Supplemental Material for:

The Application of ^{18}F-Labelling to the Staudinger Ligation for the Labelling of Peptides

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SUPPORTING INFORMATION

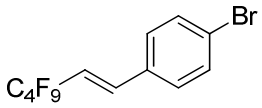
Contents:

General Procedures

^{1}H NMRs were reported on Bruker DPX 200, DPX 400, AV 400 and AV 500 spectrometers, at a frequency of 200, 400 and 500 MHz respectively. ^{13}C NMRs were recorded on Bruker AV 400 and AV 500 spectrometers at a frequency of 100 or 125 MHz respectively. Mass spectra (*m/z*) were obtained on a Bruker MicroTOF in Electrospray (ESI). Analytical thin layer chromatography (TLC) was performed on Merck Silica 60 F_{254} plates. Crude reaction mixtures were analysed by TLC and HPLC. HPLC analysis was performed with a Gilson 322 or Dionex Ultimate 3000 systems, equipped with a NaI/PMT radiodetector and a UV-detector. Radio-TLC was performed on Macherey-Nagel Polygram Silica Plates and eluted with EtOAc or 95% aq. MeCN. Analysis was performed with a plastic scintillator/PMT detector. FSPE separation was carried out using pre-assembled Waters Sep-Pak cartridges (Waters, Milford, MA) and FluoroFlash Silica gel (Fluorous Technologies Inc., Pittsburgh, PA). Pre-assembled Sep-Pak C_{18}SPE cartridges (Waters, Milford, MA) were used in the same way. [^{18}F]Fluoride was produced by the cyclotron of PETNET Solutions at Mont Vernon Hospital (UK) via the $^{18}O(p,n)^{18}F$ reaction and delivered as [^{18}F]fluoride in [^{18}O]water (1-2 GBq, 1-3 mL). This target solution was passed through a QMA anion exchange resin cartridge (20 mg, Waters). [^{18}F]Fluoride adsorbed on the charged-resin was eluted into a reaction vial with a solution of Kryptofix 222 (15 mg) and K_2CO_3 (3 mg) in 1 mL acetonitrile/water (8:2). Excess water was removed under N_2 stream at 100-110°C, and the resulting complex was dried an additional 3 times by azeotropic distillation with 0.5 mL acetonitrile each under N_2 stream. The resulting dry complex of K^{18}F/Kryptofix 222 was further dissolved by anhydrous acetonitrile (2-4 mL) and dispensed into reaction vials containing the precursor for nucleophilic fluorination.

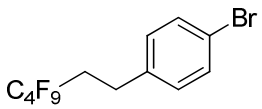
Preparation of a Fluorous Variant

(*E*)-1-Bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)benzene



A solution of 3,3,4,4,5,5,6,6,6-nonafluorohex-1-ene (3.5 mL, 20.2 mmol) in methanol (10 mL) was added dropwise to a stirred solution of 4-bromobenzenediazonium tetrafluoroborate (5.46 g, 20.2 mmol) and palladium(II) acetate (0.023 g, 0.10 mmol) in methanol (10 mL) at room temperature under nitrogen. The resulting mixture was stirred at 40 ^{O}C until the bubbling ceased. The reaction mixture was extracted into DCM, washed successively with water (30 mL) and brine (30 mL) and then concentrated *in vacuo*. The residue was dissolved in pentane, filtered through silica gel and evaporated to afford desired product (*E*)-1-bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)benzene as a colourless oil (7.58 g, 94 %); δ_H (400 MHz, $CDCl_3$) 6.14-6.24 (1H, m, CF_2CH), 7.12 (1H, d, J = 16.0 Hz, CH=C*H*), 7.35 (2H, dd, J = 8.3, 2.8 Hz, Ar-*H*), 7.55 (2H, dd, J = 8.3, 3.2 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 115.0 (t, J = 23.2 Hz), 124.5, 129.1, 132.2, 132.4, 138.6 (t, J = 9.6 Hz); δ_F (377 MHz, $CDCl_3$) -80.0 (3F, t, J = 9.5 Hz), -111.5, -124.1, -125.8; *m*/*z* (ESI) $C_{12}H_7F_9Br$ ($[M+H]^+$) *calc.* 400.9587, *found* 400.9605.

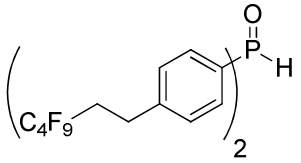
1-Bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene



A solution of (*E*)-1-bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-enyl)benzene (1 g,

2.49 mmol) in DCM (10 mL) under 5 bar H_2 was stirred with Rh/C catalyst at 30 ^oC for 24 hours. The reaction was monitored by GCMS analysis and upon consumption of the starting material, the mixture was filtered through a plug of Celite® and concentrated *in vacuo* to yield the desired product 1-bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene as a colourless oil (900 mg, 90 %); δ_H (400 MHz, $CDCl_3$) 2.34-2.37 (2H, m, CF_2CH_2), 2.86-2.90 (2H, m, CH_2Ar), 7.07-7.11 (2H, m, Ar-*H*), 7.43-7.46 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 25.9, 32.6 (t, J = 22.4 Hz), 120.6, 130.0, 131.9, 138.0; δ_F (377 MHz, $CDCl_3$) -81.0 (3F, t, J = 9.5 Hz), -114.9, -124.5, -126.1; *m*/*z* (ESI) $C_{12}H_9F_9Br$ ($[M+H]^+$) *calc.* 402.9744, *found* 402.9758.

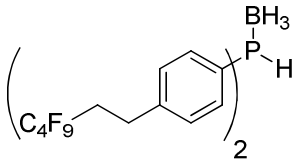
Bis(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphine oxide[2]



To a stirred solution of 1-bromo-4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)benzene (3 g, 7.4 mmol) in Et_2O (52 mL) at -78 ^oC under argon was added *t*BuLi (1.6 M solution in Et_2O, 9.3 mL, 14.9 mmol) carefully. The resulting mixture was slowly warmed to 0 ^oC (> 30 mins) before the addition of dichloro(diethylamino)phosphine (0.97 mL, 6.7 mmol) dropwise. The reaction mixture was stirred at 0 ^oC for 16 hours, then concentrated hydrochloric acid (0.99 mL, 11.9 mmol) was added the mixture warmed to room temperature for 4 hours. The reaction was quenched by the addition of H_2O (20 mL) and the aqueous layer extracted with Et_2O (100 mL). The combined organic layer was washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by silica column chromatography (97:3 DCM:MeOH) afforded the

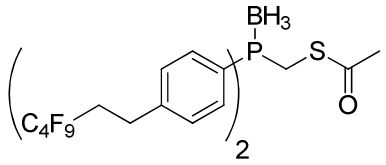
desired product *bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphine oxide as a white solid (1.76 g, 68 %); δ_H (400 MHz, $CDCl_3$) 2.30-2.46 (4H, m, CF_2CH_2), 2.92-3.05 (4H, m, CH_2Ar), 7.38 (4H, dd, J = 5.0, 2.7 Hz, Ar-*H*), 7.47 (½H, d, J = 481.8 Hz, P-*H*), 7.61-7.74 (4H, m, Ar-*H*), 8.68 (½H, d, J = 481.8 Hz, P-*H*); *m*/*z* (ESI) $C_{24}H_{17}F_{18}NaOP$ ($[M+H]^+$) *calc*. 717.0622, *found* 717.0628.

(*Bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphonio)trihydroborate



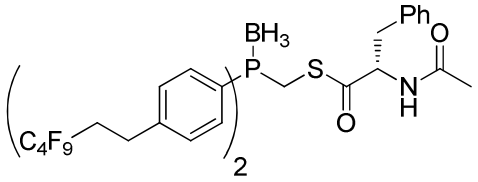
To a stirred solution of *bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphine oxide (1.86g, 2.7 mmol) in THF (56 mL) under argon was added H_2O (0.48 mL, 26.8 mmol). The mixture was allowed to homogenise and then cooled to 0 ^oC before the slow addition of $BH_3{\cdot}SMe_2$ (2 M solution in Et_2O, 26.8 mL, 53.6 mmol) [Note: evolution of gas]. The resulting mixture was allowed to warm to room temperature and stirred for 5 hours, after which it was concentrated *in vacuo* and the residue purified using silica column chromatography (98:2 Hexane:EtOAc) to afford the desired product (*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphonio) trihydroborate as a white solid (1.75 g, 94 %); δ_H (400 MHz, $CDCl_3$) 0.45-1.57 (3H, m, BH_3), 2.27-2.46 (4H, m, CF_2CH_2), 2.88-3.03 (4H, m, CH_2Ar), 5.76-5.88 (½H, dm, J = 379.3 Hz, P-*H*), 6.72-6.88 (½H, dm, J = 379.3 Hz, P-*H*), 7.33 (4H, d, J = 6.8 Hz, Ar-*H*), 7.58-7.68 (4H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 26.4, 32.4 (t, J = 22.0 Hz), 124.6 (d, $J_{C\text{-}P}$ = 57.5 Hz), 129.2 (d, $J_{C\text{-}P}$ = 11.2 Hz), 133.4 (d, $J_{C\text{-}P}$ = 9.6 Hz), 143.2 (d, $J_{C\text{-}P}$ = 2.4 Hz); δ_F (377 MHz, $CDCl_3$) -81.1, -114.8, -124.5, -126.1; δ_P (162 MHz, $CDCl_3$) -0.1; *m/z* (ESI) Unobtainable due to decomposition.

(((Acetylthio)methyl)*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphonio) -trihydroborate



To a stirred solution of (*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphonio) trihydroborate (500 mg, 0.72 mmol) in DMF (2.5 mL) at 0 ^{o}C under argon was added sodium hydride (60 % in mineral oil, 43 mg, 1.1 mmol). The resulting mixture was stirred at 0 ^{o}C until bubbling ceased. A solution of **3** (183 mg, 1.1 mmol) in DMF (0.5 mL) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred overnight. The mixture was then concentrated *in vacuo* and purified using silica column chromatography (96:4 Hexane:Et_2O) to afford the desired product (((acetylthio)methyl)*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl) phenyl)phosphonio)trihydroborate as a colourless oil (233 mg, 41 %); δ_H (400 MHz, $CDCl_3$) 0.48-1.48 (3H, m, BH_3), 2.26 (3H, s, CH_3), 2.30-2.47 (4H, m, CF_2CH_2), 2.91-3.01 (4H, m, CH_2Ar), 3.70 (2H, dd, J = 6.7, 2.7 Hz, PCH_2S), 7.28-7.37 (4H, m, Ar-*H*), 7.60-7.71 (4H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (d, $J_{C\text{-}P}$ = 36.0 Hz), 26.4, 30.0, 32.3 (t, J = 22.0 Hz), 125.9 (d, $J_{C\text{-}P}$ = 56.7 Hz), 128.9 (d, $J_{C\text{-}P}$ = 11.2 Hz), 132.9 (d, $J_{C\text{-}P}$ = 9.6 Hz), 143.3 (d, $J_{C\text{-}P}$ = 1.6 Hz), 193.2; δ_F (377 MHz, $CDCl_3$) -81.1, -114.8, -124.5, -126.1; δ_P (162 MHz, $CDCl_3$) 18.2; *m*/*z* (ESI) $C_{27}H_{24}BF_{18}NaOPS$ ($[M+H]^+$) *calc.* 803.0988, *found* 803.0983.

