

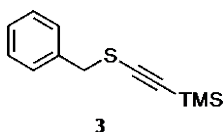
Supplementary Material

Fluorovinyl thioethers as putative steric and electronic thioester enolate mimetics: Chemoselective HF addition to acetylene thioethers

Davide Bello, Rodrigo A. Cormanich and David O'Hagan*

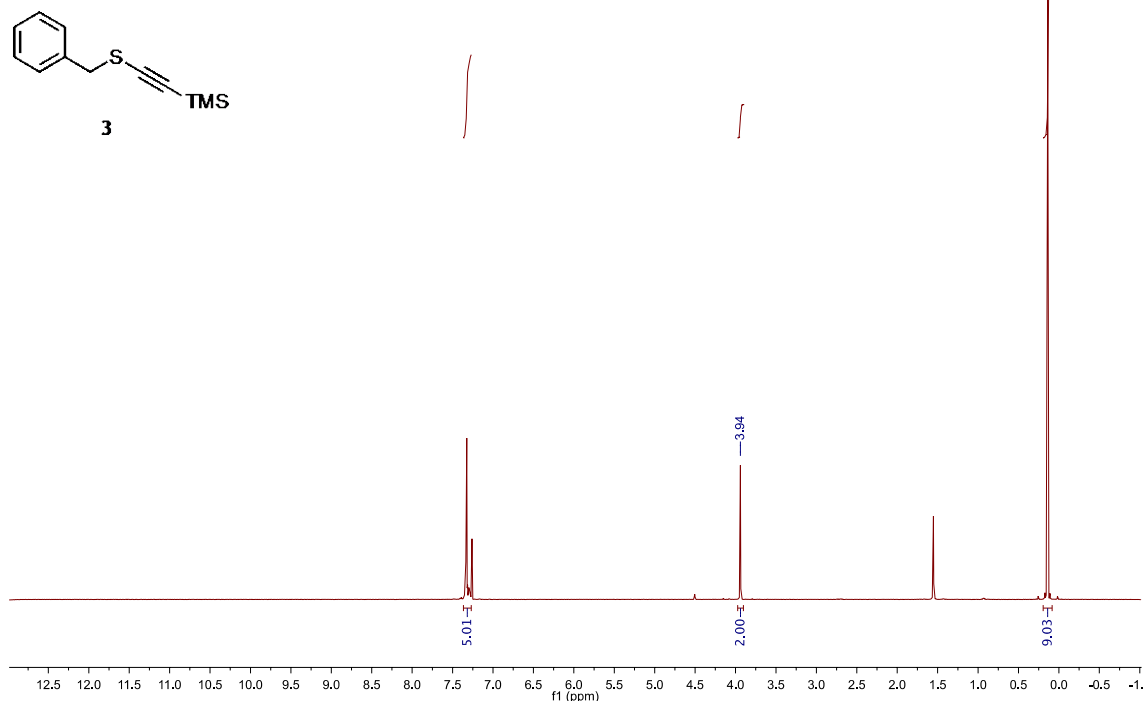
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*Email: do1@st-andrews.ac.uk

- **Experimental section**

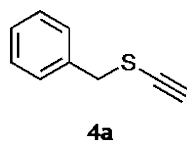
Benzylthioethynyl trimethylsilane (3)

Trimethylsilyl acetylene (5.5 mL, 39.0 mmol, 1.0 equiv) was dissolved in diethylether (50 mL) and the resulting mixture cooled to -78 °C. Buthyllithium (1.6 M in hexanes, 24.0 mL, 39.0 mmol, 1.0 equiv) was slowly added dropwise with stirring, and the mixture stirred at -78 °C for a further 15 minutes. Molecular sulphur (1.25 g, 39 mmol, 1.0 equiv) was then added portionwise at -78 °C, and the resulting mixture allowed to warm to room temperature and stirred for a further hour, upon which time the sulfur completely dissolved to yield an orange colour. The mixture was then re-cooled to 0 °C and benzyl bromide (4.6 mL, 39.0 mmol, 1.0 equiv) was added dropwise, and the resulting mixture allowed to warm to room temperature and stirred for 16 hours. The resulting turbid mixture was concentrated under reduced pressure to yield a yellow paste, which was extracted with taken up with hexane (30 mL) and filtered. This procedure was repeated three times, and the combined hexane layers were concentrated under reduced pressure to furnish the title compound (orange oil, 7.7 g, 89% yield). The material obtained was used in the next synthetic step without any further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.30 (m, 5H), 3.94 (s, 2H), 0.14 (s, 9H). These data are in good agreement with the literature values.¹

01112013-3-doh-db44-F
1H Observe
DB112_crude

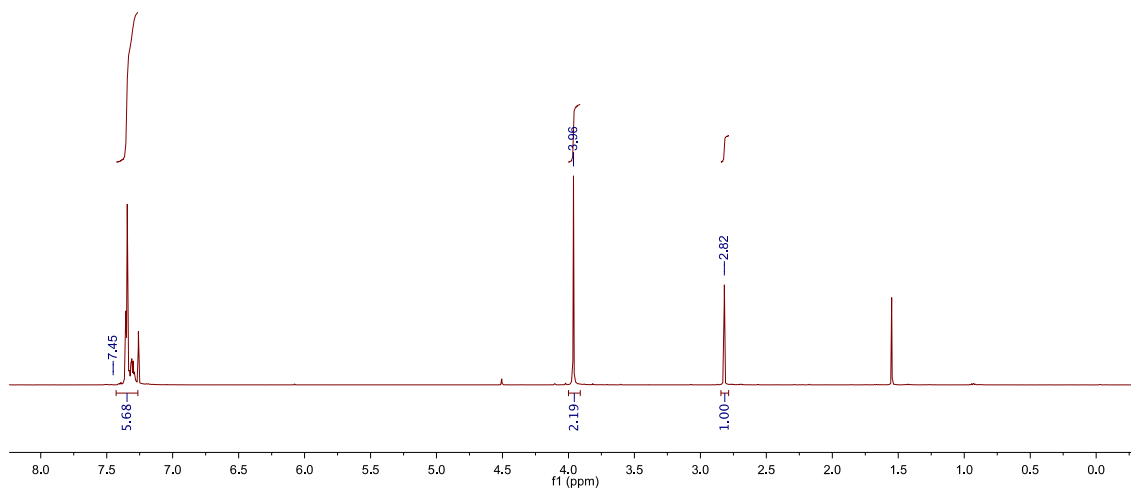
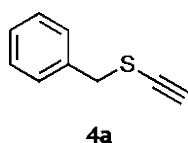


Benzyl ethynyl sulfane (4a)

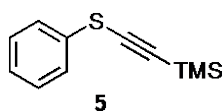


Benzylthioethynyl trimethylsilane **3** (4.0 g, 18.1 mmol, 1.0 equiv) was dissolved in a 3:1 mixture of tetrahydrofuran and methanol (40 mL), and tetrabutylammonium fluoride trihydrate (33.0 mg, 0.104 mmol, 0.006 equiv) was added in one portion. The resulting mixture was stirred at room temperature for 16 hours. The mixture was then concentrated under reduced pressure, the residue taken up in dichloromethane (30 mL) and the resulting solution washed with brine (3 x 10 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure, to furnish the title compound as a light orange oil (2.48 g, 92% yield). The material obtained was used in the next synthetic step without any further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.28 (m, 5H), 3.96 (s, 2H), 2.82 (s, 1H). These data are in good agreement with the literature values.¹

01142013-11-doh-db44-A
1H Observe
DB113_crude

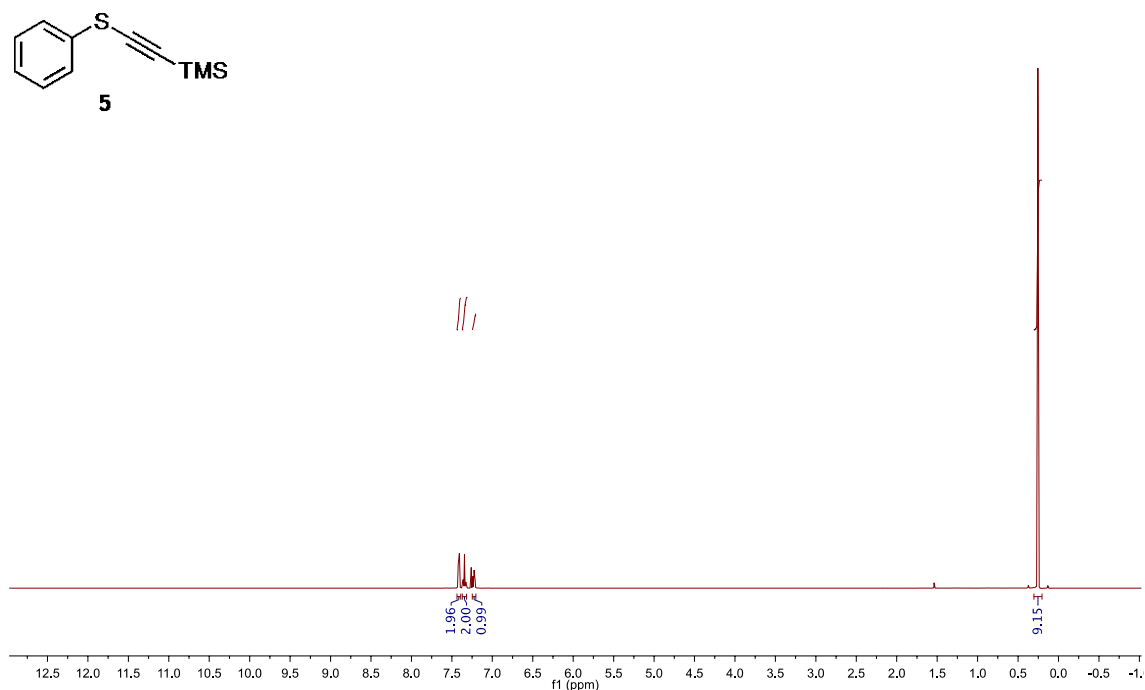


Phenylthioethynyl trimethylsilane (5)

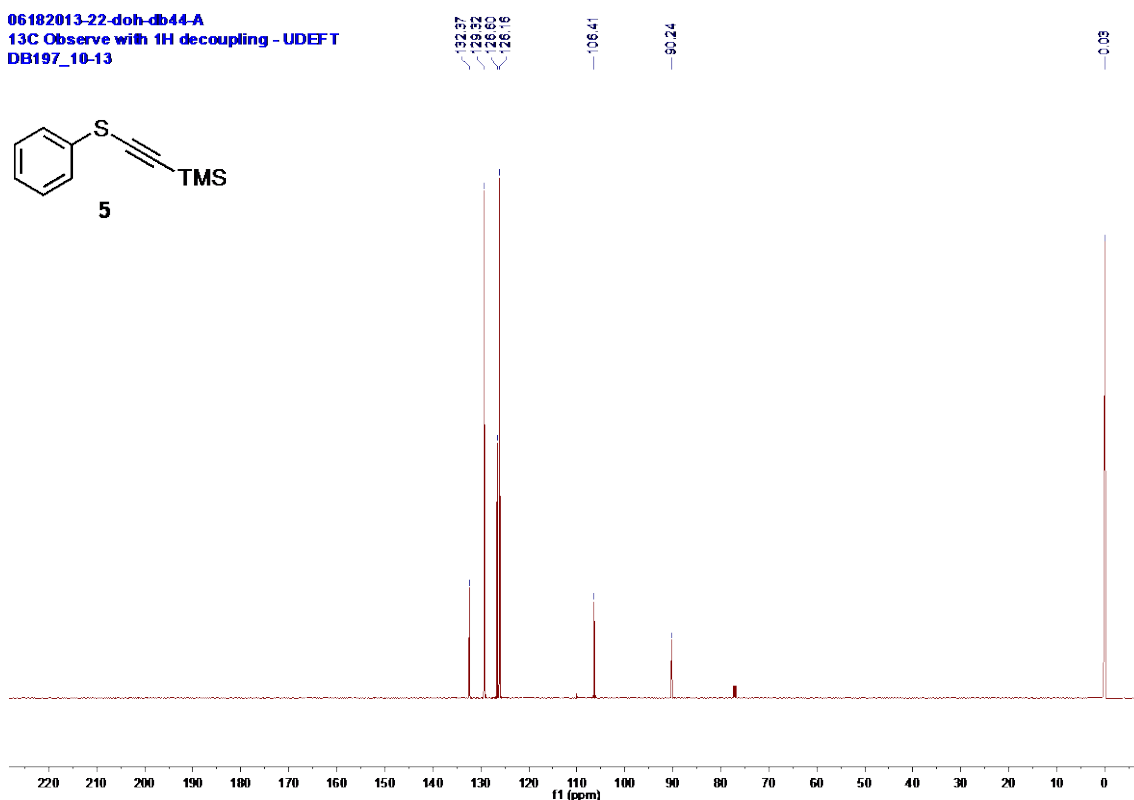


Trimethylsilyl acetylene (1.42 mL, 10.1 mmol, 1.1 equiv) was dissolved in diethylether (15 mL) and the resulting mixture cooled to -78 °C. Butyllithium (1.5 M in hexanes, 6.7 mL, 10.1 mmol, 1.1 equiv) was slowly added dropwise with stirring, and the mixture stirred at -78 °C for a further 15 minutes. Diphenyl disulfide (2.0 g, 9.2 mmol, 1.0 equiv) was then added portionwise at -78 °C, and the resulting mixture allowed to warm to room temperature and stirred for 16 hours. The mixture was diluted with diethyl ether to 30 mL, washed with a saturated aqueous solution of sodium hydrogen carbonate (20 mL), brine (20 mL), then the layers were separated and the organic layer was dried over magnesium sulfate, filtered and carefully concentrated under reduced pressure (product **5** is highly volatile) to yield a yellow oil. Purification by silica gel column chromatography, eluting with hexane, afforded the title compound as a colourless oil (1.1 g, 58% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.42-7.40 (m, 2H), 7.36-7.33 (m, 2H), 7.24-7.21 (m, 1H), 0.26 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 132.4, 129.3, 126.6, 126.2, 106.4, 90.2, 0.03. These data are in good agreement with the literature values.²

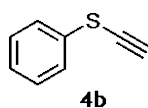
06182013-10-doh-db44-A
1H Observe
DB197_10-13



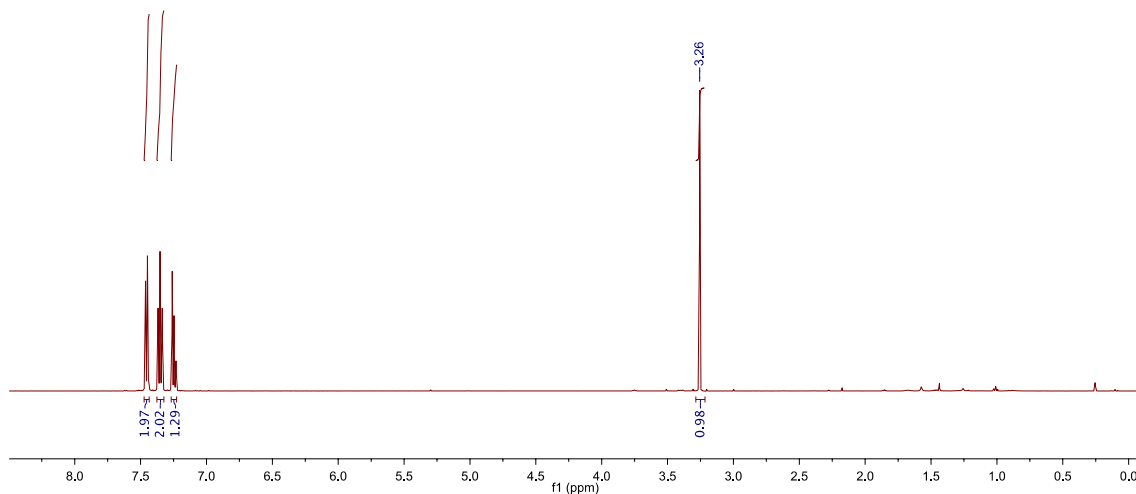
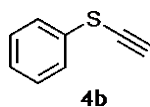
06182013-22-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB197_10-13



