A Facile Chemoenzymatic Route to Optically Active 4,5-Disubstituted-2*E*-hexenoate Derivatives. II[1)]

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The reaction of (±) methyl 4,5-*trans*-epoxy-(2*E*)-hexenoate (1) with nucleophiles having heteroatoms in the presence of $BF_3 \cdot Et_2O$ gave the 4,5-*anti*-5-hydroxy-4- and/or 2,5-*anti*-5-hydroxy-2-substituted products. Among them, the (±)-4,5-*anti*-5-hydroxy-4-thiophenoxy ester 12a was enantioselectively acetylated with acylating reagent in the presence of lipase "PL 266" from *Alcaligenes* sp. to provide the (4*S*,5*R*)-5-acetoxy ester 12b and (4*R*,5*S*)-12a quantitatively.

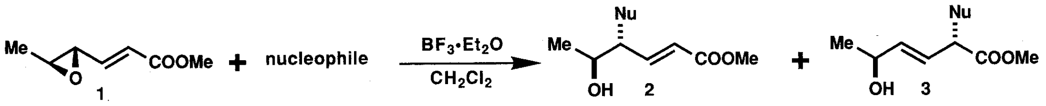
Keywords methyl 4,5-*trans*-epoxy-2*E*-hexenoate; boron trifluoride etherate; epoxy ring opening; enantioselective acetylation; lipase; 4,5-disubstituted-2*E*-hexenoate

In our previous paper,[3)] we reported that the reaction of (±) methyl 4,5-*trans*-epoxy-2*E*-hexenoate (**1**) with aromatic nucleophiles having electron-donating groups in the presence of $BF_3 \cdot Et_2O$ gave the 4,5-*anti*-5-hydroxy-4-substituted product **2** and/or the 2,5-*anti*-5-hydroxy-2-substituted product **3**. This work has aroused much interest because of its possible extension to nucleophiles having heteroatoms such as oxygen, nitrogen, sulfur and chlorine.

Optically active 4,5-*anti*-disubstituted-2*E*-hexenoates **2** are expected to be chiral intermediates for the synthesis of biologically active compounds such as amino sugars or related compounds.[4)] We now report the regioselective synthesis of (±)-4,5-*anti*-disubstituted-2*E*-hexenoates **2** having various heteroatoms and enantioselective acetylation of (±)-**2** with acylating reagent in the presence of lipase in an organic solvent.

The Reaction of (±) Methyl 4,5-*trans*-Epoxy-2*E*-hexenoate (1) with Various Nucleophiles i) The Reaction of (±)-1 and Indole In the reaction of indole and electrophiles, the C_3-position of indole is reported to be more reactive than the C_2-position. In order to allow comparison of the results with the previously reported data,[3)] the reaction conditions were the same as in the previous case. When the reaction of (±)-**1** (10 mmol) with indole (5 mmol) in the presence of boron trifluoride etherate ($BF_3 \cdot Et_2O$, 5 mmol) in CH_2Cl_2 (10 ml) was conducted for 1 h at −78 °C, the (±)-4,5-*anti*-5-hydroxy-4-(3′-indolyl)-2*E*-hexenoate **4a** (59%)[5)] and the (±)-4,5-*anti*-5-hydroxy-4-(2′-indolyl)-2*E*-hexenoate **5a** (8%) were obtained.

The structure of (±)-**4a** was determined as follows. Acetylation of (±)-**4a** provided an acetate (±)-**4b** whose nuclear magnetic resonance (NMR) spectrum showed the



