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Stereoselective Synthesis of 2-Acetamido-1,2-dideoxyallonojirimycin (DAJNAc), a New Potent Hexosaminidase Inhibitor

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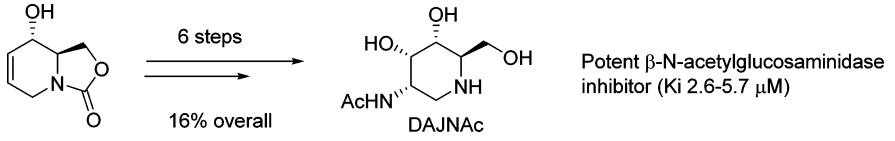
ABSTRACT



A practical synthesis of the previously unreported *N*-acetyl-D-allosamine glycomimetic DAJNAc is described. The reaction sequence involves Pd-catalyzed allylic substitution by phthalimide in an azaheterobicyclic scaffold as the key step. The new iminosugar resulted in being a stronger *β*-*N*-acetylglucosaminidase (human placenta) competitive inhibitor than the D-*gluco* (DNJNAc) and D-*galacto* (DGJNAc) stereoisomers.

Iminosugars (frequently termed azasugars) are structural analogs of monosaccharides in which the oxygen ring atom has been replaced by nitrogen.[1] Since nojirimycin (NJ, **1**; Figure 1) was first isolated from *Streptomyces* in 1966, the number of natural and synthetic iminosugars has never stopped growing. Given the instability of the hemiaminal functionality,[2] most biologically relevant representatives are 1-deoxy derivatives, such as 1-deoxynojirimycin (DNJ, **2**) or its stereoisomers (Figure 1).[3] The biological activity of these compounds may be related to their capacity to mimic the glycosyloxocarbenium cation in their protonated state, a species postulated to be close to the transition state in the reaction coordinate of enzymatic glycoside hydrolysis. Many iminosugars are competitive glycosidase inhibitors.[4] The broad range of metabolic processes in which glycosidases participate makes them

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potential candidates for the treatment of a range of diseases, including cancer, type II diabetes, lysosomal storage disorders, or viral infections such as HIV or dengue, among others.[5] Some iminosugars are currently marketed as drugs, such as miglitol (Glyset) for the treatment of type II diabetes mellitus and *N*-butyl-DNJ (Zavesca) for the treatment of Gaucher disease.[6]

Among iminosugars, the analogs of *N*-acetylhexosamines have a strong potential for the treatment of acquired and genetic diseases such as osteoarthritis,[7] allergy,[8] and Alzehimer[9] or Sandhoff, Tay-Sachs, and Schindler-Kanzaki syndromes.[10] Thus, 2-acetamido-1,2-dideoxy-D-nojirimycin (DNJNAc, **3**; Figure 1) and some of its derivatives are potent inhibitors of β-hexosaminidases[11,12] and of β-*O*-(*N*-acetyl)glucosaminidase (*O*-GlcNAcase).[13] The analogous compound with the D-*galacto* configuration, namely 2-acetamido-1,2-dideoxy-D-galactonojirimycin (DGJNAc, **4**) and its *N*-alkyl derivatives, are highly potent competitive inhibitors of α-galactosaminidases (α-GalNAcases) and β-hexosaminidases,[14,15] whereas 2-acetamido-1,2-dideoxymannonojirimycin (DMJNAc, **5**) and its derivatives are potent reversible inhibitors of UDP-*N*-acetylglucosamine 2-epimerase.[16] Given the remarkable biological activity of *N*-acetylhexosamine analogs, here we sought to complete the series with the, to date, unknown D-*allo*-configured congener, namely 2-acetamido-1,2-dideoxy-D-allonojirimycin (DAJNAc, **6**; Figure 1). In the context of our ongoing efforts to develop selective glycosidase inhibitors as drug candidates,[17] here we report the first synthesis of DAJNAc and a preliminary screening of its glycosidase inhibitory capacity.

