Electronic Supplementary Material (ESI) for ChemComm.

Highly Hindered 2-(Aryl-di-*tert*-Butylsilyl)-*N*-Methyl-Imidazoles: A New Tool for the Aqueous ^{19}F - and ^{18}F-Fluorination of Biomolecules-Based Structures.

Marion Tisseraud,[a] Jürgen Schulz,[b] Delphine Vimont,[b] Murielle Berlande,[a] Philippe Fernandez,[b] Philippe Hermange*,[a] and Eric Fouquet*,[a]

[a]*Univ. Bordeaux, Institut des Sciences Moléculaires, UMR-CNRS 5255, 351 Cours de la Libération, 33405 Talence Cedex, France.*

[b]*Department Institut des Neurosciences Cognitives et Intégratives d'Aquitaine, UMR-CNRS 5287, 146 Rue Léo Saignat, 33076 Bordeaux Cedex, France*

philippe.hermange@u-bordeaux.fr, eric.fouquet@u-bordeaux.fr

Electronic Supplementary Information

Table of Contents

A) General methods

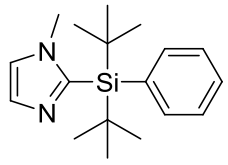
All commercial materials were used without further purification, unless indicated. ^{1}H NMR and ^{13}C NMR were recorded on BRUKER AVANCE I 300 Mhz (^{1}H: 300MHz, ^{13}C: 75.3MHz), BRUKER AVANCE II 400 Mhz (^{1}H: 400MHz, ^{13}C: 100.2 MHz) or BRUKER AVANCE III 600 Mhz (^{1}H: 600MHz, ^{13}C: 150.3 MHz) spectrometers. The chemical shifts for the NMR spectra are reported in ppm relative to the solvent residual peak[1]. Coupling constants J are reported in hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; st, sextet; m, multiplet; br, broad; dd, doublet of doublet. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC), unless specified in the text. Analytical TLC was performed on Fluka Silica Gel 60 F254. Analytical HPLC were performed on a Dionex Ultimate 3000 UHPLC with a diode array detector and analysed using the Chromeleon 7 software. Preparative HPLC were performed on a JASCO AS-1555 HPLC with a Jasco UV-2075 Plus detector. High resolution mass spectra were performed by the CESAMO (Talence, France) and were recorded on Qq-TOF tandem mass spectrometer (API Q-STAR Pulsari, Applied Biosystems). Experiments under microwave irradiation were performed using a Biotage Initiator 2.5.

[1] Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw,J. E.; Goldberg, K. I. *Organometallics* **2010**, 29, 2176

B) Organic syntheses

a) Synthesis of 2-(aryl-di-tert-butylsilyl)-N-methyl-imidazole tags

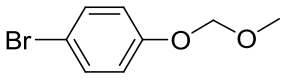
2-(di-*tert*-butyl(phenyl)silyl)-1-methyl-1*H*-imidazole 2a



2a

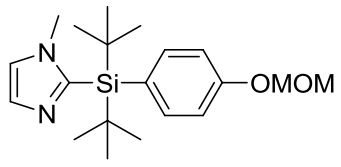
Under nitrogen, 1-methylimidazole (0.75 mmol, 61.6 mg) was dissolved in 1.75 mL of dry THF, and a *n*-butyllithium solution (1.6M in hexane, 0.825 mmol, 1.1 eq., 0.51 mL) was added at -80°C. After stirring at -80°C for 10 min, di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.125 mmol, 1.5 eq., 496 mg) and a phenyllithium solution (1.9M in dibutyl ether, 1.5 mmol, 2 eq., 0.8 mL) were successively added dropwise. The reaction was allowed to warm to room temperature and stirred for 16h at rt. The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on a silica gel (cyclohexane/EtOAc: 90/10; Rf = 0.5) to give **2a** (188.5 mg, 84%) as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.63-7.60 (m, 2H), 7.40-7.34 (m, 3H), 7.32 (s, 1H), 7.00 (s, 1H), 3.40 (s, 3H), 1.16 (s, 18H) ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 148.2, 136.3 (2C), 135.1, 130.5, 129.3, 127.7 (2C), 123.3, 36.8, 29.4 (6C), 20.7 (2C). ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) -5.90. HRMS (ESI/TOF$^+$) $C_{18}H_{29}N_2Si$ $[M+H]^+$ calculated 301.2094, found 301.2104. MP (°C): 76-77.

1-bromo-4-(methoxymethoxy)benzene



Under nitrogen, 4-bromophenol (10 mmol, 1.73g) was dissolved in 10 mL of dry dichloromethane. Chloromethyl methyl ether (11 mmol, 1.1 eq., 0.88 mg, 0.84 mL) and *N*, *N*-diisopropylethylamine (11 mmol, 1.1 eq., 1.42 g, 1.92 mL) were added at 0°C. Then, the mixture was stirred at room temperature for 48h. The reaction was quenched with an aqueous saturated solution of ammonium chloride (10 mL). The aqueous layer was extracted three times with dichloromethane (3x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on a silica gel (cyclohexane/dichloromethane: 80/20 ; Rf = 0.3) to give 1-bromo-4-(methoxymethoxy)benzene (1.85 g, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38 (d, 2H, *J* = 9.0 Hz), 6.93 (d, 2H, *J* = 9.0 Hz), 5.14 (s, 2H), 3.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.4, 132.3 (2C), 118.2 (2C), 114.3, 94.5, 56.26. HRMS (EI$^+$) $C_8H_9BrO_2$ $[M]^+$ calculated 215.9786, found 215.9785.

2-(di-*tert*-butyl(4-(methoxymethoxy)phenyl)silyl)-1-methyl-1*H*-imidazole 2b

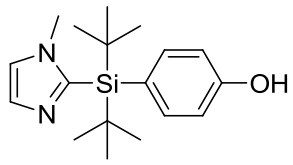


2b

Under nitrogen, 1-methylimidazole (0.75 mmol, 61.6 mg) was dissolved in 1.75 mL of dry THF, and a *n*-butyllithium solution (1.6M in hexane, 0.825 mmol, 1.1eq., 0.51 mL) was added at -80°C. After stirring at -80°C for 10 min, di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.125 mmol, 1.5 eq., 496 mg), 1-bromo-4-(methoxymethoxy)benzene (1.5 mmol, 2 eq., 326 mg) and a *n*-butyllithium solution (1.6M in hexane, 1.65 mmol, 2.2 eq., 1.03 mL) were successively added dropwise. The reaction was allowed to warm to room temperature and stirred for 16h at rt. The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on a silica gel (cyclohexane/EtOAc: 90/10; Rf = 0.3) to give **2b** (81.4 mg, 70%) as a brown powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.54 (d, 2H, *J* = 8.6 Hz), 7.31 (s, 1H), 7.03 (d,

2H, *J* = 8.6 Hz), 6.99 (s, 1H), 5.20 (s, 2H), 3.50 (s, 3H), 3.42 (s, 3H), 1.15 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.4, 148.4, 137.7 (2C), 130.5, 127.1, 123.2, 115.5 (2C), 94.3, 56.3, 36.7, 29.4 (6C), 20.7(2C). ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) -6.81. HRMS (ESI/TOF$^+$) $C_{20}H_{32}N_2O_2Si$ $[M+H]^+$ calculated 361.2305, found 361.2308. MP (°C): 100-101.

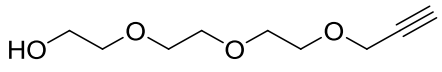
4-((1-methyl-1*H*-imidazol-2-yl)-di-*tert*-butylsilyl) phenol 2c



2c

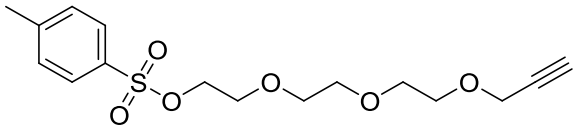
2b (0.6 mmol, 205.8 mg) was dissolved in 12 mL of methanol and 6 mL of an aqueous solution of sulfuric acid (6.2M) was added. The mixture was stirred at 50°C for 24h. The reaction was quenched with an aqueous solution of sodium bicarbonate, and extracted with dichloromethane (2x 10 mL). The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/EtOAc: 70/30; Rf = 0.3) to give **2c** (171 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, MeOD) δ (ppm) 7.44 (d, 2H, *J* = 8.6 Hz), 7.2 (d, 1H, *J* = 1.1 Hz), 7.18 (d, 1H, *J* = 1.1 Hz), 6.85 (d, 2H, *J* = 8.6 Hz), 3.43 (s, 3H), 1.13 (s, 18H). ^{13}C NMR (75 MHz, MeOD) δ (ppm) 159.8, 149.3, 138.7 (2C), 130.7, 124.9, 124.4, 116.1 (2C), 37.4, 29.8 (6C), 21.4(2C). ^{29}Si NMR (59 MHz, MeOD) (δ ppm) -6.53. HRMS (ESI/TOF$^+$) $C_{18}H_{28}N_2OSi$ $[M+H]^+$ calculated 317.2043, found 317.2053. MP (°C): 98-99.

2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethanol



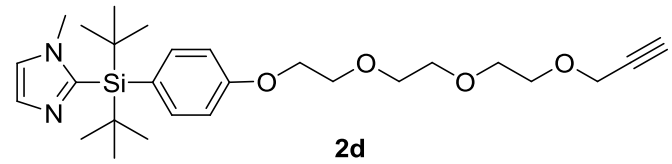
Under nitrogen, triethylene glycol (10 mmol, 1.50 g, 1.34 mL) was added to a solution of potassium *tert*-butoxide (5 mmol, 0.5 eq., 561 mg) in 40 mL of dry THF and the mixture was stirred for 30 min at rt. Propargyl bromide (5 mmol, 0.5 eq., 594.8 mg, 445.5 µL) was added and the mixture was stirred at room temperature for 24h. The reaction mixture was filtered on celite and washed with ethyl acetate (2x 10 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (EtOAc: 100%; Rf = 0.5) to give 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethanol (775 mg, 41 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.18 (d, 2H, *J* = 2.4 Hz), 3.72-3.57 (m, 12H), 2.42 (t, 1H, *J* = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 79.6, 74.7, 72.6, 70.7, 70.4, 70.4, 69.2, 61.8, 58.5.

2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate



Under argon, triethylamine (12.5 mmol, 2.5 eq., 1.74 mL) was added to a solution of 2-(2-(2-(prop-2-ynyloxy) ethoxy) ethoxy)ethanol (5 mmol, 0.94 g) and trimethylamine hydrochloride (0.5 mmol, 0.1 eq., 47.8 mg) in 6 mL of dry acetonitrile at rt. Then, a solution of *p*-toluenesulfonyl chloride (10 mmol, 2 eq., 1.90 g) in dry acetonitrile (6 mL) was added to the mixture at 0°C and stirred at room temperature for 24h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (Cyclohexane/EtOAc: 70/30; Rf = 0.4) to give 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80 (d, 2H, *J* = 8.2 Hz), 7.34 (d, 2H, *J* = 8.2 Hz), 4.19 (d, 2H, *J* = 2.3 Hz), 4.17-4.14 (m, 2H), 3.70-3.59 (m, 10H), 2.44 (s, 3H), 2.42 (t, 1H, *J* = 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 144.9, 133.2, 129.9 (2C), 128.1 (2C), 79.7, 74.7, 70.9, 70.7, 70.6, 69.4, 69.2, 68.8, 58.5, 21.8.

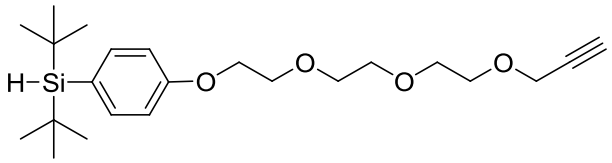
2-((4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenyl)di-*tert*-butylsilyl)-1-methyl-1*H*-imidazole 2d



2d

Compound **2c** (0.08 mmol, 27.1 mg) was dissolved in dry THF (3 mL) under argon. Then, potassium *tert*-butoxide (0.12 mmol, 1.5 eq., 13.5 mg) and a solution of 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (0.12 mmol, 1.5 eq., 41 mg) in dry THF (2 mL) were added at rt. The reaction was stirred at room temperature for 24h and a saturated aqueous solution of $NaHCO_3$ was added (10 mL). The mixture was extracted three times with ethyl acetate (3x 10 mL) and the combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane/EtOAc: 80/20; Rf = 0.3) to give **2d** (32.8 mg, 85%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.52 (d, 2H, *J* = 8.4 Hz), 7.31 (d, 1H, *J* = 1.0 Hz), 6.99 (d, 1H, *J* = 1.0 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 4.2 (d, 2H, *J* = 2.4Hz), 4.16-4.13 (m, 2H), 3.89-3.98 (m, 2H), 3.76-3.67 (m, 8H), 3.40 (s, 3H), 2.41 (t, 1H, *J* = 2.4 Hz), 1.14 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7, 148.4, 137.6 (2C), 130.4, 125.8, 123.2, 118.3, 114.0 (2C), 74.7, 70.9, 70.8, 70.6, 69.8, 69.3, 67.2, 58.5, 36.7, 29.4 (6C), 20.7 (2C). ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) -6.87. HRMS (ESI/TOF$^+$) $C_{27}H_{42}N_2O_4Si$ $[M+H]^+$ calculated 487.2986, found 487.2984.

di-*tert*-butyl(4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenyl)silane



4-(Di-*tert*-butylsilyl)phenol (3.4 mmol, 802 mg) was dissolved in dry THF (30 mL) under argon. Then, potassium *tert*-butoxide (5.1 mmol, 1.5 eq., 572.2 mg) and a solution of 2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (5.1 mmol, 1.5 eq., 1.74 g) in dry THF (15 mL) were added at rt. The reaction was stirred at room temperature for 24h and a saturated aqueous solution of $NaHCO_3$ was added (10 mL). The mixture was extracted three times with ethyl acetate (3x 10 mL) and the combined organic layers were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (cyclohexane/EtOAc: 70/30; Rf = 0.6) to give the title compound as a colorless oil. (298 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.47 (d, 2H, *J* = 8.6 Hz), 6.89 (d, 2H, *J* = 8.6 Hz), 4.19 (d, 2H, *J* = 2.4 Hz), 4.15-4.12 (m, 2H), 3.87-3.84 (m, 2H), 3.82 (s, 1H), 3.75-3.72 (m, 2H), 3.70-3.66 (m, 6H), 2.41 (t, 1H, *J* = 2.4 Hz), 1.02 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 137.2 (2C), 126.6, 114.0 (2C), 79.8, 74.6, 70.9, 70.8, 70.6, 69.9, 69.3, 67.1, 58.54, 29.1 (6C), 19.2 (2C). ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) 12.53. HRMS (ESI/TOF$^+$) $C_{23}H_{38}O_4Si$ $[M+Na]^+$ calculated 429.2431, found 429.2428.

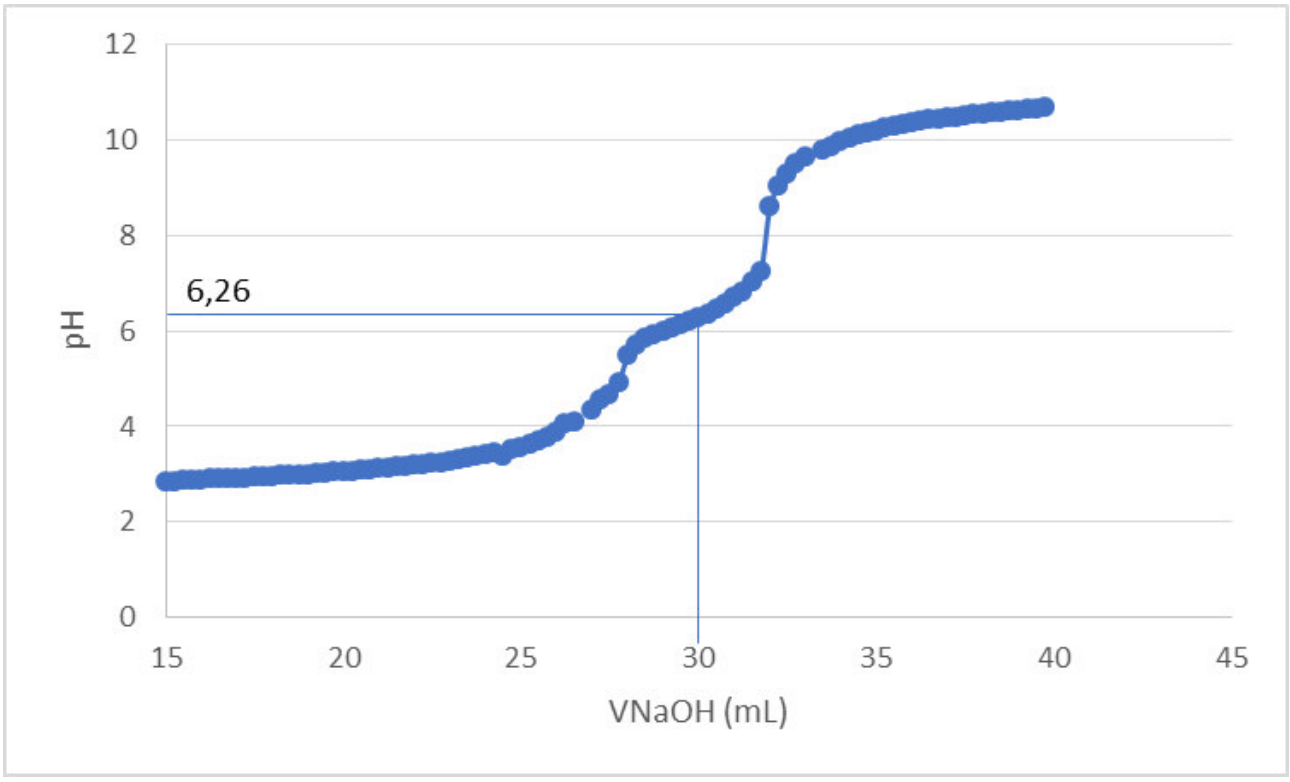
b) Determination of the pKa of ***[2b-H]$^+$/2b***

2b (0.1 mmol, 36.1 mg) and 0.4 mL of an aqueous solution of HCl (0.4 mmol, 1M) were added to 90mL of water. Then, the resulting solution was titrated with an aqueous solution of NaOH (0.02M) and after each addition, the pH was measured by a pHmeter (H12211, Hanna Instruments) to follow the titration. The pKa of **[2b-H]$^+$/2b** (6.26) was read on the pH = f(VNaOH) plotting at the half-equivalence of **[2b-H]$^+$** + HO^- → **2b** + H_2O.

The measured pH values are summarised in the following table:

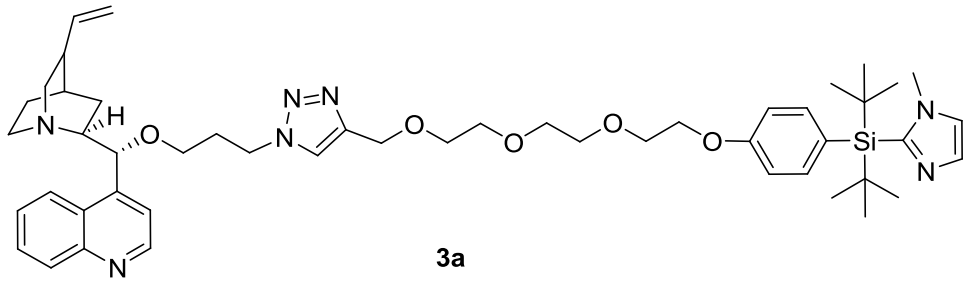
V(NaOH) mL	pH	V(NaOH) mL	pH	V(NaOH) mL	pH	V(NaOH) mL	pH	V(NaOH) mL	pH	V(NaOH) mL	pH
0	2.48	6.75	2.63	13.5	2.8	20	3.05	26.5	4.09	33.5	9.79
0.25	2.49	7	2.63	13.75	2.81	20.25	3.06	27	4.33	33.75	9.88
0.5	2.5	7.25	2.64	14	2.82	20.5	3.07	27.25	4.54	34	9.97
1	2.5	7.5	2.64	14.25	2.83	20.75	3.09	27.5	4.67	34.25	10.05
1.25	2.51	7.75	2.65	14.5	2.83	21	3.11	27.75	4.93	34.5	10.11
1.5	2.51	8	2.65	14.75	2.84	21.25	3.13	28	5.48	34.75	10.15
1.75	2.52	8.25	2.66	15	2.84	21.5	3.14	28.25	5.71	35	10.19
2	2.52	8.5	2.67	15.25	2.85	21.75	3.16	28.5	5.85	35.25	10.24
2.25	2.52	8.75	2.67	15.5	2.86	22	3.18	28.75	5.91	35.5	10.29
2.5	2.53	9	2.68	15.75	2.86	22.25	3.2	29	5.99	35.75	10.33
2.75	2.54	9.25	2.68	16	2.87	22.5	3.22	29.25	6.06	36	10.36
3	2.54	9.5	2.68	16.25	2.89	22.75	3.24	29.5	6.13	36.25	10.39
3.25	2.54	9.75	2.69	16.5	2.89	23	3.28	29.75	6.19	36.5	10.42
3.5	2.55	10	2.7	16.75	2.9	23.25	3.3	30	6.26	36.75	10.44
3.75	2.55	10.25	2.7	17	2.91	23.5	3.32	30.25	6.35	37	10.47
4	2.56	10.5	2.71	17.25	2.92	23.75	3.36	30.5	6.45	37.25	10.49
4.25	2.56	10.75	2.72	17.5	2.93	24	3.39	30.75	6.56	37.5	10.51
4.5	2.57	11	2.73	17.75	2.94	24.25	3.43	31	6.69	37.75	10.53
4.75	2.57	11.25	2.74	18	2.95	24.5	3.36	31.25	6.81	38	10.54
5	2.58	11.5	2.74	18.25	2.96	24.75	3.5	31.5	7.04	38.25	10.58
5.25	2.58	11.75	2.75	18.5	2.97	25	3.55	31.75	7.25	38.5	10.59
5.5	2.59	12	2.76	18.75	2.99	25.25	3.61	32	8.59	38.75	10.61
5.75	2.6	12.25	2.76	19	2.99	25.5	3.69	32.25	9.05	39	10.63
6	2.61	12.5	2.77	19.25	3.01	25.75	3.78	32.5	9.29	39.25	10.65
6.25	2.61	13	2.78	19.5	3.02	26	3.86	32.75	9.51	39.5	10.66
6.5	2.62	13.25	2.79	19.75	3.04	26.25	4.04	33	9.63	39.75	10.67

Plotting of the pH as a function of the volume of aqueous NaOH added:



c) Syntheses of the conjugated precursors

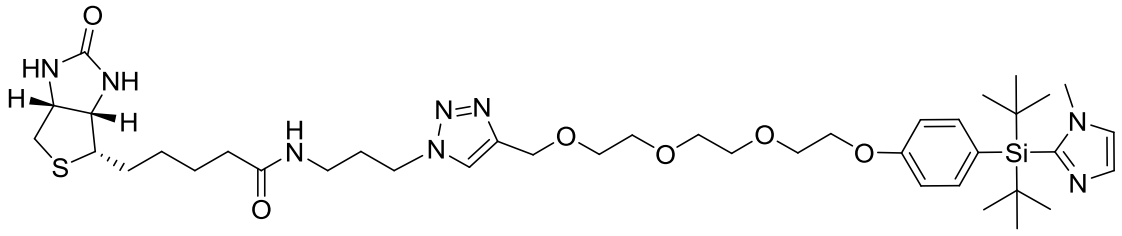
(2S)-2-(R)-*O*-[3-(4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-cinchonidine 3a



3a

O-[3-azidopropanyl)]-(2S)-2-(R)-cinchonidine (0.19 mmol, 0.95 eq., 71.6 mg), pentahydrate copper sulfate (0.04 mmol, 0.2 eq., 9.9 mg) and sodium ascorbate (0.2 mmol, 1 eq., 39.6 mg) were added to a solution of compound **2d** (0.2 mmol, 116.9 mg) in *t*BuOH/H_2O: 3/1 (4 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/MeOH/NH_3: 95/5/1; Rf = 0.5) to give compound **3a** (97.1 mg, 59%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.88 (d, 1H, *J* = 4.3 Hz), 8.14 (s, 1H), 8.13 (s, 1H), 7.71 (t, 1H, *J* = 7.6 Hz), 7.57 (t, 1H, *J* = 7.9 Hz), 7.50 (d, 2H, *J* = 8.8 Hz), 7.45 (m, 1H), 7.40 (d, 1H, J = 4.1 Hz), 7.30 (s, 1H), 6.97 (s, 1H), 6.90 (d, 2H, *J* = 8.8 Hz), 5.76-5.70 (m, 1H), 4.97-4.92 (m, 2H), 4.64 (s, 2H), 4.52-4.43 (m, 2H), 4.13 (m, 2H), 3.85 (m, 2H), 3.73-3.71 (m, 2H), 3.68-3.65 (m, 7H), 3.43-3.40 (m, 1H), 3.39 (s, 3H), 3.37-3.33 (m, 2H), 3.15 (m, 1H), 3.07 (m, 1H), 2.75-2.59 (m, 2H), 2.29 (m, 1H), 2.19 (m, 2H), 1.84 (m, 1H), 1.78-1.64 (m, 3H), 1.57 (m, 1H), 1.13 (s, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 159.7, 150.2, 148.7, 148.4, 146.0, 145.4, 141.6, 137.7 (2C), 130.7 (2C), 130.4, 129.3, 126.9, 126.5, 125.8, 123.2, 122.6, 114.7, 114.0 (2C), 70.9 (2C), 70.7 (2C), 70.7 (2C), 69.9, 69.8, 67.2, 65.9, 64.8, 60.6, 56.8, 47.5, 43.2, 39.8, 36.6, 30.8, 29.8, 29.4 (6C), 27.9, 20.7 (2C). ^{29}Si NMR (119 MHz, $CDCl_3$) (δ ppm) -6.88. HRMS (ESI/TOF$^+$) $C_{49}H_{69}N_7O_5Si$ $[M+H]^+$ calculated 864.5202, found 864.5203.

***N*-[3-(4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy) ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-biotinamide 3b**

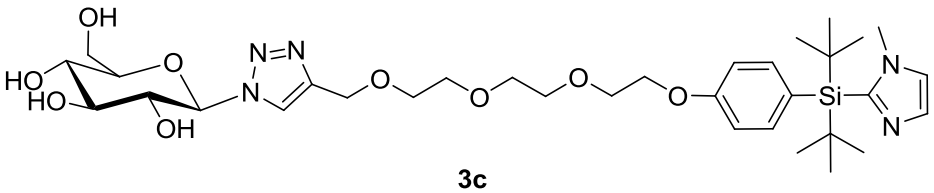


3b

1-Biotin-3-azidopropylamine (0.08 mmol, 0.95 eq., 27 mg), pentahydrate copper sulfate (0.017 mmol, 0.2 eq., 4.2 mg) and sodium ascorbate (0.084 mmol, 1 eq., 16.6 mg) were added to a solution of compound **2d** (0.084 mmol, 40.8 mg) in *t*BuOH/H_2O: 3/1 (2.5 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH: 90/10; Rf = 0.4) to give compound **3b** (34.4 mg, 53%) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.75 (s, 1H), 7.49 (d, 2H, *J* = 8.5 Hz), 7.45 (s, 1H), 7.14 (s, 1H),

7.11 (s, 1H), 6.93 (d, 2H, *J* = 8.5 Hz), 6.64 (s, 1H), 5.78 (s, 1H), 4.63 (s, 2H), 4.50-4.48 (m, 1H), 3.38 (t, 2H, J = 6.8 Hz), 4.31-4.29 (m, 1H), 4.14-4.13 (m, 2H), 3.86-3.84 (m, 2H), 3.72-3.70 (m, 2H), 3.67-3.64, (m, 6H), 3.47 (s, 3H), 3.26-3.19 (m, 2H), 3.13-3.10 (m, 1H), 2.89-2.86 (dd, 1H, *J* = 13.1 Hz, *J* = 4.9 Hz), 2.72-2.70 (m, 1H), 2.19 (t, 2H, *J* = 7.3 Hz), 2.11-2.67 (m, 2H), 1.74-1.60 (m, 4H), 1.42-1.39 (m, 2H), 1.14 (s, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 174.1, 164.3, 160.1, 147.9, 145.1, 137.5 (2C), 128.5, 128.4, 124.2, 123.6, 114.5 (2C), 70.9, 70.7, 70.6, 69.8, 69.7, 67.3, 64.6, 61.9, 60.3, 55.9, 48.1, 40.7, 37.5, 36.4, 35.8, 30.3, 29.3 (6C), 28.3, 28.1, 25.7, 20.7 (2C). ^{29}Si NMR (119 MHz, $CDCl_3$) (δ ppm) -5.32. HRMS (ESI/TOF$^+$) $C_{40}H_{64}N_8O_6SSi$ $[M+H]^+$ calculated 813.4511, found 813.4500.

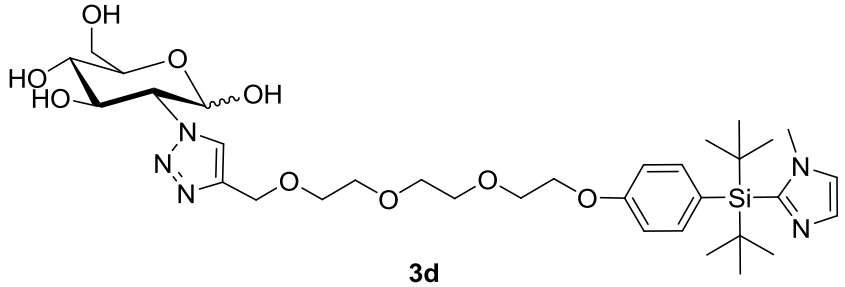
<u>*β*-D-1-Deoxy-1-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 3c</u>



3c

1-Azido-1-deoxy-*β*-D-glucopyranose (0.095 mmol, 0.95 eq., 19.5 mg), pentahydrate copper sulfate (0.02 mmol, 0.2 eq., 4.9 mg) and sodium ascorbate (0.1 mmol, 1 eq., 19.8 mg) were added to a solution of compound **2d** (0.1 mmol, 52.1 mg) in *t*BuOH/H_2O: 3/1 (3 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH: 85/15, Rf = 0.5) to give compound **3c** (29.5 mg, 45%) as a yellow oil. ^{1}H NMR (400 MHz, MeOD) (δ ppm) 8.20 (s, 1H), 7.54 (d, 2H, *J* = 8.5 Hz), 7.24 (m, 2H), 7.01 (d, 2H, *J* = 8.5 Hz), 5.60 (d, 1H, *J* = 9.1 Hz), 4.65 (s, 2H), 4.15 (m, 2H), 3.91-3.84 (m, 4H), 3.72-3.70 (m, 3H), 3.67 (m, 6H), 3.56-3.49 (m, 3H), 3.45 (s, 3H), 1.15 (s, 18H). ^{13}C NMR (100 MHz, MeOD) (δ ppm) 160.1, 147.7, 144.6, 137.3 (2C), 128.8, 124.5, 123.9, 122.9, 113.9 (2C), 88.2, 79.7, 77.1, 72.6, 70.3, 70.2 (2C), 69.5 (2C), 69.4, 66.9, 63.5, 60.9, 36.2, 28.4 (6C), 19.9 (2C). ^{29}Si NMR (79 MHz, MeOD) (δ ppm) -6.22. HRMS (ESI/TOF$^+$) $C_{33}H_{53}N_5O_9Si$ $[M+H]^+$ calculated 692.3685, found 692.3687.

<u>D-2-Deoxy-2-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 3d</u>

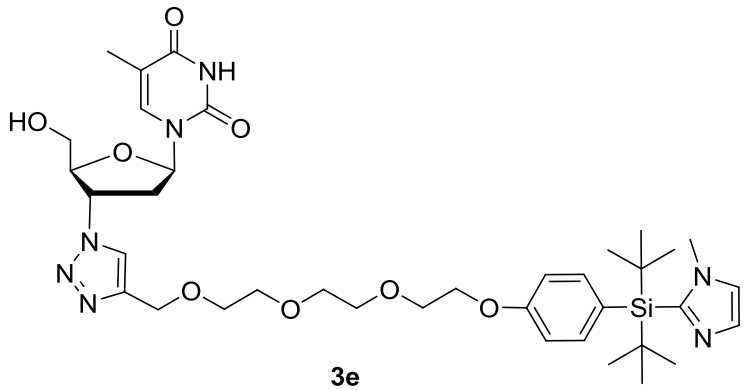


3d

2-Azido-2-deoxy-D-glucose (0.119 mmol, 0.95 eq., 24.4 mg), pentahydrate copper sulfate (0.025 mmol, 0.2 eq., 6.2 mg) and sodium ascorbate (0.125 mmol, 1 eq., 24.7 mg) were added to a solution of compound **2d** (0.125 mmol, 60.7 mg) in *t*BuOH/H_2O: 3/1 (2.5 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane/MeOH: 90/10; Rf = 0.3) to give compound **3d** (50.9 mg, 62%) as a white powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.11 (s, 0.5H), 8.02 (s, 0.5H), 7.55 (d, 2H, *J* = 8.2 Hz), 7.26 (m,

2H), 7.01 (m, 2H), 5.29 (d, 0.5H, *J* = 3.3 Hz), 5.12 (d, 0.5H, *J* = 8.2 Hz), 4.65-4.62 (m, 3H), 4.28-4.25 (m, 0.5H), 4.17-4.16 (m, 3H), 3.97-3.95 (m, 0.5H), 3.93 (dd, 0.5H, *J* = 11.6 Hz, *J* = 2.3 Hz), 3.86-3.84 (m, 2.5H), 3.80-3.73 (m, 1H), 3.71-3.69 (m, 2H), 3.67-3.64 (m, 6H), 3.55-3.44 (m, 4H), 1.15 (s, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 161.6, 149.1, 145.5, 138.7 (2C), 130.1, 126.4, 125.7, 125.4, 124.5, 115.4 (2C), 96.2, 92.7, 78.2, 75.5, 73.3, 72.4, 72.1, 71.7, 71.5, 70.7, 69.7, 68.4, 66.8, 65.0, 64.9, 62.6, 62.5, 37.7, 29.8 (6C), 21.4 (2C). ^{29}Si NMR (119 MHz, $CDCl_3$) (δ ppm) -6.03. HRMS (ESI/TOF$^+$) $C_{33}H_{53}N_5O_9Si$ $[M+H]^+$ calculated 692.3685, found 692.3698.

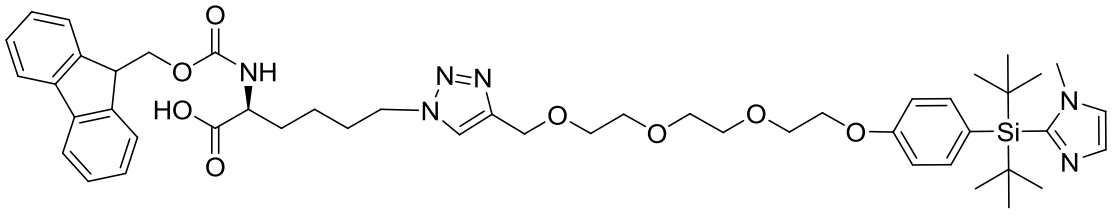
3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 3e



3e

Zidovudine (0.119 mmol, 0.95 eq., 31.8 mg), pentahydrate copper sulfate (0.025 mmol, 0.2 eq., 6.2 mg) and sodium ascorbate (0.125 mmol, 1 eq., 24.7 mg) were added to a solution of compound **2d** (0.125 mmol, 60.7 mg) in *t*BuOH/H_2O: 3/1 (2.5mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane /MeOH: 95/5; Rf = 0.3) to give compound **3e** (66.3 mg, 74%) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (s, 1H), 7.52 (d, 1H, *J* = 0.8 Hz), 7.50 (d, 2H, *J* = 8.6 Hz), 7.31 (d, 1H, *J* = 1 Hz), 7.0 (d, 1H, *J* = 0.9 Hz), 6.9 (d, 2H, *J* = 8.6 Hz), 6.25 (t, 1H, *J* = 6.6 Hz), 5.43-5.39 (m, 1H), 4.68 (s, 2H), 4.40-4.38 (m, 1H), 4.15-4.13 (m, 2H), 3.97 (dd, 1H, *J* = 12.4 Hz, *J* = 2.4 Hz), 3.87-3.85 (m, 2H), 3.77-3.66 (m, 9H), 3.42 (s, 3H), 2.92-2.88 (m, 2H), 1.9 (d, 3H, *J* = 1.1 Hz), 1.13 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.9, 159.7, 150.5, 148.3, 145.6, 137.8, 137.7 (2C), 130.1, 125.6, 123.4, 122.9, 114.1 (2C), 111.3, 88.4, 85.4, 70.9, 70.7 (2C), 70.1, 69.8, 67.2, 64.7, 61.6, 59.4, 37.7, 36.8, 29.4 (6C), 20.7 (2C), 12.6. ^{29}Si NMR (79 MHz, $CDCl_3$) (δ ppm) -6.38. HRMS (ESI/TOF$^+$) $C_{37}H_{55}N_7O_8Si$ $[M+Na]^+$ calculated 776.3773, found 776.3771. MP (°C) : 85-86.

