Table VI. Isotopic Compositions (% D) of Butenes from Thermolysis of 7 and 8 at 100 °C

precursor	1-butene	*trans*-2-butene	*cis*-2-butene
15	98.2	97.9	3.6
14	98.8	98.6	2.6
21	98.5	1.8	97.1
20	98.7	1.8	96.4

butene isomers but are not adjusted to correspond to 100% D starting material. The data in Table IV are corrected to correspond to 100% D starting material and 100% isomerically pure butene products.

Thermolysis of Tetrazene 22. 1,4-Bis(1-methylpropyl)-1,4-diphenyl-2-tetrazene (**22**) was heated for 5.5 h at 100 °C as a degassed solution in diglyme. This resulted in the formation of <0.1% C_1–C_4 hydrocarbons.

Registry No. **6**, 84695-40-9; **7**, 84695-41-0; **8**, 84695-42-1; **9**, 84695-43-2; **10**, 84695-44-3; **11**, 10277-60-8; **12**, 7429-10-9; **13**, 84695-45-4; **14**, 84695-46-5; **15**, 84695-47-6; **17**, 10277-59-5; **18**, 7429-09-6; **19**, 84695-48-7; **20**, 84695-49-8; **21**, 84695-50-1; **22**, 84695-51-2; *N*-(1-methylpropyl)aniline, 6068-69-5; nickel peroxide, 1314-06-3; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; *trans*-2-butene, 624-64-6; aniline, 62-53-3; imidogen, 13774-92-0.

Formation of Isoxazolyl Hydroperoxides via a Novel Oxidative Fragmentation of Bicyclic Isoxazolidines

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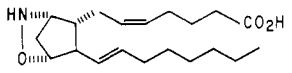
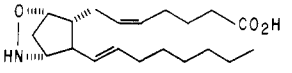
(5*Z*,9α,11α,13*E*)-9,11-(Epoxyimino)prosta-5,13-dienoic acid (**2**) and the corresponding methyl ester **3** undergo a novel oxidative fragmentation reaction in the presence of air. The resulting four isomeric isoxazolyl hydroperoxides **4a,b** and **5a,b**, formed cleanly in similar amounts and in good combined yield, have been characterized spectrally and by further chemical transformations. The novel oxidative fragmentation reaction is very facile with the strained bicyclic [2.2.1]isoxazolidine ring system (e.g., **3**) but occurs (more slowly) in less constrained substrates as well. The new isoxazolyl hydroperoxides, as well as the corresponding alcohols and ketones, are potent inhibitors of PGH_2-induced human platelet aggregation.

A variety of prostaglandin endoperoxide (PGH_2) analogues have been synthesized in which one or both of the peroxide oxygens have been replaced by methylene groups or other heteroatoms. Many of these chemically stabilized PGH_2 analogues share with PGH_2 the ability to raise blood pressure, constrict smooth muscle, and aggregate platelets. The corresponding endoperoxide mimics without the C-15 hydroxyl group usually lack the typical PGH_2 agonist activities and tend to be inhibitors or antagonists of the further metabolism of the natural endoperoxide PGH_2 (and therefore useful biochemical tools for investigations into the complex metabolism of arachidonic acid). For example, (5*Z*,9α,11α,13*E*)-11,9-(epoxyimino)prosta-5,13-dienoic acid (**1**)[1] is a potent inhibitor of the conversion of



1

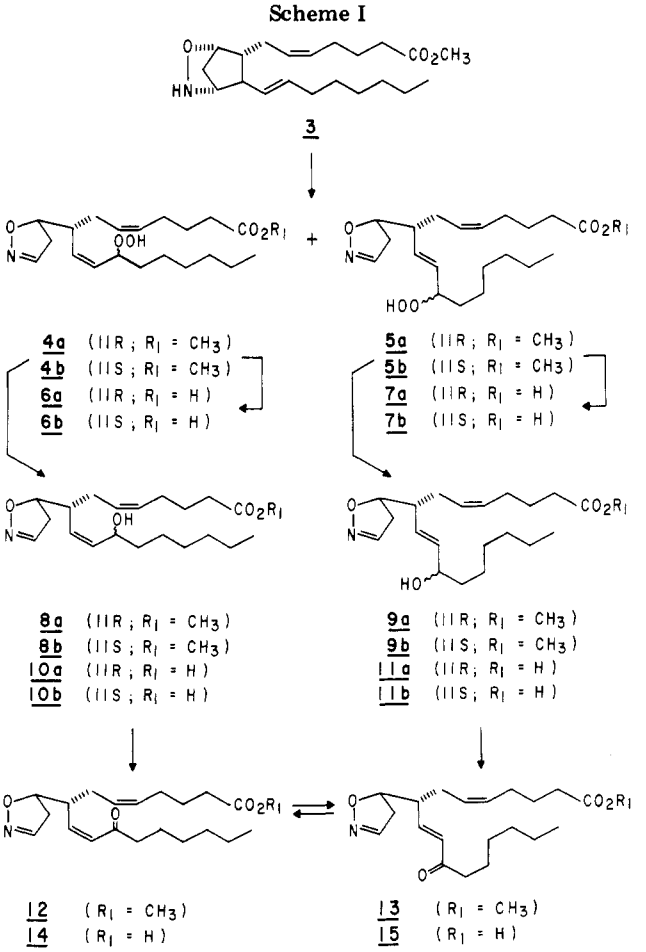


2

PGH_2 to thromboxane A_2 (TXA_2) at concentrations (10^{-4}–10^{-6} M) which have minimal effect on the formation of the endoperoxide or its conversion to prostacyclin.[2] Regioisomeric 9,11-epoxyimino analogue **2** does not inhibit the formation of TXA_2 in platelets but will prevent preformed TXA_2 from exerting its usual biological effect (i.e., **2** is a TXA_2 receptor-level antagonist).[3]

11,9-Epoxyimino isomer **1** is a crystalline solid (mp 53–54 °C) and has shown no sign of instability either neat or in solution. On the other hand, the 9,11-epoxyimino isomer **2** (and its methyl ester **3**) have never been obtained completely free from several less polar impurities.[4] Even when completely clean (by TLC) chromatographic frac-

Scheme I



(1) Bundy, G. L.; Peterson, D. C. *Tetrahedron Lett.* **1978**, 41.
(2) Fitzpatrick, F.; Gorman, R.; Bundy, G.; Honohan, T.; McGuire J.; Sun, F. *Biochim. Biophys. Acta* **1979**, *573*, 238.
(3) Fitzpatrick, F. A.; Bundy, G. L.; Gorman, R. R.; Honohan, T. *Nature (London)* **1978**, *275*, 764.

0022-3263/83/1948-0976$01.50/0

tions were combined, the presence of four less polar spots (1–5% of the total product) was evident by the time the solvent had been evaporated. Stoppered solutions of **2** in ethyl acetate (10 mg/mL) were converted cleanly and completely to the same four products in several weeks at 25 °C or overnight at reflux. These products have been isolated, via tedious chromatography, and identified as the four isoxazolyl hydroperoxides **4a,b** and **5a,b** (Scheme I), products of a novel, and to the best of our knowledge unprecedented, oxidative fragmentation reaction. Although two of the corresponding acids, **6a** and **7a**, were crystalline, it has not been possible to obtain crystals of sufficient quality for X-ray analysis. The structures of the four isomeric hydroperoxides were therefore based on the spectral considerations and further chemical transformations described below.

The four oxidative decomposition products of **3**, isolated in approximately equal amounts and in about 65–70% combined yield, all retained a single nitrogen (elemental analysis). The observation that the PG_1 series analogue of **3** (i.e., saturated at C-5,6) underwent the identical oxidative decomposition at the same rate, affording an analogous collection of products, showed that the 5,6 double bond was not involved in the reaction.

