Highly Enantioselective Reduction of 3-Chloro-2-oxoalkanoates with Fermenting Bakers' Yeast. A New Synthesis of Optically Active 3-Chloro-2-hydroxyalkanoates and Glycidic Esters

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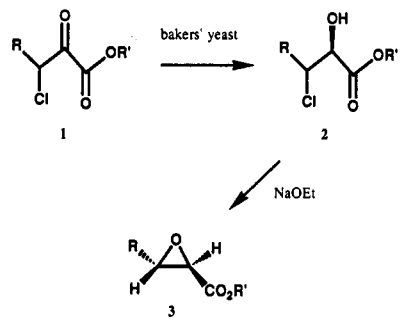
Reduction of 3-chloro-2-oxoalkanoic esters with fermenting bakers' yeast gave optically active 3-chloro-2-hydroxyalkanoic esters **2** (anti(2*S*,3*R*)/syn (2*S*,3*S*) = 52:48–90:10) in 50–85% yields with >95% ee except for 43% ee of ethyl *syn*-(2*S*,3*S*)-3-chloro-2-hydroxy-4-phenylbutanoate (**2j**). Compounds **2** were treated with NaOEt to give (*E*)-(2*R*,3*S*)-2,3-epoxyalkanoates **3** in 30–66% yields with 44–64% ee. Optically active 2,3-epoxy alcohols (*cis*-**23**, *trans*-**23**, and *trans*-**25**), key intermediates for the syntheses of (−)-disparlure (**4**), mosquito pheromone (**5**), and a component of passion fruit flavor (**6**), were prepared with more than 86% ee in high yields.

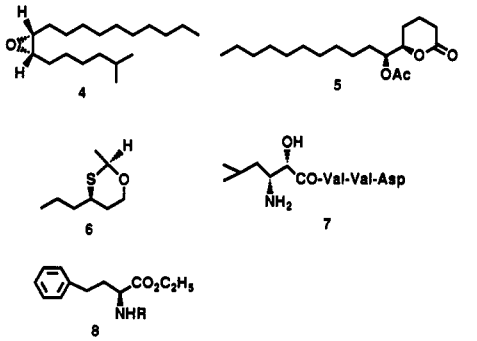
Recently, the use of actively fermenting bakers' yeast for the preparation of optically active building block in the synthesis of natural products has increased.[1] As our continuing studies on α-halo carbonyl compounds[2] and also on the asymmetric synthesis with fermenting bakers' yeast,[3] we carried out the asymmetric reduction of 3-chloro-2-oxoalkanoates **1** with bakers' yeast to give the reduced products **2**, which were converted to chiral glycidates **3**, as shown in Scheme I. In this paper we describe the results and the application of the reduced products for the synthesis of some key intermediates of natural products such as (−)-disparlure (**4**),[4] mosquito pheromone (**5**),[5] a component of passion fruit flavor (**6**),[6] virginiamycin M,[7] and Roflamycoin[8] and a precursor both for the synthesis of a stereoisomer of the unusual N-terminal amino acid

Scheme I



1 2 3

of amastatin (**7**)[9,10] and N-substituted L-homophenylalanine ethyl ester (**8**)[11] as a common structural unit of angiotensin converting enzyme (ACE) inhibitors.



4 5 6 7 8

Some asymmetric reductions of α-keto esters with fermenting bakers' yeast have been reported. Treatments of β-functionalized α-keto esters such as compounds **9**,[12] **10**,[13] **11**,[14] **12**,[15] and **13**[3b,c] with bakers' yeast have afforded chiral α-hydroxy esters in moderate yields. However, the

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(1) For example, see: (a) Mori, K.; Sugai, T. *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 1044. (b) Oishi, T.; Akita, H. *Ibid.* **1983**, *41*, 1031. (c) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163. (d) Drian, C. Le.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473. (e) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251. (f) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541. (g) Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771. (h) Ramaswamy, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 255. (i) Gopalan, A. S.; H. Jacobs, K. *Tetrahedron Lett.* **1990**, *32*, 5575. (j) Mazur, P.; Nakanishi, K. *J. Org. Chem.* **1992**, *57*, 1047. (k) Csuk, R.; Glänzer, B. J. *Chem. Rev.* **1991**, *91*, 49. (l) Servi, S. *Synthesis* **1990**, 1.

(2) (a) Takeda, A.; Wada, S.; Uno, T. *Mem. School Eng., Okayama Univ.* **1967**, *2*, 80. (b) Takeda, A.; Wada, S.; Fujii, M.; Tanaka, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2997. (c) Tsuboi, S.; Furutani, H.; Takeda, A.; Kawazoe, K.; Sato, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2475. (d) Tsuboi, S.; Furutani, H.; Takeda, A. *Synthesis* **1987**, 292. (e) Takeda, A.; Tsuboi, S.; Hongo, T. *Bull. Chem., Soc. Jpn.* **1973**, *46*, 1844. (f) Takeda, A.; Tsuboi, S.; Oota, Y. *J. Org. Chem.* **1974**, *38*, 4148. (g) Takeda, A.; Tsuboi, S.; Sakai, S. *Ibid.* **1974**, *39*, 2601.

(3) (a) Utaka, M.; Watabu, H.; Takeda, A. *Chem. Lett.* **1985**, 1475. (b) Tsuboi, S.; Nishiyama, E.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1986**, *27*, 1915. (c) Tsuboi, S.; Nishiyama, E.; Furutani, H.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1987**, *52*, 1359. (d) Tsuboi, S.; Sakamoto, J.; Sakai, T.; Utaka, M. *Synlett.* **1991**, 867. (e) Tsuboi, S.; Sakamoto, J.; Kawano, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1991**, *56*, 7177.

(4) (a) Bierl, B. A.; Beroza, M.; Collier, C. W. *Science* **1970**, *170*, 88. (b) Iwaki, S.; Marumo, S.; Saito, T.; Yamada, M.; Katagiri, K. *J. Am. Chem. Soc.* **1974**, *96*, 7842. (c) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 3471.

(5) (a) Laurence, B. R.; Pickett, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 59. (b) Mori, K.; Otsuka, T. *Tetrahedron* **1983**, *39*, 3267. (c) Yamaguchi, M.; Hirao, I. *J. Chem. Soc. Commun.* **1984**, 202. (d) Guo-qiang, L.; Hai-jian, X.; Bi-chi, W.; Guong-zhoug, G.; Wei-shan, Z. *Tetrahedron Lett.* **1985**, *26*, 1233.

(6) Pickerhagen, W.; Schindler, H. B. *Helv. Chim. Acta* **1984**, *67*, 947.

(7) Wood, R. D.; Ganem, B. *Tetrahedron Lett.* **1982**, *23*, 707.

(8) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825.

(9) Chong, J. M.; Sharpless, K. B. *Aldrichimica Acta* **1985**, *18*, 53.

(10) (a) Tobe, H.; Morishima, H.; Naganawa, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 591. (b) Tobe, H.; Morishita, H.; Aoyagi, T.; Umezawa, H.; Ishiki, K.; Nakamura, K.; Yoshioka, T.; Shimauchi, Y.; Inui, T. *Ibid.* **1982**, *46*, 1865.

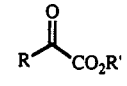
(11) (a) Brunner, H. R.; Hussberger, J.; Waeber, B. *J. Cardiovasc. Pharmacol.* **1985**, *7*, S2-S11. (b) Wyvratt, M. J.; Patchett, A. A. *Med. Res. Rev.* **1985**, *5*, 483. (c) Urbach, H.; Henning, R. *Tetrahedron Lett.* **1984**, *25*, 1143.

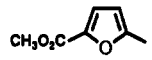
(12) Barton, D. H. R.; Brown, B. D.; Ridley, D. D.; Widdowson, D. A.; Keys, A. J.; Leaver, C. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2069.

(13) Ridley, D. D.; Stralow, M. *J. Chem. Soc., Chem. Commun.* **1975**, 400.

(14) Iriuchijima, S.; Ogawa, M. *Synthesis* **1982**, 41.

