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Synthesis and valorization of alpha-hydroxyketones through bio and organocatalysis

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PURPOSE OF THE ABSTRACT
A chemoenzymatic strategy is investigated to obtain highly valuable unsymmetrical alpha-hydroxyketones (acyloins), precursors of vinylene carbonate, useful building blocks for prodrugs synthesis such as medoxomil producing after hydrolysis non-toxic carbon dioxide and alpha-dicarbonyl derivatives.1

In the first enzymatic steps, thermostable Transketolase from Geobacillus stearothermophillus (TKgst)2 catalysing C-C bond formation is used to obtain unsymmetrical alpha-hydroxyketones from alpha-ketoacid donor which brings different functionality (R1 = aliphatic, hydroxyl), while the aldehyde acceptor (biosourced or obtained from cheap and achiral precursor) allows the modulation of the main carbon chain on its R2 group (halogenation, hydroxylation, length variation). The TK reaction enables the irreversible transfer of a ketol group from an alpha-ketoacid donor to an aldehyde acceptor with concomitant decarboxylation of the donor and release of carbon dioxide.3 The alpha-ketoacid can be generated in situ from the corresponding D-aminoacid with a novel D-aminoacid oxidase (DAAO), as already initiated.2 To improve TKgst activity toward the targeted substrates, TKgst variants were designed by rational mutagenesis based on the analysis of TKgst active site.4

Finally, organocatalysts (ORG) such as N-heterocyclic carbenes (NHC) together with a carbonyl source (DPC, DMC or carbon dioxide) could catalyze efficiently the synthesis of vinylene carbonates,5 from unsymmetrical alpha-hydroxyketones never investigated before due to the difficulty to control the regioselectivity by chemical ways. This chemo-enzymatic strategy combining enzymes and organocatalysts in a one-pot could be performed sequentially or simultaneously avoiding the purification of intermediates.

FIGURES

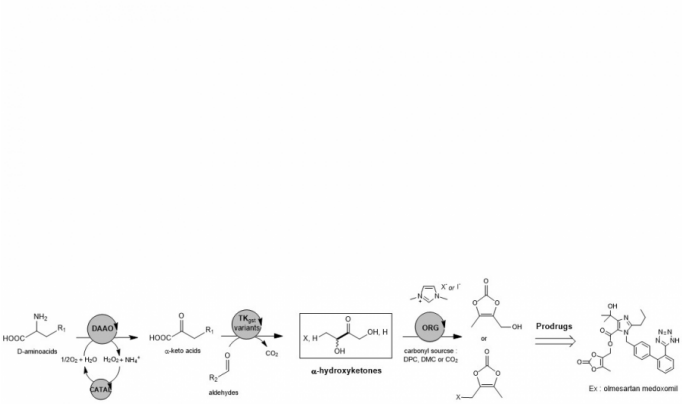

FIGURE 1

Overview of the chemoenzymatic strategy
DAAO : D-aminoacid oxydase
CATAL : Catalase
TKgst : Transketolase de Geobacillus stearothermophilus
ORG : Organocatalyst
NHC : N-heterocyclic carbene
DPC : Diphenyl carbonate
DMC : Dimethyl carbonate

FIGURE 2

KEYWORDS

chemo-enzymatic strategy | unsymmetrical alpha-hydroxyketones | transketolase | prodrugs

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