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One-Pot Efficient Synthesis of (R)-Mandelic Acids and Other Valuable Chiral Chemicals from Racemic Epoxides via Cascade Biotransformations

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PURPOSE OF THE ABSTRACT

Enzymatic cascades bear great potential for offering economical and sustainable synthesis of valuable enantiopure chemicals from cheap starting substrates, due to their advantages of mild reaction conditions, and less toxic waste generation. Enantiopure (R)-mandelic acid is a highly valuable precursor in the synthesis of many pharmaceutically active molecules such as antibiotics.. Its chemical synthesis usually requires expensive and toxic reagents while giving unsatisfactory enantiomeric excess (e.e.) and generating problematic by-products. A few existing biocatalytic routes to this compound are reported, including cascade reactions from styrene – they are greener, but also suffer low efficiencies in many cases. Here we report a novel and efficient artificial cascade consisting of enantioconvergent epoxide hydrolysis, enantioselective diol oxidation, and aldehyde oxidation to produce enantiopure (R)-mandelic acids in high yields and high ee from easily available racemic epoxides. Using coupled E. coli (StEH) and E. coli (EcALDH-Aldo(M)) strains, (R)-mandelic acid was produced in up to 175mM, 88%-92% yields, and >99% ee from racemic styrene oxide. This represents the highest (R)-mandelic acid titre produced from simple chemicals via green synthesis. The cascade reaction was also successfully applied to convert other racemic epoxides to the corresponding (R)-4-fluoromandelic acid, (R)-4-chloromandelic acid, and (R)-4-bromomandelic acid in >99% ee, demonstrating the first enzymatic syntheses of these valuable molecules. With high yields and high product concentrations, the new cascade developed in this work offers a greener and practical synthetic route to useful and valuable enantiopure hydroxy acids, being potentially applicable for industrial production.

Racemic styrene oxides could also be converted to other valuable chiral chemicals such as amino acids and amino alcohols, by cascading different enzymes after the enantioconvergent StEH. However, the yields of such cascades are still limited by one or more enzymes involved. Directed evolution of these yield-limiting enzymes using our newly developed ultrahigh-throughput microfluidics-based screening platforms are currently in progress.

FIGURES

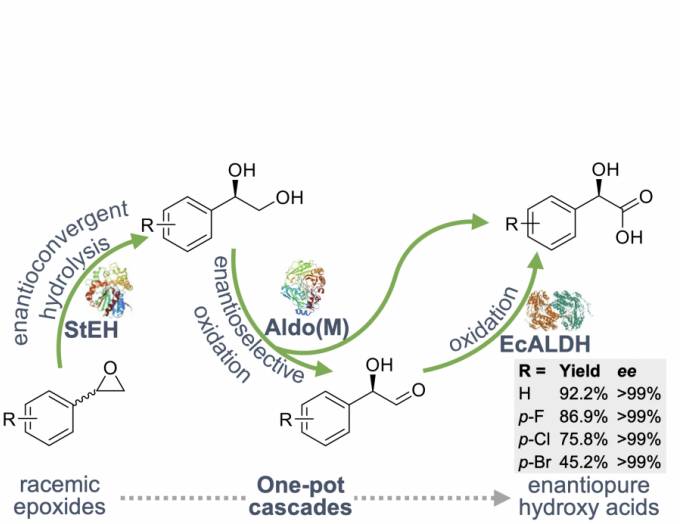

FIGURE 1

One-Pot Efficient Synthesis of (R)-Mandelic Acids from Racemic Epoxides vis Cascade Biotransformations

StEH - epoxide hydrolase from Solanum tuberosum

Aldo(M) - V133M/G236V/V250I/G399K mutant of alditol oxidase from Streptomyces coelicolor

EcALDH - phenylacetaldehyde dehydrogenase from Escherichia coli

FIGURE 2

KEYWORDS

Sustainable catalysis | Enzymatic cascade | Enantioselective synthesis | Racemic epoxides

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