Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

An Unusual Glycosylation Product from a Partially Protected Fucosyl Donor under Silver Triflate activation conditions

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Supporting information

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Experimental data - General Information

Unless otherwise stated; specific rotation was recorded in a Rudolph research autopol IV polarimeter, infrared spectra (IR) were recorded on a Perkin Elmer spectrometer. A Brüker Avance 400, and an Agilent 400 spectrometer were employed for ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) NMR spectra, a Brüker Ultrashield 600 spectrometer was employed for ^{1}H (600.13 MHz) and ^{13}C (150.90 MHz) NMR spectra. Resonances δ, are in ppm units downfield from an internal reference in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.0 ppm), MeOH (δ_H = 3.31 ppm, δ_C = 49.0 ppm). For oligosaccharides the notation a, b, c.... refers to the monosaccharide from the reducing end. Mass spectrometry analysis was performed with a Q-Tof Premier Waters Maldi-quadrupole time-of-flight (Q-Tof) mass spectrometer equipped with Z-spray electrospray ionization (ESI). X-ray crystallography was performed with a Brüker SMART APEX diffractometer. Silica gel Florisil (200 mesh; Aldrich) was used for column chromatography. Analytical thin-layer chromatography was performed using Merck 60 F_{254} silica gel (pre-coated sheets, 0.2 mm thick, 20 cm x 20 cm) and visualised by UV irradiation or molybdenum staining. DCM, MeOH, THF and toluene were dried over flame dried 3 Å or 4 Å sieves. Triethylamine (Et_3N) and trifluoroacetic acid (TFA) were used dry from sure/seal bottles. Other reagents were purchased from an industrial supplier; Sigma Aldrich, VWR, Carbosynth.

For experimental procedures and characterisation data for compounds **1**,**2**, **6** and **8** see references 19 and 35.

3-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-benzyl-α-L-fucopyranose, 3a

and,

3-(2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-benzyl-β-L-fucopyranose, 3b

Thioglycoside donor **1** (120 mg, 0.28 mmol), was dried under vacuum for 12 h, before dissolving in DCM (2 mL) containing pre-activated 3 Å ms under N_2. The mixture was cooled to 0 ^{o}C and Br_2 (104 µL, 2.80 mmol) added. The mixture was stirred under N_2 for 5 min at 0 ^{o}C after which time the bromine was removed *in vacuo*, co-evaporating with DCM (1 mL) and toluene (1 mL). The mixture was re-dissolved in anhydrous DCM (2 mL), and BnOH (29 µL, 0.28 mmol) was added. The temperature was lowered to -20 ^{o}C. AgOTf (141 mg, 0.55 mmol) in dry THF (1 mL) was cooled to -20 ^{o}C, and added. The mixture was stirred in the dark for 25 min before quenching with Et_3N (0.5 mL), and stirring for 20 min. The mixture was diluted with DCM (10 mL) and filtered through a plug of celite. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (5 mL), deionised H_2O

(3 mL) then dried over $MgSO_4$. The mixture was filtered and the solvent removed *in vacuo*. The mixture was purified by column chromatography (Et_2O:Hex, 1:19 v:v) to yield the disaccharide products **3a** (28 mg, 24 % yield), and **3b** (23 mg, 20 % yield) as clear oils;

αα anomer characterised, **3a**

$[\alpha]_D^{20}$ = 64 ^{o} (deg cm^3 g^{-1} dm^{-1}) (c = 0.1 in CH_3Cl);

ν_{max} (thin film) 3590 cm^{-1} (OH), 2928 cm^{-1} (CH);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 7.2 Hz, o-Ph), 7.33 (2H, t, *J* = 7.2 Hz, m-Ph), 7.28 (1H, t, *J* = 7.2Hz, p-Ph), 5.16 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1B), 4.85 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1A), 4.66 (1H, d, *J* = 11.8 Hz, OCHH), 4.51 (1H, d, *J* = 11.8 Hz, OCHH), 4.15 (1H, dd, $J_{2,3}$ = 10.0 Hz, $J_{2,1}$ = 3.3 Hz, H-2A), 4.10 (1H, q, $J_{5,6}$ = 6.5 Hz, H-5B), 4.05 (1H, dd, $J_{3,2}$ = 10.0 Hz, $J_{3,4}$ = 2.0 Hz, H-3A), 3.99 (1H, br s, H-4A), 3.94 (1H, ddd, $J_{3,2}$ = 9.3 Hz, $J_{3,OH}$ = 5.2 Hz, $J_{3,4}$ = 1.7 Hz, H-3B), 3.88 (2H, m, H-5A, H-2B), 3.81 (1H, d, $J_{4,3}$ = 1.6 Hz, H-4B), 1.76 (1H, *J* = 5.2 Hz, 3B-OH), 1.15 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6A), 1.14 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6B), 0.96 (18H, s, $SiC(CH_3)_3$), 0.91, 0.86 (9H, $SiC(CH_3)_3$), 0.16, 0.16, 0.13, 0.11, 0.11, 0.11, 0.04, 0.04 ((3H, s, $Si(CH_3)_2$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0 (Ar C), 128.2 (Ar CH), 128.1 (Ar CH), 127.1 (Ar CH), 100.4 (C-1B), 99.1 (C-1A), 77.7 (C-3A), 74.3 (C-4A), 74.0 (C-4B), 72.0 (C-2B), 70.5 (C-3 B), 70.4 (C-2A), 69.6 ($PhCH_2O$), 68.1 (C-5B), 68.0 (C-5A), 26.1, 26.1, 26.0, 25.9 ($SiC(\underline{C}H_3)_3$), 18.6, 18.5, 18.1, 18.1 ($Si\underline{C}(CH_3)_3$), 17.2 (C-6B), 17.0 (C-6A), -3.8, -3.9, - 4.0, - 4.1, - 4.4, - 4.7, - 4.7, -4.8, - 4.8 $Si(\underline{C}H_3)$;

M/z HRMS (ESI-TOF) calcd. for $C_{43}H_{84}O_9NaSi_4$ = 879.5090, $(M+Na)^+$. Found = 879.5068.

