C-12 Substituted Prostaglandins: Synthesis and Biological Evaluation of (±)-12-Hydroxyprostaglandin $F_{2\alpha}$ Methyl Ester

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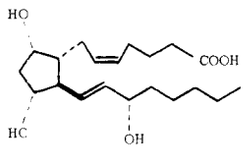
The synthesis of (±)-12-hydroxyprostaglandin $F_{2\alpha}$ methyl ester (**5**) and (±)-15-*epi*-12-hydroxyprostaglandin $F_{2\alpha}$ methyl ester (**35**) along with the corresponding 11,12-*O*-isopropylidene derivatives **33** and **34** is detailed starting from the known bromo ester **6**. Prostaglandins **5, 33, 34,** and **35** have been evaluated for pregnancy interruption in the hamster and smooth muscle stimulating effects on gerbil colon and hamster uterine strips.

Since the observation that prostaglandin $F_{2\alpha}$ (**1**) has a luteolytic action in a variety of laboratory and farm animals,[1] derivatives of natural $PGF_{2\alpha}$ possessing luteolytic activity in animals have been reported.[2] Our efforts in this area have been primarily concerned with finding prostaglandin derivatives which possess luteolytic properties with no undesirable effects (e.g., nausea, vomiting, diarrhea). We have been involved in the synthesis and biological evaluation of C-12 substituted derivatives of natural $PGF_{2\alpha}$ in order to investigate the effect on luteolytic activity. Our early work centered on the preparation of (±)-12-methyl-$PGF_{2\alpha}$ (**2**).[3] More recently we have described the synthesis of (±)-12-fluoro-$PGF_{2\alpha}$ methyl ester (**3**)[4] and (±)-12-hydroxymethyl-$PGF_{2\alpha}$ methyl ester (**4**).[5] We



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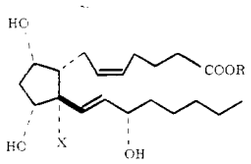
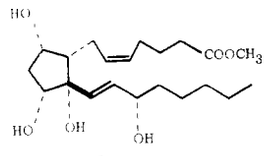


2 X = CH_3, R = H
3 X = F, R = CH_3
4 X = CH_2OH, R = CH_3

detail below the synthesis of (±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester (**5**) and present the preliminary biological data.



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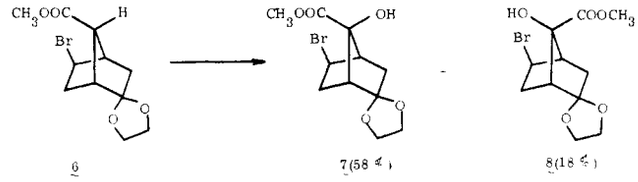
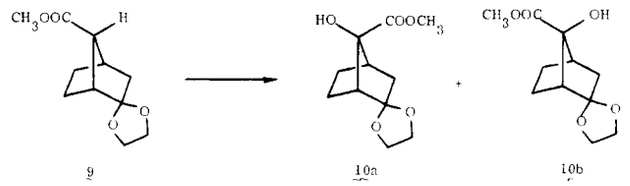
The previously described bicyclo[2.2.1]heptane derivative **6**, mp 74–75 °C, which had been employed in the synthesis of the C-12 methyl, fluoro, and hydroxymethyl derivatives,[3-6] was subjected to α-hydroxylation.[7] Treatment in tetrahydrofuran of the enolate derived from ester **6** with oxygen at low temperature provided in 76% yield a 3:1 mixture of the two crystalline hydroxy esters **7** (mp 102 °C) and **8** (mp 126 °C), respectively, along with recovered starting material (17%). In contrast, the corresponding bicyclo[2.2.1]heptane **9** upon α-hydroxylation afforded a 4:1 mixture of α-hydroxy esters **10a** and **10b**, respectively.[8] The presence of the bulky *exo*-2-bromo substituent in compound **6** is undoubtedly responsible for the observed predominance of hydroxy ester **7** during α-hydroxylation of ester **6**.

