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Articles

Synthesis and Biological Evaluation of 10-Oxa-11-deoxyprostaglandin E_1 and 10-Nor-9,11-secoprostaglandin F_1 and Their Derivatives

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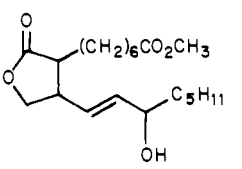
Three 10-oxa-11-deoxyprostaglandin E_1 and two 10-nor-9,11-secoprostaglandin F_1 analogues were prepared. The compounds were evaluated for pregnancy interruptions, oxytocin-like activity (uterine strip), and antiprostaglandin activity. One of the 10-nor-9,11-secoprostaglandin F_1 analogues displayed activity as a PGE_2 antagonist in the gerbil colon smooth muscle preparation.

The prostaglandins are a class of C_{20} lipids derived from arachidonic acid by enzymatic hydroxylation and cyclization. They are known to exhibit a wide spectrum of pharmacological properties.[1] In an effort to prepare prostaglandins possessing selective activity, we synthesized the 10-oxa-11-deoxyprostaglandin E_1 (**1**) and 10-nor-9,11-secoprostaglandin F_1 (**2**) analogues.[2] In this paper we describe the synthetic routes used to prepare racemic **1** and **2** and present the biological results for these compounds.

Chemistry. Analogues **1** and **2** were prepared from the readily available diethyl cyclooct-2-enylmalonate (**3a**).[3,4] Reduction of **3a** with lithium aluminum hydride gave the diol **3b**. Ozonolysis of **3b** in methanol followed by oxidation workup gave the crude hydroxy acid lactone **4a**. For purification and absolute identification purposes, compound **4a** was converted to its methyl ester and purified by chromatography to yield **4b**. Compound **4b** was homogeneous by TLC and GLC analysis (SE-30, OV-17), and its basic structure was firmly established by IR, NMR, and mass spectral analysis. Hydrolysis of **4b** back to **4a** was accomplished with no difficulty by 1 N hydrochloric acid. Spectral studies failed to establish the geometry of the substituents attached to the five-membered lactone; nevertheless, it was anticipated that this material was the more stable trans isomer since it was formed under equilibrating conditions (HCl–MeOH) and was apparently homogeneous. Chart I pictorially presents the facile interconversion of the less stable cis isomer to the more stable trans isomer under methanolysis conditions.

It is apparent that the aliphatic chain in compounds **4a** and **4b** is one methylene unit short of the desired analogue. This discrepancy could readily be overcome by using the cyclononene analogue of **3a** as starting material. Since cyclononene needed for the preparation of this analogue is not readily available, we elected the route involving chain homologation of **4a**.[5] This was accomplished by the sequence **4a** → **4c** → **4d** → **4e** → **4f** → **5a** (see the Experimental Section for details). The best procedure (78%



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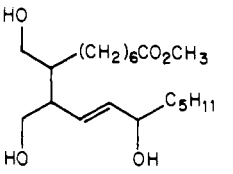

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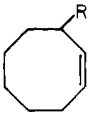
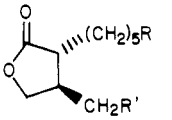
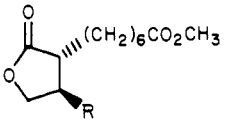


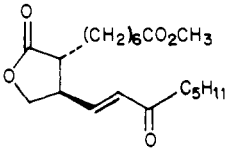
3a, R = $CH(CO_2C_2H_5)_2$
b, R = $CH(CH_2OH)_2$



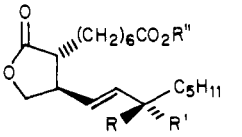
4a, R = CO_2H; R′ = OH
b, R = CO_2CH_3; R′ = OH
c, R = CO_2H; R′ = OAc
d, R = CH_2OH; R′ = OAc
e, R = CH_2OTos; R′ = OAc
f, R = CH_2CN; R′ = OAc



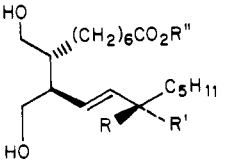
5a, R = CH_2OH
b, R = CHO



6



1a, R = OH; R′ = H; R″ = CH_3
b, R = H; R′ = OH; R″ = CH_3
c, R = OH; R′ = CH_3; R″ = CH_3
d, R = CH_3; R′ = OH; R″ = CH_3
e, R = OAc; R′ = H; R″ = H
f, R = H; R′ = OAc; R″ = H



