10-Nor-9,11-secoprostaglandins. Synthesis, Structure, and Biology of Endoperoxide Analogues

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Abstract: Prostaglandin A_2 (PGA_2) methyl ester (**4**) and PGA_2 15-acetate methyl ester (**11**) have both been converted to the corresponding derivatives of 10-nor-9,11-seco-$PGF_{2\alpha}$ (**7** and **12**, respectively) by the four-step sequence of reactions: (a) hydrogen peroxide–lithium hydroxide epoxidation, (b) borohydride reduction, (c) periodate cleavage, and (d) again, borohydride reduction. The 1,4-diol system of **7** readily formed an acetonide (**8**). Removal of protecting groups from **8** or **12** gave 10-nor-9,11-seco-PGF_2 (**1**). An X-ray crystallographic study of **7** confirmed the structural assignments. With an excess of *p*-toluenesulfonyl chloride in pyridine, diol **12** gave predominantely the ditosylate **13** while with a limited amount, 10-oxa-9,11-deoxy-PGF_2 15-acetate methyl ester (**14**) predominates. Removal of the acetate from **13** by hydrolysis gave a second ditosylate **17**. Reaction of either **13** or **17** with potassium superoxide in DMF gave the cyclic peroxides **16** or **18**, respectively. The methyl ester of **18** could be hydrolyzed with lipase to give 10-nor-9,11-seco-PGH_2 (**2**). The dimesylate (**19**) was also prepared from **12** and upon reaction with potassium thioacetate gave a mixture of the dithioacetate derivative **20** and the cyclic disulfide **21**. When this mixture was hydrolyzed with potassium carbonate and oxidized with air, the cyclic disulfide **22** was obtained. Hydrolysis of the methyl ester of **22** gave 10-nor-9,11-seco-9,11-dideoxy-9,11-epidithio-PGH_2 (**3**). Endoperoxide analogues **2** and **3**, while structurally related to PGH_2, elicit biological responses similar to thromboxane A_2 (TxA_2).

Prostaglandins modified by the formal removal of the C-10 methylene group may be defined as 10-nor-9,11-seco-prostaglandins. The preparation of several such analogues has been reported.[1-3] We were interested in molecules of this type, exemplified by 10-nor-9,11-secoprostaglandin $F_{2\alpha}$ (**1**), for several reasons. First, because these molecules have conformational freedom, we were curious what effect this would have on their biological activities. Second, we envisioned **1** as the starting material for preparation of both 10-nor-9,11-secoprostaglandin H_2 (**2**), a strain-free analogue of the endoperoxide prostaglandin H_2,[4] and 10-nor-9,11-seco-9,11-epidithioprostaglandin H_2 (**3**). Third, **1** also could serve as a precursor to other 10-nor-prostaglandin and -prostacyclin analogues. In this report, we describe the synthesis of compounds **1-3**.

10-Nor-9,11-secoprostaglandin $F_{2\alpha}$ (1). The nearest approach to **1** that has been reported to date is the synthesis of *d,l*-10-nor-9,11-seco-$PGF_{1\alpha}$ by Carroll and colleagues.[2] Their method via total synthesis is limited to preparation of the "one series" of analogues. We were interested in devising a short approach to the 10-nor system from available prostaglandins and chose PGA_2 methyl ester (**4**) as a potential starting point.

PGA_2 methyl ester **4** was converted in two steps into the 9α-hydroxy-10α,11α-epoxide **5**, a compound prepared previously by total synthesis and reported by Grieco and co-workers.[5] The hydroxy group of **4** was temporarily protected as the trimethylsilyl derivative and the 10,11 double bond then epoxidized with hydrogen peroxide–lithium hydroxide.[6] The trimethylsilyl group was removed during the reaction workup, and the crude product was submitted to reduction with sodium borohydride. Following purification of the product, these transformations provided **5** in 59% yield from **4**. The α configuration of both the 9-hydroxyl group and the epoxide in **5** was confirmed by reduction of **5** with lithium aluminum hydride to a mixture that contained 1-decarboxy-1-hydroxymethyl-$PGF_{2\alpha}$ (**6**).[7]

Our next goal was to carry out a cleavage reaction upon **5** with formation of the 10-nor-9,11-seco system as the result. Many conditions were tried in attempts to achieve this reaction, but only one, the use of periodic acid in tetrahydrofuran-water[8] followed by borohydride reduction, gave the desired result. The product of this reaction sequence, 10-nor-9,11-secoprostaglandin $F_{2\alpha}$ methyl ester (**7**), was a crystalline compound, mp 71-72 °C, obtained in 23% yield. Upon acid-catalyzed reaction with acetone, compound **7** was easily converted to acetonide **8**. A singlet at δ 1.30 in the NMR spectrum of **8**, integrating for six protons, is consistent with the acetonide structure.

Acetonide **8** was converted to the desired product **1** in two steps. The methyl ester was first saponified with potassium hydroxide in aqueous methanol, giving **9**. Then acid-catalyzed hydrolysis of the acetonide function gave 10-nor-9,11-secoprostaglandin $F_{2\alpha}$, a crystalline compound, mp 80-81 °C.

A shorter route to **1** from PGA_2 methyl ester (**4**) was developed as follows. The 15-acetate derivative (**11**) of **4** was prepared and then converted in four steps without isolation of intermediates into 10-nor-9,11-secoprostaglandin $F_{2\alpha}$ methyl ester 15-acetate (**12**). The four-step sequence was very similar to that described above and consisted of (a) hydrogen peroxide–LiOH epoxidation, (b) borohydride reduction, (c) periodate (H_5IO_6) cleavage, and (d) borohydride reduction and gave **12** in 20% yield from **11**. Simultaneous removal of the methyl ester and acetate-protecting groups from **11** gave **1**.

In order to show that acetonide formation had occurred between the hydroxyl groups at C-9 and C-11, we correlated compound **8** with **12**. Acetylation of **8** with acetic anhydride in pyridine gave **10**. The acetonide group of **10** was hydrolyzed with aqueous acid, giving a product identical with compound **12** and showing that the 15-hydroxyl group in **8** was free.

X-ray Crystallography. The structure of the triol **7** was confirmed by X-ray crystallography. The following crystal data were obtained for **7**. The space group is $P2_12_12_1$; unit cell parameters are α = 5.978 (1) Å, b = 8.815 (1) Å, and c = 39.944 (1) Å; and the final agreement index R was 0.055.[9] Final atomic coordinates

(1) A. Ishida, S. Saijo, K. Noguchi, M. Wada, O. Takaiti, and J. Himizu, *Chem. Pharm. Bull.*, **27**, 625 (1979). See also: J. Himizu, S. Harigaya, A. Ishida, K. Yoshikawa, and M. Sato, German Offen., 2229225 [*Chem. Abstr.*, **78**, 111102 (1973)].

(2) (a) F. I. Carroll, F. M. Hauser, R. C. Huffman, and M. C. Coleman, *J. Med. Chem.*, **21**, 321 (1978); (b) F. M. Hauser and R. C. Huffman, *Tetrahedron Lett.*, 905 (1974).

(3) D. Tunemoto, Y. Takahatake, and K. Kondo, *Chem. Lett.*, 189 (1978).

(4) Cf.: (a) D. H. Nugteren and E. Hazelhof, **326**, 448 (1973); (b) M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 345 (1974); (c) R. A. Johnson, E. G. Nidy, L. Baczynskyj, and R. R. Gorman, *J. Am. Chem. Soc.*, **99**, 7738 (1977); (d) N. A. Porter, J. D. Byers, K. M. Holden, and D. B. Menzel, *Ibid.* **101**, 4319 (1979).

(5) P. A. Grieco, T. Sugahara, Y. Yokoyama, and E. Williams, *J. Org. Chem.*, **44**, 2189 (1979).

(6) W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Am. Chem. Soc.* **99**, 1222 (1977).

(7) P. Crabbe, H. Carpio, and A. Guzman, *Intra-Sci. Chem. Rept.*, 6, 55 (1972).

(8) A. J. Fatiadi, *Synthesis*, 229 (1974).

