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## Synthesis of Thiaprostaglandin E<sub>1</sub> Derivatives<sup>1)</sup>

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A series of new thiaprostaglandins, 4-thia-, 5-thia-, 6-thia- and 7-thiaprostaglandin E<sub>1</sub> methyl esters (**3b**, **4b**, **5b**, and **6b**), was synthesized by a three-component coupling process using a chiral common synthon, (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**1**). Among these thiaprostaglandins, 7-thiaprostaglandin E<sub>1</sub> methyl ester showed the most potent platelet aggregation-inhibiting activity.

**Keywords**—thiaprostaglandin E<sub>1</sub>; enolate trapping; conjugate addition; organocuprate, three-component coupling process; (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone

Natural primary prostaglandins (PGs) are well-known to have potential biological activities and to play important physiological roles as autacoids. PGF<sub>2α</sub>, PGE<sub>2</sub> and PGE<sub>1</sub> are now clinically used for inducing abortion, for the treatment of peripheral circulatory failure, and so on,<sup>2)</sup> though they have several disadvantages: (1) broad-spectrum activity which occasionally results in side effects, (2) short duration of activity *in vivo*, and (3) restriction of the dosage route. To resolve these problems, numerous attempts have been made to synthesize artificial prostaglandin analogues with better pharmacological profiles.<sup>3)</sup> These prostaglandin analogues can be classified generally into two types in terms of the chemical structure. One type consists of chemically modified analogues bearing substituents on the carbon atoms of a prostanoid acid skeleton. The other type comprises analogues in which a carbon or oxygen atom of the original prostanoid is replaced by a hetero atom such as oxygen, nitrogen, or sulfur. Syntheses of sulfur-containing prostaglandins such as 1-thia-,<sup>4)</sup> 3-thia-,<sup>5)</sup> 7-thia-,<sup>6)</sup> 9-thia-,<sup>7)</sup> 11-thia-,<sup>8)</sup> 13-thia-<sup>9)</sup> and 15-thiaprostaglandins<sup>10)</sup> have been reported, and these analogues exhibited pharmacologically agonistic or antagonistic activities depending upon their chemical structures. We report here the synthesis of a series of new E-type thiaprostaglandins, 4-thia-, 5-thia-, 6-thia- and 7-thiaprostaglandin E<sub>1</sub> derivatives, which show activities similar to those of natural PGE<sub>1</sub>.

### Chemistry

The synthetic strategies for these thiaprostaglandins are characterized by the use of a chiral (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**1**) as a common starting material.<sup>11)</sup> In these synthesis, the  $\omega$ -side chain was introduced into this enone (**1**) by conjugate addition as an organocuprate reagent, and the  $\alpha$ -side chain was constructed from the appropriate  $\omega$ -mercapto fatty acid for each 4-thia-, 5-thia-, 6-thia- and 7-thia-PGE<sub>1</sub>. The chiral (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**1**),  $[\alpha]_D^{22} + 63.2^\circ$  ( $c = 1.04$ , CH<sub>3</sub>OH, 94.3% ee)<sup>12)</sup> was obtained by the resolution of racemic 4-hydroxy-2-cyclopentenone<sup>13)</sup> by using (1*R*,4*R*,5*R*)-4-hydroxy-6,6-dimethyl-3-oxabicyclo[3.1.0]hexane-2-one (**2**).<sup>14,15)</sup>

Firstly the synthesis of 4-thiaprostaglandin E<sub>1</sub> (**3**) was carried out *via* the key in-

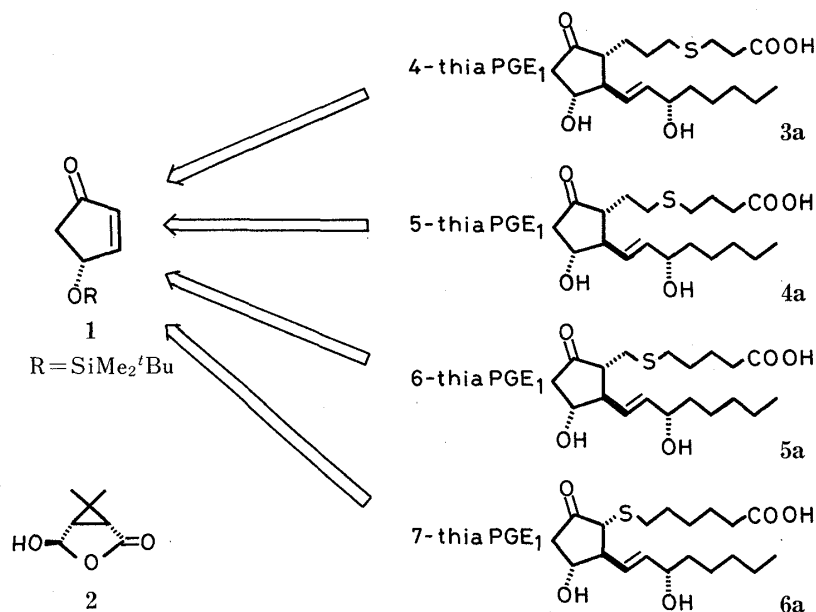


Chart 1

intermediate 2-allylcyclopentanone (8), which was obtained in two different ways. In the first route, compound (8) was prepared from the common chiral enone (1) by the following three-component coupling process. The  $\beta$ -keto allyl ester (7) was obtained by conjugate addition of the mixed cuprate to the chiral enone (1) followed by direct trapping of the resulting enolate with allyl chloroformate in 74% yield.<sup>16,17)</sup> Treatment of this ester (7) with a catalytic amount of tetrakis(triphenylphosphine)palladium afforded the  $\alpha$ -allylated intermediate (8) in 80% yield.<sup>18)</sup> The alternative route started with the conversion of 2-(1-hydroxy-3-butenyl)furan into 2-allyl-4-hydroxy-2-cyclopentenone (*dl*-9a).<sup>19,20)</sup> The chiral enone [(*R*)-9a] was prepared by resolution of its racemate utilizing the same resolving reagent as used in the preparation of the chiral 4-hydroxycyclopentenone (1) described above. Then the same key intermediate (8) was obtained by conjugate addition of the mixed cuprate to the protected chiral enone [(*R*)-9b]

