used without further purification. The ^{13}C spectrum was consistent with the presence of two isomers, epimeric at C-4, in approximately equal amounts.

(±)-Sarracenin (1). A solution of 91 mg (0.43 mmol) of crude lactol **23** in 20 mL of methylene chloride was ozonized with 1 equiv of ozone in oxygen at −78 °C. After removal of the solvent the oily residue was dissolved in 5 mL of glacial acetic acid and 84 mg (1.3 mmol) of zinc dust was added. After being stirred at room temperature for 70 min, the mixture was cooled and filtered through a layer of celite and then heated at 70 °C for 1 h. The solvent was removed under high vacuum to give 134 mg of an oil. Pure sarracenin was obtained by preparative layer chromatography (3:1 Skelly B–ethyl acetate) and could be crystallized from hot Skelly B to give very small white needles, mp 107–108 °C (lit.[2] for (+)-sarracenin, 127–128 °C dec), by ^1H and ^{13}C NMR, IR, and UV spectral analysis identikcal with that of an authentic sample.[16]

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Synthesis of (5*Z*)- and (5*E*)-6,9-Thiaprostacyclins

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Abstract: The stereospecific synthesis of (5*Z*)- and (5*E*)-6,9-thiaprostacyclins **1** and **2** from readily available prostanoid precursors is described. The key intermediates for the syntheses are the (5*Z*)- and (5*E*)-9-thia-$PGF_{2\alpha}$ methyl ester derivatives **3** and **4**, respectively, which undergo facile iodine-induced and stereospecific cyclization via sulfenyl iodide intermediates. Finally, base-induced E2 trans-type elimination of hydrogen iodide leads selectively to the desired (5*Z*)- and (5*E*)-thiaprostacyclin derivatives.

In 1976, Vane and his associates[2] reported that microsomal fractions of arterial walls transformed prostaglandin endoperoxides (PGG_2 and PGH_2) biosynthetically derived from arachidonic acid (AA) (Figure 1) into an unstable substance found to be an extremely potent inhibitor of blood platelet aggregation and a powerful vasodilator. This substance, initially termed PGX, is one of the most recently discovered[3] biosynthetic products of the arachidonic acid cascade[3,4] and together with thromboxane A_2[5] (Figure 1) constitutes two of the most important biomolecules of this metabolic pathway. The structure of PGX had first been postulated by Pace-Asciak and Wolfe[6] in 1971, but unfortunately it was neither isolated nor its biological importance recognized at that time. It was Johnson's elegant work[4,7,8] that led to the structural elucidation of PGX and its relationship to its degradation product 6-keto-$PGF_{1\alpha}$ previously reported by Pace-Asciak in 1976.[9] This important biomolecule is now recognized as 6,9α-oxido-11α,15α-dihydroprosta-5(*Z*),13(*E*)-dienoic acid and is referred to as prostaglandin I_2 (PGI_2) (Figure 1) or prostacyclin due to its second ring which distinguishes it from the primary prostaglandins.

Prostacyclin is a rather unstable molecule (chemical and biological half-lifes at pH 7.4 of a few minutes), its instability arising from the presence of the enol ether functionality and enhanced by the carboxyl group. The methyl ester of prostacyclin is more stable than prostacyclin itself, and its sodium salt is perfectly stable at ambient temperatures.

The discovery of prostacyclin and the recognition of its vasodilatory and antiaggregating properties together with the discoveries related to thromboxane A_2 and its biological actions revolutionized current concepts of thrombosis and hemostasis. Moncada and Vane[10] have shown that prostacyclin is continuously generated from the prostaglandin endoperoxides H_2 and G_2 by the inner walls of blood vessels and is responsible for the maintenance of the integrity of blood vessel walls by inhibiting the adherence of platelets as well as preventing thrombus formation. Thromboxane A_2 (TXA_2, Figure 1) is also generated from the endoperoxides H_2 and G_2, but its production is concentrated in the platelets. Its biological actions are opposite of those of prostacyclin, namely, aggregating and vasoconstricting.[5]

The potent and important physiological actions of prostacyclin on the cardiovascular system suggested its potential use as a therapeutic agent and its low natural abundance created a need for an efficient synthesis. Due to independent efforts of several groups[8,11] prostacyclin in various forms is now available in large quantities. Its instability, however, dictated the need for the design and synthesis of more stable analogues of prostacyclin. In this series of papers we describe the synthesis of a number of prostacyclins that fulfull this stability requirement. Most of these novel prostacyclins were constructed by new methodology specifically designed for their synthesis.

In this report we describe the synthesis of both the *Z* (natural) and the *E* isomers of 6,9-thiaprostacyclin in which the ring oxygen of prostacyclin has been replaced by a sulfur atom.[12] The ra-

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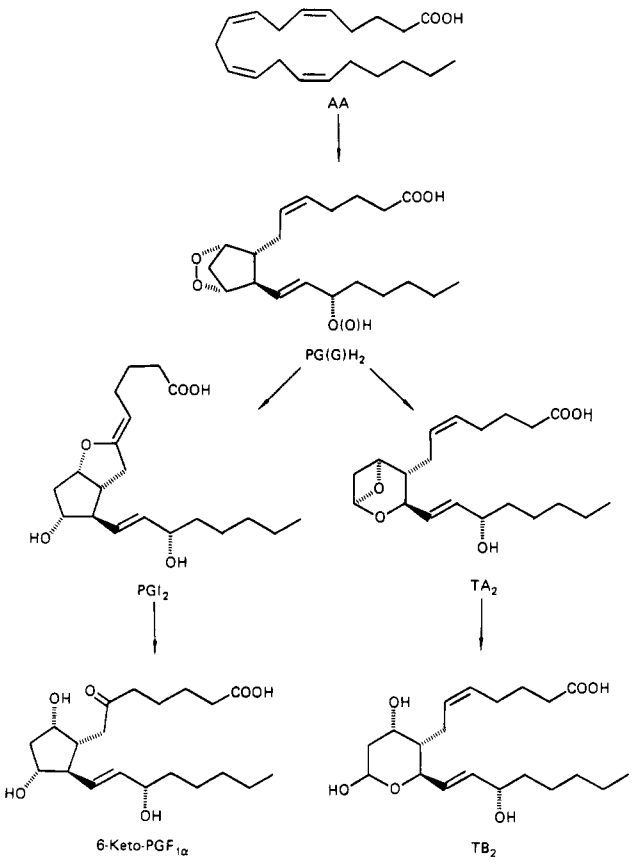

Figure 1. Biosynthesis of prostacyclin (PGI_2) and thromboxane A_2 (TA_2).

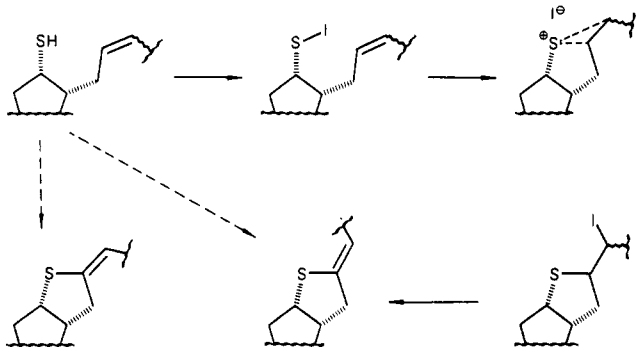

Figure 2. Stereospecific iodine-induced formation of thioenol ethers from unstaturated thiols.

tionale for this type of analogue lies in the well-known properties of thioenol ethers as considerably more stable than their oxygen counterparts[13] and the expectation that sulfur due to its similarity to oxygen would not disturb significantly the biological profile of the designed molecules.

Results and Discussion

The strategy for the synthesis of 6,9-thiaprostacyclins was based on the intramolecular addition of sulfenyl halides to olefins. Mechanistically the reaction was envisioned to proceed as indicated in Figure 2 in several stages including (i) formation of a sulfenyl iodide (source of positive sulfur) from a thiol by iodine, (ii) intramolecular electrophilic addition of sulfur to the 5,6-olefin to form an episulfonium species, (iii) nucleophilic (S_N2) opening of the episulfonium ion by iodide to form the iodo thioether, and finally (iv) base-induced elimination of hydrogen iodide to form the thioenol ether by an E2 trans-type elimination. *Earlier investigations and model studies in our own laboratories encouraged us to believe that this sequence would be completely regio- and stereospecific, leading to the desired (5Z)- and (5E)-thiaprostacyclins from the corresponding Z and E precursors.* Figure 3 shows these sulfur-containing prostacyclins (**1** and **2**) and their predicted precursor thiols (**3** and **4**). Before we proceed with the application of this methodology to the synthesis of thiaprostacyclins, however, a brief discussion on the stereochemical aspects of these reactions and a comparison with the corresponding oxygen series of transformations is deemed appropriate.

