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Synthesis of 15-*cis*-(4-*n*-Propylcyclohexyl)-16,17,18,19,20-pentanor-9-deoxy-6,9α-nitriloprostaglandin F_1 Methyl Ester (OP-2507), a Novel Anti-cerebral Ischemic Agent

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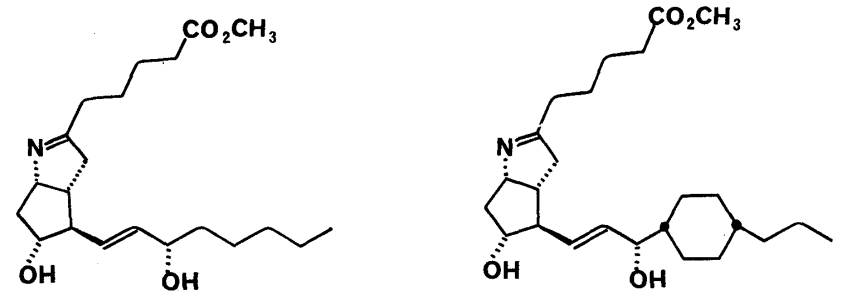
Synthesized was 15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanor-9-deoxy-6,9α-nitriloprostaglandin F_1 methyl ester (OP-2507), a novel, promising anti-cerebral ischemic agent. A key intermediate, methyl *cis*-4-*n*-propylcyclohexanecarboxylate, was prepared stereoselectively by the hydrogenation of methyl 4-*n*-propylbenzoate with commercially available dimer of chloro(1,5-cyclooctadiene)rhodium as a catalyst. Stereoselective reduction of C_{15}-ketone to $C_{15\alpha}$-alcohol was achieved with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide.

Keywords——prostacyclin analog; anti-cerebral ischemic agent; stereoselective hydrogenation; chloro(1,5-cyclooctadiene)rhodium dimer; diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide

At present there are few effective therapeutic drugs for acute cerebral ischemic edema, and considerable efforts have been devoted to the development of such drugs. Prostaglandins and prostacyclin are known to have a variety of biological activities, and many analogs of the both compounds are being synthesized as candidate drugs for the treatment of diseases. Recently beneficial effects of prostacyclin have been observed in an animal hypoxic and ischemic model[1] and in patients with ischemic stroke.[2] It has also been shown that slow reacting substances of anaphylaxis (SRS-A)[3] and thromboxane A_2 (TXA_2)[4] might play important roles in the formation of cerebral ischemic edema, and that prostacyclin, which possesses opposite bioactivity to TXA_2, inhibited SRS-A release.[5] However, prostacyclin is too unstable (half life in an aqueous solution at 37 °C is 5 min) as a drug. Therefore, much attention has been focused on the development of novel and stable prostacyclin analogs with such activities.

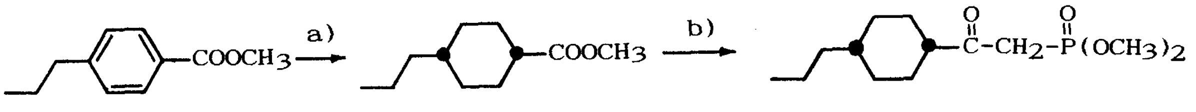
In the research for stable mimics of prostacyclin, a number of analogs have been prepared in which the unstable enol ether linkage is replaced by a more stable grouping.[6] One target molecule of this type was the nitrogen-containing prostacyclin, 9-deoxy-6,9α-nitriloprostaglandin F_1 methyl ester **1a**.[7] In order to increase the bioactivity, we have carried out the modification of its ω-chain, and have found that the highest anti-cerebral ischemic activity was obtained when a *cis*-4-*n*-propylcyclohexane ring was introduced at C_{15}.

