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Enzymatic Procedure for the Synthesis of 11-Deoxyprostaglandins

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This paper describes the enzymatic hydrolysis of the *trans*, *trans(meso)*-2-substituted 1,3-bis(acetoxymethyl)cyclopentanes (**4a**, **b**) to afford the monoacetates (**5a**, **b**) in high enantiomeric excess ((-)-**5a**: 96% ee, (-)-**5b**: >99% ee). The absolute stereochemistry of (-)-**5b** was unequivocally determined to be 1*R*,2*R*,3*S* by converting it to a known compound derived from (-)-limonen-10-ol. Starting with (-)-**5b**, a new route to the key intermediate ((-)-**20**) for the synthesis of 11-deoxyprostaglandins was established.

Keywords—prostaglandin; *meso* compound; enzymatic hydrolysis; 11-deoxyprostaglandin; *cis*-1,3-bis(acetoxymethyl)cyclopentane; 1,4-addition

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. The hydrolytic enzymes have been widely investigated because many of them are capable of transforming *meso*-diesters into chiral monoesters. One of the synthetically useful hydrolytic enzymes is pig liver esterase (PLE). Hydrolysis of *meso* compounds such as monocyclic (three-, four-, and six-membered) ring derivatives with *cis*-1,2-dimethyl esters by commercially available PLE proceeds with high enantioselectivity.¹⁾ However, *cis*-1,2- and *cis*-1,3-bis(methoxycarbonyl)cyclopentanes are hydrolyzed to the corresponding half esters with only 17^{1a)} and 34% ee,²⁾ respectively. According to Laumen and Schneider,^{1c)} and Jones *et al.*,³⁾ enzymatic hydrolysis of *cis*-1,2-bis(acetoxymethyl)cyclopentane⁴⁾ with PLE or pig pancreatic lipase (PPL) affords the corresponding hydroxy ester in good yield and with fairly good optical purity (88—89% ee). This result is in marked contrast to that of the hydrolysis of the dimethyl esters.

We now report that the enzymatic hydrolysis of the *trans*, *trans(meso)*-2-substituted 1,3-bis(acetoxymethyl)cyclopentanes proceeds in a highly enantioselective manner to afford the chiral monoacetates, which provide the new route to the synthesis of a key intermediate⁵⁾ for 11-deoxyprostaglandins (PGs).

The *trans*, *trans(meso)*-2-substituted 1,3-bis(acetoxymethyl)cyclopentanes used as substrates were synthesized from 1,3-bis(methoxycarbonyl)-1-cyclopentene (**1**)⁶⁾ as follows. The 1,4-addition of **1** with BuCuBF₃, prepared from BuLi, CuI, and BF₃ etherate, afforded a mixture of the *trans*, *trans(meso)* compound (**2a**) and the *cis*, *trans* compound (**3a**) in 70% yield in the ratio of 2 (**2a**) to 1 (**3a**), and these products could be separated by flash chromatography. In the proton nuclear magnetic resonance (¹H-NMR) spectrum of the less polar fraction (**2a**), the signals of the C₁-H and C₃-H protons were observed as a broad singlet (*W*_{1/2} = 14 Hz) at δ 2.47, and two methyl signals due to C₁- and C₃-COOCH₃ appeared as a singlet peak at δ 3.67, whereas those of the more polar fraction (**3a**) were observed as separate

Chart 1

TABLE I. Enzymatic Hydrolysis of **4a, b**

Run	Compd. ^{a)}	Enzyme (mg)	Chem. yield (%)			Reaction time (h)	5	
			4	5	6		% ee ^{b)}	[α] _D ²⁰ (CDCl ₃)
1	4a	PPL (26)	46	41	5	14	66	-1.39°
	4b	PPL (12)	39	44	4	20	63	-2.13°
2	4a	PLE (3.1)	68	4	16	1.5	23	+0.52°
	4b	PLE (1.5)	85	3	1	2.0	59	+2.10°
3	4a	RDL (14)	34	62	0	20	96	-2.31°
	4b	RDL (6.2)	18	69	5	68	>99	-3.68°
4	4a	— ^{c)}						
	4b	CCL (24.8)	65	14	1	48	21	+1.20°