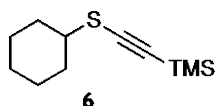
Phenyl ethynyl sulfane (**4b**)



Phenylthioethynyl trimethylsilane **5** (0.7 g, 3.39 mmol, 1.0 equiv) was dissolved in a 3:1 mixture of tetrahydrofuran and methanol (7 mL), and tetrabutylammonium fluoride trihydrate (43.0 mg, 0.135 mmol, 0.04 equiv) was added in one portion. The resulting mixture was stirred at room temperature for 16 hours. The mixture was then concentrated under reduced pressure, the residue taken up in dichloromethane (10 mL) and the resulting solution washed with brine (3 × 5 mL), dried over magnesium sulfate, filtered and carefully concentrated under reduced pressure (product is **4b** highly volatile), to furnish the title compound as a colourless oil (420 mg, 93% yield). The material obtained was used in the next synthetic step without any further purification. ¹H NMR (500 MHz, CDCl₃) δ 7.47-7.45 (m, 2H), 7.37-7.34 (m, 2H), 7.26-7.23 (m, 1H), 3.26 (s, 1H). These data are in good agreement with the literature values.²



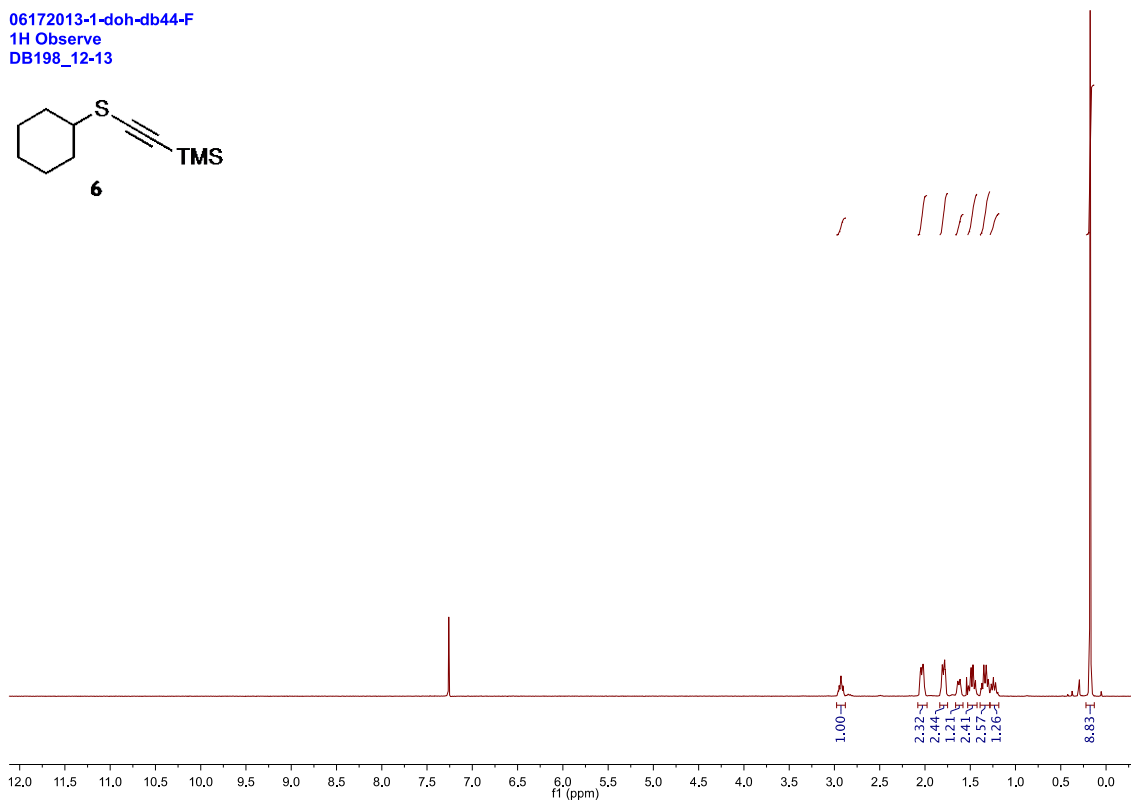
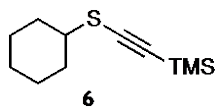
Cyclohexylthioethynyl trimethylsilane (6)



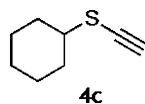
Trimethylsilyl acetylene (3.48 mL, 24.6 mmol, 1.0 equiv) was dissolved in diethylether (50 mL) and the resulting mixture cooled to -78 °C. Buthyllithium (1.5 M in hexanes, 16.4 mL, 24.6 mmol, 1.0 equiv) was slowly added dropwise with stirring, and the mixture stirred at -78 °C for a further 15 minutes. Molecular sulphur (0.8 g, 24.6 mmol, 1.0 equiv) was then added portionwise at -78 °C, and the resulting mixture allowed to warm to room temperature and stirred for a further hour, upon which time the sulfur completely dissolved to yield an orange colour. The mixture was then re-cooled to 0 °C and cyclohexyl bromide (3.0 mL mL, 24.6 mmol, 1.0 equiv) was added dropwise, the resulting mixture allowed to warm to room temperature and then stirred for 16 hours under reflux. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was taken up in ethyl acetate (30 mL) and a saturated aqueous solution of sodium hydrogen carbonate (20 mL), the layers separated, the aqueous layer extracted with ethyl acetate (2 x 10 mL), the organic layers combined, washed with brine (20 mL), then dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification by silica gel column chromatography, eluting with hexane, afforded the title compound as a colourless oil (3.24 g, 61% yield). ¹H NMR (500 MHz, CDCl₃) δ 2.98 – 2.88 (m, 1H), 2.08 – 1.96 (m, 2H), 1.84 – 1.74 (m, 2H), 1.67 – 1.59 (m, 1H), 1.53 – 1.43 (m, 2H), 1.39

– 1.28 (m, 2H), 1.28 – 1.19 (m, 1H), 0.18 (s, 9H). These data are in good agreement with the literature values.³

06172013-1-doh-db44-F
1H Observe
DB198_12-13

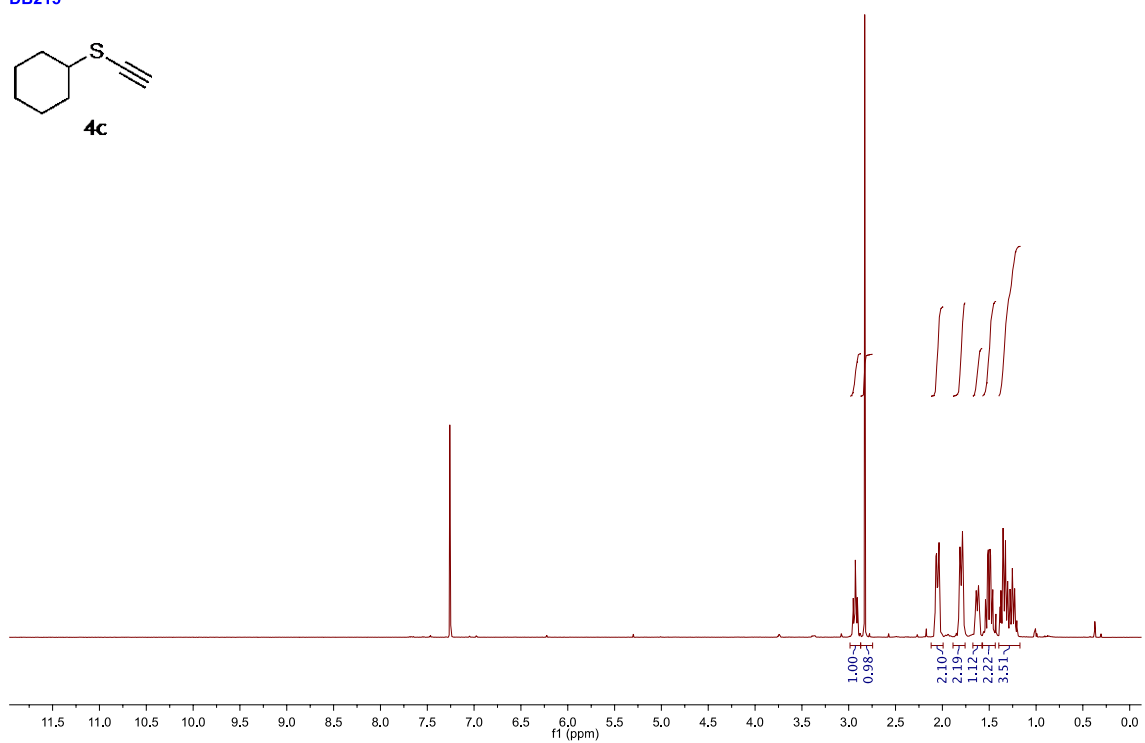
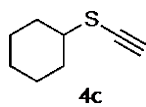


Cyclohexyl ethynyl sulfane (4c)



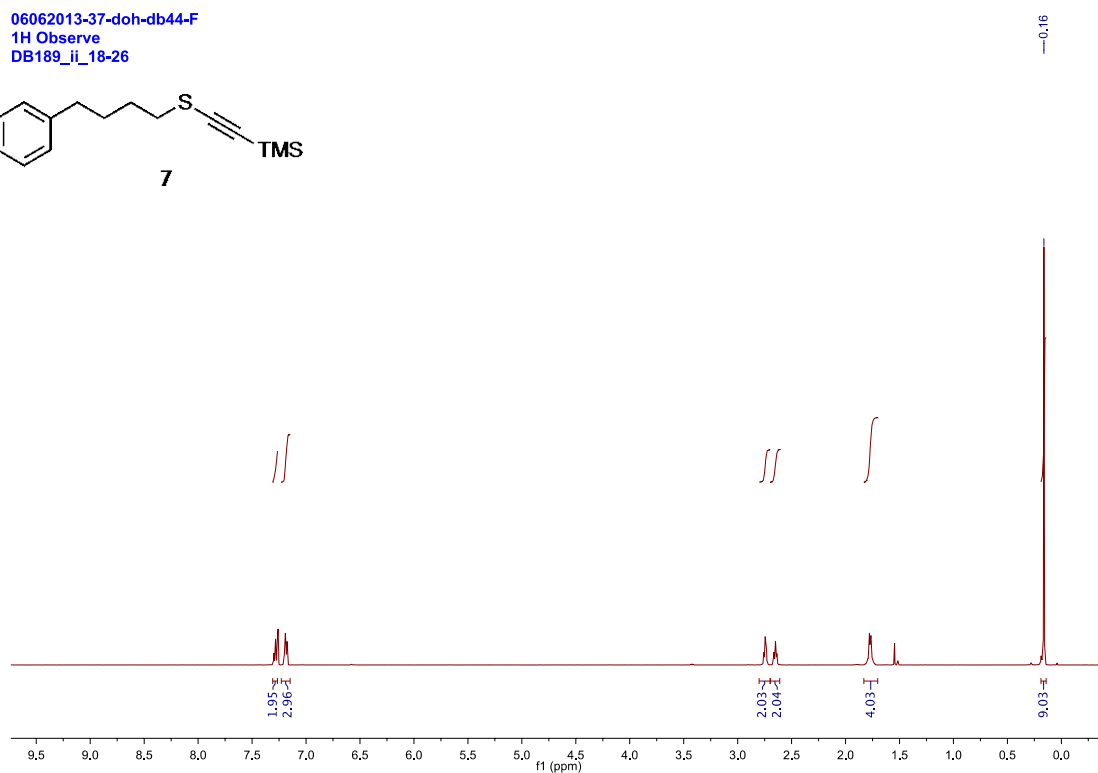
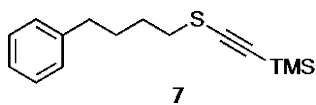
Cyclohexylthioethynyl trimethylsilane **6** (915 mg, 4.3 mmol, 1.0 equiv) was dissolved in a 3:1 mixture of tetrahydrofuran and methanol (9 mL), and tetrabutylammonium fluoride trihydrate (54.3 mg, 0.172 mmol, 0.04 equiv) was added in one portion. The resulting mixture was stirred at room temperature for 16 hours. The mixture was then concentrated under reduced pressure, the residue taken up in dichloromethane (10 mL) and the resulting solution washed with brine (3 × 5 mL), dried over magnesium sulfate, filtered and concentrated under reduced pressure, to furnish the title compound as a colourless oil (543 mg, 90% yield). The material obtained was used in the next synthetic step without any further purification. ¹H NMR (500 MHz, CDCl₃) δ 2.99 – 2.86 (m, 1H), 2.83 (s, 1H), 2.10 – 2.00 (m, 2H), 1.84 – 1.75 (m, 2H), 1.67 – 1.58 (m, 1H), 1.56 – 1.41 (m, 2H), 1.40 – 1.17 (m, 3H). These data are in good agreement with the literature values.⁴

07032013-26-doh-db44-A
1H Observe
DB215

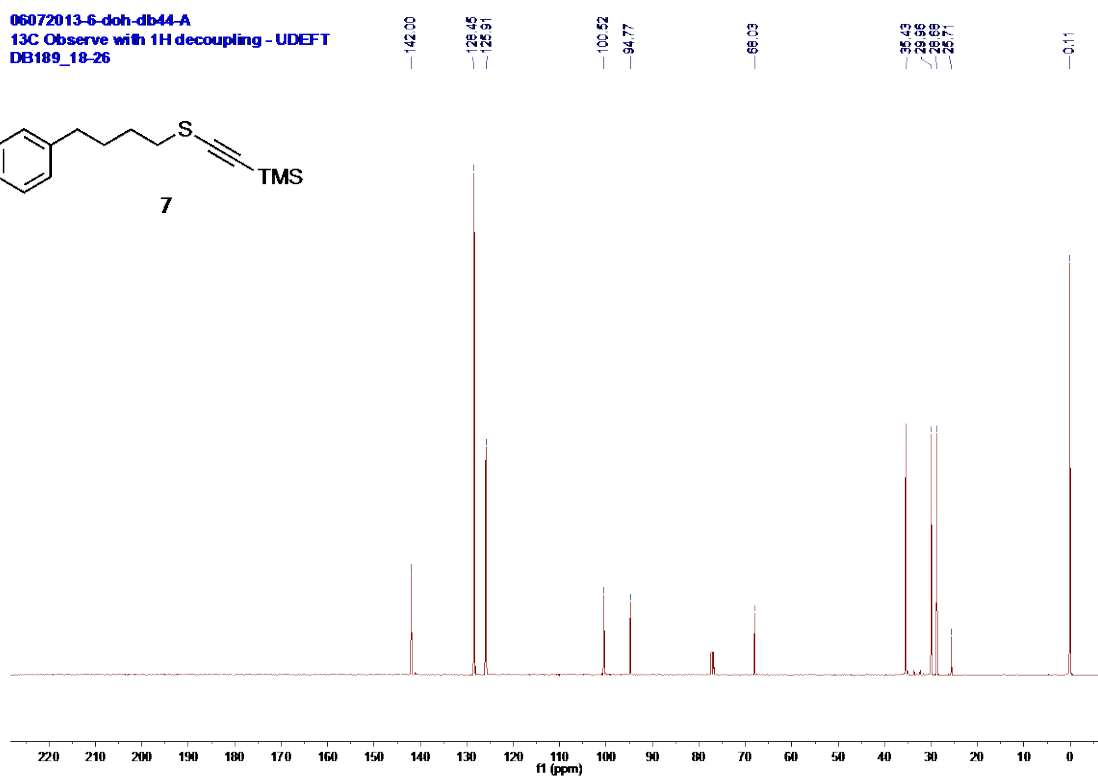
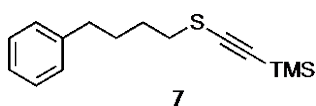