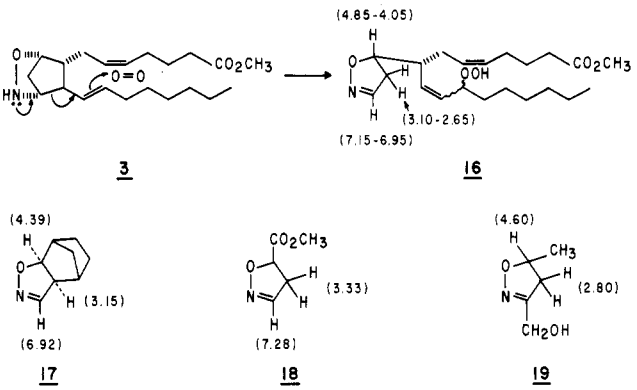
The infrared spectra of the four oxidative fragmentation products (**4a,b**, **5a,b**) all contained a new peak in the hydroxyl region, a new small peak at 1600 cm^{-1}, and a new medium-intensity peak at 845–850 cm^{-1}. In addition, the 975 cm^{-1} band, characteristic of the 13,14-trans double bond, was missing in two of the four products, indicating involvement of the 13,14-double bond.

The NMR spectra of each of the four products showed the absence of the characteristic C-9 and C-11 proton signals of **3**, and the presence of signals at δ 8.7–8.4 (exchangeable, 1 H), 7.15–6.95 (m, 1 H), 5.70–5.25 (m, 4 H, vinyl), 4.85–4.05 (m, 2 H, CHO), 3.66 (s, 3 H, CO_2CH_3), and 3.10–2.65 (m, 2 H). Although the splitting pattern for the δ 3.10–2.65 signal was distinctly different for each of the four products, these differences did not prove useful in assigning the structures.

Early attempts to analyze the unknown structures by high-resolution mass spectrometry gave results which were confusing at the time but were reasonable once the structures had been assigned. Silylation of the four unknowns under standard conditions (BSFTA, 1% Me_3SiCl, pyridine) yielded less polar compounds, mass spectral analysis of which showed no trimethylsilyl groups. Low-resolution mass spectroscopy, without silylation, indicated that the four products were isomeric and differed from the starting epoxyimino analogue **3** by the addition of two oxygen atoms.

Spraying of TLC plates containing the unknowns with a freshly prepared solution of ferrous thiocyanate[5] (intense red color instantaneously at 25 °C) showed that the newly acquired oxygens were in the form of either a peroxide or a hydroperoxide. Reduction of the unknowns with zinc in acetic acid or sodium borohydride in methanol (Scheme I, **4a** → **8a**, **4b** → **8b**, etc.) afforded in each case a monohydroxy product containing one less oxygen atom than the original unknowns (i.e., the latter were hydroperoxides, not peroxides).

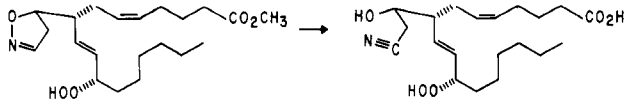
On the basis of the preceding spectral information, plus the observation that the C-13,14 double bond (but not the C-5,6 double bond) was involved, the 8-(4,5-dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoic acid structures **4a,b** and **5a,b** were tentatively assigned: two geometric isomers of the new $\Delta^{9,10}$ double bond and two hydroperoxy epimers of each. Formally (and without mechanistic implications), these products are derived from **3** via electron push from nitrogen, cleavage of the C-11,12



3 16 17 18 19

bond, reaction with oxygen at C-14 (PG numbering), and proton transfer, a process which for convenience may be designated an oxidative fragmentation reaction.[6] The isoxazoline structures were supported by NMR comparisons with several literature examples (**17**–**19**).[7,8]

Further confirmation for the isoxazoline ring system was provided by the observation that it was difficult to hydrolyze the methyl ester, e.g., **5b**, without cleaving the isoxazoline ring to some extent, yielding hydroxy nitrile **20**. An analogous isoxazoline ring cleavage was observed



5b 20

with **18** upon treatment with triethylamine at 20 °C.[7] The isoxazolyl hydroperoxy acids **6a,b** and **7a,b**, which were needed for biological evaluation, could be obtained by performing the oxidative fragmentation on acid **2**, but this route provided a mixture that was separable only with great difficulty. More advantageously, methyl esters **4a,b** and **5a,b** could be hydrolyzed to the corresponding acids in high yield and purity by using a Plexaura homomalla (soft coral) derived esterase.[9]

The further transformations in Scheme I were carried out both to complete structural characterization of the isoxazolyl hydroperoxides **4a,b** and **5a,b** and to provide material for biological evaluation. As mentioned earlier, reduction of the hydroperoxides **4a**, **4b**, **5a**, and **5b** (or the corresponding C-1 acids) was equally efficient with either

(4) Other examples of the 2-oxa-3-azabicyclo[2.2.1]heptane ring system have also proven unstable, but their simpler structures would preclude oxidative fragmentation reactions of the type reported here. See: Just, G.; Cutrone, L. *Can. J. Chem.* **1976**, *54*, 867. Kresze, G.; Schultz, G. *Tetrahedron* **1961**, *12*, 7.

(5) Abraham, M. H.; Davies, A. G.; Llewellyn, D. R.; and Thain, E. M. *Anal. Chim. Acta* **1959**, *17*, 499. Ammonium thiocyanate (1.25 g) was dissolved in 25 mL of distilled water. The solution was treated with 0.25 mL of concentrated sulfuric acid and then with 1.75 g of ferrous ammonium sulfate. The resulting pink to light tan solution was stored under nitrogen and could be used for several days.

(6) For an excellent review of fragmentation reactions, see: Becker, K. B.; Grob, C. A. In "The Chemistry of Double-bonded Functional Groups"; Patai, S., Ed.; Wiley: New York, 1977; Part 2 Chapter 8. In the strictest sense, the designation of this reaction as a "fragmentation" would imply the presence of a (nucleofugal) leaving group at C-13. In this case, the electronic "pull" is provided by the interaction of the π electrons with oxygen.

(7) Huisgen, R.; Christl, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6* (5), 456.

(8) Tartakovskii, V. A.; Onishchenko, A. A.; Lazodzinskaya, B. V.; Novikov, S. S. *Zh. Org. Khim.* **1967**, *3*, 765.

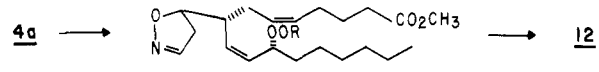
(9) Schneider, W. P.; Bundy, G. L.; Lincoln, F. H.; Daniels, E. G.; Pike, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 1222.

sodium borohydride in methanol or zinc in acetic acid (25 °C, 3 h), with no evidence for any N–O bond reduction.

Oxidation of alcohol **8a** or **8b** with either Jones reagent or Collins reagent afforded the same 9*Z* C-11 ketone **12**, thereby showing that **8a** and **8b** differed only by being epimeric at the hydroxyl-bearing carbon. Likewise, oxidation of either **9a** or **9b** provided the same 9*E* C-11 ketone **13**. The fact that the hydroxyl groups of all four alcohols (**8a,b, 9a,b**) were attached to the same carbon was evident from the facile interconversion of enones **12** and **13**. Irradiation of trans enone **13** in acetone at 350 nm for 30 min afforded a 1:1 mixture of **12** and **13**.[10] (Longer irradiation times led to more cis enone **12**, but eventually additional byproducts appeared which complicated TLC interpretation). Transformation of **12** to the thermodynamically more stable trans enone **13** was accomplished with 0.5 M HCl in 50% aqueous THF.

