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Studies on Prostaglandins. VI.[1] Synthesis of 16(*S*)-Methyl-20-methoxy-PGE_2 (YPG-209) having Oral Bronchodilator Activity and Its Analogs

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16(*S*)-Methyl-20-methoxy-PGE_2 (YPG-209) (Is), 16(*R*)-methyl-20-methoxy-PGE_2 (I_R) and several analogs, such as 16(*S*)-methyl-20-methoxy-PGA_2 (XIIIs) and -PGB_2 (XIVs), 16-methyl-20-ethoxy-PGE_2 ($XXVII_a$), 16-methyl-20-hydroxymethyl-PGE_2 ($XXVI_a$), 16-methyl-17-oxa-ω-dihomo-PGE_2 ($XXVIII_a$) and 20-hydroxymethyl-PGE_2 (XXX), were synthesized by Corey's procedure and their biological activities were investigated. Among these derivatives, I_S and I_R possessed potent oral bronchodilator activity; the bronchoselectivity of I_S was higher than that of I_R.

Keywords——16(*S*)-methyl-20-methoxy-PGE_2; 16(*R*)-methyl-20-methoxy-PGE_2; 16-methyl-20-ethoxy-PGE_2; 16-methyl-20-hydroxymethyl-PGE_2; 16-methyl-17-oxa-ω-dihomo-PGE_2; 16-methyl-19-oxa-ω-dihomo-PGE_2; Corey's method for prostaglandin synthesis; oral bronchodilator activity

The natural prostaglandins (PGs) have various well-known physiological activities, such as contractile activity on smooth muscles of the uterus, hypotensive activity, gastric antisecretory activity, antiaggregatory activity towards blood platelets, bronchodilator activity, *etc.*[3-6] Since Corey *et al.*[7] and Upjohn's group[8] succeeded in the total synthesis of natural PGs, many laboratories have attempted to obtain PG derivatives which have higher, more long-lasting, and more selective biological activities than the natural PGs as pontential therapeutically useful medicines.[1,3-13] Among such derivatives, 15(*S*)-methyl-PGE_2-methyl ester,[9] 16-

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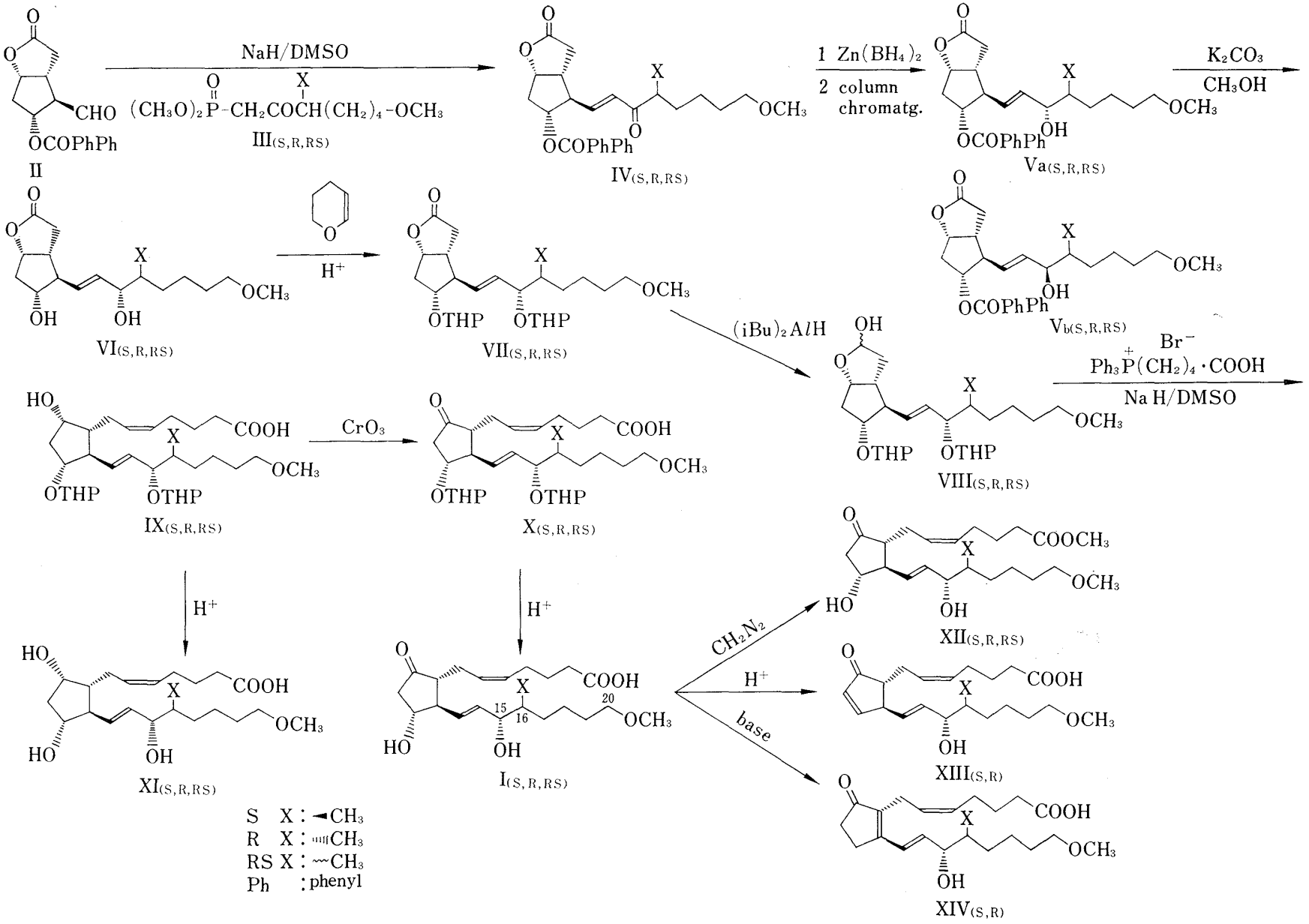

Chart 1

methyl-PGE_2,[10] 16-dimethyl-PGE_2[11] and 17-oxa-PGE_2-derivatives[12] have aroused particular interest.

Among several hundred derivatives of PGs which have been synthesized by our laboratories, this report describes the synthesis of 16(*S*)-methyl-20-methoxy-PGE_2 (YPG-209) (I_S) and 16(*R*)-methyl-20-methoxy-PGE_2 (I_R), which were shown to have oral bronchodilator activity by our laboratories,[13] and the synthesis of analogs, such as 16-methyl-20-ethoxy-PGE_2 ($XXVII_a$), 16-methyl-20-hydroxymethyl-PGE_2 ($XXVI_a$), 16-methyl-17-oxa-ω-dihomo-PGE_2 ($XXVIII_a$) and 20-hydroxymethyl-PGE_2 (XXX). Their biological activities are also discussed.

