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Kinetic resolution of (*R*,*S*)-ethyl 2-hydroxyl-4-phenylbutyrate via lipase-catalyzed hydrolysis and transesterification in isooctane

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Abstract

In the enantioselective hydrolysis of (*R*,*S*)-ethyl 2-hydroxy-4-phenylbutyrate ((*R*,*S*)-EHPB) in isooctane or in a biphasic solution, Lipase PS having an enantiomeric ratio (i.e. the E value) of 22 for the (*S*)-enantiomer was screened as the best lipase to produce the remaining (*R*)-ethyl 2-hydroxy-4-phenylbutyrate ((*R*)-EHPB). When (*R*)-2-hydroxy-4-phenylbutanoic acid ((*R*)-HPBA) was the desired product, one might employ Novozym 435, possessing (*R*)-stereoselectivity with $E = 22$, as the biocatalyst. The results of using Lipase PS in the enantioselective transesterification of (*R*,*S*)-EHPB in isooctane indicated that addition of more vinyl acetate (VA) could suppress the hydrolysis side-reaction, leading to an apparent E value >100. The result of $E > 100$ was also found when initial VA concentration was fixed at 80 mM and (*R*,*S*)-EHPB concentrations increased from 5.4 to 190 mM. Vinyl laurate was further selected as the best acyl donor after comparing the enzyme performances among all vinyl esters employed and considering the easiness of product separation in the down-stream process.

Keywords: Kinetic resolution; Lipase; Transesterification; Hydrolysis; (*R*)-ethyl 2-hydroxy-4-phenylbutyrate; (*R*)-2-hydroxy-4-phenylbutanoic acid

1. Introduction

(*R*)-Ethyl 2-hydroxy-4-phenylbutyrate or (*R*)-2-hydroxy-4-phenylbutanoic acid is an important intermediate for the synthesis of several angiotension-converting enzyme inhibitors, e.g. enanlapril or delapril [1]. It can be synthesized from the asymmetric reduction of the prochiral precursor of ethyl 2-oxo-4-phenylbutyrate (EOPB) by microbial transformation [2–5] or by chemically enantioselective hydrogenantion [6–8]. The results in terms of chemical yield (39–92%) and enantiomeric excess (80–99%) for the biotechnological methods are impressive, whereas chemical yields of 70–90% with optical purity of 50–82% were also reported on the basis of chemical methods. Yet, another simple but efficient way of producing (*R*)-EHPB or (*R*)-HPBA is the kinetic resolution of corresponding racemic 2-hydroxy esters with lipases as the biocatalyst.

Enantioselective hydrolysis (*R*,*S*)-EHPB catalyzed by lipases from *Pseudomonas cepacis* has been performed in an aqueous solution [9] or in a membrane reactor consisting of a biphasic solution [10]. For the later, the value $E = 38$ at 25 °C was estimated from the kinetic constants for both substrates. Moreover, a strong product inhibition by the resultant alcohol and acids was observed to decrease the enzyme activity. With VA as an irreversible acylation agent, the lipase-catalyzed resolution of phenylpropionaldehyde cyanohydrin in dichloromethane, giving $E = 22$, with the subsequent synthesis of (*R*)-EHPB was known [11]. The resolution of (*R*,*S*)-2-hydroxyl-4-phenylbutanoic acid using hexanoic anhydride as an irreversible acyl donor in diethylether was later proposed, where $E > 24$ was estimated from the conversion of 60% and optical purity more than 99% for the remaining substrate [12]. A higher enantiomeric excess and yield of the resulting enantiomer, and hence $E = 33$, in methyl *t*-butyl ether was also claimed when VA was employed as the acylation agent [13]. The dynamic kinetic resolution of (*R*,*S*)-EHPB using *P. cepacis* lipase and ruthenium as the catalysts in cyclohexane at 60 °C was also reported, in which a low optical purity of 30% with the yield of 62% at 48 h was obtained [14]. The above results in terms of the E value imply that more studies on improving the enzyme enantioselectivity and hence the optical purity for the desired enantiomer are needed. Therefore in the present report, an enantioselective hydrolysis of (*R*,*S*)-EHPB in isooc-

