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Chemoenzymatic Syntheses of Each Stereoisomer of (4,5)-Epoxy-(2*E*)-Hexenoates

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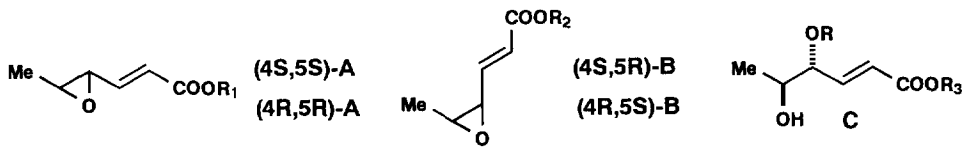
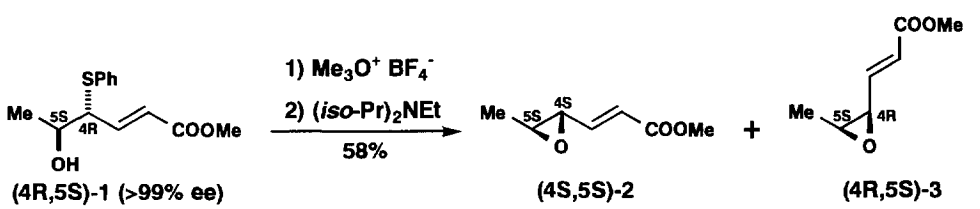
Abstract: The highly stereoselective syntheses of each of the four stereoisomers of (4,5)-epoxy-(2*E*)-hexenoate ((4S,5S)-**2**, (4R,5R)-**2**, (4S,5R)-**3** and (4R,5S)-**3**) based on a chemoenzymatic method were achieved from the achiral precursor, methyl sorbate.

In the course of our synthetic studies on chiral epoxy esters based on enzymatic function and their application to the natural products synthesis,[1] the four stereoisomers of (4,5)-epoxy-(2*E*)-hexenoate ((4S,5S)-**A**, (4R,5R)-**A**, (4S,5R)-**B** and (4R,5S)-**B**) were selected as synthetic targets. The reaction of (4,5)-epoxy (2*E*)-hexenoate **A** and alcohols[2] in the presence of a Lewis acid was reported to give selectively (4,5)-*anti*-disubstituted-(2*E*)-hexenoate **C** while the reaction of **A** and acetoacetate in the presence of a palladium catalyst[3] or methyl-metal reagent[4] was reported to produce (4,5)- or/and (2,5)-disubstituted hexenoate. Application of **C** to the stereoselective synthesis of amino sugars such as (±)-acosamine *via* intramolecular Michael additions was reported.[2] For the above mentioned reasons, enantiomerically pure stereoisomers of (4,5)-epoxy-(2*E*)-hexenoate are expected to be versatile chiral synthons for the syntheses of biologically active compounds such as amino sugars, deoxy sugars and their related compounds.