nucleophile ; phenol, poly-methoxybenzene

Chart 1

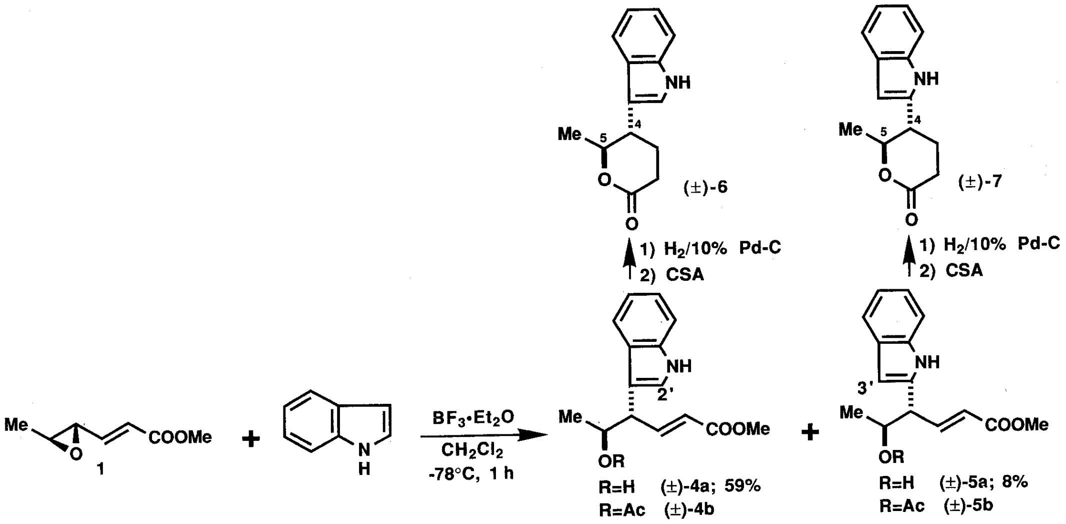


Chart 2

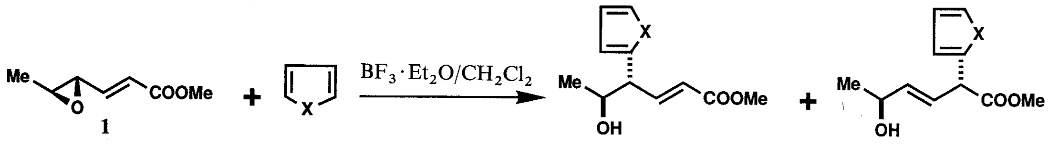
presence of an acetoxyl group at the C$_5$-position, because the signal due to C$_5$-H was a double quartet at 5.36 ppm with coupling constants of $J_{5,\mathrm{Me}}=6$ Hz and $J_{4,5}=8$ Hz. Carbon–carbon bond formation was found to take place between the C$_4$-position of (±)-**1** and the C$_3$-position of indole because the chemical shift (δ 7.06, br s) due to 2′-H of (±)-**4a** was almost the same as that (δ 6.90, br s) of 3-methylindole. The 4,5-*anti*-configuration of (±)-**4a** was determined by the following chemical evidence. Hydrogenation of (±)-**4a** and subsequent lactonization produced the lactone **6**. From a decoupling experiment on **6**, the coupling constant of C$_4$-H and C$_5$-H was 10 Hz, and this evidence indicates that (±)-**4a** possesses 4,5-*anti*-configuration.$^{6)}$ Then the structure determination of (±)-**5a** was carried out by the following method. Acetylation of (±)-**5a** gave the acetate (±)-**5b** (δ 5.35, dq, $J_{5,\mathrm{Me}}=J_{4,5}=6$ Hz) and (±)-**5a** was also converted into the lactone **7** in the same way as (±)-**4a**. From a decoupling experiment on (±)-**7**, the signal due to C$_5$-H is a double quartet at 4.60 ppm ($J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=10$ Hz) and the coupling constant of C$_4$-H and C$_5$-H was found to be 10 Hz. These data indicate that the starting (±)-**5a** possesses 4,5-*anti*-configuration. In comparison with the case of (±)-**4a**, the difference is that carbon–carbon bond formation took place between the C$_4$-position of (±)-**1** and the C$_2$-position of indole because the chemical shift (δ 6.32, br s) due to 3′-H of (±)-**5a** was almost the same as that (δ 6.20 br s) of 2-methylindole.

ii) The Reaction of (±)-1 and Five-Membered Heterocycles Furan and thiophene undergo attack by electrophilic reagents at the α-position. The reaction of (±)-**1** and furan provided (±)-**8a** (19%) and its regio-isomer (±)-**9a** (3%, δ 4.42, 1H, d, $J_{2,3}=8$ Hz, C$_2$-H) as shown in Table I. The reaction of (±)-**1** and thiophene yielded (±)-**10a** (16%) and its regio-isomer (±)-**11a** (25%, δ 4.41, 1H, d, $J_{2,3}=8$ Hz, C$_2$-H). When the reaction temperature was raised to 0 °C in order to improve the total yield of the products, no improvement of total chemical yield was obtained. The reaction of (±)-**1** and thiazole did not occur and the starting material (±)-**1** was recovered unchanged.

iii) The Reaction of (±)-1 and Thiophenol The reaction of (±)-**1** and thiophenol provided (±)-**12a** as a sole product in 95% yield. Acetylation of (±)-**12a** provided the acetate (±)-**12b** (34%, δ 5.19, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=5$ Hz, 5-H) along with dehydration products **13** (a mixture of double bond isomers) in 63% yield. As the C$_4$-hydrogen of (±)-**12a** is acidic because of the S-phenyl group at the allylic position of the α,β-unsaturated ester moiety, elimination of thiophenol takes place smoothly from a part of the resulting acetate (±)-**12b** in the presence of pyridine.

The stereochemistry of (±)-**12a** was confirmed by the following correlation. Treatment of (±)-**12a** with Meerwein's reagent (trimethyloxonium tetrafluoroborate) followed by epoxy formation from the resulting sulfonium salt **14** with diisopropylethylamine afforded an inseparable mixture (68% yield, *trans*:*cis*=4:1) of (±)-*trans*-**1** and (±)-*cis*-**1**.

Table I



X=O	−78 °C, 1 h	(±)-**8a**; 19%	(±)-**9a**; 3%
X=O	0 °C, 1 h	(±)-**8a**; 24%	(±)-**9a**; 2%
X=S	−78 °C, 1 h	(±)-**10a**; 16%	(±)-**11a**; 25%
X=S	0 °C, 1 h	(±)-**10a**; 17%	(±)-**11a**; 13%

Products **8a**, **10a**, **11a** were converted to the corresponding acetates **8b**, **10b**, **11b**.

