

Supporting Information
for
**The difluoromethylene (CF₂) group in aliphatic chains:
Synthesis and conformational preference of palmitic
acids and nonadecane containing CF₂ groups**

Yi Wang, Ricardo Callejo, Alexandra M. Z. Slawin and David O'Hagan*

Address: EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, Fife KY16 9ST, UK.

Email: David O'Hagan - do1@st-andrews.ac.uk

*Corresponding author

Contents	Page
General information	S1
Preparation and characterisation	S2
NMR spectra	S13

General information

All commercially available reagents were purchased from Acros, Alfa Aesar, Fisher Scientific, Fluorochem or Sigma-Aldrich and used without further purification unless otherwise stated. All glassware was flame-dried and allowed to cool down under high vacuum. Dry solvents DCM, Et₂O, hexane, THF were obtained from the MBraun SPS-800 Solvent Purification System, by passing the solvent through two drying columns under an argon atmosphere.

Thin layer chromatography (TLC) was performed using Merck TLC silica gel 60 F₂₅₄ aluminium-backed plates. Compounds were visualised by either UV light (254 nm) or by the use of potassium permanganate stain or molybdenum-based stain. Column chromatography was performed using Merck silica gel 60 (40–63 µm).

NMR spectra were acquired on either Bruker Avance 300 (^1H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 282 MHz), Bruker Avance II 400 spectrometer (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) or Bruker Avance III 500 spectrometer (^1H at 500 MHz, ^{13}C at 125 MHz, ^{19}F at 470.6 MHz). Chemical shifts (δ) are reported in parts per million (ppm) and are quoted relative to the residual peak of CDCl_3 or CD_2Cl_2 . Coupling constants (J) are given in Hertz (Hz). ^{13}C NMR and ^{19}F NMR spectra were recorded with ^1H decoupling. Signal splitting patterns are described as: s – singlet, t – triplet, tt – triplet of triplets, q – quartet, quin – quintet, abq – AB quartet, m – multiplet.

Mass spectrometric data was acquired by electron impact ionisation (EI), electrospray ionisation (ESI) or chemical ionisation (CI). At the University of St Andrews LRMS and HRMS examination was carried out by Mrs. C. Horsburgh on a Waters Micromass LCT (ESI) or GCT (CI) spectrometer. At the National Mass Spectrometry Service Centre, Swansea, the LRMS assessment was performed on ThermoFisher DSQ-II spectrometer (CI) and HRMS was performed on Finnigan MAT 95 XP (EI). Values are reported as a ratio of mass to charge (m/z).

Preparation and characterisation

7-Phenylheptanal (8) To a solution of methyl 7-phenylheptanoate **7** (5.5 g, 25 mmol) in CH_2Cl_2 (50 mL) was added DIBAL-H (27 mL, 1 M in THF, 27 mmol) dropwise at $-78\text{ }^\circ\text{C}$. After 30 min, the reaction was quenched with saturated Rochelle's salt solution (100 mL). The organic layer was separated and washed with 1 M HCl (30 mL) and brine (30 mL). Then it was dried over MgSO_4 and concentrated to yield the aldehyde (4.4 g, 93%) as a colourless oil; ^1H NMR (400 MHz, CDCl_3) δ_{H} 9.77 (t, J = 1.8 Hz, 1H, CHO), 7.31-7.27 (m, 3H, ArH), 7.21-7.18 (m, 2H, ArH), 2.63 (t, J = 7.7 Hz, 2H, ArCH_2), 2.43 (td, J = 7.3, 1.8 Hz, 2H, CH_2CHO), 1.69-1.61 (m, 4H, 2 x CH_2), 1.40-1.36 (m, 4H, 2 x CH_2); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 202.8 (CH), 142.6 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 43.9 (CH_2), 35.8 (CH_2), 31.2 (CH_2), 29.1(CH_2), 29.0 (CH_2), 22.0 (CH_2); LRMS (ES $^+$) calcd for $\text{C}_{13}\text{H}_{18}\text{ONa}$ [M+Na] $^+$: 213.12, found: 213.05.

1-Phenylpentadec-8-yn-7-ol (9). To a solution of 7-phenylheptanal (3 g, 15.7 mmol) in THF (50 mL) at $-78\text{ }^\circ\text{C}$ was added *n*-BuLi (10 mL, 1.58 mol/L) and warmed up to 0 $^\circ\text{C}$ over 30 mins. Then it was cooled down to $-78\text{ }^\circ\text{C}$ again and 1-octyne (1.73 g, 15.7 mmol) was added dropwise. The resulting mixture was stirred for 1 h at rt. The reaction was quenched with aq. NH_4Cl solution (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification over silica gel, eluting with 5:1 hexane/EtOAc, yielded the alcohol (4.0 g, 85%) as a colourless oil; ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.34-7.29 (m, 3H, ArH), 7.22-7.18 (m, 2H, ArH), 4.41-4.35 (m, 1H, CHOH), 2.64 (t, J = 7.4 Hz, 2H, ArCH_2), 2.27-2.10 (m, 2H, $\equiv\text{CCH}_2$), 1.76-1.61 (m, 6H, 3 x CH_2), 1.53-1.30 (m, 12H, 6 x CH_2), 0.93 (t, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 142.8 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.5 (CH), 85.6 ($\equiv\text{C}$), 81.2 ($\equiv\text{C}$), 62.7 (CH), 38.1 (CH_2), 35.9 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 18.7 (CH_2), 14.0 (CH_3); HRMS (EI $^+$) calcd for $\text{C}_{21}\text{H}_{36}\text{ON}$ [M+NH $_4$] $^+$: 318.2791, found: 318.2784.

1-Phenylpentadec-8-yn-7-one (10). To a solution of 1-phenylpentadec-8-yn-7-ol (4 g, 13.3 mmol) in acetone (20 mL) at 0 °C was slowly added a solution of CrO₃ (1.5 g, 15 mmol) in H₂SO₄ (5 mL) and H₂O (10 mL). The mixture was stirred for 30 min at rt. The reaction was quenched with H₂O (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with sat. NaHCO₃ solution, dried over MgSO₄ and concentrated in vacuo to give the ketone (3.6 g, 91%) as a yellow oil; ¹H NMR (300 MHz, CDCl₃) 7.31-7.26 (3H, m, ArH), 7.20-7.16 (2H, m, ArH), 2.61 (2H, t, J = 7.4 Hz, ArCH₂), 2.52 (2H, t, J = 7.4 Hz, O=CCH₂), 2.36 (2H, t, J = 7.0 Hz, ≡CCH₂), 1.69-1.53 (8H, m, 4 x CH₂), 1.37-1.28 (8H, m, 4 x CH₂), 0.90 (3H, t, J = 6.8 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 188.6 (C=O), 142.7 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 94.4 (≡C), 80.9 (≡C), 45.5 (CH₂), 35.8 (CH₂), 31.3 (CH₂), 31.2 (CH₂), 29.0 (CH₂), 28.8 (CH₂), 28.5 (CH₂), 27.7 (CH₂), 24.1 (CH₂), 22.5 (CH₂), 18.9 (CH₂), 14.0 (CH₃); HRMS (EI⁺) Exact mass calcd for C₂₁H₃₁O [M+H]⁺: 299.2369, found: 299.2367.

(7,7-Difluoropentadec-8-yn-1-yl)benzene (11). Neat DAST (2.33 mL, 17.6 mmol) was added to 1-phenylpentadec-8-yn-7-one (2.6 g, 8.8 mmol) under argon atmosphere. The mixture was heated at 50 °C for 4 h and cooled down to rt. It was diluted with EtOAc (50 mL), washed with saturated NaHCO₃ solution (100 mL). The organic layer was separated, dried over MgSO₄ and solvent removed in vacuo. Purification over silica with 2% EtOAc in hexane gave the difluoro product (1.9 g, 67%) as a colourless oil; {¹⁹F}¹H NMR (400 MHz, CDCl₃) 7.31-7.27 (3H, m, ArH), 7.27-7.17 (2H, m, ArH), 2.62 (2H, t, J = 7.4 Hz, ArCH₂), 2.27 (2H, t, J = 7.0 Hz, ≡CCH₂), 2.02-1.96 (2H, m, CH₂), 1.66-1.50 (8H, m, 4 x CH₂), 1.39-1.28 (8H, m, 4 x CH₂), 0.90 (3H, t, J = 7.0 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 142.6 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 115.1 (t, J = 230 Hz, CF₂), 88.6 (≡C), 74.0 (≡C), 39.4 (t, J = 26.4 Hz, CH₂), 35.9 (CH₂), 31.3 (CH₂), 31.2 (CH₂), 29.0 (CH₂), 28.8 (CH₂), 28.4 (CH₂), 27.7 (CH₂), 24.1 (CH₂), 22.9 (t, J = 3.8 Hz, CH₂), 22.5 (CH₂), 18.3 (CH₂), 14.0 (CH₃); {¹H}¹⁹F NMR (376 MHz, CDCl₃) δ_F -81.3 (CF₂). HRMS (Cl⁺) Exact mass calcd for C₂₁H₃₀F₂ [M⁺]: 320.2310, found: 320.2304.

(7,7-Difluoropentadecyl)benzene (12). Palladium on activated carbon (50 mg) was added to a solution of (7,7-difluoropentadec-8-yn-1-yl)benzene (400 mg, 1.25 mmol) in CH₂Cl₂ and stirred under hydrogen atmosphere for 18 h. The mixture was filtered through silica plug and solvent removed in vacuo. Purification over silica with 2% EtOAc in hexane gave the saturated product (380 mg, 94%) as a colourless oil; {¹⁹F}¹H NMR (500 MHz, CDCl₃) 7.29-7.26 (2H, m, ArH), 7.18-7.17 (3H, m, ArH), 2.60 (2H, t, J = 7.7 Hz, ArCH₂), 1.80-1.76 (4H, m, 2 x CH₂), 1.62 (2H, m, CH₂), 1.43 (4H, m, 2 x CH₂), 1.35 (4H, m, 2 x CH₂), 1.29-1.27 (10H, m, 5 x CH₂), 0.88 (3H, t, J = 6.6 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ_C 142.7 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 125.4 (t, J = 240 Hz, CF₂), 36.2 (2 x t, J = 25.5 Hz, 2 x CH₂), 35.9 (CH₂), 31.8 (CH₂), 31.3 (CH₂), 29.4 (2 x CH₂), 29.2 (CH₂), 29.1 (CH₂), 29.0 (CH₂), 22.6 (CH₂), 22.3 (2 x t, J = 4.4 Hz, 2 x CH₂), 14.1 (CH₃); {¹H}¹⁹F NMR (470 MHz, CDCl₃) δ_F -97.6 (CF₂). HRMS (Cl⁺) Exact mass calcd for C₂₁H₃₄F₂ [M⁺]: 324.2623, found: 324.2619.

8,8-Difluorohexadecanoic acid (6a). RuCl₃·xH₂O (20 mg, 0.08 mmol) and NaIO₄ (3.4 g, 16 mmol) was added to a solution of (7,7-difluoropentadecyl)benzene (300 mg, 0.92 mmol) in CCl₄/MeCN/H₂O (2 mL/2 mL/3 mL) and stirred at 25 °C for 18 h. The mixture

acidified with 1 M HCl (1 mL), then filtered through a pad of celite, dried over MgSO_4 and concentrated in vacuo. Purification over silica with 20% EtOAc in hexane gave the acid (190 mg, 71%) as a white crystalline solid, m.p. 52 °C; $\{^{19}\text{F}\}^1\text{H}$ NMR (300 MHz, CDCl_3) 2.37 (2H, t, J = 7.4 Hz, CH_2), 1.82-1.77 (4H, m, 2 x CH_2), 1.70-1.61 (4H, m, 2 x CH_2), 1.48-1.42 (4H, m, 2 x CH_2), 1.38-1.29 (12H, m, 6 x CH_2), 0.89 (3H, t, J = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 178.6 (C=O), 125.4 (t, J = 238 Hz, CF_2), 36.3 (2 x t, J = 25.4 Hz, 2 x CH_2), 33.7 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 24.5 (CH_2), 22.6 (CH_2), 22.3 (CH_2 , t, J = 4.4 Hz,), 22.1 (CH_2 , t, J = 4.7 Hz,), 14.1 (CH_3); $\{^1\text{H}\}^{19}\text{F}$ NMR (282 MHz, CDCl_3) δ_{F} -98.2 (CF_2). HRMS (ESI) Exact mass calcd for $\text{C}_{16}\text{H}_{29}\text{F}_4\text{O}_2$ [M-H] $^-$: 291.2141, found: 291.2133.

10-Phenyldec-1-en-4-ol (13). To a solution of 7-phenylheptanal (7.6 g, 40 mmol) in THF (200 mL) at 0 °C was added allylmagnesium bromide (45 mL, 45 mmol, 1.0 M in THF) and the resulting mixture was stirred for 30 min at rt. The reaction was quenched with aq. NH_4Cl solution (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification over silica gel, eluting with 10:1 hexane/EtOAc, yielded the alcohol (5.5 g, 59%) as a colourless oil; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.29-7.25 (m, 2H, ArH), 7.18-7.16 (m, 3H, ArH), 5.88-5.77 (m, 1H, =CH), 5.16-5.14 (m, 1H, = CH_2), 5.12-5.10 (m, 1H, = CH_2), 3.66-3.60 (m, 1H, CHOH), 2.60 (t, J = 7.6 Hz, 2H, Ar CH_2), 2.32-2.26 and 2.16-2.09 (m, 2H, HOCH CH_2), 1.64-1.43 (m, 6H, 3 x CH_2), 1.34-1.33 (m, 4H, 2 x CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.8 (C), 134.9 (CH), 128.4 (2 x CH), 128.2 (2 x CH), 125.5 (CH), 118.1 (CH₂), 70.6 (CHOH), 41.9 (CH₂), 36.7 (CH₂), 35.9 (CH₂), 31.4 (CH₂), 29.5 (CH₂), 29.2 (CH₂), 25.6 (CH₂); HRMS (ES⁺) calcd for $\text{C}_{16}\text{H}_{28}\text{ON}$ [M+NH₄]⁺: 250.2165, found: 250.2163.

10-Phenyldec-1-en-4-one (14). To a solution of 10-phenyldec-1-en-4-ol (5.5 g, 23.7 mmol) in dichloromethane (100 mL) at 0 °C was slowly added Dess-Martin periodinane (17 g, 40 mmol). The mixture was stirred for 30 min at room temperature. The reaction was quenched with H_2O (50 mL), washed with aqueous saturated NaHCO_3 solution (2 x 50 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo to give the ketone (4.5 g, 82%) as a colourless oil; ^1H NMR (400 MHz, CDCl_3) δ_{H} 7.20-7.16 (m, 2H, ArH), 7.08-7.07 (m, 3H, ArH), 5.88-5.78 (m, 1H, =CH), 5.10-5.01 (m, 2H, = CH_2), 3.07-3.05 (m, 2H, $\text{CH}_2\text{CH}=\text{}$), 2.50 (t, J = 7.7 Hz, 2H, Ar CH_2), 2.33 (t, J = 7.4 Hz, 2H, $\text{CH}_2\text{C=O}$), 1.56-1.44 (m, 4H, 2 x CH_2), 1.25-1.22 (m, 4H, 2 x CH_2); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 208.7 (C=O), 142.6 (C), 130.6 (CH), 128.2 (2 x CH), 128.1 (2 x CH), 125.5 (CH), 118.6 (CH₂), 47.6 (CH₂), 42.2 (CH₂), 35.8 (CH₂), 31.2 (CH₂), 28.9 (2 x CH₂), 23.4 (CH₂); HRMS (ES⁺) calcd for $\text{C}_{16}\text{H}_{23}\text{O}$ [M+H]⁺: 231.1743, found: 231.1745.

(7,7-Difluorodec-9-en-1-yl)benzene (15). Neat DAST (6.4 g, 40 mmol) was added to 10-phenyldec-1-en-4-one (4.5 g, 19.6 mmol) under argon atmosphere. The reaction was heated at 50 °C for 4 hours and cooled down to room temperature. The reaction mixture was diluted with EtOAc (50 mL) and carefully quenched with saturated NaHCO_3 solution (100 mL). The organic layer was separated, dried over MgSO_4 and solvent removed in vacuo. Purification over silica with 2% EtOAc in hexane gave the difluoro

product (2.2 g, 45%) as a colourless oil ; $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) δ_{H} 7.23-7.19 (m, 2H, ArH), 7.21-7.20 (m, 3H, ArH), 5.87-5.78 (m, 1H, =CH), 5.24-5.20 (m, 2H, =CH₂), 2.65 (m, 2H, $\text{CH}_2\text{CH}=$), 2.62 (t, J = 6.1 Hz, 2H, ArCH₂), 1.84-1.80 (m, 2H, CH₂), 1.63 (m, 2H, CH₂), 1.50 (m, 2H, CH₂), 1.38 (m, 4H, 2 x CH₂); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.7 (C), 129.9 (t, J = 6 Hz, =CH), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 124.3 (t, J = 241 Hz, CF₂), 119.9 (=CH₂), 65.9 (CH₂), 41.1 (t, J = 26 Hz, CH₂), 35.9 (CH₂), 31.6 (CH₂), 29.2 (CH₂), 22.6 (CH₂), 15.2 (CH₂); $\{^1\text{H}\}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} -97.2 (CF₂); HRMS (ES⁺) Exact mass calcd for $\text{C}_{16}\text{H}_{22}\text{F}_2$ [M⁺]: 252.1684, found: 252.1683.

2-(2,2-Difluoro-8-phenyloctyl)oxirane (16). To a solution of (7,7-difluorodec-9-en-1-yl)benzene (2.0 g, 7.7 mmol) in dichloromethane (50 mL) was added mCPBA (6.9 g, 40 mmol) and the mixture was stirred for 10 hour at room temperature. The reaction mixture was washed with aqueous saturated NaHCO_3 solution (3 × 50 mL) and H_2O (50 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over MgSO_4 , concentrated in vacuo and purification over silica with 5% EtOAc/hexane to give the epoxide (1.5 g, 73%) as a colourless oil; ^1H NMR (300 MHz, CDCl_3) δ_{H} 7.30-7.26 (m, 2H, ArH), 7.20-7.16 (m, 3H, ArH), 3.14-3.08 (m, 1H, OCH), 2.84-2.81 (m, 1H, OCH), 2.61 (t, J = 7.7 Hz, ArCH₂), 2.53-2.51 (m, 1H, OCH), 2.18-1.81 (m, 4H, 2 x CH₂), 1.67-1.58 (m, 2H, CH₂), 1.52-1.47 (m, 2H, CH₂), 1.39-1.35 (m, 4H, 2 x CH₂); ^{13}C NMR (75 MHz, CDCl_3) δ_{C} 142.6 (C), 128.3 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 124.2 (t, J = 241 Hz, CF₂), 46.9 (m, CH₂), 46.2 (CH₂), 39.9 (t, J = 25.8 Hz, CH₂), 36.6 (t, J = 24.6 Hz, CH₂), 35.8 (CH₂), 31.3 (CH₂), 29.1 (CH₂), 29.0 (CH₂), 22.0 (t, J = 4.5 Hz, CH₂); $\{^1\text{H}\}^{19}\text{F}$ NMR (282 MHz, CDCl_3) δ_{F} -96.7 (q, J = 250 Hz, CF₂); HRMS (ES⁻) Exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{OF}_2$ [M-H]⁻: 267.1555, found: 267.1553.

9,9-Difluoro-15-phenylpentadecan-7-ol (17). To a solution of 2-(2,2-difluoro-8-phenyloctyl)oxirane (1.0 g, 3.7 mmol) and Cul (50 mg) in THF (50 mL) at 0 °C was added pentylmagnesium chloride (2.5 mL, 5 mmol, 2.0 M in THF) and the resulting mixture was stirred for 30 min at rt. The reaction was quenched with aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification over silica gel, eluting with 5% EtOAc/hexane, yielded the alcohol (0.65 g, 52%) as a colourless oil; $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) 7.33-7.30 (2H, m, ArH), 7.01-7.20 (3H, m, ArH), 4.05-4.02 (1H, m, CHOH), 2.64 (2H, t, J = 7.7 Hz, ArCH₂), 2.05-1.86 (4H, m, 2 x CH₂), 1.67-1.65 (2H, m, CH₂), 1.52-1.32 (16H, m, 8 x CH₂), 0.93 (3H, t, J = 6.4 Hz, CH₃); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 142.6 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 125.5 (t, J = 241 Hz, CF₂), 66.8 (CH), 43.3 (t, J = 23.5 Hz, CH₂), 37.6 (CH₂), 37.2 (t, J = 25.0 Hz, CH₂), 35.9 (CH₂), 31.8 (CH₂), 31.3 (CH₂), 29.2 (CH₂), 29.1 (2 x CH₂), 25.3 (CH₂), 22.6 (CH₂), 22.2 (CH₂), 14.1 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (476 MHz, CDCl_3) δ_{F} -96.1 (abq, CF₂). HRMS (ESI⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{34}\text{F}_2\text{ONa}$ [M+Na]⁺: 363.2471, found: 363.2464.

9,9-Difluoro-15-phenylpentadecan-7-one (18). To a solution of 9,9-difluoro-15-phenylpentadecan-7-ol (0.60 g, 1.8 mmol) in acetone (20 mL) at 0 °C was slowly added a solution of CrO_3 (0.4 g, 4 mmol) in H_2SO_4 (3 mL) and H_2O (6 mL). The mixture was stirred for 30 min at rt. The reaction was quenched with H_2O (20 mL) and extracted with

diethyl ether (3×20 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo to give the ketone (0.50 g, 82%) as a colourless oil; $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) 7.21-7.17 (2H, m, ArH), 7.11-7.08 (3H, m, ArH), 2.86 (2H, s, CH_2), 2.52 (2H, t, $J = 7.7$ Hz, Ar CH_2), 2.42 (2H, t, $J = 7.3$ Hz, CH_2) 2.09 (2H, s, CH_2), 1.88-1.84 (2H, m, CH_2), 1.56-1.49 (4H, m, 2 x CH_2), 1.40-1.36 (2H, m, CH_2), 1.29-1.26 (4H, m, 2 x CH_2), 1.23-1.18 (6H, m, 3 x CH_2), 0.80 (3H, t, $J = 6.8$ Hz, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 204.7 (C=O), 142.6 (C), 128.3 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 122.8 (t, $J = 242$ Hz, CF_2), 48.7 (t, $J = 26.2$ Hz, CH_2), 44.2 (CH₂), 36.3 (t, $J = 22.0$ Hz, CH_2), 35.8 (CH₂), 31.5 (CH₂), 31.2 (CH₂), 29.0 (CH₂), 28.9 (CH₂), 28.6 (CH₂), 23.2 (CH₂), 22.4 (CH₂), 22.1 (t, $J = 4.2$ Hz, CH_2), 14.0 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (476 MHz, CDCl_3) δ_{F} -93.3 (s, CF_2). HRMS (ESI⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{32}\text{F}_2\text{ONa}$ [M+Na]⁺: 361.2315, found: 361.2312.

(7,7,9,9-Tetrafluoropentadecyl)benzene (19). Neat DAST (0.81 g, 5.0 mmol) was added to 9,9-difluoro-15-phenylpentadecan-7-one (0.50 g, 1.5 mmol) under argon atmosphere. The reaction was heated at 50 °C for 4 hours and cooled down to rt. The reaction mixture was diluted with EtOAc (20 mL), washed with saturated NaHCO_3 solution (50 mL) and extracted with EtOAc (2 x 20 mL). The organic layer was combined and dried over MgSO_4 and concentrated in vacuo. Purification over silica with 3% EtOAc in hexane gave the tetrafluoro product (0.32 g, 59%) as a colourless oil; $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) 7.32-7.29 (2H, m, ArH), 7.22-7.19 (3H, m, ArH), 2.63 (2H, t, $J = 7.7$ Hz, Ar CH_2), 2.46 (2H, s, CH_2), 1.95-1.92 (4H, m, 2 x CH_2), 1.68-1.63 (2H, m, CH_2), 1.52-1.47 (4H, m, 2 x CH_2), 1.38-1.33 (10H, m, 5 x CH_2), 0.92 (3H, t, $J = 6.8$ Hz, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 142.6 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.6 (CH), 122.5 (2 x t, $J = 242$ Hz, 2 x CF_2), 42.3 (quin, $J = 26.9$ Hz, CH_2), 36.9 (2 x t, $J = 23.8$ Hz, 2 x CH_2), 35.9 (CH₂), 31.5 (CH₂), 31.3 (CH₂), 29.1 (CH₂), 29.0 (CH₂), 22.5 (CH₂), 22.0 (2 x CH₂), 14.0 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (476 MHz, CDCl_3) δ_{F} -93.4 (m, 2 x CF_2). HRMS (ESI⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{32}\text{F}_4\text{Na}$ [M+Na]⁺: 383.2322, found: 383.2332.

8,8,10,10-Tetrafluorohexadecanoic acid (6b). $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ (10 mg, 0.04 mmol) and NaIO_4 (1.7 g, 8 mmol) was added to a solution of (7,7,9,9-tetrafluoropentadecyl)benzene (150 mg, 0.42 mmol) in $\text{CCl}_4/\text{MeCN}/\text{H}_2\text{O}$ (2 mL/2 mL/3 mL) and stirred at 25 °C for 18 h. The mixture acidified with 1 M HCl (1 mL), then filtered through a pad of celite, dried over MgSO_4 and concentrated in vacuo. Purification over silica with 20% EtOAc in hexane gave the acid (95 mg, 69%) as a white crystalline solid, m.p. 60 °C; $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) 2.45 (2H, s, CH_2), 2.36 (2H, t, $J = 7.4$ Hz, CH_2), 1.94-1.90 (4H, m, 2 x CH_2), 1.68-1.62 (2H, m, CH_2), 1.52-1.45 (4H, m, 2 x CH_2), 1.38-1.31 (10H, m, 5 x CH_2), 0.90 (3H, t, $J = 6.9$ Hz, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 179.0 (C=O), 122.5 (2 x t, $J = 245$ Hz, 2 x CF_2), 42.4 (t, $J = 26.8$ Hz, CH_2), 36.8 (m, 2 x CH_2), 33.8 (CH₂), 31.5 (CH₂), 28.9 (CH₂), 28.8 (CH₂), 28.7 (CH₂), 24.4 (CH₂), 22.5 (CH₂), 22.0 (CH₂), 21.9 (CH₂), 14.0 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (476 MHz, CDCl_3) δ_{F} -93.4 (m, 2 x CF_2). HRMS (ESI⁺) Exact mass calcd for $\text{C}_{16}\text{H}_{28}\text{F}_4\text{O}_2\text{Na}$ [M+Na]⁺: 351.1916, found: 351.1917.

9-Phenylnon-1-yn-3-ol (20). To a solution of 7-phenylheptanal (4.4 g, 23 mmol) in THF (100 mL) at 0 °C was added ethynylmagnesium bromide (60 mL, 30 mmol, 0.5 M in

THF) and the resulting mixture was stirred for 30 min at rt. The reaction was quenched with aq. NH₄Cl solution (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification over silica gel, eluting with 10:1 hexane/EtOAc, yielded the alcohol (3.6 g, 72%) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ _H 7.22-7.19 (m, 3H, ArH), 7.12-7.09 (m, 2H, ArH), 4.32-4.27 (m, 1H, CHOH), 2.53 (t, *J* = 7.6 Hz, 2H, ArCH₂), 2.39 (d, *J* = 2.4 Hz, 1H, \equiv CH), 1.72 (d, *J* = 5.5 Hz, 1H, OH), 1.67-1.61 (m, 2H, CH₂), 1.57-1.53 (m, 2H, CH₂), 1.41-1.37 (m, 2H, CH₂), 1.31-1.27 (m, 4H, 2 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ _C 142.7 (C), 128.4 (2 × CH), 128.2 (2 × CH), 125.6 (CH), 84.9 (\equiv C), 72.9 (\equiv CH), 62.3 (CHOH), 37.6 (CH₂), 35.9 (CH₂), 31.4 (CH₂), 29.1 (CH₂), 29.0 (CH₂), 24.0 (CH₂); LRMS (ES⁺) calcd for C₁₅H₂₀ONa [M+Na]⁺: 239.31, found: 239.06.

9-Phenylnon-1-yn-3-one (21). To a solution of 9-phenylnon-1-yn-3-ol (3.6 g, 16.6 mmol) in acetone (30 mL) at 0 °C was slowly added a solution of CrO₃ (2.0 g, 20 mmol) in H₂SO₄ (5 mL) and H₂O (10 mL). The mixture was stirred for 30 min at rt. The reaction was quenched with H₂O (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give the ketone (3.4 g, 96%) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ _H 7.31-7.26 (m, 2H, ArH), 7.20-7.16 (m, 3H, ArH), 3.20 (s, 1H, \equiv CH), 2.63-2.56 (m, 4H, 2 × CH₂), 1.71-1.60 (m, 4H, 2 × CH₂), 1.39-1.34 (m, 4H, 2 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ _C 187.5 (C=O), 142.6 (C), 128.4 (2 × CH), 128.2 (2 × CH), 125.6 (CH), 81.4 (\equiv C), 78.5 (\equiv CH), 45.4 (CH₂), 35.9 (CH₂), 31.3 (CH₂), 29.0 (CH₂), 28.8 (CH₂), 23.7 (CH₂); LRMS (ES⁺) calcd for C₁₅H₁₈ONa [M+Na]⁺: 237.12, found: 237.03.

