The temperature of the reaction mixture was raised to 30 °C. Stirring at room temperature was continued for 1 h. The reaction mixture was washed with 10% NaOH, dried over $MgSO_4$, and after evaporation of the solvent distilled at 175–90 °C (10 torr) to remove the unreacted benzylideneaniline. The dark residue was chromatographed and the isolated product (5%) shown to be identical with **7b**.

Synthesis of 2-Ethoxy-3-methyl-4-phenylquinoline (13b). Compound **13b** was synthesized by heating under reflux for 15 min 1 g of 2-chloro-3-methyl-4-phenylquinoline[20] and 0.01 mol of NaOEt in 10 mL of absolute ethanol. The solvent was evaporated, the residue was washed with water and extracted with ether, and the ether solution was dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a preparative silica gel plate, and 18% of 2-ethoxy-3-methyl-4-phenylquinoline (**13b**) was obtained: mp 71–72 °C (from EtOH): IR (mineral oil) 1590 cm^{-1}; ^1H NMR δ 7.1–7.9 (m, 9 H, aromatic), 4.60 (q, 2 H, J = 7.0 Hz), 2.08 (s, 3 H), 1.48 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 160.95, 147.96, 145.19, 137.57, 130.35, 129.41, 128.42, 128.10, 127.61, 127.13, 125.94, 123.49, 120.08, 61.71, 14.68, 13.81; mass spectrum, m/e 263 (m^+, 42), 248 (M – 15, 75), 234 (M –29, 100), 218 (M – 45, 46); UV λ_{max} 226 nm (ϵ 31 000), 263 (5780), 272 (5870), 282 (4880), 296 (3000), 309 (4740), 322 (5680). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.17; H, 6.43; N, 5.35.

Synthesis of 3-Ethoxy-2-methyl-4-phenylquinoline (14b). A mixture of 110 mg (1.08 mmol) of ethoxyacetone[21] and 126 mg (0.54 mmol) of 2-aminobenzophenone hydrochloride was heated in a sealed tube at 190 °C for 1 h. The dark reaction mixture was treated with water and ether and neutralized with Na_2CO_3 solution. The ether extracts were dried over $MgSO_4$. After the solvent was evaporated, the residue was purified by preparative TLC, and 21% of **14b** was isolated: mp 68–70 °C; IR (mineral oil) 1590 cm^{-1}; ^1H NMR δ 8.09–7.97 (1 H), 7.2–7.7 (m, 8 H, 3.59 (q, 2 H, J = 7.0 Hz), 2.75 (s, 3 H), 1.06 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 156.18, 153.37, 148.31, 144.87, 134.38, 130.34, 128.77, 128.58, 128.34, 128.09, 127.78, 125.84, 125.41, 69.14, 21.04, 15.53; mass spectrum, m/e 263 (M^3, 82), 248 (M – 15, 4), 235 (M – 28, 100), 234 (M – 29, 50), 206 (M – 57, 50), 204 (M – 59, 20). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.98; H, 6.45; N, 5.28.

Synthesis of 2-Ethoxy-4-phenylquinoline (13a). Compound **13a** was synthesized by heating under reflux 1 g (0.004 mol) of 2-chloro-4-phenylquinoline[22] and 0.01 mol of sodium ethoxide in 10 mL of absolute ethanol for 0.5 h. After evaporation of the ethanol the residue was treated with ether, washed with water, and dried over $MgSO_4$. After evaporation of the ether, the mixture was purified by preparative silica gel TLC. The product (**13a**) was crystallized from ethanol: mp 54–55 °C; yield 15%; IR (neat) 1620, 1600, 1575 cm^{-1}; ^1H NMR δ 7.1–8.0 (m, 9 H), 6.84 (s, 1 H), 4.58 (q, 2 H, J = 7.0 Hz), 1.45 (t, 3 H, J = 7.0 Hz); ^{13}C NMR δ 161.79, 151.03, 147.46, 138.18, 129.33, 128.42, 128.25, 127.79, 125.73, 124.04, 123.80, 113.07, 61.56, 14.64; mass spectrum, m/e 249 (M^+, 27), 234 (M – 15, 100), 220 (M – 29, 65), 205 (M – 44, 32), 204 (M – 45, 31); UV λ_{max} (ϵ 54 100), 275 (8370), 313 (5150), 326 (5700). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.07; N, 5.62. Found: C, 81.91; H, 6.01; N, 5.55.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. R01 NS 14883). We thank the donors of these funds.

Registry No. 1, 883-93-2; **2a**, 927-80-0; **2b**, 14273-06-4; **3a**, 83463-79-0; **3b**, 83463-81-4; **4b**, 83463-82-5; **5b**, 83463-83-6; **6a**, 83463-80-3; **6b**, 83463-84-7; **7b**, 83463-85-8; **13a**, 83463-88-1; **13b**, 83463-86-9; **14b**, 83463-87-0; **15**, 79091-78-4; 2-aminoacetophenone hydrochloride, 25384-14-9; α-ethoxyacetophenone, 14869-39-7; benzylideneaniline, 538-51-2; 2-chloro-3-methyl-4-phenylquinoline, 37118-76-6; ethoxyacetone, 14869-34-2; 2-aminobenzophenone hydrochloride, 40318-20-5; 2-chloro-4-phenylquinoline, 5855-56-1.

(20) Marsili, A. *Ann. Chim. (Rome)* **1962**, *52*, 3; *Chem. Abstr.* **1962**, *57*, 2193a.

(21) Cross, L. B.; Henze, H. R. *J. Am. Chem. Soc.* **1939**, *61*, 2730.

(22) Hauser, C. R.; Reynolds, G. A. *J. Am. Chem. Soc.* **1948**, *70*, 2402.

Synthesis of (5*E*)- and (5*Z*)-11-Deoxy-6,11α-epoxy-Δ^5-prostaglandin $F_{1\alpha}$ Sodium Salts: 6,11α-Enol Ether Isomers of Prostacyclin

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Received May 7, 1982

The key intermediates, (5*S*,6*R*)- and (5*R*,6*R*)-11-deoxy-6,11α-epoxy-5-hydroxy cyclic ethers, **22a,b**, were prepared from the reaction of a C-9 silyl $PGF_{2\alpha}$ derivative **12** with mercuric acetate (oxymercuration), followed by conversion of the mercurioacetate substituent to a hydroxy group. Attempts to construct the 6,11α oxygen bridge by reaction of **12** and other C-9 protected $PGF_{2\alpha}$ derivatives [9-tetrahydropyranyl (**11**), 9-acetyl (**13**)] with iodine, *N*-bromosuccinimide, and phenylselenenyl chloride were unsuccessful. Reaction of **11** and **12** with iodine resulted in removal of the C-9 blocking group and the isolation of 6,9-iodo cyclic ether products. Treatment of **13** with phenylselenenyl chloride gave the β-chlorophenylselenenyl addition adduct **18**. Conversion of alcohols **22a,b** to their mesylate derivatives, **25a,b**, and subsequent reaction with potassium methoxide in dimethyl sulfoxide afforded the labile Δ^5 enol ethers, **29a,b**. The success of this elimination reaction was critically dependent on the base, the reaction solvent, and the workup conditions. The structural assignments of **29a,b** were based on their spectral properties and hydrolysis to 6-keto-$PGF_{1\alpha}$ methyl ester. The stereoconfiguration at C-6 was assigned by conversion of the oxymercuration product obtained from **12** to the 5,6-dihydro-6,11α-cyclic ether **20**. The C-5 stereoconfiguration of alcohols **22a,b** was established by the mode of formation of enol ethers **29a,b**. In contrast to PGI_2 methyl ester, **29a,b** in aqueous acid showed a greater tendency to form the internal ketal **34** during hydrolysis to 6-keto-$PGF_{1\alpha}$ methyl ester.

Introduction

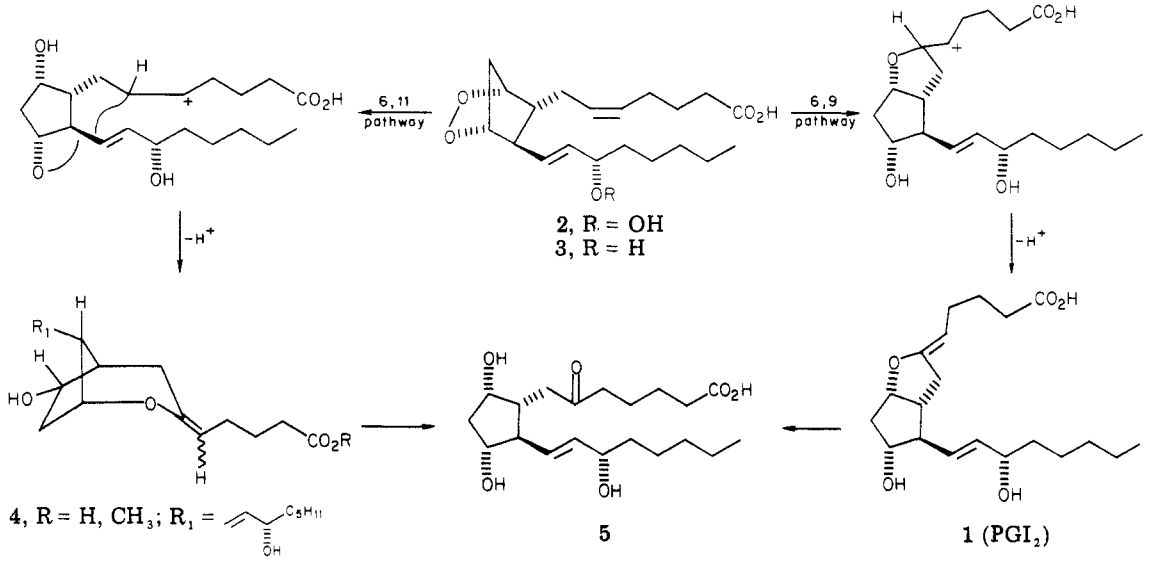
Prostacyclin (PGI_2, **1**) is derived biosynthetically from arachidonic acid by way of intermediate prostaglandin endoperoxides, PGG_2 and PGH_2 (**2** and **3**).[1] The formation of PGI_2 from endoperoxide PGH_2 can be envisioned to occur in the following manner:[2] (1) attack by an electrophilic site on the prostacyclin synthetase at the oxygen attached to C-11 causes breaking of the peroxide bond, (2) capture of the electron-deficient C-9 oxygen by the C_5–C_6 double bond, and (3) subsequent loss of the C_6 hydrogen

(1) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976).

