Synthesis of 5-Fluoroprostacyclin

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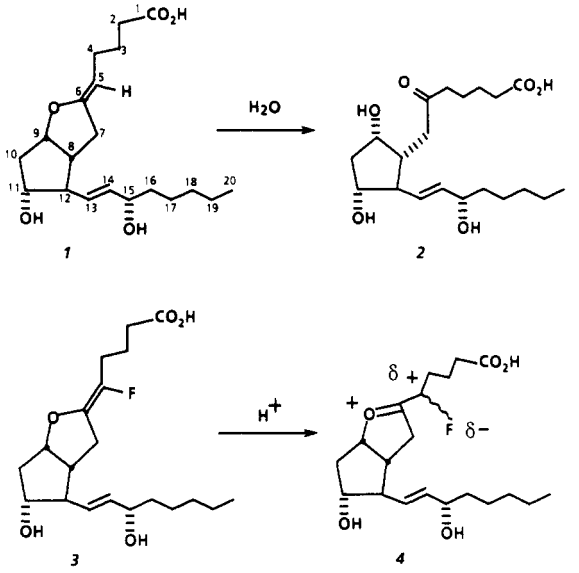
Received August 22, 1986

Protected prostacyclin derivatives were reacted with perchloryl fluoride in methanol. The resultant 5-fluoro-6-methoxy derivatives were separated and identified. Pyrolysis of the individual isomers in the presence of magnesium triflate led to 5(*R*)- or 5(*S*)-fluoro-Δ^6-PGI_1 derivatives. The 5*R* isomers also produced some 5(*E*)-fluoro-PGI_2 while the 5*S* isomers produced a lesser amount of 5(*Z*)-fluoro-PGI_2. A mechanism is proposed to explain this stereospecificity. The stereoelectronic relationship between a carbon–fluorine bond and an adjacent carbonium ion is considered. This is the first synthesis of 5(*E*)-fluoro-PGI_2, which is a stable, highly potent prostacyclin analogue. The efficiency of the synthesis was improved by recycling the 5(*R*)-fluoro-Δ^6 product.

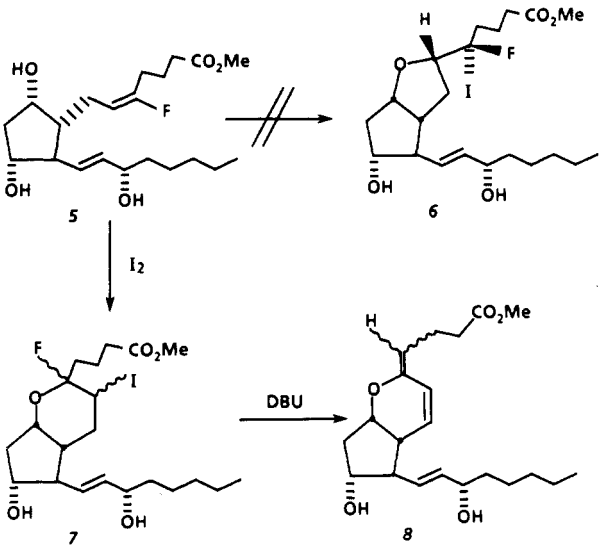
Prostacyclin (**1**) is the most potent natural inhibitor of platelet aggregation known.[1] However, the facile hydration of **1** to the relatively inactive 6-keto-$PGF_{1\alpha}$ (**2**) (Scheme I) limits its potential clinical utility. Several reviews describe prostacyclin derivatives in which an electron-withdrawing group is attached to the 5- or 7-carbon atom to achieve some chemical stabilization.[2] We felt that a fluorine atom would be the ideal group for such a purpose due to both the electron-withdrawing potency of the fluorine atom and the similarity in size to the proton being replaced.[2a,3,4] In this report we describe the first synthesis of 5-fluoroprostacyclin (**3**) in which hydration is inhibited because of the inductive destabilization of the resulting oxonium ion, **4**. Fried[5] has suggested a possible route to **3** via an iodo ether forming cyclization reaction of a 5-fluoro-$PGF_{2\alpha}$ derivative, **5**, to form **6**, followed by elimination of hydrogen iodide with base and deprotection to provide **3**. This method was shown not to follow the desired path by Hayashi,[6] who demonstrated that **5** when treated under varying conditions provided **7** rather than **6** (Scheme II). Treatment of **7** with base provided only the diene **8**. No trace of **6** was formed; thus 5-fluoroprostacyclin could not be synthesized by this route.[7]

It has recently been suggested that vinyl fluorides are important synthetic targets, even though methods for synthesis are limited.[8-10] Fluoro enol ethers in general have only recently been documented in the literature,[10] even though preparation of α-fluoro ketones by electrophilic fluorination presumably could go through this type of intermediate.[11,12] During the course of our work, we have not only achieved the synthesis of an important fluorinated enol ether but have obtained some insights as to why these compounds are so elusive.

Scheme I



Scheme II



Chemistry

Perchloryl fluoride is a useful fluorinating agent that has been used to fluorinate enol ethers to provide α-fluoro ketones after hydrolysis.[13,14] We have found perchloryl

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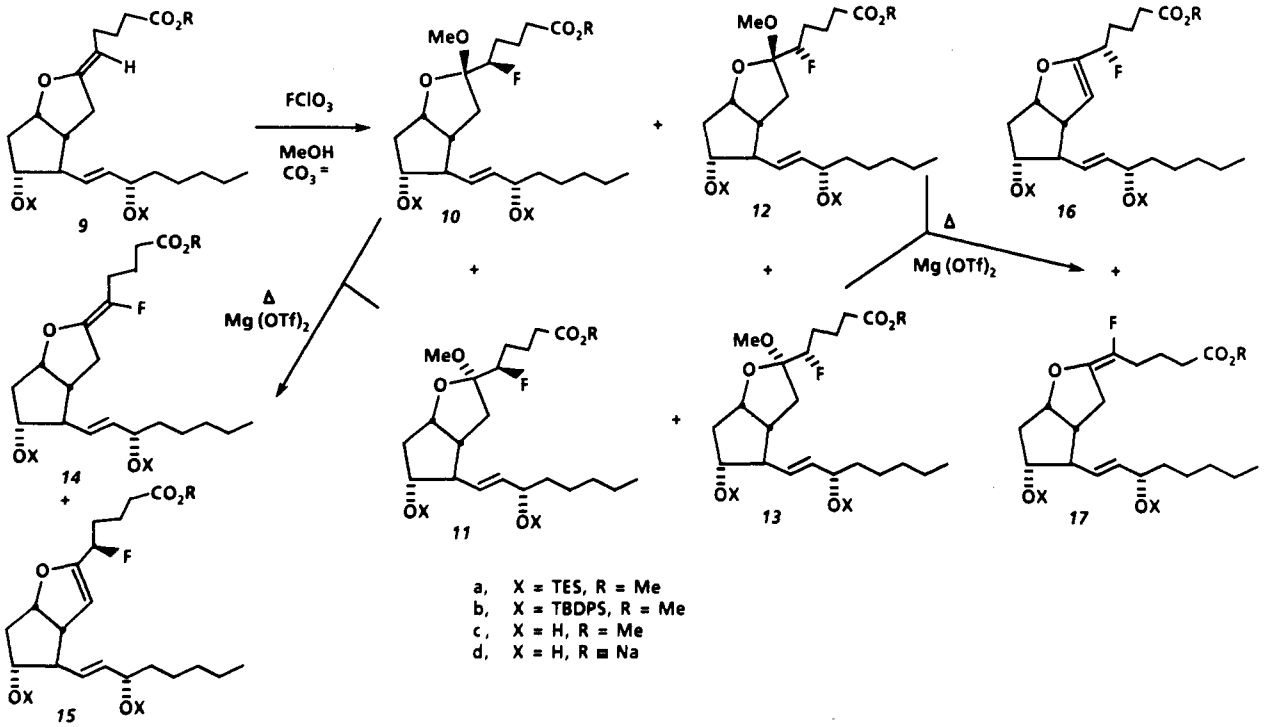
Scheme III



fluoride to be a convenient reagent for laboratory use since condensation permits measurement of a liquid volume. After many attempts, however, we were unable to obtain a fluorination of PGI_2 derivatives to prepare the 5-fluoro analogue directly. We then discovered that if an alcohol such as methanol is used as the solvent for the reaction and a base such as sodium or potassium carbonate is present to consume the acid formed, a mixture of 5-fluoro-6-methoxy derivatives is produced (Scheme III). While the unprotected methyl ester **9c** could be used for this reaction, it was necessary to protect the 11- and 15-hydroxyl groups both for ease of isomer separation and for the subsequent steps. It was found advantageous to use a protected derivative such as **9a** or **9b** in the fluoromethoxylation to minimize byproducts. Our early experiments and structural studies were done with triethylsilyl (TES) protected PGI_2 methyl ester (**9a**); subsequently we found some practical advantages in using the more stable *tert*-butyldiphenylsilyl[15] (TBDPS) derivative **9b**. These starting materials were prepared from $PGF_{2\alpha}$ methyl ester by adaptation of the methods of Johnson[16] and Whittaker.[17] Perchloryl fluoride was measured as a liquid and added slowly to avoid hazardous concentrations. The desired fluoromethoxylation takes place at temperatures as low as 15 °C but we have found more consistent results if the reaction is run without any cooling bath. While we are not certain of the exact route the reaction follows, there may be some reaction of perchloryl fluoride with methanol to produce acid faster than it can be consumed by the solid base used to neutralize the acid as it is formed. In some runs at 15 °C a substantial amount of **19a** resulting from the simple addition of methanol and a significant amount of 7-fluoro-6-methoxy isomers **21a**, **22a**, and **23a** was obtained. All of these byproducts can be explained by acidic methanolysis or isomerization of the Δ^5 bond to Δ^6 via oxonium ion **18a** before fluorination (Scheme IV). The use of methoxide as base resulted in consumption of the reagent with very little product formed. Using dry methanol and potassium carbonate and a reaction temperature in the 25–32 °C range, we have not observed these byproducts. An even better method is to employ cesium carbonate which is much more soluble in methanol, permitting the reaction to be run at 15 °C with slightly improved isomer selectivity.

The abundance of **10a**, **11a**, **12a**, and **13a** was roughly 6:2:3:1. When 7-fluoro isomers were obtained the relative order of abundance was **21a** > **22a** > **23a**. Although it may have been produced, we were not able to isolate the fourth 7-fluoro isomer, **24a**. When 7-fluoro isomers were not present, **12a** was easily separated by chromatography as a distinctly slower moving material. When present, **21a** moved just barely faster on the column than **12a**, but with care it too could be obtained pure. The separation of **10a**, **11a**, and **13a** was more troublesome. These isomers have very similar R_f values on TLC, with multiple development required for separation of the individual spots. However, the use of different solvent systems and adsorbents permitted the isolation of each pure isomer. The remaining 7-fluoro isomers, **22a** and **23a**, when present could be separated after removing the non-fluorinated materials.

