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Synthesis and Biological Activity of Prostaglandin Lactones

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Most of the primary prostaglandins and several biologically important prostaglandin analogues were converted to 1,9-, 1,11- or 1,15-lactones, in order to investigate the biological profiles of these internal esters and to assess their potential as prodrugs for the corresponding open-chain hydroxy acids. In each case, the key lactonization step was done using Corey's "double activation" procedure (cyclization of ω-hydroxy-2-pyridinethiol esters). In general, the 1,9-lactones exhibited less than 1% of the biological activity of the parent hydroxy acids in the standard prostaglandin test systems. The 1,11- and 1,15-lactones, on the other hand, were essentially equal to the parent hydroxy acids as antifertility agents (a 4-day assay which would allow time for in vivo enzymatic lactone hydrolysis). The 1,11- and 1,15-lactones exhibited very low activity in acute or in vitro screens (e.g., rat blood pressure and gerbil colon stimulation), assays which more closely reflect the intrinsic activity of the lactones themselves. These results are consistent with the observed relative ease of enzymatic hydrolysis of the prostaglandin lactones (1,15 ≥ 1,11 ≫ 1,9). Several of the lactones whose parent hydroxy acids are resistant to metabolic inactivation (e.g., 15-methyl, 16-phenoxy, and 17-phenyl) exhibited potent abortifacient activity in the hamster. These lactones, with greatly diminished activity in the blood pressure and smooth muscle assays (indicators of potential side effects), represent a therapeutically useful class of antifertility agents.

A wide variety of prostaglandin C-1 esters have been reported.[1,2] In the case of PGE_2, a relatively unstable β-hydroxy ketone, conversion of the C-1 carboxy group to any of several para-substituted phenyl esters afforded derivatives with distinctly improved solid-sate stability.[1] Aliphatic prostaglandin C-1 esters,[2] although less frequently crystalline, offered the advantage of improved intestinal absorption,[3,4] (relative to the corresponding acid) and greater potency following intravenous administration.[5] Likewise, $PGF_{2\alpha}$ C-9 and C-15 monoacylates have been synthesized and evaluated as prodrugs.[6] Some of these prostaglandin esters exhibited intrinsic biological activity, while others required enzymatic hydrolysis before their biological effects became evident. We felt that prostaglandin lactones, formed by reaction of either the C-9, C-11, or C-15 hydroxy groups with an activated form of the C-1 carboxy, might offer several further advantages, in addition to those characteristic of other prostaglandin esters. First, the alcohol portion of the lactones would obviously not pose any additional toxicology problems beyond those of the parent prostaglandin. Second, the solubility of the lactones should be better than that of esters made from high-molecular-weight aromatic alcohols.[1] Third, at least the 1,15-lactones would be protected from metabolic oxidation (and inactivation) at C-15 until the lactone was hydrolyzed. Finally, by virtue of their different conformations relative to the open-chain hydroxy acids, the lactones might exhibit diminished PG-like activity themselves but become available (as the fully active hydroxy acids) locally on a sustained release basis depending on esterase distribution and the mode of administration. In order to evaluate these hypotheses, most of the natural prostaglandins and several key analogues were converted to the corresponding lactones as described below.[7]

Over the past decade, considerable synthetic effort has been expended in the development of new, efficient methods for macrocyclic lactone formation.[8,9] One of the mildest and most generically useful lactonization procedures, developed by Corey and Nicolaou[10,11] and involving "double activation" of the appropriate ω-hydroxy acid, was used throughout the current study. This process involves

(1) Morozowich, W.; Oesterling, T. O.; Miller, W. L.; Lawson, C. F.; Weeks, J. R.; Stehle, R. G.; Douglas, S. L. *J. Pharm. Sci.* **1979**, *68*, 833.
(2) Morozowich, W.; Oesterling, T. O.; Miller, W. L.; Douglas, S. L. *J. Pharm. Sci.* **1979**, *68*, 836.
(3) Magee, W. E.; Armour, S. B.; Miller, O. V. *Biochim. Biophys. Acta* **1973**, *306*, 270.
(4) Robert, A.; Magee, W. E.; Miller, O. V.; Nezamis, J. E. *Biochim. Biophys. Acta* **1974**, *348*, 269.
(5) Wiqvist, N.; Martin, J. N.; Bygdeman, M.; Green, K. *Prostaglandins* **1975**, *9*, 255.
(6) Morozowich, W.; Oesterling, T. O.; Miller, W. L., Lawson, C. F.; Cornett, J. C.; Weeks, J. R.; Douglas, S. L. *J. Pharm. Sci.* **1979**, *68*, 949.
(7) In addition to $PGF_{2\alpha}$ 1,9-lactone and $PGF_{2\alpha}$ 1,15-lactone, which had been reported earlier by Corey (ref 11) and Mukaiyama (ref 9), N. H. Andersen has described a series of prostaglandin 1,(ω − 1)-lactones designed to constrain the prostaglandins in a "hairpin" conformation. See: (a) Andersen, N. H.; Imamoto, S.; Subramanian, N.; *Prostaglandins* **1981**, *22*, 831. (b) Andersen, N. H.; Imamoto, S.; Subramanian, N.; Picker, D. H.; Ladner, D. W.; De, B.; Tynan, S. S.; Eggerman, T. L.; Harker, L. A.; Robertson, R. P.; Oien, H. G.; Rao, Ch. V. *Ibid.* **1981**, *22*, 841.
(8) For recent reviews of macrolide syntheses, see: (a) Masamune, S. *Aldrich. Acta* **1978**, *11*,23. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, 3041. (d) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.
(9) Naraska, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885.
(10) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, *38*, 3405. (c) Corey, E. J.; Brunelle, D. J. *Ibid.* **1976**, *38*, 3409.
(11) Corey, E. J.; Nicolaou, K. C.; Melvin, Jr., L. S. *J. Am. Chem. Soc.* **1975**, *97*, 653.

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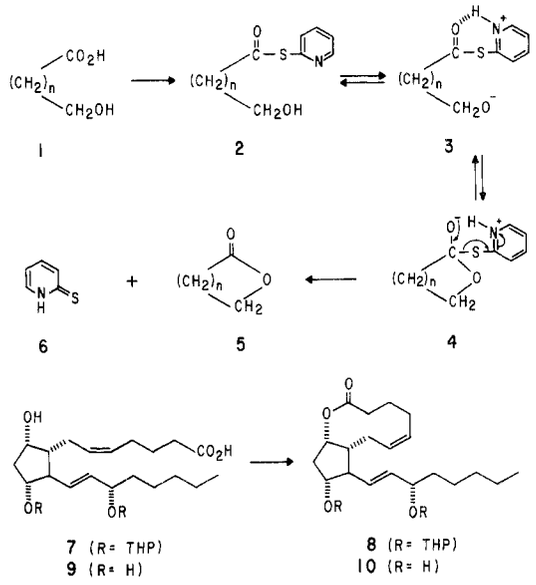
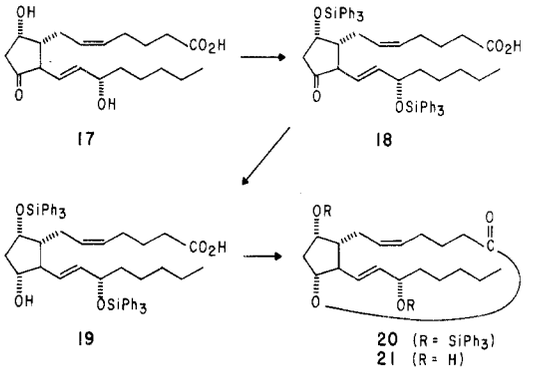
Scheme I



Scheme II



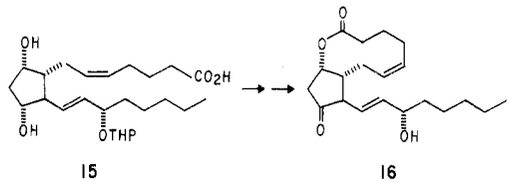
initial formation of a 2-pyridinethiol ester[12] of an ω-hydroxy acid via an oxidation–reduction condensation[12] (**1** → **2**). Internal proton transfer then affords intermediate **3**, in which both the carboxy carbonyl and the hydroxy groups have been activated, and ring closure is effected under mild conditions (at high dilution to avoid dimer formation).[10]

By using the Corey–Nicolaou lactonization procedure, $PGF_{2\alpha}$ 11,15-bis(tetrahydropyranyl ether) (**7**)[13] could be converted to the corresponding lactone (**8**)[11] and deprotected, affording $PGF_{2\alpha}$ 1,9-lactone (**10**) in good yield. Corey reported that direct lactonization of unprotected $PGE_{2\alpha}$ (**9**) (in refluxing xylene) afforded a 4:1 mixture of **10** and $PGF_{2\alpha}$ 1,15-lactone (**34**). We have found that lowering the reaction temperature (refluxing benzene) increased the ratio to at least 8:1, favoring the 1,9-lactone. Thus, yields of recrystallized **10** in the range of 60–65% were routinely obtainable on a 5–10-g scale, without protection of the C-11 and C-15 hydroxys. $PGF_{2\alpha}$ 1,9-lactone has been described as an oil that solidified upon refrigeration[11] or long standing[9] (no melting point recorded) or as a crystalline material with mp 82–84 °C[7a] (no recrystallization solvent indicated). After several recrystallizations from either ethyl acetate/hexane or ether/hexane, we obtained material that underwent an apparent change of crystalline form at about 44–46 °C and then melted sharply at 87.1–88.8 °C.

$PGF_{2\alpha}$ 1,9-lactone (**10**) and several of the analogues described below exhibited two infrared bands in the carbonyl region (at 1733 and 1707 cm^{-1} for **10** as a Nujol null; 1728 and 1718 cm^{-1} in chloroform solution). Since mass spectral analysis of **10** (both by electron impact and chemical ionization with ammonia) showed no evidence for the presence of a dimer, and since base hydrolysis of **10** afforded only $PGF_{2\alpha}$ (uncontaminated by any 5*E*, 9β, 11β, 13*Z*, or 15*R* isomers), we have tentatively ascribed this phenomenon to the presence of two conformers with similar energy but with distincty different shape or hydrogen-bonding capabilities.

Using the 2,2′-dipyridyl disulfide/triphenylphosphine procedure discussed above (Scheme I), we prepared (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (**11**), 16,16-dimethyl-$PGF_{2\alpha}$ 1,9-lactone (**12**),[14] (15*S*)-15-methyl-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ 1,9-lactone (**13**), and (15*S*)-2,2-difluoro-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (**14**) from the corresponding (unprotected) triol acids[15] (in yields of 71, 40, 63, and 32%, respectively). Although (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (**11**) was completely homogeneous in a wide variety of TLC solvents, a small sample was hydrolyzed in aqueous base back to the hydroxy acid from which it had been made, in order to ensure that undetected epimerization had not occurred at C-15 during lactonization. TLC analysis of the crude hydrolysis product (after diazomethane esterification) showed conclusively that the C-15 tertiary allylic alcohol center still possessed cleanly the 15*S* configuration.

