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Synthesis of 7-Thiaprostaglandin E_1 Congeners: Potent Inhibitors of Platelet Aggregation[1)]

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Novel 7-thiaprostaglandin E_1 derivatives and congeners were synthesized by a stepwise three-component coupling process, which involves the introduction of α-side chains (thiols) and β-side chains (organocopper reagents) into (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone. Several acid derivatives of 7-thiaprostaglandin E_1 were also prepared either by enzymatic or by chemical methods. The stereochemistry of these products was assigned on the basis of the results with chiral protected cyclopentenones and chiral ω-side chains. Some of these 7-thiaprostaglandin E_1 congeners were found to exhibit more potent platelet aggregation-inhibitory activity than PGE_1. The structure–activity relationship of these congeners is discussed.

Keywords——7-thiaprostaglandin E_1; (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone; asymmetric reduction; kinetic resolution; conjugate addition; hydrolysis; absolute configuration; inhibitor of platelet aggregation; structure–activity relationship

Total syntheses of naturally occurring prostaglandins have been successfully achieved by many groups over the past decade[2)] to provide materials for pharmacological and clinical investigations. While some of these prostaglandins, *i.e.*, $PGF_{2\alpha}$, PGE_2, PGE_1, are now clinically used for labor induction, treatment of peripheral vascular disease, and so on, several disadvantages exist, for example, (1) the broad spectrum of their biological activities occasionally leading to side effects, (2) short duration of action *in vivo*, (3) restriction regarding administration route. So far, there have been numerous syntheses of new prostaglandin analogs, and clinical evaluations have been carried out in several therapeutic fields.[3)] The structural features of these prostaglandin analogs can be classified into two categories: (i) chemical modifications at carbon atoms of the prostanoic acid skeleton, and (ii) replacement of carbon or oxygen atoms of the prostanoic acid with hetero-atoms such as oxygen, nitrogen, and sulfur.[4)] During the past few years, we have reported syntheses of several sulfur-containing prostaglandins,[5)] in which one or two methylene groups of the prostanoic acid skeleton were replaced by sulfur atoms. These thiaprostaglandins[6)] are considered to be bioisosters[7)] of the parent natural prostaglandins. Recently, we have reported the syntheses of a series of 4-thia-, 5-thia-, 6-thia-, and 7-thiaprostaglandin E_1 analogs.[8)] In this paper, we describe the synthesis and structure–activity relationship of 7-thiaprostaglandin E_1 derivatives, which exhibited more potent platelet aggregation-inhibitory activity than naturally occurring PGE_1.

The syntheses of 7-thiaprostaglandin E_1 skeletons were carried out by organocopper-conjugate addition of chiral ω-side chain moieties to chiral cyclopentenone derivatives bearing α-side chain moieties. The cyclopentenone intermediates were prepared from protected (4*R*)-4-hydroxy-2,3-epoxycyclopentanone and thiols as α-side chains (Chart 1). This stepwise three-component coupling process (introduction of the α-chain followed by the β-

chain into the chiral enone) provides a short, convergent, and versatile entry to novel 7-thiaprostaglandin E_1 congeners.

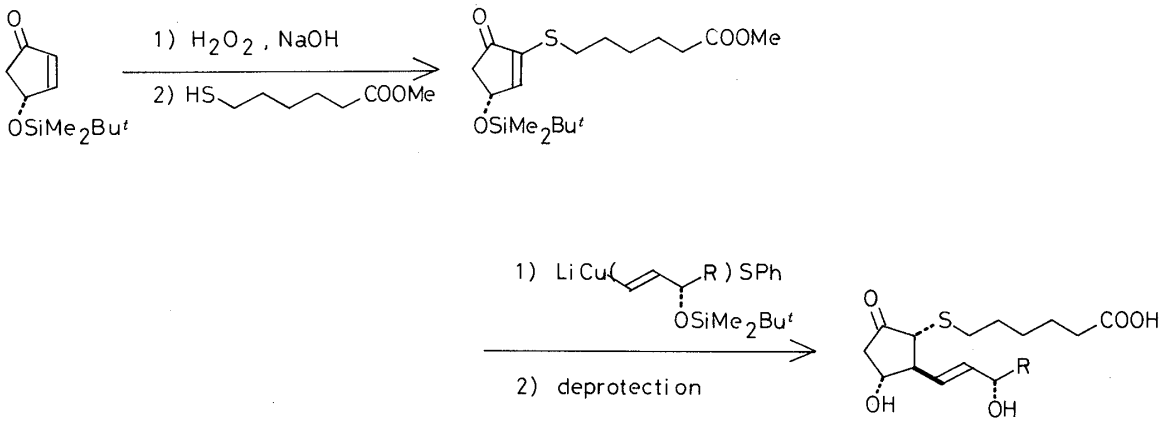


Chart 1

Preparation of Chiral Vinyl Iodides Corresponding to ω-Side Chains

In order to modify the ω-chain of 7-thiaprostaglandin E_1, eight chiral vinyl iodides (**5a**—**h** (*S*)) were prepared by the following general sequence: (1) acylation of acetylene with acyl chlorides (**1a**—**h**) in the presence of aluminum trichloride; (2) conversion of the resulting chlorides (**2a**—**h**) into iodides (**3a**—**h**); (3) asymmetric reduction of the iodovinyl ketones (**3c**—**h**) by the use of binaphthol-modified aluminium hydride reagent ((*S*)-BINAL-H)[9] prepared from lithium aluminum hydride, ethanol, and (*S*)-(−)-binaphthol; (4) protection of the alcohols (**4a**—**h**(*S*)) with the *tert*-butyldimethylsilyl group.

Two vinyl iodides **5a**(*S*),[10] **5b**(*S*)[11] were prepared by resolution methods and the other six vinyl iodides (**5c**—**h**(*S*)) were obtained by asymmetric reduction of iodovinyl ketones (**3c**—**h**) with (*S*)-BINAL-H, followed by protection. Acyl chlorides (**1g**, **h**), chlorovinyl ketones (**2g**, **h**), and iodovinyl ketones (**3g**, **h**) were prepared as racemates. Asymmetric reduction of the racemates (**3g**, **h**) afforded two diastereomers which were separated by usual chromatography to isolate each isomer, **4g** and **4h**. The optical purities of these chiral alcohols (**4b**, **c**, **g**, **h**(*S*)) were estimated by nuclear magnetic resonance (NMR) measurement of their α-methoxy-α-trifluoromethylphenylacetic (MTPA)[12] esters (**6b**, **c**, **g**, **h**(*S*)). The optical purities were also confirmed by high-performance liquid chromatographic (HPLC) analysis of the ratio of diastereomeric ether derivatives (**7c**(*S*); acylals)[13] of **4c**(*S*). The optical purities of **4c**—**f**(*S*) were estimated by HPLC analysis of the corresponding acylals (**7c**—**f**(*S*)) which were obtained from **4c**—**f**(*S*) by complete conversion (see Table VII).

The absolute configurations of the chiral allylic alcohols (**4b**—**h**(*S*)) were confirmed by circular dichroism (CD) measurement of their benzoate derivatives (**8b**—**h**(*S*)) according to the exciton chirality method developed by Nakanishi's group.[14] Allylic benzoates (**8b**—**g**(*S*)) with *S*-configuration were predicted to show positive Cotton effects. Benzoylation of the (*S*)-allylic alcohols (**4b**—**g**(*S*)) obtained by (*S*)-oriented asymmetric reduction with (*S*)-BINAL-H gave quantitatively the allylic benzoates (**8b**—**g**(*S*)) which exhibited the expected positive Cotton effects (see Table VII).

In order to determine the orientation of the branched methyl group of two diastereomers **4g**(*S*) and **4h**(*S*), each alcohol was oxidized with Jones' reagent to give the optically active iodovinyl ketones, **3g** ($[\alpha]_D^{23}$ −4.2° (*c*=3.85, MeOH)) and **3h** ($[\alpha]_D^{23}$ +4.0° (*c*=3.5, MeOH)), respectively. An authentic sample of **3h** with known absolute configuration at the branched carbon was synthesized as follows. Conjugate addition of Grignard reagent (BuMgBr) to *N*-crotyl-*l*-ephedrine (**9**) afforded the (*S*)-adduct (**10**).[15] Through hydrolysis and chlorination,

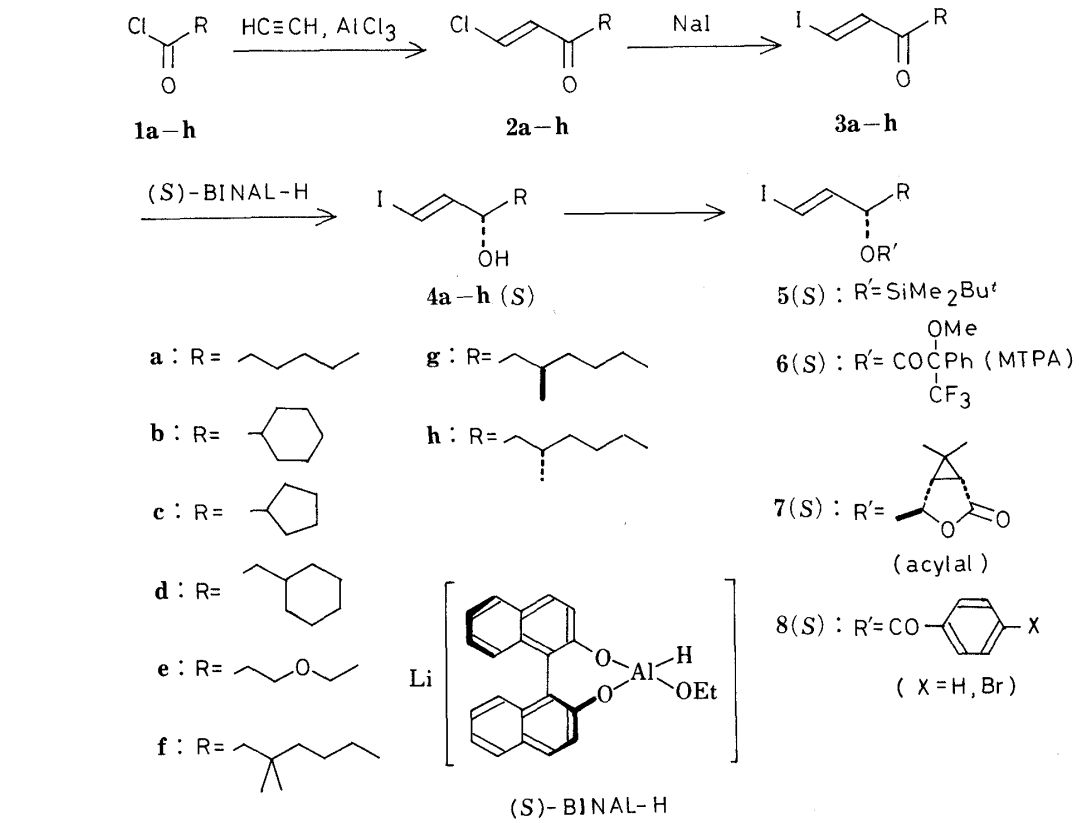
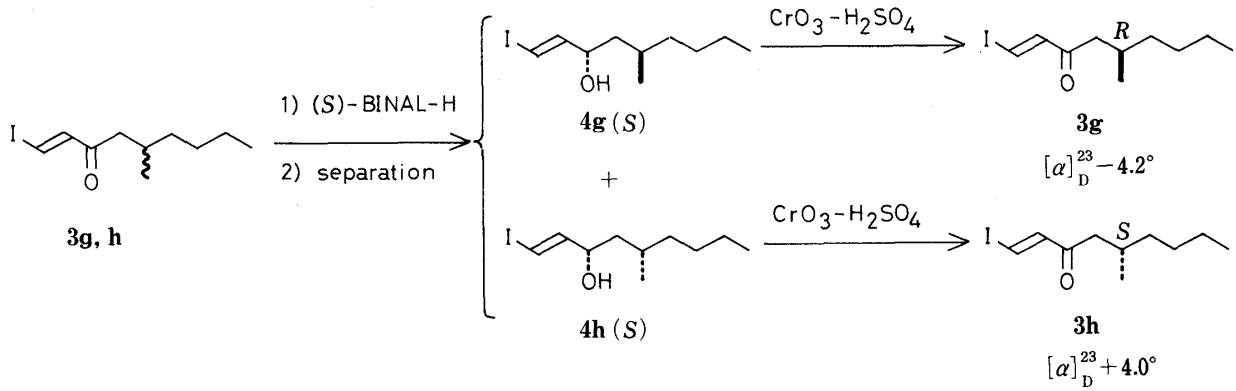


Chart 2



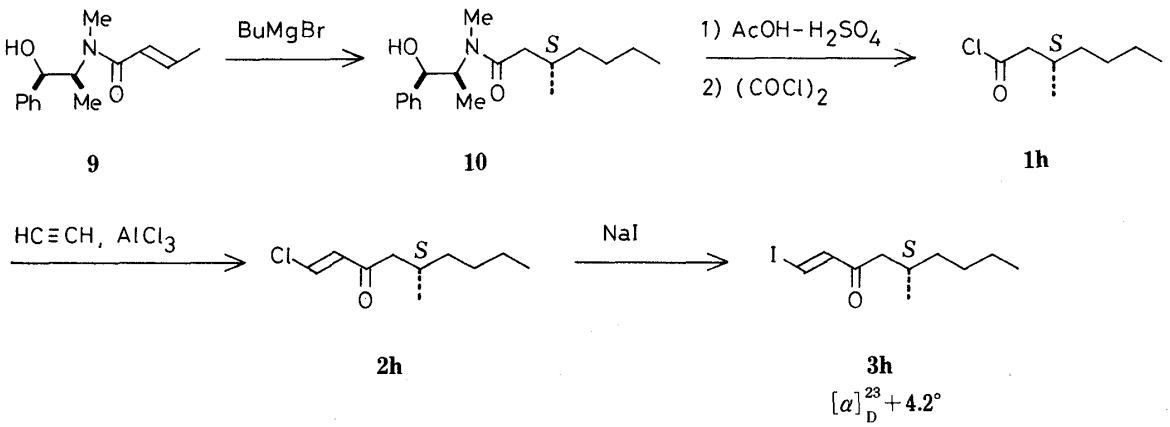


Chart 3

compound **10** was converted to the chlorovinyl ketone (**2h**), which was then transformed into the iodovinyl ketone (**3h**) with *S* chirality ($[\alpha]_D^{23}$ +4.2° (*c*=2.1, MeOH)). From this result, the diastereomer **4h**(*S*), which showed a positive optical rotation after oxidation, was concluded to possess the *S* configuration at the branched chiral carbon and thus **4g**(*S*) had the *R* absolute configuration.

In the course of an enantiomeric-excess determination by the use of (1*R*,2*S*)-*cis*-2-formyl-3,3-dimethylcyclopropane-1-carboxylic acid (**11**) (a cyclic hemiacylal form), a partial kinetic resolution of alcohol **4** was observed when the alcohol remained unreacted. Three different racemic alcohols, *dl*-**4c**—**e**, were allowed to react with equimolar amounts of optically pure **11**. After incomplete conversion of the alcohols, two diastereomeric acylals **7c**—**e**(*S*) and **7c**—**e**(*R*) were obtained accompanied by small amounts of unreacted starting alcohols (10%, 20%, 19%, respectively). These recovered alcohols **4c**—**e** showed negative optical rotations indicating that they are the *R* isomers (**4c**(*R*)); $[\alpha]_D^{27}$ −7.1° (*c*=0.70, MeOH), **4d**(*R*); $[\alpha]_D^{27}$ −13.7° (*c*=2.1, MeOH), **4e**(*R*); $[\alpha]_D^{22}$ −9.1° (*c*=0.95, MeOH), 56—84% ee *vide post.* This result indicated that the condensation reaction of **4**(*S*) with chiral **11** was easier than that of **4**(*R*).

