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Biocatalytic Resolution of 2,3-Epoxyalcohols in Organic Solvents

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Abstract: The PPL-catalysed resolution of 3-substituted *cis*-2,3-epoxyalcohols has been successfully performed in toluene and in THF. Lower enantioselectivities were observed for the *trans*-isomers. A substituent at the position 3 of an epoxyalcohol controls the enantiomeric discrimination, the 3*R* centre always occuring in the enantiomer which reacts faster.

Introduction

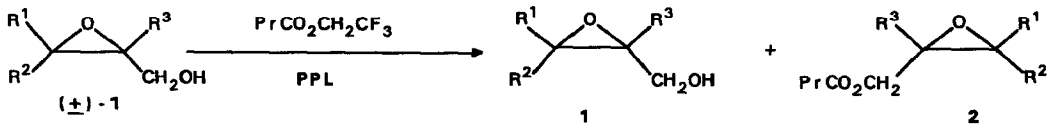
The capabilities of ester hydrolases for enantiomeric differentiation are well known. A good example of this is the production of (*R*)-(-)-glycidyl butyrate through the porcine pancreatic lipase (PPL)-catalysed hydrolysis of racemic glycidyl butyrate[1]. Lipases are known to catalyse ester hydrolysis through an acyl-enzyme mechanism, and the mechanism of enzymatic catalysis is essentially independent of the reaction medium[2,3]. Thus, the acyl group of an acyl-enzyme intermediate formed under anhydrous conditions can be transferred to suitable nucleophiles such as primary and secondary alcohols[4,5]. In organic solvents, the enzymatic resolution of racemic primary alcohols often exhibits a low enantioselectivity[6]. Accordingly, the low enantioselectivity of PPL catalysis (E<5) has been detected for the reaction of (±)-**1a** with vinyl esters in chloroform[7,8]. Similarly, the PPL-catalysed transesterification of racemic glycidyl butyrate with 1-alcohols resulted in the low values of E<5[9].

Many derivatives of optically active 2,3-epoxyalcohols are important synthons for the syntheses of biologically active or pharmaceutically important compounds. The Sharpless asymmetric epoxidation of allylic alcohols is one of the most versatile methods for the preparation of optically active epoxyalcohols[10]. A good alternative to the Sharpless reaction is the enzyme-catalysed resolution of epoxyalcohols[1,11-14]. The PPL-mediated hydrolysis of a number of acylated 3-substituted 2,3-epoxyalcohols has revealed greater enantioselectivity for the *trans*- than for the corresponding *cis*-isomers [1,11,12]. In this work, a systematic study on the utility of lipase catalysis in the preparative resolution of the *cis*- and *trans*-2,3-epoxyalcohols (±)-**1e-k** (Scheme 1) with 2,2,2-trifluoroethyl butyrate in organic solvents has been performed.

Results and Discussion

Among the lipases tested, PPL indicated the best combination of activity and selectivity in the transesterification between the 2,3-epoxyalcohols **1a-k** and 2,2,2-trifluoroethyl butyrate in organic solvents. The pure enantiomers for the alcohols **1a-c** are commercially available, enabling the

determination of the enantioselectivity ratio v_o^R/v_o^S or v_o^{RR}/v_o^{SS}. The results are summarized in Table 1. Thus, the initial rates v_o^R and v_o^S for the enantiomers of **1a** (0.1 M) were measured to be 0.48 and 0.27 μmol s^{-1} g^{-1}, respectively, at 7 mg ml^{-1} of PPL at the reaction with 2,2,2-trifluoroethyl butyrate (0.2 M) in *tert*-amyl alcohol. This result leads to the value of the enantioselectivity ratio of only 1.8. Similar low enantioselectivities were also observed for the butyrylation of the alcohols **1b** and **c**.



				Configuration	
(±)-1	R^1	R^2	R^3	1	2
a	H	H	H	(S)	(R)
b	H	H	Me	(S)	(R)
c	Ph	H	H	(2S,3S)	(2R,3R)
d	H	Ph	H	-	-
e	Pr	H	H	(-)-(2S,3S)	(+)-(2R,3R)
f	H	Pr	H	(+)-(2R,3S)	(-)-(2S,3R)
g		H	H	(-)-(2S,3S)	(+)-(2R,3R)
h	H		H	(+)-(2R,3S)	(-)-(2S,3R)
i		Me	H	(-)-(2S,3S)	(+)-(2R,3R)
j	Me		H	(+)-(2R,3S)	(-)-(2S,3R)
k	H	$PrCO_2CH_2$	H	(-)-(2S,3R)	-

Scheme 1.

It has been previously shown that the enzyme enantioselectivity in nonaqueous media can be controlled by the solvent, and PPL is one of the most suitable of the lipases to be tested in that respect because it is catalytically active in a number of water-miscible and water-immiscible organic solvents[15,16]. Thus, the ratio v_o^R/v_o^S for the PPL-catalysed transesterification of 1-phenylethanol with vinyl butyrate has been shown to decrease from the value 75 in nitromethane to the value 35 in *tert*-amyl alcohol and to 6 in decane[15]. However, the values of the enantioselectivity ratios of Table 1 for PPL catalysis clearly demonstrate that not only the two enantiomers of the alcohols **1a-c** react with almost equal rates with 2,2,2-trifluoroethyl butyrate, but also the values of the ratios are practically independent of the solvent. Only in the PPL-catalysed butyrylation of **1c**, a somewhat better enantioselectivity is achieved in THF than in the other solvents screened.

