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# Synthesis of 4-Azido-4-deoxy-Neu5,7,8,9Ac$_4$2en1Me. A Key Intermediate for the Synthesis of GG167 from D-Glucono-$\delta$-lactone

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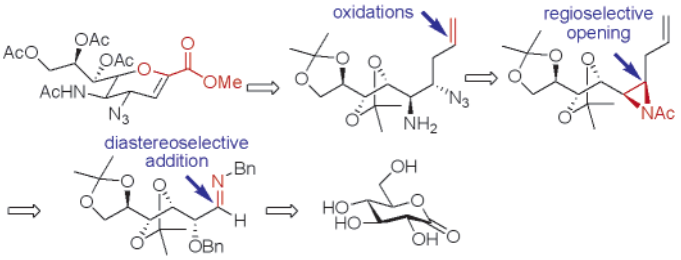
## ABSTRACT




**Stereoselective synthesis of 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-azido-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid methyl ester, an advanced key intermediate for the synthesis of neuraminidase inhibitor GG167 (Zanamivir, Relenza), was accomplished using D-glucono-$\delta$-lactone as starting material. A highly diastereoselective allylation of an imine intermediate, a regioselective azide-opening of an aziridine, and chemoselective oxidations of vicinal diols served successfully as key steps.**

Infection by influenza virus is still a major worldwide health problem today that causes substantial morbidity and mortality. Though great advances have been achieved in antiviral chemotherapies against other pathogens, such as HIV and herpes, very limited options are available for the treatment of infection by influenza virus.[1] Fortunately, notable progress has been made in recent years on development of inhibitors of influenza neuraminidase (NA),[2] which is believed to catalyze the cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids. This process is necessary for the release of newly formed virus from infected cells as well as for efficient spread of virus in the respiratory tract.[3] During the past decade, NA has become an attractive target for developing agents against influenza infection, and various small molecule-based inhibitors[4] have resulted. Among these, GG167[5,6] (zanamivir, relenza, **1**) and GS4104[7] (tamiflu, oseltamivir, **2**) represent two successful examples[8] designed as analogues of the sialic acid derivative Neu5Ac (**3**, Figure 1). Both agents have been marketed for the treatment of influenza by Glaxo-Wellcome and Roche, respectively.

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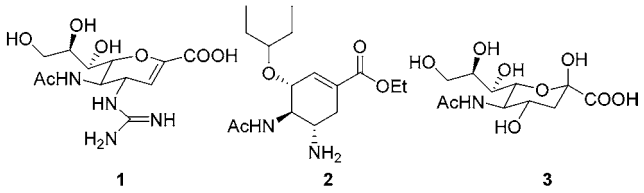


**Figure 1.** NA inhibitors GG167 (**1**), GS4104 (**2**), and Neu5Ac (**3**).

All literature approaches[9] toward GG167 (**1**) pass through common intermediates and require approximately 15 steps, starting from Neu5Ac (**3**). The major differences between these routes are the reproducibility of certain steps, reagents, and yields. Considering the cost of Neu5Ac, it would be of considerable value to establish an alternative route to GG167 that started from less costly starting materials. In recent years, we have developed a general [6 + 3] sugar-extension strategy that has been successfully applied to the syntheses of several sialic acid analogues.[10] All of these targets present common structural features such as α-ketocarboxylic acids bearing cyclic internal hemi-acetal moieties or dehydrated variants. Structurally, GG167 presents these characteristics, being a typical α-ketocarboxylic acid sugar derivative (2,6-anhydro form) with a nine-carbon skeleton (Figure 2). Presented herein is our recent synthesis of 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-azido-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid methyl ester (**19**), a key advanced intermediate en route to GG167 (**1**), using the inexpensive starting material, D-glucono-*δ*-lactone. The synthesis utilizes as key steps, addition of allylmagnesium bromide to an imine intermediate, as well as an efficient aziridine-opening by sodium azide.

The synthesis started from inexpensive commercially available D-glucono-*δ*-lactone, which was converted to the imine **4** according to ref 10b (Scheme 1). Several reagents and sets of conditions were examined with this imine before the chain extension could be achieved. Conditions examined included propargyl bromide-Zn dust, propargylmagnesium bromide, allyl bromide-Zn dust, and allylmagnesium bromide