The synthesis of 16-methyl-20-methoxy-PGE_2 ($I_{S,R,RS}$) was carried out according to Corey's procedure[7] as shown in Chart 1. Corey's intermediate (II)[7,14] was reacted with sodium dimethyl-(7-methoxy-3(*S*)-methyl-2-oxo-heptyl)-phosphonate (III_S) to provide the enone (IV_S). III_S was synthesized from *d*-2(*S*)-methyl-6-methoxyhexanoic acid (XIX_S), obtained by the resolution of *dl*-2-methyl-6-methoxyhexanoic acid (XIX) with cinchonidine (Chart 2). The *S*-configuration of XIX_S was determined to be shown in Chart 3, by comparing *d*-2-methylhexanol ($XXIV_R$) derived from *l*-2-methyl-6-methoxyhexanoic acid (XIX_R) with *l*-2(*S*)-methylhexanol ($XXIV_S$) derived from *d*-2(*S*)-methylhexanoic acid (XXV) whose absolute configuration is known.[15] 15α-Hydroxy-lactone (V_{aS}) and the 15β-epimer (V_{bS}) were obtained by the reduction of IV_S with zinc borohydride, followed by the separation of V_{aS} and V_{bS} using silica gel column chromatography. V_{aS} preceded V_{bS}, and the ratio of V_{aS} to V_{bS} was about 2.5 to 1. The configurations of the 15-hydroxy epimers (V_{aS} and V_{bS}) were determined

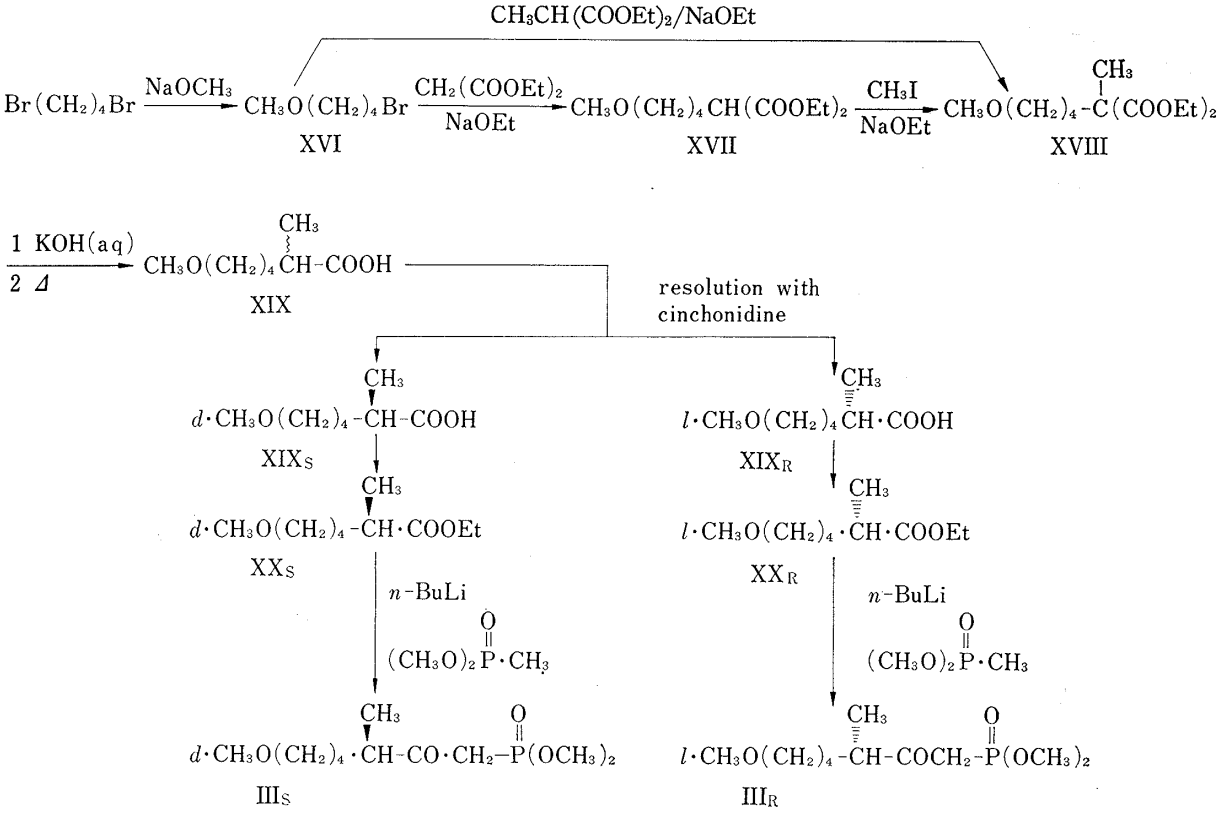

Chart 2

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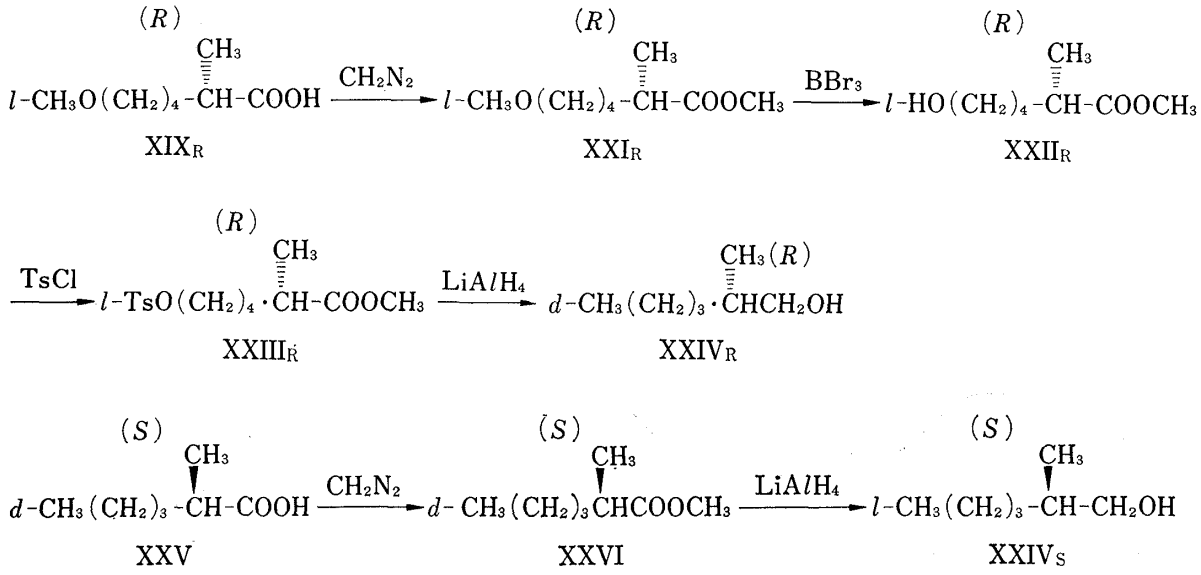

