Supporting Information for

Copper-Catalyzed Cross-Coupling of Iodobenzoates with Bromozinc-difluorophosphonate

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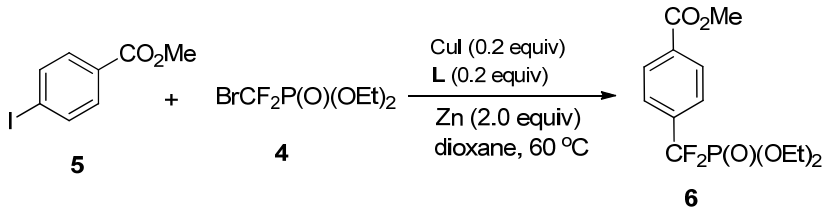
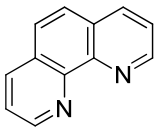
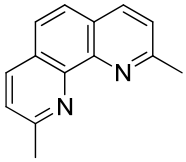
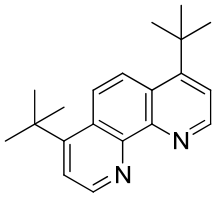
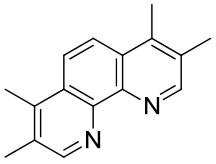
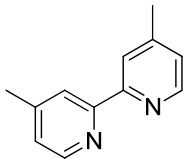
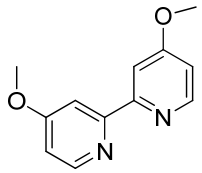
General information: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300 and AM400 spectrometer. ^{19}F NMR was recorded on a Bruker AM300 spectrometer ($CFCl_3$ as outside standard and low field is positive). Purification by reverse phase preparative HPLC was performed on a PerkinElmer 200 HPLC equipped with a PerkinElmer Series 200 UV/VIS detector and a Kromasil 100-5-C18 (250 x 10 mm) column. 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, unless specified otherwise, or prepared as described in the literature. All reagents were weighed and handled in air, and refilled with an inert atmosphere of N_2 at room temperature. DMF and DMSO were distilled under reduced pressure from CaH_2. 1,4-Dioxane was distilled from sodium and benzophenone immediately before use.

Table S1. Cross-Coupling of Methyl 4-Iodobenzoate 5 with Bromozinc-difluorophosphonate 2.

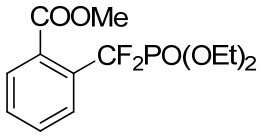


5 **4** **6**

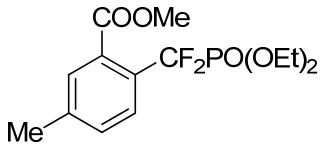
L	yield (%)[a]	L	yield (%)[a]
	16		10
	20		15
	trace		17

[a]NMR yield, determined by ^{19}F NMR using fluorobenzene as an internal standard

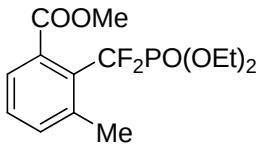
General procedure for copper-catalyzed cross-coupling of iodobenzoates with bromozinc-difluorophosphonate: To a stirred suspension of Zn dust (1.0 mmol) in dioxane (2 mL) was added bromodifluoromethanephosphonate (1.0 mmol) under N_2. After stirring for 3 h at 60 ^oC, the resulting mixture was cooled to room temperature. CuI (0.1 equiv) and phen (0.2 equiv) were added. The reaction mixture was stirred at same temperature for 30 min, iodobenzoate **1** (0.5 mmol) was then added. The reaction was warmed to 60 ^oC and stirred for 24-48 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography to provide pure product.



Methyl 2-((diethoxyphosphoryl)difluoromethyl)benzoate (3a) The product (153 mg, 95% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 3:1). This compound is known.[1] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 6.6 Hz, lH), 7.55-7.53 (m, 3H), 4.26-4.17 (m, 4H), 3.91 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.2 (2F, d, J = 112.8 Hz).

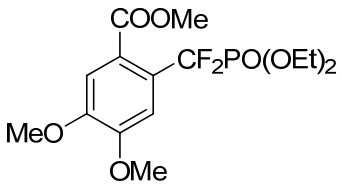


Methyl 2-((diethoxyphosphoryl)difluoromethyl)-5-methylbenzoate (3b) The product (124 mg, 74% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 4.18 (m, 2H), 3.86 (s, 3H), 2.36 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.3 (*d* = 113.1 Hz, 2F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 7.0 (t, *J* = 113.1 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.9, 141.0 (q, *J* = 1.5 Hz), 131.7 (q, *J* = 3.6 Hz), 130.6 (d, *J* = 1.5 Hz), 129.0, 128.4 (td, J_{CF} = 7.5 Hz, J_{CP} = 1.5 Hz), 127.2 (td, J_{CF} = 21.5 Hz, J_{CP} = 14.9 Hz), 119.5 (td, J_{CF} = 261.0 Hz, J_{CP} = 217.3 Hz), 64.8, 64.7, 52.5, 21.0, 16.3, 16.2. IR (thin film) ν_{max} 1739, 1436 cm^{-1}. MS (EI): *m/z* (%) 321 (M^+ - Me), 199, 165 (100). HRMS calcd. for $C_{13}H_{16}F_2O_5P$ (M^+ - Me): 321.0703; Found: 321.0704.

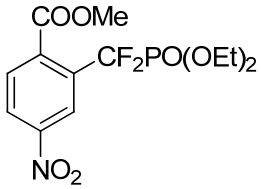


Methyl 2-((diethoxyphosphoryl)difluoromethyl)-3-methylbenzoate (3c) The product (135 mg, 80% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 2:1). This compound is unknown. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 7.24 (d, *J* = 6.6 Hz, 1H), 4.19 (m, 4H),

3.88 (s. 3H), 2.64 (s, 3H), 1.31 (t, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -98.0 (d, J = 112.8 Hz, 2F). ^{31}P NMR(121 MHz, $CDCl_3$) δ 7.67 (t, J = 112.5 Hz) ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 138.8, 133.6, 133.3 (td, J = 5.6 Hz, J = 2.9 Hz), 129.9, 128.1(td, J_{CF} = 20.4 Hz, J_{CP} = 15.0 Hz), 125.5, 119.4 (td, J_{CF} = 266.3 Hz, J_{CP} = 213.5 Hz), 64.55, 64.46, 52.2, 21.2 (t, J = 3.7 Hz), 16.04, 15.97. IR (thin film): ν_{max} 1737 cm^{-1}. MS (EI): *m/z* (%) 336 (M^+), 219, 109 (100). HRMS calcd. for $C_{14}H_{19}F_2O_5P$: 336.0938. Found: 336.0939.

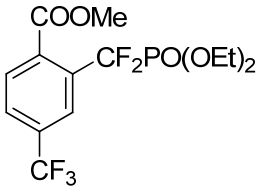


Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4,5-dimethoxybenzoate (3d). The product (103 mg, 54% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 1:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.90 (s, 1H), 4.05 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 1.16 (t, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -100.7 (d, J = 114.8 Hz, 2F). ^{31}P NMR (161 MHz, $CDCl_3$) δ 5.868 (t, J = 114.6 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 150.1, 149.9 (d, J = 18.0 Hz), 124.8 (d, J = 3.2 Hz), 122.9 (m), 117.9 (td, J_{CF} = 263.8 Hz, J_{CP} = 218.3 Hz), 111.5, 110.8 (t, J = 8.0 Hz), 65.0, 64.9, 56.1, 56.0, 52.4, 16.23, 16.18. IR (thin film): ν_{max} 1736 cm^{-1}. MS (EI): *m/z* (%) 382 (M^+), 245, 155 (100), 109, 99. HRMS calcd. for $C_{15}H_{21}F_2O_7P$: 382.0993; Found: 382.0998.

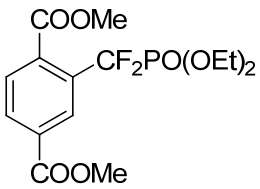


Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-nitrobenzoate (3e). The product (110 mg, 62% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 2:1). This compound is unknown. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.59 (s, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 4.30 (m, 4H), 3.96 (s, 3H), 1.38 (t, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -103.5 (d, J = 108.8 Hz, 2F). ^{31}P NMR (161 MHz, $CDCl_3$) δ 4.58 (t, J = 107.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 148.2, 137.4 (q, J = 3.5 Hz), 132.4 (td, J_{CF} = 22.5 Hz, J_{CP} = 15.5 Hz), 130.0, 125.3, 123.8 (t, J = 8.3 Hz), 117.1 (td, J_{CF} = 265.9 Hz, J_{CP} = 216.5 Hz) 65.3, 65.2, 53.1, 16.3, 16.2. IR (thin film): ν_{max} 1740 cm^{-1}. MS (EI): *m/z* (%) 352 (M^+ - Me), 214, 196 (100), 109. HRMS calcd. for $C_{12}H_{13}F_2NO_7P$ (M^+ - Me): 352.0398; Found: 352.0403.

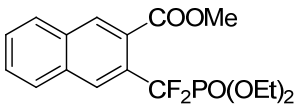


Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-(trifluoromethyl)benzoate (3f). The product (113 mg, 56% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 3:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 4.25 (m, 4H), 3.94 (s, 3H), 1.34 (t, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -59.3 (s, 3F), -98.7 (d, J = 110.8 Hz, 2F). ^{31}P NMR (161 MHz, $CDCl_3$) δ 4.97 (t, J = 109.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 135.4, 132.3 (q, J = 33.2 Hz), 131.5 (m), 129.3, 127.5, 125.7, 123.0 (q, J = 271.5 Hz), 118.6 (td, J_{CF} = 264.3 Hz, J_{CP} = 215.7 Hz), 65.15, 65.09, 53.0, 16.3, 16.2. IR (thin film): ν_{max} 1742 cm^{-1}. MS (EI): *m/z* (%) 375 (M^+ - Me), 219 (100), 109. HRMS calcd. for $C_{13}H_{13}F_5O_5P$ (M^+ - Me): 375.0421; Found: 375.0425.

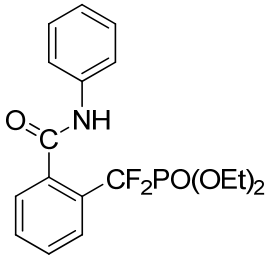


Dimethyl 2-((diethoxyphosphoryl)difluoromethyl)terephthalate (3g). The product (121 mg, 64% yield) as a colorless oil was purified with silica gel chromatography

(Petroleum ether: EtOAc = 1:1). This compound is unknown. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 4.16 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 1.26 (t, J = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.8 (d, J_{PF} = 110.8 Hz). ^{31}P NMR (161 MHz, $CDCl_3$) δ 5.20 (t, J = 110.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 165.0, 135.6 (q, J = 3.1 Hz), 131.6, 131.4, 130.5 (td, J = 22.1 Hz, J = 15.1 Hz), 129.4 (t, J = 7.5 Hz), 128.6, 117.6 (td, J_{CF} = 265.2 Hz, J_{CP} = 216.5 Hz), 64.9, 64.8, 52.6, 52.4, 16.1, 16.0. IR (thin film): ν_{max} 1732 cm^{-1}. MS (EI): *m/z* (%) 365 (M^+ - Me), 243, 223, 209 (100), 109. HRMS calcd. for $C_{14}H_{16}F_2O_7P$ (M^+ - Me): 365.0602; Found: 365.0606.

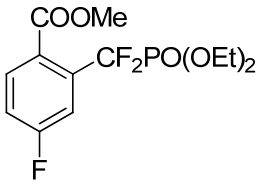


Methyl 3-((diethoxyphosphoryl)difluoromethyl)-2-naphthoate (3h.) The product (162 mg, 87% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.10 (s, 1H), 7.90 (m, 1H), 7.85 (m, 1H), 7.56 (m, 2H), 4.20 (m, 4H), 3.92 (s, 3H), 1.28 (t, J = 6.8 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -99.6 (d, J = 112.6 Hz, 2F). ^{31}P NMR (161 MHz, $CDCl_3$) δ 6.15 (t, J = 112.6 Hz).^{13}CNMR (100 MHz, $CDCl_3$) δ 168.5, 132.9, 132.8, 130.0, 129.4 (t, J = 7.0 Hz), 128.7, 128.6, 128.3, 128.1, 127.4 (td, J_{CF} = 21.8 Hz, J_{CP} = 15.4 Hz), 118.4 (td, J_{CF} = 263.6 Hz, J_{CP} = 216.2 Hz), 64.9, 64.8, 52.6, 16.32, 16.26. IR (thin film): ν_{max} 1738 cm^{-1}. MS (EI): *m/z* (%) 372 (M^+), 137, 109 (100), 81. HRMS calcd. for $C_{17}H_{19}F_2O_5P$: 372.0938; Found: 372.0943.

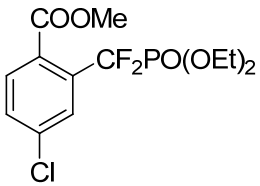


Diethyl difluoro(2-(phenylcarbamoyl)phenyl)methylphosphonate (3i). The product (101 mg, 53% yield) as a colorless oil was purified with silica gel

chromatography (Petroleum ether/EtOAc = 2:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.59-7.51 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 4.24 (m, 4H), 1.36 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -105.1 (d, *J* = 113.7 Hz, 2F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 8.6 (t, *J* = 113.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 138.8, 136.8 (m), 131.3 (d, *J* = 1.7 Hz), 130.4, 129.4 (d, J = 1.5 Hz), 128.8, 128.0 (td, J_{CF} = 21.5 Hz, J_{CP} = 14.2 Hz), 126.8 (td, *J* = 7.3 Hz, *J* = 1.9 Hz), 123.9, 119.6, 118.4 (td, J_{CF} = 266.3 Hz, J_{CP} = 214.3 Hz), 65.8, 65.7, 16.3, 16.2. IR (thin film): ν_{max} 3266, 1679 cm^{-1}. MS (EI): *m/z* (%) 383 (M^+), 286, 206, 109 (100). HRMS calcd. for $C_{18}H_{20}F_2NO_4P$: 383.1098; Found: 383.1100.



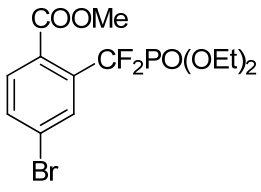
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-fluorobenzoate (3j). The product (139 mg, 82% yield) as an oil was purified with silica gel chromatography (Petroleum ether/ ethyl acetate = 3:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.7 Hz, *J* = 5.4 Hz, 1H), 7.46 (d, *J* = 9.0 Hz, lH), 7.25 (t, *J* = 7.8 Hz, 1H), 4.26 (m, 4H), 3.91 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.0 (d, J = 108.8 Hz, 2F), -108.1 (m, 1F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.46 (t, *J* = 109.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 162.9 (d, *J* = 250.9 Hz), 133.4 (m), 131.3 (d, *J* = 8.5 Hz), 128.1, 117.7 (d, J = 21.4 Hz), 117.3 (td, J_{CF} = 264.4 Hz, J_{CP} = 215.5 Hz), 115.8 (td, *J* = 24.8 Hz, *J* = 8.2 Hz), 65.0, 64.9, 52.6, 16.22, 16.17. IR (thin film): ν_{max} 1741 cm^{-1}. MS (EI): *m/z* (%) 325 (M^+ - Me), 203, 169 (100). HRMS calcd. for $C_{12}H_{13}F_3O_5P$ (M^+ - Me): 325.0453; Found: 325.0449 .



Methyl 4-chloro-2-((diethoxyphosphoryl)difluoromethyl)benzoate (3k). The product (140 mg, 79% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/ethyl acetate = 3:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.50 (s, 2H), 4.23 (m, 4H), 3.89 (s, 3H), 1.33 (t, *J* = 7.5 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.2 (d, *J* = 110.8 Hz, 2F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.38 (t, *J* = 109.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 136.4, 132.2 (td, J_{CF} = 21.3 Hz, J_{CP} = 16.1 Hz), 130.7, 130.2, 128.5 (td, *J* = 8.0 Hz, 1.2 Hz), 117.3 (td, J_{CF} = 264.1 Hz, J_{CP} = 216.2 Hz), 65.0, 64.9, 52.7, 16.2, 16.1. IR (thin film): ν_{max} 1740 cm^{-1}. MS (EI): *m/z* (%) 341 (M^+ - Me), 219, 185 (100). HRMS calcd. for $C_{13}H_{16}ClF_2O_5P$: 356.0392; Found: 356.0391.

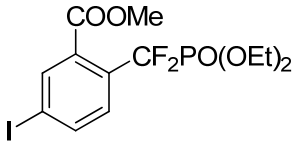
2-g-scale synthesis of 3k.

To a stirred suspension of Zn dust (13.5 mmol, 0.878g) in dioxane (8 mL) was added bromodifluoromethanephosphonate (13.5 mmol, 3.604 g) under N_2. After stirring for 3 h at 60 ^{o}C, the resulting mixture was cooled to room temperature and filtered with a syringe filter. To the filtrate were added CuI (0.1 equiv) and phen (0.2 equiv). The reaction mixture was stirred at same temperature for 30 min, methyl 4-chlorobenzoate (6.75 mmol, 2 g) was then added. The reaction was warmed to 60 ^{o}C and stirred for 24 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether/ethyl acetate = 3:1) to provide pure product (2.403 g, 64% yield).



Methyl 4-bromo-2-((diethoxyphosphoryl)difluoromethyl)benzoate (3l). The product (146 mg, 73% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/ethyl acetate = 3:1). This compound is unknown. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 8.1

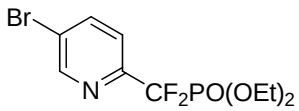
Hz, 1H), 4.24 (m, 4H), 3.91 (s, 3H), 1.35 (t, J = 7.5 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.3 (d, J = 108.8 Hz, 2F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.39 (t, J = 110.2 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 133.7, 132.3 (td, J = 22.1 Hz, 15.5 Hz), 131.3 (td, J = 8.1 Hz, J = 1.5 Hz), , 130.8 (q, J = 4.0 Hz), 130.3, 124.4 (d, J = 1.6 Hz), 117.2 (td, J_{CF} = 265.6 Hz, J_{CP}= 217.5 Hz), 65.1, 65.0, 52.7, 16.3, 16.2. IR (thin film): ν_{max} 1740 cm^{-1}. MS (EI): *m/z* (%) 387 (M^+ - Me), 385 (M^+ - Me), 231, 229, 169 (100), 109. HRMS calcd. for $C_{13}H_{16}BrF_2O_5P$: 399.9887; Found: 399.9882.



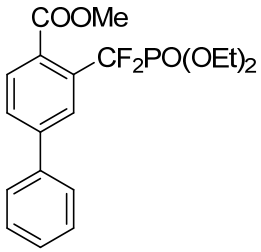
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-5-iodobenzoate (3m). The product (186 mg, 83% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: EtOAc=3:1). This compound is known.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 4.21 (m, 4H), 3.89 (s, 3H), 1.33 (t, J = 7.2 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.8 (d, J = 112.8 Hz, 2F).

2-g-scale synthesis of 3m.

To a stirred suspension of Zn dust (10.3 mmol, 0.672 g) in dioxane (8 mL) was added bromodifluoromethanephosphonate (10.3 mmol, 2.76 g) under N_2. After stirring for 3 h at 60 ^{o}C, the resulting mixture was cooled to room temperature and filtered with a syringe filter. To the filtrate were added CuI (0.1 equiv) and phen (0.2 equiv). The reaction mixture was stirred at same temperature for 30 min, methyl 2,5-diiodobenzoate (5.17 mmol, 2 g) was then added. The reaction was warmed to 60 ^{o}C and stirred for 24h. The reaction mixture was cooled to room temperature, and diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether/ethyl acetate = 3:1) to provide pure product (2.316 g, 70% yield).

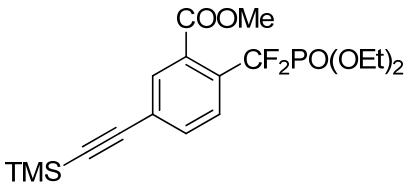


Diethyl (5-bromopyridin-2-yl)difluoromethylphosphonate (3n). The product (101 mg, 59% yield) as a light yellow oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 4.30 (m, 4H), 1.36 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.2 (d, *J* = 106.0 Hz, 2F). ^{31}P NMR (121 MHz, $CDCl_3$) δ 6.01 (t, *J* = 106.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 150.1 (m), 139.8, 123.0, 116.1 (td, J_{CF} = 263.9 Hz, J_{CP} = 212.5 Hz), 65.13, 65.07, 16.34, 16.30. IR (thin film): ν_{max} 1463, 1274, 1021 cm^{-1}. MS (EI): *m/z* (%) 345 (M^+), 343 (M^+), 288, 286, 208, 206, 109 (100). HRMS calcd. for $C_{10}H_{13}F_2O_3PNBr$: 342.9784; Found: 342.9782.



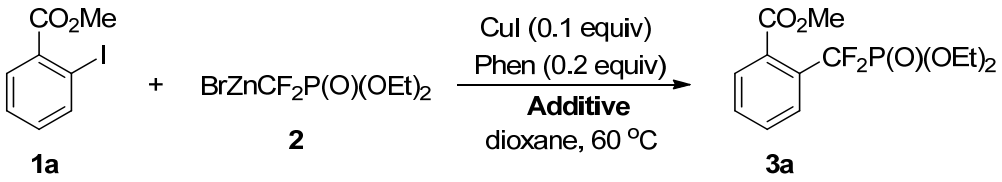
Methyl-3-((diethoxyphosphoryl)difluoromethyl)biphenyl-4-carboxylate 7. To a solution of $Pd_2(dba)_3$ (23 mg, 0.025 mmol), SPhos (20.5 mg, 0.05 mmol) in dioxane (1 mL) was added a solution of methyl 4-chloro-2-((diethoxyphosphoryl) difluoromethyl)benzoate **3k** (89 mg, 0.25 mmol) in dioxane (1 mL). After stirring for 10 min, K_3PO_4 (159 mg, 0.75 mmol) and $PhB(OH)_2$ (45.8 mg, 0.375 mmol) were added. The resulting mixture was heated to 100 °C and stirred for 15 hours. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The product (92 mg, 92% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether/EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.62 (m, 3H), 7.50-7.41 (m, 3H), 4.24 (m, 4H), 3.94 (s, 3H), 1.34 (t, *J* = 6.9 Hz, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -101.9 (d, *J* = 112.8 Hz, 2F). ^{31}P NMR (161MHz, $CDCl_3$) δ 5.84 (t, *J* = 111.4 Hz). ^{13}CNMR (75 MHz,

$CDCl_3$) δ 168.5, 143.0, 138.8, 130.8 (td, J_{CF} = 21.6 Hz, J_{CP} = 15.2 Hz), 130.5 (q, J = 3.5 Hz), 130.4, 129.3, 128.9, 128.3, 127.1, 127.0 (m), 126.8, 118.0 (td, J_{CF} = 265.5 Hz, J_{CP} = 216.7 Hz), 64.9, 64.8, 52.5, 16.24, 16.17. IR (thin film): ν_{max} 1738 cm^{-1}. MS (EI): *m/z* (%) 398 (M^+), 261, 227 (100). HRMS calcd. for $C_{19}H_{21}F_2O_5P$: 398.1095. Found: 398.1098.



Methyl-2-((diethoxyphosphoryl)difluoromethyl)-5-((trimethylsilyl)ethynyl)benzoate 8. To a solution of $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (3.6 mg, 0.02 mmol) in TEA (1 mL) was added **3m** (9 0mg, 0.2 mmol) and ethynyltrimethylsilane (50 mg, 0.4 mmol). After stirring for 6 h at room temperature, the reaction mixture was concentrated. The residue was purified with silica gel chromatography (Petroleum ether: EtOAc=5:1) to give **8** (78 mg, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 1H), 7.59 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H) , 4.19 (m，4H), 3.88 (s，3H), 1.30 (t, J = 7.2，6H), 0.22 (s，9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -102.7 (d, J = 110.8 Hz, 2F). ^{31}P NMR (161 MHz, $CDCl_3$) δ 5.45 (t, J = 110.9 Hz) .^{13}CNMR (100 MHz, $CDCl_3$) δ 167.8, 133.0, 132.1 (m), 132.0, 129.7 (td, J_{CF} = 21.9 Hz, J_{CP} = 15.3 Hz), 128.5 (t, J = 7.3 Hz), 126.0, 117.9 (td, J_{CF} = 264.2 Hz, J_{CP}= 215.2 Hz), 102.6, 98.0, 65.0, 64.9, 52.7, 16.3, 16.2, 0.3. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 133.0, 132.1 (q, J = 3 Hz), 131.9, 129.7 (td, J_{CF} = 21.9 Hz, J_{CP} = 15.3 Hz), 128.5 (t, J = 7.3 Hz), 126.0, 117.8 (td, J_{CF} = 264.2 Hz, J_{CP}= 215.2 Hz), 102.6, 98.0, 65.0, 64.9, 52.7, 16.3, 16.2, -0.3. IR (thin film): ν_{max} 2160, 1743 cm^{-1}. MS (EI): *m/z* (%) 418 (M^+), 403, 281, 247 (100). HRMS calcd. for $C_{18}H_{25}F_2O_5PSi$: 418.1177. Found:418.1181.

Effects of Additives on Copper-Catalyzed Cross-Coupling of Iodobenzoate with Bromozinc-difluorophosphonate.



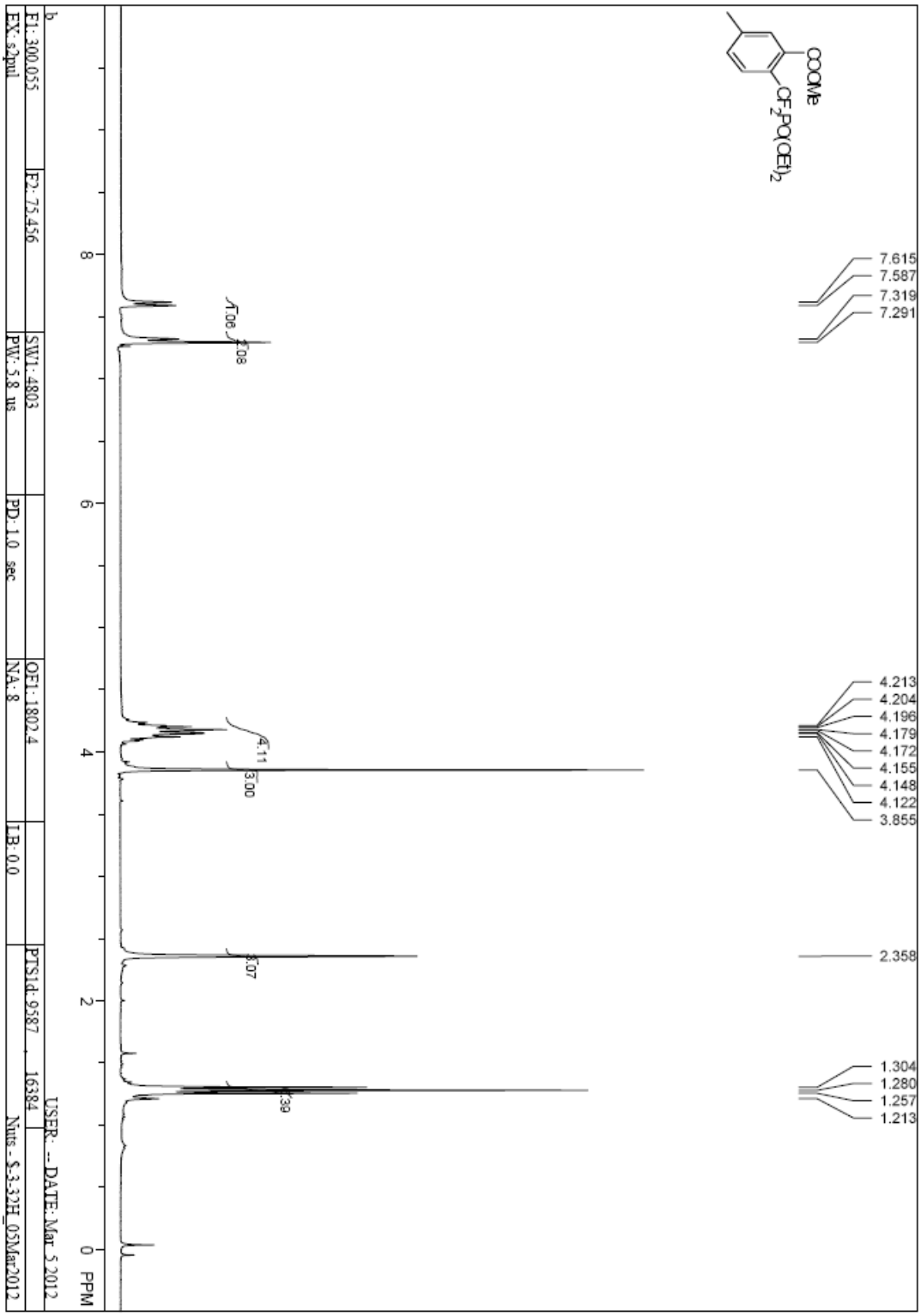
To a stirred suspension of Zn dust (1.0 mmol) in dioxane (2 mL) was added bromodifluoromethanephosphonate (1.0 mmol) under N_2. After stirring for 3 h at 60 ^oC, the resulting mixture was cooled to room temperature. CuI (0.1 equiv) and phen (0.2 equiv) were added. The reaction mixture was stirred at same temperature for 30 min, iodobenzoate **1** (0.5 mmol) and additive (0.2 -1.0 equiv) were then added. The reaction was warmed to 60 ^oC and stirred for 24h. The reaction mixture was cooled to room temperature. The yield was determined by ^{19}F NMR before working up.

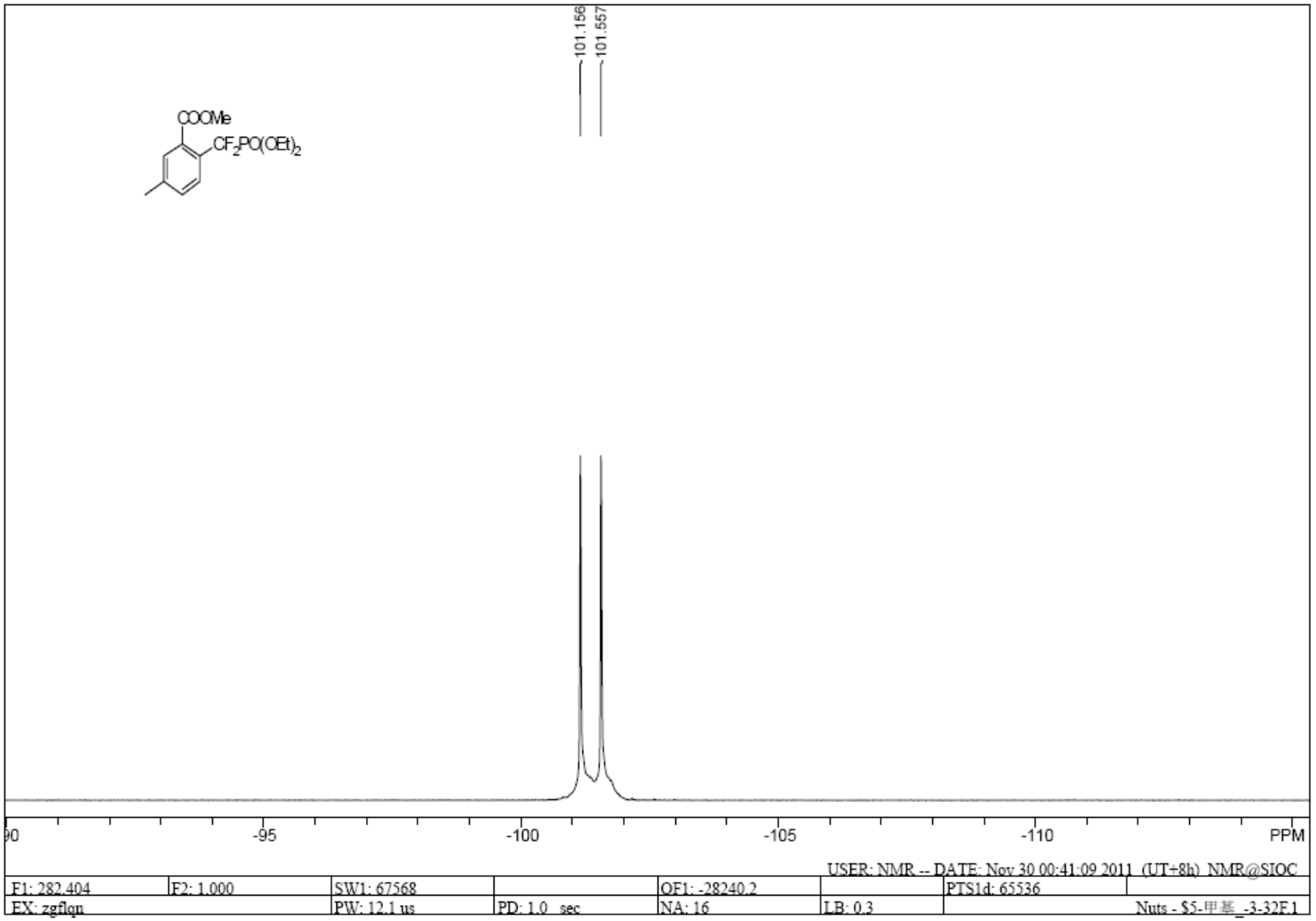
References:

(1) Yokomatsu, T.; Murano, T.; Suemune, K.; Shibuya, S. *Tetrahedron.* **1997**, *53*, 815.

