*Tetrahedron* Vol 39, No. 22, pp. 3807 to 3819, 1983
Printed in Great Britain

0040 4020/83 $3.00 + .00
Pergamon Press Ltd.

# SYNTHESIS OF CHEMICALLY STABLE PROSTACYCLIN ANALOGS†

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(*Received in Japan* 4 *August* 1983)

Abstract - Syntheses of several stable $PGI_2$ analogs substituted by an electron-withdrawing substituent at C-5 or C-7 are described. Reaction of $PGI_2$ methyl ester (1) with benzenesulfenyl chloride gave (5*E*)-5-phenylthio-$PGI_2$ (2) or (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ (5) according to the reaction condition employed. Allyl sulfide 5 was transformed into (7*S*)-7-hydroxy-$PGI_2$ (11) and (7*S*)-7-acetoxy-$PGI_2$ (12) *via* stereocontrolled sulfoxide-sulfenate rearrangement, and alcohol 11 was further transformed into (7*S*)-7-fluoro-$PGI_2$ (14). These $PGI_2$ analogs were found much more stable than $PGI_2$.

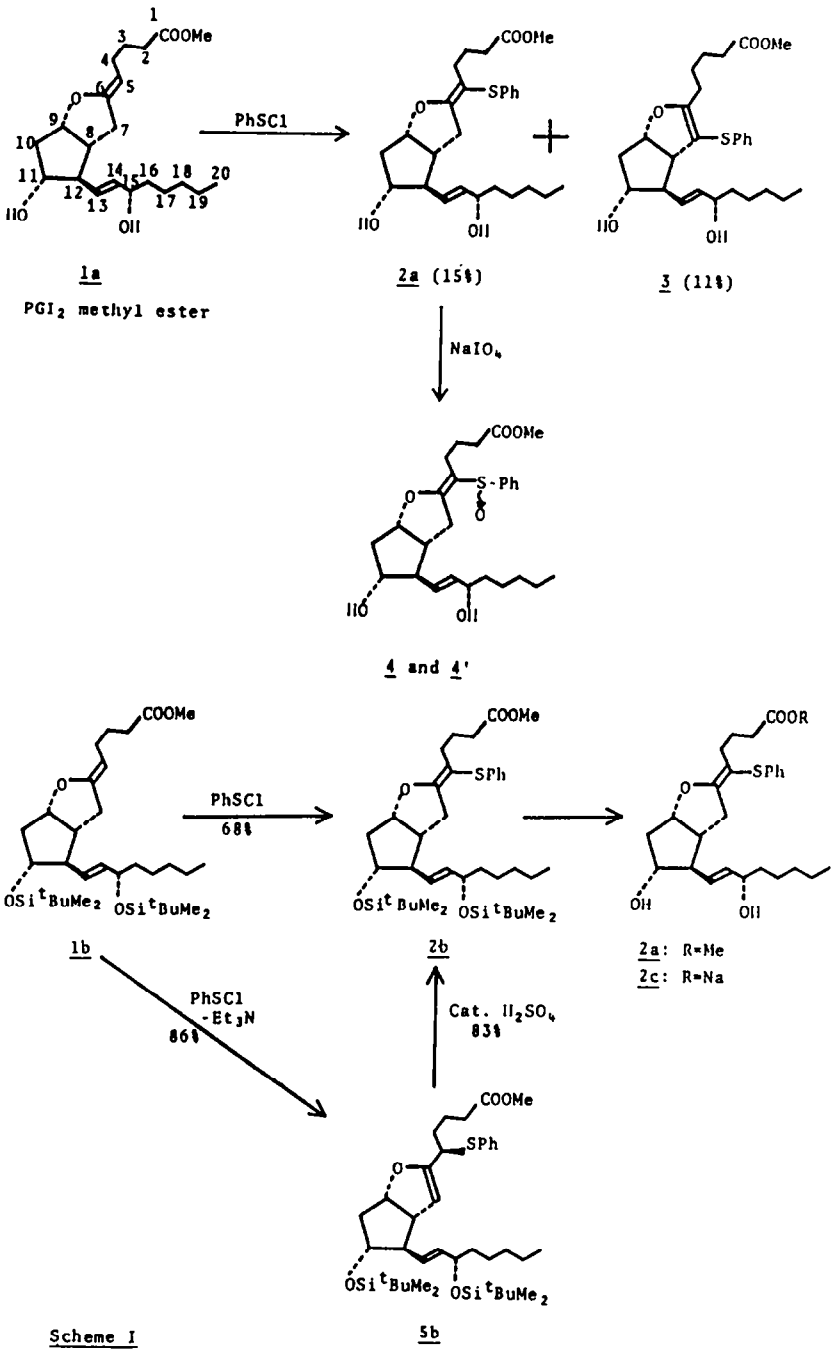
Prostacyclin ($PGI_2$) is a remarkably attractive compound as a therapeutic agent for several serious vascular diseases since it is a potent inhibitor of platelet aggregation as well as a powerful vasodilator[1]. Nevertheless, the chemical instability of $PGI_2$, that it is easily hydrolyzed to inactive 6-oxo-$PGF_{1\alpha}$ in acidic or neutral media[2], limits its clinical application. In this hydrolysis the electrophilic attack of hydroxonium ion to the enol ether double bond of $PGI_2$ is considered to be a rate determining step[3,4]. Thus reducing the electron density of the enol ether double bond should lead to the stabilization of $PGI_2$ against hydrolysis. To achieve this, introduction of an electron-withdrawing group at the position on or adjacent to enol ether double bond was planned[5]. Examination of the electrophilic reaction of benzenesulfenyl chloride toward $PGI_2$ enol ether lead to the finding of selective formation of (5*E*)-5-phenylthio-$PGI_2$ (2) or (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ (5) according to the reaction condition employed[6]. In this report is discussed the above reaction including the mechanistic and stereochemical consideration. We also describe the stereocontrolled transformation of (5*R*)-5-phenylthio-$\Delta^6$-$PGI_2$ (5) into (7*S*)-7-hydroxy-$PGI_2$ (11) or (7*S*)-7-acetoxy-$PGI_2$ (12)[6] and fluorination of 11 into (7*S*)-7-fluoro-$PGI_2$ (14)[6]. The chemical stability of these stable $PGI_2$ analogs are also described briefly.

## I. Reaction of $PGI_2$ methyl ester with benzenesulfenyl chloride.

### Synthesis of 5-phenylthio-substituted $PGI_2$ derivatives

First we directed our efforts to incorporating a phenylthio group into the enol ether function of $PGI_2$. This strategy encompasses two beneficial facets; (i) stabilizing effect of the electron-withdrawing phenylthio group on the enol ether linkage against hydrolysis is expected, and (ii) transformation of the phenylthio group into other electron-withdrawing functional groups is possible. In order to introduce a phenylthio group into the $PGI_2$ skeleton, we examined

†Prostaglandin Chemistry XX. For Part XIX; Atsuo Hazato, Toshio Tanaka, Takeshi Toru, Noriaki Okamura, Kiyoshi Bannai, Satoshi Sugiura, Kenji Manabe and Seizi Kurozumi, Submitted to Nippon Kagaku Kaishi.




Scheme I

the reaction of the enol ether of $PGI_2$ with benzenesulfenyl chloride. The electrophilic reaction of arylsulfenyl chloride with enol ethers is known to give usually α-arylthio ketones[7,8,9].

When benzenesulfenyl chloride was added to $PGI_2$ methyl ester (1a) in methylene chloride at -78°C, there were isolated two products, (5*E*)-5-phenylthio-$PGI_2$ methyl ester (2a)[10] (15%) and 7-phenylthio-$\Delta^6$-$PGI_1$ methyl ester (3) (11%) accompanied with several unidentified products.

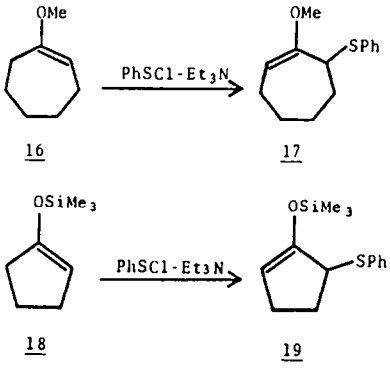
Since the C-11 and C-15 hydroxyl groups could be responsible for the low yield of the products, these two hydroxyl groups were protected with *t*-butyldimethylsilyl groups to avoid undesired side reactions. The addition of benzenesulfenyl chloride to the methylene chloride solution of $PGI_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (1b) at -78°C resulted in the formation of desired (5*E*)-5-phenylthio-$PGI_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (2b)[10] in 68% yield with

little formation of side reaction products. It is interesting that only *E*-isomer of 5-phenylthio-$PGI_2$ analog 2 was obtained in this reaction.