Chart 3

on the basis of their biological activities after completion of the syntheses of I_S and its 15-epimer using V_{aS} and V_{bS}, respectively.[16] The conversion of V_{bS} to V_{aS} was achieved by a modified Robinson procedure using diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid,[17] or by the reoxidation of V_{bS} to IV_S, followed by reduction of IV_S as described above. Deacylation of V_{aS} with potassium carbonate in methanol gave the dihydroxy lactone (VI_S), which was converted into ditetrahydropyranyl derivative (VII_S). VII_S was reduced to the lactol ($VIII_S$) with diisobutylaluminium hydride. The condensation of $VIII_S$ with the Wittig reagent derived from 5-triphenylphosphonio-pentanoic acid bromide and sodio methylsulfinylcarbanide in dimethylsulfoxide gave 11,15-ditetrahydropyranyl-16(*S*)-methyl-20-methoxy-$PGF_{2\alpha}$ (IX_S). Hydrolysis of IX_S with acetic acid gave 16(*S*)-methyl-20-methoxy-$PGF_{2\alpha}$ (XI_S). Jones oxidation of IX_S followed by removal of protecting groups gave 16(*S*)-methyl-20-methoxy-PGE_2 (YPG-209) (I_S). Esterification of I_S with diazomethane provided XII_S. I_S was also converted to 16(*S*)-methyl-20-methoxy-PGA_2 ($XIII_S$) or 16(*S*)-methyl-20-methoxy-PGB_2 (XIV_S) by treating it with strong acid or base, respectively.

16(*R*)-Methyl-20-methoxy-PGE_2 (I_R), 15-epi-16(*S*)-methyl-20-methoxy-PGE_2 and 15-epi-16-(*R*)-methyl-20-methoxy-PGE_2, which are diastereoisomers of I_S, were also synthesized in a similar manner. Data for the synthesized diastereoisomers are summarized in Table I. Furthermore, we synthesized several analogs of I_S (listed in Table II) using the Corey's procedure[7]; these include 16-methyl-20-ethoxy-PGE_2 ($XXVII_a$), 16-methyl-20-hydroxy-methyl-PGE_2 ($XXVI_a$), 16-methyl-17-oxa-ω-dihomo-PGE_2 ($XXVIII_a$), and 20-hydroxy-methyl-PGE_2 (XXX). Details of the syntheses of these analogs will be reported elsewhere. These diasteroisomers and analogs of I_S are of interest in connection with studies of the structure-biological activity relationships.

The biological activities of I_S, I_R and related compounds are summarized in Table II. PGE_2, 20-methoxy-PGE_2 (XXIX)[12c] and 20-hydroxymethyl-PGE_2 (XXX), after oral administration at 800 μg/kg, showed no bronchodilator or diarrheal effect. However, I_{RS}, and $XXVI_a$, which carry methyl groups at the 16-position of XXIX and XXX, respectively, each

16) The configuration of 15-hydroxy epimers of PG derivatives is generally determined on the basis of their biological activities. The 15α-hydroxy epimer(natural PG-type) shows strong biological activity, but the 15β-epimer shows little activity. X-Ray analysis of I_S (YPG-209) is being carried out by Dr. G.T. DeTitta and Dr. M.E. Erman of the Medical Foundation of Buffalo, Inc.

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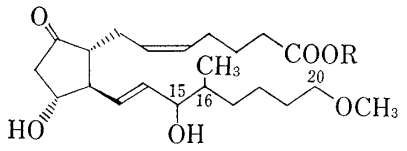
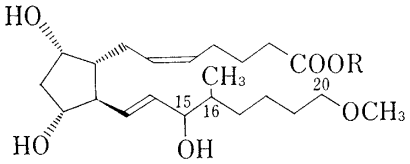
Table I. 16-Methyl-20-methoxy-PGs



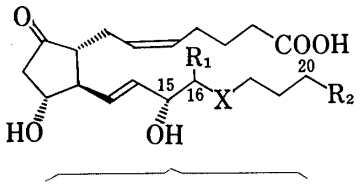
Compound	R	Configuration at C_{15}	Configuration at C_{16}	NMR ($CHCl_3$) δ	$[\alpha]_D^{22}$ (Solvent)
I_S (YPG-209)	H	····OH	—CH_3	0.88 (3H, d, J=7 cps, CH_3), 3.33 (3H, s, OCH_3), 5.28—5.52 (2H, –CH=CH-), 5.52—5.72 (2H, –CH=CH–), 3.8—4.2 (2H, broad, –C<u>H</u>–OH)	−65° (c=0.5, $CHCl_3$)
I_R	H	····OH	····CH_3	0.91 (3H, d, J=7 cps, CH_3), 3.32 (3H, s, OCH_3), 5.30—5.52 (2H, –CH=CH–), 5.56—5.76 (2H, –CH=CH–), 3.90—4.24 (2H, broad, –C<u>H</u>–OH)	−58.5° (c=1.5, $CHCl_3$)
I_{RS}	H	····OH	∿CH_3	0.70—1.10 (3H, CH_3), 3.33 (3H, s, OCH_3), 5.20—5.52 (2H, –CH=CH–), 5.52—5.84 (2H, –CH=CH–), 3.80—4.30 (2H, broad, –C<u>H</u>–OH)	−51.5° (c=0.78, CH_3OH)
	H	—OH	∿CH_3		−60.2° (c=0.82, CH_3OH)
XII_S	CH_3	····OH	—CH_3	0.88 (3H, d, J=7 cps, CH_3), 3.34 (3H, s, OCH_3), 3.64 (3H, s, $COOCH_3$), 5.20—5.48 (2H, –CH=CH–), 5.48—5.70 (2H, –CH=CH–), 3.80—4.20 (2H, –C<u>H</u>–OH)	−66.4° (c=0.4, $CHCl_3$)
XII_R	CH_3	····OH	····CH_3	0.88 (3H, d, J=7 cps, CH_3), 3.33 (3H, s, OCH_3), 3.66 (3H, s, $COOCH_3$), 5.20—5.50 (2H, –CH=CH–), 5.50—5.70 (2H, –CH=CH–), 3.80—4.20 (2H, –C<u>H</u>–OH)	−58.0° (c=0.6, $CHCl_3$)



XI_{RS}	H	····OH	∿CH_3	0.7—1.1 (3H, broad, CH_3), 3.3 (3H, s, OCH_3), 5.2—5.8 (4H, –CH=CH–), 3.7—4.0 (2H, broad, –C<u>H</u>–OH)	+26.3° (c=0.56, CH_3OH)
	H	—OH	∿CH_3	4.0—4.3 (1H, broad, –C<u>H</u>–OH)	+13.0° (c=0.37, CH_3OH)

showed a more potent bronchodilator effect than the parent compound. $XXVII_a$ and $XXVIII_a$ also showed bronchodilator activity. Their ED_{50} values, however, were 5 times and 2 times, respectively, lower than that of I_{RS}. I_{RS} is a mixture of I_S and I_R (1:1). I_S (YPG-209), I_R and I_{RS} showed potent bronchodilator action. The bronchoselectivity of I_S was higher than that of I_R. Further details of the bronchodilator activity of I_S, I_R and I_{RS} have already been published by our laboratories[13] and details of the biological activities of other compounds listed in Tables I and II will be reported shortly.

