Reaction of N-Acetylneuraminic Acid Derivatives with Perfluorinated Anhydrides: a Short Access to N-Perfluoracylated Glycals with Antiviral Properties

Paola Rota, Pietro Allevi, Roberto Mattina and Mario Anastasia*

Department of Medical Chemistry, Biochemistry and Biotechnology
University of Milan. Via Saldini 50-I-20133-Milano (Italy)
Fax: (+39) 0250316040
E-mail: mario.anastasia@unimi.it

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1. General Methods

Solvents were dried using standard methods and distilled before use. The reactions are thermostated by block heater -BBA- Grant Boekel apparatus. The progress of all reactions was monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F254) using UV light, 50% sulphuric acid, anisaldehyde/H2SO4/EtOH solution or 0.2% ninhydrin in ethanol and heat as developing agent. The flash chromatography was performed with normal phase silica gel (E. Merck 230-400 mesh silica gel), following the general protocol of Still[1]. GLC was performed by Hewlett 5890 PACKARD Series II using HP-5 30 m x 0.32 mm, 0.25 μm film-thickness column. Melting points were measured on a SMP3 mp apparatus (Stuart Scientific, USA) and are not corrected. NMR spectra were recorded at 25°C on a Bruker AM-500 spectrometer operating at 500.13 MHz for 1H and 125.76 MHz for 13C. The chemical shifts are reported in ppm and coupling constants are given in Hz, relative to CD3OD signal fixed at 3.31 ppm for 1H spectra and to CD2OD signal fixed at 49.05 ppm for 13C spectra, relative to CDCl3 signal fixed at 7.26 ppm for 1H spectra and to CDC13 signal fixed at 77.00, relative to CD3CN signal fixed at 1.94 ppm for 1H spectra and to CD3CN signal fixed at 1.24 ppm for 13C spectra. Proton and carbon assignments were established, if necessary, with 1H-1H and 1H-13C correlated NMR experiments. Data for 1H NMR are recovered as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) in Hz, number of protons, assignment of proton(s). In some cases, reported in the text, the 1H NMR inspection was performed on the total reaction mixture using CD3CN as a solvent. Optical rotations were taken on a Perkin-Elmer 241 polarimeter equipped with a 1 dm tube; [α]D values are given in 10−1deg cm2 g−1 and the concentrations are given in g/100 mL.

Infrared (IR) spectra were recorded for CH2Cl2 solution using a Perkin-Elmer 1420 instrument. Mass spectrometry was performed using Finnigan LCQdeca quadrupole ion-trap mass spectrometer equipped with an ESI ion source (Finnigan ThermoQuest, San Jose, CA, USA). The spectra were collected in continuous flow mode by connecting the infusion pump directly to the ESI source. Solutions of compounds were infused at a flow rate of 5 μL/min. The spray voltage was set at 5.0 kV in the positive and at 4.5 kV in the negative ion mode with a capillary temperature of 220 °C. Full-scan mass spectra were recorded by scanning a m/z range of 100-2000. Work-up refers to successive washing of the organic layer with an ice cold aqueous NaHCO3 saturated solution and water, to drying over Na2SO4, and evaporation of the solvent under reduced pressure.

2. Preparation of N-Perfluoroacylneuraminic Acid Glycals: General Procedure

The acylamide (0.2 mmol) dissolved in CH3CN (0.60 mL) was reacted with the appropriate perfluorinated anhydride (0.6-1.4 mmol, 3-7 molar equivalents) at 135 °C for 5-15 min in a sealed tube. Then the reaction mixture was cooled, added of methanol (0.20 mL) and evaporated under reduced pressure to afford a crude residue which, after usual work-up, and rapid chromatography, using the designed solvent system, afforded the appropriate glycal. This procedure was used both for the exclusive N-transacylation and for the N-transacylation coupled with elimination reaction.
2.1 Glycal 5: 4,7,8,9-tetra-O-Acetyl-2,3-dehydro-2-deoxy-5-N-(2,2,2-trifluoroacetyl)-β-neuraminic acid methyl ester

![Image of Glycal 5]