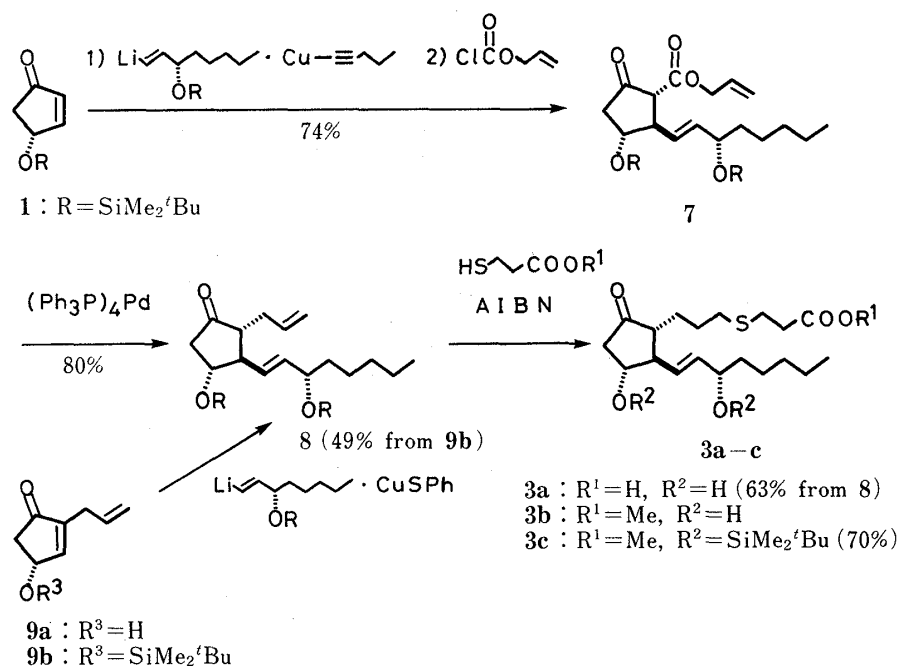


Chart 2

in 49% yield. Radical addition of methyl 3-mercaptopropionate<sup>21)</sup> to the resulting key intermediate (**8**) in the presence of  $\alpha,\alpha'$ -azobis(isobutyronitrile) (AIBN)<sup>22)</sup> was carried out to give the protected 4-thiaprostaglandin E<sub>1</sub> methyl ester (**3c**) in 70% yield. Removal of the silyl protective groups under the standard conditions (CH<sub>3</sub>COOH-THF-H<sub>2</sub>O) completed the synthesis of 4-thiaprostaglandin E<sub>1</sub> methyl ester (**3b**). The acid form of 4-thiaprostaglandin E<sub>1</sub> (**3a**) was also obtained in the same manner using 3-mercaptopropionic acid.<sup>21)</sup> The overall yield of **3a** from **8** was 63%.

Next, the synthesis of 5-thiaprostaglandin E<sub>1</sub> (**4**) was effectively achieved by two kinds of vicinal carba-condensation (three-component coupling process) using the common chiral enone (**1**). The first method was analogous to the synthetic procedure for prostaglandin E<sub>1</sub> reported by Noyori *et al.*<sup>15)</sup> Trapping the enolate generated by the organocopper conjugate addition with methyl 7-oxo-5-thiaheptanoate<sup>23,24)</sup> allowed direct construction of a 5-thiaprostanoic acid skeleton, *i.e.*, the 7-hydroxy-5-thiaprostaglandin E<sub>1</sub> derivative (**10**), in 65% yield. Dehydration of **10** followed by 1,4-reduction of the resulting enone (**11**) with tri-*n*-butyltin hydride gave the desired protected 5-thiaprostaglandin E<sub>1</sub> methyl ester (**4c**) in 47% yield from **10**.

In the second method, trapping of the enolate generated by addition of the organocuprate to **1** with phenylselenoacetaldehyde afforded the cross-aldol condensation product (**12**) in 46% yield. The product (**12**) was converted into the 2-vinylcyclopentanone (**13**) *via* mesylation in the presence of triethylamine in 41% yield.<sup>25)</sup> Treatment of this  $\alpha$ -vinyl ketone (**13**) with methyl 4-mercaptobutanoate<sup>24)</sup> in the presence of AIBN<sup>22)</sup> afforded the desired protected 5-thiaprostaglandin E<sub>1</sub> methyl ester (**4c**) as a minor product accompanied by the iso-

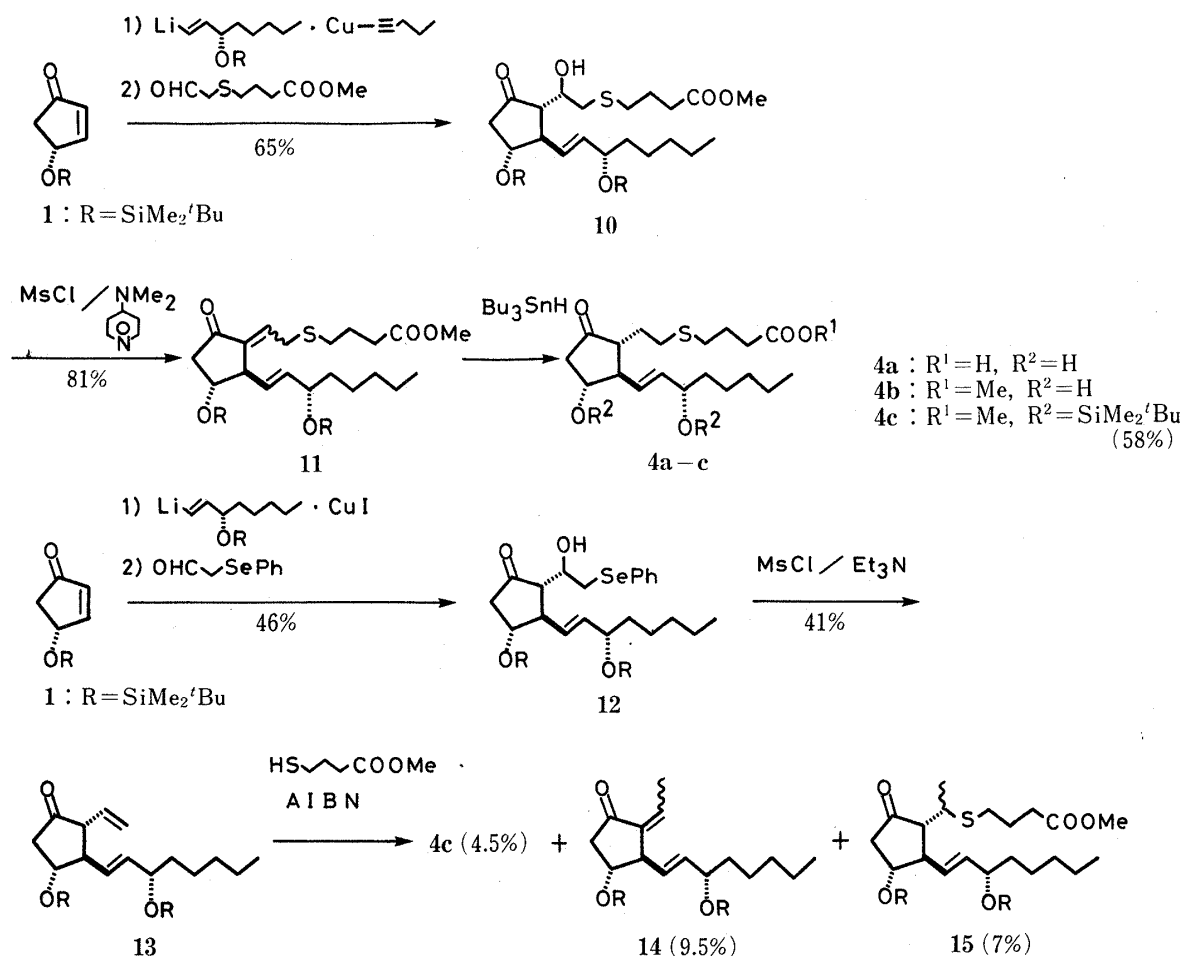
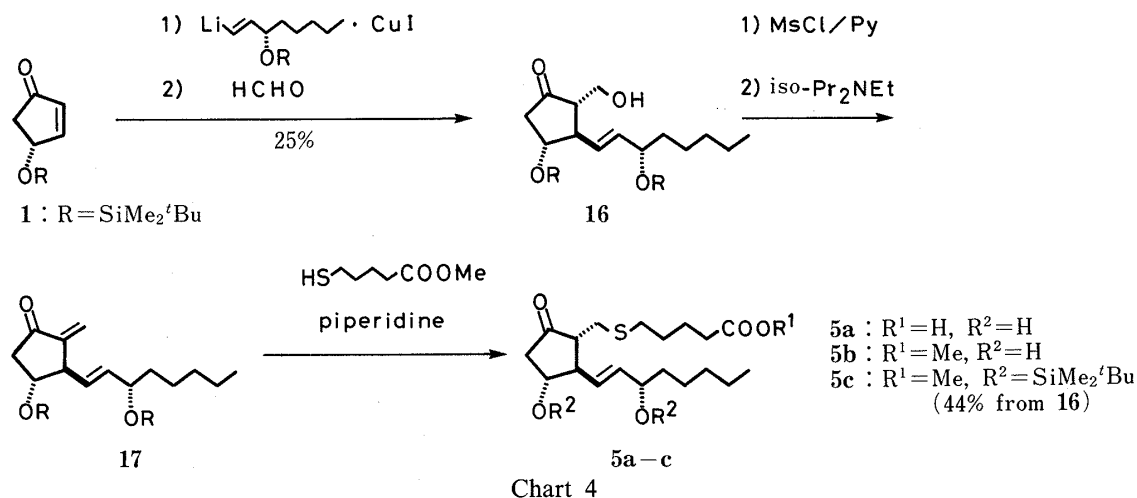