Table II. Biological Activities



	R_1	R_2	X	Broncho-dilator effect ED_{50} (μg/kg, *p.o.*) (a)	Diarrhea ED_{50} (μg/kg, *p.o.*) (b)	Broncho-selectivity b / a	lit.
PGE_2	H	–H	CH_2	>800	>800	—	
XXIX	H	$-OCH_3$	CH_2	>800	>800	—	12 *c*
XXX	H	$-CH_2OH$	CH_2	>800	>800	—	
$XXVI_a$	~~CH_3	$-CH_2OH$	CH_2	>800	>800	—	
I_{RS}	~~CH_3	$-OCH_3$	CH_2	9.8	120	12.2	
I_S (YPG-209)	—CH_3	$-OCH_3$	CH_2	7.0	140	20	
I_R	····CH_3	$-OCH_3$	CH_2	9.0	44	4.9	
$XXVII_a$	~~CH_3	$-OCH_2CH_3$	CH_2	52	480	9.2	
$XXVIII_a$	~~CH_3	$-CH_2CH_3$	O	25	12.5	0.5	

Experimental[18]

4β-[8-Methoxy-4(*S*)-methyl-3-oxo-1-(*trans*)octenyl]-2-oxo-5α-*p*-phenylbenzoyloxy-3,3aβ,4α,5β,6,6aβ-hexahydro-2H-cyclopenta[*b*]furan (IV_S)——a) A suspension of 528 mg of 50% oily NaH in 45 ml of dry dimethoxyethane (DME) was prepared under a nitrogen stream and after adding dropwise a solution of 2.93 g of dimethyl-(7-methoxy-3(*S*)-methyl-2-oxo)heptylphosphonate (III_S) in 20 ml of dry DME, the whole was stirred for 90 minutes at room temperature. Next, a solution of 4.04 g of Corey's intermediate (II) in 80 ml of dry tetrahydrofuran (THF) was further added dropwise and the resulting mixture was stirred for 90 minutes at room temperature. The reaction mixture was neutralized with dry ice powder, and after adding 150 ml of H_2O and saturating with NaCl, the resulting mixture was extracted 4 times with 50 ml each of CH_2Cl_2. The extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The oily product obtained was subjected to silica gel column chromatography and developed using a mixture of ether and *n*-hexane (3: 1 by volume ratio) to provide 3.3 g of IVs showing $[\alpha]_D^{23}$ −86.3° (*c*=1.0, $CHCl_3$). IR(film) cm^{-1}: 2950, 2875, 1780, 1720, 1710, 1680, 1630, 1615. NMR of IVs δ: 1.07 (3H, d, *J*=7 cps, CH_3), 3.28 (3H, s, OCH_3), 6.32 (1H, d, *J*=16 cps, –CH=CH–CO–), 6.74 (1H, dd, *J*=16 cps, –CH=CH–CO–), 5.35 (1H, m, –CH–OCO–PhPh).

b) In a similar manner, the 4(*R*)-isomer of IVs (IV_R) was synthesized from dimethyl-(7-methoxy-3(*R*)-methyl-2-oxo)-heptylphosphonate (III_R): $[\alpha]_D^{25}$ −118° (*c*=3.8, $CHCl_3$). IR (film) cm^{-1}: 2950, 2875, 1780, 1720, 1710, 1675, 1630, 1615.

4β-[3(*S*)-Hydroxy-8-methoxy-4(*S*)-methyl-1-(*trans*)octenyl]-2-oxo-5α-*p*-phenylbenzoyloxy-3,3aβ,4α,5β,6,-6aβ-hexahydro-2H-cyclopenta[*b*]furan (V_{aS}) and Its 3(*R*)-Hydroxy-isomer (V_{bS})——a) A suspension of 1.65 g of $NaBH_4$ and 2.98 g of anhydrous $ZnCl_2$ in 200 ml of dry ether was prepared, and after stirring for 90 minutes at room temperature, a solution of 3.3 g of IVs in 50 ml of dry THF was added dropwise, followed by stirring for 2 hours at room temperature. The reaction mixture was neutralized with dry ice powder and after adding 150 ml of H_2O, the resulting mixture was extracted 3 times with 50 ml each of ether. The extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to provide 2.8 g of an oily product. The oily product was subjected to silica gel column chromatography and developed using a mixture of ether and *n*-hexane (4: 1 by volume) as the eluting solution to provide 1.26 g of V_{aS} showing $[\alpha]_D^{24}$ −126.1° (*c*=0.3, $CHCl_3$) and 0.5 g of the 3(*R*)-hydroxy-isomer (V_{bS}) showing

18) All boiling points and melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated, using tetramethylsilane as an internal standard, on a JEOL JNM-MH-100 instrument. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

$[\alpha]_D^{23}$ −110.5° (c=2, $CHCl_3$). IR (film) cm^{-1}: 3450, 2940, 2870, 1770, 1710, 1605. NMR of V_a δ: 0.82 (3H, d, J=7 cps, CH_3), 3.27 (3H, s, OCH_3), 3.95 (1H, m, -C<u>H</u>-OH), 5.5—5.7 (2H, -CH=CH-), 5.25 (1H, m, -C<u>H</u>-OCO-PhPh).

b) The 4(R)-isomer (V_{aR}) and 4(RS)-isomer (V_{aRS}) of V_{aS} were synthesized from IV_R and IV_{RS}, respectively, by the same procedure. V_{aR}: $[\alpha]_D^{25}$ −83° (c=1.5, $CHCl_3$). IR(film) cm^{-1}: 3500, 2950, 2875, 1780, 1720, 1605. V_{aRS}: $[\alpha]_D^{25}$ −74.1° (c=2.37, $CHCl_3$).

