Mono- and multivalent iminosugar-based α-amino acids as new organocatalysts

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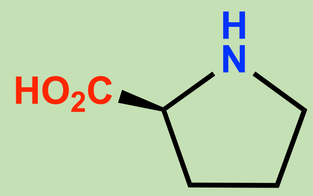
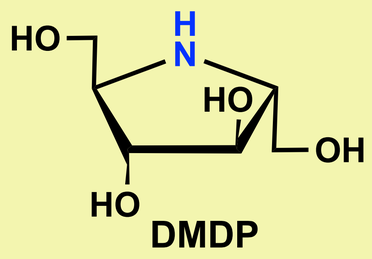
The asymmetric synthesis through organocatalysis, i.e. exploiting low molecular weight organic molecules as the catalyst (very often the natural amino acid L-proline), allows the preparation of pharmacologically active chiral compounds not contaminated by residual noxious metals. The profound impact of the organocatalysis on the asymmetric synthesis has been emphasized by the Nobel prize in Chemistry 2021, which has been awarded jointly to B. List and D. W. C. MacMillan. Recently, natural carbohydrates (e.g. D-glucosamine) and synthetic sugar derivatives (e.g. sugar thioureas, sugar ketones, sugar prolinamides) have also been employed[1] as organocatalysts in various enantioselective transformations, such as aldol reaction, Mannich reaction, Michael addition and aza-Henry reaction. However, other natural enantiopure products, i.e. the iminosugars (sometimes erroneously called azasugars) have never been exploited as organocatalysts.



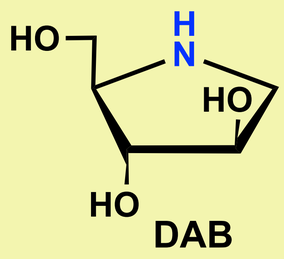
L-proline

Iminosugars are naturally occurring monocyclic and bicyclic compounds closely related to carbohydrate since they feature a basic nitrogen instead of the endocyclic oxygen atom (Figure 1). It is worth noting that most iminosugars are 1-deoxy (*e.g.* DAB and DNJ) or *C*-glycoside (*e.g.* DMDP) derivatives and therefore their chemical and enzymatic stability largely exceeds that of the natural carbohydrates, the latter existing as hemiacetals (aldoses) and hemiketals (ketoses) or acetals and ketals (*O*-glycosides).

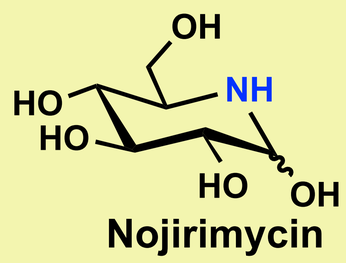
The iminosugars are mainly known to be strong inhibitors of both the glycosidases,[2] the enzymes that catalyze the cleavage of glycosidic bonds in oligosaccharides and glycoconjugates, and the glycosyltransferases,[2] the enzymes that catalyze the formation of the glycosidic bond starting from a sugar donor bearing a leaving group at the anomeric position.



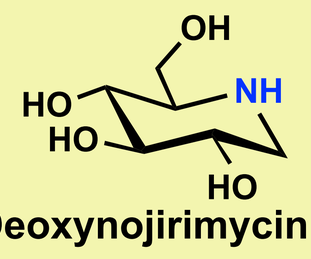
DMDP



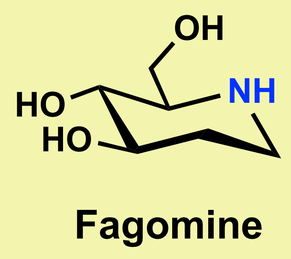
DAB



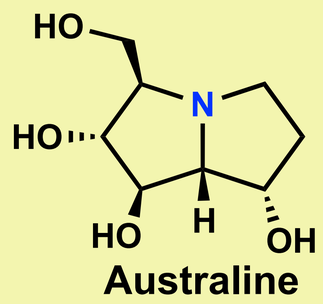
Nojirimycin



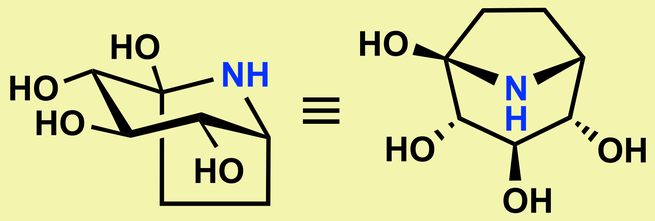
1-Deoxynojirimycin (DNJ)



