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Lipase-Catalysed Transesterification in the Preparation of Optically Active Monobutyrate of *cis*-2,3-Epoxybutane-1,4-diol

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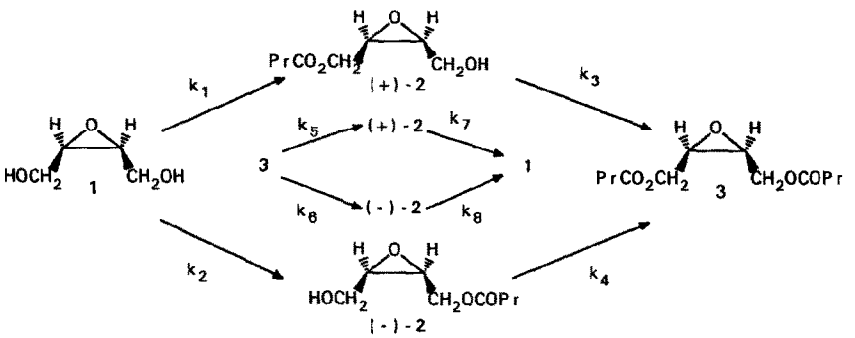
Abstract: The PPL-catalysed resolution of 4-hydroxy-2,3-epoxybutyl butyrate resulted in the (2*S*,3*R*)-(-)-enantiomer with high optical purity (>90% e.e.). The two acylation (or deacylation) steps from diol to dibutyrate (or from dibutyrate to diol) were shown to have reverse stereoselectivities.

Since the discovery that enzymes can work in organic solvents as well as in aqueous media, lipase-catalysed esterifications and transesterifications have gained increasing value in resolving racemic alcohols and carboxylic acids[1]. Epoxyalcohols are important target molecules in the synthesis of natural products. The enzyme-catalysed resolution of racemic compounds is one of the best alternatives for the preparation of optically active *cis*-epoxyalcohols[2-7].



Scheme 1

(2*R*,3*S*)-(+)-4-Hydroxy-2,3-epoxybutyl butyrate (**2**) - a possible starting material for pheromone syntheses[7,8] - has been previously prepared using enzymatic hydrolysis of the *meso*-dibutyrate **3**[5,6]. It has also been reported that enzymatic transesterification of the *meso*-diol **1** with vinyl butyrate leads to the same monobutyrylated (+)-enantiomer with low yield and enantiomeric purity (*ca.* 50% e.e.)[6]. In this work, we have performed a detailed study on the PPL-catalysed acylation of **1**[9] (0.1 M) with 2,2,2-trifluoroethyl butyrate (0.3 M) in THF (outer arrows of Scheme 1) as well as on the PPL-catalysed deacylation of **3** (0.2 M) with 1-hexanol in 1-hexanol (inner arrows of Scheme 1). The PPL-catalysed resolution of racemic **2** (0.1 M) with 2,2,2-trifluoroethyl butyrate (0.3 M) or 1-hexanol has also been

performed. PPL (porcine pancreatic lipase, type II, Sigma) was proven to be a useful biocatalyst in the preparation of optically active epoxyalcohols[2-7].

The use of a Chirasil-L-Val column in GLC allowed us routinely to follow the enantiomeric purity of the product **2** with time. In this method, the enantiomeric excess of samples taken from the reaction mixture at intervals can be directly analyzed[10]. The enantioselectivity results for the desymmetrization of **1** and **3** as the reaction proceeds are shown in Figures 1 and 2, respectively.

