3.68 (s, 3H), 3.25 – 3.03 (m, 2H), 1.38 (s, 9H), 1.05 – 0.91 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.5 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.1 (t, $J = 30.1$ Hz), 171.7, 155.0, 143.7, 130.6, 129.6, 106.6 (t, $J = 244.1$ Hz), 98.4 (t, $J = 5.4$ Hz), 96.3 (t, $J = 36.5$ Hz), 80.2, 54.1, 52.3, 38.4, 28.2, 18.3, 10.8. IR (thin film) max 3374.2, 2947.1, 2867.7, 1747.8, 1715.7 cm^{-1} . MS (DRAT): m/z (%) 555 ($\text{M}+\text{NH}_4$) $^+$. HRMS (DRAT): calcd for $\text{C}_{28}\text{H}_{41}\text{O}_5\text{F}_2\text{NSi}$: 537.2722; Found: 555.3061 ($\text{M}+\text{NH}_4$) $^+$.

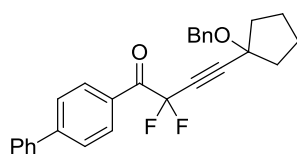


1-([1,1'-Biphenyl]-4-yl)-2,2-difluorodec-3-yn-1-one (5a). The product (59 mg, 57% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.26 (d, $J = 8.3$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.66 (d, $J = 7.2$ Hz, 2H), 7.50 (t, $J = 7.3$ Hz, 2H), 7.44 (t, $J = 7.2$ Hz, 1H), 2.37 – 2.26 (m, 2H), 1.60 – 1.49 (m, 2H), 1.38

– 1.30 (m, 2H), 1.29 – 1.18 (m, 4H), 0.86 (t, $J = 6.8$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -86.9 (t, $J = 5.6$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.5 (t, $J = 30.6$ Hz), 147.2, 139.5, 131.0 (t, $J = 2.1$ Hz), 129.7, 129.1, 128.6, 127.3, 127.2, 107.7 (t, $J = 243.4$ Hz), 95.9 (t, $J = 6.6$ Hz), 72.0 (t, $J = 38.2$ Hz), 31.1, 28.4, 27.4 (t, $J = 1.9$ Hz), 22.4, 18.7 (t, $J = 2.4$ Hz), 14.0. IR (thin film) max 2955.4, 2858.4, 2247.0, 1709.8, 1604.2 cm^{-1} . MS (EI): m/z (%) 340 (M^+), 181 (100). HRMS calcd. for $\text{C}_{22}\text{H}_{22}\text{OF}_2$: 340.1639; Found: 340.1643.

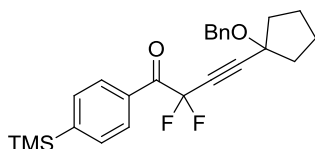


8-([1,1'-Biphenyl]-4-yl)-7,7-difluoro-8-oxooct-5-yn-1-yl acetate (5b). The product (64 mg, 57% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, $J = 8.2$ Hz, 2H), 7.72 (d, $J = 8.3$ Hz, 2H), 7.63 (d, $J = 8.3$ Hz, 2H), 7.48 (t, $J = 7.7$ Hz, 2H), 7.44 – 7.37 (m, 1H), 4.03 (t, $J = 6.0$ Hz, 2H), 2.36 (p, $J = 5.9$ Hz, 2H), 2.00 (s, 3H), 1.73 – 1.56 (m, 4H). ^{19}F NMR (376 MHz, CDCl_3) δ -86.9 (t, $J = 5.4$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.4 (t, $J = 30.6$ Hz), 171.1, 147.2, 139.4, 131.0 (t, $J = 2.3$ Hz), 129.1, 128.7, 127.3, 127.2, 115.7, 107.7 (t, $J = 243.9$ Hz), 94.7 (t, $J = 6.7$ Hz), 72.4 (t, $J = 38.1$ Hz), 63.6, 27.6, 24.1 (t, $J = 2.0$ Hz), 20.9, 18.4 (t, $J = 2.3$ Hz). IR (thin film) max 3399.9, 2955.5, 2247.9, 1738.4, 1708.9 cm^{-1} . MS (EI): m/z (%) 370 (M^+), 181 (100). HRMS calcd. for $\text{C}_{22}\text{H}_{20}\text{O}_3\text{F}_2$: 370.1381; Found: 370.1387.

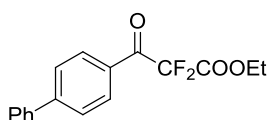


1-([1,1'-Biphenyl]-4-yl)-4-(1-(benzyloxy)cyclopentyl)-2,2-difluorobut-3-yn-1-one (5c). The product (109 mg, 84% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, $J = 8.4$ Hz, 2H), 7.70 (d, $J = 8.4$ Hz, 2H), 7.60 (d, $J = 7.2$ Hz, 2H), 7.49 (t, $J = 7.3$ Hz, 2H), 7.43 (t, $J = 7.2$ Hz, 1H), 7.29 – 7.19 (m, 5H), 4.47 (s, 2H), 2.18 – 2.09 (m, 2H), 2.03 – 1.91 (m, 2H), 1.86 – 1.65 (m, 4H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.2 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.0 (t, $J = 30.1$ Hz), 147.4, 139.3,

138.0, 131.0 (t, $J = 2.1$ Hz), 129.4, 129.1, 128.7, 128.4, 127.61, 127.60, 127.33, 127.25, 107.7 (t, $J = 244.8$ Hz), 95.8 (t, $J = 6.6$ Hz), 80.3 (t, $J = 1.7$ Hz), 76.2 (t, $J = 38.3$ Hz), 67.6, 39.1, 23.3. IR (thin film) max 2962.3, 2872.2, 2237.9, 1708.8, 1603.3 cm^{-1} . MS (EI): m/z (%) 324 ($[\text{M-BnO}] + \text{H}^+$), 181 (100). HRMS calcd. for $\text{C}_{21}\text{H}_{18}\text{OF}_2$ ($[\text{M-BnO}] + \text{H}^+$): 324.1326; Found: 324.1335.

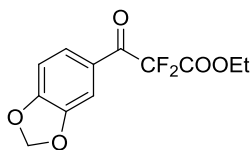


4-(1-(Benzyloxy)cyclopentyl)-2,2-difluoro-1-(4-(trimethylsilyl)phenyl)but-3-yn-1-one (5d). The product (82 mg, 74% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 5:1). ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.34 – 7.16 (m, 5H), 4.44 (s, 2H), 2.16 – 2.07 (m, 2H), 2.01 – 1.91 (m, 2H), 1.83 – 1.66 (m, 4H), 0.28 (s, 9H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.2 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.7 (t, $J = 29.9$ Hz), 149.7, 138.0, 133.5, 130.8, 129.1 (t, $J = 2.0$ Hz), 128.3, 127.64, 127.60, 107.6 (t, $J = 244.8$ Hz), 95.7 (t, $J = 6.6$ Hz), 80.3 (t, $J = 1.8$ Hz), 76.1 (t, $J = 38.3$ Hz), 67.6, 39.2, 23.3, -1.5. IR (thin film) max 2956.9, 2873.4, 2238.9, 1714.6, 1595.5, 1545.1 cm^{-1} . MS (EI): m/z (%) 336 ($[\text{M-Bn}] + \text{H}^+$), 335 (100). HRMS calcd. for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{F}_2\text{Si}$ ($[\text{M-Bn}] + \text{H}^+$): 335.1279; Found: 335.1285.

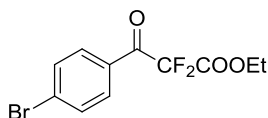


Ethyl 3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-oxopropanoate (5e). The product (75 mg, 82% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 15:1). ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 7.1$ Hz, 2H), 7.50 (t, $J = 7.3$ Hz, 2H), 7.44 (t, $J = 6.7$ Hz, 1H), 4.41 (q, $J = 7.2$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.6 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 185.0 (t, $J = 27.7$ Hz), 161.9 (t, $J = 30.7$ Hz), 147.8, 139.3, 130.6 (t, $J = 2.8$ Hz), 129.7 (t, $J = 1.9$ Hz), 129.1, 128.8, 127.5, 127.3, 109.9 (t, $J = 265.4$ Hz), 63.8, 13.8. IR (thin film) max 3060.7, 2984.6, 1774.0, 1696.9,

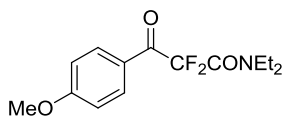
1603.9 cm^{-1} . MS (EI): m/z (%) 304 (M^+), 181 (100). HRMS calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_3\text{F}_2$: 304.0911; Found: 304.0912.



Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-3-oxopropanoate (5f). The product (78 mg, 94% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 15:1). ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, J = 8.4 Hz, 1H), 7.48 (s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.07 (s, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.0 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.4 (t, J = 27.1 Hz), 161.9 (t, J = 29.7 Hz), 153.6, 148.5, 127.3 (t, J = 3.6 Hz), 125.4, 109.9 (t, J = 265.3 Hz), 109.1, 108.4, 102.3, 63.7, 13.8. IR (thin film) max 2928.7, 2912.8, 1774.0, 1694.0, 1606.2 cm^{-1} . MS (EI): m/z (%) 272 (M^+), 149 (100). HRMS calcd. for $\text{C}_{12}\text{H}_{10}\text{O}_5\text{F}_2$: 272.0496; Found: 272.0498.

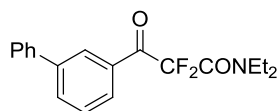


Ethyl 3-(4-bromophenyl)-2,2-difluoro-3-oxopropanoate (5g). The product (60 mg, 65% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 15:1). ^1H NMR (400 MHz, CDCl_3) δ 7.93 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -107.7 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 184.7 (t, J = 27.9 Hz), 161.6 (t, J = 30.4 Hz), 132.4, 131.3 (t, J = 2.8 Hz), 130.9, 129.7 (t, J = 2.0 Hz), 109.7 (t, J = 264.8 Hz), 63.9, 13.8. IR (thin film) max 2986.0, 1774.8, 1704.2, 1584.9 cm^{-1} . MS (EI): m/z (%) 305 (M^+), 183 (100). HRMS calcd. for $\text{C}_{11}\text{H}_9\text{O}_3\text{F}_2\text{Br}$: 305.9703; Found: 305.9709.

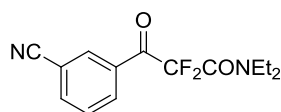


N,N-Diethyl-2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanamide (5h). The product (71 mg, 83% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether /

EtOAc = 10:1). ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 3.41 (q, J = 7.2 Hz, 2H), 3.38 (q, J = 7.2 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -102.6 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 185.1 (t, J = 27.0 Hz), 164.8, 161.1 (t, J = 27.3 Hz), 132.7 (t, J = 2.4 Hz), 124.6, 114.1, 111.8 (t, J = 264.5 Hz), 55.6, 41.8 (t, J = 4.1 Hz), 41.4, 14.0, 12.2.

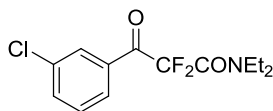


3-([1,1'-Biphenyl]-3-yl)-N,N-diethyl-2,2-difluoro-3-oxopropanamide (5i). The product (88 mg, 88% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 7:1). ^1H NMR (400 MHz, CDCl_3) δ 8.32 (s, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.86 (ddd, J = 7.7 Hz, 1.6 Hz, 1.0 Hz, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 3.50 (q, J = 7.0 Hz, 2H), 3.44 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -102.9 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 186.8 (t, J = 27.2 Hz), 161.1 (t, J = 27.0 Hz), 141.9, 139.7, 133.2, 132.4, 129.2, 129.0, 128.8 (t, J = 2.5 Hz), 128.6 (t, J = 1.8 Hz), 128.0, 127.2, 111.7 (t, J = 265.3 Hz), 41.9 (t, J = 4.4 Hz), 41.5, 14.2, 12.3. IR (thin film) max 3062.6, 2978.5, 1716.2, 1658.9, 1479.8 cm^{-1} . MS (EI): m/z (%) 331 (M^+), 181 (100). HRMS calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_2\text{NF}_2$: 331.1384; Found: 331.1382.

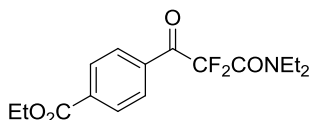


1-(3-Cyanophenyl)-N,N-diethyl-2,2-difluoro-3-oxopropanamide (5j). The product (76 mg, 91% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 7:1). ^1H NMR (400 MHz, CDCl_3) δ 8.24 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.41 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -103.4 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 185.3 (t, J = 28.2 Hz), 160.9 (t, J = 26.7 Hz), 136.9, 133.8 (t, J = 2.4 Hz), 133.5 (t, J = 2.7 Hz), 133.2, 129.8, 117.6, 113.3, 111.5 (t, J = 269.4 Hz), 41.8 (t, J = 4.8 Hz), 41.5, 14.3, 12.2. IR (thin film)

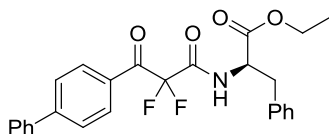
max 3412.5, 2980.0, 2234.2, 1723.3, 1654.4 cm^{-1} . MS (EI): m/z (%) 280 (M^+), 130 (100). HRMS calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_2\text{N}_2\text{F}_2$: 280.1023; Found: 280.1024.



3-(3-Chlorophenyl)-N,N-diethyl-2,2-difluoro-3-oxopropanamide (5k). The product (53 mg, 61% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 7:1). ^1H NMR (400 MHz, CDCl_3) δ 7.99 (s, 1H), 7.91 (d, $J = 7.7$ Hz, 1H), 7.63 – 7.52 (m, 1H), 7.42 (t, $J = 8.1$ Hz, 1H), 3.50 (q, $J = 6.8$ Hz, 2H), 3.42 (q, $J = 7.0$ Hz, 2H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.15 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -103.1 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 185.7 (t, $J = 27.7$ Hz), 160.9 (t, $J = 26.7$ Hz), 135.0, 134.3, 133.5, 130.0, 129.8 (t, $J = 2.0$ Hz), 128.1 (t, $J = 2.2$ Hz), 111.5 (t, $J = 266.7$ Hz), 41.8 (t, $J = 4.6$ Hz), 41.5, 14.2, 12.2. IR (thin film) max 3402.8, 2979.1, 1720.7, 1654.9, 1507.2 cm^{-1} . MS (EI): m/z (%) 289 (M^+), 139 (100). HRMS calcd. for $\text{C}_{13}\text{H}_{14}\text{NO}_2\text{F}_2\text{Cl}$: 289.0681; Found: 289.0686.

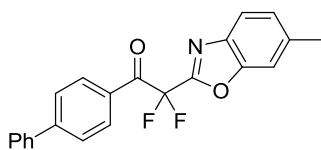


Ethyl 4-(3-(diethylamino)-2,2-difluoro-3-oxopropanoyl)benzoate (5l). The product (68 mg, 70% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 5:1). ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 8.7$ Hz, 2H), 8.08 (d, $J = 8.6$ Hz, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 3.52 (q, $J = 7.0$ Hz, 2H), 3.42 (q, $J = 7.1$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.15 (t, $J = 7.1$ Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -103.3 (s, 2F). ^{13}C NMR (101 MHz, CDCl_3) δ 186.5 (t, $J = 27.7$ Hz), 165.4, 161.0 (t, $J = 26.8$ Hz), 135.24, 135.18, 129.9 (t, $J = 2.4$ Hz), 129.7, 111.6 (t, $J = 267.7$ Hz), 61.6, 41.7 (t, $J = 4.6$ Hz), 41.4, 14.25, 14.20, 12.2. IR (thin film) max 3426.3, 2980.9, 1720.5, 1659.1 cm^{-1} . MS (EI): m/z (%) 327 (M^+), 177 (100). HRMS calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{F}_2$: 327.1282; Found: 327.1275.



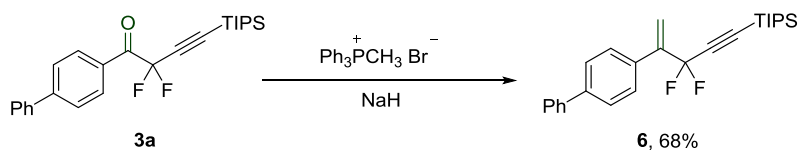
(R)-Ethyl-2-(3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-oxopropanamido)-3-phen-ylpropanoate

(5m). The product (94 mg, 72% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 7.0 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.45 – 7.39 (m, 1H), 7.28 – 7.16 (m, 3H), 7.13 – 7.08 (m, 2H), 4.91 (dd, J = 13.9 Hz, 5.9 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.13–3.26 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -108.2 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 186.2 (t, J = 26.8 Hz), 170.1, 161.1 (t, J = 28.1 Hz), 147.5, 139.4, 135.0, 131.0 (t, J = 2.7 Hz), 130.2, 129.3, 129.1, 128.71, 128.66, 127.36, 127.35, 127.34, 110.8 (t, J = 266.2 Hz), 62.0, 53.6, 37.6, 14.1. IR (thin film) max 3334.5, 2926.5, 1740.6, 1713.2, 1603.6 cm^{-1} . MS (EI): m/z (%) 451 (M^+), 181 (100). HRMS calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_4\text{F}_2$: 451.1595; Found: 451.1588.

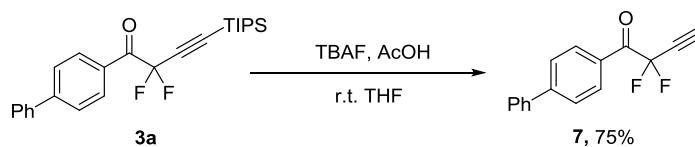


1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-2-(6-methylbenzo[d]oxazol-2-yl)ethanone (5n). The product (87 mg, 80% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether / EtOAc = 20:1). ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.63 – 7.59 (m, 3H), 7.52 – 7.43 (m, 3H), 7.41 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 2.47 (s, 3H). ^{19}F NMR (376 MHz, CDCl_3) δ -101.6 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.7 (t, J = 28.2 Hz), 155.5 (t, J = 32.0 Hz), 149.2, 147.6, 140.1, 139.3, 135.6, 131.0 (t, J = 2.6 Hz), 129.9 (t, J = 1.4 Hz), 129.1, 128.7, 128.5, 127.5, 127.3, 121.3, 110.9, 110.8 (t, J = 256.0 Hz), 21.5. IR (thin film) max 3059.4, 2924.3, 1708.5, 1603.4, 1484.1 cm^{-1} . MS (EI): m/z (%) 363 (M^+), 181 (100). HRMS calcd. for $\text{C}_{22}\text{H}_{15}\text{NO}_2\text{F}_2$: 363.1071; Found: 363.1067.

Transformation of Compound 3a

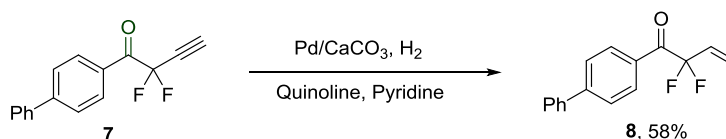


(4-([1,1'-Biphenyl]-4-yl)-3,3-difluoropent-4-en-1-yn-1-yl)triisopropylsilane (6). To a 50 mL of round-bottom flask were added $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$ (250 mg, 0.7 mmol), NaH (28 mg, 0.705 mmol, 60 % NaH) and THF (10 mL). The resulting solution was stirred for 0.5 h at 0 °C. **3a** (144 mg, 0.35 mmol) was then added dropwise at the same temperature. After stirring for 12 h at room temperature, the reaction mixture was quenched by H_2O , and extracted with EtOAc for 3 times. The combined organic layers were washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated and the residue was purified with silica gel chromatography (Petroleum ether/EtOAc = 20:1) to give compound **6** (98 mg, 68% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.65 – 7.56 (m, 6H), 7.48 (t, J = 8.0 Hz, 2H), 7.39 (d, J = 7.6 Hz, 1H), 6.04 (t, J = 1.7 Hz, 1H), 5.71 (s, 1H), 1.02-1.12 (m, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -78.9 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 143.7 (t, J = 25.8 Hz), 141.3, 140.7, 134.5, 128.8, 128.5, 127.5, 127.1, 126.9, 120.1, 118.77 (t, J = 7.3 Hz), 111.2 (t, J = 233.2 Hz), 98.56 (t, J = 39.6 Hz), 92.64 (t, J = 5.0 Hz), 18.37, 10.91. IR (thin film) max 3273.6, 2944.8, 2866.5, 1652.7, 1488.0 cm^{-1} . MS (EI): m/z (%) 410 (M^+), 215 (100). HRMS calcd. for $\text{C}_{26}\text{H}_{32}\text{F}_2\text{Si}$: 410.2241; Found: 410.2238.

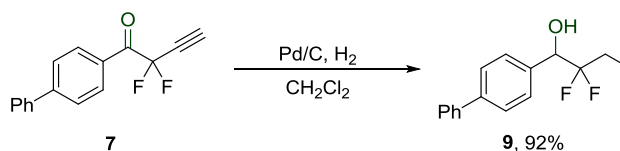


1-([1,1'-biphenyl]-4-yl)-2,2-difluorobut-3-yn-1-one (7). To a 25 mL of Schlenk tube equipped with a magnetic stir bar were added TBAF (1.0 M in THF, 4.4 mL, 4.4 mmol, 2.2 equiv), AcOH (6 mmol, 3.0 equiv) and wet THF (15 mL). The reaction mixture was stirred at room temperature for 30 min. And then a THF solution (5 mL) of **3a** (2.0 mmol) was added slowly at room temperature and the mixture stirred at room temperature for 3 h. After this time, it was quenched with water and extracted with EtOAc (3 \times 10 mL). The organic layer was washed with brine and dried over Na_2SO_4 . The residue was purified by flash chromatography (Hexane) to afford terminal alkyne **7** (384 mg, 75% yield).

yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.4$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.43-7.52 (m, 3H), 3.13 (t, $J = 5.4$ Hz, 1 H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.9 (d, $J = 5.4$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 183.6 (t, $J = 29.6$ Hz), 147.5, 139.3, 131.0 (t, $J = 2.4$ Hz), 129.2 (t, $J = 1.3$ Hz), 129.1, 128.7, 127.3, 107.36 (t, $J = 246.0$ Hz), 81.1 (t, $J = 6.8$ Hz), 74.2 (t, $J = 38.3$ Hz). IR (thin film) max 3274.7, 3060.0, 2129.6, 1706.8, 1603.6, 1558.9 cm^{-1} . MS (EI): m/z (%) 256 (M^+), 181 (100). HRMS calcd. for $\text{C}_{16}\text{H}_{10}\text{OF}_2$: 256.0700; Found: 256.0703.

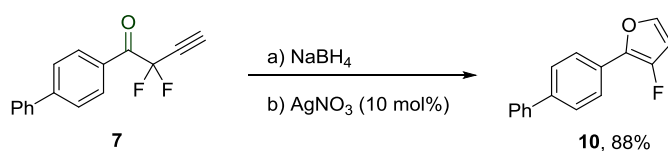


1-([1,1'-Biphenyl]-4-yl)-2,2-difluorobut-3-en-1-ol (8). A mixture of Pd/CaCO_3 (5%, 42 mg), quinoline (10 mg) and **7** (0.41 mmol) in 10 mL of pyridine was stirred under 1 atm H_2 atmosphere at room temperature for 24 h. The reaction mixture was filtered by a short silica gel column. The filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The product **8** (62 mg, 58% yield) was purified with silica gel chromatography (Petroleum ether/EtOAc = 5:1) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, $J = 8.4$ Hz, 2H), 7.73 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 7.6$ Hz, 2H), 7.50 (t, $J = 7.2$ Hz, 2H), 7.39 – 7.47 (m, 1H), 6.23-6.35 (m, 1H), 5.92 (dt, $J = 17.2$ Hz, 2.4 Hz, 1H), 5.72 (d, $J = 11.2$ Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -99.8 (d, $J = 11.2$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 188.3 (t, $J = 31.0$ Hz), 147.0, 139.4, 130.8 (t, $J = 3.2$ Hz), 130.7 (t, $J = 1.8$ Hz), 129.9 (t, $J = 25.2$ Hz), 129.1, 128.6, 127.3, 127.3, 122.8 (t, $J = 9.7$ Hz), 115.6 (t, $J = 251.0$ Hz). IR (thin film) max 3446.1, 2925.4, 1700.2, 1604.0, 1582.4 cm^{-1} . MS (EI): m/z (%) 258 (M^+), 181 (100). HRMS calcd. for $\text{C}_{16}\text{H}_{12}\text{F}_2\text{O}$: 258.0856; Found: 258.0857.

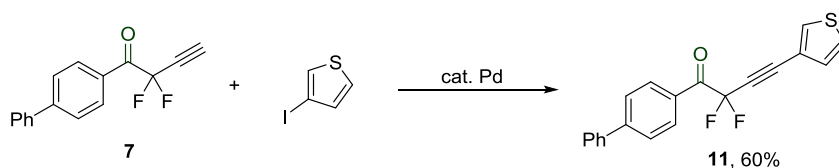


1-([1,1'-Biphenyl]-4-yl)-2,2-difluorobutan-1-ol (9). A mixture of Pd/C (10%, 85 mg) and **7** (0.41 mmol) in 20 mL of DCM was stirred under 1 atm H_2 atmosphere at room temperature for 24 h. The reaction mixture was filtered by a short silica gel column. The filtrate was washed with brine, dried

over Na₂SO₄ and concentrated. The product **9** (99 mg, 92% yield) was purified with silica gel chromatography (Petroleum ether/EtOAc = 5:1) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.64 (m, 9H), 4.92 (t, *J* = 10.4 Hz, 1H), 2.91 (br, 1H), 2.29 – 1.56 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -111.64 – -111.98 (m, 2F). ¹³C NMR (101 MHz, CDCl₃) δ 141.4, 140.5, 135.7, 128.8, 127.8, 127.42, 127.03, 126.95, 123.7 (t, *J* = 247.0 Hz), 74.98 (t, *J* = 28.8 Hz), 25.37 (t, *J* = 24.9 Hz), 5.5 (t, *J* = 5.4 Hz), 1.0. IR (thin film) max 2947.9, 2253.0, 1488.0, 1466.3 cm⁻¹. MS (EI): *m/z* (%) 262 (M⁺), 183 (100). HRMS calcd. for C₁₆H₁₆F₂O: 262.1169; Found: 262.1167.



2-([1,1'-biphenyl]-4-yl)-3-fluorofuran (10). To a 50 mL of round-bottom flask were added **7** (0.8 mmol, 1 equiv), NaBH₄ (1.2 mmol, 1.5 equiv) and THF (10 mL). The resulting solution was stirred for 5 h at room temperature. The resulting reaction mixture was quenched by H₂O, and extracted with EtOAc for 3 times. The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated. The residue was filtered through a pad of MgSO₄ and the filtrate was concentrated. It was purified with silica gel chromatography with Petroleum ether/EtOAc (10:1) as an eluent to give compound **10** (168 mg, 88% yield) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.65-7.70 (m, 4H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.37-7.40 (m, 1H), 7.29 – 7.27 (m, 1H), 6.47 (s, 1H). ¹⁹F NMR (376 MHz, CDCl₃) δ -164.5 (d, *J* = 3.4 Hz, 2F). ¹³C NMR (126 MHz, CDCl₃) δ 149.4 (d, *J* = 253.6 Hz), 140.6, 139.9 (d, *J* = 9.2 Hz), 139.7 (d, *J* = 1.6 Hz), 136.5 (d, *J* = 20.7 Hz), 128.8, 128.02 (d, *J* = 5.0 Hz), 127.40, 127.36, 126.9, 123.9 (d, *J* = 5.3 Hz), 104.6 (d, *J* = 19.9 Hz). IR (thin film) max 3433.8, 2925.8, 2252.5, 1778.9, 1633.0 cm⁻¹. MS (EI): *m/z* (%) 238 (M⁺), 84 (100). HRMS calcd. for C₁₆H₁₁FO: 238.0794; Found: 238.0799.

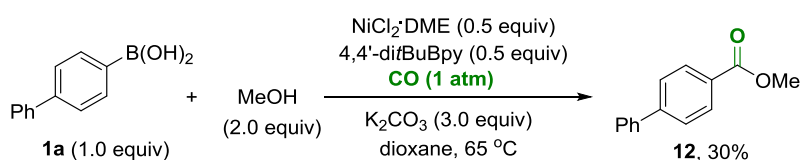


1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-4-(thiophen-3-yl)but-3-yn-1-one (11). To a septum capped

25 mL of Schlenck tube were added $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol %) and CuI (10 mol %) under Ar. The alkyne **7** (0.4 mmol, 1.0 equiv), Et_3N (2 mL), heteroaryl iodide (0.6 mmol, 1.3 equiv) and THF (2 mL) were then added. The reaction mixture was stirred for 16 h at 50 °C and concentrated. The crude product was purified by silica gel chromatography (Petroleum ether/EtOAc = 10:1) to give product **11** (82 mg, 60% yield) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 8.30 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 6.0 Hz, 3H), 7.50 (t, J = 7.2 Hz, 2H), 7.47 – 7.42 (m, 1H), 7.31 (s, 1H), 7.17 (d, J = 4.8 Hz, 1H). ^{19}F NMR (376 MHz, CDCl_3) δ -87.4 (s, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 184.2 (t, J = 30.5 Hz), 147.3, 139.4, 132.7 (t, J = 2.9 Hz), 131.04 (t, J = 2.0 Hz), 129.65 (t, J = 1.6 Hz), 129.6, 129.1, 128.7, 127.33, 127.29, 126.2, 118.5 (t, J = 3.0 Hz), 108.3 (t, J = 244.8 Hz), 88.2 (t, J = 6.7 Hz), 79.2 (t, J = 38.4 Hz). IR (thin film) max 3395.6, 3110.1, 2236.6, 1705.9, 1603.7, 1559.0 cm^{-1} . MS (EI): m/z (%) 338 (M^+), 181 (100). HRMS calcd. for $\text{C}_{20}\text{H}_{12}\text{OSF}_2$: 338.0577; Found: 338.0574.

Mechanistic Studies

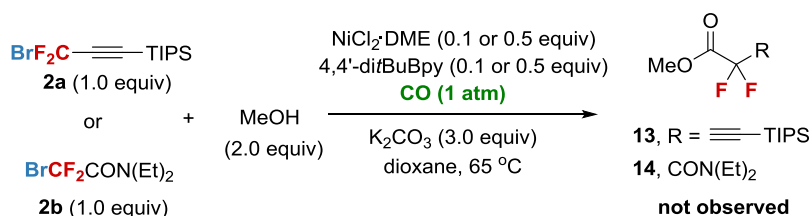
a) Reaction of Aryl Boronic Acid **1a** with MeOH under 1atm of CO in the Presence of $\text{NiCl}_2\cdot\text{DME}/4,4'\text{-di}t\text{BuBpy}$



Procedure: To a 25 mL of Schlenck tube were added aryl boronic acid **1** (0.3 mmol, 1.0 equiv), $\text{NiCl}_2\cdot\text{DME}$ (50 mol%), 4,4'-di-*t*BuBpy (50 mol%), and K_2CO_3 (4.0 equiv). The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). To the Schlenck tube were added MeOH (0.6 mmol, 2.0 equiv.) and dioxane (2 mL). The tube was screw capped and put into a preheated oil bath (65 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ethyl acetate and H_2O . The resulting mixture was then extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The

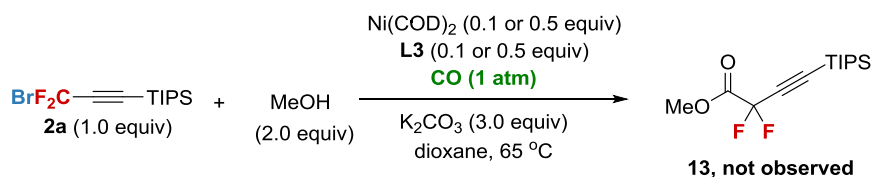
residue was purified with silica gel chromatography to give product **12** (19 mg, 30% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.11 (d, J = 8.2 Hz, 2 H), 7.67 (d, J = 8.2 Hz, 2 H), 7.63 (d, J = 7.5 Hz, 2 H), 7.47 (m, 2 H), 7.40 (m, 1 H), 3.94 (s, 2 H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.0, 145.6, 140.0, 130.1, 128.89, 128.85, 128.1, 127.2, 127.0, 52.1. IR (thin film) max 2922.9, 1719.1, 1607.4, 1452.0 cm^{-1} . MS (EI): m/z (%) 212 (M^+), 181 (100). HRMS calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2$: 212.0837; Found: 212.0841.

b) Reaction of Difluoroalkyl Bromides 2a or 2b with MeOH under 1 atm of CO in the Presence of $\text{NiCl}_2\cdot\text{DME}/4,4'\text{-di}t\text{BuBpy}$



Procedure: To a 25 mL of Schlenk tube were added $\text{NiCl}_2\cdot\text{DME}$ (0.1 or 0.5 equiv), 4,4'-di-*t*BuBpy (0.1 or 0.5 equiv), and K_2CO_3 (3.0 equiv). The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). To the Schlenk tube were added difluoroalkyl bromide **2** (0.3 mmol, 1.0 equiv), MeOH (2.0 equiv) and dioxane (2 mL). The tube was screw capped and put into a preheated oil bath (65°C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The resulting mixture was analyzed by ^{19}F NMR and showed no desired product **13** or **14** was observed.

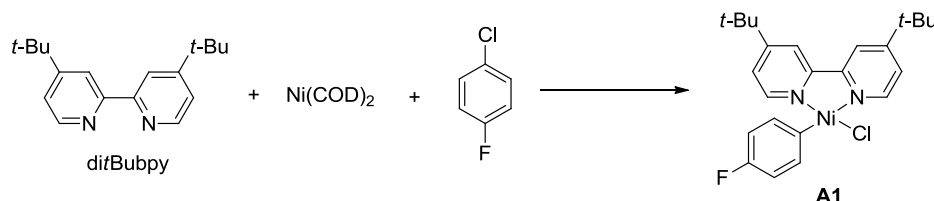
c) Reaction of Difluoroalkyl Bromides 2a with MeOH under 1 atm of CO in the Presence of $\text{Ni}(\text{COD})_2/4,4'\text{-di}t\text{BuBpy}$



Procedure: To a 25 mL of Schlenk tube were added $\text{Ni}(\text{COD})_2$ (0.1 or 0.5 equiv), 4,4'-di-*t*BuBpy

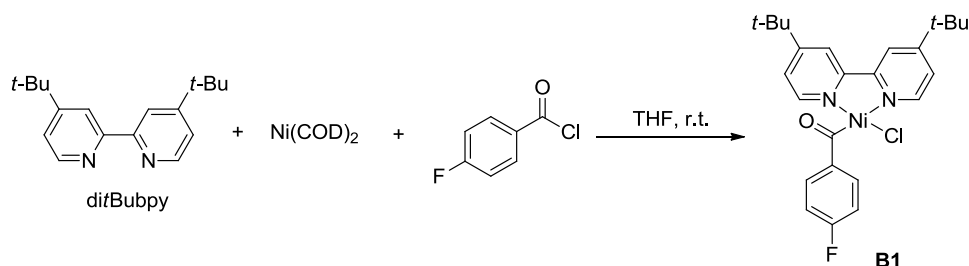
(0.1 or 0.5 equiv), and K_2CO_3 (3.0 equiv). The reaction mixture was then evacuated and backfilled with Ar (3 times). The resulting mixture was evacuated again and backfilled with CO (1 atm, balloon). To the Schlenk tube were added difluoroalkyl bromide **2a** (0.3 mmol, 1.0 equiv), MeOH (2.0 equiv) and dioxane (2 mL). The tube was screw capped and put into a preheated oil bath (65 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The resulting mixture was analyzed by ^{19}F NMR and showed no desired product **13** was observed.

d) Preparation of Nickel Complex **A1**⁶



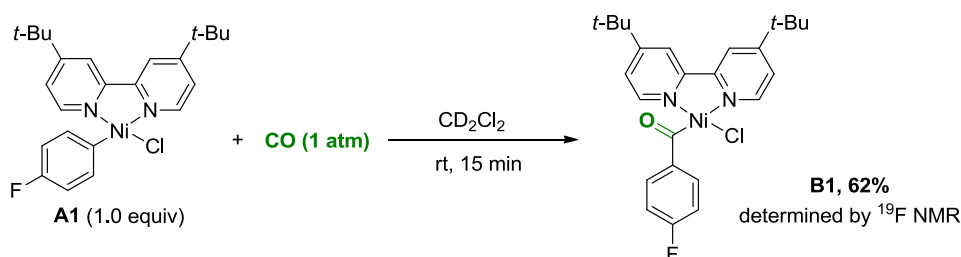
Procedure: The preparation of nickel complex (**A1**) is a modification of the literature method.⁶ To a Schlenk tube was charged with $\text{Ni}(\text{COD})_2$ (275 mg, 1.0 mmol), 4,4'-di-tert-butyl-2,2'-pyridine (268 mg, 1.0 mmol) and degassed dry THF (5 mL) under Ar. The resulting deep purple solution was left to stir for 1 hour at ambient temperature. 1-Chloro-4-fluorobenzene (1.06 mL, 10 mmol) was then added and the reaction mixture was stirred until the color of solution become dark red. The resulting dark red solution was triturated with degassed dry pentane and the precipitate was collected on a frit immediately, because the nickel complex (**A1**) deteriorated easily in the THF. And then the complex rinsed with pentane and dried under vacuum to give nickel complex (**A1**) as a light yellow powder (365 mg, 75% yield). The exact purity of complex **A1** is 78%, which was determined by ^{19}F NMR by using fluorobenzene as an internal standard. ^1H NMR (400 MHz, CD_2Cl_2) δ 9.01 (s, 1 H), 7.86 (s, 2 H), 7.49 (m, 3 H), 7.27 (s, 1 H), 7.15 (s, 1 H), 6.79 (s, 2 H), 1.42 (s, 9 H), 1.37 (s, 9 H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -125.1 (s, 1 F). IR (thin film) max 3054.3, 2962.7, 1544.4, 1507.8, 1473.3 cm^{-1} .

e) Preparation of Nickel Complex **B1**⁷



Procedure: The preparation of nickel complex (**B1**) is a modification of the literature method.⁷ To a Schlenk tube was charged with Ni(COD)_2 (550 mg, 2.0 mmol), 4,4'-di-tert-butyl-2,2'-pyridine (537 mg, 2.0 mmol) and degassed dry THF (5 mL) under Ar. The resulting deep purple solution was left to stir for 1 hour at ambient temperature. 4-Fluorobenzoyl chloride (2.1 mmol, 1.05 equiv) was then added and the reaction mixture was stirred for 4 min. The resulting dark red solution was triturated with degassed dry pentane and the precipitate was collected on a frit immediately. And then the complex rinsed with pentane and dried under vacuum to give nickel complex (**B1·THF**) as a dark red powder (760 mg, 78% yield). ^1H NMR (400 MHz, CD_2Cl_2) δ 8.87 (s, 1 H), 8.66 (s, 2 H), 7.92 (s, 2 H), 7.71 (s, 1 H), 7.53 (s, 1 H), 7.22 (s, 1 H), 7.13 (s, 2 H), 3.69 (s, 4 H), 1.87 (s, 4 H), 1.43 (s, 9 H), 1.37 (s, 9 H). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -109.2 (s, 1 F). IR (thin film) max 2964.2, 1627.5, 1614.6, 1586.1, 1495.0 cm^{-1} .

f) Reaction of Nickel Complex **A1** with CO



Procedure: To a NMR tube was charged with nickel complex (**A1**) (0.025 mmol) and CD_2Cl_2 (0.5 mL) under Ar at room temperature. Fluorobenzene (0.014 mmol) was added into the NMR tube as an internal standard [Note: the ratio between Fluorobenzene and nickel complex (**A1**) is not 1:1, but it doesn't affect us to monitor the reaction]. The NMR tube was evacuated and backfilled with CO

balloon (1 atm). The reaction was monitored by ^{19}F NMR and showed a 62% yield (determined by ^{19}F NMR) of acyl nickel complex **B1** was generated after consuming of **A1**.

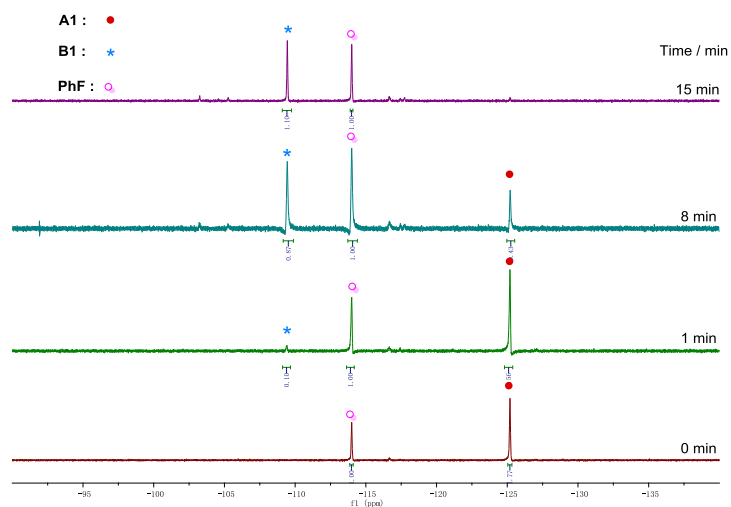


Figure S1. Reaction of Nickel Complex A1 with CO Monitored by ^{19}F NMR

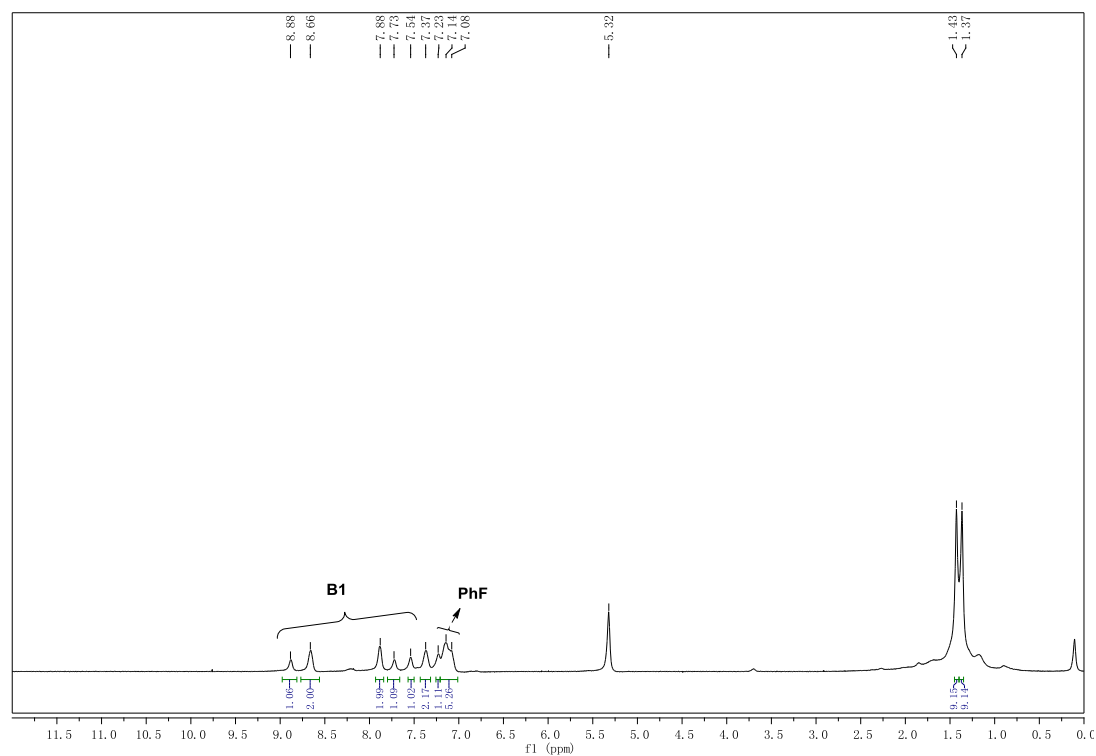


Figure S2. The ^1H NMR Spectra of Nickel Complex B1 After the Reaction of A1 with CO (Fluorobenzene as an Internal Standard and the Mole Ratio of B1/PhF = 1.1/1.0)

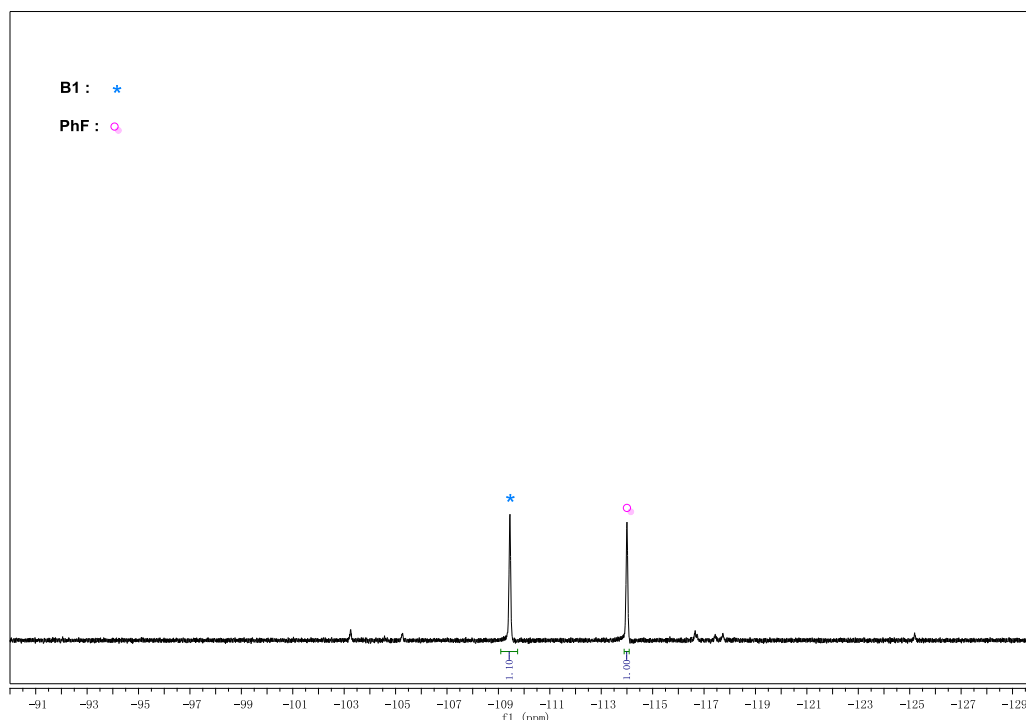
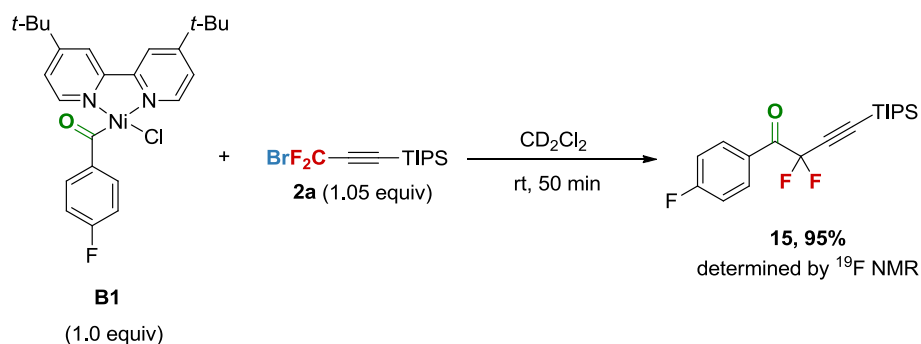


Figure S3. The ^{19}F NMR Spectra of Nickel Complex **B1** After the Reaction of **A1** with CO (Fluorobenzene as an Internal Standard and the Mole Ratio of **B1**/**PhF** = 1.1/1.0)

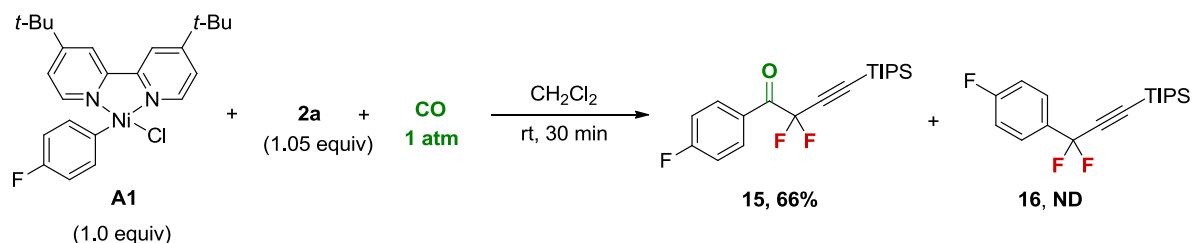
e) Reaction of Acyl Nickel Complex **B1 with *gem*-Difluoroalkyl Bromide **2a****



Procedure: To a NMR tube was charged with nickel complex (**B1**) (0.025 mmol) and CD_2Cl_2 (0.5 mL) under Ar at room temperature. Then **2a** (0.026 mmol, 1.05 equiv) was added into the NMR tube. Fluorobenzene (0.03 mmol) was added into the NMR tube as an internal standard. The reaction was monitored by ^{19}F NMR and showed a 95% yield (determined by ^{19}F NMR) of carbonyl compound **15** was generated after consuming of **B1**. Compound **15** as a light yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 8.24-8.20 (m, 2 H), 7.78 – 6.62 (m, 2 H), 1.35 – 0.43 (m, 21 H). ^{19}F NMR (376 MHz, CDCl_3) δ -88.5 (s, 2 F), -101.6 – -101.7 (m, 1 F). ^{13}C NMR (101 MHz, CDCl_3) δ 183.0 (t, J = 30.3 Hz), 166.5 (d, J = 259.6 Hz), 133.3 (dt, J = 10.1 Hz, 2.0 Hz), 127.2 (d, J = 3.0 Hz), 115.9 (d, J = 22.2 Hz), 106.5 (t, J = 245.4 Hz), 98.7 (t, J = 6.1 Hz), 96.1 (t, J = 37.4 Hz), 18.3, 10.8. IR (thin film) max

2945.6, 2867.6, 1715.5, 1600.3 cm^{-1} . MS (EI): m/z (%) 354 (M^+), 311 (100). HRMS calcd. for $\text{C}_{19}\text{H}_{25}\text{OF}_3\text{Si}$: 354.1627; Found: 354.1633.

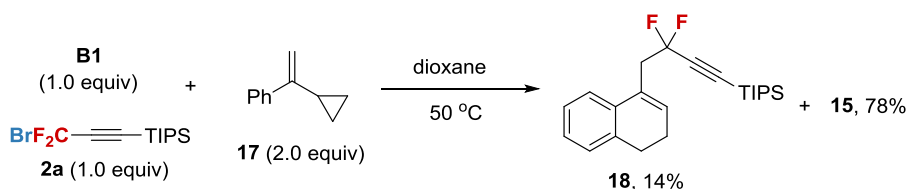
f) Reaction of Nickel Complex **A1** with **2a** under 1 atm of CO



Procedure: To a 25 mL of Schlenk tube was added **A1** (0.04 mmol, 1.0 equiv). The tube was then evacuated and backfilled with Ar (3 times). The schlenk tube was put into a $-78\text{ }^\circ\text{C}$ dry ice bath. The mixture was evacuated again and backfilled with carbon monoxide CO (1 atm, balloon). Fluorobenzene (0.04 mmol) was added into tube as an internal standard. The solution of compound **2a** in CH_2Cl_2 (0.42 mL, 0.1M) was added into the tube quickly at $-78\text{ }^\circ\text{C}$. The reaction mixture was then warmed to room temperature and stirred for 30 min. ^{19}F NMR showed the nickel complex **A1** was consumed and a 66% yield of compound **15** was produced.

Radical Clock Experiments

a) Reaction of **2a** with **17** in the Presence of **B1**

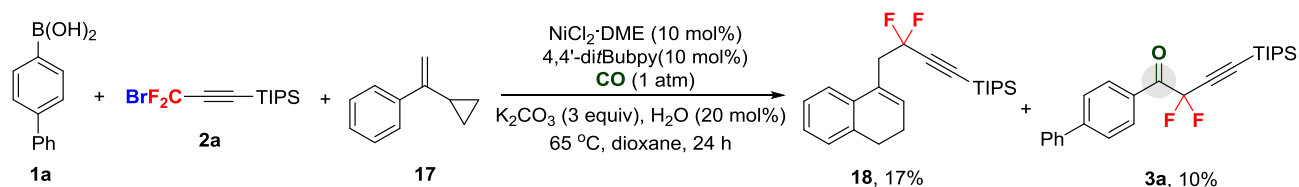


Procedure: To a 25 mL of Schlenk tube was added **B1** (0.1 mmol, 1.0 equiv). The tube was then evacuated and backfilled with Ar (3 times). The compound **2a** (0.1 mmol, 1.0 equiv), compound **17** (0.2 mmol, 2.0 equiv) and dioxane (2 mL) were added subsequently. The tube was screw capped and put into a preheated oil bath ($50\text{ }^\circ\text{C}$). After stirring for 50 min, the reaction mixture was cooled to

room temperature. The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard (**18**: 14% yield. **15**: 78% yield). **(3,4-Dihydronaphthalen-1-yl)-3,3-difluorobut-1-yn-1-yl triisopropylsilane (18)**. This compound is known.⁹ ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, $J = 7.5$ Hz, 1H), 7.22-7.15 (m, 1H), 7.17 – 7.10 (m, 2H), 6.17 (t, $J = 4.4$ Hz, 1H), 3.21 (t, $J = 14.4$ Hz, 2H), 2.77 (t, $J = 8.0$ Hz, 2H), 2.35 – 2.27 (m, 2H), 1.04 (s, 21H). ^{19}F NMR (376 MHz, CDCl_3) δ -79.1 (t, $J = 14.3$ Hz, 2F). ^{13}C NMR (126 MHz, CDCl_3) δ 136.2, 134.3, 131.7, 128.2 (t, $J = 4.0$ Hz), 127.6, 126.9, 126.3, 123.1 (t, $J = 1.3$ Hz), 113.5 (t, $J = 234.7$ Hz), 98.8 (t, $J = 38.7$ Hz), 90.4 (t, $J = 5.2$ Hz), 41.56 (t, $J = 27.6$ Hz), 28.1, 23.3, 18.4, 10.9.

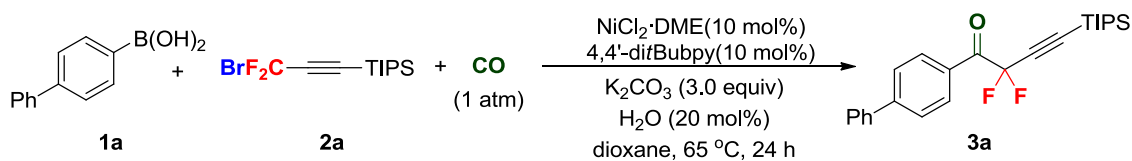
b) Reaction of **2a** with **17** in the Presence of Aryl Boronic Acid **1a** under Standard Reaction

Conditions



Procedure: To a 25 mL of Schlenk tube were added 4-biphenylboronic acid **1a** (0.45 mmol, 1.5 equiv), $\text{NiCl}_2 \cdot \text{DME}$ (10 mol%) and 4,4'-di-Bubpy (10 mol%) under air, followed by K_2CO_3 (0.9 mmol, 3.0 equiv). The mixture was then evacuated and backfilled with Ar (3 times). The mixture was evacuated again and backfilled with carbon monoxide CO (1 atm, balloon), compound **2a** (0.3 mmol, 1.0 equiv), compound **17** (0.36 mmol, 1.2 equiv), H_2O (20 mol%) and dioxane (2 mL) were added subsequently. The tube was screw capped and put into a preheated oil bath (65°C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The yield was determined by ^{19}F NMR using fluorobenzene as an internal standard (**18**: 17% yield based on the compound **2a**. **3a**: 10% yield based on the compound **2a**).

Radical Inhibition Experiments:



Entry	additive	3a Yield (%) ^b
1	1,4-dinitrobenzene (0.2 equiv)	4
2	1,4-dinitrobenzene (1 equiv)	ND

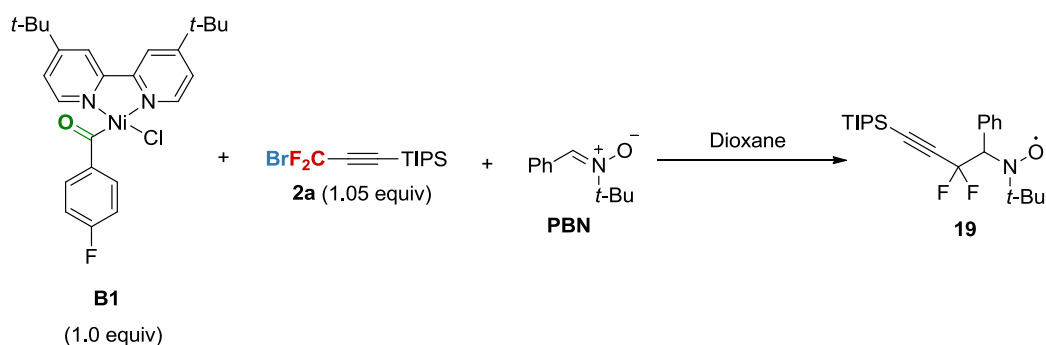
^aReaction conditions (unless otherwise specified): **1a** (0.45 mmol, 1.5 equiv), **2a** (0.3 mmol, 1.0 equiv), NiCl₂·DME (10 mol%), 4,4'-di-*t*-Bubpy (10 mol%), K₂CO₃ (3.0 equiv), H₂O (20 mol%), dioxane (2 mL).

^bDetermined by ¹⁹F NMR using fluorobenzene as an internal standard.

Procedure: To a 25 mL of Schlenk tube were added arylboronic acid **1a** (0.45 mmol, 1.5 equiv), NiCl₂·DME (10 mol %) and 4,4'-di-*t*-Bubpy (10 mol %) under Ar, followed by K₂CO₃ (0.9 mmol, 3.0 equiv) and 1,4-dinitrobenzene (0.2-1.0 equiv) under air. The mixture was then evacuated and backfilled with Ar (3 times). The mixture was evacuated again and backfilled with carbon monoxide CO (1 atm, balloon), compound **2a** (0.3 mmol, 1.0 equiv), H₂O (20 mol %) and dioxane (2 mL) were added subsequently. The tube was screw capped and put into a preheated oil bath (65 °C). After stirring for 24 h, the reaction mixture was cooled to room temperature. The yield was determined by ¹⁹F NMR using fluorobenzene as an internal standard.

EPR Studies

a) EPR Study of the Reaction of *gem*-Difluoroalkyl Bromide **2a** with **B1** in the Presence of PBN



Procedure:

A mixture of nickel complex (**B1**) (0.03 mmol), PBN (0.06 mmol) and **2a** (1.05 equiv) in dioxane (1 mL) was stirred at room temperature for 30 min. The resulting mixture was then analyzed by EPR at

room temperature. The EPR showed an e.p.r. triplet spectrum of nitroxide **19** ($g = 2.00559$; $a_N = 14.25$ G) (Figure S4).

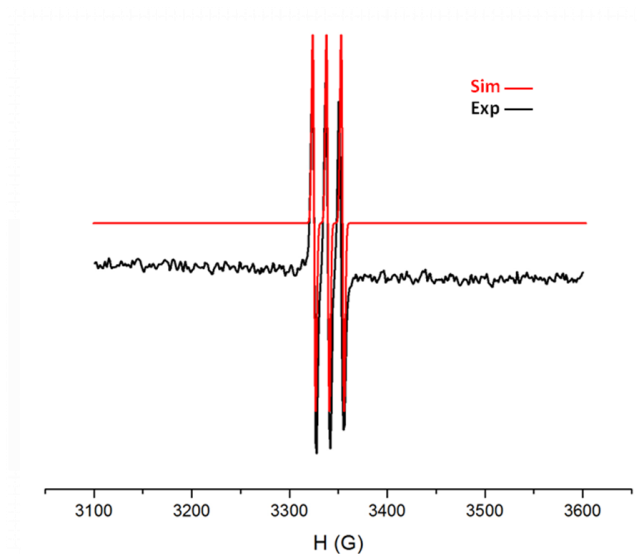
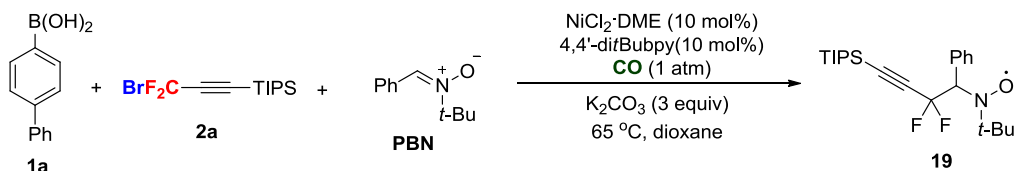


Figure S4. EPR Spectra of the mixture of PBN, B1, and 2a in 1,4-dioxane at room temperature

b) EPR Study of the Reaction of *gem*-Difluoroalkyl Bromide 2a with PBN in the Presence of Aryl Boronic Acid 1a under Standard Reaction Conditions



Procedure: A mixture of phenylboronic acid **1a** (30 mg, 0.15 mmol, 1.5 equiv), $\text{NiCl}_2(\text{DME})$ (10 mol %), 4,4'-di-*tert*-butylbipyridine (10 mol %), K_2CO_3 (3.0 equiv), PBN (35.4 mg, 0.2 mmol, 2.0 equiv) and **2a** (0.1 mmol, 1.0 equiv) in dioxane (1 mL) was stirred at 65 °C for 30 min. The resulting mixture was then analyzed by EPR at 65 °C. The EPR showed an e.p.r. triplet spectra of nitroxide **19** ($g = 2.00559$; $a_N = 14.25$ G) (Figure S5).

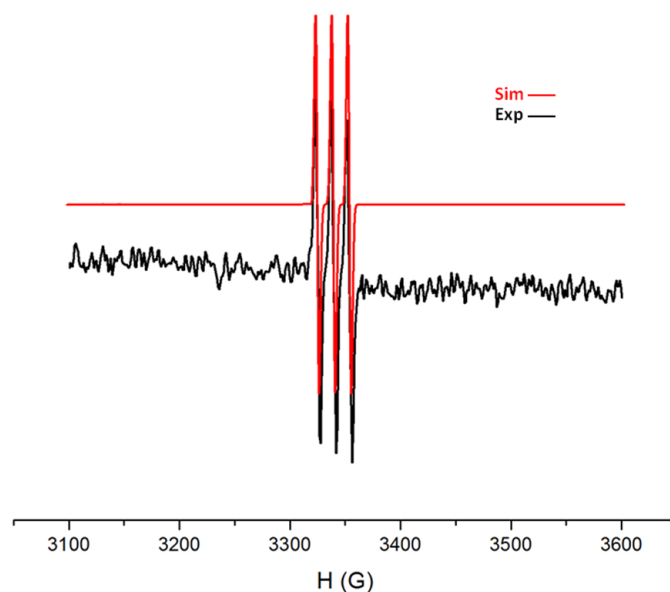


Figure S5. The EPR Spectra of the mixture of PBN, **1a**, $\text{NiCl}_2 \cdot \text{DME}$, 4,4'-di-*t*-Bubpy, K_2CO_3 and **2a** in 1,4-dioxane at 65 °C

Cyclic Voltammetry

Cyclic voltammograms were recorded with a CHI660E potentiostat at room temperature. Cyclic voltammetry was performed in a 3-electrode cell consisting of a 3mm glassy carbon disc working electrode, a Ag/Ag^+ reference electrode with a Ag wire in a fritted chamber containing a solution of AgNO_3 (0.01 M, CH_2Cl_2) and a Pt wire counter electrode. To an electrochemical cell was added a 10 mL solution of $n\text{-Bu}_4\text{NPF}_6$ (0.1 M) in CH_2Cl_2 , which was used as the supporting electrolyte. Cyclic voltammetry scans were taken at selected scan rates (from 10 to 400 mV/s) and in the selected potential window. (Note: Complex **B1** decomposes immediately in THF at room temperature)

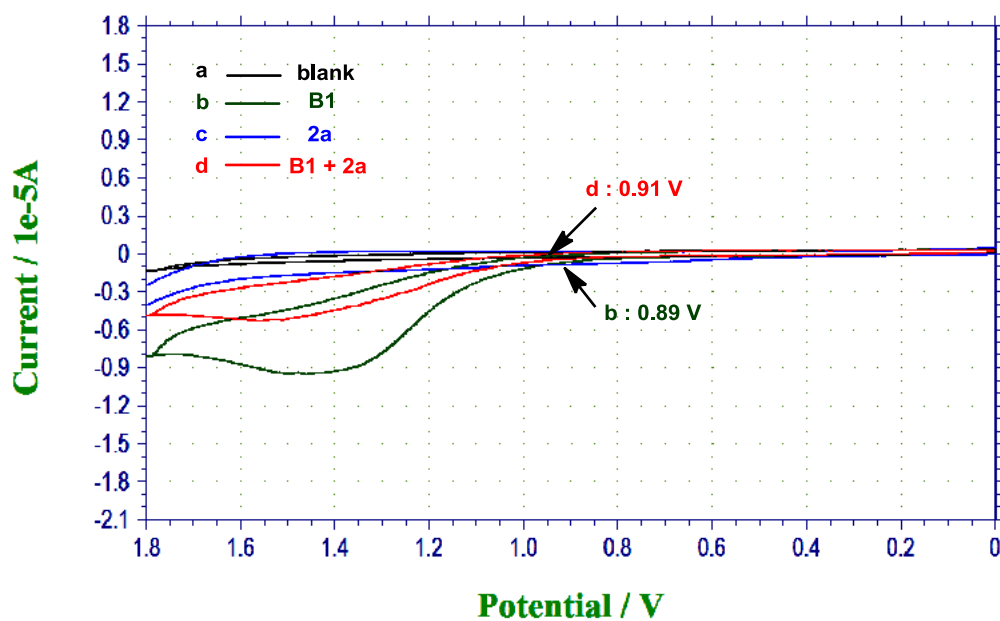
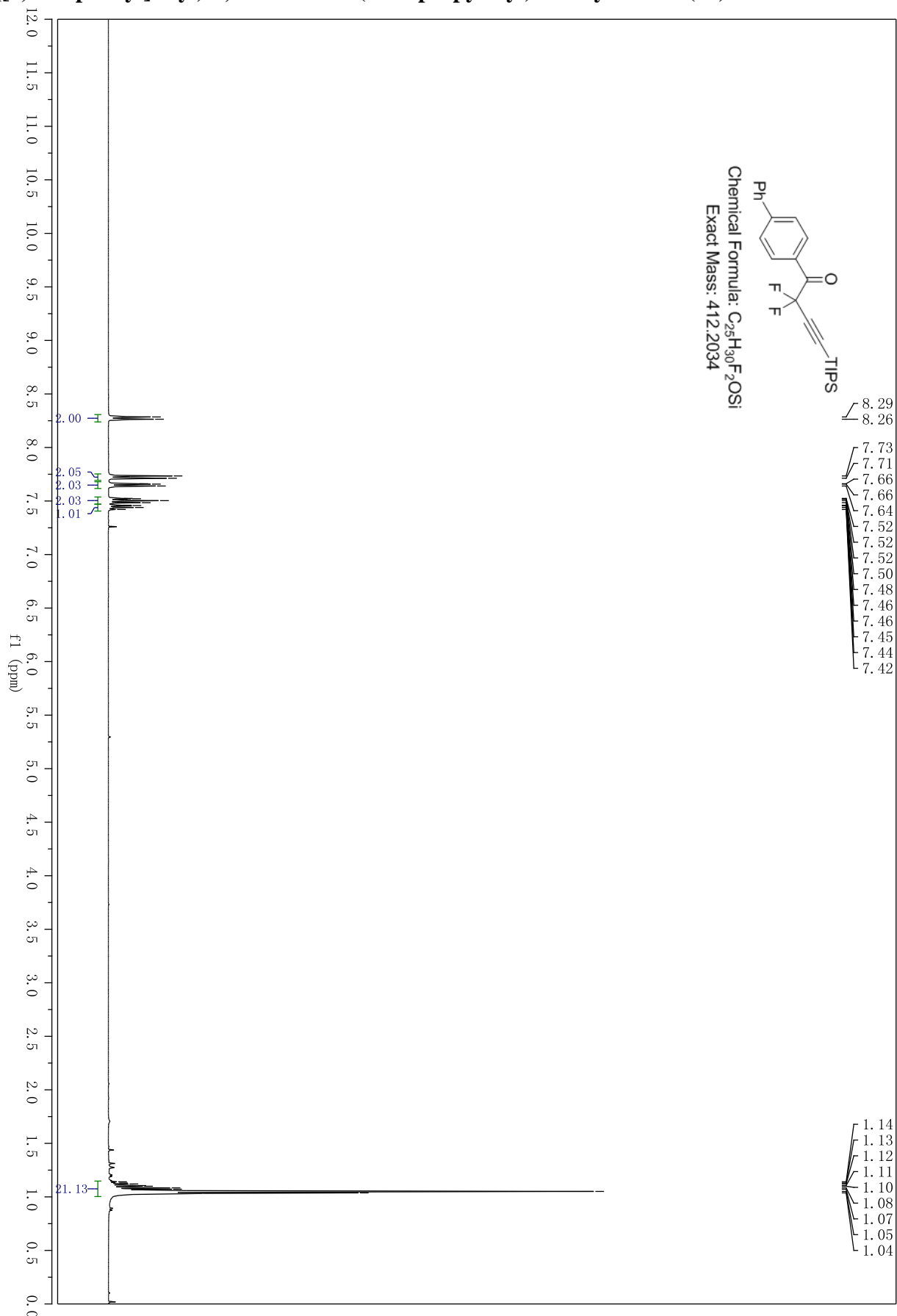


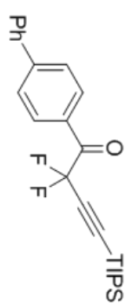
Figure S6. Cyclic voltammograms recorded on a Pt electrode (area = 0.03 cm²): (a) CH₂Cl₂ containing 0.1 M n-Bu₄NPF₆; (b) The solution (a) after addition of 5 mM **B1**, E⁺=0.89 V vs Ag/AgCl; (c) The solution (a) after addition of 5 mM **2a**; (d) The solution (a) after addition of 5 mM **B1** and 5 mM **2a**, E⁺= 0.91 V vs Ag/AgCl.

