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Synthesis of a Six-Carbon Sialic Acid Using an Indium-Mediated Coupling

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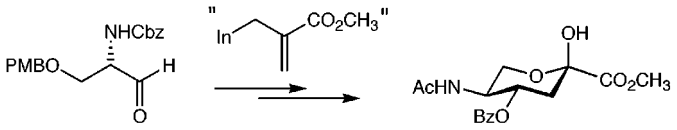
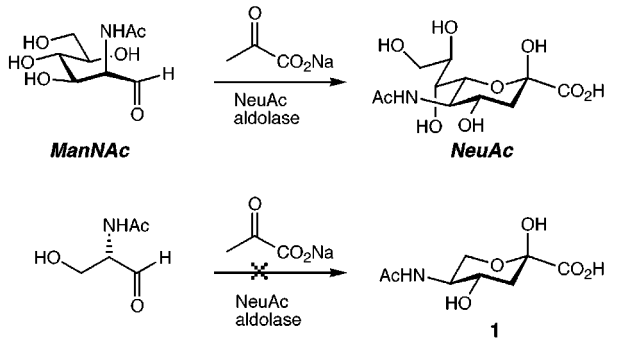
ABSTRACT



The synthesis of a six-carbon truncated sialic acid is described. A key step in the synthesis was an indium-mediated allyl addition to a serine-derived aldehyde. Careful choice of protecting groups was found to be necessary in order to prevent unwanted side reactions throughout the sequence. The truncated sialic acid was obtained in a form suitable for activation as a glycosyl donor.

Sialic acids are a class of monosaccharides that are found at the termini of oligosaccharides in many mammalian cellular systems.[1] Sialic acids are represented by the prototypical congener *N*-acetylneuraminic acid (NeuAc, Scheme 1).

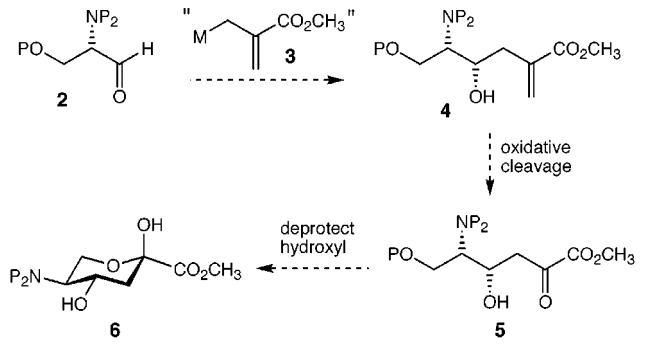
Scheme 1



During the course of research in this laboratory into the biochemical roles of oligosaccharides that contain sialic acids, there arose a need for synthetic access to natural and unnatural derivatives of this residue.[2] Specifically, there was a need for the truncated six-carbon sialic acid **1**, especially in a form that would be a suitable glycosyl donor or an immediate precursor thereof. Investigations of oligosaccharides which contain **1** could provide information concerning the role of the three-carbon glycerol side chain of sialic acids in biochemical and cellular processes, such as those that are mediated by carbohydrate−protein recognition events.

Sialic acids are generally prepared from derivatives of *N*-acetylmannosamine (ManNAc) by an aldol condensation with pyruvate which is catalyzed by NeuAc aldolase.[3] However, compound **1** could not be prepared by this

Scheme 2



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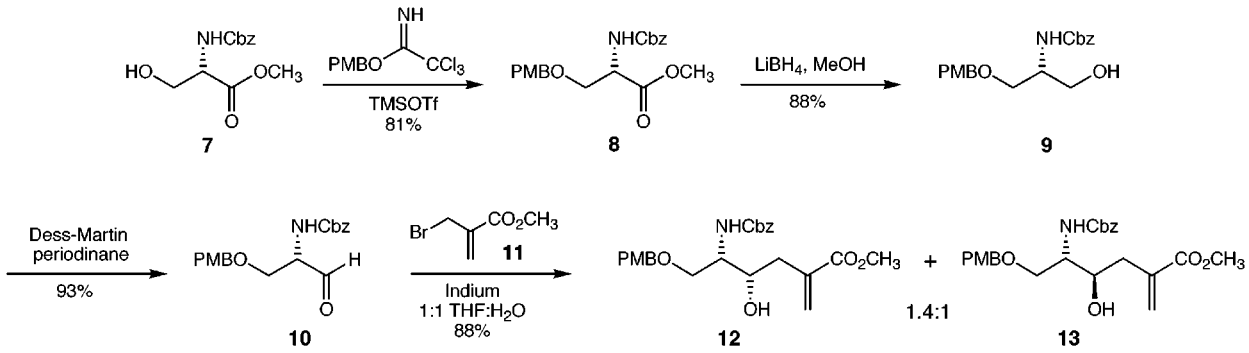
Scheme 3