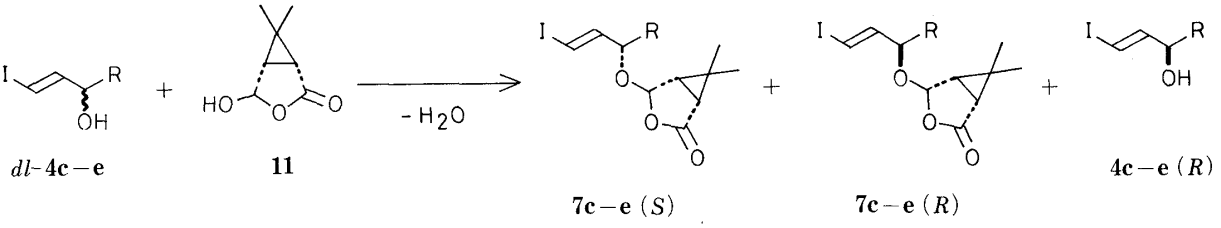


Chart 4

Preparation of Cyclopentenone-Synthons

Several cyclopentenone-synthons with different α-side chains were prepared. Chiral cyclopentenone-synthons (**17i**—**k**(*R*)) were synthesized by reaction of the epoxide (**13**(*R*)) of (*R*)-4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (**12**(*R*))[16,17] with thiols (**16i**—**k**) according to the reported method (56—70% yields).[5b] Racemic synthons (*dl*-**17l**—**o**) were also prepared by reaction of the epoxide (*dl*-**13**) with **16l**—**o** (63—67% yields). Esters (*dl*-**18p**—**r**) or amide (*dl*-**17s**, **w**) derivatives were obtained in 51—98% yields by the condensation of acids (*dl*-**17o**, **18o**) with the corresponding alcohols or amines by using dicyclohexylcarbodiimide or isobutyl chloroformate in the usual manner. Reaction of the epoxide **13** with hydroxy thiols (**16t**, **u**) gave the corresponding cyclopentenone-alcohols (**17t**, **u**). The alcohol (*dl*-**17t**) was acetylated or silylated to protect its hydroxyl group during the following organocopper-conjugate addition. Oxidation of the chiral alcohol (**17u**(*R*); $[\alpha]_D^{20}$ −25.0° (*c*=1.03, MeOH)) in dimethyl sulfoxide in the presence of oxalyl chloride and triethylamine gave the chiral aldehyde (**19**(*R*); $[\alpha]_D^{19}$ −26.6°, (*c*=1.15, MeOH)), which was then converted into the enoic ester (*E*-**17v**(*R*); $[\alpha]_D^{20}$ −20.9° (*c*=1.18, MeOH)) by treatment with trimethyl phosphonoacetate and sodium hydride in benzene.

Synthesis of 7-Thiaprostaglandin E_1 Derivatives

Combination of the above cyclopentenone-synthons with several types of ω-side chains allowed us to prepare various types of modified 7-thiaprostaglandin E_1 analogs and to assess the structure–activity relationship in this series. The parent 7-thiaprostaglandin E_1 methyl ester (**23a**(*S*)**j**(*R*); $[\alpha]_D^{21}$ −26.9° (*c*=0.36, MeOH)) was synthesized from chiral cyclopentenone-synthon (**17j**(*R*); $[\alpha]_D^{23}$ −23.2° (*c*=0.60, MeOH)) and chiral vinyl iodide (**5a**(*S*); $[\alpha]_D^{21}$ −30.6° (*c*=1.57, CCl_4)) by the following sequences:[5c,11] (1) lithiation of **5a**(*S*) with *tert*-butyllithium at −78 °C for 2 h in ether; (2) mixed-cuprate formation of the resulting

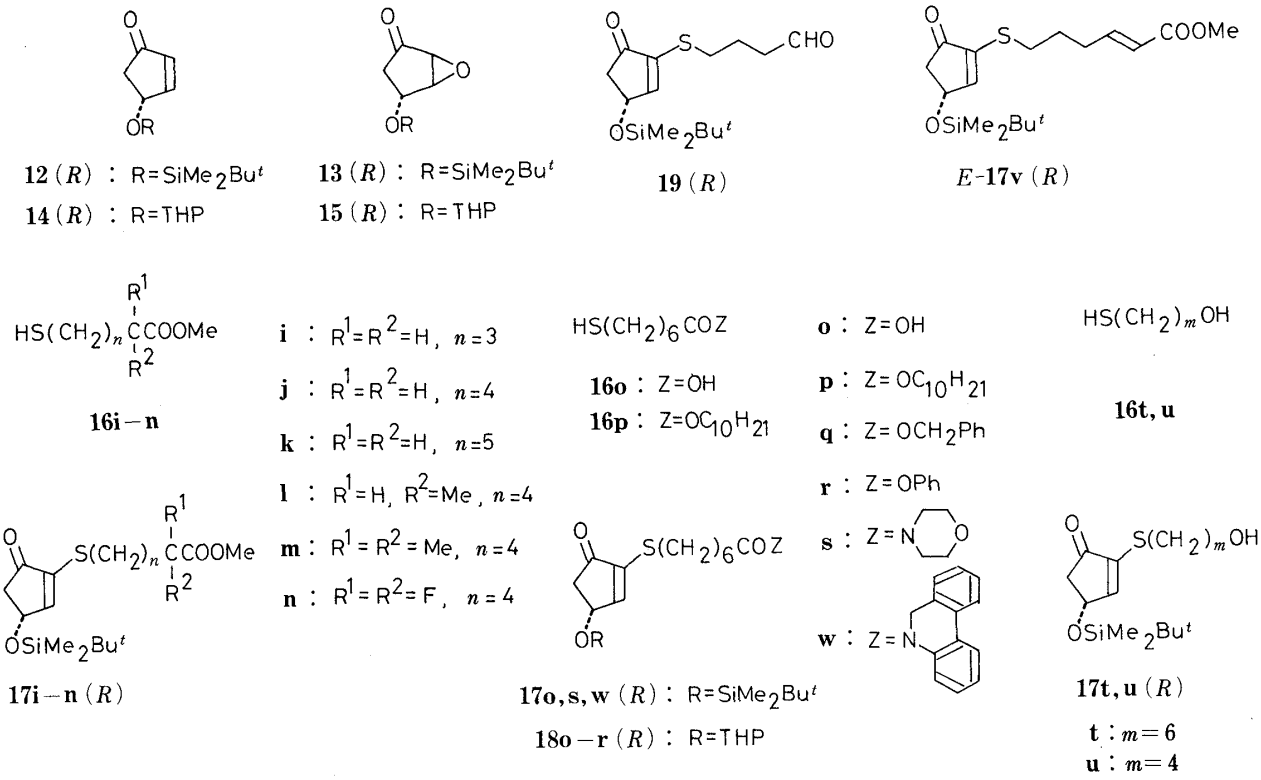


Chart 5

vinyllithium with phenylthiocopper[18] using hexamethylphosphorus triamide as a ligand; (3) conjugate addition of the resulting mixed cuprate to **17j**(*R*); (4) desilylation of the resultant conjugate-adduct (**21a**(*S*)**j**(*R*); $[\alpha]_D^{21}$ $-27.5°$ ($c=1.00$, MeOH)) with aqueous hydrogen fluoride in acetonitrile. In a similar manner, 7-thiaprostaglandin E_1 derivatives (**23b**—**h**(*S*)**j**(*R*)) modified in the ω-side chain were prepared from **17j**(*R*) using the corresponding chiral vinyl iodides (**5b**—**h**(*S*)).[19]

In order to evaluate the effect of α-side chain length of the products, α-nor and α-homo derivatives (**23b**(*S*)**i**(*R*) and **23b**(*S*)**k**(*R*)) were obtained from **17i**(*R*) and **17k**(*R*), respectively. In view of the role of β-oxidation in prostaglandin metabolism, we designed three types of 2-substituted 7-thiaprostaglandin E_1 (2-methyl, 2,2-dimethyl, and 2,2-difluoro derivatives) which were synthesized from the corresponding thiols (**16l**—**n**) through the above-mentioned procedures. Another modification in the α-side chain was the introduction of a double bond between the C-2 and C-3 positions in the prostaglandin skeleton, and the Δ^2-derivatives (**23b**(*S*)**v**(*R*) and **23h**(*S*)**v**(*R*)) were synthesized. Modification of the C-1 position is also important for structure–activity relationship studies, and two types of modified 7-thiaprostaglandin E_1 were synthesized. One example was the conversion of the methyl ester (**23b**(*S*)**j**(*R*)) into decyl (**23b**(*S*)**p**(*R*)), benzyl (**23b**(*S*)**q**(*R*)), and phenyl (**23b**(*S*)**r**(*R*)) esters, and morpholine amide (**23b**(*S*)**s**(*R*)). Another modification was the conversion of the ester function to a hydroxymethyl function and its derivatives. The alcohol (**23b**(*S*)**t**(*R*)) and its acetylated derivative were thus synthesized. The sulfoxide (**24**) was also synthesized from **23b**(*S*)**j**(*R*) by treatment with sodium periodate in 61% yield. The dihydrogenated analog (**25**) was obtained from **23b**(*S*)**j**(*R*) by catalytic hydrogenation in the presence of Adams catalyst (PtO_2) in 68% yield.

Synthesis of 7-Thiaprostaglandin E_1 (Acid Form)

In general, synthesis of PGE-type prostanoic acid requires milder conditions than usual

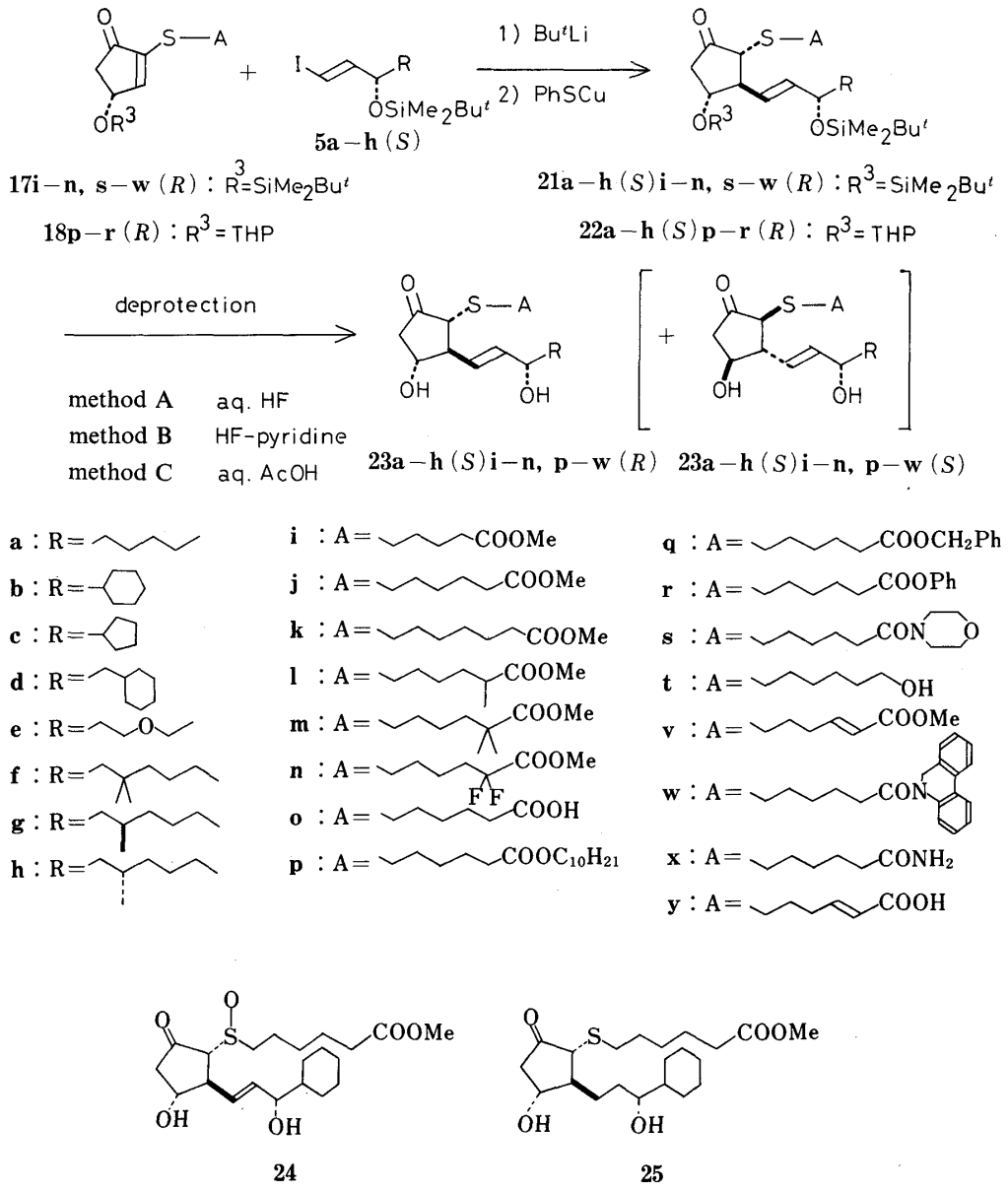
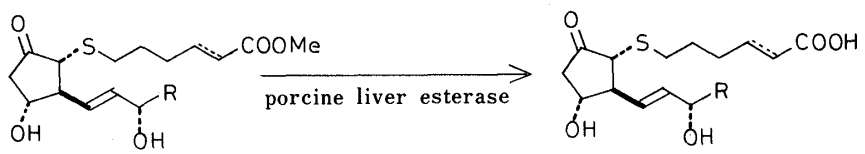


Chart 6

because the PGE skeleton has a β-hydroxy ketone moiety in the molecule, which is sensitive to acidic or basic conditions. One possible approach to synthesize the acid from its methyl ester was to utilize enzymatic hydrolysis with partially purified hog pancreatic lipase[10,20] or yeast.[21] A more convenient method[22] to hydrolyze E-type prostaglandin esters has been developed by us using porcine liver esterase.[23] Hydrolysis of several methyl ester derivatives (**23a**—**c**, **g**, **h**(*S*)**j**(*R*), **23b**(*S*)**v**(*R*)) by treatment with porcine liver esterase in phosphate buffer containing 10% acetone gave the corresponding acids (**23a**—**c**, **g**, **h**(*S*)**o**(*R*), **23b**(*S*)**y**(*R*)) in high yields. This procedure should be suitable for the large-scale preparation of these E-type prostaglandins.

An alternative approach is to use mild chemical methods. We prepared the key intermediate (*dl*-**17w**), in which the carboxylic acid function was protected with 5,6-dihydrophenanthridine in the amide labile to oxidation.[24] The successful conjugate addition of the chiral mixed cuprate to *dl*-**17w** afforded a diastereomeric adduct (**21b**(*S*)**w**(*R*) and **21b**(*S*)**w**(*S*)), which was then desilylated with aqueous hydrogen fluoride in acetonitrile to



23a–c,g,h (*S*)**j,v** (*R*) **23a–c,g,h** (*S*)**o,y** (*R*)

Chart 7

give two amides (**23b**(*S*)**w**(*R*) and **23b**(*S*)**w**(*S*)). Successful oxidation of the amide (**21b**(*S*)**w**(*R*) and **21b**(*S*)**w**(*S*)) with ceric ammonium nitrate in aqueous acetonitrile gave the corresponding carboxylic acid (**21b**(*S*)**o**(*R*) and **21b**(*S*)**o**(*S*)) in 85% yield. Desilylation of this product with aqueous hydrogen fluoride furnished the natural isomer (**23b**(*S*)**o**(*R*)) and its 15-*epi-ent* isomer (**23b**(*S*)**o**(*S*)) after chromatographic separation. Reaction of (**21b**(*S*)**o**(*R*) and **21b**(*S*)**o**(*S*)) with isobutyl chloroformate in the presence of triethylamine followed by aqueous ammonia provided the corresponding amide (**21b**(*S*)**x**(*R*) and **21b**(*S*)**x**(*S*)), which was converted into the final desilylated amide (**23b**(*S*)**x**(*R*) and **23b**(*S*)**x**(*S*)).