References

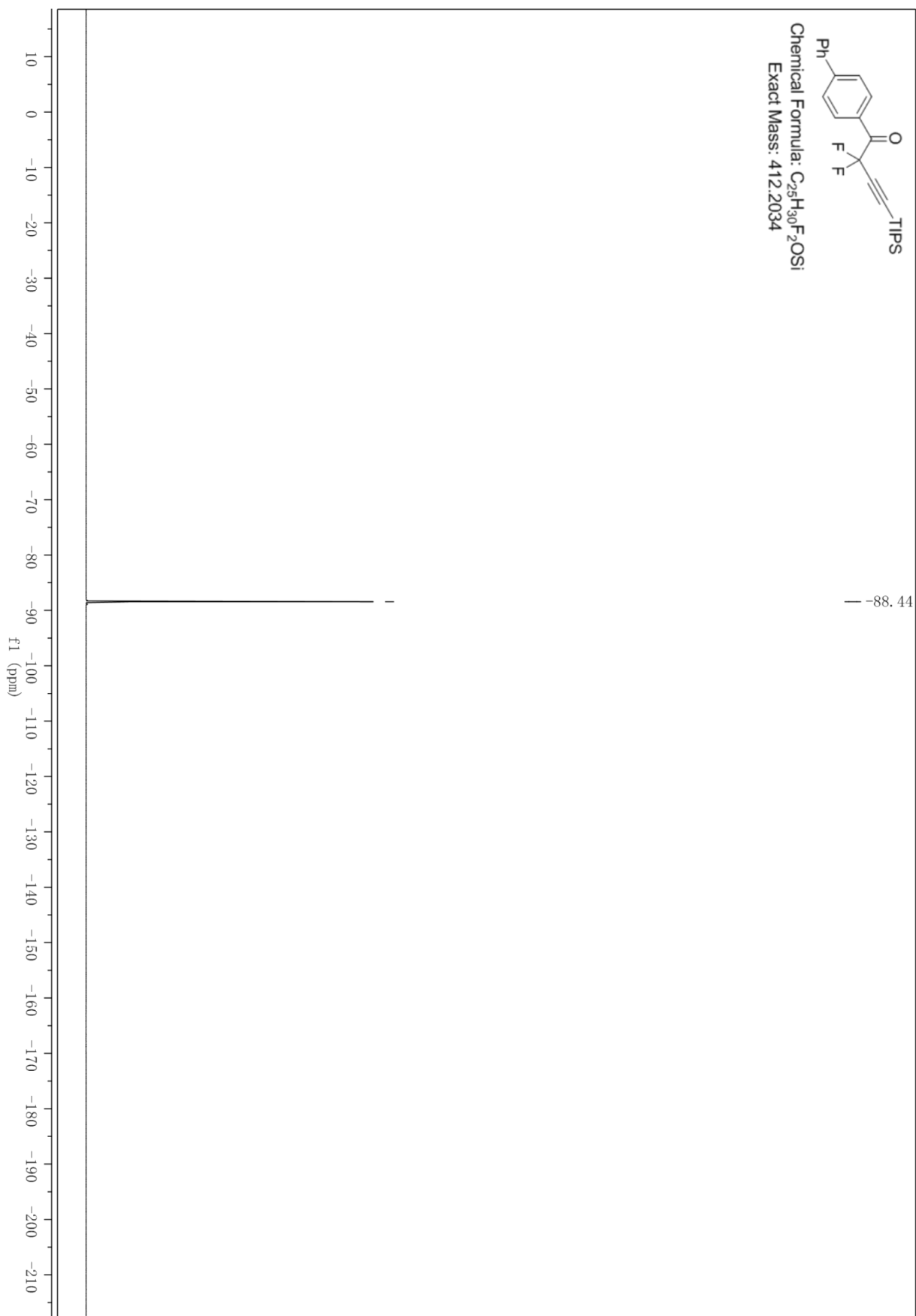
- (1) Guo, W.-H.; Luo, Z.-J.; Zeng, W.; Zhang, X. Access to Difluoromethylene-Skipped 1,4-Diynes with *gem*-Difluoropropargyl Bromide. *ACS Catal.* **2017**, 7, 896.
- (2) Ge, S.; Arlow, S. I.; Mormino, M. G.; Hartwig, J. F. Pd-Catalyzed α -Arylation of Trimethylsilyl Enolates of α,α -Difluoroacetamides. *J. Am. Chem. Soc.* **2014**, 136, 14401.
- (3) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B. Zhang, X. Palladium-Catalyzed Difluoroalkylation of Aryl Boronic Acids: A New Method for the Synthesis of Aryldifluoromethylated Phosphonates and Carboxylic Acid Derivatives. *Angew. Chem., Int. Ed.* **2014**, 53, 1669.
- (4) Dolbier Jr., W. R.; Burkholder, C. R.; Medebielle, M. Syntheses of 2-(Bromodifluoromethyl)benzoxazole and 5-(Bromodifluoromethyl)-1,2,4-oxadiazoles. *J. Fluorine Chem.* **1999**, 95, 127.
- (5) Xiao, Y.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. Nickel-Catalyzed Difluoroalkylation of (Hetero)Arylborons with Unactivated 1-Bromo-1,1-difluoroalkanes. *Angew. Chem., Int. Ed.* **2016**, 55, 5873.
- (6) Xu, C.; Guo, W.-H.; He, X.; Guo, Y.-L.; Zhang, X.-Y.; Zhang, X. Difluoromethylation of (Hetero)aryl Chlorides with Chlorodifluoromethane Catalyzed by Nickel. *Nat. Commun.* **2018**, 9, 1170.
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- (8) Chen, F.; Hashmi, A. S. Silver-Catalyzed Decarboxylative Alkynylation of α,α -Difluoroarylacetic Acids with Ethynylbenziodoxolone Reagents. *Org. Lett.*, **2016**, 18, 2880.
- (9) An, L.; Xu, C.; Zhang, X. Highly Selective Nickel-Catalyzed *gem*-Difluoropropargylation of Unactivated Alkylzinc Reagents. *Nat. Commun.* **2017**, 8, 1460.

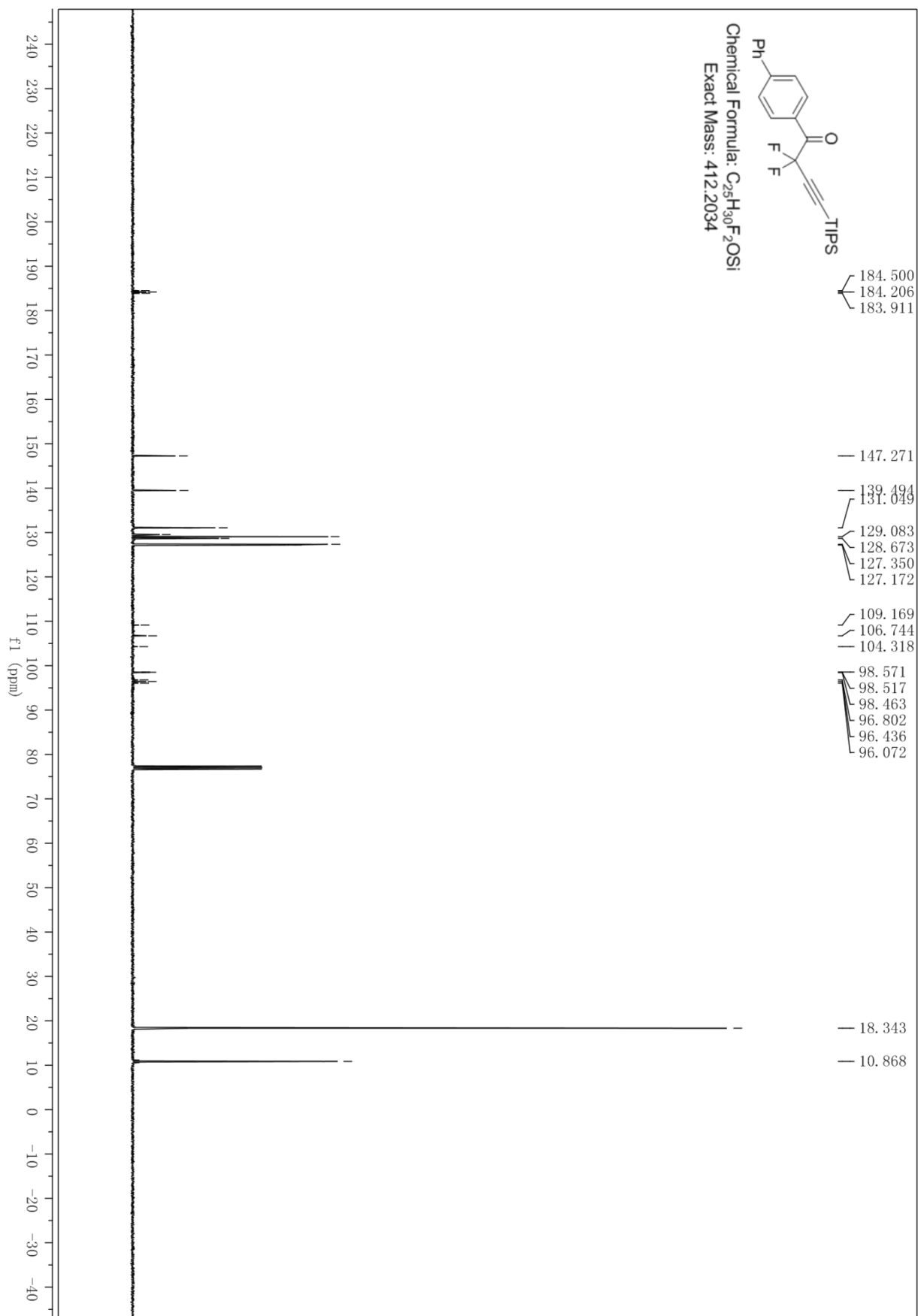
1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3a).



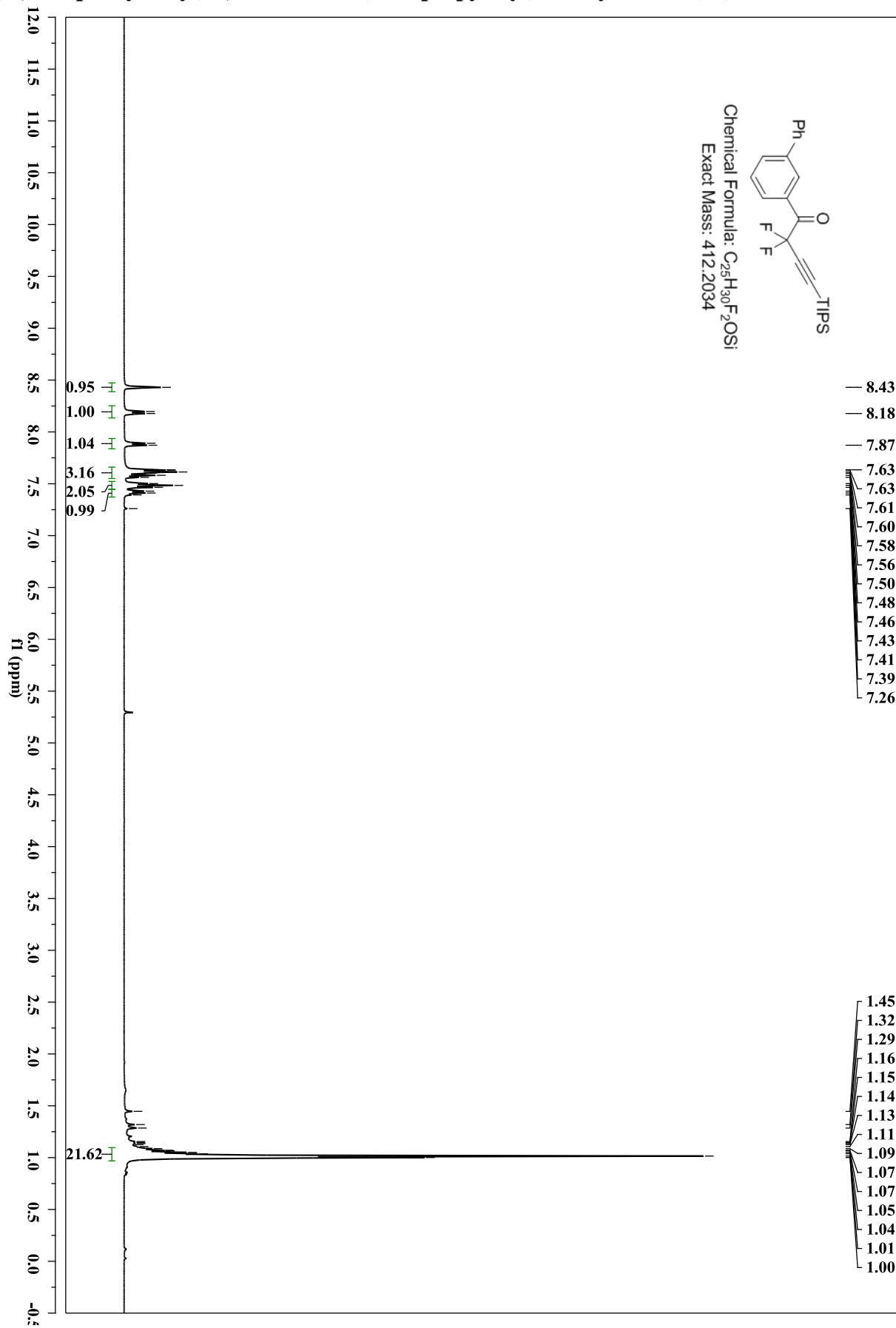


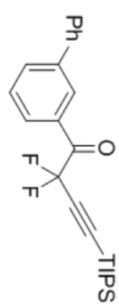
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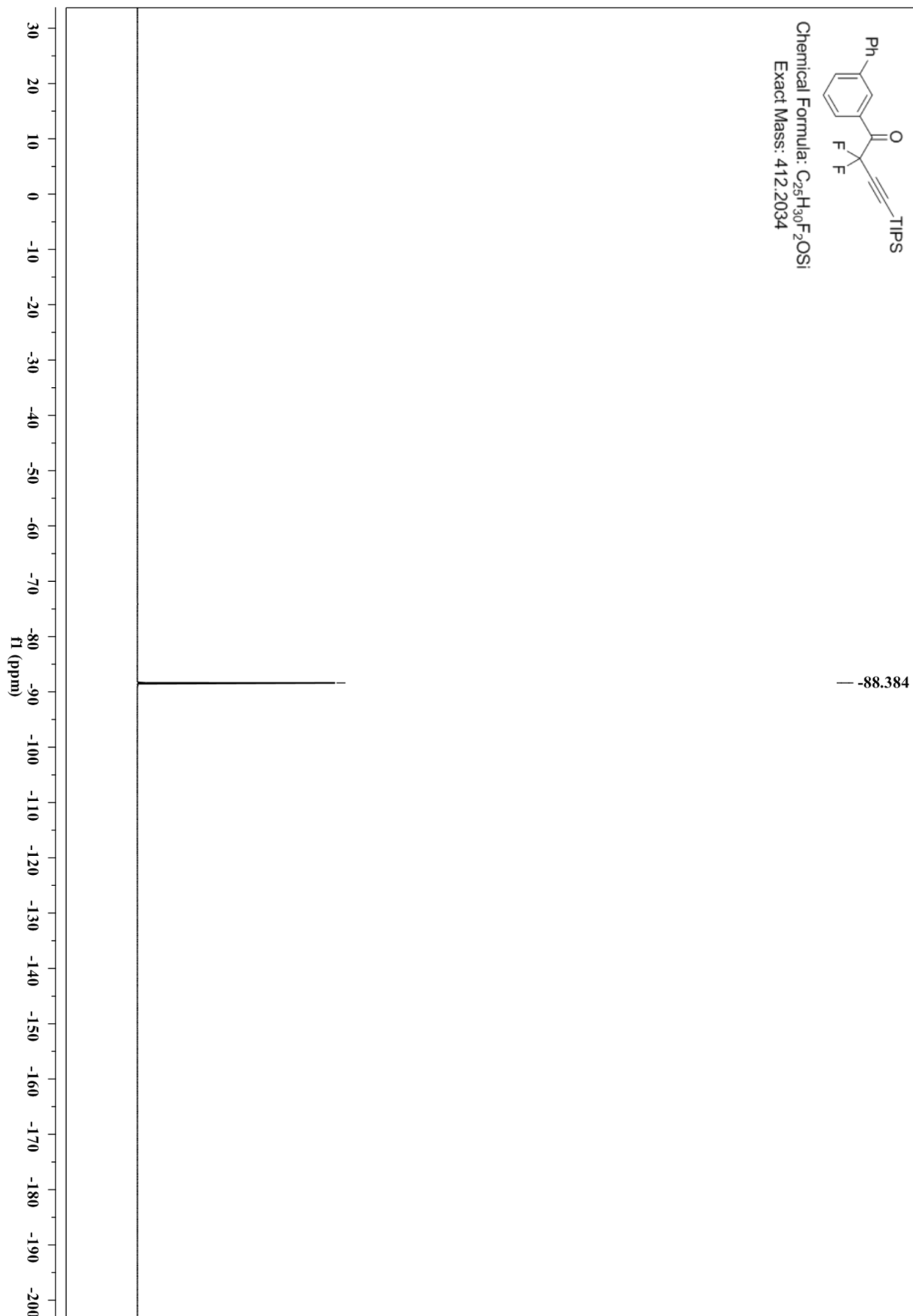


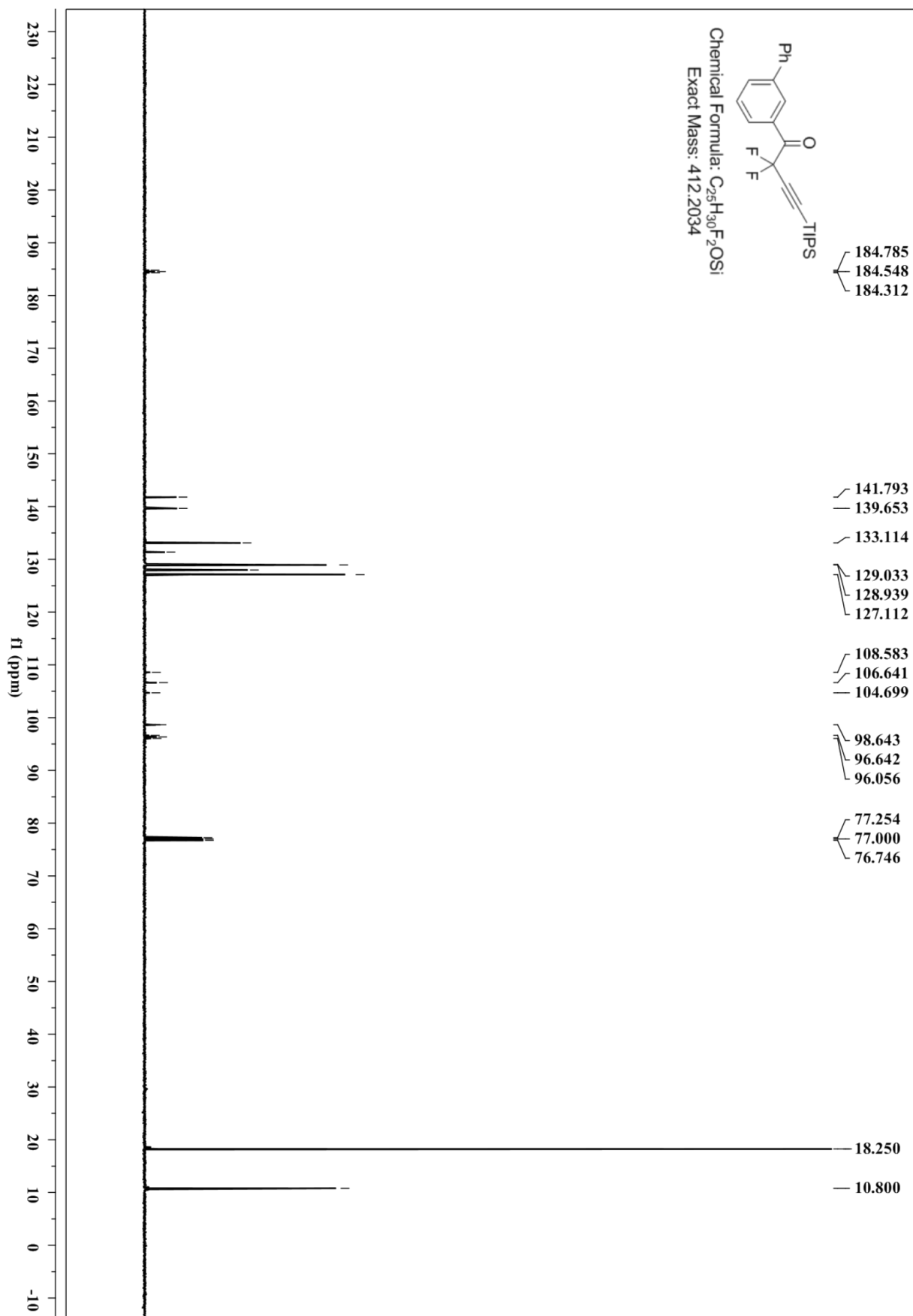
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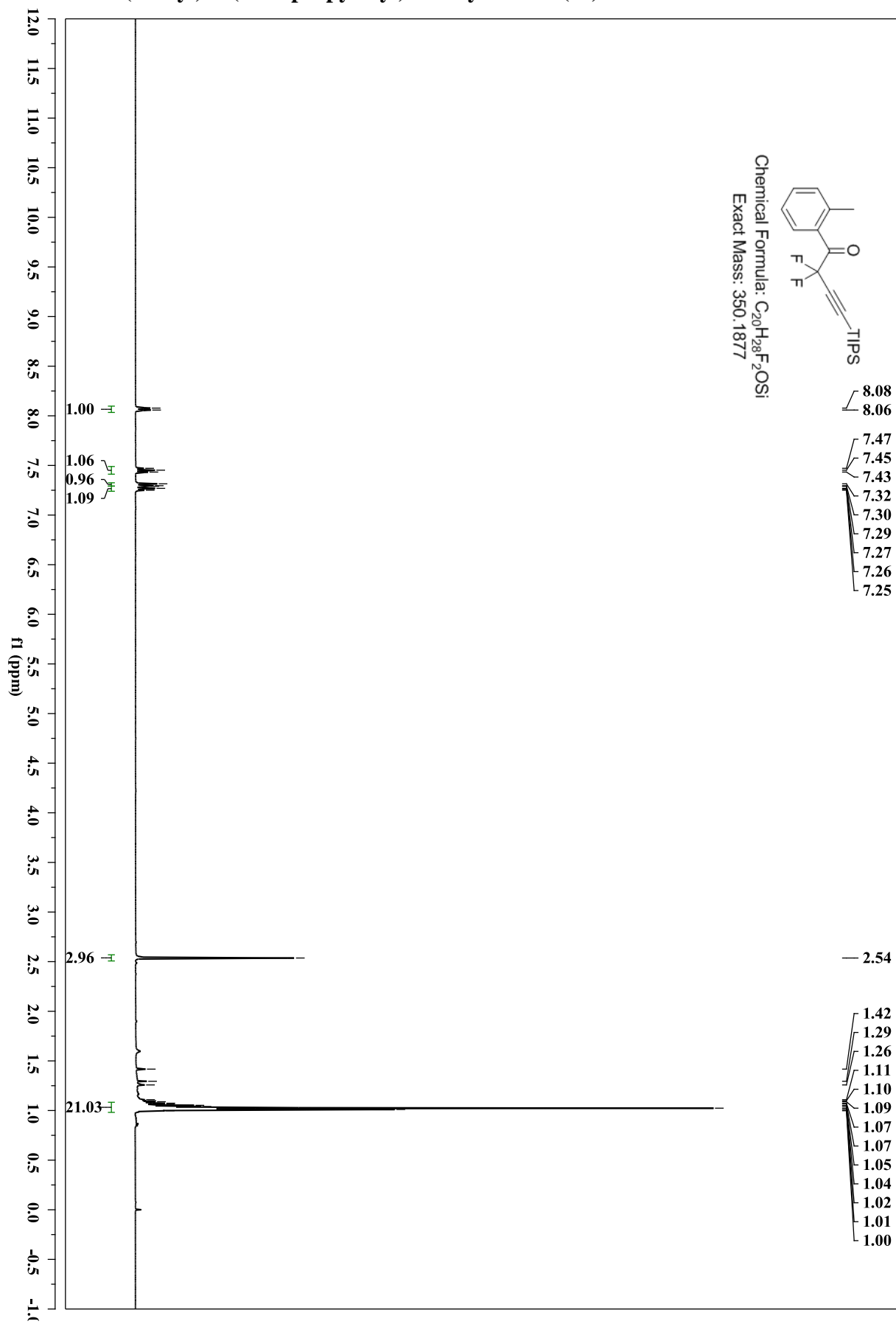


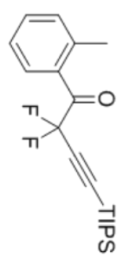
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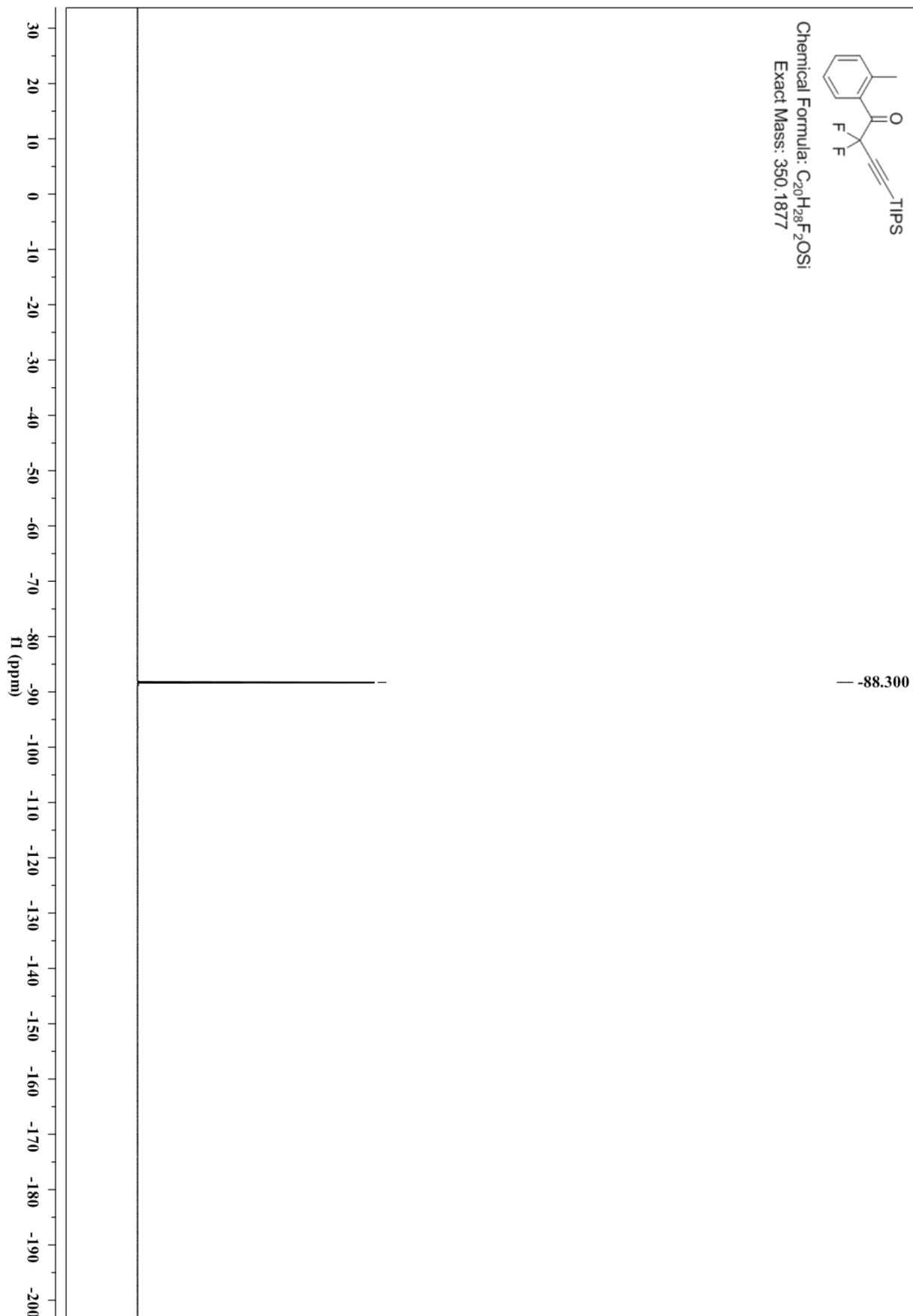


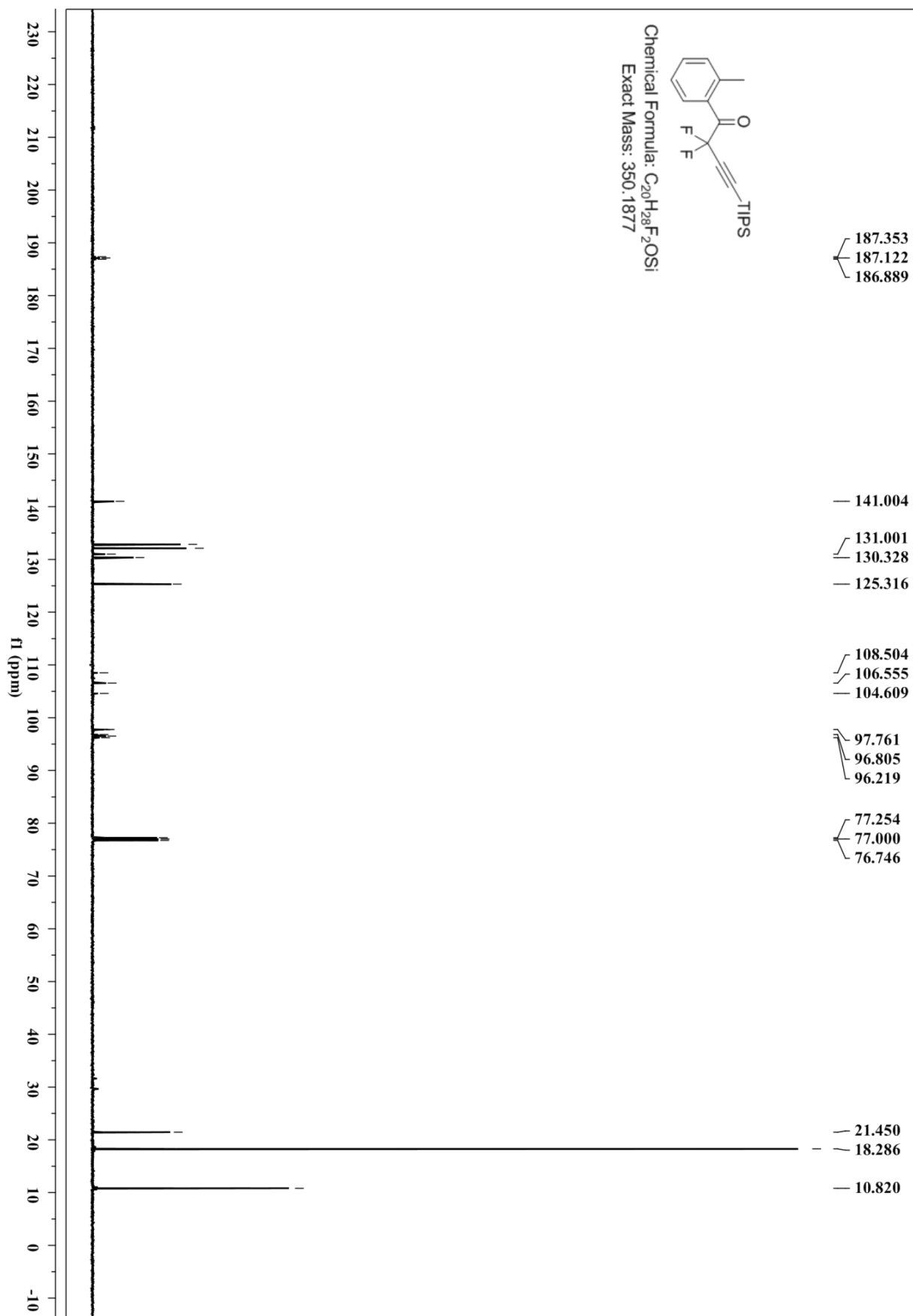
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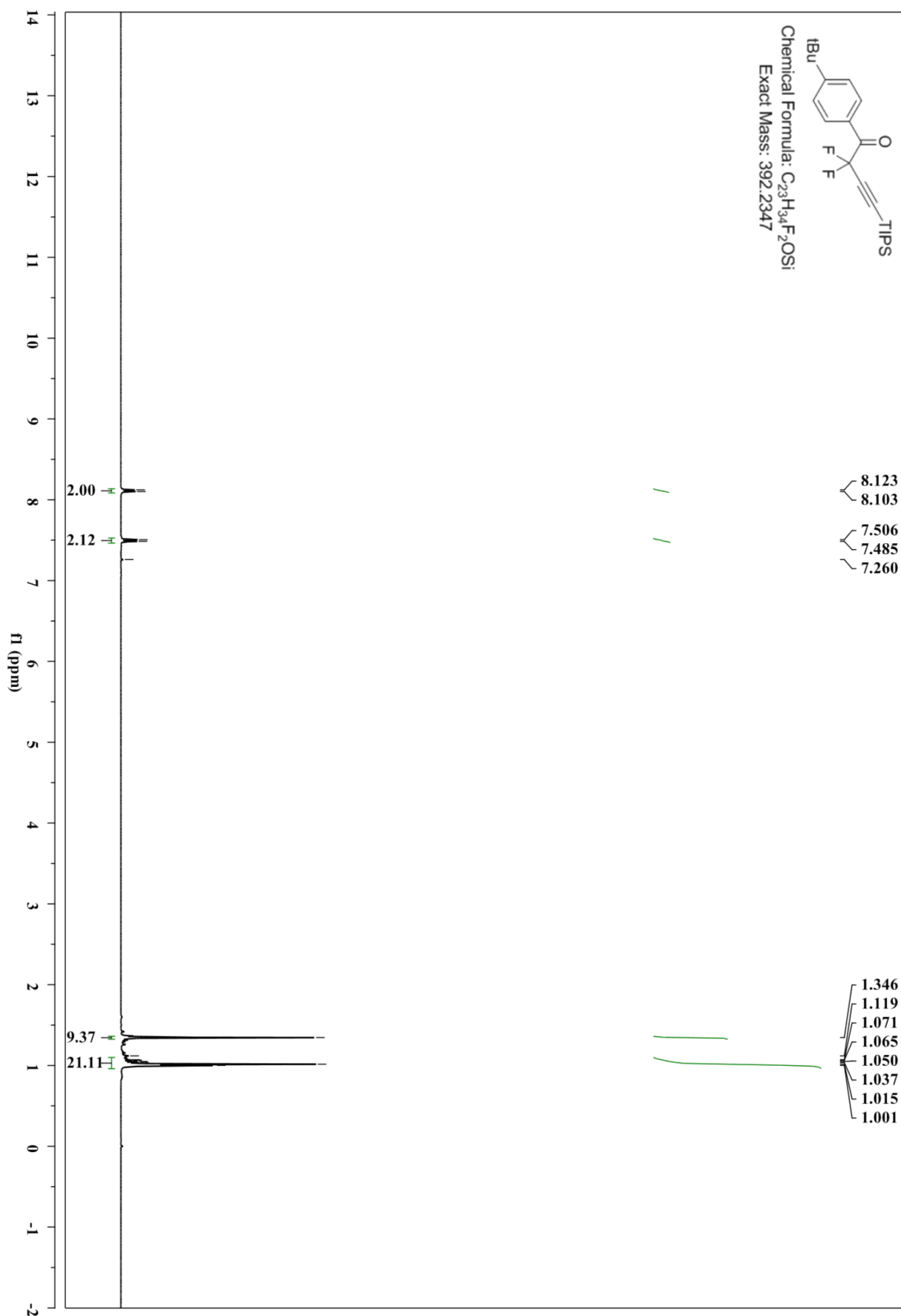


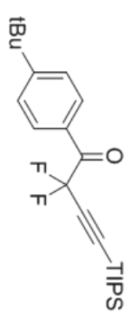
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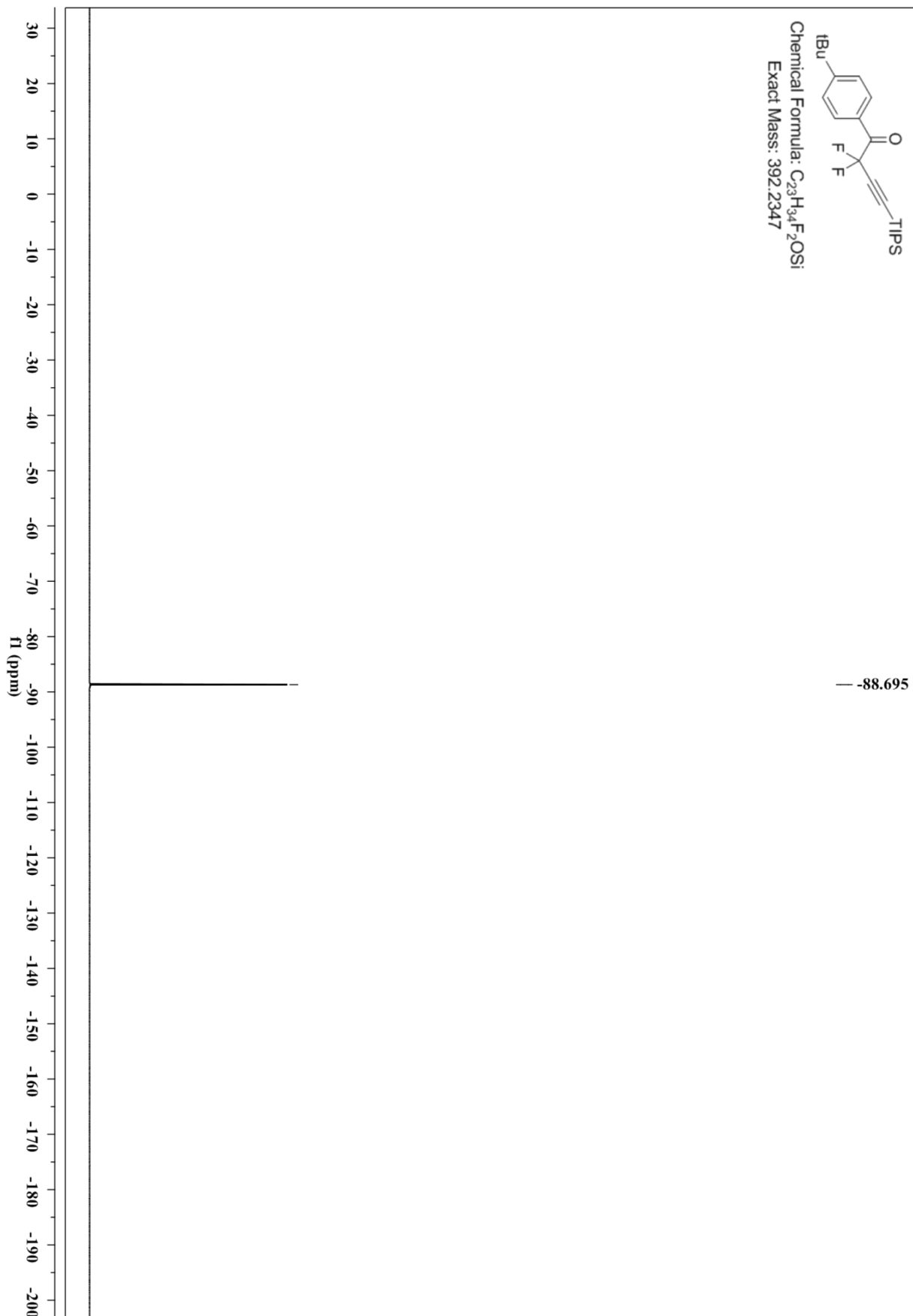


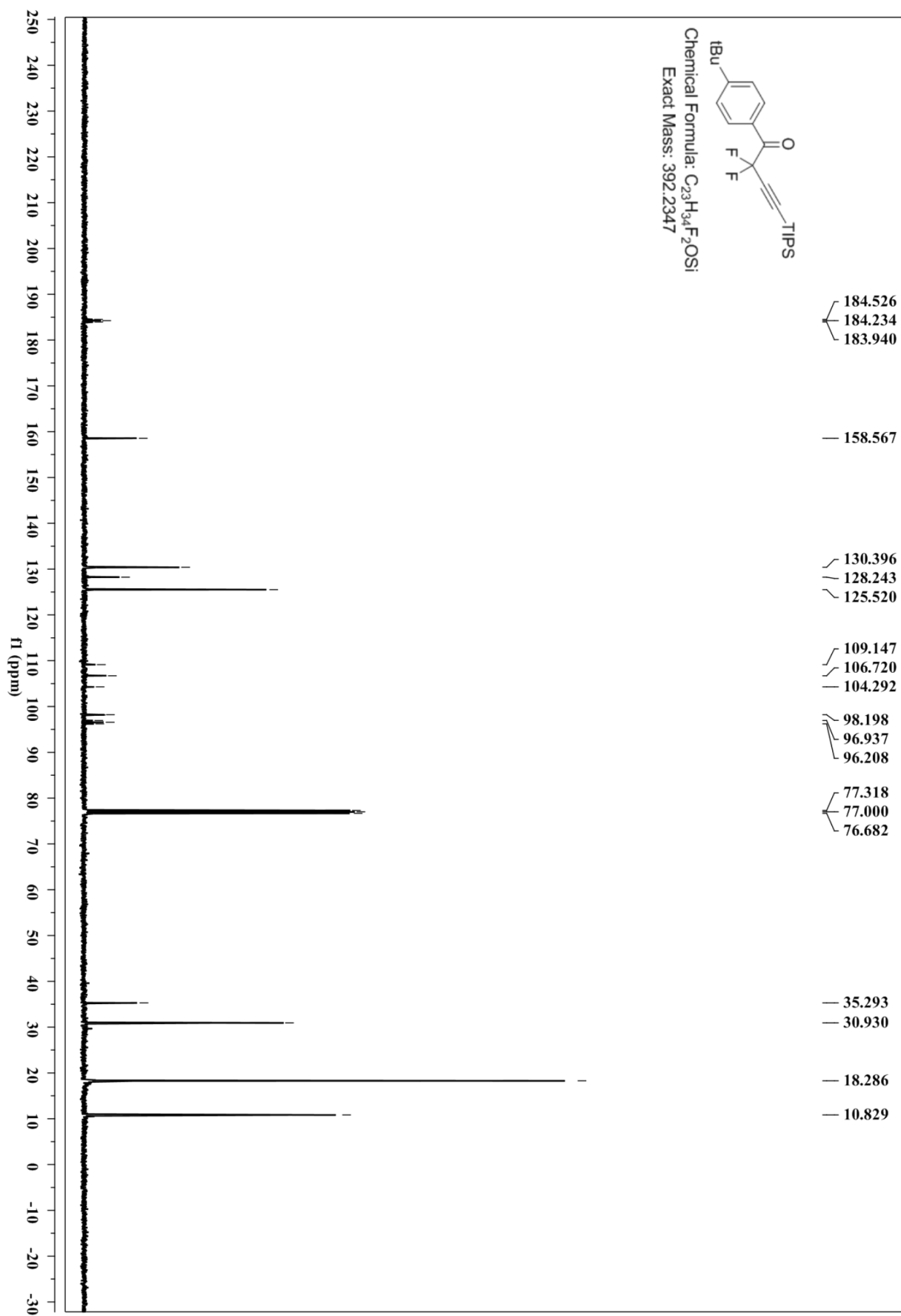
1-(4-(*tert*-Butyl)phenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3d).



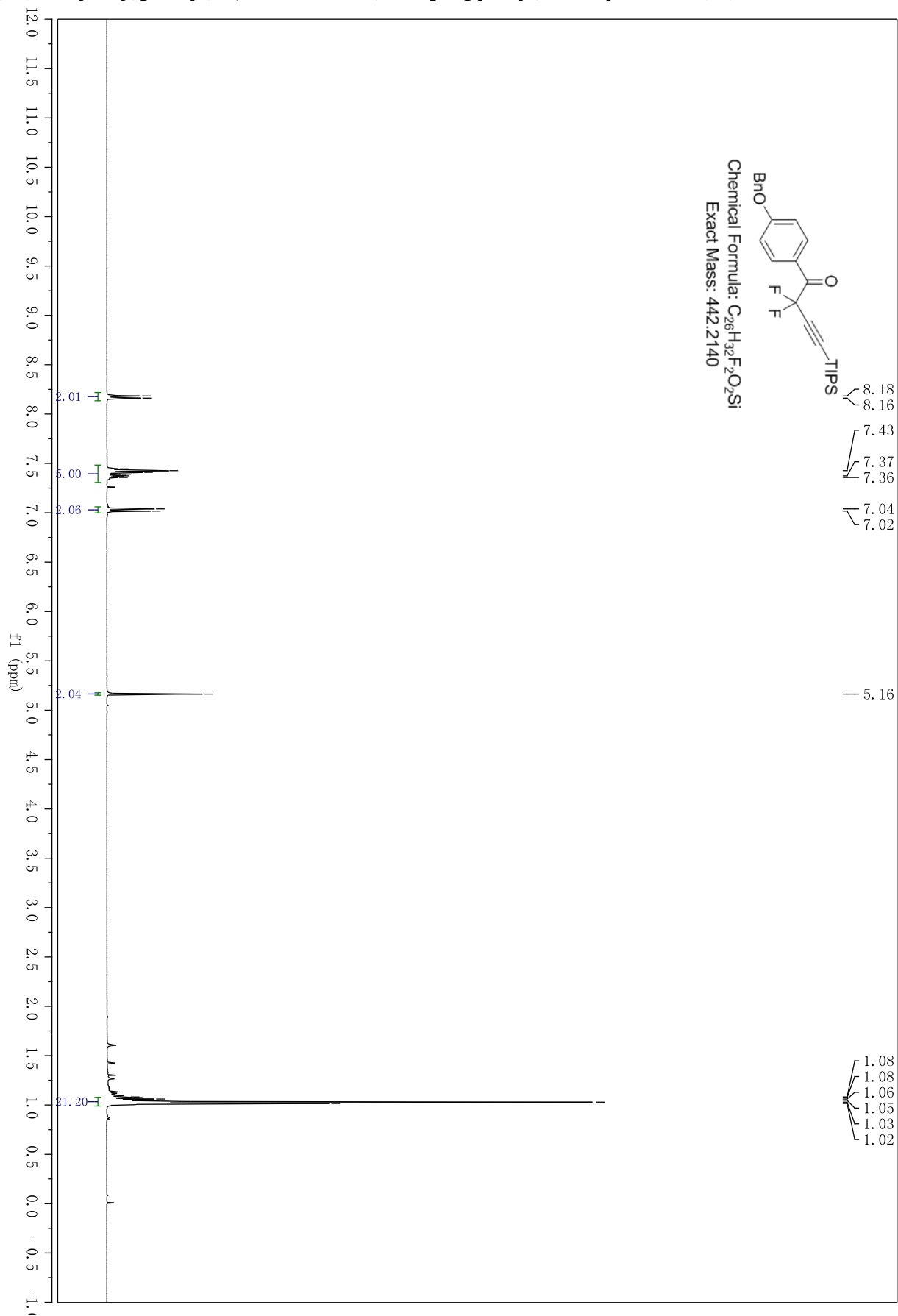


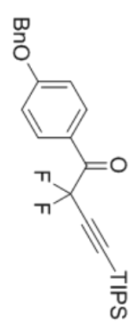
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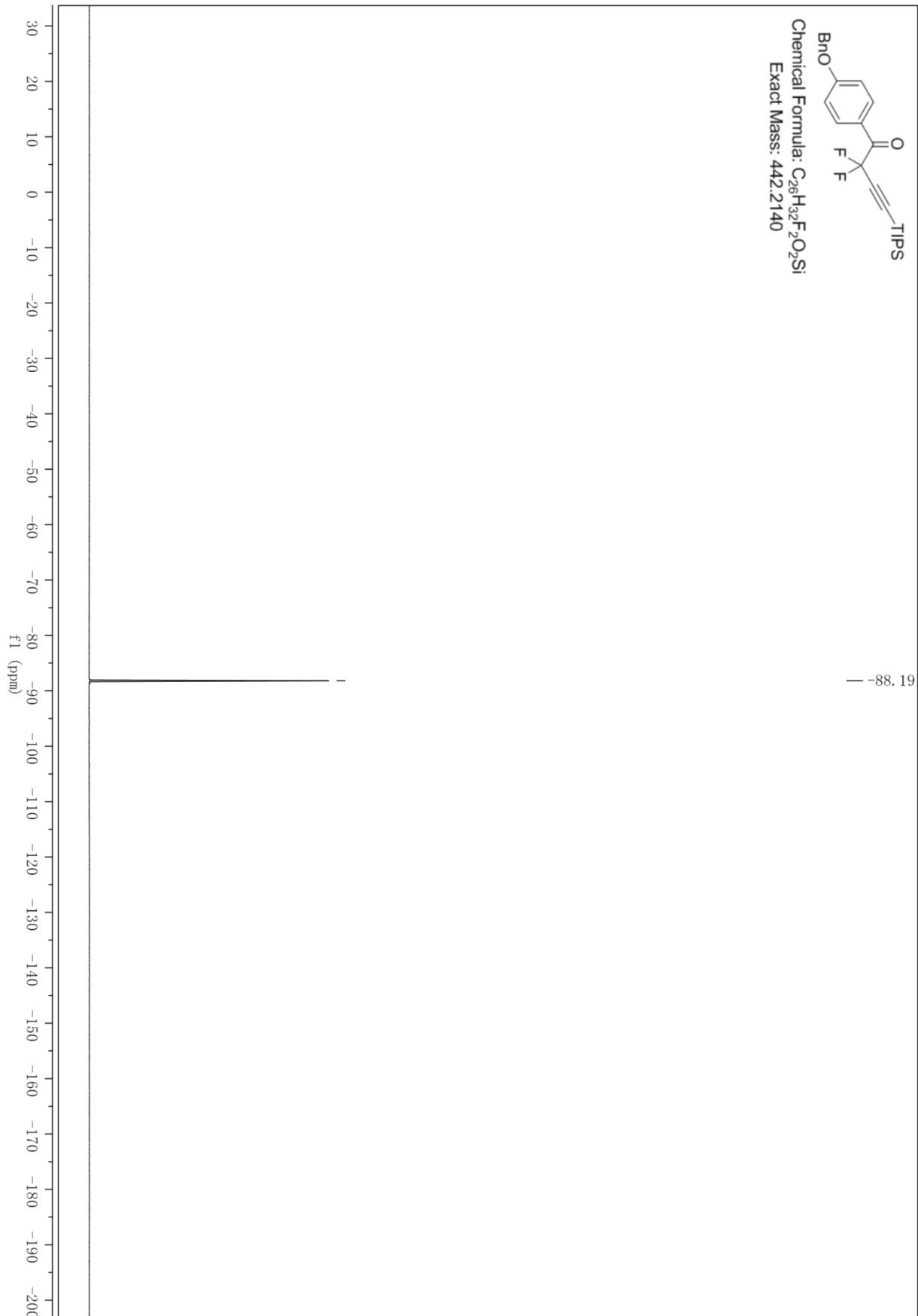


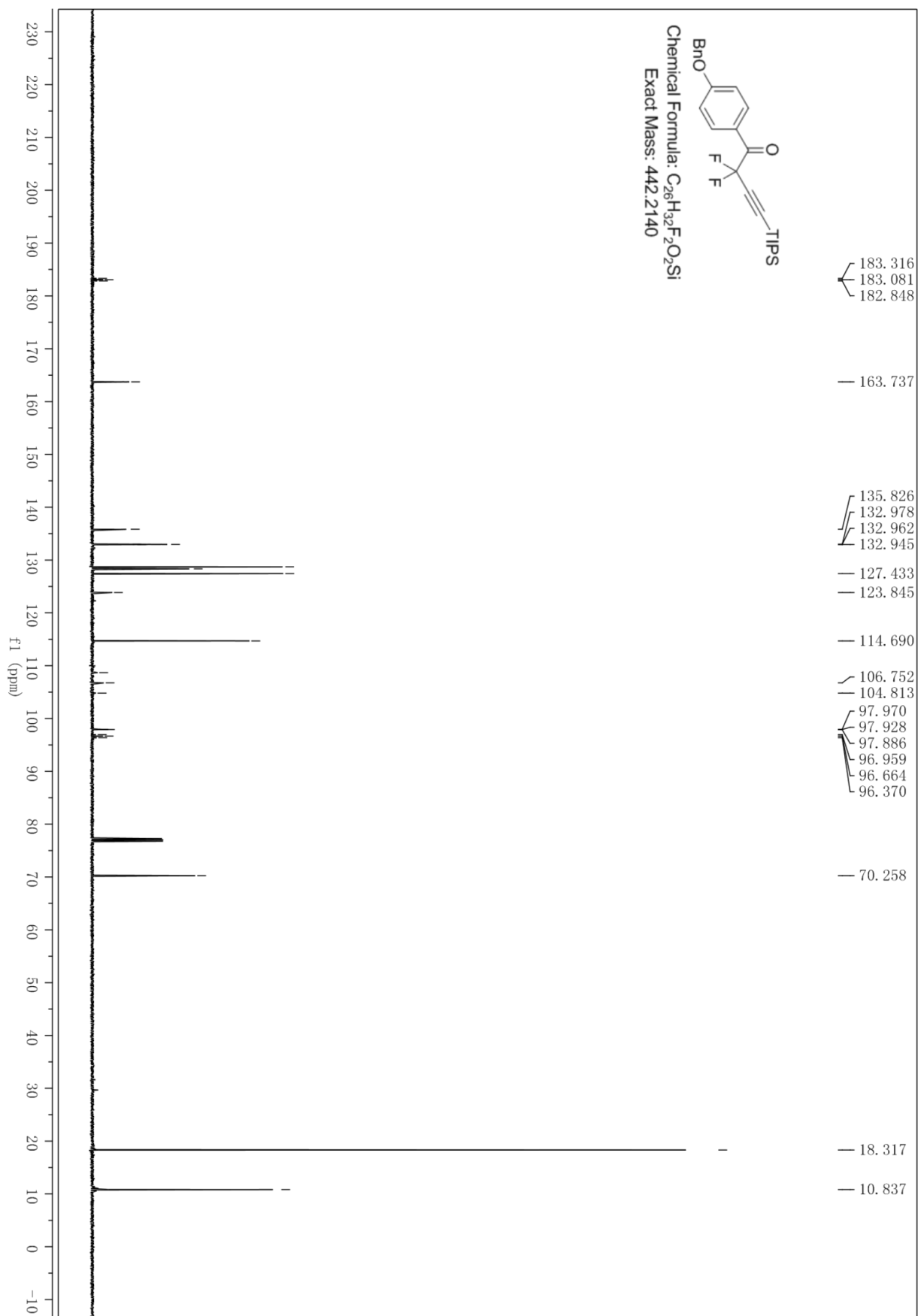
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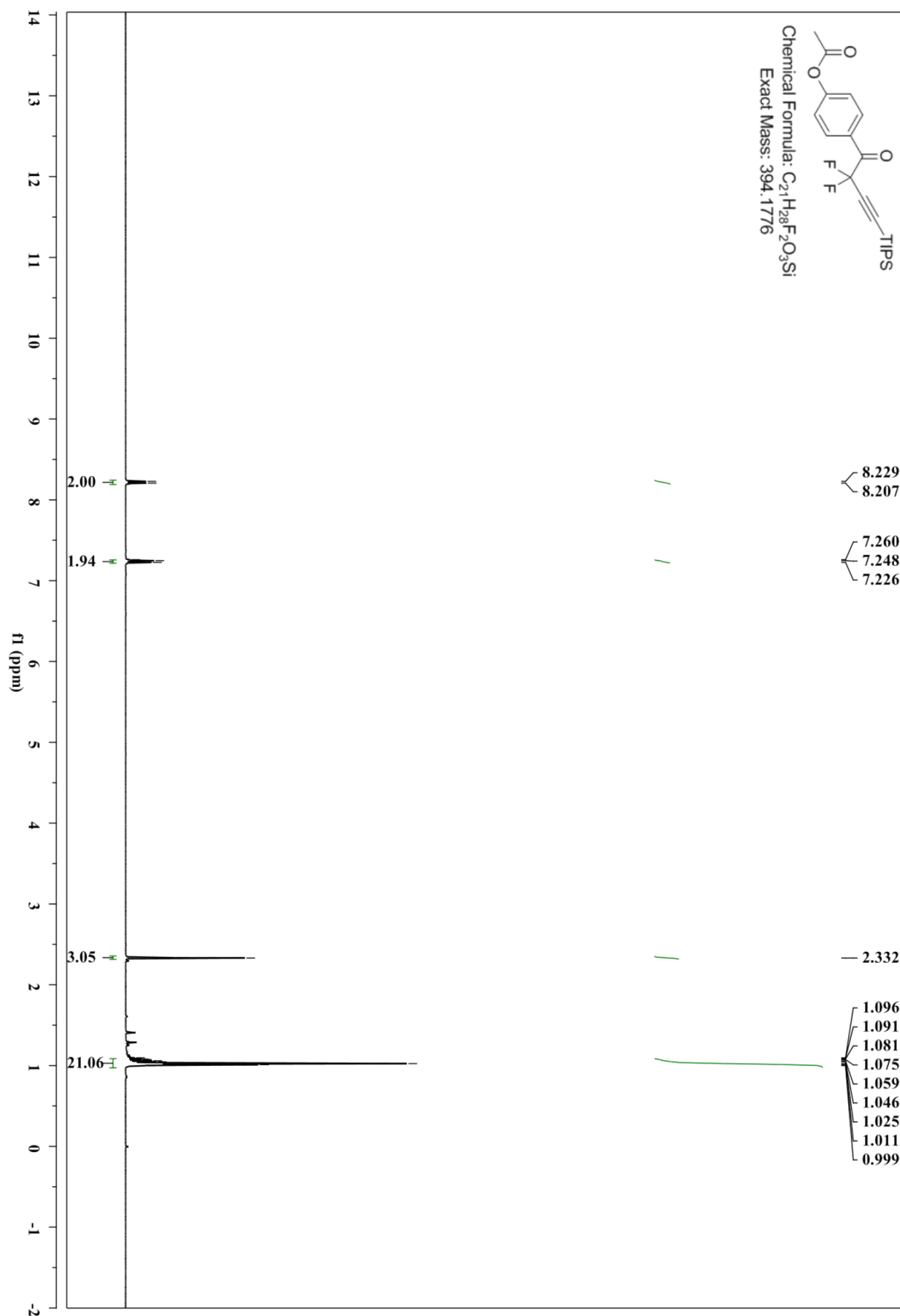


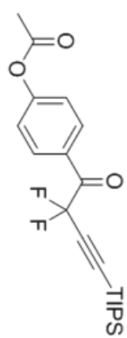
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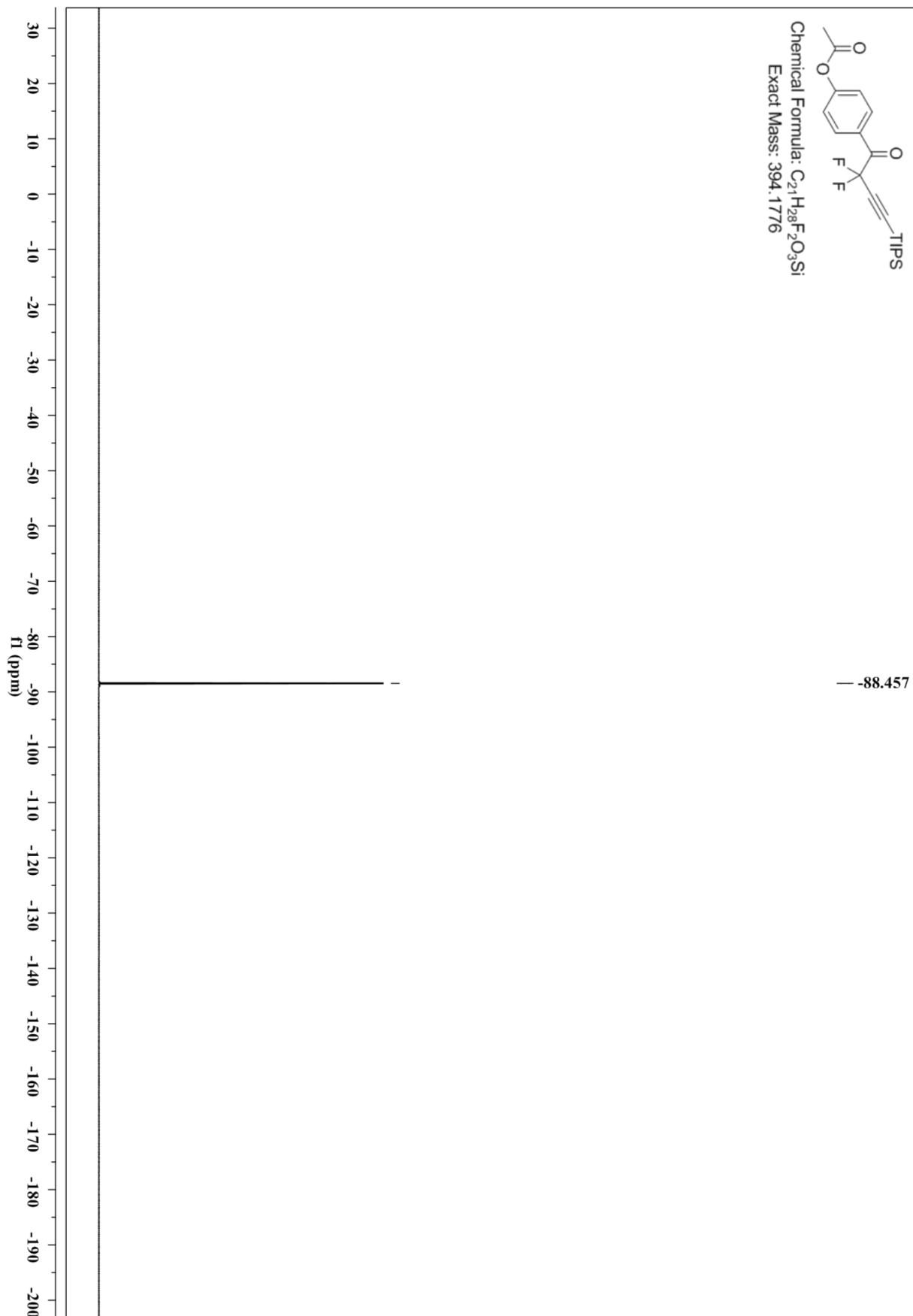


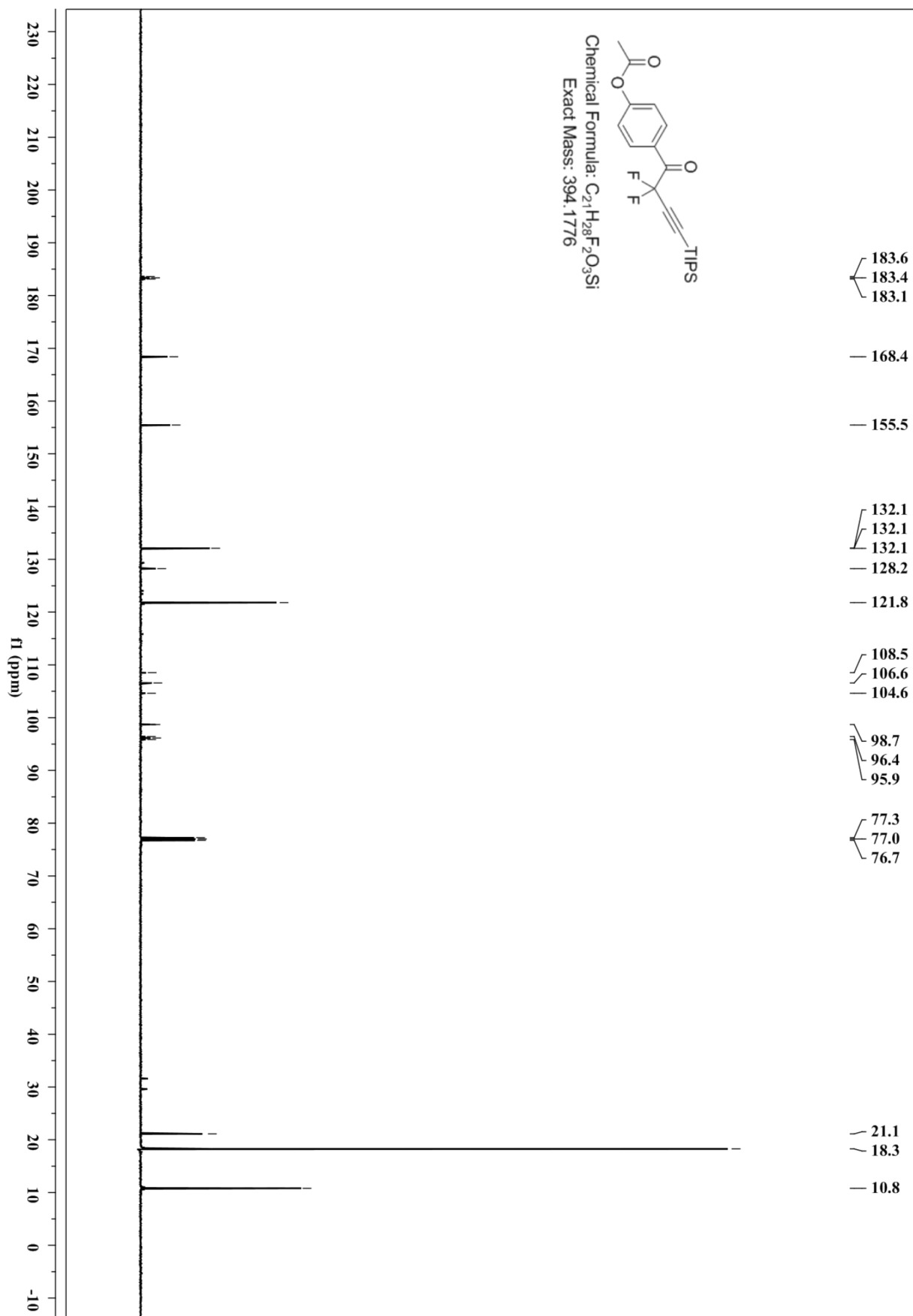
4-(2,2-Difluoro-4-(triisopropylsilyl)but-3-ynoyl)phenyl acetate (3f).



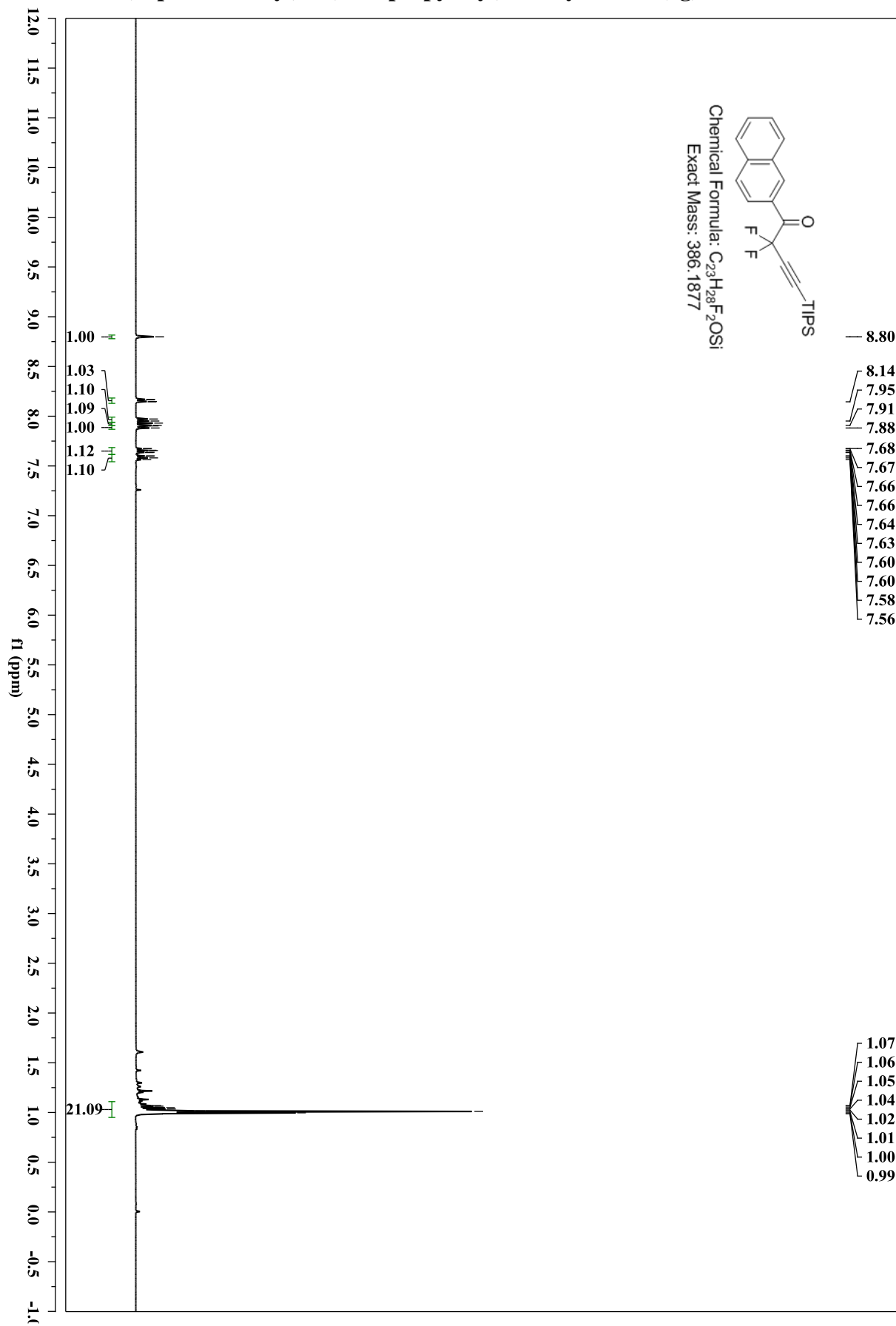


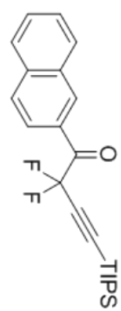
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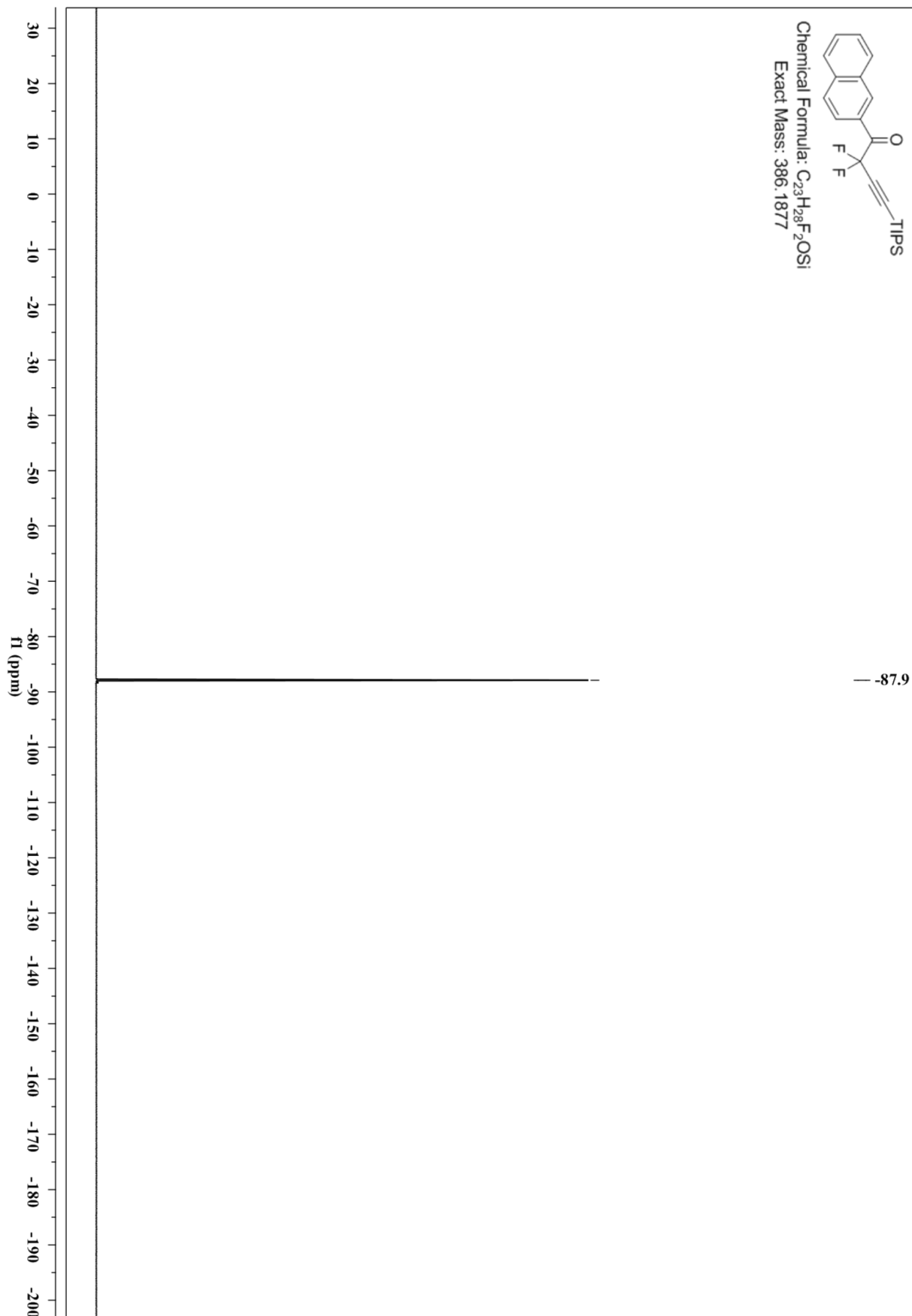


2,2-Difluoro-1-(naphthalen-2-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3g).