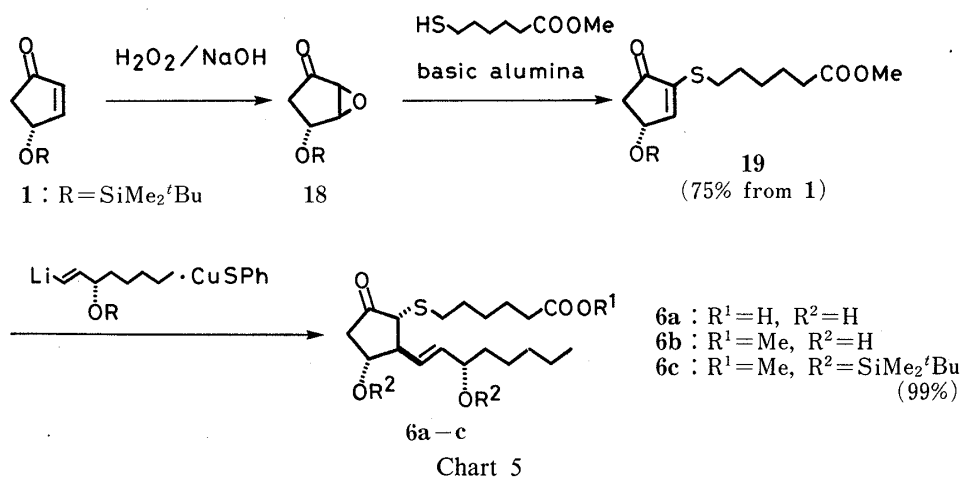
Chart 3

merized enone (**14**) and its thiol adduct (**15**) in 4.5%, 9.5% and 7% yields, respectively. From this protected product (**4c**), 5-thiaprostaglandin E<sub>1</sub> methyl ester (**4b**) was obtained by using aqueous hydrogen fluoride as a deprotecting reagent.<sup>26)</sup>

Thirdly, synthesis of 6-thiaprostaglandin E<sub>1</sub> (**5**) was also achieved from the common enone (**1**) as a starting material. The conjugate addition of the organocuprate followed by trapping with formaldehyde afforded the tandem alkylated cyclopentanone (**16**) in 25% yield according to the procedure of Stork *et al.*<sup>27)</sup> The product (**16**) was converted into the  $\alpha$ -methylene ketone (**17**) *via* mesylation.<sup>27)</sup> The Michael addition of methyl 5-mercaptopentanoate<sup>24)</sup> to the  $\alpha$ -methylene ketone (**17**) in the presence of piperidine gave the adduct (**5c**) in 44% yield based on **16**, and removal of the silyl protective group under the standard conditions (CH<sub>3</sub>COOH-THF-H<sub>2</sub>O) completed the synthesis of 6-thiaprostaglandin E<sub>1</sub> methyl ester (**5b**) (70%).



Finally, synthesis of 7-thiaprostaglandin E<sub>1</sub> (**6**) was carried out according to our previous paper<sup>9a)</sup> starting from the common enone (**1**). Epoxidation of the chiral enone (**1**) with hydrogen peroxide in the presence of a catalytic amount of sodium hydroxide gave the epoxy ketone (**18**). Exposure of **18** to methyl 6-mercaptohexanoate<sup>24)</sup> in the presence of activated basic alumina<sup>28)</sup> afforded the enone intermediate (**19**)<sup>9a)</sup> in 75% yield from **1**. Conjugate addition of the mixed organocuprate to this enone (**19**) gave the protected 7-thiaprostaglandin E<sub>1</sub> methyl ester (**6c**) (99%), and removal of the silyl protecting groups yielded the desired product (**6b**) (90%). Ester hydrolysis of 7-thiaprostaglandin E<sub>1</sub> methyl ester (**6b**) was accomplished by the convenient method reported in our previous paper using an enzymatic process.<sup>29)</sup>



These synthetic methods *via* a three-component coupling process using a chiral common synthon, (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**1**), thus enabled us to synthesize a series of new thiaprostaglandins, 4-thia-, 5-thia-, 6-thia-, and 7-thiaprostaglandin E<sub>1</sub> derivatives, in only a few steps.<sup>30)</sup>

### Pharmacology

The *in vitro* inhibitory effects of these synthetic thia-prostaglandins (**3b**—**6b**, **20**—**25**)<sup>31)</sup>

