Indium-Mediated Allylations of Unprotected Carbohydrates in Aqueous Media: A Short Synthesis of Sialic Acid

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Received August 2, 1993

Background

The carbohydrates on the surface of cells play a central role in cellular recognition events. Sialic acid (Neu5Ac, I), an element of gangliosides, sialyl Lewis x, and many other glycoconjugates, is arguably the most important of these critical mediators of intercellular and cell—virion recognition. A recent review describes synthetic approaches to sialic acid and its derivatives. Recent reports have established the potential of in-and-indium-mediated allylations of aliphatic aldehydes and ketones, amidines, acid anhydrides, and aldoses, and aldoses.1 Our laboratory has focused on the development of protocols for the elaboration of unprotected aldoses to higher carbon


Discussion of Results

Heating a suspension of indium, or tin, N-acetyl-β-D-mannosamine (9), and ethyl α-(bromomethyl)acrylate13 in aqueous ethanol, at temperatures less than or equal to 100°C for up to 24 h, resulted in no detectable products derived from the addition of a carbon nucleophile to C-1 of 3. When the reaction was repeated in a mixture of ethanol and 0.1 N aqueous hydrochloric acid (6:1 v/v), the metal dissolved rapidly: the slow formation of an adduct identified as enoates 4 was observed in the reactions that included indium. We hypothesized that the major component of 4 possessed a threo relationship between the stereocenters at C-4 and C-5 based on the established threo diastereoselectivity of related transformations involving monosaccharides bearing a hydroxyl group at C-2.11-12 This paper describes the allylation of N-acetyl-β-D-mannosamine (3) (with a bromoacrylate and indium and the subsequent preparation of a protected form, 2, of sialic acid.

Application of optimized reaction conditions to 3 produced an inseparable mixture of enoates 4 (4:1 threo/erythro, based on the integration of the acetate singlets in the 1H NMR spectrum) in 90% yield (see Scheme I). Ozonolysis of enoates 4, followed by oxidative decomposition of the ozonide,14 and exhaustive acetylation provided protected β-sialoside 2 in 51% yield. Synthetic 2 was indistinguishable (1H and 13C NMR spectroscopy, mass spectrometry, and TLC in a number of solvents) from authentic material derived from sialic acid isolated from...
Figure 1.

edible bird’s nest.\footnote{15} The formation of 2 supported our hypothesis that the major product of the allylation of 3 was the \textit{threo} diastereomer of 4. This sequence has been carried out on a gram scale with no decrease in yield.

Figure 1 depicts our current hypothesis for the \textit{threo} diastereoselectivity observed in the formation of 4. Initial formation of Cram chelate 5 under the reaction conditions, followed by attack of the nucleophilic allylindium reagent at the activated carbonyl group, either inter- or intramolecularly, would selectively produce the \textit{threo} diastereomer of the product. This simple model can also account for the \textit{threo} diastereoselectivity observed previously in allylations of aldoses bearing a hydroxyl group at C-2.\footnote{11}

The fact that the diastereoselectivity of the allylation reactions appears to be insensitive to the configuration at centers \textit{\beta} to the carbonyl group, or more distant, leads us to discount, at this time, explanations that imply a role for these groups in the diastereoselectivity of these reactions.

\section*{Conclusion}

We report a short synthesis of sialic acid (Neu5Ac, 1) in a protected form, 2, in two steps and 46\% yield from N-acetyl-\textit{\beta}-d-mannosamine (3). The synthesis is the result of the extension of our previously disclosed methodology for the tin- or indium-mediated allylation of unprotected carbohydrates in hydroxylic solvents to a pyranose bearing an N-acetyl group at C-2.

The practicality of this route to sialic acid compares favorably with that of previous nonenzymatic syntheses of sialic acid\footnote{6} and its isolation from bird’s nest.\footnote{15} The enzymatic synthesis of sialic acid\footnote{16} is limited by the availability of Neu5Ac aldolase while the route we report favorsably with that of previous nonenzymatic syntheses. The practicality of this route to sialic acid compares favorably with that of previous nonenzymatic syntheses of sialic acid and its isolation from bird’s nest.

\section*{Acknowledgment}

This work was supported by NIH Grant GM 30367. NMR spectra were obtained in the Harvard University NMR Laboratory which was supported in part by NIH Grant 1 S10 RR04870 and NSF Grant CHE 88 14019. Mass spectrometry was performed by Dr. A. Tyler and Ms. N. Niedowski. The Harvard University Mass Spectrometry Facility was supported by NSF Grant CHE 90 20042 and NIH Grant 1 S10 RR06716.

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  \item \footnote{17} Sparks, M. A.; Williams, K. W.; Lulake, C.; Schrell, A.; Priebe, G.; Spaltenstein, A.; Whitesides, G. M. \textit{Tetrahedron} 1993, 49, 1.
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