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Nomenclature

ee_S	enantiomeric excess for the substrate
E	enantiomeric ratio in hydrolysis or the apparent enantiomeric ratio in transesterification estimated from the conversion and ee_S of (*R*,*S*)-EHPB
EOPB	ethyl 2-oxo-4-phenylbutyrate
(*R*)-,(*S*)-, (*R*,*S*)-EHPB	(*R*)-,(*S*)-,(*R*,*S*)-ethyl 2-hydroxy-4-phenylbutyrate, respectively
(*R*)-HPBA	(*R*)-2-hydroxyl-4-phenylbutanoic acid
t	time (h)
$V_{S,h}$, $V_{S,t}$, $V_{S,\text{total}}$	initial rates for the formation of (*S*)-*HPBA* (equal to the depletion rate of (*S*)-EHPB in enantioselective hydrolysis) and (*S*)-EHPB ester as well as depletion of (*S*)-EHPB in enantioselective transesterification, respectively (mM/h)
VA	vinyl acetate
$X_{R,h}$	conversion of (*R*)-EHPB in enantioselective hydrolysis
$X_{S,h}$, $X_{S,t}$, $X_{S,\text{total}}$	conversions for the formation of (*S*)-*HPBA* (equal to the depletion rate of (*S*)-EHPB in enantioselective hydrolysis) and (*S*)-EHPB ester as well as depletion of (*S*)-EHPB (i.e. $X_{S,\text{total}} = X_{S,h} + X_{S,t}$) in enantioselective transesterification, respectively

tane and then in a biphasic solution as shown in the lower part of Scheme 1 was employed for screening the lipase from various sources. In order to maintain the enzyme in high stability in hydrophobic organic solvents, isooctane was selected as the reaction medium. An enantioselective transesterification with hydrolysis side-reaction for (*R*,*S*)-EHPB in isooctane (Scheme 1) was further carried out to study the effect of substrate concentration on the lipase performance. To drive the reaction to completion, various vinyl esters as the acyl donor were employed ([15], and references herein).

2. Material and methods

2.1. Materials

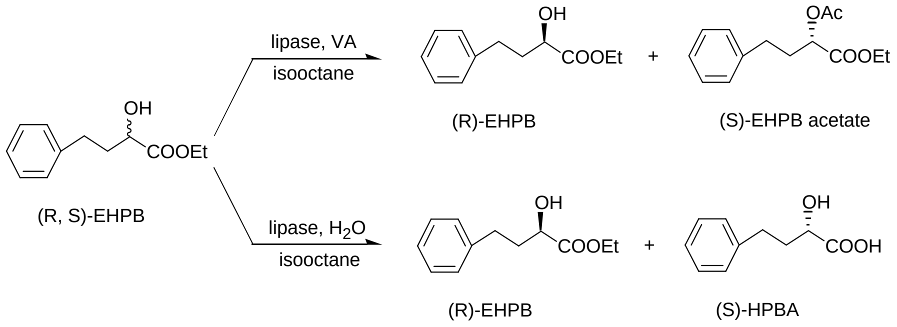
Lipases (triacylglycerol ester hydrolases, EC 3.1.1.3) from various sources were used: Lipase MY from *Candida rugosa* (Meito Sangyo, Tokyo); Lipase PS from *P. cepacia* and Lipase M-AP10 from *Mucor javanicus* (Amano, Nagoya); *Candida rugosa* lipase (Type VII) from Sigma (St. Louis, MO); *Aspergillus niger* lipase from Fluka (Buchs, Switzerland); Novozyme 435 from Novo (Bagsvaerd, Denmark). Other chemicals of analytical grade were commercially available and used without further purification as follows: ethyl 2-oxo-4-phenylbutyrate (EOPB) from Aldrich (Milwaukee, WI); silica gel 60 and hydrochloric acid from Merck (Darmstadt, Germany); isooctane, acetic acid, *n*-hexane, isopropanol, ethyl acetate and tetrahydrofuran from Tedia (Fairfield, OH); sodium borohydride from Sigma; vinyl acetate (VA) and (*R*)-ethyl 2-hydroxy-4-phenylbutyrate ((*R*)-EHPB) from Fluka; vinyl propionate from TCI (Tokyo, Japan); (*R*)-1-phenylethanol, vinyl butyrate, vinyl pivalate, vinyl octanoate, vinyl decanoate and vinyl laurate from Wako (Tokyo, Japan).

