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Formal synthesis of (–)-*N*-acetylneuraminic acid (Neu5Ac) via desymmetrization by ring-closing metathesis

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Abstract—A formal total synthesis of (–)-*N*-acetylneuraminic acid (Neu5Ac), the most naturally abundant sialic acid, has been accomplished using a rigid 6,8-dioxabicyclo[3.2.1]octane template for stereoselective introduction of all oxygen and nitrogen functionality. The template was obtained via a novel ketalization/ring-closing metathesis bond construction strategy, taking advantage of an advanced intermediate in our KDN synthesis to complete the efficient assembly of Neu5Ac. © 2001 Elsevier Science Ltd. All rights reserved.

We recently reported an efficient route to (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN, Fig. 1) exploiting the rigid 6,8-dioxabicyclo[3.2.1]octane ring system for the rapid stereoselective introduction of all oxygen functionality.[1] To further showcase the utility of our intermolecular ketalization/intramolecular C–C bond formation strategy for substrate desymmetrization,[1,2] the synthesis of 5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid [*N*-acetylneuraminic acid (Neu5Ac, **1**), Fig. 1] has been pursued. Neu5Ac was first isolated in 1951[3] and has since become the most studied member of the many known sialic acids primarily due to its vital biological role as a terminal residue in glycoproteins, glycolipids, and oligosaccharides in cellular membranes and nerve tissue.[4]

The chemical synthesis of Neu5Ac has been carried out by several groups due to the fact that enzymatic syntheses provide only very limited access to Neu5Ac analogs.[5] Each of these chemical syntheses relies on four sugar-derived stereocenters or lengthy and low yielding reaction sequences. The efficient total synthesis of Neu5Ac therefore remains an important goal.

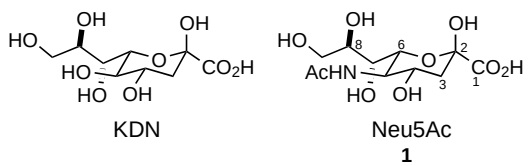

Figure 1. Sialic acids.

Neu5Ac differs from KDN only at C-5 (Fig. 1) in the presence of an acetamido group in place of the C-5 hydroxyl of KDN. In our retrosynthesis of Neu5Ac (Fig. 2), azidoalcohol **2**, with its four axial substituents and electron rich 3,4-dimethoxyphenyl carboxyl surrogate at the anomeric carbon, was seen as a suitable precursor to **1**.[1] Tetraacetate **3**,[1] a late stage KDN intermediate, was chosen as a suitable convergency point, requiring a double inversion at C-5 via an intermediate epoxide to obtain **2**. Diene **4** was previously converted to inverted tetraacetate **3** via bis-dihydroxyla-

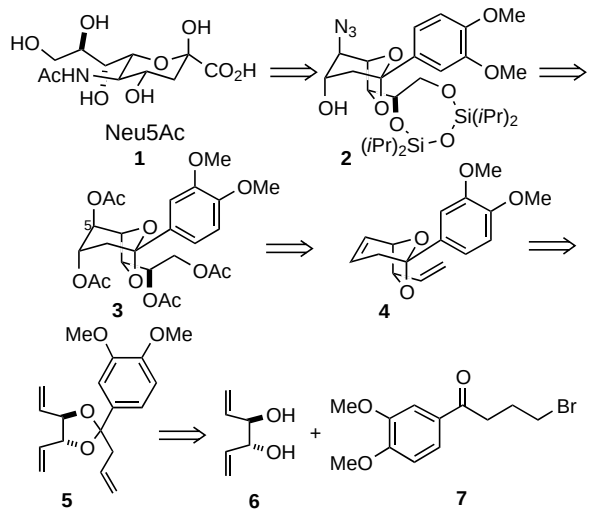

Figure 2. Retrosynthetic analysis.

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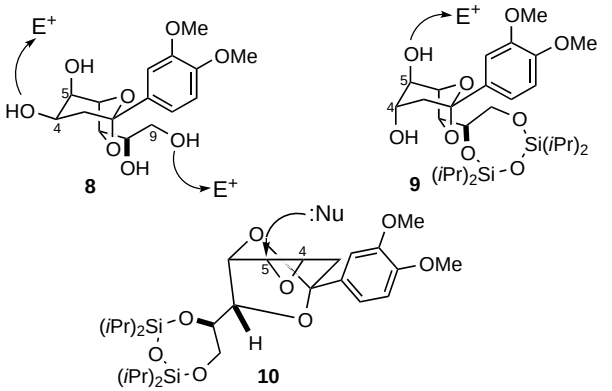
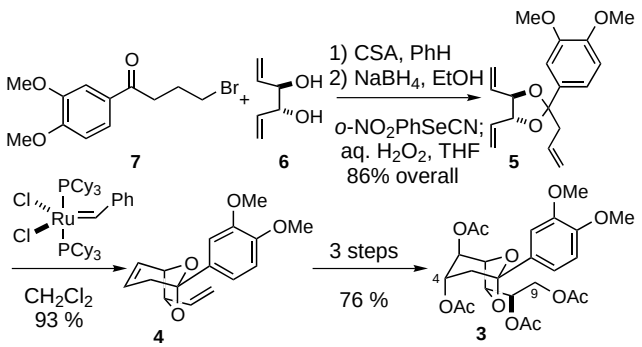