(2) Shakespeare, W. C.; Bohacek, R. S.; Narula, S. S.; Azimioara, M. D.; Yuan, R. W.; Dalgarno, D. C.; Madden, L.; Botfield, M. C.; Holt, D. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3109.

Methyl 2-((diethoxyphosphoryl)difluoromethyl)-5-methylbenzoate (3b)

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-110
PPM
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LB: 0.3
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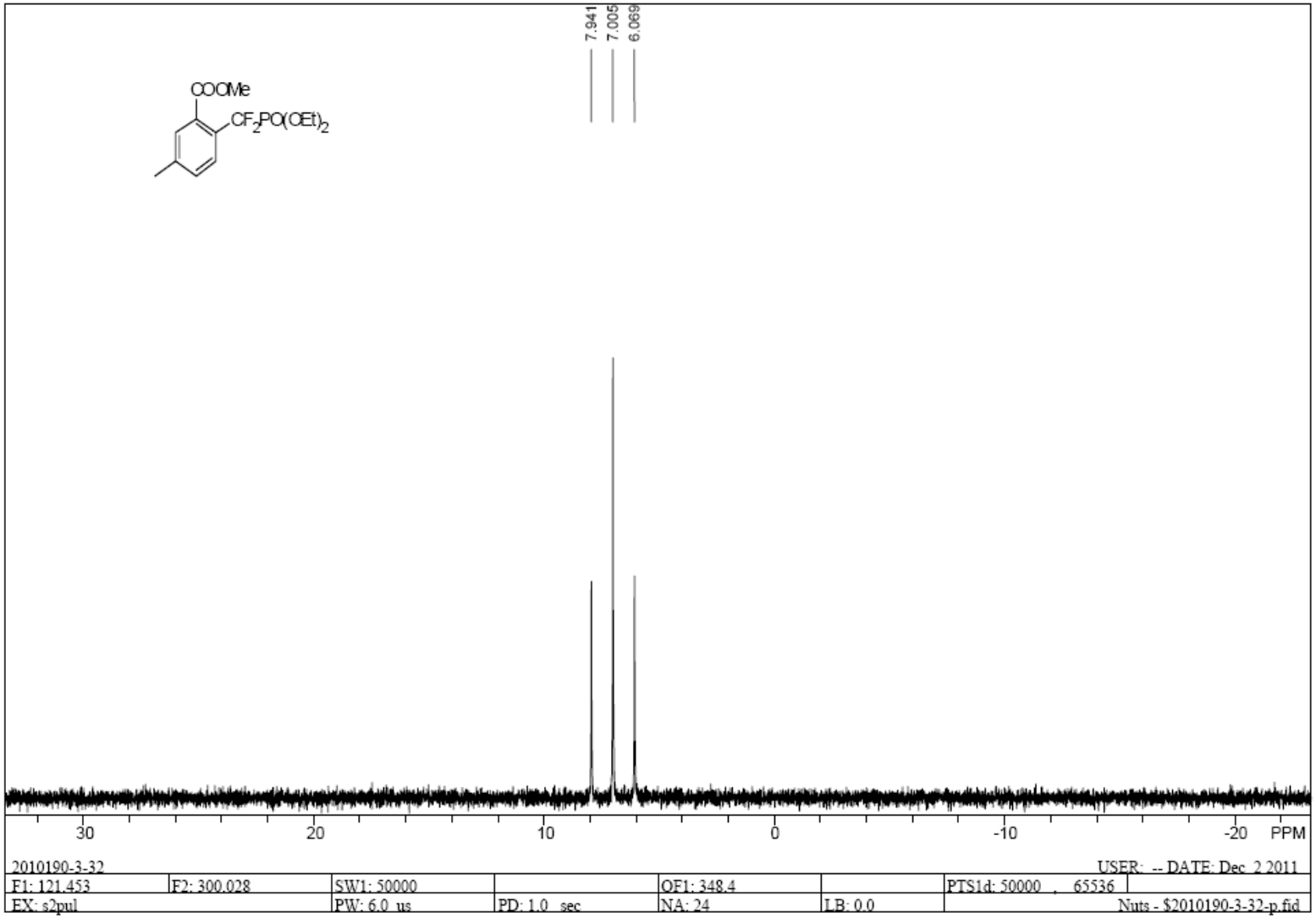
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2010190-3-32
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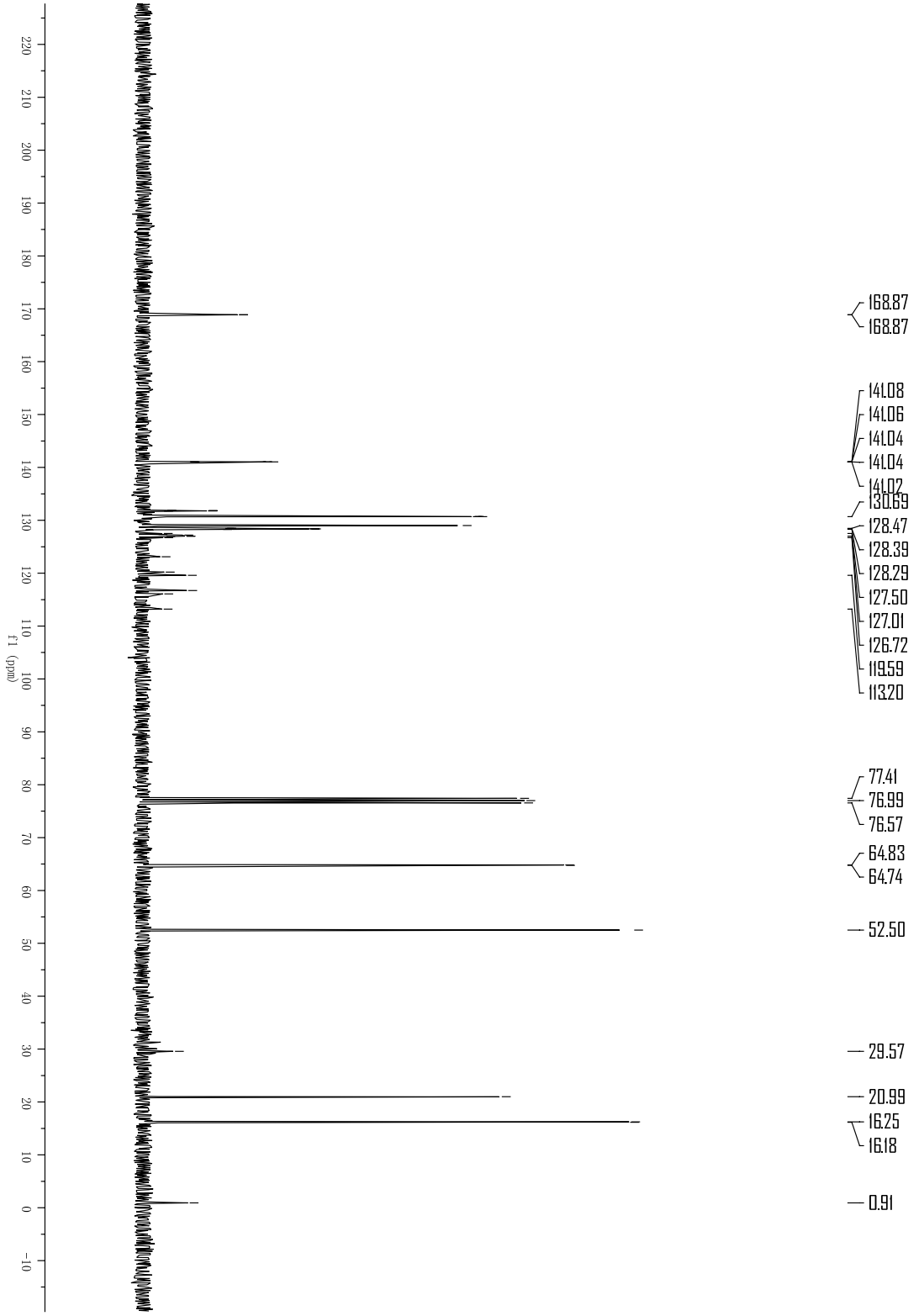
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30
20
10
0
−10
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168.87
141.08
141.06
141.04
141.04
141.02
130.69
128.47
128.39
128.29
127.50
127.01
126.72
119.59
113.20
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76.99
76.57
64.83
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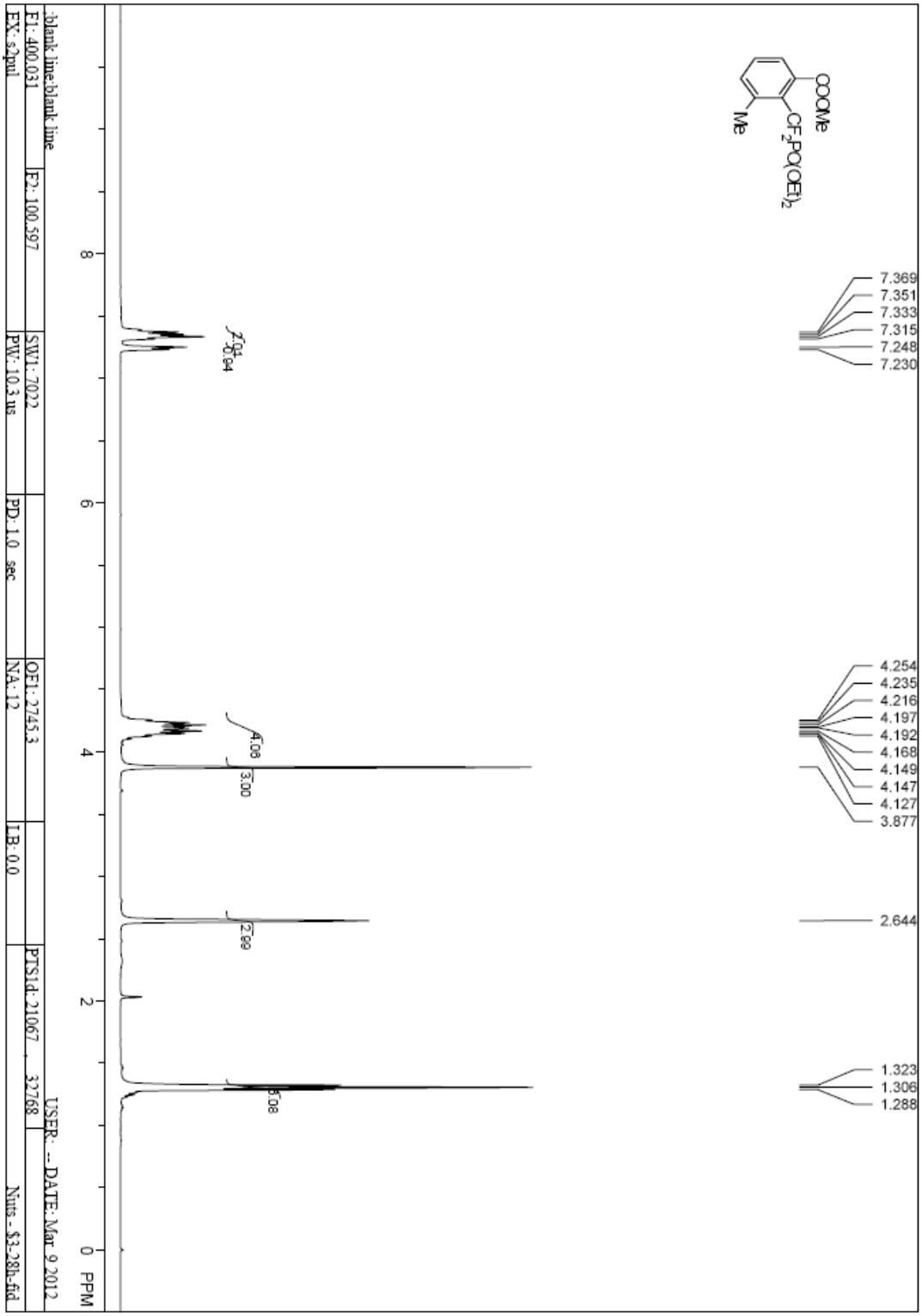
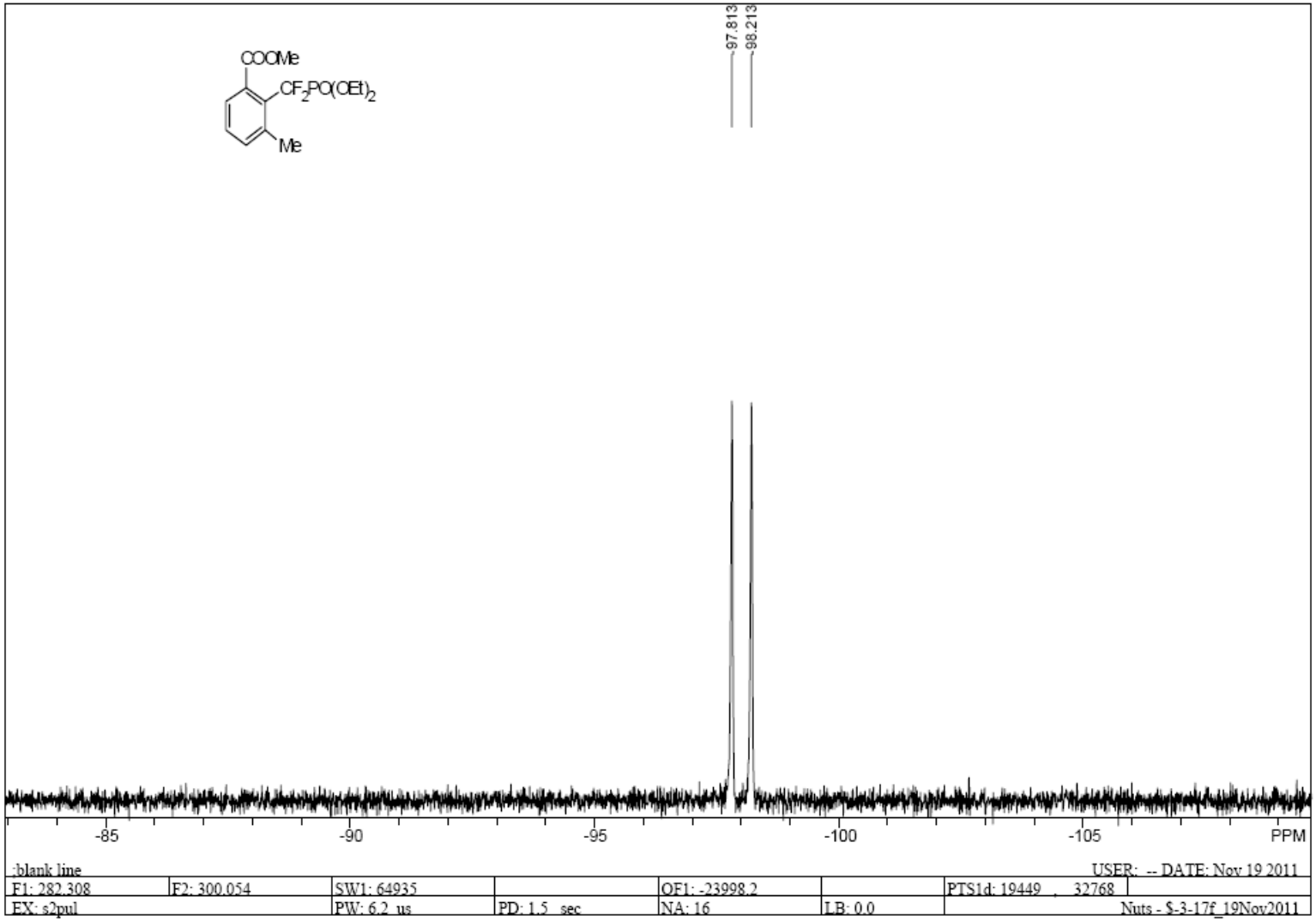
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-3-methylbenzoate (3c)

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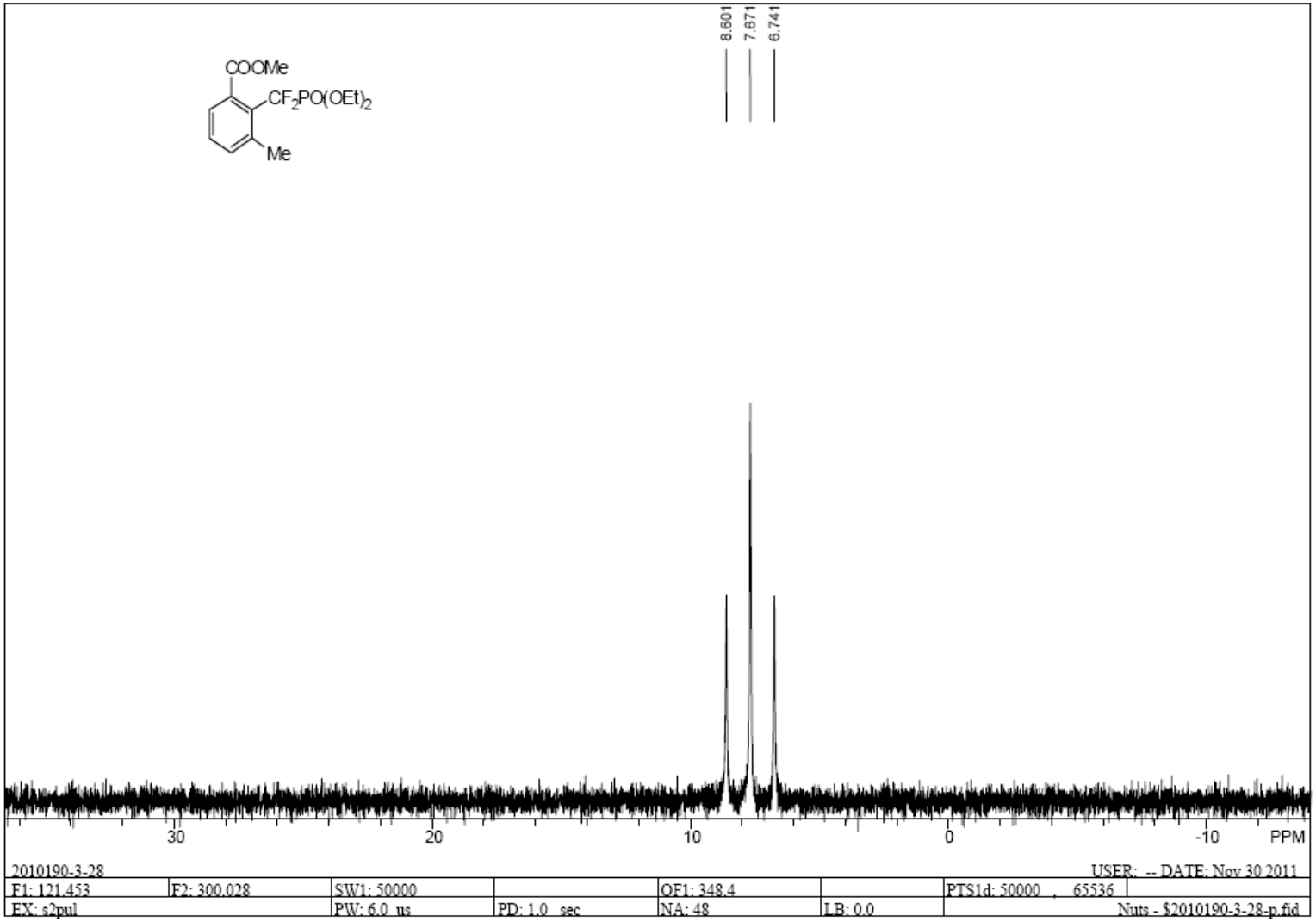
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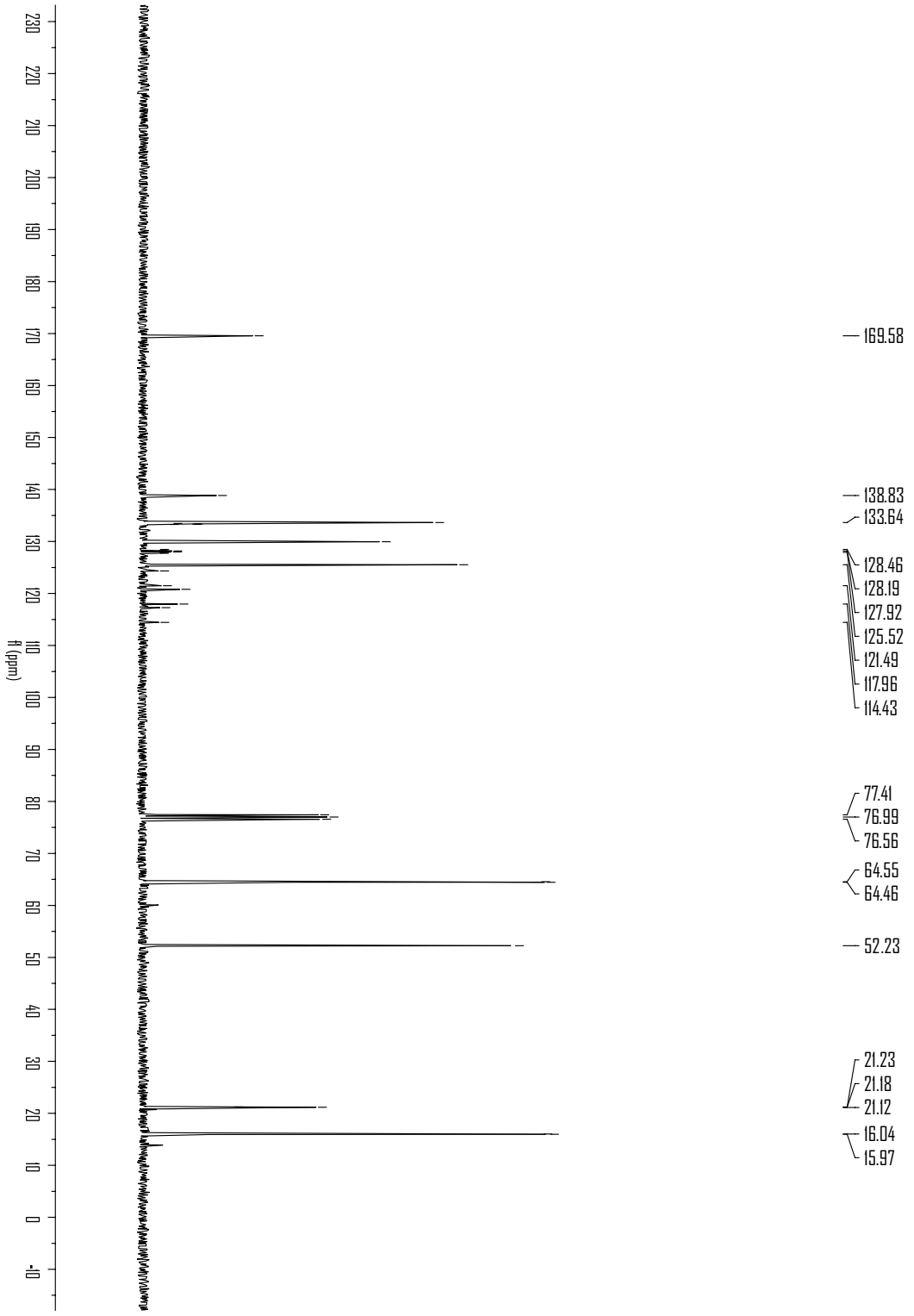
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64.55
64.46
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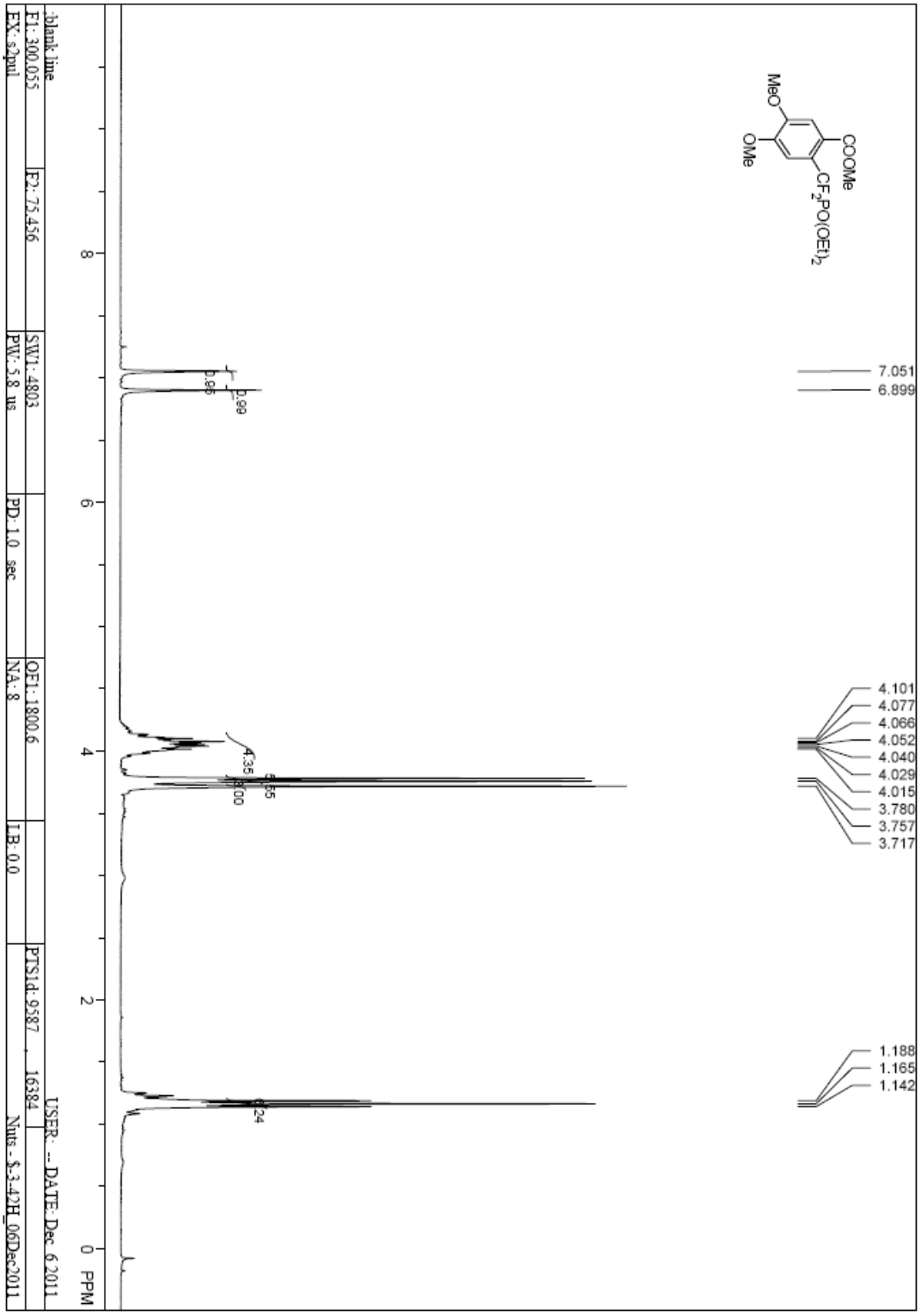
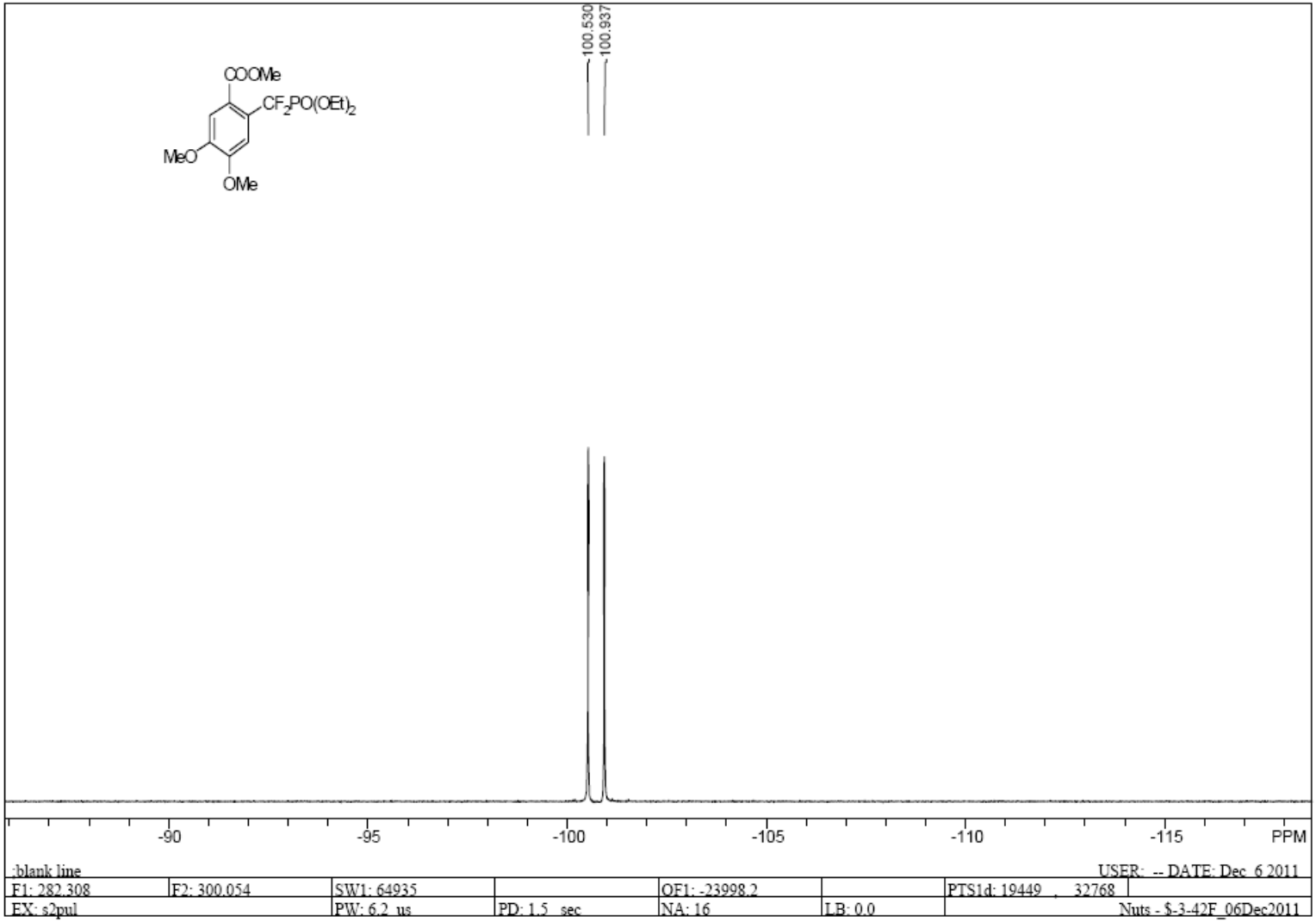
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4,5-dimethoxybenzoate (3d).