2.2. Analysis

Hydrolysis and/or transesterification of (*R*,*S*)-EHPB in isooctane or a biphasic solution were monitored by HPLC using a Chiralcel OD column (Daicel, Japan) capable of separating the internal standard of (*R*)-1-phenylethanol, (*R*)- and (*S*)-EHPB, (*R*)- and (*S*)-EHPB acetate with the retention time as 24.5, 30.2, 19.1, 12.8 and 11.7 min, respectively. The mobile phase was a mixture of *n*-hexane/isopropanol/acetic acid (100/0.8/0.35, v/v) at a flow rate of 1.0 ml/min. UV detection at 254 nm was for quantification at the column temperature of 25 °C.

2.3. Synthesis of (R,S)-EHPB from EOPB

By following a standard procedure, 0.77 g of sodium borohydride in 25 ml of tetrahydrofuran was added drops by drops to 175 ml of tetrahydrofuran containing 4.24 g of EOHP at −10 °C and reacted for 40 min. To the resultant



Scheme 1.

solution was slowly added 10 ml of an aqueous solution containing hydrochloric acid (2 mM) and reacted for 15 min at the room temperature. Hexane of 75 ml was successively employed two times to extract (*R*,*S*)-EHPB from the aqueous phase. The recovered organic phase was collected, then added to 10 ml of the aqueous solution containing 2 mM sodium carbonate at 0 °C with stirring for 5 min. The organic layer was separated, dried over magnesium sulfate, filtered and concentrated under vacuum. After purification in silica gel chromatography with the mobile phase of hexane/ethyl acetate (5/1, v/v) and concentrated by vacuum, the desired (*R*,*S*)-EHPB was obtained and identified from the residence time of authentic compounds in HPLC.

2.4. Enantioselective hydrolysis of (R,S)-EHPB in isooctane and biphasic solution

Unless specified, 5.4 mM of (*R*,*S*)-EHPB and 20 mg of lipases from different sources were added to 1 ml of isooctane containing 11.3 mM of saturated deionized water at pH 6.8 at 37 °C [16]. Samples were removed at 12 h and injected onto the above HPLC system for analysis, with which a suitable lipase was selected and employed in the following experiments. A similar experiment was carried out except that 15 ml of isooctane and Lipase PS were employed with samples withdrawn at different time intervals. From the time-course conversions of (*R*)- and (*S*)-EHPB, the initial rate of (*S*)-EHPB and *E* value were estimated [17]. An enantioselective hydrolysis in a biphasic solution was also performed where 2 ml of deionized water was added to the above reaction system.

2.5. Enantioselective transesterification of (R,S)-EHPB in isooctane

To 15 ml of isooctane was added 5.4 mM of (*R*,*S*)-EHPB, VA of concentrations varied from 5 to 200 mM and 20 mg/ml of Lipase PS that has been lyophilized for 8 h. The resultant solution was stirred with a magnetic stirrer at 37 °C. Samples were removed and injected onto above HPLC system at different time intervals for analysis. From the time-course results, the initial rates for the acetate product and acid byproduct of the (*S*)-substrate were estimated. The apparent *E* value was further estimated from the conversion and enantiomeric excess ee_s of the racemic substrate [17]. Similar experiments were carried out except that 80 mM of VA and (*R*,*S*)-EHPB concentrations varied from 5.4 to 190 mM were employed. In order to study the effect of carbon length of the acyl donor on the lipase performance, similar experiments with VA replaced with other vinyl esters were performed.