The *E*-geometry of $\Delta^5$-olefin of 5-phenylthio-$PGI_2$ 2a was determined on the basis of $^1$H-NMR study of the corresponding two diastereomeric sulfoxides 4 and 4' which were obtained by the oxidation of 2a with sodium metaperiodate. The C-7 methylene protons of the less polar sulfoxide 4 appeared in a field lower by 0.32 ppm (two protons) than those of parent sulfide 2a, and those of the more polar sulfoxide 4' appeared in fields lower by 0.48 ppm (one proton) and 0.10 ppm (the other proton) than those of 2a. Since allylic methylene protons *cis* to sulfoxide group are known to appear markedly lower than those *cis* to sulfide group[11,12] the $\Delta^5$-olefin geometry of 5-phenylthio-$PGI_2$ 2a was analogously assigned to be 5E.

Removal of the silyl-protecting groups of 2b with tetrabutylammonium fluoride afforded (5*E*)-5-phenylthio-$PGI_2$ methyl ester (2a) in 70% yield. Hydrolysis of the ester 2a with sodium hydroxide in ethanol-water gave (5*E*)-5-phenylthio-$PGI_2$ sodium salt solution (2c), which was used directly for chemical stability and pharmacological tests.

Our effort was then focused on the formation of the allyl sulfide isomer, 5-phenylthio-$\Delta^6$-$PGI_1$ derivative 5, which is a key intermediate for other types of stable $PGI_2$ analogs. We postulated that the formation of the allyl sulfide required the use of a base in the sulfenyl chloride addition reaction to eliminate the C-7 proton. When benzenesulfenyl chloride was added to the silyl-protected $PGI_2$ 1b at room temperature in the presence of a base (3 equiv.) such as triethylamine, 4-dimethylaminopyridine or 2,2,6,6-tetramethylpiperidine, the allyl sulfide type compound, (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (5b)[10], was obtained. This reaction proceeded stereoselectively to give only 5*R*-isomer (*vide post*) and no formation of the vinyl sulfide type compound 2b was observed. Triethylamine recorded the best yield (86%) of 5b among the bases tested[13]. This reaction was extended to other enol ethers such as 1-methoxycycloheptene (16) and



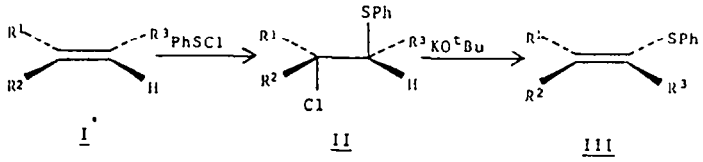

Scheme II

1-trimethylsilyloxycyclopentene (18) to result in the formation of allyl sulfide type compounds, 1-methoxy-7-phenylthiocycloheptene (17) and 5-phenylthio-1-trimethylsilyloxycyclopentene (19), in 60% and 63% yield, respectively.

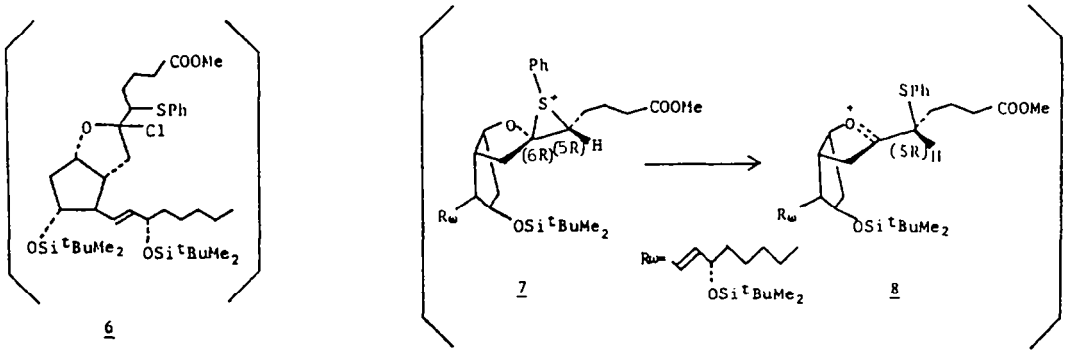
Isomerization of allyl sulfide 5b to vinyl sulfide 2b was easily realized using acid instead of bases[14]. The treatment of (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ 5b with a catalytic amount of concentrated sulfuric acid in chloroform at room temperature gave (5*E*)-5-phenylthio-$PGI_2$ 2b (83%) stereospecifically without any evidence of the formation of 5Z-isomer.

Mechanistic consideration

The reaction of $PGI_2$ methyl ester (1) with benzenesulfenyl chloride without base resulted in the formation of (5*E*)-5-phenylthio-$PGI_2$ (2) with retention of the $\Delta^5$-olefin geometry. Masaki *et al.* have reported that the reaction to olefin I with benzenesulfenyl chloride and the subsequent treatment of the adduct II with base such as potassium *t*-butoxide gave vinyl sulfide III *via* complete inversion of the olefin geometry as shown in Scheme III[12]. The *trans* addition of the sulfenyl chloride to olefin I first occurred to form olefin-sulfenyl chloride adduct II, which is then dehydrochlorinated in a *trans* manner by the base giving the inversed vinyl sulfide III. Our result on the reaction of the enol ether with benzenesulfenyl chloride can not be explained by the Masaki's mechanism. It was considered that 2b should have been




Scheme III




formed not *via* enol ether-sulfenyl chloride adduct 6, but presumably *via* oxonium ion intermediate 8 derived from episulfonium ion 7[8]. From the molecular model study the approach of benzenesulfenyl chloride from the β-side of the $\Delta^5$-enol ether double bond of $PGI_2$ should be much more favorable than from the sterically more hindered α-side[15]. Thus the more plausible configurations of both C-5 and C-6 of the episulfonium ion intermediate 7 should be *R*, and consequently the configuration of C-5 of 8 should be *R*.

In order to form $\Delta^5$-olefin from oxonium ion intermediate 8, the C-5 carbon-proton bond should be parallel to the C-6 vacant *p*-orbital. Between the two possible conformers 8-I and 8-II shown in Fig. 1, conformer 8-I would be formerd kinetically much more favorably by the least motion (60° counterclockwise rotation from the firstly formed conformer 8-A) than conformer 8-II (120° clockwise rotation from the conformer 8-A is necessary). Thus it was considered that 5*E*-isomer of 5-phenylthio-$PGI_2$ 2b was formerd through conformer 8-I under

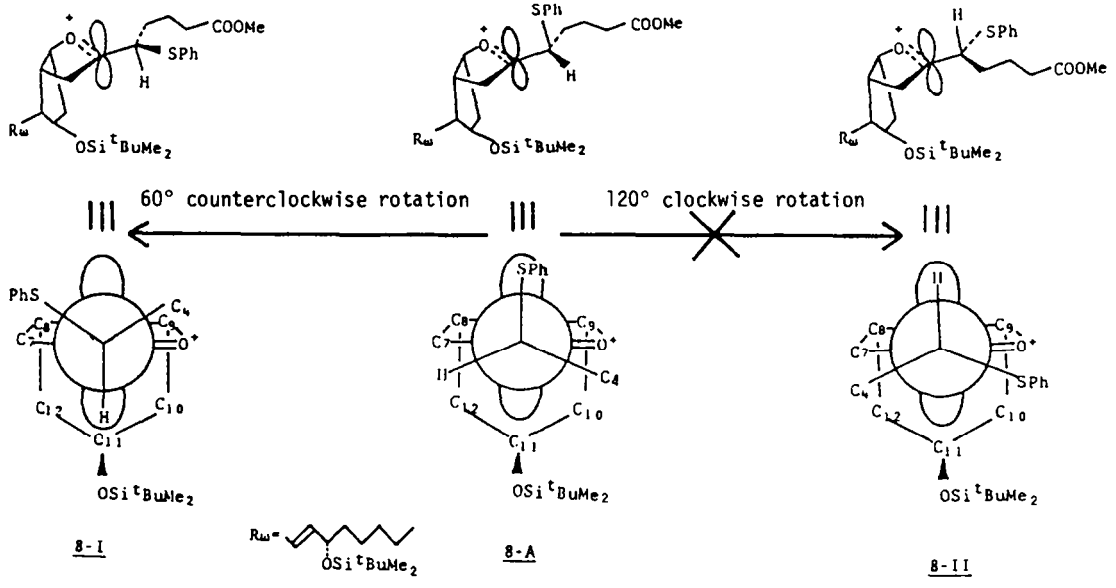



Fig. 1. Conformers of oxonium ion 8

kinetic control based on the restriction of the rotation between C-5 and C-6 bond in 8-A. The stereospecific acid-catalyzed isomerization of (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ 5b to (5*E*)-5-phenylthio-$PGI_2$ 2b could be explained by the same mechanism *via* the episulfonium ion and the oxonium ion intermediates, 7 and 8.