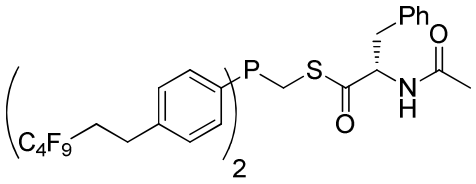
(*S*)-6-Benzyl-2,2-*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)-5,8-dioxo-4-thia-7-aza-2-phospha-1-boranonan-2-ium-1-uide



To a stirred solution of (((acetylthio)methyl)*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl) phenyl)phosphonio)trihydroborate (400 mg, 0.51 mmol) in degassed MeOH (2.4 mL) at room temperature under argon was added sodium methoxide (36 mg, 0.67 mmol). The reaction was followed by TLC and upon consumption of starting material, the mixture was quenched by the addition of 1 N HCl (2 mL). The resulting mixture was extracted with EtOAc (15 mL) and the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was re-dissolved in DCM (3.2 mL) under argon and *N*-acetylphenylalanine (116 mg, 0.56 mmol), DCC (121 mg, 0.59 mmol) and DMAP (3 mg, 0.03 mmol) were added sequentially. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then filtered through a plug of Celite® and the filtrate concentrated *in vacuo*. Purification by silica column chromatography (90:10 Hexane:EtOAc) afforded the desired product (*S*)-6-benzyl-2,2-*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)-5,8-dioxo-4-thia-7-aza-2-phospha-1-boranonan-2-ium-1-uide as a white solid (176 mg, 37 % over two steps); δ_H (400 MHz, $CDCl_3$) 0.54-1.47 (3H, m, B*H*$_3$), 1.92 (3H, s, C*H*$_3$), 2.28-2.46 (4H, m, CF_2CH_2), 2.79-2.86 (1H, m, C*H*HPh), 2.90-3.08 (5H, m, CH_2Ar and CH*H*Ph), 3.58-3.67 (1H, m, PC*H*HS), 3.71-3.81 (1H, m, PCH*H*S), 4.83-4.92 (1H, m, C*H*CH_2Ph), 5.63 (1H, d, *J* = 8.1 Hz, N*H*), 7.00-7.08 (2H, m, Ph-*H*), 7.23-7.29 (3H, m, Ph-*H*), 7.30-7.39 (4H, m, Ar-*H*), 7.60-7.71 (4H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 23.0, 23.5 (d, $^1J_{CP}$ = 35.1 Hz), 26.4, 32.3 (t, $^3J_{CF}$ = 22.0 Hz), 37.7, 59.5, 125.8, (d, $^1J_{CP}$ = 56.3 Hz), 125.9 (d, $^1J_{CP}$ = 56.3 Hz), 127.4, 128.8, 128.9, 129.0, 129.0, 132.9 (d, $^3J_{CP}$ = 9.8 Hz), 133.0 (d, $^3J_{CP}$ = 9.8 Hz), 135.0, 143.3 (d, $^4J_{CP}$ = 2.4

Hz), 143.4 (d, $^4J_{CP}$ = 2.4 Hz), 169.9, 198.1; δ_F (377 MHz, $CDCl_3$) -81.0, -114.8, -124.4, -126.0; δ_P (162 MHz, $CDCl_3$) 18.4; *m/z* (ESI) $C_{36}H_{33}BF_{18}NNaO_2PS$ ($[M+H]^+$) *calc.* 950.1674, *found* 950.1667.

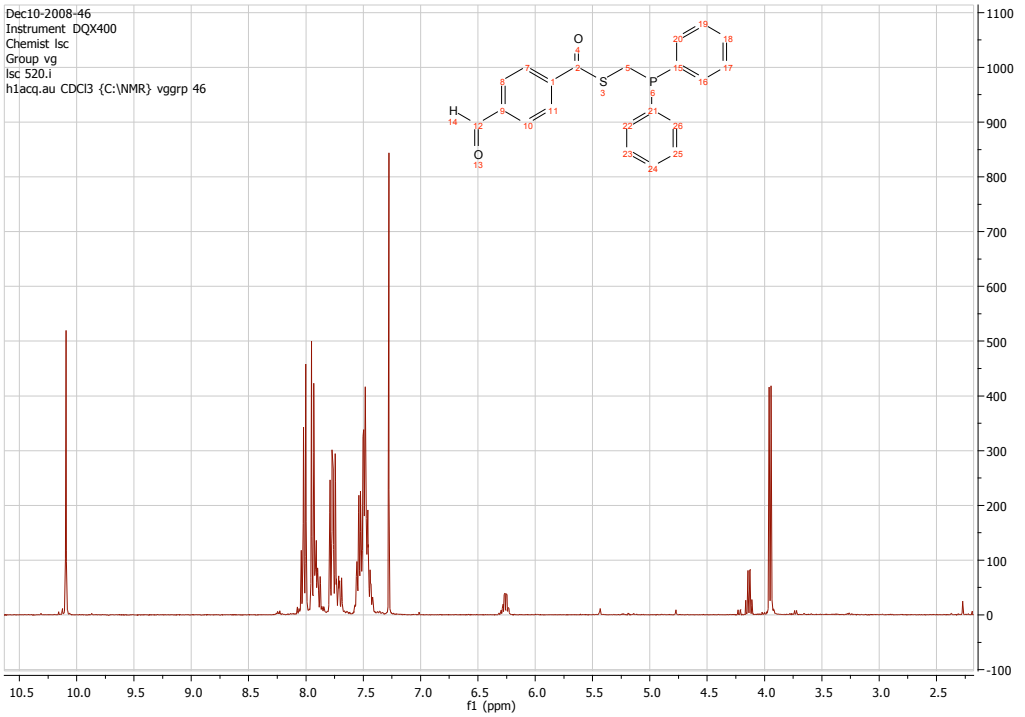
(*S*)-*S*-((*Bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)phosphino)methyl) 2-acetamido-3-phenylpropanethioate (7)

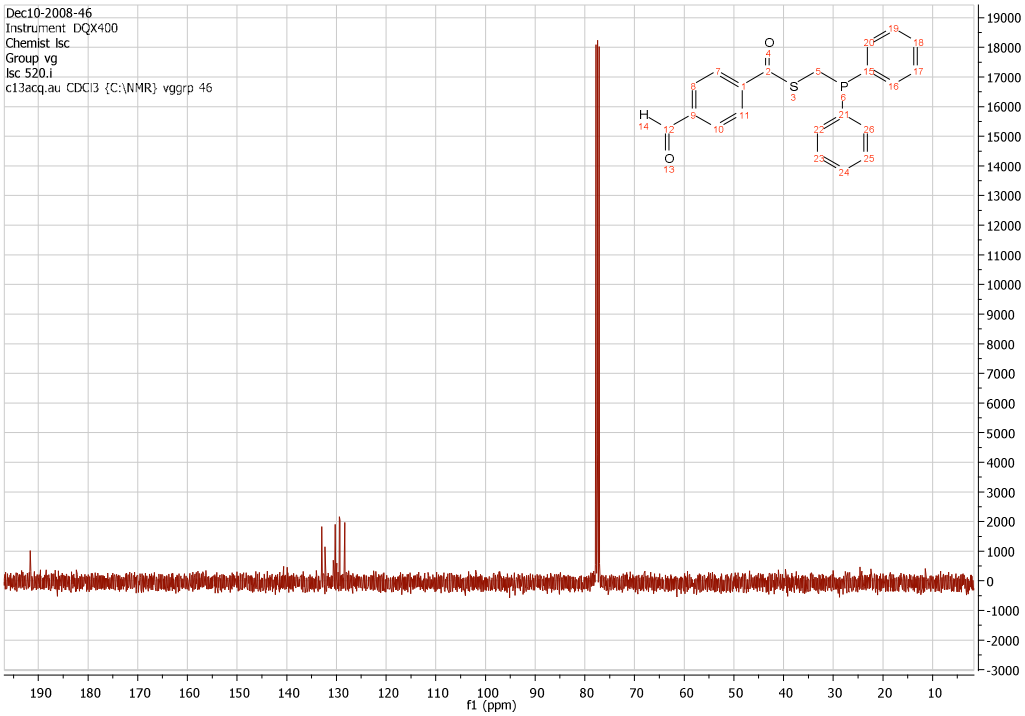


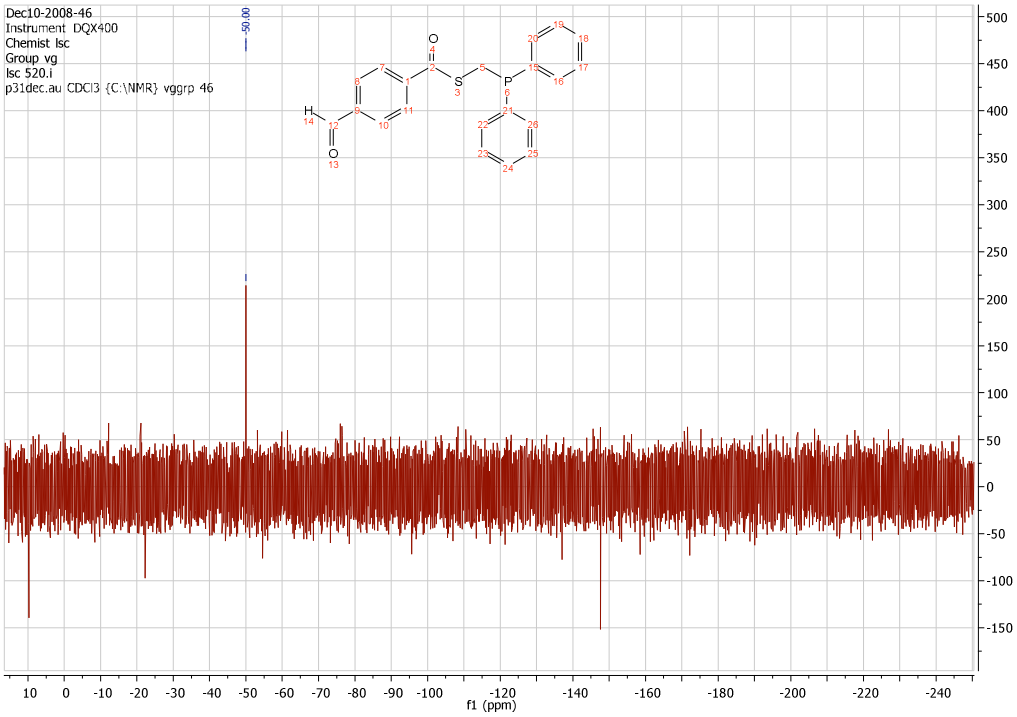
A solution of (*S*)-6-benzyl-2,2-*bis*(4-(3,3,4,4,5,5,6,6,6-nonafluorohexyl)phenyl)-5,8-dioxo-4-thia-7-aza-2-phospha-1-boranonan-2-ium-1-uide (103 mg, 0.11 mmol) and DABCO (12 mg, 0.22 mmol) in toluene (1.1 mL) under Argon was stirred at 60 ^oC for 5 hours. The reaction mixture was then concentrated in vacuo and purified using silica column chromatography (under a stream of nitrogen) to afford the desired product as a pale yellow oil (73 mg, 50 %). By ^1H and ^{31}P NMR recorded immediately, ratio of oxidised product P=O to **7** found to be 30:70; δ_H (400 MHz, $CDCl_3$) 1.92 (1H, s, C*H*$_3$(P=O)), 1.94 (2H, s, C*H*$_3$(P)), 2.28-2.47 (4H, m, CF_2CH_2), 2.80 (0.3H, dd, *J* = 14.5, 7.6 Hz, C*H*HPh(P=O)), 2.88-3.06 (5H, m, CH_2Ar; CH*H*Ph(P=O) and CH*H*Ph(P)), 3.10 (0.7H, dd, *J* = 14.4, 6.1 Hz, C*H*HPh(P)), 3.45 (0.7H, dd, *J* = 14.3, 3.3 Hz, PC*H*HS), 3.51 (0.7H, dd, *J* = 14.3, 3.3 Hz, PCH*H*S), 3.65 (0.3H, dd, *J* = 14.8, 8.9 Hz, P(O)C*H*HS), 3.83 (0.3H, dd, *J* = 14.8, 8.6 Hz, P(O)C-H*H*S), 4.86-4.93 (0.7H, m, C*H*CH_2Ph(P)), 4.94-5.01 (0.3H, m, C*H*CH_2Ph(P=O)), 5.65-5.73 (1H, m, N*H*), 6.98-7.12 (2H, m, Ph-*H*), 7.19-7.31 (5H, m, Ph-*H* and Ar-*H*), 7.32-7.43 (4H, m, Ar-*H*), 7.68-7.79 (2H, m, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 23.0, 23.1, 26.4, 26.5, 32.3, 37.6, 38.2, 59.5, 59.7, 127.2, 127.3, 128.6, 128.7, 128.8, 128.9,

129.0, 129.3, 131.6, 131.7, 133.1, 133.3, 135.3, 144.0, 170.0; δ_F (377 MHz, $CDCl_3$) -81.0, -114.8, -124.4, -126.0; δ_P (162 MHz, $CDCl_3$) -16.9 (0.7P, *P*), 28.7 (0.3P, *P*=O); *m/z* (ESI) $C_{36}H_{30}F_{18}NNaO_2PS$ ($[M+H]^+$) *calc.* 936.1340, *found* 936.1336.