TABLE I. Effects of ThiaPGE<sub>1</sub> Methyl Esters on Platelet Function

Compd.	Structure	Conc. <sup>a)</sup> (μg/ml)	Percent <sup>b)</sup> inhibition	Percent aggregation
4-ThiaPGE <sub>1</sub>		30 10 3	86.5 ± 0.8 58.1 ± 6.3 14.2 ± 0.5	
<i>ent</i> -15- <i>epi</i> -ThiaPGE <sub>1</sub>		100 30 10	56.9 ± 1.9 29.3 ± 2.3 7.2 ± 4.5	
5-ThiaPGE <sub>1</sub>		10	17.8 ± 1.1	
<i>ent</i> -15- <i>epi</i> -5-ThiaPGE <sub>1</sub>		10	9.9 ± 1.7	
6-ThiaPGE <sub>1</sub>		30 10 3	85.9 ± 3.5 67.0 ± 0.8 26.3 ± 2.4	
<i>ent</i> -15- <i>epi</i> -6-ThiaPGE <sub>1</sub>		10 3 1		62.1 ± 1.5 8.4 ± 0.8 0
7-ThiaPGE <sub>1</sub>		1 0.3 0.1	72.6 ± 10.2 36.7 ± 7.5 14.2 ± 4.0	
<i>ent</i> -15- <i>epi</i> -6-ThiaPGE <sub>1</sub>		30 10 3	78.4 ± 0.4 54.1 ± 1.9 23.5 ± 2.5	
6 <i>S</i> -Oxide (6-ThiaPGE <sub>1</sub> )		100 30	72.3 ± 1.5 16.0 ± 0	
6 <i>S</i> -Oxide ( <i>ent</i> -15- <i>epi</i> -6-ThiaPGE <sub>1</sub> )		100 30		0 0

a) Drug concentration. b) 10 μM ADP was used as the aggregating agent.

on platelet aggregation are listed in Table I. The novel thiaprostaglandin  $E_1$  methyl esters (**3b**–**6b**)<sup>32)</sup> with natural configuration showed agonistic activity towards prostaglandin  $E_1$  methyl ester, and inhibited adenosine diphosphate (ADP)-induced aggregation of rabbit platelets in a dose-dependent manner. Of these thiaprostaglandins, 7-thiaprostaglandin  $E_1$  methyl ester (**6b**) was the most potent ( $IC_{50}$ : 0.47  $\mu\text{g/ml}$ ). The others were one or two orders of magnitude less active than **6b**.

The enantiomers of the 15-*epi* isomers which were obtained from the *dl* enone (*dl*-**1**) in the same ways as described above,<sup>31)</sup> i.e. *ent*-15-*epi*-7-thiaprostaglandin  $E_1$  (**23**) and *ent*-15-*epi*-4-thiaprostaglandin  $E_1$  (**20**), showed far weaker activity than the compounds with natural configuration, and *ent*-15-*epi*-5-thiaprostaglandin  $E_1$  (**21**) was inactive up to 10  $\mu\text{g/ml}$ . On the other hand *ent*-15-*epi*-6-thiaprostaglandin (**22**) was interestingly found to have platelet-aggregating activity. The aggregatory activity of **22** was characterized by the use of several aggregation inhibitors. The aggregation induced by **22** was inhibited by 6-thiaprostaglandin  $E_1$  (**5b**) and prostacyclin while indomethacin, a cyclooxygenase inhibitor, failed to inhibit the aggregation by this unique prostaglandin (**22**). The aggregatory activity of *ent*-15-*epi*-6-thiaprostaglandin  $E_1$  (**22**) disappeared when the sulfur atom at the 6 position was oxidized, though the sulfoxide (**24**) retained a weak inhibitory activity as compared with the parent 6-thiaprostaglandin  $E_1$  methyl ester (**5b**).

From these observations, 7-thiaprostaglandin  $E_1$  methyl ester (**6b**) was concluded to be the most potent inhibitor of platelet aggregation among the compounds tested. We are now searting for highly active and long-lasting analogues of the 7-thiaprostaglandin  $E_1$  series.

### Experimental

Infrared (IR) spectra were recorded on a JASCO A 102 spectrometer. Proton nuclear magnetic resonance ( $^1\text{H}$ -NMR) spectra were obtained on a JEOL JNM-PS-100 (100 MHz) or a Varian EM 360A (60 MHz) spectrometer. Chemical shifts are reported as parts per million (ppm) relative to internal tetramethylsilane. Mass spectra (MS) were taken at 70 or 20 eV on an LKB-9000 mass spectrometer. Thin-layer chromatography (TLC) was performed using Merck silica gel (Kieselgel 60 F<sub>254</sub>) analytical or preparative plates. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents.

**Allyl[(1*R*,4*R*,5*R*)-4-*tert*-butyldimethylsilyloxy-5-[(3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-octenyl]-2-oxocyclopentyl]methanoate (**7**)**—A pentane solution of 2.1 M *tert*-butyllithium (5.2 ml, 11 mmol) was added to an ether solution (15 ml) of (3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene<sup>33)</sup> (2.02 g, 5.5 mmol) at  $-78^\circ\text{C}$  under an argon atmosphere, and the mixture was stirred for 2 h. A solution of pentynylcopper(I)<sup>34)</sup> (0.72 g, 5.5 mmol) and hexamethylphosphorus triamide (1.8 g, 11 mmol) in ether (10 ml) was then added, and the whole was stirred for 1 h at  $-78^\circ\text{C}$ . Next, a solution of **1**<sup>12)</sup> (1.06 g, 5.0 mmol) in ether (10 ml) was added, and the reaction mixture was stirred at  $-78^\circ\text{C}$  for 15 min and then at  $-40^\circ\text{C}$  for 1 h. A mixture of the resulting solution an ether solution (5 ml) of allyl chloroformate (1.5 g, 12.5 mmol) was stirred for 1 h at  $-40^\circ\text{C}$ , and poured into pH 4 acetate buffer solution (100 ml), then the aqueous layer was extracted with ether. The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and purified by silica gel column chromatography (hexane :  $\text{AcOEt}$  = 10 : 1) to give **7** (2.0 g, 74%). IR  $\nu_{\text{max}}^{\text{liq.}}$   $\text{cm}^{-1}$ : 3100, 1760 (CO), 1735 (CO), 1655, 1460, 1360, 1255, 1120, 1080.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.08 (12H, s), 0.82 (21H, s), 1.3 (8H, m), 1.9–2.7 (3H, m), 3.1 (1H, m), 3.9–4.2 (2H, m), 4.6 (2H, d,  $J$  = 5 Hz), 5.0–5.7 (5H, m). MS  $m/e$ : 538 ( $\text{M}^+$ ), 497, 423, 397, 383, 323, 292, 266, 240, 239.

**(2*R*,3*R*,4*R*)-2-Allyl-3-[(3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-octenyl]-4-*tert*-butyldimethylsilyloxycyclopentanone (**8**)**—Method A: Tetrakis(triphenylphosphine)palladium(O) (10 mg, 0.009 mmol) was added to a solution of the above ester (**7**) (97 mg, 0.18 mmol) in 1 ml of *N,N*-dimethylformamide (DMF) under a nitrogen atmosphere, and the mixture was stirred for 2 h at room temperature. Brine was added and the reaction mixture was treated with  $\text{AcOEt}$ . The organic layer was dried over  $\text{MgSO}_4$  and then purified by TLC (hexane :  $\text{AcOEt}$  = 10 : 1) to give **8** (70 mg, 80%). IR  $\nu_{\text{max}}^{\text{liq.}}$   $\text{cm}^{-1}$ : 3100, 1745 (CO), 1640, 1460, 1360, 1255, 1110.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.04 (12H, s), 0.86 (21H, s), 1.1–1.5 (8H, m), 1.6–2.8 (6H, m), 3.8–4.3 (2H, m), 4.75–4.95 (1H, m), 4.95–5.15 (1H, m), 5.35–5.60 (3H, m). MS  $m/e$ : 494 ( $\text{M}^+$ ), 479, 437, 379.