NMR and mass spectral analysis of enones **12** and **13** allowed firm assignment of the oxygen functionality (in ketones **12** and **13**, hydroperoxides **4a,b–7a,b**, and alcohols **8a,b–11a,b**) to C-11, and not C-9, which would have resulted if all of the products had undergone allylic rearrangement. The mass spectra of both **12** and **13** (as well as those of the corresponding acids **14** and **15**) showed a major ion (in some cases, the base peak) at *m/e* 113, assignable to the bottom-side chain fragment $C_6H_{13}C{\equiv}O^+$. In the NMR spectrum of cis enone **12**, the signal for the allylic C-8 proton (δ 3.65) was considerably downfield from the comparable C-8 proton in trans enone **13** (δ <2.75). (An analogous downfield shift has been noted for the C-12 proton of 13-*cis*-15-oxo-$PGF_{2\alpha}$ relative to the 13-trans 15-ketone.[11]) Simple decoupling experiments demonstrated that this C-8 proton signal was adjacent to the isoxazoline >CHO signal.

Enones **12** and **13** were also generated during attempts to silylate hydroperoxides **4a/4b** or **5a/5b**, respectively, under commonly used GC derivatization conditions. This is the explanation for the early anomalous high-resolution mass spectral observations on the hydroperoxides. The hydroperoxides could be converted to the corresponding *tert*-butyldimethylsilyl ethers[12] (e.g., **4a** → **21**) under mild

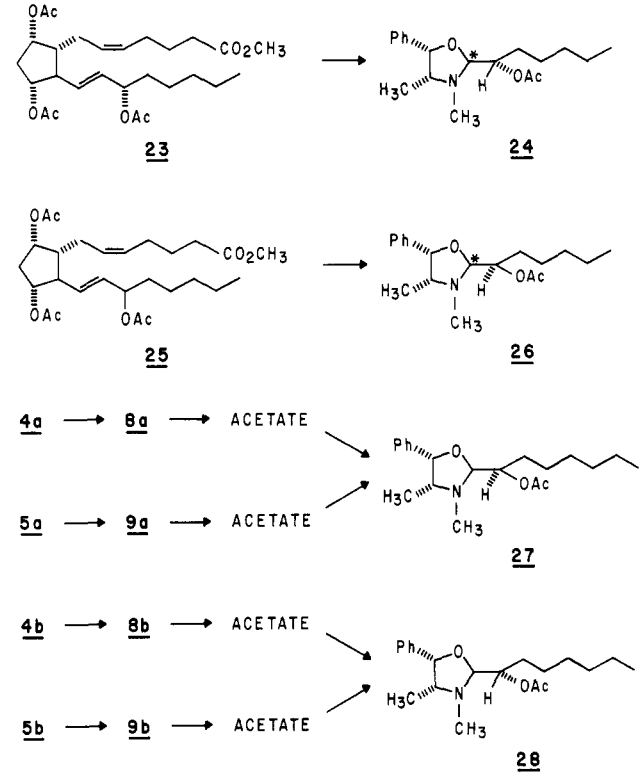


21 (R = $tBuMe_2Si$)
22 (R = TMS)

conditions (imidazole, *tert*-butyldimethylsilyl chloride, DMF, 0 °C, 2 h). Even after chromatographic purification, however, the silyl peroxide **21** was unstable and lost *tert*-butyldimethylsilanol on gentle warming, thereby yielding ketone **12**. Likewise, trimethylsilyl peroxide **22** was unstable both to heat and to the more vigorous silylating reagents.

The only remaining uncertainty regarding the structures of hydroperoxides **4a,b** and **5a,b**, namely, the configuration of each at the hydroperoxy carbon (C-11), was resolved by using the convenient micro method of Just and Oh[13] (Scheme II). To provide the required reference standards, $PGF_{2\alpha}$ triacetate methyl ester **23** and the corresponding 15*R* isomer **25** were each subjected to the following sequence: (a) ozonolysis, (b) reduction with dimethyl sulfide to the α-acetoxyheptanal, (c) oxazolidine formation with *l*-ephedrine.[13] By this procedure, oxazolidines **24** and **26** were obtained, each one a 6:1 mixture of diastereomers at the starred carbon and all four readily resolvable by TLC.

Scheme II

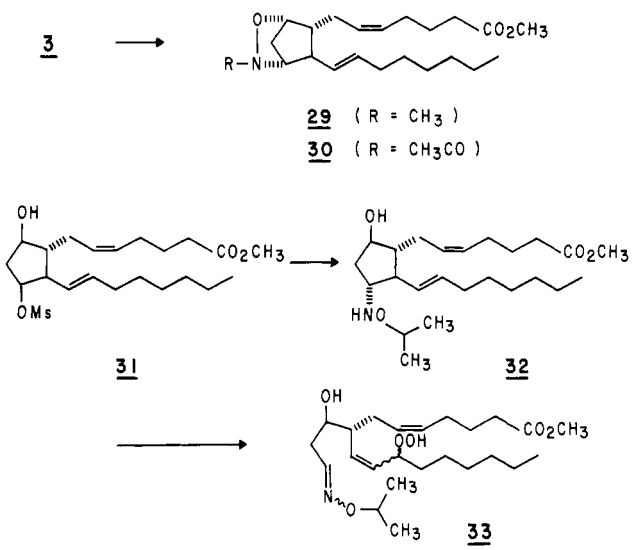


Identical treatment of alcohols **8a** and **9a** afforded oxazolidine **27** indistinguishable by TLC from the 2*R* standard **26**. Since the configuration at C-11 in hydroperoxides **4a** and **5a** would be unaffected by reduction to alcohols **8a** and **9a**, the C-11 configuration of **4a** and **5a** was unambiguously established as 11*R*. In analogous fashion, alcohols **8b** and **9b**, following the same sequence, both yielded oxazolidine **28**, identical by TLC with reference standard **24**, thereby establishing **8b** and **9b** as the 11*S* epimers. The fact that oxazolidines **27** and **28** contain an extra methylene group in their alkyl side chain relative to the prostaglandin-derived standards was, as anticipated, not detectable by TLC.

Several additional substrates related to epoxyimino analogue **3** were prepared (Scheme III) to determine the generality of the novel oxidative fragmentation reaction. Alkylation of **3** with methyl iodide and diisopropylethylamine in methanol afforded *N*-methyl derivative **29** in 45% yield. (With acetonitrile or tetrahydrofuran as the solvent, the reaction could not be stopped at the monoalkylation stage.) Acylation of **3** with acetic anhydride/pyridine gave *N*-acetyl derivative **30** in 94% yield. Both **29** and **30** were recovered completely unchanged after 2 weeks at 50 °C in oxygen-saturated ethyl acetate. (By comparison, the oxidative fragmentation of **3** was complete in less than 16 h under the same conditions.) The inertness of *N*-acetyl derivative **30** was not surprising, undoubtedly reflecting

(10) Buchi, G.; Yang, N. C. *Helv. Chim. Acta* **1955**, *28*, 1338.
(11) Yankee, E. W. U.S. Patent 4 026 909, May 31, 1977.
(12) Corey, E. J.; Venkateswarlu, A. *J. Chem. Soc.* **1972**, *94*, 6190.
(13) Just, G.; Oh, H. *Tetrahedron Lett.* **1980**, *21*, 3667. This method had the major advantages of being unambiguous and applicable to very small scale work. Other procedures are available.[14]
(14) (a) Nugteren, D. H.; Van Dorp, D. A.; Bergstrom, S.; Hamberg, M.; Samuelsson, B. *Nature (London)* **1966**, *212*, 38. (b) Johnson, R. A.; Krueger, W. C.; Nidy, E. G.; Pschigoda, L. M.; Garry, M. J. *J. Org. Chem.* **1980**, *45*, 1528. This procedure was investigated briefly but gave ambiguous results on these substrates. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (d) Konig. W. A.; Sievers, S.; Schulze, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 910.