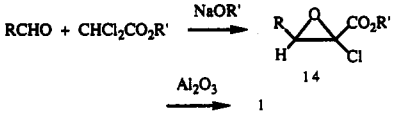
0022-3263/93/1958-0486$04.00/0



No.	R	R'
8		CH_3
9	C_6H_5	CH_3
10	BzO_2CNHCH_2	CH_3
11	$C_6H_5CH(CH_3)$-	CH_3
12		C_2H_5

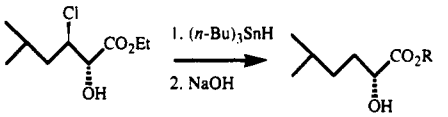
reduction of α-keto esters with no substituent gave α-hydroxy esters in a poor yield. For example, reduction of ethyl 2-oxohexanoate with fermenting bakers' yeast gave ethyl (*R*)-(−)-2-hydroxyhexanoate in 5% yield because it is labile.[16]

Recently, we found that 3-chloro-2-oxoalkanoates **1** were reduced with fermenting bakers' yeast to give optically active 3-chloro-2-hydroxyalkanoates **2** in good yields. The absolute configuration of the α-carbon was proven to be *S*, as shown below. The starting material **1** can be easily obtained by Darzen's type condensation of aldehydes and dichloroacetate[2a-c] or by the following thermal rearrangement of 2-chloro-2,3-epoxyalkanoates **14** to **1** promoted with alumina which was recently developed by us.[2d]



The reduction of **1** with fermenting bakers' yeast was carried out at 31–35 °C until the starting materials were completely consumed as shown by TLC. The products **2** were purified by column chromatography and analyzed by HPLC and NMR spectra. Several 3-chloro-2-oxoalkanoates were reduced, and the results are tabulated in Table I. The reaction afforded *anti*-**2** predominantly. Ethyl esters of **1** were reduced to give **2** in 55–67% yields, but in the case of methyl ester **1d** the yield decreased. Aromatic ketone **1j** was also reduced with bakers' yeast, giving the alcohols **2j** (anti/syn = 66/34) in 50% yield. The optical purity was determined by ^1H NMR analysis in the presence of chiral shift reagent, Eu(hfc)$_3$, and/or by HPLC analysis after converting **2** to 3,5-dinitrophenylcarbamates (DNPC) or chiral α-methoxy-α-(trifluoromethyl)phenylacetates and compared with racemic **2** prepared by the reduction of **1** with $NaBH_4$. Both of *syn*- and *anti*-**2** were shown to be enantiomerically pure except for 43% ee of aromatic *syn*-**2j**. The configurational determination of the reduced products was accomplished by conversion of **2** to the known epoxides, as shown below.

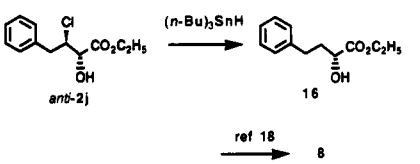
Reduction of ethyl 3-chloro-2-hydroxy-5-methylhexanoate (**2e**) with (*n*-$C_4H_9)_3SnH$ yielded ethyl (2*R*)-2-hydroxy-5-methylhexanoate (**15a**), which was subsequently hydrolyzed to give sodium (2*R*)-2-hydroxy-5-methylhexanoate (**15b**). The absolute configuration of **15b** was determined by comparison of its optical rotation with that of an authentic sample.[17]



anti-**2e**

15a, R=Et
15b, R=Na

Phenyl-substituted diastereomers **2j** were easily separated by column chromatography on silica gel. *anti*-**2j** with the optical purity of 95% ee was also reduced with (*n*-$C_4H_9)_3SnH$ to afford ethyl (*R*)-2-hydroxy-4-phenylbutanoate (**16**) with 94% ee in 77% yield. Reaction of the triflate of **16** with amines is known to give L-homophenylalanine ethyl ester moiety **8**[11] with the stereospecific inversion in high yields.[11c,18]



Glycidic esters and their synthetic equivalent 2,3-epoxy alcohols are versatile and important intermediates in organic synthesis. However, procedures for the synthesis of the chiral compounds are scarcely known. The best known among them is probably the asymmetric epoxidation of allylic alcohols by Sharpless et al.[19] Here we provide a new method for the synthesis of chiral 2,3-epoxyalkanoate **3**. Compounds **2** were efficiently converted to **3**, and the results are shown in Table II. Treatment of crude **2** with NaOEt in EtOH gave optically active *trans*-(2*R*,3*S*)-2,3-epoxyalkanoates (**3**), which will be produced from *anti*-**2**, in 30–66% yield. Even though the chlorohydrin **2** contains the syn isomer, the reaction gave only *trans*-glycidate **3** with 44–64% ee. Any cis isomer could not be detected, although ethyl 2-ethoxy-2,3-epoxyalkanoates (**17**) derived from the starting material **1** were isolated.

Hydrolysis of chiral glycidic ester **3e** will give (2*R*,3*S*)-5-methyl-2,3-epoxyhexanoic acid (**18**), which is a precursor for the synthesis of stereoisomers of the unusual N-terminal amino acid of amastatin, a tripeptide competitive inhibitor of aminopeptidase.[10] Sharpless et al.[9] also reported the synthesis of **18** with Ti(O-i-Pr)$_4$-(+)- or

(15) Akita, H.; Furuichi, A.; Koshiji, H.; Horikoshi, K.; Oishi, T. *Chem. Pharm. Bull.* **1983**, *31*, 4384.

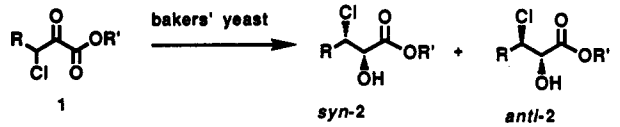
(16) In the course of the present study, bakers' yeast reduction of 2-oxo esters in organic solvent in acceptable yields has been reported: Nakamura, K.; Kondo, S.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.* **1991**, *32*, 7075.

(17) Katsura, H.; Kaneko, T. *J. Inst. Polytech. Osaka City Univ. Ser. C* **1956**, *5*, 152.

(18) (a) Henning, R.; Urbach, H. Ger. Offen. **1984**, 3315464; *Chem. Abstr.* **1985**, *102*, 149796w. (b) Campbell, S. F.; Kobylecki, R. J. Eur. Patent **1986**, 186431; *Chem. Abstr.* **1986**, *105*, 153548w. (c) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Koike, H.; Tsujita, Y. Eur. Patent **1985**, 161801; *Chem. Abstr.* **1986**, *104*, 207317v. (d) Attwood, M. R.; Hassall, C. H.; Krohn, A.; Lawton, G.; Redshaw, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1011. (e) Boyer, S. K.; Pfund, R. A.; Portman, R. E.; Sedelmeir, G. H.; Wetter, H. F. *Helv. Chim. Acta* **1988**, *71*, 337.

(19) (a) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. (b) Behrens, C. H.; Ko., S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.

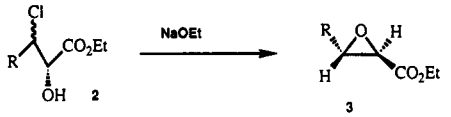
Table I. Asymmetric Reduction of 3-Chloro-2-oxoalkanoates 1 with Bakers' Yeast



no.	R	R'	chem yield (%)	anti/syn[a]	$[\alpha]^{23}_D$ ($CHCl_3$) anti	$[\alpha]^{23}_D$ ($CHCl_3$) syn	ee (%)[c] anti	ee (%)[c] syn
a	n-C_3H_7	C_2H_5	74	77/23	+0.77	+0.38	86[b]	92[b]
b	i-C_3H_7	C_2H_5	62	75/25	-6.02	-15.4	>95	>95
c	n-C_4H_9	C_2H_5	67	67/33	+0.31	-15.5	>99	>99
d	i-C_4H_9	CH_3	56	90/10	-1.26	+6.94	>99	>99
e	i-C_4H_9	C_2H_5	62	83/17	+5.61	+3.37	>95	>95
f	n-C_5H_{11}	C_2H_5	67	80/20	+1.34	-23.1	>95	>95
g	n-C_6H_{13}	C_2H_5	85	62/38	+2.28	-17.3	>95	>95
h	n-C_7H_{15}	C_2H_5	73	65/35	+1.54	-20.9	>95	>95
i	n-$C_{10}H_{21}$	C_2H_5	75	52/48	+1.76	-17.9	>95	>95
j	$C_6H_5CH_2$	C_2H_5	50	66/34	-19.63	-16.72	95[d]	43[d]

[a] Determined by HPLC analysis. [b] Determined after the conversion to the epoxide. [c] Unless indicated, determined by ^1H NMR analysis (>95% ee) or by HPLC analysis (>99% ee) for the corresponding MTPA ester. [d] Determined by HPLC packed with Chiralcel OB column.

