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Note

Synthesis and glycosidase inhibition evaluation of (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol

En Zhang [a, b, *], Peng-Yan Bai [a], Wei Sun [a], Shang Wang [a], Ming-Ming Wang [a], Shuai-Min Xu [a], Hong-Min Liu [a, b, **]

[a] School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou, 450001, PR China
[b] Collaborative Innovation Center of New Drug Research and Safety Evaluation, Henan Province, Zhengzhou, 450001, PR China

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ABSTRACT

A new azasugar (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol (**1**) was obtained from commercially available D-glucose using one-pot reductive cyclization as a key step. The target product, i.e., the iminosugar isomer, was obtained in 10 steps and 24.3% overall yield. Only three column chromatography purifications were needed in this synthesis. The biological activity of the target molecule as glycosidase inhibitor was studied, but the inhibitory activity against four glycosidases was not good (IC_{50} > 100 μM).

1. Introduction

Many sugars with the ring oxygen replaced by nitrogen, i.e., azasugars or iminosugars [1], occur widely in plants and microorganisms [2]. Azasugars are carbohydrate analogs in which the anomeric hydroxyl group has been preserved or removed, and they include polyhydroxylated pyrrolidines and piperidines [3].

Iminosugars are potent inhibitors of common carbohydrate-processing enzymes and have significant glycosidase and glycosyltransferase inhibitory activities [4]. Glycosidases and glycosyltransferases participate in sugar processing and synthesis. It is therefore important to study and develop compounds that inhibit glycosidases. Glycosidase inhibitors have attracted much attention because they are potentially antidiabetic [5], antiviral [6], and anticancer agents [7], and they have potential in obesity therapy [5]. Recently, many novel glycosidase inhibitors used in herbal medicine, including polysaccharides, alkaloids, glycosides and polypeptides, have been screened [8]. Because of their important biological activities and potential applications, the study of azasugars and their derivatives has become an important research topic in organic and pharmaceutical chemistry [9]. Recent studies have shown that azasugars can be used to treat a wide range of conditions, including diabetes, viral infections, tumor metastasis, lysosomal storage disorders and cystic fibrosis [10,11].

As a result from their potent inhibitory activities, a large number of natural and non-natural structural analogs have been prepared and tested as therapeutically potent inhibitors. Chiral carbohydrate or non-sugar compounds are useful for studying azasugar synthesis [12].

Some azasugars are used as drugs, e.g., *N*-hydroxyethyl **DNJ** (miglitol, Fig. 1) [13] and **NB-DNJ** (miglustat, Fig. 1) [14] are widely used in clinical practice for the treatment of type-II diabetes and Gaucher's disease (a severe genetic disease caused lysosomal storage disorder), respectively. The galactofuranose pyrrolidine analog **2**, which is an inhibitor of UDP-Gal mutase and intervenes in the biosynthesis of mycobacterial galactan, has been obtained [15]. The synthesis and biological evaluation of new inhibitors (**3** and **4**, Fig. 1) of UDP-Galf transferase, which is a significant enzyme in *Mycobacterium tuberculosis* cell wall biosynthesis, have been reported [16];

* Corresponding author. School of Pharmaceutical Sciences, Institute of Drug Discovery and Development, Key Laboratory of Advanced Pharmaceutical Technology, Ministry of Education of China, Zhengzhou University, Zhengzhou, 450001, PR China.
** Corresponding author. Collaborative Innovation Center of New Drug Research and Safety Evaluation, Henan Province, Zhengzhou, 450001, PR China.
E-mail addresses: zhangen@zzu.edu.cn (E. Zhang), liuhm@zzu.edu.cn (H.-M. Liu).

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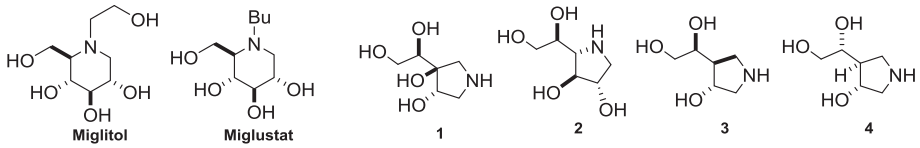


Fig. 1. Structures of some iminosugars.

ring-closing metathesis reactions were the key step in generating novel compounds. A considerable number of nitrogen-containing azasugar isomers have attracted attention because of their importance as glycosidase inhibitors. Polyhydroxylated piperidines are excellent glycosidase inhibitors [17]. Azasugar isomers have the potential to be good glycosidase inhibitors.

In terms of diversity-oriented synthesis, it is important to develop new strategies for synthesizing novel azasugar isomers, especially with high stereoselectivity. During our investigations of α-glucosidase inhibitors [18] and their synthesis from sugars [19], we developed an effective synthetic method for the preparation of new azasugars based on deprotection and reductive amination in one pot. The target compound (**1**) was obtained in 10 steps and 24.3% overall yield. Only three column chromatography purifications were needed in this synthesis. The biological activity of the target molecule as a glycosidase inhibitor was studied but the inhibitory activity against four glycosidases was not good (IC_{50} > 100 μM).