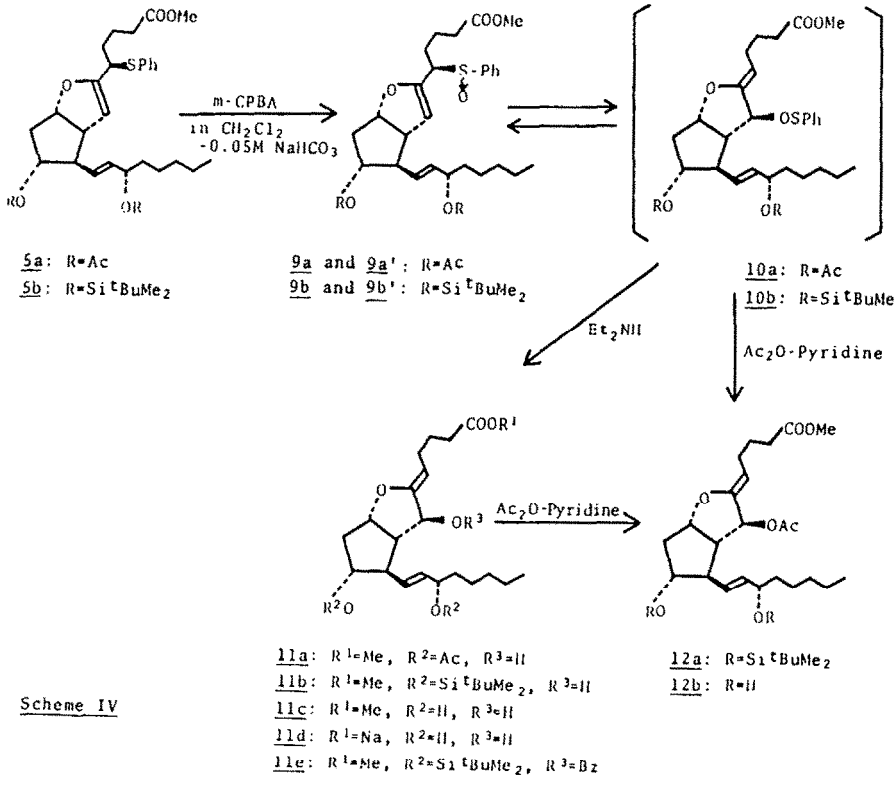
The reaction of $PGI_2$ methyl ester with benzenesulfenyl chloride in the presence of triethylamine would proceed also *via* oxonium ion intermediate 8, which lead to the formation of (5*R*)-5-phenylthio-$\Delta^6$-$PGI_1$ 5b through the C-7 proton abstruction by base. It can not be ruled out that another reaction species such as a complex formed from benzenesulfenyl chloride and triethylamine might be involved in this reaction because the reaction of 1b with benzenesulfenyl chloride in the presence of triethylamine proceeded slower than with benzenesulfenyl chloride only.

The formation of 7-phenylthio-$\Delta^6$-$PGI_1$ 3 would be also explained by similar 6,7-episulfonium ion and 7-phenylthio-oxonium ion intermediates derived from $\Delta^6$-$PGI_1$ methyl ester, which would possibly be formed from $PGI_2$ methyl ester 1a by isomerization[16].

II. Transformation of 5-substituted $PGI_2$ into 7-substituted $PGI_2$.

Synthesis of 7-hydroxy-$PGI_2$

Studies on the transformation of 5-phenylthio-$\Delta^6$-$PGI_1$ derivative into other stable $PGI_2$ analogs with an electron-withdrawing substituent at C-7 were carried out. Transformation of 5-phenylthio-$\Delta^6$-$PGI_1$ 5b into 7-hydroxy-$PGI_2$ 11b was performed by the sulfoxide-sulfenate rearrangement[17]. Attempts to oxidize 5b into the corresponding sulfoxide with *m*-chloroperbenzoic acid in methylene chloride or sodium metaperiodate in methanol failed to result in the formation of complex mixtures. The successful oxidation of 5b was achieved with *m*-chloroperbenzoic acid in a two phase solvent system of methylene chloride and 0.05 M aqueous sodium bicarbonate giving an isomeric mixture of sulfoxides 9b and 9b' in 53% yield. The product ratio of 9b and 9b' was *ca.* 1:1 on thin layer chromatography, however isolation of each epimeric sulfoxide was unsuccessful due to the rapid isomerization of an epimer to the other *via* sulfenate ester 10b (9b ⇄ 10b ⇄ 9b')[17,18]. The mixture of sulfoxides 9b and 9b' was then treated with a thiophile (diethylamine) to give




5a: R=Ac
5b: R=Si$^t$BuMe$_2$

9a and 9a': R=Ac
9b and 9b': R=Si$^t$BuMe$_2$

10a: R=Ac
10b: R=Si$^t$BuMe$_2$

11a: $R^1$=Me, $R^2$=Ac, $R^3$=H
11b: $R^1$=Me, $R^2$=Si$^t$BuMe$_2$, $R^3$=H
11c: $R^1$=Me, $R^2$=H, $R^3$=H
11d: $R^1$=Na, $R^2$=H, $R^3$=H
11e: $R^1$=Me, $R^2$=Si$^t$BuMe$_2$, $R^3$=Bz

12a: R=Si$^t$BuMe$_2$
12b: R=H

Scheme IV

(7*S*)-7-hydroxy-$PGI_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (11b)[10] in 68% yield. Treatment of the mixture of sulfoxides 9b and 9b' with acetic anhydride and pyridine[19] afforded (7 *S*)-7-acetoxy-$PGI_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (12a)[10] in 62% yield. The compound 12a was also obtained by acetylation of (7*S*)-7-hydroxy-$PGI_2$ 11b with acetic anhydride and pyridine. Removal of the silyl protecting groups of 11b and 12a with tetrabutylammonium fluoride in tetrahydrofuran afforded (7*S*)-7-hydroxy-$PGI_2$ methyl ester (11c) (87%) and (7 *S*)-7-acetoxy-$PGI_2$ methyl ester (12b) (60%), respectively. Hydrolysis of the ester 11c with sodium hydroxide in ethanol-water gave (7 *S*)-7-hydroxy-$PGI_2$ sodium salt solution (11d).

The absolute configuration of the C-7 of 7-hydroxy-$PGI_2$ 11 was determined from the circular dichlomism (CD) spectrum of the corresponding benzoate 11e. The positve Cotton effect of 11e ($[\theta]_{224}$+5.6×10$^4$) indicated 7*S*-configuration of 11[20]. In the $^1$H-NMR spectrum of 11b, the C-5 vinyl proton appeared at 4.46 ppm, while that of $PGI_2$ methyl ester 1a and its 5*E*-isomer, (5*E*)-$PGI_2$ methyl ester, have been reported to appear at 4.16 and 4.67 ppm, respectively[21]. The hydroxyl group substitution at the allyl position is known to cause the downfield effect on the γ-*cis* and γ-*trans* vinyl proton by about 0.24 and 0.14 ppm, respectively[22]. The fact that the C-5 vinyl proton of 11b appeared 0.30 ppm lower than that of $PGI_2$ methyl ester 1a and higher than that of (5*E*)-$PGI_2$ methyl ester lead to determination of 5*Z*-geometry of 11b. Furthermore these stereochemical assignements are in good accord with the following possible reaction pathway; 5*R*-phenylsulfinyl group of 9b and 9b' migrated concertedly[18] to the less hindered β-side of C-7 to form 5*Z*,7*S*-sulfenate ester intermediate 10b, which was transformed into corresponding 5*Z*,7*S*-alcohol 11b.

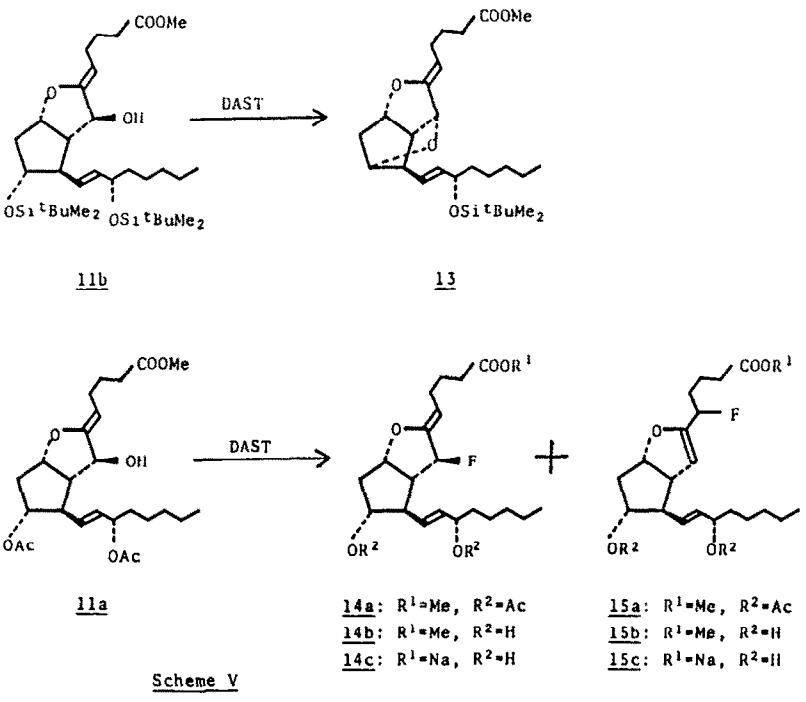
The stereochemistry of 7-acetoxy-$PGI_2$ 12a obtained directly from the mixture of sulfoxides 9b and 9b' was also assigned to 5*Z* and 7*S*, because the product was the same as that obtained by acetylation of 5*Z*,7*S*-alcohol 11b. The 5*Z*-configuration of 12a was also confirmed from the $^1$H-nmr study in which the C-5 vinyl proton appeared at 4.56 ppm, between that of $PGI_2$ methyl ester 1a and (5*E*)-$PGI_2$ methyl ester.

