Stereoselective Synthesis of α-C-Sialyl Compounds

Jin-Hwan Kim, Fei Huang, Sayaka Masuko, Deepak Sait,† and Robert J. Linhardt*  

CONTENTS  
Introduction .................................................................................................................. 239  
Experimental Methods ............................................................................................... 240  
General Methods ......................................................................................................... 240  
Sml₂-Mediated C-Sialylation: 4,4-Dimethyl-1-{Methyl (5-Acetamido-4,7,8,9-Tetra-O-Acetyl-3,5-Dideoxy-d-Glycero-α-D-Galacto-Non-2-  
Uropyranosyl)onate}cyclohexanol (3) ..................................................................... 240  
References ...................................................................................................................... 242  

INTRODUCTION  
Sialic acids (or neuraminic acids) are often found at the outmost ends of the oligosaccharide components of cell-surface glycoproteins and glycolipids. They are involved in a number of important biological events including cell recognition and interaction, neuronal transmission, ion transport, reproduction, differentiation, epitope masking, and protection. They are also involved in pathological processes including infection, inflammation, cancer, neurological, cardiovascular, endocrine, and autoimmune diseases.  

Cell surfaces containing sialic acids interact with receptors, hormones, enzymes, toxins, and viruses and other pathogens that use them to localize on the surface of cells they infect. The linkage of sialic acid to oligosaccharide is among the most labile glycosidic linkages and is cleaved in vitro under mildly acidic conditions.  

In vivo, sialic acid–containing glycoconjugates are catabolized through the removal of the terminal sialic acid residue by the action of hydrolase-type enzymes called neuraminidases. A nonhydrolyzable glycosidic linkage to sialic acid is an attractive approach to design reagents for glycobiology and immunology. The replacement of the interglycosidic oxygen atom with a hydroxymethylene group using Sml₂ chemistry affords hydrolytically and metabolically inert α-C-sialyl analogues of natural glycoconjugates. This stable linkage is being studied to improve our understanding of biological recognition and to enhance or suppress biological events at the molecular level.
A method for the stereoselective preparation of α-C-sialyl compounds was pioneered in our laboratory. Since 1997, this method has been applied for the diastereoccontrolled synthesis of α-C-sialyl compounds, using samarium iodide under Barbier conditions, a method that had been previously used to prepare C-glycosyl compounds. This approach is tolerant of a wide variety of protecting groups. The reducing potential of SmI₂ is exploited through the in situ generation of a neunaminal samarium (III) species and its coupling to carbonyl compounds. Through a simple, high-yielding reaction, this same chemistry could be used to couple different ketones or aldehydes with peracetylated sialic acid sulfone and form α-C-sialyl compounds (Scheme 26.1).

EXPERIMENTAL METHODS

GENERAL METHODS

All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted. Column chromatography was performed on silica gel 60 (EM Science, 70-230 mesh). Reaction was monitored by TLC on Kieselgel 60F₂₅₄ (EM Science) and the compounds were detected by UV light and visualized by dipping the plates in a cerium sulfate-ammonium molybdate solution followed by heating. Solutions in organic solvents were concentrated by rotary evaporation below 40°C under reduced pressure. ¹H NMR and ¹³C NMR spectra were recorded with a Bruker, 600MHz instrument. When reporting NMR data, nuclei associated with the sugar are denoted with a prime ('). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = double of doublet, ddd = doublet of doublet of doublet, dt = double of triplet, m = multiplet and/or multiple resonances), integration, and coupling constant in Hertz (Hz). High-resolution mass spectra were run in a JMS SX/SX102A tandem mass spectrometer, equipped with FAB source. The matrix used was DHB and the internal standards ultramark 16211 and PEG. SmI₂ solution was purchased from Aldrich.