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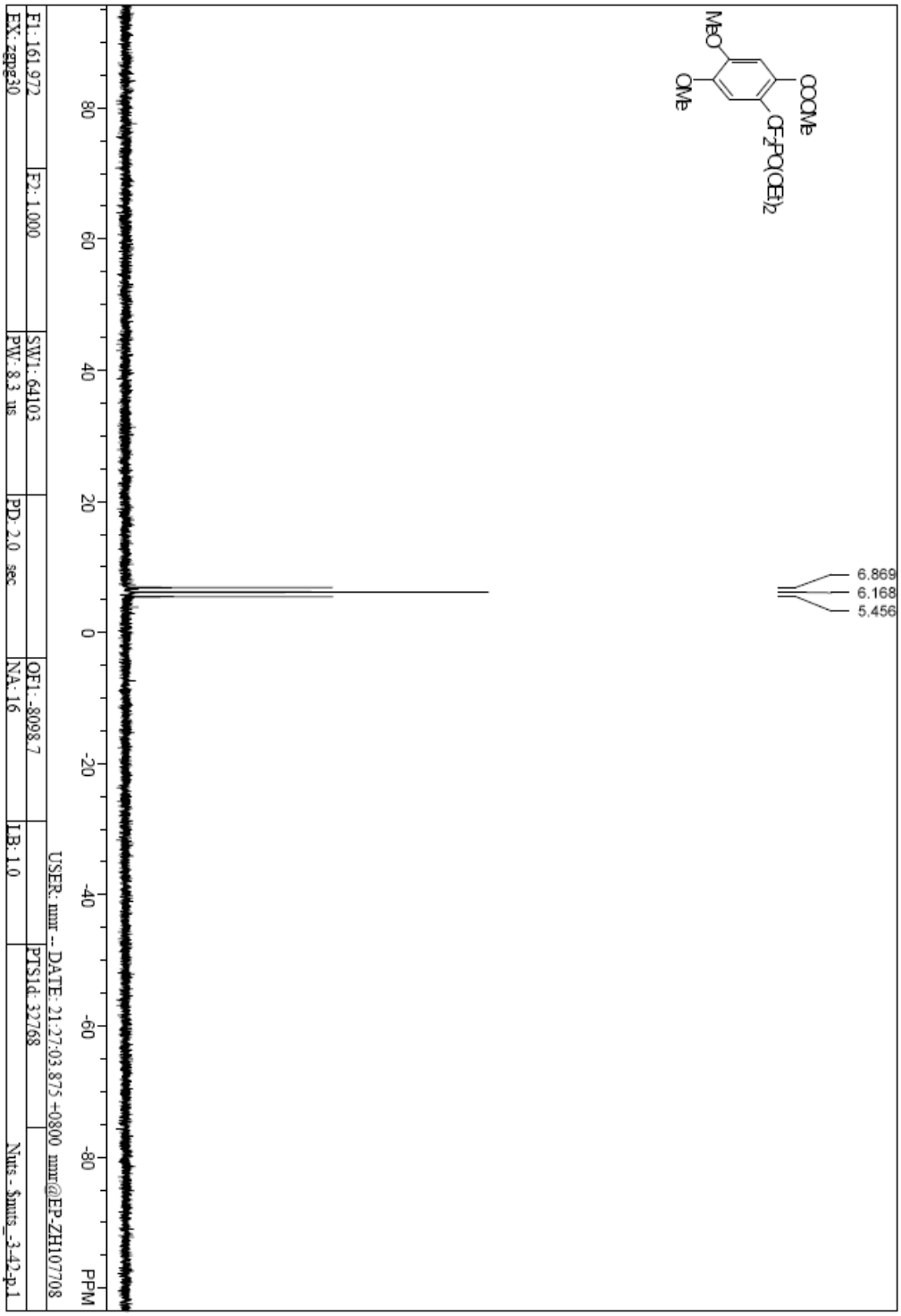
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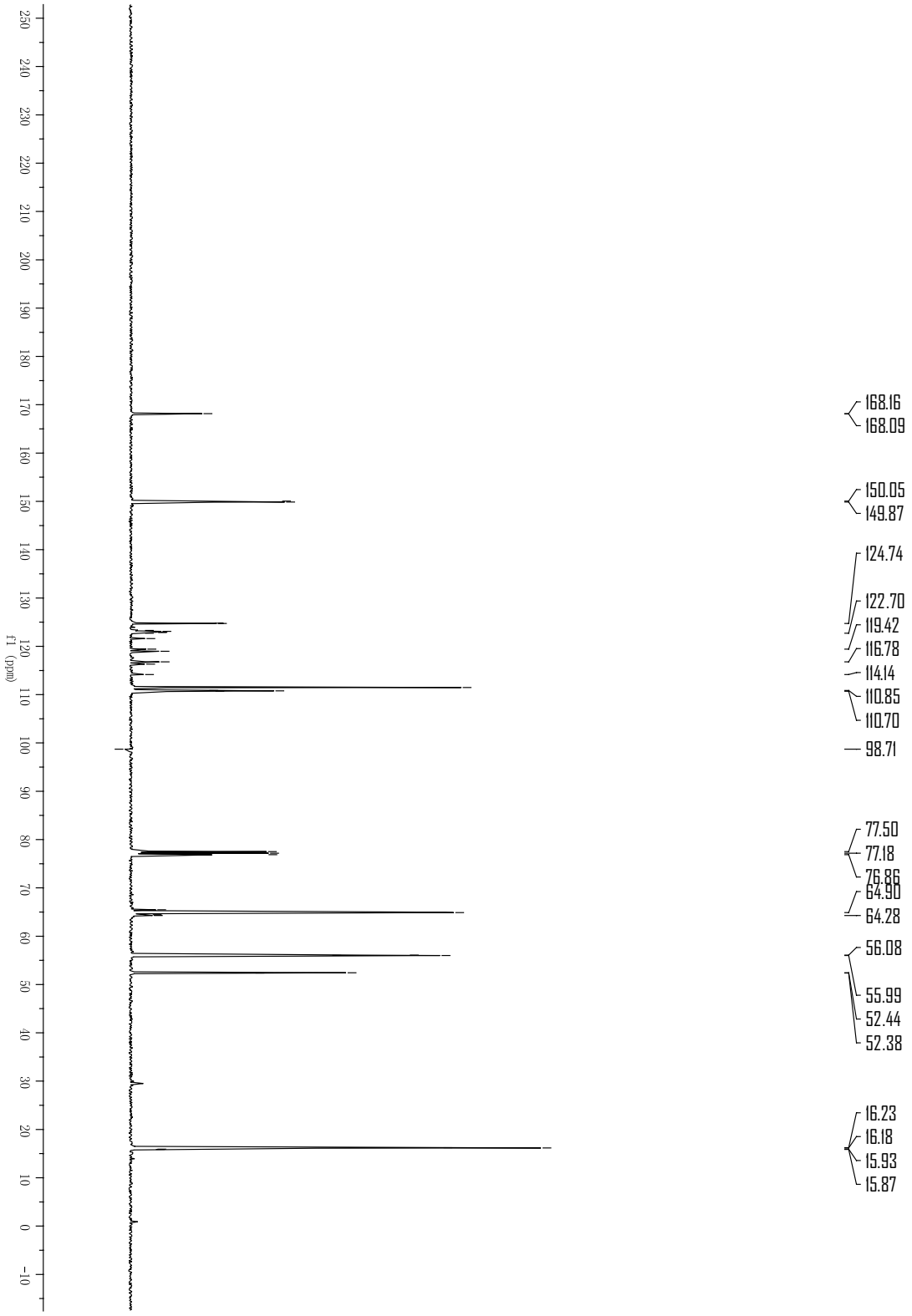
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149.87
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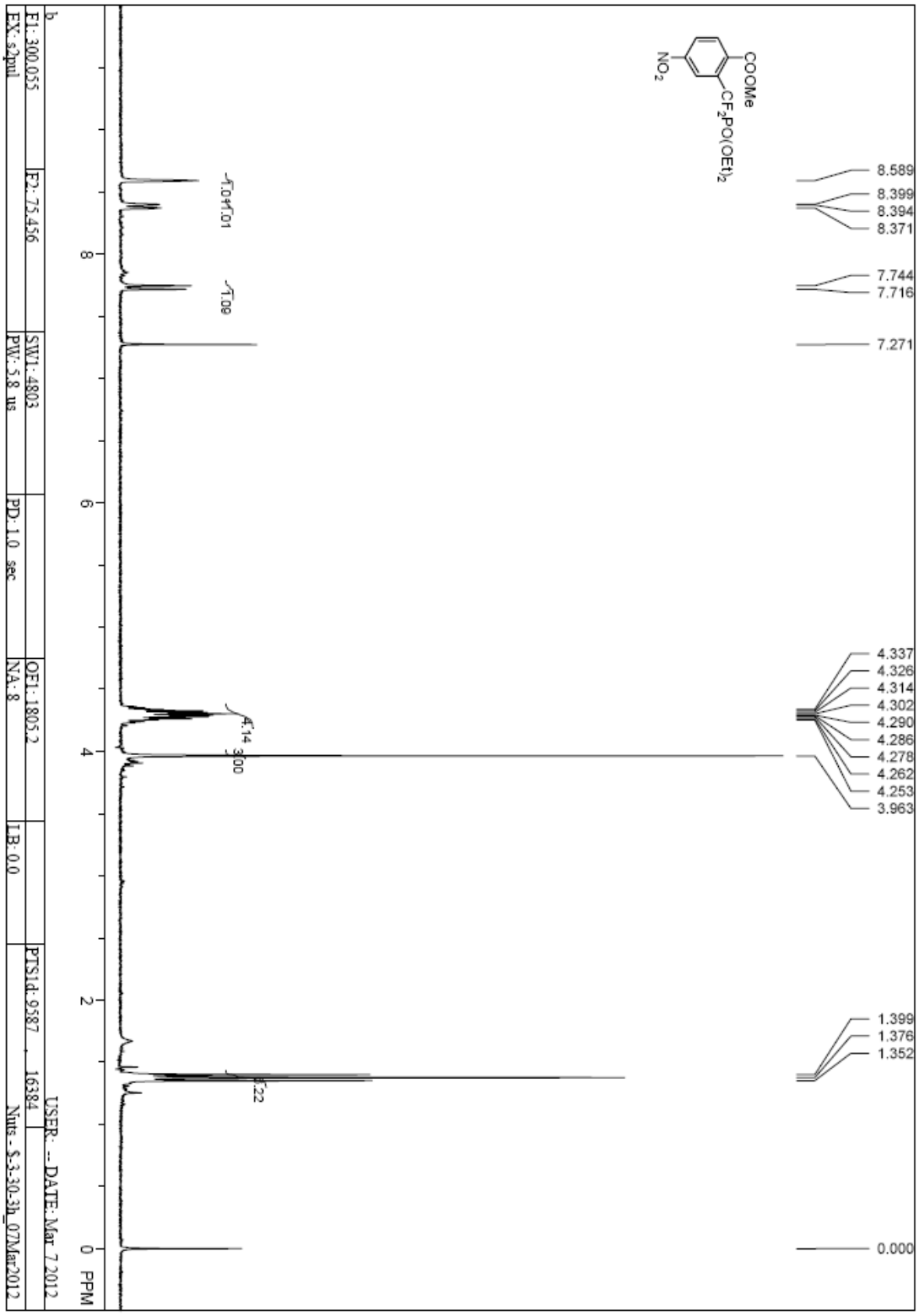
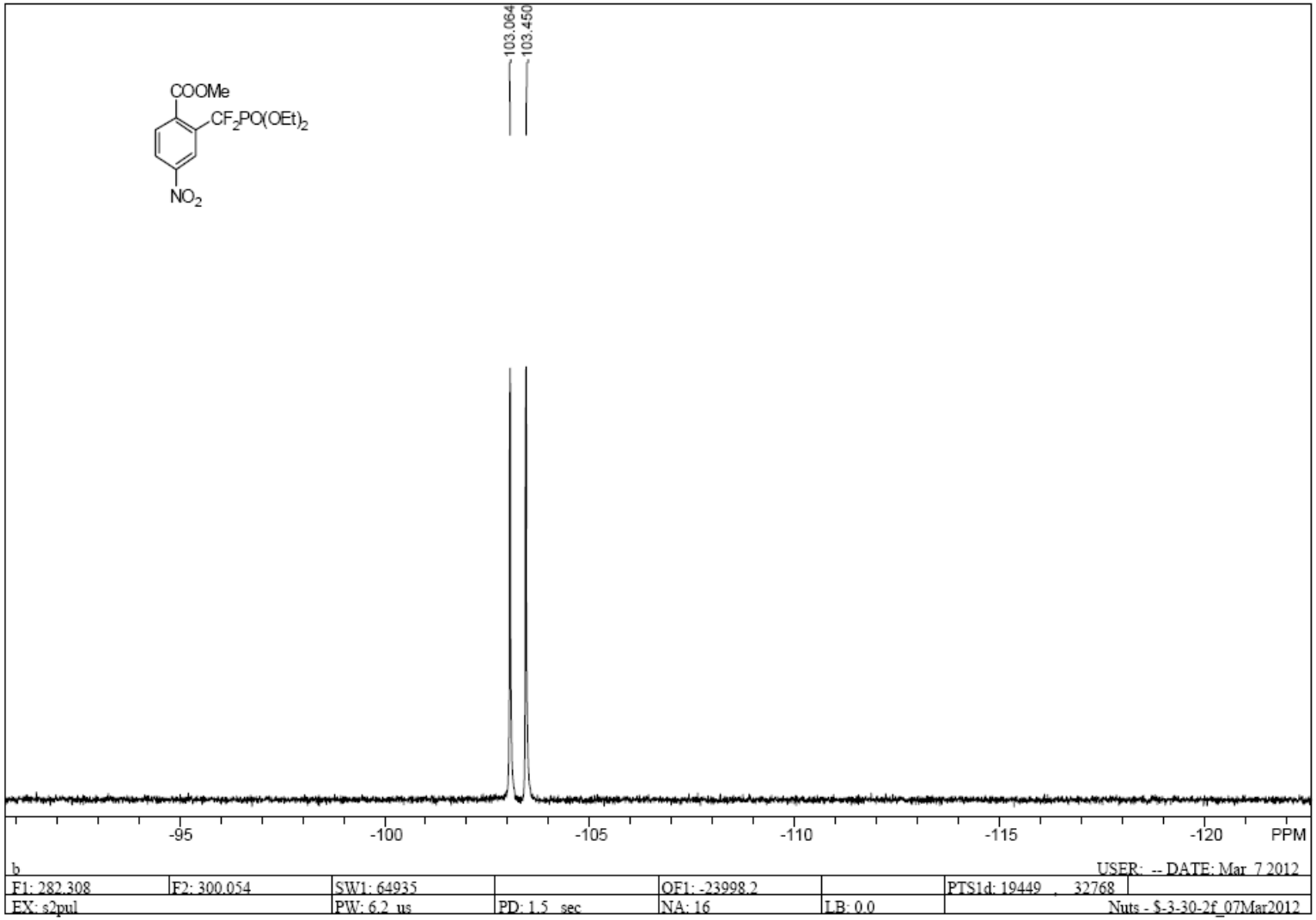
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-nitrobenzoate (3e).

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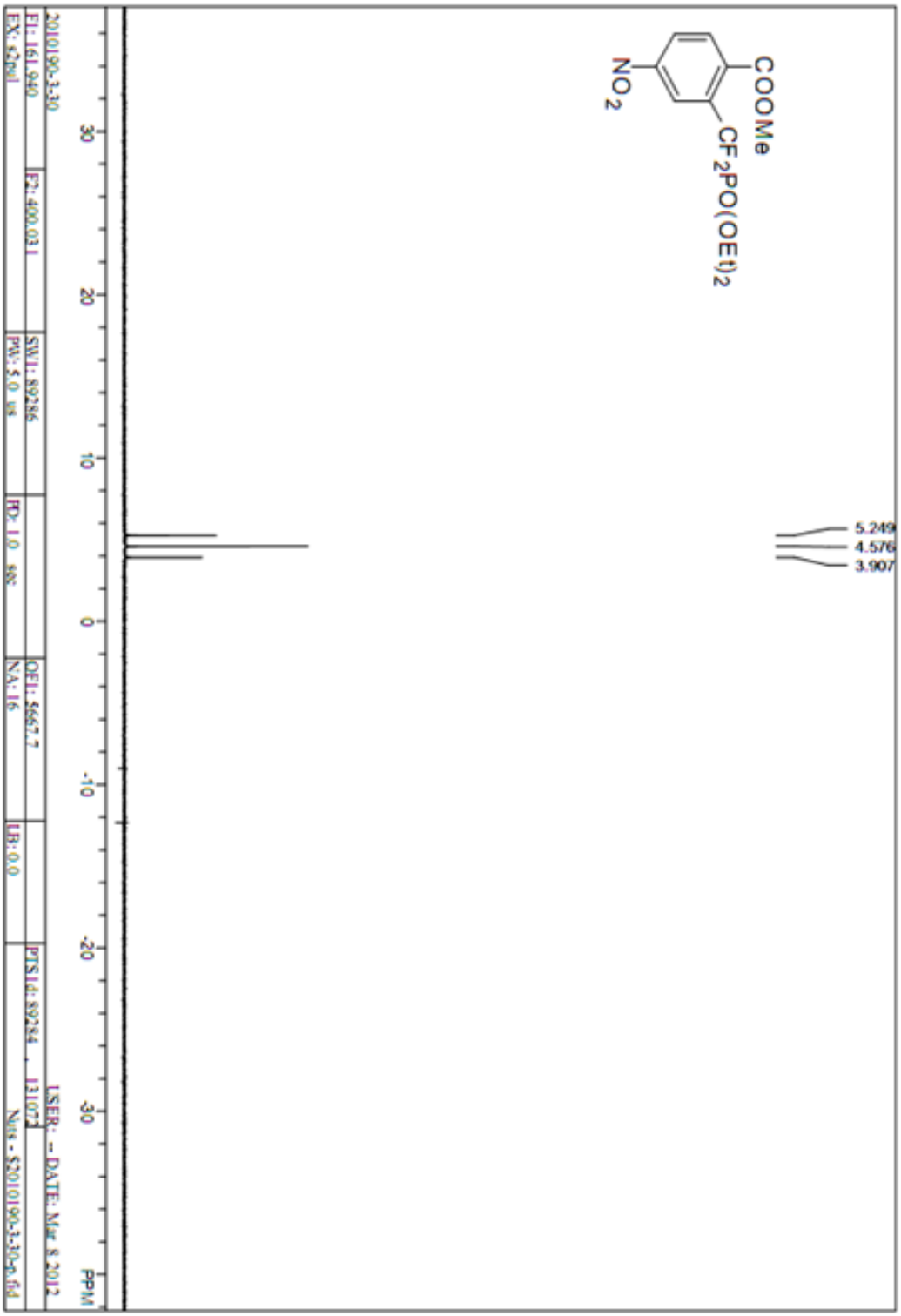
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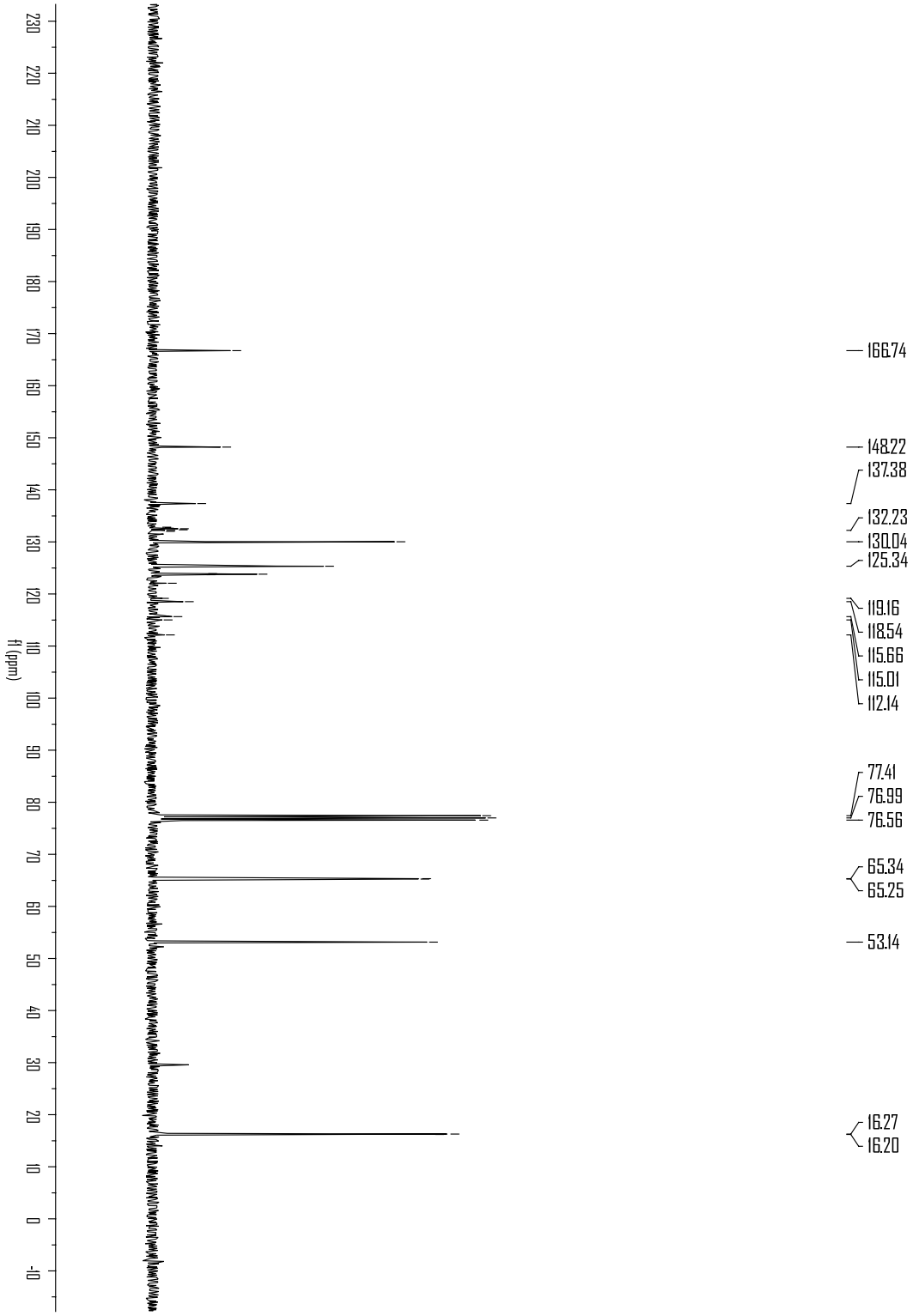
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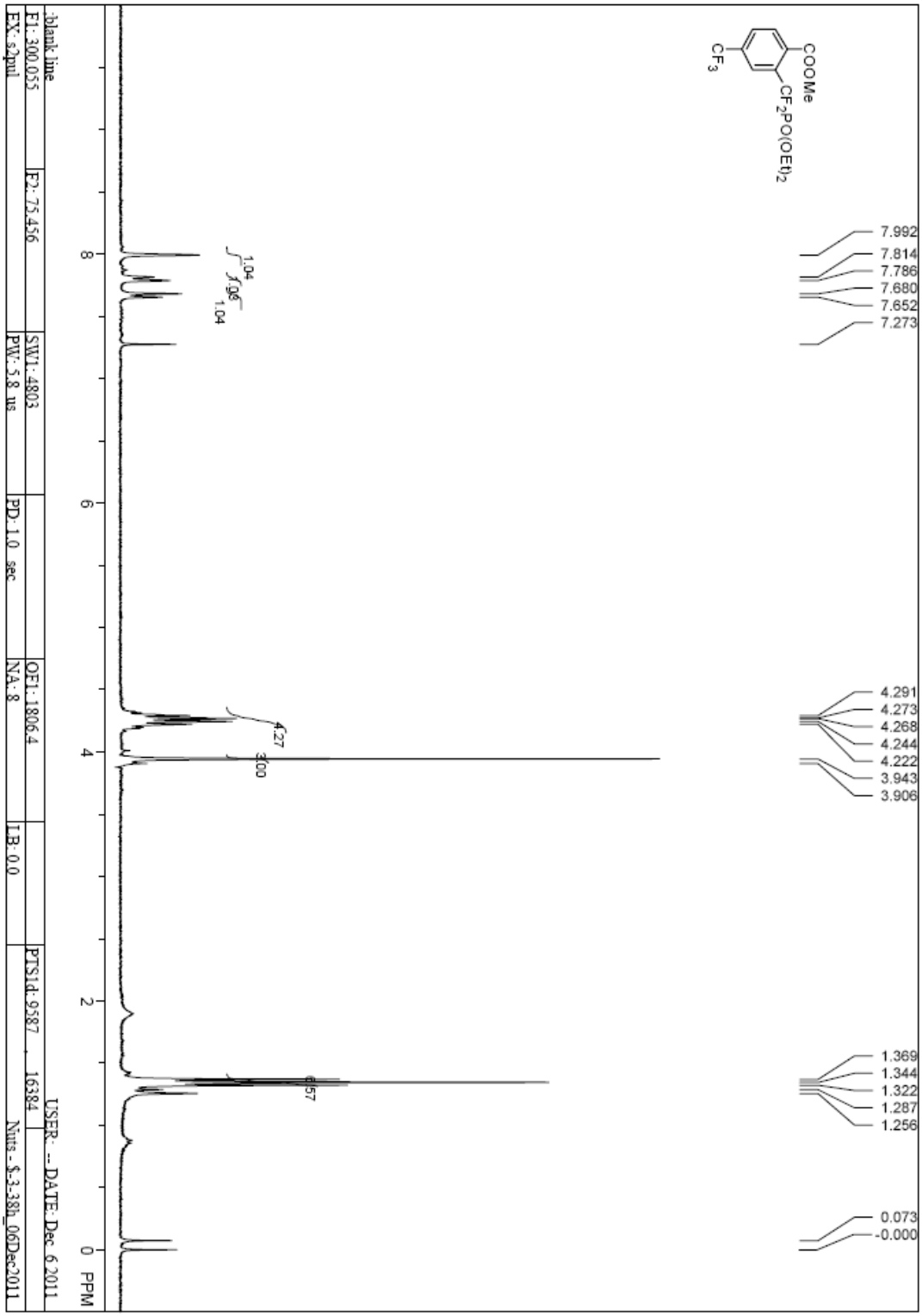
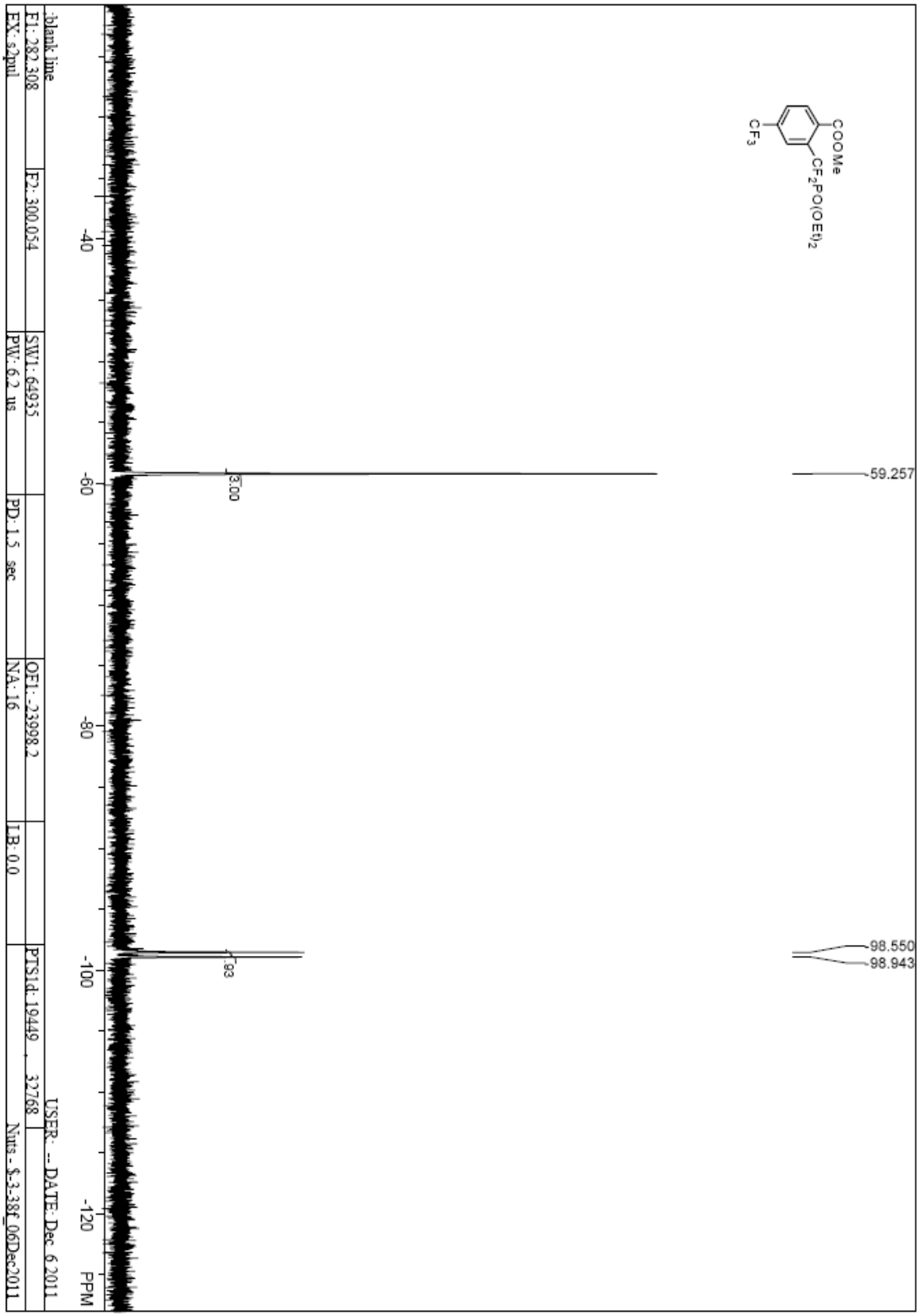
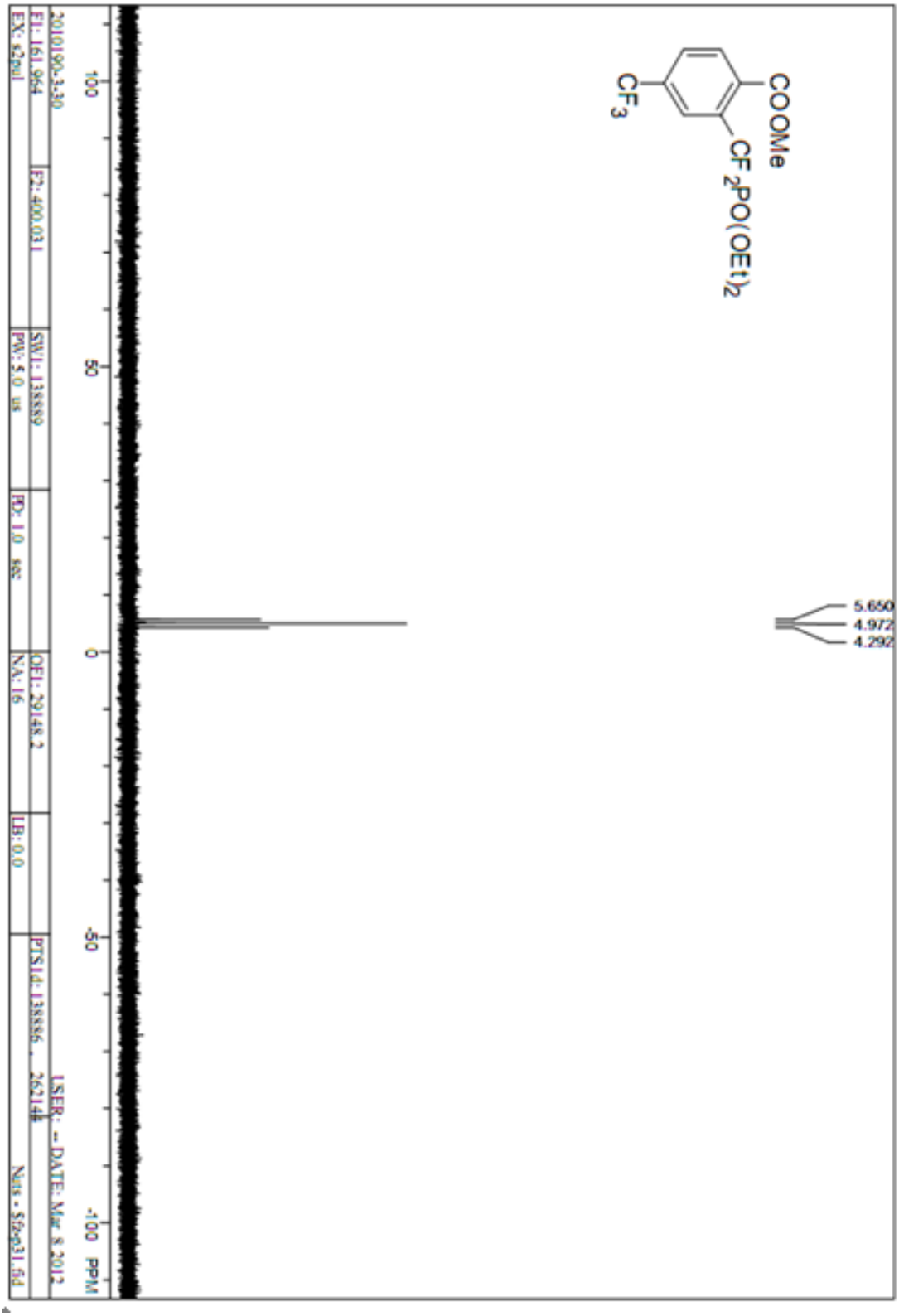
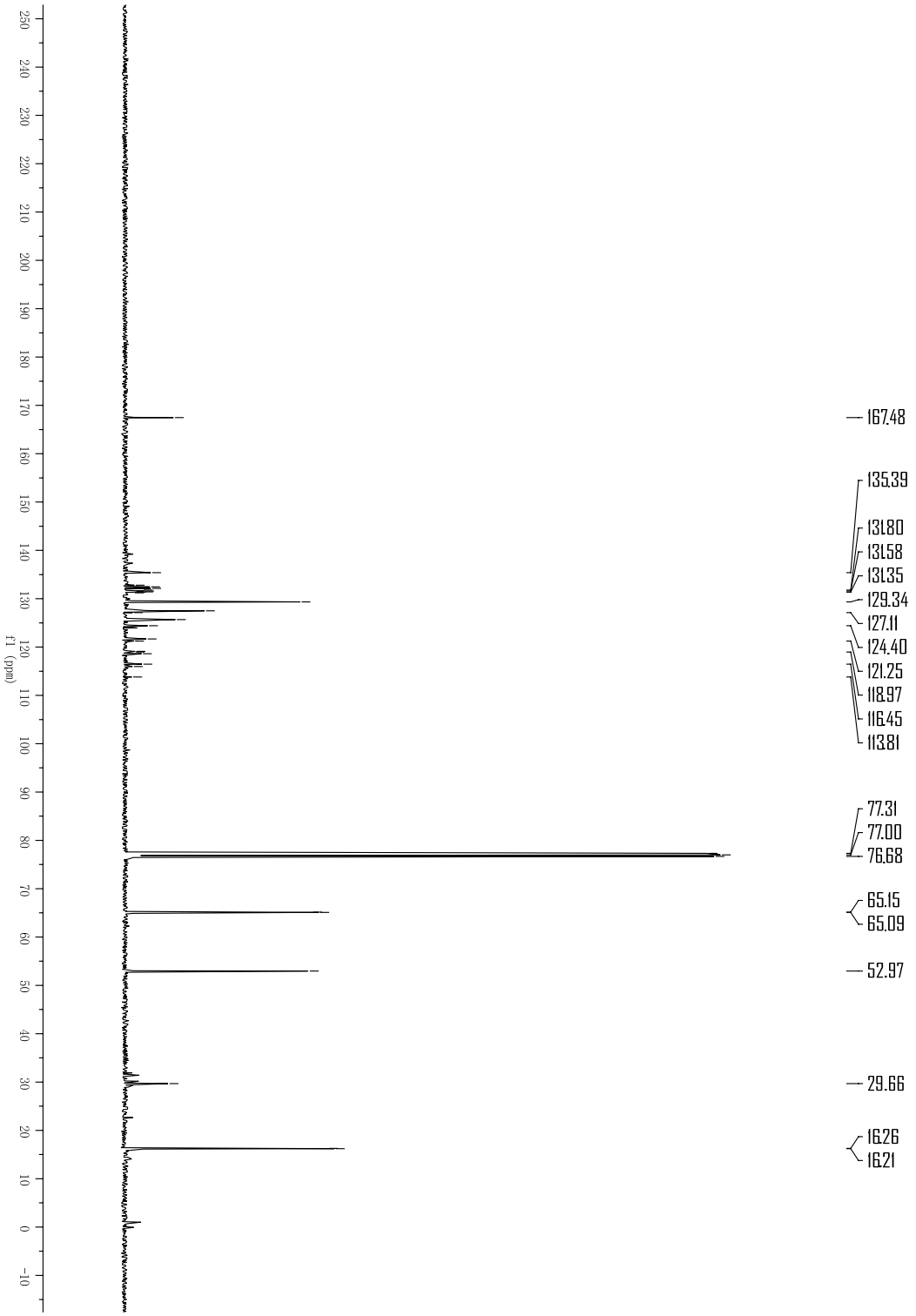
166.74
148.22
137.38
132.23
130.04
125.34
119.16
118.54
115.66
115.01
112.14
77.41
76.99
76.56
65.34
65.25
53.14
16.27
16.20

Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-(trifluoromethyl)benzoate (3f).

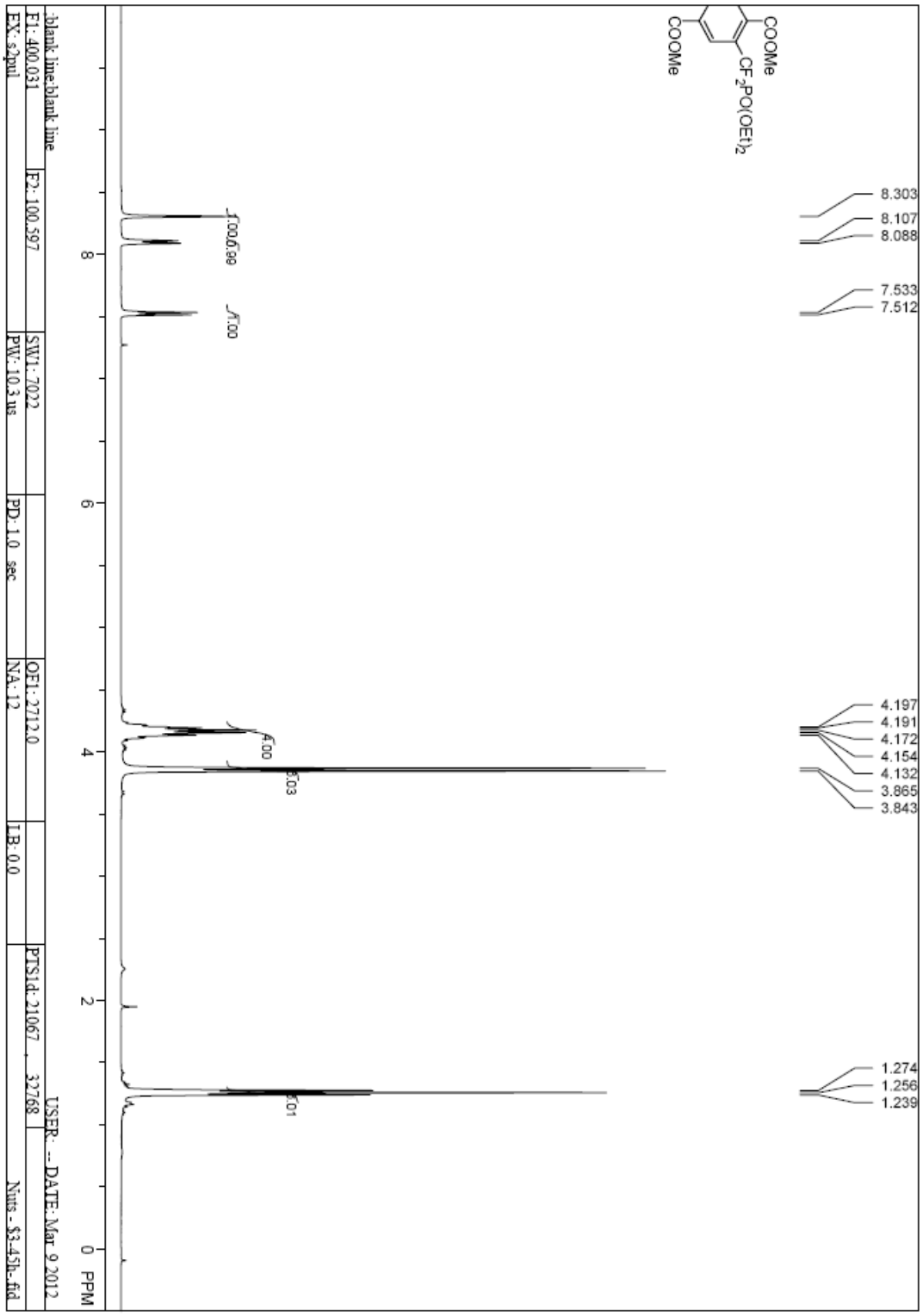


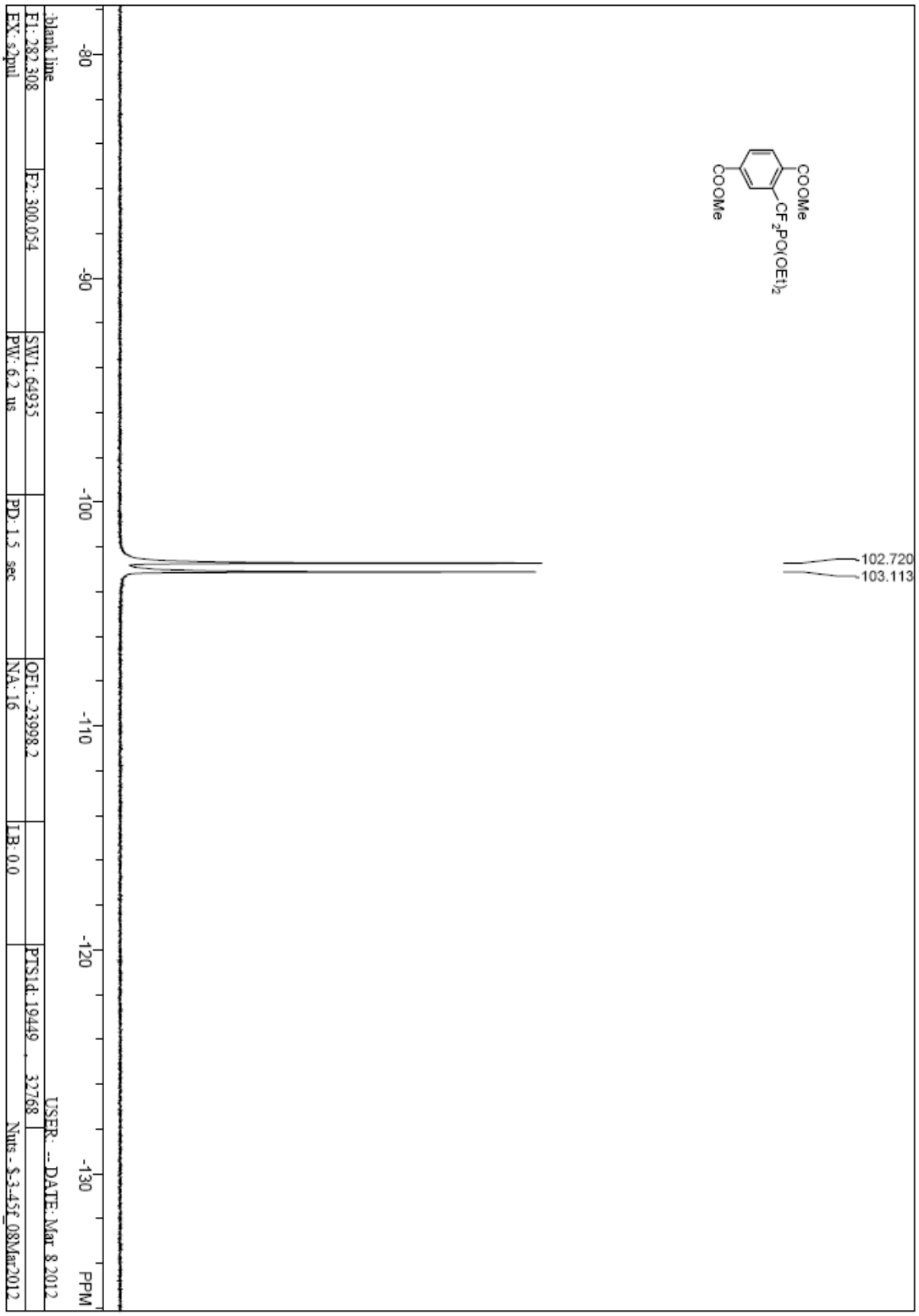

COOMe
CF2PO(OEt)2
CF3
59.257
98.550
98.943
3.00
1.93
-40
-60
-80
-100
-120
PPM
blank line
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
USER: -- DATE: Dec 6 2011
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-38f_06Dec2011

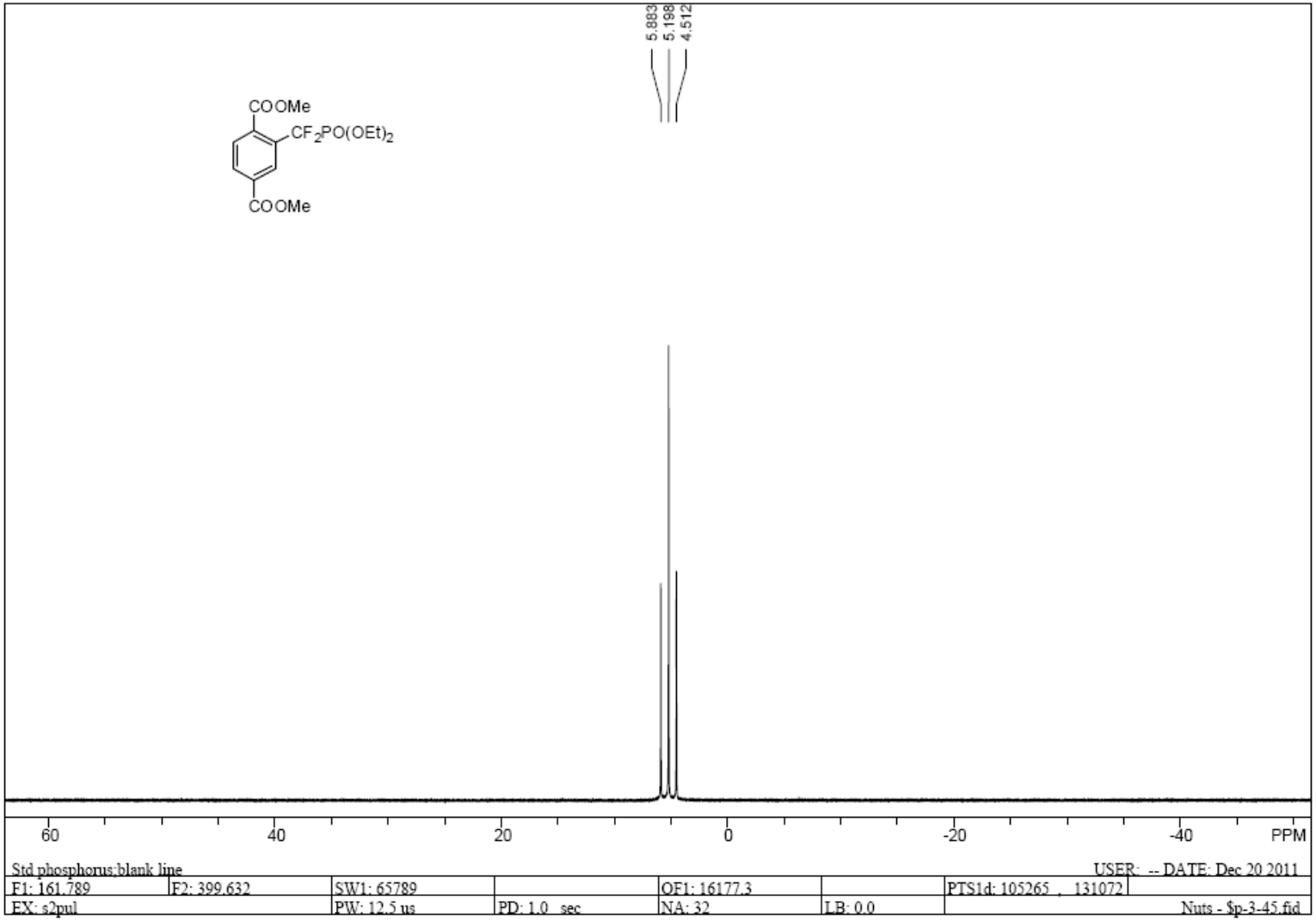

COOMe
CF2PO(OEt)2
CF3
5.650
4.972
4.292
100
50
0
-50
-100
PPM
20100190-3-30
F1: 161.964
F2: 400.031
EX: s2pul
SW1: 13888.9
PW: 5.0 us
RD: 1.0 sec
OE1: 29148.2
NA: 16
LB: 0.0
PTS1d: 13886
26214
LSER: -- DATE: Mar 8 2012
Nuts - S6p31.fid

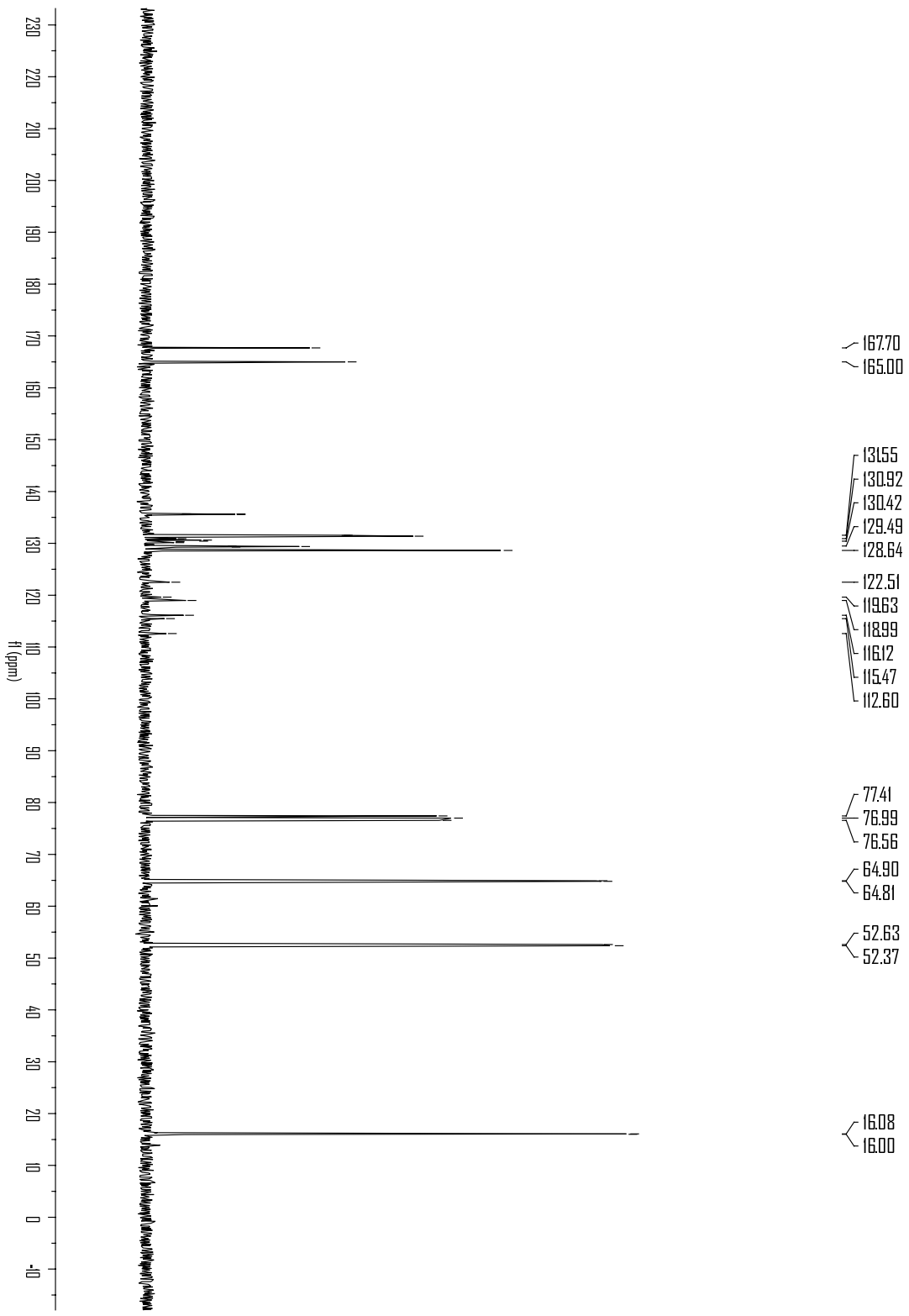

167.48
135.39
131.80
131.58
131.35
129.34
127.11
124.40
121.25
118.97
116.45
113.81
77.31
77.00
76.68
65.15
65.09
52.97
29.66
16.26
16.21
f1 (ppm)

Dimethyl 2-((diethoxyphosphoryl)difluoromethyl)terephthalate (3g).

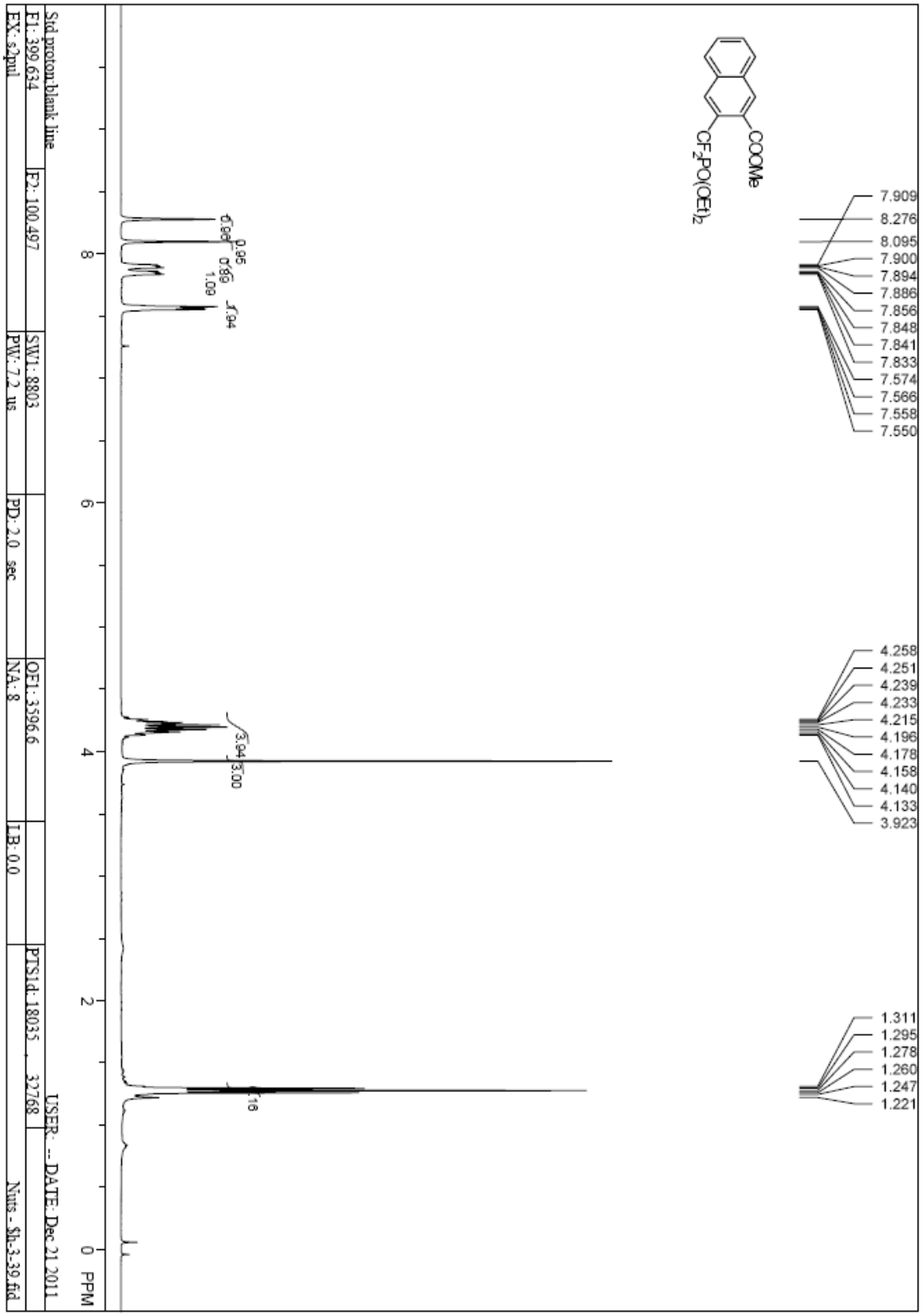


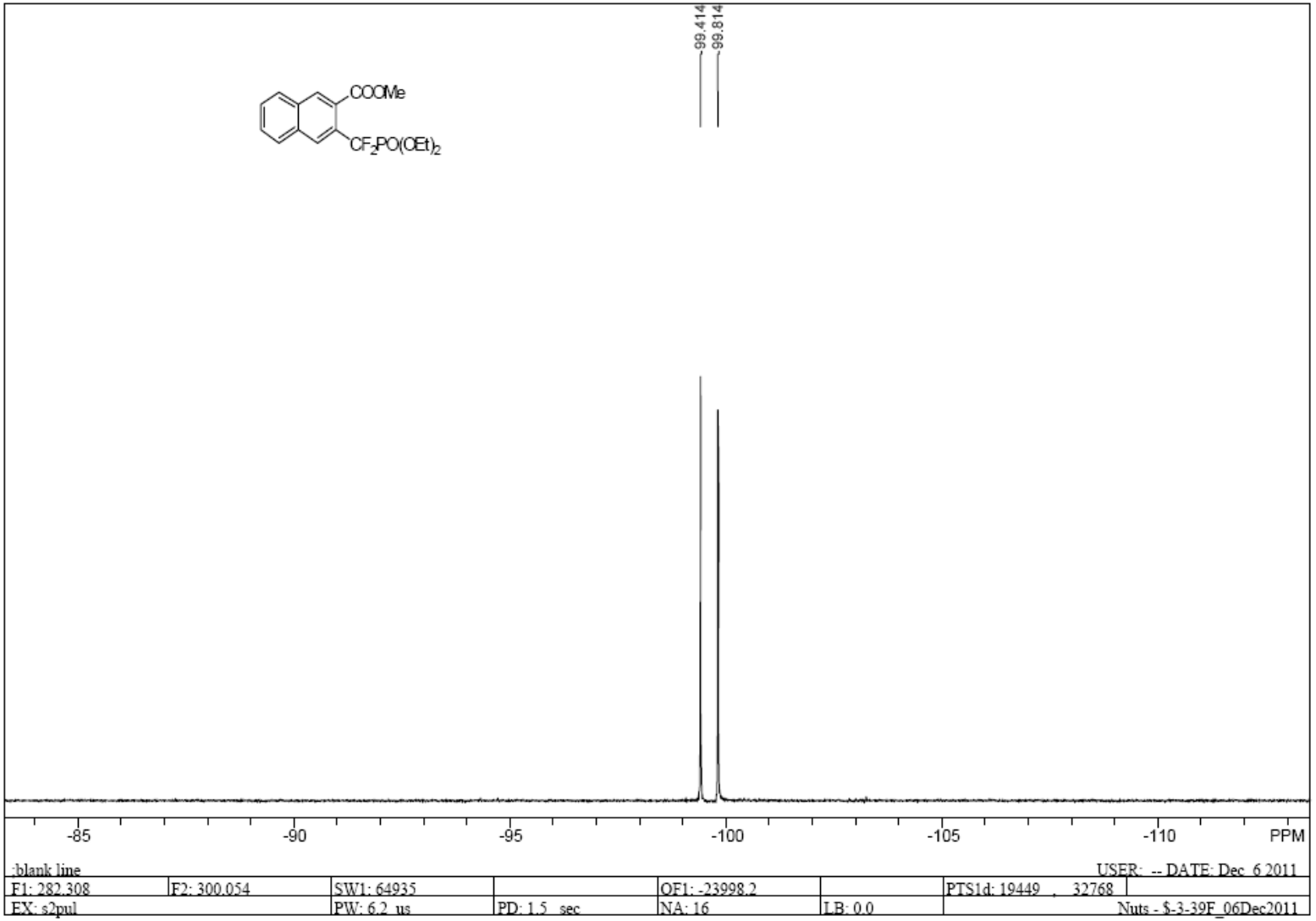

COOMe
CF2PO(OEt)2
COOMe
102.720
103.113
-80
-90
-100
-110
-120
-130
PPM
blank line
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
USER: -- DATE: Mar 8 2012
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-345f_08Mar2012