2a, R = OH; R′ = H; R″ = CH_3
b, R = H; R′ = OH; R″ = CH_3
c, R = OAc; R′ = H; R″ = CH_3
d, R = H; R′ = OAc; R″ = CH_3

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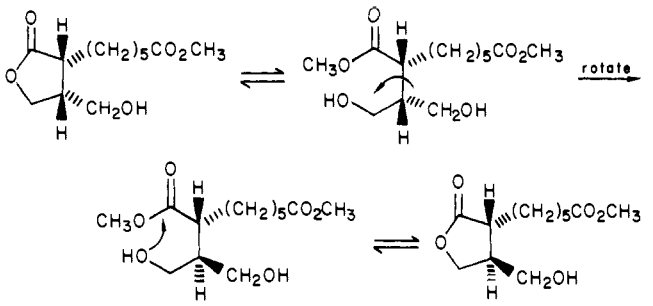
Chart I



yield) found for the oxidation of the alcohol **5a** to the aldehyde **5b** was the Collins reagent.[6] Coupling of **5b** with the sodio derivative of dimethyl 2-oxoheptylphosphonate afforded the 15-ketoprostaglandin analogue **6** in 78% yield.[7,8] The structural assignment was based on IR, NMR, and mass spectral analyses described in the Experimental Section.

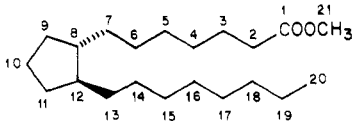
Reduction of **6** with sodium borohydride in methanol at 0 °C afforded the position-15 alcohols **1a** (less polar) and **1b** (more polar)(the structure of only one epimer in each case is shown) which were separated by column chromatography on silica gel. The isomeric nature of **1a** and **1b** is apparent from the similarity of their ^{13}C chemical shifts listed in Table I, as well as their elemental analyses and ^1H NMR chemical shifts given in the Experimental Section. The stereochemical assignments at C-15 of **1a** and **1b** are tentative and based solely on relative mobilities on TLC of natural and 15-epiprostaglandins;[9] the more polar isomer has been assigned the natural 15*S* configuration.

Treatment of **6** with methylmagnesium chloride gave the alcohol **1c** or **1d**. TLC analysis of the crude reaction mixture showed only a single spot, indicating that only one alcohol was formed. The NMR spectrum of **1c** (**1d**) showed only one singlet each for the C-15 and OCH_3 methyl groups, indicating that the methyl Grignard addition to the ketone **6** was stereoselective.

It is apparent that regioselective reduction of **1a** and **1b** with sodium borohydride would be expected to give **2a** and **2b**, respectively. However, preliminary studies indicated that both the methyl ester and C_{13} double bond underwent partial reduction under conditions strong enough to reduce the lactone ring. This difficulty could be overcome by converting **1a** and **1b** to the acid acetate derivatives **1e** and **1f**, respectively, before reduction. The major products from the reduction of **1e** and **1f** were esterified with diazomethane to give the open-chain structures **2c** and **2d**, respectively. The structure assignment of products **2c** and **2d** was confirmed by comparative integration of the acetate methyl absorption of **2c** and **2d**, as well as their triacetate derivatives against various other proton entities in the compounds. Subjection of **2c** and **2d** to mild hydrolysis with sodium methoxide gave the triols **2a** and **2b**.

Biological Results. Compounds **1a–d** and **2a,b** were evaluated for interruption of pregnancy in hamsters[10] by a slight modification of the method of Giannina and coworkers[11] and for oxytocin-like activity in vitro (hamster uterine strip) by the method of Holton[12] and were found to be inactive in both tests. The doses were 1.0 mg per animal (single subcutaneous injection of the compound dissolved in ethanol on day 3 of pregnancy using ten hamsters for each compound) for the interruption of pregnancy test and 20 μg in the oxytocin-like activity test. In addition, analogues **1c,d** and **2a,b** were tested for antiprostaglandin activity in the gerbil colon smooth muscle assay.[12] Compound **2b** was active showing 0, 14, 26, and 41% inhibition of 40 ng of PGE_2 using a gerbil colon smooth muscle preparation at dose levels of 20, 40, 80, and 125 μg/15 mL. Compound **2a** was inactive at these dose levels, and analogue **1c** or **1d** was inactive at 25 mg/15 mL, the highest level tested. Since compound **2b** showed antagonist activity and **2a** was inactive, a high order of stereoselectivity is apparent. This stereoselectivity is of interest since **2b** has an open cyclopentane ring and thus very little structural rigidity when compared to the natural prostaglandins.