We found that it was possible to effect a pyrolytic elimination of methanol from **10a** and **12a** by refluxing in *tert*-butylbenzene (ca. 170 °C) for 20–40 min. The other isomers were slow to eliminate under these conditions and even **10a** and **12a** gave erratic results with the extent of elimination varying widely in different runs. We suspected that a catalyst must be present in some batches. Since we had used Florisil chromatography in a number of the separations, it was possible that magnesium ions could be present as a catalyst. Since magnesium sulfate[16,18] has been used as a catalyst for dehydration of 6-keto-$PGF_{1\alpha}$ derivatives, we added a small amount to the pyrolysis mixture but again obtained erratic results. Recently, magnesium triflate has been used as a Lewis acid catalyst.[19] We found

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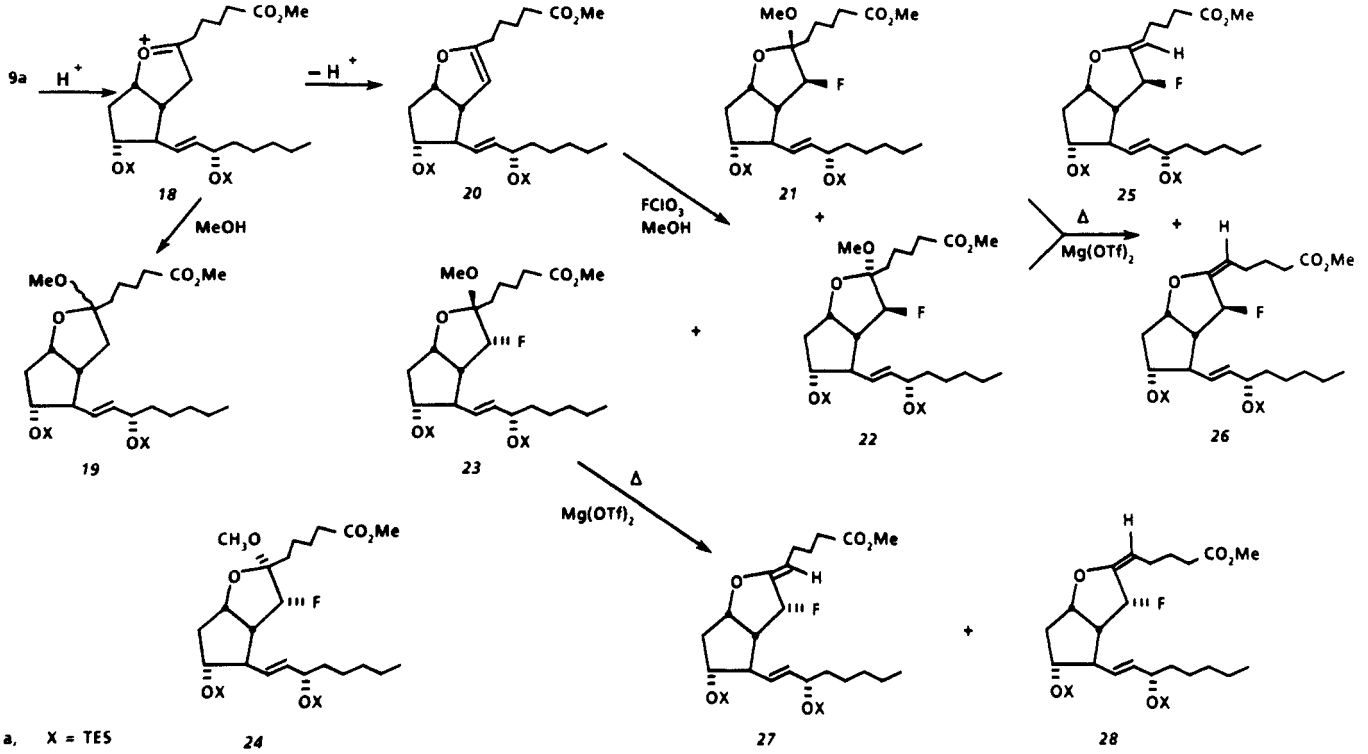
Scheme IV



that this reagent serves as an efficient catalyst. Thus, we were able to lower the temperature required for the elimination (refluxing xylene) and obtained reproducible results with different batches. Under these conditions, isomers **11a**, **13a**, **21a**, **22a**, and **23a** also provided elimination products, although longer heating times were required. Magnesium triflate, which can be handled in air without problems, functions as an efficient Lewis acid even in the presence of a weak base such as 2-picoline or 2,6-lutidine. This is doubtless due to the great affinity the magnesium ion has for oxygen. The presence of base helps to avoid acid-catalyzed decomposition of products. The main decomposition products we have observed appear to have suffered loss of the 15-silyloxy group to provide a mixture of conjugated dienes. With 2-picoline or 2,6-lutidine present and care taken not to drive the reaction beyond completion (about 90% to completion is optimal), decomposition is not a serious problem even with isomers that require long reflux times or when high boiling solvents (up to 190 °C) are used.

Both **10a** and **11a** gave a mixture of products consisting of about 6% of **14a**, 70% of **15a**, and the respective starting material, while **12a** and **13a** produced only **16a**. The pyrolysis of all three 7-F isomers gave only 7-fluoro-Δ^5 derivatives, with no evidence found for the presence of any 7-fluoro-Δ^6 compounds. The pyrolysis of the 7β-F isomers **21a** and **22a** to give a mixture of 5(Z)- and 5(E)-Δ^5 compounds, **25a** and **26a** was slower than that of any of the 5-fluoro-6-methoxy isomers. The pyrolysis of the 7α-F isomer **23a** was considerably faster than that of the 7β-F isomers and only slightly slower than that of the endo 5-fluoro-6-methoxy isomers **10a** and **12a**. In this case we were able to separate the 5Z (**27a**) and 5E (**28a**) isomers.

Two syntheses of 7(S)-fluoroprostacyclin have been described.[2f,20] The ^{1}H NMR evidence for the 5Z configuration was presented by Kurozumi et al.[2f] Our results are consistent with their assignment. The synthesis of 7(R)-fluoroprostacyclin has also been reported.[21]

Being convinced that the 5-fluoro-Δ^5 product we obtained, **14a**, was indeed the desired 5E structure and encouraged by preliminary biological results, we sought methods for improving the overall yield. One of the methods we considered was recycling the endocyclic olefin material, **15a**. When **15a** was dissolved in dry methanol and a small amount of pyridinium tosylate was added, the triethylsilyl groups were cleaved in about 20 min on the basis of a TLC analysis and methanol added slowly to the double bond overnight to produce a mixture of **10c** and **11c** that could be silylated and then pyrolyzed.

Since the loss of the silyl groups made this process inefficient, we tried the more stable *tert*-butyldiphenylsilyl protecting group.[15] Quite comparable results were obtained in the fluoromethoxylation reaction, which again provided a mixture of the four isomers. As before, isomer **12b** was easily separated by chromatography. Isomer **13b** was not completely separated from **10b** and **11b** but it was concentrated in the first part of this major fraction. These early fractions were conveniently equilibrated with camphorsulfonic acid in anhydrous methanol to provide extensive isomerization of **13b** to **12b**, which is readily separated. In this manner it was easy to obtain a mixture of **10b** and **11b** suitable for pyrolysis to **14b** and **15b**. After chromatographic separation **15b** could be recycled to a mixture of **10b** and **11b** by camphorsulfonic acid in dry methanol.[22] No noticeable loss of protecting groups was observed and chromatography was not required before pyrolysis.

We also hoped to increase the proportion of Δ^5 product in the pyrolysis. Since this was the minor product we

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(22) In this case, pyridium tosylate can be used as well but the reaction can require 3 or 4 days for completion.

Table I. ^{13}C NMR Data for Triethylsilyl-Protected Esters

	carbon									
no.	3	4	5	6	7	8	9	10	11	12
					Chemical Shifts					
10a	21.4	29.9	93.1	110.4	39.2	45.3	82.5	41.2	78.7	56.2
11a	21.3	29.8	92.3	111.2	34.2	45.2	82.4	42.8	77.6	54.8
12a	21.2	29.9	91.7	110.9	37.1	45.0	81.7	41.3	78.5	55.9
13a	21.3	29.3	94.9	110.0	35.9	45.2	82.4	42.6	77.8	55.1
15a	20.5	32.1	87.7	154.3	101.7	57.9	83.7	42.8	76.4	50.6
16a	20.5	32.2	87.9	154.3	102.0	58.1	83.8	42.9	76.4	50.7
14a	21.8	26.9	142.8	141.9	29.7	44.8	84.0	41.8	77.6	54.4
17b[a]	22.0	28.3	137.5	137.7	30.6	44.7	85.1	41.1	78.5	54.5
21a	25.1	22.9	32.2	106.2	100.0	51.9	80.2	40.5	79.1	54.4
22a	25.2	23.7	29.3	112.9	97.9	51.7	80.5	42.5	76.9	51.1
23a	25.2	23.4	28.5	112.5	93.0	48.5	78.4	41.4	78.3	46.4
25a	24.8	24.8	103.8	153.7	94.9	51.6	82.6	41.7	77.6	50.7
26a	26.7	25.7	103.3	154.6	91.2	51.9	81.9	41.4	77.6	51.0
27a	24.5	24.8	100.9	153.9	90.6	47.6	81.6	42.1	77.5	47.7
28a	25.5	25.6	102.5	154.8	88.4	48.3	81.3	41.7	77.6	47.6
					C–F Coupling Constants					
10a		21	177	22						
11a		21	179	22						
12a		21	179	22						
13a		21	177	24						
15a	4	22	169	22	6					
16a	4	25	169	22	6					
14a		25	222	48						
17b[a]	2	25	235	12						
21a				15	197	22	8			
22a			5	25	182	22			2	10
23a				25	190	19				13
25a		9	11	15	176	22				6
26a	3	4	10	14	177	21			2	7
27a	2	4	7	19	188	18	3			7
28a			7	17	186	19				5

[a] *tert*-Butyldiphenylsilyl protected.

sought conditions that would be less selective, namely, higher temperature. Since the major problem we had encountered at higher temperatures was the loss of the 15-silyloxy group, the more bulky and more stable *tert*-butyldiphenylsilyl group was advantageous for these conditions as well. Increasing the temperature from 140 °C (xylene) to 170 °C (*tert*-butylbenzene) did increase the proportion of Δ^5 material from 8% to 14%. Going to even higher temperatures (190 °C, *tert*-butyltoluene) gave a slightly better ratio (18%). When these same conditions (190 °C) were applied to **12b** still no **14b** could be detected but 8% of the elimination product was the isomeric **17b**.

Structure Elucidation

All four possible 5-fluoro-6-methoxy-PGI_1 isomers and three of four possible 7-fluoro-6-methoxy-PGI_1 isomers were isolated in the triethylsilyl series. The isomers are most easily distinguished by careful inspection of the ^{13}C NMR spectra. The presence of fluorine could be readily ascertained from the characteristic ^{13}C NMR chemical shifts of the carbons bearing fluorine and the one- and two-bond C–F couplings. The signals of aliphatic methine carbons –CHF– were between δ 85 and 100, with $J_{CF} \simeq$ 165–195 Hz and $J_{CCF} \simeq$ 20 Hz. In this series of compounds, the δ 85–100 region did not contain signals from other types of carbons and thus the number of fluorinated compounds in mixtures could be ascertained, and the individual isomers could usually be identified. In the 5-fluoro-Δ^5 compounds the olefinic carbons bearing fluorine had signals near δ 140 with $J_{CF} \simeq$ 220–240 Hz, $J_{CCF} \simeq$ 20 Hz, and $J_{C=CF} \simeq$ 12 or 48 Hz. Table I lists the ^{13}C NMR chemical shifts and carbon–fluorine coupling constants for carbons 3 through 12 of the triethylsilyl-protected esters.

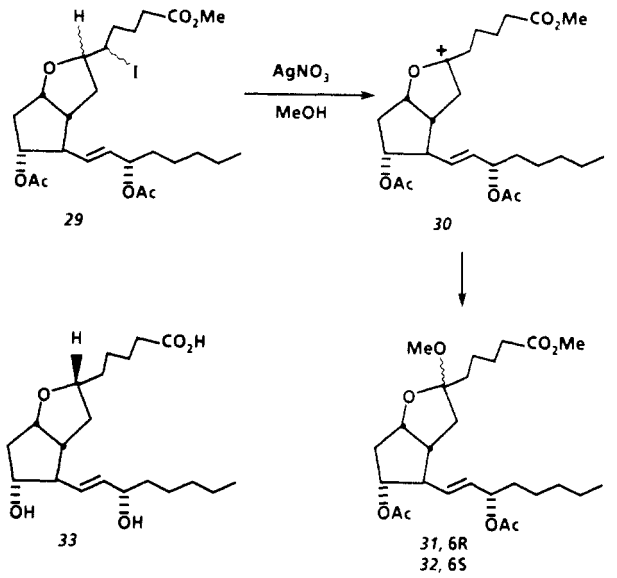
The position of the fluorine (C-5 or C-7) in these prostacyclin derivatives was determined from the chemical shifts of the adjacent carbons, which were identified by the two-bond C–F coupling of about 20 Hz. In the 6-methoxy-PGI_1 compounds, **10–13** and **21–23**, a 20-Hz splitting of the C-6 ^{13}C NMR signal near δ 110 confirmed the presence of fluorine on C-5 or C-7. With the fluorine on C-5, a two-bond C–F coupling to C-4, which has a chemical shift of about δ 30, can be observed. If the fluorine is on C-7, the C-8 signal near δ 50 is split. A 7-F also has observable three- and four-bond C–F couplings to other ring carbons. The magnitudes of these long-range couplings depend on the configuration of the fluorine and the conformation of the bicyclic ring system, which in turn depends on the configuration at C-6.

The ^1H NMR data were not as useful as the ^{13}C NMR data for characterizing these compounds and establishing the composition of mixtures. However, some of the isomers had characteristic 6-methoxy signals that could be used for identification. In some isomers a small (ca. 1 Hz) splitting of the 6-methoxyl signal by fluorine was noted.