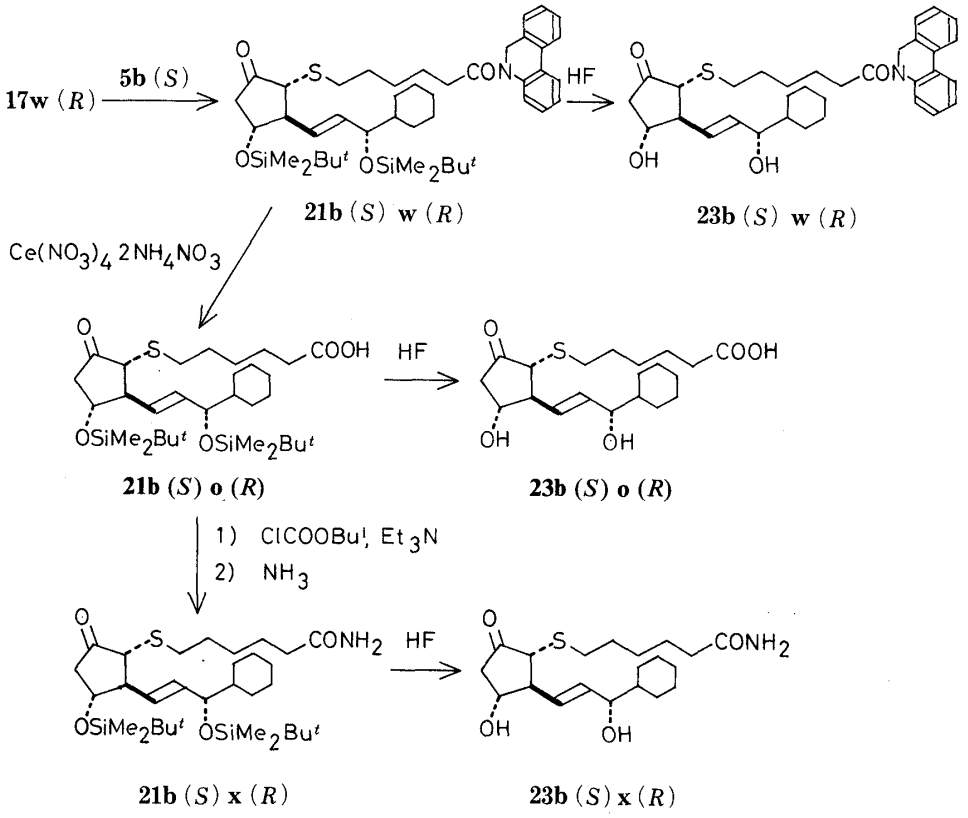


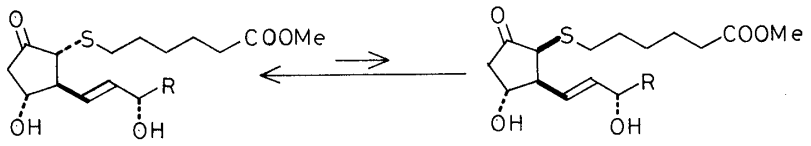
Chart 8

Stereochemistry of 7-Thiaprostaglandin E_1 Derivatives

Reaction of the racemic synthon (*dl*-**17j**) with chiral mixed cuprate, generated from **5a**(*S*), gave a mixture of two diastereomeric methyl esters (**23a**(*S*)**j**(*R*) and **23a**(*S*)**j**(*S*)) in equal amounts after desilylation. These isomers showed two main spots on thin-layer chromatography (TLC) and were isolated by chromatography. Since the more polar product coincided with an authenic sample (**23a**(*S*)**j**(*R*)) possessing the same configuration as natural PGE_1 in physical and spectral properties, the compound was assigned as 7-thiaprostaglandin E_1 methyl ester (**23a**(*S*)**j**(*R*)) and the less polar compound was assigned as 15-*epi-ent*-7-thiaprostaglandin E_1 methyl ester (**23a**(*S*)**j**(*S*)). In cases when similar conjugate additions

were carried out on other racemic synthons (*dl*-**17l—n**, **s**, **t**, **w** and *dl*-**18p—r**), the more polar products were analogously assigned the same configuration as natural PGE.

Natural prostaglandin E_1 is known to epimerize at the C-8 position under basic conditions to result in the formation of an equilibrium mixture, and the reported ratio of 8-*epi*-PGE_1 to PGE_1 was 1 : 9.[25] In the case of the present 7-thiaprostaglandin E_1, this kind of epimerization was also observed on the thin-layer chromatogram where four equilibrated spots were observed by the method of two-dimensional development with an interval (room temperature, 2 h) after the first development. The thin-layer chromatogram after the second development showed only two major and two minor spots. It was found that epimerization at the C-8 position of 7-thiaprostaglandin E_1 occurred much more easily than in the case of PGE_1 under the same conditions, and the ratio of 8-*epi*-7-thiaprostaglandin E_1 to 7-thiaprostaglandin E_1 was about 1 : 2 under various conditions. The ratio was determined by HPLC analysis (210 nm).[26] Thus, it was considered that replacement of a methylene group by a sulfur atom at the C-7 position of PGE_1 caused both the C-8 proton to be more acidic and the α-side chain to be less sterically hindered in relation to the vicinal β-side chain. The presence of such equilibration at the C-8 position was also indicated by the ^{13}C-NMR spectrum of an equilibrated sample, which showed eight pairs of signals due to C(6) and C(8) through C(14). The spectral data for **23b**(*S*)**j**(*S*), **23g**(*S*)**j**(*R*), and their 8-*epi* isomers are listed in Table XI in the experimental section. The values of specific optical rotation of 7-thiaprostaglandin E_1 derivatives were dependent on the ratio between the natural-form isomer and its 8-epimer. For example, 7-thiaprostaglandin E_1 methyl ester (**23a**(*S*)**j**(*R*)) exhibited the following specific optical rotations depending upon the content of 8-epimer:[26] $[\alpha]_D^{21}$ −26.9° (*c* = 0.36, MeOH; natural: 8-*epi* = 91 : 9), $[\alpha]_D^{20}$ −21.4° (*c* = 0.36, MeOH; natural: 8-*epi* = 61 : 39), $[\alpha]_D^{20}$ −13.5° (*c* = 0.36, MeOH; natural: 8-*epi* = 18 : 82).



natural form 8-*epi* form

Chart 9

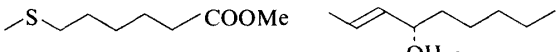
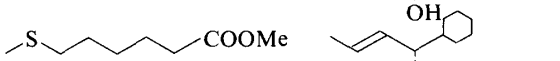
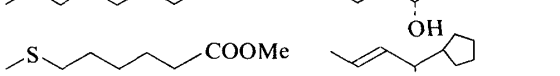
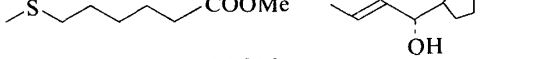
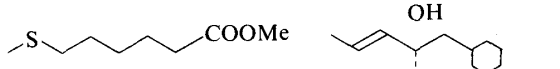
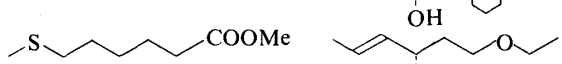
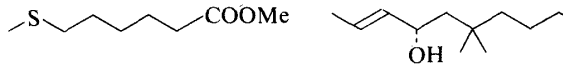
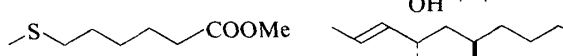
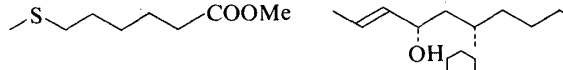
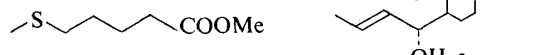
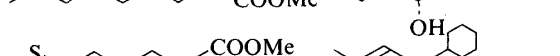
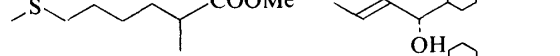
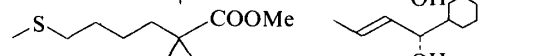
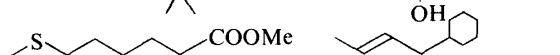
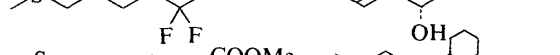
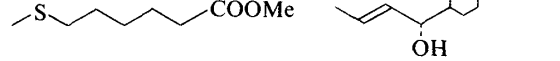
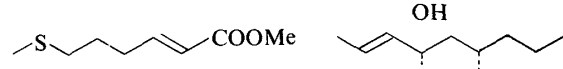
Structure–Activity Relationships of 7-Thiaprostaglandin E_1 Derivatives

On the basis of a preliminary pharmacological evaluation *in vitro*,[27] these 7-thiaprostaglandin E_1 derivatives inhibited platelet aggregation induced by various aggregating agents in platelet-rich plasma, as shown in Table I. The parent 7-thiaprostaglandin E_1 (**23a**(*S*)**j**(*R*)) showed about one-tenth of the activity of PGE_1. Some kinds of modification of the ω-side chain resulted in marked enhancement of the activity, which corresponded to that of prostacyclin (PGI_2). Several modifications at the α-position with respect to the carboxylic ester in the α-chain lowered the activity. Increase and decrease of the α-chain length resulted in reduction of the inhibitory activity. Carboxylic acid and some ester derivatives retained the activity, while hydroxymethyl and amide derivatives showed moderate activity. Sulfoxide and 13,14-dihydro derivatives showed weaker activity. In summary, some of chemically modified 7-thiaprostaglandin E_1 analogs were found to show more potent activity than PGE_1. These results suggest that it might be possible to develop a new synthetic cardiovascular drug.

Experimental

All melting points and boiling points are uncorrected. Melting points were observed with a Yanaco micro melting point apparatus. Infrared (IR) spectra were recorded on a JASCO A120 spectrometer. ^{1}H-NMR and ^{13}C-

TABLE I. Inhibitory Activity of 7-Thia PGE_1 Congeners on Rabbit Platelet Aggregation Induced by ADP

Compd. No.	α-Side chain	ω-Side chain	IC_{50} (μg/ml)
23a(*S*)**j**(*R*)			0.47
23b(*S*)**j**(*R*)			0.004
23c(*S*)**j**(*R*)			0.053
23d(*S*)**j**(*R*)			0.23
23e(*S*)**j**(*R*)			7.5
23f(*S*)**j**(*R*)			0.16
23g(*S*)**j**(*R*)			0.002
23h(*S*)**j**(*R*)			0.001
23b(*S*)**i**(*R*)			2.3
23b(*S*)**k**(*R*)			39
23b(*S*)**l**(*R*)			0.52
23b(*S*)**m**(*R*)			>100
23b(*S*)**n**(*R*)			0.37
23b(*S*)**v**(*R*)			0.091
23h(*S*)**v**(*R*)			0.64
23b(*S*)**p**(*R*)			0.058
23b(*S*)**q**(*R*)			0.054
23b(*S*)**r**(*R*)			0.015
23b(*S*)**s**(*R*)			>100
23b(*S*)**t**(*R*)			>100
24			13.5
25			0.12
23b(*S*)**o**(*R*)			0.004
23b(*S*)**x**(*R*)			43
PGE_1			0.02—0.05

NMR spectra were taken on a Varian EM 360A (60 MHz) and a JEOL JNM-PS-100 (100 MHz) spectrometer, respectively, with TMS as an internal standard in $CDCl_3$ (unless otherwise noted). The chemical shifts and coupling constants (J) are given in δ (ppm) and Hz, respectively. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Mass spectra (MS) were obtained on a Shimadzu LKB 9000 spectrometer (at 20 eV unless otherwise noted). When molecular ions were too weak to be detected, other characteristic peaks are given. High-resolution MS were measured on a JEOL JMS D 300 mass spectrometer for molecular peaks or other characteristic peaks. Optical rotations were measured in MeOH on a Union Giken PM-101 automatic polarimeter. CD spectra were recorded on a JASCO J-20 automatic recording spectropolarimeter. HPLC was carried out with a Shimadzu LC-3A liquid chromatograph with a Shimadzu C-R1B chromatopac.

Layer chromatography was performed on Merck silica gel (Kiesel gel 60 F_{254}) analytical (thickness 0.25 mm) and preparative (0.5 mm and 2.0 mm) plates. Column chromatography was carried out on Wako gel C-200 and C-300 silica gel or silica Woelm TSC (silica gel for dry-column chromatography). Unless otherwise specified, all reactions were carried out under an atmosphere of argon or nitrogen. As the esterase for enzymatic hydrolysis, porcine liver esterase purchased from Sigma Chemical Co. was used.

Chromatographed compounds were prepared for analysis and biological testing by being heated at 40 °C *in vacuo* for 1—2 h in order to remove the last traces of solvents, and in each case the purity was checked by TLC. The final products were confirmed to be homogeneous by TLC and HPLC except for the 8-*epi* isomer.

General Procedure for the Preparation of Chiral Vinyl Iodides (5c—h(S)) from Iodovinyl Ketones (3c—h)——The starting iodovinyl ketones (**3c—h**) were prepared[10,11] by acylation of acetylene with acyl chlorides (**1c—h**) in the presence of $AlCl_3$ followed by conversion of the resulting chlorovinyl ketones (**2c—h**) to **3c—h**. Yields, physical and spectral data of **2c—h** and **3c—h** are given in Tables II and III, respectively.

(1*E*)-(3*S*)-3-*tert*-Butyldimethylsilyloxy-3-cyclohexyl-1-iodo-1-propene (5b(S)) (by Optical Resolution)——**5b**(S) was prepared by silylation of (+)-(1*E*)-(3*S*)-3-cyclohexyl-3-hydroxyl-1-iodo-1-propene, which was obtained by a procedure similar to that used for the preparation of **5a**(S) and resolved by using (−)-α-methylbenzylamine.[10,11] Physical and spectral data for intermediates (**1b**, **2b**, **3b**, and **4b**(S)) and the product (**5b**(S)) are given in Tables II—V and VII.

(1*E*)-(3*S*)-3-*tert*-Butyldimethylsilyloxy-3-cyclopentyl-1-iodo-1-propene (5c(S)) (by Asymmetric Reduction)——According to the cited procedure,[9] a 1.0 M solution of dry ethanol in dry tetrahydrofuran (THF) (83.8 ml, 83.8 mmol) was added at 0 °C to a 1.04 M solution of $LiAlH_4$ in THF (80.6 ml, 83.8 mmol), and the mixture was stirred at room temperature for 10 min. To the resulting mixture was added at 0 °C a solution of (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthol (24 g, 83.8 mmol) in THF (120 ml), and the whole was stirred at room temperature for 30 min. Then a solution of iodovinyl ketone (**3c**; 14.1 g, 55.8 mmol) in dry THF (60 ml) was added at −100 °C, and the mixture was stirred at −100 °C for 2 h, then at −78 °C for 1 h. The reaction was quenched at −78 °C by the addition of MeOH (24 ml) followed by the addition of water (28 ml) at room temperature, and the resulting mixture was stirrred for 30 min, diluted with ethyl acetate, and dried by the addition of $MgSO_4$ (200 g). The resulting cake was filtered off

TABLE II. Yields, Physical and Spectral Data for Chlorovinyl Ketones (**2b—h**)

Compd. No.	Yield (%)	bp °C (mmHg)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
2b	74	92—93 (6)	3080, 1685, 1580, 940	1.1—2.0 (10H, m), 2.15—2.70 (1H, m), 6.72 (1H, d, J=15 Hz), 7.42 (1H, d, J=15 Hz)
2c	76	80—82 (1.5)	3080, 1685, 1580, 940	1.5—1.9 (8H, m), 2.95 (1H, m), 6.63 (1H, d, J=14 Hz), 7.36 (1H, d, J=14 Hz)
2d	83	83—86 (0.15)	3080, 1685, 1580, 940	0.7—2.0 (11H, m), 2.37 (2H, d, J=7 Hz), 6.60 (1H, d, J=13 Hz), 7.35 (1H, d, J=13 Hz)
2e	30	54—56 (0.15)	3080, 1680, 1590, 1105, 940	1.14 (3H, t, J=7 Hz), 2.78 (2H, t, J=5.5 Hz), 3.49 (2H, q, J=7 Hz), 3.72 (2H, t, J=5.5 Hz), 6.60 (1H, d, J=13 Hz), 7.35 (1H, d, J=13 Hz)
2f	68	62—64 (0.12)	3080, 1685, 1580, 940	0.94 (9H, s+t), 1.23 (6H, br s), 2.34 (2H, s), 6.47 (1H, d, J=14 Hz), 7.21 (1H, d, J=14 Hz)
2g[a] (**2h**)	80	68—70 (0.20)	3080, 1685, 1580, 940	0.8—1.0 (6H, m), 1.1—1.4 (7H, m), 2.25—2.45 (2H, m), 6.47 (1H, d, J=13 Hz), 7.20 (1H, d, J=13 Hz)

a) Racemic mixture.

