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Enzymatic Procedure for the Synthesis of Prostaglandin A_2

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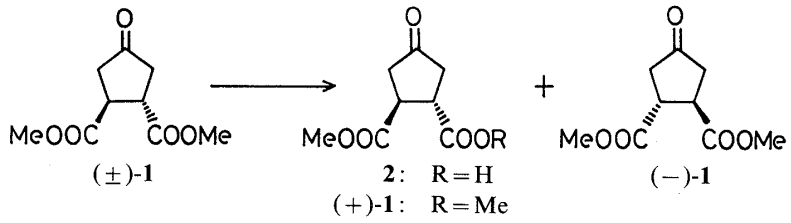
Synthesis of prostaglandin A_2 (PGA_2) by means of a route involving enzymatic reactions is described. Enantioselective reduction and hydrolysis of *trans*-3,4-bis(methoxycarbonyl)cyclopentanone (**1**) were examined using yeasts or enzymes, and it was found that (+)- and (−)-**1** are easily obtained by an enzymatic procedure. Compound (+)-**1** was converted to the Corey intermediate for PGA_2 *via* the regioselective hydrolysis of the (+)-diacetate (**8**) with porcine pancreatic lipase. This synthesis based on the enzymatic approach was proved to be useful for the synthesis of both PGA and PGE from (−)-**1**.

Keywords——prostaglandin A_2; enantioselective hydrolysis; microbial reduction; enzymatic hydrolysis; kinetic resolution; regioselective hydrolysis

Primary prostaglandins (PGs) have been an attractive target for chemical synthesis from the early stages of PG research, because of their unique biological properties and relatively simple framework in addition to the low natural abundance. $PGF_{2\alpha}$, PGE_2, and their analogues have developed into drugs for inducing labour and terminating pregnancy. Prostacyclin (PGI_2) may also be applicable in the future. A number of synthetic sequences for primary PGs have been developed by many research groups.[1] Our own synthetic route for primary PGs started with *trans*-3,4-bis(methoxycarbonyl)cyclopentanone (**1**), obtained by a slight modification of the reported procedure,[2] and (±)-11-deoxy-11-hydroxymethyl-PGE and (±)-PGE[3] were synthesized. The optically active forms were synthesized from (−)-(3*R*,4*R*)-**1** obtained by optical resolution[4] of the ethylene acetal of the monoacid ((±)-**2**) with *d*-ephedrine.

We now report the chemical synthesis of PGA_2 involving the use of enzymatic procedures. The ability of enzymes to discriminate between enantiotopic groups of symmetrical substrates such as *meso* compounds is highly attractive for the synthesis of natural products. Enzymatic hydrolyses of *meso* compounds such as monocyclic (three-, four-, five-, and six-membered ring) compounds with a *cis*-1,2-dimethyl ester moiety have been investigated by Jones *et al.*,[5] and hydrolyses of these compounds with pig liver esterase (PLE) were found to proceed with high enantioselectivity, except for the case (17% ee) of *cis*-1,2-bis(methoxycarbonyl)cyclopentane. Hydrolyses of (±)-*trans*-1,2-diacetoxycycloalkanes (four-, five-, and six-membered ring) were also examined by Schneider *et al.*[6] using PLE, and *trans*-1,2-diacetoxycyclopentane was found to give low enantioselectivity (63% ee), in remarkable contrast to the case of four- and six-membered ring systems. Thus, we have examined the hydrolysis of *trans*-3,4-bis(methoxycarbonyl)cyclopentanone (**1**) with PLE. The results are shown in Table I; (−)-(3*R*,4*R*)-**1** with high enantiomeric excess (>99% ee)[7] was recovered in 40% yield, and the (+)-(3*S*,4*S*)-enantiomer (95% ee) was obtained as the monohydrolyzed product (**2**) in 34% yield. As shown in Table I, shortening the hydrolysis time (60 min) seems to afford (+)-**1** with higher optical purity. On the other hand, elongation

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



Entry	Time (min)	Compound (+)-**1**		Compound (−)-**1**	
		Yield (%)	Optical purity (% ee)	Yield (%)	Optical purity (% ee)
1	110	32	71	40	>99
2	60	34	95	45	95

TABLE II. Reduction of (±)-**1** with Yeast

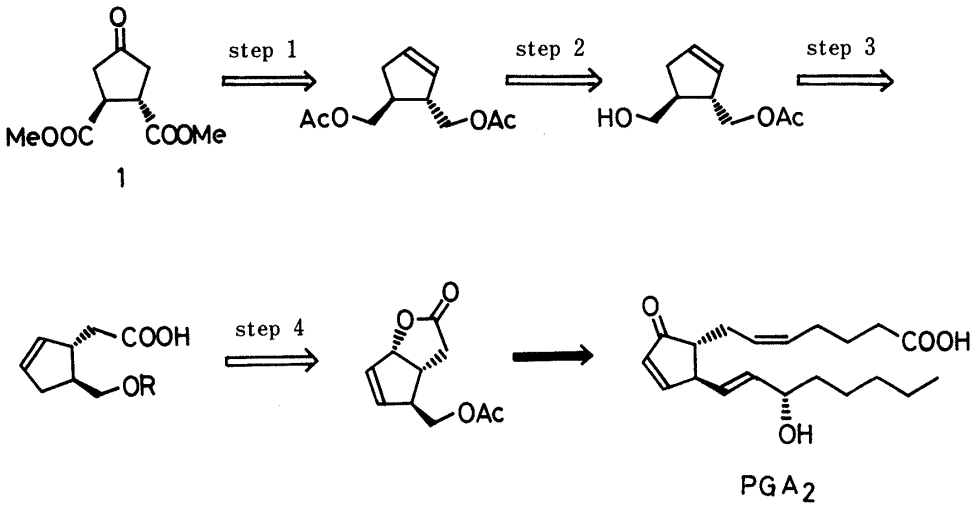
Yeast	Recovery			Reduction product		
	Product	Chem. yield (%)	Optical purity (% ee)	After oxid.	Chem. yield (%)	Optical purity (% ee)
Saccharomyces sp.	(−)-**1**	25	38	(+)-**1**	43	29
Torulopsis sp. Jyozo Kyokai 17	(+)-**1**	58	11	(+)-**1**	18	15
Saccharomyces cerevisiae	(−)-**1**	23	44	(+)-**1**	28	41
Candida humicola CCY 29-11-1	(+)-**1**	20	>99	(−)-**1**	45	28

of the hydrolysis time (110 min) increased the optical purity of (−)-**1**.

The enantioselective reduction of (±)-**1** with yeasts of forty species was next examined. Among the tested yeasts, *Saccharomyces* sp., *Torulopsis* sp., *Saccharomyces cerevisiae*, and *Candida humicola* were effective for kinetic resolution in the process of microbial reduction. In particular, *Candida humicola* CCY 29-1-1 afforded (+)-(3*S*,4*S*)-**1** with the highest optical purity (>99% ee) in 20% yield, in addition to the reduction product (45% yield, 28% ee)[8] as shown in Table II. Next, we planned the synthesis of the Corey intermediate (**18**)[9] for PGA_2 from (+)-**1** with the undesired configuration for the synthesis of PGE and related compounds.[3]

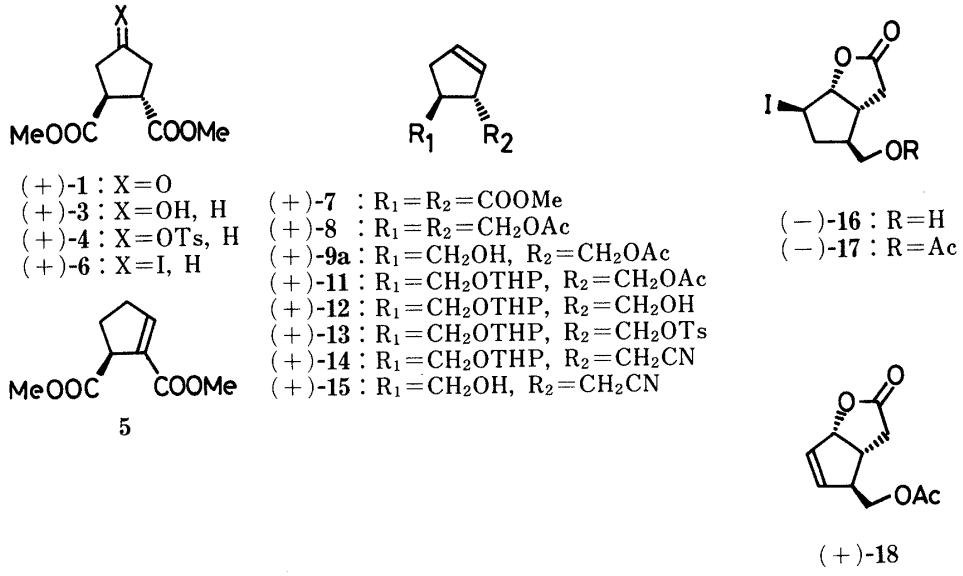
As shown in Chart 1, this sequence seems to have several advantages. For example, in the conversion (step 1) of the carbonyl function in compound **1** to the double bond, dehydration of the corresponding alcohol should afford a single product, because of the presence of the C_2-axis in **1**. Although the regioselective hydrolysis (step 2) of the acetoxy function is considered to be the most difficult step in the designed sequence, this difficulty may be overcome by the use of an enzymatic procedure. Elongation (step 3) by one carbon followed by iodolactonization (step 4) seem to proceed without difficulty.

Reduction of (+)-**1** with $NaBH_4$/MeOH (Chart 2) afforded the (+)-alcohol (**3**) as a sole product in 87% yield. To avoid the rearrangement of the double bond under acidic conditions to the conjugated ester (**5**), the alcohol function was first converted to the (+)-tosylate (**4**) in



1

Chart 1



(+)-**1** : X=O
(+)-**3** : X=OH, H
(+)-**4** : X=OTs, H
(+)-**6** : X=I, H

(+)-**7** : $R_1=R_2=COOMe$
(+)-**8** : $R_1=R_2=CH_2OAc$
(+)-**9a** : $R_1=CH_2OH$, $R_2=CH_2OAc$
(+)-**11** : $R_1=CH_2OTHP$, $R_2=CH_2OAc$
(+)-**12** : $R_1=CH_2OTHP$, $R_2=CH_2OH$
(+)-**13** : $R_1=CH_2OTHP$, $R_2=CH_2OTs$
(+)-**14** : $R_1=CH_2OTHP$, $R_2=CH_2CN$
(+)-**15** : $R_1=CH_2OH$, $R_2=CH_2CN$

(−)-**16** : R=H
(−)-**17** : R=Ac

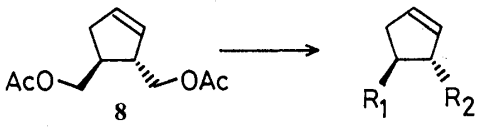
5

(+)-**18**

Chart 2

the standard manner. However, reflux of (+)-**4** in benzene in the presence of DBU resulted in the formation (47% yield) of (−)-**5**, the structure of which was supported by the signal at δ 6.95 (1H, m) attributable to the β-hydrogen of the α,β-unsaturated ester, in addition to the absorption bands at 1730, 1710, 1630 cm^{-1} in the infrared (IR) spectrum. The desired (+)-cyclopentene (**7**) was obtained in 74% yield, by converting the tosyl function of **4** with NaI to the iodide followed by dehydroiodination with DBU in benzene at 40 °C for 20 h. The presence of the deconjugated double bond in (+)-**7** was supported by the signals of olefinic H at δ 5.73 (2H, m) and two CH–COO at δ 3.55 and 3.98 (each m). By reduction with $LiAlH_4$ followed by acetylation with Ac_2O/pyridine, (+)-**7** was converted into the (+)-diacetate (**8**) in 90% yield. In a preliminary experiment for the regioselective hydrolysis of the diacetate, (±)-**8** was subjected to hydrolysis with K_2CO_3/MeOH. The hydrolyzed products were obtained as a mixture of the diol (36%) and the monoacetate (29%), in addition to the recovered diacetate (33%), which could be separated by column chromatography on silica gel. The (±)-monoacetate (**9**) was observed as one spot on thin layer chromatography (TLC), and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum also provided no indication to

TABLE III. Enantioselective Hydrolysis of the Diacetate (**8**)



8

9a: $R_1=CH_2OH$, $R_2=CH_2OAc$
9b: $R_1=CH_2OAc$, $R_2=CH_2OH$
10a: $R_1=COOMe$, $R_2=CH_2OAc$
10b: $R_1=CH_2OAc$, $R_2=COOMe$

Entry	Origin of lipase	Time (h)	Monoacetate	
			Yield (%)	**9a**/**9b**
1	*Rhizopus javanicus*	17	30	72/28
2	*Mucol javanicus*	72	7	74/26
3	*Pseudomonas fluorescens*	1	29	58/42
4	*Aspergillus niger*	50	23	57/43
5	Pig liver esterase (PLE)	2	56	50/50
6	*Candida cylindracea*	45	33	43/57
7	*Rhizopus delemar*	12	38	69/31
8	Porcine pancreas (PPL)	9	40 ($[\alpha]_D^{23}$ +96.4°)	84/16
9	Porcine pancreas (PPL)	20	84 ($[\alpha]_D^{23}$ +134.6°)	86/14

Compounds (±)-**8** and (+)-**8** were used as substrates for entries 1—8 and entry 9, respectively.

suggest that it is a mixture of acetates. Jones oxidation of (±)-**9** followed by esterification with CH_2N_2 afforded the (±)-monoester (**10**), which was also observed as one spot on TLC. However, the 400 MHz ^{1}H-NMR spectrum showed that this compound is a 1 : 1 mixture of two compounds ((±)-**10a** and (±)-**10b**). Thus, we were forced to consider the use of an enzymatic procedure for the hydrolysis of **8**. The results of selective hydrolysis of (±)-**8** with several enzymes are shown in Table III. The 400 MHz ^{1}H-NMR spectral analysis of the product ester (**10**) indicated that porcine pancreatic lipase (PPL) was effective for the regioselective hydrolysis (entry 8, **9a**(84)/**9b**(16)). However, the specific rotation (+96°) (see entry 9; +134.6°) of the hydrolyzed product (entry 8) suggests that PPL was not very effective for the enantioselective hydrolysis. The regioselective hydrolysis of the (+)-diacetate (**8**) with PPL afforded the (+)-monoacetate (**9**) ($[\alpha]_D^{23}$ +134.6°), which was an 86 : 14 mixture (see Experimental) of optically active **9a** and **9b**, in accordance with our expectations. The hydrolysis at C_4-CH_2OCOCH_3 was determined by comparison of the 400 MHz ^{1}H-NMR spectrum of the corresponding methyl ester with that of the methyl ester (**10**) (C_4-H at δ 3.3305 (**10a**) and C_3-H at δ 3.3856 (**10b**)). Further increase of the selectivity in the hydrolysis with enzymes could not be attained. According to the designed sequence, the alcohol function in (+)-**9** was protected as the tetrahydropyranyl ether by treatment with dihydropyran/*p*-TsOH. Elongation by one carbon, required for PGA_2, was accomplished in 88% yield from the (+)-tetrahydropyranyl ether (**11**) *via* the sequence of hydrolysis (K_2CO_3/MeOH), tosylation (*p*-TsCl/Py), and then substitution with NaCN. After removal of the tetrahydropyranyl function with AcOH/H_2O/THF, the (+)-nitrile (**15**) was subjected to hydrolysis in refluxing MeOH/NaOH/H_2O to afford the corresponding acid, which was converted to the (−)-lactone (**16**) (60% from **15**) by treatment with KI–I_2. In this lactonization process, the undesired alcohol (**9b**) contaminating (+)-**9** was removed. After acetylation with Ac_2O/Py, the dehydroiodination of the (−)-acetate (**17**) with DBU afforded the Corey lactone (**18**) for PGA_2 synthesis in excellent yield. The structure was confirmed by comparison of the ^{1}H-NMR and IR spectra, and the specific rotation with the reported data.[9] Thus, the above synthesis, involving the enzymatic procedure, proved to be useful for the synthesis of PGA and PGE.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on JEOL JNM-GX 400 and JEOL JNM-FX 100 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Specific rotations were measured on a JASCO DIP-400 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 230—400 mesh) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). For enzymatic hydrolysis, PLE (Sigma, type I) and PPL (Sigma, type II (pfs)) were used. All organic solvent extracts were washed with brine, and dried on anhydrous magnesium sulfate.

Enantioselective Hydrolysis of (±)-1 with PLE (Entry 1 in Table I)——Compound (±)-**1** (300 mg) in acetone (3 ml) and PLE (0.25 ml) were successively added with stirring to 0.1 M phosphate buffer (54 ml, pH 7). The whole was stirred for 110 min at 30 °C, and hydrolysis was terminated by extracting the mixture with AcOEt. 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 (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (−)-**1** (120 mg, 40%). $[\alpha]_D^{26}$ −133.3° (c=1.18, $CHCl_3$).[4] The aqueous layer was made acidic (pH 3) with 10% HCl, extracted with AcOEt, then dried. Removal of the solvent *in vacuo* afforded the monoester (**2**), which, after treatment with CH_2N_2, was subjected to column chromatography on silica gel to afford (+)-**1** (96 mg, 32%). $[\alpha]_D^{26}$ +91.1° (c=0.85, $CHCl_3$).

Reduction of (±)-1 with Yeast (Table II)——Test tubes (25×200 mm) containing 10 ml of the culture medium [5% glucose, 0.1% KH_2PO_4, 0.1% $(NH_4)_2SO_4$, 0.05% $MgSO_4 \cdot 7H_2O$, 0.1% yeast extract and tap water (pH 7.0)] were inoculated with microorganisms and cultured at 30 °C for 3 d with continuous shaking. The above-mentioned seed cultures (2 ml) were transferred to 100 ml of the same culture medium. After cultivation at 30 °C for 3 d, compound **1** (100 mg) was added to this seed culture, and the cultivation was continued for a further 3 d under the same conditions. The reaction mixture was filtered with the aid of celite and the filtrate was extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford a mixture of **1** and **3**, which could be separated by column chromatography on silica gel. The alcohol **3** was converted to **1** with Jones oxidation.

In the case of *Candida humicola* CCY 29-11-1, (+)-**1** (20 mg, 20%) ($[\alpha]_D^{23}$ +134.4° (c=0.99, $CHCl_3$)) was recovered and (−)-**1** (45 mg, 45%) ($[\alpha]_D^{23}$ −36.2° (c=0.88, $CHCl_3$)) was obtained *via* **3**.

(3*S*,4*S*)-Bis(methoxycarbonyl)cyclopentanol (3)——$NaBH_4$ (348 mg) was added portionwise to a stirred solution of (+)-**1** (1.836 g) in MeOH (30 ml) at 0 °C. After 0.5 h, the reaction mixture was diluted with brine, and extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (50 g). The fraction eluted with 50% AcOEt in hexane (v/v) afforded (+)-**3** (1.615 g, 87%) as a colorless oil. $[\alpha]_D^{23}$ +66.4° (c=1.36, $CHCl_3$). IR (neat): 3450, 1730, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10—3.60 (2H, m, CHCOO×2), 3.70 (6H, s, $COOCH_3$×2), 4.40 (1H, m, CHO–). MS m/z: 203 (M^++1), 170, 153.

(3*S*,4*S*)-1-Tosyloxy-3,4-bis(methoxycarbonyl)cyclopentane (4)——*p*-Toluenesulfonyl chloride (1.415 g) and 4-dimethylaminopyridine (DMAP, *ca.* 50 mg) were successively added to a stirred solution of (+)-**3** (1.004 g) in pyridine (10 ml) at less than 10 °C. After being stirred at room temperature for 15 h, the rection mixture was diluted with brine, and extracted with Et_2O–CH_2Cl_2 (4:1, v/v). The Et_2O–CH_2Cl_2 extract was washed, and dried, then concentrated *in vacuo* to give a white solid, which was subjected to column chromatography on silica gel (30 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded (+)-**4** (1.351 g, 76.4%) as colorless needles, mp 88 °C, recrystallized from AcOEt–hexane. $[\alpha]_D^{25}$ +50.5° (c=1.01, $CHCl_3$). IR (Nujol): 1725, 1595, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, CH_3), 3.15 (1H, q, J=10 Hz, CHCOO), 3.43 (1H, q, J=10 Hz, CHCOO), 3.70 (6H, s, $COOCH_3$×2), 7.35 (2H, d, J=9 Hz, aromatic H), 7.76 (2H, d, J=9 Hz, aromatic H).

(3*S*,4*S*)-1-Iodo-3,4-bis(methoxycarbonyl)cyclopentane (6)——NaI (1.54 g) was added to a solution of (+)-**4** (2.820 g) in hexamethylphosphoramide (HMPA, 6 ml) and benzene (20 ml) at room temperature under an Ar atmosphere. The whole was stirred for 2 h at 70 °C, and diluted with brine, then extracted with ether. The ether extract was washed with 5% $Na_2S_2O_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (50 g). The fraction eluted with 10% AcOEt in hexane (v/v) gave (+)-**6** (2.355 g, 95%) as a colorless oil. $[\alpha]_D^{24}$ +23.4° (c=0.98, $CHCl_3$). IR (neat): 1730, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (1H, q, J=9 Hz, CHCOO), 3.49 (1H, q, J=9 Hz, CHCOO), 3.71 (3H, s, $COOCH_3$), 3.73 (3H, s, $COOCH_3$), 4.22 (1H, m, CHI).

(*S*)-2,3-Bis(methoxycarbonyl)cyclopent-1-ene (5)——1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 0.1 ml) was added to a stirred solution of (+)-**4** (70 mg) in benzene (3 ml), and the whole was heated at reflux for 10 h. The reaction mixture was diluted with brine, and extracted with AcOEt, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was subjected to column chromatography on silica gel (3 g). The fraction eluted with 5% AcOEt in hexane (v/v) afforded (−)-**5** (17 mg, 47%) as a colorless oil. $[\alpha]_D^{26}$ −56.5° (c=0.65, $CHCl_3$). IR (neat): 1730, 1710, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s, $COOCH_3$), 3.72 (3H, s, $COOCH_3$), 6.95 (1H, m, CH=). MS m/z: 184 (M^+), 152, 124.

(3*S*,4*S*)-3,4-Bis(methoxycarbonyl)cyclopent-1-ene (7)——The mixture of DBU (5.6 ml) and (+)-**6** (2.535 g) in benzene (80 ml) was stirred at 40 °C under an Ar atmosphere. After 20 h, the reaction mixture was diluted with brine, and extracted with ether. The organic layer was successively washed with 5% HCl, 5% $Na_2S_2O_3$, and brine, then

dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (100 g). The fraction eluted with 10% ether in hexane (v/v) afforded (+)-**7** (1.015 g, 73.7%) as a colorless oil. $[\alpha]_D^{26}$ +233.0° (c=0.216, $CHCl_3$). IR (neat): 1730, 1615, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (1H, m, CHCOO), 3.72 (6H, s, $COOCH_3 \times 2$), 3.98 (1H, m, CHCOO), 5.73 (2H, m, CH=CH). MS m/z: 184 (M^+), 152, 125.

(3*S*,4*S*)-3,4-Bis(acetoxymethyl)cyclopent-1-ene (8)——Compound (+)-**7** (419 mg) in ether (10 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (200 mg) in ether (50 ml) under ice water cooling. After being stirred for 3 h at room temperature, the reaction mixture was decomposed with 4% NaOH (1 ml), and the resulting precipitate was filtered off and washed with $CHCl_3$. The combined organic layer was concentrated *in vacuo* to afford an oily residue (400 mg), which was acetylated in the standard manner. The crude diacetate was purified by column chromatography on silica gel (20 g). The fraction eluted with 50% AcOEt in hexane (v/v) gave (+)-**8** (432 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$ +125.2° (c=0.91, $CHCl_3$). IR (neat): 1735, 1440, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (6H, s, $COCH_3 \times 2$), 4.03 (4H, d, J=6 Hz, $CH_2O \times 2$), 5.57 (1H, m, CH=), 5.77 (1H, m, CH=). MS m/z: 213 ($M^+ + 1$), 169, 152.

Hydrolysis of (±)-8 with K_2CO_3——K_2CO_3 (50 mg) was added portionwise to a stirred solution of (±)-**8** (300 mg) in MeOH (30 ml) at room temperature. After 0.5 h, AcOH (0.5 ml) was added, and the solvent was removed *in vacuo* to afford an oily residue, which was extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (8 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded the monoacetate (70 mg, 29%), which was subjected to Jones oxidation followed by esterification with CH_2N_2. 400 MHz ^{1}H-NMR ($CDCl_3$) δ: 2.0583, 2.0531 ($COCH_3$ in the same ratio), 3.7154, 3.7093 ($COOCH_3$ in the same ratio), 5.5761, 5.6763, 5.7575, 5.8344 (olefinic H in the same ratio).

General Method for the Enzymatic Hydrolysis of 8 (Table III). A Typical Example: Hydrolysis of (+)-8 with PPL——PPL (10 mg) was added to a stirred suspension of (+)-**8** (144 mg) in acetone (0.8 ml) and 0.1 M phosphate buffer (pH 7, 7 ml). The whole was stirred for 20 h at 30 °C, and the hydrolysis was terminated by extracting with AcOEt. The AcOEt extract was dried, and concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (10 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded (+)-**9a** (97 mg, 84%) contaminated with **9b** (**9a**/**9b**: 86/14, based on **10a**/**10b**). $[\alpha]_D^{23}$ +135° (c=1.08, $CHCl_3$). IR (neat): 3425, 1730, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, $COCH_3$), 3.58 (2H, d, J=6 Hz, CH_2O), 4.03 (2H, d, J=6 Hz, CH_2OCO). Jones oxidation of (+)-**9a** followed by esterification with CH_2N_2 afforded the monoester **10a** contaminated with **10b**. **10a**(+**10b**); 400 MHz ^{1}H-NMR ($CDCl_3$) δ: 2.0531, 2.0583 ($COCH_3$), 3.3305 (C_4-H in **10a**), 3.3856 (C_3-H in **10b**), 3.7093, 3.7154 ($COOCH_3$), 5.5761, 5.7575 (olefinic H in **10a**), 5.6763, 5.8344 (olefinic H in **10b**). Each signal was observed in the ratio of 86/14.

(3*S*,4*S*)-3-Acetoxymethyl-4-(tetrahydropyran-2-yl)oxymethylcyclopent-1-ene (11)——2,3-Dihydropyran (0.15 ml) and *p*-toluenesulfonic acid (*ca.* 10 mg) were successively added to a stirred solution of (+)-**9a** (184 mg) in CH_2Cl_2 (20 ml). After being stirred for 3 h at room temperature, the reaction mixture was washed with 5% $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 10% ether in hexane (v/v) afforded (+)-**11** (284 mg, 99%) as a colorless oil. $[\alpha]_D^{24}$ +103.5° (c=0.97, $CHCl_3$). IR (neat): 1740, 1240, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, $COCH_3$), 4.59 (1H, m, OCHO–), 5.57 (1H, m, CH=), 5.77 (1H, m, CH=). MS m/z: 152 (M^+ −THP−OH), 110, 92.

(3*S*,4*S*)-3-Hydroxymethyl-4-(tetrahydropyran-2-yl)oxymethylcyclopent-1-ene (12)——K_2CO_3 (150 mg) was added portionwise to a stirred solution of (+)-**11** (284 mg) in MeOH (5 ml). After being stirred for 12 h at room temperature, the reaction mixture was diluted with brine (20 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (25 g). The fraction eluted with 20—25% AcOEt in hexane afforded (+)-**12** (232 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ +41.4° (c=0.66, $CHCl_3$). IR (neat): 3425, 1120, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.00—4.00 (6H, m, CH_2O), 4.68 (1H, m, OCHO–).

(3*S*,4*S*)-3-Tosyloxymethyl-4-(tetrahydropyran-2-yl)oxymethylcyclopent-1-ene (13)——*p*-Toluenesulfonyl chloride (291 mg) and DMAP (*ca.* 10 mg) were successively added to a stirred solution of (+)-**12** (216 mg) in pyridine (8 ml). The whole was stirred for 12 h at 0 °C, and diluted with brine, then extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed, and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (30 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded (+)-**13** (356 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ +90.9° (c=0.95, $CHCl_3$). IR (neat): 1650, 1600, 1360 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.50 (1H, m, CH=), 5.70 (1H, m, CH=), 7.33 (2H, d, J=9 Hz, aromatic H), 7.78 (2H, d, J=9 Hz, aromatic H).

(3*S*,4*S*)-3-Cyanomethyl-4-(tetrahydropyran-2-yl)oxymethylcyclopent-1-ene (14)——The mixture of NaCN (3.2 mg) and (+)-**13** (16 mg) in dimethylsulfoxide (DMSO, 8 ml) was stirred for 3.5 h at 80 °C under an Ar atmosphere. The reaction mixture was diluted with brine, and extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (5.0 g). The fraction eluted with 10% ether in hexane (v/v) afforded (+)-**14** (9.1 mg) as a colorless oil. $[\alpha]_D^{21}$ +125.7° (c=0.99, $CHCl_3$). IR (neat): 1650, 1120, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.10—3.95 (4H, m, $CH_2O \times 2$), 5.60 (1H, m, CH=), 5.80 (1H, m, CH=). MS m/z: 221 (M^+), 192, 119.

(3*S*,4*S*)-3-Cyanomethyl-4-hydroxymethylcyclopent-1-ene (15)——Compound (+)-**14** (164 mg) in AcOH–H_2O–THF (3 : 1 : 1, 15 ml) was stirred for 3 h at 50 °C. The reaction mixture was diluted with brine, and extracted with AcOEt, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was chromatographed on silica gel (10 g). The fraction eluted with 40% ether in hexane (v/v) afforded (+)-**15** (99 mg, 97%) as a colorless oil. $[\alpha]_D^{24}$ +168° (c=0.80, $CHCl_3$). IR (neat): 3425, 2250, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (2H, m, CH_2O), 5.60 (1H, m, CH=), 5.80 (1H, m, CH=). MS m/z: 137 (M^+), 119.

(1*R*,5*R*,6*S*,8*R*)-6-Hydroxymethyl-8-iodo-2-oxa-3-oxobicyclo[3.3.0]octane (16)——A mixture of NaOH (140 mg), (+)-**15** (79.8 mg), MeOH (5 ml), and H_2O (2 ml) was heated at reflux for 15 h. After neutralization with CO_2, KI–I_2 (I_2 450 mg, KI 2.0 g, H_2O 3 ml) was added to the solution, and the whole was stirred for 5 h at 0 °C, and for 2 h at room temperature. Then, the solution was cooled to 0 °C, diluted with 5% $Na_2S_2O_3$ (20 ml), and extracted with AcOEt. The AcOEt extract was washed with 5% $NaHCO_3$, and then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (5 g). The fraction eluted with 60% AcOEt in hexane (v/v) afforded (−)-**16** (97.8 mg, 59.5%). $[\alpha]_D^{19}$ −56.3° (c=1.20, $CHCl_3$). IR (neat): 3425, 1780, 1160, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (1H, br, OH), 3.79 (2H, d, J=5 Hz, CH_2O), 4.23 (1H, m, CHI), 5.14 (1H, dd, J=3, 7 Hz, COOCH). MS m/z: 282 (M^+), 264, 137.

(1*R*,5*R*,6*S*,8*R*)-6-Acetoxymethyl-8-iodo-2-oxa-3-oxobicyclo[3.3.0]octane (17)——Acetylation was accomplished in 97% yield with the standard procedure (Ac_2O and pyridine). $[\alpha]_D^{18}$ −48.2° (c=1.16, $CHCl_3$). IR (neat): 1780, 1735, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $COCH_3$), 4.20 (2H, d, J=6 Hz, CH_2OCO), 4.23 (1H, m, CHI), 5.14 (1H, dd, J=4, 7 Hz, COOCH). MS m/z: 324 (M^+), 197, 137.

(1*S*,5*R*,6*S*)-6-Acetoxymethyl-2-oxa-3-oxobicyclo[3.3.0]oct-7-ene (18)——DBU (0.14 ml) was added to a stirred solution of (−)-**17** (64 mg) in benzene (5 ml) at room temperature under an Ar atmosphere. The whole was stirred for 3 h at 70 °C, diluted with 5% HCl, and extracted with AcOEt. The AcOEt extract was successively washed with 5% $Na_2S_2O_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was subjected to column chromatography on silica gel (3 g). The fraction eluted with 40% AcOEt in hexane (v/v) afforded (+)-**18** (41 mg, 99%) as a colorless oil. $[\alpha]_D^{19}$ +225.5° (c=1.10, $CHCl_3$) (reported value +226.7°).[9] IR (neat): 1770, 1730, 1240, 1165, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $OCOCH_3$), 4.06 (2H, d, J=6 Hz, CH_2O), 5.54 (1H, m, COOCH), 6.01 (2H, m, CH=CH). MS m/z: 196 (M^+), 136, 91. High-MS for $C_{10}H_{12}O_4$ (M^+): Calcd m/z 196.07356; Found 196.07446.

References and Notes

1) S. M. Roberts and F. Scheinmann, "New Synthetic Routes to Prostaglandins and Thromboxanes," Academic Press, London, 1982.
2) L. J. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *J. Org. Chem.*, **36**, 1277 (1971).
3) K. Sakai, J. Ide, and O. Oda, *Tetrahedron Lett.*, **1975**, 3021.
4) O. Oda, K. Kojima, and K. Sakai, *Tetrahedron Lett.*, **1975**, 3709; O. Oda and K. Sakai, *ibid.*, **1975**, 3705.
5) G. Sabbioni, M. L. Shea, and J. B. Jones, *J. Chem. Soc., Chem. Commun.*, **1984**, 236.
6) D. H. G. Grout, V. S. B. Gaudet, K. Laumen, and M. Schneider, *J. Chem. Soc., Chem. Commun.*, **1986**, 808.
7) Optical purity and absolute stereochemistry were determined, based on the specific rotations.[4]
8) Optical purity and absolute stereochemistry were determined, based on the specific rotations of the oxidation products.[4]
9) E. J. Corey and P. A. Grieco, *Tetrahedron Lett.*, **1972**, 107.