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SYNTHESIS OF NEW STABLE FLUOROPROSTACYCLIN ANALOGS WITH POTENT ANTI-ANGINAL ACTIVITY

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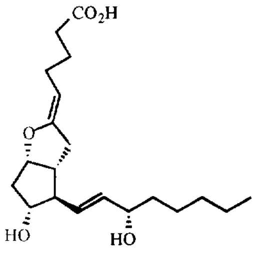
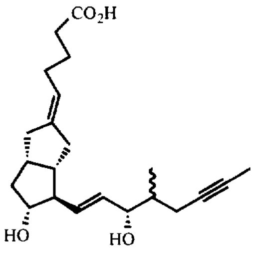
Abstract: Synthesis of new stable fluoroprostacyclins, 7-fluoro-2,4-methylene-17,20-dimethylprostacyclins (**1**, **2**) with potent and long-lasting anti-anginal activities has been achieved via three-component coupling reaction and stereospecific fluorination.

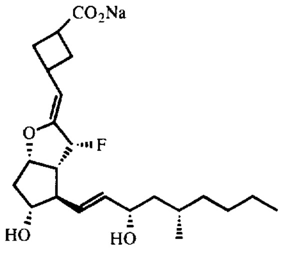
In search for chemically and metabolically stable prostacyclin mimics with high therapeutic utilities a large number of efforts have been concentrated to the synthesis of structurally modified analogs.1) Introduction of fluorine atoms to a variety of biologically important compounds2) has often brought significant improvement in their physiological properties mainly taking advantage of its exceptional electron negativity and small atomic size. Several prostacyclin analogs possessing fluorine atoms neighboring to the acid labile enol ether have emerged with a view of retarding the hydrolysis.3) We have focused on the synthesis of a novel type of fluoroprostacyclins by using stereo-controlled fluorination at the 7-position and introducing methylene group into the upper side chain to prevent from β-oxidation. We herein report new stable prostacyclin analogs, 7-fluoro-2,4-methylene-17,20-dimethylprostacyclins (**1**, **2**), which administered intravenously or orally showed potent and long-lasting anti-anginal activities.