The anti relationship between the 7-hydroxy group and the *exo*-2-bromo substituent in compound **7** was based primarily

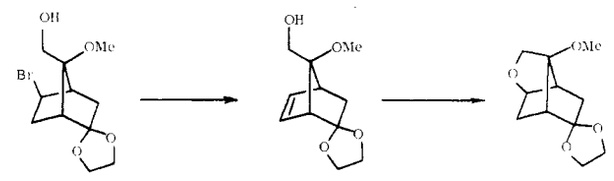


6 **7** (58 %) **8** (18 %)



9 **10a** **10b**

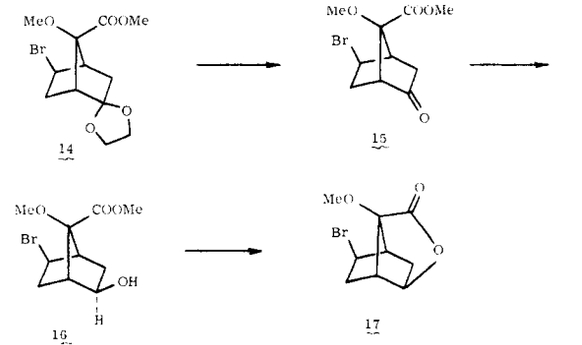
(vide infra) on two sets of experiments. The lower melting isomer (**7**) was methylated (sodium hydride, tetrahydrofuran, methyl iodide, room temperature, 13 h) and reduced (90% overall) in refluxing anhydrous ether with lithium aluminum hydride. The resulting bromo alcohol **11** was dehydrobrominated (80%) with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing toluene providing the bicyclo[2.2.1]heptene **12.**



11 **12** **13**

Oxymercuration–demercuration[9] [a, mercuric acetate (1.0 equiv), tetrahydrofuran–water (1:1), 25 °C; b, sodium hydroxide, sodium borohydride] gave cyclic ether **13** (83%) whose spectral data were in complete agreement with the assigned structure.

In a second series of experiments the higher melting hydroxy ester **8** was methylated (94%) [sodium hydride, tetrahydrofuran, methyl iodide, room temperature, 21 h] giving rise to methyl ether **14.** Hydrolysis [acetic acid–water (1:1), 95 °C, 3 h] of the ketal function provided (90%) keto ester **15** [IR ($CHCl_3$) 1760, 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.08 (q, 1 H, J = 5 Hz, 8 Hz, –CHBr), 3.81 (s, 3 H, $-COOCH_3$), 3.40 (s, 3 H,



14 **15** **16** **17**

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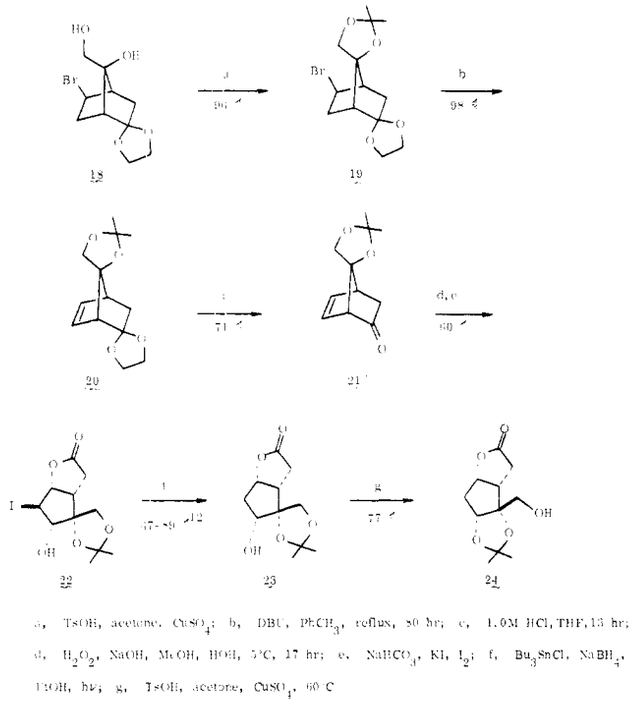
Scheme I



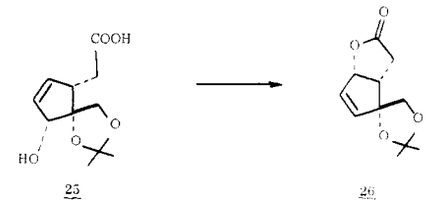
a, TsOH, acetone, $CuSO_4$; b, DBU, $PhCH_3$, reflux, 30 hr; c, 1.0 M HCl, THF, 13 hr; d, H_2O_2, NaOH, MeOH, H_2O, 5°C, 17 hr; e, $NaHCO_3$, KI, I_2; f, Bu_3SnCl, $NaBH_4$, EtOH, hν; g, TsOH, acetone, $CuSO_4$, 60°C

OCH_3)]. Reduction of bicyclo[2.2.1]heptanone **15** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at 0 °C gave (85%) the exo alcohol **16** [IR ($CHCl_3$) 3615, 3500, 1735] which upon treatment with *p*-toluenesulfonic acid in refluxing benzene (1 h) gave exclusively in near quantitative yield γ-lactone **17** [IR ($CHCl_3$) 1790 cm^{-1}; NMR ($CDCl_3$) δ 4.44 (t, 1 H, J = 3 Hz, –CHO–), 4.17 (t, 1 H, J = 5 Hz, –CHBr), 3.60 (s, 3 H, $-OCH_3$)].

