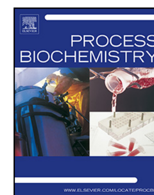
Process Biochemistry 50 (2015) 759–770

Contents lists available at ScienceDirect

Process Biochemistry

journal homepage: www.elsevier.com/locate/procbio



Enzymatic synthesis of chiral 2-hydroxy carboxylic acids

Xi Chen, Qiaqing Wu, Dunming Zhu *

National Engineering Laboratory for Industrial Enzymes and Tianjin Engineering Center for Biocatalytic Technology, Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, 32 Xi Qi Dao, Tianjin Airport Economic Area, Tianjin 300308, China

ARTICLE INFO

Article history:
Received 10 October 2014
Received in revised form 26 January 2015
Accepted 29 January 2015
Available online 16 February 2015

Keywords:
Enzymatic catalysis
2-Hydroxy carboxylic acid
Dynamic resolution
Hydrolysis
Asymmetric reduction

ABSTRACT

Optically active 2-hydroxy carboxylic acids are widely used not only as key building blocks for the synthesis of various organic compounds, but also as chiral resolving reagents. This review focuses on the recent advances in enzymatic preparation of enantiomerically pure 2-hydroxy carboxylic acids, which mainly includes two approaches: (dynamic) kinetic resolution of racemic 2-hydroxy carboxylic acids and derivatives by hydrolase enzymes, and asymmetric reduction of α-keto acids and esters by carbonyl reductases.

© 2015 Elsevier Ltd. All rights reserved.

Many 2-hydroxy carboxylic acids are naturally occurring compounds in various biological sources. Glycolic acid (sugar cane), lactic acid (milk), citric acid (citrus fruits), and malic acid (apples) are present in various foods. 2-Hydroxy fatty acids are found in plants (chain from 12 up to 24 carbon atoms), and in animal wool waxes, skin lipids and specialized tissues, mainly in brain. For example, 2-hydroxylinoleic and 2-hydroxyoleic were detected in the Labiatae *Salvia nilotica* [1]. Several 2-hydroxy fatty acids were also reported in polar lipids of the alga *Grateloupia turuturu* from Brittany, France [2]. 2-Hydroxy carboxylic acids stimulate the exfoliation of epidermal cells in the stratum corneum by interfering with the ionic bonding between these cells, thus resulting in the sloughing off dull, rough skin and promoting cellular renewal [3]. As such, 2-hydroxy carboxylic acids are widely used as additives in cosmetics [4–6]. In addition, chiral 2-hydroxy carboxylic acids are useful building blocks for the production of a diversity of fine chemicals. For example, the applications of chiral lactic acid, mandelic acid, malic acid and tartaric acid as starting material for the synthesis of fine chemicals have been summarized in literature [7]. Ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPBE) is a key chiral building block for the commercial synthesis of angiotensin converting enzyme (ACE) inhibitors [8]. (*R*)-*o*-Chloromandelic acid was the intermediate for the synthesis of Clopidogrel [9]. Therefore, chemical and biocatalytic methods have been developed for the preparation of optically pure 2-hydroxy carboxylic acids. In this review the enzymatic preparation of chiral 2-hydroxy carboxylic acids and esters is surveyed with an emphasis on the recent advances in this field because the works before 2001 were summarized in an excellent review article by Gröger [10]. The enzymatic preparation of chiral 2-hydroxy carboxylic acids mainly includes two approaches: kinetic resolution and asymmetric synthesis. This review first discusses the kinetic resolution of racemic 2-hydroxy carboxylic acids, esters, amides and nitriles by hydrolases and oxidases, and then summarizes the application of carbonyl reductases in the synthesis of optically pure 2-hydroxy carboxylic acids and esters.

1. Enzymatic kinetic resolution of racemic 2-hydroxy carboxylic acids and esters

2-Hydroxy carboxylic acids have two functional groups: the hydroxyl and carboxylic acid groups. Therefore, the kinetic resolution can proceed through the reactions of either the hydroxyl group or the carboxylic acid group.

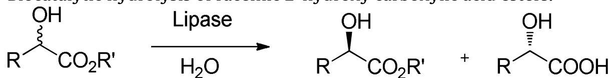
While the enzymatic hydrolysis of carboxylic acid esters has been widely employed to achieve the chiral resolution of racemic 2-hydroxy carboxylic acids, the reverse esterification of racemic 2-hydroxy carboxylic acids with alcohols has been rarely studied. Some recent examples of biocatalytic hydrolysis of racemic 2-hydroxy carboxylic acid esters are presented in Table 1.

The commercially available lipase Novozym 435, lipozyme RM IM and lipozyme TL IM were studied for their activity and selectivity for the hydrolysis of racemic (*R*,*S*)-methyl mandelate. After optimization of the reaction conditions (*R*)-mandelic acid was

* Corresponding author. Tel.: +86 22 84861962; fax: +86 22 84861996.
E-mail address: zhu_dm@tib.cas.cn (D. Zhu).

http://dx.doi.org/10.1016/j.procbio.2015.01.027
1359-5113/© 2015 Elsevier Ltd. All rights reserved.

Table 1
Biocatalytic hydrolysis of racemic 2-hydroxy carboxylic acid esters.