SmI₂-Mediated C-Sialylation: 4,4-Dimethyl-1-[Methyl](5-Acetamido-4,7,8,9-Tetra-O-Acetyl-3,5-Dideoxy-α-O-Galacto-Non-2-Ulopyranosyl)onate[cyclohexanol (3)]

To a solution of sulfone donor 1₂ (308 mg, 0.5 mmol) and 4,4-dimethylcyclohexanone 2 (94 mg, 0.75 mmol) in anhydrous THF (7.5 mL) was added molecular sieves 4 Å,
500 mg). After stirring for 2 h at room temperature under a positive pressure of Argon, SnI₂ solution (30.0 mL, 0.1 M in THF, 3.0 mmol) was added to the reaction mixture and stirring was continued for 1 h under argon. During initial addition of the SnI₂, the solution decolorized and the mixture turned yellow but when the addition was complete the reaction mixture turned dark green and maintained that color for ~1 h. TLC (3:2 hexane-acetone) then showed reaction to be complete. The mixture was diluted with Et₂O (50 mL), and washed successively with aqueous 1 N HCl (50 mL), aqueous 0.1 M Na₂S₂O₃ (50 mL), and saturated aqueous NaHCO₃ (50 mL). The organic phase was dried over anhydrous MgSO₄, filtered, the filtrate was concentrated, and chromatography (2:1 hexane–acetone) afforded 3 (219 mg, 73%); Rf = 0.4 (3:2 hexane–acetone), c.f. Rf = 0.3 for the starting material; [α]D = –19° (c = 0.7, CHCl₃).

1H NMR (600 MHz, CDCl₃) δ 5.41 (ddd, 1H, J = 8.0, 6.5, 2.7 Hz, H-8'), 5.35–5.24 (m, 2H, H-7, NH), 4.78–4.73 (m, 1H, H-4'), 4.35 (dd, 1H, H-9a, J = 12.4, 2.7 Hz), 4.07 (dd, 1H, J = 12.4, 6.4 Hz, H-9b), 4.03–3.98 (m, 2H, H-5', H-6'), 3.79 (s, 3H, CO₂CH₂), 2.56 (s, 1H, OH), 2.48 (dd, 1H, J = 12.8, 4.6 Hz, H-3'ç), 2.17 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.05 (s, 3H, Ac), 2.03 (s, 3H, Ac), 1.97 (t, 1H, J = 12.4 Hz, H-3'å), 1.88 (s, 3H, NAc), 1.68–1.16 (m, 8H, 4×CH₂), 0.92 (s, 3H, CH₃), 0.84 (s, 3H, CH₃); 13C NMR (151 MHz, CDCl₃) δ 171.1, 170.70, 170.68, 170.35, 170.18, 170.02, 86.0 (C-2'), 74.9 (C-1), 73.2 (C-6'), 70.4 (C-4'), 68.7 (C-8'), 67.8 (C-7'), 62.6 (C-9'), 52.3 (CO₂CH₂), 49.5 (C-5'), 34.1, 33.9 (C-3, 5), 32.9 (C-3'), 32.5 (CH₃), 29.3 (C-4'), 27.6, 27.3 (C-2, 6), 23.2 (CH₃), 23.1 (NAc), 21.2 (Ac), 20.9 (Ac), 20.74 (Ac), 20.72 (Ac); HR MALDI-TOF MS: m/z; calcd for C₉₃H₅₂NNaO₃ [M + Na]+: 624.2627; found: 624.2624. Anal. Calcd for C₉₃H₅₂NO₃: C, 55.90; H, 7.20; N, 2.33; O, 34.57. Found: C, 56.07; H, 7.23; N, 2.42.

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1 Molecular sieves (4 Å) were crushed and activated in vacuo >160°C for 5 h before use.

2 Commercial 0.1 M samarium iodide solution in THF should be clear blue with only small amount of solid samarium present, which is used as stabilizer.

3 Blue, instead of green color was observed when the reaction was carried out on much smaller scale.

4 Frequent monitoring of progress of the reaction by TLC is not recommended, to prevent the mixture from exposure to atmospheric air and moisture.
REFERENCES