Synthesis of 7-fluoro-$PGI_2$

Transformation of (7*S*)-7-hydroxy-$PGI_2$ 11 into fluorinated $PGI_2$ analogs is an attractive subject because fluorine atom has a strong electron-withdrawing character. It is known that 10,10-difluoro substituents stabilized the enol ether of $PGI_2$ against hydrolysis even though these fluorine atoms are remote from the enol ether linkage[23]. It was considered that a fluorine atom substituted closer to the enol ether linkage would have a much better effect on the stabilization, so we examined the transformation of (7*S* )-7-hydroxy-$PGI_2$ 11 into 7-fluorinated $PGI_2$ 14[24].

Diethylaminosulfur trifluoride (DAST)[25] is a good fluorinating agent for hydroxylated compounds. Treatment of silyl-protected (7*S*)-7-hydroxy-$PGI_2$ methyl ester (11b) with DAST in methylene chloride gave no fluorinated product but (7 *R*,11 *R*)-11-deoxy-7,11-epoxy-$PGI_2$ 15-*O*-(*t*-butyldimethylsilyl) methyl ester (13) was obtained in 52% yield. This result seemed to be due to the nucleophilic affinity of a fluoride anion for the silyl group[26]. The silyl protecting group of C-11 hydroxyl group would be suffered by the attack of the fluoride anion, giving anionic oxygen at the C-11 position which would make the 7,11-epoxide. To avoid this cyclization reaction, diacetyl-protected (7 *S*)-7-hydroxy-$PGI_2$ methyl ester (11a) was chosen as a substrate for the fluorination. The diacetate 11a was derived from $PGI_2$ diacetate methyl ester in the same manner as the synthesis of 11b. Fluorination of 11a with DAST gave the expected (7*S*)-7-fluoro-$PGI_2$ diacetate methyl ester (14a)[10] (22%) accompanied by 5-fluoro-$\Delta^6$-$PGI_1$ diacetate methyl ester (15a) (32%).

The 7*S* stereochemistry of 7-fluoro-$PGI_2$ 14 was determined as follows. The 7α-methine protons of (7*S*)-7-substituted-$PGI_2$ analogs such as (7*S*)-7-hydroxy-$PGI_2$ 11 or (7*S*)-7-acetoxy-$PGI_2$ 12 coupled with their 8β-methine protons by less than one Hz. Since the coupling constant between 7α- and 8β-methine protons of 14b was nearly zero Hz[27], the configuration of C-7 of 14 was analogously assigned to *S*. The $\Delta^5$-olefin geometry of 14 was also determined from $^1$H-NMR study. The C-5 vinyl proton of 14b appeared at 4.75 ppm much lower than that of $PGI_2$ methyl ester 1a, which indicated the *Z*-geometry of the




11b 13

11a

14a: $R^1$=Me, $R^2$=Ac
14b: $R^1$=Me, $R^2$=H
14c: $R^1$=Na, $R^2$=H

15a: $R^1$=Me, $R^2$=Ac
15b: $R^1$=Me, $R^2$=H
15c: $R^1$=Na, $R^2$=H

Scheme V

$\Delta^5$-double bond as in the case of 11 and 12. It was found that 5-fluoro-$\Delta^6$-$PGI_1$ 15 obtained above was a diastereomeric mixture of unseparable 5*R*- and 5*S*-isomers (*ca*. 2:1) because its $^{13}$C-NMR spectrum showed several pairs of absorptions corresponding to C-4, C-5, C-6, C-7 and C-9 carbons.

It is likely that the reaction of 7-hydroxy-$PGI_2$ 11a with DAST firstly formed allyl carbonium ion intermediate which would be attacked by fluoride anion at C-5 or C-7 position[28]. Since the α-side of C-7 position of 11a was sterically hindered, fluoride anion would approach from the β-side of C-7 position to form (7*S*)-7-fluoro-$PGI_2$ derivative 14a. On the other hand, fluoride anion would approach from the both sides at C-5 position to afford a mixture of (5*R*)- and (5*S*)-5-fluoro-$\Delta^6$-$PGI_1$ derivative 15a.

Removal of the acetyl groups of 14a and 15a by treatment with sodium methioxide in absolute methanol afforded (7*S*)-7-fluoro-$PGI_2$ methyl ester (14b) and 5-fluoro-$\Delta^6$-$PGI_1$ methyl ester (15b) in 82% and 80% yields, respectively. Hydrolysis of 14b and 15b with sodium hydroxide in ethanol-water gave the sodium salt solutions of (7*S*)-7-fluoro-$PGI_2$ (14c) and 5-fluoro-$\Delta^6$-$PGI_1$ (15c).

III. Chemical stability of 5- and 7-substituted $PGI_2$ analogs

Several $PGI_2$ analogs substituted by an electron-withdrawing substituent at C-5 or C-7 were synthesized. The chemical half life in pH 4.7 and 7.4 buffer solutions, and the inhibitory activity of platelet aggregation were summarized in Table I comparing with the $^{13}$C-NMR chemical shift of C-5.

In $^{13}$C-NMR of these 7-substituted $PGI_2$ analogs, 7-hydroxy-$PGI_2$ 11b and 7-fluoro-$PGI_2$ 14a, the C-5 carbon appeared in fields lower by 2.3 ppm and 7.6 ppm than that of $PGI_2$[21], respectively. These observations indicated that these electron-withdrawing substituents at C-7 reduced the electron density at C-5[29]. The reduction of the electron density at C-5 correlated with the stabilization of the enol ether of these compounds against hydrolysis, because the electrophilic attack of hydroxonium ion to the vinyl carbon β to ether oxygen (C-5 in the case of $PGI_2$ molecule) is rate determining step in enol ether hydrolysis[3,4]. Indeed these 7-substituted $PGI_2$

Table I. Chemical Stability of $PCI_2$ analogs

| Compound | $^{13}$C-NMR Chemical Shift of C-5 | Chemical Half Life ($T_{1/2}$) | | Inhibitory Activity of Platelet Aggregation[f] ($IC_{50}$ μg/ml) | |
|---|---|---|---|---|---|
| | | pH=7.4 | pH=4.7 | 0 h | 4 h |
| 5-PhS-$PGI_2$ 2a | 98.2[a] | NT[d] | 1.5 days | 1.7 | NT[d] |
| 7-OH-$PGI_2$ 11d | 99.2[b] | NT[d] | 3 h | >10 | >10 |
| 7-F-$PGI_2$ 14c | 104.5[b] | >1 month | 2.5 days | 0.05 | 0.05 |
| $PGI_2$ | 96.9[c] | 10.5 min[e] (pH=7.46) | 22.4 sec[e] (pH=5.98) | 0.005 | >5 |

(a) The chemical shift of the corresponding methyl ester is presented.

(b) The chemical shift of the corresponding 11,15-bis(*t*-butyldimethylsilyl ether) methyl ester 11b or 11,15-diacetate methylester 14a is presented.

(c) Data cited in ref. 21.

(d) Not tested.

(e) Data from ref. 2.

(f) Rabbit platelet aggregation induced by ADP (10 μM).

analogs were found to be much more stable than $PGI_2$. The chemical half life ($T_{1/2}$) of 11d and 14c in pH 4.7 buffer solution was 3 hours and 2.5 days, respectively, while that of $PGI_2$ even in pH 5.98 buffer solution has been reported to be 22.4 seconds[2]. Moreover 7-fluoro-$PGI_2$ 14c has a half life more than one month in pH 7.4 buffer solution, while that of $PGI_2$ in pH 7.46 has been reported to be only 10.5 minutes[2]. These results were further demonstrated by the biological activity of inhibitory action on rabbit platelet aggregation. The activity of 14c was maintained after standing in pH 7.4 at room temperature for 4 hours, whereas that of $PGI_2$ decreased to less than 1/1000 in the same condition.

