Chemoenzymatic Approach toward the Pure Enantiomers of 2-Methyl-1,3-propanediol Mono(*p*-Methoxybenzyl Ether)

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Abstract: In a route towards the enantiomerically pure 2-methylpropane-1,3-diol mono(*p*-methoxybenzyl ether), which is an important starting material for natural product synthesis, a kinetic resolution approach by means of lipase-catalyzed hydrolysis as well as acylation has been elaborated. *Candida antarctica* lipase-catalyzed hydrolysis of the corresponding racemic acetate proceeded with high enantioselectivity (E 35). During the studies, a curious phenomenon was observed, namely, that the enantioselectivity gradually declined accompanying the progress of the hydrolysis. This was due to inhibition of the enzyme-catalyzed reaction caused by the accumulation of the resultant alcohol. The rate of reaction of the more reactive enantiomer became lower. This situation prompted a new process, which would minimize the contamination of the undesired enantiomer, prior to the enzyme-catalyzed hydrolysis. This was successfully achieved with the aid of another *Pseudomonas cepacia* lipase-catalyzed desymmetrization, taking advantage of the prochiral nature of the starting material, 2-methyl-1,3-propanediol, and the subsequent *p*-methoxybenzylation under mild conditions.

Keywords: chiral building blocks; desymmetrization; hydrolysis; inhibitors; kinetic resolution; lipase; prochiral substrate

Introduction

The importance of mono-protected forms of 2-methylpropane-1,3-diol with a (substituted) benzyl group (**1a**[1] and **2a**,[2] Figure 1) has well been recognized as chiral building blocks in natural product synthesis.

Almost all the previous syntheses of enantiomerically enriched forms of **1a** and **2a** have so far started from both enantiomers of β-hydroxyisobutyric acid.[3] We report here an expeditious approach to **2a**, based on a lipase-catalyzed kinetic resolution of racemic **2a** itself and the corresponding acetate **2b**.

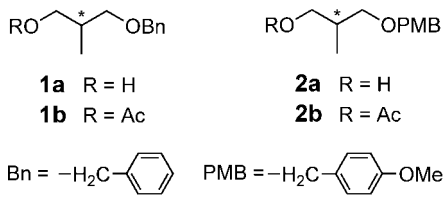

Figure 1.

Results and Discussion

Preparation of the Substrate

Towards this end, a preparative-scale synthesis of the substrate (**2a** and **2b**) was elaborated. The starting material, 2-methyl-1,3-propanediol (**3a**) was treated with *p*-anisaldehyde in the presence of *p*-TsOH under a continuously dehydrated condition with a Dean-Stark trap to give another prochiral intermediate, a substituted dioxane, six-membered ring acetal (**4**). Excessive use of the diol (3 equivalents) was essential to facilitate the separation of by-products in the subsequent steps. The product was quantitatively obtained based on *p*-anisaldehyde. The Lewis acid-promoted reductive cleavage of the acetal would provide the desired **2a** (Scheme 1, Table 1) in the following advantageous manner; 1) there is no chance of formation of a bis-benzylated byproduct; 2) the use of pungent benzyl halides could be avoided in the total benzylation scheme.

Along this line, the conditions for reductive acetal ring-opening reaction were screened, especially the combination of Lewis acid and reductant. If the coordination of the oxygen atom to Lewis acid is too strong, decomposition of the desired product, which

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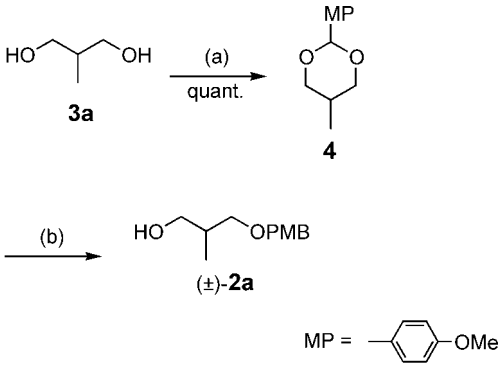


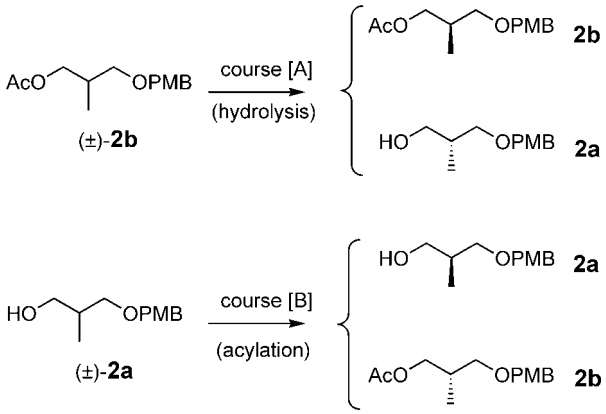
Scheme 1. (a) *p*-anisaldehyde, *p*-TsOH, toluene; (b) see Table 1.

still has the highly electron-donating *p*-methoxybenzyl ether, would result.

The results are listed in Table 1. As expected, the product was too labile towards $TiCl_4$. Indeed, Ti(O*i*-Pr)$_4$, with weakened Lewis acidity, afforded improved results, and the desired product **4** was obtained in as high as 46% yield by combining $NaBH_3CN$[4] as the reductant. $BH_3{\cdot}SMe_2$ [7] worked well, especially in a non-polar solvent such as dichloroethane (80%). The combined use with $BF_3{\cdot}OEt_2$,[7] however, only resulted in the decomposition of the product. Among these candidates, DABAL-H, which works both as Lewis acid activator and reductant,[8] gave the best result, and the desired product was obtained in quantitative yield. In this manner, a method for the large-scale preparation of racemic **2a** was established. Acetate **2b** was prepared in the conventional manner.

Enzyme-Catalyzed Enantiomeric Resolution

Santaniello et al. reported the lipase-catalyzed acylation of racemic diol **1a**.[9] In their report, the (*R*)-alcohol **1a** was enantioselectively acylated, and the enantiomeric ratio (E value)[10] was estimated to be 12.



Scheme 2. Route [A] lipase, buffer solution – organic solvent; route [B] lipase, vinyl acetate, organic solvent.

In our case, two kinds of lipases, *Candida antarctica* lipase B (Chirazyme L-2, Roche Diagnostics) and *Pseudomonas cepacia* lipase (Amano PS), which have been widely applied to the enantiomeric resolution of primary alcohols[11] and the availability of which is very high, were chosen as the candidate enzymes. The results of the lipase-catalyzed hydrolysis of (±)-**2b** [A] and acetylation of (±)-**2a** [B] as shown in Scheme 2 are summarized in Table 2. The highest E value (35) was observed in the *C. antarctica*-lipase hydrolysis of (±)-**2b**.

Next, upscaling of the reaction (substrate: between 1 to 10 g) was attempted. In the large-sale incubation, it was found that the results were reproducible only by exactly following the elaborated procedure (see Experimental Section). For example, the order of the substrate mixing was very important. The substrate should be dispersed into a pre-mixed organic co-sol-

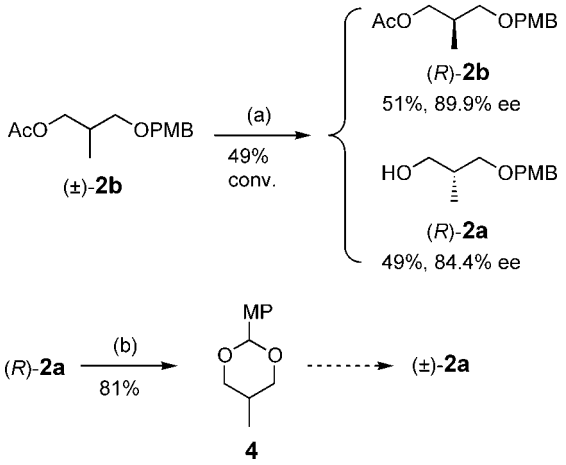
Table 1. Reductive acetal ring-opening reaction of **4**.

Lewis acid	Reducing agent	Solvent	Temperature (°C)	Time (h)	Yield of **2a** (%)
$TiCl_4$	DIBAL-H	toluene	0 – rt	4	0
$TiCl_4$	$NaBH_3CN$[a]	CH_3CN	0	4	0
$TiCl_4$	$LiAlH_4$	THF	0 – rt	16	15
$TiCl_4$	Et_3SiH[b]	CH_2Cl_2	rt	4	12
Ti(O*i*-Pr)$_4$	DIBAL-H	toluene	0 – rt	4	34
Ti(O*i*-Pr)$_4$	$NaBH_3CN$	CH_3CN	0 – rt	16	46
Ti(O*i*-Pr)$_4$	$LiAlH_4$	THF	0 – rt	4	0
Ti(O*i*-Pr)$_4$	Et_3SiH	CH_2Cl_2	40	16	0
$BH_3{\cdot}SMe_2$-THF	$BH_3{\cdot}SMe_2$-THF[c]	THF	65	3	60
$BH_3{\cdot}SMe_2$	$BH_3{\cdot}SMe_2$	$(CH_2Cl)_2$	90	16	80
$BF_3{\cdot}OEt_2$[d]	$BH_3{\cdot}SMe_2$	CH_2Cl_2	rt	0.2	0
$LiAlH_4$	$LiAlH_4$	THF	65	16	0
DIBAL-H	DIBAL-H[e]	toluene	0 – rt	2	quant.

[a] Ref.[4]
[b] Ref.[5]
[c] Ref.[6]
[d] Ref.[7]
[e] Ref.[8]

Table 2. Lipase-catalyzed kinetic resolution of **2a** and **2b**.

Lipase	Reaction course	Conversion (%)	ee (%) of alcohol	ee (%) of acetate	E value
C. antarctica	[A]	54	80	96	35
C. antarctica	[B]	45	22	28	2
P. cepacia	[A]	60	54	82	8
P. cepacia	[B]	54	93	78	26



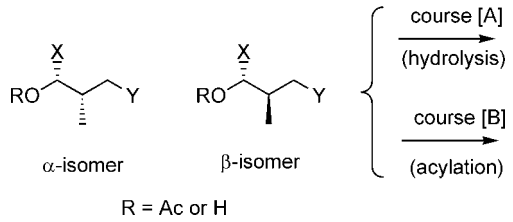
Scheme 3. (a) *Candida antarctica* lipase, buffer solution–acetone; (b) DDQ, CH_2Cl_2.

vent (acetone) and buffer solution prior to the addition of lipase. In contrast, when the incubation was started by mixing the substrate solution in acetone with the buffer, the reaction became very slow and proceeded only with very low enantioselectivity. In a preparative-scale reaction, (*R*)-**2b** (51% yield, 89.9% ee) and (*R*)-**2a**[12] (49% yield, 84.4% ee), were obtained at 49% conversion.

