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Synthesis of 7-Fluoro-2,4-methylene-17,20-dimethylprostacyclins. Novel Stable Prostacyclin Analogs as Potent Anti-anginal Agents

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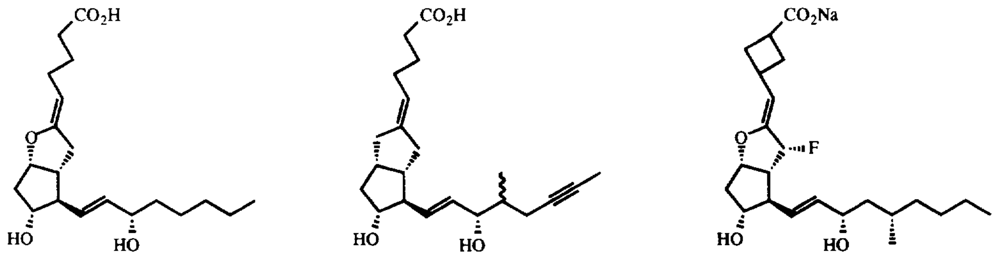
Abstract: Synthesis of new stable fluoroprostacyclins, 7-fluoro-2,4-methylene-17,20-dimethylprostacyclins (**1**, **2**) with potent and long-lasting anti-anginal activities has been achieved. The cyclobutylene prostaglandin skeleton **10** was constructed efficiently according to three-component coupling reaction. Stereospecific fluorination of silyl ether **11** and subsequent cyclization of the fluoride **12** successfully provided the desired 7-fluoro-2,4-methylene-17,20-dimethylprostacyclin.

Prostacyclin is one of the unstable metabolites of arachidonic acid which exerts a variety of actions such as inhibition of platelet aggregation and induction of vasodilation to maintain homeostasis in circulation. Its stable analogs have been regarded as potential drugs for thrombotic diseases, myocardial infarction, and arteriosclerosis.[1] In search for chemically and metabolically stable prostacyclin mimics with high therapeutic utilities a large number of efforts have been concentrated for these two decades to the synthesis of structurally modified derivatives.[2] Current progress of related studies such as elucidation of structure activity relationship based on the calculation by computer modeling,[3] or structure determination of prostacyclin receptor and suggestion of novel functions by molecular cloning,[4] has been highly stimulated discovery research of new prostacyclin agonists.[5]



prostacyclin

iloprost

1 (***trans***)
2 (***cis***)

Figure 1

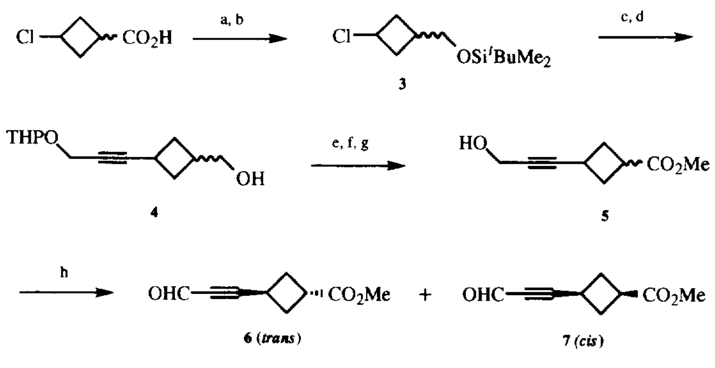
Introduction of fluorine atoms to a variety of biologically important compounds[6] has often brought significant improvement in their physiological properties mainly taking advantage of its exceptional electron negativity and small atomic size. In order to increase the stabilities several prostacyclin analogs possessing fluorine atoms neighboring to the acid labile enol ether have emerged with a view of retarding the hydrolysis.[7] We have focused on the synthesis of a novel type of fluoroprostacyclins by using stereo-controlled fluorination at the 7-position.[8]

Subsequently, our modifications have been turned toward the upper side chain to prevent it from being metabolized by β-oxidation.[9] The modifications of the chain of prostacyclin analogs have been limited in a few reports,[2f-h] probably due to the subtlety of their activities and the difficulty of the synthesis. The derivatives utilizing a ring system seem uncommon in medicinal chemistry field, and among them most examples are used as the substitutions of furan or oxetane ring, which employed for nucleosides,[10] thromboxanes,[11] and carbacyclins.[12] We have concentrated on the synthesis of the derivatives bearing a cyclobutylene group as a substituent of linear side chain to regulate its flexibility with a view of chemical approach.[13] It is supposed that regulation of the flexibility should be required for biological discrimination from undesired side effects. We preliminarily reported new stable prostacyclin analogs, 7-fluoro-2,4-methylene-17,20-dimethylprostacyclins (**1**, **2**),[14] which administered intravenously or orally showed potent and long-lasting activities as selective anti-anginal agents.[15] Here, we wish to report on the details of the study for the synthesis of fluoroprostacyclin **1** and **2**.

