Organoselenium-Based Synthesis of Sulfur-Containing Prostacyclins

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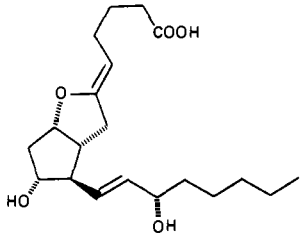
Abstract: A number of sulfur-containing prostacyclins have been synthesized stereoselectively by new organoselenium-based methodology. Thus, the key (5*Z*)- and (5*E*)-9-thioacetates **10** and **12** were converted stereospecifically to 6α- and 6β-5-phenylselenides **14** and **16**, respectively, by phenylselenenyl chloride-induced cyclization followed by desilylation. Selenide **14** served as a precursor to (5*Z*)-sulfoxaprostacyclins **17a** and **17b** and (5*Z*)-sulfonaprostacyclin **19** as well as the 6α-Δ^4-isosulfonaprostacyclin **21** whereas selenide **16** led selectively to the corresponding 5*E* series **23a**, **23b**, and **25** as well as the 6β-Δ^4-isoprostacyclin **27**. Furthermore, the (5*Z*)- or (5*E*)-9-thia-PGF$_{2\alpha}$ derivatives **10** and **12** were transformed to a series of 6,9-sulfoxa- and sulfonaprostacyclins **31ab**, **33abcd**, and **35ab** by acid-induced cyclization followed by oxidation. The stereoselectivity of these reactions and the stereochemistry of the products as well as the stability and biology of these compounds is discussed.

The biological importance and therapeutic potential of prostacyclin (**1**) have been well documented.[2,3] In the previous papers



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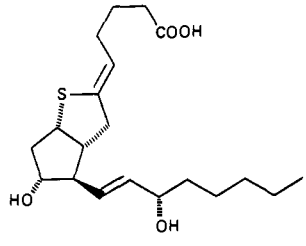

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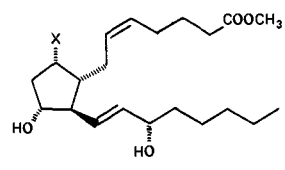
we described in detail the synthesis of the more stable 6,9-thia-prostacyclin (**2**)[4] and the application of organoselenium-based chemistry to the synthesis of a series of stable oxygen-containing prostacyclins.[5] In this report we discuss the extension of our selenium-based methodology in the stereoselective construction of a series of sulfur-containing prostacyclins[6] with increased stability.

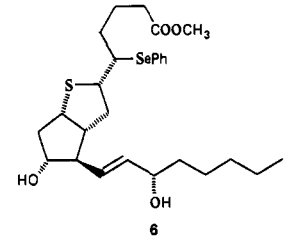
Results and Discussion

At the outset of our work in the prostacyclin area the application of the selenoetherification reaction to the construction of sulfur-containing heterocycles was not known. For the purpose of synthesizing directly prostacyclins with the α,β-unsaturated sulfoxide and sulfone groupings we investigated the induction of cyclization of unsaturated thiols and thiol derivatives by organoselenium reagents. Our successful methodological studies[7] in this area involved oxidative treatment of the cyclic thio selenides obtained by cyclization leading to unsaturated sulfoxides or sulfones depending on the conditions by concomitant oxidative removal of selenium and attack on sulfur. The strategy then involved basically (1) the selenium-induced ring-closure reaction of suitable precursors and (2) the oxidation reaction.

(1) The Ring-Closure Reaction. Recently the formation of cyclic ethers induced by organoselenium reagents has been described.[7-9] The successful cyclization of PGF$_{2\alpha}$ methyl ester (**3**) with PhSeCl



3, X = OH
4, X = SH
5, X = SSePh



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involving the C-9 hydroxy group and the C-5 olefin to afford a 5-membered ring seleno ether[5,10] encouraged us to believe that the same chemo- and regiospecificity would be observed in the case of 9-thia-PGF$_{2\alpha}$ methyl ester (**4**) or a protected equivalent. Indeed, when 9-thia-PGF$_{2\alpha}$ methyl ester (**4**) was treated with PhSeCl in methylene chloride at −78 °C, a single seleno thioether **6** was obtained in 40% yield along with an additional product presumed to be the sulfur selenide **5**. The structure of **5** was inferred from its relative instability upon chromatographic isolation and attempted concentration when it partially cyclized to **6** and partially suffered collapse liberating diphenyl diselenide. Model studies[7] were also supportive of the sulfur selenide structure obtained by direct attack of the highly nucleophilic sulfur on selenium displacing chloride. This mixed result and the lability of **4** itself (to oxidation) led us to seek alternative precursors to the seleno thioethers by this reaction. Also, in order to examine the stereoselectivity of the ring closure and oxidative elimination reactions and to prepare in a selective manner as many prostacyclins as possible, we considered synthesizing both the 5*E* and 5*Z* geometrical isomers of 9-thia-PGF$_{2\alpha}$ protected as suitable precursors. The synthesis and selenium-induced cyclizations of these compounds is depicted in Figure 1.

The readily available mesylate **7**[4] was deprotected by exposure to AcOH-THF-H_2O (3:2:2) at 45 °C (12 h) to yield diol **8** (80%) which was silylated with *tert*- butyldimethylsilyl chloride in the presence of imidazole in DMF leading to the bis(silyl ether) **9** (81%). When bis(silyl ether) **9** was irradiated with UV light in deoxygenated benzene solution in the presence of diphenyl disulfide, a photoequilibrium was established between the (5*Z*)- and (5*E*)-mesylates **9** and **11** (*Z*/*E* ca. 16:84) without appreciable loss

(1) Fellow of the A. P. Sloan Foundation 1979-1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985.
(2) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293.
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(4) Nicolaou, K. C.; Barnette, W. E., Magolda, R. L. *J. Am. Chem. Soc.*, preceding paper in this issue (paper 1 of this series).
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(10) Reich, H. J. *J. Org. Chem.* **1974**, *39*, 628. Sharpless, K. B.; Lauer, R. F. *Ibid.* **1974**, *39*, 429. Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1973**, 695; **1974**, 100.
(11) For reviews see: (a) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (c) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9.

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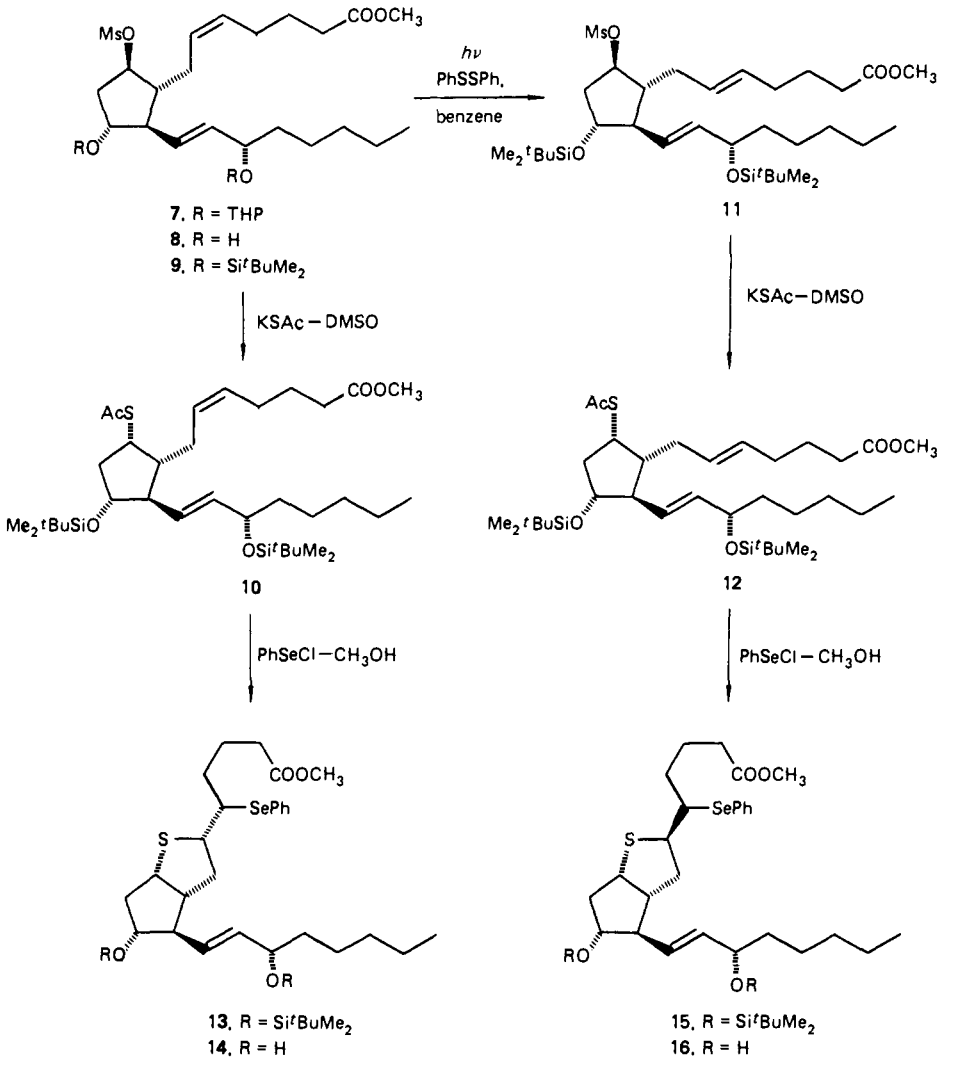

Figure 1. Synthesis and selenium-induced cyclization of 9-thia-PGF$_{2\alpha}$ and (5*E*)-9-thia-PGF$_{2\alpha}$.

of material. Irradiation of **7** itself under the above conditions was found unsatisfactory, presumably due to ready photoinduced hydrogen abstractions from the tetrahydropyranyl groups leading to extensive decomposition. The silyl groups had a further advantage in that they fascilitated chromatographic isolation of the two isomers in pure form. Thus, column chromatography on silver nitrate impregnated silica afforded pure 5*E* isomer **11** (84%) and 5*Z* isomer **9** (16%). Treatment of mesylate either **9** or **11** with excess potassium thioacetate in DMF at 45 °C (24 h) resulted in displacement with inversion of configuration at C-9 leading to thioacetates **10** and **12**, respectively (75% yield in both cases). At this point it was discovered that these 11,15-bis(silyl ether) thioacetate derivatives of (5*Z*)- and (5*E*)-PGF$_{2\alpha}$ would undergo organoselenium-induced cyclizations[7] without prior liberation of the thiol group. Thus, when either **10** or **12** was reacted with PhSeCl (1.2 equiv) in absolute methanol at −78 °C, two different selenides, each a single isomer (**13** or **15**), were obtained in 62% and 60%, respectively. This observation on the ability of the thioacetates **10** and **12** to undergo ring closure which has been found to be general[7] eliminates the problems of handling air-sensitive thiols. Furthermore, TLC analysis of the reaction mixture showed no trace of the open sulfur selenide corresponding to **5**, thus avoiding this undesired pathway earlier encountered in the case of thiol **4**. Desilylation of **13** with *tetra-n*-butylammonium fluoride in THF at 25 °C furnished **14** in 94% yield, whereas similar treatment of **15** led to **16** in 93% yield. The stereochemical assignments of these compounds as shown was based on ^{1}H NMR spectroscopic data and will be discussed later in this paper.

(2) The Oxidation Reaction. The oxidation and elimination of the PhSe group in selenides **14** and **16** was expected to be complicated by the presence of the divalent sulfur. A major and interesting question was also the nature and direction of the selenoxide elimination with respect to the sulfur group. In the case of seleno ethers (cyclic or acyclic) and seleno acetates, previous observations[10,11] have shown consistently that elimination occurs, when allowed, exclusively away from oxygen to form allylic ethers and acetates, respectively. This tendency of selenoxides which parallels that of sulfoxides[12] can be attributed to the polarity of this group which forces it to allign itself antiparallel to the oxygen lone pair of electrons, thereby positioning it favorably for an elimination away from oxygen. This selectivity was specifically applied to form stable (4*E*)-isoprostacyclins as described in the previous paper.[4] By analogy, it was anticipated that divalent sulfur would force the elimination to follow a similar course, although production of the sulfoxide function prior elimination was recognized as a possibility that could reverse the course of the reaction toward this group by virtue of the enhanced acidity of the hydrogen α to the sulfoxide.[13] The experimental results described below proved quite interesting demonstrating high selectivity.