(7,7-Difluororon-8-yn-1-yl)benzene (22). Neat DAST (3.5 g, 20 mmol) was added to 9-phenylnon-1-yn-3-one (2.3 g, 10.7 mmol) under argon atmosphere. The mixture was heated at 50 °C for 4 hours and cooled down to rt. It was diluted with EtOAc (50 mL), washed with saturated NaHCO₃ solution (100 mL). The organic layer was separated, dried over MgSO₄ and solvent removed in vacuo. Purification over silica with 2% EtOAc in hexane gave the difluoro product (2.2 g, 87%) as a colourless oil; ¹H NMR (400 MHz, CDCl₃) δ _H 7.31-7.18 (m, 5H, ArH), 2.75 (t, *J* = 5.0 Hz, \equiv CH), 2.62 (t, *J* = 7.6 Hz, ArCH₂), 2.09-1.98 (m, CH₂), 1.68-1.53 (m, 2 × CH₂), 1.40-1.37 (m, 2 × CH₂); ¹³C NMR (125 MHz, CDCl₃) δ _C 142.6 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.6 (CH), 114.4 (t, *J* = 233 Hz, CF₂), 87.9 (t, *J* = 7 Hz, \equiv CH), 77.9 (t, *J* = 41 Hz, \equiv C), 39.0 (t, *J* = 25.4 Hz, CH₂), 35.9 (CH₂), 31.2 (CH₂), 28.9 (CH₂), 28.8 (CH₂), 22.6 (t, *J* = 3.5 Hz, CH₂); HRMS (EI⁺) Exact mass calcd for C₁₅H₁₈F₂ [M⁺]: 236.1371, found: 236.1370.

9,9-Difluoro-15-phenylpentadec-7-yn-6-ol (23). To a solution of (7,7-difluororon-8-yn-1-yl)benzene (1.7 g, 7.2 mmol) in THF (7 mL) cooled down to -78 °C was added BuLi (5 mL, 7.5 mmol, 1.5 M in THF) and the resulting mixture was warmed up to 0 °C over 10 mins. Then hexanal (0.75 g, 7.5 mmol) was added to the mixture and stirred for 1 hour at rt. The solvent was removed in vacuo and purification over silica with 5% EtOAc/hexane to give the product (1.3 g, 76%) as a colourless oil; ¹⁹F¹H NMR (300 MHz, CDCl₃) 7.32-7.17 (5H, m, ArH), 4.45 (1H, m, CHOH), 2.62 (2H, t, *J* = 7.5 Hz, ArCH₂), 2.05-2.00 (2H, m, CH₂), 1.86 (1H, d, *J* = 5.8 Hz, OH), 1.77-1.71 (2H, m, CH₂), 1.66-1.53 (4H, m, 2 × CH₂), 1.49-1.30 (12H, m, 6 × CH₂), 0.91 (3H, t, *J* = 6.7 Hz, CH₃);

^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.6 (C), 128.4 (2 x CH), 128.3 (2 x CH), 125.6 (CH), 114.8 (t, J = 232 Hz, CF_2), 87.9 (C), 77.9 (C), 62.1 (CH), 39.1 (t, J = 26.0 Hz, CH_2), 37.1 (CH₂), 35.8 (CH₂), 31.3 (CH₂), 31.2 (CH₂), 28.9 (CH₂), 28.8 (CH₂), 24.6 (CH₂), 22.7 (t, J = 3.2 Hz, CH₂), 22.5 (CH₂), 13.9 (CH₃); $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (376 MHz, CDCl_3) δ_{F} -83.1 (CF₂). HRMS (Cl⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{34}\text{NOF}_2$ [M+NH₄]⁺: 354.2603, found: 354.2601.

9,9-Difluoro-15-phenylpentadec-7-yn-6-one (24). To a solution of 9,9-difluoro-15-phenylpentadec-7-yn-6-ol (1.3 g, 3.9 mmol) in acetone (20 mL) at 0 °C was slowly added a solution of CrO_3 (0.4 g, 4 mmol) in H_2SO_4 (3 mL) and H_2O (6 mL). The mixture was stirred for 30 min at rt. The reaction was quenched with H_2O (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over MgSO_4 and concentrated in *vacuo* to give the ketone (1.2 g, 93%) as a yellow oil; $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (400 MHz, CDCl_3) 7.23-7.09 (5H, m, ArH), 2.54 (2H, t, J = 7.3 Hz, ArCH₂), 2.05-1.93 (2H, m, CH₂), 1.62-1.44 (6H, m, 3 x CH₂), 1.31-1.22 (10H, m, 5 x CH₂), 0.83 (3H, t, J = 6.9 Hz, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 186.5 (C=O), 142.5 (C), 128.4 (2 x CH), 128.3 (2 x CH), 125.7 (CH), 114.5 (t, J = 235 Hz, CF₂), 82.3 (C), 80.6 (C), 45.4 (CH₂), 38.7 (t, J = 25.0 Hz, CH₂), 35.8 (CH₂), 31.2 (CH₂), 30.9 (CH₂), 28.9 (CH₂), 28.7 (CH₂), 23.2 (CH₂), 22.4 (t, J = 3.4 Hz, CH₂), 22.3 (CH₂), 13.8 (CH₃); $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (376 MHz, CDCl_3) δ_{F} -85.9 (CF₂). HRMS (ESI⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{29}\text{F}_2\text{O}$ [M+H]⁺: 335.2181, found: 335.2179.

(7,7,10,10-Tetrafluoropentadec-8-yn-1-yl)benzene (25). Neat DAST (0.96 g, 6 mmol) was added to 9,9-difluoro-15-phenylpentadec-7-yn-6-one (1.0 g, 3 mmol) under argon atmosphere. The mixture was heated at 50 °C for 4 hours and cooled down to rt. It was diluted with EtOAc (50 mL), washed with saturated NaHCO_3 solution (100 mL). The organic layer was separated, dried over MgSO_4 and solvent removed in *vacuo*. Purification over silica with 2% EtOAc in hexane gave the tetrafluoro product (0.76 g, 71%) as a colourless oil; $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (400 MHz, CDCl_3) 7.23-7.09 (5H, m, ArH), 2.54 (2H, t, J = 7.6 Hz, ArCH₂), 2.00-1.96 (2H, m, CH₂), 1.60-1.44 (4H, m, 2 x CH₂), 1.32-1.26 (4H, m, 2 x CH₂), 1.31-1.28 (8H, m, 4 x CH₂), 0.84 (3H, t, J = 7.0 Hz, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.5 (C), 128.4 (2 x CH), 128.3 (2 x CH), 125.7 (CH), 114.3 (t, J = 235 Hz, CF₂), 114.2 (t, J = 235 Hz, CF₂), 79.0 (t, J = 43.8 Hz, C), 78.9 (t, J = 44.0 Hz, C), 38.7 (m, 2 x CH₂), 35.8 (CH₂), 31.2 (CH₂), 30.9 (CH₂), 28.9 (CH₂), 28.7 (CH₂), 22.4 (CH₂), 22.3 (CH₂), 22.1 (CH₂), 13.8 (CH₃); $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (376 MHz, CDCl_3) δ_{F} -85.9 (CF₂). HRMS (EI⁺) Exact mass calcd for $\text{C}_{21}\text{H}_{28}\text{F}_4$ [M⁺]: 356.2122, found: 356.2125.

(7,7,10,10-Tetrafluoropentadecyl)benzene (26). Palladium on activated carbon (50 mg) was added to a solution of (7,7,10,10-tetrafluoropentadec-8-yn-1-yl)benzene (262 mg, 0.73 mmol) in CH_2Cl_2 and stirred under hydrogen atmosphere for 18 h. The mixture was filtered through silica plug and solvent removed in *vacuo*. Purification over silica with 2% EtOAc in hexane gave the saturated product (260 mg, 99%) as a white solid, m.p. 34 °C; $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (400 MHz, CDCl_3) 7.17-7.02 (5H, m, ArH), 2.47 (2H, t, J = 7.7 Hz, ArCH₂), 1.87 (2H, s, CH₂), 1.71-1.66 (4H, m, 2 x CH₂), 1.53-1.44 (2H, m, CH₂), 1.36-1.29 (4H, m, 2 x CH₂), 1.22-1.12 (6H, m, 3 x CH₂), 0.77 (3H, t, J = 6.5 Hz, CH₃); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 142.6 (C), 128.4 (2 x CH), 128.3 (2 x CH), 125.6 (CH), 124.5 (2 x t, J = 241 Hz, 2 x CF₂), 36.7 (2 x CH₂), 35.9 (CH₂), 31.5 (CH₂), 31.3 (CH₂),

29.2 (2 x CH₂), 29.0 (2 x CH₂), 22.4 (CH₂), 22.2 (t, *J* = 4.4 Hz, CH₂), 22.0 (t, *J* = 4.6 Hz, CH₂), 13.9 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (376 MHz, CDCl₃) δ_{F} -100.1 (2 x CF₂). HRMS (EI⁺) Exact mass calcd for C₂₁H₃₂F₄ [M⁺]: 360.2435, found: 360.2438.

8,8,11,11-Tetrafluorohexadecanoic acid (6c). RuCl₃·xH₂O (10 mg, 0.04 mmol) and NaIO₄ (1.7 g, 8 mmol) was added to a solution of (7,7,10,10-tetrafluoropentadecyl)benzene (140 mg, 0.4 mmol) in CCl₄/MeCN/H₂O (2 mL/2 mL/3 mL) and stirred at 25 °C for 18 h. The mixture acidified with 1 M HCl (1 mL), then filtered through a pad of celite, dried over MgSO₄ and concentrated in vacuo. Purification over silica with 20% EtOAc in hexane gave the acid (100 mg, 76%) as a white crystalline solid, m.p. 79 °C; $\{^1\text{H}\}^{19}\text{F}$ NMR (400 MHz, CDCl₃) 2.37 (2H, t, *J* = 7.4 Hz, CH₂), 2.02 (4H, s, 2 x CH₂), 1.86-1.81 (4H, m, 2 x CH₂), 1.70-1.62 (4H, m, 2 x CH₂), 1.52-1.42 (4H, m, 2 x CH₂), 1.38-1.22 (6H, m, 3 x CH₂), 0.91 (3H, t, *J* = 6.9 Hz, CH₃); ^{13}C NMR (100 MHz, CDCl₃) δ_{C} 179.1 (C=O), 124.5 (t, *J* = 241 Hz, CF₂), 124.4 (t, *J* = 241 Hz, CF₂), 36.7 (2 x t, *J* = 25.1 Hz, 2 x CH₂), 33.8 (CH₂), 31.5 (CH₂), 29.1 (2 x CH₂), 28.9 (CH₂), 28.7 (CH₂), 24.4 (CH₂), 22.4 (CH₂), 22.1 (CH₂), 22.0 (CH₂), 13.9 (CH₃); $\{^1\text{H}\}^{19}\text{F}$ NMR (376 MHz, CDCl₃) δ_{F} -100.1 (CF₂), -100.2 (CF₂). HRMS (ESI⁺) Exact mass calcd for C₁₆H₂₇F₄O₂ [M-H]⁺: 327.1953, found: 327.1946.

7-Octenal (28). To a solution of 7-octen-1-ol (6.0 g, 46.9 mmol) in DMSO (219 mL) was added IBX¹ (15.8, 56.3 mmol) and the resulting mixture was stirred 18h at rt. The reaction was quenched with water (516 mL) and EtOAc (516 mL). The precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with water (2 x 516 mL) and brine (516 mL), dried over anhydrous MgSO₄ and the solvent was removed in vacuo to give 7-octenal (5.73 g, 97%) as a yellow oil, which was used without further purification.²

9-Decen-1-yn-3-ol (29). To a solution of 7-octenal (3.68 g, 29.2 mmol) in THF (103 mL) at 0 °C was added ethynylmagnesium bromide (70 mL, 35 mmol, 0.5 M in THF) and the resulting mixture was stirred for 3h at rt. The reaction was quenched with aq. NH₄Cl solution (170 mL) and diethyl ether (84 mL). The aqueous layer was extracted with diethyl ether (3 x 56 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification over silica gel, eluting with 5:1 hexane/EtOAc, yielded the alcohol (2.93 g, 66%) as a yellow oil; ^1H NMR (500 MHz, CDCl₃) δ_{H} 5.81 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, =CH), 4.93-5.02 (2H, m, =CH₂), 4.37 (1H, td, *J* = 6.6, 2.0 Hz, OCH), 2.47 (1H, d, *J* = 2.2 Hz, $\equiv\text{CH}$), 2.03-2.08 (2H, m, CH₂), 1.95 (1H, bs, OH), 1.67-1.78 (2H, m, CH₂), 1.32-1.51 (6H, m, 3 x CH₂); ^{13}C NMR (125 MHz, CDCl₃) δ_{C} 138.9 (=CH), 114.3 (=CH₂), 84.9 ($\equiv\text{C}$), 72.8 ($\equiv\text{CH}$), 62.2 (OCH), 37.5 (CH₂), 33.6 (CH₂), 28.7 (CH₂), 28.6 (CH₂), 24.8 (CH₂); HRMS (Cl⁺) Exact mass calcd for C₁₀H₁₇O [M+H]⁺: 153.1274, found: 153.1270.

9-Decen-1-yn-3-one (30). To a solution of 9-decen-1-yn-3-ol (1.41 g, 9.25 mmol) in DMSO (43 mL) was added IBX (3.11 g, 11.1 mmol) and the resulting mixture was stirred

¹ Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, 64, 4537-4538.

² Rosenquist, A.; Samuelsson, B. *et al.* *Bioorg. Med. Chem.* **2007**, 15, 7184-7202.

18 h at rt. The reaction was quenched with water (102 mL) and EtOAc (102 mL). The precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with water (2 × 102 mL) and brine (102 mL), dried over anhydrous MgSO₄ and the solvent was removed in vacuo to give the propargylic ketone (1.19 g, 85%) as a yellow oil, which was used without further purification; ¹H NMR (300 MHz, CDCl₃) δ_H 5.80 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, =CH), 4.93-5.04 (2H, m, =CH₂), 3.21 (1H, s, ≡CH), 2.60 (2H, t, *J* = 7.4 Hz, CH₂), 2.02-2.10 (2H, m, CH₂), 1.65-1.75 (2H, m, CH₂), 1.27-1.47 (4H, m, 2 × CH₂); ¹³C NMR (75 MHz, CDCl₃) δ_C 187.5 (C=O), 138.6 (=CH), 114.5 (=CH₂), 81.4 (≡C), 78.3 (≡CH), 45.3 (CH₂), 33.4 (CH₂), 28.5 (CH₂), 28.3 (CH₂), 23.5 (CH₂); HRMS (Cl⁺) Exact mass calcd for C₁₀H₁₅O [M+H]⁺: 151.1117, found: 151.1114.

8,8-Difluoro-1-decen-9-yne (31). Neat DAST (7.3 mL, 8.9 g, 55.2 mmol) was added to 9-Decen-1-yn-3-one (2.07 g, 13.8 mmol) under argon atmosphere. The mixture was heated at 50 °C for 18 hours and cooled down to rt. Crude reaction was added **portionwise to a biphasic mixture of saturated aqueous NaHCO₃ solution (148 mL) and pentane (74 mL)** at 0 °C. The aqueous layer was separated and extracted with pentane (3 × 49 mL). The combined organic extracts were dried over MgSO₄ and concentrated by Vigreux distillation at atmospheric pressure. The concentrate was purified over silica gel, eluting with pentane. The solvent was removed by Vigreux distillation at atmospheric pressure yielding the highly volatile difluoro product (1.5 g, 63%) as a colourless liquid, which was rapidly used in the next step; ¹H NMR (500 MHz, CDCl₃) δ_H 5.81 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, =CH), 4.95-5.04 (2H, m, =CH₂), 2.76 (1H, t, *J* = 4.9 Hz, ≡CH), 2.00-2.09 (4H, m, 2 × CH₂), 1.52-1.61 (2H, m, CH₂), 1.36-1.46 (4H, m, 2 × CH₂); {¹⁹F}¹H NMR (500 MHz, CDCl₃) δ_H 5.81 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, =CH), 4.95-5.04 (2H, m, =CH₂), 2.76 (1H, s, ≡CH), 2.02-2.09 (4H, m, 2 × CH₂), 1.52-1.61 (2H, m, CH₂), 1.36-1.46 (4H, m, 2 × CH₂); ¹³C NMR (125 MHz, CDCl₃) δ_C 138.7 (=CH), 114.5 (=CH₂), 114.3 (t, *J* = 233 Hz, CF₂), 76.6 (t, *J* = 41.4 Hz, ≡C), 75.0 (t, *J* = 6.8 Hz, ≡CH), 38.9 (t, *J* = 25.5 Hz, CH₂), 33.5 (CH₂), 28.5 (CH₂), 28.3 (CH₂), 22.5 (t, *J* = 3.4 Hz, CH₂); {¹H}¹⁹F NMR (470 MHz, CDCl₃) δ_F -84.0 (CF₂); ¹⁹F NMR (470 MHz, CDCl₃) δ_F -84.0 (td, *J* = 15.0, 4.7 Hz, CF₂).

8-Nonenal (32). To a solution of 8-nonen-1-ol (1.7 g, 12.0 mmol) in DMSO (56 mL) was added IBX (8.0 g, 28.8 mmol) and the resulting mixture was stirred 18h at rt. The reaction was quenched with water (133 mL) and EtOAc (133 mL). The precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with water (2 × 133 mL) and brine (133 mL), dried over anhydrous MgSO₄ and the solvent was removed in vacuo. Purification over silica gel, eluting with 7:1 hexane/EtOAc, yielded 8-nonenal (1.45 g, 87%) as a yellow oil.³

12,12-Difluorononadeca-1,18-dien-10-yn-9-ol (33). To a solution of 8,8-difluoro-1-decen-9-yne (1.5 g, 8.72 mmol) in THF (13.1 mL) under argon atmosphere cooled down to -78 °C was added BuLi (6 mL, 9.6 mmol, 1.6 M in THF) and the resulting mixture was warmed up to 0 °C over 1h. Then a solution of 8-nonenal (1.34 g, 9.6 mmol) in THF (13.1 mL) was added to the mixture and stirred for 1 hour at rt. The reaction was

³ Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpińska, M. *Synthesis* **2007**, 2491-2494.

quenched with aq. NH_4Cl solution (29 mL) and extracted with EtOAc (3×12 mL). The combined organic layers were dried over MgSO_4 and concentrated in vacuo. Purification over silica gel, eluting with 7:1 hexane/ EtOAc , yielded the alcohol (1.93 g, 71%) as a yellow oil; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.77-5.86 (2H, m, 2 x =CH), 4.93-5.04 (4H, m, 2 x =CH₂), 4.43-4.48 (1H, m, OCH), 1.98-2.09 (6H, m, 3 x CH₂), 1.80 (1H, d, J = 6.0 Hz, OH), 1.72-1.78 (2H, m, CH₂), 1.33-1.59 (14H, m, 7 x CH₂); $\{^{19}\text{F}\}^1\text{H}$ NMR (500 MHz, CDCl_3) δ_{H} 5.76-5.85 (2H, m, 2 x =CH), 4.93-5.03 (4H, m, 2 x =CH₂), 4.45 (1H, q, J = 6.2 Hz, OCH), 2.01-2.09 (6H, m, 3 x CH₂), 1.69-1.80 (2H, m, CH₂), 1.33-1.59 (14H, m, 7 x CH₂); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 139.0 (=CH), 138.6 (=CH), 114.8 (t, J = 232 Hz, CF₂), 114.5 (=CH₂), 114.2 (=CH₂), 87.8 (t, J = 6.5 Hz, $\equiv\text{C}$), 77.9 (t, J = 40.9 Hz, $\equiv\text{C}$), 62.0 (OCH), 39.1 (t, J = 26.0 Hz, CH₂), 37.0 (CH₂), 33.7 (CH₂), 33.5 (CH₂), 29.0 (CH₂), 28.9 (CH₂), 28.7 (CH₂), 28.5 (CH₂), 28.3 (CH₂), 24.8 (CH₂), 22.6 (t, J = 3.2 Hz, CH₂); $\{^1\text{H}\}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} -82.7 (CF₂); ^{19}F NMR (470 MHz, CDCl_3) δ_{F} -82.7 (td, J = 14.9, 3.8 Hz, CF₂); HRMS (Cl⁺) Exact mass calcd for $\text{C}_{19}\text{H}_{34}\text{OF}_2\text{N} [\text{M}+\text{NH}_4]^+$: 330.2603, found: 330.2603.

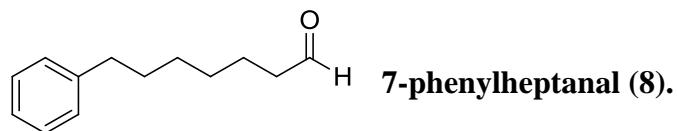
12,12-Difluorononadeca-1,18-dien-10-yn-9-one (34). To a solution of 12,12-difluorononadeca-1,18-dien-10-yn-9-ol (1.93 g, 6.19 mmol) in DMSO (29.1 mL) was added IBX (2.1 g, 7.42 mmol) and the resulting mixture was stirred 18h at rt. The reaction was quenched with water (68 mL) and EtOAc (68 mL). The precipitated white solid was filtered and the filtrate collected. The organic layer was separated and washed with water (2 x 68 mL) and brine (68 mL), dried over anhydrous MgSO_4 and the solvent was removed in vacuo to give the propargylic ketone (1.58 g, 82%) as a yellow oil, which was used without further purification; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.76-5.85 (2H, m, 2 x =CH), 4.93-5.04 (4H, m, 2 x =CH₂), 2.63 (2H, t, J = 7.4 Hz, CH₂), 2.03-2.13 (6H, m, 3 x CH₂), 1.66-1.72 (2H, m, CH₂), 1.53-1.60 (2H, m, CH₂), 1.32-1.46 (10H, m, 5 x CH₂); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 186.4 (C=O), 138.8 (=CH), 138.5 (=CH), 114.6 (=CH₂), 114.5 (t, J = 235 Hz, CF₂), 114.4 (=CH₂), 82.3 (t, J = 6.5 Hz, $\equiv\text{C}$), 80.6 (t, J = 42.3 Hz, $\equiv\text{C}$), 45.4 (CH₂), 38.7 (t, J = 25.1 Hz, CH₂), 33.6 (CH₂), 33.4 (CH₂), 28.7 (CH₂), 28.63 (CH₂), 28.58 (CH₂), 28.4 (CH₂), 28.3 (CH₂), 23.5 (CH₂), 22.3 (t, J = 3.2 Hz, CH₂); $\{^1\text{H}\}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} -85.4 (CF₂); ^{19}F NMR (470 MHz, CDCl_3) δ_{F} -85.4 (t, J = 15.2 Hz, CF₂); HRMS (Cl⁺) Exact mass calcd for $\text{C}_{19}\text{H}_{32}\text{OF}_2\text{N} [\text{M}+\text{NH}_4]^+$: 328.2446, found: 328.2443.

8,8,11,11-Tetrafluorononadeca-1,18-dien-9-yne (35). Neat DAST (0.5 mL, 0.6 g, 3.7 mmol) was added to 12,12-difluorononadeca-1,18-dien-10-yn-9-one (0.28 g, 0.91 mmol) under argon atmosphere. The mixture was heated at 50 °C for 18 hours and cooled down to rt. The reaction mixture was diluted with DCM (3.3 mL), washed with saturated NaHCO_3 solution (3.3 mL) and extracted with DCM (2 x 3.3 mL). The organic layer was combined and dried over MgSO_4 and concentrated in vacuo. Purification over silica gel with hexane gave the tetrafluoro product (0.21 g, 69%) as a colourless oil; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.76-5.85 (2H, m, 2 x =CH), 4.94-5.04 (4H, m, 2 x =CH₂), 2.02-2.16 (8H, m, 4 x CH₂), 1.52-1.59 (4H, m, 2 x CH₂), 1.30-1.46 (10H, m, 5 x CH₂); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 138.8 (=CH), 138.5 (=CH), 114.6 (=CH₂), 114.4 (=CH₂), 114.2 (t, J = 236 Hz, 2 x CF₂), 79.0 (t, J = 42.5 Hz, $\equiv\text{C}$), 78.9 (t, J = 42.3 Hz, $\equiv\text{C}$), 38.7 (t, J = 24.0 Hz, 2 x CH₂), 33.6 (CH₂), 33.4 (CH₂), 28.7 (2 x CH₂), 28.6 (CH₂), 28.4 (CH₂), 28.2 (CH₂),

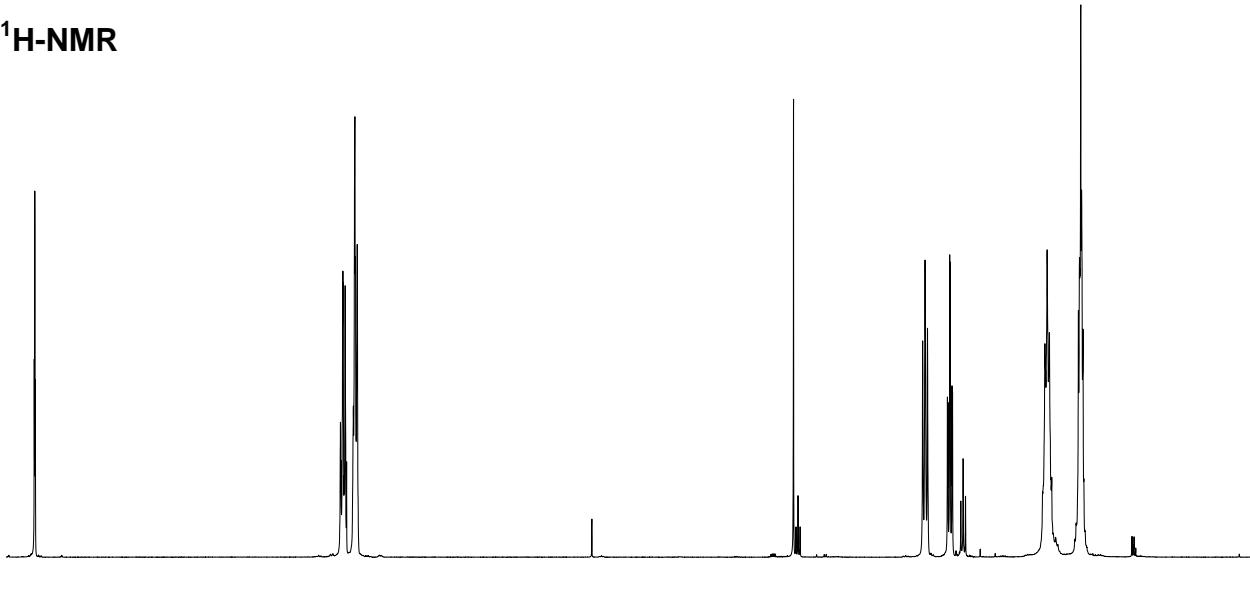
22.4 (t, J = 3.0 Hz, CH_2), 22.3 (t, J = 3.1 Hz, CH_2); $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} - 85.36 (t, J = 4.5 Hz, CF_2), -85.39 (t, J = 4.5 Hz, CF_2); ${}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} - 85.37 (tt, J = 16.0, 5.0 Hz, CF_2), -85.40 (tt, J = 15.9, 4.6 Hz, CF_2).

8,8,11,11-Tetrafluorononadecane (27). Palladium on activated carbon (21.2 mg) was added to a solution of 8,8,11,11-tetrafluorononadeca-1,18-dien-9-yne (33.0 mg, 0.1 mmol) in ethanol (1.72 mL) and stirred under hydrogen atmosphere for 18 h. The mixture was diluted with EtOAc (3 mL), filtered through a short plug of Celite and the solvent was removed in vacuo. Purification over silica gel with hexane gave the tetrafluoro alkane (29.7 mg, 90%) as a white solid, m.p. 35-37 °C; ${}^1\text{H}$ NMR (500 MHz, CDCl_3) δ_{H} 1.97-2.07 (2H, m, CH_2), 1.75-1.88 (4H, m, 2 x CH_2), 1.42-1.51 (4H, m, 2 x CH_2), 1.29-1.33 (20H, m, 10 x CH_2), 0.89 (6H, t, J = 7.1 Hz, 2 x CH_3); ${}^{13}\text{C}$ NMR (125 MHz, CDCl_3) δ_{C} 124.5 (t, J = 241 Hz, 2 x CF_2), 36.8 (t, J = 25.3 Hz, 2 x CH_2), 31.8 (CH_2), 31.7 (CH_2), 29.32 (3 x CH_2), 29.29 (CH_2), 29.1 (2 x CH_2), 29.0 (CH_2), 22.64 (CH_2), 22.60 (CH_2), 22.3 (t, J = 4.0 Hz, 2 x CH_2), 14.08 (CH_3), 14.06 (CH_3); $\{{}^1\text{H}\}{}^{19}\text{F}$ NMR (470 MHz, CDCl_3) δ_{F} -99.6 (2 x CF_2).

