# Kinetic Resolution of Acyclic 1,2-Diols Using a Sequential Lipase-Catalyzed Transesterification in Organic Solvents

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A method for the kinetic resolution of 3-(aryloxy)-1,2-propanediols *rac*-**1a–n** without additional protection–deprotection steps using a lipase-catalyzed sequential transesterification with lipase amano PS has been developed. In the first step of this one-pot procedure the racemic 1,2-diols are acylated regioselectively at the primary hydroxy group without enantioselection. The subsequent acylation at the secondary hydroxy group of the formed primary monoacetate is responsible for high enantioselection. The enantioselectivity of this transformation depends significantly on the substitution pattern of the aryl ring and the organic solvent used. 3-(Aryloxy)-1,2-propanediols with substituents in the *para*-position show a much higher enantioselectivity than the corresponding derivatives with *ortho*-substituents. Among other substrates, the pharmaceuticals Mephenesin, Guaifenesin, and Chlorphenesin have been resolved. The replacement of the aryloxy by an alkyl substituent causes a dramatic decrease of enantioselectivity.

## Introduction

Enzyme-catalyzed transformations represent an immense potential for the preparation of enantiomerically pure compounds by asymmetrization of prochiral compounds or kinetic resolution of racemic substrates.[1]

In continuation of our work on lipase-catalyzed transesterification of dihydroxy compounds,[2] we have chosen acyclic racemic 1,2-diols[3] as substrates for lipase-catalyzed transesterification in order to obtain enantiomerically pure compounds.

The 1,2-diol functionality is found in a series of synthetic intermediates,[4] pharmaceuticals, and pharmaceutical intermediates.[5] Therefore, methods for the preparation of enantiomerically pure 1,2-diols are of increasing interest.

Chemical methods for the preparation of optically active 1,2-diols include chiral-pool synthesis,[5a] asymmetric hydroxylation,[6] ring opening of epoxides,[7] and reduction of optically active 2-hydroxy carboxylic acid derivatives.[8] Enzyme-mediated synthesis of optically active 1,2-diols was achieved using a lipase-catalyzed kinetic resolution of racemic 2-hydroxy carboxylic ester followed by a subsequent reduction,[4] by lipase-catalyzed transesterification or hydrolysis of monoprotected diols or their corresponding acylated compounds,[9] respectively, or by lipase-catalyzed alcoholysis of the diacylated diols.[5b] The lipase-catalyzed transesterification of 1,2-diols is highly regioselective[10] but shows only low enantioselectivity in the monoacylation step.[11]

It was our aim to use aliphatic diols, which do not require a manipulation at the primary hydroxy group, as substrates in lipase-catalyzed sequential transesterifications.[12] We recently could demonstrate the application of this concept in the kinetic resolution of Mephenesin (*rac*-**1b**).[13] The enantioselectivity in this case was moderate ($E = 27$), but it was possible to obtain both enantiomers of **1b** in enantiomerically pure form. In order to obtain information about the influence of the structure of these diols on the enantioselectivity of the lipase-catalyzed acetylation, the 2-methylphenoxy residue of Mephenesin (*rac*-**1b**) was replaced by other substituted aryloxy groups, one aryl substituent, and alkyl residues.

Due to the influence of the organic solvent on the enantioselectivity the reaction medium was altered to improve the enantioselectivity. The results concerning the influence of the organic solvent on the enantioselectivity in enzyme-catalyzed transesterifications are contradictory.[4,14] Although there seems to exist no general rule on the influence of the structure of the solvent, in many cases the variation of the solvent is an easy way to enhance the enantioselectivity of lipase-catalyzed transesterifications.

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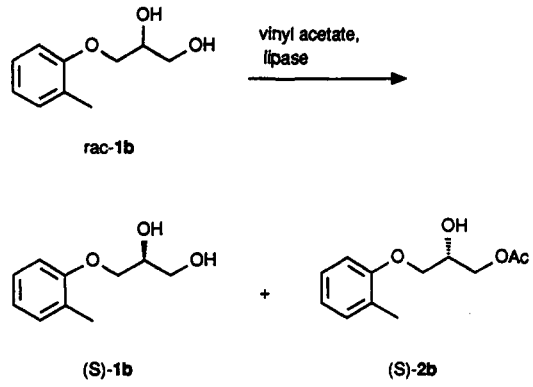
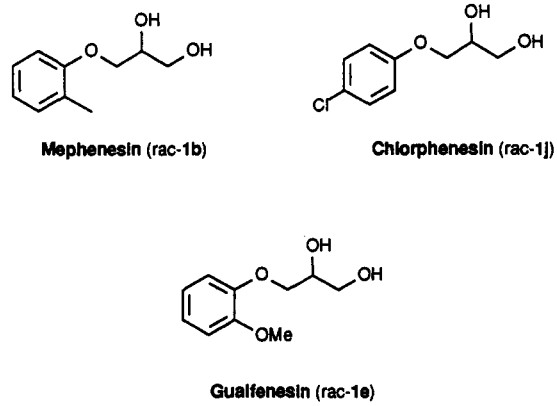
## Scheme 1