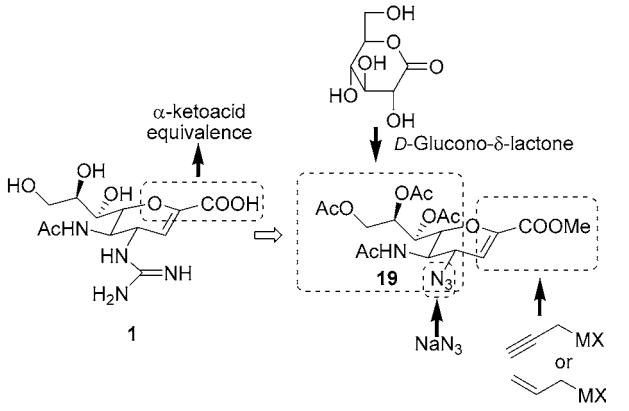
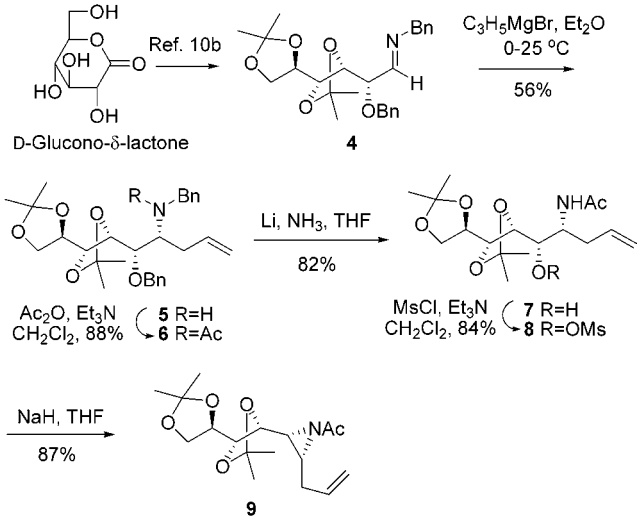


**Figure 2.** Retrosynthetic analysis of GG167 (**1**) and its key intermediate **19**.

in a range of solvents at various temperatures. Finally, it was found that the addition of allylmagnesium bromide in ether at 0−25 °C gave a single diastereomer **5** in satisfactory yield (56%).[10b] The stereochemistry of imine addition was ultimately confirmed by X-ray crystallography at a later stage (Scheme 2). N-Acetylation of amine **5** with acetic anhydride provided the acetamide **6** (88%). Deprotection of both benzyl groups in **6** was carried out using lithium−liquid ammonia (82%). The resultant alcohol **7** was then converted into the key aziridine intermediate **9** through a two-step procedure ($MsCl/Et_3N$ and NaH/THF) in 69% overall yield.

With aziridine **9** in hand, a variety of ring-opening reagents and conditions were tried in order to accomplish the transformation to the corresponding vicinal *syn*-azidoamine derivative. These conditions included $NaN_3$/DMF, $LiN_3$/DMF, $TMSN_3/ZnBr_2$, $TMSN_3/BF_3{\cdot}OEt_2$, $TMSN_3/InBr_3$,[11] and $TMSN_3$/TMSOTf. All of these gave either negative results or caused de-N-acetylation. Finally, concise and mild conditions using $NaN_3$ in refluxing EtOH−$H_2O$ in the

**Scheme 1.** Synthesis of Aziridine **9**



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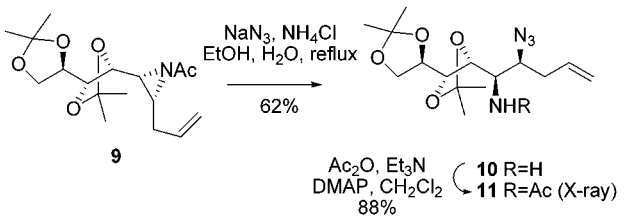
**Scheme 2.** Aziridine-Opening by Sodium Azide