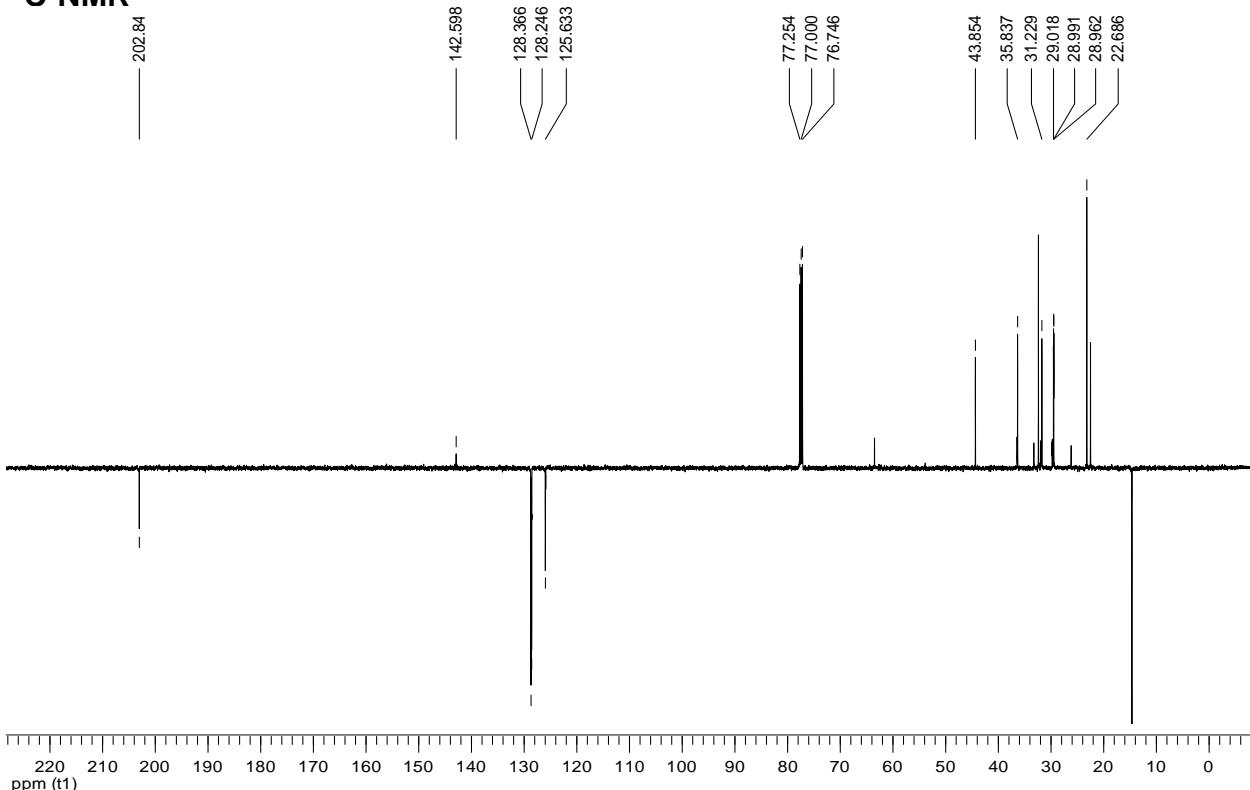
NMR spectra

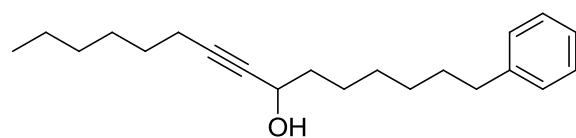


¹H-NMR

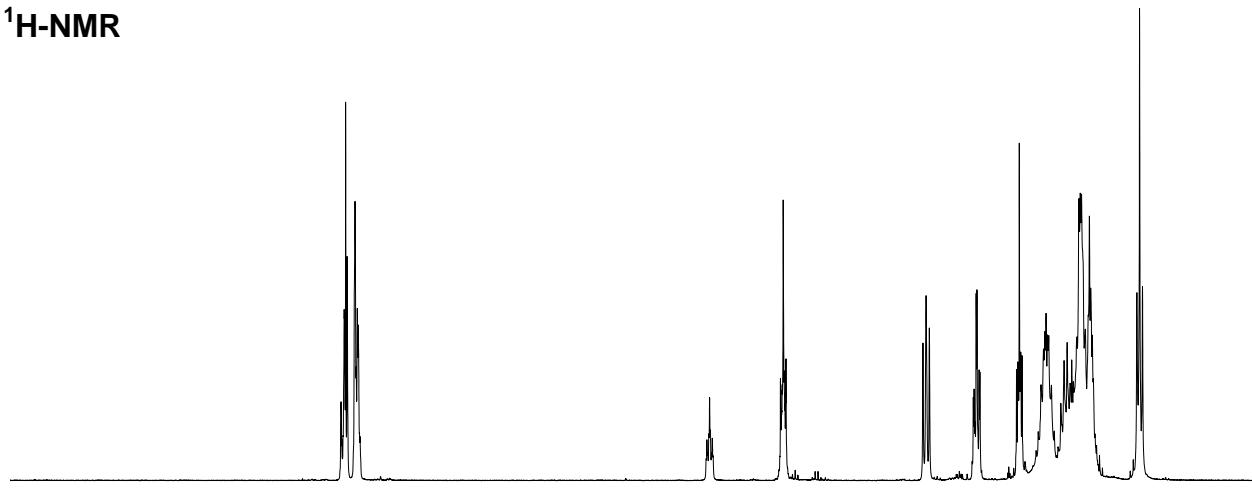


¹³C-NMR

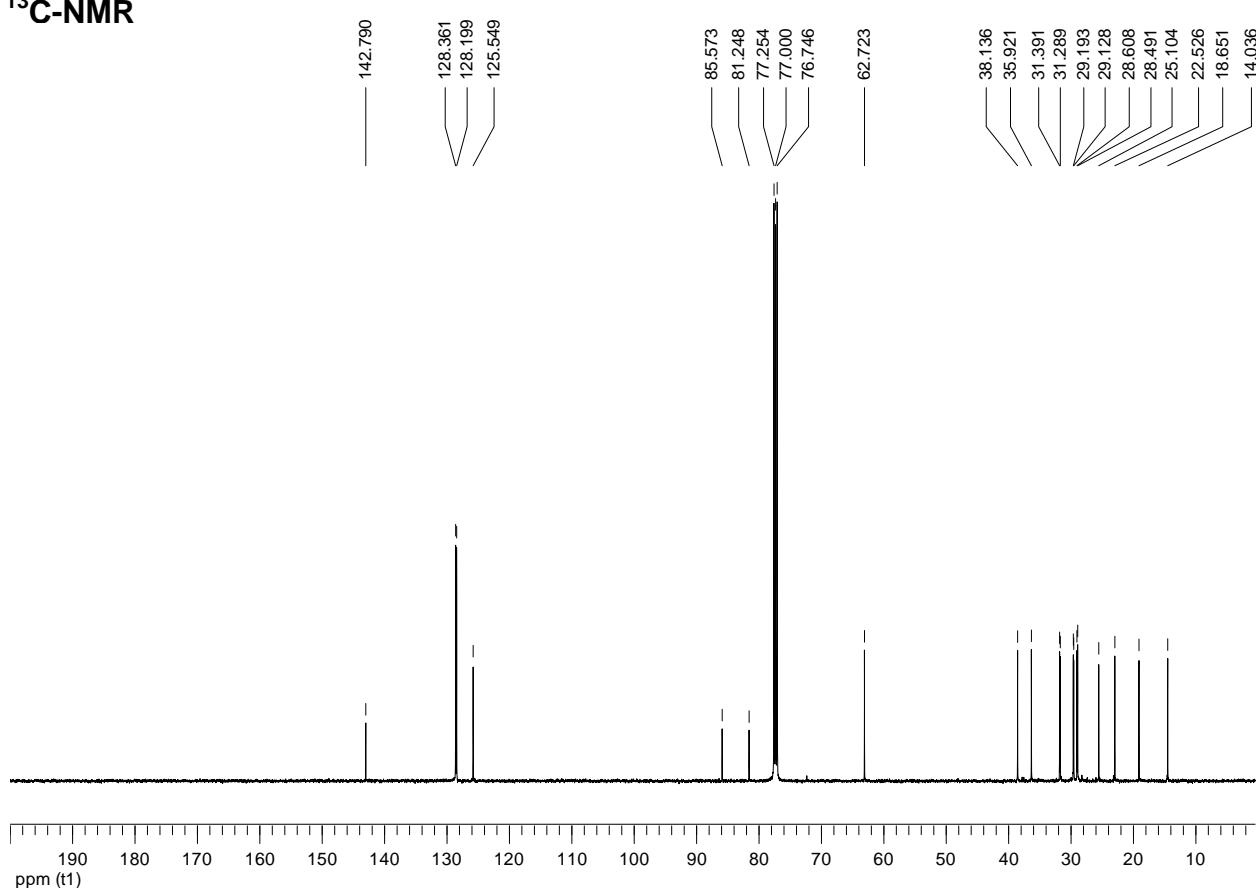


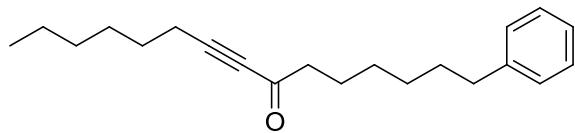


¹H-NMR



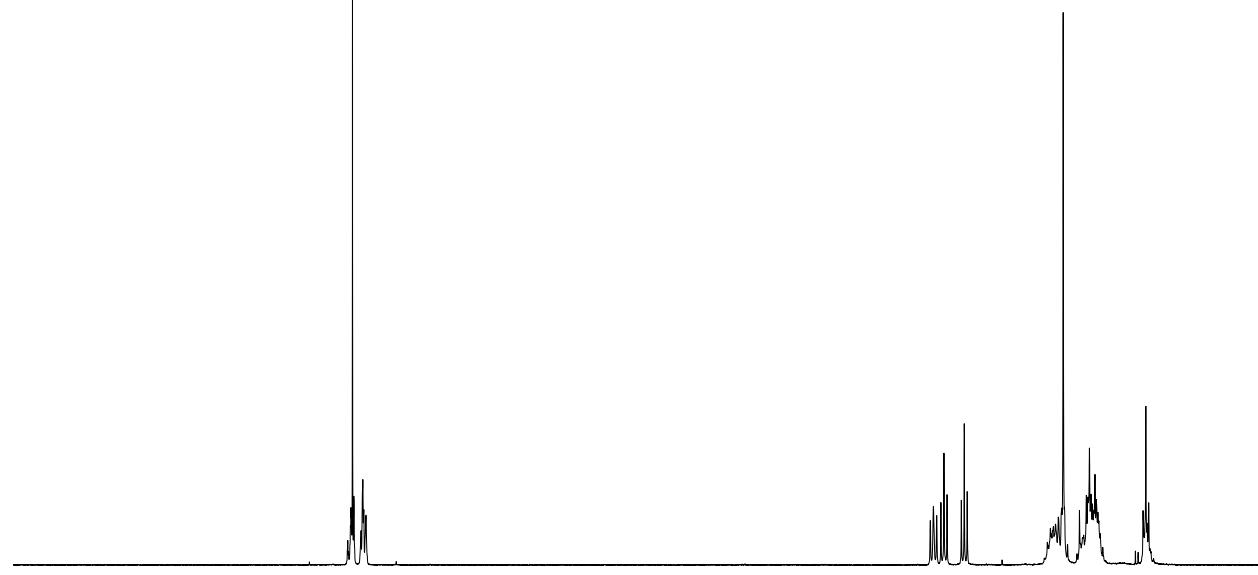
¹³C-NMR



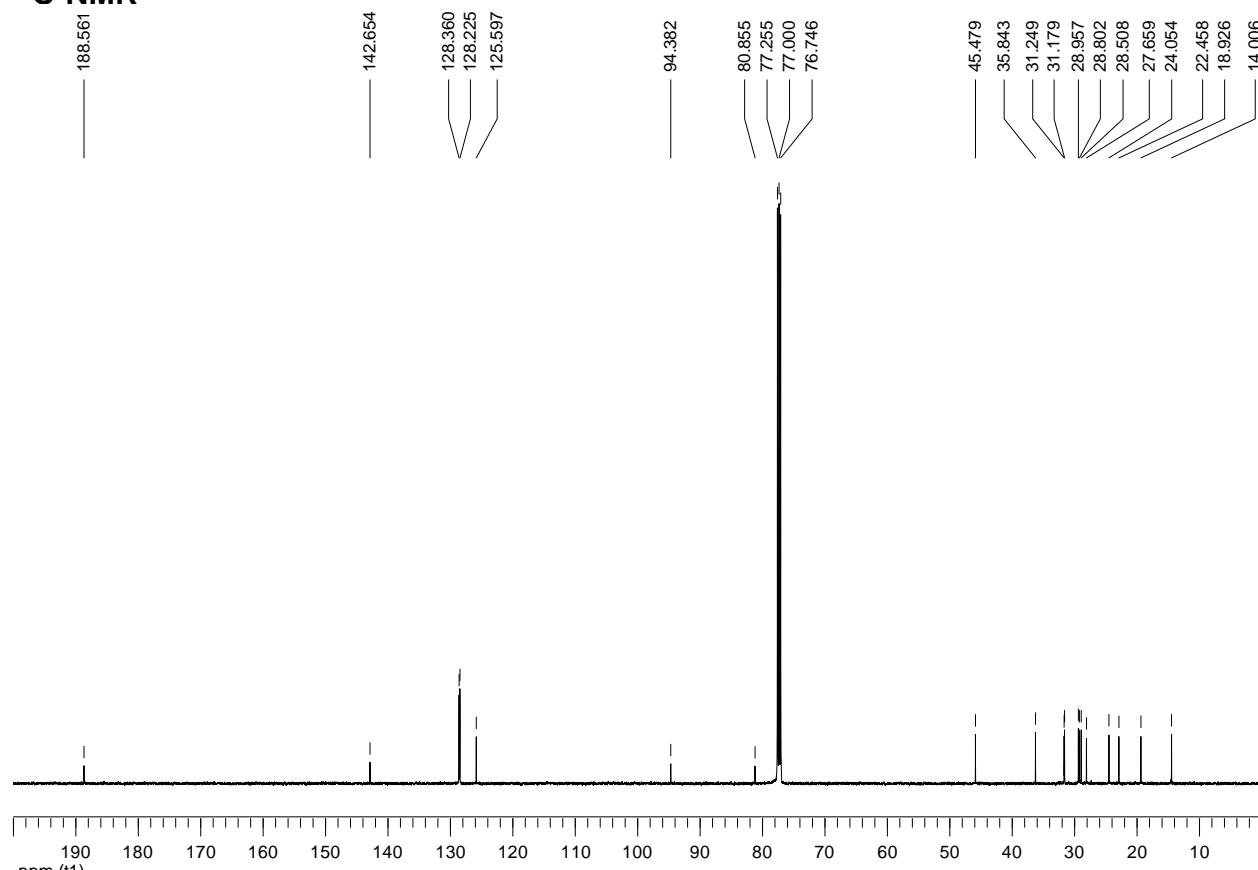


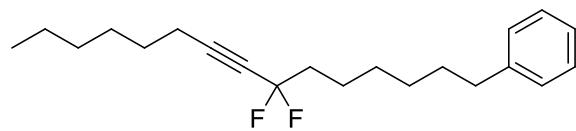
1-phenylpentadec-8-yn-7-one (10).

¹H-NMR



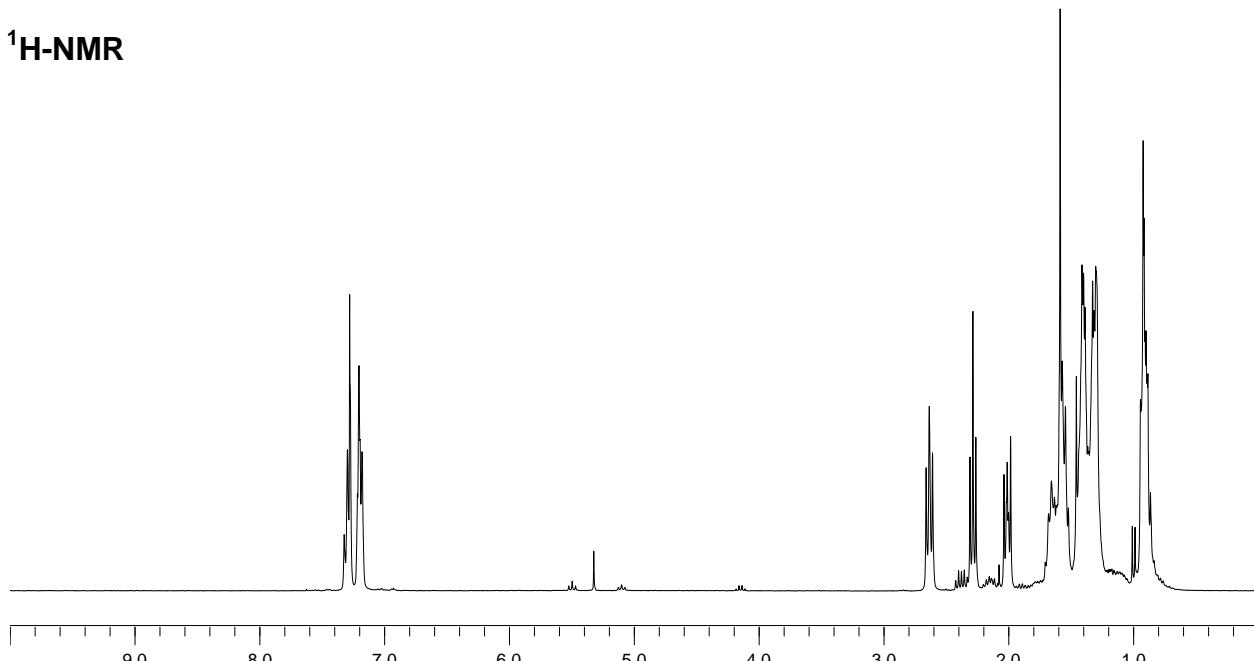
¹³C-NMR



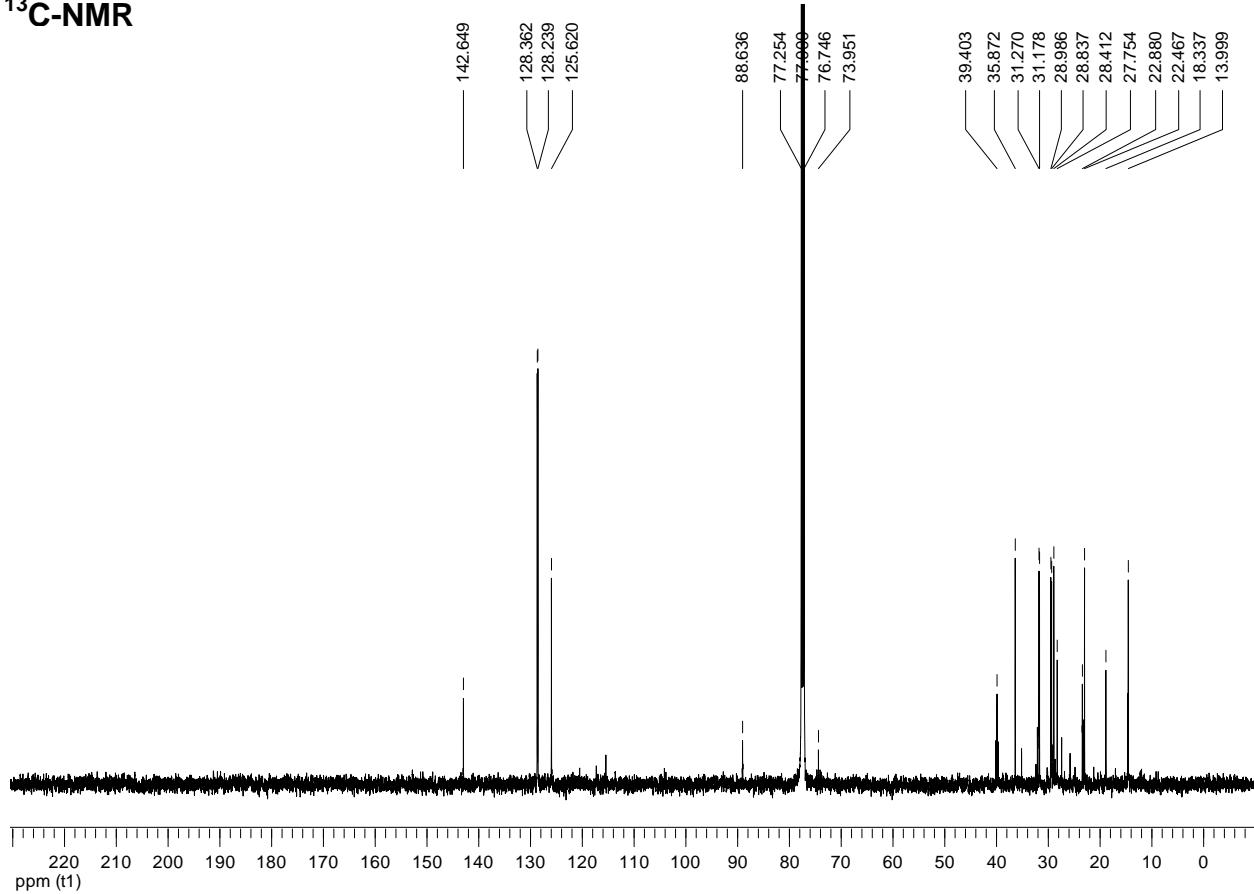


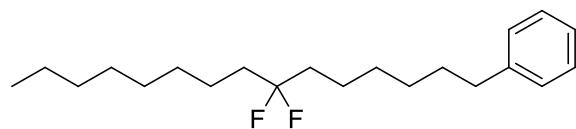
(7,7-Difluoropentadec-8-yn-1-yl)benzene (11).

¹H-NMR



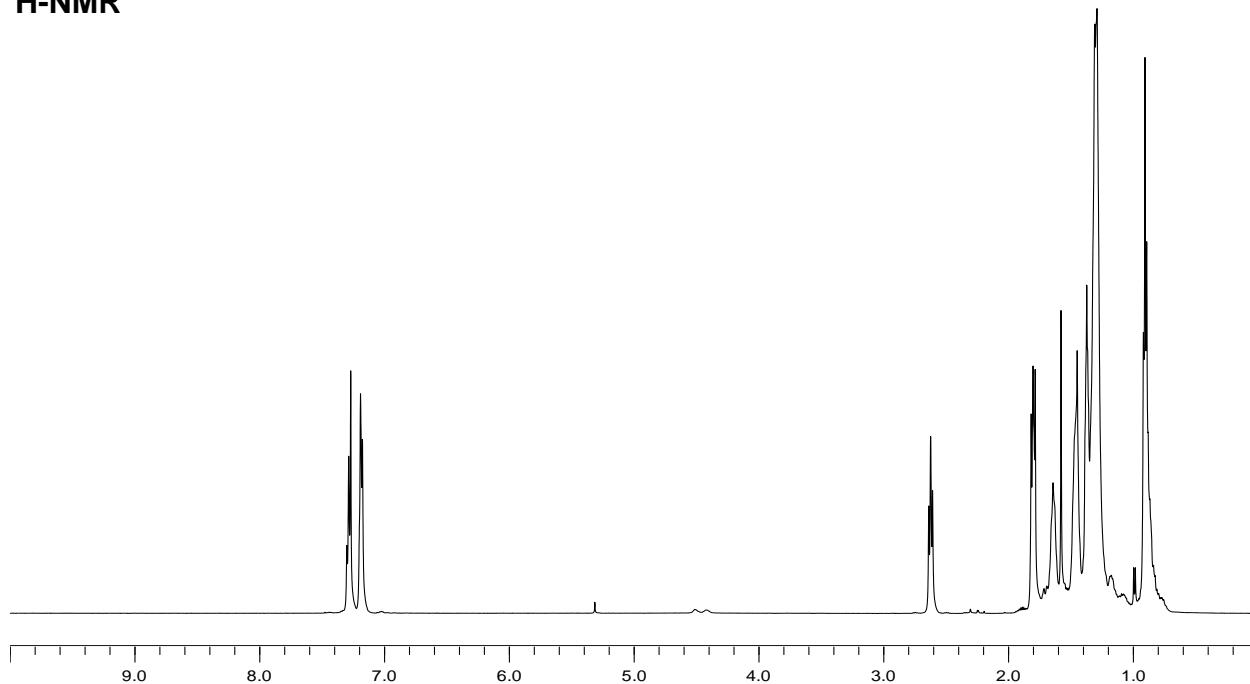
¹³C-NMR



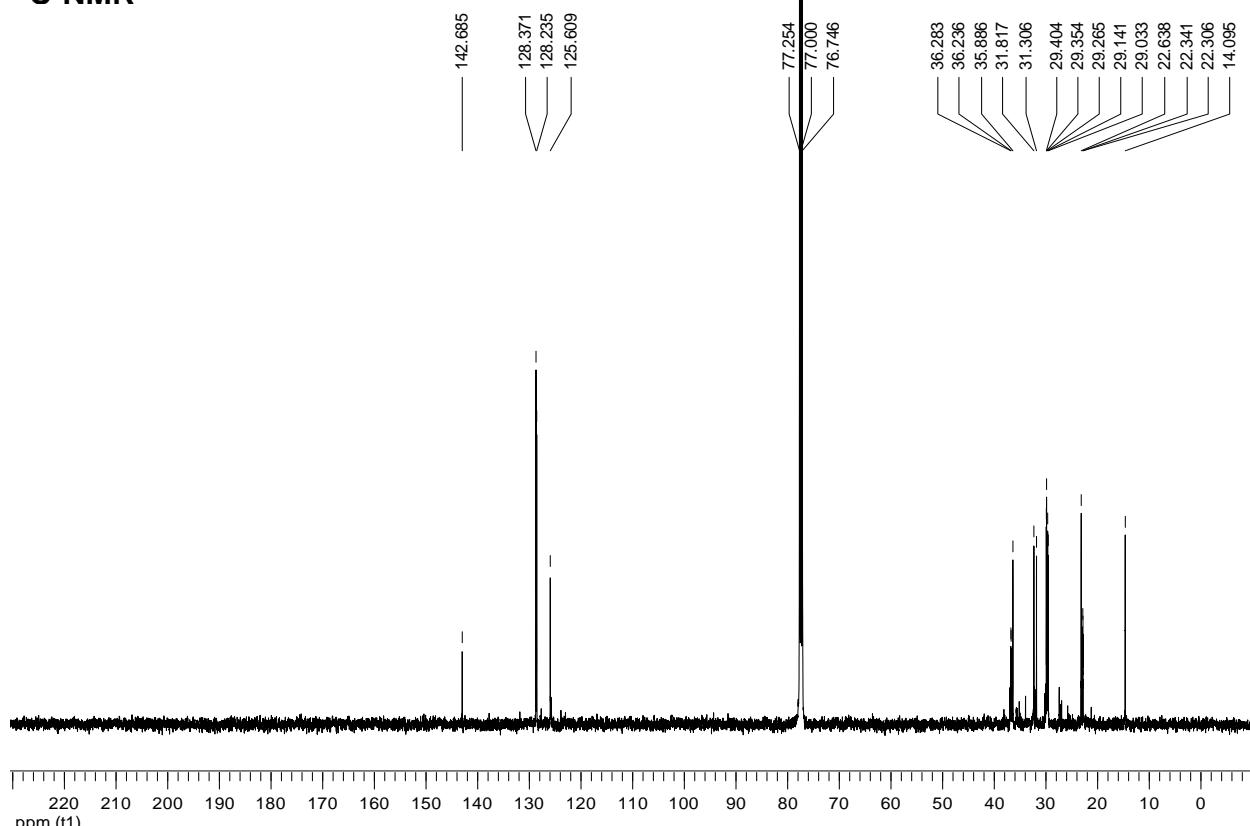


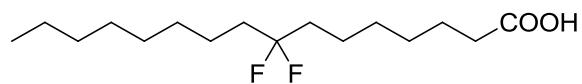
(7,7-Difluoropentadecyl)benzene (12).

¹H-NMR



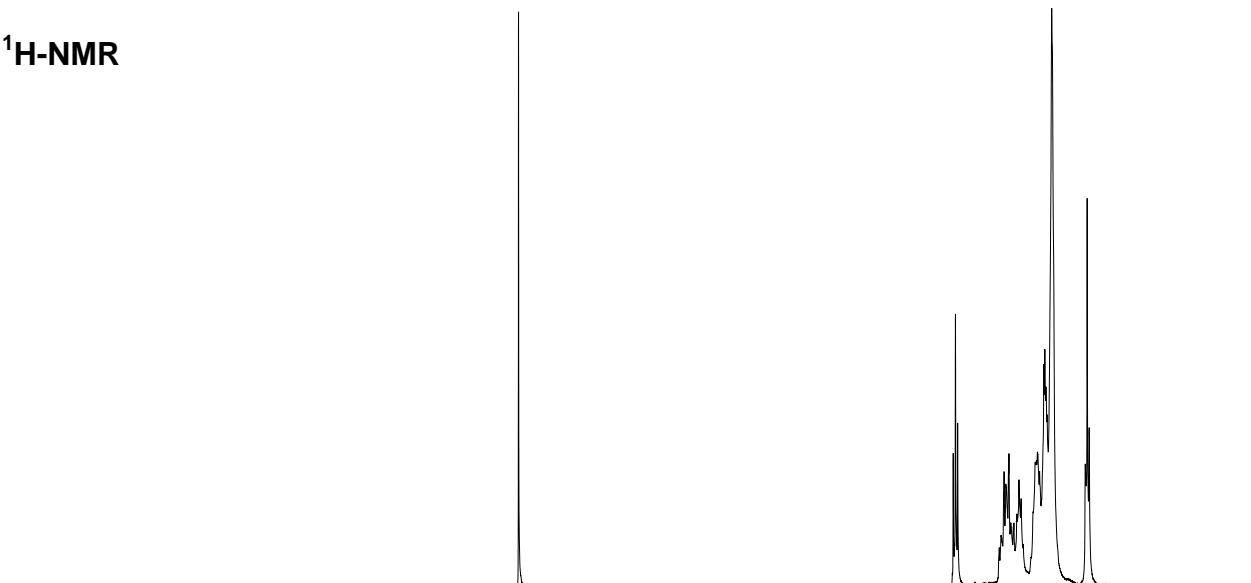
¹³C-NMR



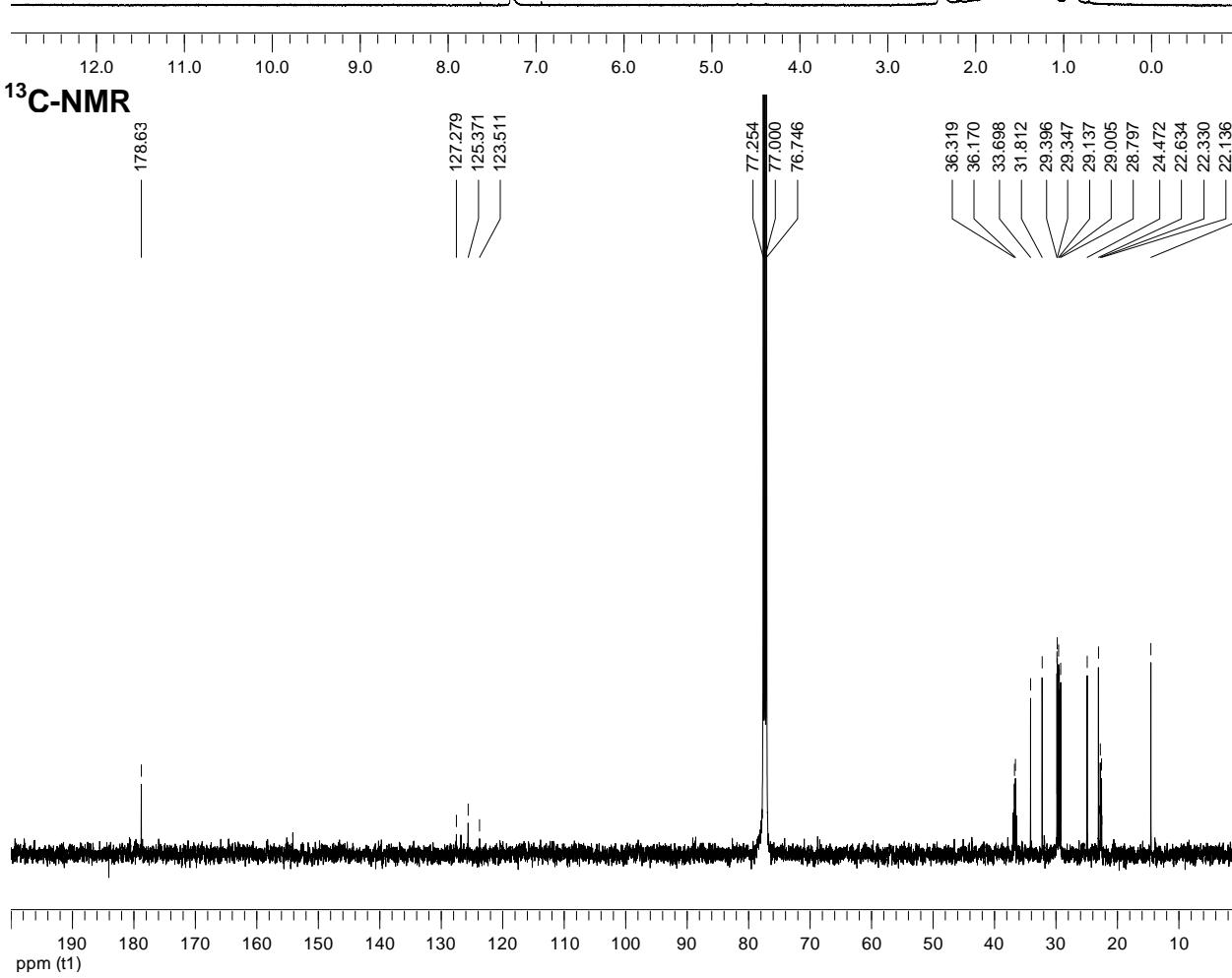


8,8-Difluorohexadecanoic acid (6a).