5-substituted $PGI_2$ analogs, 5-phenylthio-$PGI_2$ 2c, was also found much more stable than $PGI_2$. The chemical half life in pH 4.7 buffer solution was found to be 1.5 days. In the case of this compound 2c, not only the electron-withdrawing character but also the mesomeric effect[3] of phenylthio group would be considered to be responsible for the stability.

## EXPERIMENTAL

IR spectra were recorded on a JASCO A102 spectrometer. $^1$H- and $^{13}$C-NMR spectra were obtained on a JEOL JNM-PS-100 (100 MHz) or a Varian EM360A (60 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) relative to internal tetramethylsilane. Mass spectra were taken at 70 or 20 eV on a LKB-9000 mass spectrometer. Optical rotations were measured on a Union Giken PM-101 automatic polarimeter. CD spectra were recorded on a JASCO J-20 automatic recording spectropolarimeter. Thin layer chromatography was performed using Merck Silica gel (Kieselgel 60 $F_{254}$) analytical or preparative plates. All reactions were carried out under argon. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction and chromatography were GR grades.

### Preparation of benzenesulfenyl chloride solution

#### (A) 0.34 M solution in methylene chloride

To a ice-cooled solution of thiophenol (350 μL, 3.4 mmol) in anhydrous methylene chloride (10 mL) under argon was added *N*-chlorosuccinimide (476 mg, 3.6 mmol) in one portion. The reaction mixture was stirred at room temperature for 40 min, and then refluxed for 1 hr. During the reaction the color of the solution changed from yellow to orange. This solution was stored in a freezer and the supernatant solution was used for the reaction directly.

#### (B) 1.0 M solution in methylene chloride

The solution was prepared as in the case of (A) using 1.30 mL (10 mmol) of thiophenol, 10 mL of anhydrous methylene chloride and (1.40 g, 10.5 mmol) of *N*-chlorosuccinimide.

#### (C) 0.5 M solution in benzene

*N*-chlorosuccinimide (1.34 g, 10 mmol) was added

at room temperature under argon to a stirred solution of thiophenol (1.1 g, 10 mmol) in 20 mL of anhydrous benzene. The mixture was refluxed for 1 hr. At the end of this period, the color of the solution was orange. This solution was stored in a freezer and the supernatant solution was used for the reaction directly.

(5*E*)-5-Phenylthio-PGI$_2$ methyl ester (2a) and 7-phenylthio-PGI$_2$ methyl ester (3)

To a stirred solution of PGI$_2$ methyl ester (1a)[21] (60 mg, 0.16 mmol) in anhydrous methylene chloride (1.5 mL) was added dropwise at -78° C a 0.34 M solution of benzenesulfenyl chloride in anhydrous methylene chloride (0.5 mL, 0.17 mmol). During the addition the yellow color of benzenesulfenyl chloride immediately disappeared and the pale yellow color persisted in the final stage of the addition. The reaction mixture was stirred at the same temperature for additional 20 min and was poured into saturated $NaHCO_3$ solution (10 mL), and extracted with methylene chloride (2×15 mL). The combined extracts were washed with water and dried over $MgSO_4$-$K_2CO_3$. Removal of the solvent afforded an oily residue, which was chromatographed on Florisil eluting with benzene-ethyl acetate (7:3) containing 0.1% of triethylamine to isolate less polar components 3 (11 mg, 11%) and more polar component 2a (15 mg, 15%); 3 TLC Rf 0.40 (benzene-AcOEt, 3:7); IR ($CHCl_3$) 3400, 1720, 1220, 1200 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) 0.9 (3H, m), 3.09 (1H, m), 3.64 (3H, s), 3.75-4.0 (2H, m), 4.90 (1H, m), 5.38 (2H, m), 7.3 (5H, bs); MS m/e (bistrimethylsilyl ether) 618 ($M^+$), 603, 587, 547, 528, 457, 438, 427, 367, 337: Calc. for $C_{33}H_{54}O_5SSi_2$ 618.3232, Found 618.3264. 2a TLC Rf 0.30 (benzene-AcOEt, 3:7); $[\alpha]_D^{22}$+73.6° (c, 0.274, $CHCl_3$); IR ($CHCl_3$) 3400, 1722, 1650, 1435, 1220, 1200 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.9 (3H, m), 2.82 (2H, bs), 3.64 (3H, s), 3.78-4.10 (2H, m), 4.70-4.90 (1H, m), 5.53 (2H, m), 7.20 (5H, bs); $^{13}$C-NMR ($CDCl_3$) δ 22.6 ($C_3$), 34.0 ($C_4$), 98.2 ($C_5$), 164.1 ($C_6$), 30.1 ($C_7$), 45.4 ($C_8$), 86.1 ($C_9$), 40.3 ($C_{10}$), 77.2 ($C_{11}$), 55.4 ($C_{12}$); MS m/e (bis-trimethylsilyl ether) 618 ($M^+$), 603, 587, 547, 528, 457, 441, 438. Calc. for $C_{33}H_{54}O_5SSi_2$ 618.3232, Found 618.3225.

(5*E*)-5-Phenylthio-PGI$_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (2b)

To a stirred solution of PGI$_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (1b)[21] (32 mg, 0.054 mmol) in anhydrous methylene chloride (0.8 mL) was added at -78°C a 1.0 M solution of benzenesulfenyl chloride in anhydrous methylene chloride (70 μL, 0.07 mmol) over a period of 5 min. The pale yellow color of benzenesulfenyl chloride persisted in the final stage of the addition. After stirring at the same temperature for additional 15 min, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution (10 mL), and extracted with *n*-hexane (3×10 mL). The combined extracts were washed with brine and dried over $MgSO_4$-$K_2CO_3$. Removal of the solvent afforded an oily residue, which was chromatographed on Florisil eluting with *n*-hexane-ethyl acetate (99:1) containing 0.1% of triethylamine to give 27 mg of 2b (68%) as an oil; TLC Rf 0.35 (benzene); IR (film) 1740, 1650, 1255, 1122, 838, 775 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.91 (9H, s), 0.93 (9H, s), 2.85 (2H, m), 3.68 (3H, s). 3.7-4.2 (2H, m), 4.78 (1H, m), 5.45 (2H, m), 7.24 (5H, bs); $^{13}$C-NMR ($CDCl_3$) δ 23.6 ($C_3$), 34.1 ($C_4$), 97.7 ($C_5$), 164.3 ($C_6$), 30.3 ($C_7$), 44.7 ($C_8$), 85.9 ($C_9$), 41.6 ($C_{10}$), 77.9 ($C_{11}$), 54.6 ($C_{12}$); MS m/e 702 ($M^+$), 687, 671, 645, 631, 570.

2a and its sodium salt solution 2c from 2b

Tetrabutylammonium fluoride trihydrate (139 mg, 0.44 mmol) was added to a stirred solution of 2b (20.6 mg, 0.029 mmol) and triethylamine (65 μl) in 1 mL of tetrahydrofuran. After stirring the mixture at room temperature for 3 hr, saturated $NaHCO_3$ solution (10 mL) was added and extracted with ether (3×10 mL). The combined extracts were washed with brine, dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The residue was then purified by Florisil column chromatography eluting with *n*-hexane-ethyl acetate (1:1) containing 0.1% of triethylamine to yield 9.6 mg (70%) of 2a as an oil. A solution of 2a (4.8 mg, 0.01 mmol) in 0.25 M aqueous sodium hydroxide (0.2 mL) and ethanol (0.2 mL) was stirred at room temperature. After 16 hr stirring, no starting material was found monitering by TLC. This solution was stored in a freezer (-20 ° C) and used for chemical stability test and pharmacological assay as a solution of 2c.

(5*E*)-5-Phenylsulfinyl-PGI$_2$ methyl ester (4 and 4')

The solution of sodium metaperiodate (45 mg, 0.21 mmol) in 0.5 mL of water was added at room temperature to a stirred solution of 2a (80 mg, 0.17 mmol) in 1 mL of methanol. The mixture was stirred at the same temperature for 9 hr. At the end of this period, saturated $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with methylene chloride (3×10 mL). The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by preparative TLC developing with methylene chloride-acetone (7:3) containing trace amount of ammonium hydroxide giving two sulfoxides (Rf 0.36 and 0.28), less polar sulfoxide 4 (30 mg, 36%) and more polar sulfoxide 4' (20 mg, 24%); 4 $^1$H-NMR ($CDCl_3$) δ 0.85 (3H, bt, J=6 Hz), 3.14 (2H, d, J=6 Hz), 3.58 (3H, s), 3.8-4.3 (2H, m), 4.82 (1H, m), 5.58 (2H, bs); 7.46 (5H, bs); MS m/e 490 ($M^+$), 474, 472, 456, 364, 346. 4'; $^1$H-NMR ($CDCl_3$) δ 0.88 (3H, m), 2.92 (1H, dd, J=6 and 16 Hz), 3.30 (1H, d, J=16 Hz), 3.58 (3H, s), 3.90 (1H, t, J=7 Hz), 4.08 (1H, m), 4.82 (1H, m), 5.60 (2H, m), 7.44 (5H, m); MS m/e 490 ($M^+$), 474, 472, 456, 364, 346.