The configurations of fluorine could be determined by correlating pairs of fluoromethoxy isomers that produce the same products of methanol elimination. Thus, **10a** and **11a** produce the same 5-fluoro-Δ^6 product, **15a**, while **12a** and **13a** produce **16a**. The configuration of fluorine in **10a**, **11a**, and **15a** is the same but **12a**, **13a**, and **16a** have the alternative configuration. Similarly **21a** and **22a** produce the same mixture of **25a** and **26a**, indicating a common 7-F configuration. Thus, **23a** and its elimination products **27a** and **28a** must have the opposite configuration at C-7.

The configuration of the C-7 fluorine in **22a** was assigned on the basis of the observed 0-Hz coupling constant between the C-7 and C-8β protons. This vicinal proton–proton coupling constant can approach zero if the dihedral angle between the two protons is about 90°, which requires that the two protons be trans to each other. Thus, the

Scheme V



fluorine must have the 7β (*S*) configuration. Since **21a** has the same configuration it is also 7β, while **23a** must be 7α-fluoro. Attack on the less hindered exo face to give the 7β-F isomer is expected to be more facile. Thus the observed relative abundance (**21a** > **22a** > **23a**) of the 7-fluoro isomers is consistent with the assignment of the configuration on the basis of the ^{1}H NMR data.

Our assignment of configuration of the C-5 fluorine is based on the relative abundance of the isomers produced. The reaction must take place by the attack of the fluorinating agent on the double bond to provide an intermediate oxygen-stabilized carbonium ion at C-6. If the attack is from the exo face the 5(*R*)-fluoro configuration results, while attack from the endo face will produce the 5(*S*)-fluoro configuration. In studying the reaction of prostacyclin derivatives with NBS or NCS, Kurozumi et al.[18] found that in carbon tetrachloride the 5*R* isomer is the only product when a silyl-protecting group was used and the major product when an 11,15-diacetate was employed. Even succinimide adduct byproducts appear to be a single isomer from silyl-protected material but a mixture when acetyl protection is used.[23] We are uncertain as to which factors are responsible for the increased selectivity observed by Kurozumi. The *N*-halosuccinimide is probably more demanding sterically than perchloryl fluoride and the nonpolar solvent may aid in the selectivity. Our reaction takes place in a more polar solvent, methanol, which presumably solvates, and eventually adds to, the carbonium ion. Both products are obtained, but on steric grounds it is expected that the product arising from exo attack would predominate. Thus, since the total of **10a** and **11a** is about twice that of **12a** and **13a**, we assign **10** and **11** as being 5*R* with **12** and **13** being 5*S*. When the reaction was carried out on the unprotected ester **9c**, the selectivity for exo attack was only slightly diminished. The use of the bulky *tert*-butyldiphenylsilyl protecting group improved the degree of selectivity only slightly. The 5-fluoro-Δ^6-PGI$_1$ derivatives **15d** and **16d** had been obtained as a mixture of 5*R* and 5*S* isomers by Kurozumi et al.[2f]

The assignment of configuration at C-6 was based on both the NMR data and the observed relative abundances for each pair. Tomoskozi et al.[24] have described the solvolysis (Scheme V) of a 5-iodo-PGI$_1$ derivative, **29**, in methanol with silver nitrate via carbonium ion **30**. They found that the ratio of the endo/exo α-chain in their product, **31**/**32**, was 3:1. That is to say, methanol adds preferentially from the less hindered face. They also observed that the ^{1}H NMR signal for the 9-H of the exo chain compound was upfield from that of the endo chain isomer. In each of our pairs of endo/exo 5- or 7-fluoro-6-methoxy isomers the ratio was about 3:1 but the differences in 9-H chemical shifts were too small to be useful. The 9-H signals within each pair of isomers were within a 0.1 ppm range. On the basis of proportions of products, it appears that **10a**, **12a**, and **21a**, being the more abundant of each pair, are endo α-chain isomers, while **11a**, **13a**, and **22a** are exo.

On the basis of a detailed analysis of PGI$_1$ and PGI$_2$ ^{1}H NMR coupling patterns and NOE data, Kotovych et al.[25] report different conformations of the bicyclic ring for exo and endo configurations of the α-chain of prostacyclins. The coupling patterns for 9-H, in our endo isomers **10a**, **12a**, and **21a** are similar to the 6(*R*)-PGI$_1$, **33**, spectrum reported by Kotovych and Aarts.[26] The 9-H signal for these isomers is a triplet of doublets, while the corresponding signal for the exo isomers **11a**, **13a**, and **22a** is approximately a quartet. In the literature, the 9-H signal observed for a number of exo α-chain materials usually appears as a poorly defined quartet.[16] In addition, the 11-H signal of the endo isomer was found to be consistently slightly downfield from the corresponding signal of the exo isomer and to have a narrower bandwidth. Analysis of the ^{13}C NMR data of known exo–endo pairs of prostacyclins yielded correlations of the ^{13}C NMR chemical shifts of C-11 and C-12 with the C-6 configuration. The C-11 and C-12 signals were consistently downfield in the endo isomer.

The C-6 configurations of the two 7β-F isomers **21a** and **22a** can be definitively assigned on the basis of the ^{1}H NMR. The observed coupling constants between the C-7α and C-8β protons of **21a** (5.5 Hz) and **22a** (0 Hz) are consistent with the values reported by Kotovych[25] for PGI$_1$ isomers, 6*R* (endo, 5.0 Hz) and 6*S* (exo, 0.5 Hz).

In the ^{13}C NMR spectra of the 7-fluoro-6-methoxy isomers **21a**–**23a**, long-range C–F couplings can be observed to other ring carbons. The magnitudes of the three-bond C–F couplings seem to follow a Karplus relationship. The three-bond coupling is maximum for dihedral angles of 0° and 180° and minimum for 90° dihedral angles. Thus, in isomer **22a**, where the C–C–C–F dihedral angle between C-12 and 7β-F is nearly 180°, the C-12 signal is split by 10 Hz. The dihedral angle between C-9 and 7β-F is nearly 90°, and no splitting of the C-9 signal is observed. In the corresponding endo isomer **21a**, the magnitudes of the above dihedral angles are reversed. The C-9 and 7β-fluoro dihedral angle is close to 180° while the C-12 and 7β-F dihedral angle is nearly 90°. The C-9 signal is split by 8 Hz, while C-12 does not show observable coupling to the fluorine. The dihedral angles were estimated assuming the exo and endo configurations proposed by Kotovych et al.[25] In isomer **22a**, a four-bond C–F coupling of 2 Hz is observed between 7β-F and C-11.

Assignment of the C-6 configuration of the only 7α-F isomer (**23a**) isolated was difficult since the other 7α-F isomer was not available. In the ^{13}C NMR spectrum of **23a**, the C-12 carbon signal is split by 13 Hz, while C-9 shows no coupling to fluorine. In the exo configuration, 7α-F has a dihedral angle of about 130° with C-9, and

(23) Kurozumi, S. Teijin, Ltd., personal communication, 1985.
(24) Tomoskozi, I.; Galambos, G.; Kanai, K.; Gyory, P.; Gruber, L.; Tamas, J.; Bujtas, G. *Tetrahedron* **1982**, *38*, 3661–3666.
(25) Beierbeck, H.; Kotovych, G.; Sugiura, M. *Can. J. Chem.* **1985**, *63*, 1143–1149.
(26) Kotovych, G.; Aarts, G. H. M. *Can. J. Chem.* **1980**, *58*, 2649–2659.

about 10° with C-12, and thus would be expected to have a large three-bond coupling to C-12 and a smaller one to C-9. In the endo configuration, 7α-F has an approximately 90° dihedral angle with C-9, and about 10° with C-12. Thus the observed 13-Hz splitting of the C-12 signal is consistent with either configuration. The lack of splitting of the C-9 signal of **23a** is more consistent with a C-6 endo configuration (6*R*). However, the ^{1}H NMR splitting pattern (q, $J \simeq 7$ Hz) of the 9-H suggests the exo (6*S*) configuration. The observed 6.0-Hz coupling between the C-7β and C-8β protons is somewhat smaller than the C-7β–C-8β proton coupling constants of 8.1 and 9.1 Hz reported for the exo and endo PGI_1 isomers. We have tentatively assigned the endo (6*R*) configuration to **23a**. The 6*R* configuration is based on the belief that we would have found evidence for the remaining isomer **24a** if it were not less abundant than **23a**. This assignment is consistent with the ^{13}C NMR data but not with the ^{1}H NMR. Interaction of the C–F dipole with the C–O dipoles may result in a ring conformation that differs from those observed for known exo/endo pairs and thus the guidelines used above for the other isomers may not be applicable to **23a**.

The rates of elimination of methanol under Lewis acid catalysis conditions, with **10a** and **12a** being faster than **11a** and **13a**, also is consistent with the methoxyl of the major isomer of each pair being in the more accessible exo configuration. For these reasons we are confident in assigning the structures of the four 5-fluoro-6-methoxy isomers as indicated, namely: **10**, 5*R*,6*S*; **11**, 5*R*,6*R*; **12**, 5*S*,6*S*; **13**, 5*S*,6*R*.

In the ^{13}C NMR spectra of the 5-fluoro-6-methoxy prostacyclins **10–13**, the three-bond carbon–fluorine couplings generally are not resolved, although the C-3 signal is broadened in most 5-F compounds and is split by 2–3 Hz in some of the derivatives. In the 5-fluoro-Δ^6 compounds **15** and **16**, three-bond C–F couplings of 4–6 Hz to C-3 and C-7 are observed. In all the 7-fluoro-Δ^5 compounds **25–28**, three-bond C–F couplings are observed to C-12 (5–7 Hz) and to C-5 (7–11 Hz). Several four-bond C–F couplings were also observed.

The configuration of the double bonds in **25a–28a** can be assigned on the basis of the relative ^{13}C NMR chemical shifts of the 7 carbons. An allylic carbon cis to a hydrogen is generally about 5 ppm downfield from a corresponding carbon cis to an alkyl group.[27] In each of the pairs of 7-fluoro-Δ^5 isomers, the one with the downfield C-7 signal, **25a** or **27a**, was assigned the *Z* configuration. In each case the compound with the upfield C-7 signal, **26a** or **28a**, is the minor isomer produced. As expected, the ^{1}H NMR chemical shifts of the C-7 protons had the opposite relative shifts, i.e., the 5*Z* isomer has the upfield 7-H signal.

In addition, in the case where we were able to separate the isomers, the biological potency of the major isomer, **27c**, is much higher than that of the minor product, **28c**, confirming a configuration about the double bond that corresponds to **1**, namely 5*Z*.

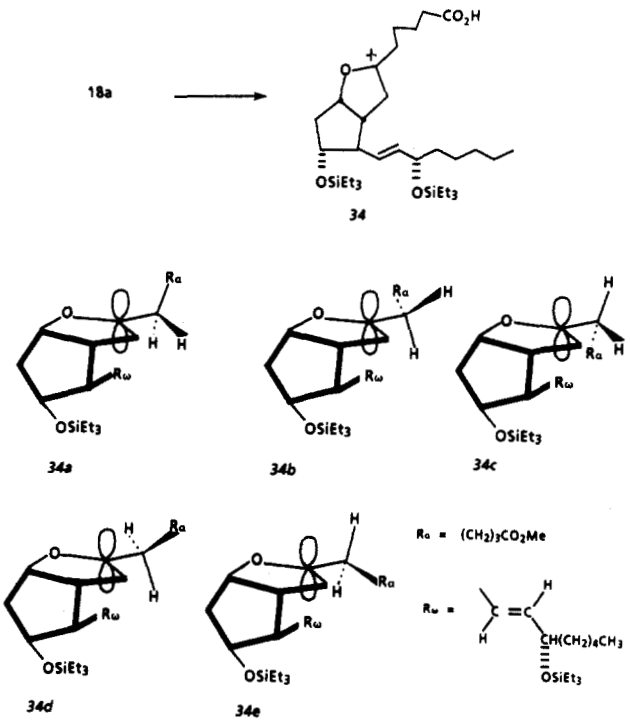
In the 5-fluoroprostacyclin derivatives **14** and **17**, the C-5 and C-6 olefinic carbons had signals near δ 140, $J_{CF} \simeq 222$ or 237 Hz, $J_{CCF} \simeq 20$ Hz, and $J_{C=CF} \simeq 48$ or 12 Hz, depending on the relative orientations of fluorine and oxygen. The reported values for $J_{C=CF}$ in *cis*- and *trans*-1,2-difluoroethene[28] indicate that the coupling is larger when the fluorines are trans. By analogy, in the 5-fluoro-PGI_2 compounds, the larger $J_{C=CF}$ coupling would be expected for the trans (*E*) configuration of the two polar double-bond substituents (5-F and 6-O). The observed values of $J_{C=CF}$ (48, 12 Hz) for the two 5-fluoroprostacyclins **14c** and **17c** are similar in magnitude to those reported for *trans*- and *cis*-1,2-difluoroethene (52, 6 Hz). Thus compound **14c**, with $J_{C=CF} = 48$ Hz, can be assigned the *E* configuration and compound **17c**, with $J_{C=CF} = 12$ Hz, the *Z* configuration. In addition, the increase in the two-bond C–F coupling between **14c** (222 Hz) and **17c** (237 Hz) is similar to the difference in the corresponding difluoroethenes C–F couplings (trans 242 Hz, cis 256 Hz). Lee and Schwartz[10] report a fluoro enol ether in which the fluorine is trans to oxygen with $J_{CF} = 234$ Hz and $J_{C=CF} = 34.5$ Hz. In 2-fluoroanisole with a cis fluorine–oxygen relationship, the C-2 signal at δ 152.6 has $J_{CF} = 245$ Hz and C-1 at δ 147.8 has $J_{CCF} = 10$ Hz.[29] These assignments agree with those made on the basis of biological activity. The more active isomer **14d** would be expected to have the same configuration of the α side chain as natural PGI_2.