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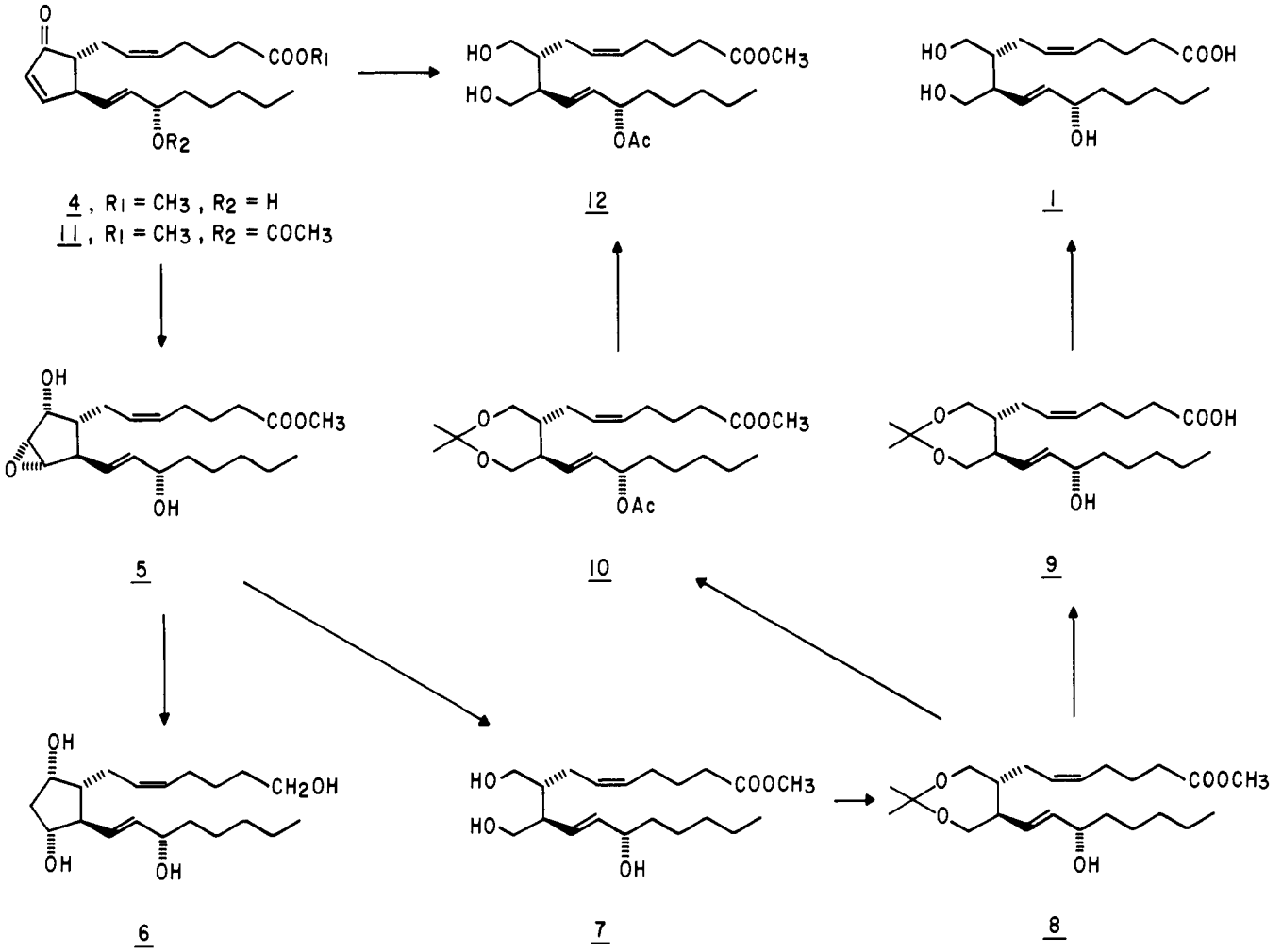
Scheme I



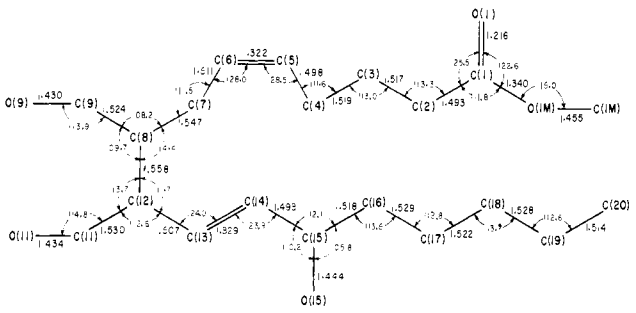


Figure 1. Bond distances (Å) and bond angles (Deg). Standard deviations are 0.003–0.006 Å for bond lengths and 0.2–0.3° for angles.

are listed in Table I, and numbering and bond distances and angles are shown in Figure 1.

The overall "hairpin" appearance of the molecule is very much like other prostaglandins with intact rings despite markedly different torsion angles. Langs, Erman, and DeTitta observed two conformers in their X-ray study of the tris salt of $PGF_{2\alpha}$.[10] In both of the conformers they studied as well as in the two conformers of the *p*-iodophenacyl ester of 15(*S*)-methyl-$PGF_{2\alpha}$ studied by Chidester and Duchamp,[11] the torsion angles at the ring junction bond, C8–C12, are simialr; this angle varies from 80° to 93° among the four molecules. In contrast, in this study of the 10-nor-9,11-seco-$PGF_{2\alpha}$ methyl ester (**7**), the torsion angle C7–C8–C12–C13 is −39°, a rotation of −120° to −130° about

Table I. Final Atomic Coordinates (×10⁴) and Standard Deviations for Compound 7

	X	Y	Z
C(1)	2350 (7)	−10059 (5)	−4674 (1)
O(1)	2255 (6)	−11433 (4)	−4651 (1)
O(1M)	3911 (5)	−9349 (4)	−4857 (1)
C(1M)	5458 (8)	−10346 (7)	−5032 (1)
C(2)	791 (7)	−8963 (5)	−4510 (1)
C(3)	−776 (7)	−9703 (5)	−4260 (1)
C(4)	−2595 (7)	−8639 (5)	−4135 (1)
C(5)	−4243 (6)	−9448 (5)	−3916 (1)
C(6)	−4933 (6)	−9077 (5)	−3612 (1)
C(7)	−4304 (5)	−7697 (4)	−3408 (1)
C(8)	−2747 (5)	−8118 (4)	−3113 (1)
C(9)	−405 (5)	−8389 (4)	−3252 (1)
O(9)	1139 (4)	−8974 (3)	−3011 (1)
C(11)	−4410 (5)	−7144 (4)	−2555 (1)
O(11)	−6670 (4)	−6852 (3)	−2657 (1)
C(12)	−2651 (5)	−6909 (4)	−2829 (1)
C(13)	−2657 (5)	−5316 (4)	−2967 (1)
C(14)	−890 (5)	−4400 (4)	−2963 (1)
C(15)	−836 (5)	−2879 (4)	−3128 (1)
O(15)	−562 (4)	−1700 (3)	−2880 (1)
C(16)	1130 (6)	−2715 (4)	−3366 (1)
C(17)	1209 (6)	−3928 (5)	−3639 (1)
C(18)	3169 (7)	−3721 (5)	−3878 (1)
C(19)	3408 (7)	−5002 (5)	−4134 (1)
C(20)	5299 (8)	−4730 (6)	−4379 (1)

(9) All calculations were carried out by using the CRYM system of crystallographic programs written by David J. Duchamp, The Upjohn Company, Kalamazoo, MI.

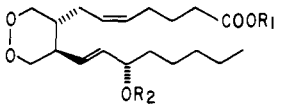
(10) D. A. Langs, M. Erman, and G. T. DeTitta, *Science (Washington, D.C.)*, **197**, 1003 (1977).

(11) C. G. Chidester and D. J. Duchamp, American Crystallographers Association Spring Meeting, Berkeley, CA, Program and Abstracts, ACA, New York, 1974, p 34.

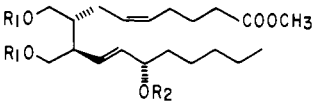
this bond. If this were the only difference, the "upper" (C1–C8) carbon chain and the "lower" (C12–C20) chain would be nowhere near each other; however another rotation, about the C6–C7 bond, brings the chains into proximity again. In the Langs, Erman, and DeTitta study, the C5=C6—C7—C8 torsion angle for the two conformers was 142° and 128°; for the two conformers in the Chidester and Duchamp study, this angle was 111° and 135°. In compound **7**, the C5=C6—C7—C8 angle was −108°, a rotation of approximately 120°. There are many differences in chain conformation among the four molecules previously studied, but one feature common to all four and also observed in compound **7** is the gauche–gauche interaction at C13=C14—C15—C16 and C13=C14—C15—O15. In compound **7** there is also a gauche interaction at C3—C4—C5=C6; a computer graphics model shows that if this torsion angle were trans instead of gauche, the chains would be farther apart. There are no contacts between upper and lower chain atoms which are less than the sum of the van der Waals radii. The closest approach is C2–C19, 4.11 Å. All three hydroxyls in compound **7** are both donors and acceptors for hydrogen bonds, involving three other molecules.

10-Nor-9,11-secoprostaglandin H_2 (2). The prostaglandin endoperoxides, PGH_2 and PGG_2, are the key intermediates in the biological conversion of arachidonic acid into a variety of important molecules including the classical prostaglandins,[4] thromboxane A_2,[12] prostacyclin,[13] and the fragmentation product 12-hydroxy-5,8,10-hepadecatrienoic acid (HHT).[12] As such, the endoperoxides are subject to a series of remarkable (bio)chemical transformations. The strain energy inherent in the bicyclo[2.2.1]heptyl ring structure of the endoperoxides may contribute to these transformations. We wished to prepare the relatively strain-free 10-nor-9,11-seco-PGH_2 molecule as an analogue of PGH_2 in order that we might attempt to determine the effect of the ring strain on both the biological and chemical properties of the latter.

