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Biocatalytic Approaches to Both Enantiomers of (2*R**,3*S**)-2-Allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol

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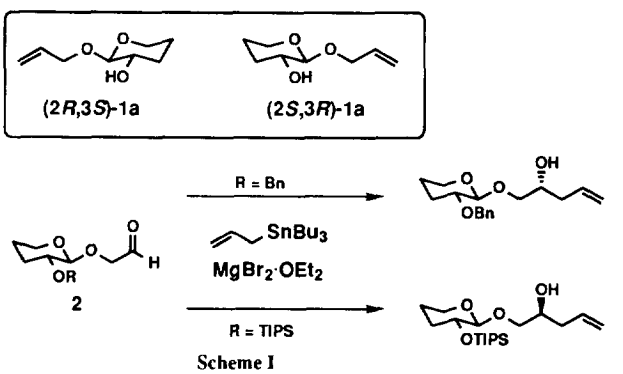
Abstract: Both enantiomers of (2*R**,3*S**)-2-allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol, a precursor of chiral auxiliary for asymmetric addition of organometallics, and its analog, (2*S*,3*S*)-2-ethoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol were prepared by biocatalytic optical resolutions. Lipase-catalyzed enantioselective acetylation of the racemate in organic solvent worked well with a high enantioselectivity. *Pseudomonas cepacia* lipase was most effective (E = 11–17) for the kinetic resolution. Under the optimized condition, the products, (2*R*,3*S*)-2-allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol and (2*S*,3*S*)-2-ethoxy analog with more than 97% *e.e.* were obtained in 31-45% yield with 52-62% conversion. The enantiomer, (2*S*,3*R*)-2-allyloxy compound was secured by two ways. The repetition of the lipase-catalyzed acetylation on partially enantiomerically enriched substrate afforded the acetate with a high *e.e.* (97%). A newly developed double resolution procedure in one-pot reaction was also successful. In this case, the apparent E value *via* two steps became as high as 71. Copyright © 1996 Elsevier Science Ltd

Introduction

Optically active cyclic alcohols play important roles as chiral auxiliaries in asymmetric syntheses.[1] Among them, Charette and co-workers have demonstrated (2*R**,3*S**)-2-allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol (**1**).[2] This alcohol works as a starting material of **2**, which is a chiral auxiliary for diastereoselective addition of organometallics on α-alkoxyaldehyde. Only by changing the protective group [R = Bn or triisopropylsilyl (TIPS)], attack of allylstannane occurs with highly diastereofacial but opposite selectivity as shown in Scheme I. Another interest is the biological function of optically active form of **1a** when it is incorporated into oligosaccharides as a highly deoxygenated carbohydrate.[3] In Charette's report, the preparation of optically active forms of **1a** and/or **2** from L-glutamic acid and both enantiomers of arabinose was also described, however, the installation of the functional groups requires multi-steps from these staring materials. Here we report on biocatalytic approaches to the optical resolution of the corresponding racemate of **1a**, which has been prepared in only a single step from dihydropyran and allyl alcohol.[2]

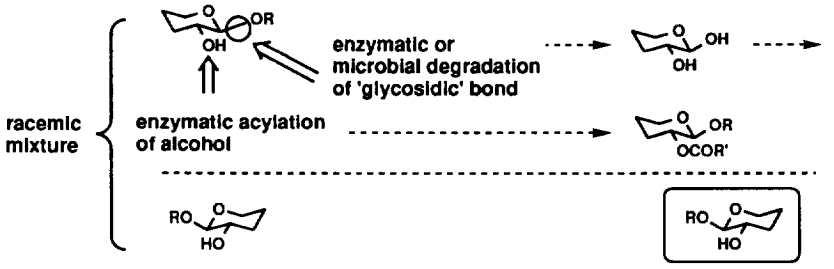


Scheme I

Results and Discussion: Glycosidase-catalyzed Reaction

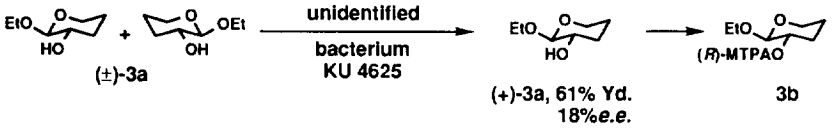
The tetrahydropyranol can be regarded as a highly deoxygenated β-glycoside. Another functional group which is inherent in this target molecule is a secondary alcohol. To achieve the optical resolution of the

tetrahydropyranol, we proposed two approaches as depicted in Scheme II: 1) biocatalytic enantioselective cleavage of the 'glycosidic' bond; 2) enzymatic enantioselective acylation of the secondary alcohol.



Scheme II

We started an investigation in the light of the first appoach. Several commercially available β-galactosidases[4] and microorganisms were applied to a simple model substrate **3a**.[5] To our disappointment, the hydrolysis of glycosidic bond and/or the microbial degradation of **3a** in every case was very slow. Even in the best case as obtained from the incubation of **3a** with a strain of unidentified bacterium KU 4625 which assimilated **3a** as a sole carbon source, the enantiomeric excess (*e.e.*) of the recovered substrate [(+)-**3a**, 61% yield], determined by NMR analysis of the corredponding MTPA ester **3b**,[6] was as low as 18% (Scheme III). We accordingly turned our attention to the second approach as described before.



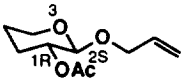
Scheme III

Lipase-catalyzed Kinetic Resolution of (±)-1a and (±)-3a

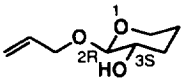
There have been reported numerous examples of lipase-catalyzed kinetic resolution of cyclic secondary alcohols *via* hydrolysis in aqueous media or transesterification in organic solvents (Scheme IV†).[7] Because of substantial solubility of **1a** and **3a** in water, a lipase-catalyzed acetylation with vinyl acetate in the presence or absence of a proper organic co-solvent was chosen for the kinetic resolution of these compounds.[8]

Toward this end, several kinds of lipases with high availability were tested for the acetylation of (±)-**1a** with vinyl acetate. Among them, Amano PS lipase (from *Pseudomonas cepacia*) was found to be the best [E(S)[9] = 15] to catalyze this reaction. While most of lipases preferred (−)-enantiomer of **1a** in acetylation, lipase Sigma L-1754 (from *Candida cylindracea*) enantioselectively acylated (+)-enantiomer.*cf.*[10] However, its selectivity was rather low [E(S) = 6].