Figure 3. Chemo- and regioselectivities facilitated by rigid 6,8-dioxabicyclo[3.2.1]octane template.

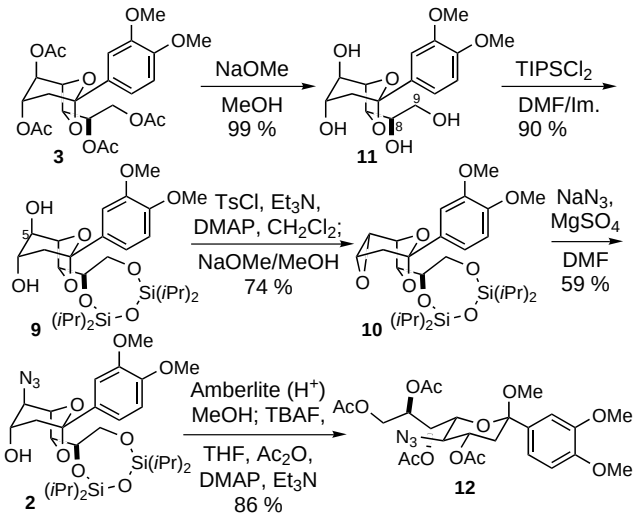
tion and selective stereochemical inversion at C-4, and **4** was obtained via a ketalization/elimination/ring-closing metathesis (RCM) sequence,[1,2] breaking the C_2 symmetry of diene diol **6**.

Fig. 3 highlights the chemo- and regioselectivities expected for hydroxyl sulfonylation (**8** and **9**) and epoxide nucleophilic ring opening (**10**) in the KDN and Neu5Ac intermediates. In the KDN synthesis, the rigid 6,8-dioxabicyclo[3.2.1]octane template in **8** allowed complete selectivity for disulfonylation at the C-4 equatorial hydroxyl and the C-9 primary alcohol using a dibutyltin oxide-catalyzed tosylation reaction.[1] For the pursuit of Neu5Ac, the C-5 *exo*-hydroxyl in **9** was expected to be more reactive towards sulfonylation than the C-4 *endo*-hydroxyl, allowing selective α-epoxide formation. Furthermore, epoxide **10** was expected to suffer nucleophilic attack selectively at C-5 in order to allow a chair-like transition state via *trans*-diaxial ring opening.[6] Each of these reactions would be dependent upon the steric and conformational constraints of the rigid 6,8-dioxabicyclo[3.2.1]octane ring system.

An improved route to **3**[1] for application to the synthesis of Neu5Ac is shown in Scheme 1. An acid catalyzed ketalization/selenoxide elimination sequence, starting with diene diol **6** and ketone **7**, afforded RCM precursor **5** in 86% overall yield (Scheme 1). It was found that the RCM reaction could be performed with only 1% Grubbs' ruthenium benzylidene catalyst[7] when the catalyst was added slowly to a CH_2Cl_2 solution of triene **5** at rt, affording 5-aryl-7-vinyl-6,8-dioxabicyclo[3.2.1]-oct-2-ene **4** in an improved yield (93%). A double Sharpless asymmetric dihydroxylation gave **8** (Fig. 3), and selective disulfonylation of the C-4 and C-9 hydroxyls, peracetylation, and C-4 inversion with cesium acetate provided inverted tetraacetate **3** in 76% overall yield.[1] At this point the KDN and Neu5Ac syntheses diverge.



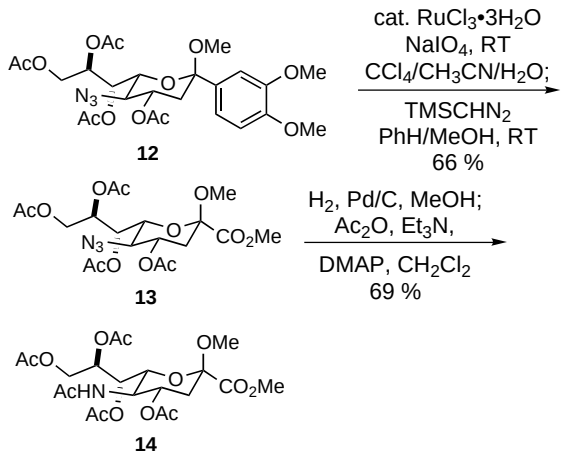
Scheme 1. Synthesis of tetraacetate **3**.



