-Supporting Information for-

Second-Generation Tags for Fluorous Chemistry Exemplified with a New Fluorous Mitsunobu Reagent

Qianli Chu, Christopher Henry and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

Email: curran@pitt.edu

Table of Contents

I. General Methods

All experiments were done under an atmosphere of argon. All proton, carbon, and fluorine NMR spectra were recorded at 300 MHz, 75 MHz, and 121.5 MHz. Chemical shifts are reported in parts per million (ppm) and the spectra were calibrated from the residual solvent signal of $CDCl_3$ (^{13}C NMR, t 77.23 ppm, ^1H NMR 7.27 ppm) or acetone-d_6 (^{13}C NMR 29.92 ppm (septet), ^1H NMR 2.04 (quintet)). All the fluorine NMR spectra were calibrated using $CFCl_3$ (0 ppm (singlet)). In reporting spectral data, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Infrared (IR) spectra were recorded on an IBM IR/32 spectrometer and ran as neat films or chloroform solutions on sodium chloride plates. Unless otherwise stated, high and low resolution mass spectra were taken under EI mode and are reported in units of *m/e*. Flash chromatography was performed using silica gel (230-400 mesh). Melting points were measured on a Temp-Melt apparatus and were uncorrected. GC analyses were performed on a Hewlett-Packard 5890 instrument (column: 30 m x 0.32 mm x 0.25 μm HP-1 methyl siloxane)

II. Experimental Procedures

Synthesis of Bis(perfluoro-*t*-butyloxypropyl)diazodicarboxylate (7p).

3-(2',2',2'-Trifluoro-1',1'-*bis*-trifluoromethylethoxy)propanol (3p): In 100 mL flask equipped with magnetic stirrer and ice bath, argon gas inlet, and addition funnel, KOH (1.4 g, 25 mmol) was suspended in methylethyl ketone (30 mL). $(CF_3)_3COH$ (**2**, 3.5 mL, 25 mmol) was added dropwise over 20 min at 0 ˚C. The ice bath was removed and the mixture was stirred vigorously for 2 h at room temperature. $BrCH_2CH_2CH_2OH$ (2.5 mL, 28.5 mmol) was add by a syringe. The mixture was under reflux for 12 hours. Then, it was cooled to r.t. Ice water (50 mL) was added. The mixture was exacted with ether (60 mL x 3). The organic layer was dried over $MgSO_4$, filtered, concentrated and distilled at ambient pressure to afford perfluoro-*t*-butyloxypropyl alcohol (**3p,** 5.8 g, 79 % yield)) as a colorless oil (b.p. 70 ˚C/80 mmHg). ^1H NMR ($CDCl_3$) δ 4.27 (b, 1H), 4.16 (t, 2H, J_{HH} = 5.5 Hz), 3.75-3.83 (m, 2H), 1.88-1.99 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 120.4 (q, J_{CF} = 288 Hz), 79.6 (m), 68.1 (s,), 59.6 (s), 32.0 (s); ^{19}F NMR ($CDCl_3$) δ –71.2 (s); IR (thin film) 3362, 1255, 1164 cm^{-1}; MS 294 (M^+, 2%), 317 (M^++23, 5%), 215 (100%).

Bis(perfluoro-*t*-butyloxypropyl)carboxyhydrazide (5p): In a 1-neck, 100 mL flask equipped with magnetic stirrer, argon gas inlet, and addition funnel, carbonyl diimidazole (1.6 g, 9.6 mmol) was suspended in THF (15 mL, anhydrous). A solution of **3p** (2.4 g, 8 mmol) in THF (10 mL, anhydrous) was added dropwise over 1 h. The mixture was stirred vigorously for 2 h. Water (0.1 ml) was added to quench, and the mixture stirred for 10 minutes. The mixture was

concentrated in vacuo to dryness to give crude **4p**. The crude intermediate **4p** was taken up in BTF (20 ml, dried over 4 Å MS). Hydrazine monohydrogen chloride (0.27 g, 4 mmol) was added, followed by addition of triethylamine (4.8 mL, 35 mmol). This was stirred at 70 °C overnight. It was then cooled to room temperature. The mixture was diluted with ether (100 mL). After transfer to a 250 mL separatory funnel, the mixture was washed with 2N HCl (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was loaded on a silica chromatography column. Hexane/ethyl acetate (6:1) was used to elute pure diperfluoro-*t*-butyloxypropyl carboxyhydrazide (**5p**, 2.3 g, 83 % yield for two steps) as a white solid (m.p. 29-31 ˚C). ^{1}H NMR ($CDCl_3$) δ 6.54 (b, 2H), 4.35 (t, J = 5.0 Hz, 4H), 4.11 (t, J = 5.8 Hz, 4H), 2.00-2.08 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.6 (s), 121.5 (q, J = 290.5 Hz), 79.8 (m), 66.3 (s), 62.1 (s), 29.4 (s); ^{19}F NMR ($CDCl_3$) δ –71.2 (s); IR (thin film) 3310, 1732 cm^{-1}; LRMS 673 (M^++1, 75%), 695 (M^++23, 100%), 711 (M^++39, 67%), 279 (16%); HRMS calculated 673.0643, found 673.0673.

Bis(perfluoro-*t*-butyloxypropyl)diazodicarboxylate (7p): In a 100 mL flask equipped with magnetic stirrer, argon gas inlet, addition funnel, **5p** (2 g, 2.4 mmol) was suspended in BTF (20 mL). Pyridine (0.6 mL, 7.5 mmol) was added, and the mixture was purged with dry argon for five minutes while stirring vigorously. A solution of bromine (0.21 mL, 3.9 mmol) in BTF (10 mL) was added dropwise slowly. The mixture was stirred at room temperature for 3 h. The mixture was filtered in fume hood. The solid was washed with BTF (2 x 10 mL) filtered. The solid waste was then washed with $Na_2S_2O_3$ solution for disposal. The all BTF was combined and concentrated. A little yellow precipitation stick to the bottle after concentration was removed by transferring the product into another container. The product was further dried under high

vacuum overnight to provide diperfluoro-*t*-butyloxyethyl carboxyhydrazide (**7p**, 2.0 g, 100 %) as yellow oil. ^{1}H NMR ($CDCl_3$) δ 4.60 (t, J = 6.1 Hz, 4H), 4.18 (t, J = 5.7 Hz, 4H), 2.16-2.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 160.2, 120.5 (q, J = 290.7 Hz), 79.9 (m), 65.6 (s), 65.0 (s), 29.0 (s); ^{19}F NMR ($CDCl_3$) δ –71.1 (s); IR (thin film) 1782 cm^{-1}; MS 670 (M^+, 3%), 693 (M^++23, 2%), 356 (100%).

