Prostanoic Acid Chemistry. II.[1] Hydrogenation Studies and Preparation of 11-Deoxyprostaglandins

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Selective hydrogenations, mainly by the homogeneous Wilkinson catalyst, were shown to convert PGE_2 to PGE_1, $PGF_{2\alpha}$ to $PGF_{1\alpha}$, and 5,6-*trans*-PGE_2 to PGE_1. In the same way, 11β-PGE_1, 15β-PGE_1, and 11β,15β-PGE_1 were also prepared from their 5,6-cis unsaturated precursors. Hydrogenation of PGA_1 and PGA_2 gave a number of 11-deoxyprostaglandins, including 11-deoxy-PGE_1, 11-deoxy-PGE_2, and 13,14-dihydro analogs. Sodium borohydride reduces the cyclopentenone system of PGA_1 and PGA_2 completely, to give pairs of epimeric alcohols **18, 19** and **26, 27**. Other reduction by-products and cyclization products of some prostaglandins are described.

Prostaglandins of the "2" series, *i.e.*, PGE_2 (**1**, 11α, R = R′ = H), $PGF_{2\alpha}$ (**15a**), and PGA_2 (**23**, R = R′ = H), differ from those of the "1" series, PGE_1 (**3**, 11α, R = R′ = H), $PGF_{1\alpha}$ (**15b**), PGA_1 (**20**), in having a cis double bond between carbon atoms 5 and 6. While the PG_1 series was the first studied[2] and is still of biological and clinical interest, compounds of the PG_2 series have become the most readily available *via* biosynthesis,[3] total synthesis,[4] and from the common gorgonian, *Plexaura homomalla*.[5] This led us to initiate studies on the selective hydrogenation of the 5,6 double bond of prostaglandins in order to interrelate the two series. These studies on reduction products of prostaglandins led also to a number of 11-deoxyprostaglandins. Such compounds are relatively stable to acidic or basic reagents in contrast to the β-hydroxy ketones PGE_1 and PGE_2. Since 11-deoxyprostaglandins also retain prostaglandin-like biological activity,[6] they have been the target for total synthesis dating back to the early days of prostaglandin research.[7] Most of these efforts have produced racemic products and epimeric mixtures rather than the "natural" antipodes described here. An early report of biological activities of some of the natural 11-deoxyprostaglandins or their methyl esters described below has been published.[8]

At the time of our first experiments, the only recorded selective hydrogenation of the 5,6-cis double bond was by Samuelsson,[9] who prepared 5,6-tritiated PGE_1 from PGE_2 (**1**, 11α, R = R′ = H) using tritium and 5% palladium on charcoal catalyst in ethyl acetate.[10] Using hydrogen, we found this reduction to proceed rapidly at 25° with little difference in rates of reduction of the 5,6 and 13,14 double bonds. No greater selectivity was achieved by lowering the temperature. Similar results were obtained using 5% rhodium on alumina catalyst. The less active 5% palladium–barium sulfate catalyst offered more selectivity, especially when the 15 acetate, methyl ester of PGE_2 (**1**, 11α, R = CH_3, R′ = Ac) was reduced. However, hydrogenolysis of the 15 acetate was an undesirable side reaction.

The soluble Wilkinson catalyst, tristriphenylphosphine rhodium chloride,[11] was not effective in benzene solution (no hydrogen uptake) but, in a mixture of benzene and acetone,[12] PGE_2 was reduced to PGE_1 (**3**, 11α, R = R′ = H), recrystallized yield of 50%, together with lesser amounts of 13,14-dihydro-PGE_1 (**5**, 11α) and the 15-ketoprostanoic acid **4**, 11α. These latter two materials have been previously encountered[12,13] on a microscale but are here fully characterized. Acid-catalyzed dehydration of **4**, 11α gave the cyclopentenone **7**.

The observed selectivity of the 5,6 double bond over the 13,14 bond is not entirely due to the fact that one is cis and the other trans, since a similar hydrogenation of 5,6-*trans*-PGE_2[14] (**2** 11α), while a little slower than that of PGE_2, also gave PGE_1 as the predominant product.

The Wilkinson catalyst was also used to reduce the 5,6 double bond of 11β,15β-PGE_2 (**12**, 11β, R = R′ = H) and the 15 acetate methyl esters of 11β-PGE_2 (**1**, 11β, R = CH_3, R′ = Ac) and 15β-PGE_2 (**12**, 11α, R = CH_3, R′ = Ac)[15] giving, after an enzymatic hydrolysis

(1) For paper I of this series, see J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).

(2) S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *Acta Chem. Scand.*, **16**, 501 (1962).

(3) E. G. Daniels and J. E. Pike in "Prostaglandin Symposium of the Worcester Foundation for Experimental Biology," P. W. Ramwell and J. E. Shaw, Ed., Interscience, New York, N. Y., 1968, p 379.

(4) (a) W. P. Schneider, *Chem. Commun.*, 304 (1969); (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969), and later papers.

(5) (a) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *ibid.*, **94**, 2122 (1972); (b) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2123 (1972).

(6) See, for example, ref 7b and 8.

(7) (a) B. Samuelsson and G. Ställberg, *Acta Chem. Scand.*, **17**, 810 (1963); (b) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, **5**, 465 (1966); (c) J. F. Bagli and T. Bogri, *ibid.*, 5 (1967); (d) *ibid.*, 1639 (1969); (e) E. Hardegger, H. P. Schenk, and E. Borger, *Helv. Chim. Acta*, **50**, 2501 (1967); (f) R. Klok, H. J. J. Pabon, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **87**, 813 (1968); (g) P. Collins, C. J. Jung, and R. Pappo, *Israel J. Chem.*, **6**, 839 (1968); (h) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968); (i) R. B. Morin, D. O. Spry, K. L. Hauser, and R. A. Mueller, *ibid.*, 6023 (1968); (i) M. Miyano, *ibid.*, 2774 (1969); (k) Y. Yura and J. Ide, *Chem. Pharm. Bull.*, **17**, 408 (1969); (l) J. Katsube and M. Matsui, *Agr. Biol. Chem.*, **33**, 1078 (1969); (m) M. Miyano, *J. Org. Chem.*, **35**, 2314 (1970); (n) R. Klok, H. J. J. Pabon, and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **89**, 1043 (1970); (o) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971); (p) P. Crabbé and A. Guzman, *ibid.*, 115 (1972); (q) M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *ibid.*, 773 (1972).

(8) J. E. Pike, F. P. Kupiecki, and J. R., Weeks, "Prostaglandins," Nobel Symposium 2, S. Bergstrom and B. Samuelsson, Ed., Almqvist and Wiksell, Uppsala, 1967, p 169.