Results and Discussion

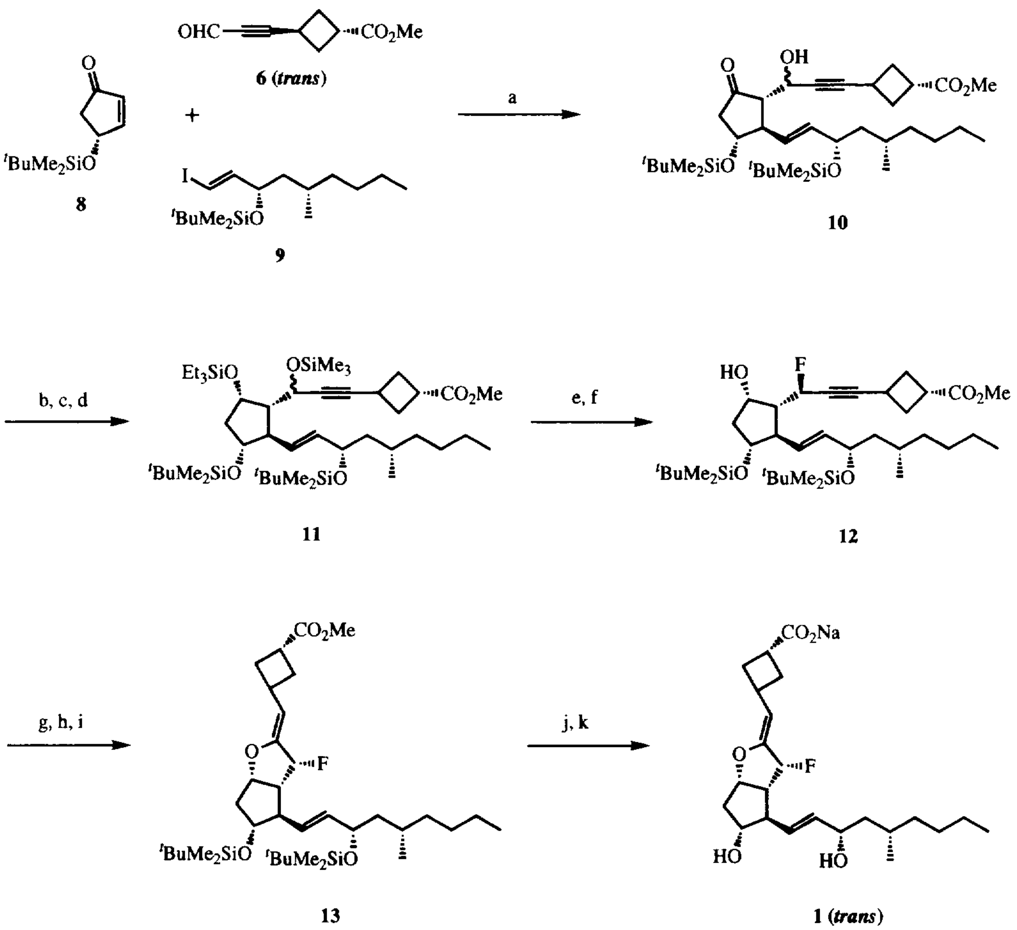
Preparation of cyclobutylene subunit and construction of prostaglandin skeleton Our strategy for generating the prostaglandin skeleton employed Noyori's three-component coupling process.[16] The convergent synthesis began with the preparation of cyclobutylene α-side chain (Scheme 1).

Scheme 1



a) $LiAlH_4$, THF, 86% b) t-$BuMe_2SiCl$, imidazol, DMF, r. t., 93% c) Mg, $BrCH_2CH_2Br$, $ZnCl_2$, $CuCN{\bullet}2LiCl$, $THPOCH_2C{\equiv}CBr$, THF, reflux d) Bu_4NF, THF, 52% (2 steps) e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 f) $AgNO_3$-NaOH, H_2O g) H_2SO_4, MeOH, 49% (3 steps) h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, **6**: 27%, **7**: 27%

Scheme 2



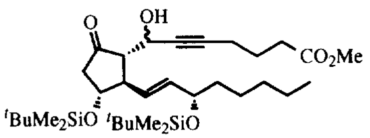
(a) i. **9**, ᵗBuLi (2.2 eq), ether, then $C_3H_7C{\equiv}CCu$, $(Me_2N)_3P$, -78°C ii. **8**, -78°C iii. **6**, -40°C, 65% (b) Me_3SiCl, Py, 0°C (c) $NaBH_4$, MeOH, -20°C (d) Et_3SiCl, Py, CH_2Cl_2, 0°C, 68% (3 steps) (e) piperidinosulfur trifluoride, $ClCF_2CFCl_2$, r. t. (f) pyridinium *p*-toluenesulfonate, EtOH, r. t., 51% (2 steps) (g) H_2 (1 atm), Pd-$CaCO_3$-Pb, 0°C (h) NIS, CH_3CN, 40°C (i) DBU, toluene, 110°C, 33% (3 steps) (j) Bu_4NF, THF, r. t. (k) NaOH, EtOH, r. t., 84% (2 steps)

3-Chlorocyclobutanecarboxylic acid[17] readily obtained in a large scale from 1,1-cyclobutanedicarboxylic acid was reduced with $LiAlH_4$ and the resulting alcohol was protected with *t*-butyldimethylchlorosilane to afford *t*-butyldimethylsilyl ether **3** in 80% yield. The Grignard reagent from the chloride **3** was transmetallated with zinc chloride, and the obtained organometallic species were coupled with 1-bromo-3-(2-tetrahydropyranyl)oxypropyne in the presence of CuCN•2LiCl.[18] The crude coupling product was deprotected with Bu_4NF in THF to give the alcohol **4** in 52% yield (2 steps). Two-step oxidation of the alcohol **4** and deprotection of THP group accompanied with simultaneous esterification provided the hydroxy ester **5** in 49% yield (3 steps). The α side chain subunit was obtained by Swern oxidation of the hydroxy ester **5** in 54% yield as a 1 : 1 mixture of *trans* and *cis* isomers (**6** and **7**), which were readily separated by silica gel chromatography.