The above-mentioned chiral building block (**2a**) has been designed to overcome the problems, such that the maximum yield of the desired enantiomer is as high as 50%, essentially accompanied with the kinetic resolution of racemate. This is well illustrated by the recycling of the undesired isomer, through taking advantage of the protecting group, *p*-methoxybenzyl ether. The resultant alcohol (*R*)-**2a** was oxidized with DDQ[13] to revert it to the precursor **4** in 81% yield (Scheme 3). This obviously serves as the racemic substrate for the enzyme-catalyzed reaction, by the reductive cleavage of acetal as shown in Scheme 1.

Change in Stereochemical Preference

It is noteworthy that there was a large difference between the E values observed in the hydrolysis of acetate and acetylation of alcohol catalyzed by *Candida antarctica* lipase. A similar change in selectivity was experienced for the recognition of the chiral center adjacent to the alcohol such as **5**[14] and **6**.[15] These



Scheme 4. Route [A] lipase, buffer solution – organic solvent; route [B] lipase, vinyl acetate, organic solvent.

Table 3. Change in stereochemical preference between lipase-catalyzed hydrolysis and acetylation.

Substrate	Reaction course	Preferred enantiomer	E value
RO OBn **1**	[A]	α	37
	[B]	α	3
RO OPMB **2**	[A]	α	35
	[B]	α	2
RO SPh **5**	[A]	α	11
	[B]	β	15
RO **6**	[A]	α	9
	[B]	α	2
RO OBn **7**	[A]	α	17
	[B]	α	3
RO Ph **8**	[A]	α	7
	[B]	β	8
RO Ph **9**	[A]	α	7
	[B]	α,β	1

results prompted us to further investigate the change in selectivity observed in the reaction shown in Scheme 4. The results are summarized in Table 3.

In the case of *C. antarctica* lipase-catalyzed hydrolysis (in buffer-acetone), stereoisomers with the absolute configuration of the carbon atom bearing a methyl group substituent, depicted as the α-isomer, were preferred, while the E values diverged between 7 – 37. In contrast, under the acylation conditions, the rate of reaction of the α-isomer became somewhat slower. In particular cases (for **5** and **8**), the reaction rate of the β-isomer exceeded that of the α-isomer and, accordingly, the apparent enantioselectivity seems to be inverted.

Lowering of the Enantioselectivity Accompanied with the Progress of Hydrolysis

Another important aspect to be carefully considered is that the enantioselectivity changes depending upon the progress of the hydrolysis. In this case, the E value apparently decreased as the conversion became higher as described in Figure 2.

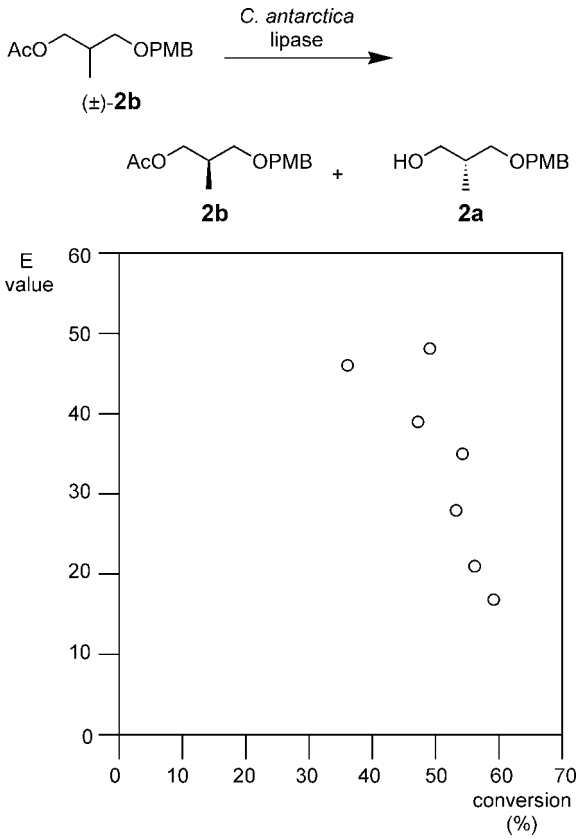


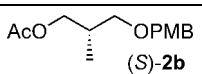
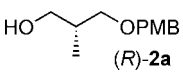
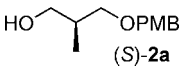
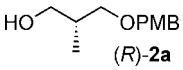
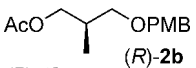
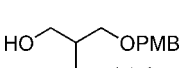
Figure 2. Lowering of the E value along with the progress of hydrolysis.

This phenomenon prompted us to clarify the mechanism of the decline, which was assumed to be due to the product inhibition on lipase during the accumulation of the resulting alcohol. The results are shown in Table 4. The incubation of (*S*)-**2b**, the reactive substrate, with the product (*R*)-**2a** at 2.5% w/v, which showed that the conversion reached 60%, indicated 55% of the original enzyme activity (entries 1 and 2).

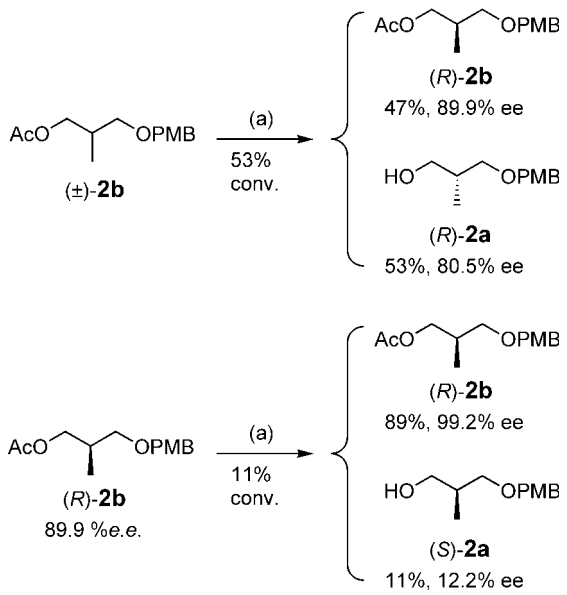
In turn, at 60% conversion, *ca*. 0.5% w/v of the less reactive isomer of the product exists in the incubation mixture. This (*S*)-alcohol also showed some inhibitory effect (80%, entries 1 and 3). No significant difference between the two enantiomers of the products [(*R*)- and (*S*)-**2a**] was observed (entries 3 and 4). On the other hand, there was little effect of the product on the less-reactive substrate (*R*)-**2b** (from 7 to 6%, entries 1 and 6, 1 and 7, respectively). It was concluded that the accumulation of the product showed a deleterious effect on the rate of hydrolysis of the more reactive enantiomer. A similar inhibitory effect had also been reported by Anthonsen et al.,[16] in the case of the *Candida* lipase-catalyzed hydrolysis of a secondary acetate. The fact that a high concentration of alcohol retarded the reaction of a "fast" enantiomer supported the observation of a higher enantioselectivity in the case of lipase-catalyzed hydrolysis, compared with the acylation of alcohol, as stated in the previous section.

To avoid this inhibition problem, the two-step resolution was effective. The reaction stopped at a lower conversion, before separation of the resulting mixture. Subsequently, the recovered unreactive substrate was incubated again with the lipase as shown in Scheme 5. In the first step, the reaction stopped at a conversion of 53%. The resultant alcohol was removed by chromatography from the mixture, and the recovered substrate was hydrolyzed by lipase

Table 4. Inhibition experiment on the *Candida antarctica* lipase-catalyzed hydrolysis of **2b**.

Entry	Substrate	Additive	w/v % of additive	Relative rate (%)[a]
1	 (*S*)-**2b**	none	0	10
2	(*S*)-**2b**	 (*R*)-**2a**	2.5	55
3	(*S*)-**2b**	 (*S*)-**2a**	0.5	81
4	(*S*)-**2b**	 (*R*)-**2a**	0.5	88
5	 (*R*)-**2b**	none	0	7
6	(*R*)-**2b**	 (±)-**2a**	2.5	6

[a] See Experimental Section.

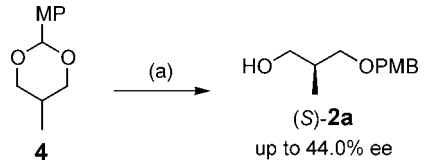


Scheme 5. (a) *Candida antarctica* lipase, buffer solution–acetone.

again. The unreacted (*R*)-acetate (**2b**) with 99.2% ee was recovered in a total yield of 42%. The E values of the first and second steps were calculated to be 28 and 40, respectively. In this way, the kinetic resolution could be achieved without loss of enantioselectivity, which is caused by the product inhibition.

Preparation of Partially Enantiomerically Enriched Substrate by Asymmetric Synthesis

The above-mentioned situation prompted a new process, which would minimize the contamination of the undesired enantiomer, prior to the enzyme-catalyzed hydrolysis. This could be achieved by the aid of desymmetrization, taking advantage of the prochiral nature of the starting material as well as the intermediate.



Scheme 6. (a) $NaBH_3CN$, (*R*)-binaphthol, titanium(IV) complex. For details, see Table 5.

The first approach was the asymmetric Lewis-acid promoted reductive cleavage of acetal **4**. The pioneering work by Harada et al. had achieved the acetal-mediated desymmetrization[17] of prochiral 2-methyl-1,3-propanediol (**3a**), whose oxygen atoms were differentiated as the diastereotopic groups, *via* the acetalization with *l*-menthone. Later, they also reported a chiral reagent-based asymmetric ring opening reaction on a five-membered 1,3-dioxolane.[18]

As we mentioned earlier, in the course of studies for the preparation of racemic substrate **2a** from **4**, titanium(IV)-based Lewis acids, especially titanium isopropoxide combined with $NaBH_3CN$ effected the ring-opening reaction in moderate yields (Table 1). This titanium(IV) Lewis acid has an advantage, namely, that chiral ligands would readily replace with the original isopropoxide. We turned our attention to a binaphthol (BINOL)-titanium(IV) complex,[19] whose availability has recently been growing.

The attempts for the reaction (Scheme 6) are summarized in Table 5. Due to the low solubility of the BINOL-Ti(IV) complex, a mixture of the solvent system (CH_3CN/CCl_4)[19e] was applied (entry 1). Although the desired desymmetrization proceeded to give enantiomerically enriched (22 – 37% ee) form of **2a**, the yield as well as ee of the product were not highly reproducible.