## Results and Discussion

In a first attempt Mephenesin (*rac*-**1b**) was converted with vinyl acetate in the presence of different lipases in the solvent system tetrahydrofuran–triethylamine.[15] The reaction was terminated after 25–50% conversion by filtration of the enzyme to give the diol (*S*)-**1b** and the corresponding primary monoacetate (*S*)-**2b** (Scheme 1). The results of the enantioselectivity of this reaction are summarized in Table 1. In general, all lipases tested show very high regioselectivity but the enantioselectivity of this transformation is very low. Lipase amano PS exhibits the highest enantioselectivity ($E = 4$).[16] Therefore, this lipase was chosen as biocatalyst in a sequential transesterification to resolve Mephenesin (*rac*-**1b**).[13]

In order to investigate the influence of the substituent *R* at the aryl ring, 14 different racemic 3-(aryloxy)-1,2-propanediols *rac*-**1a–n** were used as substrates in a kinetic resolution by a lipase-catalyzed sequential acetylation. Mephenesin (*rac*-**1b**), Chlorphenesin (*rac*-**1j**), and Guaifenesin (*rac*-**1e**) represent pharmaceuticals, and one of the diols, the naphthyloxy derivative *rac*-**1k**, is used as an intermediate in the synthesis of propanolol.




Transformations were carried out with vinyl acetate in the presence of lipase amano PS in tetrahydrofuran–triethylamine until *ca.* 50% of the fastly formed primary monoacetates *rac*-**2a–n** were converted enantioselectively into the diacetates (*S*)-**3a–n** (Scheme 2). The results are given in Table 2. The (*S*)-enantiomers of the primary monoacetates **2a–n** are converted at a higher rate into the (*S*)-diacetates **3a–n**. The corresponding (*R*)-enantiomers **2a–n**[17] are slow-reacting and resist further diacetylation in greater extent.

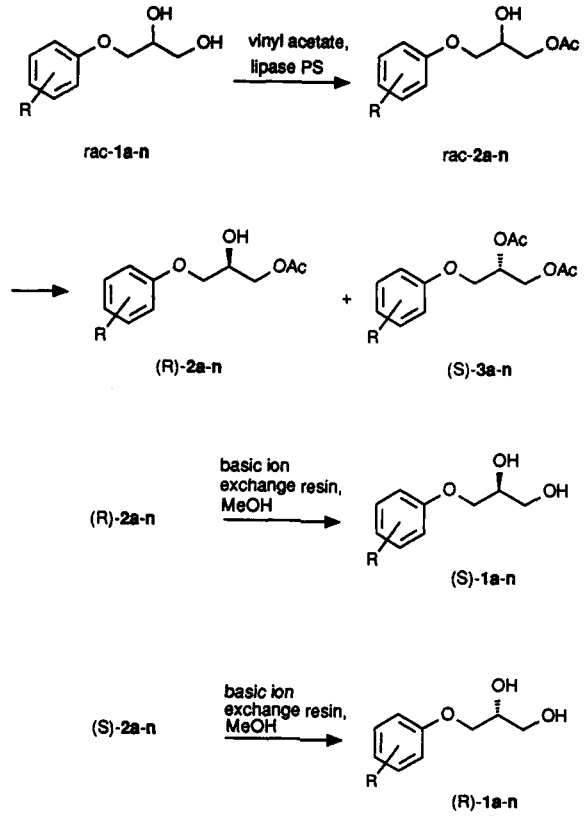
**Table 1. Kinetic Resolution of Mephenesin *rac*-1b by Monoacetylation**

| enzyme (mg) | time (h) | diol (*S*)-**1b** yield | diol (*S*)-**1b** ee | monoacetate (*S*)-**2b** yield | monoacetate (*S*)-**2b** ee | *c* | *E* |
|---|---|---|---|---|---|---|---|
| amano PS (10) | 2 | 49 | 40 | 47 | 45 | 0.47 | 4 |
| lipozyme (50) | 6 | 62 | 6 | 37 | 9 | 0.40 | ~1 |
| SP 382 (50) | 1 | | | 94 | 0 | | 1 |
| SP 382 (10) | 1 | 57 | 6 | 45 | 10 | 0.38 | ~1 |
| yarrowia lip. (100) | 8 | 67 | 12 | 35 | 23 | 0.34 | 1.8 |
| pancreatin (30) | 2.5 | 71 | 1 | 29 | 3 | 0.25 | ~1 |

**Table 2. Kinetic Resolution of the 3-(Aryloxy)propane-1,2-diols *rac*-1a–n by Sequential Acetylation in THF/$NEt_3$**

| substrate | R | time (h) | (*R*)-**2** yield (%) | (*R*)-**2** ee (%) | (*S*)-**3** yield (%) | (*S*)-**3** ee (%) | *c* | *E* |
|---|---|---|---|---|---|---|---|---|
| **1a** | H | 92 | 48 | 85 | 49 | 79 | 0.52 | 23 |
| **1b** | 2-Me | 96 | 45 | 93 | 48 | 80 | 0.54 | 27 |
| **1c** | 3-Me | 72 | 55 | 66 | 43 | 87 | 0.43 | 28 |
| **1d** | 4-Me | 48 | 57 | 66 | 42 | 93 | 0.42 | 55 |
| **1e** | 2-OMe | 44 | 58 | 63 | 42 | 87 | 0.42 | 27 |
| **1f** | 3-OMe | 29 | 49 | 91 | 47 | 95 | 0.49 | >100 (124) |
| **1g** | 4-OMe | 28 | 48 | 96 | 52 | 94 | 0.51 | >100 (127) |
| **1h** | 2-Cl | 24 | 59 | 55 | 38 | 88 | 0.38 | 27 |
| **1i** | 3-Cl | 24 | 48 | 86 | 43 | 92 | 0.48 | 67 |
| **1j** | 4-Cl | 25 | 48 | 94 | 49 | 92 | 0.50 | 85 |
| **1k** | 2,3-$C_4H_4$ | 72 | 63 | 42 | 36 | 78 | 0.35 | 12 |
| **1l** | 2-t-Bu | 78 | 82 | 3 | 17 | 34 | 0.08 | 2 |
| **1m** | 3-t-Bu | 73 | 67 | 43 | 33 | 80 | 0.35 | 14 |
| **1n** | 4-t-Bu | 50 | 50 | 99 | 50 | 93 | 0.52 | >100 (145) |