**a) By N-transacylation from the glycal 3**

Starting with the glycal 3[^2] (95 mg; 0.20 mmol), glycal 5 was obtained (83 mg, 79 % yield), after a 10 min reaction with TFAA and flash chromatography (eluting with hexane/AcOEt; 6:4, v/v). Glycal 5 showed: m.p. 115-116°C; [α]D[^20] = + 50.8 (c = 1, CHCl₃); ¹H NMR (CDCl₃) δ 7.21 (d, J_NH,2 = 9.0 Hz, 1H; N-H), 5.97 (d, J₃,4 = 2.6 Hz, 1H; H-3), 5.65 (dd, J₄,5 = 8.0, J₄,3 = 2.6 Hz, 1H; H-4), 5.47 (dd, J₇,8 = 4.3, J₇,6 = 3.0 Hz, 1H; H-7), 5.29 (m, 1H; H-8), 4.71 (dd, J₉a,9b = 12.4, J₉a,8 = 2.6 Hz, 1H; H-9a), 4.49 (dd, J₆,5 = 9.7, J₆,7 = 3.0 Hz, 1H; H-6), 4.34 (m, 1H; H-5), 4.18 (dd, J₉b,9a = 12.4, J₉b,8 = 7.3 Hz, 1H; H-9b), 3.81 (s, 3H; COOCH₃); 2.11 (s, 3H; CH₃COO at C-7), 2.06 (overlapping, 6H; 2XCH₃COO), 2.04 (s, 3H; CH₃COO); ¹³C NMR (CDCl₃) δ 170.7 (3C, CH₃COO at C-4, CH₃COO at C-8 and CH₃COO at C-9), 170.0 (CH₃COO at C-7), 161.3 (C-1), 157.4 (q, J_C:F = 38 Hz; COCF₃), 145.3 (C-2), 120.0-110.0 (1C, CF₃), 107.7 (C-3), 75.9 (C-5), 171.3 (C-1), 71.3 (C-7), 67.4 (C-4 and C-7), 61.8 (C-9), 52.7 (COOCH₃), 47.8 (C-5), 20.8 (CH₃COO), 20.6 (2C, CH₃COO), 20.5 (CH₃COO); IR 1750,1724 1660 cm⁻¹; MS (ESI positive) m/z 550.2 [M+Na][⁺], 1077.8 [2M+Na][⁺].

Anal. Calcd for C₂₀H₂₄F₃NO₁₂: C, 45.55; H, 4.59; N, 2.66. Found: C, 45.65; H, 4.49; N, 2.53.

**b) By N-transacylation-elimination from 4,7,8,9-tetra-O-acetyl-5-N-acetyl-β-neuraminic acid methyl ester 8**

Starting with 4,7,8,9-tetra-O-acetyl-5-N-acetyl-β-neuraminic acid methyl ester 8[^3] (107 mg, 0.2 mmol), after a 15 min reaction, with TFAA and flash chromatography (eluting with hexane/AcOEt; 6:4, v/v) glycal 5 was obtained (77 mg, 73% yield). Glycal 5 showed: m.p. 114-116°C; [α]D[^20] = + 50.3 (c = 1, CHCl₃). All physico-chemical properties were superimposable to those of the compound described above.

Anal. Calcd for C₂₀H₂₄F₃NO₁₂: C, 45.55; H, 4.59; N, 2.66. Found: C, 45.58; H, 4.45; N, 2.62.

2.2 Glycal 6: 4,7,8,9-tetra-O-Acetyl-2,3-dehydro-2-deoxy-5-N-(2,2,3,3,3-pentafluoropropyonil)-β-neuraminic acid methyl ester

![Image of Glycal 6]

**a) By N-transacylation, from the glycal 3**

Starting with the glycal 3[^2] (95 mg; 0.20 mmol), compound 6 (90 mg, 78% yield) was obtained, after a 10 min reaction with PFPA (0.16 mL, 0.8 mmol), and flash chromatography (eluting with hexane/AcOEt; 6:4, v/v). Glycal 6 showed: m.p. 120-122°C; [α]D[^20] = + 55.3 (c = 1, CHCl₃); ¹H NMR (CDCl₃) δ 7.10 (d, J_NH,2 = 9.3 Hz, 1H; N-H), 5.98 (d, J₃,4 = 2.8 Hz, 1H; H-3), 5.70 (dd, J₄,5 = 8.0, J₄,3 = 2.8 Hz, 1H; H-4), 5.43 (dd, J₇,8 = 4.5, J₇,6 = 3.0 Hz, 1H; H-7), 5.31 (m, 1H; H-8), 4.67 (2H; CH₃COO), 3.40 (s, 3H; COOCH₃), 2.18 (s, 3H; CH₃COO); IR 1760,1730 1650 cm⁻¹; MS (ESI positive) m/z 561.3 [M+Na][⁺], 1122.6 [2M+Na][⁺].

