treated with 0.87 mL of a 2.3 M solution of *n*-BuLi in hexane. The solution was stirred for 1 h at −50 °C, cooled to −60 °C, and treated with an ether solution (4 mL) of 260 mg of copper 1-pentyne and 640 mg of hexamethylphosphorous triamide. The reaction mixture was stirred for 10 min at −60 °C, and then an ether solution (2 mL) of 350 mg (1 mmol) of **2b** was added dropwise. The solution was stirred for 1 h and then poured into a mixture of ether and 1 N HCl. The mixture was shaken well, after which the organic layer was separated, washed with H_2O three times, and filtered, and the filtrate was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give the protected prostaglandin. This material (500 mg) was dissolved with stirring in about 20 mL of a 3:1:1 mixture of AcOH/THF/H_2O[15] and allowed to stand at room temperature for approximately 1 h. The solution was diluted with ether, washed four times with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (80% EtOAc, 20% hexane) to give 230 mg (60%) of **1b** as a colorless, viscous oil: ^{1}H NMR δ 1.19 (s, 16-CH_3), 4.09 (q, C_{11}), 5.39 (m, $C_{4,5}$), 5.42 (dd, C_{13}), 5.79 (dt, C_{14}). Anal. ($C_{22}H_{36}O_5$) C, H.

Compounds **1a** and **1c** were prepared in an analogous manner from the corresponding cyclopentenones **23** and **24**. **1a** Anal. ($C_{22}H_{34}O_5$) C, H. **1c** Anal. ($C_{22}H_{36}O_5$) C, H.

Gastric Antisecretory Studies.[25,26] Adult female mongrel dogs (15–18 kg)) surgically prepared with Heidenhain pouches (HP) and adult female Beagles (4.5–7 kg) prepared with simple gastric fistulas (GF) were used in these experiments. The dogs were trained to stand quietly in Pavlov supports and were conscious during all studies. The animals were not used more than once per week.

All prostaglandins were dissolved in absolute ethanol stock solution (1 mg/mL) and stored at −10 °C when not in use. Appropriate dilutions of the stock solution were carried out with an isoosmotic phosphate buffer so that the final alcohol concentration did not exceed 20%.

Experiments were initiated by fasting the dogs for 18 h. On the morning of an experiment, the dogs were placed in Pavlov stands and infused intravenously (iv) with 0.15 M NaCl solution. Gastric secretion was collected at 15-min intervals and measured for volume to the nearest 0.1 mL. After 15–30-min basal secretion, the dogs were infused with histamine solution at the submaximal stimulatory dose of 1.0 mg/h. The rate of infusion was kept at approximately 13.0 mL/h for the HP dogs and 6.5 mL/h for the GF dogs. Approximately 1 h after the start of histamine infusion, a steady-state plateau of gastric secretion was obtained. At this time, in the HP dogs, the prostaglandin was administered by a single intravenous bolus injection using a total volume not exceeding 3.0 mL. The iv doses usually ranged from 0.1 to 100 μg/kg and were logarithmically spaced. At least two dogs were employed at each dose.

The GF dogs were used for the intragastric administration of the prostaglandins. At the steady-state plateau of gastric secretion, the PG's were administered directly into the stomach through a specially constructed dosage plug, and the cannula was closed for 30 min to allow sufficient contact with the gastric mucosa. At the end of 30 min, gastric juice collections were resumed.

Gastric samples were measured for total acidity by titration with 0.1 N sodium hydroxide solution to pH 7.0 (Radiometer, Copenhagen). ED_{50} values were calculated from the degree of maximum inhibition of total acid output. The ED_{50} is defined as the dose that caused 50% inhibition of total acid output in the series of dogs.

Diarrheal Studies. Adult Charles River male rats weighing 210–230 g were individually housed and fasted for 24 h prior to the test. The animals (N = 6–12) were orally administered logarithmically graded doses of the prostaglandin. Immediately after administration, the animals were returned to their cages, and diarrhea, if any, was assessed on an all or none basis up to 8 h after drug treatment. The ED_{50} and relative potency values were calculated by the logistic method of Berkson.[27,28]

Acknowledgment. The authors thank Ms. E. L. Phillips and Jackie Casler for technical assistance in the antisecretory and diarrheal studies, David Calhoun for statistical assistance, the group of A. J. Damascus for spectral data, Dr. R. Bible, Ms. L. Swenton, and Ms. P. Finnegan for assistance in interpretation of spectral data, the group of E. Zielinski for microanalyses, and Dr. P. H. Jones for helpful discussions during the preparation of this manuscript.

Registry No. (±)-**1a** (isomer 1), 85168-35-0; (±)-**1a** (isomer 2), 85168-55-4; (±)-**1b** (isomer 1), 78908-16-4; (±)-**1b** (isomer 2), 78908-15-3; (±)-**1c** (isomer 1), 78908-27-7; (±)-**1c** (isomer 2), 78908-26-6; (±)-**2a**, 85168-36-1; (±)-**2b**, 78908-11-9; (±)-**2c**, 85168-37-2; (±)-**3**, 85201-89-4; (±)-**4**, 66792-28-7; (±)-**5**, 66792-29-8; (±)-**6**, 85185-20-2; **7**, 5978-08-5; **8**, 85168-38-3; **9**, 78908-03-9; **10**, 61448-22-4; **11a**, 78908-04-0; **11b**, 78908-05-1; **11c**, 85168-39-4; **12**, 78908-28-8; **12** (keto alcohol), 85168-50-9; **13**, 78908-06-2; (±)-**14**, 85168-40-7; **15**, 78908-08-4; **15**-yne, 85168-53-2; (*E*)-**15**, 85168-54-3; (±)-**16**, 78908-09-5; (±)-**17**, 85168-41-8; (±)-**17**-yne, 85168-45-2; (±)-(*E*)-**17**, 85168-47-4; (±)-**18**, 78908-10-8; (±)-**19**, 85168-42-9; **19** (4-methoxalyl derivative), 85168-51-0; (±)-**20**, 85168-43-0; **20** (4-methoxalyl derivative), 85168-52-1; (±)-**21**, 85168-44-1; (±)-**22**, 85168-46-3; (±)-**23**, 85168-48-5; (±)-**24**, 85168-49-6; 4-pentyn-1-ol THP ether, 62992-46-5.

(25) E. Z. Dajani, D. R. Driskill, R. G. Bianchi, and P. W. Collins, *Prostaglandins*, **10**, 205 (1975).
(26) E. Z. Dajani, L. F. Rozek, J. H. Sanner, and M. Miyano, *J. Med. Chem.*, **19**, 1007 (1976).
(27) D. J. Finney, "Statistical Methods in Biological Assay", 2nd ed., Harper Publishing Co., New York, 1964, Chapters 4–6.
(28) J. Berkson, *Am. Stat. Assoc. J.*, **48**, 565 (1953).

Synthesis and Platelet Aggregation Inhibiting Activity of Prostaglandin D Analogues

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Several prostaglandin D (PGD) analogues have been synthesized, incorporating the following variations: (a) varying degrees of side-chain unsaturation, (b) C-9 hydroxy removed or in the unnatural 9β configuration, (c) metabolically stabilized analogues (e.g., 15-methyl, 16,16-dimethyl, 17-phenyl, etc.), and (d) Δ^{12} isomers resulting from decomposition of PGD_2. With regard to their ability to inhibit adenosine diphosphate (ADP) induced human platelet aggregation: (a) $PGD_3 \geq PGD_2 > PGD_1 >$ 13,14-dihydro-PGD_1, (b) the 9β- and 9-deoxy-PGD_2 analogues are more potent than PGD_2, (c) metabolically stabilized analogues with bulky substituents at or near C-15 have substantially reduced antiaggregatory activity relative to PGD_2 and (d) the Δ^{12} isomers of PGD_2 are much less active than PGD_2.

Like the more thoroughly studied prostaglandins of the E series (PGE_1, PGE_2), PGD_1 and PGD_2 are important metabolic products of homo-γ-linolenic acid and arachidonic acid, respectively, via the endoperoxide pathway.[1-3]

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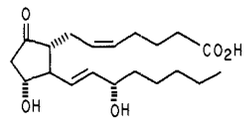
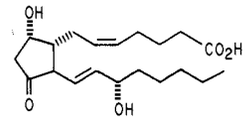


PGE_2



PGD_2

Although the biological significance of the PGDs was not fully appreciated at first,[4] particularly PGD_2 is a potent inhibitor of human platelet aggregation (about 10 times as active as PGE_1).[5,6] We report herein the synthesis and biological evaluation of a series of PGD analogues designed to determine what portions of the PGD structure are the most critical for the observed antiaggregatory activity.

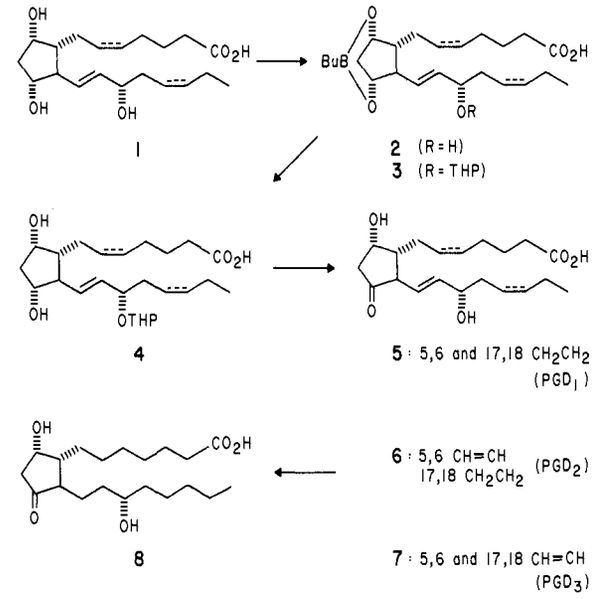
Chemistry. Of the several PGD syntheses available,[6-9] the most general approach is that of Hayashi and Tanouchi,[7] as modified by Nishizawa et al.[6] By this route (Scheme I), any PGF analogue may be converted to the corresponding PGD by (a) temporary protection of the C-9 and C-11 hydroxy groups as a cyclic butylboronate, (b) formation of the C-15 tetrahydropyranyl ether, (c) selective oxidation at C-11, and (d) removal of the C-15 protecting group. PGD_1 (**5**), PGD_2 (**6**), and PGD_3 (**7**) were prepared in this manner from $PGF_{1\alpha}$, $PGF_{2\alpha}$, and $PGF_{3\alpha}$, respectively, each in approximately 30% overall yield.

Catalytic hydrogenation of PGD_1 or PGD_2 (Pd/C, ethanol) afforded 13,14-dihydro-PGD_1 (**8**)[3] in 50% yield. (With the 13,14 trans double bond reduced, **8** exists at least in part as the cyclic 11,15-hemiacetal).