3. Results and discussion

3.1. Enantioselective hydrolysis of (R,S)-EHPB in isooctane and biphasic solution

Table 1 demonstrated the enantioselective hydrolysis of (*R*,*S*)-EHPB in isooctane saturated with deionized water at 37 °C for the lipase from various sources. For all lipases possessing (*S*)-stereoselectivity, Lipase PS was screened as the best lipase according to the enzyme activity and *E* value. On the contrary, only Novozym 435 showed (*R*)-stereoselectivity with $E = 22$. Since (*R*)-EHPB was the desired product, Lipase PS was selected as the biocatalyst in the following experiments. However, if (*R*)-HPBA was desired, one might select Novozym 435 as the biocatalyst in the kinetic resolution of (*R*,*S*)-EHPB.

Fig. 1 illustrated typical time-course conversions of (*R*)- and (*S*)-EHPB (i.e. $X_{R,h}$ and $X_{S,h}$, respectively) in isooctane, from which an initial rate of 8.91 mM/h for (*S*)-EHPB was estimated. An equilibrium conversion of $X_{S,h} = 0.75$ was also shown, which might be attributed to the limited water content for the hydrolysis in isooctane. When a biphasic solution was employed as the reaction medium, similar lipase performances as in isooctane were illustrated in Fig. 1. However, a higher equilibrium conversion of $X_{S,h} = 0.93$ was obtained, owing to more water available for hydrolysis and products extracted into the aqueous phase to shift the equilibrium to the product side. Therefore, a biphasic solution is suggested as the reaction medium for the enantioselective hydrolysis of (*R*,*S*)-EHPB in the future.

Table 1
Effects of lipase sources on the enantioselective hydrolysis of (*R*,*S*)-EHPB in isooctane saturated with deionized water at 12 h

Lipases	$X_{S,h}$	$X_{R,h}$	ee_s	E	Stereoselectivity
Lipase PS[a]	0.70	0.05	0.52	22	S
Lipase M-AP10	0.30	0.10	0.04	2	S
Lipase MY	0.44	0.23	0.16	2	S
C. rugosa lipase[b]	0.31	0.06	0.16	6	S
M. javanicus lipase	0.19	0.11	0.05	2	S
A. niger lipase	No reaction				
Novozym 435[c]	0.11	0.92	0.84	22	R

Conditions: concentrations of lipase and (*R*,*S*)-EHPB as 20 mg/ml and 5.4 mM, respectively, at 37 °C.

[a] At 0.5 h.

[b] At 3.0 h.

[c] Lipase concentration of 80 mg/ml.

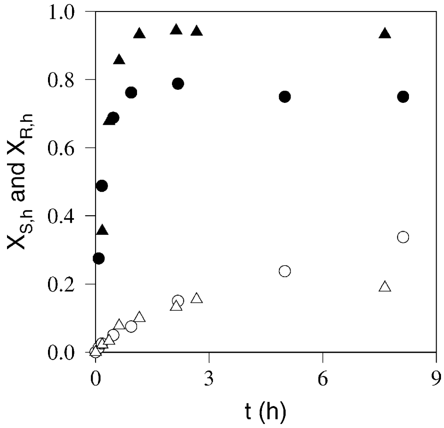


Fig. 1. Time-course conversions of (*R*)- and (*S*)-EHPB in the enantioselective hydrolysis in isooctane ($X_{S,h}$, (●); $X_{R,h}$, (○)) and in a biphasic solution ($X_{S,h}$, (▲); $X_{R,h}$, (△)); concentrations of lipase and (*R*,*S*)-EHPB as 20 mg/ml and 5.4 mM, respectively, at 37 °C.

3.2. Enantioselective transesterification of (R,S)-EHPB with VA in isooctane

Fig. 2 illustrated typical time-course conversions of (*S*)-EHPB substrate (i.e. $X_{S,\text{total}}$) and those for the (*S*)-EHPB acetate product (i.e. $X_{S,t}$) in isooctane. Thus, the time-course conversions of (*S*)-HPBA byproduct (i.e. $X_{S,h} = X_{S,total} - X_{S,t}$) due to hydrolysis side-reaction might be estimated from the difference of $X_{S,\text{total}}$ and $X_{S,t}$. At the low VA concentration of 5 mM, a lower conversion of $X_{S,t}$ (and hence the initial transesterification rate of (*S*)-EHPB, i.e. $V_{S,t}$) in comparison with $X_{S,h}$ (and hence the initial rate for the hydrolysis side-reaction of (*S*)-EHPB, i.e. $V_{S,h}$) at any specific time were found. Increasing VA concentration to 200 mM (Fig. 2) resulted in the enhancement of $X_{S,t}$ and $X_{S,\text{total}}$, and then the suppression of $X_{S,h}$ when comparing with the results for VA concentration of 5 mM. Moreover, an apparent *E* value increasing from 35 to >100 was obtained. This implied that Lipase PS has high enantioselectivity (i.e. $E > 100$) when using (*R*)- and (*S*)-EHPB as acyl acceptors in transesterification, but not as acyl donors in hydrolysis side-reaction.