(5*R*)-5-Phenylthio-$\Delta^6$-PGI$_1$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (5b)

To a stirred solution of 1b (619 mg, 1.04 mmol) in 10 mL of anhydrous benzene containing triethylamine (434 μL, 3.12 mmol) at room temperature was added dropwise a 0.5 M solution of benzenesulfenyl chloride in anhydrous benzene until the reaction mixture was colored to pale yellow (2.4 mL, 1.20 mmol). The mixture was stirred at the same temperature for additional 1 hr, quenched by the addition of saturated $NaHCO_3$ solution (10 mL) and extracted with *n*-hexane (3×10 mL). The combined extracts were washed with water (3×10 mL), dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The oily residue was chromatographed over 10 g of Florisil. Elution with 1% ethyl acetate in methylene chloride containing 0.1% of triethylamine afforded 5b (628 mg, 86%) as an oil; TLC

Rf 0.41 (*n*-hexane-AcOEt, 9:1); $[\alpha]_D^{22}$+62.5° (*C*, 0.605, $CHCl_3$); IR ($CDCl_3$) 1740, 1650, 1582, 1460, 1438, 1254, 1120, 835, 775 $cm^{-1}$; $^1H$-NMR ($CDCl_3$) δ 0.9 (21H, bs), 2.7-2.95 (1H, m), 3.67 (3H, s), 3.7-4.2 (2H, m), 4.70 (1H, d, J=3 Hz), 4.78 (1H, m), 5.43 (2H, m), 7.1-7.5 (5H, m); $^{13}C$-NMR ($CDCl_3$) δ 22.8 ($C_3$), 32.0 ($C_4$), 46.3 ($C_5$), 155.2 ($C_6$), 101.1 ($C_7$), 50.2 and 58.1 ($C_8$ or $C_{12}$), 82.5 ($C_9$), 42.7 ($C_{10}$), 75.9 ($C_{11}$); MS m/e 702 ($M^+$), 687, 645, 593, 570, 537: Calc. for $C_{39}H_{66}O_5SSi_2$ 702.4169, Found 702.4197.

(5R)-5-Phenylthio-$\Delta^6$-$PGI_2$ diacetate methyl ester (5a)

Diacetate 5a (618 mg, 78%) was prepared as in the case of 5b using a 0.5 M solution of benzenesulfenyl chloride in anhydrous benzene (3.1 mL, 1.55 mmol), $PGI_2$ diacetate methyl ester[21] (640 mg, 1.4 mmol) and triethylamine (580 μL, 0.42 mmol); TLC Rf 0.35 (*n*-hexane-AcOEt, 7:3); $^1H$-NMR ($CDCl_3$) δ 2.00 (3H, s), 2.02 (3H, s), 2.75-3.0 (1H, m), 3.67 (3H, s), 4.73 (1H, d, J=3 Hz), 4.7-5.3 (3H, m), 5.47 (2H, m), 7.2-7.6 (5H, m); MS m/e 558 ($M^+$), 498, 438, 329.

Acid catalyzed isomerization of 5b into 2b

Trace amount of concentrated sulfuric acid was added by means of glass capillary tube to a vigorously stirred solution of 5b (60 mg, 0.085 mmol) in 2 mL of chloroform, and the reaction mixture was stirred at room temperature for 10 min. Ether (40 mL) was then added and washed with saturated $NaHCO_3$ solution and brine successively. The organic solution was dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The residueal oil was purified by Florisil column chromatography eluting with *n*-hexane-ethyl acetate (99:1) containing 0.1% of triethylamine to give 2b (50 mg, 83%) as an oil, which was identical with the product obtained above on TLC behavior and in the spectral data.

(5R)-5-Phenylsulfinyl-$\Delta^6$-$PGI_1$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (9b and 9b')

A slight excess of *m*-chloroperbenzoic acid (85% purity, 227 mg, 1.1 mmol) was added to a vigorously stirred solution of 5b (650 mg, 0.93 mmol) in a two-phase solvent system of methylene chloride (20 mL) and 0.05 M aqueous $NaHCO_3$ solution (20 mL). The mixture was vigorously stirred at room temperture for 30 min. The organic phase was separated and the water phase was extracted with methylene chloride (2 × 20 mL). The combined organic solution was washed with brine and dried over $MgSO_4$-$K_2CO_3$. Removal of the solvent gave an oil which was purilfied by Florisil column chromatography. Elution with *n*-hexane-ethyl acetate (9:1) containing 0.1% of triethylamine afforded a diastereomeric mixture of sulfoxide 9b and 9b' (354 mg, 53%) as an oil; TLC Rf 0.45 0.35 (benzene-AcOEt, 8:2); $^1H$-NMR ($CDCl_3$) δ 0.87 (21H, bs), 3.2-3.6 (1H, m), 3.64 (3H, s) 4.5-4.7 (1H, m), 4.67 (0.7H, d, J=3 Hz), 4.84 (0.3H, d, J=3 Hz), 5.45 (2H, m), 7.4-7.7 (5H, m); MS m/e 592 (M-PhSOH), 535, 460.

(5R)-5-Phenylsulfinyl-$\Delta^6$-$PGI_1$ diacetate methyl ester (9a and 9a')

A diastereomeric mixture of 9a and 9a' (316 mg, 55%) was prepared in a similar manner to the case of 9b and 9b' using 202 mg of *m*-chloroperbenzoic acid (85% purity, 1.0 mmol), 562 mg of 5a (1.0 mmol) and a two-phase solvent system of methylene chloride (20 mL) and 0.05 M aqueous $NaHCO_3$ solution (20 mL); TLC Rf 0.28, 0.21 (benzene-AcOEt, 7:3); $^1H$-NMR ($CDCl_3$) δ 2.00 (6H, s), 3.1-3.4 (1H, m), 3.65 (3H, s), 4.6-5.3 (4H, m), 5.47 (2H, m), 7.4-7.7 (5H, m), MS m/e 448 (M-PhSOH), 388, 328.

(7S)-7-Hydroxy-$PGI_2$ 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (11b)

Diethylamine (1.55 mL, 15 mmol) was added dropwise at room temperature to a stirred solution of the mixture of sulfoxide 9b and 9b' (718 mg, 1.0 mmol) in tetrahydrofuran (14 mL). After stirring for 12 hr at the same temperature, the mixture was quenched by the addition of saturated $NaHCO_3$ solution (70 mL) and extracted with ethyl acetate (2×70 mL). The combined extracts were washed with water, dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The oily residue was chromatographed over Florisil. Elution with *n*-hexane-ethyl acetate (93:7) containing 0.1% of triethylamine afforded 11b as an oil (415 mg, 68%); TLC Rf 0.58 (benzene-AcOEt, 8:2); IR (film) 3450, 1740, 1692, 1460, 1252, 835, 772 $cm^{-1}$; $^1H$-NMR ($CDCl_3$) δ 0.86 (9H, s), 0.89 (9H, s), 3.66 (3H, s), 3.84 (1H, q, J=8 Hz), 4.07 (1H, m), 4.26 (1H, s), 4.46 (1H, t, J=7 Hz), 4.78 (1H, m), 5.47 (2H, m); $^{13}C$-NMR ($CDCl_3$) δ 24.7 ($C_3$), 25.0 ($C_4$), 99.2 ($C_5$), 158.7 ($C_6$), 75.5 ($C_7$), 51.4 and 53.5 ($C_8$ or $C_{12}$), 82.7 ($C_9$), 41.6 ($C_{10}$), 77.9 ($C_{11}$); MS m/e 610 ($M^+$), 592, 553, 421, 403: Calc. for $C_{33}H_{60}O_5Si_2$ (M-$H_2O$) 592.3979, Found 592.3981.

(7S)-7-Hydroxy-$PGI_2$ 11,15-diacetate methyl ester (11a)

Diacetate 11a (144 mg, 62%) was obtained similarly using 286 mg of the mixture of 9a and 9a' (0.5 mmol) and 0.88 mL of diethylamine (8.5 mmol) in 7 mL of tetrahydrofuran; TLC Rf 0.5 (benzene-AcOEt, 6:4); IR ($CHCl_3$) 3420, 1732, 1372, 1240, 1020, 972 $cm^{-1}$; $^1H$-NMR ($CDCl_3$) δ 1.99 (3H, s), 2.01 (3H, s), 3.66 (3H, s), 4.28 (1H, s), 4.50 (1H, t, J=7 Hz), 4.7-5.3 (3H, m), 5.55 (2H, m); MS m/e 448 (M-$H_2O$), 388, 328.

