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Concise and highly stereoselective syntheses of D-fagomine and 2-*epi*-fagomine

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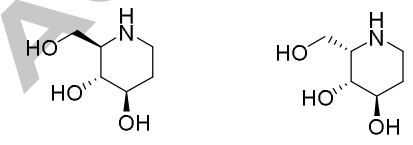
ABSTRACT

Highly stereoselective total syntheses of polyhydroxylated piperidines D-fagomine and 2-*epi*-fagomine has been developed starting from 3,4,6-tri-*O*-benzyl-D-glucal which is a derivative of D-Glucose. Key steps in the synthesis of these azasugars involved *N*-Boc-protected amine preparation from oxime followed by stereo specific iodination of alcohol and cascade cyclization triggered by *N*-Boc deprotection.

Polyhydroxyated piperidines are known for their biological activity as glycosidase inhibitors.[1] These compounds are found to possess effective therapeutic activity against a wide range of diseases including diabetes,[2] viral infection and tumor metastasis.[3] Glycosidases are the enzymes involved in carrying out several fundamental biological processes, azasugars that are either agonistic or antagonistic to these enzymes have thus acquired great significance from synthesis perspective.

D-fagomine (**1**), is a naturally occurring azasugar that was first isolated from Japanese buckwheat seeds of *Fagopyrum esculentum* austral Moench in 1974,[4] and *Castanospermum austral* (a member of *Leguminosae* family).[5] The stereo isomers of this compound were isolated from the leaves and roots of *Xanthocercis zambesiaca*.[6] This azasugar has an inhibitory activity against mammalian intestinal α-glucosidase and β-galactosidase.[7]



1 **2**

Figure-1: D-fagomine **1** and 2-*epi*-fagomine **2**

Also, it has potent antihyperglycemic effect on diabetic mice *via* potentiation of glucose induced insulin secretion.[8] The hyperglycemic condition in mice was caused by inducing Streptozocin in them. These important biological properties of D-fagomine clubbed with its structural similarity with sugars have attracted chemists as an important synthetic target. Because of its limited natural occurrence increasing the availability of its analogues with different substitution pattern and stereochemistry would benefit the scientific community to establish the structure activity relationship. Several syntheses of D-fagomine (**1**) and 2-*epi*-fagomine (**2**), both from carbohydrate[9] and from non-carbohydrate[10] precursors have been reported in the literature. Yaswanth *et al.* reported the total synthesis of D-fagomine and 2-*epi*-fagomine by intramolecular reductive amination from 2-deoxy-1-azido sugars.[9d] Yokoyama *et al.* reported the synthesis of D-fagomine by Sharpless asymmetric dihydroxylation and Pd(II)-catalyzed cyclization starting from 3-(*t*-butoxylcarbonylamino) propanol.[10e] Chemo-enzymatic synthesis of D-fagomine reported by Jesu´s Joglar and Pere Clape´s with FSA-catalyzed aldol addition of dihydroxyacetone (DHA) to *N*-Cbz-3-aminopropanal and reductive amination.[10g] Kim *et al.* reported the synthesis of D-fagomine by stereoselective intramolecular oxazine formation catalyzed by palladium(0) and piperidine formation by catalytic hydrogenation of oxazine.[10i] The diastereoselective synthesis of D-fagomine reported by Min *et al.* from D-lyxose.[10j] Bates and Shuyi Ng reported the synthesis of 2-*epi*-fagomine by gold(I)-catalysed allene cyclisation.[10k] These syntheses though resulted desired product in high yields, the use of complex reagents, reaction conditions and multistep synthetic sequences involved in these syntheses invite even simple and scalable approaches for synthesis of these natural products.

Herein we describe our successful effort towards the highly stereoselective total synthesis of D-fagomine (**1**) and its epimer 2-*epi*-fagomine (**2**) from a common intermediate **5**, which was derived from 3,4,6-tri-*O*-benzyl-D-glucal. The retrosynthetic approach for synthesis **1** and **2** is described in