Synthesis of Bis(perfluoro-*t*-butyloxyethyl) carboxyhydrazide (5e).

2-(2',2',2'-Trifluoro-1',1'-*bis*-trifluoromethylethoxy)ethanol: In 100 mL flask equipped with magnetic stirrer and ice bath, argon gas inlet, and addition funnel, KOH (1.4 g, 25 mmol) was suspended in methylethyl ketone (30 mL). $(CF_3)_3COH$ (**2**, 3.5 mL, 25 mmol) was added dropwise over 20 min at 0 ˚C. The ice bath was removed and the mixture was stirred vigorously for 2 h at room temperature. $BrCH_2CH_2OH$ (2.0 mL, 28.5 mmol) was add by a syringe. The mixture was under reflux for 12 hours. Then, it was cooled to r.t. Ice water (50 mL) was added. The mixture was exacted with ether (60 mL x 3). The organic layer was dried over $MgSO_4$, filtered, concentrated and distilled at ambient pressure to afford perfluoro-*t*-butyloxyethyl alcohol (**3b,** 5.4 g, 77 % yield) as a colorless oil (b.p. 125 ˚C, lit.[1]: 124 ˚C).

Synthesis of Bis(perfluoro-*t*-butyloxyethyl) carboxyhydrazide (5e): In a 1-neck, 100 mL flask equipped with magnetic stirrer, argon gas inlet, and addition funnel, carbonyl diimidazole (1.6 g, 9.6 mmol) was suspended in THF (15 mL, anhydrous). A solution of **3e** (2.2 g, 8 mmol) in THF (10 mL, anhydrous) was added dropwise over 1 h. The mixture was stirred vigorously

for 2 h. Water (0.1 ml) was added to quench, and the mixture stirred for 10 minutes. The mixture was concentrated in vacuo to dryness give crude **4e**.

The crude intermediate **4e** was taken up in BTF (20 ml, dried over 4 Å MS). Hydrazine monohydrogen chloride (0.27 g, 4 mmol) was added, followed by addition of triethylamine (4.8 mL, 35 mmol). This was stirred at 70 °C overnight. It was then cooled to room temperature. The mixture was diluted with ether (100 mL). After transfer to a 250 mL separatory funnel, the mixture was washed with 2N HCl (2 x 15 mL) and brine (1 x 15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was loaded on a silica chromatography column. Hexane/ethyl acetate (6:1) was used to elute pure diperfluoro-*t*-butyloxyethyl carboxyhydrazide (**5b**, 2.1 g, 82 % yield for two steps) as white oil. ^{1}H NMR (acetone-d_6) δ 8.47 (b, 2H), 4.26 (t, J = 4.2 Hz, 4H), 2.83 (t, J = 4.3 Hz, 4H); ^{13}C NMR (acetone-d_6) δ 157.1, 121.2 (q, J = 289.9 Hz), 80.5 (m), 69.7 (s), 64.2 (s); ^{19}F NMR (acetone-d_6) δ –71.6 (s); IR (thin film) 3296, 1740 cm^{-1}; MS 645 (M^++1, 60%), 667 (M^++23, 100%), 683 (M^++39, 45%).

General Procedure for the Mitsunobu Reactions: Synthesis of 4-Cyanophenyl 4-Fluorobenzyl Ether (10a): 4-Cyanophenol (**8**, 51 mg, 0.42 mmol), *p*-fluorobenzyl alcohol (**9**, 26 μL, 0.23 mmol), F-TPP (300 mg, 0.35 mmol) and F-DEAD (355 mg, 0.42 mmol) were combined by procedure B[2] in THF (10 mL) (procedure B: A solution of F-DEAD in THF (5 mL) was slowly added to a solution of phenol, alcohol, and F-TPP in THF (5 mL) at room temperature over 30 mins.). After the reaction was completed, the crude reaction mixture was concentrated and taken up in ether (100 mL) and washed with aqueous 1 M sodium hydroxide solution (2 x 10 mL) and brine (2 x 10 mL). The ether layer was dried with magnesium sulfate

and concentrated. The crude reaction mixture was loaded onto a 20 g Fluoro*Flash* cartridge using MeOH (<1 mL). Washing with 80:20 MeOH:H_2O (30 mL) eluted the organic product. A second wash with MeOH (100 mL) eluted the fluorous byproducts. The MeOH:water fraction was concentrated and dried to give 47 mg 4-cyanophenyl 4-fluorobenzyl ether (**10a**, 90 % yield; 96 % GC purity), which is a known compound. Its CAS registry number is [56442-14-9].

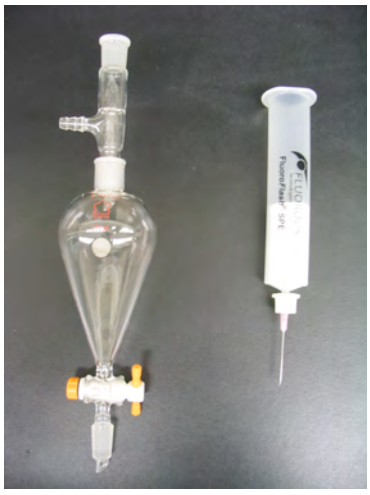
Recycling of the reagents: The crude fluorous fraction from the spe was purified by flash chromatography, as previously described.[2] The recovered hydrazide **5b** was reconverted to **7p** by the above procedure. The recovered phosphine oxide was reconverted to the phosphine by the published procedure.[3]

III. Apparatus for F-SPE

Designed by Mr. Simon Nielsen, visiting graduate student from the Danish University of Pharmaceutical Sciences.