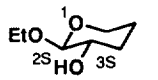
† The IUPAC nomenclature and numbering of **1a**, **1c** and **3a** is somewhat confusing:



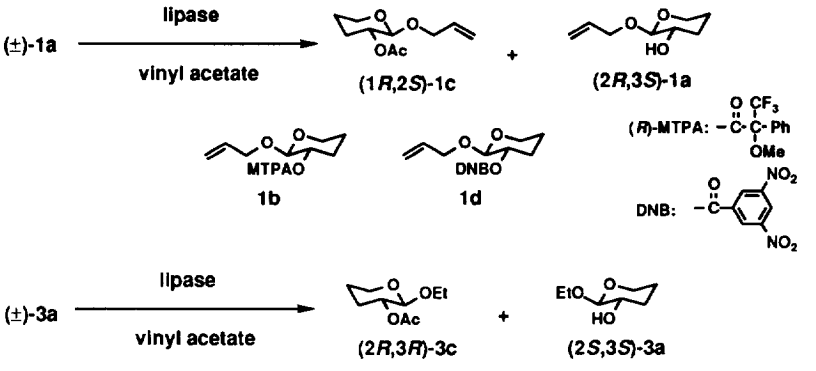
(1*R*,2*S*)-2-allyloxy-1,4,5,6-tetrahydro-2H-pyranyl acetate **1c**



(2*R*,3*S*)-2-allyloxy-3,4,5,6-tetrahydro-2H-pyran-3-ol **1a**



(2*S*,3*S*)-2-ethoxy-3,4,5,6-tetrahydro-2H-pyran-3-ol **3a**



Scheme IV

Next, the effect of co-solvent[11] on the enantioselectivity and the catalytic activity of Amano PS was investigated. The results are given in Table I. The enantioselectivity of the reaction did not depend upon the nature of added co-solvent; E(P) value being always slightly higher (*ca.* 14–17) than that without adding any co-solvent [E(P) = 11]. The rate of transesterification was, however, remarkably accelarated by the addition of hexane (80% of total volume), a linear-shaped solvent.

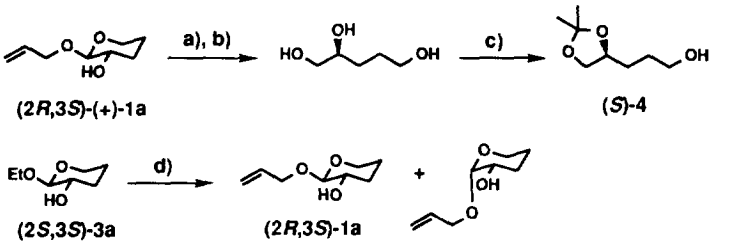
Table I. Lipase-catalyzed Kinetic Resolution of **1a** or **3a**[a]

substrate	lipase	co-solvent (80% v/v)	time (h) / conversion (%)	(–)-**1c** or **3c** Yd. (%)	% *e.e.*	(+)-**1a** or **3a** Yd. (%)	% *e.e.*	E(P)
1a	Amano PS (*P. cepacia*)	none	23 / 59	52	62	36	93	15[c]
1a	Sigma L-1754 (*C. cylindracea*)	none	25 / 51	45[b]	53	47[b]	60	6
1a	Amano PS	none	16 / 26	24	78	70	31	11
1a	Amano PS	hexane	6.5 / 44	40	79	56	62	16
1a	Amano PS	cyclohexane	10 / 42	39	81	57	59	17
1a	Amano PS	diisopropyl ether	10 / 41	38	78	55	61	14
1a	Amano PS	benzene	14 / 30	28	82	64	36	14
3a	Amano PS	none	24 / 62	55	52	31	97	8

a) All reactions were carried out at 30 °C and the conversion was determined by ^{1}H-NMR measurement of reaction mixture; b) (+)-**1c** and (–)-**1a** were obtained, respectively; c) E(S) value

We attempted the further improvement of the reaction conditions. It was thought that some change of the enantioselectivity of the reaction might be caused by lowering reaction temperature and the efficient removal of acetaldehyde, a toxic product of transesterification. From these reasons, the reaction was carried out at 23°C under an atmosphere of nitrogen gas with a continuous flow. The modification was really effective to enhance the enantioselectivity, [E(P) = 27] and we were pleased that (+)-**1a** with 97% *e.e.* was obtained in 45% yield. The result was well reproducible in a preparative scale (3-5 g of substrate). The *e.e.* of the product could be further enhanced (99%) by recrystallizing its 3,5-dinitrobenzoate **1d**.

The absolute configuration of (+)-**1a** was elucidated as shown in Scheme V. Acid hydrolysis of acetal and the subsequent reduction afforded a triol. Vicinal diol was protected as acetonide to give known (*S*)-(+)-**4**; $[\alpha]_D^{22}$ +12.0 (*c*=1.05, $CHCl_3$) [lit.[12] $[\alpha]_D^{20}$ +15.3 (*c*=2.45, $CHCl_3$)]. This result indicated that (+)-**1a** has (2*R*,3*S*)- absolute configuration.



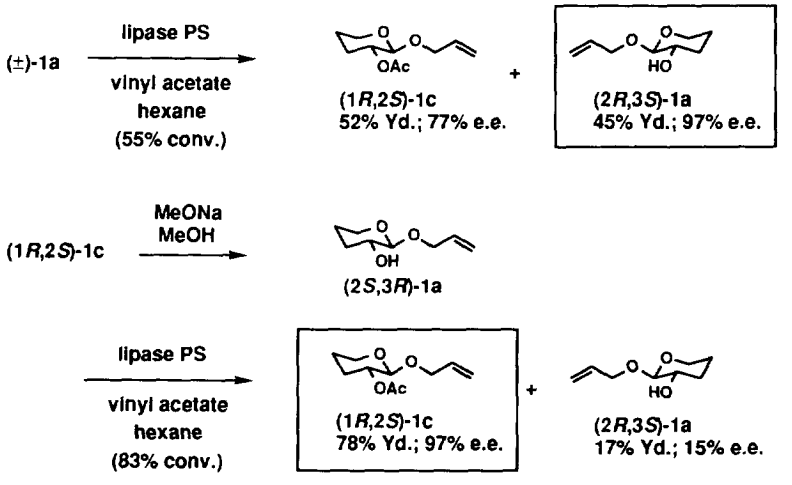
a) $HClO_4$ / H_2O; b) $NaBH_4$; c) 2,2-dimethoxypropane, *p*-TsOH / acetone; d) allyl alcohol, $HClO_4$

Scheme V

When an analogous substrate **3a** was treated with vinyl acetate and Amano PS lipase, (–)-**3c** (55% yield, 52% *e.e.*) was obtained, while leaving unreacted (+)-**3a** (31% yield, 97% *e.e.*, see Scheme IV and Table I). (2*S*,3*S*)-Absolute configuration of (+)-**3a** was confirmed by converting it into (+)-**1a**, whose absolute configuration was unambiguous as described above, by an acid-catalyzed transacetalization with allyl alcohol.