TABLE III. Yields and Spectral Data for Iodovinyl Ketones (**3b—h**)

Compd. No.	Yield (%)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
3b	98	3080, 1685, 1560, 945	1.0—1.9 (10H, m), 2.15—2.70 (1H, m), 7.21 (1H, d, J=16 Hz), 7.80 (1H, d, J=16 Hz)
3c	90	3080, 1685, 1560, 945	1.4—2.1 (8H, m), 3.0 (1H, m), 7.30 (1H, d, J=15 Hz), 7.88 (1H, d, J=15 Hz)
3d	98	3080, 1685, 1560, 945	0.7—2.0 (11H, m), 2.38 (1H, d, J=8 Hz), 7.23 (1H, d, J=15 Hz), 7.88 (1H, d, J=15 Hz)
3e	42	3080, 1685, 1565, 945	1.12 (3H, t, J=7 Hz), 2.77 (2H, t, J=6 Hz), 3.46 (2H, q, J=7 Hz), 3.70 (2H, t, J=6 Hz), 7.20 (1H, d, J=15 Hz), 7.90 (1H, d, J=15 Hz)
3f	81	3080, 1685, 1560, 950	0.93 (9H, s+t), 1.24 (6H, br s), 2.36 (2H, s), 7.13 (1H, d, J=15 Hz), 7.99 (1H, d, J=15 Hz)
3g	98[a]	3070, 1680, 1565, 945	0.8—1.0 (6H, m), 1.1—1.4 (7H, m), 2.25—2.50 (2H, m), 7.20 (1H, d, J=15 Hz), 7.83 (1H, d, J=15 Hz)
3h	98[a]	3070, 1680, 1565, 945	0.8—1.0 (6H, m), 1.1—1.4 (7H, m), 2.25—2.50 (2H, m), 7.20 (1H, d, J=15 Hz), 7.83 (1H, d, J=15 Hz)

a) The product was obtained as a racemic mixture of **3g** and **3h**.

and washed with ethyl acetate. After removal of the combined solvent from the collected filtrate and washings, recrystallized (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthol was filtered off and the resulting filtrate was subjected to column chromatography to give **4c**(*S*) (6.93 g, 27.3 mmol, 49%) accompanied by the starting **3c** (6.48 g, 25.7 mmol, 46%). Silylation (room temperature, 2 h) of **4c**(*S*) (6.93 g, 27.3 mmol) with *tert*-butyldimethylchlorosilane (4.94 g, 32.8 mmol) in the presence of imidazole (2.79 g, 41.0 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) gave **5c**(*S*) (9.24 g, 25.1 mmol, 92%) after separation by column chromatography with hexane as the eluent.

In the same manner, **5d—h**(*S*) were prepared by asymmetric reduction of the corresponding **3d—h** followed by silylation of the resulting **4d—h**(*S*). **4g**(*S*) and **4h**(*S*) were separated by silica gel column chromatography. As described later, the more polar reduction product was identical to **4h**(*S*). Yields and spectral data for **4c—h**(*S*) and **5c—h**(*S*) are listed in Tables IV and V, respectively. The optical properties for these compounds are listed in Table VII.

General Procedure for the Preparation of (+)-MTPA Esters (6b, c, g, h(*S*)). A Typical Example: (1*E*)-(3*S*)-3-(+)-MTPA-3-cyclopentyl-1-iodo-1-propene (6c(*S*))——(+)-MTPA-Cl (157 mg, 0.62 mmol) was added at room temperature to a solution of **4c**(*S*) (79 mg, 0.31 mmol) in CH_2Cl_2 (1 ml). Pyridine (62 mg, 0.78 mmol) was added to the mixture, which was stirred at room temperature for 1 h until no **4c**(*S*) was detected on TLC. Water was added and the resulting mixture was extracted with hexane. The separated organic layer was washed with 5% aq. $NaHCO_3$, 5% HCl, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford **6c**(*S*) (225 mg), which was homogeneous by TLC (hexane : ethyl acetate = 9 : 1) without further purification. The enantiomeric purity of **6c**(*S*) was estimated to be 97.5% (95% ee) from the ^{1}H-NMR peak areas corresponding to the olefinic protons at the C-1 and C-2 positions, whereas that of *dl*-**6c** was 50% (0% ee).

The other chiral compounds (**6b, g, h**(*S*)) were similarly prepared. Yields and ^{1}H-NMR spectral data are listed in Table VI.

General Procedure for the Preparation of 7c—f(*S*). A Typical Example: (1*E*)-(3*S*)-3-[(1*R*,4*R*,5*S*)-6,6-Dimethyl-2-oxo-3-oxabicyclo[3.1.0]hex-4-yloxy]-3-cyclopentyl-1-iodo-1-propene (7c(*S*))——**4c**(*S*) (176 mg, 0.7 mmol), obtained by the above asymmetric reduction, was added to a solution of **11** (110 mg, 0.77 mmol) and pyridinium *p*-toluenesulfonate (40 mg, 0.16 mmol) in benzene (20 ml) and the mixture was refluxed for 12 h with azeotropic separation of water. After removal of the solvent, the residue was taken up in ethyl acetate. This solution was washed with aq. $NaHCO_3$ and then brine, and dried over $MgSO_4$. Evaporation of the solvent left quantitatively almost pure **7c**(*S*) (258 mg). This product showed two diastereomeric peaks corresponding to racemic **7c**(*S*) and **7c**(*R*) by HPLC analysis using CH_2Cl_2–hexane (1 : 1) as an eluent, and the ratio was 97.5 : 2.5 (95% ee).

The other compounds (**7d—f**(*S*)) were similarly prepared to estimate the optical purities of asymmetrically

TABLE IV. Yields and Spectral Data for Iodovinyl Alcohols (**4b**—**h**(*S*))

Compd. No.	Yield (%)	Recovery[a] (%)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
4b(*S*)	14[b]		3380, 3060, 1610, 1170, 1040, 950	0.9—1.9 (11H, m), 2.27 (1H, br s), 3.73 (1H, m), 6.20 (1H, d, J=16 Hz), 6.40 (1H, dd, J=16 and 6 Hz)
4c(*S*)	49	46	3360, 3060, 1610, 1180, 1025, 945	1.3—2.0 (9H, m), 1.76 (1H, s), 3.90 (1H, m), 6.30 (1H, d, J=16 Hz), 6.65 (1H, dd, J=16 and 6 Hz)
4d(*S*)	56	31	3360, 3060, 1610, 1165, 1040, 945	0.7—2.1 (13H, m), 2.30 (1H, br s), 3.90 (1H, m), 6.15 (1H, d, J=14 Hz), 6.50 (1H, dd, J=14 and 5 Hz)
4e(*S*)	59	14	3430, 3060, 1610, 1170, 1040, 950	1.2 (3H, t, J=7 Hz), 1.73 (1H, br s), 1.75 (2H, m), 3.50 (4H, m), 4.20 (1H, m), 6.30 (1H, d, J=15 Hz), 6.60 (1H, dd, J=15 and 4 Hz)
4f(*S*)	76		3400, 3060, 1610, 1170, 1045, 950	0.90 (9H, s+t), 1.20 (6H, br s), 1.43 (2H, d, J=5 Hz), 1.53 (1H, br s), 4.27 (1H, m), 6.38 (1H, d, J=15 Hz), 6.58 (1H, dd, J=15 and 6 Hz)
4g(*S*)	40[c]	7	3350, 3060, 1610, 1170, 1050, 950	0.80—0.95 (6H, m), 1.1—1.7 (9H, m), 1.72 (1H, br s), 4.15 (1H, m), 6.27 (1H, d, J=15 Hz), 6.50 (1H, dd, J=15 and 5 Hz)
4h(*S*)	47[c]		3420, 3060, 1605, 1170, 1010, 945	0.8—1.00 (6H, m), 1.1—1.6 (9H, m), 1.68 (1H, br s), 4.15 (1H, m), 6.27 (1H, d, J=14 Hz), 6.50 (1H, dd, J=14 and 5 Hz)

a) Recovery of the substrate. *b*) Based on the racemate (*dl*-**4b**), which was used for the resolution. *c*) Based on the starting racemic substrate (**3g**, **h**).

reduced **4d**—**f**(*S*). The ^{1}H-NMR spectral data and optical purities for **7c**—**f**(*S*) are listed in Tables VI and VII, respectively.

General Procedure for the Preparation of 8c—f(*S*). A Typical Example: (1*E*)-(3*S*)-3-Benzoyloxy-3-cyclopentyl-1-iodo-1-propene (8c(*S*))——In a similar manner to that described for the preparation of (+)-MTPA esters, benzoylation (room temperature, 18 h) of **4c**(*S*) (40 mg, 0.157 mmol) with benzoyl chloride (44 mg, 0.314 mmol) and pyridine (124 mg, 1.57 mmol) in CH_2Cl_2 (2 ml) gave **8c**(*S*) (52 mg, 0.146 mmol, 93%) after usual work-up and separation by preparative TLC (cyclohexane : ethyl acetate = 3 : 1). This product (**8c**(*S*)) exhibited a positive Cotton effect at 233 nm; $\Delta\varepsilon = +8.28$ (cyclohexane).

The other compounds (**8d**—**f**(*S*)) were similarly prepared to determine the absolute configurations by CD measurement. Yields and ^{1}H-NMR spectral data are listed in Table VI, and CD spectral data in Table VII.

Oxidation of (1*E*)-(3*S*,5*R* and 3*S*,5*S*)-3-Hydroxy-1-iodo-5-methyl-1-nonene (4g and 4h)——The Jones reagent (2.67 M) was added at room temperature to a solution of **4g** (167 mg, 0.59 mmol) in acetone (5 ml) until the color of the reaction mixture changed to reddish from green. The reaction was quenched by the addition of 2-propanol and then aq. $NaHCO_3$. The resulting mixture was diluted with ether, then washed with brine. The separated organic layer was dried over $MgSO_4$, and concentrated *in vacuo* to give **3g** (151 mg, 0.54 mmol, 91%) as an oil showing one spot on TLC (hexane : ethyl acetate = 9 : 1). $[\alpha]_D^{23}$ −4.2° (c = 3.85, MeOH).

TABLE V. Yields and ^{1}H-NMR Spectral Data for Vinyl Iodide (**5b**—**h**(*S*))

Compd. No.	Yield (%)	^{1}H-NMR δ ($CDCl_3$)
5b(*S*)	99	0.03 (6H, s), 0.87 (9H, s), 0.9—1.9 (11H, m), 3.63 (1H, m), 6.20 (1H, d, J=15 Hz), 6.50 (1H, dd, J=15 and 6.5 Hz)
5c(*S*)	92	0.03 (6H, s), 0.87 (9H, s), 1.3—2.0 (9H, m), 3.91 (1H, m), 6.23 (1H, d, J=15 Hz), 6.60 (1H, dd, J=15 and 6 Hz)
5d(*S*)	96	0.03 (6H, s), 0.88 (9H, s), 1.0—1.8 (13H, m), 4.20 (1H, m), 6.25 (1H, d, J=15 Hz), 6.57 (1H, dd, J=15 and 6 Hz)
5e(*S*)	90	0.03 (6H, s), 0.90 (9H, s), 1.20 (3H, t, J=8 Hz), 1.75 (2H, m), 3.45 (4H, m), 4.30 (1H, dt, J=6 and 6 Hz), 6.20 (1H, d, J=15 Hz), 6.60 (1H, dd, J=15 and 6 Hz)
5f(*S*)	58	0.03 (6H, s), 0.90 (18H, s), 1.0—1.5 (8H, m), 4.20 (1H, dt, J=6 and 6 Hz), 6.20 (1H, d, J=16 Hz), 6.60 (1H, dd, J=16 and 6 Hz)
5g(*S*)	90	0.03 (6H, s), 0.87 (15H, m), 1.20 (9H, m), 4.15 (1H, m), 6.20 (1H, d, J=15 Hz), 6.50 (1H, dd, J=15 and 6 Hz)
5h(*S*)	88	0.03 (6H, s), 0.85 (15H, m), 1.1—1.5 (9H, m), 4.20 (1H, m), 6.23 (1H, d, J=14 Hz), 6.53 (1H, dd, J=14 and 6 Hz)

The same oxidation of **4h** (153 mg, 0.54 mmol) yielded **3h** (141 mg, 0.50 mmol, 93%). $[\alpha]_D^{23}$ +4.0° (c=3.50, MeOH). Spectral data for **3g** and **4g** are listed in Table IV.

(1*E*)-(5*S*)-1-Iodo-5-methylnon-1-en-3-one (3h)——According to the reported procedure,[15] (3*S*)-3-methylheptanoic acid (**10**; $[\alpha]_D^{23}$ −3.9° (c=1.0, benzene), lit[15] $[\alpha]_D^{23}$ −3.6° (neat)) was obtained from **9** in 95% yield (see Chart 3). Chlorination of **10** (151 mg, 1.05 mmol) with oxalyl chloride (200 mg) in benzene (3 ml) at room temperature for 5 h gave **1h** (170 mg) after evaporation. According to the general method mentioned above,[10] crude **1h** (170 mg, 1.05 mmol) was converted into **3h** (176 mg, 0.63 mmol, 60% based on **10**) through **2h**. Purified **3h** showed $[\alpha]_D^{23}$ +4.2° (c=2.1, MeOH). The products (**1**—**3h**) were identical (TLC, IR, and NMR) with the racemic sample (**1**—**3h**) described above (Tables II and III).

Kinetic Resolution of *dl*-4c—e with 11. A Typical Example: *dl*-(1*E*)-5-Ethoxy-3-hydroxy-1-iodo-1-pentene (*dl*-4e)——A mixture of *dl*-**4e** (119 mg, 0.46 mmol), **11** (65 mg, 0.46 mmol), and pyridinium *p*-toluenesulfonate (35 mg, 0.14 mmol) in benzene (10 ml) was refluxed for 12 h with azeotropic separation of water. Work-up and separation by preparative TLC (benzene : ethyl acetate = 4 : 1) yielded **7e**(*S*) (77 mg, 0.20 mmol, 44%), **7e**(*R*) (31 mg, 0.08 mmol, 18%), and recovered **4e**(*R*) (23 mg, 0.09 mmol, 19%). The optical rotation of **4e**(*R*) was $[\alpha]_D^{22}$ −9.1° (c=0.95, MeOH), while that of the asymmetrically reduced product **4e**(*S*) was $[\alpha]_D^{25}$ +10.8° (c=0.53, MeOH). The recovered **4c**(*R*) and **4d**(*R*) showed $[\alpha]_D^{27}$ −7.1° (c=0.70, MeOH) and $[\alpha]_D^{27}$ −13.7° (c=2.1, MeOH), respectively (see Table VII). Similar results were obtained for *dl*-**4c** and *dl*-**4d**.

