4a-$CH_3$), 5.58 (br s, 1 H, vinyl H); mass spectrum, $m/e$ (70 eV) 220.1751 (calcd 220.1821).

The GLC behavior and spectral properties of the major rearrangement product of **7** were identical with those of a sample prepared from the corresponding dienone **12b**[4] with an 11,12 double bond as follows. A solution of 75 mg of tris(triphenylphosphine)rhodium chloride in 15 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen had ceased. Then a solution of 110 mg of dienone **12b** in 2 mL of benzene was introduced and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen was absorbed. After filtration of the product through a column the containing 5 g of ammonia, ~60 mg of enone **12a** was isolated as a colorless oil.

**Reaction of Cyclopropyl Ketone 6 with Boron Trifluoride in Methylene Chloride.** Cyclopropyl ketone **6** (450 mg) was reacted with a saturated solution of boron trifluoride in methylene chloride under the same conditions as those described above for **5** and **7**. After workup of the product in the usual manner, 380 mg of a yellow oil was obtained. GLC analysis (column A)[19] of this material indicated that it contained one major component and two minor components in an 18:1:1 ratio. Preparative GLC (column B)[19] did not permit complete purification of the major component. However, preparative TLC using 0.5-mm silica plates and 20% ether–hexane as the eluant allowed the isolation of an analytical sample of 11,12-dihydrosolavetivone (**13**): UV (95% $C_2H_5OH$) 242 nm ($\epsilon$ 6400); IR ($CCl_4$) 1670 ($\alpha,\beta$-unsaturated C=O), 1616 $cm^{-1}$ (conjugated C=C); $^1H$ NMR ($CCl_4$) $\delta$ 0.89–1.01 (m, 9 H, $CH(CH_3)_2$ and $CHCH_3$), 1.89 (d, $J$ = 1.2 Hz, vinyl $CH_3$), and 5.62 (q, $J$ = 1.2 Hz, 1 H, vinyl H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 41.0 (C-1), 47.2 (C-2), 33.4 (C-3), 34.2 (C-4), 50.2 (C-5), 166.0 (C-6), 124.8 (C-7), 198.0 (C-8), 42.8 (C-9), 38.9 (C-10), 32.1 (C-11), 21.4 and 20.8 (C-12 to C-14), 15.9 (C-15); mass spectrum, $m/e$ (70 eV) 220.1813 (calcd 220.1821).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 10.96.

The sample of **13** obtained above was identical in GLC and TLC behavior and spectral properties with a sample prepared by selective reduction of the 11,12 double bond of (-)-solavetivone.[15] This reduction was performed as follows. A solution of 50 mg of tris(triphenylphosphine)rhodium chloride in 10 mL of benzene was placed under a hydrogen pressure of 1 atm and stirred until the uptake of hydrogen ceased. Then a solution of 61 mg of (-)-solavetivone in 1 mL of benzene was introduced via a syringe and the solution was stirred under a hydrogen pressure of 1 atm until 1 equiv of hydrogen had been absorbed. The solution was then passed through a column containing 5 g of silica gel and the solvent was removed in vacuo to give 54 mg of crude 11,12-dehydrosolavetivone (**13**). A pure sample of **13** was obtained by preparative TLC using 20% ether–hexane as the eluant.

**Registry No.** **1**, 74431-66-6; **5**, 61187-65-3; **6**, 74431-17-7; **7**, 74397-88-9; **8**, 53768-19-7; **9a**, 16735-08-3; **9b**, 69035-61-6; **10**, 69044-04-8; **11**, 70267-57-1; **12a**, 74397-89-0; **12b**, 74397-90-3; **13**, 74431-18-8.

# Synthesis and Stereochemistry of 9-Deoxy-5,9$\alpha$-epoxyprostaglandins: A Series of Stable Prostacyclin Analogues

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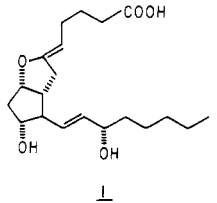
*Received April 23, 1980*

The reaction of *cis*-$\Delta^4$-prostaglandin $F_1\alpha$ methyl ester (**4**) with iodine gave (4*S*,5*S*)-4-iodo-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ methyl ester (**5**) and (4*R*,5*R*)-4-iodo-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ methyl ester (**6**). The reaction of **4** with mercuric acetate followed by reduction with sodium borohydride gave (5*R*)-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ methyl ester (**7**) and (5*S*)-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ methyl ester (**8**). Reductive removal of iodine from **5** gave **7**. The free acids (5*R*)-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ (**9**) and (5*S*)-9-deoxy-5,9$\alpha$-epoxyprostaglandin $F_1$ (**10**) were prepared by saponification of **7** and **8**, respectively. The reaction of iodo ether **5** with DBN in warm toluene gave (2*E*,5*S*)-9-deoxy-5,9$\alpha$-epoxy-$\Delta^2$-prostaglandin $F_1$ methyl ester (**13**) as the main product together with, after hydrolysis, a small amount of 5-oxoprostaglandin $F_1\alpha$ methyl ester (**14**). The $\alpha,\beta$-unsaturated ester **13** was prepared independently from **7** via preparation of the phenyl selenide, oxidation to the selenoxide, and elimination of the selenoxide to give the olefin. Reaction of iodo ether **6** with DBN gave (4*Z*)-9-deoxy-5,9$\alpha$-epoxy-$\Delta^4$-prostaglandin $F_1$ methyl ester (**15**), which was converted to the sodium salt **16** by reaction with 1 equiv of sodium hydroxide. Aqueous acid converted **15** to **14**. The configuration at $C_5$ in **7** and **8** (and all related analogues) was determined by the conversion of both compounds into like-ended molecules, (2*R*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-decahydro-2,7-dipentyl-2*H*-cyclopenta[1,2-*b*:4,3′-*b*]dipyran (**27a**) and (2*S*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-decahydro-2,7-dipentyl-2*H*-cyclopenta[1,2-*b*:4,3′-*b*]dipyran (**27b**), respectively. The $^{13}C$ NMR spectrum of **27b** contains eleven signals, reflecting the fact that the $C_2$ symmetry of the molecule reduces to 11 the number of stereochemically different carbons in the skeleton. These results reverse the previous tentative assignment of configuration given to $C_5$.[6]

Prostacyclin is the most potent, naturally occurring inhibitor of platelet aggregation yet discovered and also is a powerful vasodepressor.[1] The chemical structure of prostacyclin (**1**) features an enol–ether functional group that is susceptible to hydrolysis, giving 6-keto-$PGF_1\alpha$ (**2**).[2] Hydrolysis of the enol–ether is catalyzed by the carboxylic acid group so that prostacyclin has a half-life of only 3–4 min under physiological conditions.[3] Clearly, the preparation of chemically stable analogues of prostacyclin that

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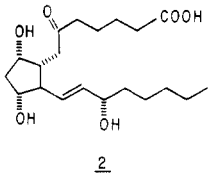



2

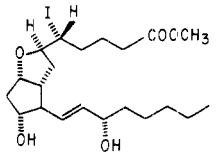
(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Moncada, S.; Vane, J. R. In "Biochemical Aspects of Prostaglandins and Thromboxanes"; Kharasch, N., Fried, J., Eds.; Academic Press: New York, 1977; pp 155–177.

(2) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915.

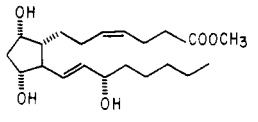
(3) (a) Cho, M. J.; Allen, M. A. *Prostaglandins* **1978**, *15*, 943. (b) Chiang, Y.; Kresge, A. J.; Cho, M. J. *J. Chem. Soc., Chem. Commun.* **1979**, 129.

0022-3263/80/1945-3802$01.00/0 

retain biological activity represents a desirable goal. The 5,6-dihydroprostacyclins, or $PGI_1$s (e.g., (5*R*,6*R*)-5-iodo-$PGI_1$ methyl ester, **3**), used in synthesis of prostacyclin are representative of one such family of analogues.[4]



**3**

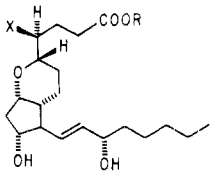


**4**

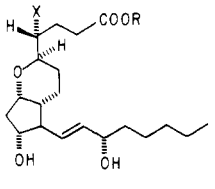
We have studied the chemistry of *cis*-$\Delta^4$-$PGF_1\alpha$ methyl ester[5] (**4**) in a series of reactions that roughly parallels those used in the synthesis and characterization of prostacyclin. This has led to the preparation of a new enol-ether analogous to prostacyclin and to a series of stable 9-deoxy-5,9α-epoxy-$PGF_1$ analogues of prostacyclin.[6] Members of the latter series do retain biological activity and in some cases the profile of activity is similar to that of prostacyclin.[7] In this report, we present a brief discussion of the synthesis, transformations, and structures of these analogues. Discussed in more detail is an unequivocal assignment of configuration to the newly generated asymmetric center ($C_5$) in these analogues. Our new results reverse our previous[6] tentative assignment of configuration at this center.

## Synthesis and Structure

The reaction of **4** with iodine in methylene chloride in the presence of aqueous sodium bicarbonate proceeded satisfactorily to give a mixture of two diastereomeric iodo ethers. The two products (**5**, 45%, and **6**, 16%) were



**5** R = $CH_3$, X = I
**7** R = $CH_3$, X = H
**9** R = X = H



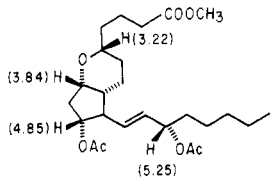
**6** R = $CH_3$, X = I
**8** R = $CH_3$, X = H
**10** R = X = H

separated chromatographically and assigned the structures (4*S*,5*S*)-4-iodo-9-deoxy-5,9α-epoxy-$PGF_1$ methyl ester and (4*R*,5*R*)-4-iodo-9-deoxy-5,9α-epoxy-$PGF_1$ methyl ester, respectively. The assignment of configuration at $C_5$ of these products is discussed in the following section. The configuration at $C_4$ is assigned on the assumption that iodo ether formation has occurred via a trans addition mode such as was observed for the analogous iodo ethers derived from $PGF_2\alpha$ methyl ester.[4b]

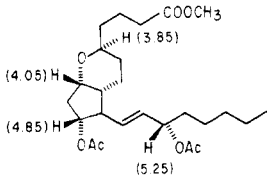
Cyclization of **4** was also achieved with mercuric acetate, again in analogy to previous work with $PGF_2\alpha$.[4b] Subsequent reduction of the intermediate mercuriacetates with sodium borohydride gave a mixture of cyclic ethers **7** and **8**. After chromatography, **7** and **8** were obtained in yields of 41 and 22%, respectively. Correlation of the iodo ether series with the mercuriacetate series was achieved by reductive removal of iodine from **5** with tri-*n*-butyltin hydride. The product from **5** was identical with compound **7** from the mercuric acetate–borohydride sequence. Saponification of **7** and **8** with sodium hydroxide in aqueous methanol gave acids **9** and **10**, respectively.

