

Highly Stereocontrolled Synthesis of *gem*-Difluoromethylenated Azasugars: D- and L-1,4,6-Trideoxy-4,4-difluoronojirimycin

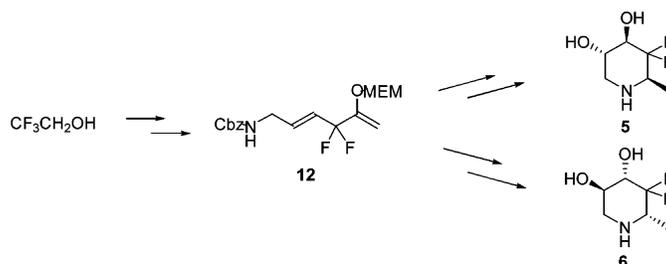
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ABSTRACT



D-1,4,6-Trideoxy-4,4-difluoronojirimycin and L-1,4,6-trideoxy-4,4-difluoronojirimycin, a novel series of *gem*-4,4-difluoromethylenated azasugars, were synthesized from $\text{CF}_3\text{CH}_2\text{OH}$ in 10 steps. A key step was the highly diastereoselective construction of the piperidine ring via reductive amination.

Azasugars (iminosugars) are polyhydroxylated piperidines that frequently act as strong and specific inhibitors of carbohydrate-processing enzymes (i.e., glycosidases and glycotransferases).¹ Notable in this category are natural 1-deoxynojirimycin (DNJ) **1** and L-1-deoxyfuconojirimycin **2** (Figure 1), both of which are excellent inhibitors of glucosidase and fucosidase, respectively.² Since glycosidases are essential for the normal cellular development of all organisms, azasugars have tremendous potential as thera-

peutic agents in a wide range of diseases.³ For example, *N*-butyl-1-DNJ (Zavesta) **3** and *N*-hydroxyethyl-DNJ (Miglitol) **4** (Figure 1) have both been approved as medicines.⁴

Fucosyltransferases are involved in a number of essential physiological or pathological processes such as fertilization, cancer, and apoptosis;⁵ thus they have been valid targets for

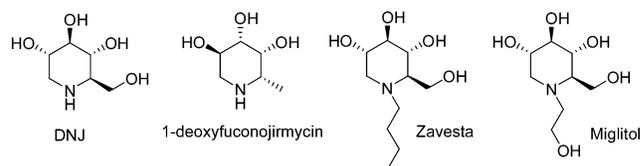


Figure 1. Structures of compounds 1–4.

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the development of potent inhibitors. With regard to the development of new inhibitors, much effort has been devoted to the synthesis and structural modification of **1**,⁶ but only several azasugars have been shown to possess fucosidase or fucosyltransferase inhibitory activity.⁷ We therefore decided to design new potential inhibitors of fucosyltransferases by structural modification of compound **2**, since **2** has proved to be an excellent inhibitor of both fucosidases and fucosyltransferases.^{2b,5a} According to past structure–activity relationships for various azasugars,^{4,8} both the C2-OH and the C3-OH groups are important for a good inhibitor binding to the carbohydrate-processing enzymes, whereas the C4-OH group is not essential for biological activity. We wondered if the presence of a CF₂ group in the C-4 position of the piperidine would affect the biological activity of the interesting analogues D-1,4,6-trideoxy-4,4-difluoronojirimycin **5** and L-1,4,6-trideoxy-4,4-difluoronojirimycin **6** (Figure 2).

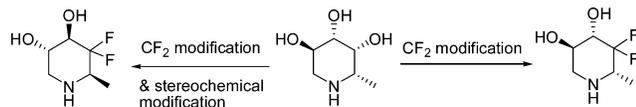


Figure 2. Design of *gem*-difluoromethylenated azasugars **5** and **6**.

Many fluorinated azasugars have been prepared for the biochemical investigations of azasugars; most of these have been monofluorinated compounds bearing a fluorine at C-2 or C-3.⁹ Only a few *gem*-difluoromethylenated azasugars

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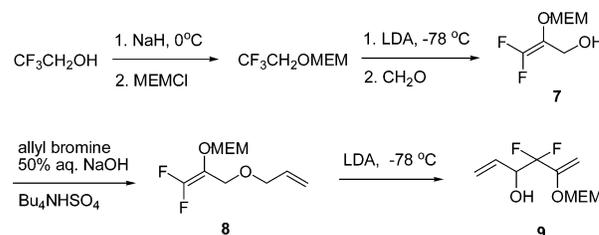
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have ever been reported because of the difficulties of their synthesis. Herein, we report a concise and highly stereocontrolled route to D-1,4,6-trideoxy-4,4-difluoronojirimycin **5** and L-1,4,6-trideoxy-4,4-difluoronojirimycin **6** using Percy's method.

