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Resolution of 2-aryloxy-1-propanols via lipase-catalyzed enantioselective acylation in organic media

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Abstract—2-Aryloxy-1-propanols, primary alcohols with an oxygen atom at the stereocenter, were resolved with good to high enantioselectivity by acylation with vinyl butanoate mediated by *Pseudomonas* sp. lipase in di-*iso*-propyl ether. Potential factors affecting the enantioselectivity of the enzymatic acylation were examined: solvents, acyl donors and temperature. Using this enantioselective acylation procedure, enantiomerically pure (*R*)-2-(4-chlorophenoxy)-1-propanol was prepared on a gram scale.

1. Introduction

Homochiral alcohols are useful building blocks for the synthesis of a wide variety of biologically active compounds and functional materials such as liquid crystals. Enzymatic methodologies have recently been recognized as the most attractive approaches for obtaining such compounds in enantiomerically pure form. Lipases from different sources have been used for the resolution of racemic alcohols via hydrolysis, transesterification or esterification.[1] However, compared to the high number of reports on the resolution of secondary alcohols using lipases, successful examples with primary alcohols have been documented far less.[2] It has been reported that most lipases show low enantioselectivity toward primary alcohols and only lipases from *Pseudomonas cepacia* and porcine pancreas resolve these substrates with moderate to high enantioselectivity.[3] In the lipase-catalyzed resolution of secondary alcohols, a simple rule based on the size of the substituents was proposed which could predict the favored enantiomer.[4] A similar rule was later introduced for the *P. cepacia* lipase-catalyzed reactions of primary alcohols,[5,†] and a revised model has recently been proposed[6] from molecular modeling studies of transition state analogs bound to the active site of the lipase, where primary alcohols are bound in a different manner to secondary alcohols. However, the rule is not reliable for primary alcohols with an oxygen atom at the stereogenic center.[5,6] Accordingly, it seemed challenging to explore the enzymatic resolution of this class of primary alcohols using lipases. We report herein the detailed results of our investigation concerning the resolution of 2-aryloxy-1-propanol analogues via the lipase-catalyzed enantioselective acylation.[7] These 2-aryloxy-1-propanols are useful chiral starting materials for the synthesis of a sorbinil homolog[8] and of juvenile hormone analogs (juvenoids) of the 2-(4-hydroxybenzyl)-1-cyclohexanone series.[9]

2. Results and discussion

Initially, lipases from microbial and pancreatic sources were screened for the acylation of the parent 2-phenoxy-1-propanol **1a** with vinyl butanoate as an acyl donor in di-*iso*-propyl ether[‡] (Scheme 1). Some of the results are shown in Table 1.

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† Other predictive active site models have also been reported for lipases from *Pseudomonas* sp. and *Alcaligenes* sp. to identify which enantiomer of an alcohol (primary or secondary) reacts faster in the lipase-catalyzed acylation (see Refs. 2a and 2b).

‡ We have reported the lipase-catalyzed highly enantioselective deacylation and acylation of mandelic acid derivatives in this solvent.[10]

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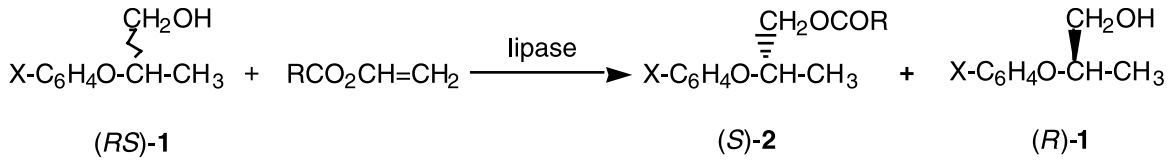

Scheme 1. Lipase-catalyzed enantioselective acylation of (±)-2-aryloxy-1-propanols [(*RS*)-**1**] with vinyl esters.

Table 1. Lipase-catalyzed acylation of (*RS*)-**1a** with vinyl butanoate in di-*iso*-propyl ether[a]

Lipase source	% Convn.	Time (min)	% E.e.$_s$[b]	*E*
Pseudomonas sp.[c]	51	110	89	35
P. cepacia[d]	60	13	92	13
Porcine pancreas[e]	62	60	94	12
C. viscosum[f]	66	19	96	11
M. javanicus[g]	56	150	66	6.0

[a] Reactions were conducted at 25°C as described in Section 4.
[b] E.e. of the remaining alcohol, whose preferred absolute configuration is *R*.
[c] Amano AK; 5 mg.
[d] Amano P; 25 mg.
[e] Sigma Type II; 25 mg.
[f] Asahi Kasei LP; 12 mg.
[g] Amano M; 25 mg.