The synthesis of 7-hydroxyprostaglandin derivative **10** was carried out according to three-component coupling reaction (Scheme 2). Michael addition of the copper reagent derived from iodide **9** to cyclopentenone **8** and successive trapping with the*trans*- cyclobutylene aldehyde **6** efficiently constructed the desired 7-hydroxyprostaglandin **10** in 65% yield as an approximately 1 : 1 mixture of the diastereomers at 7-position. After treatment of **10** with Me_3SiCl and pyridine, stereoselective reduction of the resulting cyclopentanone with $NaBH_4$ in MeOH at -30 °C followed by protection of the hydroxy group with triethylsilyl group furnished the silyl ether **11** in 68% yield.

Fluorination

Our first attempts to fluorinate the 7-hydroxyl group of the known prostaglandin derivatives **14** or **15**[19] with various fluorinating reagents resulted in obtaining the dehydrated compounds as major products. Fluorination of **16** even using diethylaminosulfur trifluoride (DAST) in CH_2Cl_2-Et_3N gave **18** only in 30% yield. Therefore, we tried to examine the modified fluorination reaction using (*R*)-2-octanol **19** as a model substrate. While fluorination of the alcohol **19a** with DAST in CH_2Cl_2 resulted in the poor selectivity (**20** : **21** = 48 : 52), modified fluorination of the corresponding silyl ether **19b** was found to give the products with high selectivity (**20** : **21** = 89 : 11). The modifed fluorination of the trimethylsilyl ether surpressed the side products probablly because the reaction formed enert trimethylsilyl fluoride *in situ*, instead of acidic hydrogen fluoride which usually caused undesirable dehydration reaction as well. The selectivities of **20** : **21** were not improved in the reported fluorination procedure[20] of the tosylate **19c** with KF or Bu_4NF (Table 1).



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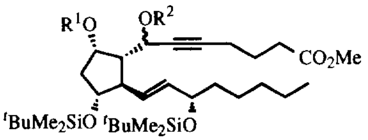

15 (R^1, R^2 : H)
16 (R^1 : $SiEt_3$, R^2 : H)
17 (R^1 : $SiEt_3$, R^2 : $SiMe_3$)

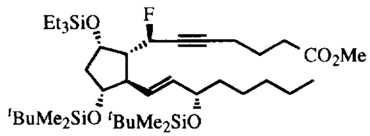

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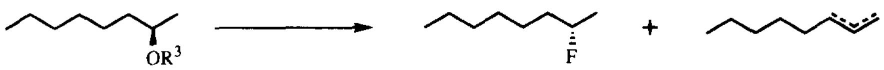
Table 1. Fluorination of (*R*)-2-Octanol Derivatives 19a-c.



19a (R^3 : H) **20** **21**

19b (R^3 : $SiMe_3$)

19c (R^3 : Ts)

Substrate	Reagent	Selectivity (**20** : **21**)	Optical purity of **20**
19a	DAST	48 : 52	97
19b	DAST	89 : 11	98
19c	KF	50 : 50 [a]	91 [a]
19c	Bu_4NF	63 : 37 [a]	79 [a]

[a] Reference 20).

Fluorination of the tetrakissilylated **17** (a 1 : 1 mixture of *C*-7 diastereomers) with DAST in CH_2Cl_2 resulted in a complex mixture including the products partly lost protective silyl groups. Instead of CH_2Cl_2, non-polar solvent was found to improve the product yield in the fluorination reaction. Desilylative fluorination of compound **17** (a 1 : 1 mixture of *C*-7 diastereomers) with piperidinosulfur trifluoride[21] in 1,1,2-trichloro-1,2,2-trifluoroethane at room temperature furnished the (7*R*)-fluoroprostaglandin derivative **18** in 61% yield as a single isolable stereoisomer. The fluoride **18** was obtained in the fluorination from both (7*S*)-**17** and (7*R*)-**17** in 72 % and 56 % yields, respectively. Dialkylaminosulfur trifluoride was known to give unexpected products, especially on the fluorination of stereochemically congested compounds.[22] It is supposed that the bulky triethylsiloxy group at the 9-position influenced the stereochemical outcome through the attack of fluoride anion to the propargylic carbonium ion. The fluoride anion would approach only from the β-side of *C*-7 position avoiding the steric hinderance of the α-face to form exclusively the (7*R*)-diastereomer. The similar fluorination of the cyclobutylene derivative **11** (a 1 : 1 diasteromeric mixture at *C*-7) and subsequent deprotection with pyridinium *p*-toluenesulfonate gave the hydroxy fluoride (7*R*)-**12** in 51% yield, accompanied with a small amount of the dehydrated product (< 10%).

Transformation to 7-fluoro-2,4-methylene-17,20-dimethylprostacyclin

A couple of methods employing the reagents $PdCl_2(C_6H_5CN)_2$-HCO_2NH_4,[23] or $Hg(OCOCF_3)_2$-Et_3N/ $NaBH_4$[24] are known for cyclization of 5,6-dehydroprostaglandin $F_{2\alpha}$ derivatives. We studied these methods to apply to the cyclization of our substrates, but we could not obtain the desired product in practical yields. Probably due to electron-deficient nature of the fluorine-containing acetylenic alcohol of **12**, the cyclization reactions retarded and complicated reductive cleavage of the vinyl intermediates was took place in some cases. We turned our attention to cyclization of the corresponding olefinic alcohol which could be obtained by selective hydrogenation of the acetylenic alcohol **12** without a loss of fluorine atom (Scheme 2).