4-Phenylbutyl-thioethynyl trimethylsilane (7)

06062013-37-doh-db44-F
1H Observe
DB189_ji_18-26

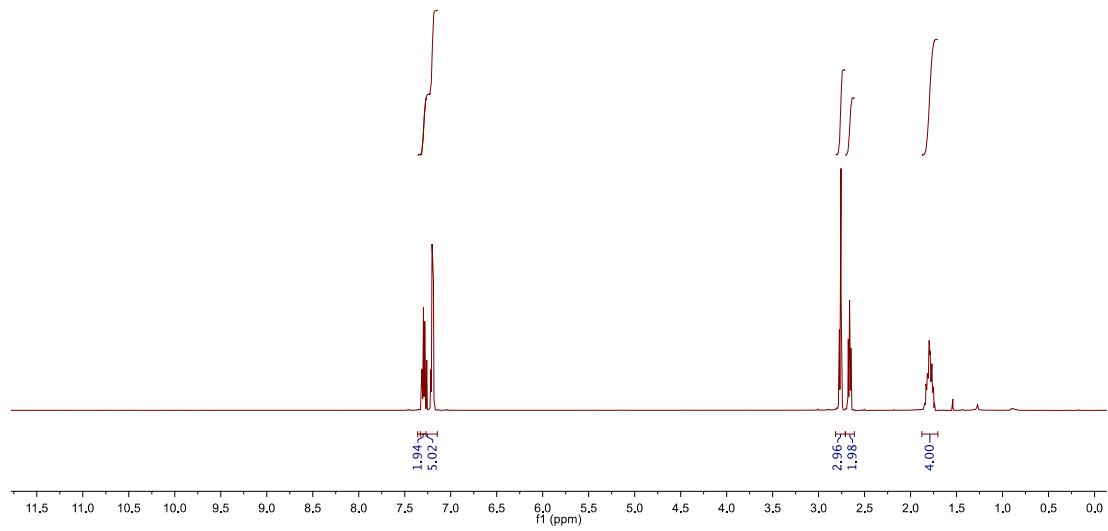
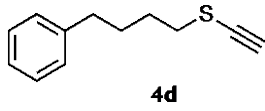


06072013-6-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB189_18-26

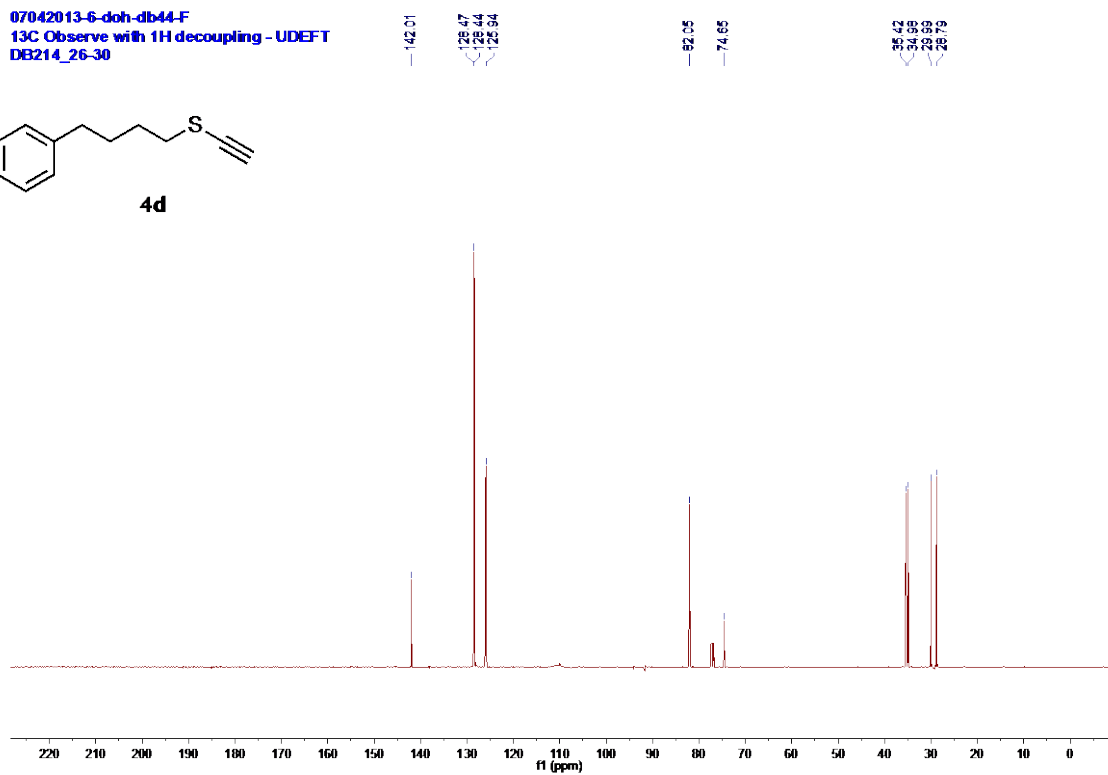
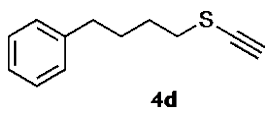


4-Phenylbutyl ethynyl sulfane (4d)

07042013-3-doh-db44-F
1H Observe
DB214_26-30

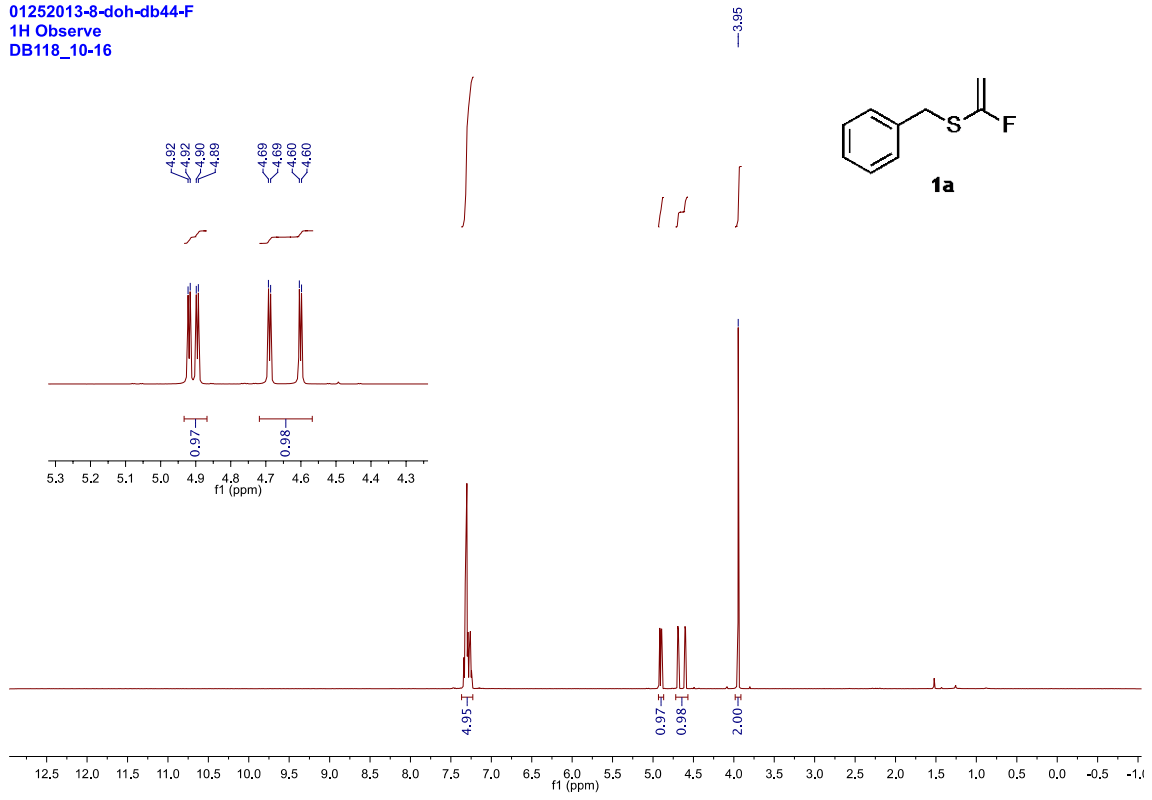


07042013-6-doh-db44-F
13C Observe with 1H decoupling - UDEFT
DB214_26-30

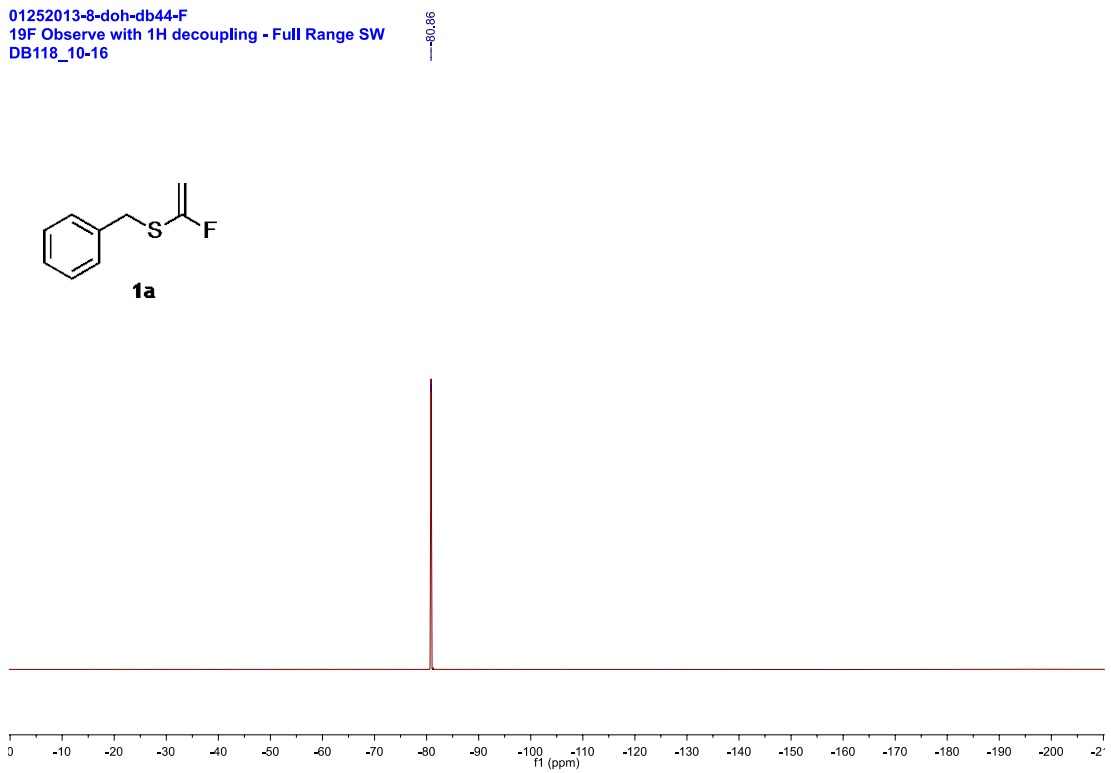


Benzyl 1-fluorovinyl sulfane (1a)

01252013-8-doh-db44-F
1H Observe
DB118_10-16



01252013-8-doh-db44-F
19F Observe with 1H decoupling - Full Range SW
DB118_10-16



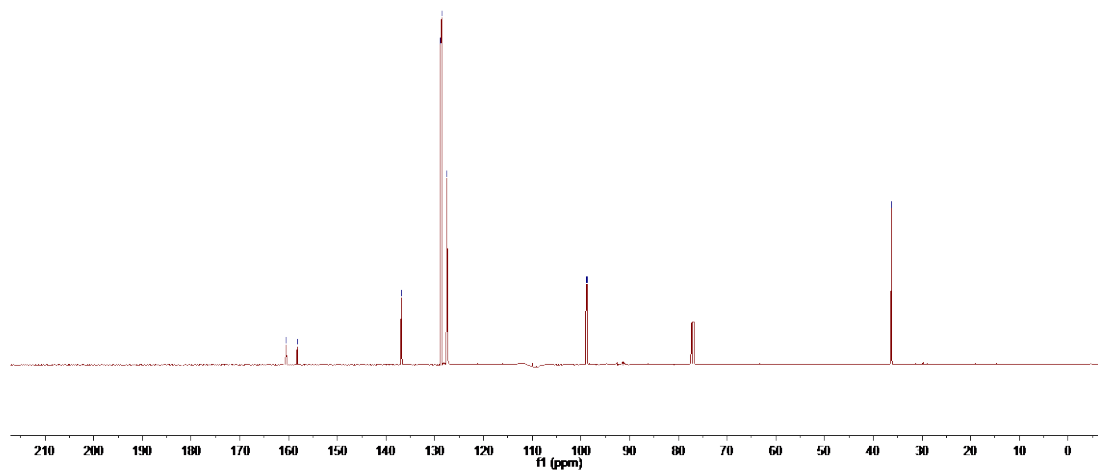
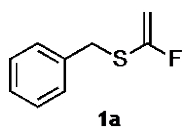
01252013-17-doh-db44-F
13C Observe with 1H decoupling - GPCFT
DB118_10-16

159.22
157.22

136.66
128.83
127.45

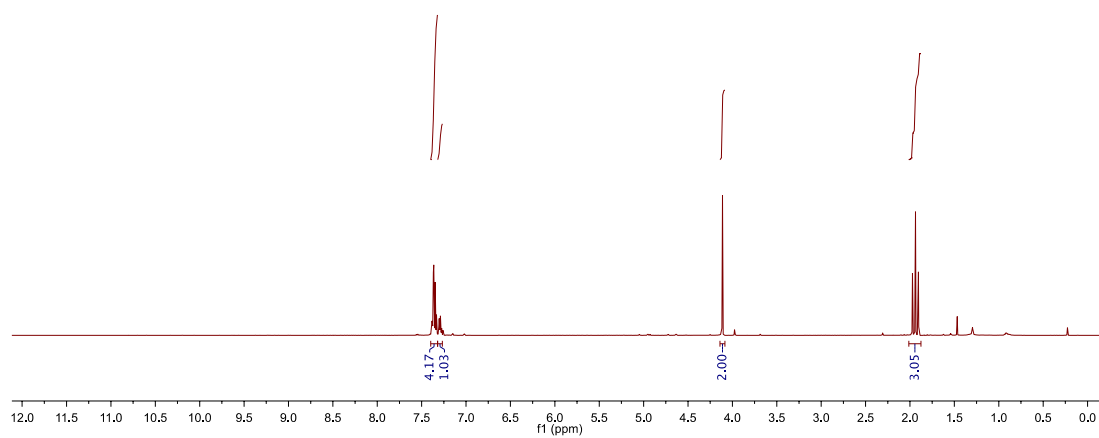
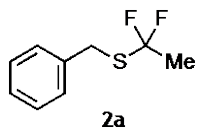
98.92
96.72