The rate and enantioselectivity of the reaction varied markedly depending on the enzyme employed, while the stereochemical preference remained unchanged, the preferred absolute configuration of the remaining alcohol being *R* (see below). Of the enzymes tested, *Pseudomonas* sp. lipase (Amano AK) showed the highest enantioselectivity as judged from the values of enantiomeric ratio, *E*.[11] A large number of examples have already been accumulated on the effect of organic solvents on lipase-catalyzed reactions.[12] However, it is still difficult to predict the solvent effect, especially on enantioselectivity, and the practical way is to select an appropriate solvent through screening experiments.

Table 2 shows the effect of solvents other than di-*iso*-propyl ether on the acylation of **1a** with vinyl butanoate mediated by *Pseudomonas* sp. lipase. The solvents examined had little influence on the enantioselectivity of the reaction, with the exception of benzene in which it deteriorated compared with the reaction in di-*iso*-propyl ether. Acylation in acetonitrile was found to proceed very slowly.

Table 2. Solvent effect on the *Pseudomonas* sp. lipase-catalyzed acylation of (*RS*)-**1a** with vinyl butanoate[a]

Solvent	% Convn.	Time (min)	% E.e.$_s$[b]	*E*
1,4-Dioxane	52	110	89	34
Acetonitrile	51	95 h	88	32
THF	51	100	88	30
Benzene	49	60	47	4.5
Tetrachloromethane	55	100	94	27
Cyclohexane	50	60	83	27
Hexane	48	300	78	27

[a] Reactions were conducted at 25°C as described in Section 4.
[b] E.e. of the remaining alcohol, whose preferred absolute configuration is *R*.

Next, the resolution of a number of aryloxy-1-propanol analogues **1** bearing different benzene ring substituents was examined in the acylation with vinyl butanoate mediated by the same lipase in di-*iso*-propyl ether. As shown in Table 3, the substituent did not have a significant effect on the reaction rate but had a considerable effect on the enantioselectivity of the reaction.

The substitution of a chlorine atom reduced the enantioselectivity without affecting the acylation rate. On the other hand, the substitution of two chlorine atoms at the *o*- and *p*-positions lowered the enantioselectivity as well as that of the *p*-ethyl or *p*-*iso*-propyl group, suggesting that the bulk of the substituent on the

Table 3. *Pseudomonas* sp. lipase-catalyzed acylation of 2-aryloxy-1-propanols [(*RS*)-**1**] with vinyl butanoate in di-*iso*-propyl ether[a]

Compound	X	% Convn.	Time (min)	% E.e.$_s$[b]	*E*
1a	H	51	110	89	35
1b	4-F	50	100	86	34
1c	2-Cl	48	100	89[c]	48
1d	3-Cl	51	130	92	55
1e	4-Cl	50	120	90	58
1f	2,4-Cl$_2$	52	110	76[c]	19
1g	4-Et	53	90	84	18
1h	4-Pr^i	50	110	73	15

[a] Reactions were conducted at 25°C as described in Section 4.
[b] E.e. of the remaining alcohol.
[c] E.e. of the ester formed.

benzene ring has a deleterious effect on the enantioselectivity. Even in these cases, however, the E values were larger than 15, with which the recovered substrate with a practically high enantiomeric excess (e.e.) can be obtained when the reaction is allowed to proceed over ca.60% conversion.[11] In all of the cases examined, the recovered alcohols were of (*R*)-configuration, as confirmed by comparison with the authentic samples, i.e. (*S*)- or (*R*)-enriched 2-aryloxy-1-propanols prepared through the reduction of the corresponding (*S*)- or (*R*)-enriched 2-aryloxypropanoic acids, respectively, obtained via the lipase-catalyzed transesterification of their racemic vinyl esters or esterification of racemic acids.[13] This indicates that the (*S*)-alcohols react preferentially to give the (*S*)-butanoates **2**. The stereochemical preference observed here is contrary to that predicted by the empirical rule mentioned above for the *P. cepacia* lipase-catalyzed reactions of primary alcohols without an oxygen atom at the stereogenic center.[5] Furthermore, gram-scale resolution of (*RS*)-2-(4-chlorophenoxy)-1-propanol **1e** was achieved. After incubation for 8 h (56% conversion) with vinyl butanoate in di-*iso*-propyl ether in the presence of *Pseudomonas* sp. lipase, (*R*)-**1e** with >99% e.e. was isolated as the unreacted substrate alcohol through column chromatography on silica gel.