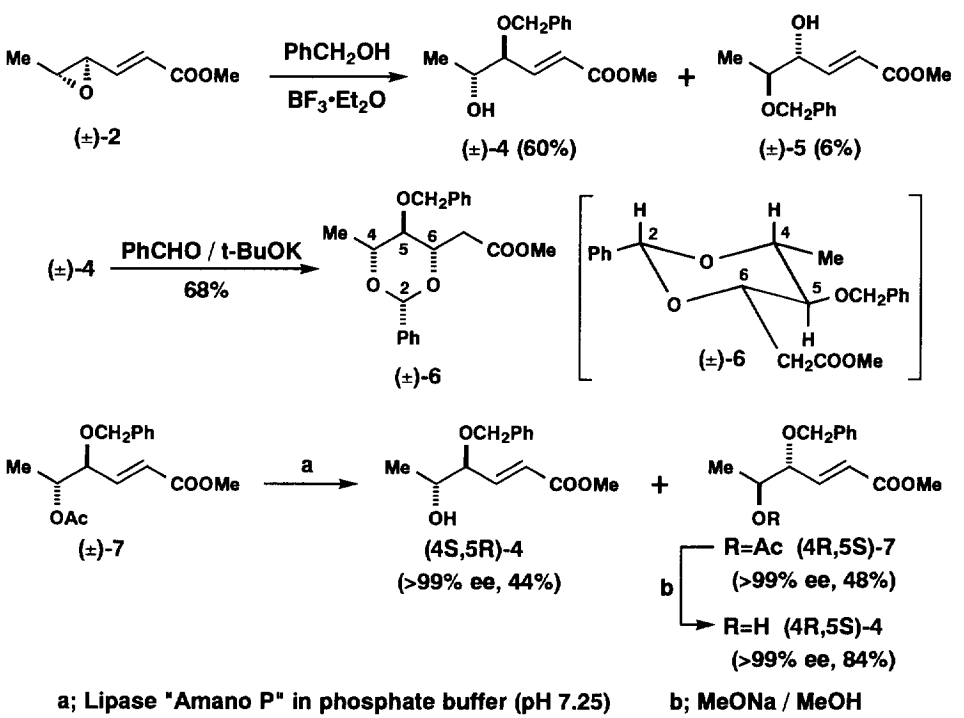


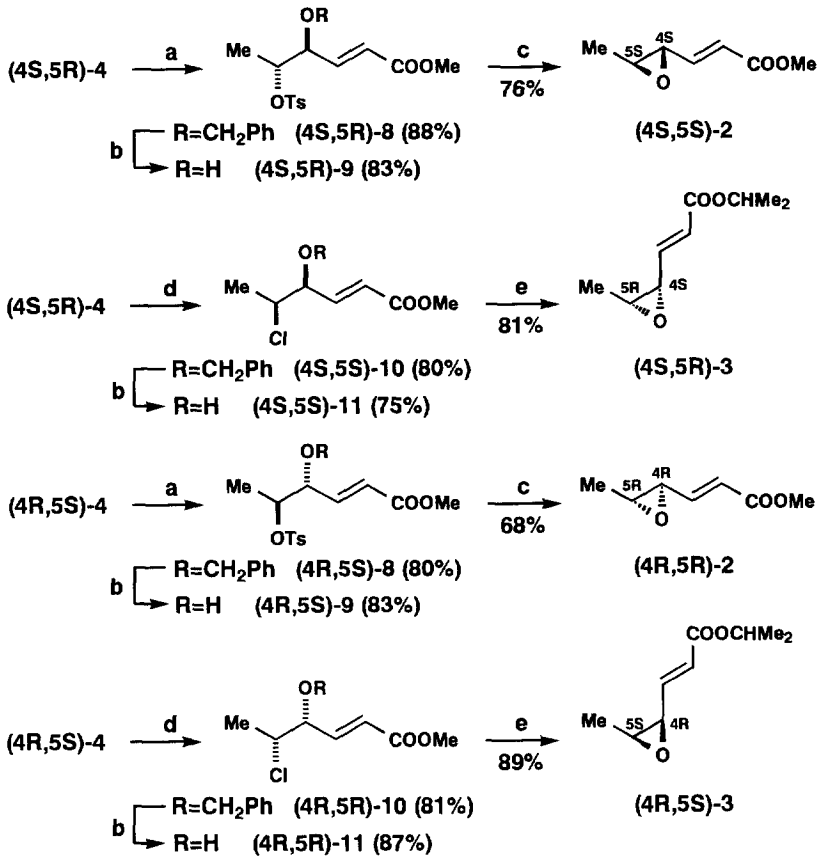
In a previous paper,[5] the sulfonium salt formation of (4R,5S)-**1** with Meerwein's reagent followed by treatment with Hunig's base gave an inseparable mixture (*trans* : *cis* =4:1) of (4S,5S)-*trans* **2** and (4R,5S)-*cis* **3** in 58% yield. In this process, the isomerization to the *cis*-epoxy ester **3** was partly observed, but no loss of enantiomeric purity was detected.



In order to overcome this drawback, we now wish to describe the highly stereoselective syntheses of the four pure diastereomers of (4,5)-epoxy-(2*E*)-hexenoate based on a chemoenzymatic method.