## Scheme 2

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(15) This solvent system was used advantageously by us earlier; see ref 2.

(16) *E* values were calculated according to: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

**Table 3. Kinetic Resolution of the 1,2-Diols *rac*-4a-d by Sequential Acetylation in THF/$NEt_3$**

| | | | monoacetate 5 | | | | diacetate 6 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| substrate | R | lipase | yield (%) | ee (%) | $[\alpha]_D$[a] | conf | yield (%) | ee (%) | $[\alpha]_D$[a] | conf | c | E |
| 4a | Et | amano PS | 45 | 61 | −10.0[b] | S[c] | 38 | 49 | +9.0[b] | R[c] | 0.55 | 5 |
| 4a | Et | pancreatin | 70 | 49 | −9.1[b] | S[c] | 27 | 94 | +17.5[b] | R[c] | 0.34 | 53 |
| 4b | n-Pr | amano PS | 40 | 19 | 0 | S[d] | 52 | 11 | 0 | R[d] | 0.63 | 1.5 |
| 4b | n-Pr | pancreatin | 58 | 6 | 0 | S[d] | 33 | 6 | 0 | R[d] | 0.50 | 1 |
| 4c | $C(OH)Me_2$ | amano PS | 63 | 17 | −3.0[e] | S[f] | 34 | 14 | +3.0[e] | R[f] | 0.55 | 1.5 |
| 4c | $C(OH)Me_2$ | pancreatin | 51 | 55 | −9.3[e] | S[f] | 41 | 61 | +12.7[e] | R[f] | 0.47 | 7 |
| 4d | Ph | amano PS | 60 | 66 | −25.3[e] | R[c] | 40 | 93 | +39.4[e] | S[c] | 0.42 | 55 |
| 4d | Ph | pancreatin | 67 | 27 | −11.0[e] | R[c] | 28 | 69 | +28.2[e] | S[c] | 0.28 | 7 |

[a] Of the corresponding diol after deacetylation. [b] *c* 2.1, EtOH. [c] Reference 11. [d] Due to no optical rotation value of the diol the assignment of the absolute configuration is not unambigious. [e] *c* 1.0, MeOH. [f] Reference 20.

**Table 4. Kinetic Resolution of the Diol *rac*-1e in Various Solvents**

| | | | monoacetate 2e | | diacetate 3e | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 100 | 70 | 29.4 | 25 | 94.6 | 0.23 | 48 |
| 1,4-dioxane | −1.1 | 100 | 78 | 17.7 | 17 | 94.2 | 0.16 | 40 |
| diethyl ether | 0.85 | 100 | 43 | 94.5 | 50 | 83.0 | 0.53 | 39 |
| *tert*-butyl methyl ether | 2.0 | 100 | 41 | 98.4 | 52 | 86.4 | 0.53 | 65 |
| toluene | 2.5 | 100 | 54 | 64.6 | 42 | 85.4 | 0.43 | 25 |
| 3-methyl-3-pentanol | ~2 | 100 | 62 | 53.5 | 37 | 93.3 | 0.36 | 49 |
| *tert*-amyl alcohol | 1.4 | 100 | 66 | 45.1 | 33 | 94.7 | 0.32 | 57 |

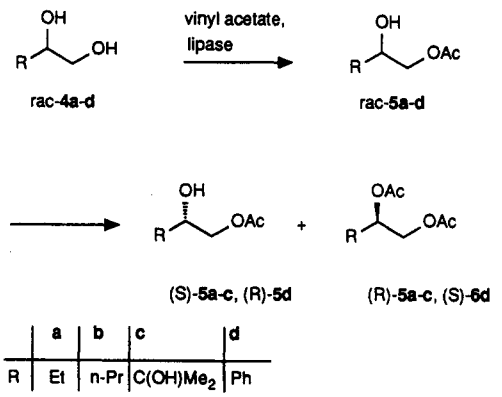
The absolute configuration of the reaction products was assigned after deacetylation on the basis of the CD spectra of the corresponding diols **1a–n** in Cupra A solution.[5a] Deacylation of (*R*)-**2a–n** afforded (*S*)-**1a–n**, and (*S*)-**3a–n** gave (*R*)-**1a–n**. All diols with a positive short-wavelength (265–285 nm) Cotton effect were assigned the (*S*)-configuration (Table 11).