αβ anomer characterised, **3b**

$[\alpha]_D^{20}$ = 92 ^{o} (deg cm^3 g^{-1} dm^{-1}) (c = 0.1 in CH_3Cl);

ν_{max} (thin film) 3599 cm^{-1} (OH), 2929 cm^{-1} (CH);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 7.2 Hz, o-Ph), 7.34 (2H, t, *J* = 7.2 Hz, m-Ph), 7.30 (1H, t, *J* = 7.2 Hz, 5.07 (1H, d, $J_{1,2}$ = 2.0 Hz, H-1B), 4.92 (1H, d, *J* = 11.6 Hz, PhCH(H)), 4.52 (1H, d, *J* = 11.6 Hz, PhCH(H)), 4.29 (1H, br s, H-1A), 4.11 (1H, q, $J_{5,6}$ = 6.8 Hz, H-5B), 4.08 (1H, br s, H-4A), 3.92 (3H, m, H-3B, 2B, 5A), 3.76 (1H, br s, H-4B), 3.62 (2H, m, H-2A,3A), 1.73 (1H, br s, OH), 1.32 (3H, br s, H-6A), 1.15 (3H, d, $J_{6,5}$ = 6.7 Hz, H-6B), 0.97, (18H, s, $SiC(CH_3)_3$), 0.94, 0.89 (9H, s, Si $C(CH_3)_3$), 0.15, 0.15, 0.14, 0.13, 0.12, 0.11, 0.11, 0.05 (3H, s, $Si(CH_3)_2$;

^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9 (Ar C), 128.2 (Ar CH), 128.0 (Ar CH), 127.3 (Ar CH), 102.6 (C-1A), 101.0 (C-1B), 81.5 (C-3A), 74.0-72.5 (br, C-4A), 72.3 (C-2B), 74.0 (C-4B), 72.0 (C-2A), 71.7 (C-5A), 70.4 (C-3B), 70.2 ($O\underline{C}H_2Ph$), 68.0 (C-5B), 26.1, 26.1, 26.1, 26.0 ($SiC(\underline{C}H_3)_3$), 18.6, 18.5, 18.3, 18.1 ($Si\underline{C}(CH_3)$), 17.3 (C-6A), 17.2 (C-6B), - 3.6, - 3.9, - 4.0, - 4.0, - 4.2, - 4.4, - 4.4, - 4.6 ($Si(\underline{C}H_3)$);

M/z HRMS (ESI-TOF) calcd. for $C_{43}H_{84}O_9NaSi_4$ = 879.5090, $(M+Na)^+$. Found = 879.5063.

Reverse Glycosylation conditions for preparation of 3a and 3b (Table 1; entry 12)

Thioglycoside donor **1** (120 mg, 0.28 mmol), was dried under vacuum for 12 h, before dissolving in DCM (2 mL) containing pre-activated 3 Å ms under N_2. The mixture was cooled to 0 ^oC and Br_2 (104 µL, 2.80 mmol) added. The mixture was stirred under N_2 for 5 min at 0 ^oC before the bromine was removed *in vacuo*, co-evaporating with DCM and toluene. The bromide donor mixture was re-dissolved in anhydrous DCM (2 mL). BnOH (29 µL, 0.28 mmol) was added to AgOTf (141 mg, 0.55 mmol) in dry THF (1 mL) at -20 ^oC. The bromide donor mixture was added to the acceptor/activator mixture dropwise, and stirred in the dark for 25 min. The mixture was quenching with Et_3N (0.5 mL), and stirred for 20 min before being worked up as general procedure to yield the disaccharide products **3a** (16 mg, 14 % yield), and **3b** (14 mg, 12 % yield) as clear oils;

O-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-propargyl-α-L-fucopyranose, 5a

and

O-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-propargyl-β-L-fucopyranose 5b

Thioglycoside donor **1** (120 mg, 0.28 mmol), Br_2 (104 µL, 2.80 mmol) and propargyl alcohol **63** (15 µL, 0.28 mmol) were reacted according to procedure described for synthesis of **3a/3b**. The crude material was purified by column chromatography (EtOAc:Hexane, 1:49 (v/v)) to yield products **5a**, as a clear oil, (50 mg, 45 %) and the product **5b**, as a clear oil (9 mg, 8 %);

αα anomer characterised, **5a**

$[\alpha]_D^{20}$ = -76 ^{o} (deg cm^3 g^{-1} dm^{-1}) (c = 0.1 in CH_3Cl);

ν_{max} (thin film) 3599 cm^{-1} (OH), 2929 cm^{-1} (CH);

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.13 (1H, d, $J_{1,2}$ = 3.1 Hz, H-1B), 4.97 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1A), 4.24 (2H OCH_2), 4.16 (1H, dd, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 3.5 Hz, H-2A), 4.10 (1H, q, $J_{5,6}$ = 6.6 Hz, H-5B), 4.01 (1H, br s, H-4A), 4.00 (1H, dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 2.2 Hz, H-3A), 3.94 (1H, ddd, $J_{3,2}$ = 9.6 Hz, $J_{3,OH}$ = 6.0 Hz, $J_{3,4}$ = 2.9 Hz, H-3B), 3.90 (1H, dd, $J_{3,2}$ = 10.0 Hz, $J_{3,4}$ = 3.1 Hz, H-2B) 3.87 (1H, q, $J_{5,6}$ = 6.6 Hz, H-5A), 3.81 (1H, d, $J_{4,3}$ = 1.9 Hz, H-4B), 2.36 (1H, t, J = 2.4 Hz, C≡CH), 1.76 (1H, d, J = 6.0 Hz, OH), 1.17 (3H, d, $J_{6,5}$ = 6.8 Hz, H-6A), 1.14 (3H, d, $J_{6,5}$ = 6.8 Hz, H-6B), 0.96, 0.95, 0.94, 0.93 (9H, s, $SiC(CH_3)_3$), 0.16, 0.15, 0.15, 0.15, 0.15, 0.11, 0.11, 0.11 (3H, s, $Si(CH_3)_2$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 100.8 (C-1B), 98.0 (C-1A), 79.6 (C≡CH), 77.9 (C-3A), 74.3 (C-4A), 74.1 (C≡CH), 74.0 (C-4B), 72.1 (C-2B), 70.5 (C-3B), 70.0 (C-2A), 68.3 (C-5A), 68.2 (C-5B), 54.2 (OCH_2), 26.1, 26.1, 26.1, 26.0 ($SiC(CH_3)_3$), 18.6, 18.6, 18.5, 18.5, 18.3, 18.3, 18.2, 18.2 ($SiC(CH_3)_3$, 17.3 (C-6B), 16.9 (C-6A), -3.8, -3.9, -3.9, -4.2, -4.4, -4.7, -4.7, -4.9 ($Si(CH_3)_2$;

M/z HRMS (ESI-TOF) calcd. for $C_{39}H_{80}O_9NaSi_4$ = 827.4777 $(M+Na)^+$. Found = 827.4770.