(7S)-7-Hydroxy-$PGI_2$ methyl ester (11c) and its sodium salt solution (11d)

Tetrabutylammonium fluoride trihydrate (110 mg, 0.35 mmol) was added at room temperature to a stirred mixture of 11b (27 mg, 0.044 mmol) and triethylamine (50 μL) in 2 mL of tetrahydrofuran. The reaction mixture was stirred at the same temperature for 2 hr and poured into saturated $NaHCO_3$ solution (10 mL), which was then extracted with ethyl acetate (3×15 mL). The combined extracts were washed with brine, dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. Chromatography of the crude product with Florisil eluted with *n*-hexane-ethyl acetate (1:1 ∿ 1:3) containing 0.1% of triethylamine furnished 14.6 mg of 11c (87%) as an oil; TLC Rf 0.18 ($CH_2Cl_2$-acetone, 7:3); $[\alpha]_D^{22}$+77.2° (*C*, 0.334, $CHCl_3$); IR (film) 3400, 1740, 1700, 1202, 1035, 970, 912, 730 $cm^{-1}$; $^1H$-NMR ($CDCl_3$) δ 3.69 (3H, s), 3.7-4.2 (2H, m), 4.24 (1H, s), 4.51 (1H, t, J=7 Hz), 4.83 (1H, m), 5.59 (2H, m); MS m/e 364 (M-$H_2O$), 346: Calc. for $C_{21}H_{32}O_5$ (M-$H_2O$) 364.2249, Found 364.2213. Methyl ester 11c (6.1 mg, 0.016 mmol) was dissolved in 0.25 M aqueous sodium hydroxide (0.32 mL, 0.08 mmol) and ethanol (0.32 mL). The mixture was stirred

at room temperature until the starting ester 11c disappeared on TLC (16 hr). This solution was used for chemical stability test and pharmacological assay as a solution of 11d.

(7S)-7-Benzoyloxy-PGI2 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (11e)

To a stirred solution of 11b (30 mg, 0.049 mmol) and pyridine (60 μL, 0.72 mmol) in 0.6 mL of anhydrous methylene chloride was added at -40 °C a solution of benzoyl chloride (11 μL, 0.095 mmol) in 0.2 mL of anhydrous methylene chloride. The reaction mixture was stirred at the same temperature for 50 min. At the end of this period, the reaction was quenched by the addition of saturated $NaHCO_3$ solution and extracted with ether (2×30 mL). The combined extracts were washed with water and dried oyer. $MgSO_4$-$K_2CO_3$. After evaporation of the solvent *in vacuo*, the residual oil was purified by preparative TLC (benzene-AcOEt, 95:5) to give 11e (21 mg, 60%) as an oil; TLC Rf 0.49 (*n*-hexane-AcOEt, 9:1); CD (cyclohexane) $[\theta]_{224}$ +56,000; $^1$H-NMR ($CDCl_3$) δ 0.87 (9H, s), 0.88 (9H, s), 3.65 (3H, s), 3.91 (1H, q, J=7 Hz), 4.09 (1H, m), 4.70 (1H, t, J=7 Hz), 4.85 (1H, m), 5.56 (2H, m), 5.59 (1H, s), 7.46 (3H, m), 8.01 (2H, m): MS m/e 714 ($M^+$), 657, 592, 535.

(7S)-7-Acetoxy-PGI2 11,15-*O*-bis(*t*-butyldimethylsilyl) methyl ester (12a)

(A) The mixture of sulfoxides 9b and 9b' (30 mg, 0.042 mmol) was dissolved in 0.3 mL of acetic anhydride-pyridine (molar ratio, 1:1.05) and the resulting solution was stirred at 60 °C for 2 hr. The reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL), extracted with ether (3×10 mL), dried over $MgSO_4$-$K_2CO_3$, and then concentrated *in vacuo*. The residual oil was purified by preparative TLC (benzene-AcOEt, 40:1) to give 12a (17 mg, 62%) as an oil;

(B) Pyridine (0.2 mL, 2.48 mmol) and acetic anhydride (0.1 mL, 1.06 mmol) was added to a methylene chloride solution (0.5 mL) of 11b (31.2 mg, 0.051 mmol) at room temperature. The mixture was stirred at the same temperature for 14 hr, quenched by the addition of ice-saturated $NaHCO_3$ solution (10 mL), and extracted with ether (2×10 mL). The combined extracts were washed with brine, dried over $MgSO_4$-$K_2CO_3$, and concentrated *in vacuo*. The residual oil was chromatographed on Florisil eluting with *n*-hexane-ethyl acetate (93:7) containing 0.1% of triethylamine to give 12a (12.6 mg, 38%) as an oil, TLC Rf 0.30 (benzene-AcOEt; 40:1); IR (film) 1734, 1700, 1240, 835 cm$^{-1}$; $^1$H-NMR ($CCl_4$) δ 0.87 (21H, bs), 2.01 (3H, s), 3.63 (3H, s), 3.6-3.9 (1H, m), 3.9-4.2 (1H, m), 4.56 (1H, t, J=7 Hz), 4.5-4.8 (1H, m), 5.25 (1H, d, J=1 Hz), 5.5 (2H, m); $^{13}$C-NMR ($CDCl_3$) δ 24.3 ($C_3$), 24.3 ($C_4$), 102.5 ($C_5$), 154.0 ($C_6$), 76.7 ($C_7$), 51.6 ($C_8$), 82.5 ($C_9$), 41.6 ($C_{10}$), 77.7 ($C_{11}$), 51.6 ($C_{12}$); MS m/e 652 ($M^+$), 637, 621, 595, 535, 462: Calc. for $C_{31}H_{55}C_7O_2$ (M-tBu) 595.3486, Found 595.3461.

(7S)-7-Acetoxy-PGI2 methyl ester (12b)

The silyl-protecting groups of (12a) (10 mg, 0.015 mmol) were removed by following the same method described above to give 3.8 mg (60%) of 12b as an oil; TLC Rf 0.48 ($CH_2Cl_2$-acetone, 6:4); $^1$H-NMR ($CCl_4$) 2.02 (3H, s), 3.66 (3H, s), 3.6-4.1 (2H, m), 4.58 (1H, t, J=7 Hz), 4.68 (1H, m), 5.16 (1H, s), 5.52 (2H, m), MS m/e 424 ($M^+$), 406, 364, 346: Calc. for $C_{21}H_{32}O_5$ (M-AcOH) 364.2249, Found 364.2288.

(7R,11R)-11-Deoxy-7,11-epoxy-PGI2 15-*O*-(*t*-butyldimethylsilyl) methyl ester (13)

A solution of 11b (10 mg, 0.016 mmol) in anhydrous methylene chloride (1 mL) was cooled to -78 ° C. Diethylaminosulfur trifluoride (DAST, 4 μL, 0.025 mmol) was added dropwise and the mixture stirred at the same temperature for 1.5 hr. Saturated $NaHCO_3$ solution (5 mL) was added to destroy excess DAST and the mixture was extracted with ethyl acetate (3×10 mL). The combined extracts were washed with water, dried over $MgSO_4$-$K_2CO_3$ and then evaporated *in vacuo*. The residual oil was purified by preparative TLC developing with benzene-ethyl acetate (97:3) containing trace amount of triethylamine to afford 13 (4.0 mg, 52%) as an oil; TLC Rf 0.51 (benzene-AcOEt, 95:5); IR ($CHCl_3$) 1732, 1705, 1252, 1052, 980, 835 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 0.88 (12H, bs), 2.94 (2H, m), 3.66 (3H, s), 4.04 (1H, m), 4.14 (1H, bs), 4.34 (1H, d, J=3 Hz), 4.55 (1H, t, J=7 Hz), 4.80 (1H, bt, J=6 Hz), 5.48 (2H, m); MS m/e 478 ($M^+$ 447, 421, 407.