Scheme III



the decreased electron density on nitrogen. The unreactivity of *N*-methyl derivative **29**, despite the higher electron density on nitrogen relative to **3**, may result from a strong preference of the methyl group to remain exo to the bicyclo[2.2.1]heptane ring system. This would prevent the trans coplanar arrangement of the nitrogen lone pair of electrons and the C-11/C-12 bond, undoubtedly the preferred (if not required) orientation for ring cleavage.[6]

In order to determine the importance of the strain inherent in the bicyclic ring system to the success of the oxidative fragmentation reaction, 11α-(isopropoxyamine) substrate **32** was synthesized (Scheme III) via displacement of mesylate **31**[1] with *O*-isopropylhydroxylamine (generated in situ by hydrazinolysis of the corresponding *N*-phthalimido derivative).[15,16] As might be expected, this displacement reaction proceeded in poor yield (8% after chromatography), but the desired product was easily recognized by NMR and was, in fact, the only product of the mixture which contained the characteristic isopropyl signals.

Solutions of 11α-(isopropoxyamino) substrate **32** in oxygen-saturated ethyl acetate at 50 °C slowly afforded a mixture of at least seven products, all positive to the ferrous thiocyanate spray reagent[5] for peroxides, presumably isomers of isopropyloxime **33** (eight isomers possible). The two most abundant of these products were isolated, and both exhibited IR and NMR spectra consistent with structure **33**. The fact that the reaction of **32** required 6 days to proceed to completion, compared to 1 day for bicyclic substrate **3**, showed that the forced orbital alignment and/or the ring strain of the bicyclic ring system were facilitating factors, but not absolute prerequisites, for the oxidative fragmentation.

Although the precise mechanism for the oxidative fragmentation of epoxyimino substrate **3** has not been determined in detail, the reaction appears to be a free radical process. The room-temperature (25–30 °C) oxidation is substantially accelerated in the presence of di-*tert*-butyl peroxyoxalate, a good radical initiator at these temperatures.[17] The presence of acids (HCl, TsA) or bases (KO-*t*-Bu, DBU, Et_3N) had little, if any, effect on reaction rate or product array. Although the rate was a little slower, no additional products were isolated when the reaction was run with cumene or isopropyl alcohol as the solvent. (The hope had been to capture possible radical intermediates with these good H· sources.) The oxidative fragmentation of **3** proceeded at the same speed in normal room light or in total darkness and also was unhindered by the presence of 10–300 mol % of Dabco (1,4-diazabicyclo[2.2.2]octane), a singlet oxygen quencher.[18] When **3** was exposed to photochemically generated singlet oxygen, hydroperoxides **4a,b** and **5a,b** were produced rapidly (<3 h, 25 °C) but were accompanied by at least four additional unidentified products (probably from reaction with the C-5,6 double bond).

The oxidative fragmentation of **3** was temperature dependent (essentially no reaction at −20 °C; several weeks to completion at 25 °C; complete in less than 16 h at 50 °C). The reaction could be avoided only by using solvents which had been thoroughly deoxygenated with nitrogen or argon and then maintaining an inert atmosphere.

In addition to representing products of an unusual reaction type, many of the compounds in Scheme I also exhibited substantial biological activity. In particular, hydroperoxides **6b** and **7a**, alcohols **10b** and **11a**, and ketone **15** all inhibited PGH_2-induced (but not ADP-induced) aggregation of human platelets,[19] with potencies from one-third to equal that of (5*Z*,9α,11α,13*E*)-9,11-azoprosta-5,13-dienoic acid[20] (1 μg/mL).

Experimental Section

General Methods. Melting points were obtained with a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with either a Perkin-Elmer Model 197 or a Digilab Model FTS-14D spectrophotometer; mulls were in Nujol, liquids were films between NaCl plates, and solutions were in $CHCl_3$. The ^1H NMR spectra were obtained with a Varian A-60A spectrometer as solutions in deuteriochloroform with tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer and low-resolution mass spectra with a Varian MAT-CH-7A instrument.

Oxidative Fragmentation of Methyl (5*Z*,9α,11α,13*E*)-9,11-(Epoxyimino)prosta-5,13-dienoate (3). A solution containing 9.0 g of 9,11-epoxyimino analogue **3**[1] in 900 mL of EtOAc was placed in a 2-L flask, stoppered, and allowed to stand at 22 ± 2 °C for 6 weeks. (Subsequent smaller scale runs afforded an identical array of products in 16 h at 50 °C.) TLC analysis (40% EtOAc/hexane) showed that no starting material remained and that four less polar spots, all strongly positive to the ferrous thiocyanate spray reagent[5] for peroxides, had formed, in approximately equal amounts. Following evaporation of the solvent, the residue was chromatographed on a column containing 1.6 kg of 40–60-μm silica gel. The chromatogram was eluted with 12 L of 20% EtOAc/hexane (discarded) and then 16 L of 30% and 10 L of 35% EtOAc/hexane (50-mL fractions). Fractions were combined as follows on the basis of TLC homogeneity.

Methyl (5*Z*,8*R*,9*Z*,11*R*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoate (4a): fractions 14–40; 852 mg; R_f 0.54 (silica gel, 50:50:1 EtOAc/hexane/HOAc); IR (neat) 3380, 3000, 1730, 1600, 850, 800 cm^{-1}; NMR ($CDCl_3$) δ 8.7 (br m, 1 H, OOH, exchangeable), 7.15–7.04 (m, 1 H, N=CH), 5.7–5.3 (m, 4 H, CH=CH), 4.80–4.25 (m, 2 H, CHOH and CHOOH), 3.66 (s, 3 H, CO_2CH_3), 3.05–2.65 (m, 2 H, N=CHCH_2); low-resolution mass spectrum, *m/e* 381 (M^+), 364, 348, 316, 278, 206, 165, 113.

(15) Chimiak, A.; Kolasa, T. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1974**, *22*, 195.
(16) Grochowski, E.; Jurczak, J. *Synthesis* **1976**, 682.
(17) Bartlett, P. D.; Benzing, E. P.; Pincock, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 1762.
(18) Ouannes, C.; Wilson, T. *J. Am. Chem. Soc.* **1968**, *90*, 6527.
(19) Unpublished data from R. R. Gorman, The Upjohn Co. The complete biological profile of this series of isoxazolylhydroperoxyheptadecadienoic acids will be published shortly by Dr. Gorman.
(20) Gorman, R. R.; Bundy, G. L; Peterson, D. C.; Sun, F. F.; Fitzpatrick, F. A. *Proc. Acad. Sci. U.S.A.* **1977**, *74*, 4007.

Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 65.73; H, 9.21; N, 3.56.

Methyl (5*Z*,8*R*,9*E*,11*S*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoate (5b): fractions 66–90; 1.81 g; R_f 0.49 (silica gel, 50:50:1 EtOAc/hexane/HOAc); IR (neat) 3400, 3000, 1730, 1600, 970, 845 cm^{-1}; NMR ($CDCl_3$) δ 8.4 (br m, 1 H, exchangeable), 7.17–6.95 (m, 1 H), 5.65–5.25 (m, 4 H), 4.85–4.05 (m, 2 H), 3.66 (s, 3 H), 3.10–2.65 (m, 2 H); low-resolution mass spectrum, *m/e* 381 (M^+), 364, 348, 316, 278, 223, 206, 165. Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 65.74; H, 9.14; N, 3.65.

Methyl (5*Z*,8*R*,9*Z*,11*S*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoate (4b): fractions 186–225; 1.47 g; R_f 0.42 (silica gel, 50:50:1 EtOAc/hexane/HOAc); IR (neat) 3380, 3000, 1730, 1600, 1020, 845, 800 cm^{-1}; NMR ($CDCl_3$) δ 8.63 (m, 1 H, exchangeable), 7.15–7.00 (m, 1 H), 5.65–5.20 (m, 4 H), 4.85–4.35 (m, 2 H), 3.66 (s, 3 H), 3.10–2.80 (m, 2 H); low-resolution mass spectrum, *m/e* 381 (M^+), 364, 349, 348, 316, 278, 165, 113. Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 65.70; H, 9.27; N, 3.66.