General Procedure for the Preparation of 17i—k, u(*R*), *dl*-17l—o, t, and *dl*-18o, p. A Typical Example: (4*R*)-4-*tert*-Butyldimethylsilyloxy-2-(5-methoxycarbonylpentylthio)-2-cyclopentenone (17j(*R*))——According to the reported procedure,[5a-c] the reaction (room temperature, 3 h) of **13**(*R*) (10.8 g, 47.2 mmol), prepared from **12**(*R*) by epoxidation with alkaline hydrogen peroxide, with **16j**[28] (7.65 g, 47.2 mmol) in the presence of triethylamine (4.77 g, 47.2 mmol) in MeOH (200 ml) gave **17j**(*R*) (12.3 g, 33.1 mmol, 70%) after chromatographic separation (hexane : ethyl acetate = 5 : 1).[29]

Analogously, chiral **17i**, **k**, **u**(*R*) and racemic *dl*-**17l**—**o**, **t** and *dl*-**18o**, **p** were prepared from the corresponding thiols[28] (see Chart 5). Other data are listed in Table VIII.

Esterification of *dl*-2-(5-Carboxypentylthio)-4-(tetrahydropyran-2-yloxy)-2-cyclopentenone (*dl*-18o)——a) Isobutyl chloroformate (281 mg, 2.06 mmol) and then triethylamine (277 mg, 2.74 mmol) were added to a stirred solution of *dl*-**18o** (450 mg, 1.37 mmol) in CH_2Cl_2 (5 ml) at −40 °C. The mixture was stirred for 30 min, then benzyl alcohol (178 mg, 1.64 mmol) was added at −40 °C, and the reaction temperature was maintained at −40 °C during the first 1 h and finally raised to room temperature for 3 h with stirring. The resulting mixture was extracted with ethyl acetate. The extract was washed with aq. $NaHCO_3$, dil. HCl, and brine, and dried over $MgSO_4$. Removal of the solvent afforded a crude product, which was chromatographed on a silica gel column with hexane–ethyl acetate (4 : 1) to furnish *dl*-**18q** (293 mg, 0.70 mmol, 51%).

TABLE VI. Yields and ^{1}H-NMR Spectral Data for **6**—**8**(*S*)

Compd. No.	Yield (%)	^{1}H-NMR δ ($CDCl_3$)
6b(*S*)	Quant.[a]	0.8—1.9 (11H, m), 3.67 (3H, br s), 5.20 (1H, m), 6.36—6.48 (2H, m), 7.3—7.6 (5H, m)
6c(*S*)	Quant.[a]	1.4—1.65 (9H, m), 3.57 (3H, m), 5.23 (1H, m), 6.37—6.50 (2H, m), 7.35—7.60 (5H, m)
6g(*S*)	Quant.[a]	0.83—0.98 (6H, m), 1.1—1.6 (9H, m), 3.58 (3H, m), 5.50 (1H, m), 6.40—6.52 (2H, m), 7.40—7.60 (5H, m)
6h(*S*)	Quant.[a]	0.85—1.00 (6H, m), 1.1—1.7 (9H, m), 3.58 (3H, br s), 5.50 (1H, m), 6.44—6.56 (2H, m), 7.40—7.64 (5H, m)
7c(*S*)	Quant.[a]	1.11 (6H, s), 1.50 (9H, m), 2.00 (2H, s), 3.90 (1H, m), 5.11 (1H, s), 6.35—6.45 (2H, m)
7d(*S*)	Quant.[a]	1.13 (6H, s), 1.3—1.8 (13H, m), 1.99 (2H, s), 4.25 (1H, m), 5.13 (1H, s), 6.33—6.43 (2H, m)
7e(*S*)	Quant.[a]	1.15 (6H, s), 1.18 (3H, t, J=7 Hz), 1.6—1.9 (2H, m), 2.01 (2H, s), 3.25—3.65 (4H, m), 4.35 (1H, m), 5.17 (1H, s), 6.4—6.55 (2H, m)
7f(*S*)	Quant.[a]	0.87 (9H, s+t), 1.15 (6H, s), 1.0—1.8 (8H, m), 1.98 (2H, s), 4.3 (1H, m), 5.12 (1H, s), 6.33—6.45 (2H, m)
8c(*S*)	93	1.1—2.2 (9H, m), 5.4 (1H, m), 6.55 (1H, d, J=14 Hz), 6.75 (1H, dd, J=14 and 3 Hz), 7.6 and 8.2 (3H and 2H, m)
8d(*S*)	82	0.7—2.0 (13H, m), 5.6 (1H, m), 6.55 (1H, d, J=14 Hz), 6.75 (1H, dd, J=14 and 3 Hz), 7.6 and 8.2 (3H and 2H, m)
8e(*S*)	91	1.2 (3H, t, J=6 Hz), 2.05 (2H, m), 3.05 (2H, q, J=6 Hz), 3.55 (2H, t, J=6 Hz), 5.70 (1H, m), 6.55 (1H, d, J=14 Hz), 6.75 (1H, dd, J=14 and 3 Hz), 7.6 and 8.2 (3H and 2H, m)
8f(*S*)	92	0.9 (9H, s+t), 1.1—1.2 (6H, m), 1.75 (2H, dd, J=14 and 5 Hz), 5.65 (1H, m), 6.50 (1H, d, J=14 Hz), 6.80 (1H, dd, J=14 and 3 Hz), 7.6 and 8.2 (3H and 2H, m)

a) Reacted until no starting alcohol was detected on TLC.

b) A solution of dicyclohexylcarbodiimide (860 mg, 4.18 mmol) in CH_2Cl_2 (10 ml) was added at 0 °C to a stirred solution of *dl*-**18o** (686 mg, 2.09 mmol), phenol (295 mg, 3.14 mmol), and pyridine (0.1 ml), and the whole was stirred at room temperature for 18 h. Work-up and separation by column chromatography (hexane : ethyl acetate = 7 : 2) yielded *dl*-**18r** (653 mg, 1.62 mmol, 77%).

Spectral data for *dl*-**18q** and *dl*-**18r** are given in Table VIII.

Amidation of *dl*-4-*tert*-Butyldimethylsilyloxy-2-(5-carboxypentylthio)-2-cyclopentenone (*dl*-17o)——In the same manner as used for the esterification with isobutyl chloroformate, condensation of *dl*-**17o** with morpholine and 5,6-dihydrophenanthridine produced *dl*-**17s** (98%) and *dl*-**17w** (86%). Spectral data are given in Table VIII.

Protection of *dl*-4-*tert*-Butyldimethylsilyloxy-2-(6-hydroxyhexylthio)-2-cyclopentenone (*dl*-17t)——a) *tert*-Butyldimethylchlorosilane (452 mg, 3.0 mmol) and imidazole (340 mg, 5.0 mmol) were added to a stirred solution of *dl*-**17t** (688 mg, 2.0 mmol) in DMF (3 ml) at room temperature, and the mixture was stirred for 2 h. Water was added and the mixture was extracted with hexane. The separated organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo* to yield almost pure 1-*tert*-butyldimethylsilylated *dl*-**17t** (898 mg, 1.96 mmol, 98%) without further purification. IR ν_{max}^{film} cm^{-1}: 1710, 1575, 1170, 1080, 835, 780. NMR ($CDCl_3$) δ: 0.10 (12H, s), 0.90 (18H, s), 1.40 (8H, br s), 2.5—3.0 (4H, m), 3.70 (2H, t, J=7 Hz), 4.90 (1H, m), 6.77 (1H, t, J=2.5 Hz).

b) *dl*-**17o** (733 mg, 2.13 mmol) was dissolved in a mixture of acetic anhydride (1.02 g, 10 mmol) and pyridine (1.58 g, 20 mmol), and then the mixture was stirred at room temperature for 2 h. MeOH was added and the whole was concentrated *in vacuo* to give almost pure 1-acetylated *dl*-**17o** (788 mg, 2.13 mmol, quantitative yield) without further purification. IR ν_{max}^{film} cm^{-1}: 1740, 1710, 1575, 1170, 1080, 835, 780. NMR ($CDCl_3$) δ: 0.13 (6H, s), 0.90 (9H, s), 1.46 (8H, br s), 2.01 (3H, s), 2.0—3.0 (4H, m), 4.00 (2H, t, J=7 Hz), 4.90 (1H, m), 6.77 (1H, d, J=3 Hz).

TABLE VII. Physical Data for Optically Active **4**—**8**(*S*)

	$[\alpha]_D$ of **4**(*S*)				$[\alpha]_D$ of **5**(*S*)			
	(°)	Temp. (°C)	*c*	Solvent	(°)	Temp. (°C)	*c*	Solvent
a	+10.2	24	2.25	MeOH[a]	−30.6	21	1.57	CCl_4
b	+18.3	22	1.10	MeOH	−23.5	24	1.59	CCl_4
c	+12.7	25	0.59	MeOH	−43.4	22	0.62	MeOH
d	+17.0	25	1.34	MeOH	−38.6	22	0.64	MeOH
e	+10.8	25	0.53	MeOH	−26.2	22	0.55	MeOH
f	+18.3	25	1.18	MeOH	−33.5	22	0.52	MeOH
g	−2.0	21	2.55	MeOH	−51.9	21	0.55	MeOH
h	+9.8	21	2.03	MeOH	−35.4	21	0.55	MeOH

	Optical purity (% ee)		CD of **8**(*S*)			Absolute configuration
	6(*S*)	**7**(*S*)	$\Delta\varepsilon$	nm	Solvent	
a						*S*
b	95		+7.91	243	Hexane[b]	*S*
c	95	95	+8.28	233	$^cC_6H_{12}$	*S*
d		94	+8.14	232	$^cC_6H_{12}$	*S*
e		78	+6.04	231	$^cC_6H_{12}$	*S*
f		95	+6.78	231	$^cC_6H_{12}$	*S*
g	94		+11.24	243	Hexane[b]	*S*
h	93					*S*

a) Lit.[10] $[\alpha]_D$ +10.2° (*c*=2.59, MeOH). *b*) Data have been reported for the *p*-bromobenzoates of **8b**(*S*) and **8g**(*S*).[14]

(4*R*)-4-*tert*-Butyldimethylsilyloxy-2-((4*E*)-5-methoxycarbonyl-4-pentenylthio)-2-cyclopentenone (*E*-17v(*R*))——Dimethylsulfoxide (DMSO) (1.78 g, 22.8 mmol) was added to a stirred solution of oxalyl chloride (1.45 g, 11.4 mmol) in CH_2Cl_2 (24 ml) at −55 °C, and the mixture was stirred for 3 min. Next, a solution of **17u**(*R*) (2.40 g, 7.59 mmol) in CH_2Cl_2 (5 ml) was added at −55 °C, and the whole was stirred for 30 min. Triethylamine (3.8 g, 38 mmol) was added to the mixture at −55 °C, and the resulting mixture was stirred at −55 °C for 30 min, and then at 0 °C for 15 min. The reaction was quenched by the addition of saturated aq. NH_4Cl. The organic layer was taken up in CH_2Cl_2, and the solution was washed with brine, dried over ($MgSO_4$), and concentrated *in vacuo* to leave an oily residue (2.28 g), which was separated by column chromatography (hexane : ethyl acetate = 5 : 1) to give **19**(*R*) (1.88 g, 6.00 mmol, 79%; data given in Table VIII).

Trimethyl phosphonoacetate (2.18 g, 12 mmol) was added to a suspension of sodium hydride (50% in mineral oil; 300 mg, 6.0 mmol) in benzene (50 ml) at 0 °C, and the mixture was stirred for 10 min. Then a solution of **19**(*R*) (1.54 g, 4.90 mmol) in benzene (30 ml) was added and the resulting mixture was stirred at room temperature for 30 min. Saturated aq. NH_4Cl was added and the whole was extracted with ethyl acetate. The separated extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue (2.54 g), which was chromatographed on silica gel with hexane–ethyl acetate (4 : 1) to yield *E*-**17v**(*R*) (1.46 g, 3.94 mmol, 80%; data given in Table VIII).

General Procedure for the Conjugate Addition of Mixed Cuprates to Cyclopentenone-Synthon (17, 18). A Typical Example: 11,15-Bis(*tert*-butyldimethylsilyl)-7-thiaprostaglandin E_1 Methyl Ester (21a(*S*)j(*R*))——A 2.0 M pentane solution of *tert*-BuLi (12 ml, 24 mmol) was added at −78 °C to a stirred solution of (1*E*)-(3*S*)-*tert*-butyldimethylsilyloxy-1-iodo-1-octene (**5a**(*S*); 4.42 g, 12 mmol) in dry ether (20 ml), and the resulting mixture was stirred at −78 °C for 2 h. A solution of phenylthiocopper[18] (2.07 g, 12 mmol) and $(Me_2N)_3P$ (3.91 g, 24 mmol) in dry ether (10 ml) was then added at −78 °C. The whole was stirred at −78 °C for 1 h, then **17j**(*R*) (3.72 g, 10 mmol) in THF (150 ml) was added at −78 °C, and the mixture was stirred at −78 °C for 15 min, then at −40 °C for 1 h. The reaction mixture was poured into 10% aq. NH_4Cl. The organic layer was taken up in hexane, and this solution was washed with water and then brine, dried over $MgSO_4$, and concentrated *in vacuo* to leave 7.2 g of an oily residue. The residue was chromatographed on silica gel (150 g) with hexane–ethyl acetate (9 : 1) to give **21a**(*S*)**j**(*R*) (5.34 g,

TABLE VIII. Cyclopentenone-Synthons (**17**—**19**)