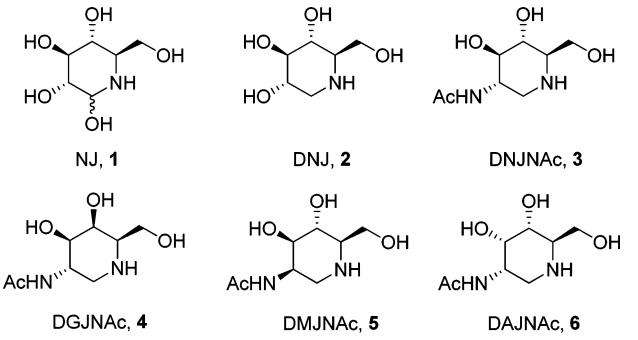

Figure 1. Structures of nojirimycin (**1**), its 1-deoxy derivative (**2**), and the diastereoisomeric 2-acetamido-1,2-dideoxyiminosugars with the D-*gluco*- (**3**), D-*galacto*- (**4**), D-*manno*- (**5**), and D-*allo*-configuration (**6**).

Most reported iminosugar syntheses rely on the chiral pool, using carbohydrates, amino acids, or tartaric acid as starting materials.[18] However, the high functional group density of these compounds and the difficulties associated with the incorporation of the acetamido group in the all-cis C2—C3—C4 segment, characteristic of D-*allo*-configured derivatives, makes the synthesis of DAJNAc **6** particularly challenging. These considerations drove us to design an asymmetric synthesis of **6** based on the key bicyclic precursor **7**, which is easily accessible in high enantiomeric purity by Sharpless epoxidation of penta-1,4-dien-3-ol.[19]

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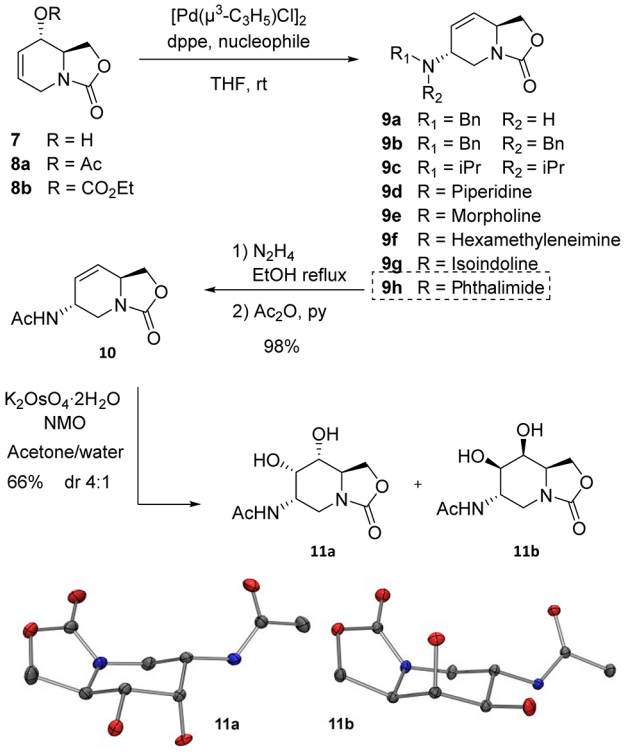
Scheme 1. Synthesis of *N*-Acetamidediolcarbamates **11a** (D-*allo*) and **11b** (D-*galacto*) from **7**[a,b]



[a] Ortep drawings of the crystal structures of **11a** and **11b** with 50% probability ellipsoids. [b] The yields of the first step can be found in Table 1.

Acetylation of **7** with acetic anhydride/Et_3N/DMAP provided **8a** in 98% yield (Scheme 1). Subsequent introduction of the amino moiety by Pd-catalyzed allylic substitution[20] was, however, problematic. Use of the azide anion or primary or secondary amines as nucleophiles and bis(allyl)palladium chloride/1,2-bis(diphenylphosphino)-ethane (dppe) as the catalyst proved unsuccessful (Table 1, entries 1–3). Of note, only cyclic secondary amines provided the desired addition products **9d**–**9g** in satisfactory yields (Table 1, entries 3–7). A single reaction product was observed in those cases, with complete control of the regio- and diastereoselectivity. Analysis of products **9d**, **9e**, and **9f** by NOESY experiments revealed that the reaction took place through a *syn* attack to the less hindered C5 position in the piperidine ring (C2 in the iminosugar nomenclature). The observed diastereoselectivity points to the complete complexation of the Pd-atom through the opposite face of the acetoxy leaving group. This hypothesis was confirmed after preparation of complex **12**, in 85% yield, by treatment of **8a** with equimolar amounts of the catalyst, followed by precipitation with ammonium hexafluorophosphate (Scheme 2). As expected, only one diastereoisomer was observed by NMR and the relative stereochemistry of **12** was established by NOESY experiments.