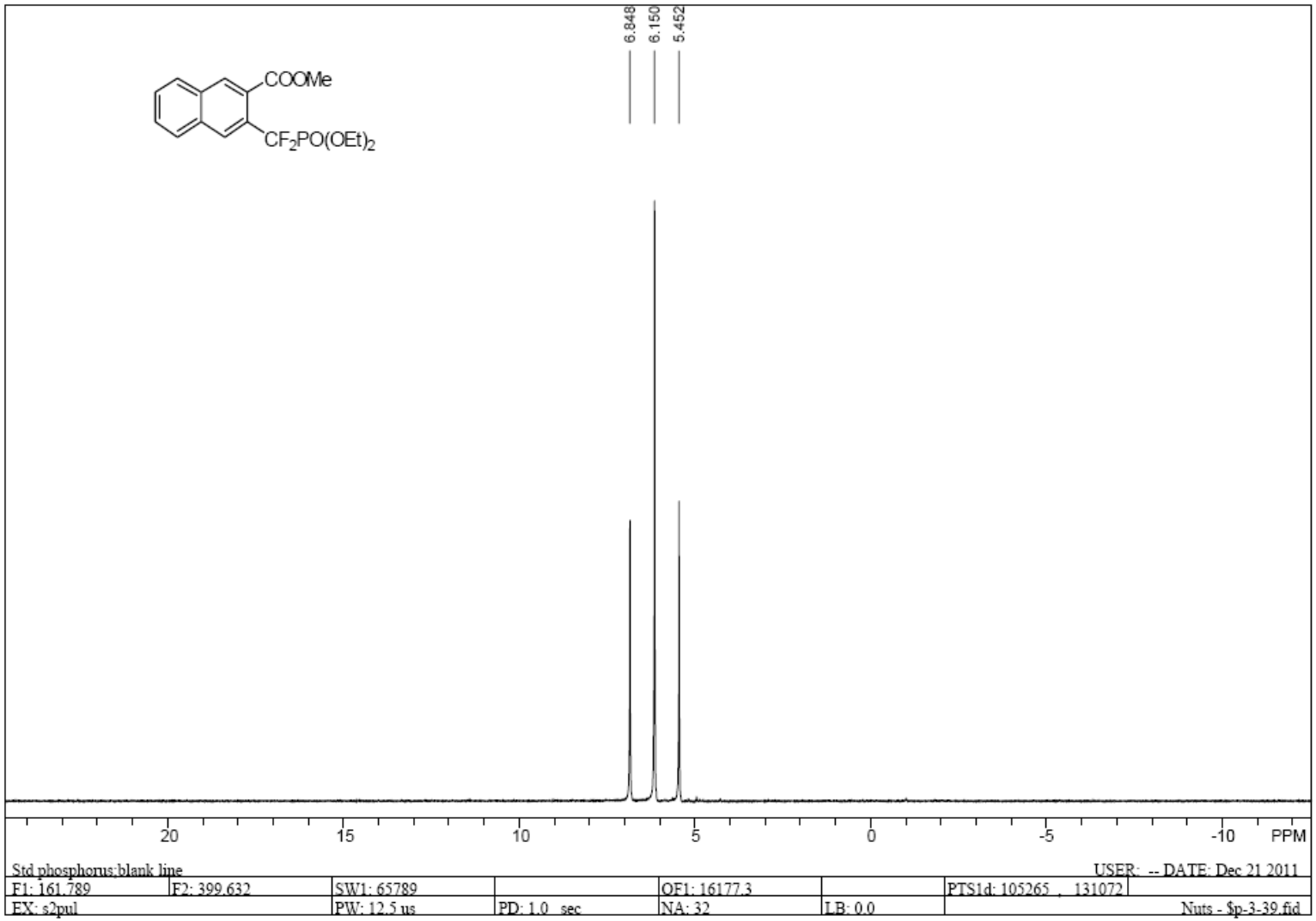

5.883
5.198
4.512
COOMe
CF2PO(OEt)2
COOMe
60
40
20
0
-20
-40
PPM
Std phosphorus;blank line
USER: -- DATE: Dec 20 2011
F1: 161.789
F2: 399.632
SW1: 65789
OF1: 16177.3
PTS1d: 105265 , 131072
EX: s2pul
PW: 12.5 us
PD: 1.0 sec
NA: 32
LB: 0.0
Nuts - $p-3-45.fid

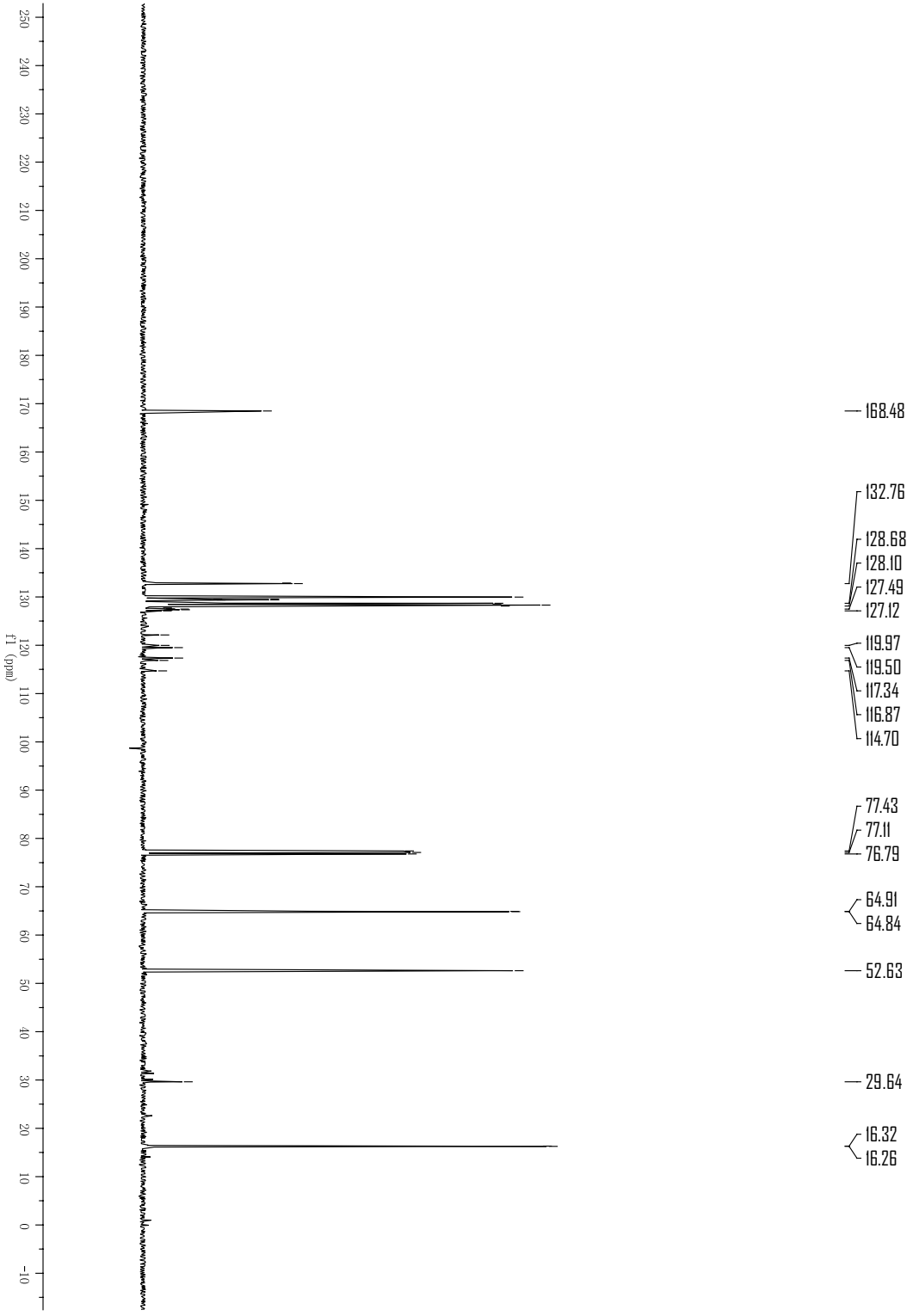

f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
167.70
165.00
131.55
130.92
130.42
129.49
128.64
122.51
119.63
118.99
116.12
115.47
112.60
77.41
76.99
76.56
64.90
64.81
52.63
52.37
16.08
16.00

Methyl 3-((diethoxyphosphoryl)difluoromethyl)-2-naphthoate (3h)

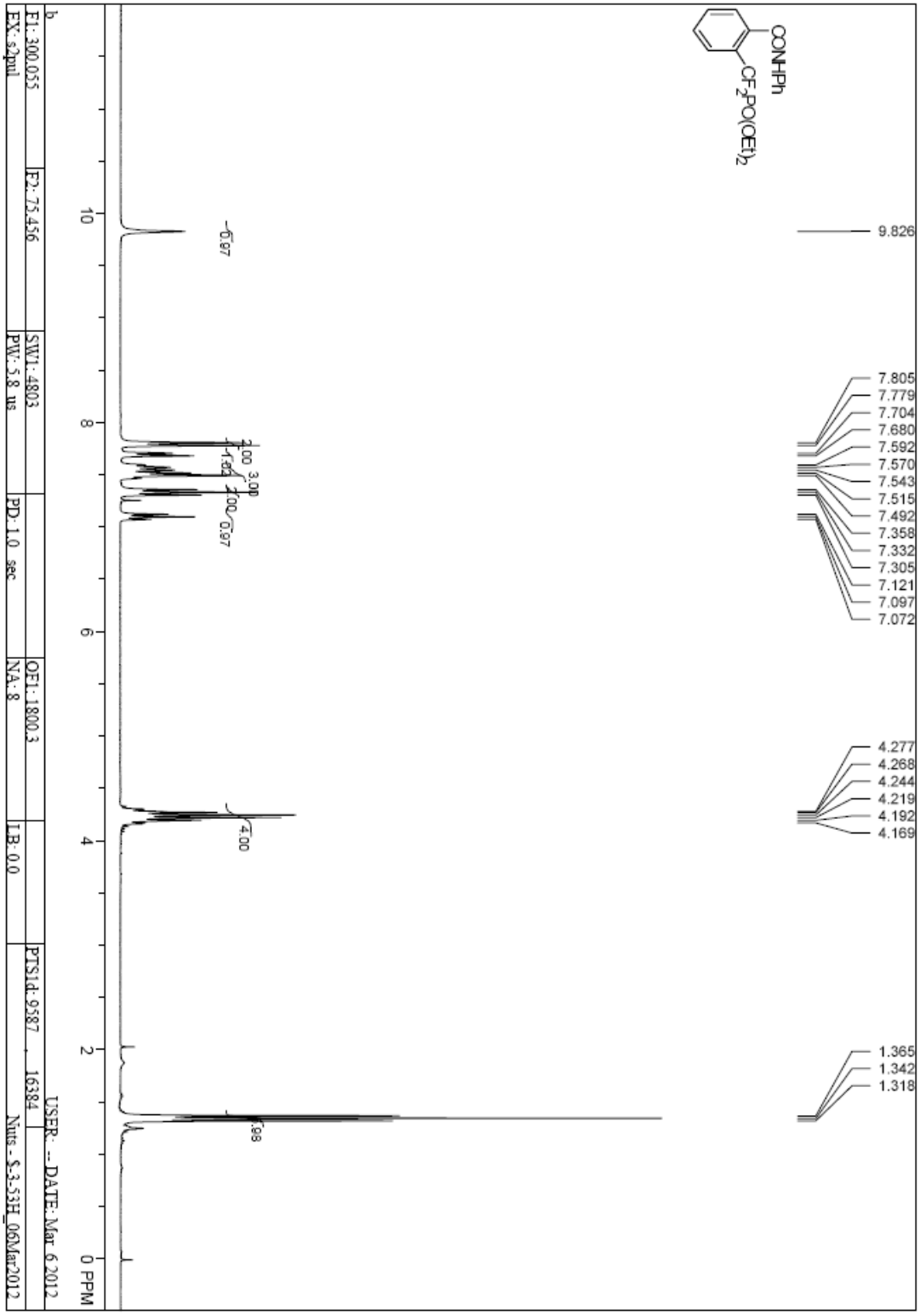


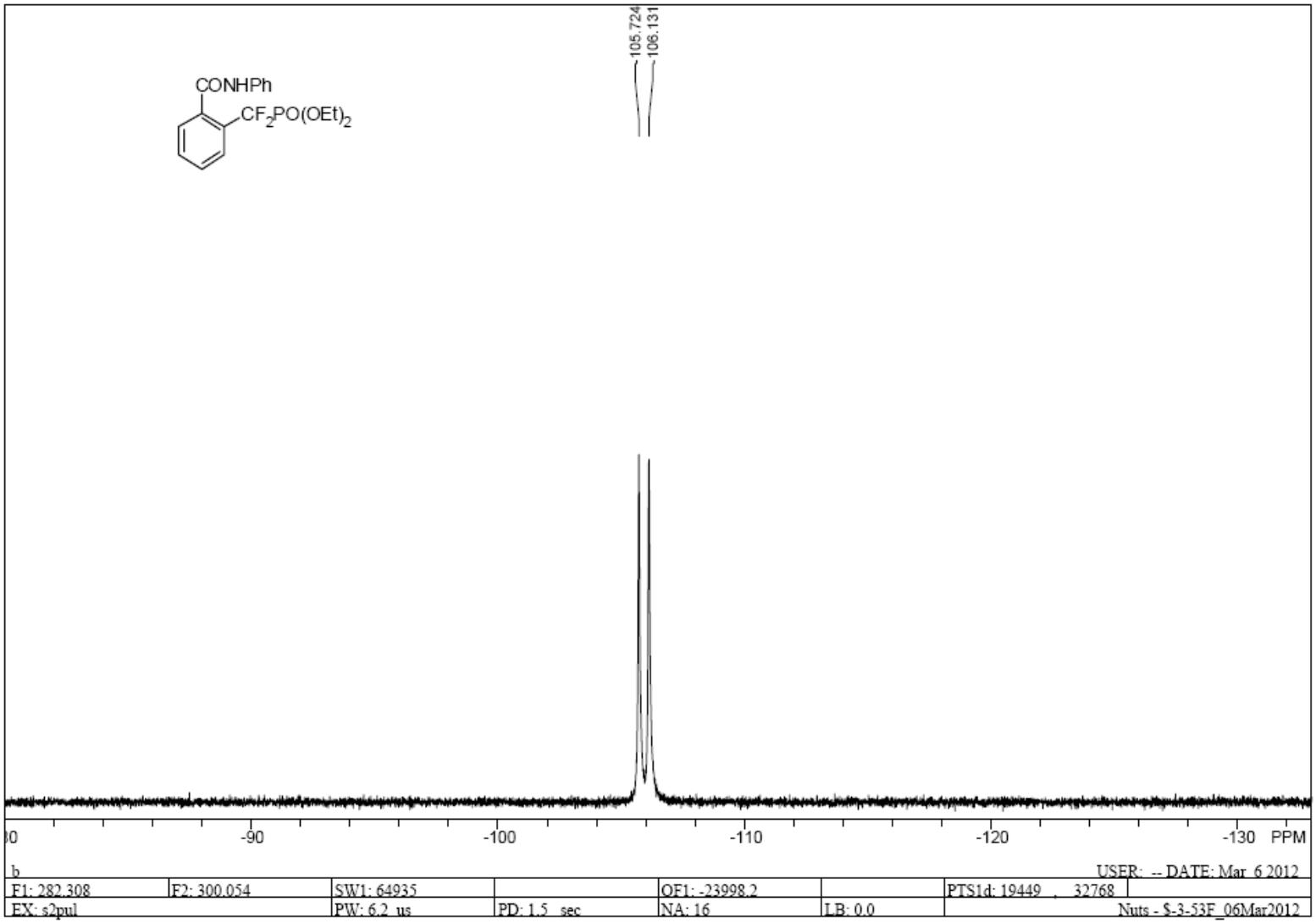

COOMe
CF2PO(OEt)2
-99.414
-99.814
-85
-90
-95
-100
-105
-110
PPM
:blank line
USER: -- DATE: Dec 6 2011
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-39F_06Dec2011

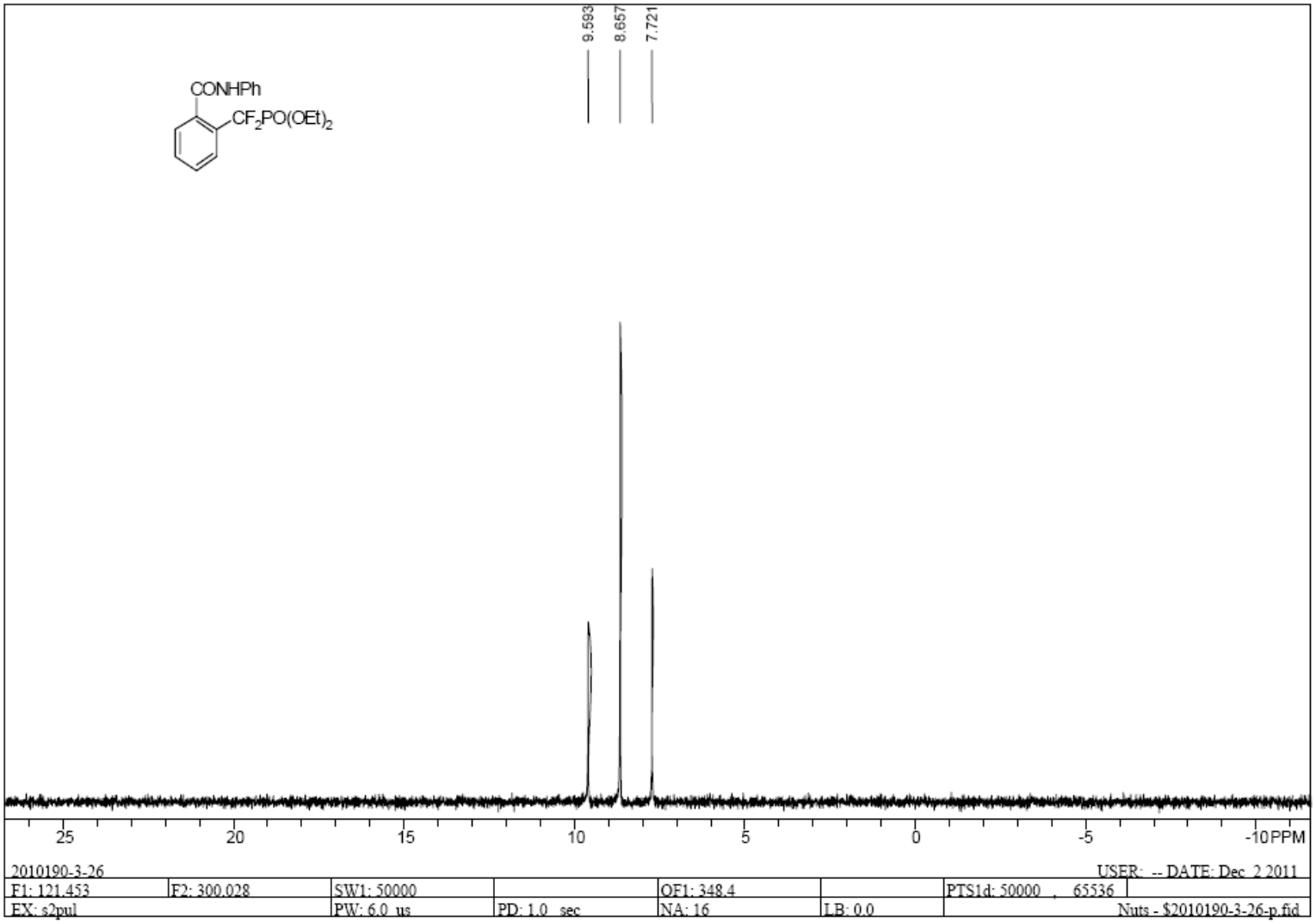

6.848
6.150
5.452
COOMe
CF2PO(OEt)2
20
15
10
5
0
-5
-10
PPM
Std phosphorus;blank line
USER: -- DATE: Dec 21 2011
F1: 161.789
F2: 399.632
SW1: 65789
OF1: 16177.3
PTS1d: 105265 , 131072
EX: s2pul
PW: 12.5 us
PD: 1.0 sec
NA: 32
LB: 0.0
Nuts - $p-3-39.fid

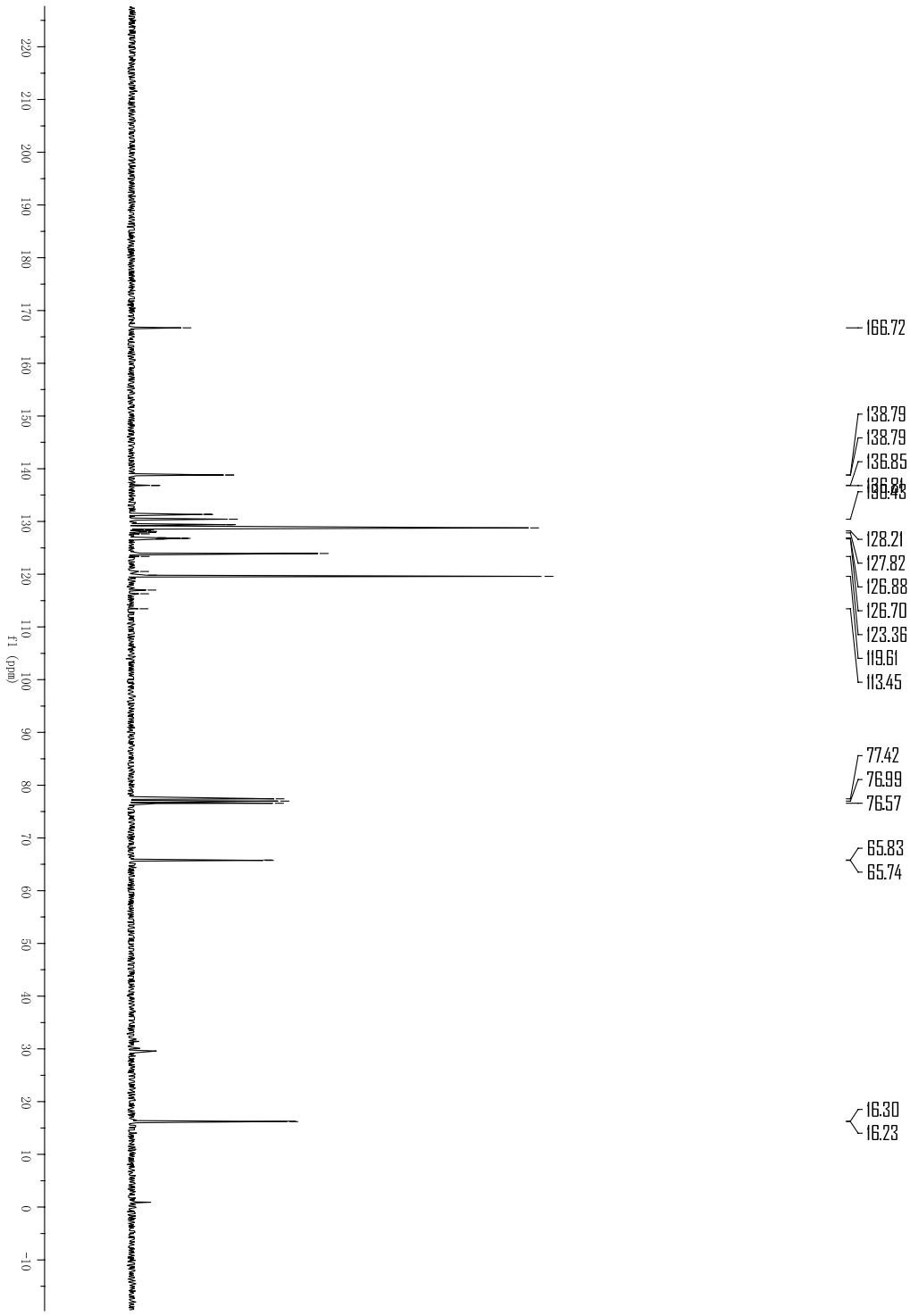

f1 (ppm)
168.48
132.76
128.68
128.10
127.49
127.12
119.97
119.50
117.34
116.87
114.70
77.43
77.11
76.79
64.91
64.84
52.63
29.64
16.32
16.26

Diethyl difluoro(2-(phenylcarbamoyl)phenyl)methylphosphonate (3i).

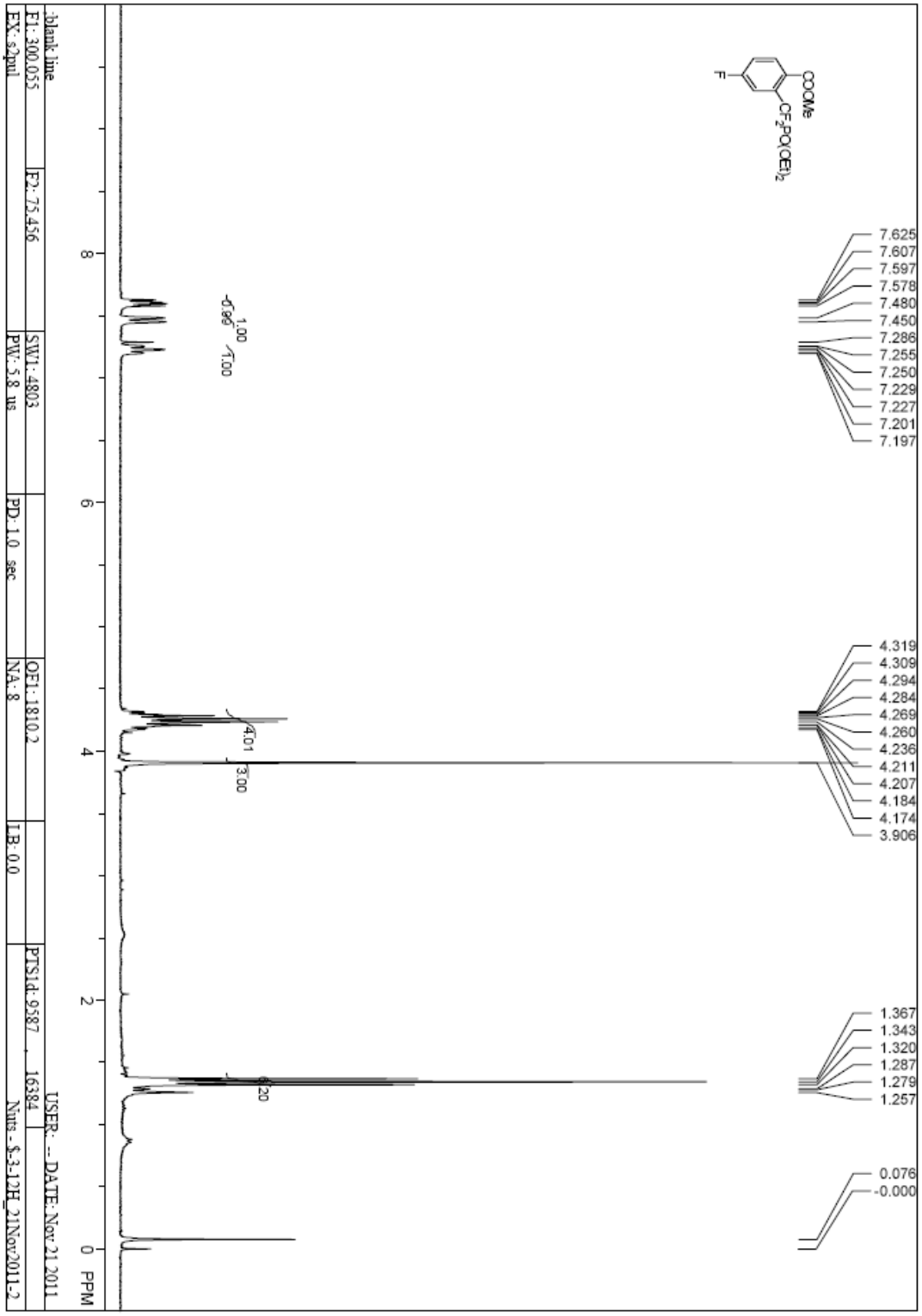


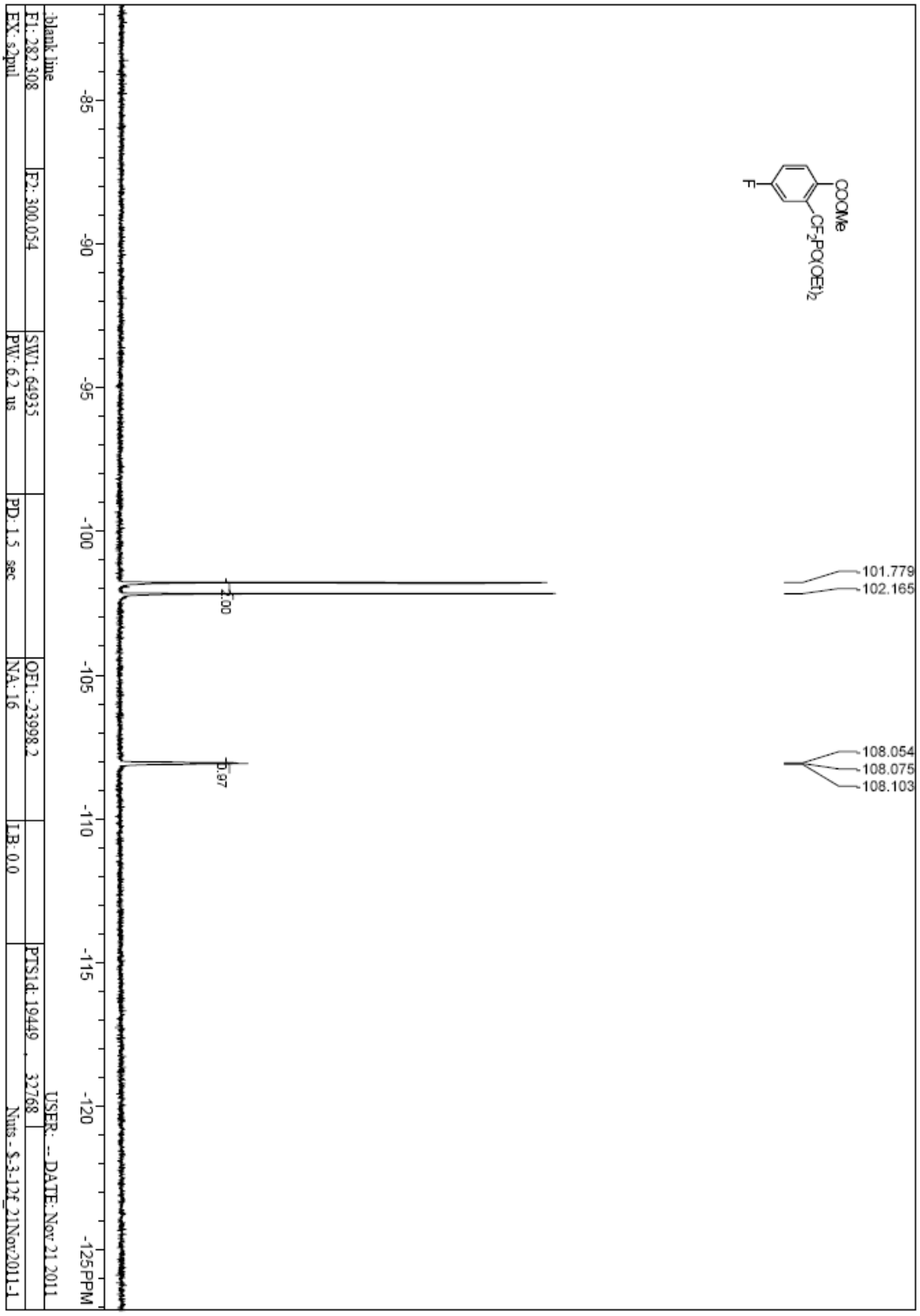

CONHPh
CF2PO(OEt)2
105.724
106.131
-90
-100
-110
-120
-130 PPM
b
USER: -- DATE: Mar 6 2012
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-53F_06Mar2012

