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

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

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

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

Acknowledgment. We wish to thank Professors J. Bryan Smith and Allan M. Lefer for the biological investigations, and Dr. M. Hayashi of the Ono Pharmaceutical Co., Japan, for generous supplies of prostanoid compounds. Financial support for this work was provided by the University of Pennsylvania, Merck Sharp and Dohme, U.S.A., and the National Institutes of Health (Heart, Lung, and Blood Institute Contract No. HV-E2931). The 360-MHz ^1H NMR spectra were recorded at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the Medical School of the University of Pennsylvania.

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Organoselenium-Based Synthesis of Oxygen-Containing Prostacyclins

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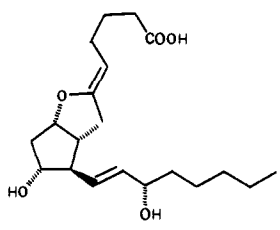
Abstract: The application of organoselenium-induced ring closures to the synthesis of stable, oxygen-containing prostacyclins is described. The strategy involves utilization of $PGF_{2\alpha}$ methyl ester (**3**) as a starting material in a PhSeCl-induced cyclization to produce the two epimeric 5-seleno-PGI_1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

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



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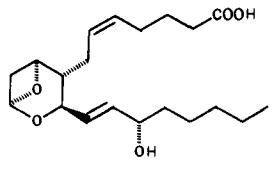

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(1) Fellow of the A. P. Sloan Foundation, 1979-1983; recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985.
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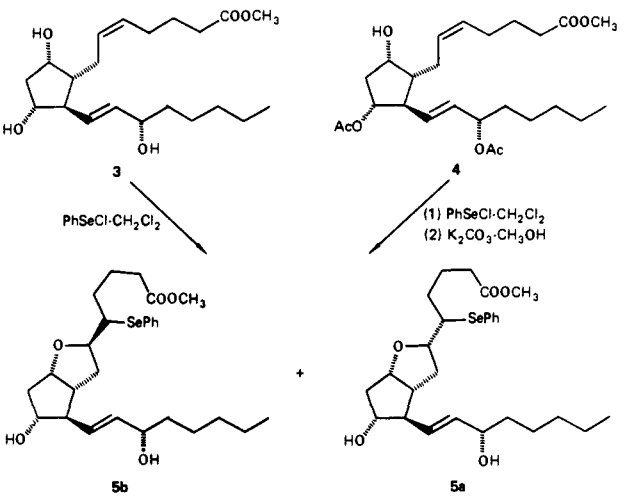
routes to specific analogues. In the case of prostacyclins the principal synthetic task is the regioselective formation of the second ring by a cyclization reaction followed by removal of any groups introduced during this operation. Halogens[5,6,8,9] and mercury[5-8] reagents have been used extensively and with good success, constructing a number of prostacyclins.[9] However, these reagents have their limitations since the mercury reagents would lead to dihydroprostacyclins while halogen-induced syntheses would lead to either dihydro analogues or enol ether-containing prostacyclins due to the tendency of halo ethers to eliminate toward the oxygen. It was clear that for the synthesis of allylic ether-containing prostacyclins, which were deemed important due to their projected chemical stability, a new type of methodology was required.

Our recent organoselenium-based methodology for inducing facile ring closures arrived very timely[10,11] and appeared to be very promising for the synthesis of prostacyclins. Our results in this area proved very rewarding in that this new methodology not only provided an entry into a variety of stable oxygen-[12] and sulfur-containing[13] prostacyclins but also proved crucial in establishing the structures of some of the final products. In this paper we describe the application of this organoselenium-based methodology to the synthesis of a series of oxygen-containing prostacyclins and discuss the stereochemical aspects of the reactions and products involved. The accompanying paper describes our results in the corresponding sulfur series.[14]

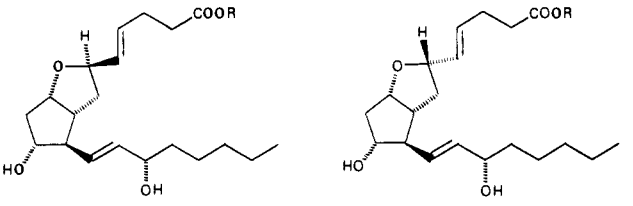
Results and Discussion

The strategy of our synthesis involved (a) phenylselenonium ion ($PhSe^+$)-induced ring closure of the C-9 hydroxy group with the upper side chain double bond of prostaglandin $F_{2\alpha}$ derivatives, (b) oxidative removal of the phenylseleno (PhSe) group offering a unique entry into the Δ^4-prostacyclin series, and (c) reductive removal of the PhSe group leading to 5,6-dihydroprostacyclins. The structures of the products were firmly established by chemical and spectroscopic means. A detailed discussion follows.

(1) The Selenium-Induced Ring-Closure Reaction. Steric, topological, and reactivity considerations led us to expect the facile construction of the prostacyclin 6,9-oxygen bridge by PhSeCl-induced cyclization without interference from the other potentially reactive functionalities of the $PGF_{2\alpha}$ system under the proper conditions. Particularly crucial factors for the expected success of this operation were (a) the reversibility of the phenylselenonium ion addition to a double bond and (b) the proximity of the C-9 hydroxyl group to the C-5 olefin. Indeed, 1.2 equiv of PhSeCl (or PhSeBr or NPSP)[15] reacted with $PGF_{2\alpha}$ methyl ester (**3**) in methylene chloride at −78 °C to afford a mixture (ca. 65:35) of diastereomeric phenylseleno ethers **5a** and **5b** in 80% total yield.[6,12] The two isomers were separated by preparative layer chromatography on silica gel by using 20% acetone in methylene chloride and multiple elutions. The major isomer (slow moving $R_f = 0.11$) was assigned the 6β (exo) configuration, whereas the minor isomer (fast moving $R_f = 0.14$) was assigned the 6α (endo) stereochemistry. The basis for these assignments is discussed below and is in accordance with findings of other workers in the area. To demonstrate the involvement of the C-9 hydroxy group with the Δ^5 and not the C-11 or C-15 hydroxy groups in this ring closure, we subjected the 11,15-diacetoxy-$PGF_{2\alpha}$ methyl ester (**4**) to the phenylselenoetherification reaction. After removal of the acetates (anhydrous potassium carbonate in absolute methanol) the cyclization product was identical with that obtained from $PGF_{2\alpha}$ methyl ester (**3**), thus, confirming our initial assumptions on the course of this reaction. The formation of a tetrahydrofuran rather than a tetrahydropyran system was proved by chemical means as discussed below.