PGD_2 1,9-lactone (**16**) could not be synthesized by direct

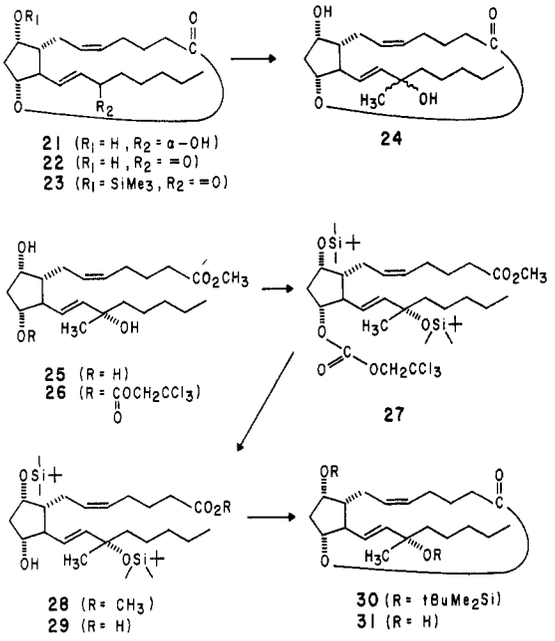


lactonization of PGD_2. Conditions vigorous enough to effect ring closure in every instance led to concomitant rearrangement of the β,γ-unsaturated C-11 ketone (i.e., PGD_2 itself) to the more stable α,β-unsaturated (Δ^{12}) isomer.[16] As described in detail elsewhere,[16] PGD_2 1,9-lactone (**16**) was prepared starting from $PGF_{2\alpha}$ 15-(tetrahydropyranyl ether) (**15**)[17] via the following sequence: (a) Corey–Nicolaou lactonization, (b) Jones oxidation (−30 °C, 1 h), and (c) deprotection at C-15 ($THF/H_2O/HOAc$, 40 °C, 1 h) in 31% overall yield. Lactone **16**, an oil, could be purified by chromatography only on Mallinckrodt CC-4 acid-washed silica gel. On "neutral" silica gel (e.g., silica gel 60, EM Reagents), rapid elimination of the carboxylate afforded 9-deoxy-9,10-didehydro-PGD_2 in good yield.

Lactone formation utilizing the C-11 hydroxy group of $PGF_{2\alpha}$, the least accessible of the three, relative to the C-1

(12) Mukaiyama, T. *Synth. Commun.* **1972**, *2*, 243, and earlier references cited therein.
(13) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.
(14) This experiment was performed by Dr. Douglas R. Morton, Department of Experimental Sciences, The Upjohn Co.
(15) (a) 15-Methyl-$PGF_{2\alpha}$: Yankee, E. W.; Axen, U. F.; Bundy, G. L. *J. Am. Chem. Soc.* **1974**, *96*, 5865. (b) 16,16-dimethyl-$PGF_{2\alpha}$: Magerlein, B. J.; DuCharme, D. W.; Magee, W. E.; Miller, W. L.; Robert, A.; Weeks, J. R. *Prostaglandins* **1973**, *4*, 143. (c) 15-methyl-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$: Bundy, G. L. U.S. Patent 3 987 087, 1976, example 54. (d) (15*S*)-2,2-difluoro-15-methyl-$PGF_{2\alpha}$: Axen, U. F. U.S. Patent 4 001 300, 1977, example 26.
(16) Bundy, G. L.; Morton, D. R.; Peterson, D. C.; Nishizawa, E. E.; Miller, W. L. *J. Med. Chem.* **1983**, *26*, 790.
(17) Nishizawa, E. E.; Miller, W. L.; Gorman, R. R.; Bundy, G. L.; Svensson, J.; Hamberg, M. *Prostaglandins* **1975**, *9*, 109.

Scheme III

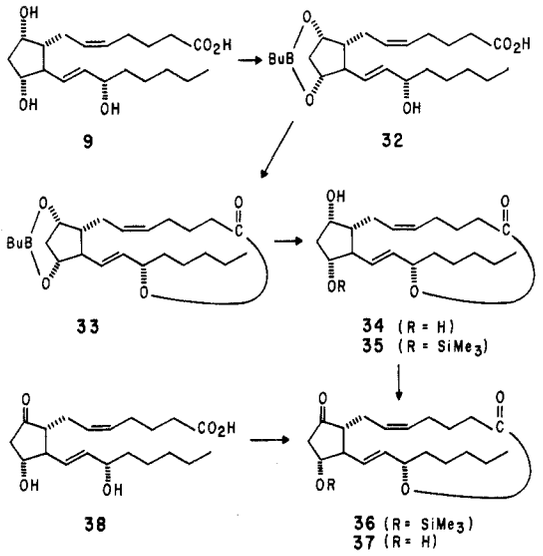


carboxy group,[18] has not been reported. In order to induce lactonization at C-11, the C-9 and C-15 hydroxy groups had to be masked temporarily (Scheme II). PGD_2[17] was converted to the 9,15-bis(triphenylsilyl ether) **18** in 87% isolated yield by using triphenylsilyl chloride in pyridine. (The triphenylsilyl ester that formed simultaneously was cleanly hydrolyzed during a modified workup by the pyridine hydrochloride formed during the silylation.) Reduction of ketone **18** with sodium borohydride then afforded a mixture of epimeric C-11 alcohols, with the desired 11α-isomer greatly predominant[19] (71% isolated yield of **19**). Lactonization (77%) and desilylation (71%) gave $PGF_{2\alpha}$ 1,11-lactone **21**. While silylated intermediate **20** exhibited a single carbonyl band in its infrared spectrum (1730 cm^{-1}), $PGF_{2\alpha}$ 1,11-lactone itself (**21**), like most of the 1,9-lactones, had a double carbonyl absorption (1735, 1715 cm^{-1}).

It appeared at first that the efficient synthesis of (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,11-lactone would prove reasonably uncomplicated (Scheme III). $PGF_{2\alpha}$ 1,11-lactone (**21**) was oxidized at C-15 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 82% yield. Following silylation of the remaining (C-9) alcohol (to keep the substrate soluble in the next reaction), trimethylaluminum addition gave 15-methyl-$PGF_{2\alpha}$ 1,11-lactone (**24**) in essentially quantitative yield. Unfortunately, product **24** consisted of a 1:1 mixture of C-15 epimers, which proved inseparable chromatographically. (The fact that **24** was a mixture was shown by conversion of lactone **24** to the corresponding open-chain hydroxy ester. At that point, the C-15 epimers, for which authentic standards were available,[15a] were readily resolvable by TLC.) The synthesis of (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,11-lactone, configurationally homogeneous at C-15, therefore required a considerably more circuitous route, outlined in Scheme III.

Selective protection of the C-11 hydroxy group of (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester (**25**) as the trichloroethyl carbonate derivative[20,21] was accomplished in

Scheme IV



81% yield. Conversion of **26** to the 9,15-bis(*tert*-butyldimethylsilyl ether) **27** required relatively vigorous conditions (*t*-$BuMe_2SiCl$,[22] imidazole, DMF, 80 °C, 16 h) but proceeded fairly cleanly (60%).[23] Removal of the C-11 protecting group (zinc, methanol, reflux, 75 min, 89%) and basic hydrolysis of the C-1 ester (95%) then afforded hydroxy acid **29**, lactonization of which yielded 1,11-lactone **30** (70%).

Clean desilylation of **30** proved unexpectedly challenging. While the C-15 silyl group was hydrolyzed very readily (even contact with acid-washed silica gel was sufficient), the more acidic conditions necessary to desilylate the C-9 hydroxy led to epimerization of the C-15 tertiary allylic alcohol.[15a] With tetrabutylammonium fluoride, desilylation at C-9 was efficient, but the more vigorous conditions necessary to desilylate C-15 (1,2-dimethoxyethane, reflux, 16 h) led to considerable cleavage of the strained lactone by attack of fluoride at C-1 (leading after workup to 15-methyl-$PGF_{2\alpha}$). The isolated yield of **31** was therefore only 46%, but 79% if account was taken of recovered (and theoretically recycleable) (15*S*)-15-methyl-$PGF_{2\alpha}$. Examination of this byproduct (or that obtained by lactone cleavage of **31** with methoxide) by TLC showed that the sensitive tertiary allylic alcohol had survived configurationally intact through the somewhat vigorous silylation–lactonization–desilylation sequence.

The general route used for the synthesis of prostaglandin 1,15-lactones is summarized in Scheme IV and involved temporary protection of the C-9 and C-11 hydroxys as a cyclic butyl boronate (**32**), lactonization, and mild hydrolytic workup. By this route, $PGF_{2\alpha}$ 1,15-lactone (**34**)[11] (mp

(18) CPK space-filling models confirm that the 1,11-lactone (**21**) is by far the most hindered of the three possible monomeric lactones of $PGF_{2\alpha}$.

(19) The configurational assignments at C-11 were established by desilylation and comparison with authentic $PGF_{2\alpha}$ and 11β-$PGF_{2\alpha}$ standards.

(20) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555.

(21) The *p*-phenylbenzoate was equally useful as the C-11 protecting groups in this sequence. The Me_3Si group, although readily introduced regioselectively, did not survive during *tert*-butyldimethylsilylation of the remaining hydroxys, and complex mixtures were obtained.

(22) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

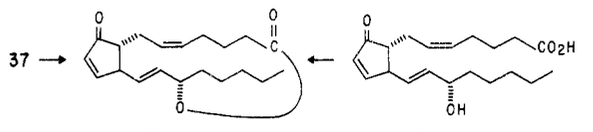
(23) In earlier work, we had found that protection of the C-15 alcohol was indeed necessary. Even though the C-15 hydroxy is hindered, attempted formation of the 1,11-lactone from 15-methyl-$PGF_{2\alpha}$ 9-*tert*-butyldimethylsilyl ether apparently involved such a highly strained intermediate that reaction at C-15 was the predominant process. The product thereby obtained was unstable to the reaction conditions, undergoing elimination at C-15, followed finally by lactonization at C-11.

110.0–111.7 °C) was obtained in 46% overall yield. (Corey's synthesis of **34** proceeded via $PGF_{2\alpha}$ 9-acetate. In the case of the analogues reported herein, the unprotected PGF triol acids were generally the more accessible intermediates.) Using the same boronate protection procedure, we prepared $PGF_{1\alpha}$ 1,15-lactone (**39**), (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,15-lactone (**40**), 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ 1,15-lactone (**41**), and 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ 1,15-lactone (**42**) from the corresponding PGFs.[24]

The standard lactonization procedure worked very poorly in the case of the hindered 15-methyl or 16,16-dimethyl substrates. Using either benzene or xylene as solvent, we obtained complex mixtures, the only major component of which was the starting material. In these difficult cases, an alternative ring closure of the ω-hydroxy-2-pyridinethiol ester intermediates with silver perchlorate or fluoroborate in benzene[25] likewise proceeded in only very low yield. Despite the low yield and the complexity of the product mixture, chromatographic purification of (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,15-lactone (**40**) proved straightforward. Methanolic sodium methoxide lactone cleavage, generating only (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester, proved that no inadvertent epimerization had occurred at C-15.