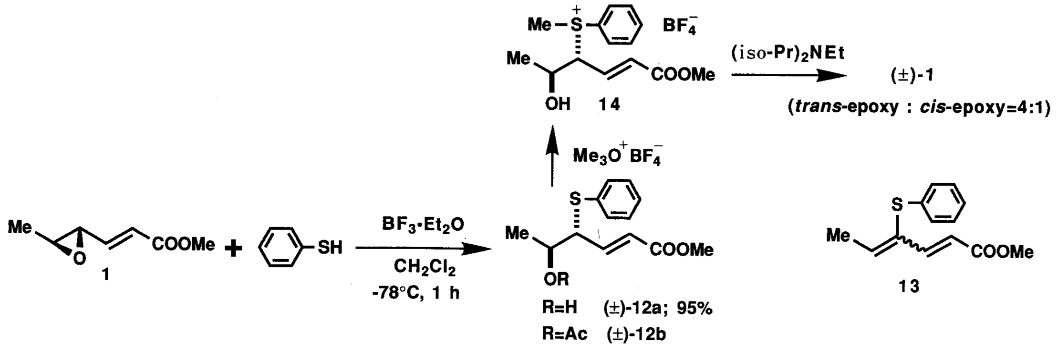


Chart 3

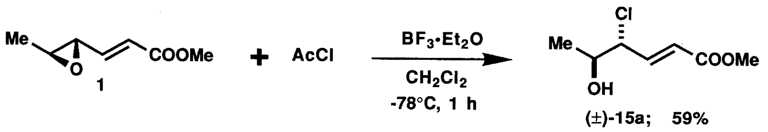


Chart 4

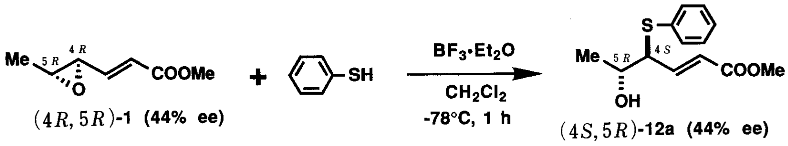
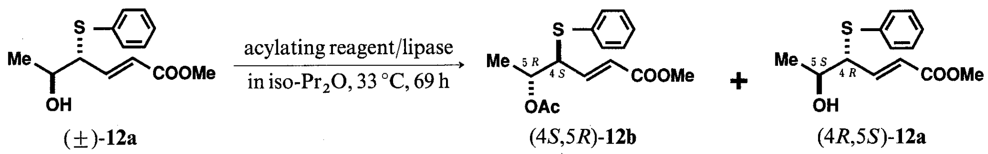


Chart 5

TABLE II



Entry	Substrate (mg)	Lipase	Acylating reagent	Product (yield, %; optical purity, % ee)	
1	103	PL 266 (*Alcaligenes* sp.)	A	(4*S*,5*R*)-**12b** (50.2%, 98% ee)	(4*R*,5*S*)-**12a** (49.7%, >99% ee)
2	97	PL 679 (*Alcaligenes* sp.)	A	(4*S*,5*R*)-**12b** (61.1%, 58% ee)	(4*R*,5*S*)-**12a** (34.6%, 90% ee)
3	107	PL 266 (*Alcaligenes* sp.)	B	(4*S*,5*R*)-**12b** (49.5%, 99% ee)	(4*R*,5*S*)-**12a** (49.8%, 97% ee)
4	109	PL 679 (*Alcaligenes* sp.)	B	(4*S*,5*R*)-**12b** (41.5%, 95% ee)	(4*R*,5*S*)-**12a** (57.8%, 67% ee)

A, Isopropenyl acetate. B, PhSAc.

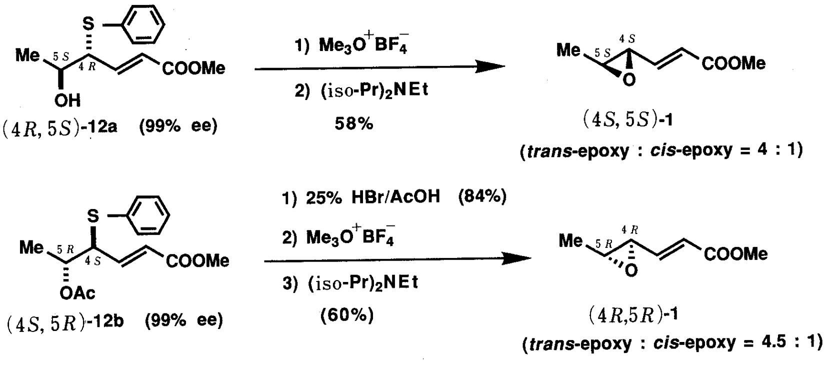


Chart 6

iv) The Reaction of (±)-1 and Acetyl Chloride For the introduction of chlorine at the C_4-position, the reaction of (±)-**1** and acetyl chloride was carried out to provide (±)-**15a** as a sole product in 59% yield. The 4,5-*anti*-configuration of (±)-**15a** was deduced by comparison with the results so far obtained.[3]

The reaction of (±)-**1** and other nucleophiles such as thioanisole, allyltrimethylsilane, ethyl vinyl ether and LiCN in dimethylformamide (DMF) did not occur to any significant extent and the starting material (±)-**1** was recovered unchanged.

Enantioselective Acetylation of the (±)-4,5-*anti*-5-Hydroxy-4-thiophenoxy Ester 12a with Lipase First, in order to determine the absolute structure and optical purity of the enzymatic reaction products, an optically active authentic sample (4*S*,5*R*)-**12a** (44% ee) was obtained by the reaction of the known (4*R*,5*R*)-**1** (44% ee)[7] and thiophenol in the presence of $BF_3 \cdot Et_2O$ at 0 °C.

i) Enantioselective Acetylation of (±)-12a with Lipases The treatment of (±)-**12a** and acylating reagents (isopropenyl acetate and phenylthioacetate) with lipase "PL-266" from *Alcaligenes* sp. in isopropyl ether provided quantitatively the (4*S*,5*R*)-5-acetoxy ester **12b** (98—99% ee) and the (4*R*,5*S*)-5-hydroxy ester **12a** (97—99% ee) as shown in Table II (entries 1 and 3). When the lipase "PL 679" from *Alcaligenes* sp. was employed (entries 2 and 4), optical yields of products ((4*R*,5*S*)-**12a** or (4*S*,5*R*)-**12b**) were found to be less than in the previous case. The stereochemistry of (4*R*,5*S*)-**12a** was confirmed by comparison with authentic (4*S*,5*R*)-**12a** by means of high-performance liquid chromatography (HPLC) using a chiral column[8] and the optical purity of (4*R*,5*S*)-**12a** was determined by HPLC analysis. The stereochemistry and the optical purity of the acetate (4*S*,5*R*)-**12b** were also determined by HPLC analysis after hydrolysis of (4*S*,5*R*)-**12b** with 25% HBr–AcOH (v/v).