^{a)} Scale of hydrolysis, **a** = 350, **b** = 200 mg. ^{b)} Optical purities were determined by examination of the 400 MHz ¹H-NMR spectra after conversion of the products to the esters of (+)- α -methoxy- α -trifluoromethylphenylacetic acid (MTPA).⁸⁾ ^{c)} Not tested.

peaks (see Experimental). These data suggest that compound **2a** is a *meso* form. By assuming approach of the reagent from the less-hindered side of the sterically hindered double bond, the structure of **2a**⁷⁾ and **3a** were determined to be 1,2-*trans*-2,3-*trans*(*meso*) and 1,2-*cis*-2,3-*trans*, respectively. In a similar manner, **2b** and **3b** were synthesized from **1** and the cuprate reagent, prepared from 8-bromo-1-octene *via* 8-lithio-1-octene. Reduction of **2** with LiAlH₄ followed by treatment with Ac₂O/Py afforded the *trans, trans*(*meso*)-2-substituted 1,3-bis(acetoxy-methyl)cyclopentanes (**4**).

Enzymatic hydrolyses of **4** were performed in 0.1 M phosphate buffer solution (pH 7) at 30 °C (Table I). Among the four tested enzymes, PLE, PPL, *Rhizopus delemar* lipase (RDL), and *Candida cylindracea* lipase (CCL), RDL afforded the (–)-monoacetate (**5**) in fairly good yield and with high enantiomeric excess ((–)-**5a**: 96% ee, (–)-**5b**: >99% ee). It is noteworthy

that the hydrolysis of **4b** with CCL (or PLE) afforded the (+)-monoacetate (**5b**), whereas PPL (or RDL) gave the (–)-monoacetate (**5b**), although the absolute values of specific rotation are not always identical (see Table I).

The absolute stereochemistry of the hydrolyzed product ((–)-**5b**) was unambiguously determined by converting it to a known compound (**12**)⁹ derived from (–)-limonen-10-ol, *via* the removal of the unnecessary hydroxymethyl function. Upon catalytic hydrogenation with H₂/Pt in EtOH and subsequent Swern oxidation ((COCl)₂/dimethyl sulfoxide (DMSO)) in the presence of triethylamine, (–)-**5b** afforded the aldehyde (**8**) in 86% yield. The aldehyde function in **8** was smoothly removed by heating in benzonitrile in the presence of Wilkinson complex, and the acetoxy function was reductively transformed into the corresponding

Chart 2

alcohol by treatment with LiAlH₄. Mesylation of the alcohol (**9**) with methanesulfonyl chloride/Py followed by substitution with NaCN/DMSO afforded the nitrile (**11**) in 78% yield from **9**. By reduction with diisobutylaluminum hydride (DIBAL-H) and subsequent hydrolysis with 10% H₂SO₄, **11** was converted into the aldehyde ((–)-**12**). The aldehyde (–)-**12** was identical with the standard sample (+)-**12**⁹ in terms of the ¹H-NMR spectrum, the infrared (IR) spectrum and thin-layer chromatographic (TLC) behavior, except for the sign of specific rotation. Thus, the absolute stereochemistry of (–)-**5b** was unequivocally determined to be 1*R*,2*R*,3*S*.

In the synthesis of 11-deoxy PGs, the absolute stereochemistry of (–)-**5b** suggests that the C₁-CH₂OCOCH₃ group in (–)-**5b** should be converted to the ketone in the five-membered ring. Conversion of (–)-**5b** to the intermediate ((–)-**20**) for 11-deoxy PGs proceeded smoothly with retention of the stereochemistry at C₂ and C₃ in (–)-**5b**. The alcohol function in (–)-**5b** was first protected with 2-methoxyethoxymethyl chloride (MEM chloride)/*N,N*-diisopropylethylamine to afford the MEM ether (**13**), and the acetoxy function was converted to the corresponding alcohol with LiAlH₄. In order to facilitate the elimination of the alcohol to form the double bond, the alcohol (**14**) was subjected to mesylation with methanesulfonyl chloride/Et₃N and subsequent substitution with NaI in hexamethylphosphoramide (HMPA). Dehydroiodination of the iodide (**16**) with *tert*-BuOK in DMSO at room temperature afforded the diene (**17**) in 68% yield from (–)-**5b**. Concurrent cleavage of the two double bonds in **17** with ozone in CH₂Cl₂, followed by treatment with Zn/AcOH, gave the keto-aldehyde (**18**) in 76% yield. By Jones oxidation of the aldehyde function to the corresponding acid, followed by treatment with CH₂N₂, **18** was converted to