(S)-6-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1H-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy) ethoxy)methyl)-1H-1,2,3-triazol-1-yl]-2-(9-fluorenylmethoxycarbonyl)aminohexanoic acid 3f

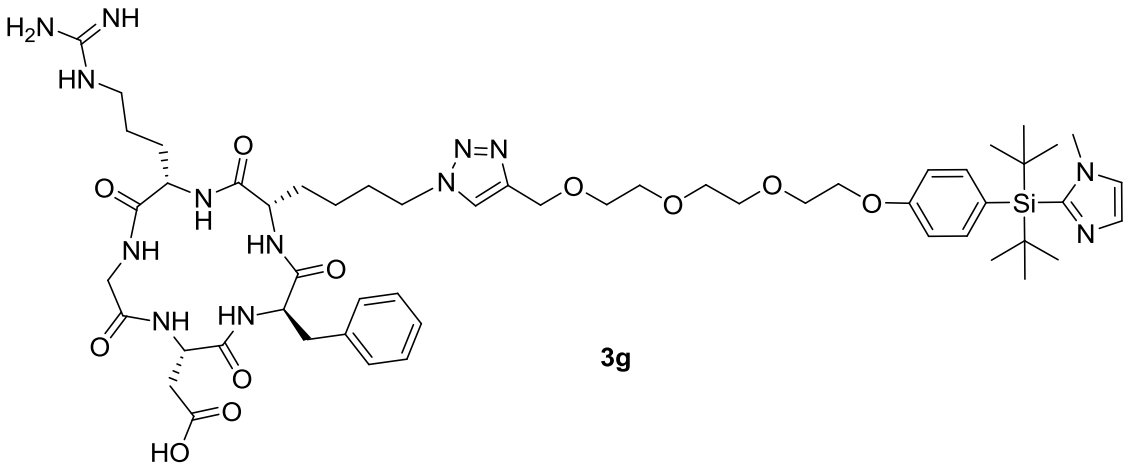


3f

N'-Diazo-L-Fmoc-lysine (0.19 mmol, 0.95 eq., 74.9 mg), pentahydrate copper sulfate (0.04 mmol, 0.2 eq., 10 mg) and sodium ascorbate (0.2 mmol, 1 eq., 39.6 mg) were added to a solution of compound

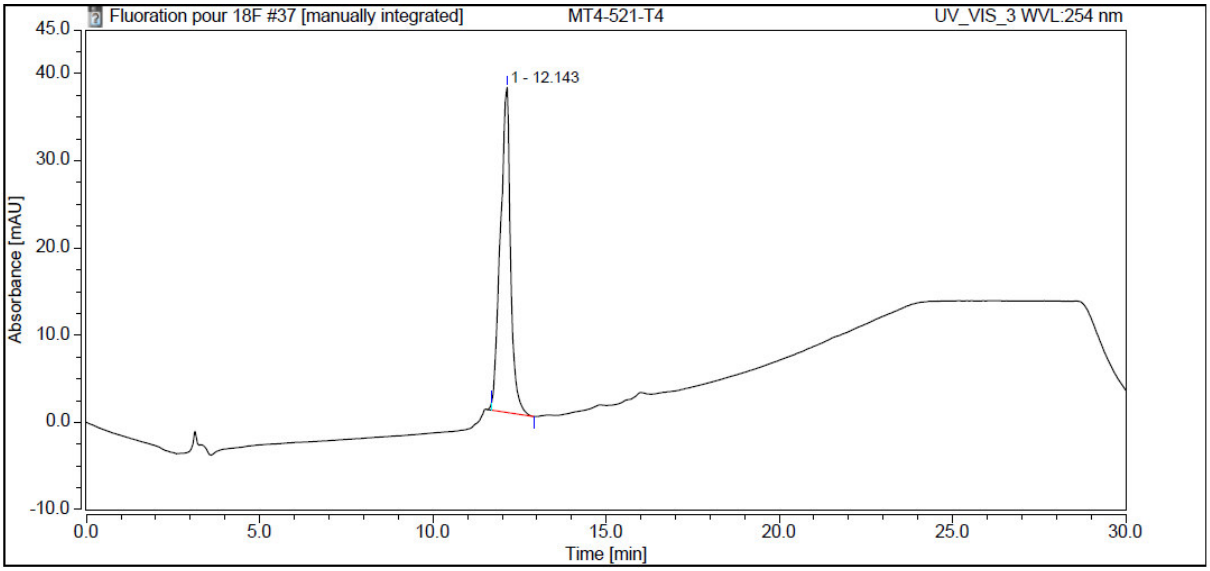
2d (0.2 mmol, 98.9 mg) in *t*BuOH/H_2O: 3/1 (4 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane /MeOH: 85/15; Rf = 0.5) to give compound **3f** (58.5 mg, 35%) as a yellow oil. ^{1}H NMR (600 MHz, MeOD) δ (ppm) 7.92 (s, 1H), 7.75 (d, 2H, *J* = 7.2 Hz), 7.62 (m, 2H), 7.49 (d, 2H, *J* = 8.5 Hz), 7.38-7.34 (m, 4H), 7.27 (t, 2H, *J* = 7.2 Hz), 6.97 (d, 2H, *J* = 8.5 Hz), 4.54 (s, 2H), 4.33 (m, 2H), 4.27 (m, 1H), 4.16 (m, 1H), 4.08 (m, 3H), 3.79 (m, 2H), 3.64 (m, 2H), 3.59 (m, 7H), 3.48 (s, 3H), 1.88 (m, 3H), 1.75-1.69 (m, 1H), 1.36 (m, 2H), 1.12 (s, 18H). ^{13}C NMR (150 MHz, MeOD) δ (ppm) 161.7, 158.9, 148.8, 145.4 (2C), 145.2, 142.5 (2C), 138.6 (2C), 128.8 (2C), 128.2, 128.1 (2C), 126.3 (2C), 126.2, 125.1, 124.5, 121.0 (2C), 115.6 (2C), 71.7 (2C), 71.5, 71.5, 70.7, 70.7, 68.4, 67.7, 65.0, 51.2, 48.4, 38.3, 33.0, 30.9, 29.7 (6C), 23.8, 21.3 (2C). The signal for CO_2H was not detected. ^{29}Si NMR (119 MHz, MeOD) (δ ppm) -4.76. HRMS (ESI/TOF$^+$) $C_{48}H_{64}N_6O_8Si$ $[M+H]^+$ calculated 881.4627, found 881.4622.

[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy) methyl)-1*H*-1,2,3-triazol-1-yl]-Cyclo-RGD 3g

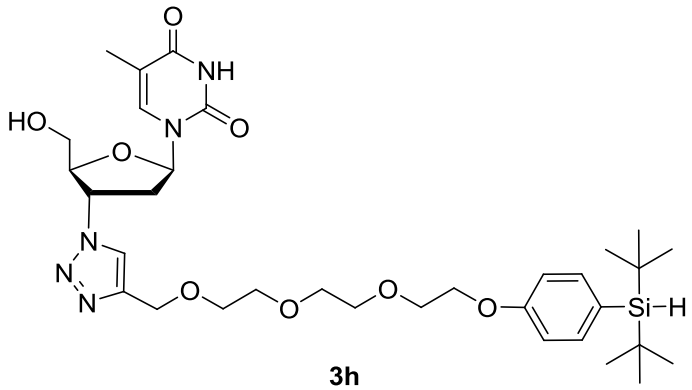


Cyclo-RGDN$_3$ (0.04 mmol, 0.95 eq., 25.2 mg), pentahydrate copper sulfate (0.008 mmol, 0.2 eq., 2 mg) and sodium ascorbate (0.042 mmol, 1 eq., 8.3 mg) were added to a solution of compound **2d** (0.042 mmol, 20.4 mg) in *t*BuOH/H_2O: 3/1 (2 mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by semi-preparative HPLC (Luna C18, 10µm, 10*250mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA: 95/5 to 24/76 linear gradient (0-15 min) then 24/76 to 5/95 linear gradient (15-17 min), 5 mL/min, $t_{\mathbf{3g}}$ = 11.87 min) to give compound **3g** (32.1 mg, 72%) as a colorless oil. The sample purity was checked by analytical HPLC (Luna C18, 5µm, 4.6*250mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA: 90/10 gradient to 10/90 (0-20 min) then isocratic (20-25 min), 1 mL/min, $t_{\mathbf{3g}}$ = 12.14 min). ^{1}H NMR (600 MHz, CD_3CN/D_2O) δ (ppm) 8.44 (s, 1H), 8.18 (m, 1H), 8.15 (m, 1H), 8.12 (d, 2H, *J* = 8.4 Hz), 7.82 (m, 2H), 7.77-7-74 (m, 3H), 7.60 (d, 2H, *J* = 8.4 Hz), 5.24 (m, 1H), 5.16 (s, 2H), 5.13-5.11 (m, 1H), 4.42-4.39 (m, 1H), 4.37 (m, 2H), 4.22 (m, 2H), 4.20-4.16 (m, 9H), 3.95 (m, 1H), 3.67 (m, 2H), 3.48 (m, 2H), 3.37 (dd, 1H, *J* = 16.9 Hz, *J* = 8.4 Hz), 3.16 (dd, 1H, *J* = 16.7 Hz, *J* = 6.3 Hz), 2.55 (m, 5H), 2.38-2.33 (m, 1H), 2.31-2.26 (m, 2H), 2.17-2.09 (m, 2H), 2.05-1.96 (m, 3H), 1.73 (m, 1H), 1.69 (s, 18H), 1.53-1.49 (m, 2H). ^{13}C NMR (150 MHz, CD_3CN/D_2O) δ (ppm) 176.6, 176.5, 176.2, 175.3, 175.1, 173.7, 173.6, 163.3, 159.5, 149.3, 146.9, 140.4 (2C), 139.1, 132.0 (2C), 131.4 (2C), 129.7, 127.1, 124.7, 123.5, 117.6 (2C), 72.8, 72.6, 72.5, 71.9, 71.8, 69.9, 66.1, 57.8, 57.6, 55.1, 52.5, 52.20, 46.1, 43.4, 41.6, 39.8, 37.0, 32.6, 31.5, 31.0 (6C), 30.1, 27.3, 25.1, 22.6 (2C). ^{29}Si NMR (119 MHz, CD_3CN/D_2O) (δ ppm) 1.06. HRMS (ESI/TOF$^+$) $C_{54}H_{81}N_{13}O_{11}Si$ $[M+H]^+$ calculated 1116.6020, found 1116.6004.

Analytic HPLC chromatogram of 3g:



3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-*tert*-butylsilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 3h

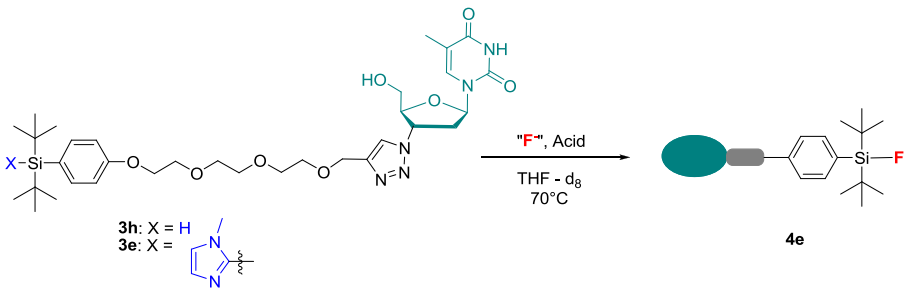


3h

Zidovudine (0.047 mmol, 0.95 eq., 12.6 mg), pentahydrate copper sulfate (0.01 mmol, 0.2 eq., 2.5 mg) and sodium ascorbate (0.05 mmol, 1 eq., 11.9 mg) were added to a solution of di-*tert*-butyl(4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenyl)silane (0.05 mmol, 20 mg) in *t*BuOH/H_2O: 3/1 (1.5mL). The mixture was stirred for 5 min at 100°C under microwave irradiation (40 W). The crude reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane /MeOH: 97/3; Rf = 0.1) to give compound **3h** (22.1 mg, 70%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (s, 1H), 7.47-7.43 (m, 3H), 6.86 (d, 2H, *J* = 8.6 Hz), 6.22 (t, 1H, *J* = 6.5 Hz), 5.44-5.38 (m, 1H), 4.67 (s, 2H), 4.39-4.37 (m, 1H), 4.14-4.10 (m, 2H), 3.99-3.96 (m, 1H), 3.86-3.83 (m, 2H), 3.80 (s, 1H), 3.74-3.64 (m, 9H), 2.90-2.87 (m, 2H), 1.90 (s, 3H), 1.00 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 163.9, 159.5, 150.6, 145.7, 137.9, 137.3 (2C), 126.8, 123.0, 113.9 (2C), 111.3, 88.5, 85.4, 70.8, 70.7, 70.6, 70.0, 69.8, 67.1, 64.7, 61.6, 59.3, 37.6, 29.0 (6C), 19.1 (2C), 12.6. ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) 12.47. HRMS (ESI/TOF$^+$) $C_{33}H_{51}N_5O_8Si$ $[M+Na]^+$ calculated 696.3399, found 696.3389.

d) Optimization of the conditions of ^{19}F-fluorination

General procedure



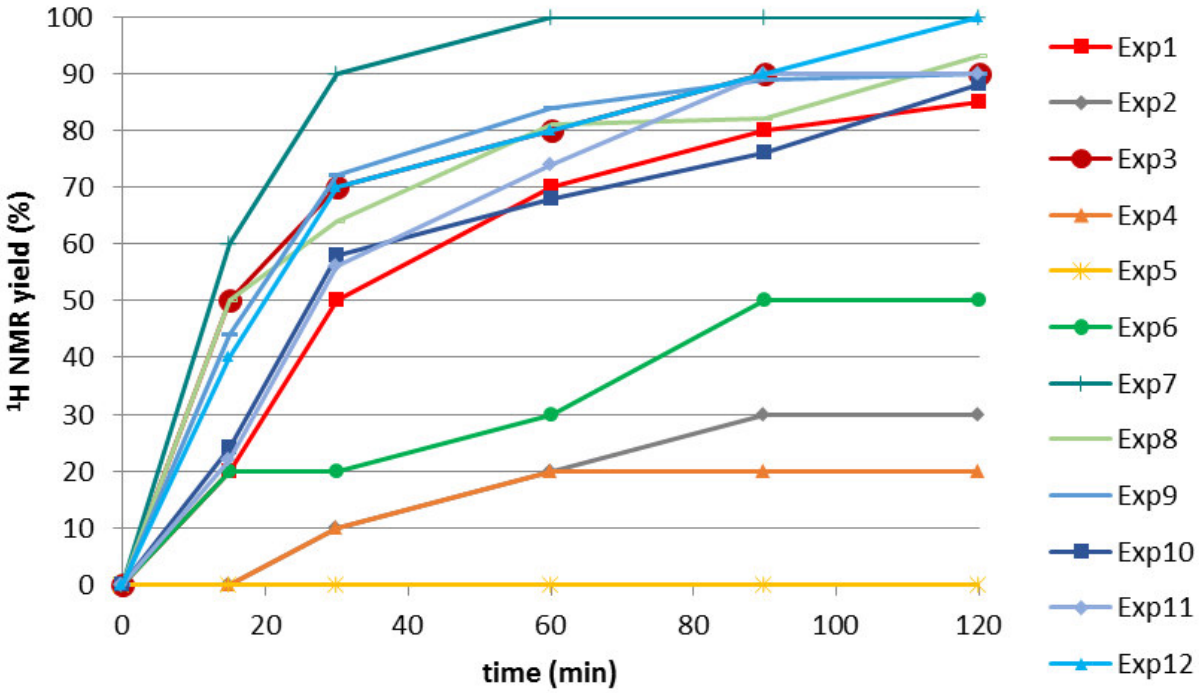
Mesitylene (0.198 mmol, 6eq., 27 µL) and precursor **3e** or **3h** (0.033 mmol) were dissolved in 1 mL of THF-d_8. The fluoride source (x eq.) and the acid (y eq.) were added. The mixture was stirred at 70°C for 2h. The reaction was followed by ^{1}H-NMR at t = 0, 15, 30, 60, 90 and 120 min, and the corresponding ^{1}H NMR yields were determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard.

Experiments

Experience	Precursor	"F⁻" (x equiv)	Acid (y equiv)	^{1}H NMR Yields					
				t = 0 min	t = 15 min	t = 30 min	t = 60 min	t = 90 min	t = 120 min
1	3e	TBAF (1.5 equiv)	AcOH (10 equiv)	0	20	50	70	80	85
2	3h	TBAF (1.5 equiv)	AcOH (10 equiv)	0	0	10	20	30	30
3	3e	KF/ Kryptofix (1.5 equiv)	AcOH (10 equiv)	0	50	70	80	90	90
4[a]	3e	TBAF (1.5 equiv)	AcOH (10 equiv)	0	0	10	20	20	20
5	3e	TBAF (1.5 equiv)	-	0	0	0	0	0	0
6	3e	TBAF (1.5 equiv)	NH_4Cl (10 equiv)	0	20	20	30	50	50
7	3e	TBAF (1.5 equiv)	CH_3SO_3H (1.5 equiv)	0	60	90	100	100	100
8[b]	3e	TBAF (1.5 equiv)	PS-SO_3H (1.5 equiv)[d]	0	50	64	81	82	93
9	3e	0.1 M HF_{aq} (1.5 equiv)	-	0	44	72	84	89	90
10[c]	3e	0.1 M HF_{aq} (0.5 equiv)	-	0	24	58	68	76	88
11	3e	0.1 M NaF_{aq} (0.5 equiv)	1.0 M HCl_{aq} (0.5 equiv)	0	22	56	74	90	90
12	3e	0.1 M NaF_{aq} (0.5 equiv)	AcOH (10 equiv)	0	40	70	80	90	100

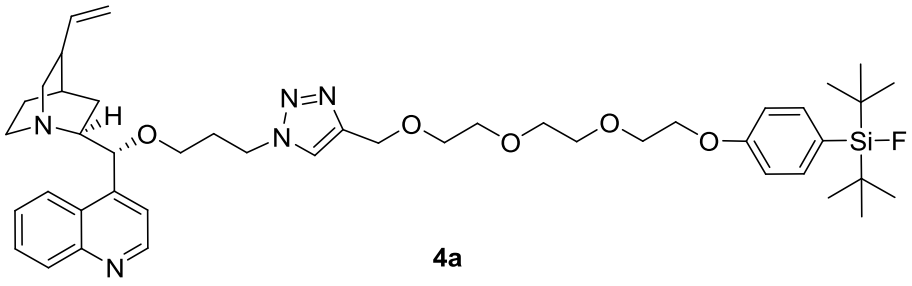
[a]DMSO-d_6 was used as solvent. [b]PS-SO_3H = Sulfonic acid functionalized polystyren resin (1.18 mmol/g). [c]A 1:1 mixture of H_2O and THF-d_8 was used as solvent, trimethoxybenzene was used as internal standard.

Evolution in time of the ^{1}H NMR yields of 4e under various conditions of fluorination:



e) *^{19}F-Fluorination of precursors **3a-g***

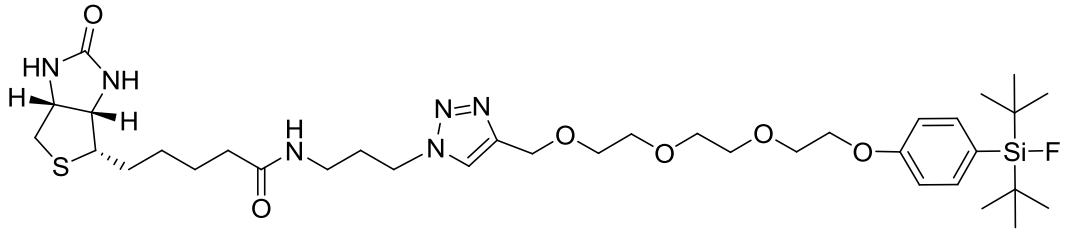
(2S)-2-(R)-*O*-[3-(4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-cinchonidine 4a



4a

Mesitylene (0.06 mmol, 6eq., 8.3 µL) and compound **3a** (0.01 mmol, 8.8 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (15 µmol, 1.5eq., 0.1 M, 150 µL) was added. The mixture was stirred at 70°C for 2h. A 100% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel ($CHCl_3$/MeOH: 95/5; Rf = 0.2) to give compound **4a** (2.3 mg, 29%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.90 (d, 1H, *J* = 4.4 Hz), 8.25 (m, 1H), 8.15 (d, 1H, *J* = 8.4 Hz), 7.74 (t, 1H, *J* = 6.8 Hz), 7.62 (m, 1H), 7.50 (m, 3H), 7.42 (d, 1H, *J* = 4.2 Hz), 6.92(d, 2H, *J* = 8.4 Hz), 5.69 (m, 1H), 4.96 (m, 2H), 4.66 (s, 2H), 4.50 (m, 2H), 4.13 (m, 2H), 3.85 (m, 2H), 3.74-3.66 (m, 9H), 3.49-3.42 (m, 3H), 3.20 (m, 2H), 2.82 (m, 2H), 2.39 (m, 1H), 2.22 (m, 2H), 1.91 (m, 3H), 1.25 (m, 2H), 1.03 (s, 18H), 0.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.1, 150.2, 148.7, 145.5, 135.6 (2C, d, *J* = 4.2 Hz), 130.7, 129.5, 127.3, 126.2, 124.8 (2C, d, *J* = 14.1 Hz), 123.3, 122.6, 118.6, 114.1 (2C), 77.4, 70.9 (2C), 70.8 (2C), 70.7 (2C), 69.9, 69.8, 67.2, 66.4, 66.1, 64.8, 60.5, 56.5, 47.6, 43.4, 30.8, 29.7, 27.7, 27.5 (6C), 20.5 (2C, d, *J* = 12.8 Hz). ^{29}Si NMR (79 MHz, $CDCl_3$) (δ ppm) 14.39 (d, *J* = 297 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) (δ ppm) -183.7. HRMS (ESI/TOF$^+$) $C_{45}H_{64}N_5O_5SiF$ $[M+H]^+$ calculated 802.4733, found 802.4725.

***N*-[3-(4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-biotinamide 4b**

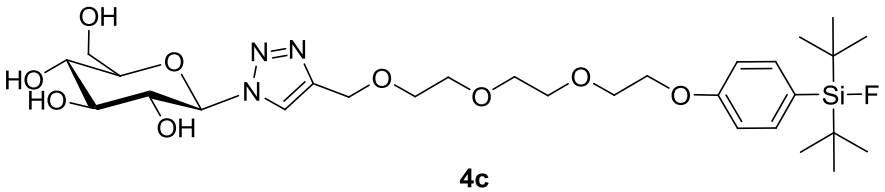


4b

Mesitylene (0.06 mmol, 6eq., 8.3 µL) and compound **3b** (0.01 mmol, 8.2 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (15.0 µmol, 1.5eq., 0.1 M, 150 µL) was added. The mixture was stirred at 70°C for 2h. A 100% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (dichloromethane/MeOH : 90/10; Rf = 0.5) to give compound **4b** (2.3 mg, 31%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.72 (s, 1H), 7.50 (d, 2H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 8.4 Hz), 6.68 (t, 1H, *J* = 6.1 Hz), 6.39 (s, 1H), 5.44 (s, 1H), 4.66 (s, 1H), 4.50 (m, 1H), 4.40 (t, 2H, *J* = 6.5 Hz), 4.30

(m, 1H), 4.14 (m, 2H), 3.86 (m, 2H), 3.86 (m, 2H), 3.74-3.65 (m, 9H), 3.27-3.23 (m, 2H), 3.15-3.11 (m, 1H), 2.90 (dd, 1H, *J* = 12.7 Hz, *J* = 5.2 Hz), 2.72 (m, 1H), 2.19 (m, 2H), 2.11 (m, 2H), 1.42 (m, 2H), 1.03 (d, 18H, *J* = 1.05 Hz. ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.7, 163.9, 159.9, 135.5 (2C, d, J = 4.0 Hz), 124.7 (d, J = 13.5 Hz), 113.9 (2C), 70.8 (2C), 70.6 (2C), 70.5, 69.8, 69.7, 67.0, 64.7, 61.8, 60.2, 55.7, 48.0, 40.6, 36.4, 35.7, 30.0, 28.1, 27.9, 27.4 (6C), 25.5, 20.3 (2C, d, *J* = 11.9 Hz). ^{29}Si NMR (79 MHz, $CDCl_3$) (δ ppm) 14.40 (d, *J* = 294 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) (δ ppm) -188.7. HRMS (ESI/TOF$^+$) $C_{36}H_{59}N_6O_6SSiF$ $[M+Na]^+$ calculated 773.3862, found 773.3862.

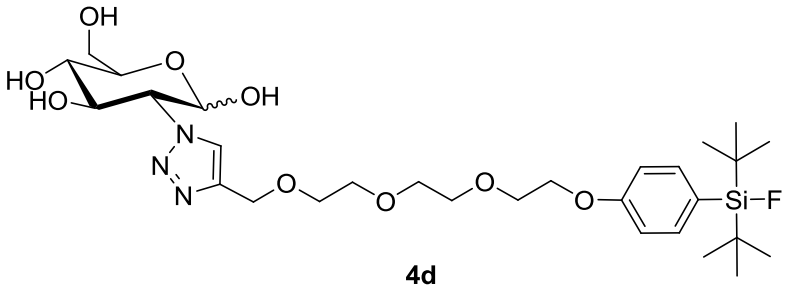
<u>*β*-D-1-Deoxy-1-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 4c</u>



4c

Mesitylene (0.084 mmol, 6eq., 11.6 µL) and compound **3c** (0.014 mmol, 10 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (21.0 µmol, 1.5eq., 0.1 M, 210 µL) was added. The mixture was stirred at 70°C for 2h. A 100% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (dichloromethane/MeOH: 90/10) to give compound **4c** (4.2 mg, 48%) as a colorless oil. ^{1}H NMR (600 MHz, MeOD) δ (ppm) 8.19 (s, 1H), 7.52 (d, 2H, *J* = 8.5 Hz), 6.98 (d, 2H, *J* = 8.5 Hz), 5.59 (d, 1H, *J* = 9.3 Hz), 4.65 (s, 2H), 4.15 (m, 2H), 3.90-3.84 (m, 4H), 3.72-3.69 (m, 3H), 3.67-3.65 (m, 6H), 3.57-3.54 (m, 2H), 3.51-3.48 (m, 1H), 1.04 (d, 18H, *J* = 0.2 Hz). ^{13}C NMR (150 MHz, MeOD) δ (ppm) 161.7, 146.0, 136.6 (2C, d, *J* = 4.10 Hz), 125.6 (d, *J* = 13.5 Hz), 124.4, 115.2 (2C), 89.6, 81.2, 78.5, 74.1, 71.7, 71.6, 71.5, 70.6, 70.8 (2C), 68.3, 64.9, 62.4, 27.8 (6C), 21.1(2C, d, *J* = 13.2 Hz). ^{29}Si NMR (119 MHz, MeOD) (δ ppm) 14.26 (d, *J* = 293 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) (δ ppm) -189.6. HRMS (ESI/TOF$^+$) $C_{29}H_{48}N_3O_9SiF$ $[M+Na]^+$ calculated 652.3036, found 652.3032.

<u>D-2-Deoxy-2-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 4d</u>

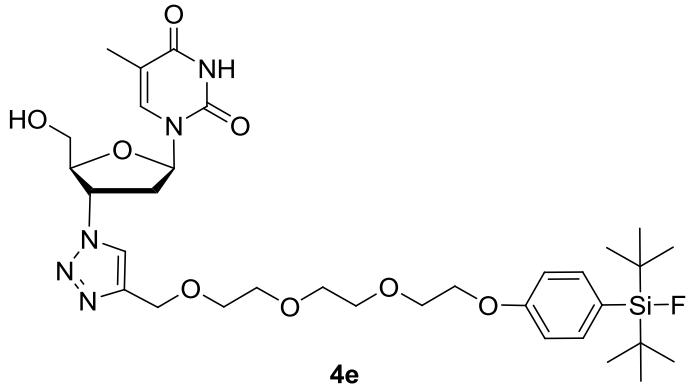


4d

Mesitylene (0.132 mmol, 6eq., 18.4 µL) and compound **3d** (0.022 mmol, 15 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (33.0 µmol, 1.5eq., 0.1 M, 330 µL) was added. The mixture was stirred at 70°C for 5h. A 100% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (dichloromethane/MeOH: 90/10; Rf = 0.3) to give compound **4d** (5.0 mg, 36%) as a yellow oil. ^{1}H NMR (600 MHz, MeOD) δ (ppm) 8.10 (s, 0.5H), 8.0 (s, 0.5H, s), 7.52 (d, 2H, *J* = 8.6 Hz), 6.99 (d,

2H, *J* = 8.6 Hz), 5.28 (m, 0.5H), 5.12 (s, 0.5H), 4.65 (m, 2.5H), 4.58 (m, 1H), 4.27-4.24 (m, 0.5H), 4.17-4.13 (m, 3H), 3.99-3.92 (m, 1H), 3.87-3.84 (m, 2H), 3.80-3.73 (m, 1H), 3.72-3.70 (m, 2H), 3.67-3.64 (m, 6H), 3.55-3.43 (m, 1H), 1.08 (d, 18H, *J* = 1.1 Hz). ^{13}C NMR (150 MHz, MeOD) δ (ppm) 161.7, 145.5, 145.3, 136.6 (2C, d, *J* = 3.9 Hz), 126.4, 125.5 (d, *J* = 14.6 Hz), 124.5, 115.2 (2C), 96.2, 92.7, 78.2, 75.6, 73.3, 72.4, 72.2, 71.8, 71.7, 71.6, 71.5, 70.8, 70.7, 69.7, 68.3, 66.9, 65.1, 65.0, 62.7, 62.5, 59.5, 27.8 (6C), 24.8, 21.1 (2C, d, *J* = 12.7 Hz), 20.7, 13.9. ^{29}Si NMR (119 MHz, MeOD) (δ ppm) 14.26 (d, *J* = 294 Hz). ^{19}F NMR (282 MHz, MeOD) (δ ppm) -189.6 HRMS (ESI/TOF$^+$) $C_{29}H_{48}N_3O_9SiF$ [M+Na]$^+$ calculated 652.3036, found 652.3046.

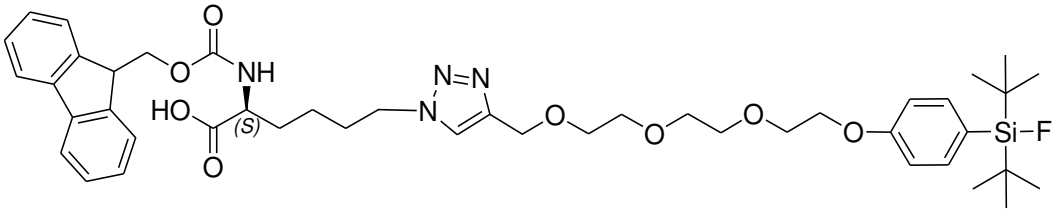
3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 4e



4e

Mesitylene (0.198 mmol, 6eq, 27 µL) and compound **3e** (0.033 mmol, 25 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (49.5 µmol, 1.5eq., 0.1 M, 495 µL) was added. The mixture was stirred at 70°C for 2h. A 90% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (dichloromethane/MeOH: 95/5; Rf = 0.3) to give compound **4e** (19.9 mg, 87%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (s, 1H), 7.50-7.47 (m, 3H), 6.90 (d, 2H, *J* = 8.6 Hz), 6.22 (t, 1H, *J* = 6.6 Hz), 5.44-5.38 (m, 1H), 4.68 (s, 2H), 4.40-4.38 (m, 1H), 4.1-4.12 (m, 2H), 4.00-3.95 (dd, 1H, *J* = 12.1 Hz, *J* = 2.3 Hz), 3.87-3.84 (m, 2H), 3.79-3.65 (m, 9H), 2.91 (t, 2H, *J* = 6.9 Hz), 1.91 (s, 3H), 1.02 (d, 18H, *J* = 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 164.0, 159.9, 150.6, 145.7, 137.9, 135.56 (2C, d, *J* = 4.9 Hz), 124.9 (d, *J* = 14.3 Hz), 123.10, 114.1 (2C), 111.3, 88.7, 85.4, 70.9, 70.7, 70.6, 70.04, 69.8, 67.2, 64.9, 61.6, 59.4, 37.6, 27.46 (6C), 20.4 (2C, d, *J* = 12.8 Hz), 12.5. ^{29}Si NMR (59 MHz, $CDCl_3$) (δ ppm) 14.37 (d, *J* = 297 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) (δ ppm) -188.6. HRMS (ESI/TOF$^+$) $C_{33}H_{50}N_5O_8SiF$ [M+Na]$^+$ calculated 714.3304, found 714.3304.

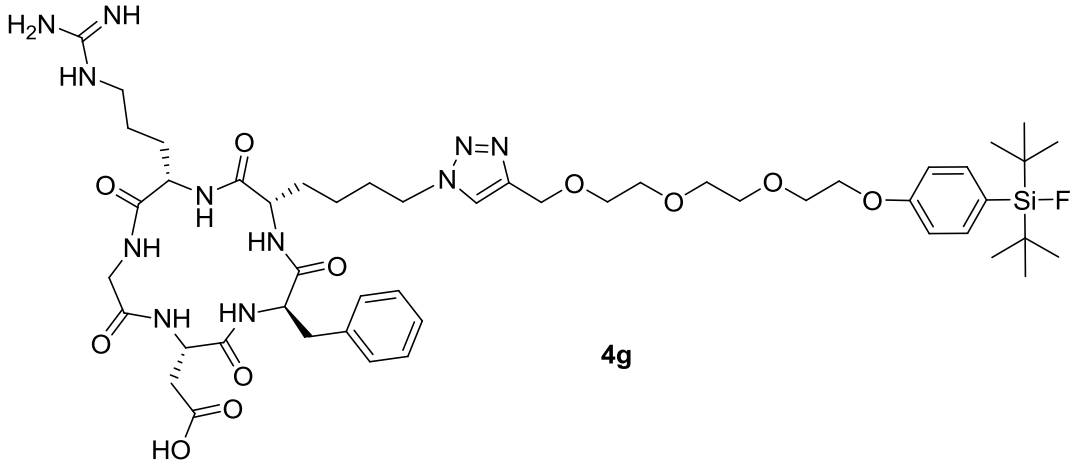
(S)-6-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl]-2-(9-fluorenylmethoxycarbonyl)aminohexanoic acid 4f



4f

Mesitylene (0.09 mmol, 6eq, 12.5 µL) and compound **3f** (0.015 mmol, 13.3 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (22.5 µmol, 1.5eq., 0.1 M, 225 µL) was added. The mixture was stirred at 70°C for 3h. A 100% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by column chromatography on a silica gel (dichloromethane/MeOH: 95/5; Rf = 0.1) to give compound **4f** (4.1 mg, 33%) as a yellow oil. ^{1}H NMR (600 MHz, MeOD) δ (ppm) 7.93 (s, 1H), 7.78 (d, 2H, *J* = 7.7 Hz), 7.67-7.64 (m, 2H), 7.50 (d, 2H, *J* = 8.3 Hz), 7.38 (m, 2H), 7.30 (m, 2H), 6.95 (d, 2H, *J* = 8.3 Hz), 4.57 (s, 2H), 4.38-4.31 (m, 4H), 4.20 (t, 1H, *J* =6.2 Hz), 4.11 (m, 2H), 4.07 (m, 1H), 3.81 (m, 2H), 3.66 (m, 2H), 3.61 (m, 7H), 1.90 (m, 2H), 1.70 (m, 1H), 1.38 (m, 2H), 1.03 (d, 18H, *J* = 1.0 Hz). ^{13}C NMR (150 MHz, MeOD) δ (ppm) 161.7, 158.5, 145.9, 145.4, 145.2, 142.6 (2C), 136.5 (2C, d, *J* = 4.2 Hz), 128.8 (2C), 128.2 (2C), 126.3 (2C), 125.5 (d, *J* = 13.7 Hz), 125.0, 120.9 (2C), 115.2 (2C), 71.7 (2C), 71.5, 71.5, 70.8, 70.8, 68.3, 67.8, 64.9, 51.2, 48.5, 32.6, 30.8, 27.8 (6C), 23.8, 21.1 (2C, d, *J* = 12.7 Hz). The signal for CO_2H was not detected. ^{29}Si NMR (119 MHz, MeOD) (δ ppm) 14.26 (d, *J* = 294 Hz). ^{19}F NMR (282 MHz, MeOD) (δ ppm) -189.5. HRMS (ESI/TOF$^+$) $C_{44}H_{59}N_4O_8SiF$ $[M+Na]^+$ calculated 841.3978, found 841.3982.