Method B: A pentane solution of 1.2 M *tert*-butyllithium (5.8 ml, 7 mmol) was added to an ether solution (20 ml) of (3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene<sup>33)</sup> (1.29 g, 3.5 mmol) at  $-78^\circ\text{C}$  under a nitrogen atmosphere. The mixture was stirred for 2 h, then a solution of phenylthiocopper(I)<sup>35)</sup> (0.6 g, 3.5 mmol) and hexamethylphosphorus triamide (1.2 g, 7.3 mmol) in ether (5 ml) was added, and the whole was stirred for 1 h at  $-78^\circ\text{C}$ . Next, a

solution of (4*R*)-2-allyl-*tert*-butyldimethylsilyloxy-2-cyclopentenone [(*R*)-9a] (0.8 g, 3.2 mmol) in ether (5 ml) was added, and the reaction mixture was stirred for 1 h at  $-78^{\circ}\text{C}$  and then at  $-40^{\circ}\text{C}$  for 3 h, quenched by the addition of  $\text{NH}_4\text{Cl}$  solution containing  $\text{NH}_4\text{OH}$ , and extracted with ether. The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and then purified by silica gel column chromatography (cyclohexane :  $\text{AcOEt}$  = 15 : 1) to give **8** (775 mg, 49%).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-4-thiaprostaglandin  $\text{E}_1$  Methyl Ester (3c)**—A mixture of **8** (118 mg, 0.24 mmol) and methyl 3-mercaptopropionate<sup>21)</sup> (120 mg, 1.0 mmol) was heated at  $60^{\circ}\text{C}$  for 5 h with stirring in the presence of 5 mg of AIBN. After the reaction, the crude product was purified by silica gel column chromatography to give 103 mg (70%) of **3c**.  $^1\text{H-NMR}$  ( $\text{CCl}_4$ )  $\delta$ : 0.89 (18H, s), 0.9 (3H, t,  $J = 7\text{ Hz}$ ), 1.0–1.7 (12H, m), 1.8–2.8 (10H, m), 3.6 (3H, s), 3.6–4.1 (2H, m), 5.5 (2H, m). MS  $m/e$ : 614 ( $\text{M}^+$ ). High-MS for  $\text{C}_{28}\text{H}_{53}\text{O}_5\text{SSi}_2$ : Calcd  $m/e$  557.3156; Found  $m/e$  557.3150.

**4-Thiaprostaglandin  $\text{E}_1$  Methyl Ester (3b)**—**3c** (200 mg, 0.33 mmol) was dissolved in a mixture of 2 ml of tetrahydrofuran, 2 ml of water and 6 ml of acetic acid, and the solution was stirred at  $40^{\circ}\text{C}$  for 24 h. The solvent was evaporated off under reduced pressure, and the residue was purified by TLC (cyclohexane :  $\text{AcOEt}$  = 1 : 4) to give **3b** (88 mg, 70%).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (3H, m), 1.0–1.7 (12H, m), 1.7–2.9 (10H, m), 3.65 (3H, s), 3.5–4.2 (4H, m), 5.55 (2H, m). MS  $m/e$ : 368 ( $\text{M}^+ - 18$ ).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-4-thiaprostaglandin  $\text{E}_1$  (3a)**—**3a** was obtained in the same manner as described above using 3-mercaptopropionic acid.<sup>21)</sup> The overall yield of **3a** from **8** was 63%.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.90 (3H, m), 1.0–1.8 (12H, m), 1.8–2.95 (10H, m), 3.8–4.2 (2H, m), 5.55 (2H, m), 10.3 (3H, brs).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-7-hydroxy-5-thiaprostaglandin  $\text{E}_1$  Methyl Ester (10)**—A pentane solution of 2.0 M *tert*-butyllithium (16.5 ml, 33 mmol) was added to an ether solution (30 ml) of (3*S*)-(*E*)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene<sup>33)</sup> (6.07 g, 16.5 mmol) at  $-78^{\circ}\text{C}$  under an argon atmosphere, and the mixture was stirred for 2 h. Then a solution of pentynylcopper(I)<sup>34)</sup> (2.15 g, 16.5 mmol) and hexamethylphosphorus triamide (5.4 g, 33 mmol) in ether (25 ml) was added, and the whole was stirred for 1 h at  $-78^{\circ}\text{C}$ . Next, a solution of **1**<sup>12)</sup> (3.18 g, 15 mmol) in ether (20 ml) was added. The mixture was stirred at  $-78^{\circ}\text{C}$  for 30 min and then at  $-40^{\circ}\text{C}$  for 10 min, and an ether solution (10 ml) of methyl 7-oxo-5-thiaheptanoate<sup>23)</sup> (2.9 g, 16.5 mmol) cooled to  $-40^{\circ}\text{C}$  was added. The reaction mixture was stirred for 40 min at  $-40^{\circ}\text{C}$ , poured into pH 4 acetate buffer solution (300 ml) and extracted with hexane. The extract was washed with brine, dried over  $\text{MgSO}_4$ , and then purified by silica gel column chromatography (hexane :  $\text{AcOEt}$  = 10 : 1) to give **10** (6.1 g, 65%).  $R_f$  (TLC): 0.45 (hexane :  $\text{AcOEt}$  = 3 : 1). IR  $\nu_{\text{max}}^{\text{liq. cm}^{-1}}$ : 2950, 1740 (CO), 1460, 1440, 1360.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.9 (18H, s), 0.9–1.7 (11H, m), 1.7–3.1 (10H, m), 3.7 (3H, s), 3.7–4.4 (3H, m), 5.65 (2H, m).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-5-thia- $\Delta^7$ -prostaglandin  $\text{E}_1$  Methyl Ester (11)**—4-Dimethylaminopyridine (1.65 g, 13.5 mmol) and then methanesulfonyl chloride (0.5 ml, 6.7 mmol) were added to a solution of **10** (1.25 g, 1.98 mmol) in dichloromethane (10 ml) at  $0^{\circ}\text{C}$ . The mixture was stirred for 5 h at  $0^{\circ}\text{C}$  and then for 1 h at  $0^{\circ}\text{C}$ . Water was added and the whole was extracted with dichloromethane. The organic layer was washed with saturated  $\text{NaHCO}_3$  solution,  $\text{KHSO}_4$  solution and brine, then dried over  $\text{MgSO}_4$ . The extract was purified by silica gel column chromatography (hexane :  $\text{AcOEt}$  = 10 : 1) to give **11** (982 mg, 81%) (4 : 1 mixture of 7*E* form and 7*Z* form).  $R_f$  (TLC) hexane :  $\text{AcOEt}$  = 3 : 1. 0.65 (7*E*), 0.68 (7*Z*). 7*E*-**11**: IR  $\nu_{\text{max}}^{\text{liq. cm}^{-1}}$ : 2980, 1740 (CO), 1640, 1460.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.9 (18H, s), 0.7–2.1 (13H, m), 2.1–2.8 (6H, m), 3.0–3.5 (3H, m), 3.70 (3H, s), 3.9–4.3 (2H, m), 5.55 (2H, m), 6.8 (1H, dt,  $J = 7.5\text{ Hz}$ , 2.0 Hz). 7*Z*-**11**: IR  $\nu_{\text{max}}^{\text{liq. cm}^{-1}}$ : 2980, 1740 (CO), 1450.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.9 (18H, s), 0.7–2.1 (13H, m), 2.1–2.7 (6H, m), 3.0–3.6 (3H, m), 3.7 (3H, s), 3.7–4.4 (2H, m), 5.3–5.9 (1H, m), 5.55 (2H, m).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-5-thiaprostaglandin  $\text{E}_1$  Methyl Ester (4c)**—Di-*tert*-butyl peroxide (ca. 20 mg) was added to a solution of **11** (210 mg, 0.34 mmol) in tributyltin hydride (2 ml), and the mixture was stirred for 1.5 h at  $100^{\circ}\text{C}$ . The reaction mixture was directly purified by silica gel column chromatography (hexane ~ hexane :  $\text{AcOEt}$  = 10 : 1) to give **4c** (122 mg, 58%).  $R_f$  (TLC): 0.60 (hexane :  $\text{AcOEt}$  = 3 : 1).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.9 (18H, s), 1.1–1.6 (15H, m), 1.7–2.8 (9H, m), 3.7 (3H, s), 4.15 (2H, m), 5.65 (2H, m).

