Biocatalytic Asymmetric Synthesis Of Heterocyclic Alpha, Alpha-Disubstituted Amino Acids
Tech ID: 32888 / UC Case 2022-990-0

BACKGROUND

Amino acids (AAs) play a central role in making proteins and diverse metabolites in nature. They are also essential building blocks for therapeutics, such as peptides and peptidomimetics. Among all AAs, α,α-disubstituted α-AAs are unique in that they are sterically and conformationally constrained and have the additional advantage of being resistant to racemization and proteolysis when incorporated in peptides. Despite their promising role in pharmaceuticals, the applications of α,α-disubstituted α-AAs are limited by inefficient routes of production. Biocatalytic methods to prepare structurally complex AAs are an increasingly attractive approach. However, only a handful of biocatalysts are available for synthesizing α,α-disubstituted α-AAs, and all currently available enzymes are limited to synthesizing acyclic α,α-disubstituted α-AAs. An efficient technique for asymmetric synthesis of different α,α-disubstituted α-AAs would be a boon for next-gen therapeutics research.

DESCRIPTION

Researchers at the University of California, Santa Barbara have bridged a gap in the biocatalysis field by devising an efficient technique for synthesizing heterocyclic α,α-disubstituted α-amino acids. This two-step artificial biocatalytic route uses recombinant Lo1T to catalyze Mannich cyclization on a variety of imine substrates which are spontaneously formed in situ. This Lo1T-based biocatalytic technique affords access to a variety of pyrrolidine and piperidine-based α,α-disubstituted α-AAs from simple, commercially available aldehyde and diamino acid substrates. Moreover, Lo1T demonstrated excellent diastereomeric and enantiomeric excess towards a broad range of imine substrates. Beyond noncanonical amino acids, this technique can also make strained heterocycles, such as pyrrolizidine, indolizidine, and quinolizidine, which are important pharmacophores for making new therapeutics. This novel approach of using a PLP-dependent enzyme to catalyze intramolecular Mannich reactions in order to make heterocyclic alpha-quaternary amino acids provides the basis for future protein engineering work that will improve catalytic efficiency and stereoselectivity towards further substrates.

ADVANTAGES

▶ Enables synthesis of heterocyclic α,α-disubstituted α-amino acids
▶ Excellent stereoselectivity (diastereomeric excess >95) towards a broad range of imine substrates
▶ Able to synthesize strained heterocycles, such as pyrrolizidine, indolizidine, and quinolizidine

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OTHER INFORMATION

KEYWORDS
amino acids, synthesis, heterocyclic, α,α-disubstituted α-amino acids, Lo1T, biocatalysis, biocatalyst, Mannich cyclization, indolizidine, quinolizidine, pyrrolidine, piperidine, imine substrates, protein engineering

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