

A Facile Chemoenzymatic Route to Optically Active 4,5-Disubstituted-2*E*-hexenoate Derivatives. I¹⁾

Hiroyuki AKITA,*^a Isao UMEZAWA,^a Michika TAKANO,^b Chiiko OHYAMA,^b
Hiroko MATSUKURA,^b and Takeshi OISHI^{b,2)}

School of Pharmaceutical Science, Toho University,^a 2-2-1, Miyama, Funabashi, Chiba 274, Japan and Riken Institute (The Institute of Physical and Chemical Research),^b 2-1, Hirosawa, Wako-shi, Saitama 351-01, Japan.

Received June 3, 1992

The reaction of (±) methyl 4,5-*trans*-epoxy-2*E*-hexenoate (**2**) with aromatic nucleophiles having an electron-donating group in the presence of BF₃·Et₂O gave the 4,5-*anti*-5-hydroxy-4- or/and 2,5-*anti*-5-hydroxy-2-substituted products. The 5-acetates of the 4,5-*anti*-4-substitution products were subjected to enantioselective hydrolysis with lipase to provide the optically active 4,5-disubstituted 2-hexenoate derivatives.

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

In connection with our work directed towards the synthesis of optically active 2,3-disubstituted butyrate derivatives **A**, which were obtained by the reaction of an optically active 2,3-*trans*-epoxy butyrate **1** and nucleophilic reagents in the presence of Lewis acid,^{3a,b)} the reaction of (±)-4,5-*trans*-epoxy-2*E*-hexenoate (**B**), a vinylogous derivative of **1**, with various kinds of nucleophiles has aroused our interest. The reaction of (±)-**B** and alcohols in the presence of Lewis acid was reported to give selectively (±)-4,5-*anti* **C**,^{4a,b)} while the reaction of (±)-**B** and acetoacetate in the presence of palladium catalyst⁵⁾ or methyl-metal reagent^{6a,b)} was reported to produce the (±)-4,5- or/and 2,5-disubstituted compounds (**C** or/and **D**).

Optically active 4,5-*anti*-disubstituted-2*E*-hexenoate derivatives **C** are expected to be chiral intermediates for the synthesis of biologically active compounds such as amino sugars or related compounds.^{4b)} We now report the regioselective synthesis of (±)-4,5-*anti* **C** and enantioselective hydrolysis of the 5-acetate of (±)-4,5-*anti* **C** with lipase.

The Reaction of (±) Methyl 4,5-*trans*-Epoxy-2*E*-hexenoate (2**) with Various Nucleophiles** By applying the reported method,^{6a)} the epoxide (±)-**2** was obtained by the epoxidation of methyl sorbate with *m*-chloroperbenzoic acid (MCPBA) in 85% yield.

i) The Reaction of (±)-**2** and Phenol Analogues: In a preliminary experiment, when the reaction of (±)-**2** (5 mmol) with *p*-methoxyphenol (5 mmol) in the presence of boron trifluoride etherate (BF₃·Et₂O, 5 mmol) in CH₂Cl₂ (10 ml) was carried out for 1 h at -78 °C, the (±)-4,5-*anti*-4-aryl ether (*O*-substituted compound) **3a** (14%) and the (±)-4,5-*anti*-4-aryl substitution products (*C*-substituted

compounds **4a** (24%) and **5a** (4%)) were obtained along with the starting (±)-**2** (4%) and *p*-methoxyphenol (30%). To ensure complete consumption of the nucleophile (*p*-methoxyphenol), 2 molar eq of (±)-**2** and BF₃·Et₂O with respect to *p*-methoxyphenol were employed under the same conditions as above, giving (±)-**3a** (25%), (±)-**4a** (48%) and (±)-**5a** (6%). In this case, chemical yields of the products were calculated based on the amount of *p*-methoxyphenol.

The structure of (±)-**3a** was determined as follows. Acetylation of (±)-**3a** provided an acetate (±)-**3b** whose nuclear magnetic resonance (NMR) spectrum showed the presence of an acetoxyl group at the C₅-position, because the signal due to C₅-H was a double quartet at 5.11 ppm with two coupling constants (*J*_{5,Me} = 6 Hz, *J*_{4,5} = 4 Hz). The 4,5-*anti*-configuration of (±)-**3a** (or (±)-**3b**) was deduced by comparison with the reported reaction result^{4a,b)} using (±)-**B** and alcohol. Structure elucidations of (±)-**4a** and (±)-**5a** were carried out as follows. Acetylation of (±)-**4a** and (±)-**5a** gave the corresponding acetates (±)-**4b** and (±)-**5b**, respectively. The substitution pattern in the aromatic ring of (±)-**4b** and (±)-**5b** was determined by a nuclear Overhauser effect (NOE) experiment as shown in Chart 2. These determinations were supported by the fact that methylation (Me₂SO₄/K₂CO₃ in acetone) of (±)-**4a** or (±)-**5a** afforded the same (±)-4,5-*anti*-dimethoxy compound **6a**, whose structure determination is described below. Then the reaction of (±)-**2** with phenol analogues was examined, and the same results as in the previous case were obtained, as shown in Table I. The similarity of the NMR spectra of these products ((±)-**7a**—(±)-**14a**) to those