αβ anomer characterised, **5b**

$[\alpha]_D^{20}$ = -57 ^{o} (deg cm^3 g^{-1} dm^{-1}) (c = 0.1 in CH_3Cl);

ν_{max} (thin film) 3587 cm^{-1} (OH), 2931 cm^{-1} (CH);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1H, d, $J_{1,2}$ = 2.8 Hz, H-1b), 4.37 (1H, dd, J = 15.5 Hz, J = 2.4 Hz, OCH(H)) 4.34 (1H, d, $J_{1,2}$ = 6.5 Hz, H-1a), 4.31 (1H, dd, J = 15.6 Hz, J = 2.2 Hz, OCH(H)), 4.10 (1H, q, $J_{5,6}$ = 6.6 Hz, H-5b), 4.03 (1H, br s, H-4a), 3.97 (1H, ddd, $J_{3,2}$ = 10.0 Hz, $J_{3,OH}$ = 6.5 Hz, $J_{3,4}$ = 2.6 Hz, H-3b), 3.92 (1H, dd, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 3.1 Hz, H-2b), 3.85 (1H, dd, $J_{2,3}$ = 8.9 Hz, $J_{2,1}$ = 6.4 Hz, H-2a), 3.81 (1H, br s, H-4b), 3.60 (1H, dd, $J_{3,2}$ = 8.6 Hz, $J_{3,4}$ = 1.2 Hz, H-3a), 3.57 (1H, m, H-5a), 2.39 (-C≡CH), 1.24 (3H, d, $J_{6,5}$ = C-6a), 1.15 (3H, d, $J_{6,5}$ = C-6b), 1.00, 0.95, 0.95, 0.94 (9H, s, $SiC(CH_3)_3$), 0.15, 0.15, 0.14, 0.14, 0.14, 0.14, 0.12, 0.12 (3H, s, $Si(CH_3)_2$;

^{13}C NMR (100 MHz, $CDCl_3$) δ 101.4 (C-1a), 101.0 (C-1b), 82.1 (C-3a), 78.8 (-C≡CH), 74.5 (-C≡CH), 74.1 (C-4b), 72.5 (C-4a), 72.1 (C-2b), 71.9 (C-2a), 70.1 (C-3b), 68.0 (C-5b), 55.0 (OCH_2), 26.0, 25.9, 25.9, 25.7 ($SiC(CH_3)_3$), 18.5, 18.4, 18.4, 18.53, 18.1, 18.1, 18.0, 18.0 ($SiC(CH_3)_3$), 17.8, 17.8 (C-6b, C-6a) -3.7, -3.7, -3.9, -4.1, -4.2, -4.5, -4.6, -4.7 ($Si(CH_3)_2$;

M/z HRMS (ESI-TOF) calcd. for $C_{39}H_{80}O_9NaSi_4$ = 827.4777 $(M+Na)^+$. Found = 827.4736.

2-Acetamido-2-deoxy-3,4-di-O-acetyl-6-O-(3-O-(2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-1-O-propargyl-β-D-glucopyranose, 7

Thioglycoside donor **1** (128 mg, 0.30 mmol), Br_2 (104 µL, 2.80 mmol) and acceptor **6** (100 mg, 0.30 mmol) reacted according to procedure described for synthesis of **3a/3b.**. The crude material was purified by column chromatography (EtOAc:Hex, 1:1 (v/v)) to yield the product as a clear oil (13 mg, 8 %);

$[\alpha]_D^{20}$ = -83 ^{o} (deg cm^3 g^{-1} dm^{-1}) (c = 0.1 in CH_3Cl);

ν_{max} (thin film) 3530 cm^{-1} (OH), 3276 cm^{-1} (C≡CH), 3035 cm^{-1} (NH), 2929 cm^{-1} (CH), 1753 cm^{-1} C=O, 1663 cm^{-1} (NHC=O);

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.39 (1H, d, J = 9.1 Hz, NH), 5.24 (1H, app t, $J_{3,4} = J_{3,2}$ = 9.8 Hz, H-3A), 5.10 (1H, d, $J_{1,2}$ = 2.3 Hz, H-1C), 5.00 (1H, app t $J_{4,3} = J_{4,5}$ = 9.6 Hz, H-4A), 4.76 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1A), 4.74 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1B), 4.37 (2H, m, $\underline{CH_2}C{\equiv}CH$), 4.08 (1H, dd, $J_{2,3}$ = 9.6 Hz, $J_{2,1}$ = 2.7 Hz, H-2B), 4.06 (2H, m, H-5C, H-4B), 4.00 (1H, app q, $J_{2,NH} = J_{2,1} = J_{2,3}$ =8.9 Hz, H-2A), 3.93 (4H, m, H-3B, H-3C, H-2C, H-5B), 3.83 (1H, br s, H-4C), 3.75 (1H, br d, $J_{6',6}$ = 11.6 Hz, H-6'A), 3.73 (1H, m, H-5A), 3.60 (1H, dd, $J_{6,6'}$ = 11.5 Hz, $J_{6,5}$ = 5.8 Hz, H-6A), 2.46 (1H, s, $C{\equiv}\underline{CH}$), 2.05, 2.03, 1.98 (3H, s, $COCH_3$), 1.79 (1H, d, J = 4.5Hz, 3C-OH), 1.19 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6B), 1.15 (3H, d, $J_{6,5}$ = 6.4 Hz, H-6C), 0.97, 0.97, 0.95, 0.92 (9H, s, $SiC(CH_3)_3$), 0.20, 0.17, 0.16, 0.15, 0.13, 0.11, 0.11, 0.10 (3H, s, $SiCH_3$);

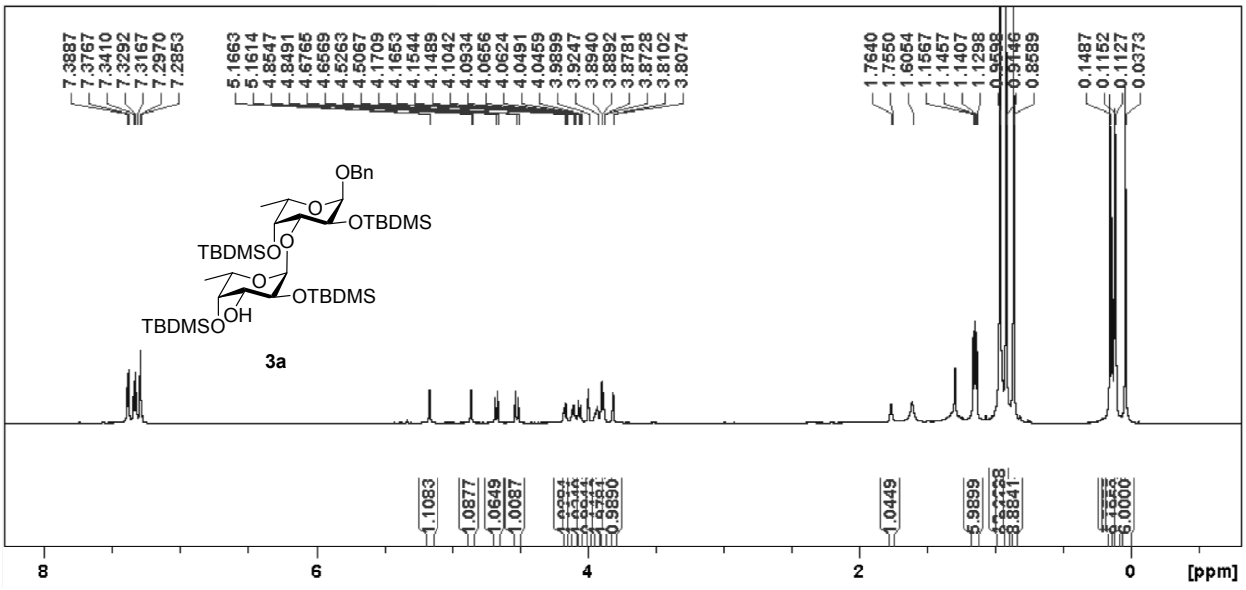
^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 169.9, 168.9 (C=O), 100.6 (C-1C), 99.0 (C-1B), 98.2 (C-1A), 78.7 ($HC{\equiv}\underline{C}$), 77.6 (C-3B), 74.9 ($C{\equiv}\underline{CH}$), 73.8 (C-4C), 73.4 (C-5A), 73.3 (C-4B), 72.7 (C-3A), 71.6 (C-3C), 70.3 (C-2C), 70.1 (C-2B), 68.9 (C-4A), 68.5 (C-5B), 68.0 (C-5C), 66.8 (C-6A), 55.4 ($CH_2C{\equiv}CH$), 54.0 (C-2A), 25.9, 25.9, 25.9, 25.8 ($SiC(CH_3)_3$), 23.2 ($NHCO\underline{C}H_3$), 20.5, 20.5 ($COCH_3$), 18.4, 18.3, 18.2, 18.0 ($Si\underline{C}(CH_3)_3$), 17.1 (C-6C), 16.6 (C-6B), -3.6, -4.0, -4.0, -4.4, -4.6, -4.9, -4.9, -4.9 ($Si\underline{C}H_3$);