Oxidation of **14** (Figure 2) with *m*-CPBA (1.0 equiv) in methylene chloride at −78 °C resulted in selective oxidation of sulfur (as judged by TLC). Further addition of *m*-CPBA (1.0 equiv) at −78 °C and warming to −20 °C effected oxidation at selenium (as judged by TLC). Subsequent warming to 20 °C yielded isomeric (5*Z*)-sulfoxides **17a** (18%) and **17b** (53%) by

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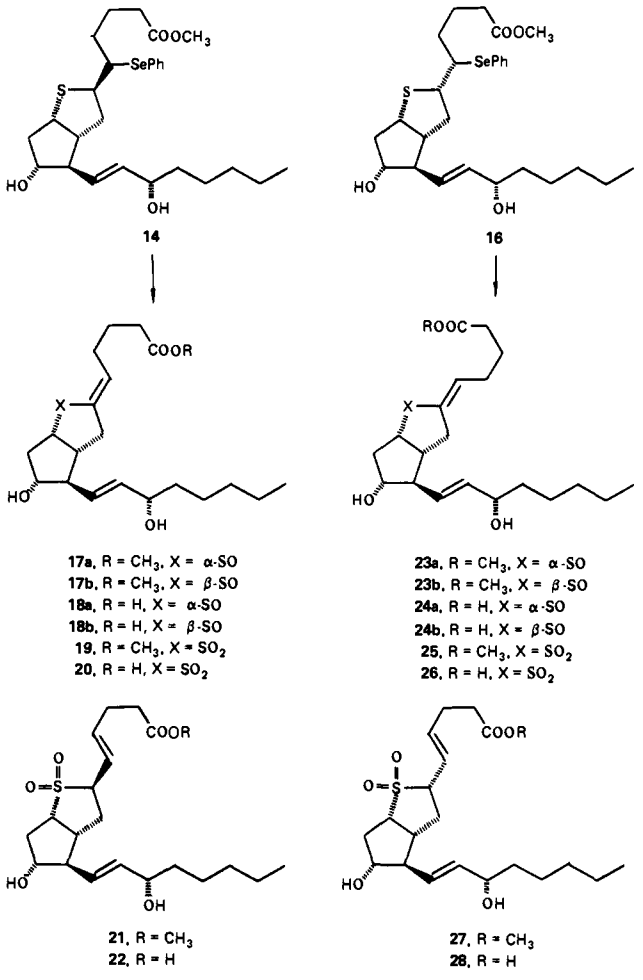

Figure 2. Synthesis of sulfoxa- and sulfona-PGI_2 analogues.

syn elimination toward the sulfoxide (method A). The addition of a third equivalent of *m*-CPBA at −20 °C prior to warming to ambient temperature resulted in further oxidation at sulfur and exclusive formation of the (5*Z*)-sulfone **19** (86%) (method B). Alternatively this sulfone (**19**) could be obtained by addition of hydrogen peroxide (4 equiv) to the reaction mixture of method A (83%, method C). This observed facile sulfoxide → sulfone oxidation is presumably effected by benzeneperoxyseleninic acid (PhSe(O)OOH)[6,14,15] generated in situ under the reaction conditions (H_2O_2 + liberated PhSeOH). Finally, the oxidation of the thio selenide **14** with excess hydrogen peroxide (8 equiv) in tetrahydrofuran at room temperature gave directly the sulfone **19** as the major product (ca. 70–75%) together with smaller varying amounts of the unconjugated (4*E*)-sulfone **21** (17–22%) depending on the initial peroxide concentration (method D). This nonselectivity in the direction of the elimination of the selenoxide is presumably due to indiscriminate oxidation of sulfur and selenium by hydrogen peroxide resulting in a mixture of selenoxide–sulfide, selenoxide–sulfoxide which could eliminate by different pathways. Base hydrolysis (excess LiOH in aqueous tetrahydrofuran) of the methyl ester series led to the corresponding acids **18a**, **18b**, **20**, and **22** in good yields.

Exposure of the isomeric thio selenide **16** to the above oxidation methods furnished similar results leading to the corresponding 5*E* series of compounds **23a**, **23b**, **25**, and the 4*E* unconjugated sulfone **27**: method A, **23a** (25%) and **23b** (53%); method B, **25** (82%); method C, **25** (80%); method D, **25** (65–70%) and **27** (10–15%). Basic hydrolysis of this series of compounds with excess lithium hydroxide in aqueous tetrahydrofuran again produced the corresponding acids **24a**, **24b**, **26**, and **28** in good yields.

Thus, despite the introduction of the sulfur parameter, conditions were found to produce selectively a number of sulfoxa- and sulfonaprostacyclins. It appears that elimination of selenoxide occurs by a *syn mechanism* (see later discussion) and at least partially away from divalent sulfur, whereas, the same type of elimination occurs selectively toward the sulfoxide group. The relatively high acidity of the hydrogen α to the sulfoxide[13] is proposed as the overriding factor for the direction of the elimination.

(3) Synthesis of Sulfur-Containing PGI_1 Analogues. In the course of our investigations with 9-thia-$PGF_{2\alpha}$ and its derivatives we observed that these thiols had a tendency to form the corresponding disulfide and also produce substantial amounts of tetrahydrothiophene derivatives such as **31ab** (Figure 3). These reactions occurred rapidly upon attempted chromatography on silica or on standing at ambient temperature for prolonged periods of time. This observation encouraged us to explore this ring-closure reaction in the hope of developing a synthetic entry into the sulfur-containing prostaglandin I_1 (PGI_1) series.

Although the addition of thiols to olefins is typically a free radical reaction catalyzed by oxygen, peroxides, light, or other initiators, attempted intramolecular addition of the thiol to the C-5 olefin under photolytic conditions or in the presence of azobis(isobutyronitrile) (AIBN), a radical initiator, failed. On the other hand, however, a carefully degassed solution of freshly prepared thiol **29** (from methanolysis of **10** with 2.0 equiv of sodium methoxide in absolute methanol) in AcOH–THF–H_2O (3:2:2) at 45 °C produced the cyclic sulfide **31a** and **31b** (ca 1:2.7 by ^1H NMR, τ 6.13 and 6.29 (H-11)) by ring closure and concomitant desilylation. Interestingly, precisely the same mixture of C-6 diastereoisomers **31a** and **31b** was obtained by similar treatment of the (5*E*)-thiol **30** (prepared similarly from the thioacetate **12**). Since this mixture of **31ab** was unseparable by TLC, it was oxidized without separation to the corresponding sulfoxides (**33ac** and **33bd**) with *m*-CPBA (1.0 equiv) in methylene chloride at −20 °C. These four sulfoxides were separated on silica as two pairs: mixture A (33%), R_f = 0.11 (5% methanol in methylene chloride), presumed on the basis of ^1H NMR (see experimental) to be the α-sulfoxides (stereochemistry at sulfur) and mixture B (29%), R_f = 0.08 (5% methanol in methylene chloride), presumed to be the β-sulfoxides (stereochemistry at sulfur). The corresponding 6,9-sulfona-PGI_1 methyl esters (**35a** and **35b**) were prepared by hydrogen peroxide oxidation of **31ab** (mixture of C-6 epimers) in the presence of catalytic amounts of PhSeSePh (10 mol%).[6,15] These sulfones were separated chromatographically on silica with 3% methanol in ether as eluant **35b** (R_f = 0.33, 65%) and **35a** (R_f = 0.27, 24%) and their stereochemistry is discussed below. Hydrolysis of the methyl esters again with excess lithium hydroxide in aqueous tetrahydrofuran at ambient temperature afforded the corresponding acids **32ab** (mixture of C-6 epimers), **34abcd** (two isomeric pairs), **36a** (pure isomer), and **36b** (pure isomer) in good yields.

(4) Stereochemistry of Prostacyclins. Having proven the 5-membered ring (rather than a 6-membered ring) nature of the heterocycle of the discussed prostacyclins by model studies,[7] similarities in ^1H NMR spectra and direct comparisons of the sulfoxides **17ab** and **23ab** with those obtained from (5*Z*)- and (5*E*)-6,9-thiaprostacyclin methyl esters,[4] we now focus discussion on (a) the geometry of the 5-olefin and (b) the configuration at C-6 of these synthetic, sulfur-containing prostacyclins. Although mechanistic considerations served as excellent guidelines with regard to geometrical isomerism, it was again, as in the case of the oxygen-containing prostacyclins,[4] ^1H NMR spectroscopy that provided the basis for the stereochemical assignments for both the 5-olefin geometry and the C-6 stereochemistry.

The 5*E* and 5*Z* geometries of the final 6,9-sulfoxa- and 6,9-sulfonaprostacyclins were initially assumed on mechanistic grounds. Thus, since it has been well established that PhSeCl induces the addition of alcohols both inter- and intramolecularly

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(15) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299.
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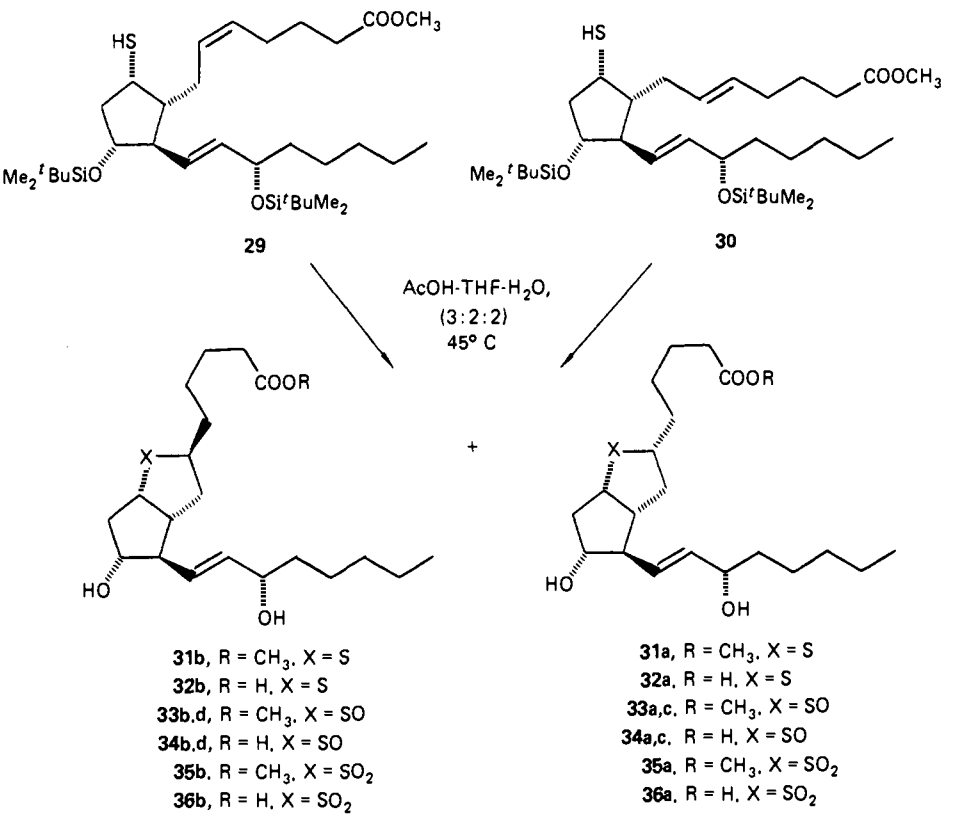

Figure 3. Synthesis of sulfur-containing PGI_1 analogues.

Table I. ^1H NMR Chemical Shifts for H-5 in the Sulfur-Containing Prostacyclin (PGI_2) Series

compd	^1H NMR ($CDCl_3$, 360 MHz), τ(H-5)
(5*E*)-sulfoxa-PGI_2 methyl ester (α) (23a)	3.72
(5*E*)-sulfoxa-PGI_2 methyl ester (β) (23b)	3.59
(5*E*)-sulfona-PGI_2 methyl ester (25)	3.56
(5*Z*)-sulfoxa-PGI_2 methyl ester (α) (17a)	3.98
(5*Z*)-sulfoxa-PGI_2 methyl ester (β) (17b)	3.92
(5*Z*)-sulfona-PGI_2 methyl ester (19)	4.00
(5*E*)-thia-PGI_2 methyl ester[4]	4.60
(5*Z*)-thia-PGI_2 methyl ester[4]	4.69

in a clean trans stereospecific manner,[7-10,11] it was assumed that the same mechanism operates in the case of thiols or their derivatives. Hence a trans stereospecific addition of selenium-induced cyclization reaction involving a (*Z*)-olefin followed by a syn elimination of a selenoxide would result in the formation of an (*E*)-thia-, -sulfoxa-, or -sulfonaenol ether, whereas the corresponding *Z* series should result from the (*E*)-olefin by the same sequence. These predictions are illustrated in Figure 4 and were demonstrated in appropriate model compounds.[7] The ^1H NMR spectra of these α,β-unsaturated sulfoxide- and sulfone-containing prostacyclins were also supportive of their assigned geometries. Table I shows the chemical shifts of H-5 and compares them withthose of (5*E*)- and (5*Z*)-thia-PGI_2 methyl esters. Figure 5 presents the low-field ^1H NMR region of these compounds. In every pair of *Z* and *E* geometrical isomers there was a consistent downfield shift (averaging ca. 0.35 ppm) observed for H-5 for the expected *E* isomer relative to the Z isomer. This effect presumably results from the closer proximity of this proton to the sulfoxide or sulfone group in the E isomer and has been extensively used previously for assigning the geometries of enol ethers[17] including prostacyclins.[18] Furthermore, oxidation of (5*E*)- and (5*Z*)-

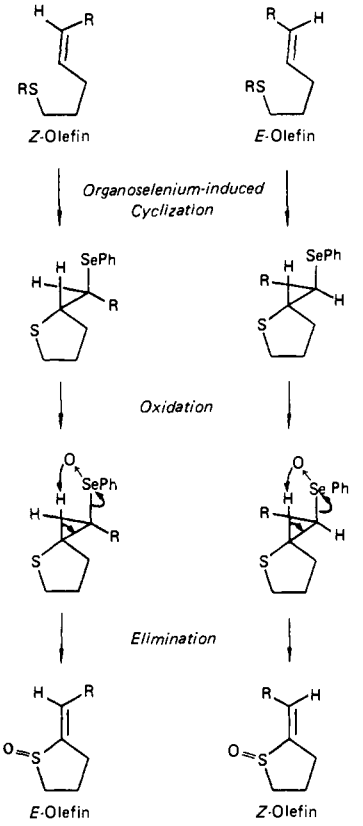

Figure 4. Stereochemical course of the cyclization and elimination reactions.

thia-PGI_2,[4] the stereochemistries of which have been established, to sulfoxides **17ab** and **23ab** respectively, strengthens these assignements.

