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Note

Regioselective synthesis of 4azido-Neu2en5,7Ac$_2$1Me and its intramolecular transformation to 4azido-Neu2en5,9Ac$_2$1Me

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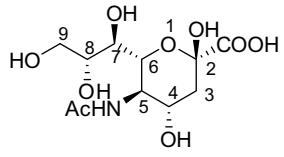
ABSTRACT

Methyl 5-*N*-acetyl-7-*O*-acetyl-4-azido-2,3-didehydro-2,4-dideoxy-neuraminic acid (4azido-Neu2en5,7Ac$_2$1Me) was synthesized regioselectively starting from 4azido-Neu2en5Ac1Me in high yield. The transformation of 4azido-Neu2en5,7Ac$_2$1Me to the corresponding thermodynamically stable 4azido-Neu2en5,9Ac$_2$1Me via intramolecular acetyl migration was confirmed by single-crystal X-ray diffraction analysis. The proposed rearrangement mechanism is discussed.

5-Acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulopyranoso nic acid (Neu5Ac, **1**) and its derivatives are significant carbohydrates that play important roles in the construction of biological molecules.[1–3] In an effort to learn more about the involvement of Neu5Ac derivatives substituted in the glycerol chain in biological processes with retention of amino or guanido groups at C-4,[4–10] an efficient preparation of this class of compounds would provide easy access to various structural congeners required for further structure–activity relationships study. 4Azido-Neu2en5Ac1Me (**2**) was a versatile intermediate for such kind of research since it can be easily transformed into amino or guanido derivatives. Herein, we report our efforts on the first efficient and regioselective synthesis of the 7-O-acetylated form of 4azido-Neu2en5Ac1Me (Schemes 1 and 2).



1
Neu5Ac

4-Azido-Neu2en5,7,8,9Ac$_4$1Me, prepared from Neu5Ac in good yield,[11] was deacetylated with NaOMe in MeOH to give compound **2**[12] in 96% yield. Without separation, compound **2** was reacted with acetone using Dowex 50W-X8 (H^+) resin as a catalyst to give protected compound **3**[13] in 80% yield. Treatment of compound **3** with either propionic, butyric, methoxyacetic, benzoic or acetic anhydride in pyridine under the catalysis of 4-dimethylaminopyridine (DMAP)[14] afforded the corresponding acylated compounds **4a–e** in 95–98% yield.

Hydrolysis of **4a–d** with water in the presence of Dowex 50W-X8 (H^+) resin yielded the corresponding 7-O-acylated compounds. Due to their unstable character, these compounds were difficult to purify via crystallization and column chromatography, as indicated by LC–MS. Fortunately, compound **4e** could be converted into pure compound **5** by hydrolysis and crystallization from EtOAc. Compound **5** was stable when stored in desiccators or in common solvents such as MeOH, CH_2Cl_2, and EtOAc at room temperature, while it was unstable in acidic media. It is interesting to note that compound **5** in MeOH began to transform into the thermodynamically stable compound **6** at 40 °C (Scheme 2). Furthermore, no 8-O-acetylated product was found during the rearrangement. It was postulated that the intramolecular transfer of the acetyl group proceeded via the cyclic intermediates of orthoesters **7** and **8** (Scheme 3).[15]

All structures of new compounds were confirmed by elemental analysis, ^{1}H NMR, and ^{13}C NMR spectroscopy. The evident

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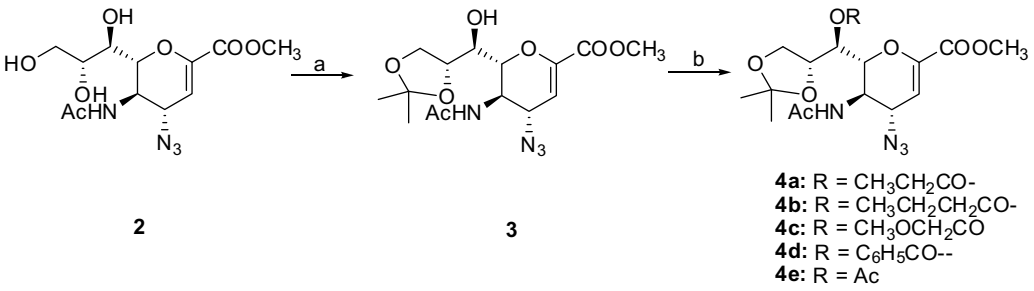
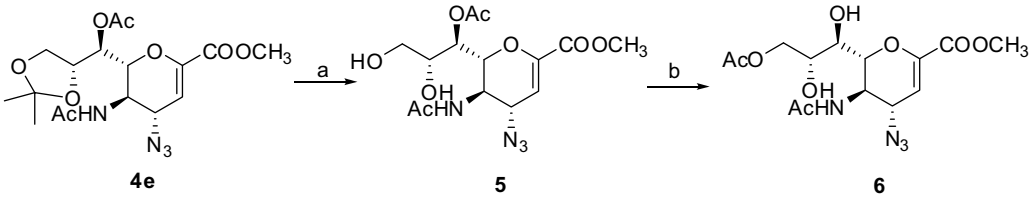
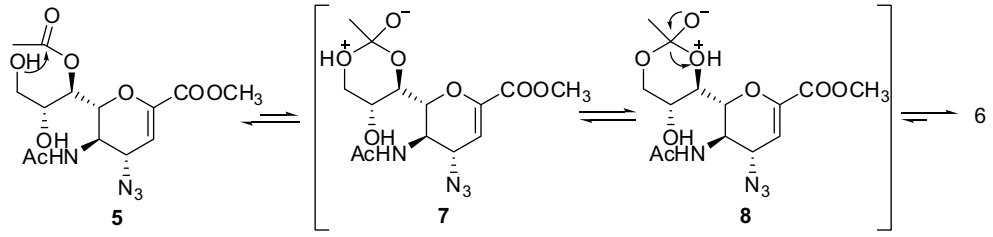