¹H-NMR

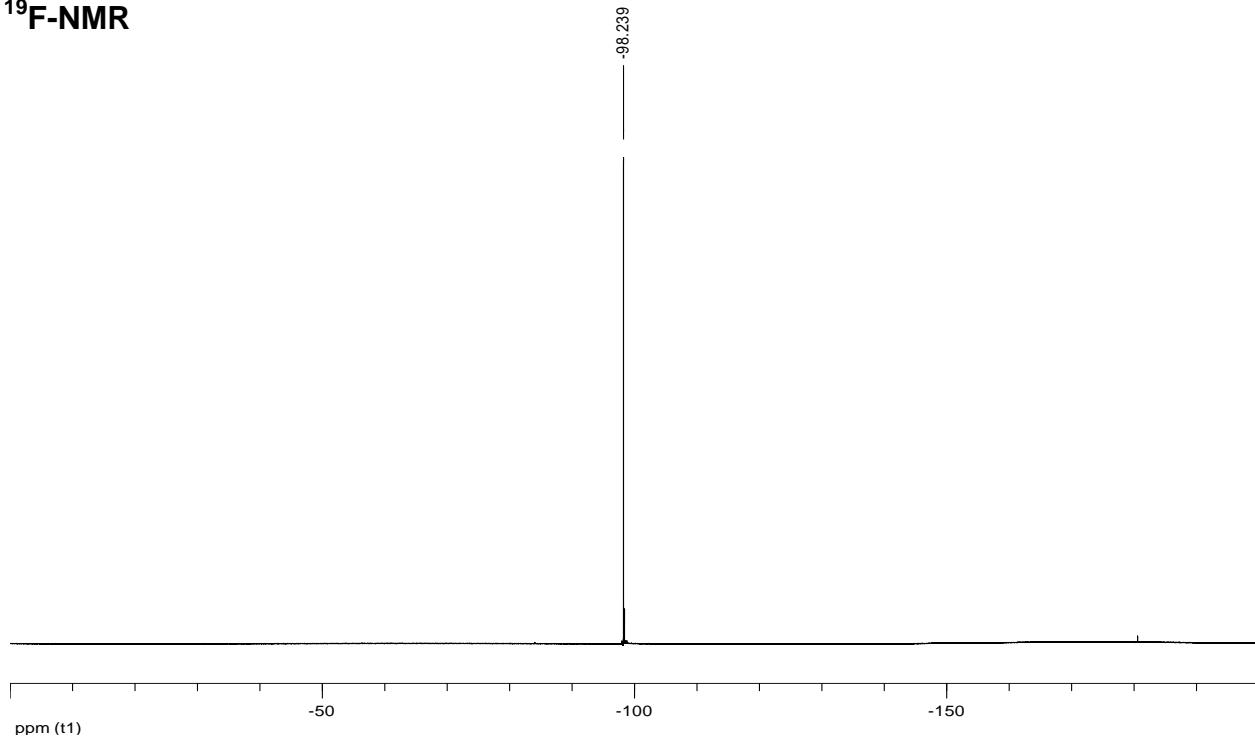


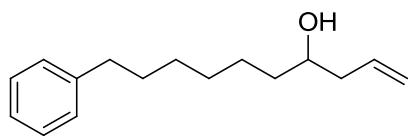
¹³C-NMR



ppm (t1)

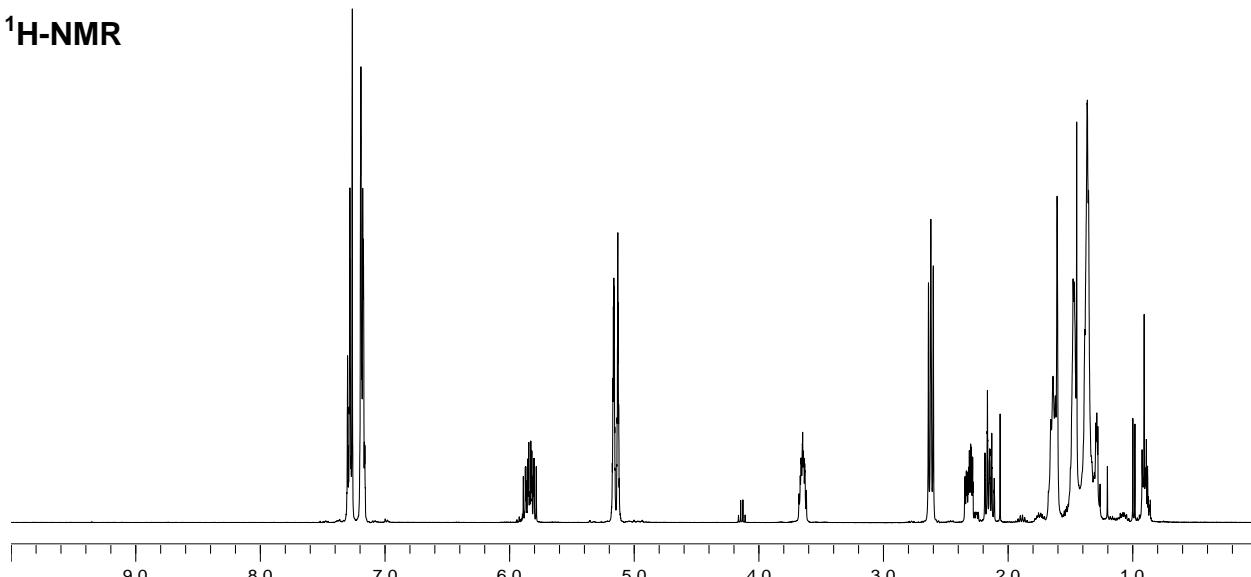
¹⁹F-NMR



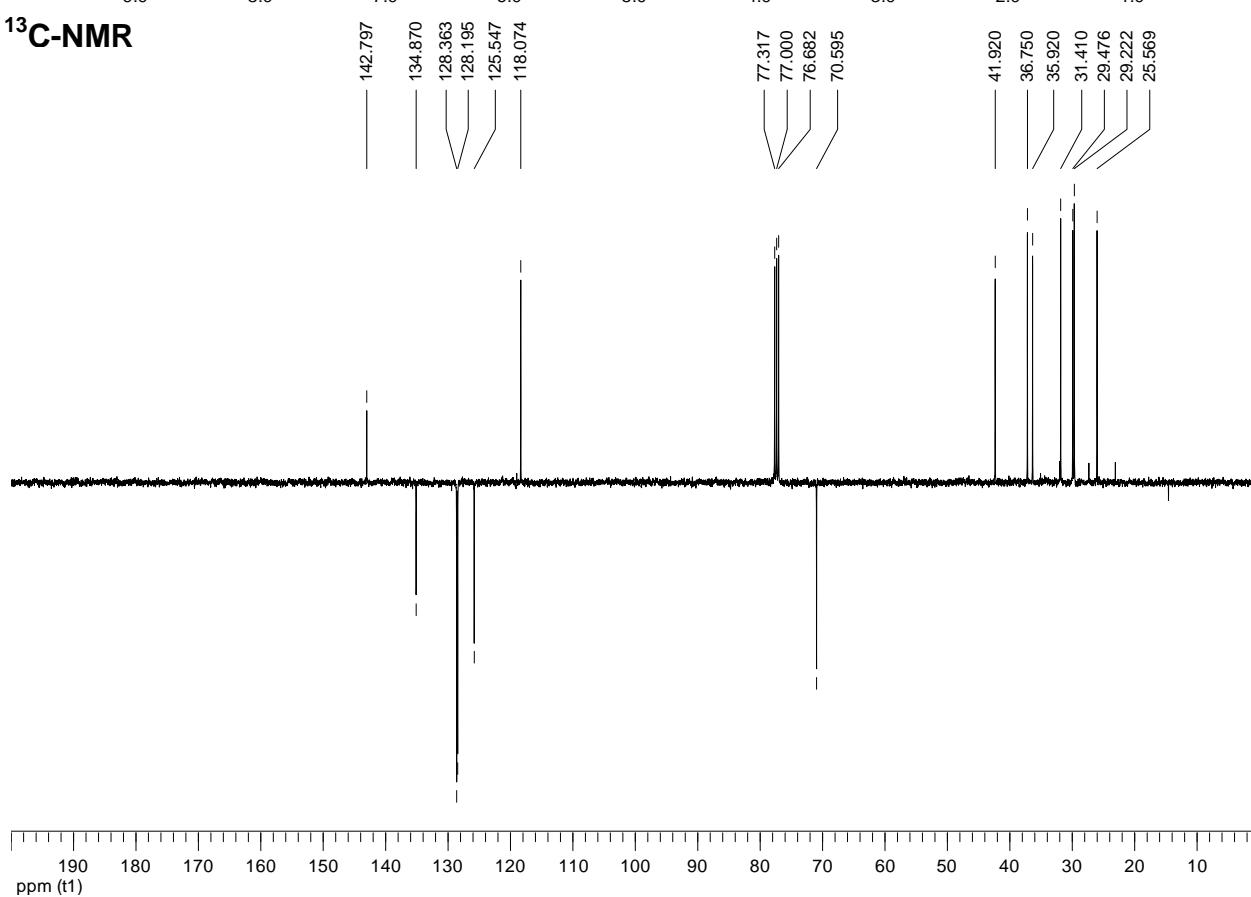


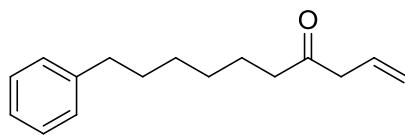
10-Phenyldec-1-en-4-ol (13).

¹H-NMR



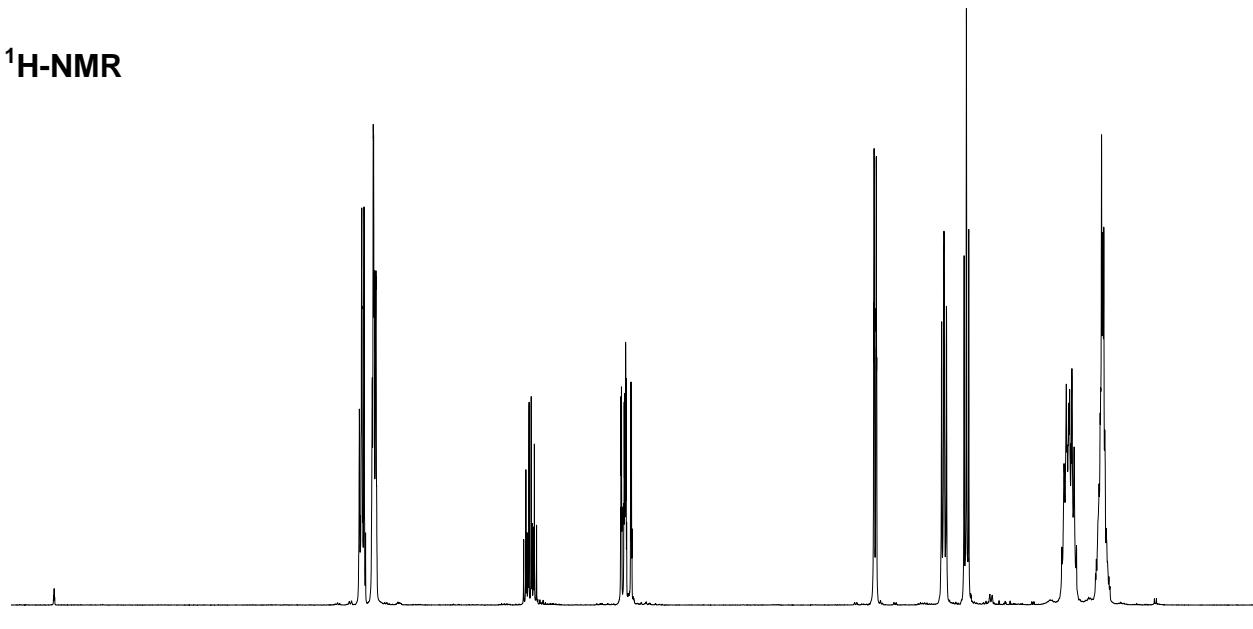
¹³C-NMR



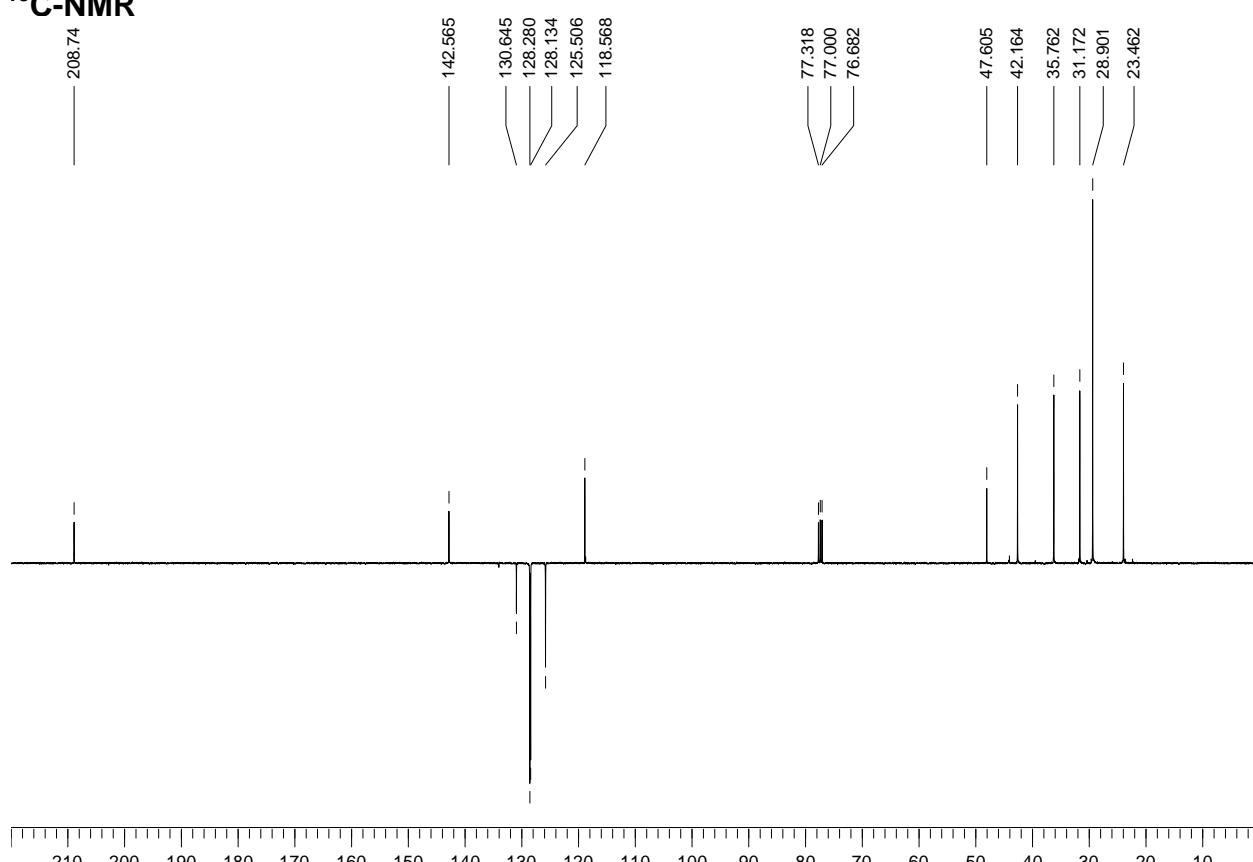


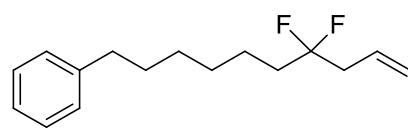
10-phenyldec-1-en-4-one (14).

¹H-NMR



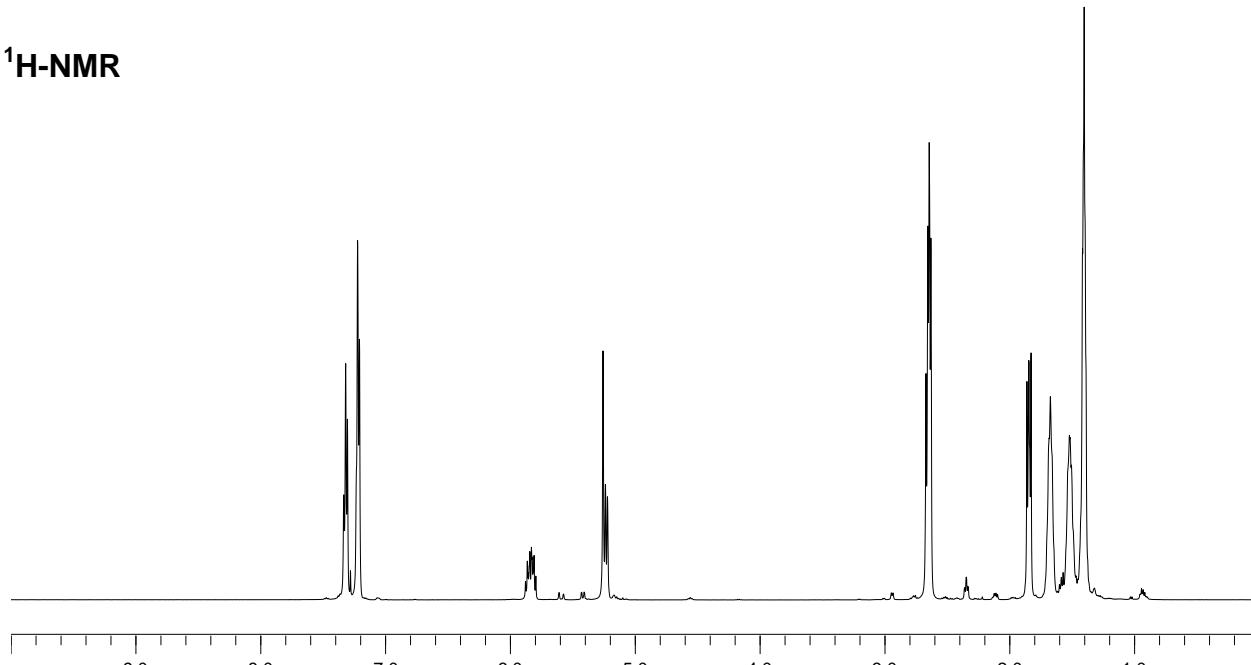
¹³C-NMR



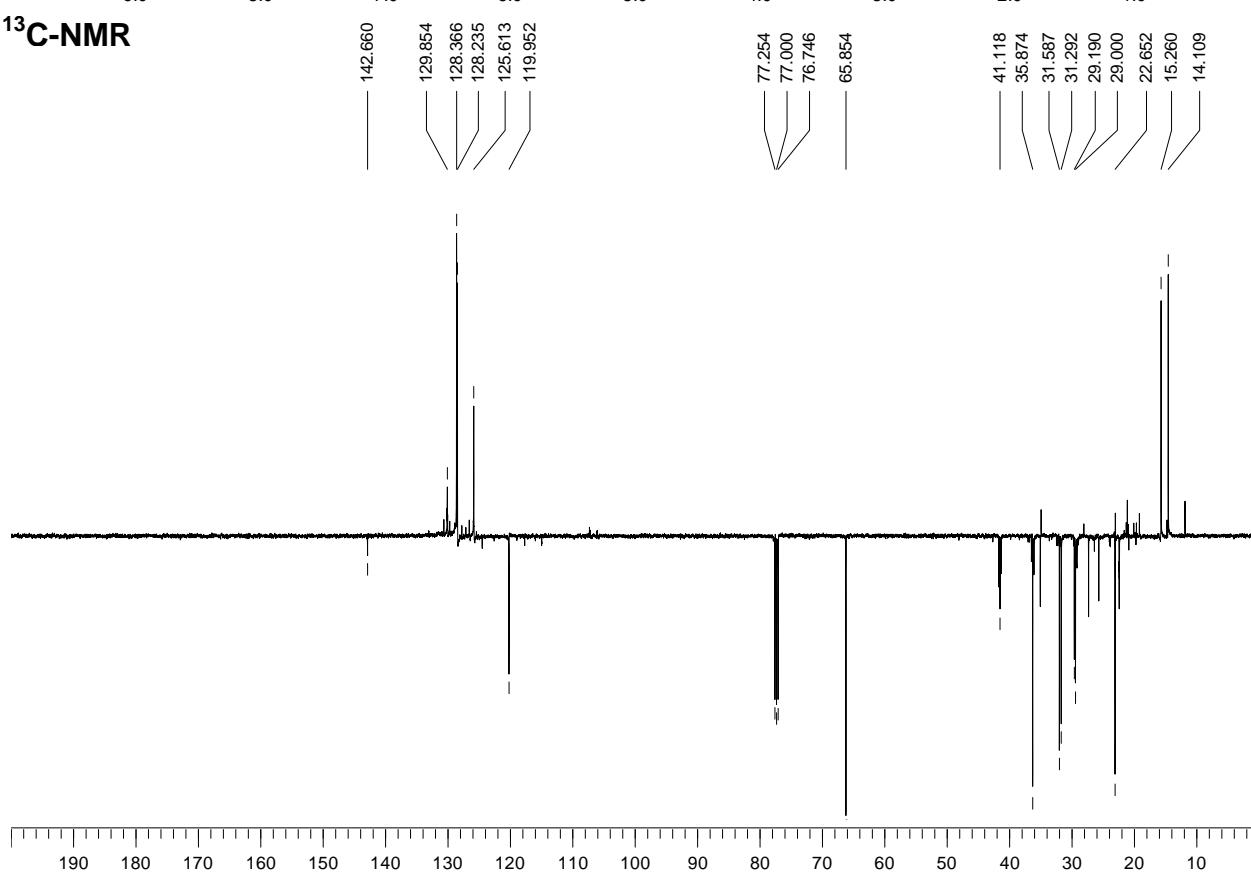


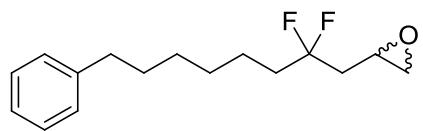
(7,7-difluorodec-9-en-1-yl)benzene (15).

¹H-NMR



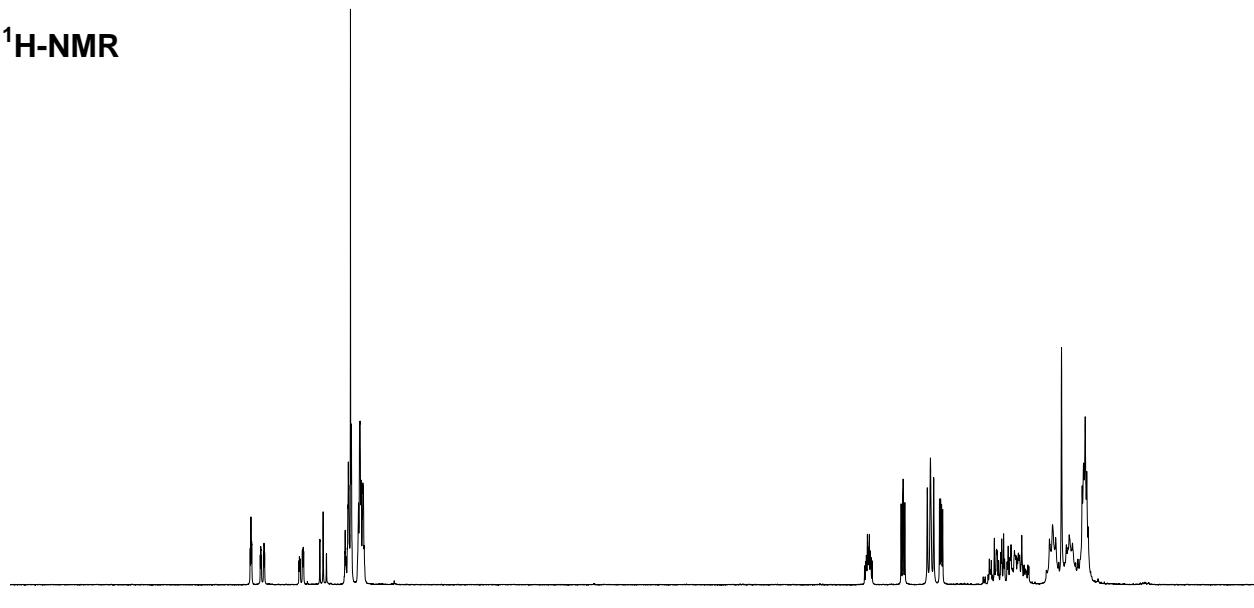
¹³C-NMR



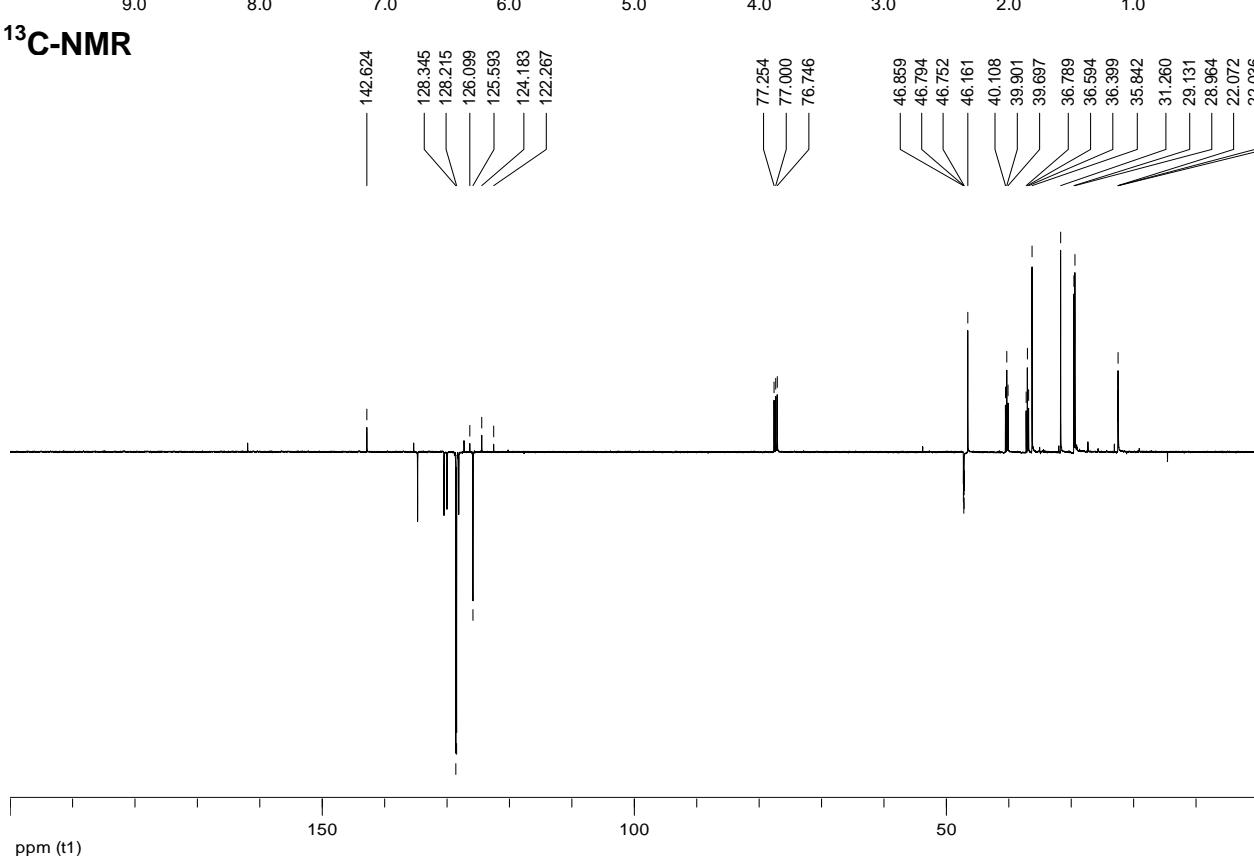


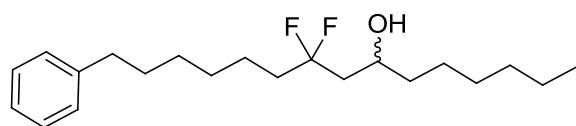
2-(2,2-difluoro-8-phenyloctyl)oxirane (16).