(2) Oxidative Removal of the Phenylseleno Group. Δ^4-Isoprostacyclins. Having formed the desired tetrahydrofuran system with concomitant introduction of the phenylseleno group into the molecule at C-5, the task of removing this moiety, in the first instance by oxidation was undertaken. Previous observations led us to expect that oxidative removal of the phenylseleno group as the selenoxide would proceed away from the ring oxygen leading to an allylic rather than an enol ether with a trans double bond.[16,17,11a] Our expectations were realized when a mixture of selenides **5a** and **5b** was oxidized with hydrogen peroxide in tetrahydrofuran at 25 °C and the resulting selenoxide allowed to decompose at ambient temperature. A mixture of the (4*E*)-isoprostacyclin methyl esters **6a** and **6b** (**6b**:**6a** ca. 65:35) was formed selectively and in high yield (95%). These C-6 epimers were separated by preparative layer chromatography on silica gel by using 20% acetone in methylene chloride and multiple elutions. The more polar isomer **6b** ($R_f = 0.05$, major) was assigned the 6β (exo) and the less polar isomer **6a** ($R_f = 0.09$, minor) the 6α (endo) stereochemistry on spectroscopic and chromatographic mobility data as will be discussed below. Pure selenide **5b** led to pure 6-*exo*-(4*E*)-isoprostacyclin methyl ester **6b** (95%), whereas pure selenide **5a** afforded pure 6-*endo*-(4*E*)-isoprostacyclin methyl



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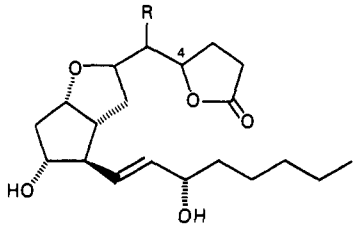
ester **6a** (95%). Saponification (lithium hydroxide in aqueous methanol, 25 °C) of **6a** and **6b** or a mixture of the two (35:65) led in essentially quantitative yield to the acids **7a** and **7b** or a mixture of the two (35:65) after acidification, extraction, and chromatographic isolation.

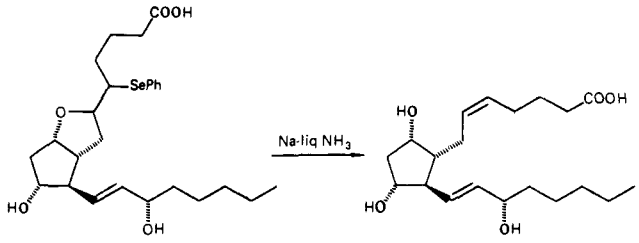
The position of the newly generated double bond and, therefore, the five-membered ring nature of the cyclic ether in these systems was firmly estabilished by phenylselenolactonization[10] of **7b** to afford the γ-lactone **8b** (68% yield). The gross structure of this



8b, R = SePh
9b, R = H

compound (epimeric mixture of C-4) was apparent from its spectral data, particularly the IR spectrum revealing the γ-lactone moiety at ν_{max} (neat) 1765 cm^{-1}. Reductive removal of the phenylseleno group[9,10b,18,19] from **8b** with *tri-n*-butyltin hydride in toluene at 110 °C in the presence of small amounts (2 mol %) of azobis(isobutyronitrile) (AIBN) furnished, in 80% yield, the γ-lactone **9b**. The application of this new and selective method for the reductive removal of the phenylseleno group to the synthesis of 5,6-dihydroprostacyclins is described below.

(3) Reductive Removal of the Phenylseleno Group. 5,6-Dihydroprostacyclins. The readily available 5-phenylselenoprostacyclins **5a** and **5b** besides serving as precursors to the Δ^4-isoprostacyclins **6ab** and **7ab** could, in principle, lead to 5,6-dihydroprostacyclins **10ab** and **11ab** if a practical and efficient way was to be found for the replacement of the phenylseleno group with hydrogen. Although the reductive removal of the phenylseleno (PhSe) group from organic substrates could be accomplished by hydrogenolysis (e.g., Raney Ni),[10,11] this methodology was clearly not applicable to the present case due to the presence of the unsaturation and the allylic oxygen at C-15. Attempted removal of the PhSe group using sodium in liquid ammonia from the acids **13a**, **13b**, or **13ab** (a mixture of the two) (obtained from



13b, 6β
13a, 6α
14

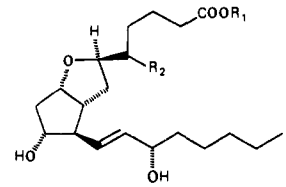
the corresponding methyl esters **5a**, **5b**, or **5ab** by hydrolysis with lithium hydroxide in aqueous methanol) resulted in the high yield (75%) formation of $PGF_{2\alpha}$ (**14**) contaminated with ca. 25% of its 5*E* geometrical isomer.[20] This reaction, although it did not provide the desired 5,6-dihydroprostacyclins, demonstrated the reversibility[10b,20] of the phenylselenoetherification reaction in a synthetically useful manner. Furthermore, it suggests that the selenide **13ab**, due to its efficient formation and reversal to the $PGF_{2\alpha}$ system, could be useful as an internally protected form of this important and readily available prostaglandin for chemical elaborations of the free functionalities.