Early investigations[14,15] of the stereochemistry of the sulfenyl halide addition to olefin found it to be exclusively trans stereospecific and stereochemically independent of temperature. Examinations[16] of the intramolecular addition of sulfenyl halides to olefins have determined that it is also trans stereospecific and tends to favor 5-membered ring formation where possible.[16] However, the regiospecificity and, therefore, ring selectivity of the reaction is complicated by the ability of cyclic halo thioethers to undergo rearrangement to a more thermodynamically stable system.[16] Such rearrangements are a consequence of the readiness of divalent sulfur to reverse back to an episulfonium species which suffers redisplacement by halide ion leading to the most stable ring isomer. Whereas, the corresponding haloetherification reactions are extremely sensitive to olefin substitution, such rearrangements are not favorable in cyclic halo ethers due to the inability of oxygen to undergo octet expansion. The conversion of halo thioethers to thioenol ethers is analogous to the corresponding reaction leading to enol ethers but more facile. Thus treatment of halo thioethers with base results in an E2 type elimination of hydrogen halide toward the heteroatom leading stereospecifically to the thioenol ether. This is apparently a consequence of abstracting the most acidic proton, that is to say the one adjacent to the heteroatom.[17]

The chosen synthetic strategy then for the synthesis of (5Z)-6,9-thiaprostacyclin **1** requires as a key precursor the $PGF_{2\alpha}$ derivative 9-thia-$PGF_{2\alpha}$ methyl ester **3**. This compound was prepared by two alternative and efficient routes as illustrated in Figure 4. The first approach utilized 15-acetoxy-PGE_2 methyl ester (**5**) which is readily available from the coral *Plexaura homomalla* by a known procedure.[18,19] Treatment of **5** with dihydropyran (1.5 equiv) in the presence of catalytic amounts of *p*-toluenesulfonic acid (2 mol %) in methylene chloride resulted in the formation of the tetrahydropyranyl ether **6** in 78% yield. Reduction of **6** with excess zinc borohydride (dimethoxyethane, 25 °C, 15 h) afforded two epimeric alcohols in 66% total yield with the desired 9β-isomer **7** slightly predominating (ratio ca. 55:45 by weight after separation). The two isomers were separated by preparative layer chromatography (silica, ether; R_f(α-isomer) = 0.51, R_f(β-isomer) = 0.28). The 9β configuration was assigned to the major, more polar isomer **7** initially on chromatographic mobility grounds (less hindered hydroxyl) and later confirmed

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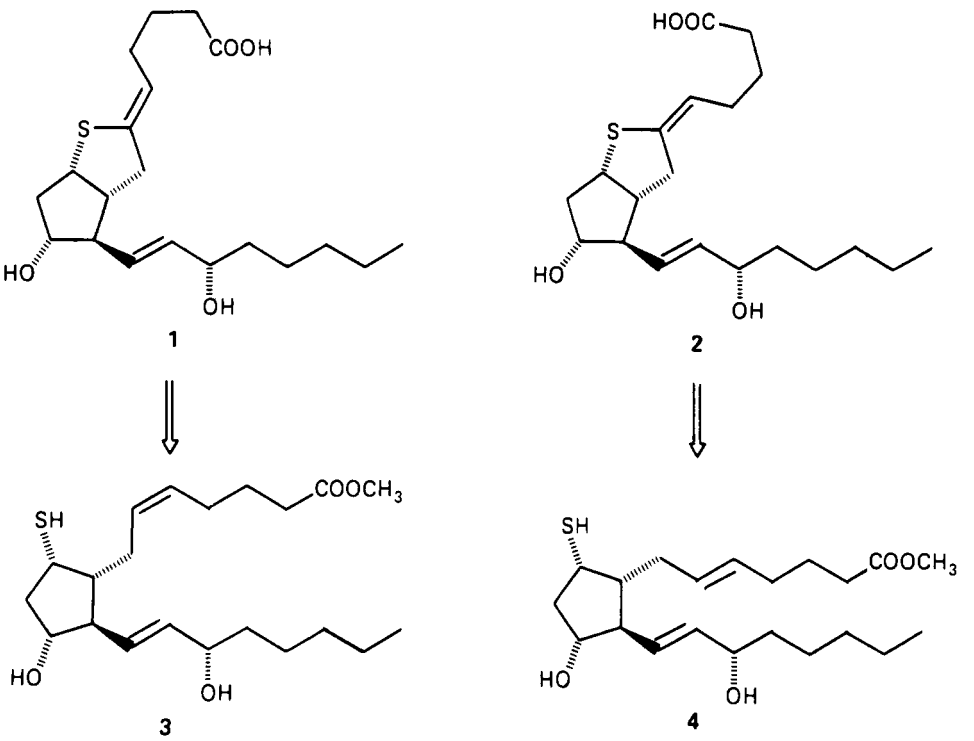

Figure 3. (5*Z*)- and (5*E*)-Thiaprostacyclins and their precursors.

by conversion of the minor, less polar isomer to $PGF_{2\alpha}$ methyl ester. Mesylation of **7** with mesyl chloride–triethylamine at −20 °C proceeded smoothly to give the mesylate **8** (72%) which was displaced (S_N2 inversion) by potassium thioacetate in dimethylformamide at 45 °C (24 h) leading to the thioacetate **9** (94%) with the correct 9α configuration. The deprotection of **9** was carried out unexceptionally and in a stepwise fashion. Thus, treatment with AcOH–THF–H_2O (3:2:2) at 45 °C for 20 h removed the tetrahydropyran protecting group leading to **10** (90%), whereas methanolysis with sodium methoxide (4 equiv) in absolute, deoxygenated methanol at 25 °C (30 min) led to the thiol **3** (100%). 9-Thia-$PGF_{2\alpha}$ methyl ester (**3**) was found to be highly sensitive to air oxidation forming the disulfide particularly on silica during chromatography. It was, therefore, used for subsequent steps directly and without purification or delay.

The second route to 9-thia-$PGF_{2\alpha}$ methyl ester (**3**) was developed starting with the readily available 11,15-bis(THP)-$PGF_{2\alpha}$ methyl ester (**11**) (Figure 4). This substance was first converted to its mesylate **12** by the standard conditions and then inverted at C-9 by displacement with potassium superoxide in the presence of 18-Crown-6 in dimethyl sulfoxide–dimethoxyethane (2:1) at 25 °C (70% yield overall).[20]

The 9β-11,15-bis(THP)-$PGF_{2\alpha}$ methyl ester (**13**) was then mesylated again in the usual way (93%) and subjected to thioacetate displacement accompanied by inversion of configuration (excess KSAc) in dimethylformamide at 45 °C (18 h) leading to the 9α-thioacetate **15** in 93% yield. Deprotection of **15** with AcOH–THF–H_2O (3:2:2) at 45 °C for 20 h yielded the dihydroxy thioacetate **16** (91%). Finally methanolysis of **16** with sodium methoxide (3 equiv) in absolute, deoxygenated methanol at 25 °C (30 min) furnished the labile thiol **3** in quantitative yield.

With the requisite 9-thia-$PGF_{2\alpha}$ (**3**) at hand, we then proceeded to construct the 6,9-thia bridge via the sulfenyl iodide. Addition of iodine (1 equiv) to a dilute methylene chloride solution of **3** at −78 °C in the presence of anhydrous potassium carbonate (4 equiv) led to the formation of the iodo thioether **19** (Figure 5) as a major product together with some disulfide **18**. The reaction presumably proceeds via the sulfenyl iodide **17** by intramolecular addition to the C-5 double bond as discussed above. An alternative pathway for the sulfenyl iodide to take would be, of course, disulfide formation by interaction with unreacted thiol although this reaction should be subject to dilution. Although the sulfenyl iodide **17** was too unstable for isolation, indirect evidence for its intermediacy was provided by (i) the bright orange-red coloration of the reaction mixture immediately after the addition of iodine and (ii) the formation of the disulfide **18** even after vigorous exclusion of oxygen. It was also observed that higher concentrations favored the disulfide whereas under very dilute solutions the iodide predominated as expected for an intermolecular vs. an intramolecular process. It is clear, however, that the strategic location of the sulfur group in relation to the C-5 bond is responsible for the success of this cyclization process.

The iodo thioether **19** was found to be rather unstable itself, particularly on concentration even below 0 °C, and could not be purified by silica chromatography. It's instability may be the result of sulfur-induced rearrangements leading to reactive species such as the episulfonium ion and sulfenyl iodide followed by decomposition. The formation of the tetrahydrothiophene nucleus rather than its 6-membered ring isomer was presumed by analogy to model compounds synthesized in our laboratories,[21] the structures of which were firmly established by ^1H NMR spectroscopy. Since the iodo ether **19** was rather labile, no extensive spectroscopic studies could be carried out to determine its stereochemistry at C-6 although it is presumed to be a single isomer with the exo stereochemistry by analogy to the corresponding selenium-induced cyclization which leads to the exo isomer as discussed in an accompanying paper.[22]

Treatment of the crude iodo thioether **19** with excess 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at 25 °C for 12 h furnished the desired (5*Z*)-6,9-thiaprostacyclin methyl ester (**20**) in 50% overall yield from thiol **3** after preparative layer chromatography together with disulfide **18** (25%). Hydrolysis of the methyl ester **20** with lithium hydroxide (10 equiv) in aqueous tetrahydrofuran (3:1) at 25 °C yielded (5*Z*)-6,9-thiaprostacyclin (**1**) in 75% yield. The sodium salt **21** could also be obtained quantitatively in solution by hydrolysis of the ester **20** in a 1 M sodium ethoxide (10 equiv) solution in 90% ethanol. The resulting sodium salt solutions were found to be a stable and convenient source of **1** for direct use in biological investigations.