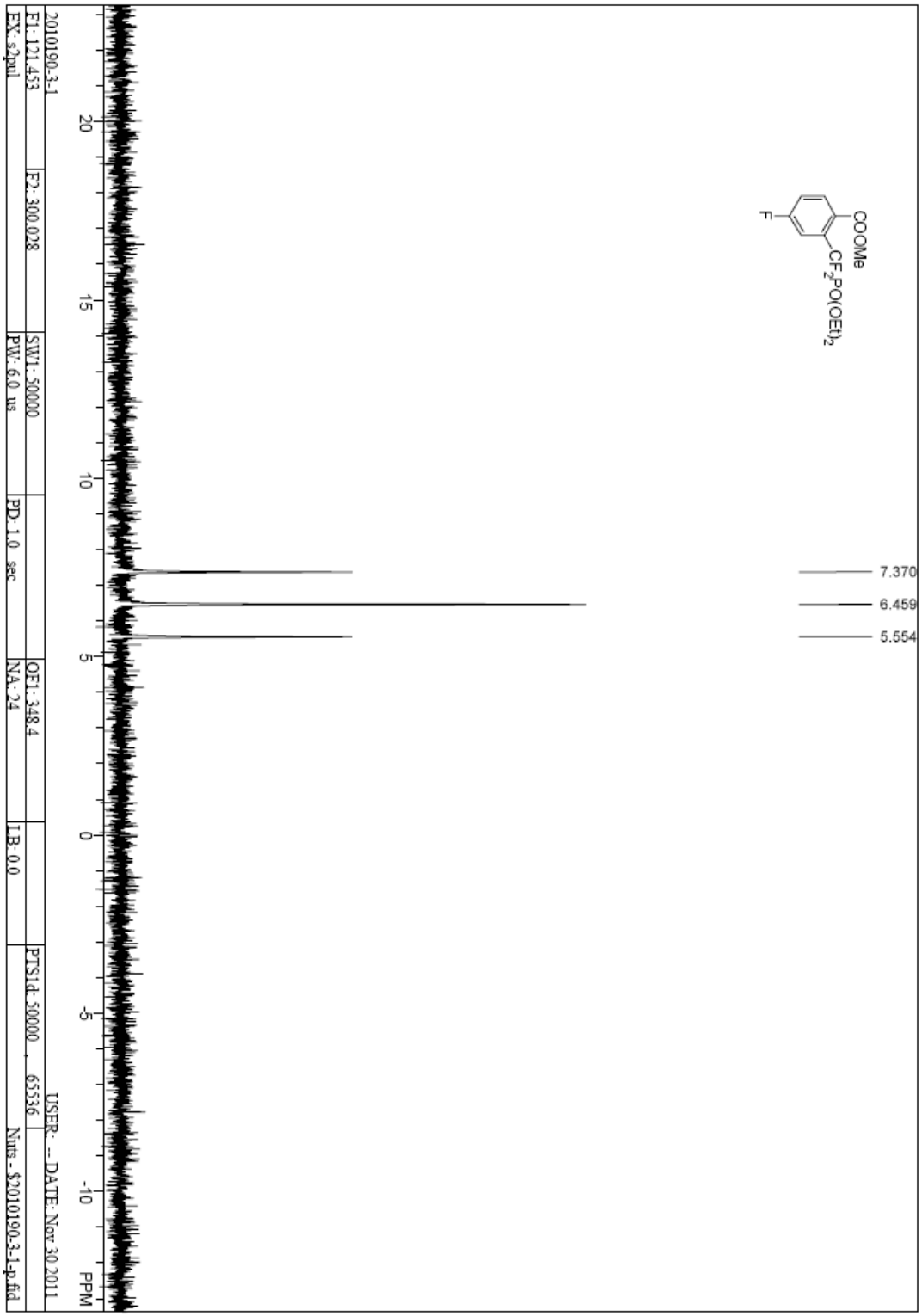

9.593
8.657
7.721
CONHPh
CF2PO(OEt)2
25
20
15
10
5
0
-5
-10PPM
2010190-3-26
USER: -- DATE: Dec 2 2011
F1: 121.453
F2: 300.028
SW1: 50000
OF1: 348.4
PTS1d: 50000 , 65536
EX: s2pul
PW: 6.0 us
PD: 1.0 sec
NA: 16
LB: 0.0
Nuts - $2010190-3-26-p.fid

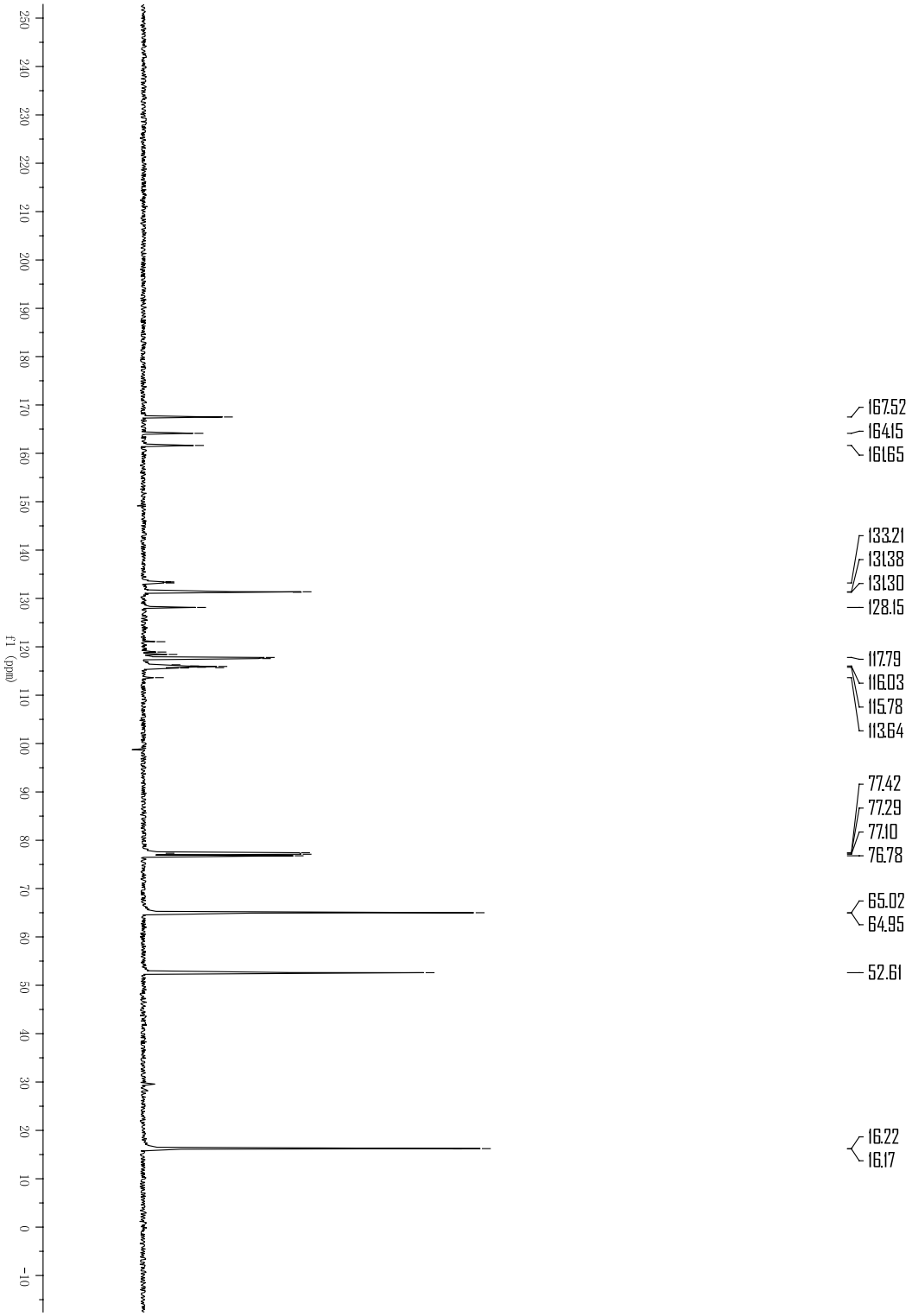

166.72
138.79
138.79
136.85
136.84
136.48
135.45
128.21
127.82
126.88
126.70
123.36
119.61
113.45
77.42
76.99
76.57
65.83
65.74
16.30
16.23
f1 (ppm)

Methyl 2-((diethoxyphosphoryl)difluoromethyl)-4-fluorobenzoate (3j).

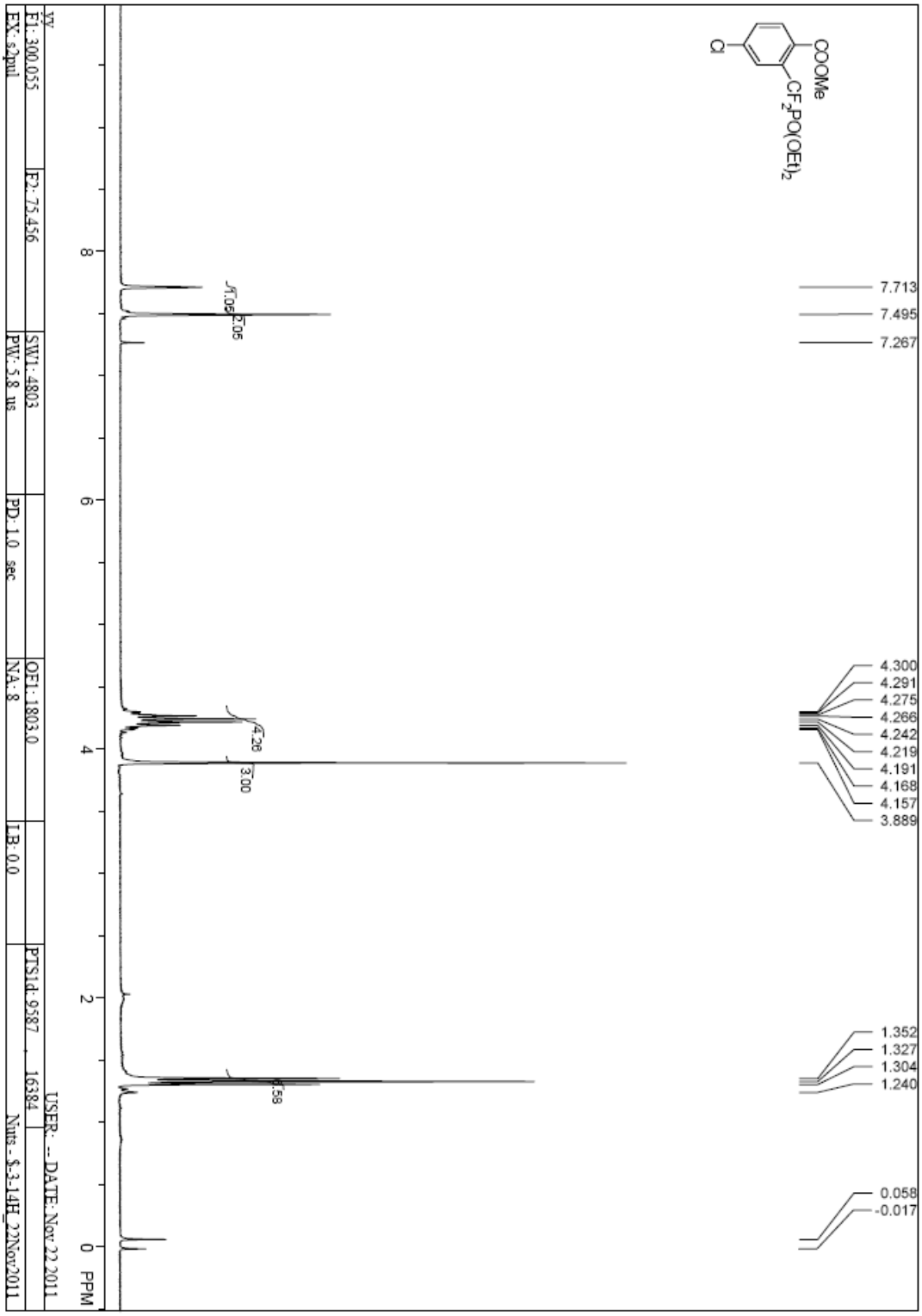


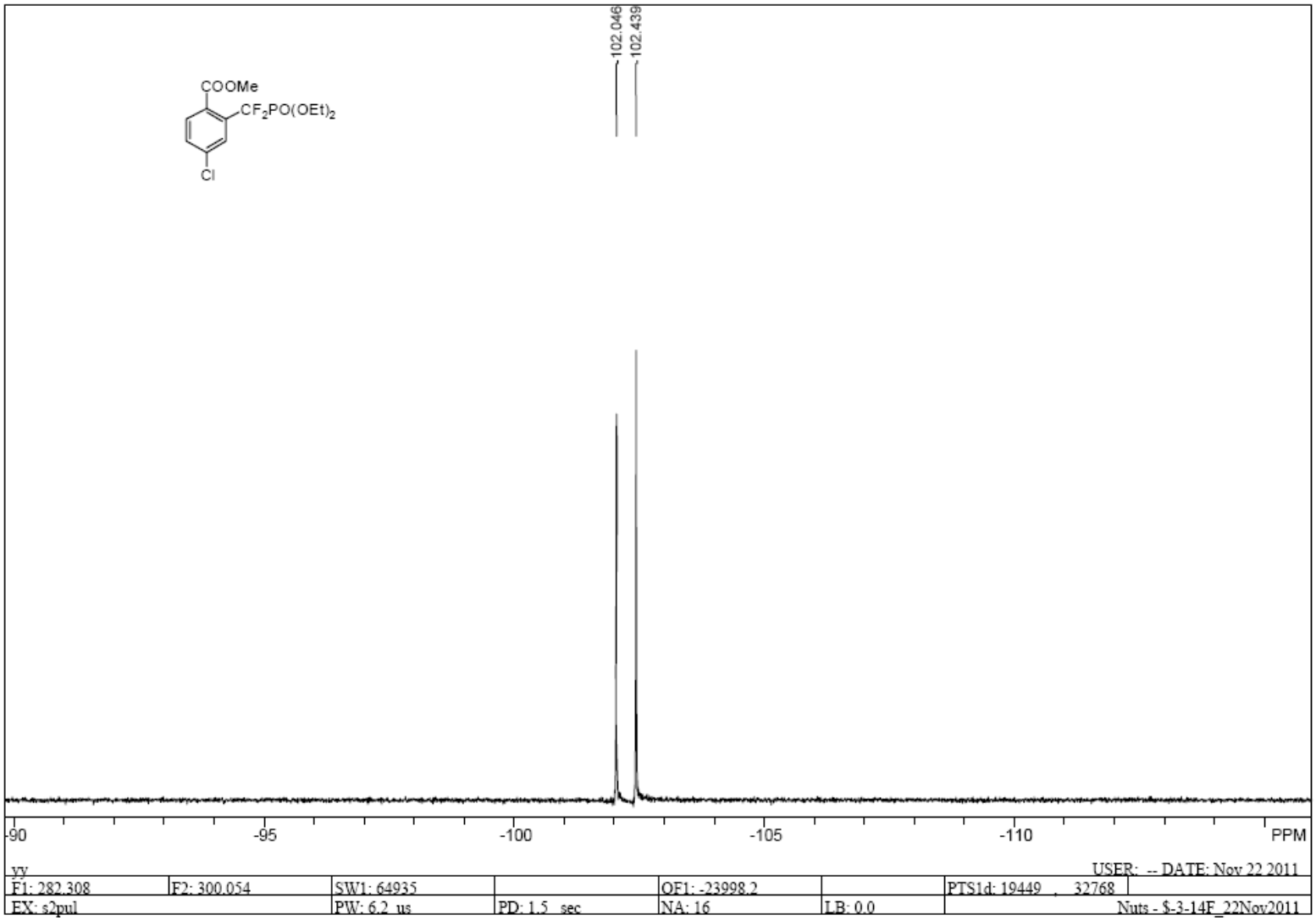

COOMe
CF2PO(OEt)2
F
101.779
102.165
108.054
108.075
108.103
2.00
0.97
-85
-90
-95
-100
-105
-110
-115
-120
-125 PPM
:blank_line
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTSIA: 19449 , 32768
USER: -- DATE: Nov 21 2011
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $3-12f_21Nov2011-1

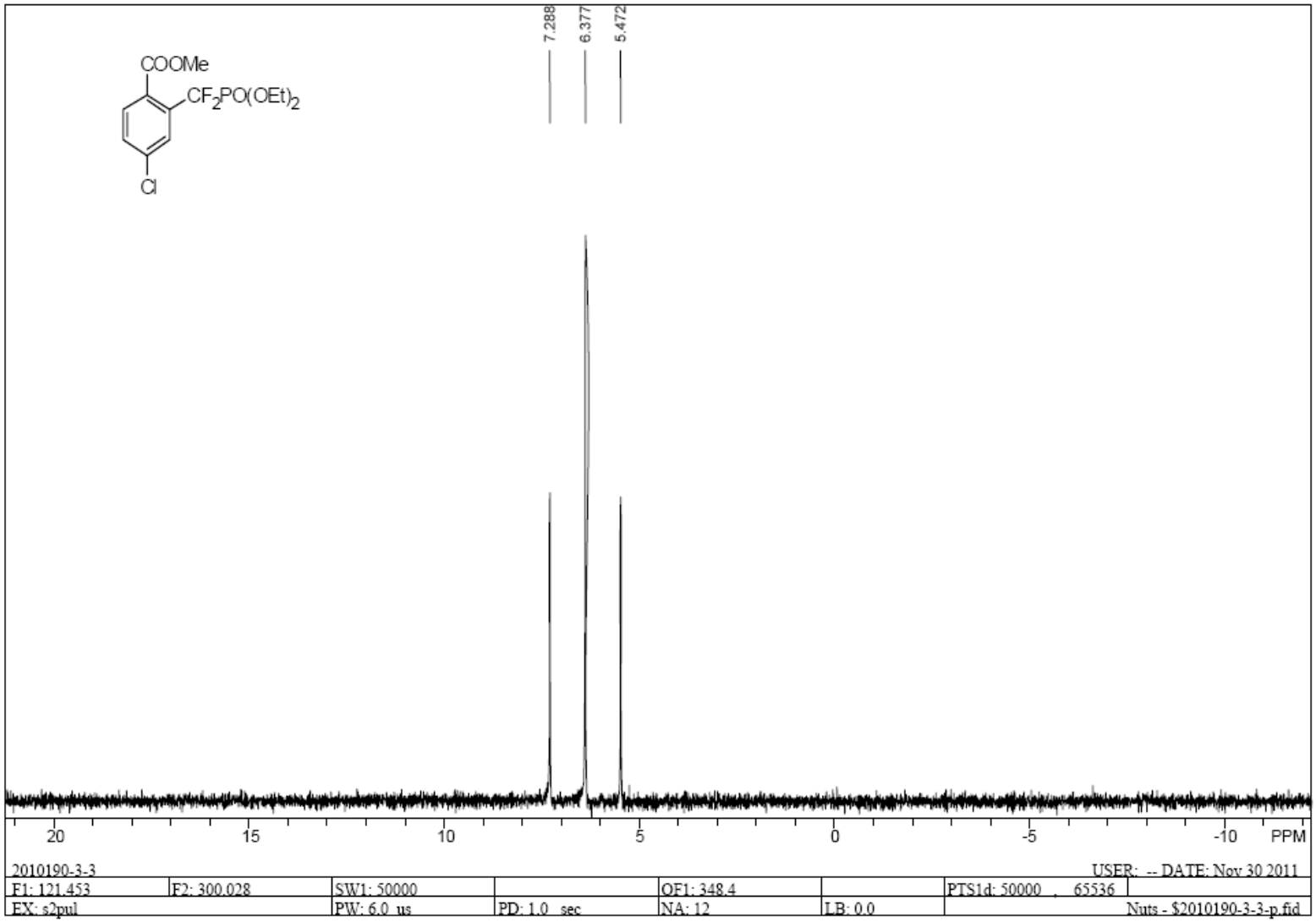

COOMe
CF2PO(OEt)2
F
7.370
6.459
5.554
20
15
10
5
0
-5
-10
PPM
2010190-3-1
F1: 121.453
F2: 300.028
SW1: 50000
OF1: 348.4
PTS1d: 50000 , 65536
USER: -- DATE: Nov 30 2011
EX: s2pul
PW: 6.0 us
PD: 1.0 sec
NA: 24
LB: 0.0
Nuts - $2010190-3-1-p.fid

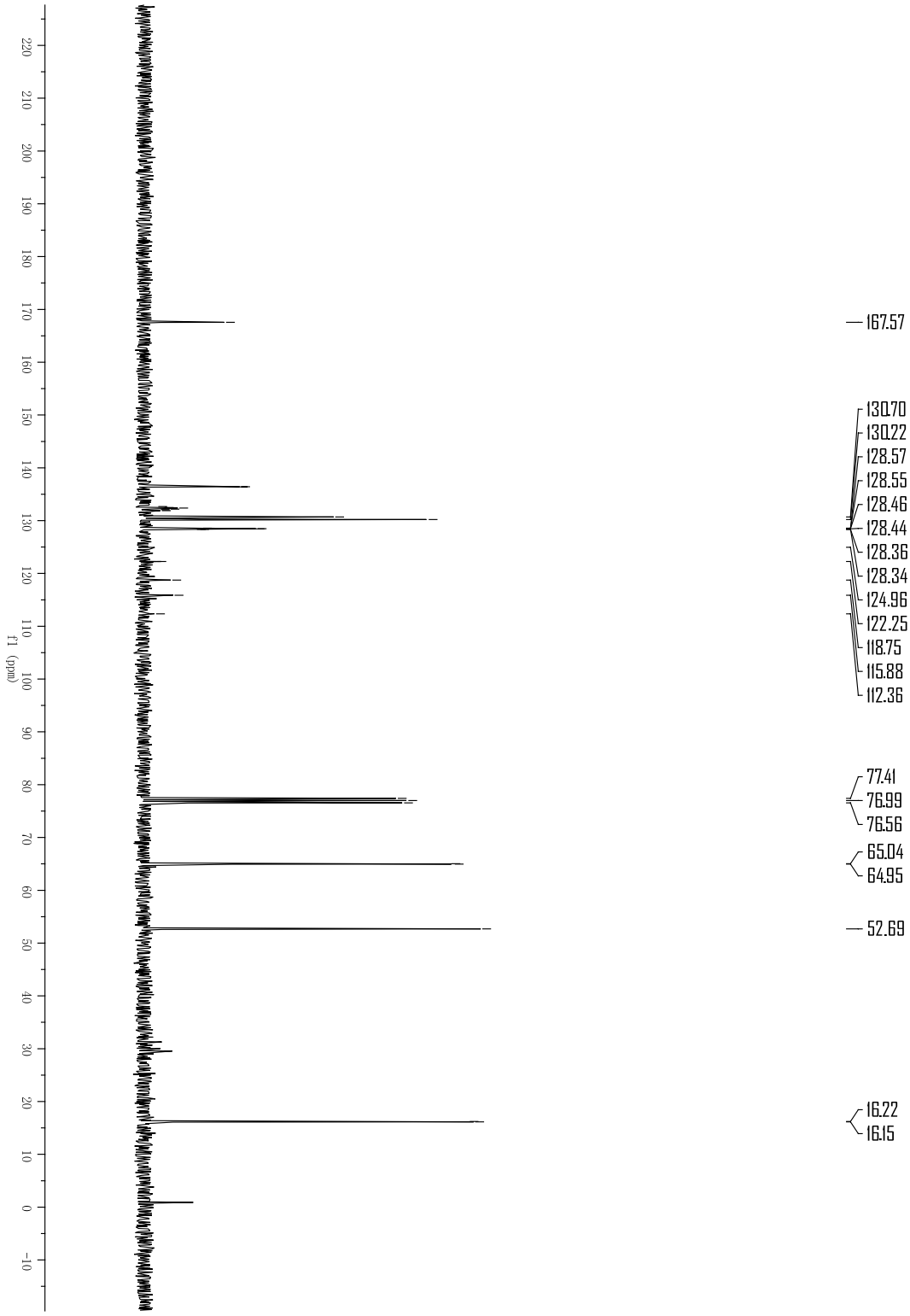

167.52
164.15
161.65
133.21
131.38
131.30
128.15
117.79
116.03
115.78
113.64
77.42
77.29
77.10
76.78
65.02
64.95
52.61
16.22
16.17
f1 (ppm)

Methyl 4-chloro-2-((diethoxyphosphoryl)difluoromethyl)benzoate (3k).

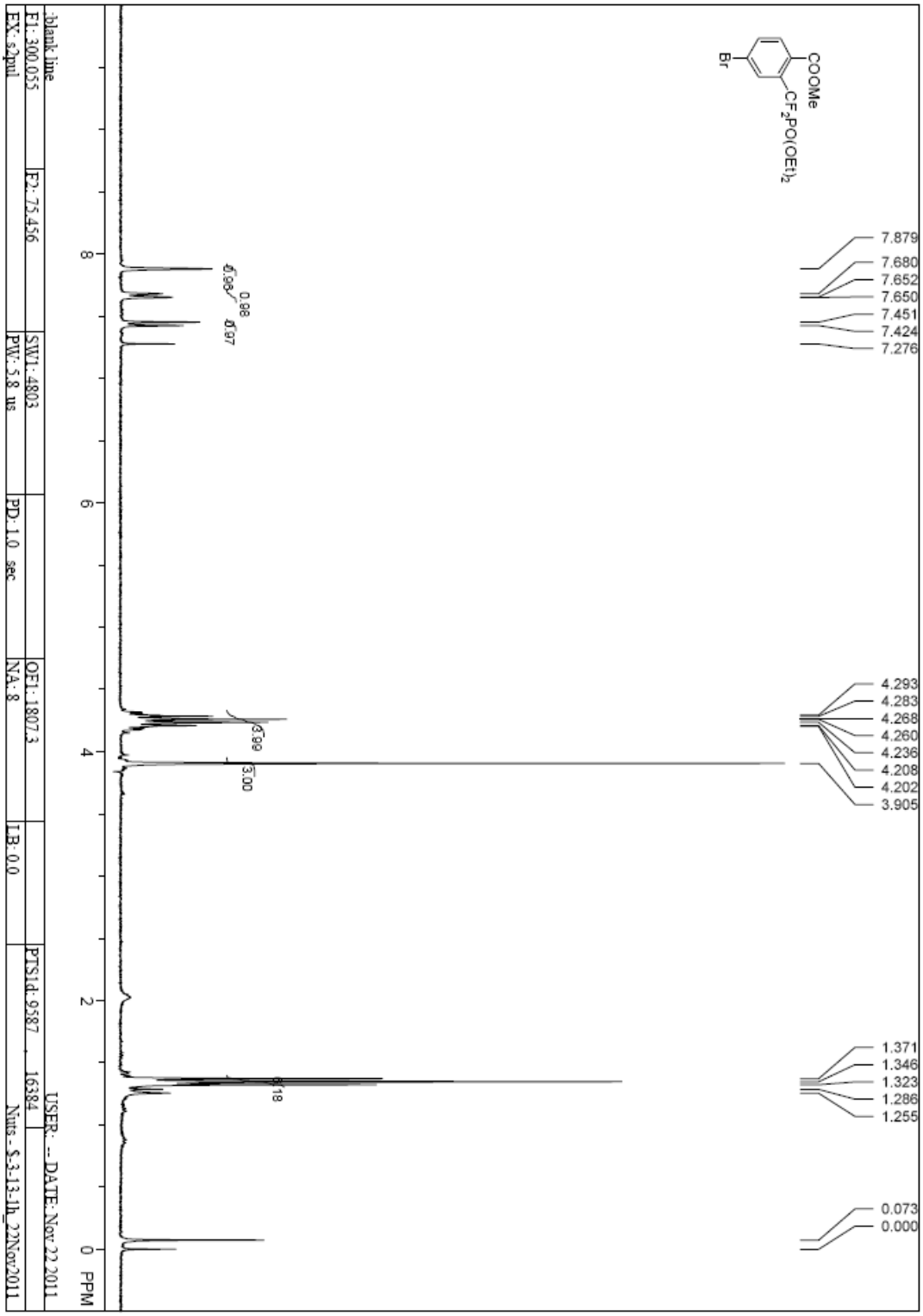


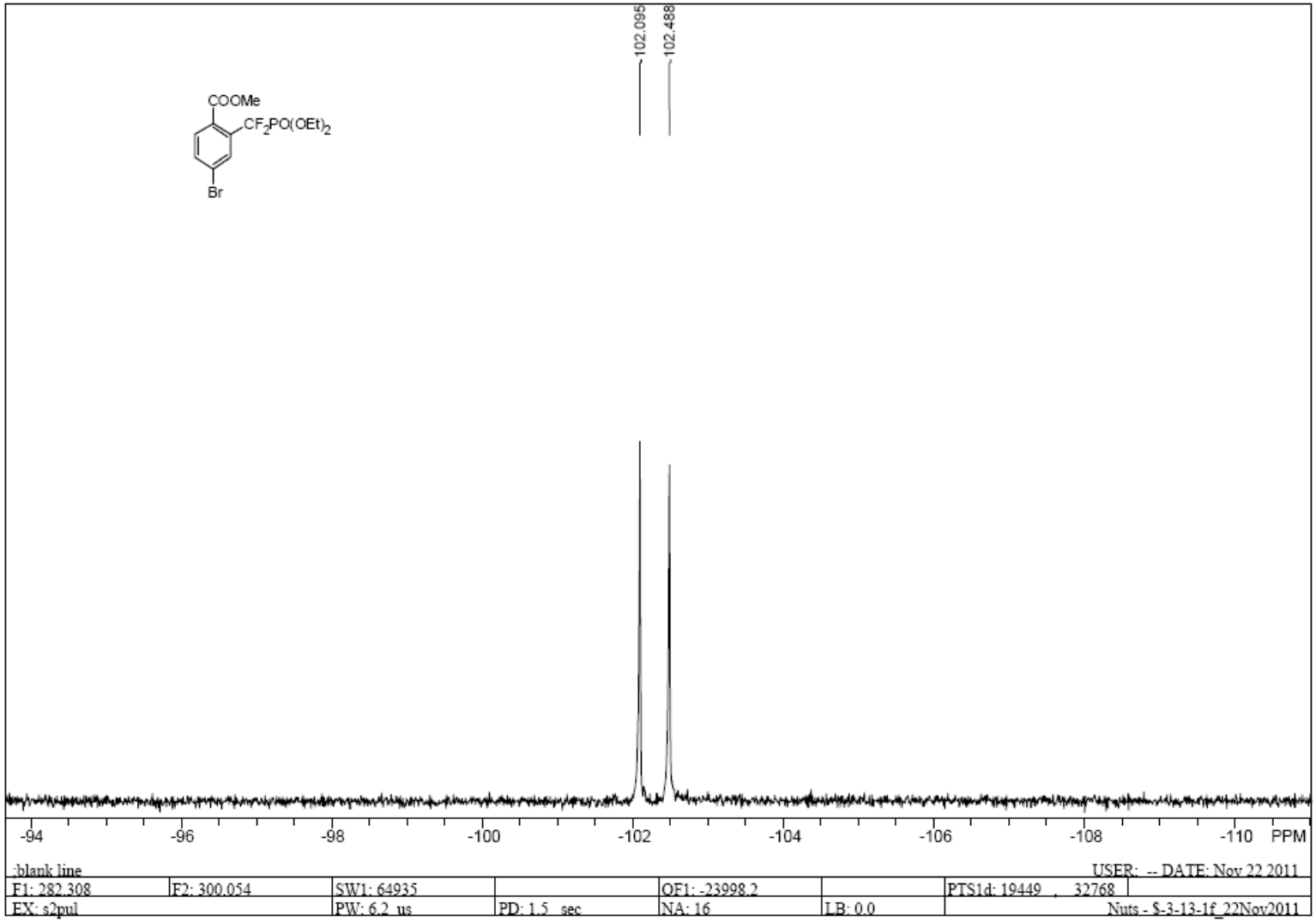

COOMe
CF2PO(OEt)2
Cl
102.046
102.439
-90
-95
-100
-105
-110
PPM
yy
USER: -- DATE: Nov 22 2011
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-14F_22Nov2011