Discussion

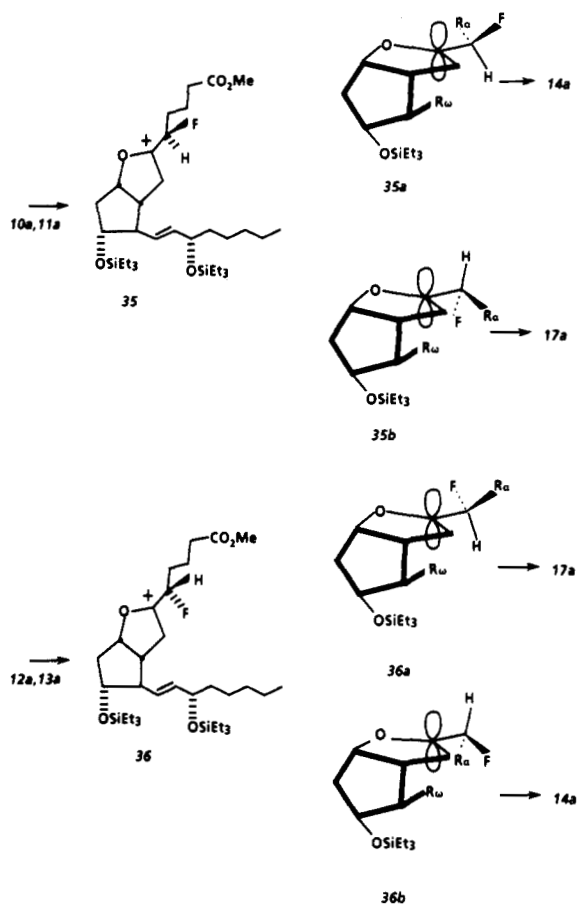
Methanol elimination from 5-fluoro-6-methoxy compounds proceeds so that 5(*R*)-fluoro compounds produce some 5*E* olefin but no 5*Z*, while 5(*S*)-fluoro compounds can produce 5*Z* but not 5*E*. We need to note that pyrolysis of **19a**, which lacks a fluorine atom, produces mainly Δ^6 product. However, in the 7-fluoro compounds, **21a**, **22a**, and **23a**, no Δ^6 product is formed during elimination. In these cases the ratio of 5*Z* to 5*E* was about 85:15. The assignment of the major isomer as being 5*Z* in each case is based on NMR data and on the work of Johnson[16] in the similar magnesium sulfate catalyzed elimination of water from 6-keto-$PGF_{1\alpha}$, where the major product isolated was the Δ^6 compound and of the Δ^5 compounds the *Z* isomer predominated. In our own work, we found that pyrolytic elimination of methanol from **19b** produced a 2:1 ratio of Δ^6 compound **20b** to 5*Z* compound **9b**.[30] Pyrolysis of **19c** in hexamethylphosphoric triamide at 180 °C was reported to give **20c**.[31] Since the elimination reaction is clearly catalyzed by the Lewis acid magnesium triflate, and in each pair of isomers studied the methoxyl configuration has no significant effect on the product composition, we suspect that we are dealing with a carbonium ion type intermediate. In the nonpolar solvents we use there is little reason to expect a concerted elimination that would require the loss of a poorly solvated proton. The fact that the methoxyl configuration affects the rate of reaction but not the product composition is evidence for a two-step reaction path in which the rate is controlled in the first step, but the product composition is determined in the second. Thus we must consider the factors related to the relative stability of conformations of the carbonium ion intermediate, **34**. Scheme VI shows several conformations of **34** with emphasis on the bond from C-6 to C-5. It would appear that a conformation resembling **34a** would have the least interactions between the α-chain and the rest of the molecule and therefore be the most abundant form. However, neither C–H bond is coplanar with the vacant p orbital of C-6, so loss of a C-5 proton from this conformation is unlikely. Unless rotation to one of the other conformations suggested takes place, it is apparent that

(27) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; p 80.
(28) den Otter, G. J.; MacLean, C. *J. Magn. Reson.* **1975**, *20*, 11–18.
(29) The other signals we observed in $CDCl_3$ were δ 116.0, $J_{CF} = 18$ Hz (C-3); 120.9, $J_{CF} = 7$ Hz (C-4); 124.4, $J_{CF} = 4$ Hz (C-5); 113.4, $J_{CF} = 2$ Hz (C-6); 56.0 (CH_3).
(30) A third material was present to the extent of about 7%, but it could not unambiguously be assigned the 5*E* structure by our ^{13}C NMR analysis since critical signals corresponding particularly to C-5 were obscured by the more abundant isomers.
(31) Shimoji, K.; Konishi, Y.; Arai, Y.; Hayashi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1978**, *100*, 2547–2548.

Scheme VI



Scheme VII



the loss of a C-5 proton is not possible.[32] The remaining conformations depicted are those in which one of the C-5 hydrogen atoms is ideally situated for elimination. Of these four conformations, **34b** appears to be the most favored since both **34c** and **34e** have some interference between the α-chain and the 11-triethylsilyloxy group and both **34d** and **34e** have a degree of interference between the α-chain and the ω-chain. Thus, if the loss of a proton from C-5 is to take place, it is most likely to occur from **34b** to form a *Z* olefin. Loss from **34c** also would provide a *Z* olefin, while **34d** and the less likely **34e** would provide an *E* olefin. The observed distribution of Δ^5 isomers is consistent with this expectation. For exocyclic elimination, the same factors are at work with all of our 7-fluoro materials. The fact that in this case no endocyclic product is obtained is probably related to ring conformation changes due to interactions of the C–F bond with the π-bonding orbital at C-6. These results suggest that an interaction of the polar C–F bond with the π orbitals of the adjacent oxonium ion can prevent the 7-H from assuming a coplanar orientation with the C-6 p orbital. Since all of the 5-fluoro-6-methoxy compounds as well as the non-fluorinated materials favor elimination to an endocyclic product, at least one of the 7-fluoro isomers should give a Δ^6 product if such a stereoelectronic effect did not exist. These same types of factors may serve to further minimize Δ^5 products from the 5-fluoro isomers.

When a similiar type of steric consideration is given to the carbonium ions derived from the 5-fluoro isomers, we find that for each pair of isomers only two conformations are ideally set up for the loss of the C-5 proton (Scheme VII). When **10a** or **11a** are pyrolyzed the carbonium ion **35** would need to be in form **35a** or **35b** for loss of the C-5 proton. Of these, **35a** is favored and would provide the 5*E* product.[33] Thus from these two isomers, we would expect any Δ^5 product to be mainly 5*E*. When **12a** and **13a** are similarly considered the conformation **36a**, expected to provide the 5*Z* product, has interaction between the α-chain and the ω-chain while **36b**, expected to provide 5*E*, has an interaction between the α-chain and the triethylsilyloxy group. It is clear that neither conformation is as favorable as **35a**. Only at 190 °C was a small amount of **17b** formed from **12b**, but no **14b** was detectable. This fact along with studies using molecular models suggest that the most important interference is between the α-chain and the 11-silyloxy group. The interference with the ω-chain is less but still significant.

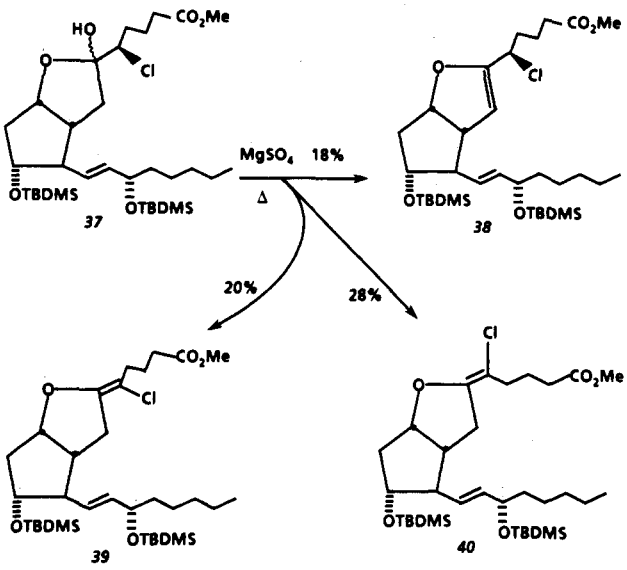
In the course of our studies using the *tert*-butyldiphenylsilyl protecting group, we obtained some physical evidence that there is indeed some interaction between the α- and ω-chains. The C-13 and C-14 protons in the triethylsilyl-protected isomers **10a**, **11a**, **12a**, and **13a** had very similiar chemical shifts, centered at about δ 5.5. In the *tert*-butyldiphenylsilyl-protected compounds, the 14-H signals of isomers **10b** and **12b** with an endo α-chain are shifted upfield by about 0.1 ppm, while those of **11b** and **13b** with an exo α-chain remain at δ 5.5. The 13-H signals of all four isomers are shifted upfield, but those of **10b** and **12b** are shifted by twice as much as those of **11b** and **13b**. Thus the relative conformation of the Δ^{13} olefinic protons and phenyl groups in the ω-chain depends on the configuration of the α-chain. While the isomers were not separated, similar results were observed with the mixed nonfluorinated derivatives **19b**.

It is instructive to note the differences in our results compared with the work of Kurozumi et al.[18] on the dehydration of a mixture of 5(*R*)-chloro-6-hydroxy compounds, **37**, with magnesium sulfate in refluxing benzene (Scheme VIII), products were Δ^6, **38** (18%); 5*E*, **39** (20%); and 5*Z*, **40** (28%). It is apparent that not only does the elimination

(32) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983; p 190.

(33) Because replacing hydrogen by fluorine changes the priority in sequencing, it should be noted that 5(*E*)-fluoro corresponds geometrically to 5*Z* hydrogen.

Scheme VIII



occur more readily (lower temperature) but loss of a proton to produce a vinyl chloride is a more favorable process than that required to produce a vinyl fluoride. The lack of stereoselectivity in the Δ^5-chloro compounds produced might well be due to another mechanism being responsible for a portion of the reaction products. Possibilities would include a concerted elimination with syn or anti orientation of the hydroxyl and hydrogen controlling the product distribution. The observed product composition requires either a different path or some type of electronic interaction in the 5(*R*)-chloro compounds to overcome the steric factors which are similar to those we have observed with the 5(*R*)-fluoro compounds.

Our results with the 7-fluoro-6-methoxy isomers raise some puzzling theoretical questions. These three isomers, especially the 7*S* isomers **21a** and **22a** eliminate methanol more slowly than the 5-fluoro compounds with the corresponding configuration at C-6. This is illustrated by the amount of recovered starting material after pyrolyses of endo α-chain isomers in refluxing xylene: **10a**, 2 h, 6%; **12a**, 2 h, 5%; **21a**, 22 h, 11%; **23a**, 4 h, 6%. Similarly, the recoveries for the exo α-chain isomers were **11a**, 18 h, 22%; **13a**, 20 h, 28%; **22a**, 44 h, 21%.[34] Since these are presumably magnesium triflate assisted E_1 processes, the rate must be determined by the transition state en route to the carbonium ion. The 7(*S*)-fluorine clearly destabilizes this transition state to a greater extent than the 5-fluorine. The 7(*R*)-fluorine appears to be less effective than 7(*S*), but lacking the other 6*S*,7*R* isomer, we cannot draw firm conclusions. The 7(*S*)-fluorine must have an orientation that is particularly unfavorable for the transition state.