Racemic ester	Microbial origin	Enzyme	Conversion (Yield%)	E (ee%) configuration	Ref.
	Candida antarctica	Novozym 435	19	(78) *R*[a]	[11]
	Aspergillus oryzae	Amano M	50	>200 (98) *R*[b]	[12]
	Aspergillus oryzae	Amano A	51	>200 (99) *R*[b]	[12]
	Aspergillus melleus	Protease	(35)	60 (94) *R*[a]	[13]
	Pseudomonas cepacia	Amano PS	(39)	(99) *R*[a]	[14]

[a] The ee of the product acid.
[b] The ee of the unreacted ester.

obtained with 78% ee when the reaction was carried out in a non-aqueous media using lipase Novozym 435 as the catalyst (Table 1) [11]. The proteases from *Aspergillus oryzae* were used for the hydrolysis of the methyl esters of (*R,S*)-3-phenyllactic acid and (*R,S*)-3-(4′-chlorophenyl)lactic acid (Table 1) [12]. Methyl 3-phenyllactate and methyl 3-(4′-chlorophenyl)lactate were resolved excellently with *E* >200. However, these enzymes showed low enantioselectivity for methyl mandelate with ee of the product acid being <10% at about 40% conversion. An industrially scalable process was developed for the enantioselective hydrolysis of tetrahydrofuran-2-carboxylate ester by using the protease from *Aspergillus melleus*. (*R*)-Tetrahydrofuran-2-carboxylic acid was obtained with 93.9% ee and 34.9% yield when the concentration of substrate was 1.0 M (Table 1) [13].

The lipases, esterases and proteases have widely used in the hydrolysis of 2-hydroxy carboxylic acid esters, but these enzymes do not always show satisfying performance for the specific substrates. In order to improve the conversion and stereoselectivity or simplifying the separation step, a variety of methods have been developed. Membrane reactor was applied for the kinetic resolution of ethyl 2-hydroxy-4-phenylbutyrate (HPBE) at high substrate concentration of 1.2 M by using lipase Amano PS as the catalyst, and the reaction time for the product to reach >99% ee was reduced from 50 h to 12.5 h by integrating *in situ* diafiltration [14].

Wang et al. developed an aqueous/organic biphasic reaction system for the enantioselective resolution of ethyl (*R,S*)-mandelate [15] and ethyl (*R,S*)-*o*-chloromandelate [16]. When the hydrolase (SNSM-87) from *Klebsiella oxytoca* was used as the catalyst, no reaction was observed in water-saturated *iso*-octane, while in a biphasic reaction system at substrate concentrations of 5 mM for ethyl mandelate and 1 mM for ethyl *o*-chloromandelate, the ee value of the unreacted substrates were 83.8% for ethyl (*R*)-mandelate and 100% for ethyl (*R*)-2-chloromandelate, respectively.

Lee et al. developed a novel whole cell biocatalyst system for the production of enantiomerically enriched compounds by displaying the *Pseudomonas fluorescens* lipase on the surface of *Escherichia coli* cells using the truncated *Salmonella typhimurium* OmpC as an anchoring motif. When racemic methyl mandelate and *cis*-3-acetoxy-4-phenylazetidin-2-one were treated with this whole cell biocatalyst, (*S*)-mandelic acid and (3*S*,4*R*)-*cis*-3-hydroxy-4-phenylazetidin-2-one were successfully obtained with the ee value greater than 99% [17].

The immobilization is often used to improve the stability and reuse of the enzyme. The enantioselectivity of lipases was also affected by the immobilization protocols and the support materials. The lipase from *Candida rugosa* (CRL) showed very different *E* value from 1.2 to >200 toward *S* isomer of methyl mandelate when it was absorbed by PEI-coated support. However, a high enantioselectivity ($E = 400$) toward *R* isomer was observed for CRL modified with glutaraldehyde [18,19]. In addition to these methods, some other good approaches have been summarized by Bornscheuer [20].

The acylation of the hydroxyl group of racemic 2-hydroxy carboxylic acids/esters (Scheme 1) or the reverse hydrolysis of the acylated 2-hydroxy carboxylic acids/esters (Scheme 2) were also investigated for the kinetic resolution of racemic 2-hydroxy carboxylic acids.

Campbell et al. examined the resolution of a series of substituted mandelic acids through the acylation of the hydroxyl group catalyzed by Lipase PS "Amano" [21]. For all the aromatic substituted substrates (3′-SMe, 3′-NO_2, 3′-Cl-5′-NO_2, 3′-Cl-5′-NMe_2, 3′-NMe_2-5′-CF_3, 3′-Cl-5′-(1*H*-pyrrol-1-yl)), the ee values of the unreacted substrates were >95% at 1 M substrate concentration. The acylation of methyl mandelate was carried out in isopropyl ether (non-aqueous solution) by using free *Pseudomonas* sp. lipase or the immobilized enzyme on poly(ethylene) oxide (PEO) and agar gel. Conversion of the reaction with the enzyme immobilized on PEO was nearly 50% and both enantiomers were obtained with practically 100% of optical purity in 96 h, although at low substrate concentration of 1.5 mM [22].

The immobilized *Candida antarctica* lipase A (CAL-A) showed high enantioselectivity and activity for the acylation of methyl (*S*)-*o*-chloromandelate under a solvent-free condition. As such, methyl (*R*)-*o*-chloromandelate was obtained in enantiomerically pure form (>99% ee) and 41% yield. CAL-A maintained its catalytic activity for 13 cycles of repeated use without significant decrease in enantioselectivity [23].

An esterase, rPPE01, from *Pseudomonas putida* ECU1011 was heterologously expressed in *E. coli* and employed for enzymatic resolution of 2-hydroxy carboxylic acids *via* *O*-deacetylation (Scheme 2) [24]. The esterase had organic-solvent tolerance, good thermostability and high enantioselectivity toward 2-acetoxy carboxylates. A series of 2-*O*-acetyl carboxylates substrates (2-phenyl, 3-phenyl, 4-phenyl, 2-(*o*-chlorophenyl), 2-(*m*-chlorophenyl),

Download English Version:

https://daneshyari.com/en/article/34333

Download Persian Version:

https://daneshyari.com/article/34333

Daneshyari.com