2.1. Effect of acyl donors

The lipase-catalyzed enantioselective acylation of a racemic alcohol with an achiral donor ester proceeds via the acyl–enzyme intermediate and the enantiodiscrimination of the alcohol should occur during the subsequent alcoholysis of the intermediate. Accordingly, it is reasonable to anticipate that the enantioselectivity as well as the rate of the acylation reaction must be significantly affected by the donor ester, particularly by its acid moiety. However, systematic investigations have scarcely been carried out. We previously examined the effect of a series of vinyl esters in the *Pseudomonas* sp. lipase-catalyzed acylation of methyl (*RS*)-mandelate and found that the chain length of the fatty acid moiety of the vinyl esters had a marked effect on the conversion rate, with those carrying a shorter alkyl chain serving as better acyl donors. The enantioselectivity was highest with vinyl butanoate.[10a] More recently, Ema et al. also studied the effect of different vinyl esters on the lipase-catalyzed acylation of 2-[(*N*,*N*-dimethylcarbamoyl)methyl]-3-cyclopenten-1-ol and observed a similar change in enantioselectivity with the chain length of the acyl moiety of the donor esters.[14]

As shown in Table 4 for the *Pseudomonas* sp. lipase-catalyzed acylation of **1a** in di-*iso*-propyl ether, the enantioselectivity was the highest with vinyl acetate and it tends to become lower with the chain length of the fatty acid moiety, though the difference between the acetate and the butanoate, for example, was not very large. With vinyl chloroacetate the enantioselectivity decreased and with vinyl trifluoroacetate it deteriorated greatly. The results obtained here and those mentioned above[10,14] indicate that acyl donors strongly affect the lipase's enantioselectivity due to both steric and electronic factors.

Table 4. Effect of acyl donors on the *Pseudomonas* sp. lipase-catalyzed acylation of (*RS*)-**1a** in di-*iso*-propyl ether[a]

R of vinyl ester[b]	% Convn.	Time (min)	% E.e.$_S$[c]	E
CH_3	52	50	93	42
C_2H_5	52	80	90	35
n-C_3H_7	51	110	89	35
n-C_5H_{11}	51	120	87	36
n-C_7H_{15}	55	40	94	28
n-$C_{11}H_{23}$	46	50	74	28
$ClCH_2$	47	10	63	11
CF_3	40	120	11	1.5

[a] Reactions were conducted at 25°C as described in Section 4.
[b] See Scheme 1.
[c] E.e. of the remaining alcohol.

2.2. Effect of temperature

Temperature is another factor which can potentially affect the rate and enantioselectivity of enzymatic reactions, and there is a general belief that enzymes exhibit their highest selectivity at low temperature. In the *Aspergillus oryzae* protease-catalyzed hydrolysis of the *iso*-butyl esters of some aliphatic amino acids, we observed previously that the enantioselectivity was improved greatly at 5°C compared with the reaction at 25°C.[15] However, it has been pointed out that the higher enantioselectivity at lower temperature is not always the case; a temperature-dependent reversal of stereochemistry has been reported in a few enzymatic reactions.[16] A rational understanding of this phenomenon has also been proposed.[17] Accordingly, the acylations of **1a** were investigated using vinyl butanoate or vinyl chloroacetate as the acyl donor in di-*iso*-propyl ether at different temperatures (0–40°C). The enantioselectivity was found to improve with decreasing temperature, though the reaction rate was diminished considerably. The best compromises in terms of both the acylation rate and the enantioselectivity were obtained at 5°C in the acylation with vinyl butanoate (45% conversion after 200 min; $E=60$) and at 0°C in the acylation with vinyl chloroacetate (37% conversion after 180 min; $E=15$). When $-RT\ln E$, representing the activation free energy difference ($\Delta\Delta G^{\ddagger}$) between the enantiomers, was plotted against the absolute temperature, T, approximately linear correlations were obtained between them (Fig. 1), although the slope was very small for the chloroacetylation.

The linear plots depicted in Fig. 1 indicate that there should have been no change in the reaction mechanism, i.e. in the lipase's active conformation in the temperature range examined.[§] In these acylations the racemic

[§] If the differences in the activation enthalpy and activation entropy ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) remain constant in a certain temperature range, the temperature dependence of enantioselectivity can be given by the equation $\Delta\Delta G^{\ddagger}=-RT\ln E=\Delta\Delta H^{\ddagger}-T\Delta\Delta S^{\ddagger}$. Thus, in such a case $-RT\ln E$ should be linearly correlated with T.[17]