Anal. Calcd for C₂₀H₂₄F₅NO₁₂: C, 47.93; H, 4.32; N, 2.43. Found: C, 47.85; H, 4.28; N, 2.39.
(dd, $J_{9a,9b} = 12.4$, $J_{9a,8} = 2.9$ Hz, 1H; H-9a), 4.51 (dd, $J_{6,5} = 9.7$, $J_{6,7} = 3.0$ Hz, 1H; H-6), 4.37 (m, 1H; H-5), 4.19 (dd, $J_{9b,9a} = 12.4$, $J_{9b,8} = 6.4$ Hz, 1H; H-9b), 3.84 (s, 3H; COOCH$_3$), 2.13 (s, 3H; CH$_3$COO), 2.08 (s, 3H; CH$_3$COO), 2.06 (s, 3H; CH$_3$COO), 2.05 (s, 3H; CH$_3$COO); 13C NMR (CDCl$_3$) $\delta$ 170.7-170.5 (3C, CH$_3$COO at C-4, CH$_3$COO at C-8 and CH$_3$COO at C-9), 170.0 (CH$_3$COO at C-7), 161.3 (C-1), 158.1 (t, $J_{C-F} = 26$ Hz; COCF$_2$CF$_3$), 145.2 (C-2), 120.0-112.0 (2C, CF$_2$CF$_3$), 107.7 (C-3), 75.6 (C-6), 70.9 (C-8), 67.3 (C-4 and C-7), 61.8 (C-9), 52.2 (COOCH$_3$), 47.7 (C-5), 20.8 (CH$_3$COO), 20.6 (CH$_3$COO), 20.5 (2C,CH$_3$COO); IR 1747, 1728, 1661 cm$^{-1}$; MS (ESI positive) $m/z$ 600.1 [M+Na]$^+$, 1176.4 [2M+Na]$^+$. Anal. Calcd for C$_{21}$H$_{24}$F$_5$NO$_{12}$: C, 43.68; H, 4.19; N, 2.43. Found: C, 43.50; H, 4.35; N, 2.50.

b) By N-transacylation-elimination from 4,7,8,9-tetra-O-acetyl-N-acetyl-$\beta$-neuraminic acid methyl ester $^8$

Starting from 4,7,8,9-tetra-O-acetyl-5-N-acetyl-$\beta$-neuraminic acid methyl ester $^8[3]$ (0.107 g, 0.2 mmol) and PFPAA (0.16 mL, 0.8 mmol) after a reaction for 15 min at 135°C the glycal 6 was obtained (86.6 mg, 75% yield) after column chromatography (eluting with hexane/AcOEt; 6:4, v/v). Glycal 6 showed: m.p. 120-122°C; $\lbrack \alpha \rbrack_D^{20} = + 55.3$ (c = 1, CHCl$_3$) with all physico-chemical properties superimposable to those of the compound described above. Anal. Calcd for C$_{21}$H$_{24}$F$_5$NO$_{12}$: C, 43.68; H, 4.19; N, 2.43. Found: C, 43.50; H, 4.35; N, 2.50.

2.3 Glycal 7: 4,7,8,9-tetra-O-Acetyl-2,3-dehydro-2-deoxy-5-N-(2,2,3,3,4,4,4-heptafluorobutanoyl)-$\beta$-neuraminic acid methyl ester