As an approach to **2**, we planned to attempt peroxide formation

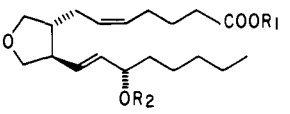


2, $R_1 = R_2 = H$
16, $R_1 = CH_3$, $R_2 = COCH_3$
18, $R_1 = CH_3$, $R_2 = H$



13, R_1 = Tos, $R_2 = COCH_3$
17, R_1 = Tos, $R_2 = H$

by using the displacement reaction of potassium superoxide on tosylates.[14] To this end, we prepared the 9,11-ditosylate derivative (**13**) of intermediate **12**. Besides formation of the desired ditosylate, reaction of **12** with *p*-toluenesulfonyl chloride in pyridine produced a second product (**14**). We suspected that these reaction conditions might result in dehydration of the 1,4-diol with formation of a tetrahydrofuran. This suspicion was shown to be correct by the physical properties of **14**. There was no hydroxyl absorption in the infrared spectrum of **14** and no protons typical of a tosyl group in the NMR spectrum. These results taken with the analytical data for the compound confirm that **14** is 10-oxa-9,11-dideoxy-$PGF_{2\alpha}$ 15-acetate methyl ester. Hydrolysis of **14** with potassium hydroxide in aqueous methanol gave the parent 10-oxa-9,11-dideoxy-$PGF_{2\alpha}$ (**15**).



14, $R_1 = CH_3$, $R_2 = COCH_3$
15, $R_1 = R_2 = H$

The ratio of **13** and **14** formed in the tosylation reaction depends on the reaction conditions used and therefore can be controlled to a considerable extent. When the reaction is kept at 0–10 °C and a large excess of *p*-toluenesulfonyl chloride is used, **13** and **14** are obtained in 75% and 3% yields, respectively. However, when the reaction is done at room temperature and only 1 equiv of *p*-toluenesulfonyl chloride is added at a time, **13** and **14** are obtained in yields of 11% and 76%, respectively.

The reaction of ditosylate **13** with potassium superoxide in DMF gave only one peroxidic product as determined by reaction of the TLC plate to ferrous thiocyanate spray reagent.[14] This peroxidic product (**16**) was also the main reaction product and after purification was obtained in 56% yield. Reduction of this product with triphenylphosphine slowly converted it into a single new product having the same R_f on TLC as diol **12**, confirming the structure as **16**. The possibility that **16** may have either a hydroperoxide structure or a dimeric structure can be ruled out by the characteristics of the compound. If either a monohydroperoxide (at C-9 or C-11) or a dihydroperoxide had formed in the reaction of **13** with KO_2, it would be expected to be more polar on silica gel TLC than **13**, but the product was a less polar material. Formation of a dimeric peroxide structure seems unlikely since five different dimers are possible (three monoperoxy dimers are possible by joining C-9 to C-9, C-9 to C-11, or C-11 to C-11 and two diperoxy dimers are possible by joining C-9 to C-9 and C-11 to C-11 or by joining C-9 to C-11 and C-11 to C-9), but no more than one peroxidic product was ever detected while the reaction was in progress or in the final product mixture.

In order to reduce the number of chemical manipulations required after peroxide formation, we modified the ditosylate **13** by removal of the acetate-protecting group. This was done by dissolving **13** in methanol and using sodium methoxide to catalyze exchange of the acetate group with the solvent. The reaction was complete in 2 h at room temperature, and the tosylate functions were unaffected by this treatment. The product **17** was then converted to the cyclic peroxide **18** by using KO_2 in DMF. The yield of **18** after chromatographic purification was 69%. As above, the product gave a positive color test with ferrous thiocyanate and was the only peroxidic product formed by the reaction.

Conversion of **18** to the desired carboxylic acid **2** was achieved efficiently by the use of lipase in pH 8.0 buffer.[4d] 10-Nor-9,11-seco-PGH_2 (**2**) was obtained from this reaction in 87% yield following chromatographic purification on acid-washed silica gel.

10-Nor-9,11-seco-9,11-dideoxy-9,11-epidithioprostaglandin H_2 (3). The disulfide analogue of PGH_2 has been prepared and interesting biological properties have been suggested for the analog.[15] With the ready availability of intermediate **12**, we have carried out the preparation of the analogue **3** as described below.

The bis(mesylate) derivative (**19**) of **5** was prepared and, without further purification, was heated (50 °C) with potassium thioacetate in 1:1 Me_2SO–DMF[15] for 16 h. The 9,11-dithioacetate derivative **20** was obtained from this reaction in 60% yield together with 20% of a second, unexpected product (**21**). The anticipated structure of the major product **20** was confirmed by signals for the three acetyl groups at δ 1.98 (*O*-acetyl) and δ 2.27 and 2.29 (two *S*-acetyls). The multiplet of signals at δ 2.7–3.1 (4 protons) also is consistent with the presence of two methylene groups next to sulfur.

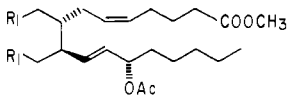
(12) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 3400 (1974).

(13) (a) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976); (b) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976).

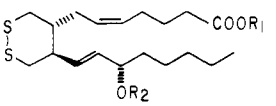
(14) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975); (b) R. A. Johnson, E. G. Nidy, and M. V. Merritt, *J. Am. Chem. Soc.*, **100**, 7960 (1978); (c) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).

(15) H. Miyake, S. Iguchi, H. Itoh, and M. Hayashi, *J. Am. Chem. Soc.*, **99**, 3536 (1977).

The nature of minor product **21** was elucidated during con-



19, R_1 = -OMs
20, R_1 = -SCOCH$_3$

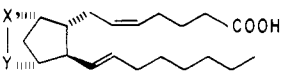


3, $R_1 = R_2 = H$
21, $R_1 = CH_3$, $R_2 = COCH_3$
22, $R_1 = CH_3$, $R_2 = H$

version of bis(thioacetate) **20** into cyclic disulfide **22**. The first step of this conversion was the hydrolysis of the acetyl groups using potassium carbonate in methanol. The *S*-acetyl groups apparently are hydrolyzed more rapidly than the *O*-acetate. When both *S*-acetyl groups are removed, the resulting bis(thiol) is rapidly oxidized by atmospheric oxygen to the cyclic disulfide, which has the same R_f on silica gel TLC as does the minor product **21** isolated above. Hydrolysis of the *O*-acetyl group proceeds more slowly, but when complete the cyclic disulfide **22** is isolated in 87% yield.

Further hydrolysis of the methyl ester with aqueous potassium hydroxide in *tert*-butyl alcohol served to convert **22** into the desired disulfide analogue **3**.

Biological Properties of 2 and 3. The activities of both **2** and **3** were measured in several biological systems and compared with those of their natural counterpart, PGH_2. As shown in Figure 2, PGH_2 is a proaggregatory agent toward human platelet rich plasma (PRP).[16] Approximately 5 times as much of either **2** or **3** is required to induce an aggregation equal to that of PGH_2 (also in Figure 2). The aggregation induced by PGH_2 is blocked by the thromboxane synthetase inhibitor, 9α,11α-iminoepoxy-prosta-5(*Z*),13(*E*)-dienoic acid (**23**, 9,11-IEP)[17,18] as shown in Figure 3. This inhibitor does not, however, block the aggregations induced by either **2** or **3**. The aggregations induced by all three, PGH_2, **2**, and **3**, are blocked by the receptor level TxA_2 antagonist, 9α,11α-epoxyiminoprosta-5(*Z*),13(*E*)-dienoic acid (**24**, 9,11-EIP)[17,19] (see Figure 3).



23, X = NH, Y = O
24, X = O, Y = NH

A second assay sensitive to PGH_2 and thromboxane A_2 is the rat aorta strip. Authentic TxA_2 (generated from PGH_2 with human platelet microsomes)[20] contracts the rat aorta strip with an ED_{50} value of 5 ng/mL while PGH_2 itself has an ED_{50} of approximately 400 ng/mL. Both **2** and **3** induced dose dependent contractions of the rat aorta and had ED_{50} values of 20 and 5 ng/mL, respectively. However, neither compound gave larger contractions after incubation with human platelet microsomes.

The preceding results suggest that both **2** and **3** have intrinsic "TxA_2-like" activity since they both induce platelet aggregation and contract rat aorta strips. They apparently are not biochemically converted to "TxA_2-like" molecules because their proaggregatory activity is not blocked by a thromboxane synthetase inhibitor and their aorta contracting activity is not enhanced by incubation with human platelet microsomes. Although **2** and **3** differ very little structurally from PGH_2, their biology more closely approximates TxA_2.

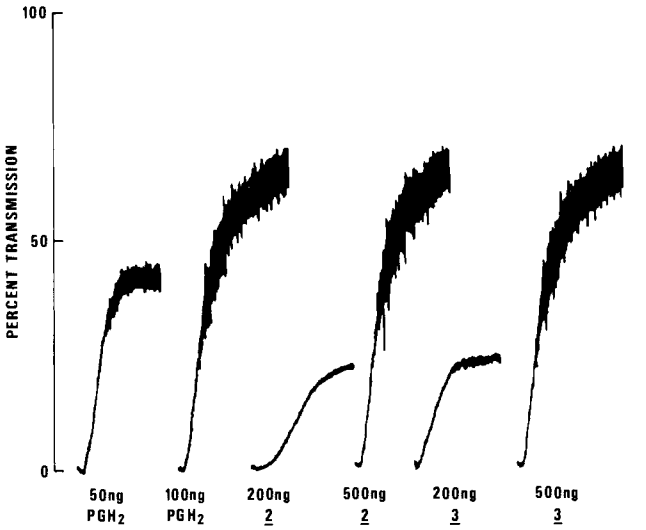


Figure 2. Platelet aggregation induced by two concentrations each of PGH_2, **2**, and **3** in human platelet rich plasma.