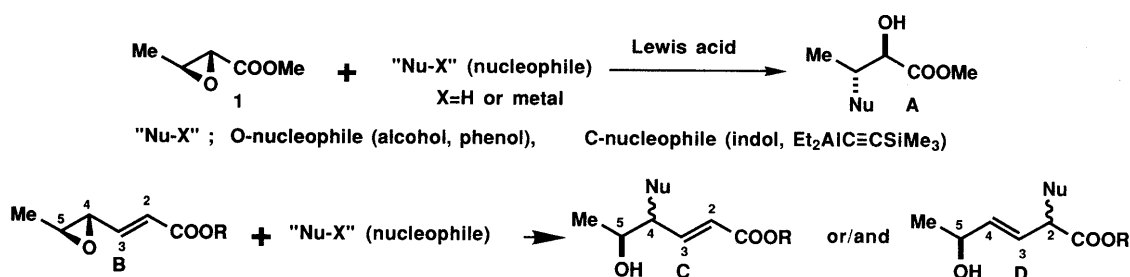


Chart 1

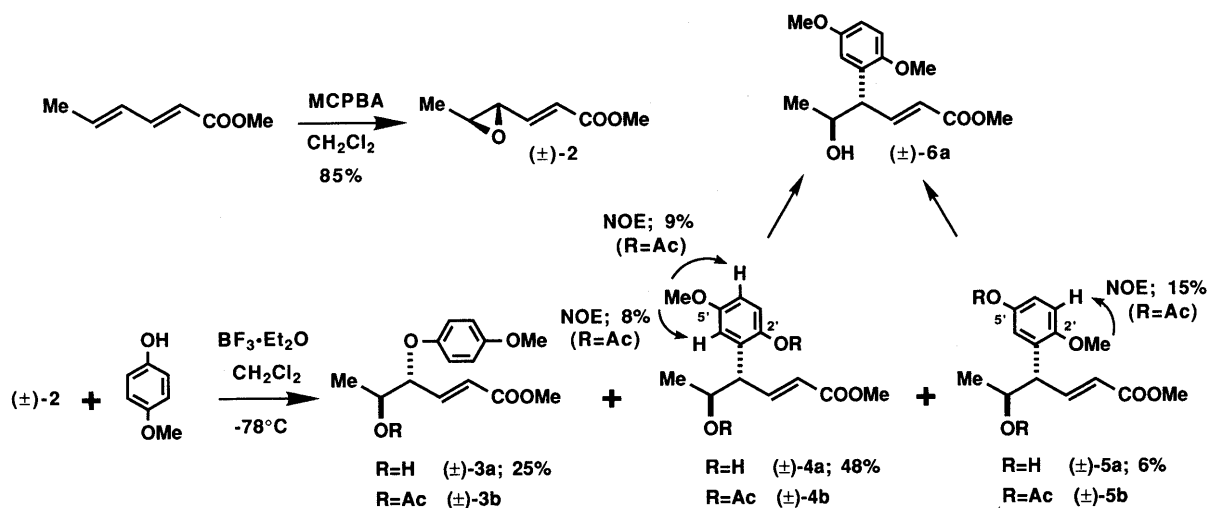
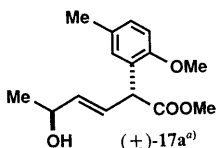


TABLE I

Entry	R ₁	R ₂	R ₃	Products
1	H	H	H	(±)-7a ^a (8%), (±)-8a ^a (31%), (±)-9a ^a (12%)
2	H	H	Me	(±)-10a ^a (17%), (±)-11a ^a (69%)
3	H	Me	H	(±)-12a ^a (9%), (±)-14a ^a (26%), (±)-13a ^a (48%)
4	Me	H	H	(±)-15a ^a (33%)
5 ^b	Me	H	Me	(±)-16a ^a (15%)



a) Products 7a—17a were converted to the corresponding acetates 7b—17b. b) In entry 5, the (±)-2,5-disubstituted product 17a (5%) was additionally obtained.

of (±)-3a, (±)-4a and (±)-5a suggested the structures shown in Table I. In the case of the reaction of (±)-2 and *p*-chlorophenol, the starting materials were recovered.