Mikami et al. had extensively studied the effects on the Diels–Alder reaction, of the status, method of preparation, equivalents of components, and additives

Table 5. Asymmetric reductive acetal ring-opening reaction of **4** with $NaBH_3CN$.

Entry	Lewis	Solvent	Additive etc.	Yield of **2a** (%)	% ee
1	$Ti(Oi\text{-}Pr)_4$ [a]	CH_3CN/CCl_4	none	41 – 43	22 – 37
2	$Ti(Oi\text{-}Pr)_4$ [a]	CH_3CN/CCl_4	3 Å MS	35	11
3	$Ti(Oi\text{-}Pr)_4$ [a]	CCl_4	3 Å MS	11	8
4	$Ti(Oi\text{-}Pr)_4$ [a]	CH_2Cl_2	H_2O (1 equiv.)	11	8
5	$Ti(Oi\text{-}Pr)_4$ [a]	CCl_4	PhCN (1 equiv.)	25	0
6	$Ti(Oi\text{-}Pr)_4$ [a]	CH_2Cl_2	none	22	10
7	$Ti(Oi\text{-}Pr)_4$ [a]	CH_2Cl_2	*i*-PrOH (1 equiv.)	20	3
8	$Ti(Oi\text{-}Pr)_4$ [a]	CH_3CN/CCl_4	– *i*-PrOH[b]	28	44
9	$Ti(Oi\text{-}Pr)_4$ [c]	CH_3CN/CCl_4	none	43	9
10	$Ti(Oi\text{-}Pr)_4$ [d]	CH_3CN/CCl_4	none	18	35
11	$TiCl_2(Oi\text{-}Pr)_2$	CCl_4	none	0	–
12	$TiCl(Oi\text{-}Pr)_5$	CH_3CN/CCl_4	none	68	0

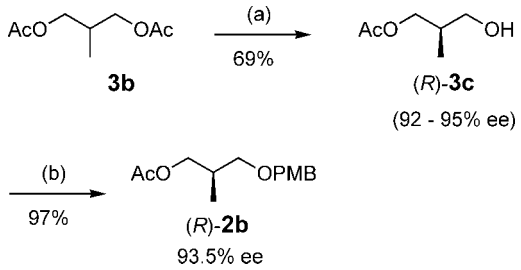
[a] $Ti(Oi\text{-}Pr)_4$ (2 equiv.) and binaphthol (2 equiv.).
[b] Isopropyl alcohol was removed prior to use.
[c] $Ti(Oi\text{-}Pr)_4$ (2 equiv.) and binaphthol (3 equiv.).
[d] $Ti(Oi\text{-}Pr)_4$ (2.2 equiv.) and binaphthol (2 equiv.)

for the BINOL-Ti(IV) complex.[19d] In our case, indeed, a coordinative agent such as the solvent (CH_3CN) or a trace of water in the reaction mixture affected the enantioselection, in a somewhat confusing manner (entries 2 – 6). Isopropyl alcohol, which inevitably forms, accompanying the formation of BINOL-Ti(IV) showed considerable influence. When the isopropyl alcohol was removed prior to use, the ee of the product reached as much as 44.0% (entry 8), while an extra addition of isopropyl alcohol (plus 1.0 equiv.) in the mixture showed apparently a deleterious effect (entry 7). An excess of BINOL also lowered the ee (entry 9) of the product.

The introduction of an electron-withdrawing chlorine atom in the BINOL-Ti(IV) complex showed no advantage (entries 11 and 12). Change of the reductant from $NaBH_3CN$ to DIBAL-H resulted in the decomposition of both the starting material and the desired product. As examples, except for the titanium-based complex, BINAL-H[20] or CBS-oxazaborolidine[21] produced no fruitful results. In summary, enantiotopic group-selective coordination on the *pro*-(*R*) acetal oxygen atom was observed in at most *ca.* 2.5:1, in our experimentation, by the use of the (*R*)-BINOL-Ti(IV) complex and the reductive cleavage proceeded with $NaBH_3CN$ in 28% yield. This partially enantiomerically enriched alcohol would work as the more effective substrate for the *Pseudomonas* lipase-catalyzed enantioselective acylation as shown in Table 2.

The second approach, an alternative and successfully established pathway, was the enzyme-catalyzed desymmetrization of **3a** as the key step.[9,22] Towards this end, according to the Wirz procedure,[22b] the *Pseudomonas* lipase-catalyzed enantiotopic group-selective hydrolysis of prochiral diacetate **3b** was carried out, and the desired product (*R*)-**3c** was obtained in 69% yield as shown in Scheme 7. At this stage, its ee was estimated to be 92 – 95% based on the Wirz report.

The final, but still challenging task was the protection of the liberated primary alcohol in **3c** as the *p*-methoxybenzyl ether without the migration of acetate under the reaction conditions. This could hardly be achieved by the conventional benzylation procedure, the use of *p*-methoxybenzyl bromide in the presence of a base such as NaH, Ag_2O, or diisopropylethylamine. The procedure has another drawback, the extremely labile nature of the product under strongly acidic conditions. None of the attempts for benzylation with benzyl alcohol and bismuth bromide[23] or the acid-catalyzed trichloroacetimidate protocol[24] worked well. This was overcome by means of a trichloroimidate-PPTS procedure[2h] under very weakly acidic conditions, which proceeded in 97% yield. Nearly no migration of the acetate during this step was observed under the above-mentioned mild conditions, to give the (*R*)-**3b** with 93.5% ee. This should



Scheme 7. (a) *Pseudomonas cepacia* lipase; (b) *p*-methoxybenzyltrichloroacetimidate, PPTS.

work well as the substrate in the *Candida* lipase-catalyzed kinetic resolution, as the contamination of the undesired enantiomer is as low as 3–4%. In a practical sense, the production efficiency of lipase-catalyzed desymmetrization of the diacetate in regard to the so-called "space-time-yield" should be further improved.[22b]

Conclusion

Candida antarctica lipase-catalyzed hydrolysis of the racemic acetate of 2-methylpropane-1,3-diol mono(*p*-methoxybenzyl ether) proceeded with high enantioselectivity (E 35). The enantioselectivity, however, gradually declined, accompanying the progress of the hydrolysis, due to product inhibition. The two-step resolution, while avoiding the high accumulation of the product, was the key to obtain the desired product with as high as 99.2% ee.

In turn, this inhibition problem provided a new chemoenzymatic desymmetrization process for the enantiomerically enriched substrate. With the aid of the *Pseudomonas cepacia* lipase-catalyzed desymmetrization of 2-methyl-1,3-propanediol diacetate and subsequent *p*-methoxybenzylation, the desired substrate with 93.5% ee was obtained.

The combined use of an enzyme-catalyzed kinetic resolution and desymmetrization approach is effective to access the "highly enantiomerically pure" form of the desired product. The remaining task is the recycle use of the enzyme, by applying a solvent-resistant, immobilized form[25] of lipases for an enhanced productivity.

Experimental Section

General Methods

IR spectra were measured as films on a Jasco FT/IR 410 spectrometer. NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 400 MHz for ^1H and at 100 MHz for ^{13}C on a JEOL JNM GX-400 or at 400 MHz on a JEOL JNM α-400 spectrometer. Wako Gel B-5F and silica gel

60 K070-WH (70 – 230 mesh) of Katayama Chemical Co. were used for preparative TLC and column chromatography, respectively.

2-(4-Methoxyphenyl)-5-methyl-1,3-dioxane (4)

To a mixture of diol **3a** (12.01 g, 133.3 mmol) and *p*-anisaldehyde (6.02 g, 44.2 mmol) in toluene (100 mL), *p*-toluenesulfonic acid monohydrate (58 mg, 0.3 mmol) was added and the mixture refluxed for 1 day, while being equipped with a Dean-Stark water separator. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc, and the organic layer was washed with H_2O, brine, dried with Na_2SO_4, and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (100 g). Elution with hexane/EtOAc/Et_3N (700/100/1) afforded **4** as a colorless oil;[13] yield: 9.20 g (quant.). Analytical sample: bp 125 °C/1.5 torr; ^{1}H NMR: δ = 0.77 (d, *J* = 6.8 Hz, 3H), 2.22 (m, 1H), 3.50 (dd, *J* = 11.4, 11.6 Hz, 2H), 3.80 (s, 3H), 4.17 (dd, *J* = 4.6, 11.6 Hz, 2H), 5.37 (s, 1H), 6.89 (m, 2H), 7.41 (m, 2H); ^{13}C NMR: δ = 159.8, 130.9, 127.3, 113.6, 101.2, 73.6, 55.2, 29.3, 12.3; IR: ν = 2950, 2825, 1610, 1515, 1460, 1390, 1300, 1250, 1160, 1110, 1070, 1030, 990, 920, 890, 830 cm^{-1}; anal. calcd. for $C_{12}H_{16}O_3$ (208.3): C 69.21%, H 7.74%; found: C 69.10%, H 7.89%.

Judging from its ^{1}H NMR spectrum in comparison with that of a closely related molecule, 2-(2-methoxyphenyl)-5-methyl-1,3-dioxane,[26] the *trans*-configuration of the present **4** was concluded.

(±)-3-(4-Methoxybenzyloxy)-2-methyl-1-propanol (2a); Reduction of 4 with DIBAL-H

The reaction was carried out in a similar manner to the procedure reported previously.[8] To a solution of acetal **4** (15.04 g, 72.2 mmol) in toluene (36 mL) was added DIBAL-H (128 mL, 1.0 M in hexane) with stirring at 0 °C. The mixture was then allowed to warm to room temperature before being quenched by the addition of aqueous NaOH solution (1.0 M, 517 mL) at 0 °C. The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated under vacuum. The residue was distilled to give the alcohol **2a** as a colorless oil; yield: 15.2 g (quant.); bp 132 °C/1.5 torr; ^{1}H NMR: δ = 0.86 (d, *J* = 7.0 Hz, 3H), 2.06 (m, 1H), 3.39 (dd, *J* = 8.2, 9.0 Hz, 1H), 3.53 (dd, *J* = 4.6, 9.0 Hz, 1H), 3.62 (dd, *J* = 4.5, 10.7 Hz, 1H), 3.62 (dd, *J* = 4.5, 10.7 Hz, 1H), 3.81 (s, 3H), 4.45 (s, 2H), 6.88 (m, 2H), 7.25 (m, 2H); IR: ν = 3350, 2925, 2850, 1610, 1580, 1510, 1460, 1360, 1300, 1245, 1170, 1080, 1030, 820, 750, cm^{-1}; anal. calcd. for $C_{12}H_{18}O_3$ (210.3): C 68.55%, H 8.63%; found: C 68.43%, H 8.50%.