a) New apparatus for F-SPE

b) standard apparatus



c) close up view

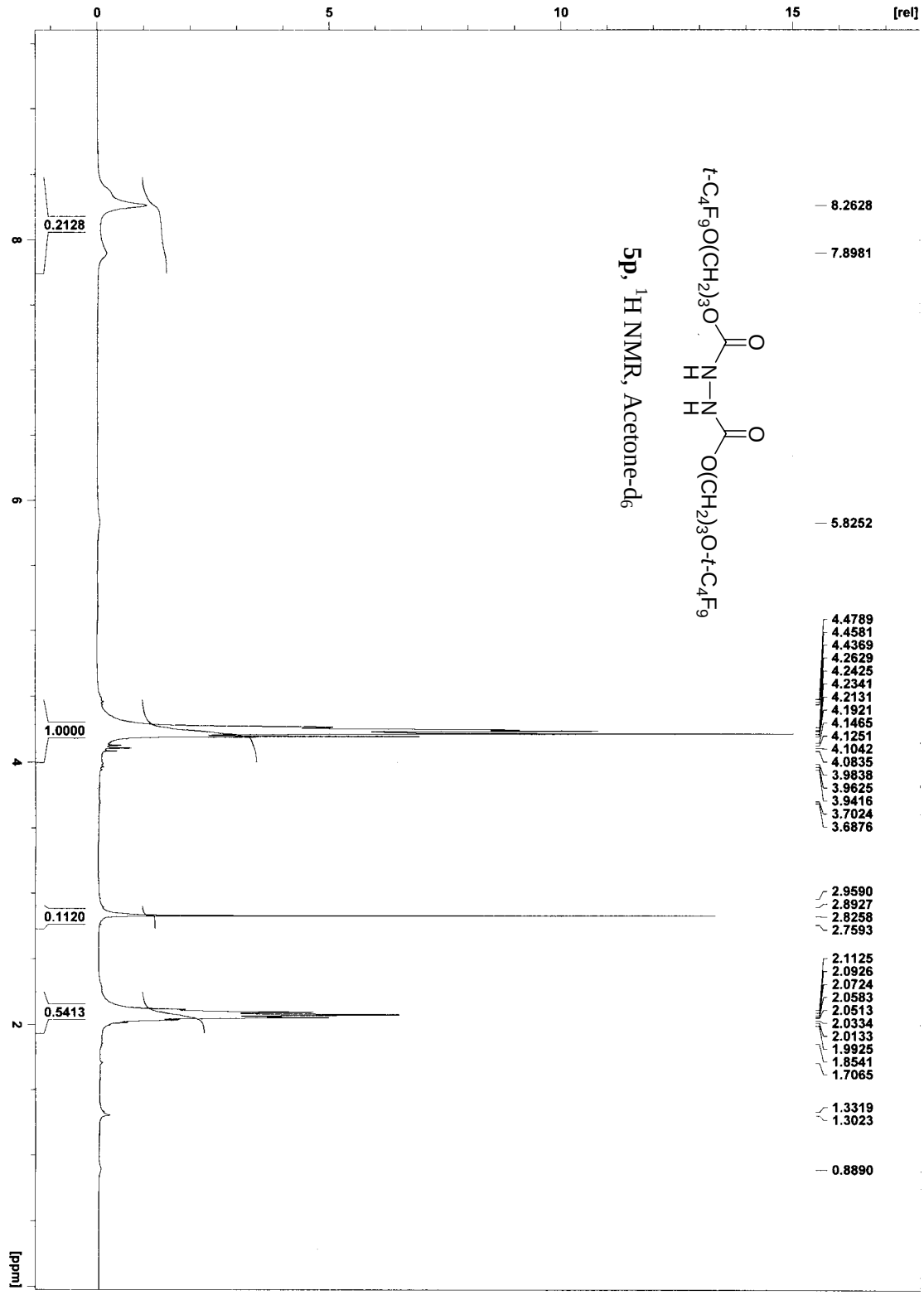
d) component parts

Figure 1. Standard and new apparatus for F-SPE with its parts

As shown in Figure 1, the new F-SPE apparatus consists of 1) a Fluoro*Flash* cartridge; 2) a septum stopper with its top part cropped; 3) a needle; 4) a vacuum adapter; 5) a separatory funnel.