The reaction of (±)-**2**[6] with benzyl alcohol in the presence of BF_3•Et_2O afforded regioselectively the (±)-(4,5)-*anti* **4** (60% yield) and its regioisomer (±)-**5** (6% yield). In order to determine the *anti*-stereochemistry of (±)-**4**, compound (±)-**4** was converted into the acetal (±)-**6** by applying Evans method.[7] The coupling constant of the C_4-axial and the C_5-axial protons of (±)-**6** was 9 Hz, clearly indicating that the starting (±)-**4** possessed the *anti*-configuration. For the purpose of chiral induction, an acetate (±)-**7** derived from (±)-**4** was subjected to the enantioselective hydrolysis using the lipase "Amano P" from *Pseudomonas* sp. in phosphate buffer solution (pH=7.25) to afford the (4S,5R)-5-hydroxy ester **4** ($[\alpha]_D$ +68.2 (c=1.33, $CHCl_3$), >99% ee, 44% yield) and the (4R,5S)-5-acetoxy ester **7** ($[\alpha]_D$ -74.9 (c=1.35, $CHCl_3$), >99% ee, 48% yield). The enantiomeric excess (ee) of the optically active compounds was determined by HPLC on a chiral column (250 X 4.6 mm). The stereochemistry of (4S,5R)-**4** was determined by comparison with an authentic sample (4S,5R)-**4** ($[\alpha]_D$ +30.2 (c=1.27, $CHCl_3$), 44% ee) prepared by the reaction of the known (4R,5R)-**2** ($[\alpha]_D$ +4.0 (c=1.5, $CHCl_3$), 44% ee)[6,8] and benzyl alcohol in the presence of BF_3•Et_2O. Methanolysis of (4R,5S)-**7** with MeONa in MeOH provided the (4R,5S)-**4** ($[\alpha]_D$ -69.5 (c=1.31, $CHCl_3$), >99% ee) in 84% yield.





Thus obtained enantiomerically pure (4S,5R)-**4** was separately converted into the *trans* (4S,5S)-**2** and *cis* (4S,5R)-**3**. Tosylation ((4S,5R)-**8**, $[\alpha]_D$ +49.6 (c=1.39, $CHCl_3$), >99% ee, 88% yield) of (4S,5R)-**4** followed by deprotection of benzyl group with $AlCl_3$ in the presence of *m*-xylene gave the (4S,5R)-**9** ($[\alpha]_D$ +6.0 (c=1.17, $CHCl_3$)) in 83% yield, which was treated with Hunig's base to afford the *trans* (4S,5S)-**2** ($[\alpha]_D$ -9.5 (c=0.60, $CHCl_3$), >99% ee) in 76% yield. In general, benzyl ethers including an inner double bond are cleaved by Birch reduction. In the present deprotection reaction, phenyl-*m*-xylylmethane was isolated as a main product. It can therefore be presumed after formation of an oxonium ion by the assistance of $AlCl_3$ and subsequent trapping of the benzyl cation generated phenyl-*m*-xylylmethane in the manner of a Friedel-Crafts reaction.[9] On the other hand, inversion of C_5-stereochemistry of (4S,5R)-**4** was achieved by applying the modification of Mitsunobu' method.[10] Namely, treatment of (4S,5R)-**4** with N-chlorosuccimide (NCS) in the presence of triphenylphosphine (Ph_3P) produced the (4S,5S)-5-chloride **10** ($[\alpha]_D$ +34.9 (c=0.67, $CHCl_3$), >99% ee) in 80% yield. Deprotection ((4S,5S)-**11**, $[\alpha]_D$ -21.4 (c=1.10, $CHCl_3$), >99% ee, 75% yield) of

benzyl group of (4S,5S)-**10** by the same way as previous case followed by the treatment of NaH in *iso*-PrOH gave the *cis* (4S,5R)-isopropyl ester **3** ($[\alpha]_D$ +46.0 (c=0.94, $CHCl_3$), >99% ee) in 81% yield. No epimerization was observed in the conversions of (4S,5R)-**4** to the *trans* (4S,5S)-**2** and the *cis* (4S,5R)-**3**. By applying the same procedure, the (4R,5S)-**4** was also separately converted to the enantiomerically pure *trans* (4R,5R)-**2** ($[\alpha]_D$ +10.2 (c=0.43, $CHCl_3$), >99% ee) and *cis* (4R,5S)-**3** ($[\alpha]_D$ -49.9 (c=1.10, $CHCl_3$), >99% ee) in essentially the same yields as the previous case.

In conclusion, the highly stereoselective syntheses of the four diastereomers of (4,5)-epoxy-(2*E*)-hexenoate ((4S,5S)-**2**, (4R,5R)-**2**, (4S,5R)-**3** and (4R,5S)-**3**) based on a chemoenzymatic method were achieved from methyl sorbate.