Conversion of the (4*R*,5*S*)-5-Hydroxy Ester 12a to Methyl (4*S*,5*S*)-*trans*-Epoxy-(2*E*)-hexenoate (1) and Conversion of the (4*S*,5*R*)-5-Acetoxy Ester 12b to Methyl (4*R*,5*R*)-*trans*-Epoxy-(2*E*)-hexenoate (1) The (4*R*,5*S*)-**12a** (99% ee) was subjected to epoxide formation in the same way as (±)-**12a** to give an inseparable mixture (*trans*:*cis*=4:1) of (4*S*,5*S*)-*trans*-**1** and (4*R*,5*S*)-*cis*-**1** in 58% overall yield. The (4*S*,5*R*)-**12b** (99% ee) was treated with 25% HBr–AcOH (v/v) to give (4*S*,5*R*)-**12a** in 84% yield, and this was also converted into an inseparable mixture (*trans*:*cis*=4.5:1) of (4*R*,5*R*)-*trans*-**1** and (4*S*,5*R*)-*cis*-**1** in 60% overall yield (two steps). In these processes, partial isomerization to the undesired *cis* epoxy ester was observed, but no loss of optical purity was detected. These conversions mean that chiral synthesis of (4,5)-disubstituted-2*E*-hexenoate derivatives can be achieved.

Experimental

IR spectra (CCl_4) were measured on a JASCO A-3 spectrophotometer. NMR spectra were measured on a JEOL GX-400 instrument. Spectra were taken with 5—10% (w/v) solutions in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 MC polarimeter. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). All the reactions were carried out in an atmosphere of argon. For column chromatography, silica gel (Wakogel C-200) was employed. All organic solvents were washed with saturated brine and dried over anhydrous magnesium sulfate ($MeSO_4$). All evaporations were performed under reduced pressure.

General Procedure of the Reaction of (±)-1 and Various Kinds of Nucleophiles in the Presence of $BF_3 \cdot Et_2O$ and Acetylation of Each Product $BF_3 \cdot Et_2O$ (10 mmol) was added to a solution of (±)-**1** (10 mmol) and a nucleophile (5 mmol) in CH_2Cl_2 (10 ml) under dry ice/acetone cooling and the whole was stirred for 1 h at the same temperature. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with aqueous saturated $NaHCO_3$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (50 g) to afford a homogeneous oil from the AcOEt : *n*-hexane (1 : 9—1 : 3, v/v) eluate. The chemical yield of each product was calculated based on the nucleophile used. All products were treated with excess Ac_2O in pyridine at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 10% aqueous HCl, and aqueous saturated $NaHCO_3$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel to provide the corresponding acetate from the AcOEt : *n*-hexane (1 : 9—1 : 4, v/v) eluate.

(±) Methyl (4,5)-*anti*-5-Hydroxy-4-(3′-indolyl)-(2*E*)-hexenoate (4a) and Its Acetate (±)-4b (±)-**4a**: Pale yellow oil. 59% yield. *Anal.* HRMS Calcd for $C_{15}H_{17}NO_3$ (M$^+$; *m/z*): 259.120. Found: 259.117. IR: 3600, 3510, 1730, 1720 (sh), 1650 (sh) cm^{-1}. NMR δ: 1.21 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 1.88 (1H, br s, 5-OH), 3.71 (3H, s, COOMe), 3.77 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=6$ Hz, 4-H), 4.24 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.98 (1H, d, $J_{2,3}=16$ Hz, 2-H), 7.06 (1H, br s, 2′-H), 7.35 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=9$ Hz, 3-H), 8.30 (1H, br s, 1′-H). (±)-**4b**: Pale yellow oil. 89% yield. *Anal.* HRMS Calcd for $C_{17}H_{19}NO_4$ (M$^+$; *m/z*): 301.131. Found: 301.128. IR: 3500, 1730, 1740 (sh), 1720 (sh), 1650 cm^{-1}. NMR δ: 1.20 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.04 (3H, s, 5-OAc), 3.70 (3H, s, COOMe), 3.88 (1H, t, $J_{3,4}=J_{4,5}=8$ Hz, 4-H), 5.36 (1H, dq, $J_{4,5}=8$ Hz, $J_{5,\mathrm{Me}}=6$ Hz, 5-H), 5.90 (1H, d, $J_{2,3}=16$ Hz, 2-H), 7.10 (1H, br s, 2′-H), 8.29 (1H, br s, 1′-H).

(±) Methyl (4,5)-*anti*-5-Hydroxy-4-(2′-indolyl)-(2*E*)-hexenoate (5a) and Its Acetate (±)-5b (±)-**5a**: Pale yellow oil. 8% yield. *Anal.* HRMS Calcd for $C_{15}H_{17}NO_3$ (M$^+$; *m/z*): 259.120. Found: 259.123. IR: 3630, 3475, 1730, 1720 (sh), 1650 cm^{-1}. NMR δ: 1.25 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.06 (1H, br s, 5-OH), 3.71 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=4$ Hz, 4-H), 3.74 (3H, s, COOMe), 4.22—4.25 (1H, m, 5-H), 5.96 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.32 (1H, br s, 3′-H), 7.24 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=9$ Hz, 3-H), 8.70 (1H, br s, 1′-H). (±)-**5b**: Pale yellow oil. 70% yield. *Anal.* HRMS Calcd for $C_{17}H_{19}NO_4$ (M$^+$; *m/z*): 301.131. Found: 301.134. IR: 3500, 1730, 1740 (sh), 1720 (sh), 1650 cm^{-1}. NMR δ: 1.22 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.07 (3H, s, 5-OAc), 3.74 (3H, s, COOMe), 3.81 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=6$ Hz, 4-H), 5.35 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.97 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.35 (1H, br s, 3′-H), 8.29 (1H, br s, 1′-H).

