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Stereodivergent synthesis 2-hydroxy-3-substituted-4-butyrolactones by tandem of aldolases and oxidoreductases.

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PURPOSE OF THE ABSTRACT

Stereodivergent synthesis 2-hydroxy-3-substituted-4-butyrolactones by tandem of aldolases and oxidoreductases.

Homochiral 2-hydroxy-4-butyrolactone derivatives are important structural motifs frequently found in naturally occurring biologically active products, synthetic drugs, biodegradable polymers as well as building blocks and chiral auxiliaries in asymmetric organic synthesis (1). Among the methods described in the literature, the stereoselective reduction of 4-hydroxy-2-oxoacid derivatives to produce 2-hydroxy-4-butyrolactone derivatives remains unexplored.

In this communication we report a tandem biocatalytic stereodivergent route for the preparation of these compounds using two stereocomplementary aldolases and oxidoreductases, using simple and achiral starting materials. The strategy comprises (Scheme 1) (i) aldol addition reaction of 2-oxoacids to formaldehyde using both 3-methyl-2-oxobutanoate hydroxymethyltransferase and 2-keto-3-deoxy-L-rhamnonate aldolase and variants thereof, and (ii) subsequent 2-oxogroup reduction of the aldol adduct by both ketopantoate reductase and a delta-1-piperidine-2-carboxylate/delta-1-pyrroline-2-carboxylate reductase with uncovered promiscuous ketoreductase activity. Finally, the formation of the corresponding lactone takes place during the work up and purification steps.

Yields, enantiomeric excesses and diasteromeric ratios for a total of 23 structurally diverse 2-hydroxy-3-substituted-4-butyrolactones will be discussed. Moreover, one-pot one-step cascade reactions with the aldolases and reductases operating in tandem will be presented.

FIGURES

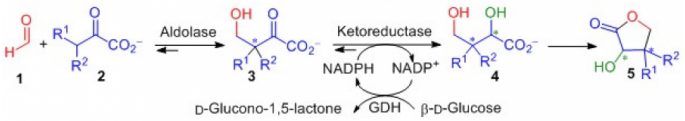

FIGURE 1

Scheme 1.

Biocatalytic synthesis of 3-substituted-2-hydroxy-4-butyrolactones 5 by tandem aldolase-ketoreductase biocatalytic reactions starting from formaldehyde 1 and 2-oxoacids 2.

FIGURE 2

KEYWORDS

2-Oxoacid aldolase | Ketoreductases | Aldol addition | 2-Hydroxy-4-butyrolactones

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