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HI/Acetic Acid Reduction of Peracetylated *N*-Acetyl Neuraminic Acid Esters to Stereoselectively Provide α-2-Deoxy-2-hydrido Derivatives[1]

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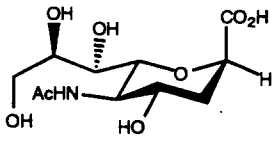
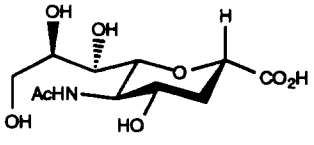
Abstract: Peracetylated ester derivatives of *N*-acetyl neuraminic acid were reacted with hydrogen iodide in acetic acid to stereoselectively provide α-2-deoxy-2-hydrido analogs. The reaction proceeds through formation of an anomeric iodide which, in the presence of excess HI, is reduced to give an enol intermediate. Kinetic protonation of the intermediate enol gives a 3.4:1 α:β mixture of 2-deoxy-2-hydrido derivatives. Under thermodynamic conditions the α-anomer is formed exclusively. © 1997 Elsevier Science Ltd.

N-Acetyl neuraminic acid (NeuAc) is an important cellular component involved in numerous biological processes. Derivatives of NeuAc have been targeted as inhibitors of important metabolic enzymes including neuraminidases, CMP-sythetases, and hemagglutinins of the influenza virus.[2] NeuAc is most often presented to these enzymes as an α-linked glycolipid conjugate with the carboxylate occupying the axial position, however these are not always necessary requirements for inhibitor activity. For example, the equatorial 2-deoxy-2-hydrido derivative **1** is an inhibitor of X-31 HA hemagglutinin,[3] and the axial derivative **2** is an inhibitor of *Vibio cholerae* sialidase.[4] Because NeuAc is a 3-deoxy sugar, stereocontrolled glycosylation can be problematic, and the presence of the anomeric carboxy functionality makes these compounds particularly susceptible to elimination. For this reason, the structurally simplified 2-deoxy analogs represent attractive targets for inhibitor design and numerous derivatives have been prepared using several different methods (Table 1).