Their application in natural product syntheses is being investigated.

Experimental

General. ^1H NMR spectra were recorded on JEOL EX 4000 spectrometer in $CDCl_3$. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D 300 spectrometer. The fast atom bombardment mass spectra (FAB MS) were obtained with JEOL JMS-DX 303 spectrometer. IR spectra were recorded a JASCO FT/IR-300 spectrometer. The HPLC system was composed of two SSC instruments (ultraviolet (UV) detector 3000B and flow system 3100). Optical rotations were measured in $CHCl_3$ with a JASCO DIP-370 digital polarimeter. For column chromatography , silica gel (Kieselgel 60) was employed.

Methyl (4S*,5R*)-4-Benzyloxy-5-hydroxy-(2*E*)-hexenoate (±)-4 and Methyl (4R*,5S*)-5-Benzyloxy-4-hydroxy-(2*E*)-hexenoate (±)-5 To a solution of (±)-**2** (2.86 g, 20 m mol), benzyl alcohol (4.36 g, 2 equiv) in CH_2Cl_2 (40 ml) at -20°C, BF_3•Et_2O (2.5 ml, 2 equiv) was added and whole mixture was stirred at rt for 1 h, and then diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure. The residue was chromatographed on silica gel (120 g, n-Hexane-EtOAc=5:1) to give (±)-**4** (3.03 g, 60%) and (±)-**5** (0.3 g, 6%) as colorless oils, respectively. (±)-**4**: IR (neat): 3445 cm^{-1} (OH), 1724 (COOMe); ^1H NMR : δ 1.15 (3H, d, *J*=6 Hz, 5-CH_3), 2.50 (1H, br.s, 5-OH), 3.75 (3H, s, COOMe), 3.90 (1H, ddd, *J*=1, 5.5, 7 Hz, 4-H), 3.92-3.97 (1H, m, 5-H), 4.41, 4.63 (each 1H, d, *J*=12 Hz, OCH_2Ph), 6.08 (1H, dd, *J*=1, 16 Hz, 2-H), 6.92 (1H, dd, *J*=7, 16 Hz, 3-H), 7.25-7.38 (5H, m, aromatic-H). HRMS: Found: 251.1260. Calcd. for $C_{14}H_{18}O_4$ $(M+1)^+$; 251.1283. (±)-**5**: IR (neat): 3445 cm^{-1} (OH), 1723 (COOMe); ^1H NMR : δ 1.14 (3H, d, *J*=6 Hz, 5-CH_3), 2.60 (1H, br.s, 4-OH), 3.65 (1H, dq, *J*=4, 6 Hz, 5-H), 3.72 (3H, s, COOMe), 4.40-4.43 (1H, m, 4-H), 4.51, 4.61 (each 1H, d, *J*=12 Hz, OCH_2Ph), 6.13 (1H, dd, *J*=1, 16 Hz, 2-H), 6.91 (1H, dd, *J*=5, 16 Hz, 3-H), 7.25-7.37 (5H, m, aromatic-H). *Anal.* Found: C, 67.07; H,7.50. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H,7.25 %. The racemate (±)-**4** was analyzed to provide well separated peaks (31.0 and 34.8 min) of each enantiomer using a CHIRALCEL OD under the following analytical conditions (eluent, n-Hexane-EtOH (100:1); detection, UV at 254 nm; flow rate, 1.0 ml/min).

(2R*,4R*,5R*,6S*)-5-Benzyloxy-4-methyl-6-methoxycarbonylmethyl-2-phenyl-1,3-dioxane (±)-6 To a solution of (±)-**4** (0.1 g, 0.4 m mol) in 1ml of THF at 0°C was added benzaldehyde (0.15 g, 3 equiv), followed by 4 mg of *t*-BuOK, and the resulting yellow solution was stirred for 45 min at 0°C. The reaction mixture was diluted with H_2O and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (10 g, n-

Hexane-EtOAc=20:1) to afford (±)-**6** (0.1 g, 68%) as a colorless oil. (±)-**6**: ^{1}H NMR : δ 1.45 (3H, d, *J*=6 Hz, 4-CH_3), 2.60 (1H, dd, *J*=8, 16 Hz, CH_2COOMe), 2.82 (1H, dd, *J*=4, 16 Hz, CH_2COOMe), 3.16 (1H, t, *J*=9 Hz, 5-H), 3.65 (3H, s, COOMe), 3.81-3.88 (1H, m, 4-H), 4.12-4.18 (1H, m, 6-H), 4.63, 4.72 (each 1H, d, J=12 Hz, OCH_2Ph), 5.59 (1H, s, 2-H), 7.26-7.50 (5H, m, aromatic-H). *Anal.* Found: C, 70.62; H,6.77. Calcd. for $C_{21}H_{24}O_5$: C, 70.77; H,6.79 %.