(17) (a) House, H. O.; Kramer, V. *J. Org. Chem.* **1963**, *28*, 3362. (b) Rhoads, S. J.; Chattopadhyay, J. K.; Waali, E. E. *Ibid.* **1970**, *35*, 3352. (c) Nidy, E. G.; Johnson, R. A. *Ibid.* **1975**, *40*, 1415.

(18) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690.

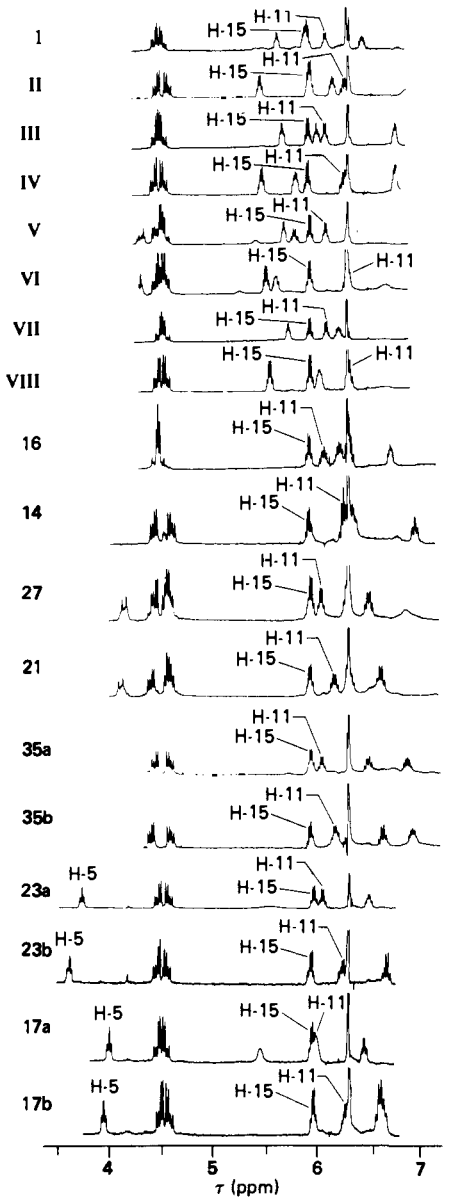

Figure 5. Partial ^1H NMR spectra of prostacyclins of Table II (360 MHz, $CDCl_3$).

In the case of oxygen-containing prostacyclins the chemical shift of H-9 and the R_f values of the two epimers were recognized as useful criteria for assigning the C-6 stereochemistry.[5,18,19] In the sulfur series, however, these criteria were not very useful since no consistent trends were recognized with respect to these two parameters. On the other hand, it was recognized that the endo epimers in the sulfur-containing prostacyclin series exhibited invariably a downfield shift for H-11 relative to the exo isomer (Table II). This trend is also evident in the oxygen-containing prostacyclin series[5] which are included in Table II for comparison reasons. Since the C-6 stereochemistry of the oxygen series has been rigorously established[5,19] and because this chemical shift difference for H-11 is common in the two series (as shown in Table II, which contains 14 compounds; chemical shift difference for exo–endo isomers ca. 0.10–0.22 ppm) we have used this as an empirical criterion to assign the C-6 stereochemistry of both oxygen- and sulfur-containing prostacyclins. We then used this as an empirical criterion to assign the C-6 stereochemistry of both

Table II. Chemical Shifts[a] of H-15 and H-11 of Prostacyclins

compd	no.	H-15	H-11
6α-5-iodo-PGI_1	I[5]	5.94	6.12
6β-5-iodo-PGI_1	II[5]	5.96	6.29
6α-5-phenylseleno-PGI_1	III[5]	5.95	6.12
6β-5-phenylseleno-PGI_1	IV[5]	5.96	6.32
6α-Δ^4-iso-PGI_2	V[5]	5.94	6.10
6β-Δ^4-iso-PGI_2	VI[5]	5.96	6.32
6α-PGI_1	VII[5]	5.96	6.12
6β-PGI_1	VIII[5]	5.96	6.34
6α-5-phenylselenothia-PGI_1	16	5.98	6.13
6β-5-phenylselenothia-PGI_1	14	5.97	6.30
6α-Δ^4-isosulfona-PGI_2	27	5.98	6.08
6β-Δ^4-isosulfona-PGI_2	21	5.98	6.18
6α-sulfona-PGI_1	35a	5.95	6.05
6β-sulfona-PGI_1	35b	5.97	6.21
(5*E*)-sulfoxa-PGI_2 (α)	23a	5.98	6.06
(5*E*)-sulfoxa-PGI_2 (β)	23b	5.95	6.28
(5*Z*)-sulfoxa-PGI_2 (α)	17a	5.97	6.00
(5*Z*)-sulfoxa-PGI_2 (β)	17b	5.98	6.27

[a] Spectra were recorded in $CDCl_3$ at 360 MHz, and chemical shifts are in τ values.

oxygen- and sulfur-containing prostacyclins.

Table II also includes the four sulfoxides **23a**, **23b**, **17a**, and **17b** which also show similar differences in the H-11 chemical shifts. This difference, taken together with the relative R_f values of these compounds, allows a tentative assignment of the sulfoxide configurations. Thus, we assigned to the less polar (silica, 5% methanol in methylene chloride) isomers **23a** (R_f = 0.19) and **17a** (R_f = 0.19) the α (endo) configuration and to the more polar isomers **23b** (R_f = 0.08) and **17b** (R_f = 0.08) the β (exo) configuration. The low-field region of the ^1H NMR spectra of a number of oxygen- and sulfur-containing prostacyclins are displayed in Figure 3 and show clearly these differences of the H-11 proton whereas H-15 remains more or less at a constant field (see also Table II).

Further support for the above exo/endo assignments was obtained from the fact that both Δ^4-isosulfonaprostacyclins **21** and **27** were hydrolyzed to the same acid **22** on treatment with aqueous base, indicating that one of them suffered epimerization at C-6. Clearly the 6-endo isomer **27** is expected to be the one to isomerize to the thermodynamically most stable exo isomer **21** and this was indeed the case as revealed by the similarity of the ^1H NMR spectra of the acid **22** and the methyl ester of the exo isomer **21** (also diazomethane treatment of **22** led to the C-6 exo methyl ester **21**).

(5) Chemical Stability and Biological Activity of Sulfur-Containing Prostacyclins. Although all the sulfur-containing prostacyclins synthesized were found to be quite stable as the acids, it was much more convenient to prepare their sodium salts from the methyl ester in aqueous ethanolic solutions for biological evaluations. The hydrolysis was carried out with 1 M sodium ethoxide (10 equiv) in 90% ethanol at 25 °C for 24 h followed by appropriate dilutions before testing. The biological evaluations on blood platelets were carried out by Professor J. B. Smith[20] and those on the cat coronary artery by Professor A. M. Lefer.[21] The stability of the prostacyclins in saline solution were determined by bioassay. A summary of the results in these studies is shown in Table III.

Conclusion

In this study, we have demonstrated the application of organoselenium-induced ring closures[6,7] in the synthesis of a series of complex sulfur-containing prostacyclins. Unlike the selenium-induced cyclization of $PGF_{2\alpha}$ methyl ester (**3**) which leads to a mixture of C-6 epimers,[4,22,23] cyclization of 9-thia-$PGF_{2\alpha}$ deriv-

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(20) Cardeza Foundation and Department of Pharmacology, Thomas Jefferson University, Philadelphia, PA 19174.

(21) Department of Physiology, Thomas Jefferson University, Philadelphia, PA 19174.

(22) Nicolaou, K. C.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* (1977) 331.

Table III. Biological Properties of Sulfur-Containing Prostacyclins

prostacyclin		$T_{1/2}$ (saline, 25 °C)[b]	biological activity[a]	
			platelet aggregation	cat coronary artery
natural prostacyclin (PGI_2)	1	2 min	(1) inhibitor (P)	dilator (P)
6,9-thia-5(*Z*)-prostacyclin	2	>3 h	(0.2-0.5) inhibitor (P)	constrictor (P)
6,9-sulfoxa-5(*E*)-prostacyclin (α)	24a	>24 h	very little activity, if any	very little activity, if any
6,9-sulfoxa-5(*E*)-prostacyclin (β)	24b	>24 h		
6,9-sulfoxa-5(*Z*)-prostacyclin (α)	18a	>24 h	little activity	little activity
6,9-sulfoxa-5(*Z*)-prostacyclin (β)	18b	>24 h		
6,9-sulfo-5(*E*)-prostacyclin	26	>24 h	very little activity, if any	very little activity, if any
6,9-sulfo-5(*E*)-prostacyclin	20	>24 h	little activity	little activity
6,9-thia-5,6-dihydroprostacyclin	30ab	>24 h	little activity	constrictor (M)
6,9-sulfoxa-5,6-dihydroprostacyclin	32ab	>24 h	antagonist of prostacyclin (M)	constrictor (M)
6,9-sulfo-5,6-dihydroprostacyclin	36ab	>24 h	antagonist of prostacyclin (M)	constrictor (M)
6,9-sulfo-4(*E*)-isoprostacyclin, 6β isomer	22	>24 h	inhibitor	constrictor (M)

[a] P = potent; M = moderate (concentrations ca. 10^{-6} M); very little activity means at concentrations $<10^{-6}$ M; compounds may show more activity at concentrations $>10^{-6}$ M. [b] $T_{1/2}$ = half-life.

atives **10** and **12** is completely stereoselective resulting in the exclusive formation of the endo and exo bicyclic seleno esters **13** and **15**, respectively. This selectivity reflects a change from a thermodynamic to a complete kinetic control of these reactions by changing from oxygen to sulfur as the nucleophile. An examination of Dreiding models of the thioacetate substrates **10** and **12** reveals no obvious steric reasons for the conformation of the two molecules to follow different reaction pathways. To account for the complete stereospecificity, however, one can postulate a complexation of both the olefin and the sulfur group by selenium prior to selenonium ion formation. This simultaneous complexation is apparently strong and geometrically demanding enough, so as to be sensitive to the geometry of the C-5 olefin. The stronger affinity of sulfur toward selenium as compared to that of oxygen is evident from the isolation of sulfur selenides[7] but not oxygen selenides. Whereas, a fully formed sulfur selenide such as **5** is possible in the cyclization of thiols, this is doubtful in the case of thioacetates, since such intermediate was detected only in the case of thiol cyclization. As a corollary, the lack of stereoselectivity in the cyclization of $PGF_{2\alpha}$ methyl ester (**3**) itself implies the absence of such a strong simultaneous coordination of the olefin and oxygen to selenium prior to formation of the intermediate selenonium ion.

As a result of these organoselenium-induced and other ring closure reactions, a series of 5*Z* and 5*E* and α,β and β,γ-unsaturated as well as 5,6-dihydro sulfur-containing prostacyclins were synthesized with high degree of stereoselectivity. All new prostacyclins synthesized in this study showed enhanced chemical stability and varying degrees of biological activity although non exhibited the potency of the natural prostacyclin. In terms of structure-activity relationships these and other[2,4,5] observations suggest the following: (a) oxidation of the 6,9 bridge results in decreased biological activity and (b) the absence of an sp^2 hybridization at C-6 coincides with diminished activity.

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 in 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, Univeristy 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 preformed 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, 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_3-Si refers to the trimethylsilyl group and HRMS refers to high-resolution mass spectra.

Microanalyses were preformed by Galbraith Laboratories.

Methyl (5*Z*,9β,11α,13*E*,15*S*)-11,15-Dihydroxy-9-[(methylsulfonyl)oxy]prosta-5,13-dien-1-oate (8). The mesylate **7** (1082 mg, 1.76 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 × 40 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent, and purification by column chromatography (silica, 5% methanol in ether) yielded the dihydroxy mesylate **8** (630 mg, 80%), **8**: oil; R_f = 0.26 (silica, 5% methanol in ether); $[\alpha]^{25}_D$ −15.8° (methanol, *c* = 0.017); IR (liquid film) ν_{max} 2900 (OH, m), 3000 (w), 2940 (s), 2920 (s), 2850 (m), 1730 (ester, s), 1430 (m), 1410 (w), 1350 (SO_2, s), 1240 (m), 1170 (s), 1080 (w), 1015 (w), 965 (s), 910 (s), 875 (m), 810 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.70 (m, 4 H, olefinic), 5.39 (m, 1 H, H-9), 6.14 (m, 2 H, H-11, H-15), 6.51 (s, 3 H, ester), 7.18 (s, 3 H, OSO_2CH_3), 7.73–9.00 (m, 22 H), 9.32 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 494 (M^+ − MesOH, $2Me_3Si$, 0.1%), 479 (M^+ − MesOH − CH_3, 1.4%), 423 (4.6%), 404 (M^+ − MesOH − Me_3SiOH, 5.6%), 333 (15.3%), 314 (M^+ − MesOH − $2Me_3SiOH$, 12.5%), 199 (39.9%), 173 (48.0%), 153 (63.9%), 147 (61.1%), 129 (58.2%), 117 (56.5%), 81 (91.4%), 79 (base peak); HRMS (M − H_2O) calcd. for $C_{22}H_{36}O_6S$ 428.2232, found 428.2236.