Table I. Chemical Shifts[a] for H-9, H-11, and H-15 and R_f Values[b] of Prostacyclins 5ab, 6ab, 10ab, and 12ab

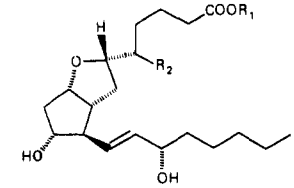
compd	H-9	H-11	H-15	R_f[b]
6β-5-seleno-PGI_1 (5b)	5.51	6.32	5.96	0.11
6α-5-seleno-PGI_1 (5a)	5.70	6.12	5.95	0.14
6β-(4*E*)-iso-PGI_2 (6b)	5.50	6.32	5.96	0.05
6α-(4*E*)-iso-PGI_2 (6a)	5.68	6.10	5.94	0.09
6β-PGI_1 (10b)	5.57	6.34	5.96	0.08
6α-PGI_1 (10a)	5.75	6.12	5.96	0.09
6β-5-iodo-PGI_1 (12b)	5.52	6.29	5.96	0.10
6α-5-iodo-PGI_1 (12a)	5.63	6.12	5.94	0.13

[a] Spectra were recorded in $CDCl_3$ at 360 MHz, and chemical shifts are in τ values. [b] Silica: 20% acetone in methylene chloride.

Successful, reductive removal of the PhSe group[9,10b,11b] from the selenides **5a** and **5b** was carried out by using tri-*n*-butyltin hydride in dry, deoxygenated toluene at 110 °C in the presence of traces (2 mol %) of azobis(isobutyronitrile) (AIBN) as a radical initiator. This new methodology for the selective removal of the PhSe group also reported by Corey[18] and Clive[19] provided **10a**



10b, $R_1 = CH_3$, $R_2 = H$
11b, $R_1 = R_2 = H$
12b, $R_1 = CH_3$, $R_2 = I$



10a, $R_1 = CH_3$, $R_2 = H$
11a, $R_1 = R_2 = H$
12a, $R_1 = CH_3$, $R_2 = I$

(85%) from pure **5a** and **10b** (61%) from pure **5b**. The same products **10a** and **10b** were obtained by similar *tri-n*-butyltin hydride based procedures from the iodo ethers **12a** and **12b**, respectively, by Johnson et al.[5,21] Saponification (lithium hydroxide–aqueous methanol, 25 °C) of the methyl ester **10b** afforded 6-*exo*-5,6-dihydroprostacyclin (6-*exo*-PGI_1) (**11b**), whereas saponification of **10a** led to 6-*endo*-5,6-dihydroprostacyclin (6-*endo*-PGI_1) (**11a**) with both processes proceeding in essentially quantitative yield. The C-6 stereochemistry of these PGI_1 epimers as well as other prostacyclin isomers is discussed below.

(4) C-6 Stereochemistry of Prostacyclins. The C-6 stereochemistry of the epimeric pairs **5ab**, **6ab**, and **10ab** was assigned on the basis of ^1H and ^{13}C NMR spectral data and chromatographic properties and are in accordance to the arguments developed by Johnson et al.,[5,23] Nelson,[22] Corey et al.,[18] and Tomoskozi et al.[24]

Strong indication of the C-6 stereochemical nature of these prostacyclins came from both their ^1H and ^{13}C NMR spectral data. In all cases the 6-exo (6β) isomer exhibited in its ^1H NMR spectrum a distorted quartet (J = ca. 6 Hz) centered at relatively low field (τ 5.50–5.57; Table I) in $CDCl_3$ and at 360 MHz. The corresponding 6-endo (6α) isomer had this signal appearing at considerably higher field, usually superimposed on other resonances. The relatively low chemical shift for this signal which is assigned to H-9[22-24] is presumably due to the 1,3-diaxial-like relationship of this proton and the 6-exo alkyl substitutent ordinarily resulting in downfield shifts.[25] Furthermore, as Table I shows, while H-15 remains at a constant chemical shift in both C-6 epimers, there is a consistent upfield shift (0.17–0.22 ppm) for the exo (6β) epimer. The ^{13}C NMR data (Table II) revealed,

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Table II. ^{13}C NMR Spectral Data of Prostacyclins 5ab, 6ab, 10ab, and 12ab[a]

	compds							
carbon no.	5b	5a	6b	6a	10b	10a	12b	12a
1	173.76	173.76	173.36	173.16	174.01	174.01	173.49	173.36
2	34.35	33.76	33.57	33.31	31.75	31.69	33.18	32.98
3	22.59	22.60	27.46	29.47	25.06	24.91	25.19	25.06
4	34.55	36.43	130.90	132.00	25.12	25.13	36.17	37.01
5	50.39	50.00	130.77	131.29	36.69	37.08	40.32	39.09
6	79.67	82.85	76.10	78.10	79.15	81.25	81.49	84.15
7	33.83	33.31	31.75	31.55	34.78	33.96	35.84	36.17
8	47.53	47.40	47.53	47.33	47.27	47.14	47.66	46.88
9	80.97	83.44	79.99	81.81	79.67	81.55	80.97	81.75
10	41.23	39.48	40.97	38.37	40.91	39.93	41.23	39.09
11	76.29	74.15	77.85	77.00	76.10	78.24	76.55	77.92
12	56.12	57.20	56.04	57.59	56.30	57.92	56.23	56.88
13	132.00	131.74	132.26	132.00	132.20	132.33	131.68	131.81
14	135.84	134.60	135.77	135.12	135.64	135.12	135.90	135.25
15	72.92	72.85	73.05	72.77	72.92	72.98	72.92	72.79
16	37.34	37.34	37.20	37.01	37.33	37.98	37.33	37.01
17	25.19	25.17	25.19	25.00	25.06	24.93	25.19	25.00
18	31.75	31.75	24.47	27.47	25.97	25.91	31.75	31.56
19	23.57	23.63	22.60	22.40	22.60	22.60	22.59	22.47
20	14.02	14.02	14.02	13.83	14.02	14.02	14.02	13.89
21	51.49	51.49	51.56	51.36	51.42	51.42	51.55	51.42
Ph	134.41	134.08						
	129.79	129.02						
	129.02	129.02						
	127.33	127.26						

[a] Spectra were recorded in CD_2Cl_2 at 25.72 Hz, and chemical shifts are in δ values from tetramethylsilane.

without exception, a significant upfield shift for C-6 (2.08–3.18 pmm) and C-9 (0.78–2.47 pmm) in the 6-exo series. This consistent upfield shift for these carbons in **5a**, **6a**, **10a**, and **12a** relative to their 6-endo epimers is presumed to be due to the well-known δ effect.[26] Tables I and II contain data for iodo ethers **12a** and **12b** for comparison reasons.