A distinctive signal is seen in the nuclear magnetic resonance (NMR) spectra of **7** and **9** and also, with the exception of iodo ether **5**, in the spectra of all other compounds that will be shown to have a 5α-carboxylic acid side chain. This signal is a broad multiplet in the range of δ 3.10–3.25 and integrates for one proton. The related compounds of the 5β series are completely free of any signal in this region of their NMR spectra.

The proton responsible for the signal at δ ~3.25 has been identified in the following manner. First, the 11,15-diacetate derivatives **11** and **12** were prepared from



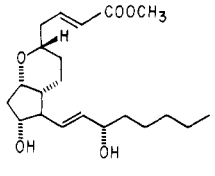
**11**



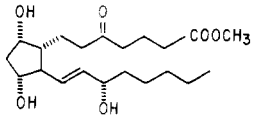
**12**

**7** and **8**, respectively. The signals for the $C_{11}$ and $C_{15}$ protons are now shifted downfield in the NMR spectra of these derivatives. Unaffected by this procedure were signals at δ 3.22 and 3.84 in **11** and at δ 3.85 and 4.05 in **12**. Further modification of these spectra by irradiation of one of the $C_{10}$ protons (at δ 2.54) resulted in partial decoupling of the signal at δ 3.84 in **11** and at δ 4.05 in **12**. These signals must, therefore, be due to the protons at $C_9$ in these compounds, and we can conclude that the $C_5$ proton is the source of the signal at δ 3.22 in **11** and at δ 3.85 in **12**. We will return to these NMR data in the discussion of configurational assignments below.

Elimination of HI was attempted first with the major iodo ether **5** and, with DBN as the base, gave two products in a ratio of 5:1. The main product (**13**, 44%) was a



**13**



**14**

crystalline solid (mp 60–62 °C) that was stable to acid hydrolysis conditions. The NMR spectrum of **13** clearly indicated the presence of an olefin in conjugation with the carboxylate group. Such an α,β-unsaturated ester functionality could arise if HI elimination occurred from $C_3$–$C_4$ and was followed by base-catalyzed isomerization of the resultant double bond into conjugation with the ester carbonyl.

The structure of **13** was confirmed by synthesis from cyclic ether **7**. Compound **7** was first converted to the bis(tetrahydropyranyl) ether derivative and then submitted to the sequence (a) base, (b) diphenyl diselenide, and (c) hydrogen peroxide.[8] Following removal of the

(4) (a) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 4182. (b) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *Ibid.* **1978**, *100*, 7690. (c) Corey, E. J.; Keck, G. E.; Szekely, I. *Ibid.* **1977**, *99*, 2006. (d) Fried, J.; Barton, J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 2199.

(5) Green, K.; Samuelsson, B.; Magerlein, B. J. *Eur. J. Biochem.* **1976**, *62*, 527.

(6) A preliminary account of portions of this article has been presented previously: Johnson, R. A.; Nidy, E. G. In "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids"; Roberts, S. M., Scheinmann, F., Eds.; Pergammon Press: London, 1979; pp 274–285.

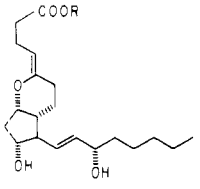
(7) Johnson, R. A.; Lincoln, F. H.; Smith, H. W.; Ayer, D. E.; Nidy, E. G.; Thompson, J. L.; Axen, U.; Aiken, J. W.; Gorman, R. R.; Nishizawa, E. E.; Honohan, T. In "Prostacyclin"; Bergstrom, S., Vane, J. R., Eds.; Raven Press: New York, 1979; pp 17–29.

(8) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

THP protecting groups, this sequence gave an authentic sample of (2*E*,5*S*)-9-deoxy-5,9α-epoxy-$\Delta^2$-$PGF_1$ methyl ester that was identical with **13**.

The minor product formed in the elimination of HI from **5** was sensitive to acid and was converted to a more polar product when the TLC plate was developed in an acidic solvent system. Consequently, the total reaction product mixture was first treated with aqueous acid before the products were separated by chromatography. The minor product (**14**, 8.5%) isolated after this treatment was identified (see spectral data in the Experimental Section) as 5-oxo-$PGF_1\alpha$ methyl ester and was presumed to arise from hydrolysis of the desired enol–ether.

Elimination of HI from minor iodo ether **6** with DBN was then attempted and gave the desired (4*Z*)-9-deoxy-5,9α-epoxy-$\Delta^4$-$PGF_1$ methyl ester (**15**) as an essentially pure product (91% yield). A trace of **13** was detected in the product by TLC, but further purification was not attempted due to the instability of **15**.



**15** R = $CH_3$
**16** R = Na

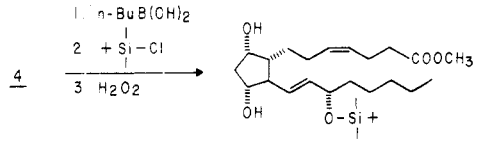
The structure of **15** is supported by the spectral data (see Experimental Section) and by hydrolysis to 5-oxo-$PGF_1\alpha$ methyl ester (**14**). The stereochemistry of the $\Delta^4$ double bond is assigned as 4*Z* on the basis of the assumption that elimination of HI from **6** has occurred via a trans mechanism.[4b]

The sodium salt **16** was prepared from **15** by saponification with sodium hydroxide followed by lyophilization of the reaction solution. As an inhibitor of $PGH_2$-induced platelet aggregation, **16** was 90% as effective as the prostacyclin sodium salt.[9]

## Assignment of Configuration at $C_5$

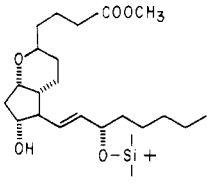
The potent biological properties of various analogues[7] derived from **7** and **8** made desirable an unequivocal assignment of configuration to the $C_5$ position of these compounds. To do so, we devised a series of transformations which would convert **5** and **6** into two like-ended molecules differing by only one epimeric center. The symmetry properties of these two molecules would allow us to make the configurational assignments in question. In the following discussion, the letter "a" is incorporated with the numerals to indicate compounds derived from the major epimeric series (also having the NMR signal at δ ~3.25) and the letter "b" is used with compounds from the minor epimeric series.

As a starting point we prepared the 15-(*tert*-butyldimethylsilyl) ether derivative (**17**) of cis-$\Delta^4$-$PGF_1\alpha$ methyl ester (**4**). The sequence of reactions (a) protection of the

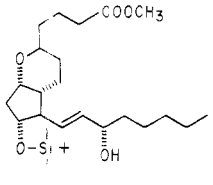



**17**

9- and 11-hydroxyls as the *n*-butyl boronate, (b) derivatization of the 15-hydroxyl group with *tert*-butyldimethylsilyl chloride, and (c) deprotection of the 9- and 11-hydroxyls with hydrogen peroxide[10] was used to prepare **17**. Reaction of **17** with mercuric acetate in tetrahydrofuran followed by reduction of the intermediate mercuriacetate with sodium borohydride gave the epimeric cyclic ethers **18a** and **18b** (total yield 65%, ratio 2.5:1). Just as in the parent structure **7**, the major product **18a** has a characteristic signal at δ 3.20 in its $^1H$ NMR spectrum.

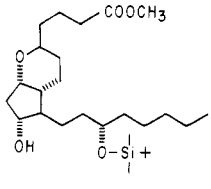



**18a** (δ 3.20)
**18b**

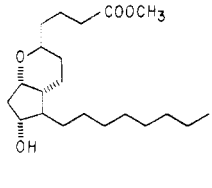



**19** (δ 3.25)

Compound **18a** also was correlated chemically with **7** in the following way. The 11,15-bis(*tert*-butyldimethylsilyl) ether derivative of **7** was desilylated with a controlled portion of tetra-*n*-butylammonium fluoride.[11] The 15-(*tert*-butyldimethylsilyl) ether derivative obtained from this reaction was identical with **18a**. The 11-silyl ether **19** was also isolated from this reaction.[12] Reduction of **18a** was done with hydrogen over palladium on carbon and gave the desired **20a** (69%) together with a smaller amount

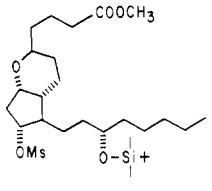



**20a** (δ 3.13)
**20b**

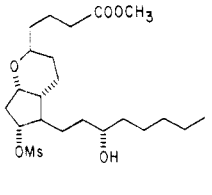



**21**

of the hydrogenolysis product **21** (17%). In the case of **18b**, the catalyst used was platinum, and the reaction was nearly free of any hydrogenolysis product. Reduction product **20b** was obtained in 67% yield. The remaining hydroxyl group at $C_9$ in **20a** and **20b** was converted to the mesylate by reaction with methanesulfonyl chloride in pyridine. Desilylation of **22a** and **22b** by hydrolysis in acetic acid–tetrahydrofuran–water–HCl gave **23a** and **23b** with free 15-hydroxyl groups.




**22a** (δ 3.23)
**22b**




**23a** (δ 3.23)
**23b**

We now wished to carry out a ring closure between positions 11 and 15 so that a new tetrahydropyran ring would form with a cis fusion to the central cyclopentane ring and with known stereochemistry at $C_{15}$. The best conditions found for cyclization of **23a** and **23b** were simply heating the compounds in benzene for 16–22 h. Under

(9) We thank Dr. Robert R. Gorman for measuring inhibition of platelet aggregation.