Methyl (5*Z*,9β,11α,13*E*,15*S*)-11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[(methylsulfonyl)oxy]prosta-5,13-dien-1-oate (9). The mesylate **8** (600 mg, 1.34 mmol) and imidazole (220 mg, 3.23 mmol) were dissolved in anhydrous dimethylformamide (3 mL). *tert*-Butyldimethylchlorosilane (484 mg, 3.23 mmol) was added and the solution stirred at room temperature under argon for 30 min. The reaction mixture was diluted with ether (60 mL), washed with water (15 mL) and 10% potassium bicarbonate solution (15 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, 25% ether in hexane) yielded the product **9** (730 mg, 81%). **9**: oil; R_f = 0.12 (silica, 25% ether in hexane); $[\alpha]^{25}_D$ −18.2° (methanol, *c* = 0.059); IR (liquid film) ν_{max} 3000 (w), 2940 (s), 2920 (s), 2850 (s), 1730 (ester, s), 1455 (m), 1430 (m), 1355 (SO_2, s), 1250 (s), 1175 (s), 1120 (m), 1005 (m), 960 (s), 880 (s), 840 (s), 775 (s); ^1H NMR (220 MHz, $CDCl_3$) τ 4.58 (m, 4 H, olefinic, 5.24 (m, 1 H, H-9), 6.00 (m, 2 H, H-11, H-15), 6.36 (s, 3 H, ester), 7.04 (s, 3 H, OSO_2CH_3), 7.50–8.91 (m, 20 H), 9.14 (m, 21 H, *tert*-butyl, H-20), 9.98 (m, 12 H, $SiCH_3$); mass spectrum *m/e* (relative intensity) 617 (M^+ − C_4H_9, 1.7%) 5.63 (2.3%), 522 (base peak), 446 (5.4), 389 (15%), 305 (14.3%), 241 (32.5%), 147 (39.5%); HRMS calcd for $C_{34}H_{66}O_7SSi_2$ 674.4062, found 674.4039.

Methyl (5*E*,9β,11α,13*E*,15*S*)-11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[(methylsulfonyl)oxy]prosta-5,13-dien-1-oate (11). The mesylate **8** (700 mg, 1.04 mmol) and diphenyl disulfide (113 mg, 0.052

(23) Corey, E. J.; Keck, G. E.; Szekely, I. *J. Am. Chem. Soc.* **1977**, *99*, 2006.

mmol) were dissolved in anhydrous benzene (75 mL) and the solution deoxygenated with argon. The reaction flask was then immersed in a water bath maintained at 25 °C and irradiated for 6 h under argon. Removal of solvent under reduced pressure and purification by column chromatography (silver nitrate impregnated silica, 25% ether in hexane) yielded the (5*E*)-mesylate **11** (590 mg, 84%), along with recovered (5*Z*)-mesylate **8** (110 mg, 16%): *Z*, R_f = 0.43; *E*, R_f = 0.49 (Ag^+ silica, ether–hexane 1:1). The silver-impregnated silica gel was prepared by suspending standard column grade silica gel (100 g) in a solution of silver nitrate (10 g) in water (200 mL). Simultaneous mixing and removal of water were achieved by rotovapping the mixture at 60 °C. The remaining water was removed by drying at 60 °C under vacuum for 4 h followed by oven drying at 115 °C for 24 h. In all cases light was excluded by wrapping the flask in aluminum foil and the silica thus prepared was stored in the dark in a brown bottle. The actual reaction and chromatographic purification was monitored by thin-layer chromatography utilizing plates immersed for 5 s in a silver nitrate in acetonitrile solution (10% by weight) after being dried for 45 min. These plates were then stored in the dark until needed. **11**: oil; R_f = 0.12 (silica, 25% ether in hexane); $[\alpha]^{25}_D$ −15.9° (methanol, *c* = 0.021); IR (liquid film) ν_{max} 3000 (w), 2950 (s), 2900 (m), 2850 (s), 1730 (ester, s), 1460 (m), 1430 (m), 1355 (SO_2, s), 1250 (s), 1175 (s), 1050 (s), 1000 (m), 970 (s), 890 (s), 835 (s), 775 (s) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.57 (m, 4 H, olefinic), 5.20 (m, 1 H, H-9), 5.98 (m, 2 H, H-11, H-15), 6.35 (s, 3 H, ester), 7.04 (s, 3 H, OSO_2CH_3), 7.50–8.91 (m, 20 H), 9.14 (m, 21 H, *tert*-butyl, H-20), 9.98 (m, 12 H, $SiCH_3$); mass spectrum, *m/e* (relative intensity) 617 ($M^+ - C_4H_9$, 2.9%), 563 (1.4%), 522 (base peak), 448 7.0%), 315 (12.1%), 241 (20.0%), 215 (36.4%), 171 (30.4%), 147 (31.7%), HRMS calcd for $C_{34}H_{66}O_7SSi_2$ 674.4062, found 674.4033.

Methyl (5*Z*,9α,11α,13*E*,15*S*)-9-(Acetylthio)-11,15-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]prosta-5,13-dien-1-oate (10). The (5*Z*)-mesylate **9** (450 mg, 0.66 mmol) was dissolved in anhydrous dimethylformamide (15 mL). Potassium thioacetate (1140 mg, 9.9 mmol) was added and the mixture stirred at 45 °C under argon for 15 h. The reaction mixture was diluted with water (30 mL) and extracted with ether (3 × 40 mL). The combined extracts were washed with water (2 × 25 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, 10% ether in hexane yielded the thioacetate **10** (328 mg, 76%). **10**: oil; R_f = 0.29 (silica, 10% ether in hexane); $[\alpha]^{25}_D$ −21.7° (methanol, *c* = 0.056); IR (liquid film) ν_{max} 3000 (w), 2950 (s), 2920 (s), 2890 (s), 2850 (s), 1740 (ester, s), 1688 (thioester, s), 1470 (m), 1460 (m), 1430 (m), 1355 (m), 1250 (s), 1100 (s), 1000 (m), 960 (m), 890 (m), 830 (s), 800 (m), 770 (s) cm^{-1}; ^1H NMR (360 HMz, $CDCl_3$) τ 4.65 (m, 4 H, olefinic), 5.97 (m, 2 H, H-11, H-15), 6.14 (q, *J* = 7 Hz, 1 H, H-9), 7.70 (s, 3 H, $SCOCH_3$), 7.50–8.92 (m, 20 H), 9.12 (m, 21 H), *tert*-butyl, H-20), 9.97 (m, 12 H, $SiCH_3$); mass spectrum, *m/e* (relative intensity) 597 ($M^+ - C_4H_9$, 40.6%), 447 (4.5%), 389 (5.4%), 375 (9.5%), 315 (20.3%), 133 (38.0%), 75 (84.7%), 73 (base peak); HRMS ($M^+ - C_4H_9$) calcd for $C_{31}H_{57}O_5SSi_2$ 597.3464, found 597.3390.

Methyl (5*E*,9α,11α,13*E*,15*S*)-9-(Acetylthio)-11,15-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]prosta-5,13-dien-1-oate (12). The (5*E*)-mesylate **11** (570 mg, 0.845 mmol) was dissolved in anhydrous dimethylformamide (17 mL). Potassium thioacetate (1466 mg, 12.69 mmol) was added and the mixture stirred at 45 °C under argon for 15 h. The reaction mixture was then diluted with water (34 mL) and extracted with water (2 × 25 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by column chromatography (silica, 10% ether in hexane) yielded the thioacetate **12** (409 mg, 74%). **12**: oil; R_f = 0.29 (silica, 10% ether in hexane); $[\alpha]^{25}_D$ −6.1° (methanol, *c* = 0.033); IR (liquid film) ν_{max} 3000 (w), 2950 (s), 2920 (s), 2890 (s), 2850 (s), 1740 (ester, s), 1685 (thioester, s), 1450 (m), 1425 (m), 1350 (m), 1250 (s), 1100 (s), 1005 (m), 965 (m), 885 (m), 835 (s), 770 (s) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.64 (m, 4 H, olefinic), 5.98 (m, 2 H, H-11, H-15), 6.10 (q, *J* = 7 Hz, H-9), 6.34 (s, 3 H, ester), 7.68 (s, 3 H, $SCOCH_3$), 7.34–8.86 (m, 20 H), 9.11 (m, 21 H), *tert*-butyl, H-20), 9.98 (m, 12 H, $SiCH_3$); mass spectrum, *m/e* (relative intensity) 639 ($M^+ - CH_3$, 0.3%), 597 ($M^+ - C_4H_9$, 22.7%), 521 (12.8%), 315 (22.1%), 241 (13.9%), 215 (18.1%), 133 (29.8%), 75 (50.1%), 73 (base peak); HRMS calcd for $C_{35}H_{66}O_5SSi_2$ 654.4164, found 654.4162.

Methyl (6*S*,9α,11α,13*E*,15*S*)-11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,9-epithio-5-(phenylseleno)prosta-13-en-1-oate (13). The (5*E*)-thioacetate **10** (335 mg, 0.512 mmol) was dissolved in absolute methanol (51 mL) and cooled to −78 °C under argon. Phenylselenenyl chloride (119 mg, 0.615 mmol) was added and the mixture stirred until all of the solid had dissolved (about 3 h). The reaction mixture was then diluted with methylene chloride (200 mL), washed with 10% potassium bicarbonate solution (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, methylene chloride) yielded the selenide **13** (244 mg, 62%). **13**: oil; R_f = 0.33 (silica, methylene chloride); $[\alpha]^{25}_D$ −26.4° (methanol, *c* = 0.0165); IR (liquid film) ν_{max} 3050 (w), 2960 (s), 2920 (s), 2890 (s), 2850 (s), 1738 (ester, s), 1575 (aromatic, w), 1470 (m), 1460 (m), 1435 (m), 1360 (m), 1255 (s), 1110 (s), 965 (m), 900 (m), 830 (s), 770 (s), 730 (s), 690 (m), 660 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.43 (m, 2 H, aromatic), 2.75 (m, 3 H, aromatic), 2.53 (m, 2 H, olefinic), 5.97 (m, 1 H, H-15), 6.12 (q, *J* = 7 Hz, 1 H, H-11), 6.27 (m, 1 H, H-9), 6.37 (s, 3 H, ester), 6.43 (q, *J* = 9 Hz, 1 H, H-6), 6.78 (m, 1 H, H-5), 7.42–9.00 (m, 20 H), 9.14 (m, 21 H, *tert*-butyl, H-20), 9.97 (m, 12 H, $SiCH_3$); mass spectrum, *m/e* (relative intensity) 711 ($M^+ - C_4H_9$, 0.1%), 611 (M^+ – SePh, 0.4%), 554 ($M^+ - C_4H_9$ – SePh), 479 (2.1%), 305 (2.6%), 189 (2.9%), 158 (18.5%), 105 (11.9%), 84 (35.3%), 78 (49.1%), 75 (base peak), 73 (75.1%); HRMS (M^+ – SePh) calcd for $C_{33}H_{63}O_4SSi_2$ 611.3985, found 611.3956.

Methyl (6*R*,9α,11α,13*E*,15*S*)-11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,9-epithio-5-(phenylseleno)prosta-13-en-1-oate (15). The (6*R*)-thioacetate **12** (305 mg, 0.466 mmol) was dissolved in absolute methanol (50 mL) and cooled to −78 °C under argon. Phenylselenenyl chloride (108 mg, 0.56 mmol) was added and the mixture stirred until all of the solid had dissolved (about 3 h). The reaction mixture was then diluted with methylene chloride (200 mL), washed with 10% potassium bicarbonate solution (50 mL) and water (50 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, methylene chloride) yielded the selenide **15** (215 mg, 60%). **15**: oil; R_f = 0.33 (silica, methylene chloride); $[\alpha]^{25}_D$ −27.4° (methanol, *c* = 0.056); IR (liquid film) ν_{max} 2940 (s), 2900 (s), 2860 (m), 2840 (s), 1730 (ester, s), 1570 (aromatic, w), 1450 (m), 1430 (m), 1350 (w), 1250 (s), 1115 (s), 1000 (w), 965 (m), 830 (s), 775 (s), 740 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.48 (m, 2 H, aromatic), 2.79 (m, 3 H, aromatic), 4.47 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.62 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 5.92 (q, *J* = 7 Hz, 1 H, H-15), 6.28 (q, *J* = 7 Hz, 1 H, H-11), 6.34 (s, 3 H, ester), 6.37 (m, 2 H, H-6, H-9), 6.97 (b t, *J* = 12 Hz, 1 H, H-5), 7.47–8.83 (m, 20 H), 9.13 (m, 21 H, *tert*-butyl, H-20), 9.97 (m, 12 H, $SiCH_3$); mass spectrum *m/e* (relative intensity) 711 ($M^+ - C_4H_9$, 0.2%), 611 (M^+ – SePh, 8.2%), 554 ($M^+ - C_4H_9$ – SePh, 6.3%), 497 ($M^+ - 2C_4H_9$ – SePh, 0.6%), 241 (16.1%), 209 (13.0%), 157 (48.3%), 149 (32.0%), 115 (26.8%), 105 (64.0%), 79 (53.4%), 78 (93.6%), 77 (85.4%), 75 (base peak, 73 (94.3%); HRMS calcd for $C_{39}H_{68}O_4SSi_2Se$ 768.3537, found: 768.3534.

