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Diastereocontrolled Synthesis of Carbon Glycosides of *N*-Acetylneuraminic Acid *via* Glycosyl Samarium(III) Intermediates

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α-*O*-Glycosides of *N*-acetylneuraminic acid (Neu5Ac, **1**, Scheme 1) are often found terminating the oligosaccharide component of cell-surface glycoproteins and glycolipids. Neu5Ac is involved in a number of important biological events: intercellular interactions such as adhesion, aggregation, and agglutination; masking of antigenic oligosaccharides and suppressing undesired immune reactions (antirecognition phenomena); influencing the cell membrane permeability for ions, amino acids, and proteins; and protection of glycoproteins against proteolysis.[1] Terminal Neu5Ac is an attachment site of pathogens to the cells, and often catabolic and inflammatory processes are initiated on the removal of this carbohydrate group.[2] In general the "right" life time of a cell is a reflection of a delicate balance between the introduction and removal of terminal Neu5Ac or other sialic acids.

The glycosidic bond of Neu5Ac is cleaved *in vivo* by hydrolase type enzymes, called neuraminidases.[3] Therefore, designing nonhydrolyzable analogs of Neu5Ac-α-*O*-glycosides is an attractive approach to control, at the molecular level, events of crucial importance to glycobiology and immunology. The replacement of the interglycosidic oxygen atom by a methylene group, for example, generates a class of hydrolytically and metabolically inert isosteres, the Neu5Ac *C*-glycosides. Despite several elegant methods for direct carbon–carbon (C–C) bond formation at the anomeric center in aldoses and ketoses,[4] no major advances have been reported in the synthesis of Neu5Ac *C*-glycosides.[5] The major problem confounding their synthesis is the requirement that the C–C bond being formed results in a quaternary C-atom.

Herewith, we report our findings of a general method for diastereocontrolled preparation of α-*C*-glycosides of Neu5Ac. This approach is tolerant of a wide variety of protecting groups. The reducing potential of SmI_2 is exploited through the *in situ* generation of an *N*-acetylneuraminyl samarium(III) species and its coupling to carbonyl compounds under Barbier conditions.[6]

In model studies that led to this method, the SmI_2-promoted generation of the anomeric capto-dative free radical **3** was attempted, employing an ester tethered Neu5Ac-sulfone **2**[7]

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Supporting Information Available: Experimental procedures for the synthesis of **10** and **11**, supporting ^{1}H-NMR spectra and ^{1}H–^{1}H ROSY spectra for **10** and analytical data (7 pages). See any current masthead page for ordering information and Internet access instructions.

(Scheme 1). It was anticipated that **3** would collapse into a mixture of *C*-glycosides by cyclization through an *exo*- and/or *endo*-mode.[8] Surprisingly, instead of the anticipated cyclic *C*-glycosides (**5** and/or **6**), the 2-deoxy compound **7**[9] was isolated in excellent yield and stereoselectivity. No trace of the C-2-epimer having an equatorial carboxy function was observed. This exceptional stereoselectivity suggested an intermediate second electron transfer providing the organosamarium(III) derivative **4**, in which the bulky I_2Sm(III)-substituent adopts the more thermodynamically stable equatorial position.

A diastereocontrolled synthesis of α-linked *C*-disaccharides was designed using this C-2-samariated Neu5Ac derivative as a C_9-nucleophile to react with a *C*-formyl sugar (a C_7-electrophile) (Scheme 2). The proposed C_9-nucleophile precursor **8** was obtained in four steps from Neu5Ac as previously described.[7] A 2-pyridyl sulfone, similar to that suggested by Mazeas *et al*,[8] replaced the phenyl sulfone moiety, decreasing the LUMO-energy level of the SO_2Ar, facilitating one electron-transfer and homolytic fragmentation to the intermediate free radical of type **3**. The C_7-electrophile **9** was prepared in seven steps from methyl α-D-galactopyranoside as described by Schmidt *et al.*[10]

Treatment of a neat mixture of sulfone **8** and aldehyde **9** (1.5 equiv) in inert atmosphere with 3.1 equiv of freshly prepared 0.1 M SmI_2 solution in THF at 20 °C gave a nearly instantaneous conversion to the *C*-disaccharide **10** in excellent yield.

Addition of the aldehyde immediately after the SmI_2 solution does not lead to a condensation with **8** clearly demonstrating the Barbier conditions of the reaction. Under these conditions, only protonation (presumably from THF) of the intermediate organosamarium(III) species was observed.