We found that the hydrogenation on Lindler catalyst at 0°C gave better results than those of Pd/C or Pd/$BaSO_4$. After quantitative hydrogenation with Lindler catalyst, rather sluggish cyclization of the resulted olefinic alcohol with *N*-iodosuccinimide (NIS)[25] in acetonitrile at 40 °C for 16 h and subsequently dehydroiodination of the resulting iodide with DBU afforded the desired vinyl fluoride **13** in 33% yield (3 steps). Deprotection of **13** and following saponification finally provided the prostacyclin derivative **1** containing *trans*-cyclobutylene moiety in 84% yield. The *cis*-isomer **2** was synthesized in a similar synthetic pathway starting from the corresponding *cis*-aldehyde **7**.

In conclusion, we have demonstrated a convergent synthesis of 7-fluoro-2,4-methylene-17,20-dimethylprostacyclins **1** and **2**, which exerted potent and long-lasting activities as selective anti-anginal agents.[15] The cyclobutyleneprotacyclin skeleton was prepared through both three-component coupling process and desilylative fluorination method of trimethylsilylated alcohol as key steps. Novel cyclobutyleneprostacyclin derivatives may bring a key to understand the conformational elucidation of structure-activity relationship.

Experimental Section

General. ^1H and ^{19}F NMR spectra were recorded on JEOL JNM-FX-90Q, and JEOL JNM-GSX-270 spectrometers with tetramethylsilane for ^1H NMR as an internal standard, and trichlorofluoromethane for ^{19}F NMR as an external standard. IR spectra were recorded on JASCO IR-810 spectrometer. Mass spectra were obtained on a JEOL SX-102A mass spectrometer. Melting points were determined by Mettler FP80 melting point apparatus. All 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. Analytical gas liquid chromatography (GLC) was carried out with a Hitachi Gas Chromatograph 163 model instrument, equipped with a thermal conductivity detector. The column used was PEG 20M on Chromosorb WAW DMCS (80-100 mesh). GLC peak integrals were calculated by Shimadzu Chromatopack C-RIA. HPLC analysis was performed on Shimadzu liquid chromatograph LC-9A, SPD-6A UV detector, and Chromatopack C-R4A.

All reactions were carried out under argon atmosphere except for aqueous hydrolysis. Ether and tetrahydrofuran were distilled from Na metal and benzophenone. CH_2Cl_2, 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. (4*R*)-4-Hydroxy-2-cyclopentenone was perchased from Sumitomo Chemical Co., Ltd., and used for the *t*-butyldimethylsilyl ether. (1*E*, 3*S*, 5*S*)-3-*t*-Butyldimethylsilyl-1-iodo-5-methylnonene was available from Nissan Chemical Co., Ltd.

3-Chlorocyclobutane-1-methanol *t*-butyldimethylsilyl ether (3). A solution of 3-chlorocyclobutane-1-carboxylic acid (176 g, 1.31 mol) in ether (700 ml) was added dropwise to a suspension of $LiAlH_4$ (49.7 g, 1.31 mol) in ether (700 ml) at -50 °C. The mixture was allowed to warm to room temperature and stirred for 14 h, then 10% H_2SO_4 was carefully added at 0 °C. The mixture was extracted with AcOEt, and the organic phase was washed with 10% $NaHCO_3$, dried, and evaporated. The residue was distilled *in vacuo* to furnish the alcohol (105-110 °C / 26 mmHg, 137 g, 1.12 mol, 86%). ^1H NMR ($CDCl_3$) δ = 2.0-2.8 (m, 5H), 3.59 (m, 2H), 4.20-4.55 (m, 1H). The alcohol (47.1 g, 390 mmol) was dissolved in DMF (800 ml), and then imidazole (39.7 g, 584 mmol) and *t*-$BuMe_2SiCl$ (64.5 g, 428 mmol) were added at 0 °C. The mixture was stirred at room temperature for 1 h and poured into a mixture of 10% $NaHCO_3$ (800 ml) and hexane (800 ml). The organic phase was separated and washed with brine, dried and chromatographed on silica gel (hexane : AcOEt = 30 : 1) to give the silyl ether **3** (86 g, 366 mmol, 93%). ^{1}H NMR ($CDCl_3$) δ = 0.02-0.05 (m, 6H), 0.90 (s, 4.5 H), 0.91 (s, 4.5H), 2.0-2.8 (m, 5H), 3.59 (m, 2H), 4.20-4.55 (m, 1H).

3-[3-(2-Tetrahydropyranyl)oxy-1-propynyl]-1-cyclobutanemethanol (4) Compound **3** (705 g, 3 mol) and 1,2-dibromoethane (282 g, 1.5 mol) were mixed and added dropwise to magnesium turning (146 g, 6 mol) in tetrahydrofuran (2 l) with heating at reflux. After heating at reflux for 3.5 h, zinc chloride (408 g, 3 mol) in tetrahydrofuran (1.5 l) was added dropwise during 1.5 h and the heating was continued for 30 min. The mixture was cooled to -10 °C and added to a suspension of CuCN (188 g, 2.1 mol) and LiCl (178 g, 4.2 mol) in tetrahydrofuran (2.1 l) at -10 °C. The mixture was stirred at 0 °C for 5 min and cooled to -65 °C, to which was added dropwise a solution of 1-bromo-3-(2-tetrahydropyranyl)oxypropyne (329 g, 1.5 mol) in tetrahydrofuran (750 ml) cooled at -78 °C. The mixture was stirred at -65 °C for 1 h and -40 °C for 12 h, then allowed to warm to room temperature. The reaction mixture was poured into saturated ammonium chloride (4 l) and extracted with ether. The organic layer was washed with brine (500 ml), dried and evaporated. The residue was filtered through silica gel eluted with 5% AcOEt in hexane to give a crude silyl ether (488 g). The silyl ether was dissolved in tetrahydrofuran (1.1 l) and tetrabutylammonium fluoride (Bu_4NF) (1 M in tetrahydrofuran, 1.44 l) was added at 0 °C. The mixture was stirred at 5 °C for 4 h, then the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt = 3 : 2, then 1 : 2) to afford **4** (176 g, 786 mmol, 52%). ^{1}H NMR ($CDCl_3$) δ = 1.40-2.65 (m, 11H), 2.90-3.11 (m, 1H), 3.50-3.70 (m, 3H), 3.84 (m, 1H), 4.15-4.38 (m, 2H), 4.90 (m, 1H).