Methyl (6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxy-5-(phenylseleno)prosta-13-en-1-oate (14). The (6*S*)-selenide **13** (200 mg, 0.26 mmol) was dissolved in anhydrous tetrahydrofuran (3.9 mL). Tetra-*n*-butylammonium fluoride (780 μL of a 1 M solution in tetrahydrofuran, 0.78 mmol) was added and the solution stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with ether (60 mL), washed with water (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 selenide **14** (132 mg, 94%). **14**: oil; R_f = 0.17 (silica, 2.5% methanoi in ether); $[\alpha]^{25}_D$ −107.9° (methanol, *c* = 0.025); IR (liquid film) ν_{max} 3380 (OH, m), 3060 (w), 2950 (s), 2930 (s), 2850 (s), 1730 (ester, s), 1575 (aromatic, w), 1475 (w), 1450 (m), 1435 (s), 1375 (m), 1255 (m), 1195 (m), 1170 (m), 1105 (s), 1020 (m), 965 (m), 905 (s), 730 (s), 690 (m), 640 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.46 (m, 2 H, aromatic), 2.75 (m, 3 H, aromatic), 4.52 (m, 2 H, olefinic), 5.98 (q, *J* = 7 Hz, 1 H, H-15), 6.13 (q, *J* = 7 Hz, 1 H, H-11), 6.30 (m, 1 H, H-9), 6.37 (s, 3 H, ester), 6.38 (m, 1 H, H-6), 6.78 (m, 1 H, H-5); mass spectrum, *m/e* (relative intensity) 540 (M^+, 0.2%), 525 ($M^+ - CH_3$, 0.1%), 522 ($M^+ - H_2O$, 2.3%), 504 ($M^+ - 2H_2O$, 1.8%), 383 (M^+ – SePh, 2.4%), 365 (M^+ – SePh – H_2O, 11.9%), 347 (M^+ – SePh – $2H_2O$, 23.1%), 211 (26.4%), 157 (25.7%), 105 (29.7%), 97 (44.1%), 93 (37.5%), 91 (56.7%), 81 (59.6%), 79 (69.0%), 67 (81.7%), 55 (base peak); HRMS calcd for $C_{27}H_{40}O_4SSe$ 540.1809, found 540.1805.

Methyl (6*R*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxy-5-(phenylseleno)prosta-13-en-1-oate (16). The (6*R*)-selenide **15** (170 mg, 0.22 mmol) was dissolved in anhydrous tetrahydrofuran (3.3 mL). Tetra-*n*-butylammonium fluoride (664 μL of a 1 M solution in tetrahydrofuran, 6.6 mmol) was added and the solution stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with ether (60 mL), washed with water (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 selenide **16** (111 mg, 93%). **16**: oil; R_f = 0.17 (silica, 2.5% methanol in ether); $[\alpha]^{25}_D$ −97.3° (methanol, *c* = 0.0285); IR (liquid film) ν_{max} 3380 (OH, m), 3060 (w), 2940 (s), 2910 (s), 2840 (s), 1730 (ester, s), 1575 (aromatic, w), 1470 (m), 1450 (m),

1430 (s), 1330 (m), 1260 (m), 1200 (m), 1165 (s), 1120 (m), 1090 (m), 1060 (m), 1015 (m), 960 (m), 905 (m), 730 (s), 685 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 2.48 (m, 2 H, aromatic), 2.75 (m, 3 H, aromatic), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.63 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.97 (q, J = 7 Hz, 1 H, H-15), 6.30 (m, 1 H, H-11), 6.35 (s, 3 H, ester), 6.35 (m, 2 H, H-6, H-9), 7.00 (b d, J = 6 Hz, 1 H, H-5), 7.33–9.00 (m, 22 H), 9.12 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 540 (M^+, 0.1%), 383 (M^+ – SePh, 7.4%), 365 (M^+ – SePh – H_2O, 20.1%), 347 (M^+ – SePh – $2H_2O$, 10.1%), 211 (16.1%), 157 (25.9%), 123 (20.1%), 117 (26.8%), 105 (40.2%), 99 (56.3%), 91 (56.0%), 81 (58.3%), 78 (86.4%), 67 (71.5%), 55 (base peak); HRMS calcd for $C_{27}H_{40}O_4SSe$ 540.1809, found 540.1796. Anal. ($C_{27}H_{40}O_4SSe$) C, H.

Methyl [5*Z*,6(*R*),9α,11α,13*E*,15*S*]- and [5*Z*,6-(*S*),9α,11α,13*E*,15*S*]-6,9-epithio-11,15-dihydroxyprosta-5,13-diene 1-Oxides (17a and 17b). Method A. The (6*R*)-selenide **16** (80 mg, 0.148 mmol) was dissolved in anhydrous methylene chloride (5 mL) and cooled to −78 °C under argon. *m*-Chloroperbenzoic acid (33 mg, 85% by wt, 0.163 mmol) was dissolved in methylene chloride (1 mL) and added dropwise to the cooled selenide solution. The resulting mixture was stirred for 15 min at −78 °C before a second equivalent of *m*-chloroperbenzoic acid (33 mg, 0.163 mmol) in methylene chloride (1 mL) was added. The mixture was then warmed to −20 °C and stirred for an additional 15 min before being warmed to room temperature. Once at 25 °C, diisopropylamine (56 mg = 77 μL, 0.55 mmol) was added to destroy any excess peracid. Stirring was continued at 25 °C for 15 h after which the reaction mixture was diluted with ether (75 mL). The ether solution was washed with 10% sodium thiosulfate solution (20 mL), saturated sodium bicarbonate solution (2 × 10 mL), and water (20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in methylene chloride, four developments) yielded the epimeric sulfoxides **17a** (faster moving, 31 mg, 53%) and **17b** (slower moving, 15 mg, 25%). **17a**: white crystals, mp 64–66 °C (benzene–hexane); R_f = 0.19 (silica, 5% methanol in methylene chloride); $[\alpha]^{25}_D$ + 66.5° (methanol, c = 0.0135); IR ($CHCl_3$) ν_{max} 3380 (OH, m), 2990 (s), 2940 (s), 2920 (s), 2850 (s), 1725 (ester, s), 1655 (thioenol ether, w), 1450 (m), 1430 (s), 1360 (m), 1355 (m), 1305 (m), 1200 (s), 1165 (m), 1080 (m), 1000 (s), 965 (s), 900 (w), 715 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.98 (t, J = 6 Hz, 1 H, H-5), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.53 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.46 (b, 2 H, OH), 5.97 (q, J = 7 Hz, 1 H, H-15), 6.00 (m, 1 H, H-11), 6.32 (s, 3 H, ester), 6.49 (m, 1 H, H-9), 7.00–8.00 (m, 10 H), 8.18 (m, 2 H), 8.33–9.00 (m, 10 H), 9.10 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 399 (M^+ + 1, 0.3%), 383 (M^+ – CH_3, 0.1%), 382 (M^+ – O, 1.1%), 380 (M^+ – H_2O, 1.3%), 367 (2.9%), 363 (2.7%), 360 (M^+ – $2H_2O$, 4.3%), 345 (5.8%), 313 (7.3%), 231 (7.1%), 191 (10.5%), 135 (14.7%), 123 (21.0%), 99 (56.6%), 91 (47.5%), 79 (55.2%), 71 (62.2%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_5S$ 398.2125, found 398.2120. **17b**: oil; R_f = 0.08 (silica, 5% methanol in methylene chloride); $[\alpha]^{25}_D$ −57.3° (methanol, c = 0.0070); IR (liquid film) ν_{max} 3380 (OH, s), 3050 (w), 2950 (s), 2930 (s), 2850 (s), 1735 (ester, s), 1660 (thioenol ether, w), 1435 (s), 1360 (m), 1340 (m), 1255 (s), 1225 (m), 1195 (m), 1165 (s), 1095 (s), 1000 (s), 905 (w), 880 (w), 735 (s), 700 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.92 (t, J = 7 Hz, 1 H, H-5), 4.47 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.54 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.98 (q, J = 7 Hz, 1 H, H-15), 6.27 (q, J = 6 Hz, 1 H, H-11), 6.31 (s, 3 H, ester), 6.61 (q, J = 9 Hz, 1 H, H-9), 6.65 (b, 2 H, OH), 7.00–9.00 (m, 20 H), 9.10 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 399 (M^+ + 1, 0.8%), 383 (M^+ – CH_3, 0.5%), 382 (M^+ – O, 2.5%), 380 (M^+ – H_2O, 1.3%), 367 (2.4%), 363 (3.3%), 362 (M^+ – $2H_2O$, 4.6%), 346 (5.3%), 313 (10.0%), 275 (10.4%), 211 (13.5%), 187 (14.5%), 135 (18.5%), 129 (22.8%), 123 (33.6%), 105 (49.8%), 99 (59.5%), 91 (50.7%), 79 (91.1%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_5S$ 398.2125, found 398.2116.

[5*Z*,6(*R*),9α,11α,13*E*,15*S*]- and [5*Z*,6(*S*),9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid *S*-Oxides (18a and 18b). The methyl ester **17a** or **17b** (10 mg. 0.025 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1 mL). Lithium hydroxide (250 μL of a 1 M solution in water, 0.25 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 (250 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 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 (15 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yielded the free acid **18a** or **18b** (5.8 mg, 60%).

Stable stock solutions of the sodium salt of **18a** or **18b** could be prepared by dissolving the methyl ester **17a** or **17b** (3.98 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 provides standard solutions of the sodium salt of 10^{-3} M. **18a**: oil; R_f = 0.07 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3320 (OH, m), 3000 (COOH, b), 2950 (s), 2920 (s), 2850 (s), 1720 (acid, s), 1455 (m), 1430 (m), 1410 (m), 1375 (m), 1340 (m), 1300 (m), 1260 (s), 1170 (m), 1090 (s), 1005 (s), 965 (s), 900 (w), 795 (w), 730 (s), 695 (m) cm^{-1}; ^1H NMR 360 MHz, $CDCl_3$) τ 3.95 (t, J = 7 Hz, 1 H, H-5), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.54 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.07 (b, 3 H, OH), 5.95 (q, J = 7 Hz, 1 H, H-15), 6.01 (q, J = 18 Hz, 1 H, H-11), 6.47 (m, 1 H, H-9), 7.00–9.00 (m, 20 H), 9.12 (m, 3 H, CH_3). **18b**: oil; R_f = 0.04 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3350 (OH, m), 3000 (COOH, b), 2960 (s), 2930 (s), 2850 (s), 1720 (acid, s), 1450 (m), 1430 (m), 1405 (m), 1370 (m), 1340 (m), 1260 (m), 1175 (m), 1085 (m), 1005 (s), 965 (s), 900 (w), 795 (w), 730 (w), 695 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.90 (m, 1 H, H-5), 4.40 (m, 2 H, olefinic), 5.90 (m, 1 H, H-15), 6.18 (m, 1 H, H-11), 4.60 (m, 1 H, H-9), 7.00–9.00 (m, 23 H), 9.10 (m, 3 H, CH_3).

Methyl (5*Z*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate *S*,*S*-Dioxide (19). Method B. The (6*R*)-selenide **16** (54 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (2 mL) and cooled to −78 °C under argon. *m*-Chloroperbenzoic acid (20.2 mg, 85% by wt, 0.1 mmol) was dissolved in methylene chloride (1 mL) and added dropwise to the cooled selenide solution. The resulting mixture was stirred for 15 min at −78 °C before a second equivalent of *m*-chloroperbenzoic acid (20.2 mg, 0.1 mmol) was added in methylene chloride (1 mL). The mixture was then warmed to −20 °C and stirred for an additional 15 min before being warmed to room temperature. Once at 25 °C, a third equivalent of *m*-chloroperbenzoic acid (20.2 mg, 0.1 mmol) in methylene chloride solution (1 mL) was added and the solution stirred at room temperature for 15 h. The reaction mixture was then diluted with ether (75 mL), washed with 10% sodium thiosulfate solution (20 mL), saturated sodium bicarbonate solution (2 × 10 mL), and water (20 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in methylene chloride, three developments) yielded the sulfone **19** (34 mg, 82%).

Method C. The (6*R*)-selenide **16** (54 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (2 mL) and cooled to −78 °C under argon. The solution was treated with 2 equiv of *m*-chloroperbenzoic acid as described for method B. After being stirred for 15 min at −20 °C, the reaction mixture was warmed to room temperature and most of the methylene chloride removed under reduced pressure. The residue was then immediately redissolved in distilled tetrahydrofuran (2.5 mL) and hydrogen peroxide (500 μL of a 1 M solution in tetrahydrofuran prepared by dilution of a 30% peroxide in water solution, 0.5 mmol) was added and the solution stirred at room temperature under argon for 15 h. The reaction mixture was diluted with ether (75 mL), washed with 10% potassium bicarbonate solution (2 × 20 mL), 10% sodium thiosulfate solution (20 mL), and water (20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride, three developments) yielded the sulfone **19** (33 mg, 80%). **19**: oil; R_f = 0.09 (20% acetone in methylene chloride); $[\alpha]^{25}_D$ +22.4° (methanol, c = 0.0355); IR (liquid film) ν_{max} 3410 (OH, m), 2960 (s), 2930 (s), 2860 (m), 1735 (ester, s), 1665 (thioenol ether, w), 1455 (m), 1435 (m), 1325 (m), 1295 (s), 1160 (m), 1120 (s), 1105 (s), 1020 (m), 970 (m), 910 (m), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.00 (t, J = 8 Hz, 1 H, H-5), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.60 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.96 (q, J = 7 Hz, 1 H, H-15), 6.13 (q, J = 8 Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.58 (q, J = 7 Hz, 1 H, H-9), 7.00–9.00 (m, 22 H), 9.11 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 558 (M^+, $2Me_3$-Si, 0.4%), 468 (M^+ – Me_3SiOH, 2.2%), 397 (25.6%), 378 (M^+ – $2Me_3SiOH$, 1.1%), 263 (9.1%), 199 (13.2%), 129 (25.8%), 99 (8.7%), 91 (14.6%), 75 (37.9%), 73 (base peak); HRMS (M^+·$2Me_3Si$ – CH_3) calcd for $C_{20}H_{29}O_6S$·$2Me_3Si$ 543.2631, found 543.2538. Anal. ($C_{21}H_{34}O_6S$) C, H.

