Preparation of Optically Active γ-Hydroxyethyl α,β-Unsaturated γ-Lactone Using an Enzymatic Procedure

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γ-Hydroxyethyl α,β-unsaturated γ-lactone (2) is a promising intermediate for the synthesis of eldanolide and *cis,cis*-1,2,3-trisubstituted cyclopentane, which could be converted to 11-deoxyprostaglandins. In order to prepare optically active 2, enzymatic hydrolysis of (±)-*trans*-cyclohexene-4,5-diacetate with *Pseudomonas fluorescens* lipase was examined, and the monoalcohol ((−)-6, >99% ee) with *R*-configuration was obtained in accord with prediction based on the three-site model proposed by us. Compound (−)-6 could be converted to the chiral lactone ((−)-2) *via* a sequence of reactions involving ring cleavage.

Keywords enzymatic hydrolysis; *Pseudomonas fluorescens* lipase; pig liver esterase; enantioselective hydrolysis; cosolvent; γ-substituted α,β-unsaturated γ-lactone; kinetic resolution; *trans*-cyclohexene-4,5-diol

γ-Hydroxyethyl α,β-unsaturated γ-lactone (**2**) is a key intermediate for the synthesis of eldanolide,[1] and can be readily prepared from 2,6-dioxabicyclo[3.3.0]octane-3,7-dione, which is available from *trans*-3-hexenedioic acid by our method.[1] Previously, we described the synthesis of *cis,cis*-1,2,3-trisubstituted cylopentanes in a stereocontrolled manner from this lactone, and its application to the synthesis of 11-deoxyprostaglandins.[2] In connection with these syntheses, we have undertaken the preparation of optically active **2** using an enzymatic procedure.[3]

Enantioselective hydrolysis of the acetate ((±)-**1**) was examined using 11 species of enzymes (Table I). However, this hydrolysis resulted in low enantioselectivity, and even the highest optical purity[4] was only 59.4% ee, which was observed in the acetate ((−)-**1**) recovered from hydrolysis with pig liver esterase (PLE) (entry 1). *Pseudomonas fluorescens* lipase[5] (PFL) also afforded merely the alcohol ((−)-**2**) of low optical purity (58.2% ee), in addition to the acetate ((+)-**1**) of 33% ee (entry 2). The effect[6] of an organic cosolvent on hydrolysis with PEL was also studied. Addition of isopropylether in the ratio (v/v) of 1 to 6 (buffer solution) considerably raised the optical purity (63.8% ee) of the recovered acetate ((+)-**1**), but the optical purity of (−)-**2** was not affected under the conditions employed (entry 3).

Next, our attention was directed to the hydrolysis of (±)-*trans*-cyclohexene-4,5-diacetate((±)-**5**) with PFL, because the three-site model[7] proposed by us for the hydrolysis with PFL predicts formation of the alcohol with *R*-configuration. Cyclohexa-1,4-diene (**3**) was converted to the (±)-*trans*-diol ((±)-**4**, 65%) *via* epoxidation with *m*-chloroperbenzoic acid (MCPBA) followed by treatment with 1% aqueous H_2SO_4. The diacetate (**5**) fits the requirements for the three-site model. Hydrolysis of (±)-**5** with PFL afforded the monoalcohol ((−)-**6**) (>99% ee) and the recovered acetate ((+)-**5**) (93% ee) (Table II, entry 2).[8] The

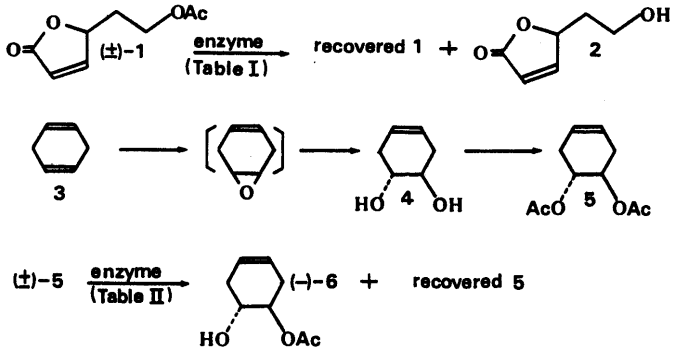

Chart 1

TABLE I. Enantioselective Hydrolysis of (±)-**1**

Entry	Enzyme	Recovered acetate (**1**)			Product (**2**)		
		Yield (%)	ee (%)	Ab. conf.	Yield (%)	ee (%)	Ab. conf.
1	A	30.0	59.4	*R*	62.7	21.2	*S*
2	B	65.9	33.0	*S*	18.0	58.2	*R*
3[a]	B	42.8	63.8	*S*	56.0	50.8	*R*
4	C	46.0	16.5	*S*	19.9	5.6	*R*
5	D	71.2	5.2	*S*	5.5	24.8	*R*
6	E	65.0	25.4	*S*	30.0	40.9	*R*
7	F	77.5	4.0	*R*	6.6	14.7	*S*

A, pig liver esterase; B, *Pseudomonas fluorescens* lipase (Amano P); C, *Aspergillus niger* lipase (Amano A-6); D, *Mucol javanicus* lipase (Amano M); E, *Pseudomonas P. fragi* (Lipase Thermophilic); F, porcine pancreas lipase. *a*) Enzyme B (120 mg) was used for substrate ((±)-**1**) (50 mg), and isopropyl ether was added in the ratio (v/v) of 1 to 6 (buffer solution).

