Multivalent iminosugars as new organocatalysts

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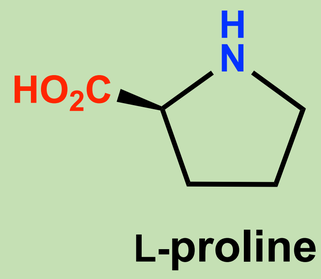
The asymmetric synthesis through organocatalysis, i.e. exploiting low molecular weight organic molecules as the catalyst (very often the natural amino acid L-proline), allows the preparation of pharmacologically active chiral compounds not contaminated by residual noxious metals. The profound impact 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. As recently reviewed by us,[1] natural carbohydrates (*e.g.* D-glucosamine) and synthetic sugar derivatives (*e.g.* sugar thioureas, sugar ketones) have also been employed as organocatalysts in various enantioselective transformations, such as aldol and Mannich reaction, Michael addition. Amazingly, the natural, enantiopure iminosugars (sometimes called azasugars) have never been exploited as organocatalysts.



L-proline

Iminosugars are naturally occurring monocyclic and bicyclic compounds closely related to carbohydrates 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 and the glycosyltransferases,[2] the enzymes that catalyze the cleavage or the formation of the glycosidic bonds.

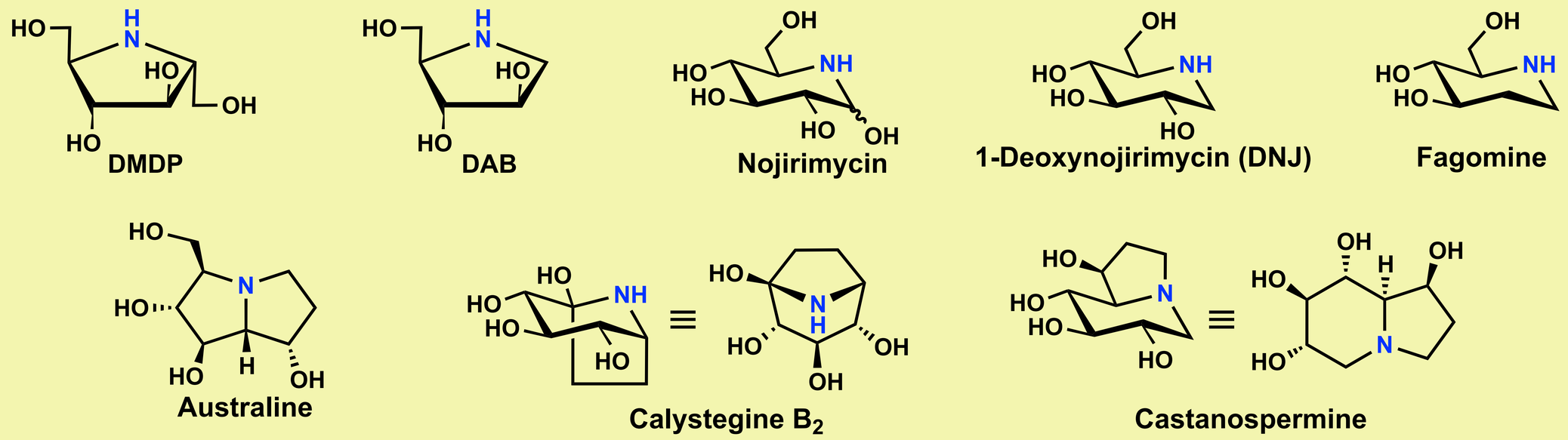


FIGURE 1

The present project will be focused on the synthesis of six-member ring cyclic α-amino acids such as the piperidine derivative 1 (Figure 2), an oxidized iminosugar that will be obtained from D-glucose via the intermediate 1-deoxynojirimycin (DNJ), and their use as new organocatalysts to study the effect of both the ring enlargement (5 *versus* 6 atoms) and the presence of three more stereocenters on the yield and enantiomeric excess of the products usually synthesized using the α-amino acid L-proline as the organocatalyst.