Scheme 1. Reagents and conditions: (a) Dowex 50W-X8 (H^+) resin, Me_2CO, 80%; (b) anhydrides, Py, DMAP, 10–24 h; 95–98%.



Scheme 2. Reagents and conditions: (a) Dowex 50W-X8 (H^+) resin, water, 76%; (b) MeOH, reflux, 80%.



Scheme 3. Plausible mechanism for the transformation of **5** to thermodynamically stable **6**.

Table 1
Chemical shifts (ppm) in the ^1H NMR spectra (Me_2SO-d_6) of **2**,[12] **5**, and **6**

	4-H	5-H	6-H	7-H	8-H	9-H_a	9-H_b
2	4.50	3.95	4.15	3.44	3.65	3.65	3.44
5	4.30	4.02	4.86	4.37	3.79	3.33	3.20
6	4.42	3.94	3.41	4.17	3.83	4.27	3.94

difference between compounds **2**,[12] **5**, and **6** was elucidated by the chemical shifts of C–H in the ^1H NMR spectra (Table 1). The obvious deviation of proton chemical shift was consistent with introduction and the position change of the *O*-acetyl group. An unambiguous confirmation of compound **6** was provided by X-ray crystal analysis. Figure 1 illustrates the structure, conformation, and atom numbering system of compound **6**.

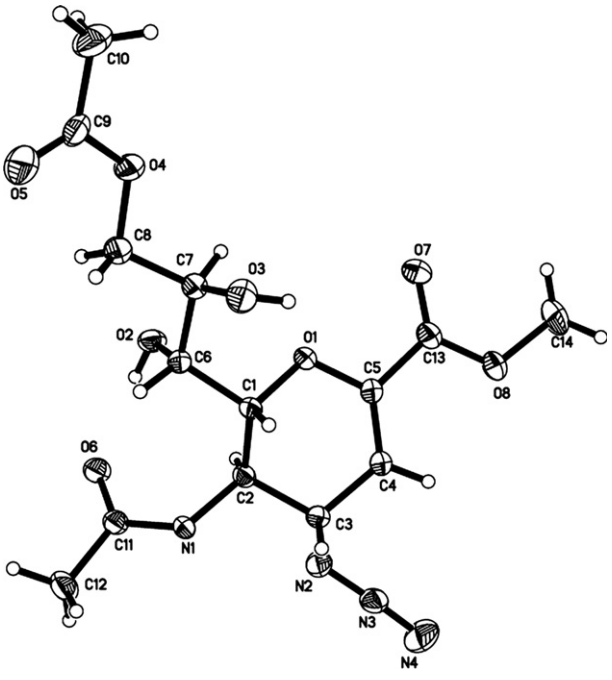


Figure 1. Crystal structure of **6** showing 50% probability displacement for ellipsoids.

1. Experimental

1.1. General methods

The reactions were performed with the use of commercial reagents and distilled solvents purified according to standard procedures. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. ^1H NMR spectra and ^{13}C NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 on a Bruker AMX-400/600 equipment at 300 MHz or 400 MHz using TMS as an internal standard at room temperature. The chemical shifts (δ) are recorded in ppm relative to $CDCl_3$ ($\delta = 7.26$) or Me_2SO-d_6 ($\delta = 2.50$) for proton and $CDCl_3$ ($\delta = 77.0$) or Me_2SO-d_6 ($\delta = 39.5$) for carbon. Melting points were determined by using the capillary method on a Buchi-510 melting point apparatus and are uncorrected. The mass spectrum was