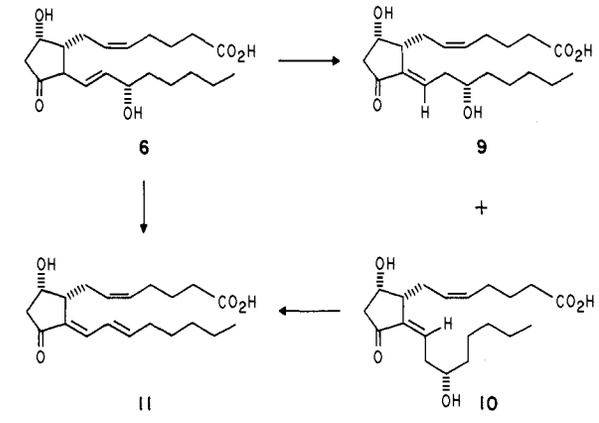
PGE_2, by virtue of its β-hydroxy ketone structure, has well-documented problems of chemical instability, affording PGA_2 and PGB_2 under acidic and basic conditions, respectively.[10] PGD_2 and most related 11-keto analogues are even less stable than PGE_2, due in large part to their more acidic C-12 proton (α to a ketone and allylic). Isomerization of PGD_2 (a β,γ-unsaturated ketone) to the more stable α,β-unsaturated isomers **9** and **10** [UV λ_{max} (EtOH) 244 nm (ϵ 7500)] could be accomplished under sufficiently mild conditions that the β-hydroxy ketone system remained unaltered (Scheme II). The isomerization took place upon prolonged storage of PGDs (even in the cold), upon exposure of the PGDs to silica gel or Florisil, and under the influence of either mild acid or base. Under slightly more vigorous conditions, dehydration of either **6** or **9** and **10** afforded unstable trienone **11** [UV λ_{max} (EtOH) 297 nm (ϵ 16800)], while strongly basic conditions (e.g., 1 M KOH) yielded a complex inseparable mixture of unstable tetraenone isomers.[3]

The assignment of stereochemistry in enones **9** and **10** was based on the chemical shift of the C-13 proton, 6.70 ppm for the 12*E* isomer **9** and 6.10 ppm for 12*Z* isomer **10**.[11] Treatment of PGD_2 with triethylamine in chloroform yielded a 4:1 mixture of **9** and **10**, while either potassium acetate/95% ethanol, DBN/THF, Florisil/ethyl acetate,

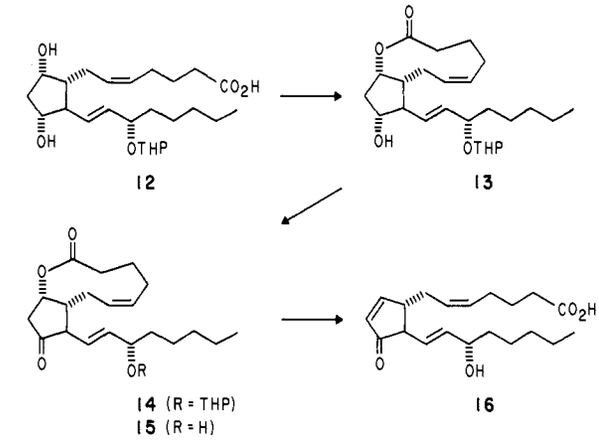
Scheme I



Scheme II

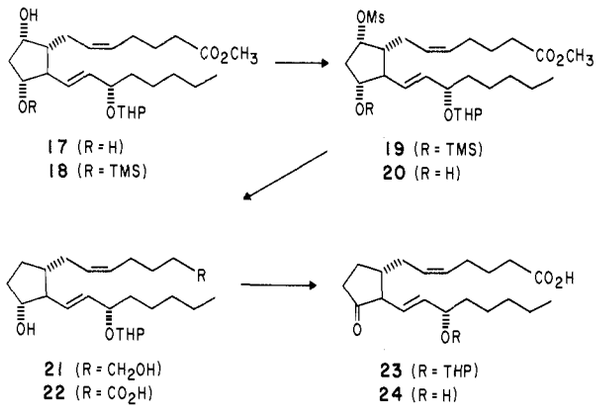


Scheme III



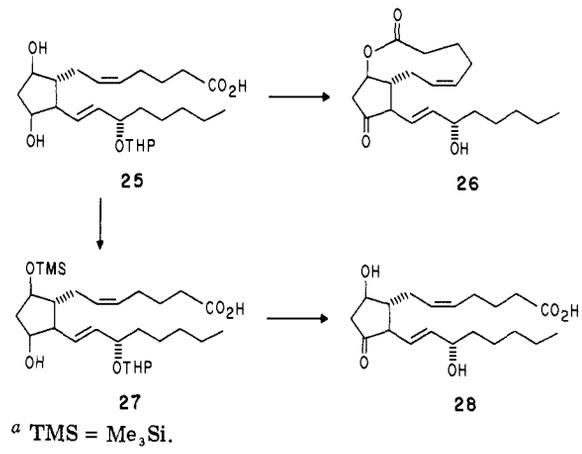
(1) D. H. Nugteren, R. K.; Beerthius, and D. A. Van Dorp, *Recl. Trav. Chim. Pays-Bas*, **85**, 405 (1966).
(2) E. Granström, W. E. M. Lands, and B. Samuelsson, *J. Biol. Chem.*, **243**, 4104 (1968).
(3) P. S. Foss, C. J. Sih, C. Takeguchi, and H. Schnoes, *Biochemistry*, 11, 2271 (1972).
(4) As recently as 1973, the PGDs were reported as "biologically inactive": D. H. Nugteren and E. Hazelhof, *Biochim. Biophys. Acta*, **326**, 448 (1973).
(5) J. B. Smith, M. J. Silver, C. M. Ingerman, and J. J. Kocsis, *Thromb. Res.*, **5**, 291 (1974).
(6) E. E. Nishizawa, W. L. Miller, R. R. Gorman, G. L. Bundy, J. Svensson, and M. Hamberg, *Prostaglandins*, **9**, 109 (1975).
(7) M. Hayashi and T. Tanouchi, *J. Org. Chem.*, **38**, 2115 (1973).
(8) T. W. Hart, D. A. Metcalfe, and F. Scheinmann, *J. Chem. Soc., Chem. Commun.*, 156 (1979).
(9) E. F. Jenny, P. Schäublin, H. Fritz, and H. Fuhrer, *Tetrahedron Lett.*, 2235 (1974).
(10) (a) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *J. Biol. Chem.*, **238**, 3555 (1963). (b) N. H. Anderson, *J. Lipid Res.*, **10**, 320 (1969). (c) D. C. Monkhouse, L. Van Campen, A. J. Aguiar, *J. Pharm. Sci.*, **62**, 576 (1973).
(11) The greater downfield shift observed for a proton cis to a ketone carbonyl (such as the C-13 proton in **9**), relative to a proton trans to a carbonyl (as in **10**), is a well-precedented phenomenon. See, for example, F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York and London, 1969, and other references cited therein.

Scheme IV[a]



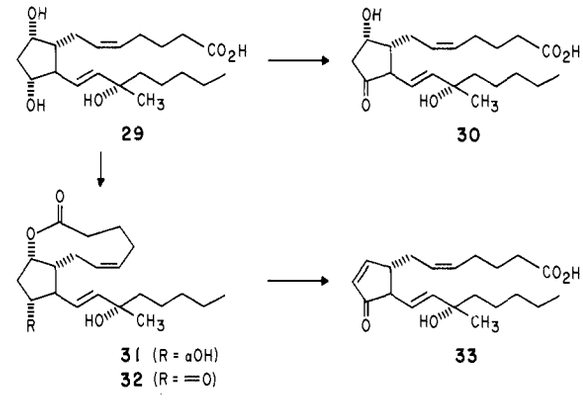
[a] TMS = Me_3Si.

Scheme V[a]



[a] TMS = Me_3Si.

Scheme VI



or sodium bicarbonate/methanol gave essentially only the 12*E* isomer **9**. (12*Z* isomer **10** was rather unstable and was not submitted for biological evaluation).

F. Fitzpatrick[12] has found that the half-life of PGD_2 in a pH 7.4 physiological (0.9%) saline buffer at 37 °C is about 12 h.

The synthesis of ring-dehydrated PGD derivatives (analogous to PGAs) required an indirect approach (Scheme III), since no conditions were found that would cleanly dehydrate the β-hydroxy ketone portion of PGD_2 directly without concomitant isomerization to the Δ^{12} isomers mentioned above.[13] The C-15 tetrahydropyranyl ether of $PGF_{2\alpha}$ (**12**)[6] was first converted to the 1,9-lactone by using 2,2′-dipyridyl disulfide and triphenylphosphine in refluxing benzene,[14] and the remaining free hydroxy group was oxidized with Jones reagent (−30 °C, 1 h), thereby affording **14** in 45% overall yield from **12**. Removal of the C-15 tetrahydropyranyl ether (1:3:6 THF/H_2O/HOAc; 40 °C, 1 h) then yielded PGD_2 1,9-lactone **15** (68% after purification). Lactone **15** could be recovered intact following chromatography only if acid-washed silica gel was used (e.g., Mallinckrodt CC-4). Chromatography of **15** on standard silica gel (silica gel 60, EM Reagents) led to clean elimination of the carboxylate, affording the desired enone **16** (75% yield) with no detectable rearrangement of the Δ^{13} double bond.[15]

Although a wide variety of procedures exist for reduction of the olefinic bond of α,β-unsaturated carbonyl compounds, it appeared that most of these procedures were not sufficiently mild to allow survival of the β,γ-unsaturation (i.e., at C-13,14).[16] 9-Deoxy-PGD_2 (**24**) was therefore synthesized by the more circuitous, but foolproof, route illustrated in Scheme IV. Since the C-11 hydroxyl was the more accessible of the two in diol **17**, its temporary protection was required, a selective transformation accomplished with the sterically discriminating silylating reagent trimethylsilyldiethylamine.[17,18] Conversion of hydroxy intermediate **18** to the methanesulfonate and desilylation (citric acid, aqueous methanol, 0 °C, 1 h) then afforded 9α-mesylate **20** (66% from **17**). Reduction of **20** with lithium aluminum hydride (ether, 30 min, 25 °C) gave the 9-deoxy 1,11-diol **21** (75%), selective reoxidation of which yielded the C-1 acid **22** (O_2, PtO_2, $NaHCO_3$, H_2O, acetone, 60 °C, 4.5 h, 51%). Oxidation at C-11 with either Collins or Jones reagent and standard THP hydrolysis finally led to 9-deoxy-PGD_2 (**24**). 9-Deoxy analogue **24** showed no UV absorption at 244 nm, thus demonstrating that the C-13,14 double bond had remained in place.[19]

9β-PGD_2 analogues **26** and **28** were synthesized as outlined in Scheme V. The starting 9β,11β-diol **25** was obtained from 9α,11α-diol **17** by using a Mitsunobu diethyl azodicarboxylate mediated inversion process,[20] followed

(12) F. A. Fitzpatrick, the Upjohn Co., unpublished observation. Dr. Fitzpatrick will report shortly on the nature of PGD_2 degradation under these more nearly physiological conditions.

(13) For an alternative, elegant, but less generic and longer, approach to Δ^9-11-ketones of this type, see (a) S. M. Ali, C. B. Chapleo, M. A. W. Finch, S. M. Roberts, G. T. Woolley, R. J. Cave, and R. F. Newton, *J. Chem. Soc., Perkin Trans 1*, 2093 (1980); (b) M. A. W. Finch, S. M. Roberts, G. T. Woolley, and R. F. Newton, *ibid.*, 1725 (1981). The present procedure obviously is more general only to the extent that one assumes the ready availability of various PGF analogues.

(14) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).

