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Asymmetric mono-reduction of 1,2-dicarbonyls by Old Yellow Enzyme and glucose dehydrogenase

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PURPOSE OF THE ABSTRACT

Chiral α-hydroxy ketones are valuable molecules that can be used as fine chemicals or as building blocks for asymmetric synthesis to obtain bioactive compounds [1]. These enantiopure molecules can be obtained via asymmetric reduction of one carbonyl from a vicinal diketone or other (enzymatic) approaches [2]. Alcohol dehydrogenases typically catalyse the double reduction of diketones to the corresponding diols, with some exception for the mono-reduction of certain aliphatic and aromatic 1,2-diketones [3]. Recent studies on flavin-dependent ene reductases from the Old Yellow Enzyme family (OYE) have revealed compelling non-conventional activity without illumination, in particular oxime reduction [4] and C-C bond formation [5], that are distinct from the typical asymmetric reduction of α,β-unsaturated compounds. Evidence alludes to yet another variant reaction, where OYEs might catalyse the reduction of 1,2-dicarbonyl substrates [6]. In this study we demonstrate that certain OYEs can catalyse the non-conventional diastereoselective mono-reduction of 1,2-dicarbonyls to the corresponding hydroxy carbonyl enantiomer (Figure 1). Purification of these enzymes, use of stoichiometric amounts of native cofactor, synthetic cofactor, and mechanistic studies confirmed formation of the α-hydroxy ketone product with full conversion, in high enantiomeric and diastereomeric excess. We also highlight the serendipitous discovery of promiscuous GDH activity on these vicinal dicarbonyls.

FIGURES

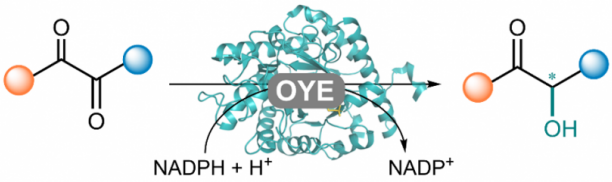

FIGURE 1

Figure 1

Stereoselective mono-reduction of vicinal dicarbonyls catalysed by an OYE to the corresponding alpha-hydroxyl carbonyl.

FIGURE 2

KEYWORDS

asymmetric reduction | ene reductases | hydroxy ketones | dicarbonyls

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