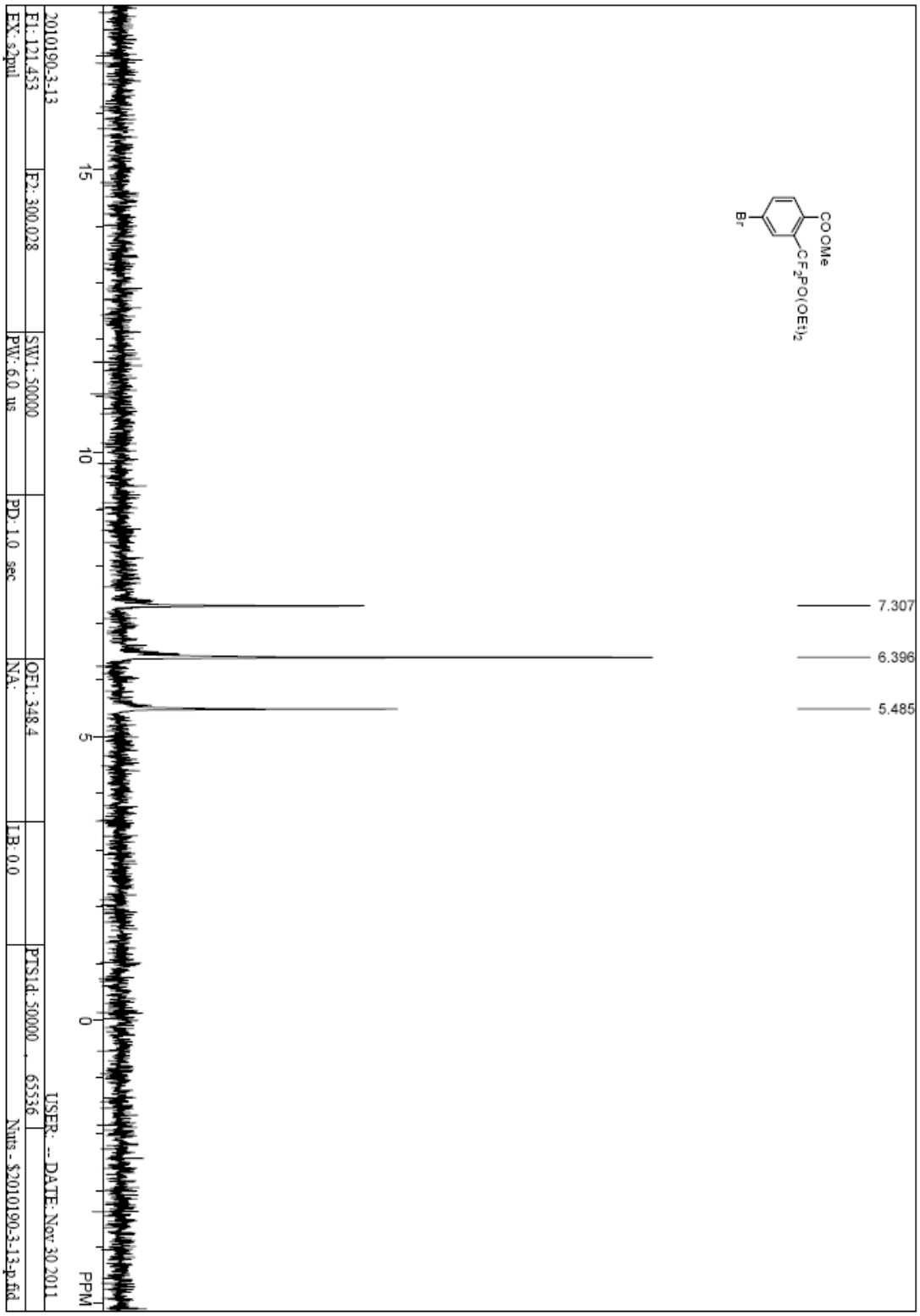

COOMe
CF2PO(OEt)2
Cl
7.288
6.377
5.472
20
15
10
5
0
-5
-10
PPM
2010190-3-3
USER: -- DATE: Nov 30 2011
F1: 121.453
F2: 300.028
SW1: 50000
OF1: 348.4
PTS1d: 50000 , 65536
EX: s2pul
PW: 6.0 us
PD: 1.0 sec
NA: 12
LB: 0.0
Nuts - $2010190-3-3-p.fid

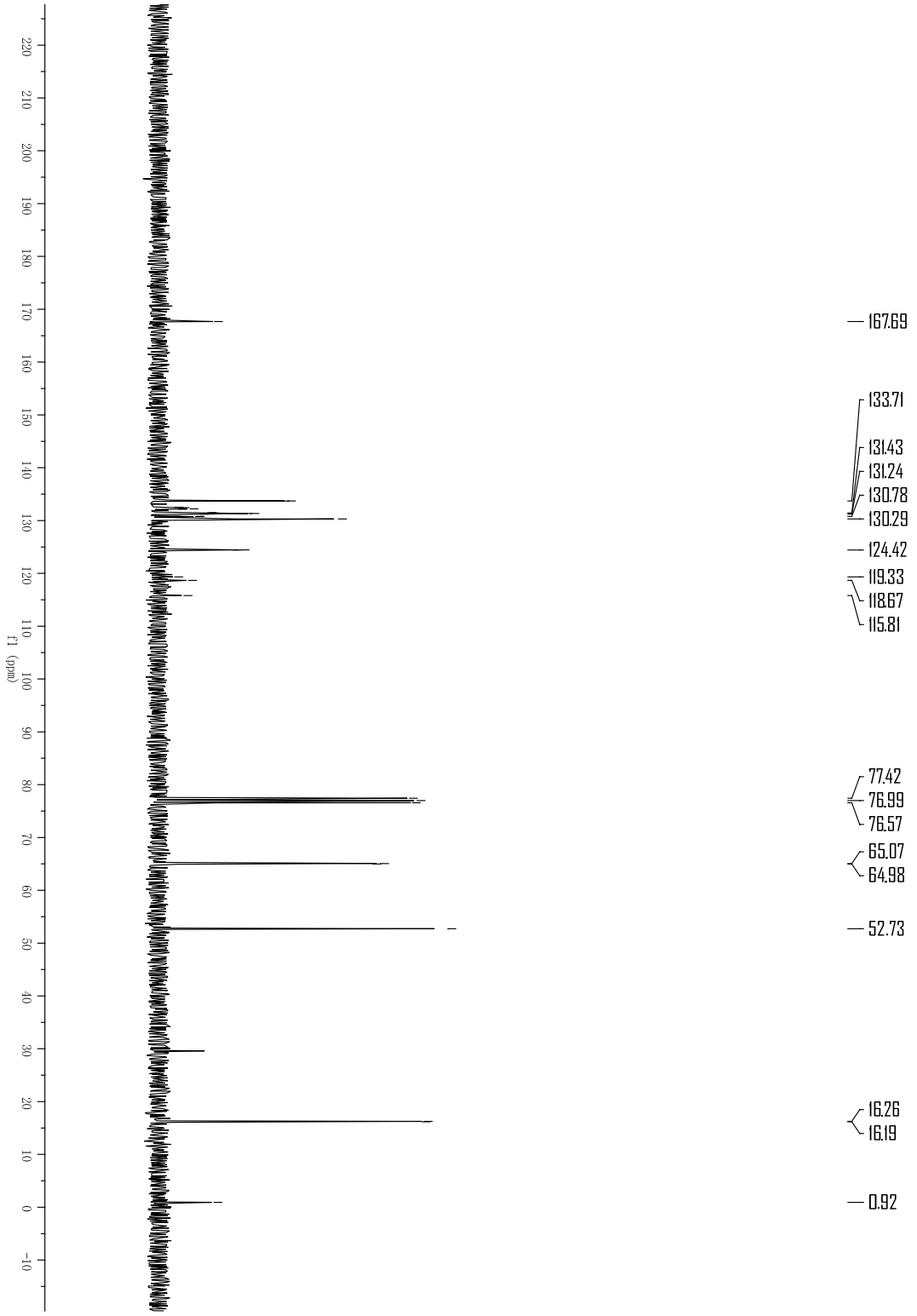

167.57
130.70
130.22
128.57
128.55
128.46
128.44
128.36
128.34
124.96
122.25
118.75
115.88
112.36
77.41
76.99
76.56
65.04
64.95
52.69
16.22
16.15
f1 (ppm)

Methyl 4-bromo-2-((diethoxyphosphoryl)difluoromethyl)benzoate (3l).

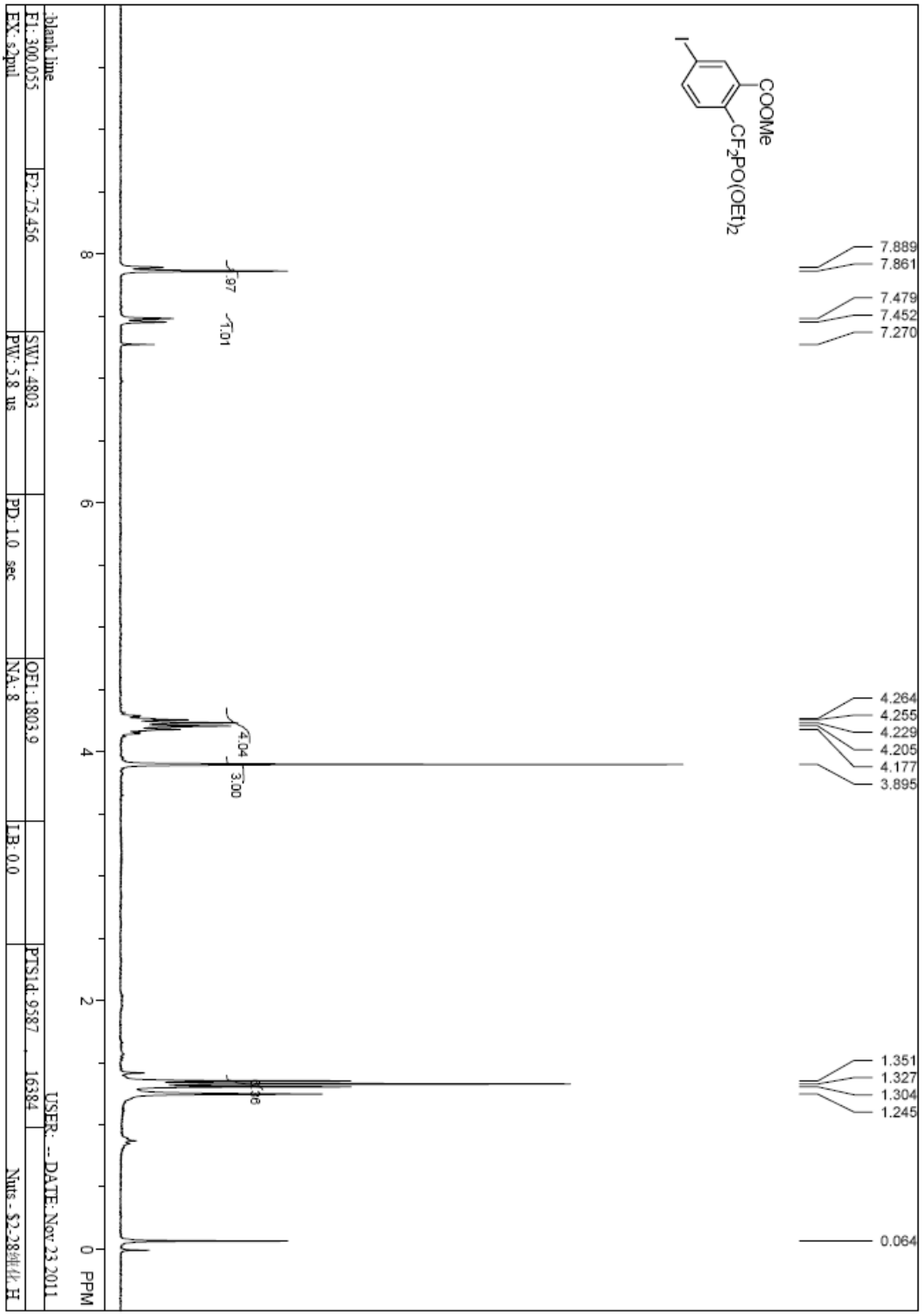


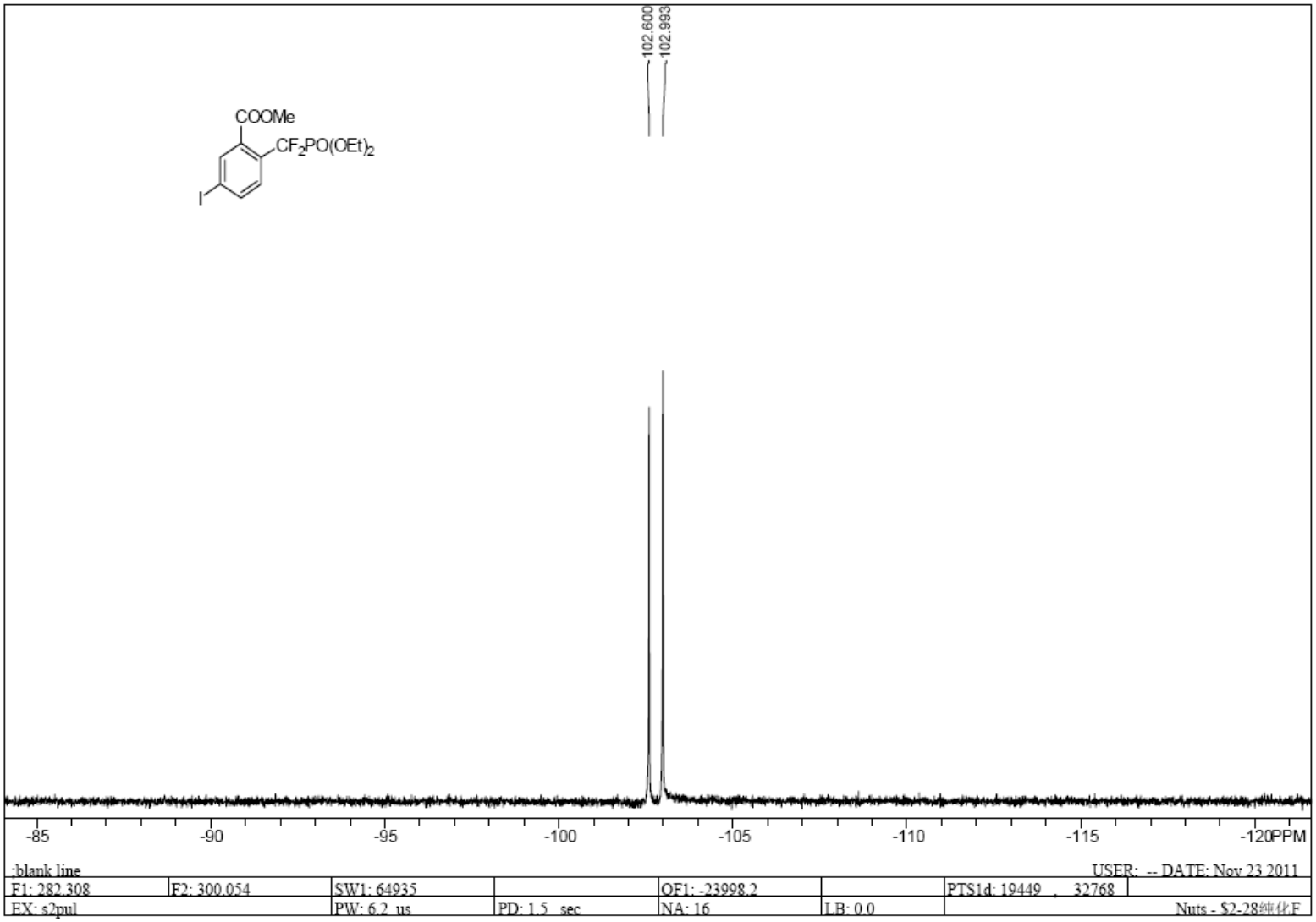

COOMe
CF2PO(OEt)2
Br
102.095
102.488
-94
-96
-98
-100
-102
-104
-106
-108
-110
PPM
:blank line
USER: -- DATE: Nov 22 2011
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-13-1f_22Nov2011


COOMe
Br
CF2PO(OEt)2
7.307
6.396
5.485
15
10
5
0
PPM
2010190-3-13
F1: 121.453
F2: 300.028
EX: s2pul
PW: 6.0 us
SW1: 50000
PD: 1.0 sec
OF1: 348.4
NA:
LB: 0.0
PTS1d: 50000 , 65536
USER: -- DATE: Nov 30 2011
Nuts - $2010190-3-13-p.fid

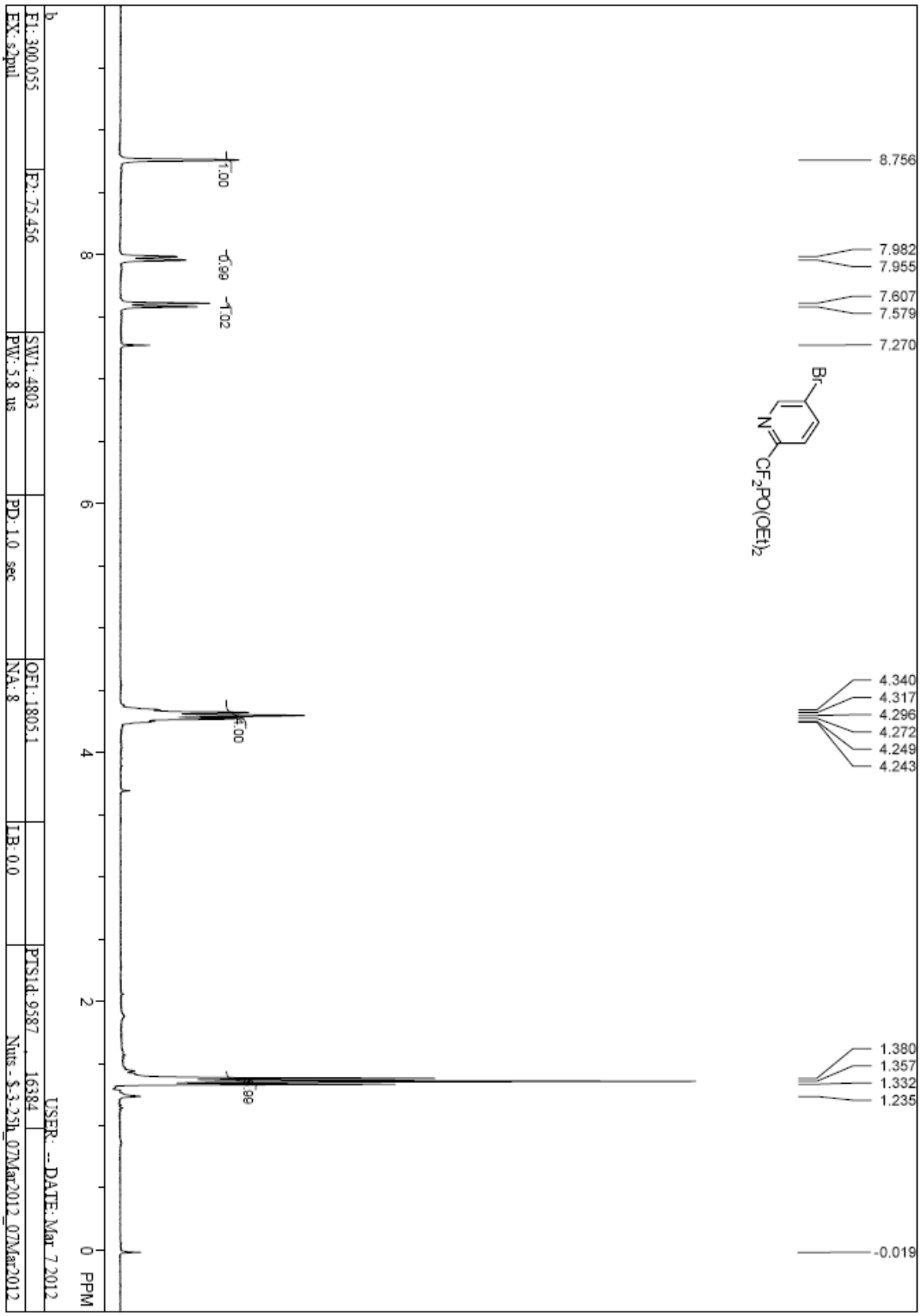

167.69
133.71
131.43
131.24
130.78
130.29
124.42
119.33
118.67
115.81
77.42
76.99
76.57
65.07
64.98
52.73
16.26
16.19
0.92
f1 (ppm)

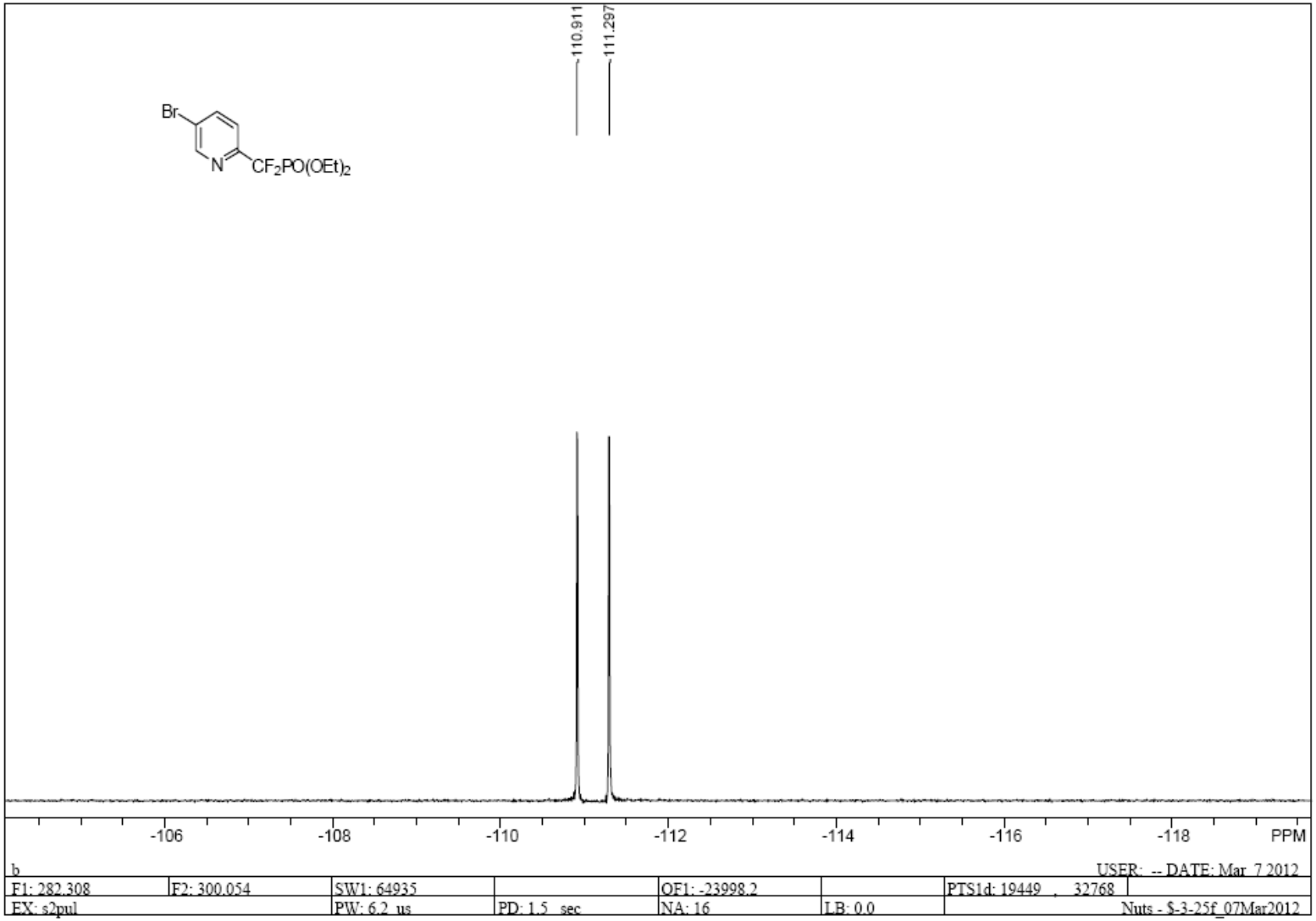
Methyl 2-((diethoxyphosphoryl)difluoromethyl)-5-iodobenzoate (3m).

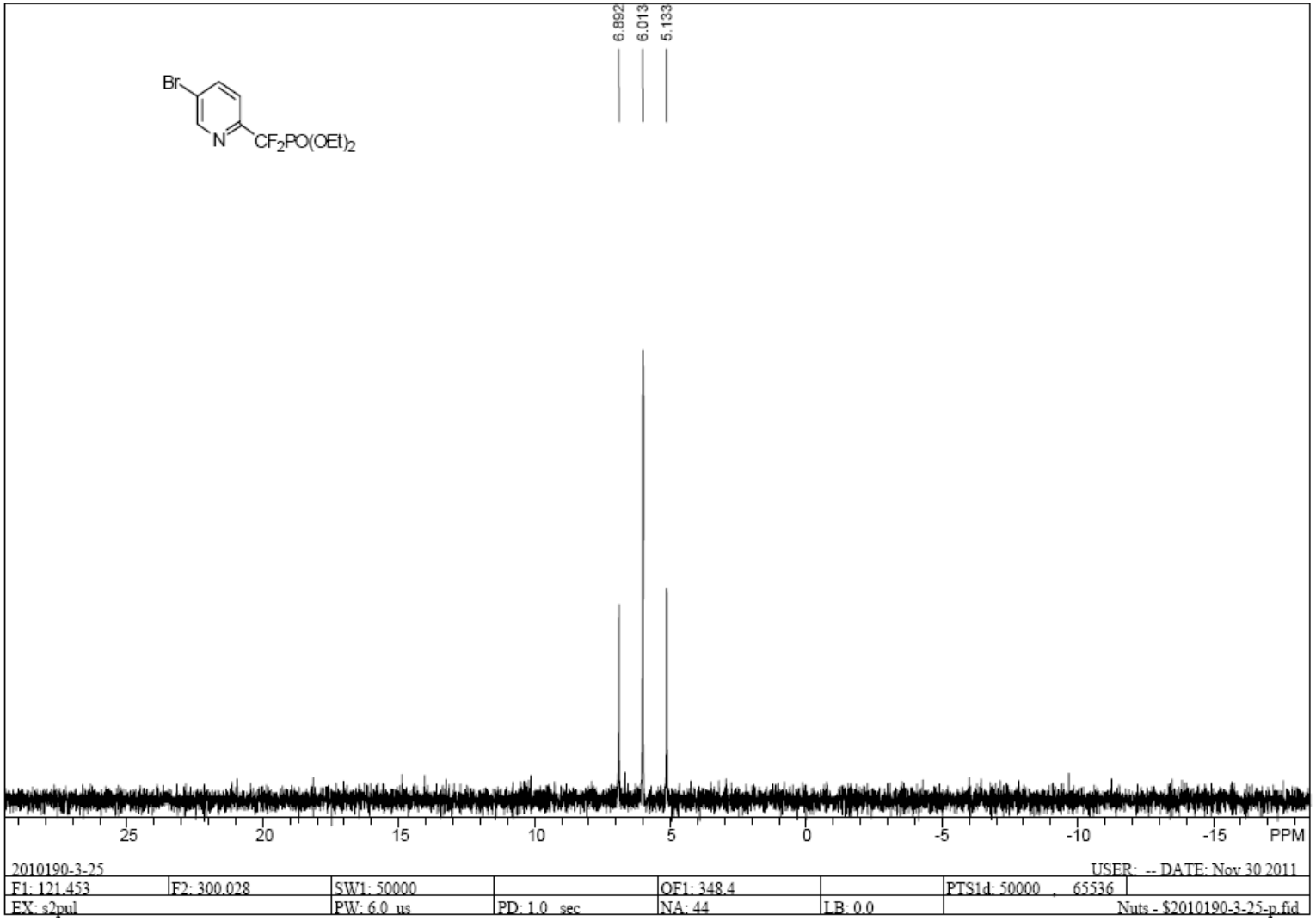


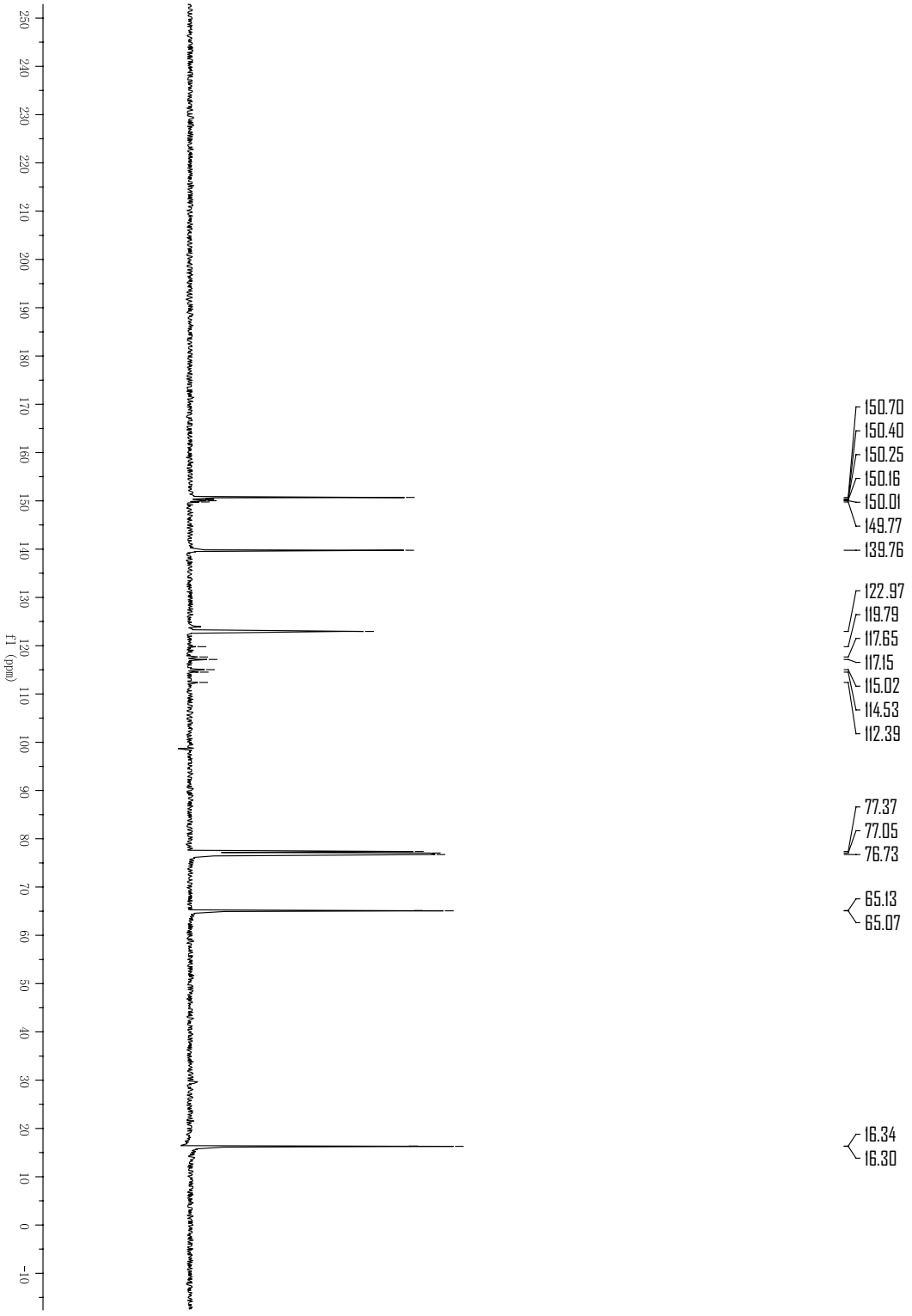

102.600
102.993
COOMe
CF2PO(OEt)2
I
-85
-90
-95
-100
-105
-110
-115
-120PPM
:blank line
USER: -- DATE: Nov 23 2011
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $2-28纯化F

Diethyl (5-bromopyridin-2-yl)difluoromethylphosphonate (3n).