(5*Z*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid *S*,*S*-Dioxide (20). The methyl ester **19** (15 mg, 0.036 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1.4 mL). Lithium hydroxide (360 μL of a 1 M solution in water, 0.36 mmol) was added and the mixture stirred at room temperature under argon for 3 h. The base was neutralized by the addition of oxalic acid (360 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 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 **20** (10.5 mg, 75%).

Stable stock solutions of the sodium salt of **20** could be prepared by dissolving the methyl ester **19** (4.12 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 provides standard solutions of the sodium salt of 10^{-3} M. **20**: oil; R_f = 0.16 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3360 (OH, m), 3000 (COOH, b), 2960 (s), 2930 (s), 2850 (s), 1710 (acid, s), 1665 (thioenol ether, w), 1455 (m), 1435 (m), 1405 (m), 1375 (m), 1290 (s), 1260 (s), 1165 (m), 1110 (s), 1050 (m), 1015 (m), 960 (m), 865 (m), 800 (m), 735 (s), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.98 (t, J = 7 Hz, 1 H, H-5), 4.38 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.62 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.97 (b, 3 H, OH), 5.95 (q, J = 7 Hz, 1 H, H-15), 6.13 (q, J = 8 Hz, 1 H, H-11), 6.58 (q, J = 9 Hz, 1 H, H-9), 7.00–9.00 (m, 20 H), 9.10 (m, 3 H, CH_3).

Methyl (4*E*,6*R*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-4,13-dien-1-oate *S*,*S*-Dioxide (21). Method D. The (6*R*)-selenide **16** (80 mg, 0.148 mmol) was dissolved in anhydrous tetrahydrofuran (7.4 mL). Hydrogen peroxide (1.48 mL of a 1 M solution in tetrahydrofuran prepared by dilution of 30% peroxide solution in water, 1.48 mmol) was added and the mixture stirred at room temperature under argon for 48 h. The reaction mixture was diluted with ether (75 mL), washed with 10% potassium bicarbonate solution (2 × 20 mL), 10% sodium thiosulfate solution (20 mL), and water (20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride, four developments) yielded the isosulfone **21** (12 mg, 20%) and the α,β-unsaturated sulfone **19** (45 mg, 73%). **21**: oil; R_f = 0.06 (silica, 20% acetone in methylene chloride); $[\alpha]^{25}_D$ +12.4° (methanol, c = 0.0125); IR (liquid film) ν_{max} 3400 (OH, s), 2960 (s), 2930 (s), 2860 (s), 1734 (ester, s), 1438 (m), 1350 (w), 1305 (s), 1200 (m), 1165 (s), 1115 (s), 1015 (w), 970 (m), 912 (m), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.10 (m, 1 H, olefinic), 4.39 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.57 (m, 2 H, olefinic), 5.95 (q, J = 7 Hz, 1 H, H-15), 6.18 (q, J = 8 Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.34 (m, 1 H, H-6), 6.64 (q, J = 9 Hz, 1 H, H-9), 7.00–9.00 (m, 20 H), 9.12 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 558 (M^+, $2Me_3Si$, 2.3%), 543 ($M^+ - CH_3$, 37.5%), 487 (46.4%), 468 ($M^+ - Me_3SiOH$, 11.8%), 404 (26.3%), 400 (24.5%), 398 (98.4%), 378 ($M^+ - 2Me_3SiOH$, 1.0%), 332 (69.4%), 244 (48.9%), 216 (58.1%), 200 (69.3%), 174 (73.4%), 130 (74.5%), 91 (63.7%), 73 (87.4%), 55 (base peak); HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{29}O_6S \cdot 2Me_3Si$ 543.2631, found 543.2668.

(4*E*,6*R*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-4,13-dien-1-oic Acid *S*,*S*-Dioxide (22). The methyl ester **31** (10 mg, 0.024 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1 mL). Lithium hydroxide (240 μL of a 1 M solution in water, 0.24 mmol) was added and the mixture stirred at room temperature under argon for 3 h. The base was neutralized by the addition of oxalic acid (240 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 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 **22** (6 mg, 63%).

Stable stock solutions of the sodium salt of **22** could be prepared by dissolving the methyl ester **21** (4.12 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 provides standard solutions of the sodium salt of 10^{-3} M. **35**: oil; R_f = 0.09 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3400 (OH, m), 3100 (COOH, b), 2960 (s), 2920 (s), 2850 (s), 1720 (acid, s), 1490 (w), 1455 (m), 1410 (m), 1375 (m), 1260 (s), 1150 (s), 1110 (s), 1015 (s), 965 (m), 860 (m), 795 (m), 735 (s), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.08 (m, 1 H, olefinic), 4.38 (m, 1 H, olefinic), 4.53 (m, 2 H, olefinic), 5.93 (m, 1 H, H-15), 6.13 (q, J = 7 Hz, 1 H, H-11), 6.28 (m, 1 H, H-6), 6.50 (b, 3 H, OH), 6.61 (q, J = 9 Hz, 1 H, H-9), 7.33–9.00 (m, 18 H), 9.11 (m, 3 H, CH_3).

Methyl [5*E*,6(*R*),9α,11α,13*E*,15*S*]- and [5*E*,6-(*S*),9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate *S*-Oxides (23a and 23b). Method A. The (6*S*)-selenide **14** (60 mg, 0.11 mmol) was dissolved in anhydrous methylene chloride (2 mL) and cooled to −78 °C under argon. *m*-Chloroperbenzoic acid (22.5 mg, 85% by wt, 0.11 mmol) was dissolved in anhydrous methylene chloride (1 mL) and added dropwise to the cooled selenide solution. The resulting mixture was stirred for 15 min at −78 °C before a second equivalent of *m*-chloroperbenzoic acid (22.5 mg, 85% by wt, 0.11 mmol) in methylene chloride (1 mL) was added. The mixture was then warmed to −20 °C and stirred for an additional 15 min before being warmed to room temperature. Once at 25 °C, diisopropylamine (56 mg = 77 μL, 0.55 mmol) was added to destroy any excess peracid. Stirring was continued at 25 °C for 15 h after which the reaction mixture was diluted with ether (75 mL). The ether solution was washed with 10% sodium thiosulfate solution (20 mL), saturated sodium bicarbonate solution (2 × 10 mL), and water (20 mL) and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in methylene chloride, four developments) yielded the epimeric sulfoxides **23a** (faster moving, 23 mg, 53%), and **23b** (slower moving, 8 mg, 18%). **23a**: white crystals, mp 75–76 °C (benzene–hexane); R_f = 0.19 (silica, 5% methanol in methylene chloride); $[\alpha]^{25}_D$ +48.4° (methanol, c = 0.016); IR ($CHCl_3$) ν_{max} 3380 (OH, m), 2990 (s), 2945 (s), 2920 (s), 2850 (m), 1725 (ester, s), 1660 (thioenol ether, w), 1450 (m), 1430 (m), 1360 (m), 1310 (m), 1200 (s), 1165 (m), 1085 (m), 1000 (s), 965 (m), 900 (w), 875 (w), 715 (m), 650 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.72 (t, J = 6 Hz, 1 H, H-5), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.55 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.98 (q, J = 7 Hz, 1 H, H-15), 6.06 (q, J = 7 Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.52 (m, 1 H, H-9), 7.33 (m, 3 H), 7.65 (m, 3 H), 7.77 (m, 5 H), 8.21 (m, 2 H), 8.20–8.92 (m, 9 H), 9.11 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 399 (M^+ + 1, 0.1%), 382 ($M^+ - O$, 1.5%), 380 ($M^+ - H_2O$, 1.8%), 364 ($M^+ - H_2O - O$, 9.0%), 362 ($M^+ - 2H_2O$, 9.3%), 346 ($M^+ - 2H_2O - O$, 14.1%), 249 (19.6%), 211 (20.9%), 189 (25.1%), 129 (40.5%), 123 (47.9%), 105 (61.0%), 99 (63%), 97 (59%), 71 (71.1%), 55 (base peak); HRMS ($M^+ - 2H_2O$) calcd for $C_{21}H_{30}O_3S$ 362.1915, found 362.1923; Anal. ($C_{21}H_{34}O_5S$) C, H. **23b**: oil, R_f = 0.08 (5% methanol in methylene chloride); $[\alpha]^{25}_D$ −76.4° (methanol, c = 0.011); IR (liquid film) ν_{max} 3380 (OH, s), 2975 (s), 2925 (s), 2860 (s), 1735 (ester, s), 1710 (w), 1660 (thioenol ether, w), 1450 (m), 1435 (m), 1365 (m), 1315 (m), 1260 (m), 1220 (m), 1200 (m), 1165 (m), 1095 (m) 1000 (s), 880 (w), 800 (w), 730 (m), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.59 (t, J = 6 Hz, 1 H, H-5), 4.45 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.54 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.95 (q, J = 6 Hz, 1 H, H-15), 6.28 (q, J = 6 Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.68 (q, J = 7.5 Hz, 1 H, H-9), 6.92 (dd, J = 7.15 Hz, 1 H), 7.20 (q, J = 9 Hz, 1 H), 7.37 (d, J = 15 Hz, 1 H), 7.43 (m, 1 H), 7.62 (m, 2 H), 7.75 (m, 2 H), 8.18 (m, 2 H), 8.25–8.92 (m, 12 H), 9.10 (m, 3 H, CH_3); mass spectrum, m/e (relative intensity) 399 (M^+ + 1, 2.4%), 398 (M^+, 0.3%), 382 ($M^+ - O$, 4.7%), 380 ($M^+ - H_2O$, 2.5%), 364 ($M^+ - H_2O - O$, 4.1%), 362 ($M^+ - 2H_2O$, 7.7%), 346 ($M^+ - 2H_2O - O$, 9.0%), 313 (16.1%), 275 (17.9%), 211 (23.2%), 187 (23.9%), 129 (29.5%), 111 (38.2%), 99 (87.8%), 97 (53.9%), 91 (60.1%), 71 (71.6%), 55 (base peak); HRMS (M^+ + 1) calcd for $C_{21}H_{35}O_5S$ 399.2204, found 399.2230.

[5*E*,6(*R*),9α,11α,13*E*,15*S*]- and [5*E*,6(*S*),9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid *S*-Oxides (24a and 24b). The methyl ester **23a** or **23b** (10 mg, 0.025 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1 mL). Lithium hydroxide (250 μL of a 1 M solution in water, 0.25 mmol) was added and the mixture stirred at room temperature under argon for 3 h. The base was neutralized by the addition of oxalic acid (250 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 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 **24a** or **24b** (6.5 mg, 68%).

Stable stock solutions of the sodium salt of **24a** or **24b** could be prepared by dissolving the methylester **23a** or **23b** (3.98 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 temperture overnight before being diluted with absolute ethanol (9 mL). This procedure then provides standard solutions of the sodium salt of 10^{-3} M. **24a**: oil; R_f = 0.07 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3350 (OH, m), 3050 (m), 3000 (COOH, b), 2960 (s), 2920 (s), 2850 (s), 1715 (acid, s), 1490 (w), 1450 (m), 1405 (m), 1375 (m), 1260 (s), 1175 (m), 1090 (s), 1010 (s), 970 (s), 910 (w), 880 (w), 790 (w), 730 (s), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.72 (t, J = 6 Hz, 1 H, H-5), 4.52 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.72 (dd, J = 7, 15 Hz, 1 H, olefinic), 6.05 (m, 1 H, H-15), 6.10 (m, 1 H, H-11), 6.42 (q, J = 8 Hz, 1 H, H-9), 7.18–9.00 (m, 23 H), 9.12 (m, 3 H, CH_3). **24b**: oil; R_f = 0.04 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3350 (OH, m), 3000 (COOH, b), 3150 (m), 2950 (s), 2920 (s), 2850 (s), 1715 (acid,

s), 1455 (m), 1265 (s), 1170 (m), 1090 (s), 1015 (s), 970 (s), 880 (w), 795 (w), 735 (s), 700 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.57 (m, 1 H, H-5), 4.48 (m, 2 H, olefinic), 5.90 (m, 1 H, H-15), 6.22 (m, 1 H, H-11), 6.67 (m, 1 H, H-9), 6.83–9.00 (m, 23 H), 9.11 (m, 3 H, CH_3).

Methyl (5*E*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oate *S*,*S*-Dioxide (25). Method B. The (6*S*)-selenide **14** (54 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (2 mL) and cooled to −78 °C under argon. *m*-Chloroperbenzoic acid (20.2 mg, 85% by wt, 0.1 mmol) was dissolved in methylene chloride (1 mL) and added dropwise to the cooled selenide solution. The resulting mixture was stirred for 15 min at −78 °C before a second equivalent of *m*-chloroperbenzoic acid (20.2 mg, 0.1 mmol) was added in methylene chloride solution (1 mL). The mixture was then warmed to −20 °C and stirred for an additional 15 min before being warmed to room temperature. Once at 25 °C, a third equivalent of *m*-chloroperbenzoic acid (20.2 mg, 0.1 mmol) in methylene chloride solution (1 mL) was added and the solution stirred at room temperature for 15 h. The reaction mixture was then diluted with ether (75 mL), washed with 10% sodium thiosulfate solution (20 mL), saturated sodium bicarbonate solution (2 × 10 mL) and water (20 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in methylene chloride, three developments) yielded the sulfone **25** (36 mg, 86%).