(±) Methyl (4,5)-*anti*-4-(2′-Furyl)-5-hydroxy-(2*E*)-hexenoate (8a) and Its Acetate (±)-8b (±)-**8a**: Pale yellow oil. 19% yield. *Anal.* HRMS Calcd for $C_{11}H_{14}O_4$ (M$^+$; *m/z*): 210.089. Found: 210.087. IR: 3570, 1720, 1645 cm^{-1}. NMR δ: 1.18 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.04 (1H, d, $J_{5,\mathrm{OH}}=4$ Hz, 5-OH), 3.56 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=6$ Hz, 4-H), 3.74 (3H, s, COOMe), 4.17 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.94 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.16 (1H, dd, $J_{3',4'}=3.3$ Hz, $J_{3',5'}=0.8$ Hz, 3′-H), 6.34 (1H, dd, $J_{3',4'}=3.3$ Hz, $J_{4',5'}=1.8$ Hz, 4′-H), 7.15 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=9$ Hz, 3-H), 7.37 (1H, dd, $J_{4',5'}=1.8$ Hz, $J_{3',5'}=0.8$ Hz, 5′-H). (±)-**8b**: Pale yellow oil. 61% yield. *Anal.* HRMS Calcd for $C_{13}H_{16}O_5$ (M$^+$; *m/z*): 252.100. Found: 252.101. IR: 1723 (sh), 1718, 1640 cm^{-1}. NMR δ: 1.19 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.02 (3H, s, 5-OAc), 3.71 (1H, t, $J_{3,4}=J_{4,5}=8$ Hz, 4-H), 3.74 (3H, s, COOMe), 5.26 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=8$ Hz, 5-H), 5.91 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.13 (1H, dd, $J_{3',5'}=0.8$ Hz, $J_{3',4'}=3.5$ Hz, 3′-H), 6.32 (1H, dd, $J_{4',5'}=1.8$ Hz, $J_{3',4'}=3.5$ Hz, 4′-H), 7.04 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=8$ Hz, 3-H), 7.36 (1H, dd, $J_{4',5'}=1.8$ Hz, $J_{3',5'}=0.8$ Hz, 5′-H).

(±) Methyl (2,5)-*anti*-2-(2′-Furyl)-5-hydroxy-(3*E*)-hexenoate (9a) (±)-**9a**: Pale yellow oil. 3% yield. *Anal.* HRMS Calcd for $C_{11}H_{14}O_4$ (M$^+$; *m/z*): 210.089. Found: 210.088. IR: 3550, 1715, 1640 cm^{-1}. NMR δ: 1.28 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 3.74 (3H, s, COOMe), 4.35 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 4.42 (1H, d, $J_{2,3}=8$ Hz, 2-H), 5.73 (1H, dq, $J_{4,5}=6$ Hz, $J_{3,4}=16$ Hz, 4-H), 5.96 (1H, dq, $J_{2,3}=8$ Hz, $J_{3,4}=16$ Hz, 3-H), 6.20 (1H, d, $J_{3',4'}=3.2$ Hz, 3′-H), 6.33 (1H, dd, $J_{3',4'}=3.2$ Hz, $J_{4',5'}=2$ Hz, 4′-H), 7.36 (1H, d, $J_{4',5'}=2$ Hz, 5′-H).

(±) Methyl (4,5)-*anti*-5-Hydroxy-4-(2′-thienyl)-(2*E*)-hexenoate (10a) and Its Acetate (±)-10b (±)-**10a**: Pale yellow oil. 16% yield. *Anal.* HRMS Calcd for $C_{11}H_{14}O_3S$ (M$^+$; *m/z*): 226.066. Found: 226.066. IR: 3580, 1720 cm^{-1}. NMR δ: 1.20 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 1.90 (1H, d, $J_{5,\mathrm{OH}}=4$ Hz, 5-OH), 3.71 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=6$ Hz, 4-H), 3.74 (3H, s, COOMe), 4.09 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.95 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.90 (1H, dd, $J_{3',5'}=1.2$ Hz, $J_{3',4'}=3.6$ Hz, 3′-H), 6.99 (1H, dd, $J_{3',4'}=3.6$ Hz, $J_{4',5'}=5.2$ Hz, 4′-H), 7.19 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=9$ Hz, 3-H), 7.23 (1H, dd, $J_{3',5'}=1.2$ Hz, $J_{4',5'}=5.2$ Hz, 5′-H). (±)-**10b**: Pale yellow oil. 91% yield. *Anal.* HRMS Calcd for $C_{13}H_{16}O_4S$ (M$^+$; *m/z*): 268.077. Found: 268.075. IR: 1718, 1723 (sh), 1640 cm^{-1}. NMR δ: 1.22 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.06 (3H, s, 5-OAc), 3.74 (3H, s, COOMe), 3.87 (1H, dd, $J_{3,4}=9$ Hz, $J_{4,5}=6$ Hz, 4-H), 5.19 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.91 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.88 (1H, dd, $J_{3',5'}=1.3$ Hz, $J_{3',4'}=3.6$ Hz, 3′-H), 6.97 (1H, dd, $J_{3',4'}=3.6$ Hz, $J_{4',5'}=5.1$ Hz, 4′-H), 7.09 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=9$ Hz, 3-H), 7.22 (1H, dd, $J_{3',5'}=1.3$ Hz, $J_{4',5'}=5.1$ Hz, 5′-H).

