# Study on Efficient Synthetic Routes for 7-Fluoroprostaglandin $F_{2\alpha}$ and 7-Fluoro-17,20-dimethyl-2,4-methyleneprostacyclin

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New and facile syntheses of 7-fluoroprostaglandin $F_{2\alpha}$ **1** and chemically stable 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin **2** from commercially available methylenecyclopentanone are described. Construction of the key 7-hydroxyprostaglandin skeleton has been efficiently accomplished by the coupling of acetylenic acids with cyclopentanecarbaldehyde **4** under mild conditions.

The unique physical properties of the fluorine atom, such as its small atomic size, strong electron negativity, and high carbon-fluorine bond energy, have been taken into consideration in order to refine the nature of the parent compounds in medicinal chemistry field.[1] Extensive studies for modification utilizing fluorine atoms of biologically important constituents, for instance, steroids,[2] nucleic acids,[3] amino acids, and peptides,[4] have resulted in significant success discovering new drug candidates.

We have been interested in a series of prostaglandin-related compounds, because of their potent and versatile actions.[5] Prostaglandin $F_{2\alpha}$ has a potent luteolytic effect, and is used by veterinary surgeons to synchronize estrous prior to artificial-insemination programs (Chart 1). It can also reduce the intraocular pressure, and the derivatives are therapeutically employed as antiglaucoma agents.[6] Meanwhile, natural prostacyclin exerts a variety of actions to maintain homeostasis in circulation as a potent inhibitor of platelet aggregation, and also as a strong vasodilator. Over the decade since its discovery, a number of its stable analogs have been synthesized in order to overcome its intrinsic chemical and metabolical instability; some of them have already been used clinically as efficient antiplatelet agents.[7] However, since the biological roles of prostaglandin derivatives and their receptors are not yet well understood at the molecular level, it is necessary for a further elucidation, or even discovery, of their functions[8] in order to develop more selective novel prostaglandin agonists or antagonists by means of chemical synthesis.

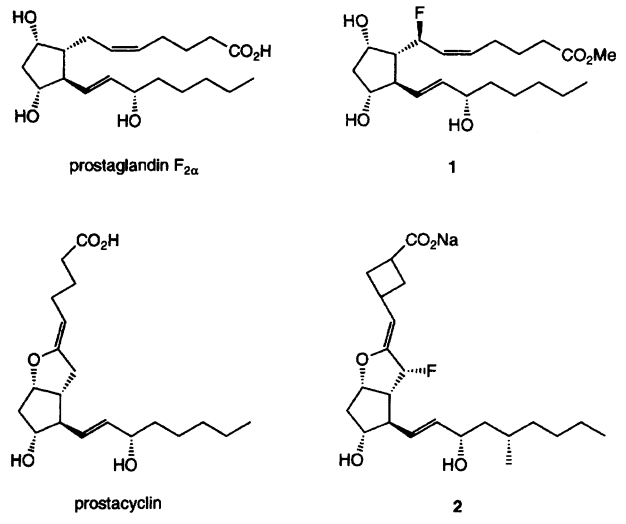
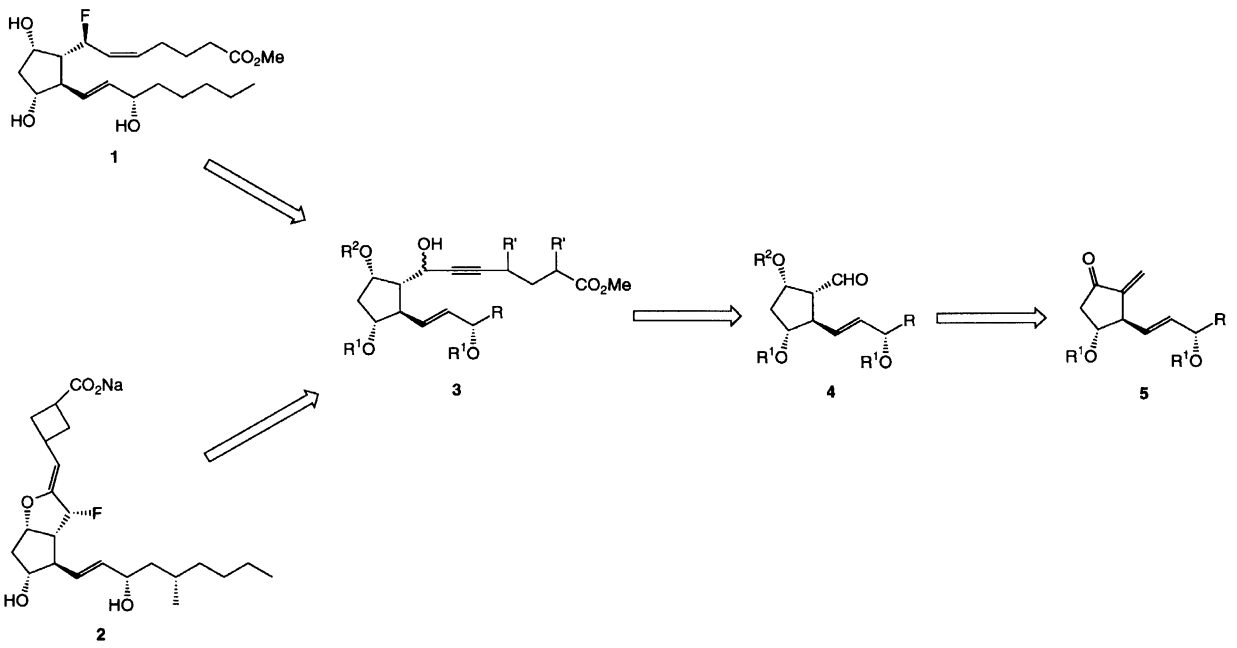



Chart 1.

We have studied fluorine-containing prostaglandin analogs,[9] and especially the synthesis of 7-fluoroprostacyclin analogs, to stabilize chemically labile vinyl ether by introducing an electron-withdrawing fluorine atom. We recently reported on the synthesis of fluoroprostacyclin analogs with modified cycloalkylenyl chains by applying a three-component coupling process[10] and stereospecific fluorination.[11] We found that the modifying the upper side chain ($\alpha$-chain) with a cyclic structure prevented metabolism by $\beta$-oxidation in vivo; also, among the derivatives, 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin **2** showed most potent antianginal activities with long duration.[11b] We herein report on a new synthetic method to construct the 7-substituted prostaglandin skeleton, which is a useful process for various $\alpha$-chain modified analogs from commercially available methylenecyclopentanone. We also describe its application to the synthesis of 7-fluoroprostaglandin $F_{2\alpha}$ **1** and 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin **2**.[12]

Our retrosynthetic pathway is shown in Scheme 1. In designing a synthetic plan, we searched for a useful intermediate which would serve as a key compound for a number of $\alpha$-chain modified analogs, which would simply produce the 7-hydroxyprostaglandin framework **3**. Our preliminary attempts aimed at the 7-hydroxyprostaglandin structure have provided useful guidance for proper assembly. Neither $\alpha$-hydroxylation of the Corey lactone–Wittig olefination sequence nor the regioselective allylic oxidation of prostaglandin $F_{2\alpha}$




Scheme 1.