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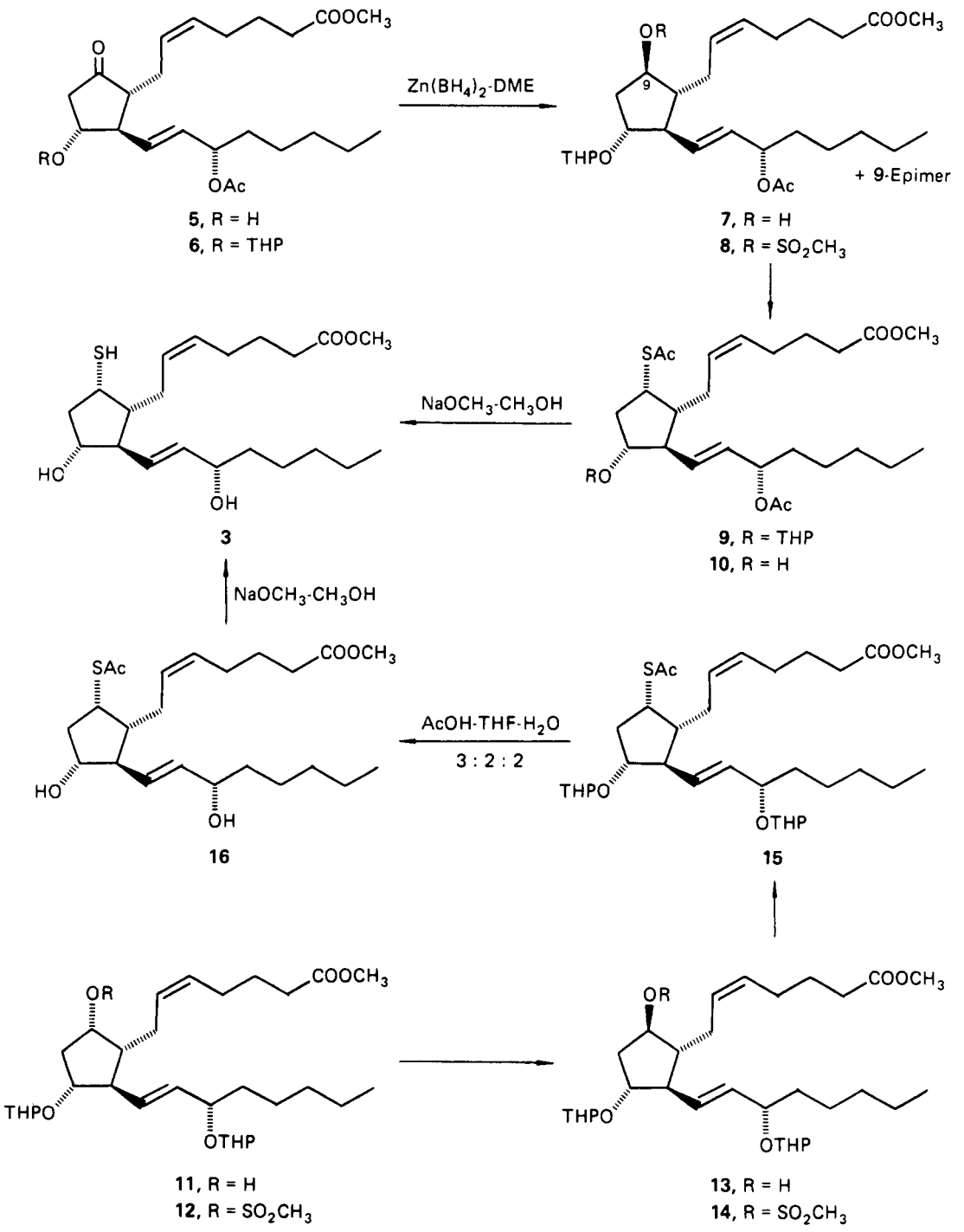


Figure 4. Synthesis of 9-thia-$PGF_{2\alpha}$ methyl ester **3**.

The 5*Z* geometry of 6,9-thiaprostacyclin **1** and its derivatives was assigned on mechanistic grounds and was supported by ^1H NMR spectral data of the methyl ester **20** and the two diastereomeric sulfoxides **22a** and **22b** (derived from **20** by hydrogen peroxide oxidation in THF) as well as comparisons with the corresponding 5*E* series of compounds, the synthesis of which is described below.

To confirm the stereospecificity of the 6,9-thiaprostacyclin formation but also to complete the series for biological considerations, we then sought to synthesize stereospecifically the (5*E*)-6,9-thiaprostacyclin (**2**). As already discussed above, the requisite key intermediate for this synthesis was the (5*E*)-9-thia-$PGF_{2\alpha}$ methyl ester **4** which was constructed as shown in Figure 6. The starting point for this sequence was the (5*E*)-11,15-bis(silyl ether)-9-thioacetate-$PGF_{2\alpha}$ methyl ester **23**, the synthesis of which is described in an accompanying paper.[22] Deprotection of the bis(silyl ether) **23** proceeded smoothly in AcOH–THF–H_2O (3:2:2) at 45 °C (24 h), affording the dihydroxy thioacetate **24** in 90% yield. Methanolysis of **24** with sodium methoxide (3 equiv) in absolute, deoxygenated methanol provided the desired, air-sensitive thiol **4** which was isolated (98% yield crude) and used directly in the subsequent step without purification. Addition of iodine (1 equiv) to a dilute solution of **4** in methylene chloride at −78 °C in the presence of anhydrous potassium carbonate (4 equiv) led to the rather labile iodo thioether **27** (stereochemistry not rigorously assigned but presumed to be a single isomer with an endo configuration at C-6) again presumably via the sulfenyl iodide **25**.

Workup and treatment of **27** without purification with excess diazabicyclo[5.4.0]undec-5-ene in benzene at 25 °C resulted in elimination of hydrogen iodide and the formation of (5*E*)-6,9-thiaprostacyclin methyl ester (**28**) in 26% overall yield from **4** along with disulfide **26** (19%). (5*E*)-6,9-Thiaprostacyclin (**2**) and its sodium salt **29** were generated from the methyl ester **28** exactly

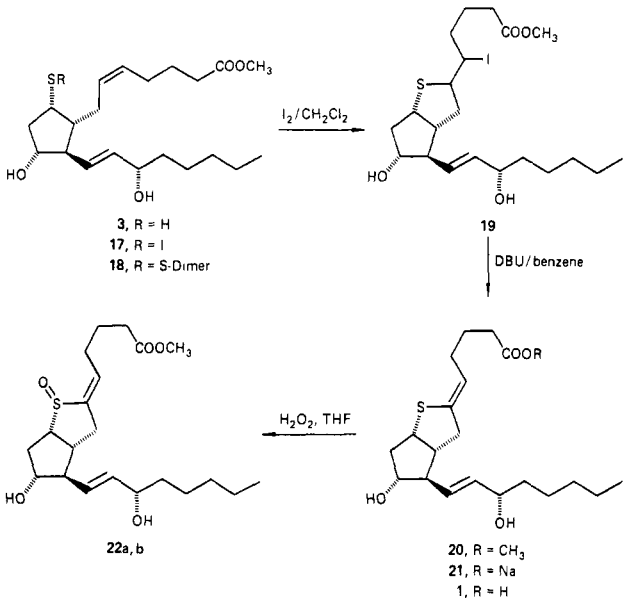


Figure 5. Synthesis of (5*Z*)-6,9-thiaprostacyclin.

Table I. Chemical Shift for Vinyl Proton (H-5) of (5*Z*)- and (5*E*)-Prostacyclins and (5*Z*)- and (5*E*)-Thiaprostacyclins

compd	τ(H-5) ($CDCl_3$)
(5*Z*)-prostacyclin methyl ester	5.84
(5*E*)-prostacyclin methyl ester	5.52
(5*Z*)-6,9-thiaprostacyclin methyl ester	4.69
(5*E*)-6,9-thiaprostacyclin methyl ester	4.60

in the same way as described above for the natural series. Oxidation of **28** in *tert*-butyl hydroperoxide at 25 °C (0.5 h) furnished two diastereomeric sulfoxides **30a** and **30b** chromatographically separated and compared to those obtained by the selenium-based methodology.[22]

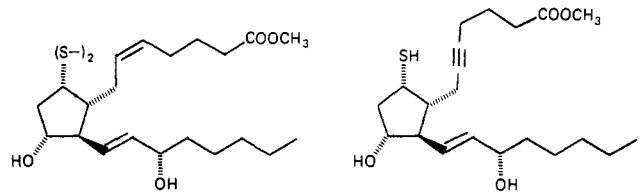
For support of the geometrical assignments of the two isomeric thiaprostacyclins the analogy to prostacyclin itself and its 5*Z* isomer was made. Table I shows the chemical shifts of the H-5 vinyl proton in the four compounds. As can be seen in the *E* isomers, H-5 (which is cis to the oxygen or sulfur atom of the ring) occurs at lower field due to deshielding by the heteroatom, although the effect is less dramatic in the case of sulfur. These differences, however, are enhanced in the sulfoxide and sulfone series as will be discussed in an accompanying paper.[22]

As anticipated from the chemical point of view at the planning stage, replacement of the enol ether grouping of prostacyclin with a thioenol linkage led to increased stability with regard to hydrolysis. Both (5*Z*)- and (5*E*)-thiaprostacyclin methyl esters **20** and **28** are perfectly stable compounds, both in solution and in the neat liquid state for prolonged periods of time at ambient temperatures. The corresponding acids **1** and **2** also exhibit enhanced stability compared to prostacyclin and like their methyl esters can be isolated by chromatography without appreciable decomposition after extraction from pH 4 buffer solutions. The sodium salts **21** and **29** were prepared as stable solutions and used directly for bioassays.