(±) Methyl (2,5)-*anti*-5-Hydroxy-2-(2′-thienyl)-(3*E*)-hexenoate (11a) and Its Acetate (±)-11b (±)-**11a**: Pale yellow oil. 25% yield. *Anal.* Calcd for $C_{11}H_{14}O_3S$ (M$^+$; *m/z*): 226.066. Found: 226.062. IR: 3580, 1720, 1645 cm^{-1}. NMR δ: 1.27 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 3.71 (3H, s, COOMe), 4.33 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 4.41 (1H, d, $J_{2,3}=8$ Hz, 2-H), 5.66 (1H, dd, $J_{3,4}=15$ Hz, $J_{4,5}=6$ Hz, 4-H), 6.00 (1H, dd, $J_{3,4}=15$ Hz, $J_{2,3}=8$ Hz, 3-H), 7.02 (1H, dd, $J_{3',5'}=1$ Hz, $J_{4',5'}=5$ Hz, 5′-H), 7.13 (1H, dd, $J_{3',4'}=3$ Hz, $J_{3',5'}=1$ Hz, 3′-H), 7.29 (1H, dd, $J_{3',4'}=3$ Hz, $J_{4',5'}=5$ Hz, 4′-H). (±)-**11b**: Pale yellow oil. 86% yield. *Anal.* HRMS Calcd for $C_{13}H_{16}O_4S$ (M$^+$; *m/z*): 268.077. Found: 268.075. IR: 1725, 1640 cm^{-1}. NMR δ: 1.31 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.04 (3H, s, 5-OAc), 3.72 (3H, s, COOMe), 4.41 (1H, d, $J_{2,3}=8$ Hz, 2-H), 5.37 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=6$ Hz, 5-H), 5.61 (1H, dd, $J_{3,4}=16$ Hz, $J_{4,5}=6$ Hz, 4-H), 6.04 (1H, $J_{2,3}=8$ Hz, $J_{3,4}=16$ Hz, 3-H), 7.01 (1H, dd, $J_{3',5'}=1.2$ Hz, $J_{4',5'}=5$ Hz, 5′-H), 7.13 (1H, dd, $J_{3',5'}=1.2$ Hz, $J_{3',4'}=2.5$ Hz, 3′-H), 7.29 (1H, dd, $J_{3',4'}=2.5$ Hz, $J_{4',5'}=5$ Hz, 4′-H).

(±) Methyl (4,5)-*anti*-5-Hydroxy-4-thiophenoxy-(2*E*)-hexenoate (12a) and Its Acetate (±)-12b (±)-**12a**: Pale yellow oil. 95% yield. *Anal.* HRMS Calcd for $C_{13}H_{16}O_3S$ (M$^+$; *m/z*): 252.082. Found: 252.078. IR: 3560, 3500, 1715, 1635 cm^{-1}. NMR δ: 1.28 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.26 (1H, d, $J_{5,\mathrm{OH}}=3$ Hz, 5-OH), 3.70 (1H, dd, $J_{4,5}=4$ Hz, $J_{3,4}=10$ Hz, 4-H), 3.72 (3H, s, COOMe), 4.03 (1H, dq, $J_{4,5}=4$ Hz, $J_{5,\mathrm{Me}}=6$ Hz, 5-H), 5.75 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.94 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=10$ Hz, 3-H), 7.28—7.43 (5H, m, aromatic-H), (±)-**12b**: Pale yellow oil. 34% yield. *Anal.* Calcd for $C_{15}H_{18}O_4S$ (M$^+$; *m/z*): 294.093. Found: 294.095. IR: 1740, 1727, 1645 cm^{-1}. NMR δ: 1.34 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.03 (3H, s, 5-OAc), 3.71 (1H, dd, $J_{3,4}=10$ Hz, $J_{4,5}=5$ Hz, 4-H), 3.72 (3H, s, COOMe), 5.19 (1H, dq, $J_{5,\mathrm{Me}}=6$ Hz, $J_{4,5}=5$ Hz, 5-H), 5.63 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.88 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=10$ Hz, 3-H), 7.24—7.42 (5H, m, aromatic-H).

(±) Methyl (4,5)-*anti*-4-Chloro-5-hydroxy-(2*E*)-hexenoate (15a) (±)-**15a**: Pale yellow oil. 59% yield. *Anal.* HRMS Calcd for $C_7H_{11}ClO_3$ (M$^+$; *m/z*): 143.071. Found: 143.072. IR: 3550, 1720, 1640 cm^{-1}. NMR δ: 1.26 (3H, d, $J_{5,\mathrm{Me}}=6$ Hz, 5-Me), 2.29 (1H, br s, 5-OH), 3.77 (3H, s, COOMe), 4.0—4.10 (1H, m, 5-H), 4.48 (1H, ddd, $J_{2,4}=1$ Hz, $J_{3,4}=8$ Hz, $J_{4,5}=4$ Hz, 4-H), 6.11 (1H, dd, $J_{2,3}=16$ Hz, $J_{2,4}=1$ Hz, 2-H), 6.95 (1H, dd, $J_{3,4}=8$ Hz, $J_{2,3}=16$ Hz, 3-H).