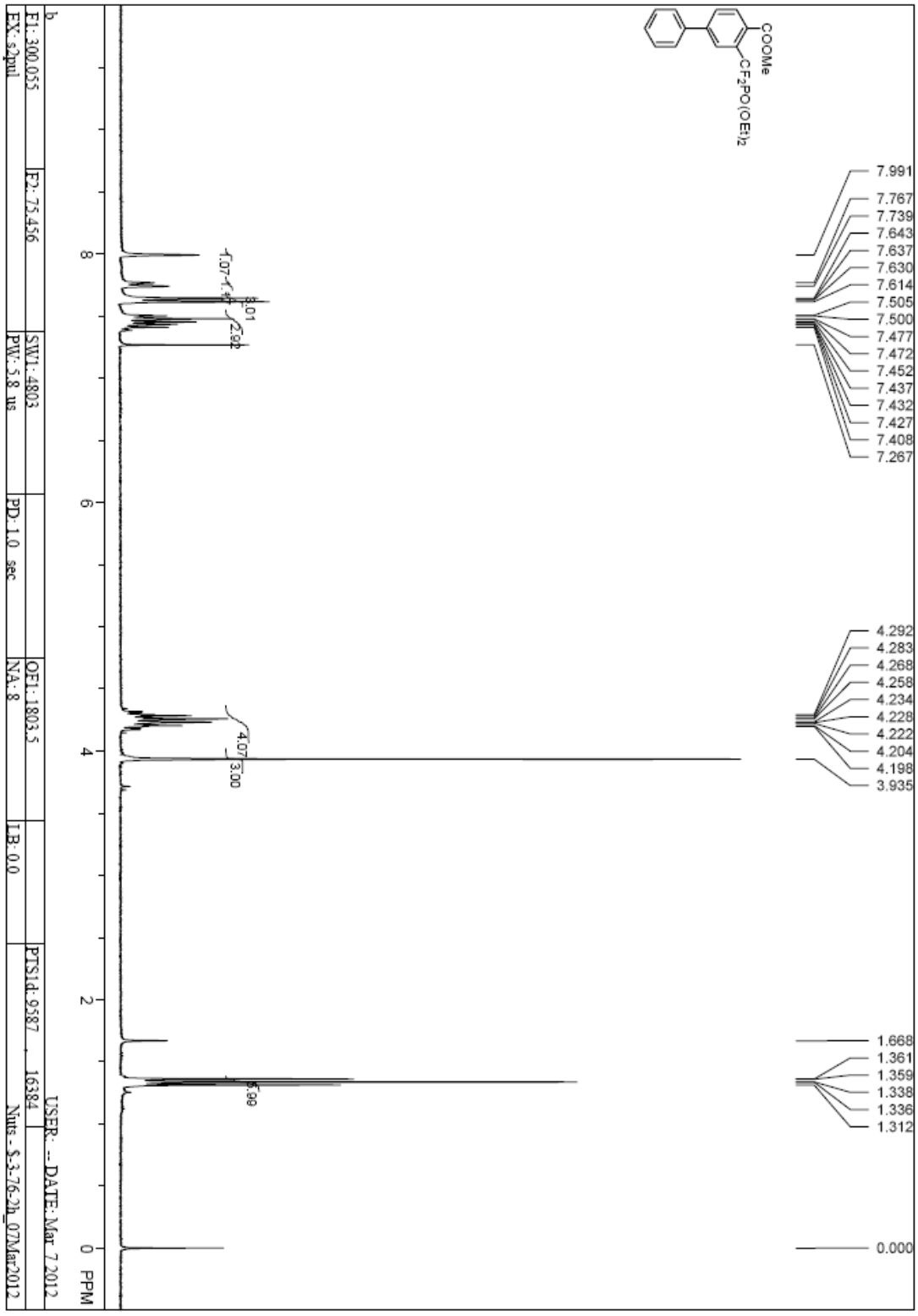


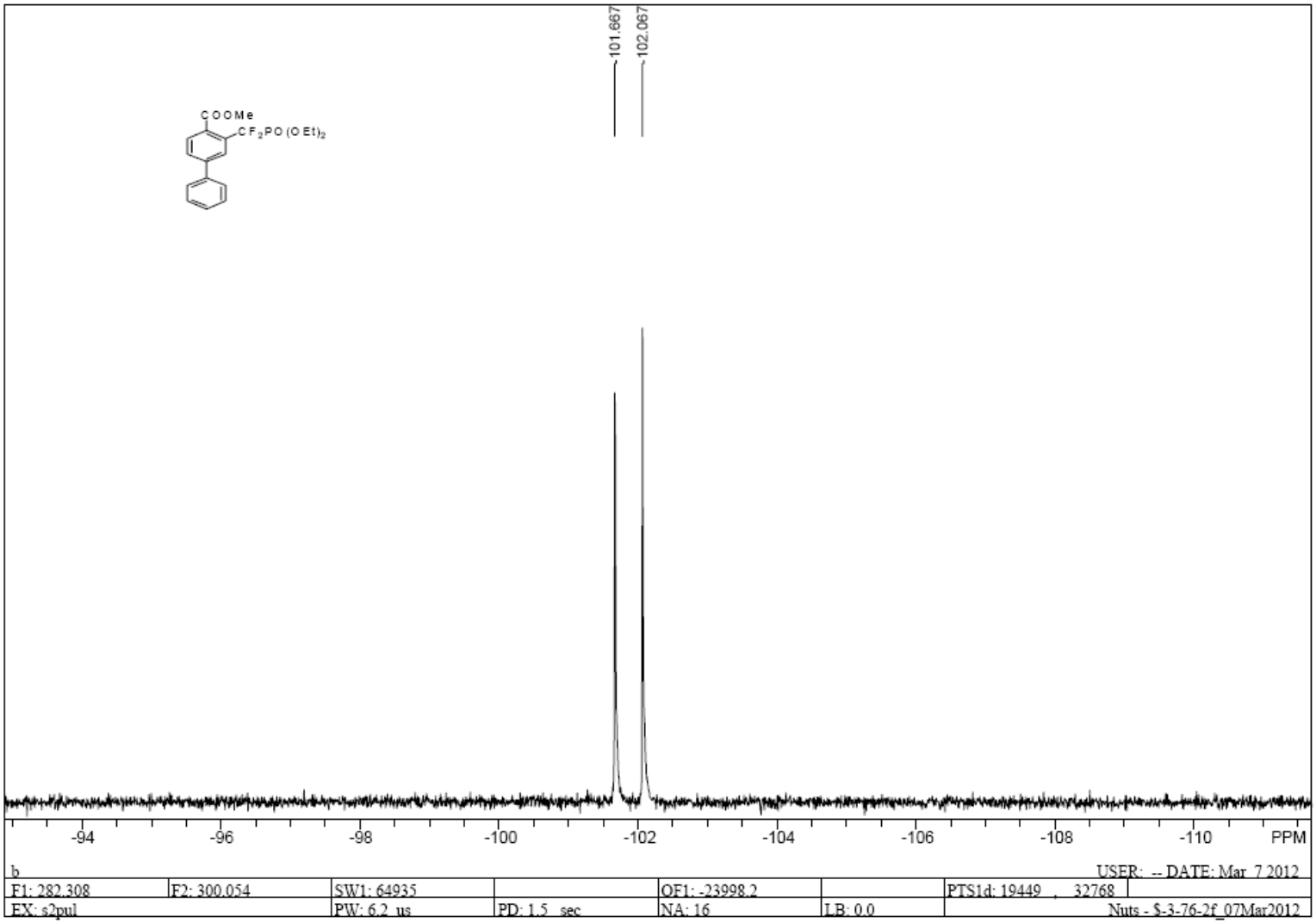

110.911
111.297
Br
N
CF2PO(OEt)2
-106
-108
-110
-112
-114
-116
-118
PPM
b
USER: -- DATE: Mar 7 2012
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-25f_07Mar2012

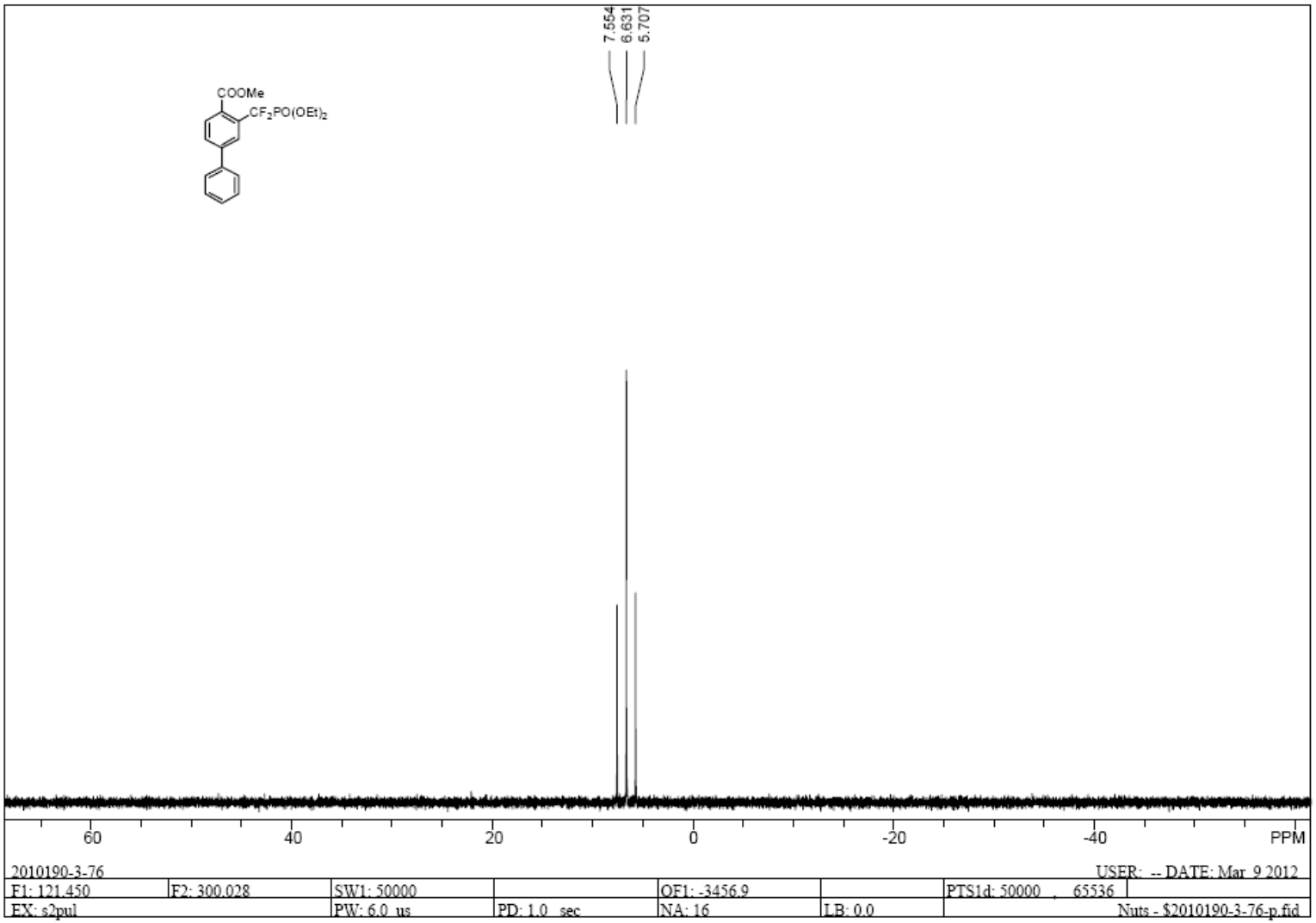

6.892
6.013
5.133
Br
N
CF2PO(OEt)2
25
20
15
10
5
0
-5
-10
-15
PPM
2010190-3-25
USER: -- DATE: Nov 30 2011
F1: 121.453
F2: 300.028
SW1: 50000
OF1: 348.4
PTS1d: 50000 , 65536
EX: s2pul
PW: 6.0 us
PD: 1.0 sec
NA: 44
LB: 0.0
Nuts - $2010190-3-25-p.fid

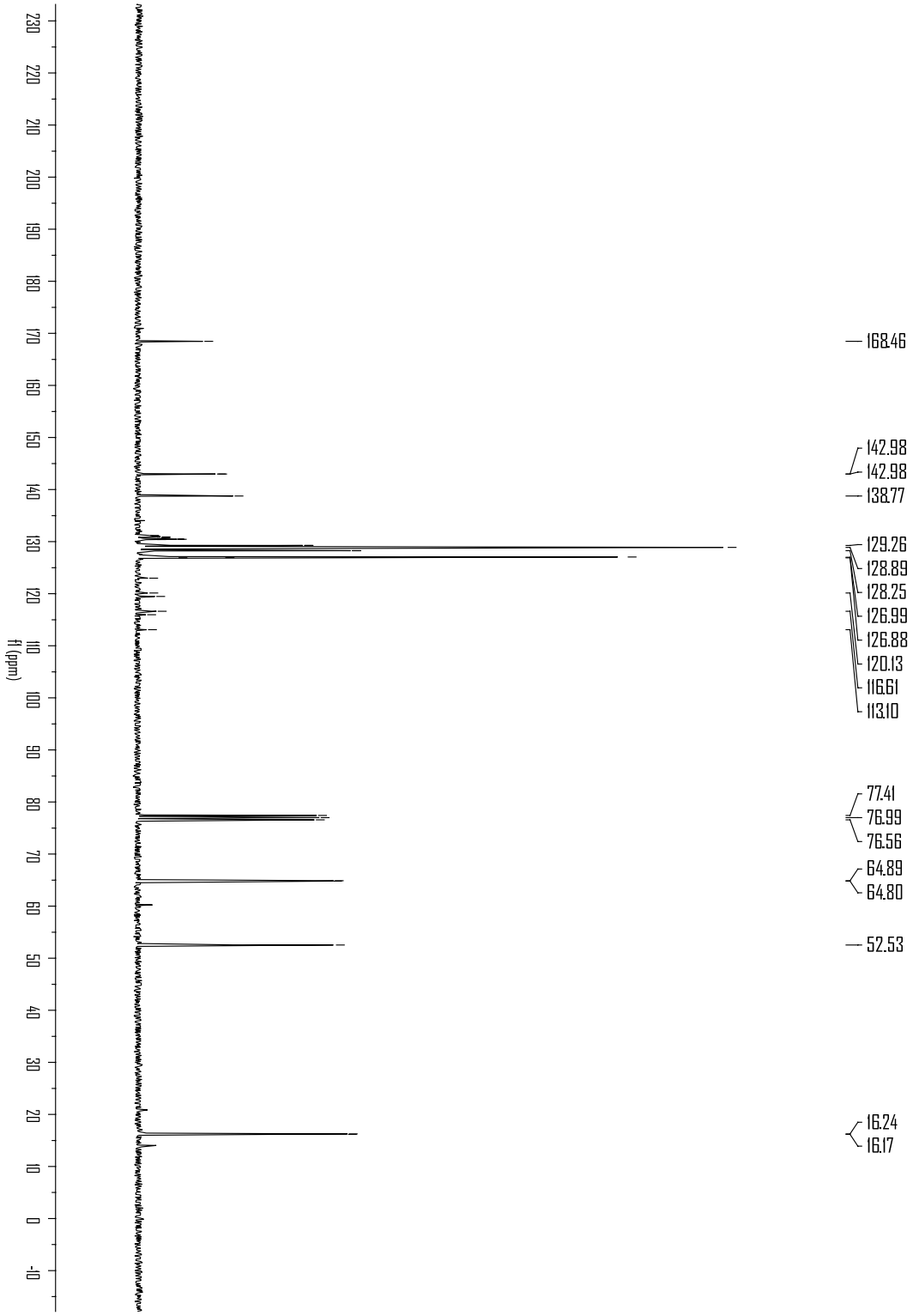

f1 (ppm)
150.70
150.40
150.25
150.16
150.01
149.77
139.76
122.97
119.79
117.65
117.15
115.02
114.53
112.39
77.37
77.05
76.73
65.13
65.07
16.34
16.30

Methyl-3-((diethoxyphosphoryl)difluoromethyl)biphenyl-4-carboxylate 7.

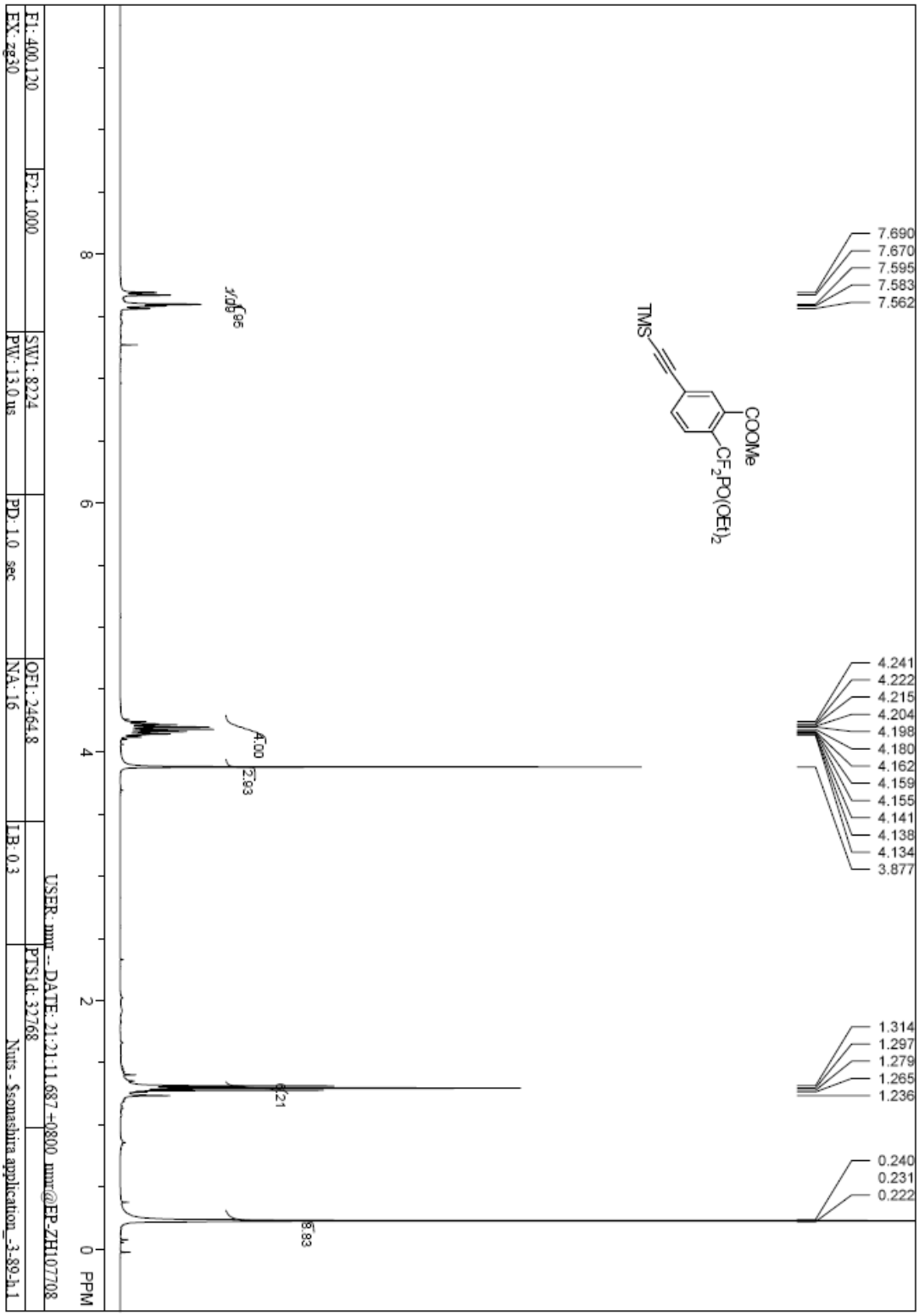


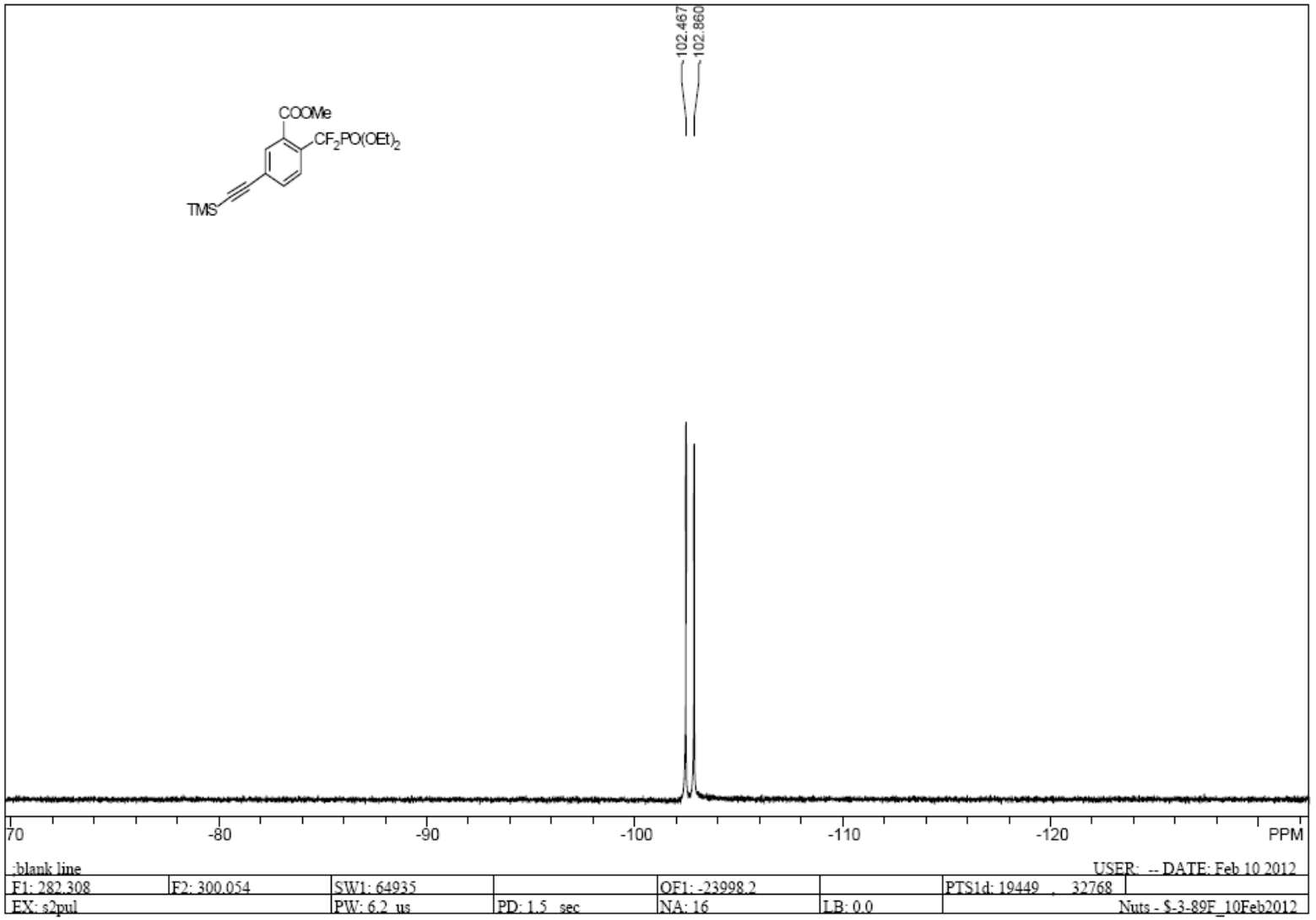

101.667
102.067
COOMe
CF2PO(OEt)2
-94
-96
-98
-100
-102
-104
-106
-108
-110
PPM
b
USER: -- DATE: Mar 7 2012
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-76-2f_07Mar2012

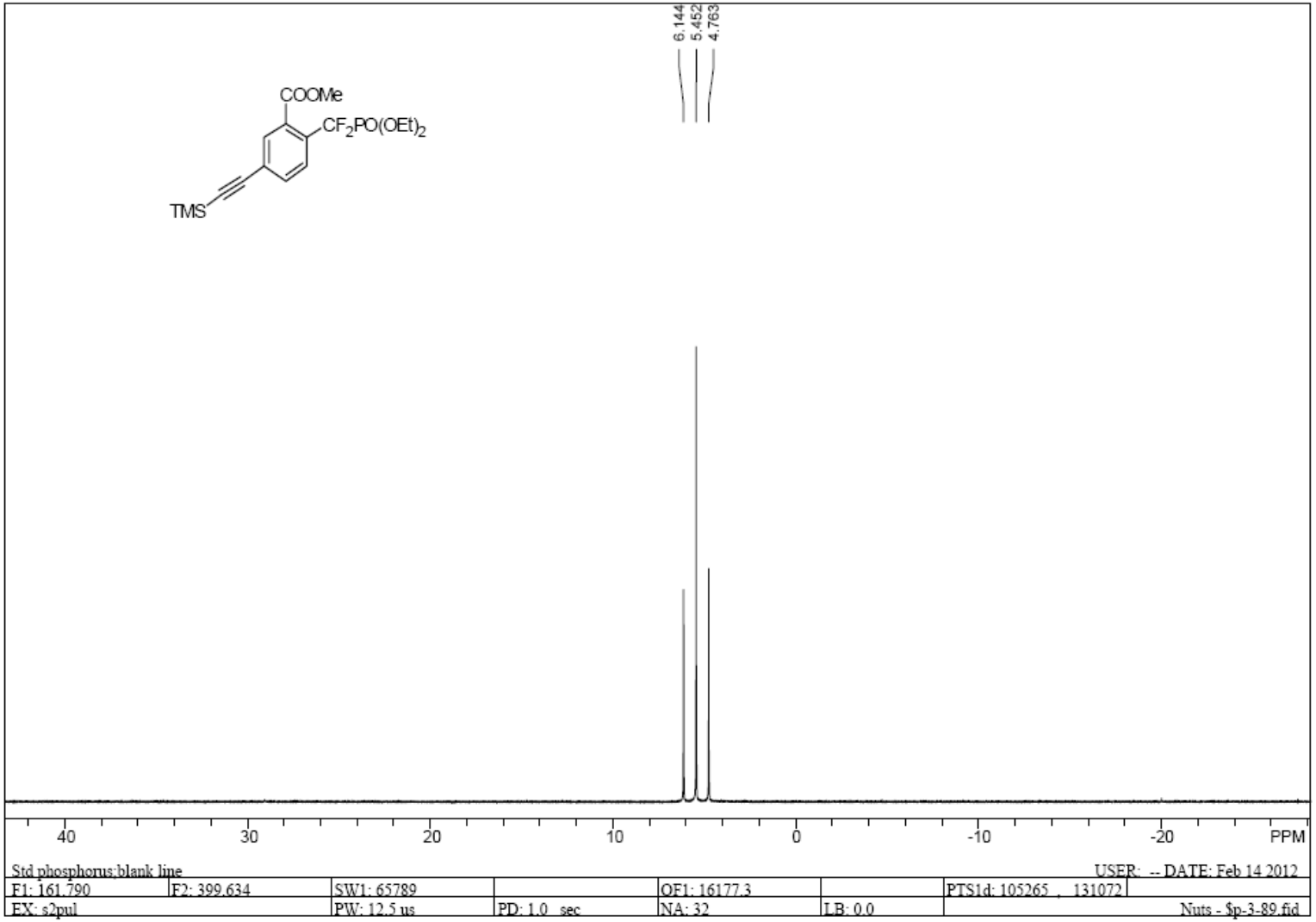

7.554
6.631
5.707
COOMe
CF2PO(OEt)2
60
40
20
0
-20
-40
PPM
2010190-3-76
USER: -- DATE: Mar 9 2012
F1: 121.450
F2: 300.028
SW1: 50000
OF1: -3456.9
PTS1d: 50000 , 65536
EX: s2pul
PW: 6.0 us
PD: 1.0 sec
NA: 16
LB: 0.0
Nuts - $2010190-3-76-p.fid

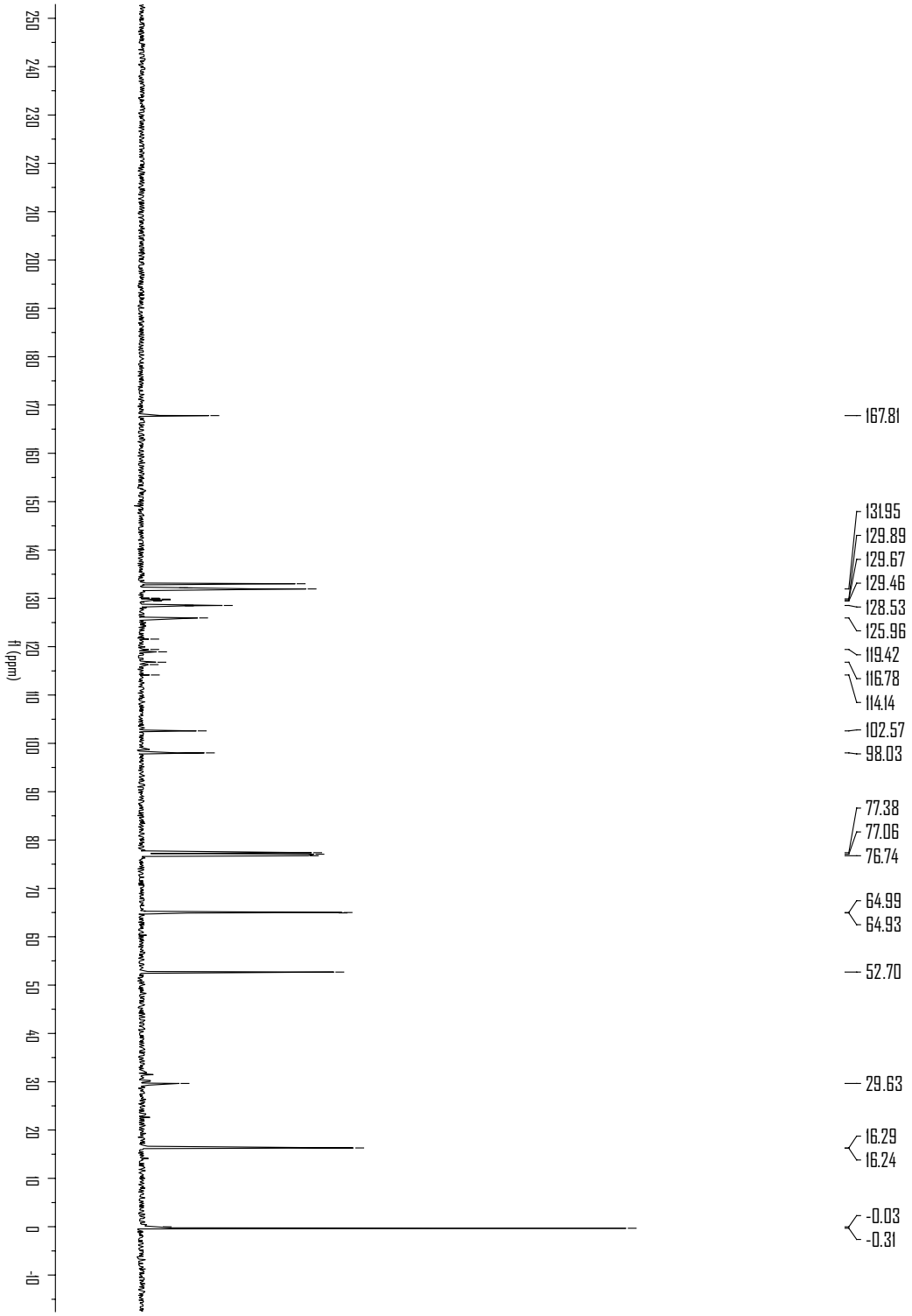

f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
168.46
142.98
142.98
138.77
129.26
128.89
128.25
126.99
126.88
120.13
116.61
113.10
77.41
76.99
76.56
64.89
64.80
52.53
16.24
16.17

Methyl-2-((diethoxyphosphoryl)difluoromethyl)-5-((trimethylsilyl)ethynyl)benzo ate 8.




102.467
102.860
COOMe
CF2PO(OEt)2
TMS
70
-80
-90
-100
-110
-120
PPM
;blank line
USER: -- DATE: Feb 10 2012
F1: 282.308
F2: 300.054
SW1: 64935
OF1: -23998.2
PTS1d: 19449 , 32768
EX: s2pul
PW: 6.2 us
PD: 1.5 sec
NA: 16
LB: 0.0
Nuts - $-3-89F_10Feb2012


6.144
5.452
4.763
COOMe
CF2PO(OEt)2
TMS
40
30
20
10
0
-10
-20
PPM
Std phosphorus;blank line
USER: -- DATE: Feb 14 2012
F1: 161.790
F2: 399.634
SW1: 65789
OF1: 16177.3
PTS1d: 105265 , 131072
EX: s2pul
PW: 12.5 us
PD: 1.0 sec
NA: 32
LB: 0.0
Nuts - $p-3-89.fid


f1 (ppm)
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
167.81
131.95
129.89
129.67
129.46
128.53
125.96
119.42
116.78
114.14
102.57
98.03
77.38
77.06
76.74
64.99
64.93
52.70
29.63
16.29
16.24
-0.03
-0.31