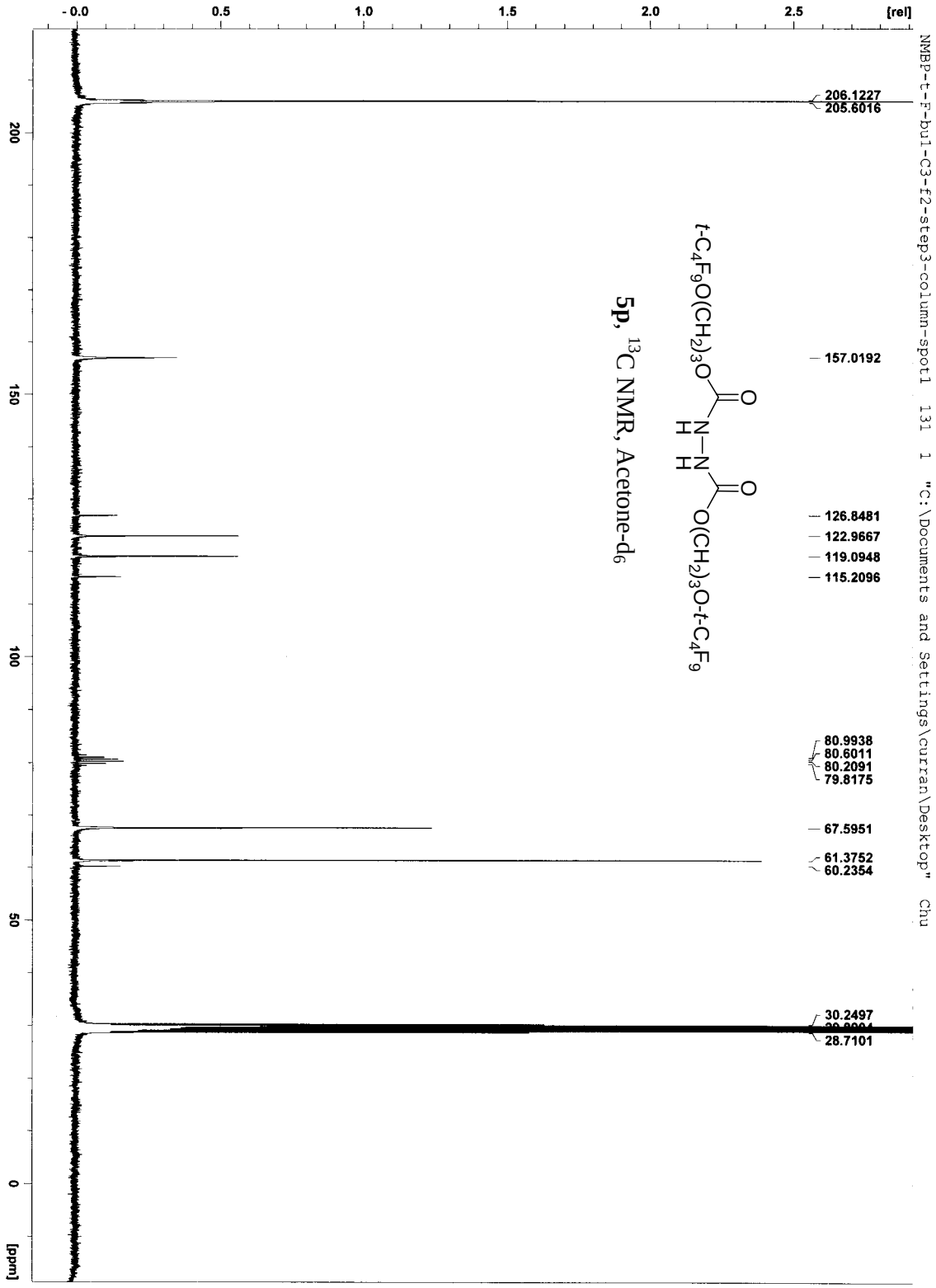
IV. References

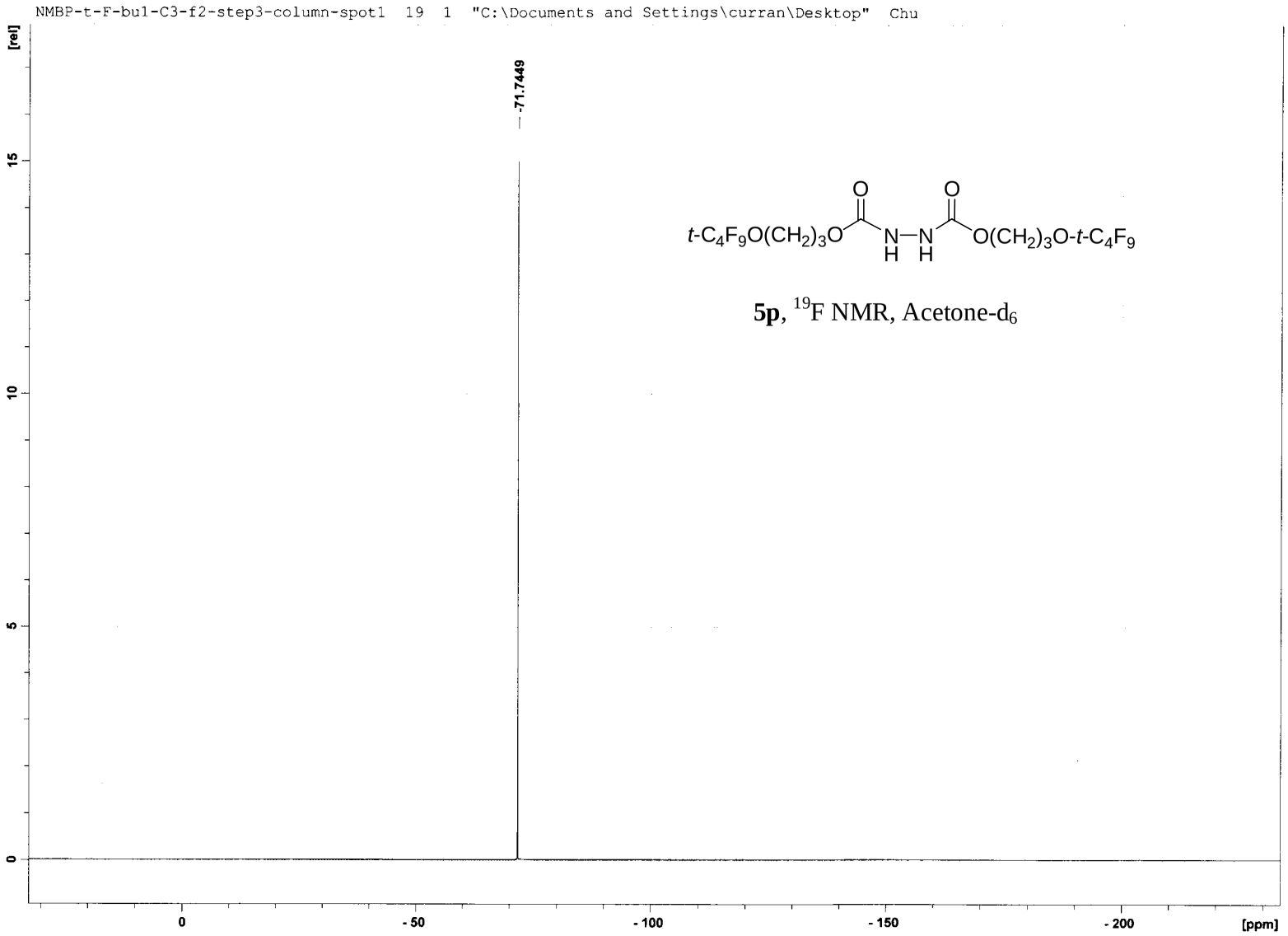
1. Szabó, D.; Mohl, J.; Bálint, A.-M.; Bodor, A.; Rábai, J. *J. Fluorine Chem.* **2006**, *127*, 1496-1504.
2. Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855-3864.
3. Zhang, Q.; Luo, Z.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866-8873.