Table I. Carbon-13 Chemical Shifts of 1a and 1b in $CDCl_3$[a]



Carbon[b,c]	1a	1b	Carbon[b,c]	1a	1b
1, s	174.21	174.09	12, d	45.08[e]	45.11[e]
2, t	33.82	33.80	13, d	127.20	127.62
3, t	24.55	24.63	14, d	137.20	137.18
4, *	28.89[d]	28.97[d]	15, d	71.81	71.93
5, *	28.60[d]	28.68[d]	16, t	37.14	37.17
6, t	26.16	26.25	17, t	24.84	24.92
7, *	28.46[d]	28.44[d]	18, t	31.58	31.56
8, d	44.83[e]	44.82[e]	19, t	22.46	22.44
9, s	178.30	178.28	20, q	13.88	13.86
10			21, q	51.37	51.36
11, t	70.00	69.99			

[a] Chemical shifts are in parts per million relative to tetramethylsilane. [b] Identification and multiplicity of carbon. Chemical shift assignments are based on single-frequency off-resonance decoupling and correlation to chemical shifts of prostaglandins [see G. F. Cooper and J. Fried, *Proc. Natl. Acad. Sci. U.S.A.*, 70, 1579 (1973); G. Lukacs, F. Piriou, S. D. Gero, D. A. Van Dorp, E. W. Hagaman, and E. Wenkert, *Tetrahedron Lett.*, 515 (1973)]. [c] Signal multiplicity was obtained from single-frequency off-resonance experiments: s = singlet, d = doublet, t = triplet, q = quartet, * indicates that the signals were too close together to determine multiplicity. [d,e] Assignments in vertical columns may be reversed.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope using a calibrated thermometer. IR spectra were measured with a Perkin-Elmer Model 467 grating infrared spectrophotometer. UV absorption spectra were obtained on a Cary Model 14 spectrometer. Mass spectra were determined using an Associated Electrical Industries MS-902 instrument. Gas–liquid chromatographic analysis was carried out using either Varian Model 1400 or Hewlett-Packard Model 700 instruments with columns containing 3% SE-30 on Chromosorb W and 2% OV-17 on Gaschrom G, respectively. Proton NMR spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane (Me_4Si) as an internal standard. The ^{13}C NMR spectra were determined at 24.92 MHz on a modified JEOL JNM-PS-100 FT-NMR interfaced with a Nicolet 1085 Fourier-transform computer system. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

2-(2-Cyclooctenyl)-1,3-propanediol (3b). To a stirred solution of lithium aluminum hydride (16.88 g, 0.44 mol) in ether (500 mL), under nitrogen, was added diethyl cyclooct-2-enylmalonate[4] (60 g, 0.22 mol) at such a rate as to maintain the solution at reflux. When the addition was completed, the reaction mixture was heated at reflux an additional 4 h.

Water was cautiously added to destroy the excess hydride reagent. More water (300 mL) was then added, followed by a saturated solution of tartaric acid to dissolve the alumina salts. The reaction was poured into a separatory funnel and repeatedly extracted with ether (4 × 300 mL). After drying (Na_2SO_4) and evaporation of the ether at reduced pressure, there remained a viscous oil which slowly crystallized. The crude diol was further purified by vacuum distillation to yield 34.4 g (81%) of pure diol

(**3b**): mp 44–48 °C; bp 142 °C (0.1 mm); IR ($CHCl_3$) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.9–1.9 (9 H, m, $-CH_2-$), 1.9–2.8 (3 H, m, CH, $CH_2C=$), 2.98 (2 H, s, OH) disappears with D_2O, 3.7 (4 H, m, $-CH_2O$), 5.4 (1 H, q, J = 4 Hz, =CH), and 5.85 (1 H, m, J = 4 Hz, =CH). Anal. ($C_{11}H_{20}O_2$) C, H.

2-(5-Carboxypentyl)-3-(hydroxymethyl)-γ-butyrolactone (4a). Ozone was passed into a solution of diol **3b** (20 g, 0.11 mol) in methanol (1 L) at −70 °C (dry ice–2-propanol) until the blue color of ozone persisted. The solvent was removed at reduced pressure behind a safety shield. Residual traces of methanol were then removed under high vacuum.

The crude ozonide was treated with 90% formic acid (150 mL) and hydrogen peroxide (40 mL, 30%) and then warmed gently until a vigorous reaction ensued. When the violent reaction ceased, the solution was heated at reflux an additional hour on the steam bath.