Scheme 2. Synthesis of Configurationally Stable Pd Allyl Complex **12**

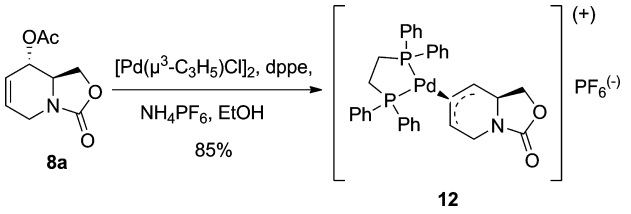


Table 1. Isolated Yields of the Products Arising from Pd-Catalyzed Addition of Nitrogen Nucleophiles to the Allylic-Type Esters **8a** and **8b**[a]

entry	substrate	nucleophile	product	yield/%
1	**8a**	butylamine	**9a**	0
2	**8a**	dibenzylamine	**9b**	0
3	**8a**	diisopropylamine	**9c**	0
4	**8a**	piperidine	**9d**	88
5	**8a**	morpholine	**9e**	91
6	**8a**	hexamethyleneimine	**9f**	88
7	**8a**	isoindoline	**9g**	74
8	**8a**	phthalimide	**9h**	25
9[b]	**8a**	cesium phthalimide	**9h**	48
10[b]	**8b**	cesium phthalimide	**9h**	75

[a] Unless otherwise stated, the reaction conditions were those indicated in Scheme 1. [b] The reactions were performed in DME at 85 °C.

Although the above procedure was satisfactory in view of the synthesis of iminosugar hexosamine analogs, none of the amines **9b**–**9g** were suitable to introduce the acetamide fragment of the target *N*-acetylallosamine mimic **6**. The use of phthalimide as the nucleophile[21] afforded the *N*-phthalimido derivative **9h** in 25% yield, a potential precursor of DAJNAc (Scheme 1; Table 1, entry 8). The conditions developed by Trost et al.[22] involving generation of the corresponding cesium salt in DME allowed the synthesis of **9h** in 48% yield. Replacing acetate **8a** by carbonate **8b**, prepared from **7** in 90% yield by treatment with ethyl chloroformate/pyridine, further increased the yield of the addition product **9h**, obtained as a single diastereoisomer (entry 10) in 75% yield. The phthalimido group was deprotected by treatment with hydrazine in EtOH at reflux, affording the corresponding primary amine, which was acetylated *in situ* to give acetamide **10** in 98% overall yield. Dihydroxylation of **10** using NMO and catalytic amounts of $K_2OsO_4 \cdot 2H_2O$ in acetone/water afforded a 4:1 mixture of the diastereomeric *N*-acetamide-diolcarbamates **11a** (D-*allo*) and **11b** (D-*galacto*) in 66% yield. The use of "Sharpless asymmetric dihydroxylation" conditions did not improve the yield or the diastereomeric ratio. Both isomers were crystalline solids easily separable by chromatography, and the configuration assignments

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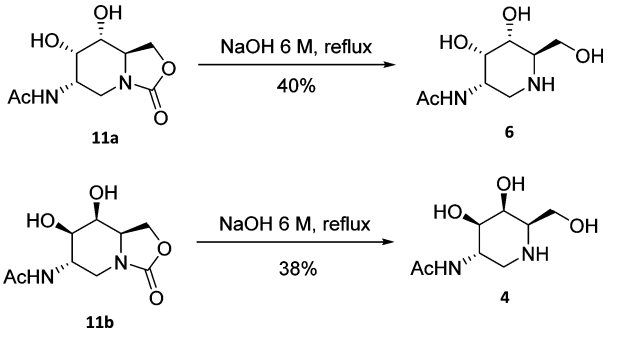
were confirmed by X-ray diffraction. Final hydrolysis of the 2-oxazolidinone ring of **11a** and **11b** by treatment with 6 M NaOH at reflux gave the title iminosugar DAJNAc **6** (40% yield) and the known *N*-acetylgalactosamine mimic DGJNAc **4**[14,15] in 38% yield, respectively (Scheme 3).