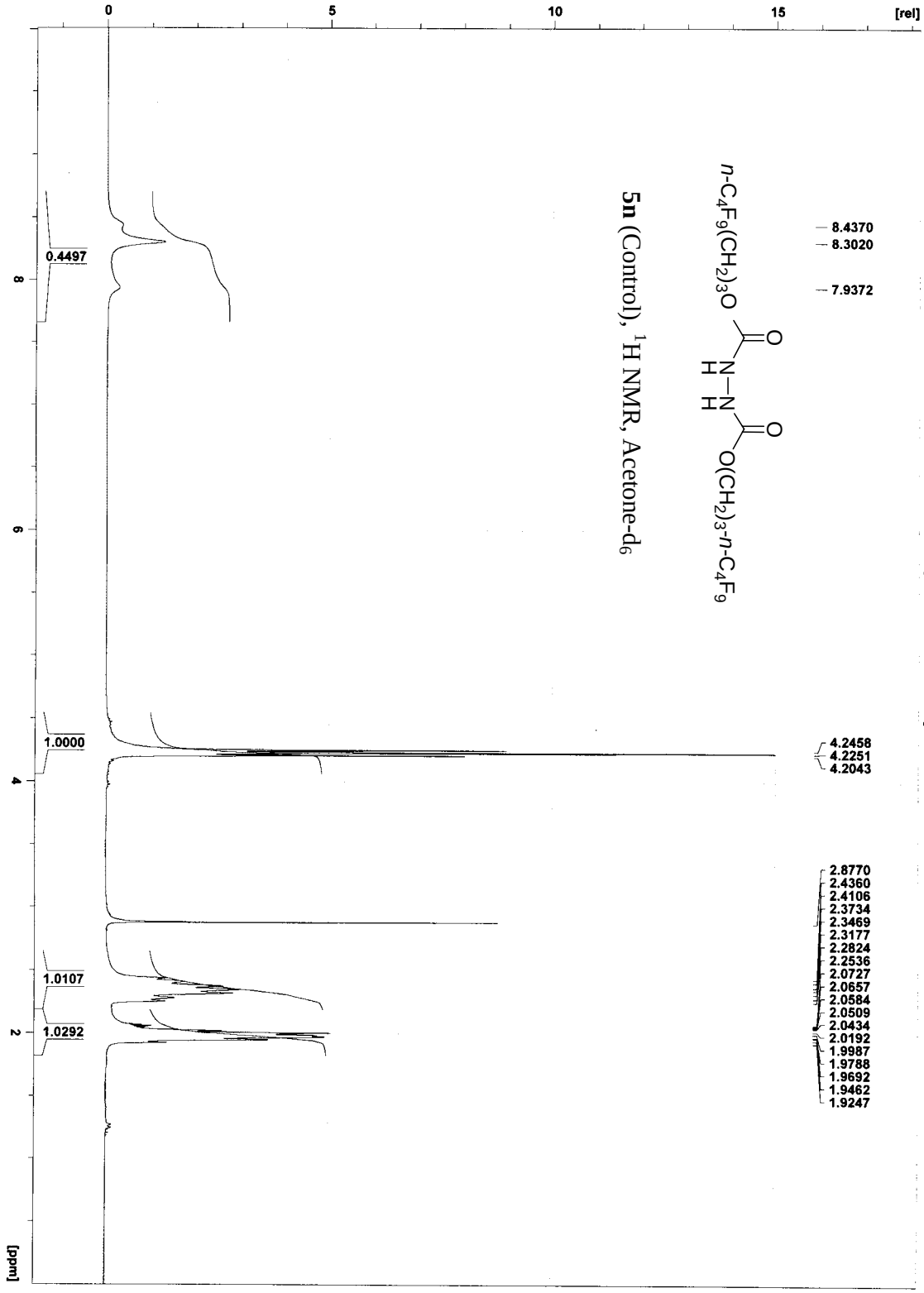
t-$C_4F_9O(CH_2)_3O$ O N–N H H O $O(CH_2)_3O$-t-C_4F_9