(10) Johnson, R. A.; Nidy, E. G.; Baczynskyj, L.; Gorman, R. R. *J. Am. Chem. Soc.* **1977**, *99*, 7738.
(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(12) This reaction is selective for the removal of the 11-silyl group in certain cases (J. C. Sih and D. R. Graber, unpublished results, The Upjohn Company, 1977), but this was not the case here.

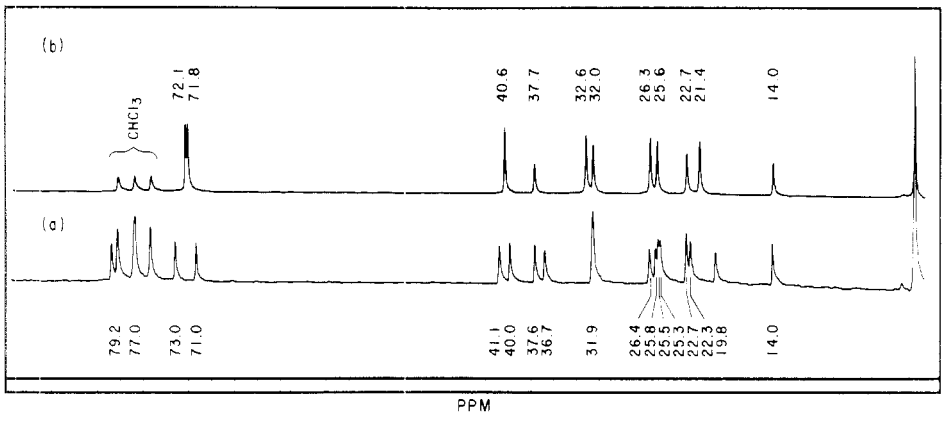
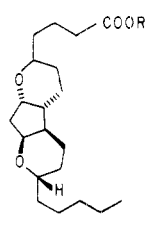
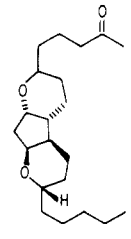



**Figure 1.** $^{13}C$ NMR spectra of (a) compound **27a** and (b) compound **27b**.

these conditions, however, we could not be certain that the cyclization was stereospecific, i.e., that it had proceeded by an $S_N2$ reaction. Several bases were used (including *tert*-butoxide and sodium hydride) in attempting to catalyze the reaction before we found that potassium hydride[13] was an effective catalyst for the cyclization (~10–30 min at room temperature in THF). The products (**24a**) obtained from cyclization of **23a** by either method were identical, as were those (**24b**) obtained from **23b**. Consequently, we can be certain that the products of the thermal cyclization have the desired 11β,15*S* stereochemistry.



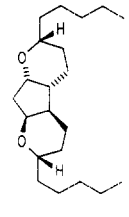



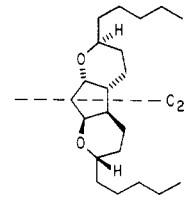
24a R = $CH_3$ (δ 3.17)
24b R = $CH_3$
25a R = H (δ 3.20)
25b R = H

26a (δ 3.17)
26b

To make the molecules completely like-ended, we found it necessary to homologate and reduce the carboxylic acid side chain in each series. To do this, we first converted methyl esters **24a** and **24b** to acids **25a** and **25b**. Reaction of the latter with methyllithium served to convert the carboxylic acid groups into the homologous methyl ketones **26a** and **26b**. Signals at δ 2.45 (t, $J$ = 6.5 Hz) and 2.10 (singlet) in the NMR spectra of **26a** and **26b** are consistent with the methyl ketone structure.

Finally, reduction of the carbonyl groups of **26a** and **26b** to methylenes was carried out by using the Huang–Minlon modification of the Wolff–Kishner method. This reduction proceeded satisfactorily with the exception that the desired products, **27a** and **27b**, were obtained in only modest yields (30 and 41%).

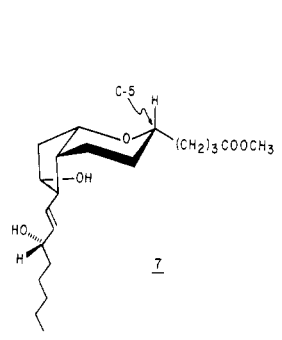




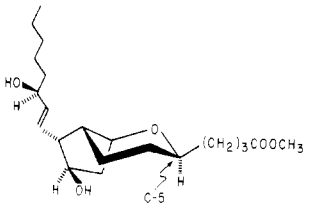

27a (δ 3.15)

27b

(13) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.




7




8

**Figure 2.** Conformational drawings of compounds **7** and **8**.

Structures **27a** and **27b** can be distinguished unequivocally on the basis of their symmetry properties. Of the two structures, **27b** has $C_2$ symmetry while **27a** does not. Consequently, all 21 carbon atoms of **27a** are stereochemically different whereas **27b** has only 11 such different carbons. This difference between the two compounds should be reflected in their $^{13}C$ NMR spectra. Compound **27a** should have 21 signals in its $^{13}C$ NMR spectrum while compound **27b** should have only 11 signals in its spectrum.

The actual spectra of **27a** and **27b** are reproduced in Figure 1. The spectrum of **27a** has 17 distinguishable signals whereas the spectrum of **27b** has only 11 signals. Therefore, **27b** must have $C_2$ symmetry and must be assigned the 5β or 5*S* configuration (prostaglandin numbering). Compound **27a** is assigned the 5α or 5*R* configuration.

The effect of these symmetry properties is also seen in the $^1H$ NMR spectra of **27a** and **27b**. The $^1H$ NMR of **27a** contains four different signals (δ 4.19, 3.93, 3.76, and 3.15) for the protons on carbon next to oxygen while the spectrum of **27b** contains only two signals (δ 4.39 and 3.65, two protons each).

Our earlier assumption[6] that the 5α-proton (see **8** in Figure 2) may be shielded and its NMR signal therefore shifted upfield is not supported by the literature. In fact, several observations[14] have demonstrated that when an axial proton is situated in a 1,3-relationship to an axial alkyl group (generally a methyl group in the literature examples), the signal for that proton is shifted downfield

(14) (a) Eliel, E. L.; Gianni, M. H.; Williams, T. H.; Stothers, J. B. *Tetrahedron Lett.* **1962**, 741. (b) Eliel, E. L.; Biros, F. J. *J. Am. Chem. Soc.* **1966**, *88*, 3334. (c) This was also evident in the spectra of some *N*-benzoylpiperidines but was not recognized at the time: Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627.

(15) Cf.: Cooper, E. L.; Yankee, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5876.

relative to the case where it is situated 1,3 to an axial hydrogen. Our rationalization that the signal found between δ 3.10 and 3.25 was the result of shielding by carbon was incorrect. However, we still have not found an adequate precedent for this signal which now is assigned to the 5β-proton in these compounds (see **7** in Figure 2).

## Experimental Section

**General Methods.** Melting points were obtained with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded with either a Perkin-Elmer Model 137 or a Digilab Model FTS-14D spectrophotometer; mulls were in Nujol, liquids and oils were films between salt plates, and solutions were in $CHCl_3$. The $^1H$ NMR spectra were obtained with a Varian A-60A, a Varian HFT-80, or a Varian XL-100 spectrometer as solutions in chloroform with tetramethylsilane as an internal standard. First-order analysis of the NMR spectra are presented. The $^{13}C$ NMR spectra were obtained with a Varian CFT-20 spectrometer in chloroform solution and are reported in parts per million from tetramethylsilane. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer. Brine refers to a saturated aqueous solution of sodium chloride.

**(4*S*,5*S*)-4-Iodo-9-deoxy-5,9α-epoxy-PGF$_1$ Methyl Ester (5) and (4*R*,5*R*)-4-Iodo-9-deoxy-5,9α-epoxy-PGF$_1$ Methyl Ester (6).** A solution of iodine in methylene chloride (112 mL, 2.5%, 10.9 mmol) was added dropwise (35 min) at room temperature to a stirred mixture of *cis*-Δ$^4$-PGF$_1$α methyl ester (**4**; 2.01 g, 5.45 mmol) dissolved in methylene chloride (260 mL) and a saturated aqueous solution of sodium bicarbonate (82 mL). The reaction was worked up after 2 h by first adding methylene chloride (1300 mL) and then shaking with aqueous 0.2 M sodium thiosulfate solution (80 mL). The layers were separated quickly, and the organic layer was washed successively with water (360 mL), pH 2 buffer (140 mL), and water (360 mL). Following being dried over magnesium sulfate, the organic layer was concentrated and the residue chromatographed over three series-connected Merck B Lobar LC columns. Elution with acetone–hexane (1:3) yielded first **(4*S*,5*S*)-4-iodo-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester** (1.215 g, 0.00246 mol, 45%) as a colorless oil: $R_f$ 0.38 (TLC on silica gel in acetone–hexane, 40:60); mass spectrum [bis(trimethylsilyl) ether], *m/e* 638.2308 (calcd for $C_{27}H_{51}Si_2O_5I$ 638.2321), 623, 567, 548, 517, 511, 477, 451, 173; $^1H$ NMR ($CDCl_3$) δ 5.50 (m, 2 H, CH=CH), 3.98 (m), 3.67 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, *J* = 5 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ 173.0, 135.3, 132.4, 79.6, 79.0, 78.1, 72.8, 52.5, 51.6, 42.7, 41.3, 37.1, 34.0, 32.2, 31.7, 25.9, 25.2, 22.6, 21.7, 14.0; IR (film) $\nu_{OH}$ 3380, $\nu_{C=O}$ 1735, $\nu_{C=C}$ 1670 cm$^{-1}$.

Anal. Calcd for $C_{21}H_{35}O_5I$: C, 51.01; H, 7.14. Found: C, 50.47; H, 7.22.

Eluted second was **(4*R*,5*R*)-4-iodo-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester** (0.440 g, 0.000 89 mol, 16%) as a crystalline material: fine needles from ether–hexane; mp 72–74 °C; $R_f$ 0.32 (TLC on silica gel in acetone–hexane, 40:60); $^1H$ NMR ($CDCl_3$) δ 5.49 (m, 2 H, CH=CH), 4.34 (m), 4.10 (m), 3.67 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, *J* = 5 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ 173.0, 135.8, 132.6, 75.9, 73.0, 71.3, 54.4, 51.7, 41.6, 40.0, 37.0, 34.2, 31.7, 31.2, 25.2, 24.4, 22.6, 20.7, 14.0; mass spectrum [bis(trimethylsilyl) ether], *m/e* 638.2346 (calcd for $C_{27}H_{51}Si_2O_5I$ 638.2321), 623, 607, 567, 517, 511, 477, 451, 421, 173; IR (Nujol mull) $\nu_{OH}$ 3400, $\nu_{C=O}$ 1740, 1715, $\nu_{CH}$ 965 cm$^{-1}$.