Double Resolution Procedure in One Pot

One unsolved problem in this resolution is a moderate [E(P) = 27] enantioselectivity even in the most selective case by combining Amano PS lipase and hexane, which makes the preparation of (2*S*,3*R*)-**1a** with high enantiomeric purity difficult. The *e.e.* of (1*R*,2*S*)-**1c** obtained in a preparative-scale resolution was 77%. So far, to obtain the product with a higher *e.e.*, so-called "double resolution" have been reported.[9,13]

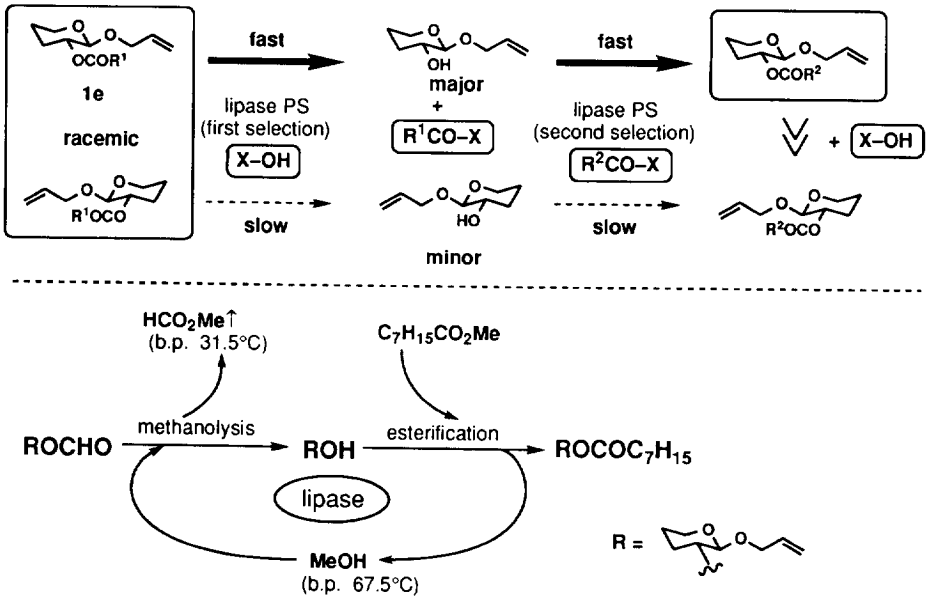


Scheme VI

Indeed, in the present case, (1*R*,2*S*)-**1c** with 77% *e.e.* was converted to (2*S*,3*R*)-**1a** by methanolysis. This was subsequently re-acetylated by the same lipase PS at a conversion of 83%, while leaving the contaminating (2*R*,3*S*)-**1a** intact. In this way, the *e.e.* of (1*R*,2*S*)-**1c** could be enhanced to as high as 97% (Scheme VI). This

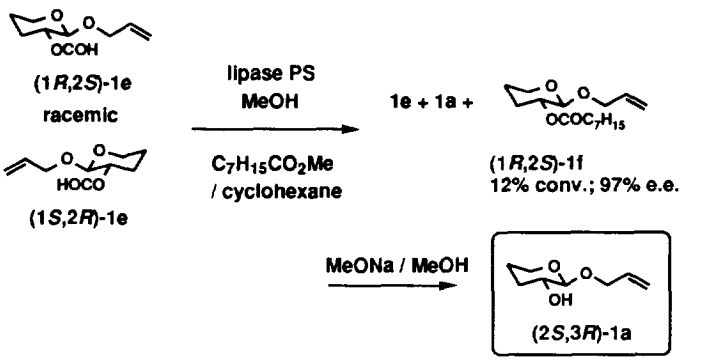
process worked successfully; however, the repeating enzymatic reaction and separation of the product was necessary.

We proposed one-pot double resolution procedure*cf.*[14] as shown in Scheme VII. The starting ester [acyl part: R^1CO–] is mixed with alcohol (X–OH) and lipase PS, an enantioselective transesterification would occur to give the corresponding alcohol where (2*S*,3*R*)-enantiomer is enriched. If another ester R^2CO–X co-exists simultaneously in the reaction mixture, the further enantioselective transesterificaion whould be expected to give the desired product [acyl part: R^2CO–] in a more enantiomerically enriched form. To achieve this proposed scheme, two important aspect should be emphasized: 1) the desired product must be isolated from the starting material, intermediates, and all other reagents by chromatography and/or distilliation; 2) the lipase-catalyzed transesterification, which is essentially a reversible process, should proceed to the desired direction. We accordingly chose a formate **1e** [acyl part: HCO–] as the starting material, methanol as the nucleophile in the first step (X–OH), and methyl octanoate as an ester used for the second step. It was expected that methyl formate (b.p. 31.5°C), a resulting ester in the first step [R^1CO_2X] in Scheme VII would be gradually released as a vapor from the reaction mixture even at the room temperature to work for moving the equilibrium to the desired reaction. While sequential double resolutions with the tandem use of same enzyme have been reported, the present procedure has an advantage that these sequential steps can be performed within the same reaction apparatus.



Scheme VII

This idea was realized by designing a reaction system using cyclohexane as a co-solvent, (2*S*,3*R*)-**1f** with a high *e.e.* being obtained. The *e.e.* (97%) of **1f** was confirmed by converting into **1a**. Although the yield (and conversion) was as low as 12%, an enhanced "apparent" E(P) = 74 value through two steps was observed. In single step procedure [E(P) = 17 in cyclohexane; as described above], at 12% conversion, an estimated *e.e.* of the acylated product is around 88%.