In general, the derivatives with substituents in the 4-position of the aromatic ring show significantly higher enantioselectivities than the corresponding derivatives with substituents in the 2-position. Such a relationship could not be observed for compounds substituted in the 3-position of the aromatic ring. A substituent in the 4-position, independently of its electronic properties, seems to be a prerequisite for a high enantioselectivity of the resolution procedure, because the unsubstituted derivative *rac*-**1a** shows an enantioselectivity comparable to the 2-substituted compounds. A similar behavior was observed recently by Schneider[18] in the resolution of the corresponding chlorohydrins by a lipase-catalyzed transesterification. Surprisingly, Sharpless *et al.*[6] found a comparable relationship in the asymmetric dihydroxylation of (aryloxy)allyl ethers to give (*S*)-3-(aryloxy)-1,2-propanediols.

In comparison, the resolution of the racemic diols *rac*-**4a–d** was attempted under the same conditions in the presence of lipase amano PS and pancreatin (Scheme 3). 1-Phenyl-1,2-ethanediol (*rac*-**4d**) was converted with a fairly high enantioselectivity into the monoacetate (*R*)-**5d** and the diacetate (*S*)-**6d**.[19] However, the diols with an aliphatic substituent *R* are very poor substrates in an enantioselective sequential transacetylation reaction in the presence of lipase amano PS (Table 3).

By using pancreatin as the biocatalyst in the sequential transesterification only 1,2-butanediol (*rac*-**4a**) was converted with a reasonable enantioselectivity (*E* = 53) into the monoacetate (*S*)-**5a** and the diacetate (*R*)-**6a**. 1,2-Pentanediol (*rac*-**4b**) and the triol *rac*-**4c** are poor substrates in the pancreatin-catalyzed reaction as well. The latter compound is a building block for vitamin $D_3$ metabolites.[20] The absolute configurations of the products (*S*)-**5a–c**, (*R*)-**6a–c**, (*R*)-**5d**, and (*S*)-**6d** were determined after deacetylation to the corresponding diols on the basis of their optical rotation values reported in the literature.

**Scheme 3**




The results documented in Tables 2 and 3 clearly demonstrate that lipase amano PS requires an aromatic substituent in the 1,2-diols for a high enantioselection between both enantiomeric primary monoacetates which are formed as intermediates in this sequential reaction. The enantioselectivity of the kinetic resolution of the racemic 1,2-diols is in accordance with Kazlauskas' rule.[21]

To study the influence of the organic solvent on the enantioselectivity of the above-described kinetic resolution procedure the methoxy- and *tert*-butyl-substituted 3-(aryloxy)-1,2-propanediols *rac*-**1e–g** and *rac*-**11–n**, respectively, were selected as substrates.

The results of the influence of the different solvents on the enantioselectivity summarized in Tables 4–9 show that

(17) In most cases the primary monoacetates were contaminated with a trace (<5%) of the corresponding regioisomeric secondary monoacetate as indicated by TLC.

(18) Ader, U.; Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 521.

(19) Simultaneously with our investigations a comparable result using *rac*-**4** with a carboxylic anhydride as acylating agent was published: Bosetti, A.; Bianchi, D.; Cesti, P.; Golini, P.; Spezia, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2395.

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(21) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.

**Table 5. Kinetic Resolution of the Diol *rac*-1f in Various Solvents**

| | | | monoacetate 2f | | diacetate 3f | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 135 | 45 | 95.4 | 43 | 99.1 | 0.49 | >100 (848) |
| 1,4-dioxane | −1.1 | 135 | 48 | 85.9 | 44 | 98.5 | 0.46 | >100 (369) |
| diethyl ether | 0.85 | 135 | 43 | 85.8 | 48 | 96.0 | 0.47 | >100 (136) |
| *tert*-butyl methyl ether | 2.0 | 100 | 45 | >99.9 | 49 | 97.1 | 0.51 | >100 (>514) |
| toluene | 2.5 | 100 | 34 | 99.4 | 61 | 56.2 | 0.64 | 19 |
| 3-methyl-3-pentanol | ~2 | 100 | 45 | 99.6 | 47 | 96.8 | 0.51 | >100 (381) |
| *tert*-amyl alcohol | 1.4 | 100 | 46 | 98.5 | 47 | 98.2 | 0.50 | >100 (541) |

**Table 6. Kinetic Resolution of the Diol *rac*-1g in Various Solvents**

| | | | monoacetate 2g | | diacetate 3g | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 100 | 50 | 91.6 | 50 | 97.9 | 0.49 | >100 (308) |
| 1,4-dioxane | −1.1 | 100 | 52 | 82.6 | 48 | 97.9 | 0.46 | >100 (244) |
| diethyl ether | 0.85 | 100 | 46 | 99.6 | 53 | 88.8 | 0.53 | >100 (103) |
| *tert*-butyl methyl ether | 2.0 | 100 | 42 | 99.7 | 54 | 81.9 | 0.55 | 63 |
| toluene | 2.5 | 100 | 43 | 99.9 | 55 | 83.9 | 0.54 | 84 |
| 3-methyl-3-pentanol | ~2 | 100 | 46 | 97.9 | 54 | 88.6 | 0.52 | 75 |
| *tert*-amyl alcohol | 1.4 | 100 | 44 | 98.4 | 53 | 90.4 | 0.52 | 95 |