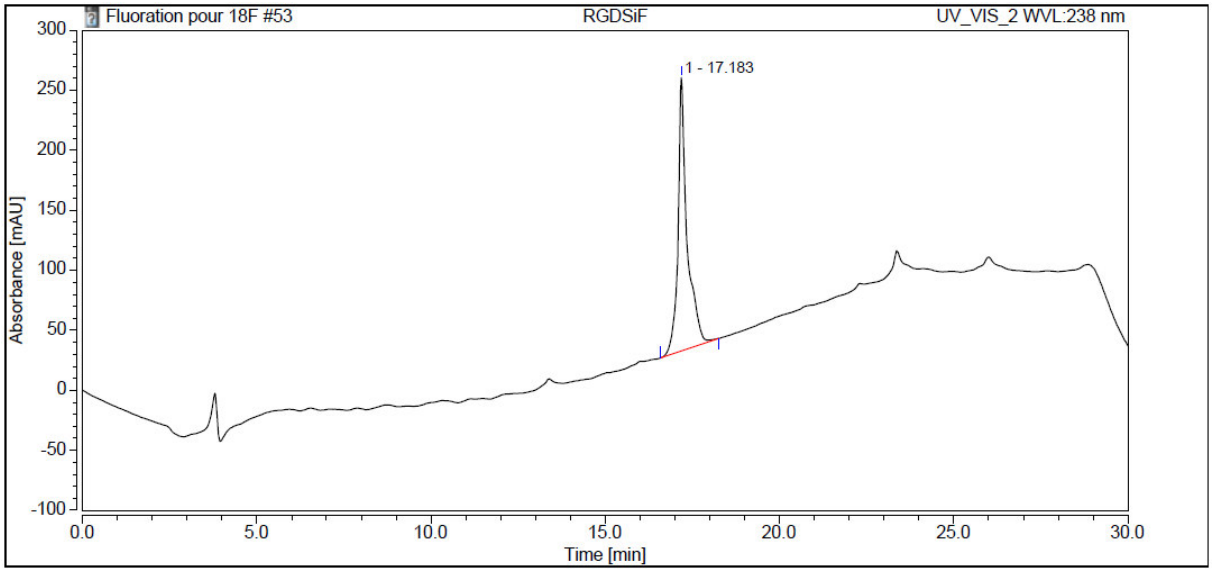
[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-Cyclo-RGD 4g



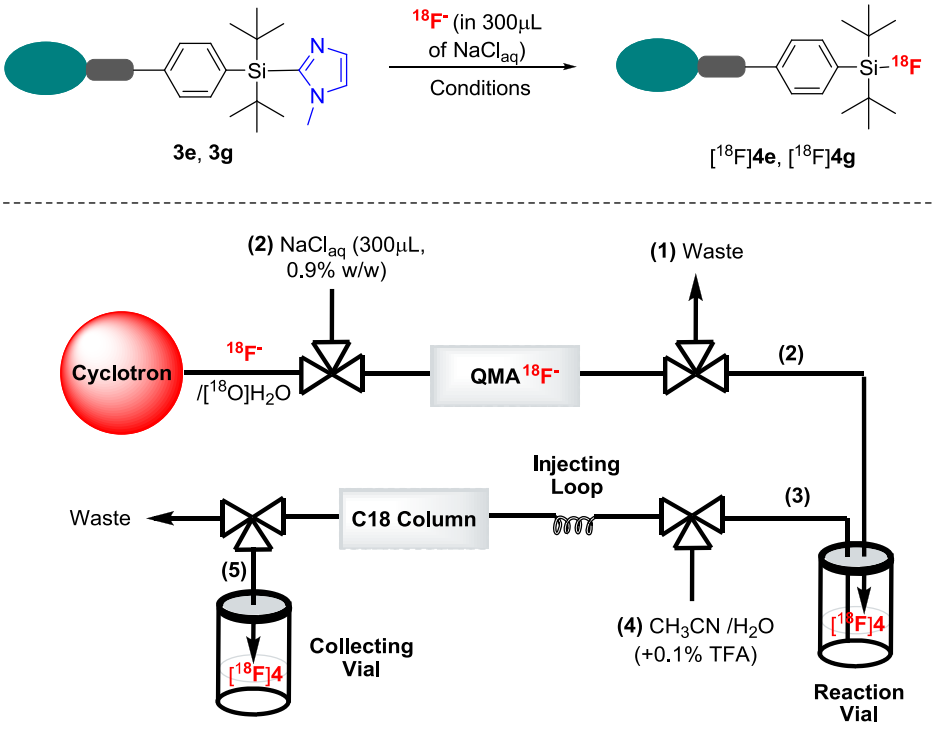
4g

Mesitylene (0.042 mmol, 6eq, 5.8 µL) and compound **3f** (7.0 µmol, 8.5 mg) were dissolved in 1 mL of THF-d_8. Aqueous hydrofluoric acid (10.5 µmol, 1.5eq., 0.1 M, 105 µL) was added. The mixture was stirred at 70°C for 3h. A 90% ^{1}H NMR yield was determined by ^{1}H NMR analysis of an aliquot of the mixture using mesitylene as the internal standard. The solvent was removed under reduced pressure and the residue was purified by semi-preparative HPLC (Luna C18, 10µm, 10*250mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA: 95/5 to 5/95 linear gradient (0-20 min), 5 mL/min, t_{3g} = 16.67 min) to give compound **4g** (5.3 mg, 72%) as a colorless oil. The sample purity was checked by analytical HPLC (Luna C18, 5µm, 4.6*250mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA: 90/10 gradient to 10/90 (0-20 min) then isocratic (20-25 min), 1 mL/min, t_{3g} = 17.18 min). ^{1}H NMR (400 MHz, CD_3CN/D_2O) δ (ppm) 7.79 (m, 1H), 7.52 (d, 2H, *J* = 8.3 Hz), 7.27 (m, 2H), 7.22 (m, 3H), 6.96 (d, 2H, *J* = 8.3 Hz, 4.59 (t, 1H, *J* = 6.9 Hz), 4.56 (m, 2H), 4.29 (t, 2H, *J* = 6.3 Hz), 4.21-4.18 (m, 2H), 4.12 (m, 2H), 3.95 (m, 1H), 3.79-3.77 (m, 3H), 3.64-3.57 (m, 9H), 3.33 (m, 1H), 3.10 (m, 2H), 3-2.96 (m, 1H), 2.90-2.85 (m, 1H), 1.78 (t, 1H, *J* = 6.3 Hz), 1.59 (m, 1H), 1.52 (m, 1H), 1.25-1.20 (m, 6H), 1.09 (m, 2H), 1.02 (d, 18H, *J* = 1.1 Hz), 0.86 (m, 1H). ^{29}Si NMR (119 MHz, CD_3CN/D_2O) (δ ppm) 14.78 (d, *J* = 297 Hz). ^{19}F NMR (282 MHz, CD_3CN/D_2O) (δ ppm) -185.6. HRMS (ESI/TOF$^+$) $C_{50}H_{76}N_{11}O_{11}SiF$ $[M+Na]^+$ calculated 1076.5371, found 1076.5382.

Analytic HPLC chromatogram of 4g:



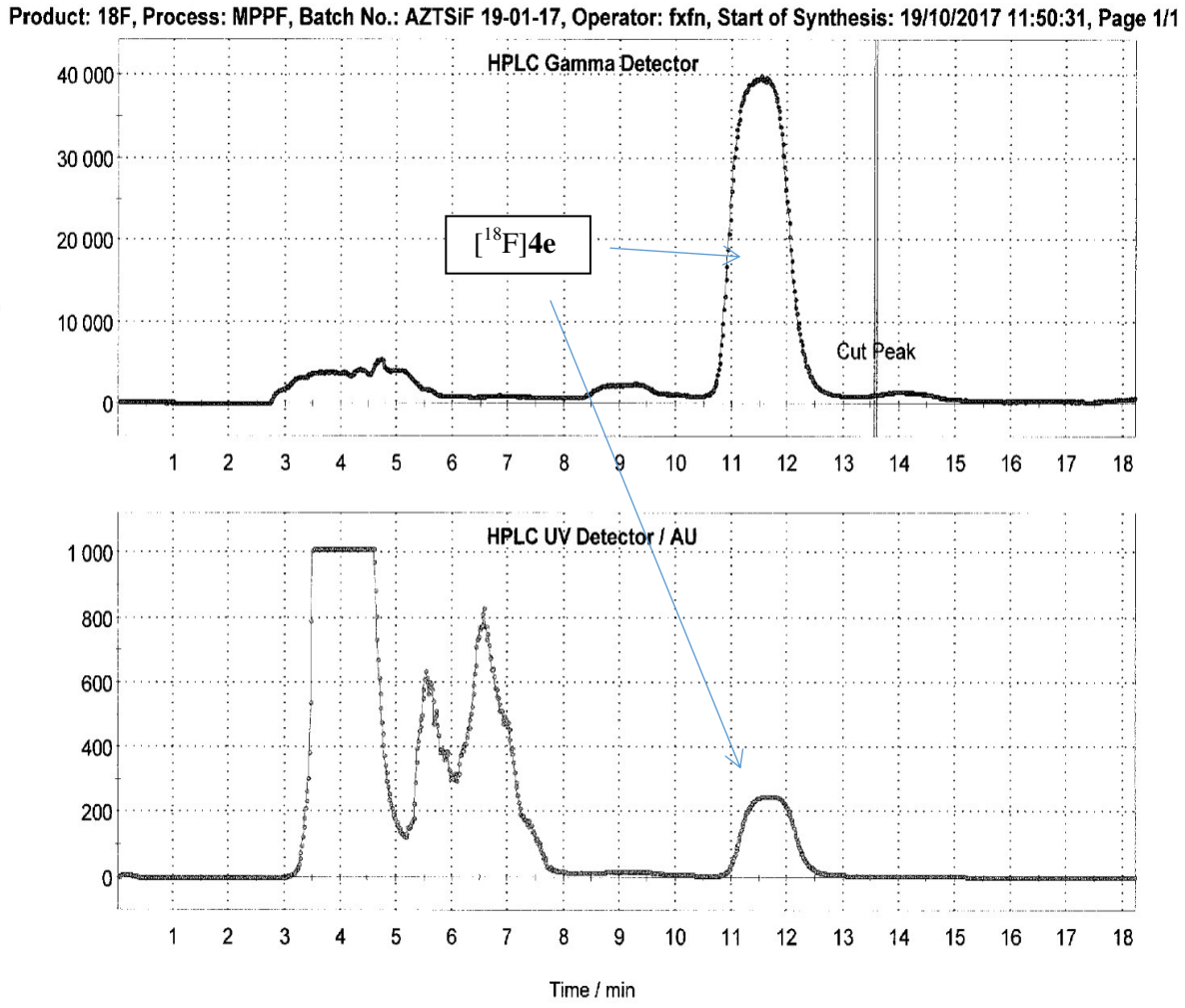
C) Radiosyntheses



*a. Radiosynthesis of [^{18}F] **4e***

No-carrier-added [^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of enriched [^{18}O]H_2O.[^{18}F]Fluoride production: Bombardment: 30-60 min; 30-60 µA; target volume 1.8-2.5 mL; 24-110 GBq were obtained. [^{18}F]Fluoride was trapped on an anion-exchange resin cartridge (Sep-Pak QMA light, Waters). The cartridge was eluted with an aqueous solution of NaCl (0.9% w/w, 300 µL) and the resulting saline solution was transferred to the reaction vial previously loaded with a THF solution of the silylated precursor and the acid. The resulting mixture was allowed to react at 70 or 100 °C under constant stirring for 15 min. After this time, the mixture was diluted with mobile phase (4 mL), and the resulting solution was injected into a semi-preparative HPLC (Luna C18, 5µm, 10*250mm, H_2O+0.1% TFA/CH_3CN+0.1% TFA: 30/70 isocratic (0-20 min), 2.5 mL/min, $t_{[18F]\mathbf{4e}}$ = 11.7 min). Then, the activity of the collected fraction of [^{18}F]**4e** was measured and the purity of a precise fraction of the sample was checked by analytical HPLC (Luna C18, 5µm, 4.6*250mm, H_2O+0.1% TFA/CH_3CN: 35/65 isocratic (0-30 min), 1 mL/min, $t_{[18F]\mathbf{4e}}$ = 11.53 min). The molar quantity in the sample was determined by fitting the UV pic area into a calibration line previously realized, then allowing to calculate the molar activity of the whole collected fraction containing [^{18}F]**4e**.

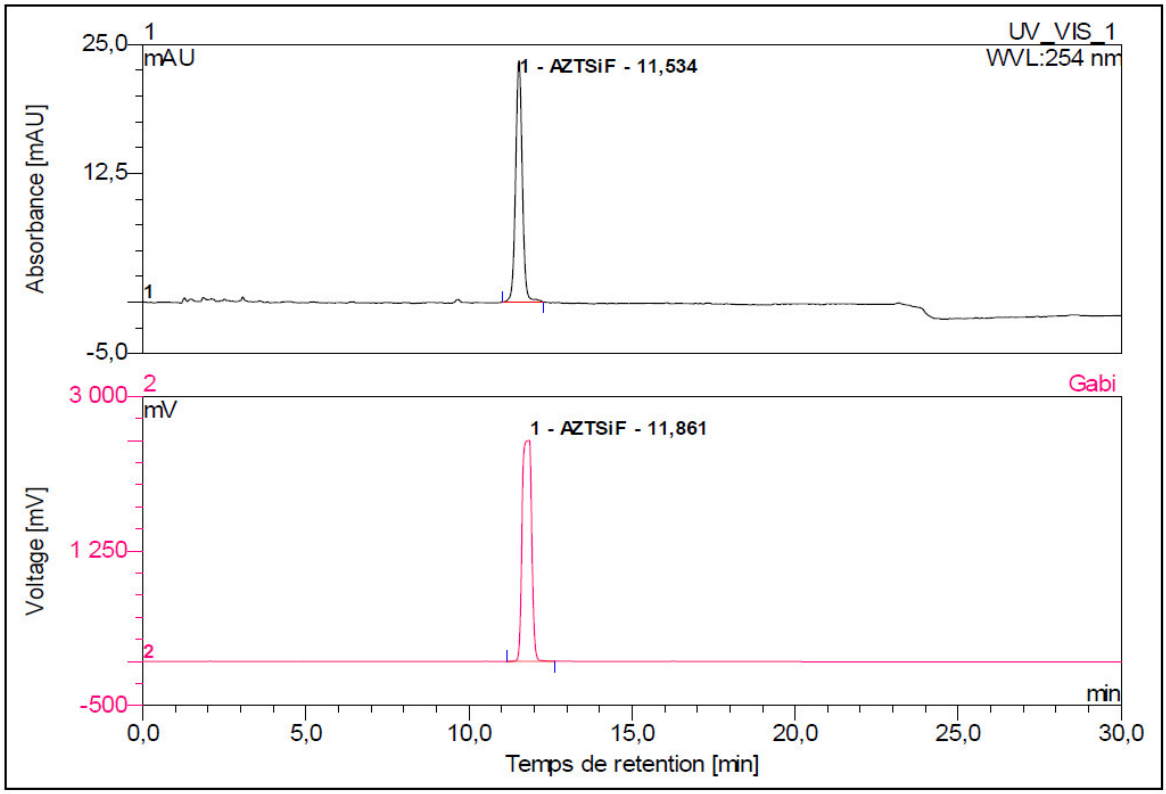
Preparative HPLC chromatogram of [^{18}F]4e obtained from 3e:



Analytic HPLC chromatogram of the collected fraction of [^{18}F]4e obtained from 3e:

2	19-10-17

Sample Name:	**28-04-10**	*Injection Volume:*	**20,0**
Vial Number:	**2**	*Channel:*	**UV_VIS_4**
Sample Type:	**unknown**	*Wavelength:*	**260**
Control Program:	**AZTSiF iso colonne Luna CQ 35 65 TFA /**	*Bandwidth:*	**1**
Quantif. Method:	**DEFAULT**	*Dilution Factor:*	**1,0000**
Recording Time:	**19/10/2017 12:40**	*Sample Weight:*	**1,0000**
Run Time (min):	**30,00**	*Sample Amount:*	**1,0000**



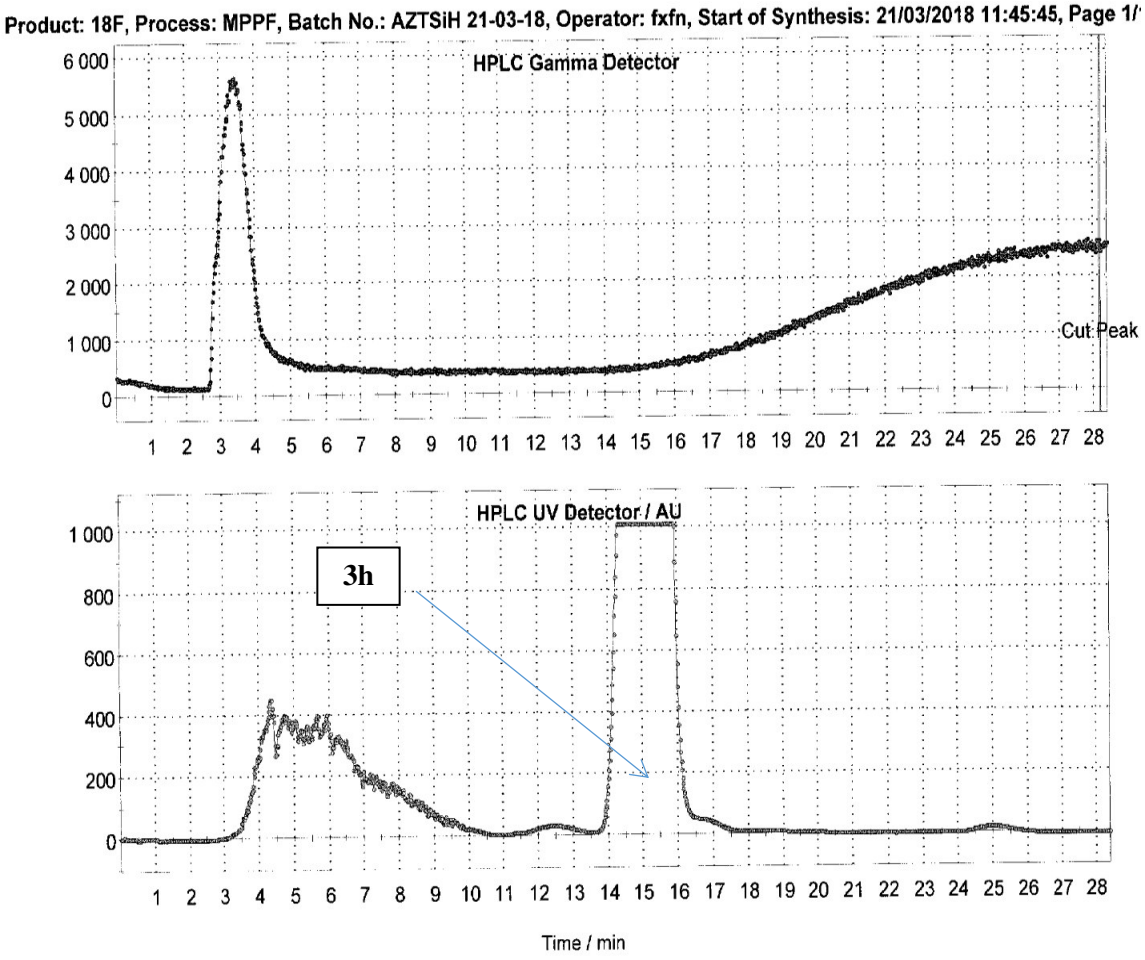
No. V_VIS	Ret.Time UV_VIS_1 min	Peak Name UV_VIS_1	Height UV_VIS_1 mAU	Area UV_VIS_1 mAU*min	Rel.Area UV_VIS_1 %	Amount UV_VIS_1	Type UV_VIS_1
n.a.	11,53	AZTSiF	23,428	5,561	100,00	n.a.	BMB*^
Total:			23,428	5,561	100,00	0,000	

Screening of conditions for the radiosynthesis of [^{18}F]4e

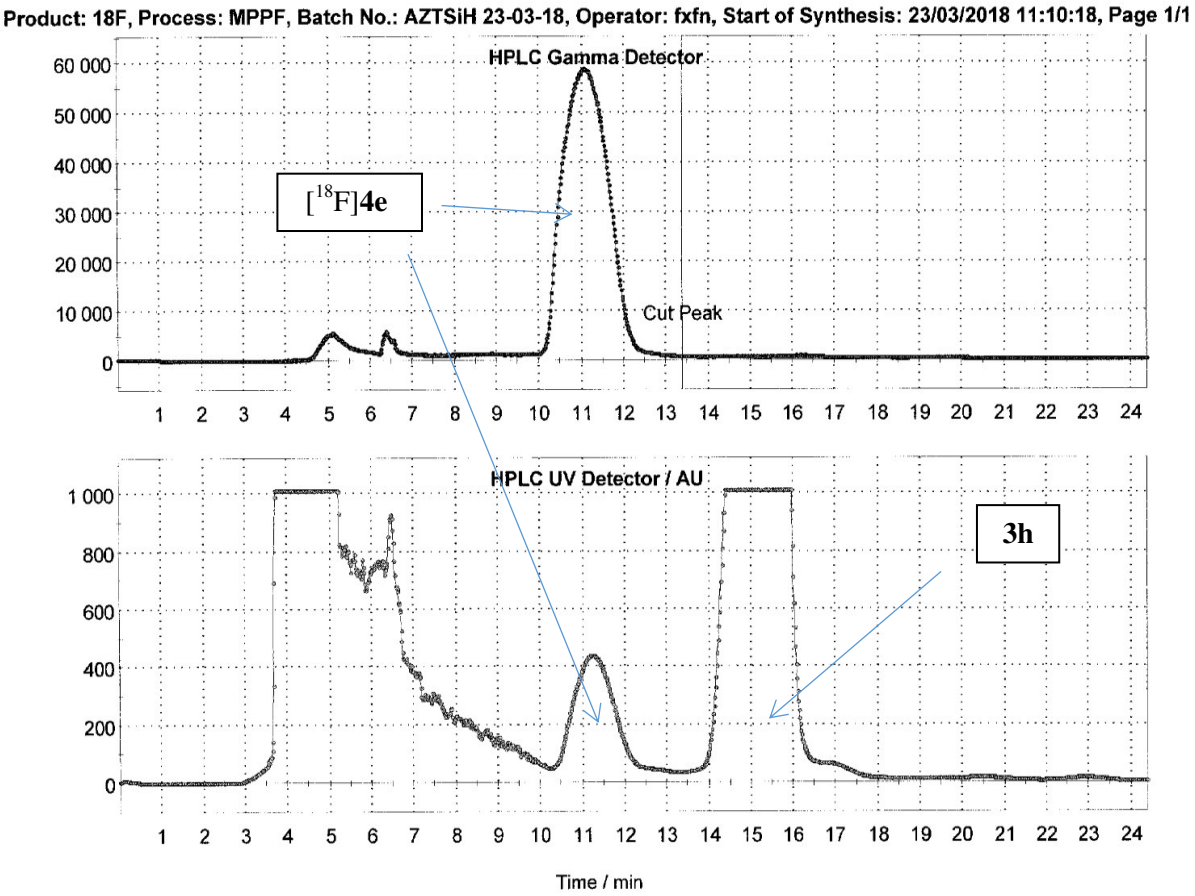
Exp	Bom-bard-ment	Aqueous solution for QMA elution (% w/w)	Reacting Vial	Condi-tions	Activity at the end of bombar-dment in GBq	Activity of [^{18}F]4e in GBq (Time,[a] decay corrected)	Activity yield (AY)[b] (Radio-chemical yield)	Molar activity (GBq/µmol)[c]	Mean[d] of AY (Mean of RCY)	Mean[d] of molar activity (GBq/µmol)
1	30min - 30µA	300µL NaCl (0.9%)	**3e** (10 mg, 13.3µmol), THF (400µL), HCl_{aq} (1M, 1 equiv, 13.3µL), H_2O (82.7µL)	70°C - 15min	24	0.72 (35 min, 0.89)	**3.0% (3.7%)**	**6**		
2	42min - 55µA	300µL NaCl (0.9%)	**3e** (10 mg, 13.3µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 13.3µL)	100°C - 15min	79	11.6 (29 min, 13.8)	14.6% (17.5%)	188	**14.6 ± 0.03% (17.5 ± 0.02%)**	**188 ± 5**
3	58min - 55µA	300µL NaCl (0.9%)	**3e** (10 mg, 13.3µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 13.3µL)	100°C - 15min	78,5	11.5 (29 min, 13.8)	14.7% (17.6%)	181		
4	59min - 55µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	110,6	38.5 (31 min, 46.1)	**34.8% (41.7%)**	166	**28.6 ± 5.9% (34.4 ± 7.0%)**	**130 ± 31**
5	59min - 55µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	88,7	20.4 (29 min, 24.5)	23.0% (27.7%)	115		
6	58min - 55µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	94	26.4 (30 min, 31.8)	28.0% (33.8%)	109		
7	58min - 55µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), PS-SO_3H (6 mg, 1 equiv)	100°C - 15min	96,5	22.5 (29 min, 27.0)	23.3% (28.0%)	61		
8	51min - 60µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), AcOH (10 equiv, 3.8µL)	100°C - 15min	105	32 (29 min, 38.7)	30.5% (36.9%)	103	**28.8 ± 2.3% (34.9 ± 2.8%)**	**89 ± 20**
9	54min - 60µA	300µL NaCl (0.9%)	**3e** (5 mg, 6.6µmol), THF (300µL), AcOH (10 equiv, 3.8µL)	100°C - 15min	101,6	27.6 (31 min, 33.4)	27.2% (32.9%)	75		
10	55min - 55µA	300µL NaCl (0.9%)	**4e** (4,6 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	94	0.4 (30 min, 0.5)	**0.4% (0.5%)**	**nd**		
11	59min - 60µA	300µL NaCl (0.9%)	**3h** (4,5 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	75	0 (39 min, 0)	**0**	**nd**		
12	58min - 60µA	300µL NaCl (0.9%)	**3h** (4,5 mg, 6.6µmol), THF (300µL), AcOH (10 equiv, 3.8µL)	100°C - 15min	80	0 (39 min, 0)	**0**	**nd**		
13	65min - 55µA	600µL H_2O, 1mL CH_3CN (K_2CO_3 + K2.2.2.) Azeotropic drying	**3h** (7,3 mg, 10 µmol), DMSO (300µL), AcOH (5 equiv, 3.0µL)	60°C - 15min	182.6	60.9 (**52 min**, 84.6)	**33.4% (46.3%)**	**nd**		
14	57min - 55µA	300µL Na_2SO_4 (2.1%)	**3e** (5 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	110	33.5 (40.4)	**30.4% (36.7%)**	**111**		

[a]From the end of bombardment to the measurement of the activity of [^{18}F]**4e**. [b]Calculated as the activity in the collected vial divided by the activity at the end of bombardment (x100). [b]Molar activity determined by HPLC/radio HPLC. [c]mean ± standard deviation of the *n* experiments. nd = Non determined. PS-SO_3H = Sulfonic acid functionalized polystyren resin (1.18 mmol/g).

Preparative HPLC chromatogram of [^{18}F]4e obtained from 3h in aqueous conditions (entry 12):



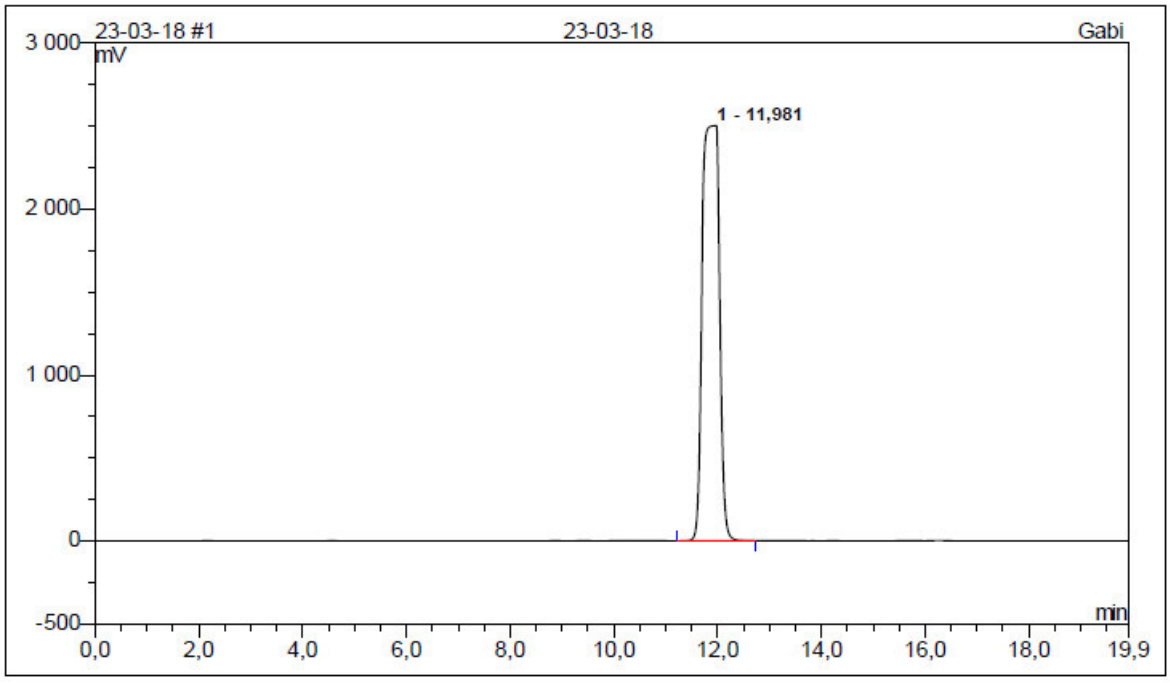
Preparative HPLC chromatogram of [^{18}F]4e obtained from 3h in anhydrous conditions (entry 13):



Analytic HPLC chromatogram of the collected fraction of [^{18}F]4e obtained from 3h in anhydrous conditions (entry 13):

1 23-03-18

Sample Name:	**23-03-18**	*Injection Volume:*	**20,0**
Vial Number:	**3**	*Channel:*	**Gabi**
Sample Type:	**unknown**	*Wavelength:*	**n.a.**
Control Program:	**AZTSiF iso colonne Luna CQ 35 65 TFA ACN sans**	*Bandwidth:*	**n.a.**
Quantif. Method:	**DEFAULT**	*Dilution Factor:*	**1,0000**
Recording Time:	**23/03/2018 12:25**	*Sample Weight:*	**1,0000**
Run Time (min):	**19,91**	*Sample Amount:*	**1,0000**



System Suitability Test Results:

No.	Test Name	Sample Condition	Peak Condition	Test Result
	Number of executed single tests:	n.a.	Total test result:	n.a.

*b. Radiosynthesis of [^{18}F]**4g***

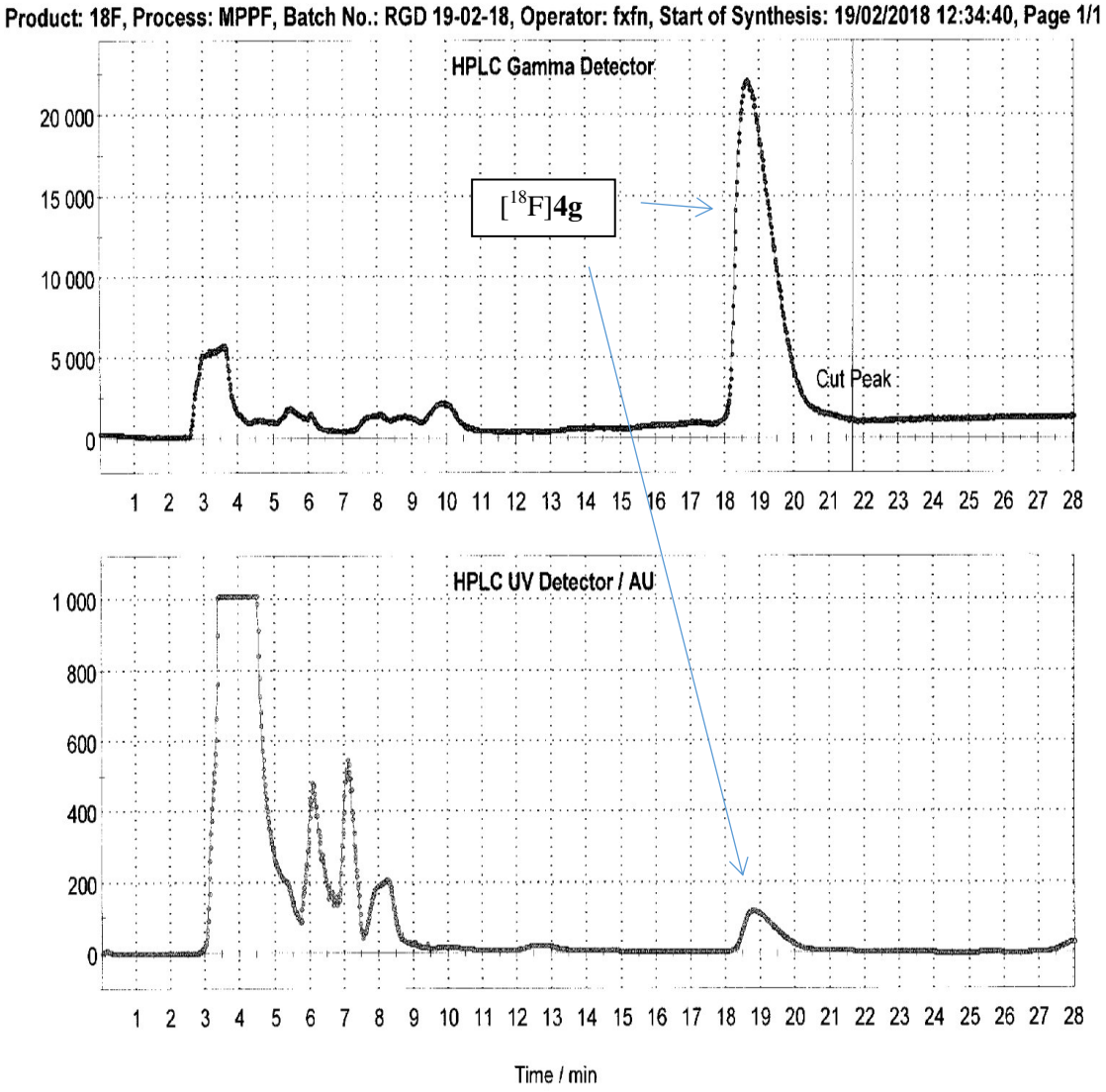
No-carrier-added [^{18}F]fluoride was produced by the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of enriched [^{18}O]H_2O.[^{18}F]Fluoride production: Bombardment: 50-60 min; 60-65 µA; target volume 1.8-2.5 mL; 48-94 GBq were obtained. [^{18}F]Fluoride was trapped on an anion-exchange resin cartridge (Sep-Pak QMA light, Waters). The cartridge was eluted with an aqueous solution of NaCl (0.9% w/w, 300 µL) and the resulting saline solution was transferred to the reaction vial previously loaded with a THF solution of the silylated precursor and the acid. The resulting mixture was allowed to react at 100 °C under constant stirring for 15 min or 30 min. After this time, the mixture was diluted with mobile phase (4 mL), and the resulting solution was injected into a semi-preparative HPLC (Luna C18, 5µm, 10*250mm, H_2O+0.1% TFA/CH_3CN: 50/50 isocratic (0-30 min), 2.5 mL/min, $t_{[18F]\mathbf{4g}}$ = 18.6 min). Then, the activity of the collected fraction of [^{18}F]**4g** was measured and the purity of a known amount of the sample was checked by analytical HPLC (Luna C18, 5µm, 4.6*250mm, H_2O+0.1% TFA/CH_3CN: 50/50 isocratic (0-30 min), 1 mL/min, $t_{[18F]\mathbf{4g}}$ = 16.23 min). The molar quantity was determined by fitting the UV pic area into a calibration line previously realized, allowing to calculate the molar activity of the whole collected fraction containing [^{18}F]**4g**.