For the purpose of obtaining selectively the *C*-substituted compound, the reaction of (±)-2 and various kinds of polymethoxybenzene analogues was examined.

ii) The Reaction of (±)-2 and Methoxybenzene Analogues: The reaction of (±)-2 and anisole provided (±)-15a in 33% yield while the reaction of *p*-methoxytoluene yielded (±)-16a (15%) and its regio-isomer (±)-17a (5%, δ 4.57, 1H, d, $J_{2,3}$ = 8 Hz; C₂-H), as shown in Table I. Structure elucidation of (±)-15a and (±)-16a was the same as the case of i). The structure elucidation of (±)-17a will be dealt with in connection with that of the similar compound (±)-18a (see below, and Table II).

iii) The Reaction of (±)-2 and Dimethoxybenzene Analogues: The reaction of (±)-2 and 1,4-dimethoxybenzene provided the two *C*-substitution products ((±)-6a (27%) and (±)-18a (25%, δ 4.57, 1H, d, $J_{2,3}$ = 8 Hz; C₂-H)). Hydrogenation of (±)-6a and the subsequent lactonization produced the (±)- δ -lactone 19. From a decoupling ex-

periment with (±)-19, the coupling constant due to C₄-H and C₅-H was 10 Hz and this result indicates that (±)-6a possessed 4,5-*anti*-configuration.⁷⁾ Compound (±)-18a was also converted into the δ -lactone (±)-20 in the same way as (±)-6a. From a decoupling experiment with (±)-20, the signal due to C₅-H appears as a double quartet at 4.60 ppm ($J_{5,Me}$ = 6 Hz, $J_{4,5}$ = 11 Hz, $J_{4,5}$ = 2 Hz) and the signal due to C₂-H as a double doublet at 3.54 ppm ($J_{2,3}$ = 11 Hz, $J_{2,3}$ = 7 Hz). These data indicate that the starting (±)-18a possessed 2,5-*anti*-configuration. The reaction of (±)-2 and 1,2-dimethoxybenzene afforded (±)-4,5-*anti* 21a (77%), while the reaction of (±)-2 and 1,3-dimethoxybenzene provided (±)-4,5-*anti* 22a (75%) together with (±)-2,5-*anti* 23a (10%, δ 4.53, 1H, d, $J_{2,3}$ = 8 Hz; C₂-H) as given in Table II.

iv) The Reaction of (±)-2 and Trimethoxybenzene Analogues: In order to increase the chemical yield of *C*-substitution product, the reaction of (±)-2 and trimethoxybenzene analogues having greater nucleophilicity of the aromatic ring as compared with mono- or dimethoxybenzene analogues was examined. The results are

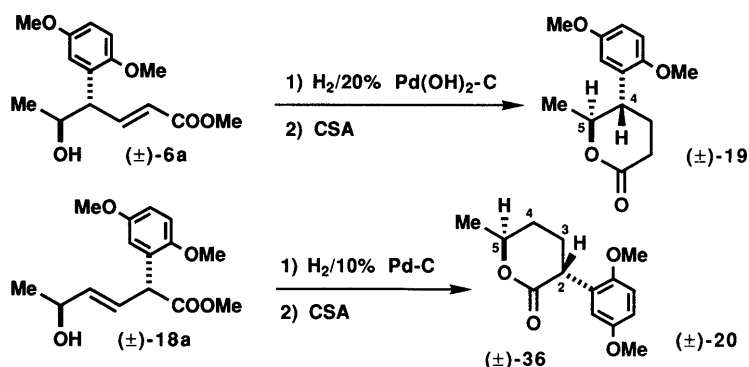
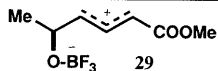


Chart 3

TABLE II

Entry	R ₁	R ₂	R ₃	R ₄	(±)- 6a (27%)	(±)-21a (77%)	(±)-18a (25%)
1	H	H	OMe	H	(±)- 6a (27%)	—	(±)-18a (25%)
2	OMe	H	H	H	—	(±)-21a (77%)	—
3	H	OMe	H	H	(±)-22a (75%)	—	(±)-23a (10%)
4	H	OMe	H	OMe	(±)-24a (91%)	—	—
5	H	OMe	OMe	H	(±)-25a (89%)	—	(±)-26a (7%)
6	OMe	OMe	H	H	(±)-27a (7%)	(±)-28a (7%)	—



Products 6a, 18a, 21a—28a were converted to the corresponding acetates 6b, 18b, 21b—28b.