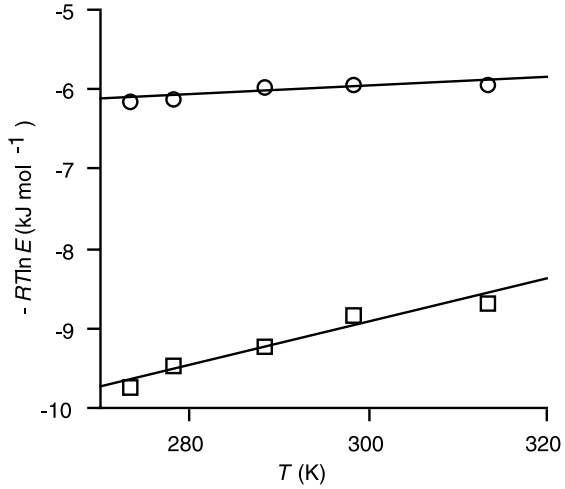

Figure 1. Influence of temperature on the difference in the activation free energy ($\Delta\Delta G^{\ddagger} = -RT \ln E$) between the enantiomers for the *Pseudomonas* sp. lipase-catalyzed acylation of (*RS*)-**1a** with vinyl butanoate (□) or vinyl chloroacetate (○) in di-*iso*-propyl ether.

temperatures defined as $T_r = \Delta\Delta H^{\ddagger}/\Delta\Delta S^{\ddagger}$, at which there occurs no enantiomeric discrimination, lie far above the ordinary temperature and thus the reversion of enantioselectivity was never observed. Such a situation must often be the case and the enantioselectivity increases with decreasing temperature, as is usually believed.[18] Thus, lower temperature can often cause the enhancement of enzyme's enantioselectivity.

3. Conclusion

In summary, 2-aryloxy-1-propanols, which belong to primary alcohols with an oxygen atom at the stereocenter, were resolved with good to high enantioselectivity via the *Pseudomonas* sp. lipase-catalyzed acylation procedure. The acyl donor and temperature affected the enantioselectivity of the present enzymatic transesterification considerably. The results obtained here, together with those reported earlier, demonstrate that *Pseudomonas* lipases are useful enzymes for the resolution of primary alcohols.

4. Experimental

(±)-2-Phenoxypropanoic, (±)-2-(2-chlorophenoxy)-propanoic, (±)-2-(3-chlorophenoxy)propanoic and (±)-2-(2,4-dichlorophenoxy)propanoic acids were purchased from Tokyo Chemical Industry, (±)-2-(4-chlorophenoxy)propanoic acid from Aldrich, and (±)-2-(4-fluorophenoxy)propanoic acid from Lancaster. (±)-2-(4-Ethylphenoxy)propanoic and (±)-2-(4-*iso*-propylphenoxy)propanoic acids were prepared from 4-ethyl- and 4-*iso*-propylphenols, respectively, according to the literature method.[13,19] All the organic solvents were distilled and dried over molecular sieves prior to use. The following lipases were screened as transesterification catalysts, which were obtained from Amano Pharmaceutical Co., Meito Sangyo Co., Asahi Chemical Industry Co., or Sigma: ex *Pseudomonas* sp. (Amano AK), *Achromobacter* sp. (Meito AL), *P. cepacia* (Amano P), *Chromobacterium viscosum* (Asahi Kasei LP), *Mucor javanicus* (Amano M), *Rhizopus delemar* (Amano D) and porcine pancreas (Sigma Type II).

TLC was run on precoated silica gel plates (Merck). IR spectra were recorded on a Nicolet N-750B FT-IR spectrometer using attenuated total reflectance (ATR). ^{1}H NMR spectra (300 MHz) were recorded on a Varian Unity 300 spectrometer using $CDCl_3$ as a solvent with TMS as an internal standard. Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter. Elemental analyses of new compounds are compiled in Table 5.

4.1. Preparation of racemic (±)-2-aryloxy-1-propanols 1a–1h

These compounds were prepared by the reduction of the corresponding 2-aryloxypropanoic acids using borane–THF complex. The preparation of **1a** is described as a typical example. To a stirred solution of 2-phenoxypropanoic acid (10.0 g, 60 mmol) in dry THF (20 mL) was added BH_3 in THF (1 M, 84 mL, 84 mmol; Aldrich) dropwise over a period of 80 min with ice-cooling and the atmosphere of nitrogen, and the mixture was stirred at ambient temperature overnight. A 1:1 (v/v) mixture of THF and water (24 mL) was added and the resulting mixture was stirred for 90 min. After THF had been removed in vacuo, the residue was diluted by adding water (30 mL), brought to pH 9 by adding solid K_2CO_3, and extracted with ether (3×100 mL). The ethereal extracts were combined, washed with water (3×30 mL), and dried over Na_2SO_4. After evaporation of the solvent in vacuo the residual oil was distilled under reduced pressure to give a colorless oil (7.4 g, 81%). The 2-aryloxy-1-propanols **1b**–**1h** were likewise prepared and purified by distillation under reduced pressure to give oils in 77–85% yield. The physical and ^{1}H NMR data of **1** thus prepared are compiled in Table 6.