4β-[3(S)-Hydroxy-8-methoxy-4(S)-methyl-1-(*trans*)octenyl]-2-oxo-5α-hydroxy-3,3aβ,4α,5β,6,6aβ-hexahydro-2H-cyclopenta[*b*]furan (VI_S)——a) A solution of 1.21 g of V_{aS} in 40 ml of dry methanol (MeOH) was prepared, and after adding 169 mg of anhydrous K_2CO_3, the mixture was stirred for 3 hours at room temperature. The reaction mixture was then neutralized with 147 mg of glacial acetic acid (g-AcOH) and MeOH was distilled off under reduced pressure. After adding 30 ml of H_2O to the residue thus obtained and saturating with NaCl, the mixture was extracted 3 times with 30 ml each of ether. The extracts were combined, washed with saturated saline solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The oily product thus obtained was subjected to silica gel column chromatography and developed using a mixture of $CHCl_3$ and ethyl acetate (AcOEt) (1: 4 by volume) to provide 651.7 mg of VI_S showing $[\alpha]_D^{23}$ −1.73° (c=1.2, $CHCl_3$). IR(film) cm^{-1}: 3400, 2950, 2875, 1770. NMR of VI_S δ: 0.85 (3H, d, J=7 cps, CH_3), 3.32 (3H, s, OCH_3), (2H, m, -C<u>H</u>-OH), 5.3—5.7 (2H, -CH=CH-).

b) The 4(R) and 4(RS)-isomers of VI_S were synthesized from V_{aR} and V_{aRS}, respectively, in a similar manner. 4(R)-Isomer (VI_R): $[\alpha]_D^{25}$ +7.1° (c=1.6, $CHCl_3$). IR(film) cm^{-1}: 3400, 2950, 2875, 1765. 4(RS)-Isomer (VI_{RS}): $[\alpha]_D^{25}$ +2.43° (c=1.85, $CHCl_3$).

4β-[8-Methoxy-4(S)-methyl-3(S)-tetrahydropyran-2-yloxy-1-(*trans*)octenyl]-2-oxo-5α-(tetrahydropyran-2-yloxy)-3,3aβ,4α,5β,6,6aβ-hexahydro-2H-cyclopenta[*b*]furan (VII_S)——a) A solution of 650 mg of VIs in 13 ml of dry CH_2Cl_2 was prepared, and after adding 699 mg of 2,3-dihydropyran and 4 mg of p-toluenesulfonic acid monohydrate, the whole was stirred for 30 minutes at room temperature. When the reaction was over, 50 ml of $CHCl_3$ and 20 ml of dilute aqueous $NaHCO_3$ solution were added to the reaction mixture, followed by shaking. The organic layer was separated, washed with H_2O, and dried over anhydrous $MgSO_4$, then the solvent was distilled off under reduced pressure. The residue obtained was applied to a silica gel column and developed using a mixture of ether and n-hexane (1: 2 by volume) as an eluting solution to provide 869 mg of oily VII_S which crystallized gradually (mp 40—53°): IR(film) cm^{-1}: 2940, 2860, 1775. NMR of VII_S δ: 0.85 (3H, d, J=7 cps, CH_3), 3.32 (3H, s, OCH_3), 3.9 (2H, m, -C<u>H</u>-OTHP), 5.3—5.6 (2H, -CH=CH-).

b) In a similar manner, the 4(R) and 4(RS)-isomers of VII_S were synthesized from VI_R and VI_{RS}, respectively. 4(R)-Isomer (VII_R): $[\alpha]_D^{27}$ −27.4° (c=1.75, $CHCl_3$). IR(film) cm^{-1}: 2950, 2875, 1780.

4β-[8-Methoxy-4(S)-methyl-3(S)-(tetrahydropyran-2-yloxy)-1-(*trans*)octenyl]-2-hydroxy-5-(tetrahydropyran-2-yloxy)-3,3aβ,4α,5β,6,6aβ-hexahydro-2H-cyclopenta[*b*]furan ($VIII_S$)——A solution of 555 mg of VII_S in 40 ml of dry toluene was prepared under a nitrogen stream and the solution was cooled to −60° with dry ice-acetone. Next, 3.36 ml of a toluene solution containing 328.3 mg of diisobutylaluminum hydride was added dropwise under a nitrogen stream and the mixture was stirred for 30 minutes; 0.3 ml of AcOEt and 0.3 ml of MeOH were then added successively to the mixture at the same temperature. After warming to room temperature, 50 ml of H_2O was added to the mixture, yielding a white precipitate. This was filtered off and the filtrate was separated into an aqueous layer and an organic layer. The aqueous layer was extracted twice with 50 ml each of benzene and the extracts were combined with the organic layer. The mixture was washed with saturated saline solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure below room temperature to provide 492.2 mg of $VIII_S$. IR(film) cm^{-1}: 3400, 2940, 2860.

The 4(R)-isomer ($VIII_S$) and 4(RS)-isomer ($VIII_{RS}$) of VIIIs were synthesized by the same procedure using VII_R and VII_{RS}, respectively. IR of $VIII_R$ (film) cm^{-1}: 3400, 2940, 2875.

11,15-Ditetrahydropyranyl-16(S)-methyl-20-methoxy-PGF$_{2\alpha}$ (IX_S)——a) Dry dimethyl sulfoxide (DMSO) (7 ml) was added to 211.5 mg of 50% oily NaH under a nitrogen stream, and after heating to 60—65°, the mixture was stirred for about 1 hour until the evolution of hydrogen gas ceased. The mixture was then cooled to room temperature and 1.01 g of 4-carboxybutyl-triphenylphosphonium bromide was added. A solution of 442.9 mg of VIIIs in 5 ml of dry DMSO was then added to the clear red solution thus obtained and the mixture was stirred for 1 hour at room temperature. The reaction mixture was neutralized with dry ice powder and then a mixture of 60 ml of ether and 30 ml of H_2O saturated with dry ice was further added. The organic layer was separated and the aqueous layer was extracted 3 times with 30 ml each of AcOEt. The extracts were combined with the organic layer and the mixture was washed with ice water, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography and developed using a mixture of AcOEt and n-hexane (1: 1 by volume) to provide 262 mg of IX_S showing $[\alpha]_D^{22}$ +76.8° (c=2.0, $CHCl_3$). IR(film) cm^{-1}: 3450, 2950, 2875, 1740, 1720. NMR of IX_S δ: 0.85 and 0.9 (3H, d, J=7 cps, CH_3), 3.32 (3H, s, OCH_3), 5.2—5.7 (4H, -CH=CH-).

b) The 16(R) and 16(RS)-isomers of IX_S were synthesized from $VIII_R$ and $VIII_{RS}$, respectively, in a similar manner. 16(R)-Isomer (IX_R): $[\alpha]_D^{23}$ +5.8° (c=1.25, $CHCl_3$). 16(RS)-Isomer (IX_{RS}): $[\alpha]_D^{25}$ +1.32° (c=1.14, $CHCl_3$).