Screening of conditions for the radiosynthesis of [^{18}F]4g

Exp	Bom-bard-ment	Aqueous solution for QMA elution (% w/w)	Reacting Vial	Condi-tions	Activity at the end of bombar-dment in GBq	Activity of [^{18}F]4g in GBq (Time,[a] decay corrected)	Activity yield (AY)[b] (Radio-chemical yield)	Molar activity (GBq/µmol)[c]	Mean[d] of AY (Mean of RCY)	Mean[d] of molar activity (GBq/µmol)
1	58min - 60µA	300µL NaCl (0.9%)	**3g** (7.4 mg, 6.6µmol), THF (300µL), HCl_{aq} (1M, 1 equiv, 6.6µL)	100°C - 15min	84	0.6 (42 min, 0.8)	**0.7% (1.0%)**	**100**		
2	59min - 60µA	300µL NaCl (0.9%)	**3g** (7.4 mg, 6.6µmol), THF (300µL), H_2O (100 µL), AcOH (10 equiv, 3.8µL)	100°C - 15min	100	4.1 (40 min, 5.3)	**4.1% (5.3%)**	**86**		
3	59min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (20 equiv, 3.8µL)	100°C - 15min	84	3.5 (38 min, 4.5)	**4.2% (5.3%)**	**189**		
4	50min - 65µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (20 equiv, 3.8µL)	100°C - 30min	64	3.8 (60 min, 5.6)	**5.9% (8.7%)**	**82**		
5	60min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL)	100°C - 30min	48	1.4 (61 min, 2.4)	**2.9% (5.0%)**	**80**		
6	60min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (2 equiv, 0.38µL)	100°C - 30min	94	5.5 (60 min, 8.5)	5.8% (9.0%)	116	**13.8 ± 5.4% (20.4 ± 7.7%)**	**129 ± 37**
7	60min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (2 equiv, 0.38µL)	100°C - 30min	101	16.5 (58 min, 23.9)	16.4% (23.8%)	184		
8	53min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (2 equiv, 0.38µL)	100°C - 30min	99	15.2 (62 min, 22.4)	15.4% (22.8%)	115		
9	60min - 60µA	300µL NaCl (0.9%)	**3g** (3.7 mg, 3.3µmol), THF (300µL), AcOH (2 equiv, 0.38µL)	100°C - 30min	89	15.7 (61 min, 23.1)	17.6% (25.9%)	101		

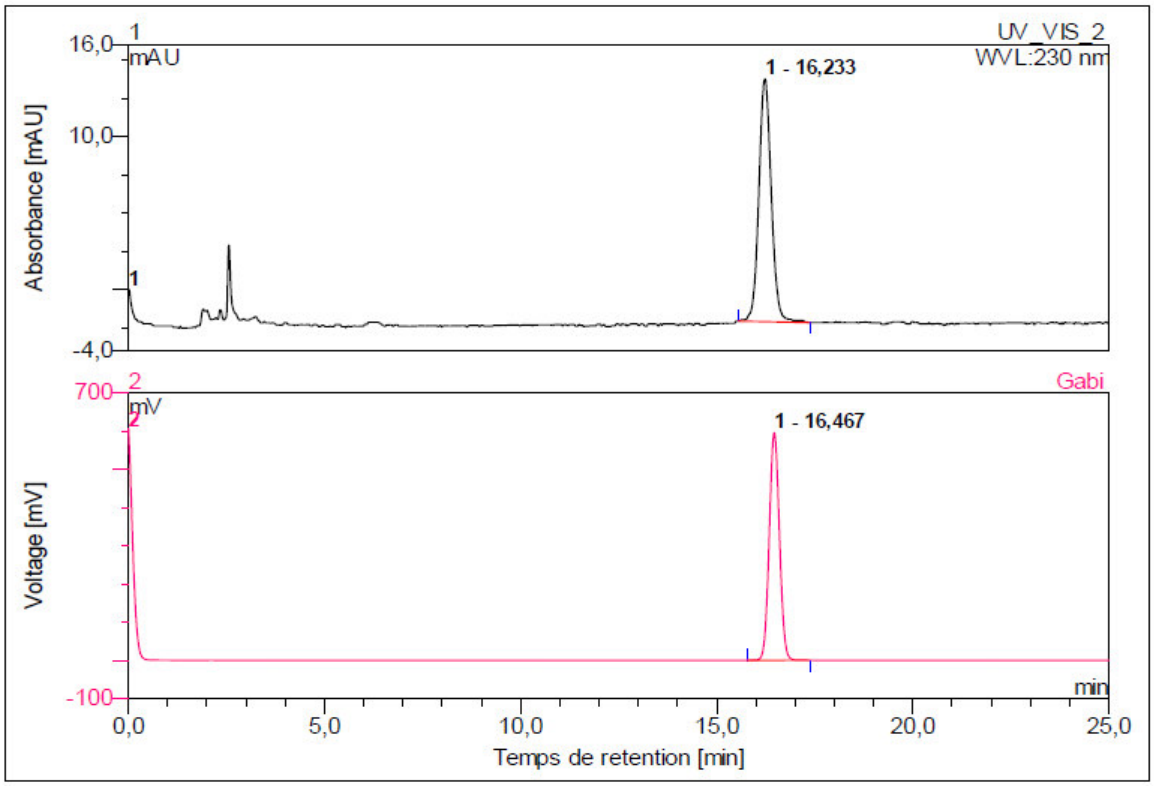
[a]From the end of bombardment to the measurement of the activity of [^{18}F]**4g**. [b]Calculated as the activity in the collected vial divided by the activity at the end of bombardment (x100). [b]Molar activity determined by HPLC/radio HPLC. [c]mean ± standard deviation of the *n* experiments. nd = Non determined.

Preparative HPLC chromatogram of [^{18}F]4g:



Analytic HPLC chromatogram of the collected fraction of [^{18}F]4g:

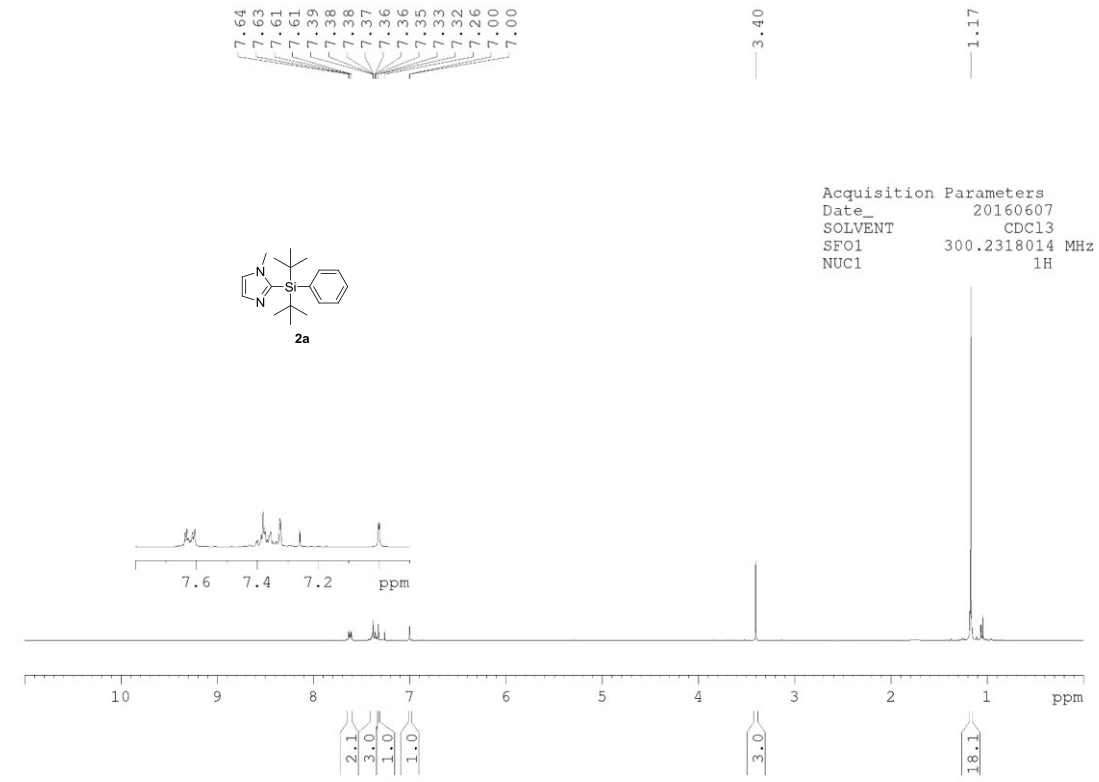
2	RGD 19-02		
Sample Name:	**28-04-10**	*Injection Volume:*	**20,0**
Vial Number:	**2**	*Channel:*	**UV_VIS_4**
Sample Type:	**unknown**	*Wavelength:*	**260**
Control Program:	**AZTSiF iso colonne Luna CQ 50 50 TFA A**	*Bandwidth:*	**1**
Quantif. Method:	**DEFAULT**	*Dilution Factor:*	**1,0000**
Recording Time:	**19/02/2018 14:31**	*Sample Weight:*	**1,0000**
Run Time (min):	**25,00**	*Sample Amount:*	**1,0000**

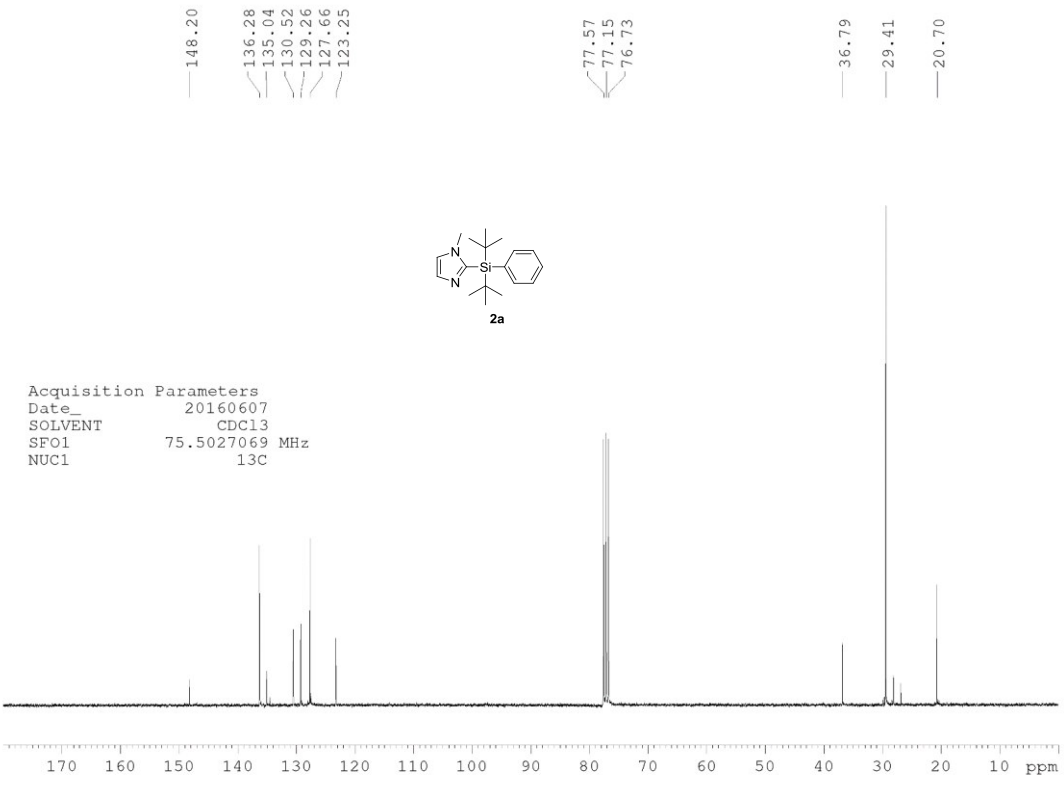


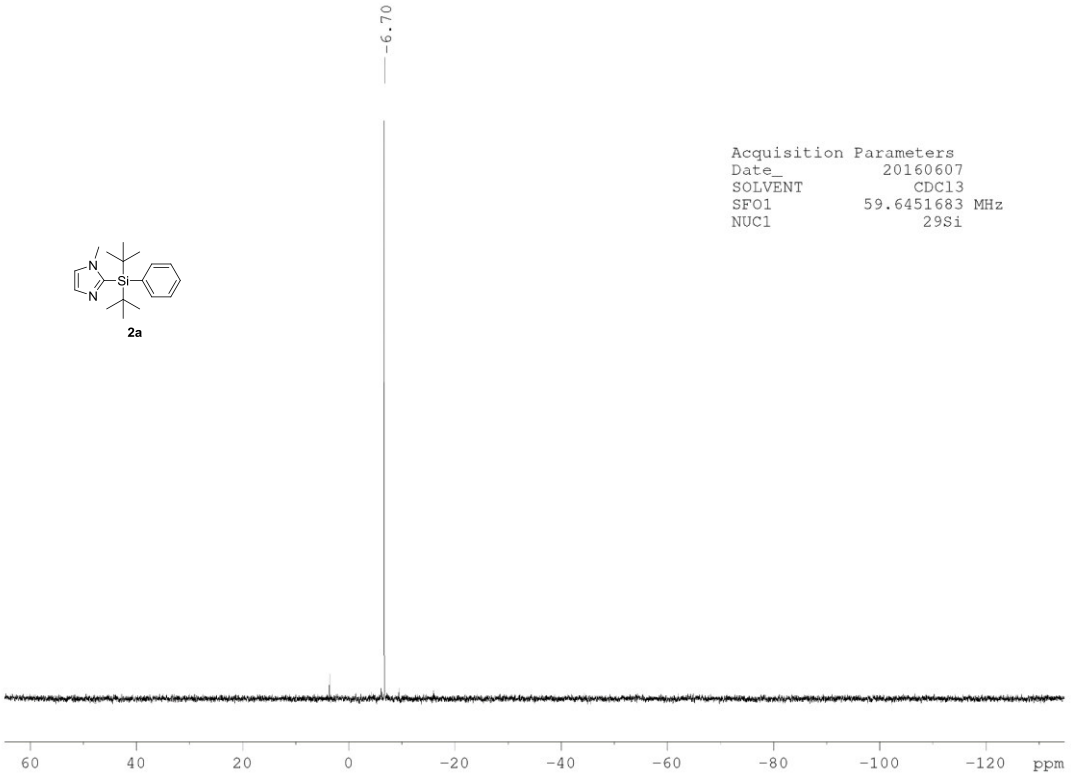
No. V_VIS_	Ret.Time UV_VIS_2 min	Peak Name UV_VIS_2	Height UV_VIS_2 mAU	Area UV_VIS_2 mAU*min	Rel.Area UV_VIS_2 %	Amount UV_VIS_2	Type UV_VIS_2
n.a.	16,23	n.a.	15,876	5,847	100,00	n.a.	BMB*
Total:			15,876	5,847	100,00	0,000	

D) ^{1}H, ^{13}C, ^{29}Si and ^{19}F NMR spectra

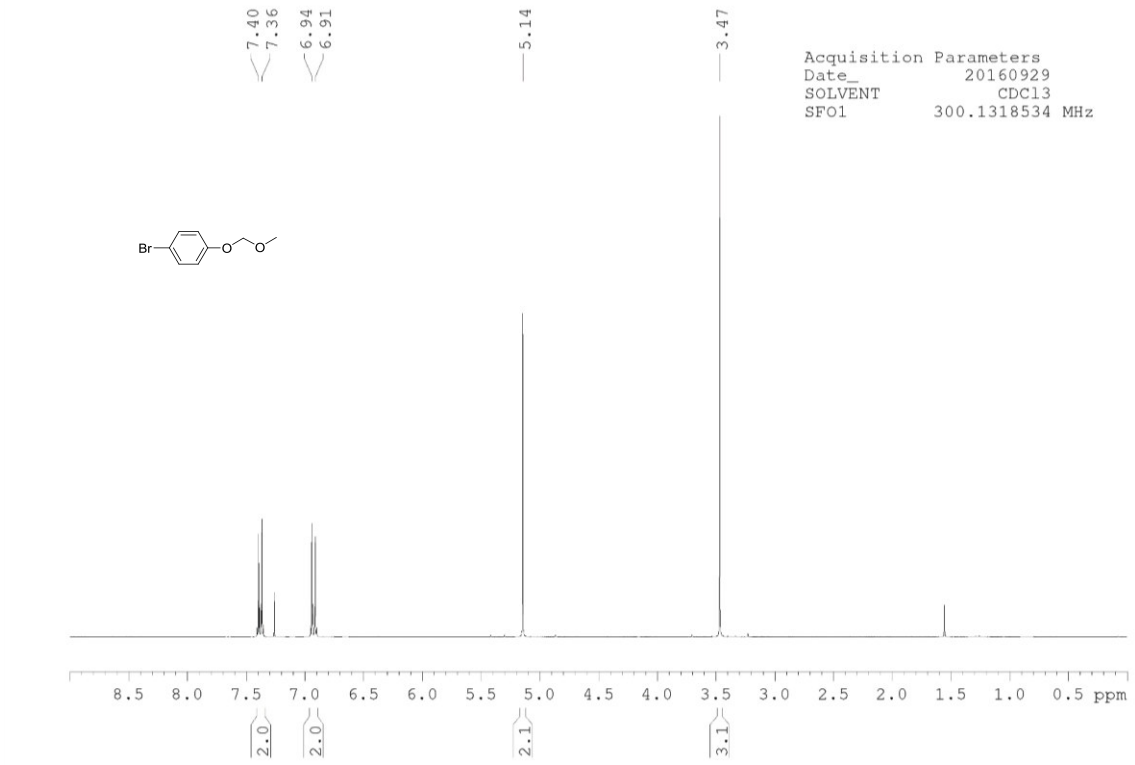
2-(di-*tert*-butyl(phenyl)silyl)-1-methyl-1*H*-imidazole 2a

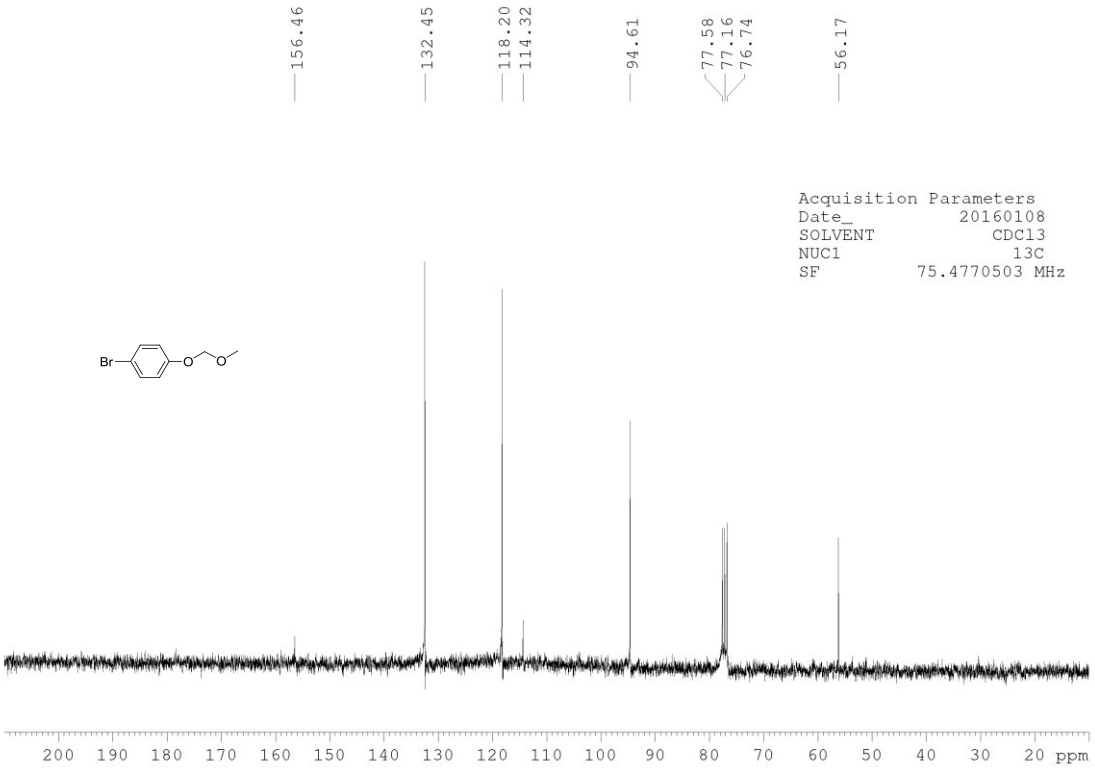




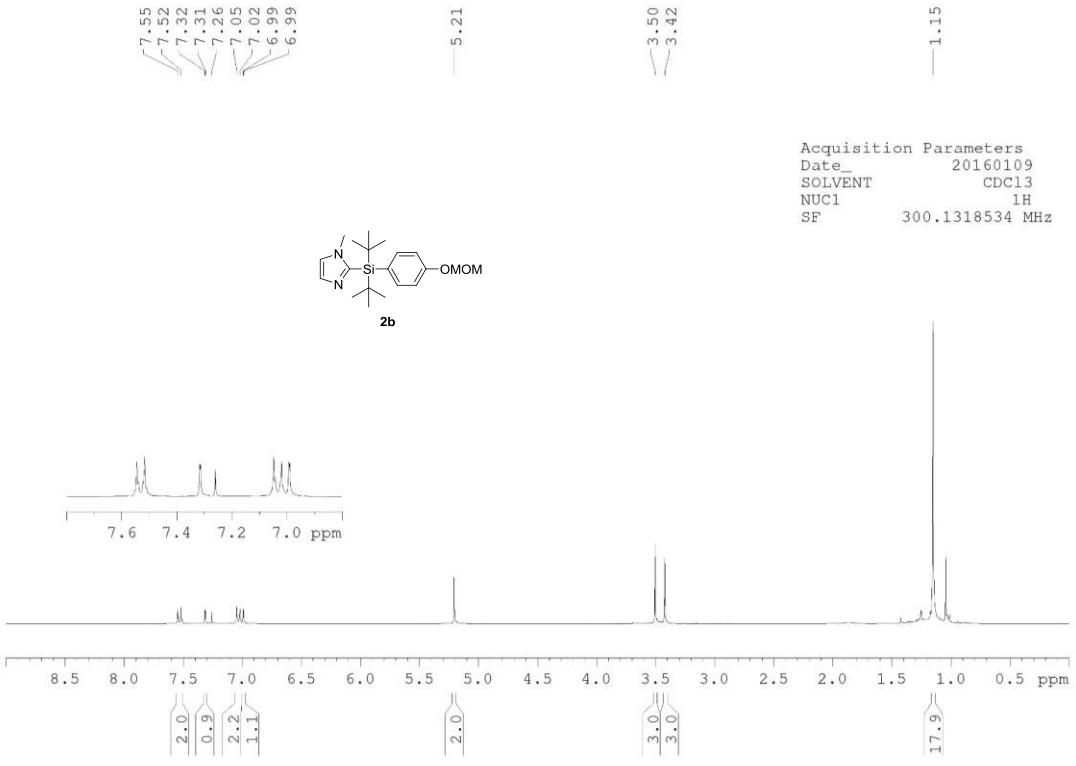


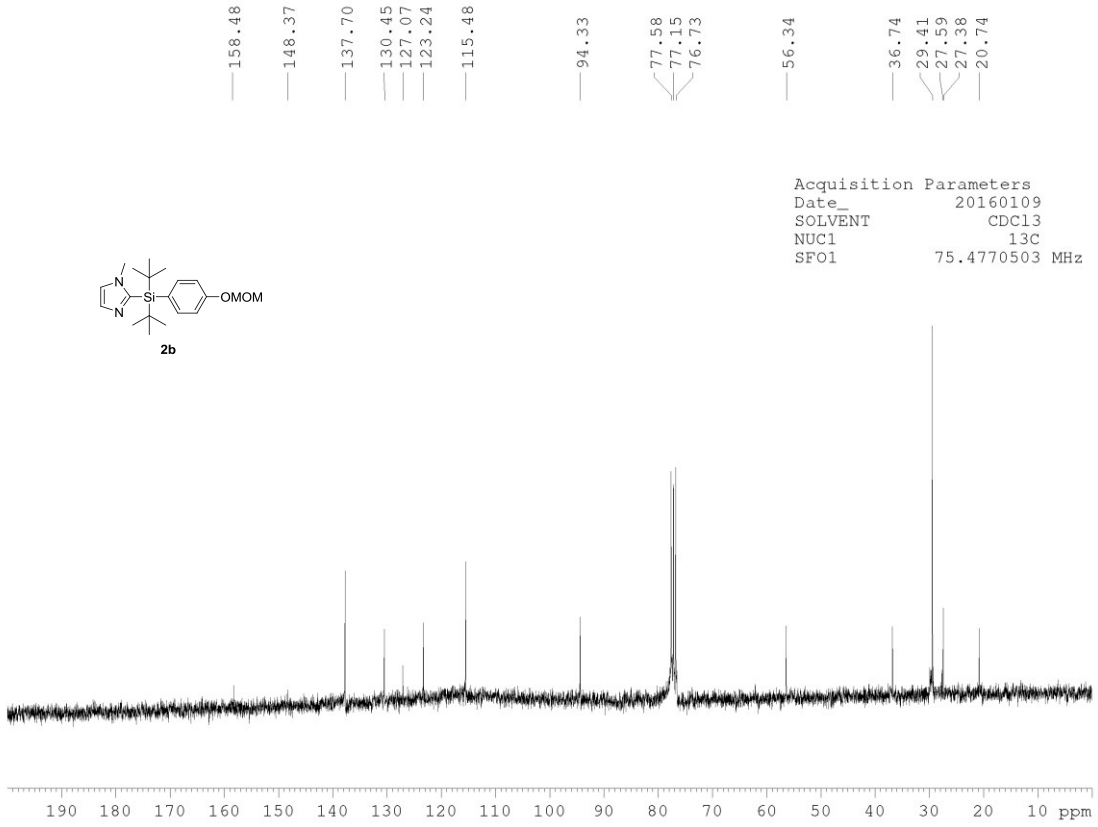
1-bromo-4-(methoxymethoxy)benzene

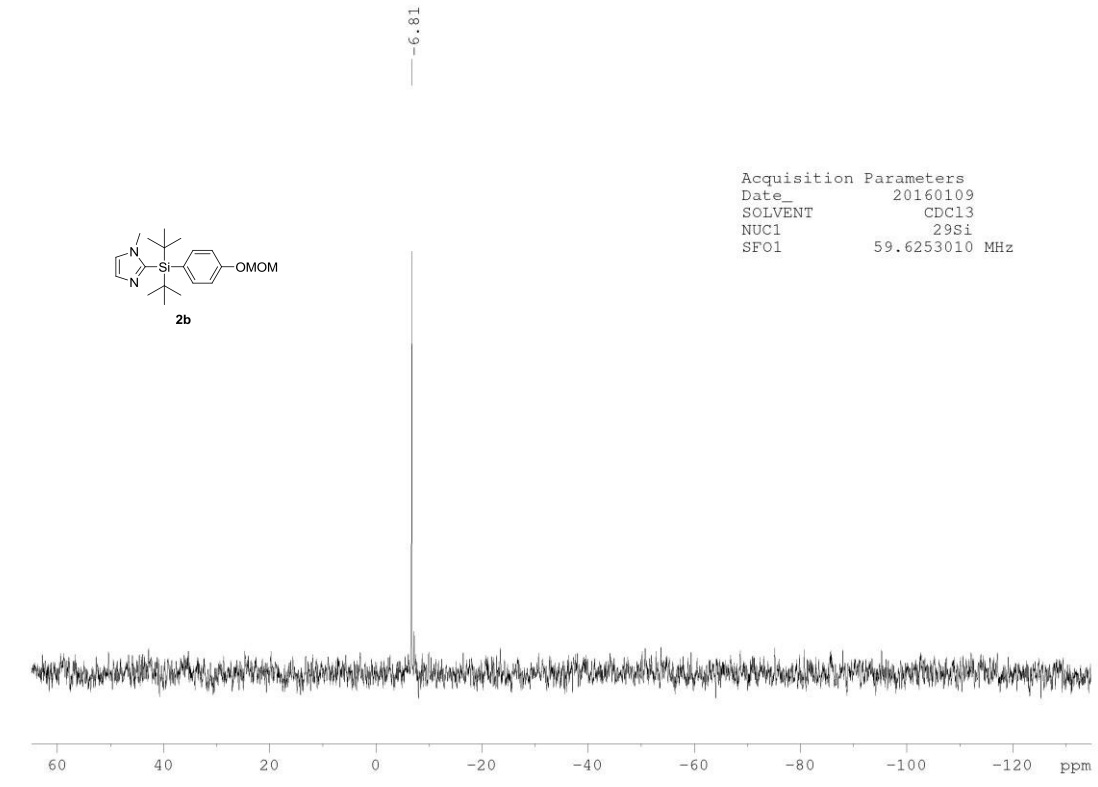




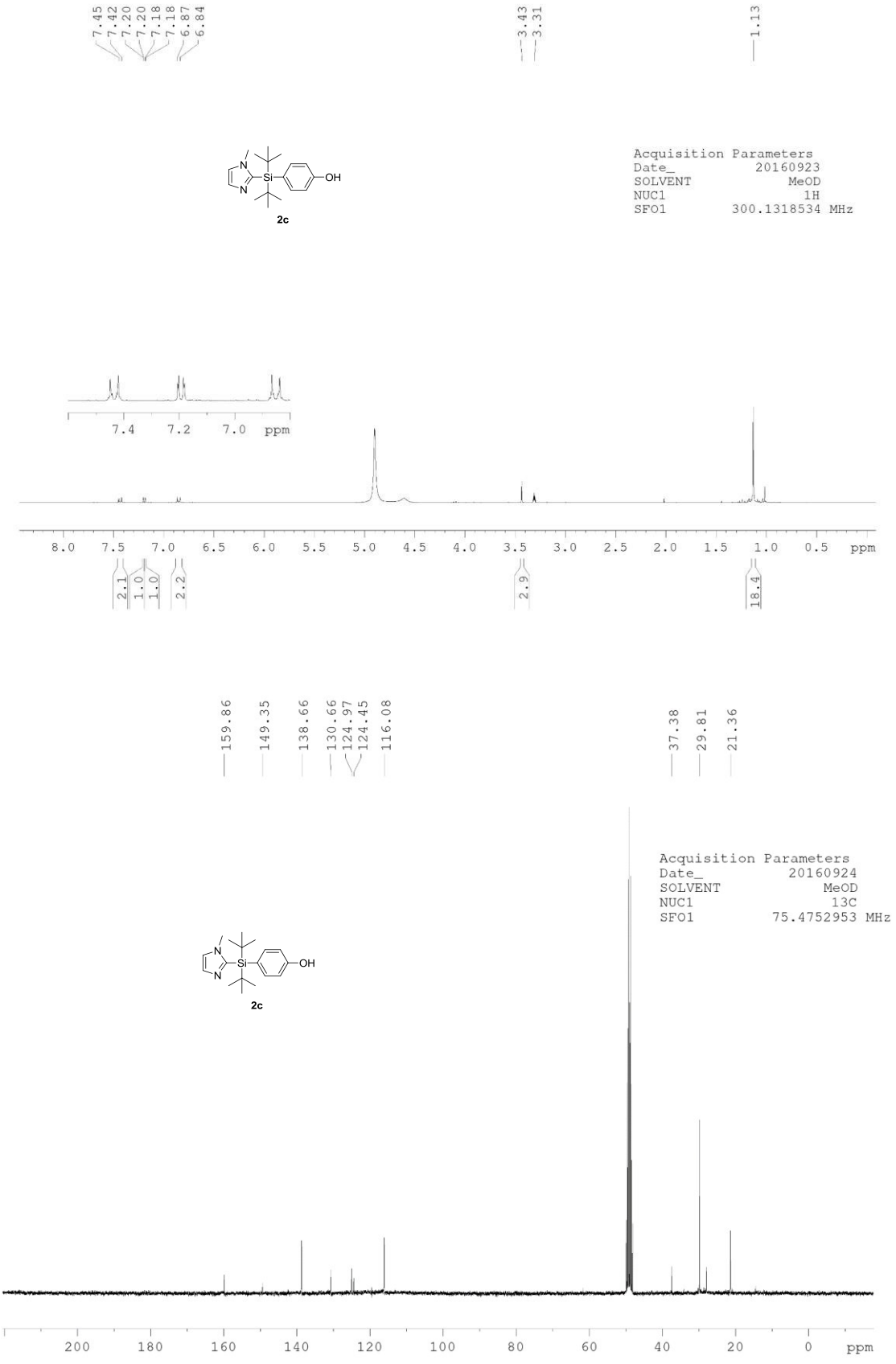
2-(di-*tert*-butyl(4-(methoxymethoxy)phenyl)silyl)-1-methyl-1*H*-imidazole 2b

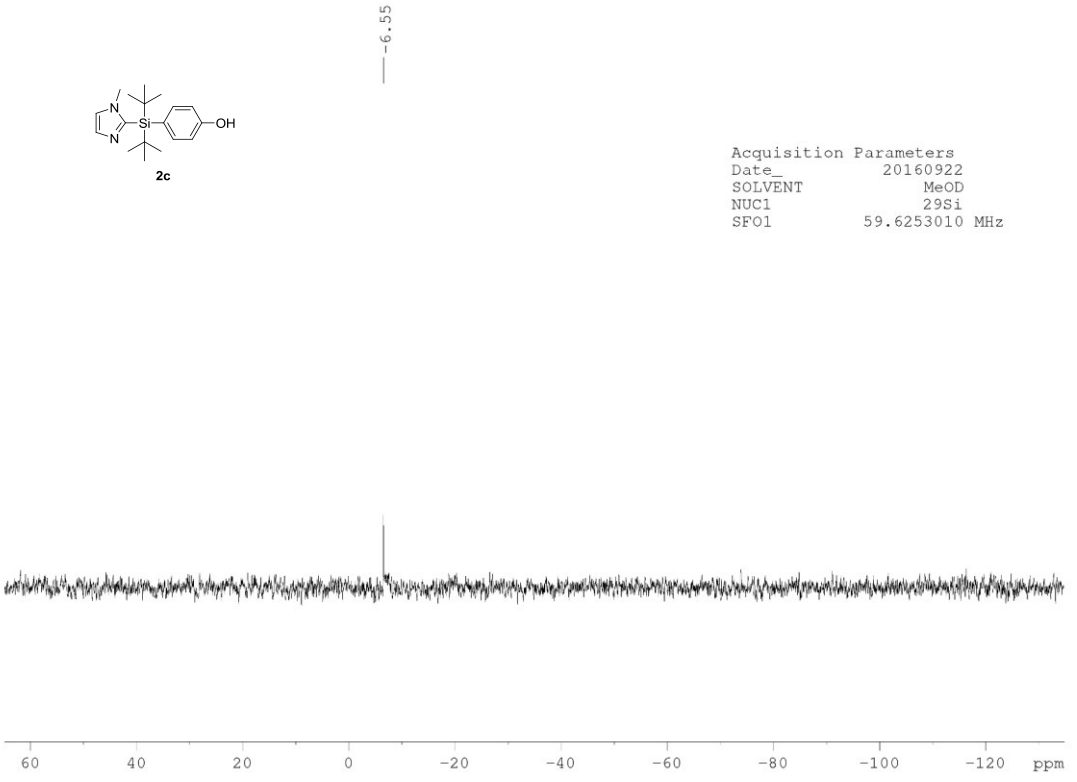



158.48
148.37
137.70
130.45
127.07
123.24
115.48
94.33
77.58
77.15
76.73
56.34
36.74
29.41
27.59
27.38
20.74
Acquisition Parameters
Date_ 20160109
SOLVENT CDCl3
NUC1 13C
SFO1 75.4770503 MHz
OMOM
2b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

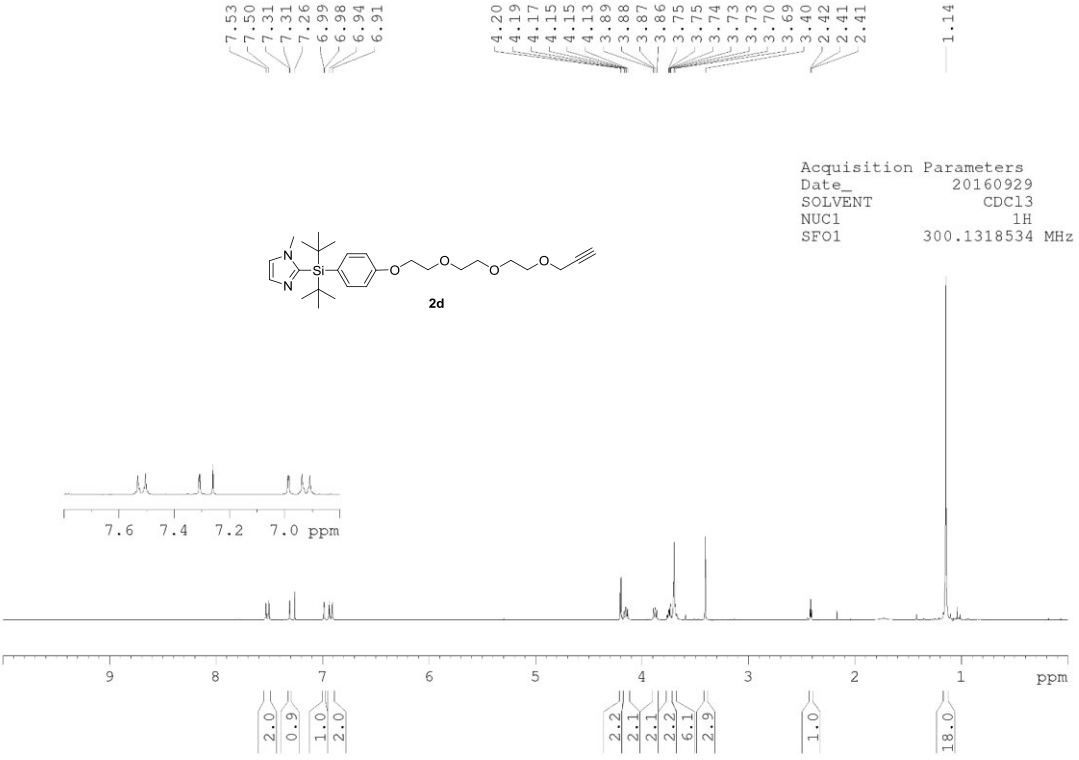

-6.81
Acquisition Parameters
Date_ 20160109
SOLVENT CDCl3
NUC1 29Si
SFO1 59.6253010 MHz
OMOM
2b
60 40 20 0 -20 -40 -60 -80 -100 -120 ppm