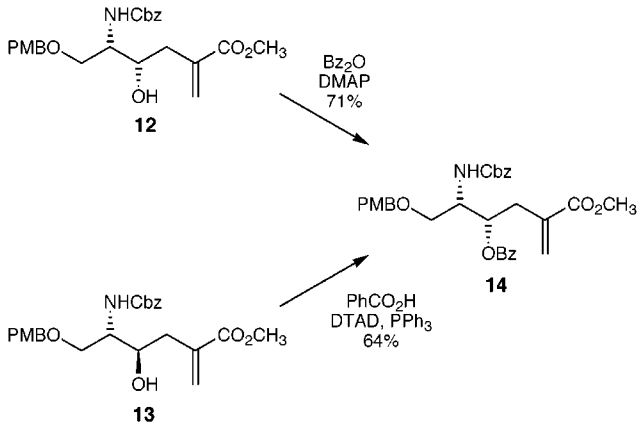


enzymatic method because aldehyde precursors under five carbons in length, such as *N*-acetylserinal needed here (Scheme 1), are generally poor substrates for Neu5Ac aldolase.[4] Consequently, a nonenzymatic approach was developed for the construction of compound **1**.[5]

In designing a synthesis plan (Scheme 2), it was recognized that the basic components required for the hypothetical enzyme-mediated aldol condensation shown in Scheme 1 might be useful for a nonenzymatic route. It was then surmised that the protected target compound, represented by **6** in Scheme 2, could be derived from building blocks such as **2** and **3**. A key step upon which the synthesis would hinge is the addition of a nucleophile, represented by **3**, to the serine-derived aldehyde **2** to provide **4**. In actuality, an indium-mediated nucleophilic addition (M = InL_n) was chosen to accomplish this transformation, primarily because this method had previously been used to synthesize full length sialic acids.[6] These indium-mediated reactions are known to be compatible with a variety of functional groups, including those which are not orthogonal to more reactive organometallic reagents.[7] An ozonolysis of compound **4** would then afford the α-keto ester **5**. Upon removal of its blocking group, the primary alcohol was anticipated to spontaneously cyclize onto the resulting ketone to afford the hemiketal **6**.

The aldehyde starting material **2** was ultimately derived from D-serine. The synthesis sequence began with protection of serine derivative **7**[8] as a *p*-methoxybenzyl ether to afford **8** in 81% yield (Scheme 3). Reduction of the methyl ester with $LiBH_4$ smoothly provided alcohol **9** (88%), which was subsequently oxidized with the Dess−Martin periodinane[9] to give aldehyde **10** (93%). Exposure of aldehyde **10** to the reagent derived from methyl (bromomethyl)acrylate **11**[10] and indium led to the production of a mixture of diastereomeric adducts **12** and **13** in excellent yield. The relative configurations of **12** and **13** were determined by conversion to **16** and the corresponding epimer at the benzoyloxy-bearing carbon, respectively, and subsequent analysis of coupling constants in the NMR spectra. There was no evidence for racemization of **10** during the course of the reaction.[11] The initial trials of this reaction, which were conducted using THF as solvent, afforded compounds **12** and **13** in essentially equal quantities. The poor diastereoselectivity was somewhat unexpected because it had been reported that with related 2-aminoaldehydes involving carbamate protecting groups, the desired *syn*

Scheme 4



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(5) A synthesis of a similar compound, which utilized D-gluconolactone as the starting material, was previously reported: Vlahov, I. R.; Vlahova, P. I.; Schmidt, R. R. *Tetrahedron Lett*. **1991**, *32*, 7025. For recent synthetic studies, see: Burke, S. D.; Sametz, S. M. *Org. Lett*. **1999**, *1*, 71 and references therein.