11,15-Ditetrahydropyranyl-16(*S*)-methyl-20-methoxy-PGE$_2$ (X_S)——a) A solution of 262 mg of IX_S in 7.7 ml of ether was prepared and cooled to 0° to −5°, then 7.7 ml of a solution prepared from 2.0 g of CrO_3, 9.65 g of $MnSO_4 \cdot nH_2O$, 2.13 ml of conc. H_2SO_4 and H_2O to make the total volume 50 ml, precooled to 0°, was added. The whole was stirred for 3 hours at the same temperature. When the reaction was over, 10 ml of H_2O was added and the mixture was extracted 3 times with 30 ml each of ether. The extracts were combined, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to provide 260 mg of X_S. The crude oil (X_S) obtained was used for the next steps without further purification.

b) Using the same procedure, the 16(*R*)- and 16(*RS*)-isomers of X_S were synthesized by oxidation of IX_R and IX_{RS}, respectively.

16(*S*)-Methyl-20-methoxy-PGE$_2$ (YPG-209) (I_S)——A solution of 260 mg of X_S in 4 ml of a mixture of AcOH, H_2O and THF (19: 11: 3 by volume) was prepared and stirred for 3 hours at 40°. The solvent was distilled off under reduced pressure and the residue obtained was applied to a silica gel column chromatography and developed using AcOEt to provide 119.2 mg of I_S (YPG-209), which was crystallized in a deep-freeze as needles having low melting point: IR($CHCl_3$) cm^{-1}: 3350, 2925, 2850, 1730, 1710. *Anal.* Calcd for $C_{22}H_{34}O_5$ (M^+-18): mass, 378.24042. Found: mass, 378.23912.

16(*R*)-Methyl-20-methoxy-PGE$_2$ (I_R) was synthesized from X_R in the manner described above. IR($CHCl_3$) cm^{-1}: 3400, 2950, 2880, 1750, 1720.

16(*RS*)-Methyl-20-methoxy-PGE$_2$ (I_{RS}) was also synthesized. IR($CHCl_3$) cm^{-1}: 3350, 2925, 2850, 1725, 1700. MS *m/e*: 378 (M^+-18), 360 (M^+-36).

16-Methyl-20-methoxy-PGF$_{2\alpha}$ (XI_{RS})——A solution of 122.3 mg of IX_{RS} in 5 ml of mixture of AcOH, H_2O and THF (19: 11: 3 by volume) was prepared and stirred for 3 hours at 40°. The solvents were distilled off under reduced pressure and the residue obtained was subjected to silica gel column chromatography using a mixture of AcOEt and *n*-hexane as the eluting solution to provide 45.3 mg of XI_{RS}. IR($CHCl_3$) cm^{-1}: 3350, 2920, 2850, 1700. MS *m/e*: 380 (M^+-18), 372 (M^+-36).

The 15-epimer of XI_{RS} was synthesized from V_{RS} by the same procedure. IR($CHCl_3$) cm^{-1}: 3380, 2920, 2850, 1700. *Anal.* Calcd for $C_{22}H_{36}O_5$ (M^+-18): mass, 380.25602. Found: mass, 380.25422.

16(*S*)-Methyl-20-methoxy-PGE$_2$ Methyl Ester (XII_S) and 16(*R*)-Methyl-20-methoxy-PGE$_2$ Methyl Ester (XIIs)——a) A solution of 124.6 mg of I_{RS} in 20 ml of ether was prepared and then an ether solution containing CH_2N_2 was added dropwise until the mixture became yellow, indicating completion of the reaction. The solvent was then distilled off under reduced pressure and the residue obtained was subjected to silica gel column chromatography using a mixture of AcOEt and *n*-hexane as the eluting solution to provide 40.6 mg of 16(*R*)-methyl-20-methoxy-PGE$_2$ methyl ester (XII_R) from the first eluate, followed by 28.8 mg of 16(*S*)-methyl-20-methoxy-PGE$_2$ methyl ester(XII_S). IR($CHCl_3$) cm^{-1}; 3350, 2920, 2850, 1720, 1680. MS *m/e* 392 (M^+-18), 374 (M^+-36), 361 ($M^+-18-OCH_3$).

b) 16(*S*)-Methyl-20-methoxy-PGE$_2$ (I_S) was dissolved in ether and the solution was treated with CH_2N_2 as described above. The solvent was evaporated off to give XII_S in quantitative yield. Using the same procedure, XII_R was also prepared from I_R.

16(*S*)-Methyl-20-methoxy-PGA$_2$ ($XIII_S$)——I_S (396 mg) was dissolved in a mixture of AcOH (20 ml) and H_2O (3 ml). The solution was allowed to stand overnight at 65° under a nitrogen stream. The reaction solution was concentrated under reduced pressure and the residual oil was purified by silica gel column chromatography using a mixture of AcOEt and *n*-hexane as the eluting solvent. A yellowish oil (320 mg) showing $[\alpha]_D^{22}$ +110.2° (*c*=1.0, $CHCl_3$) was obtained. IR($CHCl_3$) cm^{-1}: 3400, 2920, 2850, 1695, 1580. NMR of XIIIs δ: 0.72—0.96 (3H, $-CH_3$), 3.8—4.1 (1H, broad, $-C\underline{H}-OH$). 3.31 (3H, s, $-OCH_3$), 5.20—5.7 (4H, $-CH=CH-$), 6.18 and 7.51 (each 1H, dd, *J*=7 cps, $-C_{10}\underline{H}=C_{11}\underline{H}-$). *Anal.* Calcd for $C_{22}H_{34}O_5$: mass, 378.24043. Found: mass, 378.24353.

16(*S*)-Methyl-20-methoxy-PGB$_2$ (XIV_S)——A solution of 396 mg of I_S in a mixture of ethanol (EtOH) (16 ml) and 1 N NaOH aqueous solution (16 ml) was prepared and left for 1 hour at 30—40° under a nitrogen stream. The solution was concentrated to remove EtOH under reduced pressure and the residual aqueous solution was acidified with 1 N HCl solution. The oil precipitated was extracted with AcOEt. The extracted solution was washed with H_2O and dried over anhydrous $MgSO_4$, then AcOEt was evaporated off. The residual oil was purified by column chromatography on silica gel using a mixture of AcOEt and *n*-hexane as the eluting solvent. A colorless oil (289 mg) was obtained: $[\alpha]_D^{22}$ +38.9° (*c*=1.5, $CHCl_3$). IR($CHCl_3$) cm^{-1}: 3350, 2920, 2850, 1700, 1680, 1630, 1590. *Anal.* Calcd for $C_{22}H_{34}O_5$: mass, 378.24048. Found: mass, 378.24268. NMR of XIV_S δ: 0.9 (3H, d, *J*=7 cps, $-CH_3$), 3.31 (3H, s, $-OCH_3$), 4.1—4.32 (1H, broad, $-C\underline{H}-OH$), 6.30 (1H, dd, *J*=16 cps, $=C_{14}\underline{H}$), 6.89 (1H, d, *J*=16 cps, $C_{13}\underline{H}=$).