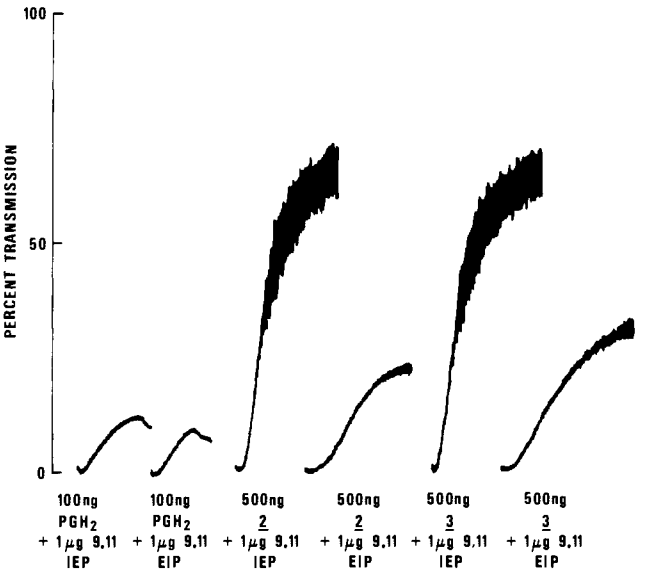


Figure 3. The effect of the thromboxane A_2 synthetase inhibitor 9,11-IEP (**23**) and the receptor level thromboxane A_2 antagonist 9,11-EIP (**24**) on platelet aggregation induced by PGH_2, **2**, or **3**.

Experimental Section

General Remarks. Melting points were obtained with either a Fisher-Johns or Thomas-Hoover 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 either 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 analyses of the NMR spectra are presented. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer. Brine refers to a saturated aqueous solution of sodium chloride. Preparative HPLC columns used were prepared by packing silica gel 60 (40–63 μm, E. Mercek) or CC-4 silica gel (Mallinkrodt) in various sizes of Michel-Miller column (Ace Glass, Inc.). The elution solvents were driven by either Milton-Roy mini or D pumps. Detection of the products was done by TLC analyses.

10α,11α-Epoxy-11-deoxyprostaglandin $F_{2\alpha}$ Methyl Ester (5). A solution of prostaglandin A_2 methyl ester (**4**, 13.9 g, 40 mmol), hexa-

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methyldisilazane (19 mL), and chlorotrimethylsilane (1 mL) in tetrahydrofuran (80 mL) was stirred at room temperature under nitrogen for 4 h. The solvent was removed in vacuo. Benzene was added to the residue, and the mixture was filtered through Celite to remove a white precipitate. The solvent was again removed in vacuo. The residue was dissolved in isopropyl alcohol (300 mL). The solution was placed under nitrogen and cooled to −40 °C, and 30% aqueous hydrogen peroxide (24 mL) was added. Aqueous 3 N lithium hydroxide (34 mL) was added dropwise over a period of 30 min. The mixture was warmed to −25 °C and stirred for 3 h. If reaction is not complete as detected by TLC, additional LiOH solution (5 mL) may be added and stirring continued another hour. The reaction mixture was neutralized to pH ~7 with 1 N hydrochloric acid. Isopropyl alcohol was removed in vacuo, and the residue was extracted with ethyl acetate (1 L). The organic extract was washed with aqueous sodium bisulfate, 1 N HCl, sodium bicarbonate, and brine and was dried over sodium sulfate. Filtration and concentration in vacuo gave crude epoxy ketone, which was stored in the freezer.

A solution of the above epoxy ketone in methanol (200 mL) was added over a period of 30 min to a stirred mixture of sodium borohydride (4.62 g, 0.12 mol) in methanol (200 mL) cooled to −15 °C under nitrogen. After the solution was stirred for 1 h, TLC analysis showed that some starting material remained so additional $NaBH_4$ (1.51 g, 0.04 mol) was added. After the solution was stirred 1 h, one more addition of $NaBH_4$ (1.51 g) was required to complete the reaction. Saturated aqueous ammonium chloride (100 mL) was added, and the reaction mixture was allowed to warm to room temperature. The pH was adjusted to ~7.5 by addition of aqueous $NaHSO_4$. Methanol was removed in vacuo, and the aqueous concentrate was extracted with ethyl acetate (2 L total). The organic extract was washed with aqueous sodium bisulfate, sodium bicarbonate, and brine and was dried over magnesium sulfate. Filtration and concentration in vacuo gave 13.6 g of a crude product which was purified by chromatography over silica gel (250 g) using HPLC techniques. Chloroform–acetone (10:1) was used for 100 fractions (40 mL each) and $CHCl_3$–acetone (5:1) was used for 50 fractions. The product (**5**, 8.74 g, 59%) was eluted in fractions 36–110 as a colorless oil: $[\alpha]^{25}_D$ + 93° (*c* 0.9960, 95% EtOH); IR 3400, 3000, 2930, 2850, 1735, 1435, 1315, 1245, 1220, 1200, 1150, 1085, 1020, 920, 860 cm^{-1}; NMR (δ, $CDCl_3$) 5.76–5.25 (m, 4 H, olefinic protons), 4.56–4.32 (d of d centered at δ 4.44, 1 H, (O)CHCCO), 4.26–3.78 (m, 1 H, *CH*OH), 3.68 (s, 3 H, $COOCH_3$), 3.68 (d, 1 H, J = 2.5 Hz, OCCHCO), 3.36 (d, 1 H, J = 1 H, J = 2.5 Hz, OCHCCO), 2.78–2.55 (m, 1 H, CHCCO), 0.88 (t, 3 H, J = 5.5 Hz, CH_3); mass spectrum, *m/e* 510.3203 (calcd for bis(Me_3Si) ether, $C_{27}H_{50}Si_2O_5$, *m/e* 510.3196).

Reduction of 10α,11α-Epoxy-11-deoxyprostaglandin $F_{2\alpha}$ Methyl Ester with Lithium Aluminum Hydride. A solution of **5** (0.183 g, 0.5 mmol) in ether (10 mL) was added dropwise to a mixture of lithium aluminum hydride (0.152 g, 40 mmol) and ether (10 mL). The mixture was stirred 2 h at room temperature and 2 h at 40 °C. The reaction mixture was cooled in ice and carefully quenched with 1 N HCl until pH ~4.5 was reached. The mixture was saturated with NaCl, extracted with ethyl acetate (3 × 100 mL), and dried. The crude product (0.175 g) was separated into three components by preparative TLC on six Analtech silica gel (250 μm thickness) plates. Chloroform–acetone (1:1) was used as solvent, and the plates were developed twice in this system. The most polar fraction (0.065 g, 38%) was by TLC mobility and NMR spectrum identical with an authentic sample of the tetraol (**6**) obtained from reduction of $PGF_{2\alpha}$ methyl ester with $LiAlH_4$.

The second fraction (0.053 g, 31%) was crystallized from ethyl acetate–hexane, mp 53–54 °C. This compound formed an acetonide (NMR, δ 1.26 and 1.42) in acetone containing *p*-toluenesulfonic acid as a catalyst. The compound was assigned the structure having a 10α-hydroxyl group.

The third, least polar fraction (0.018 g, 10%) retained the epoxide group (NMR) and was tentatively assigned the structure in which only the methyl ester group of **5** has been reduced to the primary alcohol.

10-Nor-9,11-secoprostaglandin F_2 Methyl Ester (7). A solution of 10α,11α-epoxy-11-deoxy $PGF_{2\alpha}$ methyl ester (**5**, 5.5 g, 15 mmol) and periodic acid (10.2 g, 45 mmol) in tetrahydrofuran–water (4:1, 450 mL) was heated at 60 °C for 5 h. Saturated sodium bicarbonate was then added to neutralize the acid, and the THF was removed in vacuo. The residue was extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. Filtration and concentration gave the crude product. The crude product was dissolved in isopropyl alcohol (150 mL), and the solution was cooled to 0–5 °C with an ice–water bath. Sodium borohydride (2.78 g, 75.0 mmol) was added over a period of 5 min. The mixture was stirred at room temperature for 2 h. The solution was again cooled with an ice–water bath and 10% aqueous sodium bisulfate was added until the pH <7. The isopropyl alcohol was removed in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with 10% aqueous sodium bisulfate, with saturated sodium bicarbonate, and with brine and was dried over anhydrous magnesium sulfate. Filtration and concentration gave the crude product. The product mixture was separated by chromatography over a size C Merck Lobar silica gel column. The column was eluted with ethyl acetate, and fractions of 50-mL volume were collected. Fractions 4–11 contained 1.2 g of an unidentified product; fractions 13–18 contained 0.4 g of recovered **5**; and fractions 60–200 contained 1.25 g (3.5 mmol, 23%) of the desired product **7**. The product (**7**) was recrystallized from ethyl acetate–hexane, giving 10-nor-9,11-secoprostaglandin F_2 methyl ester as colorless crystals: mp 71–72 °C; IR (Nujol mull) 3260, 1745, 1665, 1165, 1040, 1025, 985 cm^{-1}; ^1H NMR (δ, $CDCl_3$) 5.74–5.32 (m, 4 H, olefinic protons), 4.26–3.88 (m, 1 H, CHO), 3.66 (s, 3 H, $COOCH_3$), 3.88–3.48 (m, 4H, CH_2O); high-resolution mass spectrum (tris(Me_3Si) derivative), *m/e* 557.3517 (calcd for $M^+ - CH_3$, $C_{28}H_{57}Si_3O_5$, *m/e* 557.3514).

Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.63; H, 10.36.

10-Nor-9,11-secoprostaglandin F_2 9,11-Acetonide Methyl Ester (8). A solution of **7** (0.712 g, 2.0 mmol) in acetone (20 mL) was cooled to 0–5 °C in an ice bath. *p*-Toluenesulfonic acid (0.020 g) was added, and the solution was stirred at 0–5 °C for 3 h. Saturated sodium bicarbonate was added, and acetone was removed in vacuo. The residue was extracted with ether, and the organic layer was washed with saturated sodium bicarbonate. After the layer was dried over anhydrous magnesium sulfate, filtered, and concentrated, acetonide **8** was obtained. Purification of the acetonide was achieved by chromatography over silica gel (one Merck size B Lobar column) with ethyl acetate as the eluant. The pure product **8** was obtained as a colorless oil: IR (cm^{-1}, neat) 3460, 1740, 1220, 1160, 1040, 970, 850; ^1H NMR (δ, $CDCl_3$) 5.68–5.24 (m, 4 H, CH=CH) 4.28–3.78 (m, 1 H, CHO), 3.68 (s, 3 H, $COOCH_3$), 3.78–3.26 (m, 4 H, CH_2O); 1.30 (s, 6 H, $CH_3(O)C(O)CH_3$); high-resolution mass spectrum (Me_3Si derivative), *m/e* 453.3025 (calcd for $M^+ - CH_3$, $C_{25}H_{45}SiO_5$, *m/e* 453.3036).

Anal. Calcd for $C_{23}H_{40}O_5$; C, 69.66; H, 10.17. Found: C, 69.37; H, 10.39.

10-Nor-9,11-secoprostaglandin F_2 9,11-Acetonide (9). A solution of **8** (0.213 g, 0.54 mmol) in methanol (1 mL), water (0.1 mL), and 1 N potassium hydroxide in methanol (1 mL) was stirred at room temperature for 24 h. Methanol was removed in vacuo, and the aqueous residue was acidified with cold 10% aqueous sodium bisulfate. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over $MgSO_4$. Filtration and concentration gave the crude product which was chromatographed over acid-washed silica gel (Mallinckrodt CC-4, 50 g, packed in an HPLC glass column), using acetone–methylene chloride (1:2) for elution. The pure product **9** (0.187 g, 0.49 mmol, 90%) was obtained as an oil: IR (cm^{-1}, neat) 3385, 3158, 2665, 1731, 1710, 1219, 1158, 1080, 1039, 972, 852; ^1H NMR (δ, $CDCl_3$) 6.92 (br s, 3 H, OH, CO_2H), 5.68–5.22 (m, 4 H CH=CH), 4.26–3.80 (m, 1 H CHO), 3.80–3.35 (m, 4 H, CH_2O); 1.30 (s, 6 H, $CH_3(O)C(O)CH_3$); high-resolution mass spectrum (bis(Me_3Si) derivative), *m/e* 511.3303 (calcd for $C_{27}H_{51}Si_2O_5$, *m/e* 511.3275).

Anal. Calcd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. Found: C, 68.68, H, 9.98.

10-Nor-9,11-secoprostaglandin F_2 (1). A. From 9. A solution of **9** (0.103 g, 0.27 mmol) in acetic acid–water (2:1, 1.5 mL) was stirred at room temperature for 16 h and at 40 °C for 30 min. The acetic acid–water was removed in vacuo, and the crystalline residue was recrystallized from ethyl acetate–hexane, giving **1** as colorless crystals (0.078 g, 0.227 mmol, 84%): mp 79–80 °C; IR (cm^{-1}, Nujol) 3240, 1720, 1685, 1665, 1190, 1040, 1025, 985; ^1H NMR (δ, $CDCl_3$) 5.78–5.28 (m, 4 H, CH=CH) 4.28–3.80 (m, 1 H, CHO), 3.80–3.32 (m, + Br sh 8 H, CH_2O, OH, CO_2H); high-resolution mass spectrum (tetrakis(Me_3Si) derivative), *m/e* 615.3726 (calcd for $M^+ - CH_3$, $C_{30}H_{63}Si_4O_5$, *m/e* 615.3753).

Anal. Calcd for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.88; H, 10.18.

B. From 12. A solution of **12** (0.398 g, 1 mmol) in methanol containing KOH (1 N, 4.0 mL, 4.0 mmol) was stirred at room temperature for 16 h. The solution was acidified with 10% aqueous sodium hydrogen sulfate and the excess methanol removed in vacuo. The aqueous residue was extracted with ethyl acetate, and the organic extract was washed with brine, dried, filtered, and concentrated. The crystalline residue was recrystallized from ethyl acetate–hexane, giving 0.170 g of **1**. The mother liquors were chromatographed. The desired product was combined with the above crystals and recrystallized, giving a total of 0.175 g (0.51 mmol, 51%) with **1**, mp 80–81 °C. The spectral properties of this compound were identical with the sample of **1** described in part A, above.

10-Nor-9,11-secoprostaglandin F_2 9,11-Acetonide 15-Acetate Methyl Ester (10). The acetonide **8** was dissolved in a solution of pyridine (1 mL) and acetic anhydride (1 mL). The solution was stirred at room

temperature for 2 h. The solution was cooled to 0–5 °C, and 0.2 mL of water was added. After being stirred for 0.5 h, the mixture was extracted with ether. The ether layer was washed with 10% aqueous sodium bisulfate, saturated sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration gave the crude product. HPLC (silica gel, 30–50 μm 125 g; collecting 50 mL/fraction eluting with hexane, fractions 1–10; hexane–ethyl acetate (10:1) fractions 10–70; (5:1) fractions 71+) gave pure **10** (720 mg from 712 mg of **8**, 82%) as a colorless oil: IR (cm^{-1}, neat) 1740, 1370, 1241, 1220, 1159, 1082, 1040, 1020, 972, 853; ^1H NMR (δ, $CDCl_3$) 5.68–5.00 (m, 5 H, CH=CH, CHOAc), 3.66 (s, 3 H, CO_2CH_3), 3.72–3.22 (m, 4 H, CH_2O), 2.02 (s, 3 H, $OCOCH_3$), 1.28 (s, 6 H, $CH_3(O)C(O)CH_3$); high-resolution mass spectrum, *m/e* 423.2766 (calcd for $M^+ - CH_3$, $C_{24}H_{39}O_6$, *m/e* 423.2746).

Anal. Calcd for $C_{25}H_{42}O_6$: C, 68.46; H, 9.65. Found: C, 68.42; H, 9.69.

10-Nor-9,11-secoprostaglandin F_2 15-Acetate Methyl Ester (12). A. From 10. The acetonide **10** (0.525 g, 1.2 mmol) was dissolved in acetic acid–water (2:1, 3.6 mL). The solution was stirred at room temperature for 4 h after which no starting material remained (TLC). The acetic acid–water was removed in vacuo and the residue was taken up in ethyl acetate. This solution was washed in succession with saturated aqueous sodium bicarbonate and with brine and then dried over $MgSO_4$. Filtration and concentration gave the crude product which was chromatographed over one Merck size B Lobar silica gel column with 80% ethyl acetate–hexane (50 mL/fraction). Fractions 8–15 contained pure **12** (0.468 g, 1.17 mmol, 98%) IR (cm^{-1}, neat) 3428, 3005, 1738, 1437, 1371, 1243, 1174, 1155, 1047, 1021, 978; ^1H NMR (δ, $CDCl_3$) 5.78–5.00 (m, 5 H CH=CH, CHOAc), 3.66 (s, 3 H, CO_2CH_3), 3.92–3.50 (m, 4 H, CH_2O), 2.94 (br s, 2 H, OH), 2.02 (s, 3 H, $-OCOCH_3$); high-resolution mass spectrum (bis(Me_3Si) derivative), *m/e* 542 (M^+), 482.3251 (calcd for $M^+ - HOAc$, $C_{26}H_{50}Si_2O_4$, *m/e* 482.3247).

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.57; H, 9.30.

B. From Prostaglandin A_2 15-Acetate Methyl Ester. A stirred solution of prostaglandin A_2 15-acetate methyl ester (**11**, 60.1 g, 0.15 mol) in isopropyl alcohol (1.3 L) was cooled to −30 to −40 °C and aqueous 30% hydrogen peroxide (110 mL) was added over a period of 5 min. Aqueous 3 N lithium hydroxide (140 mL) was added over a period of 30 min with vigorous stirring while the temperature of the solution was maintained at −30 to −40 °C. The solution was stirred an additional 90 min at this temperature and monitored by TLC to check for completion of reaction (an aliquot is treated with aqueous $NaHSO_3$–$NaHSO_4$ and extracted with ethyl acetate). Sodium borohydride (23 g, 0.6 mol) was added over a period of 10 min, and the mixture was stirred an additional 30 min. The mixture was cooled to −50 to −60 °C and excess reagent destroyed by addition of 10% aqueous sodium bisulfate until the pH <7. Isopropyl alcohol was removed in vacuo, and the residue was extracted with ethyl acetate (2 L). The ethyl acetate was washed with $NaHSO_3$ (200 mL), $NaHSO_4$ (200 mL), saturated $NaHCO_3$, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed over a column of silica gel (1.3 kg) packed in 1:2 ethyl acetate–hexane. TLC of the product (57.5 g, 91%) indicated a mixture of isomeric epoxides: IR (cm^{-1}, neat) 3457, 1738, 1437, 1372, 1242, 1156, 1082, 1045, 1021, 973, 879, 862; ^1H NMR (δ, $CDCl_3$) 5.80–4.95 (m, 5 H, CH=CH, CHOAc), 4.56–3.24 (m, 3 H, CHO, $\overleftarrow{CH-CHO}$), 3.64 (s, 3 H, CO_2CH_3), 2.02 (s, 3 H, $OCOCH_3$); high-resolution mass spectrum (Me_3Si derivative), *m/e* 480, 465, 449, 420.2718 (calcd for $M^+ - HOAc$, $C_{24}H_{40}SiO_4$, *m/e* 420.2696).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.34; H, 9.02.

