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Lipase-catalysed Kinetic Resolution of Phenylethan-1,2-diol by Sequential Transesterification – the Influence of the Solvent

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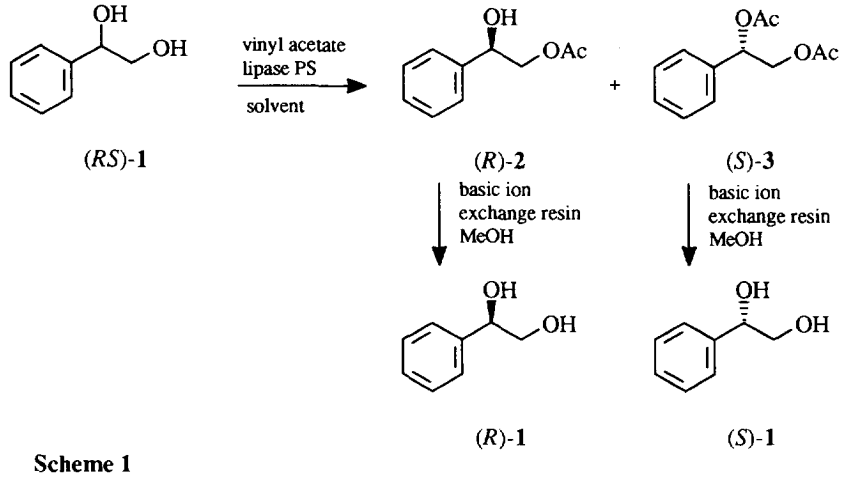
Abstract: The enantiomer selectivity of the kinetic resolution of phenylethan-1,2-diol [(*RS*)-**1**] by sequential acetylation with vinyl acetate in the presence of lipase from *Pseudomonas cepacia* (Amano PS) was investigated for dependence on the solvent. Optimal conditions for the resolution of (*RS*)-**1** are presented. Copyright © 1996 Elsevier Science Ltd

Enantiomerically pure or enriched phenylethan-1,2-diol can be prepared by asymmetric dihydroxylation of styrene,[1] hydrolysis of styrene oxide with epoxide hydrolases,[2] PLE-catalysed hydrolysis of the cyclic carbonate of racemic phenylethan-1,2-diol,[3] or kinetic resolution of racemic phenylethan-1,2-diol (*RS*)-**1** by lipase-catalysed acylation.[4a-c]

We recently found that a variety of 1,2-diols could be separated into their enantiomers by the lipase-catalysed transesterification with vinyl acetate in THF/NEt_3 in the presence of lipase PS from Amano.[4b,c] The *E*-value in the case of phenylethan-1,2-diol was 55 but the conversion did not reach more than 42 %. That means the monoacetate (*R*)-**2** was isolated with an ee of 66 % and the diacetate (*S*)-**3** with an ee of 93 % (Scheme 1). Deacetylation of both (*R*)-**2** and (*S*)-**3** yielded enantiomerically enriched (*R*)- and (*S*)-**1**, respectively. The *S*-enantiomer furnished by recrystallisation enantiomerically pure (*S*)-**1**. In the case of the *R*-enantiomer recrystallisation is ineffective, because the binary phase diagram shows an eutectic at about 60 % ee.[5]



Scheme 1

It is known that solvent variation in many cases of lipase-catalysed acylations can influence the enantiomer or enantiotopic selectivity as well as the reaction rate.[4c,6] Therefore, it seemed to be worth to reinvestigate the kinetic resolution of phenylethan-1,2-diol with vinyl acetate and lipase from *Pseudomonas cepacia* in the presence of different solvents. The aim was to obtain some more information on the influence of the solvent on the outcome of this reaction and to improve the enantiomer selectivity. Because of its cheapness and simplicity, the lipase-catalysed resolution of phenylethan-1,2-diol (*RS*)-**1** represents an alternative to other methods for the preparation of both enantiomers in non-racemic form.

Table 1: Solvent-dependent Resolution of (*RS*)-**1**[a]

		Monoacetate (*R*)-**2**		Diacetate (*S*)-**3**			
Solvent	Time (h)	Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)	*c*	*E*
THF/NEt_3	48	60	66.0	40	93.0	0.42	55[c]
THF	53	58	67.1	42	94.7	0.42	74
1,4-Dioxan	142	59	62.8	41	92.3	0.40	48
t-Butyl methyl ether	20	53	85.8	47	95.5	0.47	>100 (120)
Diethyl ether	31	52	87.2	48	95.7	0.48	>100 (130)
1,4-Dioxan	142	59	62.8	41	92.3	0.40	48
t-Amylalcohol	50	60	63.5	40	95.1	0.40	77
3-Methyl-3-pentanol	50	59	65.2	41	92.5	0.41	50
n-Hexane	19	52	84.0	47	89.7	0.48	49
Acetone	99	65	48.2	35	91.2	0.35	35
Dichloromethane	31	68	46.8	32	97.7	0.32	>100 (137)[d]
Dichloromethane	92	58	62.9	42	88.9	0.41	32[d]
Vinyl acetate	31	65	49.3	34	96.0	0.34	80[e]
Vinyl acetate	46	56	66.0	42	91.5	0.42	45[e]
1,1,1-Trichloro-trifluoroethane	16	51	81.4	49	85.9	0.49	33
1,1,2-Trichloro-1,2,2-trifluoroethane	19	52	82.6	48	93.7	0.47	76
Toluene/THF (4:1)	28	54	82.3	46	95.2	0.46	>100 (105)
n-Hexane/THF (4:1)	20	50	90.7	49	92.2	0.49	78
n-Hexane/THF (7:1)	22	44	92.3	55	82.0	0.53	33
Cyclohexane/THF (4:1)	31	52	85.2	48	91.6	0.48	62
t-Butyl methyl ether/ THF (4:1)	22	42	85.7	56	66.8	0.56	13

