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

Ruo-Wen Wang[†] and Feng-Ling Qing*[,†,‡]

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and College of Chemistry and Chemical Engineering, Donghua University, 1882 West Yanan Lu, Shanghai 200051, China

flq@mail.sioc.ac.cn

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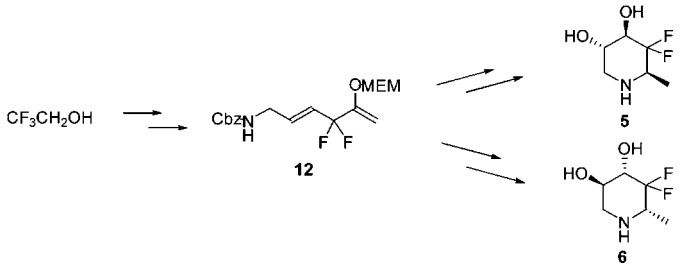
ABSTRACT



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 CF_3CH_2OH 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 therapeutic 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

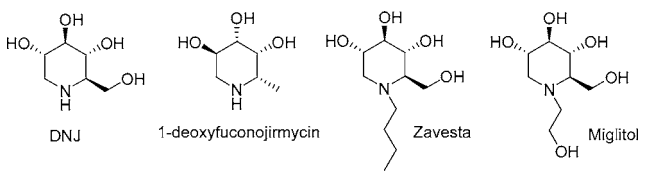


Figure 1. Structures of compounds **1**−**4**.

* To whom correspondence should be addressed. Fax: 86-21-64166128.
† Shanghai Institute of Organic Chemistry.
‡ Donghua University.

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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 CF_2 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).

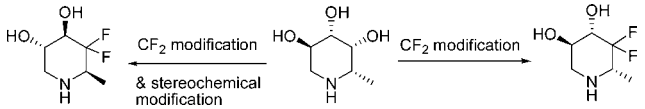
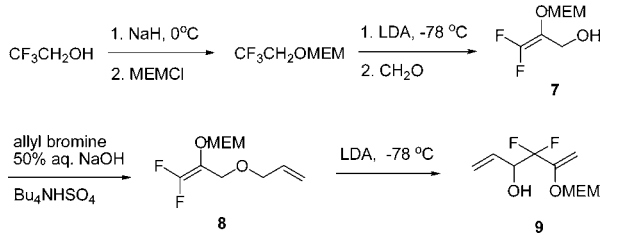


Figure 2. Design of *gem*-difluoromethylenated azasugars **5** and **6**.

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 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 °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 resolution[12] and kinetic resolution via Sharpless epoxidation,[13] but this turned out to be unsuccessful.[14]

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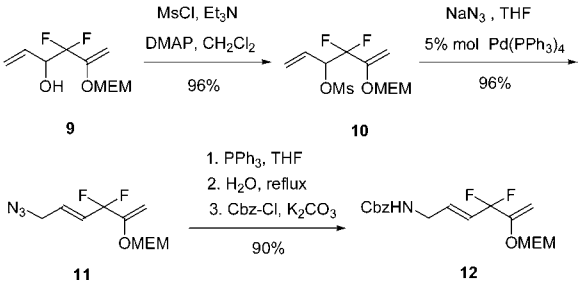
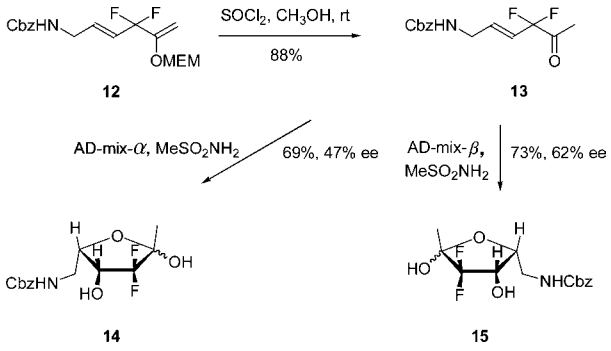
Alcohol **9** was therefore converted to the mesylated product **10** by treatment with mesyl chloride and Et_3N in CH_2Cl_2 at room temperature. When a mixture of **10**, NaN_3, and catalytic $Pd(PPh_3)_4$ was stirred for 10 h in THF/H_2O (4:1) at room temperature, a smooth and regioselective Pd(0)-catalyzed 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 PPh_3 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).