¹H-NMR



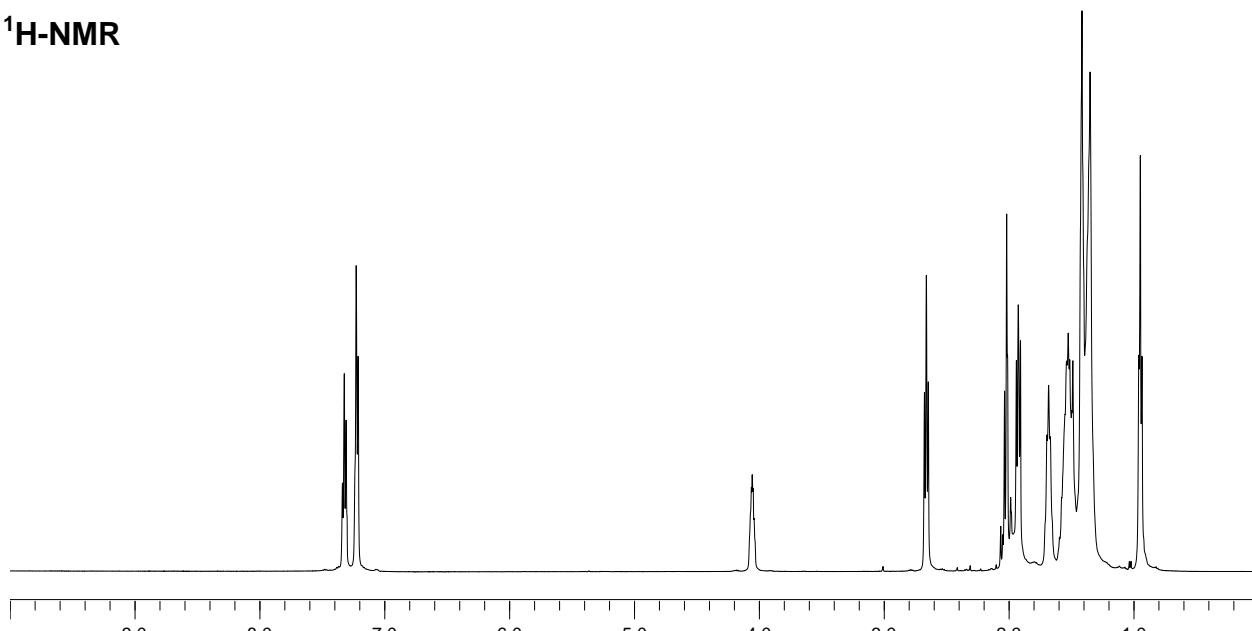
¹³C-NMR



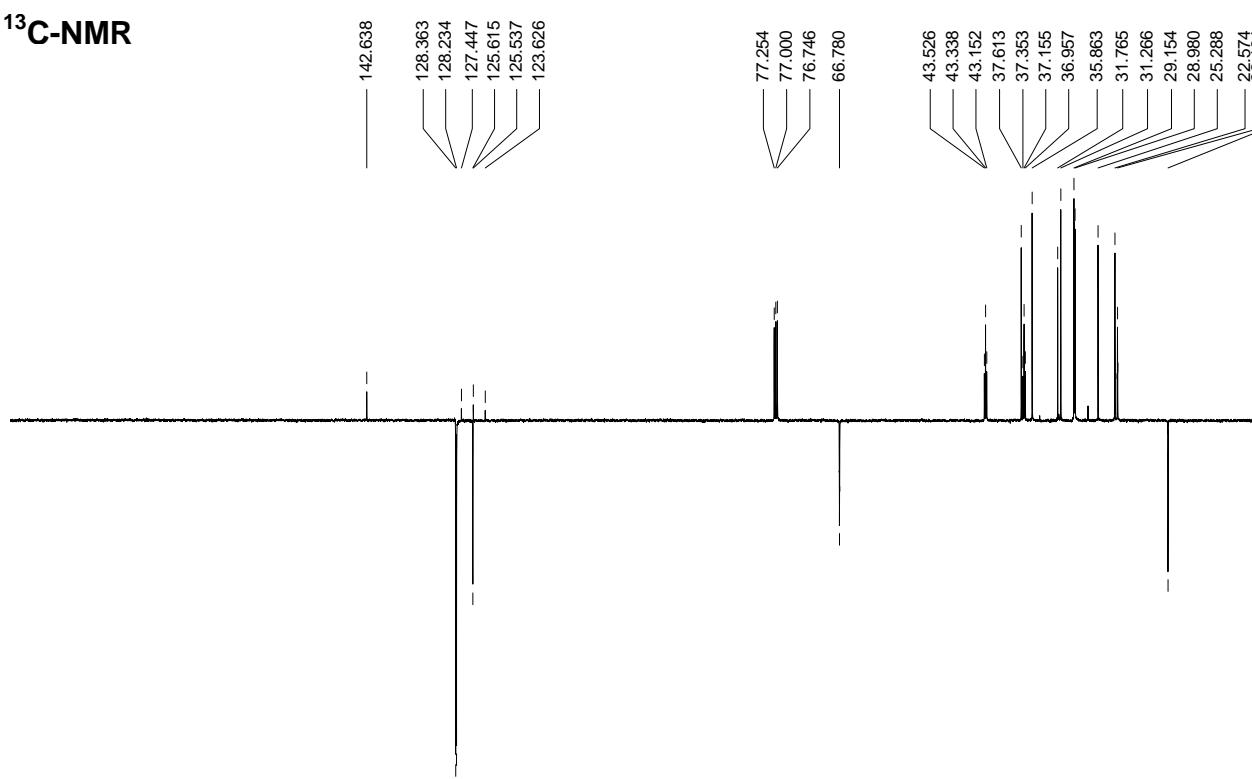


9,9-difluoro-15-phenylpentadecan-7-ol (17).

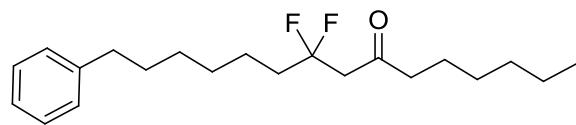
¹H-NMR



¹³C-NMR

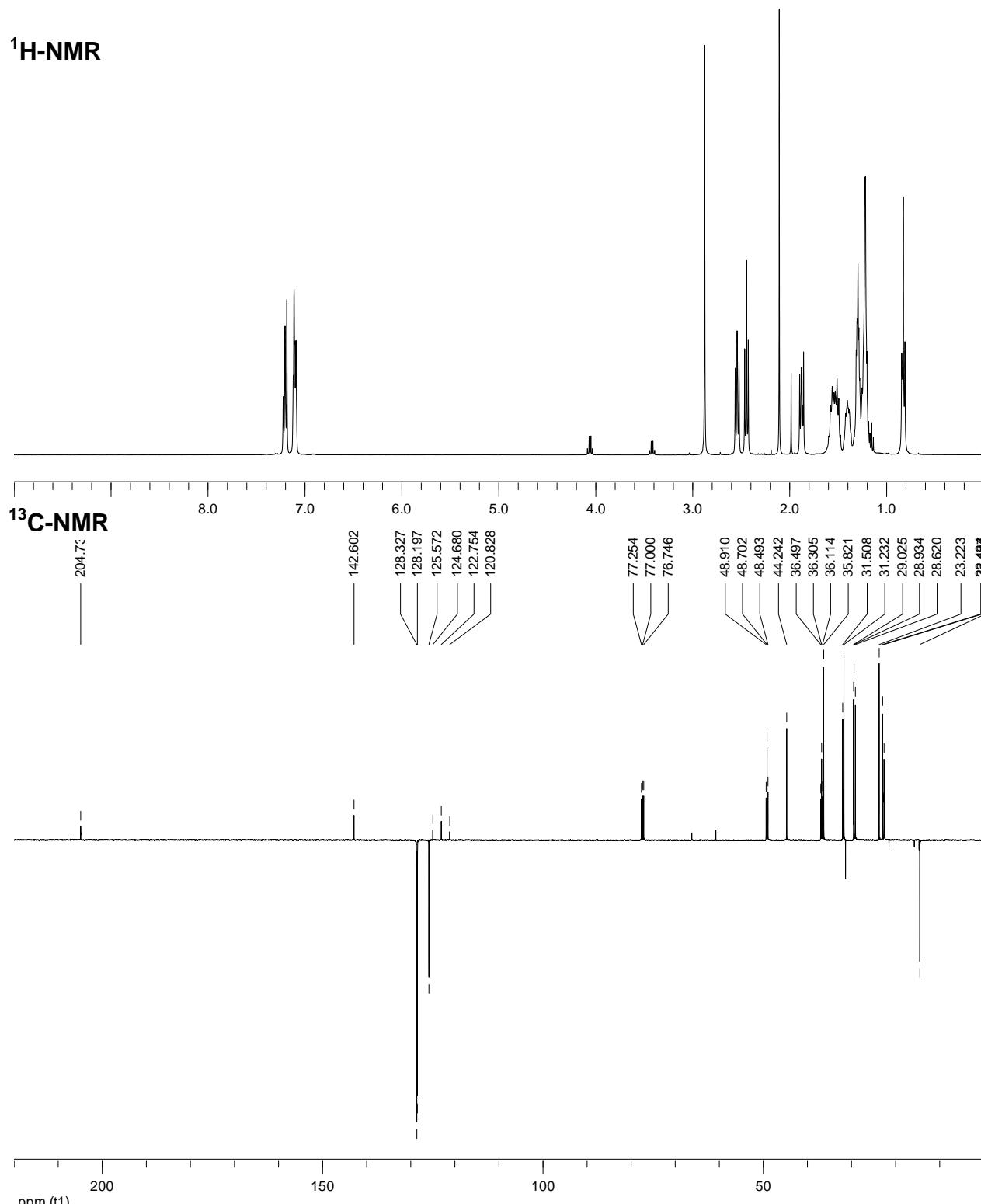


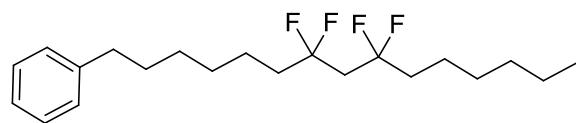
ppm (t1)



9,9-difluoro-15-phenylpentadecan-7-one (18).

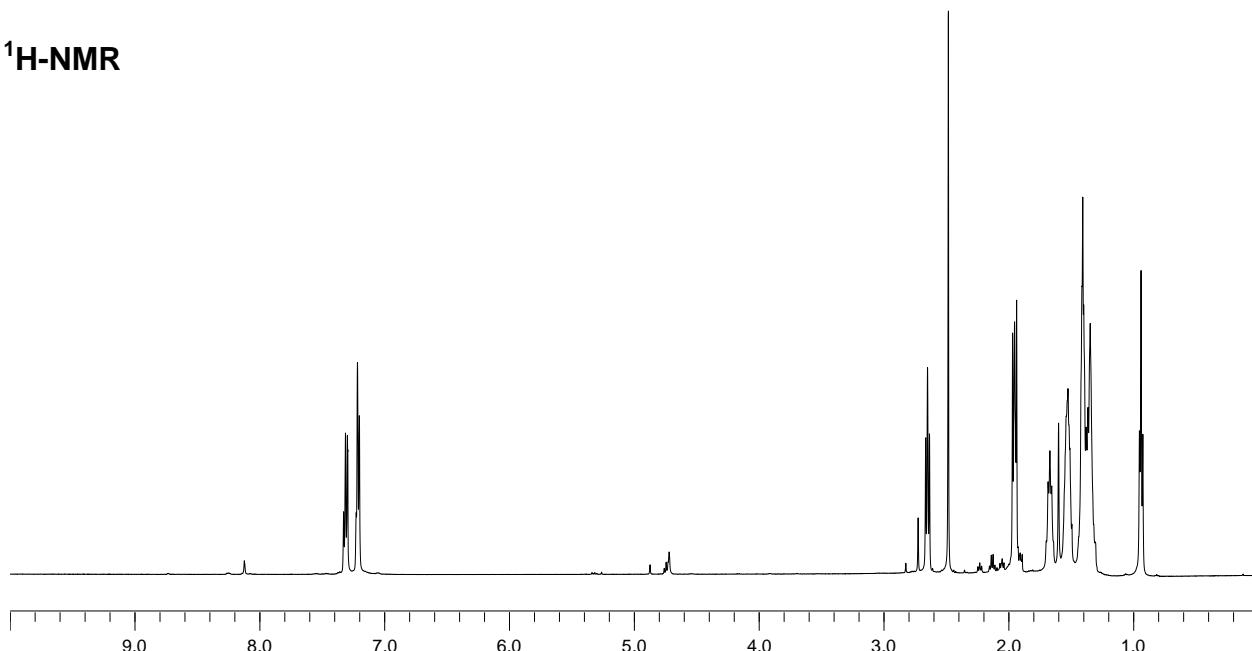
¹H-NMR



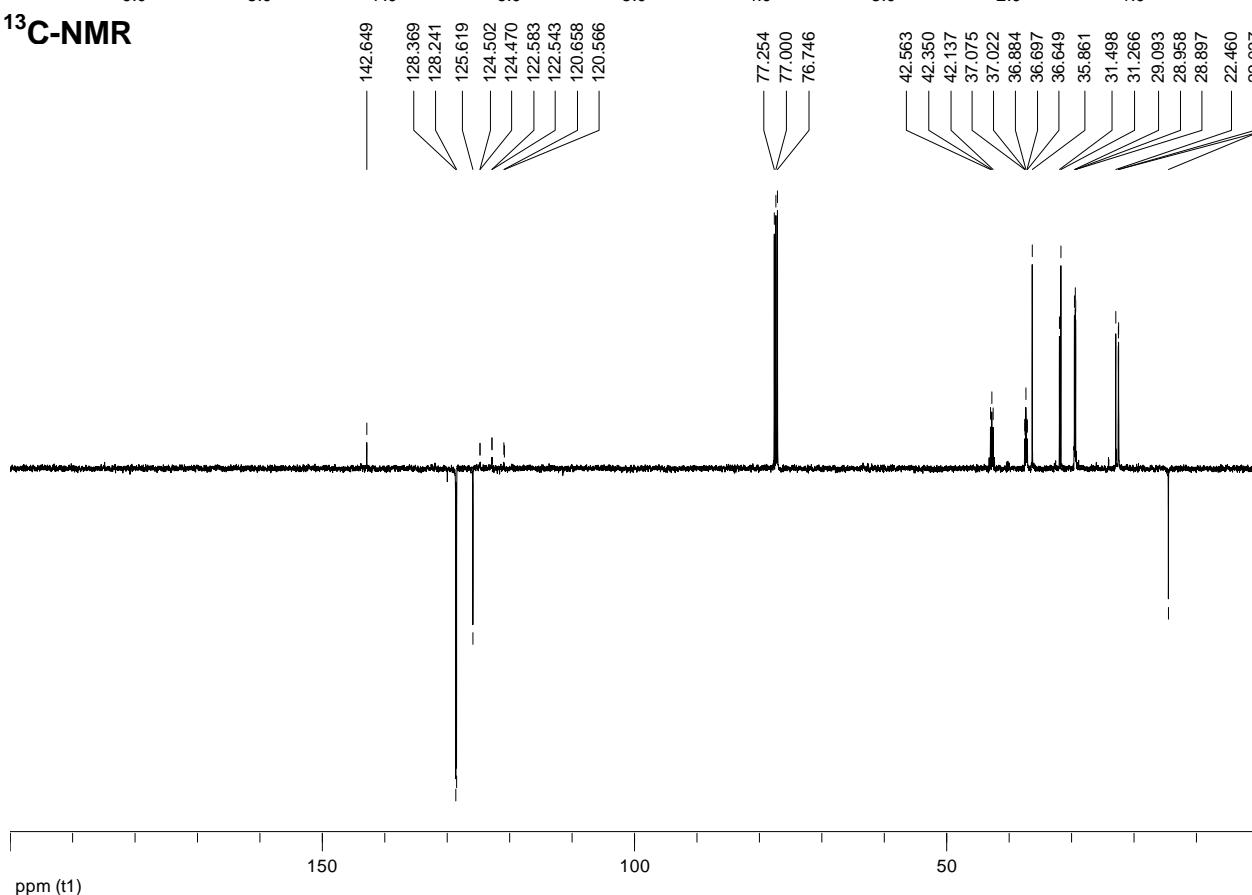


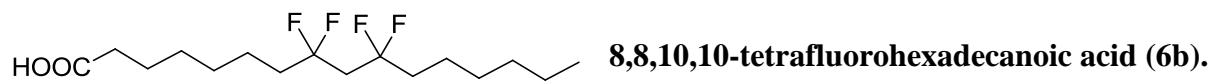
(7,7,9,9-tetrafluoropentadecyl)benzene (19).

¹H-NMR

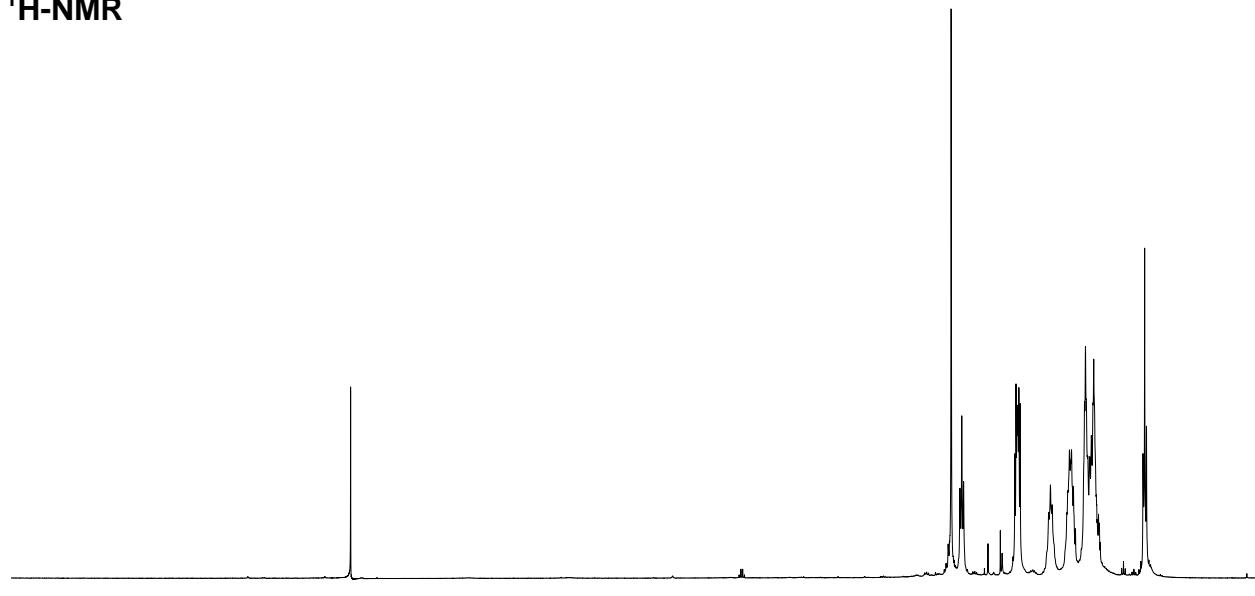


¹³C-NMR

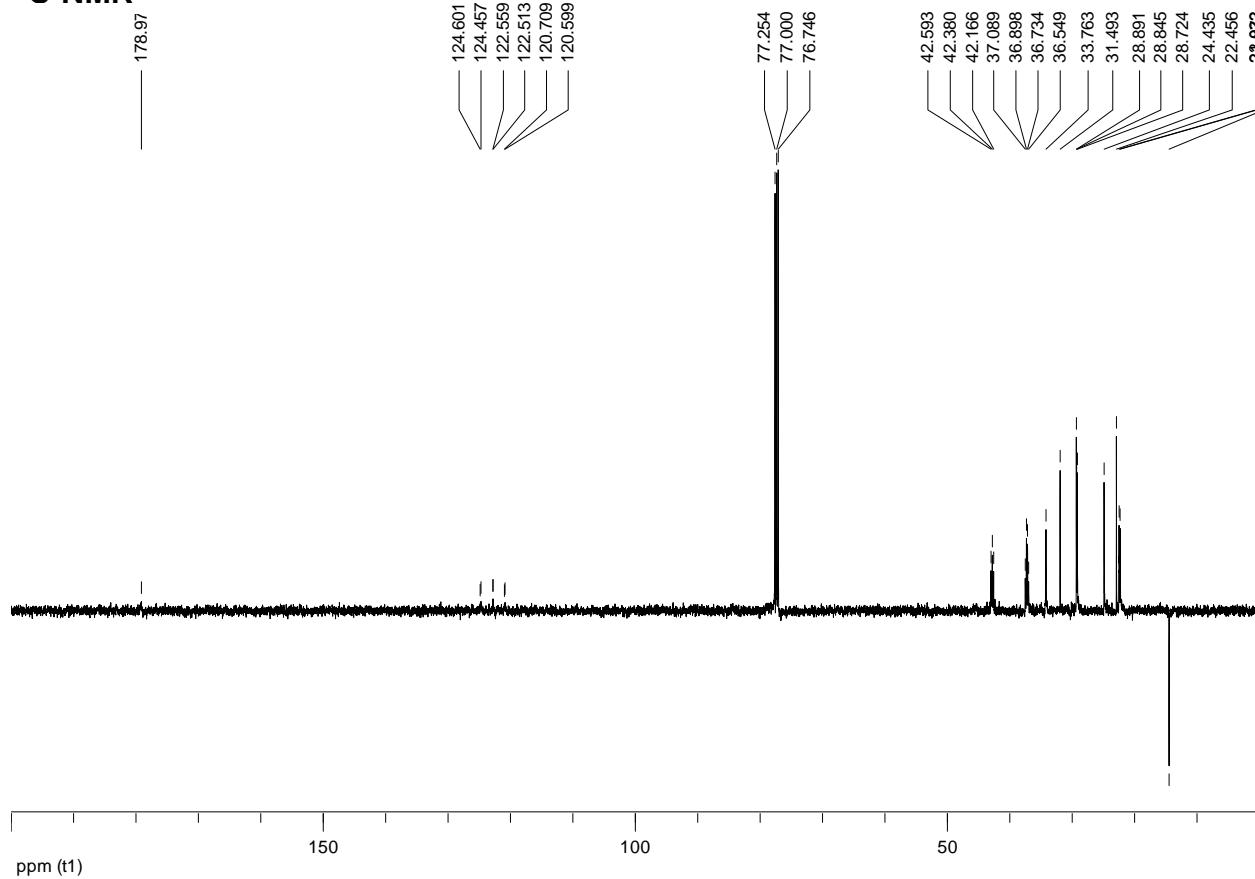




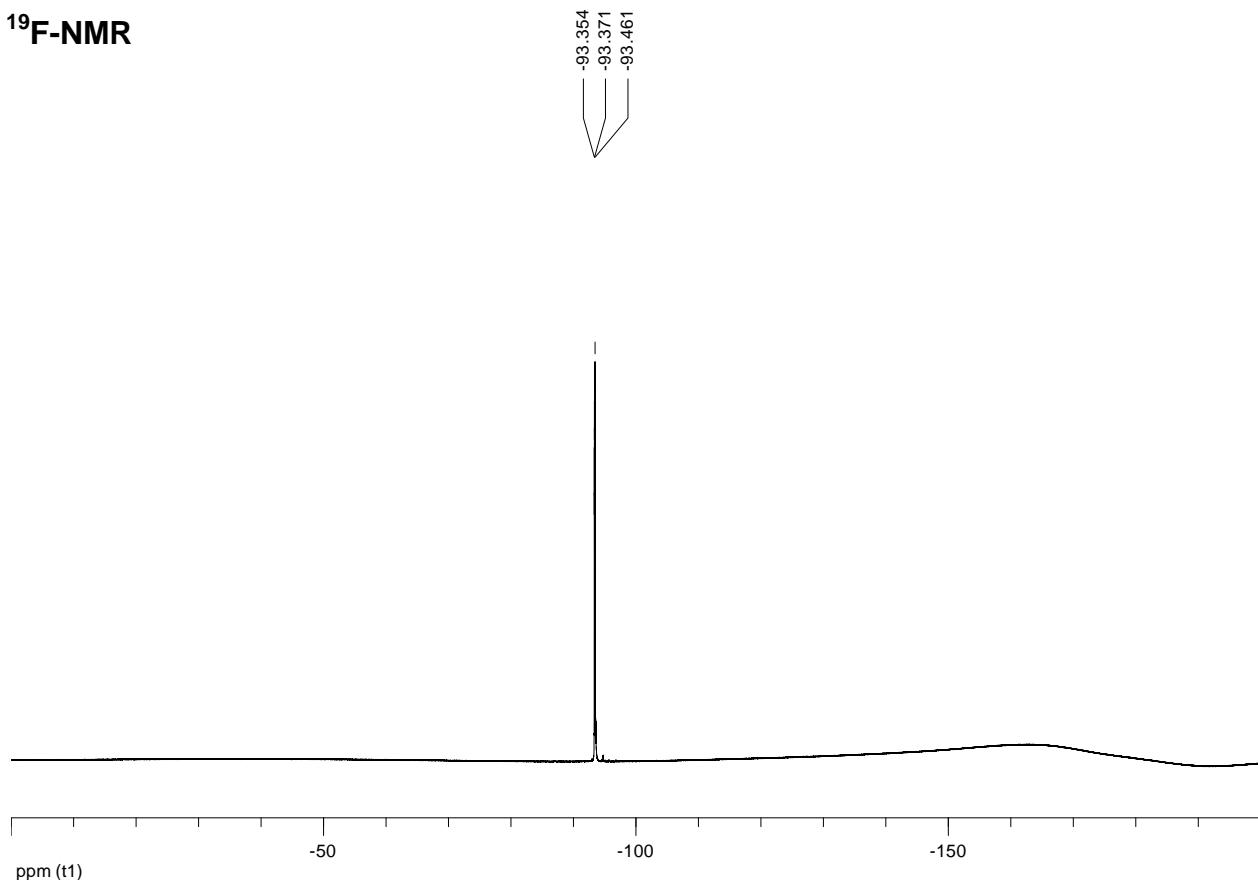
¹H-NMR

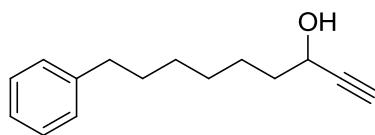


¹³C-NMR



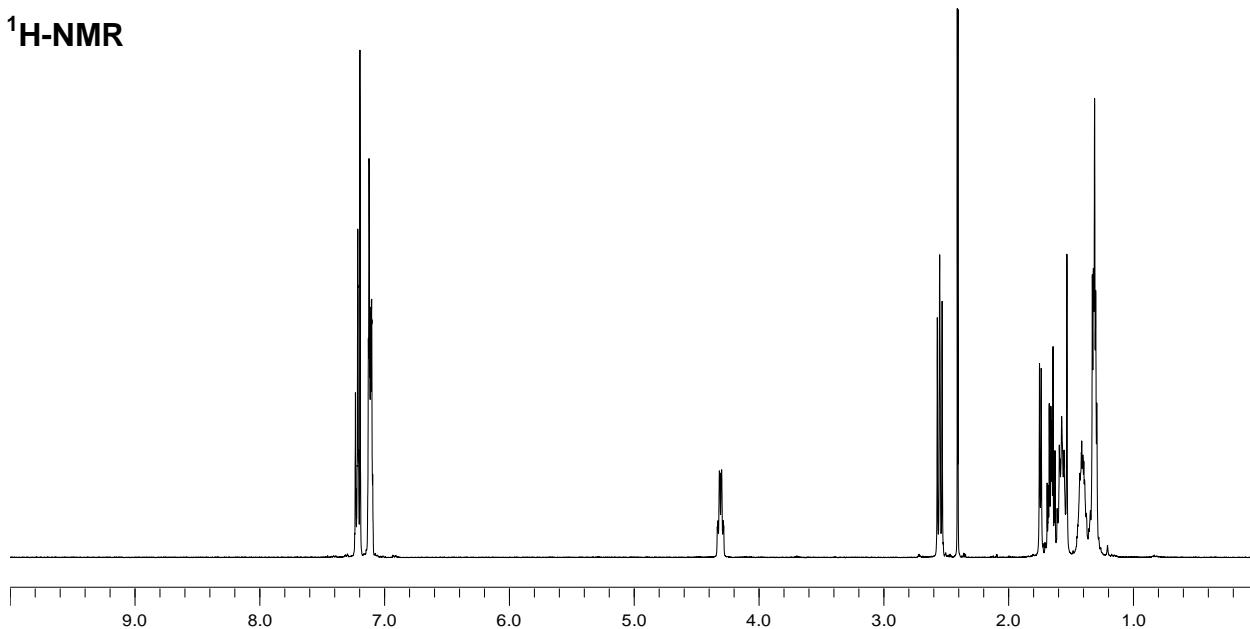
¹⁹F-NMR



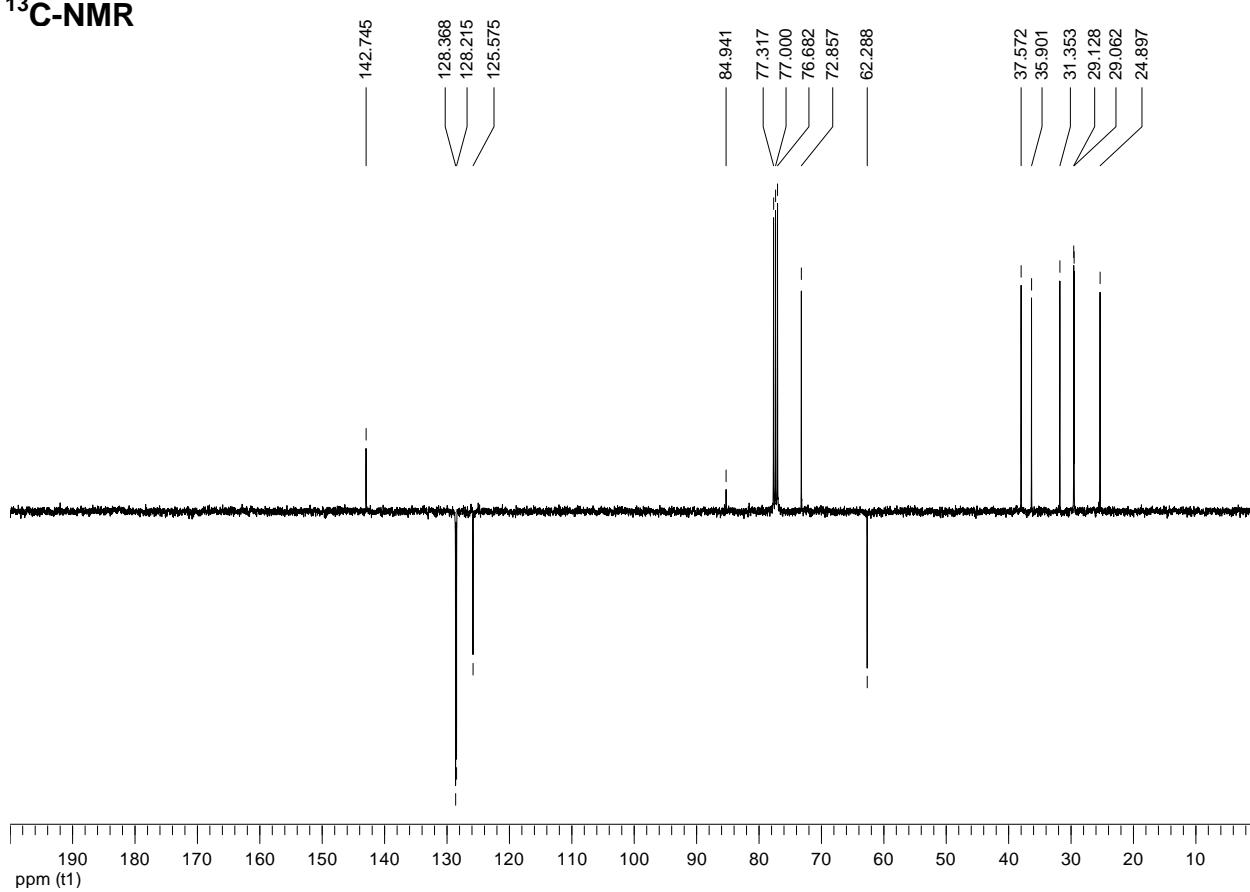


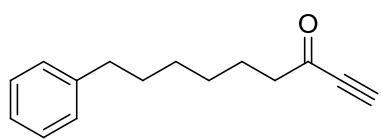
9-phenylnon-1-yn-3-ol (20).