M/z HRMS (ESI-TOF) calcd. for $C_{51}H_{96}NO_{16}Si_4$ = 1090.5806, $(M-H)^-$. Found = 1090.5806.

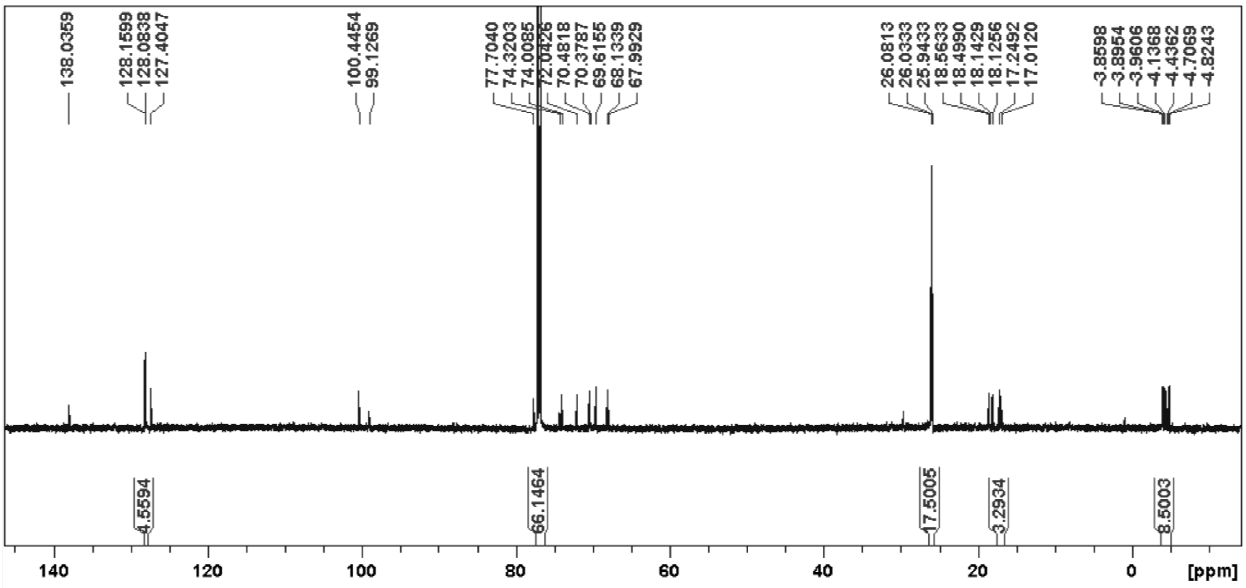
Supplemental – S3 NMR data

3-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-benzyl-α-L-fucopyranose, 3a