Anal. Calcd for $C_{21}H_{35}O_5I$: C, 51.01; H, 7.14. Found: C, 50.75; H, 7.19.

**(5*R*)- and (5*S*)-9-Deoxy-5,9α-epoxy-PGF$_1$ Methyl Esters 7 and 8. (A) Via Mercuriacetates.** Mercuric acetate (1.86 g, 5.85 mmol) was dissolved in water (20 mL). Tetrahydrofuran (20 mL) was added, and a yellow precipitate formed. A solution of *cis*-Δ$^4$-PGF$_1$α methyl ester (**4**; 1.44 g, 3.9 mmol) in THF (20 mL) was added to the mixture. The reaction was stirred at room temperature for 6 h. Sodium borohydride (0.40 g) in 1 N NaOH (20 mL) was added dropwise, and then brine and ether were added. The layers were separated, and the aqueous layer was extracted thoroughly with ether. The ether extracts were pooled, washed with water and brine, dried ($MgSO_4$), filtered, and evaporated (yield 1.30 g). The aqueous layer was acidified (pH <3) with 10% $KHSO_4$ and extracted with ether. The ether extracts contained 1.9 g of oil, which was esterified with excess diazomethane in ether. The product of this esterification was combined with the above extract and the total was chromatographed on silica gel (180 g) by using high-pressure liquid chromatography (LC). The sample was applied to the column in methylene chloride. The column was eluted with 25% acetone–hexane. Fractions of 25 mL were collected. Fractions 55–80 contained (5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (**7**; 0.796 g, 1.6 mmol, 41%), and fractions 95–126 contained (5*S*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (**3**; 0.319 g, 0.867 mmol, 22%). Isomer **7** was a viscous oil: NMR ($CDCl_3$) δ 5.49 (m, 2 H, CH=CH), 4.23–3.60 (m, 3 H, $C_9H$, $C_{11}H$, $C_{15}H$), 3.65 (s, 3 H, $COOCH_3$), 3.25 (m, 1 H, $C_5HO$), 0.88 (t, 3 H, *J* = 5 Hz, $CH_3$); mass spectrum [bis(trimethylsilyl) ether], *m/e* 512.3320 (calcd for $C_{27}H_{52}Si_2O_5$ 512.3353), 497, 441, 422, 412, 391, 351, 325, 235, 173.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.49; H, 10.10.

Isomer **8** was a viscous oil: NMR ($CDCl_3$) δ 5.50 (m, 2 H, CH=CH), 4.23–3.60 (m, 4 H, $C_5H$, $C_9H$, $C_{11}H$, $C_{15}H$), 3.66 (s, 3 H, $COOCH_3$), 0.88 (5, 3 H, *J* = 5 Hz, $CH_3$); mass spectrum [bis(trimethylsilyl) ether], *m/e* 512.3331 (calcd for $C_{27}H_{52}Si_2O_5$ 512.3353), other peaks similar to those of isomer **7**.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.02; H, 10.03.

**(B) Preparation of 7 from Iodo Ether 5.** To a solution of **5** (0.29 g, 0.587 mmol) in methanol (15 mL) under nitrogen was added with stirring, first, tri-*n*-butyltin chloride (30 drops) and, second, sodium borohydride (0.3 g, over 5 min). The resulting mixture was stirred under $N_2$ for 1 h at room temperature. The reaction was complete as determined by TLC (30% acetone–hexane). The reaction was worked up by pouring of the mixture into brine (75 mL) and extracting this with ethyl acetate (3 × 50 mL). The pooled extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed over a column of silica gel (30 g) packed in 25% acetone–hexane. There was obtained 0.17 g (0.46 mmol, 78%) of **(5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (7)**, identical when compared by TLC and NMR spectrum with the major, less polar compound **7** described above.

**(5*R*)-9-Deoxy-5,9α-epoxy-PGF$_1$ (9).** A solution of **7** (0.410 g, 1.111 mmol) in methanol (15 mL) was mixed and stirred at room temperature with an aqueous 0.1 N sodium hydroxide solution (12 mL). After several hours, the reaction was incomplete, so additional 0.1 N NaOH (3 mL) was added, and stirring was continued overnight. The reaction now was complete so the excess methanol was removed under reduced pressure. The aqueous residue was acidified (pH <2) with 10% $KHSO_4$ and extracted with ethyl acetate (4×). The pooled extracts were washed with water and brine and then dried ($MgSO_4$). Following filtration and concentration under reduced pressure, the residue was chromatographed on acid-washed silica gel (Malinckrodt CC-4, 60 g). The column was dry packed after equilibration with 50% ethyl acetate–hexane (30 mL). The column was eluted first with 50% ethyl acetate–hexane (400 mL) and then with 65% ethyl acetate–hexane (3:1). Fractions of 25 mL were collected, and the product was eluted in fractions 31–42 (0.285 g) and 43–95 (0.034 g; total 0.319 g, 0.90 mmol, 81%). The product, **(5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ (9)**, is a colorless oil: NMR ($CDCl_3$) δ 5.54 (m, 2 H, CH=CH), 4.29–3.73 (m, 3 H, $C_9H$, $C_{11}H$, $C_{15}H$), 3.27 (m, 1 H, $C_5HO$), 0.90 (5, 3 H, 5 Hz, $CH_3$); mass spectrum [tris(trimethylsilyl) ether], *m/e* 570.3575 (calcd for $C_{29}H_{58}Si_3O_5$ 570.3592), remainder of breakdown pattern similar to that of isomer **10**.

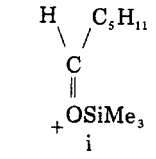
**(5*S*)-9-Deoxy-5,9α-epoxy-PGF$_1$ (10).** A solution of **8** (0.207 g, 0.56 mmol) in methanol (8 mL) was stirred at room temperature with aqueous 0.1 N sodium hydroxide (12 mL) for 24 h. The reaction was complete as shown by TLC examination. After partial removal of excess methanol, the mixture was acidified (pH <2) with 10% $KHSO_4$ and extracted with ethyl acetate. The combined extracts were washed with water and brine and were dried over $MgSO_4$. Filtration and removal of the solvent gave 0.199 g of crude product (**10**). The product was chromatographed on a column of acid-washed silica gel (30 g, CC-4), which was dry packed after addition of and equilibration with 15 mL of 70% ethyl acetate–hexane. The column was eluted with 70–80% ethyl acetate–hexane and gave 0.165 g (0.467 mmol, 83%) of pure **(5*S*)-9-deoxy-5,9α-epoxy-PGF$_1$ (10)** as a viscous, colorless oil: NMR ($CDCl_3$) δ 5.52 (m, 2 H, CH=CH), 4.27–3.60 (m, 4 H, $C_5H$,

$C_9H$, $C_{11}H$, $C_{15}H$), 0.88 (t, 3 H, $J$ = 5 Hz, $CH_3$); mass spectrum [tris(trimethylsilyl) ether], $m/e$ 570.3598 (calcd for $C_{29}H_{58}Si_3O_5$ 570.3592), 555, 499, 480, 465, 409, 390, 383, 364, 173.

**(5*R*)-9-Deoxy-5,9α-epoxy-PGF$_1$ Diacetate Methyl Ester (11).** A solution of (5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (**7**; 0.10 g, 0.27 mmol) in 3:1 (v/v) pyridine–acetic anhydride (1 mL) was stirred at room temperature for 4 h. The reaction was mixed with water (5 mL) and was extracted with ether (4×). The ether extracts were pooled and washed with 1 N HCl until the aqueous layer remained acidic. The organic layer was washed twice with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was placed under vacuum to remove any remaining acetic anhydride. The product, (5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ diacetate methyl ester (**11**, 0.078 g), consisted of a single spot when examined by TLC analysis: NMR ($CDCl_3$, 100 MHz) δ 5.52 (m, 2 H, CH=CH), 5.26 (m, 1 H, $C_{15}H$), 4.85 (eight-line pattern, 1 H, $C_{11}H$), 3.84 (four-line pattern, 1 H, $J_{9,10}$ = 6 Hz, $C_9H$), 3.68 (s, 3 H, $OCH_3$), 3.22 (broad five-line pattern, 1 H, $J \simeq 6$ Hz, $C_5H$), 2.56 (portions of the signal for one of the $C_{10}$ protons), 2.35 (m, 2 H, $CH_2C(O)$), 0.88 (t, 3 Hz, $J$ = 5 Hz, $CH_3$). Irradiation at δ 3.84 caused simplification of the signal at δ 2.56, whereas irradiation at δ 2.56 caused simplification of the signals at δ 3.84 and 4.85. The results of the double-irradiation experiments allow assignment of the signal at δ 3.84 to the $C_9$ proton and of the signal at δ 4.85 (shifted downfield by acetate formation) to the $C_{11}$ proton. The signals at δ 5.26 and 3.22 may now be assigned to the $C_{15}$ (acetate has shifted this downfield) and the $C_5$ protons, respectively.

**(5*S*)-9-Deoxy-5,9α-epoxy-PGF$_1$ Diacetate Methyl Ester (12).** The procedure used for the preparation of **11** was used to convert (5*S*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (0.10 g, 0.00027 mol) into (5*S*)-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester diacetate (**12**): 0.057 g; NMR ($CDCl_3$, 100 MHz) δ 5.52 (m, 2 H, CH=CH), 5.25 (m, 1 H, $C_{15}H$), 4.87 (eight-line pattern, 1 H, $C_{11}H$), 4.05 (m, 1 H, $C_9H$), 3.85 (m, 1 H, $C_5H$), 3.69 (s, 3 H, $OCH_3$), 2.54 (a portion of the signal for one of the $C_{10}$ protons), 2.38 (m, 2 H, $CH_2C(O)$), 0.88 (5, 3 H, $J$ = 5 Hz, $CH_3$). Irradiation of the signal at δ 2.54 caused simplification of the signals at δ 4.05 and 4.87, which therefore must be due to the $C_9$ and $C_{11}$ protons, respectively.