The fact that none of the 7-fluoro isomers form any Δ^6 product also must be related to the orientation of the C–F bond relative to the vacant p orbital. Work of Barton et al.[35] on base treatment of the CF_3OF adducts of stilbenes shows that HF is eliminated more readily than CF_3OH. Thus loss of a proton from a carbon bearing fluorine may not be favorable. However, the fact that it does occur to some extent with the 5-fluoro compounds suggests that a stereoelectronic factor inhibits 7-H loss from 7-fluoro compounds. This would be accomplished if the C-7–H bond is forced out of coplanarity with the vacant p orbital. Zupan and Sket[36] have suggested that a fluorine adjacent to a carbonium ion may be more stable in a conformation where the C–F bond is orthogonal to rather than eclipsed by the vacant p orbital. However, this orientation places the C-7–H bond virtually coplanar with the vacant p orbital, thus predicting Δ^6 products.

While it is clear that a carbonium ion is destabilized by a fluorine on a neighboring carbon atom, Peterson and Bopp[37] have demonstrated that fluorine enhances the rate of a reaction involving a positive charge on the carbon to which it is attached, relative to either hydrogen or chlorine. They also observed a 1,4 fluorine migration to a carbonium ion, indicating that fluorine can donate electrons to a positive center. Electrophilic attack on fluorobenzene is known to produce para and ortho substitution.[38] It has also been shown[39,40] that in the gas phase fluorine stabilizes a carbonium ion relative to hydrogen. Thus it is apparent that fluorine can provide some p orbital back-bonding. This could provide for an orientation preference with an adjacent carbonium ion even though the small size and short bond length of the fluorine atom prevent formation of a bridged fluoronium ion.

Work of Olah and Bollinger[41] suggests that fluorine can rapidly equilibrate with a β-carbonium ion. For this rapid equilibration to occur, the C–F bond and the vacant orbital on the adjacent carbon atom must be coplanar. This equilibration is only observed when the two carbonium ions are similarly stabilized. In our compounds this not the case, so we do not expect to find the fluorine atom migrating to the adjacent positive center. However, the conformation of 7-fluoro intermediates may be controlled by a pseudoanomeric effect which favors C–F bond coplanarity with the vacant p orbital at C-6. This prevents the C-7–H bond from assuming a configuration in which the proton can be lost. We suspect that in the case of the 5-fluoro isomers the aliphatic chain has greater rotational freedom. Movements within the chain at the temperatures we employ prevent locking the 5-carbon atom into a rigid configuration. Stabilization of conformations with the C–F bond coplanar with the vacant p orbital will tend to reduce the amount of Δ^5 product produced. At the temperatures we have employed, the barriers to rotation about the 5,6 bond must be relatively insignificant. The fact that the eliminations are not concerted suggests that the proton loss is dependent on assistance by some other agent. At the point in time when this agent is present, the amount of any given conformation depends on its relative stability.

If the carbonium ion derived from pyrolysis of **21a** and **22a** has the same ring conformation that Kotovych et al.[25] assign to prostacyclin, the C–F bond would be nearly coplanar with the vacant p orbital. The fact that ratio of **21a** to **22a** formed in methanol is about the same as the ratio of **10a** to **11a** or **12a** to **13a** suggests similar carbonium ion conformations. If this configuration corresponds to prostacyclin, the 7α-H is not suitably oriented for elimination. However, the carbonium ion derived from **23a** would have the 7β-H oriented parallel to the vacant p orbital at C-6 if it corresponds to the configuration of

(34) The rate of elimination from **22a** was complicated by decomposition such that only 38% of elimination products was obtained from this prolonged pyrolysis.

(35) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Ogunkoya, L.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 739–742.

(36) Zupan, M.; Sket, B. *J. Org. Chem.* **1978**, *43*, 696–700.

(37) Peterson, P. E.; Bopp, R. J. *J. Am. Chem. Soc.* **1967**, *89*, 1283–1284.

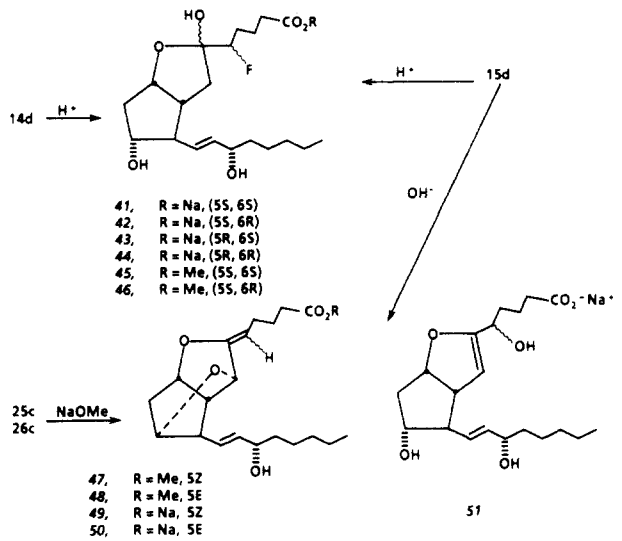
(38) Olah, G.; Pavlath, A.; Varsanyi, G., *J. Chem. Soc.* **1957**, 1823–1829.

(39) Taft, R. W.; Martin, R. H.; Lampe, F. W. *J. Am. Chem. Soc.* **1965**, *87*, 2490–2492.

(40) McMahon, T. B.; Blint, R. J.; Ridge, D. P.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 8934–8936.

(41) Olah, G. A.; Bollinger, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 947–953; **1967**, *89*, 4744–4752.

Scheme IX



prostacyclin. If, on the other hand, the ring assumes a conformation with the C-7–F bond approaching coplanarity with the vacant p orbital at C-6, the 7β-H is no longer suitably oriented for elimination. If this type of change in conformation does take place, there would have to be enough energy benefit to overcome the interaction between the 7α-F and the 12α-H. The fact that this type of interaction exists in the endo α-chain isomers **10**, **12**, and **21** as well as in 6(R)-PGI$_1$ **33** indicates that this energy requirement is not great. The orientation of a C–F bond relative to an adjacent carbonium ion is a question worthy of further study.

Biological Activity

Biological potency was compared in the inhibition of rat platelet aggregation induced by ADP. The molar concentrations required to reduce aggregation by 50% were determined: PGI$_2$ sodium salt, 1.6×10^{-9}; **10d**, $>10^{-4}$; **11d**, 1.6×10^{-5}; **12d**, $>10^{-4}$; **13d**, 5×10^{-5}; **14d**, 2.9×10^{-9}; **15d**, 6.7×10^{-8}; **16d**, 1.3×10^{-6}; **17d**, 1.03×10^{-6}; **27c**, 1.8×10^{-9}; **28c**, 3.5×10^{-7}. Additional details on the biological activities of these compounds will be published elsewhere.

Stability

Solutions of **14d**, **15d**, and **16d** did not show any significant loss of biological potency after 24 h at pH 9. Solutions of **14d** and **15d** were deliberately decomposed (Scheme IX). After storage for 72 h at ca. 24 °C and pH 5.3, **14d** had decomposed to a mixture containing ca. 20% **14d**, 34% **41**, 18% **42**, 15% **43**, and 13% **44**. It is interesting to note that protonation of **14d** takes place predominantly from the exo face. The decomposition of **15d** was studied under varying conditions as it proved to be less stable than **14d**. At pH 4.2 for 16 h, a mixture of ca. 20% **15d**, 45% **43**, and 35% **44** was obtained. After 48 h at pH 6.0 a mixture containing **15d**, **43**, **44**, and **49** in a ratio of about 3:3:2:2 with small amounts of other materials was formed. After 48 h at pH 11 the mixture contained ca. 10% **15d**, 30% **49**, 45% of **51** (the 5S configuration is likely), and 10% and 5% of other materials with unsaturation at the 6-carbon, perhaps the other isomer of **51**, and a 7-hydroxy compound. The 7,11-epoxy compounds **49** had been observed in some samples that had been stored for long periods with moisture present. In one such sample of **16d** about 20% of **49** had formed; acidification, extraction, esterification, and chromatographic separation provided crude **47** and a mixture of isomers **45** and **46**. Saponification of this mixture provided **41** and **42** as a mixture. We had observed that saponification of the mixture **25c** and **26c** in aqueous methanol even at 0 °C produced significant amounts of **49**. We prepared a mixture of isomers **47** and **48** by refluxing the mixture of **25c** and **26c** in methanol with sodium methoxide. In dry methanol this reaction is very slow. DBU in refluxing benzene also failed to produce **47**. Apparently, solvation by water greatly facilitates the ease of fluorine displacement. The 7,11-epoxy compounds **47** and **48** had previously been prepared by Kovacs et al.[42] and found to be devoid of interesting anti-aggregatory potency. Saponification of the mixture of **47** and **48** produced a mixture of **49** and **50**.

Experimental Section

Caution. While we have experienced no problems with the use of perchloryl fluoride under the conditions described here, its use has resulted in explosions with various organic materials and extreme caution is recommended. After finding that the reaction was very slow at low temperatures, we did not use a temperature below 15 °C to avoid building up perchloryl fluoride concentration. We used only Teflon-coated magnetic stirring bars to minimize grinding the chlorate salts that precipitate during the reaction. A referee has suggested that methoxyxenon fluoride[43] might well serve the same purpose under much safer conditions.

Reagents. All solvents were either Burdick and Jackson high purity solvents or were redistilled prior to use. Anhydrous methanol was freshly distilled from magnesium methoxide. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Perchloryl fluoride was measured as a liquid by condensation in a graduated centrifuge tube cooled in a dry ice–acetone bath. It was added as a gas by means of a tube just below the liquid surface of the reaction. The rate of addition was controlled by gradually raising the tube from the cooling bath.

Chromatography. MPLC (medium pressure liquid chromatography)[44] except where noted was run on a Woelm pH Controlled Scientific silica gel column unless Florisil is specified. A 25 mm × 1 m column was prewashed with 95:5 EtOAc–Et_3N (500 mL) and then with the solvent system (500 mL) which is given as a percentage of EtOAc in hexane. About 0.2% Et_3N was added to each solvent mixture except for non-fluorinated prostacyclins where 1% Et_3N was added. Where two concentrations are given a step gradient elution was employed. The column was regenerated by washing with a small amount of EtOAc and then with 500 mL of EtOAc that had been saturated with water. DCLC (dry column liquid chromatography) was carried out in the manner of Loev[45] except that elution was continued and fractions were collected and monitored by TLC. The adsorbent was Mallinckrodt CC-7 which had been pretreated with 10% EtOAc and 1% Et_3N. About 1% Et_3N was added to each solvent mixture. TLC (thin layer chromatography) monitoring was carried out by using Sybron/Brinkmann Polygram SIL G/UV plates developed with 10% EtOAc in hexane for silylated products and pure EtOAc for deprotected products. For distinction of the isomeric products generally a multiple development (3 to 6 times) on 20-cm plates was employed. In this manner all of the isomers could be distinguished in column fractions even when the R_fs for a single development were essentially the same.