3-(3-Hydroxy-1-propynyl)cyclobutanecarboxylic acid methyl ester (5). To a solution of oxalyl chloride (20.5 ml) in CH_2Cl_2 (483 ml) in -78 °C was added DMSO (35.8 ml) in CH_2Cl_2 (78 ml). After stirring for 15 min, a solution of **4** (35.7 g, 159 mmol) in CH_2Cl_2 (159 ml) was added at -78 °C. The mixture was stirred at -78 °C for 40 min, then Et_3N (145 ml) was added. The stirring was continued at -78 °C for 15 min, at room temperature for 30 min. The mixture was poured into water (1 l) and extracted with CH_2Cl_2. The extract was washed with brine and evaporated to give a crude aldehyde. To a mixture of NaOH (26.2 g, 655 mmol) in water (112 ml) and $AgNO_3$ (56.9 g, 334 mmol) in water (115 ml) was added the aldehyde at 0 °C with vigorous stirring. The viscous mixture was stirred for 15 min, filtered through Celite, and washed with hot water. The filtrate was acidified with concentrated HCl and extracted with ether. The ether extracts were combined and evaporated to provide the crude acid (29.5 g). The acid was dissolved in benzene (125 ml) and MeOH (125 ml) and concentrated H_2SO_4 (1 ml) was added. The mixture was heated at reflux for 14 h, then poured into saturated $NaHCO_3$, and extracted with CH_2Cl_2. The crude ester was purified by silica gel chromatography (hexane : AcOEt = 1 : 1) to yield **5** (13.0 g, 49%). ^{1}H NMR ($CDCl_3$) δ = 2.25-2.65 (m, 4H), 3.00 (m, 1H), 3.20 (m, 1H), 3.68 (s, 1.5H), 3.70 (s, 1.5H), 4.30 (m, 2H).

3-(3-Oxo-1-propynyl)-*trans*-cyclobutanecarboxylic acid methyl ester (6) and 3-(3-oxo-1-propynyl)-*cis*-cyclobutanecarboxylic acid methyl ester and (7). To a solution of oxalyl chloride (83.7 ml, 975 mmol) in CH_2Cl_2 (1 l) at -78 °C was added DMSO (138 ml, 1.9 mol) in CH_2Cl_2 (300 ml). After 30 min, a solution of the alcohol **5** (105 g, 625 mmol) in CH_2Cl_2 (300 ml) was added at -78 °C and the mixture was stirred for 40 min. After Et_3N (500 ml, 3.6 mol) was added, the reaction temperature was raised to 10 °C. The mixture was poured into ice-water and extracted with CH_2Cl_2. The extracts were combined, washed with 1N HCl, 5% $NaHCO_3$, and brine. Drying and evaporation gave a crude aldehyde. The *trans* and *cis* isomers were separated by silica gel chromatography (hexane : AcOEt = 6 : 1, then 4 : 1).

The *trans* isomer **6** (27.7 g, 167 mmol, 27%): TLC Rf : 0.67 (hexane : AcOEt = 2 : 1). ^{1}H-NMR ($CDCl_3$) δ = 2.40-2.56 (m, 2H), 2.60-2.75 (m, 2H), 3.20-3.45 (m, 2H), 3.71 (s, 3H), 9.21 (s, 1H). The *cis* isomer **7** (27.9 g, 168 mmol, 27%) : TLC Rf 0.58 (hexane : AcOEt = 2 : 1). ^{1}H-NMR ($CDCl_3$) δ = 2.44-2.66 (m, 4H), 3.02-3.24 (m, 2H), 3.70 (s, 3H), 9.20 (s, 1H).

(7*RS*, 17*S*)-5,6-Dehydro-7-hydroxy-2,4-*trans*-methylene-17,20-dimethylprostaglandin E_2 methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl) ether (10).

t-Butyllithium (1.5 M, a pentane solution, 75,2 ml, 106.1 mmol) was added to ether (100 ml) at -78 °C. (1*E*, 3*S*, 5*S*)-3-*t*-Butyldimethylsilyl-1-iodo-5-methylnonene (**9**) (20.6 g, 52 mmol) was dissolved in ether (100 ml) and added dropwise thereto over a period of 30 min. The mixture was stirred at -78 °C for 2 h. In another flask pentynyl copper (6.79g, 52 mmol) and hexamethylphosphorous triamide (18.9 ml, 104 mmol) were mixed and dissolved in ether (200 ml) at room temperature, which was added dropwise to the vinyllithium at -78 °C over a period of 15 min. After 30 min, to the mixture was added a solution of (4*R*)-4-*t*-butyldimethylsiloxy-2-cyclopentenone (**8**) (10.6 g, 50 mmol) in ether (200 ml) at -78 °C during 1 h. After stirring at -78 °C for 20 min, the mixture was warmed to -40 °C. A solution of **6** (9.13 g, 55 mmol) in ether (200 ml) was added dropwise to the reaction mixture at -40 °C. The mixture was stirred at -40 °C for 1 h, then poured into a mixture of acetate buffer (pH 4, 400 ml) and hexane (400 ml) with vigorous stirring. The organic layer was separated, and the aqueous layer was extracted with hexane (2 x 200 ml). The organic extracts were combined and washed with a mixture of saturated ammonium chloride (200 ml) and 28% NH_3 in water (3 x 200 ml), saturated ammonium acetate (400 ml), and then brine (400 ml), and dried over $MgSO_4$. After evaporation, the residue was chromatographed on silica gel (hexane : AcOEt = 9 : 1, then 6 : 1) with cooling below 5 °C to afford acid labile compound **10** (21.4 g, 65%). ^{1}H NMR ($CDCl_3$) δ = 0.01 (m, 12H), 0.80-0.95 (m, 24H), 1.0-1.5 (m, 10H), 2.2-2.9 (m, 9H), 3.66 (s, 3H), 4.0-4.2 (m, 2H), 4.5-4.6 (m, 1H), 5.50-5.70 (m, 2H).