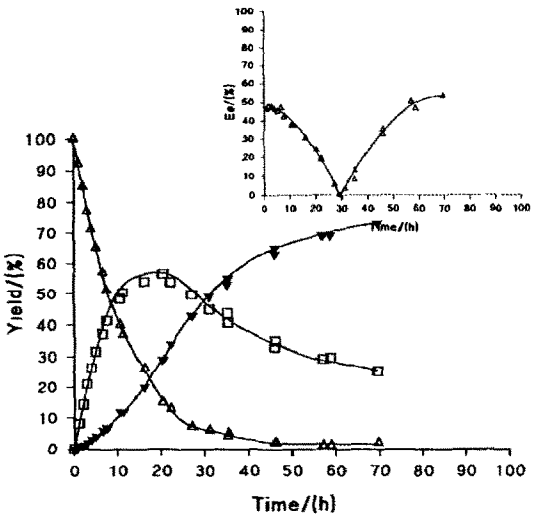


Figure 1.The progress of the butyrylation of **1** with time. **1** (△), **2** (□) and **3** (▾) Insert: Enantiomeric composition of **2** with time.

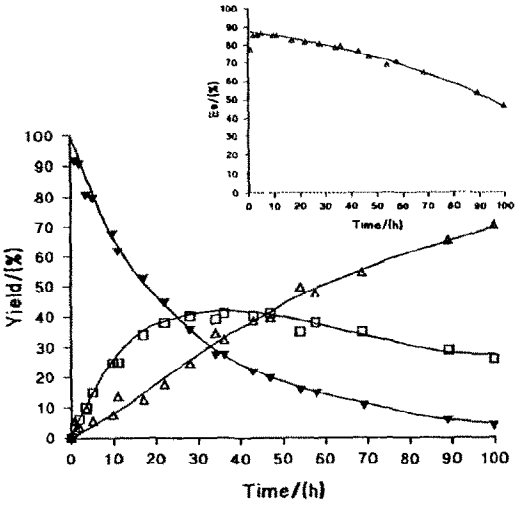


Figure 2. The progress of the debutyrylation of **3** with time. **1** (△), **2** (□) and **3** (▾). Insert: Enantiomeric composition of **2** with time.

The acylation of **1** with 2,2,2-trifluoroethyl butyrate results in the kinetic ratio 2.8 for $\alpha = k_1/k_2$. The low value of that ratio is the primary reason to the low optical purity of (2*R*,3*S*)-(+)-**2** initially observed (*ca.* 50% e.e. at best, Figure 1)[11]. In the acylation of **1** to **3**, the two acylation steps proceed approximately at the same rate. Furthermore, the results of Figure 1 (insert) clearly demonstrate the change of the major (2*R*,3*S*)-(+)-enantiomer to prevailing (2*S*,3*R*)-(−)-**2** through a racemic mixture with time. Thus, in the butyrylation of **1** through **2** to **3** $k_3 > k_4$ is expected. This is opposite to the general expectation that the enzyme should show the same stereochemical preference in the second acylation step (as well as in the second deacylation step) of a *meso*-compound (*i.e.* $k_4 > k_3$), and as a consequence the optical purity of the monoacetate should further be enhanced by the kinetic resolution which follows[12-15].

The kinetic consideration of the PPL-catalysed resolution of racemic **2**[16] with 2,2,2-trifluoroethyl

butyrate to **3** results in the enantioselectivity ratio[17] $E = k_3/k_4 = 21$ in THF (Table 1). The resolution in the other solvents proceeds slowly and with low enantioselectivity. Thus, in the resolution of **2** through an acylation reaction, PPL shows a preferred (*S*)-selectivity. This is a strong indication for the different enantioselectivities of PPL catalysis in the two acylation steps (Scheme 1; Figure 1).

The PPL-catalysed reaction between **1** and **3** in THF is significant, resulting in (2*R*,3*S*)-(+)-**2** with 66% e.e. and 25% yield within 17 hours. On the other hand, the resolution of (±)-**2** with **3** under the same conditions is unsuccesful. These results further confirm the *pro*-(*R*)-selectivity for the acylation of **1** and (*S*)-selectivity for the acylation of **2**.