Chart 3

the ester (**19**), and the MEM function was removed by treatment with TiCl_4 to afford the intermediate ((-)-**20**),¹⁰ whose ^1H -NMR spectrum and IR spectrum were identical with those of a standard sample.¹¹⁾

Thus, this synthetic method using enzymatic hydrolysis of *meso* compounds seems to be useful for the synthesis of the optically active target (-)-**20**.

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^1H -NMR spectra were measured on a JEOL-PS-100 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography and flash chromatography, silica gel 70—230 mesh (Merck, Kieselgel 60) and 230—400 mesh (Nakarai Chemicals, Silica gel 60) were used, respectively. TLC was performed on Silica gel 60 F_{254} plates (Merck). For enzymatic hydrolysis, PLE (Sigma, type I), PPL (Sigma, type II (pfs)), CCL (Sigma, type VII (pfs)) and RDL (Seikagaku Kogyo, fine grade) were used. All organic solvent extracts were washed with satd. brine and dried over anhydrous sodium sulfate.

(*r*-1,*r*-2,*c*-3)-1,3-Bis(methoxycarbonyl)-2-butylcyclopentane (2a) and (*r*-1,*r*-2,*r*-3)-1,3-Bis(methoxycarbonyl)-2-butylcyclopentane (3a)—BuLi (1.5 M in hexane, 10.9 ml) solution was added dropwise with stirring to a suspension of CuI (3.11 g) in ether (30 ml) at -40°C under an Ar atmosphere. After 0.5 h, BF_3 etherate (2.12 ml) was added dropwise at -78°C . The mixture was stirred for 0.5 h, the diester (**1**, 1.003 g) in ether (3 ml) was added dropwise, and the whole was stirred for 1 h at -78°C , then for 1 h at -10°C . The reaction mixture was diluted with satd. NH_4Cl , and extracted with ether. The ether extract was washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was roughly chromatographed on silica gel (10 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded a mixture of **2a** and **3a** (1.10 g), which was subjected to flash chromatography using 2% AcOEt in hexane (v/v). **2a** (702 mg, 53%) and **3a** (344 mg, 26%) were obtained from the less polar fraction and the more polar fraction, respectively. **2a**: IR (neat): 1735, 1430, 1155 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.87 (3H, t, $J=6\text{ Hz}$, CH_3), 2.47 (2H, br s, $\text{CHCO} \times 2$), 3.67 (6H, s, $\text{COOCH}_3 \times 2$). MS m/z : 242 (M^+), 211, 102. **3a**: IR (neat): 1735, 1435, 1160 cm^{-1} . ^1H -NMR (CDCl_3) δ : 0.86 (3H, t, $J=6\text{ Hz}$, CH_3), 2.71 (1H, m, $\text{C}_3\text{-H}$),¹²⁾ 3.00 (1H, m, $\text{C}_1\text{-H}$), 3.64 (3H, s, COOCH_3), 3.67 (3H, s, COOCH_3). MS m/z : 242 (M^+), 210, 182.

(*r*-1,*r*-2,*c*-3)-1,3-Bis(methoxycarbonyl)-2-(7-octenyl)cyclopentane (2b) and (*r*-1,*r*-2,*r*-3)-1,3-Bis(methoxycarbonyl)-2-(7-octenyl)cyclopentane (3b)—8-Bromo-1-octene (5.00 g) in ether (20 ml) was added dropwise with stirring to a suspension of lithium (high sodium, 25% (w/w) dispersion in mineral oil, 2.45 g) in ether (50 ml) in the presence of 1,2-dibromoethane (0.2 ml) at -40°C under an Ar atmosphere. The resulting 8-lithio-1-octene solution was added dropwise to a stirred solution of CuI (4.29 g) in ether (50 ml) at -40°C . After 0.5 h, BF_3 etherate (2.93 ml) was added dropwise at -78°C , and the mixture was stirred for 0.5 h, then the diester (**1**, 1.381 g) in ether (5 ml) was