Scheme 3. Synthesis of DAJNAc **6** and DGJNAc **4** from **11a** and **11b**



With DAJNAc in hand, a preliminary screening of its inhibitory properties against a panel of commercial glycosidases, including three *β*-*N*-acetylglucosaminidases of mammalian (human placenta and bovine kidney) and plant (jack beans) origin, was conducted. With the exception of modest activity against *β*-mannosidase (K_i 150 μM), DAJNAc was found to be a selective inhibitor of the *β*-*N*-acetylglucosaminidases. The corresponding inhibition constants (K_i) are shown in Table 2 and compared with data for the D-*gluco* and D-*galacto* epimers DNJNAc (**3**) and DGJNAc (**4**), respectively. The K_i values (5.6−2.6 μM) were comparable to those obtained for DNJNAc and DGJNAc. In fact, the inhibitory capacity of compound **6** against the enzyme from human placenta was 1.3−1.5-fold stronger than that of the "matching" iminosugar **3** or its C4-epimer **4**. Figure 2 depicts the structures of the strongest inhibitors reported to date for the three enzymes evaluated in this work, namely **13**,[23] **14**,[24] and **15**,[25] and the corresponding K_i or IC_{50} values.

The results demonstrate that *β*-*N*-acetylglucosaminidases accept conformational modifications at the C3 and C4 centers in the glycone moiety of substrate analogs without affecting the binding affinity. The efficiency of the synthetic strategy described here and its suitability for molecular diversity-oriented strategies warrants further research.

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Table 2. Inhibition Contants (K_i, μM) against Commercial *β*-*N*-Acetylglucosaminidases for DAJNAc (**6**) Determined from the Slope of Lineweaver−Burk Plots and Double Reciprocal Analysis[a]

β-*N*-acetylglucosaminidase[b]	**3**[15]	**4**[15]	**6**
human placenta	7.0 ± 0.2	8.3 ± 0.3	5.6 ± 0.1
bovine kidney	7.4 ± 0.3	4.2 ± 0.1	2.6 ± 0.1
jack beans	2.9 ± 0.1	1.8 ± 0.1	2.6 ± 0.1

[a] Data for the corresponding analogs with D-*gluco*- (DNJNAc, **3**) and D-*galacto*-configuration (DGJNAc, **4**) are included for comparative purposes. No inhibition was observed for any of the compounds at a concentration of 2 mM on almonds and bovine liver *β*-glucosidases, yeast α-glucosidase, jack bean α-mannosidase (except for **6**; K_i 150 mM), *Helix pomatia* *β*-mannosidase, *Aspergillus niger* amyloglucosidase, *Penicillium decumbens* naringinase, green coffee α-galactosidase, *E. coli* *β*-galactosidase, or yeast isomaltase. [b] Inhibition was competitive for compound **6** against *β*-*N*-acetylglucosaminidase from human placenta and noncompetitive for the enzymes from bovine liver and jack beans (see the Supporting Information).

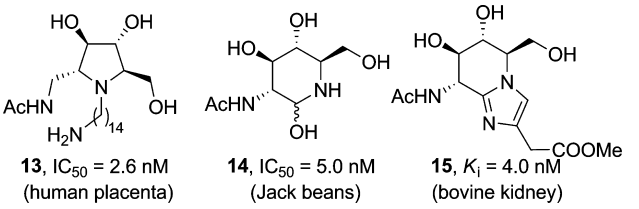

Figure 2. Structures of pyrrolidine **13**, 2-acetamido-2-deoxynojirimycin **14**, and nagstatin derivative **15**, the strongest inhibitors reported to date for the *β*-*N*-acetylglucosaminidase from human placenta, Jack beans, and bovine kidney, respectively.

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Supporting Information Available. General experimental methods, experimental procedures, compound characterization data, NMR spectra for all new compounds, X-ray data for compounds **11a** and **11b**, and Lineweaver−Burk representations for K_i determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.