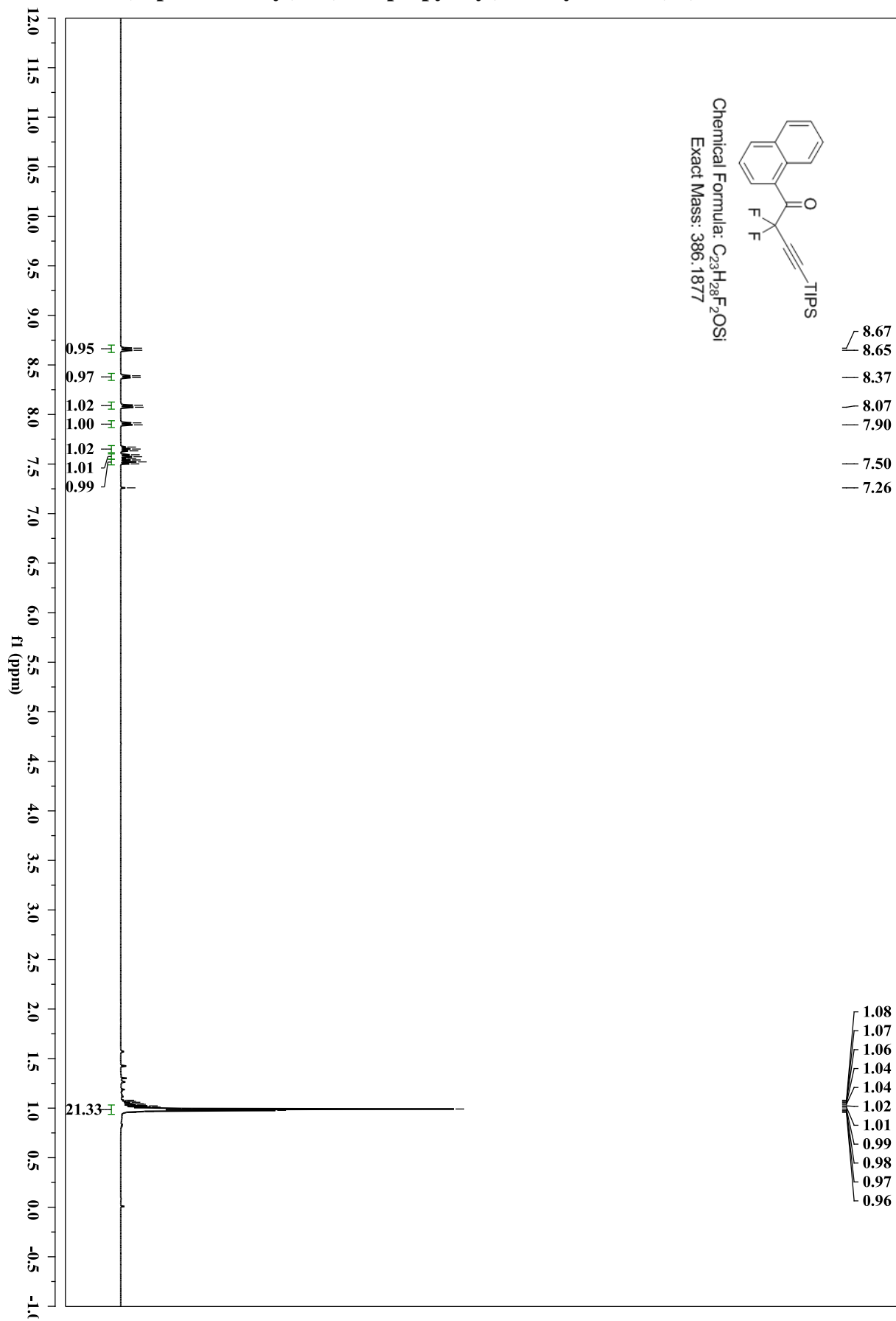


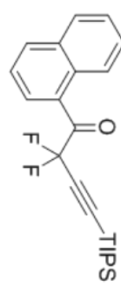


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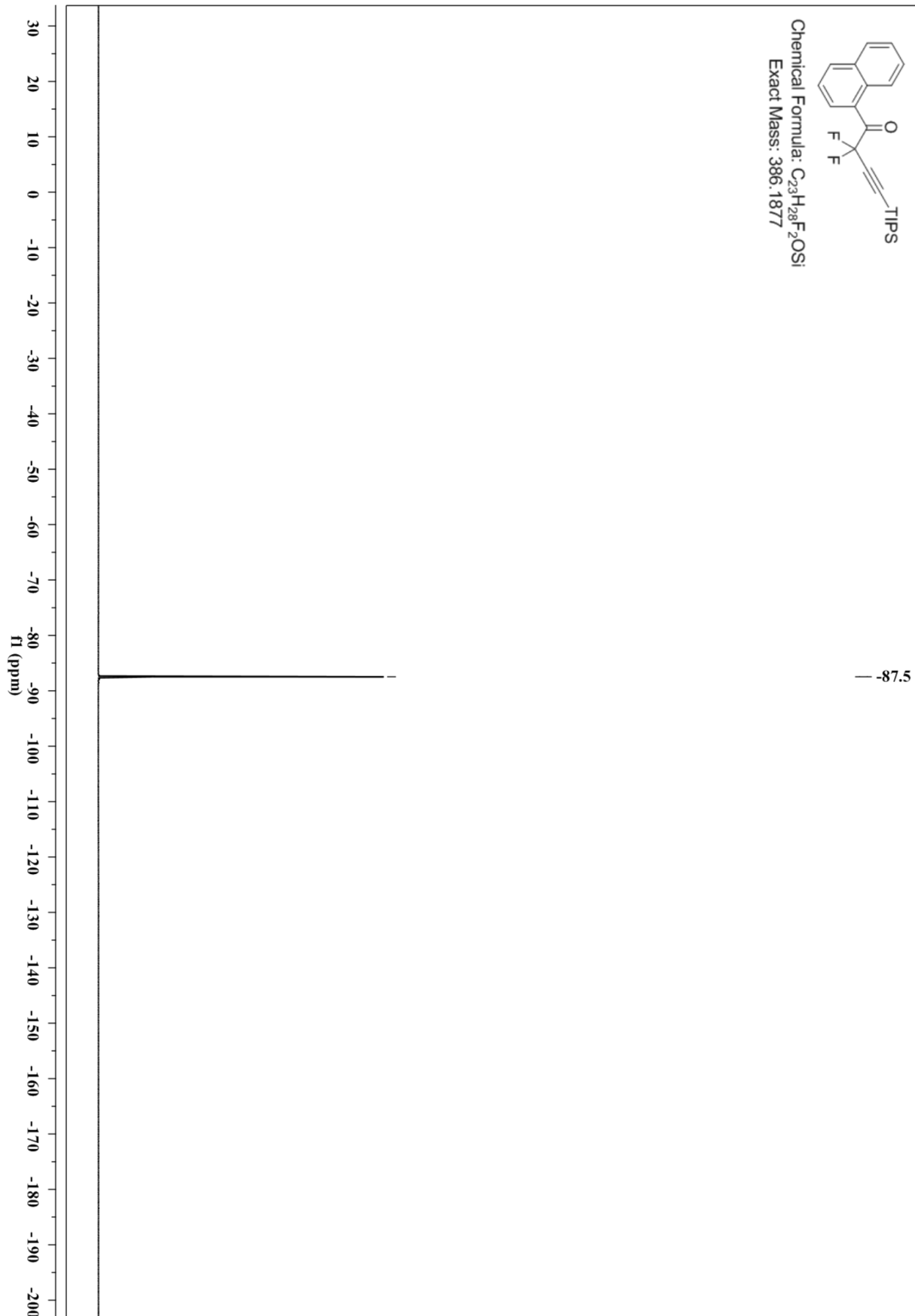


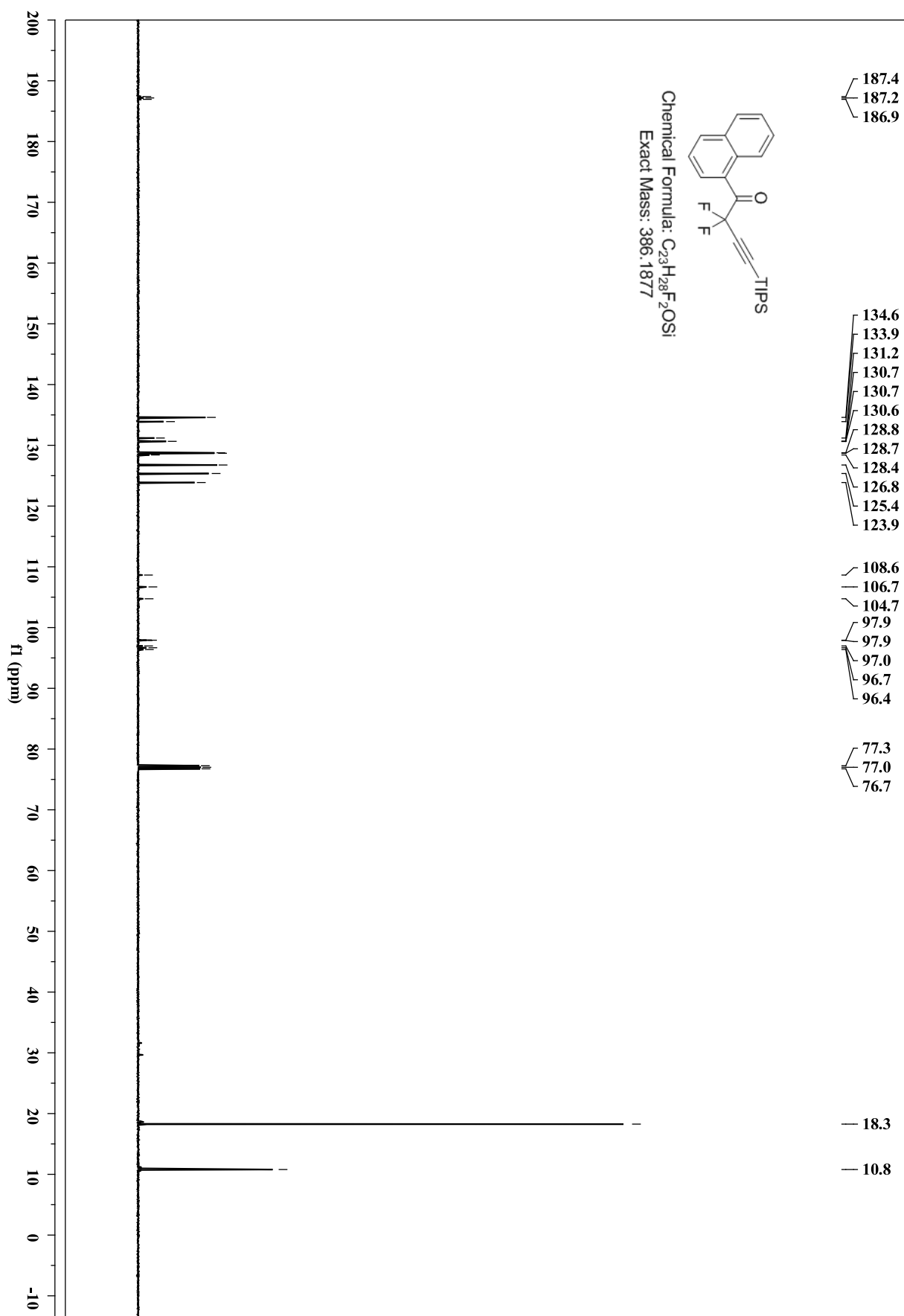
2,2-Difluoro-1-(naphthalen-1-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3h).



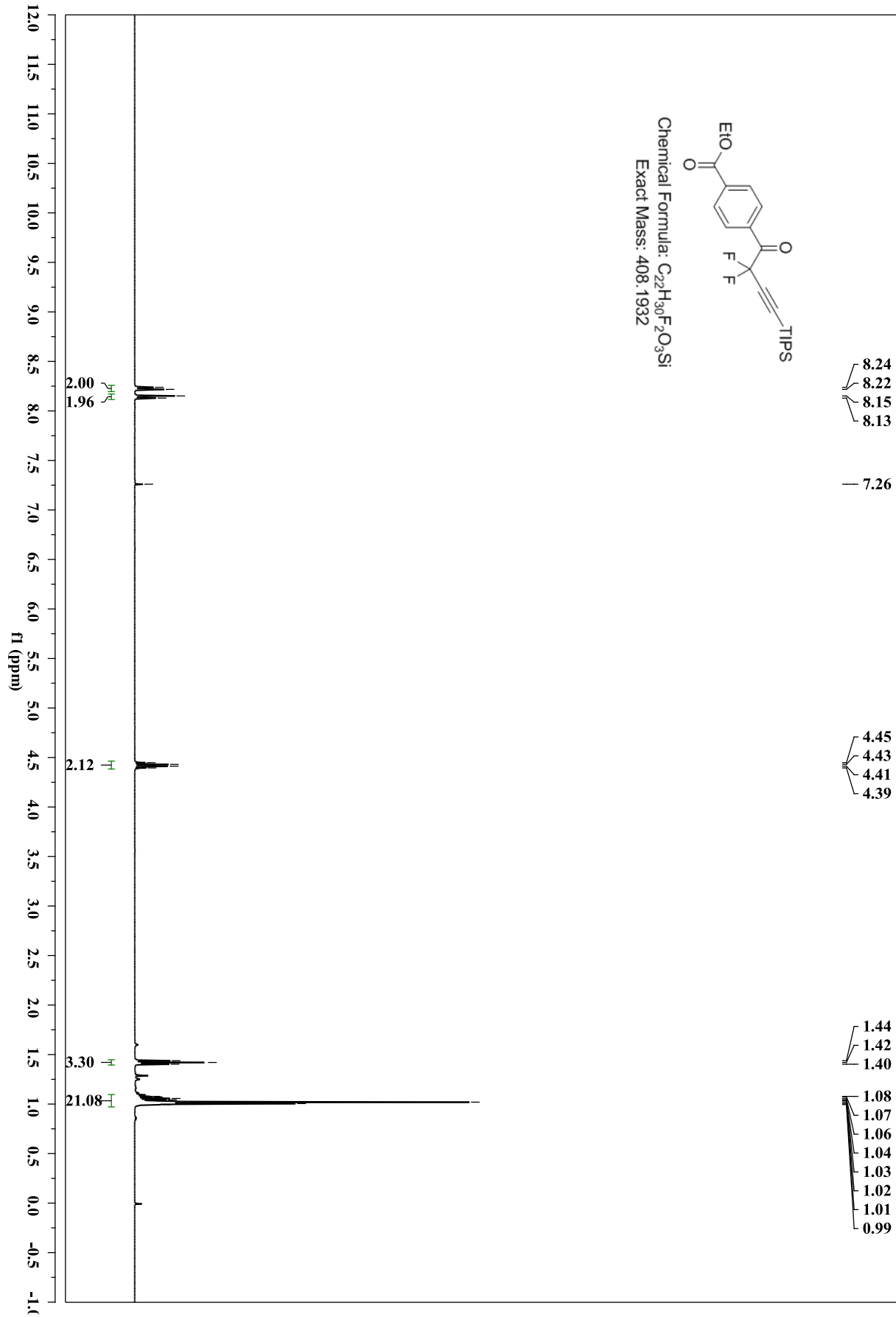


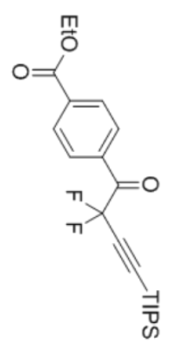
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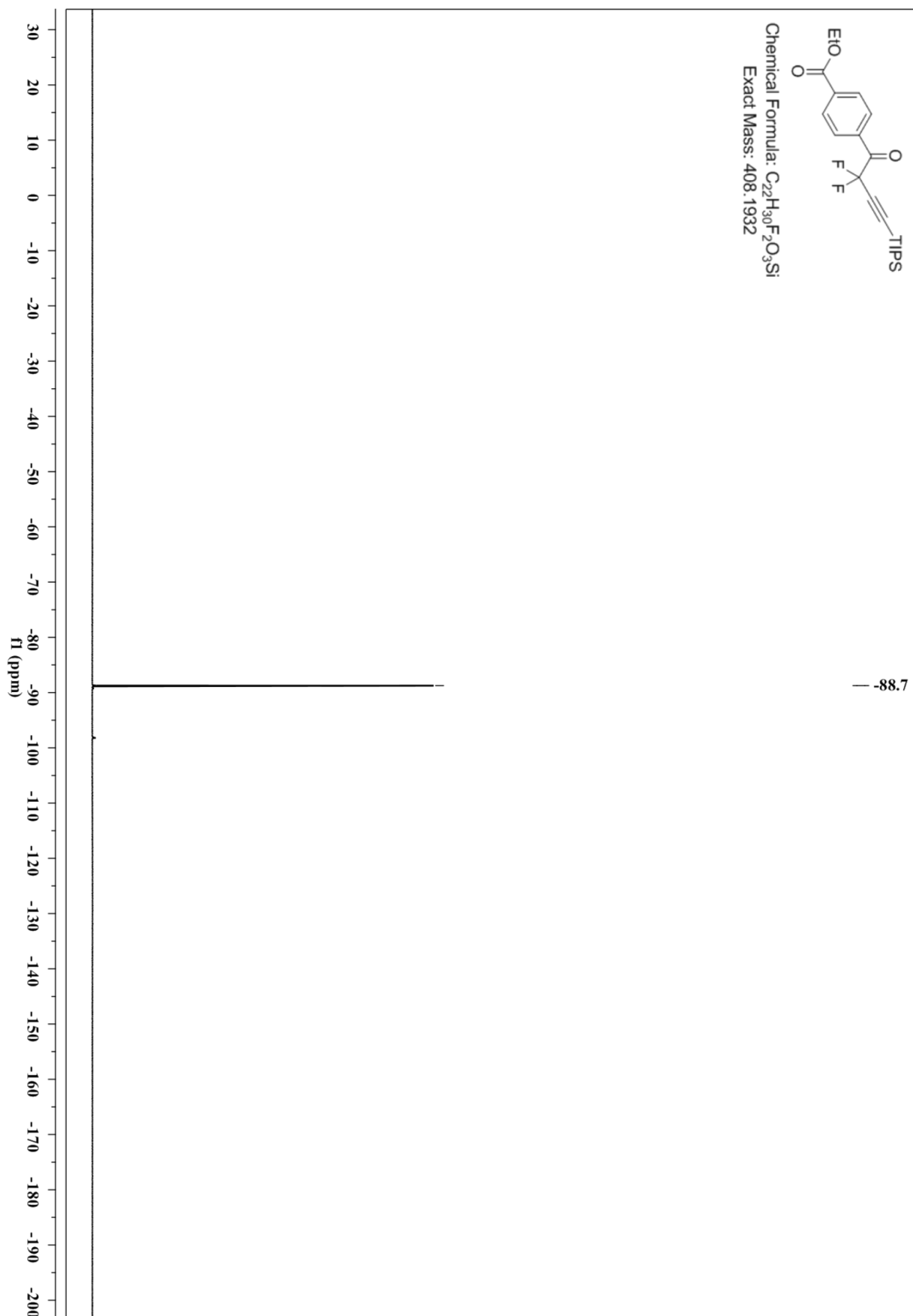


Ethyl 4-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzoate (3i).

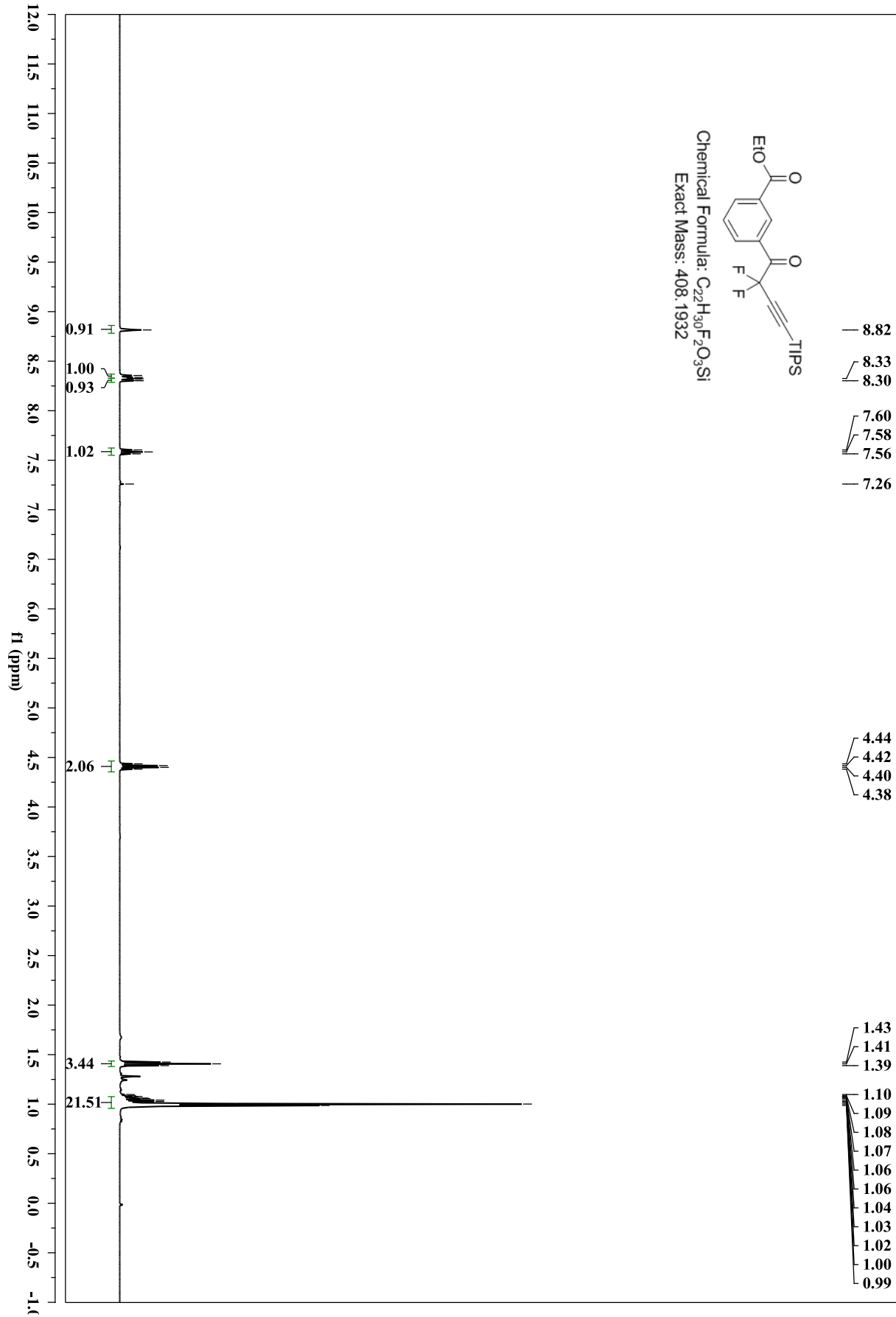


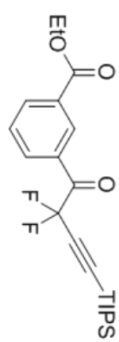


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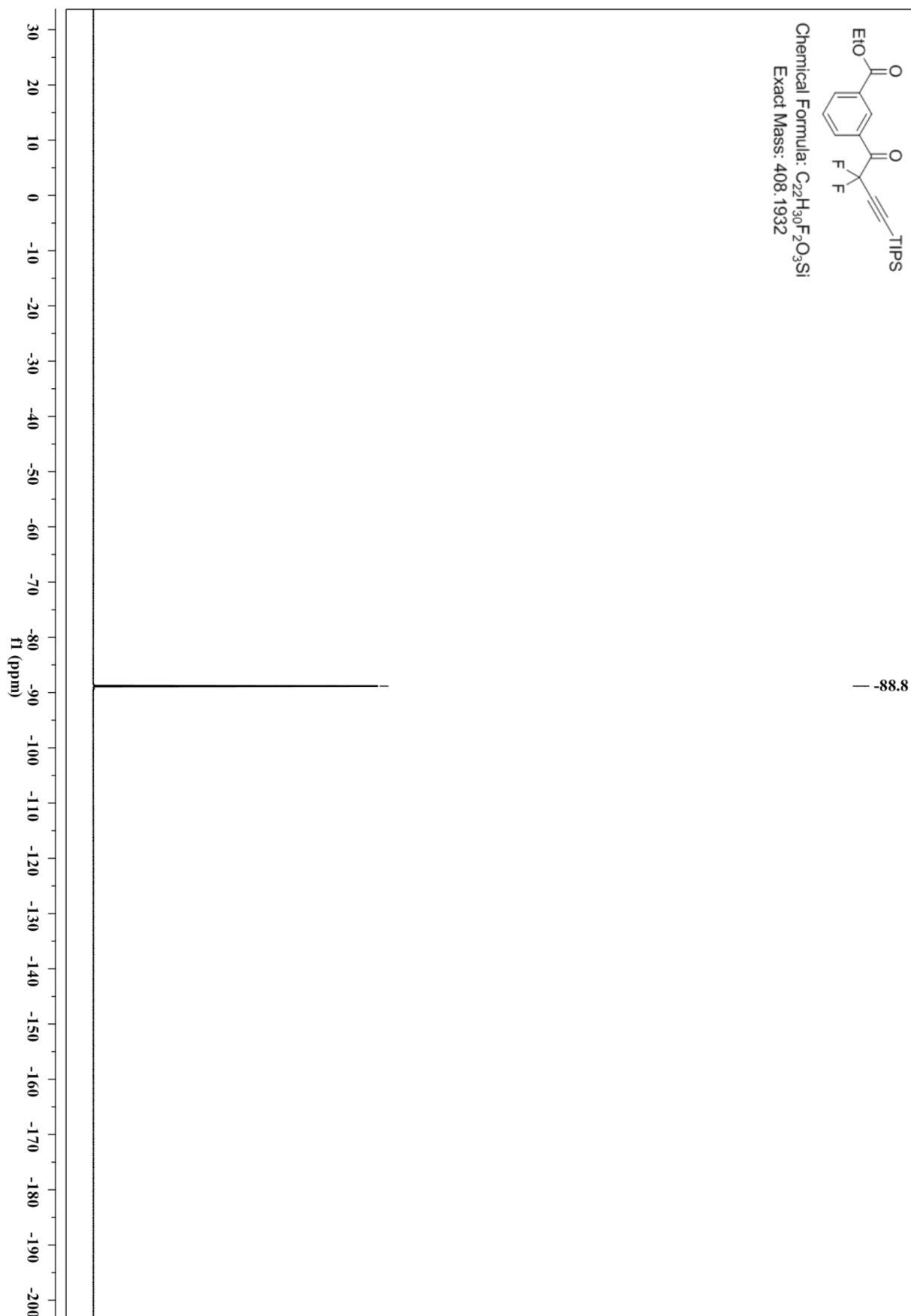


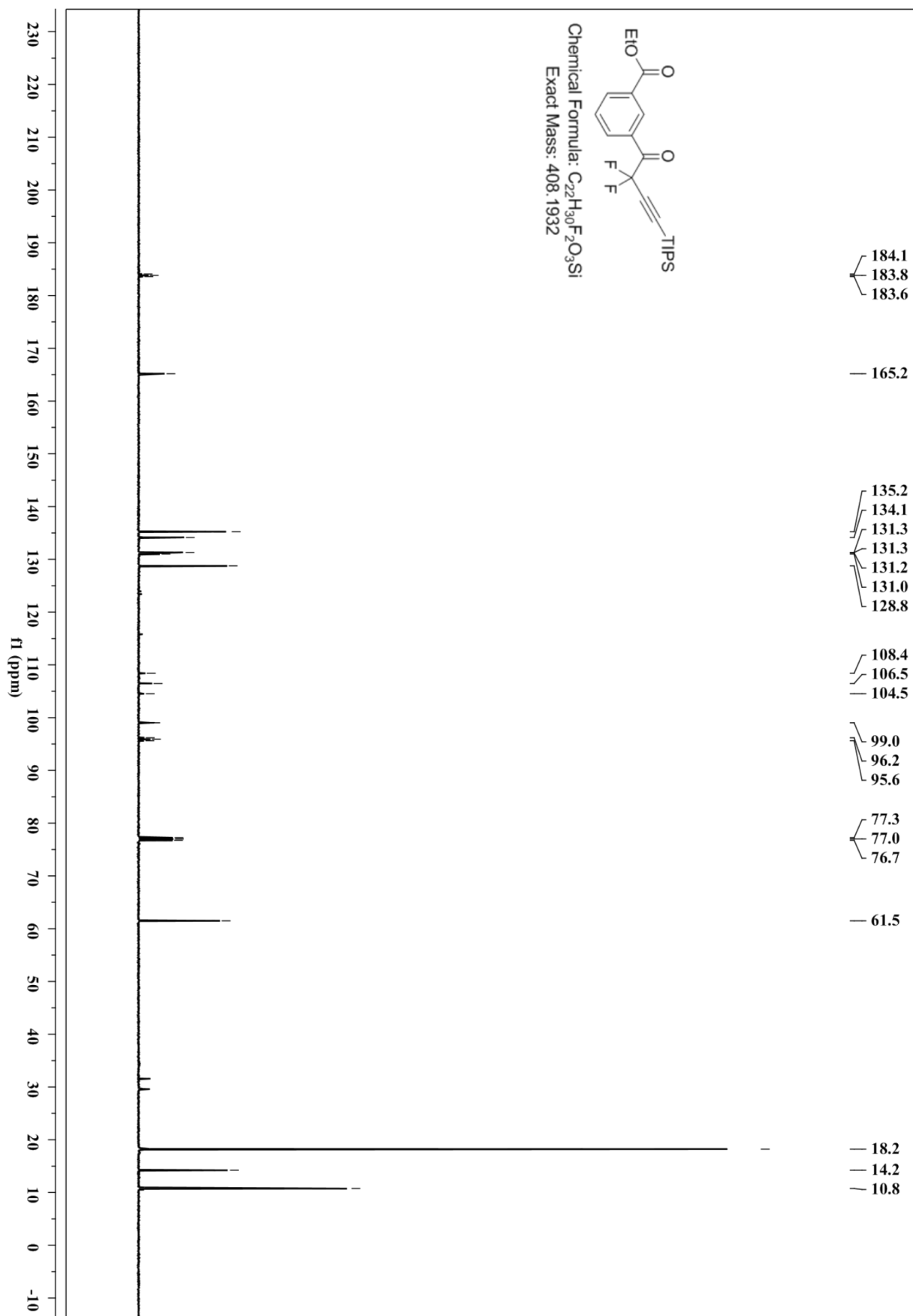
Ethyl 3-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzoate (3j).



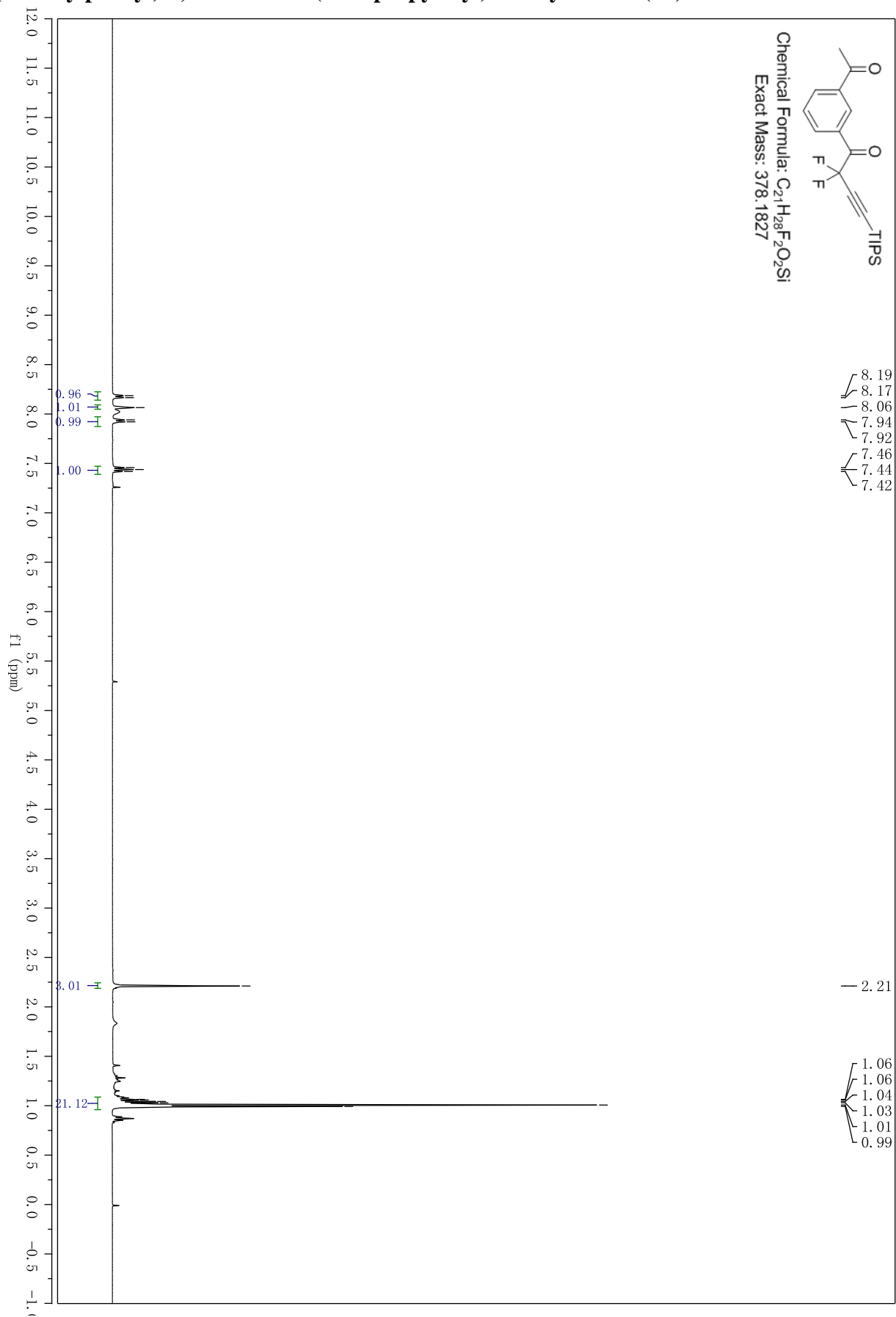


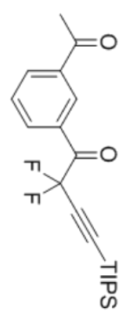
Chemical Formula: $C_{22}H_{30}F_2O_3Si$
Exact Mass: 408.1932



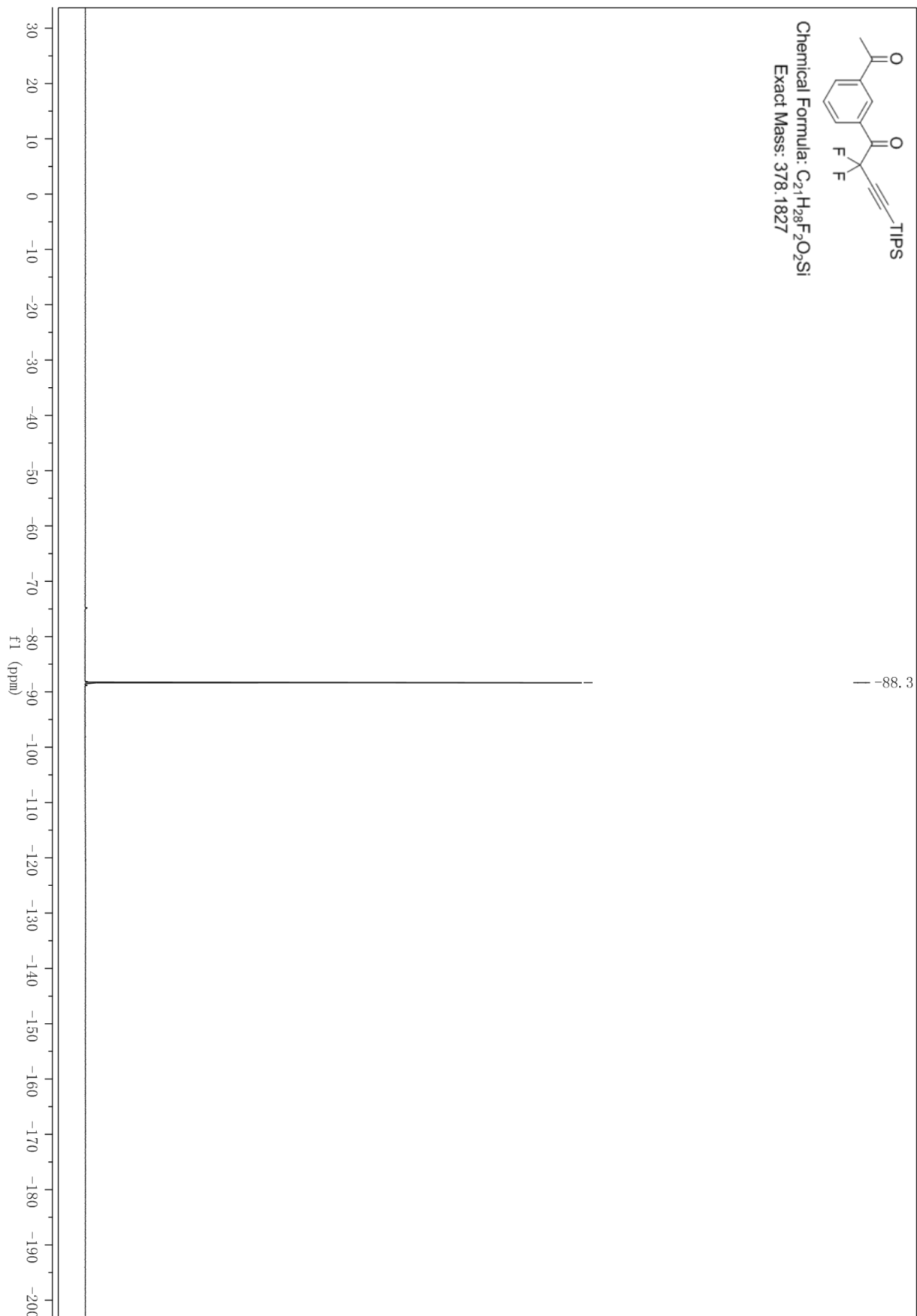


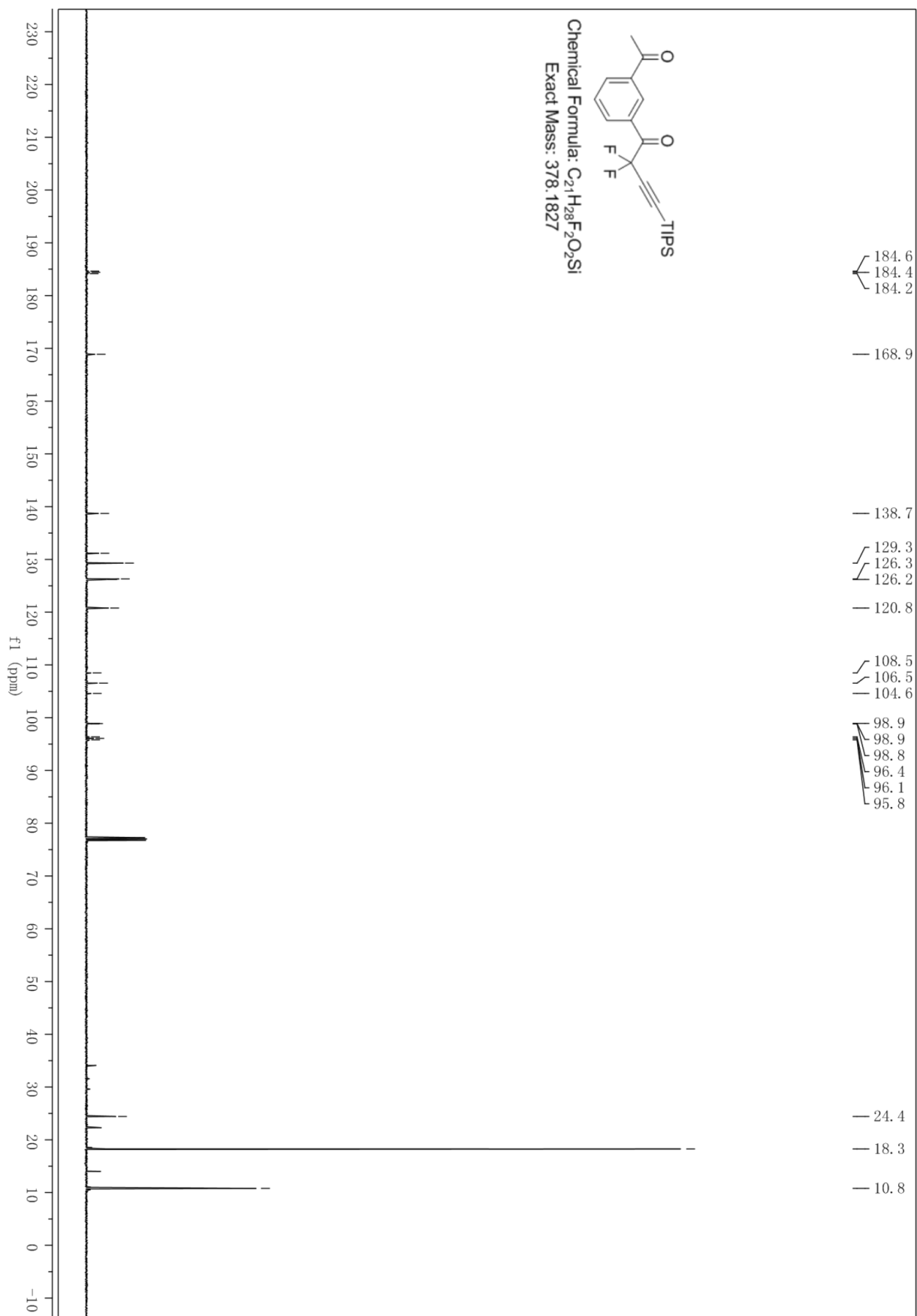
1-(3-Acetylphenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3k).



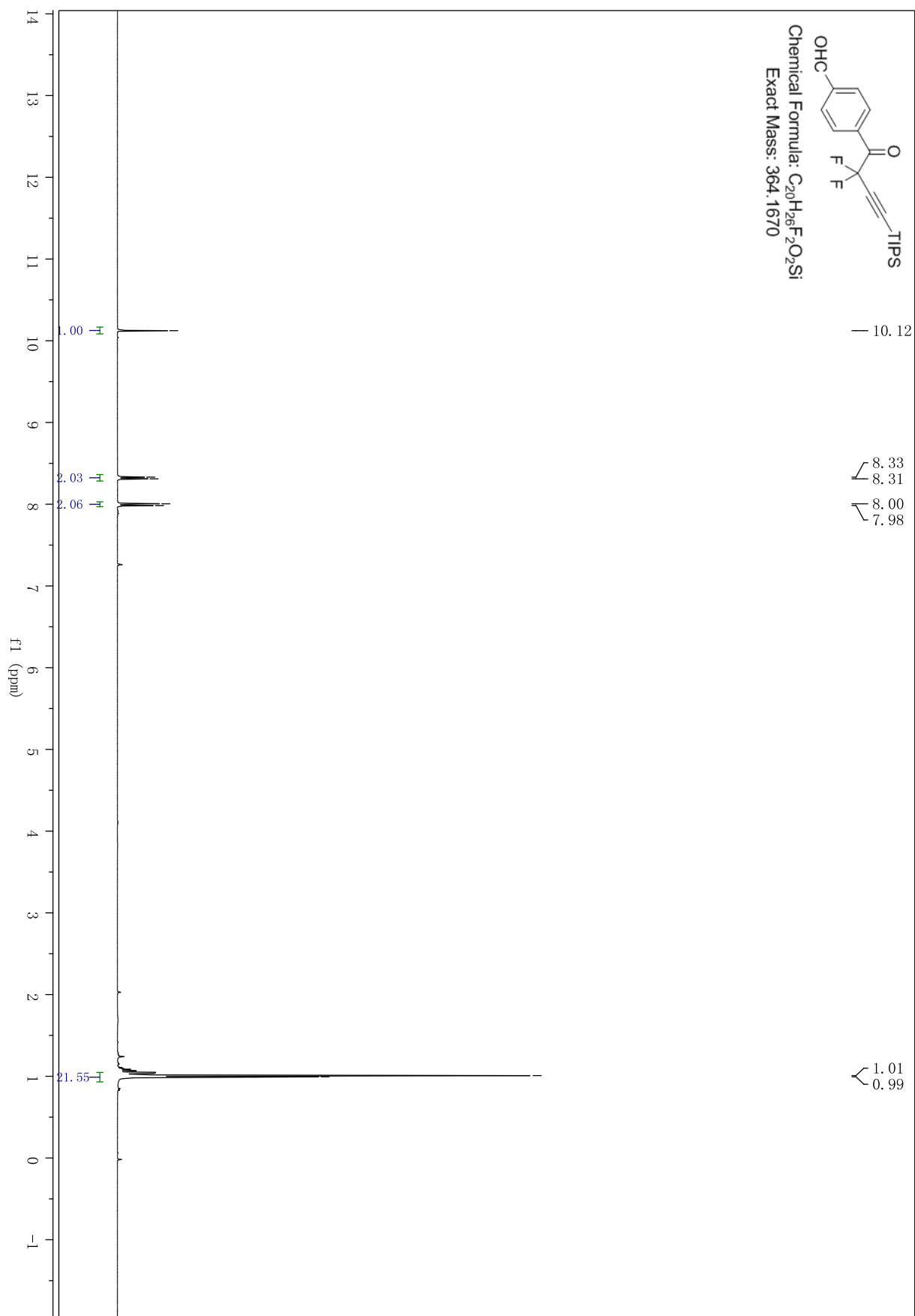


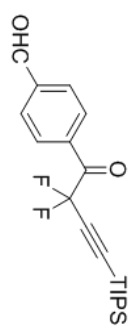
Chemical Formula: $C_{21}H_{28}F_2O_2Si$
 Exact Mass: 378.1827



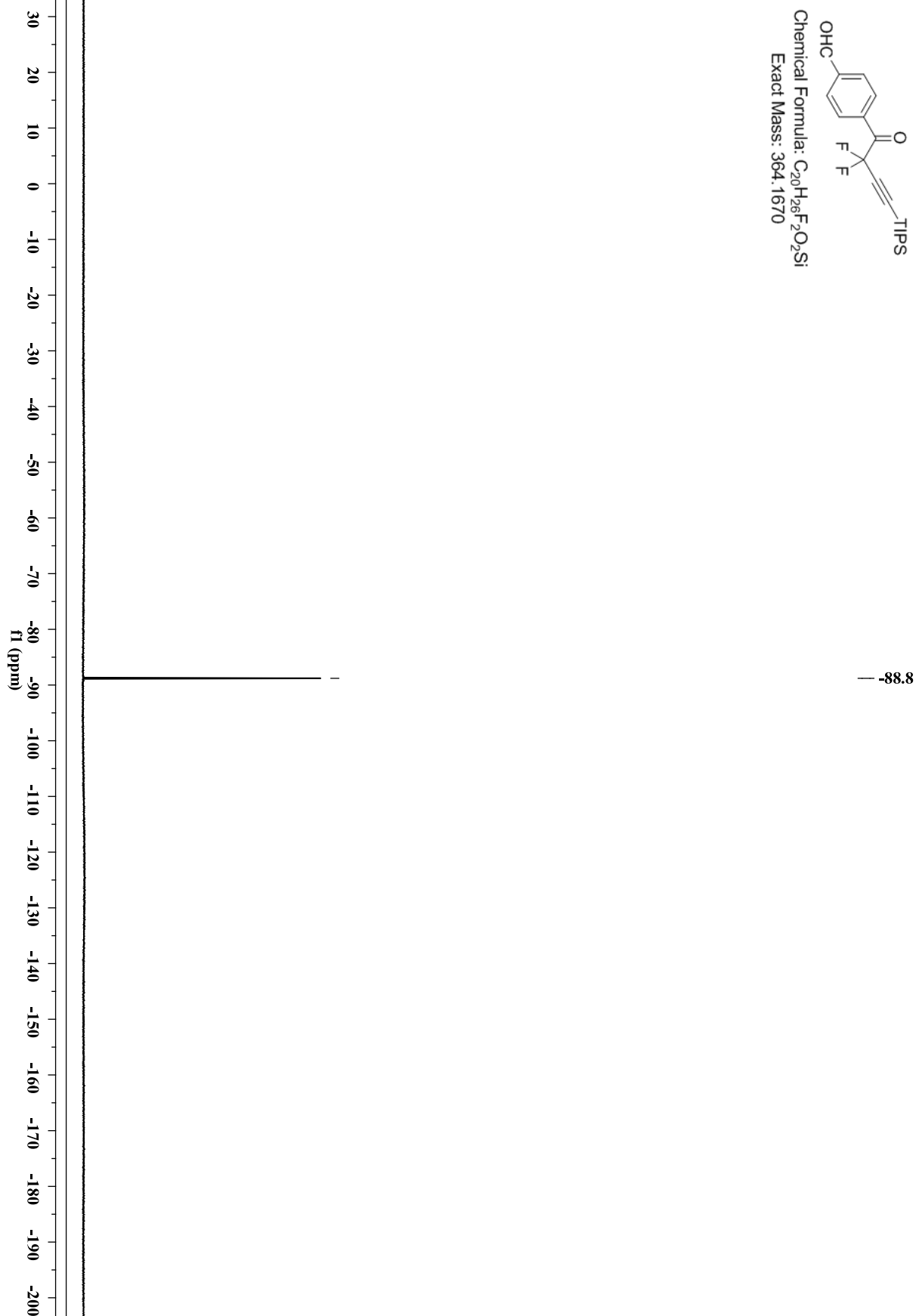


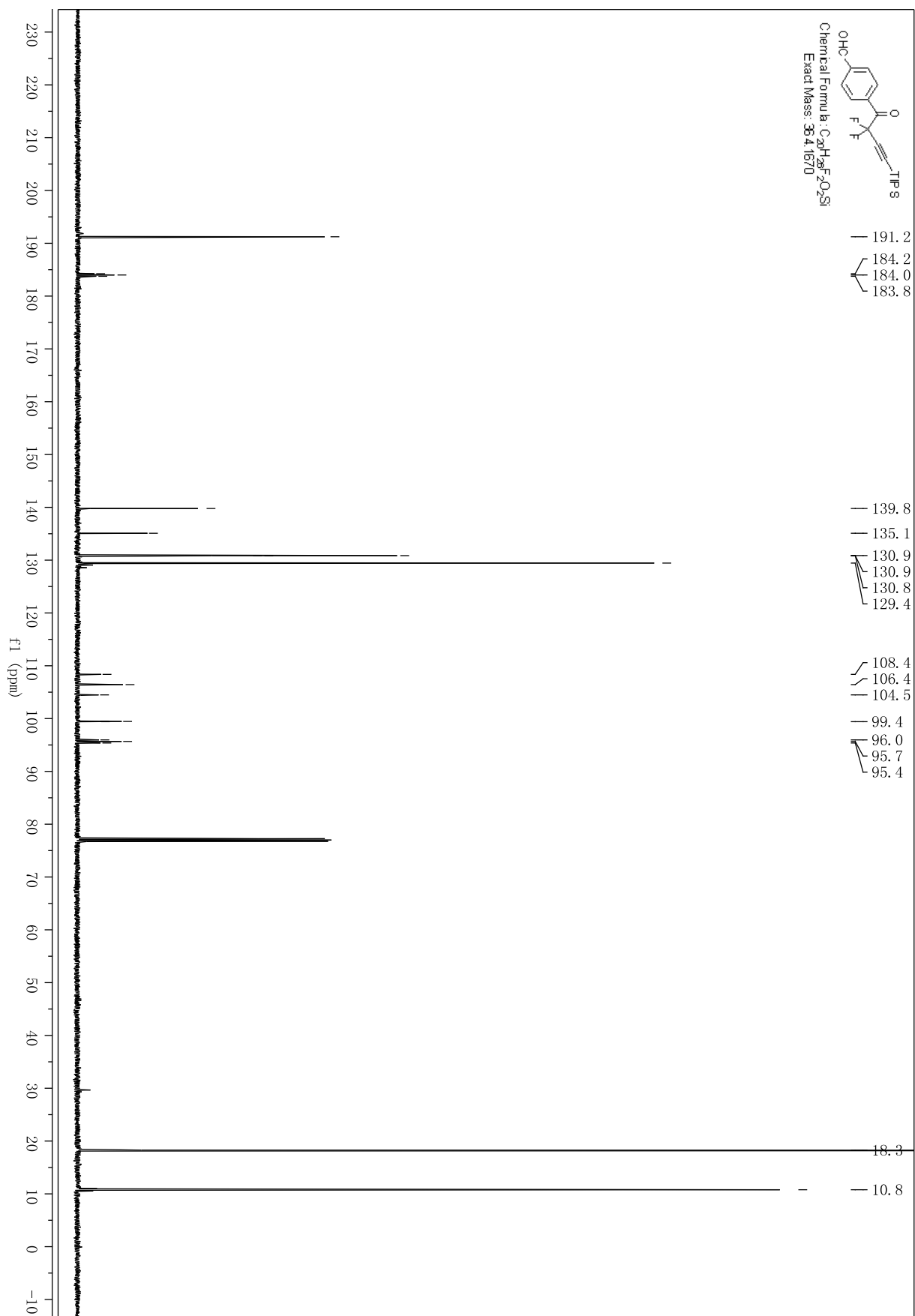
4-(2,2-Difluoro-4-(triisopropylsilyl)but-3-ynoyl)benzaldehyde (3l).



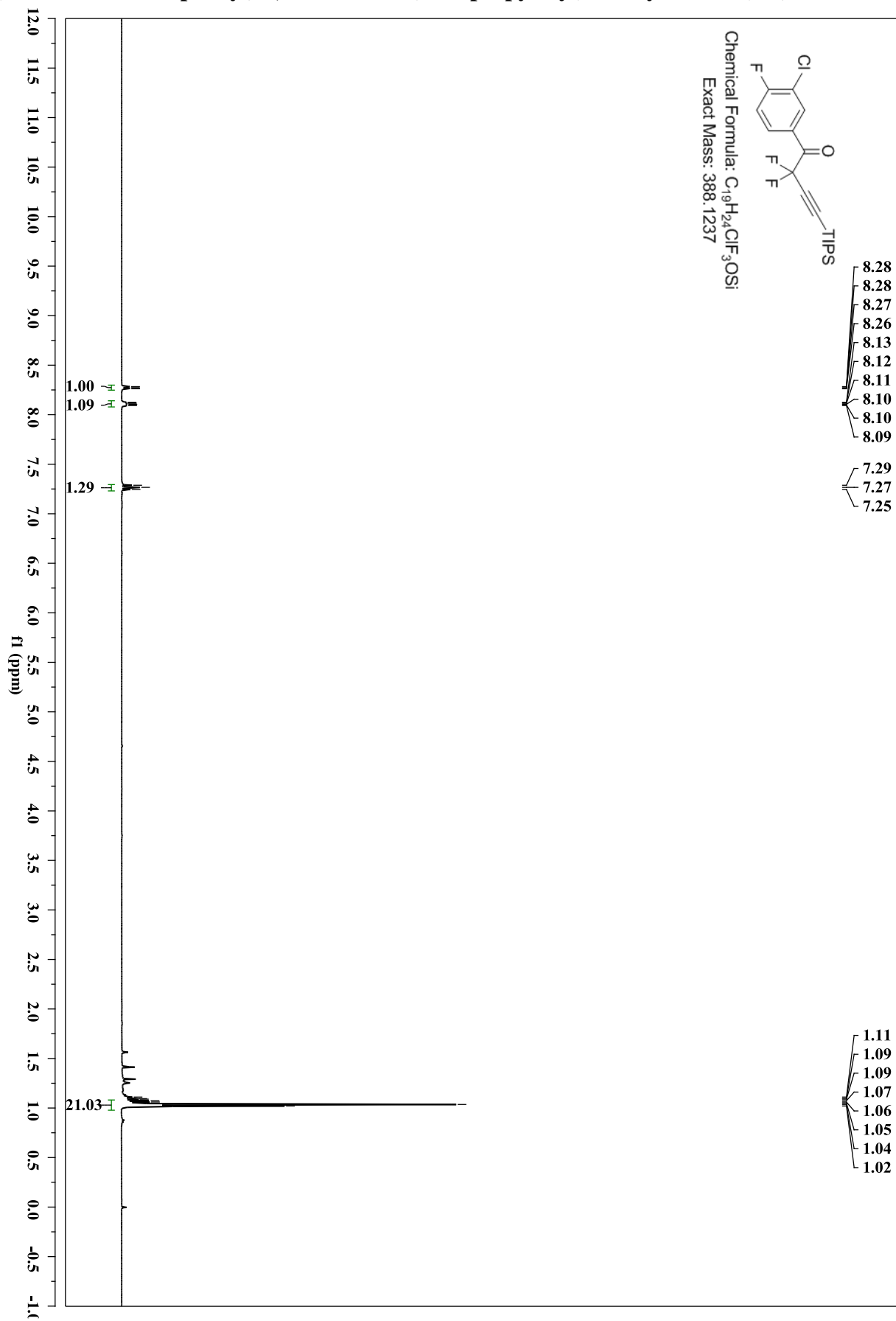


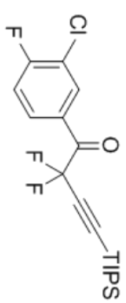
Chemical Formula: $C_{20}H_{26}F_2O_2Si$
 Exact Mass: 364.1670



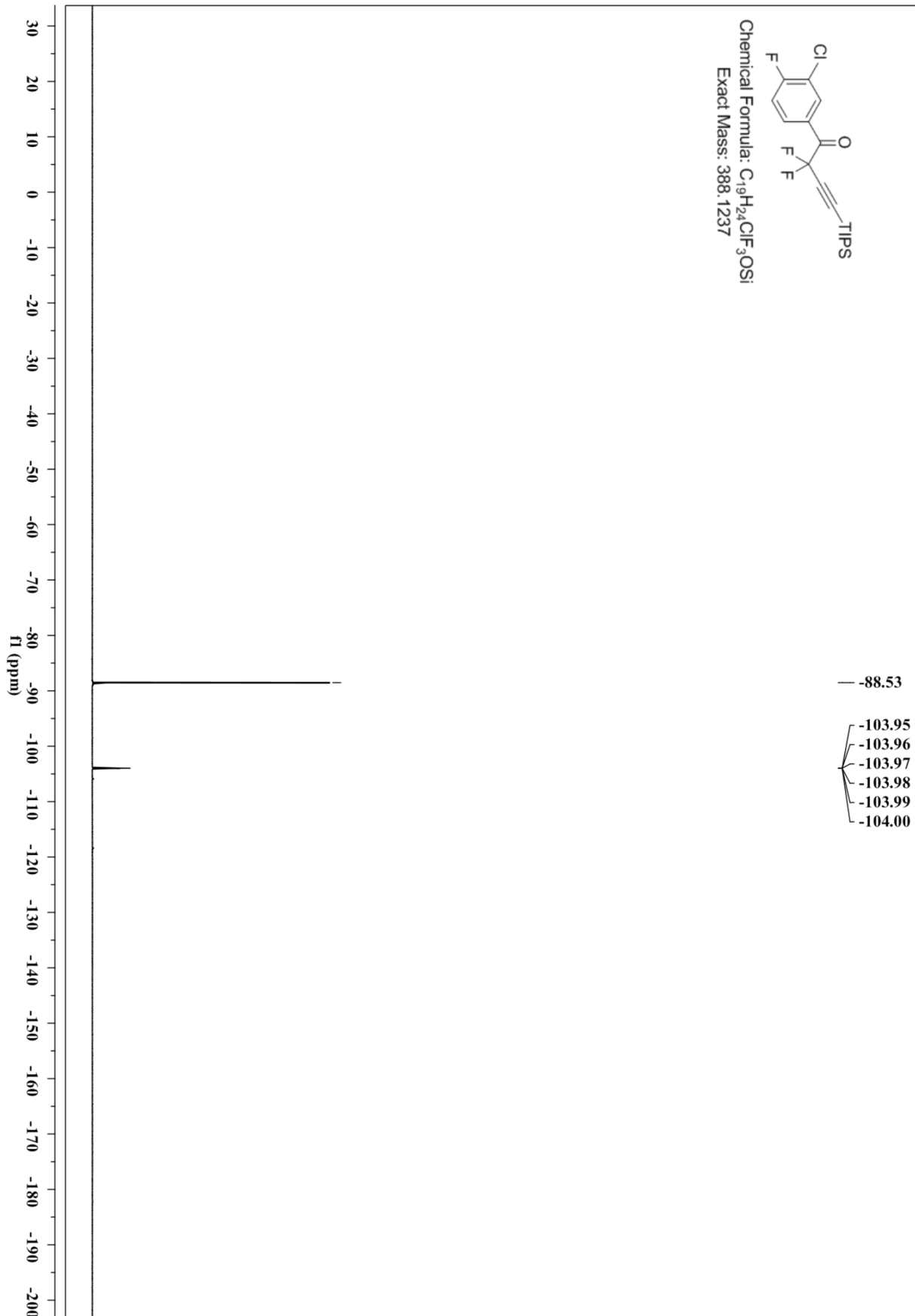


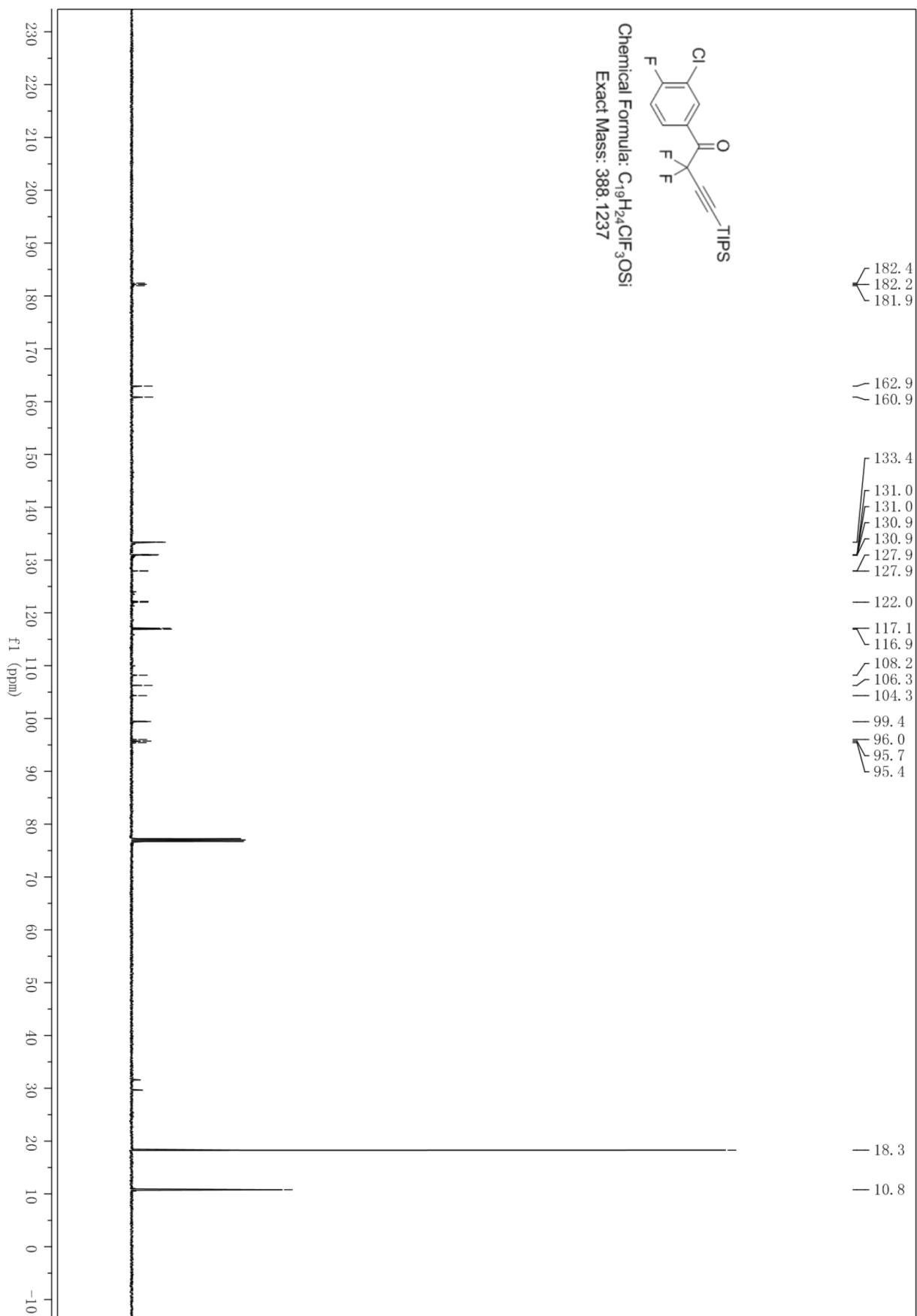
1-(3-Chloro-4-fluorophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one-(3m).



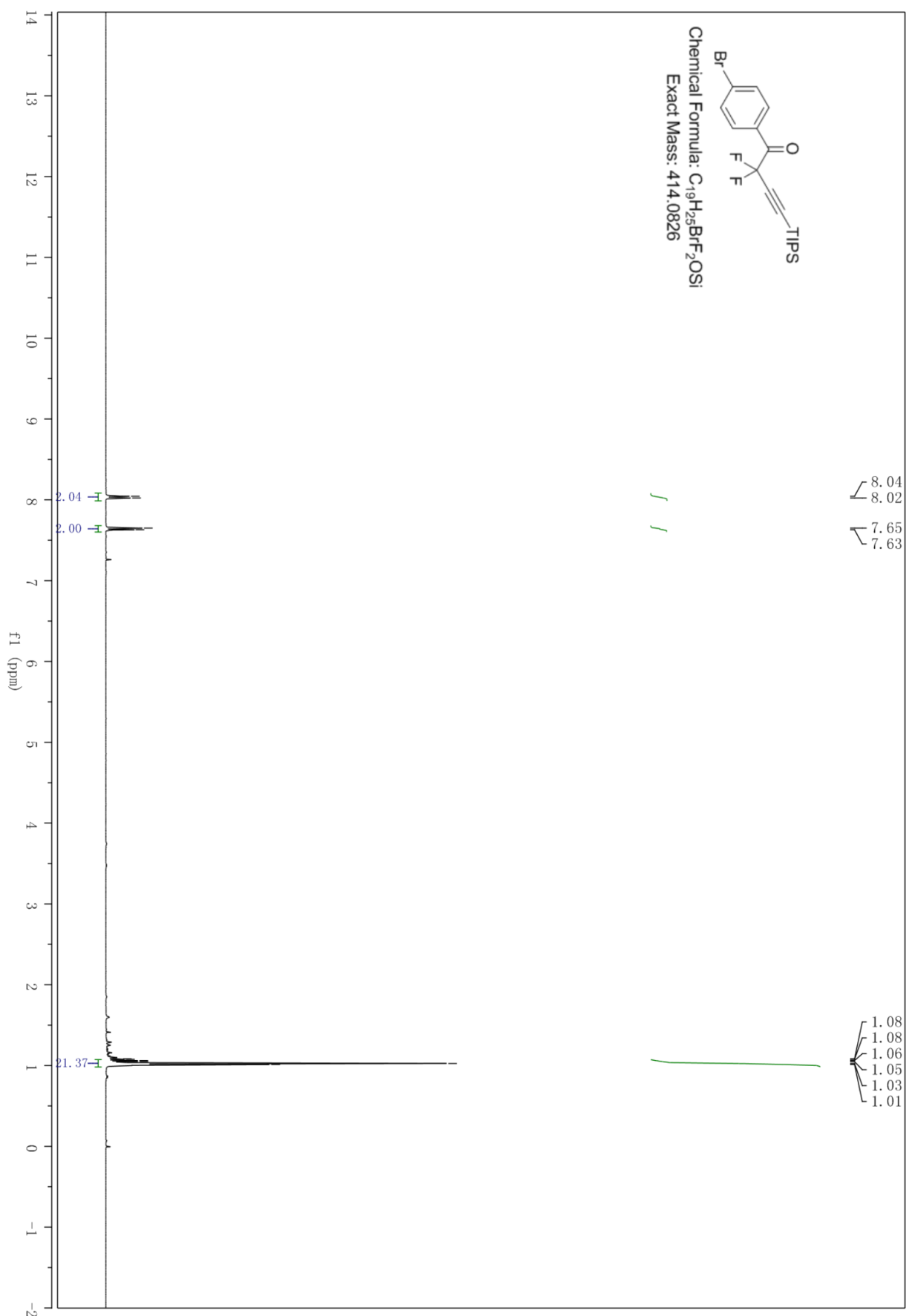


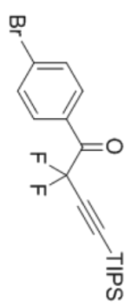
Chemical Formula: $C_{19}H_{24}ClF_3OSi$
Exact Mass: 388.1237



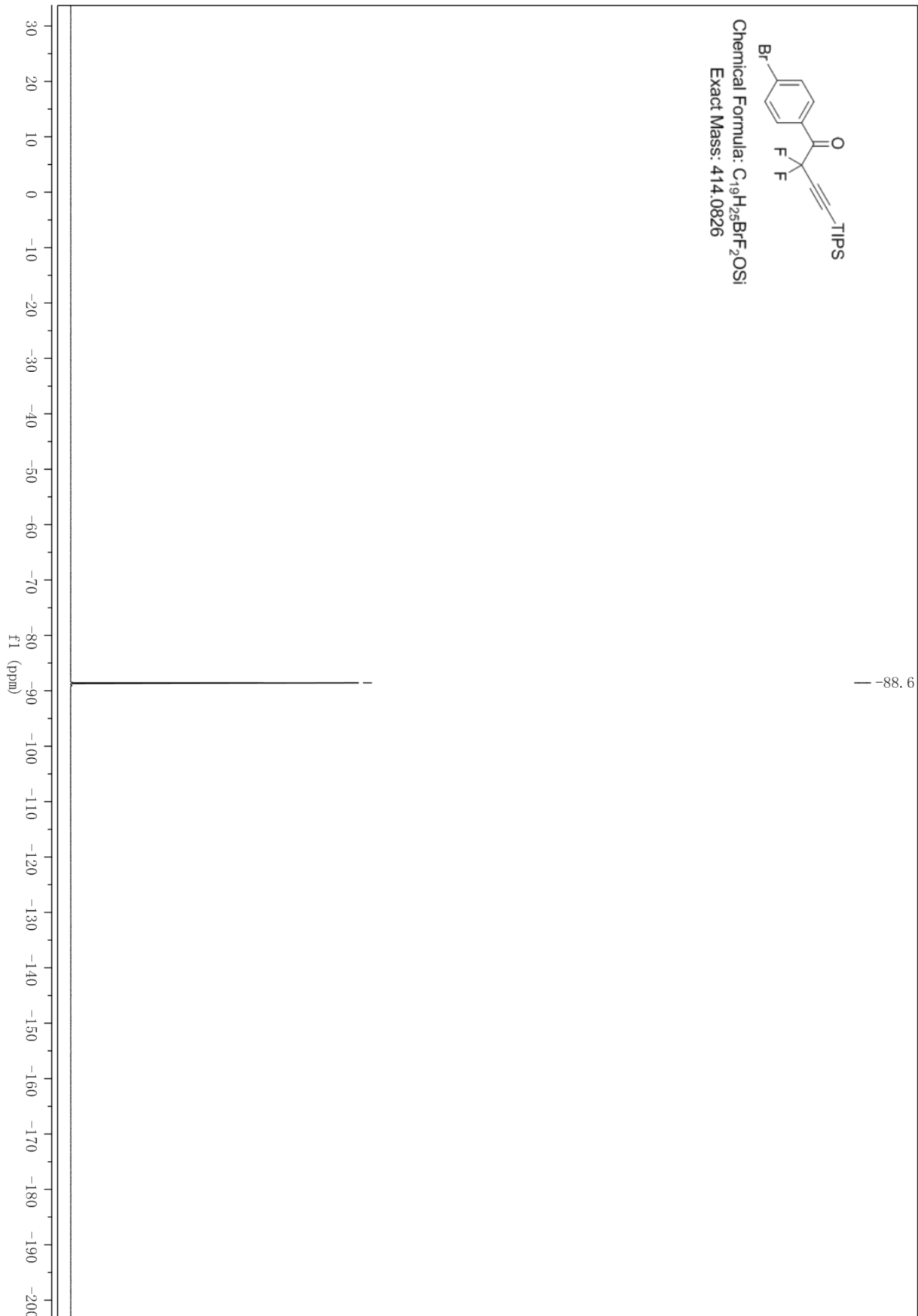


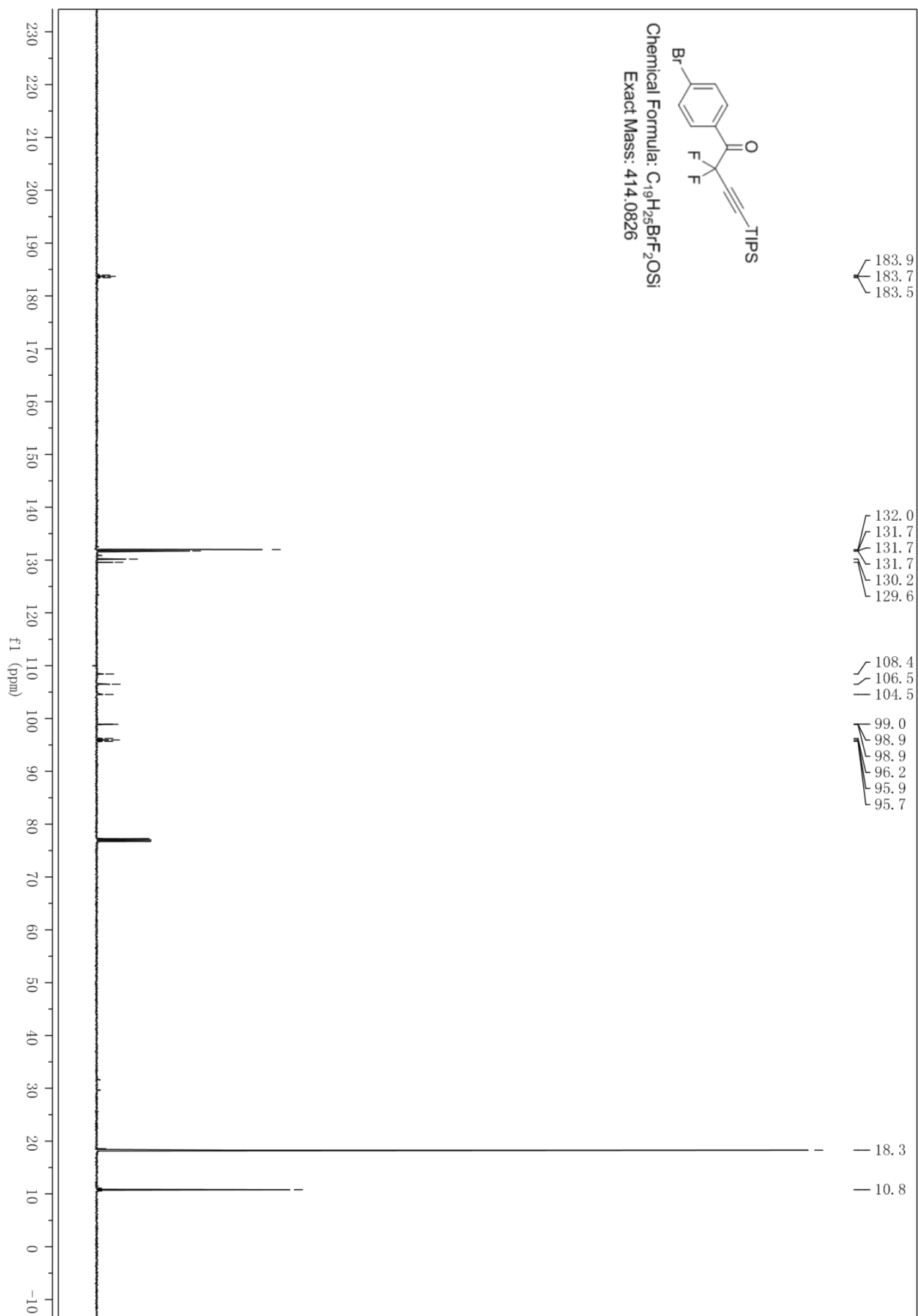
1-(4-Bromophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3n).