(2) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 2199 (1977).

0022-3263/82/1947-4919$01.25/0

Scheme I



(Scheme I). However, if the initial endoperoxide cleavage gave instead a C-11 electron-deficient oxygen, the same sequence of events would lead to 11-deoxy-6,11α-epoxy-Δ^5-prostaglandin $F_{1\alpha}$ (**4**, R = H).

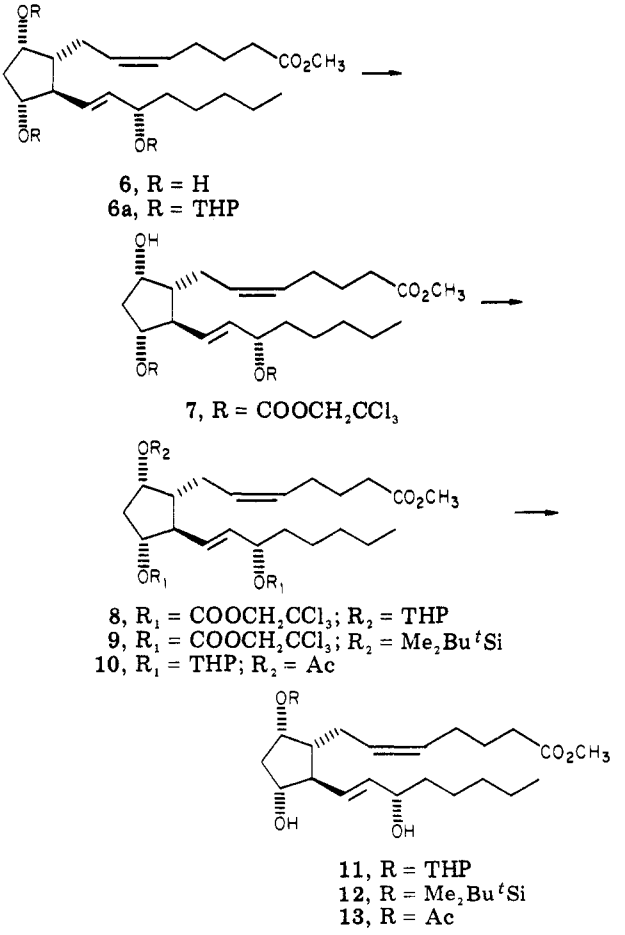
Prostacyclin formation in biological systems is often measured after conversion to its stable hydrolysis product, 6-keto-$PGF_{1\alpha}$ (**5**).[3] Similar to PGI_2, enol ether **4** (R = H) would also be expected to hydrolyze rapidly to **5** in the biosynthetic milieu. Aside from the intriguing possibility that **4** (R = H) may be produced enzymatically, we were interested in the chemical, physical, and biological properties of this substance. For these reasons, we decided to synthesize **4** ($R = CH_3$) and compare its chemical stability and spectral properties to that of PGI_2 methyl ester. Also reported are some preliminary biological activities obtained with the sodium salt of **4**.

Results and Discussion

Synthesis. We anticipated that the synthesis of the title compounds could be accomplished starting with an appropriate C-9 hydroxy protected $PGF_{2\alpha}$ methyl ester derivative by carrying out a similar sequence of reactions used for PGI_2 synthesis,[4] i.e., iodoetherification to form a 6,11α oxygen bridge, removal of the C-9 blocking group, elimination of HI with base, and base hydrolysis.

For this study, the C-9 tetrahydropyranyl (THP), the C-9 dimethyl-*tert*-butylsilyl (Me_2Bu^tSi), and the C-9 acetyl derivatives **11**–**13** were prepared from $PGF_{2\alpha}$ methyl ester (**6**, Scheme II). Reaction of **6** with trichloroethyl chlorocarbonate (2 equiv, −45 °C, 50 min) afforded the 11,15-bis(carbonate) derivative **7** in 80% yield. Silylation of **7** with DMBS chloride and imidazole gave **9**, which was then treated with zinc in MeOH to provide **12** in 77% overall yield. In a similar manner, **11** was obtained in 63% yield from **8** by reaction of **7** with dihydropyran and pyridine hydrochloride, followed by removal of the C-11 and C-15 blocking groups. The 11,15-bis(THP) derivative **6a**, a readily available intermediate in $PGF_{2\alpha}$ synthesis, was employed for the preparation of the C-9 acetyl derivative **13**. Acetylation of **6a** and acid hydrolysis gave **13** in 57% yield. As will become evident later on under Discussion, the key 6,11-cyclic ether intermediate utilized in the synthesis may have possibly been obtained from any one of these three C-9 derivatives. The decision to select **12**[5] for completion of the synthesis was based on the favorable chromatographic and spectral (NMR, MS) properties of Me_2Bu^tSi ether intermediates.

Scheme II

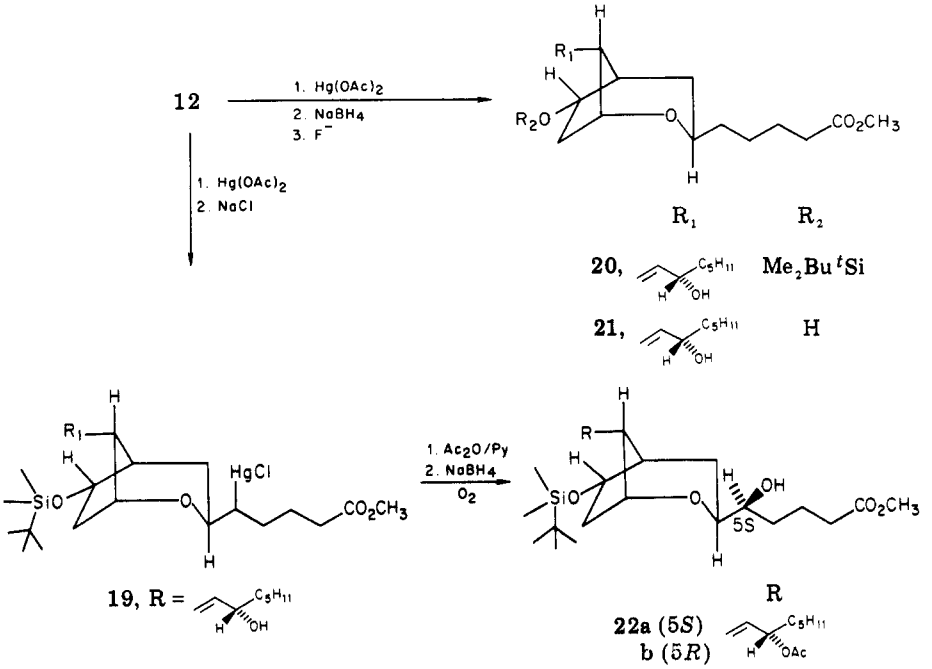


(3) C. Pace-Asciak, *J. Am. Chem. Soc.*, **98**, 2348 (1976).

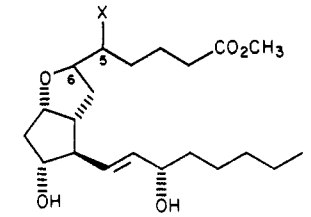
(4) R. A. Johnson, F. H. Lincoln, E. G. Nidy, W. P. Schneider, J. L. Thompson, and U. F. Axen, *J. Am. Chem. Soc.*, **100**, 7690 (1978), and references cited therein.

(5) The regio assignment of the DMBS group to the C-9 position was unequivocally determined by chemical conversion of **12** to PGE_2 (9-deoxy-9-keto-$PGF_{2\alpha}$) methyl ester via (a) pyranylation, (b) removal of DMBS with F^-, (c) Jones oxidation, and (d) acid hydrolysis. No PGD_2 (11-deoxy-11-keto-$PGF_{2\alpha}$) methyl ester was detected.

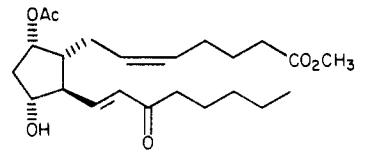
Scheme III



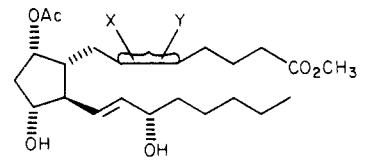
It soon became apparent that the facile iodoetherification reaction observed with $PGF_{2\alpha}$ methyl ester (6) to produce iodo ethers 14[4] was not applicable with 11



14, X = I (5*R*,6*R* and 5*S*,6*S* mixture)
15a, X = H (6*S*)
b, X = H (6*R*)



16



17, X = I; Y = OH
18, X = Cl; Y = PhSe

or 12 for the preparation of the 6,11-oxygen ring system. Treatment of 11 or 12 with iodine gave a complex mixture of products. Acid hydrolysis of these crude mixtures yielded, after chromatography, two iodo ether containing fractions. Reductive removal of iodine from the individual fractions afforded the previously reported (6*R*)- and (6*S*)-PGI_1 compounds,[4] **15a** and **15b**. Since these 6,9-cyclic ether products were derived from **6**, their formation resulted from loss of the C-9 protective groups of **11** and **12** under the iodination conditions.