**(2*E*,5*S*)-9-Deoxy-5,9α-epoxy-Δ$^2$-PGF$_1$ Methyl Ester (13) and 5-Oxo-PGF$_1$α Methyl Ester (14).** A solution of (4*S*,5*S*)-4-iodo-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (**5**; 1.126 g, 2.27 mmol) in 60 mL of toluene was purged with nitrogen followed by the addition of 2 mL of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). The solution was heated at 40–45 °C under a nitrogen atmosphere. The reaction was heated for 72 h, during which time another 0.5 mL of DBN was added. The reaction was then cooled to room temperature and diluted with toluene. The reaction was washed with water (2×), dried ($Na_2SO_4$), filtered, and evaporated to give 832 mg of an oil. The oil was dissolved in 15 mL of THF and treated with 15 mL of pH 1.5 buffer solution. The solution was stirred at room temperature for 1.5 h. The solution was then shaken with brine plus ethyl acetate (3×). The pooled ethyl acetate layers were washed with water, dried ($MgSO_4$), filtered, and evaporated to give an oil. The oil was chromatographed on three Merck B Lobar columns connected in series. The sample was applied with methylene chloride, and the column was eluted with 400 mL of 20% acetone–hexane, 1.1 L of 25% acetone–hexane, 750 mL of 30% acetone–hexane, 2.5 L of 40% acetone–hexane, and with 50% acetone–hexane. Eluted first was **(2*E*,5*S*)-9-deoxy-5,9α-epoxy-Δ$^2$-PGF$_1$ methyl ester** (369 mg, 0.0010 mol, 44%) as an oil: $R_f$ 0.55 (TLC on silica gel in 30% acetone–methylene chloride); $^1$H NMR ($CDCl_3$) δ 6.95 (dt, 1 H, $C_3$ olefinic, $J_{H2}$ = 15.5 Hz, $J_{H4}$ = 7 Hz), 5.85 (dt, 1 H, $C_2$ olefinic, $J_{H3}$ = 15.5 Hz, $J_{H4}$ = 1.5 Hz), 5.50 (m, 2 H, $C_{13}$–$C_{14}$ olefinic), 4.20–3.65 (m, 3 H, OCH), 3.70 (s, 3 H, $OCH_3$), 3.33 (m, 1 H, $C_5H$), 0.88 (t, 3 H, $CH_3$, $J$ = 5 Hz); mass spectrum [bis(trimethylsilyl) ether], $m/e$ 510.3188 (calcd for $C_{27}H_{50}Si_2O_5$ 510.3197), 495 ($M^+ - CH_3$), 479 ($M^+ - OCH_3$), 439 ($M^+ - C_5H_{11}$), 420 ($M^+ - Me_3SiOH$), 411 [$M^+ - (CH_2CH{=}CHCO_2CH_3)$], 349 [$M^+ - (C_5H_{11} + Me_3SiOH)$], 321 ($411^+ - Me_3SiOH$), 199 [$(HC{=}CHCH_5H_{11})^+$], 173 (i).



i

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.96; H, 9.61.

Eluted second was **5-oxo-PGF$_1$α methyl ester** (94 mg, 0.000 194 mol, 8.5%) as a colorless oil: $R_f$ 0.21 (TLC on silica gel in 30% acetone–methylene chloride); mass spectrum [bis(trimethylsilyl) ether], $m/e$ 510.3173 [calcd for $C_{27}H_{50}Si_2O_5$ ($M^+ - Me_3SiOH$) 510.3197], 495 ($510^+ - CH_3$), 479 ($510^+ - OCH_3$), 439 ($510^+ - C_5H_{11}$), 420 ($510^+ - Me_3SiOH$), 394 ($510^+ - CH_2{=}CH - OSiMe_3$), 181.0856 (large, $C_{10}H_{13}O_3$, calcd 181.0865); mass spectrum of methoxime–trimethylsilyl ether derivative gave $M^+$ at 629 mass units; IR (film) $\nu_{OH}$ 3360, $\nu_{C=O}$ 1735, 1710, $\nu_{trans\text{-}CH=CH}$ 970 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.48 (m, 2 H, CH=CH), 4.54–3.59, 3.65 (s, 3 H, $CH_3$), 0.88 (t, 3 H, $CH_3$, $J$ = 5 Hz).

Anal. Calcd for $C_{21}H_{30}O_6$: C, 65.59; H, 9.44. Found: C, 65.00; H, 9.55.

**Synthesis of 13 from 7. (A) Preparation of Phenyl Selenide.** The bis(tetrahydropyranyl) ether derivative of **7** was prepared by standard procedures.[15] This derivative was converted to the α-phenylseleno compound by the procedure of Reich and co-workers.[8] A solution of diisopropylamine (658 mg, 6.5 mmol) in THF (5 mL) was cooled to −78 °C under a $N_2$ atmosphere. *n*-Butyllithium (6.14 mmol) was added over a 10-min period and the solution stirred an additional 15 min. The diTHP (2.03 mmol) in THF (2 mL) was added dropwise (10 min) to the cold (−78 °C) solution. Stirring at −78 °C was continued for 90 min, diphenyl diselenide (0.811, 2.6 mmol) in THF (4 mL) was added dropwise, and stirring was continued for 60 min. After this time the solution was allowed to warm to room temperature. The reaction was poured into 30 mL of saturated aqueous ammonium chloride. The mixture was extracted with ether (4×). The pooled ether extracts were washed with water and brine and then were dried over $Na_2SO_4$. The crude product was filtered through silica gel with ethyl acetate. The resulting amber oil was chromatographed on three Merck size B Lobar columns by using pressure chromatography. The sample was applied to the column in methylene chloride, and the column was eluted with 10% ethyl acetate–toluene, collecting fractions of 25 mL. The epimeric phenyl selenides partially separated, the least polar being found in fractions 53–60, a mixture in fractions 61–69, and the more polar compounds in fractions 70–96 (total 0.646 g, 46%).

**(B) Oxidation of Phenyl Selenide and Elimination of Selenoxide.** Both epimers of the phenyl selenide (0.634 g, 0.916 mmol) in methylene chloride (20 mL) were oxidized with aqueous 30% hydrogen perioxide (10 mL plus 15 mL of water). After the mixture was stirred 2 h at room temperature, more $CH_2Cl_2$ was added, and the mixture was added to 20 mL of 5% $NaHCO_3$. The layers were separated, and the organic solution was washed with 10% $NaHCO_3$ (25 mL), water, and brine, dried ($MgSO_4$), filtered, and concentrated, giving a pale yellow oil (0.504 g) that was used directly in the next step.

**(C) Hydrolysis of THP Groups.** The preceding crude compound (0.504 g) was treated with 20 mL of a glacial acetic acid–water–tetrahydrofuran (20:10:3) solution and heated at 40 °C for 4 h. Azeotropic removal of the solvents with toluene gave an oil which was chromatographed on three series-connected Merck size B columns. The compounds were eluted with 1.4 L of 25% acetone–hexane and then 30% acetone–hexane. Fractions with a volume of 25 mL each were collected. Fractions 1–106 contained 155 mg of material which was assumed to be the incomplete THP hydrolysis product, and fractions 107–126 contained the desired product (163 mg). The material in fractions 1–106 was again subjected to hydrolysis conditions. There was obtained after chromatography another 42 mg of product to give a total of 205 mg (61% of theory) of **13**, having spectral properties identical with the **13** isolated above.

**(4*Z*)-9-Deoxy-5,9α-epoxy-Δ$^4$-PGF$_1$ Methyl Ester (15).** A solution of (4*R*,5*R*)-4-iodo-9-deoxy-5,9α-epoxy-PGF$_1$ methyl ester (**6**; 200 mg, 0.4 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 0.4 mL) in toluene (10 mL) was heated at 40–45 °C under nitrogen for 48 h. The reaction mixture was diluted with toluene and

washed twice with water. The organic layer was dried over sodium sulfate, filtered, and concentrated to give 133 mg of **(4*Z*)-9-deoxy-5,9α-epoxy-Δ⁴-PGF$_1$ methyl ester** (0.000 365 mol, 91%) as a semisolid: $R_f$ 0.56 (TLC on silica gel in acetone–hexane, 2:3); $^1$H NMR ($CDCl_3$) δ 5.50 (m, 2 H, CH=CH), 4.43 (m), 4.24–3.76 (m, 2 H), 3.66 (s, 3 H, $COOCH_3$), 3.58–3.20 (m, 2 H), and 0.88 (t, 3 H, $J$ = 5 Hz, $CH_3$); mass spectrum [bis(trimethylsilyl) ether], $m/e$ 510.3183 (calcd for $C_{27}H_{50}Si_2O_5$ 510.3197), 495, 479, 439, 420, 389, 349, 330, 181, 173; IR (Nujol) $\nu_{OH}$ 3450, $\nu_{C=O}$ 1735, $\nu_{C=C}$ 1700, 1680 cm$^{-1}$.

**(4*Z*)-9-Deoxy-5,9α-epoxy-Δ⁴-PGF$_1$ Sodium Salt (16).** A solution of (4*Z*)-9-deoxy-5,9α-epoxy-Δ⁴-PGF$_1$ methyl ester (**15**; 133 mg, 0.36 mmol) in methanol (4 mL) and aqueous 0.1 M sodium hydroxide (4 mL) was stirred at room temperature for 16 h. The excess methanol was removed under reduced pressure. The remaining aqueous solution was frozen and lyophilized to give **(4*Z*)-9-deoxy-5,9α-epoxy-Δ⁴-PGF$_1$α sodium salt** as a semisolid material.

***cis*-Δ⁴-PGF$_1$α 15-(*tert*-Butyldimethylsilyl) Ether Methyl Ester (17).** By use of a previously described procedure,[10] *cis*-Δ⁴-PGF$_1$α methyl ester (**4**; 6.40 g, 0.0173 mol) and 1-butaneboronic acid (1.97 g) in benzene (425 mL) were heated to reflux. Water was removed from the reaction azeotropically with a Dean–Stark trap. After 3 h of reflux, dimethylformamide (30 mL) was added, refluxing was continued 30 min, and then the mixture was cooled to room temperature.

Imidazole (4.69 g) and *tert*-butyldimethylsilyl chloride (5.19 g) were added to the mixture. The benzene was removed from the reaction under reduced pressure. The remaining solution was stirred 16 h at room temperature.