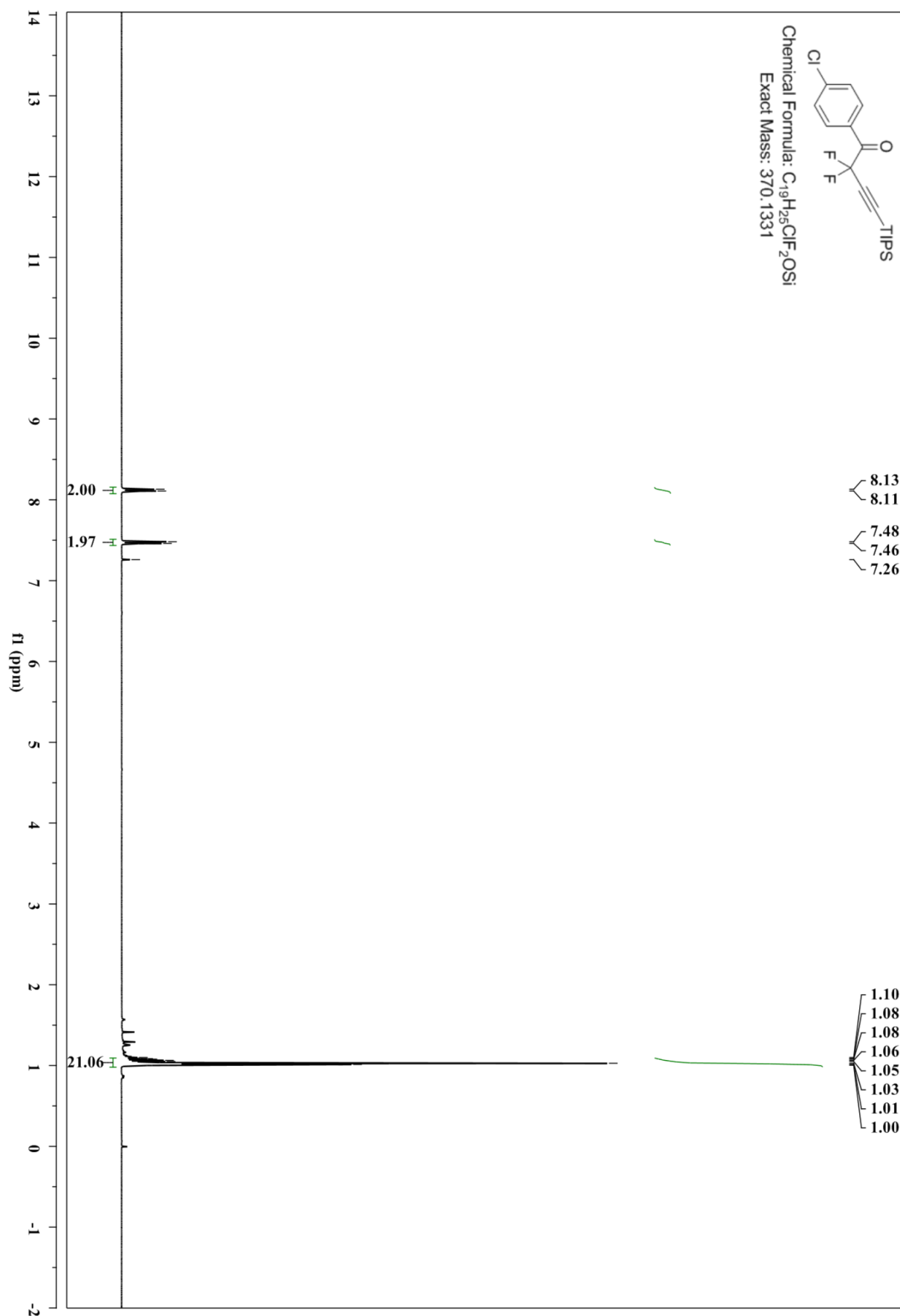


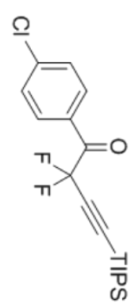
Chemical Formula: $C_{19}H_{25}BrF_2OSi$
 Exact Mass: 414.0826



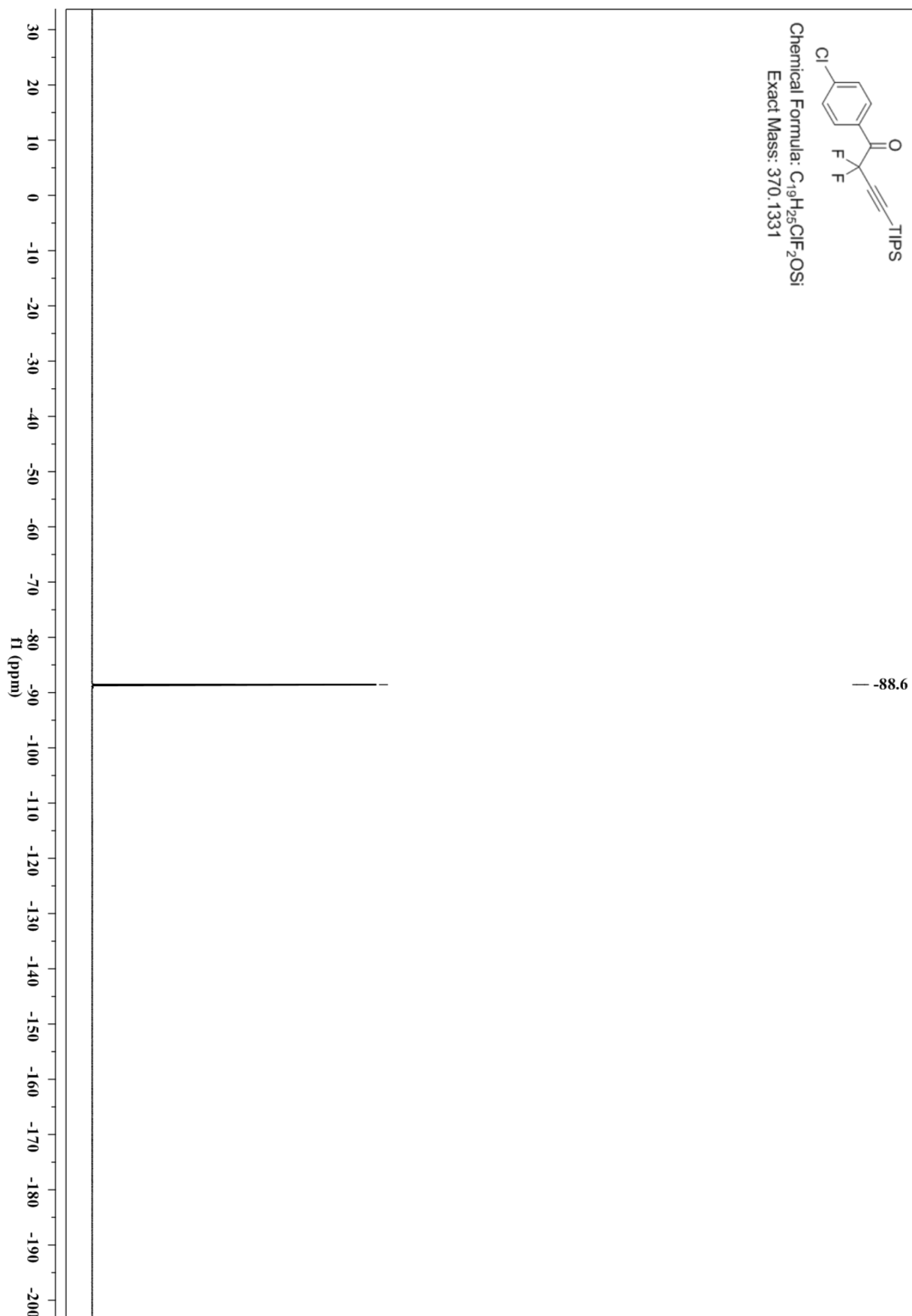


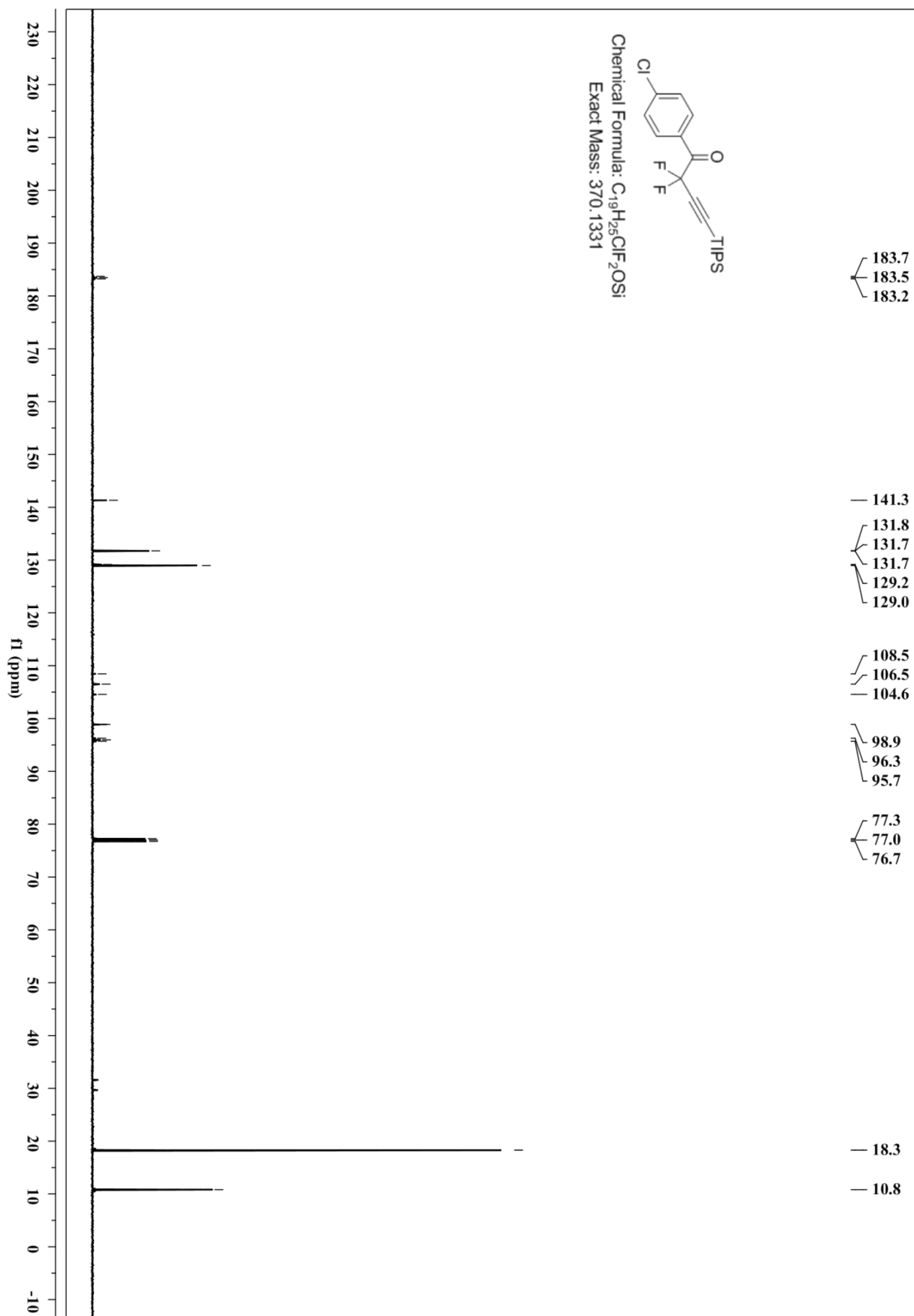
1-(4-Chlorophenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3o).



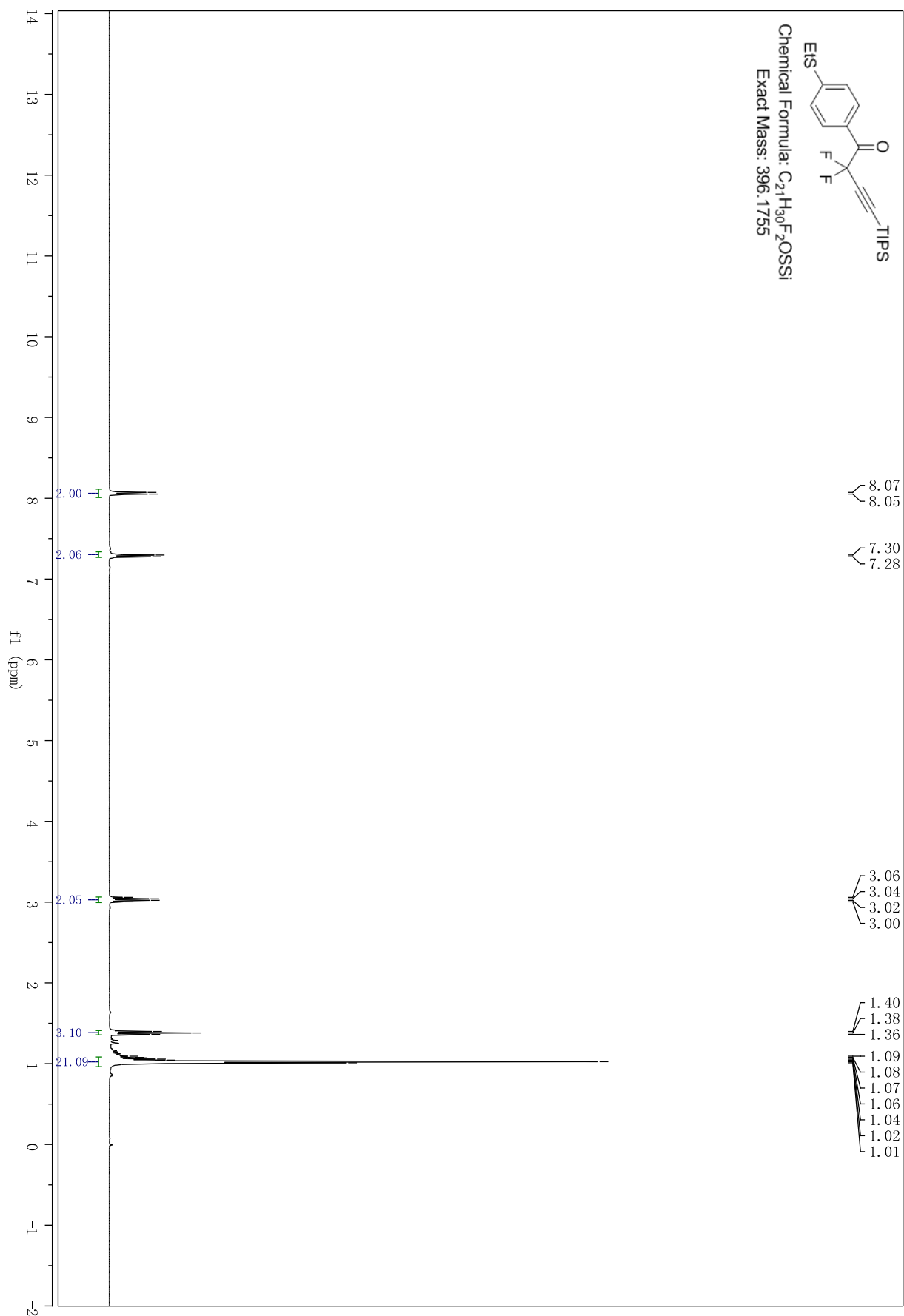


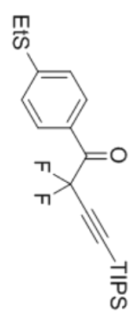
Chemical Formula: $C_{19}H_{25}ClF_2OSi$
Exact Mass: 370.1331



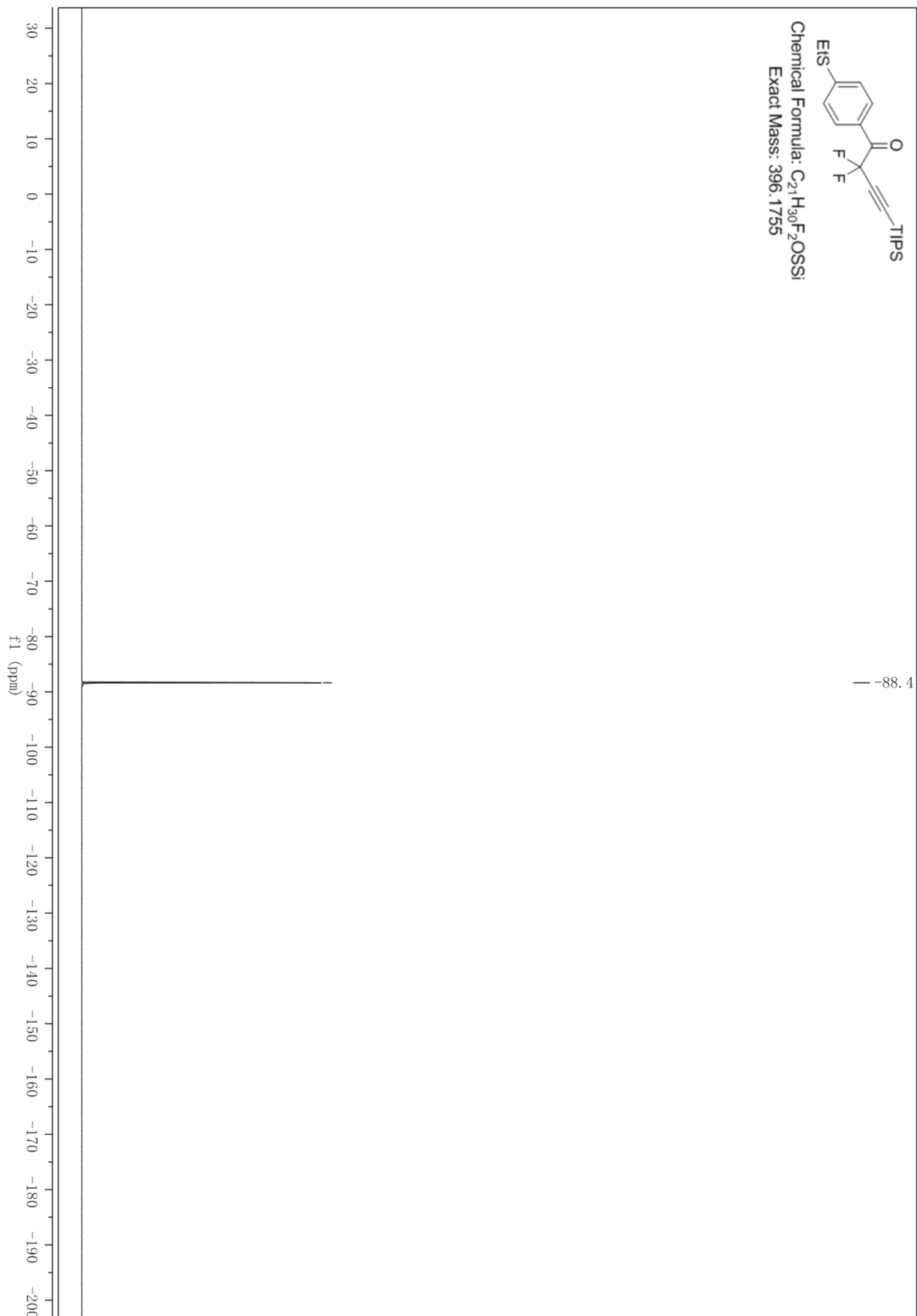


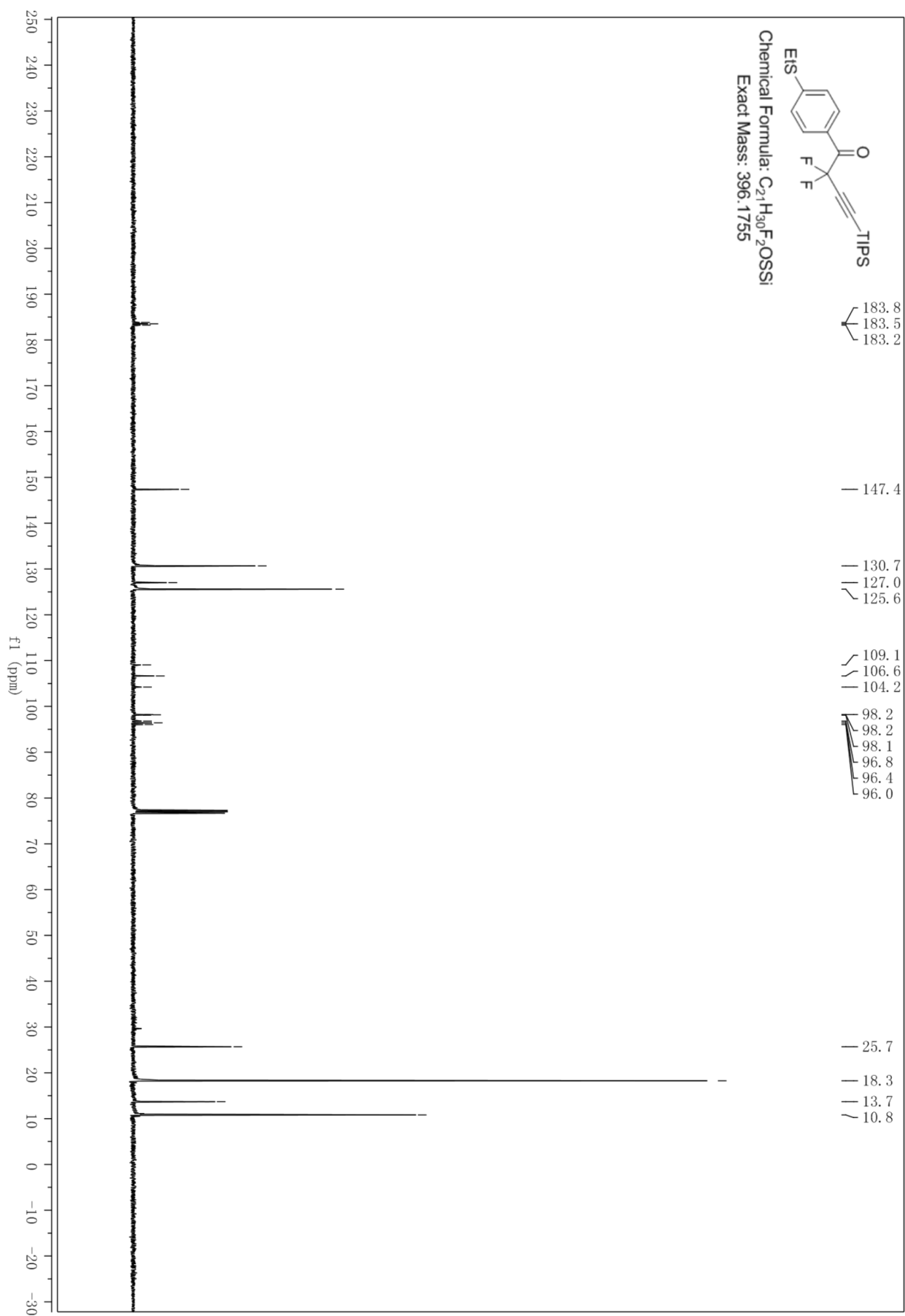
1-(4-(Ethylthio)phenyl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3p).



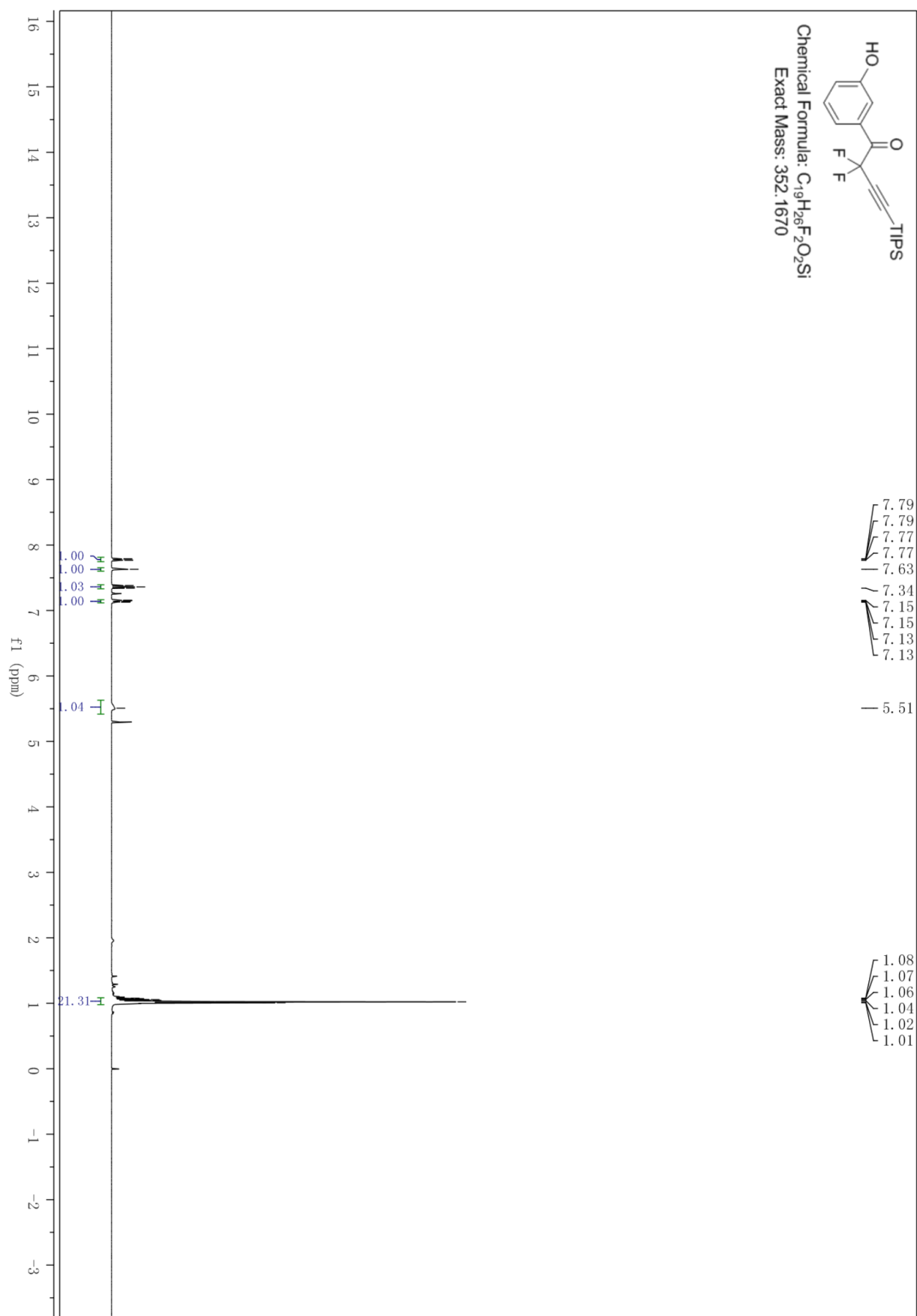


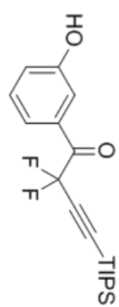
Chemical Formula: $C_{21}H_{30}F_2OSSI$
 Exact Mass: 396.1755



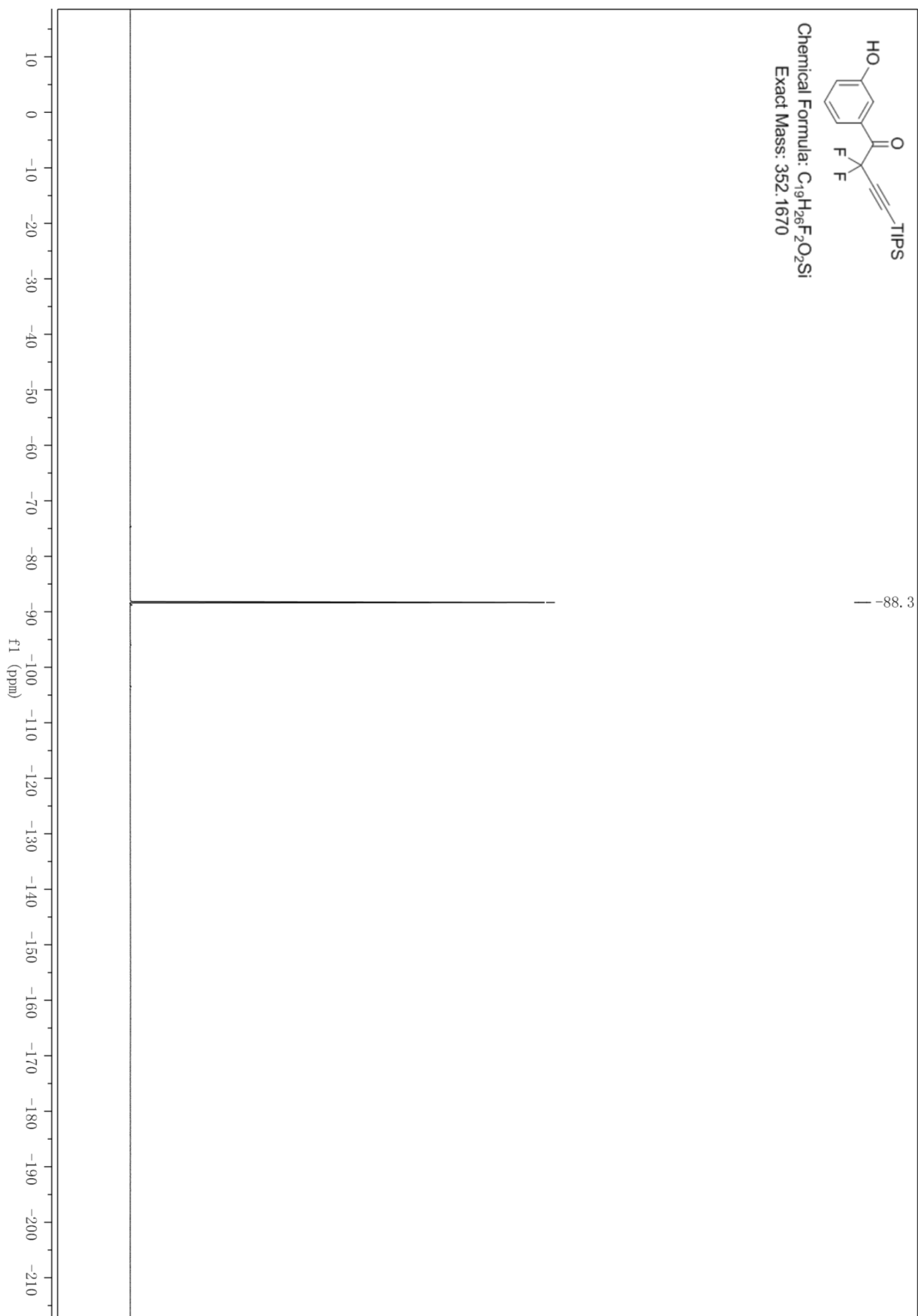


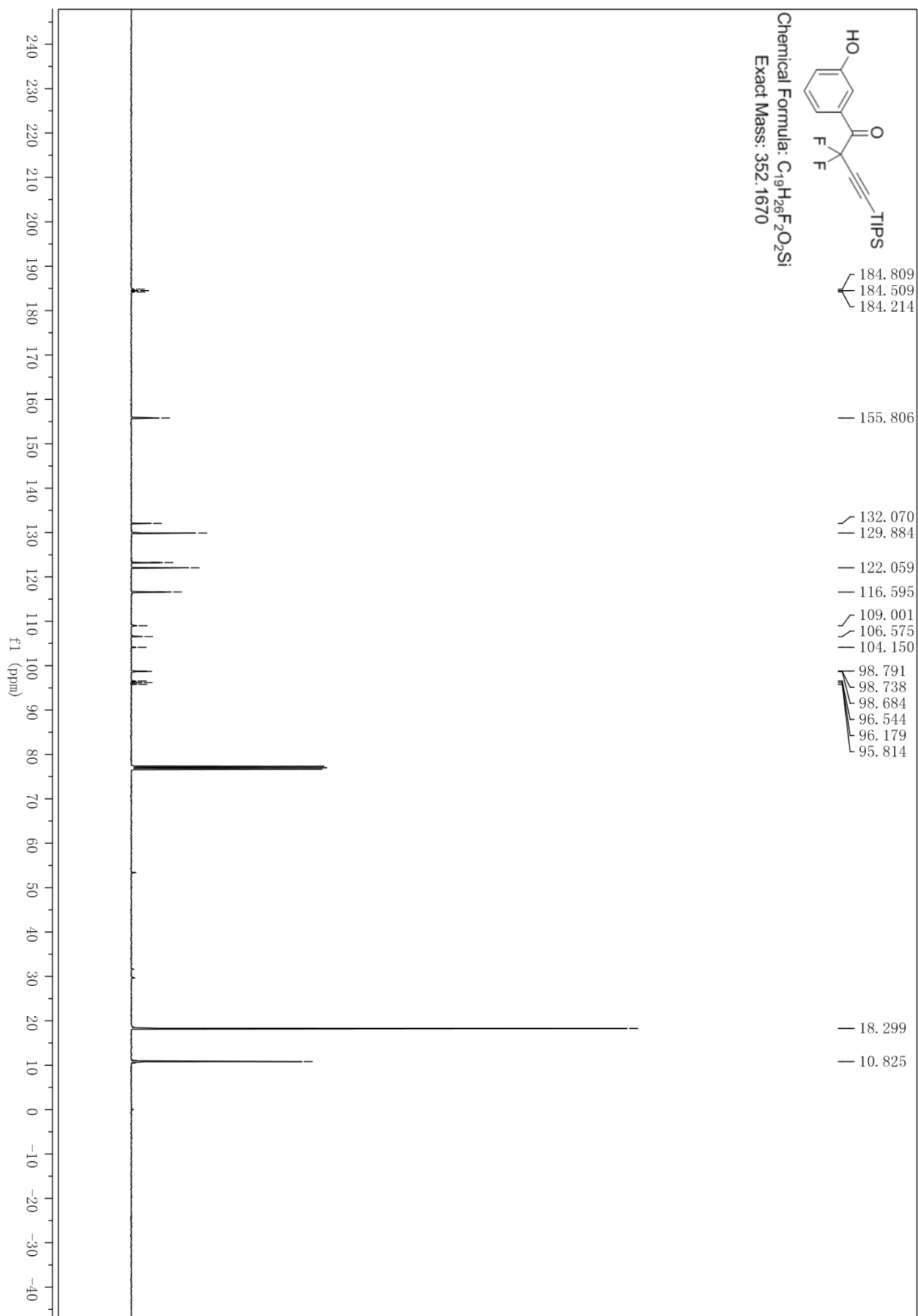
2,2-Difluoro-1-(3-hydroxyphenyl)-4-(triisopropylsilyl)but-3-yn-1-one (3q).



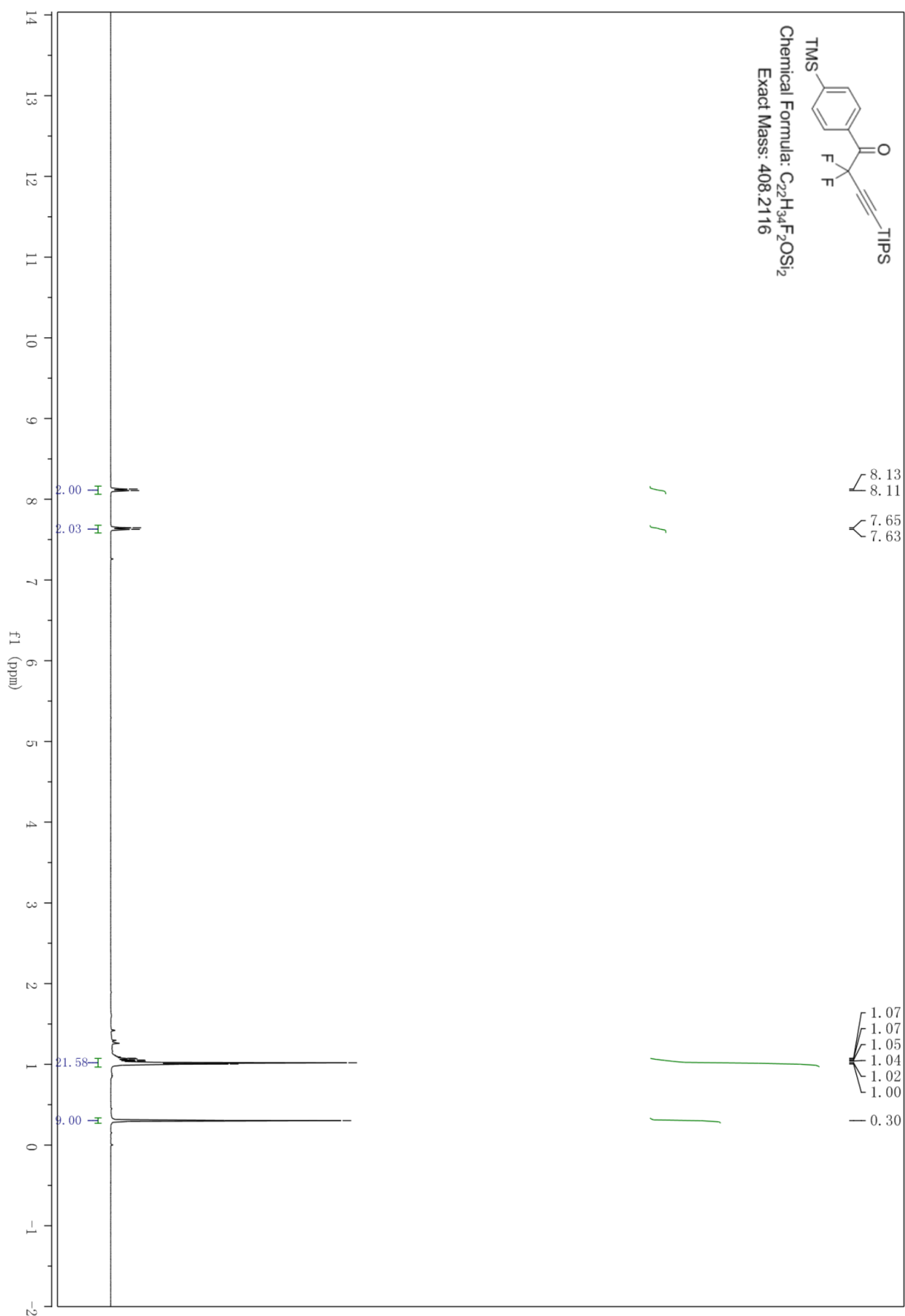


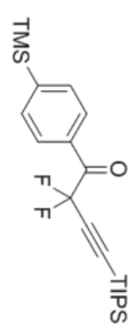
Chemical Formula: $C_{19}H_{26}F_2O_2Si$
Exact Mass: 352.1670



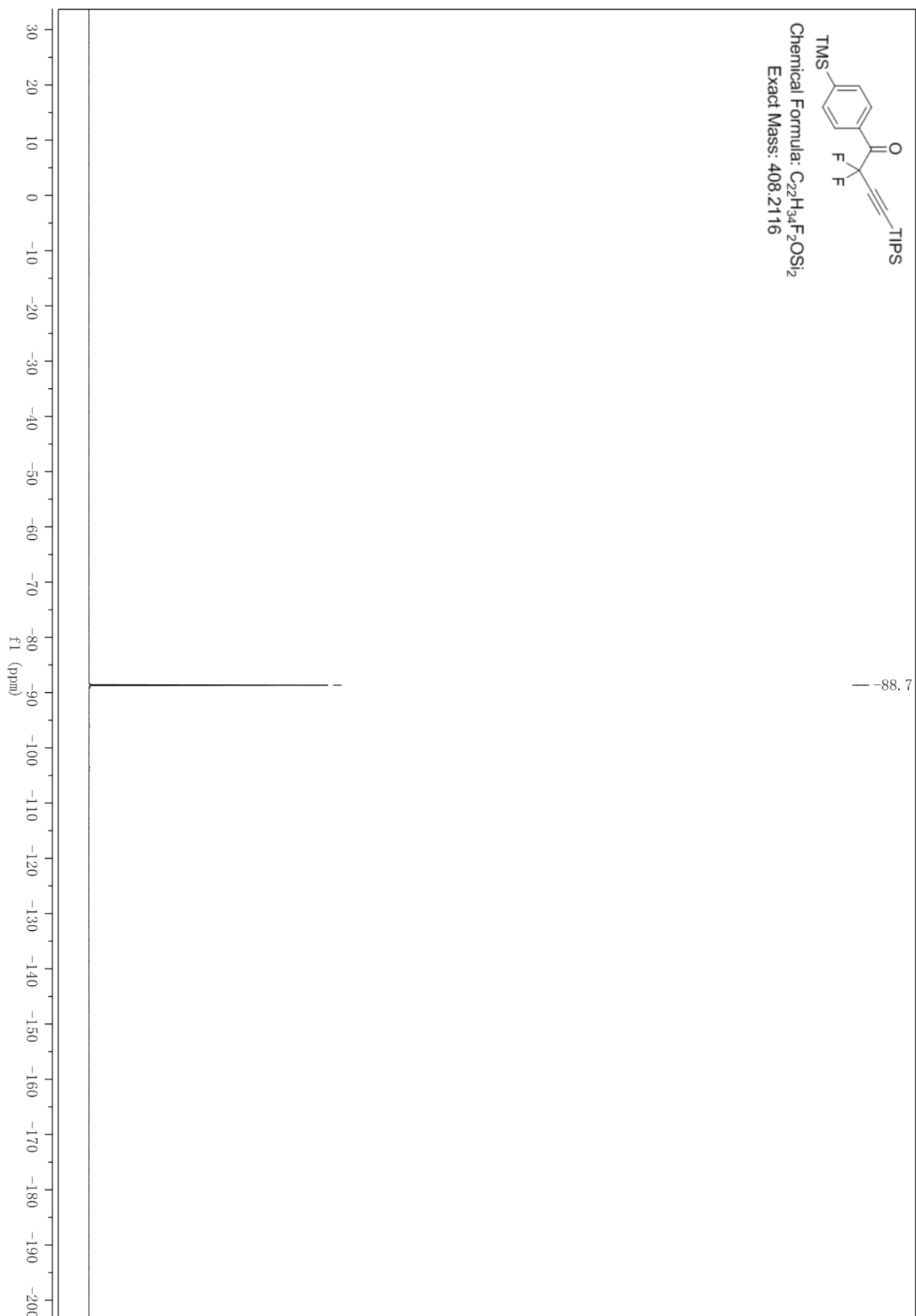


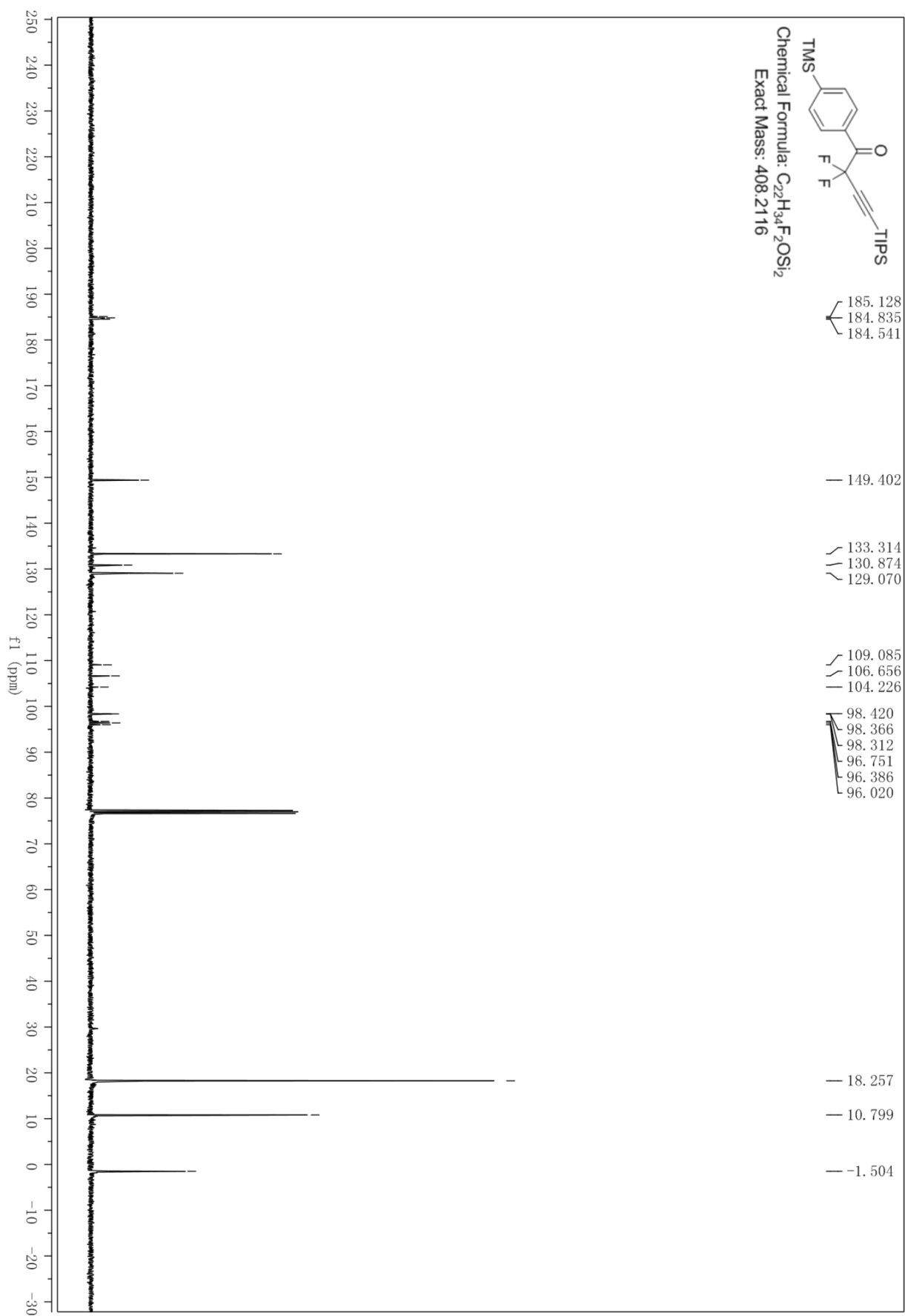
2,2-Difluoro-4-(triisopropylsilyl)-1-(4-(trimethylsilyl)phenyl)but-3-yn-1-one (3r).



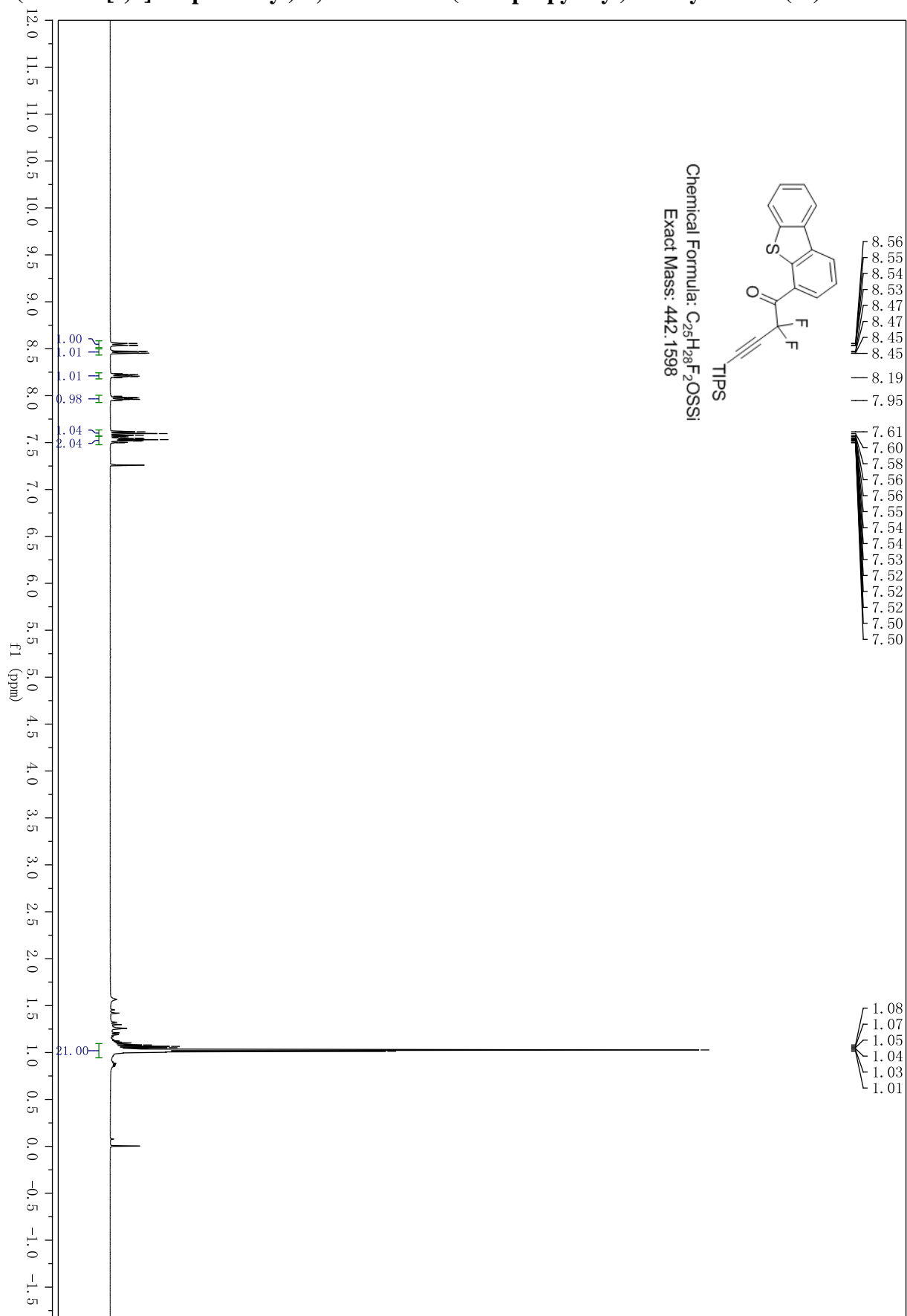


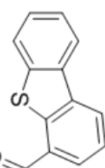
Chemical Formula: C₂₂H₃₄F₂OSi₂
Exact Mass: 408.2116





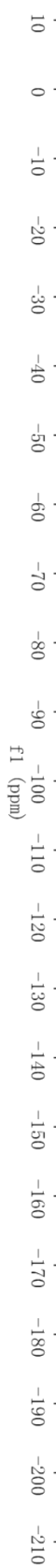
1-(Dibenzo[*b,d*]thiophen-2-yl)-2,2-difluoro-4-(triisopropylsilyl)but-3-yn-1-one (3s).

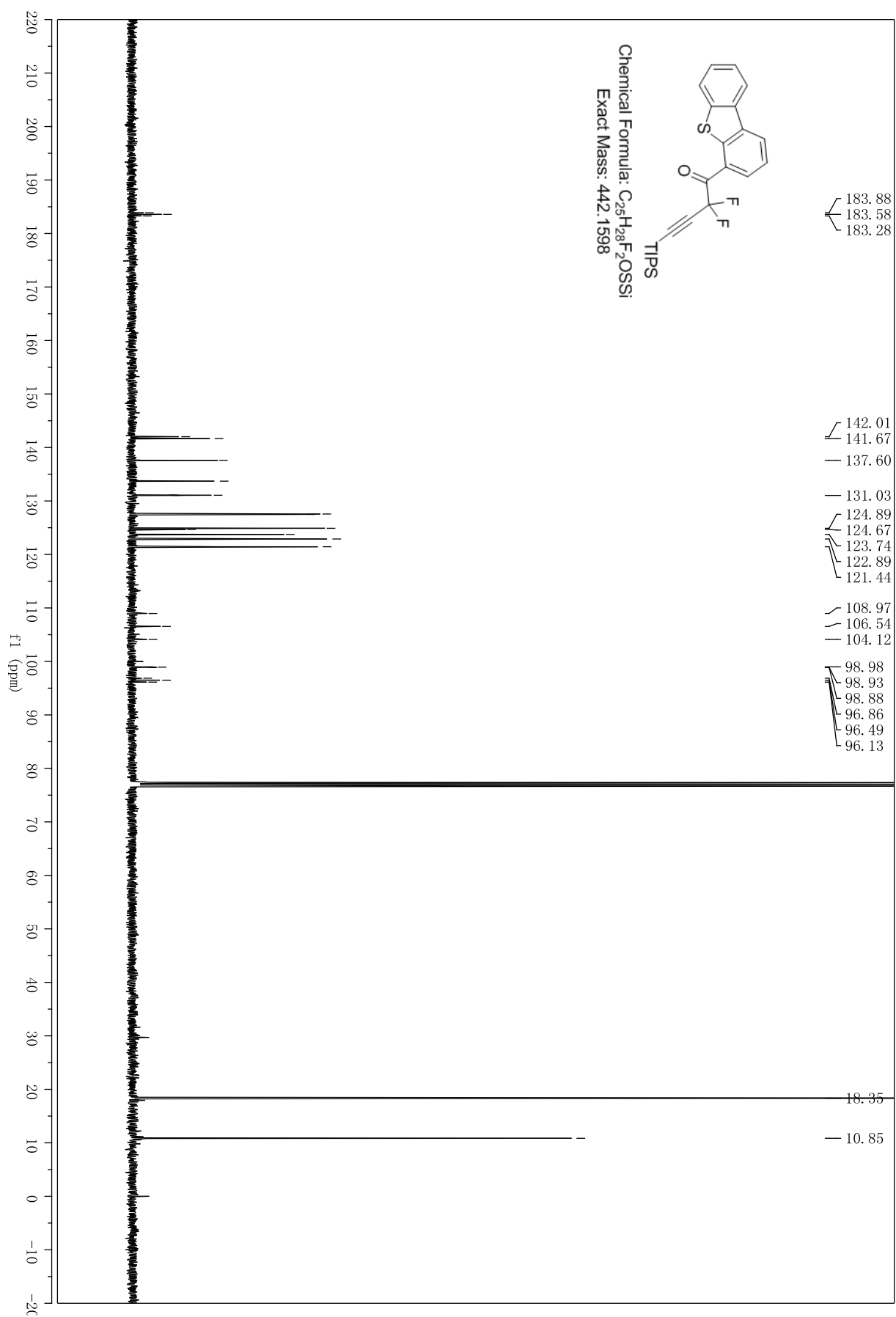




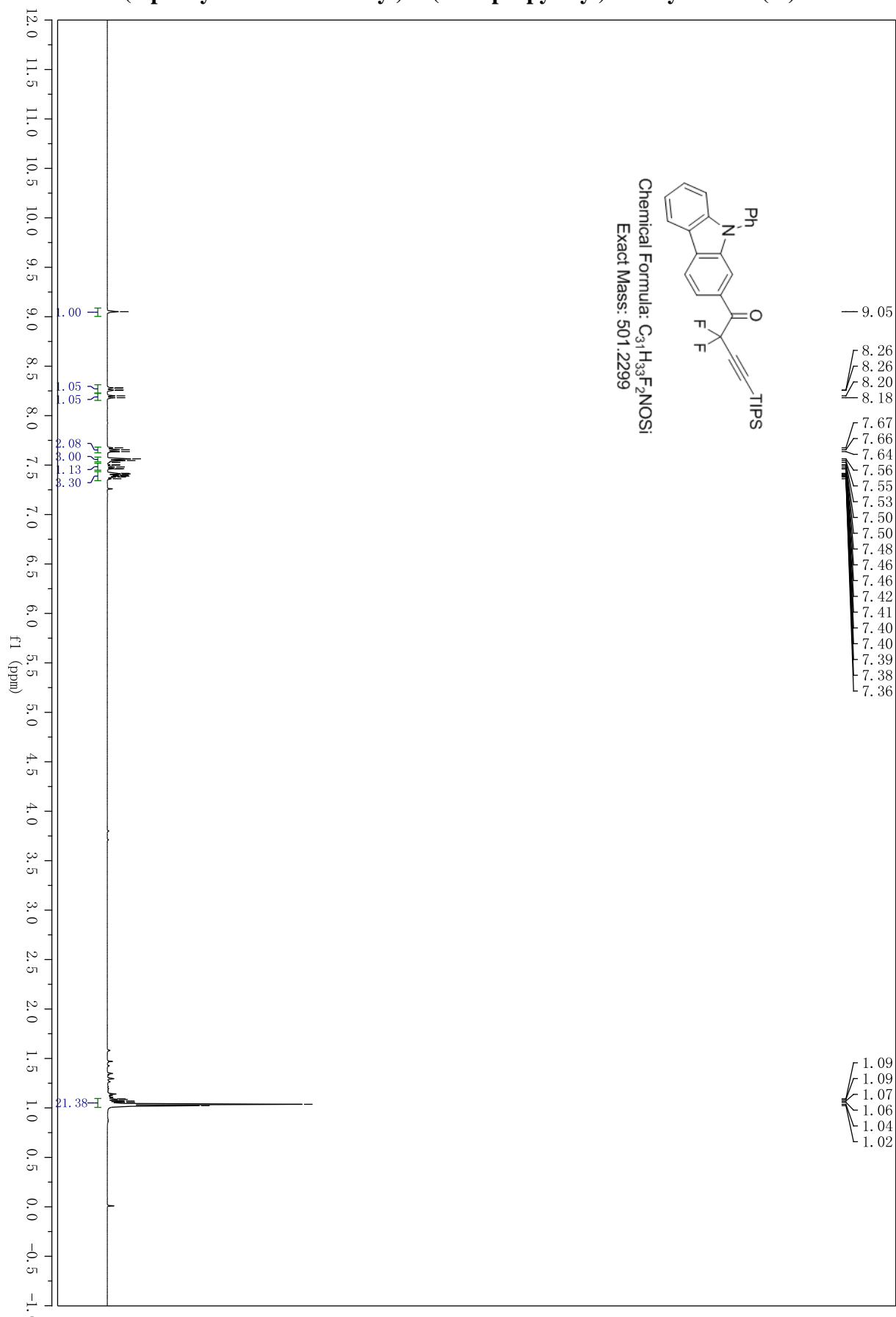
Chemical Formula: $C_{25}H_{28}F_2OSSI$
 Exact Mass: 442.1598

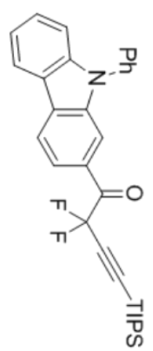
— -86.6



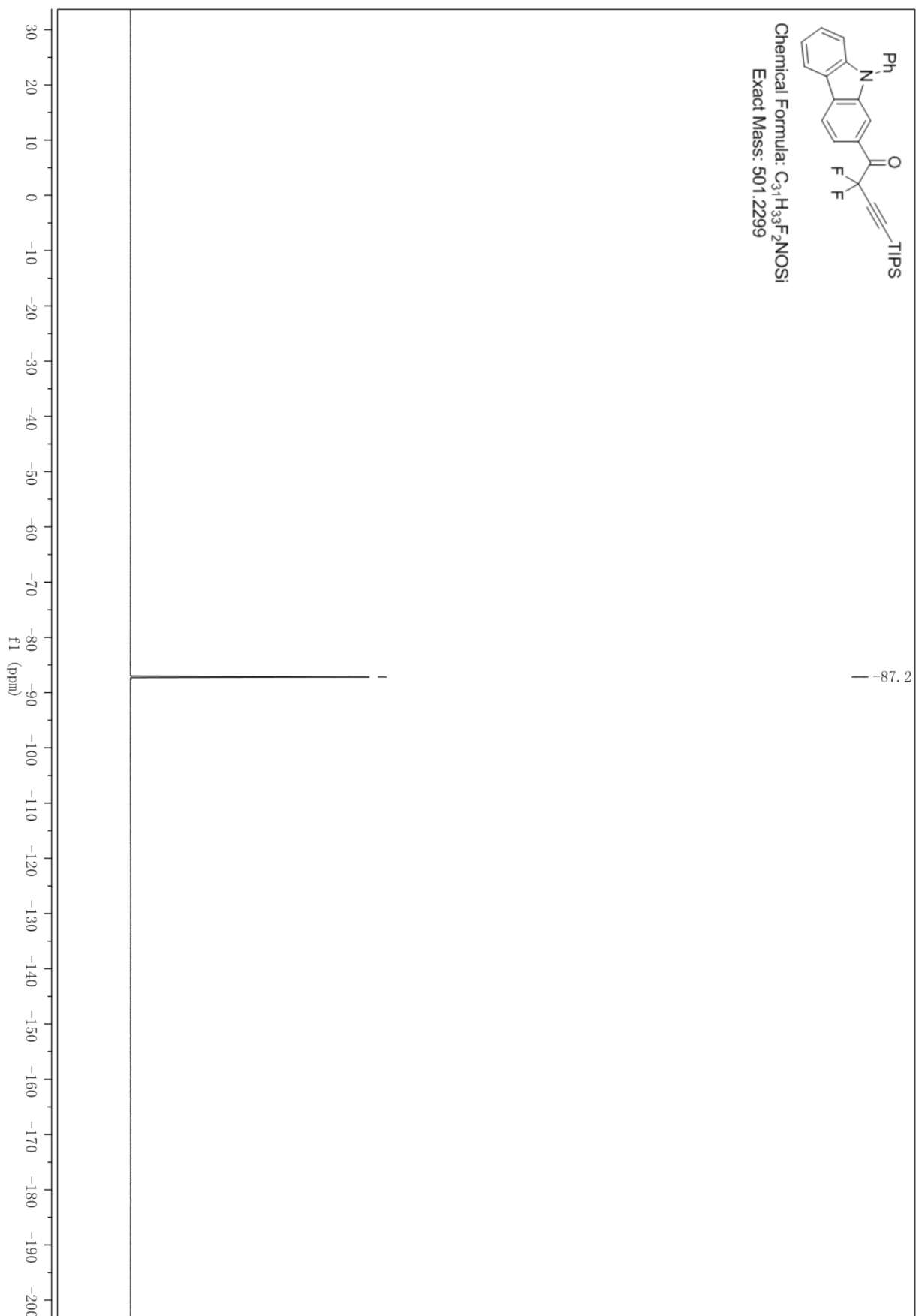


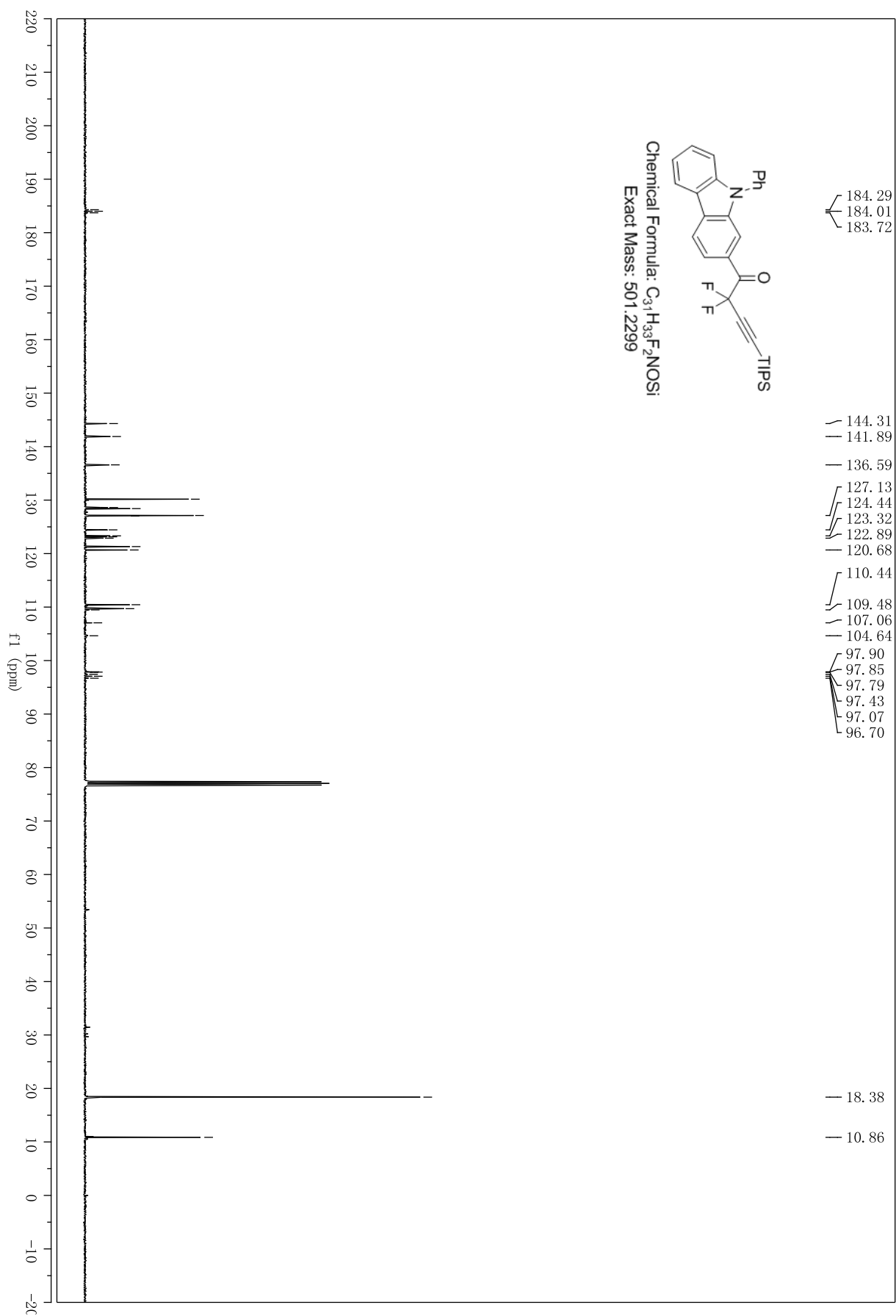
2,2-Difluoro-1-(9-phenyl-9H-carbazol-2-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3t).



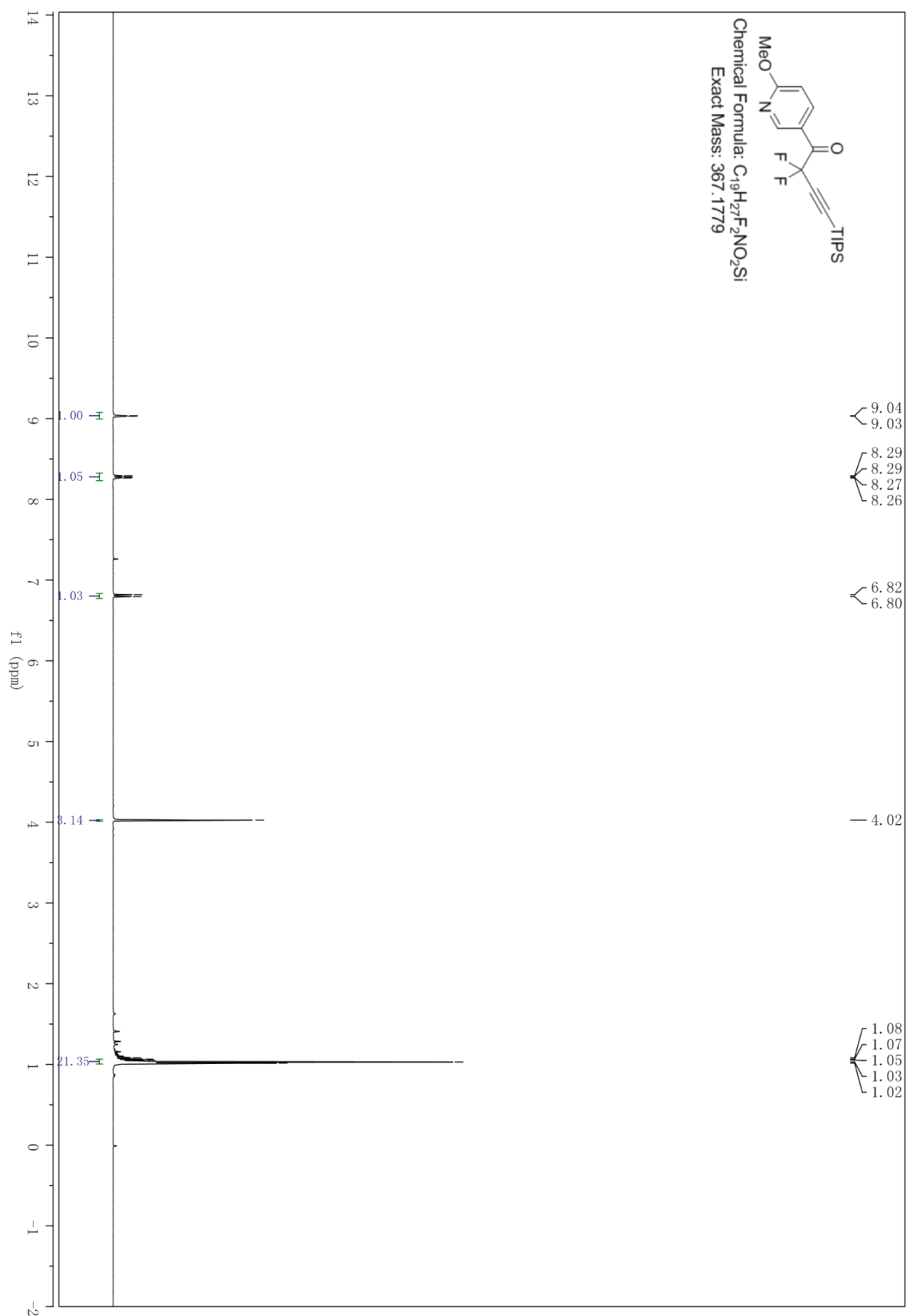


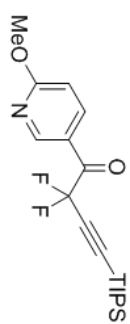
Chemical Formula: $C_{31}H_{33}F_2NO$
Exact Mass: 501.2299





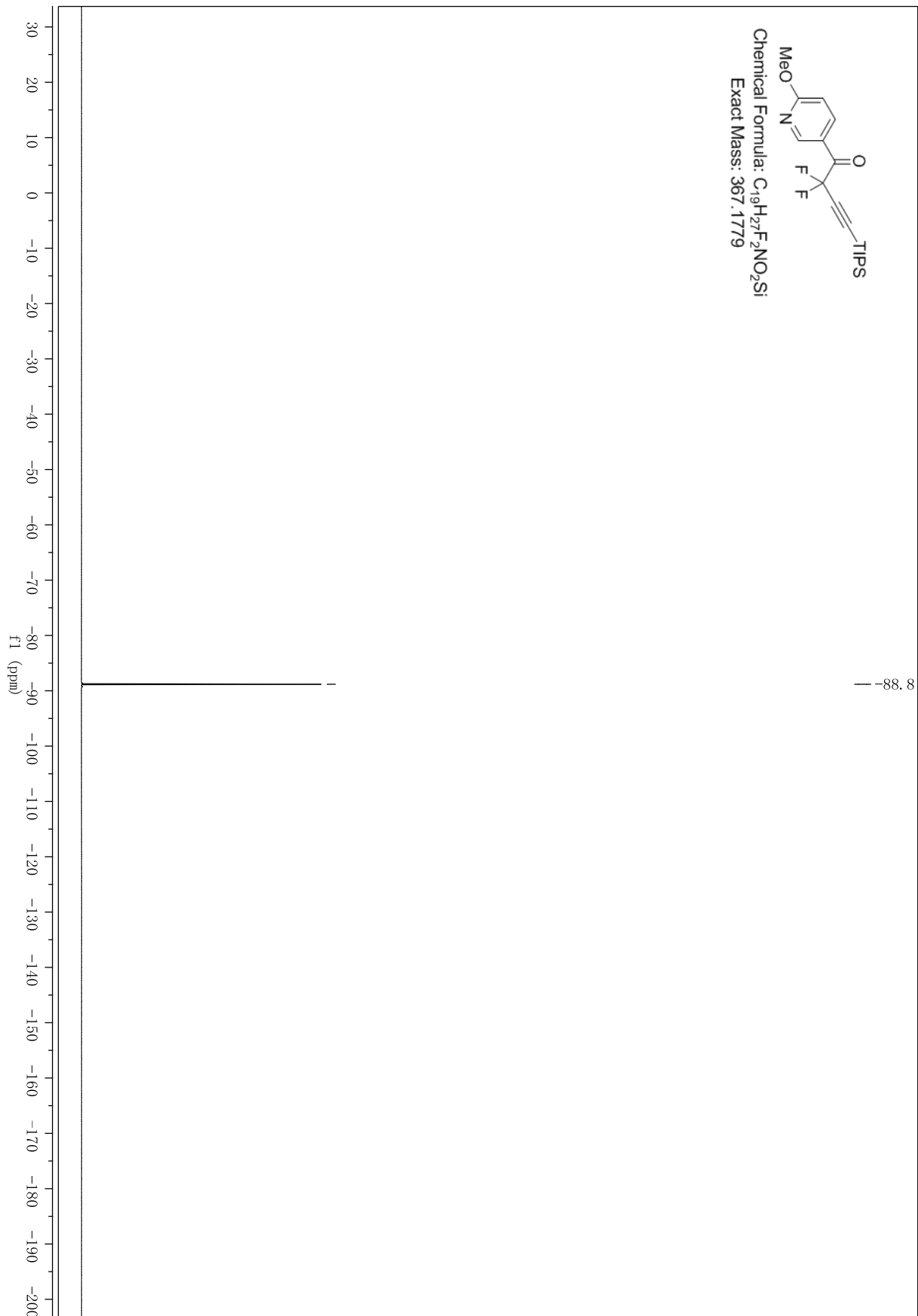
2,2-Difluoro-1-(6-methoxypyridin-3-yl)-4-(triisopropylsilyl)but-3-yn-1-one (3u).