PGE_2 1,15-lactone (**37**) was initially prepared from $PGF_{2\alpha}$ 1,15-lactone (**34**) (Scheme IV) by the three-step sequence originally designed for $PGF_{2\alpha}$ itself,[26] i.e., selective silylation at C-11, Collins oxidation at C-9, and desilylation (57% overall yield in the case of **37**, mp 73–76 °C). We have since found that PGE_2 1,15-lactone (**37**) could also be made directly from PGE_2 itself (**38**) via the pyridinethiol ester, even in refluxing xylene, without appreciable dehydration of the sensitive β-hydroxy ketone ring functionality in an isolated yield of 53%. In analogous fashion, PGE_1 1,15-lactone (**43**, mp 87–88 °C) and 17-phenyl-18,19,20-trinor-PGE_2 1,15-lactone (**44**, mp 81–83 °C) were synthesized either from the corresponding PGF 1,15-lactones (**39** and **42**, respectively) or directly from PGE_1 and 17-phenyl-18,19,20-trinor-PGE_2.[24c] The survival of the relatively labile PGE ring system during the direct pyridinethiol ester lactonization attests to the exceptional mildness of these reaction conditions.[10,11]

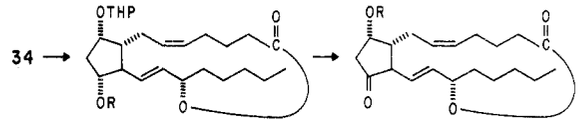
The synthesis of PGA_2 1,15-lactone (**45**, mp 60–61 °C)



45 46

was best accomplished by conversion of PGE_2 1,15-lactone (**37**) to the C-11 acetate (acetic anhydride, pyridine), followed by elimination of acetic acid on silica gel. Although direct lactonization of PGA_2 (**46**) afforded the same product (**45**), the yield was considerably lower, undoubtedly due to attack of the lactonization reagents at the relatively electrophilic C-11 carbon.[27] Direct lactonization of PGB_2 (which undergoes conjugate addition by nucleophiles less readily) afforded PGB_2 1,15-lactone (**47**) in 63% yield.[28] Isomerization of PGA_2 lactone **45** under mildly basic conditions led not to **47** but primarily to products resulting from elimination of the C-15 oxygen functionality.

The previously mentioned instability of PGD_2 to the Corey lactonization conditions precluded direct formation of PGD_2 1,15-lactone (**51**). This unstable lactone was



48 (R = tBuMe2Si) 50 (R = THP)
49 (R = H) 51 (R = H)

available in good yield from $PGF_{2\alpha}$ 1,15-lactone (**34**) via the following sequence: (a) selective *tert*-butyldimethylsilation, (b) THP formation, (c) desilylation with fluoride, (d) Jones oxidation, and (e) THP removal.[16] Lactone **51** could be readily purified by recrystallization (mp 93–94 °C) but did not survive chromatography on silica gel (elimination at C-15).

Lactone Hydrolysis. Since the prostaglandin lactones described herein possess shapes and polarities considerably different from their corresponding uncyclized congeners, it seems likely that they might go unrecognized by many of the normal prostaglandin-processing enzyme systems. Thus, in addition to whatever intrinsic biological activity these lactones may possess, a substantial portion of their therapeutic usefulness will depend on the facility with which they can be hydrolyzed enzymatically back to their prostaglandin parents (ideally with some biological site selectivity and at a biologically useful rate). Evidence for the first statement was provided by the observation that the lactones in this report were inert to hydrolysis by a soft coral (*Plexaura homomalla*) derived esterase.[29] This enzyme has proven fairly nondiscriminating over a wide variety of other prostaglandin-related structural types.

A rough measure of the relative susceptibility of $PGF_{2\alpha}$ lactones **10**, **21**, and **34** to enzymatic hydrolysis in vitro was obtained by incubating these lactones with the (esterase-containing) blood plasma from rats, monkeys, and humans and then measuring the hydrolysis product ($PGF_{2\alpha}$) by radioimmunoassay.[30] $PGF_{2\alpha}$ (**9**) and $PGF_{2\alpha}$ 15-acetate[30] were also incubated under the same conditions, the former as a positive control for the radioimmunoassay procedure and the latter for comparison with the lactones. (A commercially available hog liver esterase preparation was also included as a typical, efficient, and nonspecific hydrolyzing enzyme.)

Several conclusions are apparent from the data in Table I. $PGF_{2\alpha}$ 1,9-lactone (**10**) (the most easily formed of the three lactones) was not hydrolyzed to any appreciable extent by the esterase systems utilized here. (The C-9 acetate and butyrate of $PGF_{2\alpha}$ were likewise resistant to enzymatic hydrolysis in vitro.[6]) In contrast, the 1,15-lactone (**34**) was readily hydrolyzed under all four conditions, more easily in most cases than $PGF_{2\alpha}$ 15-acetate.

(24) (a) 15-methyl-$PGF_{2\alpha}$: ref 15a. (b) 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$: Binder, D.; Bowler, J.; Brown, E. D.; Crossley, N. S.; Hutton, J.; Senior, M.; Slater, L.; Wilkinson, P.; Wright, N. C. A. *Prostaglandins* **1974**, *6*, 87. (c) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$: Magerlein, B. J.; Bundy, G. L.; Lincoln, F. H.; Youngdale, G. A. *Prostaglandins* **1975**, *9*, 5.

(25) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*(8), 2661.

(26) Yankee, E. W.; Lin, C. H.; Fried, J. *J. Chem. Soc., Chem. Commun.* **1972**, 1120.

(27) For the addition of a wide variety of nucleophiles at C-11 in PGA_2, see: Grudzinskas, C. V.; Weiss, M. J. *Tetrahedron Lett.* **1973**, 141.

(28) This experiment was performed by Dr. Norman A. Nelson, Cardiovascular Diseases Research, The Upjohn Co.

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

(30) This technique has been used successfully with a variety of prostaglandin C-1 esters and C-9 (or C-15) acylates. See: Morozowich, W.; Oesterling, T. O.; Miller, W. L.; Lawson, C. F.; Cornette, J. C.; Weeks, J. R.; Douglas, S. L. *J. Pharm. Sci.* **1979**, *68*, 4315, and ref 31.

(31) Miller, O. V.; Magee, W. E. *Prostaglandins* **1974**, *7*, 29.

Table I. Plasma Hydrolysis of PGF Lactones

compd	% cross-reaction of substrate with $PGF_{2\alpha}$ antisera	% hydrolysis[a] following 2-h incubation with					% hydrolysis[a] following 20-h incubation with				
		saline control	hog liver esterase	rat plasma	monkey plasma	human plasma	saline control	hog liver esterase	rat plasma	monkey plasma	human plasma
$PGF_{2\alpha}$ 1,9-lactone (10)	<0.05	<0.05	0.2	0.2	0.06	0.06	0.2	1.8	0.8	0.3	0.4
$PGF_{2\alpha}$ 1,11-lactone (21)	0.09	0.1	28.3	43.0	2.4	0.2	0.2	100	80.6	15.5	0.6
$PGF_{2\alpha}$ 1,15-lactone (34)	0.9	1.3	55.3	51.4	8.4	55.6	4.4	75.6	58.7	41.7	57.9
$PGF_{2\alpha}$ 15-acetate[b]	2.4	4.1	59.1	18.0	3.6	3.3	14.2	85.0	25.7	9.4	6.8
$PGF_{2\alpha}$ (9)	100	100	100	100	100	100	100	100	100	100	100

[a] As measured by cross-reactivity with $PGF_{2\alpha}$ antisera. [b] Reference 30.

Table II. Urinary Excretion of $PGF_{2\alpha}$ Metabolite in Rats Treated with $PGF_{2\alpha}$ Lactones

compd administered (1 mg/rat sc)	urinary excretion, μg	
	day 1	day 2
$PGF_{2\alpha}$ 1,9-lactone (10)	1.4 (1.3-1.6)[a]	0.9 (0.7-1.1)
$PGF_{2\alpha}$ 1,11-lactone (21)	27.2 (23.1-31.1)	1.6 (1.2-2.0)
$PGF_{2\alpha}$ 1,15-lactone (34)	77.1 (31.9-155)	3.9 (2.2-5.6)
$PGF_{2\alpha}$	252 (220-285)	14.5 (11.4-16.5)
vehicle control	1.2 (0.9-1.6)	0.9 (0.7-1.3)

[a] Average (and range) for three rats; measured by radioimmunoassay.[33]

(Note that both the lactone **34** and $PGF_{2\alpha}$ 15-acetate were slowly hydrolyzed in the saline control solutions.) $PGF_{2\alpha}$ 1,11-lactone (**21**) was intermediate in its susceptibility to enzymatic hydrolysis by rat or monkey plasma but was notably inert in human plasma.

A measure of the relative hydrolyzability of the $PGF_{2\alpha}$ lactones in vivo was provided by injecting the lactones (1 mg) subcutaneously in rats and then measuring the urinary excretion of the major metabolite of $PGF_{2\alpha}$ (viz., 5α,7α-dihydroxy-11-ketotetranorprosta-1,16-dioic acid[32]) by radioimmunoassay.[33] (This metabolism should occur only after hydrolysis of the lactones to $PGF_{2\alpha}$ itself.) As indicated by the data in Table II, $PGF_{2\alpha}$ 1,9-lactone (**10**) was not hydrolyzed by the rat in vivo, while the 1,15-lactone (**34**) yielded substantial amounts of the $PGF_{2\alpha}$ metabolite (approximately 30% of the amount recovered from rats given $PGF_{2\alpha}$ itself). (Both $PGF_{2\alpha}$ 9-acetate and 9-butyrate were readily hydrolyzed in analogous in vivo experiments.[6]) As in the in vitro plasma hydrolysis studies described above, $PGF_{2\alpha}$ 1,11-lactone (**21**) was intermediate between the 1,9- and 1,15-lactones with respect to the ease of hydrolysis. From these data, it was evident that substantial amounts of $PGF_{2\alpha}$ were available following administration of either the 1,11- or the 1,15-lactone (**21** and **34**) to rats. The biological profiles of these lactones (described below) closely paralleled this relative order of "availability after hydrolysis". The ratio of the amounts of $PGF_{2\alpha}$ metabolite formed on day 1 vs. day 2 following administration of lactones **21** or **34** was virtually identical with the day 1/day 2 ratio observed after $PGF_{2\alpha}$ administration. Thus, in the rat at least, where esterase activity is fairly efficient, there was no evidence for dramatically prolonged metabolic stability for these lactones. The sustained release of the parent hydroxy acids from the corresponding PG lactones should be more evident in species where the lactone hydrolysis is slower.

Biology. The biological activities of the prostaglandin lactones reported above were determined in a number of commonly used prostaglandin test systems[40] (described in brief below).

Rat Blood Pressure. Mature female albino rats were anesthetized with sodium pentobarbital (30 mg/kg ip), supplemented as needed, and given atropine sulfate (0.08 mg sc) and pentolinium tartrate (2 mg iv). A femoral vein was exposed for injections of solutions or emulsions of the test compounds, and blood pressure was recorded from a common carotid artery by means of a Statham P23G transducer and Grass polygraph. The change in blood pressure (millimeters of Hg, rise or fall) was measured and compared with standard compounds (PGE_1 for depressors and $PGF_{2\alpha}$ for pressors).

Isolated Gerbil Colon Stimulation. The isolated ascending colon of male gerbils (*Meriones unguiculatus*) were mounted in de Jalon's solution (NaCl, 154 mM; KCl, 0.54 mM; $CaCl_2$, 0.27 mM; $NaHCO_3$, 1.78 mM; glucose, 5.55 mM), and isotonic contractions were recorded by means of Phipps and Bird linear transducers (5-mL baths). Test compounds were dissolved in ethanol (minimum amount)/physiological saline and compared with PGE_1 as the standard.

Hamster Antifertility. Mature female hamsters (80–100 g) in estrus were caged overnight with males (two females with one male) of proven fertility. Those animals with sperm in the vagina the following morning were injected subcutaneously with the test compound (in 0.5 mL of 10–30% ethanol–aqueous saline) the 4th day after mating. On the 8th day, animals were sacrificed and considered pregnant if one or more implantation sites were found in the uterus. All of 52 control hamsters receiving vehicle injections were pregnant.