Having established the structures of the two α-hydroxy esters **7** (vide infra) and **8**, we proceeded with conversion of **7** into the key cyclopentanoid intermediate **24** (Scheme I) which possesses the necessary functionality for elaboration of the α and ω side chains. Reduction of ester **7** with lithium aluminum hydride in refluxing tetrahydrofuran provided diol **18**, mp 84.5–86.0 °C. Treatment of crystalline diol **18** with anhydrous *p*-toluenesulfonic acid in acetone containing anhydrous copper sulfate gave rise to a 96% yield of crystalline acetonide **19**,[10] mp 103.0–103.5 °C, as evidenced by the presence of a six-proton singlet (broad) located at δ 1.42 and an AB quartet (J = 9 Hz, $\Delta\nu_{AB}$ = 15.6 Hz) centered at 4.22 in the NMR spectrum. Dehydrobromination was carried out utilizing DBU in refluxing toluene in near quantitative yield giving rise to the crystalline bicyclo[2.2.1]heptene **20**, mp 33.0–34.5 °C. The NMR spectrum clearly revealed the presence of a two-proton multiplet at δ 6.29, indicative of the olefinic protons. Selective hydrolysis of the ketal function in compound **20** was achieved in 71% yield with 1.0 M hydrochloric acid in tetrahydrofuran. The acetonide moiety was reasonably stable to the reaction conditions for short periods of time; however, prolonged treatment with acid resulted in cleavage of the acetonide as well.

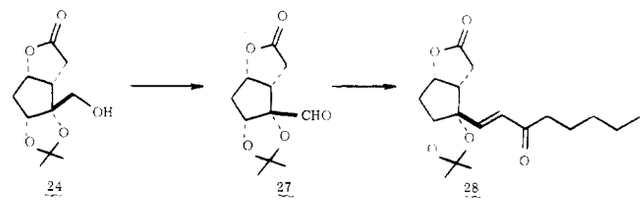
Baeyer-Villiger oxidation of ketone **21** followed by iodolactonization gave in ca. 60% overall yield the crystalline iodo lactone **22**, mp 133.5–134.5 °C. The above two-step sequence was necessary due to the sensitive nature of the Baeyer-Villiger product **25** which cyclized upon standing to the bicyclic lactone **26**. Deiodination employing the recently described procedure by Corey and Suggs[11] furnished the bicyclic acetonide **23**, mp 129.0–129.5 °C, in varying yields.[12]

Of critical importance to the success of our scheme was the ability at some point in the synthesis to transform **23** into the corresponding acetonide **24**. We were gratified to find that



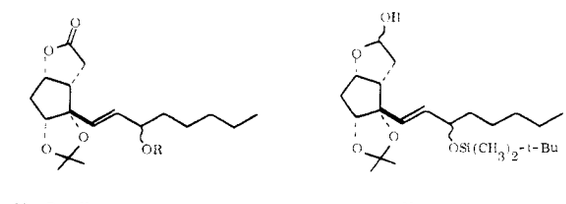
treatment of a solution of acetonide **23** in acetone with anhydrous *p*-toluenesulfonic acid in the presence of anhydrous copper sulfate at 55 °C gave, as evidenced by TLC analysis, a single product (ca. 80%) which was not starting material. The spectral data are completely consistent with the assigned structure **24**. The smooth transformation of **23** into acetonide **24** further supports the α configuration of the hydroxyl group at C-12 (prostaglandin numbering).

It was anticipated that once alcohol **24** was in hand the completion of the synthesis of 12-hydroxy-$PGF_{2\alpha}$ methyl ester would proceed in a straightforward manner (cf. **24** → **28**). It