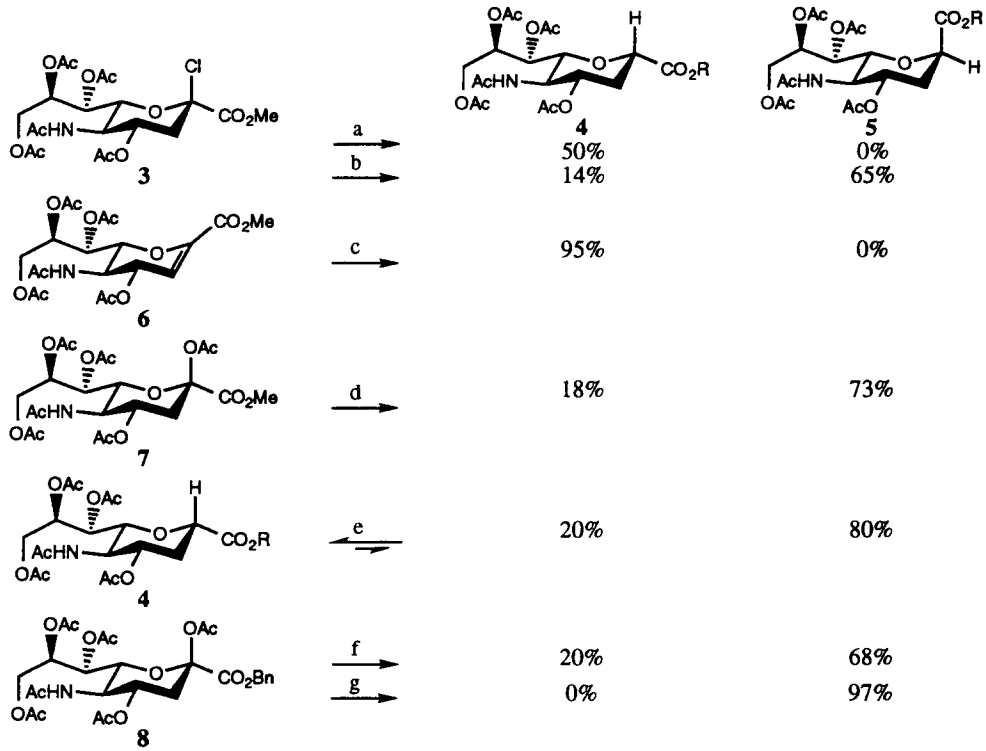
1 Inhibitor of X-31 HA hemagglutinin



2 Inhibitor of Vibrio cholerae

Radical reduction of NeuAc derived anomeric halide **3** gives exclusively the axial product **4** as does reduction of the glycal **6**.[5] The equatorial hydride derivative **5** can be preferentially obtained from catalytic hydrogenation of the anomeric chloride **3**,[4] or by base catalyzed equilibration of the axial hydride **4**.[3] The required anomeric halide and glycal precursors are typically prepared from the anomeric acetate **7** using hydrogen chloride/acetyl chloride[6] and trimethylsilyl triflate,[7] respectively. The glycal may also be prepared from the chloride by elimination using DBU.[8] More recently, Hanessian reported that direct reduction of the anomeric acetate **7** could be achieved using samarium diiodide to give a 4:1 α:β mixture of 2-deoxy-2-hydrido derivatives.[9] However, until this report, exclusive formation of **5** had not been achieved.

Table 1



Reagents: a)[4] Bu_3SnH, AIBN, toluene 80°C. b)[4] 10% Pd/C H_2, toluene/pyridine. c)[4] 10% Pd/C H_2, iprOH. d)[8] SmI_2, (2.5 eq.) ethylene glycol, THF r.t. e)[3] Lithium *N*-cyclohexylisopropylamide, aq. NH_4Cl, -50°C, THF. f) 8eq. HI in acetic acid/CH_2Cl_2, -20°C, 7h. g) 8eq. HI in acetic acid/CH_2Cl_2, r.t., 4h.

Recently we reported the stereoselective synthesis of glycosyl iodides from anomeric acetates by reaction with trimethylsilyl iodide at low temperatures.[10] Quantitative and instantaneous conversion to the iodide was achieved, providing useful intermediates for nucleophilic displacement reactions.[11] Wishing to

extend this methodology to the synthesis of NeuAc analogs, we reacted peracetylated NeuAc benzyl ester under similar conditions. Unfortunately, this protocol did not produce the anomeric iodide (**9**) but rather it led to the quantitative production of the eliminated glycal.

In 1950 Ness et al. reported that anomeric iodides could be obtained by reaction of perbenzoylated sugars using hydrogen iodide and acetic acid.[12] An excess of HI was typically employed in these reactions. We reacted the peracetylated benzyl ester of NeuAc under similar conditions and we were pleased to find that no elimination occurred. However rather than forming the anomeric iodide **9**, two new products were obtained corresponding to a 3.4:1 α:β mixture of anomeric hydrides. We reasoned that the 2-deoxy-2-hydrido derivatives could result from *in situ* reduction of the anomeric iodide as shown in figure 1, and that this reaction would be more likely to occur in the presence of excess hydrogen iodide. Indeed we found that careful reaction of the peracetylated benzyl ester of NeuAc with 1 equivalent of hydrogen iodide in acetic acid at 0°C, quantitatively produced the β-iodide (**9**) in 3 h.[13] The iodide was cleanly converted to a 3.4:1 α:β ratio of hydrido analogs upon addition of excess hydrogen iodide in acetic acid at -20°C after an additional 4h reaction time. The anomeric hydrides could be easily separated using flash column chromatography. The methyl ester derivative was also subjected to the above reaction conditions to give a similar hydride ratio, however the reaction was slower and 12% starting material remained after 12h.