Scheme 2. Synthesis of Imine **12**



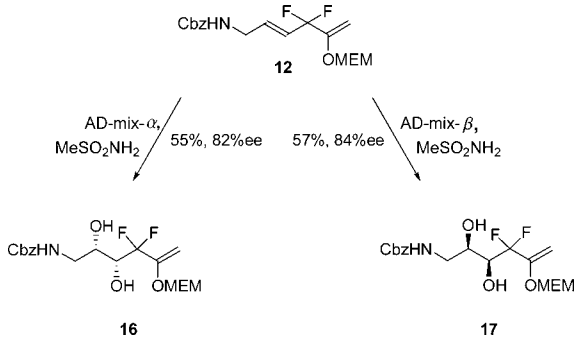
Initially we planned to prepare **14** and **15** directly by the Sharpless asymmetric dihydroxylation (AD) of compound **13**. Therefore, compound **12** was treated with $SOCl_2$ in CH_3OH to obtain ketone **13** in 88% yield. Then the AD of **13** was carried out. As a result of the strong electron-withdrawing effect of the CF_2 group, the reaction occurred slowly to give cyclic hemiketals **14** and **15** in low enantiomeric excesses (ee's) (47−62%) (Scheme 3).

Scheme 3. Preparation of **14** and **15** from **13**



Fortunately, the AD reaction of compound **12** could be carried out selectively and diols **16** and **17** were obtained with good ee's (82−84%) using either $(DHQ)_2PHAL$ 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 $MeSO_2NH_2$ 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 $MeSO_2NH_2$. 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).

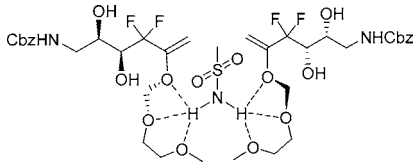
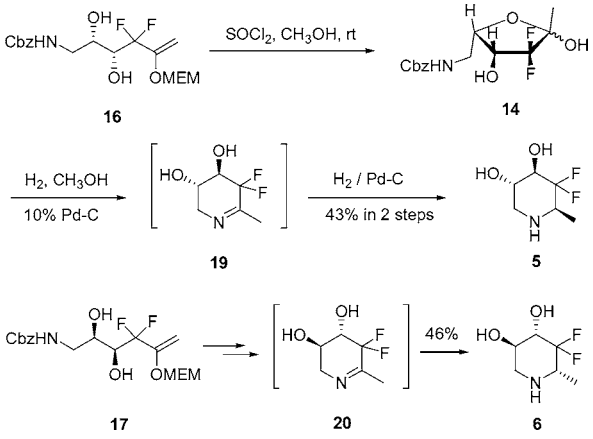


Figure 3. Sandwich structure of compound **17** with $MeSO_2NH_2$.

Treatment of diol **16** with $SOCl_2$ in CH_3OH for about 12 h followed by the removal of CH_3OH in vacuo provided a

Scheme 5. Preparation of Azasugars **5** and **6**



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

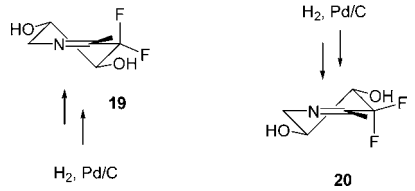

Figure 4. Demonstration of diastereoselective hydrogenation.

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

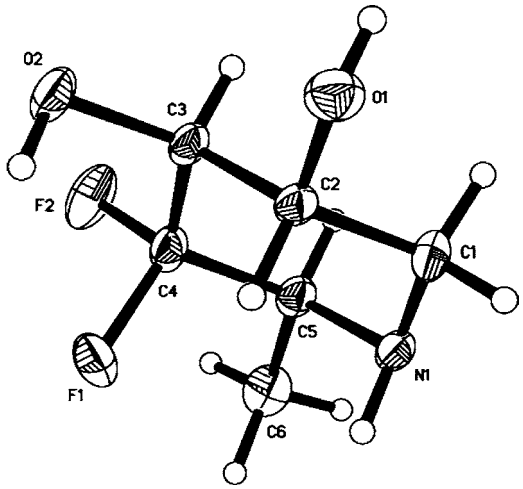

Figure 5. ORTEP drawing of the X-ray crystallographic structure of **6**.

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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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