Compd. No.	Yield (%)	mp (°C) or $[\alpha]_D$ (*c*, MeOH)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
17i(*R*)	68		3060, 1735, 1710, 1570, 1170, 1075, 835, 780	0.15 (6H, s), 0.87 (9H, s), 1.4—1.8 (4H, m), 2.1—3.1 (6H, m), 3.67 (3H, s), 4.83—5.06 (1H, m), 6.83 (1H, d, J=3 Hz)
17j(*R*)	70	57.5—59 °C (MeOH) $[\alpha]_D^{23}$ −23.2° (0.60)	3060, 1740, 1710, 1570, 1165, 1080, 835, 770[a]	0.16 (6H, s), 0.87 (9H, s), 1.4—1.8 (6H, m), 2.1—3.1 (6H, m), 3.63 (3H, s), 4.80—5.03 (1H, m), 6.77 (1H, d, J=3 Hz)
17k(*R*)	56	55—57 °C (MeOH) $[\alpha]_D^{22}$ −19.7° (0.595)	3060, 1735, 1710, 1570, 1170, 1075, 835, 780[a]	0.15 (6H, s), 0.88 (9H, s), 1.2—1.9 (8H, m), 2.1—3.1 (6H, m), 3.66 (3H, s), 4.83—5.06 (1H, m), 6.82 (1H, d, J=3 Hz)
dl-**17l**	67		3060, 1735, 1720, 1575, 1170, 1075, 835, 780	0.11 (6H, s), 0.87 (9H, s), 1.11 (3H, d, J=7 Hz), 1.25—1.8 (6H, m), 2.3—3.0 (5H, m), 3.61 (3H, s), 4.75—5.00 (1H, m), 6.72 (1H, d, J=2.5 Hz)
dl-**17m**	64		3060, 1735, 1720, 1570, 1170, 1075, 835, 780	0.11 (6H, s), 0.90 (9H, s), 1.14 (6H, s), 1.3—2.0 (6H, m), 2.2—3.1 (4H, m), 3.65 (3H, s), 4.92 (1H, m), 6.79 (1H, d, J=2.5 Hz)
dl-**17n**	63		1775, 1720, 1575, 1180, 1090, 835 780	0.13 (6H, s), 0.88 (9H, s), 1.4—2.2 (6H, m), 2.3—3.1 (4H, m), 3.83 (3H, s), 4.90 (1H, m), 6.79 (1H, d, J=2.5 Hz)
dl-**17o**	67		3100, 1715, 1575, 1080, 835, 780	0.13 (6H, s), 0.90 (9H, s), 1.45—1.85 (6H, m), 2.1—3.1 (6H, m), 4.8—5.05 (1H, m), 6.78 (1H, d, J=3 Hz), 8.50 (1H, br)
dl-**18o**	33		3100; 1715, 1575, 1025	1.3—1.9 (12H, m), 2.15—3.1 (6H, m), 3.3—4.1 (2H, m), 4.65—5.05 (2H, m), 6.97 (1H, t, J=2.5 Hz), 10.33 (1H, br s)
dl-**18p**	76		1735, 1720, 1575, 1030	0.87 (3H, m), 1.24 and 1.61 (28H, m), 2.1—2.9 (6H, m), 3.35—4.20 (4H, m), 4.50—5.10 (2H, m), 7.02 (1H, t, J=3 Hz)
dl-**18q**	51		3080, 3040, 1735, 1720, 1575, 1030	1.3—1.9 (12H, m), 2.1—3.0 (6H, m), 3.3—4.1 (2H, m), 4.6—5.0 (2H, m), 5.09 (2H, s), 6.93 (1H, t, J=2.5 Hz), 7.32 (5H, br s)
dl-**18r**	77		3080, 1760, 1720, 1595, 1575, 1110, 1030	1.3—2.1 (12H, m), 2.5—3.1 (6H, m), 3.3—4.2 (2H, m), 4.7—5.1 (2H, m), 7.0—7.6 (6H, m)
dl-**17s**	98		3080, 1720, 1645, 1575, 1080, 835, 780	0.13 (6H, s), 0.88 (9H, s), 1.4—1.8 (6H, m), 2.0—3.0 (6H, m), 3.3—3.7 (8H, m), 4.77—5.00 (1H, m), 6.76 (1H, d, J=3 Hz)
dl-**17t**	36		3460, 1710, 1575, 1170, 1080, 835, 780	0.13 (6H, s), 0.90 (9H, s), 1.40 (8H, br s), 2.5—3.0 (5H, m), 3.60 (2H, t), 4.90 (1H, m), 6.77 (1H, d, J=2.5 Hz)
17u(*R*)	81	$[\alpha]_D^{20}$ −25.0° (1.03)	3440, 1715, 1570, 1080, 830, 775	0.13 (6H, s), 0.89 (9H, s), 1.6—2.2 (5H, m), 2.1—3.1 (4H, m), 3.69 (3H, s), 4.9—5.1 (1H, m), 6.90 (1H, d, J=3 Hz)
19(*R*)	79	$[\alpha]_D^{19}$ −26.6° (1.15)	3060, 2720, 1715, 1570, 1080, 830, 770	0.11 (6H, s), 0.89 (9H, s), 1.8—2.2 (2H, m), 2.4—3.1 (6H, m), 4.85—5.1 (1H, m), 6.97 (1H, d, J=3 Hz), 9.96 (1H, br s)
E-**17v**(*R*)	80	$[\alpha]_D^{20}$ −20.9° (1.18)	3060, 1720, 1660, 1575, 1080, 830, 780	0.14 (6H, s), 0.90 (9H, s), 1.6—2.1 (2H, m), 2.1—3.1 (6H, m), 3.74 (3H, s), 4.87—5.10 (1H, m), 5.89 (1H, dt, J=15 and 2 Hz), 6.87 (1H, d, J=3 Hz), 7.00 (1H, dt, J=15 and 6.5 Hz)
dl-**17w**	86		3080, 1720, 1660, 1600, 1260, 1180, 1080, 945, 910, 835, 780, 740	0.12 (6H, s), 0.88 (9H, s), 1.2—1.8 (6H, m), 2.3—3.0 (6H, m), 4.75—5.00 (3H, br s), 6.72 (1H, d, J=2.5 Hz), 7.2—7.4 and 7.6—7.9 (6H and 2H, m)

a) KBr.

8.7 mmol, 87%). The physical and spectral data for **21a**(*S*)**j**(*R*) are given in Table X.

Similarly, **21b**—**h**(*S*)**j**(*R*), **21b**(*S*)**i**, **k**(*R*), and **21b**, **h**(*S*), **v**(*R*) were prepared from the corresponding **17i**—**k**, **v**(*R*). Diastereomeric **21b**(*S*)**l**—**n**, **s**(*RS*) and **22b**(*S*)**p**—**r**(*RS*) were similarly prepared from *dl*-**17l**—**n**, **s** and *dl*-**18p**—**r**, respectively. Yields and physical and spectral data for these compounds are listed in Table IX.

1-*tert*-Butyldimethylsilylated and 1-acetylated **21b**(*S*)**t**(*RS*) were similarly prepared (58% and 63%, respectively) from the corresponding 1-protected *dl*-**17t**. 1-*tert*-Butyldimethylsilylated **21b**(*S*)**t**(*RS*); IR ν_{max}^{film} cm^{-1}: 1735, 840, 780. NMR ($CDCl_3$) δ: 0.09 (18H, s), 0.90 (27H, m), 1.0—2.0 (19H, m), 2.1—2.9 (6H, m), 3.4—3.8 (4H, m), 5.65 (2H, m). 1-Acetylated **21b**(*S*)**t**(*RS*); IR ν_{max}^{film} cm^{-1}: 1740, 1240, 840, 780. NMR ($CDCl_3$) δ: 0.88 (18H, s), 1.0—2.0 (17H, m), 2.03 (3H, s), 2.2—2.9 (6H, m), 4.05 (2H, t, J=7 Hz), 3.7—4.2 (2H, m), 5.58 (2H, m).

Deprotection of the Conjugate Adducts (21, 22). Method A. An Example: 7-Thiaprostaglandin E_1 Methyl Ester (23a(*S*)j(*R*))——A stirred solution of the bis-silyl ether (**21a**(*S*)**j**(*R*); 3.07 g, 5.0 mmol) in CH_3CN (100 ml) was treated with 47% aq. HF (10 ml) at room temperature. The mixture was stirred at room temperature for 2 h, neutralized with saturated $NaHCO_3$, and extracted twice with ethyl acetate. The combined extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvents *in vacuo* left an oily residue. Purification by silica gel (100 g) column chromatography using hexane–ethyl acetate (2 : 3) for elution gave an equilibrium mixture (1.58 g, 4.1 mmol, 82%) of **23a**(*S*)**j**(*R*) and its 8-epimer, which were identical with the set of more polar diastereomers obtained by the same reaction with *dl*-**17j** as described before. The physical and spectral data are given in Table X.

The other products obtained by method A were prepared in the same manner. Desilylation of **21b**(*S*)**l**—**n**, **s**, **t**(*RS*) afforded diastereomeric mixtures of **23b**(*S*)**l**—**n**, **s**, **t**(*R*) and **23b**(*S*)**l**—**n**, **s**, **t**(*S*), which were separable into their components by usual chromatography. Yields and the physical and spectral data are also listed in Table X.

Acetylated **23b**(*S*)**t**(*R*) and its 15-*epi-ent* **23b**(*S*)**t**(*S*) were also deprotected and separated in a similar manner in 21% and 26% yields, respectively. 1-Acetylated **23b**(*S*)**t**(*R*); IR ν_{max}^{film} cm^{-1}: 3420, 1740, 970, 890. NMR ($CDCl_3$) δ: 0.8—2.0 (19H, m), 2.03 (3H, s), 2.1—3.0 (6H, m), 3.4 (2H, m), 4.02 (2H, t, J=7 Hz), 5.60 (2H, m). MS *m/e*: 412 (M^+), 394, 376, 83 (100). High-resolution MS for $C_{22}H_{34}O_4S$ (dehydration peak from molecular ion): Calcd *m/e*: 394.2180; Found: 394.2171. 1-Acetylated **23b**(*S*)**t**(*S*); IR ν_{max}^{film} cm^{-1}: 3400, 1740, 970, 890. NMR ($CDCl_3$) δ: 0.8—2.0 (19H, m), 2.02 (3H, s), 2.2—3.1 (8H, m), 4.05 (2H, t, J=7 Hz), 5.68 (2H, m). MS *m/e*: 412 (M^+), 394, 376, 83 (100). High-resolution MS for $C_{22}H_{34}O_4S$ (dehydration peak from molecular ion): Calcd *m/e*: 394.2180; Found: 394.2221.

Method B. An Example: 17(*R*),20-Dimethyl-7-thiaprostaglandin E_1 Methyl Ester (23g(*S*)j(*R*))——Pyridine (5 ml) and then hydrogenfluoride–pyridine (10 ml) were added to a stirred solution of the bis-silyl ether (**21g**(*S*)**j**(*R*); 3.21 g, 5.0 mmol) in CH_3CN (100 ml) at room temperature, and the resulting mixture was stirred for 2 h. Work-up and purification by column chromatography as in method A yielded an equilibrium mixture (1.90 g, 4.6 mmol, 92%) of **23g**(*S*)**j**(*R*) and its 8-epimer. The physical and spectral data are indicated in Table X.

Method C. An Example: 15-Cyclohexyl-ω-pentanor-7-thiaprostaglandin E_1 Decyl Ester (23b(*S*)p(*R*)) and its 15-*epi* Enantiomer (23b(*S*)p(*S*))——The protected ester (**22b**(*S*)**p**(*RS*); 1.29 g, 1.79 mmol) was dissolved in a mixture of AcOH (30 ml), water (10 ml), and THF (10 ml). After being stirred at room temperature for 48 h, the mixture was diluted with ethyl acetate, and neutralized with saturated aq. $NaHCO_3$. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to leave a crude product, which was chromatographed on silica gel (50 g) with hexane–ethyl acetate (1 : 1) to give more polar **23b**(*S*)**p**(*R*) (290 mg, 0.55 mmol, 31%) and the less polar 15-*epi* enantiomer (**23b**(*S*)**p**(*S*); 330 mg, 0.63 mmol, 35%).

The other compounds obtained by method C were similarly prepared and separated. Yields and the physical and spectral data for these compounds are listed in Table X.

Oxidation of 15-Cyclohexyl-ω-pentanor-7-thiaprostaglandin E_1 Methyl Ester (23b(*S*)j(*R*)) with Sodium Periodate——A solution of sodium periodate (400 mg, 1.9 mmol) in water (3.5 ml) was added at room temperature to a solution of **23b**(*S*)**j**(*R*) (211 mg, 0.53 mmol) in methanol (15 ml). After being stirred for 2 h, the mixture was diluted with ethyl acetate, then washed with brine. The separated organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was chromatographed on a silica gel (20 g) column with ethyl acetate–methanol (29 : 1) as an eluent to yield the sulfoxide **24** (147 mg, 0.355 mmol, 67%). The spectral data are listed in Table X.

Hydrogenation of 23b(*S*)j(*R*)——PtO_2 (9 mg) was added to a solution of **23b**(*S*)**j**(*R*) (47 mg, 0.118 mmol) in MeOH (3 ml), and the mixture was stirred at room temperature for 3 d under a hydrogen atmosphere. The catalyst was filtered off and washed with ethyl acetate, then the filtrate and washings were concentrated *in vacuo* to give an oily residue, which was separated by preparative TLC (ether : ethyl acetate = 1 : 3) to yield **25** (32 mg, 0.080 mmol, 68%). The spectral data for **25** are given in Table X.

General Procedure for the Hydrolysis of Methyl Esters (23a—c, g, h(*S*)j(*R*) and 23b(*S*)v(*R*)) with Porcine Liver Esterase. A Typical Example: 7-Thiaprostaglandin E_1 (23a(*S*)o(*R*))——A solution of **23a**(*S*)**j**(*R*) (133 mg, 0.345 mmol) in acetone (1.25 ml) and then porcine liver esterase (0.5 ml) were added to a phosphate buffer solution (12.5 ml, pH 8). After being stirred at room temperature for 18 h, the mixture was acidified to pH 5 with 0.1 N HCl, saturated with $(NH_4)_2SO_4$, and extracted with ethyl acetate. The separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated to leave a crude product. Separation by silica gel column chromatography (20 g, hexane: ethyl acetate : acetic acid = 20 : 80 : 1) gave **23a**(*S*)**o**(*R*) (117 mg, 0.315 mmol, 91%).

The other acids were obtained in a similar manner. Reaction conditions, yields, and spectral data are listed in

TABLE IX. 11,15-Protected 7-Thiaprostaglandin E_1 Derivatives (**21**, **22**)

Compd. No.	Yield (%)	$[\alpha]_D$ (MeOH) (°C, *c*)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
21b(*S*)**i**(*R*)	61		1745, 1250, 1110, 835, 775	0.05 (12H, s), 0.89 (18H, s), 0.9—1.9 (15H, m), 2.1—3.1 (8H, m), 3.63 (3H, s), 3.6—4.3 (2H, m), 5.4—5.65 (2H, m)
21a(*S*)**j**(*R*)	87	−27.5° (21, 1.00)	1740, 1260, 1120, 965, 835, 775	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), 3.8—4.1 (2H, m), 5.43—5.65 (2H, m)
21b(*S*)**j**(*R*)	85	−13.6° (21, 0.93)	1740, 1255, 1110, 840, 780	0.06 (12H, s), 0.84 (18H, s), 1.0—1.9 (17H, m), 2.1—3.0 (8H, m), 3.56 (3H, s), 3.75 (2H, m), 5.3—5.6 (2H, m)
21c(*S*)**j**(*R*)	86	−17.3° (20, 1.65)	1745, 1255, 1115, 840, 775	0.06 (12H, s), 0.88 (18H, s), 1.3—1.8 (15H, m), 2.1—3.2 (8H, m), 3.71 (3H, s), 3.8—4.5 (2H, m), 5.6—5.75 (2H, m)
21d(*S*)**j**(*R*)	88		1740, 1255, 1110, 840, 775	0.06 (12H, s), 0.86 (18H, s), 1.0—1.9 (19H, m), 2.1—3.0 (8H, m), 3.63 (3H, s), 3.8—4.3 (2H, m), 5.43—5.67 (2H, m)
21e(*S*)**j**(*R*)	58		1740, 1255, 1110, 885, 835	0.06 (12H, s), 0.89 (18H, s), 1.16 (3H, t, J=8 Hz), 1.4—1.9 (8H, m), 2.1—3.0 (8H, m), 3.2—3.6 (4H, m), 3.63 (3H, s), 4.0—4.5 (2H, m), 5.47—5.70 (2H, m)
21f(*S*)**j**(*R*)	69		1745, 1255, 1110, 835, 775	0.06 (12H, s), 0.90 (27H, s), 1.1—1.9 (14H, m), 2.1—2.8 (8H, m), 3.63 (3H, s), 4.0—4.5 (2H, m), 5.53—5.73 (2H, m)
21g(*S*)**j**(*R*)	91		1745, 1260, 1110, 835, 775	0.07 (12H, s), 0.85 (18H, s), 0.9 (6H, m), 1.0—1.8 (15H, m), 2.1—3.0 (8H, m), 3.65 (3H, s), 4.0—4.4 (2H, m), 5.6 (2H, m)
21h(*S*)**j**(*R*)	84		1745, 1260, 1110, 835, 775	0.07 (12H, s), 0.85 (18H, s), 0.9 (6H, m), 1.0—1.8 (15H, m), 2.2—3.0 (8H, m), 3.65 (3H, s), 4.0—4.4 (2H, m), 5.6 (2H, m)
21b(*S*)**k**(*R*)	91		1745, 1255, 1110, 835, 775	0.07 (12H, s), 0.88 (18H, s), 0.8—2.0 (19H, m), 2.0—3.1 (8H, m), 3.67 (3H, s), 3.75—4.10 (2H, m), 5.5—5.7 (2H, m)
21b(*S*)**l**(*RS*)	56		1740, 1260, 1110, 1070, 970, 840, 780	0.08 (12H, s), 0.87 (18H, s), 1.0—1.9 (17H, m), 1.12 (3H, d, J=7 Hz), 2.2—3.3 (7H, m), 3.61 (3H, s), 3.7—4.1 (2H, m), 5.5—5.8 (2H, m)