The structural assignment of **10** was based on 1D and 2D ^{1}H-NMR. The formation of the α-anomer was confirmed using empirical rules for the determining of the anomeric configuration of Neu5Ac glycosides.[12] The chemical shift of H-4′ (4.90 ppm), the $J_{7',8'}$-value (7.7 Hz) and the $\Delta\delta$H-9′$_A$-H-9′$_B$/-value (0.26 ppm) clearly indicated the α-configuration of the Neu5Ac residue in **10**. The ^{1}H–^{1}H ROESY spectra (τ_m = 700 or 100 ms) showed negative NOEs between H-4′, H-6′ and the protons of the methyl ester group and between H-3′$_{ax}$, H-3′$_{eq}$ and H-3, confirming the α-configuration. The same spectra were used for indirect assignment of the stereochemistry at the newly formed hydroxymethylene bridge. The lack of any NOE between H-4 and H-3′$_{eq}$ indicated a restricted mobility around both the interglycosidic bonds and the negative cross peaks between the proton at the bridging carbon atom, and both the C-6 protons of the *galacto* moiety showed that they are spatially close.

The observed diastereoselectivity of the reaction could be rationalized based on the Felkin-Anh model[13] for predicting the stereochemical outcome of a kinetically controlled addition of a nucleophile to a chiral aldehyde (Scheme 2, **A**). The bulkiest ligand α to the carbonyl group in **9** is the C-2 atom containing an equatorial benzyloxy group and attached to the C-1 atom bearing an axial α-OMe glycosidic substituent. This ligand has a perpendicular relationship to the plane of the carbonyl group and is *anticlinal* to the Bürgi-Dunitz trajectory[14] of the incoming nucleophile. Only traces of other diastereomers (<1% based

on ^{1}H-NMR) were observed after silica gel separation of product **10** and unreacted aldehyde **9**.

The coupling of a ketone with **8** was also investigated to establish the scope of this reaction. An excellent yield of *C*-glycoside **11** was obtained (Scheme 2).

These preliminary results suggest the future incorporation of the *C*-glycosidic pseudodisaccharide fragment **10** into larger, biologically important oligosaccharides, affording carbon bridged sialyl Lewis X derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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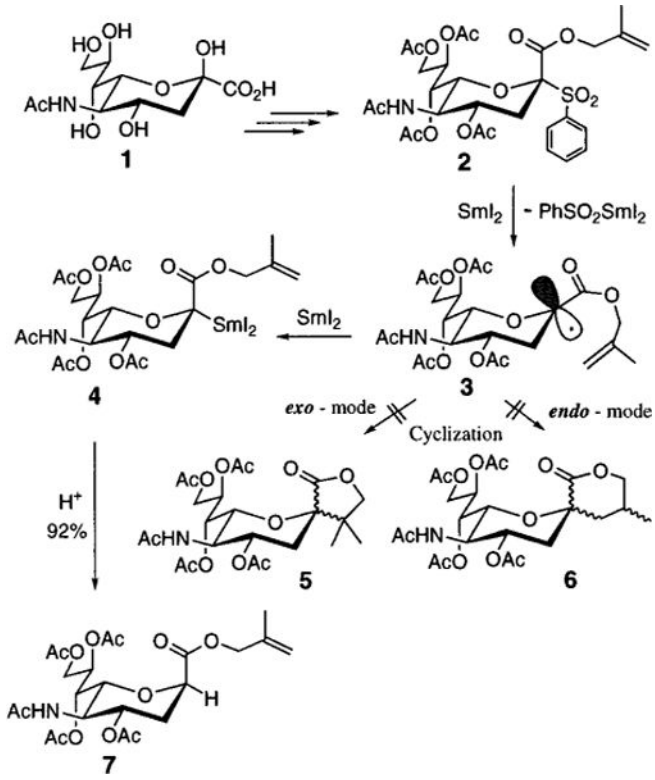
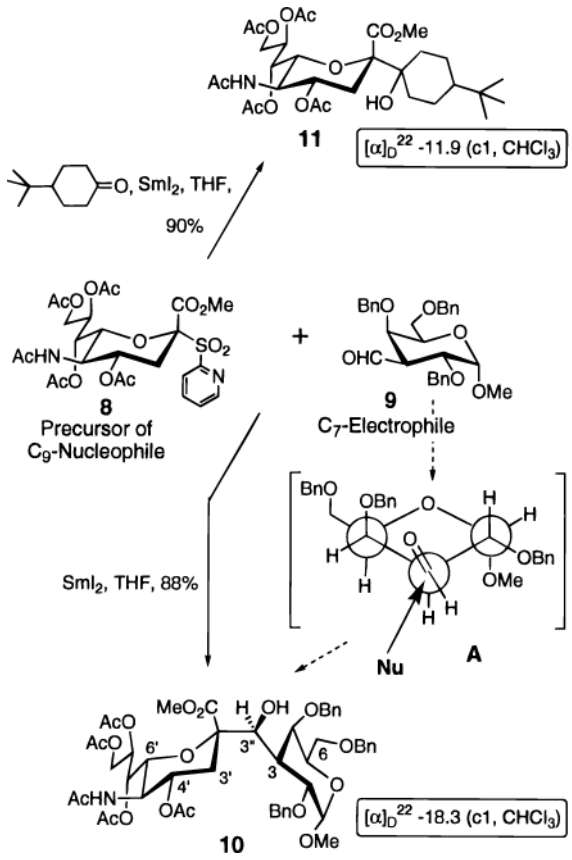


Scheme 1.



Scheme 2.