We have evaluated the activity of a novel, stable prostacyclin analog, 15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanor-9-deoxy-6,9α-nitriloprostaglandin F_1 methyl ester **1b** (OP-2507), on the acute cerebral ischemic edema using the middle cerebral artery occlusion model in cats.[8] The specific gravity of the cortex showed a significant reduction after the middle cerebral artery occlusion, and this reduction was prevented by the intravenous infusion of OP-2507. In addition, OP-2507 was highly potent in its effect on cerebral energy metabolites in hypoxic mice, and also significantly prolonged the time of the gasping



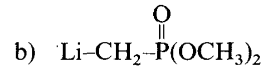
1a **1b**: OP-2507

Fig. 1



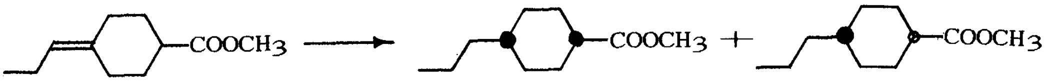
2 **3** **4**

a) H_2-chloro(1,5-cyclooctadiene)rhodium dimer



b) $\mathrm{Li{-}CH_2{-}\overset{O}{\overset{\|}{P}}(OCH_3)_2}$

Chart 1



5 **3** *trans* isomer of **3**

Chart 2

movement by s.c. or *p.o.* administration in complete ischemia in mice.[9] Furthermore, it was found to be effective on normoboric hypoxia in mice.[9]

Herein we describe the total synthesis of OP-2507, which possesses a methyl ester, an imino group and a *cis*-cyclohexane ring in a molecule. Chart 1 shows the synthetic route to the important intermediate, the *cis*-phosphonate **4**, for the construction of the ω-chain. The most crucial step in this synthesis was the stereoselective preparation of methyl *cis*-4-*n*-propylcyclohexanecarboxylate (**3**). At first, the catalytic hydrogenation of methyl 4-(1-propylidene)cyclohexanecarboxylate (**5**) using many kinds of the commercially available catalysts did not afford the satisfactory *cis*-selectivity: methyl *cis*-4-*n*-propylcyclohexanecarboxylate (**3**) was obtained in a slight excess over its *trans* isomer (Chart 2).

The catalytic hydrogenation of methyl 4-*n*-propylbenzoate (**2**) utilizing the common catalysts, Raney Ni or Pd–C, led predominantly to the undesired methyl *trans*-4-*n*-propylcyclohexanecarboxylate (*cis*/*trans*, 1/5). Various catalysts were tried to use in vain in this hydrogenation involving Ir-black, $IrCl(CO)(PPh_3)_2$, $RuCl_3$, $PdCl_2(PPh_3)_2$, and $(C_5H_5)_2Ni$. After these extensive trials had given unsatisfactory *cis*-selectivities, we found that *cis*-selective hydrogenation could be achieved by use of a catalytic amount of commercially available dimer of chloro(1,5-cyclooctadiene)rhodium, $[RhCl(COD)]_2$,[10] hydrogen (50 atm), hexane as an organic phase and a buffer solution at pH 7.6 containing a quaternary salt as a phase-transfer catalyst[11] at room temperature. Table I lists the results of hydrogenation of **2** using several types of rhodium catalysts and phase-transfer catalysts. Among them, a