4.2. Preparation of alkanoates of (±)-2-aryloxy-1-propanols

Authentic samples of the butanoates of (±)-2-aryloxy-1-propanols were prepared by the reaction of each (±)-2-aryloxy-1-propanol with butanoyl chloride. The butanoylation of **1a** is described as a typical example. To a stirred solution of **1a** (200 mg, 1.3 mmol) and pyridine (120 μL, 1.5 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise from a syringe a solution of butanoyl chloride (140 μL, 1.3 mmol) in CH_2Cl_2 (0.4 mL) under ice-cooling, and the mixture was stirred at ambient temperature overnight. Ether (30 mL) was added and the white precipitates were filtered off, and then the

Table 5. Elemental analyses of new compounds

Compound	Molecular formula	C (%) found (required)	H (%) found (required)
1a	$C_9H_{12}O_2$	70.92 (71.03)	8.00 (7.95)
1b	$C_9H_{11}FO_2$	63.78 (63.52)	6.58 (6.51)
1c	$C_9H_{11}ClO_2$	57.76 (57.92)	5.93 (5.94)
1d	$C_9H_{11}ClO_2$	57.83 (57.92)	5.99 (5.94)
1e	$C_9H_{11}ClO_2$	58.21 (57.92)	5.75 (5.94)
1f	$C_9H_{10}Cl_2O_2$	48.85 (48.90)	4.82 (4.56)
1g	$C_{11}H_{16}O_2$	73.65 (73.30)	9.06 (8.95)
1h	$C_{12}H_{18}O_2$	73.96 (74.19)	9.07 (9.34)
Acetate of **1a**	$C_{11}H_{14}O_3$	68.27 (68.02)	7.21 (7.26)
Propanoate of **1a**	$C_{12}H_{16}O_3$	68.95 (69.21)	8.02 (7.74)
Butanoate of **1a**	$C_{13}H_{18}O_3$	69.87 (70.25)	8.28 (8.16)
Hexanoate of **1a**	$C_{15}H_{22}O_3$	72.04 (71.97)	8.70 (8.86)
Octanoate of **1a**	$C_{17}H_{26}O_3$	72.99 (73.35)	9.56 (9.41)
Dodecanoate of **1a**	$C_{21}H_{34}O_3$	75.66 (75.41)	10.47 (10.24)
Chloroacetate of **1a**	$C_{11}H_{13}ClO_3$	57.91 (57.78)	5.53 (5.73)
Butanoate of **1b**	$C_{13}H_{17}FO_3$	65.14 (64.99)	7.16 (7.13)
Butanoate of **1c**	$C_{13}H_{17}ClO_3$	60.80 (60.82)	6.56 (6.67)
Butanoate of **1d**	$C_{13}H_{17}ClO_3$	61.14 (60.82)	6.39 (6.67)
Butanoate of **1e**	$C_{13}H_{17}ClO_3$	60.69 (60.82)	6.88 (6.67)
Butanoate of **1f**	$C_{13}H_{16}Cl_2O_3$	53.32 (53.63)	5.57 (5.54)
Butanoate of **1g**	$C_{15}H_{22}O_3$	69.87 (70.07)	8.28 (8.13)
Butanoate of **1h**	$C_{16}H_{24}O_3$	72.97 (72.69)	9.04 (9.15)

Table 6. Physical and ^{1}H NMR data of 2-aryloxy-1-propanols **1**

Compound	Bp/°C	n_D^{20}	R_f[a]	IR (ATR) ν_{max}/cm^{-1} (OH)	^{1}H NMR δ_H ($CDCl_3$)
1a	65–68 (0.25 mmHg)	1.5244	0.38	3379	1.27 (3H, d, *J* 6.3), 2.05 (1H, br s), 3.68–3.79 (2H, d of ABq, *J* 11.4, 6.3 and 3.9), 4.50 (1H, d of quint., *J* 6.3 and 3.9), 6.91–7.32 (5H, m)
1b	64–71 (0.07 mmHg)	1.5012	0.38	3411	1.24 (3H, d, *J* 6.3), 2.11 (1H, dd, *J* 5.4 and 5.1), 3.65–3.78 (2H, m), 4.40 (1H, d of quint., *J* 6.3 and 3.9), 6.84–7.01 (4H, m)
1c	78–84 (0.04 mmHg)	1.5380	0.42	3398	1.32 (3H, d, *J* 6.3), 2.37 (1H, br s), 3.76 (2H, d-like, *J* 5.1), 4.48 (1H, d of quint., *J* 6.3 and 5.1), 6.89–7.38 (4H, m)
1d	96–102 (0.2 mmHg)	1.5403	0.39	3416	1.27 (3H, d, *J* 6.3), 2.07 (1H, t-like, *J* 6.0), 3.66–3.79 (2H, m), 4.48 (2H, d of quint., *J* 6.3 and 4.2), 6.79–7.22 (4H, m)
1e	93–99 (0.03–0.04 mmHg)	1.5379	0.37	3381	1.24 (3H, d, *J* 6.3), 2.20 (1H, br s), 3.66–3.76 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.43 (1H, d of quint., *J* 6.3 and 4.2), 6.82–7.26 (4H, m)
1f	106–111 (0.07 mmHg)	1.5505	0.40	3360	1.30 (3H, d, *J* 6.3), 2.28–2.32 (1H, m), 3.74–3.78 (2H, m), 4.45 (1H, d of quint., *J* 6.3 and 5.4), 6.92–7.37 (3H, m)
1g	69–80 (0.05–0.06 mmHg)	1.5159	0.41	3388	1.18–1.26 (6H, m), 2.24 (1H, br s), 2.59 (2H, q, *J* 7.5), 3.64–3.77 (2H, m), 4.44 (1H, d of quint., *J* 6.3 and 3.9), 6.84–7.12 (4H, m)
1h	64–75 (0.04–0.05 mmHg)	1.5119	0.41	3385	1.21–1.26 (9H, m), 2.15 (1H, br s), 2.86 (1H, sept., *J* 6.9), 3.65–3.76 (2H, d of ABq, *J* 11.7, 6.3 and 3.6), 4.45 (1H, d of quint., *J* 6.3 and 3.6), 6.84–7.16 (4H, m)