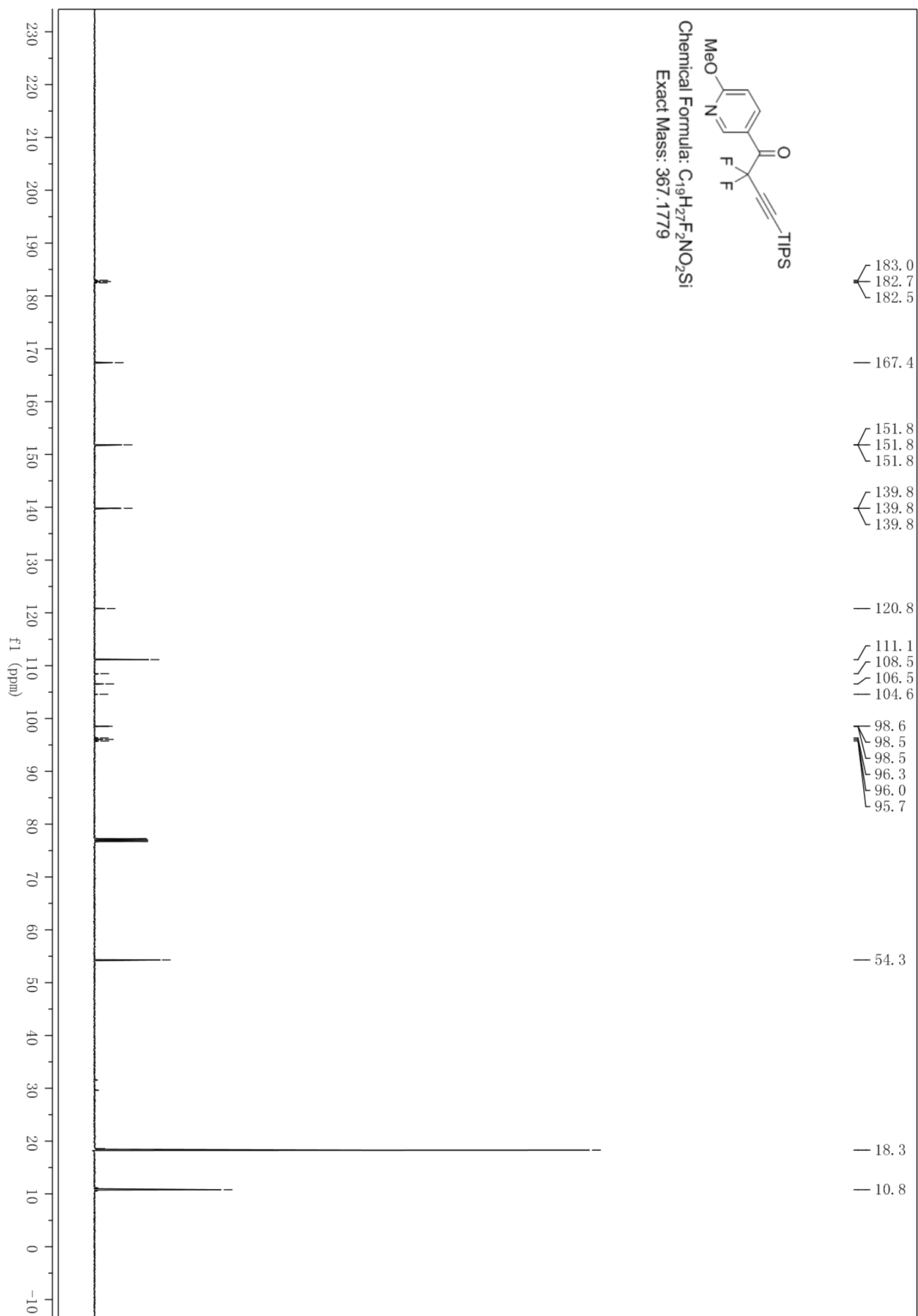




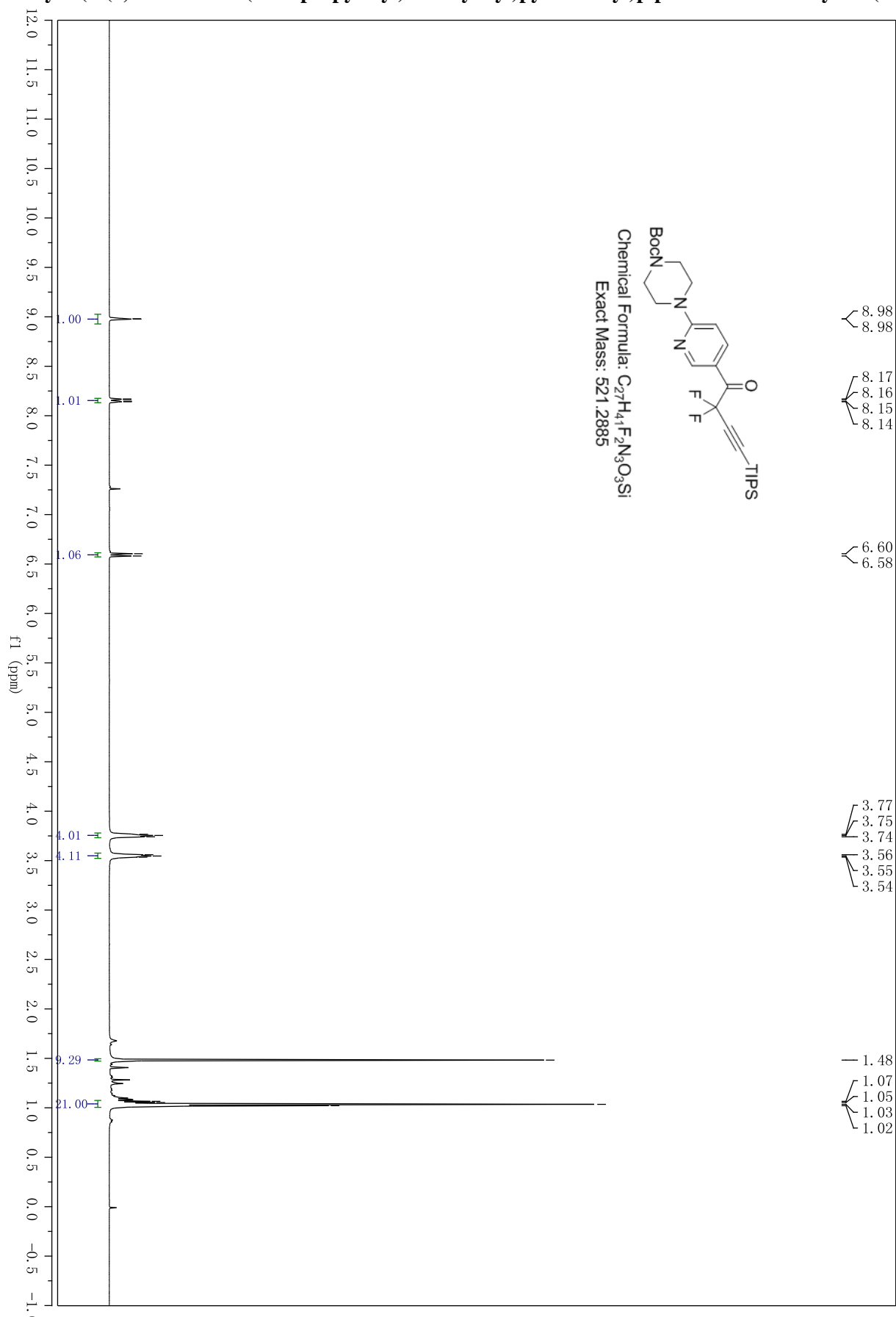
Chemical Formula: $C_{19}H_{27}F_2NO_2Si$

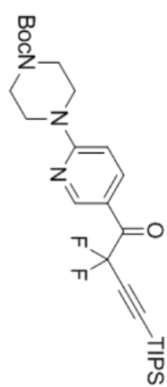
Exact Mass: 367.1779



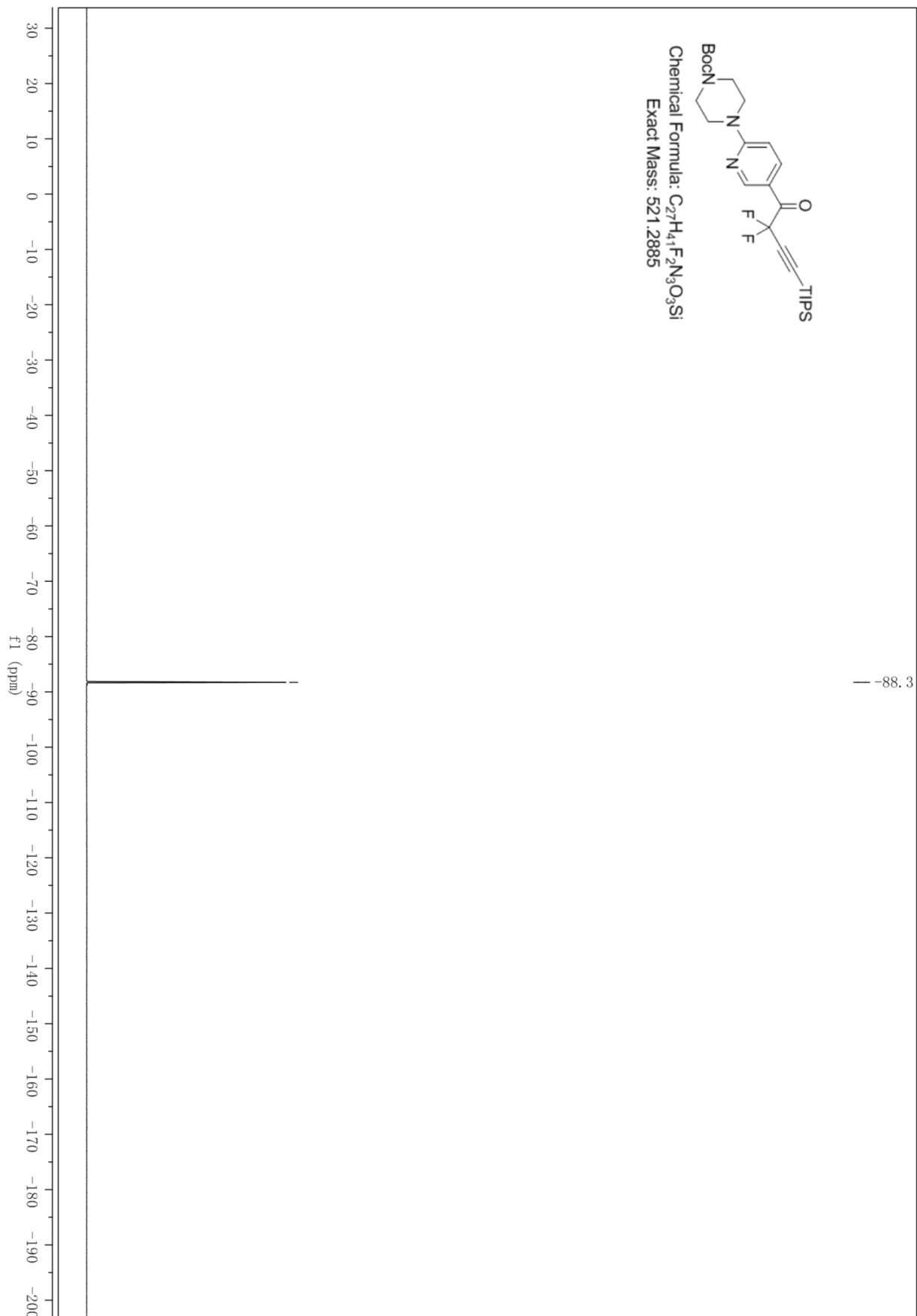


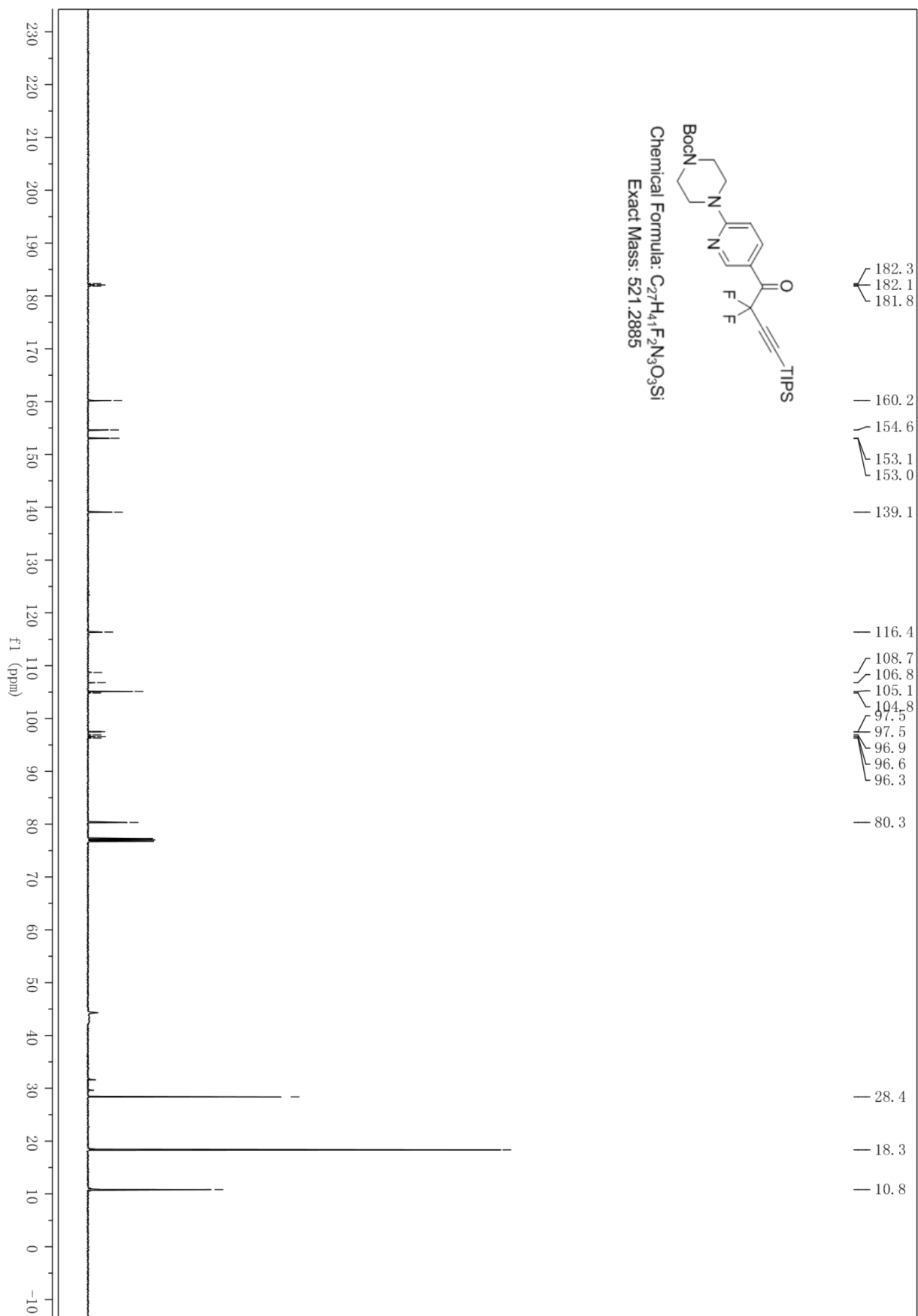
***tert*-Butyl 4-(5-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)pyridin-2-yl)piperazine-1-carboxylate (**3v**).**



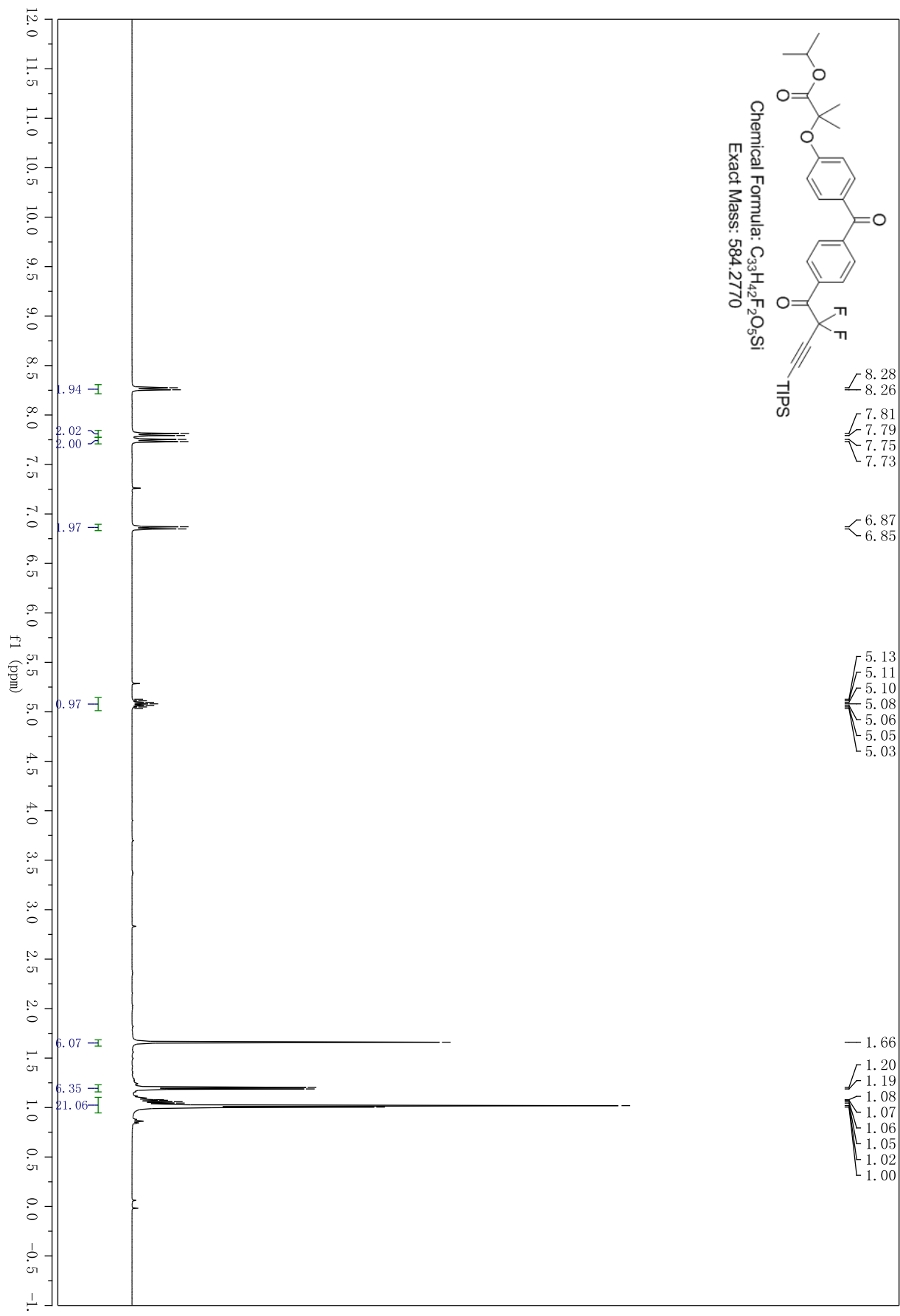


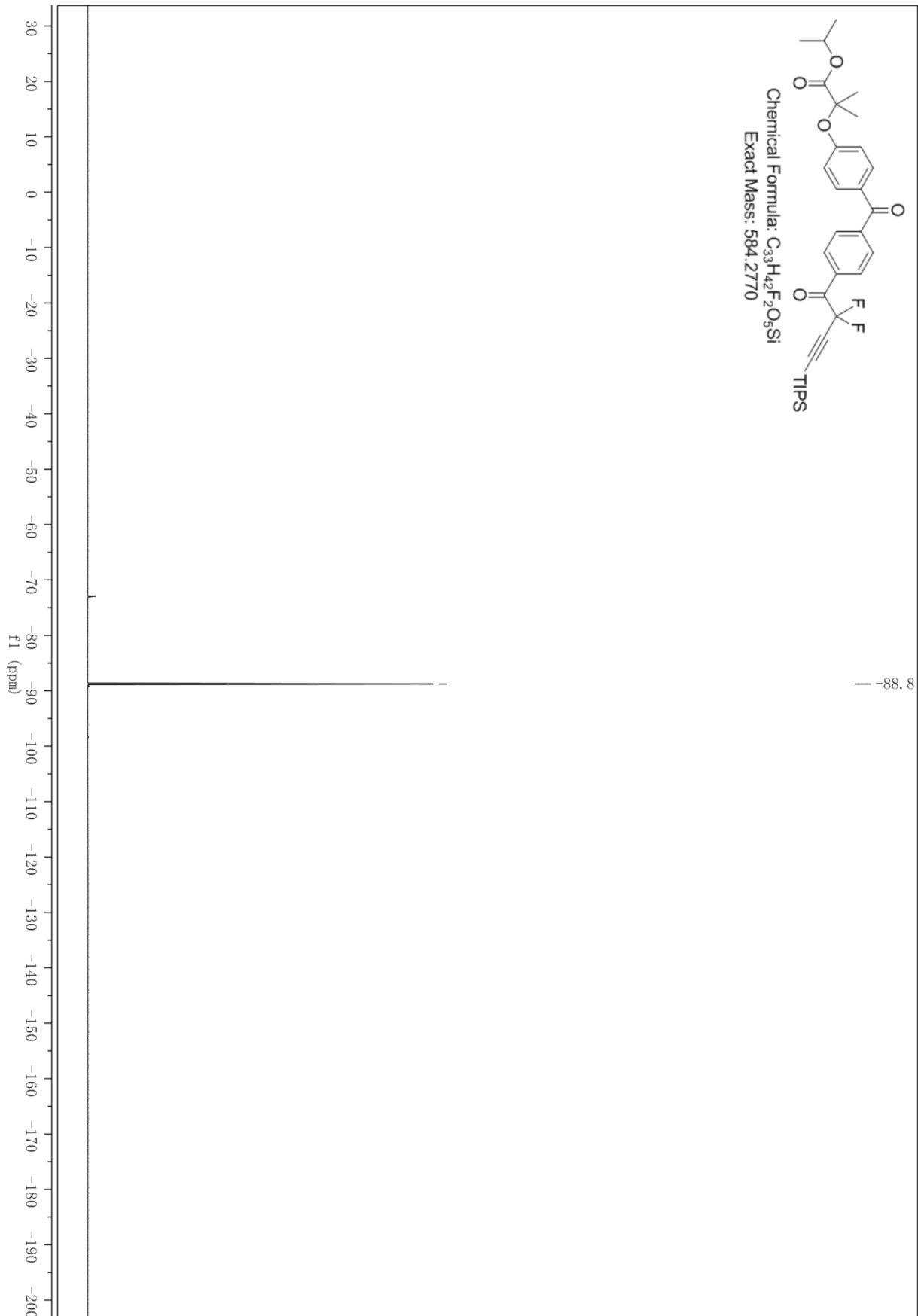
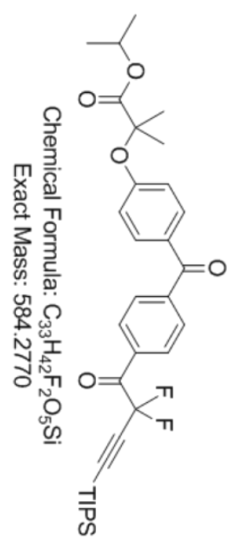
Chemical Formula: $C_{27}H_{41}F_2N_3O_3Si$
Exact Mass: 521.2885

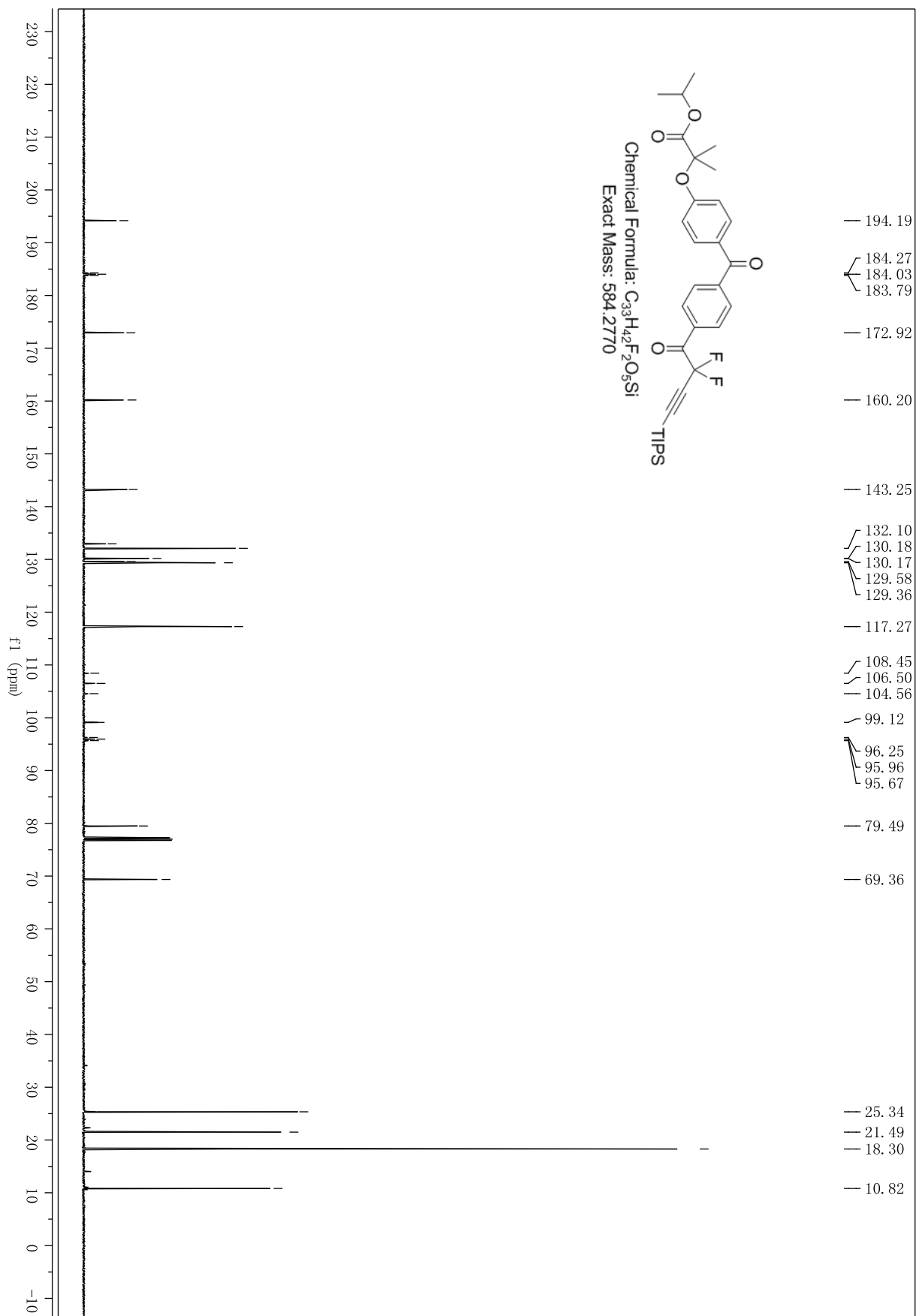




Isopropyl 2-(4-(4-(2,2-difluoro-4-(triisopropylsilyl)but-3-ynoyl)-benzoyl)phenoxy)-2-methyl-propanoate (3w).







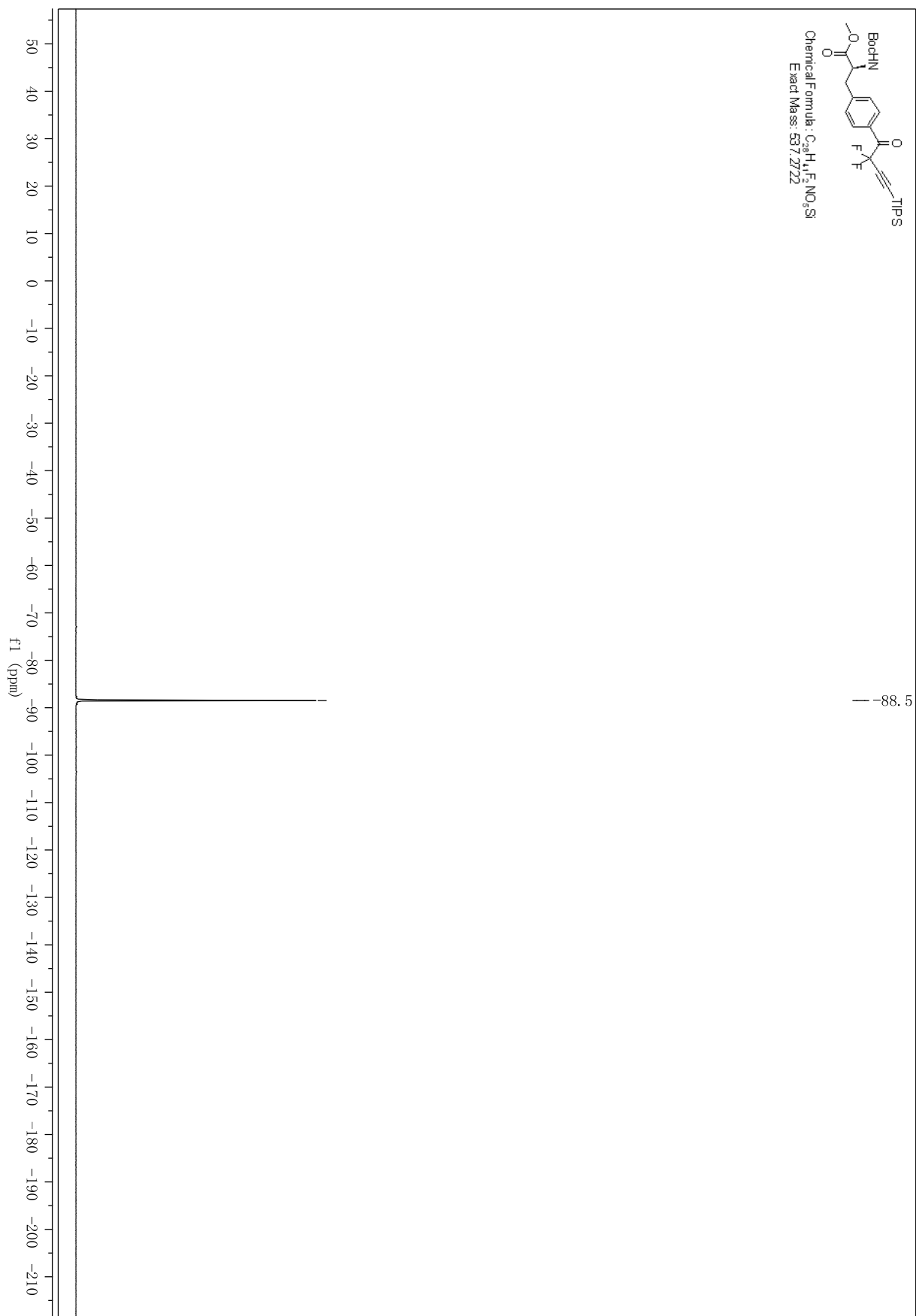
Chemical Formula: $C_{28}H_{41}F_2NO_5Si$
Exact Mass: 537.2722

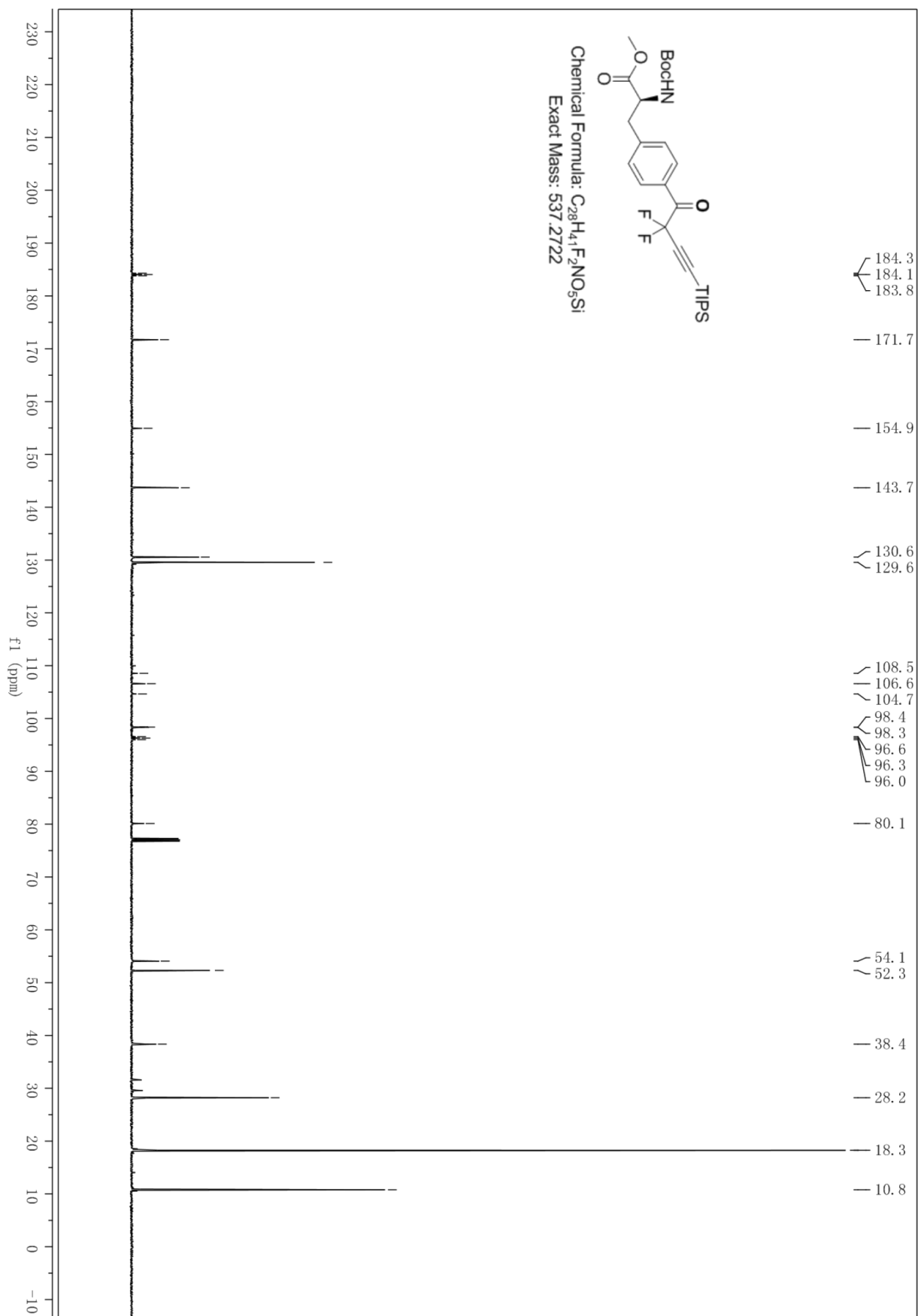
1H NMR spectrum (CDCl₃) of compound 10. The x-axis represents the chemical shift in ppm, ranging from -1.0 to 12.0. The spectrum shows several peaks corresponding to the structure of compound 10, which is a Boc-protected amino acid derivative with a fluorinated side chain and a TIPS group.

Chemical structure of compound 10 is shown above the spectrum. The structure is a Boc-protected amino acid derivative, specifically a Boc-L-phenylalanine derivative, with a fluorinated side chain and a TIPS group.

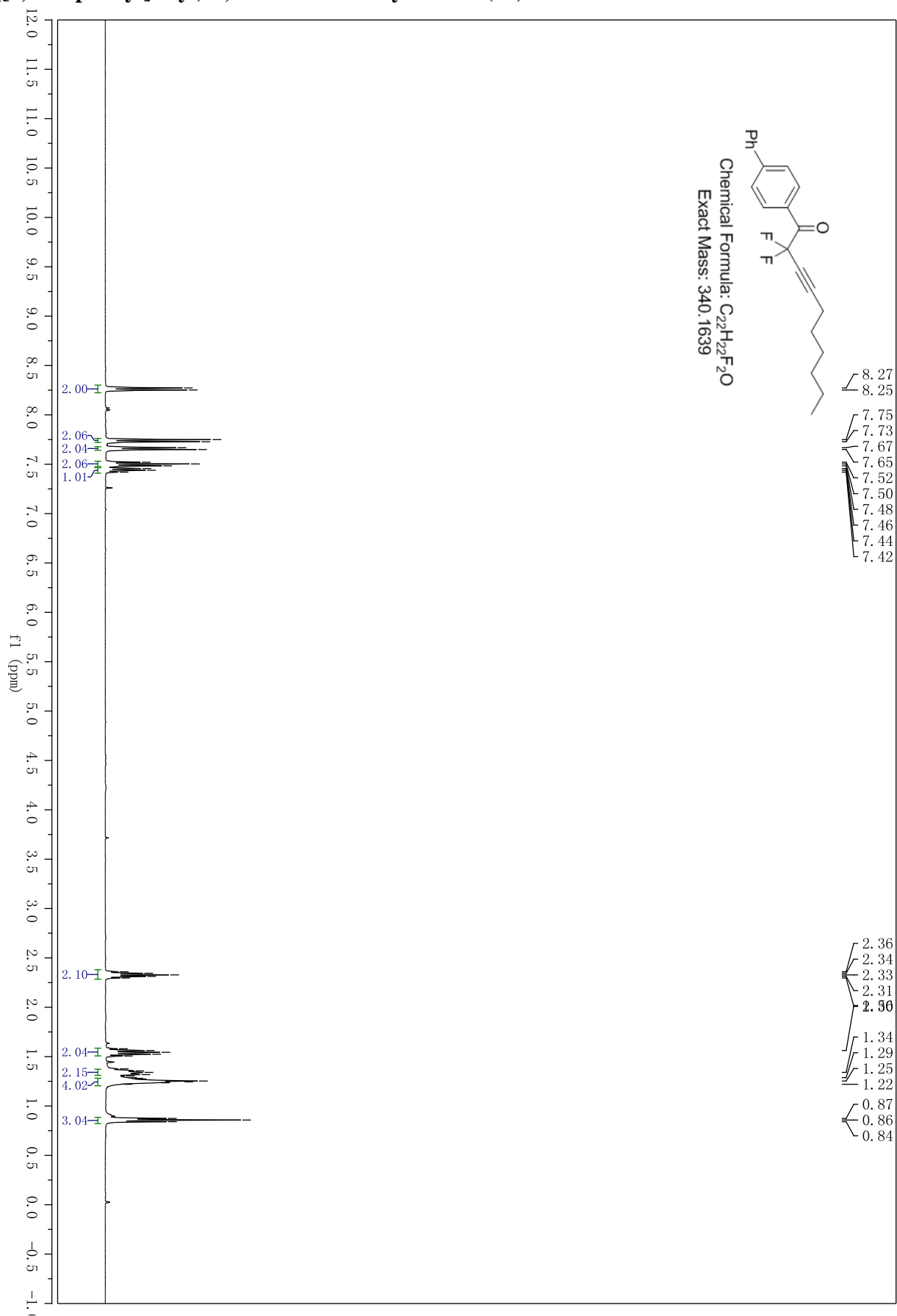
Key peaks in the spectrum are labeled with their chemical shifts and integrations:

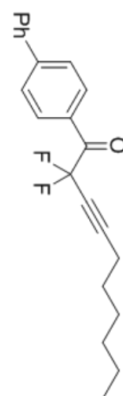
- 8.08, 8.06 ppm (2.00H): Aromatic protons (H_a).
- 7.23, 7.21 ppm (2.04H): Aromatic protons (H_b).
- 5.04, 5.02 ppm (0.93H): Methylene protons (H_c).
- 4.60, 4.58 ppm (0.95H): Methylene protons (H_d).
- 3.68 ppm (2.19H): Methylene protons (H_e).
- 3.21, 3.20, 3.18, 3.17, 3.10, 3.09, 3.07, 3.06 ppm (8.07H): Methylene protons (H_f).
- 1.38 ppm (9.04H): Methyl protons (H_g).
- 0.99, 0.97 ppm (21.20H): Methyl protons (H_h).





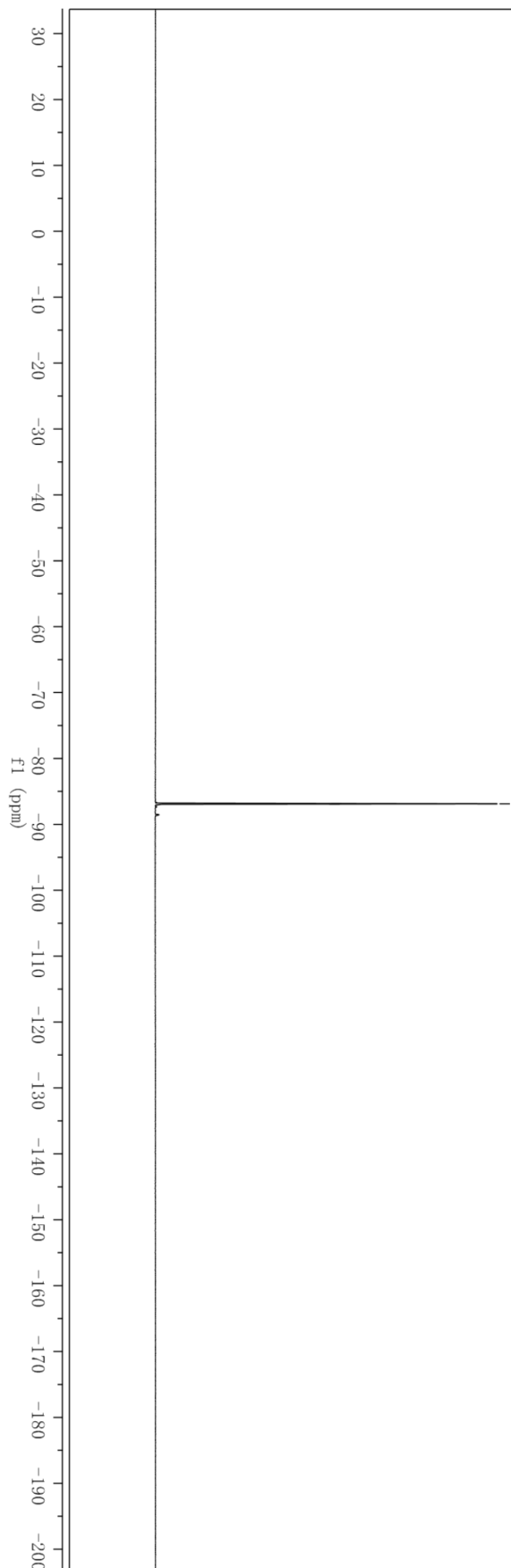
1-([1,1'-Biphenyl]-4-yl)-2,2-difluorodec-3-yn-1-one (5a).

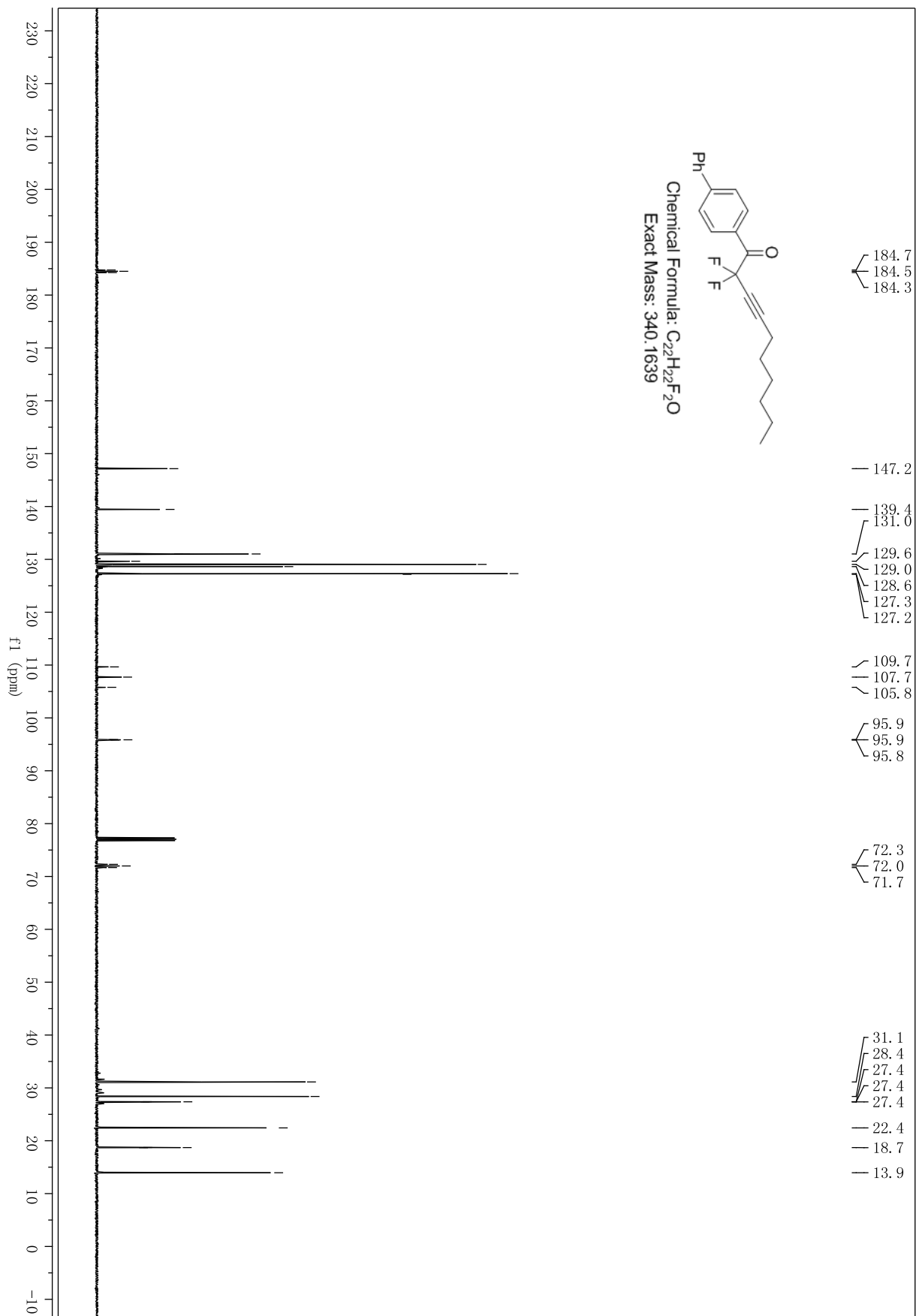




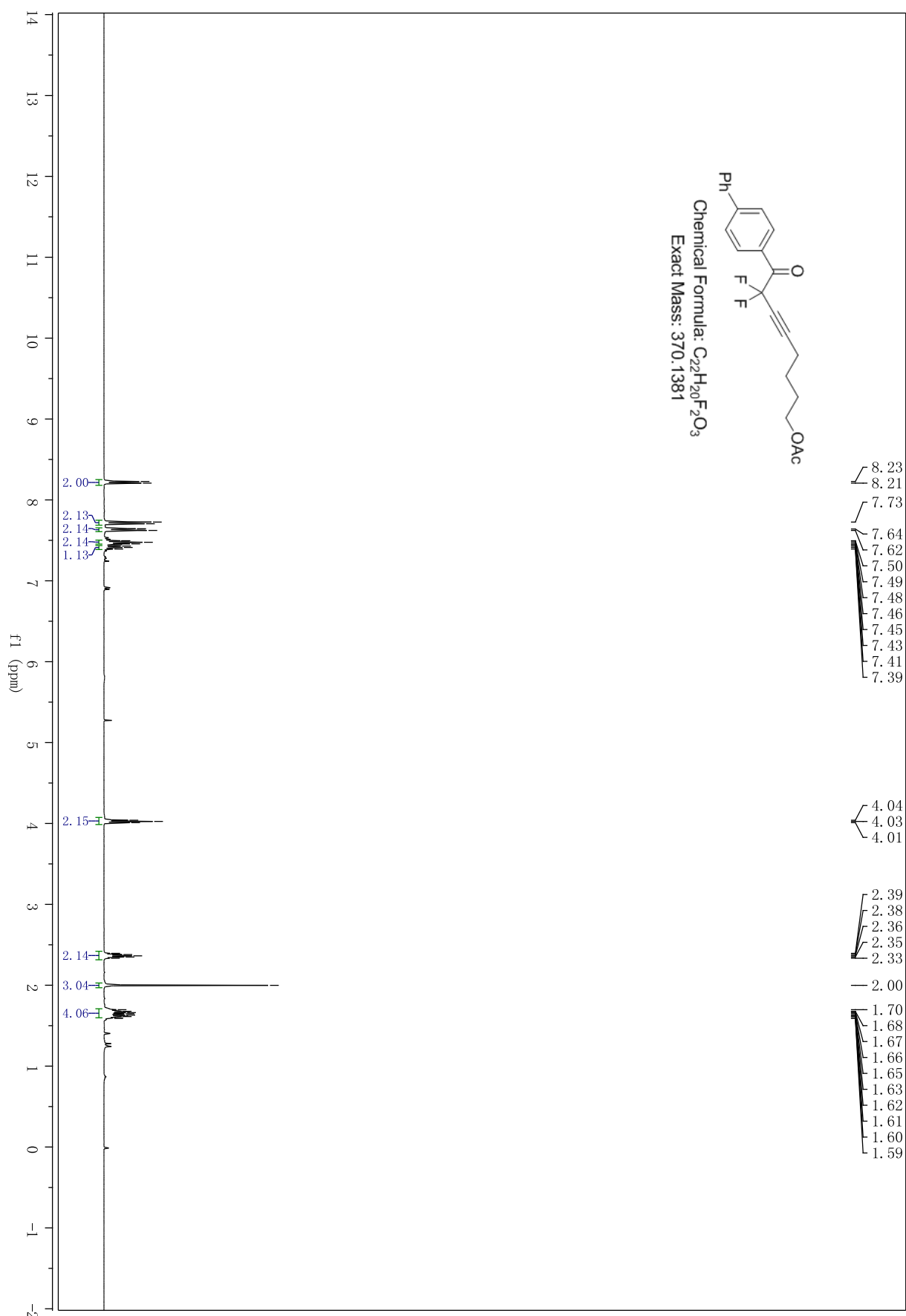
Chemical Formula: $C_{22}H_{22}F_2O$
Exact Mass: 340.1639

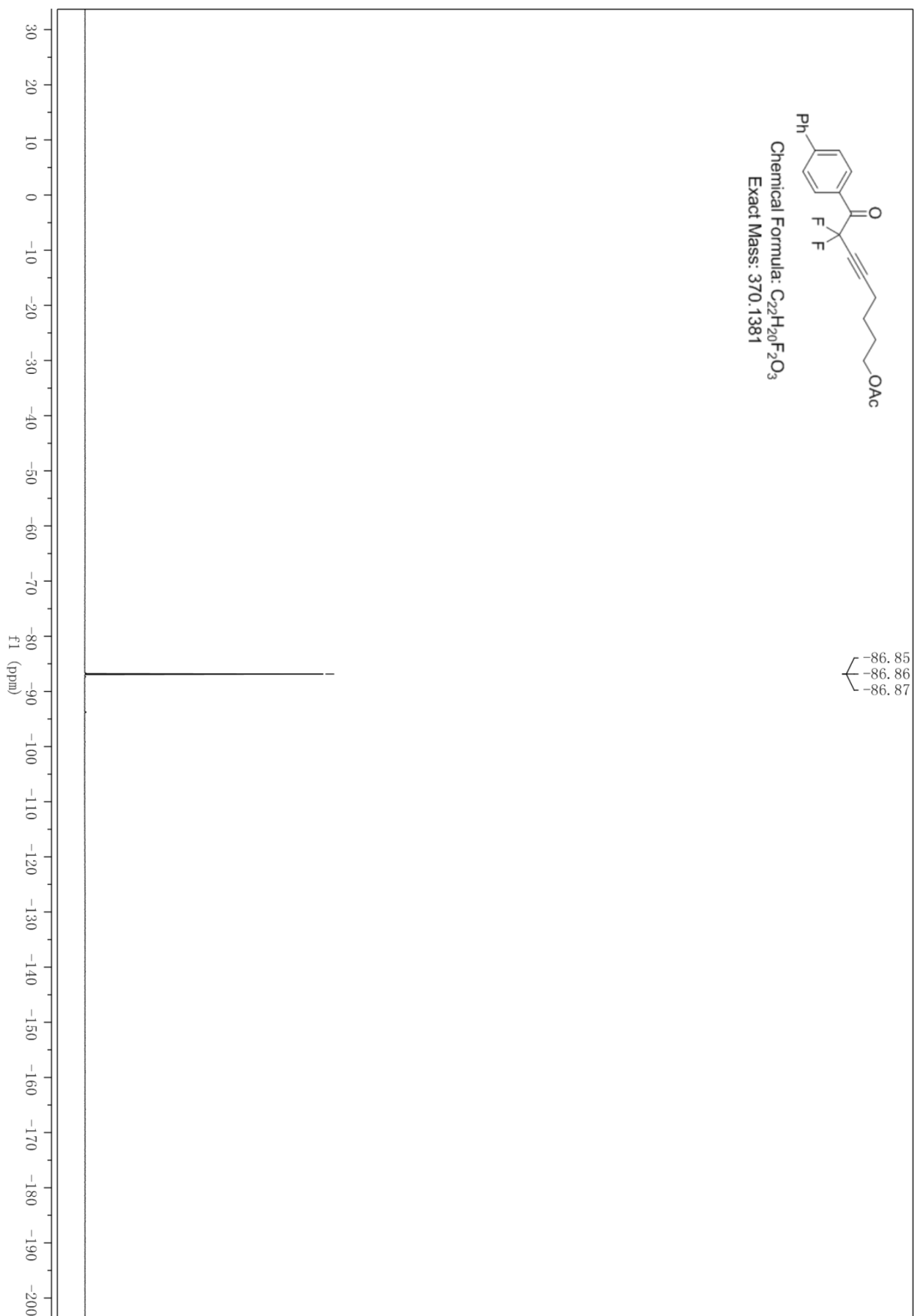
-86.88
-86.90
-86.91

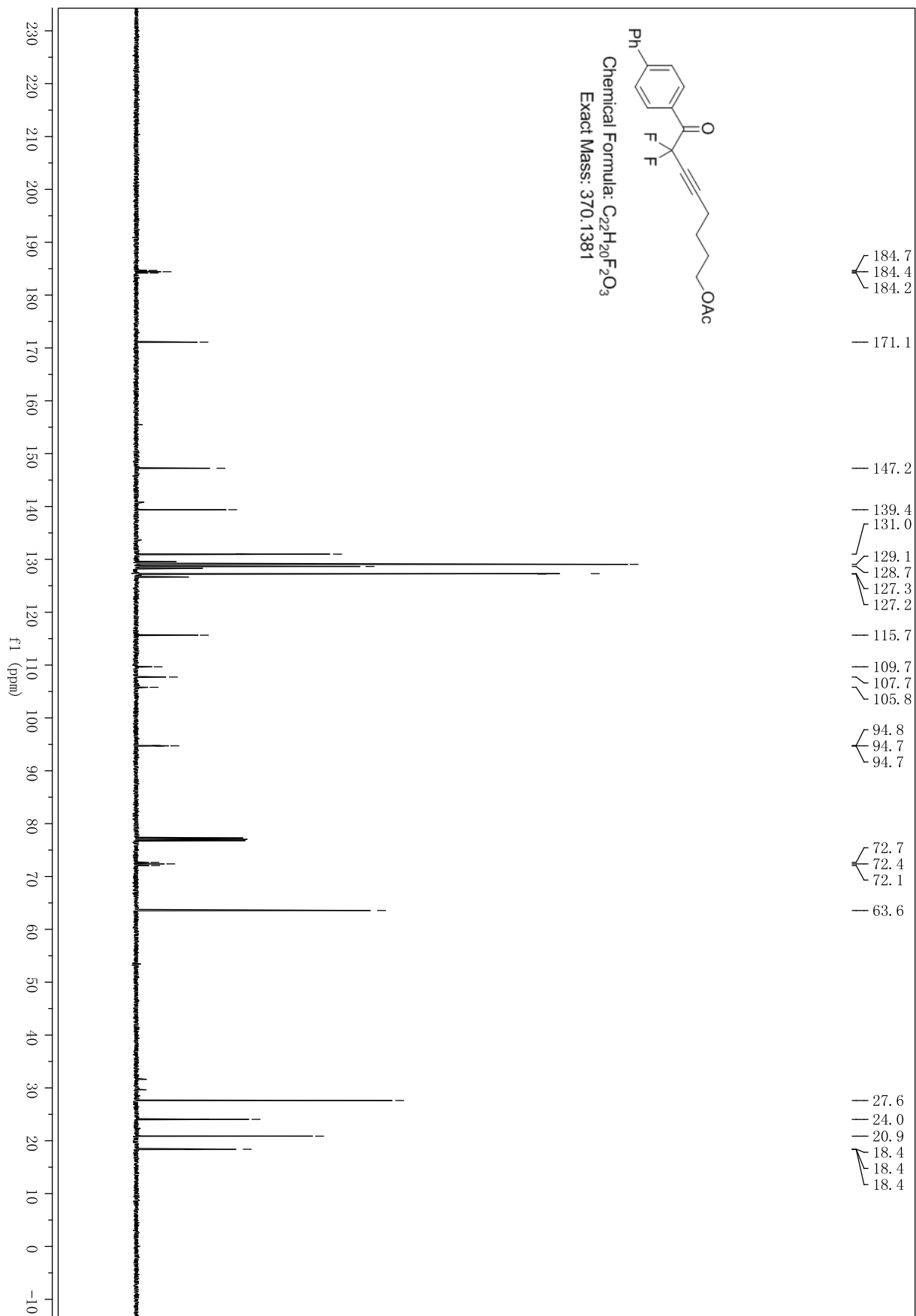




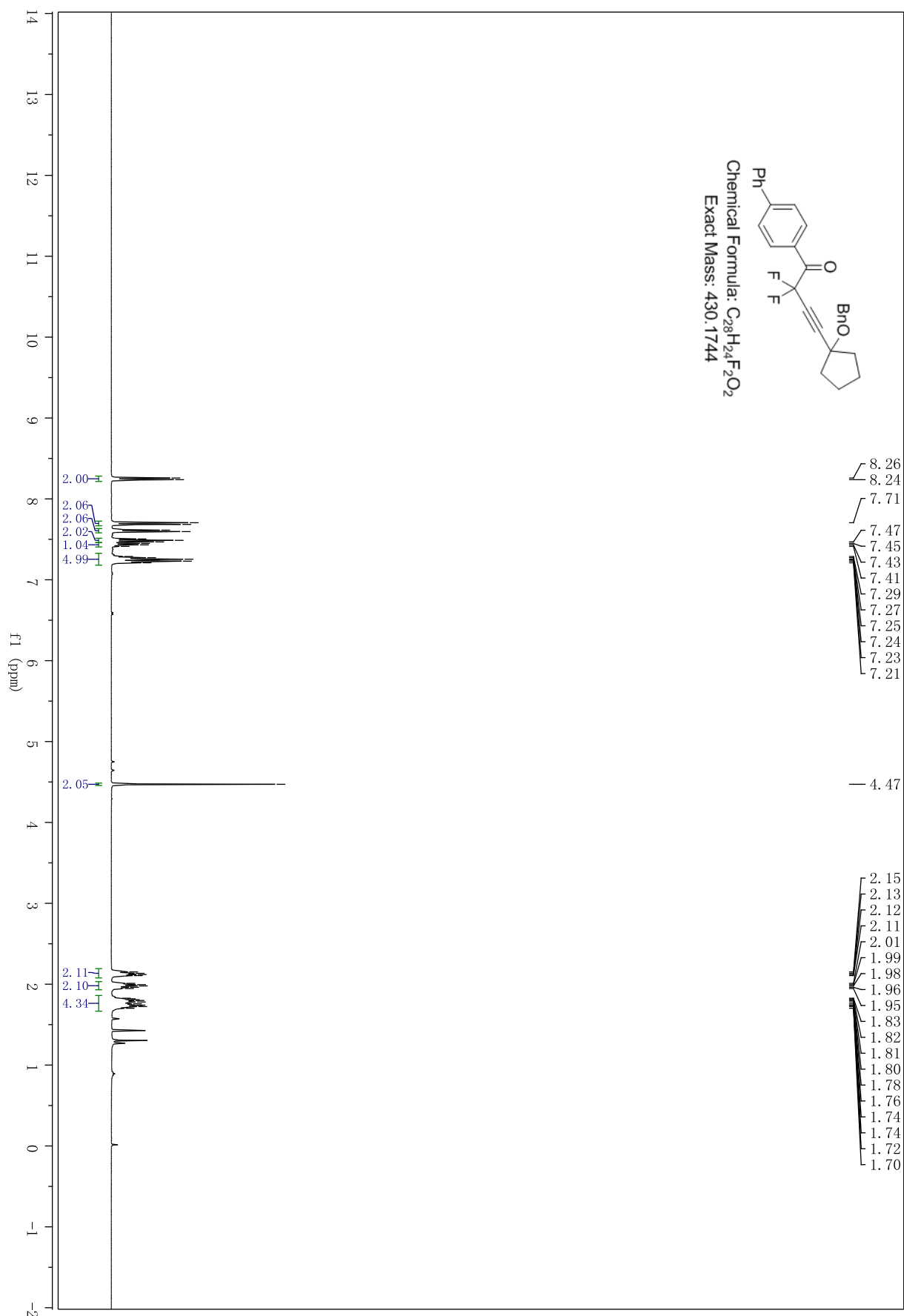
8-([1,1'-Biphenyl]-4-yl)-7,7-difluoro-8-oxooct-5-yn-1-yl acetate (5b).

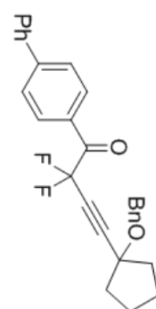






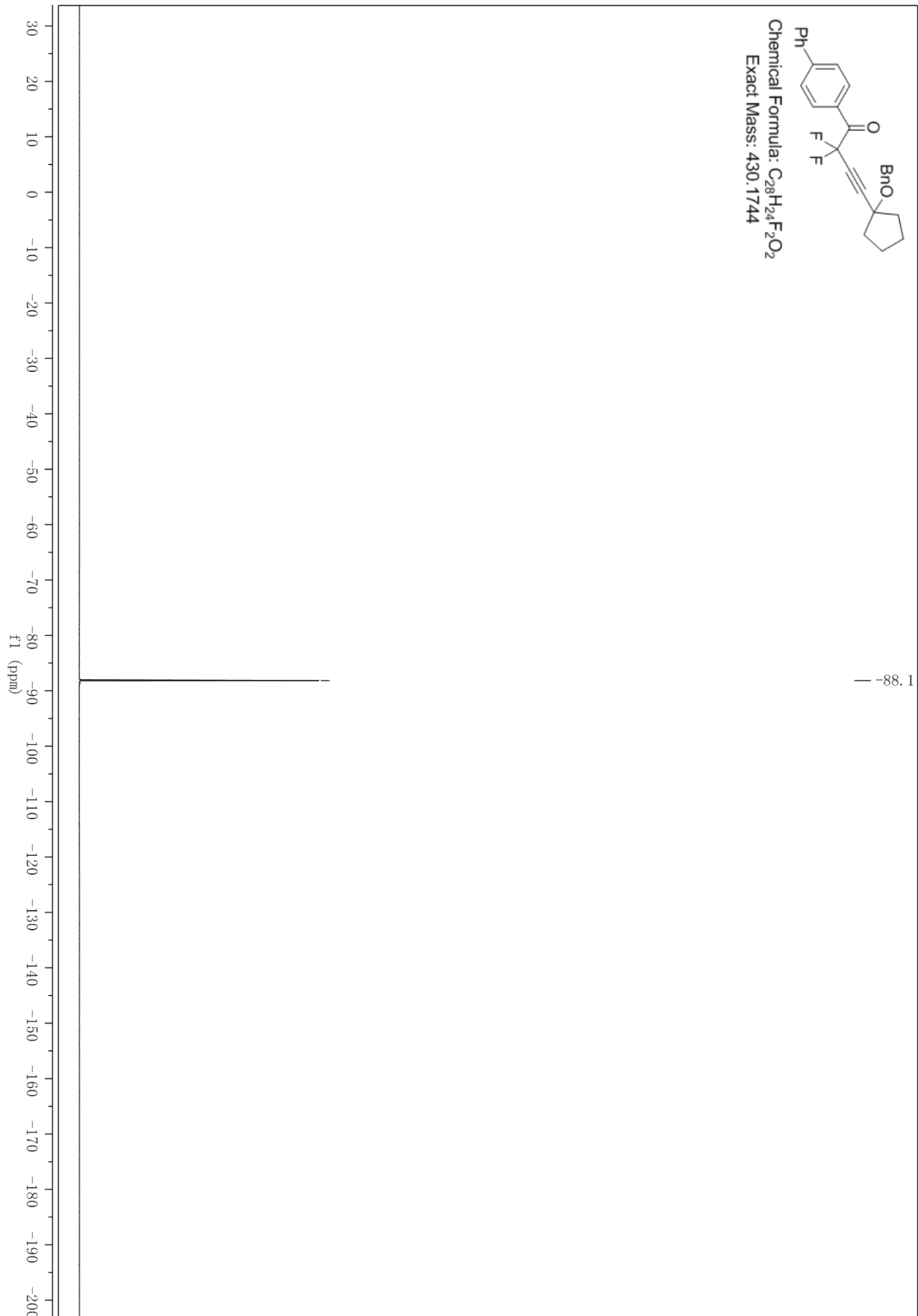
1-([1,1'-Biphenyl]-4-yl)-4-(1-(benzyloxy)cyclopentyl)-2,2-difluorobut-3-yn-1-one (5c).