In light of these problems, we next examined the reactions of the C-9 acetyl derivative **13** with iodine, *N*-bromosuccinimide (NBS), and phenylselenenyl chloride (PhSeCl). Although the acetyl protecting group remained intact during these reactions, we again failed to observe any 6,11 products. Some unexpected side reactions were observed. For example, reaction of **13** with iodine gave predominantly recovered starting material, enone **16** and some iodohydrin **17**. Addition of PhSeCl to **13** yielded the β-chloro phenylselenenyl adduct **18**.[6] During prolonged contact with silica gel, **18** was reconverted to **13**. Exposure of **18** to MeOH–$NaOCH_3$ afforded $PGF_{2\alpha}$ methyl ester (**6**).

The construction of a 6,11α-oxygen ring was at last achieved with a reaction that was earlier employed in the synthesis of 5-hydroxy-PGI_1.[7] This method[8] involved a mercuric acetate promoted cyclization (oxymercuration), followed by transformation of a mercurio chloride substituent with sodium borohydride in the presence of oxygen to a hydroxy group. When **12** was subjected to these reaction conditions, we obtained in good yield a pair of chromatographically separable, diastereomeric alcohols, **22a** and **22b** (Scheme III). The oxymercuration procedure used here was slightly modified by acetylation of **19** prior to oxygenation. This additional step was introduced to differentiate between the C-15 and C-5 hydroxy groups in the subsequent reactions. In the subsequent discussion, evidence will be presented to show that oxymercuration proceeded exclusively via the 6,11 and not the 5,11 pathway.[9]

Assignment of the 6*R* configuration to the carbomethoxy side chain of **22a** and **22b** was based on conversion of **12** to **20** and **21**. Treatment of **12** with mercuric acetate, followed by reductive removal of the mercury substituent with sodium borohydride,[10] gave **20**. Desilylation of **20** with tetra-*n*-butylammonium fluoride[11] afforded **21** (R_f of **21**,

(6) D. Kiotta and G. Zima, *Tetrahedron Lett.*, 4977 (1978).
(7) J. C. Sih, R. A. Johnson, E. G. Nidy, and D. R. Graber, *Prostaglandins*, 15, 409 (1978).
(8) C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, 96, 870 (1974).
(9) Based on the very high degree of strain, a cyclization of **12** to produce 6,15α- and 5,15α-cyclic ethers is highly unlikely. Supportive evidence is found in the mass spectra (Me_3Si derivative) of **12**, **20**, **21**, and other C-15 hydroxy intermediates. They all shared an intense *m/e* 173 peak, $CH(=OSiMe_3)C_5H_{11}$.
(10) G. M. Whitesides and J. San Filippo, *J. Am. Chem. Soc.*, 92, 6611 (1970).

Table I. Reactions of Mesylates 25a and 25b with Base

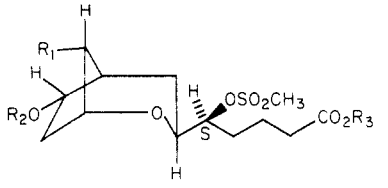
substrate	base (equiv)	solvent	temp, °C (h)	results[a]
(1) 25a (25b)	*t*-BuOK	*t*-BuOH	60 (5)	5-15%[b] of 29a (29b) and 31
(2) 25b	sublimed *t*-BuOK	*t*-BuOH	60 (17)	10% of 29b[c]
(3) 25b	DBN[d] (15)	toluene	reflux (24)	recovered 29b
(4) 25a (25b)	$KOCH_3$ (5)	MeOH	reflux (22)	5-10% of 29a (29b) and recovered 25a (25b)
(5) 25a (25b)	$NaOCH_3$ (4)	MeOH	reflux (4)	recovered 25a (25b)
(6) 25b	$NaOCH_3$ (5)	Me_2SO	25 (5)	1:1 mixture of 29b and 25b by TLC
(7) 25a (25b)	$KOCH_3$ (5)	Me_2SO	25 (5)	40-45% of 29a (29b)

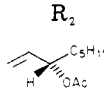
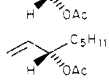
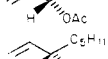
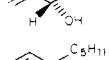
[a] Unless otherwise indicated, yields given are for isolated products. [b] This range in yield represents the results obtained from several different experiments using different lots of commercial *t*-BuOK purchased from MSA Research Corp. [c] Isolated as its *tert*-butyl ester. [d] 1,5-diazabicyclo[4.3.0]non-5-ene.

0.55; R_f of **15a** and **15b**, 0.35 and 0.40, 50% acetone in methylene chloride). In each instance, **20** and **21** were obtained as a single 6,11-cyclic ether.

Examination of Dreiding models reveals that the conformation leading to the 6*R* isomer of **20** (Figure 1) should be favored because of fewer steric interactions during the cyclization. One would also predict the 6*R* isomer as the thermodynamically controlled product of oxymercuration. The bicyclic [3.2.1] system of (6*R*)-**20** can adopt a six-membered chair conformation with the carbomethoxy side chain residing in a preferred equatorial orientation. In contrast, the 6*S* isomer would place the carbomethoxy side chain in a sterically crowded 1,3-diaxial relationship to the $C_{8,9}$ and $C_{10,11}$ alkyl substituents. The 6*S* isomer would require an interconversion of the chair to an energetically less favored boat conformation to accomodate an equatorial carbomethoxy side chain. On this basis, we have assigned the 6*R* configuration to **20** (**21**). Therefore, it is reasonable to conclude that the diastereomeric pair of alcohols, **22a,b**, produced from **19** possessed the same configuration at C-6 and differed only at C-5. The configuration at C-5 was later established with the preparation of enol ether, **29a,b**, by a route of definable stereochemistry.

With the synthesis of **22a,b** in hand, we turned our attention to the introduction of the Δ^5 enol ether double bond. Attempts to transform the hydroxy group of **22a,b** to a halogen (Br, I) met with limited success. At best, we never obtained the desired product in a synthetically useful yield. As an alternative leaving group, we prepared the mesylate derivatives, **23a,b**. The key mesylate intermediates, **25a,b**, were then obtained from **23a,b** after removal of the C-9 and C-15 blocking groups. Base hydrolysis of



	R_2	R_2	R_3
23a (5*S*)		Si	CH_3
b (5*R*)			
24a (5*S*)		H	CH_3
b (5*R*)			
25a (5*S*)		H	CH_3
b (5*R*)			
26a (5*S*)		H	H
b (5*R*)			

(11) E. J. Corey and A. Venkatesuwarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

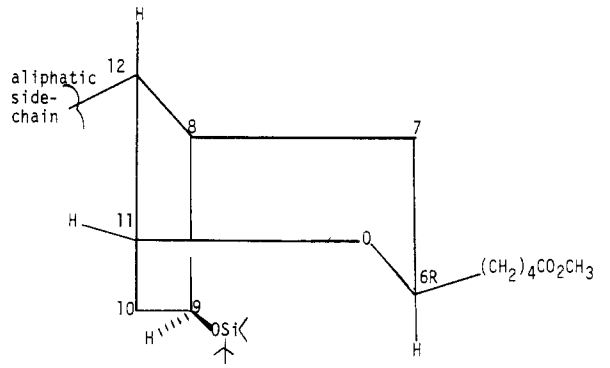
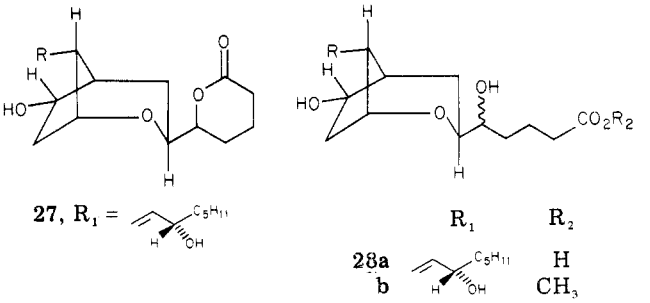


Figure 1. 6*R* isomer of compound **20**.

esters **25a,b** under standard conditions led to the formation of 1,5-lactone **27**. After aqueous workup, one obtained a mixture of **27** and hydroxy acid **28a**. Unknowingly at the

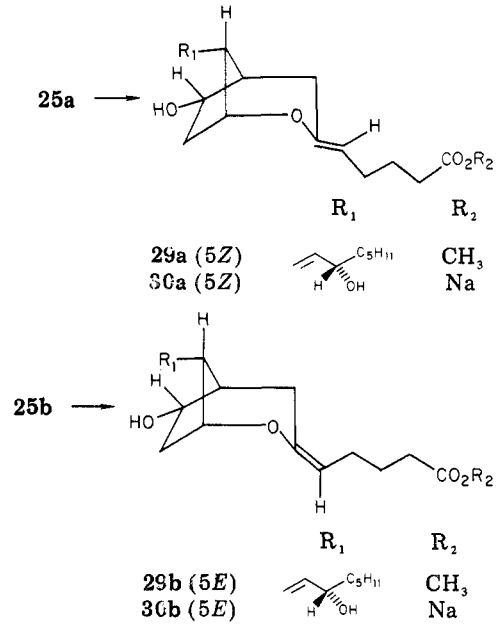


	R_1	R_2
28a		H
b		CH_3

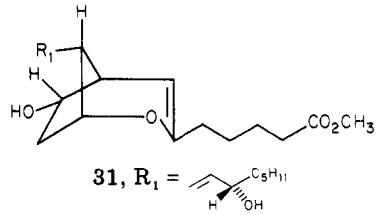
time, these side products, arising from the facile lactonization of acids **26a,b**, would later be of concern in the subsequent reactions of **25a,b**. Acids **26a,b** could be cleanly obtained by carrying out the hydrolysis of **25a,b** with lithium hydroxide in aqueous methanol at 0–5 °C.