(9) B. Samuelsson, *J. Biol. Chem.*, **239**, 4091 (1964).

(10) Since that time, the hydrogenation of the 11,15-bistetrahydropyranyl ether of $PGF_{2\alpha}$ and the 11,15-bisdimethylisopropylsilyl ether of PGE_2 over 5% palladium/charcoal catalyst has been reported in communication form: (a) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970); (b) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971). Selectivity of reduction of the 5,6 double bond over the 13,14 one is said to be good in these sterically hindered derivatives.

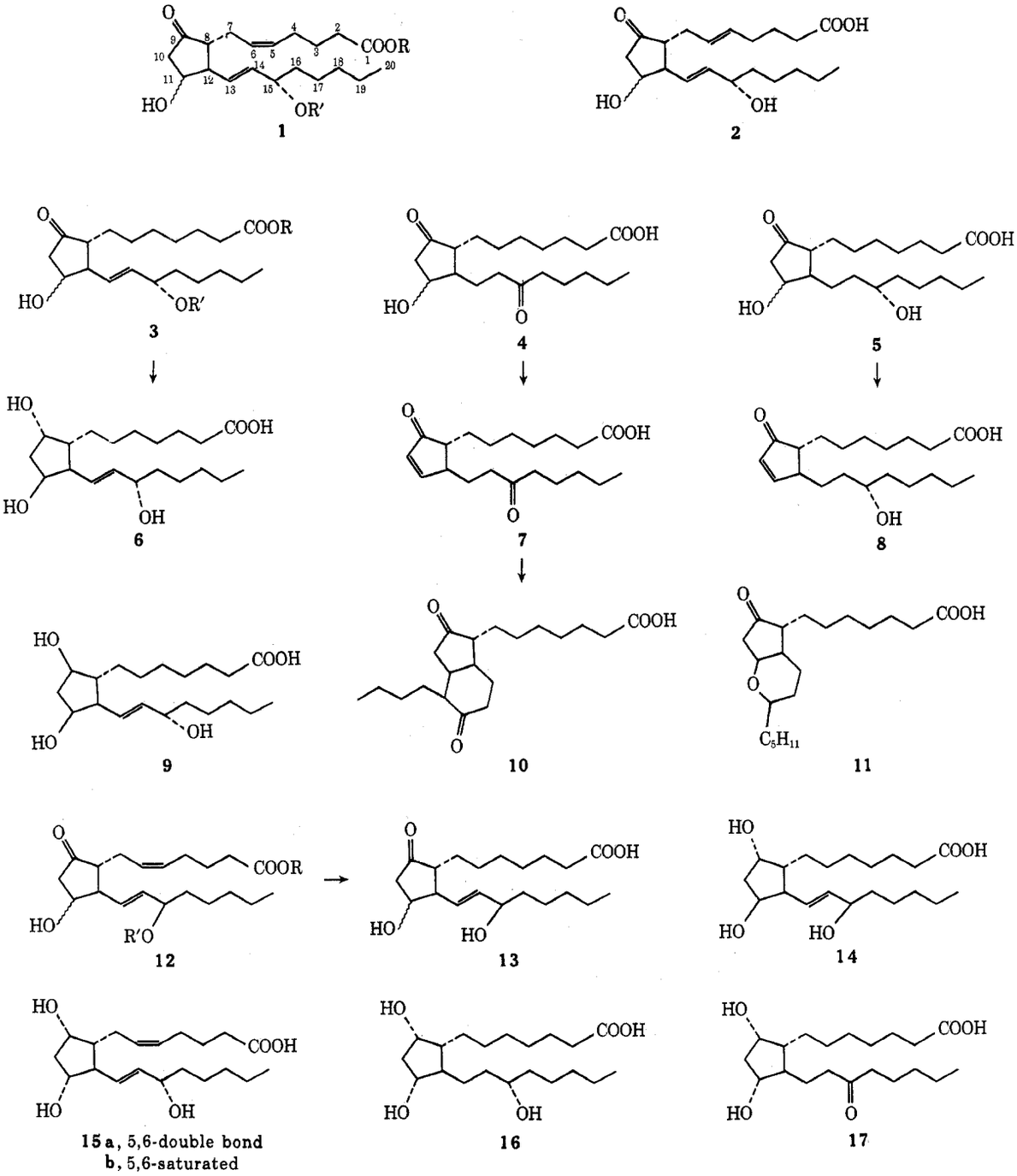
(11) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

(12) This is a procedure used by G. K. Koch and J. W. Dalenberg, *J. Label. Compounds*, VI, 395 (1970), for tritiation of PGE_2 on a microscale.

(13) E. Anggård and B. Samuelsson, *J. Biol. Chem.*, **239**, 4097 (1964).

(14) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *J. Amer. Chem. Soc.*, **94**, 2124 (1972).

(15) These materials are readily available in several steps from coral-derived prostaglandins; see ref 5b.