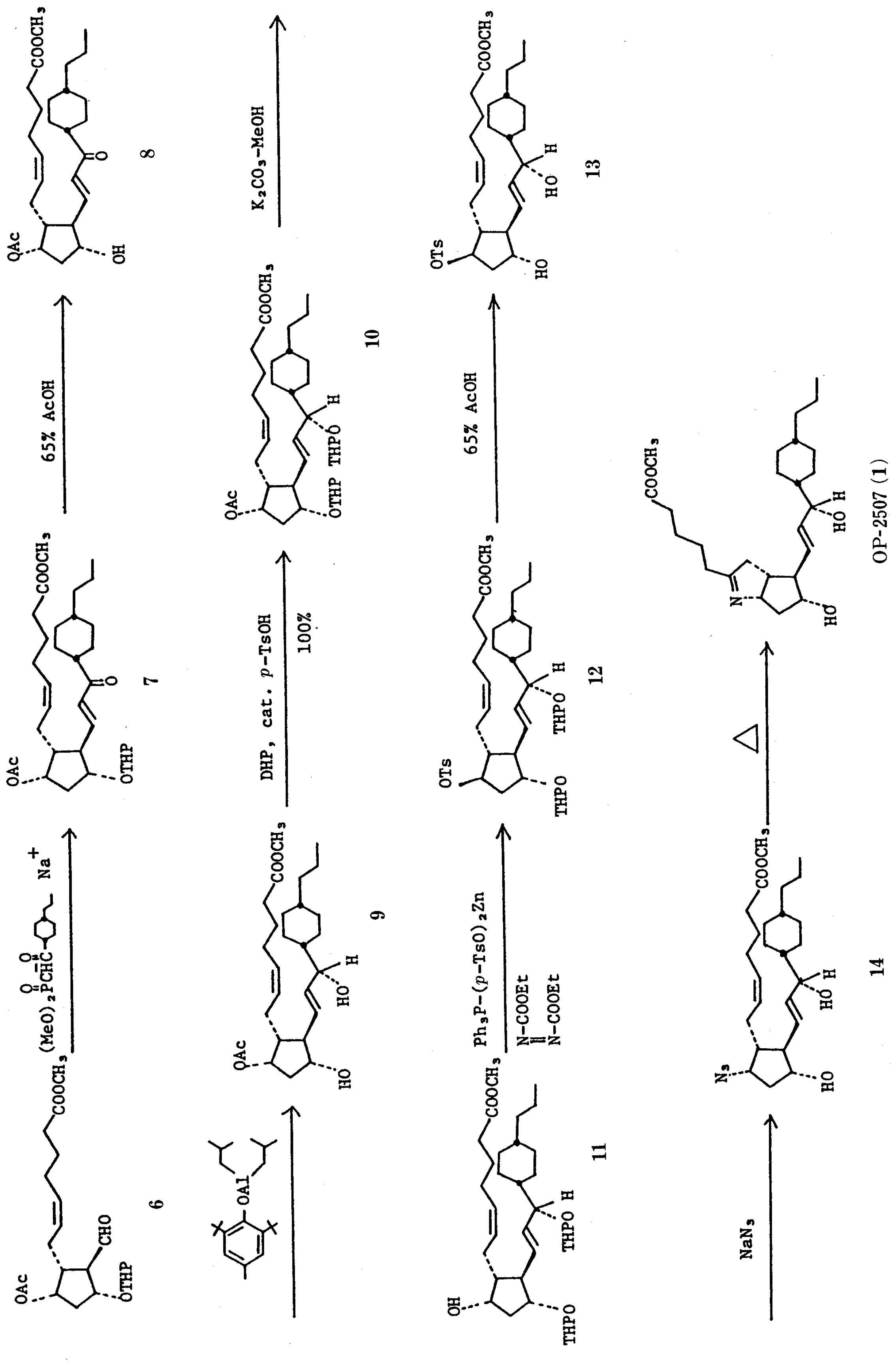


Chart 3. Synthetic Route to OP-2507

combination of $[RhCl(COD)]_2$ as a hydrogenation catalyst and tetra-*n*-butylammonium hydrogensulfate afforded the best result: **2** was converted smoothly to the desired methyl *cis*-4-*n*-propylcyclohexanecarboxylate **3** and its *trans*-isomer (the ratio, 84/16). The both isomers could be separated cleanly by column chromatography on silica gel. Their structures were confirmed by ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) analysis: the ^{1}H-NMR spectrum of each isomer was identical with that of the corresponding authentic sample[12)] and the ^{13}C-NMR chemical shifts of each isomer were in good agreement with those of methyl 4-*cis*- and 4-*trans*-methylcyclohexanecarboxylate reported by Senda *et al.*[13)] Table II shows the chemical shifts in the ^{13}C-NMR spectra of the both isomers.

The treatment of the *cis*-ester **3** with the anion derived from dimethyl methylphosphonate and *n*-butyllithium in tetrahydrofuran (THF) at −78 °C gave the *cis*-phosphonate **4** in 84% yield without isomerization at the cyclohexane ring according to the NMR analysis and thin layer chromatographic (TLC) mobility.