added dropwise. Stirring was continued for 3 h at -78°C , and for 1 h at 0°C , and work-up similar to that described for the synthesis of **2a** and **3a** afforded **2b** (1.40 g, 63%) and **3b** (515 mg, 23%) as colorless oils. **2b**: IR (neat): 1740, 1640, 910 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.46 (2H, br s, $\text{CHCO} \times 2$), 3.67 (6H, s, $\text{COOCH}_3 \times 2$), 4.84–5.15 (2H, m, $=\text{CH}_2$), 5.80 (1H, m, $\text{CH}=\text{}$). MS m/z : 297 ($\text{M}^+ + 1$), 296 (M^+), 265, 232. **3b**: IR (neat): 1735, 1640, 910 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.70 (1H, m, $\text{C}_3\text{-H}$),¹² 3.02 (1H, m, $\text{C}_1\text{-H}$), 3.64 (3H, s, COOCH_3), 3.66 (3H, s, COOCH_3), 4.82–5.10 (2H, m, $=\text{CH}_2$), 5.80 (1H, m, $\text{CH}=\text{}$). MS m/z : 297 ($\text{M}^+ + 1$), 296 (M^+), 264, 232.

(*r*-1,*t*-2,*c*-3)-1,3-Bis(acetoxymethyl)-2-butylcyclopentane (4a) and (*r*-1,*t*-2,*c*-3)-1,3-Bis(acetoxymethyl)-2-(7-octenyl)cyclopentane (4b)—The diester **2a** (484 mg) in ether (5 ml) was added dropwise with stirring to a suspension of LiAlH_4 (114 mg) in ether (5 ml) at 0°C . After 2 h, the reaction mixture was subjected to usual work-up to afford the crude diol (310 mg), which was acetylated in a usual manner. The crude diacetate (450 mg) was purified by column chromatography on silica gel (10 g), and the fraction eluted with 20% AcOEt in hexane (v/v) afforded **4a** (352 mg, 92%) as a colorless oil. Similarly, **4b** was obtained in 94% yield from **2b**. **4a**: IR (neat): 1740, 1240, 1030 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.89 (3H, t, $J=6\text{ Hz}$), 2.06 (6H, s, $\text{COCH}_3 \times 2$). MS m/z : 270 (M^+), 223, 211. **4b**: IR (neat): 1735, 1635, 1230 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.05 (6H, s, $\text{COCH}_3 \times 2$), 4.82–5.12 (2H, m, $=\text{CH}_2$), 5.78 (1H, m, $\text{CH}=\text{}$). MS m/z : 325 ($\text{M}^+ + 1$), 264, 222.

General Method for the Enzymatic Hydrolysis. A Typical Example: Hydrolysis of 4b to (1*R*,2*R*,3*S*)-1-Acetoxymethyl-2-(7-octenyl)-3-hydroxymethylcyclopentane (5b) with RDL—Compound **4b** (200 mg) in acetone (1 ml) and RDL (6.2 mg) were successively added with stirring to 0.1 M phosphate buffer (10 ml, pH 7). The whole was stirred at 30°C , and hydrolysis was terminated by extracting the mixture with AcOEt when a spot of the diol (**6b**) appeared on TLC. 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 (6 g). The fraction eluted with 3% AcOEt in hexane (v/v) afforded (–)-**5b** (120 mg, 69%) as a colorless oil. $[\alpha]_D^{20} - 3.68^{\circ}$ ($c=2.18$, CHCl_3). IR (neat): 3400, 1735, 1635, 1240 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.06 (3H, s, COCH_3), 3.42 (1H, dd, $J=11, 7\text{ Hz}$, $\text{CH}_A\text{H}_B\text{-OH}$), 3.82 (1H, dd, $J=11, 5\text{ Hz}$, $\text{CH}_A\text{H}_B\text{-OH}$), 3.88 (1H, dd, $J=10.5, 6.5\text{ Hz}$, $\text{CH}_A\text{H}_B\text{-OAc}$), 4.04 (1H, dd, $J=10.5, 5.5\text{ Hz}$, $\text{CH}_A\text{H}_B\text{-OAc}$). MS m/z : 283 ($\text{M}^+ + 1$), 252, 234. Anal. Calcd for $\text{C}_{17}\text{H}_{30}\text{O}_3$: C, 72.30; H, 10.71. Found: C, 72.43; H, 10.77.

