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A divergent approach for the synthesis of some polyhydroxy pyrrolidines and piperidines from ribosylamine

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ABSTRACT

A simple and efficient synthesis of 1,4-dideoxy-1,4-imino-D-ribitol, 1,4-dideoxy-1,4-imino-L-lyxitol, *N*-benzyl derivative of D-ribitol, 3,4,5-trihydroxy-piperidine, L-4-*epi*-isofagomine and D-3-*epi*-isofagomine, which are glycosidase inhibitors has been described from the commercially available D-ribose as a starting material.

1. Introduction

Iminosugars or azasugars have attracted the attentions of both chemists and biologists because of their prodigious biological activity against Gaucher disease,[1] diabetes,[2] hereditary lysosomal storage disorder,[3] cancer metathesis,[4] viral infections like HIV,[5] influenza[6] etc. Iminosugar shows the biological activity when it binds directly to host-cell carbohydrate receptors.[7a] The presence of lipophilic chain on nitrogen atom in iminosugar improves its ability to penetrate the cell membrane and chaperoning activity.[7b,c] The protonated nitrogen atom of the iminosugar at the enzymatic site mimics the glycopyronosyl cation or oxocarbenium ion intermediate, thus inhibiting the enzyme to catalyse glycosyl transferase reactions.[8]

1,4-Dideoxy-1,4-imino-D-ribitol **1**, a natural compound isolated from roots of mulberry tree of the species *Morus alba*,[9] is a potent inhibitor of glucosidase and of eukaryotic DNA polymerases.[10] ADP-HPD [adenosine diphosphate(hydroxymethyl) pyrrolidine diol] moiety bearing structure **1** used for determination of effects of structure on inhibitor potency by PARG [poly (ADP-ribose) glycohydrolase],[11] and inhibition of this target enzyme can be useful to treat the various diseases such as telomere-associated immortality,[12] cardiac or cerebral ischaemia,[13] Parkinson's disease.[14] 1,4-Dideoxy-1,4-imino-L-lyxitol **2**[15] is known as mannosidase inhibitor,[16] and also it is a competitive inhibitor of α-D-galactosidase of the coffee bean. The *N*-benzyl derivative **3**, synthesized by Fleet and co-workers is a strong competitive inhibitor of naringinase and α-L-rhamnosidase.[17a] Inhibitors of this enzyme are potential therapeutic agents for the treatment of bacillary dysentery, cancer,[17b] tuberculosis and leprosy.[17c] Due to the therapeutic importance of **1** and **2**, different approaches have been reported using different strategies.[16,18]

Trihydroxy-piperidine **4** isolated from *Eupatorium fortunei* TURZ plant has many applications in medicines[19] and it shows the inhibition of β-glucosidase and α and β-galactosidase. Ganem and co-workers were the first group to synthesize compound **4** before its isolation.[20] Later, several approaches have been developed for its synthesis.[7b,21] Isofagomine **5** (associated with tartarate salt) is a designed drug for the treatment of Gaucher disease, which failed in phase III clinical trials.[22] Moreover, the diastereomers of isofagomine, L-4-*epi*-isofagomine **6** and D-3-*epi*-isofagomine **7** are showing glycosidase inhibitory activities.[21i]

In continuation of our efforts in the synthesis of azasugars[23] and aminocyclitols,[24] herein we report the convenient synthesis of hydroxylated pyrrolidines **1**–**3** and isofagomine derivatives **4**, **6** and **7** (Fig. 1) by simple reaction conditions from the key intermediate **8**. Compound **8** was prepared from commercially available D-ribose in excellent yield (Scheme 2).

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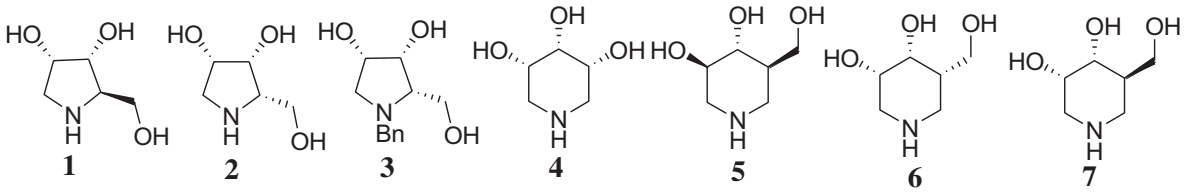


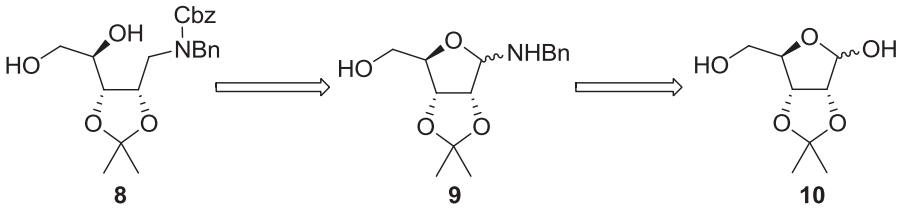
Fig. 1. Structures of some important iminosugars.