[a] 1 mmol (138 mg) (*RS*)-**1**, 2.5 ml of solvent, 0.65 ml of vinyl acetate, 100 mg of lipase PS; [b] Determined by HPLC on Chiralcel OF (0.46 × 25 cm) after conversion into the diol; [c] Ref 4c, [d] This difference can be explained due to the reversibility of the reaction. Compare ref. 7, [e] This difference is within the accuracy of the determination of the ee_p. For instance, the ee of 94 % for ee_p gives an *E*-value of 52.

Using a variety of solvents the diol (*RS*)-**1** was resolved according to Scheme 1 by transesterification with vinyl acetate in the presence of lipase PS. The acyl derivatives (*R*)-**2** and (*S*)-**3** were deacetylated to give the enantiomeric diols (*R*)- and (*S*)-**1** (Scheme 1). The results regarding the influence of the organic solvent used are depicted in Table 1.

The data from Table 1 clearly indicate that the enantiomeric ratio *E* for most of the solvents is in the range of 50–100. That means, it is possible to prepare both enantiomers of (*RS*)-**1** with high ee by conversion control. There seems to exist no relationship between the nature of the solvent and the *E*-values of the reaction. However, solvents such as acetone, dichloromethane and 1,4-dioxan compared with other solvents require very long reaction times to achieve conversion of 40 % or higher. From a practical point of view the best solvents regarding enantiomer selectivity and conversion rate are diethyl ether, *t*-butyl methyl ether, 1,1,2-trichloro-1,2,2-trifluoroethane, and 1:4 mixtures of THF with toluene, *t*-butyl methyl ether or hexane, respectively. THF was added to improve the solubility of the substrate. In all these cases a conversion of about 50 % is reached within 30 hours. *E*-values are higher than 70.

The solvent mixture *n*-hexane/THF (4:1) was selected in order to find out the optimal conditions for the preparation of (*R*)-**2** and (*S*)-**3** with high enantiomeric excess. Furthermore, this experiment was carried out in order to investigate whether this reaction is reversible as very recently found by Högberg *et al.*[7] for another substrate in the presence of the irreversible acylating agent vinyl acetate. Reversibility is assumed in the reaction in dichloromethane, where the *E*-value decreases with increasing degree of conversion. The results are summarised in Table 2.

Table 2: Kinetic Resolution of the Alcohol (*RS*)-**1** in *n*-Hexane/THF (4:1): Dependence on the Conversion

	Monoacetate (*R*)-**2**		Diacetate (*S*)-**3**			
Time (h)	Yield (%)	ee (%)	Yield (%)	ee (%)	*c*	*E*
7	61	59.2	39	95.5	0.38	79
20	50	90.7	49	92.2	0.49	78
26	51	90.3	49	92.0	0.49	75
48	45	99.5	54	86.9	0.53	84

The results from Table 2 indicate that the *E*-value is independent of the conversion. Hence, the reaction is irreversible within the time period investigated. Termination of the reaction at 38 % conversion (calculated from ee_p and ee_s) yielded the diacetate (*S*)-**3** with an ee of 95.5 % in 39 % chemical yield. Termination of the reaction at 53 % conversion furnished the monoacetate (*R*)-**2** with an ee of 99.5 % in 45 % chemical yield. This behaviour is in accordance with the theoretical relationship between the enantiomeric excess of the product and the substrate with the conversion as found by Sih *et al.*[8]

The lipases A and B from *Candida antarctica* catalyse the acylation of (*RS*)-**1** as well, however, with very poor enantiomer selectivity ($E < 5$).

Lipase PS-catalysed acetylation of phenylethan-1,2-diol with vinyl acetate in *n*-hexane/THF (4:1) allows to prepare both the monoacetate (*R*)-**2** and the diacetate (*S*)-**3** with a very high enantiomeric excess. Deacetylation by transesterification with methanol in the presence of the strong basic ion exchange resin

Wofatit SBW (OH^-) yielded (*R*)- and (*S*)-**1** which upon recrystallisation from ethyl acetate/*n*-hexane become enantiomerically pure.

The described procedure represents a cheap and simple access to both enantiomers of phenylethan-1,2-diol (*R*)- and (*S*)-**1** in enantiomerically pure form.

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