TABLE IX. (continued)

Compd. No.	Yield (%)	$[\alpha]_D$ (MeOH) (°C, *c*)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
21b(*S*)**m**(*RS*)	99		1735, 1255, 1110, 1065, 835, 775	0.06 (12H, s), 0.86 (18H, s), 1.0—1.9 (17H, m), 1.13 (6H, s), 2.3—3.1 (6H, m), 3.60 (3H, s), 3.7—4.3 (2H, m), 5.4—5.6 (2H, m)
21b(*S*)**n**(*RS*)	20[a]			
21b(*S*)**v**(*R*)	90	−12.5° (20, 2.30)	1727, 1655, 1260, 1110, 840, 780	0.05 (12H, s), 0.87 (18H, s), 0.8—2.0 (13H, m), 2.0—3.1 (8H, m), 3.64 (3H, s), 3.6—4.3 (2H, m), 5.4—5.7 (2H, m), 5.80 (1H, d, J=16 Hz), 6.85 (1H, dt, J=16 and 6 Hz)
21h(*S*)**v**(*R*)	73		1730, 1660, 1260, 1110, 840, 780	0.09 (12H, s), 0.7—0.9 (6H, m), 0.90 (18H, s), 1.0—1.9 (13H, m), 2.00—2.85 (6H, m), 3.65 (3H, s), 3.95—4.30 (2H, m), 5.50 (2H, m), 5.80 (1H, d, J=15 Hz), 6.90 (1H, dt, J=15 and 6 Hz)
22b(*S*)**p**(*RS*)	68		1740, 1260, 1180, 1080, 975, 840, 780	0.04 (6H, s), 0.84 (12H, s+t), 1.1—1.8 (39H, m), 2.1—2.5 (8H, m), 3.3—4.2 (6H, m), 4.61 (1H, m), 5.47—5.67 (2H, m)
22b(*S*)**q**(*RS*)	77		3050, 1740, 1260, 1130, 1080, 1040, 975, 840, 780, 750, 700	0.04 (6H, s), 0.84 (9H, s), 0.9—1.9 (23H, m), 2.1—3.1 (8H, s), 3.2—4.3 (4H, m), 4.64 (1H, m), 5.07 (2H, s), 5.4—5.7 (2H, m), 7.31 (5H, s)
22b(*S*)**r**(*RS*)	48		1760, 1595, 1500, 1255, 1200, 1125, 1075, 1035, 970, 840, 775, 690	0.03 (6H, s), 0.88 (9H, s), 1.1—1.9 (23H, m), 2.25—3.05 (8H, m), 3.2—4.3 (4H, m), 4.55—4.75 (1H, m), 5.5—5.7 (2H, m), 6.7—7.6 (5H, m)
21b(*S*)**s**(*RS*)	45		1740, 1650, 1255, 1120, 970, 840, 775	0.07 (12H, s), 0.88 (18H, s), 0.9—1.9 (17H, m), 2.1—2.8 (8H, m), 3.3—4.2 (10H, m), 5.4—5.65 (2H, m)
21b(*S*)**w**(*RS*)	80		3090, 3050, 1740, 1660, 1605, 1255, 1190, 1110, 835, 775, 740	0.07 (12H, s), 0.89 (18H, s), 1.1—1.9 (17H, m), 2.3—2.8 (8H, m), 3.7—4.2 (2H, m), 4.9 (2H, br s), 5.4—5.7 (2H, m), 7.2—7.5 and 7.6—7.9 (6H and 2H, m)
21b(*S*)**o**(*RS*)	85		1745, 1715, 1260, 1115, 840, 780	0.04 (12H, s), 0.83 (18H, s), 0.9—1.9 (17H, m), 2.1—3.5 (8H, m), 3.6—4.4 (2H, m), 5.3—5.6 (2H, m), 9.50 (1H, br)
21b(*S*)**x**(*RS*)	78		3370, 3220, 1750, 1670, 1260, 1115, 840, 780	0.06 (12H, s), 0.86 (18H, s), 0.9—1.9 (17H, m), 2.0—3.2 (8H, m), 3.7—4.4 (2H, m), 5.55—5.80 (2H, m), 6.08 and 6.40 (1H×2, br s×2)

a) This compound was too unstable to isolate in pure form.

TABLE X. 7-Thiaprostaglandin E_1 Derivatives (**23**)

Compd. No.	Method	Yield (%)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)	MS (*m/e*)	High-resolution MS Calcd (Formula) (Found)	Others
23b(*S*)**i**(*R*)	A	71	3450, 1740, 1200, 1170, 1125, 1055, 1000, 980[a]	0.8—2.0 (15H, m), 2.2—3.2 (10H, m), 3.69 (3H, s), 3.7—4.2 (2H, m), 5.6—5.8 (2H, m)	384 (M^+), 366 348, 202 (100)	384.1968 ($C_{20}H_{32}O_5S$) (384.1921 (M^+))	$[\alpha]_D^{21}$ −24.4° (*c*=0.64, MeOH) mp 72—73 °C (Ether)
23a(*S*)**j**(*R*)	A	82	3400, 1735, 1255, 1200, 1165, 1125, 1075, 1010, 960	0.89 (3H, m), 1.1—1.8 (14H, m), 2.1—3.1 (10H, m), 3.61 (3H, s), 3.90—4.25 (2H, m), 5.5—5.75 (2H, m)	386 (M^+), 368, 350, 99 (100)	386.2125 ($C_{20}H_{34}O_5S$) (386.2142 (M^+))	$[\alpha]_D^{21}$ −26.9° (*c*=0.36, MeOH)
23b(*S*)**j**(*R*)	A	76	3410, 1735, 1260, 1200, 1170, 1080, 1000, 970[a]	0.9—1.9 (17H, m), 2.1—3.4 (10H, m), 3.61 (3H, s), 3.7—4.5 (2H, m), 5.47—5.73 (2H, m)	398 (M^+), 380, 362, 237 (100)	398.2125 ($C_{21}H_{34}O_5S$) (398.2143 (M^+))	$[\alpha]_D^{21}$ −19.5° (*c*=2.44, MeOH) mp 73—74 °C (Ether)
23c(*S*)**j**(*R*)	A	72	3430, 3050, 1740, 1200, 1170, 1080, 965	1.2—1.9 (15H, m), 2.2—3.2 (10H, m), 3.70 (3H, s), 3.8—4.5 (2H, m), 5.60—5.85 (2H, m)	384 (M^+), 366, 348, 97 (100)	384.1968 ($C_{20}H_{32}O_5S$) (384.1930 (M^+))	$[\alpha]_D^{20}$ −25.0° (*c*=1.03, MeOH)
23d(*S*)**j**(*R*)	A	75	3400, 1740, 1260, 1200, 1175, 1080, 970	0.8—1.85 (19H, m), 2.1—3.1 (8H, m), 3.2—3.6 (2H, m), 3.63 (3H, s), 3.8—4.5 (2H, m), 5.50—5.80 (2H, m)	412 (M^+), 394, 376, 125 (100)	412.2281 ($C_{22}H_{36}O_5S$) (412.2256 (M^+))	
23e(*S*)**j**(*R*)	A	83	3420, 1740, 1260, 1205, 1170, 1100, 970	1.17 (3H, t, *J*=7 Hz), 1.3—1.9 (8H, m), 2.1—3.1 (10H, m), 3.25—3.67 (4H, m), 3.60 (3H, s), 3.8—4.5 (2H, m), 5.53—5.77 (2H, m)	388 (M^+), 370, 352, 59 (100)	370.1814 ($C_{19}H_{30}O_5S$) (370.1820 ($M-H_2O$))	
23f(*S*)**j**(*R*)	A	65	3400, 1740, 1260, 1200, 1175, 1080, 970	0.90 (9H, s), 1.1—1.7 (14H, m), 2.1—3.1 (10H, m), 3.67 (3H, s), 3.8—4.5 (2H, m), 5.55—5.85 (2H, m)	428 (M^+), 410, 382, 57 (100)	428.2597 ($C_{23}H_{40}O_5S$) (428.2610 (M^+))	
23g(*S*)**j**(*R*)	B	92	3400, 1740, 1260, 1200, 1170, 1080, 965	0.8—1.0 (6H, m), 1.0—2.1 (15H, m), 2.1—2.9 (8H, m), 3.63 (3H, s), 4.0—4.3 (2H, m), 5.65 (2H, m)	414 (M^+), 396, 378, 237 (100)	414.2437 ($C_{22}H_{38}O_5S$) (414.2414 (M^+))	$[\alpha]_D^{20}$ −29.3° (*c*=1.00, MeOH)

23h(*S*)**j**(*R*)	A	80	3400, 1740, 1260, 1200, 1170, 1080, 965	0.9 (6H, m), 1.0—2.1 (15H, m), 2.1—3.0 (8H, m), 3.65 (3H, s), 4.0—4.4 (2H, m), 5.65 (2H, m)	414 (M^+), 396, 378, 237 (100)	414.2437 ($C_{22}H_{38}O_5S$) (414.2433 (M^+))	
23b(*S*)**k**(*R*)	A	82	3420, 1740, 1250, 1200, 1080, 1000, 965, 735	0.7—2.0 (19H, m), 2.15—3.15 (10H, m), 3.58 (3H, s), 3.7—4.6 (2H, m), 5.55—5.85 (2H, m)	412 (M^+), 394, 376, 83 (100)	412.2282 ($C_{22}H_{36}O_5S$) (412.2297 (M^+))	$[\alpha]_D^{22}$ −22.2° (c=0.63, MeOH)
23b(*S*)**l**(*R*)	A	35[c]	3400, 1740, 1245, 1200, 1160, 1080, 970, 895, 740	1.15 (3H, d, J=7 Hz), 1.3—2.2 (17H, m), 2.4—3.2 (9H, m), 3.67 (3H, s), 3.8—4.2 (2H, m), 5.5—5.8 (2H, m)	412 (M^+), 394, 376, 83 (100)	394.2180 ($C_{22}H_{34}O_4S$) (394.2239 ($M-H_2O$))	
23b(*S*)**l**(*S*)	A	40[c]	3400, 1740, 1245, 1205, 1160, 1080, 975, 740	1.12 (3H, d, J=7 Hz), 1.3—1.8 (17H, m), 2.2—3.2 (9H, m), 3.63 (3H, s), 3.7—4.3 (2H, m), 5.6—5.8 (2H, m)	412 (M^+), 394, 376, 83 (100)	394.2180 ($C_{22}H_{34}O_4S$) (394.2089 ($M-H_2O$))	
23b(*S*)**m**(*R*)	A	38[c]	3420, 1730, 1240, 1195, 1150, 1080, 1000, 970, 890, 735	1.11 (6H, s), 1.2—1.8 (17H, m), 2.3—3.2 (8H, m), 3.62 (3H, s), 3.7—4.2 (2H, m), 5.47—5.73 (2H, m)	426 (M^+), 408, 390, 202 (100)	426.2444 ($C_{23}H_{38}O_5S$) (426.2453 (M^+))	
23b(*S*)**m**(*S*)	A	40[c]	3450, 1730, 1240, 1200, 1145, 1080, 975, 890, 735	1.12 (6H, s), 1.1—1.8 (17H, m), 2.3—3.1 (8H, m), 3.63 (3H, s), 3.7—4.3 (2H, m), 5.6—5.77 (2H, m)	426 (M^+), 408, 390, 97 (100)	408.2337 ($C_{23}H_{36}O_4S$) (408.2301 ($M-H_2O$))	
23b(*S*)**n**(*R*)[b]	A	24[c]	3500, 1765, 1740, 1200, 1165, 1095, 1020, 970	0.9—2.3 (17H, m), 2.3—3.0 (6H, m), 3.80 (3H, s), 3.8—4.2 (2H, m), 5.60 (2H, m)	434 (M^+), 416, 398, 202 (100)		
23b(*S*)**n**(*S*)[b]	A	26[c]	3400, 1760, 1200, 970	0.9—2.3 (17H, m), 2.3—2.9 (6H, m), 3.80 (3H, s), 3.8—4.2 (2H, m), 5.65 (2H, m)			
23b(*S*)**v**(*R*)	A	89	3400, 1740, 1725, 1660, 1270, 1200, 1080, 975, 910, 730[a]	0.8—2.0 (13H, m), 2.0—3.1 (10H, m), 3.71 (3H, s), 3.6—4.3 (2H, m), 5.4—5.8 (2H, m), 5.82 (1H, d, J=10 Hz), 6.87 (1H, dt, J=16 and 6.5 Hz)	396 (M^+), 378, 360, 83 (100)	396.1970 ($C_{21}H_{32}O_5S$) (396.1961 (M^+))	$[\alpha]_D^{20}$ −23.8° (c=0.67, MeOH) mp 84—85 °C (Ether)

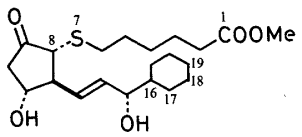
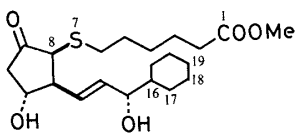
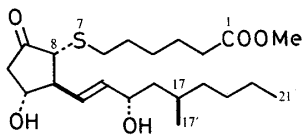
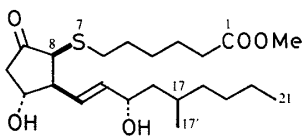
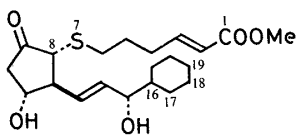
TABLE X. (continued)

Compd. No.	Method	Yield (%)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)	MS (*m/e*)	High-resolution MS Calcd (Formula) (Found)	Others
23h(*S*)**v**(*R*)	A	63	3450, 1740, 1720, 1660, 1270, 1200, 1080, 970	0.8—1.0 (6H, m), 1.0—2.8 (13H, m), 2.1—2.9 (6H, m), 3.65 (3H, s), 4.0—4.3 (2H, m), 5.65 (2H, m), 5.85 (1H, d, J=15 Hz), 6.95 (1H, dt, J=15 and 6 Hz)	412 (M^+), 394, 376	412.2282 ($C_{22}H_{36}O_5S$) (412.2289 (M^+))	
23b(*S*)**p**(*R*)	C	31[c]	3420, 1740, 1265, 1180, 1080, 1005, 975, 895, 740	0.86 (3H, m), 1.1—1.9 (33H, m), 2.1—3.4 (10H, m), 3.7—4.2 (4H, m), 5.45—5.75 (2H, m)	506 ($M-H_2O$), 488, 395, 237 (100)	506.3434 ($C_{30}H_{50}O_4S$) (506.3520 ($M-H_2O$))	
23b(*S*)**p**(*S*)	C	35[c]	3440, 1740, 1260, 1180, 1080, 1000, 975, 890, 735	0.87 (3H, m), 1.1—1.8 (33H, m), 2.0—3.1 (10H, m), 3.7—4.2 (4H, m), 5.55—5.75 (2H, m)	506 ($M-H_2O$), 488, 395, 237 (100)	506.3434 ($C_{30}H_{50}O_4S$) (506.3344 ($M-H_2O$))	
23b(*S*)**q**(*R*)	C	26[c]	3420, 3080, 1740, 1265, 1170, 1080, 1000, 970, 910, 735, 700	0.8—1.9 (17H, m), 2.2—3.1 (10H, m), 3.7—4.0 (2H, m), 5.06 (2H, s), 5.47—5.73 (2H, m), 7.29 (5H, s)	474 (M^+), 456, 438, 91 (100)	456.2473 ($C_{27}H_{36}O_4S$) (456.2473 ($M-H_2O$))	
23b(*S*)**q**(*S*)	C	31[c]	3430, 3080, 1740, 1275, 1180, 1080, 980, 920, 740, 705	0.8—1.9 (17H, m), 2.1—3.1 (10H, m), 3.6—4.0 (2H, m), 5.07 (2H, s), 5.53—5.73 (2H, m), 7.27 (5H, s)	474 (M^+), 456, 438, 91 (100)	474.2455 ($C_{27}H_{38}O_5S$) (474.2524 (M^+))	
23b(*S*)**r**(*R*)	C	21[c]	3400, 3080, 1755, 1595, 1500, 1200, 1165, 1125, 970, 745, 690	0.9—2.0 (17H, m), 2.3—3.5 (10H, m), 3.6—4.4 (2H, m), 5.5—5.8 (2H, m), 6.9—7.6 (5H, m)	460 (M^+), 442 424, 219 (100)	442.2181 ($C_{26}H_{34}O_4S$) (442.2216 ($M-H_2O$))	
23b(*S*)**r**(*S*)	C	26[c]	3430, 3080, 1755, 1595, 1500, 1200, 1165, 1125, 970, 735, 690	0.9—1.9 (17H, m), 2.3—3.3 (10H, m), 3.7—4.2 (2H, m), 5.6—5.8 (2H, m), 6.9—7.4 (5H, m)	460 (M^+), 442, 424, 284 (100)	442.2181 ($C_{26}H_{34}O_4S$) (442.2174 ($M-H_2O$))	