Method C. The (6*S*)-selenide **14** (54 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (2 mL) and cooled to −78 °C under argon. The solution was treated with 2 equiv of *m*-chloroperbenzoic acid as described for method B. After being stirred for 15 min at −20 °C, this reaction mixture was warmed to room temperature and most of the methylene chloride removed under reduced pressure. The residue was then immediately redissolved in distilled tetrahydrofuran (2.5 mL) and hydrogen peroxide (500 μL of a 1 M solution in tetrahydrofuran made by dilution of 30% peroxide in water solution, 0.5 mmol) was added and the solution stirred at room temperature under argon for 15 h. The reaction mixture was diluted with ether (75 mL), washed with 10% potassium bicarbonate solution (2 × 20 mL), 10% sodium thiosulfate solution (20 mL), and water (20 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride, three developments) yielded the sulfone **25** (34 mg, 83%). **25**: oil; R_f = 0.09 (silica, 20% acetone in methylene chloride); $[\alpha]^{25}_D$ +7.6° (methanol, *c* = 0.0455); IR (liquid film) ν_{max} 3430 (OH, s), 2960 (s), 2930 (s), 2860 (s), 1735 (ester, s), 1680 (thioenol ether, w), 1450 (m), 1435 (s), 1370 (m), 1300 (SO_2, s), 1165 (s), 1125 (s), 1100 (s), 1015 (m), 970 (m), 905 (w), 740 (m), 690 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.56 (t, *J* = 7.5 Hz, 1 H, H-5), 4.43 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.60 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 5.98 (q, *J* = 7 Hz, 1 H, H-15), 6.18 (q, *J* = 7 Hz, 1 H, H-11), 6.20 (s, 3 H, ester), 6.63 (q, *J* = 7 Hz, 1 H, H-9), 6.77 (b s, 2 H, OH), 7.32 dd, *J* = 7.5, 12 Hz, 1 H), 7.43 (q, *J* = 10 Hz, 1 H), 7.55 (m, 2 H), 7.65 (t, *J* = 7 Hz, 2 H), 7.78 (q, *J* = 9 Hz, 2 H), 7.96 (dd, *J* = 7, 10 Hz, 1 H), 8.03 (d, *J* = 7 Hz, 2 H), 8.20–8.97 (m, 9 H), 9.12 (m, 3 H, CH_3); mass spectrum $2Me_3Si$, *m/e* (relative intensity) 558 (M^+, 0.6%), 543 ($M^+ - CH_3$, 11.3%), 468 ($M^+ - Me_3SiOH$, 6.5%), 397 (51.8%), 378 ($M^+ - 2Me_3SiOH$, 7.4%), 331 (31.5%), 307 (32.1%), 169 (56.2%), 158 (54.2%), 156 (73.2%), 141 (82.2%), 129 (56.7%), 111 (75.9%), 99 (64.4%), 73 (82.0%), 55 (base peak); HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{29}O_6S \cdot 2Me_3Si$ 543.2631, found 543.2693.

(5*E*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-5,13-dien-1-oic Acid *S*,*S*-Dioxide (26). The methyl ester **25** (15 mg, 0.036 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1.4 mL). Lithium hydroxide (360 μL of a 1 M solution in water, 0.36 mmol) was added and the mixture stirred at room temperature under argon for 3 h. The base was neutralized by the addition of oxalic acid (360 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 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 **26** (11 mg, 80%).

Stable stock solutions of the sodium salt of **26** could be prepared by dissolving the methyl ester **25** (4.12 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 provides standard solutions of the sodium salt of 10^{-3} M. **26**: oil; R_f = 0.016 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3400 (OH, m), 3000 (COOH, b), 2940 (s), 2920 (s), 2840 (s), 1710 (acid, s), 1665 (thioenol ether, w), 1425 (m), 1400 (m), 1275 (s), 1175 (s), 1110 (s), 1085 (s), 1005 (m), 960 (m), 895 (w), 790 (w), 725 (m), 685 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 3.52 (t, *J* = 7 Hz, 1 H, H-5), 4.40 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.62 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.67 (b, 3 H, OH), 5.97 (q, *J* = 7 Hz, 1 H, H-15), 6.18 (q, *J* = 7 Hz, 1 H, H-11), 6.62 (q, *J* = 9 Hz, 1 H, H-9), 7.00–9.00 (m, 20 H), 9.10 (m, 3 H, CH_3).

Methyl (4*E*,6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-4,13-dien-1-oate *S*,*S*-Dioxide (27). Method D. The (6*S*)-selenide **14** (150 mg, 0.28 mmol) was dissolved in anhydrous tetrahydrofuran (2.8 mL). Hydrogen peroxide (2.8 mL of a 1 M solution in tetrahydrofuran prepared by dilution of 30% peroxide solution in water, 2.8 mmol) was added and the mixture stirred at room temperature under argon for 15 h. The reaction mixture was diluted with ether (75 mL), washed with 10% potassium bicarbonate solution (2 × 20 mL), 10% sodium thiosulfate solution (20 mL), and water (20 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride, four developments) yielded the isosulfone **27** (15 mg, 13%) and the α,β-unsaturated sulfone **25** (77 mg, 66%). **27**: white crystals, mp 92–93 °C (benzene–hexane); R_f = 0.06 (silica, 20% acetone in methylene chloride); $[\alpha]^{25}_D$ +42.3° (methanol, *c* = 0.0075); IR ($CHCl_3$) ν_{max} 3400 (OH, w), 3000 (m), 2970 (s), 2930 (s), 2850 (m), 1730 (ester, s), 1435 (m), 1315 (s), 1205 (m), 1165 (m), 1125 (s), 1095 (m), 1005 (m), 965 (m), 905 (w), 715 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.13 (m, 1 H, olefinic), 4.43 (m, 1 H, olefinic), 4.57 (m, 2 H, olefinic), 5.98 (q, *J* = 7 Hz, 1 H, H-15), 6.08 (q, *J* = 7 Hz, 1 H, H-11), 6.32 (m, 1 H, H-6) 6.33 (s, 3 H, ester), 6.54 (q, *J* = 9 Hz, 1 H, H-9), 6.75–9.00 (m, 20 H), 9.13 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 558 (M^+, 0.1%), 543 ($M^+ - CH_3$, 2.1%), 487 (2.4%), 468 ($M^+ - Me_3SiOH$, 0.9%), 403 (3.8%), 397 (9.6%), 378 ($M^+ - 2Me_3SiOH$, 0.4%), 333 (17.0%), 331 (30.4%), 192 (26.4%), 140 (83.2%), 129 (43.7%), 117 (28.3%), 91 (47.2%), 79 (64.5%), 75 (71.0%), 73 (base peak), 67 (56.8%); HRMS ($M^+ - CH_3$) calcd for $C_{26}H_{47}O_6SSi_2$ 543.2631, found 543.2653.

Methyl (6*R*,9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oate (31ab). The (5*Z*)- or (5*E*)-thioacetate **10** or **12** (360 mg, 0.55 mmol) was dissolved in absolute methanol (2.5 mL) and the solution deoxygenated with argon. Powdered sodium methoxide (60 mg, 1.1 mmol) was added and the resulting solution stirred at room temperature under argon for 30 min. The reaction mixture was diluted with saturated sodium chloride solution (10 mL) and adjusted to pH 4 with 1 N oxalic acid solution. The acidified mixture was extracted with ether (3 × 40 mL), and the combined extracts were washed with water (30 mL) and dried over anhydrous magnesium sulfate. Filtration and removal of solvent under reduced pressure yieleded the crude, air-sensitive thiol **29** or **30** (323 mg, 96%) which was immediately dissolved without purification in a mixture of acetic acid–tetrahydrofuran–water (3:2:2, 25 mL). The resulting mixture was deoxygenated with argon and stirred at 45 °C under argon for 20 h. The reaction mixture was then diluted with water (50 mL) and extracted with methylene chloride (3 × 40 mL). The combined extracts were washed with water (3 × 30 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 product **31ab** (137 mg, 65%) as an inseparable mixture of C-6 epimers. **31ab**: oil; R_f = 0.21 (silica, 2.5% methanol in ether), $[\alpha]^{25}_D$ −16.6° (methanol, *c* = 0.029); IR (liquid film) ν_{max} 3380 (OH, m), 2950 (s), 2920 (s), 2850 (s), 1735 (s), 1450 (m), 1435 (m), 1255 (m), 1200 (m), 1170 (m), 1090 (m), 1010 (m), 965 (m), 910 (m), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.52 (m, 2 H, olefinic), 5.97 (m, 1 H, H-15), 6.13 (q, *J* = 7 Hz, 0.27 H, H-11), 6.29 (q, *J* = 7 Hz, 0.73 H, H-11), 6.32 (s, 3 H, ester), 6.38 (m, 1 H, H-6), 6.50 (m, 2 H, OH), 6.58 (m, 1 H, H-9), 7.33–9.00 (m, 22 H), 9.12 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 528 (M^+, $2Me_3Si$, 0.2%), 513 ($M^+ - CH_3$, 1.8%), 497 (2.4%), 438 ($M^+ - Me_3SiOH$, 82.2%), 367 (69.4%), 348 ($M^+ - 2Me_3SiOH$, 42.5%), 277 (36.9%), 252 (57.1%), 187 (63.8%), 97 (60.8%), 91 (73.8%), 81 (66.7%), 75 (85.0%), 73 (99.2%), 67 (73.7%) , 55 (base peak); HRMS ($M^+ - Me_3SiOH$) calcd for $C_{21}H_{33}O_3S \cdot Me_3Si$ 438.2624, found 438.2641.

(6*R*,9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oic Acid (32ab). The methyl ester **31ab** (15 mg, 0.039 mmol was dissolved in a mixture of tetrahydrofuran–water (3:1, 1.5 mL). Lithium hydroxide (390 μL of a 1 M solution in water, 0.39 mmol) was added and the mixture stirred at room temperature under argon for 3 h. The base was neutralized by the addition of oxalic acid (390 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 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 **32ab** (10 mg, 72%).

Stable stock solutions of the sodium salt of **32ab** could be prepared by dissolving the methyl ester **31ab** (3.84 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 provides standard solutions of the sodium salt of 10^{-3} M. **32ab**: oil; $R_f = 0.29$ (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3350 (OH, m), 3100 (COOH, b), 2960 (s), 2920 (s), 2850 (s), 1705 (acid, s), 1455 (m), 1400 (m), 1355 (m), 1260 (s), 1090 (s), 1010 (s), 965 (m), 795 (m), 725 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.48 (m, 2 H, olefinic), 5.93 (m, 1 H, H-15), 6.10 (q, $J = 8$ Hz, 0.34 H, H-11), 6.24 (q, $J = 8$ Hz, 0.66 H, H-11), 6.30 (q, $J = 9$ Hz, 1 H, H-6), 6.55 (m, 1 H, H-9), 7.33–9.00 (m, 25 H), 9.10 (m, 3 H, CH_3).