Scheme VIII

Conclusion

Among the biocatalytic procedures for preparing both enantiomers of (2*R**,3*S**)-2-allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol, a precursor of Charette's chiral auxiliary, *Pseudomonas* Amano PS lipase-catalyzed transesterification was found to be the best way in a preparative manner.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-202 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ with TMS as the internal standard at 270 MHz on a JEOL JNM EX-270 spectrometer unless otherwise stated. Mass spectra were recorded on Hitachi M-80B spectrometer at 70 eV. Optical rotations were recorded on a Jasco DIP 360 polarimeter. 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*R**,3*S**)-2-Allyloxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol (±)-**1a**. The reaction was carried out in a similar manner as the reported procedure.[2,5] To a stirred and ice-cooled solution of dihydropyran (1.1 mL, 12.2 mmol) and allyl alcohol (8.5 mL, 125 mmol, 10 eq) in benzene (60 mL) was added portionwise mCPBA (2.0 g, 70% purity, 8.1 mmol) at 0 °C. The mixture was stirred at room temperature overnight. After confirming the consumption of peracid with KI-starch test paper, the mixture was filtered and the residue on the filter paper was washed with chloroform. The filtrate was concentrated *in vacuo* and the residue was triturated with chloroform. The solution was washed with 0.2 N NaOH aq solution (100 mL). The aqueous solution was extracted with chloroform, and the combined organic solution was dried over Na_2SO_4, and concentrated *in vacuo*. The residue was distilled to give (±)-**1a** as an oil (1.05 g 81.6 %), b.p. 135 °C / 20 Torr (bulb-to-bulb distillation); IR vmax 3420, 2960, 2920, 2850, 1640, 1420, 1330, 1260, 1200, 1120, 1080, 1035, 910, 870, 810 cm^{-1}; ^{1}H NMR δ 1.45-1.78 (3H, m), 1.98-2.12 (1H, m), 2.37 (1H, br), 3.45 (1H, ddd, *J* = 3.3, 8.8, 11.4 Hz), 3.44-3.54 (1H, m), 3.88 (1H, dddd, *J* = 1.2, 3.6, 5.1, 11.4 Hz), 4.04 (1H, dddd, *J* = 1.3, 1.3, 6.3, 12.7 Hz), 4.30 (1H, d, *J* = 5.6 Hz), 4.30 (1H, dddd, *J* = 1.3, 1.3, 5.2, 12.7 Hz), 5.19 (1H, dddd, *J* = 1.3, 1.3, 1.6, 10.3 Hz), 5.30 (1H, dddd, *J* = 1.3, 1.3 1.6, 17.2 Hz), 5.91 (1H, dddd, *J* = 5.2, 6.3, 10.3, 17.2 Hz). The (2*R**,3*S**)-(*trans*) configuration was confirmed as follows: **1a** was stirred with allyl alcohol in the presence of *p*-toluenesulfonic acid to give a mixture of **1a** and the corresponding (2*R**,3*R**)- (*cis*) isomer. After a conventional workup, the mixture was separated by a silica gel column chromatography. **1a**: Rf 0.44 [silica gel, Merck 5715, hexane-ethyl acetate (1 : 1)]; (2*R**,3*R**)- (*cis*) isomer: Rf 0.50 (same solvent). ^{1}H NMR of (2*R**,3*R**)- (*cis*) isomer: δ 1.62-1.88 (4H, m), 1.99 (1H, d, *J* = 10.1 Hz), 3.49 (1H, ddd, *J* = 3.5, 3.5, 11.5 Hz), 3.58-3.68 (1H, m), 3.68 (1H, ddd, *J* = 4.7, 11.4, 11.4 Hz), 4.03 (1H, dddd, *J* = 1.2, 1.2, 6.1, 12.9 Hz), 4.27 (1H, dddd, *J* = 1.2, 1.2, 5.1, 12.9 Hz), 4.73 (1H, d, *J* = 3.5 Hz), 5.20 (1H, dddd, *J* = 1.2, 1.2, 1.4, 10.3 Hz), 5.31 (1H, dddd, *J* = 1.2, 1.2, 1.4, 17.2 Hz), 5.94 (1H, dddd, *J* = 5.1, 6.1, 10.3, 17.2 Hz); The observed coupling constants $J_{2,3}$ = 5.6 Hz (270 MHz) supported (2*R**,3*S**)- (*trans*) configuration of **1a**; while $J_{2,3}$ = 5.2 Hz (60 MHz) for (2*R**,3*R**)- (*trans*)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol and $J_{2,3}$ = 3.2 Hz (60 MHz) for (2*R**,3*S**)- (*cis*)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol have been reported previously.[5]

(2*R**,3*R**)-2-Ethoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol (±)-**3a**. According to the reported procedure,[5] this was prepared in the almost same manner as described for (±)-**1a**. (±)-**3a**: b.p. 130 °C / 20 Torr (bulb-to-bulb distillation); IR νmax 3450, 2940, 2880, 1640, 1440, 1380, 1270, 1210, 1140, 1110, 1080, 1050, 1030, 990, 880, 810 cm^{-1}; ^1H NMR δ 1.24 (3H, dd, *J* = 7.1, 7.1 Hz), 1.43-1.76 (3H, m), 2.0-2.1 (1H, m), 2.28 (1H, d, *J* = 4.0 Hz), 3.4-3.5 (2H, m), 3.55 (1H, dq, *J* = 9.7, 7.1 Hz), 3.89 (1H, dq, *J* = 9.7, 7.1 Hz), 3.85-3.95 (1H, m), 4.23 (1H, d, *J* = 6.0 Hz). Its IR spectrum was in good accordance with that of (2*R**,3*R**)- (*trans*)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol reported previously.[5] The observed coupling constant $J_{2,3}$ = 6.0 Hz (270 MHz) also supported (2*R**,3*R**)- (*trans*) configuration of **3a**.

Hydrolysis of (±)-**3a** with β-D-galactosidases. β-D-Galactosidase (10 units) from either one of *Aspergillus oryzae* (Sigma, G7138), *Escherichia coli* (Sigma, G6008), and *Bacillus circulans* (Daiwa Kasei, Biolacta) was added to a solution of (±)-**3a** (50 mg, 0.32 mmol) in buffer (0.01 M, 2 mL, pH 4.5 for *A. oryzae*, 7.4 for *E. coli*, and 6.0 for *B. circulans*) and the mixture was stirred at 30 °C for 48 h, respectively. After removal of enzyme, the mixture was extracted with $CHCl_3$, and the starting material (*ca.* 50% recovery) was purified by silica gel column chromatography. No sample showed any optical rotation. The low recovery was due to a high solubility of **3a** in water.