It was also observed that in this series of compounds the 6-exo epimer was invariably more polar chromatographically on silica gel than its 6-endo counterpart (see Table I). This chromatographic mobility difference for the exo/endo epimers can be explained by (and provides further support for the stereochemical assignments at C-6) the steric environment of the C-11 hydroxy group considerably influenced by the C-6 side chain. In the exo series this hydroxyl group is more exposed to silica gel and, therefore, behaves as more polar than its endo epimer due to stronger binding.

Similar and further chemical evidence supporting the above stereochemical assignments have been expressed by other groups. The spectroscopic and chromatographic differences between the 6-exo and 6-endo isomers of prostacyclin analogues should serve as rapid and reliable criteria for assigning the stereochemistry of any new such analogues although caution should be exercised to allow for individual and unusual structural features. The accompanying article[14] describes further examples of such C-6 pairs of compounds.

Conclusion

Stable analogues of prostacyclin are useful biological tools in studying the physiological role of prostacyclin and other prostaglandins in mammals and could, eventually, even become useful therapeutic agents. We have demonstrated that organoselenium-based methodology developed in these laboratories offers efficient procedures for the synthesis of a number of such analogues. Of particular interest is the demonstration of the regioselective formation of the two allylic ether isomers of prostacyclin [6α- and 6β-(4*E*)-isoprostacyclins **6a** and **6b**] by this route as opposed to the generation of prostacyclin (enol ether) by similar halogen-based methodology. This is a rather unique methodology for the generation of these isomers of prostacyclin and is clearly an excellent complementary method to its halogen counterpart for the construction of unsaturated cyclic ethers. Selenium-induced lactonization (phenylselenolactonization) was also crucial in defining partially the structures of these isomeric prostacyclins. 5,6-dihydroprostacyclins **10a** and **10b** were also synthesized in high overall yield by this new selenium-based methodology. Complete and unambiguous stereochemical assignments of the synthesized prostacyclin analogues were made by ^1H and ^{13}C spectroscopic data as well as chromatographic mobility and are consistent with previous reports. The spectroscopic and chromatographic data can be used reliably as first means for assigning the C-6 stereochemistry of these molecules. Although none of the reported compounds are as biologically potent as prostacyclin, their higher stability makes them useful agents for biological studies and potential candidates for therapeutic uses. Finally, we like to mention here the independent and elegant works of Corey et al. in the synthesis of (4*E*)-isoprostacyclins[6] and 5,6-dihydroprostacyclins[6,18] and of Johnson et al. in the synthesis of the 5,6-dihydroprostacyclins[5] among other compounds in this series.

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. ^{13}C NMR spectra were recorded on a JEOL FX-60Q spectrometer equipped with a microprobe in $CDCl_3$ and are reported in ppm from Me_4Si. IR spectra were obtained with a Perkin-Elmer Model 237 or a Perkin-Elmer Model 281B spectrophotometer and the IR figures reported are ν_{max} in cm^{-1}. Mass spectra were provided by the Mass Spectral Service of Merck Sharp and Dohme, Rahway, NJ, or the Chemistry Department, University of Pennsylvania, and are within acceptable limits unless otherwise stated. Optical rotations were measured with a Hitachi Perkin-Elmer Model 241C instrument at the sodium D line by using a 1-mL, 10-cm long cell. The designation *c* refers to concentration in g/mL.

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

All reactions were carried out under an argon atmosphere by using dry freshly distilled solvents under anhydrous conditions unless otherwise stated. Ethereal and hydrocarbon solvents were dried and distilled under

(26) (a) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972. (b) Maciel, G. E. In "Topics in Carbon-13 NMR Spectroscopy"; Levy, G. C., Ed.; Wiley-Interscience: New York, 1974; Vol. 1, p 54. (c) Grover, S. H.; Stothers, J. B. *Can. J. Chem.* **1974**, *52*, 870.

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

Microanalyses were performed by Galbraith Laboratories.