(±)-(4,5)-*trans*-4-(3′-Indolyl)-5-methyl-5-pentanolide (6) A solution of (±)-**4a** (108 mg) in EtOH (8 ml) was subjected to hydrogenation in the presence of 10% Pd–C (40 mg). After hydrogen absorption had ceased, the reaction mixture was filtered off and the filtrate was evaporated. A solution of the crude product and camphorsulfonic acid (CSA, 2 mg) in toluene (10 ml) was refluxed for 30 min with stirring. The reaction mixture was diluted with AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (20 g) to afford a homogeneous oil (±)-**6** (72 mg) from the 30% AcOEt in the *n*-hexane eluate. (±)-**6**: *Anal.* Calcd for $C_{14}H_{15}NO_2$ (M^+; *m/z*): 229.110. Found: 229.113. IR ($CHCl_3$): 3475, 1720 cm^{-1}. NMR δ: 1.29 (3H, d, $J_{5,Me}=6$ Hz, 5-Me), 2.16—2.84 (4H, m, 2-H_2, 3-H_2), 3.07 (dt, $J_{4,5}=10$ Hz, 4-H), 4.71 (1H, dq, $J_{4,5}=10$ Hz, $J_{5,Me}=6$ Hz, 5-H), 7.07 (1H, br s, 2′-H), 7.13—7.61 (4H, m, aromatic-H), 8.30 (1H, br s, 1′-H).

(±)-(4,5)-*trans*-4-(2′-Indolyl)-5-methyl-5-pentanolide (7) A solution of (±)-**5a** (59 mg) in EtOH (10 ml) was subjected to hydrogenation in the presence of 10% Pd–C (31 ml). The reaction mixture was worked up in the same way as described above to give a crude lactone, which was subjected to preparative thin-layer chromatography (silica gel; eluent, *n*-hexane: AcOEt = 2 : 1, v/v) to afford a homogeneous oil (±)-**7** (5 mg). (±)-**7**: *Anal.* HRMS Calcd for $C_{14}H_{15}NO_2$ (M^+; *m/z*): 229.110. Found: 229.113. IR: 3475, 1740 cm^{-1}. NMR δ: 1.34 (3H, d, $J_{5,Me}=6$ Hz, 5-Me), 2.15—2.85 (4H, m, 2-H_2, 3-H_2), 2.91 (1H, dt, $J_{4,5}=10$ Hz, 4-H), 4.60 (1H, dq, $J_{4,5}=10$ Hz, $J_{5,Me}=6$ Hz, 5-H), 6.36 (1H, br s, 3′-H), 7.10—7.58 (4H, m, aromatic-H), 8.07 (1H, br s, 1′-H).

(±) Methyl (4,5)-*trans*-Epoxy-(2*E*)-hexenoate (1) and (±) Methyl (4,5)-*cis*-Epoxy-(2*E*)-hexenoate (1) A mixture of (±)-**12a** (172 mg) and Meerwein's reagent ($Me_3O^+BF_4^-$; 155 mg) in CH_2Cl_2 (10 ml) was stirred for 2.5 h at room temperature and for 3 h at the same temperature after addition of diisopropylethylamine (0.5 ml). The reaction mixture was directly subjected to silica gel column chromatography to give an inseparable mixture (66 mg, 68% yield, *trans* : *cis* = 4 : 1) of (±)-*trans*-**1** and (±)-*cis*-**1** from 5% AcOEt in the *n*-hexane eluate. NMR data of (±)-*trans*-**1** were identical with those of an authentic sample.[3] (±)-*cis*-**1**: NMR δ: 1.29 (3H, d, $J_{5,Me}=5.5$ Hz, 5-Me), 3.32 (1H, dq, $J_{5,Me}=5.5$ Hz, $J_{4,5}=4.6$ Hz, 5-H), 3.52 ($J_{3,4}=6.7$ Hz, $J_{4,5}=4.6$ Hz, 4-H), 3.76 (3H, s, COOMe), 6.14 (1H, d, $J_{2,3}=16$ Hz, 2-H), 6.82 (1H, dd, $J_{2,3}=16$ Hz, $J_{3,4}=6.7$ Hz, 3-H).

Synthesis of Authentic (4*S*,5*R*)-12a Authentic (4*R*,5*R*)-**1** (44% ee, $[\alpha]_D^{27}$ +4° (*c* = 1.5, $CHCl_3$))[8] was allowed to react with thiophenol in the presence of $BF_3 \cdot Et_2O$ to give authentic (4*S*,5*R*)-**12a** in 93% yield. (4*S*,5*R*)-**12a**: $[\alpha]_D^{24}$ +92.8° (*c* = 4.76, $CHCl_3$), corresponds to 44% ee.

HPLC Analysis of (±)-12a by Using a Chiral Column The racemic (±)-**12a** gave two well separated peaks (38.41 and 40.87 min) corresponding to the enantiomers under the following analytical conditions (eluent, *n*-hexane : EtOH : iso-PrOH (1000 : 2 : 1); detection, UV at 280 nm; flow rate, 1 ml/min). The assignment of these peaks was achieved by comparing them with those of the above-mentioned authentic (4*S*,5*R*)-**12a**. Namely, the peak with shorter retention time ($t_R = 38.41$ min) was found to correspond to that of the (4*S*,5*R*)-**12a** enantiomer.