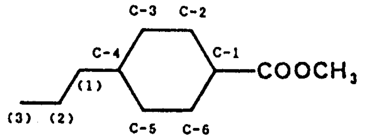
The synthetic route to the final OP-2507 is straight-forward as shown in Chart 3. The ω-chain was introduced by the Wadsworth–Emmons reaction of the aldehyde **6**[14)] with the anion derived from the *cis*-phosphonate **4** and sodium hydride in THF at room temperature in 81% yield. After the removal of the tetrahydropyranyl (THP) group in the enone **7** with 65% aqueous acetic acid and THF at 45 °C, the resulting C_{11}-hydroxy enone **8** was reduced stereoselectively with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide[15)] in toluene at −78°C to furnish the 15α-alcohol **9** in 69% yield accompanied with the undesired 15β-alcohol in 13% yield after easy column chromatography on silica gel.[16)] The diastereoselective reduction of the enone **7** with (*S*)-binaphthol–EtOH–$LiAlH_4$ ((*S*)-BINA1-H)[17)] in THF at −78 °C proceeded very slowly and the more than half of the enone remained in a period of

Table I. Catalytic Hydrogenation of Methyl 4-*n*-Propylbenzoate Using Rh Catalysts[a)]

Rh catalyst	Phase transfer catalysts	*cis*/*trans*	Total yield (%)
$(RhCl(COD))_2$	TBAHS	5.3/1.0	>98
	18-Crown-6	4.0/1.0	>98
	BTEAC	[b)]	
	TMAB	[b)]	
	LPC	[b)]	
$Rh(C_5H_7O_2)(CO)_2$	TBAHS	[b)]	
$Rh(COD)(PPh_3)_2BF_4$	TBAHS	[b)]	
$(Rh(OAc)(COD))_2$	TBAHS	3.6/1.0	>98
	18-Crown-6	3.9/1.0	>98

Abbreviations: TBAHS, tetra-*n*-butylammonium hydrogensulfate; BTEAC, benzyltriethylammonium chloride; TMAB, tetramethyl ammonium bromide; LPC, *N*-laurylpyridium chloride. *a*) All reactions were carried out on a 5 mmol scale for 5 h. *b*) No reaction in 5 h.

Table II. ^{13}C-NMR Chemical Shifts of *cis*- and *trans*-Methyl 4-*n*-Propylcyclohexanecarboxylates



	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	CO	(1)	(2)	(3)
cis	40.37	26.19	29.46	35.29	29.46	26.19	51.24	175.90	37.40	20.16	14.24
trans	43.52	29.06	32.31	36.67	32.31	29.06	51.24	176.49	39.46	19.32	14.19

18 h although the stereoselectivity was fairly good (15α/15β-alcohol, 96/4). Sodium borohydride reduction of **7** afforded a 1 : 1 mixture of 15α- and 15β-alcohols. Tetrahydropyranylation of the two hydroxy functions in the 15α-alcohol **9** with dihydropyran in methylene chloride in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the bisTHP compound **10** quantitatively. The compound **10** was treated with anhydrous potassium carbonate in methanol at room temperature to produce the C_9-alcohol **11** in 85% yield.

The ring-closure to produce the cyclic imine was carried out by the known method[7] utilizing a slight improvement of tosylation with inversion at C_9. Tosylation of **11** with the inversion at C_9 was accomplished by the Still method[18] using zinc tosylate, diethyl azodicarboxylate, and triphenylphosphine in benzene to furnish the $C_{9\beta}$-tosylate **12** in 74% yield. After the removal of the THP groups in **12** with *p*-toluenesulfonic acid in methanol, displacement of the tosylate **13** by sodium azide in dimethylsulfoxide at 40 °C for 14 h gave the azide **14**, which underwent intramolecular cycloaddition with loss of nitrogen on heating in toluene at 70 °C for 16 h to the final OP-2507 in 73% yield after column chromatography on silica gel.

By using a sequence of reactions similar to that described for the synthesis of OP-2507, the *trans*-isomer of **3** was led to the final *trans*-OP-2507, whose biological activity was 1/10 of that of OP-2507.