(2*S*,3*S*)-2-Ethoxy-3,4,5,6-tetrahydro-2*H*-pyran-3-ol (+)-**3a**. The screening of microorganisms was as follows. An inorganic medium was prepared from K_2HPO_4 (2 g), $(NH_4)H_2PO_4$ (10 g), $MgSO_4$ (0.3 g), $FeSO_4$ (10 mg), $MnSO_4$ (8 mg), $ZnSO_4$ (8 mg), yeast extract (0.2 g), and deionized water. Total volume was made up to 1000 mL and pH was adjusted to 6.8. After sterilization, a 10 mL portion of this medium containing (±)-**3a** (25 mg) in 100 mL test tube, was inoculated with the microorganism from stock culture or a sample of soil. The test tubes were shaken for several days at 30 °C to check the turbidity. In the case of the sample from soil, an aliquot was withdrawn from the turbid incubation broth and transferred into the same sterilized medium with (±)-**3a**. In this way, microorganisms which had assimilated **3a** were enriched, and the single cell colony was isolated by the incubation of turbid broth on LB-agar plate.

The degradation of (±)-**3a** by using an isolated bacterium, strain KU 4625 was carried out in a similar manner as described above. To a 200 mL of sterilized medium involving D-glucose as an adjunctive carbon source (400 mg), (±)-**3a** (500 mg) was added and was inoculated with KU 4625. After 96 h, the mixture was worked up in the same manner as described for the attempted hydrolysis by using galactosidases, and the recovered substrate was purified by silica gel column chromatography (305 mg, 61%). An analytical sample was obtained by distillation, b.p. 130 °C / 20 Torr (bulb-to-bulb distillation); $[\alpha]_D^{21}$ +17.8 (*c*=1.1, chloroform)]. Its IR and ^1H NMR spectra were identical with those reported for the corresponding racemate. HRMS Found: 128.0852. Calc. for $C_7H_{12}O_2$ (M^+-H_2O): 128.0837:

For determining the *e.e.* of the product, the corresponding (*R*)-MTPA ester was prepared in a conventional manner. The diastereomeric (*R*)-MTPA esters from (±)-**3a** appeared as two spots on TLC; fast-moving isomer of **3b**: Rf 0.47 [silica gel, Merck 5715, hexane-ethyl acetate (10 : 1), developed twice]; ^1H NMR δ 1.23 (3H, dd, *J* = 7.1, 7.1 Hz, H-2'), 1.51-1.63 (2H, m, H-5a and H-6a), 1.73 (1H, m, H-5e), 2.13 (1H, dddd, *J* = 4.3, 4.3, 8.8, 13.7 Hz, H-6e), 3.45-3.56 (1H, m, H-4e), 3.52 (1H, dq, *J* = 9.4, 7.1 Hz, H-1'), 3.60 (3H, s, -OMe) 3.84 (1H, dq, *J* = 9.4, 7.1 Hz, H-1'), 3.88 (1H, ddd, J = 3.9, 7.9, 11.4 Hz, H-4a), 4.60 (1H, d, *J* = 4.3 Hz, H-2a), 4.90 (1H, ddd, *J* = 4.3, 4.3, 6.3 Hz, H-1a), 7.41-7.55 (5H, aromatic); slow-moving isomer of **3b**: Rf 0.37 (same solvent). ^1H NMR δ 1.18 (3H, dd, *J* = 7.1, 7.1 Hz, H-2'), 1.55-1.78 (3H, m, H-5 and H-6a), 2.17 (1H, dddd, *J* = 4.1, 4.1, 8.5, 14.9 Hz, H-6e), 3.45 (1H, dq, *J* = 9.4, 7.1 Hz, H-1'), 3.46-3.54 (1H, m, H-4e), 3.56 (3H, s, -OMe), 3.78 (1H, dq, *J* = 9.4, 7.1 Hz), 3.88 (1H, ddd, *J* = 3.1, 7.9, 11.4 Hz, H-4a), 4.51 (1H, d, *J* = 4.1 Hz, H-2), 4.94 (1H, ddd, *J* = 4.1, 4.1, 6.1 Hz, H-1), 7.41-7.55 (5H, aromatic). In the case of **3b** of microbial origin, [from (+)-**3a**], a 41 : 59 ratio of fast-moving isomer and slow-moving isomer was observed, by the integration of signals of δ 4.60 and 4.51. HPLC analysis: column, Senshu Science Co. Ltd Pegasil silica 25 cm x 4.6 mm; solvent, hexane-ethyl acetate (12:1); flow rate: 1.0 mL/min, detected at 254 nm: t_R 12.9 min (41.2%) 15.5 min (58.8%).

Pseudomonas cepacia (Amano PS) lipase-catalyzed transterification of (±)-**1a**. A mixture of (±)-**1a** (200.8 mg, 1.27 mmol), Amano PS lipase (100 mg) in vinyl acetate (4 mL) was stirred at 30 °C for 23 h. The mixture was filtered and the residue was washed with chloroform. The combined filtrate and washings were

concentrated in *vacuo*, and a small portion of the residue was analyzed by ^{1}H NMR for determining the conversion. The conversion (59%) was estimated by the integration of signals of **1a** (δ 5.91) and **1c** (δ 4.60, 4.73, 5.91). The residue was further purified by silica gel column chromatography (5 g). Elution with hexane-ethyl acetate (5 : 1) afforded (–)-**1c** (133.2 mg, 52%). Analytical sample: b.p. 150 °C / 24 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ –63.7 (*c*=0.99, chloroform)]; IR νmax 2930, 2870, 1740, 1440, 1370, 1240, 1200, 1140, 1100, 1030, 970, 910, 880, 820 cm^{-1}; ^{1}H NMR δ 1.44 (1H, ddddd, *J* = 2.9, 3.8, 3.8, 3.8, 13.4 Hz), 1.65-1.74 (1H, m), 1.80-2.08 (2H, m), 2.09 (3H, s), 3.55 (1H, dddd, *J* = 1.3, 3.8, 3.8, 11.0), 3.85 (1H, ddd, *J* = 2.9, 11.0, 11.0 Hz), 4.01 (1H, dddd, *J* = 1.5, 1.5, 5.8, 13.1 Hz), 4.22 (1H, ddd, *J* = 1.5, 1.5, 5.0, 13.1 Hz), 4.60 (1H, d, *J* = 2.8 Hz), 4.73 (1H, ddd, *J* = 2.8, 3.2, 4.3 Hz), 5.18 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.4 Hz), 5.29 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.2 Hz), 5.91 (1H, dddd, *J* = 5.0, 5.8, 10.4, 17.2 Hz). (Found: C, 59.86; H, 8.39. Calc. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.)