**2-(1-Phenylseleno-2-hydroxyethyl)-3-[(3*S*)-(*E*)-*tert*-butyldimethylsilyloxy-1-octenyl]-4(*R*)-*tert*-butyldimethylsilyloxycyclopentanone (12)**—A pentane solution of 1.3 M *tert*-butyllithium (3.1 ml, 4 mmol) was added to an ether solution (4 ml) of (3*S*)-(*E*)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene<sup>33)</sup> (736 mg, 2 mmol) at  $-78^{\circ}\text{C}$  under an argon atmosphere, and the mixture was stirred for 2 h. Then a solution of copper(I) iodide (836 mg, 4.4 mmol) and tri-*n*-butylphosphine (1.78 g, 8.8 mmol) in ether (4 ml) was added, and the whole was stirred for 1 h at  $-78^{\circ}\text{C}$ . Next, a solution of **1**<sup>12)</sup> (385 mg, 1.81 mmol) in ether (5 ml) was added. The reaction mixture was stirred at  $-78^{\circ}\text{C}$  for 1 h and then at  $-40^{\circ}\text{C}$  for 10 min, then an ether solution (4 ml) of phenylselenoacetaldehyde<sup>25)</sup> (458 mg, 2.30 mmol) was added and the whole was stirred for 1 h at  $-40^{\circ}\text{C}$ , by the addition of  $\text{NH}_4\text{Cl}$  solution, and extracted with ether. The extract was dried, concentrated and purified by silica gel chromatography (hexane :  $\text{AcOEt}$  = 8 : 1) to give **12** (545 mg, 46%). IR  $\nu_{\text{max}}^{\text{liq. cm}^{-1}}$ : 2950, 2900, 1745 (CO), 1580, 1480.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.9 (18H, s), 1.1–1.6 (11H, m), 2.2–3.5 (6H, m), 3.8–4.3 (3H, m), 5.5 (2H, m), 7.25 (3H, m), 7.50 (2H, m).

**2-Vinyl-3-[(3*S*)-(*E*)-*tert*-butyldimethylsilyloxy-1-octenyl]-4(*R*)-*tert*-butyldimethylsilyloxycyclopentanone (13)**—**12** (211 mg, 0.32 mmol) was dissolved in 4 ml of carbon tetrachloride, then triethylamine (225  $\mu\text{l}$ , 1.6 mmol) and methanesulfonyl chloride (100  $\mu\text{l}$ , 1.3 mmol) were added. The mixture was stirred for 1 h at room temperature

and then quenched by addition of water. The aqueous layer was extracted with ether and the extract was dried, concentrated and purified by silica gel column chromatography (hexane:AcOEt=6:1) to give **13** (63 mg, 41%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.91 (18H, s), 1.1–1.6 (11H, m), 2.2–3.1 (4H, m), 3.8–4.3 (2H, m), 5.1–5.6 (5H, m).

**11,15-O-Bis(tert-butyldimethylsilyl)-5-thiaprostaglandin E<sub>1</sub> Methyl Ester (4c)**—A mixture of **13** (141 mg, 0.29 mmol) and methyl 4-mercaptopentanoate<sup>24</sup> (120 mg, 0.9 mmol) was heated at 80 °C in the presence of AIBN (15 mg, 0.09 mmol) in toluene (1 ml). The mixture was stirred for 5 h and the solvent was removed under reduced pressure. The residue was purified by TLC (benzene:ether=20:1) to give **4c** (8 mg, 4.5%), the isomerized enone (**14**) (14 mg, 9.5%) and the thiol adduct of **14** (**15**) (13 mg, 7%). **14**: <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.9 (18H, s), 1.1–1.6 (11H, m), 1.75 (3H, d, *J*=7 Hz), 1.8 (1H, m), 2.2–2.5 (2H, m), 4.2 (2H, m), 5.5 (2H, m), 6.9 (1H, dd, *J*=7 Hz, 2 Hz). **15**: <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.9 (18H, s), 1.1–1.6 (13H, m), 1.35 (3H, d, *J*=6 Hz), 1.8–2.8 (8H, m), 3.65 (3H, s), 4.1 (2H, m), 5.65 (2H, m).

**5-Thiaprostaglandin E<sub>1</sub> Methyl Ester (4b)**—A solution of **4c** (36 mg, 0.059 mmol) in acetonitrile (14 ml) was treated with a 47% aqueous solution of hydrogen fluoride (0.7 ml), and the mixture was stirred for 30 min at room temperature. The reaction mixture was neutralized with NaHCO<sub>3</sub> solution and extracted with AcOEt. The extract was dried, concentrated and purified by TLC (AcOEt) to give **4b** (16 mg, 70%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.9 (3H, m), 1.2–1.6 (12H, m), 1.8–2.8 (10H, m), 3.7 (3H, s), 4.1–4.2 (2H, m), 5.7 (2H, m). MS *m/e*: 368 (M<sup>+</sup> – 18), 350, 267, 235.

**5-Thiaprostaglandin E<sub>1</sub> (4a)**—A solution of **4b** (13 mg, 0.034 mmol) in then quenched with NH<sub>4</sub>OH solution. The aqueous layer was extracted with ether. The resulting organic layer was washed with NH<sub>4</sub>Cl solution containing NH<sub>4</sub>OH, NH<sub>4</sub>Cl solution and brine, then dried over MgSO<sub>4</sub>. The extract was purified by silica gel column chromatography (cyclohexane:AcOEt=9:1) to give **16** (230 mg, 25%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.88 (21H, m), 1.0–1.7 (8H, m), 2.0–2.6 (5H, m), 3.70 (2H, m), 4.00 (2H, m), 5.50 (2H, m).