**Table 7. Kinetic Resolution of the Diol *rac*-1l in Various Solvents**

| | | | monoacetate 2l | | diacetate 3l | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 100 | 95 | | 2 | | | |
| 1,4-dioxane | −1.1 | 100 | 75 | | 1 | | | |
| diethyl ether | 0.85 | 100 | 68 | 26.1 | 18 | 94.6 | 0.20 | 46 |
| *tert*-butyl methyl ether | 2.0 | 100 | 54 | 38.7 | 29 | 63.0 | 0.38 | 6 |
| toluene | 2.5 | 100 | 74 | 12.8 | 18 | 73.9 | 0.15 | 8 |
| 3-methyl-3-pentanol | ~2 | 100 | 77 | 15.6 | 12 | 93.9 | 0.15 | 37 |
| *tert*-amyl alcohol | 1.4 | 100 | 78 | | 6 | | | |

**Table 8. Kinetic Resolution of the Diol *rac*-1m in Various Solvents**

| | | | monoacetate 2m | | diacetate 3m | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 100 | 58 | 61.7 | 40 | 98.3 | 0.39 | >100 (220) |
| 1,4-dioxane | −1.1 | 100 | 62 | 45.6 | 30 | 98.6 | 0.32 | >100 (223) |
| diethyl ether | 0.85 | 100 | 48 | 99.1 | 49 | 96.8 | 0.50 | >100 (332) |
| *tert*-butyl methyl ether | 2.0 | 113 | 38 | 96.8 | 58 | 63.3 | 0.60 | 17 |
| toluene | 2.5 | 113 | 48 | 93.0 | 47 | 92.4 | 0.50 | 86 |
| 3-methyl-3-pentanol | ~2 | 113 | 51 | 92.2 | 48 | 97.1 | 0.49 | >100 (226) |
| *tert*-amyl alcohol | 1.4 | 113 | 52 | 90.3 | 48 | 97.9 | 0.48 | >100 (295) |

**Table 9. Kinetic Resolution of the Diol *rac*-1n in Various Solvents**

| | | | monoacetate 2n | | diacetate 3n | | | |
|---|---|---|---|---|---|---|---|---|
| solvent | log *P* | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| THF | 0.49 | 100 | 47 | 99.1 | 49 | 98.4 | 0.50 | >100 (671) |
| 1,4-dioxane | −1.1 | 100 | 40 | >99.9 | 41 | 98.1 | 0.50 | >100 (>790) |
| diethyl ether | 0.85 | 100 | 48 | 99.8 | 49 | 93.9 | 0.51 | >100 (217) |
| *tert*-butyl methyl ether | 2.0 | 100 | 49 | 99.0 | 51 | 94.9 | 0.51 | >100 (202) |
| toluene | 2.5 | 100 | 48 | 98.8 | 50 | 92.4 | 0.52 | >100 (129) |
| 3-methyl-3-pentanol | ~2 | 100 | 49 | 99.0 | 51 | 94.4 | 0.51 | >100 (183) |
| *tert*-amyl alcohol | 1.4 | 100 | 47 | 99.2 | 50 | 92.6 | 0.52 | >100 (198) |

alteration of the solvent in most cases caused a significant enhancement of the enantioselectivity compared with the standard solvent system tetrahydrofuran–triethylamine. However, *E* values greater than 100 should be judged with care because they are very sensitive to small errors in measurement of ee. The relationship concerning the enantioselectivity between the compounds with a substituent in the 2-position and in the 4-position is unaffected by variation of the solvent. But in contrast to other cases[14a,c] there is no relationship between the 1-octanol–water partition coefficient (log *P*)[22] as a term of hydrophobicity of the solvent and the enantioselectivity. Due

(22) Taft, R. W.; Abraham, M. H.; Famini, G. R.; Doherty, R. M.; Abboud, J.-L. M.; Kamlet, M. J. *J. Pharm. Sci.* 1985, *74*, 807.

**Table 10. Kinetic Resolution of the Diols *rac*-1b and *rac*-1k by Sequential Acetylation in *tert*-Butyl Methyl Ether**

| | | | (*R*)-2 | | (*S*)-3 | | | |
|---|---|---|---|---|---|---|---|---|
| substrate | R | time (h) | yield (%) | ee (%) | yield (%) | ee (%) | *c* | *E* |
| **1b** | 2-Me | 60 | 61 | 54 | 37 | 95 | 0.36 | 67 |
| **1k** | 2,3-$C_4H_4$ | 124 | 62 | 64 | 38 | 95 | 0.40 | 75 |

to the amplification of the enantioselectivity by an alteration of the solvent the kinetic solution of Mephenesin (*rac*-**1b**) and the naphthyloxy derivative *rac*-**1k** was reinvestigated in *tert*-butyl methyl ether (Table 10) instead of tetrahydrofuran–triethylamine as solvent in order to improve the enantioselectivity which for these substrates

