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Iminosugars

Stereodivergent Syntheses of *altro* and *manno* Stereoisomers of 2-Acetamido-1,2-dideoxynojirimycin

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Abstract: A stereoselective synthesis of 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer **9** is described. The synthetic approach is based on key bicyclic carbamate **7**, which is easily accessible with high enantiomeric purity on a multigram scale by Sharpless asymmetric epoxidation of 1,4-pentadien-3-ol or 2,4-pentadien-1-ol. This procedure completes an efficient stereodivergent approach to five isomers of 2-acetamido-1,2-dideoxyiminosugars in high overall yields starting from the same key intermediate **7**. The approach described in this paper is based on control of the stereoselectivity of the sulfite ring-opening reaction to give retention of configuration through anchimeric assistance from the endocyclic amine.

Introduction

Carbohydrates are involved in a variety of metabolic processes. Inhibitors of enzymes related to carbohydrate metabolism, such as glycosidases or glycosyltransferases, have potential applications in the treatment of several diseases, including diabetes, viral and bacterial infections, and cancer. Iminosugars — saccharides in which the ring oxygen has been substituted by a nitrogen — are potent glycosidase inhibitors, acting as mimics of the corresponding glycosidic substrates.[1,2] Derivatization of iminosugars by modification of the nitrogen and the pseudo-anomeric carbon has been widely reported.[3] However, the introduction of other substituents, such as halogens or amines, to replace some of the hydroxyl groups of the skeleton, is relatively uncommon and synthetically challenging.[4] Iminosugars in which an acetamido moiety replaces a hydroxyl group have received considerable attention in recent years, due to their high selectivity for hexosaminidases. This makes them potentially useful for the treatment of lysosomal storage disorders,[5] Alzheimer's disease,[6] some cancers,[7] and other *O*-GlcNAcase-related diseases.[8] The acetamido moiety is crucial for the high affinity of these compounds.[9] Natural products of this family, such as siastatin B (**1**),[10] nagstatin (**2**),[11] and pochonicine (**3**),[12] have been reported to show inhibitory activities that range from low micromolar to nanomolar. Among the synthetic compounds that have been reported,[13] *N*-acetylglucosamine analogues such as 2-acetamido-1,2-dideoxynojirimycin (**4**),[14] and their *galacto* (**5**)[15] and *allo* (**6**)[16] isomers, have received special attention (Figure 1). Most procedures for the synthesis of iminosugars that have been described to date are based on the chiral pool, starting from sugars or amino acids.[17] Conversely, our approach to iminosugar synthesis is based on the key precursor **7**, which is easily accessible in high enantiomeric purity on a multigram scale by Sharpless asymmetric epoxidation of 2,4-pentadien-1-ol[18] or 1,4-pentadien-3-ol.[19a] Carbamate **7** is a versatile intermediate that has been widely used for the synthesis of several carbohydrate-related compounds.[19] Following this approach we have reported efficient stereoselective procedures to obtain (2*S*)-2-acetamido iminosugars **4**, **5**, and **6**.[14f,16] In our previous work, the (*S*) configuration of the acetamide substituent at the 2-position was secured by substitution reactions that took place with complete inversion of configuration.

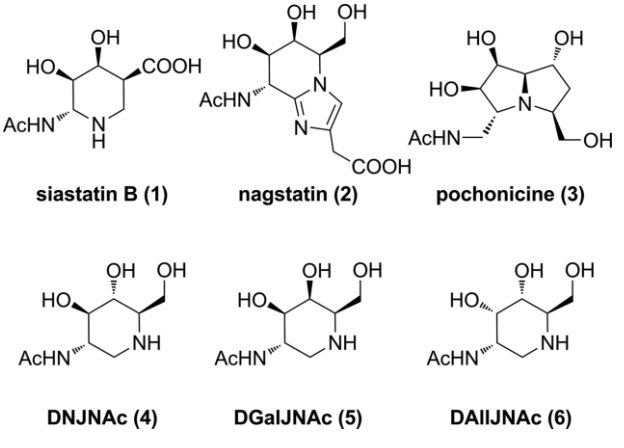

Figure 1. Natural and synthetic examples of acetamido iminosugars.

In this paper, we describe a new approach to the previously unknown 2-acetamido-1,2-dideoxyaltronojirimycin (**8**) and its *manno* epimer **9**, both with the (*R*) configuration at the 2-position (Figure 2). To achieve this, we took advantage of the anchi-

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