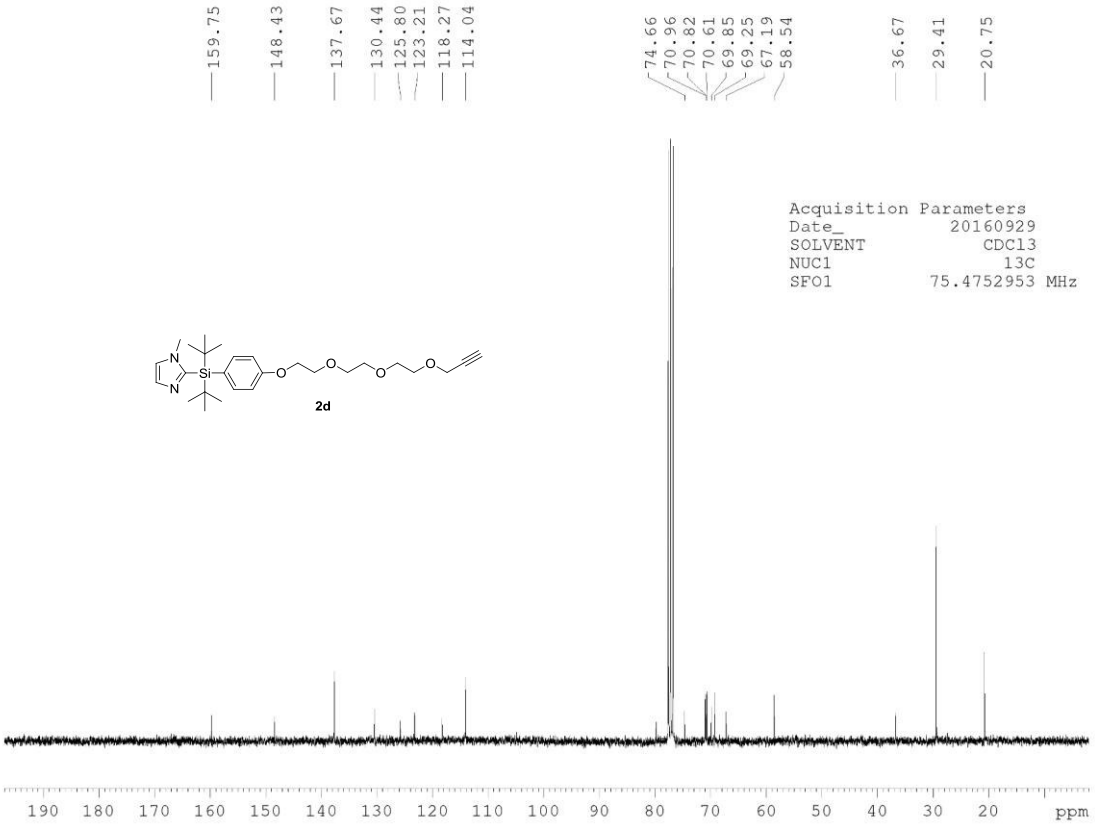
4-((1-methyl-1*H*-imidazol-2-yl)-di-*tert*-butylsilyl) phenol 2c

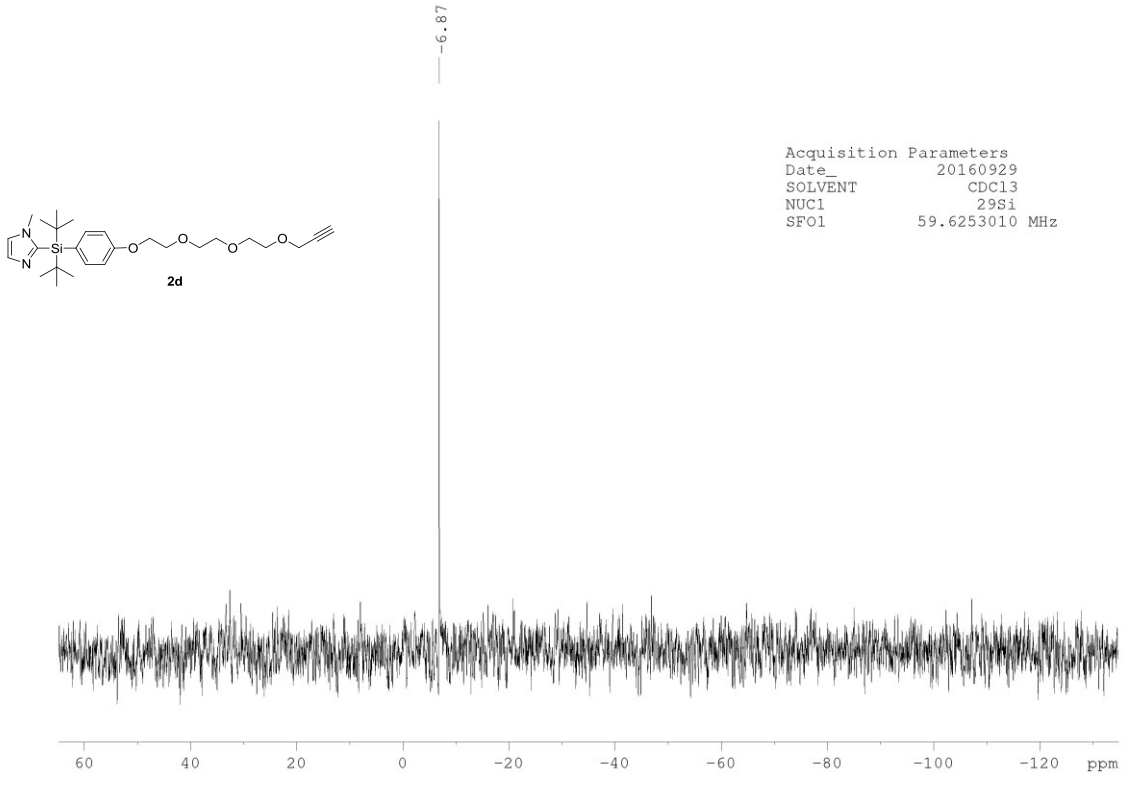




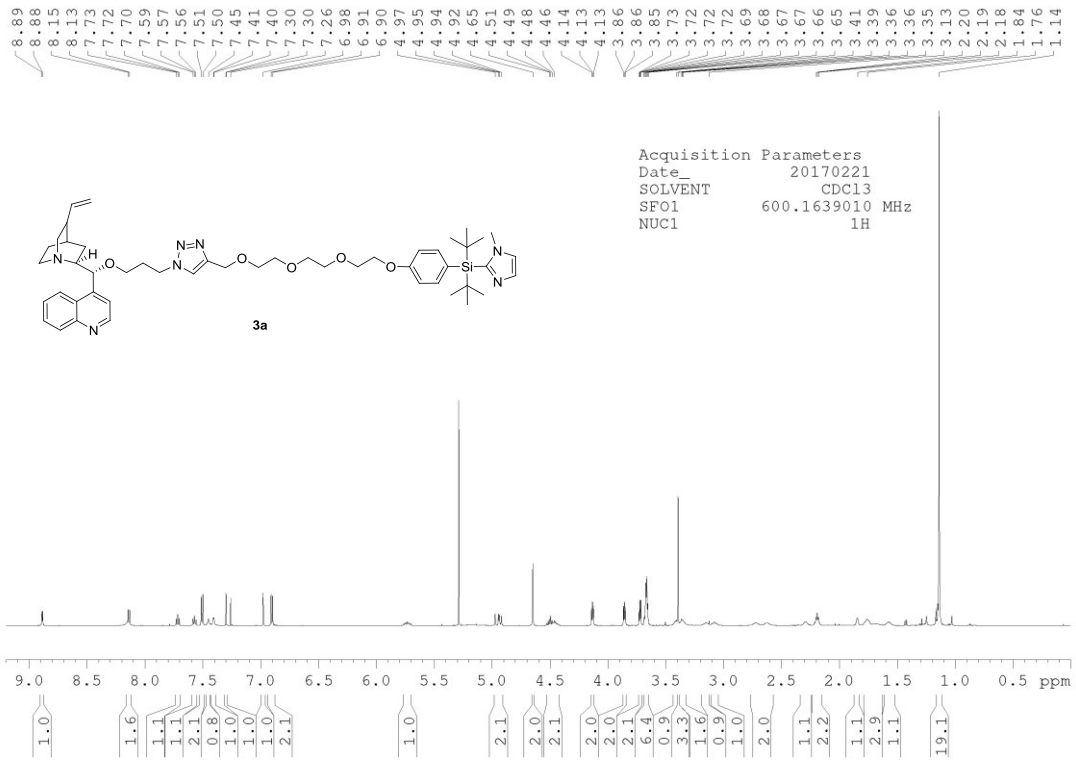
2-((4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenyl)di-*tert*-butylsilyl)-1-methyl-1*H*-imidazole 2d

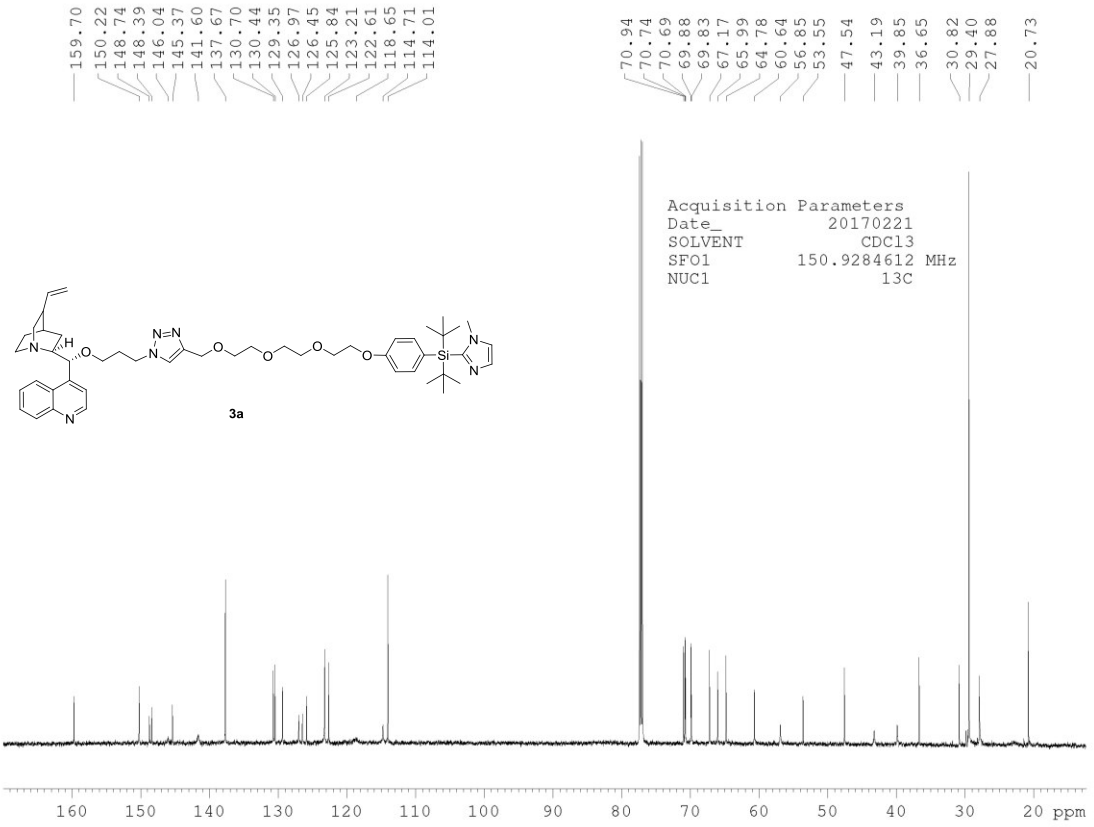


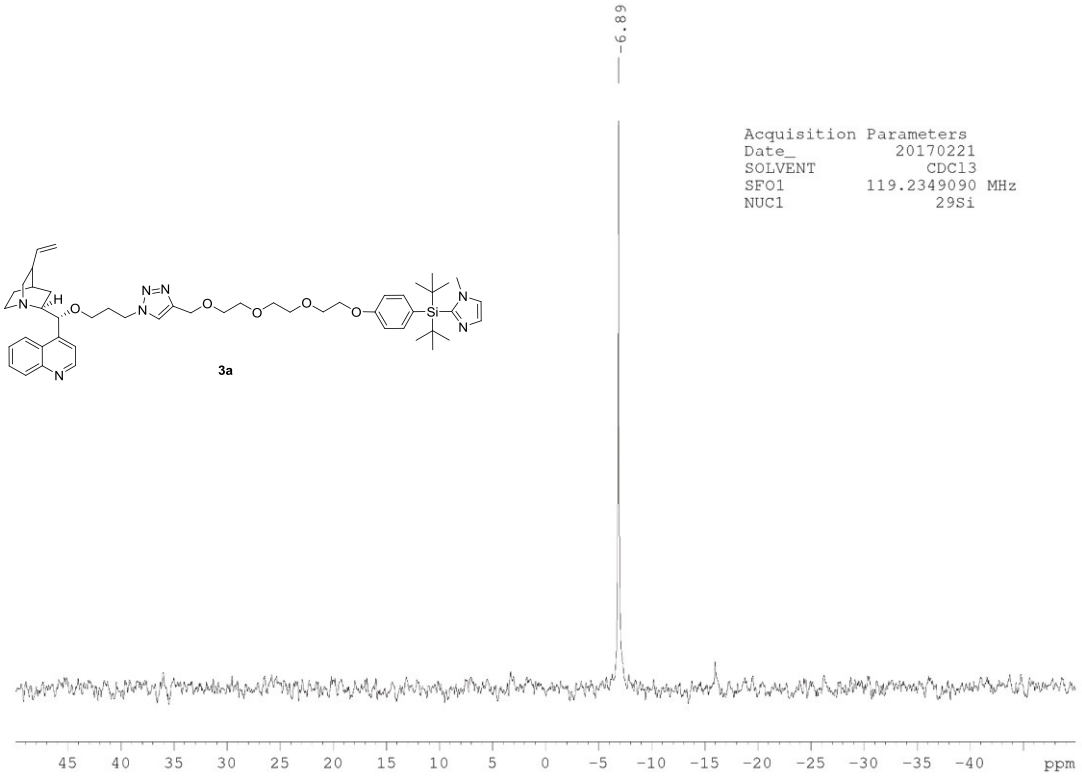

159.75
148.43
137.67
130.44
125.80
123.21
118.27
114.04
74.66
70.96
70.82
70.61
69.85
69.25
67.19
58.54
36.67
29.41
20.75
Acquisition Parameters
Date_ 20160929
SOLVENT CDCl3
NUC1 13C
SFO1 75.4752953 MHz
2d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


-6.87
Acquisition Parameters
Date_ 20160929
SOLVENT CDCl3
NUC1 29Si
SFO1 59.6253010 MHz
2d
60 40 20 0 -20 -40 -60 -80 -100 -120 ppm

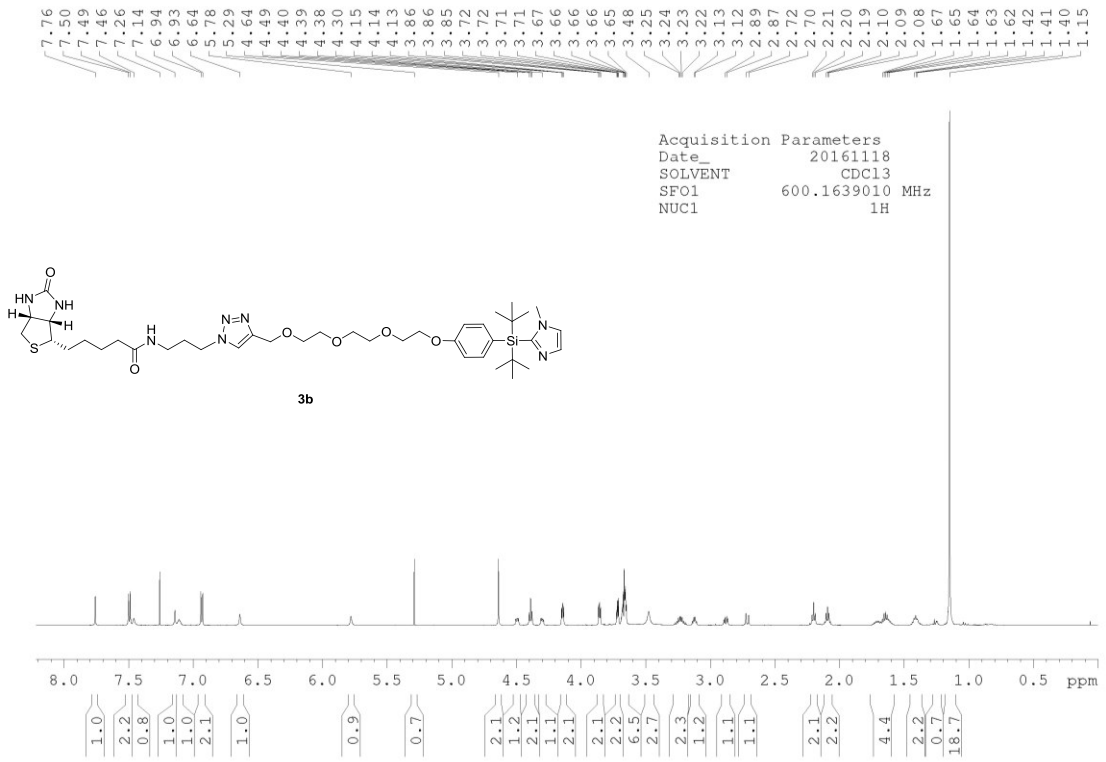
(2S)-2-(R)-*O*-[3-(4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-cinchonidine 3a

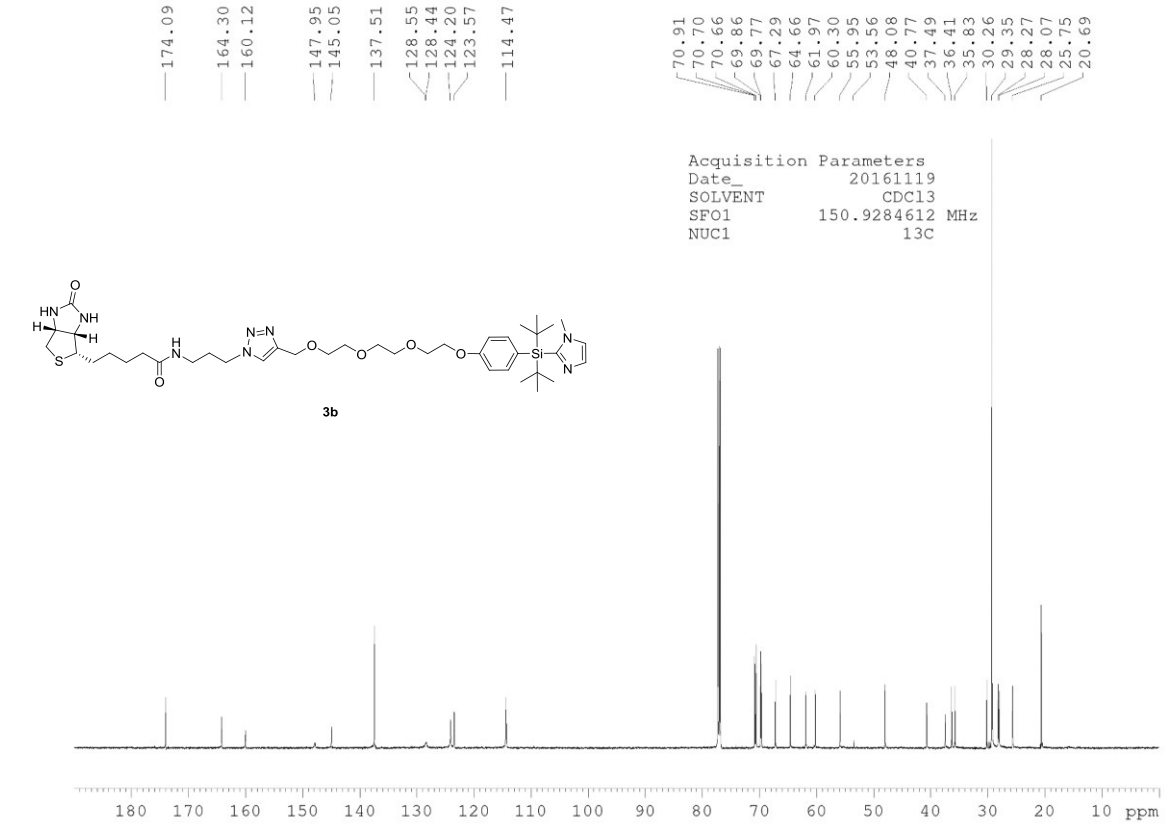


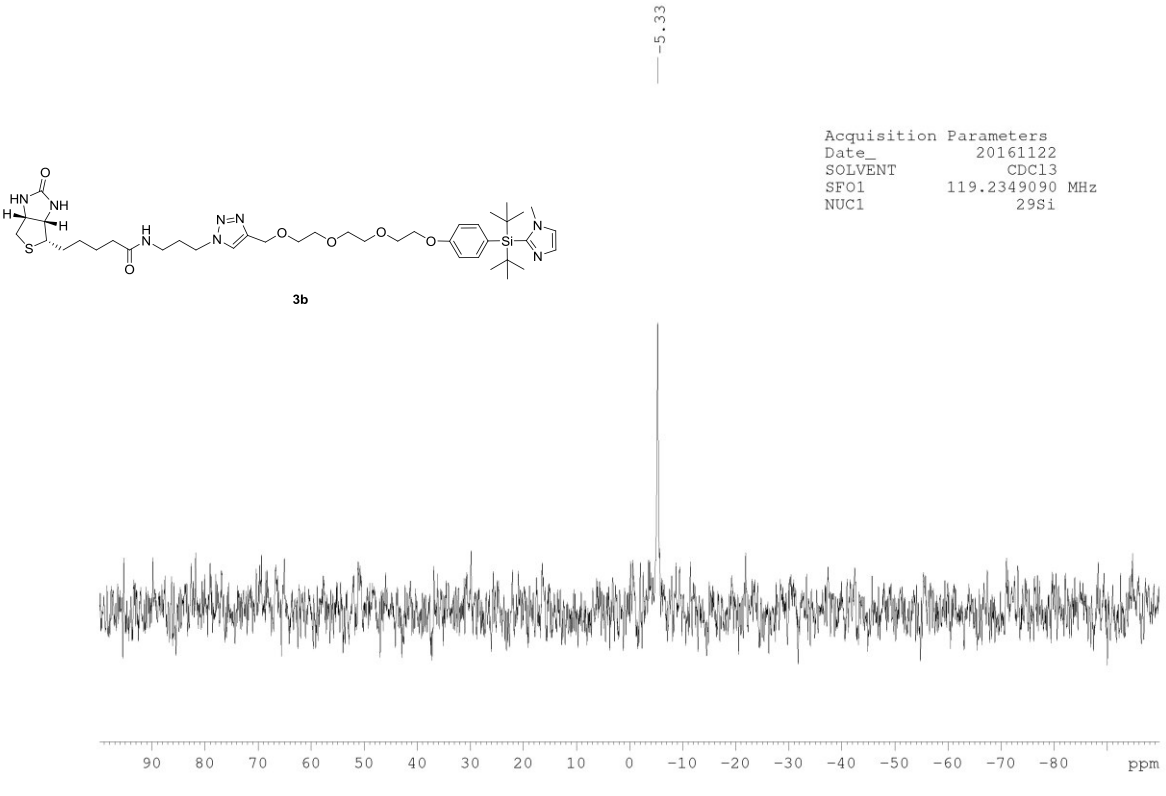




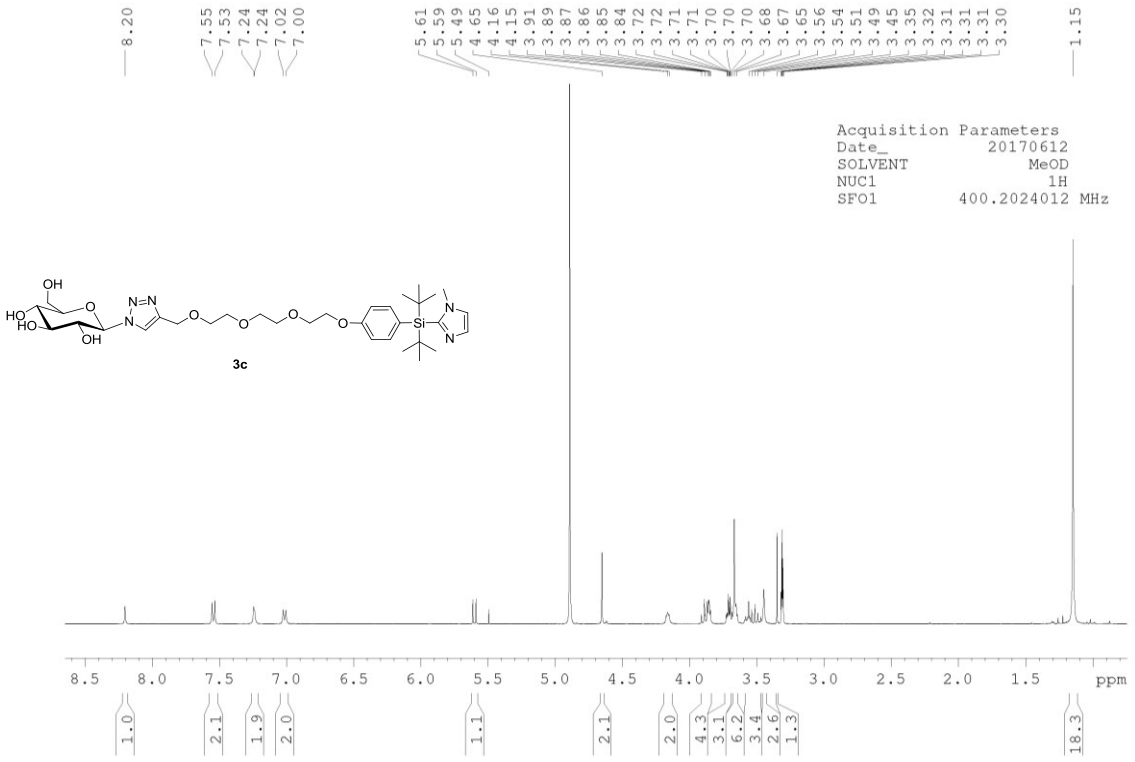
<u>*N*-[3-(4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-biotinamide 3b</u>

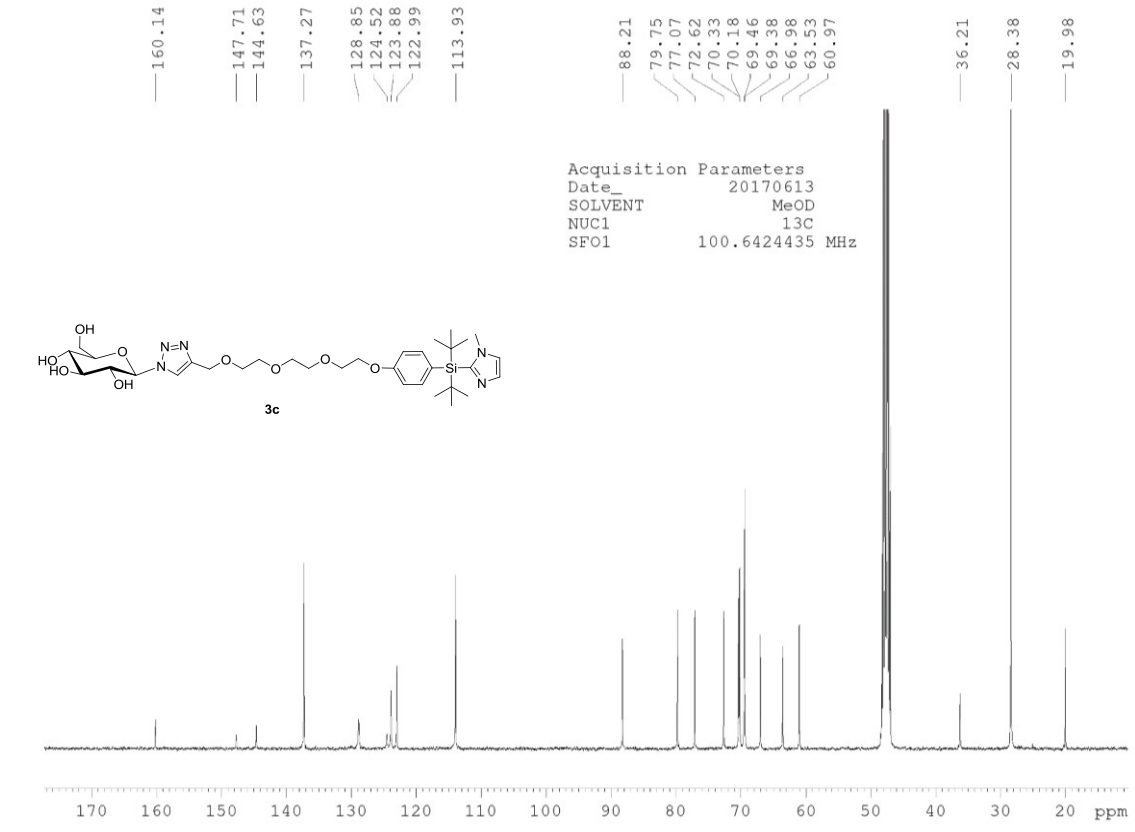


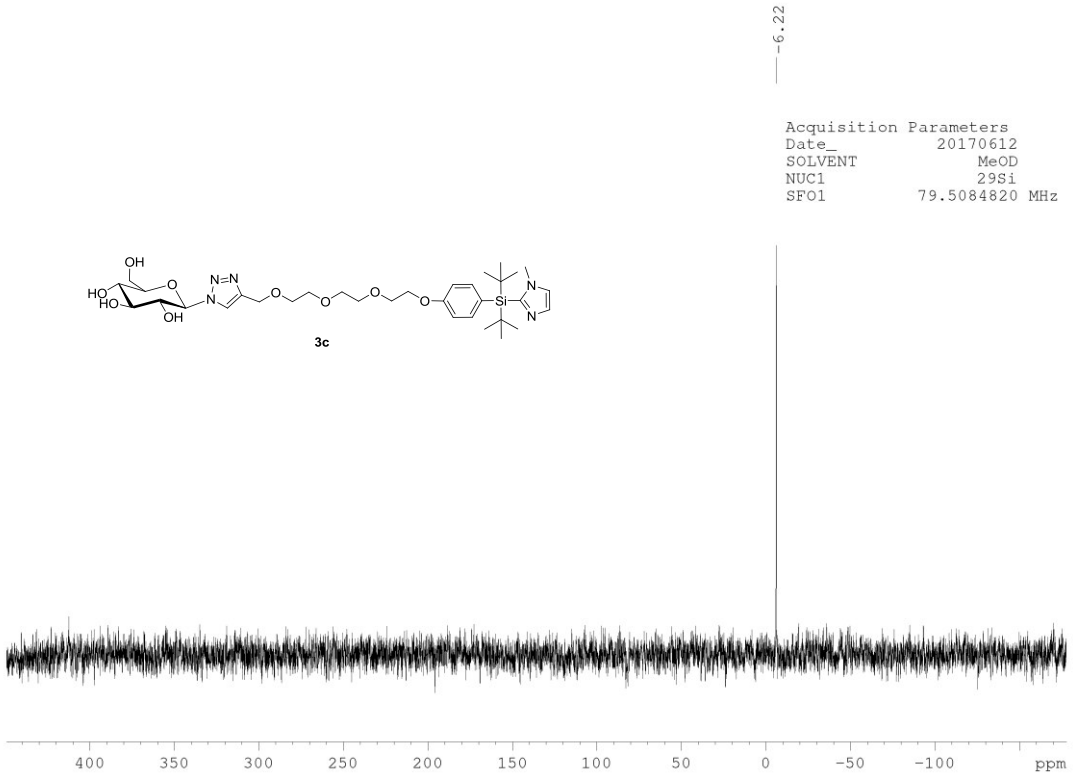

174.09
164.30
160.12
147.95
145.05
137.51
128.55
128.44
124.20
123.57
114.47
70.91
70.70
70.66
69.86
69.77
67.29
64.66
61.97
60.30
55.95
53.56
48.08
40.77
37.49
36.41
35.83
30.26
29.35
28.27
28.07
25.75
20.69
Acquisition Parameters
Date_ 20161119
SOLVENT CDCl3
SFO1 150.9284612 MHz
NUC1 13C
3b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


-5.33
Acquisition Parameters
Date_ 20161122
SOLVENT CDCl3
SFO1 119.2349090 MHz
NUC1 29Si
3b
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm

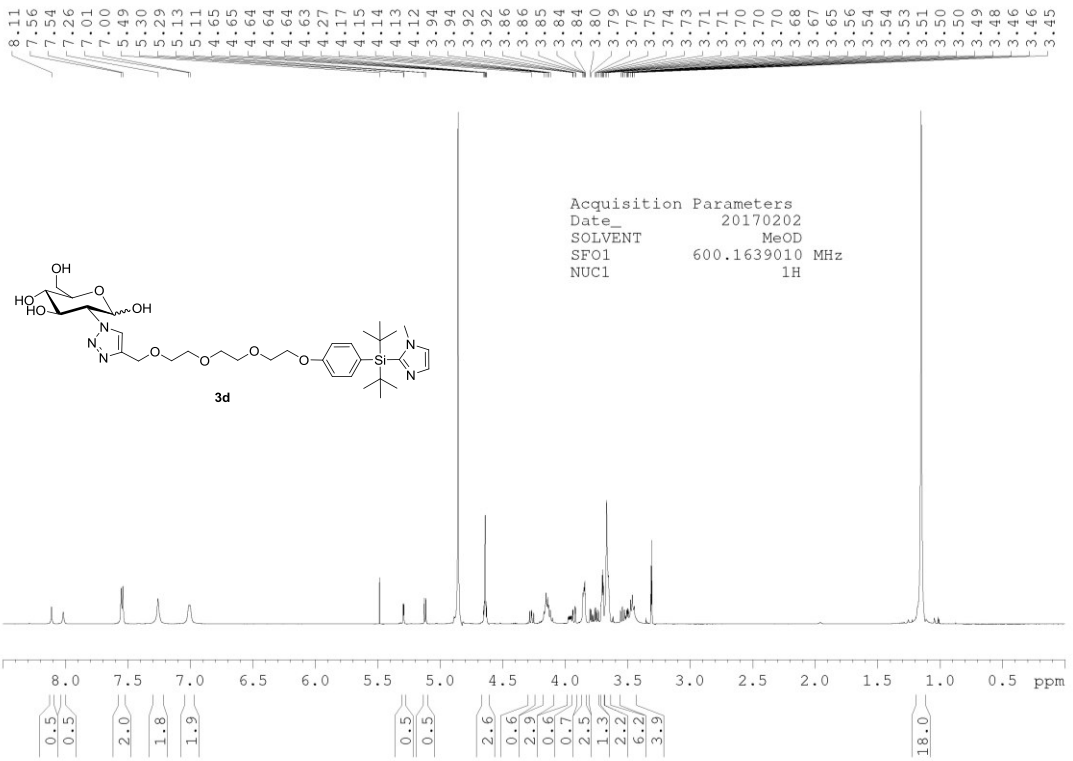
_β_-D-1-Deoxy-1-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 3c