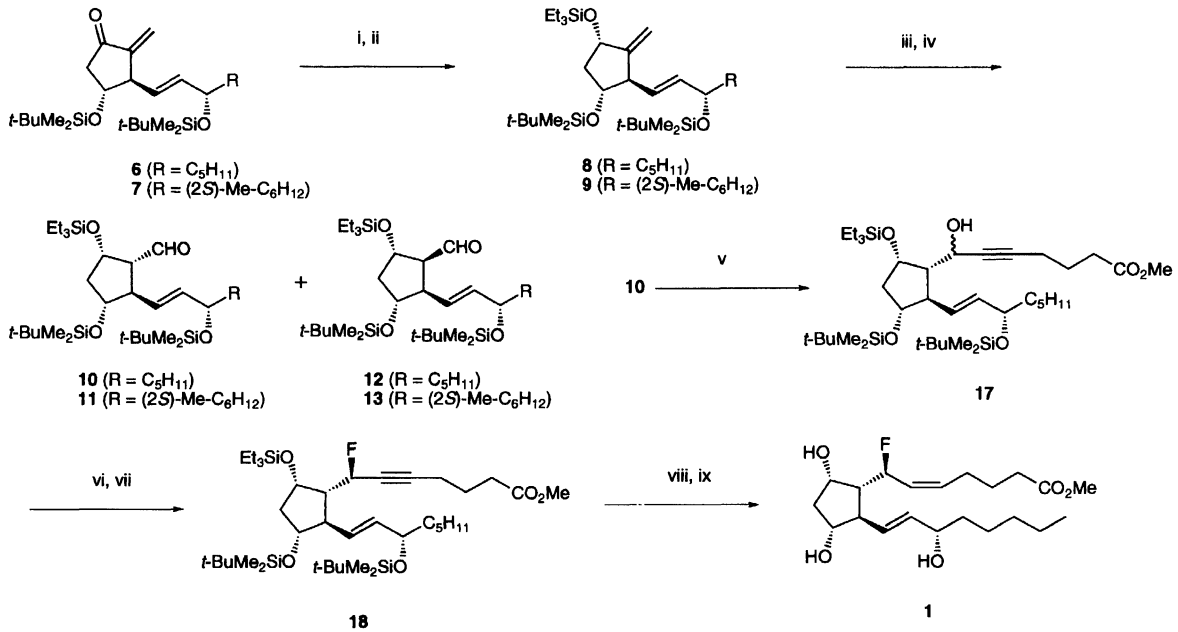
could be easily accomplished. Recently, a new class of methodologies for prostaglandin synthesis featuring methylenecyclopentanone **5**[13] has appeared. The commercial availability of the chiral starting material was a strong reason to us to examine its applicability in our prostaglandin synthesis. We opted for stereochemically defined cyclopentanecarbaldehyde **4** as a key intermediate, because a simple reaction with various nucleophiles, such as acetylenic acid, could afford the corresponding prostaglandin derivatives. The functionalities at C-8 and C-9 (prostaglandin numbering) could be stereoselectively controlled by utilizing the C-11 and C-12 stereochemistry of the starting methylenecyclopentanone **5**. If we obtained 7-hydroxyprostaglandin **3**, we could synthesize **1** or **2** in the application of the stereospecific fluorination and cyclization to the prostacyclin derivative.[11]

## Results and Discussion

**Synthesis of (7*R*)-Fluoroprostaglandin F$_{2\alpha}$.** We started the synthesis from methylenecyclopentanone having a natural lower side chain ($\omega$-chain) **6** (Scheme 2). The reduction of **6** with sodium borohydride in the presence of cerium(III) chloride, and the following protection of the alcohol with $Et_3SiCl$ in pyridine, provided the desired tris(silyl ether) **8** in 93% yield with 10 : 1 stereoselectivity. The stereoselectivity could be rationalized by a facile approach of the hydride from the $\beta$-face, thus avoiding the steric bulk of the *t*-butyldimethylsilyloxy group at C-11. We next examined the hydroboration of the *exo*-olefin **8** employed with $BH_3$·$SMe_2$, thexylborane, and 9-borabicyclo[3.3.1]nonane (9-BBN) to make the corresponding alcohol. Although the reactions of the *exo*-olefin proceeded rather slowly, due to the sterically congested neighboring groups, among them the reaction with 9-BBN at room temperature gave the best yield and stereoselectivity without affection to the double bond in the $\omega$-chain. The hydroboration of **8** with 9-BBN in THF, and the subsequent oxidation with pyridinium chlorochromate (PCC) in $CH_2Cl_2$ in the presence of molecular sieves 4A, yielded a 4 : 1 mixture of the desired triethylsilyloxy aldehyde **10** and the isomer **12**. The key compound **10** was isolated after conventional column chromatography in 62% yield (2 steps).

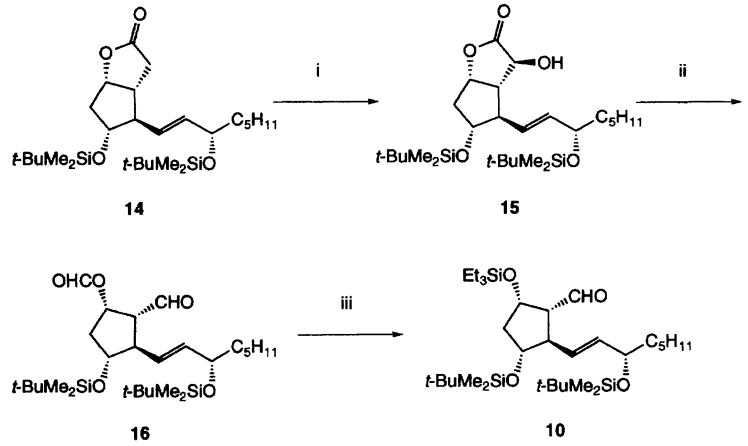
The stereochemistry of **10** was confirmed by alternative synthesis from the Corey lactone **14** (Scheme 3). The hydroxylation of **14** in a treatment with lithium *N*,*N*-bis(trimethylsilyl)amide and oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) ($MoO_5$–Py–HMPA)[14] in THF provided **15**[15] in 52% yield. After reduction of the lactone **15** with diisobutylaluminum hydride in toluene, the resulting lactol was subjected to oxidative cleavage with Pb(OAc)$_4$ to give aldehyde **16** in 54% yield (2 steps). The hydrolysis of the formyl group of **16**, and subsequent triethylsilylation, gave the aldehyde **10**, which was identical with that prepared from **6**.

In a crucial step, after the treatment of 5-hexynoic acid with 2.2 molar amounts of EtMgBr in THF at room temperature, the resulting acetylide reacted with the aldehyde **10** in THF at 0 °C and room temperature for 2 h to afford the 7-hydroxy-5,6-dehydroprostaglandin F$_{2\alpha}$ derivative as an approximately 1 : 1 diastereomeric mixture at the 7-position (Scheme 2). The product was isolated as the methyl ester **17** in 50% yield (2 steps). The alcohol **17** was silylated with $Me_3SiCl$ and treated with piperidinosulfur trifluoride in 1,1,2-trichloro-1,2,2-trifluoroethane at room temperature to furnish the (7*R*)-fluoro-5,6-dehydroprostaglandin F$_{2\alpha}$ derivative **18**,[16] as reported previously.[11] The fluorination of the trimethylsilyl ether effectively surpressed the dehydrated side products because the reaction proceeded well without formation in situ acidic hydrogen fluoride which often caused the dehydration. The sterically favorable attack of the fluoride anion from the $\beta$-face, thus avoiding the bulky triethylsilyloxyl group at




i, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; ii, $Et_3SiCl$, pyridine, 0 °C; iii, 9-BBN, THF, 0 °C ~ room temperature, then $NaOH\text{-}H_2O_2$; iv, PCC, molecular sieves 4A, $CH_2Cl_2$ room temperature; v, 5-hexynoic acid, EtMgBr, THF, room temprature, then $CH_2N_2$; vi, $Me_3SiCl$, pyridine, 0 °C; vii, piperidinosulfur trifluoride, $ClCF_2CFCl_2$, room temperature; viii, 1 atm $H_2$, Pd-$CaCO_3$-Pb, 0 °C; ix, $Bu_4NF$, 90%

Scheme 2.