NMR of Novel Compounds



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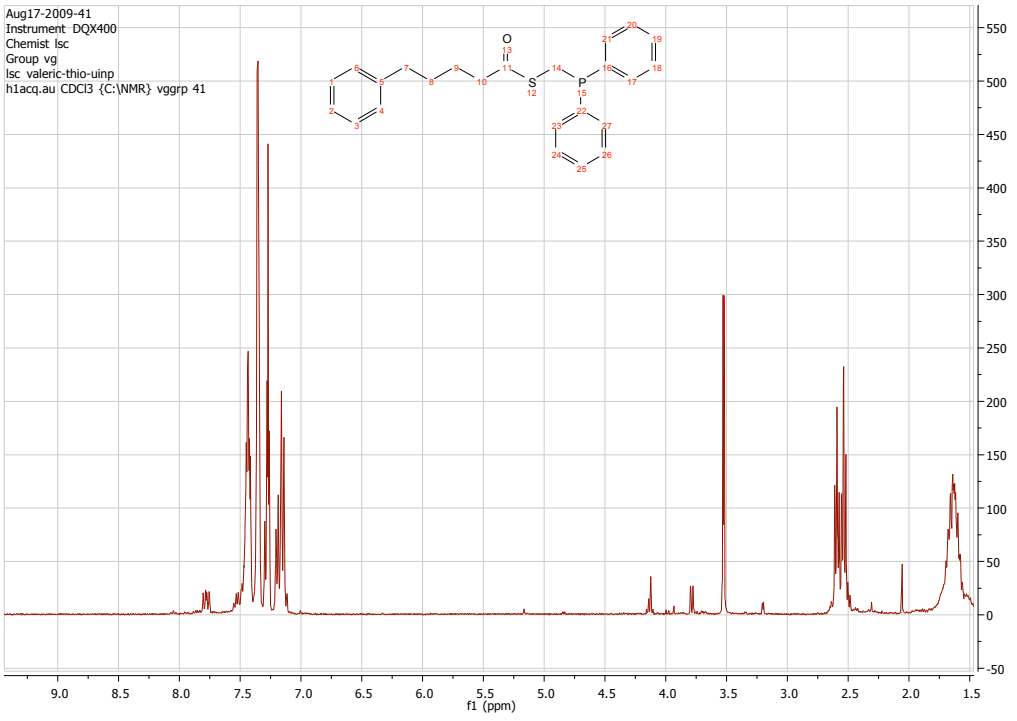
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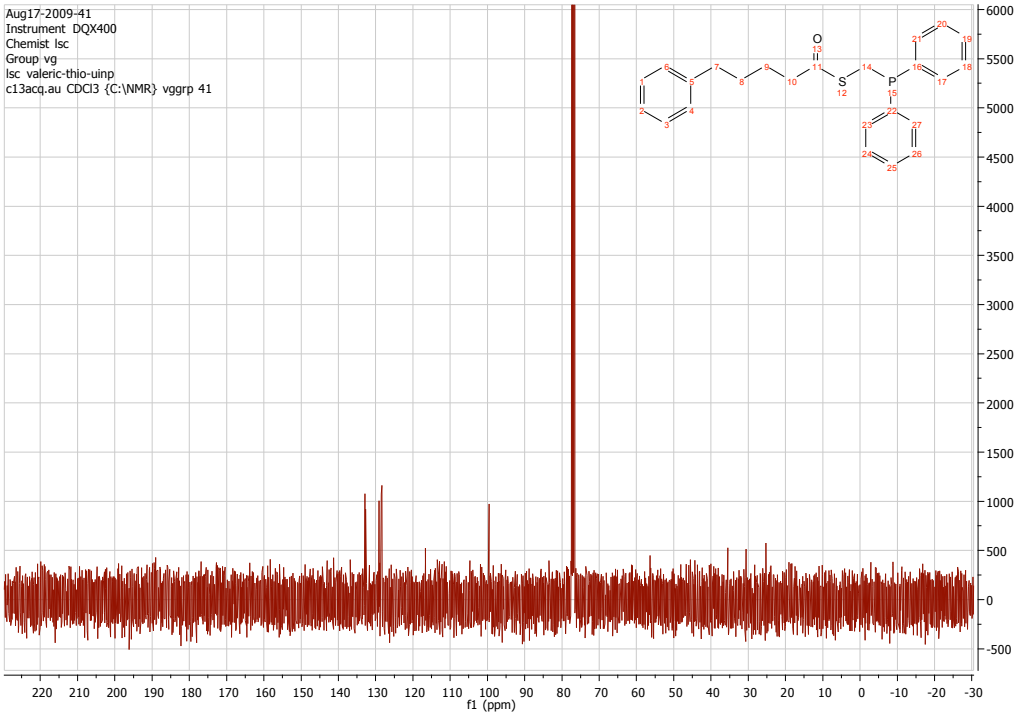
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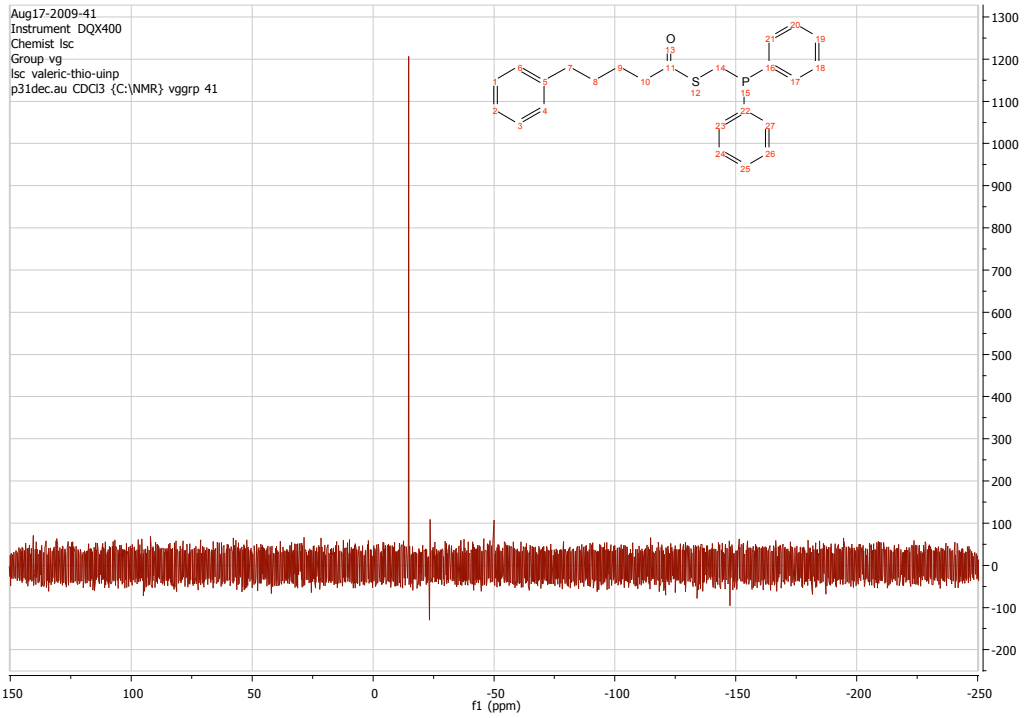
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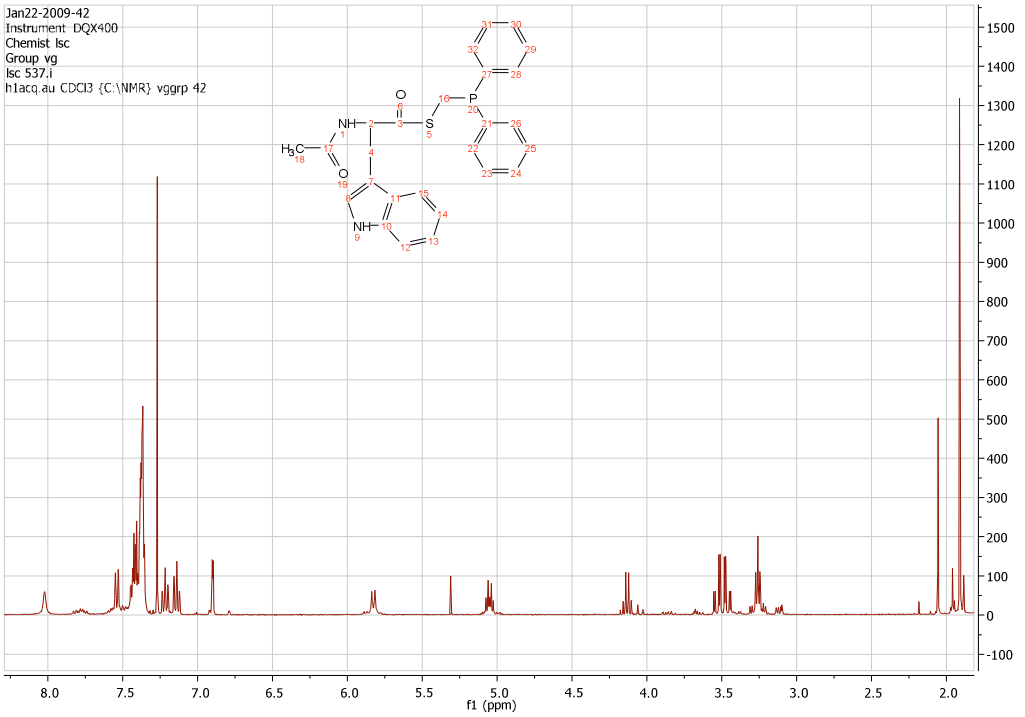
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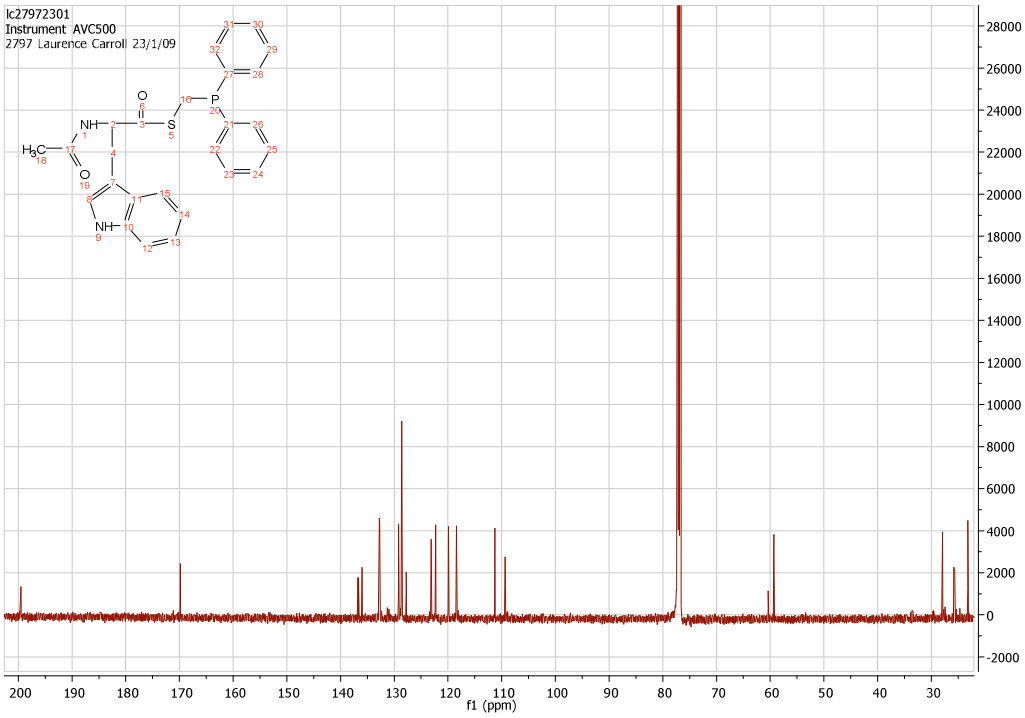
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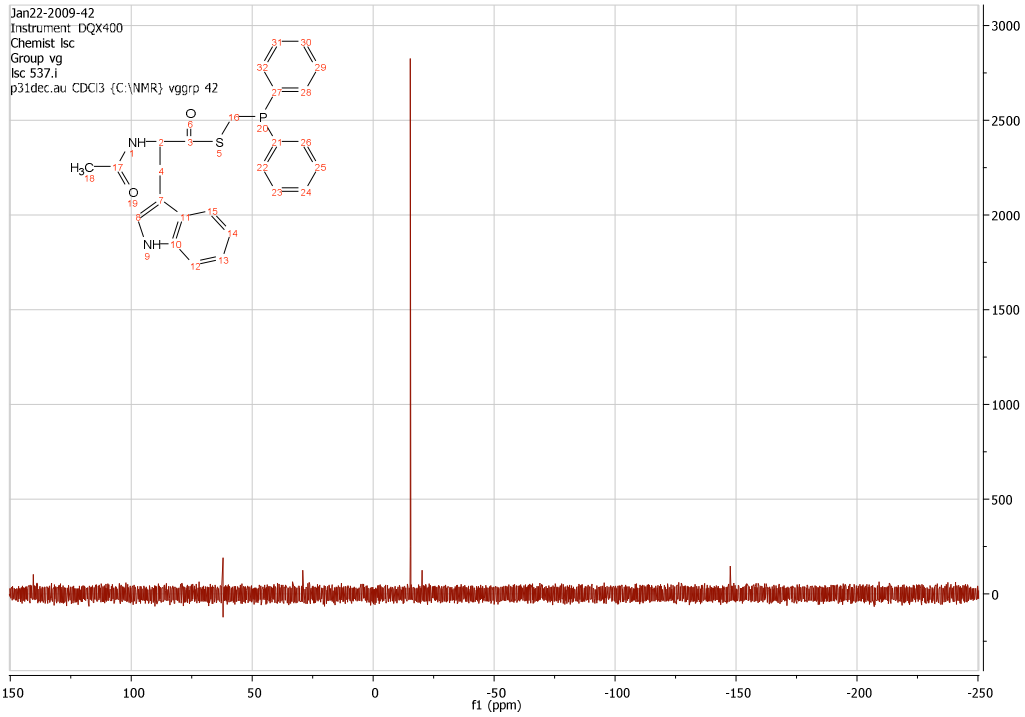
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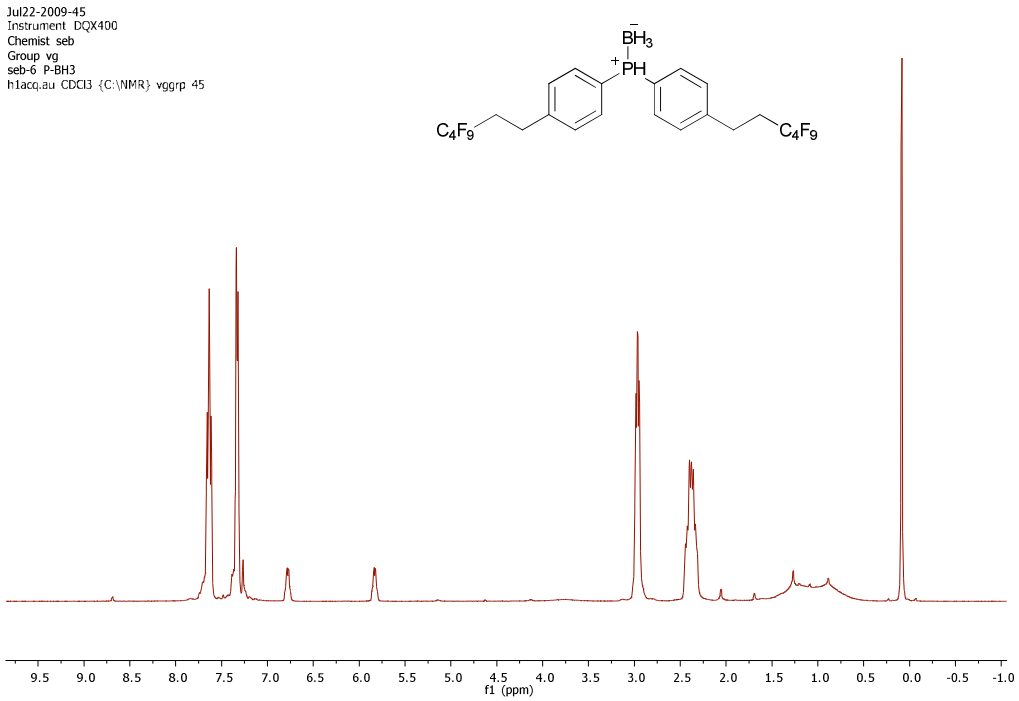