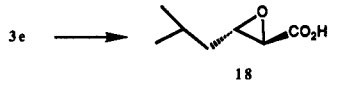
Table II. Synthesis of (2*R*,3*S*)-2,3-Epoxyalkanoates (3) by the Reaction of 2 with NaOEt



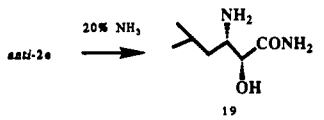
no.	R	reactn time (h)	3 chem yield (%)	3 optical purity (ee)
a	n-C_3H_7	13	47	64
b	i-C_3H_7	18	45	50
c	n-C_4H_9	10	46	56
e	i-C_4H_9	3	30	44
f	n-C_5H_{11}	7	56	53
g	n-C_6H_{13}	13	66	56
h	n-C_7H_{15}	10	52	54 (82)[a]

[a] Purity after one recrystallization.

(-)-DIPT system and the subsequent oxidation with $RuCl_3$–H_5IO_6.

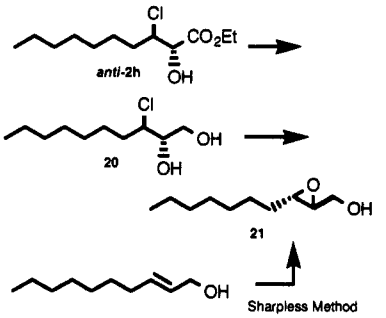


Optically pure ethyl (2*S*,3*R*)-3-chloro-2-hydroxy-5-methylhexanoate (*anti*-**2e**) purified by column chromatography was treated with an ammonia solution to give (2*R*,3*S*)-3-amino-2-hydroxy-5-methylhexanamide (**19**) in 70% yield, which is a precursor for the synthesis of a stereoisomer of **7**.[9,10]



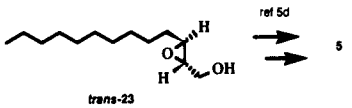
Katsuki and Sharpless[19] reported a stereospecific synthesis of (2*S*,3*S*)-2,3-epoxydecanol (**21**) by the epoxidation of *trans*-2-decenol. Here we describe a convenient synthesis of **21** from the reduced product **2h**. The reaction sequence is shown in Scheme II. Reduction of *anti*-**2h** with $NaBH_4$ gave diol **20** in 90% yield. Treatment of **20** with 2 equiv of NaOEt yielded **21** in 60% yield.[20] Enantiomeric excess was estimated as >91% ee by ^1H NMR analysis in the presence of $Eu(hfc)_3$ and also by comparison of the optical rotation with that of the literature data.[19b]

Scheme II



The synthesis of (+)-disparlure, the sex attractant of the gypsy moth, is quite attractive for an organic chemist. The present paper describes the formal synthesis of (-)-disparlure (**4**) vis (2*S*,3*R*)-2,3-epoxytridecanol (*cis*-**23**). Reduction of *syn*-**2i** with $NaBH_4$ gave diol **22** in 78% yield, which was subsequently treated with NaOEt to give optically pure *cis*-**23** quantitatively (Scheme III). Epoxy alcohol *cis*-**23** can be converted to **4** by the known method.[19a]

Similarly, trans isomer **23** was also prepared via *anti*-**22** with high optical purity. Mosquito pheromone **5** can be obtained from *trans*-**23** via several steps.[5d] Furthermore,



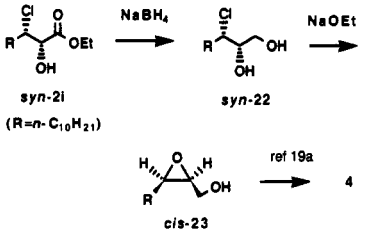
chiral chlorohydrin **2** was used for the synthesis of a component of passion fruit flavor **6** as shown in Scheme IV. The synthesis of **6** via (2*S*,3*S*)-2,3-epoxyhexanol (*trans*-**25**)[6] was carried out as shown below. Reduction of *anti*-**2a** with $NaBH_4$ and the subsequent treatment of *anti*-**24** with NaOEt gave epoxy alcohol *trans*-**25** with 86% ee in high yields. The *cis*-**25** was also prepared from *syn*-**2a**.

The absolute configuration of α-carbons of **2a**, **2d**, **2e**, and **2i** was determined to be *S* from that of known compounds which were prepared as described above. Therefore, the absolute configuration of all of **2** can be deduced to be 2*S*,3*S* or 2*S*,3*R*.

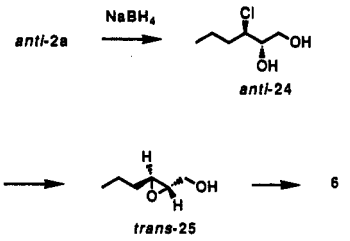
Our system provides a convenient route to chiral 2-hydroxy-3-chloroalkanoic esters, glycidic esters, and 2,3-

(20) In a similar manner, (2*S*,3*S*)-2,3-epoxyoctanol was prepared, which was converted to (2*R*,3*S*)-2,3-epoxyoctanal, a key intermediate of (5*Z*,8*Z*,-10*E*,12*E*)-14,15-epoxy-5,8,10,12-eicosatetraenoic acid (14,15-LTA$_4$): Tsuboi, S.; Furutani, H.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 833.

Scheme III



Scheme IV



epoxy alcohols, which are very useful for organic synthesis, because of easy access of the starting material, simplicity of the experiment, no use of heavy metals, and economical efficiency.

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Infrared (IR) spectra were obtained with a JASCO Model A-102 infrared spectrophotometer. ^{1}H NMR spectra (60 MHz) were recorded with a JEOL JNM-PMX60SI apparatus. ^{1}H NMR (100 MHz) and ^{13}C NMR spectra (25 MHz) were obtained with a JEOL JNM-FX100 apparatus, using $CDCl_3$ as a solvent. All chemical shifts are reported in δ units downfield from internal Me_4Si, and J values are given in hertz. Optical rotations were measured on a JASCO DIP-4 spectrometer. Column chromatography was accomplished with 100–200-mesh Wakogel C-200. Analytical determinations by GLC were performed on a Hitachi Model 163 gas chromatograph fitted with 10% Silicone SE-30 on Chromosorb W column (3-mm o.d. × 1 m). High-performance liquid chromatograph L-2000 fitted with Yanapak SA-I (6-mm o.d. × 250 mm) and with Sumipax OA-3000 (4-mm o.d. × 250 mm) for the determination of enantioselectivity. Optical purities of **2j** were determined by HPLC analysis on a LC-9A Shimazu Liquid Chromatograph using a Diacel CHIRALCEL OB column (size 0.46 × 25 cm) at 220 μm (UV detection).

Fermentation was carried out in a thermostat at 31–35 °C using pressed bakers' yeast purchased from Oriental Yeast Co. LTD. All glasswares were sterilized by boiling water before use.

3-Chloro-2-oxoalkanoates (1) were obtained by the method described in the previous paper.[2d]

Ethyl 3-Chloro-2-oxo-4-phenylbutanoate (1j). Copper(II) chloride (0.315 g, 2.39 mmol), LiCl (0.050 g, 1.17 mmol), and DMF (5 mL) were placed in a two-necked flask under nitrogen atmosphere. After heating at 100 °C (oil bath temperature), ethyl 2-oxo-4-phenylbutanoate[21] (0.2 g, 0.974 mmol) in 2 mL of DMF was added, and the whole content was stirred at 100–110 °C (oil bath temperature) for 1 h. The dark reaction mixture was diluted with ice, followed by sufficient amount of DMF to redissolve the precipitated CuCl. The solution was worked up with EtOAc (3 × 25 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated in vacuo to give a viscous oil (0.182 g) which was chromatographed over a silica gel (9.0 g) column using hexane/EtOAc (5/1; v/v) as eluent to give 0.125 g (53%) of **1j** as a clean liquid: TLC (hexane/EtOAc = 4/1) R_f 0.19; IR (neat) 3500, 1760, 1745, 1600, 1500, 1450, 1390, 1370, 1250, 1090, 1010, 870, 845, 750, and 700 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.32 (t, J = 7 Hz, 3 H), 3.44 (dd, J = 14 and 6 Hz, 1 H), 3.97 (dd, J = 14 and 7 Hz, 1 H), 4.27 (q, J = 7 Hz, 2 H), 5.10 (dd, J = 7 and 6 Hz, 1 H), and 7.17 (s, 5 H).

Some reductions of chloro keto esters 1 with bakers' yeast were shown below representatively.