![Diagram of glycal 7]

a) By N-transacylation, from the glycal 3

Starting with the glycal 3$^{[2]}$ (95 mg; 0.20 mmol), compound 7 was obtained (102 mg, 81% yield), after a 10 min reaction with HFBAA (0.16 mL, 0.8 mmol) and flash chromatography (eluting with hexane/AcOEt; 6:4, v/v). Glycal 7 showed: m.p. 115-116°C; $\lbrack \alpha \rbrack_D^{20} = + 49.1$ (c = 1, CHCl$_3$); 1H NMR (CDCl$_3$) $\delta$ 7.21 (d, $J_{NH,2} = 9.0$ Hz, 1H; N-H), 5.97 (d, $J_{3,4} = 2.6$ Hz, 1H; H-3), 5.70 (dd, $J_{4,5} = 9.0$, $J_{4,3} = 2.6$ Hz, 1H; H-4), 5.43 (dd, $J_{7,8} = 4.4$, $J_{7,6} = 2.8$ Hz, 1H; H-7), 5.30 (m, 1H; H-8), 4.66 (dd, $J_{9a,9b} = 12.4$, $J_{9a,8} = 2.6$ Hz, 1H; H-9a), 4.53 (dd, $J_{6,5} = 9.8$, $J_{6,7} = 2.8$ Hz, 1H; H-6), 4.35 (q app., $J_{5,4} = J_{5,6} = J_{5,NH} = 9.0$ Hz, 1H; H-5), 4.19 (dd, $J_{9b,9a} = 12.4$, $J_{9b,8} = 6.8$ Hz, 1H; H-9b), 3.81 (s, 3H; COOCH$_3$), 2.14 (s, 3H; CH$_3$COO at C-7), 2.07 (s, 3H; CH$_3$COO), 2.06 (s, 3H; CH$_3$COO), 2.00 (s, 3H; CH$_3$COO); 13C NMR (CDCl$_3$) $\delta$ 170.6 (3C, CH$_3$COO at C-4, CH$_3$COO at C-8 and CH$_3$COO at C-9), 170.1 (CH$_3$COO at C-7), 161.2 (C-1), 157.8 (t, $J_{C-F} = 27$ Hz; COCF$_2$CF$_2$CF$_3$), 145.1 (C-2), 122.0-109.0 (3C, CF$_2$CF$_2$CF$_3$), 107.3 (C-3), 75.6 (C-6), 70.9 (C-8), 67.4 (C-4 and C-7), 61.8 (C-9), 52.7 (COOCH$_3$), 47.8 (C-5), 20.8 (CH$_3$COO), 20.6 (2C, CH$_3$COO), 20.5 (CH$_3$COO); IR 1746, 1729, 1668 cm$^{-1}$; MS (ESI positive) $m/z$ 650.0 [M+Na]$^+$, 1276.2 [2M+Na]$^+$. Anal. Calcd for C$_{22}$H$_{24}$F$_7$NO$_{12}$: C, 42.11; H, 3.86; N, 2.23. Found: C, 42.20; H, 3.70; N, 2.40.

b) By N-transacylation-elimination from 4,7,8,9-tetra-O-acetyl-5-N-acetyl-$\beta$-neuraminic acid methyl ester $^8$

Starting from 4,7,8,9-tetra-O-acetyl-5-N-acetyl-$\beta$-neuraminic acid methyl ester $^8[3]$ (0.107 g, 0.2 mmol) and PFPAA (0.16 mL, 0.8 mmol) after a reaction for 15 min at 135°C the glycal 7 was obtained (86.6 mg, 75% yield) after column chromatography (eluting with hexane/AcOEt; 6:4, v/v).
Glycal 7 showed: m.p. 114-117°C; [α]D20 = + 50.3 (c = 1, CHCl3) with all physico-chemical properties superimposable to those of the compound described above. Anal. Calcd for C22H24F7NO12: C, 42.11; H, 3.86; N, 2.23. Found: C, 42.08; H, 3.90; N, 2.35.