¹H-NMR



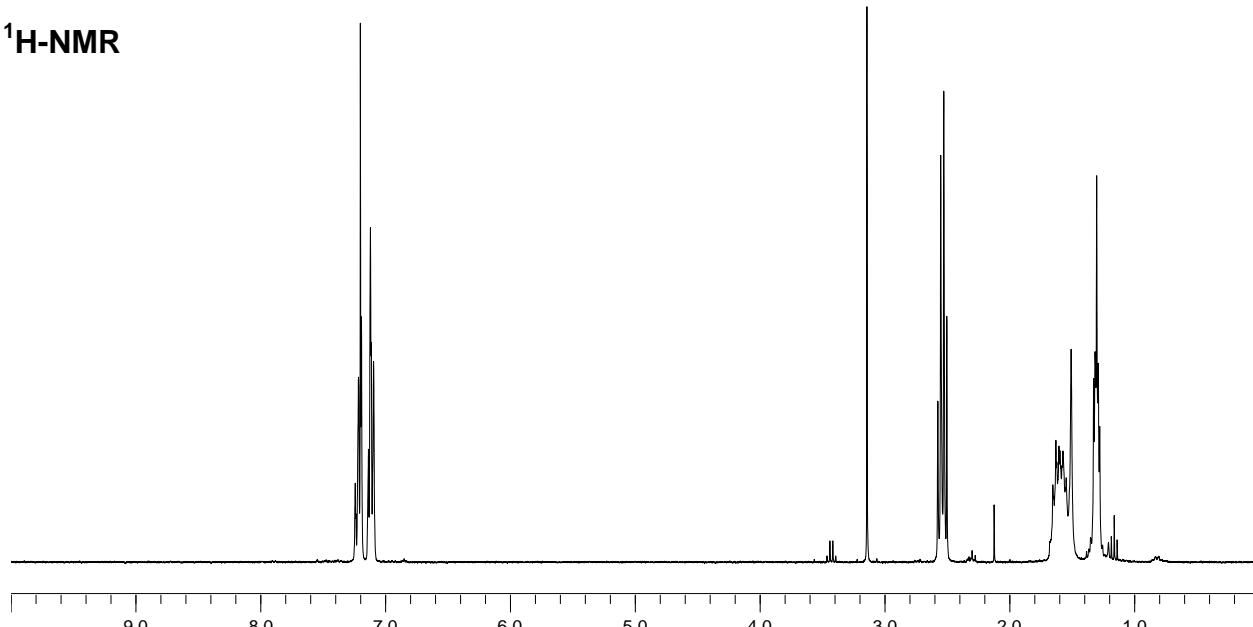
¹³C-NMR



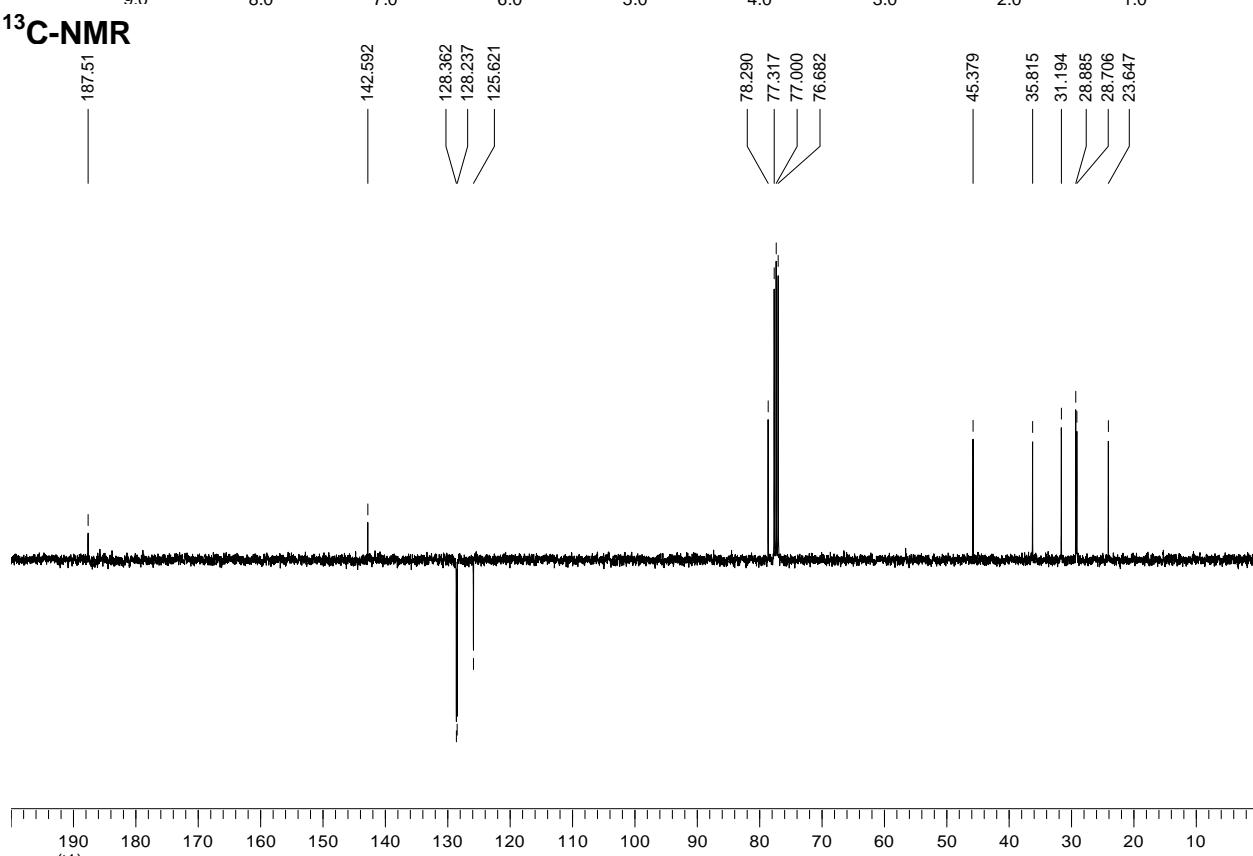


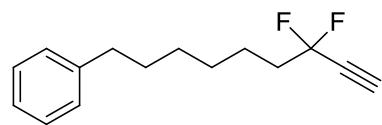
9-phenylnon-1-yn-3-one (21).

¹H-NMR



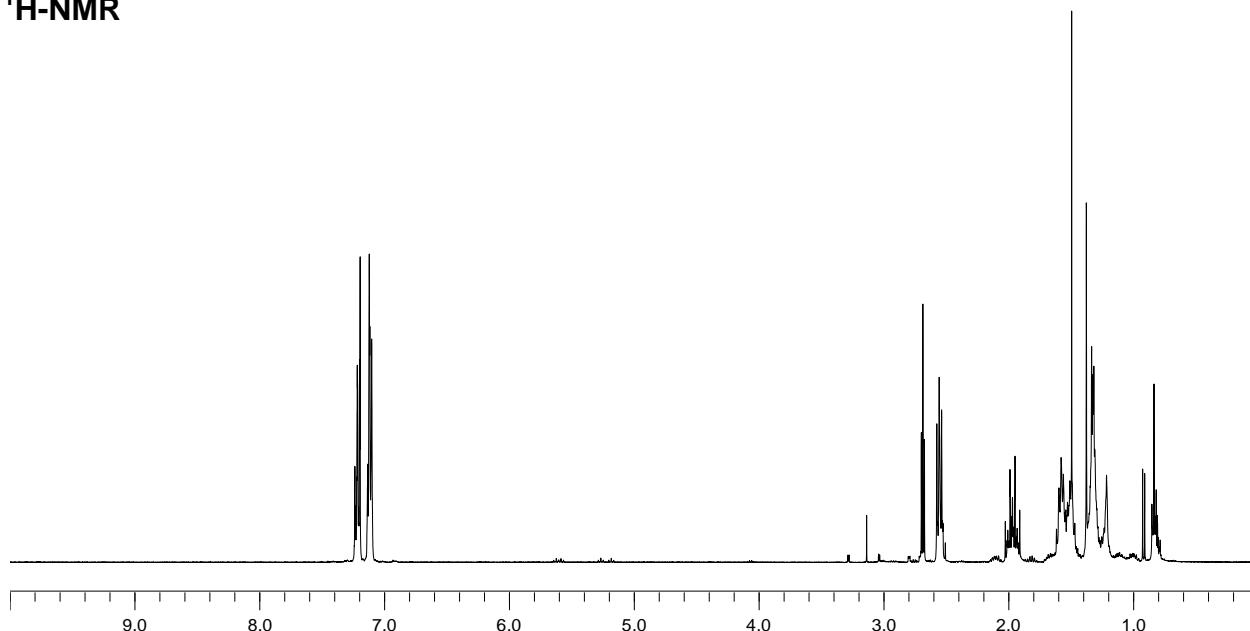
¹³C-NMR



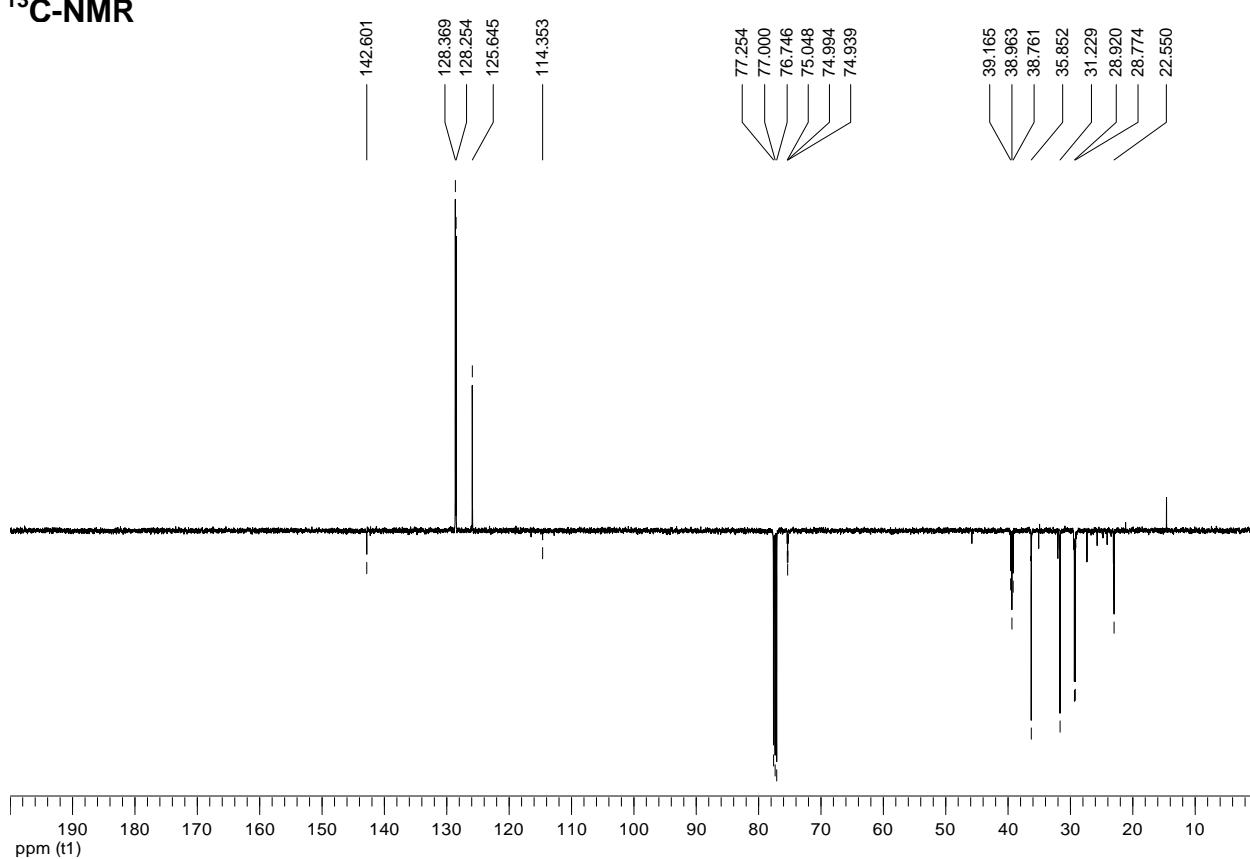


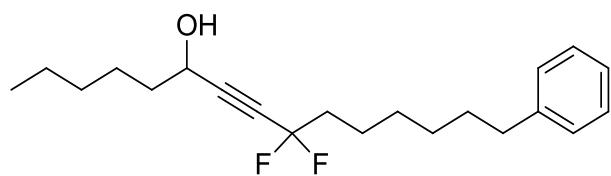
(7,7-difluoronon-8-yn-1-yl)benzene (22).

¹H-NMR



¹³C-NMR

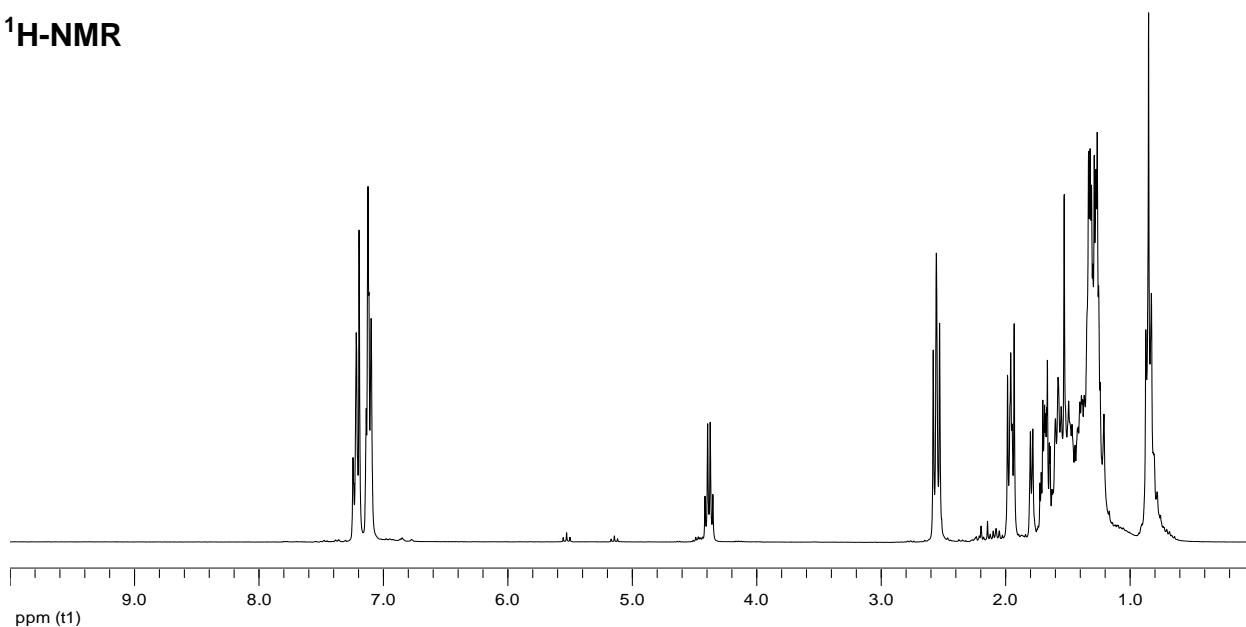




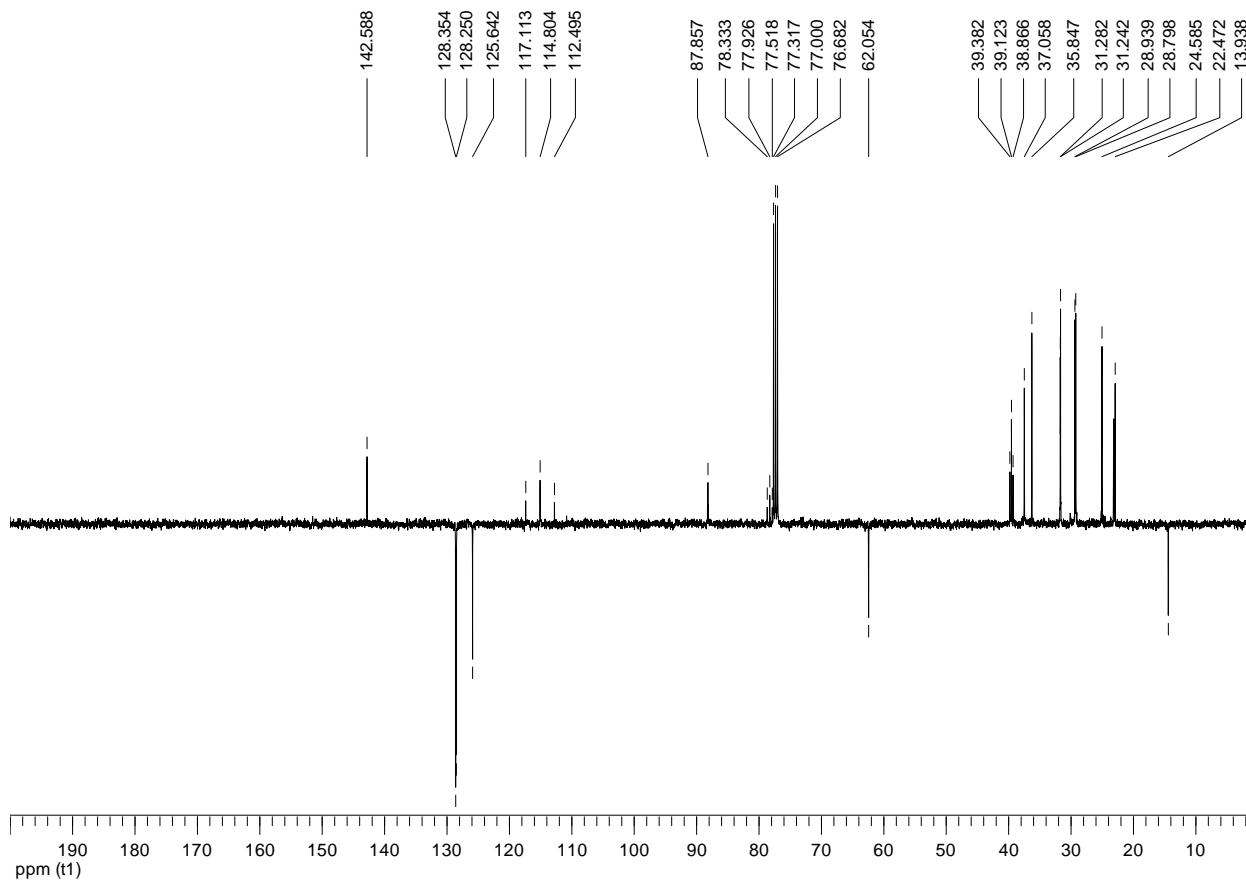
9,9-difluoro-15-phenylpentadec-7-yn-6-ol

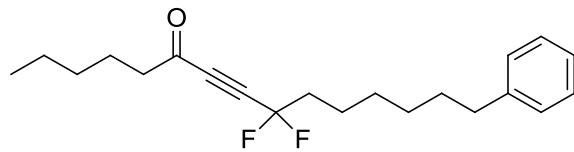
(23).

¹H-NMR



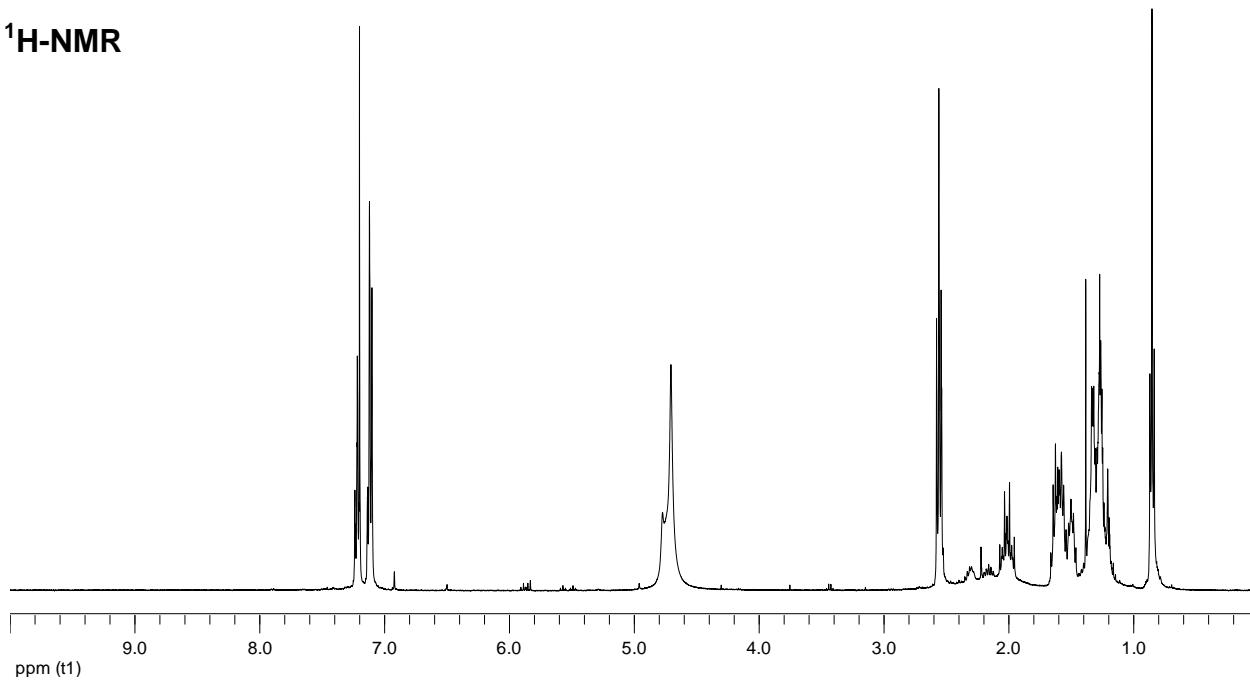
¹³C-NMR



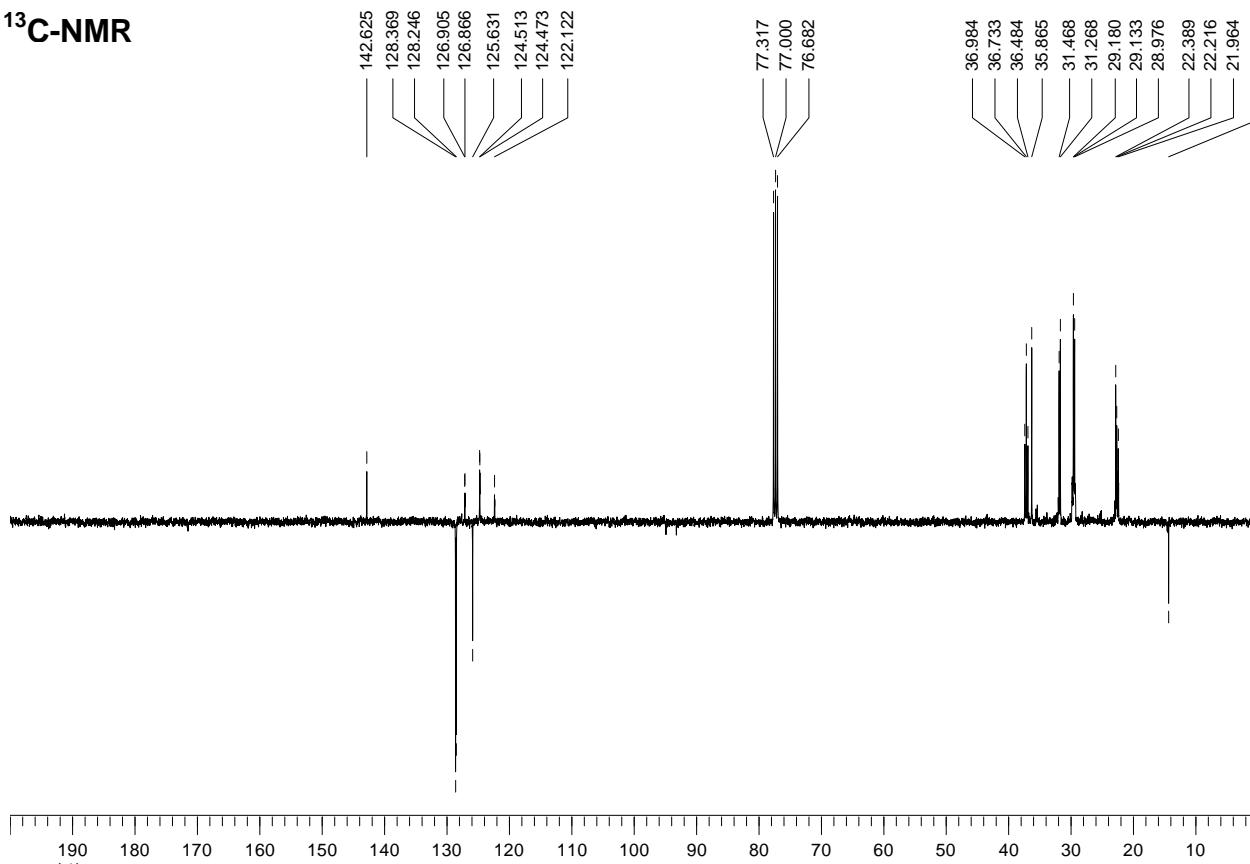


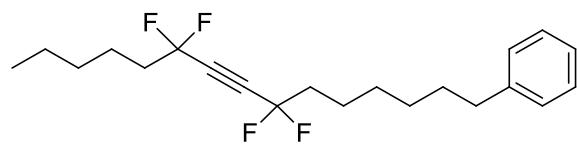
**9,9-difluoro-15-phenylpentadec-7-yn-6-one
(24).**