Methyl (4S*,5R*)-5-Acetoxy-4-benzyloxy-(2*E*)-hexenoate (±)-7 The secondary hydroxyl group of (±)-**4** (2.01 g, 8 m mol) was acetylated with Ac_2O (1 g) in pyridine (5 ml) in the usual manner to give (±)-**7** (2.1 g, 90%) as a colorless oil. (±)-**7**: IR (neat): 1730 cm^{-1} (OAc, COOMe); ^{1}H NMR : δ 1.23 (3H, d, *J*=6 Hz, 5-CH_3), 2.01 (3H, s, 5-OAc), 3.77 (3H, s, COOMe), 4.03 (1H, ddd, *J*=1, 4, 6 Hz, 4-H), 4.46, 4.64 (each 1H, d, *J*=12 Hz, OCH_2Ph), 5.03 (1H, dq, *J*=4, 6 Hz, 5-H), 6.10 (1H, dd, *J*=1, 16 Hz, 2-H), 6.86 (1H, dd, *J*=6, 16 Hz, 3-H), 7.26-7.36 (5H, m, aromatic-H). *Anal.* Found: C, 65.79; H,6.90. Calcd. for $C_{16}H_{20}O_5$: C, 65.39; H,6.78 %. The racemate (±)-**7** was analyzed to provide well separated peaks (7.4 and 8.6 min) of each enantiomer using a CHIRALCEL AD under the following analytical conditions (eluent, n-Hexane-EtOH (10:1); detection, UV at 254 nm; flow rate, 1.0 ml/min).

Kinetic Hydrolysis of (±)-7 A suspension of (±)-**7** (4.5 g) and lipase "Amano P" (500 mg) in 0.1M phosphate buffer (pH 7.25, 400 ml) was incubated at 33°C for 3 d. After the reaction mixture was filtered through a Celite pad, the filtrate was extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (100 g, n-Hexane-EtOAc=9:1 - 5:1) to give acetate (-)-(4R,5S)-**7** (2.16 g, 48%, $[\alpha]_D^{24}$ -74.9 (c=1.35, $CHCl_3$) corresponds to >99% ee) and alcohol (+)-(4S,5R)-**4** (1.70 g, 44%, $[\alpha]_D^{26}$ +68.2 (c=1.33, $CHCl_3$) corresponds to >99% ee) as colorless oils, respectively. The retention times of (-)-**7** and (+)-**4** were 8.6 and 31.0 min by means of HPLC analysis, respectively.

Synthesis of authentic (+)-(4S,5R)-4 In the same manner as preparation of (±)-**4**, treatment of the reported (+)-(4R,5R)-**2**[6] (0.12 g, 0.87 m mol, $[\alpha]_D$ +4.0 (c=1.5, $CHCl_3$) corresponds to 44% ee) with benzyl alcohol (0.19 g) in the presence of BF_3•Et_2O (0.1 ml) yielded (+)-(4S,5R)-**4** (0.13 g, 67%) as a colorless oil. (+)-**4**: $[\alpha]_D^{22}$ +30.2 (c=1.27, $CHCl_3$) corresponds to 44% ee. The spectral data of (+)-**4** were identical with those of (±)-**4**. The retention times of the present (+)-(4S,5R)-**4** were 31.0 min (72%) and 34.8 min (28%) by means of HPLC analysis.

Methanolysis of (-)-(4R,5S)-7 A solution of (-)-**7** (1.65 g, 6 m mol) in MeOH (4 ml) was added to a solution of 0.5M NaOMe in MeOH (10 ml) at 0°C and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was worked up in the same manner as preparation of (±)-**4** to afford (-)-(4R,5S)-**4** (1.19 g, 84%) as a colorless oil. (-)-**4**: $[\alpha]_D^{21}$ -69.5 (c=1.31, $CHCl_3$) corresponds to >99 % ee. The spectral data of (-)-**4** was identical with tthose of (±)-**4**.