In the PPL-catalysed debutyrylation of **3**[18] with 1-hexanol (inner arrows of Scheme 1), 1-hexanol was used also as a solvent to make the reaction virtually irreversible. In this case, the enantioselectivity of the desymmetrization step is relatively high ($\alpha = k_5/k_6 = 14$, Figure 2) whereas that of the resolution is opposite and negligible ($E = k_7/k_8 = 3$, Table 1). Thus, in spite of almost equal rates of the two deacylation steps, the drop of e.e. of (2*R*,3*S*)-(+)-**2** now stays negligible with time (Figure 2, insert) while the yield of **2** is only approximately 40 % at its best.

Table 1. The PPL-catalysed kinetic resolution of **2**.

Solvent	Substrate	Conversion/%	Time/h	E	Product
THF	$PrCO_2CH_2CF_3$	54[a]	28	21	(2*S*,3*R*)-**2**
Toluene	$PrCO_2CH_2CF_3$	12[a]	54	9	(2*S*,3*R*)-**2**
1-Hexanol	$CH_3(CH_2)_5OH$	58[b]	70	3	(2*R*,3*S*)-**2**

Enzyme concentration [a]5 mg/ml; [b]30 mg/ml

The reverse stereochemical preference observed for the two consecutive acylation (or deacylation) steps of Scheme 1 may be attributed to the different hydrolytic enzymes in crude PPL . On the other hand, THF is an unfavourable solvent for the catalytic activity of most enzymes. That is the case, *e.g.*, for α-chymotrypsin which is one of the main impurities of PPL[18]. The same reversal of enantioselectivity, and consequently the similar dependence of e.e. with time (the insert in Figure 1) was observed also in the lipase PS (*Pseudomonas cepacia*, Amano)- and SAM 2 (*Pseudomonas fluorescens*, Fluka)-catalysed acylations of **1** in THF, the value of α being 2 in the both cases.

Encouraged by the relatively high E value of 21 for the PPL-catalysed butyrylation of racemic **2** with 2,2,2-trifluoroethyl butyrate in THF a gram-scale preparation of (2*S*,3*R*)-(-)-**2** was performed. A solution of **2** (1.66 g, 9.5 mmol) and 2,2,2-trifluoroethyl butyrate (4.85 g, 29 mmol) in 95 ml of THF was added on 0.475 g of PPL. After 28 h the reaction was stopped at 54% conversion by filtering off the enzyme. The evaporation of the solvent followed by flash chromatography[19] with ethyl acetate:hexane (1:9) as an eluent resulted in 1.2 g (4.6 mmol; 52% of the theory) of the dibutyrate **3**. The subsequent elution with ethyl acetate gave 0.76 g (4.3 mmol; 46% of the theory) of unreacted **2** with the optical rotation

$[\alpha]_D^{25}$ = −14 (*c* 0.8, CH_2Cl_2) and with 93% e.e. according to the chiral GLC.

As a conclusion, the PPL–catalysed resolution of **2** with 2,2,2–trifluoroethyl butyrate is a suitable method to prepare (2*S*,3*R*)–(−)–**2** with high optical purity of more than 90% e.e To prepare (2*R*,3*S*)–(+)–**2**, the PPL–catalysed hydrolysis of **3** is the best method[5]. The reverse stereoselectivity of the two acylation (or deacylation) steps observed for the desymmetrization of **1** (or **3**) followed by the resolution of **2** leads to the lowering of optical purity of **2** obtained (Figures 1 and 2).

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9. The diol **1** was prepared from (Z)–2–butene–1,4–diol by epoxidation with 36% aqueous hydrogen peroxide using tungstic acid as a catalyst.
10. At 120 °C with N_2 as a carrier gas (flow rate 0.9 ml/min) the retention times for (2*S*,3*R*)–(−)– and (2*R*,3*S*)–(+)–**2** are 11.13 and 11.66 minutes, respectively
11. Absolute configurations of **2** are based on the specific rotations observed in this work, on the value of $[\alpha]_D^{24}$ = +17.9 (*c* 0.81, CH_2Cl_2) observed for (+)–(2*S*,3*R*)–**2** (ref. 5) and on the GLC results.
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