5p, ^{1}H NMR, Acetone-d_6

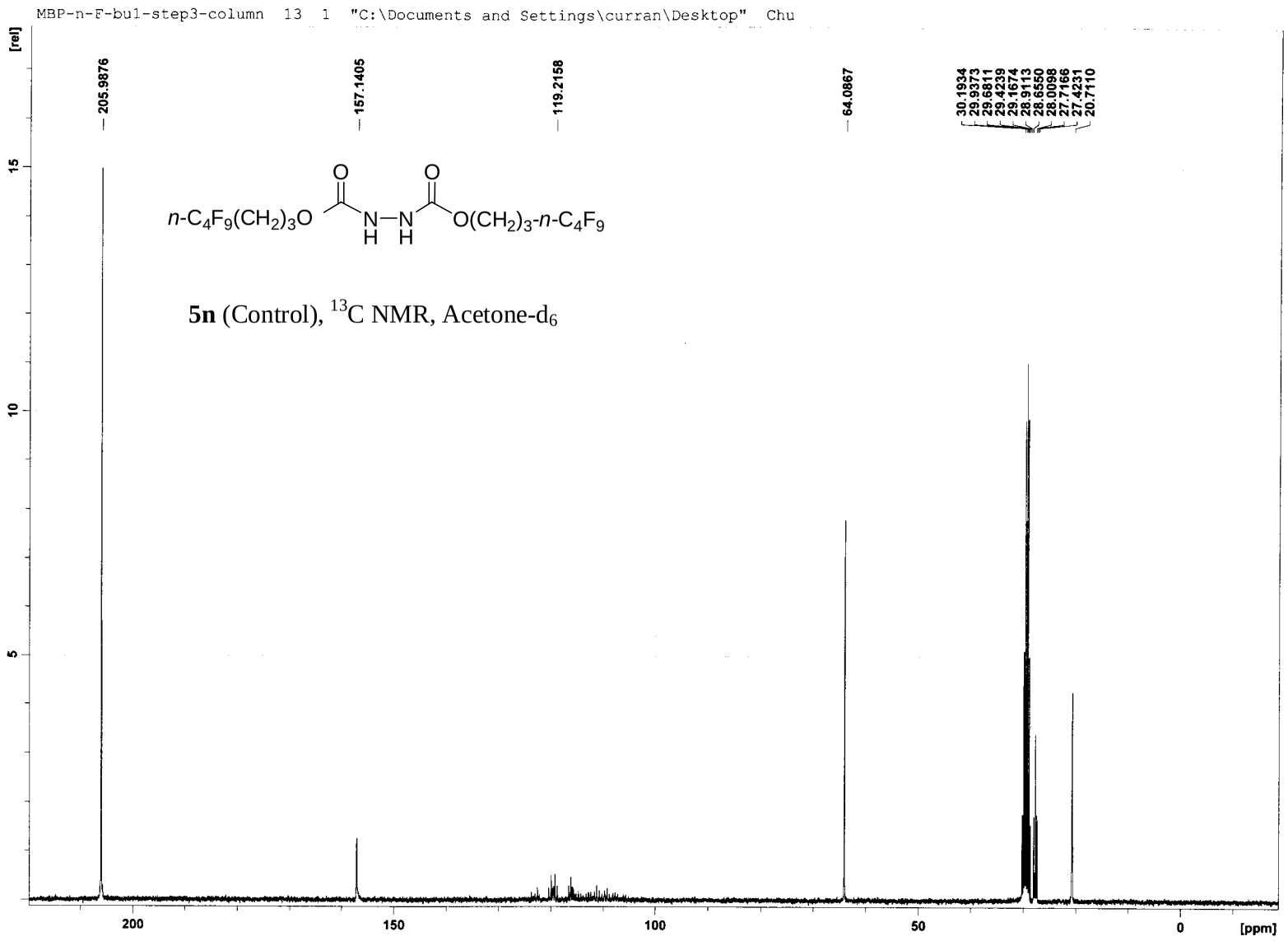

- 0.0
0.5
1.0
1.5
2.0
2.5
[rel]
200
150
100
50
0
[ppm]
206.1227
205.6016
157.0192
126.8481
122.9667
119.0948
115.2096
80.9938
80.6011
80.2091
79.8175
67.5951
61.3752
60.2354
30.2497
28.7101
NMBP-t-F-bu1-C3-f2-step3-column-spot1 131 1 "C:\Documents and Settings\curran\Desktop" Chu
t-C4F9O(CH2)3O
O
N—N
H H
O
O(CH2)3O-t-C4F9
5p, 13C NMR, Acetone-d6