Methyl (6*R*, 9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epoxy-11,15-dihydroxy-5-(phenylseleno)-prosta-13-en-1-oates (5b and 5a). The $PGF_{2\alpha}$ methyl ester (**3**) (36.8 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (10 mL) and cooled to −78 °C under argon. Solid phenylselenenyl chloride (23 mg, 0.12 mmol) was then added in one portion and the mixture stirred until all of the solid had dissolved. The reaction mixtures was diluted with methylene chloride (50 mL), washed with 10% potassium bicarbonate solution (10 mL) and saturated sodium chloride solution (10 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride, four developments) afforded the (6α) selenide **5a** (faster moving, 15 mg, 28%) and the (6β) selenide **5b** (slower moving, 27 mg, 52%). **5a**: oil, R_f = 0.14 (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +9.9° (methanol, *c* = 0.0065); IR (liquid film) ν_{max} 3300 (s, OH), 2900 (s), 2850 (s), 1725 (s, ester), 1570 (w), 1475 (m), 1430 (s), 1160 (s), 1150 (s), 960 (s), 900 (w) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 2.45 (m, 2 H, aromatic), 2.75 (m, 3 H, aromatic), 4.45 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.52 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 5.70 (m, 1 H, H-9), 5.95 (q, *J* = 7 Hz, 1 H, H-15), 6.04 (m, 1 H, H-6), 6.12 (q, *J* = 8 Hz, 1 H, H-11), 6.35 (s, 3 H, OCH_3), 6.82 (m, 1 H, H-5), 7.17–8.80 (m, 22 H), 9.10 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.76 (C-1), 33.76 (C-2) 22.60 (C-3), 36.43 (C-4), 50.00 (C-5), 82.85 (C-6), 33.31 (C-7), 47.40 (C-8), 83.44 (C-9) 39.48 (C-10), 74.15 (C-11), 57.20 (C-12), 131.74 (C-13), 134.60 (C-14), 72.85 (C-15), 37.34 (C-16), 25.17 (C-17), 31.75 (C-18), 23.63 (C-19), 14.02 (C-20), 51.49 (C-21), 134.08 (aromatic), 129.02 (aromatic) 127.26 (aromatic); mass spectrum, *m/e* (relative intensity) 653 ($M^+ - CH_3$, $2Me_3Si$, 0.1%), 578 ($M^+ - Me_3SiOH$, 1.9%), 506 (2.0%, 488 ($M^+ - 2Me_3SiOH$, 2.8%), 403 (12.0%), 331 (10.9%), 313 (11.7%), 277 (15.1%), 269 (10.3%), 217 (12.2%), 188 (62.0%), 158 (19.5%), 143 (30.6%), 111 (54.2%), 99 (44.2%), 91 (52.4%), 81 (64.2%), 73 (base peak), 55 (97.3%); HRMS calcd for $C_{27}H_{40}O_5Se$ 524.2038, found 524.2041. **5b**: oil, R_f = 0.11 (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +44.0° (methanol, *c* = 0.0066); IR (liquid film) ν_{max} 3300 (s, OH), 3020 (m), 2900 (s), 2800 (s), 1725 (s, ester), 1575 (m), 1470 (m), 1430 (s), 1175 (m), 1050 (m), 1020 (m), 965 (m), 910 (w); ^{1}H NMR (360 MHz, $CDCl_3$) τ 2.47 (m, 2 H, aromatic), 2.77 (m, 3 H, aromatic), 4.44 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.55 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 5.51 (q, *J* = 8 Hz, 1 H, H-9), 5.83 (m, 1 H, H-6), 5.96 (q, *J* = 7 Hz, 1 H, H-15), 6.32 (q, *J* = 8 Hz, 1 H, H-11), 6.35 (s, 3 H, ester), 6.69 (m, 1 H, H-5), 7.13–8.83 (m, 22 H), 9.10 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) 173.76 (C-1), 34.35 (C-2), 22.59 (C-3), 34.55 (C-4), 50.39 (C-5), 79.67 (C-6), 33.83 (C-7), 47.53 (C-8), 80.97 (C-9), 41.23 (C-10), 76.29 (C-11), 56.12 (C-12), 132.00 (C-13), 135.84 (C-14), 72.92 (C-15), 37.34 (C-16), 25.19 (C-17), 31.75 (C-18), 23.57 (C-19), 14.02 (C-20), 51.49 (C-21), 134.41 (aromatic), 129.79 (aromatic), 129.02 (aromatic), 127.33 (aromatic); mass spectrum, *m/e* (relative intensity) 524 (M^+, 0.8%), 506 ($M^+ - H_2O$, 1.1%), 488 ($M^+ - 2H_2O$, 0.2%), 367 (M^+ – PhSe, 4.3%), 331 (5.9%), 239 (4.1%), 235 (5.0%), 203 (5.5%), 195 (4.9%), 185 (5.4%), 175 (6.8%), 157 (22.6%), 143 (23.9%), 111 (40.8%), 99 (60.3%), 91 (50.0%), 79 (53.3%), 55 (base peak); HRMS calcd for $C_{27}H_{40}O_5Se$: 524.2038, found 524.2056. Anal. ($C_{27}H_{40}O_5Se$) C, H.

Methyl (4*E*,6*R*,9α,11α,13*E*,15*S*)- and (4*E*,6*S*,9α,11α,13*E*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-4,13-dien-1-oates (6a and 6b). The (6α) selenide **5a** or (6β) **5b** (52.8 mg, 0.1 mmol) was dissolved in freshly distilled tetrahydrofuran (5 mL). Hydrogen peroxide (150 μL of a 1 N solution in tetrahydrofuran, 0.15 mmol) was added and the solution stirred at room temperature for 15 h. The reaction mixture was diluted with ether (50 mL), washed with 10% potassium bicarbonate solution (10 mL), 10% sodium thiosulfate solution (10 mL), and saturated sodium chloride solution (10 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 20% acetone in methylene chloride) yielded the endo (6α) product **6a** as a white solid (35 mg, 95%) or the exo (6β) isomer **6b** as an oil (35 mg, 95%). **6a**: white crystals, mp 61–63 °C (ether–hexane); R_f = 0.09 (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +11.0° (methanol, *c* = 0.006); IR ($CHCl_3$) ν_{max} 3400 (OH, w), 3000 (m), 2950 (s), 2930 (s), 2850 (m), 1730 (ester, s), 1435 (m), 1360 (w), 1290 (w), 1260 (m), 1205 (s), 1180 (m), 1065 (m), 1050 (m), 970 (s), 905 (w), 880 (w), 825 (w), 720 (s), 655 (w) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.28 (m, 1 H, olefinic), 4.46 (m, 3 H, olefinic), 5.68 (m, 1 H, H-9), 5.79 (q, *J* = 9 Hz, 1 H, H-6), 5.94 (q, *J* = 7 Hz, 1 H, H-15), 6.10 (q, *J* = 7 Hz, 1 H, H-11), 6.32 (s, 3 H, ester), 7.50–8.83 (m, 20 H), 9.10 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.16 (C-1), 33.31 (C-2), 29.47 (C-3), 132.00 (C-4), 131.29 (C-5), 78.10 (C-6), 31.55 (C-7), 47.33 (C-8), 81.81 (C-9), 38.37 (C-10), 77.00 (C-11), 57.59 (C-12), 132.00 (C-13), 135.12 (C-14), 72.79 (C-15), 37.01 (C-16), 25.00 (C-17), 27.47 (C-18), 22.40 (C-19), 13.83 (C-20), 51.36 (C-21); mass spectrum, *m/e* (relative intensity) 366 (M^+, 0.5%); 348 ($M^+ - H_2O$, 1.9%), 330 ($M^+ - 2H_2O$, 2.5%), 304 (7.3%), 279 (11.7%), 276 (39.3%), 208 (19.3%), 182 (30.6%), 152 (54.8%), 140 (56.7%), 105 (43.3%), 99 (96.4%), 91 (70.8%), 81 (74.0%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_5$ 366.2404, found 366.2405. **6b**: oil, R_f = 0.05 (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +40.2° (methanol, *c* = 0.021); IR (liquid film) ν_{max} 3380 (OH, m), 2950 (s), 2930 (s), 2850 (s), 1730 (ester, s), 1665 (olefin, w), 1440 (s), 1360 (m), 1340 (m), 1295 (m), 1255 (m), 1200 (m), 1165 (m), 1130 (m), 1080 (m), 1055 (s), 1101 (m), 965 (s), 905 (s), 875 (w), 830 (w), 725 (s), 640 (m) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.29 (m, 1 H, olefinic), 4.51 (m, 3 H, olefinic), 5.50 (q, *J* = 6 Hz, 1 H, H-9), 5.60 (m, 1 H, H-6), 5.96 (q, *J* = 7 Hz, 1 H, H-15), 6.32 (m, 1 H, H-11), 6.34 (s, 3 H, ester), 7.60–8.83 (m, 20 H), 9.11 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.36 (C-1), 33.57 (C-2), 27.46 (C-3), 130.90 (C-4), 130.77 (C-5), 76.10 (C-6), 31.75 (C-7), 47.53 (C-8), 79.99 (C-9), 40.97 (C-10), 77.85 (C-11), 56.04 (C-12), 132.26 (C-13), 135.77 (C-14), 73.05 (C-15), 37.20 (C-16), 25.12 (C-17), 24.47 (C-18), 22.60 (C-19), 14.02 (C-20), 51.56 (C-21); mass spectrum, *m/e* (relative intensity) 366 (M^+, 0.1%), 348 ($M^+ - H_2O$, 0.7%), 330 ($M^+ - 2H_2O$, 1.0%), 293 (3.0%), 279 (7.4%), 276 (9.2%), 208 (7.6%), 182 (18.8%), 165 (17.1%), 152 (31.8%), 140 (44.0%), 117 (24.6%), 105 (38.9%), 99 (86.9%), 91 (59.3%), 81 (75.3%), 71 (83.2%), 67 (61.6%), 55 (base peak); HRMS calcd for $C_{21}H_{34}O_5$ 366.2404, found 366.2405.