Lactone Hydrolysis Studies in Monkeys. Rhesus monkeys were given a single im dose of the test compound (lactone) in 1 mL of 95% ethanol on day 22 of the menstrual cycle. Blood samples were taken at 1, 2, 4, and 8 h, and plasma levels of 15-methyl-$PGF_{2\alpha}$ (the hydrolysis product in each case) were measured by radioimmunoassay. The lactones did not cross-react with the 15-methyl-$PGF_{2\alpha}$ antibodies.

Thermogenicity Studies in Monkeys. A calibrated MKIVLL-type telemeter (Biodynamics Laboratories, Franklin Institute, Philadelphia) was surgically placed between the intestinal folds of an anesthetized 4.8-kg fe-

(32) Granstrom, E.; Samuelsson, B. *Eur. J. Biochem.* **1969**, *10*, 411.
(33) Cornette, J. C.; Kirton, K. T.; Schneider, W. P.; Sun, F. F.; Johnson, R. A.; Nidy, E. G. *Prostaglandins* **1975**, *9*, 323.

Table III. Biological Activities of PG Lactones

no.	compound	rat BP[a] (rel potency): $\downarrow PGE_1 = 100$ $\uparrow PGF_{2\alpha} = 100$	gerbil colon[a] stimulation (rel potency): $PGE_1 = 100$	hamster antifertility[b] no. nonpreg./ no. treated (dose, μg sc)
10	$PGF_{2\alpha}$ 1,9-lactone	↓0.1-0.3	1-3	1/6 (1000)
11	(15*S*)-15-Me-$PGF_{2\alpha}$ 1,9-lactone	↑3-10	1-3	4/6 (50) 2/6 (10)
12	16,16-Me_2-$PGF_{2\alpha}$ 1,9-lactone	↓0.1-0.3	32-100	1/6 (1000)
13	(15*S*)-15-Me-17-Ph-18,19,20-trinor-$PGF_{2\alpha}$ 1,9-lactone	↑3-10	1-3	4/6 (50)
14	(15*S*)-2,2-F_2-15-Me-$PGF_{2\alpha}$ 1,9-lactone	↓0.1-0.3	1-3	6/6 (10) 0/6 (1)
16	PGD_2 1,9-lactone	↓10-32	0.3-1	4/6 (1000)
21	$PGF_{2\alpha}$ 1,11-lactone	↑0.3-1	0.3-1	6/6 (1000) 4/6 (50)
31	(15*S*)-15-Me-$PGF_{2\alpha}$ 1,11-lactone	↑0.3-1	<0.1	6/6 (1) 2/6 (0.5)
34	$PGF_{2\alpha}$ 1,15-lactone	<0.1	0.1-0.3	6/6 (100) 0/6 (50)
37	PGE_2 1,15-lactone	↓1-3	1-3	6/6 (1000) 1/6 (50)
39	$PGF_{1\alpha}$ 1,15-lactone	<0.1	<0.1	5/6 (1000) 0/6 (50)
40	(15*S*)-15-Me-$PGF_{2\alpha}$ 1,15-lactone	not tested	not tested	6/6 (5) 4/6 (1)
41	16-PhO-17,18,19,20-tetranor-$PGF_{2\alpha}$ 1,15-lactone	100 μg: inact 1000 μg: toxic	0.1-0.3	6/6 (0.1) 2/6 (0.05)
42	17-Ph-18,19,20-trinor-$PGF_{2\alpha}$ 1,15-lactone	↑32-100	<0.1	5/6 (10) 0/6 (1)
43	PGE_1 1,15-lactone	<0.1	<0.1	1/6 (1000)
44	17-Ph-18,19,20-trinor-PGE_2 1,15-lactone	biphasic (weak)	0.3-1	6/6 (1000) 0/6 (50)
45	PGA_2 1,15-lactone	↓0.1-0.3	0.1-0.3	not tested
47	PGB_2 1,15-lactone	<0.1	0.1-0.3	not tested
51	PGD_2 1,15-lactone	↓0.1-0.3	0.1-0.3	5/6 (1000) 2/6 (50)

[a] A 100-fold difference in relative potency is considered significant ($p < 0.05$). [b] A score of 1/6 or 2/6 *may* represent a drug effect; scores of 3/6 and better are statistically significant ($p < 0.05$).

male rhesus monkey. Solutions of test compounds (20 mg total dose) were administered subcutaneously. During the temperature-recording experiments, the monkeys were housed in special Plexiglas chambers, surrounded with an omidirectional antenna system for receiving radio transmission. Temperature was recorded on a strip-chart recorder from which an area of significant increase (hyperthermia) or decrease (hypothermia) was calculated.

Results and Discussion

The rat blood pressure, gerbil colon stimulation, and hamster antifertility activities for the lactones in this report are summarized in Table III. Of these three test systems, the hamster antifertility assay is the most closely related to the anticipated clinical utility of particularly the PGF lactones. The blood pressure and gerbil colon data can be significant as indicators of areas for potential concern (i.e., side effects) in the clinical development of these analogues.

With only two exceptions (mentioned below), the rat blood pressure and gerbil colon activities of the lactones in this report represent at least a 10-fold (and more frequently a 30- to 100-fold) decrease relative to those of the corresponding open hydroxy acid structures. Since the short time frame of these biological tests would preclude lactone hydrolysis during the experiment, these data reflect the lactones' general lack of intrinsic activity. The two exceptions—the gerbil colon activity of lactone **12** and the blood pressure effects of lactone **16**, both virtually identical with the non-lactone parent—presumably are cases where the observed effects are attributable to the lactone themselves. This explanation seems reasonable in view of the greatly dimished activities of **12** and **16** in the other test systems.

With regard to hamster antifertility efficacy, the 1,9-lactones, with one exception, exhibit dramatically reduced (usually >100-fold) activity compared to the corresponding open-chain hydroxy acids. This observation is consistent with the above-mentioned reluctance of these lactones to undergo enzymatic hydrolysis, even over the 4-day time span of this experiment. The potent hamster antifertility activity retained in lactone **14** is undoubtedly due to the facile *non*enzymatic hydrolysis of the activated (2,2-difluoro) lactone in vivo.

In sharp contrast to the 1,9-lactones, the 1,11- and 1,15-lactones in Table III possess hamster antifertility activity essentially equal to (**31**, **34**, **37**, **39**, **40**, **41**, and **51**) or only slightly lower (**21**, **42**, **43**, and **44**) than the corresponding hydroxy acids. Again, these data correlate well with the observed ease of hydrolysis of the 1,11- and 1,15-lactones both in vitro and in vivo. Andersen[7] has observed similar trends in his 1,9- and 1,15-lactones.

With regard to substituent effects on hamster antifertility activity, the most active of the PGF lactones were those which possessed alkyl side chains chemically protected from metabolic inactivation, e.g., 15-methyl (**31** and **40**), 16-phenoxy (**41**), and 17-phenyl (**42**). The corresponding non-lactone parents of these particular analogues have likewise exhibited potent hamster antifertility activity[24] but appear considerably more prone to cardiovascular and smooth muscle related side effects (i.e., blood pressure changes and diarrhea).

A more thorough study of $PGF_{2\alpha}$ 1,15-lactone (**34**) in the fertility area by Spilman et al.[34] revealed that it was ca-

(34) Spilman, C. H.; Beuving, D. C.; Forbes, A. D.; Kimball, F. A. *Prostaglandins* **1977**, *14*, 477.

pable of interrupting early pregnancy in rhesus monkeys at doses (2 × 5 mg) where $PGF_{2\alpha}$ itself was not effective. Lactone **34** also decreased menstrual cycle length in nonpregnant monkeys. Rall et al.[35,36] observed shortened cycles and significantly depressed peripheral progesterone levels in the baboon as well (without side effects) following treatment with **34** (2 mg/kg im).

The formation of $PGF_{2\alpha}$ metabolites following the administration of the $PGF_{2\alpha}$ lactones to rats (discussed in the preceding section) demonstrated that the parent prostaglandins were "bioavailable" following in vivo lactone hydrolysis. In order to obtain a more quantitative understanding of the time course of this in vivo hydrolysis in mammals, blood levels of the metabolically stabilized analogue (15*S*)-15-methyl-$PGF_{2\alpha}$ were measured (by radioimmunoassay) as a function of time following im administration of the corresponding 1,9-, 1,11-, and 1,15-lactones (**11**, **31**, and **40**) in rhesus monkeys. Following treatment with (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,11-lactone (**31**, (100 μg) or (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,15-lactone (**40**, 500 μg), peripheral plasma concentrations of (15*S*)-15-methyl-$PGF_{2\alpha}$ reached a peak between 1 and 2 h, then declined sharply to levels of <20% of the peak within 4 h, and were undetectable by 8 h. This blood level profile was virtually the same as that obtained following intramuscular administration of (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester (or free acid) in monkeys and indicated that these lactones did not afford significantly prolonged blood levels of the biologically active ring-opened analogue.

The intramuscular injection of (15*S*)-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (**11**, 100 μg) resulted in a moderate rise in plasma levels of (15*S*)-15-methyl-$PGF_{2\alpha}$ (ca. 200 pg/mL, compared to a peak level of 700 pg/mL following the same dose of 1,11-lactone **31**). The blood levels remained fairly constant, however, for at least 4 h (8 h in one of the two monkeys; more variability between animals was noted with **11** relative to **31** and **40**). After a much larger intramuscular dose (12 mg total; 2 mg/kg) of **11**, blood levels of (15*S*)-15-methyl-$PGF_{2\alpha}$ peaked at about 4 h (4000 pg/mL), but significant amounts (200–300 pg/mL) persisted over the next 4 days. Not unexpectedly, the initially high blood levels resulted in slight diarrhea in some of the animals.

The thermogenic (fever producing) effects of the $PGF_{2\alpha}$ lactones **10**, **21**, and **34** were investigated in the rhesus monkey by using a radio-telemetry method described earlier.[17,37] The use of surgically implanted telemeters allows sensitive measurement of core (abdominal) temperatures in unrestricted, unanesthetized animals, with continuous automatic recording. Treatment of monkeys subcutaneously with an abortifacient dose of $PGF_{2\alpha}$ (4 mg/kg, 20 mg total dose) produced moderate hypothermia for 2–5 h in the majority of animals (some responded with mild hyperthermia, however).[37] Administration of the same dose of $PGF_{2\alpha}$ 1,9-lactone (**10**) led to no change in body temperature. The 1,11-lactone **21** produced a mild fever (1.2 °C) in one monkey and no response in another following the same 20 mg subcutaneous dose. Somewhat surprisingly, the 1,15-lactone **34** caused an initially intense fever (2.0 ± 0.5 °C), followed by a moderate fever which persisted up to 4 days after injection. These responses parallel the relative ease of enzymatic hydrolysis of the lactones discussed earlier but may also be attributable in part to distinctive absorption and transport characteristics of these lactones resulting from their dramatically different polarity and solubility.

Conclusion

We have prepared the 1,9-, 1,11-, or 1,15-lactones of a variety of biologically interesting prostaglandins. In each case, the lactonization step was accomplished by using the Corey ω-hydroxy-2-pyridinethiol ester ring closure on suitably modified and protected substrates. With the few exceptions noted in the text, the prostaglandin lactones themselves appeared to possess only very low levels of intrinsic biological activity in the rat blood pressure and gerbil colon stimulation assays. The observed hamster antifertility effects of especially the 1,11- and 1,15-PGF lactones were most likely the result of enzymatic hydrolysis of the lactones, yielding the pharmacologically active hydroxy acid parents. Our in vitro and in vivo studies showed that the 1,15-lactones underwent facile enzymatic hydrolysis, while the 1,11-lactones hydrolyzed with intermediate ease and the 1,9-lactones were virtually inert under our test conditions. The hamster antifertility data correlate well with this order of enzymatic hydrolyzability. With their diminished blood pressure and gerbil colon stimulating activity, several of the PGF lactones (e.g., **14**, **31**, **34**, and **40–42**) represent potentially useful prodrugs for potent fertility-active prostaglandins.