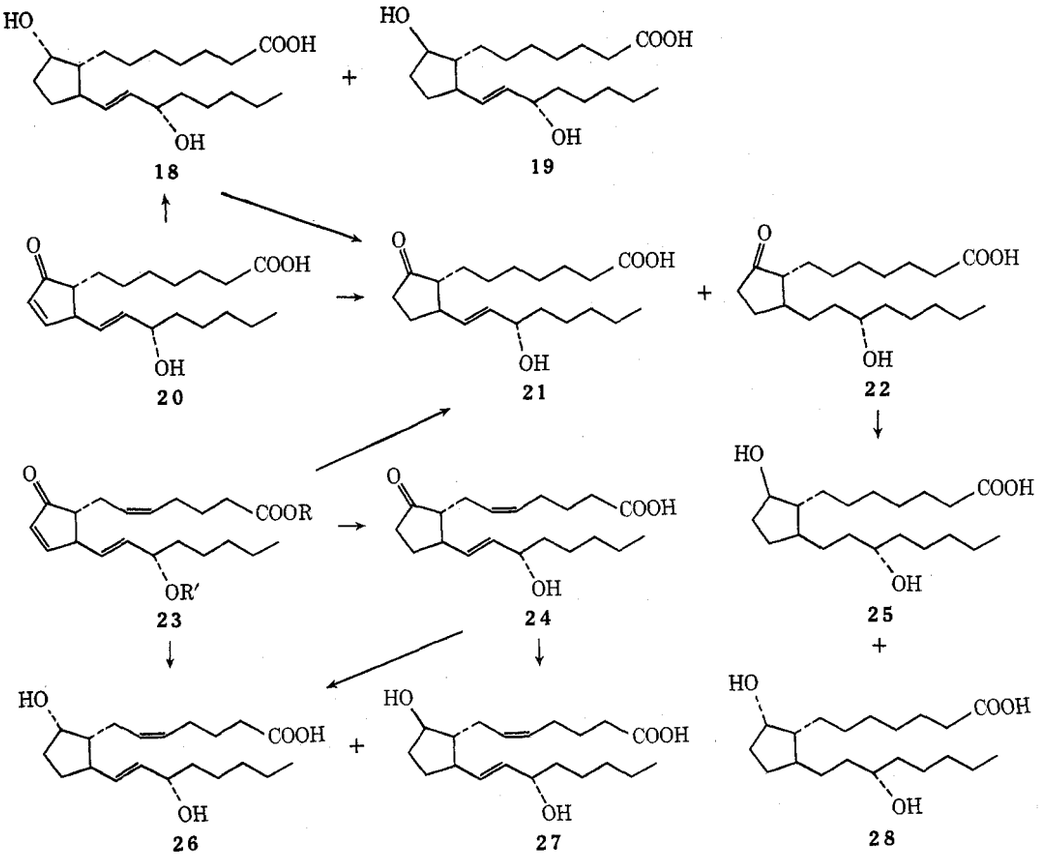
of the latter two, 11β-PGE_1 (**3**, 11β, R = R′ = H), 15β-PGE_1 (**13**, 11α), and 11β,15β-PGE_1 (**13**, 11β). The first of these products was also further reduced by sodium borohydride to give 11β-$PGF_1\alpha$ (**6**) and 11β-$PGF_1\beta$ (**9**). Both were crystalline and structural assignments were made on the basis of enhancement of thin layer or column chromatographic mobility of the 1,3-cis glycol by boric acid. This could be seen either on boric acid impregnated silica gel plates[16] or with untreated silica gel developed in a methanol–chloroform–boric acid solvent system. 11β-PGE_1 (**3**, 11β, R = R′ = H) also serves as a source of PGA_1 (**20**) by virtue of acid-catalyzed dehydration.

Strangely enough, when the above hydrogenation conditions were applied to $PGF_2\alpha$ (**15a**), no uptake of hydrogen occurred. However, substitution of ethanol for the acetone in the solvent mixture[17] allowed hydrogenation to proceed as before, giving largely $PGF_1\alpha$ (**15b**) in isolated yield of about 50%, and lesser amounts of 13,14-dihydro-$PGF_1\alpha$ (**16**) and the 15 ketone (**17**).[17]

Attempts to hydrogenate PGA_2 (**23**, R = R′ = H) to PGA_1 (**20**) under these conditions were unsuccessful. With palladium and rhodium catalysts, the 10,11 double bond was the most readily reduced, and the major products were 11-deoxy-PGE_1 (**21**), 11-deoxy-PGE_2 (**24**), and the tetrahydro derivative **22**. Minor amounts of hydrogenolysis products (15 deoxy) and 15 ketones were also produced. With the Wilkinson catalyst, no uptake of hydrogen occurred in benzene or acetone–benzene. In ethanol–benzene, hydrogenation was slow and gave 11-deoxy-PGE_1 (**21**) as the major product. The latter was also produced by palladium-

(16) L. J. Morris, *Lipids*, **1**, 41 (1966); *J. Chromatogr.*, **12**, 321 (1963).

(17) A. S. Hussey and Y. Takiuchi, *J. Org. Chem.*, **35**, 643 (1970).



catalyzed hydrogenation of PGA_1 (**20**) at $-10°$. At higher temperatures the tetrahydro compound **22**[8] predominated. This tetrahydro-PGA_1 (**22**) was further reduced with sodium borohydride to a mixture of two epimeric 9 alcohols, **25** and **28**,[8] the less polar of which (**28**) was crystalline. A racemic mixture of epimers of the methyl esters of this structure had previously been prepared by total synthesis.[7d]

11-Deoxy-PGE_2 (**24**) could also be prepared by first reducing PGA_2 acetate methyl ester (**23**, R = CH_3, R′ = Ac) with excess sodium borohydride.[18] This results in complete 1,4 reduction of the cyclopentenone system giving a mixture of two epimeric 9 alcohols, **26** and **27**, as their 15 acetate methyl esters. Oxidation of this mixture with Jones reagent[19] followed by base hydrolysis of ester groups gave 11-deoxy-PGE_2 (**24**) in about 50% yield. Sodium borohydride reduction of either PGA_1 (**20**) or 11-deoxy-PGE_1 (**21**) gave the same mixture of 11-deoxy-$PGF_1\alpha$ (**18**) and 11-deoxy-$PGF_1\beta$ (**19**), both crystalline. Structures of these and of **25** and **28** above were assigned by comparison of nmr shifts of the 9-proton signal with analogous 9 epimers and previous work.[7c,20] In the same way, 11-deoxy-$PGF_2\alpha$ (**26**) and 11-deoxy-$PGF_2\beta$ (**27**) were also prepared.

Internal additions to the cyclopentenone system occur readily when the 13,14-trans double bond has been reduced. For example, dehydration of dihydro-PGE_1 (**5**, 11α) in dilute hydrochloric acid gave a mixture of the expected 13,14-dihydro-PGA_1 (**8**) and the 11,15-cyclic ether (**11**). This was also recently observed by other workers.[21] Also, treatment of **7** or **4** with base gave the cyclized Michael product **10**.

Experimental Section[22]

A. Hydrogenations Using Homogeneous Catalysis. 1. Preparation of PGE_1 (3, 11α, R = R′ = H), 13,14-Dihydro-PGE_1 (5, 11α), and 11α-Hydroxy-9,15-diketoprostanoic Acid (4, 11α).—Prostaglandin E_2 (containing about 15% 5,6-*trans*-PGE_2[14]), 21.2 g, in 240 ml of acetone and 160 ml of benzene was purged with nitrogen and 2 g of tris(triphenylphosphine)rhodium chloride was added. This mixture was shaken under hydrogen at 20–30-psi pressure for 7 hr, when a thin layer chromatogram (tlc) (silver nitrated impregnated silica gel plate developed twice with the AIX[23] solvent system) showed the disappearance of PGE_2. Slightly more than 1 equiv of hydrogen had been consumed. The solvents were evaporated and the dark oily residue was dissolved in 200 ml of 3A alcohol and poured into 500 ml of 0.2 *M* Na_2HPO_4 buffer solution with stirring. The mixture was extracted twice with toluene, which was back-washed with a mixture of 200 ml of the same phosphate buffer and 50 ml of 3A alcohol. The combined aqueous layers were acidified to pH 3 with 2 *M* citric acid and extracted 3–4 times with ethyl acetate. The extracts were washed with saline, dried with Na_2SO_4, and evaporated to give 19.5 g of partially crystalline residue. This was dissolved in methylene chloride and chromatographed over

(18) For other 1,4 reductions of unsaturated carbonyl compounds, see, for example, S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966). 11-Deoxy-PGE_2 was first prepared in these laboratories by a longer route by Dr. N. A. Nelson.