[a] Solvent: benzene–EtOAc (4:1, v/v).

filtrate was washed successively with 1 M HCl (2×7 mL), water (7 mL), aq. $NaHCO_3$ (1 M, 2×7 mL), and brine (2×7 mL), and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residual oil was purified by preparative TLC on silica gel (Wakogel B-5F) using ether–hexane (3:20, v/v) as an eluent to give the butanoate of **1a** as a colorless oil (180 mg, 61%). The butanoates of **1b**–**1h** were likewise prepared and purified by preparative TLC on silica gel to give oils in 57–70% yield.

Other alkanoates of **1a** were prepared by the reaction of **1a** with the corresponding alkanoyl chloride (or ethyl trifluoroacetate in the case of trifluoroacetylation) in the presence of pyridine in the same manner as above and purified by preparative TLC on silica gel to give oils in 47–77% yield. The trifluoroacetate of **1a** was obtained as an oil through purification by Kugelrohr distillation (bp 105°C/1.8 mmHg) in 60% yield. The physical and ^{1}H NMR data of the alkanoates of **1** thus prepared are compiled in Table 7.

Table 7. Physical and ^{1}H NMR data of alkanoates of **1**

Compound	n_D^{20}	R_f[a]	IR (ATR) ν_{max}/cm^{-1} (C=O)	^{1}H NMR δ_H ($CDCl_3$)
Acetate of **1a**	–[b]	0.31	1732	1.33 (3H, d, *J* 6.3), 2.06 (3H, s), 4.14–4.29 (2H, d of ABq, *J* 11.4, 6.3 and 4.2), 4.61 (1H, d of quint., *J* 6.3 and 4.2), 6.91–7.31 (5H, m)
Propanoate of **1a**	1.4904	0.35	1740	1.12 (3H, t, *J* 7.5), 1.34 (3H, d, *J* 6.3), 2.33 (2H, q, *J* 7.5), 4.14–4.31 (2H, d of ABq, *J* 11.7, 6.3 and 4.5), 4.61 (1H, d of quint., *J* 6.3 and 4.5), 6.92–7.31 (5H, m)
Butanoate of **1a**	1.4858	0.39	1738	0.93 (3H, t, *J* 7.2), 1.34 (3H, d, *J* 6.3), 1.64 (2H, sext., *J* 7.2), 2.29 (2H, t, *J* 7.2), 4.14–4.30 (2H, d of ABq, *J* 11.4, 6.3 and 4.5), 4.61 (1H, d of quint., *J* 6.3 and 4.5), 6.91–7.31 (5H, m)
Hexanoate of **1a**	1.4832	0.43	1739	0.87 (3H, t, *J* 6.6), 1.24–1.30 (4H, m), 1.33 (3H, d, *J* 6.3), 1.56–1.63 (2H, m), 2.30 (2H, t, *J* 7.5), 4.14–4.30 (2H, d of ABq, *J* 11.4, 6.3 and 4.5), 4.61 (1H, d of quint., *J* 6.3 and 4.5), 6.91–7.31 (5H, m)
Octanoate of **1a**	1.4808	0.43	1739	0.87 (3H, t, *J* 6.9), 1.21–1.31 (8H, m), 1.33 (3H, d, *J* 6.3), 1.55–1.64 (2H, m), 2.30 (2H, t, *J* 7.5), 4.13–4.30 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.61 (1H, d of quint., *J* 6.3 and 4.2), 6.91–7.30 (5H, m)
Dodecanoate of **1a**	1.4787	0.45	1740	0.88 (3H, t, *J* 6.6), 1.25–1.30 (16H, m), 1.33 (3H, d, *J* 6.3), 1.56–1.61 (2H, m), 2.30 (2H, t, *J* 7.5), 4.13–4.30 (2H, d of ABq, *J* 11.7, 6.3 and 4.5), 4.61 (1H, d of quint., *J* 6.3 and 4.5), 6.91–7.30 (5H, m)
Chloroacetate of **1a**	1.5126	0.28	1760	1.35 (3H, d, *J* 6.3), 4.05 (2H, s), 4.25–4.42 (2H, d of ABq, *J* 11.4, 6.6 and 4.2), 4.64 (1H, d of quint., *J* 6.6 and 4.2), 6.91–7.31 (5H, m)
Trifluoroacetate of **1a**	1.4562[c]	0.41	1788	1.38 (3H, d, *J* 6.3), 4.38–4.57 (2H, d of ABq, *J* 11.4, 6.3 and 3.9), 4.67 (1H, d of quint., *J* 6.3 and 3.9), 6.89–7.33 (5H, m)