TABLE II. Enantioselective Hydrolysis of (±)-**5**

Entry	Enzyme	Recovered acetate (**5**)			Product (**6**)		
		Yield (%)	ee (%)	Ab. conf.	Yield (%)	ee (%)	Ab. conf.
1	A	60.0	10.5	*S,S*	40.0	15.7	*R,R*
2	B	51.5	93.0	*S,S*	46.5	99.0	*R,R*

A, pig liver esterase; B, *Pseudomonas fluorescens* lipase (Amano P). Reaction times: 1—5 h.

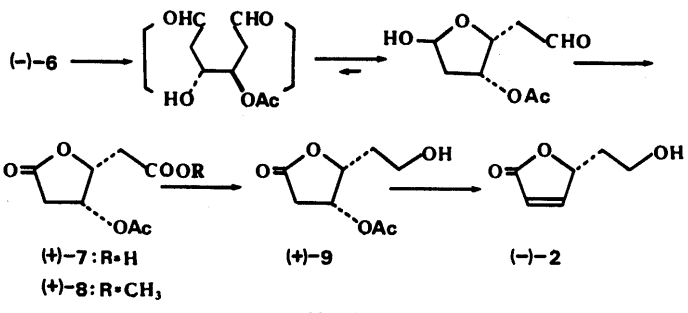

Chart 2

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absolute stereochemistry of (−)-**6** was determined to be (1*R*,2*R*) by converting it to the enantiomer ($[\alpha]_D^{28}$ −37.3° (H_2O)) of a known compound[9] ((1*S*,2*S*)-cyclohexane-1,2-diol, $[\alpha]_D^{22}$ +46.5° (H_2O)) *via* catalytic hydrogenation (H_2/5%Pd–C/EtOH) followed by hydrolysis with K_2CO_3/MeOH. This conclusion is in good agreement with our prediction.

Conversion of (−)-**6** to the optically active alcohol ((−)-**2**) was achieved as follows (Chart 2). Compound (−)-**6** (>99% ee) was subjected to ozone oxidation at −78°C. The acetal structure of the oxidation product was confirmed by the signals of aldehyde proton at δ 9.68 (1H) and hemi-acetal proton at δ 5.65 (1H) in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. Jones oxidation of the crude lactol afforded the lactone ((+)-**7**) (62% from (−)-**6**) ($[\alpha]_D^{23}$ +9.77° ($CHCl_3$)). The structure of (+)-7 was determined by converting it to the ester ((+)-**8**) (95%, $[\alpha]_D^{22}$ +10.3° ($CHCl_3$)), the ^{1}H-NMR spectrum of which showed the signals of COOMe δ 3.37 (3H, s) and OCOMe δ 2.10 (3H, s), in addition to absorption bands at 1780 and 1740 cm^{-1} in the infrared (IR) spectrum. Reduction of the carboxyl function in (+)-7 with $BH_3 \cdot Me_2S$ to give the alcohol ((+)-**9**) ($[\alpha]_D^{20}$ +49.4° ($CHCl_3$)), followed by elimination of the acetoxy function with 1,8-diazabicyclo-[5.4.0]undec-7-ene(DBU)/tetrahydrofuran (THF) provided the optically active alcohol ((*R*)-(−)-**2**) ($[\alpha]_D^{21}$ −46.4° ($CHCl_3$)) (35% from (+)-**7**). The optical purity of (−)-**2** was reconfirmed to be >99% ee by converting it to the (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester.[4] Thus, the chiral lactone ((−)-**2**) may be useful as a synthon for the synthesis of eldanolide and 11-deoxy-prostaglandins.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer, ^{1}H-NMR spectra on a JEOL JNM-FX 100 spectrometer unless otherwise stated, and mass spectra (MS) on a JEOL JMS-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel 60F_{254} plates (Merck). All organic solvent extracts were washed with saturated brine and dried over anhydrous sodium sulfate. The percentage ratios of solvent systems in column chromatography refer to v/v.