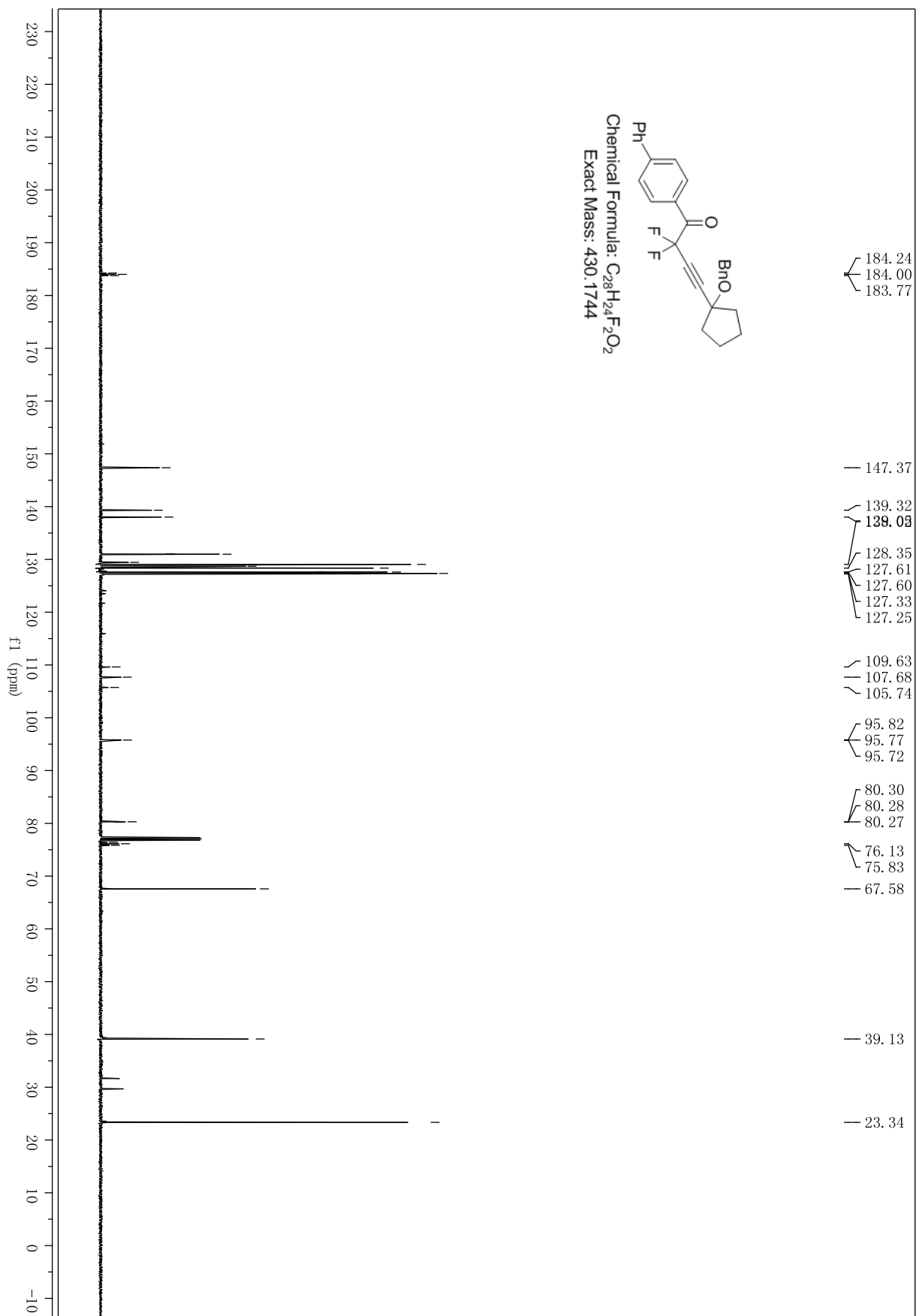




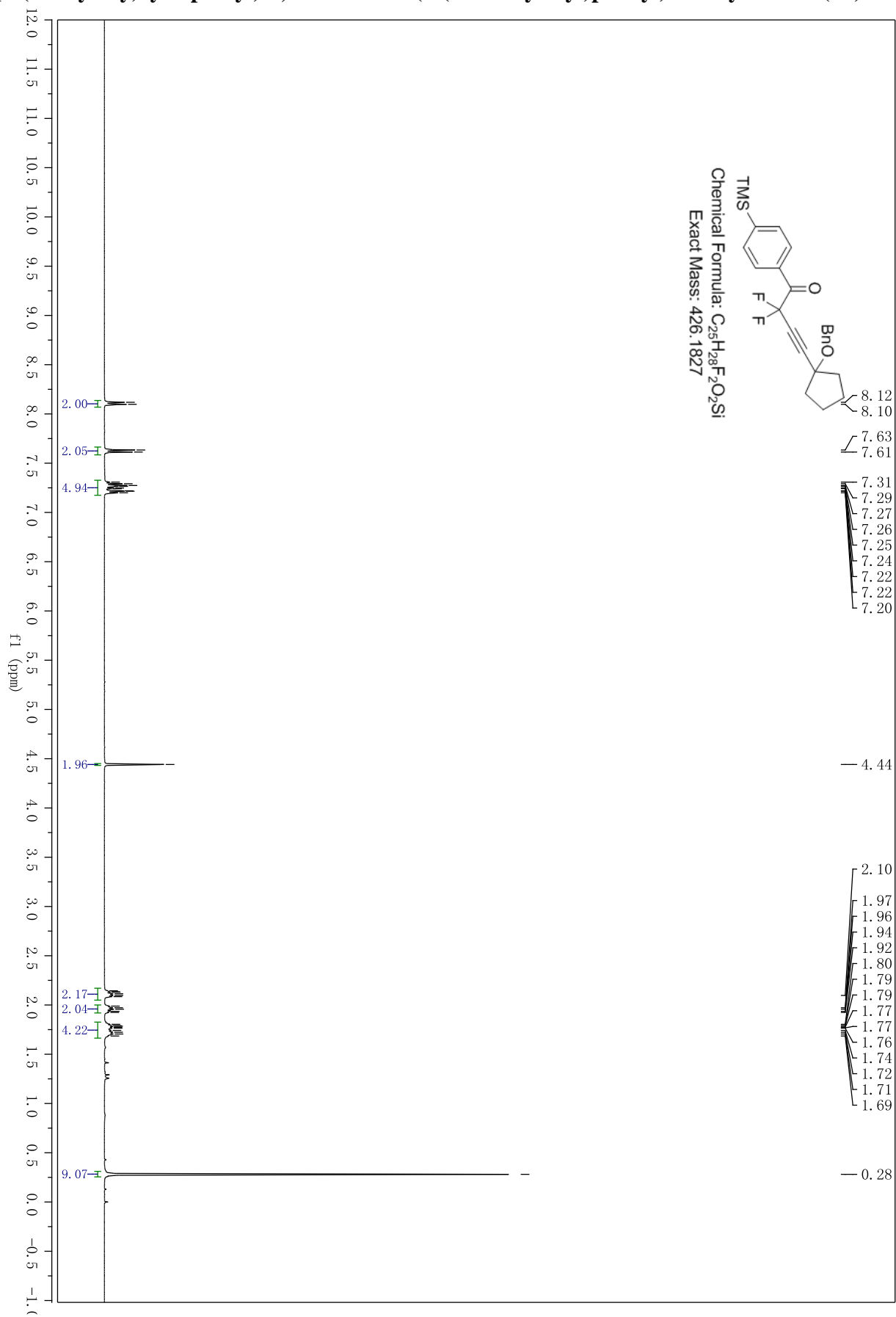
Chemical Formula: $C_{28}H_{24}F_2O_2$

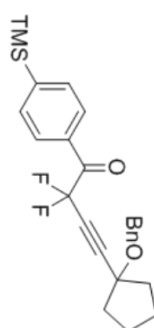
Exact Mass: 430.1744



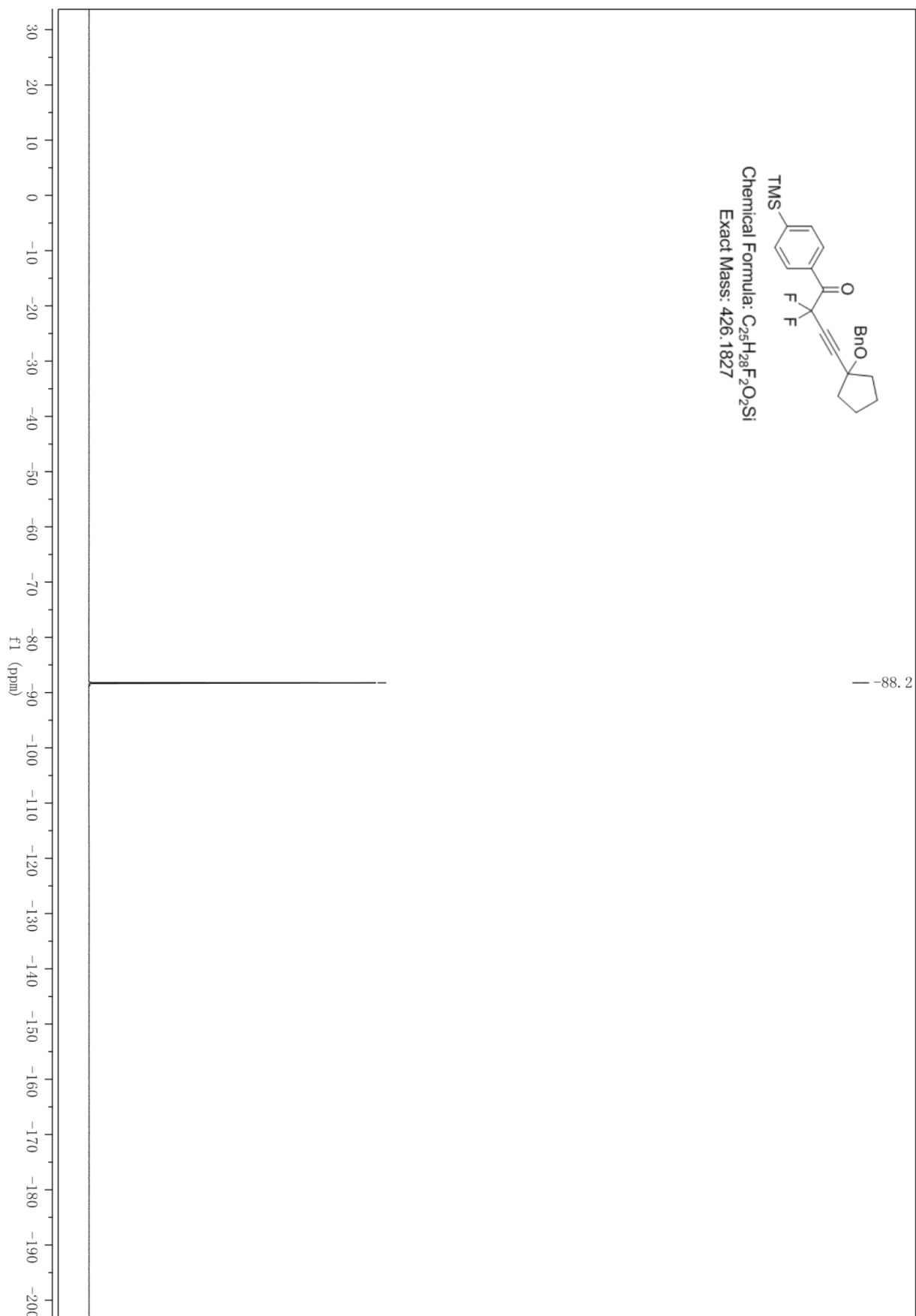


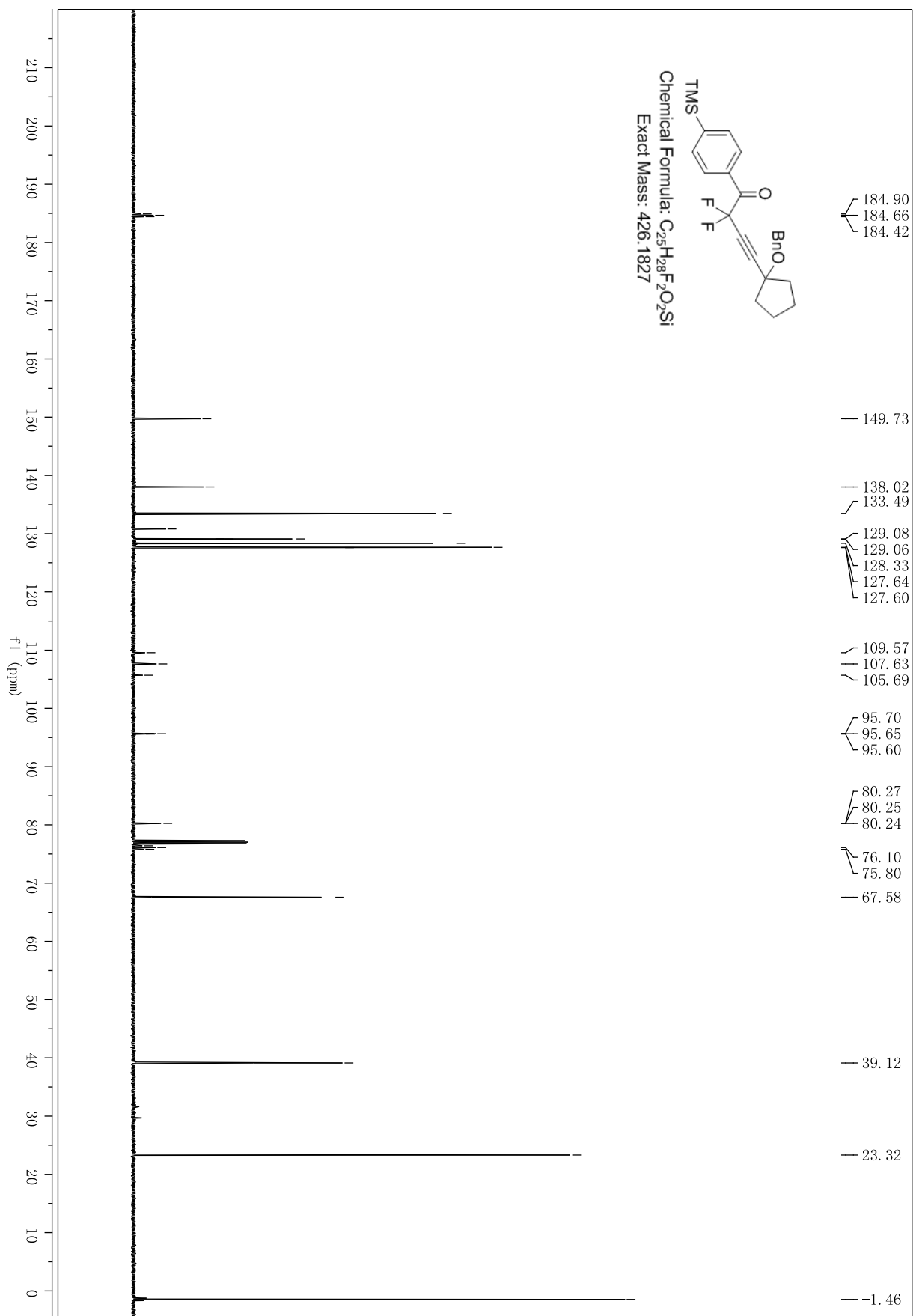
4-(1-(Benzyloxy)cyclopentyl)-2,2-difluoro-1-(4-(trimethylsilyl)phenyl)but-3-yn-1-one (5d).



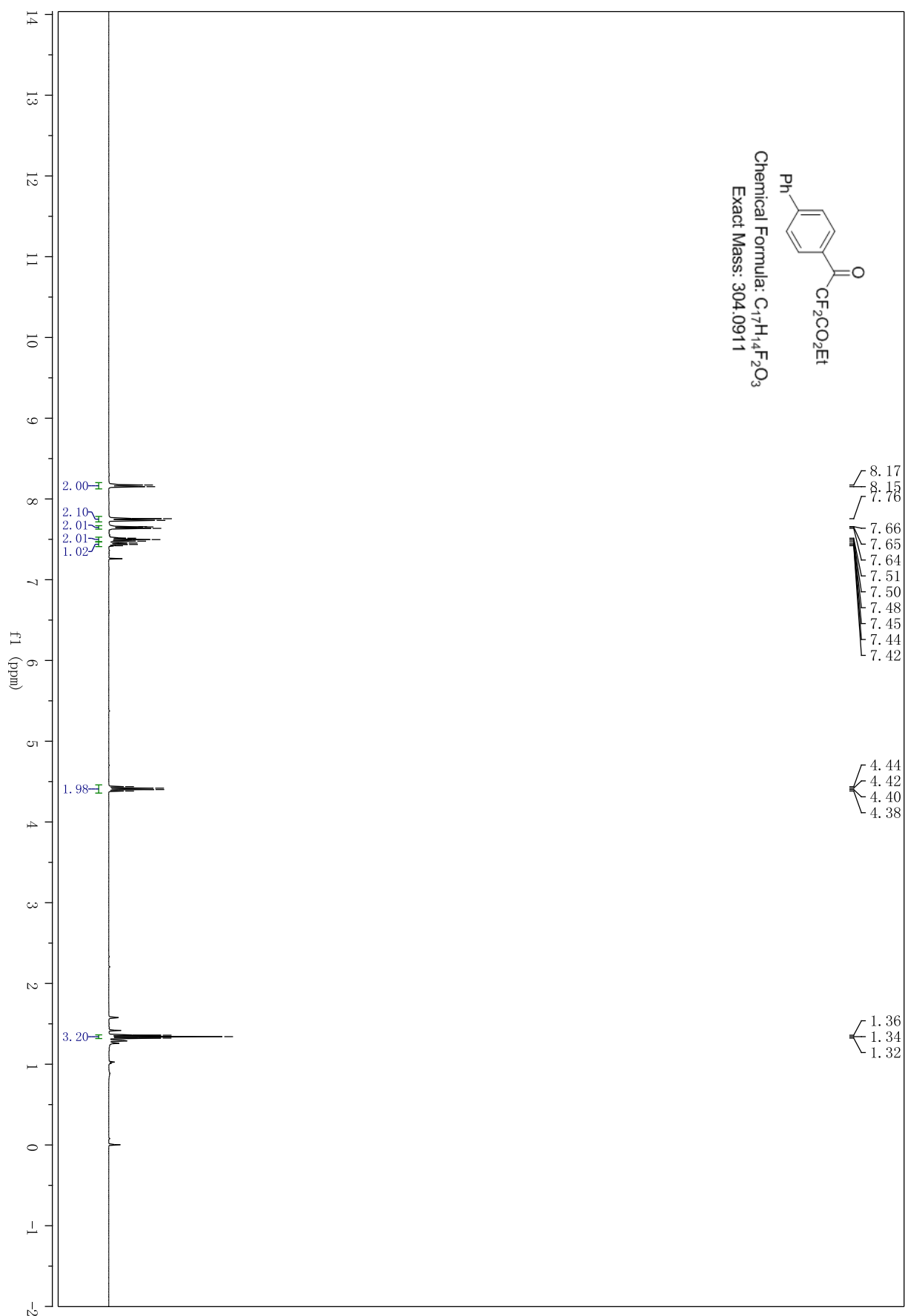


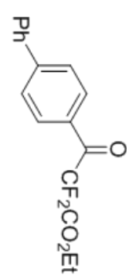
Chemical Formula: $C_{25}H_{28}F_2O_2Si$
Exact Mass: 426.1827



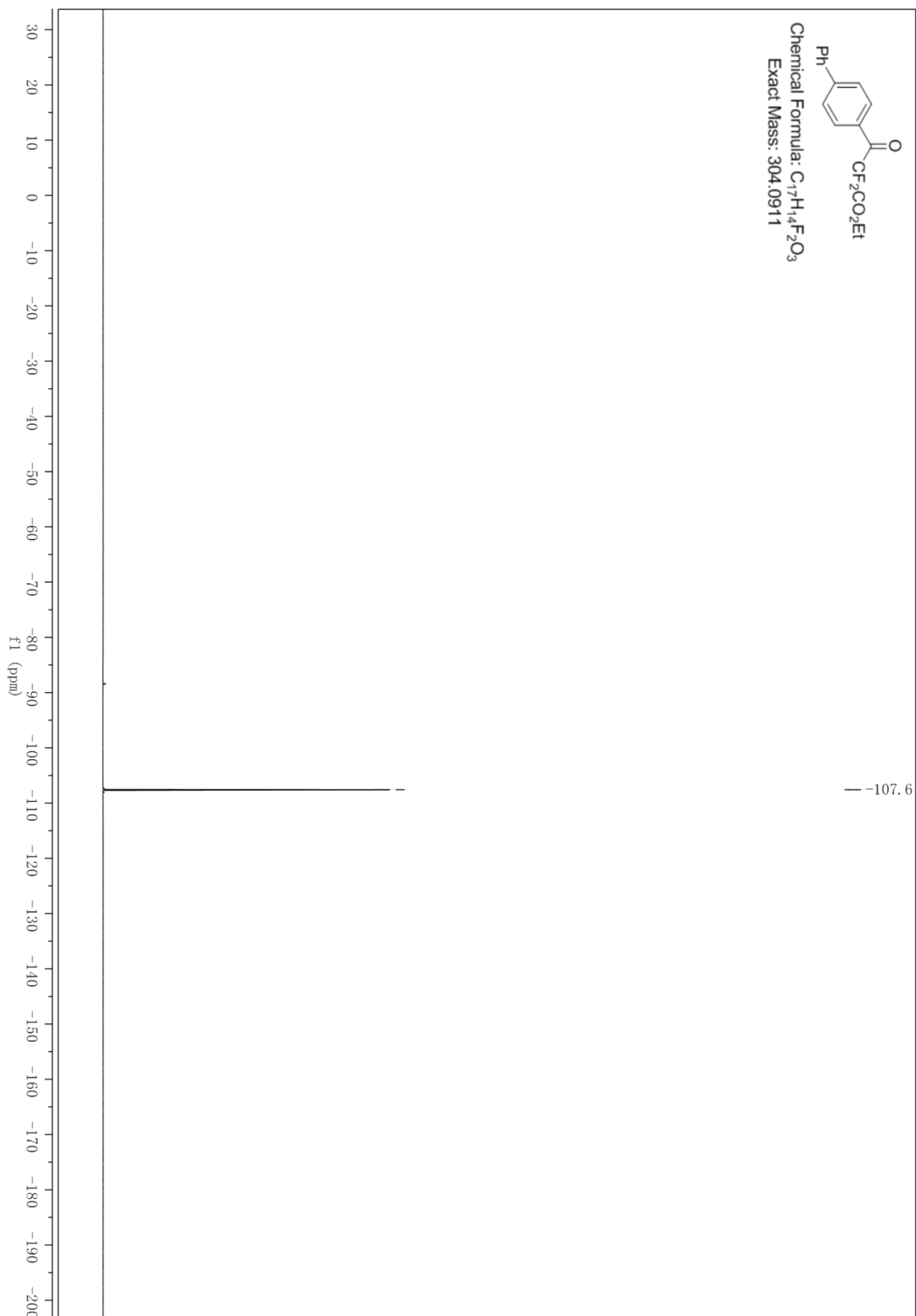


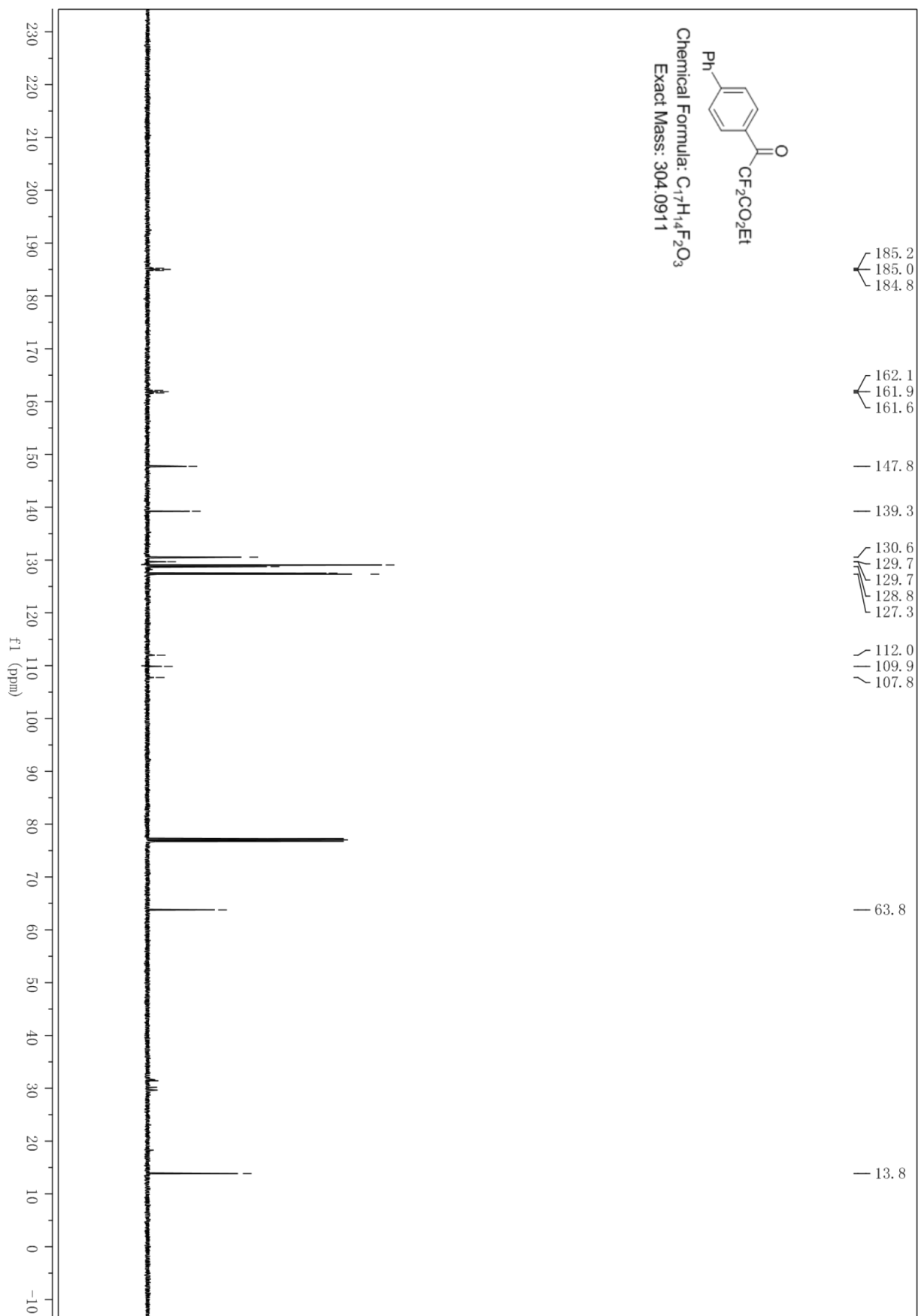
Ethyl 3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-oxopropanoate (5e).



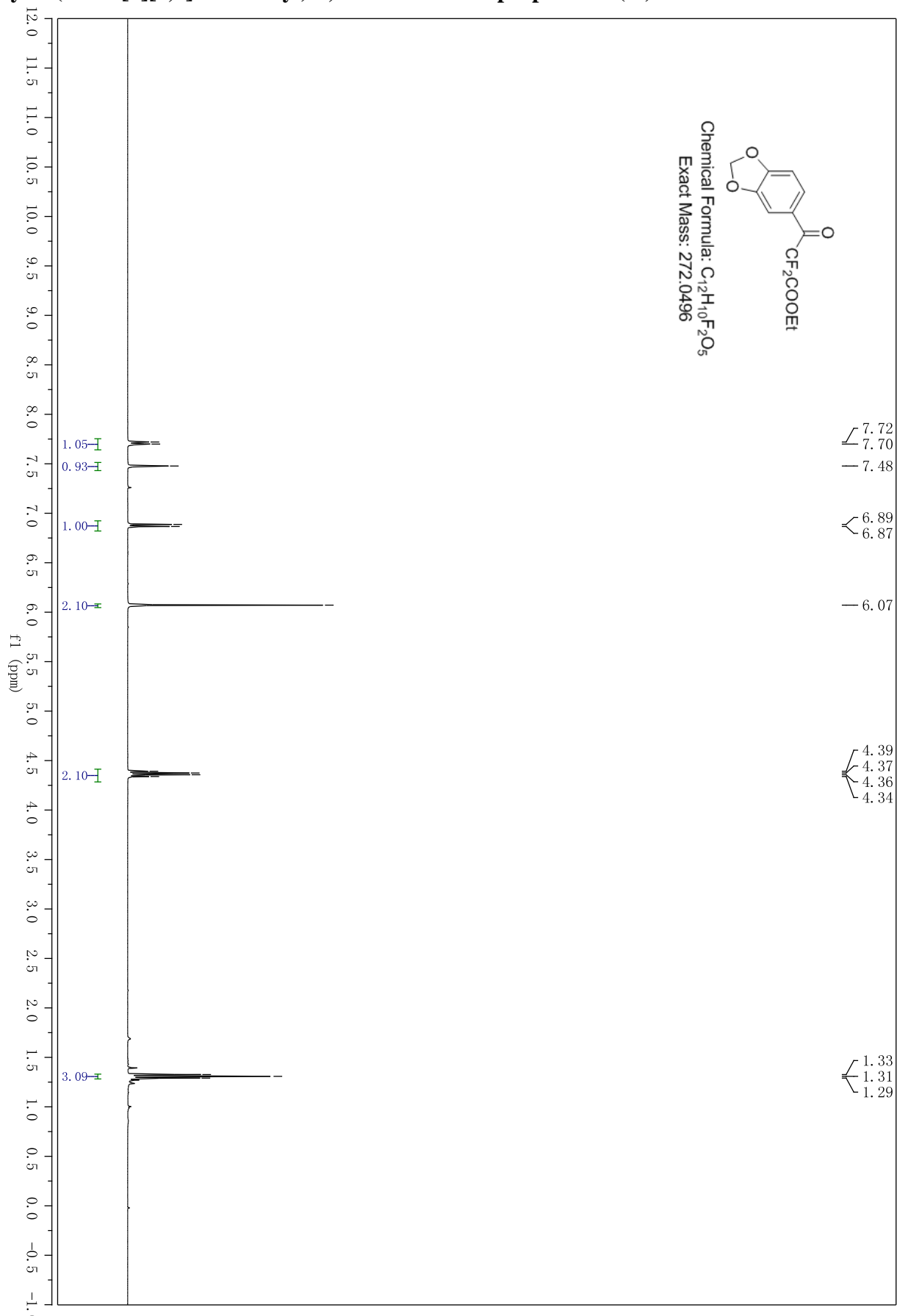


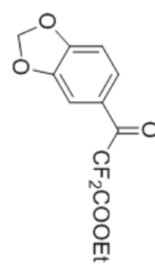
Chemical Formula: $C_{17}H_{14}F_3O_3$
Exact Mass: 304.0911



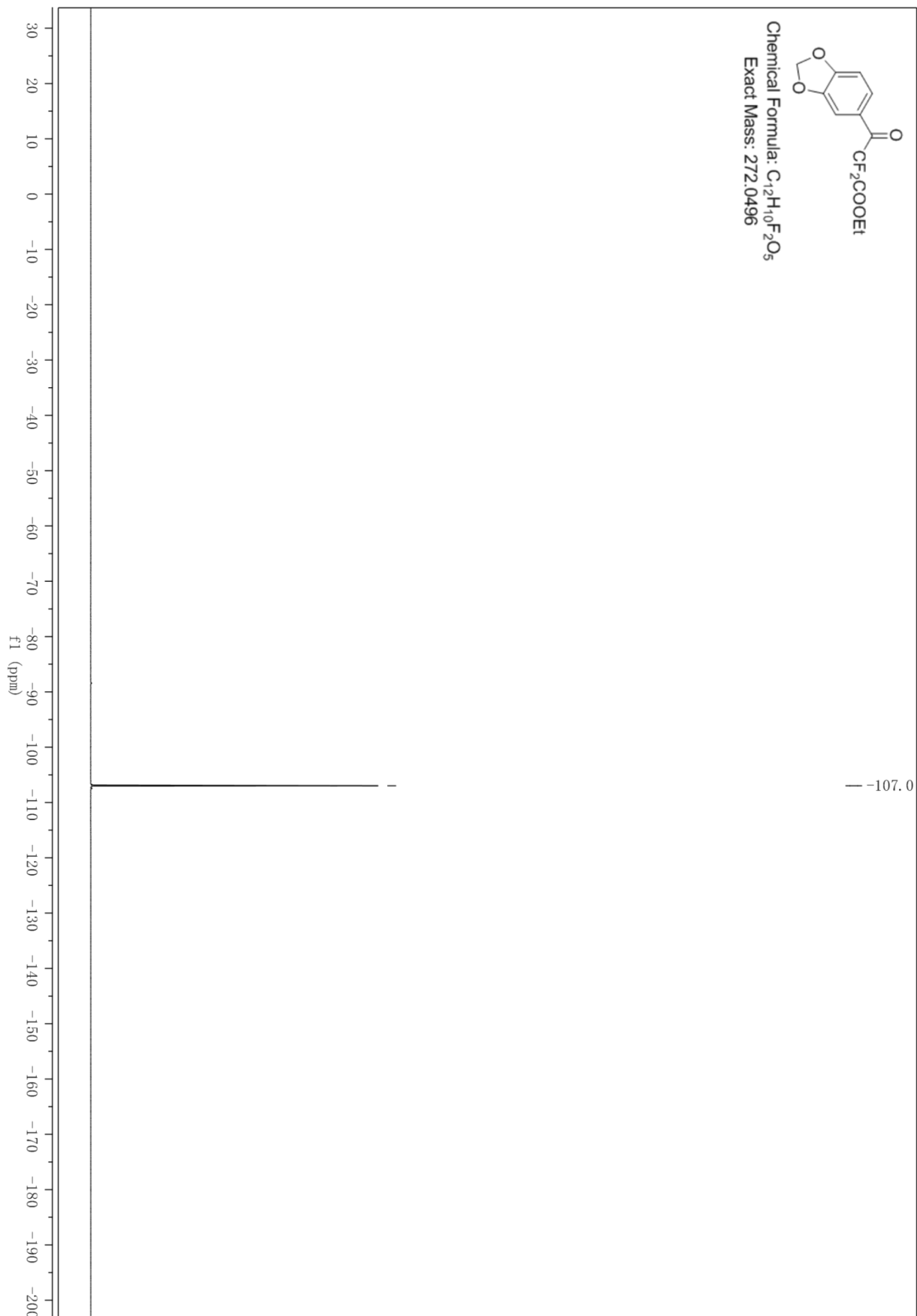


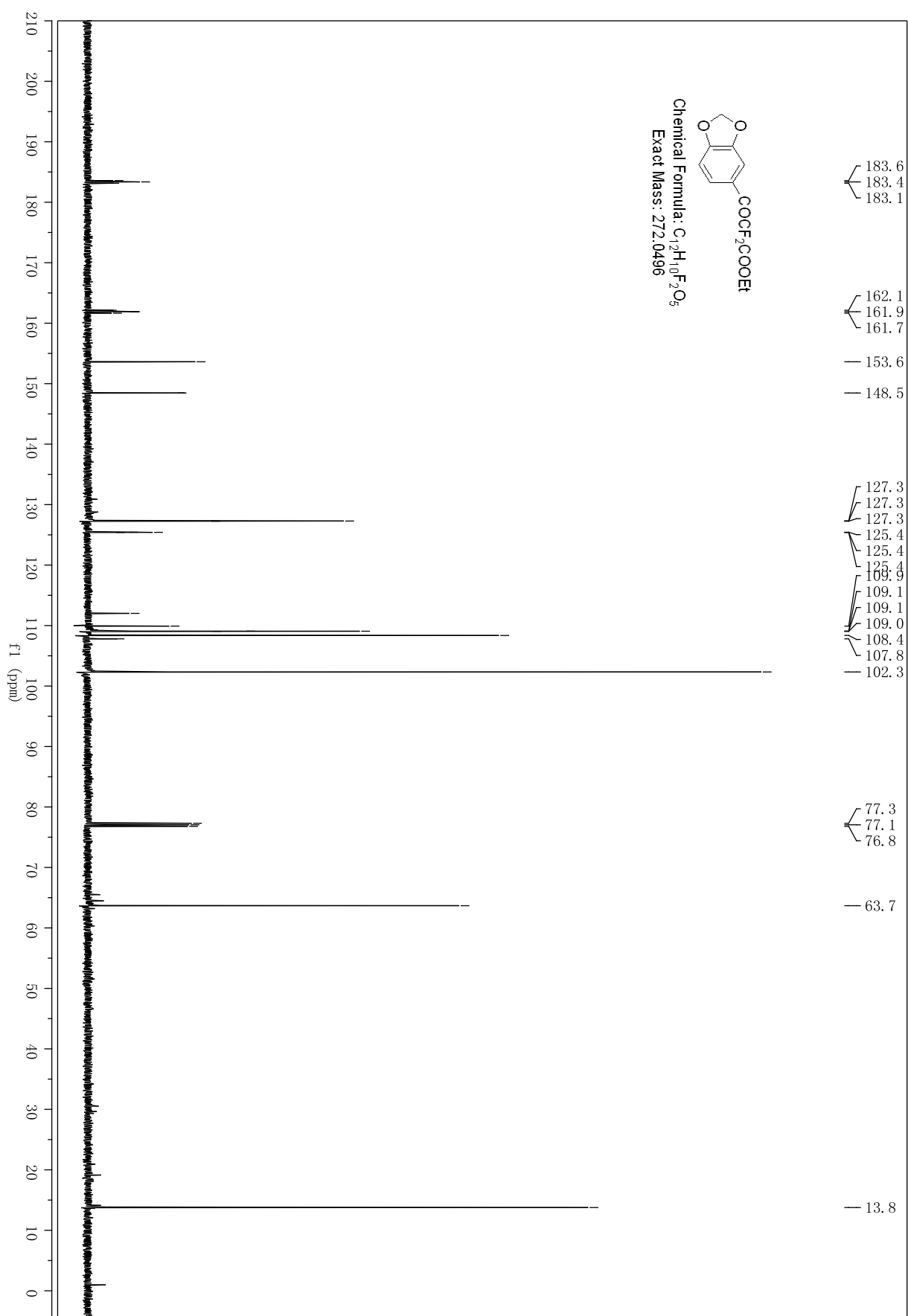
Ethyl 3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-3-oxopropanoate (5f).



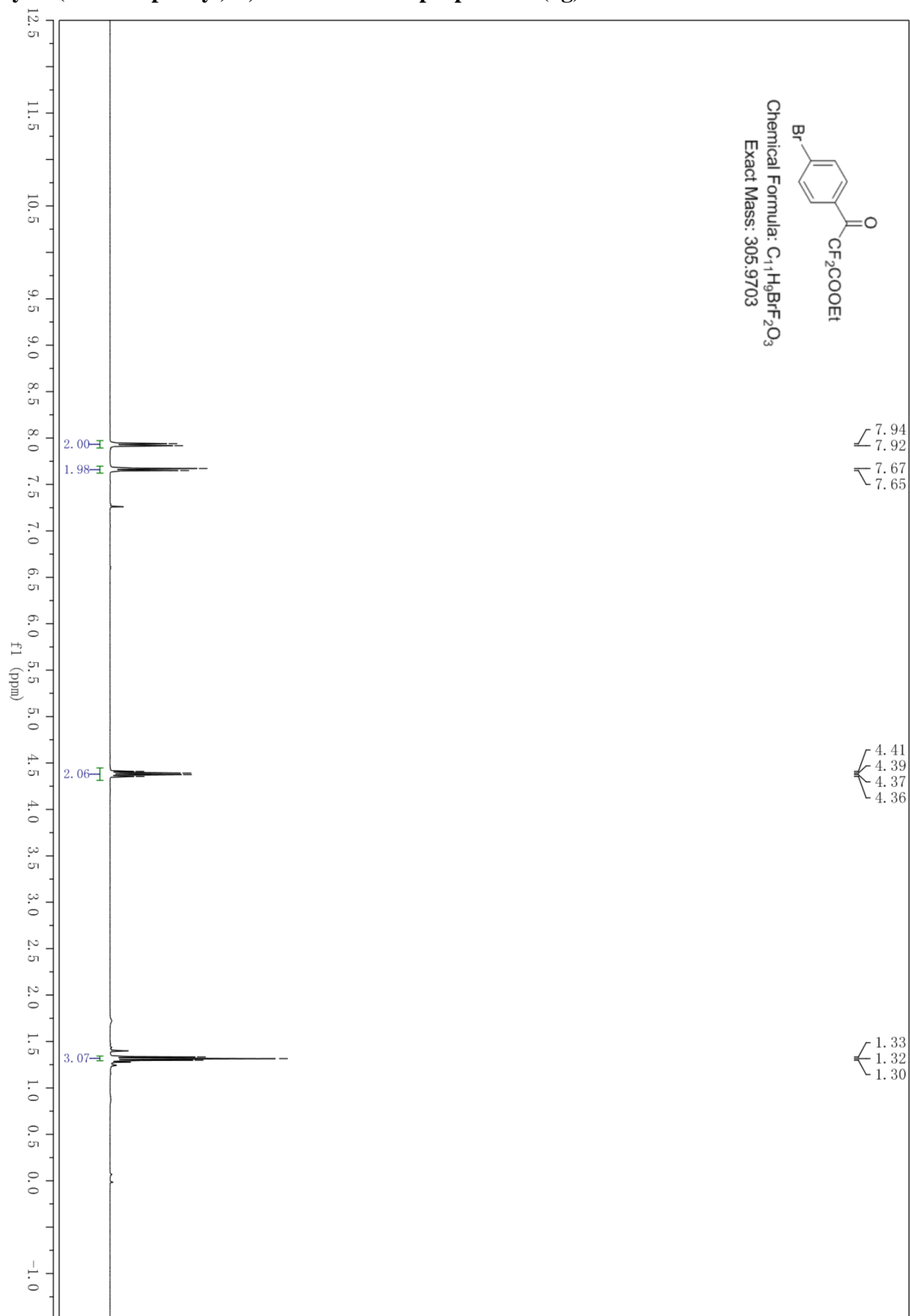


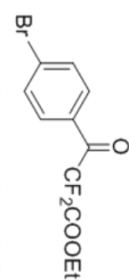
Chemical Formula: $C_{12}H_{10}F_2O_5$
Exact Mass: 272.0496



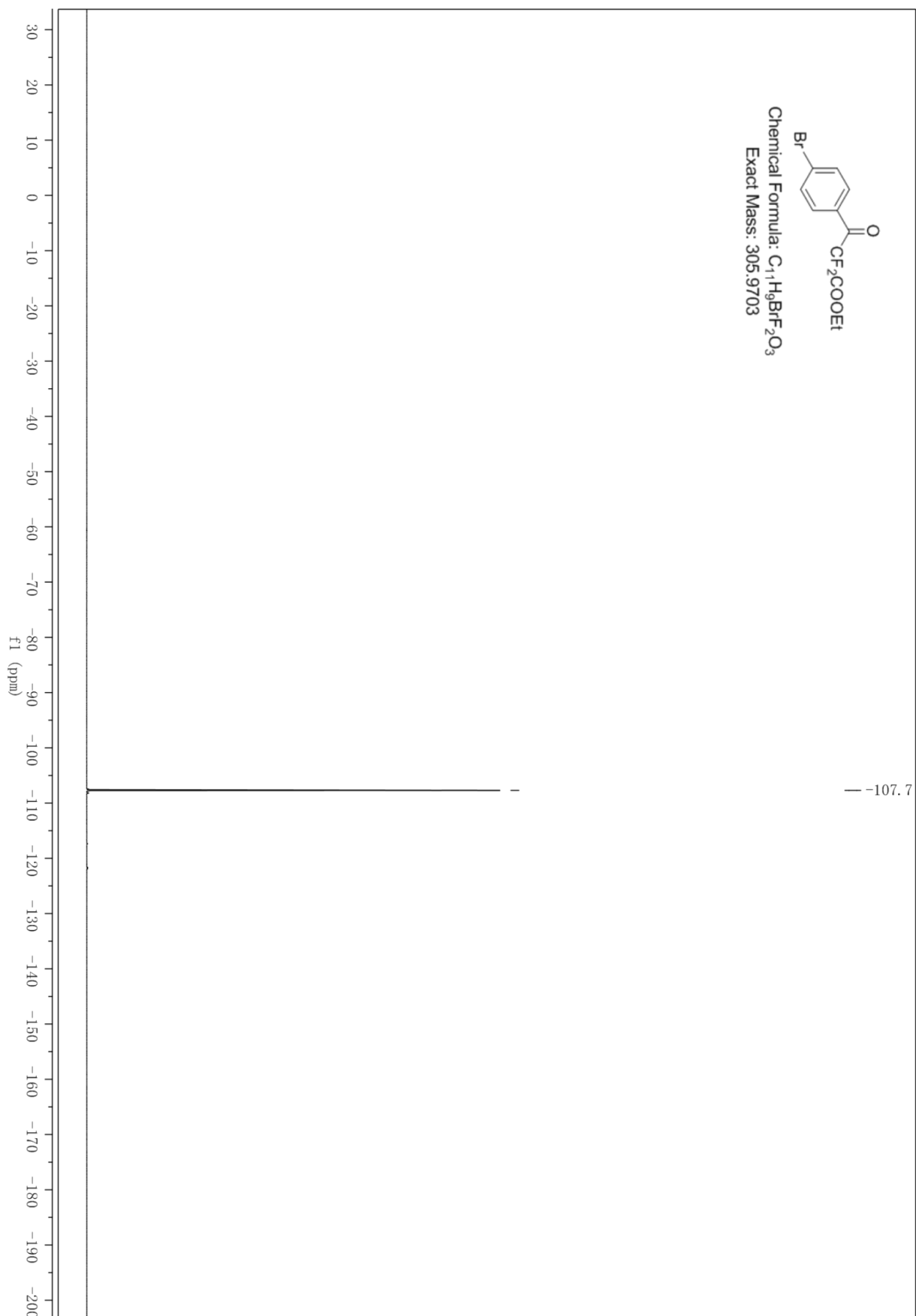


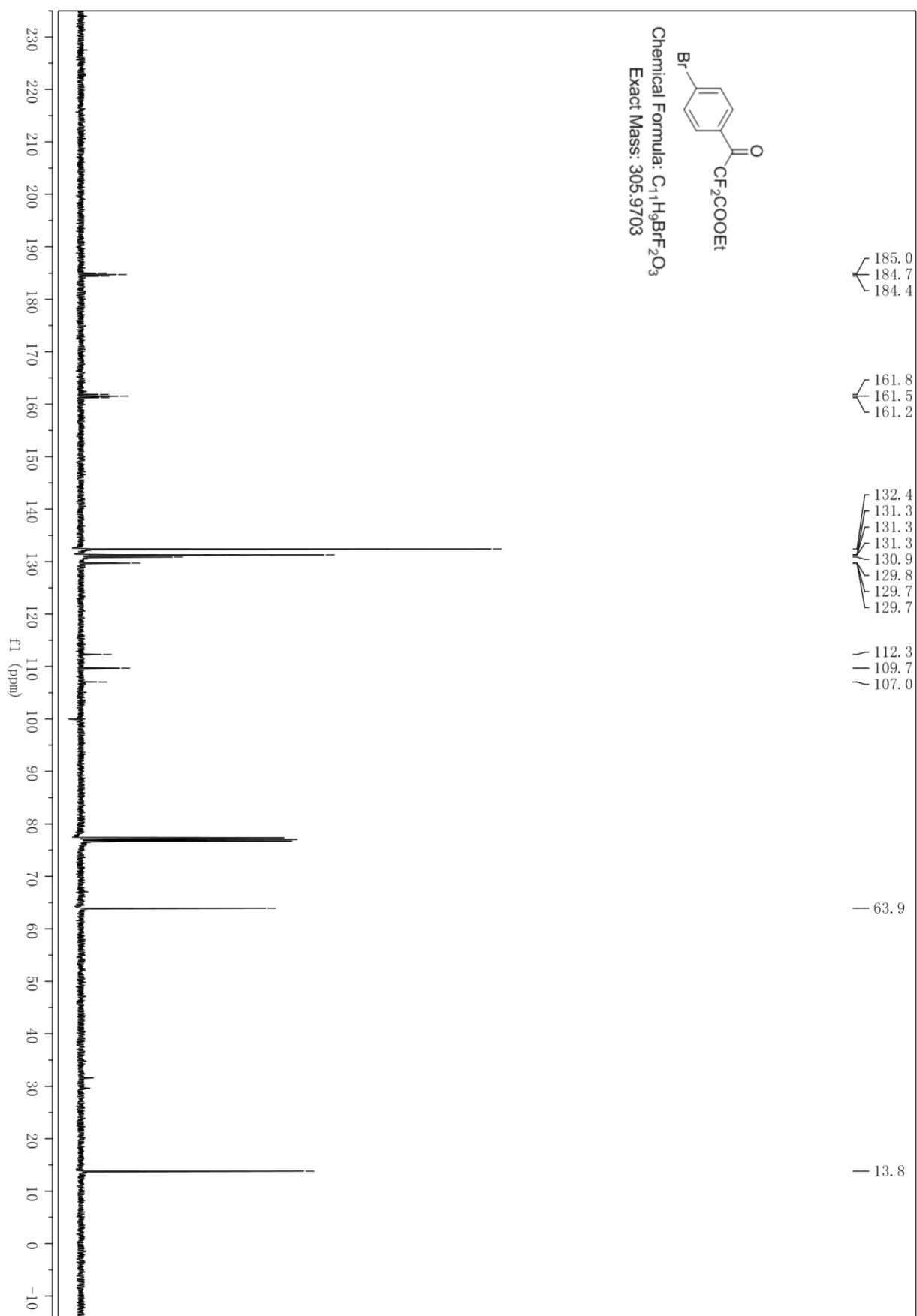
Ethyl 3-(4-bromophenyl)-2,2-difluoro-3-oxopropanoate (5g).



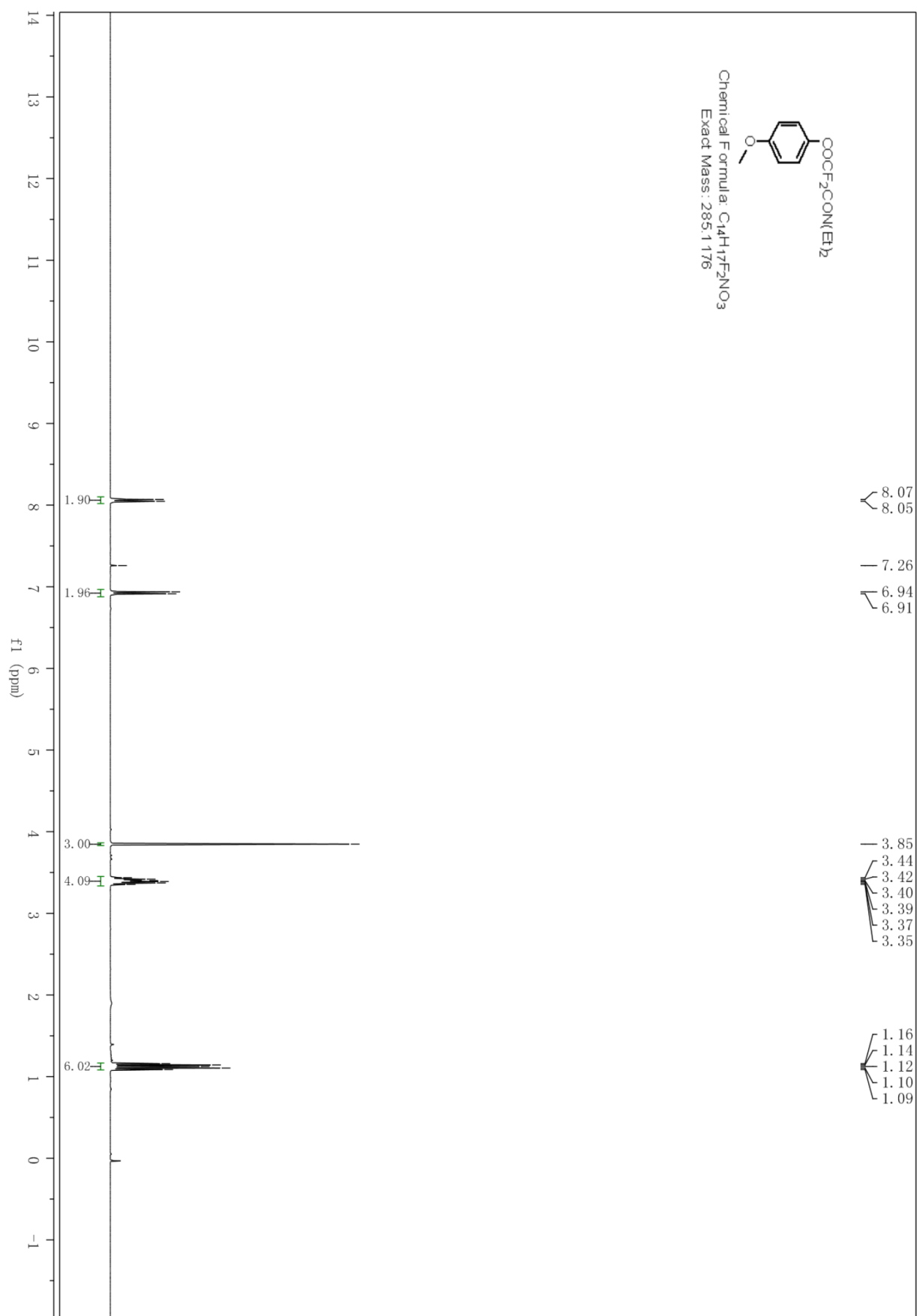


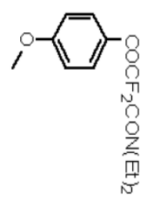
Chemical Formula: $C_{11}H_9BrF_2O_3$
Exact Mass: 305.9703



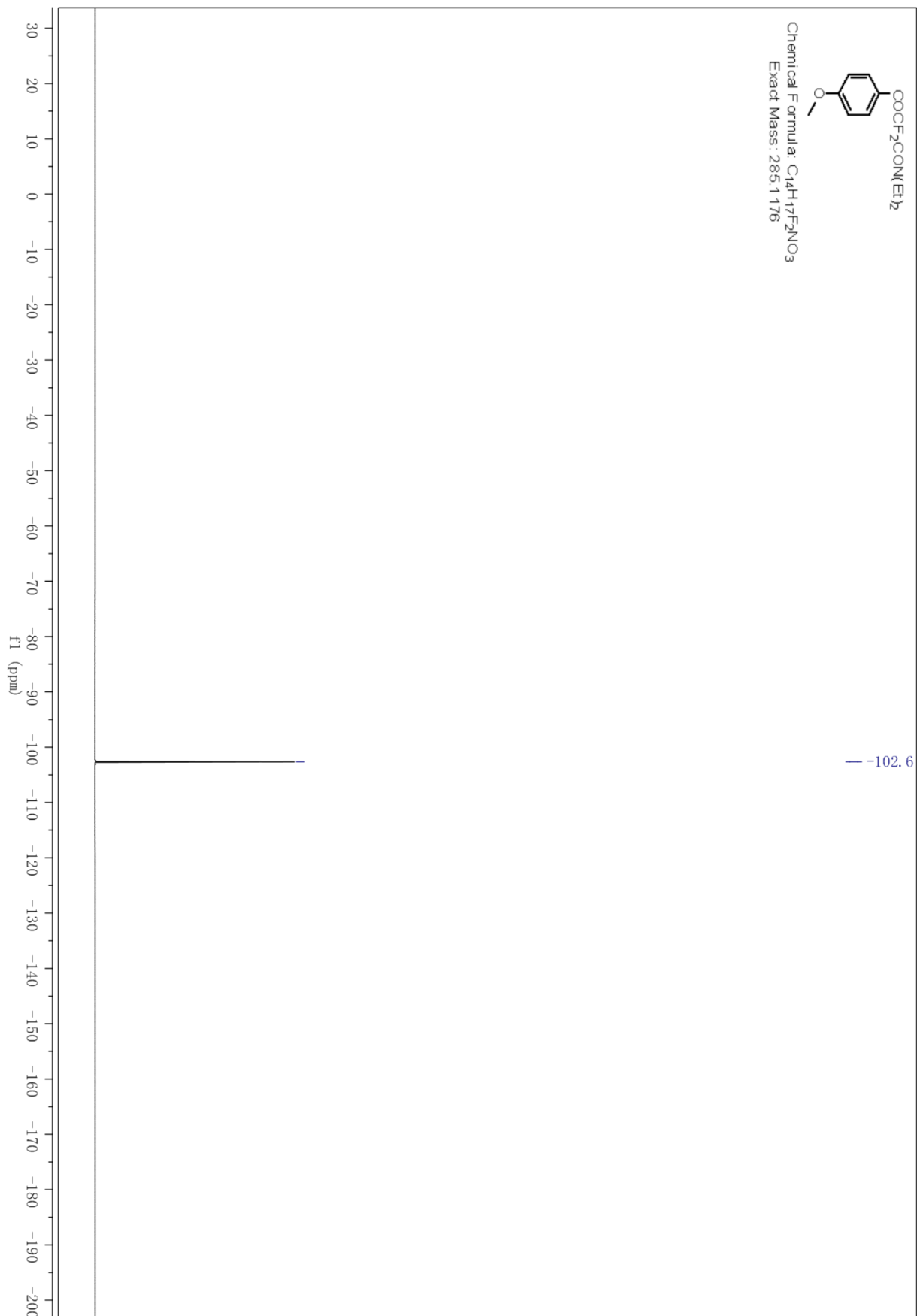


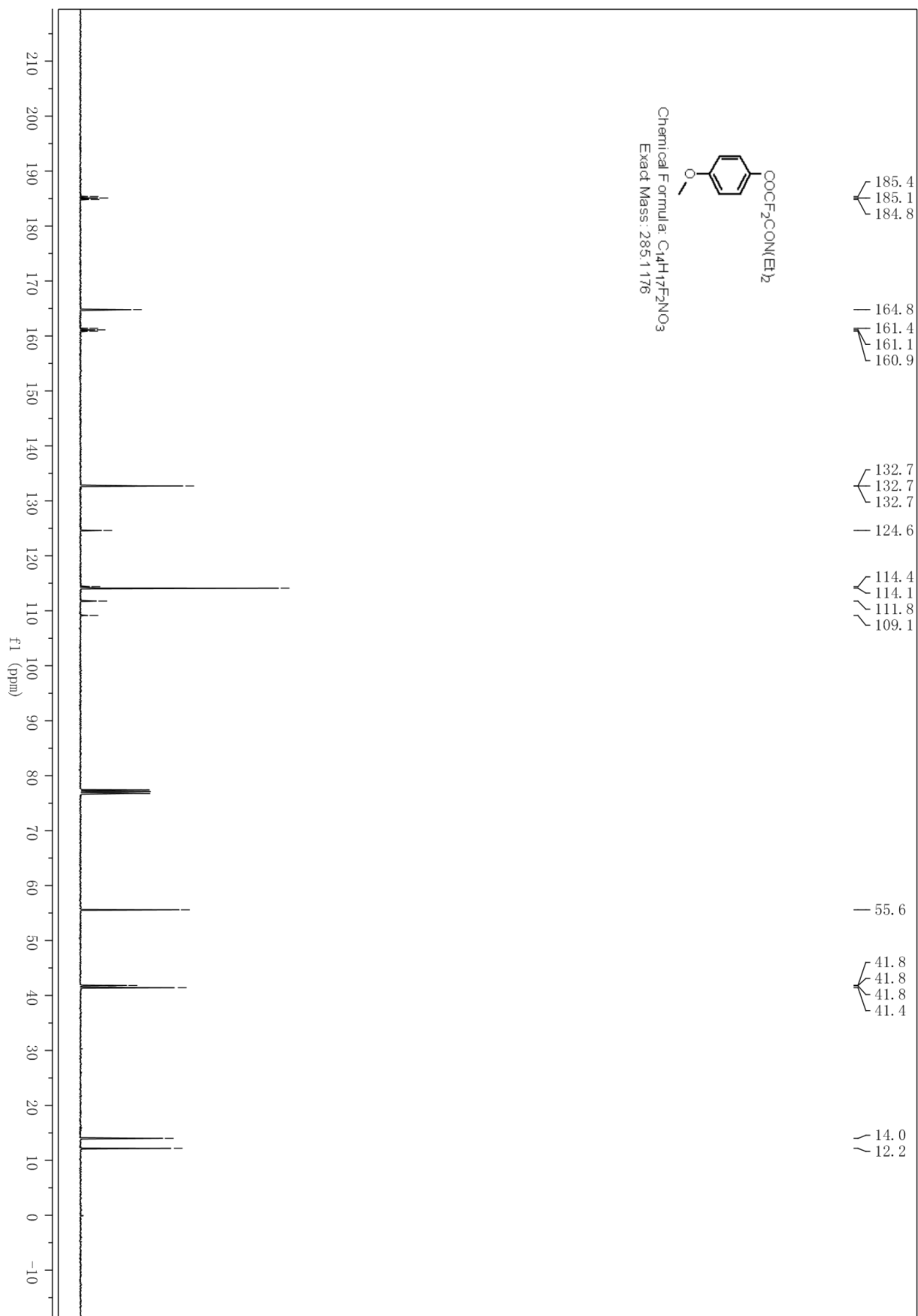
***N,N*-Diethyl-2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanamide (5h).**



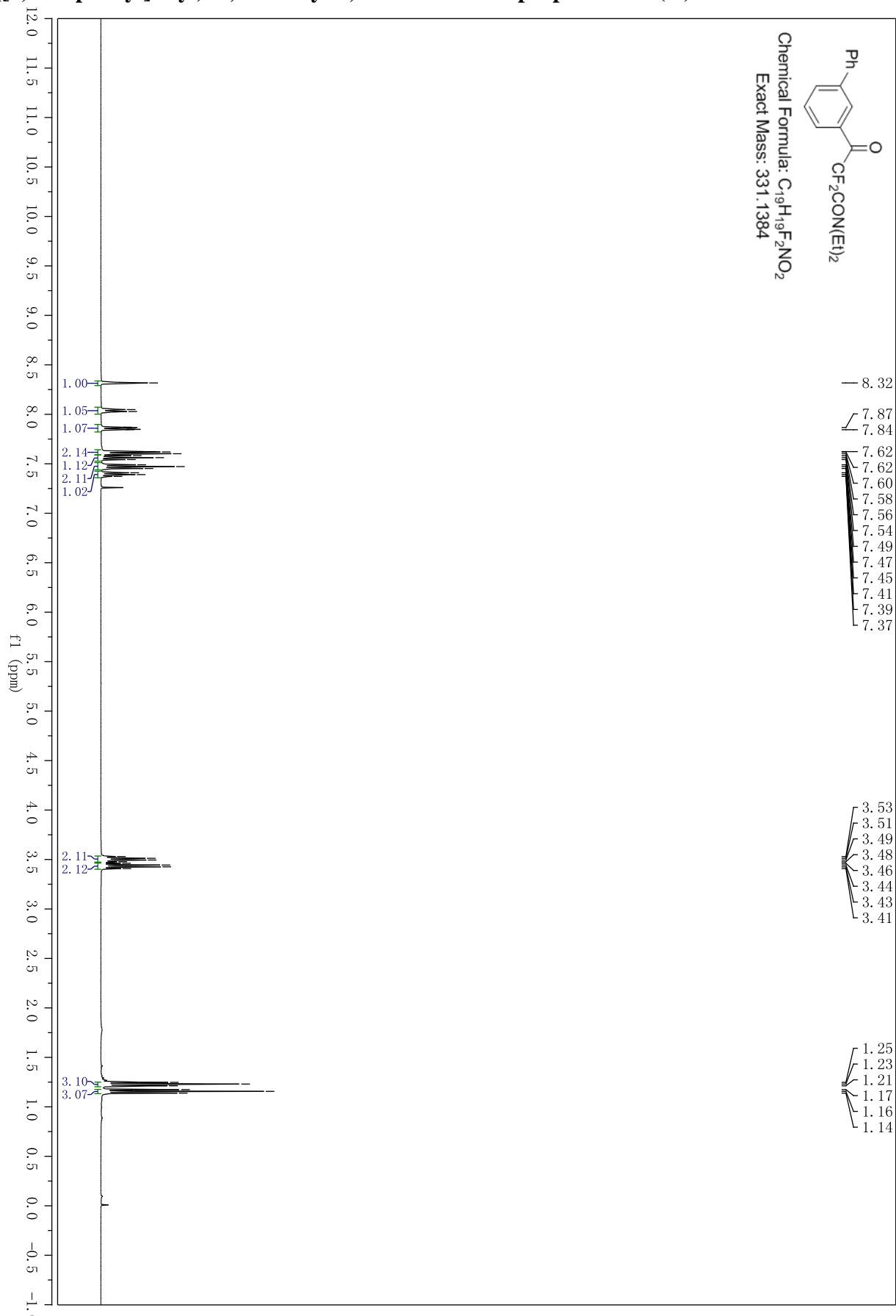


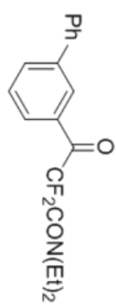
Chemical Formula: $\text{C}_{14}\text{H}_{17}\text{F}_2\text{NO}_3$
 Exact Mass: 285.1176



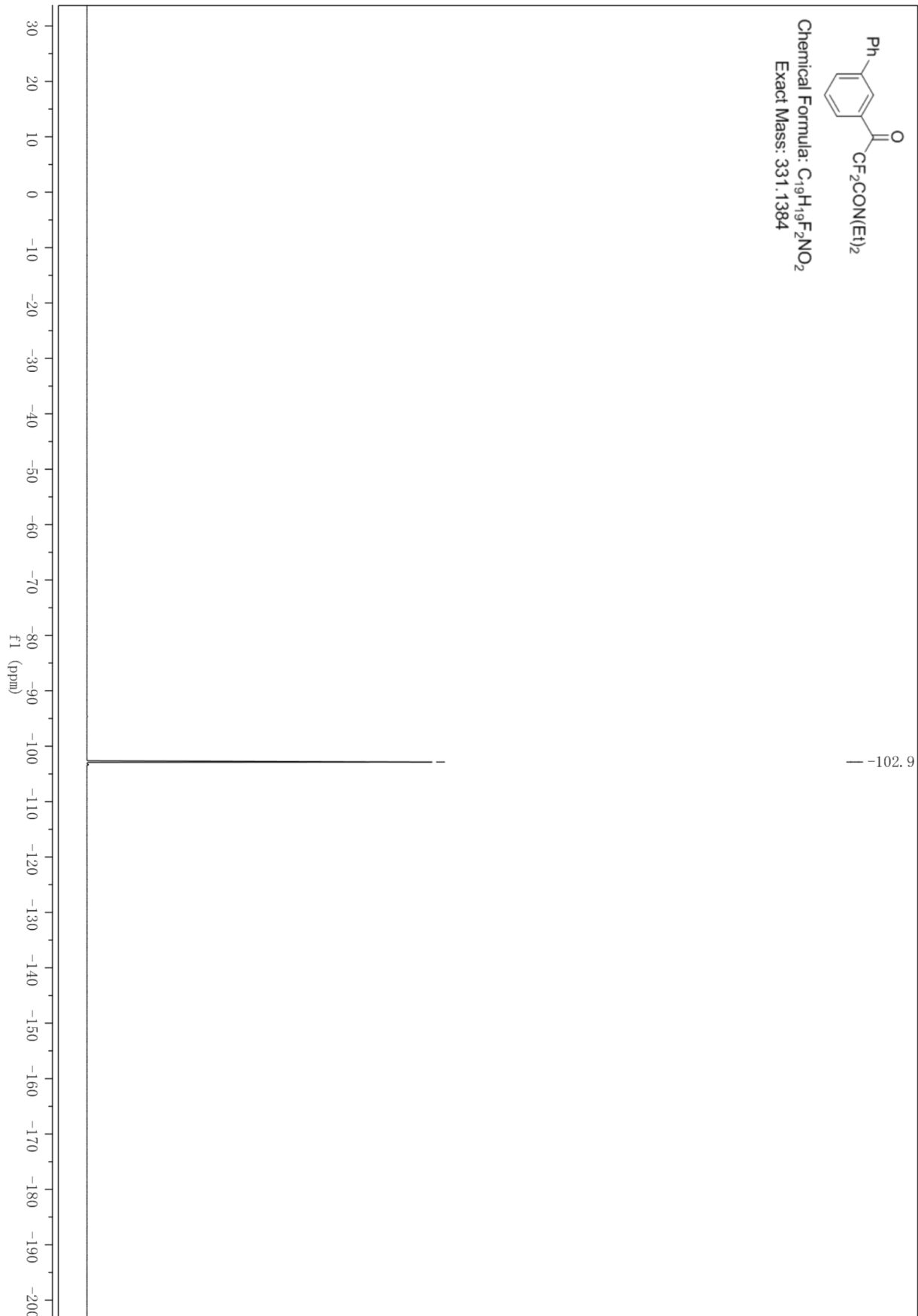


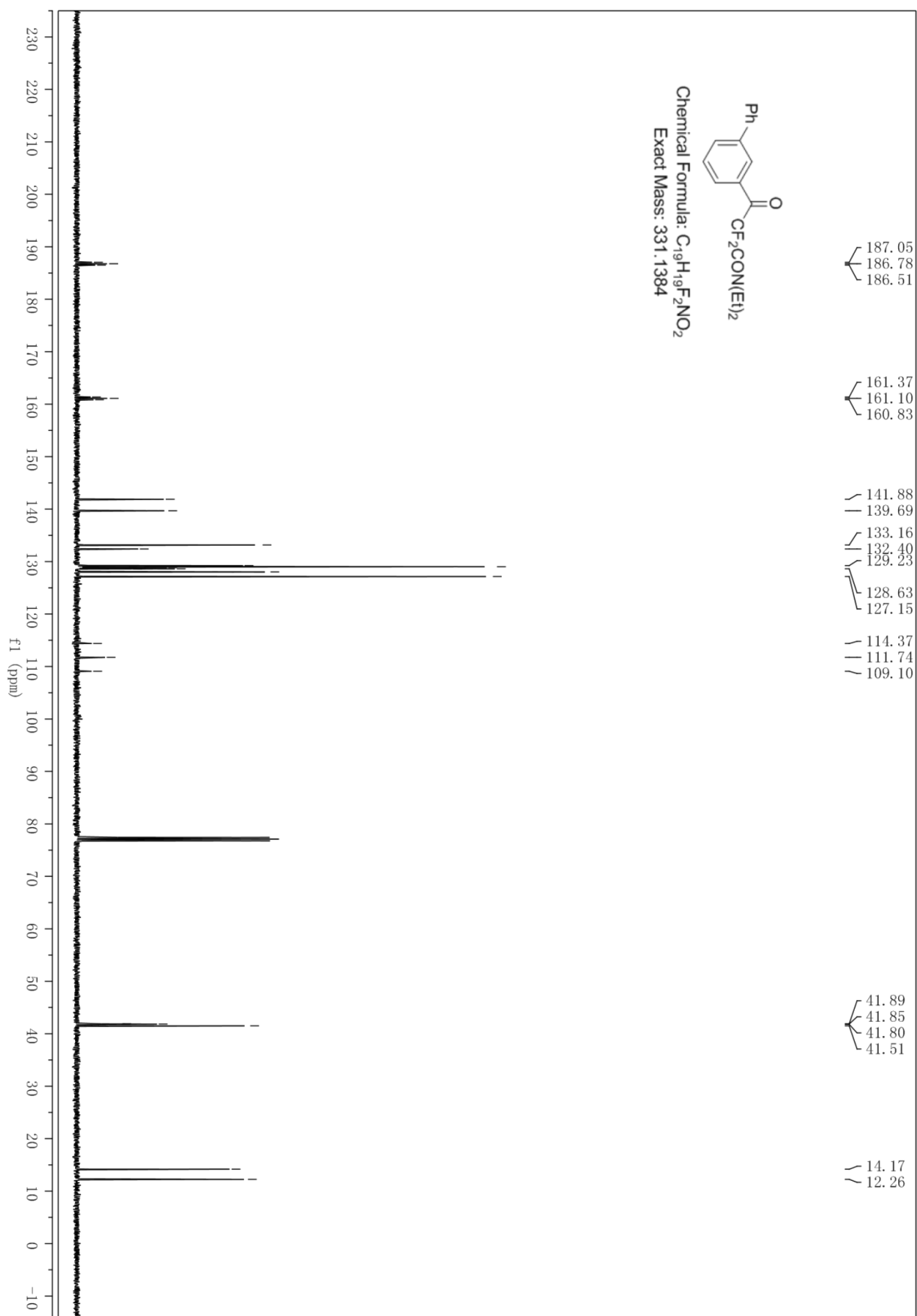
3-([1,1'-Biphenyl]-3-yl)-N,N-diethyl-2,2-difluoro-3-oxopropanamide (5i).