Table 1. Enantioselectivity ratios for the PPL–catalysed butyrylations of the enantiomers of **1a–c**.

Solvent	**1a** v_0^R/v_0^S	**1b** v_0^R/v_0^S	**1c** v_0^{RR}/v_0^{SS}
Toluene	1.2	1.2	0.8
3-Methyl-3-pentanol	1.2	1.3	1.2
Ethyl butyrate[a]	1.7	1.4	1.3
Triethylamine	1.2	0.9	–
tert-Amyl alcohol	1.8	1.2	1.1
Tetrahydrofuran	1.0	1.0	3.0
Acetonitrile	1.3	1.0	1.0

[a] the solvent and the substrate

Table 2. PPL–catalysed kinetic resolution of (±)-**1d–k**.

Compound	Solvent	Time /h	Conversion /%	**1d–k** ee /%	**1d–k** $[\alpha]_D^{25,a}$	**1d–k** Yield /%	**2d–k** ee /%	**2d–k** $[\alpha]_D^{25,a}$	**2d–k** Yield /%	E
(±)-**1d**	Toluene	18	42		0	62		0	40	1
(±)-**1e**	Toluene	18	55	11	−6.9	39	–	+6.9	24	1.3
	THF	18	57	16	−6.9	37	–	+6.5	37	1.5
(±)-**1f**	Toluene	17	50	66	+2.9	49	77	−9.6	49	9.5
	THF	19	61	90	+4.3	40	64	−7.5	65	11
(±)-**1g**	Toluene	11	40	34	−8.9	56	30	+13.3	42	4.2
	THF	11	60	65	−17.6	48	35	+14.0	62	4.7
(±)-**1h**	Toluene	22	51	80	+2.4	41	81	−6.8	52	19
	THF	8	54	90	+2.5	43	82	−6.6	56	23
(±)-**1i**	Hexane	18	33	26	−1.4	29	43	+13.3	22	4.1
	Toluene	16	66	68	−3.5	32	51	+10.0	36	4.0
	THF	4	60	59	−3.2	29	37	+14.2	21	4.0
(±)-**1j**	Toluene	28	47	71	+14.4	49	86	−20.8	46	19
	THF	19	50	79	+16.2	50	88	−21.4	41	20
	THF	42	55	>>95[b]	+19.7	42	78	−18.4	58	>29
(±)-**1k**[c]	THF	28	55	93	−13.9[d]	46				21

[a](*c* 2–7, $CHCl_3$); [b]According to GLC only one enantiomer is detected; [c]Ref. 14; [d](*c* 0.8, CH_2Cl_2).

Assuming that the different behaviour of PPL catalysis in the resolution of (±)-**1a** through the hydrolysis of glycidyl butyrate[1] on the one hand and through transesterification[7,9] (Table 1) on the other hand is due to the similarity of the substituents at the asymmetric centre of the reagent and to the conformational rigidity of enzymes in organic solvents, the greater enantioselectivity can be expected in the case of suitably substituted glycidols. Based on this assumption, the PPL–catalysed butyrylations of the

3–substituted 2,3–epoxyalcohols (±)–**1d–k** were performed in toluene and in THF. The results are shown in Table 2. When R^1 or R^2 at the position 3 is a phenyl group (**1c** and **d**, Tables 1 and 2, respectively) the resolution is unsuccessful while an aliphatic R^1 or R^2 substituent (straight or branched chain, saturated or unsaturated) enhances the enzymatic enantioselectivity. This enhancement is clearly more pronounced with increasing size of the substituent R^1 or R^2 as can be seen by comparing the E values of Table 2 for **1e**, **g** and **i** or for **1f**, **h** and **j**. Furthermore, the results of Table 2 clearly demonstrate considerably higher E values for the *cis*–epoxyalcohols **1f**, **h** and **j** than for the corresponding *trans*–counterparts. This favour of the *cis* over *trans* stereochemistry is opposite to that found for the Sharpless epoxidation of allylic alcohols as well as for the PPL–catalysed enantioselective hydrolysis of the esters of 3–substituted 2,3–epoxyalcohols[1,10–12]. Thus, the PPL–catalysed resolution of 2,3–epoxyalcohols by acylation in organic solvents is a usable method for the preparation of optically active *cis*–stereoisomers.

