

# An improved stereoselective synthesis of (1*R*,2*S*,3*S*,4*R*,5*R*)-4-amino-5-(hydroxymethyl)-cyclopentane-1,2,3-triol

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Iminosugars are sugar mimetics present in plants and microorganisms that were first reported in the 1960s [1]. They can formally result from the replacement of the endocyclic oxygen atoms of monosaccharides by a basic nitrogen and the lack of the anomeric hydroxy group (Figure 1). Taking into account their ability to inhibit carbohydrate-processing enzymes such as glucosidases, they have been proposed as a source for therapeutic agents [2]. Thus, two derivatives of the natural iminosugar deoxyojirimycin (DNJ) are now marketed drugs: miglitol for the treatment of type 2 diabetes and miglustat for the treatment of the lysosomal storage disorders Gaucher's and Nieman-Pick type 2 diseases.

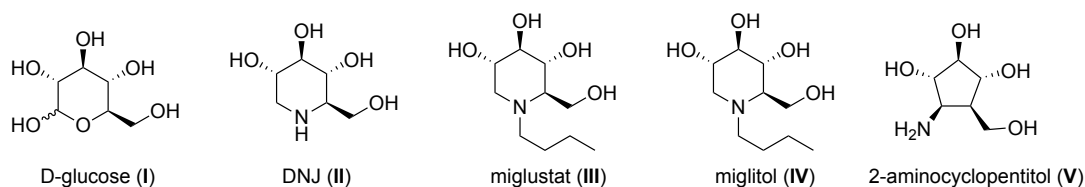
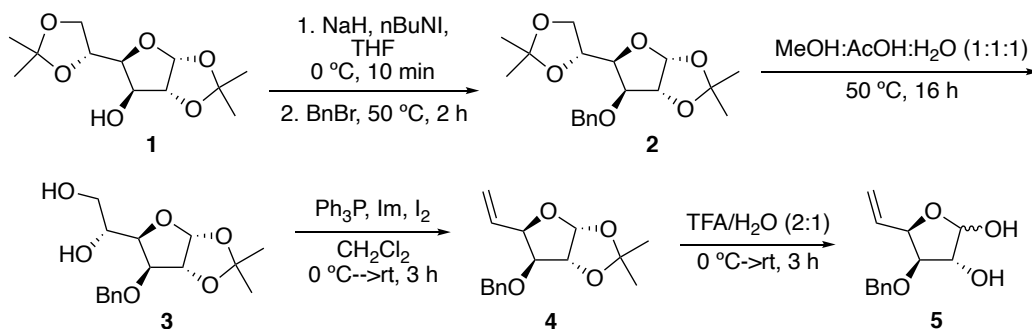


Figure 1

Aminocyclopentitols are also inhibitors of glucosidases that can be considered as carbohydrate mimics resulting from the lack of the endocyclic oxygen atom of furanoses and that carry an exocyclic amino group [3]. Similarly to the deoxyojirimycins, they are mimicking either the protonated glycoside [4] or the intermediate glycosyl (oxycarbenium) cation [5].

As part of our continued interest on glycosidase inhibitors, we report here an improved stereoselective synthesis of aminocyclopentitol **V** (Figure 1).

As shown in Scheme 1, protection of the OH group of the starting diaceton-D-glucose (**1**) as OBn, was followed by the selective deprotection of the exocyclic acetonide group of the resulting compound **2** to give compound **3** [6]. Treatment of this compound with Björn-Classon conditions, provided sugar olefin **4**, in good yield [7]. Reaction of this compound with a 2:1 TFA/H<sub>2</sub>O mixture resulted in the removal of the acetonide protecting group, a process that allowed to obtain compound **5** with its anomeric position free, as required for further transformations.