Methyl (5*Z*,8*R*,9*E*,11*R*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoate (5a): following fractions 226–245, which contained 707 mg of a mixture of **4b** and **5a**, were obtained fractions 246–305; 1.27 g; R_f 0.40 (silica gel, 50:50:1 EtOAc/hexane/HOAc); IR (neat) 3400, 3000, 1730, 1600, 970, 845 cm^{-1}; NMR ($CDCl_3$) δ 8.44 (m, 1 H, exchangeable), 7.10–7.00 (m, 1 H), 5.60–5.25 (m, 4 H), 4.85–4.05 (m, 2 H), 3.66 (s, 3 H), 3.10–2.75 (m, 2 H); low-resolution mass spectrum, *m/e* 381 (M^+), 364, 349, 348, 278, 223, 206, 165. Anal. Calcd for $C_{21}H_{35}NO_5$: C, 66.11; H, 9.25; N, 3.67. Found: C, 65.82; H, 9.65; N, 3.63.

(5*Z*,8*R*,9*Z*,11*R*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroperoxy-5,9-heptadecadienoic Acid (6a). A solution containing 635 mg of methyl ester **4a** in 6.35 mL of ethanol was diluted with 130 mL of water and treated with 6.35 g of Plexaura homomalla derived esterase powder.[9] The resulting brown suspension was stirred vigorously at 25 °C for 24 h, diluted with 800 mL of acetone, and stirred 30 min longer. The reaction mixture was filtered through a pad of Celite on a medium-porosity sintered-glass funnel, and the filtrate (with acetone washes) was concentrated in vacuo. The residue was partitioned between EtOAc and brine containing 0.5 mL of 2 M $KHSO_4$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed on an 80-g column of silica gel, packed with 20/80/0.5 EtOAc/hexane/HOAc and eluted (15-mL fractions) with 40/60/0.5 EtOAc/hexane/HOAc. Fractions 21–30 yielded 360 mg of pure **6a**. Upon trituration, the product crystallized; recrystallization of 200 mg of this from 3:1 EtOAc/hexane yielded 145 mg of **6a** as a colorless solid: mp 49–51 °C; R_f 0.37 (silica gel, 50:50:1 EtOAc/hexane/HOAc), 0.44 (silica gel, 20:80:1 acetone/CH_2Cl_2/HOAc); IR (neat, prior to crystallization) 3280, 3000, 2670, 1705, 1605, 855, 790 cm^{-1}; NMR ($CDCl_3$) δ 8.15 (br s, 2 H, exchangeable), 7.13 (br s, 1 H), 5.80–5.30 (m, 4 H), 4.90–4.24 (m, 2 H), 3.01–2.65 (m, 2 H); low-resolution mass spectrum, *m/e* 350, 316, 291, 204, 165 (M^+ not observed). This material, as well as acids **6b** and **7a,b**, still showed a strong positive reaction with the ferrous thiocyanate spray reagent.[5] Acids **6a,b** and **7a,b** could also be prepared by oxidative fragmentation of acidic substrate **2**; however, efficient chromatographic purification of the crude product proved virtually impossible.

Attempted Base Hydrolysis of 5b. Formation of (5*Z*,8*R*,9*E*,11*S*)-8-(2-Cyano-1-hydroxyethyl)-11-hydroperoxy-5,9-heptadecadienoic Acid (20). A solution of 65 mg of ester **5b** in 5 mL of CH_3OH was cooled to 0 °C and treated wtih 5 mL of cold aqueous 0.5 M LiOH. The resulting mixture was stirred for 1 h at 0 °C and 1 h at 25 °C, recooled to 0 °C, and poured into a mixture of brine, ice, and 2.5 mL of 1 M HCl. The product was isolated by extraction with 1:1 EtOAc/hexane. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on a column containing 18 g of Mallinckrodt CC-4 acid-washed silica gel, packed with 25% EtOAc/hexane and eluted (3 mL fractions) with 100 mL of 35%, 100 mL of 40%, and 100 mL of 45% EtOAc/hexane. Fractions 54–71 yielded 40 mg of pure **20**, a viscous, colorless oil (positive test with ferrous thiocyanate spray): R_f 0.38 (silica gel, 50:50:1 EtOAc/hexane/HOAc); IR (neat) 3380, 3000, 2650, 2250, 1705, 1240, 1045, 980, 860 cm^{-1}; NMR ($CDCl_3$) δ 6.6 (br s, 3 H, exchangeable), 5.75–5.25 (m, 4 H), 4.50–3.85 (m, 2 H), 2.54 (d, J = 6 Hz, 2 H, CH_2CN).

Methyl (5*Z*,8*R*,9*Z*,11*R*)-8-(4,5-Dihydro-5-isoxazolyl)-11-[(*tert*-butyldimethylsilyl)peroxy]-5,9-heptadecadienoate (21). A solution of 25 mg of hydroperoxide **4a** in 5 mL of dry DMF was cooled to 0 °C and treated with 214 mg of imidazole, followed by 235 mg of *tert*-butyldimethylsilyl chloride. The colorless homogeneous solution was stirred at 0 °C under nitrogen for 2 h, poured in 1:1 brine/water, and extracted with 40% EtOAc/hexane. The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a column containing 18 g of silica gel, packed with 20% EtOAc/hexane and eluted with 50 mL of 20% EtOAc/hexane (discarded), followed by 100 mL of 30% EtOAc/hexane (3-mL fractions). Fractions 5–9 yielded 22 mg of pure *tert*-butyldimethylsilyl peroxide **21**, viscous colorless oil (still positive to ferrous thiocyanate spray; as expected, the color took longer to develop than with hydroperoxide **4a**): R_f 0.37 (silica gel, 20% EtOAc/hexane); IR (neat) 1735, 1600, 1460, 1440, 1360, 1250, 1165, 870, 840, 785 cm^{-1}; NMR ($CDCl_3$) δ 7.15–7.00 (m, 1 H), 5.75–5.15 (m, 4 H), 4.80–4.30 (m, 2 H), 3.66 (s, 3 H), 3.00–2.60 (m, 2 H), 0.91 (s, 9 H), 0.11 (s, 6 H); mass spectrum (M^+ not observed), *m/e* 438.2637 (calcd for $C_{23}H_{40}NO_5Si$, $M^+ - C_4H_9$, 438.2676), 348, 316, 298, 247, 229.

In the above silylation (as well as with the other isomers) later fractions from the chromatogram afforded variable amounts of enone **12** (and **13**; characterized in a subsequent experiment).

Methyl (5*Z*,8*R*,9*Z*,11*R*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroxy-5,9-heptadecadienoate (8a). A solution of 75 mg of hydroperoxide **4a** in 3 mL of HOAc was treated with 50 mg of zinc dust, and the resulting gray suspension was stirred at 25 °C for 3 h. The reaction mixture was poured into a mixture of brine, ice, and aqueous sodium bicarbonate and extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was chromatographed on a column containing 20 g of silica gel, packed with 20% EtOAc/hexane and eluted with 200 mL of 30% EtOAc/hexane (20 mL and then 3-mL fractions). Fractions 35–48 afforded 65 mg of pure alcohol **8a**, a viscous, colorless oil, negative to the ferrous thiocyanate spray for peroxides: R_f 0.32 (silica gel, 30% EtOAc/hexane; corresponding hydroperoxide **4a** had R_f 0.42 on the same plate); IR (neat) 3440, 3000, 1730, 1600, 1360, 1160, 1030, 1010, 850, 800 cm^{-1}; NMR ($CDCl_3$) δ 7.15–7.05 (m, 1 H), 5.85–5.05 (m, 4 H), 4.85–4.05 (m, 2 H), 3.66 (s, 3 H), 3.05–2.60 (m, 2 H), 1.80 (br s, 1 H, exchangeable); mass spectrum (Me_3Si derivative), *m/e* 437 (M^+, weak), 422.2746 (calcd for $C_{23}H_{40}NO_4Si$, $M^+ - CH_3$, 422.2726), 352.1927 ($M^+ - C_6H_{13}$).