(15) This approach had been suggested by our earlier observation that PGE_2 methyl ester 11,15-diacetate was cleanly converted to PGA_2 methyl ester 15-acetate upon chromatography.

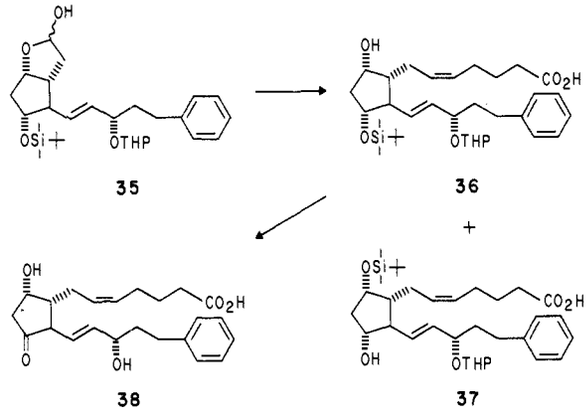
(16) (a) N. A. Cortese and R. F. Heck, *J. Org. Chem.*, **43**, 3985 (1978). (b) M. Yamashita, Y. Kato, and R. Suemitsu, *Chem. Lett.*, 847 (1980). (c) J. P. Collman, R. G. Finke, P. L. Matlock, R. Wahren, R. G. Komoto, and J. I. Brauman, *J. Am. Chem. Soc.*, **100**, 1119 (1978), and references cited therein.

(17) I. Weisz, K. Felföldi, and K. Kovács, *Acta Chim. Acad. Sci. Hung.*, **58**, 189 (1968).

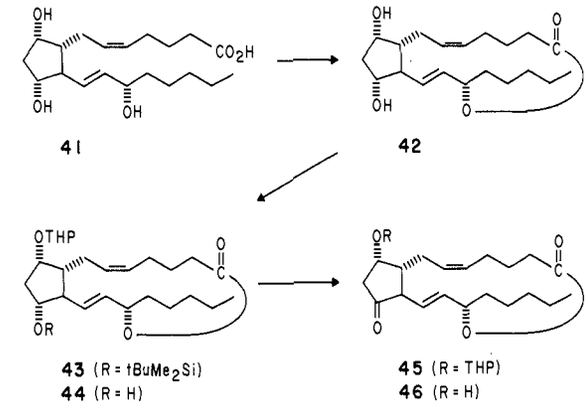
(18) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974).

(19) An obvious way to ensure chemical stability of the 13,14 double bond is to install a substituent at C-12. For example, *12-fluoro*: P. A. Grieco, W. Owens, C.-L. J. Wang, E. Williams, W. J. Schillinger, K. Hirotsu, and J. Clardy, *J. Med. Chem.*, **23**, 1072 (1980); *12-hydroxy*: N. A. Nelson and T. A. Scahill, *J. Org. Chem.*, **44**, 2790 (1979) and P. A. Grieco, Y. Yokoyama, G, P. Withers, F. J. Okuniewicz, and C.-L. J. Wang, *ibid.*, **43**, 4178 (1978); *12-methyl*: P. A. Grieco, C. S. Pogonowski, M. Nishizawa and C.-L. J. Wang, *Tetrahedron Lett.*, 2541 (1975). We chose not to incorporate C-12 substituents in this series of analogues in order to simplify interpretation of the biological results.

Scheme VII



Scheme VIII



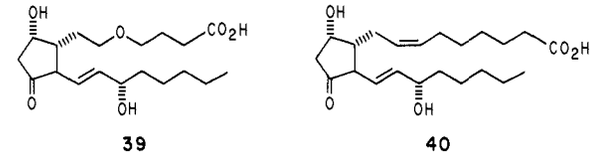
by base hydrolysis of the two benzoates and the C-1 ester. Alternatively, **25** could be obtained via borohydride reduction of 11β-PGE_2,[21] followed by selective 15-THP formation.[6] Lactonization[14] of **25** (with the 9β-alcohol, the only one the carboxy group can reach intramolecularly), followed by Jones oxidation and THP removal, gave crystalline 9β-PGD_2 1,9-lactone (**26**, mp 54–55 °C). Selective silylation, as mentioned earlier, again proceeded cleanly with the most accessible hydroxy of diol **25** (in this case at C-9, trans to the adjacent side chain), yielding 9-silyl derivative **27**. Collins oxidation (in order to retain the Me_3Si group) and THP removal under the usual conditions gave 9β-PGD_2 (**28**, mp 62–64 °C). (In contrast to the selective oxidation of diol 4, which provided a PGD/PGE ratio of about 4:1, attempted direct selective oxidation of diol **25** yielded predominantly the 11β-PGE_2 analogue.)

Although PGD_2 is a poor substrate for the prostaglandin 15-dehydrogenase relative to the other primary prostaglandins,[22,23] a majority of the PGD_2 metabolites isolated from the monkey[24] have indeed undergone oxidation to the C-15 ketone. We have therefore synthesized several PGD analogues incorporating structural features that have successfully hindered metabolism at C-15 in the PGE and PGF series.[25] 15-Methyl-PGD_2 (**30**, Scheme VI) was prepared by Jones oxidation (−30 °C, 20 min, 30% yield) of readily available 15-methyl-$PGF_{2\alpha}$ (**29**).[18] Then, following the same sequence as described earlier (Scheme III), lactonization, Jones oxidation, and chromatography of 11-keto lactone **32** on silica gel produced the 9-deoxy-Δ^9-11-keto-15-methyl analogue **33** in good yield. 16,16-Dimethyl-PGD_2 (**34**) was prepared from 16,16-dimethyl-$PGF_{2\alpha}$[25b] via the four-step sequence outlined in Scheme I.

The synthesis of 17-phenyl-18,19,20-trinor-PGD_2 (**38**) is outlined in Scheme VII. This alternative general approach to PGD synthesis may be useful particularly in cases where the corresponding PGF is not available. Standard elaboration of the carboxy side chain onto lactol intermediate **35**[26] [using the ylide from (4-carboxybutyl)-triphenylphosphonium bromide[27]] afforded a mixture of the expected 11-silyl intermediate **36** (42%) and 9-silyl intermediate **37** (22%).

The scrambling of the silyl group between the C-9 and C-11 hydroxys of the Wittig product was unexpected but in retrospect not surprising, since the silicon–oxygen bond of trimethylsilyl ethers is easily cleaved with sodium methoxide. In addition, the relatively close proximity of these hydroxy substituents may enhance transfer. Rosen[28] has reported that faster reaction rates for the upper side-chain Wittig reactions are possible when hexamethylphosphoramide (HMPA) is used as the solvent instead of Me_2SO. Rosen's conditions were therefore employed in the hope that a faster rate of product formation would not necessarily be paralleled by a rate increase for silyl group scrambling. Although the Wittig reaction did proceed considerably faster in HMPA, silyl scrambling remained a problem.[29] Intermediate **36** was converted to 17-phenyl-18,19,20-trinor-PGD_2 (**38**) by formation of a C-9 THP, desilylation (Bu_4NF), base hydrolysis of the THP ester, Jones oxidation, and THP ether hydrolysis. Silyl migration product **37** could undoubtedly be converted to PGD analogue **38** as well, but this would require a slightly different sequence (thus necessitating prior chromatographic separation of **36** and **37**).

Two PGD analogues were synthesized incorporating carboxy side chain modifications that should influence the usual prostaglandin β-oxidative metabolism.[24] 5-Oxa-PGD_1 (**39**) was synthesized from 5-oxa-$PGF_{1\alpha}$[30] via the four-step



(20) (a) O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, **40**, 2380 (1967). (b) O. Mitsunobu, K. Kato, and J. Kimura, *J. Am. Chem. Soc.*, **91**, 6510 (1969). (c) A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973).

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

(22) H. Ohno, Y. Morikawa, and F. Hirata, *J. Biochem. (Tokyo)*, **84**, 1485 (1978).

(23) F. F. Sun, S. B. Armour, V. R. Bockstanz, and J. C. McGuire, *Adv. Prostaglandin Thromboxane Res.*, 1, 163 (1976).

(24) C. K. Ellis, M. D. Smigel, J. A. Oates, O. Oelz, and B. J. Sweetman, *J. Biol. Chem.*, **254**, 4152 (1979).

(25) (a) *15-Methyl*: ref 18. (b) *16,16-dimethyl*: B. J. Magerlein, D. W. DuCharme, W. E. Magee, W. L. Miller, A. Robert, and J. R. Weeks, *Prostaglandins*, **4**, 143 (1973). (c) *17-phenyl*: B. J. Magerlein, G. L. Bundy, F. H. Lincoln, and G. A. Youngdale, *ibid.*, **9**, 5 (1975).

(26) Readily available from intermediate II in ref 25c (a C-11 benzoate, C-15 ketone) by the well-precedented sequence (a) benzoate hydrolysis, (b) silylation, (c) reduction of ketone, (d) conversion to 15-THP, (e) dibal reduction of lactone.

(27) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

(28) P. Rosen, Hoffmann-LaRoche, 9th International Symposium on the Chemistry of Natural Products (IUPAC), Ottawa, Canada, June 24–28, 1974.

(29) An analogous migration of a C-11 acetate during this Wittig reaction has also been reported; see ref 9.

(30) N. A. Nelson, R. W. Jackson, and W. L. Miller, *Adv. Prostaglandin Thromboxane Res.*, **2**, 873 (1976).

Table I. Biological Evaluation of PGD Analogues

no.	compd	inhibn of ADP-induced human platelet aggregn: [a] IC_{50}, ng/mL	rat BP (rel potency): $\uparrow PGF_{2\alpha} = 100$; $\downarrow PGE_1 = 100$	gerbil colon stim (rel potency): [b] $PGE_1 = 100$	hamster antifertility: [c] no. nonpreg/ no. treated (dose, μg)
5	PGD_1	320	↓ 0.1-0.3	3-10	4/6 (1000)
6	PGD_2	3.2	↓ 10-32	3-10	6/6 (1000) 3/6 (50)
7	PGD_3	3.2 [d]	↓ 10-32	1-3	0/6 (1000)
8	13,14-dihydro-PGD_1	3200	↑ 0.3-1	0.1-0.3	0/6 (1000)
9	Δ^{12}-PGD_2	100	↓ 10-32	1-3	3/6 (1000)
11	$\Delta^{12,14}$-PGD_2	320	↓ 0.1-0.3	<0.1	0/6 (1000)
15	PGD_2 1,9-lactone	32	↓ 10-32	0.3-1	4/6 (1000)
16	9-deoxy-Δ^9-PGD_2	3.2	↓ 10-32	0.1-0.3	0/6 (1000)
24	9-deoxy-PGD_2	1.0	↓ 10-32	1-3	2/6 (1000)
26	9β-PGD_2 1,9-lactone	32	↓ 1-3	0.3-1	0/6 (1000)
28	9β-PGD_2	0.1	↓ 10-32	0.3-1	2/6 (1000)
30	15-methyl-PGD_2	320	↑ 32-100	10-32	6/6 (50) 1/6 (10)
33	15-methyl-Δ^9-PGD_2	1000	↓ 0.1-0.3	0.3-1	4/6 (1000)
34	16,16-dimethyl-PGD_2	enhances aggregn	↑ 32-100	3-10	6/6 (1000) 0/6 (50)
38	17-phenyl-PGD_2	3200	↑ 32-100	10-32	6/6 (10) 2/6 (1)
39	5-oxa-PGD_1	32	biphasic (potent)	0.3-1	4/6 (1000)
40	2a,2b-dihomo-PGD_2	1000	biphasic (weak)	<0.1	6/6 (1000) 3/6 (50)
46	PGD_2 1,15-lactone	1000	↓ 0.1-0.3	0.1-0.3	5/6 (1000) 2/6 (50)

[a] Tenfold differences in IC_{50} are considered significantly different ($p < 0.05$). [b] A 100-fold difference in relative potency is considered significantly different ($p < 0.05$). [c] While scores of 1/6 or 2/6 may reflect drug effects, scores of 3/6 and better are statistically significant ($p < 0.05$). [d] Reference 33.

sequence in Scheme I, while 2a,2b-dihomo-PGD_2 (**40**) was prepared by the Scheme VII sequence [using a lactol intermediate corresponding to **35** but possessing the natural prostaglandin alkyl side chain; treatment with (6-carboxyhexyl)triphenylphosphorane].