¹H-NMR



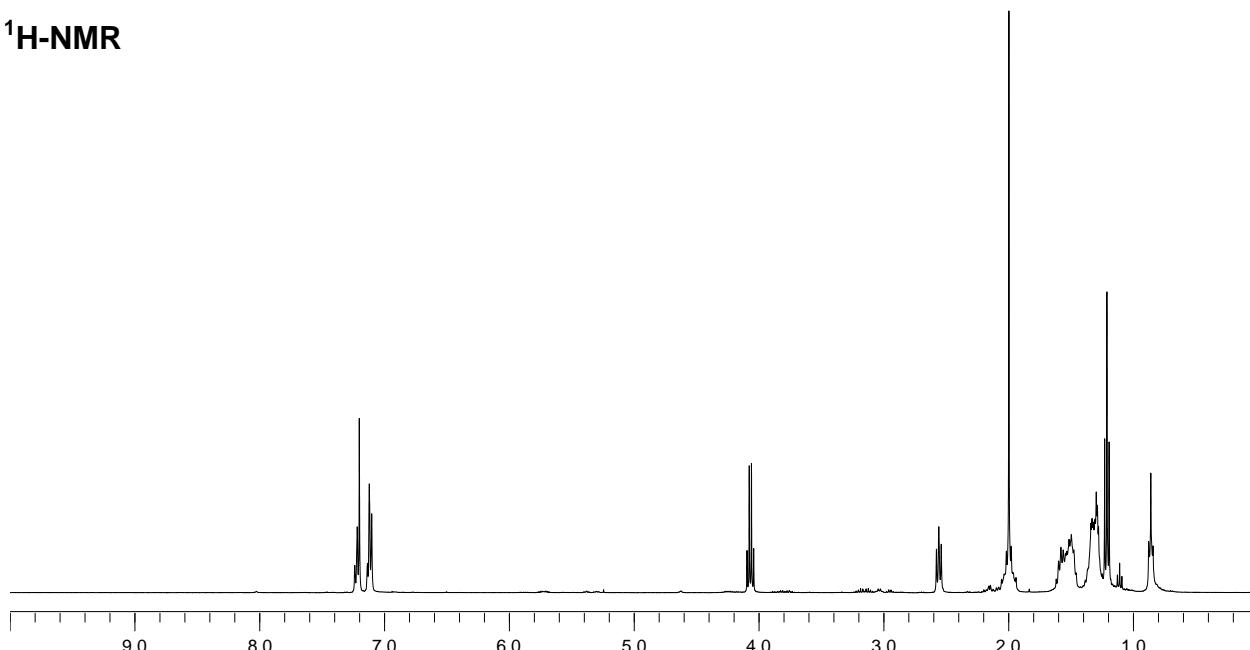
¹³C-NMR



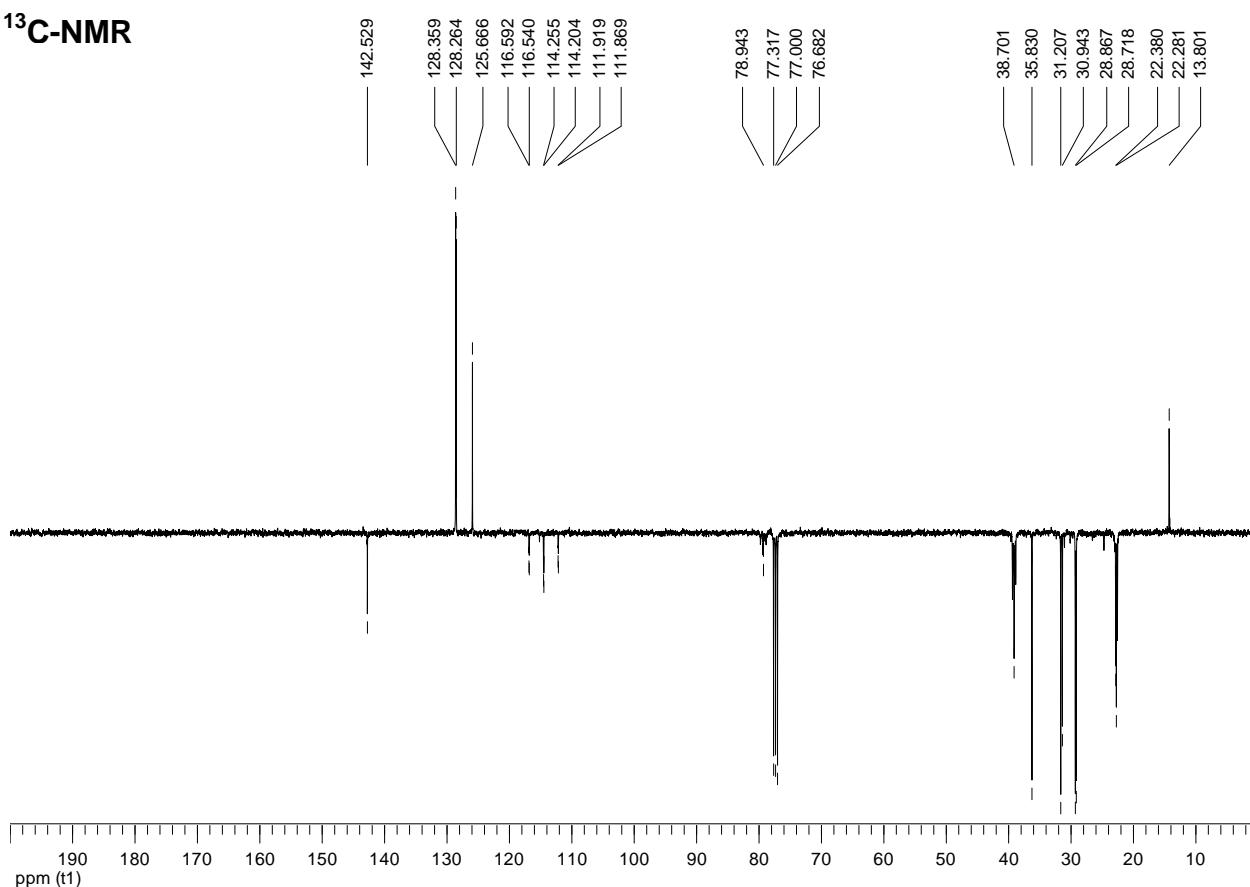


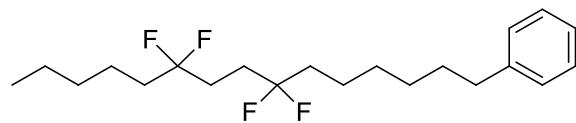
(7,7,10,10-tetrafluoropentadec-8-yn-1-yl)benzene (25).

¹H-NMR



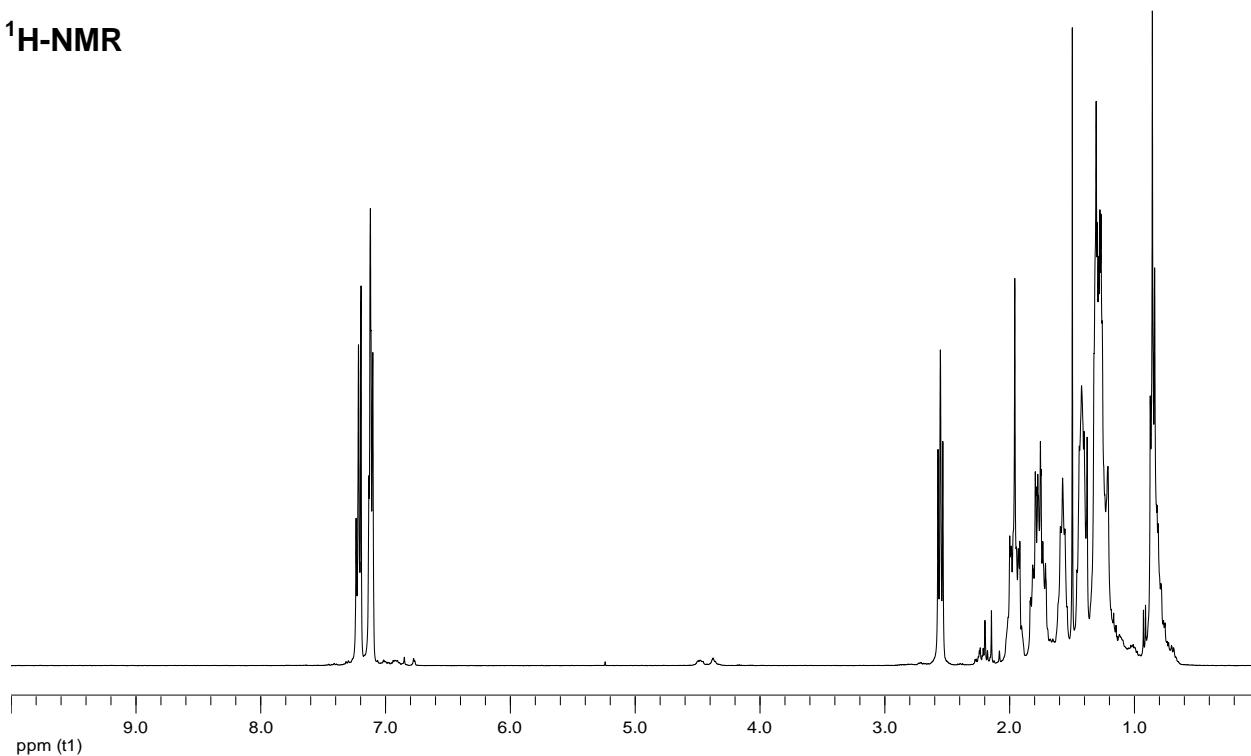
¹³C-NMR



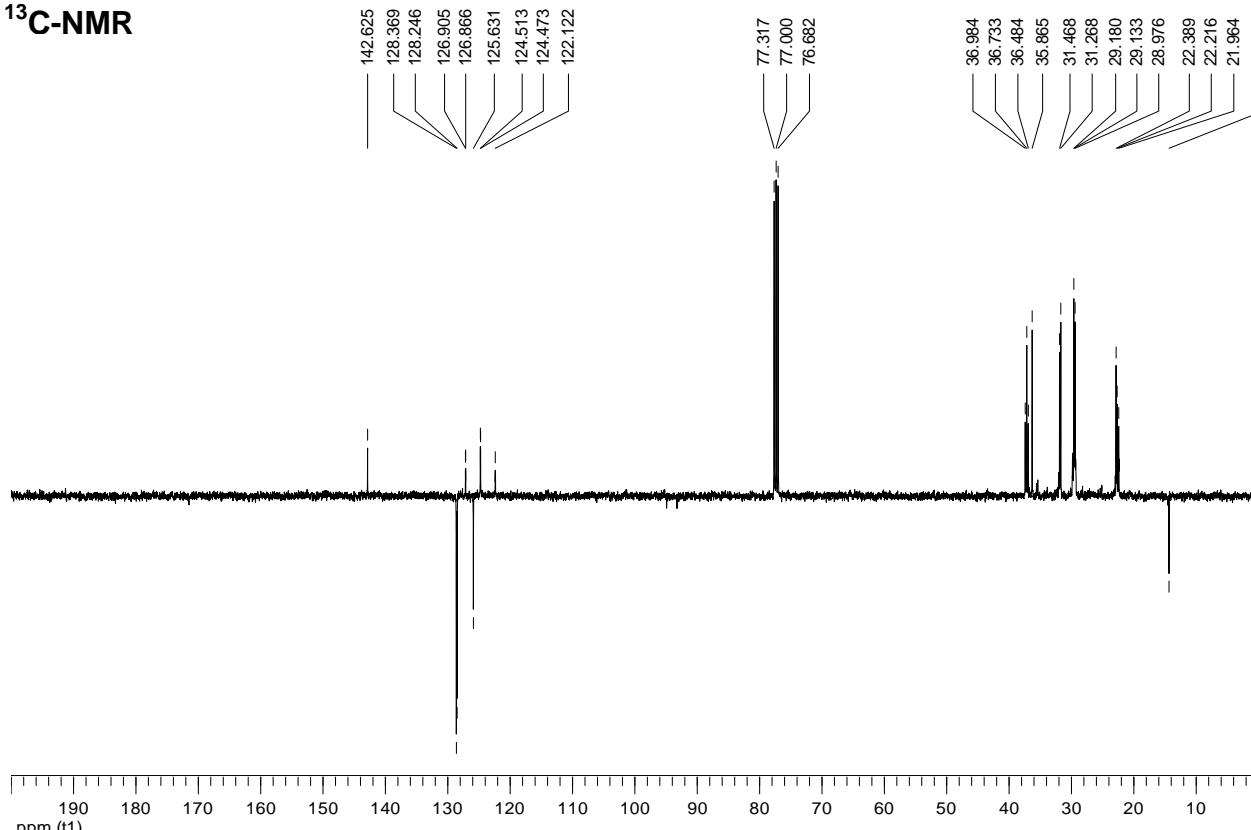


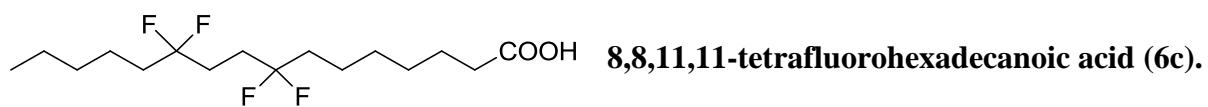
(7,7,10,10-tetrafluoropentadecyl)benzene (26).

¹H-NMR

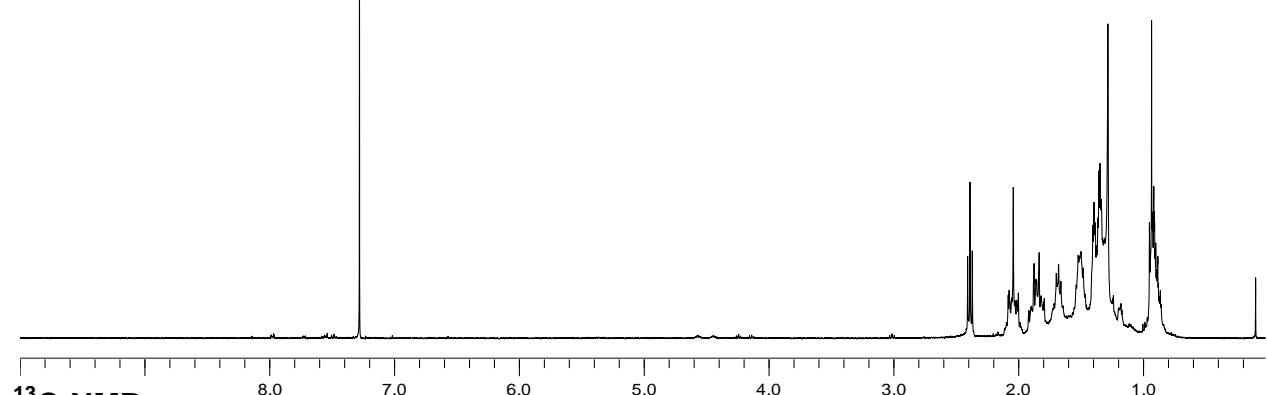


¹³C-NMR

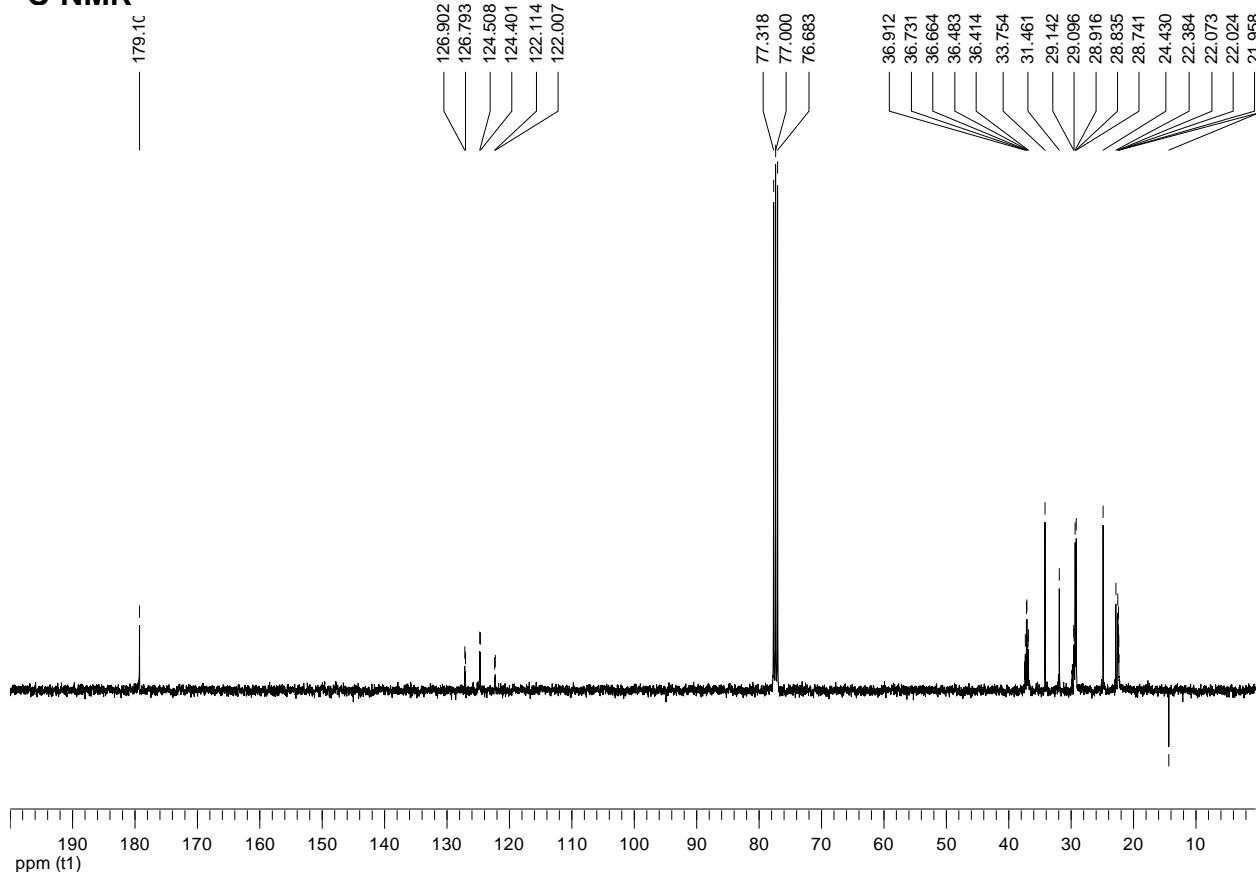




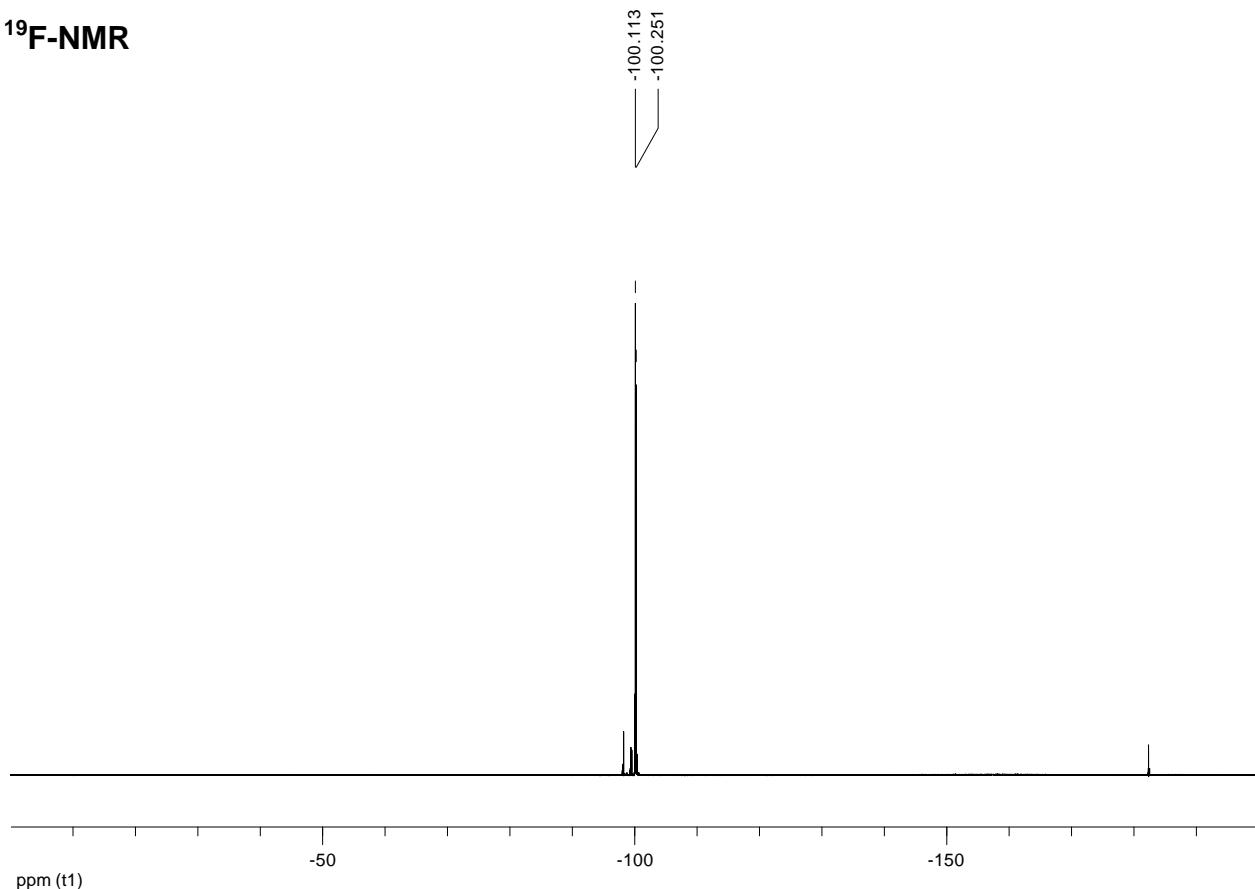
¹H-NMR

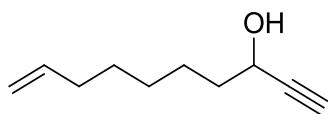


¹³C-NMR



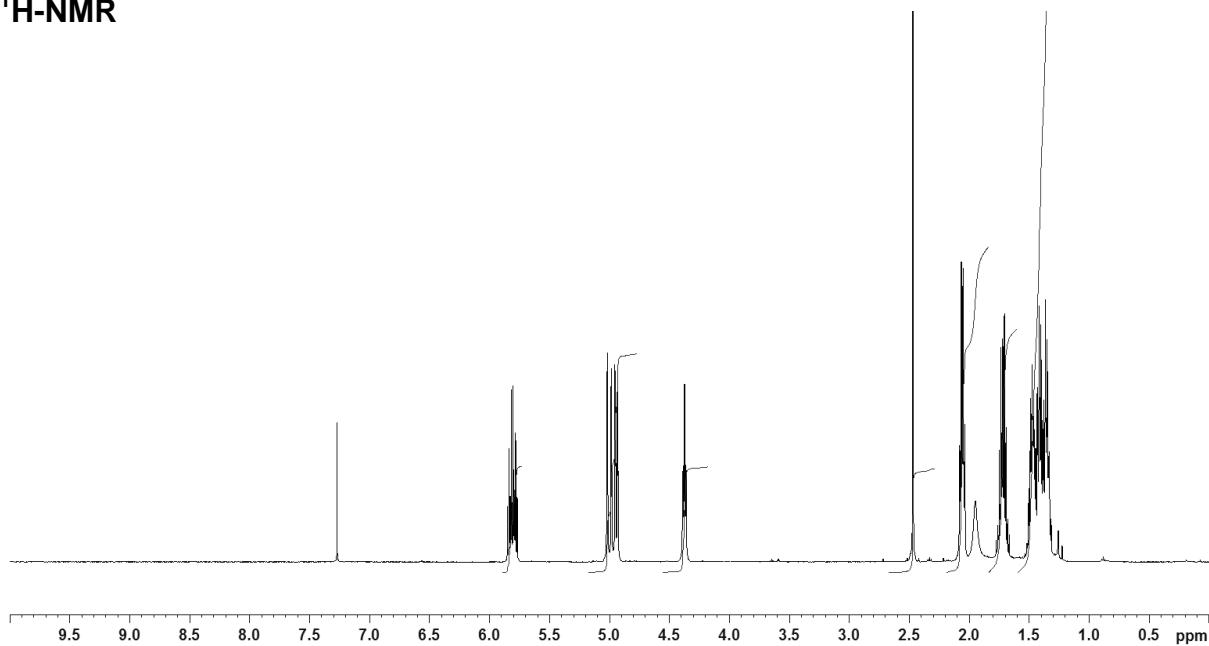
¹⁹F-NMR



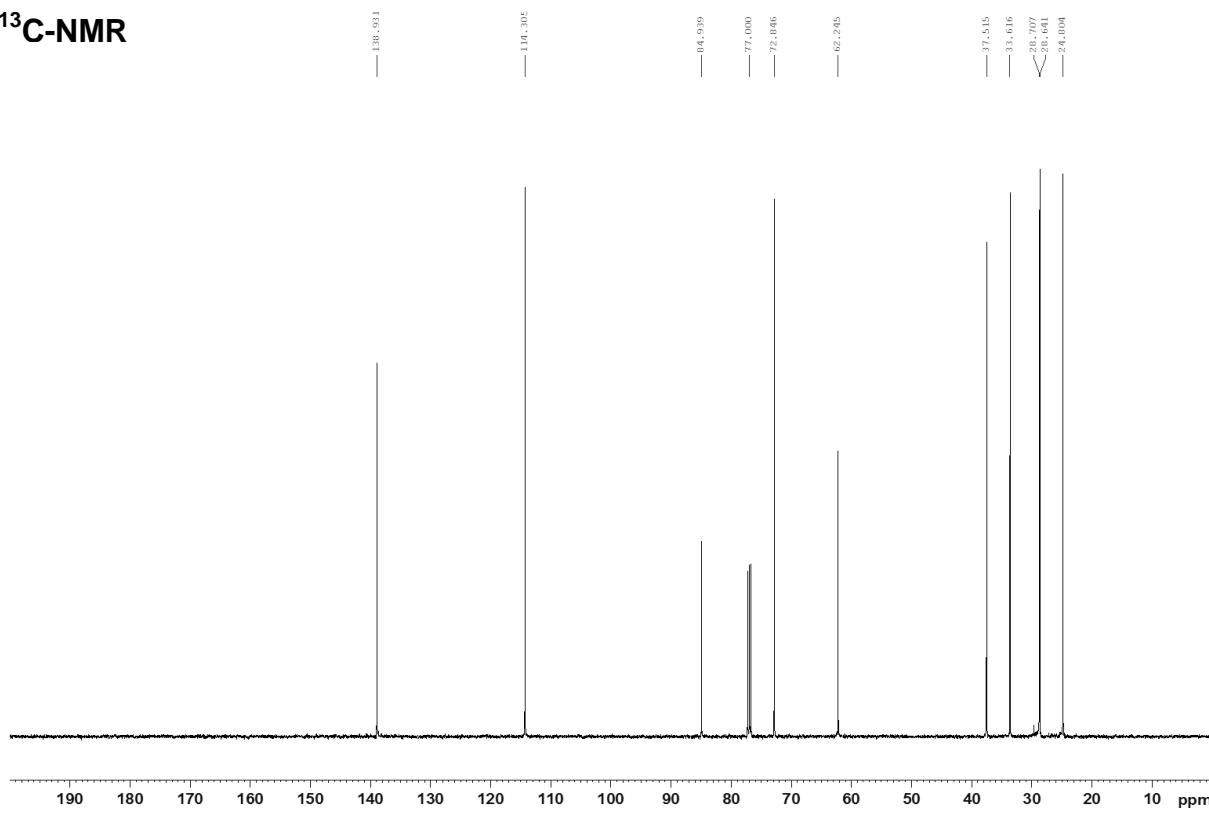


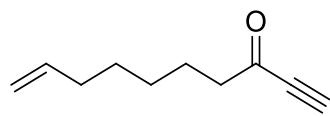
9-Decen-1-yn-3-ol (29).

¹H-NMR



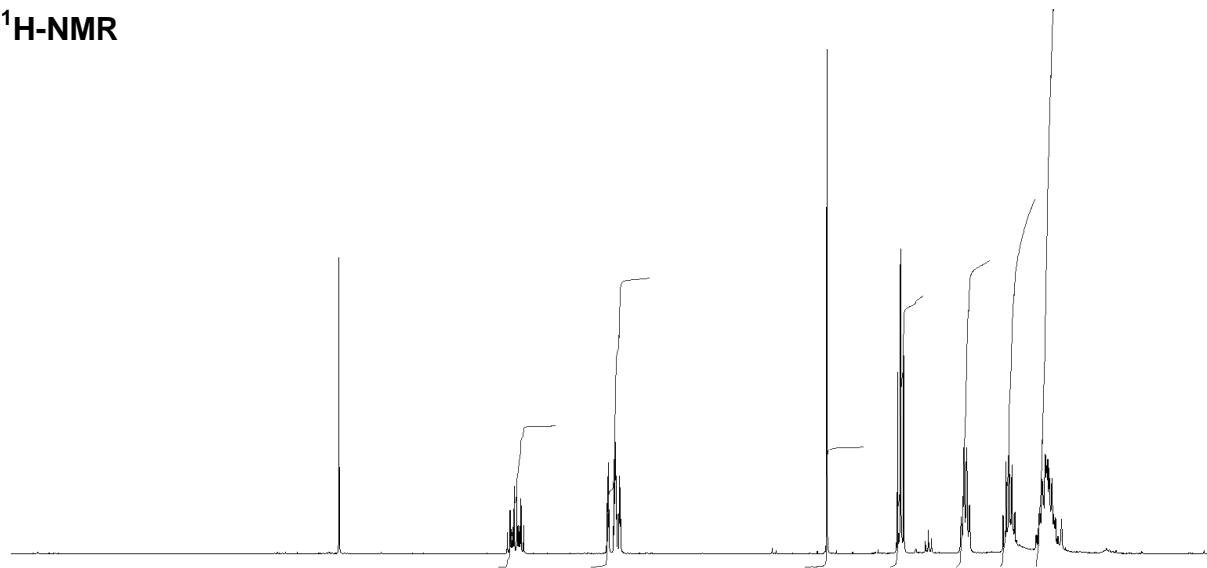
¹³C-NMR



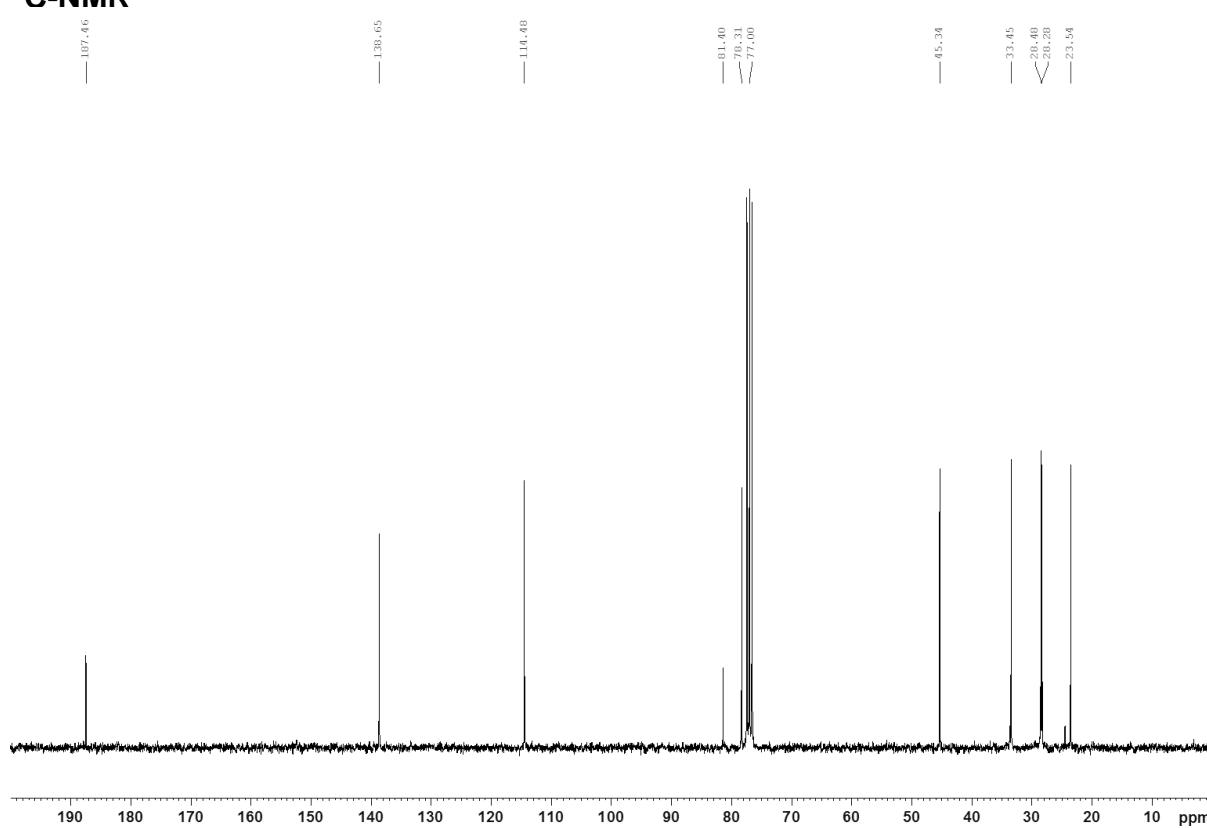


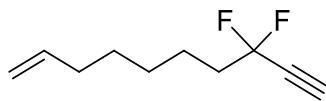
9-Decen-1-yn-3-one (30).