Experimental

^{1}H- and ^{13}C-NMR spectra were taken on a Varian XL-200 or a JEOL FX-90 FT spectrometer in $CDCl_3$. Chemical shifts are reported as parts per million relative to tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a Hitachi EPI-G2 model. Mass spectra (MS) were obtained on a JMS-01SG double-focussing mass spectrometer.

For TLC analysis throughout this work, Merck TLC plates (Kiesel gel $60F_{254}$, precoated, layer thickness 0.2 mm) were used. Column chromatography was carried out on silica gel (Merck, particle size 0.063—0.20 mm).

Unless otherwise specified, all reactions were carried out under an atmosphere of argon.

Methyl *cis*-4-*n*-Proylcyclohexanecarboxylate (3)——In a 500 ml autoclave were placed methyl 4-*n*-propylbenzoate (**2**) (50 g, 0.282 mol), *n*-hexane (180 ml), pH 7.6 phosphate buffer (1 M) solution (120 ml), tetra-*n*-butylammonium hydrogensulfate (2.3 g, 6.80 mmol), and $[RhCl(COD)]_2$ (1.50 g, 3.00 mmol). The autoclave was filled with hydrogen twice, and the mixture was reduced by shaking with hydrogen at 50 atm pressure. In 5 h, the theoretical amount of hydrogen was taken up and the absorption ceased. The mixture was filtered and the filtrate was washed with water, dried on $MgSO_4$, and concentrated *in vacuo*. Silica gel column chromatography (2.5 kg, *n*-hexane–AcOEt, 200 : 1) afforded **3** (38.9 g, 75% yield), the *trans*-isomer of **3** (7.41 g, 14% yield), and a mixture of the both isomers (4.22 g, 8% yield). **3**: TLC: *Rf* 0.697 (*n*-hexane–AcOEt, 9 : 1). ^{1}H-NMR δ: 3.67 (3H, s, $COOCH_3$), 2.53 (1H, m, CHCOO), 0.87 (3H, t, $J=7.3$ Hz). IR ($CHCl_3$): 1720 cm^{-1}. MS *m/z*: 184 (M^+), 153, 152. High-resolution MS *m/z*: Calcd for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1465. The *trans*-isomer of **3**: TLC: *Rf* 0.604 (*n*-hexane–AcOEt, 9 : 1). ^{1}H-NMR δ: 3.65 (3H, s, $COOCH_3$), 2.23 (1H, tt, $J=12.2$, 4.0 Hz, CH–COO), 0.87 (3H, t, CH_3). The IR spectrum and MS were identical with those of **3**. ^{13}C-NMR of the both isomers: Table II.

Dimethyl 2-Oxo-2-*cis*-(4-*n*-propylcyclohexyl)ethyl Phosphonate (4)——To a solution of dimethyl methylphosphonate (1.35 g, 10.8 mmol) in anhydrous THF (30 ml) cooled to −78 °C was added *n*-BuLi (1.45 M in hexane, 7.44 ml, 10.8 mmol) dropwise. The resulting mixture was stirred at −78 °C for 15 min. A solution of the ester **3** (1.00 g, 5.43 mmol) in anhydrous THF (2 ml) was added dropwise while maintaining the temperature below −60 °C. The mixture was stirred at −78 °C for 2.5 h, then acidified by addition of AcOH to pH 4, and diluted with AcOEt (200 ml). The mixture was washed with a small amount of water, dried on $MgSO_4$, and concentrated *in vacuo*. The residue was column-chromatographed on silica gel (30 g) using AcOEt to give the *cis*-phosphonate **4** (1.25 g, 84% yield). TLC: *Rf* 0.521 (AcOEt).[19] ^{1}H-NMR δ: 3.77 (6H, d, $J=11.2$ Hz, CH_3O), 3.13 (2H, d, $J=22.1$ Hz, CH_2CO), 2.68 (1H, m, CHCO),[19] 0.86 (3H, t, CH_3). MS *m/z*: 276 (M^+), 151, 123.