Acetone (250 mL), sodium bicarbonate (1.9 g), and aqueous 30% hydrogen peroxide (55 mL) were added to the reaction, which was stirred for 6.5 h at room temperature. Water (250 mL) was then added, and excess acetone was removed under reduced pressure. The reaction solution was extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with water (3 × 200 mL) and then dried over magnesium sulfate. The dry solution was filtered and concentrated, giving 7.72 g of crude product **17**. The $^1$H NMR spectrum of the crude product was consistent with the presence of one *tert*-butyldimethylsilyl group in the molecule.

**(5*R*)- and (5*S*)-9-Deoxy-5,9α-epoxy-PGF$_1$ 15-(*tert*-Butyldimethylsilyl) Ether Methyl Esters 18a and 18b.** A mixture of mercuric acetate (6.43 g) in THF–water (90 mL each) was prepared and stirred at room temperature for 30 min. The crude product **17** (7.71 g) in THF (90 mL) was added, and the resulting mixture was stirred 5 h at room temperature. The reaction was monitored by TLC (40% ethyl acetate–hexane) and when complete was cooled in an ice bath. Sodium borohydride (1.46 g) was added in portions to the stirred solution. Brine (180 mL) was then added, and the mixture was extracted with ether (2 × 200 mL). The combined extracts were washed with water (140 mL) and with brine (140 mL), dried, filtered, and concentrated. The crude extract weighed 7.29 g and was chromatographed over two Merck Lobar size C columns of silica gel. The compound was applied to the column in 25% ethyl acetate–hexane, and the column was eluted with the same solvent mixture. Fractions of 25 mL were collected and were monitored by TLC (40% ethyl acetate–hexane). Fractions 50–120 contained **(5*R*)-9-deoxy-5,9α-epoxy-PGF$_1$ 15-(*tert*-butyldimethylsilyl) ether methyl ester (18a)** and were pooled to give 3.91 g (0.0081 mol, 47% based on **4**) of a viscous oil: $^1$H NMR ($CDCl_3$) δ 5.46 (m, 2 H, CH=CH), 3.70–4.25 (m, 3 H, $H_9$, $H_{11}$, $H_{15}$), 3.63 (s, 3 H, $COOCH_3$), 3.20 (m, 1 H, $H_5$), 2.34, 2.30 (2 t, 2 H, $J$ = 6.0, 6.5 Hz, $CH_2COOCH_3$), 0.87 (m, 12 H, $CH_2CH_3$, $(CH_3)_3$). Fractions 126–202 contained **(5*S*)-9-deoxy-5,9α-epoxy-PGF$_1$ 15-(*tert*-butyldimethylsilyl) ether methyl ester (18b)** and were pooled to give 1.50 g (0.0031 mol, 18% based on **4**) of a viscous oil: $^1$H NMR ($CDCl_3$) δ 5.47 (m, 2 H, CH=CH), 3.60–4.25 (m, 4 H, $H_{5,9,11,15}$), 3.65 (s, 3 H, $COOCH_3$), 2.35 (t, 2 H, $CH_2COOCH_3$), 0.88 (m, 12 H, $CH_2CH_3$, $C(CH_3)_3$).

**(5*R*)-9-Deoxy-5,9α-epoxy-PGF$_1$ 11,15-Bis(*tert*-butyldimethylsilyl) Ether Methyl Ester.** The literature method[11] for the preparation of *tert*-butyldimethylsilyl ethers was used. (5*R*)-9-Deoxy-5,9α-epoxy-PGF$_1$ methyl ester (8.69 g, 0.0235 mol) was converted to the bis(*tert*-butyldimethylsilyl) ether by reaction with *tert*-butyldimethylchlorosilane (10.1 g, 0.0670 mol) and imidazole (8.13 g, 0.134 mol) in DMF (60 mL). After workup, there was obtained 13.57 g (0.0227 mol, 96%) of crude product: $^1$H NMR ($CDCl_3$) δ 5.40 (m, 2 H, CH=CH), 3.55–4.22 (m, 3 H, $H_{9,11,15}$), 3.60 (s, 3 H, $COOCH_3$), 3.15 (m, 1 H, $H_5$), 2.25 (5, 2 H, $CH_2COOCH_3$), 0.88 (m, 21 H, $CH_2CH_3$, 2 $C(CH_3)_3$).

**Hydrolysis of the Bis(*tert*-butyldimethylsilyl) Ether with Tetra-*n*-butylammonium Fluoride. Formation of 7, 19, and (5*R*)-9-Deoxy-5,9α-epoxy-PGF$_1$ 11-(*tert*-Butyldimethylsilyl) Ether Methyl Ester (18a).** The procedure of Sih and Graber[12] was followed. The crude product from the preceding experiment (13.3 g) was dissolved in dry THF (100 mL), cooled in an ice bath, and stirred under $N_2$. A solution of tetra-*n*-butylammonium fluoride (30 mL, 0.75 M, 0.022 mol) was added. The cooling bath was removed, and the reaction was stirred at room temperature. TLC after 3.5 h indicates a mixture containing starting bis(*tert*-butyldimethylsilyl) ether and two more polar spots (probably monosilyl ethers). The reaction was stored overnight in the refrigerator. Additional tetra-*n*-butylammonium fluoride (10 mL) was added to the reaction. After being stirred an additional 6 h at room temperature, the reaction was worked up by addition of brine and extraction with ether. The crude product was chromatographed on a column of silica gel (750 g) packed as a slurry in 10% ethyl acetate–hexane. Elution of the column was begun with the same solvent mixture and was continued with increasing proportions of ethyl acetate until 100% ethyl acetate was used. Fractions of 350 mL were collected. Fractions 26–36 contained 1.21 g of compound **19**, fractions 43–52 contained 0.73 g of **18a** ($^1$H NMR spectrum is identical with that of described in a preceding experiment), and fractions 104–124 contained 5.50 g of **7**.

**(5*R*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 15-(*tert*-Butyldimethylsilyl) Ether Methyl Ester (20a) and (5*R*)-9,15-Dideoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ Methyl Ester (21).** A solution of the silyl compound **18a** (1.20 g, 2.48 mmol) in ethyl acetate (60 mL) with 120 mg of 5% palladium on charcoal was hydrogenated at atmospheric pressure for 55 min. A total of 69.2 mL of hydrogen was consumed. The reaction mixture was then filtered, and the solvent was removed under reduced pressure to give 1.16 g of a colorless oil. The oil was pooled with that from a 0.25-mmol experiment and chromatographed on three series-connected size B Merck Lobar columns. The column was irrigated with 15% ethyl acetate–hexane (1.9 L) followed by 20% ethyl acetate–hexane, and fractions of 25 mL each were collected. Product **20a** was found in fractions 71–96 (912 mg, 69% of theory) as an oil: $R_f$ (30% ethyl acetate–hexane) 0.51; $^1$H NMR ($CDCl_3$) δ 4.06–3.13 (m, 3 H, OCH), 3.68 (s, 3 H, $OCH_3$), 3.13 (m, 1 H, OCH), 2.39, 2.35 (2 t, 2 H, $C_2$ protons, $J$ = 6 Hz), 0.91 (m, 12 H, $CH_3$), $C(CH_3)_3$); mass spectrum [11-(trimethylsilyl) ether], $m/e$ 499.3300 [calcd for $C_{27}H_{51}Si_2O_5$ ($M^+ - C_4H_9$) 499.3275], 541, 525, 485, 424, 409, 345, 327, 313, 215. Eluted second from the column was **21** in fractions 106–120 (171 mg, 17% of theory) as an oil: $R_f$ (30% ethyl acetate in hexane) 0.41; $^1$H NMR ($CDCl_3$) δ 4.05–3.59 (m, 3 H, OCH), 3.68 (s, 3 H, $CH_3$), 3.20 (m, 1 H, OCH), 2.33 (t, 3 H, $C_2$ protons), 0.89 (t, 3 H, $CH_3$, $J$ = 6 Hz); mass spectrum [11-(trimethylsilyl) ether], $m/e$ 426.3179 (calcd for $C_{24}H_{46}SiO_4$ 426.3165), 411, 408, 395, 336, 325 ($M^+ - CH_2CH_2CH_2COOCH_3$), 267.2136 (calcd for $C_{16}H_{31}SiO$ 267.2144).

**(5*S*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 15-(*tert*-Butyldimethylsilyl) Ether Methyl Ester (20b).** A solution of **18b** (1.67 g, 3.5 mmol) in ethyl acetate (200 mL) with platinum oxide (180 mg) was hydrogenated on an atmospheric hydrogenation apparatus for a period of 1.5 h. The reaction was monitored by TLC on silica gel (30% ethyl acetate–hexane). The reaction mixture was then filtered, and the ethyl acetate was removed under reduced pressure. The residue was chromatographed on three series-connected size B Merck columns. The solvent used for elution was 15% ethyl acetate–hexane (600 mL) followed by 20% ethyl acetate–hexane, and fractions with a volume of 20 mL each were collected. The pure product **20b** was obtained in fractions 109–156 (1.134 g, 67% of theory). Product containing a more polar impurity was found in fractions 157–188 (0.101 g). The pure product **20b** was a viscous oil: $R_f$ (30% ethyl acetate–hexane) 0.46; $^1$H NMR (shifts from $Si(CH_3)C(CH_3)_3$, $CDCl_3$) δ 4.04 (m, 1 H, OCH), 3.92–3.43 (m, 3 H, OCH), 2.64 (s, 3 H, $OCH_3$), 2.32 (t, 2 H, $C_2$ protons, $J$ = 5.5 Hz), 0.86 (m, 12 H, $CH_3$, $C(CH_3)_3$).

**(5*R*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 15-(*tert*-Butyldimethylsilyl) Ether 11-Methanesulfonate Methyl Ester (22a).** A solution of **20a** (912 mg, 1.88 mmol) in pyridine (9 mL) under a nitrogen atmosphere was treated with 0.58 mL (7.52 mmol) of methanesulfonyl chloride added dropwise. The reaction was stirred at room temperature for 3 h. The reaction mixture was then poured into an ice water–ether mixture with stirring. The ether layer was separated, and the aqueous was extracted with ether (3×). The combined ether layers were washed with ice-cold 1 N HCl until acidic followed by saturated $NaHCO_3$ and water. The ether layer was dried ($Na_2SO_4$), filtered, and evaporated to give 1.067 g of **22a** as a pale yellow oil; $R_f$ (20% ethyl acetate in hexane) 0.27; $^1$H NMR ($CDCl_3$) δ 4.77 (m, 1 H, $C_{11}$ proton), 3.99–3.57 (m, 2 H, OCH), 3.66 (s, 3 H, $OCH_3$), 3.23 (m, 1 H, OCH), 2.99 (s, 3 H, $SO_2CH_3$), 0.89 (m, 12 H, $CH_3$, C-$(CH_3)_3$).