2.4 Glycal 13: 4,7,8,9-tetra-O-Acetyl-2,3-dehydro-2-deoxy-5-N-(2,2,2-trifluoroacetyl) -β-neuraminic acid

Starting from 4,7,8,9-tetra-O-acetyl-5-N-acetyl-β-neuraminic acid 12[4] (0.107 g, 0.2 mmol) and TFAA (0.11 mL, 0.8 mmol) after a reaction for 15 min at 135°C, the glycal 13 was obtained as a white solid (73 mg, 71% yield) after flash chromatography (eluting with AcOEt/MeOH; 85:15, v/v). Glycal 13 showed: m.p. 115-116°C; [α]D20 = + 50.8 (c = 1, CH3OH); 1H NMR (CD3OD) δ 5.75 (d, J3,4 = 2.5 Hz, 1H; H-3), 5.62 (dd, J4,5 = 8.6, J4,3 = 2.5 Hz, 1H; H-4), 5.49 (m, 1H; H-8), 5.43 (dd, J7,8 = 7.0, J7,6 = 2.1 Hz, 1H; H-7), 4.55 (dd, J9a,9b = 12.5, J9a,8 = 2.7 Hz, 1H; H-9a), 4.42 (dd, J6,5 = 10.6, J6,7 = 2.1 Hz, 1H; H-6), 4.24-4.19 (overlapping, 2H, H-5 and H-9b), 2.08 (s, 3H; CH3COO), 2.04 (s, 3H; CH3COO), 2.01 (overlapping, 6H; CH3COO); 13C NMR (CD3OD) δ 172.6 (CH3COO at C-9), 172.2 (CH3COO at C-4), 171.7 (CH3COO at C-8), 169.2 (C-1), 159.2 (q, J CF = 38 Hz; COF3), 151.6 (C-2), 105.3 (C-3), 71.4 (C-8), 71.1 (C-4), 68.7 (C-7), 63.1 (C-9), 20.8 (CH3COO), 20.7 (3C, CH3COO); IR 1741, 1730, 1662cm-1; MS (ESI negative) m/z 511.8 [M-H]-. Anal. Calcd for C20H24F3NO12: C, 45.55; H, 4.59; N, 2.66. Found: C, 45.44; H, 4.60; N, 2.50.

3. Saturated N-Perfluoroacylneuraminic Acid: General Procedure

3.1 Compound 9: 2,4,7,8,9-Penta-O-Acetyl-5-N-(2,2,2-trifluoroacetyl)-β-neuraminic acid methyl ester

Compound 9, as a glass, showed: [α]D20 = - 22.3 (c = 1, CHCl3); 1H NMR (CDCl3) δ 6.60 (d, JNH,2 = 9.2 Hz, 1H; N-H), 5.43 (m, 1H; H-4), 5.37 (m, 1H; H-7), 5.12 (m, 1H; H-8), 4.51 (d, J9a,9b = 12.5, 1H; H-9a), 4.31 (br d, J6,5 = 10.5, 1H; H-6), 4.17 (dd, J9b,9a = 12.5, J9b,8 = 5.8 Hz, 1H; H-9b), 4.08 (m, 1H; H-5), 3.83 (s, 3H; COOCH3); 2.62 (br d, J3a,3b = 13.4 Hz, 1H; H-3a) 2.18 (overlapping, 6H; 2XCH2COO), 2.16-2.02 (overlapping, 4H; CH3COO and H-3b), 2.06 (overlapping, 6H; 2XCH3COO); 13C NMR (CDCl3) δ 171.1, 170.8, 170.6, 170.1, 168.2, 166.1, 157.4 (q, JCF = 38 Hz; COF3), 116.6 (1C, JCF = 287 Hz; CF3), 97.3, 71.8, 71.7, 67.7, 67.5, 62.0, 53.3, 49.9, 35.8, 20.9, 20.7, 20.6, 20.5; IR 1752, 1725, 1662cm-1; MS (ESI positive) m/z 610.0 [M+Na]+, 1197.1 [2M+Na]+. Anal. Calcd for C22H28F3NO14: C, 45.55; H, 4.59; N, 2.66. Found: C, 45.44; H, 4.60; N, 2.50.