Reduction of 4 with Borane-Dimethyl Sulfide Complex

To a solution of **4** (100 mg, 0.48 mmol) in $ClCH_2CH_2Cl$ (1 mL), 3 Å molecular sieves (100 mg) were added and the mixture was stirred at room temperature for 3 h. Then borane-dimethyl sulfide complex (10.5 M, 90 μL, 2.0 equiv.) was added and the mixture was stirred under reflux for 16 h. After cooling, the reaction was quenched by the addition of methanol. The workup and purification as mentioned above furnished **2a**; yield: 80.5 mg (80%). The ^{1}H NMR spectrum was identical with that obtained as above.

(±)-3-(4-Methoxybenzyloxy)-2-methylpropyl Acetate (2b)

In a conventional manner, alcohol **2a** (3.50 g, 16.6 mmol) was converted to acetate **2b** as a colorless oil; yield: 4.20 g (quant.). Analytical sample: bp 146 °C/0.5 torr; ^{1}H NMR: δ = 0.96 (d, *J* = 6.8 Hz, 3H), 2.02 (s, 3H), 2.11 (m, 1H), 3.33 (dd, *J* = 5.8, 9.2 Hz, 1H), 3.37 (dd, *J* = 6.5, 9.2 Hz, 1H), 3.80 (s, 3H), 3.98 (dd, *J* = 6.2, 10.8 Hz, 1H), 4.07 (dd, *J* = 6.0, 10.8 Hz, 1H), 6.88 (m, 2H), 7.25 (m, 2H); ^{13}C NMR: δ = 171.2, 159.1, 130.4, 129.1, 113.7, 72.7, 71.7, 66.5, 55.2, 33.2, 20.9, 14.1; IR: ν = 2925, 2850, 1735, 1610, 1580, 1510, 1460, 1365, 1300, 1240, 1170, 1090, 1030, 820, 750 cm^{-1}; anal. calcd. for $C_{14}H_{20}O_4$ (252.3): C 66.65%, H 7.99%; found: C 66.42%, H 8.19%.

Hydrolysis of (±)-2b with *Candida antarctica* Lipase

The reaction was carried out in a similar manner to the procedure reported previously.[14] To acetate **2b** (1.07 g, 4.2 mmol) was added a mixture of acetone and 0.1 M (pH 7.0) phosphate buffer (2:3, 20 mL), and the mixture was stirred at 0 °C for 10 min. Then, to the mixture, *Candida antarctica* lipase [Roche diagnostics (Novo Nordisk), Chirazyme L-2, 22.5 mg] was added and the mixture was stirred for 25 h at 0 °C. After having been filtered through a pad of Celite, the filtrate was extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution, brine, dried with Na_2SO_4, and concentrated under vacuum. The conversion (49%) was estimated by the integration of ^{1}H NMR signals of **2b** (δ = 0.96, 51%), **2a** (δ = 0.86, 49%). The crude residue was purified by silica gel column chromatography (25 g). Elution with hexane/EtOAc (5/1) yielded (*R*)-**2b** (546 mg, 51%) and (*R*)-**2a** (437 mg, 49%).

Analytical sample of (*R*)-**2a**: $[\alpha]_D^{20}$: –2.8° (*c* 0.67, EtOH); anal. calcd. for $C_{12}H_{18}O_3$ (210.3): C 68.55%, H 8.63%; found: C 68.33%, H 8.47%. Its ee (84.4%) was confirmed by HPLC analysis of the corresponding benzoate **2c** [DAICEL CHIRALCEL OJ, 0.5 cm × 25 cm, 0.5 mL/min, 1.5 MPa; *R*: 32.3 min, 7.8% for (*S*)-**2a**; *S*: 34.4 min, 92.2% for (*R*)-**2a**].[12] Its absolute configuration was unambiguously determined by the conversion of the (–)-isomer of **2a** to the known (*S*)-(+)-**1a**, as mentioned later.

Analytical sample of (*R*)-**2b**: $[\alpha]_D^{22}$: –5.0° (*c* 0.80, EtOH); anal. calcd. for $C_{14}H_{20}O_4$ (252.3): C 66.65%, H 7.99%; found: C 66.52%, H 8.01%.

The acetate (*R*)-**2b** was treated overnight with K_2CO_3 in MeOH at room temperature, and then H_2O was added. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by preparative TLC (hexane/EtOAc = 1/1) to afford (*S*)-**2a** as a colorless oil.

Analytical sample of (*S*)-**2a**: $[\alpha]_D^{23}$: +2.4° (*c* 0.40, EtOH). Its ee (89.9%) was confirmed by HPLC analysis of the corresponding benzoate **2c**. In a small-scale (substrate: 100 mg) preliminary experiment, the reaction proceeded at 54%

conversion in 24 h, and the products were obtained as shown in Table 2.

Acetylation of (±)-2a with *Candida antarctica* Lipase

The reaction was carried out in a similar manner to the procedure reported previously.[14] To a mixture of **2a** (210.8 mg, 0.835 mmol) in vinyl acetate (5 mL), *Candida antarctica* lipase (Chirazyme L-2, 40.4 mg) immobilized with Florisil[27] was added and the mixture was stirred for 2.5 h at 30 °C. After having been filtered through a pad of Celite, the filtrate was concentrated under vacuum. The conversion (45%) was estimated as described before. The crude residue was purified by silica gel column chromatography (2.5 g). Elution with hexane/EtOAc (5/1) yielded (*S*)-**2a** (116.2 mg, 55%, 22.4% ee) and (*S*)-**2b** (113.5 mg, 45%, 27.5% ee).

Analytical sample of (*S*)-**2a**: $[\alpha]_D^{24}$: +0.5° (*c* 1.4, EtOH).

Analytical sample of (*S*)-**2b**: $[\alpha]_D^{25}$: +1.4° (*c* 1.1, EtOH). The acetate (*S*)-**2b** was converted to (*R*)-**2a** as a colorless oil. Analytical sample of (*R*)-**2a**: $[\alpha]_D^{25}$: –0.69° (*c* 0.79, EtOH).

Hydrolysis of (±)-2b with *Pseudomonas cepacia* Lipase

The reaction was carried out in a similar manner to the procedure as above. To a mixture of **2b** (107.9 mg, 0.428 mmol) in acetone and pH 7.0 phosphate buffer (2:3, 2 mL), *Pseudomonas cepacia* lipase (Amano PS, 21.7 mg) was added and the mixture was stirred for 21 h at 0 °C (60% conversion). The workup was carried out in the same manner to afford (*R*)-**2a** (53.9 mg, 60%, 53.9% ee) and (*R*)-**2b** (43.2 mg, 40%, 82.3% ee).

Analytical sample of (*R*)-**2a**: $[\alpha]_D^{21}$: –1.6° (*c* 0.75, EtOH).

Analytical sample of (*R*)-**2b**: $[\alpha]_D^{26}$: –3.3° (*c* 0.41, EtOH). The acetate (*R*)-**2b** was converted to (*S*)-**2a** as described before. Analytical sample of (*S*)-**2a**: $[\alpha]_D^{20}$: +1.7° (*c* 0.86, EtOH).

Acetylation of (±)-(2a) with *Pseudomonas cepacia* Lipase

The reaction was carried out in a similar manner to the procedure reported previously.[9] To a mixture of **2a** (190.3 mg, 0.905 mmol) in vinyl acetate (1 mL) and $CHCl_3$ (9 mL), *Pseudomonas cepacia* lipase (Amano PS, 147.8 mg) was added and the mixture was stirred for 3 h at 30 °C. The conversion (54%) was estimated as described before. The workup was carried out in the same manner as described before and afforded (*S*)-**2a** (87.0 mg, 46%, 92.6% ee) and (*S*)-**2b** (124.0 mg, 54%, 77.8% ee).

Analytical sample of (*S*)-**2a**: $[\alpha]_D^{24}$: +2.1° (*c* 0.67, EtOH).

Analytical sample of (*S*)-**2b**: $[\alpha]_D^{25}$: +3.9° (*c* 1.1, EtOH). The acetate (*S*)-**2b** was converted to (*R*)-**2a** as a colorless oil. Analytical sample of (*R*)-**2a**: $[\alpha]_D^{25}$: –1.4° (*c* 0.92, EtOH).

(±)-3-Benzyloxy-2-methyl-1-propanol (1a).

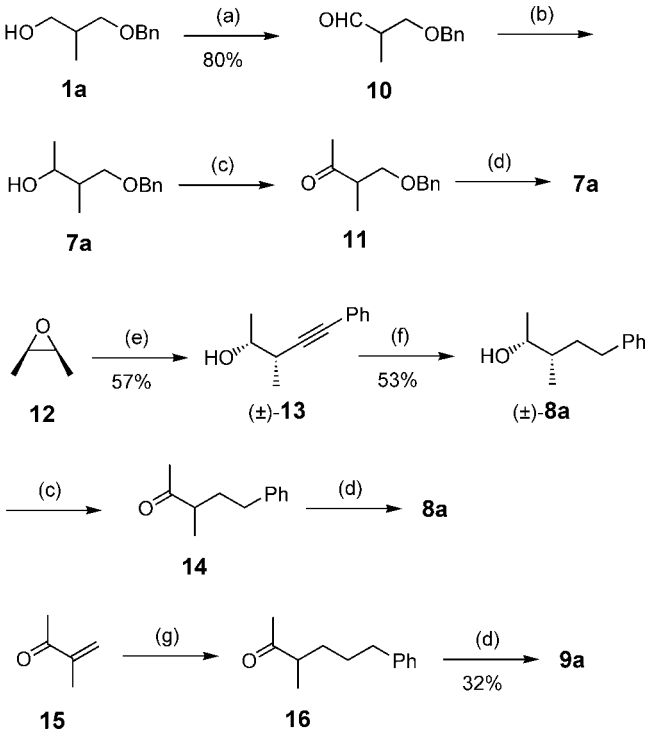
The two-step conversion was carried out in a similar manner to the procedure reported as described for **2a**. Starting from **3a** (10.0 g, 111 mmol) and benzaldehyde (11.77 g, 111 mmol), alcohol **1a** (15.1 g, 75 %) was obtained in two steps as a colorless oil. Analytical sample: ^{1}H NMR: δ = 0.88 (d, *J* = 7.0 Hz, 3H), 2.10 (dtt, *J* = 7.0, 4.3, 9.2 Hz, 1H), 2.54 (br.s, 1H), 3.43 (dd, *J* = 8.2, 9.2 Hz, 1H), 3.56 (dd, *J* = 4.5, 9.2 Hz, 1H), 3.61 (dd, *J* = 4.3, 6.5 Hz, 1H), 3.62 (dd, *J* = 4.3, 6.5 Hz), 1H), 4.52 (br.s, 2H), 7.30–7.39 (m, 5H); IR: ν_{max} = 3400, 3060, 3030, 2930, 2870, 1500, 1450, 1360, 1260, 1210, 1160, 1100, 1080, 1040, 990, 900, 740, 700 cm^{-1}. Its NMR and IR spectra were in good accordance with those reported previously.[1a]

4-Benzyloxy-3-methyl-2-butanol (7a)

The substrates **7a**, **8a** and **9a** were prepared as illustrated in Scheme 8.