Methyl (5*Z*,8*R*,9*E*,11*S*)-8-(4,5-Dihydro-5-isoxazolyl)-11-hydroxy-5,9-heptadecadienoate (9b). A solution of 80 mg of hydroperoxide **5b** in 10 mL of MeOH was cooled to 0 °C and treated with 50 mg of sodium borohydride. The reaction mixture was stirred for 15 min at 0 °C and then 1 h at 25 °C, poured into ice and brine (containing a little citric acid), and extracted with 1:1 EtOAc/hexane. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product (79 mg) was chromatographed on an 18-g column of silica gel, packed with 25% EtOAc/hexane and eluted with 100 mL of 35%, 100 mL of 40%, and 100 mL of 50% EtOAc/hexane (25 mL and then 3-mL fractions). Fractions 45–59 gave 40 mg of pure alcohol **9b**, a viscous, colorless oil, negative to ferrous thiocyanate: R_f 0.25 (silica gel, 40:60:1 EtOAc/hexane/HOAc; hydroperoxide **5b** had R_f 0.36 on the same plate); IR (neat) 3450, 3000, 1735, 1600, 1360, 1030, 980, 850 cm^{-1}; NMR ($CDCl_3$) δ 7.08–6.95 (m, 1 H), 5.70–5.15 (m, 4 H), 4.85–4.30 (m, 1 H), 4.25–3.85 (m, 1 H), 3.66 (s, 3 H), 3.05–2.65 (m, 2 H), 1.85 (s, 1 H, exchangeable); mass spectrum (Me_3Si derivative), *m/e* 437 (M^+, weak), 422.2725 (calcd for $C_{23}H_{40}NO_4Si$, $M^+ - CH_3$, 422.2726), 396, 367, 352 ($M^+ - C_6H_{13}$), 296, 262, 213, 187.

Methyl (5*Z*,8*R*,9*Z*)-8-(4,5-Dihydro-5-isoxazolyl)-11-oxo-5,9-heptadecadienoate (12). (a) From Hydroperoxide 4a or 4b. A solution of 25 mg of hydroperoxide **4a**, 235 mg of *tert*-butyldimethylsilyl chloride, and 214 mg of imidazole in 5 mL of DMF was heated in a nitrogen atmosphere for 24 h at 50 °C. The reaction mixture was poured into 1:1 brine/water and extracted

with 1:1 EtOAc/hexane. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a column containing 18 g of silica gel, packed with 20% EtOAc/hexane and eluted (2–3-mL fractions) with 60 mL of 30% and 100 mL of 40% EtOAc/hexane. Fractions 40–46 afforded 16 mg of pure 9*Z* enone **12**, a viscous, colorless oil: R_f 0.41 (silica gel, 13% isopropyl alcohol/hexane), 0.66 (50% EtOAc/hexane); IR (neat) 1735, 1685, 1620, 1435, 1410, 1280, 1240, 1220, 1200, 1160, 850 cm^{-1}; NMR ($CDCl_3$) δ 7.12–6.97 (m, 1 H), 6.45–5.65 (m, 2 H), 5.55–5.27 (m, 2 H), 4.90–4.40 (m, 1 H), 3.80–3.40 (s at 3.66 superimposed on m, 4 H total, includes C-8H), 3.10–2.75 (m, 2 H); UV (EtOH) λ_{max} 230 nm; mass spectrum, *m/e* 363.2415 (M^+, calcd for $C_{21}H_{33}NO_4$ 363.2409), 346, 332, 305, 294, 261, 250, 223, 206, 155, 113 (base peak, $C_6H_{13}CO^+$), 85 (C_6H_{13}).

Treatment of 11*S* hydroperoxide **4b** in the same manner afforded **12** in the same yield, identical in all respects with material in the preceding paragraph (M^+ observed at *m/e* 363.2423). Heating purified *tert*-butyldimethylsilyl derivative **21** at 50 °C for 24 h afforded the same 9*Z* enone **12**.

(b) From Alcohol 8a or 8b. A solution of 1 mg of alcohol **8a** in 0.2 mL of acetone was cooled to 0 °C and treated with 1 drop of Jones reagent. After 15 min at 0 °C, 1 drop of isopropyl alcohol was added, and the solvents were removed with a stream of nitrogen. The residue was partitioned between 1 mL of brine and 0.2 mL of EtOAc. TLC analysis of the organic layer showed that 9*Z* enone **12** was the only product.

Alternatively, a solution of 1 mg of alcohol **8a** in 0.2 mL of CH_2Cl_2 was treated at 25 °C with 0.2 mL of Collins reagent (from 820 mg of CrO_3, 1.41 mL of pyridine, and 25 mL of CH_2Cl_2). After 15 min at 25 °C, TLC analysis of an aliquot taken directly from the reaction flask showed that 9*Z* enone **12** was again the sole product.

With either oxidation procedure 11*S* alcohol **8b** also afforded 9*Z* enone **12**.

Methyl (5*Z*,8*R*,9*E*)-8-(4,5-Dihydro-5-isoxazolyl)-11-oxo-5,9-heptadecadienoate (13). By use of procedures indentical with those in the preceding experiments, hydroperoxides **5a** and **5b** and alcohols **9a** and **9b** were converted cleanly to 9*E* -enone **13**: R_f 0.26 (silica gel, 13% isopropyl alcohol/hexane), 0.51 (50% EtOAc/hexane); IR (neat) 1735, 1690, 1675, 1630, 1600, 1370, 985, 845 cm^{-1}; NMR ($CDCl_3$) δ 7.15–7.00 (m, 1 H), 6.75–5.95 (m, 2 H), 5.60–5.20 (m, 2 H), 4.90–4.40 (m, 1 H), 3.66 (s, 3 H), 3.10–2.80 (m, 2 H); UV (EtOH) λ_{max} 230 nm; mass spectrum, ions at 363 (M^+), 332, 314, 305, 294, 223, 206, 165, 149, 113.

Interconversion of Enones 12 and 13. (a) Photochemical Isomerization. A solution of 1.5 mg of pure 9*E* enone **13** in 10 mL of acetone was irradiated at 3500 Å for 30 min in a Rayonet preparative (Type RS) photoreactor. Stirring of the mixture, as well as exclusion of oxygen, was accomplished with a gentle stream of nitrogen introduced through a small fritted disk in the bottom of the reactor. The internal temperature of the reaction mixture was maintained at about 10 °C via circulation of cold water through a cold finger condenser. After 30 min, the solvent was removed in vacuo. TLC analysis of the residue (50% EtOAc/hexane or 13% isopropyl alcohol/hexane) showed a 1:1 mixture of enones **13** and **12**. At longer irradiation times, additional cis isomer **12** was formed, but the gradual appearance of several byproducts complicated the TLC analysis.

(b) Acid-Catalyzed Isomerization. A solution of 2 mg of cis enone **12** in 0.2 mL of tetrahydrofuran and 0.2 mL of aqueous 1 M HCl was allowed to stand at room temperature for 22 h. An aliquot was then subjected to a vial workup (1:1 brine/bicarbonate and 1:1 EtOAc/hexane), and the organic layer was analyzed by TLC (20% EtOAc/hexane). The product consisted of a 1:1 mixture of starting cis enone **12** and trans enone **13**.