General Procedure for the Enzymatic Hydrolysis in Table I. A Typical Example (Entry 1) A mixture of substrate (±)-**1** (42 mg) and PLE (5 mg) was stirred in 0.1 M phosphate buffer (12 ml) at 30 °C, and hydrolysis was terminated by extracting the mixture with AcOEt, when spots of the alcohol and the acetate appeared in the same ratio on TLC. Hydrolysis times were more than 20 h except for the cases (2—3 h) of entries 1 and 3. The AcOEt extract was washed and dried, then concentrated *in vacuo* to leave an oily residue, which was purified by column chromatography on silica gel with 5—20% AcOEt in hexane.

In addition to the enzymes shown in Table I, *Aspergillus niger* lipase (Amano A), *Rizopus delemer* lipase, electric eel cholinesterase, *Rhizopus javanicus* lipase (Amano F-AP-15), and *Candida cylindracea* lipase were also examined, but noteworthy results were not obtained.

Enzymatic hydrolysis as summarized in Table II was carried out in a manner similar to the case of Table I. Hydrolysis of the diacetate (±)-**5** (110 mg) with PFL (55 mg) afforded the monoalcohol ((−)-**6**) (41 mg, 46.5%) and the recovered acetate ((+)-**5**) (57 mg, 51.5%). (−)-**6** (entry 2): mp 71 °C (from AcOEt and hexane). $[\alpha]_D^{22}$ −121.6° (c=0.86, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s, $COCH_3$), 3.90 (1H, m, CHO-), 4.84 (1H, m, CHOCO), 5.54—5.59 (2H, m, CH=CH). IR (Nujol): 3450, 1730, 1650, 1180, 1045 cm^{-1}. MS *m/z*: 157 (M+1), 156 (M^+), 138, 96. (+)-**5** (entry 2): colorless oil. $[\alpha]_D^{22}$ +50.8° (c=1.23, $CHCl_3$) (93% ee).

(±)-*trans*-1-Cyclohexene-4,5-diol ((±)-4) MCPBA (80% purity, 5.51 g, 25.5 mmol) in CH_2Cl_2 (140 ml) was added dropwise to a stirred solution of **3** (2.01 g, 25 mmol) in CH_2Cl_2 (20 ml) at 0°C over 0.5 h. After addition of 5% aqueous $NaHCO_3$ (70 ml), the whole was stirred for 2.5 h, and the CH_2Cl_2 layer was successively washed with 10% aqueous $NaHSO_3$ (40 ml) and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to cleavage of the epoxide without being purified. Then 1% aqueous H_2SO_4 (170 ml) was added dropwise to a stirred solution of the epoxide in THF (170 ml), and the whole was stirred for 4 h at 0 °C, and for 0.5 h at room temperature. Repeated extraction with AcOEt (50 ml × 10) afforded a white solid, which was subjected to silica-gel column chromatography (35 g). The fraction eluted with 50% AcOEt in hexane afforded (±)-**4** (1.85 g, 65%) as colorless needles, which were recrystallized from hexane and AcOEt, mp 95 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (2H, m, CHO-×2), 5.54 (2H, d, J=2.9 Hz, CH=CH). IR (Nujol): 3350, 1655, 1350 cm^{-1}. MS *m/z*: 114 (M^+), 96, 60.

(±)-*trans*-4,5-Diacetoxy-1-cyclohexene ((±)-5) The diacetate ((±)-**5**) was prepared from (±)-**4** by conventional acetylation (Ac_2O/pyridine). (±)-**5**: colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (6H, s, COMe), 5.08 (2H, m, CHOAc×2), 5.58 (2H, t, J=0.6 Hz, CH=CH). IR (neat): 3050, 1735, 1650, 1045 cm^{-1}. MS *m/z*: 198 (M^+), 155, 78, 43.

(4*R*,5*R*)-4-Acetoxy-5-carboxymethyl-tetrahydro-2-furanone ((+)-7) Ozone gas was bubbled into a solution of (−)-**6** (100 mg, >99% ee) in CH_2Cl_2 (16 ml) at −78 °C, and the reaction was monitored by TLC. The resulting ozonide was decomposed with Zn powder (400 mg) and AcOH (2 ml) at 10—20 °C. The Zn powder was filtered off, and the filtrate was concentrated *in vacuo* to leave an oily residue, which was subjected to Jones oxidation in acetone (10 ml) at 0 °C. The crude oil obtained in this manner was purified by column chromatography on silica gel. The fraction eluted with 50% AcOEt in hexane afforded (+)-**7** (81 mg, 62%) as a colorless oil. $[\alpha]_D^{23}$ +9.77° (c=0.45, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 5.06 (1H, m, CHOCO), 5.55 (1H, m, CHOCO). IR (neat): 3200—3300, 1700—1800, 1375 cm^{-1}.

(4*R*,5*R*)-4-Acetoxy-5-methoxycarbonylmethyl-tetrahydro-2-furanone ((+)-8) The ester ((+)-**8**) was obtained by treatment of (+)-**7** with CH_2N_2. (+)-**8**: colorless oil (95%). $[\alpha]_D^{22}$ +10.3° (c=0.73, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, OCOMe), 3.73 (3H, s, COOMe), 5.00 (1H, m, CHOCO), 5.55 (1H, m, CHOCO). IR (neat): 1780, 1740, 1380, 1160 cm^{-1}. MS *m/z*: 216 (M^+), 516, 43.

(4*R*,5*R*)-4-Acetoxy-5-(2-hydroxyethyl)-tetrahydro-2-furanone ((+)-9) $BH_3 \cdot Me_2S$ (0.05 ml, 0.5 mmol) was added to a stirred solution of (+)-**7** (50 mg, 0.248 mmol) in THF (5 ml) at 0°C. After 2 h, the reaction was terminated by addition of MeOH (2 ml), and the solvent was removed *in vacuo* to leave an oily residue, which was chromatographed on silica gel. The fraction eluted with 50% AcOEt in hexane afforded (+)-**9** (20 mg, 43%) as a colorless oil. $[\alpha]_D^{20}$ +49.4° (c=0.68, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s, OCOME), 3.82 (2H, dd, J=5.2, 6.6 Hz, CH_2O-), 4.76 (1H, m, CHOCO), 5.50 (1H, m, CHOCO). IR (neat): 3450, 1780, 1740, 1235, 1040 cm^{-1}. MS *m/z*: 189 (M+1), 157, 145, 128.

(*R*)-5-(2-Hydroxyethyl)-2,5-dihydro-2-furanone ((−)-2) Compound (+)-**9** (90 mg, 0.479 mmol) in benzene (12 ml) and THF (6 ml) was stirred in the presence of DBU (40 mg, 0.262 mmol) at 0°C. After 8 h, the reaction mixture was diluted with brine, and extracted with AcOEt. The AcOEt extract was washed with 5% aqueous HCl, and brine, then dried. The solvent was removed *in vacuo* to afford an oily residue, which was subjected to silica-gel column chromatography. The fraction eluted with 60% AcOEt in hexane afforded (−)-**2** (51 mg, 81%) as a colorless oil. $[\alpha]_D^{21}$ −46.4° (c=0.91, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 3.83 (2H, t, J=5.2 Hz, CH_2O), 5.26 (1H, m, CHOCO), 6.10 (1H, dd, J=2.0, 5.8 Hz, COCH=), 7.58 (1H, dd, J=1.5, 5.8 Hz, CH=). IR (neat): 3400, 1740, 1600, 1050 cm^{-1}. MS *m/z*: 128 (M^+), 110, 83, 82, 55, 31.

References and Notes

1) M. Hizuka, N. Hayashi, T. Kamashita, H. Suemune, and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1550 (1988).
2) M. Hizuka, C. Fang, H. Suemune, and K. Sakai, *Chem. Pharm. Bull.*, **37**, 1185 (1989).
3) For a review, see J. B. Jones, *Tetrahedron*, **42**, 3351 (1986).
4) The optical purity of **2** was determined by 270 MHz ($CDCl_3$) ^{1}H-NMR spectroscopy after conversion to the corresponding MTPA ester. The absolute stereochemistry was determined by conversion to a known compound (see R. Bloch and M. Seck, *Tetrahedron Lett.*, **28**, 5819 (1987)) *via* Jones oxidation followed by esterification with CH_2N_2. The optical purity of **1** was determined in a manner similar to the case of **2**, after hydrolysis with K_2CO_3/MeOH followed by conversion to the MTPA ester.
5) Z.-F. Xie, H. Suemune, and K. Sakai, *J. Chem. Soc., Chem. Commun.*, **1987**, 838.

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6) *a*) V. Kerscher and W. Kreiser, *Tetrahedron Lett.*, **28**, 531 (1987); *b*) G. Guanti, L. Banfi, E. Narisano, R. Riva, and S. Thea, *ibid.*, **27**, 4639 (1986); *c*) D. Breitgoff, K. Laumen, and M. Schneider, *J. Chem. Soc., Chem. Commun.*, **1986**, 1523.
7) Z.-F. Xie, I. Nakamura, H. Suemune, and K. Sakai, *J. Chem. Soc., Chem. Commun.*, **1988**, 966.
8) The optical purity of **6** was determined by 270 MHz ^{1}H-NMR spectroscopy after converson to the corrsponding MTPA ester. The optical purity of the recovered acetate (**5**) was determined by converting it to **6** after partial hydrolysis with K_2CO_3/MeOH.
9) The difference of absolute specific rotation values between (−)-37.3° and (+)-46.5° (see Th. Posternak, D. Reymond, and H. Friedli, *Helv. Chim. Acta*, **1955**, 205) can not be explained.

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