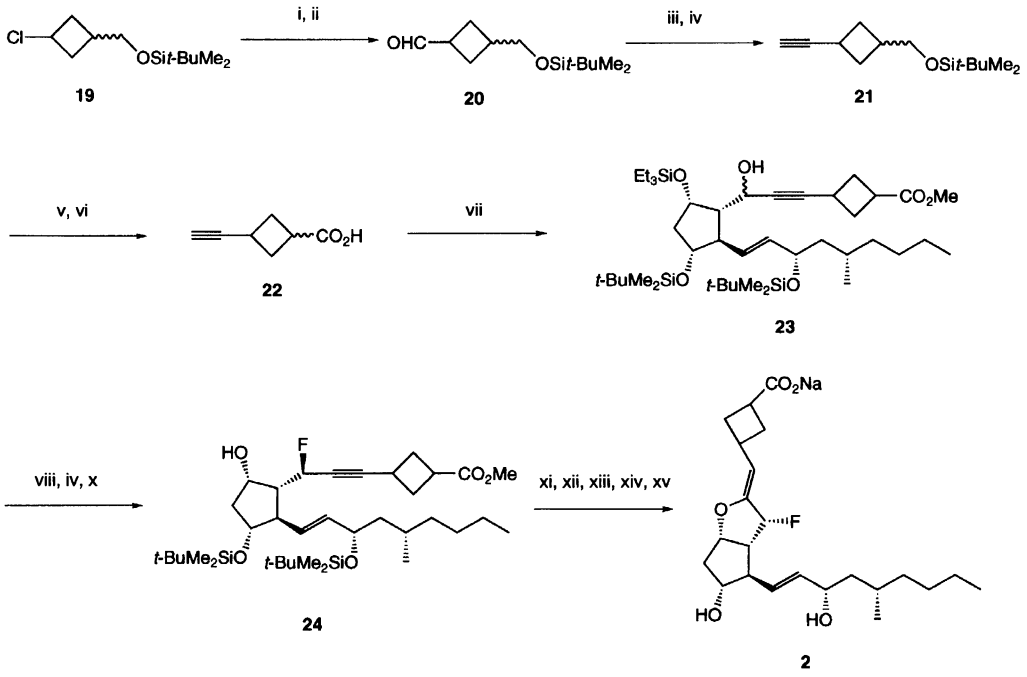

i, $LiN(SiMe_3)_2$, $MoO_5$-Py-HMPA, THF, -78 ~ -20 °C; ii, DIBAH, toluene, -78 ~ -20 °C, then $Pb(OAc)_4$, benzene; iii, NaOH aq, then $Et_3SiCl$, pyridine, 0 °C

Scheme 3.

the 9-position, resulted in the formation of the (7*R*)-isomer predominantly. Partial hydrogenation of the triple bond with the Lindlar catalyst in cyclohexane–cyclohexene–benzene at 0 °C, and a following deprotection with $Bu_4NF$, gave the desired (7*R*)-fluoroprostaglandin $F_{2\alpha}$ methyl ester **1** in 52% yield (2 steps).

**Synthesis of (7*R*)-Fluoro-17,20-dimethyl-2,4-methyleneprostacyclin.** The methodology to construct 7-fluoroprostaglandin $F_{2\alpha}$ described above can be applied to the synthesis of 7-fluoroprostacyclin derivatives having various cycloalkylene α-side chains. For the synthesis of 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin the preparation of the cyclobutyl-acetylene subunit was started from readily available silyl ether **19**[11] (Scheme 4). Grignard reaction of **19** (a mixture of *cis* and *trans* isomers) with paraformaldehyde provided the corresponding alcohol in 60% yield, which was converted to aldehyde **20** by Swern oxidation in 91% yield. The aldehyde **20** was treated with $CBr_4$-$Ph_3P$ in $CH_2Cl_2$ and then 2.1 molar amounts of *n*-BuLi in THF to yield the acetylene **21** in 82% yield (2 steps). Deprotection of the silyl group of **21** with $Bu_4NF$ and successive oxidation of the resulting alcohol with sodium hypochlorite in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidin-1-oxyl[17] afforded the desired $\alpha$-subunit **22**.

The preparation of the key intermediate **11** bearing a 17, 20-dimethyl side chain from methylenecyclopentanone **7** was




i, Mg, BrCH$_2$CH$_2$Br, (HCHO)$_n$, THF, reflux; ii, DMSO, (COCl)$_2$, CH$_2$Cl$_2$, then Et$_3$N; iii, CBr$_4$, Ph$_3$P, CH$_2$Cl$_2$; iv, n-BuLi, THF, -78 ~ 0 °C; v, Bu$_4$NF, THF, room temperature; vi, NaOCl, 2,2,6,6-tetramethylpiperidin-1-oxyl, KBr, aliquot 336, NaHCO$_3$ aq, CH$_2$Cl$_2$, room temperature; vii, **11**, n-BuLi, HMPA,THF, -20°C, then CH$_2$N$_2$; viii, Me$_3$SiCl, pyridine; iv, piperidinosulfur trifluoride, ClCF$_2$CFCl$_2$; x, pyridinium *p*-toluenesulfonate, EtOH, xi, 1 atm H$_2$, Pd-CaCO$_3$-Pb; xii, NIS, CH$_3$CN; xiii, DBU, toluene; xiv, Bu$_4$NF, THF; xv, NaOH, EtOH

Scheme 4.

carried out by a similar reaction pathway to the synthesis of aldehyde **10** (Scheme 2). The stereoselective reduction of **7** and successive protection of the alcohol with Et$_3$SiCl afforded silyl ether **9**. Hydroboration of **9** and the following oxidation provided the desired **11** and the diastereomer **13** with a 6 : 1 selectivity in 61% yield.

In the coupling process, the reaction of the aldehyde **11** with the magnesium salt which formed during the treatment of the cyclobutanecarboxylic acid **22** with EtMgBr in THF proceeded sluggishly to yield product **23** in 10—30% yield. It was assumed that the lower solubility and nucleophilicity of the magnesium salt of **22** retarded the reaction rate. The addition of HMPA or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) did not improve the yield, due to the propensity of **11** toward an in situ formation of $\alpha,\beta$-unsaturated aldehyde under basic conditions. Attempts to accelerate the reaction using diethyl ether–boron trifluoride (1/1), or cerium(III) chloride[18] ended up in failure. Although the acetylide anion[19] generated from 3-(2-trimethylsilylethynyl)cyclobutanecarboxylic acid methyl ester with catalytic Bu$_4$NF or tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF)[20] also gave a small amount of the coupling product, it was accompanied by a considerable amount of the 8, 9-dehydrated product. Finally, we found that the lithiation[21] of acetylenic acid **22** with *n*-BuLi (2.2 mol amt.) in THF with HMPA (3 mol amt.), and a following coupling reaction with the aldehyde **11** at −20 °C, effectively proceeded. The coupling product **23** was obtained in 52% yield after esterification with diazomethane as a mixture of *cis* and *trans* cyclobutylene isomers and diastereomers at C-7. After silylation of **23** with chlorotrimethylsilane, stereospecific fluorination of the trimethylsilyl ether with piperidinosulfur trifluoride and deprotection of triethylsilyl group provided **24** in 41% yield (2 steps). The acetylene **24** was hydrogenated to the olefin, cyclized, and dehydroiodinated to produce the prostacyclin derivative, which was converted to the desired 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin **2** after deprotection and hydrolysis in a previously reported manner.[11] An HPLC analysis showed that the obtained product was a 36 : 64 mixture of *cis* and *trans* cyclobutylene isomers.