The successful conversion of **25a,b** to enol ethers **29a,b** was critically dependent on the base, the reaction solvent, and the workup conditions. Table I partially summarizes some of these results. It is difficult, in retrospect, to evaluate the yield of enol ethers in the early studies. Numerous difficulties were encountered in product isolation. The problem was compounded by hydrolysis of the carbomethoxy group under the reaction conditions. As a result, workup of these reactions required acidification and methylation (CH_2N_2) prior to extraction. Different workup conditions (pH 5.5 phosphate buffer, pH 4.5 HOAc–NaOAc, 0.25–1 N $KHSO_4$) gave varying amounts of 6-keto-$PGF_{1\alpha}$ methyl ester (**32**), the decomposition product of **29a,b**. In all our studies,[12] use of *t*-BuOK in *t*-BuOH

(12) The *t*-BuOK-*t*-BuOH reaction conditions used in our studies are essentially the same as those reported by Corey in the elimination of a mesylate group for the synthesis of the 5*E* isomer of PgI_2: see E. J. Corey, I. Szekely, and C. S. Shiner, *Tetrahydron Lett.*, 3529 (1977).



afforded enol ethers **29a,b** in low and nonreproducible yields (entry 1). In these reactions, ester hydrolysis occurred, most likely, due to the presence of moisture in the reagents. However, even when precautions were taken to ensure anhydrous conditions, there was no improvement in reaction yield (entry 2). Substitution of DMF for the solvent gave ambiguous results.[13] An even more serious problem associated with using *t*-BuOK was the isomerization of **29a,b** under the reaction conditions to the endo cyclic enol ether **31**. The chromatographic properties of **31** were nearly identical with **29a,b** (see Table II), which made product isolation difficult.[14]



We were pleased to discover that the use of $KOCH_3$–Me_2SO substantially improved the isolated yield of **29a,b** (entry 7). More importantly, the formation of **31** was entirely suppressed under these conditions. The reaction also proceeded using $NaOCH_3$ but at a much slower rate (entry 6). As was initially observed with *t*-BuOK, treatment of **25a,b** with $KOCH_3$–Me_2SO again resulted in the hydrolysis of the carbomethoxy group. In the latter case, ester cleavage cannot be explained by the presence of moisture in the reagents. Strict precautions were taken to dry the Me_2SO solvent. Mesylate esters **25a,b** were recovered unchanged with $KOCH_3$–MeOH (entry 4). Therefore, we believe ester hydrolysis occurred in Me_2SO via a *O*-alkyl cleavage mechanism.[15] This reasoning is also consistent with the earlier finding that removal of the C-15 acetyl groups of **24a,b** with $NaOCH_3$–MeOH proceeded without incidence to yield cleanly the mesylate esters **25a,b**.

Table II. Comparison of TLC Mobilities in Ethyl Acetate

compd	R_f	compd	R_f
PGI_2 Me ester (33)	0.33	(5*Z*)-**29a**	0.54[b]
6-keto **32**	0.14[a]	(5*E*)-**29b**	0.50[b]
5-keto-$PGF_{1\alpha}$ Me ester	0.14[a]	5-OH ester **28b**	0.24
internal ketal **34**	0.64	lactone **27**	0.17
enol ester **31**	0.50[b]		

[a] In neutral systems, 6-keto and 5-keto derivatives exhibited the same R_f; in $CHCl_3$–MeOH–HOAc–H_2O (85:15:10:4, v/v), the 6-keto derivative showed R_f 0.29 and the 5-keto derivative showed R_f 0.16. [b] In CH_2Cl_2–acetone (4:1): **29a**, R_f 0.31; **29b**, R_f 0.25; **31**, R_f 0.28.

Besides some 6-keto-$PGF_{1\alpha}$ methyl ester (**32**) that was inevitably formed during the aqueous workup, the two major side products produced in the $KOCH_3$–Me_2SO reaction were lactone **27** and hydroxy acid **28a**. Since mesylates **25a,b** were recovered unchanged with $NaOCH_3$–MeOH and $KOCH_3$–MeOH (entries 4 and 5), **28a** was not formed via a direct displacement of the mesyl group by hydroxide but rather derived from lactone **27** during aqueous workup.

The best workup procedure for the isolation of enol ethers **29a,b** from the reaction mixture involved diluting with ether, cooling to −78 °C, acidifying with 4.9 H potassium hydrogen phthalate buffer, rapid extracting with ice-cold ether–ethyl acetate (3:1), esterifying the extract with CH_2N_2, washing the organic extract with 50% saturated brine solution, and removing the solvent in vacuo. This method consistently gave 60–70% recovery of total crude product. Interestingly enough, when PGI_2 sodium salt was subjected to this isolation procedure, PGI_2 methyl ester was recovered in nearly quantitative yield with minimal formation of 6-keto-$PGF_{1\alpha}$ methyl ester. Maximum recovery of pure enol ethers **29a,b** from chromatography was best achieved with a gravity column packed with a 1:1 Celite–silica gel mixture and elution with ethyl acetate containing 0.1% triethylamine.

Chemical and Physical Properties. Both **29a,b** were cleanly converted to 6-keto-$PGF_{1\alpha}$ methyl ester (**32**) when treated with aqueous acid. It was significant that hydrolysis did not produce any 5-keto-$PGF_{1\alpha}$ methyl ester.[16] This result firmly established that mercuric acetate cyclization occurred to give the 6,11 and not the 5,11 cyclic ether. One noticeable difference between **29a,b** and PGI_2 methyl ester (**33**) was the facile formation of the internal tricyclic ketal **34**.[17] NMR samples of **29a,b**, prepared in $CDCl_3$ containing triethylamine or pyridine and later examined by TLC, showed extensive conversion to **34**.[21] When NMR samples of **33** were prepared in the same manner and examined by TLC, **34** was not detected. This intramolecular ketalization is not unexpected from inspection of molecular models. The interatomic distance between the 9-O and the 6-C in **29a** (**29b**) is 2.8 Å; in PGI_2 methyl ester, the 11-O is 3.9 Å removed from the 6-C. On a TLC scale, treatment of **29a** or **29b** in a solvent, such as ether, with aqueous $KHSO_4$ at 25 °C for 5–10 min gave approximately a 70:30 mixture of **34** and **32**. When this hydrolysis was followed by TLC, complete conversion of **34** to **32** occurred after 1–1.5 h. In contrast, under the same conditions, **33** afforded, after 5–10 min, predominantly **32** and very little **34**.[18] For purposes of comparison, the TLC

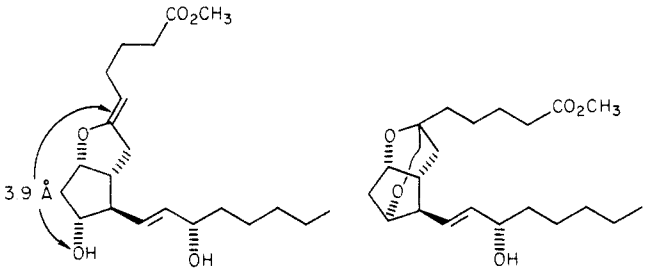
(13) Reaction of *t*-BuOK (5 equiv) with **25b** in DMF (60 °C, 0.5 h) gave predominantly lactone **27**; on another occasion, reaction of acid mesylate **26b** under these conditions yielded a 5-formyl derivative.

(14) Prolonged heating of the reactions led to an increase of **31**. This isomerization appeared more prevalent in the elimination reaction of mesylate **25a**. We were unable to obtain a pure sample of **31** free from **29a** or **29b**. The structural assignment of **31** was based on clean conversion of these mixtures to 6-keto-$PGF_{1\alpha}$ methyl ester.

(15) J. McMurry, *Org. React.* **24**, 187 (1976).

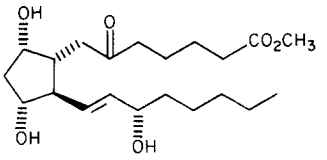
(16) An authentic sample of 5-keto-$PGF_{1\alpha}$ methyl ester was kindly supplied by Dr. R. A. Johnson of The Upjohn Co.

(17) K. Shimoji, Y. Konishi, Y. Arai, M. Hayashi, and H. Yamamoto, *J. Am. Chem. Soc.*, **100**, 2547 (1978).



33

34



32

R_f values of pertinent compounds prepared in this study are listed in Table II.

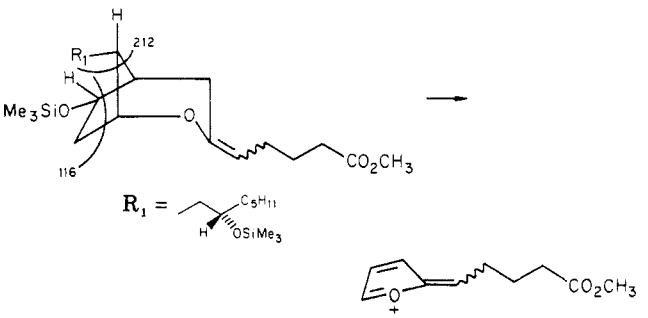
Spectral Properties. The mass spectra of **29a,b** (Me_3Si derivative) were virtually identical but totally different from the spectrum of PGI_2 methyl ester (Me_3Si derivative).[4] The base peak (*m/e* 181, calcd for $C_{10}H_{13}O_3$, 181.0865; found, 181.0874) can be envisioned to arise from the fragmentation shown in Scheme IV. Not surprisingly, the mass spectra of **25a,b** (Me_3Si derivative) all showed *m/e* 181 as their base peak and were nearly identical with that of **29a** (**29b**).

In the ^1H NMR spectra (benzene-d_6), the C-5 vinyl proton of **29a,b** appeared as a multiplet centered at δ 4.50 and 5.05, respectively. The downfield signal was assigned to the proton cis to the vinyl oxygen because of the deshielding effect of the latter atom. Therefore, **29a,b** possessed the 5*Z* and 5*E* configuration, respectively. The observed difference in chemical shifts for the C-5 vinyl protons of **29a,b** ($\Delta\delta$ = 0.55) was in agreement with that reported for (5*E*)- and (5*Z*)-PGI_2 methyl ester (5*Z*, δ 4.16; 5*E*, δ 4.67; $\Delta\delta$ = 0.51).[4] However, the C-5 vinyl proton signals of **29a,b** were unexpectedly shifted further downfield when compared to PGI_2 methyl ester and other examples in the literature.[19,20] One can speculate that this unusual downfield shift in signal is attributable to the additional deshielding influence of the C-9 hydroxy substituent.