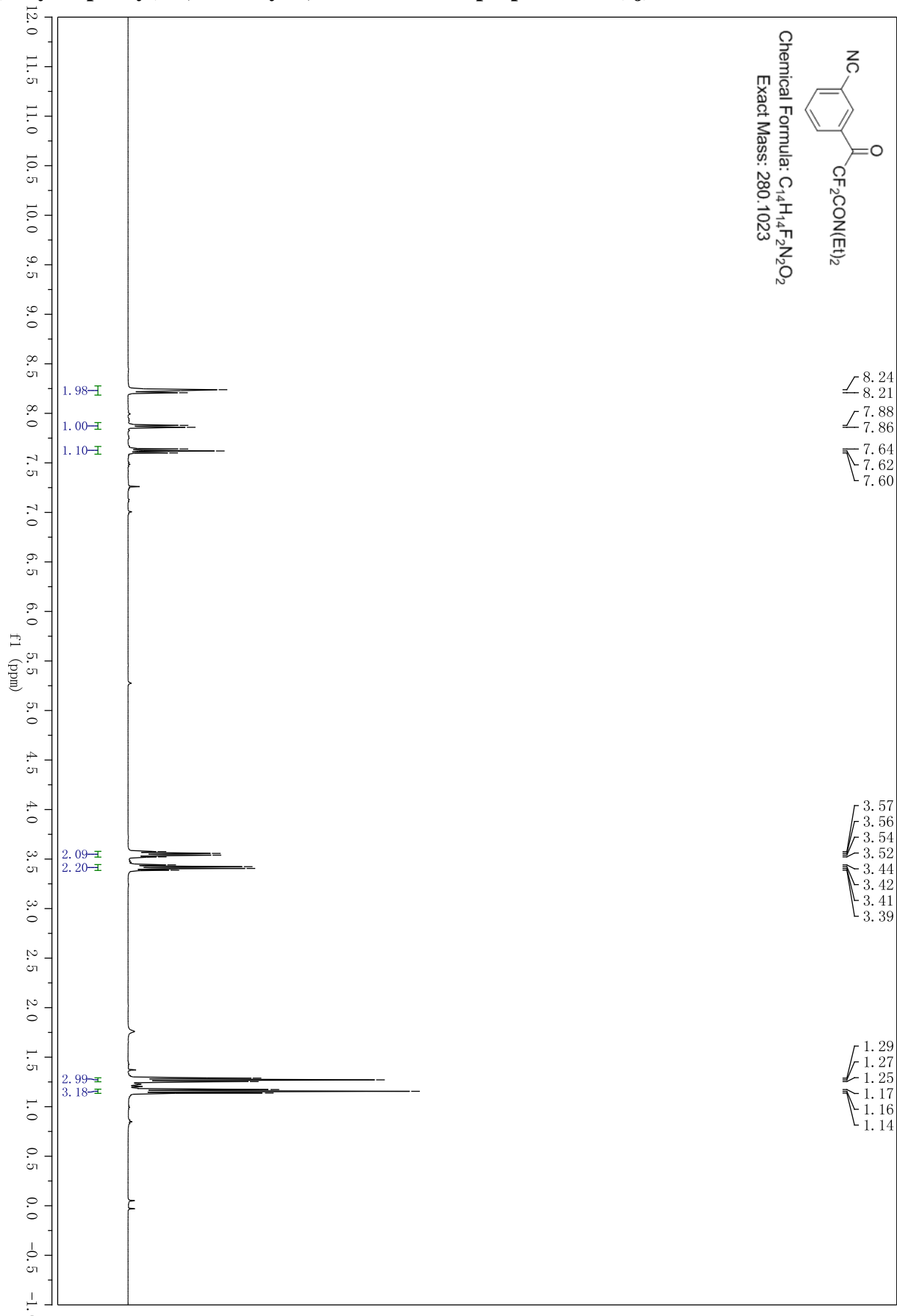


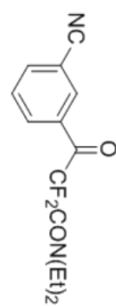
Chemical Formula: C₁₉H₁₉F₂NO₂
Exact Mass: 331.1384



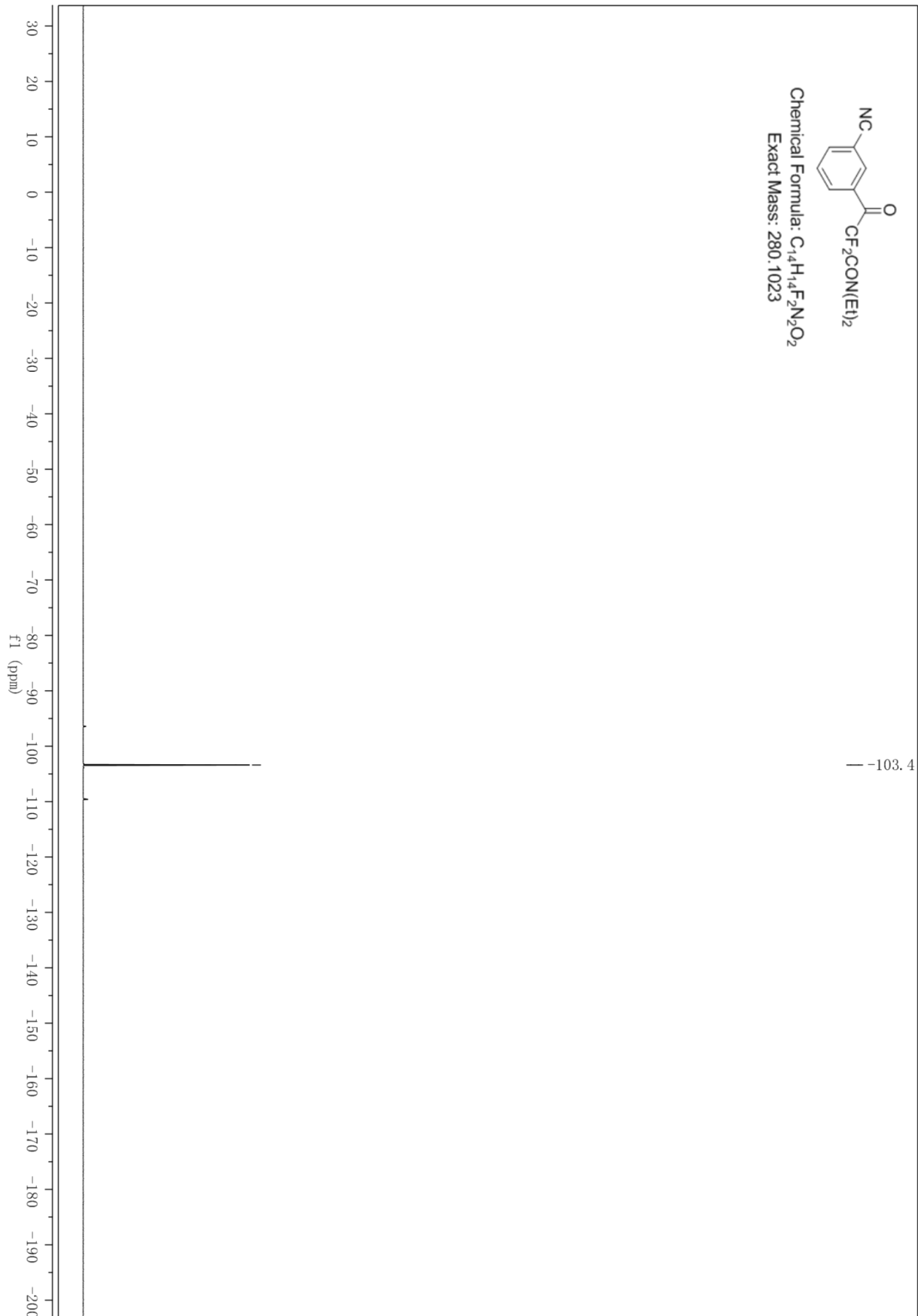


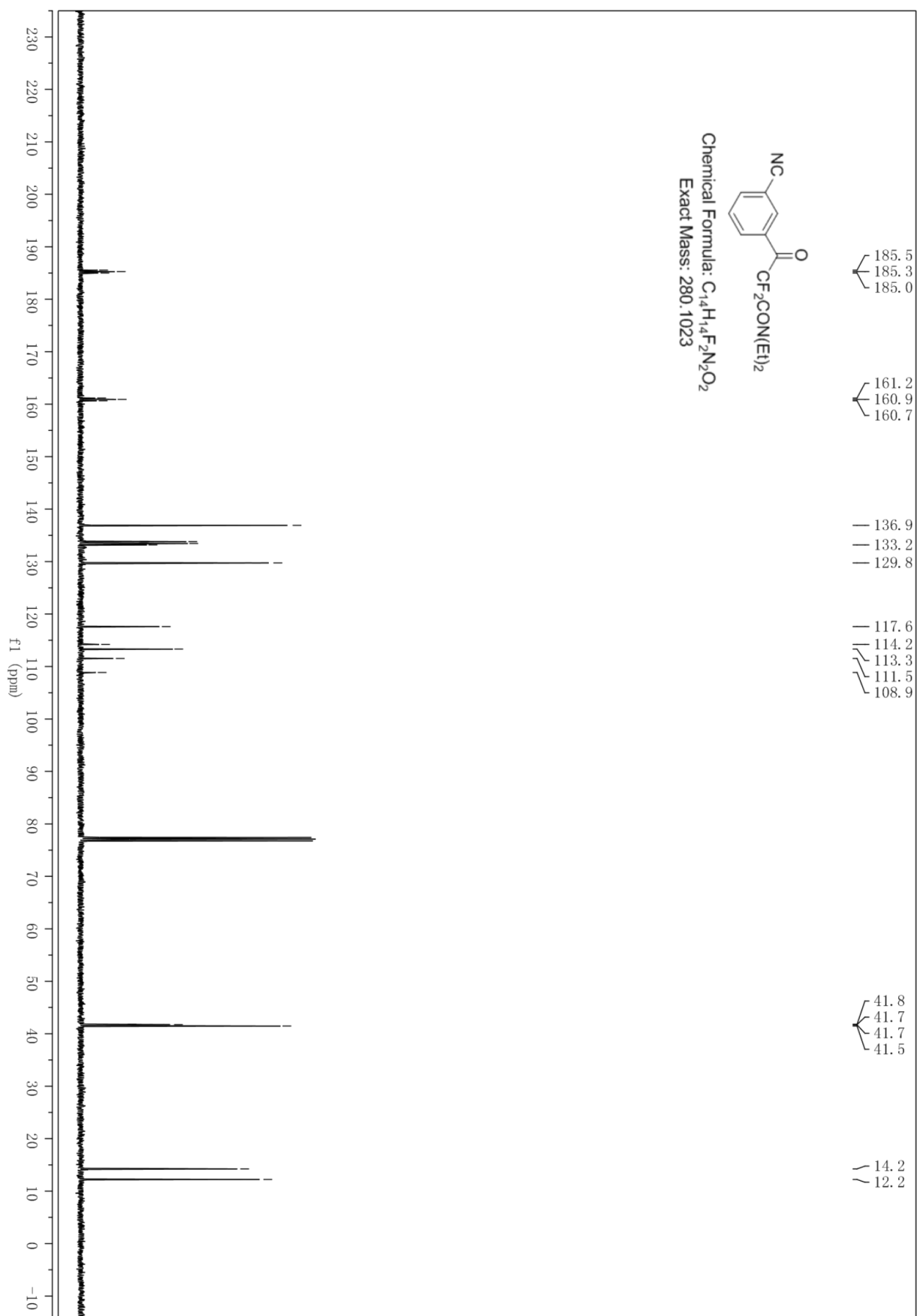
1-(3-Cyanophenyl)-N,N-diethyl-2,2-difluoro-3-oxopropanamide (5j).



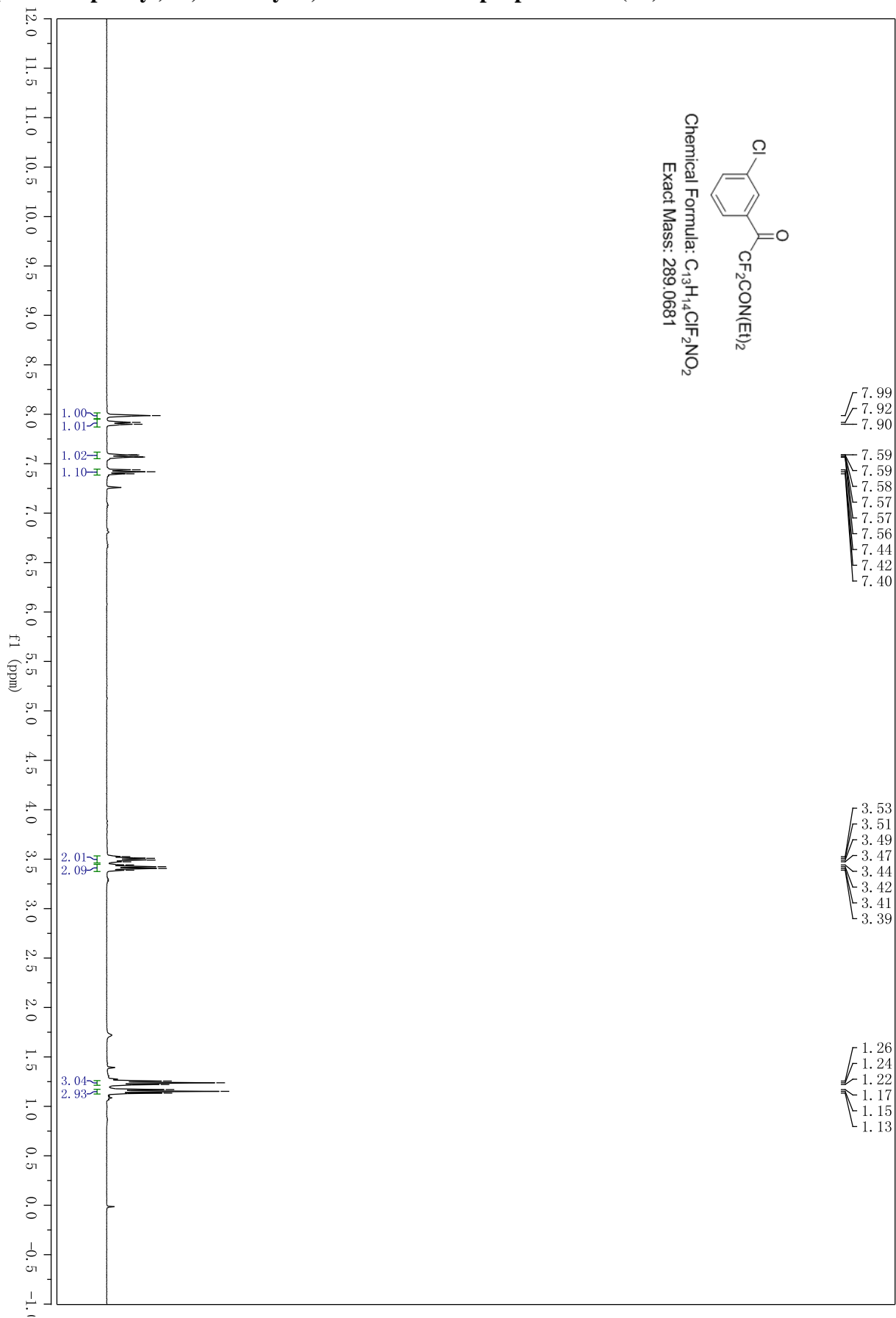


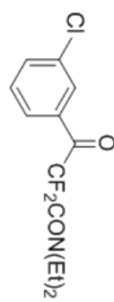
Chemical Formula: $C_{14}H_{14}F_2N_2O_2$
Exact Mass: 280.1023





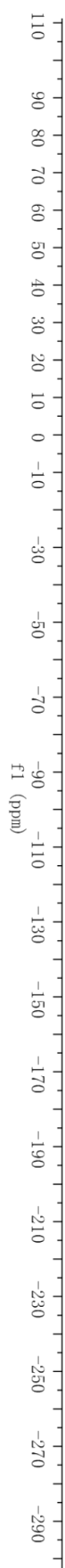
3-(3-Chlorophenyl)-*N,N*-diethyl-2,2-difluoro-3-oxopropanamide (5k).

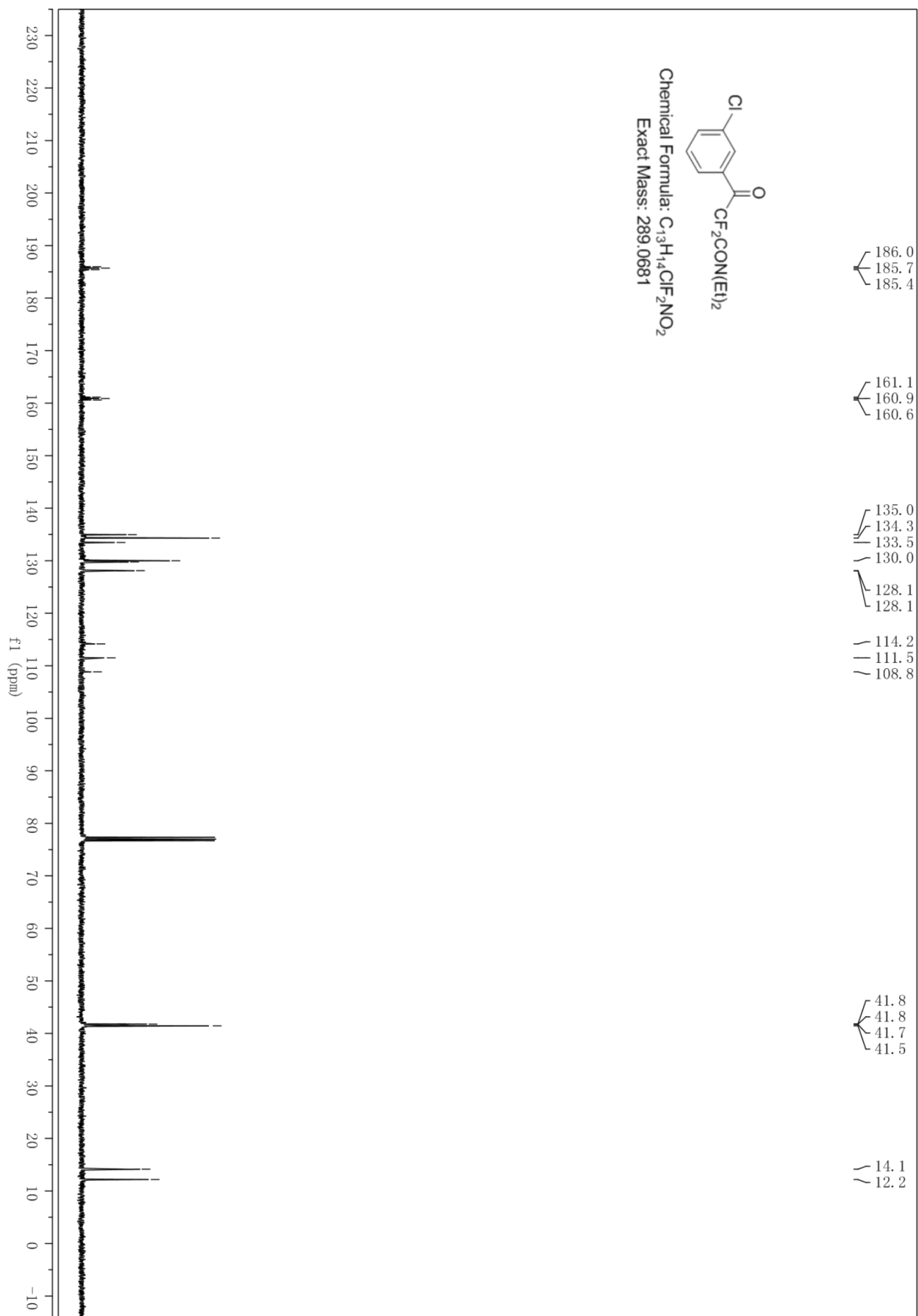




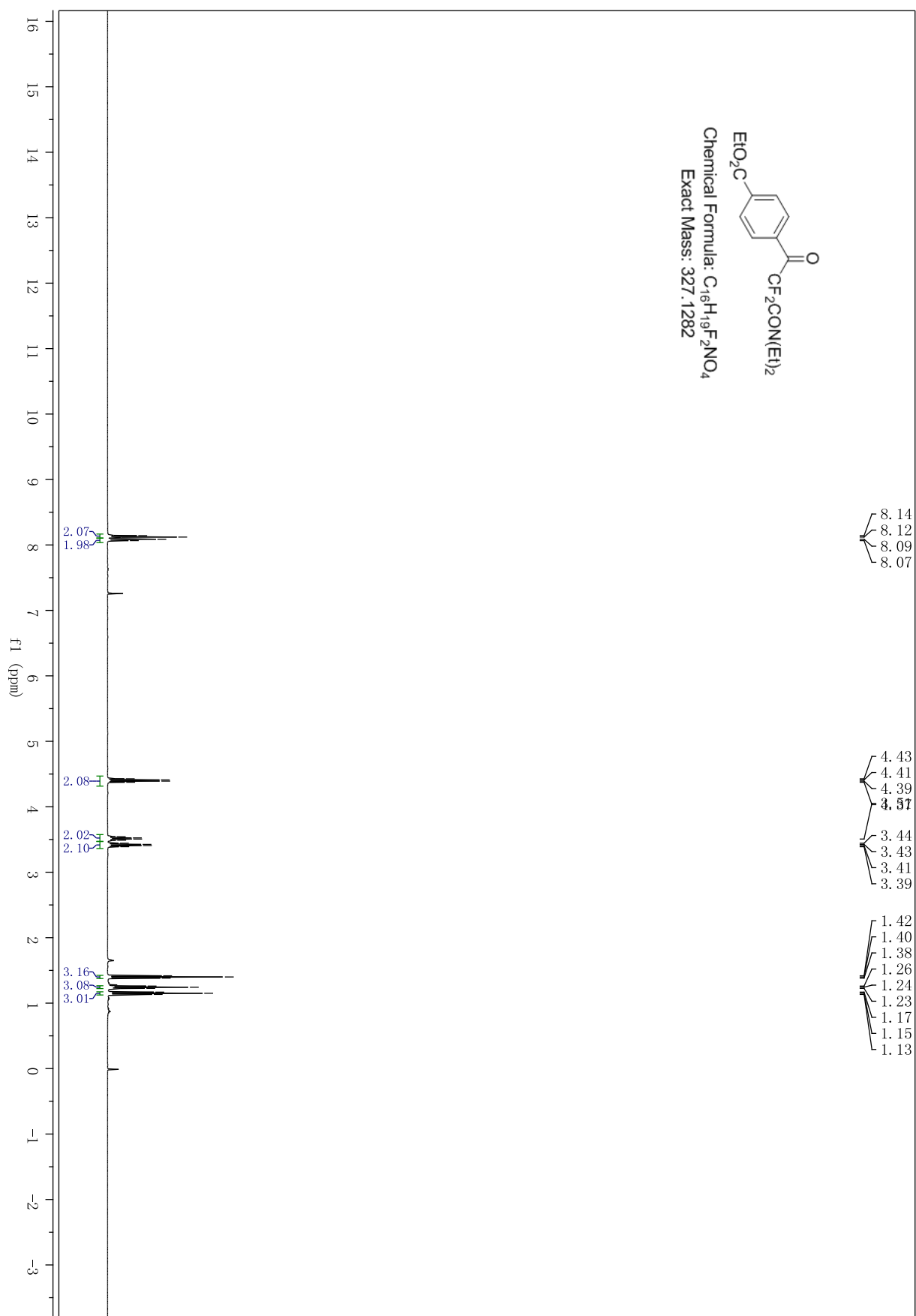
Chemical Formula: $C_{13}H_{14}ClF_2NO_2$
Exact Mass: 289.0681

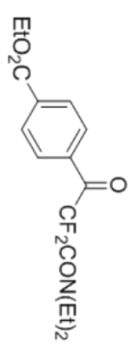
— -103.1



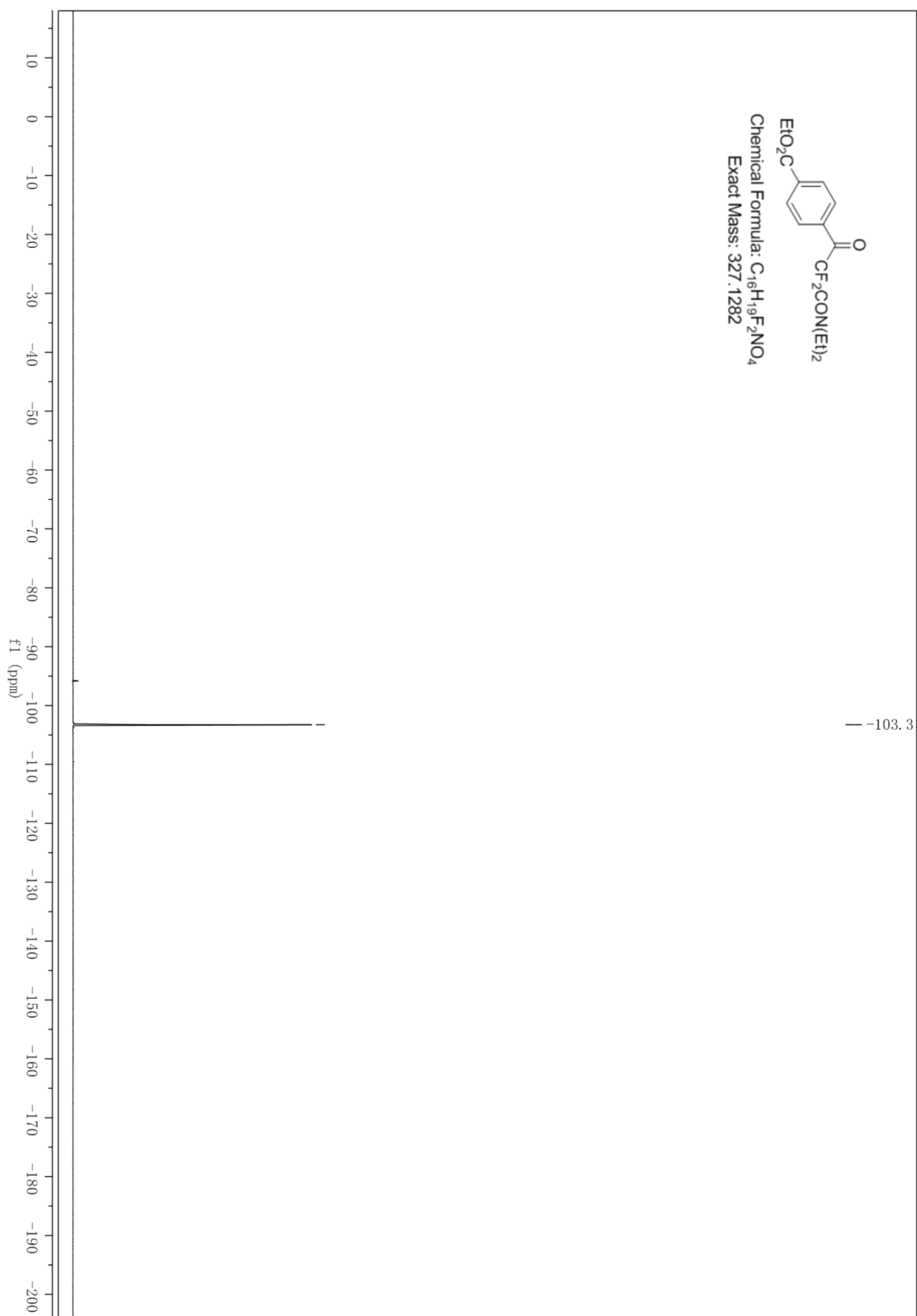


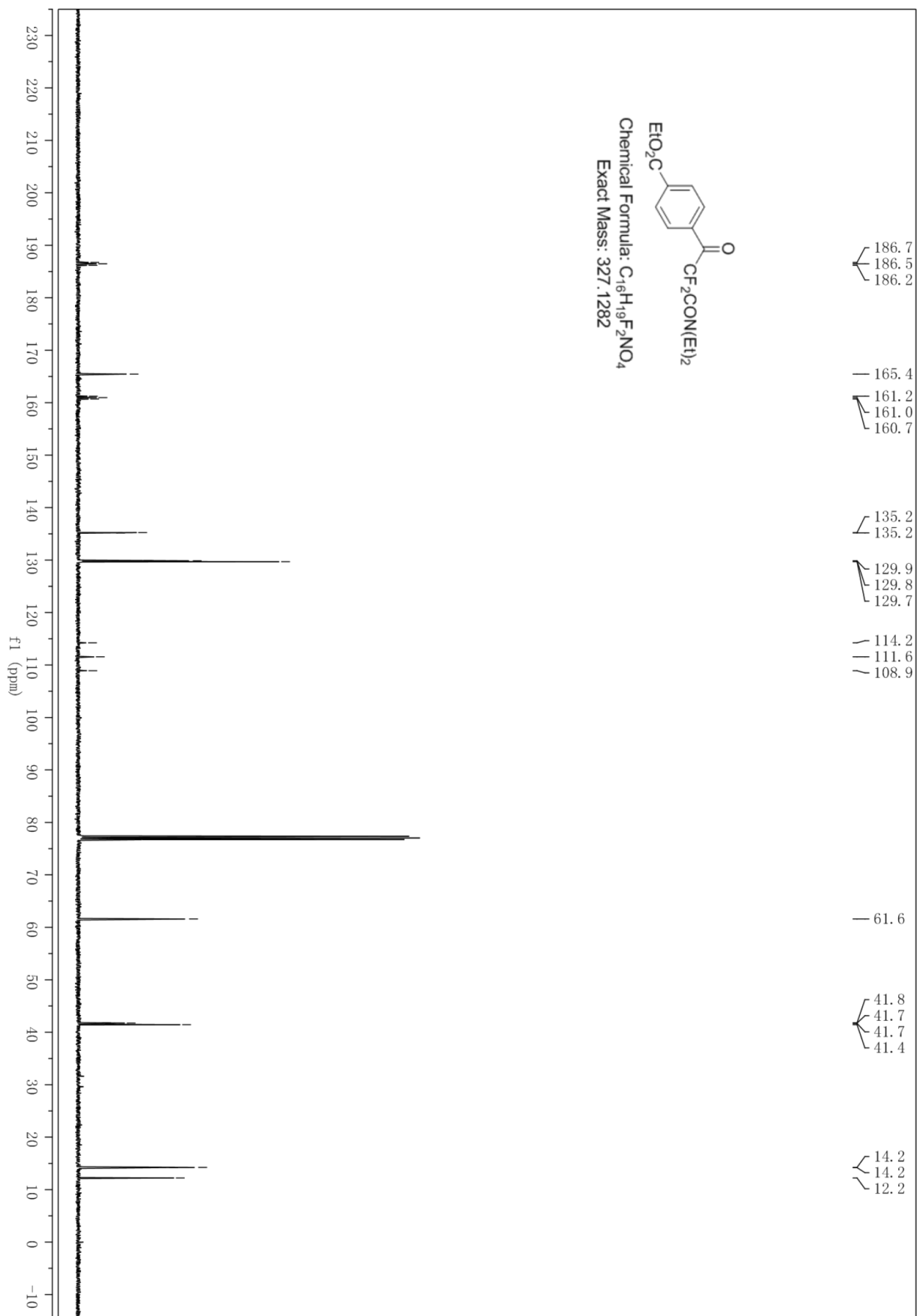
Ethyl 4-(3-(diethylamino)-2,2-difluoro-3-oxopropanoyl)benzoate (5l).



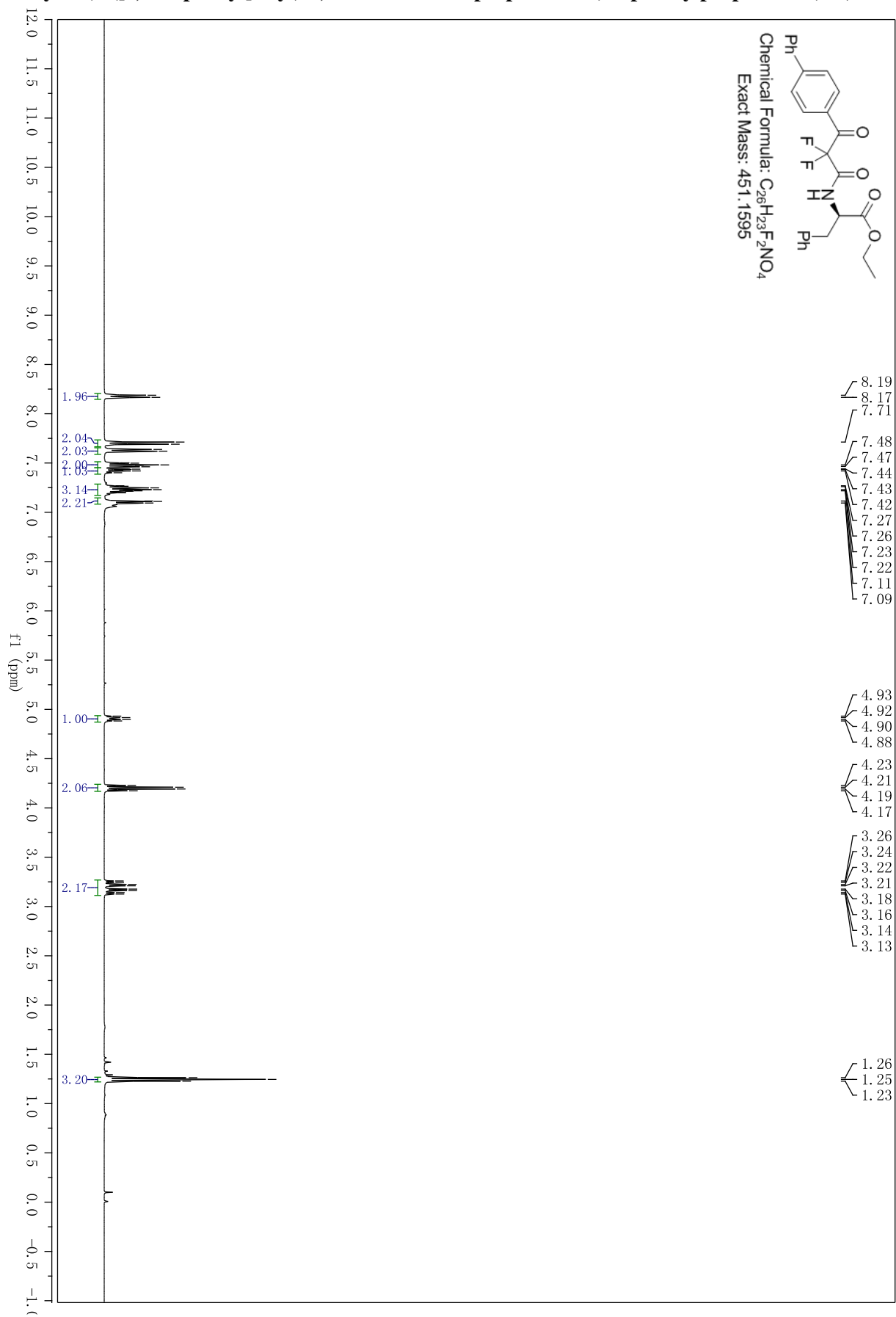


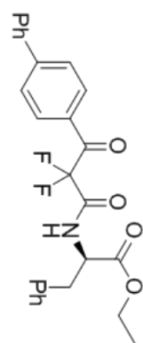
Chemical Formula: $C_{16}H_{19}F_3NO_4$
Exact Mass: 327.1282



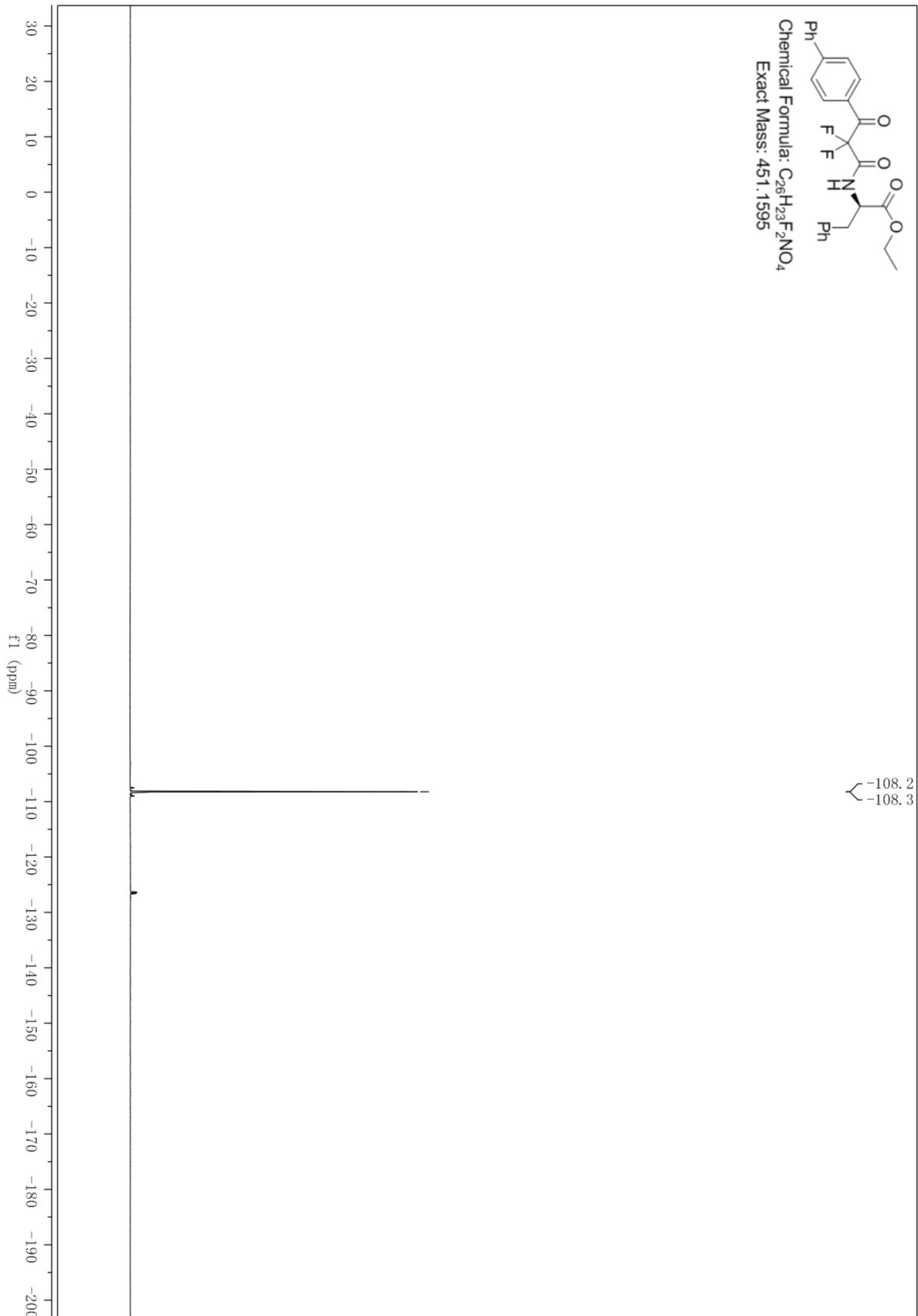


(R)-Ethyl-2-(3-([1,1'-biphenyl]-4-yl)-2,2-difluoro-3-oxopropanamido)-3-phen-ylpropanoate (5m).

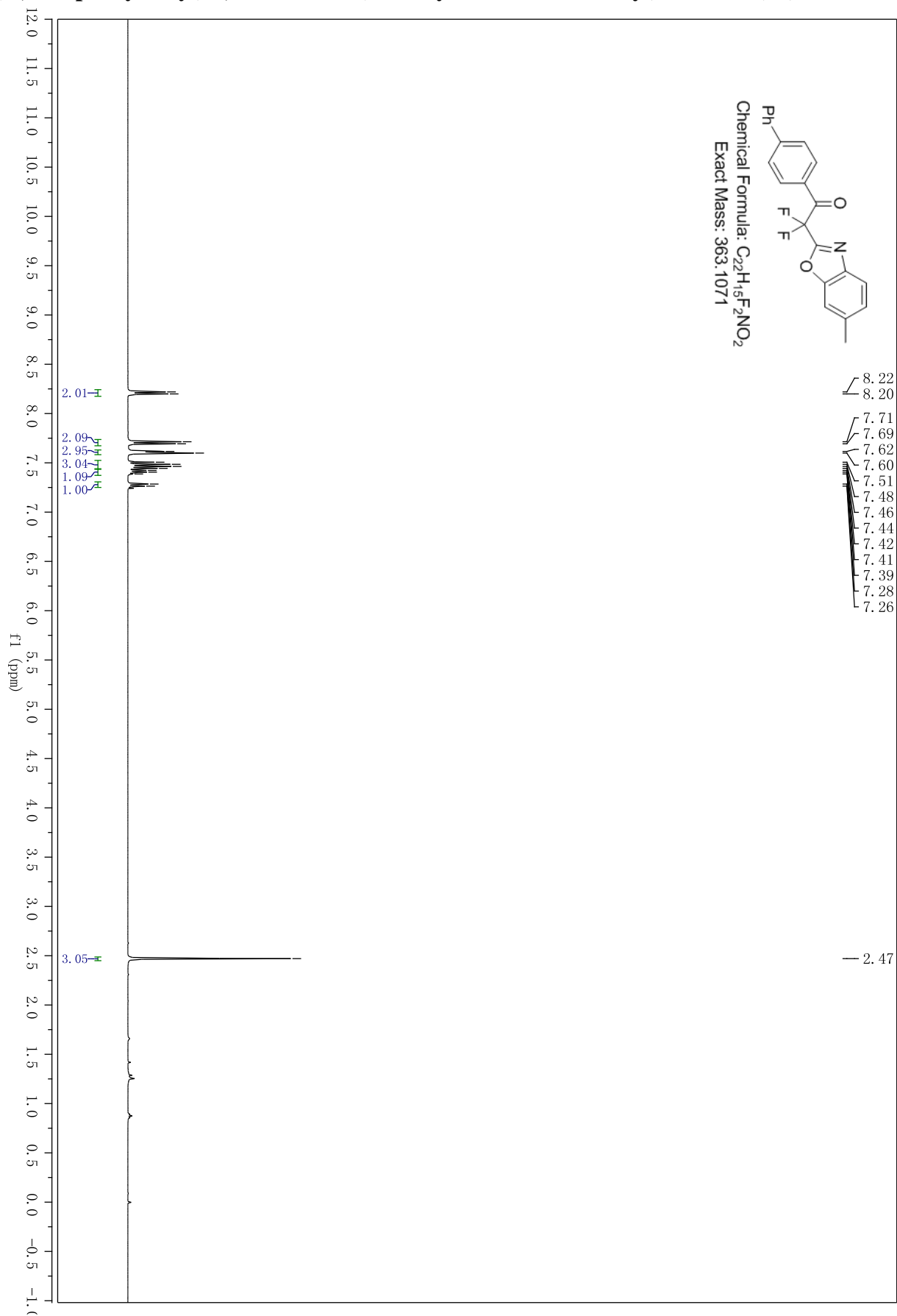




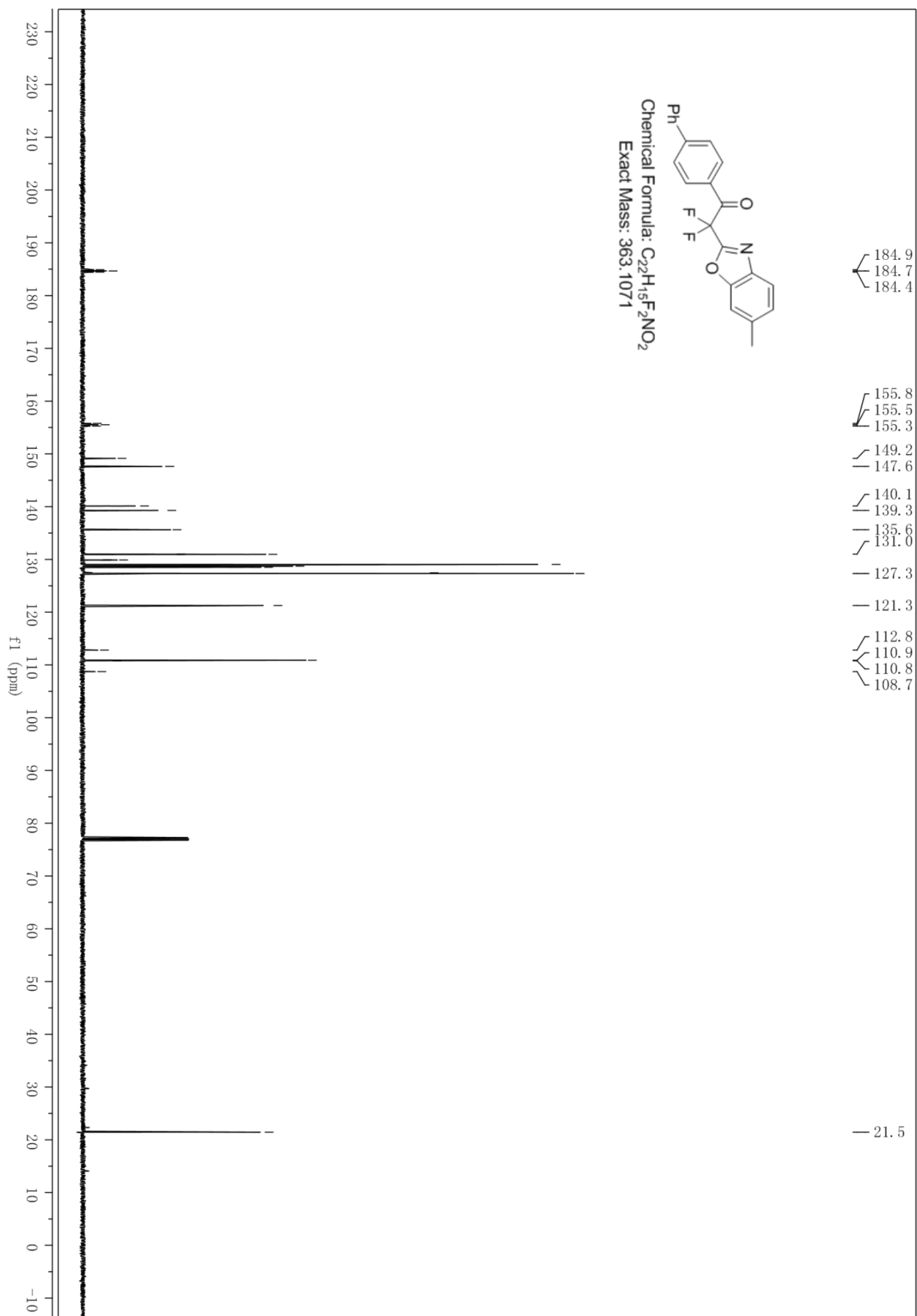
Chemical Formula: $C_{26}H_{23}F_2NO_4$
Exact Mass: 451.1595



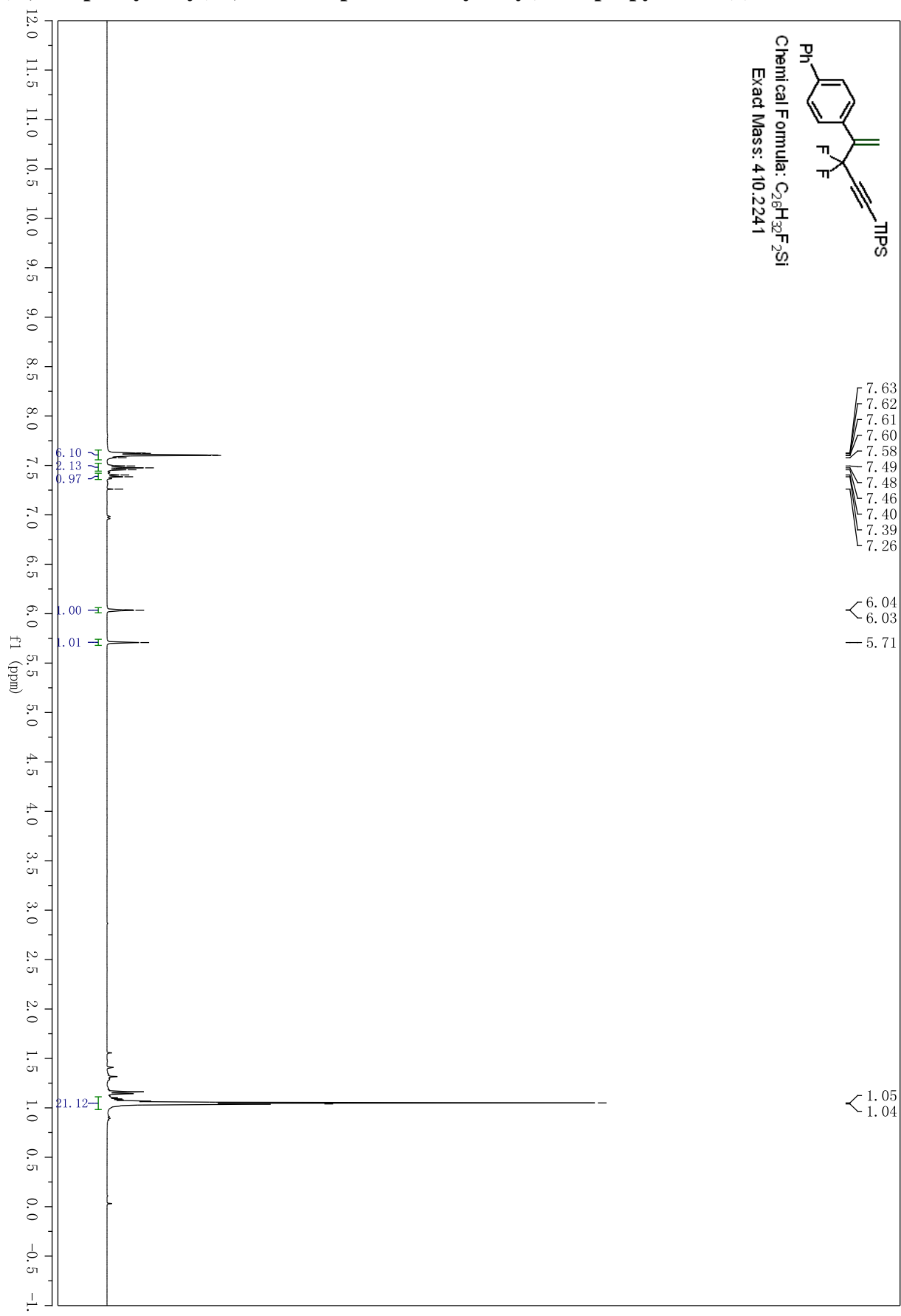
1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-2-(6-methylbenzo[d]oxazol-2-yl)ethanone (5n).

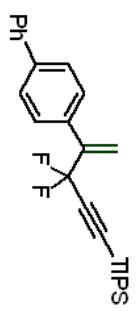




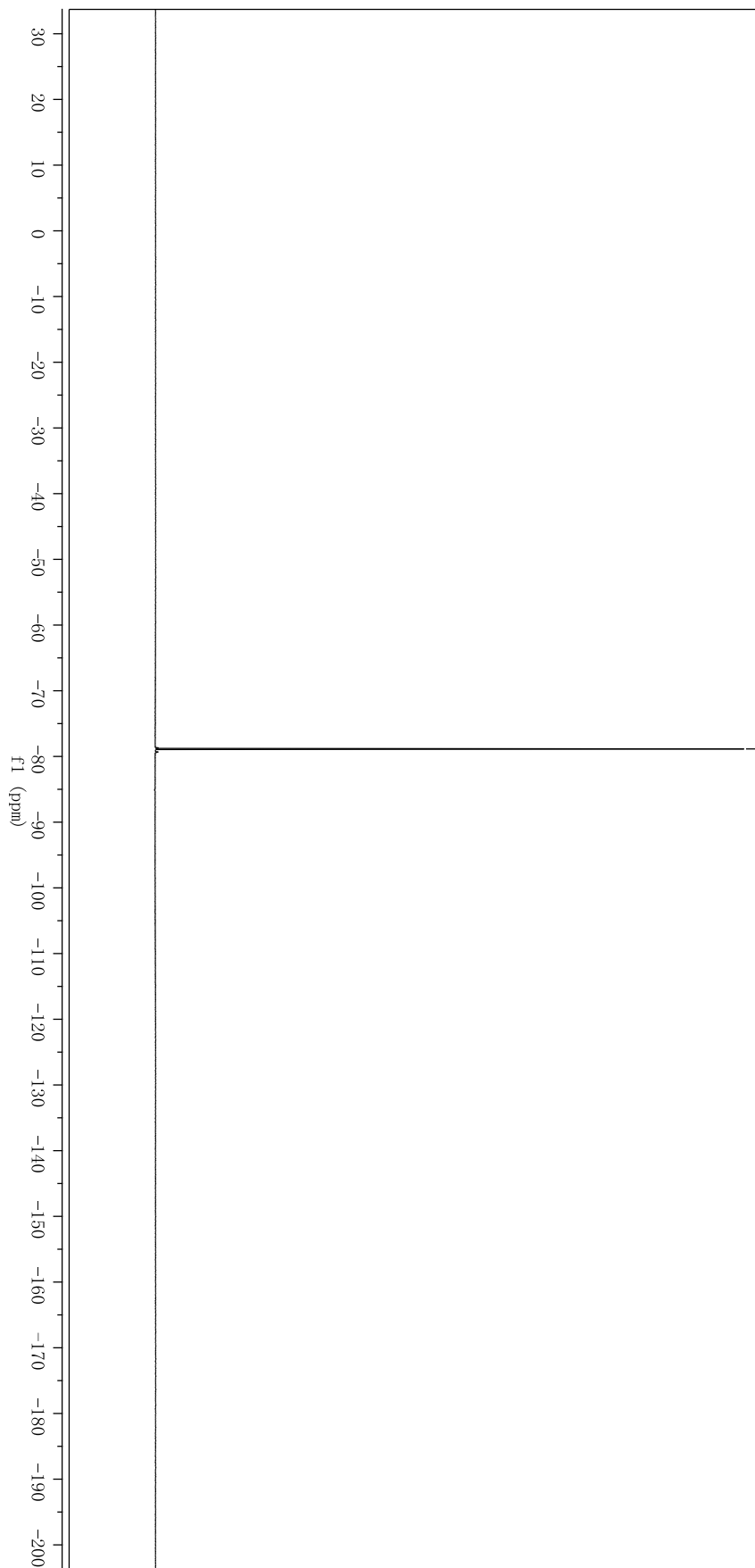


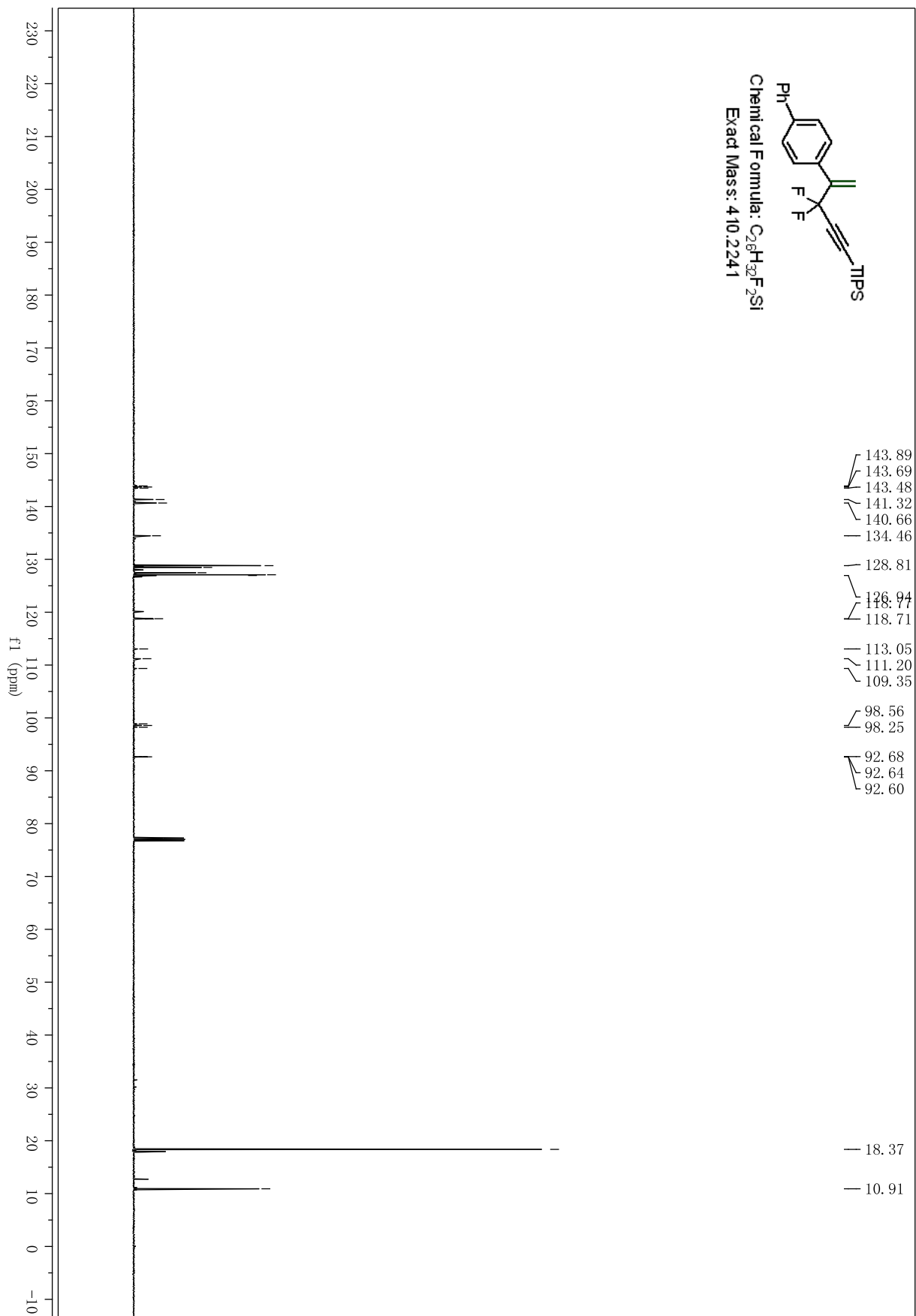
(4-([1,1'-Biphenyl]-4-yl)-3,3-difluoropent-4-en-1-yn-1-yl)triisopropylsilane (6).





— -78.9

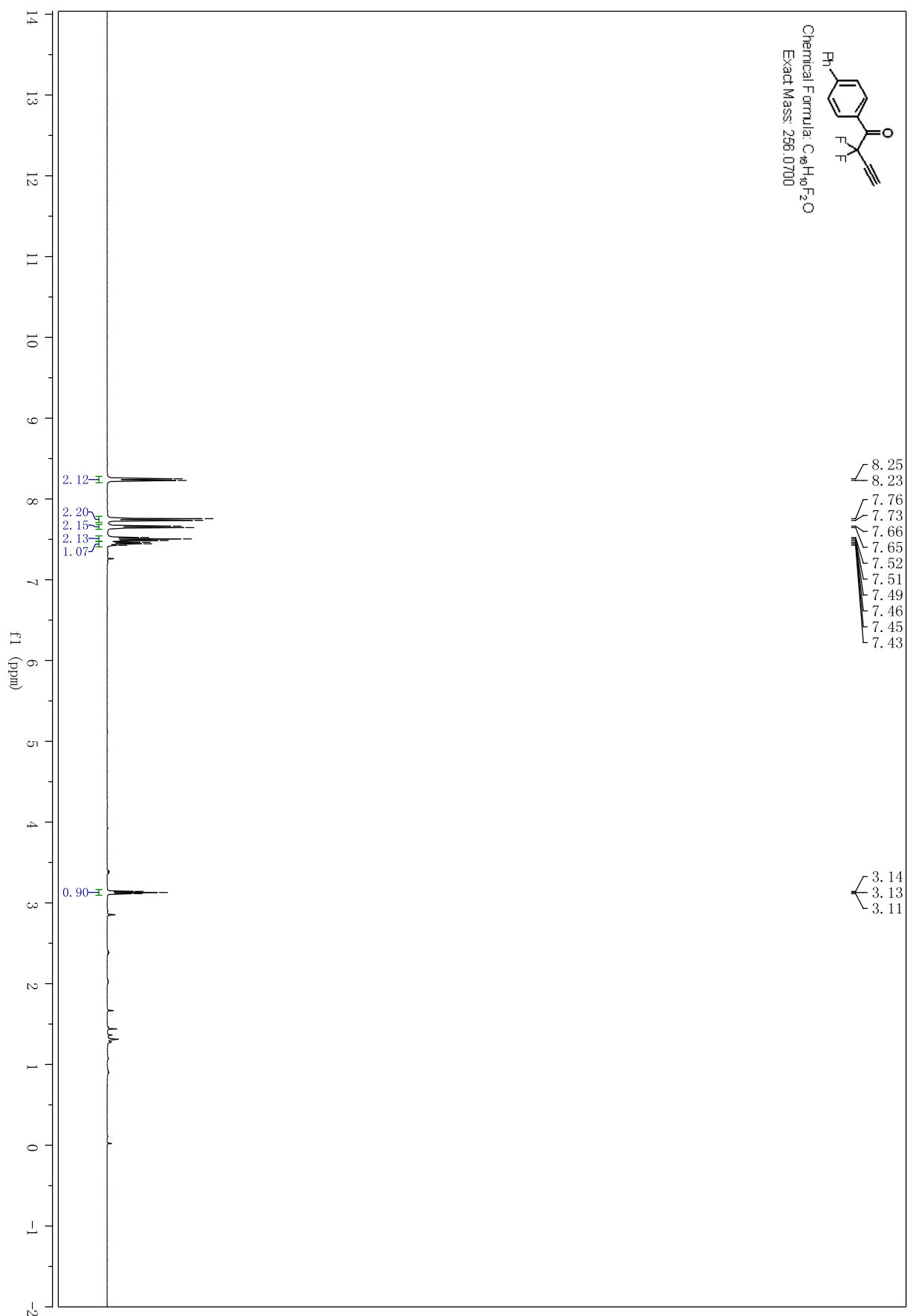


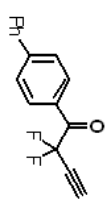


Chemical Formula: $C_{26}H_{32}F_2Si$
Exact Mass: 410.2241

Exact Mass: 410.2241

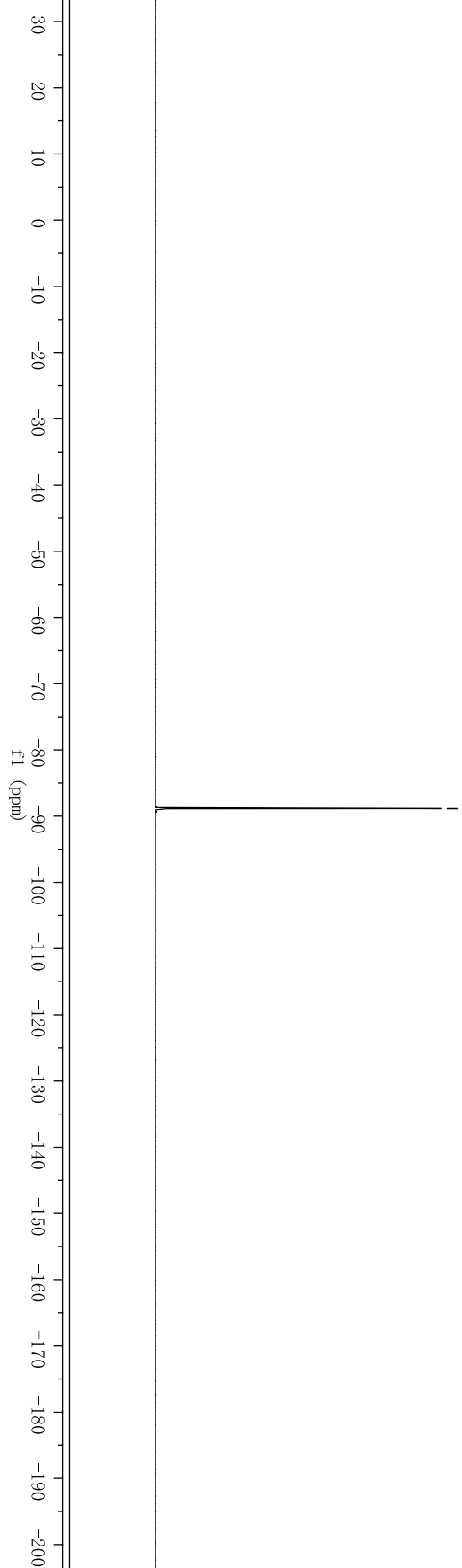
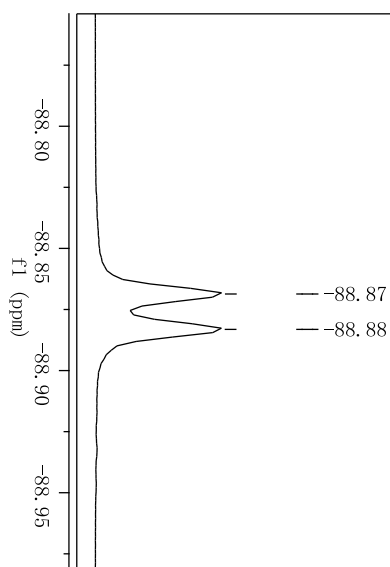
1-([1,1'-Biphenyl]-4-yl)-2,2-difluorobut-3-yn-1-one (7).

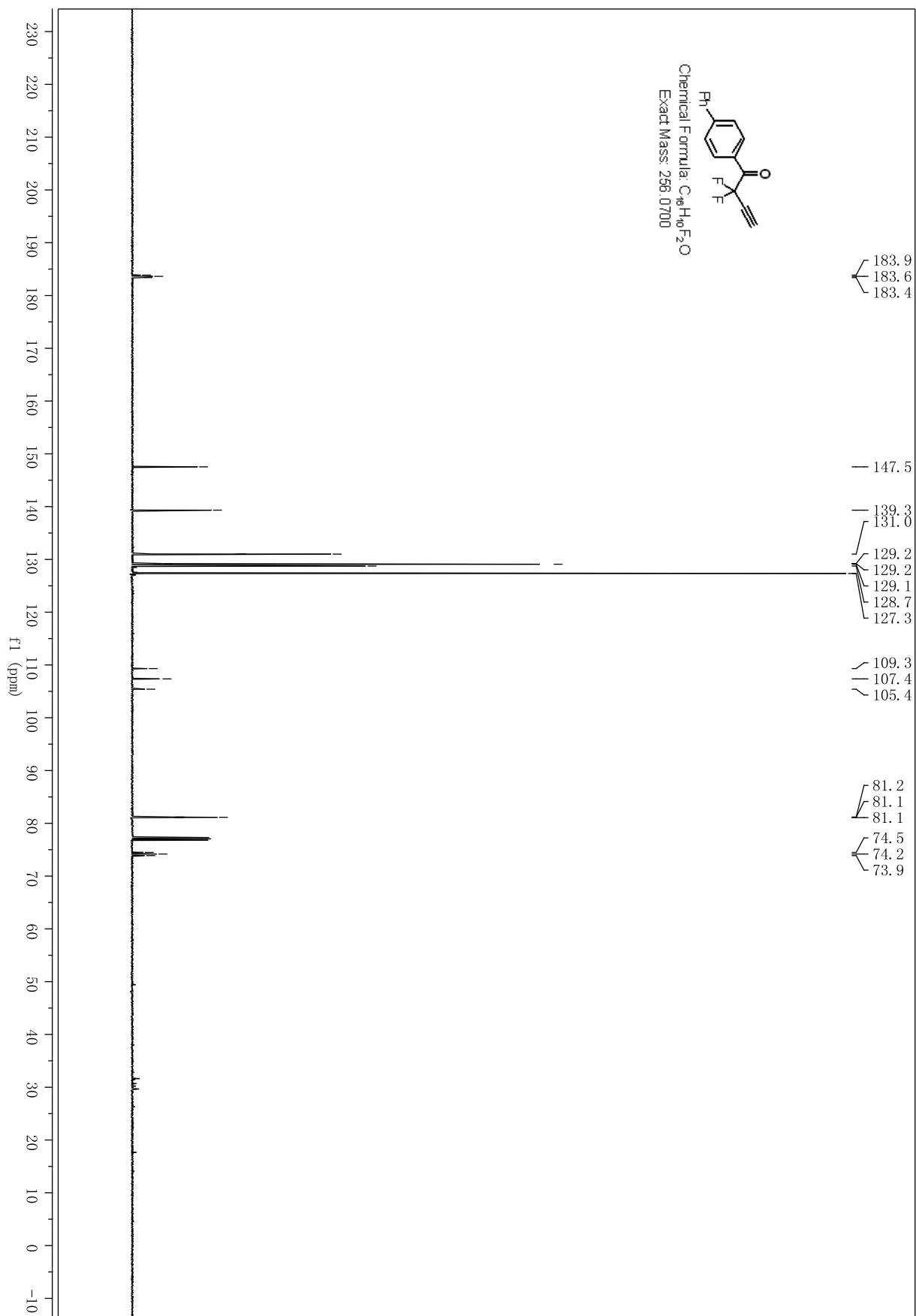




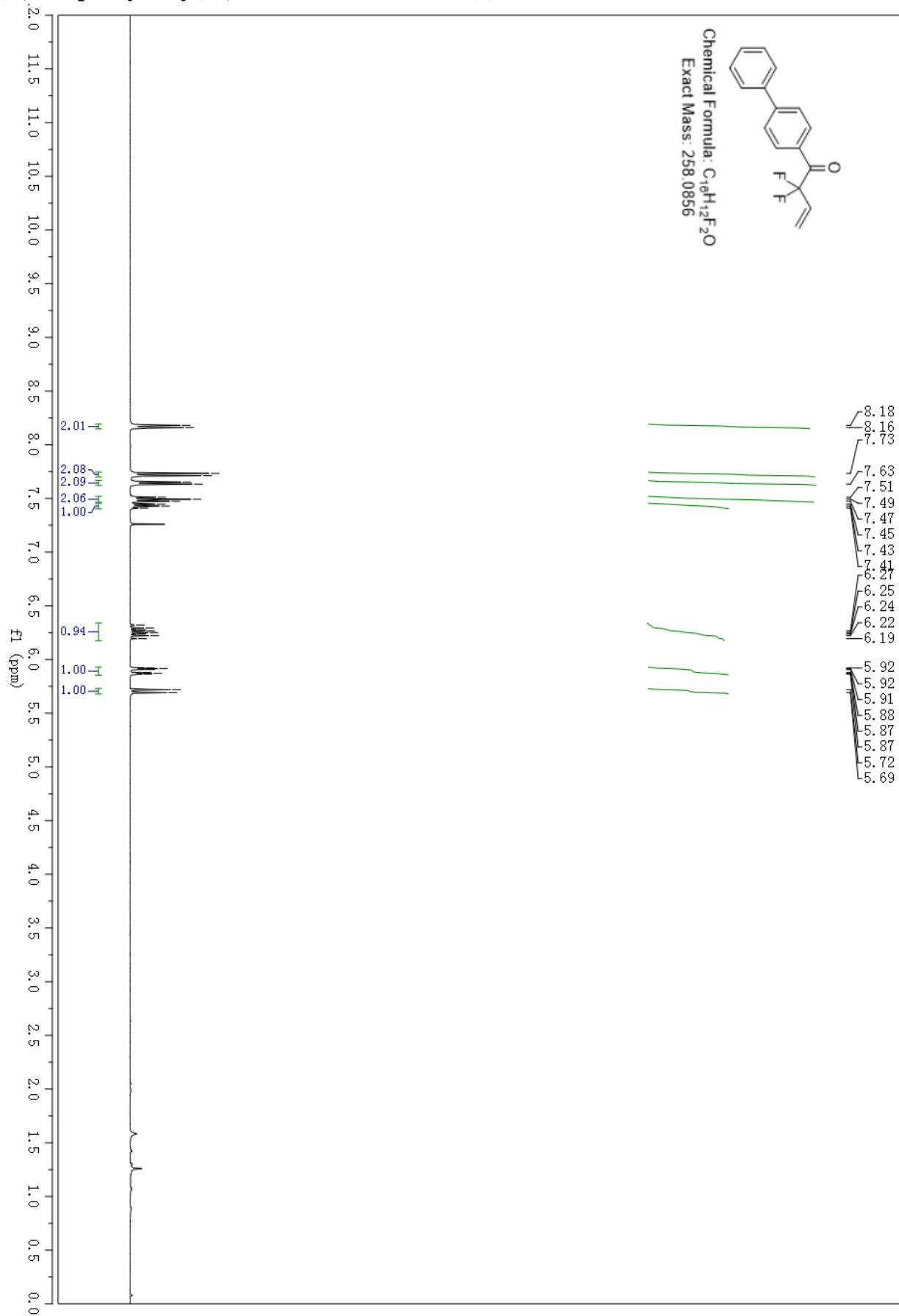
Chemical Formula: $C_{10}H_6F_4O$
Exact Mass: 256.0700

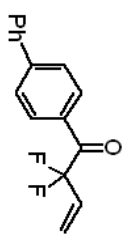
88.87
88.88





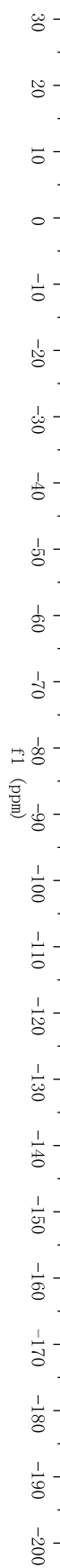
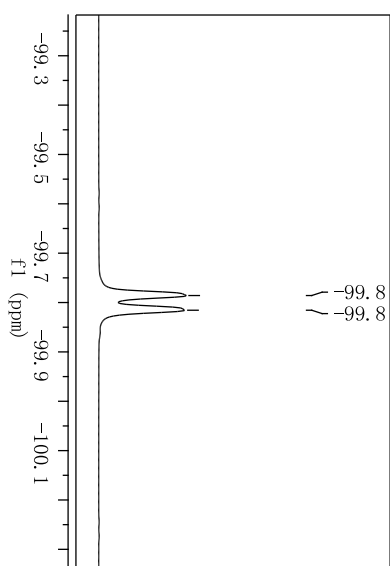
1-([1,1'-Biphenyl]-4-yl)-2,2-difluorobut-3-en-1-ol (8).