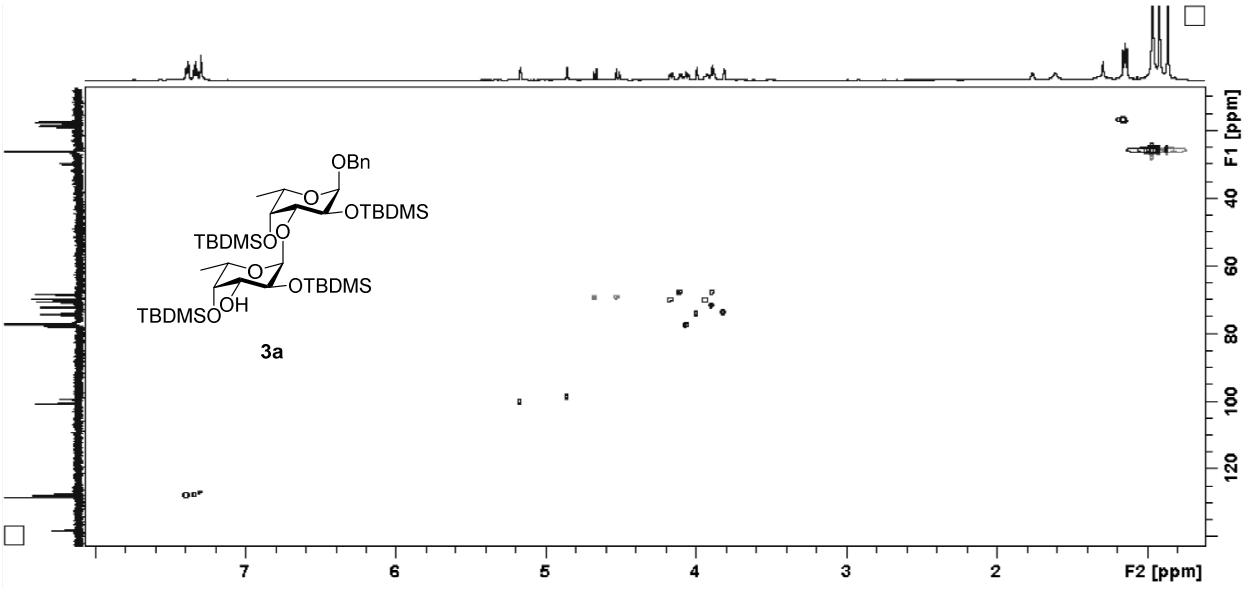
^{1}H-NMR



^{13}C-NMR

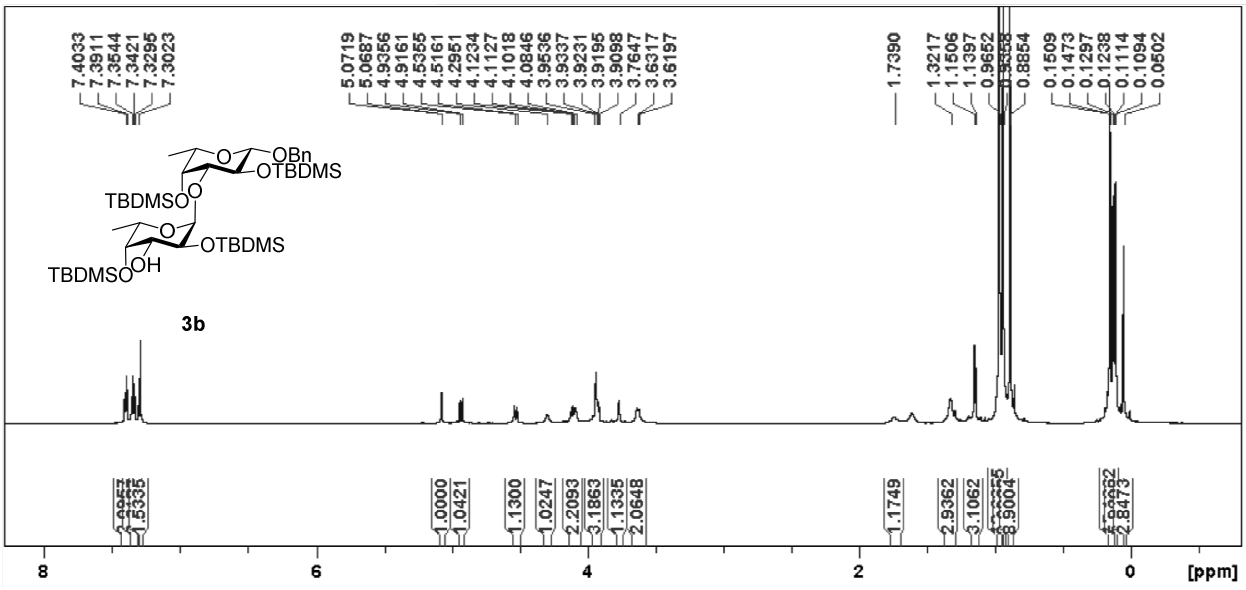


^{1}H-^{13}C HSQC



3-(2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-benzyl-β-L-fucopyranose, 3b

^{1}H-NMR



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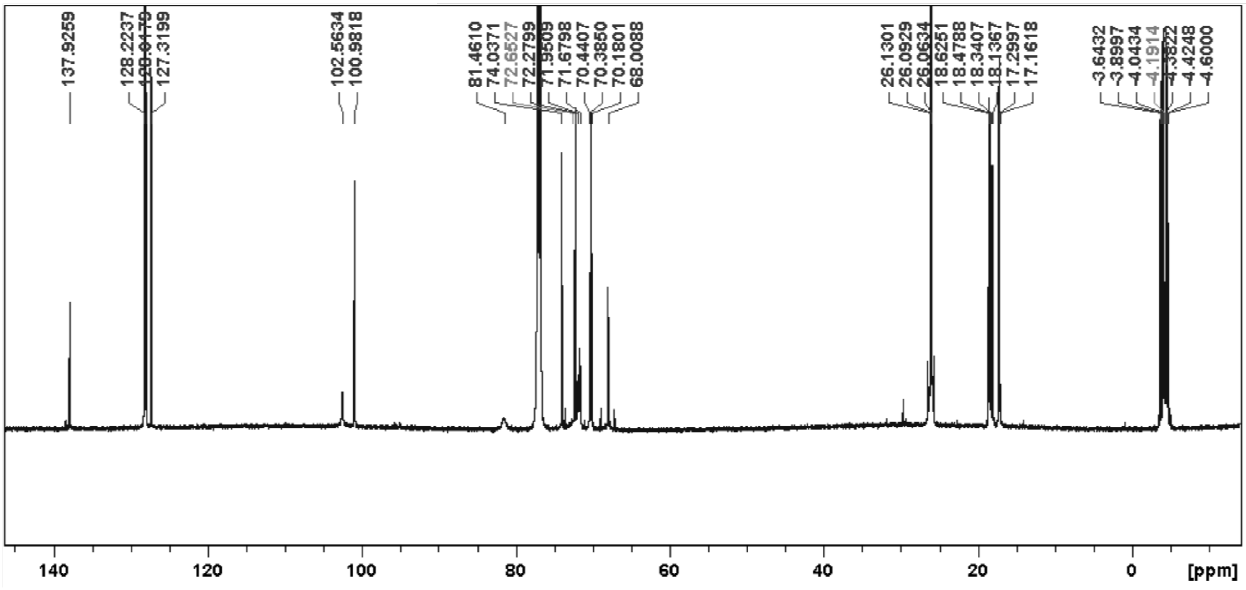
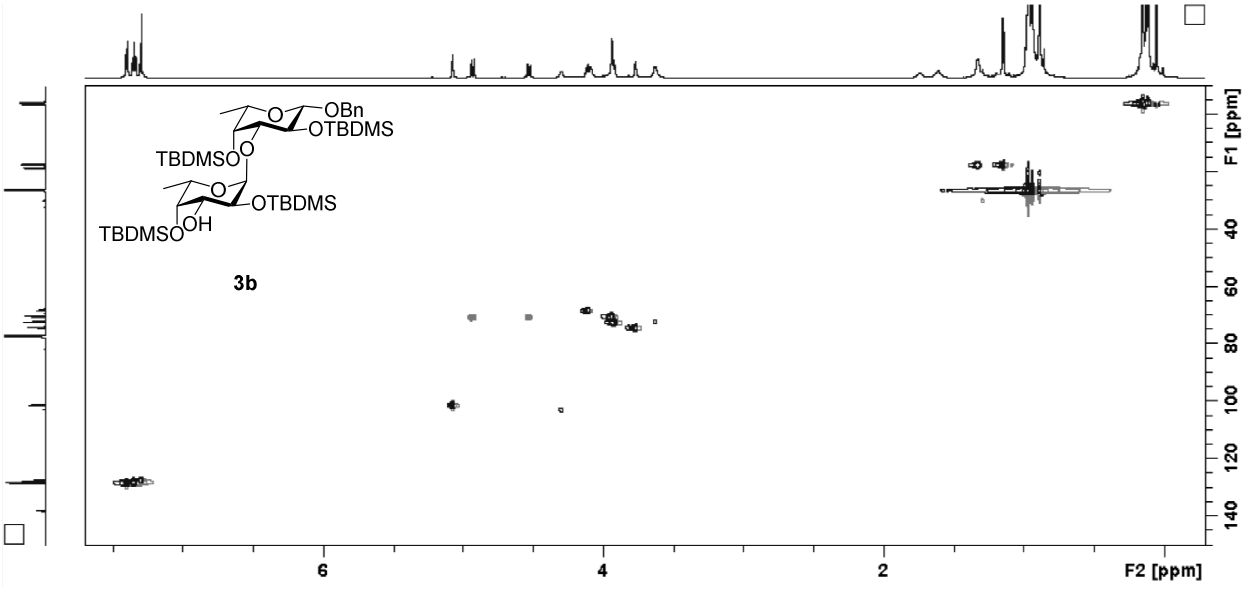
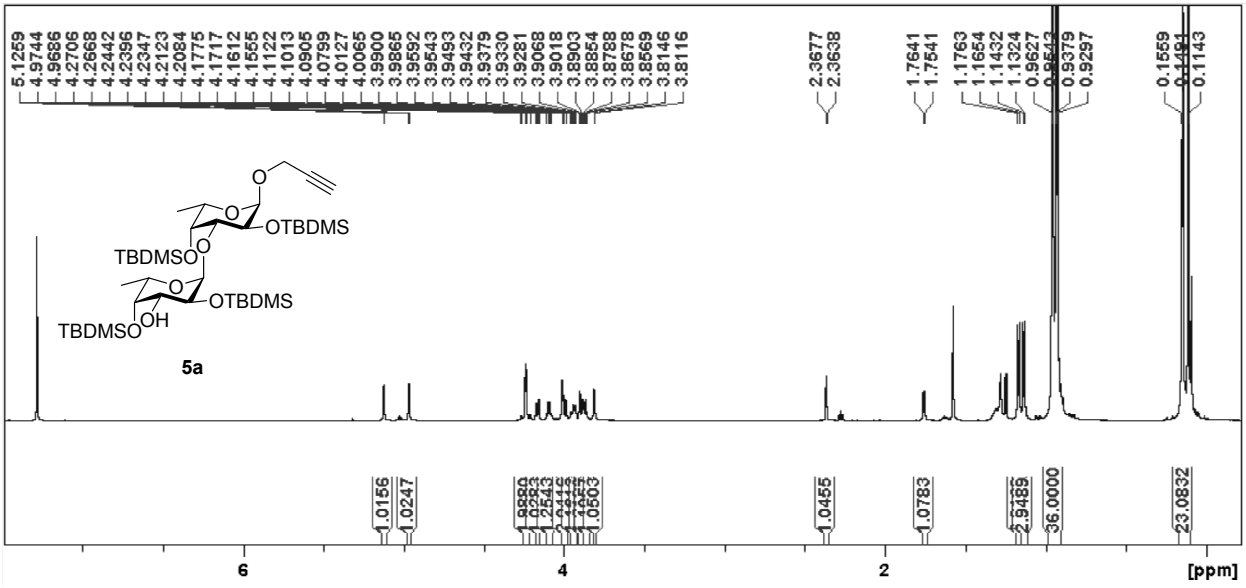