Based on the stereochemical assignments of **29a** (5*Z*) and **29b** (5*E*), the C-5 configuration of alcohols **22a,b** was readily assigned. If one assumes that **29a,b** were formed from mesylates **25a,b** via a trans elimination, mesylate **25a** bears the 5*S* configuration and **25b** the 5*R* configuration. It then follows that alcohol **22a** (less polar) must possess the 5*S* configuration and **22b** (more polar) the 5*R* configuration.

Biological Activities. Base hydrolysis of methyl esters **29a,b** (1 equiv of NaOH in MeOH–H_2O, 25 °C) gave their corresponding sodium salts **30a,b**, respectively. When these compounds were tested in vitro for inhibition of ADP-induced human platelet aggregation, both **30a** and **30b** were found inactive (ED_{50} > 1 μg/mL). In the same screen, PGI_2 sodium salt is effective at an ED_{50} of 1–2 ng/mL. In the rat blood-pressure test, **30a** was found inactive while **30b** possessed 0.1–0.32% the depressor activity of PGE_1.

Scheme IV



m/e 181

Experimental Section

General Procedures. Melting points were obtained with a Thomas-Hoover or a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded with either a Perkin-Elmer Model 137 or 139 or a Digilab Model FTS-14D. The ^1H NMR spectra were obtained with a Varian A-60A, XL-100, or HFT-80 spectrometer with tetramethylsilane as the internal standard. The chemical-shift values reported for the dimethyl-*tert*-butylsilyl derivatives were obtained in carbon tetrachloride solution without internal standard. High-resolution mass spectra were obtained on the trimethylsilyl (Me_3Si) derivatives with a CEC 21-110B spectrometer. GC–MS were obtained with a 5992A Hewlett-Packard GC/MS system. LPLP refers to low-pressure liquid chromatography employing either E. Merck prepacked silica gel Lobar columns or Michel–Miller columns (Ace Glass, Inc.) packed with silica gel 60 (40–62 μm, E. Merck). The solvents were driven by a Milton-Roy D. pump. The analysis of the column fractions was performed by TLC (silica gel GF plates, Analtech). All air- and moisture-sensitive reactions were carried out with oven-dried glassware under an inert nitrogen atmosphere.

Prostaglandin $F_{2\alpha}$ Methyl Ester 11,15-Bis(trichloroethyl carbonate) (7). To a magnetically stirred solution of $PGF_{2\alpha}$ methyl ester (6; 10.00 g, 27.20 mmol) and pyridine (43.80 mL) in 100 mL of methylene chloride, cooled to −45 to −35 °C, was added dropwise over a 20-min period a solution of trichloroethyl chlorocarbonate (11.53 g, 54.35 mmol) in 20 mL of methylene chloride. Stirring was continued at −35 to −45 °C for 35 min. At the end of this time, 10 mL of water was added, and the reaction mixture was allowed to warm to −15 °C (ca. 30 min). The solution was diluted with 500 mL of methylene chloride and washed successively with 150 mL of saturated brine, 5% HCl solution (2 × 150 mL), saturated brine (150 mL), and saturated $NaHCO_3$ solution (2 × 150 mL). The aqueous washings were reextracted with 100 mL of methylene chloride, and the combined organic extracts dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo yielded 19.60 g of crude product. This material was chromatographed with 1 kg of siilica gel, packed and eluted with 30% ethyl acetate in Skellysolve B, to give 15.47 g (79% yield) of **7** as a colorless viscous oil: TLC (Skellysolve B–ethyl acetate, 3:1) R_f 0.20; ^1H NMR ($CDCl_3$) δ 5.60 (m, 2 H), 5.40 (m, 2 H), 5.00 (m, 2 H), 4.74 and 4.72 (singlets, 4 H), 4.17 (m, 1 H), 3.66 (s, 3 H), 2.90–1.10 (m, 20 H incl OH), 0.88 (t, 3 H); IR (film) 3450, 2995, 1745 (br s), 1430, 1380, 1250 (br s), 970, 820, 780 cm^{-1}.

9-(Dimethyl-*tert*-butylsilyl)prostaglandin $F_{2\alpha}$ Methyl Ester 11,15-Bis(trichloroethyl carbonate) (9). Imidazole (2.93 g, 43.04 mmol) and dimethyl-*tert*-butylsilyl chloride (6.52 g, 43.04 mmol) was added to a magnetically stirred solution of alcohol **7** (15.47 g, 21.52 mmol) in 105 mL of dimethylformamide. After the contents were kept overnight at ambient temperature, the resulting solution was poured into 1 L of ice–water and extracted thoroughly with ether (2 × 750 mL). The ether extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 17.80 g (98%) of **9** as a colorless oil. This material, homogeneous on TLC, was used without further purification: TLC (Skellysolve B–ethyl acetate, 6:1) R_f 0.44.

(18) The synthesis of ketal **34** from PGI_2 methyl ester was accomplished by the authors in ref 17 under anhydrous acid conditions.
(19) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963).
(20) S. J. Rhodes, J. K. Chattopadhyay, and E. E. Waali, *J. Org. Chem.*, **35**, 3352 (1970).

Prostaglandin $F_{2\alpha}$ Methyl Ester 9-(Tetrahydropyranyl ether) (11). Alcohol 7 (15.89 g, 22.10 mmol) was placed in 160 mL of methylene chloride containing 7.00 mL of dihydropyran and 0.465 g of pyridinium hydrochloride and kept at room temperature for 24 h. At the end of this period, the reaction solution was diluted with 250 mL of methylene chloride and successively washed with 5% $NaHCO_3$ solution, water, and saturated brine. The methylene chloride solution was dried through anhydrous Na_2SO_4. Evaporating the solvent in vacuo and drying under high vacuum yielded 17.57 g (99% yield) of **8** as an oil: TLC (Skellysolve B–ethyl acetate, 3:1) R_f 0.51; ^1H NMR ($CDCl_3$) δ 5.80–4.40 (m, 4 H), 4.75 (s, 4 H), 4.30–3.30 (m, 3 H), 3.67 (s, 3 H), 2.90–1.10 (m, 26 H), 0.90 (t, 3 H). The crude product was placed in a 1-L three-neck flask, fitted with a condenser and a thermometer and charged with 600 mL of methanol and 90 g of zinc dust. The contents were stirred for 2.5 h at 65 °C. At the end of this period, the reaction mixture was cooled to room temperature and filtered with suction through a pad of celite, and the filtrate was concentrated in vacuo. The residual oil was placed in 450 mL of EtOAc, washed with 5% $NaHCO_3$ solution and saturated brine, and the EtOAc was dried through anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 11.12 g of crude product. Column chromatography of this material was accomplished with 450 g of silica gel packed in ethyl acetate–Skellysolve B (3:1). Taking 40-mL fractions and eluting with EtOAc yielded 6.23 g (F-48-125, 63% yield) of **11** as a semisolid: TLC (ethyl acetate–Skellysolve B, 5:1) R_f 0.28 for **11**, 0.20 for $PGF_{2\alpha}$ methyl ester; ^1H NMR ($CDCl_3$) δ 5.45 (m, 4 H), 4.60 (m, 1 H), 4.30–3.25 (m, 5 H), 3.67 (s, 3 H), 3.50 (s, OH's), 2.60–1.10 (m, 26 H), 0.90 (t, 3 H); IR (film) 3300, 2990, 1763, 1318, 1010, 980 cm^{-1}.

Prostaglandin $F_{2\alpha}$ Methyl Ester 9-(Dimethyl-*tert*-butylsilyl ether) (12). A suspension of 90 g of zinc dust and 17.80 g of 11,15-bis(carbonate) **9** (21.37 mmol) in 600 mL of methanol was magnetically stirred under nitrogen at reflux temperature for 2 h. At the end of this time, the reaction flask was cooled in an ice–water bath, the excess zinc was removed by filtration through Celite, and the filtrate concentrated in vacuo. The residual oil was dissolved in 400 mL of ethyl acetate and washed with 250 mL of saturated $NaHCO_3$, and 250 mL of saturated brine. The aqueous washings were reextracted with 400 mL of ethyl acetate, washed with saturated brine, and combined with the initial ethyl acetate solution. After the ethyl acetate solution was dried over anhydrous Na_2SO_4, concentration of the solvent in vacuo afforded 10.48 g of crude product. Chromatography of the above material with 600 g of silica gel, packed and eluted with 30% Skellysolve B in ethyl acetate, yielded 7.94 g (77%) of **12** as a colorless viscous oil: TLC (ethyl acetate–Skellysolve B, 2:1) R_f 0.30; ^1H NMR (CCl_4) δ 5.40 (m, 4 H), 4.32–3.65 (m, 3 H), 3.65 (s, 3 H), 3.48 (br s, OH's), 2.50–1.10 (m, 20 H), 0.90 (s, 12 H), 0.08 and 0.06 (singlets, 6 H); mass spectrum (Me_3Si derivative), *m/e* 626 (M^+); calcd for $C_{33}H_{66}Si_3O_5$, 626.4218; found, 626.4292. Anal. Calcd for $C_{27}H_{50}O_5Si$: C, 67.18; H, 10.44. Found C, 66.95; H, 10.66.