(5*Z*,8*R*,9*Z*)-8-(4,5-Dihydro-5-isoxazolyl)-11-oxo-5,9-heptadecadienoic Acid (14). A solution of 280 mg of a **6a**/**6b** mixture, 1.02 g of *tert*-butyldimethylsilyl chloride, and 925 mg of imidazole in 10 mL of DMF was heated at 50 °C for 65 h in a nitrogen atmosphere. The reaction mixture was cooled to 25 °C, treated with 20 mL of 1:1 HOAc/H_2O, stirred 2 h at 25 °C, poured into brine, and extracted with 1:1 EtOAc/hexane. The extracts were washed with five portions of brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on a column containing 85 g of 40–60-μm silica gel, packed with 15:85:0.5 EtOAc/hexane/HOAc and eluted (5 mL fractions) with 50:50:0.5 EtOAc/hexane/HOAc. Fractions 60–68 yielded 81 mg of pure cis enone **14**, which crystallized on standing. Trituration of a portion of the material with 15% EtOAc/hexane gave **14** as a colorless solid: mp 62–63 °C; R_f 0.32 (silica gel, 10:90:1 acetone/CH_2Cl_2/HOAc), 0.24 (10:90:1 isopropyl alcohol/hexane/HOAc), 0.42 (50:50:1 EtOAc/hexane/HOAc); IR (8% solution in $CHCl_3$) 3100, 2650, 1700, 1690, 1615, 1410, 1280, 1230, 850 cm^{-1}; NMR ($CDCl_3$) δ 9.75 (s, 1 H, exchangeable), 7.15–7.00 (m, 1 H), 6.5–5.65 (m, 2 H), 5.55–5.25 (m, 2 H), 4.90–4.45 (m, 1 H), 3.90–3.20 (m, 1 H, shown by decoupling experiments to be the C-8 proton), 3.10–2.75 (m, 2 H); mass spectrum (Me_3Si derivative); *m/e* 421 (M^+, weak), 406.2396 (calcd for $C_{22}H_{36}NO_4Si$, $M^+ - CH_3$, 406.2414), 404, 363, 352, 351, 199, 165, 113 ($C_6H_{13}C{\equiv}O^+$).

(5*Z*,8*R*,9*E*)-8-(4,5-Dihydro-5-isoxazolyl)-11-oxo-5,9-heptadecadienoic Acid (15). By the same procedure as in the preceding experiment, a mixture of hydroperoxides **7a** and **7b** was converted to 9*E* enone **15**: R_f 0.30 (silica gel, 10:90:1 acetone/CH_2Cl_2/HOAc), 0.14 (10:90:1 isopropyl alcohol/hexane/HOAc), 0.30 (50:50:1 EtOAc/hexane/HOAc); IR (neat) 3100, 2650, 1705, 1665, 1625, 1280, 1235, 980, 845 cm^{-1}; NMR ($CDCl_3$) δ 9.85 (s, 1 H, exchangeable), 7.15–7.04 (m, 1 H), 6.85–5.95 (m, 2 H), 5.65–5.25 (m, 2 H), 4.90–4.45 (m, 1 H), 3.25–2.70 (m, 2 H); mass spectrum (Me_3Si derivative), *m/e* 421 (M^+, weak), 406.2404 (calcd for $C_{22}H_{36}NO_4Si$, $M^+ - CH_3$, 406.2414), 404, 363, 352, 351, 199, 165, 113 ($C_6H_{13}C{\equiv}O^+$).

Determination of C-11 Configuration in 4a,b and 5a,b. Six compounds [$PGF_{2\alpha}$ methyl ester, (15*R*)-$PGF_{2\alpha}$ methyl ester, and hydroxy isoxazolines **8a**,**b** and **9a**,**b**] were each subjected to the series of reactions described below.[13]

(a) Acetylation. A 10-mg sample of the substrate was dissolved in 8 drops of pyridine and treated with 4 drops of acetic anhydride, and the mixture was allowed to stand at 25 °C for 4 h. Methanol (10 drops) was added, and after 10 min all of the reagents were evaporated in a gentle stream of nitrogen.

(b) Ozonolysis. The crude part a product was dissolved in 5 mL of methylene chloride (50 mL, one-necked, round-bottomed flask), cooled to −40 °C dry ice/acetonitrile bath), and treated with excess ozone (bubbled in via a gas-dispersion tube until a blue color persisted). The flask was then stoppered and allowed to stand at −40 °C for 5 min. Then via a fresh gas-dispersion tube, nitrogen was bubbled through to remove excess ozone, thereby yielding a colorless solution.

(c) Reduction to Aldehyde. To the −40 °C part b solution (after the removal of excess ozone) was added 5 mL of dimethyl sulfide, and the mixture was allowed to warm to 25 °C and stand at that temperature for 18 h. The mixture was then concentrated to dryness in vacuo.

(d) Oxazolidine Preparation. To the crude part c product was added 1 mL of methylene chloride containing 50 mg of *l*-ephedrine (from a larger stock solution). The mixture was allowed to stand for 30 min at 25 °C and was then analyzed directly by TLC. This reaction mixture was stored in the freezer without being worked up and remained the same (by TLC) 6 months later.

The six products were analyzed by TLC as shown in Table I.

Methyl (5*Z*,9α,11α,13*E*)-*N*-Methyl-9,11-(epoxyimino)-prosta-5,13-dienoate (29). A solution of 150 mg of epoxyimino ester **3** in 20 mL of methanol was cooled to 0 °C and treated with 2 mL of diisopropylethylamine and 4 mL of methyl iodide. After 2 h at 0 °C, TLC analysis of the reaction mixture (1:1 EtOAc/hexane) showed only about 10% of **3** remaining, and the mixture was poured into brine/water and extracted with 35% EtOAc/hexane. The extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. The crude product was chromatographed on a column containing 20 g of silica gel, packed with 20% EtOAc/hexane and eluted (2–3 mL fractions) with 40 mL of the same solvent and then 100 mL of 40% EtOAc/hexane. Fractions 24–31 yielded 70 mg (45% of theory) of pure *N*-methyl derivative **29**, a semiviscous, colorless oil: R_f 0.60 (silica gel, 1:1 EtOAc/hexane; **3** exhibited R_f 0.23 on the same plate); IR (neat) 1735, 1245, 1220, 1170, 1160, 970, 900, 740 cm^{-1}; NMR ($CDCl_3$) δ 5.60–5.25 (m, 4 H), 4.35–4.20 (m 1 H), 3.66 (s, 3 H), 3.15–3.04 (m, 1 H), 2.54 (s, 3 H); mass spectrum, *m/e* 363.2782 (M^+, calcd for $C_{22}H_{37}NO_3$, 363.2773), 348, 346, 332, 320, 317, 306, 292, 278, 222, 84.

Table I

starting matl	product	R_f (1:5 EtOAc/hexane)[a]	confign of hydroxyl carbon
$PGF_{2\alpha}$ methyl ester	24	0.31, 0.18	15*S*
(15*R*)-$PGF_{2\alpha}$ methyl ester	26	0.39, 0.23	15*R*
8a	27	0.39, 0.23	11*R*
9a	27	0.39, 0.23	11*R*
8b	28	0.31, 0.18	11*S*
9b	28	0.31, 0.18	11*S*

[a] Literature[13] values: **24**, 0.33, 0.18; **26**, 0.44, 0.23.

A solution of 8 mg of **29** in 0.8 mL of oxygen-saturated EtOAc was heated at 50 °C in an oxygen atmosphere. After 2 weeks, TLC analysis (1:1 EtOAc/hexane) showed only unchanged **29**.