(4*E*,6*R*,9α,11α,13*E*,15*S*)- and (4*E*,9α,11α,13*E*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-4,13-dien-1-oic Acids (7a and 7b). The ester **6a** or **6b** (18 mg, 0.05 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 2 mL). Lithium hydroxide (500 μL of a 1 N solution in water, 0.5 mmol) was added and the mixture stirred at room temperature for 12 h. The reaction mixture was adjusted to pH 4 by the addition of 1 N oxalic acid solution (ca. 500 μL) and the tetrahydrofuran removed under reduced pressure. The aqueous mixture was then diluted with saturated sodium chloride solution and extracted with ether (3 × 30 mL). The combined extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 10% methanol in methylene chloride) yielded the acid **7a** or **7b** (17 mg, 97%). **7a**: mp 121–122 °C (methanol–water 1:1); R_f = 0.17 (silica, 10% methanol in methylene chloride); IR ($CHCl_3$) ν_{max} 3300 (w, OH), 3000 (b, COOH), 3010 (m), 2940 (s), 2860 (s), 1720 (s, acid), 1460 (w), 1420 (w), 1250 (m), 1075 (s), 975 (m), 900 (w) cm^{-1}; ^{1}H NMR (220 MHz, $CDCl_3$) τ 4.64 (m, 5 H, olefinic, OH), 5.91 (m, 2 H, H-9, H-6), 6.20 (m, 1 H, H-15), 6.39 (m, 1 H, H-11), 7.68–9.23 (m, 20 H), 9.32 (m, 3 H, CH_3). **7b**: oil; R_f = 0.17 (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3300 (m, OH), 2950 (b, COOH), 2940 (s), 2900 (s), 2850 (s), 1720 (s, acid), 1450 (m), 1250 (s), 1050 (s), 1020 (s), 975 (s), 980 (w) cm^{-1}; ^{1}H NMR (220 MHz, $CDCl_3$) τ 4.45 (m, 5 H, olefinic, OH), 5.50 (m, 1 H, H-9), 5.59 (m, 1 H, H-6), 5.93 (m, 1 H, H-15), 6.29 (m, 1 H, H-11), 7.43–9.00 (m, 2 H), 9.11 (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-Epoxy-11,15-dihydroxyprosta-13-en-1-oates (10a and 10b). The (6α) selenide **5a** or (6β) **5b** (54 mg, 0.1 mmol), tri-*n*-butyltin hydride (43.5 mg, 0.15 mmol), and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (ABIN) (0.25 mg, 1 mol %) were dissolved in anhydrous toluene (1 mL) and the resulting solution deoxygenated with argon. The reaction vessel was then sealed and heated at 110 °C under argon for 2 h. The solvent was removed under reduced pressure and the residue purified directly by preparative layer chromatography (silica, 20% acetone in methylene chloride) yielding the dihydro derivative **10a** (22.4 mg, 61%) or **10b** (31 mg, 85%). These were found to be spectroscopically identical with the products formed by similar reduction of iodide **12a** or **12b**, respectively.[5] **10a**: mp 70–71 °C (ether–hexane); R_f = 0.09 (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +14.1° (methanol, *c* = 0.0082); IR (liquid film) ν_{max} 3300 (s, OH), 2900 (s), 2860 (s), 1725 (s, ester), 1430 (m), 1075 (s), 1025 (m), 965 (m), 880 (w) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) τ 4.46 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 4.55 (dd, *J* = 7, 15 Hz, 1 H, olefinic), 5.75 (m, 1 H, H-9), 5.96 (q, *J* = 7 Hz, 1 H, H-15), 6.12 (q, *J* = 8 Hz, 1 H, H-11), 6.24 (m, 1 H, H-6), 6.32 (s, 3 H, ester), 7.00–8.83 (m, 24 H), 9.11 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.01 (C-1), 31.69 (C-2), 24.91 (C-3), 25.13 (C-4), 37.08 (C-5), 81.25 (C-6),