9-Acetylprostaglandin $F_{2\alpha}$ Methyl Ester (13). Seven grams (13.06 mmol) of $PGF_{2\alpha}$ methyl ester 11,15-bis(THP ether) (**6a**) was dissolved in 45 mL of pyridine, 6.0 mL of acetic anhydride, and 50 mg of 4-(dimethylamino)pyridine. Stirring was continued at room temperature for 2.4 h. The contents were diluted with 10 mL of water and stirred for 15 min. The solution was poured into 135 mL of water and extracted with ether, and the ether was washed with ice water and saturated brine and dried through anhydrous Na_2SO_4. Removing the solvent in vacuo and drying under high vacuum yielded 7.58 g of **10** as a golden oil: ^1H NMR ($CDCl_3$) δ 5.45 (m, 4 H), 5.10 (m, 1 H), 4.70 (m, 2 H), 4.20–3.30 (m, 6 H), 3.67 (s, 3 H), 2.05 (s, 3 H), 2.80–1.10 (m, 32 H), 0.90 (t, 3 H). This material was dissolved in 6 mL of tetrahydrofuran and 60 mL of acetic acid–water (2:1) and kept overnight at room temperature. The reaction was diluted with 500 mL of ethyl acetate and poured into 250 mL of brine solution (prepared from 400 mL of saturated brine and 100 mL of ice–water). The organic layer was separated and washed with water and with saturated brine. The organic layer was carefully treated with 150 mL of saturated $NaHCO_3$ solution and solid $NaHCO_3$ to neutralize all the acetic acid. The ethyl acetate solution was separated, dried over Na_2SO_4, and concentrated in vacuo. The crude product was chromatographed with 200 g of silica gel. Elution with ethyl acetate yielded 2.93 g (57% yield) of **13** as a colorless oil: TLC (ethyl acetate) R_f 0.36; ^1H NMR ($CDCl_3$) δ 5.40 (m, 4 H), 5.10 (m, 1 H), 4.25–3.45 (m, 4 H incl OH's), 3.67 (s, 3 H), 2.10 (s, 3 H), 2.70–1.10 (m, 23 H), 0.90 (t, 3 H).

Reactions of 11–13 with Iodine. To a vigorously, magnetically stirred solution of **11** (0.904 g , 2.00 mmol) in 30 mL of methylene chloride was added 40 mL of saturated $NaHCO_3$ solution. To this heterogeneous solution, cooled in a 0–5 °C bath, was added a solution of iodine (0.559 g, 2.20 mmol) in 50 mL of methylene chloride over a 20–min period. Stirring was then continued at 25 °C for 2 h, the organic layer was separated, diluted with 150 mL of methylene chloride, washed with 10% sodium thiosulfate solution and saturated brine, and the methylene chloride solution was dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 1.11 g of an oil. This material was directly treated with 17 mL of acetic acid–water–tetrahydrofuran (20:10:3) for 3 h at 40–45 °C, and the solvents were removed in vacuo. TLC analysis of the resulting oil indicated a complex mixture (6–7 components). This material was chromatographed by LPLC (20% acetone in methylene chloride) to give 70 mg of $PGF_{2\alpha}$ methyl ester (**6**) and two less-polar fractions (87 mg, R_f 0.20 and 97 mg, R_f 0.15 in methylene chloride–acetone, 3:1). The TLC polarities of these two fractions were nearly identical when compared to an authentic sample of **14**.[21] The individual fractions were then treated with tri-*n*-butyltin hydride[22] (2 equiv) in 2–3 mL of methanol for 2 h at 25 °C. In each case, the reaction mixture was diluted with ether, the ether was washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo, and the resulting crude product was chromatographed by LPLC (20% acetone in methylene chloride). From the less polar fraction, we obtained 34 mg of (6*R*)-PGI_1 methyl ester **15b**, mp 70–72 °C (lit.[4] mp 71–73 °C); the more polar fraction yielded 21 mg of **11** and 30 mg of **15a**.[23] The ^1H NMR and TLC properties of **15a** and **15b** were identical with those of authentic samples of (6*R*)- and (6*S*)-PGI_1 methyl esters.[21]

To a magnetically stirred suspension of **12** (0.500 g, 1.04 mmol) in 7 mL of water, cooled in a 0–5 °C bath, were added Na_2CO_3 (0.129 g, 1.04 mmol), KI (0.345 g, 2.08 mmol), and iodine (0.528 g, 2.08 mmol). The contents were stirred at 0–5 °C for 30 min and then at 25 °C for an additional 1.5 h. The reaction was diluted with methylene chloride and worked up as previously described. Removal of the solvent in vacuo gave 0.600 g of a viscous golden oil. TLC analyses of the crude product showed 10–20% of unreacted **12** and 60–70% of two closely separated spots (R_f 0.15 and 0.20 in methylene chloride–acetone, 3:1), which were identical in TLC mobility with an authentic sample of **14**.[20]

Following the same iodination conditions and workup described for **11**, reaction of **13** (0.508 g, 1.24 mmol) with iodine (0.346 g, 1.36 mmol) gave, after LPLC (50% Skellysolve B in ethyl acetate), 0.217 g of recovered **13**, 69 mg of ketone **16**, and 52 mg of iodohydrin **17**: TLC (ethyl acetate) R_f 0.52 for **16**, 0.15 for **17**; ^1H NMR ($CDCl_3$) for **16** δ 7.02–6.02 (m, 2 H), 5.90–4.99 (m, 3 H), 4.37–3.62 (m, 2 H), 3.65 (s, 3 H), 3.06–1.08 (m, 20 H), 2.05 (s, 3 H), 0.88 (t, 3 H); for **17** δ 5.68–5.43 (m, 2 H), 5.35–5.03 (m, 24 H), 2.04 (s, 3 H), 0.88 (t, 3 H); IR (film) for **16** 3450 (br s), 2930, 2850, 1730, 1670, 1370, 1240, 980 cm^{-1}; for **17** 3400 (br s), 2930, 1730, 1380, 1250, 1080, 975 cm^{-1}; for **17**, mass spectrum (Me_3Si derivative), *m/e* calcd for $C_{27}H_{52}Si_3O_7I$ ($M^+ - C_5H_{11}$), 699.2067; found, 699.2094.

Reaction of 13 with Phenylselenenyl Chloride. To a magnetically stirred solution of **13** (0.500 g, 1.22 mmol) in 20 mL of methylene chloride at −78 °C was added phenylselenenyl chloride (0.257 g, 1.34 mmol) in 8 mL of methylene chloride dropwise over a 5-min period. After 30 min at −78 °C, the reaction mixture was poured into 75 mL of a saturated brine–ice mixture and extracted with ether. The organic extract was washed with saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography of the crude product with 40 g of silica gel packed and eluted with ethyl acetate furnished 0.490 g of **18**: TLC (ethyl acetate) R_f 0.29 for **18**, 0.25 for **13**; ^1H NMR ($CDCl_3$) δ 7.75–7.42

(21) Authentic samples of **14**, **15a,b**, **32**, and **34** were kindly supplied by F. H. Lincoln of The Upjohn Co.

(22) H. G. Kuivila, *Acc. Chem. Res.*, 1, 299 (1968).

(23) In this experiment, we obtained **15a** and **15b** in a 1:1 ratio; iodination of $PGF_{2\alpha}$ methyl ester, followed by treatment with tri-*n*-butyltin hydride, gives (6*S*)-**15a** and (6*R*)-**15b** in a ratio of >10:1 (see ref 4).

(m, 2 H), 7.42–7.13 (m, 3 H), 5.78–5.30 (m, 2 H), 5.30–4.92 (m, 1 H), 4.50–3.00 (m, 6 H), 3.66 (s, 3 H), 2.87–1.08 (m, 20 H), 2.03 (s, 3 H), 0.88 (t, 3 H); IR (film) 3400 (br s), 2930 (s), 1740, 1480, 1250, 975, 750 cm^{-1}. When the chromatography of the crude product was carried out over an extended time period, the product eluted from the column was acetate **13**. When a small sample of pure **18** (128 mg) in 3 mL of anhydrous methanol was treated for 15 h at 25 °C with excess $NaOCH_3$ (25 mg), we obtained, after workup, 100 mg of $PGF_{2\alpha}$ methyl ester (**6**).

(6*R*)-11-Deoxy-6,11α-epoxy-9-(dimethyl-*tert*-butylsilyl)-prostaglandin $F_{1\alpha}$ Methyl Ester (20). Silyl methyl ester **12** (0.530 g, 1.10 mmol) in 2.5 mL of tetrahydrofuran was added at room temperature to a magnetically stirred yellow suspension of mercuric acetate (0.523 g, 1.65 mmol) in 2.0 mL of tetrahydrofuran and 2.0 mL of water. After the addition, stirring as continued at ambient temperature for 22 h. At the end of this time, the contents were poured into a solution of 0.228 g of sodium borohydride in 6.50 mL of 1 N KOH and stirred occasionally for 10 min. The reaction mixture was diluted with 20 mL of saturated brine and extracted with ether, and the ether layer was dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave an oil. The crude product was chromatographed with 100 g of silica gel, packed, and eluted with (30% ethyl acetate in Skellysolve B) to afford 0.280 g (53%) of **20** as a colorless oil: TLC (Skellysolve B–ethyl acetate, 2:1) R_f 0.24; ^1H NMR ($CDCl_3$) δ 5.47 (m, 2 H), 4.50 (m, 1 H), 4.10 (m, 3 H), 3.66 (s, 3 H), 2.60–1.10 (m, 23 H incl OH), 0.90 (t, 12 H), 0.04 (s, 6 H); mass spectrum (Me_3Si derivative), *m/e* calcd for $C_{26}H_{49}Si_2O_5$ ($M^+ - C_4H_9$), 497.3118; found, 497.3108. TLC analyses in several different solvent systems indicated **20** as a single entity.