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(20) The 9β proton of 9α-hydroxyprostaglandins is consistently observed at about δ 4.2 *vs.* 3.9 for the 9 epimer.

(21) (a) D. P. Strike and H. Smith, *Ann. N. Y. Acad. Sci.*, **180**, 91 (1971); (b) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Tetrahedron Lett.*, 4085 (1971).

(22) Ir spectra were recorded with a Perkin-Elmer Model 221 ir spectrophotometer on Nujol mulls or as neat liquids between salt plates. The nmr spectra were run on a Varian A-60A spectrophotometer using deuteriochloroform solution with tetramethylsilane as internal standard. Mass spectra were recorded on an Atlas CH-4 instrument with ionization voltage of 70 eV or on a Model LKB gas chromatograph–mass spectrograph. Uv spectra were recorded in 95% ethanol using a Carey Model 14 spectrophotometer. We are grateful to Dr. A. A. Forist and associates for much of the analytical and spectral data and to J. H. Kinner and R. A. Morge for technical assistance.

(23) M. Hamberg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

1 kg of acid-washed silica gel packed in ethyl acetate–Skellysolve B (33:67). The column was eluted with increasing concentration of ethyl acetate in Skellysolve B and finally with 5% CH_3OH in ethyl acetate. The first material eluted, 1.69 g, was largely 11α-hydroxy-9,15-diketoprostanoic acid (**4**, 11α), which was rechromatographed over 150 g of acid-washed silica gel. Elution with 50% ethyl acetate–Skellysolve B gave **4**, 11α, as a pale yellow oil: R_f 0.57 on silica gel, AIX system; $[\alpha]_D$ −9° ($CHCl_3$); ir (neat) 3430, 3240, 2660, 1735, 1705, 1160, 1070 cm^{-1}; nmr ($CDCl_3$) δ 7.65 (2 H, OH, COOH), 4.1 (1 H, broad m, C-11 proton); mass spectrum M^+ *m/e* 354 (weak), 336, 318, 219, 208, 204, 190, 109, 95.

The second material eluted was 6.6 g of largely 13,14-dihydro-PGE_1 (**5**, 11α), which was also purified by rechromatography as above to give a pale yellow oil which solidified to a waxy solid on refrigeration: R_f 0.46 (AIX); nmr ($CDCl_3$) δ 6.3 (3 H, 2 OH + COOH), 4.12 (1 H, m) and 3.65 (1 H, m, carbinolic protons).

The third material eluted consisted of 9.89 g of crystalline PGE_1 (**3**, 11α, R = R′ = H), which was recrystallized from ethyl acetate (charcoal) to give 8.05 g (38%) of nearly colorless needles, mp 110–112.5°. One further recrystallization gave mp 112.5–115°; $[\alpha]_D$ −67° (95% EtOH); equiv wt 359 (calcd 354.5); uv after base treatment 278 nm (ϵ 25,350).

2. PGE_1 15 Acetate Methyl Ester (3, 11α, R = CH_3, R′ = Ac).—In the same manner as above, 500 mg of PGE_2 15 acetate methyl ester[5b] was hydrogenated in 9 ml of acetone and 6 ml of benzene and 150 mg $(PPh_3)_3RhCl$ at 1 atm hydrogen at 25° for 2 hr. The hydrogen uptake was 28 ml (calcd for 1 equiv, 27 ml). A tlc on a $AgNO_3$-impregnated silica gel plate (50% ethyl acetate–cyclohexane) showed no starting material remaining and a major new spot slightly less polar was formed. The solvents were evaporated and the residue was chromatographed on 50 g of silica gel. Elution with 40% EtAc–Skellysolve B gave 403 mg (80%) of tlc homogeneous **3**, 11α, R = CH_3, R′ = Ac, as a nearly colorless oil: nmr (CCl_4) δ 5.5 (m, 2 H, $\Delta^{13,14}$), 5.18 (m, 1 H, CHOAc), 4.0 (m, 1 H, CHOH), 3.56 (s, 3 H, OCH_3), 1.97 (s, 3 H, Ac), 0.9 (t, terminal CH_3).

3. Prostaglandin $F_{1\alpha}$ (15b).—A solution of 1.0 g of $PGF_{2\alpha}$ (**15a**) in 30 ml of 95% ethanol and 20 ml of benzene containing 250 mg of $(PPh_3)_3RhCl$ was stirred under hydrogen at 25° (1 atm). After 4 hr, 1 equiv of H_2 had been absorbed and the rate of uptake slowed. After another hour, tlc [$AgNO_3$–silica gel, CH_3OH–HOAc–$HCCl_3$ (10:10:80)] showed only a trace of $PGF_{2\alpha}$ remaining and a heavy spot corresponding to $PGF_{1\alpha}$. The mixture was filtered through Celite and evaporated. The residue was partitioned between 5% NaOH and ether. The aqueous layer was acidified, extracted with ethyl acetate, dried, and evaporated to give 1 g of an oil which crystallized from ethyl acetate–Skellysolve B, 0.36 g, mp 88–95°. The filtrate was chromatographed on 33 g of acid-washed silica gel and elution with 5% methanol in ethyl acetate gave 0.18 g of additional $PGF_{1\alpha}$ (**15b**). Recrystallization of the combined crops gave 0.40 g (40%), mp 98–100° (reported mp 101–103°).[1]

4. 11-Deoxy-PGE_1 (21).—On one-half the scale of the preceding experiment, 0.50 g of PGA_2 (**23**, R = R′ = H) was reduced. After work-up, the crude mixture showed on tlc [silica gel, EtAc–cyclohexane–acetic acid (40:60:2)] a major spot of 11-deoxy-PGE_1 (R_f 0.43), a medium spot like PGA_2 (R_f 0.37), and two minor, less polar spots. Chromatography over 50 g of acid-washed silica gel (20–60% EtAc–Skellysolve B elution) gave 263 mg of 11-deoxy-PGE_1 which melted at 90–92° after two recrystallizations from acetone–Skellysolve B. This material had a solution ir spectrum identical with that of 11-deoxy-PGE_1 (**21**) fully characterized below (Experiment B3). The Nujol mull ir spectrum was slightly different from that of the same material obtained below and a different crystal polymorph is indicated. The other major fraction from the column, 191 mg, by nmr was a mixture of PGA_2 and PGA_1.