-36.22

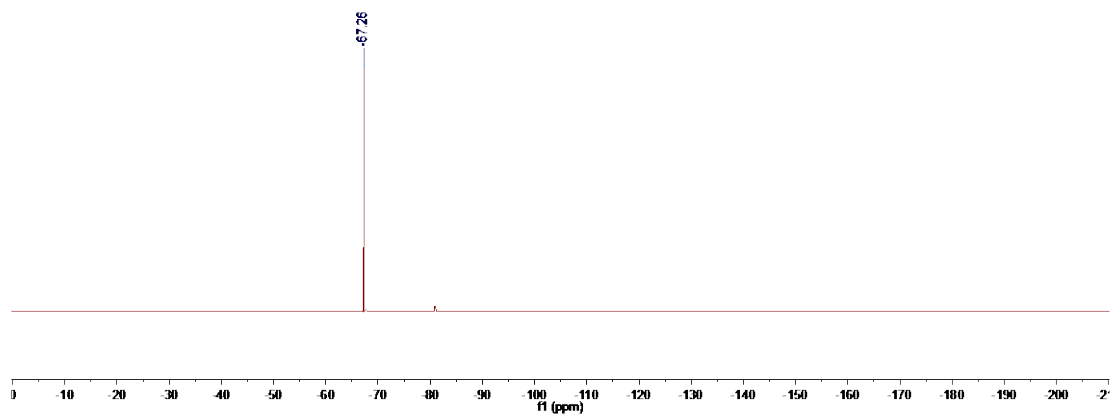
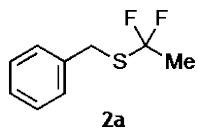


Benzyl (1,1-difluoroethyl) sulfane (2a)

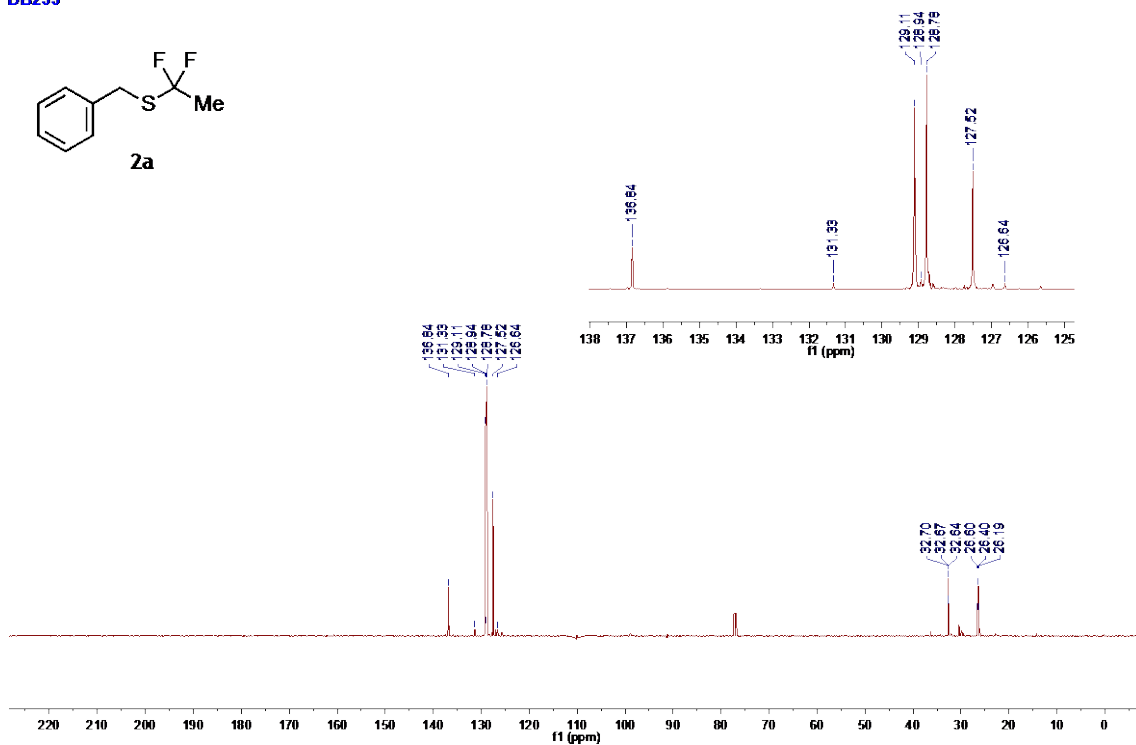
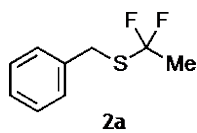
07312013-26-doh-db44-F
1H Observe
DB235



07312013-26-doh-db44-F
19F Observe with 1H decoupling - Full Range SW
DB235

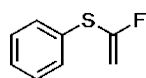


07312013-26-doh-db44-F
13C Observe with 1H decoupling - UDEFT
DB235

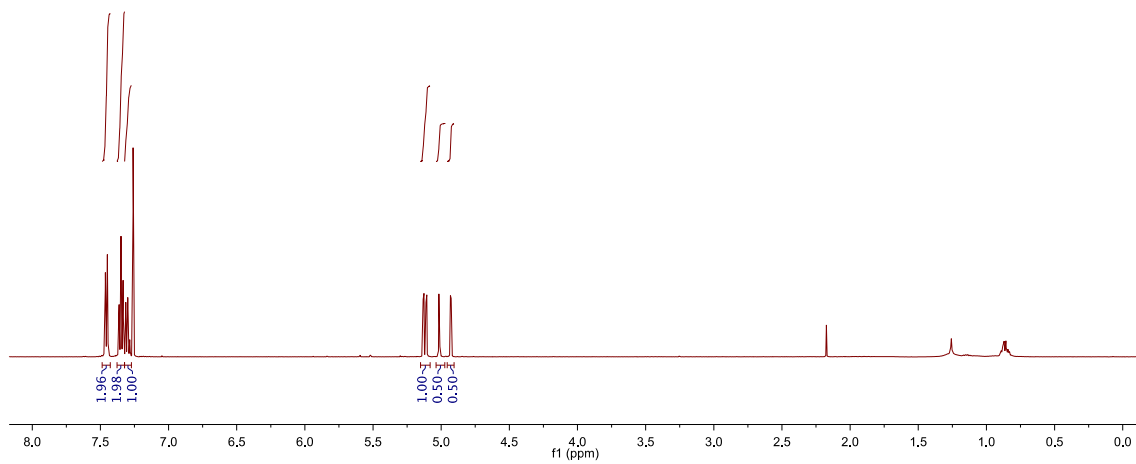


Phenyl 1-fluorovinyl sulfane (1b) and phenyl (1,1-difluoroethyl) sulfane (2b)

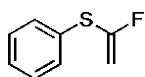
07052013-15-doh-db44-A
1H Observe
DB219_11-14



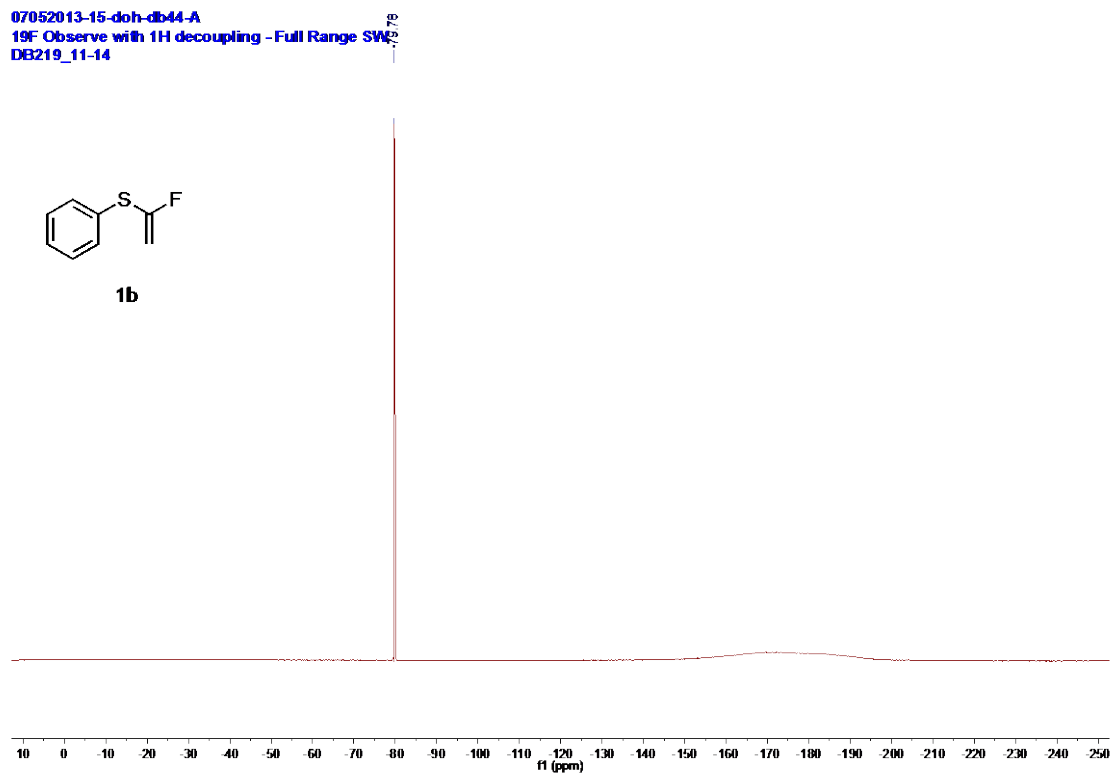
1b



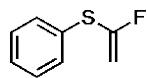
07052013-15-doh-db44-A
19F Observe with 1H decoupling - Full Range SWH
DB219_11-14



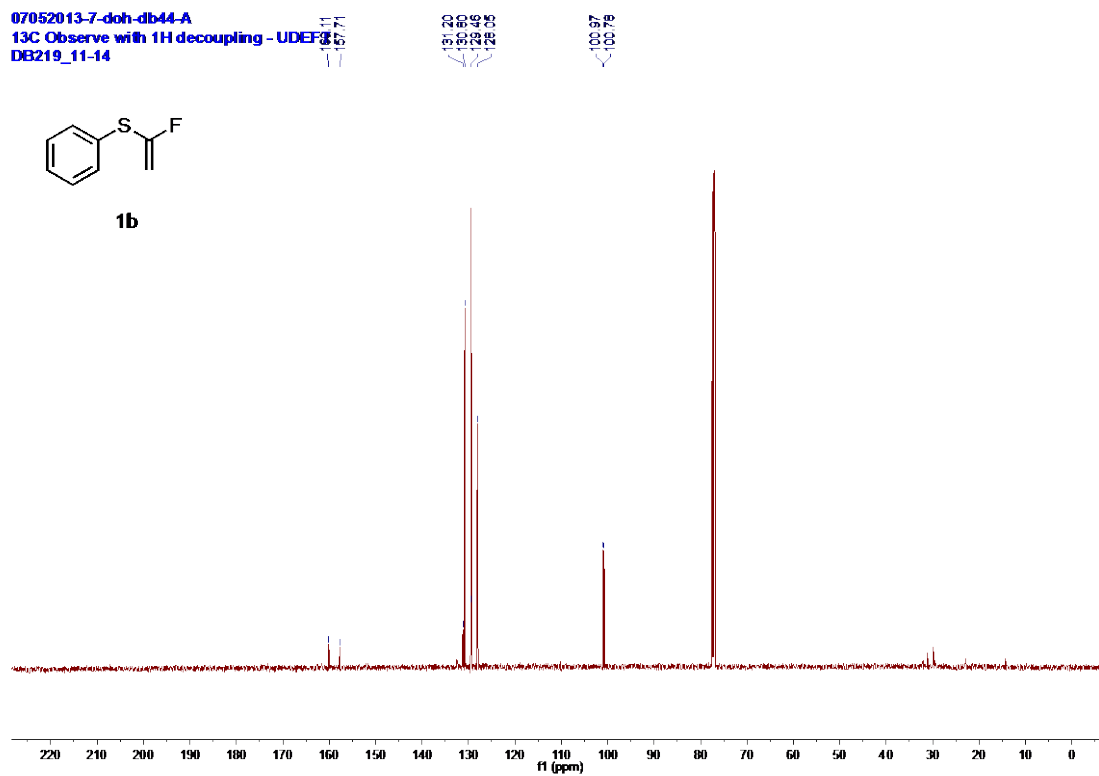
1b



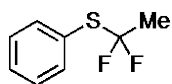
07052013-7-doh-db44-A
13C Observe with 1H decoupling - UDEF3
DB219_11-14



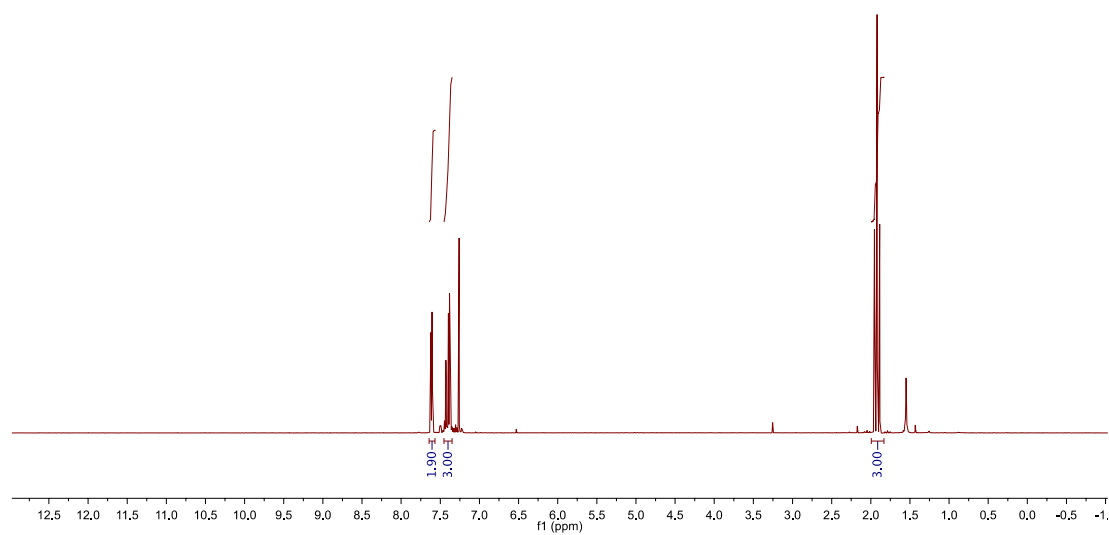
1b



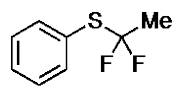
07222013-33-doh-db44-A
1H Observe
DB223_6-10