summarized in Table II. The reaction of (±)-2 and 1,3,5-trimethoxybenzene yielded exclusively (±)-4,5-*anti* 24a (91%). When 1,2,4-trimethoxybenzene was employed, (±)-2,5-*anti* 26a (7%, δ 4.59, 1H, d, $J_{2,3}$ = 8 Hz; C₂-H) and (±)-4,5 *anti* 25a (89%) were obtained. In the case of the reaction of (±)-2 and 1,2,3-trimethoxybenzene, two 4,5-*anti*-4-substitution products ((±)-27a (7%) and (±)-28a (7%)) were obtained. Substitution patterns of the benzene ring of (±)-27a (δ 6.65 and 6.84, each 1H, d, J = 9 Hz; C₅-H or/and C₆-H) and (±)-28a (δ 6.41, 2H, s; C₂-H and C₆-H) were determined as shown in Table II.

The regioselectivity of the nucleophilic reagent toward (±)-2 was found to be subtly affected by the reagents used. In the reaction of (±)-2 with nucleophiles in the presence of BF₃·Et₂O, the possibility of forming the π -allyl complex 29 (see Table II) from (±)-2 should be considered. If the complex formation takes place, then the nucleophilic attack from the less hindered side (*anti*-direction) should give the 4,5-*anti*-4-substituted compounds or the 2,5-*anti*-2-substitution products. In the reaction of (±)-2 and various kinds of methyl-copper reagents, it was reported that the harder nucleophiles attack predominantly the C₄-position while the softer reagents react predominantly at the C₂-position.^{6a)} In the present case, it is difficult to explain the regioselectivity quantitatively on the basis of differences in softness among the nucleophiles used. From the present results, it seemed more reasonable to assume that the

chemical yield of the C-substituted compound at the C₄-position of (±)-2 increases with increasing nucleophilicity of the aromatic ring and carbon-carbon bond formation takes place between the C₄-position of (±)-2 and the *ortho*- or *para*-position of the oxygen-substituted aromatic nucleophile.

Enantioselective Hydrolysis of (±)-4,5-*anti*-5-Acetoxy-4-substituted Esters with Lipase At first, in order to determine the absolute structure and optical purity of the enzymatic reaction products, optically active authentic samples ((4*S*,5*R*)-3a (44% ee), (4*R*,5*R*)-21a (44% ee), (4*R*,5*R*)-22a (44% ee), (4*R*,5*R*)-6a (43% ee), (4*R*,5*R*)-24a (44% ee)) were obtained by the reaction of the known (4*R*,5*R*)-2 (44% ee)⁸⁾ and nucleophiles as described for the racemic compounds (Chart 4).

i) Enantioselective Hydrolysis of (±)-3b with Lipases: Compound (±)-3b was exposed to various kinds of lipases and the results of the enzymatic reaction are shown in Table III. The best result was obtained when the lipase Amano M-10 from *Mucol javanicus* was employed (entry 3). It was found that the stereochemistry of the products depended upon the enzymes used. The absolute structure and optical purity of the hydrolyzed products were confirmed by an analysis of the 400 MHz NMR spectra of their (+)- α -methoxy- α -trifluoromethylacetates ((+)-MTPA ester)⁹⁾ in comparison with the spectra of the authentic (4*S*,5*R*)-3a-(+)-MTPA (δ 3.73, 3H, s; COOMe) and a mixture of two

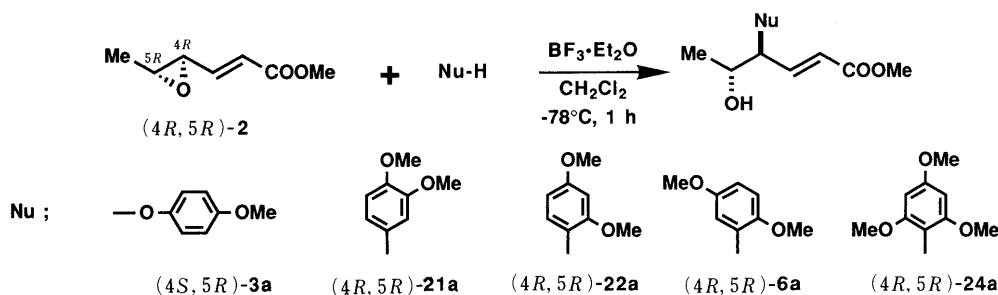
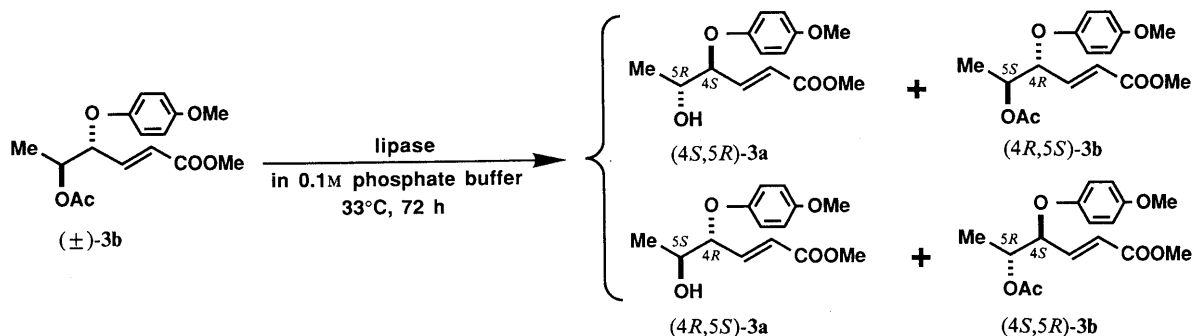