3.2 Compound 10: 2,4,7,8,9-Penta-O-Acetyl-5-N-(2,2,3,3,3-pentafluoropropyonil)-β-neuraminic acid methyl ester

3. Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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Compound 10, as a glass, showed: \([\alpha]_D^{20} = -18.5 \text{ (c = 1, CHCl}_3\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.00 (d, \(J_{NH,2} = 9.2\) Hz, 1H; N-H), 5.42 (ddd, \(J_{4,3b} = J_{4,5} = 10.8, J_{4,3a} = 4.8\) Hz, 1H; H-4), 5.32 (m, 1H; H-7), 5.04 (br s, 1H; H-8), 4.51 (d, \(J_{9a,9b} = J_{9b,8} = 6.5\) Hz, 1H; H-9b), 4.08 (m, 1H; H-5), 3.85 (s, 3H; COOCH\(_3\)), 3.80 (s, 3H; COOCH\(_3\)), 3.36 (m, 1H; H-3a) 2.15 (overlapping, 6H; 2XCH\(_3\)COO), 2.09-2.05 (overlapping, 4H; CH\(_3\)COO and H-3b), 1.96 (s, 3H; CH\(_3\)COO), 1.98 (s, 3H; CH\(_3\)COO). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 170.8, 170.6, 170.5, 170.1, 168.2, 166.1, 158.1 (COCF\(_2\)CF\(_3\)), 116.6-110.0 (2C, COC\(_2\)CF\(_2\)CF\(_3\)), 97.1, 71.6, 71.4, 67.6, 67.3, 61.9, 53.3, 50.1, 35.9, 20.9, 20.7, 20.6, 20.5; IR 1747, 1718, 1669 cm\(^{-1}\); MS (ESI positive) \(m/z\) 610.0 [M+Na\(^+\)], 1298.3 [2M+Na\(^+\)]\(^+\).

Anal. Calcd for C\(_{23}\)H\(_{28}\)F\(_5\)NO\(_{14}\): C, 43.34; H, 4.43; N, 2.20. Found: C, 43.28; H, 4.47; N, 2.23.

3.3 Compound 11: 2,4,7,8,9-Penta-O-Acetyl-5-N-(2,2,3,3,4,4,4-heptafluorobutanoyl)-β-neuraminic acid methyl ester

Compound 11 showed: \([\alpha]_D^{20} = -22.5 \text{ (c = 1, CHCl}_3\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.83 (d, \(J_{NH,2} = 9.1\) Hz, 1H; N-H), 5.48 (ddd, \(J_{4,3b} = J_{4,5} = 11.0, J_{4,3a} = 5.0\) Hz, 1H; H-4), 5.28 (dd, \(J_{7,8} = 5.7, J_{7,6} = 1.7\) Hz 1H; H-7), 5.09 (ddd, \(J_{8,9b} = J_{8,7} = 5.7, J_{8,9a} = 2.4\) Hz 1H; H-8), 4.47 (dd, \(J_{9a,9b} = 12.5, J_{9b,8} = 5.7\) Hz Hz, 1H; H-9a), 4.36 (dd, \(J_{6,5} = 10.5, J_{6,7} = 1.7\) Hz, 1H; H-6), 4.14 (dd, \(J_{9b,9a} = 12.5, J_{9b,8} = 5.7\) Hz, 1H; H-9b), 4.06 (s, 3H; CH\(_3\)COO) 1.96 (s, 3H; COOCH\(_3\)), 1.98 (s, 3H; CH\(_3\)COO), 1.98 (s, 3H; CH\(_3\)COO). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 170.5, 170.4, 170.3, 170.1, 168.2, 166.1, 157.9 (1C, COC\(_2\)CF\(_2\)CF\(_3\)), 120.0-108.0 (3C, COC\(_2\)CF\(_2\)CF\(_3\)), 97.1, 71.3, 70.9, 67.6, 67.1, 61.8, 53.3, 50.6, 35.9, 20.7, 20.6 (3C) 20.5; IR 1752, 1715, 1669 cm\(^{-1}\); MS (ESI positive) \(m/z\) 710.6 [M+Na\(^+\)], 1429.3 [2M+Na\(^+\)]\(^+\).

Anal. Calcd for C\(_{24}\)H\(_{28}\)F\(_7\)NO\(_{14}\): C, 43.34; H, 4.43; N, 2.20. Found: C, 43.28; H, 4.47; N, 2.23.

4. 1,7-Lactonization and N-transacylation of sialic acids by action of HFBAA

4. Treatment of Neu5Ac (1) with HFBAA

The reaction was performed treating Neu5Ac 1 (30 mg, 0.1mmol), dissolved in CD\(_3\)CN (0.300 mL), with HFBAA (0.034 mL, 1.4 mmol) at 135°C for 15 min, and the reaction mixture was subjected to NMR analyses. The \(^1\)H-NMR spectrum showed the absence of any olefinic signal between 5.6-6.5 ppm, attributable to the proton at C-3 of sialic glycals. On the contrary it showed diagnostic\(^5\) signals for the presence of a 1,7-lactone (detailed in the following). \(^13\)C analyses of the reaction mixture,
performed after evaporation of CD$_3$CN and dilution of the reaction mixture with CDCl$_3$, confirmed the presence of the lactone ring and of the perfluorinated amide group in place of the starting acetyl group.