The absolute configurations for the resolution products of Table 2 are shown in Scheme 1. According to the kinetic data of Table 1, it is obvious that PPL shows an (*R*)–over (*S*)–specificity in the butyrylations of (±)–**1a–c** except the case of *trans*–3–phenylglycidol in toluene where the reversed enantioselectivity is observed. According to the specific rotations, $[\alpha]_D$, observed in this work (Table 2) and to the results of the Sharpless epoxidations of *trans*–2–hexenol, geraniol and nerol the absolute configurations of **1e**, **i** and **j** (as well as **2e**, **i** and **j**) are known[10b,c]. The other configurations of Scheme 1 are based on the analogy with the above results and with the absolute configurations of the products obtained in the PPL–catalysed resolutions of *cis*– and *trans*–2,3–epoxypentanols[11], *cis*–2,3–epoxytridecanol[13] and *cis*–2,3–epoxy–8–methylnonanol[13] by hydrolysis or transesterification[17]. In accordance with the earlier proposals there is not one simple active site model for PPL which could universally explain all asymmetric synthetic applications of the enzyme[18].

As is shown in Scheme 1, the PPL–catalysed butyrylations of (±)–**1c–j** tend to take place so that the 3*R* centre always occurs in the optically active reaction products **2c–j**. This indicates the importance of the controlling effect of the substituent R^1 or R^2 on the enantiomeric discrimination. This effect is more important in the case of the *cis*–isomers as indicated by the higher enantioselectivity of PPL catalysis observed (Table 2). PPL also catalyses the butyrylations of the *cis*–isomers more effectively than the transformations of the corresponding *trans*–isomers. Moreover, for the butyrylations of **1c–j** PPL works with somewhat higher enantioselectivity and catalytic activity in THF than in toluene. This solvent effect is more evident for the PPL–catalysed butyrylation of **1k**[14]. This predicts the importance of the partition of the hydrophobic side chain at the 3*R* centre into a hydrophobic binding pocket of the enzyme in more hydrophilic THF. It is also worth noticing that if (±)–**1k** is viewed as a glycidol derivative rather than as a butyrate, the butyryloxymethyl substituent (then at the carbon atom 3) causes the same proper stereochemical steering effect as the aliphatic hydrocarbon substitents, the "3*R* centre" occuring in the *meso*–dibutyrate formed. The stereoselectivity reversal observed for the two acylation steps from diol to dibutyrate through the monobutyrate **1k** by PPL–catalysis is also worth mentioning[14]. Similar reversing

influence on the enzymatic enantioselectivity has been noted also in the case of some other heterocyclic *meso*-compounds[19].

In conclusion, the kinetically controlled resolution of 2,3-epoxyalcohols using PPL-catalysed acylation in organic solvents is a versatile method for the preparation of optically active *cis*-epoxyalcohols with high optical purity (Table 2). This enzymatic approach in organic solvents is complementary to the PPL-catalysed hydrolysis of the esters of 2,3-epoxyalcohols[1,11,12] as well as to the Sharpless epoxidation of allylic alcohols[10] in that the two last-mentioned methods usually give a lower enantioselectivity for the formation of optically active *cis*-isomers compared to the corresponding *trans*-counterparts.

Experimental

Materials. Porcine pancreatic lipase (type II, Sigma) was used as received. The solvents were of the best analytical grade and were dried over molecular sieves (3 Å) overnight before the use. 2,2,2-Trifluoroethyl butyrate was prepared from butyric anhydride and 2,2,2-trifluoroethanol. The pure enantiomers of glycidol, 2-methylglycidol and *trans*-3-phenylglycidol were the products of Aldrich. Racemic **1d-j** were prepared from the corresponding *cis*- and *trans*-allylic alcohols by epoxidation with 36% aqueous hydrogen peroxide using tungstic acid as a catalyst[20,21]. To that purpose, *trans*-2-nonenol was obtained by converting 1-octyne first to 2-nonynol which was then reduced by $LiAlH_4$[22,23]. *Cis*-cinnamic alcohol and *cis*-2-nonenol were prepared from phenyl acetylene and 1-octyne, respectively, by converting them to 2-alkynols followed by hydrogenation (H_2, $Pd/BaSO_4$)[24]. The other allylic alcohols were commercially available. (±)-**1k** was prepared as previously described[14].

Methods. Initial rates and the progress of the reactions were determined by taking samples from the reaction mixture at intervals and analysing them by GLC[16]. The e.e. values for **1e** as a Mosher ester and for **1f-h** and **1j-k** as such were determined using GLC equipped with a 25 m Chirasil-L-Val capillary column. In the case of **1i**, the enantiomeric composition was obtained by ^1H NMR (80 MHz) as an acetylated derivative in the presence of $Eu(hfc)_3$. The corresponding compounds **2f-j** were hydrolysed with K_2CO_3 (0.5 M) in methanol/water (70/30) before the e.e. determination by the methods mentioned above.

Enzymatic transesterification. Typically, 50-85 ml of a solution of an epoxyalcohol (0.1 M) and 2,2,2-trifluoroethyl butyrate (0.2 M) in an organic solvent was added on 4-15 mg ml^{-1} of PPL. After sonication the reaction mixture was shaken in an orbital shaker at the room temperature. At the valid conversions, the reactions were stopped by filtering off the enzyme. The unreacted epoxyalcohol **1d-k** and the corresponding butyrate **2d-j** were separated by chromatography in a sintered glass funnell[25]. The ester product was eluted first followed by the elution of the epoxyalcohol with EtOAc/hexane (5/95 and 4/6, respectively).

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