33.96 (C-7), 47.14 (C-8), 81.55 (C-9), 39.93 (C-10), 78.24 (C-11), 57.92 (C-12), 132.33 (C-13), 135.12 (C-14), 79.98 (C-15), 37.98 (C-16), 24.93 (C-17), 25.91 (C-18), 22.60 (C-19), 14.02 (C-20), 51.42 (C-21); mass spectrum, *m/e* (relative intensity) 422 ($M^+ - Me_3SiOH$, $2Me_3Si$, 2.3%), 351 (3.4%) 332 ($M^+ - 2Me_3SiOH$, 1.3%), 307 (11.5%), 306 (36.0%), 279 (27.2%), 173 (12.4%), 158 (10.5%), 145 (40.3%), 121 (20.8%), 109 (24.4%), 99 (38.1%), 91 (42.7%), 79 (59.4%), 73 (base peak), 67 (61.3%), 55 (83.1%); HRMS calcd for $C_{21}H_{30}O_5 \cdot 2Me_3Si$ 512.3352, found 512.3315. **10b**: mp 39–41 °C (ether–hexane); $R_f = 0.08$ (silica, 20% acetone in methylene chloride); $[\alpha]_D^{25}$ +27.7° (methanol, c = 0.0165); IR (liquid film) ν_{max} 3300 (s, OH), 2920 (s), 2850 (s), 1725 (s, ester), 1430 (s), 1175 (s), 1075 (s), 1010 (m), 960 (m), 875 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) τ 4.44 (dd, J = 7, 15 Hz, 1 H, olefinic), 4.53 (dd, J = 7, 15 Hz, 1 H, olefinic), 5.57 (q, J = 7 Hz, 1 H, H-9), 5.96 (q, J = 7 Hz, 1 H, H-15), 6.10 (m, 1 H, H-6), 6.32 (s, 3 H, ester), 6.34 (q, J = 8 Hz, 1 H, H-11), 6.58–8.83 (m, 24 H), 9.10 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.01 (C-1), 31.75 (C-2), 25.06 (C-3), 25.12 (C-4), 36.69 (C-5), 79.15 (C-6), 34.78 (C-7), 47.27 (C-8), 79.67 (C-9), 40.91 (C-10), 76.10 (C-11), 56.30 (C-12), 132.20 (C-13), 135.64 (C-14), 72.92 (C-15), 37.33 (C-16), 25.06 (C-17), 25.97 (C-18), 22.60 (C-19), 14.02 (C-20), 51.42 (C-21); mass spectrum *m/e* (relative intensity) 512 (M^+, $2Me_3Si$, 0.2%), 497 ($M^+ - CH_3$, 0.1%), 441 (2.2%), 422 ($M^+ - Me_3SiOH$, 2.3%), 332 ($M^+ - 2Me_3SiOH$, 1.0%), 322 (37.2%), 279 (14.8%), 233 (11.1%), 225 (12.4%), 201 (13.0%), 173 (44.3%), 143 (34.7%), 111 (37.8%), 81 (62.5%), 73 (77.0%), 67 (50.2%), 55 (base peak); HRMS calcd for $C_{21}H_{30}O_5 \cdot 2Me_3Si$ 512.3352, found 512.3341. Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.58; H, 9.85.

(6*R*,9α,11α,13*E*,15*S*)- and (6*S*,9α,11α,13*E*,15*S*)-6,9-Epoxy-11,15-dihydroxyprosta-13-en-1-oic Acids (11a and 11b). The ester **10a** or **10b** (18 mg, 0.05 mol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 2 mL). Lithium hydroxide (500 μL of a 1 N solution in water, 0.5 mmol) was added and the mixture stirred at room temperature for 12 h. The reaction mixture was adjusted to pH 4 by the addition of 1 N oxalic acid solution (ca. 50 μL) and the tetrahydrofuran removed under reduced pressure. The aqueous mixture was then diluted with saturated sodium chloride solution and extracted with ether (3 × 30 mL). The combined extracts were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 10% methanol in methylene chloride) yielded the acid **11a** or **11b** (17 mg, 97%). **11a**: mp 96–98 °C (methanol–water); $R_f = 0.17$ (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3300 (b, OH), 2940 (s), 2850 (s), 2750 (s), 1720 (s, acid), 1450 (m), 1250 (m), 1085 (m), 1050 (s), 975 (s), 880 (m), 815 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.43 (b, 3 H, OH), 4.75 (m, 2 H, olefinic), 5.98 (m, 1 H, H-9), 6.18 (m, 1 H, H-15), 6.36 (m, 1 H, H-11), 6.43 (m, 1 H, H-6), 7.73–9.18 (m, 22 H), 9.32 (m, 3 H, CH_3). **11b**: mp 78–80 °C (methanol–water); $R_f = 0.17$ (silica, 10% methanol in methylene chloride); IR (liquid film) ν_{max} 3300 (b, OH), 2940 (s), 2900 (s), 2850 (s), 1720 (s, acid), 1450 (m), 1250 (s), 1060 (s), 975 (m), 880 (w), 800 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.02 (b, 3 H, OH), 4.52 (m, 2 H, olefinic), 5.57 (m, 1 H, H-9), 5.88 (m, 1 H, H-15), 6.07 (m, 1 H, H-6), 6.36 (m, 1 H, H-11), 7.36–8.91 (m, 20 H), 9.11 (m, 3 H, CH_3).

γ-(6*R*,9α,11α,13*E*,15*S*)-6,9-Epoxy-4,11,15-trihydroxy-5-(phenylseleno)-prosta-13-en-1-oic Acid Lactone (8b). The (6β) isoprostacyclin **7b** (35 mg, 0.1 mmol) was dissolved in anhydrous methylene chloride (10 mL) and cooled to −78 °C under argon. Phenylselenenyl chloride (23 mg, 0.12 mmol) was added in one portion and the mixture stirred until all of the solid had dissolved. The reaction mixture was diluted with methylene chloride (50 mL), washed with 10% potassium bicarbonate and saturated sodium chloride solutions, and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 5% methanol in ether) yielded the selenolactone **8b** (35 mg, 68%). **8b**: oil; $R_f = 0.28$ (silica, 5% methanol in ether); IR (liquid film) ν 3330 (m, OH), 2920 (s), 2900 (s), 2846 (m), 1765 (s, γ-lactone), 1575 (w), 1470 (m), 1430 (m), 1325 (m), 1165 (s), 1060 (m), 1015 (m), 970 (m), 905 (w) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 2.43 (m, 2 H, aromatic), 2.73 (m, 3 H, aromatic), 4.45 (m, 2 H, olefinic), 5.17 (m, 1 H, H-4), 5.49 (m, 2 H, H-9, H-6), 5.93 (q, 1 H, J = 5.0 Hz, H-15), 6.27 (q, 1 H, J = 7.5 Hz, H-11), 6.77 (d, 1 H, J = 10.0 Hz, H-5), 7.00–9.00 (m, 20 H), 9.10 (m, 3 H); mass spectrum, *m/e* (relative intensity) 652 (M^+, $2Me_3Si$, 5%), 637 ($M^+ - CH_3$, 1%), 581 (15%), 562 ($M^+ - Me_3SiOH$, 4%), 495 ($M^+ - PhSe$, 95%), 490 (11%), 423 (71%), 405 ($M^+ - Me_3SiOH - PhSe$, 99%), 398 (52%), 315 ($M^+ - 2MeSiOH - PhSe$, 22%), 309 (50%), 254 (base peak); HRMS calcd for $C_{26}H_{36}O_5Se \cdot 2Me_3Si$ 652.2517, found 652.2488.