2. Results and discussion

2.1. Synthesis of a new azasugar isomer (3S,4S)-3-((R)-1,2-dihydroxyethyl) pyrrolidi-ne-3,4-diol (*1*)

In this study, a new azasugar (**1**) was synthesized from D-glucose in 10 steps (Scheme 1). 1,2; 5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**5**) was obtained in 95% yield from commercially available D-glucose using a previously reported method [20]. Then, compound **5** was oxidized with pyridinium dichromate (PDC) to give the furan-3-ulose **6**. Compound **7** was obtained via the highly stereoselective Henry reaction [20], treated with HCO_2NH_4 in the presence of Pd/C and then converted to the N-benzyloxycarbonyl (Cbz)-protected compound **8** in one pot [21]. The nitro group in compound **7** was hydrogenated using the method reported in the literature [22,23]. However, we could not identify the main thin-layer chromatography spot. Based on a literature search [21,24,25], we chose Pd/C as the catalyst and HCO_2NH_4 as the hydrogen source for nitro group reduction. The reduction product was used directly in the next step, without purification.

Selective deprotection of the 5,6-acetonide group in **8** using 75% acetic acid [26], gave triol **9** in 79% yield. Treatment of **9** with sodium metaperiodate gave the N-protected aminoaldehyde **10** in good yield. A proton signal from the aldehyde group was not observed in the NMR spectrum. We deduced that **10** is unstable and the nitrogen atom may attack the aldehyde group to give a hemiacetal (Fig. 2). Compound **10** was reduced with sodium borohydride in one pot, without purification, to give the N-protected amino alcohol **11**. Removal of the 1,2-acetonide group of **11** with trifluoroacetic acid/water and subsequent reductive aminocyclization using ammonium formate and 5% Pd/C in methanol under reflux conditions afforded product **1** as a thick liquid. This one-pot three-step process involves hydrogenolysis of a N-Cbz group to give in situ formation of a primary amine, which concomitantly undergoes reductive aminocyclization with a C1 aldehyde to give the target molecule **1** [27].

2.2. Biological activity evaluation of the (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidi-ne-3,4-diol (*1*)

Biological studies showed that the glycosidase inhibitory activity of compound (**1**) was not good (IC_{50} > 100 μM). The inhibition percentage against four glycosidases for compound **1** at 100 μM

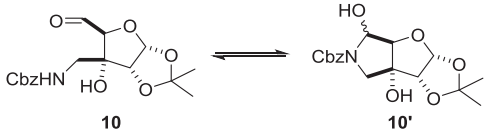
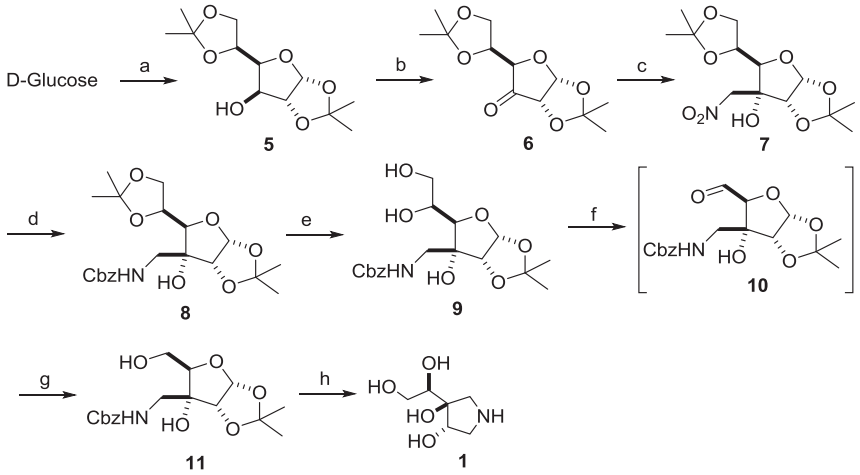


Fig. 2. Possible structure of aminoaldehyde **10**.



Scheme 1. Synthesis of (3S,4S)-3-((R)-1,2-dihydroxyethyl) pyrrolidine-3,4-diol (**1**). Reagents and conditions: (a) $ZnCl_2$, phosphoric acid, acetone; (b) PDC, Ac_2O, CH_2Cl_2; (c) CH_3NO_2, KF, THF, rt.; (d) 1) 5% Pd/C, HCO_2NH_4, CH_3OH, reflux, 1 h and 2) CH_3OH/H_2O (5:1), $NaHCO_3$, CbzCl, 0 °C → room temperature, 2 h; (e) 75% CH_3CO_2H, 55 °C, 3 h; (f) $NaIO_4$, acetone/H_2O (9:1), 0 °C, 40 min; (g) $NaBH_4$, THF/H_2O (v/v = 4/1), 0 °C; (h) 1) TFA/H_2O (3:1), 0 °C and 2) 5% Pd/C, HCO_2NH_4, CH_3OH, reflux, 1 h.