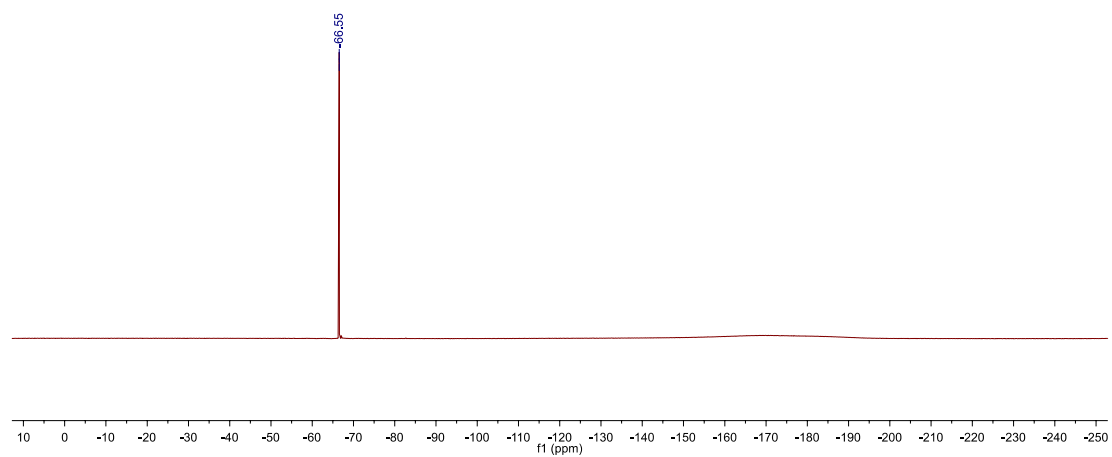
2b



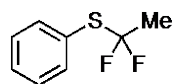
07222013-33-doh-db44-A
19F Observe with 1H decoupling - Full Range SW
DB223_6-10



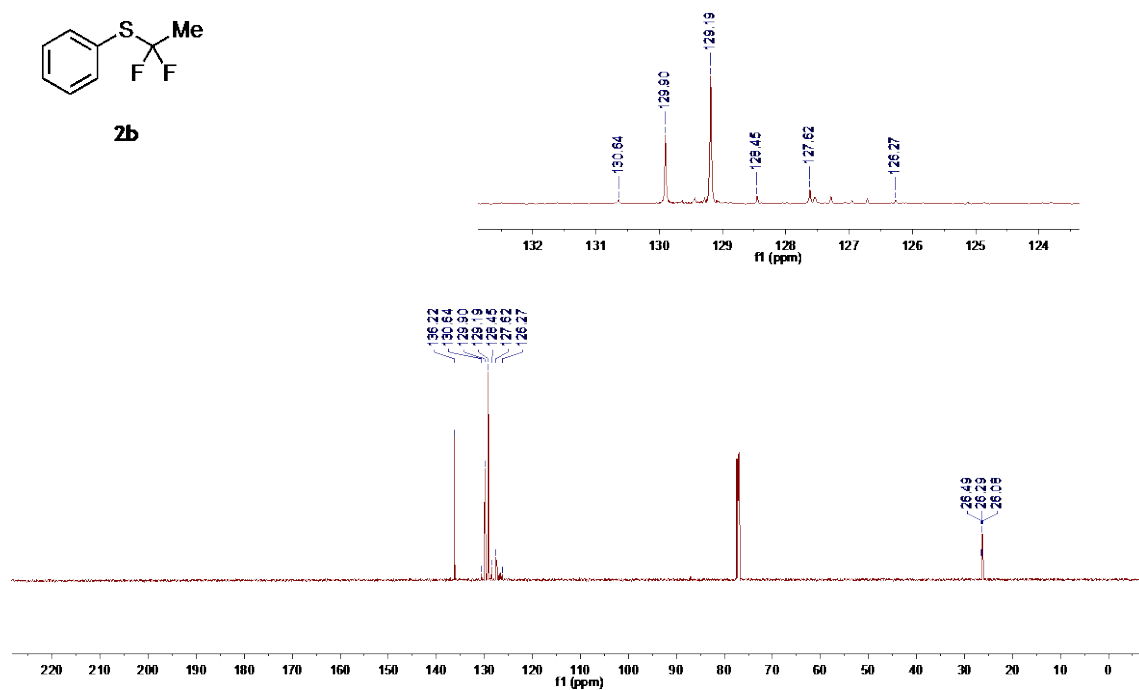
2b



07222013-40-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB223_6-10

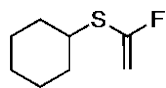


2b

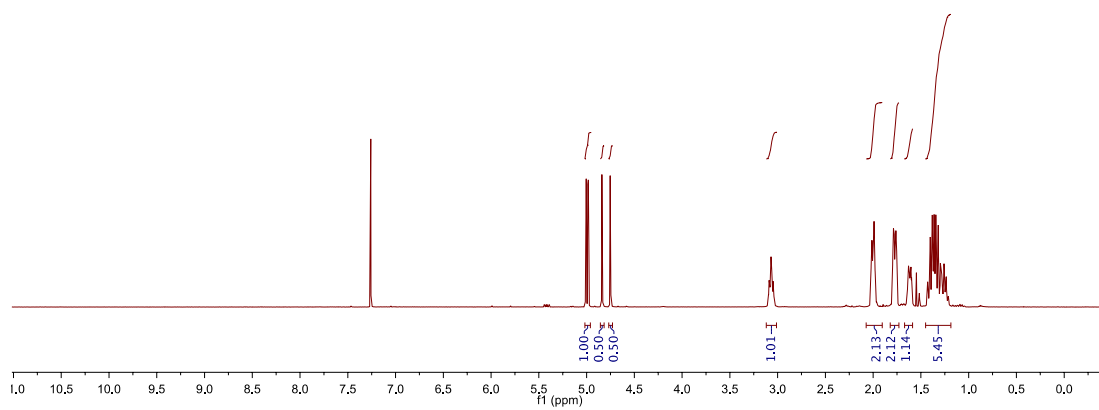


Cyclohexyl 1-fluorovinyl sulfane (1c)

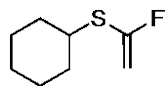
08092013-19-doh-db44-A
1H Observe
DB242_5-7



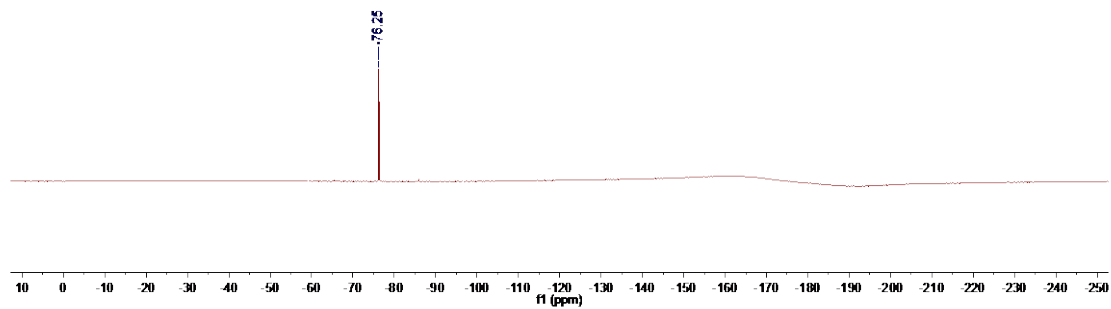
1c



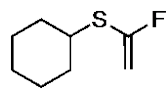
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19F Observe with 1H decoupling - Full Range SW
DB242_5-7



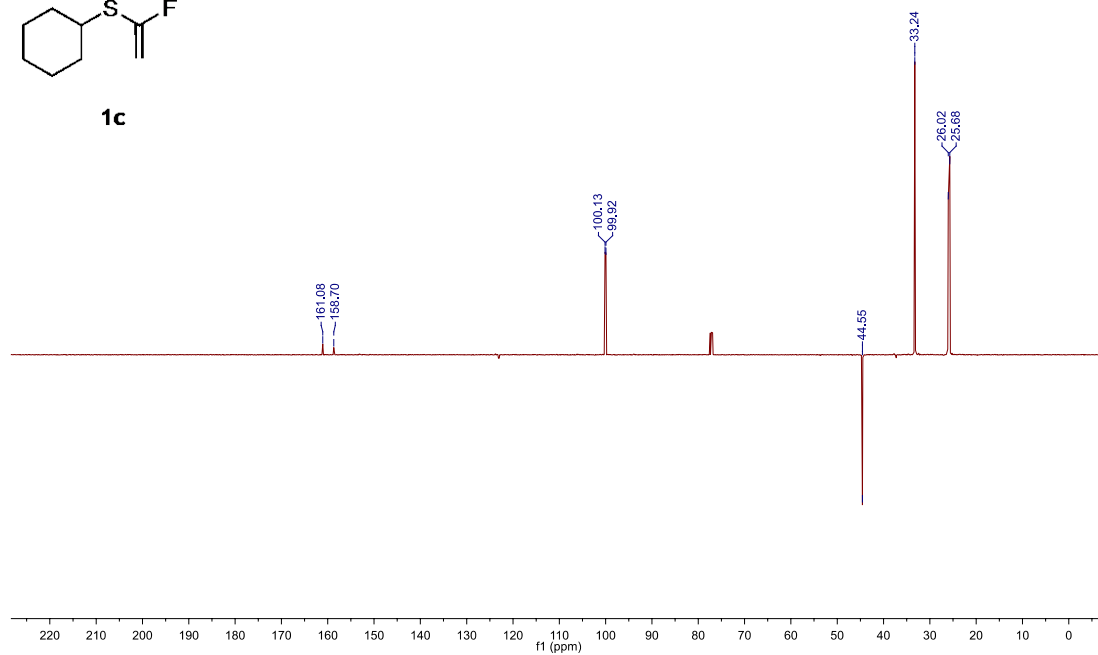
1c



08092013-32-doh-db44-A
13C Observe with multiplicity editing - DEPTQ
DB242_5-7

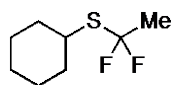


1c

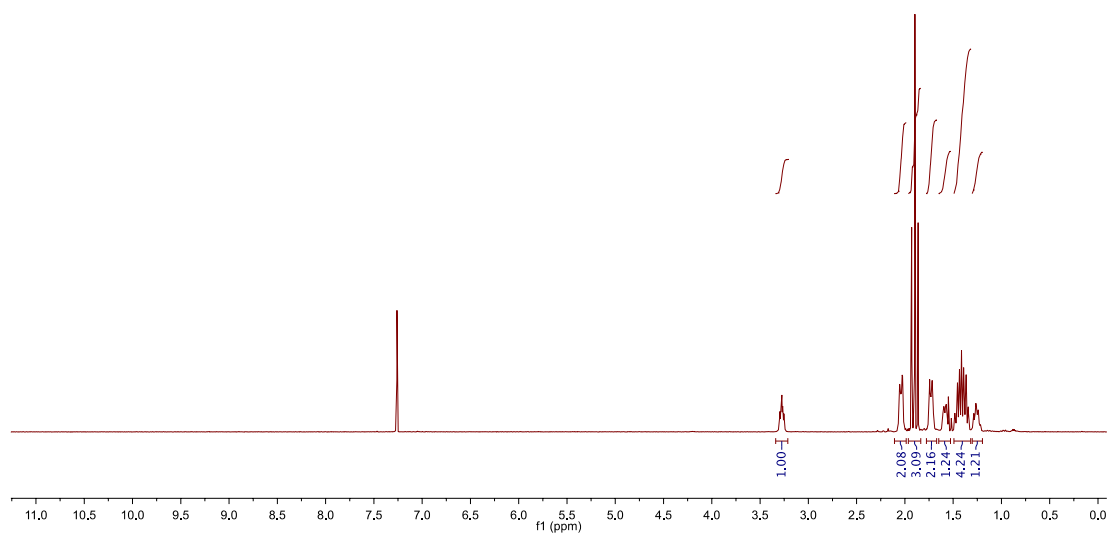


Cyclohexyl (1,1-difluoroethyl) sulfane (2c)

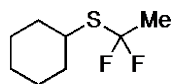
08132013-11-doh-db44-F
1H Observe
DB243_7-8



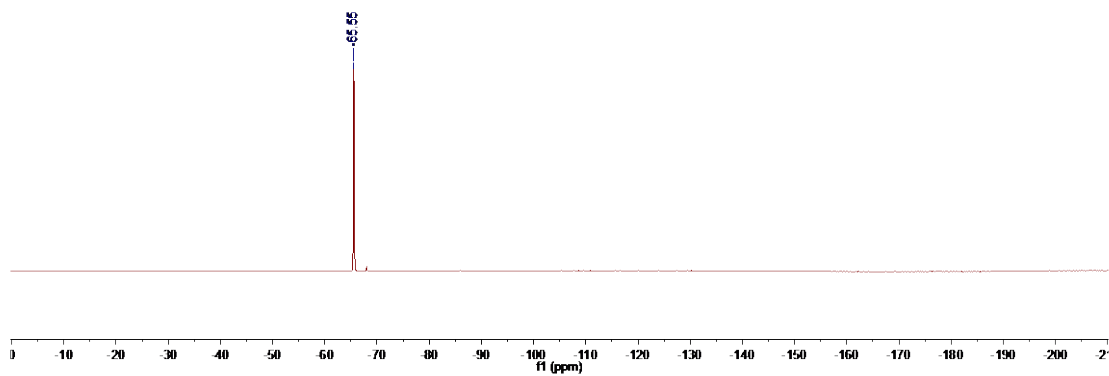
2c



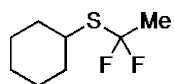
08132013-11-doh-db44-F
19F Observe with 1H decoupling - Full Range SW
DB243_7-8