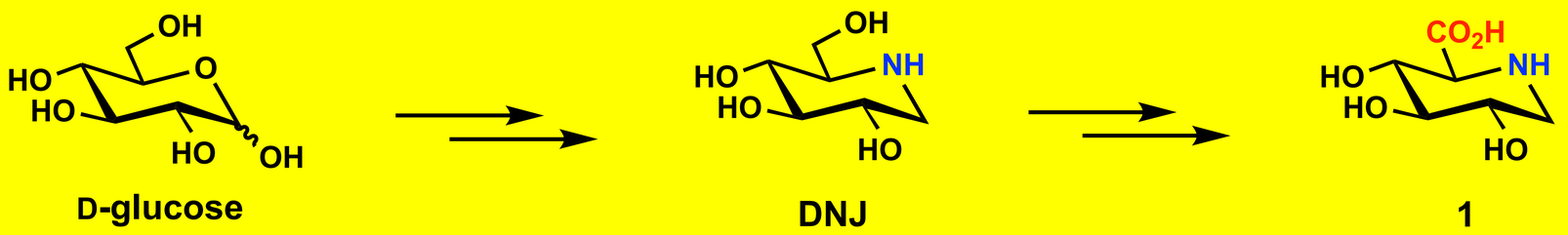


FIGURE 2

Moreover, to increase the local concentration of catalysts, we envisage to take advantage of one hydroxyl function of the iminosugar to prepare multivalent iminosugars (until now employed only as enzyme inhibitors[3]) featuring at least four copies of the organocatalyst covalently linked to a pre-organized scaffold such as the calixarene derivatives 2 and 3 (Figure 3). Our team has a vast experience in the design and synthesis of molecular platforms displaying different valency and topology (calixarenes, silsesquioxanes, dendrimers, cyclopeptides) to which sugars and iminosugars were linked through *O*-glycosylation, Cu-mediated azide-alkyne cycloaddition (CuAAC), thiol-ene (TEC) and thiol-yne couplings (TYC), oxime ligation, and sulfur(VI) fluoride exchange (SuFEx).

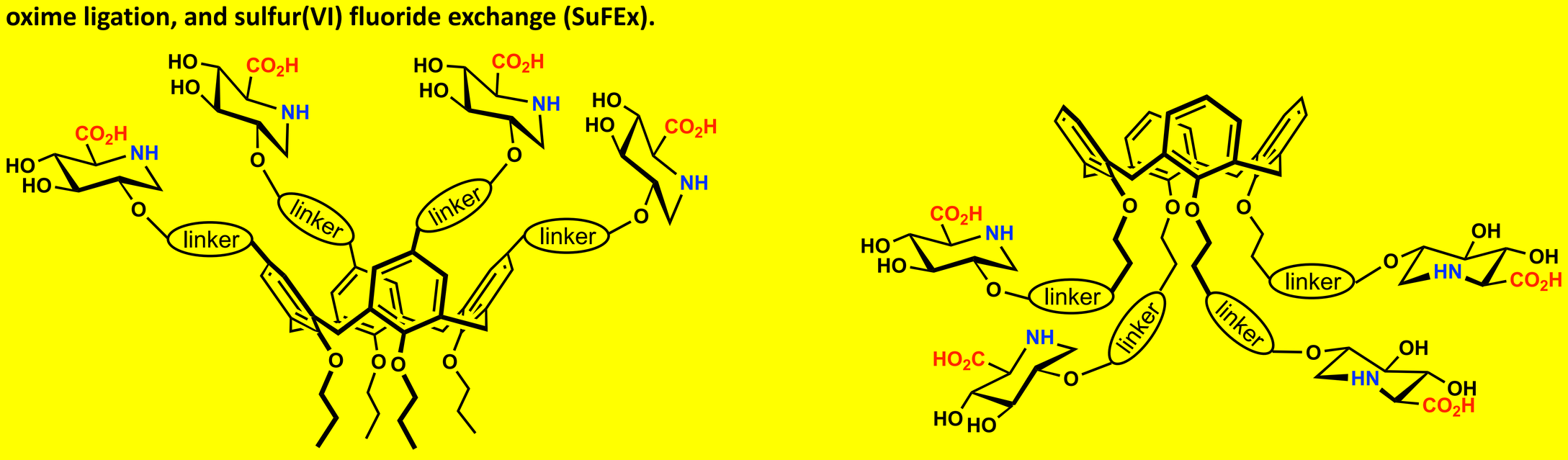


FIGURE 3

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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.