Further elution with hexane-ethyl acetate (5 : 1) afforded (+)-**1a** (73.2 mg, 36%). Analytical sample: b.p. 135 °C / 19 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +88.2 (*c*=0.95, chloroform)]. Its IR and NMR spectra were identical with those of the corresponding racemate. HRMS Found: 140.0855. Calc. for $C_8H_{12}O_2$ (M^+-H_2O): 140.0837. Due to its high volatility, a correct elemental analysis could not be obtained. For determining the *e.e.* of the product, the corresponding (*R*)-MTPA ester was prepared in a conventional manner.

The diastereomeric (*R*)-MTPA esters from (±)-**1a** appeared as two spots on TLC; fast-moving isomer of **1b**: Rf 0.42 [silica gel, Merck 5715, hexane-ethyl acetate (5 : 1)]; ^{1}H NMR δ 1.44-1.56 (2H, m), 1.68-1.78 (2H, m), 2.08-2.20 (1H, m), 3.47-3.57 (1H, m), 3.59 (3H, -OMe), 3.89 (1H, ddd, *J* = 3.6, 8.7, 14.5 Hz), 4.03 (1H, dddd. *J* = 1.5, 1.5, 6.0, 12.9 Hz), 4.28 (1H, dddd, *J* = 1.5, 1.5, 5.2, 12.9 Hz), 4.65 (1H, d, *J* = 3.9 Hz), 4.94 (1H, ddd, *J* = 3.9, 3.9, 5.9 Hz), 5.20 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.3 Hz), 5.30 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.2 Hz), 5.91 (1H, dddd, *J* = 5.2, 6.0, 10.3, 17.2 Hz), 7.37-7.60 (5H, aromatic); slow-moving isomer of **1b**: Rf 0.37 (same solvent). ^{1}H NMR δ 1.48-1.60 (2H, m), 1.73-1.89 (2H, m), 2.10-2.24 (1H, m), 3.47-3.57 (1H, m), 3.55 (3H, -OMe), 3.88 (1H, ddd, *J* = 3.5, 8.5, 14.5 Hz), 3.97 (1H, dddd. *J* = 1.5, 1.5, 6.0, 12.9 Hz), 4.22 (1H, dddd, *J* = 1.5, 1.5, 5.2, 12.9 Hz), 4.56 (1H, d, *J* = 3.9 Hz), 4.98 (1H, ddd, *J* = 3.9, 3.9, 5.8 Hz), 5.17 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz), 5.27 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.2 Hz), 5.84 (1H, dddd, *J* = 5.2, 6.0, 10.5, 17.2 Hz), 7.37-7.57 (5H, aromatic) HPLC analysis: t_R 13.1 min (3.3%) 15.7 min (96.7%).

In the case of **1b** from (+)-**1a**, a 3.5 : 96.5 ratio of fast-moving isomer and slow-moving isomer was observed, by the integration of signals of 4.56 and 4.66. Therefore the *e.e.* of **1a** concluded to be 93%.

The present sample of (+)-**1a** (93% *e.e.*) was converted to the corresponding acetate (+)-**1c**. Analytical sample: b.p. 150 °C / 24 Torr (bulb-to-bulb distillation); $[\alpha]_D^{21}$ +98.1 (*c*=1.19, chloroform)]. Its IR and NMR spectra were identical with those of (–)-**1c**. By comparing its optical rotation with that of (–)-**1c** obtained by the lipase-catalyzed reaction, the *e.e.* of (–)-**1c** was concluded to be 61%.

In the case by using other lipase, the reaction was carried out in a similar manner as described above. (+)-**1c** and (–)-**1a** were obtained by using *Candida cylindracea* lipase (Sigma, L-1754). Analytical sample of (+)-**1c**: b.p. 150 °C / 24 Torr (bulb-to-bulb distillation); $[\alpha]_D^{21}$ +54.8 (*c*=1.02, chloroform)]. Its IR and NMR spectra were identical with those already described. Analytical sample of (–)-**1a**: b.p. 140 °C / 22 Torr (bulb-to-bulb distillation); $[\alpha]_D^{21}$ –57.2 (*c*=1.03, chloroform)]. Its IR and NMR spectra were identical with those already described.

In all cases by using *Aspergillus niger* Amano A, *Pseudomonas fluorescens* Amano P, *Candida cylindracea* Meito OF, *Candida antarctica* Novo sp 525, pig pancreatic Sigma L-3126 lipases, the conversion was less than 30% even after long reaction time (over 144 h).

In the experiments by using co-solvent, a mixture of each co-solvent (3.2 mL) and vinyl acetate (0.8 mL) was used instead of vinyl acetate (4 mL). The conversion, isolated yield, and *e.e.* of the products were determined in the same manner as described above.

Preparative-scale synthesis of (+)-**1a** and (–)-**1c**. A large-scale experiment was carried out as follows. A mixture of (±)-**1a** (5.0 g 31.6 mmol), Amano PS lipase (2.5 g) in vinyl acetate (20 mL) and hexane (80 mL) was stirred at 23 °C for 39 h. During the reaction, acetaldehyde was purged by a continuous flow of nitrogen (20 mL/min) in the flask. The mixture was worked-up (at 55% conversion, determined as above) in the same manner as described before. The crude residual mixture was purified by silica gel column chromatography and subsequent distillation to give **1a** (2.26 g, 45%) and **1c** (3.3 g, 52%). (+)-**1a**: b.p. 150 °C / 20 Torr (bulb-

to-bulb distillation); $[\alpha]_D^{21}$ +88.2 (*c*=1.08, chloroform)]. (–)-**1c**: b.p. 150 °C / 20 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ –78.7 (*c*=1.02, chloroform)]. Those spectral data were identical with those obtained above. The *e.e.* of (+)-**1a** was determined to be 97% by HPLC analysis of corresponding MTPA ester **1b**, while the *e.e.* of (–)-**1c** was estimated after converting to **1b** through **1a** (see the next section).