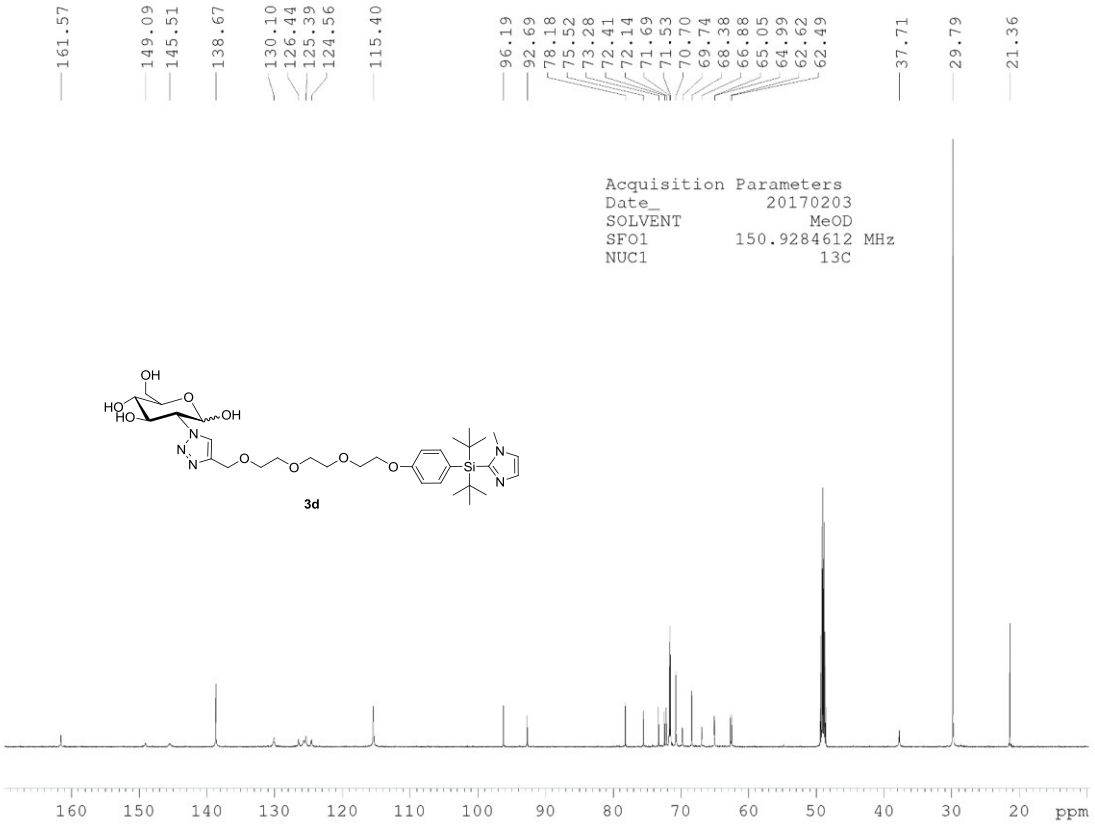


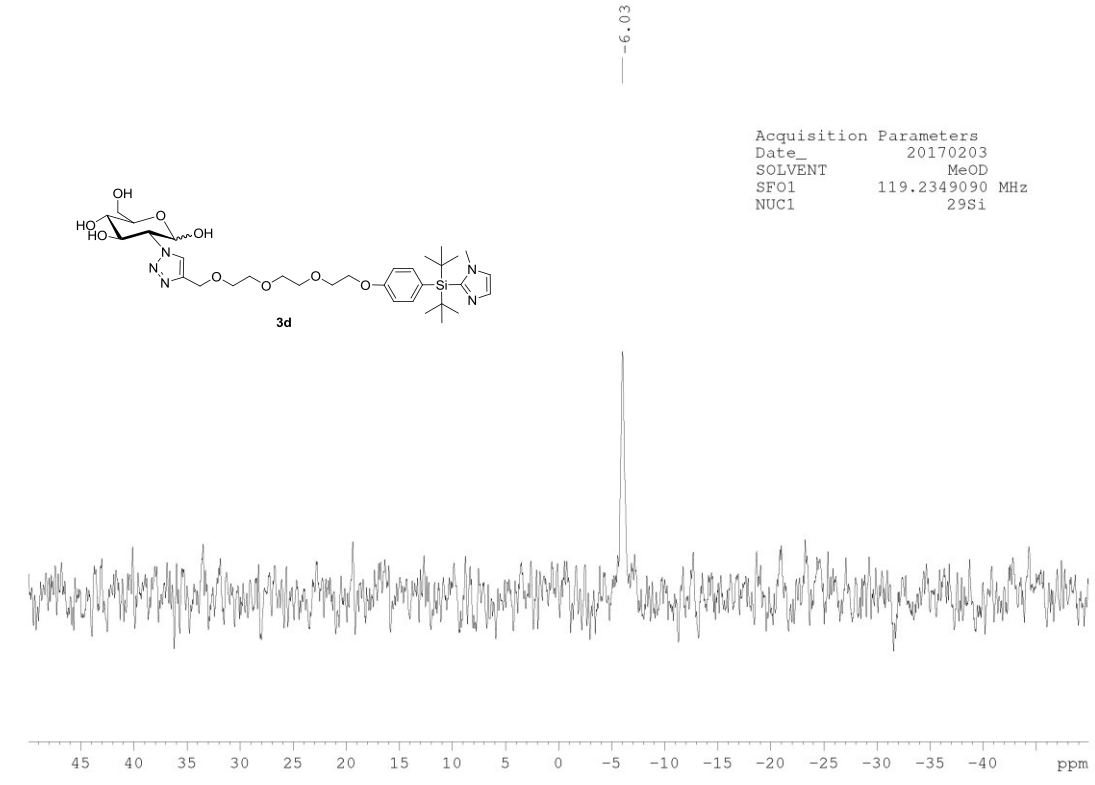




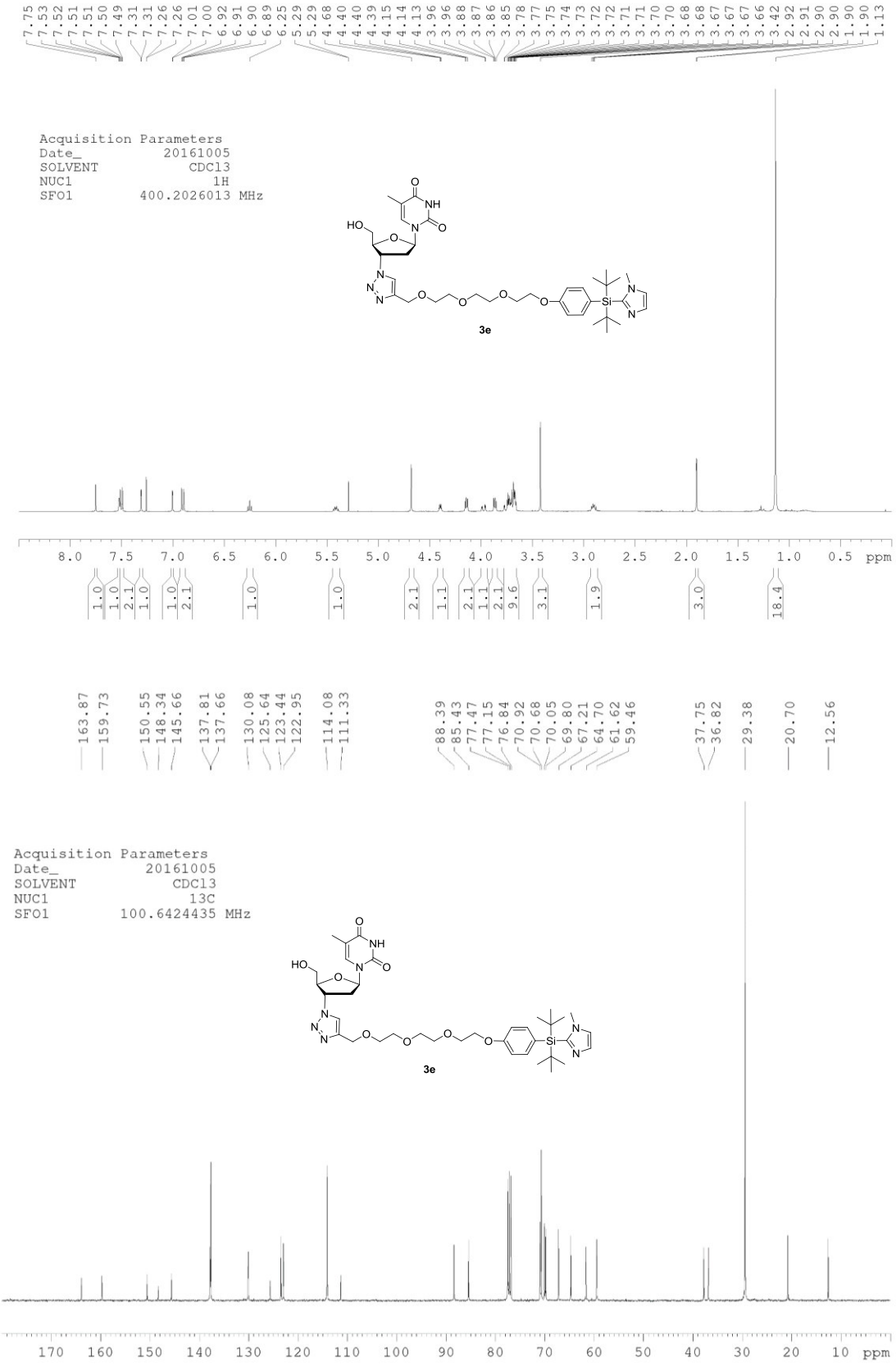
D-2-Deoxy-2-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 3d

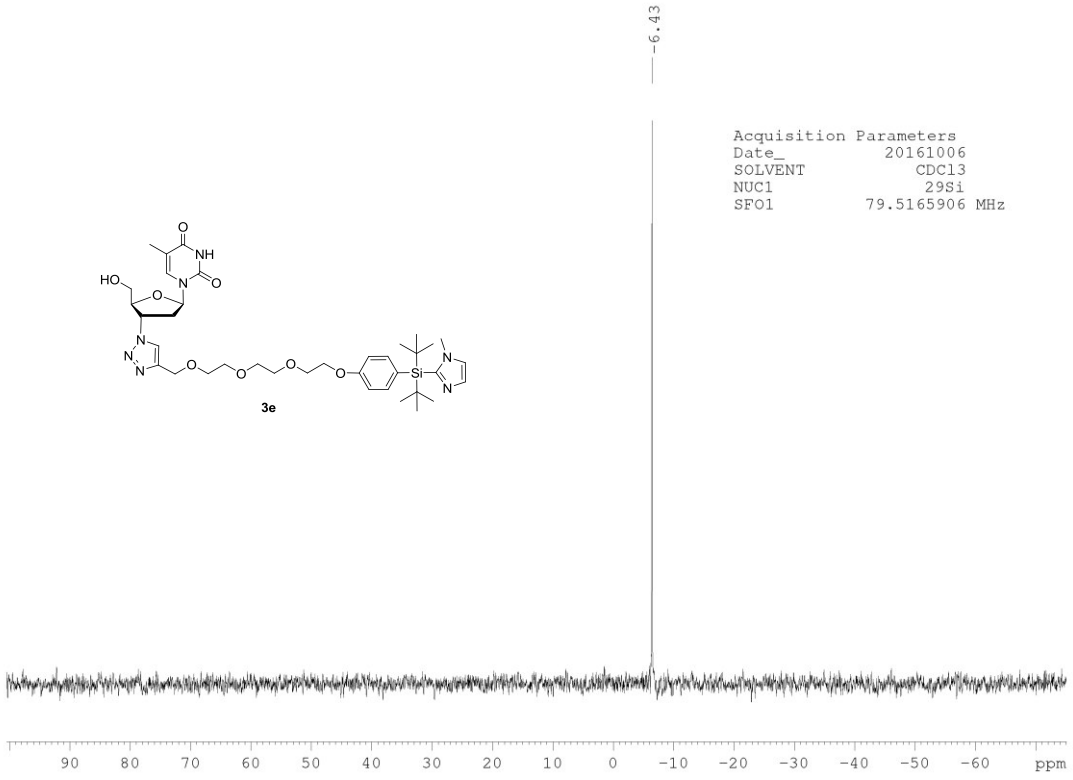



161.57
149.09
145.51
138.67
130.10
126.44
125.39
124.56
115.40
96.19
92.69
78.18
75.52
73.28
72.41
72.14
71.69
71.53
70.70
69.74
68.38
66.88
65.05
64.99
62.62
62.49
37.71
29.79
21.36
Acquisition Parameters
Date_ 20170203
SOLVENT MeOD
SFO1 150.9284612 MHz
NUC1 13C
3d
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

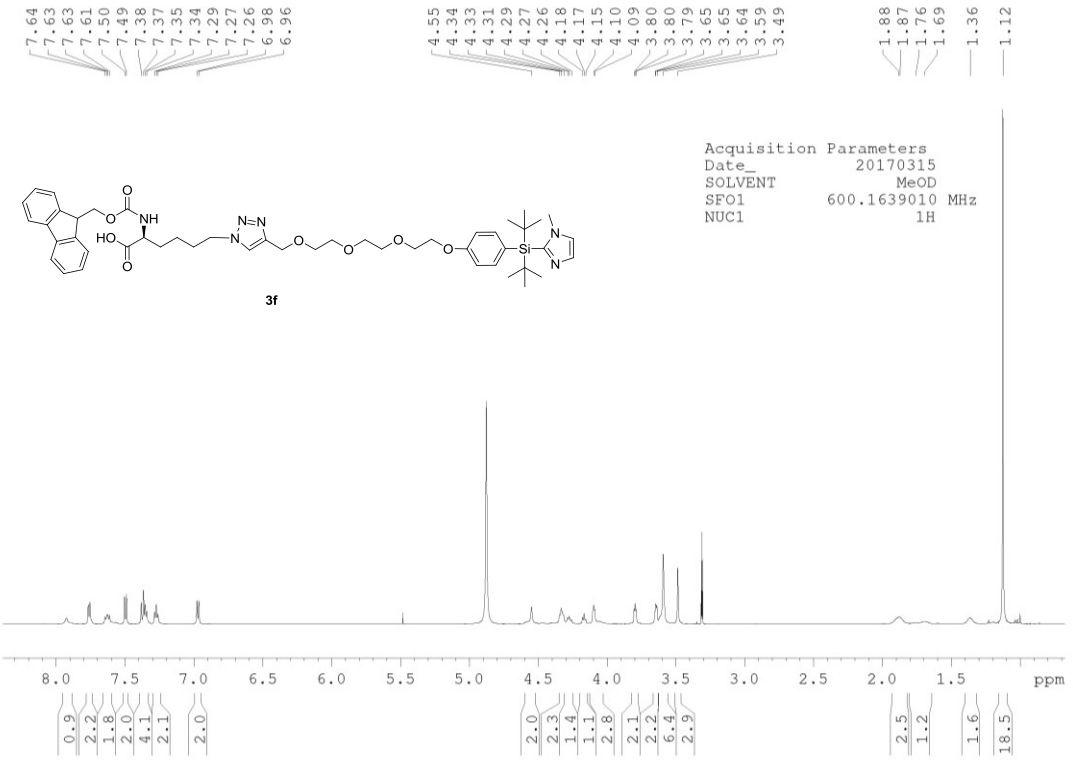

-6.03
Acquisition Parameters
Date_ 20170203
SOLVENT MeOD
SFO1 119.2349090 MHz
NUC1 29Si
3d
45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 ppm

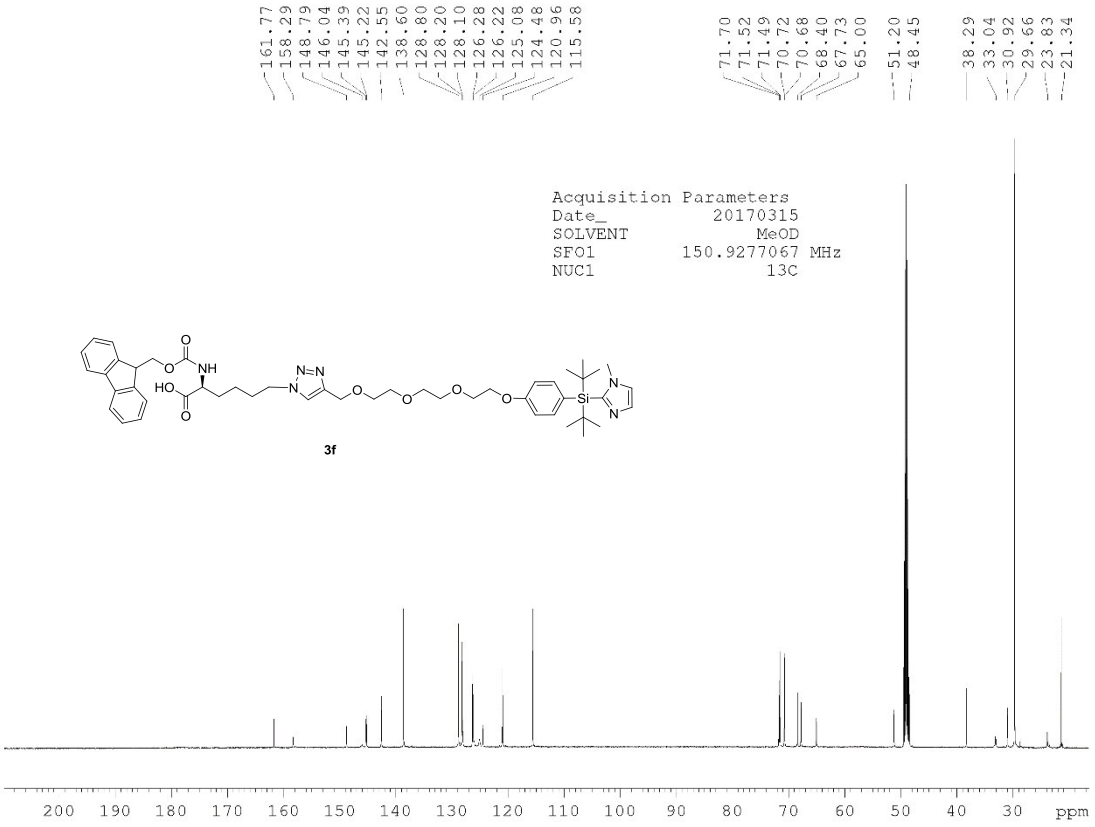
3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 3e

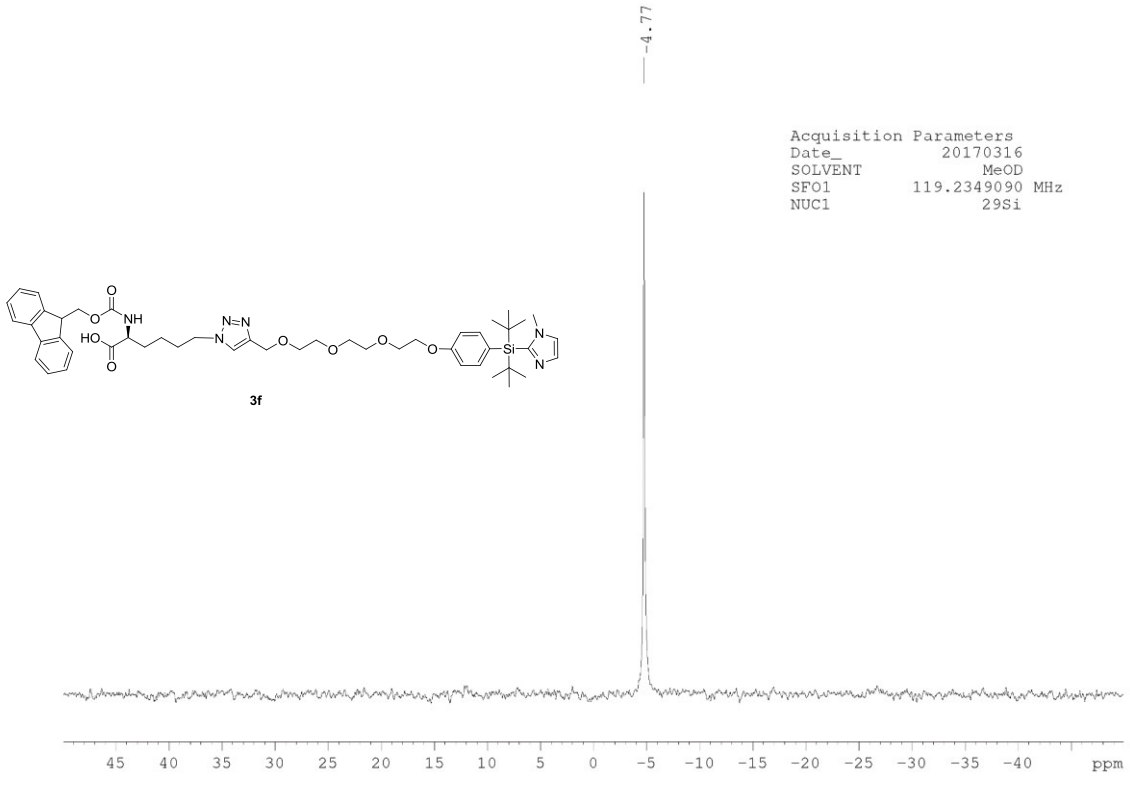




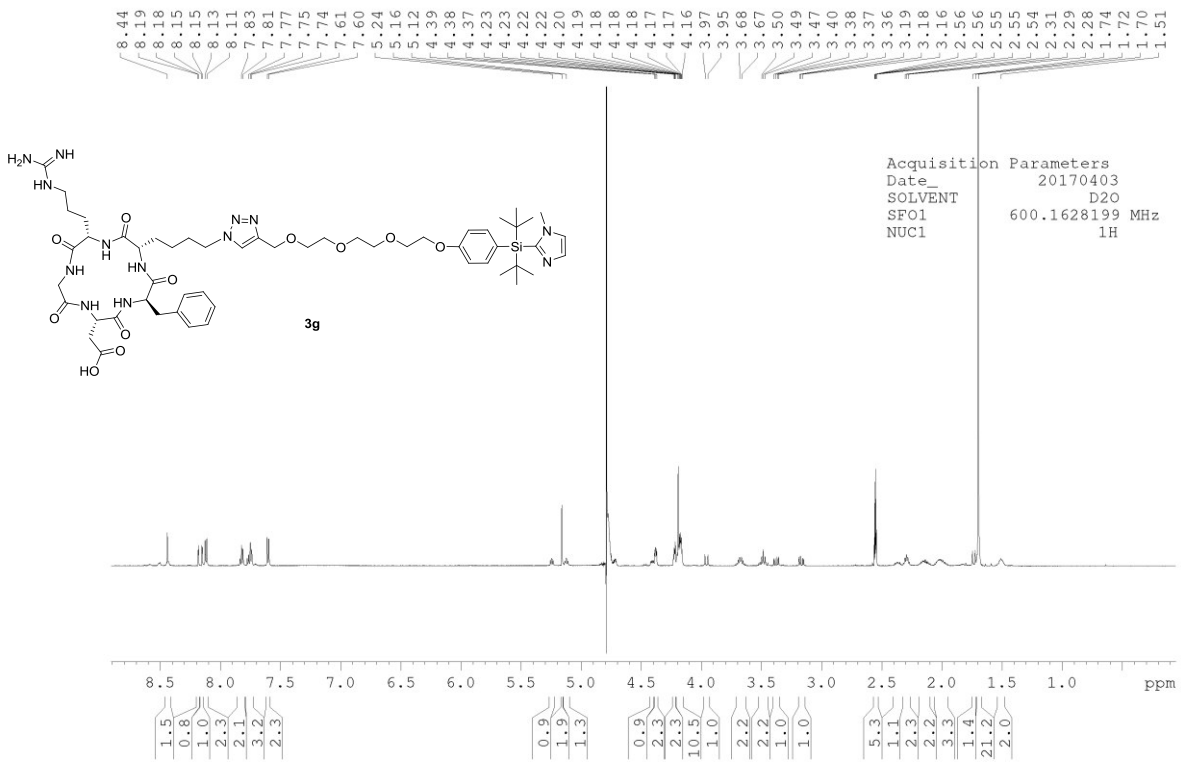
(S)-6-[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1H-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl]-2-(9-fluorenylmethoxycarbonyl)aminohexanoic acid 3f

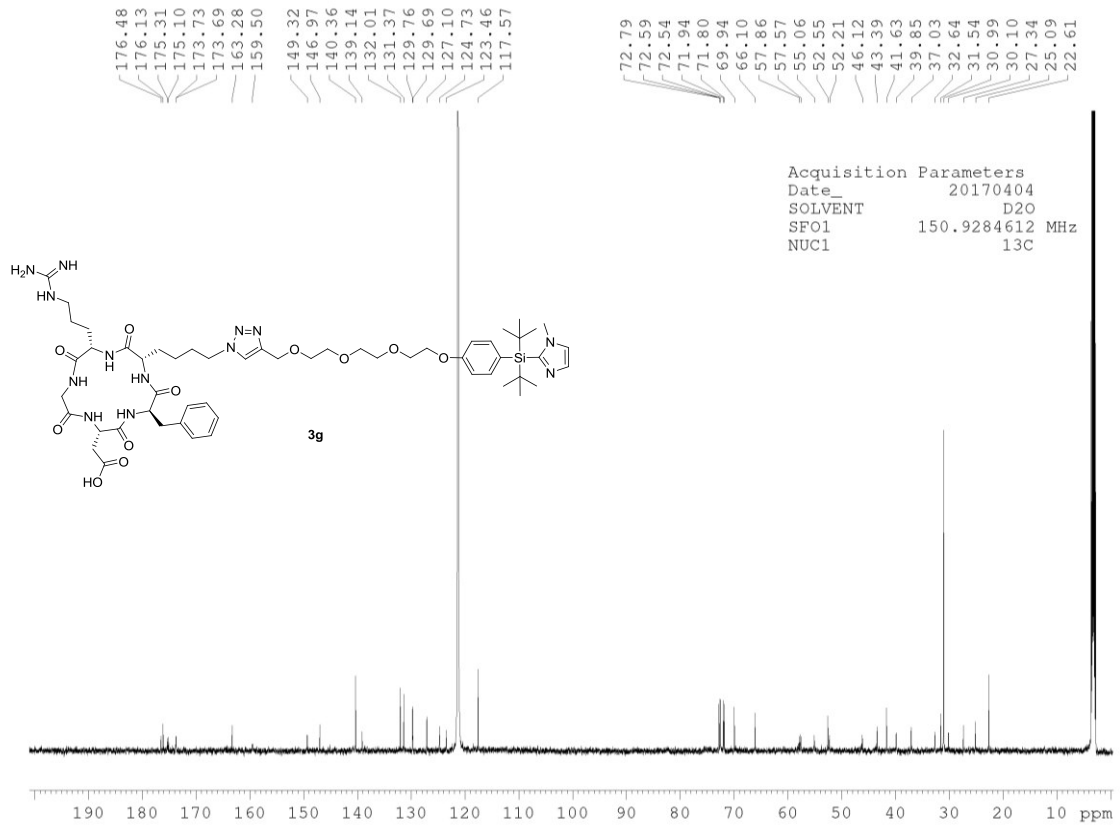


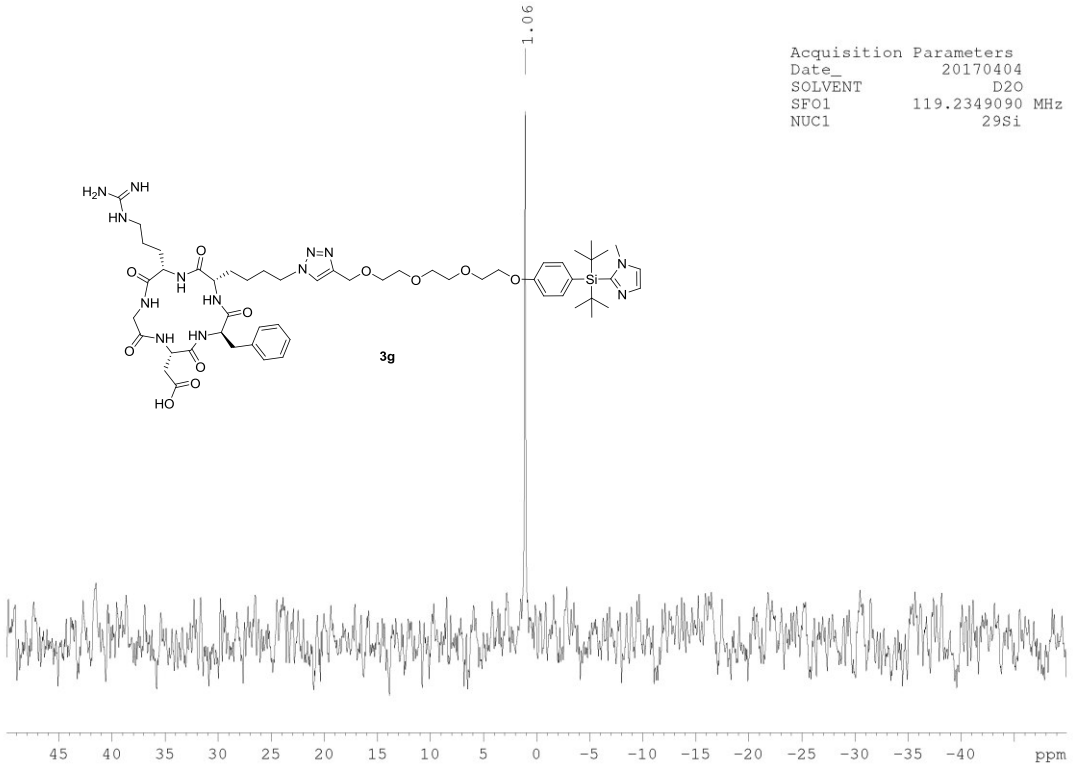

161.77
158.29
148.79
146.04
145.39
145.22
142.55
138.60
128.80
128.20
128.10
126.28
126.22
125.08
124.48
120.96
115.58
71.70
71.52
71.49
70.72
70.68
68.40
67.73
65.00
51.20
48.45
38.29
33.04
30.92
29.66
23.83
21.34
Acquisition Parameters
Date_ 20170315
SOLVENT MeOD
SFO1 150.9277067 MHz
NUC1 13C
3f
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm


-4.77
Acquisition Parameters
Date_ 20170316
SOLVENT MeOD
SFO1 119.2349090 MHz
NUC1 29Si
3f
45 40 35 30 25 20 15 10 5 0 -5 -10 -15 -20 -25 -30 -35 -40 ppm

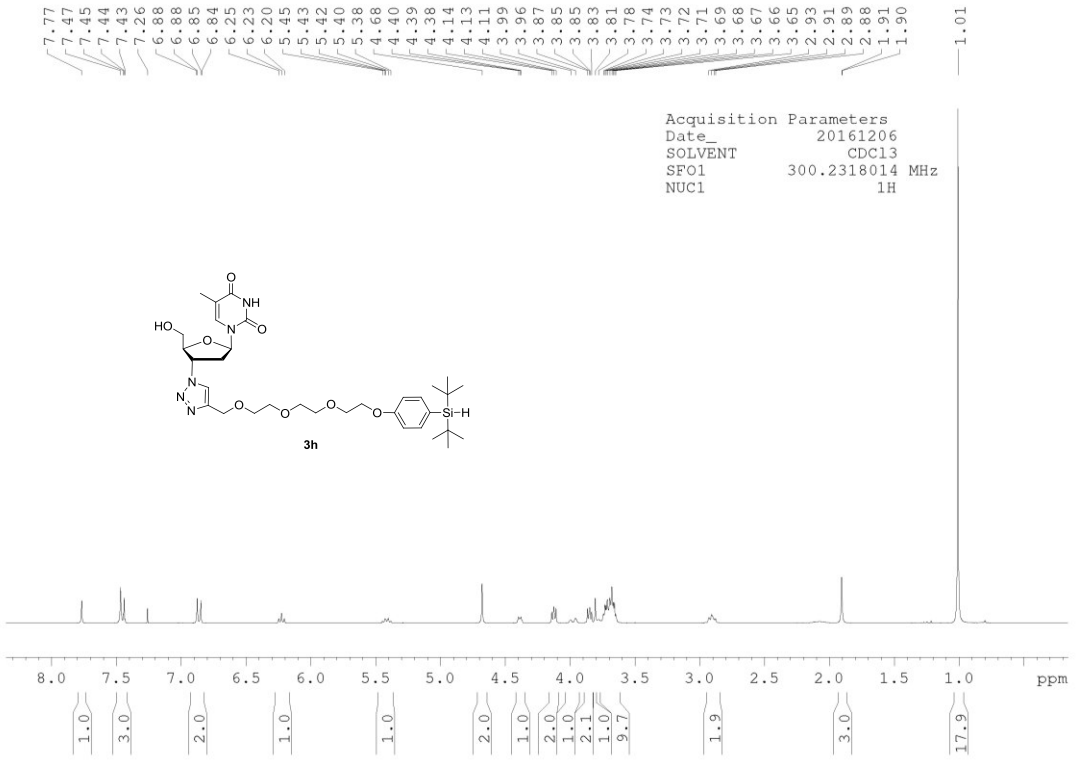
[4-((2-(2-(2-(4-(di-*tert*-butyl(1-methyl-1*H*-imidazol-2-yl)silyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-Cyclo-RGD 3g

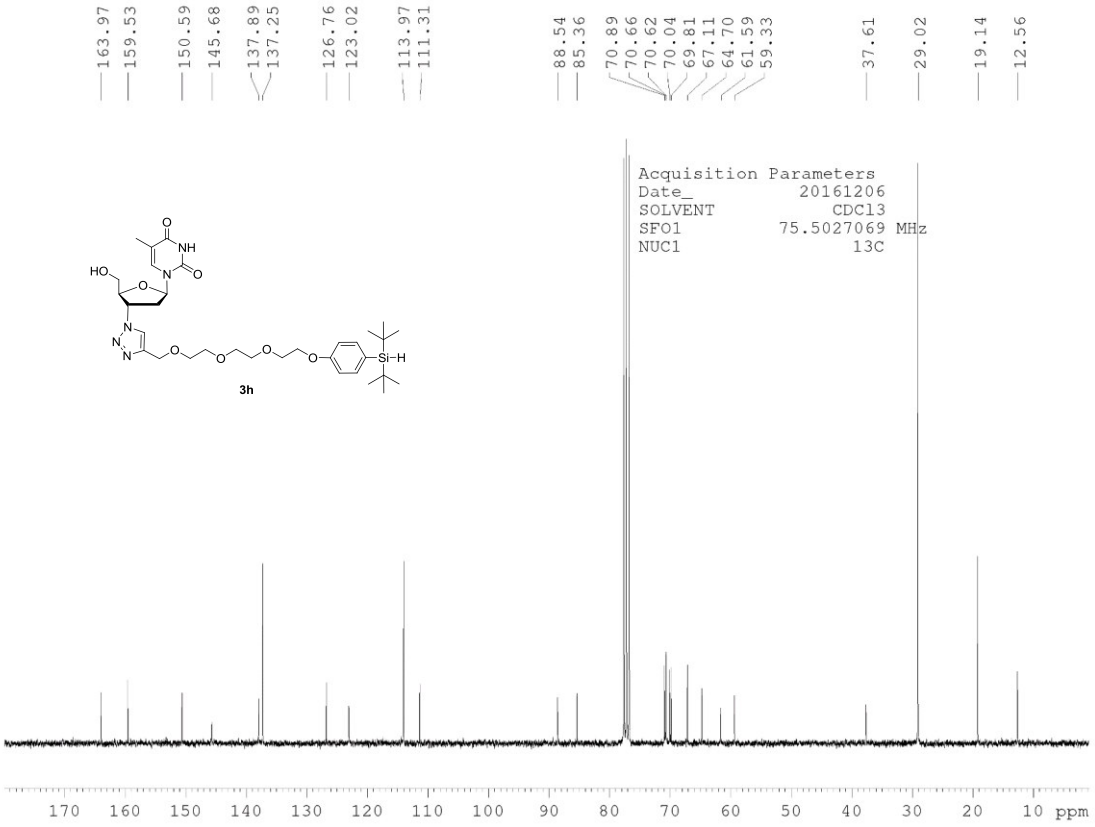


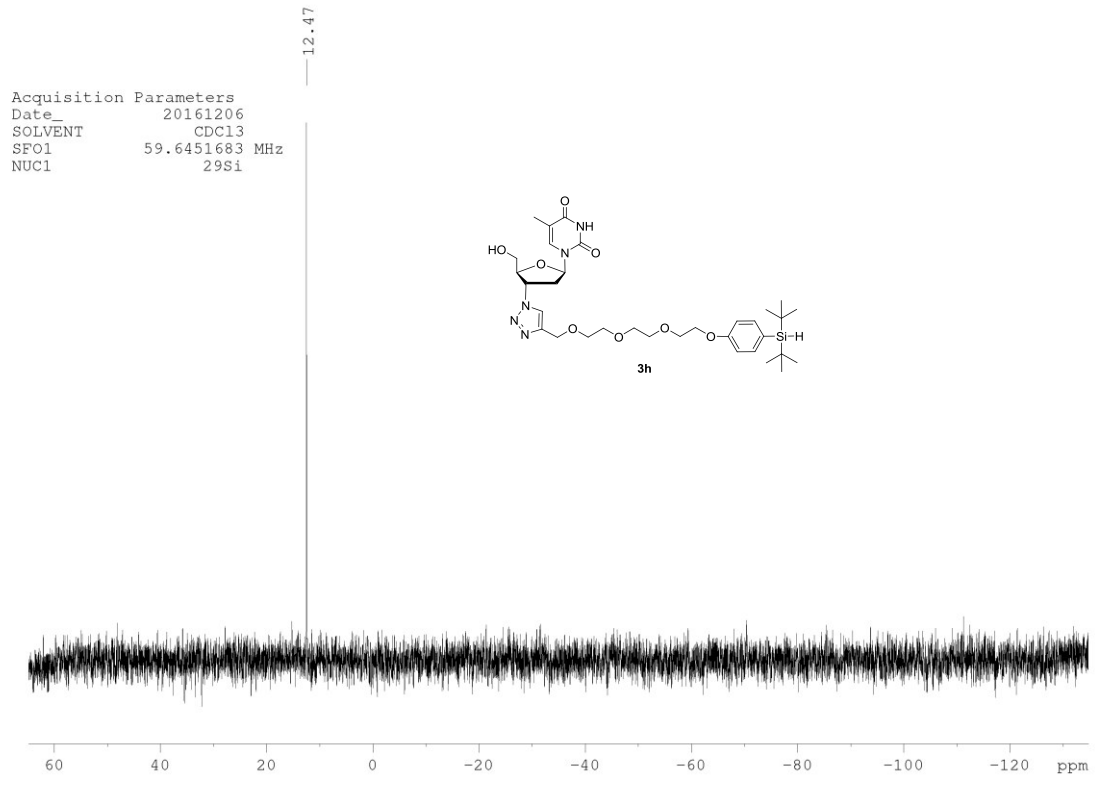




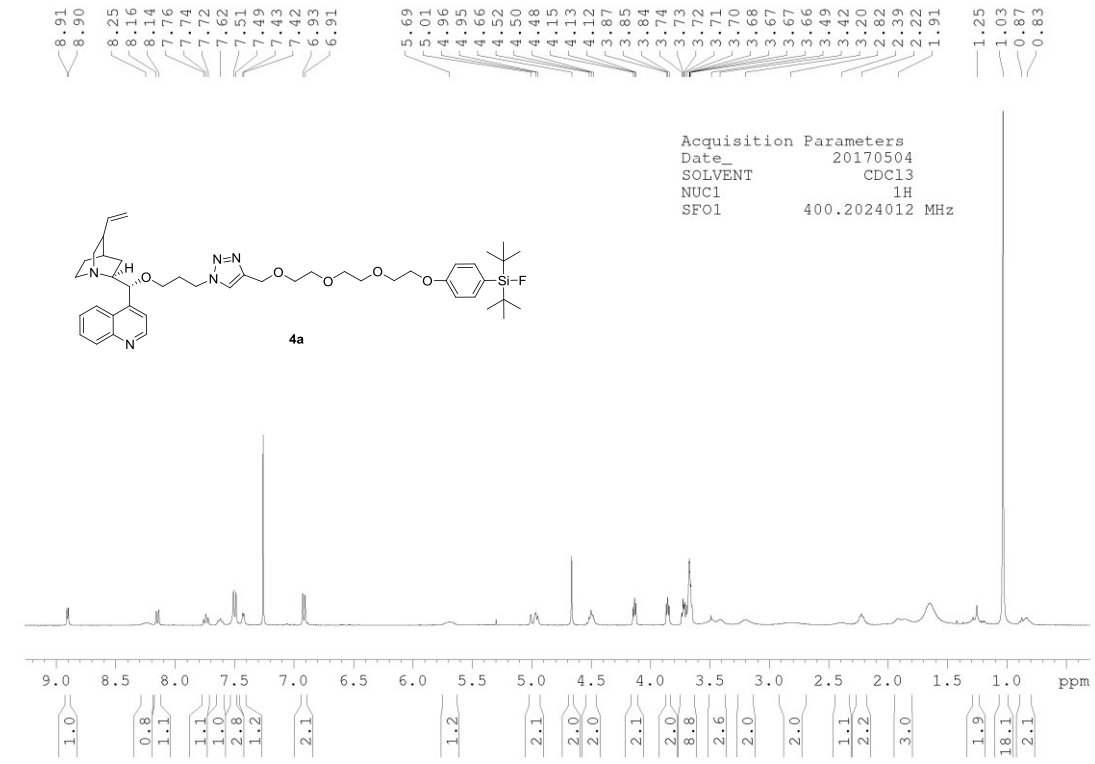
3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-*tert*-butylsilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 3h