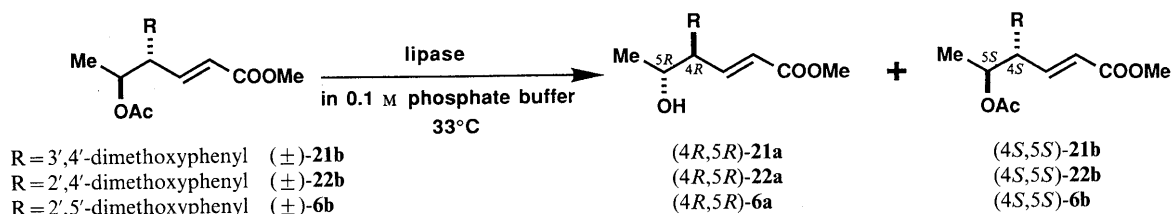
Chart 4

TABLE III



Entry	Substrate (mg)	Lipase	Product (yield, (%), optical purity (% ee))	
1	(93)	Amano A-6 (<i>Aspergillus niger</i>)	(4S,5R)-3a (43%, 68% ee)	(4R,5S)-3b (50%, 47% ee)
2	(92)	Amano A (<i>Aspergillus niger</i>)	(4S,5R)-3a (37%, 75% ee)	(4R,5S)-3b (53%, 34% ee)
3	(95)	Amano M-10 (<i>Mucol javanicus</i>)	(4S,5R)-3a (25%, 92% ee)	(4R,5S)-3b (59%, 28% ee)
4	(120)	Amano F-AP-15 (<i>Rhizopus javanicus</i>)	(4S,5R)-3a (43%, 61% ee)	(4R,5S)-3b (21%, 61% ee)
5	(95)	Amano D-10 (<i>Rhizopus delemar</i>)	(4R,5S)-3a (36%, 42% ee)	(4S,5R)-3b (53%, 48% ee)
6	(95)	OF-360 (<i>Candida cylindracea</i>)	(4R,5S)-3a (37%, 59% ee)	(4S,5R)-3b (8%, 60% ee)