5p, ^{19}F NMR, Acetone-d_6

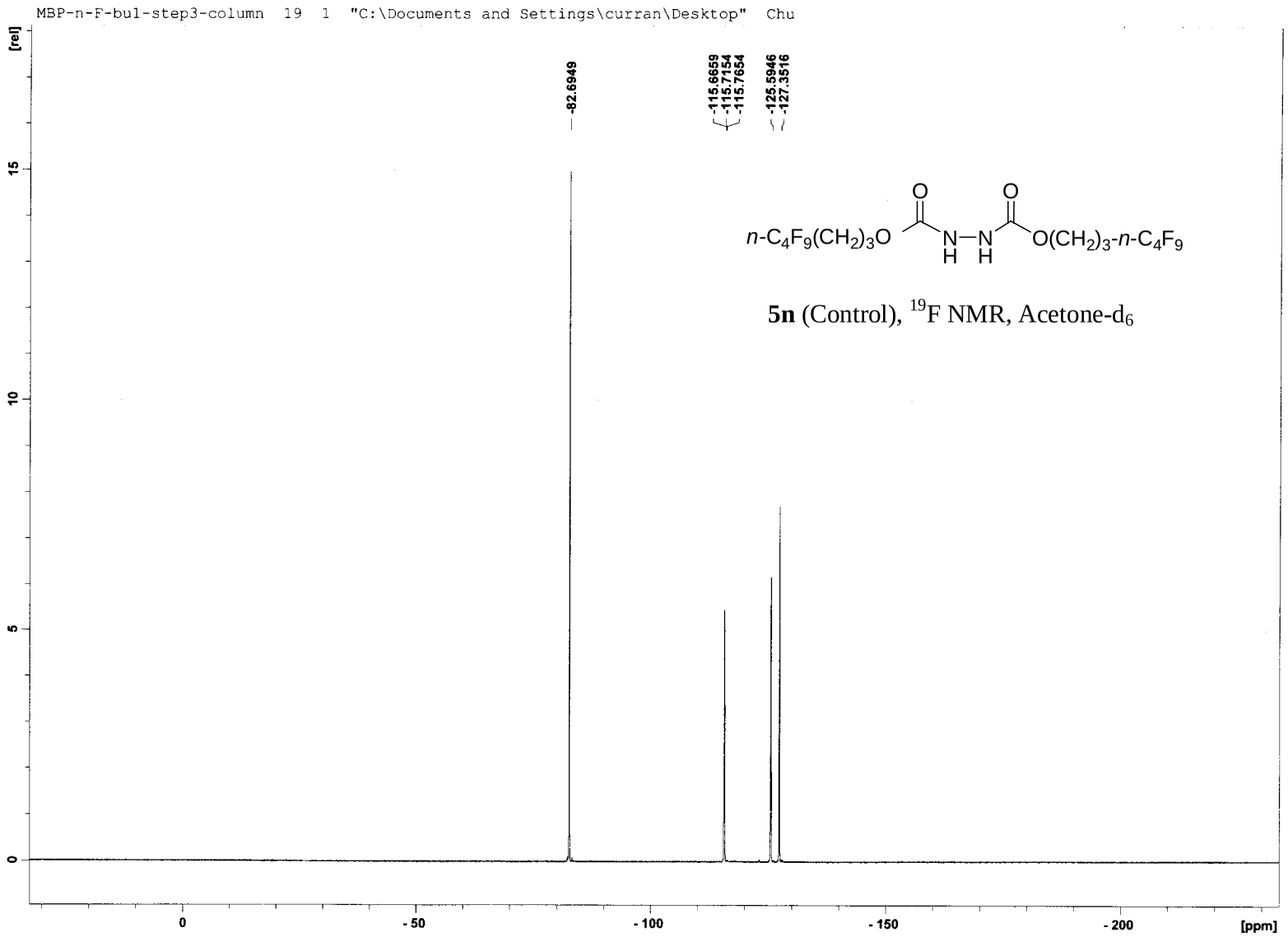


5n (Control), ^{1}H NMR, Acetone-d_6



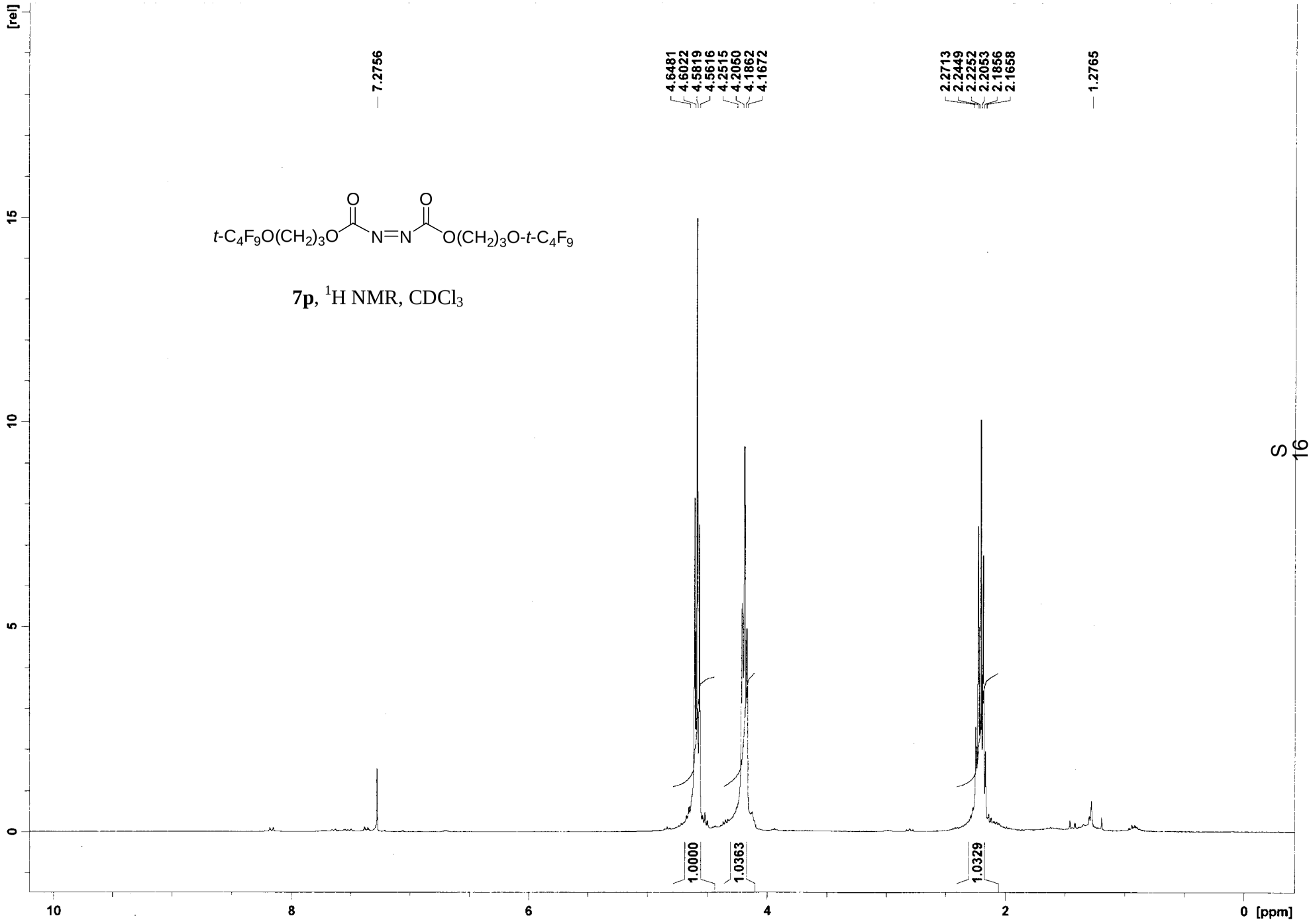
n-$C_4F_9(CH_2)_3O$ $O(CH_2)_3$-n-C_4F_9