Methyl (4S,5R)-4-Benzyloxy-5-tosyloxy-(2*E*)-hexenoate 8 A mixture of (+)-**4** (5.29g, 20 m mol), TsCl (6.86g, 40 m mol) in pyridine (20 ml) was heated at 40°C for 1 d with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with 1M aqueous HCl, saturated aqueous $NaHCO_3$, saturated brine and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (100 g, n-Hexane-EtOAc = 1:1) to provide (+)-(4S,5R)-**8** (7.50 g, 88%) as a colorless oil. (+)-**8**: $[\alpha]_D^{22}$ +49.6 (c=1.39, $CHCl_3$) corresponds to >99 % ee. IR (neat): 1726 cm^{-1} (COOMe); ^{1}H NMR : δ 1.30 (3H, d, J=6 Hz, 5-CH_3), 2.42 (3H, s, Aromatic-CH_3), 3.75 (3H, s, COOMe), 4.02 (1H, ddd, *J*=2, 4, 6 Hz, 4-H), 4.39, 4.53 (each 1H, d, *J*=12 Hz,

OCH_2Ph), 4.61 (1H, dq, *J*=4, 6 Hz, 5-H), 6.00 (1H, dd, *J*=2, 16 Hz, 2-H), 6.67 (1H, dd, *J*=6, 16 Hz, 3-H), 7.24-7.36 (7H, m, aromatic-H), 7.72 (2H, d, *J*=9 Hz, aromatic-H). FAB MS m/z: 405 $(M+1)^+$.

Methyl (4R,5S)-4-Benzyloxy-5-tosyloxy-(2*E*)-hexenoate 8 A mixture of (-)-**4** (3.4 g, 14 m mol), TsCl (5.2 g, 28 m mol) in pyridine (20 ml) was heated at 40°C for 1 d with stirring. The reaction mixture was worked up by the same way as preparation of (4S,5R)-**8** to afford (-)-(4R,5S)-**8** (4.40 g, 80%) as a colorless oil. (-)-**8**: $[\alpha]_D^{24}$ -49.3 (c=1.17, $CHCl_3$) corresponds to >99 % ee. The spetral data were identical with those of (4S,5R)-**8**.

Methyl (4S,5R)-4-Hydroxy-5-tosyloxy-(2*E*)-hexenoate 9 To a well stirred solution of $AlCl_3$ (4.95 g, 37 m mol) in CH_2Cl_2 (60 ml) at -20°C, a solution of (4S,5R)-**8** (7.50 g, 18 m mol) in *m*-xylene (20 ml) was added and whole mixture was stirred for 1 h at the same temperature. The reaction mixture was poured on ice and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. Evaporation of the organic layer under reduced pressure gave a residue, which was chromatographed on silica gel (160 g, n-Hexane-EtOAc = 5:1) to afford (+)-(4S,5R)-**9** (4.84 g, 83%) as a colorless oil. (+)-**9**: $[\alpha]_D^{23}$ +6.0 (c=1.17, $CHCl_3$) corresponds to >99 % ee. IR (neat): 3500 cm^{-1} (OH), 1725 (COOMe); ^1H NMR : δ 1.20 (3H, d, *J*=6 Hz, 5-CH_3), 2.46 (3H, s, aromatic-CH_3), 2.64 (1H, d, *J*=5 Hz, 4-OH), 3.74 (3H, s, COOMe), 4.45-4.50 (1H, m, 4-H), 4.67 (1H, dq, *J*=3, 6 Hz, 5-H), 6.12 (1H, dd, *J*=2, 16 Hz, 2-H), 6.78 (1H, dd, *J*=4, 16 Hz, 3-H), 7.36, 7.80 (each 2H, d, *J*=9 Hz, aromatic-H). FAB MS m/z: 315 $(M+1)^+$.

Methyl (4R,5S)-4-Hydroxy-5-tosyloxy-(2*E*)-hexenoate 9 In the same manner as preparation of (4S,5R)-**9**, treatment of (-)-**8** (4.73g, 12 m mol) with $AlCl_3$ (3.1 g, 23 m mol) in a mixed solvent of *m*-xylene (20 ml) and CH_2Cl_2 (100 ml) yielded (-)-(4R,5S)-**9** (3.07 g, 83%) as a colorless oil. (-)-**9**: $[\alpha]_D^{23}$ -6.0 (c=1.28, $CHCl_3$) corresponds to >99 % ee. The spectral data were identical with those of (4S,5R)-**9**.