**(3R,4R)-4-tert-Butyldimethylsilyloxy-3-[(3S)-(E)-tert-butyldimethylsilyloxy-1-octenyl]-2-methylene-cyclopentanone (17)**—Methanesulfonyl chloride (288 mg, 2.5 mmol) was added to a solution of **16** (476 mg, 0.98 mmol) in 2 ml of anhydrous pyridine at 0 °C, and the mixture was stirred for 4 h at 0 °C. Ice water was added, and the reaction mixture was extracted with ether. The extract was dried and concentrated to give crude (2S,3R,4R)-4-tert-butyldimethylsilyloxy-3-[(3S)-(E)-tert-butyldimethylsilyloxy-1-octenyl]-2-methanesulfonyloxy-methylcyclopentanone (550 mg). This crude product was dissolved in ether (7 ml) and diisopropylethylamine (280 μl) was added at room temperature. The mixture was stirred for 15 min. The reaction mixture was quenched with ice water and extracted with ether. The extract was concentrated to give acetone (0.4 ml) and 0.1 M pH 8 phosphate buffer (4 ml) was treated with porcine liver esterase (40 μl, 70 units, Sigma Chemical Co.) under stirring for 4 h. After the reaction, the mixture was acidified with HCl, saturated with (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> and then extracted with AcOEt. The extract was dried, concentrated and purified by silica gel column chromatography (1% AcOH in AcOEt) to give **4a** (9 mg, 72%). IR  $\nu_{\text{max}}^{\text{liq}}$  cm<sup>-1</sup>: 3400, 2950, 2860, 1740, 1400, 1240, 1070. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.7–1.0 (3H, m), 1.0–1.7 (8H, m), 1.7–2.0 (4H, m), 2.0–2.8 (10H, m), 3.8–4.3 (2H, m), 5.6 (2H, m).

**(2S,3R,4R)-4-tert-Butyldimethylsilyloxy-3-[(3S)-(E)-tert-butyldimethylsilyloxy-1-octenyl]-2-hydroxy-methylcyclopentanone (16)**—A pentane solution of 1.2 M *tert*-butyllithium (3.4 ml, 4 mmol) was added to an ether solution (10 ml) of (3S)-(E)-tert-butyldimethylsilyloxy-1-iodo-1-octene<sup>33</sup> (736 mg, 2 mmol) at –78 °C under an argon atmosphere, and the mixture was stirred for 2 h. Then a solution of copper(I) iodide (382 mg, 2 mmol) and tri-*n*-butylphosphine (1 ml, 4 mmol) in ether (4 ml) was added, and the whole was stirred for 1 h at –78 °C. Next, a solution of **1**<sup>12</sup> (403 mg, 1.9 mmol) in ether (1 ml) was added. The reaction mixture was stirred at –78 °C for 10 min and at –40 °C for 1 h, then 2 ml of tetrahydrofuran and a solution of formaldehyde (100 mg, 3.3 mmol) in ether (5 ml)<sup>27</sup> were added at –78 °C and the whole was stirred for 15 min, **17** (436 mg) as a crude product. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 5.2 (1H, m), 5.5 (2H, m), 6.05 (1H, d).

**11,15-O-Bis(tert-butyldimethylsilyl)-6-thiaprostaglandin E<sub>1</sub> Methyl Ester (5c)**—Crude **17** (436 mg) obtained above was dissolved in methanol (5 ml), and methyl 5-mercaptopentanoate<sup>24</sup> (700 mg, 5.2 mmol) and piperidine (100 μl) were added. The mixture was stirred for 1.5 h at room temperature. Ice water was added and the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was chromatographed on a silica gel column (hexane:AcOEt=19:1) to give **5c** (262 mg, 44% from **16**). IR  $\nu_{\text{max}}^{\text{liq}}$  cm<sup>-1</sup>: 1740 (CO). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.05 (12H, s), 0.88 (21H, s), 1.0–1.8 (12H, m), 2.0–3.0 (10H, m), 3.61 (3H, s), 3.8–4.3 (2H, m), 5.45–5.7 (2H, m).

**6-Thiaprostaglandin E<sub>1</sub> Methyl Ester (5b)**—**5c** (103 mg, 0.17 mmol) was dissolved in a mixture of tetrahydrofuran (0.5 ml), water (0.5 ml) and acetic acid (1.5 ml), and the solution was stirred at room temperature for 22 h. The solvent was evaporated off under reduced pressure. The residue was chromatographed on a silica gel column (AcOEt) to give **5b** (45 mg, 70%). IR  $\nu_{\text{max}}^{\text{liq}}$  cm<sup>-1</sup>: 3410 (OH). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.88 (3H, m), 1.1–2.0 (12H, m), 2.0–3.0 (12H, m), 3.65 (3H, s), 4.10 (2H, m), 5.65 (2H, m).

**6-Thiaprostaglandin E<sub>1</sub> Methyl Ester 6-Oxide (24)**—Sodium periodate (38 mg, 0.18 mmol) in water (0.25 ml) was added to a solution of **5b** (18 mg, 0.047 mmol) in methanol (1.2 ml). The mixture was stirred for 2 h at room temperature, then brine was added and the reaction mixture was extracted with AcOEt. The extract was dried and



concentrated, and the residue was purified by silica gel column chromatography (AcOEt: MeOH = 97: 3) to give **24** (19 mg, quantitatively).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.88 (3H, m), 1.0–1.9 (12H, m), 2.0–2.9 (8H, m), 3.2 (2H, m, -OH), 3.62 (3H, s), 3.8–4.3 (2H, m), 5.5–5.75 (2H, m).

**Methyl 6-[(4*R*)-*tert*-Butyldimethylsilyloxy-2-oxo-5-cyclopenten-1-ylthio]hexanoate (19)**—**1**<sup>12)</sup> (10 g, 47.2 mmol) was dissolved in methanol (100 ml). The solution was cooled to 0°C, and 31% aqueous hydrogen peroxide (21 ml, 189 mmol) was added, followed by 0.2 ml of 1 N NaOH solution. The mixture was stirred for 1 h, then saturated  $\text{NH}_4\text{Cl}$  solution (5 ml) was added, and methanol was removed under reduced pressure. Water was added to the residue and the mixture was extracted with ether. The extract was dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure to give (4*R*)-*tert*-butyldimethylsilyloxy-2,3-epoxycyclopentanone (**18**) as a crude product. A solution of methyl 5-mercaptopentanoate<sup>24)</sup> (7.65 g, 47.2 mmol) in hexane (20 ml) was added to a solution of crude product in hexane (180 ml), and the mixture was cooled to 0°C. Active basic alumina (Woelm, activity I, 50 g) was added, and the whole was stirred for 1 h, then filtered, and the alumina was washed with dichloromethane. The filtrate and washings were evaporated under reduced pressure and the residue was recrystallized from methanol to give **19** (13.1 g, 75%). mp 57.5–59°C.  $[\alpha]_D^{21}$  –22.8° ( $c=0.6$ , MeOH). IR  $\nu_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 1740, 1715.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.15 (6H, s), 0.90 (9H, s), 1.4–1.8 (6H, m), 2.0–3.0 (6H, m), 3.61 (3H, s), 4.90 (1H, m), 6.73 (1H, d,  $J=3$  Hz).