(1*R*,2*R*,3*S*)-1-Acetoxymethyl-3-hydroxymethyl-2-octylcyclopentane (7)—A solution of (–)-**5b** (638 mg) in EtOH (50 ml) was hydrogenated in the presence of PtO_2 (100 mg) under an H_2 atmosphere for 5 h. 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 (13 g). The fraction eluted with 3% AcOEt in hexane (v/v) afforded **7** (613 mg, 95%) as a colorless oil. $[\alpha]_D^{17} - 2.73^{\circ}$ ($c=1.21$, CHCl_3). IR (neat): 3400, 1735, 1235 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.87 (3H, t, $J=6\text{ Hz}$, CH_3), 2.05 (3H, s, COCH_3), 3.28–3.72 (2H, m, CH_2OH), 3.76–4.24 (2H, m, CH_2OAc). MS m/z : 285 ($\text{M}^+ + 1$), 254, 241.

(1*R*,2*S*,3*S*)-1-Acetoxymethyl-3-formyl-2-octylcyclopentane (8)—DMSO (375 mg) in CH_2Cl_2 (1 ml) was added to a stirred solution of $(\text{COCl})_2$ (305 mg) in CH_2Cl_2 (3 ml) at -60°C under an Ar atmosphere. After 5 min, **7** (620 mg) in CH_2Cl_2 (2 ml) was added, and the whole was stirred for 15 min, then triethylamine (1.11 g) in CH_2Cl_2 (5 ml) was added at -60°C . After 20 min, the reaction mixture was warmed to room temperature, diluted with brine (20 ml), and then extracted with AcOEt. The AcOEt extract was successively washed with 3% aq. HCl, 5% aq. 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 (15 g). The fraction eluted with 2% AcOEt in hexane (v/v) afforded **8** (559 mg, 91%) as a colorless oil. $[\alpha]_D^{17} - 19.6^{\circ}$ ($c=1.04$, CHCl_3). IR (neat): 2700, 1735, 1720, 1235 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.06 (3H, s, COCH_3), 2.48 (1H, m, CH-CHO), 9.61 (1H, d, $J=2\text{ Hz}$, CHO). MS m/z : 281 ($\text{M}^+ - 1$), 253, 237, 210.

(1*R*,2*R*)-1-Hydroxymethyl-2-octylcyclopentane (9)—A mixture of **8** (577 mg) and Wilkinson complex (2.08 g) in benzonitrile (25 ml) was heated with stirring for 5 h at 160°C . The solvent was removed *in vacuo*, and EtOH (20 ml) was added to yield a precipitate, which was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue which was roughly chromatographed on silica gel (20 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded the monoacetate contaminated with triphenylphosphine. The crude acetate (250 mg) in ether (5 ml) was added dropwise with stirring to a suspension of LiAlH_4 (56 mg) in ether (5 ml) at room temperature, and the whole was stirred for 1 h. The usual work-up afforded a crude oil (183 mg), which was purified by column chromatography on silica gel (20 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **9** (185 mg) as a colorless oil. $[\alpha]_{546}^{17} - 55.7^{\circ}$ ($c=1.12$, CHCl_3). IR (neat): 3310, 1020 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, t, $J=6\text{ Hz}$, CH_3), 3.30–3.76 (2H, m, CH_2OH). MS m/z : 211 ($\text{M}^+ - 1$), 194, 179.

(1*R*,2*R*)-1-Mesyloxymethyl-2-octylcyclopentane (10)—Methanesulfonyl chloride (142 mg) in benzene (2 ml) was added dropwise to a stirred solution of **9** (175 mg) in benzene (5 ml) in the presence of Et_3N (167 mg) at room temperature. After 2 h, the reaction mixture was diluted with 5% aq. HCl (10 ml), and extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. NaHCO_3 , 5% aq. HCl, and brine, then dried. Removal of the solvent *in vacuo* afforded 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 **10** (207 mg, 87%) as a colorless oil. $[\alpha]_D^{22} - 39.1^{\circ}$ ($c=1.03$, CHCl_3). IR (neat): 1355, 1170, 945 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, t, $J=6\text{ Hz}$, CH_3), 3.00 (3H, s, SO_2CH_3), 3.93–4.32 (2H, m, CH_2O).