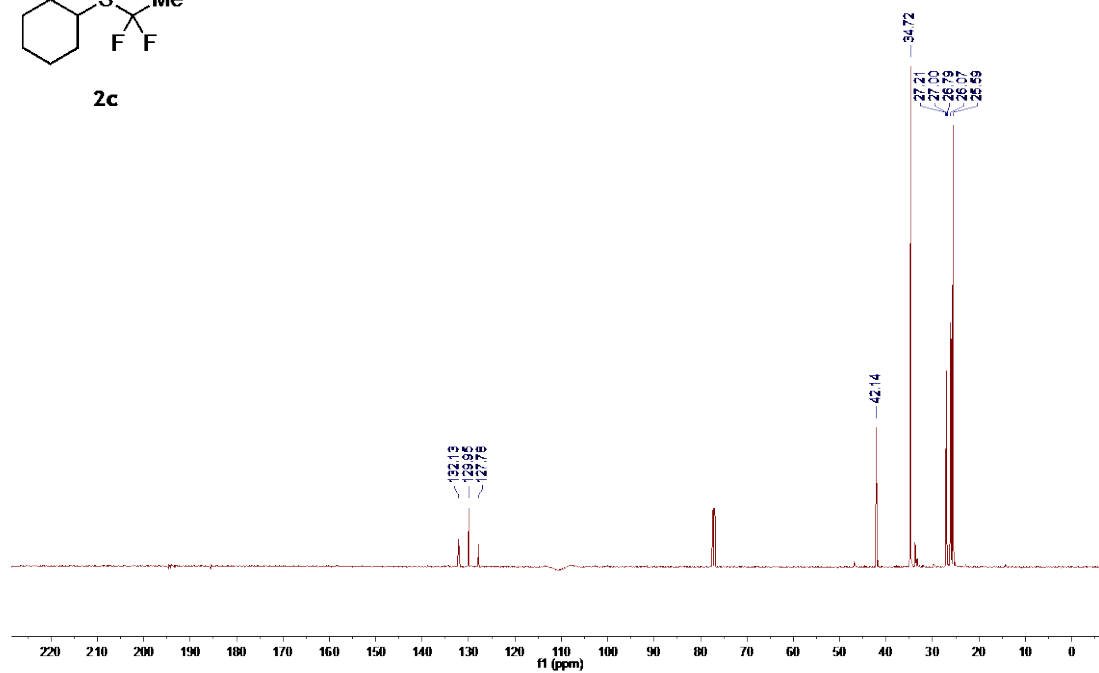
2c



08132013-15-doh-dh44-F
13C Observe with 1H decoupling - UDEFT
DB243_7-8

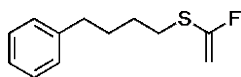


2c

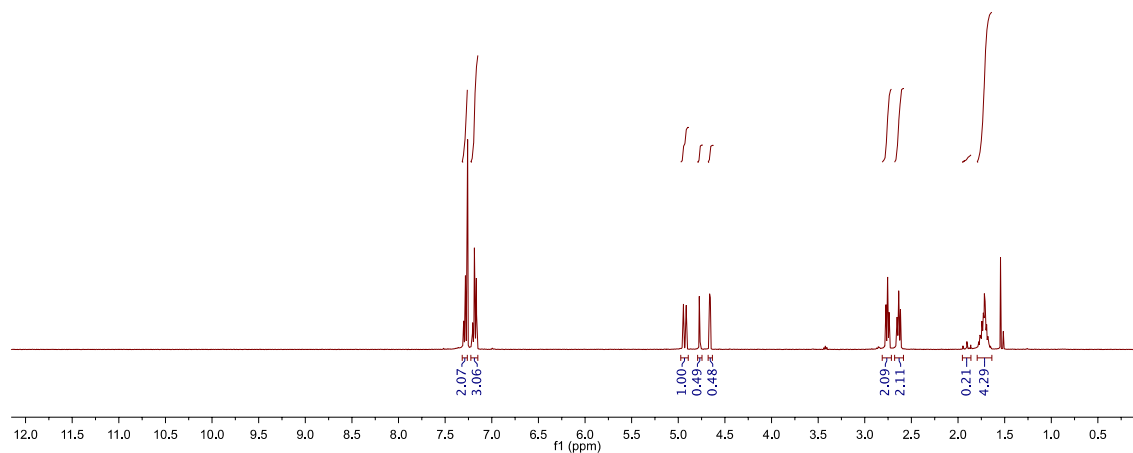


4-Phenylbutyl 1-fluorovinyl sulfane (1d)

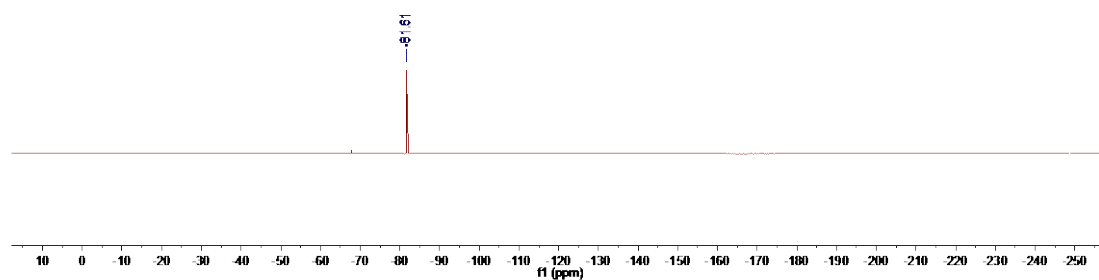
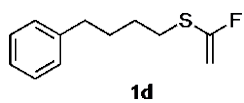
09022013-1-davideM
DB253_14-32



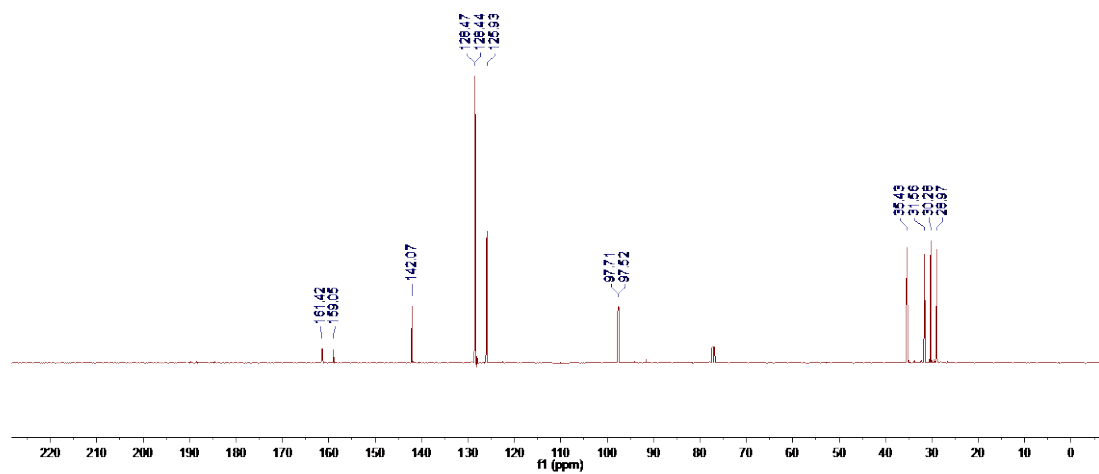
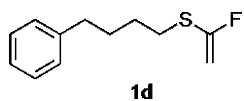
1d



09022013-1-davideM
DB253_14-32

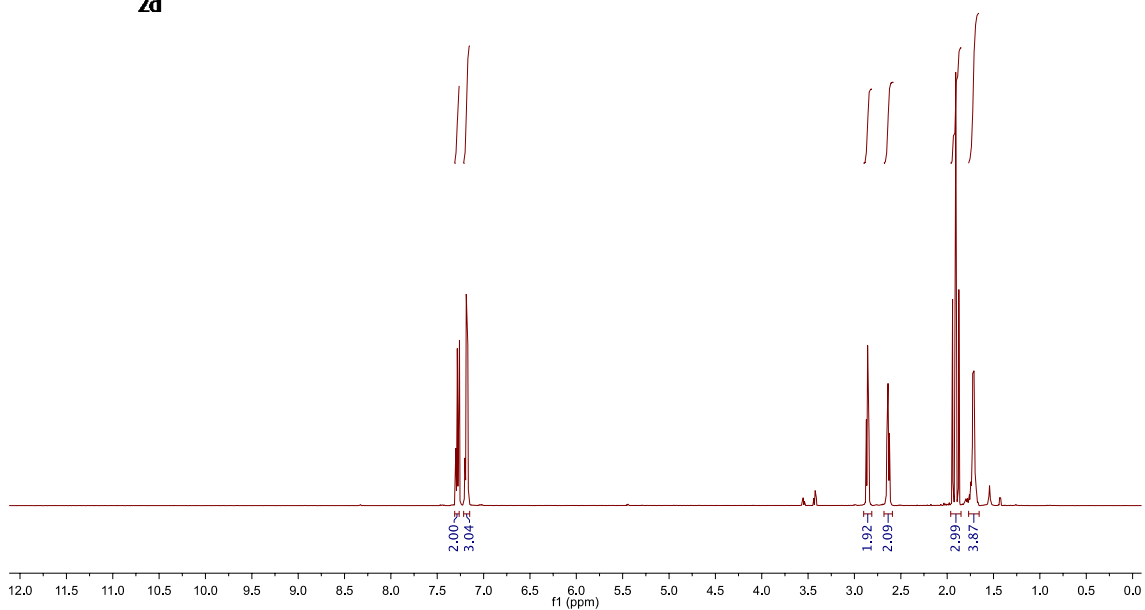
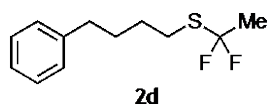


09022013-4-doh-ms966-F
13C Observe with 1H decoupling - UDEFT
DB253_14-32

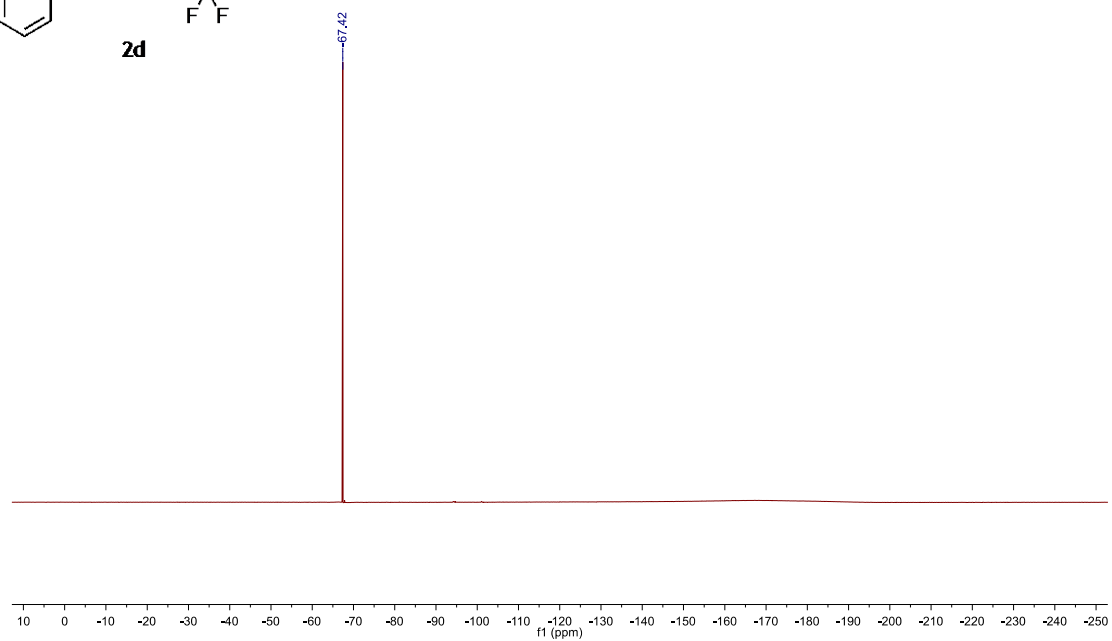
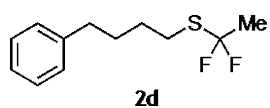


4-Phenylbutyl (1,1-difluoroethyl) sulfane (2d)

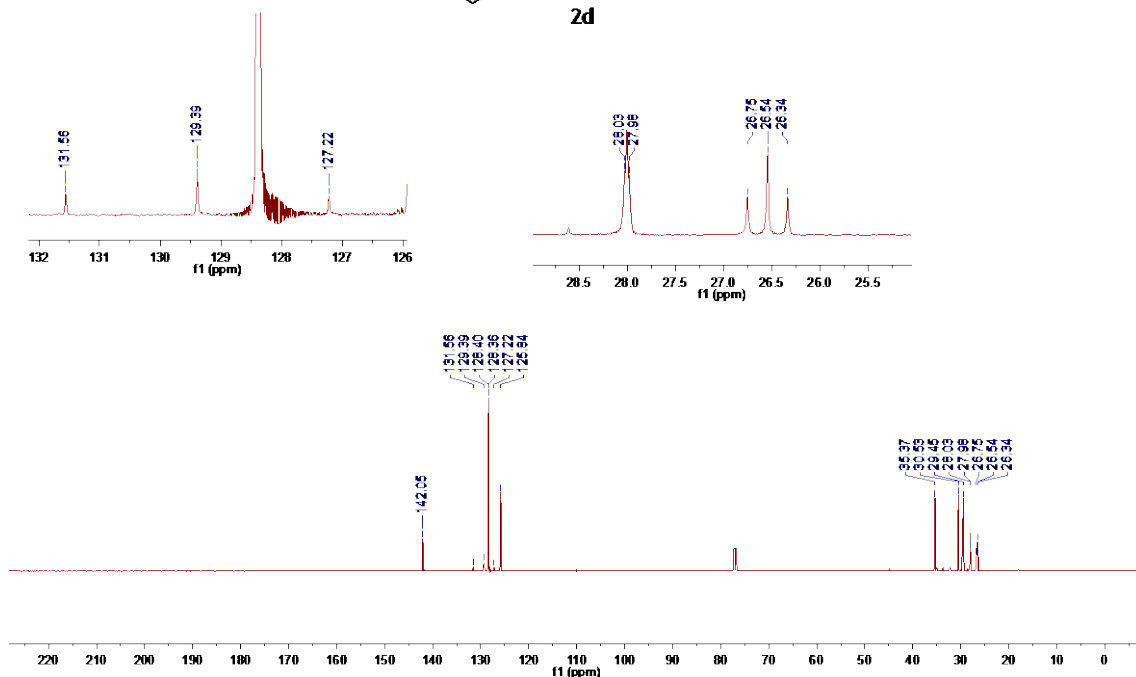
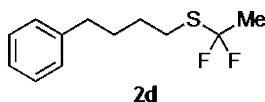
07222013-32-doh-db44-A
1H Observe
DB226b_7



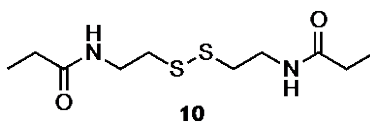
07222013-32-doh-db44-A
19F Observe with 1H decoupling - Full Range SW
DB226b_7



07222013-41-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB226b_7

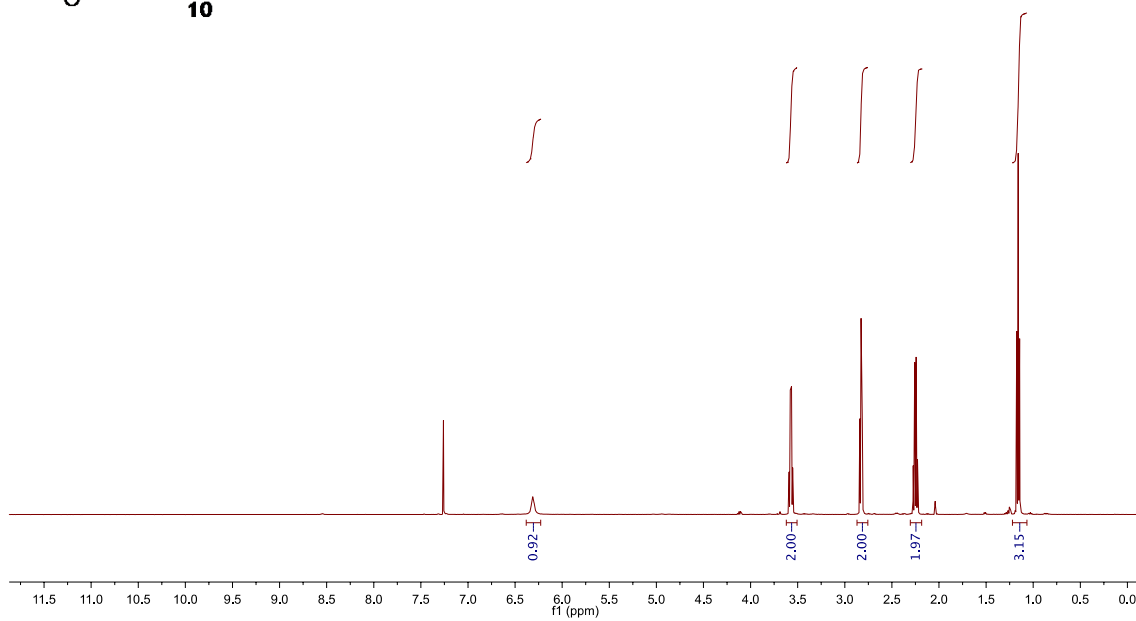
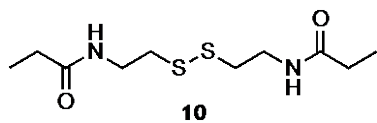