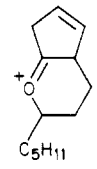
**(5*S*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 15-(*tert*-Butyldimethylsilyl) Ether 11-Methanesulfonate Methyl Ester (22b).** Using the method described above for **22a**, compound **20b** (1.134 g, 2.34 mmol) was converted to the mesylate to give 1.23 g (93% of theory) of **22b** as an oil: $R_f$ (20% acetone in hexane) 0.53; $^1$H NMR ($CDCl_3$) δ 4.67 (m, 1 H, $C_{11}$ proton), 4.08 (m, 1 H, OCH), 3.86–3.45 (m, 2 H, OCH), 3.63 (s, 3 H, $OCH_3$), 2.96 (s, 3 H, $SO_2CH_3$), 2.21 (t, 2 H, $C_2$ protons, $J$ = 7 Hz), 0.83 (m, 12 H, $CH_3$, $C(CH_3)_3$).

**(5*R*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 11-Methanesulfonate Methyl Ester (23a).** A solution of **22a** (1.047 g, 1.86 mmol) in 15 mL of an acetic acid–water–tetrahydrofuran–1 N HCl (27 mL/9 mL/9 mL/24 drops) mixture was stirred at room temperature for 2 h. The solution was then worked up by the addition of brine (20 mL) plus water (20 mL). The resulting solution was extracted well with ethyl acetate (4×). The pooled ethyl acetate layers were then washed with water, saturated $NaHCO_3$, water, and brine. The organic layers were then dried ($Na_2SO_4$), filtered, and evaporated to give 963 mg of an oil. The oil was chromatographed on three size B Merck Lobar columns by using 20% acetone–hexane to elute the product. Fractions with a volume of 25 mL each were collected. The product **23a** was obtained in fractions 71–96 (678 mg, 81% of theory) as an oil: $^1$H NMR ($CDCl_3$) δ 4.79 (m, 1 H, $C_{11}$ proton), 3.97–3.41 (m, 2 H, OCH), 3.65 (s, 3 H, $OCH_3$), 3.23 (m, 1 H, OCH), 3.00 (s, 3 H, $SO_2CH_3$), 0.90 (t, 3 H, $CH_3$, $J$ = 5.5 Hz).

**(5*S*)-9-Deoxy-5,9α-epoxy-13,14-dihydro-PGF$_1$ 11-Methanesulfonate Methyl Ester (23b).** Using the method described above for the preparation of **23a**, the silyl group was removed from **22b** (1.23 g, 2.2 mmol). The crude product was purified by column chromatography on three series-connected size B Merck Lobar columns. Elution was with 30% ethyl acetate–hexane (650 mL), 50% ethyl acetate–hexane (1.9 L), and 75% ethyl acetate–hexane. Fractions with a volume of 25 mL each were collected. The product (**23b**) was obtained as a solid in fractions 97–120 (0.885 g, 84% of theory). Recrystallization of a small portion from ether–pentane gave white crystals: mp 48–49 °C; $^1$H NMR ($CDCl_3$) δ 4.74 (m, 1 H, $C_{11}$ proton), 4.10 (m, 2 H, OCH), 3.92–3.37 (m, 1 H, OCH), 3.65 (s, 3 H, $OCH_3$), 3.00 (s, 3 H, $SO_2CH_3$), 0.90 (t, 3 H, $CH_3$, $J$ = 5 Hz).

Anal. Calcd for $C_{20}H_{40}O_7S$: C, 58.90; H, 8.99. Found: C, 59.06; H, 9.08.

**(5*R*,15*S*)-9,11,15-Trideoxy-5,9α:11β,15-diepoxy-PGF$_1$ Methyl Ester (24a). (A) Via Thermal Cyclization.** A solution of the mesylate **23a** (574 mg, 1.28 mmol) in benzene (230 mL) was heated at reflux temperature under a nitrogen atmosphere overnight (~16 h). The reaction was cooled to room temperature and the benzene removed under reduced pressure. The residue was chromatographed on three size B Merck Lobar columns. The columns were irrigated with 5% acetone–hexane (125 mL) followed by 10% acetone–hexane. Fractions with a volume of 25 mL each were collected. The product (**24a**) was obtained in fractions 26–28 (300 mg, 66% of theory) as an oil: IR ($CHCl_3$) $\nu_{C=O}$ 1730, $\nu_{CO}$/other 1220, 1130, 1110, 1050 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.18 (m, 1 H, OCH), 3.92 (m, 1 H, OCH), 3.65 (m, 1 H, OCH), 3.65 (s, 3 H, $OCH_3$), 3.17 (m, 1 H, OCH), 0.89 (t, 3 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 173.96, 79.15, 76.26, 72.92, 70.90, 51.29, 40.97, 39.94, 37.59, 35.88, 34.04, 31.88, 26.32, 25.74, 25.48, 22.67, 22.18, 21.11, 19.75, 14.04; mass spectrum, $m/e$ 352.2609 (calcd for $C_{21}H_{36}O_4$ 352.2613), 334 ($M^+ - H_2O$), 321 ($M^+ - OCH_3$), 303 ($M^+ - OCH_3 - H_2O$), 281 ($M^+ - C_5H_{11}$), 263 ($281^+ - H_2O$), 193.1584 (see structure I; calcd for $C_{13}H_{21}O$ 193.1592).



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**(B) Via Base-Catalyzed Cyclization.** Four drops of a 23.6% suspension in oil of potassium hydride was placed in a 15-mL, round-bottomed flask equipped with a $N_2$ inlet and was rinsed with dry tetrahydrofuran (THF) to remove excess oil. A solution of **23a** (0.026 g, 0.08 mmol) in THF (5 mL) was added to the potassium hydride. The resulting mixture was stirred under $N_2$ at room temperature. The reaction was complete (i.e., no **10a** remained as detected by TLC in 30% acetone–hexane) within 2.5 h. Half-saturated brine solution was added, and the reaction solution was extracted with ether (3×). The combined ether extracts were washed with water, dried ($Na_2SO_4$), filtered, and concentrated. The crude product was chromatographed over a Merck size A Lobar column of silica gel by using 10% ethyl acetate–hexane (fractions 1–13, 6 mL each), 20% ethyl acetate–hexane (fractions 14–32), and finally 50% ethyl acetate–hexane. The main product of the reaction (5 mg) was found in fractions 10–13 and had $^1$H NMR and mass spectra identical with those for **24a** obtained by thermal cyclization.

**(5*S*,15*S*)-9,11,15-Trideoxy-5,9α:11β,15-diepoxy-PGF$_1$ Methyl Ester (24b). (A) Via Thermal Cyclization.** A solution of the mesylate **23b** (774 mg, 1.72 mmol) in benzene (300 mL) was heated at reflux temperature under a nitrogen atmosphere for 21 h. The reaction was cooled and the benzene removed under reduced pressure. The residue was chromatographed on three size B Merck Lobar columns. Elution was with 5% acetone–hexane (325 mL) followed by 10% acetone–hexane. Fractions with a volume of 25 mL each were collected. The product (**24b**) was obtained in fractions 35–38 (497 mg, 82% of theory) as an oil: $^1$H NMR ($CDCl_3$) δ 4.27 (m, 2 H, OCH), 3.96–3.42 (m, 2 H, OCH), 3.65 (s, 3 H, $OCH_3$), 2.35 (t, 2 H, $C_2$ protons, $J$ = 7 Hz), 0.89 (t, 3 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 173.89, 72.00, 71.75, 51.33, 40.55, 37.67, 32.89, 32.59, 31.96, 26.32, 25.63, 22.68, 21.38, 14.04; mass spectrum, $m/e$ 352.2623 (calcd for $C_{21}H_{36}O_4$ 352.2613), other peaks similar to those for **24a**.

**(B) Via Base-Catalyzed Cyclization.** A solution of **23a** (0.032 g, 0.07 mmol) in THF (3 mL) was added to potassium hydride (3 drops of a 23.6% suspension in oil, rinsed with THF to remove excess oil) under $N_2$. The resulting mixture was stirred at room temperature, and the reaction was monitored by TLC (30% acetone–hexane, 50% ethyl acetate–hexane). The starting material was consumed within 2.5 h. The reaction was worked up and chromatogrpahed as described previously for **24a**. There was obtained as the main product (6 mg) a compound having $^1$H NMR and mass spectra identical with those of **11b** obtained by thermal cyclization. A second reaction product (5 mg) was more polar than **24b** but less polar than the starting material **23b**. The $^1$H NMR spectrum of this compound indicated that a mesylate functionality (δ 3.0) remained in the molecule.

**(5*R*,15*S*)-9,11,15-Trideoxy-5,9α:11β,15-diepoxy-PGF$_1$ (25a).** A solution of **24a** (300 mg, 0.85 mmol) in methanol (7 mL) was treated with 4.4 mL of 0.5 N NaOH. Another 3 mL of methanol was added. The reaction was stirred at room temperature for ~20 h. The methanol was partially removed under reduced pressure, and the reaction mixture was acidified with 2 M $NaHSO_4$. The aqueous layer was then extracted with ethyl acetate (4×). The pooled ethyl acetate layers were combined, washed with half-saturated brine, dried ($Na_2SO_4$), filtered, and evaporated to give 300 mg of an oil which solidified. The solid was recrystallized twice from pentane to give **25a** as a white solid: mp 80–81.5 °C; $^1$H NMR ($CDCl_3$) δ 4.18, 3.93, 3.78, 3.20 (four multiplets, 4 H, OCH), 2.35 (m, 2 H, $C_2$ protons), 0.89 (t, 3 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 179.15, 79.26, 76.39, 73.03, 71.05, 40.85, 39.90, 37.61, 35.68, 34.04, 31.93, 31.83, 26.29, 25.72, 25.42, 22.68, 22.14, 20.93, 19.68, 14.04; mass spectrum, $m/e$ 338.2465 (calcd for $C_{20}H_{34}O_4$ 338.2457), 320 ($M^+ - H_2O$), 267 ($M^+$

$-C_5H_{11}$), 251 [$M^+ - (CH_2)_3CO_2H$], 249 ($267^+ - H_2O$), 231 ($249^+ - H_2O$), 193.