(7*RS*, 17*S*)-5,6-Dehydro-2,4-*trans*-methylene-7-trimethylsilyloxy-17,20-dimethylprostaglandin $F_2\alpha$ methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl)-9-triethylsilyl ether (11). To a solution of the alcohol **10** (34.7g, 53 mmol) in CH_2Cl_2 were added pyridine (21.6 ml, 267 mmol) and Me_3SiCl (10.1 ml, 80 mmol) at 0 °C. After stirring at 0 °C for 1 h, the mixture was diluted with CH_2Cl_2 (160 ml) and poured into ice cooled saturated $NaHCO_3$ (300 ml). The organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 150 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated. The crude silyl ether (38.3 g) was dissolved in MeOH (533 ml) and cooled to -30 °C. To the solution $NaBH_4$ (7.05 g, 187 mmol) was added portionwise and the mixture was stirred for 1 h. After completion of the reaction monitored by TLC, saturated ammonium chloride (210 ml) was added dropwise, then allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2, washed with brine, dried and evaporated. The residual liquid (39.8 g) was dissolved in pyridine (210 ml) and cooled to -5 °C. To the solution Et_3SiCl (13.4 ml, 80 mmol) was added dropwise and the mixture was stirred at -5 °C for 45 min. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ (1500 ml) and hexane (1000 ml) with ice-cooling. The organic layer was separated and aqueous layer was extracted with hexane. The combined organic material was dried over $MgSO_4$, evaporated, and chromatographed on silica gel (hexane: AcOEt = 30 : 1) to give **11** (30.3 g, 36.2 mmol, 68%). ^{1}H NMR ($CDCl_3$) δ = 0-0.2 (m, 21H), 0.55 (m, 6H), 0.8-1.0 (m, 33H), 1.1-1.7 (m, 10H), 1.9-2.9 (m, 9H), 3.73 (s, 3H), 3.89 (m, 1H), 4.10-4.25 (m, 2H), 4.61 (m, 1H), 5.40-5.70 (m, 2H). HRMS Calcd for $C_{41}H_{79}O_6Si_4$: 779.4954 (M^+-*t*-Bu); found: 779.4824.

Fluorination of (*R*)-2-octanol trimethylsilyl ether (19b). To a solution of **19b** (1.01 g, 5.0 mmol) in CH_2Cl_2 (25 ml) was added DAST (0.67 ml, 5.5 mmol) dropwise at -78 °C, and stirred at -78 °C for 10 min and -20 °C for 10 h, The solution was diluted with ether and quenched with saturated potassium bicarbonate. The organic phase was washed with saturated potassium bicarbonate and brine, and dried over $MgSO_4$. The crude product was analyzed by GLC at 70 °C. The ratio of 2-fluorooctane (t_R : 9.56 min) to total olefins (1-octene; t_R : 4.08 min, *cis*-2-octene; t_R : 4.87 min, *trans*-2-octene; t_R : 4.98 min) was calculated to be 89 : 11. The mixture was treated with bromine to brominate the olefins, and distilled to give **20** (541 mg, 4.1 mmol, 82% yield) as a colorless oil. $[\alpha]_D^{25}$ 14.5 ° (in $CHCl_3$, 98% optical purity).[20]

(7*R*, 17*S*)-5,6-Dehydro-7-fluoro-prostaglandin F$_{2}\alpha$ methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl)-9-triethylsilyl ether (18). To a solution of the silyl ether **17** (317 mg, 0.39 mmol) in 1,1,2-trichloro-1,2,2-trifluoroethane (8 ml) was added piperidinosulfur trifluoride (62.9 µl) at 0 °C. The mixture was stirred at room temperature for 6 h. After cooling to 0°C, Et_3N (0.5 ml) was added. The mixture was diluted with CH_2Cl_2 (5 ml), 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 the fluoride **18** (192 mg, 0.24 mmol, 61%). ^{1}H NMR ($CDCl_3$) δ = 0-0.1 (m, 12H), 0.5-0.6 (m, 6H), 0.8-1.00 (m, 30H), 1.2-1.5 (m, 9H), 1.6-2.7 (m, 7H), 1.82 (t, J = 7.3 Hz, 2H), 3.66 (s, 3H), 3.86 (m, 1H), 4.04 (m, 1H), 4.26 (m, 1H), 5.30 (dd, J = 9.5, 47.5 Hz, 1H), 5.45-5.50 (m, 2H). ^{19}F NMR ($CDCl_3$) δ = -169 (m). HRMS Calcd for $C_{35}H_{66}FO_5Si_3$: 669.4202 (M^+-*t*-Bu); found: 669.4283.