N,N'-(Disulfanediylobis(ethane-2,1-diyl))dipropionamide (10)



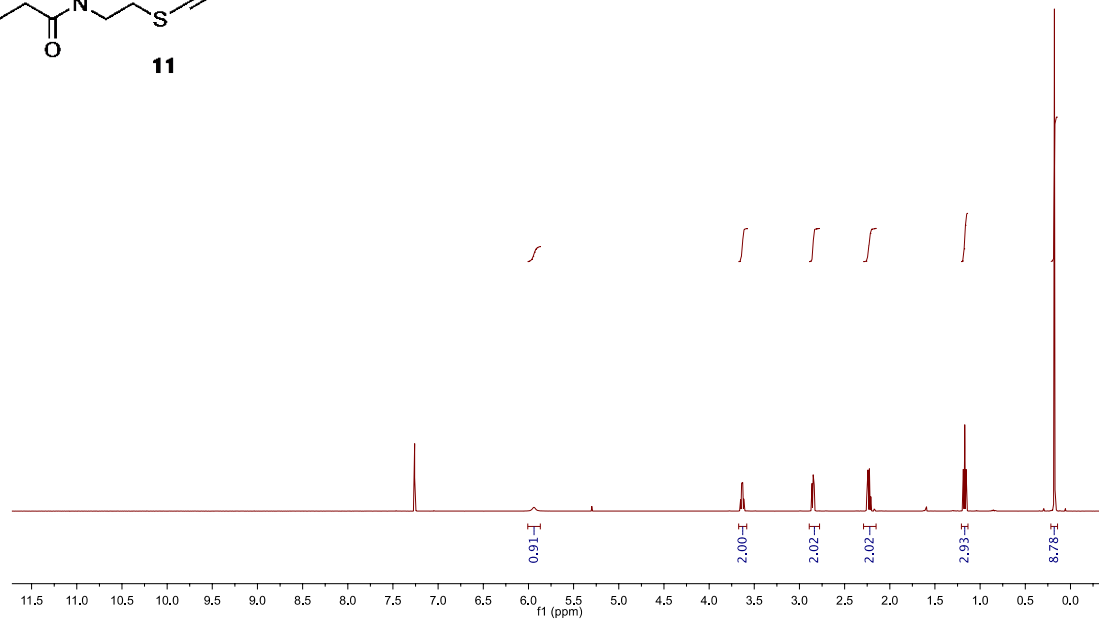
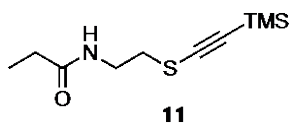
Cystamine hydrochloride **9** (20 g, 88.8 mmol, 1.0 equiv) was suspended in dry dichloromethane (150 mL) under an atmosphere of argon. Pyridine (30 mL, 373 mmol, 4.2 equiv) was added, and the resulting mixture cooled to 0 °C. Propionyl chloride (18.6 mL, 213 mmol, 2.4 equiv) was added dropwise, then the resulting mixture was allowed to warm to room temperature and stirred for 4 hour. The mixture was then re-cooled to 0 °C and methanol (30 mL) added. The resulting mixture was warmed to room temperature and stirred for a further 30 minutes. The mixture was then concentrated under reduced pressure, the residue re-suspended in dichloromethane, washed with 1M hydrochloric acid (50 mL), saturated sodium hydrogen carbonate aqueous solution (50 mL), brine (50 mL), dried onto magnesium sulfate and concentrated under reduced pressure, to furnish the title compound as a waxy solid (5.9 g, 25% yield); ¹H NMR (500 MHz, CDCl₃) δ 6.31 (s, 2H), 3.57 (q, *J* = 6.3, 4H), 2.83 (t, *J* = 6.4, 4H), 2.25 (q, *J* = 7.6, 4H), 1.16 (t, *J* = 7.6, 6H); These data are in good agreement with the literature values.⁵

03012013-1-doh-db44-A
1H Observe
DB135

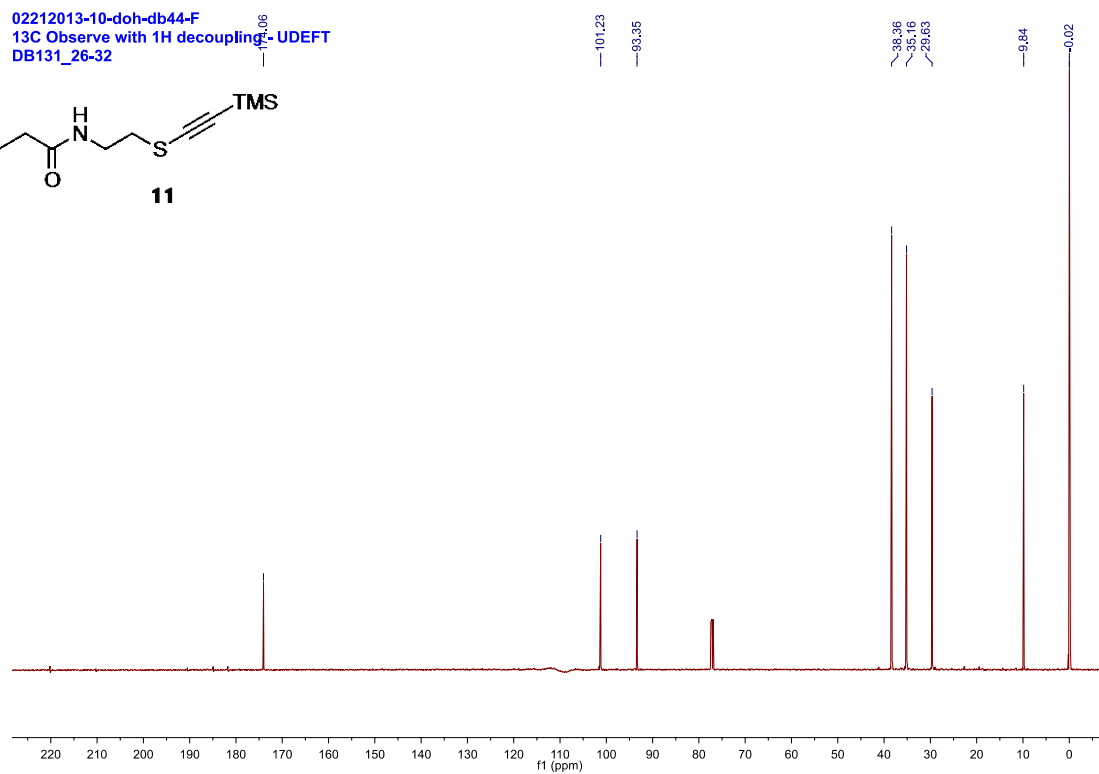
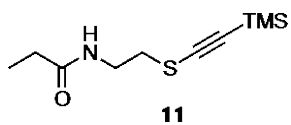


N-(2-Trimethylsilylethynyl)thioethyl propionamide (11)

02192013-18-doh-db44-A
1H Observe
DB131_26-32

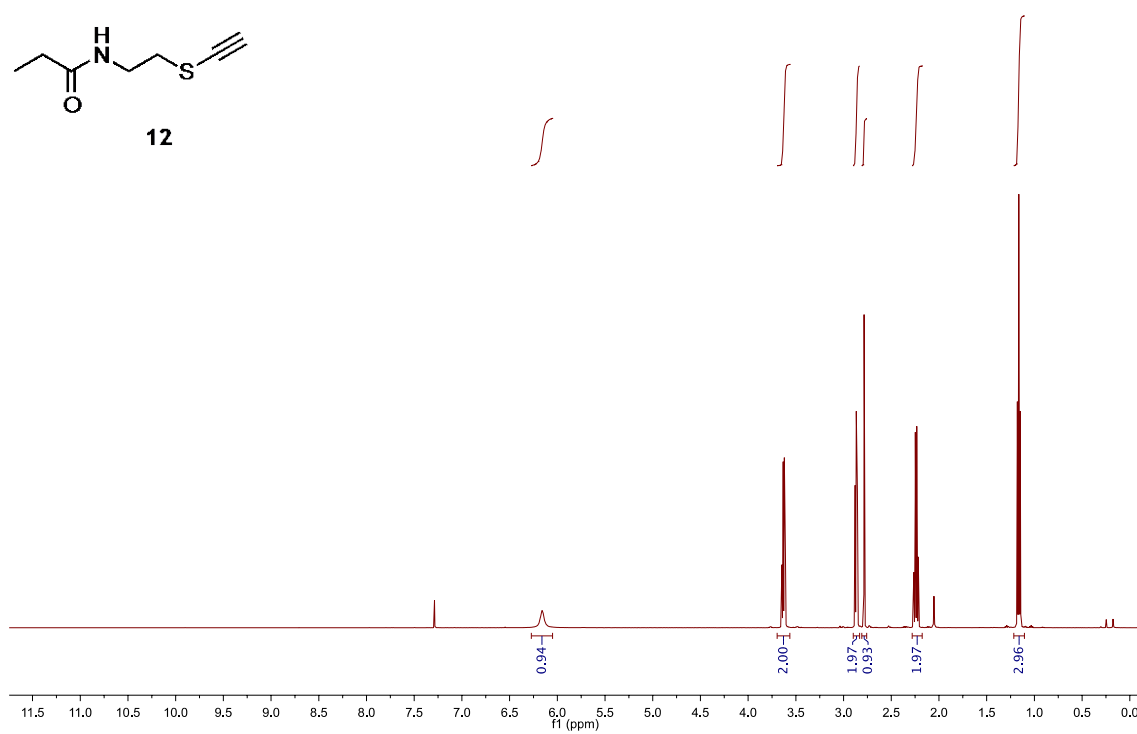
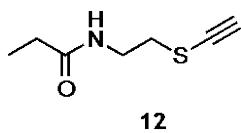


02212013-10-doh-db44-F
13C Observe with 1H decoupling UDEFT
DB131_26-32

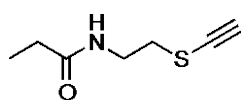


N-(2-(Ethynthio)ethyl)propionamide (12)

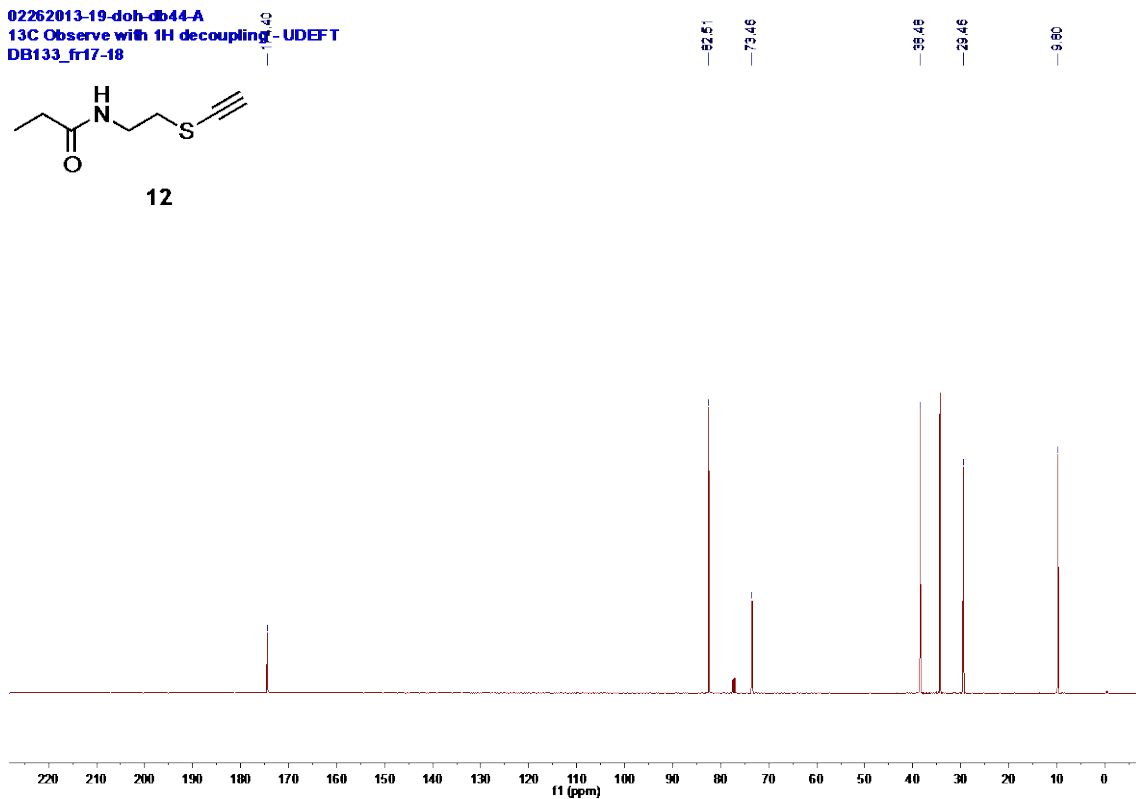
02252013-23-doh-db44-A
1H Observe
DB133_17-18



02262013-19-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB133_fr17-18

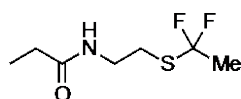


12

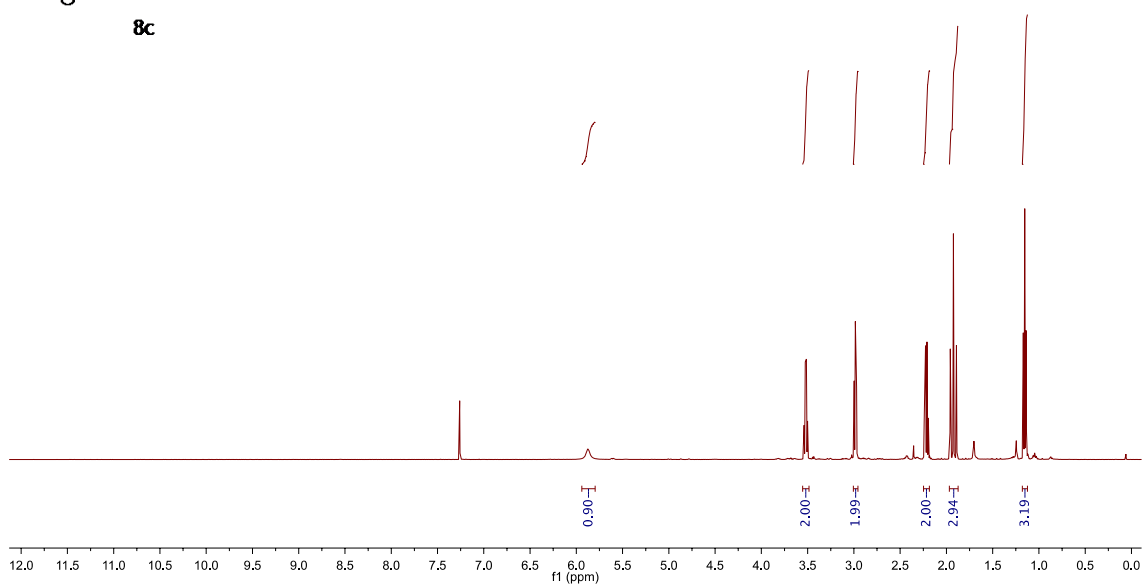


N-(2-((1,1-Difluoroethyl)thio)ethyl)propionamide (8c)