5. 11β-Prostaglandin E_1 (3, 11β, R = R′ = H).—A solution of 45 g of 11β-PGE_2 15 acetate methyl ester[5b] in 360 ml of acetone and 240 ml of benzene was purged with nitrogen and shaken in an atmosphere of hydrogen (30 psi) in the presence of 4.5 g of $(PPh_3)_3RhCl$ for 7 hr. At this time tlc [$AgNO_3$–silica gel, EtAc–cyclohexane (50:50) developed twice] showed no remaining starting material. The solvents were removed *in vacuo* and the dark residue was dissolved in 110 ml of ethyl acetate and diluted with 440 ml of Skellysolve B. The flocculent rhodium precipitate was removed by filtration and the filtrate was evaporated. The residue was dissolved in 50 ml of 3A ethanol and added to a rapidly stirred suspension of acetone-insoluble esterase-containing material prepared from frozen soft coral, *Plexaura homomalla*,[24] in 3 l. of water. The pH of the mixture was adjusted to 6.5–7.0 with phosphoric acid and the mixture was stirred for 24 hr, when tlc (silica gel, AIX system) showed no ester remaining. Acetone (6 l.) was added, and the mixture was stirred for 45 min longer and filtered. The filtrate and acetone wash was concentrated, acidified to pH 3 with citric acid, and extracted with methylene chloride. The washed and dried extracts were evaporated, the residue was equilibrated between phosphate buffer and toluene, and the acidic products were isolated as in the above experiment 1 to afford 39 g of partially crystalline residue. Crystallization from ether after decolorization with charcoal gave 13.3 g of 11β-PGE_1 (**3**, 11β, R = R′ = H), mp 90–92°. The remainder of the material was chromatographed on 1.5 kg of acid-washed silica gel to give (a) 7.0 g of PGA_1 (**20**); (b) 4.9 g of 11β-13,14-dihydro-PGE_1 (**5**, 11β); and (c) 6.7 g of additional 11β-PGE_1 which after recrystallization gave 4.6 g: mp 91–92° (total yield 46%); ir 3360, 2950, 2750, 2660, 1720, 1710 (sh), 1135, 1035, 1000, 980 cm^{-1}; uv (after base treatment) 278 nm (ϵ 25,850); nmr δ 5.75 (2 H, m, vinylic), 4.75 (3 H, broad, 2 OH + COOH), 4.4 (1 H, m), and 4.1 (1 H, m, carbinolic); $[\alpha]^{25}_D$ 25–21° (95% EtOH). *Anal.* Calcd for $C_{20}H_{34}O_5$: C, 67.76; H, 9.67. Found: C, 67.98; H, 9.69.

Fraction b was rechromatographed to give 2.5 g of pure 11β,-13,14-dihydro-PGE_1 (**5**, 11β): R_1 0.51 (silica gel, AIX); $[\alpha]_D$ +12° ($CHCl_3$); ir 3450, 3000, 2660, 1740, 1710, 1105, 1040 cm^{-1}; nmr ($CDCl_3$) δ 6.28 (3 H, OH + COOH), 4.36 (1 H, m, carbinolic), 3.66 (1 H, m, carbinolic); mass spectrum M^+ not observed, *m/e* 338 (M − 18), 249, 210, 192, 168, 119, 117, 96, 55.

6. (15*R*)-PGE_1 (13, 11α).—The conversion of 5.0 g of (15*R*)-PGE_2 15 acetate methyl ester[5b] to (15*R*)-PGE_1 was carried out as in experiment 5 above on a reduced scale to give 2.5 g of (15*R*)-PGE_1 (**13**, 11α) as a pale yellow oil: R_f 0.39 (silica gel, AIX system), less polar then PGE_1 (R_f 0.29); nmr δ 6.05 (3 H, 2 OH + COOH), 5.65 (2 H, m, vinylic), 4.12 and 4.0 (2 H, m, carbinolic).

7. 11β-(15*R*)-PGE_1 (13, 11β).—A solution of 1.0 g of 11β-(15*R*)-PGE_2[5b] in 30 ml of acetone and 20 ml of benzene containing 100 mg of $(PPh_3)_3RhCl$ was hydrogenated and worked up as in experiment 1 above. After chromatography the product was obtained as a pale yellow oil, R_f 0.40 (silica gel, AIX), yield 0.49 g. The material was less polar than starting material on silver nitrate impregnated silica gel (R_f 0.32 *vs.* 0.21, AIX) and the nmr spectrum now showed only two vinylic protons at δ 5.7.

B. Heterogeneous Hydrogenations. 1. Prostaglandin $F_{1\alpha}$ from $PGF_{2\alpha}$ 11,15-Bistetrahydropyranyl Ether.—A solution of 7.5 g of $PGF_{2\alpha}$ 11,15-bistetrahydropyranyl ether[25] in 215 ml of ethyl acetate containing 2.1 g of 5% Rh/Al_2O_3 catalyst was stirred in 1 atm hydrogen at 0–5° for 7.5 hr. At this time hydrogen uptake had slowed and tlc ($AgNO_3$–silica gel, AIX) showed only a trace of $PGF_{2\alpha}$ diether remaining. The mixture was filtered and evaporated, and the residue was redissolved in 250 ml of HOAc, 40 ml of tetrahydrofuran, and 125 ml of water. After being heated at 40° for 4 hr, the solution was lyophilized and the residue was chromatographed on 350 g of acid-washed silica gel. Elution with 40–100% ethyl acetate–Skellysolve B and then with 5% methanol in ethyl acetate gave 2.72 g of crystalline $PGF_{1\alpha}$ (**15b**) as the most polar product. The less polar, ether-containing materials were retreated as above to give an additional 1.57 g of $PGF_{1\alpha}$. These were combined with similar fractions from another reduction of 5.22 g of starting material and recrystallized twice from ethyl acetate–Skellysolve B to give 4.63 g (54%) of $PGF_{1\alpha}$, mp 101–102° (reported[1] mp 101–103°), $[\alpha]_D$ +28° (EtOH). *Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.31; H, 9.93.

2. $PGF_{1\alpha}$ (15b), 13,14-Dihydro-$PGF_{1\alpha}$ (16), and 9α,11α-Dihydroxy-15-ketoprostanoic Acid (17) from $PGF_{2\alpha}$ (15a).—A mixture of 3.13 g of $PGF_{2\alpha}$, 75 ml of ethyl acetate, and 0.5 g of 5% Rh/Al_2O_3 was hydrogenated as above at 10° until slightly more than 1 equiv of hydrogen had been absorbed. The mixture was filtered and evaporated, and the residue was chromatographed on 150 g of acid-washed silica gel. Elution with ethyl acetate–Skellysolve and then 5% CH_3OH in ethyl acetate gave

(24) We are indebted to Dr. E. G. Daniels of these laboratories for this esterase-containing material and the procedure for its use in hydrolyzing prostaglandin ester.