Recently Percy has developed methodologies for preparation of *gem*-difluoromethylenated compounds from trifluoroethanol via [2,3]-Wittig rearrangement of difluoroallylic ethers.¹⁰ He also described that the Sharpless asymmetric dihydroxylation (AD) of *gem*-difluoromethylenated olefins led to *gem*-difluoromethylenated analogues of carbohydrates.¹¹ We were interested in extending Percy's reaction for the synthesis of target molecules **5** and **6**. Accordingly, the synthesis of azasugar **5** and **6** began from trifluoroethanol (Scheme 1), which was initially protected with MEMCl.

Scheme 1. Preparation of Alcohol **9**



Treatment with 2 equiv of LDA then brought about elimination and vinyl anion formation. Addition of an approximately 0.6 M solution of monomeric formaldehyde gave alcohol **7**,^{10a} which was purified by vacuum distillation on multigram scale. Alcohol **7** was then converted to its *O*-allyl ether **8**, and a sigmatropic rearrangement of this compound was brought about by adding its THF solution to 2.2 equiv solution of LDA in THF at $-78\text{ }^{\circ}\text{C}$. Alcohol **9** was obtained in 32% yield from trifluoroethanol (four steps).^{10b}

With alcohol **9** in hand, initial effort was focused on the separation of the enantiomer **9** by transesterification-based enzymatic resolution¹² and kinetic resolution via Sharpless epoxidation,¹³ but this turned out to be unsuccessful.¹⁴

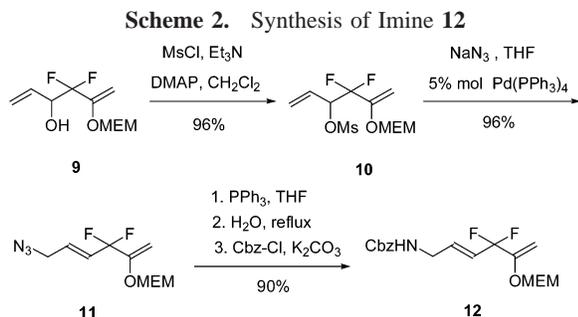
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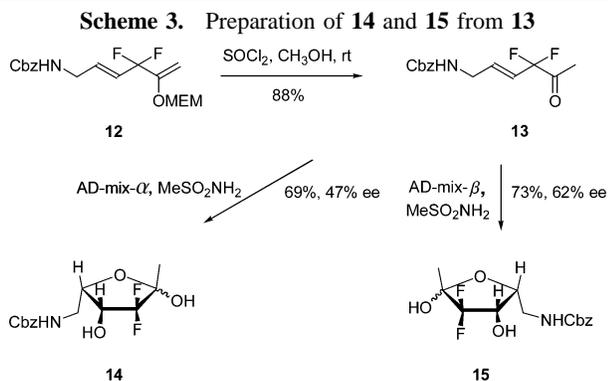
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Alcohol **9** was therefore converted to the mesylated product **10** by treatment with mesyl chloride and Et₃N in CH₂Cl₂ at room temperature. When a mixture of **10**, NaN₃, and catalytic Pd(PPh₃)₄ was stirred for 10 h in THF/H₂O (4:1) at room temperature, a smooth and regioselective Pd(0)-catalyzed allylic substitution took place and azide **11** was obtained as a clear liquid in 96% yield. Conversion of the azide **11** into the *N*-Cbz-amine **12** was accomplished by treatment with PPh₃ in dry THF followed by hydrolysis of the intermediary phosphoryl imine and addition of CbzCl. The *N*-protected amine **12** was obtained in 90% yield (Scheme 2).



Initially we planned to prepare **14** and **15** directly by the Sharpless asymmetric dihydroxylation (AD) of compound **13**. Therefore, compound **12** was treated with SOCl₂ in CH₃-OH to obtain ketone **13** in 88% yield. Then the AD of **13** was carried out. As a result of the strong electron-withdrawing effect of the CF₂ group, the reaction occurred slowly to give cyclic hemiketals **14** and **15** in low enantiomeric excesses (ee's) (47–62%) (Scheme 3).



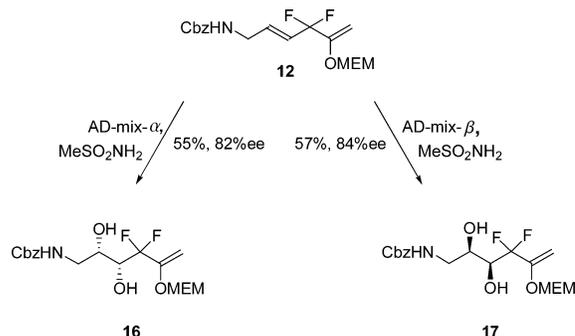
Fortunately, the AD reaction of compound **12** could be carried out selectively and diols **16** and **17** were obtained

(13) (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237–6240.

(14) When **9** was subject to the standart conditions of transesterification-based enzymatic resolution and kinetic epoxidation resolution, no reaction was observed.

with good ee's (82–84%) using either (DHQD)₂PHAL or (DHQD)₂PHAL as the ligand, respectively (Scheme 4).