For the preparation of **7a**, the first step was carried out in a similar manner to the procedure reported previously.[1c] Starting from **1a** (244.7 mg, 1.36 mmol), aldehyde **10** (193.9 mg, 80 %) was obtained as a colorless oil. Analytical sample: ^{1}H NMR: δ = 1.14 (d, *J* = 7.3 Hz, 3H), 2.67 (ddq, *J* = 5.4, 6.4, 7.3 Hz, 1H), 3.64 (dd, *J* = 5.4, 9.8 Hz, 1H), 3.69 (dd, *J* = 6.4, 9.8 Hz, 1H), 4.53 (s, 2H), 7.27–7.37 (m, 5H), 9.73 (s, 1H); IR: ν = 3050, 2980, 2950, 2840, 2740, 1730, 1600, 1500, 1455, 1390, 1365, 1320, 1280, 1250, 1210, 1100, 1030, 1000, 970, 930, 860, 810, 750, 710 cm^{-1}. Its NMR and IR spectra were in good accordance with those reported previously.[1c]

To a mixture of Mg (205 mg, 8.43 mmol) and methyl iodide (1.18 g, 8.31 mmol) in Et_2O (5 mL), aldehyde **10** (972.8 mg, 5.46 mmol) was added at room temperature with stirring. The conventional workup and chromatographic purification (silica gel, hexane/EtOAc = 12/1) afforded a mixture containing **7a** (245.0 mg). This was a inseparable mixture with unidentified contaminant.



Scheme 8. (a) Swern oxidation; (b) MeMgI; (c) Jones' oxidation; d) $NaBH_4$; (e) see ref.[29]; (f) H_2, Pd-C; (g) $PhCH_2CH_2Br$, Mg.

To obtain **7a** in the pure form, the mixture was treated with Jones' reagent for oxidation and with $NaBH_4$ for reduction. To a solution of a mixture (414.2 mg) containing **7a** in acetone (2 mL) was added Jones' reagent (8 M, 0.8 mL) at 0 °C for 1 h. After the usual workup, chromatographic purification (silica gel, hexane/EtOAc = 10/1) furnished ketone **11** as a colorless oil; yield: 323.8 mg (79%). Analytical sample: ^{1}H NMR: δ = 1.09 (d, *J* = 7.1 Hz, 3H), 2.18 (s, 3H), 2.86 (ddq, *J* = 5.4, 7.1, 7.6 Hz, 1H), 3.49 (dd, *J* = 5.4, 10.1 Hz, 1H), 3.63 (dd, *J* = 7.6, 10.1 Hz, 1H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.52 (d, *J* = 14.1 Hz, 1H), 7.27 – 7.37 (m, 5H). The NMR spectrum was in good accordance with that reported previously.[11]

To a solution of **11** (185.0 mg, 0.962 mmol) in EtOH (1 mL) was added $NaBH_4$ (30 mg, 0.793 mmol) at 0 °C for 1 h. After the usual workup, chromatographic purification (silica gel, hexane/EtOAc = 6/1) afforded **7a**[28] as a mixture of (2*R**,3*R**)-**7a** and (2*R**,3*S**)-**7a**; yield: 53.9 mg (60%). Analytical sample: ^{1}H NMR: δ = 0.86 [d, *J* = 7.1 Hz, (2*R**,3*S**)-**7a**, total 3H with δ = 0.92], 0.92 [d, *J* = 7.2 Hz, (2*R**,3*R**)-**7a**, total 3H with δ = 0.86], 1.15 [d, *J* = 6.5 Hz, (2*R**,3*R**)-**7a**, total 3H with δ = 1.17], 1.17 [d, *J* = 6.8 Hz, (2*R**,3*S**)-**7a**, total 3H with δ = 1.15], 1.76 – 1.85 [m, (2*R**,3*S**)-**7a**, total 1H with δ = 1.86 – 1.97], 1.86 – 1.97 [m, (2*R**,3*R**)-**7a**, total 1H with δ = 1.76–1.85], 3.45 [dd, *J* = 8.3, 9.3 Hz, (2*R**,3*S**)-**7a**, total 2H with δ = 3.52, 3.59], 3.52 [d, *J* = 5.6 Hz, (2*R**,3*R**)-**7a**, total 2H with δ = 3.45, 3.59], 3.59 [dd, *J* = 4.3, 9.3 Hz, (2*R**,3*S**)-**7a**, total 2H with δ = 3.45, 3.52], 3.70 [dq, *J* = 7.1, 7.1 Hz, (2*R**,3*S**)-**7a**, total 1H with δ = 3.96], 3.96 [dq, *J* = 3.8, 6.5 Hz, (2*R**,3*R**)-**7a**, total 1H with δ = 3.70], 4.53 (d, *J* = 6.5 Hz, 2H), 7.20 – 7.42 (m, 5H); IR: ν = 3450, 3030, 2970, 2860, 1490, 1450, 1410, 1360, 1300, 1200, 1100, 1020, 920, 890, 740, 700 cm^{-1}. Its IR spectrum was in good accordance with those reported previously.[28] The (2*R**,3*R**)-diastereomer was in a slight excess (12% de) judging from the integration of the signals at δ = 0.86 and 0.92.

(1*R**,2*R**)-3-Benzyloxy-1,3-dimethylpropyl Acetate (7b)

In a conventional manner, **7a** [2.30 g, 11.8 mmol, 12% de for (2*R**,3*R**)-isomer] was converted to **7b** as a colorless oil; yield: 1.81 g (65%). Analytical sample: ^{1}H NMR of (1*R**,2*R**)-**7b**: δ = 0.96 [d, *J* = 6.8 Hz, (1*R**,2*R**)-**7b**, total 3H with δ = 0.97], 0.97 [d, *J* = 6.8 Hz, (1*R**,2*S**)-**7b**, total 3H with δ = 0.96], 1.18 [d, *J* = 6.4 Hz, (1*R**,2*R**)-**7b**, total 3H with δ = 1.20], 1.20 [d, *J* = 6.8 Hz, (1*R**,2*S**)-**7b**, total 3H with δ = 1.18], 1.88 – 1.97 [m, (1*R**,2*S**)-**7b**, total 1H with δ = 1.98 – 2.10], 1.98 – 2.10 [m, (1*R**,2*R**)-**7b**, total 1H with δ = 1.88 – 1.97], 1.99 (s, 3H), 3.30 [dd, *J* = 6.4, 9.3 Hz, (1*R**,2*S**)-**7b**, total 1H with δ = 3.32], 3.32 [dd, *J* = 6.4, 9.3 Hz, (1*R**,2*R**)-**7b**, total 1H with δ = 3.30], 3.39 [dd, *J* = 6.4, 8.8 Hz, (1*R**,2*S**)-**7b**, total 1H with δ = 3.43], 3.43 [dd, *J* = 6.4, 9.3 Hz, (1*R**,2*R**)-**7b**, total 1H with δ = 3.39], 4.48 (d, *J* = 6.5 Hz, 1H), 4.52 (d, *J* = 6.5 Hz, 1H), 4.95 [dq, *J* = 6.4, 6.4 Hz, (1*R**,2*R**)-**7b**, total 1H with δ = 5.06], 5.06 [dq, *J* = 4.9, 6.4 Hz, (1*R**,2*S**)-**7b**, total 1H with δ = 5.06], 7.20 – 7.38 (m, 5H); IR: ν_{max} = 3060, 3040, 2990, 2950, 2860, 1730, 1500, 1450, 1375, 1240, 1100, 1040, 1020, 950, 910, 855, 740, 700 cm^{-1}.

Hydrolysis of 7b with *Candida antarctica* Lipase

A solution of the acetate (1*R**,2*S**)-**15b** (25.0 mg, 12% de), *Candida antarctica* lipase (5.0 mg), and acetone/pH 7.0 phosphate buffer (2:3, 0.5 mL) was stirred at room temperature for 18 h. The conversion (18%) and de were determined in the same manner as stated for the lipase-catalyzed acetylation. The workup was carried out in the same manner as described above to afford (2*R**,3*S**)-**7a** (3.0 mg, 15%, 78% de) and unreacted **7b** (14.5 mg 58%). Its NMR and IR spectra were in good accordance with those of the racemate.

Acetylation of 7a with *Candida antarctica* Lipase

To a solution of (2*R**,3*S**)-**7a** (12% de, 80.0 mg, 0.41 mmol) in vinyl acetate (2 ml) was added *Candida antarctica* lipase (20.0 mg) immobilized with Florisil and the mixture was stirred at 30 °C for 10 h. The conversion (14%) was estimated by GLC analysis [GL Science Inc., TC-1, 0.25 mm × 30 m, 140 °C, 50 mL/min, 180 kPa; **7a**: 6.0 min, **7b**: 10.1 min]. After having been filtered through a pad of Celite, the filtrate was concentrated under vacuum. The diastereomeric excess was estimated by the integration of signals of (2*R**,3*S**)-**7a** (δ = 0.86), (2*R**,3*R**)-**7a** (δ = 0.92), (1*R**,2*R**)-**7b** (δ = 4.95), and (1*R**,2*S**)-**7b** (δ = 5.06). The crude residue was purified by preparative TLC (hexane/EtOAc = 4/1) to afford (1*R**,2*S**)-**7b** (15.0 mg, 14%, 18% de) and unreacted **7a** (66.4 mg, 83%). Their NMR and IR spectra were in good accordance with those of the racemate. The (2*R*) configuration of (1*R**,2*S**)-**7b** was concluded by the comparison of the NMR spectrum of the corresponding (*R*)-MTPA ester **7c**, based on the modified Mosher method.[29]

3-Methyl-5-phenyl-2-pentanol (8a)

The first step was carried out in a similar manner to the procedure reported previously.[30] *cis*-2,3-Epoxybutane **12** (97% purity, 76.7 mg, 1.06 mmol) and phenylacetylene (168.0 mg, 1.64 mmol) were reacted to afford (2*R**,3*S**)-**13** (164.4 mg, 57%). Analytical sample: ^{1}H NMR: δ = 1.29 (d, *J* = 6.9 Hz, 3H), 1.31 (d, *J* = 5.9 Hz, 3H), 2.00 (br.s, 1H), 2.70 (dq, *J* = 5.9, 6.9 Hz, 1H), 3.74 (dq, *J* = 5.9, 5.9 Hz, 1H), 7.25–7.35 (m, 3H), 7.38 – 7.46 (m, 2H); IR: ν= 3400, 3050, 2980, 2940, 2880, 2240, 1600, 1575, 1490, 1450, 1380, 1350, 1300, 1260, 1155, 1100, 1075, 1045, 1030, 1000, 930, 890, 760, 700 cm^{-1}. This was employed in the next step without further purification.