Butanoate of **1b**	1.4731	0.37	1738	0.93 (3H, t, *J* 7.5), 1.32 (3H, d, *J* 6.3), 1.59 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 4.12–4.28 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.50 (1H, d of quint., *J* 6.3 and 4.2), 6.84–7.01 (4H, m)
Butanoate of **1c**	1.5007	0.38	1737	0.93 (3H, t, *J* 7.5), 1.39 (3H, d, *J* 6.3), 1.63 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 4.18–4.33 (2H, d of ABq, *J* 11.7, 6.3 and 4.5), 4.60 (1H, d of quint., *J* 6.3 and 4.5), 6.89–7.38 (4H, m)
Butanoate of **1d**	1.5017	0.40	1739	0.93 (3H, t, *J* 7.5), 1.33 (3H, d, *J* 6.3), 1.64 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 4.14–4.28 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 6.79–7.22 (4H, m)
Butanoate of **1e**	1.4978	0.38	1737	0.93 (3H, t, *J* 7.5), 1.32 (3H, d, *J* 6.3), 1.63 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 4.12–4.28 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.55 (1H, d of quint., *J* 6.3 and 4.2), 6.83–7.25 (4H, m)
Butanoate of **1f**	1.5114	0.36	1739	0.93 (3H, t, *J* 7.5), 1.37 (3H, d, *J* 6.3), 1.63 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 4.17–4.31 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.56 (1H, d of quint., *J* 6.3 and 4.2), 6.94 (1H, d, *J* 9.0), 7.17 (1H, dd, *J* 9.0 and 2.7), 7.37 (1H, d, *J* 2.7)
Butanoate of **1g**	1.4864	0.43	1739	0.93 (3H, t, *J* 7.5), 1.21 (3H, t, *J* 7.5), 1.32 (3H, d, *J* 6.0), 1.64 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 2.58 (2H, q, *J* 7.5), 4.12–4.29 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.56 (1H, d of quint., *J* 6.3 and 4.2), 6.83–7.13 (4H, m)
Butanoate of **1h**	1.4860	0.42	1739	0.93 (3H, t, *J* 7.5), 1.22 (6H, d, *J* 7.2), 1.32 (3H, d, *J* 6.3), 1.63 (2H, sext., *J* 7.5), 2.29 (2H, t, *J* 7.5), 2.86 (1H, sept., *J* 7.2), 4.12–4.29 (2H, d of ABq, *J* 11.7, 6.3 and 4.2), 4.56 (1H, d of quint., *J* 6.3 and 4.2), 6.83–7.15 (4H, m)

[a] Solvent: hexane–EtOAc (9:1, v/v).
[b] Semisolid.
[c] At 17°C.

4.3. HPLC analyses

Transesterification reactions were monitored by chiral HPLC on a Chiralcel OB column (4.6 mm id×250 mm) or a Chiralpak AS column (4.6 mm id×250 mm) (Daicel Chemical Industries) using hexane–propan-2-ol as an eluent. The liquid chromatograph employed was a Shimadzu LC-5A instrument, equipped with a Rheodyne 7125 sample injector and a Shimadzu SPD-2A variable wavelength UV monitor. A Shimadzu C-R1A data processor was used for data acquisition and processing. In general the enantiomers of alkanoates of 2-aryloxy-1-propanols were not separated on either column satisfactorily enough for the accurate determination of the ee value,[¶] while the corresponding alcohols were separated well on either of the columns by choosing an appropriate proportion of hexane/propan-2-ol for each compound. The void time (t_0) was estimated using 1,3,5-tri-*tert*-butylbenzene. The separation of the enantiomers of **1a**–**1h** is compiled in Table 8.