Table 11. Chiroptical Properties of the Diols 1a–n

| diol | ee | $[\alpha]^{20}_D$ | (concn, solvent) | $[\theta]$ ($\lambda_{max}$) (deg cm$^2$ mol$^{-1}$) |
|---|---|---|---|---|
| (*R*)-**1a** | 98 | −10.8 | (*c* 1, EtOH) | −667 (270) |
| (*S*)-**1a** | 91 | +10.2[a] | (*c* 1.1, EtOH) | +717 (270) |
| (*R*)-**1b** | >99 | +19.8 | [*c* 0.9, hexane–i-PrOH (4:1)] | −407 (285) |
| (*S*)-**1b** | >99 | −19.3 | [*c* 0.9, hexane–i-PrOH (4:1)] | +407 (285) |
| (*R*)-**1c** | >99 | −9.3 | (*c* 1, EtOH) | −583 (265) |
| (*S*)-**1c** | 97 | +9.5 | (*c* 1, EtOH) | +617 (270) |
| (*R*)-**1d** | 97 | −9.2 | (*c* 1, EtOH) | −380 (270) |
| (*S*)-**1d** | 71 | +7.5[b] | (*c* 1, EtOH) | +530 (270) |
| (*R*)-**1e** | 96 | −11.1 | (*c* 1, EtOH) | −500 (270) |
| (*S*)-**1e** | 88 | +11.2[c] | (*c* 1, EtOH) | +483 (270) |
| (*R*)-**1f** | 99 | −9.7 | (*c* 1, EtOH) | −500 (270) |
| (*S*)-**1f** | 98 | +10.4 | (*c* 1, EtOH) | +500 (270) |
| (*R*)-**1g** | 94 | −8.0 | (*c* 1, EtOH) | −483 (280) |
| (*S*)-**1g** | 96 | +7.9[d] | (*c* 1, EtOH) | +483 (275) |
| (*R*)-**1h** | 99 | −4.0 | (*c* 1, EtOH) | −461 (270) |
| | | +14.0 | [*c* 1, hexane–EtOH (4:1)] | |
| (*S*)-**1h** | 99 | +3.1[e] | (*c* 1, EtOH) | +277 (270) |
| | | −13.4 | [*c* 1, hexane–EtOH (4:1)] | |
| (*R*)-**1i** | >99 | −12.7 | (*c* 1, EtOH) | −544 (275) |
| (*S*)-**1i** | 98 | +13.7 | (*c* 1, EtOH) | +359 (275) |
| (*R*)-**1j** | 95 | −11.8 | (*c* 1, EtOH) | −667 (270) |
| (*S*)-**1j** | 97 | +12.3[f] | (*c* 1, EtOH) | +605 (270) |
| (*R*)-**1k** | 94 | −7.4 | (*c* 1, EtOH) | [g] |
| (*S*)-**1k** | [h] | [h] | | [h] |
| (*R*)-**1l** | 94 | [h] | | −157 (275) |
| (*S*)-**1l** | [h] | [h] | | [h] |
| (*R*)-**1m** | 99 | −8.11 | (*c* 1, EtOH) | −314 (270) |
| (*S*)-**1m** | 99 | +8.9 | (*c* 1, EtOH) | +302 (270) |
| (*R*)-**1n** | 98 | −7.1 | (*c* 1, EtOH) | −305 (275) |
| (*S*)-**1n** | >99 | +7.5 | (*c* 1, EtOH) | +355 (270) |

[a] Reference 6, +8.6 (*c* 1.1, EtOH). [b] Reference 6, +14.7 (*c* 0.49, EtOH). [c] Reference 6, +12.9 (*c* 1.2, EtOH). [d] Reference 6, +5.9 (*c* 1.2, EtOH). [e] Reference 6, +2.7 (*c* 1, EtOH). [f] Reference 6, +46.9 (*c* 0.32, EtOH), +8.1 (*c* 1.5, MeOH). [g] Insoluble in Cupra A. [h] Not determined.

was only poor or moderate. In both cases the enantioselectivity of the transesterification reaction was enhanced significantly. For Mephenesin *rac*-**1b** the $E$ value was increased from $E = 27$ in tetrahydrofuran–triethylamine to $E = 67$ in *tert*-butyl methyl ether and for *rac*-**1k** from $E = 12$ to $E = 75$, respectively. This enhancement in both cases allows the separation of the enantiomers in a more efficient manner.

## Conclusions

Aliphatic racemic 1,2-diols are only poor substrates in lipase-catalyzed transesterification. A dramatic amplification of the enantiodifferentiation is caused by application of the concept of a sequential acylation. In the first step of this sequential procedure the racemic diol is converted into a racemic primary monoacetate. This monoacetate is a much better substrate in the following enantiodifferentiation step which is caused by a preferential diacylation of one of its enantiomers.

3-(Aryloxy)-1,2-propanediols are very useful substrates for this transformation to give products in high optical purity. Besides the presence of an aromatic residue the substitution pattern at the aromatic ring determines the enantioselectivity. Diols or rather their corresponding primary monoacetates with *para*-substituents in the aromatic part fit very well with the active site of lipase amano PS to realize a high enantioselection. On the other hand, *ortho*-substituents in the aromatic part seem to disturb an optimal interaction with the active site to achieve a high enantioselection. A very impressive example for this mismatching is the behavior of the *ortho*-substituted *tert*-butyl derivative **1l** which shows neither a high conversion rate nor a reasonable enantioselectivity whereas the corresponding *para*-substituted derivative **1n** is an excellent substrate.

The phenomenon that diols are worse substrates than their corresponding monoacylated derivatives in lipase-catalyzed transesterification was observed also for racemic diols with $C_2$ symmetry[2b,12] where the first acylation step is less enantioselective than the second one. An analogous behavior was observed for many prochiral diols[2a,c,d,14b,23] in which the monoacylation step shows a low or only moderate enantioselectivity. In the second step the "wrong" enantiomeric monoacetate is acylated to give a prochiral diacylated product and one unaffected monoacetate with high ee.

It seems that different types of diols in many cases are much worse substrates than their corresponding monoacyl derivatives in lipase-catalyzed enantioselective transesterifications. But in many cases the low enantioselectivity can be overcome by application of a sequential lipase-catalyzed acylation procedure.