A number of other lactones in Table III exhibited noteworthy biological activity in other areas. For example, PGD_2 1,9-lactone (**16**), was a relatively potent inhibitor of ADP-induced platelet aggregation ($IC_{50} \approx 32$ ng/mL),[16] while PGE_2 1,15-lactone (**37**) decreased gastric secretion by 90% in the dog when administered intravenously at a dose of 100 μg/kg.[38] A more detailed description of the biological profiles of selected members of this series will be forthcoming.

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 proton NMR spectra were obtained with a Varian A-60A spectrometer as solutions in deuteriochloroform with tetramethylsilane as internal standard. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer, low-resolution mass spectra with a Varian MAT-CH-7A instrument. Prior to their submittal for C, H, and/or high-resolution mass spectral analysis, all of the products in Table III were purified to the point where they were homogeneous by TLC in at least the following four solvent systems: (A) EtOAc/hexane/HOAc; (B) acetone/CH_2Cl_2/HOAc; (C) AIX[39]/hexane; (D) isopropyl alcohol/hexane/HOAc. In each case, the ratio of components was adjusted to yield R_fs in the 0.2–0.6 range. These mixtures have traditionally been very effective for analysis of the purity of a wide variety of prostaglandins. Unless otherwise noted, TLC analyses were performed on 250-μm silica gel GF plates from Analtech. The rat blood pressure, gerbil colon stimulation, and hamster antifertility biological test systems have been described in detail.[40]

$PGF_{2\alpha}$ 1,9-Lactone (10).[11] Following the general procedure of Corey and Nicolaou,[10,11] a mixture of 10.14 g (28.64 mmol) of $PGF_{2\alpha}$, 11.26 g (42.95 mmol) of triphenylphosphine, and 9.46 g

(35) Rall, H. J. S.; Zuurmond, T. J.; Weidemann, A. *Int. J. Fertil.* **1979**, *24*, 21.
(36) Rall, H. J. S.; Zuurmond, T. J.; Neethling, A. C.; VanSchalkwyk, D. J. *S. Afr. Med. J.* **1981**, *25*, 637.
(37) (a) Miller, W. L.; Forbes, A. D. *Pharmacologist* **1974**, *16*, 279 (abstr 506). (b) Mackay, R. S.; "Bio-Medical Telemetry", 2nd ed.; Wiley New York, 1970; Chapter 11.
(38) Robert, A., The Upjohn Co., unpublished results.
(39) AIX is the organic phase from 90 mL of EtOAc, 20 mL of HOAc, 50 mL of isooctane, and 100 mL of H_2O. See: Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1966**, *241*, 257.
(40) Weeks, J. R.; DuCharme, D. W.; Magee, W. E.; Miller, W. L. *J. Pharmacol. Exp. Ther.* **1973**, *186*, 67.

(42.95 mmol) of 2,2'-dipyridyl disulfide in 100 mL of oxygen-free benzene was stirred in an atmosphere of nitrogen for 3.5 h at 35 °C.[41] The reaction mixture, containing no remaining $PGF_{2\alpha}$ by TLC (acetone), was transferred under nitrogen to a 5-L flask containing 3.78 L of oxygen-free benzene, and the mixture was heated at reflux for 18 h. (The benzene had been deoxygenated with a vigorous stream of argon introduced through a gas dispersion tube for at least 15 min prior to use.) The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was triturated with a small volume of ether and filtered, thereby removing substantial amounts of triphenylphosphine oxide. The filtrate was reconcentrated and chromatographed on a 600-g column of silica gel. The column was packed with 10% acetone/CH_2Cl_2 and eluted (600-mL fractions) with 2 L of 10%, 6 L of 20%, 6 L of 30%, and 4 L of 40% acetone/CH_2Cl_2. Fractions 12–27 were homogeneous by TLC (EtOAc) and upon combination afforded 6.84 g of $PGF_{2\alpha}$ 1,9-lactone (**10**), which crystallized upon standing in the freezer. Recrystallization from ether/hexane gave 5.94 g (62% of theory) of pure lactone **10**. Further recrystallization from the same solvents or from EtOAc/hexane led to no change in melting point or spectral characteristics: mp 87.1–88.8 °C (with an apparent change of crystalline form at 44–45 °C); IR (mull) 3466, 1733, 1707, 1456, 1208, 1180, 1147, 1086, 1066 1027, 969 and 717 cm^{-1}; IR ($CHCl_3$ solution) 3600, 3410, 1728, 1718, 1450, 1349, 1267, 1179, 1146, 1120, 1084, 1030 and 972 cm^{-1}; NMR ($CDCl_3$) δ 5.8–5.00 (m, 5 H, vinyl and C-9), 4.25–3.60 (m, 2 H, C-11, C-15); mass spectrum (Me_3Si derivative), m/e 480.3064 (calcd for $C_{28}H_{48}O_4Si_2$, M^+, 480.3091), 409, 390, 319, 263, 217, 199, 173, 147, 129, 117, 103, 91, 73; chemical-ionization mass spectrum (with NH_3), m/e 354 [$(M + NH_4)^+$], 336 [$(M + NH_4)^+ - H_2O$], 319, 301 (no peaks above 354, scanned to 800); R_f 0.25 (20% acetone/CH_2Cl_2, developed twice before visualization), R_f 0.23 (70% EtOAc/hexane, developed twice). Anal. ($C_{20}H_{32}O_4$) C, H.

A 2-mg sample of lactone **10** in 0.5 mL of CH_3OH was treated with 0.5 mL of 3 N aqueous NaOH and stirred for 2 h at 25 °C. The mixture was then acidified and extracted with 0.5 mL of EtOAc. TLC analysis of the extract showed only $PGF_{2\alpha}$ in the following solvents: AIX[39] and 5 HOAc/10 CH_3OH/85 $CHCl_3$, using standard silica plates, silver nitrate impregnated plates, and boric acid impregnated plates. Under these conditions, any inadvertent isomerization at C-5, -9, -11, -13, or -15 would have been clearly evident by comparison with authentic standards of these isomers (none had occurred).

Using essentially the same procedure as described above, we synthesized the following PGF 1,9-lactones.

(15*S*)-15-Methyl-$PGF_{2\alpha}$ 1,9-Lactone (11). Following formation of the intermediate pyridinethiol ester as above but using xylene as solvent, lactonization was completed by refluxing for 3 h in xylene. The yield of **11**, a viscous, colorless oil, was 71% of theory: IR (neat) 3400, 1740, 1715, 1450, 1370, 1350, 1265, 1225, 1205, 1180, 1145, 1125, 1085, 1030, 970, 935, 905 and 715 cm^{-1}; NMR ($CDCl_3$) δ 5.80–5.00 (m, 5 H), 4.00–3.60 (m, 1 H), 1.29 (s, 3 H); mass spectrum (Me_3Si derivative), m/e 494 (M^+, weak), 423.2407 (calcd for $C_{22}H_{39}O_4Si_2$, $M^+ - C_5H_{11}$, 423.2386), 404, 389, 333, 314, 288, 278, 213, 178; R_f 0.39 (75% EtOAc/hexane developed twice), 0.23 (20% acetone/CH_2Cl_2 developed twice).

Hydrolysis of **11** as described in the preceding experiment, followed by diazomethane treatment, or direct ester interchange with methanolic sodium methoxide yielded only (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester. TLC analysis was done with EtOAc or with 35% acetone/CH_2Cl_2, solvents in which the 15*R* and 15*S* isomers are well resolved (no 15*R* detectable).

16,16-Dimethyl-$PGF_{2\alpha}$ 1,9-lactone (12):[14] toluene solvent; 9-h reflux; 40% isolated yield; pale yellow viscous oil; IR (neat) 3420, 1735, 1710, 1450, 1345, 1260, 1220, 1200, 1020, 975, 720 cm^{-1}; R_f 0.16 (AIX solvent[39]); NMR ($CDCl_3$) δ 6.00–5.05 (m, 5 H), 4.10–3.55 (m, 2 H), 0.90, 0.85 (s, 3 H each); mass spectrum (Me_3Si derivative), m/e 508 (M^+, weak), 493.3147 (calcd for $C_{27}H_{49}Si_2O_4$, $M^+ - CH_3$, 493.3169), 409, 403, 319, 99.

(15*S*)-15-Methyl-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ 1,9-lactone (13): benzene solvent; 24 h reflux; 63% isolated yield; viscous colorless oil; IR (neat) 3400, 1735, 1710, 1605, 1495, 1450, 1365, 1265, 1225, 975, 720, 700 cm^{-1}; R_f 0.29 (25% acetone/CH_2Cl_2); NMR ($CDCl_3$) δ 7.27 (s, 5 H), 5.8–5.1 (m, 5 H), 4.30–3.75 (m, 1 H), 1.40 (s, 3 H); mass spectrum (Me_3Si derivative), m/e 528.3112 (calcd for $C_{30}H_{48}Si_2O_4$, M^+, 528.3091), 513, 438, 423, 333, 91.

(15*S*)-2,2-Difluoro-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (14): benzene solvent; lactonization occurred in 20 min at 25 °C; 32% yield; viscous colorless oil; R_f 0.41 (25% acetone/CH_2Cl_2); IR (neat) 3350, 1760, 1230, 1220, 1105, 975, 720 cm^{-1}; NMR ($CDCl_3$) δ 5.90–5.10 (m, 5 H), 4.10–3.65 (m, 1 H), 1.26 (s, 3 H); mass spectrum (Me_3Si derivative), M^+ (observed) 530.3078 (calcd for $C_{27}H_{48}Si_2O_4F_2$, 530.3059).

PGD_2 1,9-Lactone (16). Full details of the synthesis and spectral characterization of lactone **16** are found in ref 16: R_f 0.37 (50% EtOAc/hexane).

PGD_2 9,15-Bis(triphenylsilyl ether) (18). A stirred 0 °C solution of 1 g of PGD_2[17] in 25 mL of anhydrous pyridine was treated with 3 g of triphenylsilyl chloride (added in one portion), and the resulting mixture was stirred for 6 h at 25 °C under nitrogen. The mixture was then cooled to 0 °C, diluted with 100 mL of cold THF and 40 mL of cold water, and stirred 45 min longer at 0 °C. The mixture was poured into brine, acidified (325 mL of cold 1 M $NaHSO_4$), and extracted immediately with 1:1 EtOAc/hexane. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was chromatographed on a 300-g column of Mallinckrodt CC-4 acid-washed silica gel, packed with 10% EtOAc/hexane and eluted (50 mL fractions) with 700 mL of the same solvent, followed by 2000 mL of 20% EtOAc/hexane. Fractions 45–67 afforded 2.15 g (87% yield) of PGD_2 9,15-bis(triphenylsilyl ether) **18**: R_f 0.24 (EtOAc/hexane/HOAc, 20:80:1) IR (neat) 3300, 3100, 2700, 1750, 1720, 1600, 1490, 1430, 1240, 1120, 1045, 1000, 970, 740, 710, 700 cm^{-1}; NMR ($CDCl_3$) δ 10.75 (s, 1 H, exchangeable), 7.90–7.20 (m, 30 H), 5.75–5.05 (m, 4 H), 4.75–4.15 (m, 2 H).