(1*R*,2*R*)-1-Cyanomethyl-2-octylcyclopentane (11)—A mixture of **10** (83 mg) and NaCN (20 mg) in DMSO (5 ml)

was heated with stirring at 100 °C. After 4 h, the reaction mixture was diluted with H₂O (10 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (3 g). The fraction eluted with 5% AcOEt in hexane (v/v) gave **11** (57 mg) as a colorless oil. $[\alpha]_D^{25} - 62.7^\circ$ ($c=0.81$, CHCl₃). IR (neat): 2240, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (3H, t, $J=6$ Hz, CH₃), 2.10–2.64 (2H, m, CH₂CN). MS m/z : 220 ($M^+ - 1$), 206, 192.

(1R,2R)-1-Formylmethyl-2-octylcyclopentane (12)—DIBAL-H (tetrahydrofuran solution) (0.4 ml) was added dropwise to a stirred solution of **11** (45 mg) in hexane (5 ml) at –70 °C. The whole was stirred for 0.5 h at –60 °C, and for 5 h at 0 °C, then diluted with 10% H₂SO₄ (10 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 (3 g). The fraction eluted with 10% ether in hexane (v/v) afforded (–)-**12** (19 mg) as a colorless oil. $[\alpha]_D^{20} - 47.6^\circ$ ($c=0.84$, CHCl₃) (the reported value: +43.6°).⁸⁹ IR (neat): 2710, 1730, 1030 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (3H, t, $J=6$ Hz, CH₃), 2.25 (1H, ddd, $J=16, 8, 2.5$ Hz, CH_AH_B-CHO), 2.59 (1H, ddd, $J=16, 6.5, 2.5$ Hz, CH_AH_B-CHO), 9.77 (1H, t, $J=2.5$ Hz, CHO). MS m/z : 225 ($M^+ + 1$), 224 (M^+), 206, 193. Anal. Calcd for C₁₅H₂₈O: C, 80.29; H, 12.58. Found: C, 80.10; H, 12.71.

(1R,2R,3S)-1-Acetoxyethyl-3-(2-methoxyethoxymethoxymethyl)-2-(7-octenyl)cyclopentane (13)—MEM chloride (618 mg) in CH₂Cl₂ (3 ml) was added dropwise to a stirred solution of (–)-**5b** (350 mg) in the presence of *N,N*-diisopropylethylamine (650 mg). After 3 h, the reaction mixture was diluted with brine (15 ml), and extracted with AcOEt. The AcOEt extract was washed, and dried, then removal of the solvent *in vacuo* afforded an oily residue, which was chromatographed on silica gel (30 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **13** (410 mg, 89%) as a colorless oil. $[\alpha]_D^{27} + 5.56^\circ$ ($c=2.16$, CHCl₃). IR (neat): 1735, 1635, 1105 cm⁻¹. ¹H-NMR (CDCl₃) δ : 2.04 (3H, s, COCH₃), 3.39 (3H, s, OCH₃), 4.70 (2H, s, OCH₂O). MS m/z : 371 ($M^+ + 1$), 370 (M^+), 339, 281.

(1R,2S,3S)-1-Hydroxymethyl-3-(2-methoxyethoxymethoxymethyl)-2-(7-octenyl)cyclopentane (14)—Compound **13** was added dropwise with stirring to a suspension of LiAlH₄ (65 mg) in ether (20 ml) at 0 °C, and stirred for 4 h at room temperature. The work-up afforded a crude oil (449 mg), which was subjected to column chromatography on silica gel (15 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded **14** (347 mg, 93%) as a colorless oil. $[\alpha]_D^{28} + 7.50^\circ$ ($c=2.10$, CHCl₃). IR (neat): 3425, 1640, 1110 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.64 (1H, s, OH), 3.38 (3H, s, OCH₃), 4.84–5.12 (2H, m, =CH₂), 5.82 (1H, m, CH=). MS m/z : 329 ($M^+ + 1$), 252, 239, 221.

