Simple and efficient synthesis of triazole-based iminosugars with potential anti-glucosidase activity

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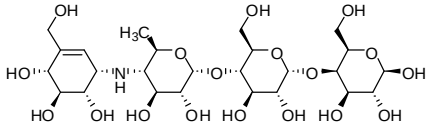
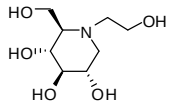
INTRODUCTION

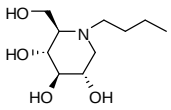
Glucosidases are enzymes involved in key steps of the processing of oligosaccharides or glycoconjugates by cleaving *O*-glucose residues. Inhibitors of glucosidase are agents with high therapeutic potential since many of them show application for the treatment of diabetes, obesity, glycosphingolipid lysosomal storage disease, HIV infections, and tumors in general. Currently, there are three anti-glucosidases drugs: acarbose (**1**) (Precose®), miglitol (**2**) (Glyset®), and *N*-butyl-1-deoxynojirimycin (**3**) (Zavesca®) (Fig. 1), being these last two drugs *N*-substituted iminosugar.[1,2]



Acarbose (1)



Miglitol (2)



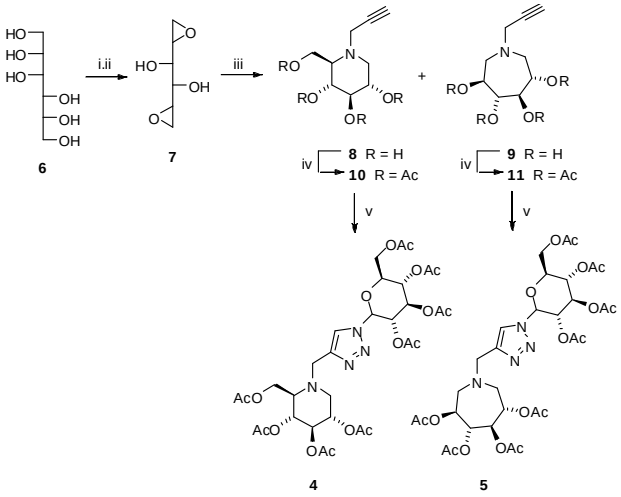
N-butyl-1-deoxynojirimycin (3)

Figure 1. Glucosidase inhibitors related to drugs to treat diabetes (**1**), and (**2**) and Gaucher's disease (**3**).

We herein present the synthesis of 1,2,3-triazole *N*-linked iminosugars, from D-mannitol, with potential anti-glucosidase and anti-viral activities.

RESULTS AND DISCUSSION

The synthesis of **4** and **5** began with selective protection of primary hydroxyl groups of D-mannitol (**6**) with tosyl chloride,[3] followed by the treatment with NaOH,[4] which resulted in the bis-epoxide **7**, the key intermediate for the synthesis of iminosugar core. The aminocyclization reaction of **7** with propargyl amine in MeOH afforded an inseparable mixture of deoxynojirimycin **8** and azepane **9** products. Thus, the mixture was per-*O*-acetylated with Ac_2O and pyridine to give deoxynojirimycin **10** and azepane **11** with 32% and 35% yields, respectively, after column chromatography. Then, the compound **10** or **11** were submitted to CuAAC (Copper(I)-catalysed azide/alkyne cycloaddition), "click chemistry", in the presence of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide over microwave irradiation, which furnished 1,2,3-triazole *N*-linked iminosugars **4** and **5** in 73% and 60% yields, respectively (scheme 1).



Scheme 1. Synthesis of iminosugars **4** and **5**. Reagents and conditions: (i) TosCl, py, 71%; (ii) NaOH, CH_3CN:H_2O, 40°C, 25%; (iii) propargyl amine, MeOH, MW, 90°C; (iv) Ac_2O, py, **10** (32%) and **11** (35%), (v) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide, DMF, $CuSO_4$, sodium ascorbate, MW, 90°C, **4** (73%); **5** (60%).

CONCLUSION

A simple and efficient synthesis of 1,2,3-triazole *N*-linked iminosugars**,** from D-mannitol, was successfully performed using microwave irradiation. The studies will be expanded for others azide compounds. Furthermore, the products obtained will be submitted to enzymatic assays involving glucosidase inhibition and anti-HIV tests.

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