The mixture of isomeric epoxides (4.08 g, 0.010 mol) from the preceding reaction was dissolved in THF–water (2:1, 300 mL). Periodic acid (6.81 g, 0.030 mol) was added and the solution was stirred at 70 °C for 2.5 h. Additional periodic acid (2.3 g) was added, and heating was continued another 2.5 h. The solution was cooled and neutralized to pH 7 with the addition of saturated sodium bicarbonate solution. The THF was removed in vacuo, and the residue was extracted with ethyl acetate (1 L). The extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The product, an oil, was dissolved in isopropyl alcohol (100 mL), and the solution was cooled (0–5 °C) in an ice bath. Sodium borohydride (3.7 g, 0.10 mol) was added as the powder. The ice bath was removed, and the mixture was stirred at room temperature for 1.5 h. The mixture was again cooled in an ice bath, and the excess sodium borohydride was carefully destroyed by addition of 10% sodium bisulfate. The isopropyl alcohol was removed in vacuo, and the residue was extracted with ethyl acetate (1 L). The ethyl acetate layer was washed with 10% sodium bisulfate, sodium bicarbonate, and brine. The solution was dried ($MgSO_4$), filtered, and concentrated, giving the crude product which was purified by chromatography over one Merck size C (180 g) Lobar silica gel column with 1:1 ethyl acetate–hexane (50-mL fractions). Fractions 17–28 contained recovered starting material (**11**, 1.0 g) and fractions 50–120 contained the desired product **12** (0.9 g, 2.26 mmol, 22%). If necessary, **12** may be rechromatographed over silica gel using pure ethyl acetate for elution. The product **12** was identical with that obtained by procedure A above.

10-Nor-9,11-secoprostaglandin F_2 15-Acetate 9,11-Ditosylate Methyl Ester (13) and 10-Oxa-9,11-dideoxyprostaglandin $F_{2\alpha}$ 15-Acetate Methyl Ester (14). A. Conditions Favoring Formation of 13. A solution of 10-nor-9,11-seco-$PGF_{2\alpha}$ 15-acetate methyl ester (**12**, 0.474 g, 0.001 19 mol) in pyridine (3 mL) was cooled in an ice bath. *p*-Toluenesulfonyl chloride (1.81 g, 0.00952 mol) was added and the mixture placed in the refrigerator for 24 h. Water (0.3 mL) was added, and the resulting mixture was stirred 1.5 h at room temperature. Additional water (50 mL) was added, and the mixture was extracted with ether (3 × 35 mL). The ether extracts were pooled, washed sequentially with brine–water, aqueous potassium hydrogen sulfate, aqueous sodium carbonate, and brine. The ether extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was chromatographed by HPLC on one Merck Lobar silica gel column (size B) using 5–15% acetone in hexane to elute the column. Eluted first was 0.015 g (0.000 040 mol, 3%) of **10-oxa-9,11-dideoxy-$PGF_{2\alpha}$ 15-acetate methyl ester (14)** as a colorless viscous oil, identical with the sample of **14** prepared and characterized below. Eluted next was **10-nor-9,11-seco-$PGF_{2\alpha}$ 15-acetate, 9,11-ditosylate methyl ester** (**13**, 0.630 g, 0.000 89 mol, 75%) as a colorless oil which crystallized when cooled in the freezer. Recrystallization from acetone–hexane gave colorless crystals of **13**: mp 62.5–63 °C; ^1H NMR (δ, $CDCl_3$), 7.78 (d, 2 H, J = 8.5 Hz, aromatic protons), 7.37 (d, 2 H, J = 8.5 Hz, aromatic protons), 5.28 (br m, 4 H, olefinic protons), 3.97 (d, 4 H, J = 6.5 Hz, CH_2O), 3.92 (m, 1 H, CHO), 3.67 (s, 3 H, $COOCH_3$), 2.47 (s, 4 H, $ArCH_3$), 2.28 (t, 2 H, J = 7 Hz, CH_2COO), 2.02 (s, 3 H, $OCOCH_3$), 0.90 (t, 3 H, J = 5 Hz, CH_3).

Anal. Calcd for $C_{36}H_{50}O_{10}S_2$: C, 61.16; H, 7.13. Found: C, 61.10; H, 7.10.

B. Conditions Favoring Formation of 14. A round-bottomed flask equipped with magnetic stirring bar was dried and flushed with nitrogen. Diol acetate **12** (199 mg, 0.50 mmol) was placed in 10 mL of pyridine, 95 mg (0.5 mmol) of *p*-toluenesulfonyl chloride was added, and the solution was stirred for 16 h at room temperature. Another equiv. of *p*-toluenesulfonyl chloride (0.5 mmol) was added, and the solution was stirred for an additional 8 h. Then about 1 mL of water was added, and the solution was stirred for 10 min. The extraction was carried out with ether. The ether layer was washed with water, 10% aqueous sodium bisulfate, saturated sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave the crude product. HPLC purification was carried out by using one Merck Lobar column (size B, 60 g; collecting 30 mL/fraction using hexane–ethyl acetate (10:1), fractions 1–25, (5:1) fractions 26–50 as eluant). The less polar product (fractions 23–36), 144.3 mg (76%) was identified as cyclic ether **14**. In addition 40 mg (11.4%, fractions 37–44) of bis(tosylate) **13** was obtained. Cyclic ether **14** was a colorless oil: IR (cm^{-1}, neat) 1740, 1440, 1370, 1240, 1160, 1050, 1020, 970, 925; ^1H NMR (δ, $CDCl_3$) 5.72–5.00 (m, 5 H, CH=CH, CHOAc), 4.18–3.84, 3.62–3.28 (m, 4 H, CH_2O), 3.64 (s, 3 H, CO_2CH_3), 2.02 (s, 3 H, $OCOCH_3$); high-resolution mass spectrum, *m/e* 320.2338 (calcd for $M^+ - HOAc$, $C_{20}H_{32}O_3$, 320.2351).

Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.29; H, 9.63.

10-Oxa-9,11-dideoxyprostaglandin $F_{2\alpha}$ (15). A solution of **14** (140.6 mg, 0.37 mmol) in 1.48 mL of 1 N KOH in methanol was stirred at room temperature for 16 h. Methanol was then removed in vacuo, and the residue was acidified with 10% aqueous sodium bisulfate. The mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded the crude product. The purification was carried out by HPLC by using CC-4 silica gel (50 g; eluting with hexane–ethyl acetate (4:1), fractions 1–10; (2.1), fractions 11–50; collecting 40 mL/fraction) to give pure **15** (fractions 27–45, 86.3 mg, 72% yield) as a colorless oil: IR (cm^{-1}, neat) 3400, 1710, 1240, 1040, 970; ^1H NMR 6.38 (br s, 2 H, OH, CO_2H), 5.78–5.08 (m, 4 H, CH=CH), 4.38–3.90 (m, 1 H, CHO), 4.02 (t, J = 7.5 Hz, 2 H, CH_2O), 3.50 (t, J = 7.5 Hz, 2 H, CH_2O); high-resolution mass spectrum (bis(Me_4Si) derivative), *m/e* 463 (M^+), 453.2844 (calcd for $M^+ - CH_3$, $C_{24}H_{45}Si_2O_4$, *m/e* 453.2856), 437, 423, 397, 379, 367, 307, 277.

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 69.94; H, 9.90.

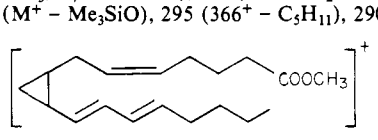
10-Nor-9,11-secoprostaglandin H_2 15-Acetate Methyl Ester (16). A solution of **13** (0.041 g, 0.058 mmol) in DMF (1 mL) was added to a cold (ice–methanol bath temperature) sample (3 mL of supernatent) of po-

tassium superoxide (KO_2) in DMF that was prepared as follows. A mixture of crushed KO_2 (0.45 g) in DMF (10 mL) containing dicyclohexyl 18-crown-6 (0.75 g) was stirred 2 h at room temperature. The solids were allowed to settle for 15 min, and the resulting supernatent was used for the reaction. Samples of the reaction were quenched after 5 and 22 min. Examination by the TLC showed no difference in the two and that some starting material remained unreacted. Additional KO_2–DMF supernatent (2 mL) was added. After 5 min, the reaction was quenched by pouring into water and ether (25 mL). The ether layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography over one Merck Lobar silica gel column (size A) using 5% acetone in hexane gave a main fraction of a peroxidic product (positive reaction on TLC to ferrous thiocyanate spray reagent): 0.013 g (0.0328 mmol, 56%); ^1H NMR (δ, $CDCl_3$) 5.32 (m, 4 H, olefinic protons), 4.00 (d, 4 H, J = 7 Hz, CH_2O), 3.66 (s, 3 H, $COOCH_3$), 2.29 (t, 2 H, J = 7 Hz, CH_2COO), 2.06 (s, 3 H, $OCOCH_3$), 0.88 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum, m/e 336.2273 (calcd for $C_{20}H_{32}O_4$, $M^+ - CH_2OOCH_2$, m/e 336.2300).