$PGF_{2\alpha}$ 9,15-Bis(triphenylsilyl ether) (19). To a stirred 0 °C solution of 4.10 g of **18** in 250 mL of CH_3OH was added 3 g of $NaBH_4$, in 100-mg portions over 15 min. After 15 min longer at 0 °C, the reaction mixture was carefully poured into a rapidly stirred mixture of ice, water, dilute $NaHSO_4$, 1:1 EtOAc/hexane. After separation of the phases, the aqueous phase was extracted with more 1:1 EtOAc/hexane. The extracts were washed with brine, dried (Na_2SO_4), and evaporated, and the crude product was chromatographed on 450 g of CC-4 silica gel. The column was packed with 10% EtOAc/hexane and eluted (1 × 800 mL, then 19-mL fractions) with 20% EtOAc/hexane. Fractions 40–75 yielded 2.90 g (71%) of $PGF_{2\alpha}$ 9,15-bis(triphenylsilyl ether) (**19**).

A 2-mg portion of **19** was stirred for 2 h at 45 °C in a mixture of 6 drops of THF, 3 drops of H_2O, and 1 drop of 85% H_3PO_4. The mixture was then diluted with brine (2 mL) and extracted with 0.3 mL of EtOAc in a vial. TLC analysis of the EtOAc layer on boric acid impregnated silica plates showed only $PGF_{2\alpha}$ and none of the 11β-epimer (authentic sample was available for comparison).

$PGF_{2\alpha}$ 1,11-Lactone (21). A solution of 2.90 g (3.33 mmol) of **19**, 1.10 g (5 mmol) of 2,2'-dipyridyl disulfide, and 1.31 g (5 mmol) of triphenylphosphine in 40 mL of dry, oxygen-free xylene was stirred at 25 °C under nitrogen for 10 h. The mixture was then diluted with 800 mL of xylene and heated at reflux for 24 h. After the mixture was cooled, the xylene was removed in vacuo (rotovac, vacuum pump, 30–35 °C), and the dark residue was chromatographed on 450 g of silica gel. The column was packed and eluted with benzene (1 × 200 mL, then 50-mL fractions). Fractions 30–48 afforded 2.20 g (77%) of 9,15-disilyl-1,11-lactone (**20**): IR 1730 cm^{-1}.

A mixture of 2.2 g of lactone **20**, 100 mL of THF, 80 mL of H_2O, and 20 mL of 85% H_3PO_4 was heated at 45 °C for 2 h. The reaction mixture was then concentrated to about one-half of the original volume, diluted with H_2O, and extracted with 3:1 EtOAc/hexane. The extracts were washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on a 125-g column of silica gel, packed with 25% EtOAc/hexane and eluted (14 mL of fractions) with 800 mL of 40%, 800 mL of 55%, and 1000 mL of 70% EtOAc/hexane. Fractions 103–135 gave 615 mg (71%) of $PGF_{2\alpha}$ 1,11-lactone (**21**), a viscous, colorless oil: R_f 0.54 (20% acetone/CH_2Cl_2, developed twice), 0.52 (70% EtOAc/hexane, developed twice); IR (neat) 3400,

(41) This experiment was performed by John H. Kinner, The Upjohn Co.

1730, 1710, 1450, 1350, 1335, 1270, 1225, 1185, 1145, 1100, 1085, 1005, 965, 705 cm^{-1}; NMR ($CDCl_3$) δ 5.8–4.95 (m, 5 H), 4.85–4.35 (m, 2 H), 4.20–3.85 (m, 1 H), 1.65 (s, 2 H, exchangeable); mass spectrum (Me_3Si derivative), m/e 480.3073 (calcd for $C_{26}H_{48}Si_2O_4$, M^+, 480.3091), 465, 409, 390, 375, 319, 199.

(15*RS*)-15-Methyl-PGF$_{2\alpha}$ 1,11-Lactone (24). A solution of 50 mg of 1,11-lactone **21** (0.149 mmol) and 40 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.178 mmol) was stirred under nitrogen at 25 °C for 66 h. The reaction mixture was filtered through a medium-porosity sintered glass funnel, and the solids were washed with CH_2Cl_2. The combined filtrate was concentrated in vacuo, and the residue was chromatographed on 10 g of silica gel. Elution (2–3-mL fractions) with 50% EtOAc/hexane afforded (fractions 12–28) 42 mg (82% yield) of 15-keto-PGF$_{2\alpha}$ 1,11-lactone **22**: IR (neat) 3400, 1730, 1670, 1625, 975 cm^{-1}; NMR ($CDCl_3$) δ 6.85–6.00 (m, 2 H), 5.55–5.00 (m, 2 H), 5.00–4.25 (m, 2 H), R_f 0.08 (20% EtOAc/hexane).

A solution of 42 mg (0.126 mmol) of **22** in 4 mL of THF was treated with 0.4 mL of hexamethyldisilazane and 0.1 mL of chlorotrimethylsilane, and the resulting mixture was stirred under nitrogen for 18 h at 25 °C. The solvent and excess reagents were removed in vacuo, and the residue was taken up in 20 mL of xylene and filtered through Celite. The filtrate was concentrated on the rotary evaporator with the aid of the vacuum pump (maximum temperature 30 °C). Two additional 20-mL portions of xylene were added and evaporated to ensure complete removal of the hexamethyldisilazane. The product, silyl derivative **23** (50 mg; 100% of theory), was greater than 98% pure by TLC (20% EtOAc/hexane, R_f 0.51) and was used without further purification in the next step.

A solution of 50 mg (0.126 mmol) of 15-keto derivative **23** in 5 mL of benzene was treated under nitrogen via syringe with 0.23 mL of 1.69 M trimethylaluminum in toluene (0.378 mmol, threefold excess), and the resulting light yellow solution was stirred for 30 min at 25 °C. Analysis of an NH_4Cl-quenched aliquot by TLC (20% EtOAc/hexane) showed that no starting material (R_f 0.51) remained—only a single more polar product (R_f 0.35). Saturated aqueous NH_4Cl (5 mL) was added to the reaction, and, after 10 min, the product was isolated by extraction with ether. The extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo.

The crude product was taken up in 15 mL of methanol, treated with 7 mL of 2% aqueous citric acid, and stirred 30 min at 25 °C. The reaction mixture was then poured into brine and extracted thoroughly with EtOAc. The extracts were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The product **24** was completely homogeneous by TLC (60% EtOAc/hexane and 20% acetone/CH_2Cl_2).

To a solution of 5 mg of lactone **24** in 1 mL of CH_3OH was added 0.5 mL of 25% methanolic sodium methoxide, and the resulting mixture was stirred for 3 h at 25 °C under nitrogen. The reaction mixture was cooled to 0 °C and treated with 5 mL of cold 2 M aqueous $KHSO_4$ and 2 mL of EtOAc. After a brief stirring at 0 °C, the layers were allowed to separate, and the EtOAc layer was analyzed immediately by TLC (40% acetone/CH_2Cl_2). The product consisted of a 1:1 mixture of (15*R*)- and (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester, indicating that lactone **24** was an inseparable mixture of C-15 epimers and that there had been no stereoselectivity in the trimethylaluminum addition.

(15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester 11-(Trichloroethyl carbonate) (26). A stirred solution of 382 mg (1 mmol) of (15*S*)-15-methyl-PGF$_{2\alpha}$ methyl ester[15a] (**25**) in 3 mL of anhydrous pyridine was cooled to 0 °C and treated dropwise with 0.137 mL (1 mmol) of trichloroethyl chloroformate.[20] The reaction mixture was stirred for 5 h at 0 °C and for 18 h at 25 °C, then poured into cold brine, and extracted with EtOAc. The extracts were washed with aqueous $NaHSO_4$, H_2O, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Chromatography of the crude product (75 g of silica gel, 30% EtOAc/hexane, 6.5-mL fractions) afforded (fractions 82–140) 450 mg (81%) of pure **26**, a viscous, colorless oil: IR 3500, 1750, 1370, 1240, 970, 825, 785, 730 cm^{-1}; NMR ($CDCl_3$) δ 5.70–5.20 (m, 4 H), 5.10–4.68 (s at 4.72, superimposed on m, 3 H), 4.35–3.95 (m, 1 H), 3.65 (s, 3 H), 1.25 (s, 3 H); R_f 0.73 (80% EtOAc/hexane).

(15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester 9,15-Bis(*tert*-butyldimethylsilyl ether) 11-(Trichloroethyl carbonate) (27). A solution of 450 mg (0.81 mmol) of **26**, 1.91 of *tert*-butyldimethylsilyl chloride,[22] and 1.73 g of imidazole in 15 mL of DMF was heated at 80 °C for 16 h. The reaction mixture was cooled to 0 °C, poured into cold brine, and extracted with 60% EtOAc/hexane. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the crude product (75 g of silica gel, 10% EtOAc/hexane, 17-mL fractions) afforded, in fractions 11–15, 375 mg (60%) of pure **27**, a semiviscous, colorless oil: IR (neat) 1745, 1360, 1240, 1060, 1000, 970, 860, 835, 775 cm^{-1}; NMR ($CDCl_3$) δ 5.65–5.20 (m, 4 H), 5.05–4.65 (m, 3 H), 4.40–4.15 (m, 1 H), 3.70 (s, 3 H), 1.30 (s, 3 H), 0.95, 0.91 (s, 9 H each), 0.06 (s, 12 H).

Continued elution of the above chromatogram yielded 67 mg (15%) of recovered starting diol **26**.

(15*S*)-15-Methyl-PGF$_{2\alpha}$ Methyl Ester 9,15-Bis(*tert*-butyldimethylsilyl ether) (28). A solution of 370 mg of **27** in 60 mL of CH_3OH was treated with 3.7 g of zinc dust, and the resulting suspension was heated at reflux with vigorous stirring for 75 min. The reaction mixture was cooled to 25 °C and filtered through Celite, and the solids were washed with additional CH_3OH. The combined filtrate was concentrated to about one-fourth of its original volume, then poured into brine and aqueous $NaHCO_3$, and extracted with 1:1 EtOAc/hexane. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. Chromatographic purification of the crude product (70 g of silica gel, 10% EtOAc/hexane, 7-mL fractions) afforded (fractions 42–65) 255 mg (89% yield) of pure **28**, a semiviscous, colorless oil: IR (neat) 3550, 1745, 1460, 1430, 1360, 1250, 1160, 1060, 1000, 975, 940, 860, 835, 805, and 775 cm^{-1}; NMR ($CDCl_3$) δ 5.60–5.15 (m, 4 H), 4.35–3.70 (m, 2 H), 3.64 (s, 3 H), 1.26 (s, 3 H), 0.90, 0.86 (s, 9 H each), 0.20–0.0 (m, 12 H).

(15*S*)-15-Methyl-PGF$_{2\alpha}$ 1,11-Lactone 9,15-Bis(*tert*-butyldimethylsilyl ether) (30). A solution of 255 mg (0.418 mmol) of **28** in 10 mL of CH_3OH and 2 mL of THF was treated with 1 mL of aqueous 2 N KOH, and the resulting cloudy mixture was stirred at 25 °C under nitrogen. As the solution became clear, additional 2 N KOH was added in 0.5-mL increments until 3 mL total had been added. After 4 h, the reaction mixture was poured into a stirred mixture of ice, brine, EtOAc, and 4 mL of 2 N $KHSO_4$ and then extracted rapidly with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product **29** (250 mg) was approximately 95% pure by TLC (AIX[39]) and used immediately without purification. (The 5% impurity was the C-15 alcohol.)