Formic acid and excess hydrogen peroxide were removed under high vacuum. The crude product was then twice taken up in methylene chloride (30 mL), diluted with benzene (300 mL), and evaporated at reduced pressure. Finally methylene chloride was evaporated from the product to give crude lactone **4a**: IR (CH_2Cl_2) 3500, 3600, 2600–3400 (OH, COOH), 1770 (lactone C=O), 1735 (CO_2R), and 1710 cm^{-1} (CO_2H). The IR deserves some comment. The acid absorption (1710 cm^{-1}) is less intense than expected; the ester absorption (1735 cm^{-1}) was unexpected and indicates that some esterification occurs during ozonolysis.

The product of the ozonolysis was dissolved in dioxane (100 mL) and aqueous hydrochloric acid (200 mL, 1 N). The solution was heated for 10 min on a steam bath and then stirred overnight at room temperature. The solution was saturated with sodium chloride and extracted with ethyl acetate (5 × 200 mL) and then chloroform (50 mL). The combined extracts were dried (Na_2SO_4) and evaporated at reduced pressure to give 24.98 g (100%) of acid lactone **4a** containing no ester: IR (CH_2Cl_2) 1760 (lactone C=O) and 1710 cm^{-1} (CO_2H). Anal. ($C_{11}H_{18}O_5$) C, H.

2-(5-Carboxypentyl)-3-(acetyloxymethyl)-γ-butyrolactone (4c). Hydroxy acid **4a** (24.98 g, 0.11 mol) was dissolved in pyridine (100 mL) and acetic anhydride (50 mL). The solution was stirred overnight at room temperature under nitrogen, then diluted with water, and stirred an additional 0.5 h. After acidification with cold hydrochloric acid (150 mL, 6 N), the solution was immediately extracted with ethyl acetate (4 × 200 mL, 2 × 100 mL). The combined extracts were dried (Na_2SO_4) and then evaporated to yield 26.49 g (90%) of **4c**: IR (CH_2Cl_2) 1760 (C=O, lactone), 1740 (CH_3CO_2), and 1710 cm^{-1} (CO_2H). Anal. ($C_{13}H_{20}O_6$) C, H.

2-(6-Hydroxyhexyl)-3-(acetyloxymethyl)-γ-butyrolactone (4d). The acetate **4c** (5.05 g, 0.19 mol) was dissolved in freshly distilled tetrahydrofuran (125 mL) with stirring and placed under a nitrogen atmosphere. The solution was cooled to 0 °C, and diborane (21 mL, 1 M BH_3, 21 mmol) was added by syringe. During the initial addition of diborane, considerable foaming due to the evolution of hydrogen occurred. After completing the addition of diborane, the reaction was stirred for 10 min at 0 °C. Water (5 mL) was added to destroy the excess diborane, and the tetrahydrofuran was then removed at reduced pressure. The resultant residue was taken up in water (20 mL) and saturated bicarbonate solution (20 mL) and extracted with ethyl acetate (4 × 100 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure. The resulting viscous oil (4.32 g, 89%) was chromatographed (silica gel, 8–18% acetone–chloroform) to yield 2.45 g (50%) of pure **4d**: IR (CH_2Cl_2) 3600 (OH), 1770 (lactone, C=O), and 1740 cm^{-1} (CH_3CO_2). Anal. ($C_{13}H_{22}O_5$) C, H.

2-(6-Cyanohexyl)-3-(acetyloxymethyl)-γ-butyrolactone (4f). Alcohol **4d** (2.95 g, 0.011 mol) was dissolved in pyridine (55 mL) with stirring, and the solution, under nitrogen, was cooled to 0 °C. *p*-Toluenesulfonyl chloride (5.89 g, 0.031 mol, 2.7 equiv) was added, and stirring at 0 °C was continued until solution was achieved. The reaction was allowed to stand in the refrigerator (~10 °C) for 20 h. After diluting with cold water (100 mL), the aqueous solution was extracted with ether (3 × 100 mL). The combined ether extracts were washed with cold dilute hydrochloric acid and then water until neutral. The ester solution was dried ($MgSO_4$) and evaporated at reduced pressure to yield 3.63 g of **4e** (77%): IR (CH_2Cl_2) 1775 (lactone, C=O), 1745 (CH_3CO_2), 1180 and 1190 cm^{-1} (SO_2PhCH_3).

The tosylate (3.63 g, 0.009 mol) was dissolved in dimethyl sulfoxide (36 mL) and placed under a nitrogen atmosphere. Sodium cyanide (1.02 g, 0.021 mol) was added, and the solution was stirred for 2 days. After dilution with water (36 mL), the reaction was extracted with chloroform (3 × 80 mL). The combined extracts were backwashed with water (50 mL), dried ($MgSO_4$), and evaporated to give an oil. The remaining traces of dimethyl sulfoxide were removed to give 2.70 g of crude product: IR (CH_2Cl_2) 2260 cm^{-1} (C≡N). The analytical sample of **4f** was prepared by preparative thin-layer chromatography (silica gel, 10% EtOAc–CH_2Cl_2). Anal. ($C_{14}H_{21}O_4N$) C, H, N.

