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A biocatalytic cascade for the synthesis of ephedrine ana-logues

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PURPOSE OF THE ABSTRACT

Nor(pseudo)ephedrines are vicinal amino alcohols possessing a sympathomimetic function in the human body; due to the presence of two 1,2 chiral centers, they constitute valuable intermediates and chiral building blocks for the organic synthesis of active pharmaceutical ingredients[1]. Their conventional chemical asymmetric syntheses often involve long multi-step procedures, frequently with the use of expensive and harmful metal catalysts or organic precursors/intermediates, in which high yields and optical purities are very difficult to achieve overall. For this reason, biocatalysis can be a promising solution in the development of a stereoselective synthesis of analogues of (1S,2S)-norpseudoephedrine and (1S,2R)- norephedrine. A two-steps biocatalytic cascade was therefore designed and carried out, consisting of a benzoin-type condensation catalysed by the (S)-selective acetoin:dichloro-phenolindophenol oxidoreductase (Ao:DCPIP OR, EC 2.3.1.190)[2] and a reductive amination mediated by an amine transaminase ((S)- or (R)-ATA, EC 2.6.1.x)[3][4]. A multistep, non-selective chemical synthesis for nor(pseudo)ephedrines was also performed in order to obtain reference material for evaluating the performance of the biocatalysed reactions. The novel bienzymatic synthesis afforded the desired products with acceptable yields and good diastereo- and enantiomeric excesses, thus opening the way for a greener production of such important building blocks.

FIGURES

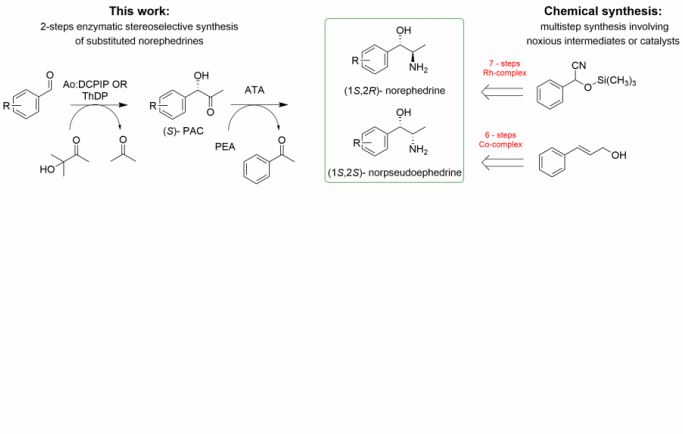

FIGURE 1

FIGURE 2

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Enzymatic two-step synthesis of norephedrine in comparison with literature chemical synthesis.

KEYWORDS

norephedrine | dichloro-phenolindophenol oxidoreductase | transaminase

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