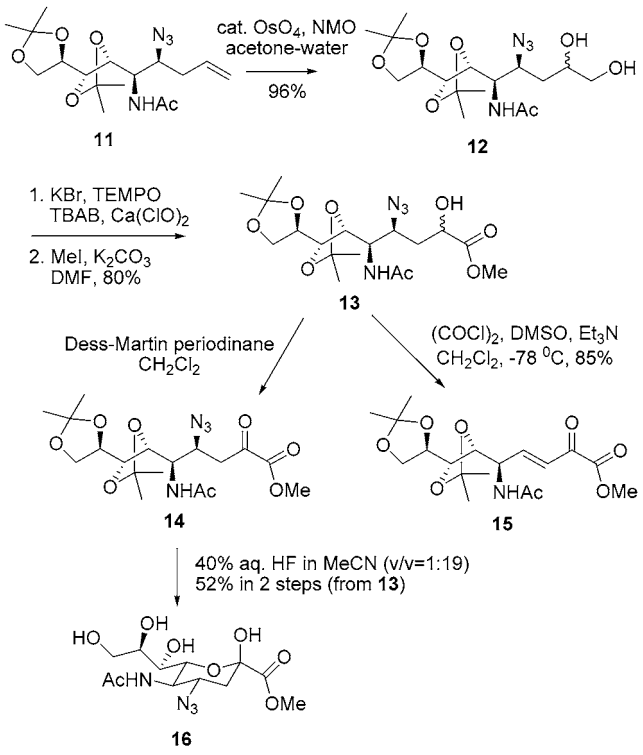

presence of $NH_4Cl$ proved to be optimal, opening aziridine **9** regioselectively at the less hindered position. This afforded the desired azide **10** in 62% yield (Scheme 2). One advantage of this reaction is its ease of scale-up. Acetylation of amine **10** gave compound **11** as a highly crystalline solid (88%). X-ray crystallographic studies on **11** (see Supporting Information) confirmed its absolute stereochemistry of **11** unambiguously. This also defined the stereochemistry of the previous addition product **5**.

Next, the terminal olefin in **11** was efficiently dihydroxylated by catalytic $OsO_4$ in the presence of NMO in acetone−$H_2O$; diol **12** was formed in 96% yield (Scheme 3). The primary hydroxyl of diol **12** was selectively oxidized under TEMPO-based conditions[12] using $Ca(ClO)_2$ as a co-oxidant. The resulting acid was immediately converted into its methyl ester **13** (80%). Dess−Martin oxidation of the remaining hydroxyl group of **13** provided the α-ketocarboxylic acid methyl ester **14**. Interestingly, elimination of one molecule of $HN_3$ occurred during silica gel purification of **14**, giving the conjugated olefin **15**. It is noteworthy that Swern oxidation of **13** also afforded **15** as the sole product in high yield. Without purification, crude **14** derived from Dess−Martin oxidation was directly treated with 40% HF in MeCN (5% in volume)[10a] to give the sugar derivative **16** (52% for two steps).

The sugar derivative **16** was fully acetylated with acetic anhydride in pyridine to yield **17** (Scheme 4).[13] By analogy to referenced methods,[14] replacement of the α-acetoxyl group of **17** with chloride (**18**, 76%) was accomplished by bubbling HCl (g) in DCM. Subsequent elimination of HCl from **18** was achieved, employing DBU in DCM to afford azide **19** (97%), which is a known advanced intermediate for the synthesis of GG167 (**1**). All the physical data on **19** coincided with literature reports.[9]

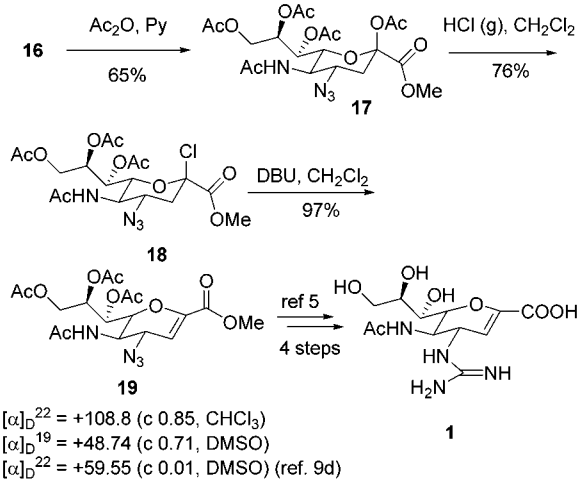
In summary, we have accomplished a new synthesis of 5-acetamido-7,8,9-tri-*O*-acetyl-2,6-anhydro-4-azido-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid methyl ester (**19**), which is an advanced intermediate in the preparation of the influenza drug GG167 (Zanamivir, Relenza, **1**). A highly diastereoselective imine addition, a regioselective and mild aziridine ring-opening using sodium azide, and a series

**Scheme 3.** Synthesis of Sugar Derivative **16**




of chemoselective oxidations were developed and/or optimized as the key steps in the synthesis. An advantage of this route is its use of an inexpensive sugar as a starting material, which may strengthen industrial interest in this route. The presented work also represents a successful application of our general [6 + 3] approach toward sialic acids and their analogues. Finally, all the intermediates produced in this route provide further opportunities to develop new NA inhibitors for related antiviral chemotherapy.

**Scheme 4.** Completion of Synthesis of 4-Azido-4-deoxy-Neu5,7,8,9Ac$_4$2en1Me (**19**)

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**Supporting Information Available:** Experimental details with full characterization of compounds, copies of $^{1}H$ NMR of compounds **7**−**11**, **14**, and **17**−**19**, a copy of $^{13}C$ NMR of compound **19**, and an ORTEP drawing of compound **11** derived from X-ray crystallographic analysis and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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