(25) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).

three fractions, the least polar, 210 mg eluted with 75% ethyl acetate, consisted of **17** as a pale yellow oil: ir 3400, 2650, 1705, 1725, 1240, 1195, 1180, 1115, 1070, 1025 cm^{-1}; nmr δ 5.6 (2 H, OH, COOH), 4.2 (1 H, m), 3.9 (1 H, m) (carbinolic protons), enhanced absorption 2.1–2.7 ($-CH_2C{=}O$); mass spectrum as tristrimethylsilyl (tris-TMS) derivative, calcd for $C_{29}H_{60}O_5Si_3$ 572.3746, found 572.3714, other major peaks at *m/e* 557, 554, 501, 482.

The second peak, eluted with ethyl acetate, contained 757 mg of 13,14-dihydro-$PGF_1\alpha$ (**16**) which crystallized on standing, and after recrystallization twice from EtAc–Skellysolve B gave mp 66–68°; ir 3370, 3210, 2700, 2580, 2560, 2570, 1695, 1135, 1080, 1020, 960, 845 cm^{-1}; $[\alpha]D$ +41° ($CHCl_3$). *Anal.* Calcd for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68. Found: C, 67.14; H, 11.15.

The third peak, 1.428 g, was crystalline $PGF_1\alpha$ (**15b**) which readily recrystallized from ethyl acetate–Skellysolve B to give material of essentially the same quality as the preceding experiment.

3. Hydrogenation of PGA_1. 11-Deoxy-PGE_1 (21) and 15α-Hydroxy-9-ketoprostanoic Acid (22).—A mixture of 1.0 g of PGA_1 and 150 mg of 5% Pd/C catalyst in 50 ml of ethyl acetate was stirred with H_2 at 1 atm and −18 to −10°. After 5 hr tlc indicated conversion to two slightly less polar spots [silica gel, EtAc–cyclohexane–HOAc (40:60:2)] and hydrogen uptake was 1.2 equiv. The crude products were chromatographed on 100 g of acid-washed silica gel. Elution with 40% ethyl acetate–Skellysolve B gave two main substances. The first, 207 mg, was predominately 15α-hydroxy-9-ketoprostanoic acid (**22**), which was further purified by rechromatography and obtained as a colorless oil: ir 3430, 3150, 2650, 1730, 1710, 1270, 1210, 1105, 725 cm^{-1}; nmr δ 6.68 (2 H, OH, COOH), 3.68 (1 H, broad, carbinolic, 0.9 (t, $-CH_3$); mass spectrum as trimethylsilyl derivative, M^+ *m/e* 484, 469, 413, 394, 384, 379, 355, 284.

The second material eluted was 11-deoxy-PGE_1 (**21**), 541 mg, which was also rechromatographed for purification and was crystallized from acetone–Skellysolve B as colorless flakes: mp 95–96°; ir 3360, 2900, 2820, 2770, 2680, 1730, 1705, 1185, 1020, 980 cm^{-1}; nmr δ 6.05 (2 H, OH, COOH), 5.6 (2 H, m, vinylic), 4.15 (1 H carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+), 320, 302, 292, 267, 249, 231; $[\alpha]D$ −51° ($CHCl_3$). *Anal.* Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.46; H, 10.58.

4. Hydrogenation of PGA_2 (23, R = R′ = H).—Hydrogenation of 4.0 g of PGA_2 as in the preceding example gave a mixture of products which on chromatography as above gave among other things 627 mg of 15α-hydroxy-9-ketoprostanoic acid (**22**) identical with that characterized above; 1.378 g of a mixture of 11-deoxy-PGE_1 (**21**), isolated by crystallization from acetone–Skellysolve B, mp 88–91°; and a small amount of 11-deoxy-PGE_2 (**24**), separated by silver nitrate impregnated silica gel chromatography and recrystallization from ethyl acetate–Skellysolve B, mp 41–43°. This is further characterized in an alternate preparation below. Less polar fractions gave evidence (ir and nmr) of hydrogenolysis of the 15-hydroxyl group and also the presence of 15-keto compounds.

11-Deoxy-PGE_2 (24).—A solution of 3.4 g of PGA_2 acetate methyl ester[5a] (**23**, R = CH_3, R′ = Ac) in 68 ml of CH_3OH at −20° was treated with an equally cold solution of 4.7 g of $NaBH_4$ in 6.8 ml of water and 61 ml of methanol, added in portions over 5 min. After a further 15 min, 4.7 ml of HOAc and 68 ml of water were added, and the mixture was concentrated and extracted with methylene chloride. The washed and dried extract was evaporated, redissolved in 170 ml of acetone, and cooled to −5°. Then 6.8 ml of Jones chromic oxide mixture[19] was added over 5 min, and after an additional 10 min 1.4 ml of isopropyl alcohol was added. Five minutes later the solution was decanted, concentrated, and extracted with methylene chloride to give 3.5 g of residue. This was chromatographed on 300 g of silica gel and eluted with 20% ethyl acetate in Skellysolve B to give 1.90 g of tlc-homogeneous 11-deoxy-PGE_2 15 acetate methyl ester. The material was treated for 1 hr under N_2 with 0.9 g of NaOH in 30 ml of methanol and 6 ml of water. After acidification and concentration, the product was isolated by methylene chloride extraction. Purification by chromatography on 170 g of acid-washed silica gel (50% ethyl acetate–Skellysolve B) gave 1.40 g of colorless **14**, R_f 0.74 (silica, AIX), which crystallized from ethyl acetate–Skellysolve B in heavy prisms: mp 42–43°; $[\alpha]D$ −54° ($CHCl_3$); ir 3360, 2710, 2650, 1725, 1275, 1185, 1020, 980 cm^{-1}; nmr δ 7.08 (2 H, OH, COOH), 5.6 (2 H, vinylic), 5.37 (2 H, m, vinylic), 4.1 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3). *Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.77.