Scheme 2. Synthesis of methyl glycoside **12**.

With multigram quantities of **3** in hand, methanolysis of tetraacetate **3** proceeded readily employing NaOMe (0.25 equiv.) in MeOH (99%, Scheme 2). Selective protection of the C-8 and C-9 hydroxyls of the resulting tetraol **11** was best achieved under basic conditions using 1,3-dichlorotetraisopropyl disiloxane (1.5 equiv.) and imidazole (3 equiv.) in DMF, affording the tetraisopropyl disiloxane **9** (90%).[8] Selective sulfonylation using *p*-toluenesulfonyl chloride (2.1 equiv.) and triethyl amine (4.2 equiv.) with catalytic 4-dimethylaminopyridine gave a C-5 tosylate that could be displaced by the C-4 hydroxyl using NaOMe (4.2 equiv.) in MeOH to provide epoxide **10** (74%).[9,10] After some experimentation, it was found that epoxide azidolysis could best be accomplished using sodium azide (10.6 equiv.) and magnesium sulfate (2.1 equiv.) in DMF (0.1 M) at 90–95°C, giving azidoalcohol **2** (59%).[11] Without magnesium sulfate, only 50% conversion could be achieved after 2 days, giving a 2:1 ratio of epoxide opening regioisomers. Methanolysis of **2** proceeded readily employing Amberlite IR-120 (plus) acid resin,[12] providing methyl glycoside **12** after removal of the TIPS group and peracetylation.

To complete the synthesis of Neu5Ac, oxidative cleavage of the 3,4-dimethoxyphenyl carboxyl surrogate was achieved using RuO_4, formed in situ by adding a catalytic amount of $RuCl_3 \cdot 3H_2O$ (0.05 equiv.) to a 2:2:3 $CCl_4/CH_3CN/H_2O$ mixture containing **12** and $NaIO_4$ (12 equiv.),[1] providing azidoNeu5Ac derivative **13** (66%, Scheme 3). Reductive acetylation of the azide in **13** gave **14** (69%),[5d] which has been previously con-



Scheme 3. Completion of the formal synthesis of Neu5Ac.

verted to Neu5Ac **1** using 1N aq. sodium hydroxide followed by acidification with aq. HCl (70%).[13a,d] The ^{1}H NMR, TLC R_f, IR, MS, and optical rotation data for **14** matched those reported in the literature.[13,14] The formal total synthesis of Neu5Ac has thus been achieved in 9.3% overall yield from diene diol **6** employing our convergent ketalization/ring-closing metathesis strategy and exploiting the resulting rigid 6,8-dioxabicyclo[3.2.1]octane template. The development and application of this strategy to other natural products and ring systems is currently being explored.

Acknowledgements

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14. Data for **14**: ^{1}H NMR ($CDCl_3$) δ 5.41 (dd, J=4, 2 Hz, 1H), 5.31 (d, J=10 Hz, 1H), 5.25 (ddd, J=11.5, 10.5, 5 Hz, 1H), 5.23 (ddd, J=7.5, 2.5, 2 Hz, 1H), 4.81 (dd, J=12.5, 2.5 Hz, 1H), 4.13 (ddd, J=10.5, 10.5, 10 Hz, 1H), 4.12 (dd, J=12.5, 7.5 Hz, 1H), 3.93 (dd, J=10.5, 2.5 Hz, 1H), 3.82 (s, 3H), 3.27 (s, 3H), 2.44 (dd, J=13, 5 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H), 1.89 (dd, J=13, 11.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.0 (C), 170.7 (C), 170.6 (C), 170.2 (C), 170.1 (C), 167.3 (C), 98.9 (C), 72.0 (CH), 71.7 (CH), 68.8 (CH), 68.4 (CH), 62.4 (CH_2), 52.7 (CH_3), 51.3 (CH_3), 49.3 (CH), 37.3 (CH_2), 23.2 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3×2); IR (thin film) 1745, 1664, 1541, 1371, 1225, 1038 cm^{-1}; $[\alpha]_D^{22}$ −12° (c=0.67, $CHCl_3$); mp 131–133°C; HRMS (ESI) calcd. for $C_{21}H_{31}O_{13}NaN$ (M+ Na^+) 528.1693, found 528.1675.