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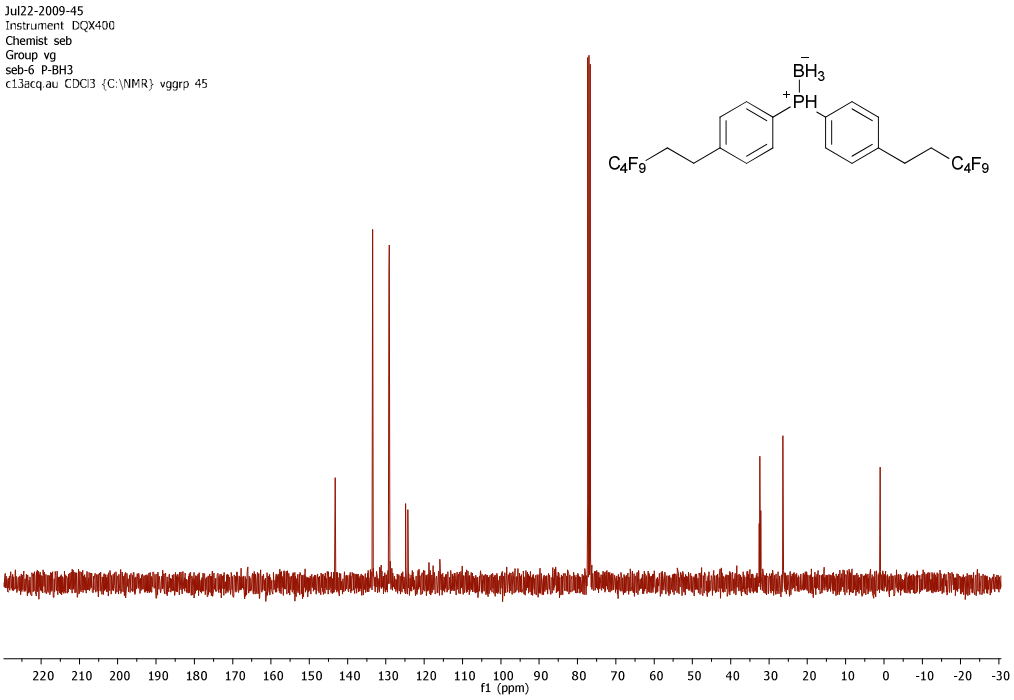
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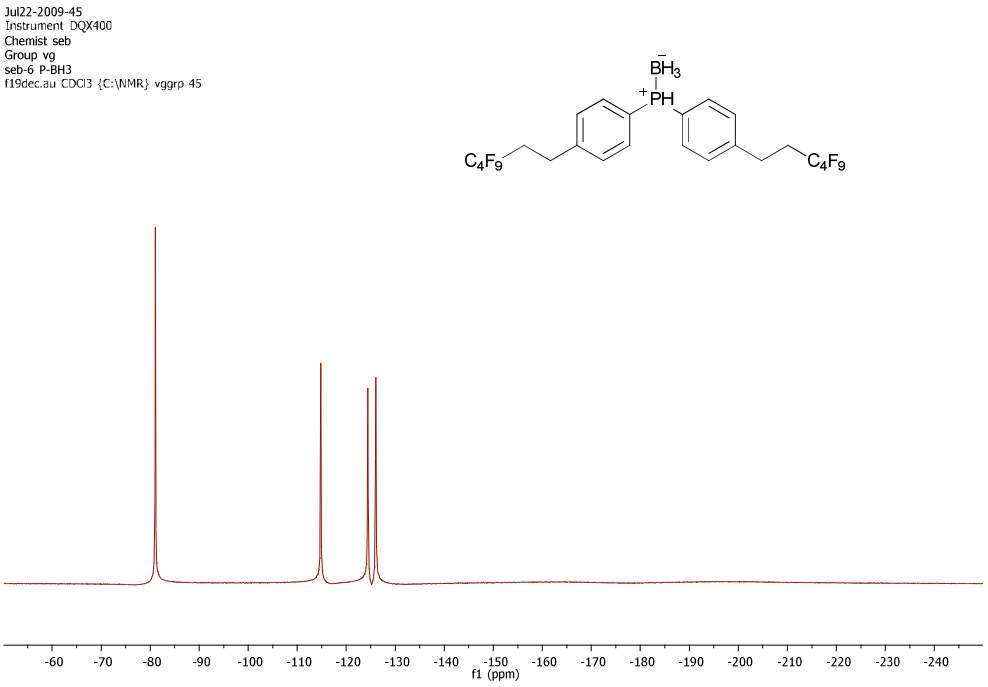
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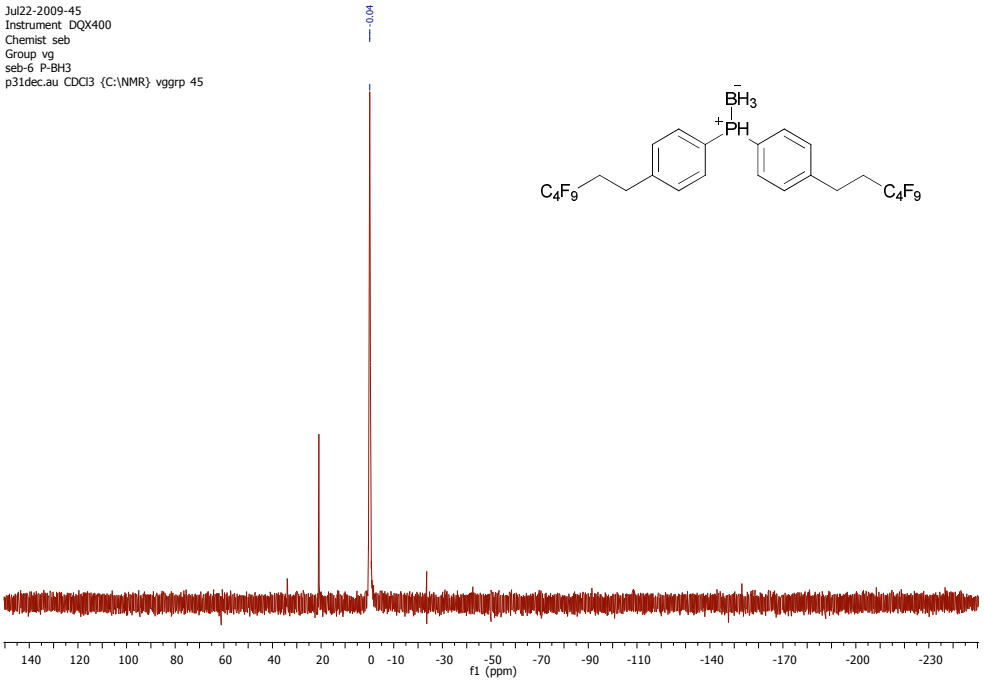
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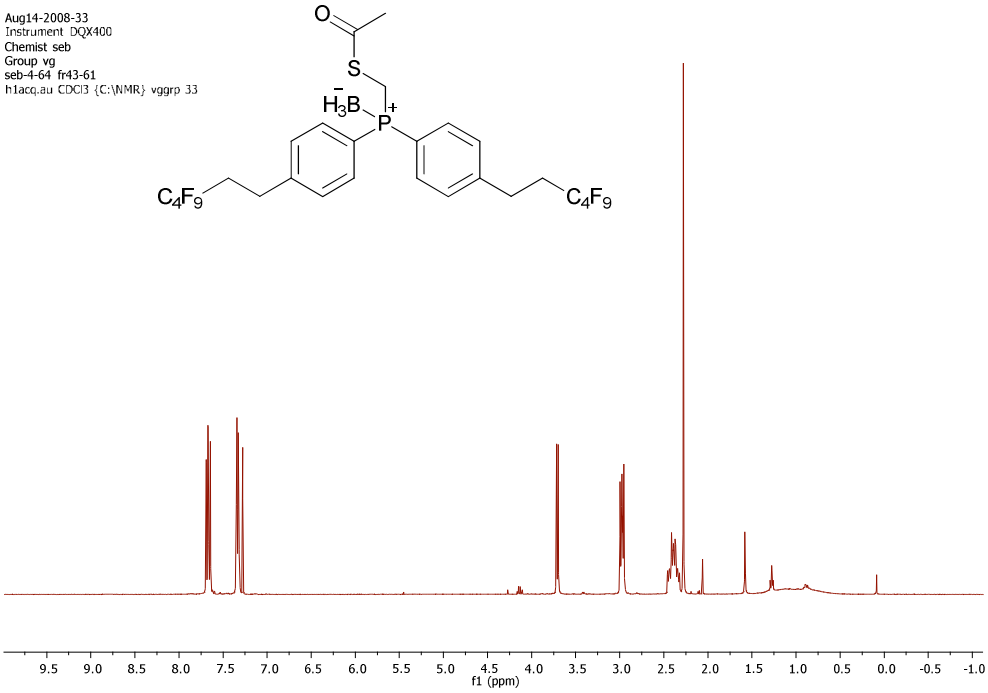
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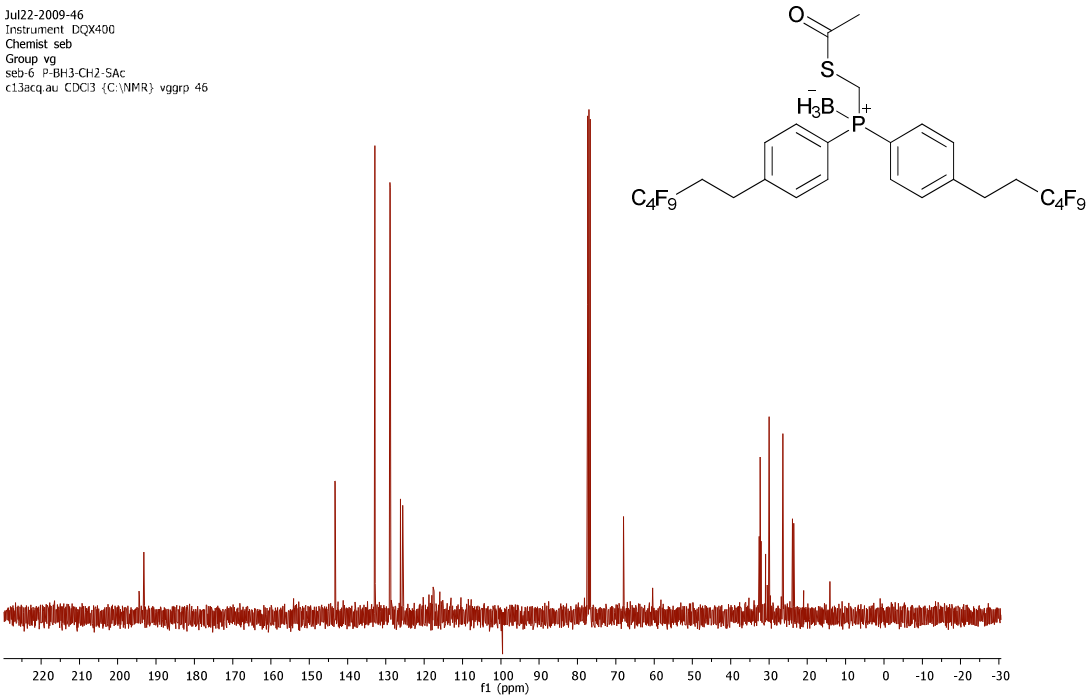
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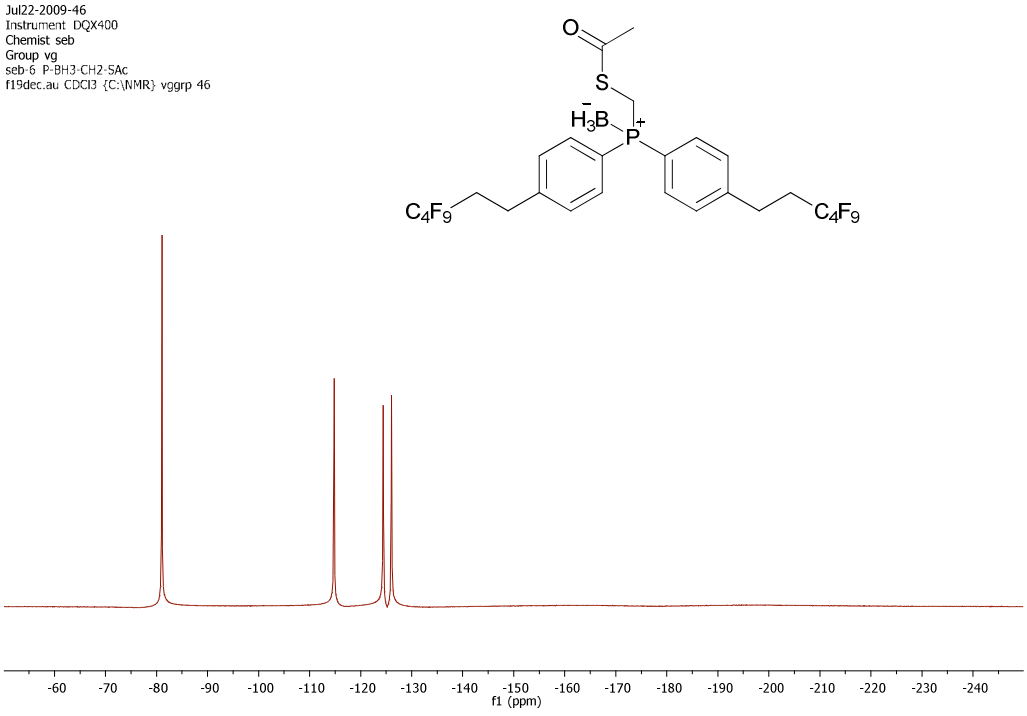
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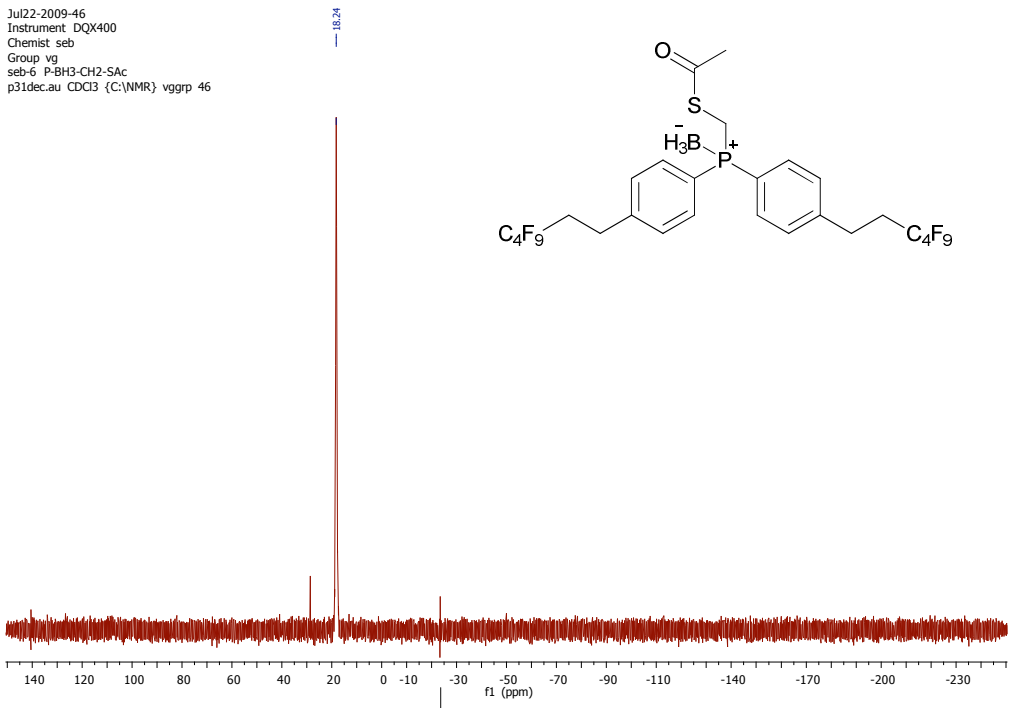
f1 (ppm)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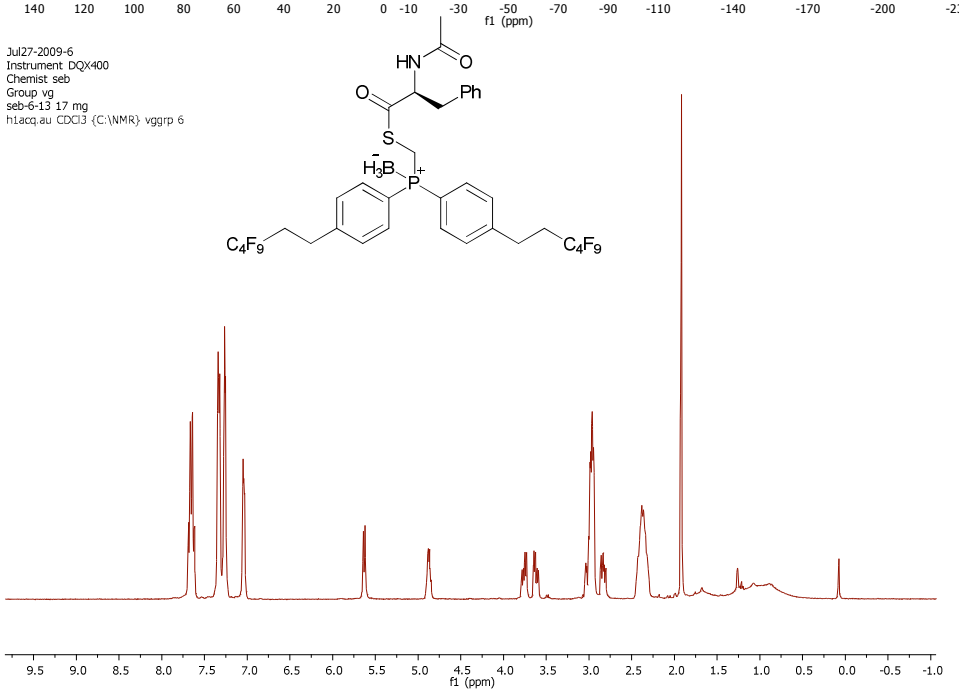
