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BIOCATALYTIC CASCADES TOWARDS IMINOSUGAR SCAFFOLDS REVEAL PROMISCUOUS ACTIVITY OF SHIKIMATE DEHYDROGENASES

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PURPOSE OF THE ABSTRACT

Iminosugar are highly polar polyhydroxylated N-heterocycles which displays a multitude of bioactivity such as glycosidase inhibitors, antivirals, or pharmaceutical chaperones but their chemical synthesis is lengthy and suffers from poor scalability and purification.1-3 To circumvent all these issues we develop here protecting group-free chemoenzymatic and biocatalytic cascades to synthesize iminosugars from sugar aminopolyols, using Galactose oxidase (GOase) variant F2 followed by a chemical or an enzymatic imine reduction (Figure 1).
The cascade has been developed applying biocatalytic retrosynthesis.4,5 The major challenge of this route was to identify a reductase able to reduce the hydroxylated cyclic imine to the iminosugar product for the final step.
A first screening on oxidase activity is performed and the GOase variant F2 was identified as the most promising biocatalyst with various substrates. Then putative iminosugar reductases were ‘created' and developed via Genome Mining. After what a cascade screening was done to identify reductases. Combining GOase F2 with a shikimate dehydrogenase (SDH), provided an efficient one-pot route to various targets, with conversions > 70%.
Expanding the reaction system to the whole substrate panel and to circumvent narrow substrate spectrum of SDH, several iminosugar products were obtained using the GOase-NaCNBH3 chemoenzymatic cascade. Iminosugar products were isolated from biotransformations in a single step through development of a gradient-elution ion exchange purification.

FIGURES

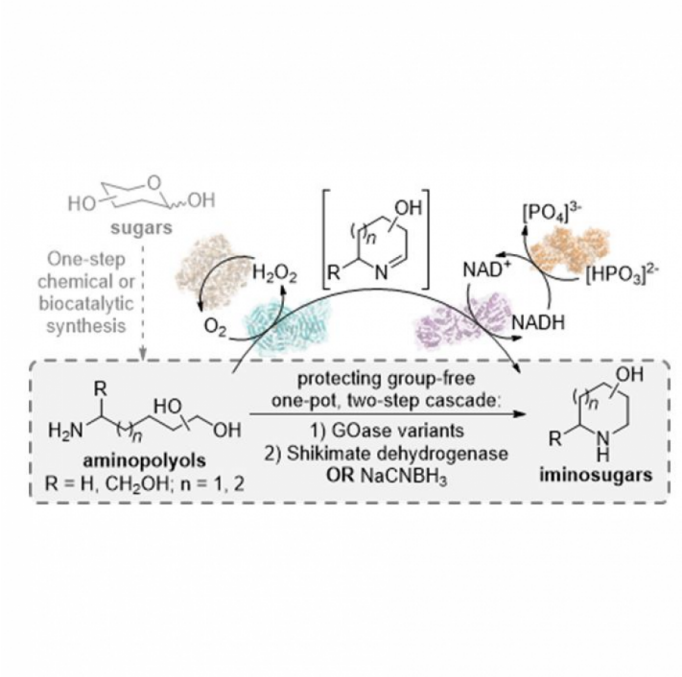

FIGURE 1

Chemoenzymatic and biocatalytic cascades to synthesize iminosugars from sugar aminopolyols.

FIGURE 2

KEYWORDS

iminosugars | biocatalytic cascades | shikimate dehydrogenase

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