The biological evaluations of (5*Z*)- and (5*E*)-thiaprostacyclins as potential biological mimics of prostacyclin in blood platelets, coronary artery, and the cardiovascular system in general were carried out in collaboration with Professors J. Bryan Smith[23] and Allan M. Lefer[24] of Thomas Jefferson University, Philadelphia, PA. It was rewarding to find that the *Z* isomer **1** with the natural geometry of prostacyclin showed potent activity as an inhibitor of blood platelet aggregation,[23] whereas the *E* isomer like its oxygen counterpart was relatively inactive in that test.

In the perfused isolated cat coronary artery test, however, (5*Z*)-thiaprostacyclin showed potent vasoconstricting properties unlike prostacyclin which is a powerful vasodilator.[24] This result is surprising in view of the fact that in vivo this compound mimics prostacyclin very closely in its action on the cardiovascular system.[25]

Finally, this report will not be complete without mention of the elegant works of Shibasaki and Ikegami[26] and Hayashi et al.[27] in two alternative syntheses of 6,9-thiaprostacyclin. The first group utilized the disulfide **31** as their key starting material leading to



the final product on cleavage with bromine, cyclization of the intermediate sulfenyl bromide, and subsequent base-induced elimination of hydrogen bromide, whereas the second group used the acetylenic thiol **32** as starting material which stereospecifically reacted intramolecularly to form (5*Z*)-6,9-thiaprostacyclin. In both cases the chemical and biological properties reported were in accord with our own observations.

Conclusion

To test the hypothesis of improved chemical stability and similar biological profile to prostacyclin, we undertook the synthesis of (5*Z*)-6,9-thiaprostacyclin (**1**) and its (5*E*)-isomer **2**. We have demonstrated that these compounds can be synthesized rapidly and efficiently from readily available prostanoid precursors and indeed they exhibited the expected increase in chemical stability. Furthermore, their biological profiles also confirmed our expectations in that the *Z* isomer showed potent antithrombotic action both in vitro and in vivo whereas the *E* isomer was relatively inactive as is its oxygen counterpart. (5*Z*)-6,9-Thiaprostacyclin (**1**) also exhibited antihypertensive properties similar to prostacyclin although it is different from it in its action on the perfused isolated cat coronary artery possessing vasoconstricting rather than vasodilatory properties.

Experimental Section

General Data. Melting points were recorded on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian 220-MHz or Bruker 360-MHz NMR spectrometer in $CDCl_3$ unless otherwise stated and are reported in τ values. IR spectra were obtained with a Perkin-Elmer Model 237 or a Perkin-Elmer Model 281B spectrophotometer, and the IR figures reported are ν_{max} in cm^{-1}. Mass spectra were provided by the Mass Spectral Service of Merck Sharp and Dohme, Rahway, NJ, or the Chemistry Department, University of Pennsylvania, and are within acceptable limits unless otherwise stated. Optical rotations were measured with a Hitachi Perkin-Elmer Model 241C instrument at the sodium D line by using a 1-mL, 10-cm long cell. The designation *c* refers to concentration in g/mL.

Thin-layer chromatography (TLC) was carried out on 0.25-mm E. Merck precoated silica gel plates (60F-254) by using UV light and/or 7% polyphosphomolybdic acid in ethanol–heat as developing agent. Preparative layer chromatography (PLC) was performed on 0.25, 0.5, or 2 mm × 20 × 20 cm E. Merck precoated silica gel plates (60F-254).

All reactions were carried out under an argon atmosphere by using dry freshly distilled solvents under anhydrous conditions unless otherwise stated. Ethereal and hydrocarbon solvents were dried and distilled under argon from sodium benzophenone ketyl. Methylene chloride was distilled under argon from calcium hydride. Reaction temperatures were measured externally. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; o,

(23) Platelet studies: Cardeza Foundation and Department of Pharmacology, Thomas Jefferson University, Philadelphia, PA 19174.
(24) Coronary artery studies: Department of Physiology, Thomas Jefferson University, Philadelphia, PA 19174.
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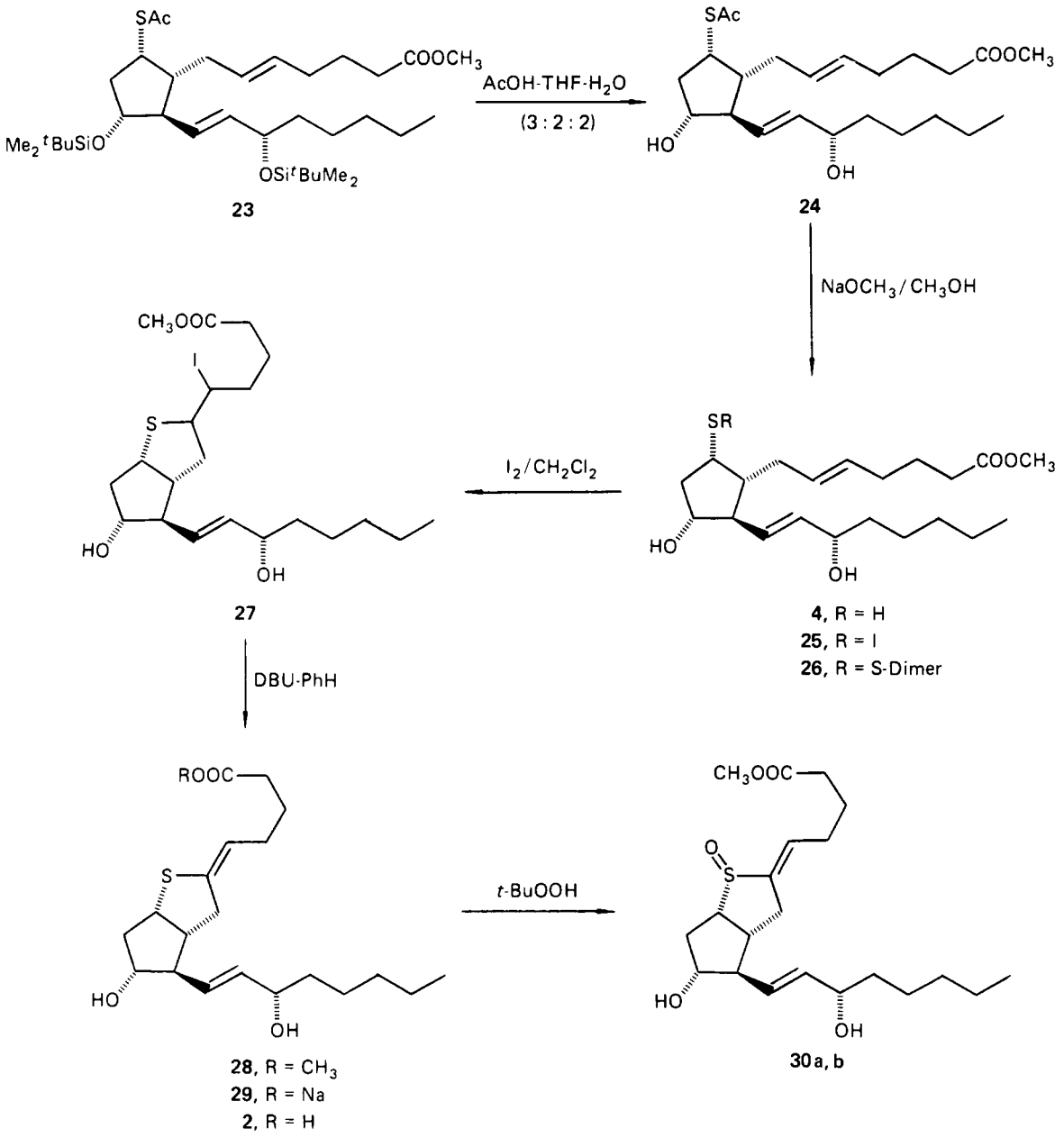

Figure 6. Synthesis of (5*E*)-6,9-thiaprostacyclin.

octet; m, multiplet; b, broad; *J*, coupling constant in Hz. IR spectra are reported by using the following convention: w, weak; m, medium; s, strong; b, broad. Only the strongest and/or structurally most important peaks are reported for the IR and mass spectra. The abbreviation Me_3Si refers to the trimethylsilyl group and HRMS refers to high-resolution mass spectra.

Microanalyses were performed by Galbraith Laboratories and were within acceptable limits.