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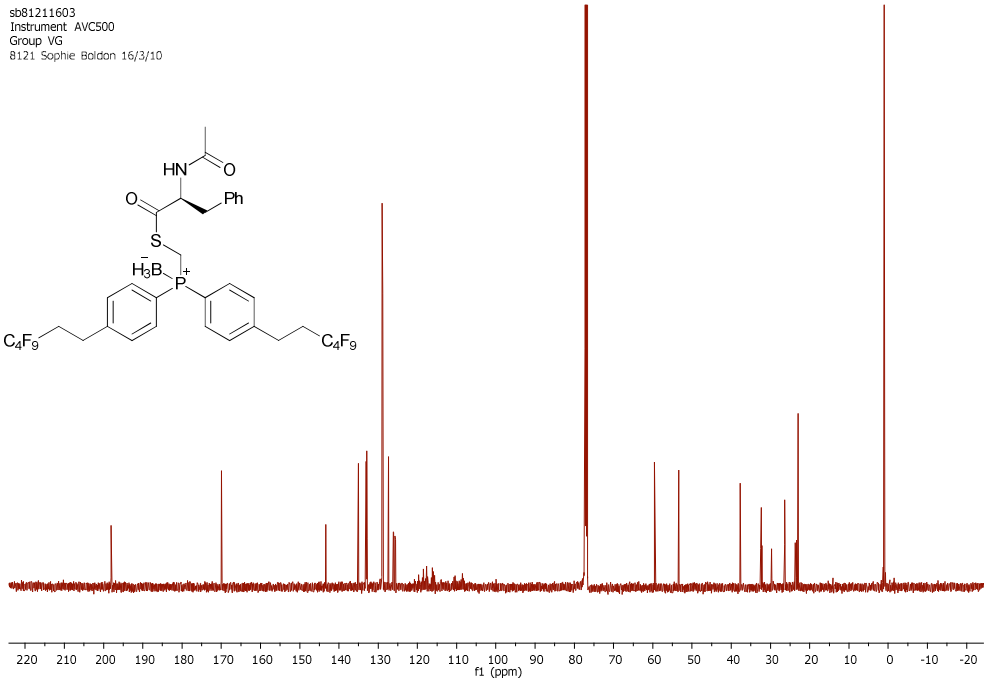
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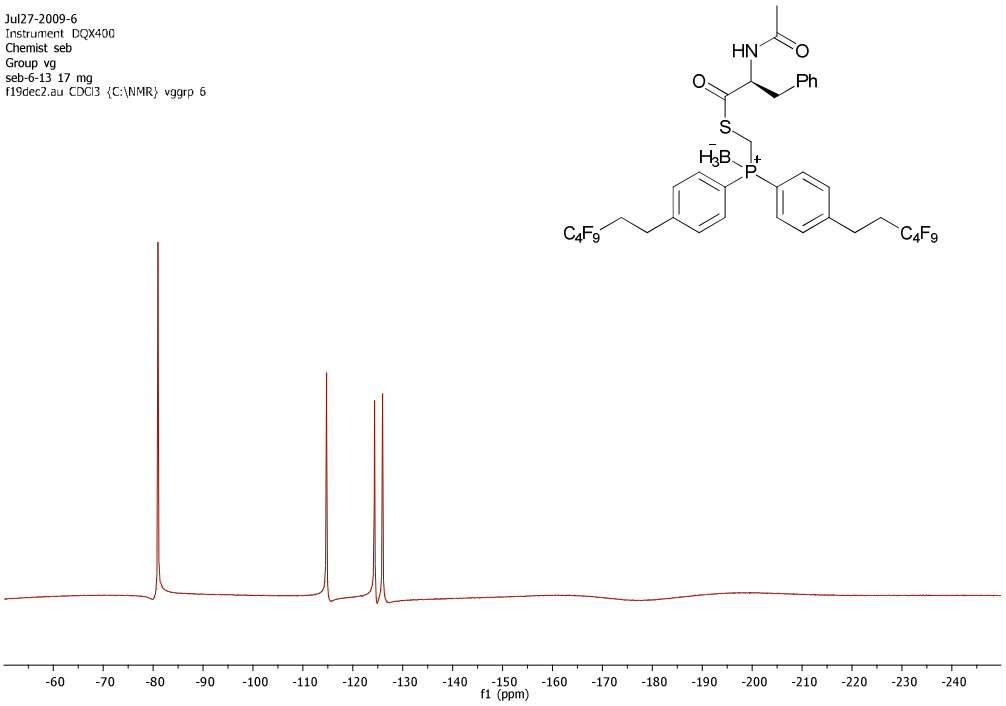
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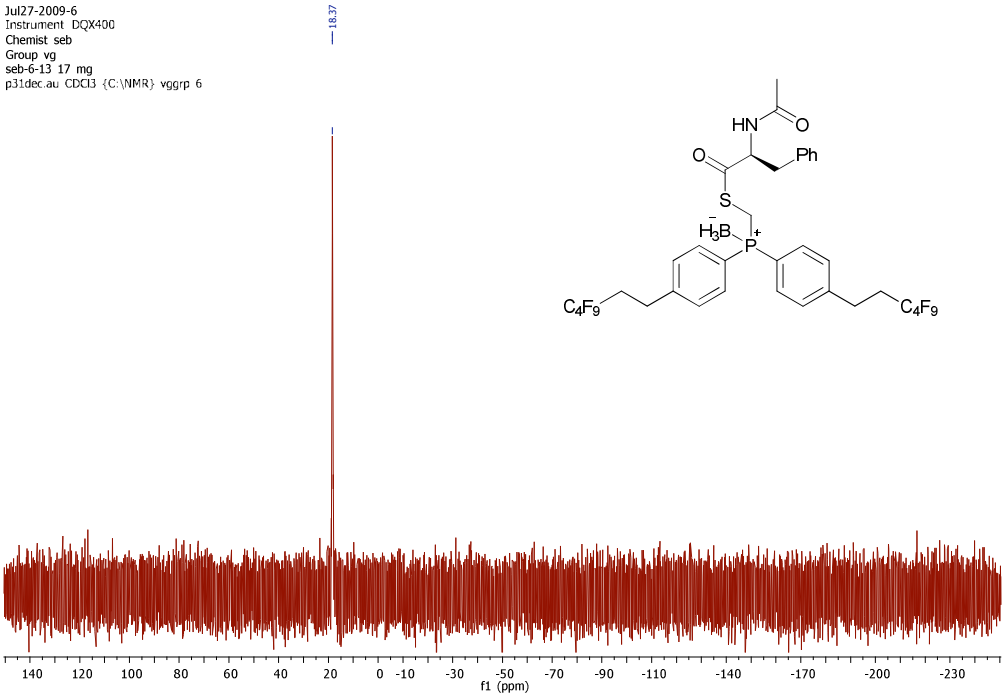
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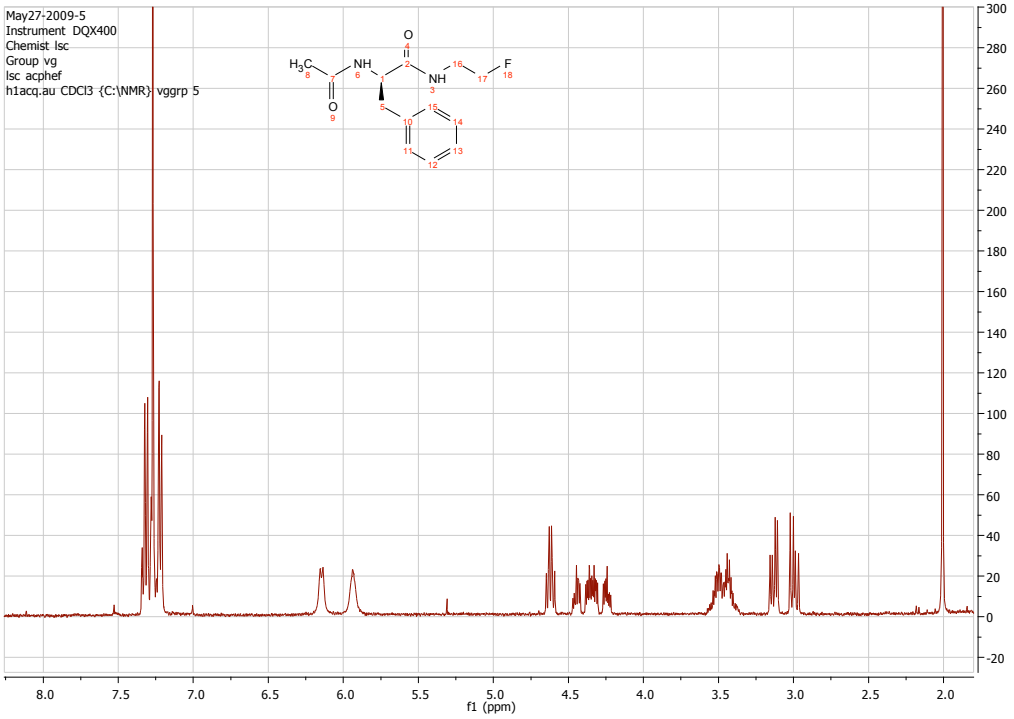
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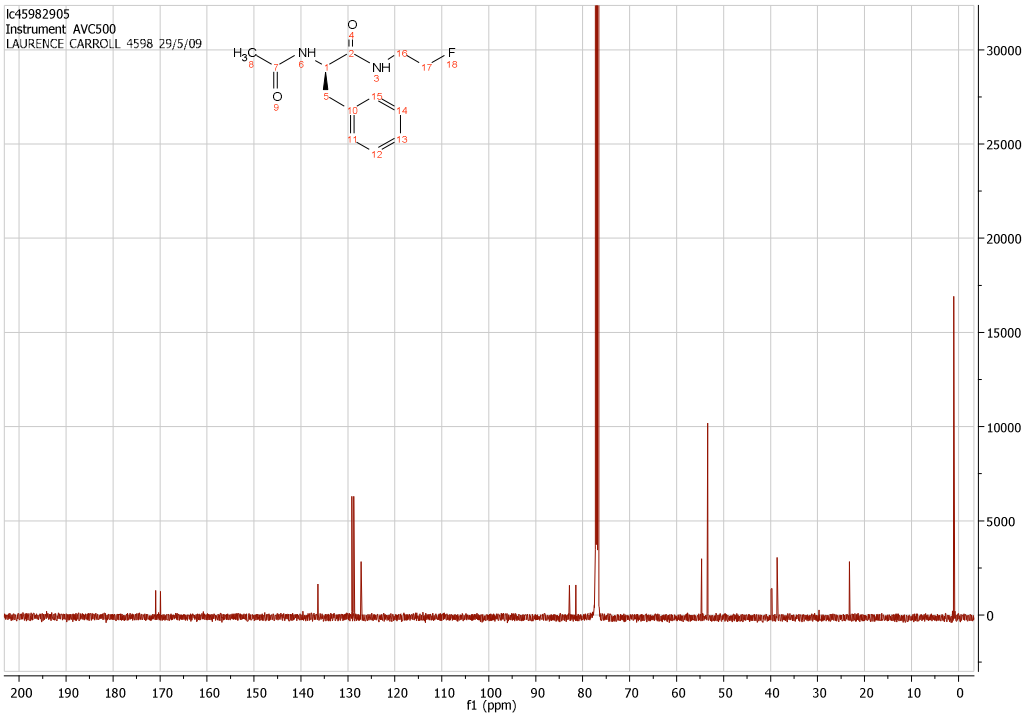
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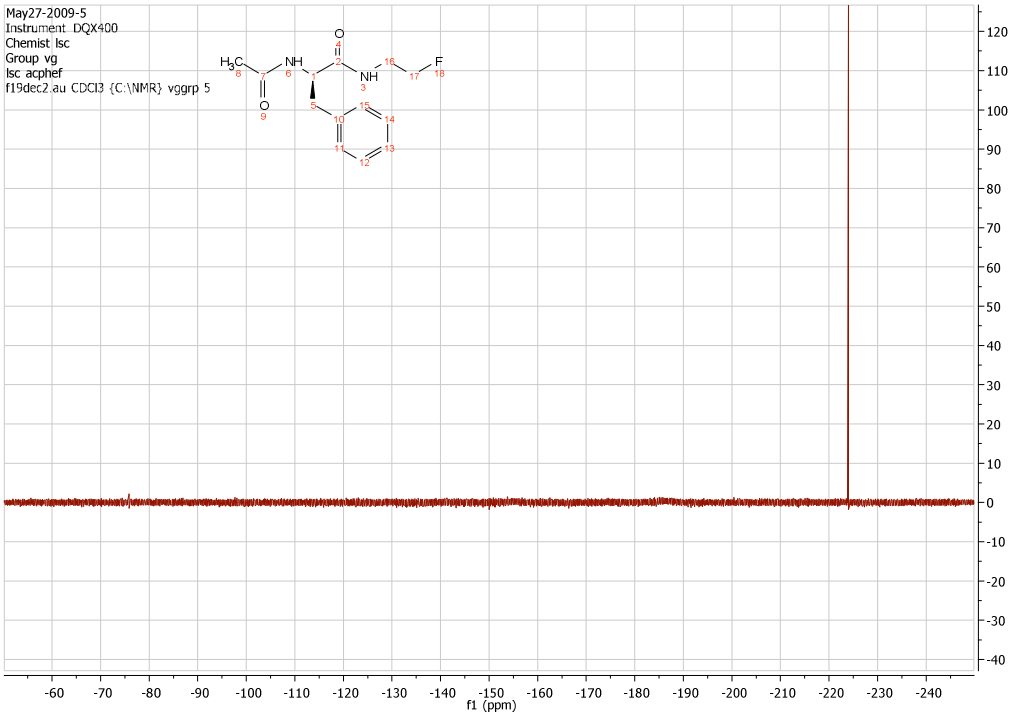
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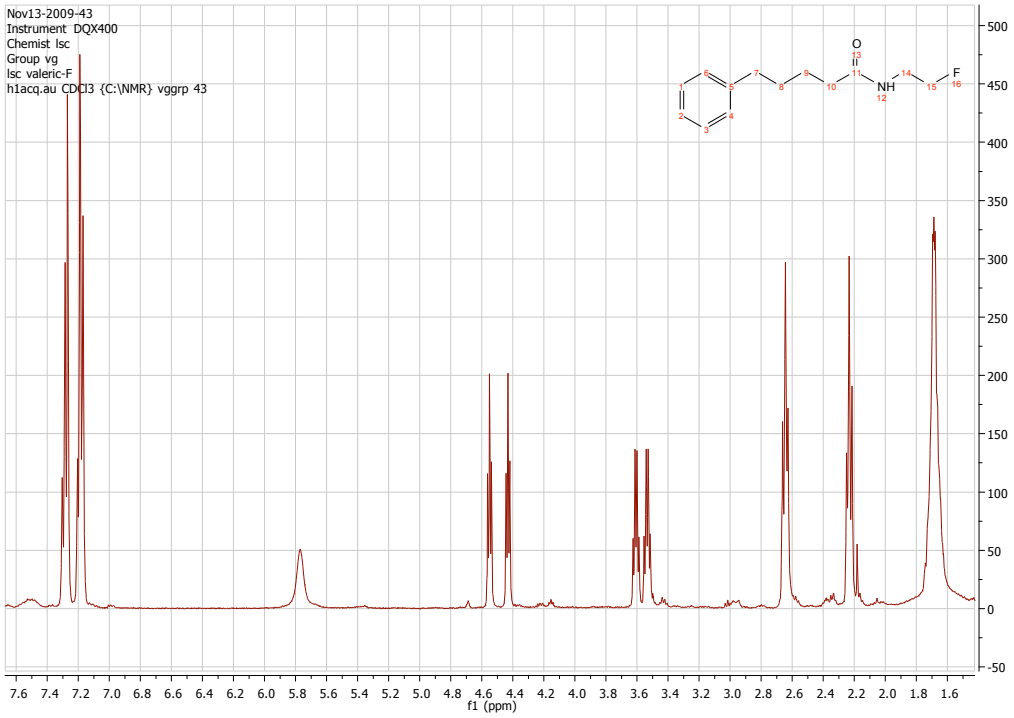