The acetate (–)-**1c** was treated overnight with a sodium methoxide-methanol solution at room temp. The mixture was neutralized by adding a small amount of Amberlyst 15 (H^+ form) and filtered through a filter paper. The combined filtrate and washings were concentrated *in vacuo* and the residue was distilled to give (–)-**1a**, b.p. 140 °C / 15 Torr (bulb-to-bulb distillation); $[\alpha]_D^{21}$ –71.1 (*c*=1.06, chloroform)]. The *e.e.* of this product was 77% by ^1H NMR and HPLC analysis of corresponding MTPA ester **1b**.

A mixture of (–)-**1a** (1.82 g 11.5 mmol), Amano PS lipase (900 mg) in vinyl acetate (8 mL) and hexane (32 mL) was stirred at 23 °C for 19 h. During the reaction, acetaldehyde was purged by a continuous flow of nitrogen (20 mL/min) in the flask. The mixture was worked-up (at 83% conversion) in the same manner as described before. The crude residual mixture was purified by silica gel column chromatography and subsequent distillation to give **1a** (312 mg, 17%) and **1c** (1.80 g, 79%). (+)-**1a**: b.p. 150 °C / 15 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +14.0 (*c*=1.00, chloroform)]. (–)-**1c**: b.p. 140 °C / 15 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ –100.2 (*c*=1.00, chloroform)]. Those spectral data were identical with those obtained above. The *e.e.* of (+)-**1a** was determined to be 15% by the comparison of its optical rotation, while the *e.e.* of (–)-**1c** was estimated to be 97.5%, after converting to **1b** through **1a** as above.

(1*S*,2*R*)-(+)-2-Allyoxy-1,4,5,6-tetrarahydro-2H-pyranyl 3',5'-dinitrobenzoate **1d**. This was prepared in a conventional manner from (+)-**1a** of 97% *e.e.* in a quantitative yield. Recrystallization from diiopropyl ether afforded pure **1d** as plates (81% recovery), m.p. 99.8-100.6°C, $[\alpha]_D^{22}$ +61.6 (*c*=0.97, chloroform)]; IR νmax 3120, 2970, 2900, 1730, 1635, 1550, 1460, 1350, 1280, 1180, 1150, 1110, 1080, 1040, 1000, 965, 920, 880, 810, 780, 740, 730 cm^{-1}; ^1H NMR δ 1.53-1.67 (1H, m), 1.84-2.09 (2H, m), 2.19-2.33 (1H, m), 3.65 (1H, dddd, *J* = 1.0, 3.5, 3.5, 11.2), 3.96 (1H, ddd, *J* = 3.2, 10.0, 11.2 Hz), 4.07 (1H, dddd, *J* = 1.5, 1.5, 6.1, 13.0 Hz), 4.29 (1H, dddd, *J* = 1.5, 1.5, 5.6, 13.0 Hz), 4.78 (1H, d, *J* = 3.2 Hz), 5.06 (1H, ddd, *J* = 3.2, 3.2, 4.8 Hz), 5.23 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.4 Hz), 5.33 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.2 Hz), 5.92 (1H, dddd, *J* = 5.6, 6.1, 10.4, 17.2 Hz), 9.17 (2H, d, *J* = 2.0 Hz), 9.24 (1H, dd, *J* = 2.0, 2.0 Hz). (Found: C, 51.12; H, 4.57, N, 7.78. Calc. for $C_{15}H_{16}O_8N_2$: C, 51.14; H, 4.58, N, 7.95%.) Its *e.e.* was determined to be 99% by HPLC analysis of corresponding MTPA ester **1b**.

Pseudomonas cepacia (Amano PS) lipase-catalyzed transterification of (±)-**3a**. In the same manner as described for the resolution of (±)-**1a**, (±)-**3a** was treated by *Pseudomonas* Amano PS lipase and vinyl acetate. The conversion was estimated by the integration of signals of **3a** (δ 4.23) and **3c** (δ 4.55). There were obtained (+)-**3c** (55% yield) and (–)-**3a** (31% yield). Analytical sample of (+)-**3c**: b.p. 140 °C / 20 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ –50.6 (*c*=2.11, chloroform)]; IR νmax 2960, 2880, 1740, 1440, 1370, 1240, 1200, 1140, 1100, 1080, 1050, 1010, 970, 930, 880 820 cm^{-1}; ^1H NMR δ 1.21 (3H, dd, *J* = 7.1, 7.1 Hz), 1.43 (1H, ddddd, *J* = 3.2, 3.6, 3.6, 3.6, 13.2 Hz), 1.62-1.72 (1H, m), 1.80-1.94 (1H, m), 1.98-2.06 (1H, m), 2.09 (3H, s), 3.49 (1H, dq, *J* = 7.1, 9.7 Hz), 3.50-3.58 (1H, m), 3.78 (1H, dq, *J* = 7.1, 9.7 Hz), 3.84 (1H, ddd, *J* = 3.2, 11.0, 11.0 Hz), 4.55 (1H, d, *J* = 3.0 Hz), 4.69 (1H, ddd, *J* = 3.0, 3.3, 4.5 Hz). HRMS Found: 147.1043. Calc. for $C_7H_{15}O_3$ (M^++1-CH_3CO): 147.1020. Due to its high volatility, a correct elemental analysis could not be obtained.

Analytical sample of (+)-**3a**: b.p. 140 °C / 22 Torr (bulb-to-bulb distillation); $[\alpha]_D^{20}$ +88.3 (*c*=1.07, chloroform)]. Its IR and NMR spectra were identical with those already described. The *e.e.* was determined to be 97% by ^1H NMR analysis of corresponding MTPA ester **3b** as described above. HPLC analysis: t_R 12.6 min (1.4%) 14.9 min (98.4%). The present sample of (+)-**3a** (97% *e.e.*) was converted to the corresponding acetate (+)-**3c**. Analytical sample: b.p. 140 °C / 22 Torr (bulb-to-bulb distillation); $[\alpha]_D^{19}$ +94.8 (*c*=1.24, chloroform)]. Its IR and NMR spectra were identical with those of (–)-**3c**. By comparing its optical rotation with that of (–)-**3c** obtained by the lipase-catalyzed reaction, the *e.e.* of (–)-**3c** concluded to be 52%.