Reduction of 16 with Triphenylphosphine. Triphenylphosphine (excess) was added to a solution of **16** (1.4 mg) in acetone (0.1 mL). The reaction was monitored by TLC (30% acetone–hexane) and the quantity of a product having the same R_f as authentic 10-nor-9,11-seco-$PGF_{2\alpha}$ 15-acetate methyl ester (**12**) was seen to increase slowly with time. After 4 days, the ratio of this product (**12**) to starting material (**16**) was approximately 1:3. No other products were detected by this TLC system.

10-Nor-9,11-secoprostaglandin F_2 9,11-Ditosylate Methyl Ester (17). Compound **13** (0.630 g, 0.89 mmol) was dissolved in methanol (Burdick and Jackson, 25 mL). Anhydrous sodium methoxide (0.30 g) was added. A cloudy solution resulted and was stirred at 25 °C. TLC after 2 h (30% acetone–hexane) showed that the reaction already was complete. Ether (100 mL) was added, and the solution was washed with brine–water (1:1, 3 × 30 mL). The pooled aqueous washes were extracted with ether (2 × 35 mL), and the ether was combined with the main organic methanol–ether solution. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The product **17** (0.560 g, 0.845 mmol, 95%) so obtained was essentially pure as determined by TLC and was used without further purification. The product (**17**) had the following spectral properties: ^1H NMR (δ, $CDCl_3$) 7.77 (d, 2 H, J = 8 Hz, aromatic protons), 7.35 (d, 2 H, J = 8 Hz, aromatic protons), 5.32 (m, 4 H, olefinic protons), 4.00 (d, 4 H, J = 7 Hz, 2 CH_2O), 3.92 (m, 1 H, CHO), 3.66 (s, 3 H, $COOCH_3$), 2.45 (s, 6 H, $ARCH_3$), 2.27 (t, 2 H, J = 7 Hz, CH_2COO), 0.88 (t, 3 H, J = 5 Hz, CH_3).

10-Nor-9,11-secoprostaglandin F_2 Methyl Ester (18). A mixture of potassium superoxide (0.67 g) in DMF (18 mL) containing dicyclohexyl 18-crown-6 (1.2 g) was stirred at 25 °C for 4 h. A solution of **17** (0.56 g, 0.845 mmol) in DMF (10 mL) was prepared and cooled in an ice bath. A portion (10 mL) of the well-stirred KO_2–DMF mixture was added to the solution of **17**. TLC (30% acetone–hexane) shows unreacted **17** remaining after 6 min and 24-min reaction time. Additional KO_2–DMF mixture (4 mL) was added and, after an additional 5 min of reaction time, the reaction was complete. The reaction mixture was poured into cold water (75 mL). Brine (75 mL) was added, and the mixture was extracted with ether (3 × 50 mL). The ether extracts were pooled, washed with water–brine (1:1, 3×), and dried over $MgSO_4$. The crude reaction product was chromatographed on a silica gel (75 g) column packed as a slurry in 25% ethyl acetate–hexane. The column was eluted with the same solvent mixture, collecting fractions of 45-mL volume. The desired product 10-nor-9,11-seco-PGH_2 methyl ester (**18**, 0.207 g, 0.585 mmol, 69%) was found in fractions 12–26 and was a colorless oil: ^1H NMR (δ, $CDCl_3$) 5.45 (br m, 4 H, olefinic protons), 4.02 (m, 1 H, CHO and d, 4 H, J = 7 Hz, 2 CH_2O), 3.65 (s, 3 H, $COOCH_3$), 2.31 (t, 2 H, J = 7 Hz, CH_2COO), 0.88 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum (Me_3Si ether derivative) m/e 426, 411.2561 (calcd for $C_{22}H_{39}SiO_5$, $M^+ - CH_3$, m/e 411.2567), 366 ($m^+ - CH_2OOCH_2$), 355 ($M^+ - C_5H_{11}$), 337 ($M^+ - Me_3SiO$), 295 ($366^+ - C_5H_{11}$), 290



265 ($355^+ - Me_3SiOH$), 199 mass units.

10-Nor-9,11-secoprostaglandin H_2 (2). A mixture of lipase (0.200 g, Sigma, type II crude from hog pancreas) and tris–HCl buffer (200 mL, pH 8.0, 50 mM) were stirred and warmed to 37 °C. 10-Nor-9,11-seco-PGH_2, methyl ester (**18**, 0.060 g, 0.169 mmol) in acetone (6 mL) was added to the lipase–buffer mixture. The resulting mixture was stirred at 37 °C for 2 h. TLC (1:1 ethyl acetate–hexane + 0.5% acetic acid) after 1 and 2 h showed that the reaction was essentially complete after 2 h. Brine (50 mL) was added and the mixture was acidified to approximately pH 2 with 2 N HCl (about 105 drops). The mixture was extracted with ether (4 × 100 mL). The ether extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product (0.049 g) was chromatographed on acid-washed silica gel (7 g, Mallincrodt CC-4) packed as a slurry in 20% ethyl acetate–hexane. The column was eluted with the same solvent system with fractions of 5-mL volume being collected. The desired product 10-nor-9,11-seco-PGH_2 (**2**, 0.042 g, 0.123 mmol, 87%) was obtained in fractions 12–28 and gave the expected positive color test when sprayed with ferrous thiocyanate reagent on silica gel TLC plates. Spectral properties of **2** are as follows: ^1H NMR (δ, $CDCl_3$) 5.47 (br m, 4 H, olefinic protons), 4.10 (m, 1 H, CHO), 4.02 (d, 4 H, J = 7 Hz, CH_2O), 2.33 (t, 2 H, J = 7 Hz, $CH_2C(O)O$), 0.88 (t, 3 H, J = Hz, CH_3); high-resolution mass spectrum (bis(trimethylsilyl) derivative), m/e 484, 469.2821 (calcd for $C_{24}H_{45}Si_2O_5$, $M^+ - CH_3$, m/e 469.2805), 413 ($M^+ - C_5H_{11}$), 394 ($M^+ - Me_3SiOH$), 424 ($M^+ - CH_2OOCH_2$), 323 ($413^+ - Me_3SiOH$), 199 [HC═CHCH(OMe_3Si)C_5H_{11}]$^+$, 173 (HC═$^+$$OMe_3Si$)$C_5H_{11}$).

10-Nor-9,11-secoprostaglandin F_2 15-Acetate 9,11-Dimesylate Methyl Ester (19). Methanesulfonyl chloride (0.13 mL, 1.7 mmol) was added at once to a stirred solution of diol **12** (0.27 g, 0.68 mmol) and triethylamine (0.4 mL) in methylene chloride (10 mL) at −20 °C under a nitrogen atomosphere. The resulting solution was stirred 45 min at −20 °C and then poured into ice water (25 mL). The mixture was extracted with ethyl acetate (250 mL). The organic extract was washed with aqueous 10% sodium bisulfate (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (2 × 50 mL) and dried over $MgSO_4$. Following filtration and removal of solvent, the product (**19**) was obtained as a pale yellow oil essentially free of any contaminants and was used without further purification in the following experiment.

10-Nor-9,11-seco-9,11-dideoxy-9,11-dithioprostaglandin F_2 9,11,15-Triacetate Methyl Ester (20) and 10-Nor-9,11-seco-9,11-dideoxy-9,11-epidithioprostaglandin H_2 15-Acetate Methyl Ester (21). A solution of dimesylate **19** (crude product) and potassium thioacetate (0.41 g, 3.6 mmol) in 1:1 dimethyl sulfoxide–dimethylformamide (10 mL) was heated to 50 °C under a nitrogen atmosphere for 16 h. The solution was poured into water (50 mL) and extracted with ethyl acetate (250 mL). The organic solution was washed with water (2 × 50 mL), 10% aqueous sodium bisulfate (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (2 × 50 mL) and dried over $MgSO_4$. After filtration and removal of solvent, the crude product (0.33 g) was a dark brown oil. This material was chromatographed over a silica gel (18 g) column, eluting with 9:1 hexane–ethyl acetate. Fractions of 20-mL volume were collected. Eluted first (fractions 4–6) was compound **21** (54 mg, 0.126 mmol, 18% from **12**) as a colorless oil: IR (cm^{-1}, neat) 2940, 2860, 1735, 1435, 1370, 1240, 1020, 975, 890, 730; ^1H NMR (δ, CCl_4) 5.37 (m, 5 H, 4 olefinic protons, C*H*OAc), 3.62 (s, 3 H, $COOCH_3$), 2.6–3.1 (m, 4 H, SCH_2), 1.96 (s, 3 H, $OCOCH_3$), 0.89 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum, m/e 428.2075 (calcd for M^+, $C_{22}H_{36}O_4S_2$, m/e 428.2055), 397, 396, 369, 355, 353, 336, and 303.