Ethyl (2*S*,3*S*)- and (2*S*,3*R*)-3-Chloro-2-hydroxyhexanoate (2a). To a mixture of $NH_4H_2PO_4$ (0.6 g), $MgSO_4$ (1.5 g), $CaCO_3$ (1.0 g), KH_2PO_4 (0.6 g), glucose (25 g), and boiled water (750 mL) was added 15 g of dry bakers' yeast at 35 °C. After the fermentation started (ca. 20 min), 3 g (15.6 mmol) of ethyl 3-chloro-2-oxohexanoate (1a) was added, and the mixture was stirred for 65.5 h at 35 °C. During the reaction, 10 g of bakers' yeast was added after 16 h. Ten and 5 g of bakers' yeast was added after 16 and 23 h, respectively. The organic layer was extracted with EtOAc. The combined extracts were washed with water and dried over $MgSO_4$. Removal of the solvent gave 3.92 g of a clean oil, which was purified by column chromatography (hexane/acetone = 20/1) to give 2.25 g (74.4%) of **2a**. HPLC analysis (Unisil 10ϕ × 250 mm, hexane/EtOAc (10/1), 25 mL/min) showed two peaks at retention times 22.9 and 24.3 min. Each component was collected by preparative HPLC and identified. First fraction, (2*S*,3*S*)-**2a**: $[\alpha]^{22}_D$ +0.38 ($CHCl_3$, *c* 1.05); IR (neat) 3480, 3000, 1750, 1250, 1025, 860 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.00 (br t, J = 5 Hz, 3 H), 1.35 (t, J = 7 Hz, 3 H), 1.30–1.95 (m, 4 H), 3.10 (s, 1 H), 3.90–4.30 (m, 2 H), 4.32 (q, J = 7 Hz, 2 H). Anal. Calcd for $C_8H_{15}O_3$: C, 49.36; H, 7.77. Found: C, 49.27; H, 7.77. Second fraction, (2*S*,3*R*)-**2a**: $[\alpha]^{23}_D$ +0.77 ($CHCl_3$, *c* 1.30); IR (neat) 3500, 2980, 1745, 1470, 1225, 1090 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.95 (br t, J = 6 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.30–2.10 (m, 4 H), 3.26 (br s, 1 H), 3.85–4.20 (m, 2 H), 4.25 (q, J = 7 Hz, 2 H). Anal. Calcd for $C_8H_{15}O_3$: C, 49.36; H, 7.77. Found: C, 49.53; H, 7.68.

Ethyl (2*S*,3*S*)- and (2*S*,3*R*)-3-Chloro-2-hydroxyheptanoate (2c). To a mixture of $NH_4H_2PO_4$ (1 g), KH_2PO_4 (1 g), $CaCO_3$ (0.3 g), $MgSO_4$ (0.25 g), glucose (25 g), and boiled water (250 mL) was added bakers' yeast (25 g) at 35 °C. After 20 min, ethyl 3-chloro-2-oxoheptanoate (1c) (1.2 g, 5.81 mmol) was added, and the mixture was stirred at 35 °C. Bakers' yeast (5 g) and glucose (5 g) was added after 7 h. After 66 h, the organic material was extracted with EtOAc, and the combined extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 1.59 g of a clean oil, which was purified by column chromatography (hexane/acetone = 20/1) to give 845 mg (69.7%) of **2c**: R_f = 0.3 (hexane/acetone = 3/1). Preparative HPLC gave two fractions. Each component was separated and identified. First fraction, (2*S*,3*S*)-**2c**: $[\alpha]^{25}_D$ +0.31 ($CHCl_3$, *c* 4.50); IR (neat) 3470, 2950, 1745, 1465, 1215 cm^{-1}; ^{1}H NMR (neat) δ 0.90 (t, J = 7 Hz, 3 H), 1.40–2.30 (m, 6 H), 1.30 (t, 3 H), 4.20 (m, 2 H), 4.15 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.1 (t), 28.8 (t), 32.1 (t), 63.0 (t), 63.7 (d), 73.0 (d), 171.8 (s). Anal. Calcd for $C_9H_{17}O_3Cl$: C, 51.80; H, 8.15. Found: C, 51.58; H, 7.94. Second fraction, (2*S*,3*R*)-**2c**: $[\alpha]^{31}_D$ −15.5 ($CHCl_3$, *c* 4.21); IR (neat) 3475, 2950, 1730, 1135 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.90 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.50–2.00 (m, 6 H), 4.20 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 22.2 (t), 28.9 (t), 33.0 (t), 62.3 (t), 64.1 (d), 74.4 (d), 171.4 (s). Anal. Calcd for $C_9H_{17}O_3Cl$: C, 51.80; H, 8.15. Found: C, 52.05; H, 8.33.

Ethyl (2*S*,3*S*)- and (2*S*,3*R*)-3-Chloro-2-hydroxynonanoate (2g). To a mixture of KH_2PO_4 (1 g), $NH_4H_2PO_4$ (1 g), $MgSO_4$ (0.5 g), $CaCO_3$ (0.3 g), glucose (25 g), and water (250 mL) was added bakers' yeast (25 g) at 35 °C. After 15 min, ethyl 3-chloro-2-oxononanoate (1g) (1.2 g, 5.44 mmol) was added, and the mixture was stirred at 34 °C. The concentration of glucose was checked by a urine test paper. After 16 h, it became 0%, and glucose (10 g) was added. After 25 h, glucose (10 g) was added. After 64 h, the organic materials were extracted with EtOAc. The combined extracts were washed with water and dried over $MgSO_4$. Concentration of the solvent gave 1.40 g of an oil, which was purified by column chromatography (hexane/acetone = 20/1) to give 1.03 g (85%) of **2g**: R_f = 0.43 (hexane/acetone = 3/1). HPLC analysis shows two peaks at t_R = 12.6 and 17.9 min. Each component was collected by preparative HPLC and identified. First fraction, (2*S*,3*S*)-**2g**: $[\alpha]^{27}_D$ −17.3 ($CHCl_3$, *c* 1.80); IR (neat) 3500, 2950, 1750, 1470, 1270, 1140; ^{1}H NMR (CCl_4) δ 0.90 (br t, 3 H), 1.30 (m, 8 H), 4.15 (m, 2 H), 4.15 (q, 2 H). Anal. Calcd

(21) Prepared by the reaction of phenethylmagnesium bromide with diethyl oxalate: Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.* **1981**, *11*, 943.

for $C_{11}H_{21}O$: C, 55.81; H, 8.94. Found: C, 55.82; H, 9.28. Second fraction, (2*S*,3*R*)-**2g**: $[\alpha]^{28}_D$ +2.28 ($CHCl_3$, *c* 2.19); IR (neat) 3470, 2945, 1465, 1215, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (br t, *J* = 5 Hz, 3 H), 1.26 (m, 8 H), 1.23 (t, *J* = 6 Hz, 3 H), 3.45 (s, 1 H). Anal. Calcd for $C_{11}H_{21}ClO_3$: C, 55.81; H, 8.94. Found: C, 55.95; H, 8.93.

Other compounds **2** were prepared as described above, and these data are shown below.

Ethyl (2*S*,3*S*)-3-chloro-2-hydroxy-4-methylpentanoate (*syn*-2b): $[\alpha]^{25}_D$ −15.4 ($CHCl_3$, *c* 0.57); IR (neat) 3450, 2975, 1740, 1260, 1140, 1095, 1022, 860 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (d, *J* = 4 Hz, 3 H), 1.1 (d, *J* = 4 Hz, 3 H), 1.35 (t, *J* = 6 Hz, 3 H), 2.2 (m, 1 H), 2.95 (br s, 1 H), 4.3 (m, 1 H), 4.3 (q, *J* = 6 Hz, 2 H), 4.31 (dd, *J* = 5 and 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 19.8 (q), 20.4 (q), 32.4 (d), 62.2 (t), 70.2 (d), 71.6 (d). Anal. Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77. Found: C, 49.08; H, 7.49.

Ethyl (2*S*,3*R*)-3-chloro-2-hydroxy-4-methylpentanoate (*anti*-2b): mp 42–43 °C; $[\alpha]^{22}_D$ −6.02 ($CHCl_3$, *c* 9.60); IR (neat) 3450, 2970, 1735, 1220, 1135, 1080, 1020, 835 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (d, *J* = 4 Hz, 3 H), 1.1 (d, *J* = 4 Hz, 3 H), 1.35 (t, *J* = 6 Hz, 3 H), 2.2 (m, 1 H), 2.95 (br s, 1 H), 4.0 (dd, *J* = 2.4 Hz, 1 H), 4.3 (q, *J* = 6 Hz, 2 H), 4.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.1 (q), 20.3 (q), 30.3 (d), 61.9 (t), 69.7 (d), 72.8 (d). Anal. Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77. Found: C, 49.43; H, 7.69.

Methyl (2*S*,3*S*)-3-chloro-2-hydroxy-5-methylhexanoate (*syn*-2d): IR (neat) 3520, 2975, 1750, 1263, 1145, 1105 cm^{-1}; ^1H NMR (CCl_4) δ 1.00 (d, *J* = 6 Hz, 6 H), 1.50–2.30 (m, 1 H), 3.78 (s, 3 H), 4.15 (m, 2 H). Anal. Calcd for $C_8H_{15}ClO_3$; C, 49.36; H, 7.77. Found: C, 49.54; H, 7.53.