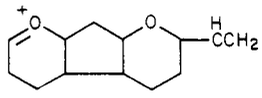
Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.16; H, 10.40.

**(5*S*,15*S*)-9,11,15-Trideoxy-5,9α:11β,15-diepoxy-PGF$_1$ (25b).** Hydrolysis of the ester **24b** (487 mg, 1.38 mmol) by use of the procedure previously described above for preparation of **25a** gave 480 mg of a solid. The solid was recrystallized twice from pentane to give **25b** as white crystals: mp 73–74.5 °C; 353 mg (75% of theory); $^1$H NMR ($CDCl_3$) δ 4.27 (m, 2 H, OCH), 3.68 (m, 2 H, OCH), 2.37, 2.35 (t, 2 H, $C_2$ protons, $J$ = 6 Hz), 0.89 (t, 3 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 178.60, 72.17, 71.87, 71.74, 40.54, 40.46, 37.59, 33.88, 32.47, 31.91, 26.18, 25.60, 22.68, 21.24, 14.05; mass spectrum, $m/e$ 338.2469 (calcd for $C_{20}H_{34}O_4$ 338.2457), other peaks similar to those in the spectrum of **25a**.

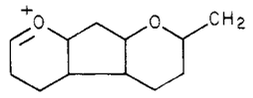
Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.16; H, 10.38.

**(2*R*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-5-(Decahydro-7-pentyl-2*H*-cyclopenta[1,2-*b*:4,3-*b*']dipyran-2-yl)-2-pentanone (26a).** A solution of **25a** (206 mg, 0.608 mmol) in ether (5 mL) was chilled to 0 °C in an ice bath under a nitrogen atmosphere. The solution was treated by the dropwise addition of methyllithium–lithium bromide complex (1.3 M in ether, 1.0 mL, 1.3 mmol) with stirring. This mixture was stirred at ice-bath temperature for 30 min and then at room temperature for 1.5 h. The reaction was quenched by being poured into a solution of saturated ammonium chloride and ether. The aqueous layer was separated and acidified to pH ~2 with 2 M $NaHSO_4$ and extracted with ether (4 × 50 mL). The combined ether layers were washed with saturated $NaHCO_3$ solution and water, dried over anhydrous sodium sulfate, filtered, and evaporated at reduced pressure to give an oil (173 mg). The product was chromatographed on one size B Merck column with 675 mL of 5% acetone–hexane followed by 10% acetone–hexane to elute the product. The product (**26a**) was obtained in fractions 14–16 (110 mg, 54% of theory) as an oil: IR ($CHCl_3$) $\nu_{C=O}$ 1710, $\nu_{CO}$/other 1220, 1040, 895, 850, 840 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 4.18, 3.92, 3.72, 3.17 (4 m, 4 H, OCH), 2.42 (m, 2 H, $CH_2C(O)$), 2.10 (s, 3 H, $C(O)CH_3$), 0.89 (t, 3 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 216.3, 79.17, 76.43, 72.97, 70.93, 43.73, 40.99, 39.92, 37.58, 35.88, 31.88, 29.76, 26.30, 25.73, 25.45, 22.67, 22.16, 20.01, 19.72, 14.04; mass spectrum, $m/e$ 336.2653 (calcd for $C_{21}H_{36}O_3$ 336.2664), 318 ($M^+ - H_2O$), 265 ($M^+ - C_5H_{11}$), 251 [$M^+ - (CH_2)_3C(O)CH_3$], 247 ($265^+ - H_2O$), 229 ($247^+ - H_2O$), 193.

**(2*S*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-5-(Decahydro-2,7-diphenyl-2*H*-cyclopenta[1,2-*b*:4,3-*b*']dipyran-2-yl)-2-pentanone (26b).** By use of the procedure described above for the preparation of **26a**, the acid **25b** (321 mg, 0.95 mmol) was converted to the methyl ketone and gave 242 mg of an oil. The crude product was chromatographed on one size B Merck Lobar column. Elution was with 20% ethyl acetate–hexane (1.2 L) followed by 50% ethyl acetate–hexane. Fractions with a volume of 25 mL each were collected. The product **26b** was obtained in fractions 23–34 (175 mg, 55% of theory) as an oil: $^1$H NMR ($CDCl_3$) δ 4.26 (m, 2 H, OCH), 3.65 (m, 2 H, OCH), 2.46 (m, 2 H, $CH_2C(O)$), 2.11 (s, 3 H, $C(O)CH_3$), 0.88 (t, 3 H, $CH_3$, $J$ = 5 H); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 216.17, 72.01, 71.70, 43.49, 40.52, 37.59, 32.60, 31.95, 29.76, 26.32, 25.60, 22.66, 21.38, 20.35, 14.03; mass spectrum, $m/e$ 336.2667 (calcd for $C_{21}H_{36}O_3$ 336.2664), 318 ($M^+ - H_2O$), 265 ($M^+ - C_5H_{11}$), 251 [$M^+ - (CH_2)_3C(O)CH_3$], 247 ($265^+ - H_2O$), 233 ($251^+ - H_2O$), 229 ($247^+ - H_2O$), 207 (structure II), 193 (structure III).



II



III

**(2*R*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-Decahydro-2,7-diphenyl-2*H*-cyclopenta[1,2-*b*:4,3-*b*']dipyran (27a).** A solution of the methyl ketone **26a** (99 mg, 0.29 mmol) in diethylene glycol (5 mL) was treated with potassium hydroxide (67 mg, 1.2 mmol) and 95% hydrazine (45 mg, 1.35 mmol) under a nitrogen atmosphere. The solution was heated at 100 °C for 35 min and then at 200 °C for 7 h. After the mixture cooled to room temperature, water was added, and the resulting mixture was extracted well (4×) with ether. The pooled ether layers were dried ($Na_2SO_4$), filtered, and evaporated to give 165 mg of an amber oil. The oil was chromatographed on one size B Merck Lobar column. The product was eluted with 2% ethyl acetate–hexane, and fractions with a volume of 25 mL each were collected. The product (**27a**) was obtained in fractions 11–13 (28 mg, 30% of theory) as a colorless oil: $^1$H NMR ($CDCl_3$) δ 4.19, 3.93, 3.76, 3.15 (4 m, 4 H, OCH), 0.89 (t, 6 H, $CH_3$, $J$ = 5.5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 79.22, 76.96, 73.03, 70.99, 41.06, 40.04, 37.62, 36.65, 31.93, 26.37, 25.76, 25.48, 25.28, 22.68, 22.27, 19.75, 14.05; mass spectrum, $m/e$ 322.2877 (calcd for $C_{21}H_{38}O_2$ 322.2871), 251 ($M^+ - C_5H_{11}$); 233 (m*, $251^+ - H_2O$), 215 (m*, $233^+ - H_2O$), 193.

**(2*S*,4a*R*,4b*R*,7*S*,8a*S*,9a*S*)-Decahydro-2,7-dipentyl-2*H*-cyclopenta[1,2-*b*:4,3-*b*']dipyran (27b).** The methyl ketone **26b** (165 mg, 0.49 mmol) was reduced in the manner described for the preparation of **27a** to yield an oil which was chromatographed on one size B Merck Lobar column. Elution was with 5% ethyl acetate–hexane (700 mL) followed by 40% acetone–hexane, and fractions with a volume of 25 mL each were collected. The product (**27b**) was obtained in fractions 8 and 9 (65 mg, 41% of theory) as an oil: $^1$H NMR ($CDCl_3$) δ 4.30 (m, 2 H, OCH), 3.65 (m, 2 H, OCH), 0.89 (t, 6 H, $CH_3$, $J$ = 5 Hz); $^{13}$C FT NMR (ppm from $Me_4Si$, $CDCl_3$) 72.07, 71.84, 40.57, 37.70, 32.65, 31.96, 26.33, 25.64, 22.69, 21.40, 14.05; mass spectrum, $m/e$ 322.2884 (calcd for $C_{21}H_{38}O_2$ 322.2871), other peaks similar to those obtained for **27a**.

**Registry No.** **4**, 50889-17-3; **5**, 69224-12-0; **5** bis(TMS), 70962-16-2; **6**, 69171-24-0; **6** bis(TMS), 69171-25-1; **7**, 68869-80-7; **7** α-phenylseleneo derivative bis(THP) isomer 1, 74397-91-4; **7** α-phenylseleneo derivative bis(THP) isomer 2, 74397-92-5; **7** bis(TMS), 70962-21-9; **8**, 68869-81-8; **8** bis(TMS), 70962-20-8; **9**, 68869-82-9; **9** bis(TMS), 74397-93-6; **10**, 68869-83-0; **10** bis(TMS), 74410-84-7; **11**, 70962-14-0; **12**, 70962-15-1; **13**, 74397-94-7; **13** bis(TMS), 74397-95-8; **13** bis(THP), 74397-96-9; **14**, 69171-30-8; **14** bis(TMS), 74411-05-5; **15**, 69171-29-5; **15** bis(TMS), 69171-38-6; **16**, 69171-34-2; **17**, 74397-97-0; **18a**, 74397-98-1; **18b**, 74397-99-2; **19**, 74398-00-8; **20a**, 74398-01-9; **20a** (11-(trimethylsilyl) ether), 74398-02-0; **20b**, 74431-19-9; **21**, 74398-03-1; **21** (11-TMS), 74398-04-2; **22a**, 74398-05-3; **22b**, 74398-06-4; **23a**, 74398-07-5; **23b**, 74398-08-6; **24a**, 74398-09-7; **24b**, 74398-10-0; **25a**, 74398-11-1; **25b**, 74398-12-2; **26a**, 74398-13-3; **26b**, 74398-14-4; **27a**, 74398-15-5; **27b**, 74398-16-6; (5*R*)-9-deoxy-5,9α-epoxy-PGF, 11,15-bis(*tert*-butyldimethylsilyl) ether methyl ester, 74398-17-7.