9-Acetyl-15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanor-15-dehydroprostaglandin $F_{2\alpha}$ Methyl Ester 11-Tetrahydropyranyl Ether (7)——To a suspension of NaH (0.152 g, 4.07 mmol) in anhydrous THF (10 ml) was added a solution of the phosphonate **4** (1.25 g, 4.53 mmol) in anhydrous THF (2 ml) at room temperature. The mixture was stirred until hydrogen gas evolution ceased and the solution turned homogeneous. After a solution of the aldehyde **6** (1.55 g, 4.07 mmol) in anhydrous THF (6 ml) was added dropwise to the above phosphonate anion solution at room temperature, the stirring was further continued at room temperature for 1 h. The mixture was acidified by addition of

AcOH to pH 3—4 and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The residue was subjected to the column chromatography on silica gel (60 g) using *n*-hexane–AcOEt (4 : 1) to furnish the enone **7** (1.79 g, 81% yield). TLC: *Rf* 0.522 (ether–*n*-hexane, 3 : 2).[20] ^{1}H-NMR δ: 6.74 (1H, dd, J = 16.2, 10.1 Hz, H_{13}), 6.34 (1H, two d, J = 16.2 Hz, H_{14}),[20] 5.33 (2H, m, *cis*-olefinic H), 5.09 (1H, m, H_9), 4.54 (1H, m, OCHO), 4.04 (1H, m, H_{11}), 3.67 (3H, s, $COOCH_3$), 2.29 (2H, t, J = 8.02 Hz, CH_2COO), 0.89 (3H, t, J = 8.1 Hz, CH_3). IR ($CHCl_3$): 2980, 1730, 960 cm^{-1}. MS *m/z*: 546 (M^+), 515, 462. High-resolution MS *m/z*: Calcd for $C_{32}H_{50}O_7$: 546.3556. Found: 546.3569.

9-Acetyl-15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanor-15-dehydroprostaglandin $F_{2\alpha}$ Methyl Ester (8)——A mixture of the enone **7** (50.0 mg, 0.0910 mmol), 65% aqueous AcOH (5 ml), and THF (0.50 ml) was stirred at 40 °C for 1.5 h. The mixture was concentrated *in vacuo* and the residue was column-chromatographed on silica gel (5 g) using CH_2Cl_2–AcOEt (4 : 1) to afford the alcohol **8** (40.1 mg, 92% yield). TLC: *Rf* 0.539 (*n*-hexane–AcOEt, 1 : 1).[21] ^{1}H-NMR δ: 6.69 (1H, dd, J = 16.2, 10.1 Hz, H_{13}), 6.36 (1H, d, J = 16.2 Hz, H_{14}),[22] 5.33 (2H, m, *cis*-olefinic H), 5.15 (1H, m, H_9), 3.67 (3H, s, $COOCH_3$), 0.89 (3H, t, J = 7.9 Hz, CH_3). IR ($CHCl_3$): 3400, 1720, 980 cm^{-1}. MS *m/z*: 462 (M^+), 444. By high performance liquid chromatography (HPLC) analysis (μ-Porasil, UV 232 nm, *n*-hexane–EtOH, 100 : 15, 0.7 ml/min), the both isomers at the cyclohexane ring could be separated and were shown to be homogeneous: t_R of *cis*- and *trans*-isomers were 28.2 and 31.5 min, respectively.