Methyl (5*Z*,11α,13*E*,15*S*)-15-(Acetyloxy)-9-oxo-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate (6). 15-Acetoxyl-PGE_2 methyl ester (**5**) (532 mg, 1.36 mmol) and dihydropyran (252 mg, 274 μL, 2.04 mmol) were dissolved in anhydrous methylene chloride (10 mL) at 0 °C. *p*-Toluenesulfonic acid (3 mg in 150 μL of THF) was added and the solution allowed to warm up to room temperature. After being stirred for 30 min, the reaction mixture was diluted with ether, washed with 10% potassium bicarbonate solution, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, ether–hexane 2:1) yielded the derivative **6** (480 mg, 72%). **6**: oil; R_f = 0.29 (silica, ether–hexane 2:1); $[\alpha]^{25}_D$ −75.1° (methanol, *c* = 0.0152); IR (liquid film) ν_{max} 3000 (m), 2920 (s), 2850 (m), 1730 (s, CO), 1430 (w), 1360 (m), 1235 (s), 1125 (m), 1075 (m), 1025 (m), 960 (m), 910 (w), 860 (w), 810 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.50 (m, 4 H, olefinic), 4.67 (m, ^1H H-15), 5.32 (m, 1 H, H-11), 5.84 (q, *J* = 5 Hz, 0.5 H, CHO), 5.98 (q, *J* = 5 Hz, 0.5 H, CHO), 6.18 (m, 1 H, CHO), 6.34 (s, 3 H, ester), 6.50 (m, 1 H, CHO), 7.20 (d, *J* = 5 Hz, 1 H, C*H*COOCH$_3$), 7.27 (d, *J* = 5 Hz, 1 H, C*H*COOCH$_3$), 7.32–8.84 (m, 27 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 432 (M^+ − HOAc, 0.2%), 330 (M^+ − HOAc − THPOH, 4.9%), 208 (10.1%), 190 (13.2%), 141 (28.0%), 85 (base peak); HRMS (M^+ − HOAc − THPOH) calcd for $C_{21}H_{30}O_3$ 330.2194, found 330.2205.

Methyl (5*Z*,9β,11α,13*E*,15*S*)-15-(Acetyloxy)-9-hydroxy-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate 7 and Its 9-Epimer. The PGE_2 derivative **6** (410 mg, 0.83 mmol) was dissolved in anhydrous dimethoxyethane (12 mL) at ambient temperature. Zinc borohydride (1.25 mL of 0.5 M solution in dimethoxyethane) was added and the mixture stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (60 mL), washed with saturated potassium tartrate solution (3 × 20 mL) and water, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, ether) yielded the desired β-alcohol **7** (126 mg, 31%) and its epimeric α-alcohol (142 mg, 35%) ($R_f(\alpha)$ = 0.51, $R_f(\beta)$ = 0.28). **7**: oil; R_f = 0.28 (silica, ether); $[\alpha]^{25}_D$ − 33.9° (methanol, *c* = 0.0056); IR (liquid film) ν_{max} 3400 (w, OH), 2950 (w), 2900 (s), 2850 (m), 1730 (ester), 1430 (m), 1170 (m), 1240 (s), 1025 (m), 965 (m), 870 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.50 (m, 4 H, olefinic), 4.80 (m, 1 H, H-15), 5.39 (b d, *J* = 7.5 Hz, 1 H, H-11), 5.95 (q, *J* = 6 Hz, 1 H, CHO), 6.00 (m, 1 H, CHO), 6.20 (m, 1 H, CHO), 6.34 (s, 3 H, ester), 6.54 (m, 2 H, CHO), 7.48–8.84 (m, 28 H), 9.14 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity)

434 (M^+ – HOAc, 0.2%), 332 (M^+ – HOAc – THPOH, 1.7%), 314 (M^+ – HOAc – THPOH – H_2O, 1.6%), 109 (15%), 105 (12.3%), 91 (23.3%), 85 (base peak), 67 (65.9%); HRMS (M^+ – HOAc) calcd for $C_{26}H_{42}O_5$ 434.4032, found 434.3144.

Methyl (5*Z*,9β,11α,13*E*,15*S*)-15-(Acetyloxy)-9-[(methylsulfonyl)oxy]-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate (8). The 9-epi-$PGE_{2\alpha}$ derivative **7** (200 mg, 0.4 mmol) and triethylamine (60 mg, 84 μL, 0.6 mmol) were dissolved in anhydrous methylene chloride (8 mL) and cooled to −20 °C under argon. Methanesulfonyl chloride (68 mg, 48 μL, 0.6 mmol) was added and the mixture stirred at −20 °C under argon for 30 min. The reaction mixture was diluted with ether (60 mL), washed with water (20 mL), 1.2 N hydrochloric acid solution (20 mL), 10% potassium bicarbonate solution (20 mL), and saturated sodium chloride solution (20 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent, and purification by column chromatography (silica, ether–hexane 1:1) yielded the mesylate **8** (172 mg, 72%). **8**: oil, R_f = 0.11 (silica, ether–hexane 1:1); $[\alpha]^{25}_D$ −29.1° (methanol, *c* = 0.008); IR (liquid film) ν_{max} 2980 (w), 2900 (s), 2840 (m), 1730 (s, esters), 1430 (w), 1340 (s, sulfonyl), 1240 (s), 1170 (s), 1120 (w), 1060 (w), 1025 (m), 965 (m), 910 (m), 810 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.50 (m, 4 H, olefinic), 4.80 (m, 1 H, H-15), 5.20 (m, 1 H, H-9), 5.40 (b d, *J* = 7 Hz, 1 H, H-11), 5.90 (m, 1 H, CHO), 6.23 (m, 1 H, CHO), 6.34 (s, 3 H, ester), 6.57 (m, 1 H, CHO), 7.02 (s, 3 H, CH_3SO_3), 7.50–8.86 (m, 29 H), 9.14 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 430 (M^+ – HOAc – THPOH, 0.5%), 334 (M^+ – HOAc – THPOH – MesOH, 0.8%), 314 (16.2%), 191 (13.8%), 117 (21.9%), 91 (33.8%), 79 (50.8%), 60 (66.8%), 55 (base peak); HRMS (M^+ – HOAc – THPOH – MesOH) calcd for $C_{21}H_{30}O_2$ 31.2245, found 314.2213.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-15-(Acetyloxy)-9-(acetylthio)-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate (9). The mesylate **8** (300 mg, 0.5 mmol) was dissolved in anhydrous dimethylformamide (5 mL). Potassium thioacetate (580 mg, 5 mmol) was added and the solution stirred at 45 °C under argon for 24 h. The reaction mixture was diluted with ether (100 mL), washed with water (30 mL) and sodium chloride solution (30 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, ether–hexane 1:1) yielded the thioacetate **9** (260 mg, 94%). **9**: oil; R_f = 0.16 (silica, ether–hexane 1:1); $[\alpha]^{25}_D$ −21.7° (methanol, *c* = 0.007); IR (liquid film) ν_{max} 3000 (w), 2920 (s), 2850 (m), 1730 (s, esters), 1690 (s, thioester), 1430 (w), 1370 (m), 1240 (s), 1125 (m), 1075 (m), 1025 (m), 965 (m), 915 (w), 870 (w), cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.50 (m, 4 H, olefinic), 4.80 (m, 1 H, H-15), 5.43 (b d, *J* = 7 Hz, 1 H, H-11), 6.14 (m, 3 H, CHO, CHS), 6.34 (s, 3 H, ester), 6.57 (m, 1 H, CHO), 7.70 (s, 3 H, CH_3SCO), 7.34–9.00 (m, 29 H), 9.14 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 314 (M^+ – HOAc – HSAc – THPOH, 0.1%), 184 (3.6%), 168 (2.1%), 155 (3.2%), 105 (18.6%), 85 (48.0%), 73 (base peak), 61 (88.9%), 55 (48.3%); HRMS (M^+ – $COCH_3$) calcd for $C_{28}H_{45}O_6S$ 509.2935, found 509.2852.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-15-(Acetyloxy)-9-(acetylthio)-11-hydroxyprosta-5,13-dien-1-oate (10). The 9-THP-thioacetate **9** (200 mg, 0.36 mmol) was dissolved in a mixture of acetic acid–tetrahydrofuran–water (3:2:2, 10 mL) and the solution stirred at 45 °C under argon for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with methylene chloride (2 × 30 mL). The combined extracts were washed with water (2 × 20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 2% methanol in ether) yielded the diacetate **10** (168 mg, 90%). **10**: oil; R_f = 0.60 (silica, 2% methanol in ehter); $[\alpha]^{25}_D$ −23.1° (methanol, *c* = 0.007); IR (liquid film) ν_{max} 3300 (m), 2900 (w), 2850 (m), 1728 (s, esters), 1690 (s, thioester), 1430 (m), 1370 (m), 1235 (s), 1110 (m), 1010 (m), 955 (m) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.50 (m, 2 H, olefinic), 4.70 (m, 2 H, olefinic), 4.84 (m, 1 H, H-15), 6.02 (m, 2 H, H-11, H-9), 6.34 (s, 3 H, ester), 7.45 (p, *J* = 4 Hz, 1 H), 7.68 (s, 3 H, CH_3SCO), 7.68–9.00 (m, 23 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 332 (M^+ – HOAc – HSAc), 184 (9.9%), 129 (10.7%), 105 (48.7%), 91 (31.7%), 85 (88.6%), 71 (53.5%), 55 (base peak); HRMS (M^+ – HOAc – HSAc) calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2370.