Scheme 4. Preparation of 16 and 17 by AD Reactions



Careful analysis of **16** and **17** revealed that these products were contaminated with MeSO₂NH₂ in the ratio of 2:1. This finding was supported by ¹H NMR from the chemical shift and the integral (3.10 ppm, 3/2 H) of the Me of MeSO₂-NH₂. Moreover, IR spectroscopy confirmed the existence of sulfamide (1329, 1152 cm⁻¹). On the basis of these data and combustion microanalytical data, we believe that a sandwich structure has been created that is held together by weak hydrogen bonds (Figure 3).

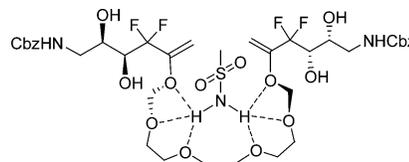
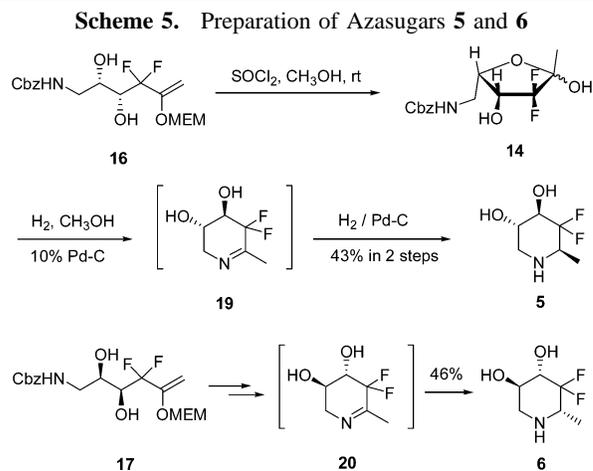


Figure 3. Sandwich structure of compound 17 with MeSO₂NH₂.

Treatment of diol **16** with SOCl₂ in CH₃OH for about 12 h followed by the removal of CH₃OH in vacuo provided a



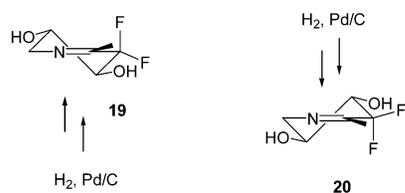


Figure 4. Demonstration of diastereoselective hydrogenation.

residue. The residue was dissolved in ethyl acetate and washed with saturated aqueous K_2CO_3 . Then ethyl acetate was removed in vacuo, and the residue was mixed with 10% Pd/C in methanol and hydrogenated at 80 psi of H_2 for 12 h. The desired azasugar **5** was obtained as a white solid in 43% yield (two steps). Following the same procedure, azasugar **6** was obtained from diol **17** in 46% yield (two steps) (Scheme 5).

The hydrogenation showed excellent diastereoselectivity. No diastereomer has ever been detected by ^{19}F NMR immediately after the reaction. The diastereoselectivity of the hydrogenation reaction, as depicted by Wong,^{6g} can be rationalized by invoking intermediates **19** and **20** (Figure 4). Taking intermediate **19** as an example, an axial attack of hydrogen from the top face is hindered by the C4 fluorine on the six-membered ring. Therefore, attack exclusively occurs from the bottom face, thus leading to the desired product **5**.

The relative configuration of azasugar **6** was determined by X-ray crystallography (Figure 5). The diastereoselectivity of the hydrogenation was also confirmed by this result.

In conclusion, we have designed and completed a 10-step synthesis of D-1,4,6-trideoxy-4,4-difluoronojirimycin **5** in

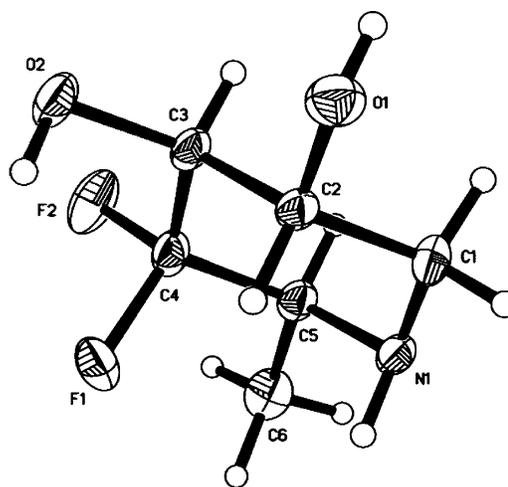


Figure 5. ORTEP drawing of the X-ray crystallographic structure of **6**.

7.0% overall yield and L-1,4,6-trideoxy-4,4-difluoronojirimycin **6** in 6.3% overall yield from trifluoroethanol.

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Supporting Information Available: Experimental procedures, characterization data, and 1H NMR spectra for all new compounds; crystallographic data for compound **6** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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