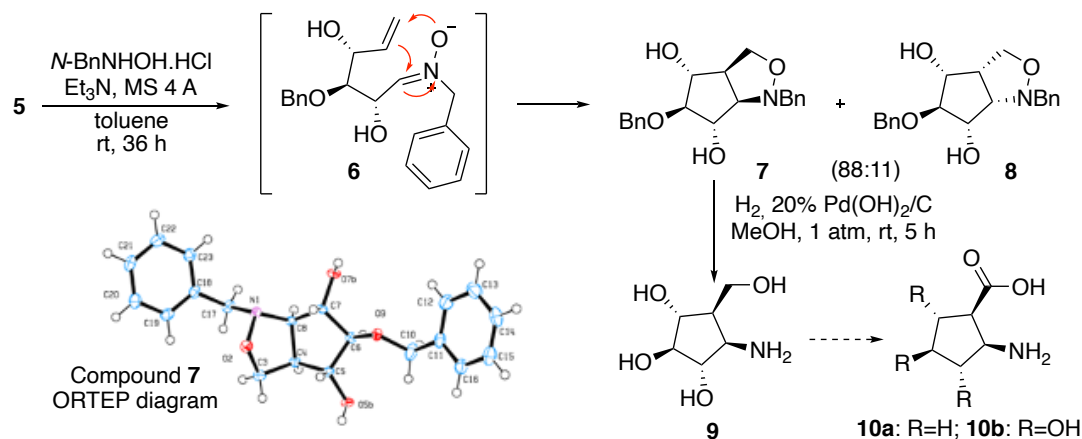


Scheme 1

When compound **5** was reacted with *N*-benzylhydroxylamine hydrochloride and triethylamine, under argon, directly provided a 81% yield of a 89:11 mixture of *cis*-fused isoxazolidines **7** and **8**, which were easily isolated by column chromatography (Scheme 2). Alternatively, when this reaction

was carried out using a 4:1 EtOH/H<sub>2</sub>O mixture, compound **7** was selectively obtained, although in a 44% yield only. The structure this compound was unequivocally confirmed by an X-Ray experiment (Scheme 2).

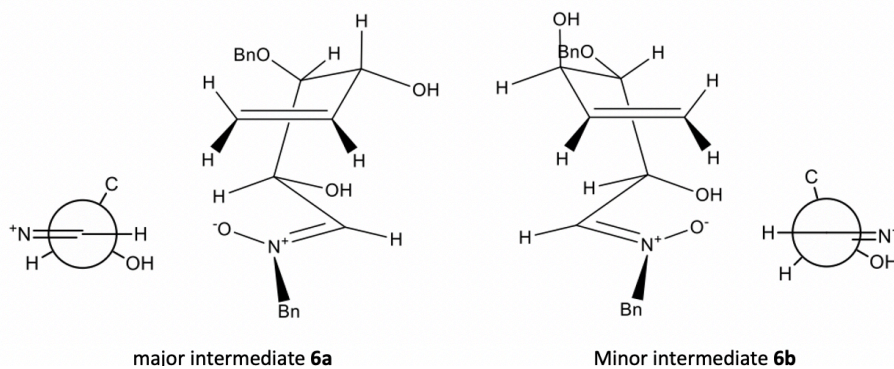
Formation of compounds **7** and **8** can be explained assuming that sugar olefin **5** provided nitrone **6**, which spontaneously undertook a nitrone-alkene cycloaddition leading to mixture **7+8** [8].



**Scheme 2**

Finally, catalytic hydrogenation of isoxazolidine **7**, using Pd(OH)<sub>2</sub>/C as the catalyst, directly provided (1*R*,2*S*,3*S*,4*R*,5*R*)-4-amino-5-(hydroxymethyl)-cyclopentane-1,2,3-triol (**9**) as a result of the opening of the heterocyclic moiety and the hydrogenolysis of the benzyloxy group [9].

Molecular modelling studies carried out allowed to explain the 88:11 ratio for compounds **7** and **8**. Calculations using the MM2 software by Allinger [10], provided a value of 19.956 Kcal/mol for compound **7** and 22.1753 for compound **8**. The difference of 2.219 kcal/mol is enough small to justify that 88:11 ratio. This suggest that this reaction could be subjected to a kinetic control.



**Figure 2**

This suggest that this reaction could be subjected to kinetic control. Two parallel reactions take place, of which the fastest is the one through the most stable intermediate, **6a** (Figure 2). Its Newman projection through the C-1 - C-2 bond shows that the conformation of its transition state is energetically more favorable than that corresponding to **6b**. The eclipsed arrangement of the nitrate and hydrogen at the C-2 positions present a lower steric hindrance than in the case of the conformation of intermediate **6b**, in which the nitrate and the hydroxy group in the C-2 position are eclipsed.

As a whole, here we report a modified route for the synthesis of aminocyclopentitol **9** [11], a known glycosidase inhibitor [12].

Work is now in progress aimed at the transformation of **9** into its β-amino acid derivative **10b** (Scheme 2) [13], a polyhydroxylated derivative of *cispentacin* (**10a**), a natural antifungal antibiotic [14].

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