γ-(6*R*,9α,11α,13*E*,15*S*)-6,9-Epoxy-4,11,15-trihydroxyprosta-13-en-1-oic Acid Lactone (9b). The selenolactone **8b** (26 mg, 0.05 mmol), tri-*n*-butyltin hydride (22 mg, 0.075 mmol), and a catalytic amount of 2,2′-azobis(2-methylpropionitrile) (ABIN) (0.1 mg, 1 mol %) were dissolved in anhydrous toluene (1 mL), and the resulting solution was deoxygenated with argon. The reaction vessel was then sealed and heated at 110 °C under argon for 1 h. Solvent was removed under reduced pressure and the residue purified directly by preparative layer chromatography (silica, 5% methanol in ether), yielding the lactone **9b** (14 mg, 80%). **9b**: oil; $R_f = 0.12$ (silica, 5% methanol in ether); IR (liquid film) ν_{max} 3360 (s, OH), 2960 (s), 2930 (s), 2860 (s), 1765 (s, γ-lactone), 1450 (m), 1345 (m), 1280 (m), 1175 (s), 1055 (s), 965 (m), 915 (m) cm^{-1}; ^1H NMR (220 MHz, $CDCl_3$) τ 4.45 (m, 2 H, olefinic), 5.31 (m, 1 H, H-4), 5.54 (m, 1 H, H-9), 5.84 (m, 1 H, H-6), 5.92 (m, 1 H, H-15), 6.32 (m, 1 H, H-11), 7.00–9.00 (m, 22 H), 9.11 (m, 3 H, CH_3); mass spectrum, *m/e* (relative intensity) 496 (M^+, $2Me_3Si$, 7.8%), 481 ($M^+ - CH_3$, 5.6%), 425 ($M^+ - C_5H_{11}$, base peak above 200), 406 ($M^+ - Me_3SiOH$, 62.1%), 335 ($M^+ - C_5H_{11} - Me_3SiOH$, 98.7%), 316 ($M^+ - 2Me_3SiOH$, 15.1%), 308 (53.0%), 290 (20.7% O, 279 (49.1%), 264 (16.8%), 252 (14.7%) 244, (22.0%), 242 (19.0%), 224 (63.4%), 216 (50.9%), 208 (19.4%), 206 (21.1%), 200 (24.1%); HRMS calcd for $C_{20}H_{32}O_5$ 352.2241, found 352.2238.

Reaction of Phenylseleno Ethers 5ab with Sodium in Liquid Ammonia. The endo selenide **5a** or exo selenide **5b** or the mixture **5ab** (52.4 mg, 0.1 mmol) was dissolved in a mixture of tetrahydrofuran–water (3:1, 4 mL). Lithium hydroxide (1 mL of a 1 M solution in water) was added and the mixture stirred at room temperature for 12 h. Oxalic acid (1 mL of a 1 N solution in water) was then added and the tetrahydrofuran removed under reduced pressure. The remaining 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 peroxide-free ether (3 × 30 mL), and the combined extracts were washed with saturated sodium chloride solution (30 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent removed under reduced pressure. The residue was redissolved in anhydrous ether (2 mL) and added to a solution of sodium (46 mg, 2 mmol) in liquid ammonia (10 mL) at −78 °C. The cooling bath was removed, and after 5 min, the reaction was quenched with solid ammonium chloride (500 mg). The mixture was then diluted with ether (50 mL) and, after the ammonia was allowed to evaporate, was washed with water (10 mL) and dried over anhydrous magnesium sulfate. This solution was filtered, concentrated, and treated with diazomethane. Removal of solvent under reduced pressure and purification by preparative layer chromatography (silica, 5% methanol in ether) yielded an oil (27.6 mg, 75%) which was spectroscopically and chromatographically similar to an authentic sample of $PGF_{2\alpha}$ methyl ester (**3**).

This oil (27.6 mg, 0.075 mmol) was then dissolved along with imidazole (46 mg, 0.675 mmol) in anhydrous dimethylformamide (1 mL). *tert*-Butyldimethylsilyl chloride (51 mg, 0.338 mmol) was added and the resulting solution stirred for 1 h under argon. The reaction mixture was diluted with ether (50 mL), washed with water (3 × 10 mL), and dried over anhydrous magnesium sulfate. Filtration, removal of solvent under reduced pressure, and purification by preparative layer chromatography (silica, 17% ether in hexane) yielded another oil (48 mg, 90%). Analysis of this material on silver nitrate-impregnated silica gel (immersion of thin-layer plate in a 10% solution of silver nitrate in acetonitrile followed by air drying for 3 h prior to use) resolved two compounds chromatographically identical with genuine samples of (5*Z*)- and (5*E*)-tris(*tert*-butyldimethylsilyl)-$PGF_{2\alpha}$ methyl ester ($R_f(Z) = 0.41$, $R_f(E) = 0.52$, 1% ether in hexane) prepared from authentic $PGF_{2\alpha}$ methyl ester (**3**) and by the photolysis of (5*Z*)-tris(*tert*-butyldimethylsilyl)-$PGF_{2\alpha}$ methyl ester as described by Corey et al.[27] 5*Z*/5*E* ratio was estimated at 1:2.5 by column chromatography by using silver nitrate impregnated silica.

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