**Compound 14** showed:

$^1$H NMR (CD$_3$CN) $\delta$ 8.23 (d, $J_{NH,5} = 7.6$ Hz, 1H; N-H), 5.80 (dt, $J_{8,7} = J_{8,9b} = 5.7$, $J_{8,9a} = 2.6$ Hz, 1H; H-8), 5.61 (br s, 1H; H-4), 5.04 (d, $J_{8,7} = 5.7$ Hz, 1H; H-7), 4.96 (dd, $J_{9a,9b} = 13.0$, $J_{9a,8} = 2.6$ Hz, 1H; H-9a), 4.75 (dd, $J_{9b,9a} = 13.0$, $J_{9b,8} = 5.7$ Hz, 1H; H-9b), 4.66 (br s, 1H; H-6), 4.54 (br d, $J_{5,NH} = 7.6$ Hz, 1H; H-5), 2.77 (dd, $J_{3a,3b} = 15.4$, $J_{3a,4} = 4.1$ Hz, 1H; H-3a), 2.51 (br d, $J_{3b,3a} = 15.4$ Hz, 1H; H-3b);

$^1$H NMR (CDCl$_3$) $\delta$ 7.34 (d, $J_{NH,5} = 7.8$ Hz, 1H; N-H), 5.69 (br d, $J_{8,7} = 9.0$ Hz, 1H; H-8), 5.53 (br s, 1H; H-4), 5.04 (br d, $J_{9a,9b} = 13.0$, 1H; H-9a), 4.85 (d, $J_{8,7} = 9.0$ Hz, 1H; H-7), 4.77 (dd, $J_{9b,9a} = 13.0$, $J_{9b,8} = 2.8$ Hz, 1H; H-9b), 4.50 (br d, $J_{5,NH} = 7.8$ Hz, 1H; H-5), 4.32 (br s, 1H; H-6), 2.62-2.59 (m, 2H, H-3a and 3b); $^{13}$C NMR (CDCl$_3$) 160.1 (C-1), 158-100 (overlapping COCF$_2$CF$_2$CF$_3$), 93.63 (C-2), 74.9 (C-7), 72.8 (C-8), 71.6 (C-6), 69.9 (C-4), 63.3 (C-9), 48.6 (C-5), 32.7 (C-3).

All attempt to isolate the formed lactone were unsuccessful.

**4. 2 Treatment of Neu5,9Ac$_2$ (15) and of Neu5,8,9Ac$_3$ (16) with HFBAA.**

The reaction was performed treating Neu5,9Ac$_2$ 15 (35 mg, 0.1mmol), dissolved in CD$_3$CN (0.300 mL), with HFBAA (0.034 mL, 1.4 mmol) at 135°C for 15 min, and the reaction mixture was subjected to NMR analyses. The $^1$H-NMR spectrum showed the absence of any olefinic signal between 5.6-6.5 ppm, attributable to the proton at C-3 of sialic glycals. On the contrary it showed diagnostic$^5$ signals for the presence of a 1,7-lactone (detailed in the following).

**Compound 17** showed: $^1$H NMR (CDCl$_3$) $\delta$ 7.11 (d, $J_{NH,5} = 8.4$ Hz, 1H; N-H), 5.58 (br m, 1H; H-8), 5.51 (br s, 1H; H-8), 4.86-4.80 (overlapping, 2H; H-7 and H-9a), 4.45-4.35 (overlapping, 2H; H-5 and H-6), 4.30 (dd, $J_{9b,9a} = 12.8$, $J_{9b,8} = 3.5$ Hz, 1H; H-9b), 2.62-2.59 (m, 2H, H-3a and 3b), 2.12 (s, 3H, COCH$_3$ at C-9).