Methyl (2*S*,3*R*)-3-chloro-2-hydroxy-5-methylhexanoate (*anti*-2d): IR (neat) 3500, 3000, 1750, 1440, 1230, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6 Hz, 3 H), 0.96 (d, *J* = 6 Hz, 3 H), 1.30–2.20 (m, 3 H), 3.45 (br s, 1 H), 3.78 (s, 3 H), 3.90–4.30 (m, 2 H). Anal. Calcd for $C_8H_{15}ClO_3$; C, 49.36; H, 7.77. Found: C, 49.41; H, 7.62.

Ethyl (2*S*,3*S*)-3-chloro-2-hydroxy-5-methylhexanoate (*syn*-2e): $[\alpha]^{27}_D$ +3.37 ($CHCl_3$, *c* 2.43); IR (neat) 3525, 2970, 1740, 1255, 1140, 1100, 1020 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (d, *J* = 6 Hz, 3 H), 1.00 (d, *J* = 6 Hz, 3 H), 1.35 (t, *J* = 7 Hz, 3 H), 1.2–2.4 (m, 3 H), 2.8 (br s, 1 H), 3.9–4.9 (m, 2 H), 4.30 (q, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 21.5 (q), 22.8 (q), 25.2 (d), 43.3 (t), 62.0 (d), 62.2 (t), 73.3 (d), 171.8 (s). Anal. Calcd for $C_9H_{17}ClO_3$: C, 51.80; H, 8.15. Found: C, 52.05; H, 8.33.

Ethyl (2*S*,3*R*)-3-chloro-2-hydroxy-5-methylhexanoate (*anti*-2e): $[\alpha]^{27}_D$ +5.61 ($CHCl_3$, *c* 1.64); IR (neat) 3500, 2975, 1735, 1220, 1090, 1032 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (d, *J* = 6 Hz, 3 H), 0.98 (d, *J* = 6 Hz, 3 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.1–2.3 (m, 3 H), 3.15 (br s, 1 H), 3.9–4.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 21.0 (q), 23.2 (q), 25.2 (d), 43.3 (t), 62.0 (d), 62.2 (t), 73.3 (d), 171.8 (s). Anal. Calcd for $C_9H_{17}ClO_3$: C, 51.8; H, 8.15. Found: C, 51.58; H, 7.94.

Ethyl (2*S*,3*S*)-3-chloro-2-hydroxyoctanoate (*syn*-2f): $[\alpha]^{25}_D$ −23.1 ($CHCl_3$, *c* 2.51); IR (neat) 3525, 2950, 1745, 1265, 1135 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (t, *J* = 6 Hz, 3 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.1–2.1 (m, 8 H), 3.07 (br s, 1 H), 3.9–4.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.2 (q), 22.4 (t), 26.3 (t), 31.1 (t), 33.2 (t), 62.3 (t), 64.2 (d), 74.2 (d), 171.4 (s). Anal. Calcd for $C_{10}H_{19}ClO_3$: C, 53.93; H, 8.60. Found: C, 54.01; H, 8.55.

Ethyl (2*S*,3*R*)-3-chloro-2-hydroxyoctanoate (*anti*-2f): $[\alpha]^{25}_D$ +1.34 ($CHCl_3$, *c* 1.94); IR (neat) 3470, 2975, 1740, 1465, 1220 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (t, *J* = 6 Hz, 3 H), 1.30 (t, *J* = 7 Hz, 3 H), 1.1–2.1 (m, 8 H), 3.35 (br s, 2 H), 3.9–4.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 22.5 (t), 26.4 (t), 31.2 (t), 34.7 (t), 63.7 (d), 73.0 (d), 171.8 (s). Anal. Calcd for $C_{10}H_{19}ClO_3$: C, 53.93; H, 8.60. Found: C, 53.99; H, 8.35.

Ethyl (2*S*,3*S*)-3-chloro-2-hydroxydecanoate (*syn*-2h): $[\alpha]^{26}_D$ −20.9 ($CHCl_3$, *c* 1.53); IR (neat) 3500, 2950, 1740, 1470, 1220, 1100, 850 cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (br t, *J* = 5 Hz, 3 H), 1.1–2.1 (m, 12 H), 1.30 (t, *J* = 7 Hz, 3 H), 2.83 (br d, *J* = 7 Hz, 1 H), 4.15 (m, 4 H). Anal. Calcd for $C_{12}H_{23}ClO_3$: C, 57.48; H, 9.24. Found: C, 57.73; H, 9.17.

Ethyl (2*S*,3*R*)-3-chloro-2-hydroxydecanoate (*anti*-2h): $[\alpha]^{26}_D$ +1.54 ($CHCl_3$, *c* 2.73); IR (neat) 3450, 2930, 1740, 1465, 1270, 1130, 790 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (br t, *J* = 6 Hz, 3 H), 1.1–2.1 (m, 12 H), 1.33 (t, *J* = 7 Hz, 3 H), 3.05 (br d, *J* = 7 Hz, 1 H), 4.10 (m, 2 H), 4.25 (q, *J* = 7 Hz, 2 H). Anal. Calcd for $C_{12}H_{23}ClO_3$: C, 57.48; H, 9.24. Found: C, 57.38; H, 9.16.

Ethyl (2*S*,3*S*)-3-chloro-2-hydroxytridecanoate (*syn*-2i): $[\alpha]^{26}_D$ −17.9 ($CHCl_3$, *c* 1.82); IR (neat) 3430, 2940, 1745, 1465, 1270, 1135 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (br t, *J* = 5 Hz, 3 H), 1.3–2.0 (m, 18 H), 1.30 (t, *J* = 7 Hz, 3 H), 3.0 (br s, 1 H), 4.2 (q, *J* = 7 Hz, 2 H). Anal. Calcd for $C_{15}H_{29}ClO_3$: C, 61.52; H, 9.98. Found: C, 61.72; H, 9.92.

Ethyl (2*S*,3*R*)-3-chloro-2-hydroxytridecanoate (*anti*-2i): $[\alpha]^{26}_D$ +1.76 ($CHCl_3$, *c* 1.82); IR (neat) 3430, 2940, 1745, 1465, 1270, 1135 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (br t, *J* = 5 Hz, 3 H), 1.3–2.0 (m, 18 H), 1.30 (t, *J* = 7 Hz, 3 H), 4.16 (m, 2 H), 4.25 (q, *J* = 7 Hz, 2 H). Anal. Calcd for $C_{15}H_{29}ClO_3$: C, 61.52; H, 9.98. Found: C, 61.70; H, 9.85.

Ethyl (2*S*,3*S*)- and (2*S*,3*R*)-3-Chloro-2-hydroxy-4-phenylbutanoate (2j). To a solution of glucose (54.5 g) in boiled cooled water (300 mL) was added 42.5 g of bakers' yeast at 30 °C. After 30 min, 0.72 g (2.99 mmol) of ester **3** was added to the solution, and the whole mixture was stirred at 30 ± 2 °C for 24 h. The reaction mixture was filtered after treating with Celite (15 g) for 1 h under stirring, and the filtrate was extracted with three times with EtOAc (total 600 mL), washed with brine, dried ($MgSO_4$), and evaporated to give a viscous oil (0.7 g), which was chromatographed on a silica gel (35 g) column (hexane/EtOAc, 90/10) to give 125 mg (17%) of (2*S*,3*S*)-**2j** as a solid (mp 62–63 °C): TLC (hexane/EtOAc, 4/1) R_f 0.42; $[\alpha]^{21}_D$ −16.72 (*c* 2.2, $CHCl_3$), 43% ee by HPLC analysis [eluent, hexane/*i*-PrOH (18/1); flow rate, 0.5 mL/min; retention times, 32.2 and 44.5 min]; IR (KBr) 3500, 1740, 1600, 1450, 1125, 1020, 750, 710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3 H), 3.33–3.11 (m, 2 H), 4.18–4.36 (2 dd, *J* = 7.27, 7.3, 1.82 Hz, 1 H), 4.25 (q, *J* = 7.0 Hz, 2 H), 4.44 (2 dd, *J* = 1.82, 7.27, 7.3 Hz), 7.31 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.10, 40.84, 62.33, 63.49, 71.12, 127.10, 128.67, 129.42, 136.91, 171.83. After elution of (2*S*,3*S*)-4, (2*S*,3*R*)-4 was obtained as a liquid (240 mg) in 33% yield: TLC (hexane/EtOAc, 4/1) R_f 0.28; $[\alpha]^{21}_D$ −19.63 (*c* 2.2, $CHCl_3$); 94.5% ee by HPLC analysis [eluent, hexane/*i*-PrOH (18/1); flow rate, 0.5 mL/min; retention times, 31.1 and 36.5 min]; IR (neat) 3500, 1745, 1500, 1455, 1210, 760, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.0 Hz, 3 H), 3.13 (dd, *J* = 8 Hz, 14 Hz, 1 H), 3.22 (dd, *J* = 7, 16 Hz, 1 H), 3.29 (br s, 1 H), 4.24 (q, *J* = 7.0 Hz, 2 H), 4.37–4.4 (m, 2 H), 7.28 (m, 5 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.16, 39.84, 62.38, 64.07, 73.23, 127.07, 128.52, 129.39, 129.47, 136.86, 171.06. Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.23. Found: C, 59.25; H, 6.42.