1-Bromo-4-methoxybutane (XVI)——A solution of 55.5 g of NaOMe in 180 ml of MeOH was prepared, and 120 g of dibromobutane was added dropwise under cooling with stirring. The resulting mixture was stirred overnight at room temperature, then refluxed for 1 hour. NaBr precipitated was removed by filtration, and the filtrate was concentrated. The residue obtained was distilled under reduced pressure to provide 45 g (yield 48.5%) of XVI having a boiling point of 52—73° (20—22 mmHg) (lit.,[19] 60—62° (15 mmHg)).

19) A. Kirrmann and L. Wartski, *Bull. Soc. Chim. France*, **1966**, 3825 [*Chem. Abstr.*, **66**, 54765*j* (1967)].

Diethyl 4-Methoxybutylmalonate (XVII)——A mixture of a solution of NaOEt (obtained from 250 ml of absolute EtOH and 4.23 g of Na) and 29.5 g of diethyl malonate, was stirred for 20 minutes at room temperature, then 30.7 g of XVI was added. After stirring overnight at room temperature, the mixture was refluxed for 2 hours. The solvent was distilled off under reduced pressure, and after adding ice-H_2O and ether to the residue, the resulting mixture was shaken well. The ether layer was separated and washed with H_2O, then dried over anhydrous $MgSO_4$. The solvent was distilled off to provide 40 g of XVII as an oily product. NMR of XVII δ: 3.30 (3H, s, OCH_3), 3.36 (2H, t, $J=7$ cps, $CH_3OC\underline{H}_2$–).

Diethyl 1-Methyl-5-methoxypentanedicarboxylate (XVIII)——a) A mixture of a solution of sodium ethylate (obtained from 200 ml of absolute EtOH and 3.74 g of Na) and 40 g of XVII was stirred at room temperature for 20 minutes, then 46.2 g of CH_3I was added dropwise. After stirring at room temperature overnight, the mixture was refluxed for 2 hours. The reaction solution was concentrated, then ice-H_2O and ether were added to the residue, and the whole was shaken well. The ether layer was separated, washed with H_2O, and then dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue obtained was distilled under reduced pressure to provide 24.8 g of XVIII having a boiling point of 92—94° (0.15 mmHg). NMR of XVIII δ: 1.4 (3H, s, CH_3), 3.30 (3H, s, OCH_3), 3.36 (2H, t, $J=7$ cps, $CH_3OC\underline{H}_2$–).

b) XVIII was also prepared by reacting XVI with diethyl methylmalonate in the presence of NaOEt in a similar manner.

2-Methyl-6-methoxyhexanoic Acid (*dl*-XIX)——KOH (49.6 g) was dissolved in a mixture of 30 ml of H_2O and 140 ml of EtOH, then 45 g of XVIII was added. The reaction mixture was refluxed for 2 hours, then concentrated, and 50 ml of ice-H_2O, was added to the residue. This solution was acidified with conc. HCl under cooling. The oily product that precipitated was extracted 3 times with 50 ml each of AcOEt. The extracts were washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue was heated at 160° for 2 hours for decarboxylation, then distilled under reduced pressure to provide 25 g (yield 90%) of XIX having a boiling point of 108—112° (0.3—0.6 mmHg). NMR of XIX δ: 1.18 (3H, d, $J=7$ cps, CH_3), 3.34 (3H, s, OCH_3), 3.40 (2H, t, $J=7$ cps, $CH_3OC\underline{H}_2$–), 2.4 (1H, m, –C$\underline{H}$–CO–).

Optical Resolution of *dl*-XIX——Cinchonidine was added to a solution of *dl*-XIX in acetone–H_2O mixture (4: 1 by volume) to provide the diastereoisomers of the cinchonidine salts of *d*- and *l*-2-methyl-6-methoxyhexanoic acid. The diastereoisomers were separated by fractional crystallization and treated in a conventional manner to provide the following two optical isomers.

d-2(*S*)-Methyl-6-methoxyhexanoic acid (XIX_S): $[\alpha]_D^{25}$ +15.0° ($c=4.0$, $CHCl_3$). Cinchonidine salt of XIX_S: $[\alpha]_D^{25}$ −77.2° ($c=1.0$, $CHCl_3$), mp 78—81°. *l*-2(*R*)-Methyl-6-methoxyhexanoic acid (XIX_R): $[\alpha]_D^{25}$ −14.0° ($c=4.0$, $CHCl_3$). Cinchonidine salt of XIX_R: $[\alpha]_D^{25}$ −83.7° ($c=1.0$, $CHCl_3$), mp 65—67°.

Assignment of the absolute configurations of XIX_S and XIX_R obtained above was accomplished as shown in Chart 3.

Ethyl *d*-2(*S*)-Methyl-6-methoxyhexanoate (XX_S) and Ethyl *l*-2(*R*)-Methyl-6-methoxyhexanoate (XX_R)——a) A solution of 5.3 g of XIX_S in 50 ml of EtOH saturated with HCl gas was prepared and allowed to stand at room temperature for 2 days, then 100 ml of saturated saline solution was added and the mixture was extracted with AcOEt. The extracts were washed with 50 ml of saline solution saturated with $NaHCO_3$ and twice with 50 ml each of saturated saline solution, and were then dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue obtained was distilled under reduced pressure to provide 4.7 g (yield 88.7%) of XX_S having a boiling point of 113° (23 mmHg): $[\alpha]_D^{25}$ +14.9° ($c=4.0$, $CHCl_3$).

b) In a similar manner, starting from the corresponding *l*-(*R*)-compound (XIX_R), XX_R having $[\alpha]_D^{25}$ −14.0° ($c=4.0$, $CHCl_3$) was obtained.

Dimethyl-(7-methoxy-3(*S*)-methyl-2-oxo)-heptyl-phosphonate (III_S) and Dimethyl-(7-methoxy-3(*R*)-methyl-2-oxo)-heptyl-phosphonate (III_R)——a) A solution of 6.2 g of dimethyl methylphosphonate in 45 ml of dry THF was prepared and 30 ml of *n*-hexane solution containing *n*-BuLi (1.58 mol/l) was added dropwise with stirring below −60° under a nitrogen atmosphere. Next, 4.7 g of a solution of XX_S in 20 ml of dry THF cooled below −60° was added dropwise. When this was completed, the reaction mixture was stirred at below −60° for 2 hours, and then at room temperature for 1—2 hours, then 3.5 ml of g-AcOH at 0° was added carefully. The solvent was evaporated off and 30 ml of ice-H_2O was added to the residue. This solution was saturated with NaCl and then extracted 3 times with 30 ml each of AcOEt. The extracts were washed twice with 30 ml of saturated saline solution and then dried over anhydrous $MgSO_4$. The solvent was evaporated off and the residue was distilled under reduced pressure. 5.0 g (yield 75%) of III_S having a boiling point of 130—142° (0.2—0.3 mmHg) was obtained: $[\alpha]_D^{25}$ +14.5° ($c=4.0$, $CHCl_3$). NMR of III_S δ: 1.12 (3H, d, $J=7$ cps, –C$\underline{H}$–C$\underline{H}_3$), 2.7 (1H, m, –C$\underline{H}$–CH_3), 3.13 (2H, d, $J=20$ cps, $-CH_2-P$), 3.30 (3H, s, OCH_3), 3.68 and 3.86 (each 3H, s, P–OCH_3).

b) In a similar manner, III_R was obtained using XX_R: $[\alpha]_D^{25}$ −13.8° ($c=2.45$, $CHCl_3$).