Methyl (5*Z*,9β,11α,13*E*,15*S*)-9-[(Methylsulfonyl)oxy]-11,15-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate (14). The 9β-alcohol **13** (1200 mg, 2.23 mmol) and triethylamine (339 mg, 467 μL, 3.36 mmol) were dissolved in anhydrous methylene chloride (50 mL) and cooled to −20 °C under argon. Methanesulfonyl chloride (383 mg, 259 μL, 3.36 mmol) was added and the mixture stirred at −20 °C under argon for 30 min. The reaction mixture was then diluted with ether (100 mL), washed with water (25 mL), 1.2 N hydrochloric acid solution (25 mL), 10% potassium bicarbonate solution (25 mL), and saturated sodium chloride solution (25 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, ether–hexane 1:1) yielded the mesylate **14** (1267 mg, 93%). **14**: oil; R_f = 0.10 (silica, ether–hexane 1:1); $[\alpha]^{25}_D$ −30.0° (methanol, *c* = 0.022); IR (liquid film) ν_{max} 2900 (s), 2850 (s), 1730 (s, ester), 1450 (m), 1430 (m), 1350 (s, sulfonyl), 1250 (m), 1180 (s), 1170 (s), 1125 (s), 1070 (s), 1030 (s), 1020 (s), 965 (s), 910 (s), 865 (m), 810 (w), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.57 (m, 4 H, olefinic), 4.67 (m, 1 H, CHO), 5.20 (m, 1 H, CHO), 5.35 (m, 1 H, CHO), 5.97 (m, 2 H, CHO), 6.17 (m, 2 H, CHO), 6.33 (s, 3 H, ester), 6.53 (m, 2 H, CHO), 7.02 (s, 3 H, SO_3CH_3), 7.62–8.92 (m, 32 H), 9.12 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 416 (M^+ – THPOH – MesOH, 0.1%), 332 (M^+ – 2THPOH – Mes, (11.1%), 315 (M^+ – 2THPOH – MesO, 15.1%), 105 (15.3%), 101 (37.3%), 93 (32.9%), 91 (33.1%), 84 (57.4%), 55 (base peak); HRMS calcd for $C_{21}H_{32}O_3$ (M^+ – 2THPOH – CH_2SO_2) 332.2351, found 332.2381.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-9-(Acetylthio)-11,15-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]prosta-5,13-dien-1-oate (15). The β-mesylate **14** (1267 mg, 2.06 mmol) was dissolved in anhydrous dimethylformamide (40 mL). Potassium thioacetate (2352 mg, 20.6 mmol) was added in one portion and the mixture stirred at 45 °C under argon for 15 h. The reaction mixture was then diluted with water (80 mL) and extracted with ether (3 × 50 mL). The combined extracts were washed with water (2 × 30 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, ether–hexane 1:1) yielded the thioacetate **15** (1135 mg, 93%). **15**: oil; R_f = 0.30 (silica, ether–hexane 1:1); $[\alpha]^{25}_D$ −18.7° (methanol, *c* = 0.020); IR (liquid film) ν_{max} 2930 (s), 2850 (m), 1730 (s, ester), 1690 (s, thioester), 1450 (m), 1435 (m), 1350 (m), 1315 (w), 1250 (m), 1200 (s), 1175 (m), 1120 (s), 1075 (s), 1020 (s), 970 (m), 910 (s), 880 (w), 865 (m), 810 (m), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.58 (m, 4 H, olefinic), 4.67 (m, 1 H, CHO), 5.35 (m, 1 H, CHO), 5.98 (m, 2 H, CHO), 6.17 (m, 3 H, CHO, CHS), 6.33 (s, 3 H, ester), 6.55 (m, 2 H, CHO), 7.42 (octet, 1 H, *J* = 6 Hz), 7.57 (octet, 1 H, *J* = 6 Hz), 7.68 (s, 3 H, SAc), 7.60–8.83 (m, 3 H), 9.12 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 314 (M^+ – HSAc – 2THPOH, 2.9%), 129 (10.1%), 105 (40.6%), 91 (51.6%), 86 (56.3%), 85 (94.5%), 67 (64.6%), 57 (88.3%), 55 (base peak); HRMS (M^+ – 2THPOH – HSAc) calcd for $C_{21}H_{30}O_2$ 314.2244, found 314.2198.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-9-(Acetylthio)-11,15-dihydroxyprosta-5,13-dien-1-oate (16). The protected thioacetate **15** (1135 mg, 1.91 mmol) was dissolved in a mixture of acetic acid–tetrahydrofuran–water (3:2:2, 50 mL) and the solution stirred at 45 °C under argon for 12 h. The reaction mixture was diluted with water (100 mL) and extracted with methylene chloride (3 × 50 mL). The combined extracts were washed with water (2 × 30 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, 2.5% methanol in ether) yielded the thioacetate **16** (737 mg, 91%). **16**: oil; R_f = 0.02 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ −0.84° (methanol, *c* = 0.0215); IR (liquid film) ν_{max} 3300 (m, OH), 2950 (s), 2920 (s), 2850 (s), 1730 (s, ester), 1690 (s, thioester), 1430 (m), 1350 (m), 1310 (m), 1250 (m), 1130 (s), 1025 (m), 970 (m), 915 (w), 860 (w), 735 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.52 (m, 2 H, olefinic), 4.72 (m, 2 H, olefinic), 5.97 (q, *J* = 6 Hz, 1 H, H-15), 6.00 (q, *J* = 6 Hz, 1 H, H-11), 6.10 (q, *J* = 6 Hz, 1 H, H-9), 6.33 (s, 3 H, ester), 7.42 (m, 2 H), 7.67 (s, 3 H, thioacetate), 7.67–8.88 (m, 20 H), 9.12 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 570 (M^+, $2Me_3Si$, 0.7%), 555 (M^+ – CH_3, 5.3%), 527 (M^+ – $COCH_3$, 11.7%), 495 (M^+ – SAc, 24.7%), 497 (M^+ – Me_3Si, 2.6%), 480 (M^+ – Me_3SiOH, 4.9%), 437 (17.8%), 423 (33.8%), 405 (88.2%), 390 (M^+ – $2Me_3SiOH$, 3.5%), 333 (base peak), 314 (M^+ – $2Me_3SiOH$ – HSAc, 31.2%); HRMS (M^+ – CH_3) calcd for $C_{22}H_{36}O_5S{\cdot}2Me_2Si$ 555.2995, found 555.2983. Anal. ($C_{23}H_{38}O_5S$) C, H.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-11,15-Dihydroxy-9-mercaptoprosta-5,13-dien-1-oate (3). (a) From 16. The thioacetate **16** (39 mg, 0.09 mmol) was dissolved in absolute methanol and the solution deoxygenated with argon. Sodium methoxide powder (14 mg, 0.27 mmol) was added and the resulting solution stirred at room temperature under argon for 1 h. The reaction mixture was diluted with saturated sodium chloride solution (20 mL) and adjusted to pH 4 with 1 N oxalic acid solution. The acidified mixture was extracted with ether (2 × 30 mL), and the combined extracts were washed with water (2 × 15 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded crude, air-sensitive thiol **3** (34 mg, 100%).

(b) From 10. The 15-acetoxy thioacetate **10** (46.8 mg, 0.1 mmol) was dissolved in absolute methanol (1 mL) and the solution deoxygenated with argon. Sodium methoxide powder (27 mg, 0.5 mmol) was added and the resulting solution stirred at room temperature under argon for 1 h. The reaction mixture was diluted with saturated sodium chloride solution and adjusted to pH 4 with 1 N oxalic acid solution. The acidified mixture was extracted with ether (2 × 35 mL), and the combined

extracts washed with water (2 × 20 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded air sensitive thiol **3** (35 mg, 100%). **3**: oil; R_f = 0.20 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ +34.4° (methanol, c = 0.026); IR (liquid film) ν_{max} 3360 (OH, m), 2975 (w), 2940 (s), 2915 (s), 2840 (m), 2550 (SH, w), 1730 (ester, s), 1430 (m), 1360 (w), 1305 (w), 1240 (m), 1190 (m), 1160 (m), 1075 (m), 1015 (m), 960 (m) cm^{-1}; ^{1}H NMR (360 MHz, benzene-d_6) τ 4.32 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.60 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.67 (m, 2 H, olefinic), 5.88 (m, 1 H, H-15), 6.15 (b, 1 H, SH), 6.20 (m, 1 H, H-11), 6.63 (s, 3 H, ester), 6.85 (m, 1 H, H-9), 7.25–8.00 (m, 22 H), 9.08 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 600 (M^+, 3Me_3Si, 0.2%), 510 ($M^+ - Me_3SiOH$), 439 (2.4%), 404 ($M^+ - Me_3SiOH - Me_3Si_4H$, 0.5%), 314 ($M^+ - 2Me_3SiOH - Me_3SiSH$, 1.0%), 348 (3%), 129 (21.4%), 91 (23.6%), 75 (41.7%), 73 (base peak); HRMS (M·3$Me_3Si - Me_3SiOH - Me_3SiSH$), calcd for $C_{21}H_{31}O_3$·Me_3Si 404.2746, found 404.2774.