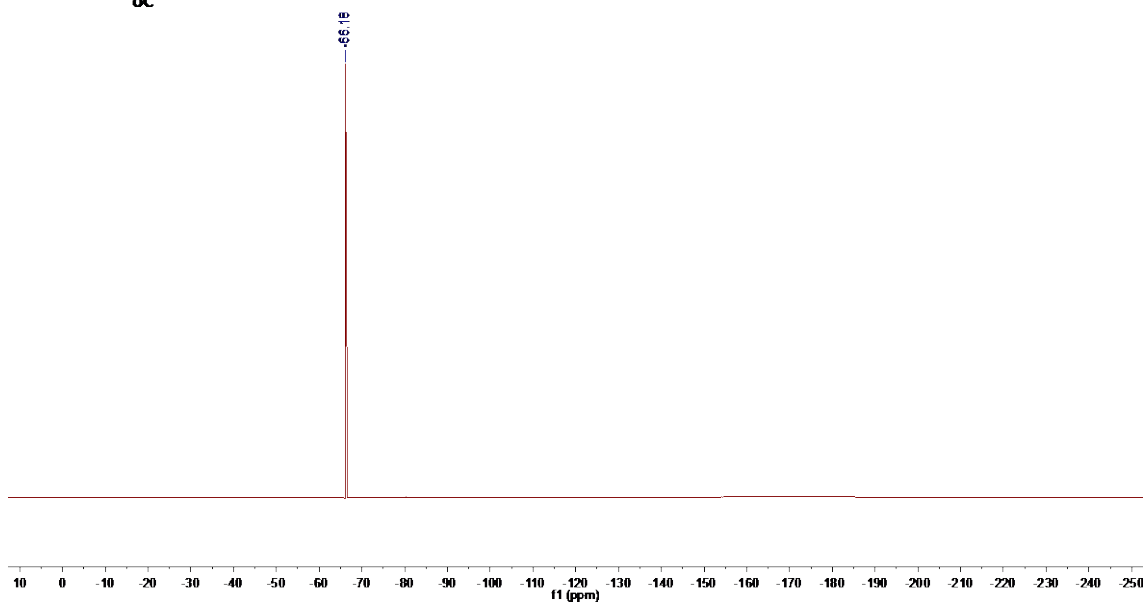
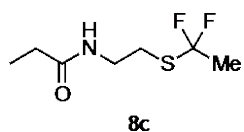
09162013-1-doh-db44-A
1H Observe
DB254_HPLC_10-11



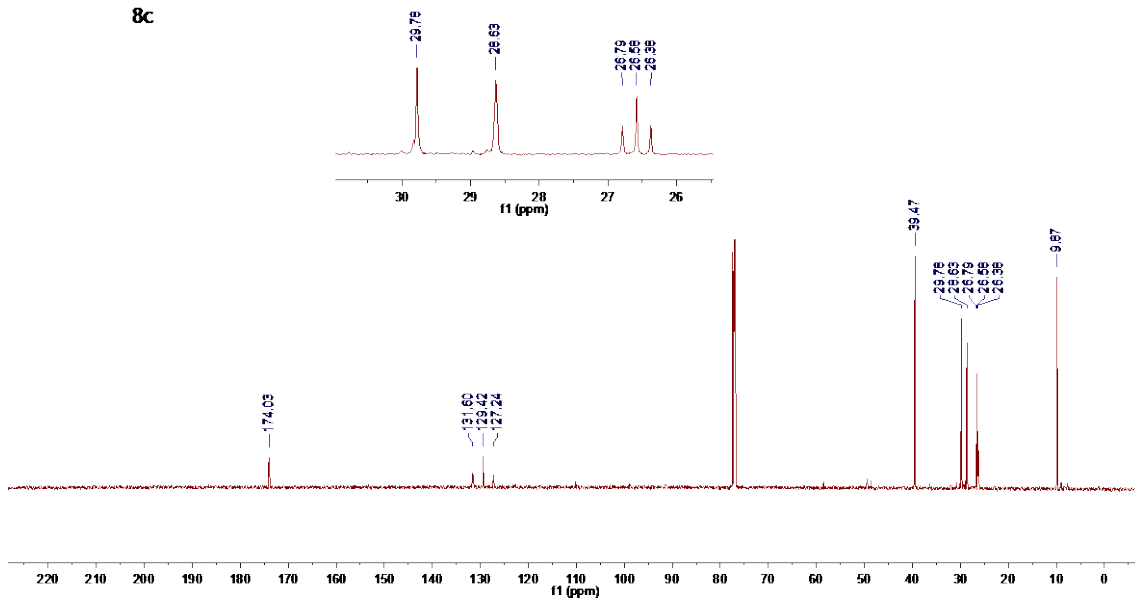
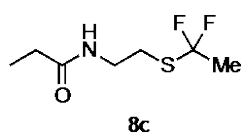
8c



09162013-1-doh-db44-A
19F Observe with 1H decoupling - Full Range SW
DB254_HPLC_10-11

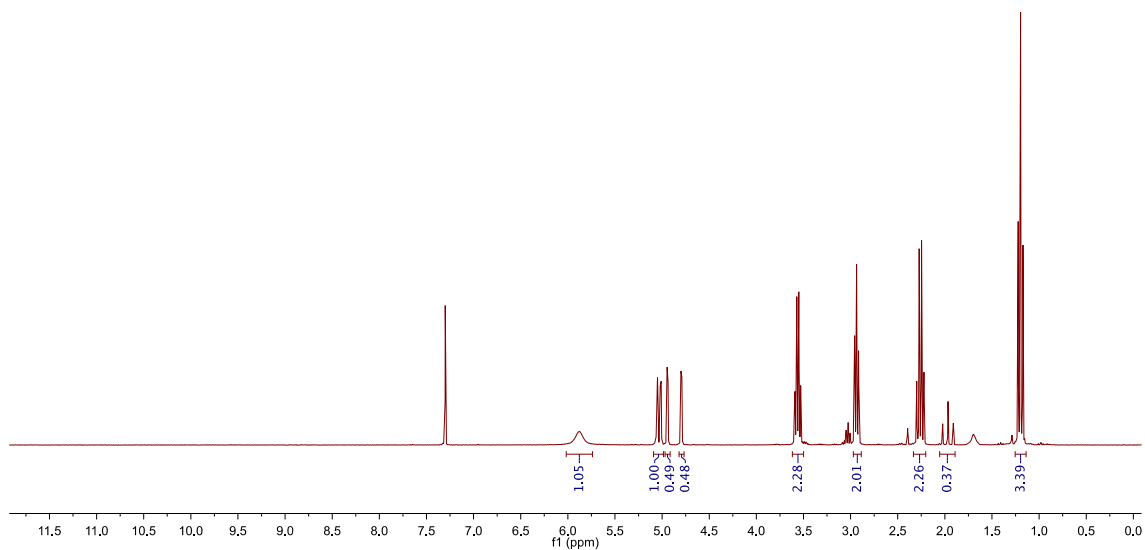
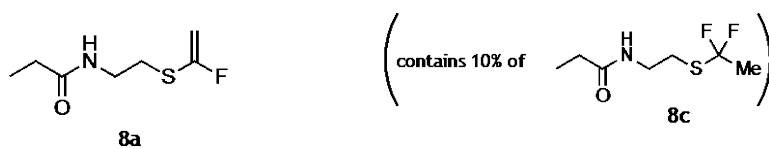


09162013-31-doh-db44-A
13C Observe with 1H decoupling - UDEFT
DB254_HPLC_10-11

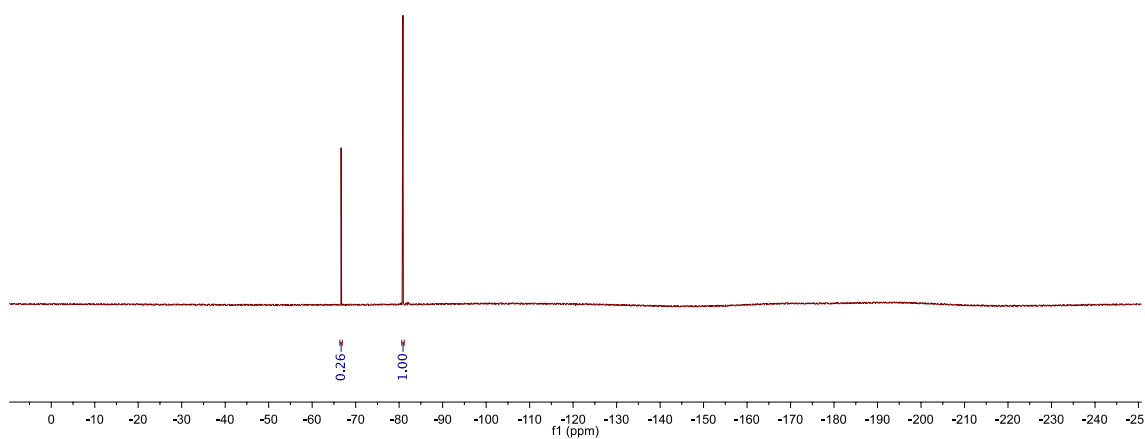
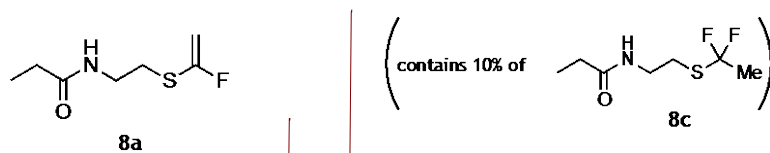


N-(2-((1-fluorovinyl)thio)ethyl)propionamide (8a)

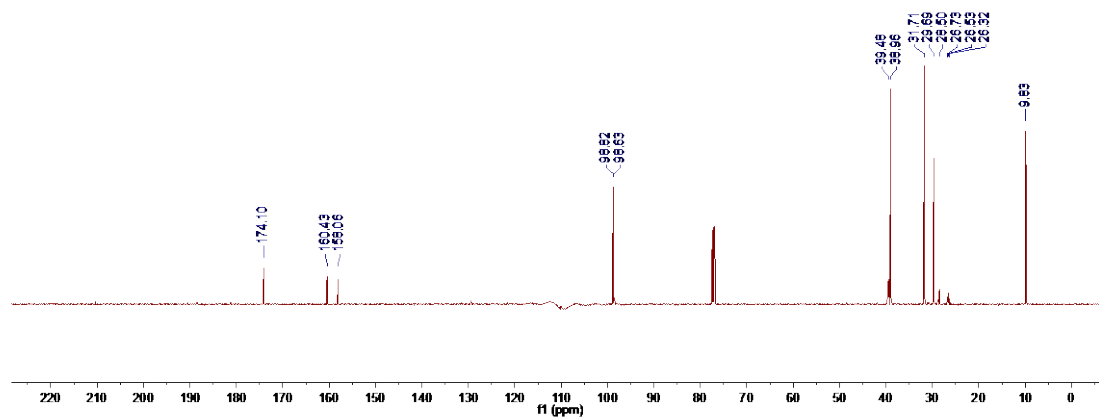
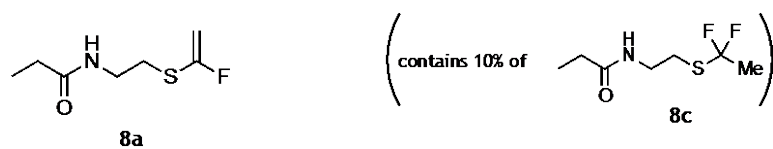
09042013-33-davidel
DB247_HPLC-II_fr3-5_DCM_extr



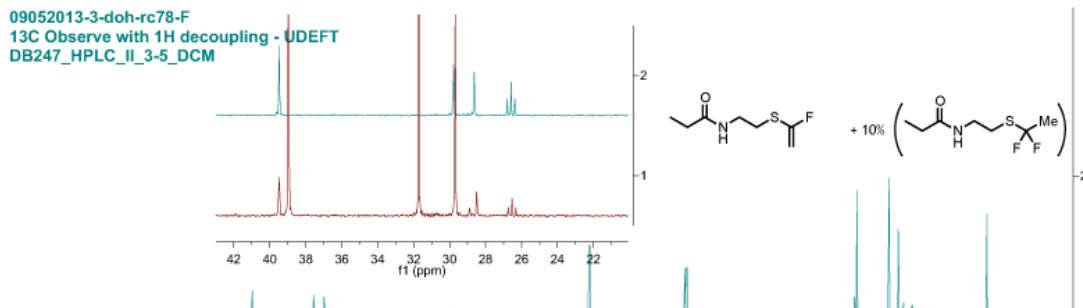
09042013-33-davidel
DB247_HPLC-II_fr3-5_DCM_extr



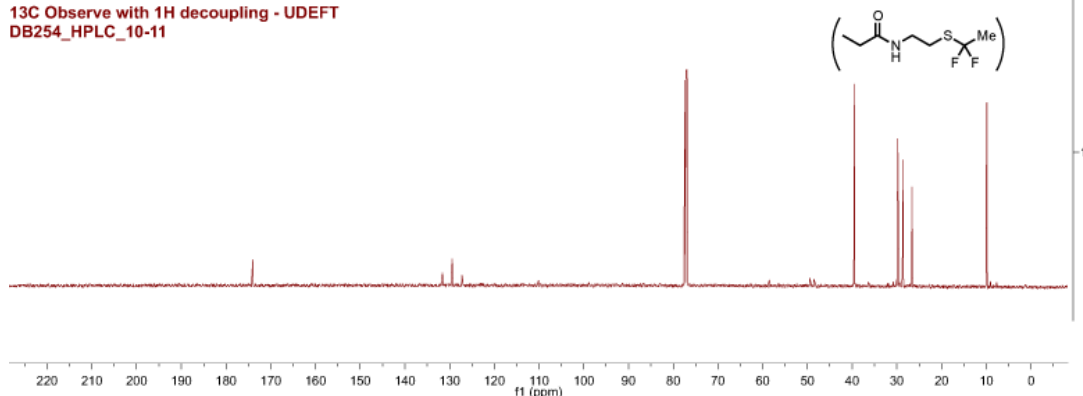
09052013-3-doh-rc78-F
 13C Observe with 1H decoupling - UDEFT
 DB247_HPLC_II_3-5_DCM



09052013-3-doh-rc78-F
 13C Observe with 1H decoupling - UDEFT
 DB247_HPLC_II_3-5_DCM



09162013-31-doh-db44-A
 13C Observe with 1H decoupling - UDEFT
 DB254_HPLC_10-11



- **References**

1. . W. W. Seidel, M. J. Meel, M. Schaffrath, T. Pape; *Eur. J. Org. Chem.*; **2007**, 3526-3532.
2. C. Eller , G. Kehr , C. G. Daniliuc , R. Fröhlich , G. Erker; *Organometallics*; **2013**, 32 (2), 384-386.
3. P. Nebois, N. Kann, A. E. Greene, *J. Org. Chem.*, **1995**, 60, 7690-7692.
4. Shchelkunov, A. V.; Krichevskii, L. A.; Shostakovskii, M. F.; *Dokl. Akad. Nauk SSSR*, **1983**, 268, (1419; *Chem. Abstr.* 1983, 99, 53053v).
5. N. Franceschini, S. Da Nascimento, M. Hugues, S. Pascal; *Heterocyclic Commun.*, **2005**, 11(6), 509-512.