^{1}H-^{13}C HSQC

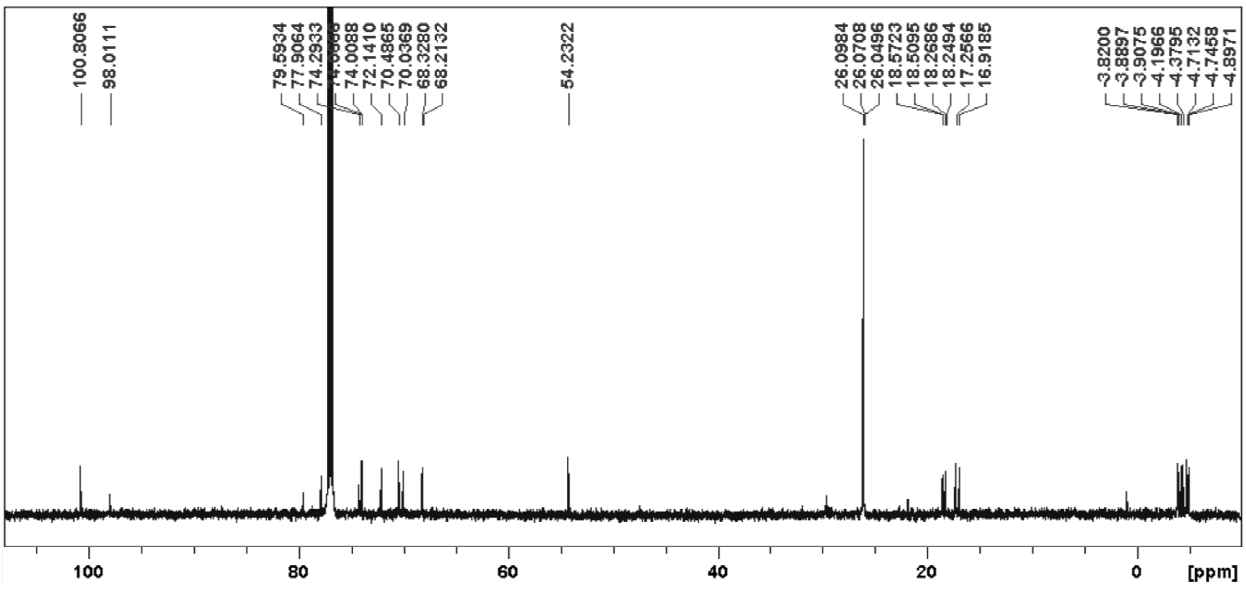


O-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-propargyl-α-L-fucopyranose, 5a