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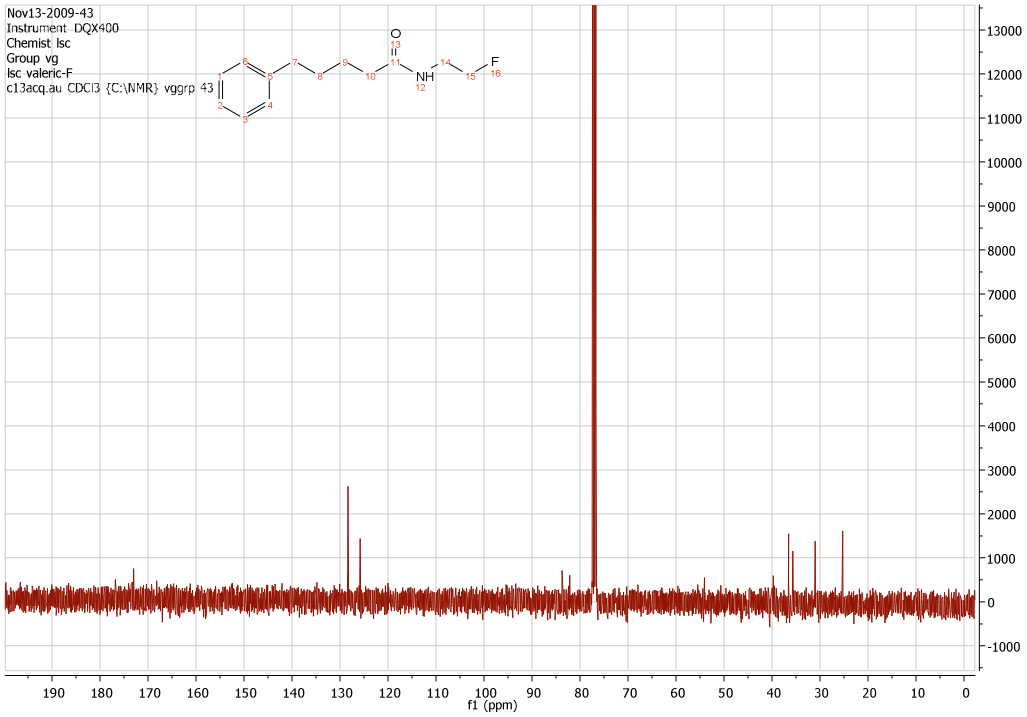
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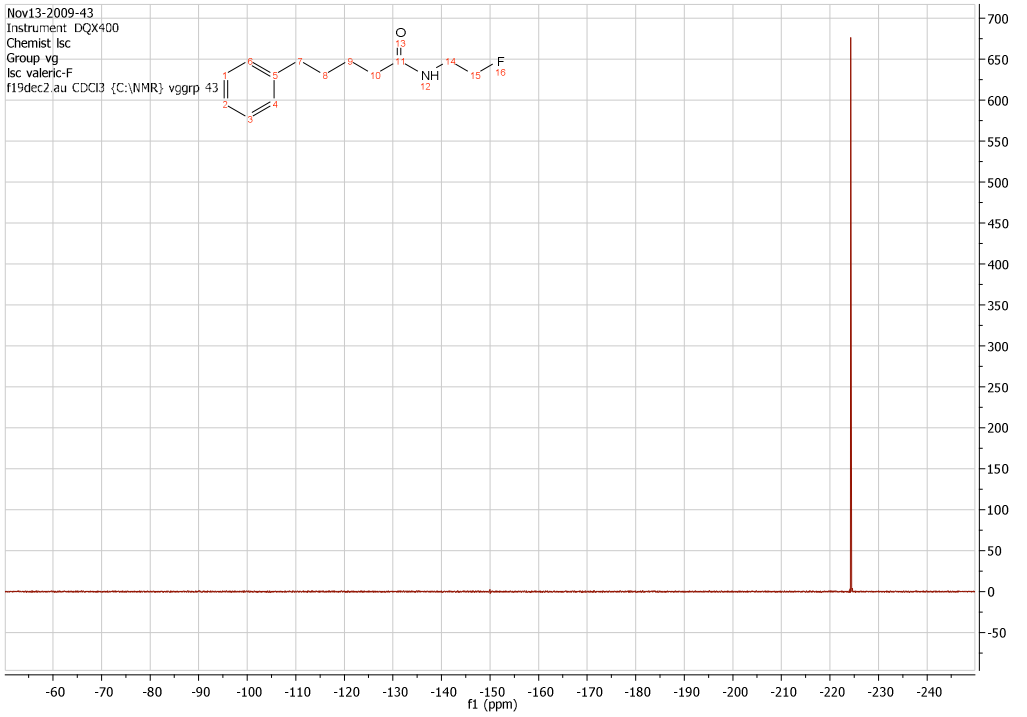
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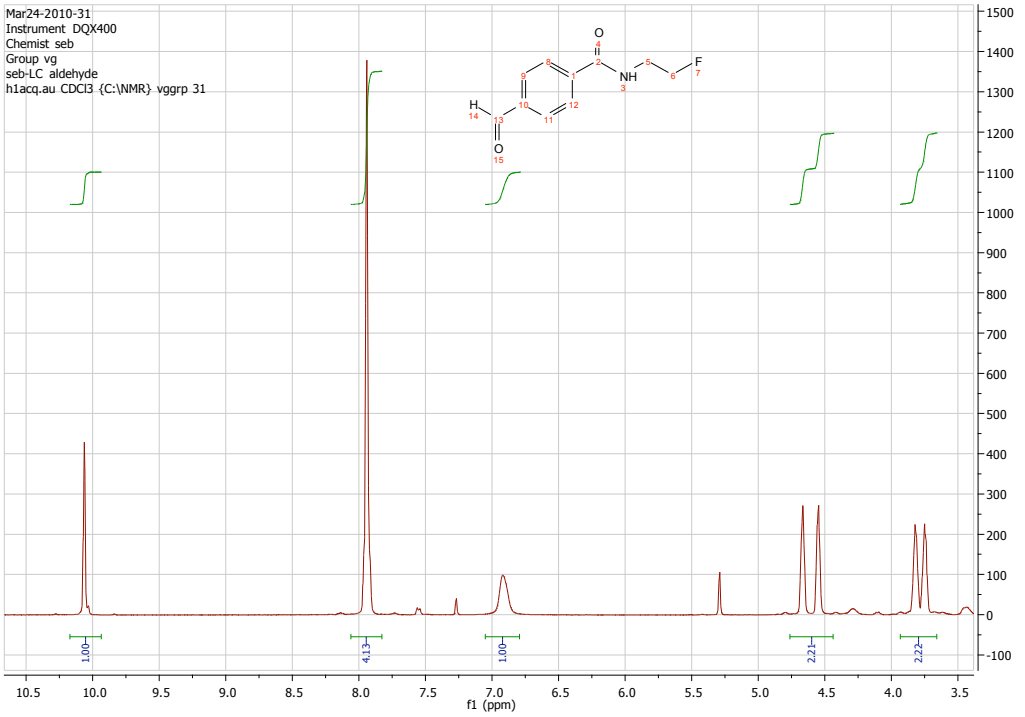
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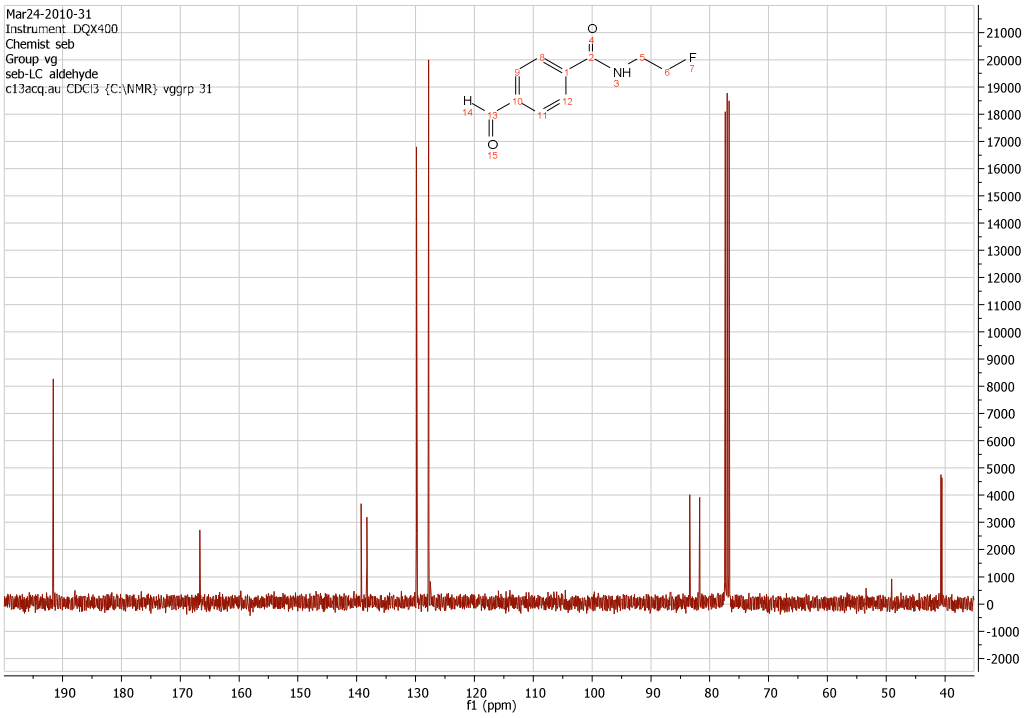
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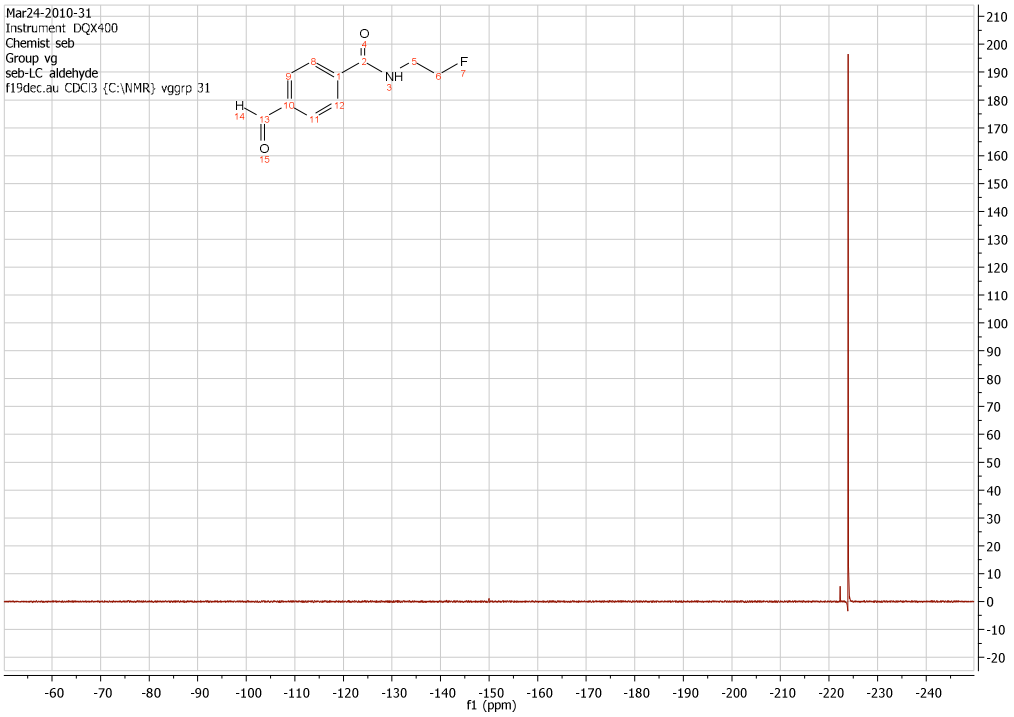
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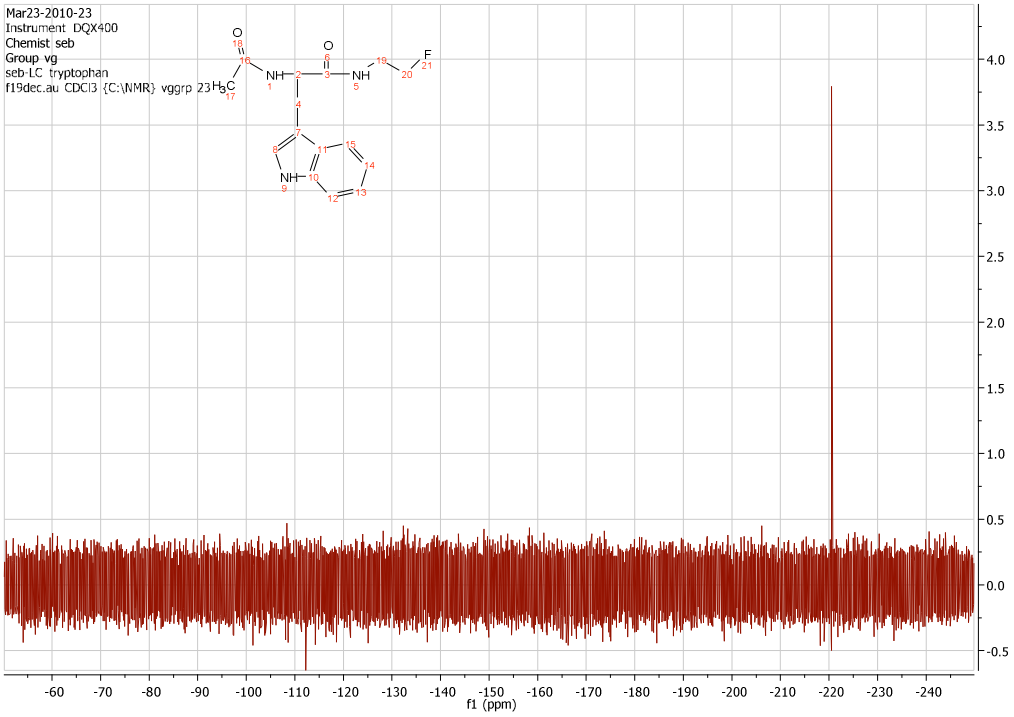
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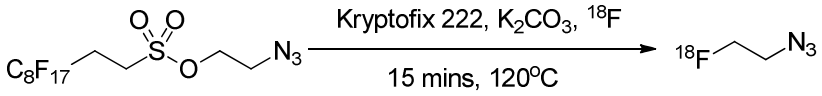
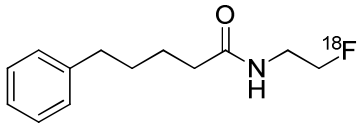
Radiochemical Procedures