PGD_2 1,9-lactone (**15**, Scheme III) and the corresponding 9β-isomer (**26**, Scheme V) were prepared as synthetic intermediates but were also of potential interest as pharmacological agents as well. In addition to whatever useful intrinsic activity lactone **15** might possess, it could possibly constitute a sustained release form (prodrug) of either PGD_2 (via esterase hydrolysis in vivo) or 9-deoxy-9,10-didehydro-PGD_2 (**16**) (via nonenzymatic elimination). Both of the latter compounds are potent inhibitors of human platelet aggregation (see below). In order to complete this series, PGD_2 1,15-lactone (**46**) was synthesized as indicated in Scheme VIII.

$PGF_{2\alpha}$ (**41**) was converted to the 1,15-lactone **42**[31] in good yield by temporary protection of the ring hydroxys as a cyclic butylboronate,[6] dipyridyl disulfide lactonization,[14,31] and aqueous workup. Direct oxidation of this lactone diol afforded the expected mixture of PGD_2 1,15-lactone and PGE_2 1,15-lactone, which was unresolvable by TLC. (It turned out that PGD_2 1,15-lactone would not have survived chromatography on silica gel anyway; see below.) Careful silylation of diol **42** (*tert*-butyldimethylsilyl chloride,[32] 5% excess; imidazole; DMF; 0 °C; 1 h) produced the C-11 monosilylated derivative (82%), which was subsequently converted to 9-THP intermediate **43** (92%). Desilylation (Bu_4NF, 100%), Jones oxidation (82%), and finally THP removal (1:1:2 THF/H_2O/HOAc, 40 °C, 3 h) afforded crystalline PGD_2 1,15-lactone (**46**), mp 93–94 °C. Fortunately, the final product **46** could be easily purified by recrystallization (ether/hexane), since it did not survive chromatography on either neutral or acid-washed silica gel. (The only products recovered from attempted chromatographic purification were trienone 11 and isomers thereof.)

Biology. The PGD analogues reported herein were evaluated in several biological test systems commonly used with the prostaglandins, with emphasis on the area of platelet aggregation inhibition (an area of major current interest with PGD_2 itself[5,6]). The ability of the analogues to inhibit ADP-induced platelet aggregation was measured in vitro in human platelet-rich plasma (see General Methods portion of the Experimental Section for details). The rat blood pressure assay (an indicator of systemic blood pressure effects), the gerbil colon stimulation assay (an in vitro system that often predicts "diarrhea potential"), and the hamster antifertility screen (a measure of luteolytic activity in that species, which correlates fairly well with abortifacient activity in humans) have all been previously described in detail.[36] Although the latter three test systems measure biological effects not generally considered clinically useful for the PGDs, the resulting data (Table I) can be significant as indicators of areas for potential concern (i.e., side effects) in the further development of some of these analogues for platelet-related indications.

With regard to the effect of side-chain unsaturation on platelet aggregation inhibiting activity, 13,14-dihydro-PGD_1 (**8**) was considerably less active than PGD_1 (**5**), which was in turn less active than PGD_2 (**6**) and PGD_3 (**7**).[33] PGD_2 and PGD_3 were both relatively potent de-

(31) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 653 (1975).
(32) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(33) More thorough evaluation of PGD_3 relative to PGD_2 (R. Gorman, Upjohn Co., unpublished observation, and P. Needleman, ref 34) showed that PGD_3 possessed an IC_{50} about one-third that of PGD_2; i.e., PGD_3 is about 0.5 log more potent. However, since most of the analogues in Table I have not yet been subjected to this closer scrutiny, all of the values in Table I represent screening data.

pressors of rat blood pressure, while only the former had significant antifertility activity.

The α,β-unsaturated ketones (i.e. Δ^{12}) **9** and **11**, which resulted from the spontaneous decomposition or mild isomerization of PGD_2, were 30–100 times less active than PGD_2 itself as inhibitors of ADP-induced aggregation.

It is apparent that the 9α-hydroxy group of PGD_2 is not required for potent antiaggregatory activity. 9-Deoxy-Δ^9-PGD_2 (**16**) was essentially equal to PGD_2, while 9-deoxy-PGD_2 (**24**) was even more potent. 9β-PGD_2 (**28**), in which the C-9 hydroxy occupies the unnatural β-configuration, was the most active of the antiaggregatory analogues reported herein, with an approximate IC_{50} of 0.1 ng/mL. The 9α-hydroxy group was apparently more responsible for good antifertility activity, since those three analogues (**16**, **24**, and **28**) all exhibited substantially diminished potency in that screen.

Interestingly, most of the metabolically stabilized PGDs, particularly those with bulky substituents at or near C-15 [15-methyl (**30**), 15-methyl-Δ^9 (**33**), and 17-phenyl (**38**)] were all much less active than PGD_2 as inhibitors of ADP-induced aggregation, while 16,16-dimethyl-PGD_2 (**34**) actually enhanced aggregation. Accompanying the diminished platelet activity, especially in **30** and **38**, was a significant increase in antifertility activity (as the 15-methyl and 17-phenyl modifications had likewise occasioned in the PGE and PGF series[35]), thus rendering these metabolically stabilized analogues unpromising for platelet applications. Of tangential interest, the metabolically stabilized analogues **30** and **38** are surprisingly potent rat blood pressure pressors, an effect that may limit their potential as selective antifertility agents as well.

Based solely on the data in Table I, there appears to be a rough parallel between platelet aggregation inhibiting ability and rat blood pressure depressor activity. The most potent antiaggregators (**6**, **7**, **16**, **24**, and **28**) are all fairly potent depressors, while the analogues that raise blood pressure (**8**, **30**, **34**, and **38**) are all very poor aggregation inhibitors. (Obviously this rough correlation should not be expected to extend to all prostaglandin analogues.)

There appears to be very little correlation between platelet activity and either gerbil colon stimulating or antifertility activity. (The latter two screens do tend to run somewhat parallel to each other within this series, however, since the most potent stimulators of gerbil colon, **30** and **38**, are among the more potent antifertility agents.)

As indicated in Table I, 1,9-lactones **15** and **26** are only 1 log less active (as antiaggregatory agents) than PGD_2 itself, while the 1,15-lactone **46** is much less potent. It should be noted, however, that these short time-frame, in vitro experiments presumably measure only the intrinsic activity of the lactones themselves. Additional aggregation studies following in vivo administration of **26** and **46** will be required to assess the potential of these lactones as sustained availability forms of 9β-PGD_2 (or 9-deoxy-Δ^9-PGD_2) and PGD_2, respectively.

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, and low-resolution mass spectra were obtained 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 I 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[37]/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.

The rat blood pressure, gerbil colon stimulation, and hamster antifertility biological test systems have been described in detail elsewhere.[36]

Platelet-aggregation evaluation was performed as follows: all prostaglandin analogues were dissolved in Emulfor/ethanol (1:1) at 20 ng/mL and subsequently diluted to the working concentration with modified Tyrode's solution (without Ca^{2+} or Mg^{2+}). Citrated platelet-rich plasma was prepared from human blood anticoagulated with sodium citrate (1 part 3.8% sodium citrate to 9 parts blood) by centrifugation at 200g for 10 min. Platelet count was adjusted to 3.0×10^5/mm^3 with autologous platelet-poor plasma. The platelet-rich plasma was incubated for 30 s at 37 °C, then treated with the test compound solution and incubated 30 s longer at 37 °C, and finally treated with ADP at concentrations predetermined to give slightly less than maximal aggregation (usually 1–4 μM). The aggregation was measured with an aggregometer from Payton Associates, Buffalo, NY. Several concentrations of the potential inhibitor were tested, as well as PGE_1, which was used as a standard to adjust for between-individual variation in the activity of the platelets. The inhibitory concentration that gave about 50% inhibiton of aggregation (IC_{50}) was determined to the nearest 0.5 log dose (concentration).

PGD_1 (5). By a procedure identical with that described by Nishizawa et al.,[6] 8.0 g (22.47 mmol) of $PGF_{1\alpha}$ was converted to 9.1 g (92% of theory) of the corresponding 15-THP. Selective oxidation with Jones reagent, following the procedure of Hayashi and Tanouchi[7] (−30 °C, 15–30 min), and subsequent THP hydrolysis afforded 2.4 g of crystalline PGD_1 (**5**): mp 71.3–72.1 °C (lit.[3] mp 62–65 °C); IR, NMR, and mass spectra were essentially identical with the published spectra.[3,9] Anal. ($C_{20}H_{34}O_5$) C, H.

PGD_2 (6). The detailed preparation of PGD_2 in our laboratories has been described elsewhere.[6] Anal. ($C_{20}H_{32}O_5$) C, H.

PGD_3 (7).[34] Following the same procedure as used above for PGD_1 and PGD_2, 500 mg of $PGF_{3\alpha}$ (1.42 mmol) was converted to 150 mg of crystalline PGD_3 (30% yield): mp 56–57 °C (after recrystallization from ether/hexane); IR (mull) 3420, 3000, 2600, 1735, 1710, 1405, 1230, 1160, 1035, 920 cm^{-1}; NMR ($CDCl_3$) δ 5.7–5.25 (m, 6 H, vinyl), 5.1 (s, 3 H, exchangeable, OH), 4.60–4.35 (m, 1 H, C-9 H), 4.35–4.05 (m, 1 H, C-15 H), 0.95 (t, J = 7 Hz, 3 H, C-20 methyl); mass spectrum (methoxime, Me_3Si derivative), ions at m/e 595 (M^+), 595 (M^+), 580.3290 (calcd for $C_{29}H_{54}NO_5Si_3$, $M^+ - CH_3$, 580.3310), 564, 548, 526, 494, 490, 454, 435, 296.