2-(6-Carbomethoxyhexyl)-3-(hydroxymethyl)-γ-butyrolactone (5a). The nitrile **4f** (23.40 g, 0.088 mol) was dissolved in dioxane (120 mL), and a solution of sodium hydroxide (38.92 g) in water (780 mL) was added. Several drops of hydrogen peroxide (30%, catalytic amount) was added to the solution, and the reaction was heated on a steam bath for 10 h. When the evolution of ammonia had ceased, the solution was cooled to room temperature and acidified to pH 1 with 12 N HCl. The solution was saturated with NaCl and extracted with ethyl acetate (3 × 200 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure, giving 20.73 g (97%) of 2-(6-carboxyhexyl)-3-(hydroxymethyl)-γ-butyrolactone as an oil: IR (CH_2Cl_2) 3600 (alcohol OH), 3600–3000 (acid OH), 1775 (lactone C=O), and 1710 cm^{-1} (acid carbonyl).

A 14.8-g (0.061 mol) sample of the acid was dissolved in methanol (500 mL), and gaseous hydrogen chloride was bubbled through the solution for 5 min. The solution was allowed to stand at room temperature for 2 h. The solvent was removed at reduced pressure, and the procedure was repeated. The solvent was again removed at reduced pressure to give 14.2 g of crude product. The ester was chromatographed (silica gel, 250 g; 5–12% acetone–chloroform) to give 11.5 g (74%) of the methyl ester **5a**: IR (CH_2Cl_2) 3600 (alcohol), 1775 (lactone, carbonyl), 1740 cm^{-1} (methyl ester carbonyl); NMR ($CDCl_3$) δ 2.1–2.8 (13 H, m, $-CH_2-$ and >CH–), 3.67 (3 H, s, CH_3O), 3.92 (2 H, q, J = 7 Hz, γ-H lactone), and 4.41 (2 H, q, J = 7 Hz, CH_2OH). Anal. ($C_{13}H_{22}O_5$) C, H.

2-(Carbomethoxyhexyl)-3-formyl-γ-butyrolactone (5b). To a stirred solution of pyridine (7.6 mL, 94 mmol) in methylene chloride (115 mL) was added chromium trioxide (4.71 g, 0.047 mol). A drying tube was placed on the flask, and the reaction was stirred for 15 min. A solution of the alcohol **5a** (1.74 g, 0.007 mol) in methylene chloride (10 mL) was added dropwise to the reaction giving a black tarry precipitate. The reaction was stirred an additional 15 min. The solution was then decanted from the precipitate, and the precipitate was washed with methylene chloride (60 mL). The combined organic solutions were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. The methylene chloride solution was dried (Na_2SO_4), and the solvent was removed at reduced pressure to yield crude aldehyde. The crude product was chromatographed (silica gel, 100 g; 8–18% acetone–chloroform) to give 1.37 g (79%) of aldehyde **5b**: IR (CH_2Cl_2) 2730 (aldehyde hydrogen), 1770 (lactone carbonyl), and 1735 cm^{-1} (methyl ester and aldehyde carbonyl); NMR ($CDCl_3$) δ 9.71 (1 H, d, J = 1 Hz, CHO). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.45; H, 7.87. Found: C, 61.52; H, 8.76.

***dl*-Methyl 9,15-Dioxo-10-oxa-13-*trans*-prostenoate (6).** Dimethyl (2-oxoheptyl)phosphonate (904.6 mg, 4.1 mmol) was dissolved in dry tetrahydrofuran (35 mL), and sodium hydride (172.5 mg, 4.1 mmol, 57% dispersion) was added under a nitrogen atmosphere with stirring. When the foaming ceased, a solution of aldehyde **5b** (1.03 g, 0.004 mol) in dry tetrahydrofuran (25 mL) was added dropwise. The reaction was allowed to stir at room temperature for 2.5 h. The solvent was then removed at reduced pressure. The oily residue was dissolved in ether (100 mL) and washed with water (3 × 50 mL). The ether solution was dried (Na_2SO_4), and the solvent was removed at reduced pressure to give 1.54 g of crude product. The material was chromatographed on a 1-in. Chromatronix pressure column (silica gel, 120 g; CH_2Cl_2, 10% EtOAc–CH_2Cl_2, 1 L) to give 1.09 g (78%) of ketone adduct **6**: IR (CS_2) 1790 (lactone C=O), 1740 (ester C=O), 1701, 1690 (α,β-unsaturated C=O), and 1640 cm^{-1} (olefin); λ_{max}^{EtOH} 224 nm (ϵ ~10 000); NMR ($CDCl_3$) δ 0.82 (3 H, t, J = 6 Hz, CH_2CH_3), 1.1–1.9 [16 H, m (br), CH_2 of aliphatic chain], 2.23 (2 H, t, J = 7 Hz, $CH_2CO_2CH_3$), 2.25–2.46 (1 H, m, CHCH=CH), 2.48 (2 H,