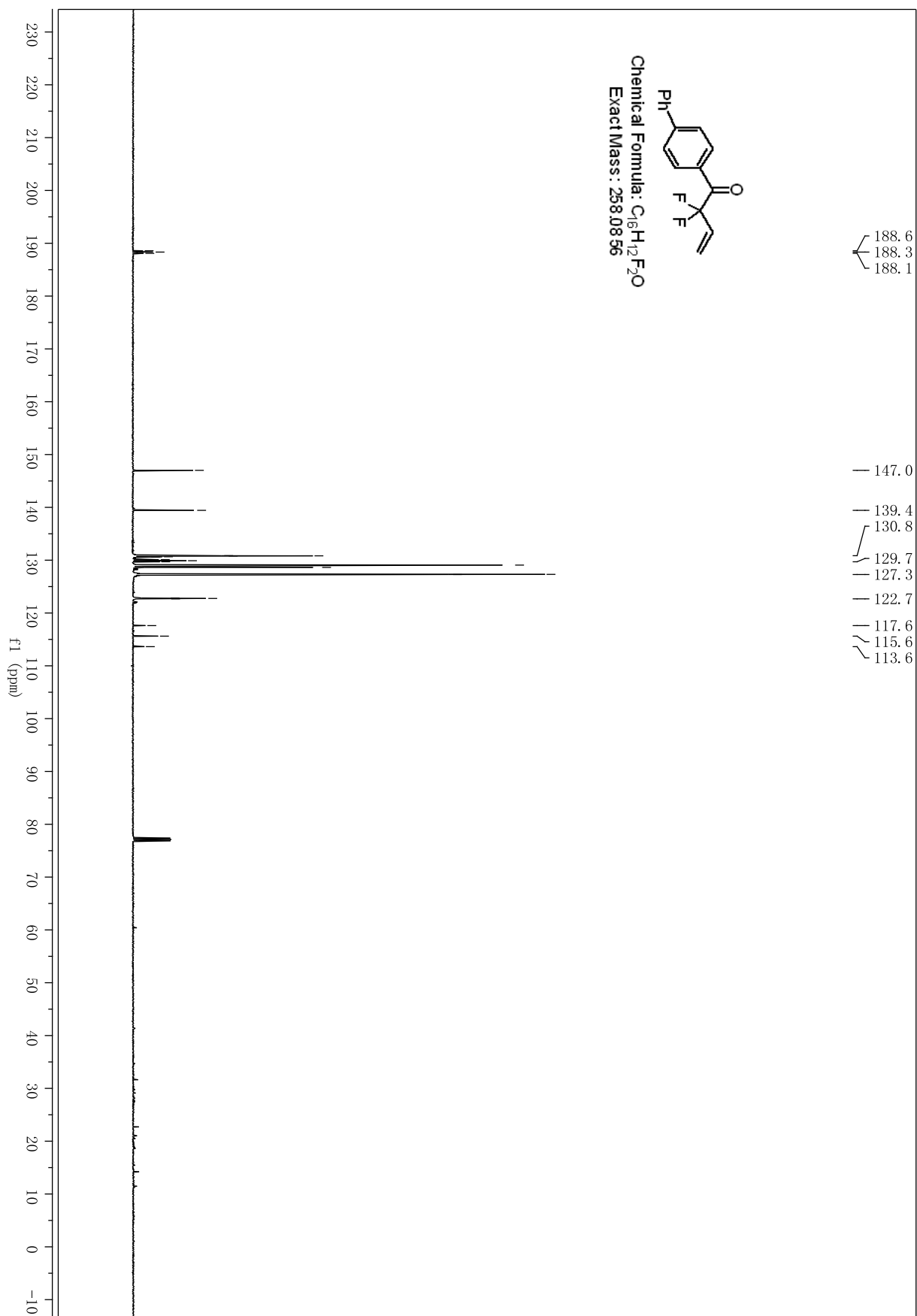




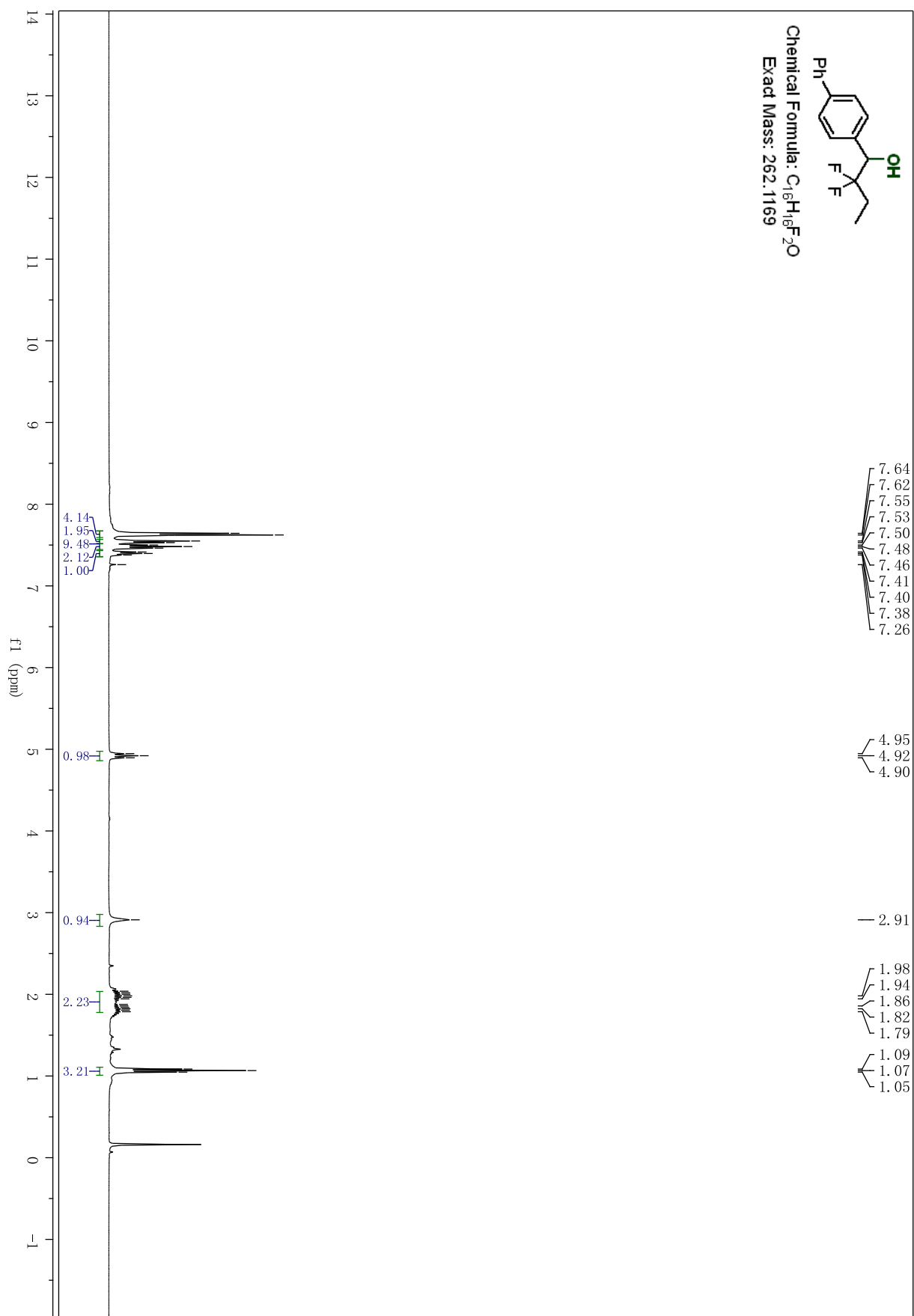
Chemical Formula: $C_{16}H_{12}F_2O$
Exact Mass: 258.0856

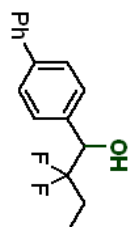
-99.8
-99.8



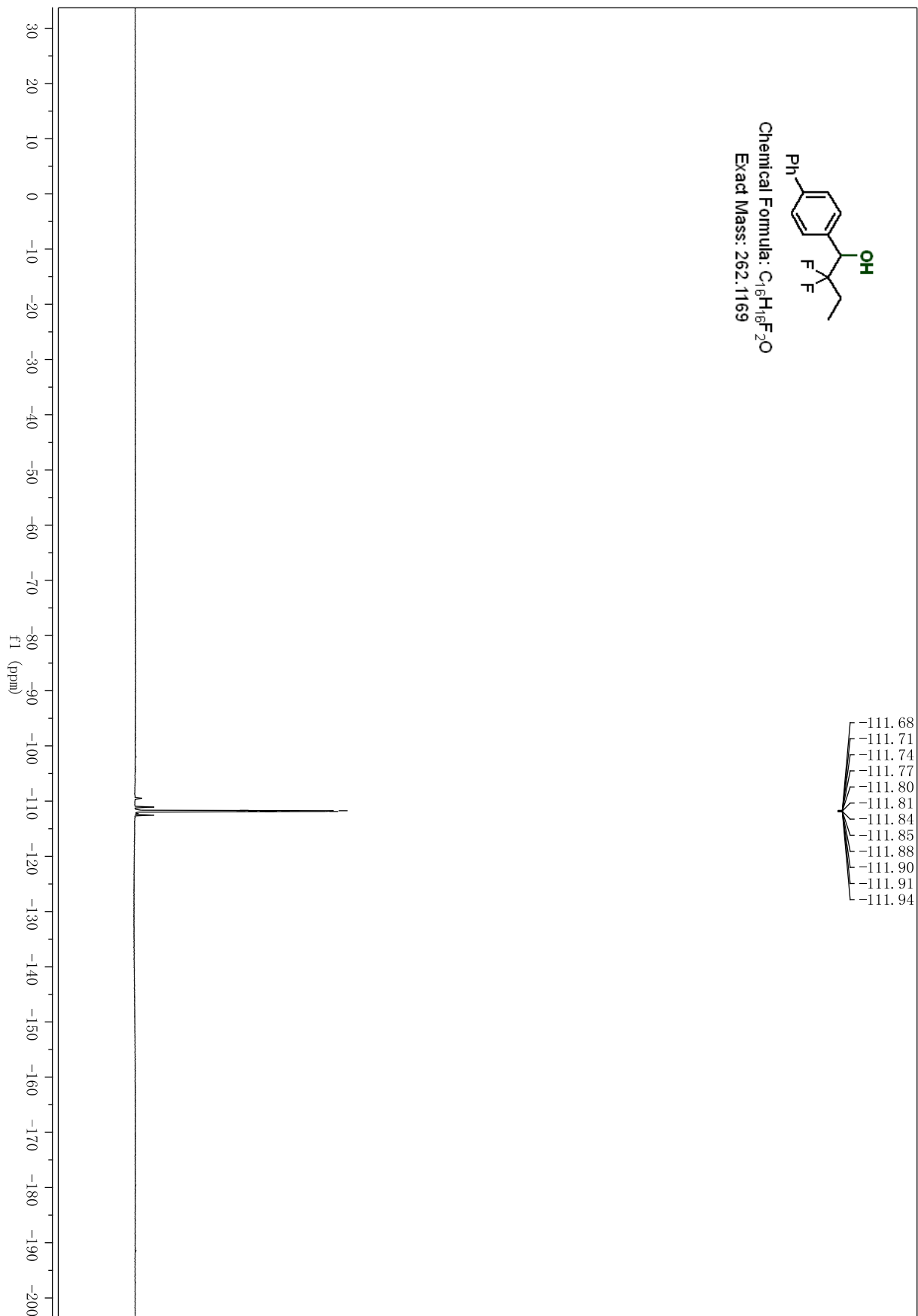


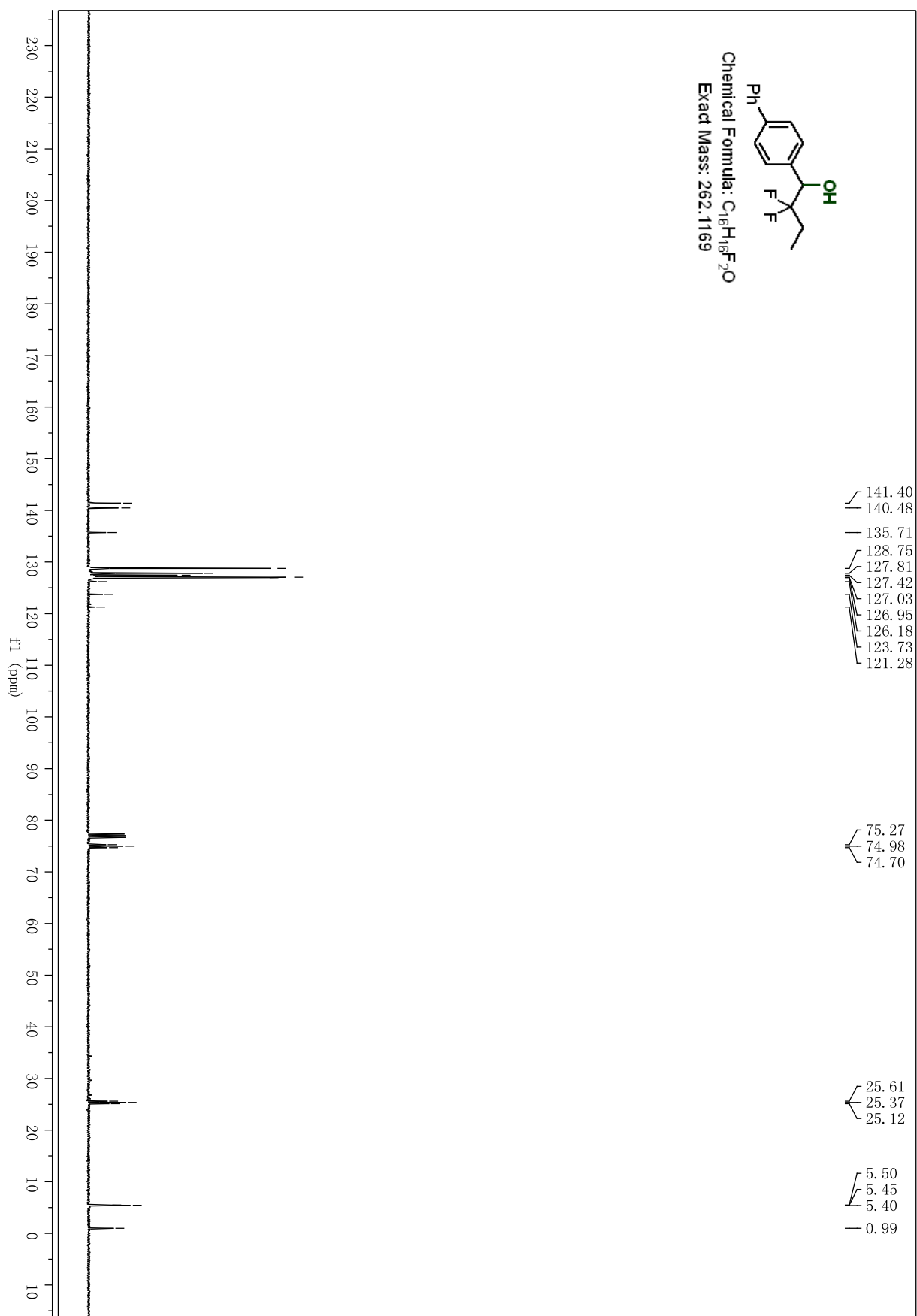
1-([1,1'-Biphenyl]-4-yl)-2,2-difluorobutan-1-ol (9).



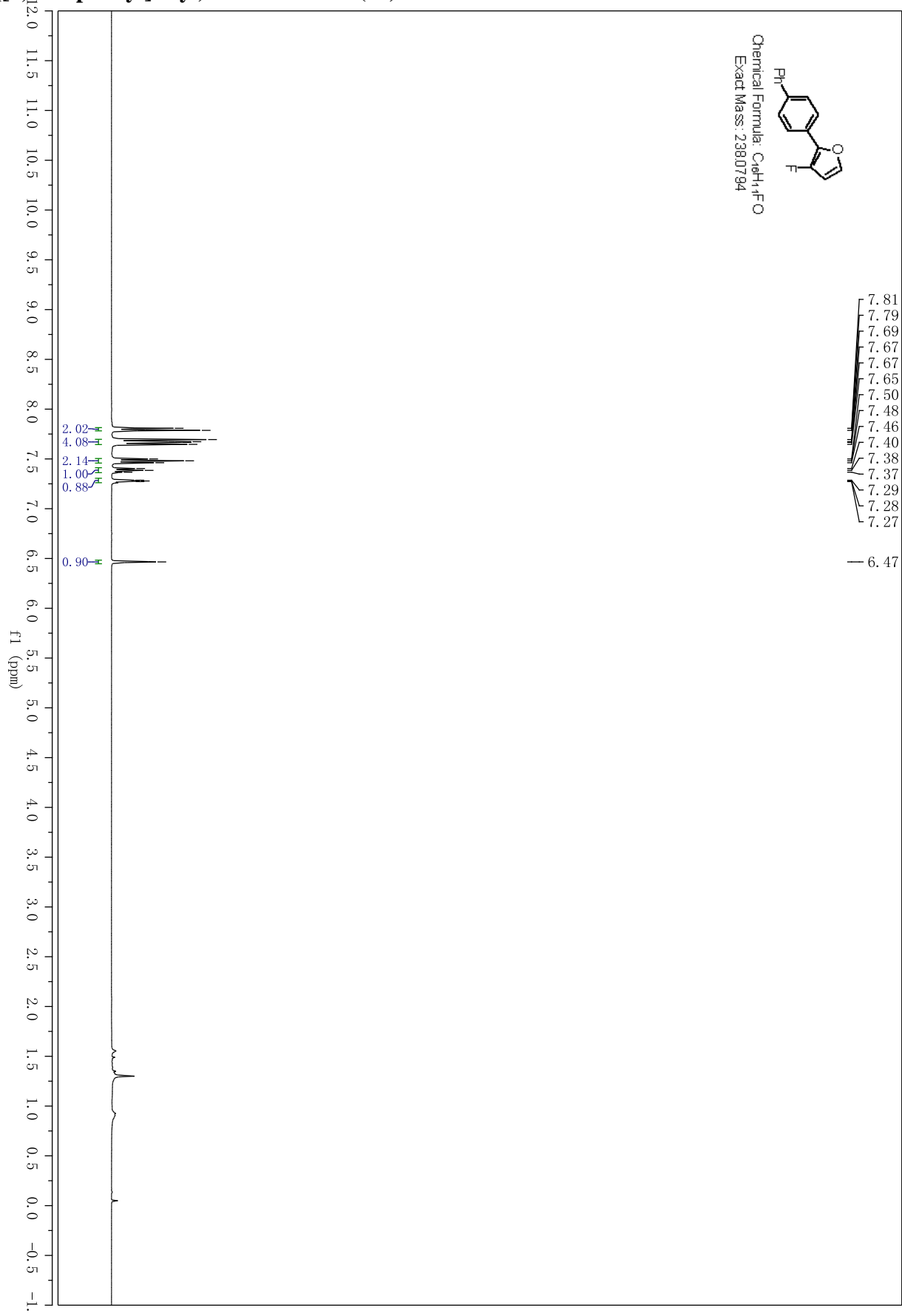


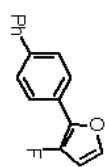
Chemical Formula: $C_{16}H_{16}F_7O$
Exact Mass: 262.1169



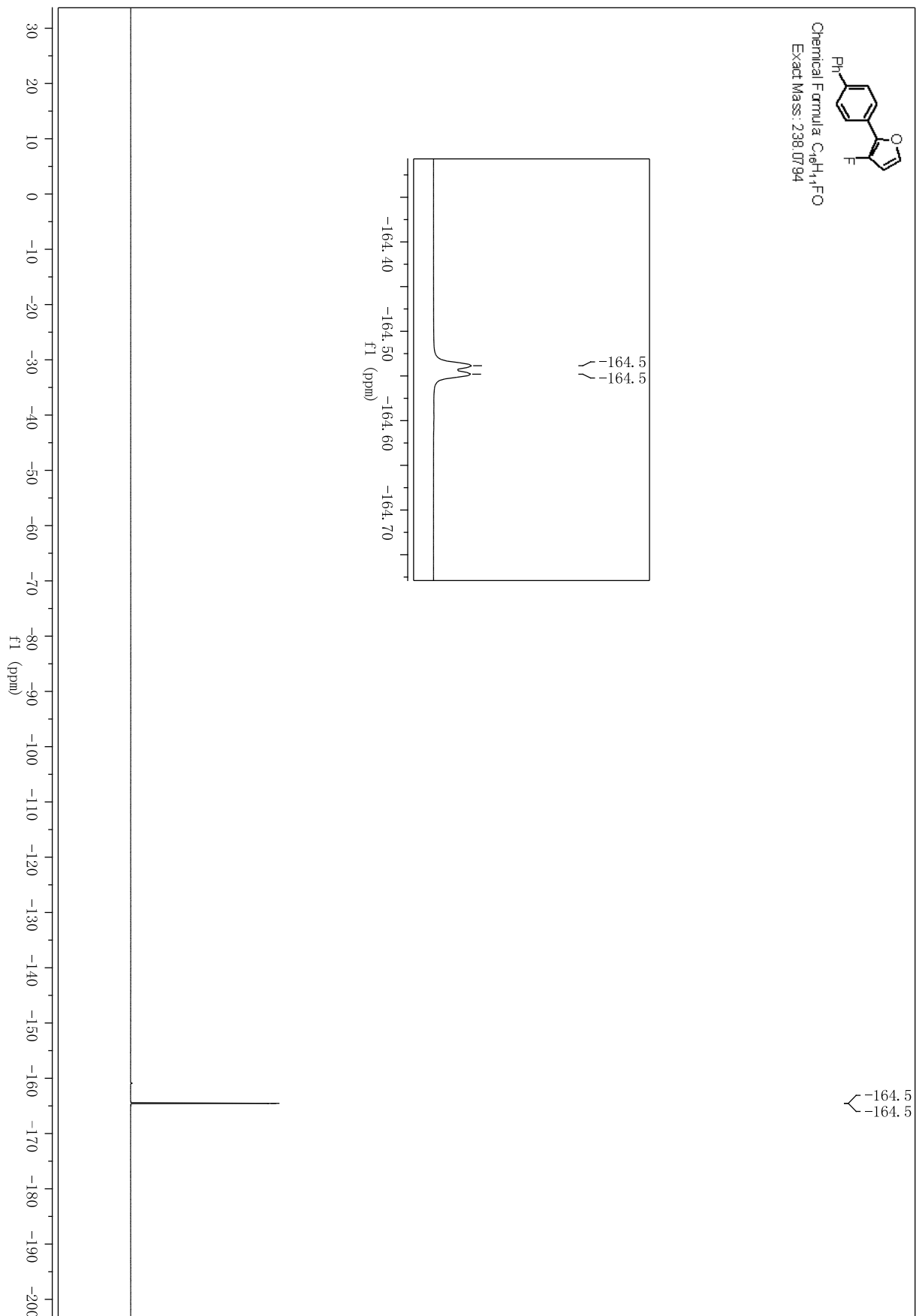


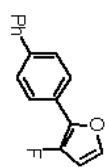
2-([1,1'-Biphenyl]-4-yl)-3-fluorofuran (10).



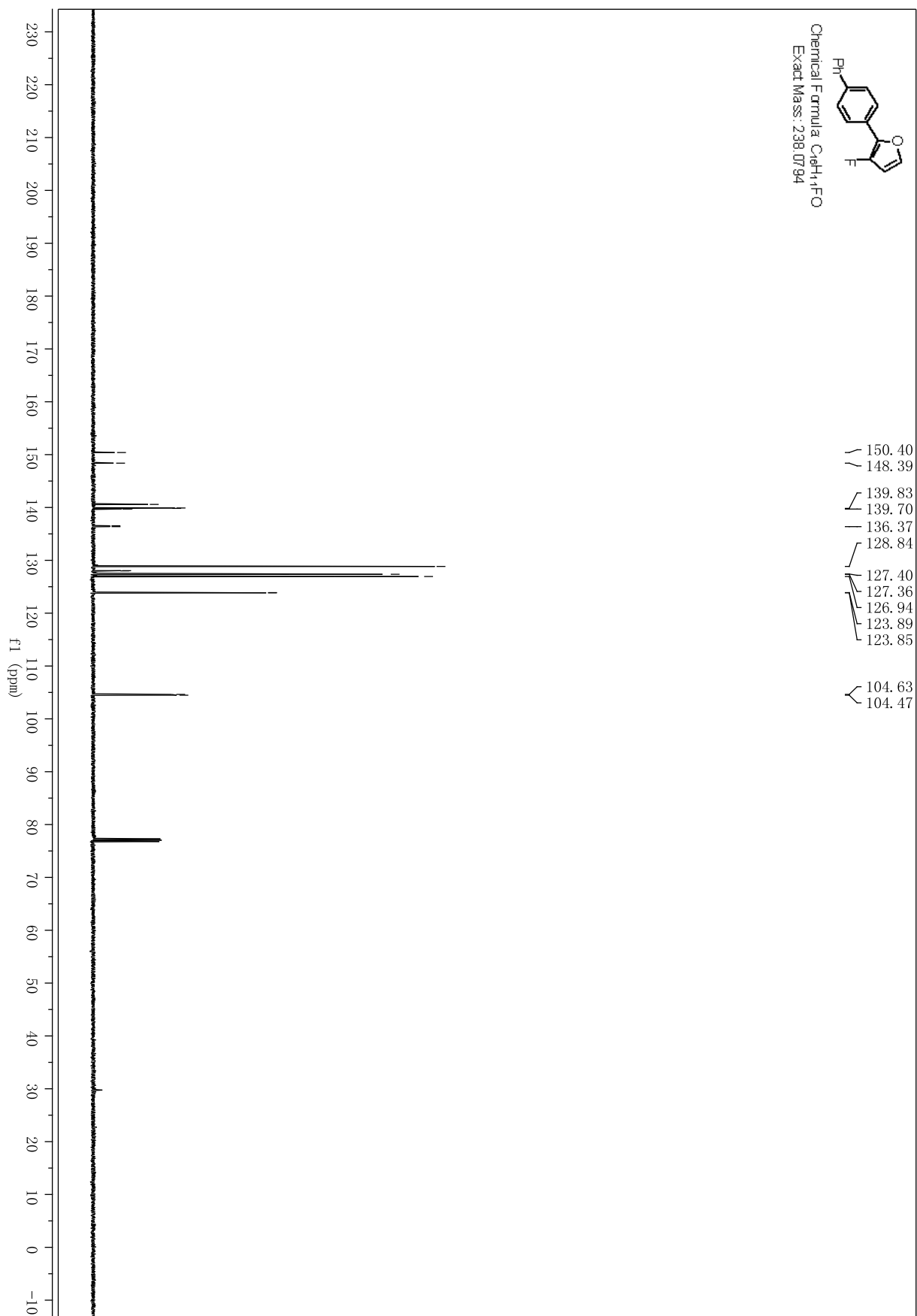


Chemical Formula: $C_{16}H_{14}FO$
Exact Mass: 238.0794

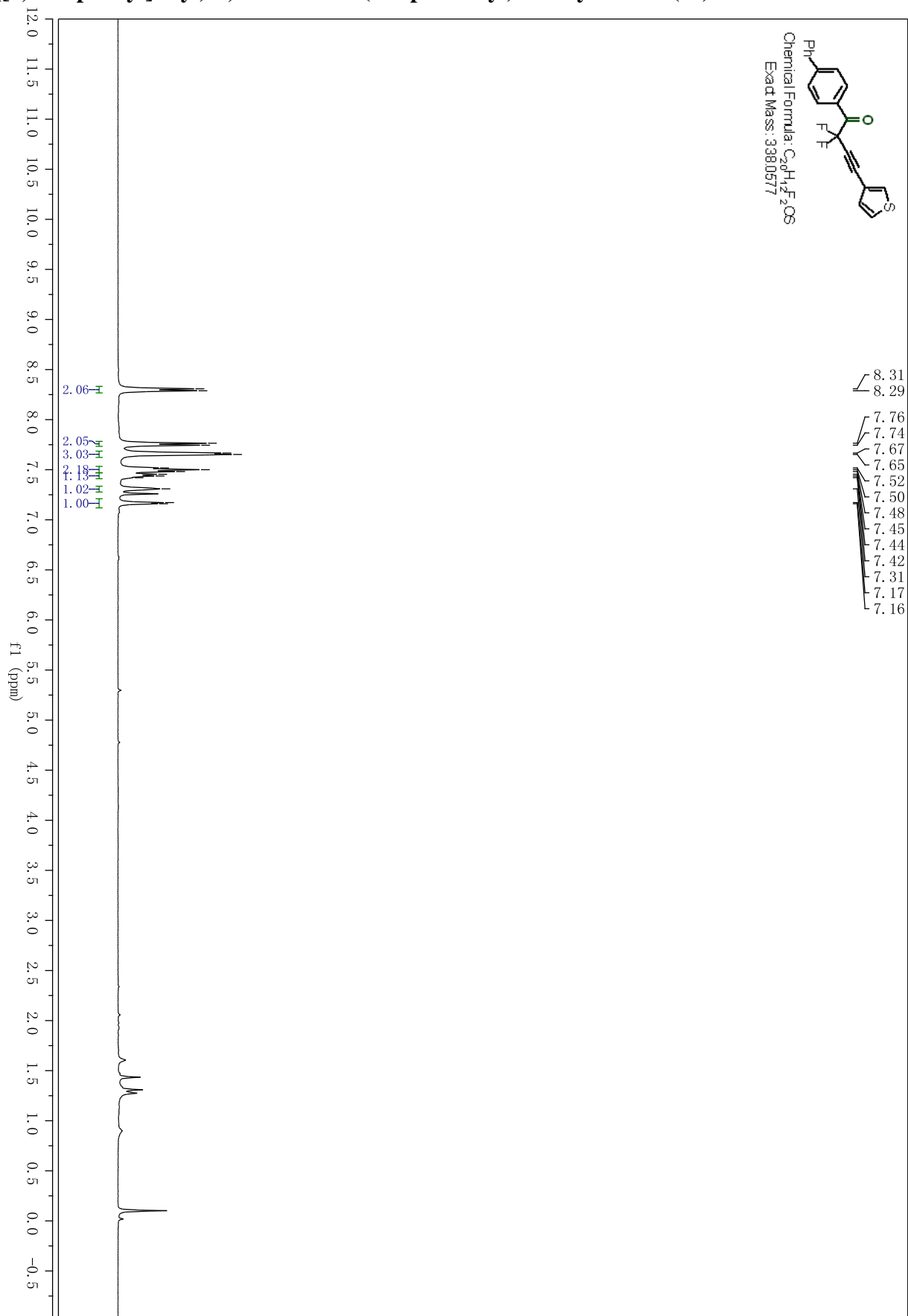


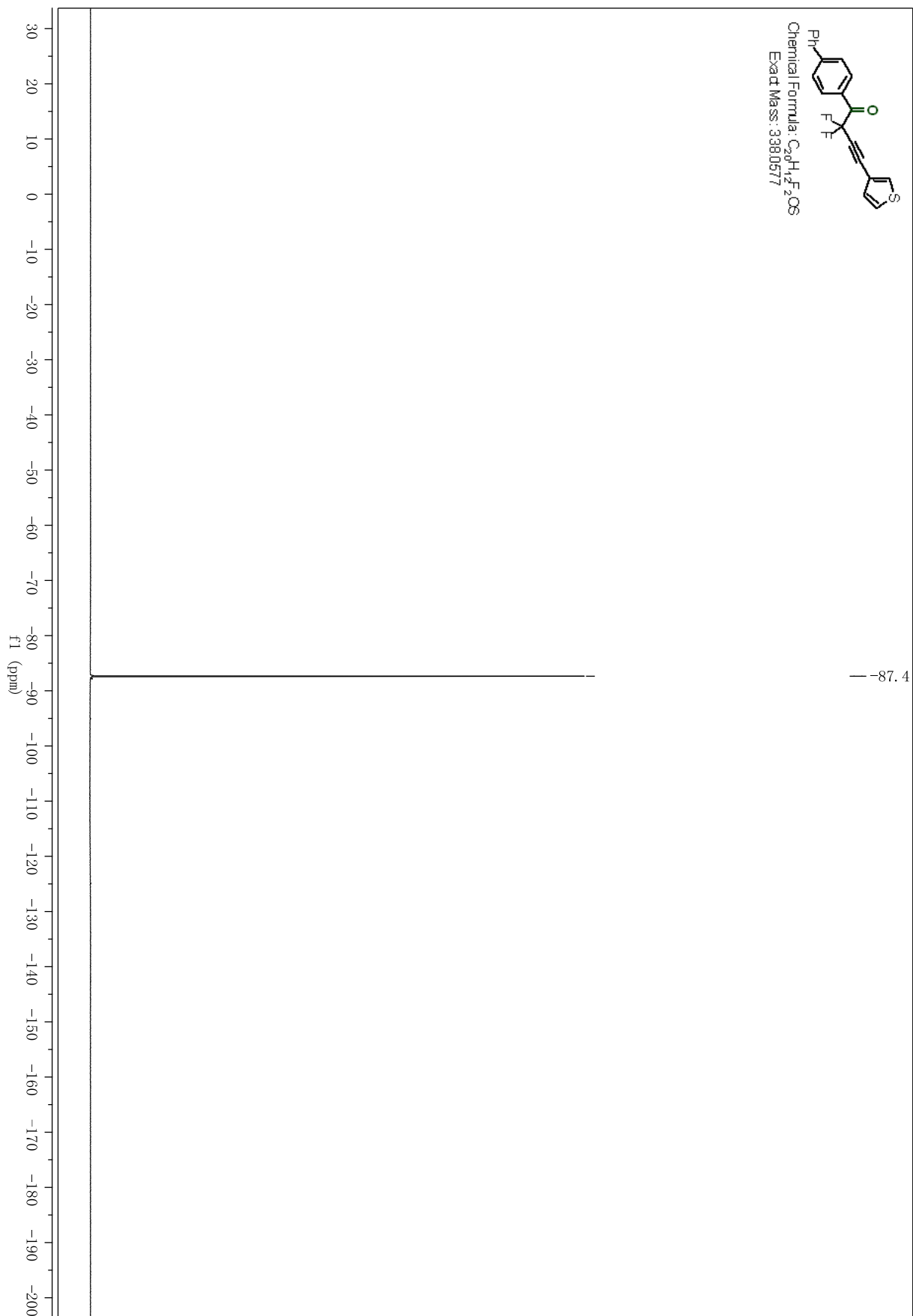
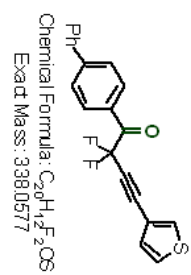


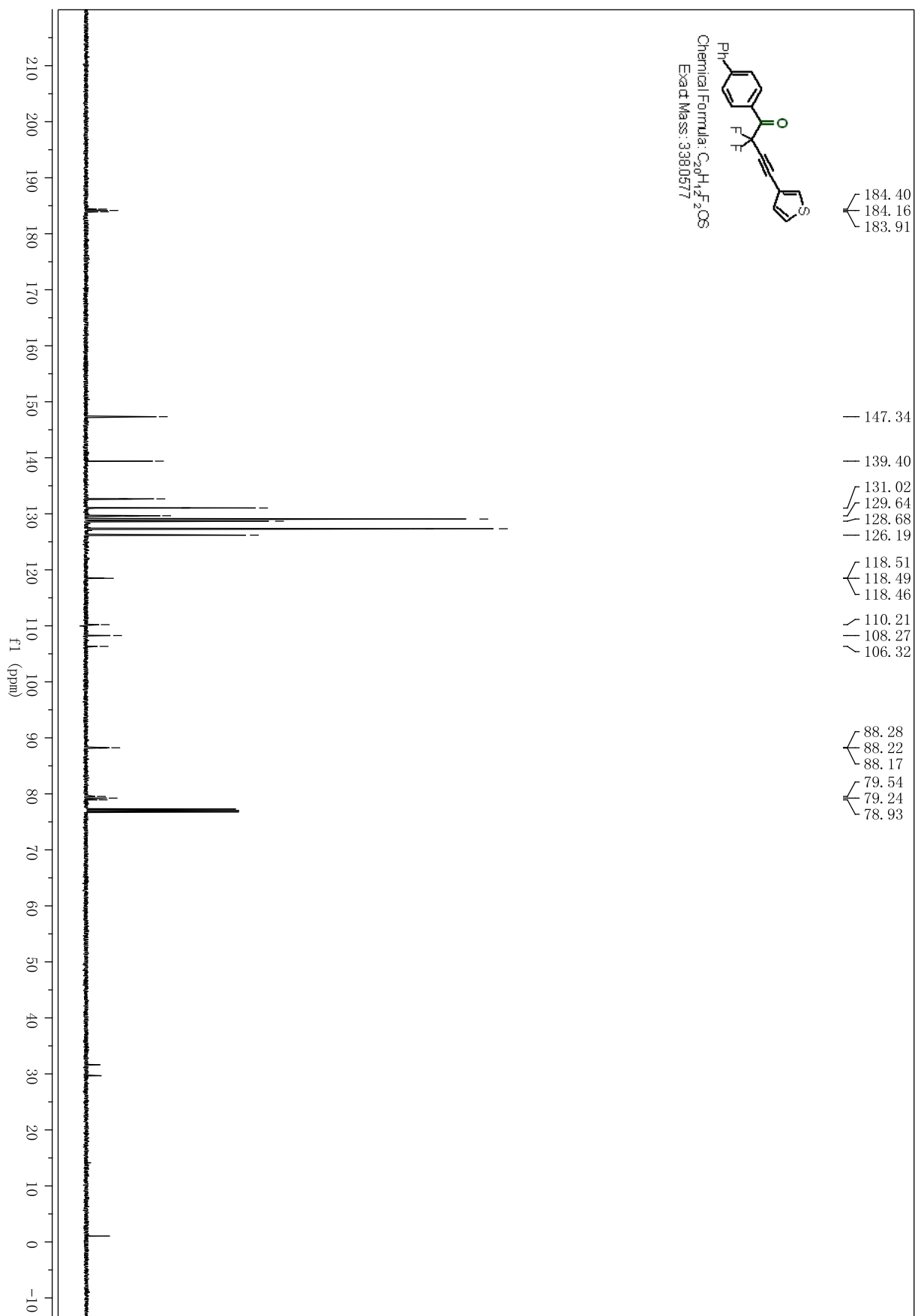
Chemical Formula: $C_{16}H_{11}FO$
Exact Mass: 238.0794



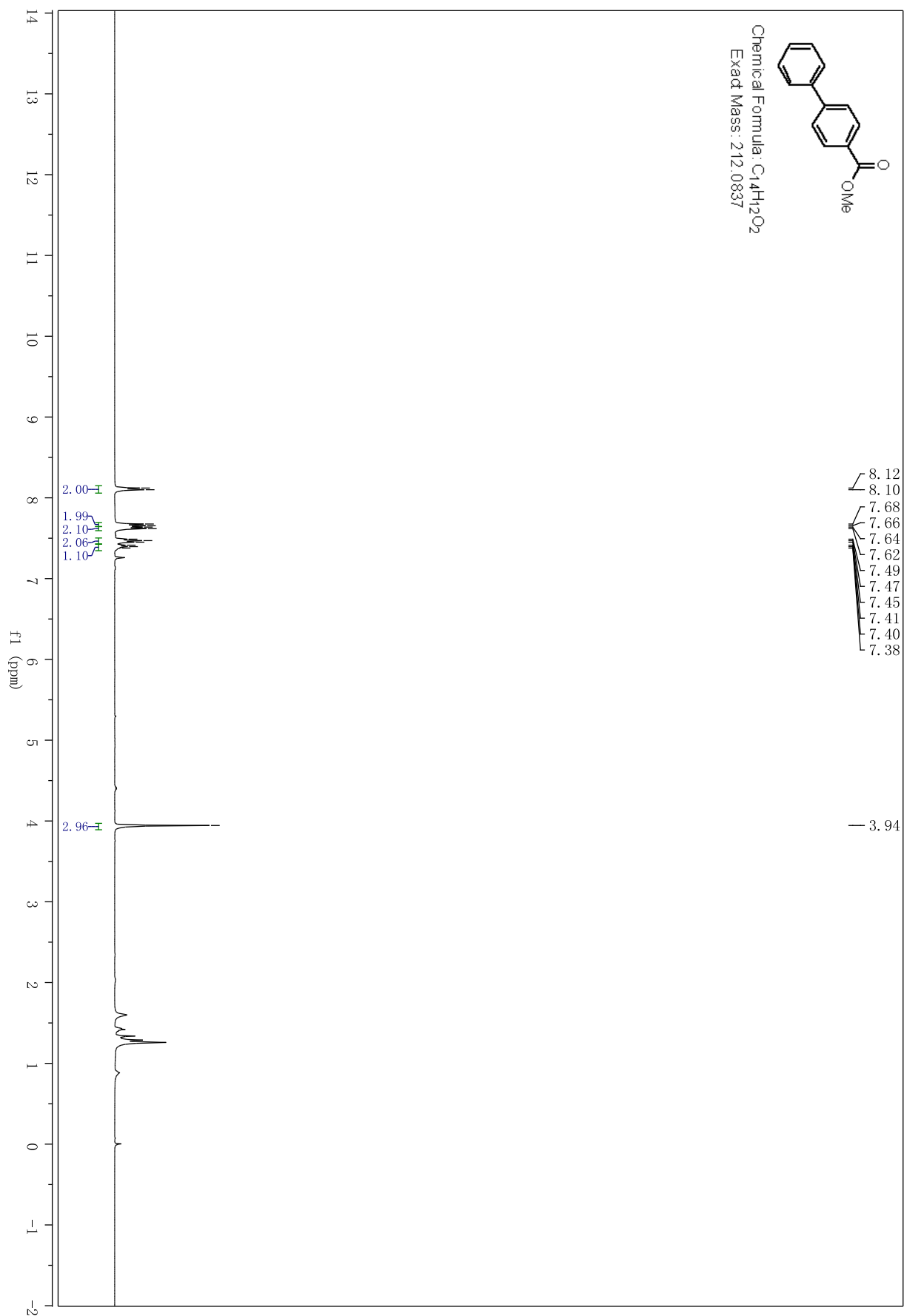
1-([1,1'-Biphenyl]-4-yl)-2,2-difluoro-4-(thiophen-3-yl)but-3-yn-1-one (11).

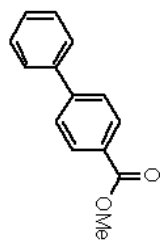




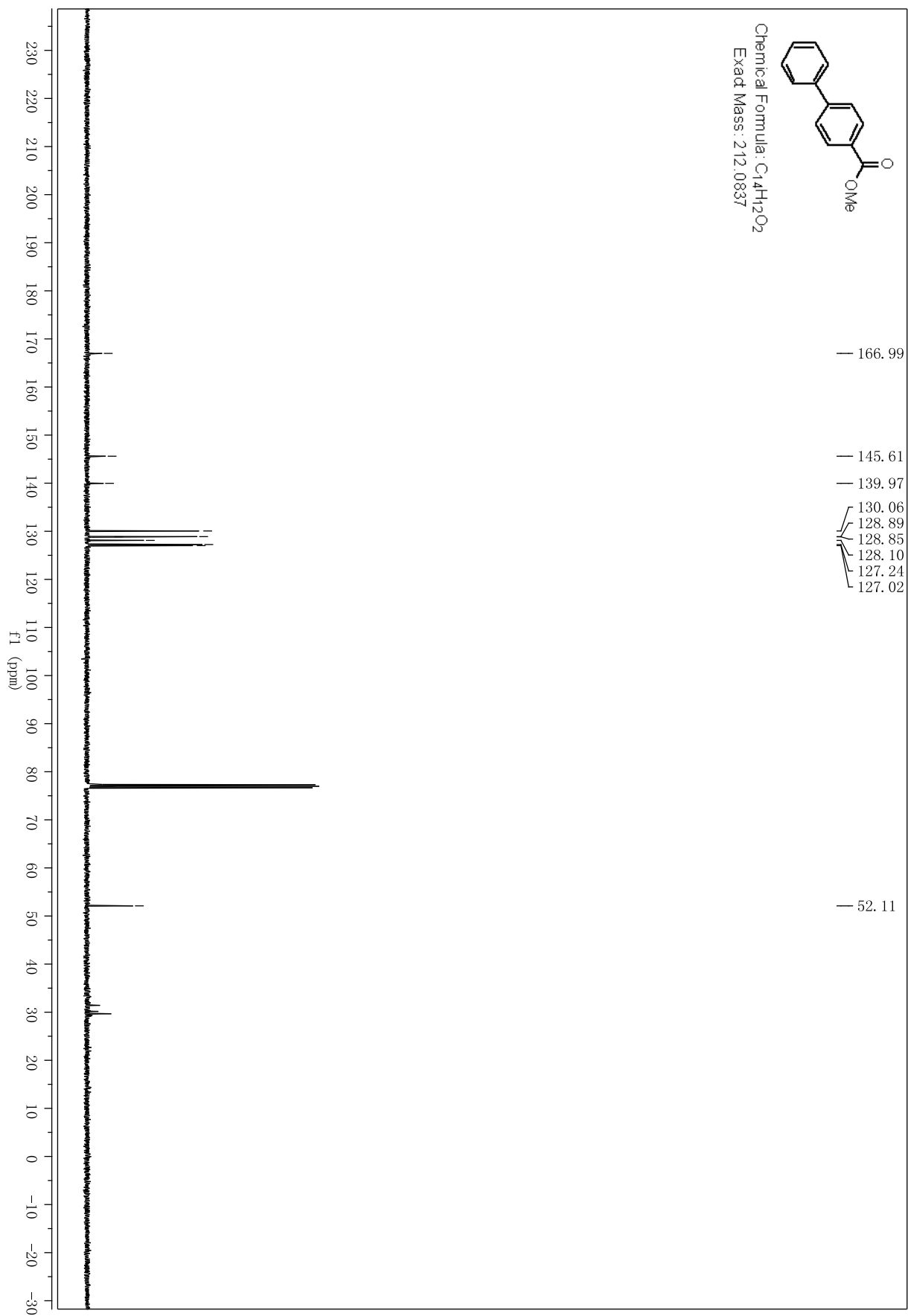


Methyl [1,1'-biphenyl]-4-carboxylate (12).

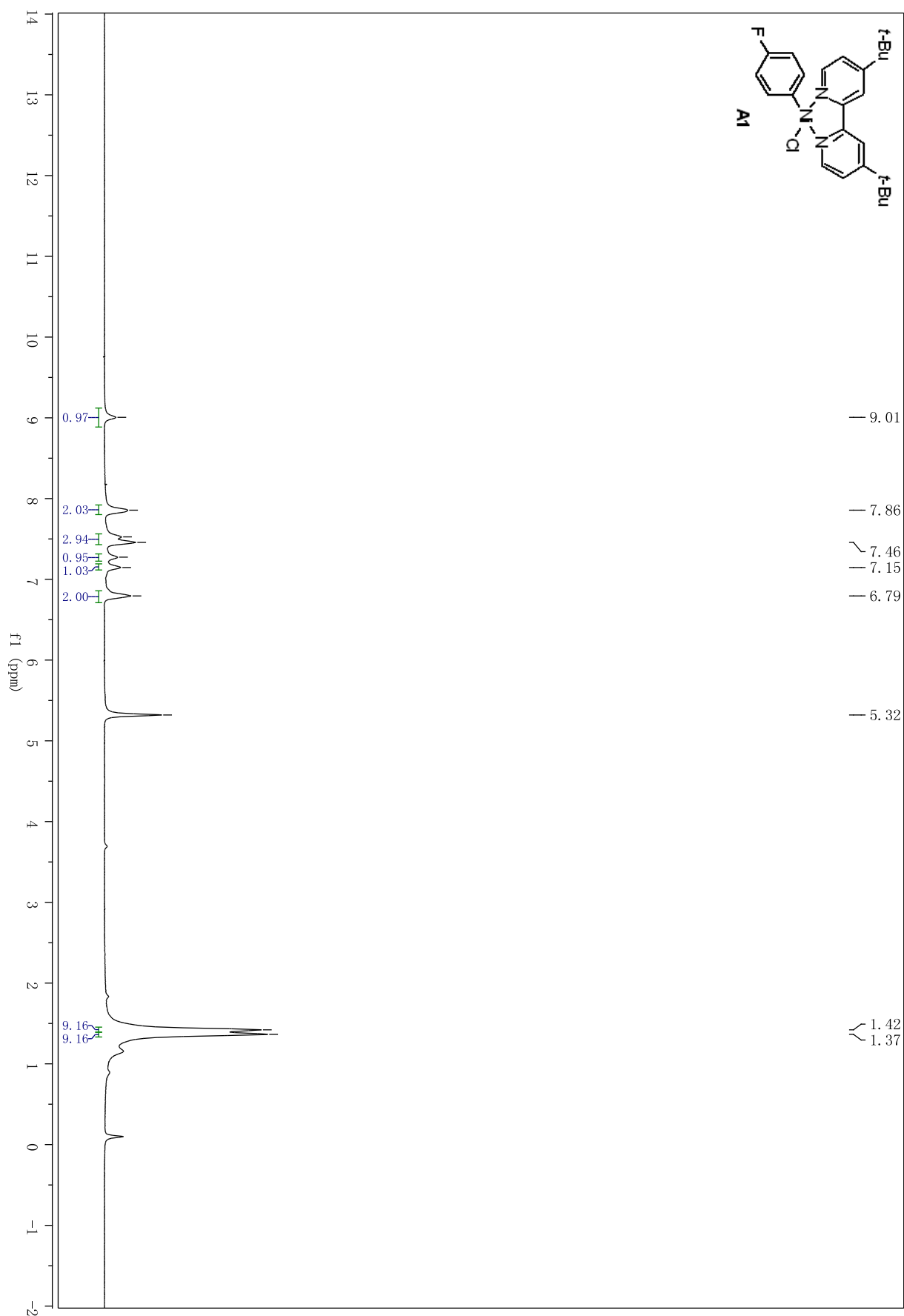


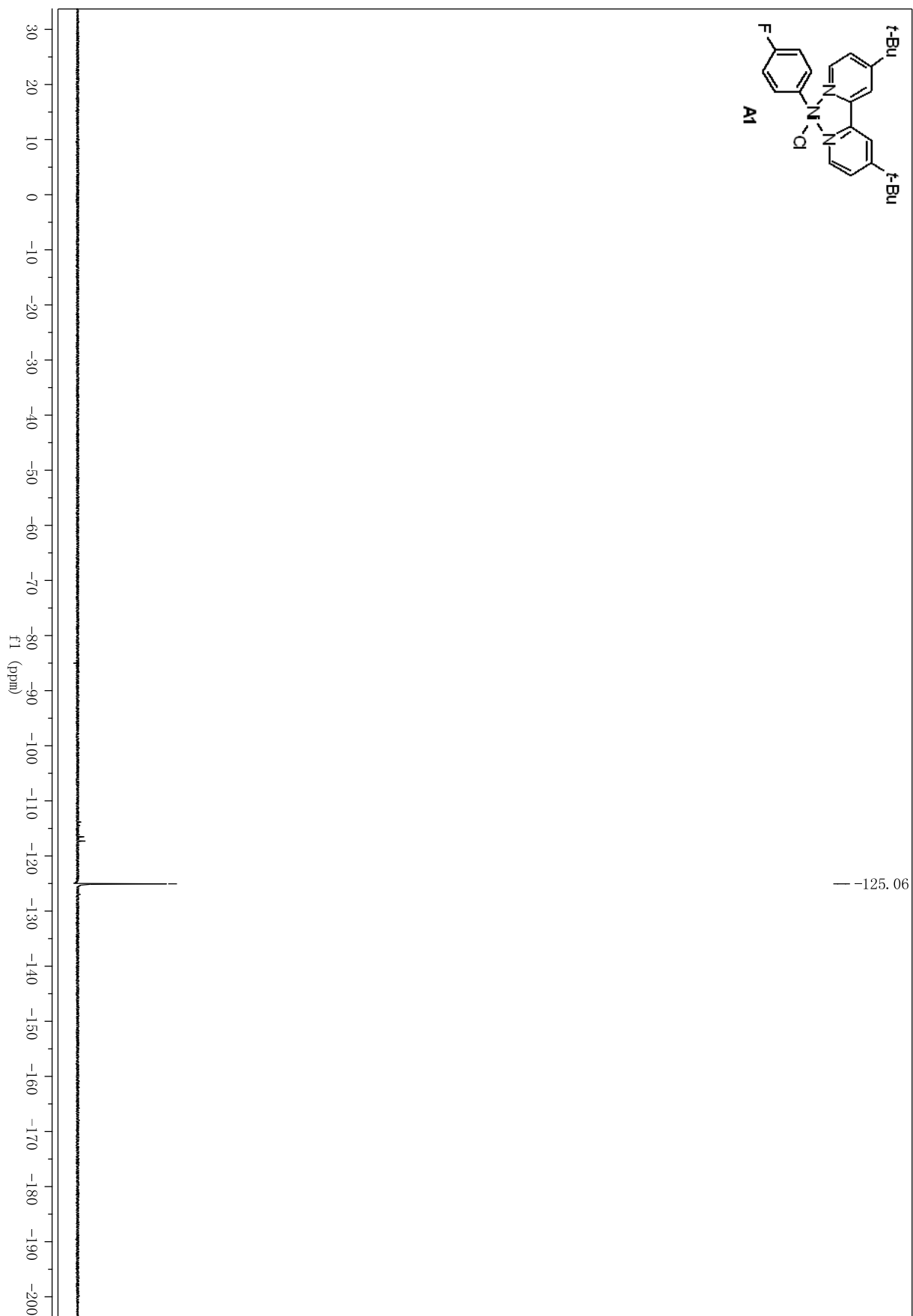


Chemical Formula: $C_{14}H_{12}O_2$
Exact Mass: 212.0837

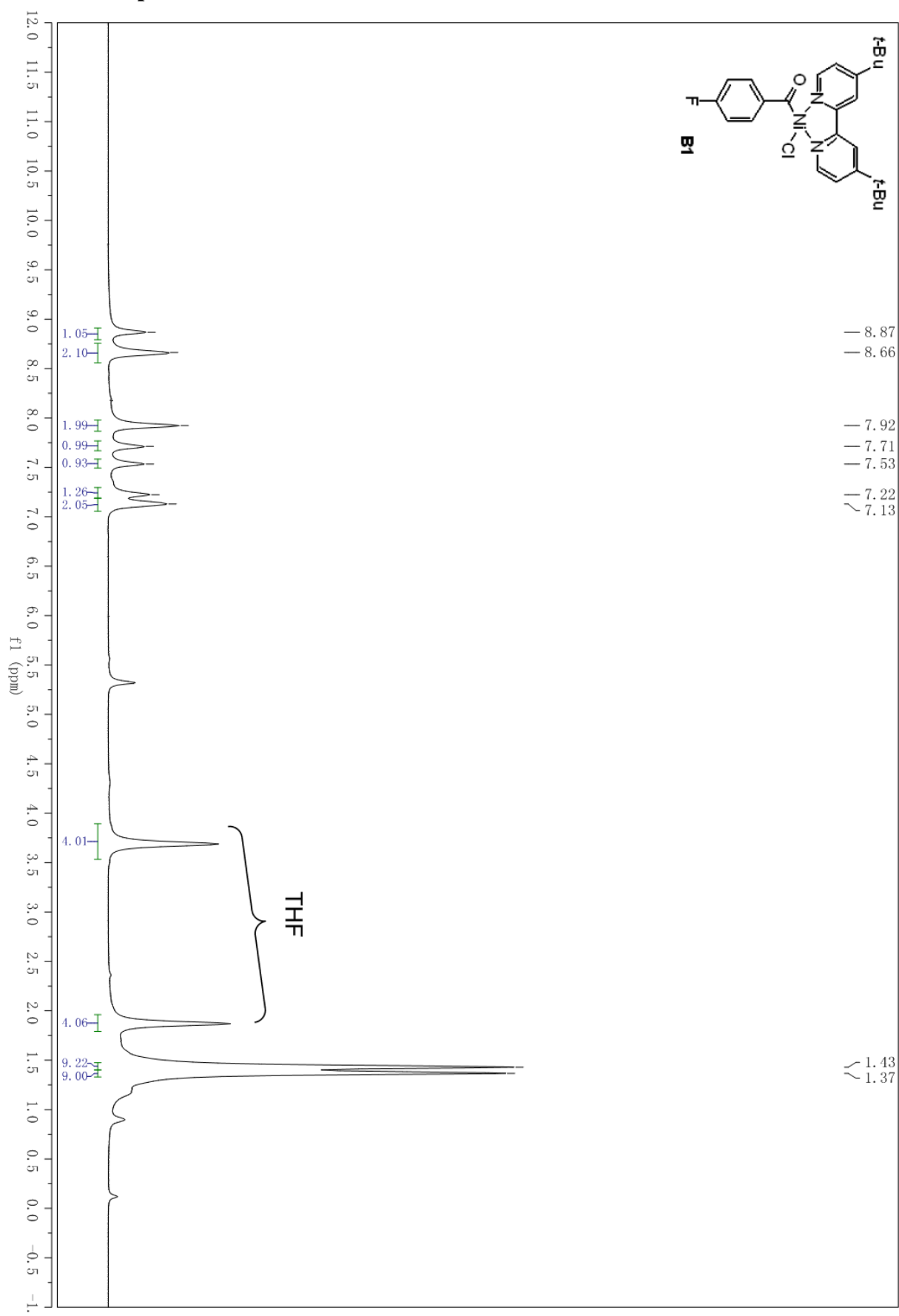


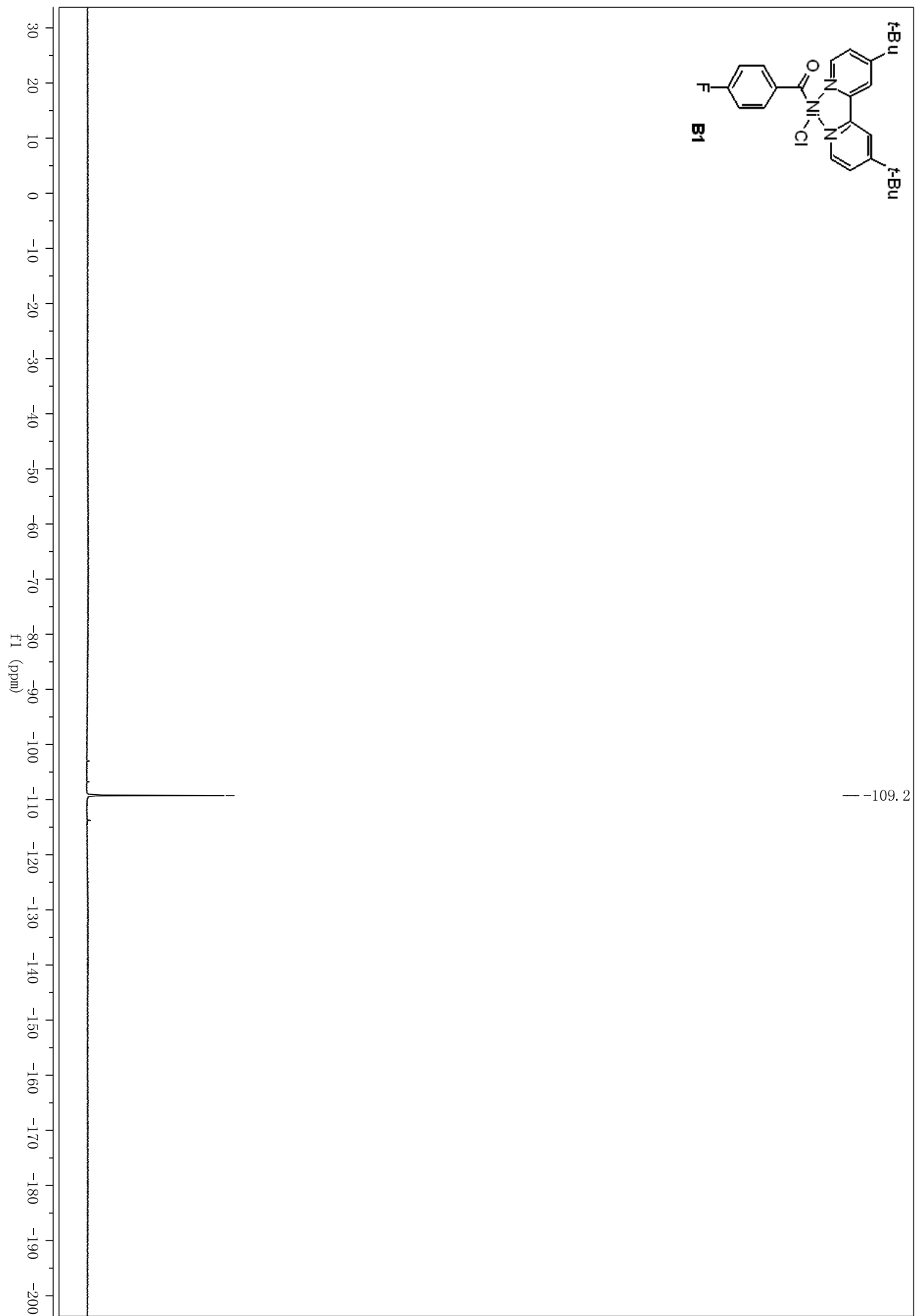
The nickel complex A1.



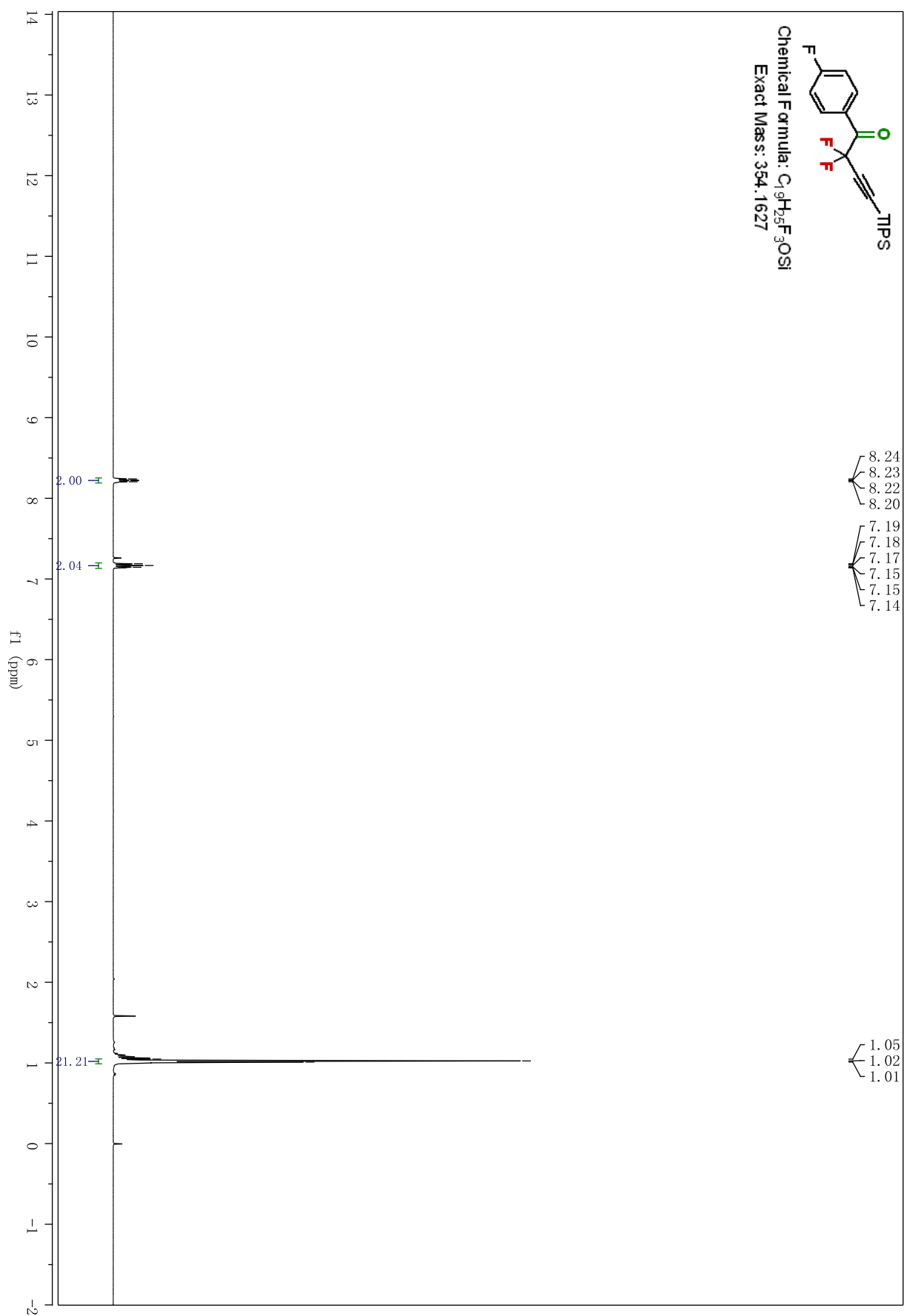


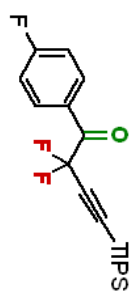
The nickel complex B1·THF.



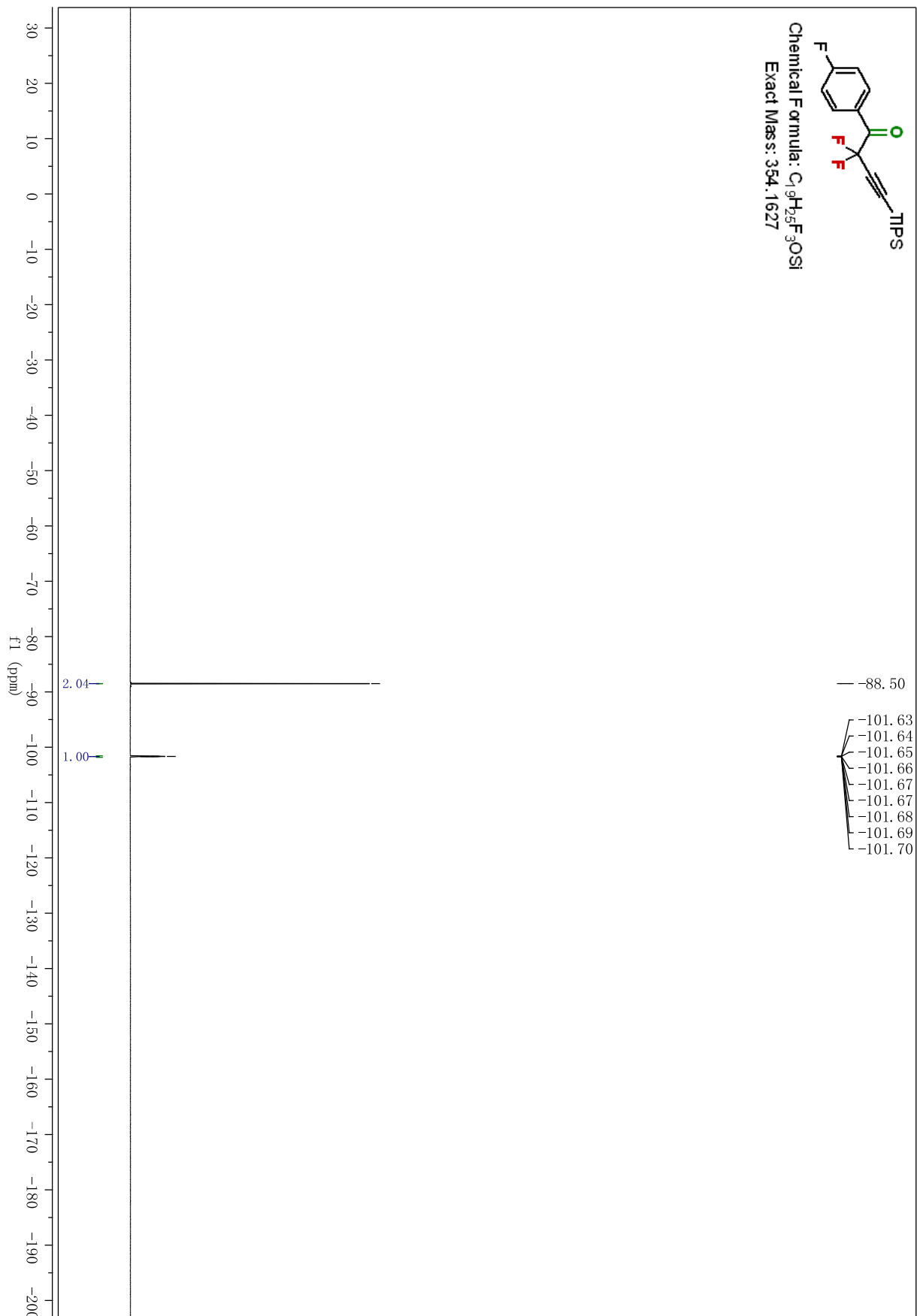


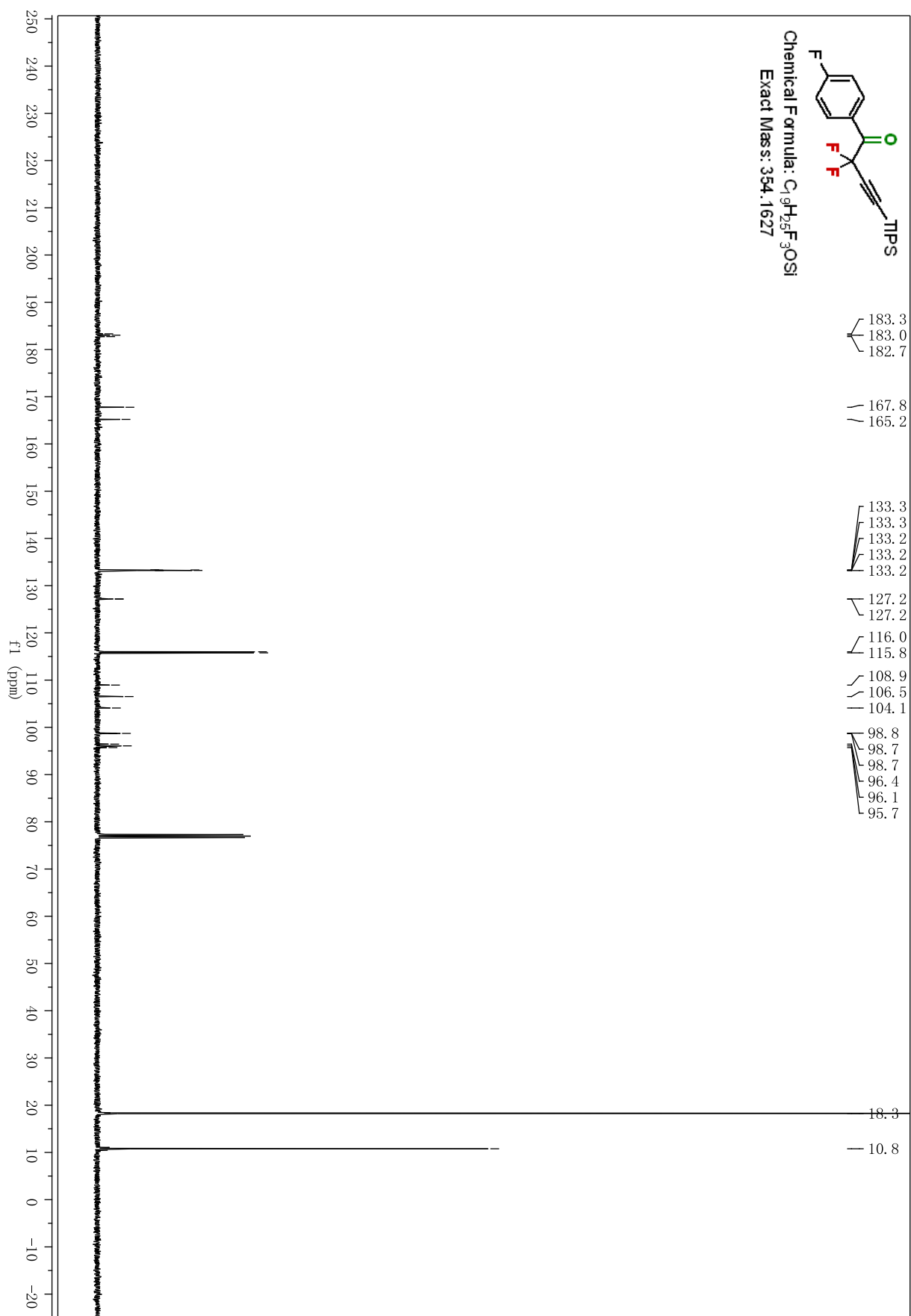
2,2-Difluoro-1-(4-fluorophenyl)-4-(triisopropylsilyl)but-3-yn-1-one (15).



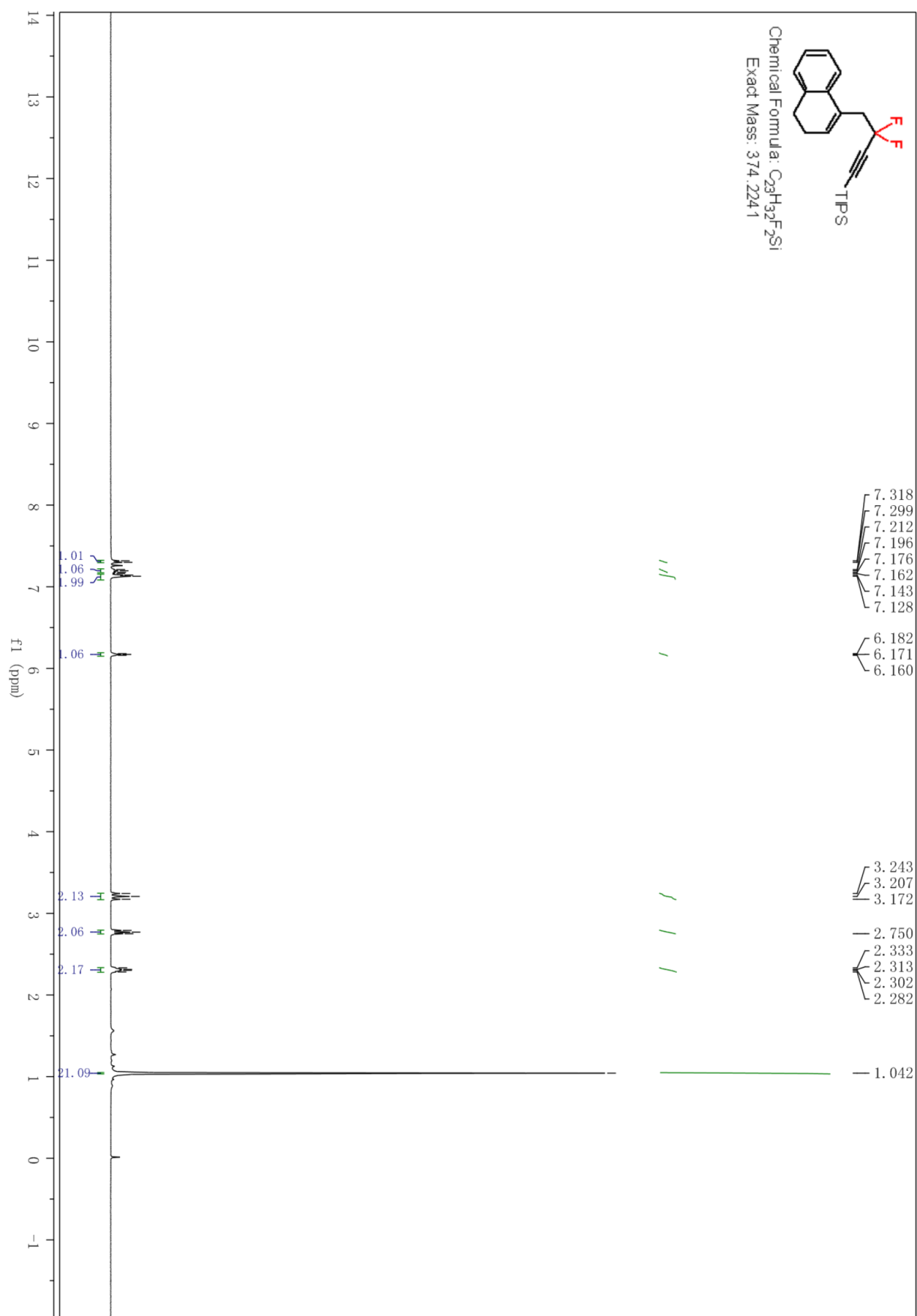


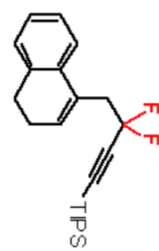
Chemical Formula: $C_{11}H_9F_3OSi$
Exact Mass: 354.1627





(3,4-Dihydronaphthalen-1-yl)-3,3-difluorobut-1-yn-1-yl triisopropylsilane (18).





Chemical Formula: $C_{29}H_{32}F_2Si$
Exact Mass: 374.2241

-79.10
-79.13
-79.17