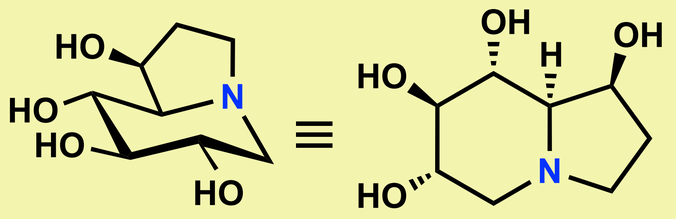
Fagomine



Australine



Calystegine B_2



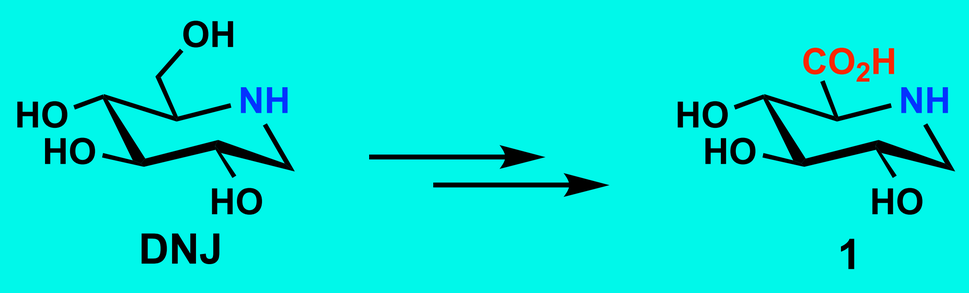
Castanospermine

FIGURE 1

The present project will be focused on the synthesis of six-member ring cyclic α-amino acids such as the iminosugar 1 (Figure 2), directly derived from 1-deoxynojirimycin (DNJ), or other epimers and their use as new organocatalysts in order to study the effect of the ring enlargement (5 *versus* 6 atoms) on the catalytic properties, i.e yield and enantiomeric excess of the obtained coupling products.

Moreover, to increase the local concentration of catalysts, we envisage to take advantage of one hydroxyl function of the iminosugar to prepare multivalent constructs such as 2 (Figure 2) featuring multiple copies of the organocatalyst covalently linked to a pre-organized scaffold.[3] Our team has a vast experience in the design and synthesis of molecular platforms displaying different valency and topology (calixarenes, dendrimers).

The monovalent and multivalent iminosugars 1 and 2 will be employed as organocatalysts in the model reactions catalysed by the L-proline.



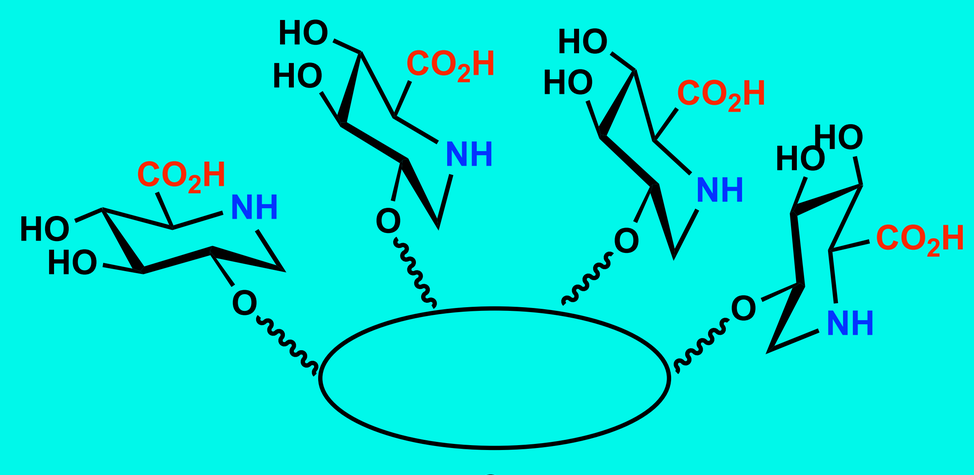


FIGURE 2

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2) I. Conforti, A. Marra *Org. Biomol. Chem*. 2021, *19*, 5439-5475.

3) R. Zelli, J.-F. Longevial, P. Dumy, A. Marra *New J. Chem*. 2015, *39*, 5050–5074.