(7*R*, 17*S*)-7-Fluoro-5,6-dehydro-2,4-*trans*-methylene-17,20-dimethylprostaglandin F$_{2}\alpha$ methyl ester 11,15-(*O*)-bis(t-butyldimethylsilyl) ether (12). To a solution of **11** (10.1 g, 12 mmol) in 1,1,2-trichloro-1,2,2-trifluoroethane (96 ml) was added piperidinosulfur trifluoride (2.08 ml) at 0 °C. The mixture was stirred at room temperature for 6 h. After cooling to 0°C, Et_3N (4.4 ml) was added. The mixture was diluted with CH_2Cl_2 (50 ml), poured into saturated $NaHCO_3$ (100 ml) and extracted with CH_2Cl_2. The organic extract was washed with brine, dried, evaporated. The residue was filtered through silica gel eluted with 5 % AcOEt in hexane to give the fluoride (7.61 g), which was dissolved in EtOH (190 ml) and cooled at 0 °C. Pyridinium *p*-toluenesulfonate (262 mg, 1.0 mmol) was added and stirred at room temperature for 6 h. The reaction mixture was poured into saturated $NaHCO_3$ (150 ml), and extracted with CH_2Cl_2. The organic extract was washed with brine, dried, evaporated and chromatographed on silica gel (hexane : AcOEt = 15 : 1, then 10 : 1) to yield **12** (3.94g, 6.07 mmol, 51%). ^{1}H NMR ($CDCl_3$) δ = 0-0.1 (m, 12H), 0.85-0.90 (m, 24H), 1.2-1.6 (m, 10H), 1.8-2.1 (m, 2H), 2.2-2.6 (m, 5H), 2.9-3.3 (m, 3H), 3.70 (s, 3H), 4.13-4.16 (m, 2H), 4.35 (m, 1H), 5.40-5.50 (m, 2H), 5.47 (d, J = 46.6 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ = -168 (d, J = 47 Hz). HRMS Calcd for $C_{32}H_{56}FO_5Si_2$: 595.3650 (M^+-*t*-Bu); found 595.3664.

(7*R*, 17*S*)-7-Fluoro-2,4-*trans*-methylene-17,20-dimethylprostacyclin methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl) ether (13). To a solution of the acetylene **12** (1.39 g, 2.1 mmol) in benzene (34 ml) and cyclohexane (34 ml) were added cyclohexene (2.12 ml) and 5% Pd-$CaCO_3$ poisoned with Pb (289 mg) at 0 °C. The mixture was hydrogenated under 1 atm hydrogen atmosphere at 0 °C for 2 h, then filtered through Celite. The filtrate was evaporated to give the corresponding olefin (1.47 g). The crude olefin was dissolved in acetonitrile (54 ml) and *N*-iodosuccinimide (2.42 g, 10.8 mmol) was added at room temperature. The mixture was heated at 40 °C for 16 h under dark, then poured into saturated NaS_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 (1.61 g). To the iodide (1.38g) in toluene (80 ml) was added 1,8-diazabicyclo[5.4.0]-7-undecene (3.12 ml) and heated at reflux for 8 h. After cooling to room temperature, the reaction mixture was poured into water (160 ml) and extracted with ether. The organic extracts were combined, dried, evaporated and chromatographed on silica gel (hexane : AcOEt = 30 : 1) to give **13** (395 mg, 0.61 mmol, 33%). ^{1}H NMR ($CDCl_3$) δ = 0-0.10 (m, 12H), 0.83-0.91 (m, 24H), 1.0-1.8 (m, 10H), 2.10 (m, 2H), 2.3-2.6 (m, 4H), 2.7-3.4 (m, 3H), 3.68 (s, 3H), 3.82 (m, 1H), 4.15 (m, 1H), 4.55-4.80 (m, 2H), 5.30 (dd, J = 7.5, 56.5 Hz, 1H), 5.53 (m, 2H). ^{19}F NMR ($CDCl_3$) δ = -184 (dd, J = 7.5, 56.5 Hz). HRMS Calcd for $C_{36}H_{65}FO_5Si_2$: 652.4355; found 652.4318.