(*S*)-(+)-3-(3',3'-Dimethyl-2',4'-dioxolanyl)-1-propanol **4**. A mixture of (2*R*,3*S*)-(+)-**1a** (90% *e.e.*, 95 mg, 0.63 mmol) and 2 N perchloric acid (3 mL) was stirred at room temp for 6 h. The mixture was neutralized by adding potassium hydroxide aq soln, and sodium borohydride (54 mg, 1.44 mmol) was added in one portion to

the mixture. After stirring at room temp for 6 h, the mixture was neutralized with acetic acid and lyophilized to give a crude mixture of pentane-1,4,5-triol. To this was added acetone (2 mL), 2,2-dimethoxypropane (0.5 mL) and a catalytic amount of *p*-toluenesulfonic acid, and the mixture was stirred at room temp overnight. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (10 g). Elution with hexane-ethyl acetate (5 : 1) and subsequent distillation gave (*S*)-(+)-**4** (45.7 mg, 48%); b.p. 130 °C / 9 Torr (bulb-to-bulb distillation); $[\alpha]_D^{22}$ +12.0 (*c*=1.05, dichloromethane)]; IR νmax 3430, 2940, 1640, 1450, 1370, 1220, 1155, 1050, 850 cm^{-1}; ^1H NMR δ 1.35 (3H, s), 1.40 (3H, s), 1.60-1.68 (4H, m), 2.14 (1H, br), 3.52 (1H, dd, *J* = 7.4, 7.4 Hz), 3.64-3.68 (2H, m), 4.04 (1H, dd, *J* = 6.0, 7.4 Hz), 4.08-4.15 (1H, m). HRMS Found: 161.1189. Calc. for $C_8H_{17}O_3$ (M^++1): 161.1176. Due to its high volatility, a correct elemental analysis could not be obtained.

(1*R**,2*S**)-2-Allyloxy-1,4,5,6-tetrahydro-2*H*-pyranyl formate (±)-**1e**. A mixture of sodium formate (1.63 g, 24 mmol), acetyl chloride (1.41 g, 18 mmol) in ether (8 mL) was stirred at room temp for 6 h. Then, a soln of (±)-**1a** (950 mg, 6 mmol) in ether (5 mL) was added and the resulting mixture was further stirred overnight. The reaction was quenched by adding sat $NaHCO_3$ aq soln and the mixture was extracted three times with ether (60 mL). The organic solution was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20 g). Elution with hexane-ethyl acetate (1 : 1) afforded (±)-**1d** as an oil, ^1H NMR δ 1.47 (1H, ddddd, *J* = 3.1, 4.2, 4.2, 4.2, 13.2 Hz), 1.74 (1H, dddd, *J* = 3.6, 4.2, 4.2, 13.8 Hz), 1.82-1.98 (1H, m), 2.10 (1H, dddd, *J* = 4.2, 4.2, 10.4, 13.8 Hz), 3.57 (1H, ddd, *J* = 4.2, 4.2, 10.9 Hz), 3.87 (1H, ddd, *J* = 3.1, 10.9, 10.9 Hz), 4.02 (1H, dddd, *J* = 1.5, 1.5, 6.0, 13.0 Hz), 4.24 (1H, dddd, *J* = 1.5, 1.5, 5.2, 13.0 Hz), 4.61 (1H, d, *J* = 3.0 Hz), 4.84 (1H, ddd, *J* = 3.0, 3.6, 4.2 Hz), 5.19 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.6 Hz), 5.30 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.2 Hz), 5.91 (1H, dddd, *J* = 5.2, 6.0, 10.6, 17.2 Hz), 8.09 (1H, s). Due to its unstability, this was employed in the next step without further purification.

(1*R*,2*S*)-(−)-2-Allyloxy-1,4,5,6-tetrahydro-2*H*-pyranyl octanoate **1f**. A mixture of (±)-**1e** (93 mg, 0.5 mmol), cyclohexane (2 mL), methanol (100 μL, 2.46 mmol), methyl octanoate (66 μL, 0.37 mmol), *Pseumomonas* Amano PS lipase (100 mg) was stirred at room temp. for 2 days. Methyl octanoate (264 μL, 1.46 mmol) was added and the resulting mixture was stirred for further 2 days. After workup as described above, the residue was purified by silica gel column chromatography (12 g). Elution with hexane-ethyl acetate (40 : 1 to 15 : 1) afforded (−)-**1f** (17.2 mg, 12%); $[\alpha]_D^{20}$ −68.3 (*c*=0.97, chlorofolm); IR νmax 2950, 2870, 1740, 1470, 1385, 1365, 1255, 1210, 1175, 1150, 1115, 1045, 1000, 930, 885, 835, 730 cm^{-1}; ^1H NMR δ 0.88 (3H, t, *J* = 6.6 Hz), 1.27-1.30 (10H, m), 1.40-1.48 (1H, m), 1.56-1.74 (2H, m), 1.80-1.98 (1H, m), 2.06 (1H, dddd, *J* = 3.0, 3.6, 11.2, 13.5 Hz), 2.34 (2H, t, *J* = 7.6 Hz), 3.56 (1H, dddd, *J* = 1.0, 3.3, 3.3, 10.9 Hz), 3.86 (1H, ddd, *J* = 3.3, 10.9, 10.9 Hz), 4.01 (1H, dddd, *J* = 1.5, 1.5, 5.9, 13.2 Hz), 4.23 (1H, dddd, *J* = 1.5, 1.5, 5.2, 13.2 Hz), 4.60 (1H, d, *J* = 3.0 Hz), 4.75 (1H, ddd, *J* = 3.0, 3.0, 4.3 Hz), 5.18 (1H, dddd, *J* = 1.5, 1.5, 1.5, 10.4 Hz), 5.30 (1H, dddd, *J* = 1.5, 1.5, 1.5, 17.1 Hz), 5.92 (1H, dddd, *J* = 5.2, 5.9, 10.4, 17.1 Hz). (Found: C, 67.35; H, 10.17. Calc. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92%.) This was converted to **1a** by methanolysis, $[\alpha]_D^{20}$ −87.3 (*c*=1.02, chlorofolm). Its *e.e.* was confirmed to be 97% by converting to MTPA ester **1b** *via* sequential methanolysis and MTPA esterification in a conventional manner.

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