**11,15-*O*-Bis(*tert*-butyldimethylsilyl)-7-thiaprostaglandin  $\text{E}_1$  Methyl Ester (6c)**—A pentane solution of 1.9 M *tert*-butyl lithium (5.1 ml, 9.6 mmol) was added to an ether solution (10 ml) of (3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene<sup>32)</sup> (1.77 g, 4.8 mmol) at –78°C under an argon atmosphere, and the mixture was stirred for 2 h. A solution of phenylthiocopper(I)<sup>35)</sup> (828 mg, 4.8 mmol) and hexamethylphosphorus triamide (1.63 g, 10 mmol) in ether (5 ml) was added, and the mixture was stirred for 1 h at –78°C. Then a solution of **19** (1.49 g, 4 mmol) in tetrahydrofuran (70 ml) cooled to –40°C was added. The reaction mixture was stirred at –78°C for 15 min and at –40°C for 1 h, then poured into 2 M pH 4 acetate buffer solution (150 ml) and extracted with hexane. The extract was washed with brine, dried over  $\text{MgSO}_4$ , and purified by silica gel column chromatography (hexane: AcOEt = 10: 1) to give 11,15-*O*-bis(*tert*-butyldimethylsilyl)-7-thiaprostaglandin  $\text{E}_1$  (2.43 g, 99%). IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 1740 (CO), 1460, 1260, 1120, 965, 835.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.07 (12H, s), 0.87 (21H, s), 1.1–1.8 (14H, m), 2.1–3.0 (7H, m), 3.37 (1H, m), 3.61 (3H, s), 3.61–4.1 (2H, m), 5.43–5.65 (2H, m).

**7-Thiaprostaglandin  $\text{E}_1$  Methyl Ester (6b)**—Pyridine (2 ml) and then hydrogen fluoride–pyridine (4 ml) were added to a solution of **6c** (2.1 g, 3.4 mmol) in acetonitrile (40 ml) at 0°C. The mixture was stirred for 2 h at room temperature, neutralized by addition of  $\text{NaHCO}_3$  solution and extracted with AcOEt. The extract was dried over  $\text{MgSO}_4$  and concentrated, and the residue was purified by silica gel column chromatography (hexane: AcOEt = 1: 2) to give **6b** (1.19 g, 90%). IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 3400, 1735 (CO), 1255, 1200, 1165, 1125.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.85 (3H, m), 1.0–1.8 (14H, m), 2.1–3.1 (10H, m), 3.60 (3H, s), 3.70–4.25 (2H, m), 5.45–5.75 (2H, m). MS  $m/e$ : 386 ( $\text{M}^+$ ), 368, 350, 337, 269, 237. High-MS for  $\text{C}_{20}\text{H}_{34}\text{O}_5\text{S}$  ( $\text{M}^+$ ): Calcd  $m/e$  386.2125; Found 386.2142.

**7-Thiaprostaglandin  $\text{E}_1$  (6a)**—A solution of **6b** (727 mg, 1.88 mmol) in acetone (6 ml) and 0.1 M pH 8 phosphate buffer (60 ml) was treated with porcine liver esterase (0.6 ml, Sigma Chemical Co.). The mixture was occasionally sonicated and stirred for 3 h, then it was acidified with 0.5 M HCl to pH 4 at 0°C and saturated with  $(\text{NH}_4)_2\text{SO}_4$ , followed by extraction with AcOEt. The extract was dried over  $\text{MgSO}_4$  and concentrated, and the residue was purified by silica gel column chromatography (0.5% AcOH in hexane: AcOEt = 1: 4) to give **6a** (650 mg, 93%). IR  $\nu_{\text{max}}^{\text{liq}}$   $\text{cm}^{-1}$ : 3400, 2950, 1740, 1720, 1460, 1410, 1080.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.85 (3H, m), 1.0–1.9 (14H, m), 2.1–3.1 (10H, m), 3.7–4.3 (2H, m), 5.45–5.75 (2H, m), 5.7–6.1 (3H, m, -OH).

**ent-15-*epi*-Thiaprostaglandin  $\text{E}_1$ s (20–23, 25)**—*ent*-15-*epi*-Thiaprostaglandin  $\text{E}_1$ s (**20–23, 25**) were obtained simultaneously in the syntheses of the natural-form thiaprostaglandins when the syntheses was started from the combination of 4(*R,S*)-*tert*-butyldimethylsilyloxy-2-cyclopentenone (*dl*-**1**) and (3*S*)-(E)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene.<sup>33)</sup> Less polar *ent*-15-*epi*-thiaprostaglandin  $\text{E}_1$ s were separated from more polar natural-form thiaprostaglandin  $\text{E}_1$ s after desilylation by TLC or silica gel column chromatography. Spectral data (IR,  $^1\text{H-NMR}$ , MS) of these *ent*-15-*epi*-thiaprostaglandin  $\text{E}_1$ s were almost identical with those of the natural-form isomers. There was a tendency that in the  $^1\text{H-NMR}$  spectra, the 13,14-vinyl protons of *ent*-15-*epi*-thiaprostaglandin  $\text{E}_1$ s appeared at about 0.1 ppm lower field compared with those of the natural-form isomers.

**Pharmacological Tests**—Blood was withdrawn into a tube containing one-tenth volume of 3.8% trisodium citrate from the ear vein of domestic white male rabbits weighing 2.3–2.5 kg. The citrated blood was centrifuged at  $100\times g$  for 10 min at room temperature, and platelet-rich plasma (PRP) was prepared. The PRP was used after standing at room temperature for about 1 h. PRP stored for more than 4 h was excluded from experiments.

Test compounds were dissolved in absolute ethanol to a concentration of 10 mg/ml and diluted with phosphate-buffered saline (PBS pH 7.4) and the responses to the corresponding vehicle were always evaluated.

Platelet aggregation study was carried out by the method of Born using Rikaden's 6-channel aggregometers as follows. A 225  $\mu\text{l}$  aliquot of PRP was added to a cuvette containing a stirring bar and the cuvette was placed in a densitometer maintained at 37°C and stirred at 1100 rpm. Twenty-five  $\mu\text{l}$  of test compound solution was added and the increase in light transmittance was recorded. Percent aggregation was calculated by the method described.<sup>35)</sup>

The platelet aggregation inhibition study was carried out as follows: A 200  $\mu\text{l}$  of PRP was added to a cuvette and

stirred at 1100 rpm. Twenty-five  $\mu\text{l}$  of inhibitor solution or vehicle was added and the cuvette was preincubated for 2 min. Aggregation was initiated by adding 25  $\mu\text{l}$  of 100  $\mu\text{g}/\text{ml}$  solution of 6-thia PGE<sub>1</sub>. Percent inhibition was calculated by the method described.<sup>36)</sup>

### References and Notes

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