(1R,2R,3S)-1-Mesyloxyethyl-3-(2-methoxyethoxymethoxymethyl)-2-(7-octenyl)cyclopentane (15)—In a manner similar to that described for the preparation of **10**, **14** (215 mg) afforded **15** (261 mg, 98%) as a colorless oil. $[\alpha]_D^{28} + 1.26^\circ$ ($c=2.11$, CHCl₃). IR (neat): 1635, 1355, 1175, 1110 cm⁻¹. ¹H-NMR (CDCl₃) δ : 3.00 (3H, s, SO₂CH₃), 3.39 (3H, s, OCH₃), 4.84–5.10 (2H, m, =CH₂), 5.82 (1H, m, CH=). MS m/z : 407 ($M^+ + 1$), 376, 361, 299.

(1R,2R,3S)-1-Iodomethyl-3-(2-methoxyethoxymethoxymethyl)-2-(7-octenyl)cyclopentane (16)—A mixture of **15** (721 mg) and NaI (532 mg) in HMPA (3 ml) was heated under reflux for 6 h, diluted with brine (10 ml), and extracted 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 (15 g). The fraction eluted with 20% AcOEt in hexane (v/v) gave **16** (692 mg, 89%) as a yellow oil. $[\alpha]_D^{25} - 12.12^\circ$ ($c=2.00$, CHCl₃). IR (neat): 1635, 1110, 905 cm⁻¹. ¹H-NMR (CDCl₃) δ : 3.38 (3H, s, OCH₃), 4.82–5.12 (2H, m, =CH₂), 5.80 (1H, m, CH=). MS m/z : 439 ($M^+ + 1$), 407, 362, 331.

(2R,3S)-1-Methylene-3-(2-methoxyethoxymethoxymethyl)-2-(7-octenyl)cyclopentane (17)—A mixture of **16** (240 mg) and *tert*-BuOK (123 mg) in DMSO (5 ml) was stirred for 10 min at room temperature, diluted with 3% aq. HCl (10 ml), and extracted with ether. The ether extract was washed, dried, and then concentrated *in vacuo* to afford an oily residue, which was chromatographed on silica gel (5 g). The fraction eluted with 20% ether in hexane (v/v) afforded **17** (160 mg, 94%) as a colorless oil. $[\alpha]_D^{25} - 1.54^\circ$ ($c=2.26$, CHCl₃). IR (neat): 1650, 1640, 1110, 1040 cm⁻¹. ¹H-NMR (CDCl₃) δ : 4.68–5.12 (4H, m, =CH₂ × 2), 4.70 (2H, s, OCH₂O), 5.82 (1H, m, CH=). MS m/z : 311 ($M^+ + 1$), 234, 220. Anal. Calcd for C₁₉H₃₄O₃: C, 73.50; H, 11.04. Found: C, 73.38; H, 11.19.

(2R,3S)-2-(6-Formylhexyl)-3-(2-methoxyethoxymethoxymethyl)-1-cyclopentanone (18)—Ozone gas was bubbled into a solution of **17** (155 mg) in CH₂Cl₂ (15 ml) at –78 °C, and the reaction was monitored by TLC. The resulting ozonide was decomposed with Zn powder (460 mg) and AcOH (3 ml) at 10 to 20 °C. The Zn powder was filtered off, and the filtrate was concentrated *in vacuo*, diluted with brine (20 ml), and then extracted with AcOEt. The AcOEt extract was washed, and dried. The solvent was removed *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (2 g). The fraction eluted with 30% AcOEt in hexane (v/v) afforded **18** (108 mg, 68%) as a colorless oil. $[\alpha]_D^{26} - 20.87^\circ$ ($c=2.18$, CHCl₃). IR (neat): 2720, 1735, 1110 cm⁻¹. ¹H-NMR (CDCl₃) δ : 3.40 (3H, s, OCH₃), 4.72 (2H, s, OCH₂O), 9.76 (1H, t, $J=2$ Hz, CHO). MS m/z : 315 ($M^+ + 1$), 314 (M^+), 299, 269.