Methyl [6(*R*),6*R*,9α,11α,13*E*,15*S*]- and [6-(*R*,6*S*9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oate *S*-Oxide (33ac) and Methyl [6(*S*,69α,11α,13*E*,15*S*]- and [6-(*S*),6*S*,9α,11α,13 *e*,15*S*]-6,9-Epithio-11,15-dihydroxprosta-13-en-1-oate *S*-Oxide (33bd). The PGI_1 derivatives **31ab** (50 mg, 0.13 mmol) were dissolved in anhydrous methylene chloride (5 mL) and cooled to −20 °C under argon. *m*-Chloroperbenzoic acid (26.5 mg, 85% by wt, 0.13 mmol) was dissolved in methylene chloride (1 mL) and added dropwise to the cooled sulfide solution. The resulting mixture was stirred at −20 °C for 20 min and then warmed to room temperature. The solution at 25 °C was diluted with ether (75 mL), washed with 10% sodium thiosulfate solution and saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in methylene chloride, four developments) yielded the product as two separable epimeric sulfoxides, both inseparable mixtures of C-6 epimers **33ac** (faster moving, 17 mg, 33%) and **33bd** (slower moving, 15 mg, 29%). **33ac**: oil; $R_f = 0.11$ (silica, 5% methanol in methylene chloride); $[\alpha]^{25}_D$ −40.5° (methanol, $c = 0.0085$); IR (liquid film) ν_{max} 3360 (OH, s), 2950 (s), 2930 (s), 2860 (s), 1735 (s), 1455 (s), 1360 (m), 1340 (m), 1300 (m), 1260 (s), 1195 (s), 1170 (s), 1130 (m), 1095 (s), 1015 (s), 965 (m), 910 (w), 875 (w), 800 (w), 730 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.47 (m, 2 H, olefinic), 5.17 (b, 2 H, OH), 5.94 (q, $J = 6$ Hz, 1 H, H-15), 6.01 (m, 1 H, H-11), 6.27 (m, 1 H, H-6), 6.32 (s, 3 H, ester), 6.07 (m, 1 H, H-9), 7.00–9.00 (m, 22 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 544 (M^+, $2Me_3Si$, 0.2%), 529 ($M^+ - CH_3$, 4.0%), 513 (2.0%), 454 ($M^+ - Me_3SiOH$, 1.2%), 438 (.4%), 367 (11.1%), 364 ($M^+ - 2Me_3SiOH$, 3.1%), 315 (37.8%), 129 (24.0%), 117 (24.6%), 75 (76.4%), 73 (base peak); HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{31}O_5S{\cdot}2Me_3Si$ 529.2838, found 529.2751. **33bd**: oil; $R_f = 0.08$ (silica, 5% methanol in methylene chloride); $[\alpha]^{25}_D$ −72° (methanol, $c = 0.007$); IR (liquid film) ν_{max} 3360 (OH, s), 2950 (s), 2930 (s), 2850 (s), 1735 (ester, s), 1455 (s), 1435 (s), 1360 (m), 1335 (m), 1255 (s), 1195 (s), 1165 (s), 1130 (m), 1095 (s), 1050 (s), 1005 (s), 980 (s), 965 (s), 905 (w), 880 (w), 730 (m), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.41 (dd, $J = 7$, 15 *Hz*, 1 H, olefinic), 4.55 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 5.95 (q, $J = 7$ Hz, 1 H, H-15), 6.10 (q, $J = 7$ Hz, 0.34 H, H-11), 6.25 (q, $J = 7$ Hz, 0.66 H, H-11), 6.32 (s, 3 H, ester), 6.37 (b, 2 H, OH), 6.60 (m, 1 H, H-9), 7.17 (m, 1 H, H-6), 7.21–9.00 (m, 22 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 544 ($M^+ - 2Me_3Si$, 0.1%), 529 ($M^+ - CH_3$, 2.0%), 454 ($M^+ - Me_3SiOH$, 0.8%), 438 (11.2%), 367 (13.4%), 364 ($M^+ - 2Me_3SiOH$, 1.8%), 315 (24.3%), 173 (18.0%), 129 (21.5%), 117 (16.4%), 75 (71.7%), 73 (base peak); HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{31}O_5S{\cdot}2Me_3Si$ 529.2838, found 529.2793.

[6(*R*),6*R*,9α,11α,13*E*,15*S*]- and [6(*R*),6*S*,9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oic Acid *S*-Oxides (34ac) and [6-(*S*),6*R*,9α,11α,13*E*,15*S*]- and [6(*S*),6*S*,9α,11α,13*E*,15*S*]-6,9-Epithio-11,15-dihydroxyprosta-13en-1-oic Acid *S*-Oxides (34bd). The methyl esters **33ac** or **33bd** (10 mg, 0.025 mmol) were dissolved in a mixture of tetrahydrofuran-water (3:1, 1 mL). Lithium hydroxide (250 μL of a 1 M solution in water, 0.25 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 (250 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 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 **34ac** or **34bd** (5 mg, 55%).

Stable stock solutions of the sodium salt of **34ac** or **34bd** could be prepared by dissolving the methyl ester **33ac** or **33bd** (4.0 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 provides standard solutions of the sodium salt of 10^{-3} M. **34ac**: oil; $R_f = 0.05$ (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3340 (OH, m), 3000 (COOH, b), 2940 (s), 2910 (s), 2840 (s), 1710 (acid, s), 1450 (m), 1405 (m), 1420 (m), 1355 (m), 1175 (m), 1090 (s), 1005 (s), 790 (w), 725 (m), 690 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.45 (m, 2 H, olefinic), 5.93 (q, $J = 7$ Hz, 1 H, H-15), 5.99 (q, $J = 6$ Hz, 1 H, H-11), 6.26 (m, 1 H, H-6), 6.65 (m, 1 H, H-9), 7.00–9.00 (m, 25 H), 9.10 (m, 3 H, CH_3). **34bd**: oil; $R_f = 0.03$ (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3440 (OH, m), 3000 (COOH, b), 2950 (s), 2920 (s), 2850 (s), 1710 (acid, s), 1455 (m), 1410 (m), 1370 (m), 1260 (s), 1095 (m), 1005 (s), 965 (m), 795 (w), 735 (s), 695 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.41 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 4.53 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 5.94 (q, $J = 7$ Hz, 1 H, H-15), 6.21 (m, 1 H, H-11), 6.58 (q, $J = 9$ Hz, 1 H, H-9), 7.12 (m, 1 H, H-6), 7.18–9.00 (m, 25 H), 9.12 (m, 3 H, CH_3).

Methyl (6*R*,9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oate *S*,*S*-Dioxides (35a and 35b). The PGI_1 derivatives **31ab** (50 mg, 0.13 mmol) were dissolved in anhydrous tetrahydrofuran (2.6 mL). Hydrogen peroxide (1.3 mL of a 1 M solution in tetrahydrofuran prepared from a 30% peroxide solution in water) and diphenyl diselenide (4 mg, 0.013 mmol) were added, and the resulting solution was stirred at room temperature under argon for 15 h. The reaction mixture was then diluted with ether (75 mL), washed with 10% potassium bicarbonate solution (2 × 30 mL) and 10% sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 3% methanol in ether, five developments) yielded the products **35b** (faster moving, 35 mg, 65%) and **35a** (slower moving, 13 mg, 24%). **35b**: oil; $R_f = 0.33$ (silica, 3% methanol in ether); $[\alpha]^{25}_D$ +16.8° (methanol, $c = 0.020$); IR (liquid film) ν_{max} 3420 (OH, s), 2950 (s), 2920 (s), 2850 (s), 1730 (ester, s), 1450 (s), 1430 (s), 1415 (m), 1360 (m), 1300 (s), 1270 (s), 1200 (s), 1170 (s), 1110 (s), 1000 (m), 965 (s), 910 (s), 730 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.38 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 4.58 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 5.95 (q, $J = 7$ Hz, 1 H, H-15), 6.21 (q, $J = 7$ Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.57 (q, $J = 9$ Hz, 1 H, H-9), 6.96 (m, 1 H, H-6), 7.37–9.00 (m, 24 H), 9.12 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 545 ($M^+ - CH_3$, $2Me_3Si$, 1.9%), 489 (1.9%), 470 ($M^+ - Me_3SiOH$, 1.2%), 399 (5.2%), 333 (30.2%), 199 (13.0%), 173 (11.9%), 129 (31.8%), 117 (17.2%), 105 (19.6%), 93 (22.8%) 91 (37.3%), 75 (58.6%), 73 (base peak), 55 (71.1%), HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{31}O_6S{\cdot}2Me_3Si$ 545.2787, found 545.2785. **35a**: white crystals, mp 100–101 °C (benzene–hexane); $R_f = 0.27$ (silica, 3% methanol in ether); $[\alpha]^{25}_D$ +16.1° (methanol, $c = 0.0075$); IR ($CHCl_3$) ν_{max} 3400 (OH, m), 3000 (m), 2950 (s), 2920 (s), 2860 (s), 1728 (ester, s), 1455 (m), 1435 (m), 1410 (m), 1375 (m), 1360 (m), 1315 (s), 1270 (s), 1205 (s), 1180 (m), 1125 (s), 1005 (m), 965 (m), 905 (m), 835 (w), 715 (m), 650 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.41 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 4.57 (dd, $J = 7$, 15 Hz, 1 H, olefinic), 5.95 (q, $J = 7$ Hz, 1 H, H-15), 6.05 (q, $J = 8$ Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 6.51 (q, $J = 9$ Hz, 1 H, H-9), 6.89 (m, 1 H, H-6), 7.37–9.00 (m, 24 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 545 ($M^+ - CH_3$, $2Me_3Si$, 3.6%), 489 (1.8%), 470 ($M^+ - Me_2SiOH$, 3.0%), 399 (14.3%), 380 ($M^+ - 2Me_3SiOH$, 1.4%), 333 (41.5%), 327 (11.1%), 314 (18.4%), 264 (10.4%), 199 (17.4%), 129 (28.2%), 105 (21.2%), 91 (34.1%), 75 (65.7%), 73 (base peak); 55 (54.1%), HRMS ($M^+ - CH_3$) calcd for $C_{20}H_{31}O_6S{\cdot}2Me_3Si$ 545.2987, found 545.2790.

(6*R*,9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epithio-11,15-dihydroxyprosta-13-en-1-oic Acid *S*,*S*-Dioxides (36a and 36b). The methyl ester **35a** or **35b** (10 mg, 0.024 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 1 mL). Lithium hydroxide (240 μL or 1 M solution in water, 0.24 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 (240 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 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 **36a** and **36b** (5.7 mg, 59%).

Stable stock solutions of the sodium salt of **36a** or **36b** could be prepared by dissolving the methyl ester **35a** or **35b** (4.16 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 the provides standard solutions of the sodium salt of 10^{-3} M. **36b**: oil; $R_f = 0.09$

(silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3400 (OH, m), 3000 (COOH, b), 2950 (s), 2930 (s), 2860 (s), 1715 (acid, s), 1455 (m), 1405 (m), 1375 (m), 1290 (s), 1270 (s), 1175 (m), 1110 (s), 1010 (m), 965 (m), 905 (w), 730 (m), 695 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.38 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.59 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.00 (b, 3 H, OH), 5.95 (q, J = 7 Hz, 1 H, H-15), 6.18 (q, J = 9 Hz, 1 H, H-11), 6.66 (q, J = 9 Hz, 1 H, H-9), 6.90 (m, 1 H, H-6), 7.33-9.00 (m, 22 H), 9.12 (m, 3 H, CH_3). **36a**: white solid, mp 107-109 °C; R_f = 0.09 (silica, 10% methanol in methylene chloride); IR ($CHCl_3$) ν_{max} 3400 (OH, w), 3100 (COOH, b), 2960 (s), 2930 (s), 2860 (s), 1710 (acid, s), 1455 (m), 1405 (w), 1375 (w), 1310 (m), 1280 (m), 1260 (m), 1205 (m), 1125 (s), 1035 (w), 1005 (w), 970 (m), 900 (w), 815 (w), 725 (s) cm^{-1}; ^1H NMR (360 MHz, acetone-d_6) τ 4.43 (m, 2 H, olefinic), 6.00 (q, J = 7 Hz, 1 H, H-15), 6.07 (q, J = 8 Hz, 1 H, H-11), 6.48 (q, J = 9 Hz, 1 H, H-9), 7.77 (m, 1 H, H-6), 7.87-9.00 (m, 25 H), 9.12 (m, 3 H, CH_3).

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A New Synthesis of Aflatoxin M_1

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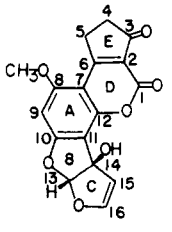
Abstract: Starting with the known and readily available phloroglucinol monobenzenesulfonate (**4**) and 1,4-anhydroerythritol (**7**), we prepared aflatoxin M_1 (**1**) in 13 steps with an overall yield of 5%. The critical features of this second synthesis of aflatoxin M_1 (**1**) include a novel approach to the tricyclic phenol **21** containing the ABC ring system, a regioselective hydrogenolysis of the benzyl protecting group at C_6 in **16**, and removal of the second benzyl group in **20** by Birch reduction. Neither the 1,3,5-trialkoxy-substituted benzene ring nor the vinyl ether function present in **20** were affected in the latter operation.

As soon as the toxic and carcinogenic properties of the naturally occurring aflatoxins[4] had been established questions were raised concerning the presence of toxic derivatives in edible products when animals ingest fodder containing aflatoxin. Lactating cattle fed sublethal doses of aflatoxin B_1 excrete in their milk a metabolite which has been named aflatoxin M_1 (milk toxin).[5] The same metabolite has also been identified in the urine of rats, sheep, monkeys, and humans.[6] A careful search for minor constituents in the original *Aspergillus flavus* mold also led to the isolation of aflatoxin M_1, and its dihydro derivative, which lacks the olefinic bond.[7] Two independent structural studies revealed aflatoxin M_1 to be 14-hydroxyaflatoxin B_1[8,9] (**1**). To probe the toxic and carcinogenic properties of M_1, substantial quantities of this metabolite are required, and the severely limited supply of natural material made it a worthwhile target for synthesis. After efforts to introduce the missing hydroxyl group into B_1 by chemical means failed, attention was focused on total synthesis. The first synthesis, published in 1971,[10] served to prepare approximately 50 mg of racemic aflatoxin M_1 for biological studies.[11] It is not an organic synthesis type of preparation! Two of the intermediates were found to be unstable, and difficult to handle, particularly on scales larger than those described; some had to be purified by chromatography, and finally, the synthesis suffered from a low overall yield.



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A superior synthesis is detailed in this paper. The basic strategy for the production of the final pentacyclic framework, a modified von Pechmann condensation of the monocyclic bromoester **23** containing ring E with a tricyclic phenol comprising the ABC portion of the molecule, was retained from the first synthesis. However, the successive annulations of the B and C rings to a derivative of phloroglucinol were replaced by a more convergent route in which a ring A component was condensed with a second, *monocyclic* intermediate representing ring C.

The first phase of the synthesis was concerned with the preparation of a suitably protected derivative of phloroglucinol (**2**). Partial alkylations, as well as acylations, of polyhydric phenols are known to be nonselective. The isolation of pure products is tedious, and usually accompanied by losses of material. Contrary to the base hydrolysis of polyesters, which again proceeds with little specificity, the partial hydrolysis of phloroglucinol triarylsulfonates was found to be an efficient process.[12,13] The presence of electron-withdrawing groups on the benzene ring increases the

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