To a solution of (2*R**,3*S**)-**13** (164 mg) in EtOH (2 mL) was added 10% palladium on charcoal (17 mg) and the mixture was hydrogenated at room temperature for 2 h. The mixture was filtered and evaporated. The crude residue was purified by silica gel column chromatography (5 g). Elution with hexane/EtOAc (4/1) furnished (2*R**,3*S**)-**8a**; yield: 145 mg (53%).

To obtain **8a** in the form of a diastereomeric mixture, (2*R**,3*S**)-**8a** was first treated with Jones' reagent for oxidation and then with $NaBH_4$ for reduction of resultant **14**.[31] The reaction was carried out in a similar manner to the procedure for **7a**. Analytical sample of **8a**: ^{1}H NMR: δ = 0.97 [d, *J* = 6.7 Hz, (2*R**,3*S**)-**8a**, total 3H with δ = 0.98], 0.98 [d, *J* = 6.3 Hz, (2*R**,3*R**)-**8a**, total 3H with δ = 0.97], 1.15 [d, *J* = 6.4 Hz, (2*R**,3*S**)-**8a**, total 3H with δ = 1.16], 1.16 [d, *J* = 6.2 Hz, (2*R**,3*R**)-**8a**, total 3H with δ = 1.15], 1.38 – 1.59 (m, 2H), 1.77 – 1.86 (m, 1H), 2.52 – 2.63 (m, 1H), 2.70 – 2.79 (m, 1H), 3.70 [dq, *J* = 6.1, 6.4 Hz, (2*R**,3*S**)-**8a**, total 1H with δ = 3.76], 3.76 [dq, *J* = 6.2, 10.4 Hz, (2*R**,3*R**)-**8a**, total 1H with δ = 3.70], 7.17 – 7.31(m, 5H).

1,2-Dimethyl-5-phenybutyl Acetate (8b)

In a conventional manner, alcohol **8a** (50.0 mg, 0.280 mmol) was converted to acetate **8b** as a colorless oil; yield: 62.1 mg (quant.). Analytical sample of **8b**: ^{1}H NMR: δ = 0.96 [d, *J* = 6.6 Hz, (1*R**,2*S**)-**8b**, total 3H with δ = 0.97], 0.97 [d, *J* = 6.7 Hz, (1*R**,2*R**)-**8b**, total 3H with δ = 0.96], 1.39 – 1.49 (m, 1H), 1.62 – 1.67 (m, 1H), 2.03 (br.s, 3H), 2.50 – 2.61 (m, 1H), 2.65 – 2.75 (m, 2H), 4.85 [dq, *J* = 6.6, 6.4 Hz, (1*R**,2*S**)-**8b**, total 1H with δ = 4.90], 4.90 [dq, *J* = 4.5, 7.0 Hz, (1*R**,2*R**)-**8b**, total 1H with δ = 4.85], 7.15 – 7.35(m, 5H); IR: ν = 3060, 3025, 2970, 2940, 2880, 1735, 1600, 1555, 1540, 1500, 1450, 1375, 1245, 1135, 1080, 1045, 1020, 950, 850, 750, 700 cm^{-1}.

Hydrolysis of 8b with *Candida antarctica* Lipase

To a mixture of **8b** (48.0 mg, 0.22 mmol) in acetone and pH 7.0 phosphate buffer (2:3, 1.0 mL), *Candida antarctica* lipase (3.9 mg) was added and the mixture was stirred for 2 h at room temperature. The conversion (7.8%) and de were determined in the same manner as stated for the lipase-catalyzed acetylation. The workup was carried out in the same manner as described above to afford (2*R**,3*S**)-**8a** (3.0 mg, 8%, 72% de) and unreacted **8b** (35.2 mg, 73%). Their NMR and IR spectra were in good accordance with those of starting materials as given above. The stereocourse of the enzyme reactions for **8** was deduced in the same manner as described for **7** with the aid of the MTPA ester **8c**.

Acetylation of 8a with *Candida antarctica* Lipase

To a mixture of **8a** (48.2 mg, 0.27 mmol), vinyl acetate (1 ml), *Candida antarctica* lipase (8.3 mg) immobilized with Florisil was added and the mixture was stirred for 3 h at 30 °C. The conversion (7.8%) was estimated by the integration of signals of (2*R**,3*S**)-**8a** (δ = 3.70), (2*R**,3*R**)-**8a** (δ = 3.76), (1*R**,2*S**)-**8b** (δ = 4.85), and (1*R**,2*R**)-**8b** (δ = 4.90). The diastereomeric excess of acetate was also estimated by GLC analysis [TC-1, 0.25 mm × 30 m; 140 °C, 15 min, 18 °C/min, 160 °C, 50 mL/min, 180 kPa; (1*R**,2*R**)-**8b**: 19.2 min, (1*R**,2*S**)-**8b**: 19.3 min]. After having been filtered through a pad of Celite, the filtrate was concentrated under vacuum. The crude residue was purified by preparative TLC (hexane/EtOAc = 4/1) to afford (1*R**,2*R**)-**8b** (3.0 mg, 5%, 74% de) and unreacted-**8a** (35.7 mg, 74%). Their NMR and IR spectra were in good accordance with those of starting materials as given above.

3-Methyl-6-phenyl-2-hexanol (9a)

To a mixture of magnesium (109 mg, 5.00 mmol) and phenethyl bromide (819 mg, 4.43 mmol) in anhydrous Et_2O (5 mL), 3-methyl-3-buten-2-one **15** (250 mg, 2.97 mmol) was added at room temperature with stirring. The conventional workup and chromatographic purification (silica gel, hexane/EtOAc = 12/1) afforded a mixture containing 3-methyl-6-phenyl-2-hexanone **16** (193.4 mg). This was employed in the next step without further purification.

To a solution of the crude **16** (193.4 mg) in EtOH (4 mL), $NaBH_4$ (40.4 mg, 1.07 mmol) was added at room temperature with stirring. The conventional workup and chromatographic purification (silica gel, hexane/EtOAc = 5/1) afforded **9a** (181.2 mg, 32% through two steps) as a mixture of (2*R**,3*S**)- and (2*R**,3*R**)-**9a**. Analytical sample: ^{1}H NMR: δ = 0.88 [d, *J* = 6.5 Hz, (2*R**,3*S**)-**9a**, total 3H with δ = 0.90], 0.90 [d, *J* = 6.4 Hz, (2*R**,3*R**)-**9a**, total 3H with δ = 0.88], 1.12 [d, *J* = 6.3 Hz, (2*R**,3*S**)-**9a**, total 3H with δ = 1.14], 1.14 [d, *J* = 6.5 Hz, (2*R**,3*R**)-**9a**, total 3H with δ = 1.12], 1.11 – 1.15 (m, 1H), 1.40 – 1.62 (m, 1H), 1.67 – 1.76 (m, 1H), 2.54 – 2.70 (m, 2H), 3.65 [dq, *J* = 4.2, 6.5 Hz, (2*R**,3*S**)-**9a**, total 1H with δ = 3.70], 3.70 [dq, *J* = 4.2, 6.5 Hz, (2*R**,3*R**)-**9a**, total 1H with δ = 3.65], 7.17 – 7.34(m, 5H).

1,2-Dimethyl-6-phenypentyl Acetate (9b)

In a conventional manner, **9a** (3.50 g, 16.6 mmol) was converted to **9b** as a colorless oil; yield: 4.20 g (quant.). Analytical sample: ^{1}H NMR: δ = 0.89 [d, *J* = 6.7 Hz, (1*R**,2*S**)-**9b**, total 3H with δ = 0.90], 0.90 [d, *J* = 6.7 Hz, (1*R**,2*R**)-**9b**, total 3H with δ = 0.89], 1.13 [d, *J* = 6.4 Hz, (1*R**,2*S**)-**9b**, total 3H with δ = 1.16], 1.16 [d, *J* = 6.3 Hz, (1*R**,2*R**)-**9b**, total 3H with δ = 1.13], 1.12 – 1.20 (m, 1H), 1.38 – 1.51 (m, 1H), 1.52 – 1.76 (m, 2H), 2.01 (br.s, 3H), 2.53 – 2.66 (m, 2H), 4.80 [dq, *J* = 6.2, 6.2 Hz, (1*R**,2*S**)-**9b**, total 1H with δ = 4.84], 4.84 [dq, *J* = 4.9, 6.3 Hz, (1*R**,2*R**)-**9b**, total 1H with δ = 4.80], 7.13 – 7.33 (m, 5H); IR: ν = 3380, 3060, 3030, 2970, 2930, 2850, 1600, 1500, 1455, 1380, 1090, 1070, 1030, 930, 890, 755, 705 cm^{-1}.

Hydrolysis of 9b with *Candida antarctica* Lipase

To a mixture of **9b** (39.7 mg, 0.17 mmol) in acetone and pH 7.0 phosphate buffer (2:3, 1.0 ml), *Candida antarctica* lipase (5.4 mg) was added and the mixture was stirred for 2 h at room temperature. The conversion (5.0%) and de were determined in the same manner as stated for the lipase-catalyzed acetylation. The workup was carried out in the same manner as described above to afford (2*R**,3*S**)-**9a** (2.0 mg, 5%, 72% de) and unreacted **9b** (31.8 mg, 80%). Their NMR and IR spectra were in good accordance with those of starting materials as given above. The stereocourse of the enzyme reactions for **9** was deduced in the same manner described for **7** with the aid of the MTPA ester **9c**.