t, J = 7 Hz, $COCH_2$), 3.0 (1 H, p, J = 10 Hz, $COCHR_2$), 3.58 (3 H, s, CO_2CH_3), 3.91 [1 H, t (ABX), J = 9 Hz, γ-H lactone], 4.35 [1 H, t (ABX), J = 9 Hz, γ-H lactone], 6.22 [1 H, d (AB), J = 16 Hz, CH=CHCOR], and 6.68 [1 H, q (ABX), J = 8 Hz, CH=CHCO]. Anal. ($C_{20}H_{32}O_5$) C, H.

***dl*-Methyl 15-Hydroxy-10-oxa-9-oxo-13-*trans*-prostenoates (1a and 1b).** To a stirred solution of the ketone **6** (415 mg, 1.2 mmol) in methanol (12.5 mL) at 0 °C was added sodium borohydride (45 mg, excess). The reaction was stirred for 15 min at 0 °C; then citrate buffer (pH 4) was added until a pH of 4 was obtained. The solvent was removed at reduced pressure, and the residue was dissolved in ether and washed with aqueous HCl (1 N) and water. The ether solution was dried (Na_2SO_4), and the solvent was removed at reduced pressure to give 508 mg of crude product which was a two-component mixture by TLC (20% EtOAc–CH_2Cl_2). The crude material was chromatographed on a 1-in. Chromatronix pressure column (silica gel, 120 g; 5–20% EtOAc–CH_2Cl_2, 1 L each) to give 217.1 mg (42%) of **1a** (higher R_f isomer) and 175.9 mg (35%) of 1b (lower R_f isomer); the IR (CH_2Cl_2) of both isomers were essentially identical and showed absorption at 3600 (OH), 1770 (lactone carbonyl), 1735 (methyl ester carbonyl), and 1600 cm^{-1} (C=C).

Isomer 1a: NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6 Hz, CH_3CH_2–), 1.1–2.1 [16 H, m (br), CH_2 of aliphatic chains], 2.31 (2 H, t, $CH_2CO_2CH_3$), 2.7–3.1 (1 H, m, CHCH=CH–), 3.65 (3 H, s, CO_2CH_3), 3.86 (1 H, t, J = 9 Hz, γ-H lactone), 4.16 (1 H, m, CH=CHCHOH), 4.33 (2 H, t, J = 9 Hz, γ-H lactone), 5.3–5.86 [2 H, m, CHCH=CHCH(OH)]. Anal. ($C_{20}H_{34}O_5$) C, H.

Isomer 1b: NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6 Hz, CH_3CH_2–), 1.1–1.9 [16 H, m (br), CH_2 of aliphatic chain], 2.30 (2 H, t, $CH_2CO_2CH_3$), 2.7–3.1 (1 H, m, –CHCH=CH–), 3.64 (3 H, s, CO_2CH_3), 3.86 (1 H, t, J = 9 Hz, γ-H lactone), 4.12 [1 H, m, CH=CHCH(OH)], 4.34 (2 H, t, J = 8 Hz, γ-H lactone), 5.36–5.84 [2 H, m, CHCH=CHCH(OH)]. Anal. ($C_{20}H_{34}O_5$) C, H.