9-Acetyl-15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester (9)——To a solution of 2,6-di-*tert*-butyl-4-methylphenol (1.17 g, 5.32 mmol) in dry toluene (10 ml) cooled in an ice-water bath was added dropwise a solution of diisobutylaluminum hydride (0.378 g, 2.66 mmol) in toluene (1.50 ml). The mixture was stirred in an ice-water bath for 30 min and then cooled to −78 °C. A solution of the enone **8** (0.123 g, 0.266 mmol) in toluene (3 ml) was added dropwise to the above reducing agent. Stirring was continued for 15 min. The mixture was warmed up to −20 °C over a period of 2 h, and then poured into cold 1 M HCl (10 ml). The products were extracted with AcOEt. The combined extracts were washed with aqueous $NaHCO_3$, dried on $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (10 g) using *n*-hexane–AcOEt (1 : 1) to provide the 15α-alcohol **9** (84 mg, 69% yield) and the 15β-alcohol (16 mg, 13% yield). **9**: TLC: *Rf* 0.163 (*n*-hexane–AcOEt, 1 : 1). ^{1}H-NMR δ: 5.56 (2H, m, *trans*-olefinic H), 5.39 (2H, m, *cis*-olefinic H), 4.88 (1H, m, H_9), 4.02 (1H, m, H_{15}), 3.99 (1H, m, H_{11}), 3.67 (3H, s, $COOCH_3$), 2.05 (3H, s, CH_3COO), 0.89 (3H, t, J = 8.0 Hz). MS *m/z*: 464 (M^+), 446, 433, 428. The 15β-alcohol: TLC: *Rf* 0.223 (*n*-hexane–AcOEt, 1 : 1). ^{1}H-NMR δ: 4.00 (2H, m, H_{11} and H_{15}). Other parts of the NMR and IR spectra and MS were quite identical with those of **9**.

15-*cis*-(4-*n*-Propylcyclohexyl)-16,17,18,19,20-pentanorprostaglandin $F_{2\alpha}$ Methyl Ester 11,15-Bistetrahydropyranyl Ether (11)——A mixture of the alcohol **9** (0.868 g, 1.87 mmol), dihydropyran (0.329 g, 3.92 mmol), *p*-toluenesulfonic acid (1 mg), and CH_2Cl_2 (8 ml) was stirred at room temperature for 10 min. The reaction was quenched by addition of Et_3N (two drops), and the mixture was concentrated *in vacuo* to give the crude **10** (1.10 g, 100% yield). TLC: *Rf* 0.865 (CH_2Cl_2–AcOEt, 4 : 1). To a solution of the crude **10** (1.10 g, 1.87 mmol) in MeOH (5 ml) was added anhydrous K_2CO_3 (0.258 g, 1.87 mmol) in one portion. The mixture was stirred at 45 °C for 1 h, and diluted with ether (50 ml). The solution was washed with water, dried on $MgSO_4$, and concentrated *in vacuo*. Column chromatography on silica gel (30 g) using CH_2Cl_2–AcOEt (9 : 1) afforded the alcohol **11** (0.872 g, 85% yield). TLC: *Rf* 0.721 (CH_2Cl_2–AcOEt, 4 : 1). ^{1}H-NMR δ: 5.39 (4H, m, olefinic H), 4.71 (2H, br, OCHO), 4.18—3.71 (5H, m, H_9, H_{11}, H_{15}, and OCH), 3.67 (3H, s, $COOCH_3$), 3.44 (2H, m, OCH), 0.88 (3H, t, J = 8.0 Hz, CH_3). IR ($CHCl_3$): 3400, 1720, 985 cm^{-1}. MS *m/z*: 488 (M^+ −OTHP), 404.

9-Deoxy-9β-tosyloxy-15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanorprostaglandin F_2 Methyl Ester 11,15-Bistetrahydropyranyl Ether (12)——To a solution of the alcohol **11** (420 mg, 0.783 mmol) in benzene (15 ml) were added at room temperature Ph_3P (1.03 g, 3.91 mmol), and zinc tosylate (188 mg, 0.470 mmol). To this suspension was added diethyl azodicarboxylate (0.621 ml, 3.91 mmol). The resulting clear light-yellow solution was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was column-chromatographed on silica gel (20 g) using *n*-hexane–AcOEt (4 : 1) to afford the tosylate **12** (392 mg, 74% yield). TLC: *Rf* 0.613 (*n*-hexane–AcOEt, 2 : 1). ^{1}H-NMR δ: 7.78 (2H, d, J = 9.0 Hz, Ar-H), 7.32 (2H, d, J = 9.0 Hz, Ar-H), 5.60—5.10 (4H, m, olefinic H), 4.63 (3H, m, H_9 and OCHO), 4.13—3.60 (7H, m and s, $COOCH_3$, H_{11}, H_{15}, and OCHO), 3.42 (2H, m, OCH), 2.44 (3H, s, CH_3-Ar), 0.89 (3H, t, CH_3). IR ($CHCl_3$): 2900, 1730, 1600, 1435, 1230 cm^{-1}. MS *m/z*: 386, 368.