(7*R*, 17*S*)-7-Fluoro-2,4-*trans*-methylene-17,20-dimethylprostacyclin sodium salt (1). To a solution of **13** (2.91 g, 4.5 mmol) in THF (20 ml) was added dropwise 1 M Bu_4NF in THF (34.9 ml) at 0 °C. The mixture was stirred at room temperature for 6 h, evaporated and chromatographed on silica gel (CH_2Cl_2 : acetone = 5 : 1) to afford (7*R*, 17*S*)-7-fluoro-2,4-*trans*-methylene-17,20-dimethylprostacyclin methyl ester (1.90 g, 4.5 mmol, 100%). ^{1}H NMR (acetone-d_6) δ = 0.86-0.90 (m, 6H), 1.1-1.8 (m, 10H), 2.3-3.3 (m, 9H), 3.60 (m, 1H), 3.65 (s, 3H), 3.89 (m, 1H), 4.03-4.15 (m, 2H), 4.61 (m, 1H), 4.75 (m, 1H), 5.44 (dd, J = 8.3, 60 Hz, 1H), 5.50-5.70 (m, 2H). ^{19}F NMR (acetone-d_6) δ = -185 (dd, J = 8.3, 60 Hz). To a solution of the ester (1.10 g, 2.61 mmol) in EtOH (63 ml) was added 0.1 N NaOH (27.4 ml) at 0 °C. The mixture was stirred at room temperature for 15 h and then evaporated to give the desired sodium salt (972 mg, 2.27 mmol, 87%) as a white solid. The salt was dissolved and precipitated again from water-acetonitrile (3 : 97). HPLC (reverse phase); t_R = 7.95 min (YMC AM-312 ODS 5 µm 150 x 6.0 mm, CH_3CN- 1% Et_3N (adjusted to pH 6.3) 40 / 60 v/v, 1.0 ml/min, UV 210 nm). Mp 184.5-185.6 °C (dec.). IR (KBr) 3400, 2970, 2935, 1560, 1420, 1236, 1060, 990 cm^{-1}. ^{1}H NMR (CD_3OD) δ = 0.95-1.05 (m, 6H), 1.18-1.82 (m, 10H), 2.00-2.02 (m, 2H), 2.50-2.78 (m, 5H), 3.10 (m, 1H), 3.35 (m, 1H), 3.95 (m, 1H), 4.20 (m, 1H), 4.68 (m, 1H), 4.90 (m, 1H), 5.46 (dd, J = 60.2, 8.4 Hz, 1H), 5.57-5.80 (m, 2H). ^{19}F NMR (CD_3OD) δ = -186.0 (d, J = 60.2 Hz). HRMS Calcd for $C_{23}H_{34}FO_5$ 409.2390 (M^+-Na); found 409.2388.

(7*RS*, 17*S*)-5,6-Dehydro-7-hydroxy-2,4-*cis*-methylene-17,20-dimethyl-prostaglandin E_2 methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl) ether (*cis*-10). ^{1}H NMR ($CDCl_3$) δ = 0.01 (m, 12H), 0.82-0.95 (m, 24H), 1.0-1.5 (m, 10H), 2.2-3.1 (m, 9H), 3.66 (s, 3H), 4.1-4.3 (m, 2H), 4.5-4.7 (m, 1H), 5.50-5.70 (m, 2H).

(7*RS*, 17*S*)-5,6-Dehydro-2,4-*cis*-methylene-7-trimethylsilyloxy-17,20-dimethylprostaglandin $F_{2}\alpha$ methyl ester 11,15-(*O*)-bis(*t*-butyldimethylsilyl)-9-triethylsilyl ether (*cis*-11). ^{1}H NMR ($CDCl_3$) δ = 0-0.2 (m, 21H), 0.58 (m, 6H), 0.8-1.0 (m, 33H), 1.1-1.7 (m, 10H), 1.9-3.1 (m, 9H), 3.71 (s, 3H), 3.90 (m, 1H), 4.05-4.22 (m, 2H), 4.62 (m, 1H), 5.40-5.70 (m, 2H).

(7*R*, 17*S*)-7-Fluoro-5,6-dehydro-2,4-*cis*-methylene-17,20-dimethylprostaglandin $F_{2}\alpha$ methyl ester 11,15-(*O*)-bis(t-butyldimethylsilyl) ether (*cis*-12). ^{1}H NMR ($CDCl_3$) δ = 0-0.1 (m, 12H), 0.85-0.89 (m, 24H), 1.2-1.6 (m, 10H), 1.8-2.1 (m, 2H), 2.3-2.6 (m, 5H), 2.9-3.4 (m, 3H), 3.68 (s, 3H), 4.13-4.16 (m, 2H), 4.37 (m, 1H), 5.35-5.55 (m, 3H). ^{19}F NMR ($CDCl_3$) δ = -169 (m).

(7*R*, 17*S*)-7-Fluoro-2,4-*cis*-methylene-17,20-dimethylprostacyclin methyl ester 11,15-(*O*)-bis(t-butyldimethylsilyl) ether (*cis*-13). ^{1}H NMR ($CDCl_3$) δ = 0-0.05 (m, 12H), 0.84-0.91 (m, 24H), 1.0-1.8 (m, 10H), 2.10 (m, 2H), 2.3-2.6 (m, 4H), 2.7-3.25 (m, 3H), 3.67 (s, 3H), 3.85

(m, 1H), 4.15 (m, 1H), 4.57-4.70 (m, 2H), 5.32 (dd, $J = 8.3, 56.3$ Hz, 1H), 5.53 (m, 2H). ^{19}F NMR ($CDCl_3$) $\delta = -184$ (dd, $J = 8.3, 56.5$ Hz).

(7*R*, 17*S*)-7-Fluoro-2,4-*cis*-methylene-17,20-dimethylprostacyclin sodium salt (2). HPLC (reverse phase); $t_R = 6.74$ min (YMC AM-312 ODS 5 μm 150 x 6.0 mm, CH_3CN- 1% Et_3N (adjusted to pH 6.3) 40 / 60 v/v, 1.0 ml/min, UV 210 nm). A white powder, mp 180.5-181.0 °C (dec.). IR (KBr): 3345, 2976, 2940, 1560, 1433, 1240, 1085, 970 cm^{-1}. ^{1}H-NMR (CD_3OD) δ : 0.94-1.05 (m, 6H), 1.18-1.85 (m, 10H), 2.03-2.19 (m, 2H), 2.33-3.20 (m, 7H), 3.93 (m, 1H), 4.19 (m, 1H), 4.60-4.75 (m, 2H), 5.45 (dd, $J = 8.4, 56.6$ Hz, 1H), 5.55-5.78 (m, 2H). ^{19}F-NMR (CD_3OD) δ : -186.1 (d, $J = 56.4$ Hz). HRMS Calcd for $C_{23}H_{34}FO_5$ 409.2390 (M^+-Na); found 409.2388.

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