(7S)-7-Fluoro-PGI2 diacetate methyl ester (14a) and 5-fluoro-$\Delta^6$-PGI1 diacetate methyl ester (15a)

To a solution of 11a (88 mg, 0.19 mmol) in anhydrous methylene chloride (8 mL) at -40 °C was added dropwise diethylaminosulfur trifluoride (152 μL, 0.9 mmol), and the mixture was stirred at -20 ° C for 13 hr. Saturated $NaHCO_3$ solution (10 mL) was added and then extracted with ethyl acetate (3×30 mL). The combined extracts were washed successively with water and brine, dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The residual oil was separated by preparative TLC developing with benzene-ethyl acetate (85:15) containing triethylamine (0.5%) to isolate less polar component 14a (19.6 mg, 22%) and more polar component 15a (28.5 mg, 32%); 14a TLC Rf 0.54 (benzene-AcOEt, 85:15); IR (film) 1740, 1700, 1438, 1370, 1240, 970 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 2.01 (3H, s), 2.05 (3H, s), 3.67 (3H, s), 4.77 (1H, t, J=7 Hz), 4.7-5.1 (2H, m), 4.95 (1H, d, J=55 Hz), 5.1-5.3 (1H, m), 5.55 (2H, m); $^{13}$C-NMR ($CDCl_3$) δ 24.8 ($C_3$), 24.8 ($C_4$), 104.5 (d, J=10.7 Hz: $C_5$), 153.3 (d, J=15.3 Hz: $C_6$), 94.4 (d, J=177.0 Hz: $C_7$), 52.1 (d, J=22.9 Hz: $C_8$), 83.2 ($C_9$), 37.9 ($C_{10}$), 78.2 ($C_{11}$), 48.3 (d, J=6.1 Hz: $C_{12}$); MS m/e 468 ($M^+$) 448, 408, 348, 328: 15a, TLC Rf 0.49 (benzene-AcOEt, 85:15); IR (film) 1735, 1665, 1365, 1240, 970 cm$^{-1}$; $^1$H-NMR ($CDCl_3$) δ 1.99 (3H, s), 2.04 (3H, s), 3.14 (1H, m), 4.6-5.3 (5H, m), 5.51 (2H, m); $^{13}$C-NMR ($CDCl_3$) δ 20.3 (d, J=3.7 Hz: $C_3$), 33.0 and 32.8 (d, J=24.4 Hz; d, J=24 Hz, respectively: $C_4$), 87.54 and 87.47 (d, J=168 Hz; d, J=172 Hz, respectively: $C_5$), 154.5 and 154.4 (d, J=20.8 Hz; d, J=20 Hz, respectively: $C_6$), 101.2 and 101.7 (d, J=6.1 Hz; d, J=7.3 Hz, respectively: $C_7$), 51.5, 54.5 ($C_8$ or $C_{12}$), 84.7 and 84.9 ($C_9$), 38.7 ($C_{10}$), 77.9 ($C_{11}$); MS m/e 468 ($M^+$), 448, 408, 348, 328.

(7S)-7-Fluoro-PGI2 methyl ester (14b) and its sodium salt solution (14c)

In a 0.12 M solution of sodium in absolute

methanol (2.0 mL, 0.24 mmol) was dissolved 14a (28 mg, 0.06 mmol). The mixture was stirred at room temperature for 12 hr and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (10 mL) and saturated $NaHCO_3$ solution (10 mL). The aqueous phase was further extracts with ethyl acetate (2×10 mL). The combined extracts were washed with brine, dried over $MgSO_4$-$K_2CO_3$ and then concentrated *in vacuo*. The residual oil was purified by Florisil column chromatography eluting with *n*-hexane-ethyl acetate (1:1) containing triethylamine (0.1%) to give 14b (19 mg, 82%) as an oil; TLC Rf 0.41 ($CH_2Cl_2$-acetone, 7:3); $[\alpha]_D^{22}$+89.2° (C=0.713, $CHCl_3$); IR (film) 3400, 1740, 1700, 1440, 1240, 970 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 3.67 (3H, s), 3.93 (1H, q, J=8 Hz), 4.00 (1H, m), 4.75 (1H, t, J=7 Hz), 4.85 (1H, m), 4.93 (1H, d, J=56 Hz), 5.59 (2H, m); MS m/e 384 ($M^+$), 366, 364, 346: Calc. for $C_{21}H_{31}O_4F$. (M-$H_2O$) 366.2202, Found 366.2292. A solution of 14c was prepared by following the same method described for 11d, using 14b (3.5 mg, 0.009 mmol), 0.26 M aqueous sodium hydroxide (0.2 mL, 0.052 mmol) and ethanol (0.2 mL).

5-Fluro-$\Delta^6$-$PGI_1$ methyl ester (15b) and its sodium salt solution (15c)

The experiment was carried out as in the case of 14b using 25.0 mg (0.053 mmol) of 15a and 1.8 mL (0.22 mmol) of a 0.12 M solution of sodium in absolute methanol. The crude product was purified by Florisil column chromatography (*n*-hexane-ethyl acetate, 1:1, 0.1% triethylamine) to give 15b (16.3 mg, 80%) as an oil; TLC Rf 0.41 ($CH_2Cl_2$-acetone, 7:3); $[\alpha]_D^{22}$+59° (C, 0.182, $CHCl_3$); IR (film) 3400, 1740, 1664, 1250, 970 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 3.07 (1H, m), 3.68 (3H, s), 3.85 (1H, q, J=7 Hz), 4.07 (1H, m), 4.92 (1H, bd, J=48 Hz), 4.85-5.15 (2H, m), 5.53 (2H, m); MS m/e 384 ($M^+$), 366, 364, 346: Calc. for $C_{21}H_{33}O_5F$ 384.2312, Found 384.2376. A solution of 15c was prepared by following the same method described for 11d, using 15b (4.4 mg, 0.011 mmol), 0.25 M aqueous sodium hydroxide (0.23 mL, 0.058 mmol) and ethanol (0.23 mL).

1-Methoxy-7-phenylthiocycloheptene(17)

To a stirred solution of 1-methoxycycloheptene (16)[30] (126 mg, 1.0 mmol) and triethylamine (101 mg, 1.0 mmol) in anhydrous benzene (2.0 mL) at 5∿10°C was added dropwise a 1.0 M solution of benzenesulfenyl chloride in anhydrous benzene (1.0 mL, 1.0 mmol). The mixture was stirred at the same temperature for additional 10 min after finishing the addition, poured into saturated $NaHCO_3$ solution (7 mL) and extracted with *n*-hexane (3×10 mL). The combined extracts were washed with brine, dried over $MgSO_4$-$K_2CO_3$ and concentrated *in vacuo*. The resulting oil was purified by preparative TLC (benzene-AcOEt, 40:1) to give 17 (140 mg, 60%); TLC Rf 0.70 (benzene-ethyl acetate, 40:1); IR (film) 1650 $cm^{-1}$; $^1$H-NMR ($CCl_3$) δ 1.1-2.7 (8H), 3.35 (3H, s), 3.87 (1H, bs), 4.75 (1H, t, J=7 Hz), 7.1-7.7 (5H, m), MS m/e 234 ($M^+$).

5-Phenylthio-1-trimethylsilyloxycyclopentene (19)

To a stirred solution of 1-trimethylsilyloxycyclopentene (18)[31] (156 mg, 1.0 mmol) and triethylamine (202 mg, 2.0 mmol) in anhydrous methylene chloride (2 mL) at -78°C was added dropwise a 1.0 M solution of benzenesulfenyl chloride in anhydrous methylene chloride (1 mL, 1.0 mmol). The mixture was stirred at room temperature for 1 hr and concentrated *in vacuo*. *n*-Hexane was added to the residue and filtered to remove undissolved material. The filtrate was concentrated *in vacuo* to afford 19 (161 mg, 63%) as an oil; TLC Rf 0.85 (benzene-AcOEt, 40:1); $^1$H-NMR ($CCl_4$) δ 1.7-2.5 (4H, m), 3.91 (1H, m), 4.57 (1H, t, J=3 Hz), 7.3 (5H, m); MS m/e 254 ($M^+$).

Measurement of chemical stability in pH 7.4 and 4.7 buffer solution

A buffer solution of pH 7.4 was prepared by mixing 13.08 mL of 0.02 M potassium phosphate monobasic and 58 mL of 0.01 M potassium phosphate dibasic. A buffer solution of pH 4.7 was prepared by mixing 41.34 mL of 0.01 M acetic acid and 19.92 mL of 0.01 M potassium hydroxide. Stable $PGI_2$ sodium salt solutions 11d and 14c (15 μL) prepared as described above were added to these buffer solutions (3 mL). 20% Ethanol-pH 4.7 buffer solution was prepared by mixing appropriate volumes of 0.01 M acetic acid, 0.01 M potassium hydroxide and ethanol (pH was adjusted by a pH meter). The stable $PGI_2$ sodium salt solution 2c (17 μL) prepared as described above was added to this solution. The hydrolysis was monitored at room temperature (15 ∿ 18°C) by following the UV spectral change of their end absorption (11d, 210 nm; 14c; 220 nm; 2c, 240 nm) accompanying the hydrolysis. The results are shown in Table I.

Measurement of inhibition of rabbit platelet aggregation induced by ADP

Stable $PGI_2$ sodium salt solutions 2a, 11d and 14c prepared as described above or $PGI_2$ sodium salt[21] were diluted to appropriate concentrations with 0.1 M phosphate buffer (pH 7.4) at room temperature. Inhibitory activity of rabbit platelet aggregation induced by ADP (10 μM) was measured immediately after dilution or 4 h after standing at room temperature according to the method previously described[32].

Acknowledgement - Authors are grateful to Professor Y. Kobayashi, Tokyo College of Pharmacy, for valuable discussion in the reaction of fluorination of 11a with DAST.

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