(6*R*)-11-Deoxy-6,11α-epoxyprostaglandin $F_{1\alpha}$ Methyl Ester (21). Tetra-*n*-butylammonium fluoride (1.2 M in THF, 0.65 mL, 0.75 mmol) was added to a magnetically stirred solution of 0.280 g (0.58 mmol) of **20** in 2.5 mL of THF. Stirring was continued at 25 °C for 24 h. At the end of this time, the reaction mixture was diluted with 100 mL of ethyl acetate, and the ethyl acetate solution was washed with 20 mL of ice–water and 15 mL of saturated brine. The aqueous washings, saturated with solid NaCl, were back-extracted with 50 mL of ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield a brown viscous oil. The crude product was chromatographed with 100 g of silica gel, packed, and eluted with 30% Skellysolve B in ethyl acetate to yield 0.172 g (80% yield) of **21** as a colorless viscous oil: TLC (methylene chloride–acetone, 1:1) R_f 0.55 for **21**, 0.40 for **15a**, 0.35 for **15b**; ^1H NMR ($CDCl_3$) δ 5.48 (m, 2 H), 4.50 (m, 1 H), 4.08 (m, 3 H), 3.67 (s, 3 H), 2.85 (br s, OH's), 2.60–1.10 (m, 20 H), 0.88 (t, 3 H); IR (film) 3350, 2990, 1710, 1420, 975 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* 512 (M^+), calcd for $C_{27}H_{52}O_5Si_2$, 512.3353; found, 512.3382. TLC analyses in several different solvent systems indicated **21** as a single entity.

(5*R*,6*R*)-11-Deoxy-6,11α-epoxy-9-(dimethyl-*tert*-butylsilyl)-5-(mercuriochloro)prostaglandin $F_{1\alpha}$ Methyl Ester (19). To a magnetically stirred yellow suspension of mercuric acetate (34.30 g, 107.5 mmol) in 130 mL of water and 130 mL of THF was added **12** (23.60 g, 48.9 mmol) in 130 mL of THF over a 5-min period. Stirring was continued at 25 °C for 18 h. The THF was then removed in vacuo, the residual oil was diluted with 350 mL of ice–water, and the aqueous solution was extracted with ether (4 × 400 mL). The combined ether extracts were washed with ice–water (2 × 200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting oil was dissolved in 500 mL of methanol and 300 mL of saturated brine and stirred for 4 h at 25 °C. The methanol was removed in vacuo, the residue was diluted with 250 mL of saturated brine, and the brine solution was thoroughly extracted with ether. The ether solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed with 1 kg of silica gel, packed and eluted with 20% ethyl acetate in Skellysolve B, to afford 20.00 g (57% yield) of **19** as a viscous colorless oil: TLC (Skellysolve B–ethyl acetate, 3:1) R_f 0.25; ^1H NMR (CCl_4) δ 5.50–5.23 (m, 2 H), 4.65–3.67 (m, 5 H), 3.56 (s, 3 H), 2.83–1.02 (m, 21 H), 0.84 (s, 12 H), 0.00 (s, 6 H); IR (film) 3430 (br m), 2940, 2920, 1730, 1460, 1250, 1160, 1100, 965, 880, 830 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* calcd for $C_{26}H_{48}Si_2O_5{}^{200}Hg^{35}Cl$ ($M^+ - C_4H_9$), 731.2411; found, 731.2380.

(5*S*,6*R*)- and (5*R*,6*R*)-15-Acetyl-11-deoxy-6,11α-epoxy-9-(dimethyl-*tert*-butylsilyl)-5-hydroxyprostaglandin $F_{1\alpha}$ Methyl Esters (22a and 22b). Alcohol **19** (20.0 g, 27.91 mmol) was treated with 120 mL of pyridine, 17 mL of acetic anhydride, and a catalytic amount of 4-(dimethylamino)pyridine (200 mg) and allowed to stand at 25 °C for 24 h. At the end of this period, 30 g of ice was added, and the contents were stirred for 20 min. The reaction mixture was poured into 600 mL of ice–water and thoroughly extracted with ether. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was obtained in quantitative yield and used without further purification. TLC (ethyl acetate–Skellysolve , 1:3) R_f 0.58; ^1H NMR (CCl_4) δ 5.47–5.16 (m, 2 H), 5.16–3.86 (m, 5 H), 3.55 (s, 3 H), 2.72–1.02 (m, 20 H), 1.88 (s, 3 H), 1.02 (s, 12 H), 0.02 (s, 6 H); mass spectrum (Me_3Si derivative), *m/e* calcd for $C_{25}H_{42}SiO_6{}^{200}Hg^{35}Cl$ ($M^+ - C_4H_9$), 701.2122; found, 701.2098.

Oxygen was vigorously bubbled into a magnetically stirred solution of $NaBH_4$ (1.48 g, 39.10 mmol) in 120 mL of DMF for 10 min. The oxygen was supplied to the bottom of the reaction fllask through a 18-gauge syringe needle. Compound **19** (21.20 g, 27.90 mmol) was dissolved in 200 mL of DMF. This solution was also saturated with oxygen and then added dropwise via an addition funnel over a 1-h period to the $NaBH_4$ solution. After complete addition, the solution was stirred and a vigorous flow of oxygen was maintained for 40 min. The contents were diluted with 1.5 L of ether and filtered with suction through Celite. The filtrate was washed with 5% $KHSO_4$ solution, ice–water, and saturated brine, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave a viscous oil, which was chromatographed with 600 g of silica gel (ethyl acetate–Skellysolve B, 1:1) to afford 12.67 g (84% yield) of **22a** and **22b** as a mixture. This mixture was separated batchwise (ca. 2 g/run) by LPLC (ethyl acetate–Skellysolve B, 1:5, using three Merck B Lobar columns connected in series) to afford 5.15 g of (5*S*)-**22a** and 5.58 g of (5*R*)-**22b**, both as viscous colorless oils: TLC (ethyl acetate–Skellysolve B, 1:3) R_f 0.15 for **22a**, 0.13 for **22b**; ^1H NMR (CCl_4), the spectra of **22a,b** were nearly identical, δ 5.54–5.18 (m, 2 H), 5.18–4.67 (m, 1 H), 4.65–3.48 (m, 21 H), 3.53 (s, 3 H), 3.40–2.97 (m, 1 H), 2.64–1.03 (m, 21 H), 1.88 (s, 3 H), 0.85 (s, 12 H), 0.01 (s, 6 H); IR (film) 3500, 2930, 2850, 1730, 1460, 1430, 1370, 1240, 1190, 1110, 880, 770 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* calcd for $C_{28}H_{51}Si_2O_7$ ($M^+ - C_4H_9$), 555.3173; found, 555.3200 (**22a**), 555.3189 (**22b**).

Conversion of Alcohols 22a,b to Their Mesylate Methyl Esters 25a,b. To a magnetically stirred solution of **22a** in 130 mL of methylene chloride, cooled in a 0–5 °C bath, was added triethylamine (1.14 g, 11.26 mmol) and methanesulfonyl chloride (1.11 g, 9.65 mmol). The cooling bath was removed, and stirring was continued at 25 °C for 30 min. The reaction was then diluted with ether, the ether solution was washed with ice–water and saturated brine, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded mesylate **23a** in quantitative yield. In the same manner, **22b** was converted to **23b**. Both **23a** and **23b** were obtained as colorless viscous oils and used without further purification: TLC (Skellysolve B–ethyl acetate, 3:1) R_f 0.29 for **23a**, 0.26 for **23b**; ^1H NMR (CCl_4) the spectra of **23a,b** were nearly identical δ 5.42–5.16 (m, 2 H), 4.65 (m, 1 H), 4.55–3.71 (m, 3 H), 3.53 (s, 3 H), 2.85 (s, 3 H), 2.55–1.00 (s, 6 H); IR (film) spectra of **23a** and **23b** were identical, 2930, 2850, 1730, 1350, 1240, 1170, 875, 770 cm^{-1}.

Tetra-*n*-butylammonium fluoride (0.75 M in THF, 13.90 mL, 10.44 mmol) was added to a magnetically stirred solution of **23a** (4.96 g, 8.03 mmol) in 70 mL of THF cooled in a 0–5 °C bath. After addition, stirring was continued at ambient temperature for 24 h. The contents were diluted with 600 mL of ether and washed with saturated brine (4 × 100 mL), and the ether dried over anhydrous Na_2SO_4. Removal of the ether in vacuo gave alcohol **24a** in quantitative yield. In the same manner, **23b** was converted to **24b**. Both **24a** and **24b** were obtained as viscous brown-colored oils, homogeneous by TLC, and used without purification: TLC (ethyl acetate–Skellysolve B, 1:1) R_f 0.20 for **24a**, 0.17 for **24b**; ^1H NMR ($CDCl_3$), the spectra of **24a** and **24b** were nearly identical, δ 5.58–5.30 (m, 2 H), 5.30–4.90 (m, 1 H), 4.90–3.87 (m, 4 H), 3.63 (s, 3 H), 3.05 (s, 3 H), 2.97–1.05 (m, 21 H), 2.00 (s, 3 H), 0.88 (t, 3 H); IR (film) the spectra of **24a** and **24b** were identical, 3510, 2930, 1730, 1350, 1240, 1170, 970 cm^{-1}.