Methyl (5*E*,9α,11α,13*E*,15*S*)-9-(Acetylthio)-11,15-dihydroxyprosta-5,13-dien-1-oate (24). The bis(silyl thioacetate) **23** (163 mg, 0.25 mmol) was dissovled in a mixture of acetic acid–tetrahydrofuran–water (3:2:2), (5 mL) and the solution stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with water (15 mL) and extracted with methylene chloride (3 × 30 mL). The combined extracts were washed with water (2 × 20 mL) and saturated sodium chloride solution (20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 2.5% methanol in ether) yielded the dihydroxy thioacetate **24** (96 mg, 90%). **24**: oil; R_f = 0.20 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ +6.0° (methanol, c = 0.0135); IR (liquid film) ν_{max} 3380 (OH, m), 2950 (s), 2920 (s), 2825 (s), 1730 (s), 1685 (s), 1430 (m), 1350 (m), 1240 (m), 1115 (s), 1015 (m), 960 (s), 905 (s), 730 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.48 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.58 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.68 (m, 2 H, olefinic), 5.97 (q, J = 7 Hz, 1 H, H-15), 6.01 (q, J = 6 Hz, 1 H, H-11), 6.11 (q, J = 7 Hz, 1 H, H-9), 6.33 (s, 3 H, ester), 7.68 (s, 3 H, $SCOCH_3$), 7.00–8.87 (m, 22 H), 9.11 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 570 (M^+, 0.1%), 555 ($M^+ - CH_3$, 0.8%), 527 (2.3%), 495 ($M^+ - SAc$, 3.4%), 480 ($M^+ - Me_3SiOH$, 1.1%), 437 (4.5%), 405 ($M^+ - SAc - Me_3SiOH$, 11.7%), 390 ($M^+ - 2Me_3SiOH$, 1.0%), 333 (57.3%), 75 (79.1%), 73 (base peak); HRMS ($M^+ - CH_3$) calcd for $C_{22}H_{33}O_5S$·2Me_3Si 555.3049, found 555.3070.

Methyl (5*E*,9α,11α,13*E*,15*S*)-11,15-Dihydroxy-9-mercaptoprosta-5,13-dien-1-oate (4). The thioacetate **24** (42.6 mg, 0.1 mmol) was dissolved in absolute methanol (1 mL) and the solution deoxygenated with argon. Sodium methoxide (16.2 mg, 0.3 mmol) was added and the solution stirred at room temperature under argon for 60 min. The reaction was diluted with saturated sodium chloride solution (20 mL) and adjusted to pH 4 with 1 N oxalic acid solution. The acidified mixture was extracted with ether (3 × 30 mL), and the ether extracts were washed with water (20 mL) and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtation and removal of solvent under reduced pressure yielded the air-sensitive thiol **4** (38.5 mg, 100%). **4**: oil; R_f = 0.20 (silica, 2.5% methanol in ether); $[\alpha]^{22}_D$ +15.3° (methanol, c = 0.0205); IR (liquid film) 3380 (OH, m), 2980 (s), 2930 (s), 2860 (m), 2700 (SH, w), 1735 (ester, s), 1450 (m), 1435 (m), 1315 (m), 1250 (m), 1200 (m), 1170 (m), 1080 (m), 1020 (m), 965 (s) cm^{-1}; ^{1}H NMR (360 MHz, benzene-d_6) τ 4.45 (m, 4 H, olefinic), 5.88 (p, J = 7 Hz, 1 H, H-15), 6.18 (q, J = 6 Hz, 1 H, H-11), 6.25 (b, 1 H, SH), 6.65 (s, 3 H, ester), 8.82 (m, 1 H, H-9), 7.17–8.83 (m, 22 H), 9.08 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 510 ($M^+ - Me_3SiOH$, 3MeSi, 0.5%), 438 (7.6%), 404 ($M^+ - Me_3SiOH - Me_3SiSH$, 0.2%), 367 (13.5%), 314 ($M^+ - 2Me_3SiOH - Me_3SiSH$, 0.7%), 252 (10.8%), 129 (17.4%), 99 (32.9%), 75 (37.9%), 73 (base peak); HRMS ($M^+ - Me_3SiOH$) calcd for $C_{21}H_{32}O_3S$·2Me_3Si 510.3019, found 510.3115.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate ((5*Z*)-6,9-Thiaprostacyclin Methyl Ester) (20). Freshly prepared thiol **3** (31 mg, 0.08 mmol) was dissolved in anhydrous methylene chloride (10 mL). Potassium carbonate (56 mg, 0.4 mmol) was suspended in this solution and the resulting mixture cooled to −78 °C under argon. Iodine (20 mg, 0.08 mmol) was then added and the mixture stirred at −78 °C under argon until the iodine crystals had dissolved (about 3 h). The orange-red reaction mixture was then diluted with ether (100 mL), washed with 10% sodium thiosulfate solution (20 mL) and 10% potassium carbonate solution (20 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of solvent yielded the crude iodo thioether **19** (R_f = 0.45, silica, 5% methanol in ether) which was immediately redissolved in anhydrous benzene (600 μL). 1,5-Diazabicyclo[5.4.0]undec-5-ene (122 mg ≡ 120 μL, 0.8 mmol) was added and the resulting solution stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with ether (75 mL), washed with water (5 × 20 mL) until the washings were neutral, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent, and purification by preparative layer chromatography (silica, 2.5% methanol in ether, two developments) yielded the product (5*Z*)-6,9-thiaprostacyclin methyl ester (**20**) (15 mg, 50%) and disulfide **18** (10 mg, 33%). **20**: oil; R_f = 0.21 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ +58.4° (methanol, c = 0.011); IR (liquid film) ν_{max} 2880 (OH, m), 2960 (s), 2920 (s), 2840 (s), 1730 (ester, s), 1640 (thioenol ether, w), 1450 (s), 1430 (s), 1370 (m), 1310 (m), 1250 (m), 1160 (s), 1095 (s), 1015 (m), 960 (m), 860 (w) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.42 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.57 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.69 (t, J = 7 Hz, 1 H, H-5), 5.93 (q, J = 7 Hz, 1 H, H-15), 6.08 (q, J = 7 Hz, 1 H, H-11), 6.10 (m, 1 H, H-9), 6.32 (s, 3 H, ester), 7.10–8.83 (m, 22 H), 9.10 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 382 (M^+, 7.5%), 364 ($M^+ - H_2O$, 6.5%), 346 ($M^+ - 2H_2O$, 10.6%), 250 (18.2%), 211 (27.2%), 197 (20.7%), 163 (20.7%), 123 (58.2%), 97 (52.2%), 91 (59.6%), 79 (73.1%), 71 (72.8%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_4S$ 382.2176, found 382.2172. Anal. Calcd for $C_{21}H_{34}O_4S$: C, 65.93; H, 8.96. Found: C, 66.05; H, 9.09. **18**: white solid, mp 70–72 °C; R_f = 0.04 (silica, 2.5% methanol in ether); $[\alpha]^{25}_S$ +51.3% (methanol, c = 0.013); IR ($CHCl_3$) ν_{max} 3400 (OH, m), 3000 (m), 2950 (s), 2915 (s), 2850 (m), 1728 (ester, s), 1455 (m), 1435 (m), 1350 (m), 1315 (m), 1260 (m), 1205 (s), 1170 (m), 1075 (m), 1015 (m), 965 (m), 905 (m), 850 (w), 715 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.43 (dd, J = 7, 15 Hz, 2 H, olefinic), 4.60 (m, 6 H, olefinic), 5.94 (q, J = 7 Hz, 2 H, H-15), 6.08 (q, J = 6 Hz, 2 H, H-11), 6.33 (s, 6 H, ester), 6.62 (m, 2 H, H-9), 7.00–9.00 (m, 44 H), 9.12 (m, 6 H, CH_3); mass spectrum, m/e (relative intensity) 383 ($M^+/2$, 0.8%), 366 ($M^+/2 + 1 - H_2O$, 8.5%), 365 ($M^+/2 - H_2O$, 3.0%), 348 ($M^+/2 + 1 - 2H_2O$, 14.9%), 347 ($M^+/2 - 2H_2O$, 4.3%), 322 (11.7%), 315 (10.0%), 277 (14.3%), 263 (23.6%), 252 (39.4%), 233 (20.8%), 187 (37.0%), 181 (37.0%), 181 (47.6%), 149 (42.2%), 135 (50.8%), 109 (59.2%), 99 (87.0%), 85 (76.7%), 71 (87.5%), 57 (86.9%), 55 (base peak); HRMS ($M^+/2$) calcd for $C_{21}H_{35}O_4S$ 383.2255, found 383.2238.