Methyl (5*Z*,9α,11α,13*E*)-*N*-Acetyl-9,11-(epoxyimino)-prosta-5,13-dienoate (30). A solution of 105 mg of epoxyimino ester **3** in 4 mL of pyridine was treated with 1 mL of acetic anhydride, and the resulting clear solution was stirred under a nitrogen atmosphere for 18 h at 25 °C. The reaction mixture was cooled to 0 °C, treated with 4 mL of methanol, and stirred 30 min at 0 °C and 30 min at 25 °C. The mixture was then poured into brine and extracted with 1:1 EtOAc/hexane. The extracts were washed with brine, cold aqueous $KHSO_4$, water, aqueous $NaHCO_3$, and brine again, dried ($MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on a column containing 20 g of silica gel, packed and eluted (2–3 mL fractions) with 40% EtOAc/hexane. Combination of fractions 35–50 yielded 110 mg of pure *N*-acetyl derivative **30**, a mobile, colorless oil: R_f 0.35 (silica gel, 1:1 EtOAc/hexane; **3** exhibited R_f 0.23 on the same plate); IR (neat) 1730, 1650, 1430, 1360, 1165, 965, 890 cm^{-1}; NMR ($CDCl_3$) δ 5.60–5.25 (m, 4 H), 4.70–4.50 (m, 2 H), 3.66 (s, 3 H), 2.07 (s, 3 H).

A solution of 10 mg of **30** in 1 mL of oxygen-saturated EtOAc was heated at 50 °C in an oxygen atmosphere. After 2 weeks, TLC analysis (1:1 EtOAc/hexane) showed only unchanged **30**.

Methyl (5*Z*,9β,11α,13*E*)-9-Hydroxy-11-(isopropoxyamino)prosta-5,13-dienoate (32). A solution of 15.38 g of *N*-isopropoxyphthalimide [prepared according to Grochowski and Jurczak;[16] mp 55–56 °C (lit.[15] mp 53–54 °C)] and 3.75 g of hydrazine hydrate in 50 mL of HMPA was heated at 70 °C for 1 h under nitrogen to generate *O*-isopropylhydroxylamine. The reaction mixture was cooled to 25 °C, and a solution of 2.95 g of hydroxymesylate **31**[1] in 5 mL of HMPA was added in one portion. The mixture was heated at 80 °C for 14 h (no **31** remained by TLC), cooled, and poured into brine. Enough 3% sodium carbonate was added to dissolve the phthalhydrazide byproduct, and the desired product was isolated by extraction with 60% EtOAc/hexane. The extracts were washed with water (four times) and brine, dried ($MgSO_4$), and evaporated. The crude product (3.1 g) was chromatographed on a column containing 285 g of 40–60-μm silica gel, equilibrated, and eluted with 10% acetone-/CH_2Cl_2 (20-mL fractions). Fractions 141–176 afforded 225 mg (8% of theory) of **32** a viscous, colorless oil: R_f 0.38 (silica gel, 1:1 EtOAc/hexane; **31**, R_f 0.24), 0.46 (18% acetone/CH_2Cl_2; **31**, R_f 0.59); IR (neat) 3400, 1730, 1435, 1360, 1240, 1220, 1150, 965, 930, 860 cm^{-1}; NMR ($CDCl_3$) δ 5.80–5.00 (m, 4 H), 4.20–3.75 (m, 2 H), 3.67 (s, 3 H), 3.60–2.90 (m, 1 H), 2.20 (br s, 1 H, exchangeable), 1.15 (d, J = 6 Hz, 6 H); mass spectrum (Me_3Si derivative), m/e 481.3593 (M^+, calcd for $C_{27}H_{51}NO_4Si$, 481.3587), 466, 450, 438, 422, 396, 332, 250, 239, 208, 202. Intermediate **32** was the only component of the above reaction mixture which exhibited the characterisitc isopropyl doublet in the NMR. The most abundant less polar product was methyl 9β-hydroxyprosta-5,11,13-trienoate, while more polar products included a mixture of diols and an unidentified prostaglandin with NMR absorptions characterisitic of aromatic protons.

Oxidative Fragmentation of 32. A solution of 160 mg of **32** in 50 mL of oxygen-saturated EtOAc was heated at 50 °C in an atmosphere of oxygen for 6 days. Following removal of the solvent in vacuo, the residue was chromatographed on a column containing 20 g of silica gel, eluted (70 mL and then 2–3 mL fractions) with 100 mL of 10%, 100 mL of 20%, 200 mL of 30%, and 100 mL of 40% EtOAc/hexane. (Although most of the components of the crude reaction product were strongly positive to the ferrous thiocyanate test for peroxides;[5] only the most abundant were isolated). Fractions 79–85 gave 16 mg of a colorless, viscous oil: R_f 0.47 (silica gel, 30% EtOAc/hexane); IR (neat) 3400 (diol intensity), 1730, 1720, 1620, 1435, 1360, 1145, 1120, 1040, 965, 855 cm^{-1}; NMR ($CDCl_3$) δ 7.60–7.27 (m, 1 H, N=CH), 5.70–5.30 (m, 4 H), 4.60–4.05 (m, 2 H), 3.95–3.55 (m, 1 H), 3.67 (s, 3 H), 1.20 (d, J = 6 Hz, 6 H).

Following fractions 86–91, which contained a mixture of the above and below products (17 mg), fractions 92–102 contained 14 mg of a viscous, colorless oil, homogeneous by TLC: R_f 0.42 (silica gel, 30% EtOAc/hexane); IR and NMR identical with those for fractions 79–85 except for minor differences in relative peak intensities. Although both of these products appeared homogeneous in a variety of TLC solvent systems, each one afforded a 1:1 mixture of isomers upon enzymatic ester hydrolysis as described earlier. All four acids, resolvable by TLC (35:65:1 EtOAc/hexane/HOAc), were still strongly positive to the ferrous thiocyanate spray test for peroxides.[5] In view of the large number of isomers expected from the oxidative fragmentation of **32**, further identification was not undertaken.

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Registry No. **2**, 66464-51-5; **3**, 66464-60-6; **4a**, 79768-80-2; **4b**, 79768-79-9; **5a**, 79740-14-0; **5b**, 79768-78-8; **6a**, 79740-17-3; **6b**, 79768-88-0; **7a**, 79768-87-9; **7b**, 79768-89-1; **8a**, 79740-15-1; **8a** acetate, 84681-52-7; **8a** Me_3Si, 84681-53-8; **8b**, 79768-82-4; **8b** acetate, 84711-21-7; **9a**, 79768-81-3; **9a** acetate, 84773-26-2; **9b**, 79768-83-5; **9b** acetate, 84711-23-9; **9b** Me_3Si, 84711-22-8; **10a**, 79740-16-2; **10b**, 79768-85-7; **11a**, 79768-84-6; **11b**, 79768-86-8; **12**, 79740-18-4; **13**, 79740-20-8; **14**, 79740-19-5; **14** Me_3Si, 84681-54-9; **15**, 79740-21-9; **15** Me_3Si, 84681-55-0; **20**, 84731-07-7; **21**, 84681-56-1; **22**, 84681-57-2; **23**, 71691-37-7; **24** (isomer 1), 76451-15-5; **24** (isomer 2), 76436-48-1; **25**, 84681-58-3; **26** (isomer 1), 76451-14-4; **26** (isomer 2), 76436-47-0; **27** (isomer 1), 84681-59-4; **27** (isomer 2), 84681-60-7; **28** (isomer 1), 84681-61-8; **28** (isomer 2), 84681-62-9; **29**, 84681-63-0; **30**, 84681-64-1; **31**, 66464-58-2; **32**, 84681-65-2; **33**, 84681-66-3; (*S*)-2-acetoxyheptanal, 75584-25-7; (*R*)-2-acetoxyheptanal, 84711-24-0; (*R*)-2-acetoxyoctanal, 84681-67-4; (*S*)-2-acetoxyoctanal, 84681-68-5.

Supplementary Material Available: Complete spectral characterization of compounds **6b**, **7a**,**b**, **8b**, **9a**, **10a**,**b**, and **11a**,**b** and *t*-$BuMe_2Si$ derivatives of **4b** and **5a**,**b** (4 pages). Ordering information is given on any current current masthead page.