Determination of Optical Purity (% ee) by ^1H NMR Analysis. The sample was purified by preparative HPLC and dissolved in a 1/3 mixture of $CDCl_3$ and CCl_4. Irradiation of a multiplet at 8–8.3 ppm due to methylene signals of ethyl esters of the spectrum of *syn*- (or *anti*-) **2** in the presence of Eu(hfc)$_3$ (60–80 mol % to **2**) showed one singlet at 3.1–3.3 ppm due to ester methyl groups of one enantiomer, indicating >95% ee. On the other hand, that of the racemates showed paired two singlets.

Determination of Optical Purity (% ee) by HPLC Analysis. Some of the alcohols were converted to 3,5-dinitrophenylcarbamates by the method described in the previous paper[3c] or to MTPA esters[22] and analyzed by HPLC equipped with Sumipax OA-3000 column. If the spectrum showed no paired peaks, its optical purity indicates >99% ee. Optical purities of **2j** were determined by HPLC analysis on a LC-9A Shimazu liquid chromatograph using a Diacel CHIRALCEL OB column (size 0.46 × 25 cm) at 220 μm (UV detection).

Ethyl (2*R*,3*S*)-2,3-Epoxyhexanoate (3a). Sodium (94 mg, 4.1 mmol) was dissolved in 10 mL of absolute EtOH. To this solution was added 658.5 mg (3.39 mmol) of **2a** at 0 °C. The mixture was stirred for 13 h at room temperature and then poured into ice water. After the mixture was acidified with dilute HCl, the organic materials were extracted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave 498 mg of an oil, which was chromatographed on silica gel (hexane/acetone, 10/1) to yield 251 mg (47%) of **3a**: $[\alpha]^{23}_D$ −14.8 ($CHCl_3$, *c* 1.52); 64% ee (determined by ^1H NMR in the presence of Eu(hfc)$_3$); IR (neat) 2975, 1758, 1450, 1280, 1190, 1030, 910; ^1H NMR

(22) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(CCl_4) δ 0.96 (br t, J = 6 Hz, 3 H), 1.26 (t, J = 7 H, 3 H), 1.30–2.50 (m, 4 H), 3.00 (br m, 2 H), 4.15 (q, J = 7 Hz, 2 H).

Ethyl (2*R*,3*S*)-2,3-Epoxy-4-methylpentanoate (3b). Sodium (30 mg, 1.3 mmol) was dissolved in 5 mL of absolute EtOH. To this solution was added dropwise 211.5 mg (1.09 mmol) of **2b** at 0 °C. The mixture was stirred for 7.3 h at room temperature and then poured into ice water. After acidification with dilute HCl, the organic materials were extracted with EtOAc. The combined extracts were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane/acetone = 10/1) to give 79 mg (97% purity by HPLC, 45% yield) of **3b**: R_f = 0.51 (hexane/acetone = 3/1). The analytical sample was obtained by preparative HPLC (eluent, hexane/EtOAc (20:1) 0.73 mL/min); t_R = 35.8 min; $[\alpha]^{22}_D$ −8.27 ($CHCl_3$, c 0.75); IR (neat) 2975, 1755, 1470, 1250, 1030 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (d, J = 6 Hz, 3 H), 1.00 (d, J = 6 Hz, 3 H), 1.25 (t, J = 7 Hz, 3 H), 1.60 (m, 1 H), 2.85 (dd, J = 1.8 and 7.0 Hz, 1 H), 3.15 (d, J = 1.8 Hz, 1 H), 4.15 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 18.1 (q), 18.7 (q), 30.0 (d), 52.1 (d), 61.5 (t), 63.4 (d), 169.4 (s); 50% ee by ^1H NMR analysis in the presence of 30% Eu(hfc)$_3$. Anal. Calcd for $C_8H_{14}O_3$: C, 60.76; H, 8.86. Found: C, 60.60; H, 8.96.

Minor component (3%) was collected by preparative HPLC and identified as **ethyl 2-ethoxy-2,3-epoxy-4-methylpentanoate (17b)**: t_R = 26.8 min; 1.1% yield; IR (neat) 2970, 1745, 1295, 1190, 950, 790 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (d, J = 7 Hz, 3 H), 1.05 (d, J = 7 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 1.80 (m, 1 H), 2.80 (d, J = 9 Hz, 2 H), 3.75 (q, J = 7 Hz, 2 H), 4.15 (q, J = 7 Hz, 2 H). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.26; H, 9.05.

Other glycidates were prepared as described above.

Ethyl (2*R*,3*S*)-2,3-epoxyheptanoate (3c): 46% yield; R_f = 0.51 (hexane/acetone = 3/1); HPLC (hexane/EtOAc = 10/1, 1.55 mL/min), t_R = 24.1 min; $[\alpha]^{26}_D$ −14.9 ($CHCl_3$, c 0.99); 56% ee by ^1H NMR in the presence of Eu(hfc)$_3$; IR (neat) 2950, 1750, 1460, 1290, 1035 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 2.90 (m, 2 H), 4.10 (q, J = 7 Hz, 2 H). Anal. Calcd for $C_9H_{16}O_3$: C, 61.71; H, 9.30. Found: C, 61.62; H, 9.28.

Ethyl (2*R*,3*S*)-2,3-epoxy-5-methylhexanoate (3e): 30% yield: R_f = 0.51 (hexane/acetone = 3/1); HPLC (hexane/EtOAc = 20/1, 1.55 mL/min), t_R = 12 min; $[\alpha]^{24.5}_D$ −11.7 ($CHCl_3$, c 1.15); 44% ee by ^1H NMR in the presence of Eu(hfc)$_3$; IR (neat) 2975, 1750, 1465, 1290, 1040 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (d, J = 6 Hz, 6 H), 1.30 (t, J = 6 Hz, 3 H), 1.5–2.4 (m, 3 H), 3.10 (m, 1 H), 3.70 (m, 1 H), 4.20 (q, J = 6 Hz, 2 H). Anal. Calcd for $C_9H_{16}O_3$: C, 62.79; H, 9.30. Found: C, 62.69; H, 9.45.

Ethyl 2,3-epoxy-2-ethoxy-5-methylhexanoate (17e): t_R = 15 min; IR (neat) 2960, 1745, 1260, 1145, 1020, 745 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (d, J = 6 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 3.10 (t, J = 6 Hz, 1 H), 3.57 (q, J = 7 Hz, 2 H), 4.20 (q, J = 7 Hz, 2 H). Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.96; H, 9.08.

Ethyl (2*R*,3*S*)-2,3-epoxyoctanoate (3f): 56% yield; R_f = 0.56 (hexane/EtOAc = 3/1); HPLC (hexane/EtOAc = 20/1, 1.55 mL/min), t_R = 13.3 min; $[\alpha]^{23}_D$ −12.8 ($CHCl_3$, c 0.81); 53% ee by ^1H NMR in the presence of Eu(hfc)$_3$; IR (neat) 2950, 1750, 1465, 1290, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (broad t, J = 7 Hz, 3 H), 1.20 (t, 3 H), 1.40 (br m, 8 H), 2.95 (br m, 2 H), 4.15 (q, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 22.5 (t), 25.4 (t), 31.4 (t), 58.4 (d), 61.5 (t), 169.3 (s). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 64.42; H, 9.78.

Ethyl 2-ethoxy-2,3-epoxyoctanoate (17f): 20% yield; HPLC (hexane/EtOAc = 20/1, 1.55 mL/min), t_R = 11.1 min; IR (neat) 2975, 1750, 1300, 1280, 955, 790, 760; ^1H NMR (CCl_4) δ 0.90 (br t, J = 6 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.27 (t, J = 7 Hz, 3 H), 1.40 (m, 8 H), 3.07 (t, J = 7 Hz, 1 H), 3.73 (q, J = 7 Hz, 2 H), 4.15 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 15.2 (q), 22.5 (t), 25.5 (t), 27.1 (t), 31.5 (t), 62.0 (t), 63.4 (t), 64.0 (d), 82.1 (s), 168.0 (s). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.36; H, 9.63.