Methyl (4S,5S)-4,5-Epoxy-(2*E*)-hexenoate 2 A mixture of (+)-**9** (3.04 g, 10 m mol), Hunig's base (*iso*-Pr)$_2$NEt (6.27 g, 50 m mol) in CH_3CN (10 ml) was heated at 60 °C for 12 h with stirring. The reaction mixture was directly subjected to chromatography on silica gel (80 g, n-Hexane-EtOAc = 9:1) to give (-)-(4S,5S)-**2** (1.05 g, 76%) as a colorless oil. (-)-**2**: $[\alpha]_D^{26}$ -9.5 (c=0.60, $CHCl_3$) corresponds to >99 % ee. *Anal.* Found: C, 58.65; H,7.08. Calcd. for $C_7H_{10}O_3$: C, 59.15; H,7.09 %. FAB MS m/z: 143 $(M+1)^+$. The spectral data of (-)-**2** was identical with those of (±)-**2**. The racemate (±)-**2** was analyzed to provide well separated peaks (13.6 and 14.6 min) of each enantiomer using a CHIRALCEL OJ under the following analytical conditions (eluent, n-Hexane-EtOH (100:1); detection, UV at 254 nm; flow rate, 1.0 ml/min). The retention time of (-)-**2** was 13.6 min.

Methyl (4R,5R)-4,5-Epoxy-(2*E*)-hexenoate 2 A mixture of (-)-**9** (1.86 g, 6 m mol), Hunig's base (*iso*-Pr)$_2$NEt (2.5 g, 19 m mol) in CH_3CN (5 ml) was heated at 60 °C for 12 h with stirring. The reaction mixture was worked up by the same way as preparation of (4S,5S)-**2** to provide (+)-(4R,5R)-**2** (0.57 g, 68%) as a colorless oil. (+)-**2**; $[\alpha]_D^{26}$ +10.2 (c=0.43, $CHCl_3$) corresponds to >99 % ee. The spectral data were identical with those of (4S,5S)-**2**. The retention time of (+)-**2** was 14.6 min.

Methyl (4S,5S)-4-Benzyloxy-5-chloro-(2*E*)-hexenoate 10 A mixture of (+)-**4** (1.85 g, 7 m mol), NCS (2.96 g, 22 m mol), Ph_3P (5.84 g, 22 m mol) in CH_3CN (15 ml) with stirred for 3 h at 0 °C. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was washed with saturated brine and dried over $MgSO_4$. The organic layer was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (50 g, n-Hexane-EtOAc = 19:1) to afford (+)-(4S,5S)-**10** (1.58 g, 80%) as a colorless oil. (+)-**10**: $[\alpha]_D^{30}$ +34.9 (c=0.67, $CHCl_3$) corresponds to >99 % ee. IR (neat): 1726 cm^{-1} (COOMe); ^1H NMR : δ 1.46 (3H, d, *J*=6 Hz, 5-CH_3), 3.78 (3H, s, COOMe), 4.07-4.14 (2H,m, 4- and

5-H), 4.46, 4.65 (each 1H, d, *J*=12 Hz, OCH_2Ph), 6.14 (1H, d, *J*=16 Hz, 2-H), 6.95 (1H, dd, *J*=6, 16 Hz, 3-H), 7.28-7.38 (5H, m, aromatic-H). FAB MS m/z: 269 $(M+1)^+$.

Methyl (4R,5R)-4-Benzyloxy-5-chloro-(2*E*)-hexenoate 10 A mixture of (-)-**4** (2.04g, 8 m mol), NCS (3.28 g, 24 m mol), Ph_3P (6.44 g, 24 m mol) in CH_3CN (20 ml) with stirred for 3 h at 0 °C. The reaction mixture was worked up by the same way as preparation of (4S,5S)-**10** give (-)-(4R,5R)-**10** (1.78 g 81%) as a colorless oil. (-)-(4R,5R)-**10**: $[\alpha]_D^{24}$ -38.3 (c=0.98, $CHCl_3$) corresponds to >99 % ee. The spectral data were identical with those of (4S,5S)-**10**.