Acetylation of 9a with *Candida antarctica* Lipase

To a mixture of **9a** (40.5 mg, 0.21 mmol), vinyl acetate (1 mL), *Candida antarctica* lipase (13.1 mg) immobilized with Florisil was added and the mixture was stirred at 30 °C for 2 h. The conversion (5.0%) was estimated by the integration of signals of (2*R**,3*S**)-**9a** (δ = 3.65), (2*R**,3*R**)-**9a** (δ = 3.70), (1*R**,2*S**)-**9b** (δ = 4.80), and (1*R**,2*R**)-**9b** (δ = 4.84). The diastereomeric excess of acetate was also estimated by GLC analysis [TC-1, 0.25 mm × 30 m; 140 °C, 15 min, 18 °C/min, 160 °C, 50 mL/min, 180 kPa; (1*R**,2*S**)-**9b:** 22.9 min, (1*R**,2*R**)-**9b:** 23.2 min]. After having been filtered through a pad of Celite, the filtrate was concentrated under vacuum. The crude residue was purified by preparative TLC (hexane/EtOAc = 4/1) to afford (1*R**,2*S**)-**9b** (2.5 mg, 5%, 8% de) and unreacted **9a** (30.8 mg, 76%). Their NMR and IR spectra were in good accordance with those of starting materials as given above.

(±)-3-Benzyloxy-2-methylpropyl Acetate (1b)

In a conventional manner, alcohol **1a** (267.6 mg, 1.48 mmol) was converted to **1b** as a colorless oil; yield: 330.0 mg (quant.). Analytical sample: ^{1}H NMR: δ = 0.98 (d, *J* = 6.9 Hz, 3H), 2.02 (s, 3H), 2.14 (m, 1H), 3.36 (dd, *J* = 5.6, 9.2 Hz, 1H), 3.40 (dd, *J* = 6.3, 9.2 Hz, 1H), 4.00 (dd, *J* = 5.9, 10.9 Hz, 1H), 4.09 (dd, *J* = 6.3, 10.9 Hz, 1H), 4.50 (br.s, 2H), 7.20–7.50 (m, 5H); IR: ν= 3080, 3040, 2970, 2870, 1740, 1600, 1590, 1500, 1455, 1370, 1240, 1105, 1020, 990, 910, 840, 740, 700, 605 cm^{-1}; anal. calcd. for $C_{13}H_{18}O_3$ (222.3): C 70.24%, H 8.16%; found: C 70.06%, H 8.13%.

Hydrolysis of 1b with *Candida antarctica* Lipase

To a mixture of **1b** (1.81 g, 8.14 mmol) in acetone and pH 7.0 phosphate buffer (2:3, 40 mL), *Candida antarctica* lipase (50 mg) was added and the mixture was stirred at 0 °C for 48 h. The conversion (58%) and ee were determined in the same manner as stated for the lipase-catalyzed acetylation. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (50 g). Elution with hexane/EtOAc (10/1) yielded (*R*)-**1b** (643 mg, 36%, >99% ee) and (*R*)-**1a** (779 mg, 53%, 74% ee).

Analytical sample of (*R*)-**1b**: $[\alpha]_D^{22}$: –5.4° (*c* 1.1, EtOH) [lit.[9] (*S*)-isomer (90% ee) $[\alpha]_D$: +4.9° (*c* 2.2, EtOH)]. Its NMR and IR spectra were in good accordance with those of the racemate. Anal. calcd. for $C_{13}H_{18}O_3$ (222.3): C 70.25%, H 8.16%; found C 70.12%, H 8.37%.

The acetate (*R*)-**1b** was converted to (*S*)-**1a** as above. Analytical sample of (*S*)-**1a**: $[\alpha]_D^{24}$: +3.7° (*c* 2.3, EtOH) [lit.[9] (90% ee) $[\alpha]_D$: +2.6° (*c* 2.2, EtOH)]. Its NMR and IR spectra were in good accordance with those of the racemate. Anal. calcd. for $C_{11}H_{16}O_2$ (180.3): C 73.30%, H 8.95%; found: C 73.18%, H 9.24%.

Analytical sample of (*R*)-**1a**: $[\alpha]_D^{20}$: –3.1° (*c* 1.0, EtOH) [lit.[9] (*R*)-isomer (90% ee) $[\alpha]_D$: –2.5° (*c* 1.5, EtOH)]. Their NMR and IR spectra were in good accordance with those of the racemate.

The alcohol (*R*)-**1a** (74% ee) obtained as above was reacetylated to the substrate (*S*)-**1b**. A mixture of the acetate (*S*)-**1b** (109.0 mg, 0.49 mmol), *Candida antarctica* lipase (2.1 mg), and acetone plus pH 7.0 phosphate buffer (2:3, 2 mL) was stirred for 24 h at 0 °C. The mixture was extracted five times with EtOAc (5 mL), and the organic layer was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (3 g). Elution with hexane/EtOAc (10/1) yielded 43.0 mg (49%, >99% ee) of (*R*)-**1a** and 41.1 mg (38%, 49% ee) of (*S*)-**1b**.

Analytical sample of (*R*)-**1a**: $[\alpha]_D^{21}$: –3.8° (*c* 1.35, EtOH); anal. calcd. for $C_{11}H_{16}O_2$ (180.3): C 73.30%, H 8.95%; found: C 73.20%, H 9.00%. Its NMR and IR spectra were in good accordance with those of the racemate.

Analytical sample of (*S*)-**1b**: $[\alpha]_D^{24}$: +2.6° (*c* 1.00, EtOH). Its NMR and IR spectra were in good accordance with those of the racemate.

Acetylation of 1a with *Candida antarctica* Lipase

To a mixture of **1a** (120.1 mg, 0.666 mmol) in vinyl acetate (3 mL), *Candida antarctica* lipase (14.5 mg) immobilized with Florisil was added and the mixture was stirred for 2 h at 30 °C. After having been filtered through a pad of Celite, the filtrate was concentrated under vacuum. The conversion (64%) was estimated by GLC analysis [TC-1, 0.25 mm × 30 m; 140 °C, 50 mL/min, 180 kPa; **1a**: 5.0 min, **1b**: 8.6 min]. The crude residue was purified by preparative TLC (hexane/EtOAc = 4/1) to afford (*S*)-**1a** (52.5 mg, 44%, 41% ee) and (*S*)-**1b** (66.8 mg, 45%, 23% ee).

Analytical sample of (*S*)-**1a**: $[\alpha]_D^{25}$: +1.5° (*c* 1.0, EtOH). Analytical sample of (*S*)-**1b**: $[\alpha]_D^{24}$: +0.8° (*c* 0.9, EtOH). The acetate (*S*)-**1b** was converted to (*R*)-**1a** as described above. Analytical sample of (*R*)-**1a**: $[\alpha]_D^{21}$: –0.8° (*c* 1.2, EtOH). Their NMR and IR spectra were in good accordance with those of the racemate. Their ee's were confirmed by ^{1}H NMR analyses of the corresponding (*R*)-MTPA ester **1c**.[12] ^{1}H NMR of (*S*)-**1c** [(*R*)-**1a**]: δ = 4.27 (dd, *J* = 5.9, 10.7 Hz, 1H), 4.39 (dd, *J* = 5.4, 10.7 Hz, 1H); of (*R*)-**1c** [(*S*)-**1a**]: δ = 4.31 (dd, *J* = 5.9, 7.6 Hz), 4.35 (dd, *J* = 5.7, 7.6 Hz).

Hydrolysis of 2b with *Candida antarctica* Lipase: E Value against the Conversion

Acetate **2b** was hydrolyzed with *Candida antarctica* lipase at 0 °C in the same manner, varying the period of reaction. For example, the substrate (1.07 g, 4.2 mmol) was hydrolyzed in acetone-phosphate buffer (2:3, total 20 mL) with lipase (22.5 mg). The reaction was stopped after the period as indicated as follows. The workup was carried out in the same manner as described before.

For 12 h hydrolysis: conversion, 36% by NMR measurement of crude mixture as described above; **2a** (36.6%, 92.9% ee by HPLC analysis after converting to **2c**); **2b** (63.5%, 52.4% ee by HPLC analysis of the corresponding **2c** as above). From these results, E value was estimated to be 46.

For 25 h hydrolysis: conversion, 49%; **4a** (47.5%, 89.2% ee as **2c**); **2b** (48.3%, 85.7% ee as **2c**); E value 48.

For 55 h hydrolysis: conversion, 53%; **2a** (53.1%, 80.2% ee); **2b** (46.4%, 90.4% ee); E value 28.

For 72 h hydrolysis: conversion, 47%; **2a** (49.6%, 88.5% ee); **4b** (50.4%, 78.5% ee); E value 39.

For 80 h hydrolysis: conversion, 59%; **2a** (59.7%, 65.8% ee); **4b** (41.7%, 94.7% ee); E value 17.

For 82 h hydrolysis: conversion, 54%; **4a** (54.3%, 81.0% ee); **4b** (46.7%, 95.1% ee); E value 35.

Another run for 82 h run: conversion, 56%; **4a** (53.4%, 72.9% ee); **4b** (46.4%, 92.8% ee); E value 21.

Hydrolysis of 2b with *Candida antarctica* Lipase: Effect of the Addition of Alcohol

To a substrate (**2b** with or without **2a**), a solution of *Candida antarctica* lipase (Chirazyme L-2) in acetone and 0.1 M, pH 7.0 phosphate buffer (2:3) was added and the mixture was stirred at 0 °C. For the more reactive acetate (*S*)-**2b** as the substrate (Table 4, entries 1 – 4), the reaction was continued for 25 min. In contrast, for the less reactive (*R*)-**1b** as the substrate (Table 4, entries 5 and 6), the incubation period

was extended to 60 min. The lipase-solvent mixture was prepared as follows: lipase, 30.0 mg; acetone, 12 mL; buffer, 18 mL. The workup as described above afforded the crude mixture. The conversion was estimated by the integration of signals of **2b** (δ = 0.96), **2a** (δ = 0.86).

Entry (1): The non-inhibition experiment: when only (*S*)-**2b** (92.9% ee, 15.7 mg) was used as the substrate, the conversion was 12.1%.

Entry (2): Under the condition that (*S*)-**2b** (92.9% ee, 15.8 mg) and (*R*)-**2a** (92.9% ee, 13.3 mg) were incubated in the solvent mixture (0.61 mL), the conversion was 6.6%.

Entry (3): Under the condition that (*S*)-**2b** (92.9% ee, 15.7 mg) and (*S*)-**2a** (99.2% ee, 2.9 mg) were incubated, the conversion was 10.7%.

Entry (4): Under the condition that (*S*)-**2b** (92.9% ee, 15.8 mg) and (*R*)-**2a** (92.9% ee, 3.3 mg) were incubated, the conversion was 9.8%.

Entry (5): When the acetate (*R*)-**2b** (99.2% ee, 15.4 mg) was incubated, the conversion was 2.1%.

