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Kinetic resolution of racemic halohydrins, precursors of optically active di- and trialkyl-substituted epoxides, with lipase from *Pseudomonas* sp.

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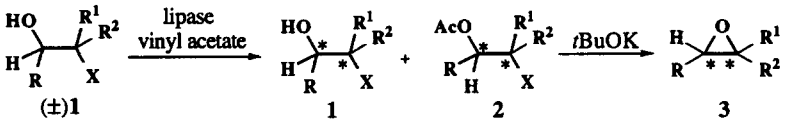
Abstract: Asymmetric acetylation of racemic halohydrins with vinyl acetate catalyzed by lipase from *Pseudomonas* sp. afforded the optically active β-halo alcohols **1** and acetates **2** in high enantiomeric excess (68 to >98%). The enzymatic kinetic resolution was performed on the preparative scale and the halo alcohols **1** and acetates **2** led to the optically active epoxides **3** after base treatment. © 1997 Elsevier Science Ltd

The synthesis of optically active halohydrins is of importance since such functionalities are convenient precursors to epoxides, which are common building blocks in the asymmetric synthesis of natural products.[1] Optically active halohydrins are accessible by two enzymatic methods, *e.g.* the reduction of α-halo ketones[2] and the acetylation of halohydrins.[3] Of the latter, only the lipase-mediated resolution of indene bromohydrin[4] and of 1-halo-2-hydroxy-substituted substrates[3] have been reported, which lead specifically to monosubstituted optically active epoxides. It was, therefore, our goal to apply the latter enzymatic kinetic resolution on halohydrins derived from unfunctionalized di- and trisubstituted alkenes, which should lead to the respective optically active epoxides (Scheme 1). Furthermore, it was of interest to compare the reactivity of chloro- and bromohydrins, as it was expected that the latter should be more enantioselective in view of steric considerations.



R = Me, iPr; R^1,R^2 = Me, *n*Pr, nC_5H_{11}; X = Br, Cl

Scheme 1.

The enzyme-catalyzed kinetic resolution of the bromohydrins **1a–c** and the chlorohydrins **1d,e**, which were prepared by standard methods (hydrobromination of the olefins with NBS/water[5] or opening of the epoxides with halogen acid[6]), was achieved with the lipase from *Pseudomonas* sp. (CHIRAZYME® L-6, Boehringer Mannheim) and vinyl acetate as acylating agent. Except for chlorohydrin **1e**, the kinetic resolutions were carried out on the preparative scale (0.5–6.0 mmol) to isolate the optically active halohydrins **1** and acetates **2**. The results are presented in Table 1. For full characterization (^{1}H and ^{13}C NMR and IR spectral data and elemental analyses), the racemic acetates **2a–d** were prepared by standard acetylation of the alcohols with acetic anhydride and triethylamine in dichloromethane with *p*-dimethylaminopyridine (DMAP) as catalyst.

To determine the absolute configuration of the compounds, the optically active products were treated with potassium *tert*-butoxide in *n*-octanol[3a,7] and the mixture distilled to obtain the optically active

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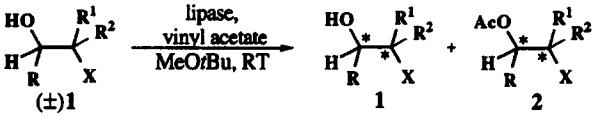
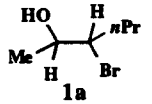
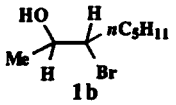
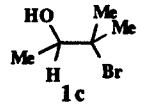
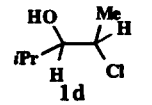
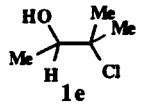
Table 1. Reaction conditions and product data for the kinetic resolution of halohydrins **1** with lipase from *Pseudomonas* sp.



(±)**1** **1** **2**

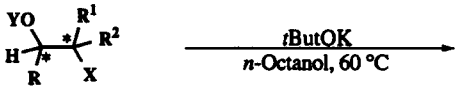
substrate	conditions[a] [mg/mmol]	[equiv.]	t [h]	conv. [%][b]	yield [%] 1	2	e.e. [%][c] 1	2	E[d]	[α]$_D$[e] 1	2
 **1a**	27	6	30	47	46	30	84	94	98	+27.7	+6.3
 **1b**	74	23	123	50	34	37	86	86	37	+16.4	+1.7
 **1c**	51	19	128	51	21	32	>98	95	180	f	+1.4
 **1d**	68	8	66	48	35	34	66	72	12	-16.5	-16.8
 **1e**	33	3	40	26	g		33	94	44	h	