[¶] The enantiomers of butanoates of **1c** and **1f** were separated better than those of their parent alcohols: $k'_S=0.77$ and $k'_R=1.18$ for the butanoate of **1c** on Chiralcel OB using hexane–propan-2-ol (95:5, v/v); $k'_S=1.46$ and $k'_R=2.27$ for the butanoate of **1f** on Chiralcel OB using hexane–propan-2-ol (99:1, v/v).

Table 8. HPLC separation of the enantiomers of 2-aryloxy-1-propanols **1**[a]

Compound	Column[b]	Mobile phase[c]	k'_S[d]	k'_R[d]	α[e]
1a	A	95:5	1.74	2.68	1.54
1b	A	95:5	1.73	3.15	1.82
1c	B	95:5	1.41	1.99	1.41
1d	A	99:1	4.89	5.64	1.15
1e	B	95:5	1.69	2.27	1.34
1f	B	99:1	4.19	4.82	1.15
1g	A	299:1	6.74	8.80	1.31
1h	A	299:1	5.16	6.44	1.25

[a] HPLC conditions: flow rate, 1.0 mL min^{-1}; column temperature, 30°C; detection, UV at 254 nm.
[b] A, Chiralpak AS; B, Chiralcel OB.
[c] The proportion of hexane/propan-2-ol.
[d] Capacity factor: $k'=(t_R-t_0)/t_0$, where t_0 = void time.
[e] Separation factor: $\alpha=k'_R/k'_S$.

4.4. Preparation of enantiomerically enriched samples of 2-aryloxy-1-propanols

(*S*)- or (*R*)-Enriched 2-aryloxy-1-propanols were prepared by reduction with borane–THF complex on a small scale (ca.0.2 mmol) of the corresponding (*S*)- or (*R*)-enriched 2-aryloxypropanoic acids, respectively, which were obtained via the *Aspergillus niger* lipase (Amano lipase A)-catalyzed transesterification of the racemic vinyl esters with methanol [(*S*)-preference] or the *Candida rugosa* lipase (Meito lipase MY or Amano lipase AY)-catalyzed esterification of the racemic acids with butanol [(*R*)-preference] in organic solvents.[13] With all the 2-aryloxy-1-propanols the (*S*)-enantiomer eluted before the (*R*)-counterpart on both Chiralcel OB and Chiralpak AS columns using hexane–propan-2-ol as an eluent. In the case of (*S*)-**1e** reduction was conducted on a semi-preparative scale as follows: (*S*)-2-(4-chlorophenoxy)propanoic acid (380 mg, 1.9 mmol; 83% e.e.) was treated with BH_3 in THF (1 M, 5 mL) in the same manner as above. After a usual work-up, the crude material was purified by preparative TLC using EtOAc–benzene (1:4, v/v) to give a colorless oil (208 mg, 59%): $[\alpha]_D^{25}=+27.9$ (*c* 1.0, $CHCl_3$); 83% e.e. by HPLC.

4.5. General procedure for the lipase-catalyzed enantioselective acylation of 2-aryloxy-1-propanols

A solution of the 2-aryloxy-1-propanol (0.3 mmol) and the vinyl alkanoate (0.9 mmol) in an organic solvent (0.8 mL) was stirred with the lipase preparation (5 mg) in a thermostated bath. Monitoring the reaction and the e.e. value of the unreacted substrate alcohol, or of the ester formed in some cases was conducted simultaneously by HPLC analysis on the chiral columns mentioned above. Aliquots (ca. 10 μL) of the reaction mixture were withdrawn at frequent intervals, diluted with di-*iso*-propyl ether (100 μL), filtered through a PTFE membrane filter, and then injected (1–5 μL) onto the column.

4.6. Gram-scale resolution of 2-(4-chlorophenoxy)-1-propanol 1e

Alcohol (±)-**1e** (3.06 g, 16.5 mmol) was dissolved in di-*iso*-propyl ether (45 mL), followed by the addition of vinyl butanoate (6 mL, 47.4 mmol) and then *Pseudomonas* sp. lipase (300 mg). The reaction mixture was stirred at 25°C. The reaction was terminated after 8 h (56% conversion) by removing the enzyme powder by filtration. The enzyme was washed with ether. Evaporation of the solvent in vacuo from the combined filtrate and the washing afforded a pale yellow oil, from which the products were isolated by column chromatography on silica gel (Wakogel C-300) using ether–hexane (1:20, v/v) as an eluent, to give initially the butanoate of (*S*)-**1e** as a colorless oil (2.01 g, 48% yield). Further elution afforded (*R*)-**1e** as a colorless oil (1.11 g, 36% yield); $[\alpha]_D^{25}=-35.1$ (*c* 1.0, $CHCl_3$); >99% e.e. by HPLC.

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