## Experimental Section

**General.** The corresponding diols **1** which have not been commercially available were synthesized from epichlorohydrin and the corresponding phenol[24] followed by a subsequent hydrolysis of the resulting glycid ether in the usual manner in water–acetone in the presence of a catalytic amount of boron trifluoride etherate. The following lipases were used: lipase PS (from *Pseudomonas cepacia*, Amano Co., Japan), pancreatin (from porcine pancreas, Fa. Belger, Germany), lipozyme 20M (from *Mucor Miehei*, Novo Nordisk, A/S, Denmark), SP 382 (from *Candida antarctica*, Novo Nordisk A/S, Denmark), and lipase from *Yarrowia lipolytica* (from the former Institute of Biotechnology of the Academy of Sciences of the GDR). THF, toluene, diethyl ether, *tert*-butyl methyl ether, and 1,4-dioxane were dried over sodium wire. 3-Methyl-3-pentanol and *tert*-amyl alcohol were distilled from $CaH_2$. Triethylamine was distilled from and stored over KOH. All reactions were monitored by thin-layer chromatography on glass plates coated with a 0.25-mm layer of silica gel. Compounds were visualized with a 3.5% solution of molybdatophosphoric acid in ethanol. Flash chromatography was performed with silica gel 60 (0.063–0.040 mm) using hexane–ethyl acetate as eluent. $^1$H NMR and $^{13}$C NMR spectra were measured in $CDCl_3$ at 200 and 75 MHz, respectively. $J$ values are given in Hz. EI mass spectra were measured at 70 eV.

**Attempted Resolution of Mephenesin *rac*-1b by Lipase-Catalyzed Monoacetylation.** A solution of *rac*-**1b** in THF (2.5 mL) and $NEt_3$ (0.1 mL) was treated with vinyl acetate (0.65 mL) and the corresponding lipase (Table 1). The mixture was stirred until 25–50% of the diol **1b** was converted into the primary monoacetate **2b** and then filtered through Celite. The filter cake was washed with ethyl acetate (3 × 10 mL). The combined filtrates were concentrated under reduced pressure. The residue was separated by flash chromatography using hexane–ethyl acetate (1:1) as eluent to give (*S*)-**1b** and (*S*)-**2b**. For the determination of the ee (*S*)-**2b** was deacetylated as described below. Results are summarized in Table 1.

**Kinetic Resolution of the Diols *rac*-1a–n by a Lipase-Catalyzed Sequential Acetylation.** A solution of the diols **1a–n** (5 mmol) in THF–$NEt_3$ (12.5 mL:0.5 mL) or the corresponding solvent (12.5–25 mL) (Table 9) was treated with vinyl

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(24) Frommelt, H.; Jedlinski, Z.; Ruebner, J.; Stolarzewicz, A.; Neumann, G.; Pradellok, W. *DD* 130419 (29. 3. 1978); *Chem. Abstr.* **1979**, *90*, 204857.

acetate (3.25 mL) and lipase amano PS (0.5 g). The reaction was stirred for the appropriate time (see Tables 2 and 4–10) until the diols **1a–n** were converted to a mixture of the primary monoacetates **2a–n** and the diacetates **3a–n**. The enzyme was filtered off through a pad of Celite. The filter cake was washed with ethyl acetate (3 × 20 mL). The combined filtrates were concentrated under reduced pressure. The remaining residue was separated by flash chromatography into a fraction of the monoacetates (*R*)-**2a–n** and a fraction of the diacetates (*S*)-**3a–n** using hexane–ethyl acetate (1:2) as eluent. Results are tabulated in Tables 2 and 4–10.

Results according to Table 2. (*R*)-Acetoxy-3-(4-methoxyphenyl)-2-propanol [(*R*)-**2g**]: oil; yield 0.53 g (48%); $^1$H NMR δ 2.05 (s, 3), 2.55 (br s, 1), 3.71 (s, 3), 3.81–4.23 (m, 5), 6.78 (s, 4); $^{13}$C NMR δ 20.80, 55.68, 65.41, 68.52, 69.48, 114.69, 115.58, 152.47, 154.23, 171.18. MS *m/z* 240 ($M^+$), 149, 124, 117 (100), 104, 95. Anal. Calcd for $C_{12}H_{16}O_4$: C, 59.99; H, 6.71. Found: C, 59.88; H, 6.81.

(*S*)-1,2-Diacetoxy-3-(4-methoxyphenyl)-propane [(*S*)-**3g**]: oil; yield 0.73 g (52%); bp 250 °C (1 Pa, Kugelrohr); $^1$H NMR δ 2.00 (s, 3), 2.03 (s, 3), 3.69 (s, 3), 4.00 (d, 2, *J* = 5), 4.20 (dd, 1, *J* = 12, 6), 4.36 (dd, 1, *J* = 12, 4), 5.27 (quintet, 1, *J* = 4), 6.77 (s, 4). $^{13}$C NMR δ 20.71, 20.94, 55.65, 62.57, 66.81, 69.83, 114.64, 115.65, 152.41, 154.26, 170.26, 170.57. MS *m/z* 282 ($M^+$), 159 (100), 124, 109, 99. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.60; H, 6.45.

For the data of the other compounds see the supplementary material.