General Procedure of Enantioselective Acetylation of (±)-12a A mixture of (±)-**12a** (*ca.* 100 mg), acylating reagent (100 mg), and lipase (100 mg) in iso-Pr_2O (20 ml) was incubated at 33 °C for 69 h as shown in Table I. The reaction mixture was dried over $MgSO_4$ and evaporated to afford a crude product, which was subjected to silica gel (40 g) column chromatography. The fraction eluted with *n*-hexane : AcOEt (19 : 1, v/v) gave (4*S*,5*R*)-**12b**. The second fraction, eluted with *n*-hexane : AcOEt (6 : 1, v/v), provided (4*R*,5*S*)-**12a**. The optically active hydroxy ester was directly analyzed by HPLC. A solution of the optically active acetoxy ester (10 mg) and 25% HBr–AcOH (v/v) in MeOH (0.2 ml) was stirred for 24 h at room temperature. The reaction mixture was diluted with AcOEt and washed with aqueous saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated to give the hydroxy ester, which was analyzed by HPLC. The results are summarized in Table II. The results with lipase "PL 266" and isopropenyl acetate (Table II, entry 1): (4*S*,5*R*)-**12b**, $[\alpha]_D^{25}$ +192.3° (*c* = 1.05, $CHCl_3$), corresponds to 98% ee; (4*R*,5*S*)-**12a**, $[\alpha]_D^{19}$ −191° (*c* = 2.03, $CHCl_3$), corresponds to >99% ee. The spectral data (IR and NMR) of the hydroxy ester (4*R*,5*S*)-**12a** and the acetoxy ester (4*S*,5*R*)-**12b** were identical with those of the racemic compounds ((±)-**12a** and (±)-**12b**), respectively.

Conversion of (4*R*,5*S*)-Hydroxy Ester 12a to Methyl (4*S*,5*S*)-*trans*-Epoxy-(2*E*)-hexenoate (1) and Methyl (4*S*,5*R*)-*cis*-Epoxy-(2*E*)-hexenoate (1) A mixture of (4*R*,5*S*)-**12a** (267 mg, corresponds to 99% ee) and Meerwein's reagent (189 mg) in CH_2Cl_2 (5 ml) was stirred for 2.5 h at room temperature and for 1.5 h at the same temperature after addition of diisopropylethylamine (0.3 ml). The reaction mixture was directly chromatographed on silica gel (80 g) to provide an inseparable mixture (88 mg, 58% yield, *trans* : *cis* = 4 : 1) of (4*S*,5*S*)-*trans*-**1** and (4*R*,5*S*)-*cis*-**1** from 10% AcOEt in the *n*-hexane eluate. NMR data of both compounds were identical with those of the above-mentioned racemic samples ((±)-*trans* **1** and (±)-*cis* **1**).

Conversion of (4*S*,5*R*)-5-Acetoxy Ester 12b to Methyl (4*R*,5*R*)-*trans*-Epoxy-(2*E*)-hexenoate (1) and Methyl (4*S*,5*R*)-*cis*-Epoxy-(2*E*)-hexenoate (1) A solution of (4*S*,5*R*)-**12b** (589 mg, corresponds to 98% ee) and 25% HBr–AcOH (4 ml, v/v) in MeOH (3 ml) was stirred for 48 h at room temperature, then diluted with water and AcOEt. The organic layer was washed with aqueous saturated $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. Evaporation of the organic solvent gave an oily product, which was chromatographed on silica gel (60 g) to give the starting (4*S*,5*R*)-**12b** (76 mg, 13% recovery) from the *n*-hexane : AcOEt (4 : 1, v/v) eluate and (4*S*,5*R*)-**12a** (427 mg, 84% yield) from the *n*-hexane : AcOEt (2 : 1, v/v) eluate. A mixture of (4*S*,5*R*)-**12a** (169 mg) and Meerwein's reagent (119 mg) in CH_2Cl_2 (4 ml) was stirred for 2.5 h at room temperature and for 1.5 h after addition of diisopropylethylamine (0.19 ml). The reaction mixture was worked up and purified in the same way as described above to give an inseparable mixture (57 mg, 60% yield, *trans* : *cis* = 4.5 : 1) of (4*R*,5*R*)-*trans*-**1** and (4*S*,5*R*)-*cis*-**1**.

Confirmation of Optical Purity of (4*S*,5*S*)-*trans*-1 and (4*R*,5*R*)-*trans*-1 In a preliminary experiment, the racemic (±)-**1** gave two well-separated peaks (29.20 min and 31.57 min) corresponding to each enantiomer under the following analytical conditions (eluent, *n*-hexane : EtOH : iso-PrOH = 1000 : 2 : 1; detection, UV 254 nm; flow rate, 1 ml/min). The assignment of these peaks was achieved by comparison with an the authentic sample of (4*R*,5*R*)-**1** (44% ee). Namely, the peak with shorter retention time ($t_R = 29.20$ min) was found to correspond to that of the (4*R*,5*R*)-**1** enantiomer. HPLC analysis showed that the purities of the present (4*S*,5*S*)-**1** and (4*R*,5*R*)-**1** were 99% ee and 98% ee, respectively.

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References and Notes

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3) H. Akita, I. Umezawa, M. Takano, C. Ohyama, H. Matsukura, and T. Oishi, *Chem. Pharm, Bull.*, **41**, 55 (1993).
4) M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, *Tetrahedron Lett.*, **26**, 4133 (1985).
5) All chemical yields of the products were calculated based on the amount of nucleophiles used unless otherwise noted in the text.
6) The same observation was reported in T. Ibuka, M. Tanaka, H. Nemoto, and Y. Yamamoto, *Tetrahedron*, **45**, 435 (1989).
7) I. Dyong, R. Knollmann, and N. Jersch, *Angew. Chem. Int. Ed. Engl.*, **15**, 302 (1976). In our case, optical resolution was carried out once. The resulting optically active acid (44% ee) was converted to the methyl ester (4*R*,5*R*)-**1**.
8) (±)-**12a** was found to be well separated by means of HPLC using a chiral column in a preliminary experiment.