Insight into the stereoselective synthesis of (1*S*)-nor(pseudo)ephedrine analogues by biocatalytic cascades

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Nor(pseudo)ephedrine (N(P)E) isomers, belonging to the amphetamine family of ephedra alkaloids, are naturally occurring compounds found in various plants such as khat (*Catha edulis*) or *Ephedra* species. Due to their biological activity and sympathomimetic properties, N(P)Es serve as crucial intermediates in active pharmaceutical ingredient synthesis, but can also be employed as auxiliaries and ligands in asymmetric organic synthesis [1,2].

The conventional chemical asymmetric syntheses of N(P)Es, compounds characterized by the presence of two chiral centers, often involve multi-step procedures, frequently relying on the use of expensive and environmentally hazardous metal catalysts, moreover achieving high yields and optical purities is challenging. These methodologies typically necessitate several stages for intermediate isolation and purification, resulting in a notable increase in the E-factor, solvent consumption, and energy usage [3].

In this work a two-step biocatalytic cascade was developed for the preparation of (1*S*)-N(P)E analogues, involving a benzoin-type condensation catalyzed by the (*S*)-selective acetoin:dichlorophenolindophenol oxidoreductase (Ao:DCPIP OR) and a reductive amination mediated by either a (*S*)- or (*R*)-selective amine transaminase (ATA). Concurrently, a multistep chemical synthesis of racemic N(P)Es was optimized to serve as reference material for evaluating the efficacy of the biocatalyzed reactions. By delivering the desired products with acceptable yields and robust diastereo- and enantiomeric excesses, this innovative bienzymatic synthesis paves the way for a more sustainable and environmentally friendly manufacturing process for these pivotal chemical compounds [4].

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