A solution of 200 mg (0.33 mmol) of **29**, 111 mg (0.5 mmol) of 2,2′-dipyridyl disulfide, and 132 mg (0.5 mmol) of triphenylphosphine in 3 mL of oxygen-free xylene was stirred at 25 °C for 90 min. TLC analysis (20% EtOAc/hexane) showed that pyridinethiol ester formation was complete (R_f 0.4; starting material **29** R_f 0.05). The reaction mixture was transferred to a flask containing 100 mL of oxygen-free xylene, and the resulting pale yellow solution was heated at reflux for 36 h. The reaction mixture was then cooled to 25 °C and concentrated in vacuo (vacuum pump), and the crude product was purified chromatographically (75 g of silica gel, 10% EtOAc/hexane, 7-mL fractions). Fractions 28–36 yielded 135 mg (70%) of pure 1,11-lactone **30**, a semiviscous colorless oil: R_f 0.58 (benzene), 0.56 (10% EtOAc/hexane).

(15*S*)-15-Methyl-PGF$_{2\alpha}$ 1,11-Lactone (31). A solution of 135 mg of lactone **30** in 5 mL of 1,2-dimethoxyethane (DME) was treated with 10 mL of 0.5 M tetrabutylammonium fluoride (in DME), and the mixture was heated at reflux under nitrogen for 16 h. The reaction mixture was then poured into a mixture of ice, brine, aqueous $NaHCO_3$, and EtOAc and extracted with EtOAc. The organic extracts were washed with aqueous $NaHCO_3$ and brine, dried, and evaporated. Chromatographic purification of the crude product (20 g of silica gel, 20% acetone/CH_2Cl_2, 2-mLfractions) afforded (fractions 31–50) 39 mg (46% yield) of pure lactone **31**, a viscous colorless oil (after Darco decolorization): R_f 0.54 (75% EtOAc/hexane, developed twice), 0.46 (20% acetone/CH_2Cl_2, developed twice); IR (neat) 3400, 1705, 1460, 1350, 1260, 1220, 1180, 1140, 1100, 1080, 1000, 965 cm^{-1}; NMR ($CDCl_3$) δ 5.65–5.00 (m, 4 H), 4.85–4.35 (m, 2 H), 1.24 (s, 3 H); mass spectrum (Me_3Si derivative), m/e 494.3244 (calcd for $C_{27}H_{50}Si_2O_4$, M^+, 494.3248), 479, 423, 333.

The aqueous layers from above were acidified with cold aqueous citric acid extracted with EtOAc. Evaporation of the combined

extracts afforded 36 mg (42% of theory) of pure (15*S*)-15-methyl-$PGF_{2\alpha}$, the product of fluoride-mediated lactone cleavage.

A 1-mg sample of lactone **31** was treated with 0.5 mL of CH_3OH and 0.2 mL of 25% methanolic $NaOCH_3$ (25 °C, 45 min). The product (**25**) was extracted with EtOAc (0.5 mL) following acidification with cold aqueous citric acid. TLC analyses of the organic layer showed 15*S* isomer **25** but no 15*R* epimer (40% acetone/CH_2Cl_2).

$PGF_{2\alpha}$ 1,15-Lactone (34).[11] A solution of 5.5 g (15.54 mmol) of $PGF_{2\alpha}$ (**9**) and 1.79 g (17.51 mmol) of 1-butaneboronic acid in 150 mL of CH_2Cl_2 was heated at reflux for 15 min. Then about half of the CH_2Cl_2 was removed by disillation at atmospheric pressure. Additional CH_2Cl_2 was added to bring the volume back to the original 150 mL. This cycle (distillation of CH_2Cl_2 followed by replacement with fresh CH_2Cl_2) was repeated three times, after which all the solvent was removed in vacuo.

The crude cyclic boronate derivative **32** was dissolved in 180 mL of anhydrous, oxygen-free xylene and treated with 5.128 g (23.31 mmol) of 2,2′-dipyridyl disulfide followed by 6.27 g (23.31 mmol) of triphenylphosphine. After 18 h at 25 °C under a nitrogen atmosphere, TLC analysis of an aliquot showed complete conversion to the pyridinethiol ester ($HOAc/CH_3OH/CHCl_3$, 10:10:80).

This ester/xylene solution was diluted with 300 mL of oxygen-free xylene and added dropwise (via addition funnel) over 10 h to 3.2 L of vigorously stirred, refluxing xylene under a nitrogen atmosphere. After the addition was complete, 100 mL of xylene was distilled off, and the solution was heated at reflux for 24 h. The reaction mixture was then cooled, and the xylene was removed in vacuo (35 °C bath temperature). The residue was taken up in 500 mL of THF and treated with 10 mL of 30% H_2O_2 and 100 mL of saturated aqueous $NaHCO_3$. The three-phase mixture was stirred vigorously for 30 min at 25 °C and then concentrated in vacuo. The residue was taken up in brine/EtOAc and extracted thoroughly with EtOAc. The combined organic layer was washed with three portions of 1 N aqueous $KHSO_4$ and once with water, aqueous $NaHCO_3$, and brine. After the solution was dried (Na_2SO_4), removal of the solvent afforded a viscous yellow oil, which was chromatographed on 500 g of Mallinckrodt acid-washed silica gel (50% EtOAc/hexane; 100-mL fractions). Fractions 26–40 were combined and yielded, after crystallization from 40 mL of 1:1 ether/hexane, 1.559 g of pure $PGF_{2\alpha}$ 1,15-lactone (**34**). The mother liquors from the crystallization were combined with side fractions from the above chromatogram and rechromatographed. The total yield of clean crystalline product **34** was 2.391 g (46% of theory). (The crystallization of **34** also worked well in EtOAc/hexane): mp 110.0–111.7 °C (lit.[11] mp 111–112 °C); R_f 0.45 (20% acetone/CH_2Cl_2, developed twice), 0.48 (70% EtOAc/hexane, developed twice), IR (mull) 3500, 3370, 3300, 3010, 1705, 1290, 1265, 1110, 1055, 1005, 970, 725 cm^{-1}; NMR ($CDCl_3$) δ 6.00–5.75 (m, 2 H), 5.75–4.95 (m, 3 H), 4.30–3.85 (m, 2 H) 2.65 (s 2 H, exchangeable); mass spectrum (Me_3Si derivative), *m/e* 480.3102 (calcd for $C_{26}H_{48}Si_2O_4$, M^+, 480.3091), 390, 380, 364, 238, 217. Anal. ($C_{20}H_{32}O_4$) C, H.

Using essentially the same procedure as described above, we prepared the following PGF 1,15-lactones.

$PGF_{1\alpha}$ 1,15-Lactone (39). Same scale as the preceding experiment. The crude product was chromatographed on a 700-g column of silica gel (50% EtOAc/hexane; 1 × 200 mL, then 100-mL fractions). Fractions 14–19 were combined and afforded 625 mg (12%) of (15*R*)-$PGF_{1\alpha}$ 1,15-lactone: IR 3520, 3480, 3380, 1710, 1300, 1290, 1265, 1250, 1235, 1160, 1110, 1075, 1055, 1000, 965 cm^{-1}; R_f 0.19 (50% EtOAc/hexane). The identity of this epimer was further established by hydrolysis as described earlier with aqueous methanolic KOH. The hydrolysis product was identical with authentic samples of (15*R*)-$PGF_{1\alpha}$ in several TLC systems and exhibited the same melting point (69–70° C) (mixed melting point with authentic sample undepressed).

Fractions 21–28 from the above chromatogram were combined and afforded 800 mg (15% of theory) of $PGF_{1\alpha}$ 1,15-lactone (**39**), which crystallized upon trituration with ether. Recrystallization from EtOAc/hexane gave the analytical sample: mp 105–106 °C; R_f 0.14 (EtOAc/hexane, 1:1); IR (mull) 3520, 3480, 3380, 1710, 1300, 1290, 1265, 1250, 1235, 1160, 1110, 1075, 1055, 1000, 965 cm^{-1}; NMR ($CDCl_3$) δ 6.00–5.75 (m, 2 H), 5.60–5.00 (m, 1 H, C-15 H), 4.25–3.80 (m, 2 H), 3.08 (s, 2 H, exchangeable); mass spectrum (Me_3Si derivative), *m/e* 482.3260 (calcd for $C_{26}H_{50}O_4Si_2$, M^+, 482.3247), 467, 392, 366, 295, 276, 266, 238, 217. Anal. ($C_{20}H_{34}O_4$) C, H.

(15*S*)-15-Methyl-$PGF_{2\alpha}$ 1,15-lactone (40): xylene solvent; reflux 7 h; yield 4% of theory; R_f 0.50 (75% EtOAc/hexane, developed twice), 0.36 (20% acetone/CH_2Cl_2, developed twice); mass spectrum (Me_3Si derivative), *m/e* 494.3234 (calcd for $C_{27}H_{50}Si_2O_4$, M^+, 494.3247), 479, 450, 423, 404, 378, 367, 314, 251, 217. More polar fractions from the chromatographic purification of **40** yielded substantial amounts of unlactonized pyridinethiol ester intermediate and (15*S*)-15-methyl-$PGF_{2\alpha}$. Although longer lactonization times led to more complete utilization of starting material, the product mixture became dramatically more complex. Cleavage of lactone **40**, as described above for **31** ($NaOCH_3$, CH_3OH, 25 °C, 3 h), afforded only (15*S*)-15-methyl-$PGF_{2\alpha}$ methyl ester (**25**), with no detectable 15*R* epimer.

16-Phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ 1,15-lactone (41): xylene; reflux 24 h; 37% yield. The product, after chromatographic purification, was recrystallized from EtOAc/hexane: mp 185–186 °C; NMR ($CDCl_3$) δ 7.6–6.90 (m, 5 H), 6.2–5.2 (m, 5 H), 4.35–3.75 (m, 4 H); R_f 0.21 (70% EtOAc/hexane), 0.22 (20% acetone/CH_2Cl_2); mass spectrum (Me_3Si derivative), *m/e* 516.2738 (calcd for $C_{28}H_{44}Si_2O_5$, M^+, 516.2727), 501, 426, 423, 409, 400, 333, 307, 217, 181.

17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$ 1,15-lactone (42): xylene; 18 h reflux; 54% yield. The chromatographically pure product was recrystallized from EtOAc/hexane, affording **42** as colorless crystals: mp 116–117 °C; R_f 0.30 (70% EtOAc/hexane), R_f 0.29 (20% acetone/CH_2Cl_2); IR (mull) 3460, 3400 (sh), 3020, 1705, 1650, 1605, 1495, 1325, 1300, 1265, 1150, 1100, 1040, 1020, 1000, 970, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.35–6.90 (m, 5 H), 5.90–4.80 (m, 5 H), 4.25–3.75 (m, 2 H); mass spectrum (Me_3Si derivative), *m/e* 514.2954 (calcd for $C_{29}H_{46}O_4Si_2$, M^+, 514.2934), 424, 398, 334, 307, 271, 259, 217, 191, 181, 147. Anal. ($C_{23}H_{30}O_4$) C, H.

PGE_2 1,15-Lactone (37). A. Via Oxidation of $PGF_{2\alpha}$ 1,15-Lactone (34). A solution of 1.07 g of $PGF_{2\alpha}$ 1,15-lactone (**34**) in 45 mL of anhydrous acetone was cooled under nitrogen to between −45 and −40 °C and treated with 4.5 mL of trimethylsilyldiethylamine. After the addition was complete (2–3 min), the mixture was stirred at −42 ± 2 °C for 2 h, by which time TLC showed only a trace of starting material (25% EtOAc/hexane). The reaction mixture was then cooled to −78 °C, diluted with 150 mL of precooled ether (−78 °C), and poured into ice/brine. After extraction with hexane (3 × 150 mL), the combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude Me_3Si derivative **35** weighed 1.47 g.