11-Deoxy-$PGF_1\alpha$ (18) and 11-Deoxy-$PGF_1\beta$ (19).—In the same manner as the preceding experiment, 2.0 g of PGA_1 was reduced with sodium borohydride in aqueous methanol. After 20 min the solution was acidified with acetic acid, concentrated, saturated with salt, and acidified to pH 3 with citric acid. Extraction with methylene chloride gave a crude product which was chromatographed on 200 g of acid-washed silica gel. From 40% EtAc–Skellysolve eluates there was obtained 270 mg of pure less polar product (**18**), determined by tlc [silica gel, EtAc–cyclohexane–acetic acid (40:60:2)]. From 50 and 60% eluates was obtained 964 mg of mixed fractions and 435 mg of pure more polar product. The mixed fractions were rechromatographed to give 186 mg of less polar, 530 mg of more polar, and 220 mg of mixed products.

The less polar product (**18**) was crystallized from ethyl acetate–Skellysolve as colorless platelets: mp 53–55°; ir 3420–3320 (OH), 2950, 2730, 2640, 1700, 1195, 1170, 1135, 1070, 1020, 970, 955, 910, 725 cm^{-1}; nmr δ 5.48 (2 H, m, vinylic), 4.75 (3 H, 2 OH + COOH), 4.25 (1 H, m), 4.1 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum as the tris-TMS derivative, *m/e* 556 (M^+), 541, 485, 466, 451, 395, 376. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.31; H, 10.81.

The more polar product (**19**) crystallized from ether–Skellysolve B and then acetone–Skellysolve B as flakes: mp 78–79°; ir 3340, 3250, 2740, 2670, 2560, 1700, 1065, 1020, 1005, 980, 970 cm^{-1}; nmr δ 5.5 (2 H, m, vinylic), 4.93 (3 H, 2 OH + COOH), 4.1 and 3.95 (2 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum as tris-TMS derivative, *m/e* 556 (M^+), 541, 485, 466, 451, 395, 305. *Anal.* Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.33; H, 10.71.

Borohydride Reduction of 11-Deoxy-PGE_1 (21).—In the same manner as the preceding experiment, 0.15 g of 11-deoxy-PGE_1 (**21**) was reduced in methanol with 0.4 g of sodium borohydride. The reaction was run at −15° for 15 min and then dilute HCl was added and the products were isolated by ether extraction. Chromatography gave 53 mg of **18** and 73 mg of **19**, identical in tlc mobility and ir spectra with the products of the preceding experiment.

11-Deoxy-$PGF_2\alpha$ (26) and 11-Deoxy-$PGF_2\beta$ (27).—As in the preceding experiment, 0.30 g of 11-deoxy-PGE_2 (**24**) was reduced with 0.8 g of sodium borohydride in methanol. After 20 min at −15°, acetic acid was added and the products were isolated by extraction with ether after concentration and acidification with dilute HCl. Chromatography on 40 g of acid-washed silica gel and elution with 20–60% ethyl acetate–Skellysolve B gave two products. The less polar, 94 mg of colorless oil, consisted of **26**: R_f 0.67 (silica gel, AIX); ir 3380, 2640, 1710, 1235, 1135, 1030, 970 cm^{-1}; nmr δ 5.53 (4 H, m, vinylic), 5.2 (3 H, 2 OH + COOH), 4.27 and 4.13 (2 H, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+, weak), 320, 302. The more polar colorless oil, 112 mg, was the 9β-hydroxy epimer **27**: R_f 0.59; ir 3350, 2640, 1710, 1305, 1235, 1075, 1020, 970 cm^{-1}; nmr same as **26**, R = R′ = H, except the carbinolic protons overlapped at δ 4.06; mass spectrum same as that of **26**, except that no M^+ was observed.

11β-$PGF_1\alpha$ (6) and 11β-$PGF_1\beta$ (9).—In the same manner as above, 2.0 g of 11β-PGE_1 was reduced with 5.0 g of sodium borohydride in 200 ml of methanol at −10° for 20 min. The crude product isolated was crystalline and showed two materials, R_f 0.45 and 0.52 by tlc on silica gel (AIX). Chromatography on 150 g of acid-washed silica gel and elution with 2 and 4% methanol in ethyl acetate afforded a minimum separation from which 0.28 g of **9**, mp 80–93°, and 0.20 g of **6**, mp 131–133°, were crystallized from the early and late fractions, respectively. The mixed fractions and mother liquors were dissolved in a small amount of 10% methanol in chloroform and adsorbed on a column of 40 g of acid-washed silica gel. The column was eluted with the filtrate obtained by mixing chloroform with $^1/_{10}$th its volume of methanol saturated with boric acid. Eluted fractions were washed with water to remove boric acid, and then dried before evaporating. The first 100 ml of eluate contained 561 mg of the less polar isomer **9**, followed by 60 mg of mixed fractions (next 50-ml eluate) and 235 mg of more polar isomer **6** (200 ml eluate). The combined like fractions were crystallized twice from acetone–Skellysolve B to give 0.99 g of the less polar isomer as shiny leaflets, mp 63–65° (another crystalline form, mp 94–95°, was seen once), and 0.36 g of the more polari somer as

colorless granules, mp 135–136°. The former was the less polar on both silica gel and boric acid impregnated silica gel plates and the separation was enhanced on both boric acid tlc plates and on column elution with boric acid containing solvents; so the less polar isomer is assigned the cis glycol structure, 11β-PGF$_1$β (**9**), ir 3460, 3440, 3220, 2630, 2520, 1675, 1080, 1065, 1050 and 1015 cm^{-1}. *Anal.* Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.19; H, 10.08.

The more polar **6** had ir absorptions at 3270, 2710, 1750, 1130, 1120, 1085, 1025, 975 cm^{-1}. *Anal.* Found: C, 67.11; H, 10.24.

9α,15α-Dihydroxyprostanoic Acid (28) and 9β,15α-Dihydroxyprostanoic Acid (25).—A solution of 370 mg of 15α-hydroxy-9-ketoprostanoic acid (**22**) in 20 ml of isopropyl alcohol and 2 ml of water was cooled to −15° and 150 mg of sodium borohydride was added portionwise. After 25 min, tlc (silica gel, AIX) showed no starting material remaining and two new materials, R_f = 0.52 and 0.46, formed. Acetone, then 1 *N* HCl, was added, and the mixture was concentrated and extracted with ethyl acetate, giving 380 mg of crude products. These were separated by chromatography on 25 g of acid-washed silica gel, eluting with 50% ethyl acetate–Skellysolve B. The less polar isomer **28**, 138 mg, was crystalline and after two recrystallizations from ethyl acetate gave mp 89–92°; ir 3450, 2650, 2400, 1705, 1040, 1015, 960, 725 cm^{-1}; nmr δ 5.01 (3 H, 2 OH, COOH), 4.20 and 3.58 (1 H each, carbinolic), and 0.9 (3 H, t, CH_3); mass spectrum *m/e* 324 (M − 18), 306 (M − 36), 295, 280, 265, 253, 235, 208, 196, 193. *Anal.* Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.58; H, 11.31.