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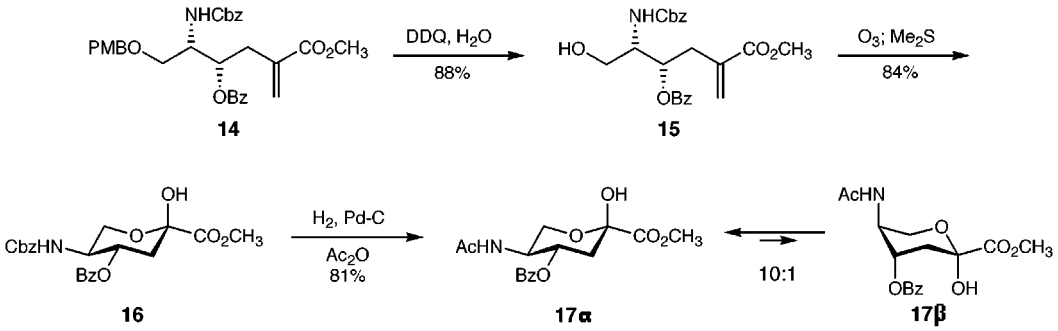
(9) Dess, D. B.; Martin, J. *J. Org. Chem*. **1983**, *48*, 4155.

(10) Anzeveno, P. B.; Campbell, J. A. *Synth. Commun*. **1986**, *16*, 387.

(11) Conversion of **12** and **13** into the corresponding *R*-(+)- and *S*-(−)-Mosher esters showed that no significant aldehyde racemization occurred before or during the indium-mediated addition. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512.

(12) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem*. **1997**, *62*, 4293.

Scheme 5



isomer was significantly more predominant.[12] It was also reported that changes in the ionic strength of the reaction solvent can provide slight increases in the *syn*:*anti* diastereomeric ratio in such systems.[7,12] Consequently, variations on the reaction were attempted using 1 M NH_4Cl as the solvent or cosolvent. Reactions conducted in 1 M aqueous NH_4Cl had significantly shortened reaction times but did not exhibit substantially different stereoselectivities. Reactions conducted in solvents composed of combinations of THF and aqueous NH_4Cl in various ratios had outcomes similar to those in THF:H_2O mixtures. Ultimately, it was found that reactions performed in 1:1 THF:H_2O provided the highest combination of diastereomeric ratios (1.4:1) and isolated yields (88%).

Fortunately, the *syn* and *anti* diastereomers **12** and **13** were easily separable by silica gel chromatography, and both compounds could both be converted to a common intermediate through a single synthesis operation (Scheme 4). Therefore, no additional attempts to optimize the diastereoselectivity beyond those discussed above were undertaken. Protection of compound **12** as its benzoate ester was accomplished by acylation with benzoic anhydride in the presence of 4-(dimethylamino)pyridine (DMAP). Compound **14** was straightforwardly obtained in 71% yield. Minor diastereomer **13** was also converted to intermediate **14** in 64% yield by implementing a Mitsunobu inversion of the alcohol stereocenter, with benzoate being employed as the nucleophile. It should be noted that di-*tert*-butyl azodicarboxylate (DTAD) was chosen over the more traditional diethyl azodicarboxylate because it provided higher yields.

Deprotection of the *p*-methoxybenzyl ether was performed by treatment of **14** with DDQ to afford alcohol **15**, with no evidence of benzoate migration (Scheme 5). Ozonolysis followed by a reductive workup provided an α-ketoester intermediate, which spontaneously cyclized to provide hemiketal **16**. Finally, the benzyl carbamate was converted to an acetamide by hydrogenolysis in the presence of acetic anhydride. The product **17** existed as an inseparable 10:1 mixture of α and *β* anomers, as determined by NMR spectroscopy and by subsequent transformations. There was no evidence of the production of any compounds derived from reductive amination pathways during the latter operation. It should be noted that synthesis pathways in which the acetamide was in place from the beginning of the sequence were not fruitful but were plagued with low yields and side reactions.

In summary, an efficient method has been developed for the synthesis of a six-carbon truncated sialic acid analogue. A key step in this synthesis was the indium-mediated coupling of an allyl nucleophile with a protected serine aldehyde, which allowed the presence of the somewhat reactive methyl ester. Despite the limited stereoselectivity of the allyl addition, a Mitsunobu inversion of the minor diastereomer made it feasible to transform both C-4 epimers into a common intermediate in the synthesis sequence. In addition, the mild deprotection chemistry and in situ acylation of the amino group should allow this sequence to be amenable to the construction of similar compounds containing a variety of C-5 amides.

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Supporting Information Available: Experimental procedures for the preparation of and spectral data for compounds **8**−**10** and **12**−**14** (by both methods) and **15**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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