2. Result and discussion

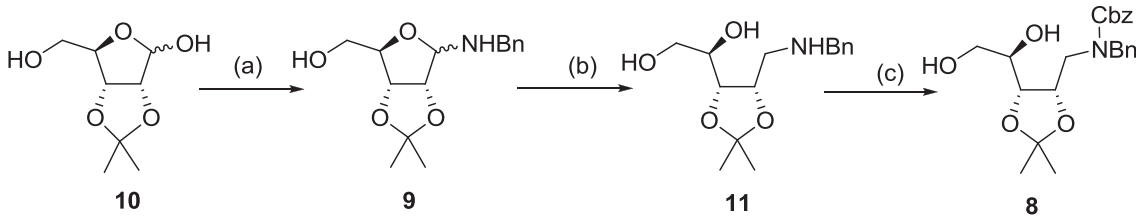
The retrosynthetic analysis for imperative intermediate **8** is depicted in Scheme 1. Compound **8** can be obtained from ribosylamine derivative **9**,[25] which in turn can be easily obtained from **10**. Consequently, our synthesis emanated from 2,3-*O*-isopropylidene-D-ribofuranose **10**,[26] which on treatment with benzylamine gave glycosylamine **9**. Reduction of imine of **9** by LAH in dry THF afforded the amino alcohol **11** in 90% yield. The amino group in **11** was protected with benzyl chloroformate (Cbz-Cl) and $NaHCO_3$ in MeOH to provide compound **8** in 95% yield. After obtaining key intermediate **8** in grams, we proceeded towards the synthesis of target compounds one by one. Initially, primary hydroxyl group in **8** was selectively protected as silyl-ether using TBDMS-Cl and imidazole in DCM to give compound **12**[27] in 90% yield (Scheme 3). Treatment of **12** in DCM with methanesulfonyl chloride and Et_3N provided mesylated compound, which on without further purification was subjected to hydrogenolysis. When hydrogenolysis was carried out on **12** for 12 h followed by global deprotection with 6 N HCl gave the pyrrolidine **2** as hydrochloric salt, whose spectral and physical data were in good agreement with the reported values.[18g] Similarly, when crude mesylated compound was kept for catalytic hydrogenolysis for 1 h gave only compound **13** in 90% yield.[21d] Removal of acetonide and silyl group by 6 N HCl afforded the *N*-benzyl derivative **3** in 95% yield, whose spectral and physical data were in good accordance with the reported values[17a] (Scheme 3).

using catalytic 10% Pd–C in MeOH followed by treatment with 6 N HCl afforded exclusively pyrrolidine **1** as hydrochloride salt via intramolecular 5-*exo*-*tet*[28] opening of epoxide, whose spectral data were in good agreement with previously reported values.[18a]

Selective tosylation of primary hydroxyl group in **8** was carried out by treatment with *p*-toluenesulfonyl chloride, Et_3N and Bu_2SnO in dichloromethane to give **16** in good yield. Hydrogenolysis of **16** in presence of catalytic Pd–C and subsequent global deprotection with 6 N HCl gave the required piperidine **4** as hydrochloride salt, whose spectral data were in good accordance with the reported values.[21g] Next, for the synthesis of **6** and **7**, oxidation of the secondary hydroxyl group in **12** was carried out using Dess–Martin periodinane in DCM to give the keto compound **17** in 85% yield. Compound **17** was subjected to one carbon Wittig olefination in dry THF at −78 °C to give **18** in 88% yield. Treatment of *exo*-olefin in **18** with $BH_3{\cdot}DMS$ in THF followed by addition of NaOH and H_2O_2 afforded primary alcohols **19** as inseparable mixture in 1:1 ratio, which on treatment with Ms-Cl, Et_3N and catalytic DMAP in DCM at 0 °C yielded the separable mesylated compounds **20** (0.48 g) and **21** (0.48 g) with 92% overall yield. Hydrogenolysis of **20** and **21** separately by catalytic 10% Pd–C in methanol followed by global deprotection with 6 N HCl afforded **6** and **7** as hydrochloride salts. Purification of these hydrochloric salts of **6** and **7** using ion exchange resin (DOWEX 50WX8) gave free forms of L-4-*epi*-isofagomine **6**[21a] and D-3-*epi*-isofagomine **7**,[21c] whose spectral data were in good agreement with the reported values (Scheme 4).



Scheme 1. Retrosynthetic pathway for intermediate **8**.



Scheme 2. Reagents and conditions: (a) $BnNH_2$, MeOH, 4 Å molecular sieves, overnight reflux at 65 °C; (b) $LiAlH_4$, THF, 0 °C to rt, 90%; (c) Cbz-Cl, $NaHCO_3$, MeOH, 0 °C to rt, 2 h, 95%.

Regioselective acylation of compound **8** with acetic anhydride and pyridine at low temperature in dichloromethane followed by deacylation with K_2CO_3 in MeOH resulted into epoxide **15** in 92% yield (over two steps). Epoxide **15** was subjected to hydrogenolysis

3. Conclusion

In conclusion, we have reported the divergent strategy for synthesis of hydroxylated pyrrolidines **1**, **2** and **3** and also