9-Deoxy-9β-tosyloxy-15-*cis*-(4-*n*-propylcyclohexyl)-16,17,18,19,20-pentanorprostaglandin F_2 Methyl Ester (13)——A mixture of **12** (0.460 g, 0.594 mmol), *p*-toluenesulfonic acid (1 mg), and MeOH (5 ml) was stirred at room temperture for 1 h. After addition of Et_3N (two drops), the mixture was concentrated *in vacuo*. Purification by column chromatography on silica gel (10 g, *n*-hexane–AcOEt, 1 : 1) afforded the diol **13** (0.330 g, 94% yield). TLC: *Rf* 0.231 (*n*-hexane–AcOEt, 1 : 1). ^{1}H-NMR δ: 7.78 (2H, d, J = 9.1 Hz, Ar-H), 7.34 (2H, d, J = 9.1 Hz, Ar-H), 5.36 (4H, m, olefinic H), 4.60 (1H, m, H_9), 3.95 (2H, m, H_{11} and H_{15}), 3.65 (3H, s, $COOCH_3$), 2.45 (3H, s, CH_3-Ar), 2.28 (2H, t, J = 8.0 Hz, CH_2COO), 0.88 (3H, t, CH_3). IR (film): 3400, 3080, 1745, 975 cm^{-1}. MS *m/z*: 404 (M^+ −TsOH), 386, 168.

15-*cis*-(4-*n*-Propylcyclohexyl)-16,17,18,19,20-pentanor-9-deoxy-6,9α-nitriloprostaglandin F_1 Methyl Ester (1b)——A mixture of the diol **13** (165 mg, 0.286 mmol), NaN_3 (37 mg, 0.573 mmol), and dimethylsulfoxide (5 ml) was stirred at 45 °C for 19 h. The mixture was poured into cold water (20 ml), and the product was extracted with AcOEt–ether (1 : 1). The combined organic layers were washed with brine, dried on $MgSO_4$, and concentrated *in vacuo* to give the azide **14** (161 mg), which was used in the next reaction without purification. A solution of **14** (161 mg) in toluene (3 ml) was heated to 70 °C with stirring for 20 h, then cooled to room temperature, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (10 g) using AcOEt and then 5% MeOH in AcOEt to afford the final product **1b** (87 mg, 73% yield). TLC: *Rf* 0.346 (AcOEt–MeOH, 10 : 1). ^{1}H-NMR δ: 5.53 (2H, m, olefinic H), 4.39 (1H, m, H_9), 3.99 (1H, m, H_{15}),[23] 3.85 (1H, dt, $J=7.0$, 6.3 Hz, H_{11}), 3.67 (3H, s, $COOCH_3$), 0.89 (3H, t, $J=8.0$ Hz, CH_3). ^{13}C-NMR δ: 14.41 (CH_3), 20.54, 35.71 (propyl group), 24.32, 24.86, 28.96, 29.06 (C_2, C_3, C_5, and C_6 in cyclohexane ring), 24.57 (C_4), 25.82 (C_3), 33.18 (C_5), 33.71 (C_7), 34.71 (C_4 in cyclohexane ring), 40.20 (C_{10}), 41.74 (C_1 in cyclohexane ring), 42.95 (C_8), 43.19 (C_2), 51.58 (CH_3 in ester function), 57.48 (C_{12}), 73.72 (C_9), 76.00 (C_{15}), 76.43 (C_{11}), 133.14 (C_{13}), 174.07 (C_6), 175.19 (C_1). IR ($CHCl_3$): 3400, 1740, 1590, 975 cm^{-1}. MS *m/z*: 419 (M^+), 401, 388. High-resolution MS *m/z*: Calcd for $C_{25}H_{41}O_4N$: 419.3035. Found: 419.3031.

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References and Notes

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