Methyl *l*-2(*R*)-Methyl-6-methoxyhexanoate (XXI_R)——XIX_R ($[\alpha]_D^{22}$ −11.6° ($c=1.0$, $CHCl_3$): e.e.=83%) was treated with CH_2N_2 in ether to obtain its methyl ester (XXI_R) in quantitative yield. $[\alpha]_D^{22}$ −13.5° ($c=2.0$, $CHCl_3$): NMR of XXI_R δ: 1.13 (3H, d, $J=7$ cps, CH_3), 2.44 (1H, m, –C$\underline{H}$–CH_3), 3.28 (3H, s, OCH_3), 3.32 (2H, t, $J=6$ cps, $-C\underline{H}_2-OCH_3$), 3.63 (3H, s, $-COOCH_3$).

Methyl *l*-2(*R*)-Methyl-6-hydroxyhexanoate ($XXII_R$)——A solution of XXI_R (1.27 g) in CH_2Cl_2 (6.5 ml) was added dropwise to 2 g of BBr_3 in CH_2Cl_2 (6.5 ml) with stirring at 0°. The stirring was continued for

1 hour at 0°, then 35 ml of 5% aqueous $NaHCO_3$ was added to the reaction solution and the mixture was shaken well. The organic layer was separated and washed with 5% aqueous $NaHCO_3$ and H_2O, then dried over anhydrous $MgSO_4$. The dried solution was concentrated under reduced pressure. The oily residue obtained was purified by column chromatography on silica gel using $CHCl_3$ followed by AcOEt as eluting solvents. A colorless oil (261 mg) was obtained: $[\alpha]_D^{20}$ −13.4° (c=3.0, $CHCl_3$). NMR of $XXII_R$ δ: 1.13 (3H, d, J=7 cps, –CH–C$\underline{H}_3$), 2.42 (1H, m, –C$\underline{H}$–CH_3), 3.6 (2H, t, J=8 cps, HO–C$\underline{H}_2$–), 3.64 (3H, s, –$COOCH_3$).

Methyl *l*-2(*R*)-Methyl-6-*p*-toluenesulfonyloxyhexanoate ($XXIII_R$)——$XXII_R$ (255 mg) and *p*-toluenesulfonyl chloride (320 mg) were dissolved in pyridine (2.35 ml) and the solution was stirred for 3.5 hours at room temperature. CH_2Cl_2 (70 ml) and H_2O were added to the reaction mixture and the whole was shaken well. The organic layer was separated and washed with 5% aqueous $NaHCO_3$ and saturated saline solution, then dried over anhydrous $MgSO_4$. The solvent was evaporated off under reduced pressure. The residual oil was purified by column chromatography using $CHCl_3$ as an eluting solvent. 338 mg of colorless oil ($XXIII_R$) showing $[\alpha]_D^{22}$ −8.44° (c=2.0, $CHCl_3$) was obtained. NMR of $XXIII_R$ δ: 1.1 (3H, d, J=7 cps, –CH–C$\underline{H}_3$), 2.4 (1H, m, –C$\underline{H}$–CH_3), 2.45 (3H, s, C$\underline{H}_3$–Ph–), 4.02 (2H, t, J=6 cps, –O–CH_2–).

***d*-2(*R*)-Methylhexanol ($XXIV_R$)**——$XXIII_R$ (173.5 mg) in THF (2.2 ml) was added to a suspension of $LiAlH_4$ (158 mg) in THF (2.2 ml). The mixture was stirred for 5.5 hours at 60—65°. The mixture was cooled to 0° in an ice-H_2O bath, then ether (50 ml) was added, followed by ice-H_2O (1.5 ml) and cold 10% H_2SO_4 (3 ml), with stirring. The ether layer was separated and washed with 5% aqueous $NaHCO_3$ and saturated saline solution, then dried over $MgSO_4$. The dried solution was concentrated under reduced pressure and the residual oil was purified by column chromatography on silica gel using $CHCl_3$ as an eluting solvent. The product was a colorless oil (57.6 mg) showing $[\alpha]_D^{20}$ +8.36° (c=3.5, $CHCl_3$). NMR of $XXIV_R$ δ: 0.88 (3H, t, J=6 cps, C$\underline{H}_3$–CH_2–), 0.9 (3H, d, J=7 cps, C$\underline{H}_3$–CH–), 2.48 (2H, m, –C$\underline{H}_2$–OH).

***l*-2(*S*)-Methylhexanol ($XXIV_S$)**——a) *d*-2(*S*)-Methylhexanoic acid (XXV) ($[\alpha]_D^{20}$ +15.8° (c=1.0, $CHCl_3$))[15] was converted to its methyl ester (XXVI) by treatment with CH_2N_2 in ether in quantitative yield; $[\alpha]_D^{20}$ +20.3° (c=1.0, $CHCl_3$). NMR of XXVI δ: 0.82 (3H, t, J=6 cps, –CH_2C$\underline{H}_3$), 1.1 (3H, d, J=7 cps, CH_3), 2.38 (1H, m, –C$\underline{H}$–$COOCH_3$), 3.60 (3H, s, -$COOCH_3$).

b) XXVI (73.8 mg) in THF (1.5 ml) was added dropwise to a suspension of $LiAlH_4$ (92.5 mg) in THF (2 ml) during 10 minutes with stirring, and the reaction mixture was further stirred for 2 hours at 70°, then cooled to 0°. Ether (10 ml) was added, followed by ice-H_2O (1.5 ml) and cold 10% H_2SO_4 (2 ml). The ether layer was washed with saturated saline solution and dried over anhydrous $MgSO_4$. The solvent was evaporated off to leave a colorless oil (56.0 mg) ($XXIV_S$) showing $[\alpha]_D^{20}$ −21.1° (c=3.5, ether), and $[\alpha]_D^{20}$ −9.2° (c=2.5, $CHCl_3$). NMR of $XXIV_S$ δ: 0.88 (3H, t, J=6 cps, –CH_2C$\underline{H}_3$), 0.9 (3H, d, J=7 cps, C$\underline{H}_3$–CH–), 2.48 (2H, m, –C$\underline{H}_2$–OH).

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