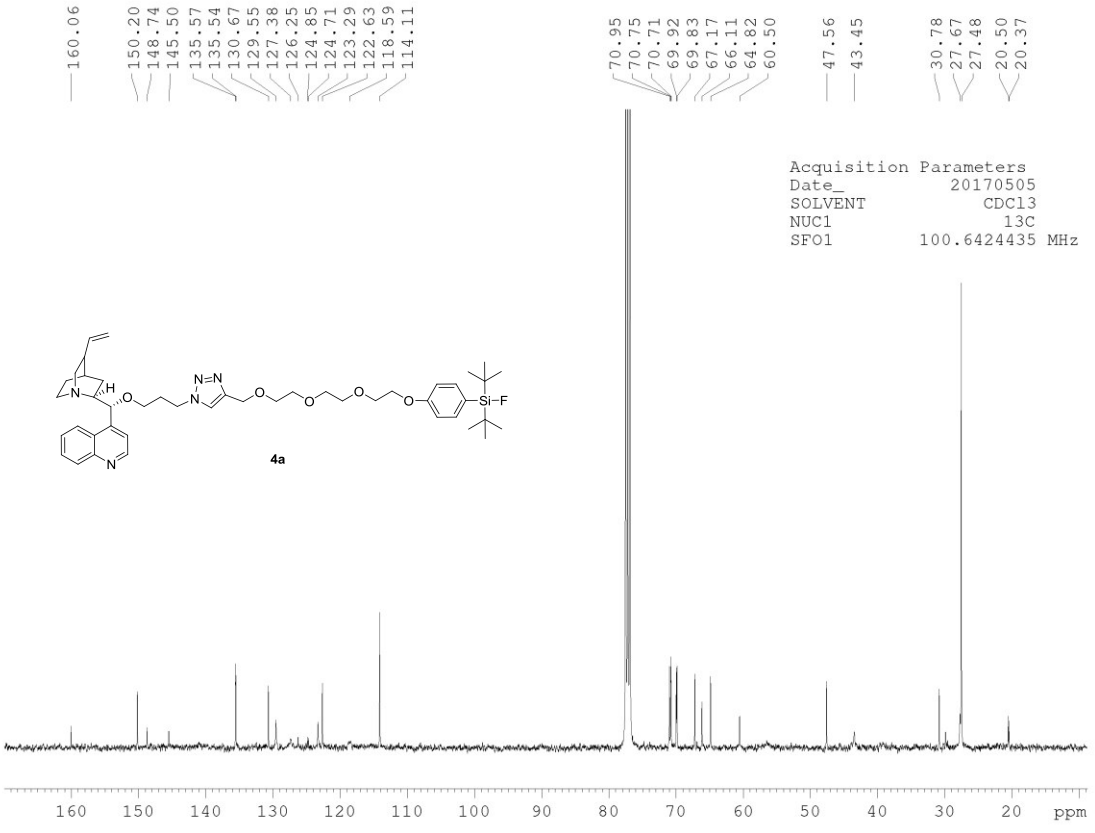


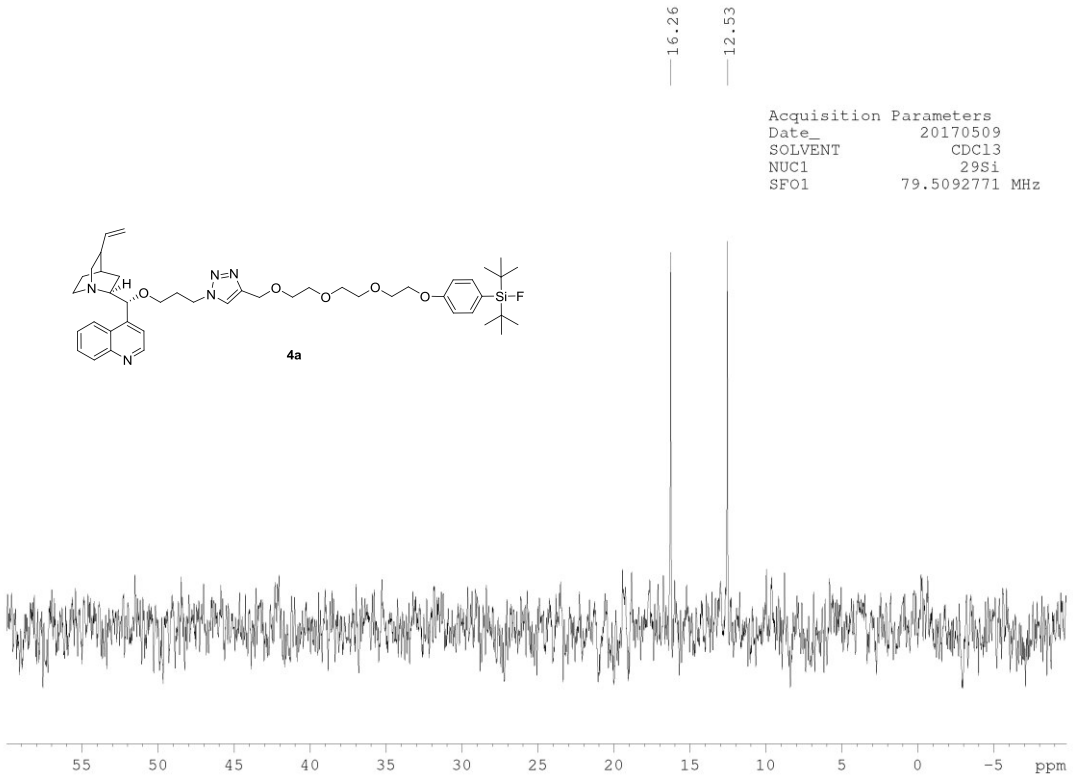

163.97
159.53
150.59
145.68
137.89
137.25
126.76
123.02
113.97
111.31
88.54
85.36
70.89
70.66
70.62
70.04
69.81
67.11
64.70
61.59
59.33
37.61
29.02
19.14
12.56
Acquisition Parameters
Date_ 20161206
SOLVENT CDCl3
SFO1 75.5027069 MHz
NUC1 13C
3h
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

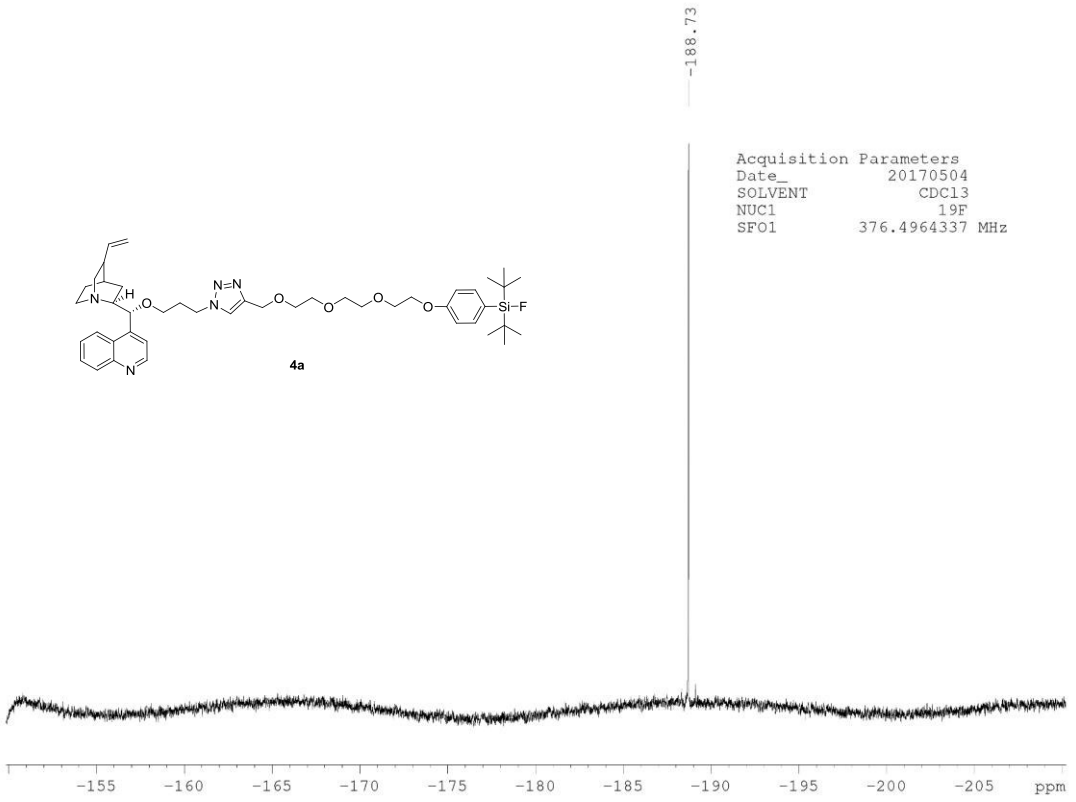

12.47
Acquisition Parameters
Date_ 20161206
SOLVENT CDCl3
SFO1 59.6451683 MHz
NUC1 29Si
3h
60 40 20 0 -20 -40 -60 -80 -100 -120 ppm

(2S)-2-(R)-*O*-[3-(4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propanyl]-cinchonidine 4a

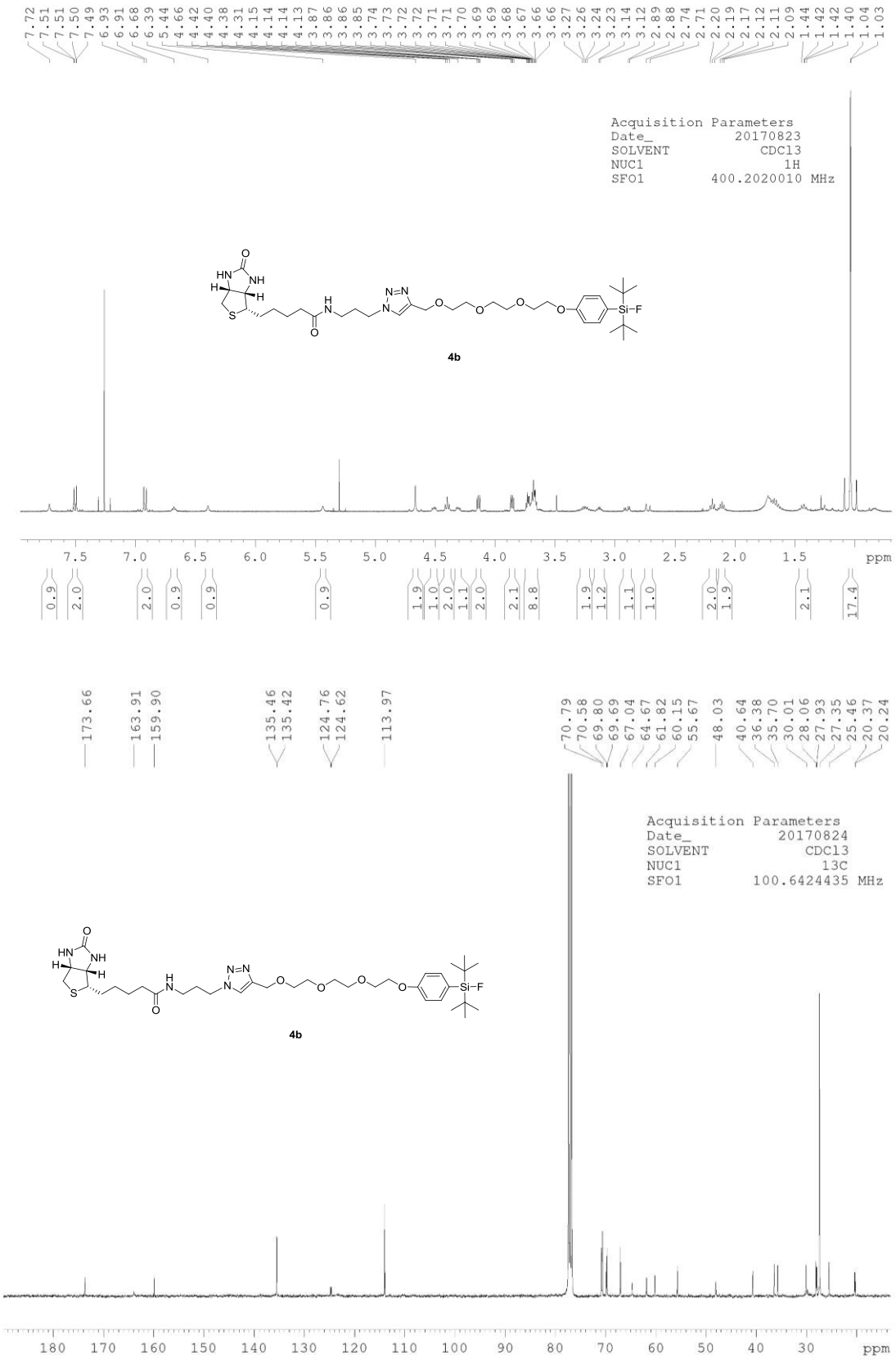


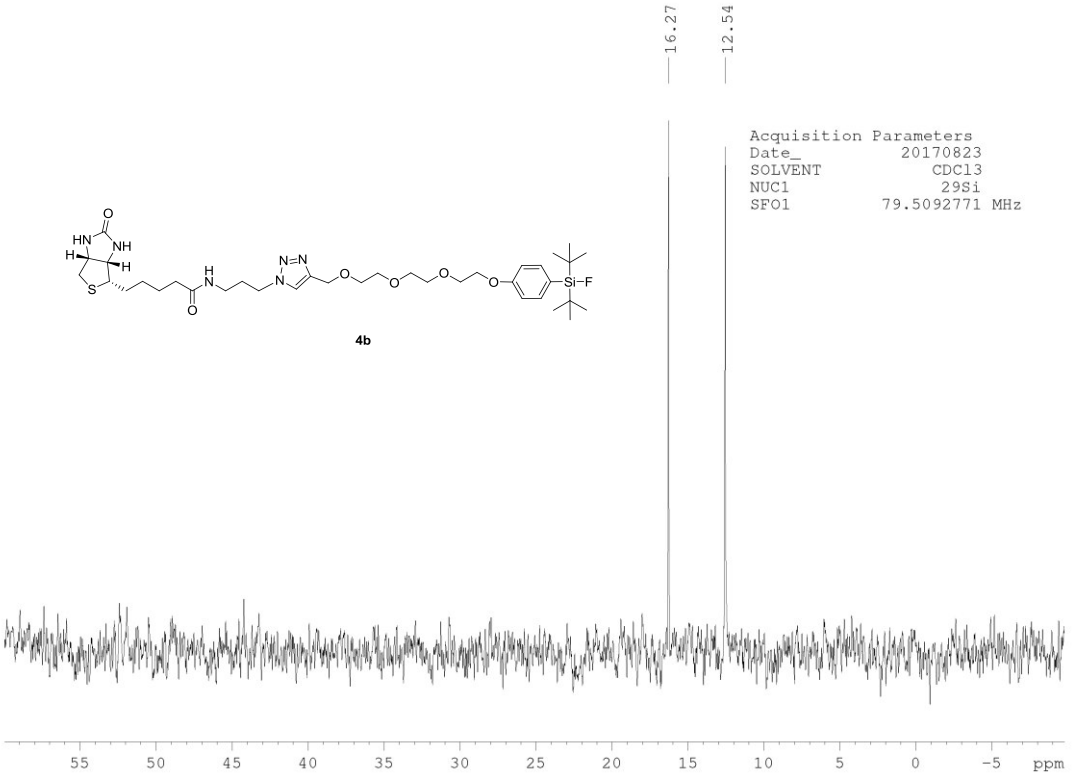


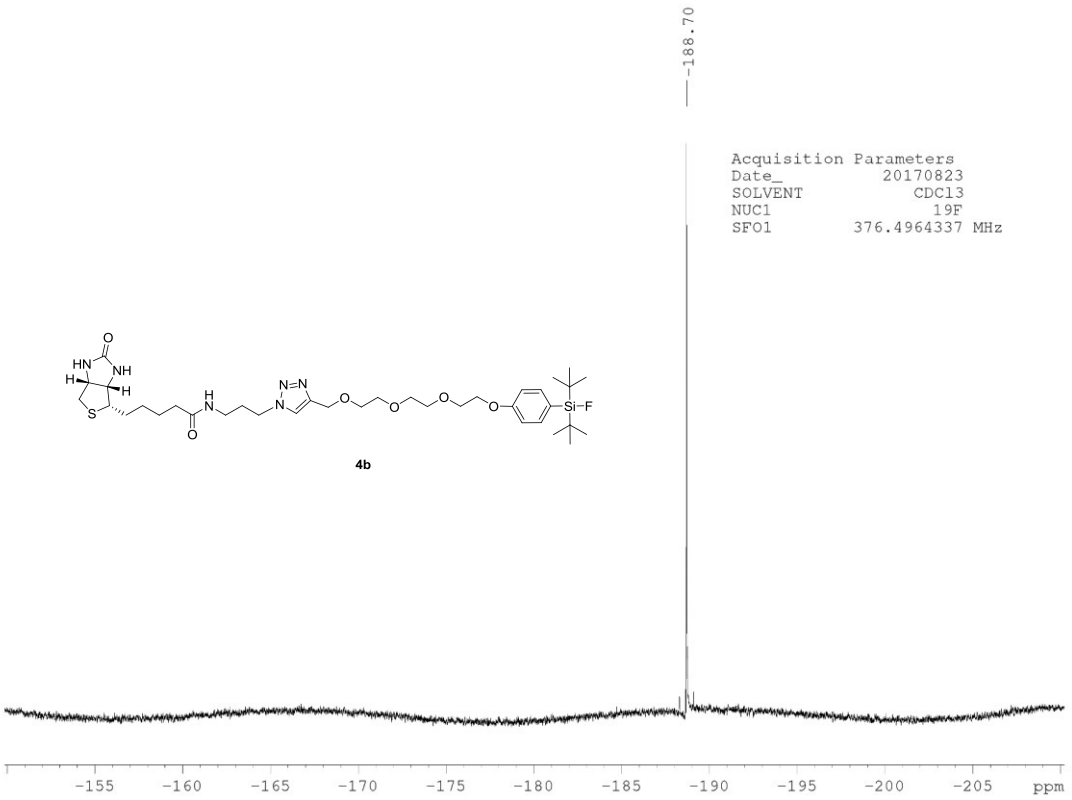

16.26
12.53
Acquisition Parameters
Date_ 20170509
SOLVENT CDCl3
NUC1 29Si
SFO1 79.5092771 MHz
4a
55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm


-188.73
Acquisition Parameters
Date_ 20170504
SOLVENT CDCl3
NUC1 19F
SFO1 376.4964337 MHz
4a
-155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 ppm

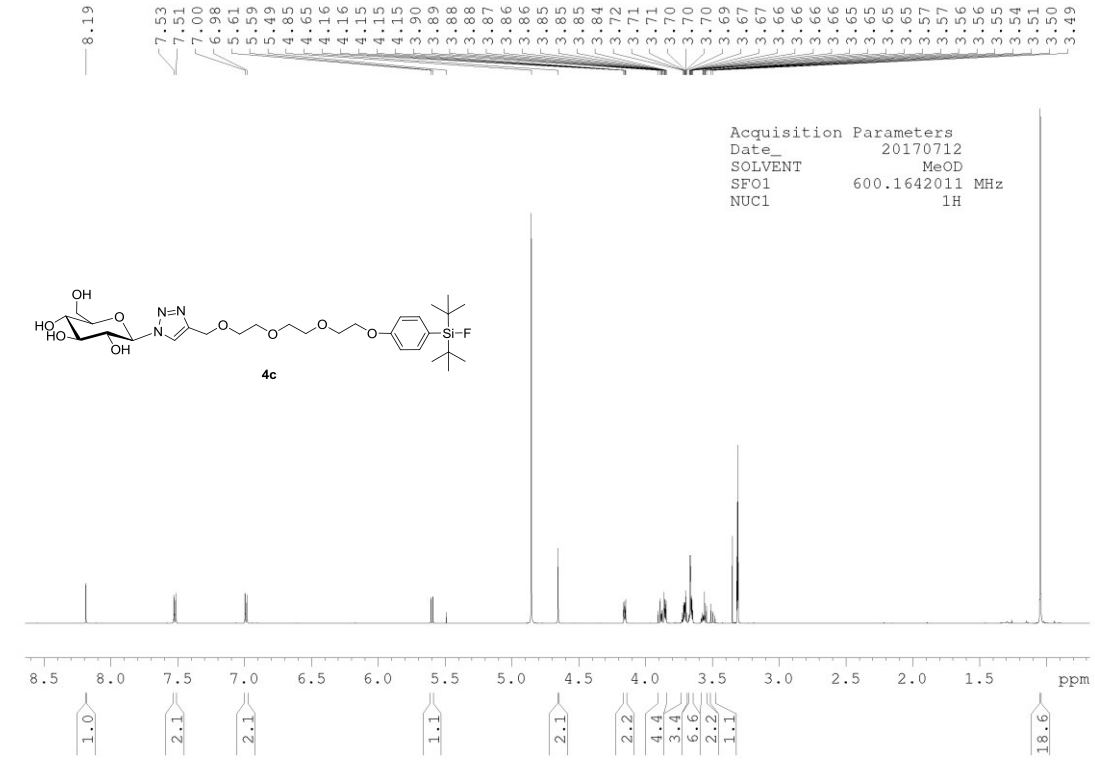
_N_-[3-(4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1_H_-1,2,3-triazol-1-yl)propanyl]-biotinamide 4b

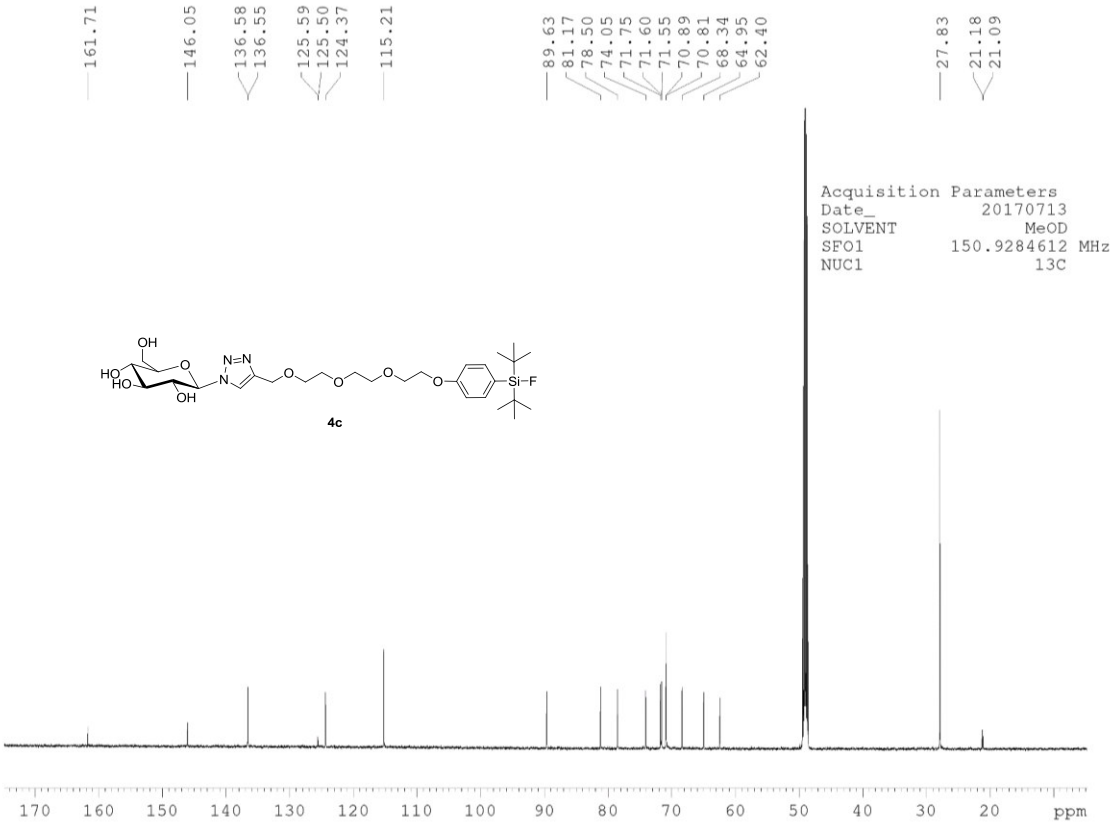


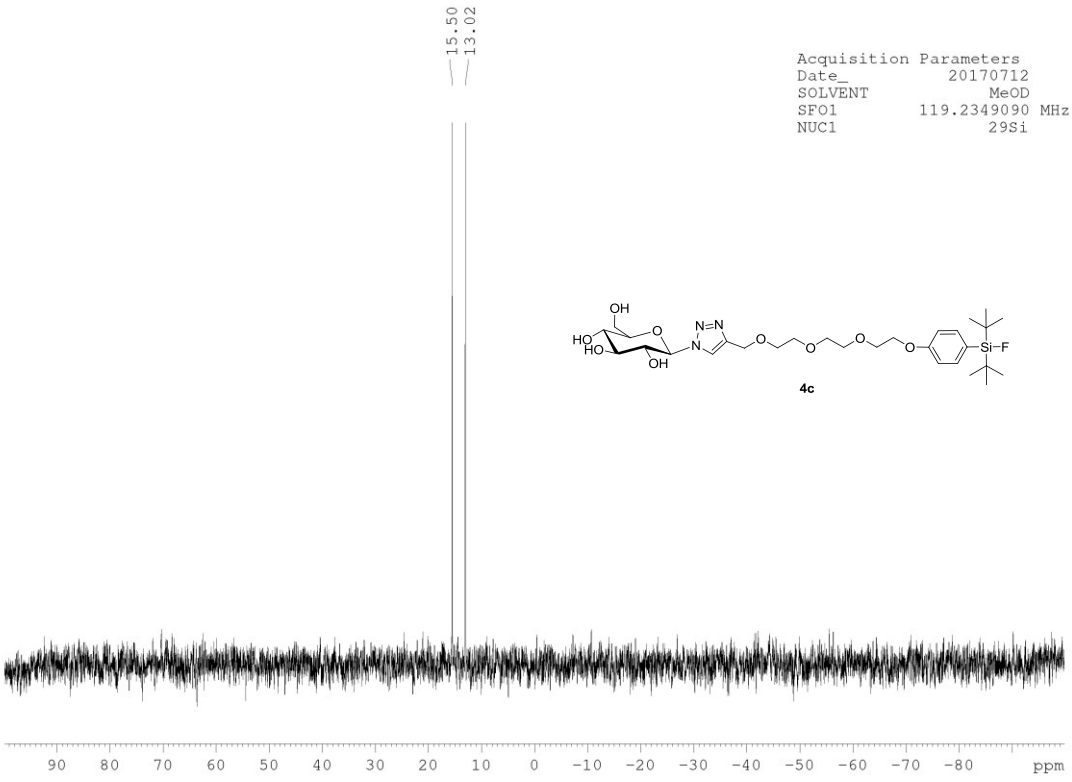

16.27
12.54
Acquisition Parameters
Date_ 20170823
SOLVENT CDCl3
NUC1 29Si
SFO1 79.5092771 MHz
4b
55 50 45 40 35 30 25 20 15 10 5 0 -5 ppm

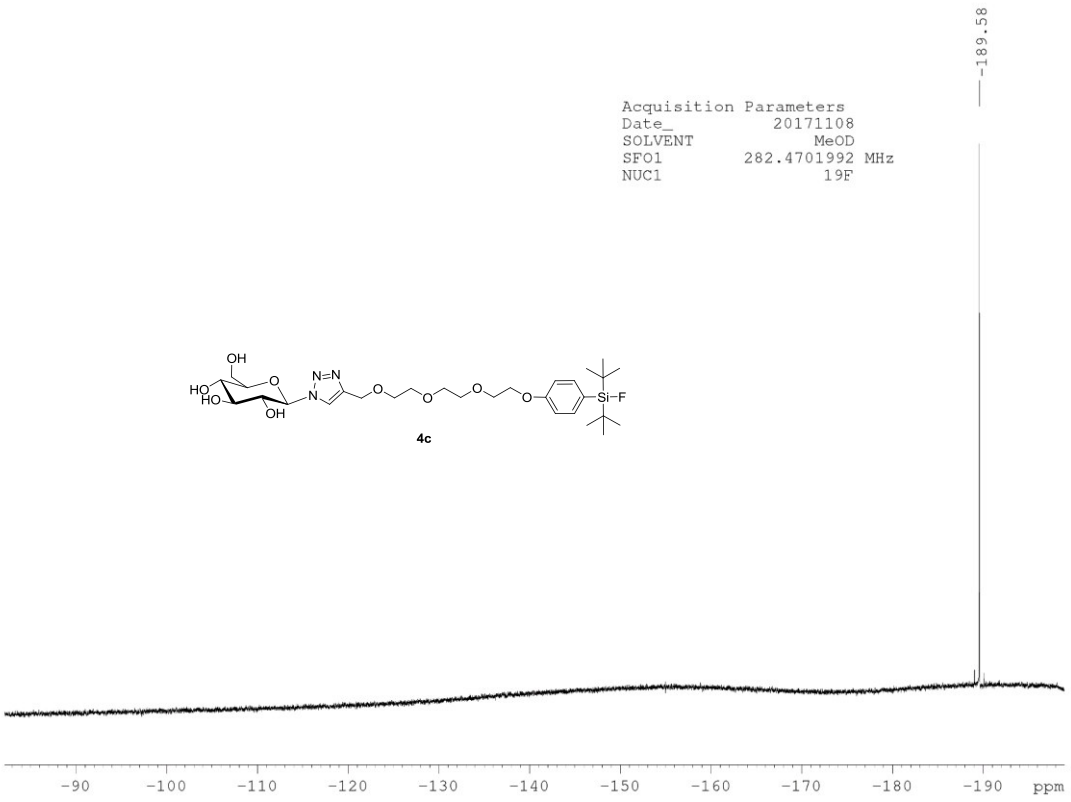

-188.70
Acquisition Parameters
Date_ 20170823
SOLVENT CDCl3
NUC1 19F
SFO1 376.4964337 MHz
4b
-155 -160 -165 -170 -175 -180 -185 -190 -195 -200 -205 ppm

_β_-D-1-Deoxy-1-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1_H_-1,2,3-triazol-1-yl]-glucopyranose 4c

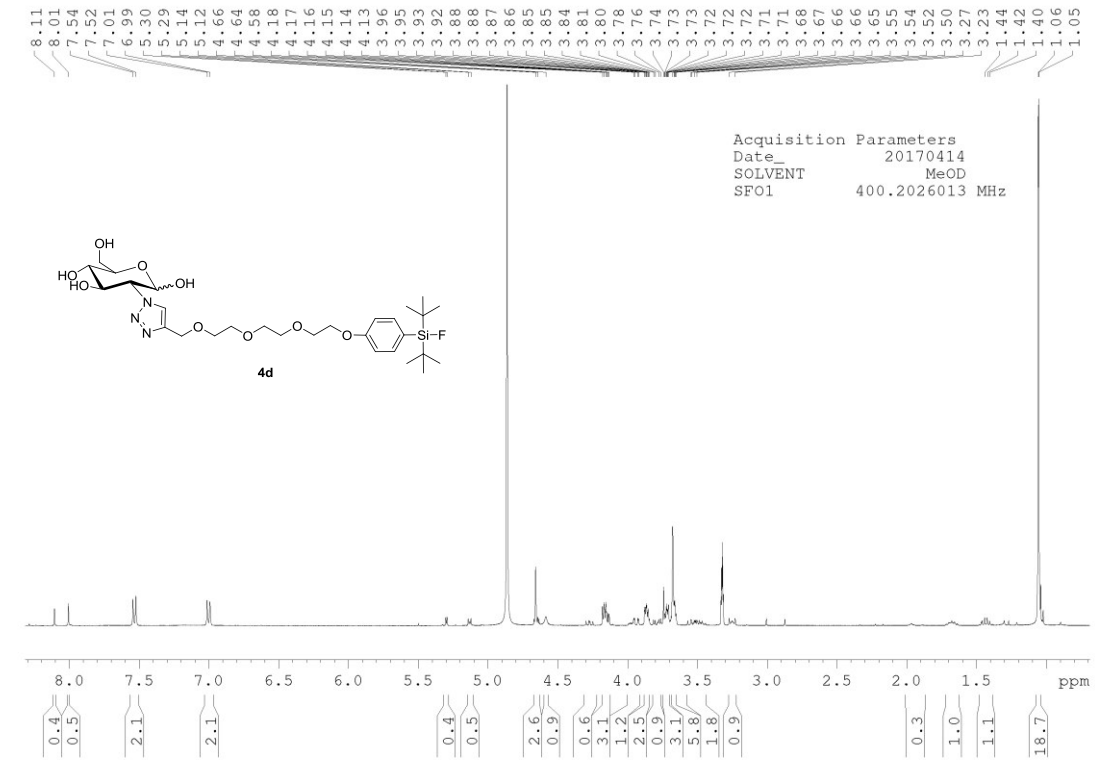


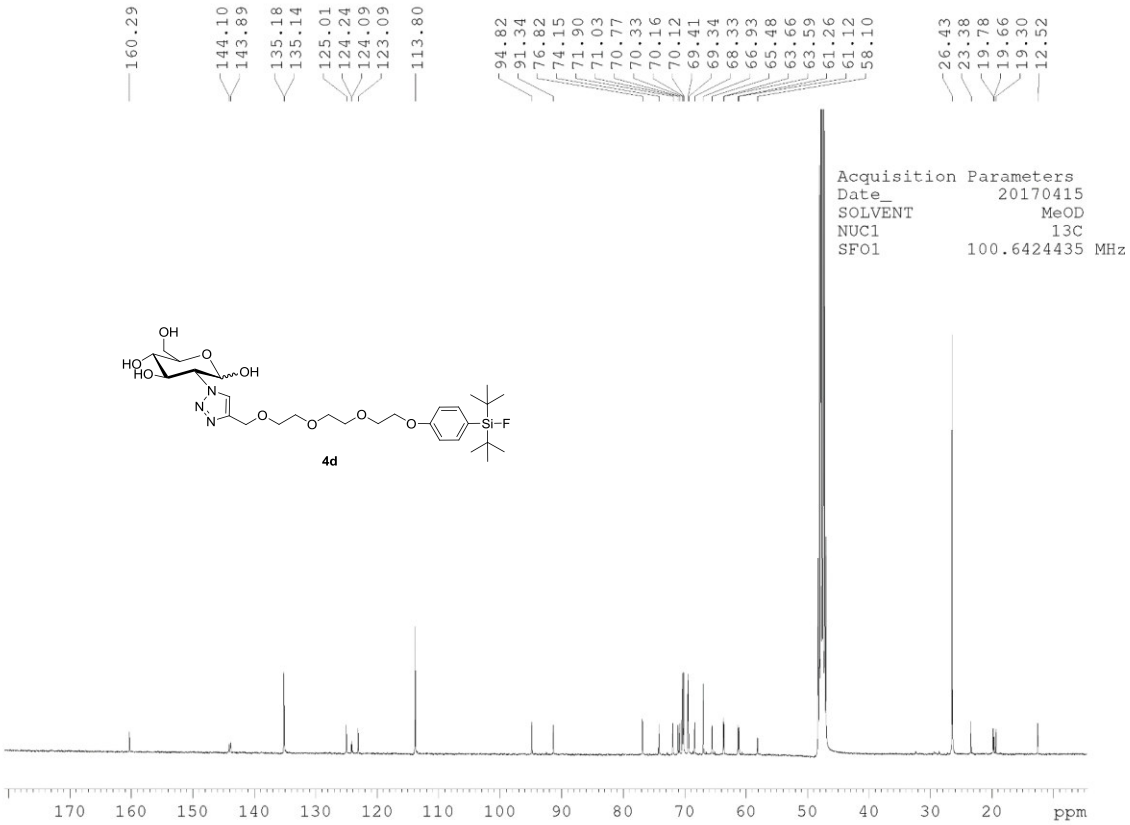


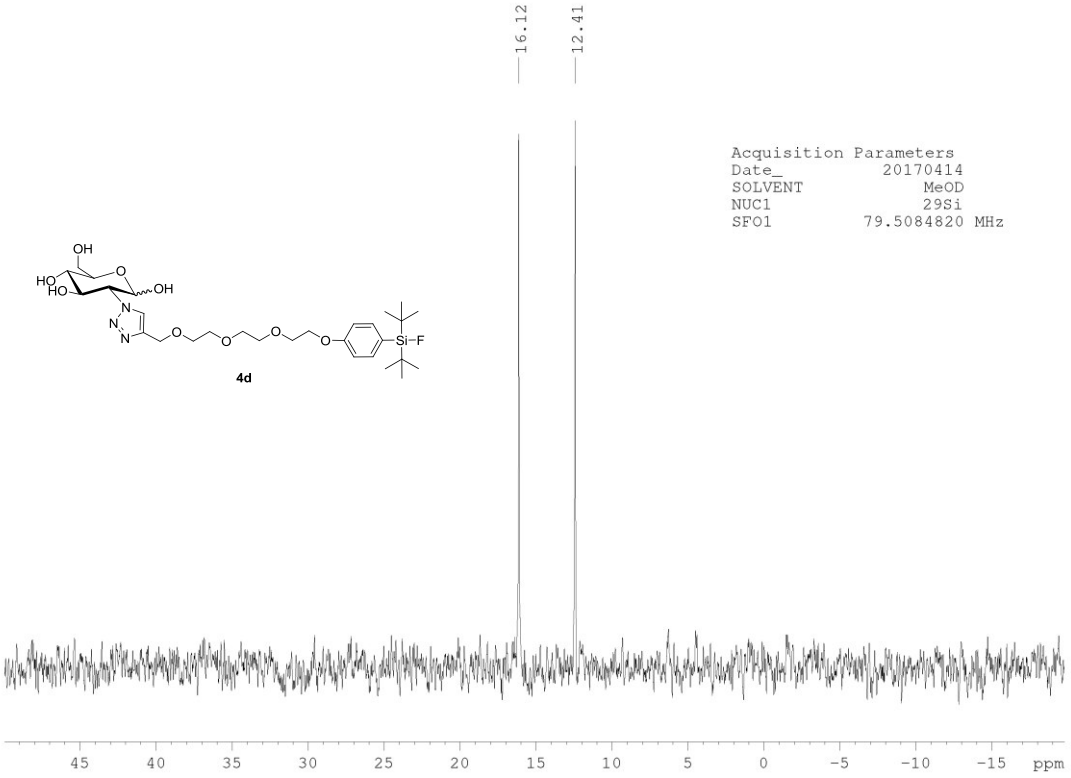

15.50
13.02
Acquisition Parameters
Date_ 20170712
SOLVENT MeOD
SFO1 119.2349090 MHz
NUC1 29Si
4c
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm

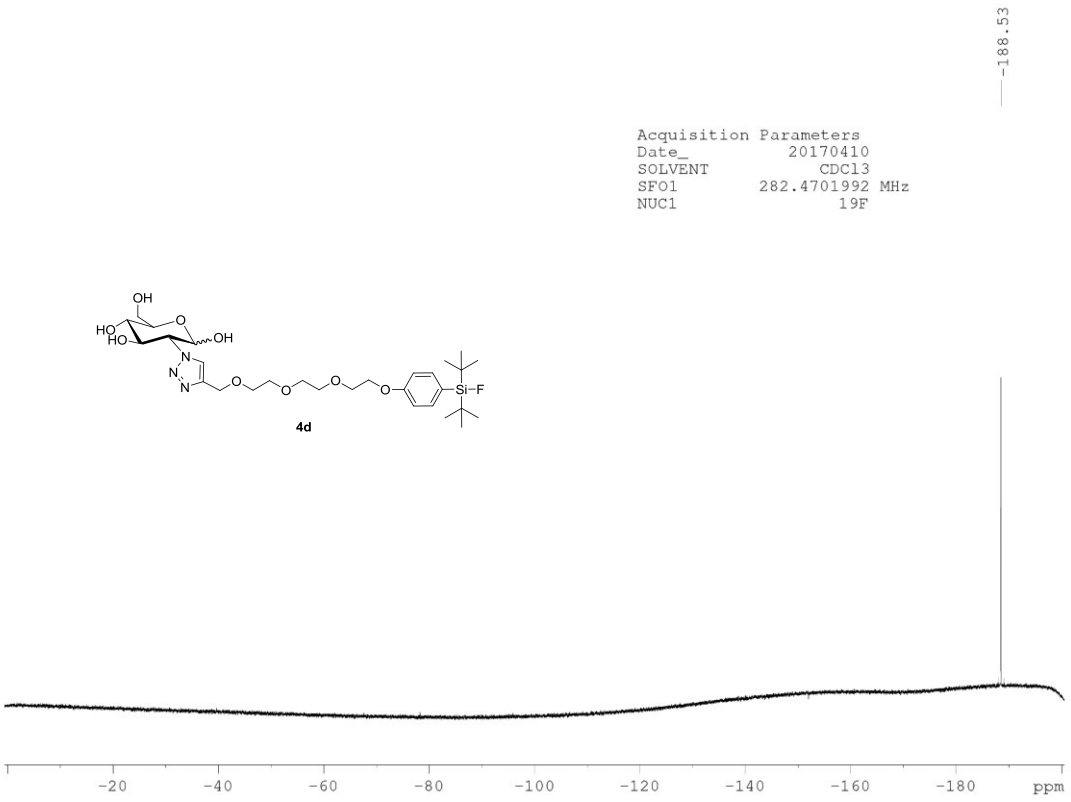

-189.58
Acquisition Parameters
Date_ 20171108
SOLVENT MeOD
SFO1 282.4701992 MHz
NUC1 19F
4c
-90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

D-2-Deoxy-2-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-glucopyranose 4d

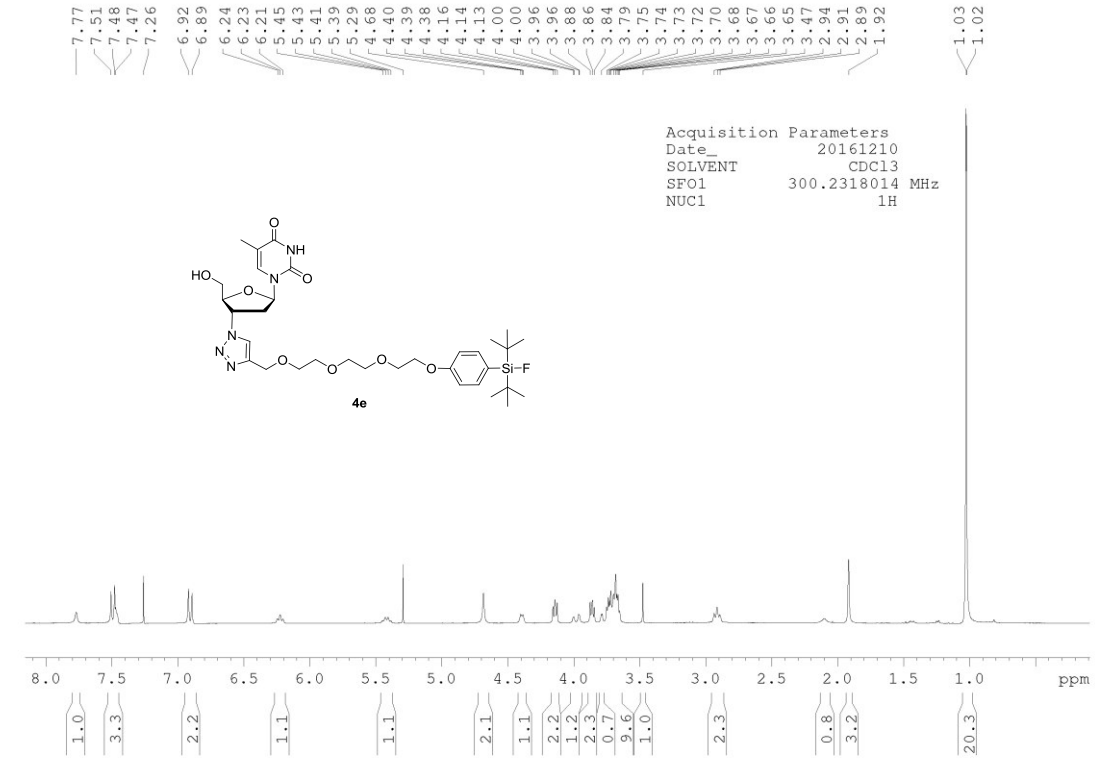


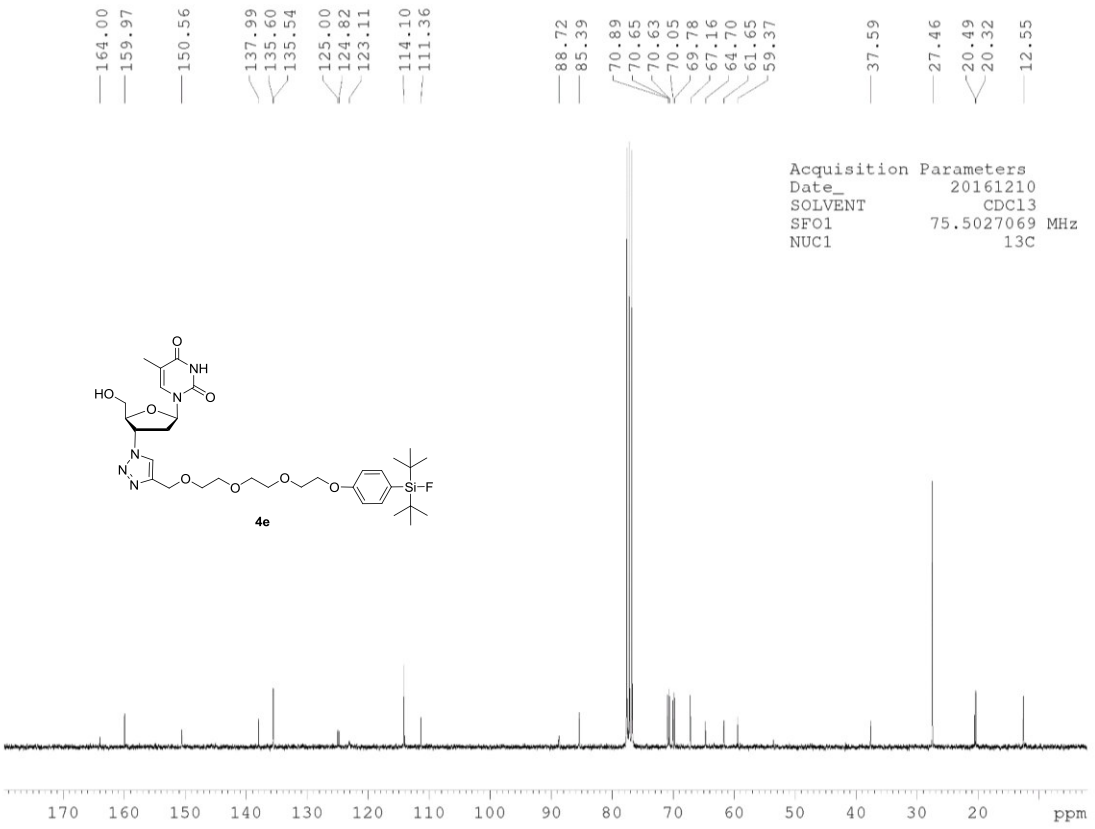


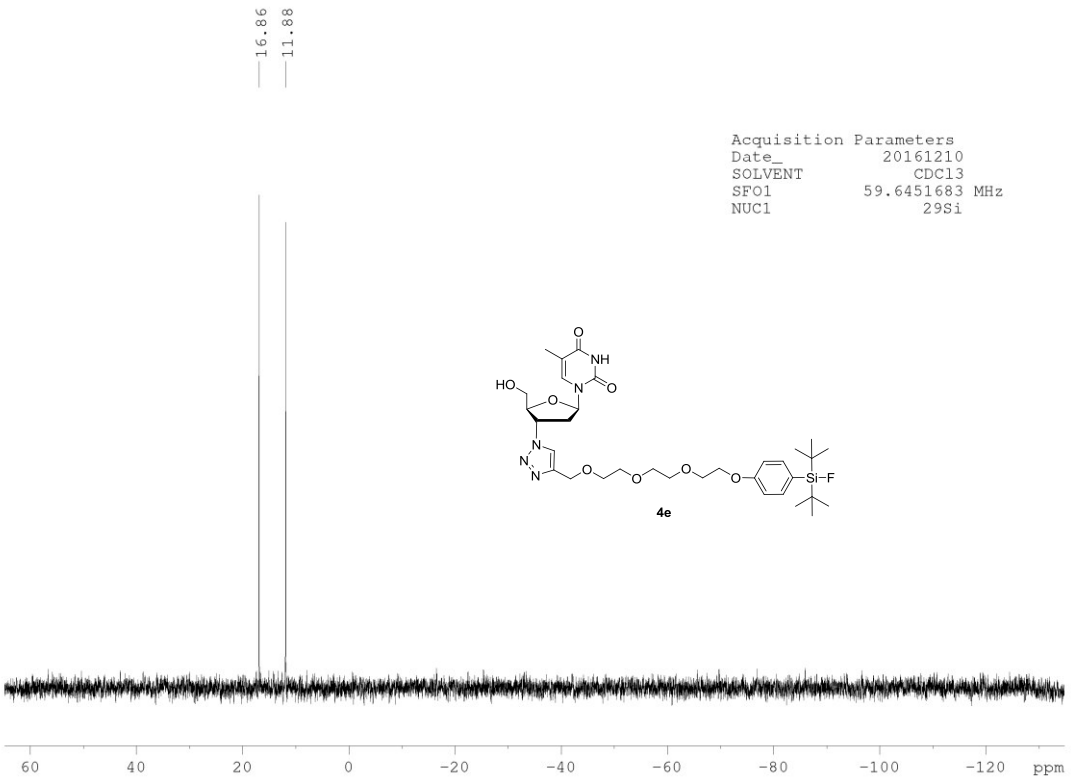

16.12
12.41
Acquisition Parameters
Date_ 20170414
SOLVENT MeOD
NUC1 29Si
SFO1 79.5084820 MHz
OH
HO
HO
OH
N
N
N
O
O
O
O
Si–F
4d
45
40
35
30
25
20
15
10
5
0
-5
-10
-15
ppm

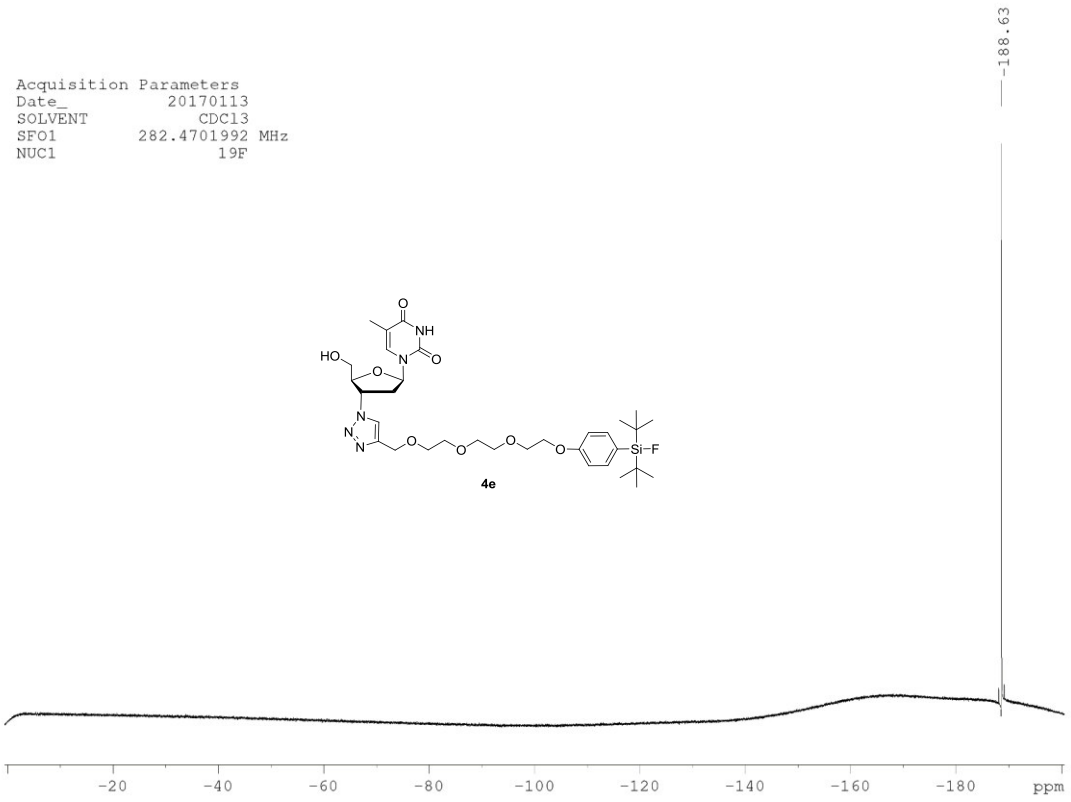

-188.53
Acquisition Parameters
Date_ 20170410
SOLVENT CDCl3
SFO1 282.4701992 MHz
NUC1 19F
OH
HO
HO
OH
N
N
N
O
O
O
O
Si–F
4d
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

3'-Deoxy-3'-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy) ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-thymidine 4e

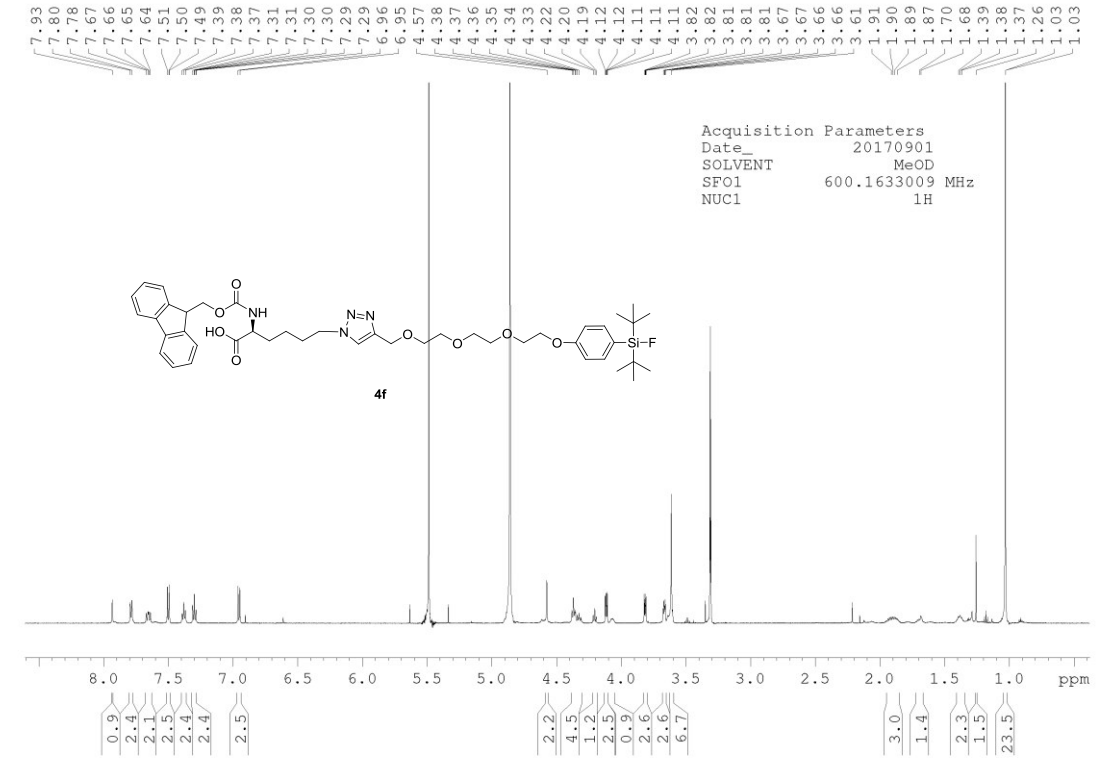


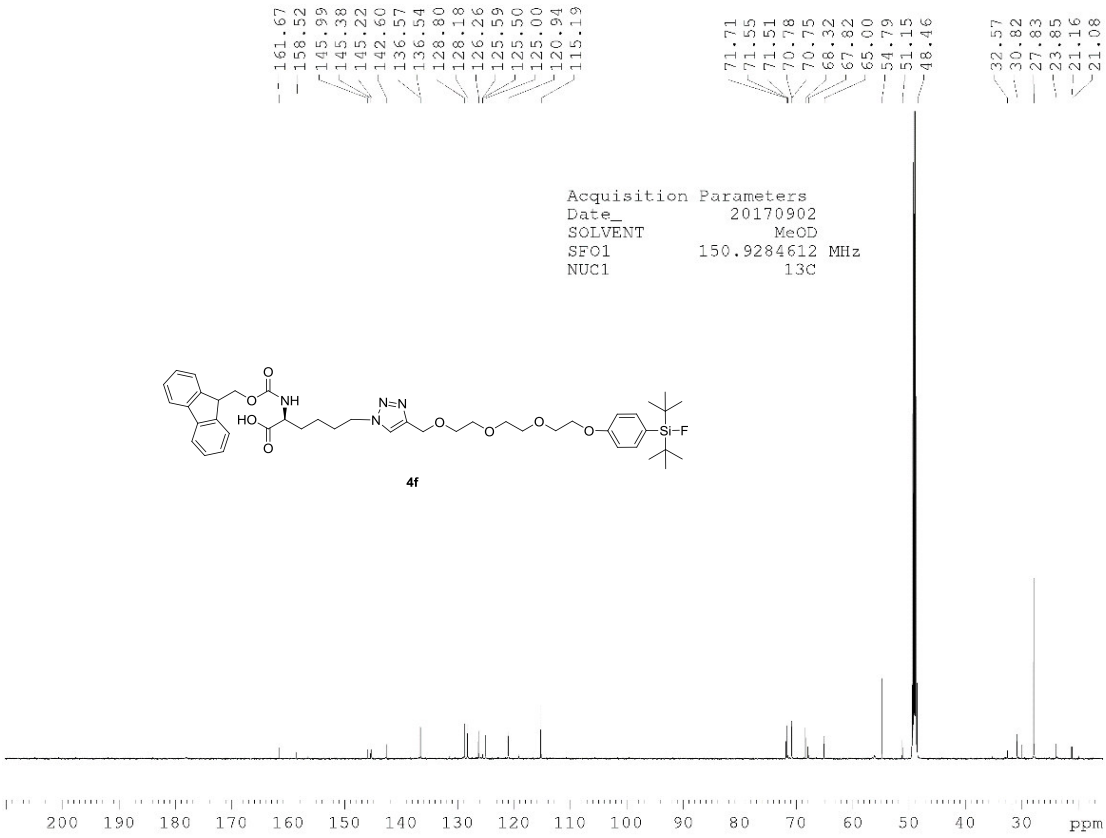


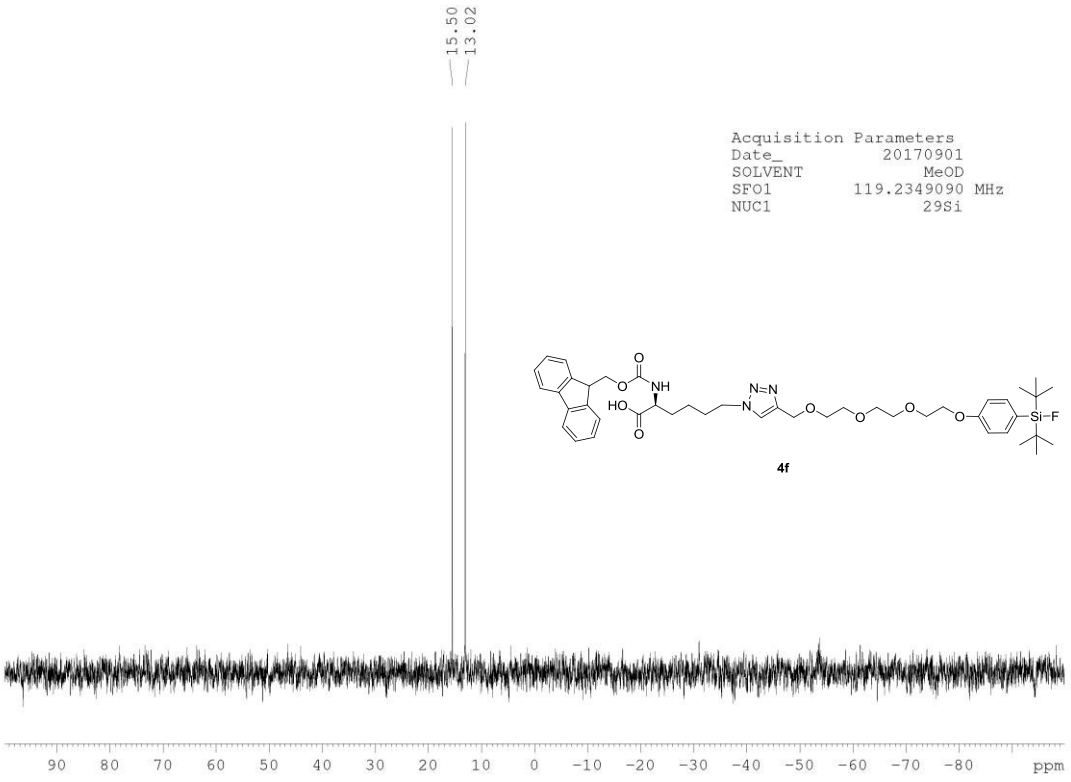

16.86
11.88
Acquisition Parameters
Date_ 20161210
SOLVENT CDCl3
SFO1 59.6451683 MHz
NUC1 29Si
4e
60
40
20
0
-20
-40
-60
-80
-100
-120
ppm

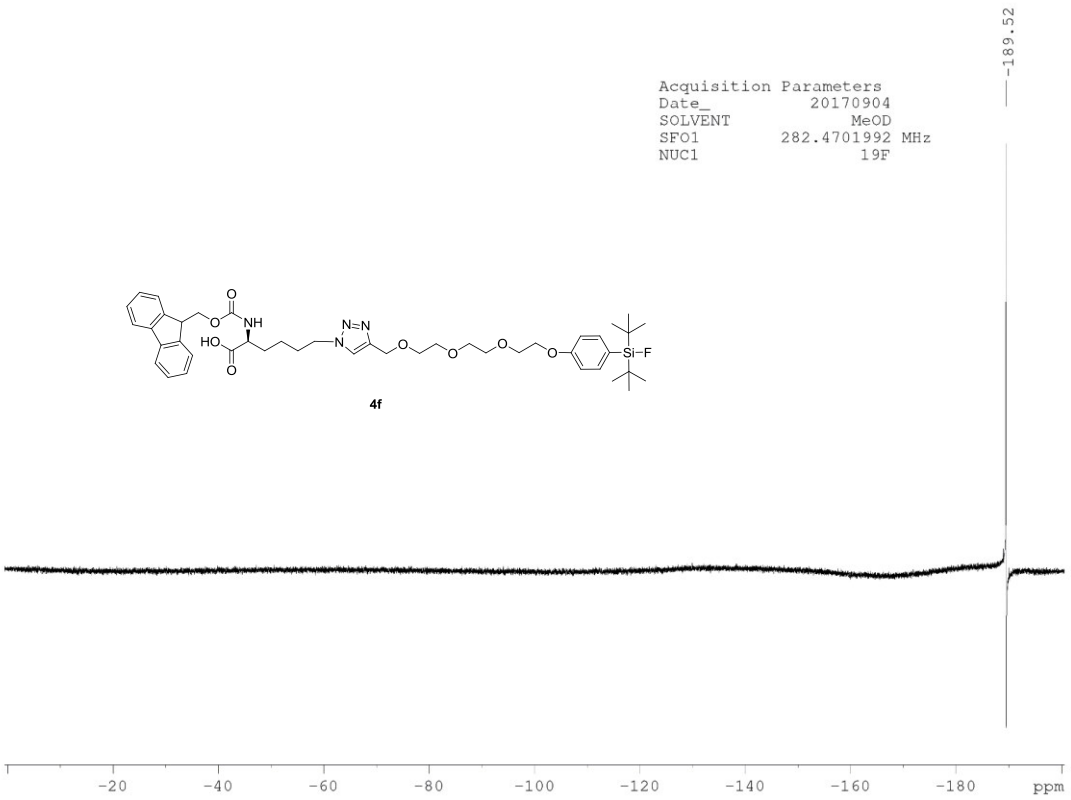

-188.63
Acquisition Parameters
Date_ 20170113
SOLVENT CDCl3
SFO1 282.4701992 MHz
NUC1 19F
4e
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

(S)-6-[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1H-1,2,3-triazol-1-yl]-2-(9-fluorenylmethoxycarbonyl)aminohexanoic acid 4f

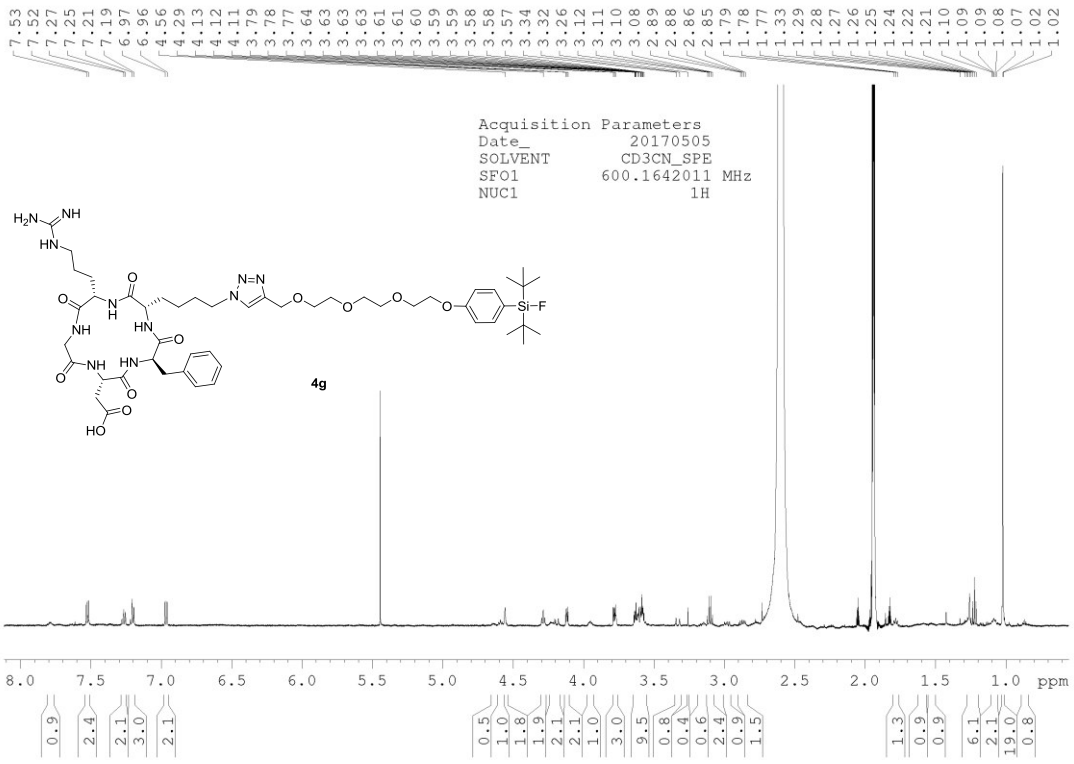


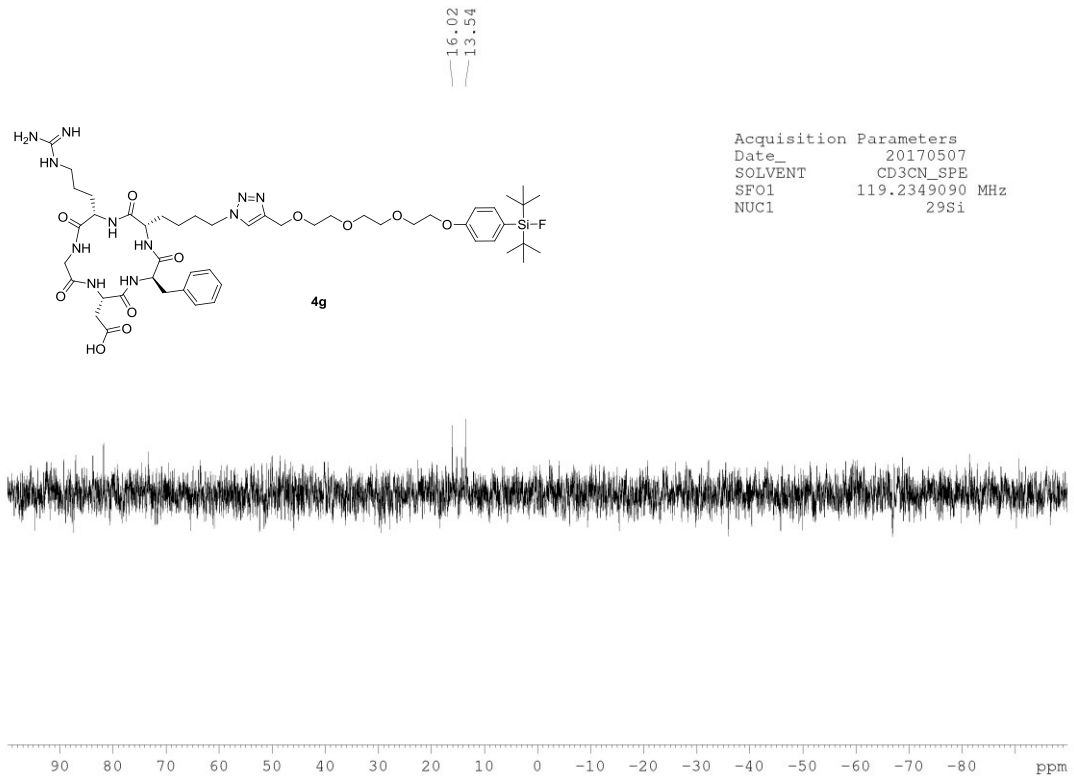


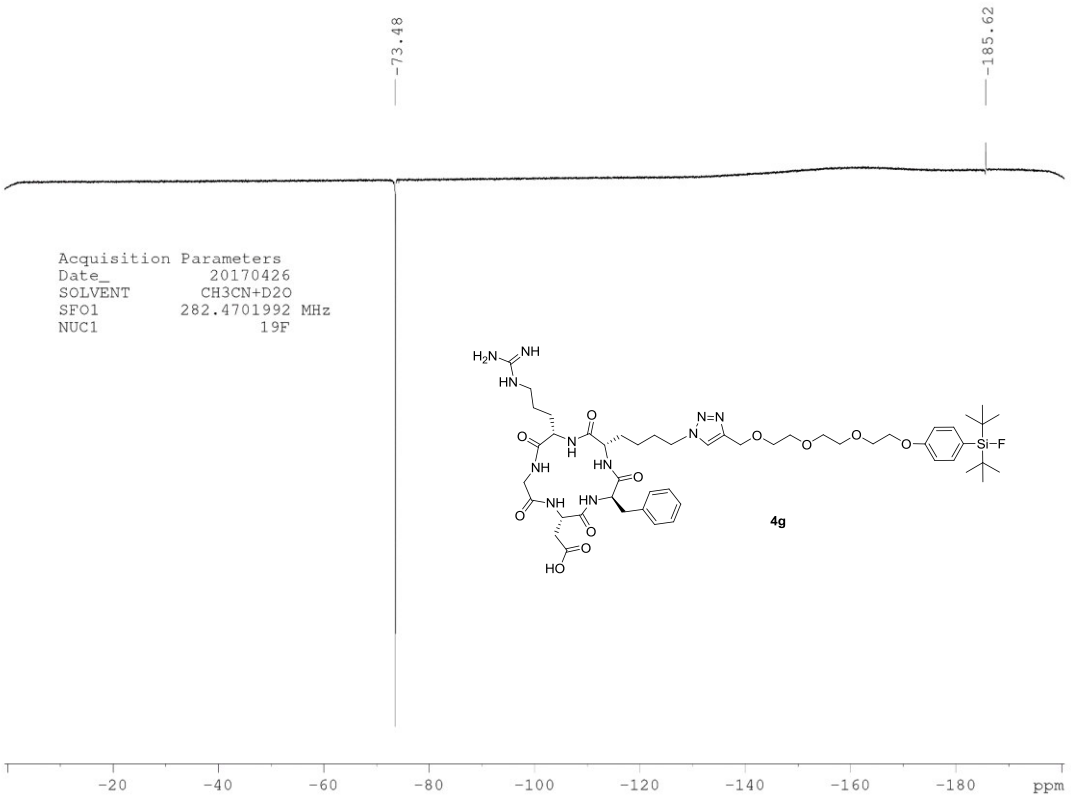

15.50
13.02
Acquisition Parameters
Date_ 20170901
SOLVENT MeOD
SFO1 119.2349090 MHz
NUC1 29Si
4f
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 ppm


-189.52
Acquisition Parameters
Date_ 20170904
SOLVENT MeOD
SFO1 282.4701992 MHz
NUC1 19F
4f
-20 -40 -60 -80 -100 -120 -140 -160 -180 ppm

[4-((2-(2-(2-(4-(di-tert-butylfluorosilyl)phenoxy)ethoxy)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl]-Cyclo-RGD 4g






-73.48
-185.62
Acquisition Parameters
Date_ 20170426
SOLVENT CH3CN+D2O
SFO1 282.4701992 MHz
NUC1 19F
4g
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm