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Preparation of Chiral, Highly Functionalized Cyclopentanes and Its Application to the Synthesis of Prostaglandin E_1

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This paper describes the preparation of the polyfunctionalized cyclopentane ((±)-5) by silica gel-catalyzed air-oxidation, and its kinetic resolution by means of microbial reduction with *Rhodotorula rubra* to afford optically pure (−)-5 (>99% ee). Starting with (−)-5, a new route to prostaglandin E_1 was established.

Keywords prostaglandin E_1; air-oxidation; microbial reduction; chemoselective oxidation; stereoselective reduction

Previously, we reported[1] that the highly functionalized cyclopentenone ((±)-**2**) was obtained by silica gel-catalyzed air-oxidation of the keto-diester ((±)-**1**) and that the kinetic resolution of (±)-**2** by microbial reduction afforded optically pure (+)-**2**. Compound (+)-**2** could be converted into (−)-α- and (+)-β-cuparenones *via* nickel-catalyzed stereoselective 1,4-addition of (p-tolyl)$_2$Zn as a key step (Chart 1). Silica gel-catalyzed air oxidation coupled with microbial reduction seems to provide optically pure, synthetically useful cyclopentanones. As a part of our synthetic studies on biologically active compounds based on a five-membered ring, we wish to report a further application of the above methodology to the synthesis of prostaglandin (PG) E_1.

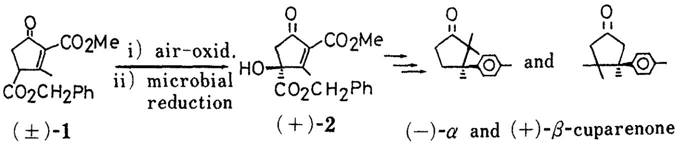


Chart 1

In analogy with (±)-**2**, the cyclopentenone ((±)-**4**) obtained by base-catalyzed cyclyzation of the 1,4-diketone ((±)-**3**) underwent facile air-oxidation during silica-gel column chromatography with the AcOEt–hexane solvent system to afford two oxygenated products, (±)-**5** (34%) and (±)-**6** (15%) (Chart 2).

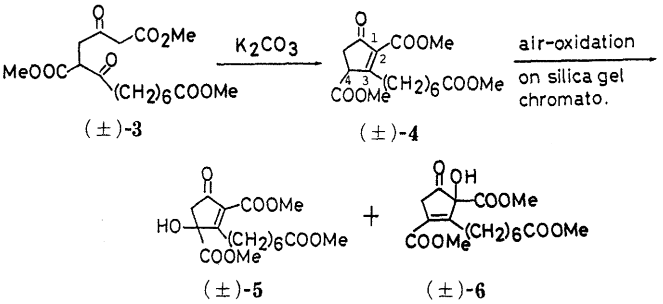


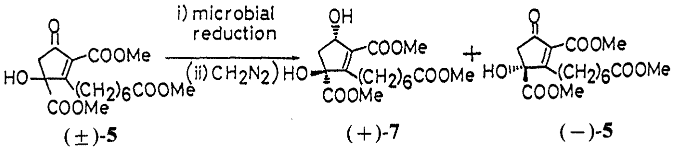
Chart 2

The structures of (±)-**5** and (±)-**6** were determined by means of spectral analysis. In the mass spectra (MS), **5** and **6** showed the molecular ion peak at m/z 356, and this finding suggests the addition of one oxygen atom to **4** (molecular weight, 340). The infrared (IR) spectra showed the absorption band of OH at 3450 cm^{-1}, in addition to the signals of hydroxy protons at δ4.05—4.09 in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The position of the hydroxy function was deduced on the basis of the ^{1}H-NMR spectra. While the signals of the C_5-geminal protons in **5** were observed separately at δ2.70 and 2.89 (1H each), the C_5-geminal protons in **6** appeared at lower field (δ3.30 and 3.35) as signals with homoallylic coupling (J=1.5 Hz) between C_5-H_2 and C_3-CH_2. Form these results, it was coucluded that the hydroxy function in **5** and **6** should be at C_4 and at C_2, respectively.

For the preparation of the chiral **5**, enantioselective reduction of (±)-**5** with microorganisms was tested. On screening of microbial reduction using 40 species of yeast, *Rhodotorula rubra* CCY 20-7-1 and *Schizosaccharomyces octosporus* were found to be effective for the kinetic resolution, and products of high optical purity were obtained. On reduction using 500 mg of the substrate (±)-**5**, *R. rubra* afforded (−)-**5** (46%, >99% ee) as a recovered substrate, and (+)-**7** (48%, >99% ee) as a reduced product after treatment with CH_2N_2[2] (Table I, entry 1), and *S. octosporus* gave (−)-**5** (80%, 8% ee) and (+)-**7** (14%, >99% ee) (Table I, entry 2). The optical purity of each product was determined from the 270 MHz ^{1}H-NMR spectral analysis by using a chiral shift reagent Tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Eu(hfc)$_3$) after conversion into (+)- or (−)-**5**.

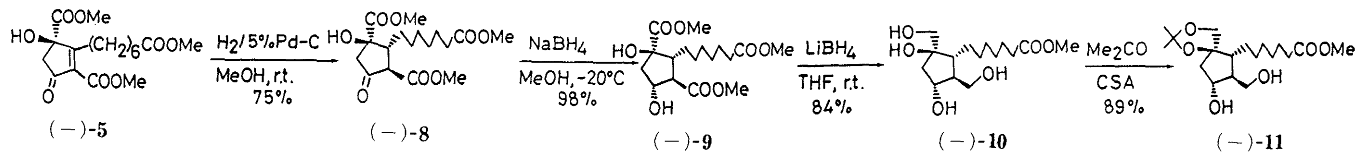
According to the quadrant rule for *R. rubra* proposed by Nakazaki,[3] the recovered (−)-**5** was concluded to be the *R*-isomer. The sequence for the synthesis of PGE_1 starts from (−)-**5** with stereoselective catalytic hydrogenation (5% Pd/C in MeOH at room temperature) to give the saturated ketone ((−)-**8**, 75%), $[\alpha]_D^{25}$ −71.1° (c=1.89, $CHCl_3$). $NaBH_4$ reduction of (−)-**8** at −20°C afforded the 1,4-*trans*-diol ((−)-**9**, 98%) as a single product, $[\alpha]_D^{24}$ −10.8°

TABLE I.



Entry	Yeast	Yield	(%)	$[\alpha]_D$[a]	% ee[b]
1	*Rodotorula*	(+)-7	48	+65.4°	>99
	rubra CCY 20-7-1	(−)-5	46	−119.6°	>99
2	*Schizosaccharomyces*	(+)-7	14	+63.1°	>99
	octosporus	(−)-5	80	−9.3°	8

a) In $CHCl_3$. *b*) Determined by 270 MHz ^{1}H-NMR analysis by using Eu(hfc)$_3$ (0.13 eq).



r.t., room temperature

Chart 3

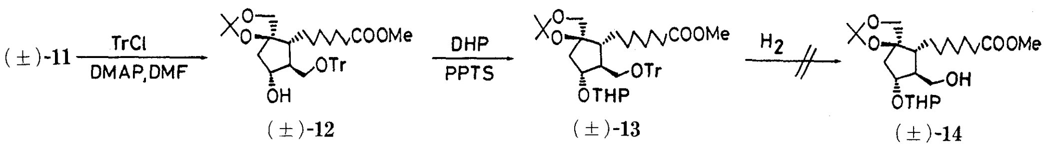


Chart 4

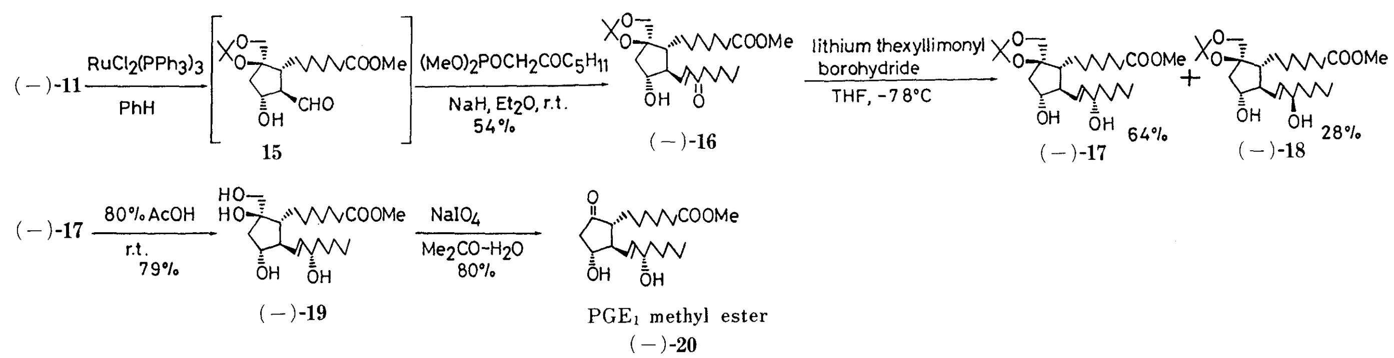


Chart 5

($c=2.54$, $CHCl_3$). These reductions proceeded stereoselectively, similarly to the case reported in the previous paper.[1] The concurrent reduction of C_2- and C_4-esters in (−)-**9** was achieved by using $LiBH_4$ in tetrahydrofuran (THF) at room temperature to afford the tetraol ((−)-**10**) in 84% yield, $[\alpha]_D^{27}$ −19.2° ($c=1.84$, MeOH). The 1,2-diol in (−)-**10** was protected as an acetonide by treatment with acetone/camphorsulfonic acid (CSA), and the acetonide (−)-**11** was obtained in 89% yield, $[\alpha]_D^{26}$ −19.2° ($c=1.57$, $CHCl_3$) (Chart 3).

To develop a method for introducing the ω-side chain into (−)-**11**, we preliminarily employed (±)-**11**. In the usual manner, the primary alcohol in (±)-**11** was protected as the trityl ether by treatment with triphenylmethyl chloride (TrCl)/dimethylformamide (DMF) in the presence of 4-dimethylaminopyridine (DMAP), and the resulting **12** was converted to the pyranyl ether (**13**) (75% yield from **11** by treatment with 3,4-dihydro-2*H*-pyran (DHP)/pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2. However, contrary to our espectation, the Tr-ether bond in (±)-**13** was not cleaved by hydrogenolysis under reducing conditions using 10% Pd/C or PtO_2 (Chart 4). Next, we tried chemoselective oxidation of the primary alcohol of (±)-**11** in the presence of the secondary alcohol with Pt black or $RuCl_2(PPh_3)_3$.[4] Oxidation of **11** with Pt black under an O_2 atmosphere for 12 h afforded the desired aldehyde-alcohol ((±)-**15**) in 49% yield and the diol **11** was recovered in 31% yield. Prolonged oxidation increased the production of the corresponding carboxylic acid, and the yield of **15** dropped. Ru complex-catalyzed oxidation of (−)-**11** afforded **15** as a single product on thin layer chromatography (TLC).[5] The crude aldehyde **15** was subjected to Horner–Emmons reaction with dimethyl (2-oxoheptyl)phosphonate to afford the enone ((−)-**16**) (54% from (−)-**11**, $[\alpha]_D^{26}$ −13.7° ($c=0.35$, $CHCl_3$)). Reduction of (−)-**16** by lithium thexyllimonylborohydride in THF at −78°C gave (−)-**17** (C_{15}-α-OH, $[\alpha]_D^{26}$ −13.2° ($c=1.99$, $CHCl_3$)) (PG numbering) as the more polar,[6] major product in 64% yield, and (−)-**18** (C_{15}-β-OH, $[\alpha]_D^{26}$ −23.1° ($c=0.59$, $CHCl_3$)) as a less polar one in 28% yield. Even on reduction at −100°C, which required 6 h, the product ratio was almost same as at −78°C (**17** : **18** = 52 : 25). The desired α-alcohol (−)-**17** was treated with 80% aqueous acetic acid to afford the tetraol ((−)-**19**, 79%), $[\alpha]_D^{26}$ −17.0° ($c=1.07$, MeOH). Oxidation of (−)-**19** with $NaIO_4$ in aqueous acetone gave PGE_1 methyl ester ((−)-**20**) in 80% yield; this product was identical with an authentic sample in terms of the spectral data ($[\alpha]_D^{26}$ −53.3° ($c=0.45$, MeOH), lit.[7] $[\alpha]_D^{23}$ −54.0° ($c=1.08$, MeOH)), (Chart 5). Agreement of the sign of optical rotation supports the correctness of our estimation of the absolute configuration of (−)-**5**.

Experimental

IR spectra were measured on a JASCO A-202 spectrometer. ^1H-NMR spectra were measured on a JEOL JMN-PS-100 spectrometer unless otherwise stated. MS were taken on a JEOL JMS-D 300 spectrometer. Specific rotations were measured on JASCO DIP-4 and DIP-360 polarimeters. The melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. For column chromatography, silica gel 70—230 mesh (Merck, Kieselgel 60) was used. TLC and preparative TLC were performed on Silica gel 60 F_{254} plates (0.25 and 2 mm) (Merck), respectively. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate unless otherwise stated.

(±)-4-Hydroxy-2,4-bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)-cyclopent-2-en-1-one (5) and (±)-2-Hydroxy-2,4-bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)cyclopent-3-en-1-one (6) K_2CO_3 (23.2 g, 167.6 mmol) was added portionwise to a stirred solution of trimethyl 2,5-dioxoundecane-1,4,11-tricarboxylate[1] (20.0 g, 55.9 mmol) in MeOH (500 ml) at room temperature. After being stirred for 1 h, the reaction mixture was neutralized with 3% aqueous HCl under ice-water cooling, and the organic solvent was evaporated off *in vacuo*. The oily residue was extracted with AcOEt (200 ml × 3), and the AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was subjected to column chromatogaphy on silica gel (500 g), and eluted slowly with 15% AcOEt in hexane (v/v) to afford (±)-**6** (3.08 g, 15%) as a yellow oil. IR (neat): 3450, 1770, 1730—1720, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.9 (10H, m), 2.30 (2H, t, J=7.2 Hz, CH_2–COO), 3.30, 3.35 (1H each, t, J=1.5 Hz, C_5-H), 3.66, 3.80, 3.82 (3H each, s, $COOCH_3$), 4.09 (1H, br s, OH). FDMS m/z: 356 (M^+), 297. The fraction eluted with 20—40% AcOEt in hexane (v/v) afforded (±)-**5** as colorless needles, mp 63.5—64.5 °C (ether). IR (Nujol): 3430, 1750—1720, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (2H, t, J=7.3 Hz, CH_2COO), 2.70, 2.89 (1H each, d, J=18 Hz, C_5-H), 3.67, 3.81, 3.87 (3H each, s, $COOCH_3$), 4.05 (1H, br s, OH). FDMS m/z: 357 (M^++1), 297.

Microbial Reduction of (±)-5, (1*S*,4*S*)-1,4-Dihydroxy-2,4-bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)cyclopent-2-ene ((+)-7 and (−)-5) In a manner similar to that described in the previous paper,$^{1)}$ (±)-**5** (500 mg) was subjected to microbial reduction with *Rhodotorula rubra* CCY 20-7-1 and with *Schizosaccharomyces octosporus*. The reaction mixture was shaken for 3 d at 30 °C, then filtered with the aid of celite. In the case of *R. rubra*, hydrolysis of one of the esters was observed. The filtrate was acidified then extracted with AcOEt (200 ml × 3). Removal of the solvent *in vacuo* gave an oily residue, which was treated with CH_2N_2. The crude products were subjected to column chromatography on silica gel (10 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (−)-**5** (241 mg, 48%, >99% ee) as a colorless oil, $[\alpha]_D^{25}$ −119.6° (c=0.51, $CHCl_3$). The fraction eluted with 30—40% AcOEt in hexane (v/v) afforded (+)-**7** (233 mg, 46%, >99% ee) as a colorless oil. IR (Nujol): 3470, 1735—1720, 1645, 1435, 1260, 1205, 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.1—2.8 (4H, m, CH_2COO, C_5-H), 3.66, 3.82, 3.88 (3H, each, s, $COOCH_3$), 3.5—3.9 (2H, br, OH × 2), 5.15 (1H, t, J=4.8 Hz, C_1-H). EIMS m/z: 357 (M^+−1), 340, 322, 308. $[\alpha]_D^{26}$ +65.4° (c=1.48, $CHCl_3$). Reduction with *S. octosporus*; (−)-**5**: 401 mg, 80%, 8% ee, $[\alpha]_D^{27}$ −9.2° (c=1.54, $CHCl_3$); (+)-**7**: 73 mg, 15%, >99% ee, $[\alpha]_D^{25}$ +63.1° (c=1.17, $CHCl_3$).

(2*R*,3*R*,4*R*)-4-Hydroxy-3-(6-methoxycarbonylhexyl)-2,4-dimethoxycarbonylcyclopentanone ((−)-8) A solution of (−)-**5** (6.65 g, 18.7 mmol) in MeOH (600 ml) was hydrogenated in the presence of 5% Pd/C (6 g) under an H_2 atmosphere at room temperature. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (60 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (−)-**8** as a colorless oil. (Recemate: colorless needles, mp 100.5—101.5 °C (AcOEt–hexane)). IR (Nujol): 3450, 1765, 1745, 1730, 1125 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (2H, t, J=7.3 Hz, CH_2COO), 2.78 (2H, s, C_5-H), 2.97 (1H, m, C_3-H), 3.30 (1H, d, J=11.7 Hz, C_2-H), 3.67, 3.78, 3.83 (3H, each, s, $COOCH_3$), 3.88 (1H, s, OH). EIMS m/z: 358 (M^+), 340, 326, 313, 308. $[\alpha]_D^{25}$ −71.1° (c=1.89, $CHCl_3$).

(1*R*,2*R*,3*R*,4*R*)-2,4-Bis(methoxycarbonyl)-3-(6-methoxycarbonylhexyl)cyclopentane-1,4-diol ((−)-9) A solution of (−)-**8** (4.00 g, 11.2 mmol) in MeOH (10 ml) was added dropwise to a stirred solution of $NaBH_4$ (423 mg, 11.2 mmol) in MeOH (50 ml) at −20°C. After 30 min, the reaction mixture was quenched with 3% aqueous HCl (10 ml) and concentrated *in vacuo*. The residue was extracted with AcOEt (50 ml × 4) and the combined extracts were dried. The solvent was removed *in vacuo* to give an oily residue, which was chromatographed on silica gel (40 g). The fraction eluted with AcOEt afforded (−)-**9** (4.00 g, 98%) as a colorless oil. IR (neat): 3470, 1740—1720 (br), 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66 (1H, dd, J=11, 6.6 Hz, C_2-H), 3.01 (2H, br s, OH × 2), 3.66, 3.74, 3.85 (3H each, s, $COOCH_3$), 4.52 (1H, dt, J=8.0, 6.6 Hz, C_1-H). EIMS m/z: 360 (M^+), 342, 328, 310, 301, 260, 251. $[\alpha]_D^{24}$ −10.8° (c=2.54, $CHCl_3$).

(1*R*,2*S*,3*R*,4*R*)-2,4-Bis(hydroxymethyl)-3-(6-methoxycarbonylhexyl)cyclopentane-1,4-diol ((−)-10) A solution of (−)-**9** (3.26 g, 9.05 mmol) in THF (10 ml) was added dropwise to a stirred suspension of $LiBH_4$ (296 mg, 13.6 mmol) in THF (40 ml) at room temperature. After 30 min, H_2O (5 ml) was added slowly and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (30 g). The fraction eluted with 10% MeOH in $CHCl_3$ (v/v) afforded (−)-**10** (2.75 g, 99%) as a colorless oil. IR (neat): 3370, 1735, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.3 (14H, m), 2.31 (2H, t, J=7.0 Hz, CH_2COO), 3.67 (3H, s, $COOCH_3$), 3.3—4.3 (8H, m, CH_2–O × 2, OH × 4), 4.29 (1H, m, C_1-H). FDMS m/z: 343 (M^++1), 342 (M^+), 327, 305. $[\alpha]_D^{27}$ −19.2° (c=1.84, MeOH).

(5*R*,6*R*,7*S*,8*R*)-8-Hydroxy-7-hydroxymethyl-6-(6-methoxycarbonylhexyl)-2,2-dimethyl-1,3-dioxaspiro[4.4]nonane ((−)-11) A catalytic amount of CSA was added to a stirred solution of (−)-**10** (121 mg, 0.40 mmol) in acetone (2 ml) at room temperature. After 1 h, the solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (4 g). The fraction eluted with 10% MeOH in $CHCl_3$ (v/v) afforded (−)-**11** (122 mg, 89%) as a colorless oil. IR (neat): 3420, 1735, 1435, 1370 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (2H, t, J=7.3 Hz, CH_2COO), 2.96 (2H, br, OH × 2), 3.4—4.0 (2H, m, CH_2–OH), 3.67 (3H, s, $COOCH_3$), 3.83, 4.02 (1H each, d, J=7.3 Hz, OCH_2O), 4.26 (1H, m, C_1-H). EIMS m/z: 344 (M^+), 329, 326, 311, 268. $[\alpha]_D^{26}$ −19.2° (c=1.57, $CHCl_3$).

(5*R,6*R**,7*S**,8*R**)-8-Hydroxy-6-(6-methoxycarbonylhexyl)-7-triphenylmethyloxymethyl-2,2-dimethyl-1,3-dioxaspiro[4.4]nonane (12)** A mixture of the diol (±)-**11** (47 mg, 0.14 mmol) and TrCl (42 mg, 0.15 mmol) in DMF (3 ml) was stirred at room temperature for 6 h in the presence of a catalytic amount of DMAP. The reaction mixture was diluted with brine (5 ml) and extracted with AcOEt (10 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 15% AcOEt in hexane (v/v) afforded (±)-**12** (62 mg, 77%) as a colorless oil. IR (neat): 3460, 1735, 1590, 750, 700, 625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (3H, s, $COOCH_3$), 3.6—4.4 (3H, m, C_8-H, OCH_2O), 7.1—7.6 (15H, m, Ar-H). FDMS m/z: 586 (M^+), 427, 243.

(5*R,6*R**,7*S**,8*R**)-6-(6-Methoxycarbonylhexyl)-8-(tetrahydropyran-2-yl)oxy-7-triphenylmethyloxymethyl-2,2-dimethyl-1,3-dioxaspiro[4.4]nonane ((±)-13)** A mixture of (±)-**12** (50 mg, 0.09 mmol) and DHP (9 mg, 0.10 mmol) in CH_2Cl_2 (2 ml) at room temperature was stirred for 2 h in the presence of a catalytic amount of PPTS. The reaction mixture was diluted with brine (5 ml) and extracted with ether (10 ml × 3). The ether extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted 5% AcOEt in hexane (v/v) afforded (±)-**13** (56 mg, 98%) as a colorless oil. IR (neat): 1735, 1595, 1440, 1030, 760, 730, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.28 (2H, t, J=7 Hz, CH_2–COO), 3.67 (3H, s, $COOCH_3$), 4.57, 4.86 (1H each, m, C_8-H, OCHO), 7.0—7.6 (15 H, m, Ar-H). FDMS m/z: 670 (M^+).

(5*R,6*R**,7*R**,8*R**)-7-Formyl-8-hydroxy-6-(6-methoxycarbonylhexyl)-2,2-dimethyl-1,3-dioxaspiro[4.4]nonane ((±)-15)** A mixture of (±)-**11** (80 mg, 0.23 mmol) and Pt black (50 mg) in acetone (10 ml) was stirred for 12 h at room temperature under an O_2 atmosphere. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 50% AcOEt in hexane (v/v) afforded (±)-**15** (39 mg, 49%) as a colorless oil. IR (neat): 3460, 2720, 1735, 1715, 1440, 1370, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—2.5 (21H, m), 2.30 (2H, t, J=6.7 Hz, CH_2COO), 3.66 (3H, s, $COOCH_3$), 3.85, 4.06 (1H each, d, J=9.0 Hz, OCH_2O), 4.57 (1H, m, C_1-H), 9.73 (1H, d, J=2.2 Hz, CHO). EIMS m/z: 342 (M^+), 327, 324, 309. The fraction eluted with AcOEt afforded the recovered diol (±)-**11** (25 mg, 31%).

9α-Hydroxymethyl-9,9a-*O*-isopropylidene-15-keto-PGF$_{1\beta}$ Methyl Ester ((−)-16) A solution of the alcohol (−)-**11** (188 mg, 0.53 mmol) and $RuCl_2(PPh_3)_3$ (393 mg, 0.41 mmol) in benzene (10 ml) was stirred for 5 h at room temperature. Removal of the solvent *in vacuo* gave a tarry residue, which was subjected to the next reaction without further purification. A solution of dimethyl (2-oxoheptyl)phosphonate (607 mg, 2.73 mmol) in ether (5 ml) was added to a stirred suspension of NaH (60% in oil; 109 mg, 2.73 mmol) in ether (5 ml) at 0°C. After 30 min, a solution of the above crude aldehyde **15** in CH_2Cl_2 (5 ml) was added and the whole was stirred for 5 h at room temperature. The reaction mixture was quenched with 3% aqueous HCl (5 ml) and extracted with AcOEt (20 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* afforded a tarry residue, which was subjected to column chromatography on silica gel (10 g). The fraction eluted with ether afforded (−)-**16** (130 mg, 54%) as a colorless oil. IR (neat): 3450, 1735, 1670, 1620, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=5.9 Hz, CH_3), 2.29 (2H, t, J=7.6 Hz, CH_2COO), 2.54 (2H, t, J=7.6 Hz, $COCH_2$), 3.66 (3H, s, $COOCH_3$), 3.6—4.3 (3H, m, C_{11}-H, OCH_2O), 6.17 (1H, d, J=15.7 Hz, =CHCO), 6.77 (1H, dd, J= 15.7, 8.5 Hz, CH=). FDMS m/z: 439 (M^++1), 438 (M^+), 423, 393. $[\alpha]_D^{26}$ −13.7° (c=0.35, $CHCl_3$).

9α-Hydroxymethyl-9,9a-*O*-isopropylidene-PGF$_{1\beta}$ Methyl Ester ((−)-17) and Its C_{15}-Epimer ((−)-18) Lithium thexyllimonyl borohydride (0.5 M in THF, 0.6 ml, 0.3 mmol) was added to a stirred solution of (−)-**16** (122 mg, 0.28 mmol) in ether (3 ml) at −78 °C. The mixture was stirred for 2 h, H_2O (2 ml) was added, and the whole was extracted with AcOEt (5 ml × 4), then the AcOEt extract was washed and 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 80% AcOEt in hexane (v/v) afforded a mixture of C_{15}-epimers (120 mg), which was subjected to preparative TLC to afford a less polar β-alcohol (−)-**18** (34 mg, 28%) and a more polar α-alcohol (−)-**17** (80 mg, 66%), each as a colorless oil.

(−)-**18**: IR (neat): 0.88 (3H, t, J=5.0 Hz, CH_3), 1.0—2.4 (30 H, m), 2.30 (2H, t, J=7.6 Hz, CH_2COO), 3.66 (3H, s, $COOCH_3$), 3.8—4.2 (2H, m, CH-O × 2), 3.77, 4.03 (1H each, d, J=8.8 Hz, $OCCH_2O$), 5.5—5.8 (2H, m, vinyls). EIMS m/z: 422 ($M^+ - H_2O$), 404, 391, 378, 346. $[\alpha]_D^{26}$ −23.1° (c=0.59, $CHCl_3$).

(−)-**17**: IR (neat): 0.89 (3H, t, J=5.7 Hz, CH_3), 0.9—2.4 (30H, m), 2.29 (2H, t, J=7.4 Hz, CH_2COO), 3.66 (3H, s, $COOCH_3$), 3.6—4.3 (4H, m, CH-O × 2, $OCCH_2O$), 5.4—5.6 (2H, m, vinyls). EIMS m/z: 440 (M^+), 422, 404, 391, 378, 364. $[\alpha]_D^{26}$ −13.2° (c=1.99, $CHCl_3$).

9α-Hydroxymethyl-PGF$_{1\beta}$ Methyl Ester ((−)-19) The acetonide (−)-**17** (18 mg, 0.04 mmol) in 80% AcOH (1 ml) was stirred at room temperature for 12 h. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 10% MeOH in $CHCl_3$ (v/v) afforded (−)-**19** (13 mg, 79%) as a colorless oil. IR (neat): 3370, 1740, 1630, 1560, 1440, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=4.6 Hz, CH_3), 1.0—2.2 (24 H, m), 2.29 (2H, t, J=7.3 Hz, CH_2COO), 3.66 (3H, s, $COOCH_3$), 3.8—4.2 (4H, m, CH-O × 2, CH_2O), 5.4—5.7 (2H, m, vinyls). EIMS m/z: 382 ($M^+ - H_2O$), 364, 346, 328. $[\alpha]_D^{26}$ −17.0° (c=1.07, MeOH).

PGE$_1$ Methyl Ester ((−)-20) A solution of $NaIO_4$ (11 mg, 0.05 mmol) in H_2O (1 ml) was added to a solution of (−)-**19** (10 mg, 0.025 mmol) in acetone (1 ml). The whole was stirred at room temperature for 1.5 h, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was diluted with brine (2 ml) and extracted with AcOEt (5 ml × 3). The AcOEt extract was washed and dried. The solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 70% AcOEt in hexane (v/v) afforded (−)-**20** (7.4 mg, 80%) as a colorless oil. IR (neat): 3400, 1740, 1460, 1435, 1165, 1070, 965, 725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=5.4 Hz, CH_3), 1.1—2.2 (18H, m, CH_2 × 9), 1.8—2.6 (7H, m, CH_2COO, CHCO, OH × 2), 2.73 (1H, dd, J=18.2, 7.4 Hz, C_{10}-H), 3.66 (3H, s, $COOCH_3$), 3.8—4.4 (2H, m, CH-O), 5.4—5.9 (2H, m, vinyls). EIMS m/z: 368 (M^+), 350, 332. $[\alpha]_D^{26}$ −53.3° (c=0.45, MeOH), lit.[7] $[\alpha]_D^{23}$ −54.0° (c=1.08, MeOH).

References and Notes

1) K. Okano, H. Suemune and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1379 (1988), and references cited therein.
2) Hydrolysis of ester **5** was observed during the screening of yeasts (see Experimental).
3) M. Nakazaki, H. Chikamatsu, K. Naemura and M. Masao, *J. Org. Chem.*, **45**, 4432 (1980).
4) H. Tomioka, K. Takai, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, **22**, 1065 (1981).
5) The aldehyde **15** obtained by oxidation with Ru complex was contaminated by a trace amount of by-product, but the low yield made it necessary to use the Ru complex.
6) In synthetic research on PGs, the polar fraction and the less polar fraction on TLC were tentatively assigned α-configuration and β-configuration, respectively.
7) M. Suzuki, T. Kawagishi, A. Yanagisawa, T. Suzuki, N. Okamura and R. Noyori, *Bull. Chem. Soc. Jpn.*, **61**, 1299 (1988).