13,14-Dihydro-PGD_1 (8).[3] A solution of 200 mg (0.57 mmol) of PGD_1 (**5**) in 15 mL of absolute ethanol was hydrogenated at atmosphere pressure over 40 mg of 10% palladium on carbon. After 35 min, the suspension was carefully filtered through Celite, and the filtrate was concentrated to an oil. The crude product was chromatographed on a 20-g column of Mallinckrodt CC-4 acid-washed silica gel, packed and eluted (4 mL fractions) with 55% EtOAc/hexane. Fractions 23–60 afforded 100 mg (50%) of 13,14-dihydro-PGD_1 (**8**) as a colorless oil: IR (neat) 3450, 2960, 2890, 1725, 1460, 1400, 1160, 1020 cm^{-1}; NMR ($CDCl_3$) δ 5.20 (s, 3 H, exchangeable, OH), 4.50 (m, 1 H, C-9 H), 3.60 (m, 1 H, C-15 H), 0.90 (m, 3 H, C-20 H); mass spectrum (Me_3Si derivative), M^+ not observed, ions at m/e 501.2872 (calcd for $C_{24}H_{49}O_5Si_3$, M^+

(34) M. O. Whitaker, A. Wyche, F. Fitzpatrick, H. Sprecher, and P. Needleman, *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 5919 (1979).

(35) (a) G. L. Bundy, E. W. Yankee, J. R. Weeks, and W. L. Miller, *Adv. Biosci.*, **9**, 125 (1973). (b) W. L. Miller, J. R. Weeks, J. W. Lauderdale, and K. T. Kirton, *Prostaglandins*, **9**, 9 (1975).

(36) J. R. Weeks, D. W. DuCharme, W. E. Magee, and W. L. Miller, *J. Pharmacol. Exp. Ther.*, **186**, 67 (1973).

(37) 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 M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1966).

– C_5H_{11}, 501.2888), 482, 467, 411, 392, 377, 354, 321, 281, 219, 199, 173, 129, 73, 55.

Δ^{12}-PGD$_2$ (9). A solution of 300 mg (0.85 mmol) of PGD_2 (**6**) in 3.5 mL of chloroform and 3.5 mL of triethylamine was allowed to stir at 25 °C for 72 h. The mixture was diluted with brine and cold 1 M $KHSO_4$ and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on a 30-g column of CC-4 acid-washed silica gel, eluted (5 mL fractions) with 30–55% EtOAc/hexane. Fractions 75–87 yield 40 mg (13%) of the 12*Z* isomer **10** [δ 6.10 (m, 1 H, C-13 H)], which decomposed fairly quickly on storage either neat or in solution. Fractions 95–135 afforded 150 mg (50%) of pure 12*E* isomer **9**, a viscous, colorless oil: IR (neat) 3400, 3010, 2930, 2860, 2660, 1710, 1645, 1575, 1405, 1240, 1180, 1080, 1035 cm^{-1}; NMR ($CDCl_3$) δ 6.90–6.55 (m, 1 H, C-13 H), 6.20–5.75 (br s, 3 H, exchangeable, OH), 5.65–5.30 (m, 2 H, vinyl), 4.70–4.20 (m, 1 H, C-9 H), 4.0–3.5 (m, 1 H, C-15 H); UV λ_{max} (EtOH) 244 nm (ϵ 7500); mass spectrum, M^+ not observed, ions at *m/e* 334, 316.

Alternatively, treatment of 700 mg (1.99 mmol) of PGD_2 with 250 mg of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in 20 mL of THF (25 °C, 16 h), followed by workup and chromatographic purification identical with that described above, afforded 500 mg (72%) of (12*E*)-Δ^{12}-PGD_2 (**9**) (no 12*Z* isomer **10** found).

15-Deoxy-$\Delta^{12,14}$-PGD$_2$ (11). During purification of a large lot of PGD_2, prepared as described earlier,[6] fractions containing several dehydrated impurities were isolated. A 1-g portion of this mixture was chromatographed on a column containing 200 g of silica gel, packed and eluted (12 mL fractions) with 96:2:2 $CHCl_3$/MeOH/HOAc. Fractions 54–74 yielded 560 mg of 9-deoxy-Δ^9-PGD_2 (**16**), contaminated with several minor impurities. (See below for clean preparation of **16**.) Fractions 91–102 gave 150 mg of clean 15-deoxy-$\Delta^{12,14}$-PGD_2 (**11**), as a viscous, colorless oil: R_f 0.24 (silica gel, 96:2:2 $CHCl_3$/MeOH/HOAc); IR 3420, 3010, 2960, 2930, 2860, 2660, 1710, 1625, 1605, 1469, 1410, 1345, 1280, 1225, 1205, 1185, 1080 (ring OH), 975 cm^{-1}; NMR δ 7.0 (s, 2 H, exchangeable, OH), 7.2–6.9 (m, 1 H, C-13 H), 6.40–6.15 (m, 2 H, C-14 and C-15 H), 5.70–5.35 (m, 2 H, C-5 and C-6 H), 4.80–4.30 (m, 1 H, C-9 H); UV λ_{max} (EtOH) 297 nm (ϵ 16800); mass spectrum (Me_3Si derivative), ions at *m/e* 478.2934 (calcd for $C_{26}H_{46}O_4Si_2$, 478.2898), 463, 407, 388.

PGD_2 1,9-Lactone (15). A solution of 1.7 g (3.88 mmol) of $PGF_{2\alpha}$, 15-THP (**12**),[6] 1.52 g (5.82 mmol) of triphenylphosphine, and 1.28 g (5.82 mmol) of 2,2′-dipyridyl disulfide[31] in 10 mL of oxygen-free benzene was stirred for 16 h at 25 °C. The reaction mixture was diluted with 1 L of oxygen-free benzene, and then heated at reflux for 23 h. The mixture was cooled to 25 °C and concentrated in vacuo, and the crude product was chromatographed on a column containing 450 g of silica gel, packed and eluted with 50–60% EtOAc/hexane (23-mL fractions). Fractions 100–150 yielded 1.23 g (73%) of pure lactone THP **13**, a colorless oil: R_f 0.26 (silica gel, 1:1 EtOAc/hexane); IR 1750 cm^{-1}.

A solution of 5.5 g of 11α-hydroxy lactone **13** (13.1 mmol, from several small-scale lactonizations) in 100 mL of actone was cooled to –30 °C and treated with 4.9 mL (1.5 equiv) of Jones reagent, and the dark solution was stirred at –30 °C for 1 h. Isopropyl alcohol (6 mL) was added, and stirring was continued 30 min at –30 °C. The reaction mixture was poured into ice–water, and extracted with 1:2 ether/hexane. The extracts were washed with brine, dried ($MgSO_4$), and concentrated, and the crude product was chromatographed on 375 g of CC-4 acid-washed silica gel. The column was eluted (23-mL fractions) with 25% EtOAc/hexane and afforded (fractions 43–64) 3.40 g (62%) of 11-keto lactone **14** (R_f 0.50, silica gel, 35:65:1 EtOAc/hexane/HOAc).

A solution of 500 mg (1.19 mmol) of lactone **14** in 25 mL of a 1:3:6 mixture of THF/H_2O/HOAc was heated at 40 °C for 1 h. The mixture was then cooled to 0 °C, poured into cold brine, and extracted with 1:1 EtOAc/hexane. The extracts were washed with brine and aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated. The crude product was chromatographed on a 20-g column of Mallinckrodt CC-4 acid-washed silica gel, packed and eluted (2 mL fractions) with 40% EtOAc/hexane. Fractions 25–42 afforded 270 mg (68%) of pure PGD_2 1,9-lactone **15**, a pale yellow, viscous oil: IR 3460, 1740, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.70–5.20 (m, 5 H, vinyl and C-9 H), 4.2–3.85 (m, 1 H, C-15 H); mass spectrum (Me_3Si derivative), ions at *m/e* 406.2539 (M^+, calcd for $C_{23}H_{38}O_4Si$, 406.2522), 391, 388, 378, 373, 355 ($M^+ - C_5H_{11}$).

9-Deoxy-Δ^9-PGD$_2$ (16). A 1.52-g sample of crude lactone **15** (above) was chromatographed on a column containing 200 g of "silica gel 60" (E.M. Reagents), packed with 20% EtOAc/hexane and eluted (20-mL fractions) with 1 L of 30% EtOAc/hexane and then 3 L of 60:40:1 EtOAc/hexane/HOAc. Fractions 111–155 were combined and concentrated to 100 mL, diluted with 300 mL of hexane, washed with several portions of brine, dried (Na_2SO_4), and concentrated, thereby affording 1.17 g (75%) of pure 9-deoxy-Δ^9-PGD_2 (**16**) as a viscous, pale yellow oil: IR 3400, 3200, 2660, 1710, 1085, 970 cm^{-1}; NMR ($CDCl_3$) δ 7.75–7.55 (m, 1 H, C-9 H), 6.30–6.10 (m, 1 H, C-10 H), 5.90 (br s, 2 H, exchangeable, OH), 5.75–5.35 (m, 4 H, vinyl H), 4.30–3.95 (m, 1 H, C-15 H); UV λ_{max} (EtOH) 216 nm (ϵ 9900), 305 (1200); mass spectrum (Me_3Si derivative), M^+ (observed) 478.2934 (calcd for $C_{26}H_{46}O_4Si_2$, 478.2912).

9-Deoxy-PGD$_2$ (24). To a stirred, –40 °C solution of 5.0 g (11.06 mmol) of $PGF_{2\alpha}$ methyl ester 15-THP[6] (**17**) in 100 mL of anhydrous acetone was added 18 mL (8.5 equiv) of trimethylsilyldiethylamine.[17,18] After 2 h at –40 °C, the reaction mixture was cooled to –78 °C, diluted with 150 mL of precooled (–78 °C) ether, poured into 200 mL of ice-cold aqueous $NaHCO_3$, and extracted with 1:2 ether/hexane. The extracts were washed with aqueous $NaHCO_3$ and brine, dried, and evaporated, thereby affording 5.5 g of crude silyl ether **18** (R_f 0.73, silica gel, 1:1 EtOAc/hexane), which was used without purification.

A solution of 5.5 g of silyl ether **18** in 80 mL of dry CH_2Cl_2 was cooled to –25 °C and treated with 1.83 mL (13.2 mmol) of Et_3N, followed by 1.0 mL (13.2 mmol) of methanesulfonyl chloride. After 10 min at –25 °C, the mixture was poured into ice-cold saturated aqueous NH_4Cl and extracted with methylene chloride. The extracts were washed with $NaHCO_3$, dried with $MgSO_4$, and evaporated, yielding 5.4 g of crude silyl mesylate **19**.

The crude product **19** was taken up in 70 mL of methanol, cooled to 0 °C, and treated with 30 mL of 2% aqueous citric acid. After 1 h, the mixture was poured into cold brine, and the product was isolated by EtOAc extraction. The crude product was chromatographed on 350 g of silica gel, eluting with 70% EtOAc/hexane (22-mL fractions). Fractions 79–130 yielded 3.84 g of pure mesylate **20**, a viscous, colorless oil (66% from **17**): R_f 0.40 (40% EtOAc/hexane); IR 3500, 1740, 1350, 1200, 1180, 1110, 1080, 1040, 980, 870, 815 cm^{-1}; NMR ($CDCl_3$) δ 5.70–5.30 (m, 4 H), 5.2–4.9 (m, 1 H), 4.8–4.6 (m, 1 H), 4.2–3.3 (s at δ 3.67 superimposed on m, 7 H total), 3.03 (s, 3 H, SO_2CH_3).

