Journal of Molecular Catalysis B: Enzymatic 122 (2015) 93–116

Contents lists available at ScienceDirect

Journal of Molecular Catalysis B: Enzymatic

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

The role of *Pseudomonas cepacia* lipase in the asymmetric synthesis of heterocyclic based compounds

Ghodsi Mohammadi Ziarani[a,*], Parisa Gholamzadeh[a], Paria Asadiatouei[a], Negar Lashgari[b]

[a] Department of Chemistry, Alzahra University, Vanak Square, P.O. Box 1993893973, Tehran, Iran
[b] School of Chemistry, College of Science, University of Tehran, Tehran 14155-6455, Iran

ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form 27 August 2015
Accepted 30 August 2015
Available online 4 September 2015

Keywords:
Pseudomonas cepacia lipase
Lipase PS
Asymmetric synthesis
Enantioselective reactions
Enzyme

ABSTRACT

Pseudomonas cepacia lipase (lipase PS) is an efficient enzyme which catalyzes the enantioselective asymmetric esterification and/or hydrolysis reactions in high yields and enantio excess of products. In this review, the role of lipase PS in the asymmetric esterification and hydrolysis of various heterocyclic compounds or their precursors is investigated.

Contents

1. Introduction

Louis Pasteur is the first scientist who could separate two enantiomers of tartaric acid and said "The universe is chiral". Many natural products are produced as chiral compounds. Asymmetric reactions produce optically active substances using one of the chiral substrates, catalysts, solvents and/or auxiliaries. In this regards, enzymes are important natural chiral catalysts [1].

Lipase is an important enzyme which catalyzes the hydrolysis of lipids and has various applications and industrial potentials. Claude Bernard was the first who discovered lipases from pancreatic juice in 1856, and since then, animal pancreases have become the main source for the commercial lipases [2]. Many industrial applications of lipases are focused on its regio- and enantio-selectivity properties since they can catalyze asymmetric hydrolysis reactions at room temperature (save energy economically) and are active in both water and/or organic solvents [3].

Pseudomonas cepacia lipase or *Pseudomonas* sp. lipase or *Burkholderia cepacia* lipase summarized as PS or PCL is an efficient lipase in the transesterification of prochiral or racemic alcohols with acetates. It has been also Immobilized on different supports such as modified ceramic (PS-C), diatomite (PS-D) and Hyflo Super Cell (PS-HSC). In continuation of our experimental researches in asymmetric synthesis using lipases [4–8], this article aims to review

Abbreviations: lipase A or ANL, *Aspergillus niger* lipase; CAL-A, *Candida antarctica* lipase A; CAL-B, *Candida antarctica* lipase B; CCL, *Candida cylindracea* lipase; CRL, *Candida rogusa* lipase; PPL, *Pancreas porcine* lipase; lipase PS or PCL, *Pseudomonas cepacia* lipase; lipase AK or PFL, *Pseudomonas fluorescens* lipase.

* Corresponding author. Fax: +98 2188041344.
E-mail addresses: gmohammadi@alzahra.ac.ir, gmziarani@hotmail.com (G. Mohammadi Ziarani).

http://dx.doi.org/10.1016/j.molcatb.2015.08.022
1381-1177/

the role of lipase PS in asymmetric esterification and/or hydrolysis of heterocyclic based compounds or their precursors. Its catalytic activity will be discussed in the next section.

1.1. Catalytic triad

A catalytic triad refers to the three amino acid residues that function together at the center of the active site of certain hydrolase enzymes. Each amino acid plays a role as an acid, base or nucleophile in hydrolysis reactions, so they constitute an acid-base-nucleophile triad catalytic center. The acidic residue is commonly aspartate (Asp) and/or glutamate (Glu). Although no natural amino acids are strongly basic, histidine (His) is an effective base since its pKa allows for base catalysis as well as hydrogen bonding to the acid residue using its imidazole moiety. Lysine (Lys) is another amino acid, which plays the role of a base. Although the 20 naturally occurring biological amino acids do not contain sufficiently nucleophilic functional groups, however the most commonly used nucleophiles are the alcohol group of serine (Ser) and the thiol group of cysteine (Cys). Ser–His–Asp, Ser–Glu–Asp and Cys–His–Asp are some examples of the classic triad-containing enzymes [9–16].

Lipase PS's active site cleft is void and has 10 Å × 25 Å across. It has a catalytic triad of Ser87, His286 and Asp264 (Ser–His–Asp) which forms a number of hydrogen bonds [17].

The mechanism of transesterification in the presence of Ser–His–Asp triad of lipase PS is shown in Scheme 1. The hydroxyl group of serine acts as a nucleophile while histidine as a basic amino acid accepts the proton from the nucleophilic atom and then the nucleophilic attack occurs. Simultaneously, the carboxylic group of aspartic acid is hydrogen bonded with histidine and makes it more electronegative. When the hydroxyl group of serine attacks to the carbonyl of ester, histidine accepts its proton (part a). By joining of serine oxygen to the carbonyl group of an ester (part b), the R^2O- group is removed as an alcohol after moving off a histidine's proton (part c). Chiral or prochiral alcohol, then attacks the carbonyl group of serine (part c) and serine-carbonyl bond is cleaved (part d). Finally, chiral ester is produced and the active cite switches back to produce more esters (part e) [18].