In summary, we have developed a convenient synthetic method for 7-hydroxyprostaglandin framework from commercially available methylenecyclopentanones. The present methodology provides simple and practical processes for 7-fluoroprostaglandin F$_{2\alpha}$ and 7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin.

## Experimental

**General.** $^1$H and $^{19}$F NMR spectra were recorded on JEOL JNM-FX-90Q, JEOL JNM-GSX-270, and JNM-EX-400 spectrometers with tetramethylsilane for $^1$H NMR as an internal standard and trichlorofluoromethane for $^{19}$F NMR as an external standard. IR spectra were recorded on a JASCO IR-810 spectrometer. Mass spectra were obtained on a JEOL SX-102A mass spectrometer. The melting points were determined using a Buchi 530 melting-point apparatus. All of the melting points were uncorrected. Purification of the products was performed by column chromatography on silica gel (Merck, Art 7734 or 9385 Kieselgel 60). Silica gel TLC was performed on a Merck TLC plate 60F-254. HPLC analysis was performed on a Shimadzu liquid chromatograph LC-9A, SPD-6A UV detector, and Chromatopack C-R4A.

All of the reactions were carried out under an argon atmosphere, except for aqueous hydrolysis. Ether and tetrahydrofuran were distilled from Na metal and benzophenone. Dichloromethane, 1,1,2-trichloro-1,2,2-trifluoroethane, and acetonitrile were distilled from $CaH_2$. Benzene, cyclohexane, and toluene were distilled from $P_2O_5$. (1*E*, 3*S*, 5*S*)-3-*t*-Butyldimethylsilyl-1-iodo-5-methylnonene, (1*S*, 3*R*, 4*R*)-4-*t*-butyldimethylsilyloxy-3-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-2-methylene-1-cyclopentanone, and (1*S*, 3*R*, 4*R*)-4-*t*-butyldimethylsilyloxy-3-[(1*E*, 3*S*, 5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-2-methylene-1-cyclopentanone were purchased from Nissan Chemical Co., Ltd.

**(1*S*, 3*R*, 4*R*)-4-*t*-Butyldimethylsilyloxy-3-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-2-methylene-1-cyclopentanol Triethylsilyl Ether 8.** To (1*S*, 3*R*, 4*R*)-4-*t*-butyldimethylsilyloxy-3-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-2-methylene-1-cyclopentanone (**6**) (1.87 g, 4 mmol) in MeOH (10 $cm^3$) were added $CeCl_3 \cdot 7H_2O$ (1.49 g, 4 mmol) and $NaBH_4$ (151 mg, 4 mmol) at −10 °C. The mixture was first stirred at 0 °C for 2 h, then poured onto saturated $NaHCO_3$, and extracted with AcOEt. The extracts were combined, dried, and evaporated to yield the crude alcohol (1.99 g) as a colorless oil. The alcohol was dissolved in pyridine (12 $cm^3$) and chlorotriethylsilane (0.806 $cm^3$, 4.8 mmol) was added. The mixture was stirred at 0 °C for 1 h, poured into saturated $NaHCO_3$, and extracted with AcOEt. The extract was dried, evaporated, and chromatographed on silica gel (hexane : AcOEt=20 : 1) to furnish silyl ether **8** (2.17 g, 93%) as a colorless oil. IR ($CHCl_3$) 2956, 2930, 2876, 2857, 1471, 1462, 1360, 1255, 1091, 1005, 970, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 0.02—0.04 (12H, m), 0.63 (6H, q, $J$ = 7.8 Hz), 0.87 (9H, s), 0.89 (9H, s), 0.8—1.0 (12H, m), 1.2—1.6 (8H, m), 1.64 (1H, dt, $J$ = 9.4, 11.5 Hz), 2.26 (1H, dt, $J$ = 6.7, 11.5 Hz), 3.05 (1H, m), 3.76 (1H, ddd, $J$ = 6.7, 9.4, 11.5 Hz), 4.10 (1H, q, $J$ = 5.7 Hz), 4.38 (1H, dt, $J$ = 2.2, 7.1, 7.1 Hz), 4.90 (1H, s), 5.14 (1H, s), 5.38 (1H, dd, $J$ = 8.1, 15.4 Hz), 5.54 (1H, dd, $J$ = 5.7, 15.4 Hz). Found: *m/z* 582.4326. Calcd for $C_{32}H_{66}O_3Si_3$: M, 582.4320.

**(1*R*, 2*R*, 3*R*, 5*S*)-3-*t*-Butyldimethylsilyloxy-5-triethylsilyloxy-2-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-1-cyclopentanecarbaldehyde 10.** To a solution of silyl ether **8** (2.17 g, 3.72 mmol) in THF (12 $cm^3$) 9-BBN (0.5 M, THF solution, 22.3 $cm^3$) was added at 0 °C. After the mixture was stirred at room temperature for 2 h, 3 M (M=mol $dm^{-3}$) NaOH (15 $cm^3$) and 30% $H_2O_2$ (15 $cm^3$) were added at 0 °C. The mixture was stirred at room temperature for 2 h, and extracted with AcOEt. After removal of the solvent, the residual oil was filtered through a silica-gel pad and eluted with 5% AcOEt in hexane to give alcohol (1.94 g) as a colorless oil. To the alcohol in $CH_2Cl_2$ were added molecular sieves 4 A (powder, 3.2 g) and pyridinium chlorochromate (2.09 g, 9.69 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h, and then filtered through Celite. The filtrate was evaporated and chromatographed on silica gel (hexane : AcOEt=20 : 1) to furnish aldehyde **10** (1.37 g, 62%) as a colorless oil. IR (neat) 3024, 2960, 2937, 2875, 2857, 1731, 1478, 1464, 1446, 1249, 1096, 1046, 972 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 0.03 (12H, m), 0.55 (6H, m), 0.8—1.0 (30H, m), 1.2—1.5 (8H, m), 1.73 (1H, ddd, $J$ = 4.9, 7.1, 13.6 Hz), 2.33 (1H, dt, $J$ = 7.1, 13.6 Hz), 2.41 (1H, ddd, $J$ = 3.4, 7.1, 10.3 Hz), 3.13 (1H, dt, $J$ = 7.1, 10.3 Hz), 3.85 (1H, q, $J$ = 7.1 Hz), 4.03 (1H, q, $J$ = 5.7 Hz), 4.50 (1H, dt, $J$ = 4.9, 7.1 Hz), 5.44 (1H, dd, $J$ = 7.1, 15.6 Hz), 5.51 (1H, dd, $J$ = 5.7, 15.6 Hz), 9.70 (1H, d, $J$ = 3.4 Hz). Found: *m/z* 599.4360. Calcd for $C_{32}H_{67}O_4Si_3$: $M^+$+H, 599.4347. The diastereomer **12**; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0.03 (12H, m), 0.55 (6H, m), 0.8—1.0 (30H, m), 1.2—1.7 (9H, m), 2.35 (2H, m), 3.11 (1H, m), 3.90 (1H, m), 4.01 (1H, m), 4.56 (1H, m), 5.33 (1H, dd, $J$ = 9.1, 14.9 Hz), 5.58 (1H, d, $J$ = 5.2, 14.9 Hz), 9.71 (1H, d, $J$ = 2.5 Hz).