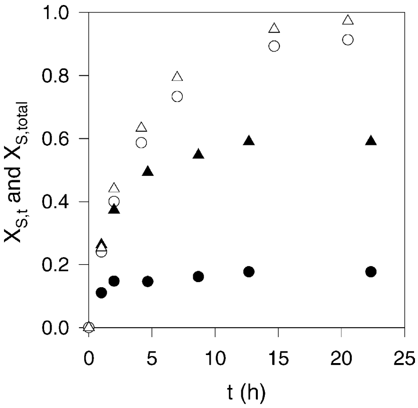


Fig. 2. Time-course yields of (*S*)-EHPB acetate and conversions of (*S*)-EHPB in isooctane for VA concentration of 5 mM ($X_{S,t}$, (●); $X_{S,\text{total}}$, (○)) and 200 mM ($X_{S,t}$, (▲); $X_{S,\text{total}}$, (△)); concentrations of lipase and (*R*,*S*)-EHPB as 20 mg/ml and 5.4 mM, respectively, at 37 °C.

Table 2
Effects of VA concentration on the initial rate for the depletion of (*S*)-EHPB formation and percents of the initial rate for the formation of (*S*)-*HPBA* byproduct and (*S*)-EHPB acetate in enantioselective transesterification (results for enantioselective hydrolysis at VA concentration of zero also included)

VA concentration (mM)	$V_{S,\text{total}}$ (mM)	$V_{S,h}$ (%)	$V_{S,t}$ (%)	*E*
0	8.910	100	0	22
5	0.9080	58.6	41.4	35
15	0.6890	29.5	70.5	64
25	0.8440	22.9	77.1	>100
50	0.8800	10.2	89.8	>100
70	0.7890	8.2	91.8	>100
80	0.7610	7.2	92.8	>100
200	0.6330	1.5	98.5	>100

Conditions: concentrations of lipase and (*R*,*S*)-EHPB as 20 mg/ml and 5.4 mM, respectively, at 37 °C.

Table 2 demonstrated the suppression of initial rate $V_{S,h}$ for hydrolysis side-reaction when VA concentration increased from 5 to 200 mM. One might attribute this behavior to the mass action effect among VA, (*S*)-EHPB and (*R*)-EHPB in binding the lipase to form enzyme-substrate complexes in the acylation step for the lipase-catalyzed reactions. A maximum $V_{S,t}$ of 0.790 mM/ml at VA concentration of 50 mM was found, which might be due to the substrate inhibition effect. However, since vinyl acetate also played an important role as an acyl donor for hydrolysis [18], the formation of acetic acid might also affect the microenvironment of lipase active center to decrease the transesterification rate at high VA concentrations. As the remaining (*R*)-EHPB was the desired enantiomer, the result in terms of apparent *E* values in Table 2 indicated that VA concentration higher than 25 mM was needed for obtaining high enantioselectivity.

In order to increase the productivity of (*R*)-EHPB, similar reactions at VA concentration of 80 mM and (*R*,*S*)-EHPB concentration varied from 5.4 to 190 mM were carried out. Table 3 demonstrated the enhancement of initial rates of

Table 3
Effects of (*R*,*S*)-EHPB concentration on the initial rates for the formation of (*S*)-*HPBA* and (*S*)-EHPB acetate as well as depletion of (*S*)-EHPB in enantioselective transesterification

(*R*,*S*)-EHPB concentration (mM)	$V_{S,\text{total}}$ (mM/h)	$V_{S,h}$ (%)	$V_{S,t}$ (%)
5.4	0.761	7.2	92.8
21	1.915	11.1	88.9
42	2.505	14.3	85.7
89	3.724	26.0	74.0
124	4.084	28.9	71.1
190	4.799	32.0	68.0

Reaction conditions: concentrations of lipase and VA as 20 mg/ml and 80 mM, respectively, at 37 °C.