(5*Z*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid ((5*Z*)-6,9-Thiaprostacyclin) (1) and Its Sodium Salt 21. The methyl ester **20** (10 mg, 0.026 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1 mL). Lithium hydroxide (260 μL of a 1 M solution in water, 0.26 mmol) was added and the mixture stirred at room temperature under argon for 12 h. The base was neutralized by the addition of oxalic acid (260 μL of a 1 N solution), and the tetrahydrofuran was removed under reduced pressure. The residual mixture was diluted with saturated sodium chloride solution (10 mL) and adjusted to pH 4 by addition of a 1 N oxalic acid solution. The acidified mixture was extracted with methylene chloride (3 × 30 mL), and the combined extracts were washed with saturated sodium chloride solution (15 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded the free acid **1** (5.2 mg, 55%). **1**: oil; R_f = 0.21 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3360 (OH, m), 3100 (COOH, b), 2960 (s), 2920 (s), 2850 (s), 1710 (acid, s), 1455 (m), 1410 (m), 1375 (m), 1260 (s), 1090 (s), 1020 (s), 865 (w), 795 (s), 735 (s), 700 (m) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.45 (m, 2 H, olefinic), 4.67 (t, J = 6 Hz, 1 H, H-5), 5.94 (q, J = 7 Hz, 1 H, H-15), 6.05 (m, 1 H, H-11), 6.10 (m, 1 H, H-9), 7.00–9.00 (m, 23 H), 9.11 (m, 3 H, CH_3).

Stable stock solutions of the sodium salt of **1** could be prepared by dissolving the methyl ester **20** (3.82 mg, 0.01 mmol) in a 0.1 M solution of sodium ethoxide in 90% ethanol (1 mL). This solution was allowed to stand at room temperature overnight before being diluted with absolute ethanol (9 mL). This procedure then provided standard solutions of the sodium salt **21** of 10^{-3} M.

Methyl (5*E*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate ((5*E*)-6,9-Thiaprostacyclin Methyl Ester) (28). Freshly prepared (5*E*)-thiol **4** (28 mg, 0.07 mmol) was immediately dissolved in anhydrous methylene chloride (10 mL). Potassium carbonate (49 mg, 0.35 mmol) was suspended in this solution and the resulting mixture cooled to −78 °C under argon. Iodine (17.8 mg, 0.07 mmol) was then added and the mixture stirred at −78 °C under argon until the iodine crystals had dissolved (about 3 h). The orange-red reaction mixture was now diluted with ether (100 mL), washed with 10% sodium thiosulfate solution (20 mL) and 10% potassium carbonate solution (20 mL), and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded the crude iodo thioether **27** (R_f = 0.45, silica, 5% methanol in ether) which was immediately redissolved in anhydrous benzene (600 μL). 1,5-Diazabicyclo[5.4.0]undec-5-ene (106 mg = 104 μL, 0.7 mmol) was added and the resulting solution stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with ether (75 mL), washed with water (5 × 20 mL) until the washings were neutral, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent, and purification by preparative

layer chromatography (silica, 2.5% methanol in ether, two developments) yielded the product (5*E*)-6,9-thiaprostacyclin methyl ester (**28**) (7 mg, 26% overall from **4**) and disulfide **26** (5 mg, 19%). **28**: oil; R_f (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ −7.5° (methanol, c = 0.0025); IR (liquid film) ν_{max} 3380 (OH, m), 2950 (s), 2920 (s), 2850 (s), 1730 (ester, s), 1625 (thioenol ether, w), 1455 (m), 1375 (m), 1260 (m), 1200 (m), 1165 (m), 1090 (m), 1015 (w), 965 (m), 730 (w), 695 (w) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.45 (m, 2 H, olefinic), 4.60 (t, J = 7 Hz, 1 H, H-5), 5.92 (m, 1 H, H-15), 6.05 (q, 7 Hz, 1 H, H-11), 6.13 (m, 1 H, H-9), 6.17 (s, 3 H, ester), 7.00–9.00 (m, 22 H), 9.10 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 382 (M^+, 5.4%), 364 ($M^+ - H_2O$, 3.8%), 346 ($M^+ - 2H_2O$, 6.7%), 250 (15.4%), 211 (25.1%), 123 (58.5%), 111 (35.8%), 99 (86.3%), 91 (54.7%), 67 (68.9%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_4S$ 382.2176, found 382.2177. **26**: white solid, mp 84–87 °C; R_f = 0.04 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ +62.2° (methanol, c = 0.0020); IR ($CHCl_3$) ν_{max} 3400 (OH, w), 2995 (m), 2950 (s), 2920 (s), 2860 (m), 2850 (m), 1725 (ester), 1620 (w), 1455 (m), 1435 (m), 1360 (w), 1240 (m), 1205 (s), 1170 (m), 1075 (m), 1010 (m), 965 (m), 720 (s) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.45 (dd, J = 7, 15 Hz, 2 H, olefinic), 4.55 (m, 6 H, olefinic), 5.94 (q, J = 7 Hz, 2 H, H-15), 6.09 (m, 2 H, H-11), 6.35 (s, 6 H, ester), 6.62 (m, 2 H, H-9), 7.42–9.00 (m, 44 H), 9.12 (m, 6 H, CH_3); mass spectrum, m/e (relative intensity) 383 ($M^+/2$ 0.4%), 366 ($M^+/2 + 1 - H_2O$, 3.6%), 365 ($M^+/2 - H_2O$, 1.2%), 3.48 ($M^+/2 + 1 - 2H_2O$, 5.8%), 347 ($M^+/2 - 2H_2O$, 1.7%), 252 (16.5%), 187 (15.4%), 149 (17.2%), 129 (19.4%), 117 (25.3%), 99 (82.1%), 91 (49.1%), 81 (52.8%), 79 (52.4%), 71 (52.7%), 67 (67.4%), 55 (base peak); HRMS ($M^+/2$) calcd for $C_{21}H_{35}O_4S$ 383.2255, found 383.2284.

(5*E*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid ((5*E*)-6,9Thiaprostacyclin) (2) and its Sodium Salt (30). (5*E*)-6,9-Thiaprostacyclin (**2**) and solutions of its sodium salt **30** were prepared from the methyl ester **29** exactly in the same manner and in similar yields as (5*Z*)-6,9-thiaprostacyclin (**1**) and its sodium salt **21**.

Methyl [5*Z*,6(*S*),9α,11α,13*E*,15*S*]- and [5*Z*,6(*R*),9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate *S*-Oxides (22a and 22b). The (5*Z*)-6,9-thia-PGI_2 methyl ester (**20**) (9.5 mg, 0.025 mmol) was dissolved in a solution of 30% hydrogen peroxide in tetrahydrofuran (250 μL, 1 M) and stirred at room temperature for 2 h. The reaction mixture was then diluted with ether (50 mL), washed with 10% sodium thiosulfate solution (10 mL), and saturated sodium chloride solution (10 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica gel, 5% methanol in methylene chloride, four developments) yielded the epimeric sulfoxides **22a** (R_f = 0.19, 4 mg, 40%) and **22b** (R_f = 0.08, 2 mg, 20%) which were in all respects identical with those described in the accompanying report.[22]

Methyl [5*E*,6(*S*),9α,11α,13*E*,15*S*)- and [5*E*,6(*R*),9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate *S*-Oxides (30a and 30b). The (5*E*)-6,9-thia-PGI_2 methyl ester (28) (9.5 mg, 0.025 mmol) was dissolved in *tert*-butyl hydroperoxide (250 μL, 70% solution in water) and the solution stirred at room temperature for 30 min. The reaction mixture was then diluted with ether (50 mL), washed with 10% sodium thiosulfate solution (10 mL) and saturated sodium chloride solution (10 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica gel, 5% methanol in methylene chloride, four developments) yielded the epimeric sulfoxides **30a** (R_f = 0.19, 4.3 mg, 42%) and **30b** (R_f = 0.08, 1.7 mg, 17%) which were in all respects identical with those described in the accompanying report.[22]

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Organoselenium-Based Synthesis of Oxygen-Containing Prostacyclins

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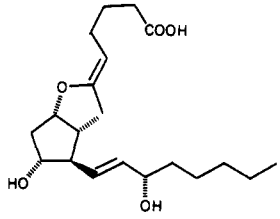
Abstract: The application of organoselenium-induced ring closures to the synthesis of stable, oxygen-containing prostacyclins is described. The strategy involves utilization of $PGF_{2\alpha}$ methyl ester (**3**) as a starting material in a PhSeCl-induced cyclization to produce the two epimeric 5-seleno-PGI_1 derivatives **5a** and **5b**. These key intermediates serve as precursors to both Δ^4-isoprostacyclins **7a** and **7b** and the 5,6-dihydroprostacyclins **13a** and **13b** by oxidative or reductive removal of the PhSe group, respectively, followed by saponification. The structures of these prostacyclins is discussed and assigned on the basis of chemistry, ^{1}H and ^{13}C NMR, and chromatographic data.

In the preceding paper[2] we outlined the biosynthesis and physiological importance of prostacyclin (**1**)[3] and thromboxane A_2 (**2**)[4] and presented the reasons for the design and synthesis of stable analogues of these important biomolecules. The novel and challenging structures of these compounds demanded the development of new methodology for rapid, selective, and flexible



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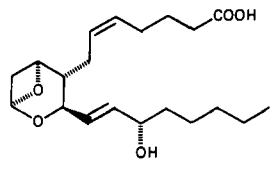

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