23b(*S*)**s**(*R*)	A	27[c]	3420, 1740, 1630, 1275, 1240, 1120, 1035, 970, 845	0.8—1.9 (17H, m), 2.1—3.2 (10H, m), 3.2—4.4 (10H, m), 5.5—5.75 (2H, m)	435 ($M-H_2O$), 417, 324, 216 (100)	435.2445 ($C_{24}H_{37}NO_4S$) (435.2448 ($M-H_2O$))
23b(*S*)**s**(*S*)	A	22[c]	3430, 1745, 1630, 1275, 1235, 1120, 1035, 970, 845	0.8—1.9 (17H, m), 2.1—3.2 (10H, m), 3.3—4.3 (10H, m), 5.55—5.75 (2H, m)	435 ($M-H_2O$), 417, 324, 216 (100)	435.2445 ($C_{24}H_{37}NO_4S$) (435.2448 ($M-H_2O$))
23b(*S*)**t**(*R*)	A	19[c]	3400, 1740, 1175, 970, 890	1.0—2.1 (19H, m), 2.3—2.95 (6H, m), 3.5—3.8 (4H, m), 5.65 (2H, m)	370 (M^+), 352, 334	352.2072 ($C_{20}H_{32}O_3S$) (352.2079 ($M-H_2O$))
23b(*S*)**t**(*S*)	A	21[c]	3420, 1740, 1180, 970, 890	1.0—2.0 (19H, m), 2.0—3.0 (6H, m), 3.4—3.8 (4H, m), 5.70 (2H, m)	370 (M^+), 352, 334	352.2072 ($C_{20}H_{32}O_3S$) (352.2063 ($M-H_2O$))
23b(*S*)**w**(*R*)	A	32[c,d]	3430, 3090, 3050, 1740, 1640, 1610 1250, 1195	0.8—1.9 (17H, m), 2.2—3.6 (10H, m), 3.6—4.5 (2H, m), 4.89 (2H, br s), 5.45—5.75 (2H, m), 7.1—7.5 and 7.6—7.9 (6H and 2H, m)	547 (M^+), 529, 511	529.2650 ($C_{33}H_{39}NO_3S$) (529.2659 ($M-H_2O$))
23b(*S*)**o**(*R*)	A	39[c]	3400, 2660, 1740, 1710, 1260, 1080, 970	0.8—1.9 (17H, m), 2.1—3.3 (8H, m), 3.5—4.3 (2H, m), 3.83 (3H, br s), 5.5—5.75 (2H, m)		
23b(*S*)**x**(*R*)	A	35[c]	3400, 1745, 1670, 1090, 970	0.8—1.9 (17H, m), 1.9—3.1 (8H, m), 3.5—4.3 (2H, m), 5.4—5.9 (6H, m)		
24		67	3400, 3060, 1740, 1245, 1045, 1020, 735, 700	0.8—2.0 (17H, m), 2.2—2.8 (7H, m), 3.0 (2H, m), 3.33 (1H, m), 3.69 (3H, s), 3.85 (1H, m), 4.17 (1H, m), 5.60—5.85 (2H, m)	396 ($M-H_2O$), 380, 111 (100)	396.1968 ($C_{21}H_{32}O_5S$) (396.1949 ($M-H_2O$))
25		68	3400, 1740, 1080, 910	0.9—1.9 (22H, m), 2.1—2.9 (9H, m), 3.2—3.5 (1H, m), 3.66 (3H, s), 3.9—4.4 (1H, m)	400 (M^+), 382, 364, 96 (100)	382.2178 ($C_{21}H_{34}O_4S$) (382.2206 ($M-H_2O$))

a) KBr. *b*) These compounds had a tendency to decompose. *c*) Based on the starting racemic substrate. *d*) The other diastereomer (**23b**(*S*)**w**(*S*)) was obtained in 34% yield after separation.

TABLE XI. ^{13}C-NMR Spectral Data for **23b**(*S*)**j**(*R*), **23g**(*S*)**j**(*R*) and Their 8-Epimers

Carbon No.	 **23b**(*S*)**j**(*R*)	 8-*epi* **23b**(*S*)**j**(*R*)	 **23g**(*S*)**j**(*R*)	 8-*epi* **23g**(*S*)**j**(*R*)	 **23b**(*S*)**v**(*R*)
COOMe	51.5 (q)	51.5 (q)	51.5 (q)	51.5 (q)	51.5 (q)
C-1	174.1 (s)	174.1 (s)	174.0 (s)	174.0 (s)	167.0 (s)
C-2	33.8 (t)	33.8 (t)	33.8 (t)	33.8 (t)	121.6 (d)
C-3	24.5 (t)	24.5 (t)	24.4 (t)	24.4 (t)	148.1 (d)
C-4	28.9 (t)	28.9 (t)	29.0 (t)	29.0 (t)	30.9 (t)
C-5	28.2 (t)	28.2 (t)	28.2 (t)	28.2 (t)	27.6 (t)
C-6	31.1 (t)	30.5 (t)	31.0 (t)	30.5 (t)	30.6 (t)
C-8	55.2 (d)	53.0 (d)	54.9 (d)	53.0 (d)	55.3 (d)
C-9	210.3 (s)	207.2 (s)	210.6 (s)	207.1 (s)	210.5 (s)
C-10	45.2 (t)	43.5 (t)	45.3 (t)	43.6 (t)	45.2 (t)
C-11	71.6 (d)	71.3 (d)	71.3 (d)	71.3 (d)	71.3 (d)
C-12	54.1 (d)	52.7 (d)	54.2 (d)	52.7 (d)	54.1 (d)
C-13	130.6 (d)	128.1 (d)	129.5 (d)	126.9 (d)	130.8 (d)
C-14	135.9 (d)	136.0 (d)	138.0 (d)	138.0 (d)	136.1 (d)
C-15	77.4 (d)	77.4 (d)	70.8 (d)	70.8 (d)	77.5 (d)
C-16	43.6 (d)	43.6 (d)	44.6 (t)	44.6 (t)	43.5 (d)
C-17	28.7 (t)	28.7 (t)	29.0 (d)	29.0 (d)	28.7 (t)
C-17′			19.6 (q)	19.6 (q)	
C-18	26.0 (t)	26.0 (t)	36.9 (t)	36.9 (t)	26.0 (t)
C-19	26.5 (t)	26.5 (t)	29.0 (t)	29.0 (t)	26.5 (t)
C-20			22.9 (t)	22.9 (t)	
C-21			14.1 (q)	14.1 (q)	

^{13}C chemical shifts: ppm downfield from internal TMS in $CDCl_3$.

TABLE XII. 7-Thiaprostaglandin E_1 Acid Derivatives (**23**)

Compd. No.	Temp. (°C)	Time (h)	Yield (%)	IR ν_{max}^{film} cm^{-1}	^{1}H-NMR δ ($CDCl_3$)
23a(*S*)**o**(*R*)	r.t.	18	91	3380, 1740, 1710, 1240, 1080, 970	0.90 (3H, t), 1.0—1.7 (14H, m), 2.1—3.1 (8H, m), 3.4—4.3 (5H, m), 5.55—5.75 (2H, m)
23b(*S*)**o**(*R*)	r.t.	5	98	3400, 1740, 1710, 1260, 1080, 970	0.8—1.9 (17H, m), 2.1—3.3 (8H, m), 3.5—4.3 (2H, m), 3.83 (3H, br s), 5.5—5.75 (2H, m)
23b(*S*)**y**(*R*)	r.t.	70	66	3480, 3250, 2670, 1740, 1690, 1635, 1280, 1065, 970[a]	0.8—2.1 (13H, m), 2.1—3.2 (8H, m), 3.4—4.3 (5H, m), 5.6—5.8 (2H, m), 5.92 (1H, d, J=15 Hz), 6.7—7.3 (1H, m)
23c(*S*)**o**(*R*)	r.t.	3	70	3400, 1740, 1710, 1240, 1080, 970	0.9—2.0 (15H, m), 2.1—3.3 (8H, m), 3.5—4.3 (5H, m), 5.5—5.75 (2H, m)
23g(*S*)**o**(*R*)	r.t.	20	94	3380, 1740, 1710, 1240, 1080, 965	0.8—1.0 (6H, m), 1.0—2.0 (15H, m), 2.0—3.1 (8H, m), 3.9—4.5 (2H, m), 5.70 (2H, m), 6.15 (3H, br s)
23h(*S*)**o**(*R*)	r.t.	20	81	3400, 1740, 1715, 1240, 1080, 970	0.8—1.0 (6H, m), 1.0—1.8 (15H, m), 2.0—3.1 (8H, m), 3.9—4.4 (5H, m), 5.55—5.85 (2H, m)

a) KBr.

Table XII.

Preparation of 15-Cyclohexyl-ω-pentanor-7-thiaprostaglandin E_1 (23b(*S*)o(*R*))—Ceric ammonium nitrate hydrate (3.62 g, 6.6 mmol) was added at 0 °C to a solution of **21b**(*S*)**w**(*RS*) (1.24 g, 1.6 mmol) in CH_3CN (38 ml), H_2O (2 ml), and THF (4 ml). The whole was stirred at 0 °C for 20 min, then at room temperature for 5 min. The mixture was taken up in ethyl acetate, and the solution was washed with 1 N HCl and then brine, dried over $MgSO_4$, and concentrated. The resulting oil (1.15 g) was purified by column chromatography (hexane : ethyl acetate = 4 : 1) to give **21b**(*S*)**o**(*RS*) (840 mg, 1.37 mmol, 85%), which was esterified with diazomethane to afford **21b**(*S*)**j**(*R*), identical with an authentic sample. Desilylation of **21b**(*S*)**o**(*RS*) was carried out by method A to give **23b**(*S*)**o**(*R*) (204 mg, 0.53 mmol, 39%) and **23b**(*S*)**o**(*S*) (169 mg, 0.44 mmol, 32%) after separation by column chromatography (hexane : ethyl acetate = 1 : 1). The spectral data for **21b**(*S*)**o**(*RS*) and **23b**(*S*)**o**(*R*) are given in Tables IX and X, respectively.

Preparation of 15-Cyclohexyl-ω-pentanor-7-thiaprostaglandin E_1 Amide (23b(*S*)x(*R*))——Isobutyl chloroformate (76 mg, 0.56 mmol) and then triethylamine (71 mg, 0.7 mmol) were added to a solution of **21b**(*S*)**o**(*RS*) (229 mg, 0.37 mmol) in CH_2Cl_2 (3 ml) at −40 °C. The mixture was stirred at −40 °C for 30 min, then aq. NH_3 (1 ml) was added, and the reaction temperature was raised to room temperature for 18 h. The whole was extracted with ethyl acetate, and the separated organic layer was washed (dil. HCl, aq. $NaHCO_3$, and brine), dried over $MgSO_4$, and concentrated *in vacuo* to give a crude product (410 mg). Column chromatographic separation (hexane : ethyl acetate = 1 : 1) provided **21b**(*S*)**x**(*RS*) (176 mg, 0.288 mmol, 78%), desilylation of which yielded **23b**(*S*)**x**(*R*) (50 mg, 0.13 mmol, 35%) and **23b**(*S*)**x**(*S*) (50 mg, 0.13 mmol, 35%) after separation by preparative TLC (ethyl acetate = 10 : 1). The spectral data for **21b**(*S*)**x**(*RS*) and **23b**(*S*)**x**(*R*) are given in Tables IX and X, respectively.

References and Notes

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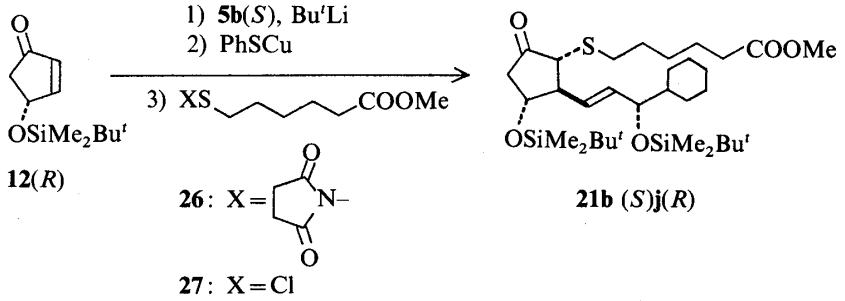
19) An alternative method to prepare the 7-thiaprostaglandin E_1 skeleton involves the one-pot direct sulfenylation[5a] of β-alkenylated enolates generated by conjugate addition of mixed cuprates to chiral cyclopentenone **12**(*R*). Reaction of the mixed cuprate, prepared from the lithiated **5b**(*S*) and phenylthiocopper, to **12**(*R*) resulted in the formation of the enolate intermediate, which was allowed to react *in situ* with *N*-(5-methoxycarbonylpentylthio)succinimide (**26**) to give the regiospecifically sulfenylated product (**21b**(*S*)**j**(*R*)) in very poor yield. Trapping of the enolate intermediate with the sulfenyl chloride (**27**) instead of **26** failed to result in adduct formation. The other attempted sulfenylations of this enolate by use of 1-pentynylcopper or cuprous iodide instead of phenylthiocopper were also unsuccessful.



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26) The ratio of 7-thiaprostaglandin E_1 methyl ester/8-*epi* isomer of the sample was 61/39 in hexane–ethyl acetate solution. Separation of the natural isomer and 8-*epi* isomer by column chromatography (hexane : ethyl acetate = 1 : 4) afforded two samples with natural/8-*epi* ratios of 91/9 and 18/82, respectively (as determined by HPLC). Detailed discussions on this equilibrium between 7-thiaprostaglandin E_1 and its 8-epimer will be presented elsewhere.

27) The detailed biological evaluation of these 7-thiaprostaglandin E_1 derivatives will also be reported elsewhere.
28) Thiols (**16i—o**) were obtained through the reaction of the corresponding bromides with thiourea. α-Methyl, α,α-dimethyl, and α,α-difluoro bromides were prepared from 2-methyl-ε-caprolactone, isobutyric acid, and 2-ethoxycarbonyl-1,3-dithiane, respectively, as starting materials. **16p** was prepared from ε,ε′-dithiodihexanoyl chloride and decyl alcohol followed by reduction with zinc. **16t** and **16u** were prepared through reduction of **16j** and methyl 4-mercaptobutyrate with lithium aluminum hydride, respectively.
29) Under these reaction conditions excess thiol resulted in the formation of 2,4-bis(5-methoxycarbonylpentylthio)-2-cyclopentenone as a by-product together with the desired enone. A similar example has appeared in the literature: L. Novák, P. Kolonits, Cs. Szántay, J. Aszódi, and M. Kajtár, *Tetrahedron*, **38**, 153 (1982).