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Review

Highly enantioselective deracemization of 1-phenyl-1,2-ethanediol and its derivatives by stereoinversion using *Candida albicans* in a one-pot process

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ABSTRACT

A very simple methodology was developed to transform racemic 1-(4-substitutedphenyl)-1,2-ethanediols using resting cells of *Candida albicans* CCT 0776 through a one-pot two-step process in which the (*R*)-stereoisomer was completely oxidized to the corresponding substituted-α-hydroxyacetophenones, which were completely reduced to produce (*S*)-1-(4-substitutedphenyl)-1,2-ethanediols in good isolated yield (60–85%) and with high enantiomeric excess (99% ee). The overall process corresponded to an enantioselective deracemization by stereoinversion of the (*R*)-enantiomer. The process was not achieved for other similar 1,2-diols using the same reaction conditions, which indicates a structural restriction of substrates by the active pocket of the enzymes of *C. albicans* involved in the stereoinversion process.

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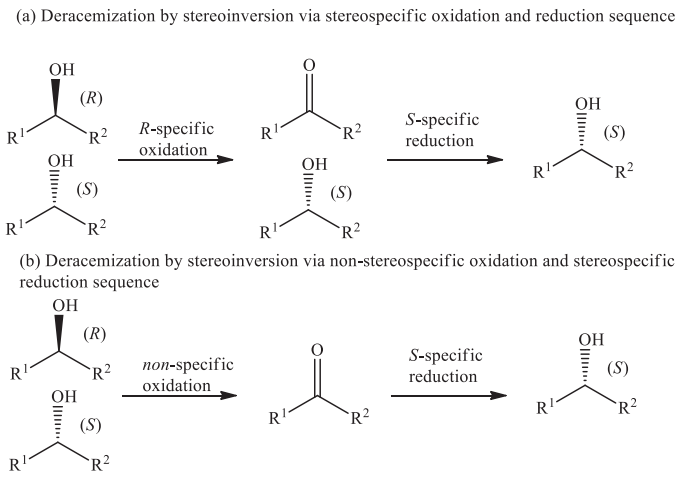

Fig. 1. Stereoinversion/deracemization technologies using alcohol dehydrogenases to transform one enantiomer into the opposite optical form.

1. Introduction

The exquisite chemo-, regio- and stereoselectivity displayed by enzymes has led to their widespread application as catalysts for stereocontrolled organic synthesis [1]. The industrial strategy most commonly used in the preparation of chiral compounds is the settlement of racemates. The separation of a racemate into its two enantiomers, commonly known as resolution, has been the most prominent way to separate two enantiomers in numerous applications. The kinetic resolution is a process in which the two enantiomers of a racemate are converted into products at different rates in an efficient process, such that only one of the enantiomers remains as the product. The limitation of this process is to obtain a maximum return of 50% of product, because only one of the enantiomers undergoes a reaction. Kinetic resolution of enantiomers occurs when $k_R \neq k_S$. To ensure high selectivity, the difference in the reactions rates in the individual enantiomers should be as large as possible (in ideal cases, $k_R/k_S = \infty$). Several strategies have been developed to overcome this limitation and allow the transformation of a racemic mixture into one of the corresponding enantiomers in theoretically 100% chemical yield and 100% optical purity, designated deracemization [2] processes. The cells of microorganisms possess several different enzymes necessary to realize their metabolism including alcohol dehydrogenases (ADHs), which lead to high oxidation, reduction and deracemization activities even toward unnatural substrates [2].

Deracemization by stereoinversion is described as a two-step interconversion reaction between the two enantiomers of the racemate in which the first step includes a stereospecific oxidation (Fig. 1a), or a non-stereospecific oxidation (Fig. 1b) of one alcohol enantiomer into the corresponding ketone and its simultaneous reduction to the mirror-image alcohol. This stereoinversions methodology, is usually achieved by employing one [3,4] or two catalysts [5]. In contrast to the chemical process, oxidation and reduction process can occur simultaneously in living cells. Several authors have reported deracemization through the stereoinversion of one alcohol enantiomer in the presence of fermenting or resting cells of microorganisms [6–10]. Different microorganisms have been tested for the deracemization of alcohols: *Geotrichum candidum* [11,12], *Candida parapsilosis* [13–15], *Alcaligenes faecallis* [16], *Serratia marcescens* [14], *Sphimgomonas* sp. [17], and *Sphingomonas paucimobilis* [18]. These reports present high substrate specificity, the requirement for low substrate concentrations to achieve high ee, high oxidation activity and long reaction times. A tandem biocatalysts system was developed for the deracemization of 1-phenylethanol using resting cells of *Microbacterium oxydans* for the oxidation step and *Rhodotorula* sp. to reduce the ketone [19]. A number of reports described only stereoselective oxidation of secondary alcohols achieving kinetic resolution [20,21].