The reaction was performed treating Neu5,8,9Ac$_3$ 16 (40 mg, 0.1mmol), dissolved in CD$_3$CN (0.300 mL), with HFBAA (0.034 mL, 1.4 mmol) at 135°C for 15 min, and the reaction mixture was subjected to NMR analyses. The $^1$H-NMR spectrum showed the absence of any olefinic signal between 5.6-6.5 ppm, attributable to the proton at C-3 of sialic glycals. On the contrary it showed diagnostic$^5$ signals for the presence of a 1,7-lactone (detailed in the following).
Compound 18 showed: $^1$H NMR (CDCl$_3$) $\delta$ 7.15 (d, $J_{\text{NH,5}}$ = 7.7 Hz, 1H; N-H), 5.52 (br d, 1H; H-4), 5.44 (m, 1H; H-8), 4.76-4.71 (overlapping, $J_{8,7}$ = 8.3 Hz, 2H; H-7 and H-9a), 4.47 (br s, 1H; H-6), 4.39 (br d, $J_{5,\text{NH}}$ = 7.7 Hz, 1H; H-5), 4.32 (dd, $J_{9b,9a}$ = 12.8, $J_{9b,8}$ = 3.5 Hz, 1H; H-9b), 2.62 (brd, $J_{3a,3b}$ = 15.4, 1H; H-3a), 2.51 (dd, $J_{3a,3b}$ = 15.4, $J_{3b,4}$ = 4.2 Hz, 1H; H-3a), 2.14 (s, 3H, COCH$_3$), 2.11(s, 3H, COCH$_3$).

All attempt to isolate the formed lactone were unsuccessful.
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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Frequency (MHz):
(f1) 500.133
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 2.8574
Spectral Width (ppm):
(f1) 11.465
Pulse Program:
ZG
Temperature:
298
Number of Scans:
16

Glycal 5
Spectrum Title: 
None 
Frequency (MHz): 
(\( f_1 \)) 500.134 
Original Points Count: 
(\( f_1 \)) 16384 
Actual Points Count: 
(\( f_1 \)) 32768 
Acquisition Time (sec): 
(\( f_1 \)) 2.3396 
Spectral Width (ppm): 
(\( f_1 \)) 14.002 
Pulse Program: 
ZO 
Temperature: 
296.6 
Number of Scans: 
16
Spectrum Title: Non
Frequency (MHz):
(f1) 500.133
Original Points Count:
(f1) 16384
Actual Points Count:
(f1) 32768
Acquisition Time (sec):
(f1) 2.8574
Spectral Width (ppm):
(f1) 11.465
Pulse Program:
ZG
Temperature:
298
Number of Scans:
16

Glycal 7
Compound 9

Spectrum Title:
None

Frequency (MHz):
(f1) 500.133

Original Points Count:
(f1) 16384

Actual Points Count:
(f1) 32768

Acquisition Time (sec):
(f1) 2.8574

Spectral Width (ppm):
(f1) 11.465

Pulse Program:
ZS

Temperature:
299.6

Number of Scans:
16
Glycal 13

- 17 -
Treatment of Neu5Ac 1 with HFBAA

crude product of reaction

Frequency (MHz):
(f1) 500.133

Original Points Count:
(f1) 16384

Actual Points Count:
(f1) 32768

Acquisition Time (sec):
(f1) 2.8574

Spectral Width (ppm):
(f1) 11.465

Pulse Program:
2G

Temperature:
300.3

Number of Scans:
16
Treatment of Neu5Ac 1 with HFBAA

Crude product of reaction
Treatment of Neu5Ac 1 with HFBAA

Crude product of reaction

CDCl₃
Treatment of Neu5Ac 1 with HFBAA

Crude product of reaction
Treatment of Neu5Ac 1 with HFBAA

Spectrum Title:
HSQC GRA

Frequency (MHz):
(f2) 500.132  (f1) 125.770

Original Points Count:
(f2) 512  (f1) 512

Actual Points Count:
(f2) 512  (f1) 512

Acquisition Time (sec):
(f2) 0.1389  (f1) 0.0207

Spectral Width (ppm):
(f2) 7.373  (f1) 196.808

Pulse Program:
HSQCETG

Temperature:
299.2

Number of Scans:
4

crude product of reaction
5. References relative to the experimental part

Treatment of Neu5Ac 1 with HFBAA

Crude product of reaction