(2R,3S)-2-(6-Methoxycarbonylhexyl)-3-(2-methoxyethoxymethoxymethyl)-1-cyclopentanone (19)—Jones reagent (0.2 ml) was added dropwise to a stirred solution of **18** (92 mg) in acetone (10 ml) at –10 °C. After 0.5 h, the excess reagent was decomposed with isopropanol, and the reaction mixture was diluted with brine (5 ml), then extracted with ether. The ether extract was dried, and esterified with CH₃N₂ in the usual manner. 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 20% AcOEt in hexane (v/v) gave **19** (86 mg, 85%) as a colorless oil. $[\alpha]_D^{24} - 18.98^\circ$ ($c=2.06$, CHCl₃). IR (neat): 1735, 1170, 1110, 1040 cm⁻¹. ¹H-NMR (CDCl₃) δ : 3.38 (3H, s, OCH₃), 3.70 (3H, s, COOCH₃),

4.72 (2H, s, OCH₂O). MS m/z : 345 ($M^+ + 1$), 313 ($M^+ - \text{OCH}_3$), 299, 269.

(2R,3S)-3-Hydroxymethyl-2-(6-methoxycarbonylhexyl)-1-cyclopentanone (20)—TiCl₄ (142 mg) in CH₂Cl₂ (1 ml) was added dropwise to a stirred solution of **19** (86 mg) in CH₂Cl₂ (2 ml) at 0 °C, and the whole was stirred for 0.5 h. The reaction mixture was diluted with brine (10 ml), and extracted with CH₂Cl₂. The CH₂Cl₂ extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (3 g). The fraction eluted with 25% AcOEt in hexane (v/v) afforded (–)-**20** (39 mg, 61%) as a colorless oil. Compound (–)-**20** was identical with the (±)-standard sample¹¹⁾ in terms of the ¹H-NMR and the IR spectra. $[\alpha]_D^{23} - 39.57$ ($c = 1.87$, CHCl₃). IR (neat): 3470, 1740, 1170, 1045 cm⁻¹. ¹H-NMR (CDCl₃) δ : 1.10–2.64 (18H, m, CH₂ × 8, CH × 2), 1.76 (1H, s, OH), 3.36–3.92 (2H, m, CH₂O), 3.65 (3H, s, COOCH₃). MS m/z : 257 ($M^+ + 1$), 256 (M^+), 238, 225. Anal. Calcd for C₁₄H₂₄O₄: C, 65.59; H, 9.44. Found: C, 65.65; H, 9.59.

References and Notes

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- 7) Preliminary hydrolysis of **2a** with PLE resulted in only 15% ee.
- 8) Optical purities of **5a, b** were determined by 400 MHz ¹H-NMR (CDCl₃) spectroscopy after conversion to the corresponding (+)-MTPA esters. In the spectrum of the (+)-MTPA ester of (±)-**5a**, methylene protons (–CH₂O–MTPA) were observed as two pairs of double-doublet signals originating from two diastereomers at δ 4.107 (dd, $J = 10.8, 7.9$ Hz), 4.182 (dd, $J = 10.8, 7.7$ Hz), 4.278 (dd, $J = 10.8, 5.1$ Hz), 4.340 (dd, $J = 10.8, 5.1$ Hz). The methylene protons in the (+)-MTPA ester of (–)-**5a** (Table I, run 3) were observed as a major pair of double-double signals at δ 4.182 and 4.278, and the other pair of double-doublet signals at δ 4.107 and 4.340 was remarkably reduced. On the basis of the relative intensity of these two pairs, the optical purity of (–)-**5a** was calculated. By using a similar technique, the optical purity of (–)-**5b** was determined. (+)-MTPA ester of (±)-**5b**: δ 4.104 (dd, $J = 10.9, 7.9$ Hz), 4.179 (dd, $J = 10.8, 7.6$ Hz), 4.274 (dd, $J = 10.8, 5.1$ Hz), 4.336 (dd, $J = 10.9, 5.1$ Hz). (+)-MTPA ester of (–)-**5b**: δ 4.179 and 4.274.
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- 10) A route to (±)-11-deoxy PGs from the corresponding (±)-aldehyde was established by Greane and Crabbe.⁵⁾
- 11) The (±)-standard sample was synthesized by an alternative method.¹³⁾
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