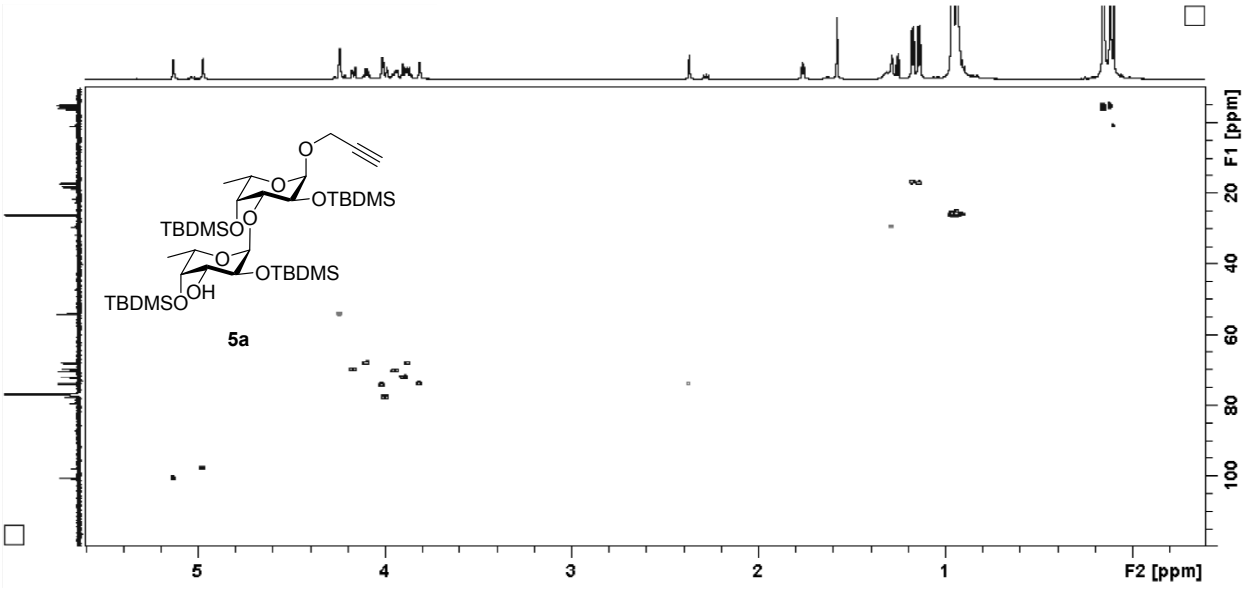
^{1}H-NMR



^{13}C-NMR

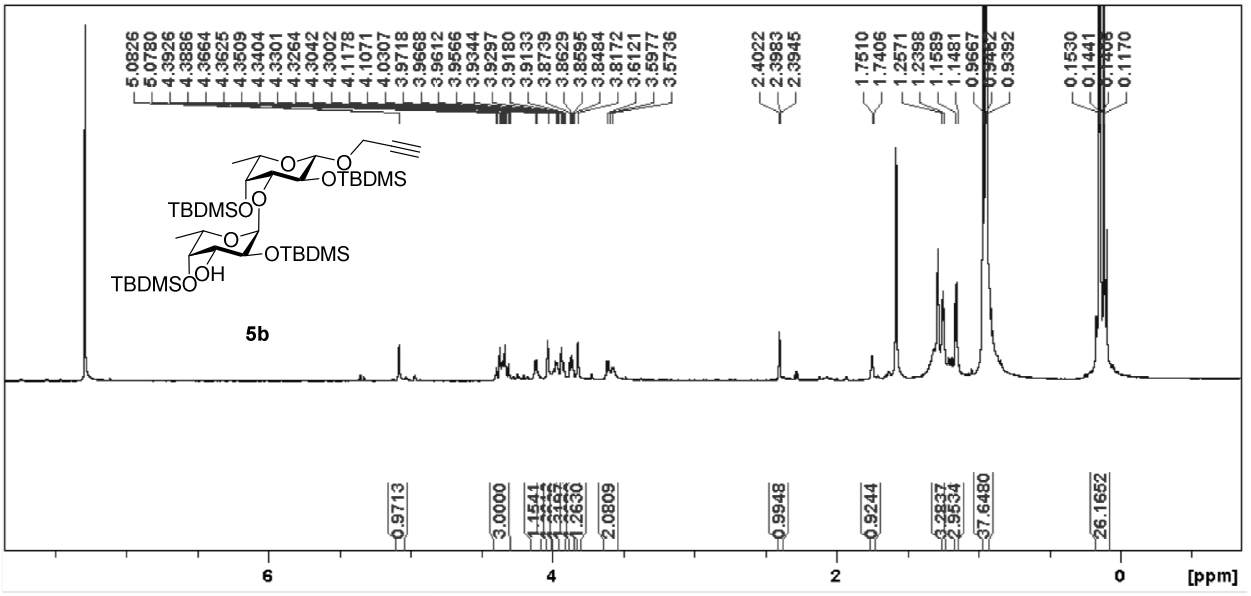


^{1}H-^{13}C HSQC

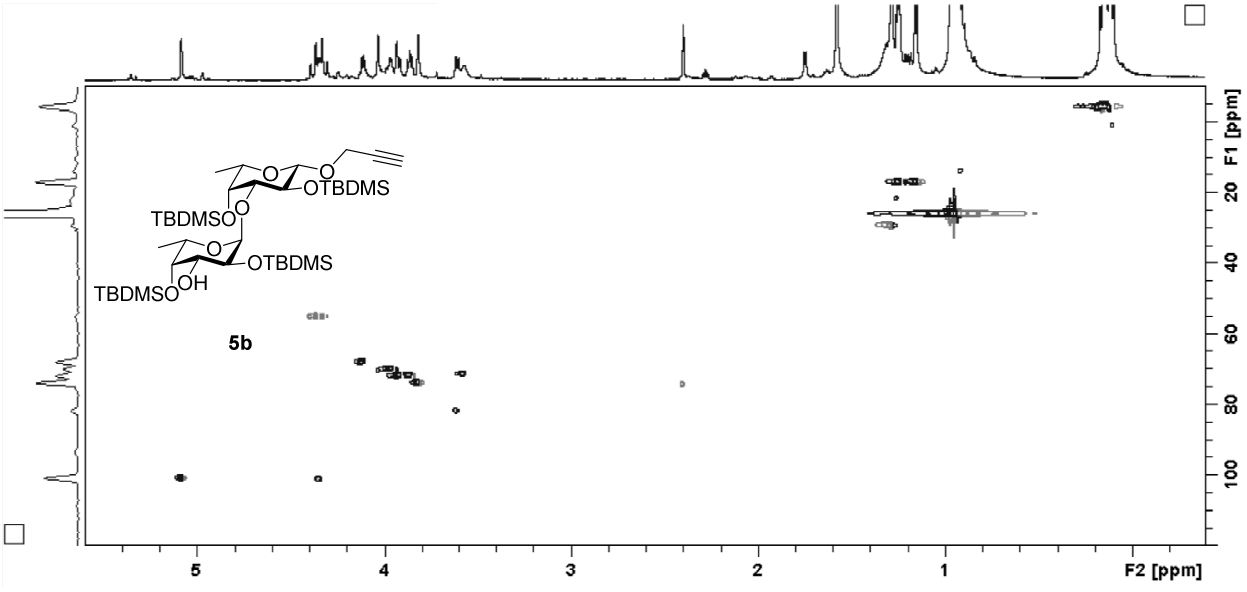


O-(2,4-Di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyl-dimethylsilyl-1-O-propargyl-β-L-fucopyranose 5b