To a stirred suspension of 1.10 g (29 mmol) of lithium aluminum hydride in 100 mL of dry ether was added (dropwise over 15 min) a solution of 3.8 g (7.2 mmol) of mesylate ester **20** in 25 mL of ether. After 1 h at at 25 °C, 2.2 mL of H_2O was added, followed by 1.75 mL of 10% aqueous KOH. After 3 h of stirring, the mixture was poured into 200 mL of 10% aqueous sodium potassium tartrate, and the layers were separated. Further ether extraction, drying ($MgSO_4$), and evaporation of the extracts gave 2.9 g of crude **21**. The crude product was chromatographed on 150 g of silica gel, eluting with 70% ethyl acetate/hexane (23-mL fractions). Fractions 19–34 afforded 2.18 g of pure 9-deoxy intermediate **21**: IR CO and OMs bands gone; R_f 0.33 (silica gel, 75% EtOAc/hexane).

Following the selective primary alcohol oxidation procedure of Fried and Sih,[38] a suspension of 500 mg of platinum oxide in 50 mL of distilled water was reduced with hydrogen. The system was flushed thoroughly with nitrogen and then oxygen. Solid $NaHCO_3$ (780 mg) was added, and the temperature of the black suspension was brought to 60 °C. To the vigorously stirred 60 °C suspension was added a suspension of 380 mg (0.93 mmol) of **21** in 30 mL of 4:1 water/acetone. An additional 53 mL of 12% acetone/water was added, and the mixture was stirred for 4.5 h at 60 °C (with oxygen being continuously bubbled through the reaction mixture via a syringe needle). The reaction mixture was cooled to 25 °C and filtered through Celite, and the filtrate was acidified with 50 mL of 2 M $NaHSO_4$ and extracted with EtOAc.

(38) J. Fried and J. C. Sih, *Tetrahedron Lett.*, 3899 (1973). See also K. Heyns and H. Paulsen, in "Newer Methods of Preparative Organic Chemistry", Vol. II, W. Foerst, Ed., Academic Press, New York, 1963, pp. 303 ff.

After the extracts were washed with brine, dried, (Na_2SO_4), and concentrated, the crude product was chromatographed on 20 g of CC-4 acid-washed silica gel. Elution of the column (5-mL fractions) with 30% EtOAc/hexane gave (fractions 21–40) 200 mg of acid **22**, a viscous, colorless oil (50%): IR 3450, 2600, 1720, 1020, 980 cm^{-1}.

Collins reagent was prepared by adding 427 mg of dry CrO_3 to a 0 °C solution of 0.69 mL of pyridine in 30 mL of CH_2Cl_2. The solution was stirred and allowed to warm to 25 °C over 30 min, and then a solution of 190 mg (0.45 mmol) of **22** in 2 mL of CH_2Cl_2 was added in one portion. After 40 min at 25 °C, the mixture was filtered through Celite directly onto a 40-g column of CC-4 silica gel. The column was eluted with 400 mL of EtOAc, concentration of which afforded 140 mg of crude 11-ketone **23**. This crude product was dissolved in a mixture of 6 mL of HOAc and 3 mL of water and warmed to 40 °C for 90 min. Water (25 mL) was added, and the solvents were removed by freeze-drying. The crude product was chromatographed on a 20-g column of CC-4 silica gel, packed with 20% EtOAc/hexane, and eluted (3 mL fractions) with 50% EtOAc/hexane. Fractions 19–24 yielded 60 mg (40%) of pure 9-deoxy-PGD_2 (**24**), a viscous, colorless oil: IR 3500, 1740, 1715, 1160, 970 cm^{-1}; NMR ($CDCl_3$) δ 6.70 (br s, 2 H, exchangeable, OH), 5.70–5.30 (m, 4 H, vinyl), 4.35–3.95 (m, 1 H, C-15 H); mass spectrum (Me_3Si derivative), ions at m/e 480.3091 (calcd for $C_{26}H_{48}O_4Si_2$, M^+, 480.3069), 465, 409, 390. (UV end absorption only.)

11β-$PGF_{2\beta}$ 15-(Tetrahydropyranyl ether) (25). (a) Via Inversion of 9α,11α-Diol. A solution of 6.7 g (14.8 mmol) of $PGF_{2\alpha}$ methyl ester 15-THP 17,[6] 15.5 g (59.2 mmol) of triphenylphosphine, and 7.2 g (59.2 mmol) of benzoic acid in 200 mL of dry THF was cooled to 0 °C under nitrogen and treated with 10.2 g (59.2 mmol) of diethyl azodicarboxylate,[20] added via pipet over 1 min to the rapidly stirred solution. After 45 min at 0 °C, the reaction mixture was poured into 400 mL of 1:1 EtOAc/hexane, washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Some triphenylphosphine oxide (18 g) was removed from the crude product by trituration with 15% EtOAc/hexane and filtration. The remaining oily product was chromatographed on a column containing 2 kg of silica gel, packed with 10% EtOAc/hexane, and eluted (250-mL fractions) with 13 L of 15%, 4 L of 20%, and 4 L of 25% EtOAc/hexane. Fractions 67–95 yielded 5.62 g (57% of theory) of the 9β,11β-dibenzoate C-1 methyl ester corresponding to **25** [R_f 0.20, 0.24 (THP diastereomers) (silica gel, 15% EtOAc/hexane)]. A 750-mg portion of the crude triester was dissolved in 60 mL of 1:1 methanol/3 N aqueous NaOH and stirred overnight at 25 °C. The mixture was poured into 50 mL of ice-cold aqueous 2 N $KHSO_4$ and extracted rapidly with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, and evaporated, thereby affording a crude product, which was chromatographed on 50 g of CC-4 acid-washed silica gel. The column was packed and eluted (5-mL fractions) with 75% EtOAc/hexane. Fractions 27–31 afforded 450 mg of clean **25**, a viscous, colorless oil: R_f 0.36 (silica gel, AIX solvent[37]); NMR ($CDCl_3$) δ 5.90–5.30 (m, 7 H, 3 H of which are exchangeable), 4.90–4.70 (m, 1 H), 4.45–3.30 (m, 5 H).

(b) Via Reduction of 11β-PGE_2. A solution of 8.3 g (22.68 mmol) of 11β-PGE_2 ester[21] in 1 L of MeOH was cooled to −20 °C and treated with 860 mg of sodium borohydride, added in several portions over 10 min. After 20 min at −20 °C, 5 mL of 1:1 HOAc/H_2O was added dropwise over 10 min, and the mixture was warmed to 0 °C. Following the removal of about 800 mL of the methanol in vacuo, the remaining solution was poured into brine, diluted with 70 mL of 2 M $NaHSO_4$, and extracted with two 500-mL portions of EtOAc. The extracts were washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The crude product (8 g) was chromatographed on a column containing 700 g of silica gel, packed and eluted (1 × 800 mL, then 70-mL fractions) with 5% MeOH/CH_2Cl_2. Fractions 57–90 yielded 4.9 g (60% of theory) of pure 11β-$PGF_{2\beta}$ methyl ester, a viscous, colorless oil: R_f 0.29 (silica gel, 5% MeOH/CH_2Cl_2). Following the standard procedure,[6] a 1.3-g (3.53 mmol) portion of this material was converted to 1.55 g of **25** (97% of theory after chromatographic purification), identical spectrally and by TLC with the material from section a above.

9β-PGD_2 1,9-Lactone (26). A solution of 1.0 g (2.28 mmol) of **25**, 900 mg (3.42 mmol) of triphenylphosphine, and 750 mg (3.42 mmol) of 2,2′-dipyridyl disulfide in 15 mL of oxygen-free benzene was stirred overnight at 25 °C under nitrogen. The mixture was then diluted with 200 mL of oxygen-free toluene and heated at reflux for 30 h. The mixture was cooled to 25 °C and concentrated in vacuo, and the crude product was chromatographed on a 300-g column of silica gel, packed with 15% EtOAc/hexane, and eluted (23-mL fractions) with 25% EtOAc/hexane. Fractions 112–200 yielded 500 mg of the 1,9-lactone corresponding to **25**: R_f 0.25, 0.32 (THP diastereomers; 25% EtOAc/hexane); IR 3550, 1750, 985 cm^{-1}. A solution of 450 mg of this lactone in 25 mL of acetone was cooled to −25 °C and treated with 0.5 mL of Jones reagent. After 45 min at −25 °C, 0.5 mL of isopropyl alcohol was added, and stirring was continued for 20 min at −25 °C. The mixture was poured into brine and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude C-11 ketone [430 mg; R_f 0.50 (25% EtOAc/hexane)] was dissolved in 25 mL of 1:3:6 THF/H_2O/HOAc and warmed at 40 °C for 90 min. Standard workup as above yielded a crude product, which was chromatographed on a 40-g column of CC-4 acid-washed silica gel, packed and eluted (4-mL fractions) with 30% EtOAc/hexane. Fractions 38–70 gave 300 mg of 9β-PGD_2 1,9-lactone (**26**), a viscous oil that crystallized on standing. Recrystallization from ether/hexane afforded 165 mg of **26** as colorless needles: mp 54–55 °C; R_f 0.25 (30% EtOAc/hexane); IR 3550, 1750, 1460, 1420, 1350, 1320, 1270, 1230, 1150, 1075, 1070, 970, 920 cm^{-1}; NMR ($CDCl_3$) δ 5.80–5.35 (m, 4 H), 5.32–4.85 (m, 1 H), 4.30–3.95 (m, 1 H); mass spectrum, M^+ (observed) 334.2173 (calcd for $C_{20}H_{30}O_4$, 334.2144).

9β-PGD_2 (28). A solution of 700 mg (1.59 mmol) of **25** in 50 mL of acetone was cooled to −20 °C, under a nitrogen atmosphere, and treated with 2.8 mL (10 equiv) of trimethylsilyldiethylamine (TMSDEA).[17] After 90 min, another 1.5 mL of TMSDEA was added, and stirring was continued for 90 min longer. The mixture was then cooled to −70 °C, diluted with 150 mL of precooled (−70 °C) ether, and poured into a mixture of 20 mL of saturated aqueous $NaHCO_3$ and 100 mL of saturated NH_4Cl. The aqueous layer was carefully acidified to pH 6 with cold 1 M $NaHSO_4$ and extracted with additional ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, affording 800 mg of C-9 Me_3Si derivative **27**, a viscous, colorless oil: R_f 0.50 (50:50:1 EtOAc/hexane/HOAc). Collins reagent was prepared by adding 1.54 g of dry CrO_3 to a stirred 0 °C solution of 2.52 mL of pyridine in 75 mL of CH_2Cl_2. After 30 min at 25 °C, a solution of 800 mg of crude **27** in 2 mL of CH_2Cl_2 was added rapidly, the dark mixture was stirred for 30 min at 25 °C, Celite (about 5 g) was added, and the crude mixture was filtered through 100 g of CC-4 acid-washed silica gel, packed and eluted with ethyl acetate. Concentration of the eluate afforded 470 mg of the C-11 ketone corresponding to **27**: R_f 0.37 (30:70:1 EtOAc/hexane/HOAc). This crude product was dissolved in 40 mL of 1:3:6 THF/H_2O/HOAc and heated at 40 °C for 1 h. The mixture was poured into brine and extracted with two 100-mL portions of 1:1 EtOAc/hexane. The extracts were washed with brine (several times), dried (Na_2SO_4), and evaporated, and the crude product was chromatographed on a 20-g column of silica gel. (Before use, the column was first washed with 150 mL of 30:60:10 acetone/hexane/HOAc and then with 100 mL of 1% acetone/hexane.) Elution was performed (5-mL fractions) with 400 mL of 20% and 400 mL of 30% acetone/hexane. Fractions 100–134 yielded 150 mg of 9β-PGD_2 (**28**), which crystallized on standing. Recrystallization from ether/hexane gave **28** as a colorless solid: mp 62–64 °C; R_f 0.31 (silica gel, 40:60:1 acetone/hexane/HOAc; for comparison, 11β-PGE_2 exhibited R_f 0.35 and PGD_2 exhibited R_f 0.38 in the same solvent system); IR 3500, 2700, 1740, 1720, 1460, 1410, 1240, 1160, 1080, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.90–5.35 (m, 4 H), 5.15 (br s, 3 H, exchangeable), 4.40–3.90 (m, 2 H); mass spectrum (Me_3Si derivative), ions at m/e 568.3420 (calcd for $C_{29}H_{56}O_5Si_3$, M^+ 568.3436) 553, 497, 478.