***α*-Hydroxylation of the Corey Lactone 14.** To a solution of lithium *N*,*N*-bis(trimethylsilyl)amide in THF, prepared from *n*-BuLi (1.6 M in hexane, 2.39 $cm^3$, 3.83 mmol) and *N*,*N*-bis(trimethylsilyl)amide (0.88 $cm^3$, 4.18 mmol), was added a solution of lactone **14** (1.73 g, 3.48 mmol) in THF (3.5 $cm^3$) at −78 °C. After stirring at −78 °C for 30 min, $MoO_5$–Py–HMPA was added portionwise at −78 °C. The mixture was stirred at −78 °C for 1 h, at −40 °C for 1 h, and −20 °C for 1 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with AcOEt. Purification with silica gel column chromatography (hexane : AcOEt=10 : 1) gave hydroxy lactone **15** (0.93 g, 52%) as a white waxy solid and recovered lactone **14** (0.31 g, 18%). Mp 38—40 °C; IR (KBr) 3243, 2955, 2929, 2857, 1776, 1766, 1471, 1256, 1189, 1117, 1086, 1035, 1004, 964, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 0.03—0.05 (12H, m), 0.86 (9H, s), 0.88 (9H, s), 0.8—0.9 (3H, m), 1.2—1.5 (8H, m), 1.98 (1H, d, $J$ = 15.1 Hz), 2.09 (1H, ddd, $J$ = 4.6, 7.1, 15.1 Hz), 2.74 (2H, m), 4.05 (2H, m), 4.46 (1H, br s), 5.11 (1H, t, $J$ = 7.1 Hz), 5.36 (1H, dd, $J$ = 7.1, 15.4 Hz), 5.50 (1H, dd, $J$ = 5.8, 15.6 Hz). Found: *m/z* 513.3442. Calcd for $C_{27}H_{53}O_5Si_2$: $M^+$, 513.3432.

**(1*R*, 2*R*, 3*R*, 5*S*)-3-*t*-Butyldimethylsilyloxy-5-formyloxy-2-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-1-cyclopentanecarbaldehyde 16.** To a solution of lactone **15** (610 mg, 1.19 mmol) in toluene (12 $cm^3$) was added DIBAH (1 M in hexane, 3.57 $cm^3$) at −78 °C. The mixture was stirred at −50 °C for 45 min, then poured into 0.1 M HCl. The mixture was extracted with AcOEt, dried, and evaporated to give crude lactol. To a soluiton of the lactol in benzene (12 $cm^3$) was added $Pb(OAc)_4$ (686 mg, 1.55 mmol) at 10 °C; the mixture was stirred at 10 °C for 30 min. After filtration to remove any insoluble material, the filtrate was washed with saturated $NaHCO_3$. Purificaiton with silica gel column chromatography (hexane : AcOEt=20 : 1—10 : 1) was performed to afford aldehyde **16** (0.33 g, 54%) as a colorless oil. IR (neat) 2928, 2856, 1730, 1688, 1471, 1463, 1419, 1388, 1361, 1255, 1170, 1121, 1085, 1005, 969, 837, 776 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 0.03—0.04 (12H, m), 0.55 (6H, m), 0.87 (9H, s), 0.88 (9H, s), 0.8—0.9 (3H, m), 1.2—1.5 (8H, m), 1.83 (1H, ddd, $J$ = 4.0, 7.1, 13.6 Hz), 2.53 (1H, dt, $J$ = 7.1, 13.6 Hz), 2.67 (1H, ddd, $J$ = 2.7, 7.1, 10.3 Hz), 3.11 (1H, dt, $J$ = 7.1, 10.3 Hz), 3.96 (1H, q, $J$ = 7.1 Hz), 4.05 (1H, q, $J$ = 5.9 Hz), 5.4—5.5 (2H, m), 5.58 (1H, dd, $J$ = 5.9, 16.1 Hz), 7.99 (1H, s), 9.69 (1H, d, $J$ = 2.7 Hz). Found: *m/z* 513.3403. Calcd for $C_{27}H_{53}O_5Si_2$: $M^+$, 513.3432.

**(1*R*, 2*R*, 3*R*, 5*S*)-3-*t*-Butyldimethylsilyloxy-5-triethylsilyloxy-2-[(1*E*, 3*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-1-cyclopentanecarbaldehyde 10.** To a solution of aldehyde **16** (45 mg, 0.088 mmol) in THF (1 $cm^3$) 0.1 M NaOH (1 $cm^3$) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 h and extracted with AcOEt. After removing the solvent, the residual oil was dissolved in pyridine (0.5 $cm^3$) and chlorotriethylsilane (0.044 $cm^3$, 0.263 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 0.5 h, poured into saturated $NaHCO_3$, and extracted with AcOEt. The extract was chromatographed on silica gel (hexane : AcOEt=20 : 1) to furnish an aldehyde **10** (33 mg, 63%) identical to the product prepared from **8**.

**(7*RS*, 17*S*)-5,6-Dehydro-7-hydroxyprostaglandin $F_{2\alpha}$ Methyl Ester 11,15-(*O*)-Bis(*t*-butyldimethylsilyl)-9-(*O*)-triethylsilyl Ether 17.** To a solution of ethylmagnesium bromide (0.93 M, THF solution, 2.80 $cm^3$) was added 5-hexynoic acid (135 mg, 1.2 mmol) in THF (3 $cm^3$) at 0 °C. After the mixture was stirred at room temperature for 1 h, aldehyde **10** (599 mg, 1 mmol) in THF was added at 0 °C. The mixture was stirred at room temperature for

2 h, then poured onto saturated ammonium chloride and extracted with AcOEt. The extract was concentrated, and the residual oil was dissolved in DMSO (5 cm$^3$). *N*-Ethyldiisopropylamine (0.523 cm$^3$, 3 mmol) and iodomethane (0.311 cm$^3$, 5 mmol) were added to the solution at room temperature. After stirring at room temperature for 1.5 h, the crude product was chromatographed on silica gel (hexane : AcOEt=10 : 1) to afford **17** (363 mg, 50%) as a colorless oil. IR ($CHCl_3$) 3017, 2956, 2930, 2857, 1733, 1521, 1471, 1419, 1389, 1072, 1047, 971 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 0.06 (12H, m), 0.60 (6H, m), 0.8—1.0 (30H, m), 1.2—1.5 (8H, m), 1.7—1.9 (4H, m), 2.1—2.5 (6H, m), 2.80 (1H, m), 3.67 (3H, s), 3.85 (1H, m), 4.05 (1H, m), 4.18 (1H, m), 4.60 (1H, m), 5.40—5.62 (2H, m). Found: *m/z* 725.5043. Calcd for $C_{39}H_{77}O_6Si_3$: M$^+$+H, 725.5028.