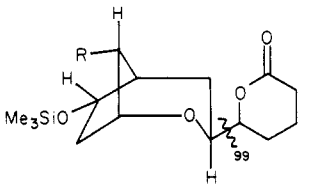
To a magnetically stirred solution of **24a** (4.04 g, 8.03 mmol) in 100 mL of anhydrous MeOH, cooled in 0–5 °C bath, was added $NaOCH_3$ (0.434 g, 8.03 mmol). After addition, the reaction was stirred at 25 °C for 5 h. The contents were then poured into 240 mL of 2 N $KHSO_4$ and 200 mL of ice–water, and the aqueous solution was extracted with ether (4 × 400 mL). The combined ether extracts were washed with saturated brine and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 4.30 g of an oil. The crude product was chromatographed by LPLC with 25% Skellysolve B in ethyl acetate to afford 2.73 g of **25a** as a viscous colorless oil (74% overall yield from **22a**). In the same manner, **24b** was converted to **25b**: mp 80–82 °C (71% overall yield from **22b**); TLC (ethyl acetate) R_f 0.42 for **25a**, 0.37 for **25b**; ^1H NMR ($CDCl_3$) for **25a**, δ 5.58–5.30 (m, 2 H), 4.80–3.77 (m, 5 H), 3.65 (s, 3 H), 3.07 (s, 3 H), 2.78 (br s, 2 H, OH), 2.67–1.06 (m, 20 H), 0.88 (t, 3 H, J = 4.5 Hz); for **25b**, δ 5.58–5.28 (m, 2 H), 4.92–3.77 (m, 5 H), 3.65 (s, 3 H), 3.09 (s, 3 H), 2.90 (br s, 2 H OH), 2.65–1.06 (m, 20 H), 0.88 (t, 3 H, J = 4.5 Hz); mass spectrum (Me_3Si derivative), m/e for **25a**, 606 (weak M^+); calcd for $C_{23}H_{43}Si_2SO_8$ ($M^+ - C_5H_{11}$), 510.3197; found, 510.3168. Anal. Calcd for $C_{22}H_{38}O_8S$ (**25b**): C, 57.13; H, 8.28. Found, C, 57.21, H, 8.28.

Preparation of Mesylate Acids 26a,b. To a magnetically stirred solution of **25a** (0.269 g, 0.582 mmol) in 20 mL of methanol, cooled in a 0–5 °C bath, was added 12.93 mL of 0.45 N LiOH (10 equiv). The contents were then kept at 0–5 °C for 20 h. At the end of this period, crushed ice (10 g) and water (10 mL) were added, and the reaction mixture was acidified with 3.5 mL of 2 N $KHSO_4$ solution. The contents were rapidly extracted with ether, and the ether extract was dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 0.257 g of **26a** as a viscous colorless oil and was homogeneous by TLC analyses. Compound **25b** was converted in the same manner to **26b**: TLC (ethyl acetate–acetic acid, 98:2) R_f 0.42 for **26a**, 0.39 for **26b**. These acids were not further characterized due to their propensity to form lactone **27** in solution. Their integrity could be maintained by storage in benzene solution at −20 °C.

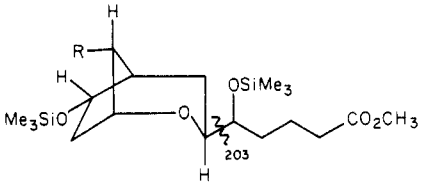
(5*Z*)- and (5*E*)-11-Deoxy-6,11α-epoxy-Δ⁵-prostaglandin $F_{1\alpha}$ Methyl Esters (29a,b). To a magnetically stirred suspension of $KOCH_3$ (0.378 g, 5.47 mmol) in 12 mL of Me_2SO (distilled from CaH and stored over 4A molecular sieves) was added a solution of **25a** (0.530 g, 1.15 mmol) in 5 mL of Me_2SO. Stirring was continued for 2 h at 25 °C. At the end of this period, the contents were transferred to a 500-mL round-bottom flask, cooled to −70 °C in an acetone–dry ice bath, and treated with 100 mL of pH 4.9 potassium hydrogen phthalate buffer (prepared from 50 mL of 0.10 M potassium hydrogen phthalate and 17.7 mL of 0.10 M sodium hydroxide). The aqueous solution was then extracted with 3:1 ether–ethyl acetate (4 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate treated with excess ethereal CH_2N_2 until the yellow color persisted. After the addition off triethylamine (ca. 0.500 g), the excess CH_2N_2 was removed by bubbling a vigorous stream of N_2 directly into the yellow solution. It was expedient to advance the work up to this stage without delay. The solution was then washed with saturated brine (3 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 0.328 g of a yellow oil. The crude product was chromatographed with a gravity column (20 mm i.d.) with 110 mL of silica gel and 110 mL of Celite, wet packed, and eluted with 0.5% triethylamine in ethyl acetate, to yield 0.192 g (46% yield) of **29a** as a viscous colorless oil. The more polar mesylate **25b** was converted to **29b**, a colorless viscous oil, in 42% yield in the same manner: TLC (EtOAc) R_f 0.54 for **29a**, 0.50 for **29b**; ^1H NMR (benzene-d_6) for **29a**, δ 5.50–5.25 (m, 2 H), 4.70–4.16 (m, 3 H), 4.16–3.60 (m, 1 H), 3.50 (s, 3 H), 2.85–1.11 (m, 22 H), 0.92 (t, 3 H); for **29b**, δ 5.52–5.32 (m, 2 H), 5.28–4.82 (m, 1 H), 4.72–4.15 (m, 2 H), 4.13–3.67 (m, 1 H), 3.45 (s, 3 H), 3.18–1.12 (m, 22 H), 0.93 (t, 3 H); IR (film) for **29a**, 3430 (br s), 2930, 2850, 1735, 1440, 970 cm^{-1}; for **29b**, 3430 (br s), 2940, 1735, 1445, 970 cm^{-1}; mass spectrum (Me_3Si derivative), m/e 510 (M^+); calcd for $C_{27}H_{50}Si_2O_5$, 510.3197; found, 510.3188 (**29a**), 510.3198 (**29b**).

Treatment of **29a** or **29b** (2–3 mg samples) in 1 mL of ether with 0.10–0.20 mL of 2 N $KHSO_4$ solution (25 °C, 1–2 h) gave by TLC examination 6-keto-$PGF_{1\alpha}$ methyl ester (**32**)[21] as the only product. When these enol ether hydrolysis reactions were followed by TLC, one observed early on (ca. 5–10 min) a 70:30 mixture of **34**[21] and **32** (See Table II in text for comparison of TLC R_f mobilities).

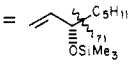
The identification of lactone **27** and hydroxy acid **28a** were



27



28a

R = 

determined by GC–MS analysis (1%, V-215, T = 90–250 °C at 5 °C/min). The mass spectrum (Me_3Si derivative) of **27** showed ions at m/e 496 (M^+), 425 ($M^+ - 71$), 397 ($M^+ - 99$) and 335 [$M^+ - (Me_3SiOH + 71)$]; the mass spectrum (Me_3Si ether methyl ester derivative) of **28a** showed ions at m/e 600 (M^+), 585 ($M^+ - CH_3O$, 529 ($M^+ - 71$), 510 ($M^+ - Me_3SiOH$), and 203 (base peak).

(5*Z*)- and (5*E*)-11-Deoxy-6,11α-epoxy-Δ⁵-prostaglandin $F_{1\alpha}$ Sodium Salts (30a,b). Methyl ester **29a** (0.135 g, 0.368 mmol) was dissolved in 3 mL of methanol. Aqueous 0.10 N sodium hydroxide (3.86 mL, 0.368 mmol) was added to the solution. The cloudy solution was magnetically stirred for 48 h at 25 °C. The methanol was then removed in vacuo, 10 mL of water was added, and the aqueous solution was lyophilized. After triturating with ether (3 × 4 mL) and drying under high vacuum, the Na salt **30a** (113 mg) was obtained as a free flowing white hygroscopic salt. Following the same procedure, **29b** (76 mg) afforded 64 mg of **30b**. The purity of **30a,b** was examined by conversion to their *p*-phenylphenacyl ester derivatives.[4] TLC analyses (25% Skellysolve B in ethyl acetate) of the *p*-phenylphenacyl esters propared from **30a,b** indicated essentially a single spot in 95% purity (R_f 0.57 from **30a** and R_f 0.50 from **30b**).

Registry No. **6**, 33854-16-9; **6a**, 55955-05-0; **7**, 83416-25-5; **8**, 83416-26-6; **9**, 83416-21-1; **10**, 63521-06-2; **11**, 83398-68-9; **12**, 83398-69-0; **12** (bis(trimethylsilyl) ether, 83416-27-7; **13**, 55022-57-6; (5*R*,6*R*)-**14**, 63557-50-6; (5*S*,6*S*)-**14**, 63557-51-7; **15a**, 63557-52-8; **15b**, 65866-08-2; **16**, 80800-65-3; **17**, 83399-05-7; tris(trimethylsilyl) ether, 83399-06-8; **18**, 83399-07-9; **19**, 83398-70-3; **19** acetate, 83398-71-4; **19** trimethylsilyl ether, 83398-72-5; **20**, 83398-73-6; **20** trimethylsilyl ether, 83398-74-7; **21**, 83398-75-8; **21** bis(trimethylsilyl) ether, 83398-76-9; **22a**, 83398-77-0; **22a** trimethylsilyl ether, 83398-78-1; **22b**, 83398-79-2; **22b** trimethylsilyl ether, 83398-80-5; **23a**, 83398-81-6; **23b**, 83398-82-7; **24a**, 83398-83-8; **24b**, 83398-84-9; **25a**, 83398-85-0; **25a** bis(trimethylsilyl) ether, 83398-86-1; **25b**, 83398-87-2; **25b** bis(trimethylsilyl) ether, 83398-88-3; **26a**, 83398-89-4; **26b**, 83398-90-7; **27**, 83398-91-8; **27** bis(trimethylsilyl) ether, 83398-92-9; **28a**, 83398-93-0; **28a** Methyl ester tris(trimethylsilyl) ether, 83398-94-1; **28b**, 83398-95-2; **29a**, 83398-96-3; **29a** bis(trimethylsilyl) ether, 83398-97-4; **29b**, 83398-98-5; **29b** bis(trimethylsilyl) ether, 83398-99-6; **30a**, 83399-00-2; **30a** *p*-phenylphenacyl ester, 83399-01-3; **30b**, 83399-02-4; **30b** *p*-phenylphenacyl ester, 83399-03-5; **31**, 83399-04-6; **32**, 63557-55-1; **34**, 66679-32-1.