Spectroscopy. The identity and purity of all products were determined on the basis of ^1H and ^{13}C NMR. Unless otherwise specified, products are single isomers by ^{13}C NMR. ^{13}C NMR data were determined at either 25.2 or 50.3 MHz, using either a Varian XL-100 or XL-200 spectrometer. $CDCl_3$ solutions were

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stabilized by a trace of Et_3N or pyridine-d_5. The 50-MHz ^{13}C NMR spectra were determined by using the APT (Attached Proton Test) pulse sequence. DEPT (Distortionless Enhancement by Polarization Transfer) spectra were determined for **10a** and **11a** to confirm 6-methoxyl assignment. The ^1H NMR data was determined either at 80 or 200 MHz, on either a Varian FT-80A or XL-200 spectrometer. Double resonance and homocorrelation experiments were used in the analysis of the ^1H NMR spectra. High resolution mass spectra were determined for representative examples of each isomer type on a Kratos MS 50 mass spectrometer at 25 °C source temperature, 70 eV, 8 kV accelerating volts, and 10 000 resolving power with perfluoro kerosene as internal reference. All quoted exact mass measurements were within 4 ppm.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxyprosta-5(*Z*),13(*E*)-dien-1-oate (9a). A solution of 5.1 g of $PGF_{2\alpha}$ methyl ester in 25 mL of CH_2Cl_2 was chilled in an ice bath and 12.5 g of sodium bicarbonate was added followed by 40 mL of water. After stirring for 30 min, a solution of 3.9 g of iodine in 125 mL of CH_2Cl_2 was added slowly over 1 h. After stirring for 1 h more at 0 °C in the dark, 25 mL of 5% sodium sulfite was added. The mixture was diluted with 100 mL of water and separated. The aqueous layer was extracted twice more with 100-mL portions of CH_2Cl_2 and the extracts were washed with water. After drying over sodium sulfate, the solvent was removed in vacuo and the residue was purified by MPLC (60–80% EtOAc) to provide 6.6 g of a mixture of iodo isomers. This mixture together with 5.4 g of imidazole was dissolved in 65 mL of DMF and the solution was cooled in an ice bath while 5.2 mL of chlorotriethylsilane was added over 5 min. The ice bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was cooled again with an ice bath and diluted with 200 mL of hexane and 200 mL of water and separated. The aqueous layer was extracted twice more with hexane and the extracts were washed four times with water and then with brine. After drying over sodium sulfate and concentrating the solution, the residue, after MPLC (5% EtOAc), provided 8.2 g of a mixture of isomers. This mixture in 50 mL of toluene was added to a solution of 5 mL of DBU in 350 mL of toluene. About 50 mL of toluene was removed by distillation to assure dryness and then refluxing under nitrogen was continued for 18 h. After the mixture was cooled to room temperature, the solid was removed by filtration and rinsed well with dry toluene. The filtrate was washed three times with 2% sodium carbonate and dried over sodium sulfate. After concentrating the solution, MPLC (Florisil, 2% EtOAc) provided 6.3 g (77%) of **9a**, R_f 0.36, followed by 0.16 g (2%) of the Δ^4-isomers,[16] R_f 0.31.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxyprosta-5(*Z*),13(*E*)-dien-1-oate (9b). In a manner similar to the preparation of **9a**, except using *tert*-butylchlorodiphenylsilane, 4.05 g of $PGF_{2\alpha}$ methyl ester provided, after MPLC (6% EtOAc), 6.8 g (73%) of **9b**, R_f 0.29, followed by 0.09 g (1%) of the Δ^4-isomers,[16] R_f 0.20.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-5-fluoro-6-methoxyprost-13(*E*)-en-1-oate Isomers (10a, 11a, 12a, and 13a). A. A mixture of 1.64 g of **9a**, 2.20 g of potassium carbonate, and 40 mL of MeOH was stirred under nitrogen at 15 °C while perchloryl fluoride (1.0 mL) was added over 30 min. The cooling bath was removed, and the mixture was stirred 30 min longer, then diluted with 200 mL of ice water, and extracted with hexane. After washing with water and then brine, the extract was dried over sodium sulfate and evaporated. The residue (1.80 g) was chromatographed by using MPLC (3% EtOAc) to provide two major fractions. The slower fraction (460 mg, 26%) was assigned to (5*S*,6*S*)-**12a**: R_f 0.18; mass spectrum, *m/z* (relative intensity) 644 (4.9), 615 (23.4), 612 (13.6), 592 (19.6), 583 (35.1), 573 (100), 512 (80.3), 481 (7.9), 460 (6.5), 441 (14.8), 399 (20.5), 383 (23.5), 329 (8.7), 267 (52.7), 215 (31.8), 193 (11.0), 171 (46.8), 145 (10.0), 115 (45.6), 87 (77.2), 75 (27.0); exact mass calcd for $C_{34}H_{65}FO_6Si_2$ 644.4304, found 644.4302. The faster fraction was rechromatographed (Florisil, 3% EtOAc) to provide two fractions. The slower fraction (faster on TLC) amounting to 150 mg (8%) was assigned to (5*S*,6*R*)-**13a**, R_f 0.28. The faster fraction was chromatographed repeatedly by using a 9.4 mm × 500 mm Partisil 10 HPLC column and developing with 3:97 EtOAc–1,1,2-trichlorotrifluoroethane to produce 820 mg (46%) of the faster isomer assigned to (5*R*,6*S*)-**10a**, R_f 0.25. The slower isomer (5*R*,6*R*)-**11a**, R_f 0.25, amounted to 265 mg (15%).

B. A mixture of 800 mg of **9c** and 1.85 g of potassium carbonate was suspended in 50 mL of MeOH at 18 °C and 0.8 mL of perchloryl fluoride was allowed to bubble in over 20 min with the temperature kept at 18–20 °C. After 30 min more the mixture was concentrated under a slow nitrogen stream. The residue in 100 mL of EtOAc was washed with water and brine, dried over sodium sulfate, and concentrated in vacuo. DCLC (60–100% EtOAc) separated 58 mg of low polarity byproducts and then 762 mg of a product fraction. This material was dissolved in 5 mL of DMF and 800 mg of imidazole and 0.85 mL of triethylchlorosilane were added. After 1 h at room temperature, the mixture was diluted with hexane and washed with water and brine. After drying over sodium sulfate and evaporation of solvent, MPLC (3% EtOAc) gave 759 mg of a mixture followed by 387 mg (27%) of **12a**. Chromatography of the mixture on Florisil (as above) provided 602 mg (43%) of a mixture of **10a** and **11a** (ca. 3:1 by ^{13}C NMR) and then 121 mg (9%) of **13a**.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-7-fluoro-6-methoxyprost-13(*E*)-en-1-oate Isomers (21a, 22a, and 23a). A mixture of 4.76 g of **9a**, 6.5 g of potassium carbonate, and 100 mL of MeOH was stirred in a 15 °C bath while 3 mL of perchloryl fluoride was added over a 20-min period. After being allowed to warm to room temperature, the mixture was concentrated under a nitrogen stream to ca. 20 mL and then diluted with 200 mL of hexane. After washing twice with water and then brine, the solution was dried over sodium sulfate and evaporated to dryness. Repeated MPLC (3% EtOAc) provided separation of 2.94 g of a mixture of isomers and non-fluorinated materials. The next fraction contained 164 mg (3%) of material assigned to (6*R*,7*S*)-**21a**: R_f 0.20; mass spectrum, *m/z* (relative intensity) 644 (2.3), 615 (18.4), 593 (10.8), 583 (5.2), 573 (100), 529 (4.4), 512 (23.8), 409 (10.1), 399 (7.1), 267 (8.1), 241 (9.8), 215 (10.4), 171 (32.5), 115 (36.7), 87 (52.4), 75 (20.7); exact mass calcd for $C_{34}H_{65}FO_6Si_2$ 644.4304, found 644.4298. The next fraction which followed closely amounted to 655 mg (13%) of **12a** identical with that described above. On flushing the column with EtOAc, 790 mg of a mixture of polar byproducts was obtained. The mixture fraction above (2.94 g) was dissolved in 25 mL of benzene containing 0.1 mL of 2-picoline. After addition of 5 mg of magnesium triflate, the mixture was refluxed under nitrogen for 18 h, then cooled to room temperature, and filtered. After the addition of 0.5 mL of Et_3N, the filtrate was evaporated and the residue chromatographed MPLC (1.5–3% EtOAc), providing first 760 mg (16%) of a mixture of **9a** and the isomeric **20a**, about 1:2 based on ^{13}C NMR analysis. The second fraction was 210 mg (4%) of **15a**, R_f 0.34 (see below). A third fraction amounting to 52 mg (1%) was assigned to (6*S*,7*S*)-**22a**, R_f 0.31. This was followed closely by a mixture of isomers that was chromatographed MPLC (Florisil, 3% EtOAc) to provide first 21 mg (0.4%) assigned (6*R*,7*R*)-**23a**, R_f 0.28, followed by 1.02 g (20%) of a mixture of **10a** and **11a** and finally 170 mg (3%) of **13a**.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-5-fluoro-6-methoxyprost-13(*E*)-en-1-oate Isomers (10b, 11b, 12b, and 13b). A. A mixture of 9.09 g of **9b** and 12.5 g of potassium carbonate in 300 mL of MeOH was stirred at 25 °C, and 4.5 mL of perchloryl fluoride was allowed to bubble in slowly over 1 h. The temperature rose to 32 °C during the addition. The mixture was allowed to evaporate under a slow nitrogen stream. The residue was taken up in a mixture of 500 mL of water and 500 mL of hexane. The hexane layer was washed again with water and brine, dried over sodium sulfate, and then evaporated to dryness. MPLC (6–10% EtOAc) provided 6.81 g of a poorly separated mixture of isomers followed by 2.19 g (23%) assigned to (5*S*,6*S*)-**12b**, R_f 0.11. The mixed fraction was taken up in 400 mL of MeOH and 10 mg of dry *d*-10-camphorsulfonic acid was added. After stirring for 18 h at room temperature under nitrogen, 0.5 mL of Et_3N was added, and the mixture was concentrated under a slow nitrogen stream to a small volume. After dilution with 500 mL of ether containing a trace of Et_3N, the mixture was washed with 5% sodium bicarbonate and then brine. After drying over sodium sulfate, the solvent was removed and the residue was chromatographed as above to provide 1.77 g of a mixture fraction, followed by 3.42 g of a mixture containing only (5*R*,6*S*)-**10b** and (5*R*,6*R*)-**11b**, and then an additional 690 mg

(7.2%) of pure **12b**. After equilibration of the 1.77 g of mixture containing **13b** in the same manner, MPLC provided 430 mg (4.5%) of a mixture of **11b** with a trace of the 5*S*,6*R* isomer **13b**, R_f 0.21, followed by 1.03 g of a mixture of **10b** and **11b** and then 120 mg of pure **12b**. The total mixture of isomers **10b** and **11b** thus obtained, 5.45 g (58%), was about 85% **10b** based on ^{13}C NMR analysis.

B. A solution of 4.49 g of **9b** in 300 mL of MeOH was chilled in an ice bath to 15 °C and 10 g of anhydrous cesium carbonate was added. When solution was complete, 2.0 mL of condensed perchloryl fluoride was allowed to distill into the mixture over a 30-min period. Stirring was continued at 15 °C for 1 h when TLC indicated the reaction was complete. The solvent was allowed to evaporate under a slow nitrogen stream. The residue was taken up in 500 mL of hexane and 200 mL of water. After separation the aqueous layer was extracted again with hexane. After being washed with water and then brine, the solution was dried over sodium sulfate and evaporated to dryness. Chromatography as above provided first 120 mg (3%) of a mixture of **15b** and **16b** (see below), followed by a partially separated mixture of **10b**, **11b**, and **13b**. Fractions were cut to provide 620 mg (13%) of ca. 6:47:47 **10b**, **11b**, and **13b**; then 2.24 g (47%) of ca. 4:1 **10b** and **11b**; and then 540 mg (11%) of **10b**. A final fraction provided 870 mg (18%) of **12b**.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-5-fluoroprosta-5(*E*),13(*E*)-dien-1-oate (14a) and Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-5(*R*)-fluoroprosta-6,13(*E*)-dien-1-oate (15a). A. To a solution of 358 mg of **10a** in 10 mL of xylene were added 2 drops of 2-picoline and 5 mg of magnesium triflate. The mixture was refluxed with stirring under nitrogen for 2 h and then cooled and filtered. The filtrate was evaporated under a nitrogen stream and the residue chromatographed (MPLC, 2% EtOAc) to provide 22 mg (6%) of **14a**, R_f 0.35, then 232 mg (68%) of **15a**, R_f 0.34, and finally 23 mg (6%) of recovered **10a**.

B. To a solution of 185 mg of **11a** in 10 mL of xylene and 2 drops of 2-picoline was added 5 mg of magnesium triflate. The mixture was refluxed for 18 h, then cooled, and filtered, and the filtrate was evaporated under a nitrogen stream. MPLC (2% EtOAc) provided 12 mg (7%) of **14a**, 122 mg (69%) of **15a**, and 41 mg (22%) of recovered **11a**.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-5-(*S*)-fluoroprosta-6,13(*E*)-dien-1-oate (16a). A. To a solution of 655 mg of **12a** in 15 mL of xylene were added 4 drops of 2-picoline and 5 mg of magnesium triflate. The mixture was refluxed for 2 h under nitrogen, cooled, and filtered, and the filtrate was evaporated under a nitrogen stream. MPLC (3% EtOAc) of the residue provided 495 mg (80%) of **16a**, R_f 0.34, and then 34 mg (5%) of recovered **12a**.