TABLE IV



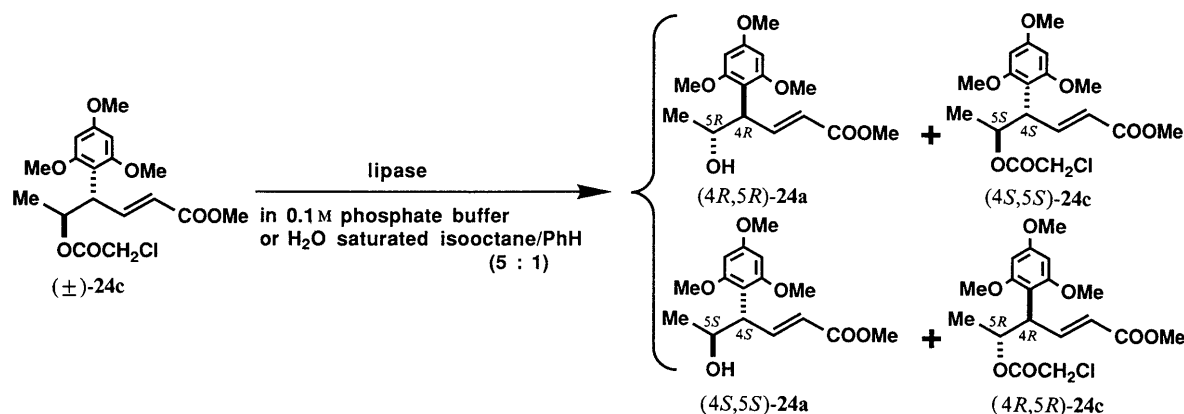
Entry	Substrate (mg)	Lipase	Time (h)	Product (yield (%), optical purity (% ee))	
1	(±)-40, (109)	MY-30 (<i>Candida cylindracea</i>)	72	(4R,5R)-21a (13.6%, >99% ee)	(4S,5S)-21b (82.6%, 16% ee)
2	(±)-40, (115)	OF-360 (<i>Candida cylindracea</i>)	72	(4R,5R)-21a (73.5%, 31% ee)	(4S,5S)-21b (24.1%, 85% ee)
3	(±)-40, (143)	Amano A-6 (<i>Aspergillus niger</i>)	72	(4R,5R)-21a (53.9%, 62% ee)	(4S,5S)-21b (30.8%, 99% ee)
4	(±)-40, (100)	PL 679 (<i>Alcaligenes</i> sp.)	72	(4R,5R)-21a (85.0%, 15% ee)	(4S,5S)-21b (13.0%, 83% ee)
5	(±)-41, (111)	PPL	72	(4R,5R)-22a (5.6%, 84% ee)	(4S,5S)-22b (87.2%, 8% ee)
6	(±)-41, (113)	Nagase P (<i>Pseudomonas</i> sp.)	72	(4R,5R)-22a (14.1%, 87% ee)	(4S,5S)-22b (83.5%, 12% ee)
7	(±)-33, (108)	Amano M-10 (<i>Mucol javanicus</i>)	166	(4R,5R)-6a (68%, 10% ee)	(4S,5S)-6b (21%, 26% ee)
8	(±)-33, (97)	W.G (<i>Wheat germ</i>)	166	(4R,5R)-6a (43%, 90% ee)	(4S,5S)-6b (52%, 67% ee)

(+)-MTPA esters ((4S,5R)-3a-(+)-MTPA and (4R,5S)-3a-MTPA (δ 3.72, 3H, s; COOMe) obtained by the reaction of (±)-3a- and (+)-MTPACl.⁹ The absolute structure and optical purity of the unchanged acetates were also confirmed by the NMR analysis of their (+)-MTPA esters obtained by hydrolysis and subsequent (+)-MTPA esterification.

ii) Enantioselective Hydrolysis of (±)-21b, (±)-22b and (±)-6b: Three kinds of acetates were exposed to the enzymatic reaction using various kinds of lipases, and

selected data are shown in Table IV. In every case, the hydrolyzed products had (4R,5R)-configuration and the unchanged acetates had (4S,5S)-configuration. In the determination of the stereochemistry and the optical purity of the enzymatic reaction products obtained from (±)-21b and (±)-22b, high-performance liquid chromatographic (HPLC) analysis with a chiral column (Chiracel OD (4.6 mm i.d. $\times$ 250 mm)) was employed. Details are given in the experimental section. The enzymatic reaction

TABLE V



Entry	Substrate (mg)	Lipase	Time (h)	Product (yield (%), optical purity (% ee))	
1	(511)	Amano A-6 (<i>Aspergillus niger</i>)	46	$(4R,5R)$ -24a (30%, 85% ee)	$(4S,5S)$ -24c (69%, 37% ee)
2	(129)	Amano A-6 (<i>Aspergillus niger</i>)/Celite	193	$(4R,5R)$ -24a (15%, 94% ee)	$(4S,5S)$ -24c (74%, 5% ee)
3	(100)	Amano M-10 (<i>Mucol javanicus</i>)/Celite	193	$(4R,5R)$ -24a (13%, 96% ee)	$(4S,5S)$ -24c (75%, 2% ee)
4	(110)	Amano A (<i>Aspergillus niger</i>)/Celite	193	$(4R,5R)$ -24a (17%, 90% ee)	$(4S,5S)$ -24c (75%, 10% ee)
5	(105)	OF-360 (<i>Candida cylindracea</i>)/Celite	193	$(4S,5S)$ -24a (49%, 16% ee)	$(4R,5R)$ -24c (43%, 35% ee)

products obtained from $(\pm)$ -6b were identified in the same way as described above [authentic $(4R,5R)$ -6a-(+)-MTPA (δ 3.70, 3H, s; COOMe), a mixture of two (+)-MTPA esters (($4S,5S$)-6a-(+)-MTPA (δ 3.68, 3H, s; COOMe) and ($4R,5R$)-6a-(+)-MTPA)]. From Table IV, it is clear that the desired absolute configuration concerning the 4,5-*anti* stereochemistry can be obtained by the differential usage of lipases.

iii) Enantioselective Hydrolysis of $(\pm)$ -24b and $(\pm)$ -24c: In a preliminary experiment on the hydrolysis of $(\pm)$ -24b with various kinds of lipases in phosphate buffer solution, hydrolysis rarely occurred. So, the substrate was changed to the chloroacetate $(\pm)$ -24c which was obtained by the reaction of $(\pm)$ -24a and chloroacetic anhydride. The enantioselective hydrolysis of $(\pm)$ -24c with lipase or immobilized enzymes on Celite¹⁰ was carried out in phosphate buffer solution or water-saturated organic media, respectively. Selected data are shown in Table V.