prostacyclin

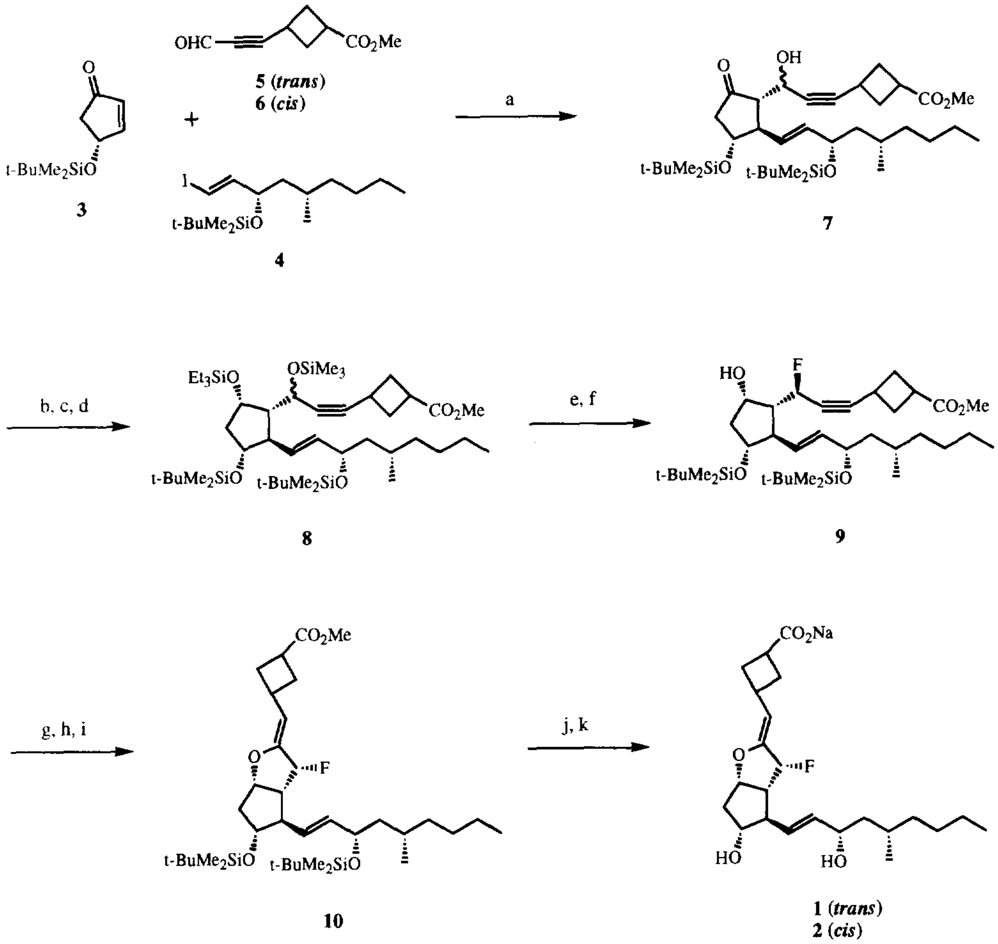


iloprost



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

Scheme 1



(a) i. **4**, t-BuLi (2.2 eq), ether, then $C_3H_7C{\equiv}CCu$, $(Me_2N)_3P$, -78°C ii. **3**, -78°C iii. **5**, -40°C (b) Me_3SiCl, Py, 0°C (c) $NaBH_4$, MeOH, -20°C (d) Et_3SiCl, Py, CH_2Cl_2, 0°C (e) piperidinosulfur trifluoride, $ClCF_2CFCl_2$, r.t. (f) pyridinium *p*-toluenesulfonate, EtOH, r.t. (g) 1atm H_2, Pd-$CaCO_3$-Pb, 0°C (h) NIS, CH_3CN, 40°C (i) DBU, toluene, 110°C (j) Bu_4NF, THF, r.t. (k) NaOH, EtOH, r.t.

The synthesis of **1** was started from cyclopentenone **3** with iodide **4** and *trans*-3-(3-oxo-1-propynyl)cyclobutanecarboxylic acid methyl ester **5**$^{4)}$ efficiently to construct 7-hydroxyprostaglandin derivative **7** as a 1 : 1 mixture of the diastereomers at 7-position according to the three-component coupling reaction$^{5)}$ in 65% yield. After treatment of **7** with Me_3SiCl-pyridine, stereoselective reduction with $NaBH_4$ followed by protection with triethylsilyl group furnished the silyl ether **8** in 75% overall yield. Fluorination of **8** with piperidinosulfur trifluoride$^{6)}$ and subsequent deprotection with pyridinium *p*-toluenesulfonate gave the (7*R*)-fluoroprostaglandin derivative **9** in 51% yield as a single stereoisomer, accompanied with a small amount of the dehydrated product (< 10 %). It should be noted the desired stereoisomer was obtained from both (7*S*)- and (7*R*)-trimethylsilyloxy isomers.$^{7)}$ 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. After selective hydrogenation with Lindler catalyst, sluggish cyclization of the olefinic alcohol **8** with *N*-iodosuccinimide in acetonitrile at 40 °C for 16 h and elimination with DBU afforded **10** in 31% yield (3 steps). Deprotection of **10** and following saponification provided the prostacyclin **1**$^{8)}$ in 84% yield. The *cis*-isomer **2**$^{8)}$ was synthesized in the same synthetic pathway starting from the corresponding *cis*-aldehyde **6**$^{4)}$.

Compound **1** and its isomer **2** indicated strong inhibition of ADP-induced platelet aggregation whose activities were almost similar to iloprost.$^{1a)}$ Anti-anginal activities of **1** and **2** evaluated by preventive effect on vassopressin-induced ST depression of rat electrocardiogram^{9} proved to be 10 - 100 fold more potent compared with iloprost. Improvement of the chemical and metabolical stabilities was well demonstrated by long duration of the activities in oral administration.^{10} The detailed results on pharmacological evaluation of **1** and **2** will be published elsewhere.

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4) Compound **5** was prepared from 3-chlorocyclobutane caboxylic acid (G. M. Lampman, J. C. Aumiller, Org. Syn. coll. vol. **VI**, 271) as follows: 1) $LiAlH_4$, ether 2) t-$BuMe_2SiCl$, imidazole, DMF 3) Mg, $ZnCl_2$, CuCN, LiCl, $THPOCH_2C{\equiv}CBr$, THF 4) Bu_4NF, THF 5) Swern oxdation 6) $AgNO_3$, NaOH 7) H_2SO_4, MeOH 8) Swern oxidation. Compound **5** and the *cis*-isomer **6** were separated by silica gel chromatography. **5**: ^{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). **6**: ^{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).

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7) The preceding results for the fluorination in reference 2c). Similar neighboring effects on fluorination of stereochemically congested compounds with diethylaminosulfur trifluoride; S. Rozen, Y. Faust, H. Ben-Yakov, *Tetrahedron Lett.*, **20**, 1823 (1979); V. V. Bezuglov, I. V. Serkov, R. G. Gafurov, L. D. Bergelson, *Dokl. Akad. Nauk*, **277**, 1400 (1984); and reference 3b).

8) **1**: a white powder, 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).

2: 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 = 56.6, 8.4 Hz, 1H), 5.55-5.78 (m, 2H). ^{19}F-NMR (CD_3OD) δ : -186.1 (d, J = 56.4 Hz).

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10) Duration of the activity at minimum effective dose; **1**: 3 h (0.01 mg/ml), **2**: 3 h (0.1 mg/ml), iloprost: 0.5 h (1.0 mg/ml).

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