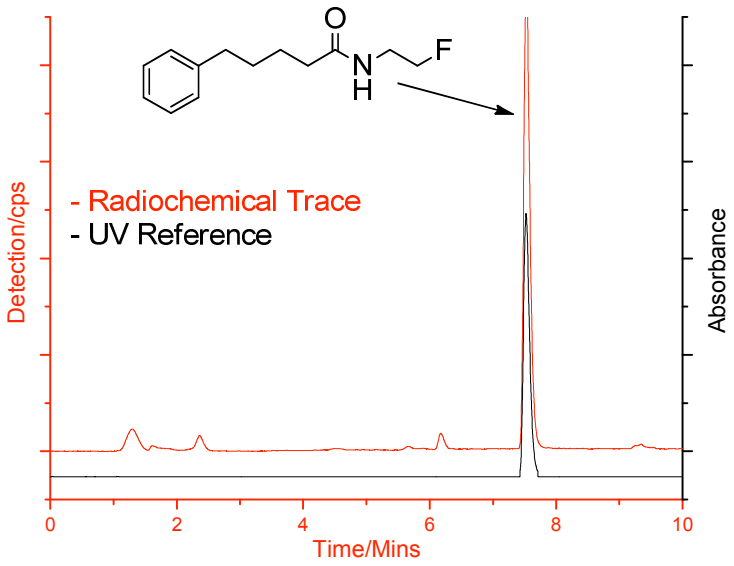
In a sealed reaction vial, 0.3 mL of $K^{18}F$/Kryptofix 222 in anhydrous MeCN (20-100 MBq) was added to 2-azidoethyl 1*H*,1*H*,2*H*,2*H*-perfluorodecane-1-sulfonate (10 mg) and heated for 15 minutes at 120°C. Determination of the radiochemical yield was by a further reaction. An aliquot (10 μL) of the crude reaction mixture was combined with *N*-propargylbenzamide (5 mg), $CuSO_{4(aq)}$ (50 μL) and sodium ascorbate$_{(aq)}$ (50 μL) and heated for 15 minutes at 80°C. Analysis by HPLC (Zorbax SB, C18, 250 x 4.6 mm, MeCN/H_2O gradient, 1 mL/min) gave a retention time of 6.70 minutes. Comparison with the cold reference HPLC trace confirmed the product to be successfully labelled [^{18}F]*N*-benzyl-3-[1-(2-fluoroethyl)-1H-[1,2,3]triazol-4-yl]propionamide. Analysis by radio-TLC (acetonitrile:water 95:5) indicated an 84 % RCY.[3] Purification was carried out by FSPE as described in the General Procedures.[4]