Ethyl (2*R*,3*S*)-2,3-epoxynonanoate (3g): 66% yield; R_f = 0.50 (hexane/acetone = 3/1); HPLC (hexane/EtOAc = 10/1, 1.5 mL/min), t_R = 8.0 min; $[\alpha]^{25}_D$ −12.8 ($CHCl_3$, c 2.05); 56% ee by ^1H NMR in the presence of Eu(hfc)$_3$; IR (neat) 2950, 1750, 1440, 1190, 1030, 900 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (br t, J = 5 Hz, 3 H), 1.29 (t, J = 7 Hz, 3 H), 1.40 (m, 10 H), 3.0 (m, 2 H), 4.15 (q, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 14.1 (q), 22.5 (t), 25.4 (t), 31.4 (t), 53.1 (d), 58.4 (d), 61.5 (t), 169.3 (s).

Ethyl (2*R*,3*S*)-2,3-epoxydecanoate (3h): 52% yield; R_f = 0.56 (hexane/acetone = 3/1); mp 43–43.5 °C (pentane); 82% ee; $[\alpha]^{25}_D$ −20.0 (EtOH, c 0.70) after one recrystallization (crude product, 54% ee, $[\alpha]^{25}_D$ −13.2 (EtOH, c 1.61)) (lit.[23] $[\alpha]^{25}_D$ −24.3 (EtOH, c 1.3); IR (neat) 2950, 1755, 1460, 1285, 1195, 1035, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (br t, J = 5 Hz, 3 H), 1.20 (t, J = 7 Hz, 3 H), 1.26 (m, 10 H), 3.15 (m, 2 H), 4.20 (q, J = 7 Hz, 2 H).

Ethyl (2*R*)-2-Hydroxy-5-methylhexanoate (15a). To a solution of *anti*-**2e** (130 mg, 0.62 mmol) in dry benzene (2 mL) was added dropwise (n-$C_4H_9)_3SnH$ (230 mg, 0.21 mL, 0.79 mmol) at room temperature. Furthermore, a solution of AIBN (10 mg) in dry benzene (2 mL) was added, and the mixture was heated at reflux temperature for 2 h. After evaporation of the solvent, short column chromatography (2 g of silica gel) of the residue gave 113 mg of an oil, which was purified with column chromatography (15 g of silica gel; eluent, hexane/acetone (20/1)) to give 60 mg (60%) of **15a**: IR (neat) 3500, 2960, 1730, 1460, 1360 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (d, J = 6 Hz, 6 H), 1.25 (t, J = 7 Hz, 3 H), 1.40–1.90 (m, 5 H), 2.65 (br d, 1 H), 4.00 (t, 1 H), 4.20 (q, J = 7 Hz, 2 H); $[\alpha]^{28}_D$ +1.15 ($CHCl_3$, c 1.57). Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.87; H, 10.26.

Sodium (2*R*)-2-Hydroxy-5-methylhexanoate (15b). To a solution of **15a** (57 mg, 0.33 mmol) in 2.5 mL of dimethoxyethane and 1 mL of water was added 132 mg of sodium hydroxide. The mixture was stirred for 45 h and then concentrated to give 229 mg of **15b**: $[\alpha]^{27.5}_D$ +9.8 (H_2O, c 1.8) (lit.[10] $[\alpha]^{22}_D$ +12.1).

Ethyl (*R*)-2-Hydroxy-4-phenylbutanoate (16). A solution of *anti*-**2j** (200 mg, 0.8 mmol) in dry benzene (30 mL) was added to a mixture of (n-$C_4H_9)_3SnH$ (360 mg, 1.23 mmol) and AIBN (8 mg) in nitrogen atmosphere, and whole content was stirred for overnight. Then, it was filtered (to remove AIBN), extracted with ethyl acetate (3 × 50 mL), washed with brine, dried ($MgSO_4$), and concentrated to give a viscous oil which was chromtographed on silica gel (hexane/ethyl acetate, 5/1) to give 130 mg (76.5%) of **16** as a colorless liquid: 94% ee optical yield, $[\alpha]^{23}_D$ −20.8 (c 1.0, $CHCl_3$) (lit.[11c] $[\alpha]^{20}_D$ −22.1); IR (neat) 3450, 1735, 1605, 1500, 1450, 1100, 1030, 745, 705 cm^{-1}; 200 MHz ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.14 Hz, 3 H), 1.84–2.21 (m, 2 H), 2.77 (t, J = 8.3 Hz, 2 H), 2.86 (br s, 1 H), 4.12–4.23 (m, 1 H), 4.21 (q, J = 7.14 Hz, 2 H), 7.26 (m, 5 H); 50-MHz ^{13}C NMR ($CDCl_3$) δ 14.20, 31.03, 36.00, 61.77, 69.88, 126.03, 128.43, 128.56.

(2*R*,3*S*)-3-Amino-2-hydroxy-5-methylhexanamide (19). To *anti*-**2e** (0.14 g, 0.67 mmol) was added ice-cooled 20% ammonia solution (2.25 mL). The mixture was stirred for 24 h at room temperature and then extracted with $CHCl_3$. The combined extracts were washed with brine and water and dried over $MgSO_4$. Concentration of the solvent gave 81 mg of the crude product, which was purified with column chromatography (hexane/EtOAc/$CHCl_3$ = 4/3/1) on silica gel (4.5 g), giving 75 mg (70%) of **19**: mp 75–76 °C; $[\alpha]^{21}_D$ +9.62 ($CHCl_3$, c 1.6); IR (KBr) 3400, 3210, 1670, 1650, 1460, and 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6 H), 1.24 (s, 1 H), 1.48 (m, 2 H), 1.83 (m, 1 H), 3.21 (m, 1 H), 3.50 (d, 1 H), 6.13 (br s, 2 H), 6.23 (br s, 2 H).

(2*S*,3*R*)-3-Chloro-1,2-decanediol (20). To a solution of **2e** (690 mg, 2.75 mmol) in 5 mL of absolute EtOH was added $NaBH_4$ (148 mg, 3.9 mmol) at room temperature. The mixture was stirred for 6 h and then poured into ice water. The organic materials were extracted with CH_2Cl_2 and worked up as usual. The crude product (577 mg) was purified by column chromatography on silica gel (hexane/acetone, 3/1) to give 515 mg (90% yield) of **20**: R_f = 0.23 (hexane/acetone = 3/1); $[\alpha]^{28}_D$ +10.2 ($CHCl_3$, c 2.40); IR (neat) 3400, 2950, 1465, 1080, 1050, 870 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (br t, J = 5 Hz, 3 H), 1.30–2.00 (m, 12 H), 3.70 (m, 4 H), 4.10 (m, 2 H). Anal. Calcd for $C_{10}H_{21}O_2Cl$: C, 57.54; H, 10.14. Found: C, 57.82; H, 10.28.

(2*S*,3*S*)-2,3-Epoxydecanol (21). To a solution of NaOEt (2.8 mmol) in absolute EtOH (7 mL) was added 515 mg (2.47 mmol) of **20** at 0 °C with stirring. The mixture was stirred for 30 min at 0 °C and for 12 h at room temperature and then poured into ice water. The organic layer was extracted with EtOAc and worked up as usual. The crude product (427 mg) was purified

(23) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.

by column chromatography on silica gel (hexane/acetone = 5/1) to give 328 mg of **21** as an oil: R_f = 0.31 (hexane/acetone = 3/1); mp 37.5–39.5 °C; $[\alpha]^{27}_D$ −19.1 ($CHCl_3$, *c* 0.90). Pure **21**: mp 37.5–38.5 °C (from pentane); $[\alpha]^{25}_D$ −23.3 ($CHCl_3$, *c* 0.78) (lit.[19b] $[\alpha]^{25}_D$ −25.5 (EtOH, *c* 1.55)); >91% ee; IR (KBr) 3425, 2950, 1460, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (br t, *J* = 5 Hz, 3 H), 1.32 (m, 12 H), 3.48 (s, 1 H), 2.95 (m, 2 H), 3.40–4.10 (m, 2 H).