The absolute structure and the optical purity of the reaction products were confirmed by the 400 MHz NMR analysis of their (+)-MTPA esters obtained in the same way as described above [authentic $(4R,5R)$ -24a-(+)-MTPA (δ 3.68, 3H, s; COOMe), a mixture of two (+)-MTPA esters (($4R,5R$)-24a-(+)-MTPA and ($4S,5S$)-24a-(+)-MTPA (δ 3.65, 3H, s; COOMe)]. The stereochemistry of the products was found to depend upon the lipases used. The optical purity of $(4R,5R)$ -24a was found to be high when immobilized enzyme was employed in water-saturated organic media (entries 2–4).

In conclusion, $(\pm)$ methyl 4,5-*trans*-epoxy-2-*E*-hexenoate (2) was reacted with aromatic nucleophiles having an electron-donating group in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to provide the 4,5-*anti*-5-hydroxy-4- or/and 2,5-*anti*-5-hydroxy-2-substituted products and the corresponding C_5 -acetates of the 4,5-*anti*-4-substituted products were exposed to the lipases to give the optically active 4,5-disubstituted-2-*E*-hexenoate derivatives. Application of these optically active compounds to the synthesis of optically active natural products is being undertaken.

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 (MgSO_4). All evaporations were performed under reduced pressure.

($\pm$) Methyl (4,5)-*trans*-Epoxy-(2-*E*)-hexenoate (2) A solution of methyl sorbate (25.2 g) and MCPBA (44 g) in CH_2Cl_2 (500 ml) was stirred for 24 h at room temperature. The reaction mixture was filtered and the filtrate was washed with aqueous saturated NaHCO_3 . The organic layer was evaporated to give a residue, which was chromatographed on silica gel (500 g) to afford 2 as a colorless oil (24.2 g, 85% yield). IR: 1720 cm^{-1} . NMR δ : 1.39 (3H, d, $J_{\text{Me},5}=5\text{ Hz}$, 5-Me), 2.97 (1H, dq, $J_{5,\text{Me}}=5\text{ Hz}$, $J_{4,5}=2\text{ Hz}$, 5-H), 3.19 (1H, dd, $J_{4,5}=2\text{ Hz}$, $J_{3,4}=7\text{ Hz}$, 4-H), 3.75 (3H, s, COOMe), 6.13 (1H, d, $J_{2,3}=16\text{ Hz}$, 2-H), 6.69 (1H, dd, $J_{2,3}=16\text{ Hz}$, $J_{3,4}=7\text{ Hz}$, 3-H).

General Procedure of the Reaction of $(\pm)$ -2 and Various Kinds of Nucleophiles in the Presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and Acetylation of Each Product $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (10 mmol) was added to a solution of $(\pm)$ -2 (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 and a catalytic amount of *p*-dimethylaminopyridine (DMAP) 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.

($\pm$) Methyl (4,5)-*anti*-5-Hydroxy-4-(*p*-methoxyphenoxy)-(2-*E*)-hexenoate (3a) and Its Acetate ($\pm$)-3b ($\pm$)-3a: pale yellow oil. 25% yield. Anal. HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5$ (M^+ ; m/z): 266.115. Found: 266.116. IR: 3560 , 1720 , 1650 cm^{-1} . NMR δ : 1.28 (3H, d, $J_{5,\text{Me}}=6\text{ Hz}$, 5-Me), 4.09 (1H, dq, $J_{5,\text{Me}}=6\text{ Hz}$, $J_{4,5}=4\text{ Hz}$, 5-H), 3.73 (3H, s, COOMe), 3.76 (3H, s, 4'-OMe), 4.62 (1H, dd, $J_{3,4}=5\text{ Hz}$, $J_{4,5}=4\text{ Hz}$, 4-H), 6.07 (1H, d, $J_{2,3}=16\text{ Hz}$, 2-H), 6.99 (1H, dd, $J_{2,3}=16\text{ Hz}$, $J_{3,4}=5\text{ Hz}$, 3-H). ($\pm$)-3b: pale yellow oil. 97%