5n (Control), ^{13}C NMR, Acetone-d_6

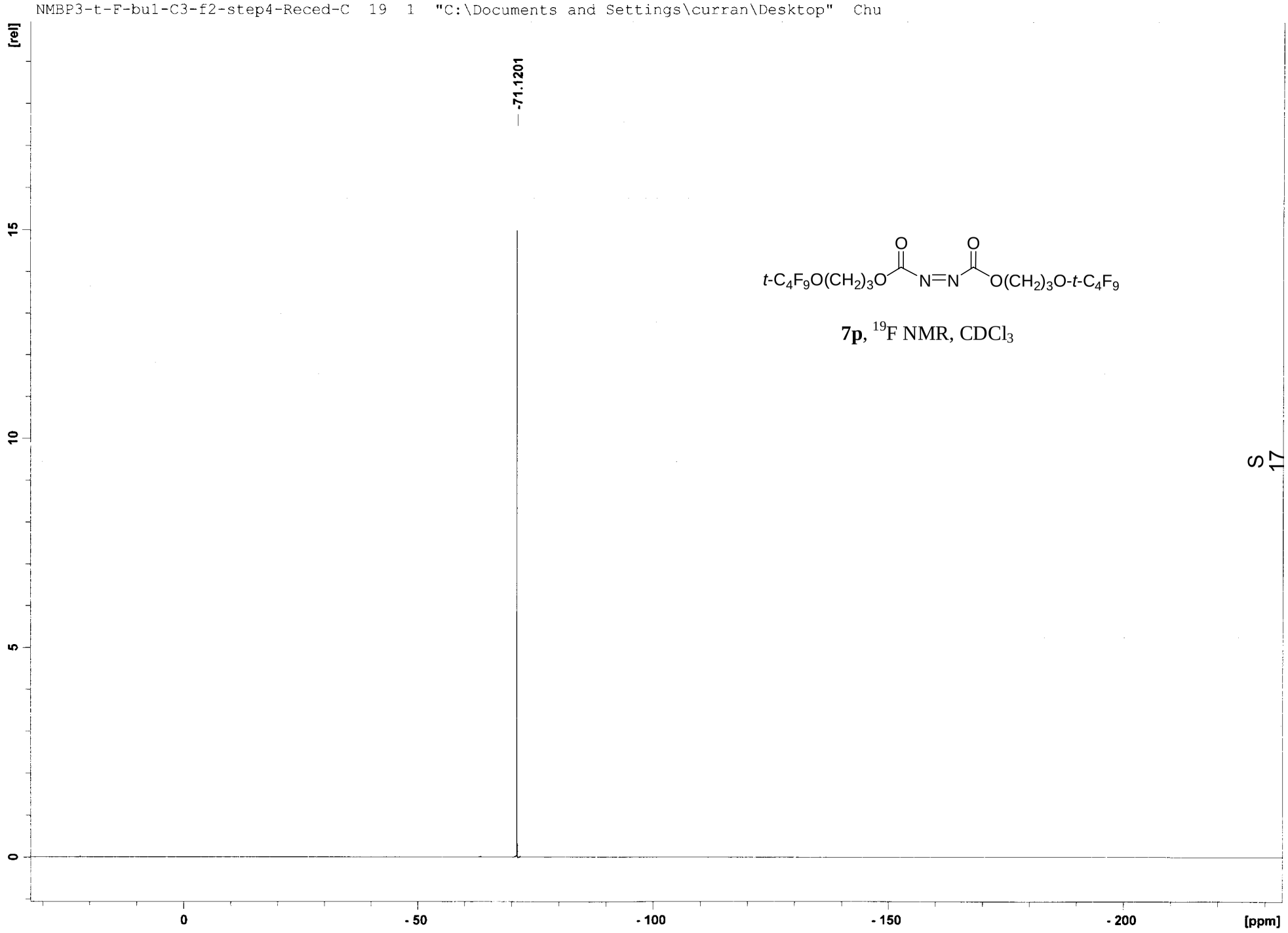


5n (Control), ^{19}F NMR, Acetone-d_6

NMBP3-t-F-bu1-C3-f2-step4-Reced-Chris 1 1 "C:\Documents and Settings\curran\Desktop" Chu

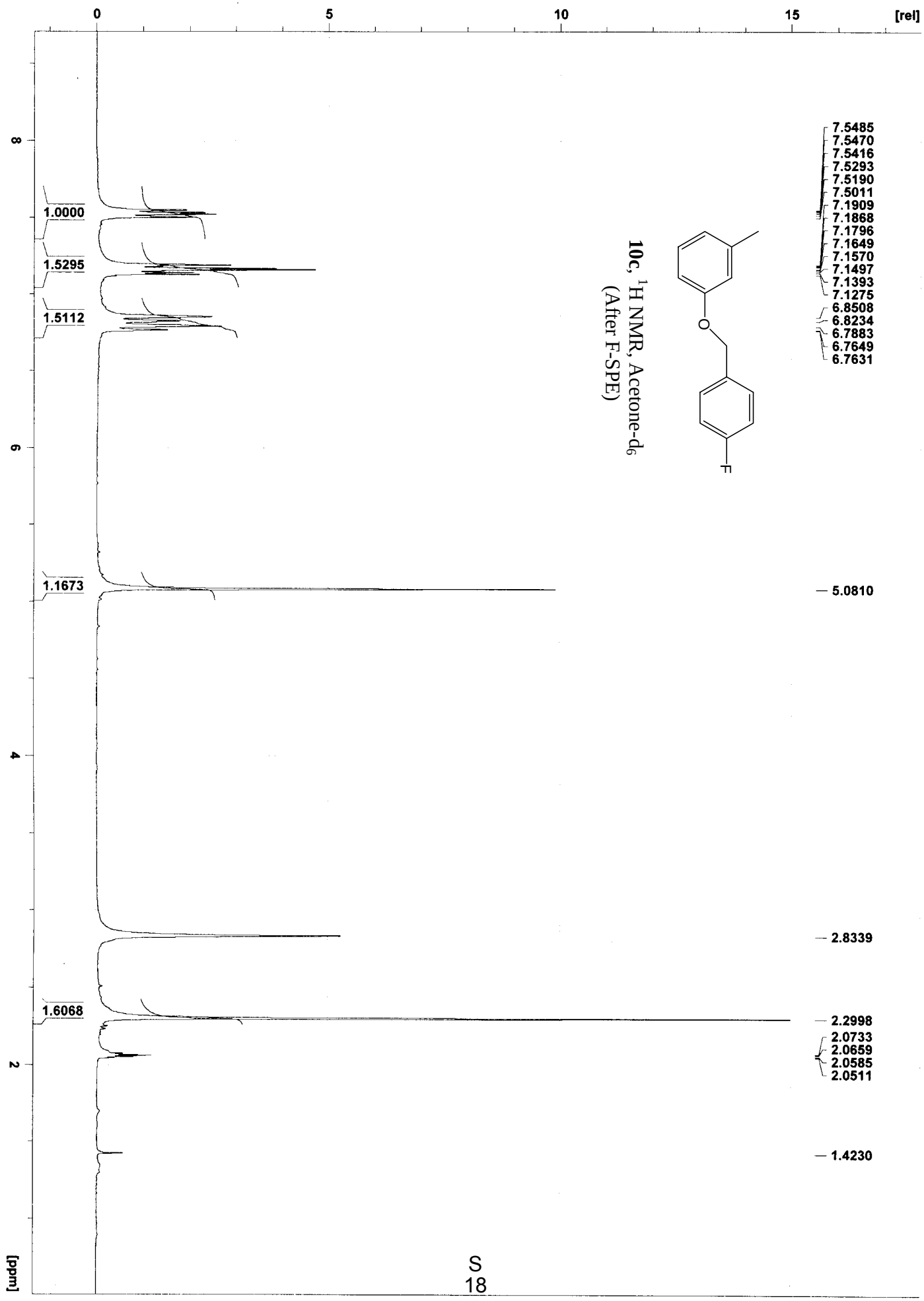


7p, ^{1}H NMR, $CDCl_3$



t-$C_4F_9O(CH_2)_3O$ O N=N O $O(CH_2)_3O$-t-C_4F_9

7p, ^{19}F NMR, $CDCl_3$


RMBP-t-F9-C3-3-Me-P 1 1 "C:\Documents and Settings\curran\Desktop" Chu
10c, ^{1}H NMR, Acetone-d$_6$
(After F-SPE)
F
7.5485
7.5470
7.5416
7.5293
7.5190
7.5011
7.1909
7.1868
7.1796
7.1649
7.1570
7.1497
7.1393
7.1275
6.8508
6.8234
6.7883
6.7649
6.7631
5.0810
2.8339
2.2998
2.0733
2.0659
2.0585
2.0511
1.4230
1.0000
1.5295
1.5112
1.1673
1.6068
0
5
10
15
[rel]
8
6
4
2
[ppm]