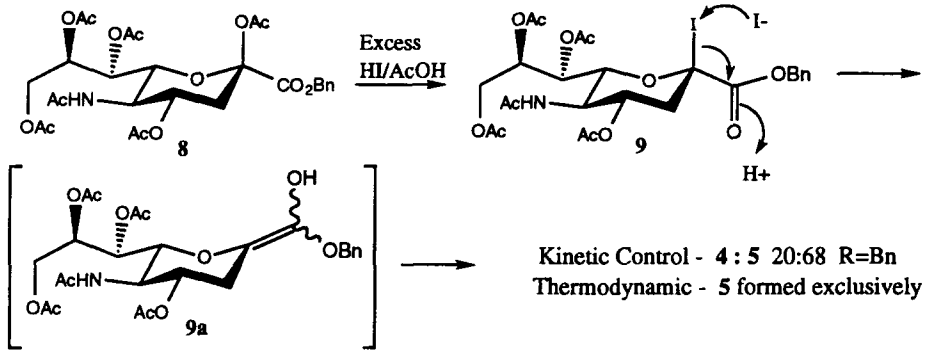


Figure 1: Proposed mechanism for the reduction of anomeric acetates in the presence of excess HI/AcOH.

Curiously, a similar distribution of anomeric hydrides (4:1 α:β) was obtained with samarium diiodide reduction[8] and with kinetic quench of a base generated enolate,[3] suggesting that the product distribution was under kinetic control. To confirm that the product ratio was due to kinetic trapping of the intermediate enol, the α and β anomers were separated and resubjected to the reaction conditions (8eq. HI/AcOH, -20°C, 12h). Neither anomer equilibrated under the reaction conditions. However, after reacting for several days, the reaction containing **4** did have a small amount of **5**, and upon warming to room temperature it anomerized completely.

We next explored the possibility of directly producing the α-hydrido derivative under thermodynamic conditions. In a typical experiment, 100 mg of **8** was added to 10 mL dichloromethane in a foil wrapped 25 mL round bottom flask. In a separate 10 mL pear shaped flask, 250 μL 47% HI/water was slowly

added to 1 mL acetic anhydride.[14] The resulting dark brown solution was added to the sugar solution at room temperature and after 4h TLC and NMR showed quantitative conversion to **5**,[15] conclusively demonstrating that the axial ester is the thermodynamic product.

In summary we have shown that treatment of the anomeric acetate of NeuAc esters with acetic acid and HI results in the quantitative conversion to the β-iodide which can be reduced in the presence of excess reagent. The intermediate enol can be kinetically trapped at -20°C to give a 3.4:1 ratio of α:β hydrido derivatives whereas under thermodynamic conditions the equatorial hydride is the only isolable product. This reaction sequence is the first report of exclusive formation of the equatorial hydrido derivative of NeuAc and firmly establishes that the axial carboxyl group is thermodynamically more stable than the equatorial carboxy ester anomer. Further theoretical and experimental studies are currently underway in our laboratory in an effort to rationalize the axial carboxyl preference.

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13. Spectral characterization of the iodide: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.92 (s, 3H, *N*-acetyl), 1.99-2.10 (s, 12H, *O*-acetyls), 2.92 (dd, 1H, *J* =14.22 & 4.5 Hz, H_{3eq}), 3.8 (dd, 1H, *J* =12.44 & 2.7 Hz, H_9), 4.04 (dd, 1H, *J* =12.5 & 5.7 Hz, H_6), 4.20 (dd, 1H, *J* =20.9 & 10.6 Hz, H_5), 4.36 (dd, 1H, *J* =12.44 & 2.7 Hz, $H_{9'}$), 5.10 (m, 1H, H_4), 5.37 (m, 1H, H_8), 5.29 (dd, 2H, *J* =28.5 & 19.7 Hz, CH_2), 5.46 (dd, 1H,*J* =6.9 & 2.3 Hz, H_7), 5.75 (d, 1H, *J* =11.1Hz, N-H). ^{13}C NMR (250 MHz, $CDCl_3$) δ 20.7-21.4 (four acetates), 22.9 (*N*-Acetate), 44.0 (C_3), 48.7 (C_5), 53.4 (CH_2), 61.7 (C_9), 67.9 (C_8), 68.3 (C_7), 69.8 (C_6), 70.9 (C_4), 78.1 (C_2), 128.2-128.7 (aromatic benzyl), 134.4 (quaternary aromatic), 166.3 (*N*-acetyl), 169.8-171.1 (four *O*-acetyls). HRFABMS calcd for $C_{26}H_{33}INO_{12}$: 678.1048; found: 678.1046.
14. Care must be taken as this reaction is extremely exothermic.
15. Compound **5** was purified using flash column chromatography (7:3 bexzene:acetone).

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