(2*S*,3*S*)-3-Chlorotridecane-1,2-diol (*syn*-22). To a solution of *syn*-**2i** (279 mg, 0.95 mmol) in 5 mL of absolute EtOH was added $NaBH_4$ (57 mg, 1.5 mmol). The mixture was stirred for 5.2 h at room temperature and poured into ice water. Usual workup gave 271 mg of an oil, which was purified with column chromatography to give 184 mg (78%) of *syn*-**22**: R_f = 0.26 (hexane/acetone = 3/1); $[\alpha]^{27}_D$ −26.1 ($CHCl_3$, *c* 0.75); IR (neat) 3450, 2950, 1465, 1050 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (br t, *J* = 5 Hz, 3 H), 1.26 (m, 18 H), 3.65 (m, 3 H), 3.89 (m, 3 H). Anal. Calcd for $C_{13}H_{27}ClO_2$: C, 62.26; H, 10.85. Found: C, 62.36; H, 10.92.

(2*S*,3*R*)-3-Chlorotridecane-1,2-diol (*anti*-22). To a solution of *anti*-**2i** (309 mg, 1.06 mmol) in 5 mL of absolute EtOH was added $NaBH_4$ (61 mg, 1.6 mmol). The mixture was stirred for 5.5 h at room temperature and then poured into ice water. Usual workup gave 283 mg of an oil, which was purified with column chromatography (hexane/acetone = 10/1) to give 181 mg (76% yield) of *anti*-**22**: R_f = 0.30 (hexane/acetone = 3/1); $[\alpha]^{28}_D$ +18.6 ($CHCl_3$, *c* 1.67); IR (neat) 3350, 2925, 1465, 1105, 1040, 875 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (br t, *J* = 6 Hz, 3 H), 1.30 (m, 18 H), 3.70 (m, 3 H), 3.90 (m, 3 H). Anal. Calcd for $C_{13}H_{27}ClO_2$: C, 62.26; H, 10.85. Found: C, 62.42; H, 10.76.

(2*S*,3*R*)-2,3-Epoxytridecanol (*cis*-23). To a solution of NaOEt (0.9 mmol) in absolute EtOH (2 mL) was added a solution of 174 mg (0.69 mmol) of *syn*-**22** in absolute EtOH (3 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C for 12 h at room temperature. After being poured into ice water, the mixture was neutralized with 10% HCl. The organic layer was extracted with CH_2Cl_2 and worked up as usual. Crude product (166 mg) was purified with column chromatography (hexane/acetone = 5/1), giving 185 mg (100%) of *cis*-**23**: mp 63–63.5 °C from pentane (lit.[19a] mp 62.5–3 °C); $[\alpha]^{25}_D$ +7.90 (EtOH *c* 0.87) (lit.[19a] $[\alpha]^{25}_D$ +7.90 (EtOH, *c* 1.0)); >95% ee; IR (KBr) 3300, 3150, 2950, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (br t, *J* = 5 Hz, 3 H), 1.30 (m, 18 H), 3.10–3.30 (m, 2 H), 3.68–3.80 (m, 3 H).

(2*S*,3*S*)-2,3-Epoxytridecanol (*trans*-23). To a solution of NaOEt (0.9 mmol) in absolute EtOH (7 mL) was added 155 mg (0.62 mmol) of *anti*-**22** at 0 °C, and the mixture was stirred for 12.5 h at room temperature and then poured into ice water. The organic layer was extracted with CH_2Cl_2 and worked up as usual. Column chromatography (hexane/acetone = 5/1) of the crude product (155 mg) gave 119 mg (90%) of *trans*-**23**: R_f = 0.38 (hexane/acetone = 3/1); mp 64.5–65 °C (from pentane); $[\alpha]^{25}_D$ −28.9 ($CHCl_3$, *c* 0.78) (lit.[24] $[\alpha]^{24}_D$ −28.8 ($CHCl_3$, *c* 1.65)); >95% ee; IR (KBr) 3300, 3150, 2950, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (br t, *J* = 5 Hz, 3 H), 1.26 (m, 18 H), 2.25 (s, 1 H), 2.88 (m, 2 H).

(2*S*,3*S*)-3-Chlorohexane-1,2-diol (*syn*-24). To a solution of *syn*-**2a** (185 mg, 0.95 mmol) in absolute EtOH (7 mL) was added $NaBH_4$ (38 mg, 1 mmol). The mixture was stirred for 3.5 h at room temperature. After the usual workup, the crude product (164 mg) obtained was purified with column chromatography (hexane/acetone = 15/1), giving 144 mg (99%) of *syn*-**24**: mp 82.5–83 °C (from hexane/acetone = 3/1); $[\alpha]^{22}_D$ +10.5 ($CHCl_3$, *c* 0.4); IR (KBr) 3300, 2950, 1400, 1030, 760 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (br t, *J* = 6 Hz, 3 H), 1.2–2.6 (m, 6 H), 3.77 (apparent s, 4 H). Anal. Calcd for $C_6H_{13}ClO_2$: C, 47.22; H, 8.58. Found: C, 47.32; H, 8.44.

(2*S*,3*R*)-3-Chlorohexane-1,2-diol (*anti*-24). To a solution of *anti*-**2a** (565 mg, 2.90 mmol) in absolute EtOH (7 mL) was added $NaBH_4$ (133 mg, 3.5 mmol). The mixture was stirred for 5.1 h at room temperature. After usual workup, the crude product (485 mg) obtained was purified with column chromatography (hexane/acetone = 15/1), giving 323 mg (73%) of *anti*-**24**: mp 67.5–69 °C (hexane/acetone = 3/1); $[\alpha]^{22}_D$ +16.5 ($CHCl_3$, *c* 0.52); IR (KBr) 3300, 2950, 1400, 1030, 760 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (br t, *J* = 6 Hz, 3 H), 1.80 (m, 2 H), 2.40 (m, 2 H), 3.80 (m, 6 H). Anal. Calcd for $C_6H_{13}ClO_2$: C, 47.22; H, 8.58. Found: C, 47.34; H, 8.61.

(2*S*,3*R*)-2,3-Epoxyhexanol (*cis*-25). To a solution of NaOEt (0.7 mmol) in dry EtOH (7 mL) was added 101 mg (0.66 mmol) of *syn*-**24**. The mixture was stirred for 12 h at room temperature and worked up as described above. The crude oil (81 mg) was purified with column chromatography (hexane/acetone = 5/1), giving 50 mg (66%) of *cis*-**25**: R_f = 0.26 (hexane/acetone = 3/1): mp 84.5–85 °C (from hexane); $[\alpha]^{22}_D$ −10.0 ($CHCl_3$, *c* 0.37); >92% ee by MTPA ester; IR (KBr) 3410, 2950, 1065 cm^{-1}; ^1H NMR (CCl_4) δ 0.93 (br t, *J* = 5 Hz, 3 H), 1.10–1.80 (m, 4 H), 2.80 (m, 2 H), 3.20–3.80 (m, 2 H).

MTPA Ester of *cis*-25. To a solution of *cis*-**25** (28 mg, 0.24 mmol) in dry CH_2Cl_2 (3 mL) and dry pyridine (3 mL) was added (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (91 mg, 0.29 mmol). The mixture was stirred for 21 h at room temperature and then poured into ice water. The organic layer was extracted with ether, washed with dilute HCl, aqueous $NaHCO_3$, and water, and dried over $MgSO_4$. After removal of the solvent, the crude product was purified with preparative TLC (hexane/acetone = 2/1), giving 56 mg (60%) of MTPA ester of *cis*-**25**: R_f = 0.50 (hexane/acetone = 2/1); IR (neat) 2970, 1762, 1453, 1240, 1022, 760 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (br t, *J* = 5 Hz, CH_3), 1.20–2.30 (m, 4 H), 3.52 (s, 3 H), 3.5–5.1 (m, 4 H). HPLC analysis (SA-I (6 φ × 250 mm), hexane/EtOAc = 20/1, 1.05 mL/min) showed two peaks at t_R 46.7 and 48.5 min with the 4/96 ratio of integrated intensity: 92% ee.

(2*S*,3*S*)-2,3-Epoxyhexanol (*trans*-25). To a solution of NaOEt (2 mmol) in absolute ethanol (7 mL) was added 272 mg (1.78 mmol) of *anti*-**24** at 0 °C. The mixture was stirred for 14 h at room temperature and then worked up as described above. The crude product (257 mg) was purified with column chromatography (hexane/acetone = 10/1), giving 161 mg (78%) of *trans*-**25**: R_f = 0.20 (hexane/acetone = 3/1); $[\alpha]^{22}_D$ −36.6 ($CHCl_3$, *c* 1.83) (lit.[6] $[\alpha]^{20}_D$ −42.4 ($CHCl_3$, *c* 0.99)); 86% ee; IR (neat) 3450, 2990, 1465, 1220, 1050, 900, 860 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (br t, *J* = 6 Hz, 3 H), 1.40 (m, 4 H), 2.78 (m, 2 H), 3.55 (m, 3 H).

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(24) Katsuki, T. Private communication.