***dl*-Methyl 15-Hydroxy-10-oxa-9-oxo-13-*trans*-15-methylprostenoate (1c or 1d).** To a stirring solution of the ketone **6** (205.3 mg, 0.58 mmol) in ether (10 mL) at −70 °C was added methylmagnesium chloride (1.16 mmol, 2 equiv) in ether. Stirring was continued for 30 min at −70 °C, and then water and ammonium chloride were added to destroy any excess Grignard reagent. The solution was diluted with ether (50 mL) and washed with water (2 × 50 mL). The ether solution was dried (Na_2SO_4), and the solvent was removed at reduced pressure to give an oil. The crude product was purified by preparative thin-layer chromatography (silica gel, 20 × 20 cm; 5% acetone–$CHCl_3$) to give 123.9 mg (58%) of the *dl*-15-methyl-15-hydroxy analogue 1c (1d): IR (CH_2Cl_2) 3600 (OH, alcohol) 1775 (lactone carbonyl), and 1740 cm^{-1} (methyl ester carbonyl); NMR ($CDCl_3$) δ 0.88 (3 H, t, CH_2CH_3), 1.1–1.9 (m, br, CH_2 of aliphatic chain), 1.26 [3 H, s, >C(OH)CH_3], 1.76 (1 H, s, OH, exchangeable with D_2O), 2.32 (3 H, m, $CH_2CO_2CH_3$ and α-H of lactone), 2.88 (1 H, m, β-H lactone), 3.65 (3 H, s, CO_2CH_3), 3.85 [1 H, t (ABX), J = 9 Hz, γ-H lactone], 4.34 [1 H, t (ABX), J = 9 Hz, γ-H lactone), 5.31 [1 H, q (ABX), J_{AB} = 15 Hz, J_{AX} = 7 Hz, >CHCH=CH–], and 5.76 (1 H, d, J_{BA} = 15 Hz, –CHCH=CH–). Anal. ($C_{21}H_{33}O_5$) C, H.

Methyl 10-Nor-9,11-seco-9,11,15-trihydroxy-13-*trans*-prostenoate (2a). The methyl 15-hydroxyprostenoate **1a** (50 mg, 0.14 mmol) was dissolved in methanol (3.5 mL), and potassium hydroxide solution (0.21 mL, 20%) was added with stirring. The reaction was stirred for 20 h and then neutralized (pH 7) with 1 N HCl solution. The methanol was removed at reduced pressure; the oily residue was acidified to pH 1 and extracted with ether (200 mL). The ether solution was extracted with saturated sodium bicarbonate (2 × 75 mL). The combined bicarbonate extracts were acidified to pH 1 and extracted with ether (3 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give 44.4 mg (92%) of 15-hydroxy-9-oxo-10-oxa-13-*trans*-prostenoic acid: IR (CH_2Cl_2) 3600 (alcohol OH), 3500 (br acid OH), 1770 (lactone carbonyl), and 1710 cm^{-1} (acid carbonyl).

The acid was dissolved in a mixture of pyridine (1 mL) and acetic anhydride (0.5 mL). The reaction was allowed to stand overnight protected from moisture with a drying tube. Water (1 mL) was then added, and the solution was poured over ice (15 g) and cold 6 N HCl (10 mL). The aqueous mixture was extracted repeatedly with ether. The combined extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure giving 44.2 mg (89%) of the acetate **1e**: IR (CH_2Cl_2) 3500 (acid OH), 1770 (lactone carbonyl), 1740 (acetate carbonyl), and 1710 cm^{-1} (acid carbonyl).

Compound **1e** (44.2 mg, 0.12 mmol) was dissolved in tetrahydrofuran (20 mL), and water (5 mL) and sodium borohydride (50 mg, excess) were added with stirring. Stirring was continued for 20 h. The solution was then acidified to pH 3 with aqueous HCl (1 N), and the solvents were removed at reduced pressure. The resultant residue was diluted with water, acidified to pH 1, and extracted with ether. The combined ether extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure giving a clear oil. The crude acid was dissolved in benzene (5 mL), and a solution of diazomethane in benzene (excess) was added until a yellow color persisted. A small amount of acetic acid (0.5 mL) was added to quench the diazomethane, and the solvent was removed at reduced pressure to give 51 mg of an oil. The oil was chromatographed on a 0.5-in. Chromatronix pressure column (silica gel, 30 g; 0–40% EtOAc–CH_2Cl_2) to give 13.1 mg (27%) of the diol analogue **2c**: IR (CH_2Cl_2) 3600 (alcohol OH) and 1740 cm^{-1} (methyl ester, acetate, carbonyls); NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7 Hz, CH_2CH_3), 1.30 [2 H, OH (br) (exchangeable with D_2O)], 2.04 (3 H, s, O_2CCH_3), 2.32 (2 H, t, $CH_2CH_2CO_2CH_3$), 3.42–3.9 (4 H, m, $-CH_2OH$), 3.67 (3 H, s, CO_2CH_3), 5.18 [1 H, m, CH=CH_2CH(OAc)R], and 5.58 (2 H, m, –CH=CH–).