Evaporation of the organic solvent gave an oily product which was subjected to silica gel (40 g) column chromatography. In case of the (+)-MTPA method, the resulting alcohol was converted to the corresponding (+)-MTPA ester and acetate was also converted to the corresponding (+)-MTPA ester after alkaline hydrolysis (K_2CO_3 in MeOH). NMR analysis of the resulting (+)-MTPA ester provided the data summarized in Tables III, IV, and V. In the case of the HPLC method, the resulting alcohol and acetate were directly analyzed and results are shown in Table IV. Chemical yields and $[\alpha]_D$ values of all reaction products were as follows: with lipase Amano M-10; ((4*S*,5*R*)-**3a**, 25% yield, 92% ee, $[\alpha]_D^{25} + 48.3^\circ$ ($c = 0.94$, $CHCl_3$), ((4*R*,5*S*)-**3b**, 59% yield, 28% ee, $[\alpha]_D^{25} - 20.14^\circ$ ($c = 2.87$, $CHCl_3$)), with lipase Amano A-6; ((4*R*,5*R*)-**21a**, 53.9% yield, 62% ee, $[\alpha]_D^{24} - 8.23^\circ$ ($c = 2.10$, $CHCl_3$)), ((4*S*,5*S*)-**21b**, 30.8% yield, 99% ee, $[\alpha]_D^{24} + 10.50^\circ$ ($c = 1.77$, $CHCl_3$)), with lipase "Nagase p; ((4*R*,5*R*)-**22a**, 14.1%, 87% ee, $[\alpha]_D^{24} + 7.30^\circ$ ($c = 1.15$, $CHCl_3$)), (4*S*,5*S*)-**22b**, 83.5% yield, 12% ee, $[\alpha]_D^{24} - 1.47^\circ$ ($c = 4.09$, $CHCl_3$)), with lipase from wheat germ; ((4*R*,5*R*)-**6a**, 43% yield, 90% ee, $[\alpha]_D^{18} - 3.55^\circ$ ($c = 1.52$, $CHCl_3$)), (4*S*,5*S*)-**6b**, 52% yield, 67% ee, $[\alpha]_D^{18} - 4.88^\circ$ ($c = 3.28$, $CHCl_3$)), with lipase Amano A-6; ((4*R*,5*R*)-**24a**, 30% yield, 85% ee, $[\alpha]_D^{27} + 3.23^\circ$ ($c = 1.3$, $CHCl_3$)), ((4*S*,5*S*)-**24c**, 69% yield, 37% ee, $[\alpha]_D^{27} - 0.6^\circ$ ($c = 1.0$, $CHCl_3$)).

Acknowledgement This work was supported by a grant for the Biodesign Research Program from The Institute of Physical and Chemical Research (RIKEN) to H. A.

References and Notes

- 1) A part of this work was published as a preliminary communication: H. Akita, I. Umezawa, M. Takano, H. Matsukura and T. Oishi, *Chem. Pharm. Bull.*, **39**, 3094 (1991).
- 2) Present address: *Meiji College of Pharmacy at Setagaya, 1-35-23, Nozawa, Setagaya-ku, Tokyo 154, Japan.*
- 3) a) H. Akita, H. Matsukura and T. Oishi, *Tetrahedron Lett.*, **27**, 5397 (1986); b) H. Akita, T. Kawaguchi, Y. Enoki and T. Oishi, *Chem. Pharm. Bull.*, **38**, 323 (1990).
- 4) a) *Chem. Abstr.*, **81**, 266 (1974); b) M. Hirama, T. Shigemoto, Y. Yamazaki and S. Ito, *Tetrahedron Lett.*, **26**, 4133 (1985).
- 5) J. Tsuji, H. Kataoka and Y. Kobayashi, *Tetrahedron Lett.*, **22**, 2575 (1981).
- 6) a) T. Ibuka, M. Tanaka, H. Nemoto and Y. Yamamoto, *Tetrahedron*, **45**, 435 (1989); b) M. Miyashita, M. Hoshino, and A. Yoshikoshi, *J. Org. Chem.*, **56**, 6483 (1991).
- 7) The same observation was reported in ref. 6a.
- 8) 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*)-**2**.
- 9) a) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2453 (1969); b) J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).
- 10) O. Hoshino, K. Itoh, B. Umezawa, H. Akita, and T. Oishi, *Tetrahedron Lett.*, **29**, 567 (1988).
- 11) H. Akita, A. Furuichi, K. Koshiji, K. Horikoshi, and T. Oishi, *Chem. Pharm. Bull.*, **31**, 4376 (1983).
- 12) This sample was obtained by the acetylation (Ac_2O -pyridine) of (4*R*,5*R*)-**21a**.
- 13) This sample was obtained by the acetylation (Ac_2O -pyridine) of (4*R*,5*R*)-**22a**.