2. Asymmetric synthesis of heterocycles using lipase PS

In asymmetric syntheses, the selectivity of the reaction is determined by enantiomeric excess (ee.) and diastereomeric excess (de.), when the products are enantiomers and/or diastereomers, respectively.

The enantioselectivity of a biocatalytic reaction is normally described by the enantiomeric excess (ee.) or the E value. In an enzymatic resolution of a racemic substrate, the E value can be calculated from Eq. (1) while the ee. value of the product is known. Where c is the conversion of substrate, and ee_p and ee_s are the obtained enantiomeric excesses of product (P) and remaining substrate (S), respectively. In order to provide both the product and the remaining substrate in high amount of ee. in one reaction step, the E-value should be high, usually around or more than 100 [19].

$$E = \frac{\ln[1 - c(1 + ee_p)}{\ln[1 - c(1 - ee_p)} \quad (1)$$

2.1. Esterification reaction

Formoterol **5**, a highly β_2-selective agonist [20], was synthesized from chiral epoxide **4** as shown in Scheme 2. For the preparation of epoxide **4**, Campos *et al.* brominated and reduced ketone **1** to the corresponding bromoalcohol **2**. Then, (S)-enantioselective esterification of racemic bromoalcohol **2** was accomplished using lipase PS and vinyl acetate. PPL was also used for this aim, but did not lead to any products after 22 h. The pure (R)-bromoalcohol **2** and (S)-bromoacetate **3** were converted to (R)- and (S)-epoxides **4**, respectively [21].

A synthetic route to 4-*O*-acetyl-L-rhodiopyranose **10** and 5-*O*-acetyl-L-rhodinofuranose **11** was described via a tandem Sharpless asymmetric dihydroxylation (AD) and lipase-catalyzed esterification (Scheme 3). In this method, alcohol **6** was oxidized to the corresponding aldehyde and went through the condensation with racemic 1,2-diphenyl-1,2-ethanediol (stilbene diol) to afford **7**, which was then dihydroxylated by AD-mix-α [$(DHQ)_2$[1], EtOAc] to provide chiral diol **8**. Esterification of diol **8** in the presence of PS lipase produced a separable mixture of acetates **9a** and **9b**, and minor amounts of diol **3**. Hydrolysis of mono acetate **9a** formed rhodiopyranose **10** and alternatively **9b** was subjected to identical reduction reaction to gain rhodinofuranose **11**. The trideoxyhexose L-rhodinose **10** and **11** are common constituents of many antibiotics, including rhodomycin, streptolydigin, vineomcyin B_2, and galtamycin [22–24]. Although, the final product of many synthetic routes towards trideoxyhexose L-rhodinose was isolated as an equilibrium mixture of pyranose **10** and furanose **11** [25], however, this lipase-catalyzed reaction gave the products separately.

Ramadas and Krupadanam reported kinetic resolution (R)-enantioselective acylation of (±)-dimethoxyethoxymethyloxy-2-acetoxymethyl-2,3-dihydrobenzofuran **13** using lipase PS to give (R)-(−)-acetate **14** and (S)-(+)-**13**. Then, (R)-(−)-acetate **14** was hydrolyzed and in some steps converted to (R)-(−)-MEM-protected arthrographol **15** as a natural product [26]. (R)-(−)-arthrographol was reported to possess antifungal and chitin synthase inhibitor activity (Scheme 4) [27].

A family of enantiomerically pure benzofurans **19a–e** was prepared by means of an asymmetric enzymatic process followed by an intramolecular chemical cyclization reaction (Scheme 5). Two lipases PS-C and CAL-B were used in this enzymatic reaction and PS-C showed an excellent selectivity toward alcohol **17a**, achieving the best stereocontrol and allowed the recovery of the (R)-acetates **18a–e** up to 99% ee in all cases. However, CAL-B showed lower stereopreference values [28].

Chenvert *et al.* reported the total synthesis of enterolactone **25** using lipase PS-catalyzed esterification of diol **21**, prepared from reduction of diester **20**. The lipase was (R)-selective with high enantio excess of the product. This synthesis was completed in 5 steps, including the hydroxyl group mesylation of compound **22**, replacement of mesylate with cyanide, hydrolyzation of cyanide, ring closing, alkylation in **24** and finally deprotection to give enterolactone **25** as human lignin (Scheme 6) [5].

Esterification of 3-hydroxy-4-trityloxybutanenitrile **27** in the presence lipase PS-C resulted in the formation of (S)-alcohol **27** and (R)-acetate **28** in good yields and high enantioselectivities. The chiral products (S)-**27** and (R)-**28** has been utilized for the synthesis of enantiomerically pure 1,3-oxazolidine-2-ones (S)-**29** and (R)-**30** as a precursor for the synthesis of β-adrenergic blocking agents and oxazolidinone based antimicrobial agents, respectively (Scheme 7). Other lipases such as CRL, AK, CCL, CAL-B, PS-D and PS were also subjected to this reaction. The E values of all these lipases were more than 200, but PS-C had $E = 1057$ in the shorter period of time than the others [29].

Difluorinated analogue of (+)-eldanolide **34**, a sex pheromone of male *Eldana saccharina*, was synthesized through the lipase-catalyzed reaction and intramolecular radical cyclization. (S)-Enantioselective acylation of (±)-**32** was achieved using lipase PS in the presence of excess amount of vinyl acetate and 2,6-di-*t*-butyl-4-methylphenol (BHT) as the antioxidant in diisopropyl ether (DIPE)

[1] Dihydroquinine.