A methanol solution (40 mL) containing a catalytic amount of sodium methoxide was added to 35 mg (0.09 mmol) of the 15-acetoxy diol analogue **2c** (obtained from combined preparations of **2c**) in methanol (5 mL) under nitrogen. The reaction mixture was stirred overnight and then acidified with acetic acid (pH 3), and the solvent was removed at reduced pressure. The residue was dissolved in ether and washed with water to neutrality. The ether solution was dried (Na_2SO_4), and the solvent was removed at reduced pressure giving 29.5 mg (83%) of **2a** as white solid: IR (CH_2Cl_2) 3600 (alcohol OH) and 1740 cm^{-1} (methyl ester carbonyl); NMR (3 H, 0.89, t, CH_2CH_3), 1.06–3.0 [CH_2 of aliphatic chain (br)], 2.31 (2 H, t, $CH_2CO_2CH_3$), 2.1–2.8 (2 H, br s, OH), 3.66 (3 H, s, CO_2CH_3), 3.4–3.9 (4 H, m, CH_2OH), 4.12 [1 H, m, CH=CHCH(OH)R], and 5.62 (2 H, m, –CH=CH–). Anal. ($C_{20}H_{38}O_5$) C, H.

Methyl 10-Nor-9,11-seco-9,11,15-trihydroxy-13-*trans*-prostenoate (2b). The title compound was prepared in 27% overall yield from **1b** by a procedure analogous to that described for the preparation of **2a**. The spectral properties of **2b** and the intermediates are listed below.

15-Hydroxy-10-oxa-9-oxo-13-*trans*-prostenoic acid: IR (CH_2Cl_2) 3600 (OH), 3200–3500 (CO_2H), 1700 (lactone carbonyl), and 1710 cm^{-1} (acid carbonyl).

15-Acetoxy-10-oxa-9-oxo-13-*trans*-prostenoic acid (1f): IR (CH_2Cl_2) 3500 (OH), 1700 (lactone carbonyl), 1735 (acetate carbonyl), and 1710 cm^{-1} (acid carbonyl).

Methyl 10-nor-9,11-seco-15-acetoxy-9,11-dihydroxy-13-*trans*-prostenoate (2d): IR (CH_2Cl_2) 3600 (alcohol OH) and 1740 cm^{-1} (methyl ester and acetate carbonyls); NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 7 Hz, CH_2CH_3, 1.1–1.8 (broad peak, aliphatic CH_2–), 2.02 (3 H, s, CH_3CO), 2.30 (2 H, t, $-CH_2CO_2CH_3$), 2.65 [2 H, s (br), OH], 3.42–3.9 (4 H, m, CH_2OH), 3.65 (3 H, s, CH_3O), 5.14 [1 H, m, CH=CHCH(OH)R], and 5.54 (2 H, m, –CH=CH–).

Methyl 10-nor-9,11-seco-9,11,15-trihydroxy-13-*trans*-prostenoate (2b): IR (CH_2Cl_2) 3600 (alcohol OH) and 1740 cm^{-1} (methyl ester carbonyl); NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7 Hz, $-CH_2CH_3$), 1.1–1.9 [m (br), aliphatic CH_2–], 2.31 (2 H, t, $-CH_2CO_2CH_3$), 2.52 [2 H, s (br), OH], 3.64 (3 H, s, CO_2CH_3), 3.4–3.9 (4 H, m, $-CH_2OH$), 4.06 [1 H, m, CH=CHCH(OH)R], and 5.58 (2 H, m, –CH=CH–). Anal. ($C_{20}H_{38}O_5$) C, H.

Biological Procedure. Interruption of Pregnancy Test. The interruption of pregnancy test[10] was carried out as described by Giannina and co-workers[11] with the exception that one male per female was used instead of one male per three females. Ten hamsters were used for each compound. The compounds were dissolved in ethanol, and a single dose of 1 mg per hamster of each compound was administered subcutaneously on day 3 of pregnancy. $PGF_{2\alpha}$ showed 100% interruption of pregnancy at a dose of 12.5 μg per hamster.

Oxytocin-Like Activity. This assay[10] was carried out as

described by Holton[12] with the exception that hamsters were used in place of rats.

Antiprostaglandin Activity in Smooth Muscle Assay. The assay[10] was carried out using the following method of Holton.[12] Male gerbils were used in place of rats. Thirty seconds after introduction of the test compound to the chamber containing the gerbil colon, 40 ng of PGE_2 was added to the chamber. Ninety seconds were allowed for the substance to act, and a 5-min interval was allowed between each test. PGE_2 (40 ng) alone was applied in the beginning two to three times and in the end of the experiment. The mean value obtained was used to calculate the percent inhibition obtained with the test compounds.

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