The more polar isomer **25**, 200 mg, was a colorless oil: ir 3400, 2700, 2600, 2350, 1705, 1220, 1155, 1050, 725 cm^{-1}; nmr δ 5.46 (3 H, 2 OH, COOH), 3.88 and 3.58 (1 H m each, carbinolic); mass spectrum *m/e* 324 (M − 18), 306 (M − 36), 265, 253, 249, 235, 208, 196, 193.

Dehydration of 11β-PGE$_1$ (3, 11β, R = R′ = H). PGA$_1$ (20).—A solution of 15.9 g of 11β-PGE$_1$ in 240 ml of tetrahydrofuran was treated under nitrogen with 160 ml of 0.5 *N* HCl at room temperature for 4 days.[26] Dilution with saturated salt and extraction with ethyl acetate gave a crude product which was purified by chromatography on 950 g of acid-washed silica gel. Elution with 30–100% ethyl acetate–Skellysolve B and 1% methanol in ethyl acetate gave 11.73 g of PGA$_1$ (**20**) and 2.03 g of recovered 11β-PGE$_1$. The PGA$_1$ fraction was crystallized from ethyl acetate–Skellysolve (1:3) to give 8.20 g of colorless crystals, mp 41–42°, and a second crop: 1.08 g; mp 40.5–41.5°; $[\alpha]_D$ +144° ($CHCl_3$); uv 217 nm (ε 10,950). *Anal.* Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.63.

Dehydration of 13,14-Dihydro-PGE$_1$ (5, 11α).—A solution of 0.50 g of 13,14-dihydro-PGE$_1$ in 10 ml of tetrahydrofuran was treated with 8 ml of 0.5 *N* HCl under nitrogen for 5 days at room temperature. Work-up as in the preceding experiment and chromatography on 50 g of acid-washed silica gel as above gave 280 mg of the cyclic compound **11**[21] as a colorless oil which solidified to a waxy mass on refrigeration: ir 2660, 1740, 1710, 1280, 1225, 1165, 1040, 735 cm^{-1}; nmr δ 8.8 (1 H, COOH), 4.35 and 3.75 (1 H each, m), 0.9 (3 H, t, CH_3); mass spectrum as the mono-TMS derivative, *m/e* 410.2821.

The next material eluted was 13,14-dihydro-PGA$_1$ (**8**), 185 mg, as a colorless oil: ir 3400, 2660, 1700, 1585, 1185, 1125, 915, 800, 735 cm^{-1}; nmr, δ 7.65 (1 H, dd, vinylic), 6.13 (1 H, dd, vinylic), 7.12 (2 H, s, OH + COOH), 3.63 (1 H, m, carbinolic), 0.9 (3 H, t, CH_3); mass spectrum *m/e* 338 (M^+), 320, 302, 277, 267, 249, 231, 210; uv 222 nm (ε 9600).

The most polar material eluted was 40 mg of recovered 13,14-dihydro-PGE$_1$.

9,15-Diketo-Δ^{10}-prostanoic Acid (7) and Its Cyclization Product 10.—During chromatographic purification of 11α-hydroxy-9,15-diketoprostanoic acid (see first experiment) a less polar fraction was obtained which consisted of its dehydration product, 9,15-diketo-Δ^{10}-prostanoic acid (**7**), as a pale yellow oil: uv 221 nm (ε 10,050); ir 3100, 2660, 1735, 1705, 1585, 1775 cm^{-1}; nmr δ 9.0 (1 H, COOH), 7.68 (1 H, dd, vinylic), 6.15 (1 H, dd vinylic), enhanced absorption between 2.1 and 2.8, and 0.9 (3 H, t, CH_3); mass spectrum as the trimethylsilyl derivative, calcd for $C_{23}H_{40}SiO_4$ 408.2695, found 408.2694, also *m/e* 393, 337, 318, 309, 208.

To a solution of the above material (0.5 g) in 25 ml of methanol under N_2 was added 4 ml of 1 *N* NaOH. After 2 hr at 25°, the solution was concentrated, acidified, and extracted with ether. An oil was obtained which showed a heavy spot on tlc [R_f 0.43, silica gel, EtAc–cyclohexane–HOAc (40:60:2)] less polar than starting material (R_f 0.34). Purification over acid-washed silica gel (30% ethyl acetate–Skellysolve B) gave a pale yellow oil (**10**): nmr δ 10.2 (1 H, COOH), enhanced absorption between 2.1 and 3.1 and 0.9 (3 H, t, CH_3). The substance gives a crystalline bisoxime: mp 84–85° from aqueous methanol; ir 3450, 3300, 1710, 1680, 960, 945 cm^{-1}. *Anal.* Calcd for $C_{20}H_{34}O_4N_2 \cdot H_2O$: C, 62.47; H, 9.44; N, 7.28. Found: C, 62.49; H, 9.68; N, 7.29.

Registry No.—11α-**1** (R = R′ = H), 363-24-6; 11α-**1** (R = CH_3, R′ = Ac), 37785-76-5; 11β-**1** (R = CH_3, R′ = Ac), 37785-77-6; 11α-**3** (R = R′ = H), 745-65-3; 11α-**3** (R = CH_3, R′ = Ac), 37785-78-7; 11β-**3** (R = R′ = H), 24570-01-2; 11α-**4**, 5094-14-4; 11α-**5**, 19313-28-1; 11β-**5**, 25140-29-8; **6**, 37818-61-4; **7**, 20721-88-4; **7** trimethylsilyl derivative, 37785-84-5; **8**, 28834-62-0; **9**, 37785-86-7; **10**, 37818-62-5; **10** bisoxime, 37785-87-8; **11**, 34389-03-2; 11α-**12** (R = CH_3, R′ = Ac), 37785-89-0; 11β-**12** (R = R′ = H), 37785-90-3; 11α-**13**, 20897-91-0; 11β-**13**, 22468-06-0; **15a**, 551-11-1; **15a** 11,15-bistetrahydropyranyl ether, 37786-09-7; **15b**, 745-62-0; **16**, 20592-20-5; **17**, 29044-75-5; **17** tris-trimethylsilyl derivative, 37785-97-0; **18**, 37785-98-1; **19**, 37785-99-2; **20**, 14152-28-4; **21**, 37786-00-8; **22**, 37786-01-9; **23** (R = R′ = H), 37503-61-0; **23** (R = CH_3, R′ = Ac), 36323-03-2; **24**, 35536-53-9; **25**, 20592-63-6; **26**, 37786-06-4; **27**, 37786-07-5; **28**, 20592-19-2.

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