**(7*R*, 17*S*)-5,6-Dehydro-7-fluoro-prostaglandin F$_{2\alpha}$ Methyl Ester 11,15-(*O*)-Bis(*t*-butyldimethylsilyl)-9-(*O*)triethylsilyl Ether 18.**[11c] To a solution of alcohol **17** (144 mg, 0.20 mmol) in pyridine (2 cm$^3$) was added $Me_3SiCl$ (0.038 cm$^3$, 0.30 mmol) at 0 °C. After the mixture was stirred at 0 °C for 1 h, it was poured into saturated $NaHCO_3$, and extracted with ether. The crude product was filtered through a silica gel pad eluted with 1—3% AcOEt in hexane to give the trimethylsilyl ether (146 mg, 0.18 mmol) as a colorless oil, and immediately used for the next reaction. To a solution of silyl ether in 1,1,2-trichloro-1,2,2-trifluoroethane (4 cm$^3$) was added piperidinosulfur trifluoride (0.029 cm$^3$) at 0 °C. After the mixture was stirred at room temperature for 6 h, $Et_3N$ (0.3 cm$^3$) was added at 0 °C. The mixture was diluted with $CH_2Cl_2$ (5 cm$^3$), poured into saturated $KHCO_3$, and extracted with $CH_2Cl_2$. The organic extract was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (hexane : AcOEt=30 : 1) to give fluoride **18** (88 mg, 61%) as a colorless oil. IR ($CHCl_3$) 3018, 2956, 2930, 2857, 1733, 1520, 1472, 1463, 1437, 1378, 1047, 1006, 969, 929 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 0—0.1 (12H, m), 0.58 (6H, q, *J* = 6.6 Hz), 0.87 (9H, s), 0.89 (9H, s), 0.8—1.0 (12H, m), 1.2—1.5 (8H, m), 1.7—2.0 (4H, m), 2.13 (1H, ddd, *J* = 5.8, 6.0, 12.5 Hz), 2.30 (2H, m), 2.44 (2H, t, *J* = 7.3 Hz), 2.70 (1H, m), 3.67 (3H, s), 3.87 (1H, q, *J* = 6.6 H), 4.05 (1H, q, *J* = 6.6 Hz), 4.28 (1H, q, *J* = 6.0 Hz), 5.35 (1H, dd, *J* = 7.1, 47.3 Hz), 5.47 (1H, dd, *J* = 7.1, 15.4 Hz), 5.52 (1H, dd, *J* = 5.6, 15.4 hz). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ = −169 (m).

**(7*R*, 17*S*)-7-Fluoro-prostaglandin F$_{2\alpha}$ Methyl Ester 1.** To a solution of acetylene **18** (30 mg, 39.7 μmol) in benzene (1 cm$^3$) and cyclohexane (1 cm$^3$) were added cyclohexene (0.042 cm$^3$) and 5% Pd–$CaCO_3$ poisoned with Pb (30 mg) at 0 °C. The mixture was hydrogenated under 1 atm hydrogen atmosphere at 0 °C for 18 h, then filtered through Celite. The filtrate was evaporated to give the corresponding olefin (25 mg). To a solution of the olefin (25 mg, 33 μmol) in THF (2 cm$^3$) was added dropwise 1 M $Bu_4NF$ in THF (0.165 cm$^3$) at 0 °C. The mixture was stirred at room temperature for 15 h, evaporated, and chromatographed on silica gel ($CH_2Cl_2$: acetone=10 : 1, then 3 : 1) to afford triol **1** (8 mg, 20.7 μmol, 52%) as a colorless oil. IR ($CHCl_3$) 3010, 2974, 1727, 1562, 1518, 1478, 1421, 1249, 1046, 929 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 0.89 (3H, t, *J* = 6.9 Hz), 1.2—1.6 (8H, m), 1.7—2.7 (10H, m), 3.68 (3H, s), 3.95—4.05 (2H, m), 4.49 (1H, br s), 5.35—5.70 (5H, m). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ = −169 (d, *J* = 54 Hz). Found: *m/z* 385.2363. Calcd for $C_{21}H_{34}FO_5$: M$^+$−H, 385.2390.

**3- (*t*- Butyldimethylsilyloxymethyl)- 1- cyclobutanecarbaldehyde 20.** To a suspension of magnesium turning (14.6 g, 0.60 mol) in THF (500 cm$^3$) at reflux was added dropwise a mixture of 3-chlorocyclobutane-1-methanol *t*-butyldimethylsilyl ether[11c] (70 g, 0.30 mol) and 1,2-dibromoethane (11.6 cm$^3$). The mixture was stirred at reflux for 3 h, then cooled to room temperature. Paraformaldehyde (18 g, 0.60 mol) was added to the mixture portionwise and the stirring was continued for 14 h. To the mixture was added saturated ammonium chloride (300 cm$^3$) at 0 °C and extracted with AcOEt. The extracts were combined and washed with water. The crude product was chromatographed on silica gel (hexane : AcOEt=10 : 1) to give the monosilyl ether (40.9 g, 60%) as a colorless oil. IR (neat) 3349, 2929, 2856, 1472, 1434, 1388, 1360, 1256, 1095, 1005, 836, 774 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 0.02 (3H, s), 0.04 (3H, s), 0.88 (9H, m), 1.4—2.1 (5H, m), 2.35 (2H, m), 3.50 (2H, m), 3.59 (2H, m). To a solution of oxalyl chloride (65 cm$^3$, 724 mmol) in $CH_2Cl_2$ (1500 cm$^3$) at −78°C was added DMSO (114 cm$^3$, 1.6 mol) in $CH_2Cl_2$ (245 cm$^3$). After 30 min, a solution of the above monosilyl ether (116 g, 505 mmol) in $CH_2Cl_2$ (505 cm$^3$) was added at −78 °C, and the mixture was stirred for 40 min. After $Et_3N$ (456 cm$^3$) was added, the temperature was raised to 10 °C. The mixture was poured into ice-water and extracted with $CH_2Cl_2$. The extracts were combined and washed with 1 M HCl, 5% $NaHCO_3$, and brine. The crude product was chromatographed on silica gel (hexane : AcOEt=30 : 1) to furnish 3-(*t*-butyldimethylsilyloxymethyl)-1-cyclobutanecarbaldehyde **20** (105 g, 459 mmol, 91%) as a colorless oil. IR (neat) 2955, 2940, 2860, 2110, 1725, 1475, 1255, 1095, 840 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 0.02—0.05 (6H, m), 0.89 (4.5H, s), 0.90 (4.5H, s), 2.0—2.6 (5H, m), 3.03 (1H, m), 3.50 (2H, d, *J* = 5.1 Hz), 3.61 (2H, d, *J* = 5.1 Hz), 9.67 (0.5H, d, *J* = 2.3 Hz), 9.79 (0.5H, d, *J* = 2.3 Hz). Found: *m/z* 228.1399. Calcd for $C_{12}H_{24}O_2Si$: M$^+$, 228.1546.

**3-Ethynylcyclobutane-1-methanol *t*-Butyldimethylsilyl Ether 21.** To a solution of aldehyde **20** (20.4 g, 89.3 mmol) in $CH_2Cl_2$ (300 cm$^3$) were added triphenylphosphine (56.2 g, 214 mmol) and a solution of $CBr_4$ in $CH_2Cl_2$ (100 cm$^3$) at −10 °C. The mixture was poured into cold saturated $NaHCO_3$ and extracted with AcOEt. The organic phase was washed with brine, dried, and evaporated. The residual oil was filtered through a short pad of silica gel and eluted with 1% AcOEt in hexane to give 3-(2,2-dibromoethenyl)-cyclobutane-1-methanol *t*-butyldimethylsilyl ether (29.2 g, 85%) as a colorless oil. The product was used for the next reaction without further purification. $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 0.04—0.06 (6H, m), 0.90 (9H, m), 1.60—2.50 (5H, m), 2.90—3.20 (1H, m), 3.50 (0.5H, d, *J* = 5.1 Hz), 3.62 (0.5H, d, *J* = 5.1 Hz), 6.43 (0.5H, d, *J* = 8.4 Hz), 6.61 (0.5H, d, *J* = 8.4 Hz). To a solution of the dibromide (476 g, 1.5 mol) in THF (4000 cm$^3$) was added *n*-BuLi (1.56 M, hexane solution, 2000 cm$^3$) at −50 °C. The mixture was stirred at −20 °C for 1 h, then quenched with aqueous ammonium chloride, and extracted with hexane. The extract was washed with water, dried, and evaporated. The residue was dissolved in hexane and filtered through silica gel to give product **21** as a colorless oil. Yield 316 g (96%). IR (neat) 3320, 2960, 2945, 2860, 2120, 1710, 1470, 1265, 1095 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 0.05—0.15 (6H, m), 0.88 (9H, m), 1.8—2.9 (7H, m), 3.55 (2H, m). Found: *m/z* 224.1606. Calcd for $C_{13}H_{24}OSi$ : M$^+$, 224.1596.