Entry (6): Under the condition that (*R*)-**2b** (99.2% ee, 14.9 mg) and (±)-**2a** (12.6 mg) were incubated, the conversion was 1.8%. For the explanation for entries 1 – 6, see text.

Hydrolysis of (±)-2b with *Candida antarctica* Lipase: Two-Step Procedure

The reaction was carried out in a similar manner to the procedure as described above. To a mixture of **2b** (10.02 g, 39.7 mmol) in acetone and 0.1 M, pH 7.0 phosphate buffer (2:3, 200 mL), *Candida antarctica* lipase (201.3 mg) was added and the mixture was stirred for 55 h at 0 °C. The order of mixing substrate, solvent and enzyme was followed in the same manner as in the small-scale reaction. The workup and the subsequent purification yielded (*R*)-**2a** (4.43 g, 53%, 80.5% ee) and (*R*)-**2b** (4.65 g, 47%, 89.9% ee).

Analytical sample of (*R*)-**2a**: $[\alpha]_D^{21}$: –2.2° (*c* 1.2, EtOH). Analytical sample of (*R*)-**2b**: $[\alpha]_D^{21}$: –3.7° (*c* 0.27, EtOH). The acetate (*R*)-**2b** was converted to (*S*)-**2a** as described above. Analytical sample of (*S*)-**2a**: $[\alpha]_D^{24}$: +2.2° (*c* 0.25, EtOH). Its ee was confirmed as described above.

To a mixture of (*R*)-**2b** (4.65 g, 89.9% ee, 18.4 mmol, recovery as above) in the same solvent system (2:3, 90 mL), *Candida antarctica* lipase (90.8 mg) was added and the mixture was stirred for 24 h at 0°C. The workup and the purification yielded (*R*)-**2b** (4.13 g, 42%, 99.2% ee) and (*S*)-**2a** (0.43 g, 5%, 12.2% ee).

Analytical sample of (*S*)-**2a**: $[\alpha]_D^{22}$: +0.21° (*c* 1.1, EtOH). Analytical sample of (*R*)-**2b**: $[\alpha]_D^{20}$: –5.2° (*c* 0.87, EtOH); anal. calcd. for $C_{14}H_{20}O_4$ (252.3): C 66.65%, H 7.99%; found: C 66.55%, H 8.05%.

The acetate (*R*)-**2b** was converted to (*R*)-**2a** as above. Analytical sample of (*S*)-**2a**: $[\alpha]_D^{20}$: +2.4° (*c* 0.54, EtOH). Its ee was confirmed as described above.

5-Methyl-2-(4-methoxyphenyl)-1,3-dioxane (4) from 2a

The reaction was carried out in a similar manner to the procedure reported previously.[13] To a mixture of **2a** (103.6 mg, 0.493 mmol) in CH_2Cl_2 (2 mL), DDQ (132.1 mg, 0.582 mmol) was added and the mixture was stirred for 6 h at room temperature. After having been filtered through a pad of Celite, the filtrate was extracted with CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (5 g). Elution with hexane/EtOAc/Et_3N (700/100/1) afforded **4** as a colorless oil; yield: 83.3 mg (81%). Its NMR and IR spectra were in good accordance with those as described above.

Confirmation of the Absolute Configuration of 2a; (*R*)-1-Benzyloxy-3-(4-methoxybenzyloxy)-2-methylpropane (1d)

To a mixture of (*R*)-**2a** [$[\alpha]_D^{21}$: –2.9°, 92.9% ee, 110.8 mg, 0.53 mmol], NaH (60% in paraffin, 69.6 mg, 1.74 mmol) in DMF (2 mL), benzyl chloride (272.3 mg, 2.15 mmol) was added at 0 °C and the mixture was stirred for 5 h at room temperature. H_2O (5 mL) was added to the mixture. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (2.5 g). Elution with hexane/EtOAc (20/1) furnished (*R*)-**1d**; yield: 129.4 mg (82 %). Analytical sample: $[\alpha]_D^{25}$: –0.18° (*c* 0.86, EtOH); ^{1}H NMR: δ = 0.98 (d, *J* = 6.8 Hz, 3H), 2.10 (m, 1H), 3.35 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.37 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.45 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.47 (dd, *J* = 6.1, 9.0 Hz, 1H), 3.80 (s, 3H), 4.43 (s, 2H), 4.49 (s, 2H), 6.85 (m, 2H), 7.22 – 7.36 (m, 6H); ^{13}C NMR: δ = 159.0, 138.7, 130.7, 129.1, 128.3, 127.5, 127.4, 113.7, 73.0, 72.8, 72.7, 55.2, 34.3, 14.5; IR: ν = 3063, 3031, 2957, 2933, 2906, 2854, 1612, 1586, 1512, 1496, 1464, 1453, 1363, 1302, 1247, 1205, 1172, 1090, 1035, 819, 734, 697 cm^{-1}; anal. calcd. for $C_{19}H_{24}O_3$ (300.4): C 75.97%, H 8.05%; found: C 75.67%, H 8.30%.

(*S*)-3-Benzyloxy-2-methyl-1-propanol (1a) from 1d

The reaction was carried out in a similar manner to the procedure reported previously.[13] To a mixture of (*R*)-**1d** (65.7 mg, 0.219 mmol) in CH_2Cl_2 and H_2O (20/1, 1 mL), DDQ (59.0 mg, 0.260 mmol) was added and the mixture was stirred for 1 h at room temperature. Saturated aqueous $NaHCO_3$ solution (10 mL) was added to it. The mixture was extracted with $CHCl_3$, and the organic layer was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (1.5 g). Elution with hexane/EtOAc (5/1) afforded (*S*)-**1a**; yield: 39.4 mg (quant.). Analytical sample: $[\alpha]_D^{24}$: +3.1° (*c* 1.0, EtOH) [lit.[9] (90% ee (*S*)-isomer) $[\alpha]_D^{24}$: +2.6° (*c* 2.2, EtOH)].

Asymmetric Acetal Ring Opening of 4

To a mixture of (*R*)-binaphthol (275 mg, 0.96 mmol) in CH_3CN (3.5 mL) and CCl_4 (0.5 mL), Ti(O*i*-Pr)$_4$ (237 mg, 0.96 mmol) was added and the mixture was stirred for 30 min at room temperature. The mixture was concentrated by a rotary evaporator under carefully dehydrated conditions. The residue was further evacuated by a vacuum pump (8 torr) for 30 min. The flask was then purged with Ar, and CH_3CN (3.5 mL) and CCl_4 (0.5 mL) were added. After cool-

ing to 0 °C, acetal **4** (100 mg, 0.48 mmol) was added and the mixture was stirred at 0 °C for an additional 1 h. Then, $NaBH_3CN$ (60 mg, 0.96 mmol) was added and the resultant mixture was stirred for 36 h at 40 °C. Saturated aqueous NH_4Cl solution (5 mL) was added to the mixture. The mixture was extracted with EtOAc, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (2.5 g). Elution with hexane/EtOAc (5/1) afforded (*S*)-**2a**; yield: 25.0 mg (22%). Analytical sample: $[\alpha]_D^{22}$: +0.24° (*c* 1.6, EtOH). Its NMR and IR spectra were in good accordance with those of the racemate. Although the rotation was very small, the ee was confirmed to be 44.0% by HPLC analysis of the benzoate **2c** as described before.

(*R*)-3-Hydroxy-2-methylpropyl Acetate (3c)

The hydrolysis was carried out essentially according to the reported procedure.[22b] A mixture of diacetate **3b** (2.0 g, 11.48 mmol), guanidine thiocyanate (0.1 M solution, 216 mL) and phosphate buffer (pH 7.0, 0.1 M, 10 mL) was stirred at 0 °C. To this was added *Pseudomonas cepacia* lipase (Amano PS, 400 mg) and the mixture was stirred at 0 °C for 5 days while its pH was maintained by a pH controller with the occasional addition of aqueous NaOH solution (1.0 M). The mixture was extracted with CH_2Cl_2 (50 mL × 5). The extract was washed with brine, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (15 g) and elution with hexane/EtOAc (2/1 – 1/1). First, the unreacted substrate **3b** (268 mg, 13.4%) was eluted.

Further elution afforded the desired product **3c**; yield: 904 mg (6.84 mmol, 59.6%). Based on the consumed starting material, the recovery of the product was 69%. ^1H NMR: δ = 0.87 (d, *J* = 6.8 Hz, 3H), 1.92 (m, 1H), 2.01 (2, 3H), 2.07 (br.s, 1H), 3.46 (m, 2H), 4.01 (m, 2H). Its NMR spectrum was in good accordance with that reported previously. This material was employed in the next step without further purification.

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropyl acetate (2b) from 3c

The derivatization was carried out in a similar manner to the procedure reported previously.[2h] *p*-Methoxybenzyltrichloroacetimidate was prepared according to Smith's procedure from *p*-methoxybenzyl alcohol. To a mixture of monoacetate **3c** (904 mg, 6.84 mmol) in a mixture of cyclohexane (28 mL) and CH_2Cl_2 (14 mL) were added 3 Å molecular sieves (1 g) and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C, a solution of the crude trichloroacetimidate (1.73 g) in CH_2Cl_2 (6 mL) and then PPTS (474 mg, 1.89 mmol) were added, and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (50 g). Elution with hexane/EtOAc (4/1) afforded (*R*)-**2b** as a colorless oil; yield: 1.674 g (97%); $[\alpha]_D^{25}$: –4.6° (*c* 1.00, EtOH); anal. calcd. for $C_{14}H_{20}O_4$ (252.3): C 66.65%, H 7.99%; found C 66.57%, H 8.03%. Its NMR and IR spectra were in good accordance with those of an authentic sample.

For the confirmation of the ee, the acetate ester was removed by transesterification with K_2CO_3-MeOH to give (*S*)-**2a**; $[\alpha]_D^{26}$: +1.87° (*c* 2.01, EtOH). Its NMR and IR spectra were in good accordance with those of an authentic sample. Its ee was estimated to be 93.5% by the HPLC analysis of the benzoate **2c** as described before.

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[12] Enzyme reaction products, acetate (*R*)-**2b** and alcohol (*R*)-**2a**, have opposite absolute configurations, however, both are described as (*R*)-enantiomers due to the IUPAC nomenclature. Also we should be careful that (*R*)-**2a** corresponds to benzoate (*S*)-**2c**. The similar relationship is noted between alcohol (*R*)-**1a**, acetate (*S*)-**1b**, and MTPA ester (*S*)-**1c**, all of which have the same absolute configuration.

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