Methyl (4S,5S)-5-Chloro-4-hydroxy-(2*E*)-hexenoate 11 In the same manner as preparation of (4S,5R)-**9**, treatment of (+)-**10** (1.38 g, 5 m mol) with $AlCl_3$ (1.37 g, 10 m mol) in a mixed solvent of *m*-xylene (6 ml) and CH_2Cl_2 (30 ml) yielded (-)-(4S,5S)-**11** (0.69 g, 75%) as a colorless oil. (-)-**11**: $[\alpha]_D^{30}$ -21.4 (c=1.10, $CHCl_3$) corresponds to >99 % ee. IR (neat): 3458 cm^{-1} (OH), 1724 (COOMe); ^1H NMR : δ 1.57 (3H, d, *J*=7 Hz, 5-CH_3), 2.51 (1H, br.s, 4-OH), 3.76 (3H, s, COOMe), 4.09 (1H, dq, *J*=5, 7 Hz, 5-H), 4.33 (1H, br.s, 4-H), 6.18(1H, dd, *J*=2, 16 Hz, 2-H), 6.95 (1H, dd, *J*=5, 16 Hz, 3-H),. FAB MS m/z: 179 $(M+1)^+$.

Methyl (4R,5R)-5-Chloro-4-hydroxy-(2*E*)-hexenoate 11 In the same manner as preparation of (4S,5R)-**11**, treatment of (-)-**10** (1.66 g, 6 m mol) with $AlCl_3$ (1.65 g, 12 m mol) in a mixed solvent of *m*-xylene (6 ml) and CH_2Cl_2 (30 ml) yielded (-)-(4R,5R)-**11** (0.96 g, 87%) as a colorless oil. (+)-**11**: $[\alpha]_D^{26}$ +19.5 (c=0.93, $CHCl_3$) corresponds to >99 % ee. The spectral data were identical with those of (4S,5S)-**11**.

Isopropyl (4S,5R)-4,5-Epoxy-(2*E*)-hexenoate 3 A mixture of (-)-**11** (0.57 g, 3 m mol), 50% NaH (0.26 g, 6 m mol) in *iso*-PrOH (12 ml) was stirred for 30 min at 0 °C. The reaction mixture was directly subjected to chromatography on silica gel (60 g, n-Hexane) to provide (+)-(4S,5R)-**3** (0.44 g, 81%) as a colorless oil. (+)-**3**: $[\alpha]_D^{26}$ +46.0 (c=0.94, $CHCl_3$) corresponds to >99 % ee. IR (neat): 1717 cm^{-1} ($COOCHMe_2$); ^1H NMR : δ 1.28 (6H, d, *J*=6 Hz, $CHMe_2$), 1.30 (3H, d, *J*=6 Hz, 5-CH_3), 3.31 (1H, dq, *J*=5, 6 Hz, 5-H), 3.51 (1H, ddd, *J*=1, 5, 6 Hz, 4-H), 5.08 (1H, septete, *J*=6 Hz, $CHMe_2$), 6.11 (1H, d, *J*=16 Hz, 2-H), 6.78 (1H, dd, *J*=6, 16 Hz, 3-H). *Anal.* Found: C, 63.11; H,8.65. Calcd. for $C_9H_{14}O_3$: C, 63.51; H,8.29 %. FAB MS m/z: 171 $(M+1)^+$. The racemate (±)-**3** was analyzed to provide well separated peaks (7.4 and 8.4 min) of each enantiomer using a CHIRALCEL OJ under the following analytical conditions (eluent, n-Hexane-EtOH (100:1); detection, UV at 254 nm; flow rate, 1.0 ml/min). The retention time of (+)-**3** was 7.4 min.

Isopropyl (4R,5S)-4,5-Epoxy-(2*E*)-hexenoate 3 A mixture of (+)-**11** (0.87 g,5 m mol), 50% NaH (0.4 g,10 m mol) in *iso*-PrOH (16 ml) was stirred for 30 min at 0 °C. The reaction mixture was worked up by the same way as preparation of (4S,5R)-**3** to provide (-)-(4R,5S)-**3** (0.74 g, 89%) as a colorless oil. (-)-**3**: $[\alpha]_D^{24}$ -49.9 (c=1.10 $CHCl_3$) corresponds to >99 % ee. The spectral data were identical with those of (4S,5R)-**3**. The retention time of (-)-**3** was 8.4 min.

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