**3-Ethynyl-1-cyclobutanecarboxylic Acid 22.** Silyl ether **21** (316 g, 1.4 mol) was dissolved in THF (500 cm$^3$) and $Bu_4NF$ (1 M, THF solution, 2500 cm$^3$) was added at −10 °C. The mixture was stirred at 0 °C for 1 h and room temperature for 2.5 h. The solvent was removed and chromatographed on silica gel (hexane : AcOEt=4 : 1) to give 3- ethynylcyclobutane-1-methanol (146 g, 95%) as colorless oil. IR (neat) 3300, 2930, 2850, 2110, 1710, 1030 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ = 1.89 (0.5H, m), 2.0—2.3 (4H, m), 2.40 (1H, m), 2.61 (0.5H, m), 2.9—3.1 (1H, m), 3.63 (2H, m). To a solution of the alcohol (11 g, 100 mmol) in $CH_2Cl_2$ (100 cm$^3$) were added methyltrioctylammonium chloride (2.02 g, 5.0 mmol) in $CH_2Cl_2$ (50 cm$^3$), then 2,2,6,6-tetramethylpiperidin-

1-oxyl (0.16 g, 1.0 mmol) in $CH_2Cl_2$ (50 $cm^3$) and KBr (1.19 g, 10 mmol) in water (20 $cm^3$) at −30 °C. Sodium hypochlorite (11.6% aqueous solution, 200 g), adjusted to pH 9.3 with the addition of $NaHCO_3$, was added to the mixture, and stirred at room temperature for 2 h. Aqueous NaOH was added to adjust the pH to 12 and extracted with $CH_2Cl_2$. The aqueous phase was acidified with concentrated HCl and extracted with $CH_2Cl_2$. The extract was dried and evaporated to afford acid **22** (6.5 g, 52%) as a colorless oil. IR (neat) 3300, 2960, 2935, 2850, 2120, 1710, 1430, 1255 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 2.20 (1H, m), 2.35—2.67 (4H, m), 3.03 (1H, m), 3.25 (1H, m), 9.0—10.05 (1H, br). Found: *m/z* 123.046. Calcd for $C_7H_7O_2$: $M^+$−H, 123.0446.

**(1*S*, 3*R*, 4*R*)-4-*t*-Butyldimethylsilyloxy-3-[(1*E*, 3*S*, 5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-2-methylene-1-cyclopentanol Triethylsilyl Ether 9.** To (1*S*, 3*R*, 4*R*)-4-*t*-butyldimethylsilyloxy-3-[(1*E*, 3*S*, 5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-2-methylene-1-cyclopentanone (**7**) (200 g, 404 mmol) in MeOH (1500 $cm^3$) were added $CeCl_3 \cdot 7H_2O$ (152 g, 408 mmol) and $NaBH_4$ (16 g, 423 mmol) at −20 °C. After the mixture was stirred at 0 °C for 2 h, it was poured onto saturated $NaHCO_3$, and extracted with AcOEt (3×500 $cm^3$). The extracts were combined, dried and evaporated to yield the crude alcohol (213 g). The alcohol was dissolved in pyridine (1000 $cm^3$) and cchlorotriethylsilane (82 $cm^3$ 489 mmol) was added at −10 °C. The mixture was stirred at 0 °C for 1 h, poured onto saturated $NaHCO_3$, and extracted with hexane (3×500 $cm^3$). The combined extracts were dried, evaporated, and chromatographed on silica gel (hexane : AcOEt=100 : 1) to furnish silyl ether **9** (246 g, 99%) as a colorless oil. IR (neat) 2960, 2935, 2875, 2860, 1475, 1462, 1380, 1360, 1255, 1095 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0.06 (12H, m), 0.62 (6H, m), 0.86—1.03 (33H, m), 1.05—1.83 (10H, m), 2.20 (1H, m), 3.15 (1H, m), 3.76 (1H, m), 4.17 (1H, m), 4.38 (1H, m), 4.89 (1H, s), 5.15 (1H, s), 5.35—5.80 (2H, m). Found: *m/z* 610.4615. Calcd for $C_{34}H_{70}O_3Si_3$: $M^+$, 610.4633.

**(1*R*, 2*R*, 3*R*, 5*S*)-3-*t*-Butyldimethylsilyloxy-5-triethylsilyloxy-2-[(1*E*, 3*S*, 5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-1-cyclopentanecarbaldehyde 11.** To a solution of silyl ether **9** (246 g, 402 mmol) in THF (12 $cm^3$) was added 9-BBN (0.5 M, THF solution, 2800 $cm^3$) at −10 °C. After the mixture was stirred at room temperature for 2 h, 3 M NaOH (500 $cm^3$) and 30% $H_2O_2$ (500 $cm^3$) were added at −20 °C. The mixture was stirred at room temperature for 1 h, poured into water and extracted with AcOEt. The extracts were combined, washed, dried, and evaporated. The crude product was filtered through silica gel and eluted with 10% AcOEt in hexane to give alcohol (219 g, 348 mmol). To the alcohol (219 g) in $CH_2Cl_2$ were added molecular sieves 4 A (powder, 180 g) and pyridinium chlorochromate (225 g, 1.04 mol) at −10 °C. The mixture was stirred at room temperature for 1 h and filtered through Florisil. The filtrate was evaporated and chromatographed on silica gel (hexane : AcOEt=10 : 1) to furnish aldehyde **11** (154 g, 61%) as a colorless oil. IR ($CHCl_3$) 3018, 2958, 2929, 2875, 1717, 1521, 1472, 1423, 1249, 1047, 928 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0.06 (12H, m), 0.57 (6H, m), 0.82—0.99 (33H, m), 1.26—1.80 (10H, m), 2.25—2.42 (2H, m), 3.13 (1H, m), 3.85 (1H, m), 4.11 (1H, m), 4.50 (1H, m), 5.38—5.48 (2H, m), 9.70 (1H, m). Found: *m/z* 569.3949. Calcd for $C_{30}H_{61}O_4Si_3$: $M^+$−*t*-Bu, 569.3878.