^{1}H-NMR

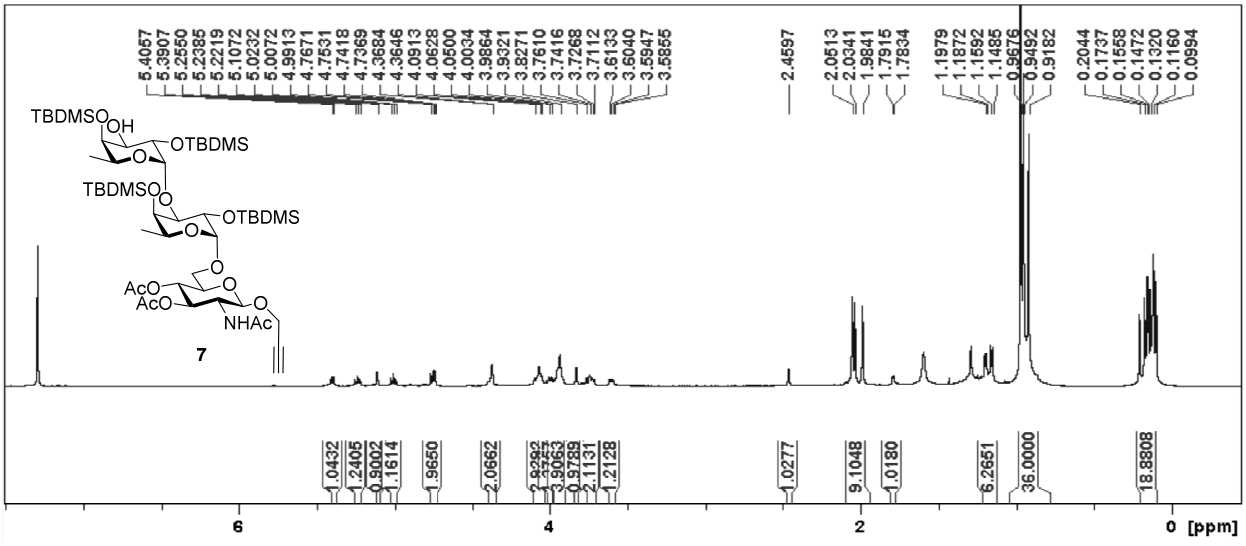


^{1}H-^{13}C HSQC

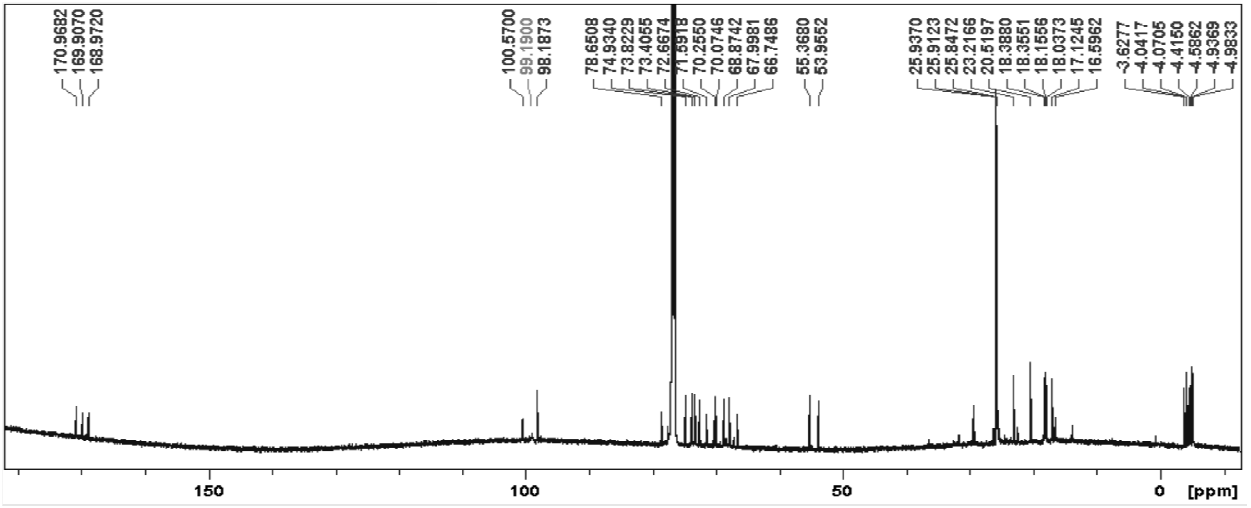


2-Acetamido-2-deoxy-3,4-di-O-acetyl-6-O-(3-O-(2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-2,4-di-O-*tert*-butyldimethylsilyl-α-L-fucopyranosyl)-1-O-propargyl-β-D-glucopyranose, 7

^{1}H-NMR



^{13}C-NMR



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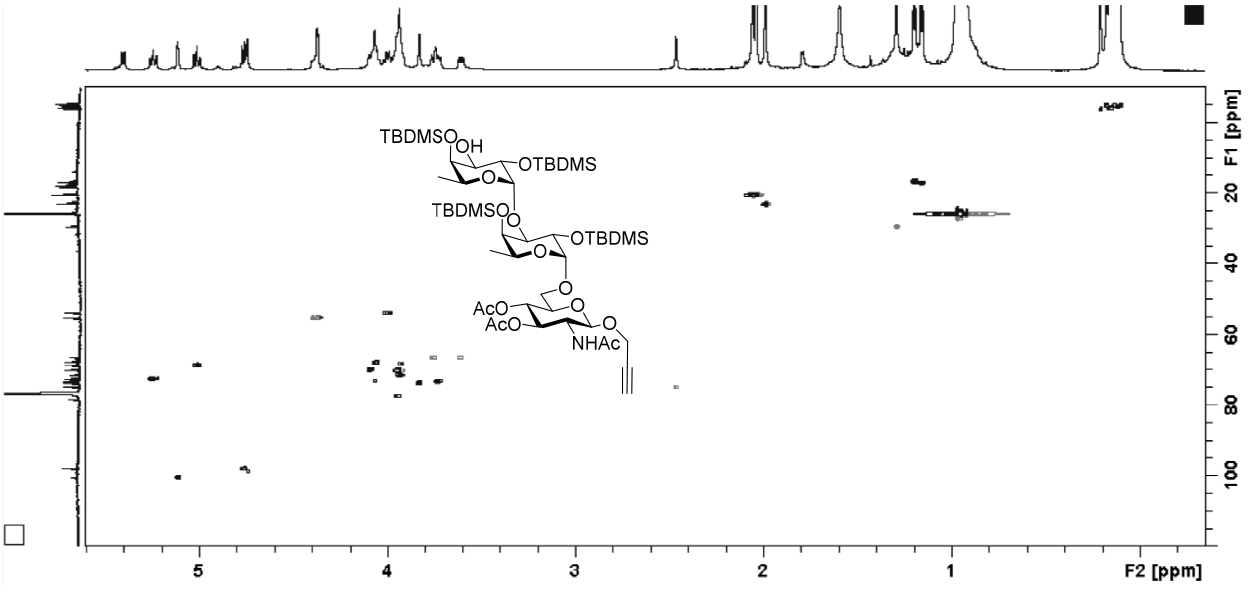
^{1}H-^{13}C HSQC



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