(15*S*)-15-Methyl-PGD_2 (30). A solution of 200 mg (0.54 mmol) of (15*S*)-15-methyl-$PGF_{2\alpha}$ (**29**)[18] in 10 mL of actone was cooled to −30 °C, treated with 0.22 mL of Jones reagent, and stirred for 20 min at −30 °C. Isopropyl alcohol (0.5 mL) was added, and after 10 min at −30 to 0 °C, the mixture was poured into brine and extracted with EtOAc. The extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product (200 mg) was chromatographed on a 20-g column of CC-4 acid-washed silica

gel, packed with 20% EtOAc/hexane and eluted with 50% EtOAc/hexane (2-mL fractions). Fractions 61–85 yielded 60 mg of pure (15S)-15-methyl-PGD_2 (**30**), a viscous, pale yellow oil: R_f 0.24 (50:50:1 EtOAc/hexane/HOAc, silica gel); IR 3500, 2700, 1740, 1720, 1460, 1420, 1390, 1240, 1170, 1140, 1080, 1040, 980, 920 cm^{-1}; NMR ($CDCl_3$) δ 5.70–5.35 (m, 4 H), 5.25 (br s, 3 H, exchangeable), 4.60–4.40 (m, 1 H), 1.28 (s, superimposed on m, C-15 methyl); mass spectrum (methoxime Me_3Si derivative), M^+ (weak) at m/e 611; $M^+ - CH_3$ (observed), 596.3627 (calcd for $C_{30}H_{58}NO_5Si_3$, 596.3622).

(15*S*)-15-Methyl-9-deoxy-Δ^9-PGD_2 (33). A solution of 4.0 g of (15S)-15-methyl-$PGF_{2\alpha}$ (**29**)[18] in 15 mL of anhydrous, oxygen-free xylene was treated with 3.45 g of 2,2′-dipyridyl disulfide and 4.12 g of triphenylphosphine. After stirring for 18 h at 25 °C, the mixture was diluted with 1000 mL of xylene and heated at reflux for 4 h. Following removal of the xylene in vacuo, the residue was partitioned between cold aqueous $NaHCO_3$ and EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated, and the crude product was chromatographed on a 1.2-kg column of silica gel, packed and eluted (125 mL fractions) with 12 L of 20%, 3 L of 25% and 6 L of 30% acetone/CH_2Cl_2. Fractions 135–180 gave 2.90 g (79% of theory) of (15S)-15-methyl-$PGF_{2\alpha}$ 1,9-lactone (**31**), a colorless, viscous oil: R_f 0.24 (silica gel, 20% acetone/CH_2Cl_2); IR 3400, 1740, 1715, 970 cm^{-1}. A solution of 2.8 g of lactone **31** (8 mmol) in 75 mL of acetone was cooled to −40 °C, treated with 2.5 mL of Jones reagent, and stirred at −40 °C for 2 h and at −30 °C for 1.5 h. Isopropyl alcohol (3 mL) was added, and stirring was continued for 20 min at −30 °C. The mixture was then poured into cold brine and extracted with 1:2 EtOAc/hexane. The extracts were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was chromatographed on 350 g of CC-4 acid-washed silica gel, eluted with 25% EtOAc/hexane (20-mL fractions). Fractions 140–180 yielded 440 mg of clean 11-keto 1,9-lactone **32**: R_f 0.35 (40:60:1 EtOAc/hexane/HOAc); IR 3550, 1750, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.75–5.10 (m, 5 H, vinyl and C-9 H), 1.28 (s, 3 H). A concentrated solution of lactone **32** (440 mg) in 3 mL of 30% EtOAc/hexane was placed on an 8-g column of silica gel packed with the same solvent mixture. The column was eluted with about 20 mL of 30% EtOAc/hexane over a 2.5-h period and then with 200 mL of 5% MeOH/EtOAc rapidly. The latter eluate was concentrated and afforded 300 mg of enone **33**, contaminated with lactone **32**. The material was chromatographed on 30 g of CC-4 acid-washed silica gel, packed and eluted (5 mL fractions) with 40% EtOAc/hexane. Fractions 19–30 yielded 130 mg of starting lactone **32**, while fractions 35–70 contained 190 mg of pure enone **33**, a viscous, colorless oil: R_f 0.20 (40:60:1 EtOAc/hexane/HOAc); IR 3500, 2700, 1720, 1600, 1460, 1380, 1250, 1020, 975, 910 cm^{-1}; NMR ($CDCl_3$) δ 7.70–7.50 (m, 1 H, C-9), 6.75 (br s, 2 H, exchangeable), 6.30–6.05 (m, 1 H, C-10), 5.75–5.30 (m, 4 H, vinyl), 1.27 (s, 3 H); UV λ_{max} (EtOH) 216 nm (ϵ 9350), 319 (1350); mass spectrum (Me_3Si derivative), ions at m/e 492 (M^+, weak), 477.2846 (calcd for $C_{26}H_{45}O_4Si_2$, $M^+ - CH_3$, 477.2856).

16,16-Dimethyl-PGD_2 (34). Following the standard four-step sequence described earlier, 16,16-dimethyl-PGD_2 (**34**) was synthesized in 44% yield from 16,16-dimethyl-$PGF_{2\alpha}$ 15-THP. (Preparation of this latter intermediate from 16,16-dimethyl-$PGF_{2\alpha}$[25b] was accomplished in 27% yield, 91% if account is taken or recovered starting material.) 16,16-Dimethyl-PGD_2 (**34**) was a viscous, colorless oil: R_f 0.48 (silica gel, AIX solvent[37]); IR 3430, 2660, 1735, 1715, 1385, 1235, 1165, 1110, 1065, 1025, 995, 975 cm^{-1}; NMR ($CDCl_3$) δ 6.0–5.2 (m, 4 H), 4.88 (br m, 3 H, exchangeable), 4.50 (m, 1 H, C-9 H), 3.86 (d, J = 6 Hz, 1 H, C-15 H), 0.87 and 0.83 (singlets, 3 H each, 16-CH_3); UV λ_{max} 220 nm (ϵ 1200), 280 (sh, 308); mass spectrum (Me_3Si derivative), ions at m/e 596 (M^+, weak), 581.3502 (calcd for $C_{30}H_{57}O_5Si_3$, $M^+ - CH_3$, 581.3514), 506, 497, 416, 407, 353, 201.

17-Phenyl-18,19,20-trinor-PGD_2 (38). A dry, 100-mL, three-necked flask equipped with addition funnel, magnetic stirring bar, and nitrogen inlet was charged with 0.42 g of 57% sodium hydride dispersion (10 mmol; washed free of oil with 2 × 20 mL of hexane). HMPA (20 mL) was added, followed by 2.22 g (5 mmol) of (4-carboxybutyl)triphenylphosphonium bromide. The resulting mixture was stirred at 70 °C for 3 h, then cooled to 15 °C, and treated dropwise with a solution of 500 mg (1 mmol) of lactol **35**[26] in 5 mL of THF (plus 2 × 3 mL THF washes). After 1.5 h at 10–15 °C, the mixture was diluted with 200 mL of ether and ice, cooled to 0 °C, acidified to pH 3 with aqueous $KHSO_4$, poured into brine, and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and evaporated. This reaction was repeated on 1.0 g (2 mmol) of lactol **35**, and the combined crude product (6.41 g) was chromatographed on a 400-g column of Mallinckrodt CC-4 acid-washed silica gel. The column was eluted (1 × 1000 mL, then 55-mL fractions) with 1000 mL each of 10, 15, 20, 25, 30, and 35% EtOAc/hexane. Fractions 45–59 afforded 740 mg (42% of theory) of pure 9α-hydroxy intermediate **36**: R_f 0.27 (24:75:1 EtOAc/hexane/HOAc); NMR ($CDCl_3$) δ 7.21 (br s, 5 H), 6.43 (br m, 2 H, exchangeable), 5.80–5.18 (m, 4 H), 4.75 (m, 1 H, acetal H of THP), 4.4–3.3 (m, 5 H), 0.87 (s, 9 H), 0.06 (s, 6 H). Fractions 60–78 yielded 380 mg (22%) of 9-silyl intermediate **37**: R_f 0.20 (24:75:1 EtOAc/hexane/HOAc).

A solution of 740 mg (1.26 mmol) of **36**, 2.1 mL of dihydropyran, and 30 mg of pyridine hydrochloride in 15 mL of CH_2Cl_2 was stirred for 48 h at 25 °C and then concentrated in vacuo. In order to hydrolyze the THP ester, the crude product was dissolved in 5 mL of MeOH and treated with 20 mL of 5% KOH in 9:1 MeOH/H_2O. After 20 h at 25 °C, the mixture was poured into brine, ice, and ether, cooled to 0 °C, acidified to pH 3 with aqueous $KHSO_4$, and extracted with ether. For desilylation, the crude product was dissolved in 10 mL of THF, treated with 1.7 g of Bu_4NF, and stirred for 2 days at 25 °C. The reaction mixture was then diluted with brine, and the product was isolated by the usual EtOAc extraction procedure. The crude product (1.15 g) was chromatographed on 115 g of CC-4 acid-washed silica gel, eluted (1 × 500 mL, then 20-mL fractions) with 675 mL of 25%, 1000 mL of 35%, and 1000 mL of 45% EtOAc/hexane. Fractions 61–95 yielded 670 mg (96% of theory) of 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$ 9,15-bis(tetrahydropyranyl ether), a colorless oil: R_f 0.50 (silica gel, AIX solvent[37]).