**Deacetylation of 2a–n and 3a–n. Determination of the Enantiomeric Excess (ee) and the Absolute Configuration of the Diols 1a–n.** The ee of the diols **1a–g**, **1i**, and **1k–m** was determined as follows: The corresponding monoacetates (*R*)-**2a–g**, **2i**, and **2k–m** and diacetates (*S*)-**3a–g**, **3i**, and **1k–m**, respectively, were dissolved in methanol (10 mL) and treated with strongly basic ion-exchange resin Wofatit SBW ($OH^-$ form) (1 g) until the deacetylation by TLC monitoring was complete. The ion-exchange resin was filtered off, and the filtrate was concentrated under reduced pressure. The resulting diols were subjected to HPLC on cellulose tris((3,5-dimethylphenyl)carbamate).

(*R*)-**2g** (0.53 g) gave 0.46 g (95%) of (*S*)-**1g**: ee 96%; mp 74–76 °C. (*S*)-**3g** (0.73 g) gave 0.50 g (97%) of (*R*)-**1g**: ee 94%; mp 75–76 °C. Recrystallization of both enantiomers did not enhance the ee. For yields and data of the other diols see the supplementary material.

The monoacetates (*R*)-**2j**, (*R*)-**2h**, and (*R*)-**2n** were acetylated with acetic anhydride in pyridine in the usual manner to give the diacetates (*R*)-**3j**, (*R*)-**3h**, and (*R*)-**3n**. The (*R*)- and (*S*)-diacetates of **3j**, **3h**, and **3n** were subjected to HPLC on cellulose tris((3,5-dimethylphenyl)carbamate).

**Kinetic Resolution of the Diols *rac*-4a–d by a Lipase-Catalyzed Sequential Acetylation.** A solution of the diols *rac*-**4a–d** in THF was treated with $NEt_3$, vinyl acetate, and lipase. After being stirred for the appropriate time the reaction mixture was worked up as described above for the reaction of the diols **1a–n**. Results are shown in Table 3. The amounts of solvents, acylating agent, and lipase used as well as the reaction time are tabulated in Table 12. According to Table 12, entry 1, 0.199 g (70%) of monoacetate (*S*)-**5a** and 0.101 g (27%) of diacetate (*R*)-**6a** were obtained. Results regarding the enantioselectivity are shown in Table 3.

**Table 12. Reaction Conditions for the Resolution of the Diols *rac*-4a-d in Table 3**

| entry | diol | amount (mmol) | THF (ml) | $NEt_3$ (ml) | vinyl acetate (ml) | pancreatin (mg) | amano PS (mg) | time (h) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4a** | 2.15 | 10 | 2 | 4.1 | 500 | | 25.5 |
| 2 | **4a** | 2 | 10 | 2 | 3.9 | | 100 | 22 |
| 3 | **4b** | 2.2 | 10 | 2 | 4.3 | 500 | | 192 |
| 4 | **4b** | 2.3 | 10 | 2 | 4.4 | | 100 | 96 |
| 5 | **4c** | 2 | 10 | 2 | 3.9 | 1000 | | 96 |
| 6 | **4c** | 2.1 | 10 | 2 | 4.0 | | 100 | 144 |
| 7 | **4d** | 1 | 2.5 | 0.5 | 0.65 | 500 | | 96 |
| 8 | **4d** | 5 | 12.5 | 0.5 | 3.25 | | 500 | 48 |

(*S*)-1-Acetoxy-2-butanol [(*S*)-**5a**]: $^1$H NMR δ 0.92 (t, 3, *J* = 7), 1.46 (quintet, 2, *J* = 7), 2.04 (s, 3), 2.28 (s, 1), 3.72 (m, 1), 3.86–4.12 (m, 2); $^{13}$C NMR δ 9.75, 20.88, 26.36, 68.38, 71.08, 171.38.

(*R*)-1,2-Diacetoxybutane [(*R*)-**6a**]: $^1$H NMR δ 0.87 (t, 3, *J* = 7), 1.56 (quintet, 2, *J* = 7), 2.00 (s, 3), 2.01 (s, 3), 4.04–4.21 (m, 2), 4.94 (m, 1); $^{13}$C NMR δ 9.48, 20.74, 21.02, 23.80, 64.74, 72.71, 170.57, 170.72.

For the data of the other compounds see supplementary material.

**Determination of the ee of Diols 4a–d.** The resulting monoacetates (*S*)-**5a–c** and (*R*)-**5d** and the diacetates (*R*)-**6a–c** and (*S*)-**6d** were deacetylated as described above with methanol and Wofatit SBW ($OH^-$ form). The ee of the diols (*R*)- and (*S*)-**4a–c** was determined after pertrifluoroacetylation in the usual manner by GLC on Lipodex E. The ee of (*R*)- and (*S*)-**4d** was determined by HPLC on cellulose tris((4-chlorophenyl)carbamate).

(*S*)-**5a** (0.180 g) gave 0.117 g (95%) of (*S*)-**4a**: ee 49%. (*R*)-**6a** (0.090 g) gave 0.048 g (97%) of (*R*)-**4a**: ee 94%.

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**Supplementary Material Available:** Compound characterization data of the compounds (*R*)-**2a**, (*R*)-**2c–f**, (*R*)-**2h–n**, (*S*)-**3a**, (*S*)-**3c–f**, (*S*)-**3h–n**, (*S*)-**5b**, (*S*)-**5c**, (*R*)-**5d**, (*R*)-**6b**, (*R*)-**6c**, and (*S*)-**6d** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfiche version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.