B. To a solution of 230 mg of **13a** in 10 mL of xylene were added 4 drops of 2-picoline and 5 mg of magnesium triflate. The mixture was refluxed for 20 h and allowed to cool, and the catalyst was removed by filtration. The filtrate was evaporated under a nitrogen stream. MPLC (3% EtOAc) of the residue provided 110 mg (50%) of **16a** and then 65 mg (28%) of recovered **13a**.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-6-methoxyprost-13(*E*)-en-1-oate (19a). To a solution of 340 mg of **9a** in 25 mL of methanol was added 0.5 g of magnesium sulfate. After 42 h, the solids were removed by filtration and rinsed with ether. The filtrate was evaporated to dryness and the residue chromatographed (MPLC, 3% EtOAc) to provide 210 mg of the mixture **19a**, R_f 0.25, ca. 70% 6*R* isomer, and 30% 6*S* isomer.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxyprosta-6,13(*E*)-dien-1-oate (20a). To a solution of 210 mg of **19a** in 25 mL of benzene containing 2 drops of 2-picoline was added 5 mg of magnesium triflate. After 18 h at reflux the mixture was cooled and filtered and the filtrate evaporated. MPLC (2% EtOAc) provided 162 mg of a mixture, R_f 0.36, of ca. 30% **9a** and 70% **20a**.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-5-fluoroprosta-5(*E*),13(*E*)-dien-1-oate (14b) and Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-5(*R*)-fluoroprosta-6,13(*E*)-dien-1-oate (15b). A. To a solution of 5.83 g of a mixture of **10b** and **11b** in 50 mL of xylene containing 1 mL of 2-picoline was added 10 mg of magnesium triflate. The mixture was refluxed for 4 h, allowed to cool, and filtered, and the filtrate was evaporated under a slow nitrogen stream. MPLC (3–6% EtOAc) of the residue produced first 403 mg (7%) of **14b**: R_f 0.28; mass spectrum, *m/z* (relative intensity) 803 (12.49), 783 (3.5), 687 (7.6), 391 (3.7), 199 (100), 135 (40.5), 77 (17.2); exact mass calcd for $C_{49}H_{60}FO_5Si_2$ (M − C_4H_9) 803.3963, found 803.3948. This was followed by 4.66 g (83%) of **15b**: R_f 0.26; mass spectrum, *m/z* (relative intensity) 841 (31.9), 803 (100), 783 (12.1), 729 (7.8), 679 (9.0), 629 (9.0), 529 (7.3), 501 (4.3), 391 (6.5), 339 (6.5), 199 (88.4), 135 (60.7), 107 (7.8), 91 (8.4), 77 (8.3), 55 (15.3); exact mass calcd for $C_{49}H_{60}FO_5Si_2$ (M − C_4H_9) 803.3963, found 803.3993. Finally the starting material fraction, which separated into 340 mg (6%) of **11b**, R_f 0.20, and then 30 mg (0.5%) of **10b**, R_f 0.19, was isolated.

B. A solution of 4.93 g of a mixture of **10b** and **11b** in 10 mL of *tert*-butylbenzene containing 0.2 mL of 2-picoline was added through an air-cooled condenser to a refluxing mixture of 40 mL of *tert*-butylbenzene, 0.2 mL of 2-picoline, and 5 mg of magnesium triflate. Reflux under nitrogen was continued for 12 min. After cooling, the mixture was filtered and the filtrate was evaporated under a nitrogen stream to a small residue. MPLC as in part A gave 388 mg (8%) of **14b**, 2.46 g (52%) of **15b**, 1.34 g (27%) of **11b**, and 480 mg (10%) of **10b**.

C. A solution of 0.47 g of **11b** in 10 mL of 4-*tert*-butyltoluene containing 0.2 mL of 2,6-lutidine was added through an air-cooled condenser to a refluxing mixture of 10 mL of 4-*tert*-butyltoluene, 0.2 mL of 2,6-lutidine, and 5 mg of magnesium triflate. Reflux under nitrogen was continued for 30 min. After cooling, the mixture was filtered and the filtrate was evaporated under a nitrogen stream to a small residue. MPLC (5% EtOAc) gave 33 mg (7%) of **14b**, 143 mg (32%) of **15b**, and 270 mg (57%) of recovered **11b**.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-5(*S*)-fluoroprosta-6,13(*E*)-dien-1-oate (16b). To a solution of 388 mg of **13b** in 15 mL of xylene containing 0.2 mL of 2-picoline was added 5 mg of magnesium triflate. The mixture was refluxed for 1.5 h under nitrogen and then allowed to cool to room temperature and the catalyst was removed by filtration. After evaporation under a slow stream of nitrogen, MPLC (5% EtOAc) provided 334 mg (89%) of **16b**, R_f 0.26, as the only significant material.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-5-fluoroprosta-5(*Z*),13(*E*)-dien-1-oate (17b). A solution of 294 mg of **12b** in 10 mL of *tert*-butyltoluene containing 0.1 mL of 2,6-lutidine was added over 3 min to a refluxing mixture of 5 mL of *tert*-butyltoluene, 0.1 mL of 2,6-lutidine, and 5 mg of magnesium triflate. After 10 min more reflux under nitrogen the mixture was cooled and filtered, and the filtrate was evaporated under a slow nitrogen stream. MPLC (5% EtOAc) provided 209 mg (74%) of **16b** identical with that described above followed by 19 mg (7%) of **17b**, R_f 0.23.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxy-6-methoxyprost-13(*E*)-en-1-oate (19b). To a solution of 440 mg of **9b** in 50 mL MeOH was added 5 mg of pyridinium *p*-toluenesulfonate. After 30 min at 24 °C, 0.5 mL of Et_3N was added and the mixture evaporated to a small volume. MPLC (10% EtOAc) provided 448 mg of the mixture, **19b**, R_f 0.22, ca. 75% 6*R* isomer, 25% 6*S* isomer.

Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)diphenylsilyl]oxy]-6,9α-epoxyprosta-6,13(*E*)-dien-1-oate (20b). A mixture of 298 mg of **19b**, 2 drops 2-picoline, 10 mL toluene, and 5 mg of magnesium triflate was refluxed for 1 h, cooled, filtered, and evaporated. MPLC (10% EtOAc) provided 278 mg of a mixture, R_f 0.29, ca. 31% **9b**, 62% **20b**, and 7% of another component: ^{13}C NMR δ 54.3, 82.8, 94.5, 156.1.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-7-(*S*)-fluoroprosta-5(*Z*),13(*E*)-dien-1-oate (25a) and Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-7(*S*)-fluoroprosta-5(*E*),13(*E*)-dien-1-oate (26a). A. A mixture of 1.015 g of **21a**, 4 drops of 2-picoline, 10 mg of magnesium triflate, and 20 mL of xylene was refluxed under nitrogen for 22 h. After being cooled to room temperature, the mixture was filtered and the filtrate was evaporated under a nitrogen stream. MPLC (3% EtOAc) produced 826 mg (84%) of a product fraction and then 110 mg (11%) of recovered **21a**. The product fraction, a single spot with R_f 0.35, was a mixture of ca. 85% **25a** and 15% **26a**, on the basis of ^{13}C NMR analysis: mass spectrum, *m/z* (relative

intensity) 612 (8.1), 592 (100), 583 (50.5), 563 (13.9), 541 (40.2), 521 (13.0), 480 (16.8), 460 (22.8), 449 (18.4), 409 (39.9), 399 (89.0), 389 (21.7), 377 (93.6), 328 (23.8), 267 (74.8), 215 (38.6), 193 (7.8), 171 (7.3), 115 (20.5), 87 (39.8), 75 (19.4); exact mass calcd for $C_{33}H_{61}FO_5Si_2$ 612.4042, found 612.4066.

B. A mixture of 489 mg of **22a**, 6 drops of 2-picoline, 10 mg of magnesium triflate, and 20 mL of xylene was refluxed under nitrogen for 44 h. After being allowed to cool to room temperature, the mixture was filtered and the filtrate was evaporated under a nitrogen stream. MPLC (3% EtOAc) provided 177 mg (38%) of a mixture of elimination products **25a** and **26a** indistinguishable from the products from **21a** above (85:15). This was followed by 101 mg (21%) of recovered **22a**.

Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-7-(*R*)-fluoroprosta-5(*Z*),13(*E*)-dien-1-oate (27a) and Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-7(*R*)-fluoroprosta-5(*E*),13(*E*)-dien-1-oate (28a). A mixture of 65 mg of **23a**, 4 drops of 2-picoline, 5 mg of magnesium triflate, and 10 mL of xylene was refluxed for 4 h and then allowed to cool to room temperature. After filtration the filtrate was evaporated under a nitrogen stream. MPLC (3% EtOAc) provided excellent separation of 47 mg (75%) of **27a**, R_f 0.35, then 8 mg (13%) of **28a**, R_f 0.32, and finally 4 mg (6%) of recovered **23a**.

Reaction of Methyl 11α,15(*S*)-Bis[(triethylsilyl)oxy]-6,9α-epoxy-5(*R*)-fluoroprosta-6,13(*E*)-dien-1-oate (15a) with MeOH and Pyridinium *p*-Toluenesulfonate. A mixture of 987 mg of **15a** and 20 mg of pyridinium *p*-toluenesulfonate in 25 mL of MeOH was stirred under nitrogen at room temperature. Solution occurred quickly and TLC analysis indicated that loss of silyl groups was complete in less than 20 min. After 24 h, TLC showed only two very close spots. After the addition of 50 mg of anhydrous sodium carbonate, the mixture was concentrated under a nitrogen stream to a small volume. The residue was dissolved in EtOAc and washed twice with water and then with brine. After drying over sodium sulfate the solvent was evaporated. DCLC on a 90-g column developed with 99:1 EtOAc–Et_3N gave 660 mg of a product mixture which by ^{13}C NMR analysis was about a 70:30 mixture of **10c** and **11c** (see below).

Reaction of Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)-diphenylsilyl]oxy]-6,9α-epoxy-5(*R*)-fluoroprosta-6,13(*E*)-dien-1-oate (15b) with MeOH and Pyridinium *p*-Toluenesulfonate. A solution of 450 mg of **15b** in 40 mL of MeOH was stirred at room temperature under nitrogen with 10 mg of pyridinium *p*-toluenesulfonate until no further change in TLC was apparent (3 days). After the addition of 2 drops of Et_3N the mixture was concentrated to a small volume under a nitrogen stream. The residue was dissolved in hexane and washed with 5% sodium bicarbonate and then brine. After being dried over sodium sulfate, evaporation left a residue of 440 mg (94%). ^{13}C NMR analysis showed this residue to be about a 76:24 mixture of **10b** and **11b**. No other material was indicated in the spectrum or on TLC analysis.

Reaction of Methyl 11α,15(*S*)-Bis[[(1,1-dimethylethyl)-diphenylsilyl]oxy]-6,9α-epoxy-5(*R*)-fluoroprosta-6,13(*E*)-dien-1-oate (15b) with MeOH and *d*-10-Camphorsulfonic Acid. A solution of 400 mg of **16b** in 100 mL of MeOH was treated with 10 mg of dried *d*-10-camphorsulfonic acid at room temperature under nitrogen for 24 h. After addition of 0.5 mL of Et_3N, the mixture was concentrated to a small volume under a nitrogen stream and the residue was taken up in hexane. After being washed with 5% sodium bicarbonate and then brine, the solution was dried over sodium sulfate and the solvent removed. MPLC (6% EtOAc) separated first 102 mg (25%) of **11b** and then 267 mg (64%) of **10b**.

General Procedure for Desilylation. Desilylations were carried out in tetrahydrofuran (THF) by using a slight excess of 1 M tetrabutylammonium fluoride (TBAF) in THF at room temperature until TLC indicated complete reaction. For triethylsilyl this required about 15 min, while *tert*-butyldiphenylsilyl required about 20 h. After evaporating most of the solvent under a slow nitrogen stream, the residue was taken up in ether, washed with 5% sodium bicarbonate and then water, and dried over sodium sulfate. After removing solvents, DCLC on a short column gave the pure product.

Methyl 6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxy-6-(*S*)-methoxyprost-13(*E*)-en-1-oate (10c). A. A solution of 548 mg of **10a** in 5 mL of THF was treated with 2 mL of TBAF for 30 min to provide 250 mg (69%) of **10c**, R_f 0.14.

B. A solution of 300 mg of **10b** in 5 mL of THF was treated with 1 mL of TBAF for 40 h to provide 134 mg (96%) of **10c**.

Methyl 6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxy-6-(*R*)-methoxyprost-13(*E*)-en-1-oate (11c). A. A solution of 410 mg of **11a** in 5 mL of THF was treated with 1.5 mL of TBAF for 30 min to provide 231 mg (85%) of **11c**, R_f 0.12.

B. A solution of 918 mg of **12b** in 10 mL of THF was treated with 2 mL of TBAF for 22 h to provide 415 mg (97%) of **11c**.