Eluted second (fractions 7–11) was compound **20** (0.209 g, 0.41 mmol, 60% from **12**) as a colorless oil: IR (cm^{-1}, neat) 2935, 2835, 2860, 1730, 1685, 1435, 1370, 1235, 1020, 960, 735, 630; ^1H NMR (δ, CCl_4) 5.43 (m, 4 H, olefinic protons), 4.87–5.28 (m, 1 H), 3.61 (s, 3 H, $COOCH_3$), 2.7–3.1 (m, 4 H, SCH_2), 2.29 (s, 3 H, $SCOCH_3$), 2.27 (s, 3 H, $SCOCH_3$), 1.98 (s, 3 H, $OCOCH_3$), 0.90 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum, m/e 471.2223 ($M^+ - CH_3CO$, calcd for $C_{24}H_{39}O_5S_2$, m/e 471.2239), 411, 381, 378, 369, 335, 303, 289, 237, 212, 195.

10-Nor-9,11-seco-9,11-dideoxy-9,11-epidithioprostaglandin H_2 Methyl Ester (22). A solution of **20** (0.21 g, 0.41 mmol) in methanol (5 mL) was stirred with potassium carbonate (0.25 g, 1.8 mmol) at room temperature for 50 min. Analysis by TLC at this time showed no starting material **20** remaining and the formation of two new compounds, one less polar than **20** and with the same R_f as compound **21**, described above, and one more polar than **20**. The reaction mixture was stirred an additional 50 min while oxygen was bubbled through the solution. After this time, only the new, more polar material was found by TLC analysis of the solution. The mixture was poured into aqueous 10% sodium bisulfate (50 mL) and extracted with ethyl acetate (300 mL). The extract was washed with saturated aqueous sodium bicarbonate (50 mL) and with brine (2 × 50 mL) and was dried over $MgSO_4$. After filtration and removal of the solvent, the crude product (0.154 g) was chromatographed (HPLC) over a silica gel column (18.6 g). The column was eluted with 10:1 hexane–ethyl acetate. Fractions of 18 mL volume were collected. Pure **22** (0.139 g, 87%) was eluted in fractions 10–17 and was a pale yellow oil: IR (cm^{-1}, neat) 3450, 2920, 2850, 1735, 1435, 1405, 1365, 1310, 1220, 1170, 1020, 975, 890, 725; ^1H NMR (δ, CCl_4) 5.48 (m, 4 H, olefinic protons), 3.82–4.20 (m, 1 H), 3.64 (s, 3 H, $COOCH_3$), 2.53–3.10 (m, 4 H, SCH_2), 0.90 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum (Me_3Si derivative) m/e 458.2332 (M^+, calcd for $C_{23}H_{42}SiO_3S_2$, m/e 458.2344), 443, 425, 387, 368, 355, 335, 321, 303, 297,

199.

Anal. Calcd for $C_{20}H_{34}O_3S_2$: C, 62.13; H, 8.86. Found: C, 62.50; H, 8.62.

10-Nor-9,11-seco-9,11-dideoxy-9,11-epidithioprostaglandin H_2 (3). A slightly turbid solution of **22** (0.091 g, 0.24 mmol) in *tert*-butyl alcohol (2.5 mL) and 3 N aqueous potassium hydroxide (0.78 ML, 2.3 mmol) was stirred at room temperature for 6 h. Hydrolysis was complete by TLC analysis. The solution was poured into 10% aqueous sodium bisulfate (40 mL) and extracted with ethyl acetate (400 mL total). The extract was washed with brine (3 × 40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by HPLC over 17.1 g of acid-washed silica gel (Mallincrodt CC-4). The column was eluted with 5:1 hexane-ethyl acetate. Fractions of 20 mL volume were collected. The product (**3**, 0.054 g, 62%) was eluted in fractions 2-18 as a pale yellow oil: IR (cm^{-1}, neat), 3600-2300, 2940, 1710, 1455, 1405, 1240, 970, and 725; ^1H NMR (δ, $CDCl_3$) 5.45 (m, 4 H, olefinic protons), 0.89 (t, 3 H, J = 5 Hz, $-CH_3$); high-resolution mass spectrum (TMS derivative, m/e) 516.2593 (M^+, calcd for $C_{25}H_{48}Si_2O_3S_2$: 516.2583), 501, 483, 445, 435, 426, 393, 361, 355, 341, 337, 313, 199 and 173.

Preparation of Human Platelet Rich Plasma. Human platelet rich plasma (PRP) was prepared by withdrawing blood directly into 0.1 volumes of 3.8% (v/v) trisodium citrate, followed by centrifugation at 200xg for 10 min at room temperature.

Analysis of Endoperoxide Analogue Aggregatory Activity. To assess the influence of the endoperoxide analogues on human platelet aggregation, 1.0 mL of PRP was prewarmed to 37 °C and stirred at 1100 rpm in a Payton Aggregometer, Payton Associates, Buffalo, NY. Following the warming period, dose-response curves were constructed by using the endoperoxide analogues and these responses were then compared with the dose-response curve of authentic PGH_2. In cases where the analogue did not exert agonist activity, platelets were preincubated for 2 min with the appropriate analogue and then challenged with PGH_2. This test uncovered any potential antagonism of PGH_2 by the analogues. Aggregation data are reported as percent transmission.

Rat Aorta Constricting Activity. The intrinsic agonist activity of the analogues was tested by using spirally cut strips of rat aorta according to the method of Furchgott.[21] The tissues were placed in 10-mL tissue baths at 37.5 °C; one end of the strip was fixed, and the other was attached to an isometric transducer (Grass FT .03) with an initial tension of 2 g. During a 1-h equilibration period, the tissue relaxed to an average basal tension of 1.55 ± 0.05 g. The Krebs solution contained 1.0 μg/mL of indomethacin to inhibit endogenous prostaglandin synthesis. Dose-response curves were constructed for the various agonists, and the data reported as ED_{50} in ng/mL.

Registry No. 1, 80559-54-2; **1** tetrakis(TMS), 80572-40-3; **2**, 80559-55-3; **2** bis(TMS), 80559-56-4; **3**, 80559-57-5; **3** bis(TMS), 80559-58-6; **4**, 31753-19-2; **5**, 80559-59-7; **5** bis(TMS), 80559-60-0; **6**, 13261-27-3; 10α-hydroxy-**5**, 80559-61-1; 10α,11α-epoxy-**6**, 80559-62-2; **7**, 80559-63-3; **7** tris(TMS), 80559-84-8; **8**, 80559-64-4; **8** TMS, 80572-41-4; **9**, 80559-65-5; **9** bis(TMS), 80559-66-6; **10**, 80559-67-7; **11**, 36323-03-2; **11** epoxide isomer 1, 38310-85-9; **11** epoxide isomer 2, 38344-07-9; **11** epoxide TMS, 80559-68-8; **12**, 80559-69-9; **12** bis(TMS), 80559-70-2; **13**, 80559-71-3; **14**, 80559-72-4; **15**, 80559-73-5; **15** bis(TMS), 80559-74-6; **16**, 80559-75-7; **17**, 80559-76-8; **18**, 80559-77-9; **18** TMS, 80559-78-0; **19**, 80559-79-1; **20**, 50559-80-4; **21**, 80559-81-5; **22**, 80559-82-6; **22** TMS, 80559-83-7.

Supplementary Material Available: A description of the X-ray crystallographic method used, tables of torsion angles, anistropic thermal parameters, hydrogen bonds and close intermolecular distances, hydrogen coordinates, and distances involving hydrogens, and a figure showing two views of compound **7** (8 pages). Ordering information is given on any current masthead page.

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Preparation and ^{13}C and ^{15}N NMR Spectroscopic Study of Cyanocarbenium Ions. Substituent Effects on the Extent of Mesomeric Nitrenium Ion Character in Cyanodiphenylmethyl Cations. The Search for Related Stable α-Cyanocarbenium Ions[1]

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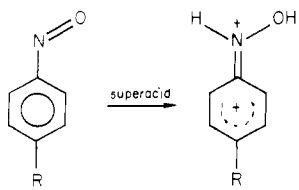
Abstract: A series of para-substituted cyanodiphenylmethyl cations have been prepared by the ionization of the corresponding benzophenone cyanohydrins in superacid solutions at -78 °C. The ^{13}C and ^{15}N NMR spectroscopic data on these ions indicate that the extent of mesomeric nitrenium character largely depends on the electronic effect of the substituent on the aryl ring. The 7-cyano-7-norbornenyl cation was found to be of bishomoaromatic nature with some charge delocalization into the cyano group. Attempts to prepare the related α-cyanocarbocations from acyclic, cyclic, bicyclic, and tricyclic precursors were, however, unsuccessful.

Nitrenium ions with divalent positive nitrogen have been claimed as intermediates in the reactions of some nitrogen-containing organic compounds.[2,3] Attempted generation of them as distinct species under long-lived stable ion conditions has thus far been unsuccessful.[4] Protonation of nitrosobenzenes **1**-R in superacidic media has led only to benzeniumiminium dications **2**-R.[4,5]



1-R 2-R

(1) (a) Stable Carbocations, Part 239. For Part 238 see: G. A. Olah, G. K. S. Prakash, and T. Nakajima, *J. Am. Chem. Soc.*, in press. (b) Appeared as a preliminary communication: G. A. Olah, G. K. S. Prakash, and M. Arvanaghi, *ibid.*, **102**, 6640-6641 (1980).

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(3) P. G. Gassman and G. D. Hartman, *J. Am. Chem. Soc.*, **95**, 449-454 (1973).

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