General Procedure for ^{18}F-Labelled Staudinger Ligation Reactions

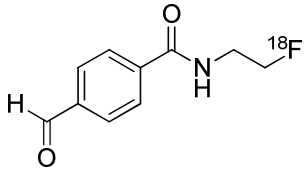
In a sealed reaction vial, the FSPE purified solution of 2-[^{18}F]Fluoroethylazide (20-100 MBq) in MeCN/H_2O (7:3, 0.5 mL) was mixed with a thiophosphane (1 mg) in either 300 μL THF:H_2O (4:1) or 300 μL DMF:H_2O (6:1) and heated for 15 minutes at 120 ^{o}C. Analysis by reverse-phase HPLC gave a retention times that correlated to the cold reference compounds, with > 95 % conversion from [^{18}F]2-fluoroethylazide to the product in each case.



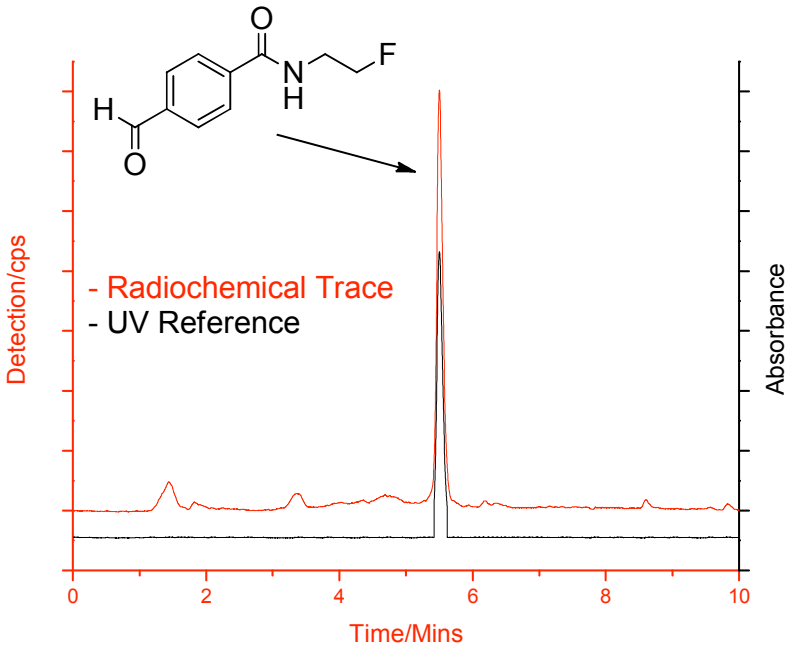
Retention Time – 7.7 minutes (Phenomenex NX 5u C18 column (150×4.60 mm) at room temperature using a gradient of acetonitrile/water (1mL/min) as the mobile phase.



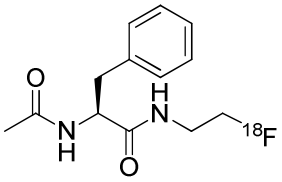
Trace 1. Radiochemical HPLC trace of [^{18}F]**6a** (red) with UV reference sample (black).



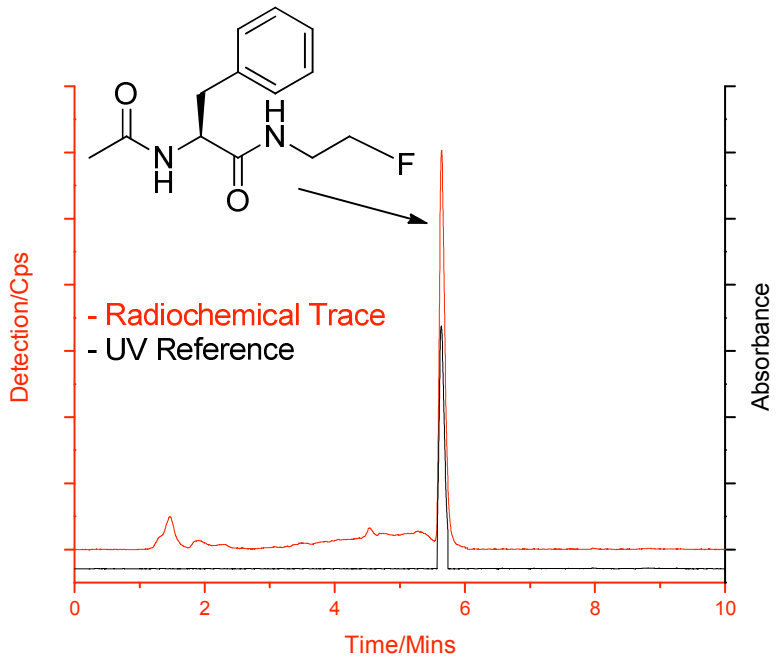
Retention Time – 5.5 minutes (Phenomenex NX 5u C18 column (150×4.60 mm) at room temperature using a gradient of acetonitrile/water (1mL/min) as the mobile phase.



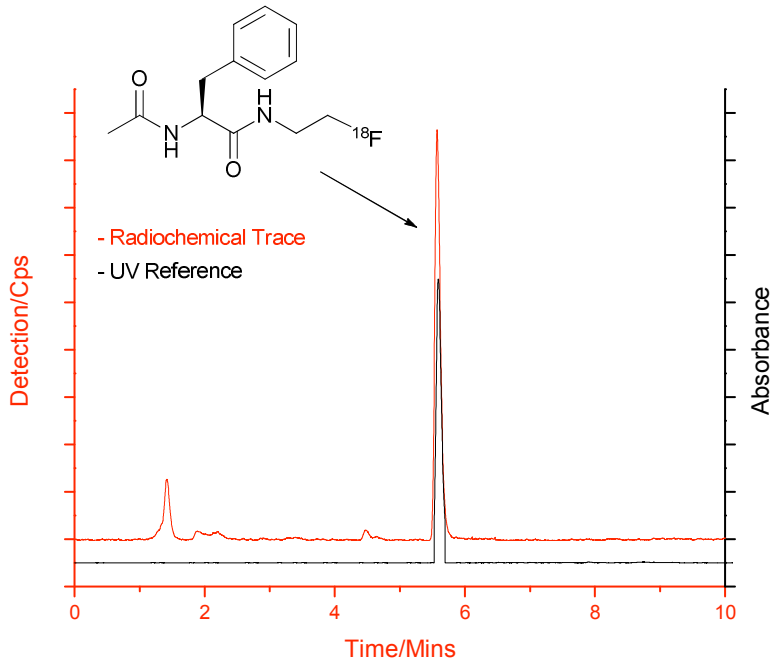
Trace 2. Radiochemical HPLC trace of [^{18}F]**6b** (red) with UV reference sample (black).



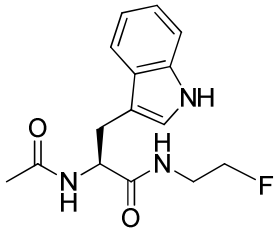
Retention Time - 5.7 minutes (Phenomenex NX 5u C18 column (150×4.60 mm) at room temperature using a gradient of acetonitrile/water (1mL/min) as the mobile phase.



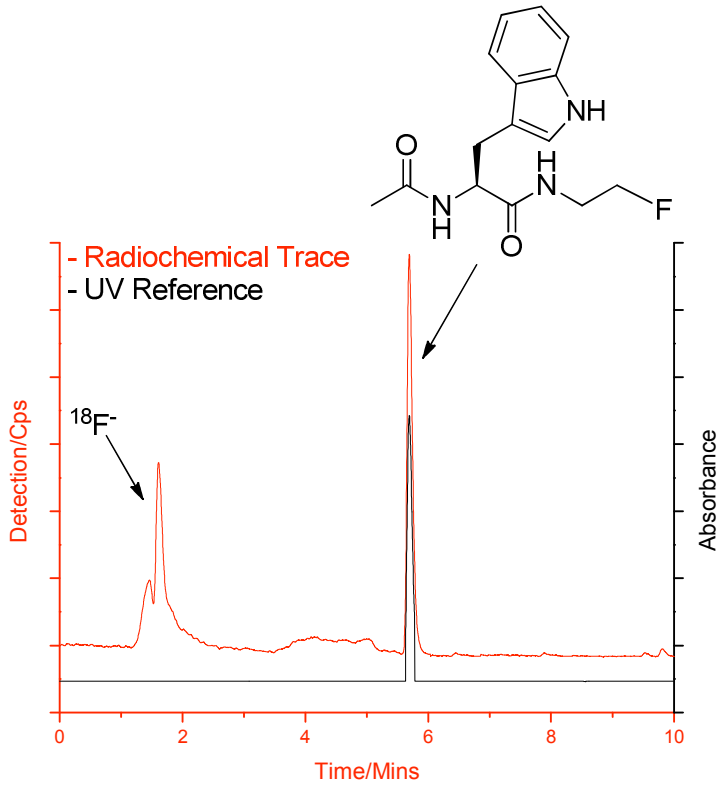
Trace 3. Radiochemical HPLC trace of [^{18}F]**6c** (red) from precursor **5c** with UV reference sample (black).



Trace 4. Radiochemical HPLC trace of [^{18}F]**6c** (red) from precursor **7** with UV reference sample (black).



Retention Time - 5.6 minutes (Phenomenex NX 5u C18 column (150×4.60 mm) at room temperature using a gradient of acetonitrile/water (1mL/min) as the mobile phase.



Trace 4. Radiochemical HPLC trace of [^{18}F]**6d** (red) with UV reference sample (black).

References

(1) Nilsson, B. L.; Kiessling, L. L.; Raines, R. T. *Organic Letters* 2001, *3*, 9-12.

(2) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *The Journal of Organic Chemistry* 2003, *68*, 6639-6645.

(3) Glaser, M.; Arstad, E. *Bioconjugate Chem.* 2007, *18*, 989-993.

(4) Bejot R.; Fowler T.; Carroll L.; Boldon S.; Moore J. E.; Declerck J.; V., G. *Angewandte Chemie International Edition* 2009, *48*, 586-589.

The Traceless Staudinger Ligation for Indirect ^{18}F-Radiolabelling

Laurence Carroll,[a] Sophie Boldon,[a] Romain Bejot,[a] Jane E. Moore,[b] Jérôme Declerck,[c] and Véronique Gouverneur*[a]

The Staudinger ligation of phosphine-substituted thioesters with 18F-fluoroethylazide has been successfully applied to access 18F-labelled molecules in radiochemical yields superior to 95 %; the first fluorous variant of a Staudinger radio-ligation has been validated.