Methyl 6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxy-6-(*S*)-methoxyprost-13(*E*)-en-1-oate (12c). A solution of 292 mg of **12a** in 5 mL of THF was treated with 1 mL of TBAF for 1 h to provide 185 mg (96%) of **12c**, R_f 0.16.

Methyl 6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxy-6-(*R*)-methoxyprost-13(*E*)-en-1-oate (13c). A solution of 85 mg of **13a** in 5 mL of THF was treated with 0.5 mL of TBAF for 1 h to provide 51 mg (91%) of **13c**, R_f 0.12.

Methyl 6,9α-Epoxy-5-fluoro-11α,15(*S*)-dihydroxyprosta-5(*E*),13(*E*)-dien-1-oate (14c). A. A solution of 154 mg of **14a** in 5 mL of THF was treated with 1 mL of TBAF for 30 min to provide 70 mg (73%) of **14c**, R_f 0.14.

B. A solution of 640 mg of **14b** in 20 mL of THF was treated with 2 mL of TBAF for 20 h to provide 279 mg (97%) of **14c**.

Methyl 6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxyprosta-6,13(*E*)-dien-1-oate (15c). A solution of 1.57 g of **15a** in 10 mL of THF was treated with 5 mL of TBAF for 1 h to provide 0.99 g (98%) of **15c**, R_f 0.17.

Methyl 6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxyprosta-6,13(*E*)-dien-1-oate (16c). A. A solution of 568 mg of **16a** in 10 mL of THF was treated with 2 mL of TBAF for 15 min to provide 324 mg (88%) of **16c**, R_f 0.17.

B. A solution of 334 mg of **16b** in 5 mL of THF was treated with 1 mL of TBAF for 22 h to provide 147 mg (98%) of **16c**.

Methyl 6,9α-Epoxy-5-fluoro-11α,15(*S*)-dihydroxyprosta-5(*Z*),13(*E*)-dien-1-oate (17c). A solution of 19 mg of **17b** in 2 mL of THF was treated with 0.5 mL of TBAF for 20 h to provide 6 mg (71%) of **17c**, R_f 0.16.

Methyl 6,9α-Epoxy-7(*S*)-fluoro-11α,15(*S*)-dihydroxyprosta-5(*Z*),13(*E*)-dien-1-oate (25c) and Methyl 6,9α-Epoxy-7(*S*)-fluoro-11α,15(*S*)-dihydroxyprosta-5(*E*),13(*E*)-dien-1-oate (26c). A solution of 553 mg of the mixture (see above) of **25a** and **26a** in 10 mL of THF was treated with 2 mL of TBAF for 30 min to provide 320 mg (90%) of a mixture, as a single spot, R_f 0.18, of **25c** and **26c**, ca. 85:15 by ^{13}C NMR analysis.

Methyl 6,9α-Epoxy-7(*R*)-fluoro-11α,15(*S*)-dihydroxyprosta-5(*Z*),13(*E*)-dien-1-oate (27c). A solution of 47 mg of **27a** in 5 mL of THF was treated with 0.5 mL of TBAF for 20 min to provide 27 mg (88%) of **27c**, R_f 0.18.

Methyl 6,9α-Epoxy-7(*R*)-fluoro-11α,15(*S*)-dihydroxyprosta-5(*E*),13(*E*)-dien-1-oate (28c). A solution of 8 mg of **28a** in 5 mL of THF was treated with 0.1 mL of TBAF for 30 min to provide 4.5 mg (87%) of **28c**, R_f 0.18.

General Method for Saponification. The methyl ester was dissolved in a minimal amount of MeOH (ca. 1 mL/200 mg). After the addition of ca. 1.05 equiv of 1 N sodium hydroxide, a total of 10 volumes of water was added in small portions each time until cloudiness developed. As the stirred mixture cleared, more of the water was added. The addition was normally complete within 2 h and stirring was continued at room temperature overnight. After evaporation under a nitrogen stream to about one-half the volume, the solution was filtered and the filtrate was lyophilized.

6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxy-6(*S*)-methoxyprost-13(*E*)-en-1-oic Acid, Sodium Salt (10d). A solution of 196 mg of **10c** in 1 mL of MeOH was treated with 0.50 mL of 1 N NaOH and 5 mL of water to provide 183 mg of **10d**.

6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxy-6(*R*)-methoxyprost-13(*E*)-en-1-oic Acid, Sodium Salt (11d). A solution of 215 mg of **11c** in 1 mL of MeOH was treated with 0.55 mL of 1 N NaOH and 5 mL of water to provide 196 mg of **11d**.

6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxy-6(*S*)-methoxyprost-13(*E*)-en-1-oic Acid, Sodium Salt (12d). A solution of 155 mg of **12c** in 1 mL of MeOH was treated with 0.40 mL of 1 N NaOH and 3 mL of water to provide 144 mg of **12d**.

6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxy-6(*R*)-methoxyprost-13(*E*)-en-1-oic Acid, Sodium Salt (13d). A solution

of 41 mg of **13c** in 1 mL of MeOH was treated with 0.11 mL of 1 N NaOH and 2 mL of water to provide 44 mg of **13d**.

6,9α-Epoxy-5-fluoro-11α,15(*S*)-dihydroxyprosta-5(*E*),13(*E*)-dien-1-oic Acid, Sodium Salt (14d). A solution of 275 mg of **14c** in 1 mL of MeOH was treated with 0.75 mL of 1 N NaOH and 5 mL of water to provide 271 mg of **14d**.

6,9α-Epoxy-5(*R*)-fluoro-11α,15(*S*)-dihydroxyprosta-6,13(*E*)-dien-1-oic Acid, Sodium Salt (15d). A solution of 347 mg of **15c** in 2 mL of MeOH was treated with 0.93 mL of 1 N NaOH and 5 mL of water to provide 325 mg of **15d**.

6,9α-Epoxy-5(*S*)-fluoro-11α,15(*S*)-dihydroxyprosta-6,13(*E*)-dien-1-oic Acid, Sodium Salt (16d). A solution of 264 mg of **16c** in 1 mL of MeOH was treated with 0.72 mL of 1 N NaOH and 5 mL of water to provide 263 mg of **16d**.

6,9α-Epoxy-5-fluoro-11α,15(*S*)-dihydroxyprosta-5(*Z*),13(*E*)-dien-1-oic Acid, Sodium Salt (17d). A solution of 5 mg of **17c** in 1 mL of MeOH was treated with 0.18 mL of 0.1 N NaOH and 2 mL of water for 24 h to provide 5 mg of **17d**.

Methyl 6,9α:7(*R*),11α-Diepoxy-15(*S*)-hydroxyprosta-5(*Z*),13(*E*)-dien-1-oate (47) and Methyl 6,9α:7(*R*),11α-Diepoxy-15(*S*)-hydroxyprosta-5(*E*),13(*E*)-dien-1-oate (48). A solution of 108 mg of the mixture of **25c** and **26c** above in 20 mL of MeOH was added to a solution prepared from 30 mg of sodium metal in 10 mL of MeOH. After 4 h at ca. 25 °C, TLC analysis showed no sign of reaction. The mixture was refluxed for 20 h until little starting material remained. After evaporation to a small volume, the mixture was diluted with ether and washed twice with water and brine. After drying over sodium sulfate and evaporation, DCLC (60% EtOAc) provided 21 mg of a mixture of isomers, ca. 82% **47** and 18% **48**, R_f 0.47.

Methyl 6,9α-Epoxy-5(*S*)-fluoro-6(*S*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oate (45) and Methyl 6,9α-Epoxy-5(*S*)-fluoro-6(*R*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oate (46). A sample of 148 mg of **16a**, which had become gummy with moisture after standing for about 8 months, was redried and found by ^{13}C NMR to contain about 20% of other materials. This sample was dissolved in 1 mL of water and chilled in an ice bath. After the addition of 20 mL of EtOAc, 5 mL of 2.5 % citric acid was added with vigorous stirring. The organic layer was separated and washed with brine. After removal of solvent the residue was dissolved in methanol and esterified with diazomethane. DCLC (20%, 50%, 100% EtOAc) provided 17 mg of crude **47**, 10 mg of a complex mixture, R_f 0.17, and 97 mg of a mixture, R_f 0.08, of ca. 55% **45** and 45% **46**.

6,9α:7(*R*),11α-Diepoxy-15(*S*)-hydroxyprosta-5(*Z*),13(*E*)-dien-1-oic Acid, Sodium Salt (49) and 6,9α:7(*R*),11α-Diepoxy-15(*S*)-hydroxyprosta-5(*E*),13(*E*)-dien-1-oic Acid, Sodium Salt (50). A solution of 21 mg of the mixture of **47** and **48** in 1 mL of MeOH was treated with 0.08 mL of 1 N NaOH and 1 mL of water to provide 23 mg of a mixture of ca. 84% **49** and 16% **50**.

Acid Decomposition of 14d. A solution of 113 mg of **14d** in 50 mL water was acidified to pH 5.3 by the addition of small pieces of dry ice and stored for 72 h at ca. 24 °C. After adding 1 N NaOH to return the pH to 8, lyophilization left a residue of 119 mg. ^{13}C NMR analysis (based on the relative intensities of the C-9 signals) indicated that the mixture contained ca. 20% **14d**, 34% 6,9α-epoxy-5(*S*)-fluoro-6(*S*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oic acid, sodium salt (**41**), 18% 6,9α-epoxy-5(*S*)-fluoro-6(*R*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oic acid, sodium salt (**42**), 15% 6,9α-epoxy-5(*R*)-fluoro-6(*S*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oic acid, sodium salt (**43**), and 13% 6,9α-epoxy-5(*R*)-fluoro-6(*R*),11α,15(*S*)-trihydroxyprost-13(*E*)-en-1-oic acid, sodium salt (**44**).

Decomposition of 15d. 1. To a solution of 259 mg of **15d** in 50 mL of water was added sufficient 1 N NaOH to raise the pH to 11. After 24 h the pH had fallen to 9.5, so additional base was added to return it to 11. After an additional 48 h (pH 9.5) lyophilization provided 282 mg of a mixture containing ca. 10% of **15d**, 30% of **49**, 45% of material that is assigned 6,9α-epoxy-5,11α,15(*S*)-trihydroxyprosta-6,13(*E*)-dien-1-oic acid, sodium salt (**51**), and 10% and 5% of two other materials. The composition was assigned on the basis of relative intensities of the C-6 signals.

2. To a solution of 267 mg of **15d** in 50 mL water were added a few small pieces of dry ice, which lowered the pH to 6.0. After 48 h at 24 °C lyophilization left a residue of 281 mg that was composed of **15d**, **43**, **44**, and **49** in ca. 3:3:2:2 as well as one or more unidentified minor impurities.

3. A solution of 270 mg of **15d** in 50 mL of water was acidified by the addition of small portions of Dowex 50W-X2 resin until a faint cloudiness developed. The resin was removed by filtration and rinsed with 50 mL of water. After 16 h at 24 °C the filtrate (pH 4.2) was returned to pH 8 and lyophilized, leaving a residue of 243 mg that was composed of ca. 20% **15d**, 45% **43**, and 35% **44**.

Acknowledgment. High resolution mass spectrometry was performed at the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln, a National Science Foundation Regional Instrumentation Facility. We are indebted to Dr. Jeremy D. Hribar for mass spectral interpretation; Nancy S. Nicholson, Susan L. Smith, and Beatrice B. Taite for biological evaluation; and Drs. Roy H. Bible, Anthony G. M. Barrett, Paul A. Grieco, and Masateru Miyano for helpful discussions.

Supplementary Material Available: The carbon and proton NMR assignments of compounds discussed and some related compounds in tabular form together with the spectrum of **14d** (14 pages). Ordering information is given on any current masthead page.

Translactonization in Erythromycins

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Received December 30, 1985

When erythromycin A is heated in diethylamine–acetic acid, an erythromycin hemiketal is obtained, which can be further transformed into a new enol ether and spiroketal. The new enol ether is also obtained in equilibrium with the normal one on heating erythromycin A or B in pyridine–acetic acid. The novel compounds, which will be called pseudoerythromycin derivatives, are characterized by a translactonization between the C_{11}-hydroxyl and the lactone group. Their structure was proved by mass and ^1H and ^{13}C NMR spectrometry, by acetylation experiments, and by degradation with lead tetraacetate.

In endeavoring to obtain a larger amount of the novel erythromycin A hemiketal, which we recently isolated from mother liquors of industrial production of erythromycin A,[1] the latter compound was treated with different com-

0022-3263/87/1952-0990$01.50/0