Collins reagent[42] was prepared by adding 2.45 g of dry CrO_3 in one portion to a cold (0 °C) stirred solution of 3.99 mL of anhydrous pyridine in 120 mL of dry CH_2Cl_2. The resulting dark red solution was stirred for 25 °C for 1 h and then recooled to 0 °C. A solution of the crude Me_3Si product (**35**; 1.47 g) in 6 mL of CH_2Cl_2 was added in one portion to the rapidly stirred Collins reagent. The ice bath was removed, and the reaction mixture was allowed to stir for 20 min longer. The mixture was then poured onto a column containing 150 g of silica gel. With the aid of a vacuum, the column was eluted rapidly into a 2-L round-bottom flask with 1000 mL of EtOAc. Removal of the solvent gave 1.357 g of PGE_2 1,15-lactone 11-(trimethylsilyl ether) (**36**).

This product was dissolved in 150 mL of CH_3OH, diluted with 60 mL of aqueous 2.5% citric acid, and stirred at 25 °C for 30 min. After removal of about half of the CH_3OH at reduced pressure, the remaining solution was diluted with brine and extracted thoroughly with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude product crystallized upon trituration and was recrystallized to constant melting point (twice) from ether/hexane, thereby affording 608 mg (57% of theory) of PGE_2 1,15-lactone (**37**): mp 73–76 °C; R_f 0.62 (70% EtOAc/hexane), 0.69 (20% acetone/CH_2Cl_2); IR (mull) 3430, 1725, 1335, 1315, 1285, 1245, 1165, 1150, 1075, 1040, 990, 975, 730 cm^{-1}; NMR ($CDCl_3$)

(42) (a) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (b) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

δ 6.30–5.00 (m, 5 H), 4.35–3.85 (m, 1 H); UV max (basic EtOH) 247 nm (ε 9800), 326 (19 800); mass spectrum (Me_3Si derivative), m/e 406.2546 (calcd for $C_{23}H_{38}O_4Si$, M^+, 406.2539), 316, 279, 262, 225, 196, 164, 143, 133, 119, 99, 73. Anal. ($C_{20}H_{30}O_4$) C, H.

B. Via Direct Lactonization of PGE_2 (38). A mixture of PGE_2 (**38**; 352 mg, 1 mmol), 393 mg (1.5 mmol) of triphenylphosphine, and 330 mg (1.5 mmol) of 2,2′-dipyridyl disulfide in 5 mL of dry, oxygen-free xylene was stirred under nitrogen at room temperature for 18 h. The reaction mixture was then diluted with 250 mL of xylene and heated at reflux for 2 h. Following removal of the xylene at reduced pressure (rotovac/vacuum pump), the residue was partitioned between brine and EtOAc. The EtOAc extracts were washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Chromatographic purification of the crude product (70 g of silica gel, 40% EtOAc/hexane, 6.5-mL fractions) afforded 176 mg of crystalline PGE_2 1,15-lactone (**37**; fractions 89–130; 53% of theory). Recrystallization from EtOAc/hexane yielded lactone **37** with mp 72–74 °C, identical spectrally and by TLC with the material obtained in part A immediately above.

Utilizing procedures analogous to those described in this experiment, we synthesized the following PGE 1,15-lactones.

PGE_1 1,15-lactone (43): via procedure A (oxidation of **39**), 70% yield; via direct lactonization of PGE_1, 54%. In each case, the chromatographically pure product (from silica gel, 50% EtOAc/hexane) was recrystallized from ether/hexane and exhibited mp 89–90 °C; R_f 0.67 (20% acetone/CH_2Cl_2); IR (mull) 3390, 3320, 1745, 1720, 1335, 1255, 1235, 1195, 1180, 1160, 1100, 1075, 980 cm^{-1}; NMR ($CDCl_3$) δ 6.1–5.85 (m, 2 H), 5.45–5.05 (m, 1 H), 4.40–3.85 (m, 1 H); UV max (basic EtOH) 242 nm (ε 9200), 270 (8150), 324 (19 750); mass spectrum (Me_3Si derivative), m/e 408.2694 (calcd for $C_{23}H_{40}O_4Si$, M^+, 408.2696), 393, 390, 380, 375, 365, 364, 318, 264, 150, 99. Anal. ($C_{20}H_{32}O_4$) C, H.

17-Phenyl-18,19,20-trinor-PGE_2 1,15-lactone (44): via procedure B (direct lactonization); xylene solvent; 2.5 h reflux; chromatographic purification on silica gel (80% ether/hexane); 37% yield. Recrystallization of the chromatographically pure product from ether/hexane gave clean lactone **44**: mp 81–83 °C; R_f 0.57 (70% EtOAc/hexane), 0.66 (20% acetone/CH_2Cl_2); IR (mull) 3400, 1725, 1605, 1500, 1330, 1240, 1160, 1145, 1085, 1045, 975, 745, 725, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.50–7.10 (m, 5 H), 6.30–5.00 (m, 5 H), 4.30–2.80 (m, 1 H); UV max (basic EtOH) 243 nm (ε 9750), 320 (18 800); mass spectrum (Me_3Si derivative), m/e 440.2351 (calcd for $C_{26}H_{36}O_4Si$, M^+, 440.2383), 350, 313, 296, 259, 241, 205, 184, 169, 143, 133, 117, 105, 91, 73. Anal. ($C_{23}H_{28}O_4$) C, H.

PGA_2 1,15-Lactone (45). A solution of 350 mg of PGE_2 1,15-lactone (**37**) in 10 mL of dry pyridine was treated with 4 mL of acetic anhydride, and the clear reaction mixture was allowed to stand at 25 °C for 3 h. The reaction mixture was then cooled to 0 °C, treated dropwise over 15 min with 20 mL of CH_3OH, and allowed to stand in a melting ice bath over 2 h. After an additional 18 h at 25 °C, the mixture was poured into ice, ether, water, and 70 mL of 2 N aqueous $KHSO_4$ and extracted thoroughly with ether. The extracts were washed with water, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. Chromatographic purification of the crude product (100 g of silica gel, 15% EtOAc/hexane, 8-mL fractions) afforded 120 mg of crystalline PGA_2 1,15-lactone (**45**) (fractions 82–108; 36% yield). The analytical sample was obtained by recrystallization from ether/hexane: mp 60.0–61.5 °C; R_f 0.76 (70% EtOAc/hexane), 0.85 (20% acetone/CH_2Cl_2); IR (mull) 3010, 1715, 1705, 1580, 1355, 1345, 1325, 1245, 1170, 1145, 1140, 1035, 970 cm^{-1}; NMR ($CDCl_3$) δ 7.35–7.20 (m, 1 H, C-11), 6.25–5.00 (m, 6 H, C-5, C-6, C-10, C-13, C-14, C-15), 3.2–2.9 (m, 1 H, C-12); UV max (neutral EtOH) 215 nm (ε 9350); UV max (basic EtOH) 240 nm (ε 9650), 255 sh (8300), 267 sh (7650), 325 (19 750); mass spectrum, m/e 316.2074 (calcd for $C_{20}H_{28}O_3$, M^+, 316.2038), 298, 288, 259, 229, 198. Anal. ($C_{20}H_{28}O_3$) C, H.

PGB_2 1,15-Lactone (47).[28] PGB_2 was converted to the 1,15-lactone by the direct lactonization procedure (B) described earlier for the PGEs (xylene, reflux 16 h). Chromatographic purification of the crude product (100 g of silica gel, 60% ether/hexane, 20-mL fractions) yielded 200 mg of lactone **47**, a viscous, pale yellow oil (fractions 14–20; 63% yield): R_f 0.37 (ether/hexane, 1:1); IR (neat) 1715, 1640, 1595, 1370, 1240, 1160, 980, 940, 760 cm^{-1}; NMR ($CDCl_3$) δ 6.80–5.97 (m, 2 H), 5.70–5.07 (m, 3 H); UV max (neutral EtOH) 277 nm (ε 16 800); mass spectrum, m/e 316.2021 (calcd for $C_{20}H_{28}O_3$, M^+, 316.2038), 298, 288, 269, 217.

PGD_2 1,15-Lactone (51). Full details of the synthesis and spectral characterization of lactone **51** are found in ref 16.

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Registry No. **9**, 551-11-1; **10**, 55314-48-2; **10**·2Me_3Si, 85720-23-6; **11**, 62411-08-9; **11** (acid), 35700-23-3; **11**·2Me_3Si, 85720-24-7; **12**, 85720-13-4; **12** (acid), 39746-23-1; **12**·2Me_3Si, 85720-25-8; **13**, 85761-26-8; **13** (acid), 57773-66-7; **13**·2Me_3Si, 85720-26-9; **14**, 62443-67-8; **14** (acid), 62411-10-3; **14**·2Me_3Si, 85720-27-0; **16**, 62410-77-9; **18**, 62410-85-9; **19**, 62410-86-0; **20**, 62410-87-1; **21**, 62410-84-8; **21**·2Me_3Si, 65627-26-1; **22**, 85720-14-5; **23**, 85720-15-6; 15(*R*)-**24**, 85720-16-7; **25**, 35700-22-2; **26**, 85720-17-8; **27**, 85720-18-9; **28**, 85720-19-0; **29**, 85720-20-3; **30**, 85720-21-4; **31**, 80029-28-3; **31**·2Me_3Si, 85720-28-1; **32**, 42161-63-7; **32** (pyridinethiol ester), 85720-22-5; **34**, 55314-49-3; **34**·2Me_3Si, 62410-21-3; **35**, 62410-94-0; **36**, 62410-95-1; **37**, 62410-93-9; **38**, 363-24-6; **39**, 62411-18-1; **39** (acid), 745-62-0; **39**·2Me_3Si, 85720-29-2; **40**, 62411-21-6; **41**, 62411-17-0; **41** (acid), 51705-19-2; **41**·2Me_3Si, 64775-50-4; **42**, 62411-15-8; **42** (acid), 38344-08-0; **42**·2Me_3Si, 85720-30-5; **43**, 62411-20-5; **43**·Me_3Si, 85720-31-6; **44**, 62411-16-9; **44** (acid), 38315-43-4; **44**·Me_3Si, 85720-32-7; **45**, 62443-66-7; **47**, 62410-97-3; **47** (acid), 13367-85-6; **51**, 62410-98-4; 2,2′-dipyridyl disulfide, 2127-03-9; PGD_2, 41598-07-6.

Synthesis of Three Potential Inhibitors of Leukotriene Biosynthesis[1]

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The syntheses of 7,7-dimethyl- (1), 10,10-dimethyl- (2), and 5,6-benzoarachidonic acid (3), potential substrate analogue inhibitors of leukotriene biosynthesis, are described. Two of these compounds (1 and 2) apparently stimulated, while 3 inhibited, the activity of lipoxygenase from intact human polymorphonuclear leukocytes in vitro when stimulated with Ca^{2+} and calcium ionophore A23187 in the presence of BSA and arachidonic acid.

Metabolism of arachidonic acid (AA) by lipoxygenase leads to the formation of a variety of products, among which the chemotactic factor LTB_4 and the spasmogenic slow-reacting substances of anaphylaxis (SRS-A's) are of particular biological importance. Consequently, specific

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