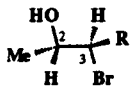
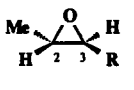
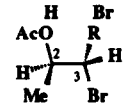
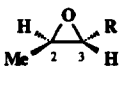
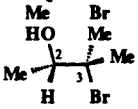
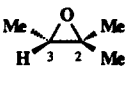
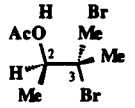
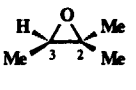
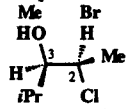
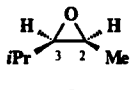
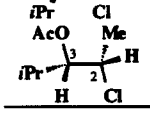
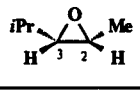
[a]Reaction conditions: mg lipase/mmol substrate, equivalents of vinyl acetate and reaction time [h]. [b]Calculated from the e.e. values of substrate and product. [c]Determined by GC analysis on a chiral β-cyclodextrin column. [d]See Ref. 10. [e]Values for the enantiomerically pure compound. [f]Exact value not determined due to decomposition of the sample, see Ref. 8b for $[\alpha]_D$ value. [g]Carried out on the analytical scale (0.15 mmol substrate) to compare its enantioselectivity with that of bromohydrin 1c. [h]See Ref. 8b for $[\alpha]_D$ value.

epoxides **3** (Table 2). The absolute configurations were assigned by comparison of the sign of the specific rotation with those described for the authentic or structurally related compounds.[2,8]

As has been previously observed,[9] the enzymatic acetylation occurs preferentially for the enantiomers of **1a–c** with the *R* configuration at the alcohol site, while for chlorohydrin **1d** the *S* enantiomer is preferentially acylated. This apparent contradiction may be rationalized if one accepts that the chloroethyl substituent is smaller than the isopropyl group and, consequently, the preferentially acylated *S* enantiomer of **1d** corresponds sterically to the *R* enantiomer of the substrates **1a–c** (Figure 1). With this steric control of the reactivity, the introduction of a bromo substituent in place of a chloro one substantially improves the enantioselectivity of the kinetic resolution, as can be seen by comparison of the E values (Table 1) for **1c** with **1e**. These data demonstrate that the bromohydrins are advantageous for the enzymatic kinetic resolution of such precursors of optically active, unfunctionalized epoxides.

Table 2. Absolute configurations of the optically active halohydrins **1**, halo acetates **2** and epoxides **3**



1 (Y=H) or 2 (Y=Ac)		config.[a]	epoxide 3[b]		config.
	(+)**1a** (R=*n*Pr)	2*S*,3*R*[c]		(+)**3a**	2*S*,3*S*[d]
	(+)**1b** (R=*n*C_5H_{11})	2*S*,3*R*[e]		(+)**3b**	2*S*,3*S*[f]
	(+)**2a** (R=*n*Pr)	2*R*,3*S*[g]		(-)**3a**	2*R*,3*R*[d]
	(+)**2b** (R=*n*C_5H_{11})	2*R*,3*S*[h]		(-)**3b**	2*R*,3*R*[f]
	(+)**1c**	2*S*[i]		(-)**3c**	3*S*[i]
	(+)**2c**	2*R*[k]		(+)**3c**	3*R*[i]
	(-)**1d**	2R,3*R*[l]		(-)**3d**	2*S*,3*R*[m]
	(-)**2d**	2S,3*S*[l]		(+)**3d**	2*R*,3*S*[n]

[a]Configuration at the oxy-substituted carbon atom given in bold. [b]Yields 30 - 50%. [c]Inferred by analogy with **1b**. [d]Inferred by analogy with **3b**, $[\alpha]_D$ = +7.6. [e]See Ref. 2a. [f]See Refs. 2a,8a. [g]Inferred from (-)**3a**. [h]Inferred from (-)**3b**. [i]See Ref. 8b. [k]Inferred from (+)**3c**. [l]Inferred from **3d**. [m]$[\alpha]_D$ = -6.3; configuration determined after reduction to (-)-3*S*-2-methylpentan-3-ol with $NaBH_4/BF_3$ in THF (yield 68%, $[\alpha]_D$ = -13.0, see. Ref. 8d). [n]$[\alpha]_D$ = +6.3.

(*R*)-**1a-c** (*S*)-**1d**

Figure 1. Preferentially acylated enantiomers.

General procedure for the lipase-catalyzed transesterification

Vinyl acetate (3 to 23 equiv.) and lipase powder (27 to 74 mg/mmol of substrate) from *Pseudomonas* sp. (CHIRAZYME® L-6 from Boehringer Mannheim) were added to the solution (approx. 0.1 M) of the racemic halohydrin **1** in *tert*-butyl methyl ether. The mixture was vigorously stirred at room temperature (ca. 20°C) and the conversion was monitored by GC analysis on a chiral β-cyclodextrin column. After the appropriate time (approx. 50% conversion, 30–128 h), the enzyme was removed by filtration and the solvent evaporated under reduced pressure (35°C, 100 Torr). Silica-gel chromatography afforded the optically active alcohol and acetate in 53–76% yield.

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