Table 4
Effects of various vinyl esters on enantioselective transesterification of (*R*,*S*)-EHPB

Vinyl esters	$V_{S,\text{total}}$ (mM/h)	$X_{S,\text{total}}$ (time, h)	E
Vinyl acetate	0.76	0.885 (12.5 h)	>100
Vinyl propionate	0.51	0.843 (11.7 h)	>100
Vinyl butyrate	0.57	0.891 (12.5 h)	>100
Vinyl pivalate	0.32	0.297 (12.1 h)	10
Vinyl octanoate	0.89	0.968 (12.5 h)	>100
Vinyl decanoate	1.08	1.00 (14.1 h)	>100
Vinyl laurate	1.16	1.00 (14.1 h)	>100

Reaction conditions: concentrations of lipase, (*R*,*S*)-EHPB and vinyl ester as 20 mg/ml, 5.4 and 80 mM, respectively, at 37 °C.

$V_{S,h}$ and $V_{S,t}$, and hence the initial rates of $V_{S,\text{total}}$, with the substrate concentration. However, the enhancement for the percentage of $V_{S,h}$ with (*R*,*S*)-EHPB concentration implied that (*S*)-EHPB acted as a better acyl donor in hydrolysis side-reaction than an acyl acceptor in transesterification. The high enantiomeric ratio of $E > 100$ for any system in Table 3 was found. Yet, the reason for the improved enantioselectivity in the hydrolysis side-reaction was unclear. Then, a detailed study on controlling the water activity of the reaction medium in studying the enhancement of E value in enantioselective hydrolysis and transesetrification is needed [19].

A successful enantioselective transesterification should further consider the easiness of product separation in the down-stream processing. In order to enlarge the difference of physical properties between (*R*)-EHPB and (*S*)-EHPB acetate, vinyl acetate was replaced with other vinyl esters containing longer carbon chain in the acyl moiety of the esters. Table 4 indicated that vinyl esters with a straight carbon chain yielded $E > 100$, whereas a slight enhancement of the initial rate of $V_{S,\text{total}}$ was shown as the carbon number increased from 3 to 12. However, low lipase activity and enantioselectivity for vinyl pivalate was found. Thus one might not use vinyl esters containing a branched carbon chain as the acyl donor for Lipase PS. After considering the lipase performance and the easiness in separating (*S*)-EHPB laurate from (*R*)-EHPB by vacuum distillation [20], vinyl laurate was selected as the best acylation agent.

4. Conclusions

A kinetic resolution process for producing (*R*)-ethyl 2-hydroxy-4-phenylbutyrate from (*R*,*S*)-ethyl 2-hydroxy-4-phenylbutyrate by using lipase-catalyzed hydrolysis in isooctane and in a biphasic solution was first investigated. The results indicated that Lipase PS was the best lipase, although the (*S*)-stereoselectivity with $E = 22$ was still not good enough. When (*R*)-2-hydroxy-4-phenylbutanoic acid was the desired enantiomer, one might employ Novozym 435, having (*R*)-stereoselectivity with $E = 22$, as the biocatalyst.

The results from the enantioselective transesterification of (*R*,*S*)-EHPB in isooctane using Lipase PS as the biocatalyst indicated that the hydrolysis side-reaction was imperative to decrease the conversion and optical purity of (*R*)-EHPB. This disadvantage could be relaxed by adding more vinyl acetate to the reaction medium, leading to $E > 100$. When VA concentration was fixed at 80 mM, the productivity and optical purity with $E > 100$ for (*R*)-EHPB was improved by increasing the (*R*,*S*)-EHPB concentration from 5.4 to 190 mM. By comparing the lipase performance for various vinyl esters and considering the easiness of product separation by vacuum distillation, vinyl laurate was selected as the best acylation donor.

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