Chiral 1,2-diols are a versatile group used in the synthesis of pharmaceuticals, agrochemicals, pheromones and other valuable molecules. In particular, (*S*)-1-phenyl-1,2-ethanediol (PED) is a precursor for the production of chiral biphosphines and an initiator for stereoselective polymerization [22]. Several methods for the preparation of chiral PED and other 1,2-diols have been developed by biocatalysis, including stereospecific dihydroxylation of styrene by naphthalene dioxygenase [23], resolution of PED by lipase-catalyzed transesterification [24], enantioselective oxidation by glycerol dehydrogenase [25], and microbial stereoinversion with a whole cell system [13,14]. This last procedure has been employed to avoid coenzyme addition or regeneration systems to obtain alcohols with high yield and ee from racemates [26–28]. For the preparation of optically active 1,2-diols from the corresponding racemates there are reports employing *C. parapsilosis* IFO0708 [14] and *C. parapsilosis* M203011 [13]. Recently, we used *Trichosporon cutaneum* to promote the deracemization of (±)-2-hydroxyindan-1-one to give (1*S*,2*R*)-1,2-indandiol in 90% yield and >99% ee by a dynamic kinetic resolution process [29]. Using the same fungus *T. cutaneum*, we achieved the diastereo- and enantioselective bioreduction of (±)-2-hydroxy-1-tetralone to the corresponding enantiopure (1*S*,2*R*)-*cis*-1,2-dihydroxy-1,2,3,4-tetrahydronaphtalene in 83% yield and >99% ee through dynamic kinetic resolution [30]. We also reported the enantioselective oxidation of (1*R*,2*S*)-1-phenyl-1,2-propanediol mediated by *Saccharomyces cerevisiae* to give (*S*)-1-phenyl-2-hydroxy-1-propanone in 64% yield and 93% ee [31].

In the present report, we investigate the deracemization of 1-phenyl-1,2-ethanediol (PED) and its derivatives with substituents at the phenyl moiety to obtain (*S*)-1-phenyl-1,2-ethanediol in high yield (80–90%) and high ee (99%), employing *Candida albicans* CCT 0776. Similar result was achieved using *C. parapsilosis* M203011 but the authors have not mentioned the reaction time, the mechanism was not studied with details and there is a misconception about the stereochemistry of the product since the structure in the scheme does not fit with assigned configuration [13]. Hasegawa et al. [14] obtained a slight better process using *C. parapsilosis* IFO0708, but they have not studied the mechanism and they have not scaled up the reaction for PED.

2. Experimental

2.1. General

The alcohols 1-phenyl-1,2-ethanediol (**1**) and 1-(2-nitrophenyl)-1,2-ethanediol (**7**) were purchased from Sigma–Aldrich. 1-(4-Methylphenyl)-1,2-ethanediol (**5**) and 1-(4-chlorophenyl)-1,2-ethanediol (**3**) were purchased from Spectra Group Limited Inc. All other commercial reagents and solvents were purchased with the highest purity available and were used as received. The NMR spectra were recorded in a Varian Gemini at 250 (^{1}H NMR) and 62.5 (^{13}C NMR) MHz, or an Avance at 500 and 600 (^{1}H NMR) and 125–150 (^{13}C NMR) MHz. The chemical shifts (δ') were reported in parts per million (ppm) and the coupling constants (*J*) were reported in Hertz (Hz). A BOMEM MB-100 FT-IR was used for the IR spectra. Optical rotations were measured using a Carl Weiss POLAMAT A polarimeter. The GC analysis was performed with an Agilent 6890 Series GC equipped with a DB1 silica capillary column from J&W Scientific (30 m × 0.25 mm ID × 0.25 μm film thickness) and helium as the carrier gas (0.9 mL/min) with a split ratio of 1:50. The temperature of the injector and the detector were maintained at 230 °C and 280 °C, respectively. The column temperature

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