The purified bis(THP ether) from the preceding paragraph was dissolved in 25 mL of actone, cooled to −25 °C, and treated with 0.45 mL of 2.67 M Jones reagent. After 1 h at −25 to −20 °C, 0.5 mL of isopropyl alcohol was added, and stirring was continued for an additional 10 min at −20 °C. The mixture was then poured into brine and extracted with EtOAc. The extracts were washed with brine (twice), dried (Na_2SO_4), and concentrated. The crude product (0.61 g) was dissolved in 10 mL of HOAc and 5 mL of H_2O and heated at 35 °C for 3.5 h. Water (80 mL) was added, and the mixture was freeze-dried to an oil (18 h). The crude product was chromatographed on a column containing 46 g of CC-4 acid-washed silica gel, eluted (1 × 250 mL, then 20-mL fractions) with 270 mL of 25% and 500 mL each of 35, 45, and 55% EtOAc/hexane. Fractions 39–71 afforded 230 mg (50%) of pure **38** as a pale yellow solid. Recrystallization from EtOAc/hexane gave 154 mg of 17-phenyl-18,19,20-trinor-PGD_2 (**38**) as colorless crystals: mp 81.5–85.9 °C; R_f 0.36 (silica gel, AIX solvent[37]); IR 3370, 2750, 2680, 1745, 1730, 1710, 1665, 1605, 1585, 1500, 1275, 1240, 1165, 1140, 1045, 1035, 990, 970, 750, 700 cm^{-1}; NMR ($CDCl_3$) δ 7.21 (br s, 5 H), 5.53 (m, 4 H), 5.10 (m, 3 H, exchangeable), 4.48 (m, 1 H, C-9 H), 4.16 (m, 1 H, C-15 H); mass spectrum (Me_3Si derivative), ions at m/e 602.3251 (calcd for $C_{32}H_{54}O_5Si_3$, M^+, 602.3279), 587, 512, 497, 407, 207, 117, 91.

5-Oxa-PGD_1 (39). Via the four-step sequence outlined in Scheme I and described earlier in detail,[6] 5-oxa-$PGF_{1\alpha}$[30] was converted to 5-oxa-PGD_1 (**39**; 20% yield), a viscous, colorless oil: R_f 0.21 (silica gel, AIX[37] solvent); IR 3420, 2720, 2660, 1735, 1715, 1255, 1225, 1180, 1110, 1010, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (m, 5 H, 3 H of which are exchaneable, 2 vinyl H, 3 OH), 4.53 (m, 1 H, C-9 H), 4.08 (m, 1 H, C-15 H), 3.57 (m, 4 H, CH_2OCH_2); mass spectrum (Me_3Si derivative), ions at m/e 572.3391 (calcd for $C_{28}H_{56}O_6Si_3$, M^+, 572.3385), 557, 501, 482, 467, 411, 173, 159.

2a,2b-Dihomo-PGD_2 (40). Starting with the lactol corresponding to **35** but with the natural prostaglandin alkyl side chain and using (6-carboxyhexyl)triphenylphosphonium bromide in the initial Wittig step, we prepared 2a,2b-dihomo-PGD_2 (**40**) in the same manner as 17-phenyl-PGD_2 (**38**) above. Following chromatographic purification on CC-4 acid-washed silica gel, the product was crystallized from EtOAc/hexane at −20 °C, thereby affording **40** as a white solid: mp 57.4–64.0 °C; R_f 0.35 (silica gel, AIX solvent[37]); IR 3380, 2680, 1720, 1705, 1315, 1280, 1230, 1155, 1080, 1045, 1015, 975 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (m, 7 H, vinyl H and 3 OH), 4.52 (m, 1 H, C-9 H), 4.12 (m, 1 H, C-15 H), 0.90 (t, J = 5 Hz, 3 H); mass spectrum (Me_3Si derivative), M^+ (ob-

served) 596.3764 (calcd for $C_{31}H_{60}O_5Si_3$, 596.3748).

PGD_2 1,15-Lactone (46). To a stirred 0 °C solution of 1.0 g (3 mmol) of $PGF_{2\alpha}$ 1,15-lactone (**42**)[31] in a 3 mL of anhydrous DMF was added a 0 °C solution of 474 mg (3.15 mmol) of *tert*-butyldimethylsilyl chloride and 428 mg (6.30 mmol) of imidazole in 3 mL of DMF.[32] The resulting colorless solution was stirred at 0 °C for 1 h, poured into cold brine, and extracted with hexane. The extracts were washed with cold aqueous $NaHSO_4$, cold $NaHCO_3$ and brine, dried, and evaporated. The crude product was chromatographed on 140 g of silica gel, eluting with 20% EtOAc/hexane (12-mL fractions). Fractions 44–56, homogeneous by TLC, were combined and yielded 1.10 g (82%) of $PGF_{2\alpha}$ 1,15-lactone, 11-*tert*-butyldimethylsilyl ether: R_f 0.33 (20% EtOAc/hexane): IR 3500, 1730, 1460, 1240, 1125, 1110, 1040, 1005, 975, 880, 854, 840, 780 cm^{-1}; NMR ($CDCl_3$) δ 5.90–4.95 (m, 5 H, vinyl and C-15 H), 4.25–3.75 (m, 2 H), 3.70 (s, 1 H, exchangeable), 0.85 (s, 9 H), 0.01 (s, 6 H).

The above product (1.05 g) was dissolved in 25 mL of CH_2Cl_2, treated with 5 mL of freshly distilled dihydropyran and 50 mg of pyridine hydrochloride, and stirred in a nitrogen atmosphere at 25 °C for 18 h. The mixture was then poured into cold brine, and the product was isolated by extraction with hexane as in the preceding paragraph. The crude product was chromatographed on a 140-g column of silica gel, packed and eluted with 10% EtOAc/hexane (12-mL fractions). Fractions 34–48 yielded 1.16 g (92%) of $PGF_{2\alpha}$ 1,15-lactone 9-(tetrahydropyranyl ether) 11-(*tert*-butyldimethylsilyl ether) (**43**): R_f 0.69 (30% EtOAc/hexane); NMR ($CDCl_3$) δ 5.95–5.50 (m, 5 H, vinyl and C-15 H), 4.75–4.50 (m, 1 H, THP acetal H), 4.30–3.25 (m, 4 H, C-9, C-11, CH_2O of THP), 0.88 (s, 9 H), 0.00 (s, 6 H).

To a stirred solution of 1.16 g of **43** in 5 mL of anhydrous THF at 25 °C was added 22 mL of a 0.3 M solution of tetrabutylammonium fluoride in THF. The reaction mixture was stirred at 25 °C for 30 min and then poured into a mixture of ice, $NaHCO_3$, brine, and hexane, and the product was isolated as described above via hexane extraction. The crude 11-hydroxy product **44** (1.10 g, 100%) was homogeneous by TLC (R_f 0.19, 30% EtOAc/hexane) and was oxidized without purification.

A solution of 920 mg (2.10 mmol) of **44** in 30 mL of actone was cooled to −30 °C and treated with 0.8 mL of Jones reagent. After 75 min at −25 ± 5 °C, 0.5 mL of isopropyl alcohol was added, and stirring was continued for 10 min at −25 °C. The mixture was diluted with 400 mL of cold water and extracted with 4:1 hexane/EtOAc. The extracts were washed with water, cold aqueous $NaHSO_4$, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The crude product (**45**) was chromatographed on a 140-g column of silica gel, packed with 5% EtOAc/hexane and eluted (1 × 300 mL, then 12-mL fractions) with 20% EtOAc/hexane. Fractions 21–35 gave 750 mg (75%) of pure PGD_2 1,15-lactone 9-THP (**45**), a viscous, colorless oil; R_f 0.62 (1:1 EtOAc/hexane).

A stirred mixture of 700 mg of **45**, 33 mL of THF, 33 mL of H_2O, and 66 mL of HOAc was heated at 40 °C for 3 h. The reaction mixture was then cooled to 0 °C, poured into 1:1 brine/water, and extracted with 1:1 EtOAc/hexane. The extracts were washed with cold aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The crude product crystallized upon trituration with ether/hexane. Two recrystallizations from ether/hexane afforded 243 mg of pure PGD_2 1,15-lactone (**46**), a white solid: mp 93–94 °C; R_f 0.34 (1:1 EtOAc/hexane); IR 3470, 3020, 1735, 1725, 1245, 1225, 1160, 1045, 1025, 960, 715 cm^{-1}; NMR ($CDCl_3$) δ 5.95–5.35 (m, 4 H, vinyl H), 5.40–4.95 (m, 1 H, C-15 H), 4.65–4.30 (m, 1 H), 2.45 (d, J = 2.5 Hz, 2 H, C-10 H); UV λ_{max} (basic EtOH) 310 nm (ϵ 16000), 260 (7900), 250 (9250), 243 (9550); mass spectrum (Me_3Si derivative), ions at m/e 406.2574 (calcd for $C_{23}H_{38}O_4Si$, M^+, 406.2539), 391, 388, 373, 335, 316, 290, 279. Anal. ($C_{20}H_{30}O_4$) C, H.

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Registry No. **5**, 17968-82-0; **5** (15-THP), 52035-44-6; **6**, 41598-07-6; **7**, 71902-47-1; **7** [methoxime, 3(Me_3Si)], 85235-09-2; **8**, 25226-29-3; **8** [3(Me_3Si)], 69079-65-8; **9**, 64072-89-5; **10**, 85235-10-5; **11**, 85235-11-6; **11** [2(Me_3Si)], 85235-12-7; **12**, 41598-01-0; **13**, 62410-78-0; **14**, 62410-79-1; **15**, 62410-77-9; **15** (Me_3Si), 62443-60-1; **16**, 60203-57-8; **16** [2(Me_3Si)], 69079-63-6; **17**, 64072-81-7; **18**, 64072-82-8; **19**, 64072-83-9; **20**, 64072-84-0; **21**, 64072-85-1; **22**, 64281-88-5; **23**, 64223-08-1; **24**, 64072-86-2; **24** [2(Me_3Si)], 85235-13-8; **25**, 62410-82-6; **25** (dibenzoate, methyl ester), 85235-14-9; **25** (1,9-lactone), 62410-83-7; **26**, 62410-80-4; **26** (THP), 62443-65-6; **27**, 85235-15-0; **27** (C-11 ketone), 85235-16-1; **28**, 64072-55-5; **28** [3(Me_3Si)], 85235-17-2; **29**, 35700-23-3; **30**, 85280-90-6; **30** [methoxime, 3(Me_3Si)], 85235-18-3; **31**, 62411-08-9; **32**, 85235-19-4; **33**, 85235-20-7; **33** [2(Me_3Si)], 85235-21-8; **34**, 85235-22-9; **34** [3(Me_3Si)], 64223-00-3; **35**, 85235-23-0; **35** (natural side chain), 64072-34-0; **36**, 85235-24-1; **36** (3THP), 85235-30-9; **36** [9,15-$(THP)_2$], 85235-31-0; **36** (9-THP-11-ol), 85235-32-1; **37**, 85235-25-2; **38**, 85280-91-7; **38** [9,11-(THP)], 85235-33-2; **38** [3-(Me_3Si)], 85235-26-3; **39**, 85235-27-4; **39** [3(Me_3Si)], 85235-28-5; **40**, 64072-63-5; **40** [3(Me_3Si)], 64072-64-6; **42**, 55314-49-3; **42** (11-TBS ether), 62410-99-5; **43**, 62411-00-1; **44**, 62411-01-2; **45**, 62411-02-3; **46**, 62410-98-4; **46** (Me_3Si), 85235-29-6; $PGF_{1\alpha}$, 745-62-0; 15-THP-$PGF_{1\alpha}$, 52035-37-7; $PGF_{3\alpha}$, 745-64-2; 11β-PGE_2 methyl ester, 38310-89-3; 11β-$PGF_{2\beta}$ methyl ester, 58407-23-1; 15-THP-16,16-dimethyl-$PGF_{2\alpha}$, 64222-95-3; 16,16-dimethyl-$PGF_{2\alpha}$, 39746-23-1; 5-oxa-$PGF_{1\alpha}$, 55444-77-4; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6; (6-carboxyhexyl)triphenylphosphonium bromide, 50889-30-0.