**(7*RS*, 17*S*)-5,6-Dehydro-7-hydroxy-17,20-dimethyl-2,4-methyleneprostaglandin $F_{2\alpha}$ Methyl Ester 11,15-(*O*)-Bis(*t*-butyldimethylsilyl)-9-(*O*)-triethylsilyl Ether 23.** Acid **22** (80.5 mg, 0.65 mmol) was dissolved in THF (2 $cm^3$) and HMPA (0.338 $cm^3$) was added *n*-BuLi (1.56 M, hexane solution, 0.90 $cm^3$, 1.4 mmol) at −78 °C. After the mixture was stirred at 0 °C for 1 h, aldehyde **11** (339 mg, 0.54 mmol) in THF (1.5 $cm^3$) was added dropwise at −78 °C. The mixture was stirred at −20 °C for 1 h, then poured onto saturated ammonium chloride, and extracted with AcOEt. The extracts were combined, dried, and evaporated. The residual crude acid was esterified with 0.5 M diazomethane in ether. The crude ester was chromatographed on silica gel (hexane, then 5% AcOEt in hexane) to give ester **23** (214 mg, 52%) as a colorless oil. IR ($CHCl_3$) 2956, 2929, 1729, 1472, 1252, 1076, 837 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0—0.2 (21H, m), 0.55 (6H, m), 0.8—1.0 (33H, m), 1.1—1.7 (10H, m), 1.9—2.9 (9H, m), 3.73 (3H, s), 3.89 (1H, m), 4.10—4.25 (2H, m), 4.61 (1H, m), 5.40—5.70 (2H, m). Found: *m/z* 764.5244. Calcd for $C_{42}H_{80}O_6Si_3$: $M^+$, 764.5263.

**(7*R*, 17*S*)-5,6-Dehydro-7-fluoro-17,20-dimethyl-2,4-methyleneprostaglandin $F_{2\alpha}$ Methyl Ester 11,15-(*O*)-Bis(*t*-butyldimethylsilyl) Ether 24.**[11c] To a solution of alcohol **23** (14.5 g, 19 mmol) in pyridine (60 $cm^3$) was silylated with chlorotrimethylsilane (5.1 $cm^3$, 40 mmol) at 0 °C for 1 h. After stirring at 0 °C for 1 h, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with ether. The extract was dried and evaporated to give the silyl ether. To a solution of the silyl ether (16.0 g) in 1,1,2-trichloro-1,2,2-trifluoroethane (380 $cm^3$) was added piperidinosulfur trifluoride (3.05 $cm^3$) at 0 °C. The mixture was stirred at room temperature for 6 h, then cooled to 0 °C. Triethylamine (6 $cm^3$) and $CH_2Cl_2$ (50 $cm^3$) were added, and the mixture was poured onto saturated $NaHCO_3$ (100 $cm^3$) and extracted with $CH_2Cl_2$ (3×200 $cm^3$). The organic extracts were filtered through silica gel, and eluted with 5% AcOEt in hexane to give the fluoride (8.42 g, 11 mmol), which was dissolved in EtOH (220 $cm^3$) and cooled at 0 °C. Pyridinium *p*-toluenesulfonate (288 mg, 1.1 mmol) was added and stirred at room temperature for 6 h. The reaction mixture was poured onto saturated $NaHCO_3$ (160 $cm^3$), and extracted with $CH_2Cl_2$. The organic extracts were combined, washed with brine, dried evaporated and chromatographed on silica gel (hexane : AcOEt=20 : 1, then 10 : 1) to yield **24** (5.03 g, 41%) as colorless oil. IR ($CHCl_3$) 3483, 3017, 2956, 2929, 2857, 1728, 1520, 1471, 1463, 1437, 1362, 1100, 1049, 928, 837 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0—0.15 (12H, m), 0.75—0.95 (24H, m), 1.2—1.6 (10H, m), 1.8—2.6 (7H, m), 2.9—3.3 (3H, m), 3.71—3.73 (3H, m), 4.08—4.20 (2H, m), 4.30—4.41 (1H, m), 5.40—5.50 (2H, m), 5.47 (1H, d, *J* = 46.6 Hz). $^{19}F$ NMR (254 MHz, $CDCl_3$) $\delta$ = −168 (m).

**(7*R*, 17*S*)-7-Fluoro-17,20-dimethyl-2,4-methyleneprostacyclin Sodium Salt 2.**[11c] To a solution of acetylene **21** (12.06 g, 19.3 mmol) in benzene (640 $cm^3$) and cyclohexane (640 $cm^3$) were added cyclohexene (20 $cm^3$) and 5% Pd–$CaCO_3$ poisoned with Pb (4.0 g) at 0 °C. The mixture was hydrogenated under a 1 atm hydrogen atmosphere at 0 °C for 5 h, then filtered through Celite. After the filtrate was evaporated to give the corresponding olefin, which was dissolved in acetonitrile (500 $cm^3$), *N*-iodosuccinimide (22.7 g, 101 mmol) was added at room temperature. The mixture was heated at 40 °C for 13 h in the dark, then poured onto saturated $Na_2S_2O_3$, and extracted with $CH_2Cl_2$. The combined extracts were washed with brine, dried, and evaporated. The residue was filtered through silica gel eluted with 10% AcOEt in hexane to afford the crude iodide (12.5 g). To the iodide in toluene (600 $cm^3$) was added 1,8-diazabicyclo[5.4.0]-7-undecene (29.6 $cm^3$, 198 mmol) and heated at reflux for 10 h. After cooling to room temperature, the reaction mixture was poured onto water and extracted with AcOEt. The organic extracts were combined, dried, evaporated and chromatographed on silica gel (hexane : AcOEt=30 : 1) to give (7*R*, 17*S*)-7-fluoro-17,20-dimethyl-2,4-methyleneprostacyclin methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl) ether (4.3 g, 6.6 mmol, 34%) as a colorless oil. $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ = 0—0.10 (12H, m), 0.75—0.95

(24H, m), 1.0—1.8 (10H, m), 2.1—2.6 (6H, m), 2.7—3.4 (3H, m), 3.66—3.69 (3H, m), 3.75—3.90 (1H, m), 4.10—4.20 (1H, m), 4.45—4.80 (2H, m), 5.30 (1H, dd, $J$ = 7.5, 56.5 Hz), 5.53 (2H, m). $^{19}$F NMR (254 MHz, $CDCl_3$) $\delta$ = −183.8 (dd, $J$ = 7.5, 56.5 Hz), −184.2 (dd, $J$ = 7.5, 56.5 Hz). To a solution of the silyl ether (4.3 g, 6.6 mmol) in THF (50 cm$^3$) was added dropwise 1 M $Bu_4NF$ in THF (55 cm$^3$) at 0 °C. The mixture was stirred at room temperature for 4 h, evaporated, and chromatographed on silica gel ($CH_2Cl_2$: acetone=5 : 1, then 3 : 1) to afford the diol (1.6 g, 3.8 mmol, 57%). To a solution of the ester (1.24 g, 2.92 mmol) in EtOH (80 cm$^3$) was added 0.1 M NaOH (31.5 cm$^3$) at 0 °C. The mixture was stirred at room temperature for 21 h and then evaporated to give the desired sodium salt. The salt was precipitated from water–acetonitrile (3 : 97) to give **2** (1.05 g, 83%) as a while solid. HPLC analysis showed a mixture of two isomers, which were identical with authentic samples.[11] (YMC AM-312 ODS 5 μm 150 × 6.0 mm, $CH_3CN$–1% $Et_3N$ (adjusted to pH 6.3) 40/60 v/v, 1.0 cm$^3$ min$^{-1}$, UV 210 nm); $t_R$=7.2 min (36%: *cis*-cyclobutylene isomer), 8.2 min (64%: *trans*-cyclobutylene isomer); $^1$H NMR (270 MHz, $CD_3OD$) $\delta$ = 0.90—1.05 (6H, m), 1.18—1.85 (10H, m), 2.0—2.2 (2H, m), 2.3—3.4 (7H, m), 3.8—4.0 (1H, m), 4.1—4.2 (1H, m), 4.6—4.9 (2H, m), 5.46 (1H, dd, $J$ = 60.2, 8.4), 5.5—5.8 (2H, m). $^{19}$F NMR (254 MHz, $CD_3OD$) $\delta$ = −186 (d, $J$ = 60.2 Hz).

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