¹H-NMR



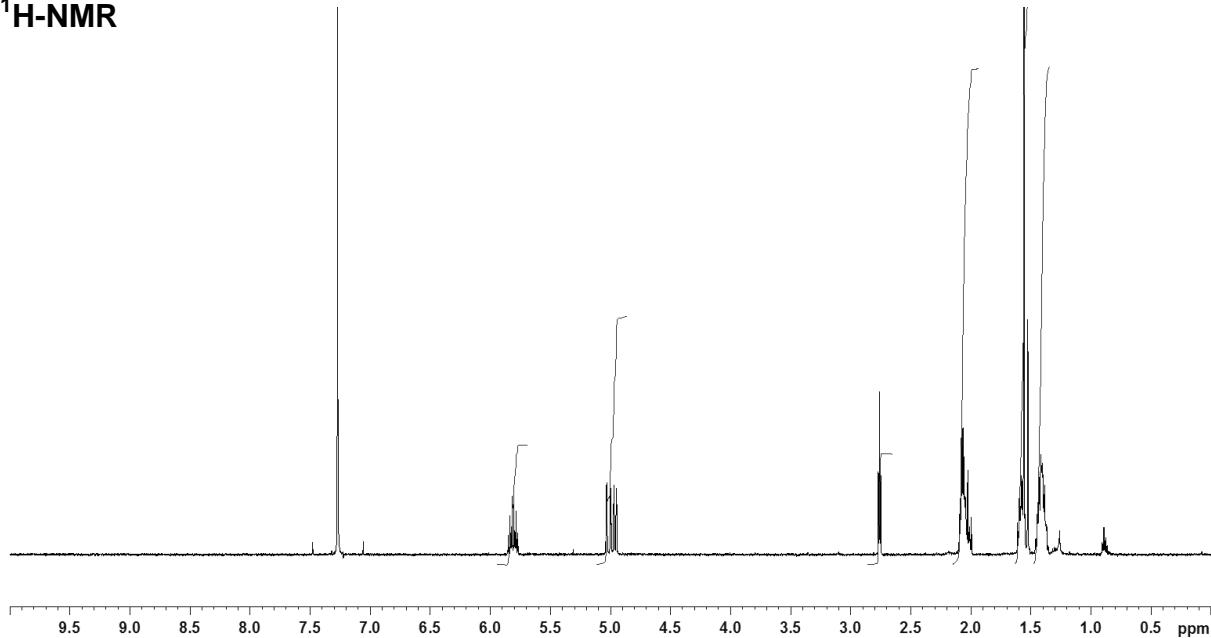
¹³C-NMR



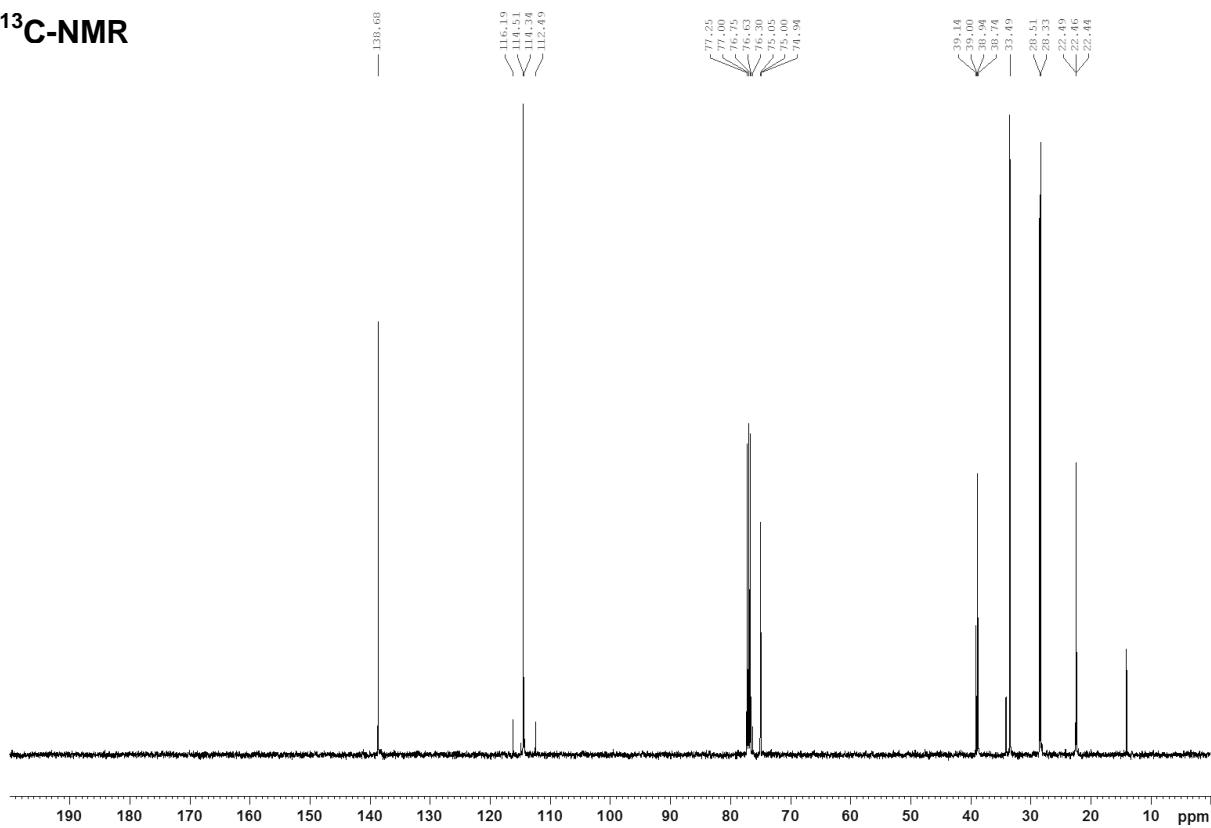


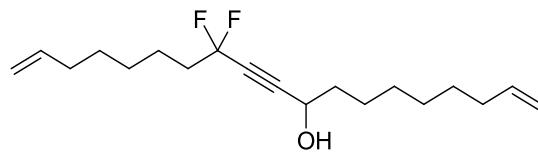
8,8-Difluoro-1-decen-9-yne (31).

¹H-NMR



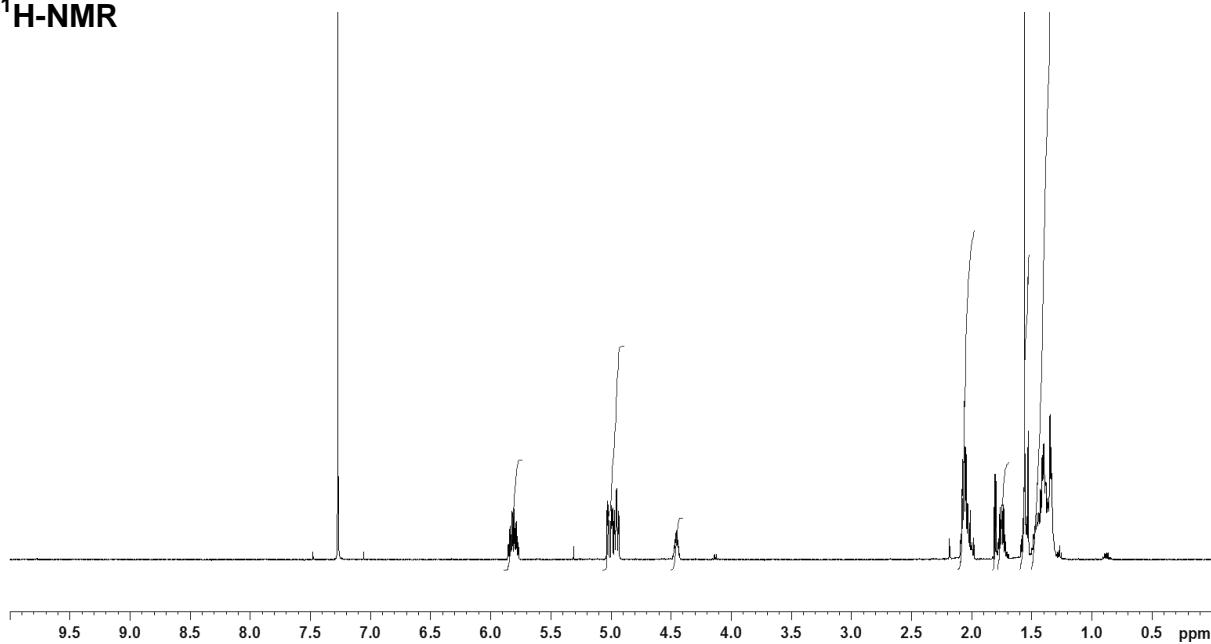
¹³C-NMR



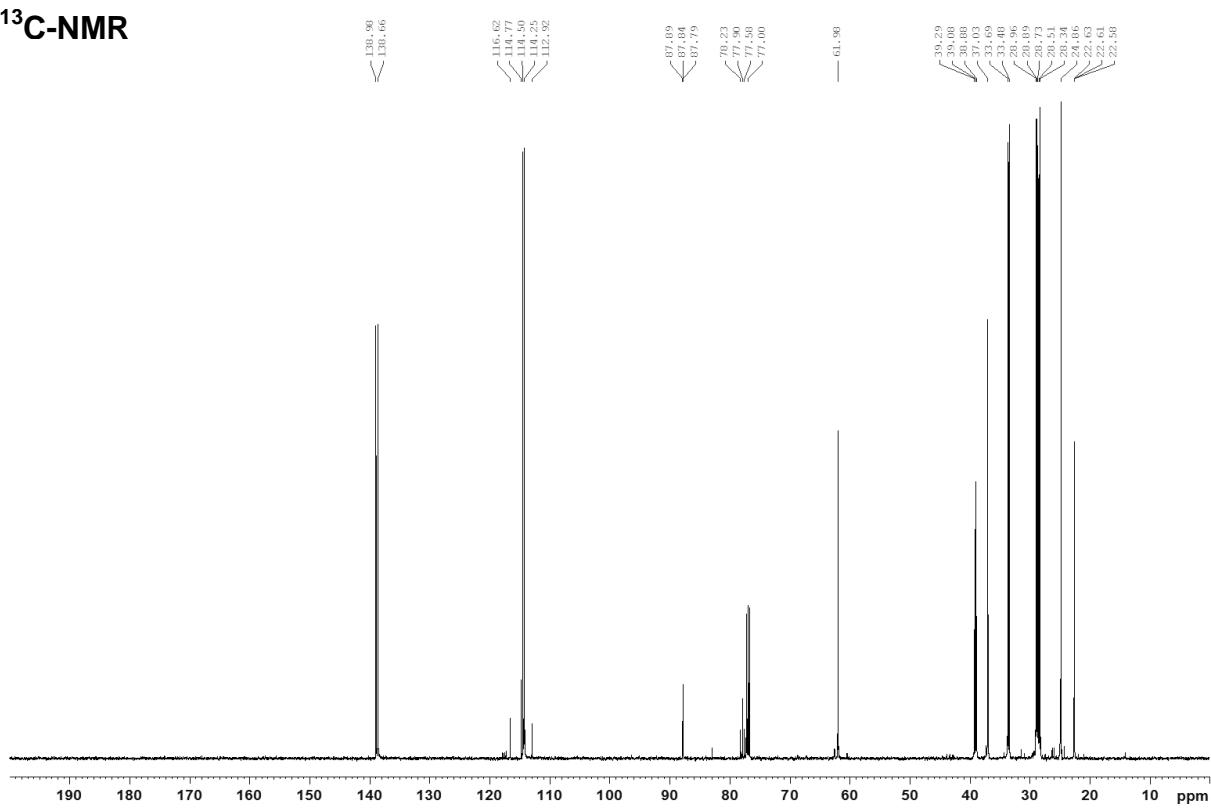


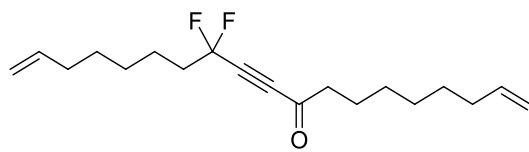
12,12-Difluorononadeca-1,18-dien-10-yn-9-ol (33).

¹H-NMR

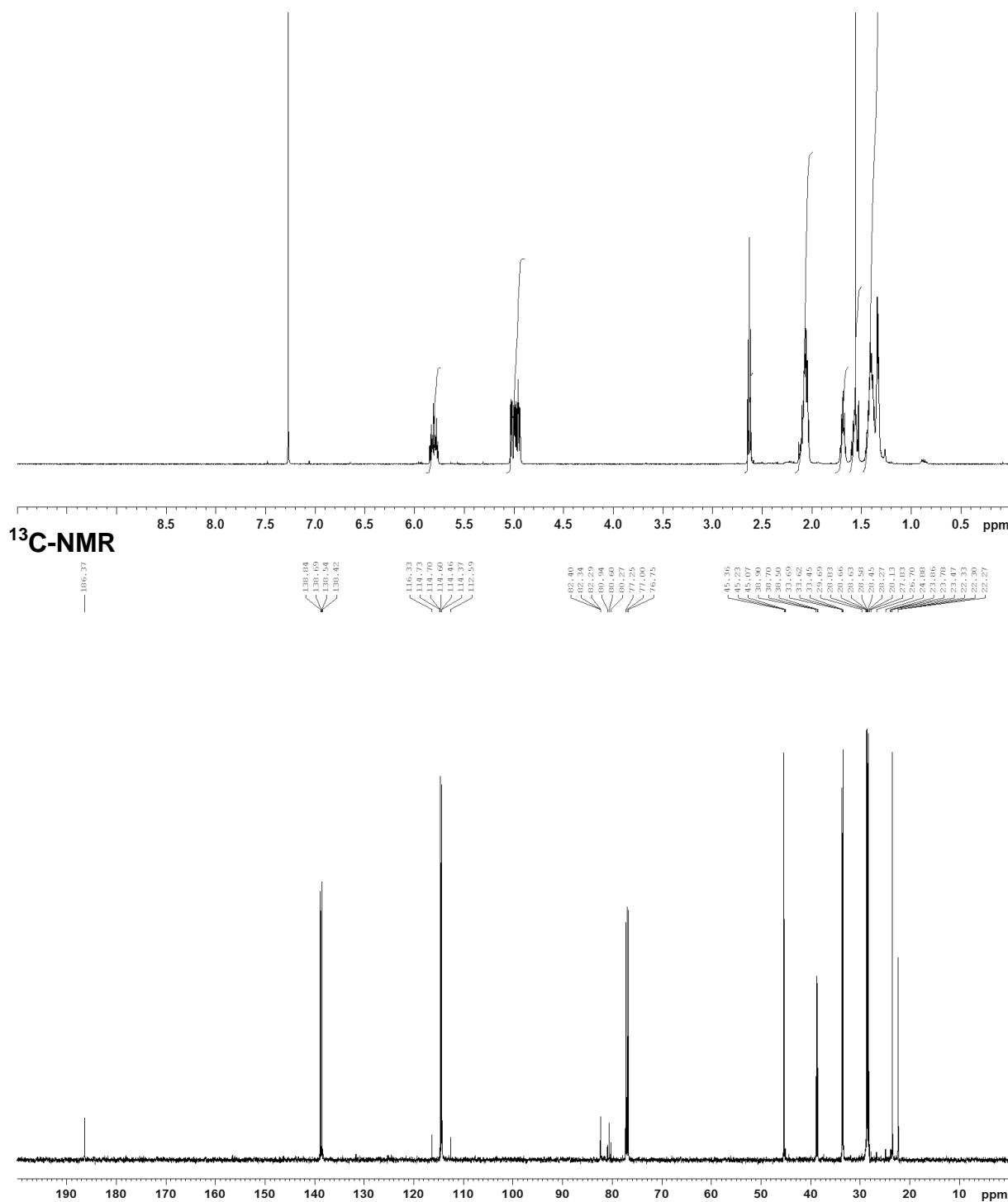


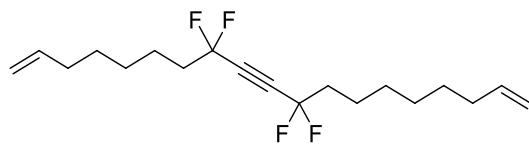
¹³C-NMR





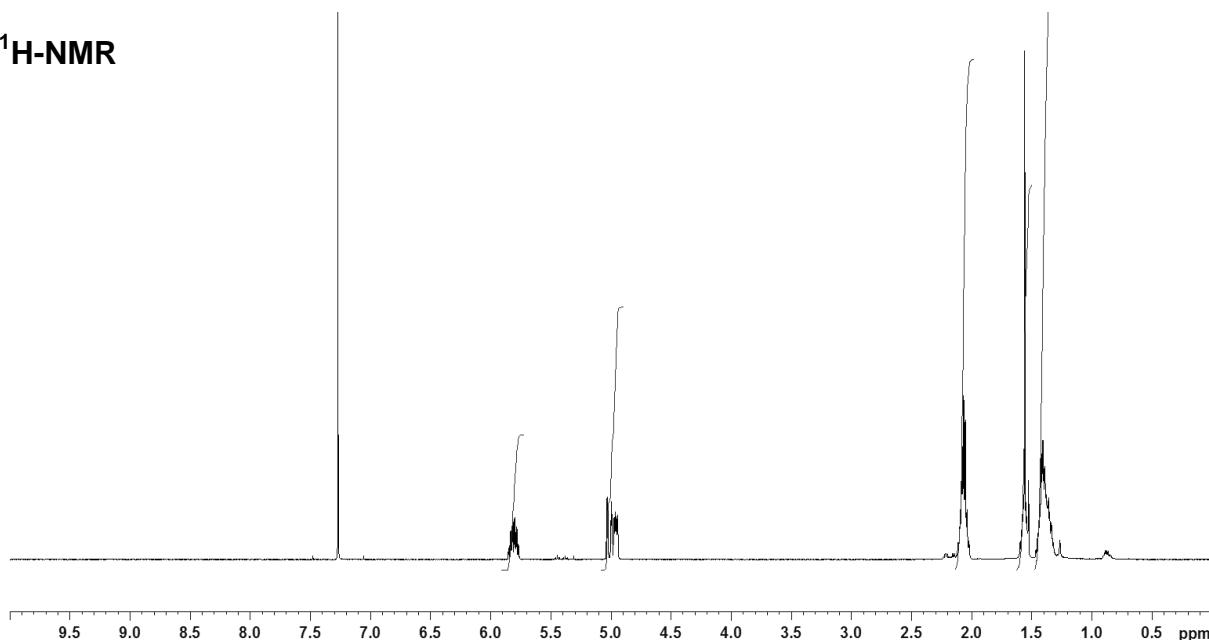
**12,12-Difluorononadeca-1,18-dien-10-yn-9-one
(34).**



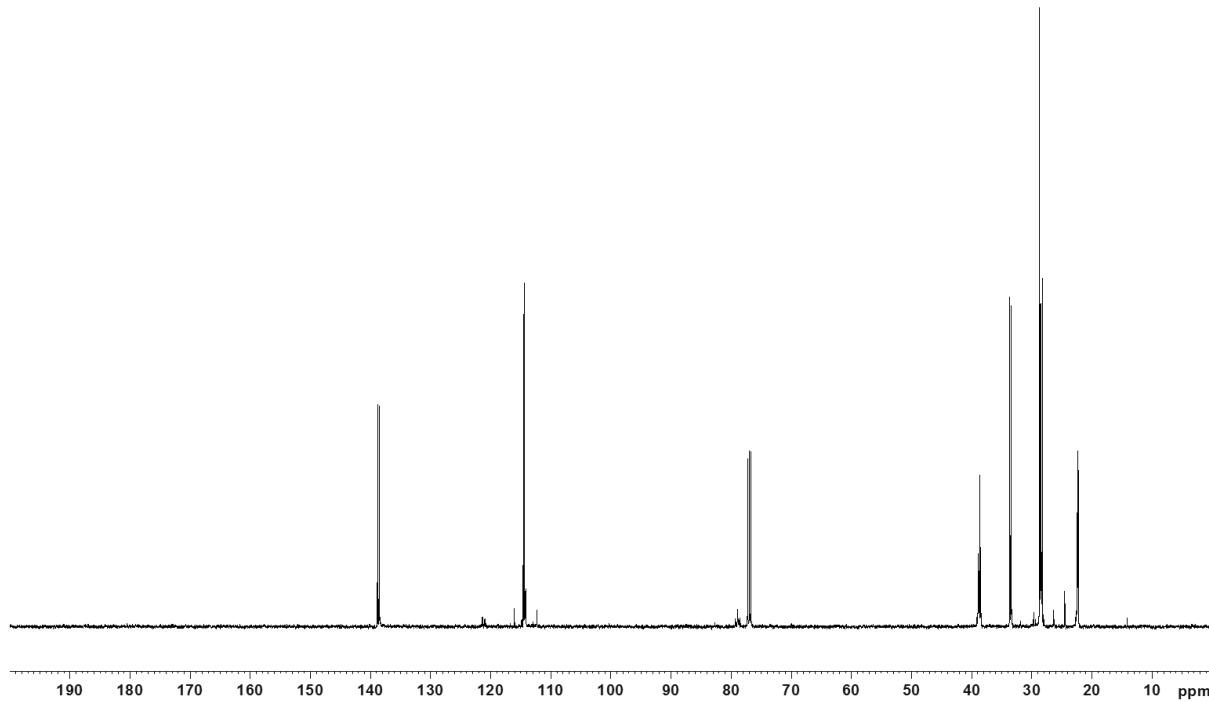


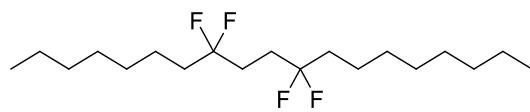
**8,8,11,11-Tetrafluoronoronadeca-1,18-dien-9-yne
(35).**

¹H-NMR



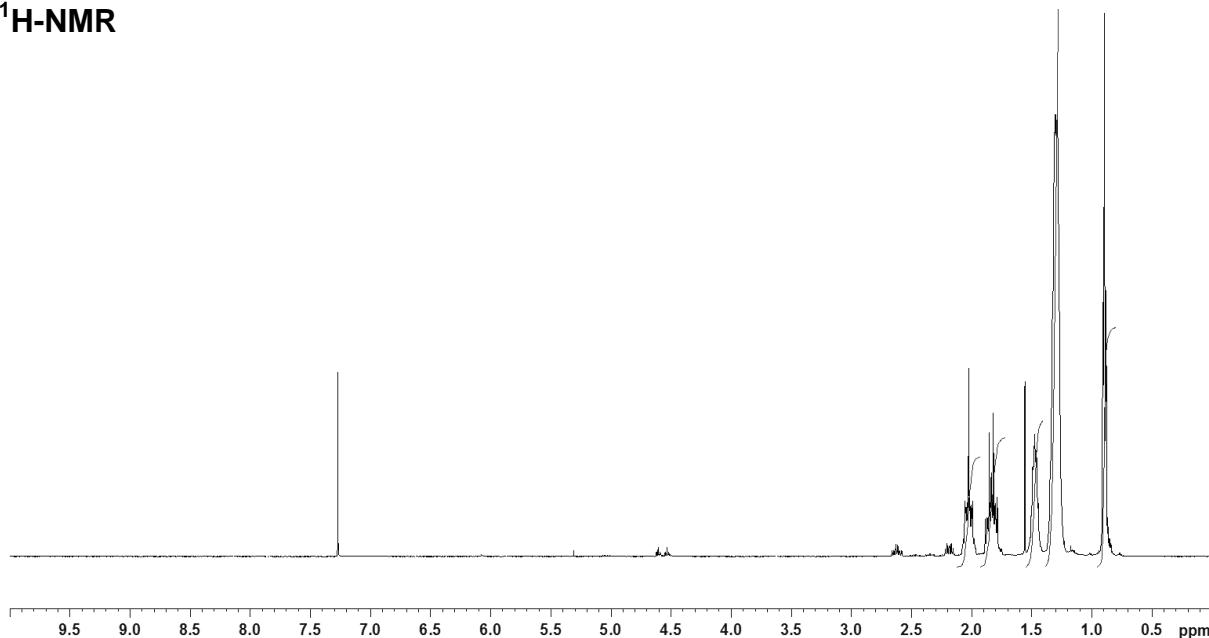
¹³C-NMR



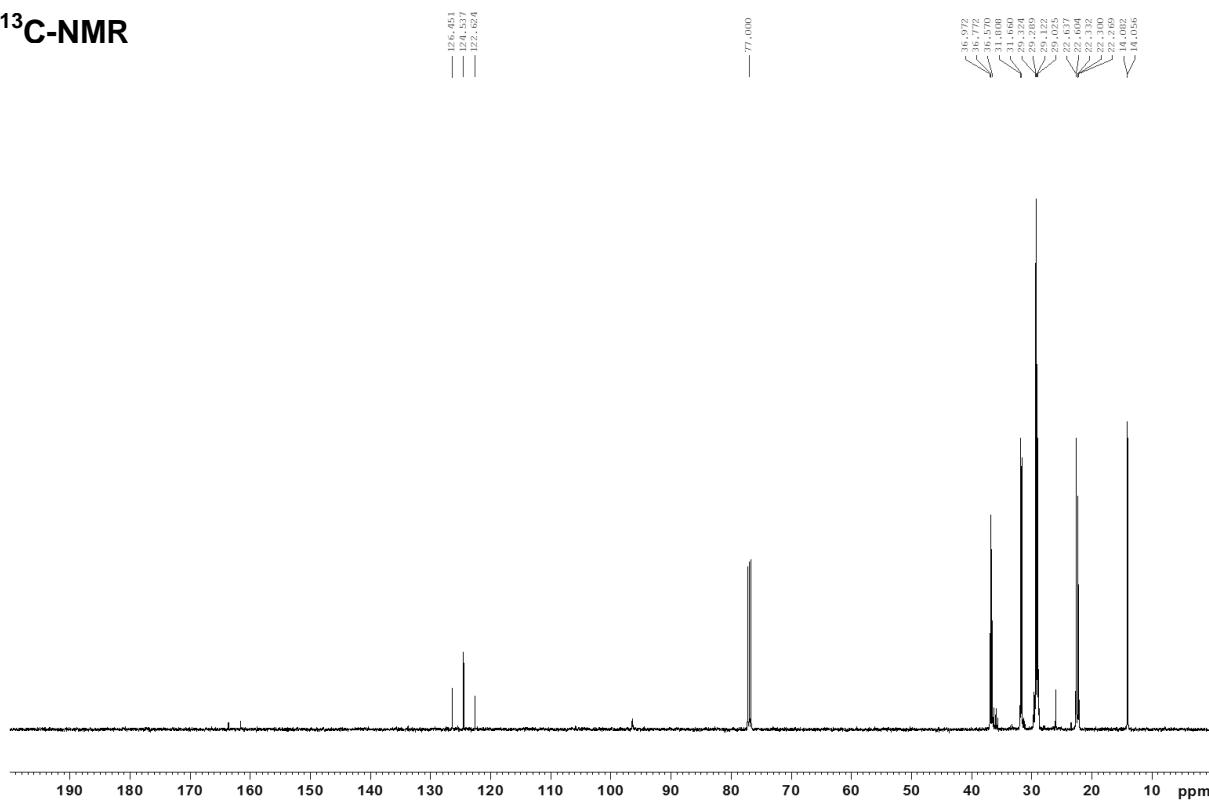


8,8,11,11-Tetrafluorononadecane (27).

¹H-NMR



¹³C-NMR



¹⁹F-NMR