was assumed that standard prostaglandin methodology[13] for elaboration of the α and ω side chains could be utilized. Indeed this was a reasonable assumption based on the vast amount of data that has now accumulated in the literature. Our assumption proved to be incorrect. Oxidation of alcohol **24** with Collins reagent[14] followed by treatment of the intermediate aldehyde **27** with the sodio derivative of dimethyl (2-oxoheptyl)phosphonate[15] gave only disappointingly low yields (0–10% overall) of enone **28**. Use of pyridinium chlorochromate,[16] *N*-chlorosuccinimide–dimethyl sulfide,[17] dimethyl sulfoxide–chlorine,[18] dimethyl sulfoxide–sulfur trioxide–pyridine,[19] dimethyl sulfoxide–acetic anhydride,[20] and dimethyl sulfoxide–dicyclohexylcarbodiimide–pyridinium trifluoroacetate[21] also gave discouraging results. Fortunately, utilization of a Moffatt-Pfitzner oxidation (Me_2SO–DCC)[22] in the presence of dichloroacetic acid[21,23] followed by a nonaqueous workup gave in 82% yield aldehyde **27** which after purification was condensed (tetrahydrofuran, 0 °C, 1 h) with the standard phosphonate carbanion giving rise to the crystalline product **28**, mp 89–90 °C, in 88% yield. Analysis of the infrared spectrum of enone **28** revealed absorptions at 1780, 1698, 1680, and 1632 cm^{-1}. Further support for the structure came from the NMR spectrum which displayed an AB quartet centered at δ 6.58 (J = 15 Hz), highly characteristic of a trans-enone system possessing no γ hydrogens.

Reduction of enone **28** gave in near quantitative yield alcohol **29** which was directly protected as its *tert*-butyldimethyl



29 R = H
30 R = $Si(CH_3)_2$-t-Bu

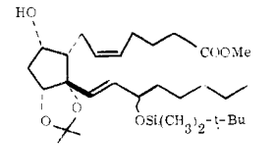
31

silyl ether.[24] Intermediate **32** was prepared from lactone **30** employing the standard sequence of reactions:[13] (a) reduction with diisobutylaluminum hydride, (b) Wittig reaction, and (c) esterification. Cleavage of silyl ether **32** with tetra-*n*-butylammonium fluoride gave in 76% yield a 1:1 mixture of

Table I. Smooth Muscle Data[28]

	registry no.	gerbil colon contraction[a] (in vitro)	hamster uterine contraction[a] (in vitro)
(±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester	67237-12-1	0.004	0.023
(±)-15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester	67237-13-2	0.001	0.004
(±)-acetonide **33**	67237-14-3	0.0005	0.0005
(±)-acetonide **34**	67237-15-4	0.0005	0.0005

[a] $PGF_{2\alpha}$ = 1.



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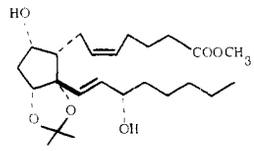

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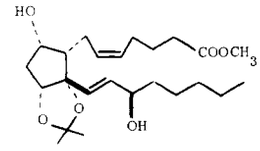

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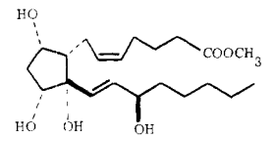

35

acetonides **33** and **34** which were separated. Cleavage of the acetonide unit in both **33** and **34** with methanol containing *p*-toluenesulfonic acid gave in only modest yield (±)-12-hydroxy-$PGF_{2\alpha}$ methyl ester **5** and (±)-15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester **35**.[25]

Preliminary results obtained with acetonide **33** and the corresponding C-15 epimer **34** indicate that both compounds are ineffective in terminating pregnancy in hamsters when dosed (125 μg/hamster) subcutaneously on day five of pregnancy.[26] Similar results were encountered with racemic 15-*epi*-12-hydroxy-$PGF_{2\alpha}$ methyl ester **35** at a dose level of 25 μg/hamster. In sharp contrast, racemic 12-hydroxy-$PGF_{2\alpha}$ methyl ester **5** gave 100% inhibition of pregnancy in the hamster at a subcutaneous dose level of 25 μg/hamster. Experiments are presently underway to determine the minimum effective dose of (±)-**5** to terminate pregnancy in hamsters. Our initial data indicate that the enantiomerically pure 12-hydroxy-$PGF_{2\alpha}$ methyl ester is at least as potent as natural $PGF_{2\alpha}$.[26]

Testing of these compounds in both the gerbil colon and hamster uterine strip smooth muscle assays revealed (Table I) that they are only very weakly effective. For example, the compound of interest, (±)-**5**, possessed only 2.3% the potency of natural $PGF_{2\alpha}$ in the hamster uterine strip assay and 0.4% the potency of $PGF_{2\alpha}$ in the isolated gerbil colon assay. Of significant interest is the dissociation in compound **5** of smooth muscle stimulating activity from antifertility (luteolytic) activity.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded on a 60-MHz (Varian A-60A or T-60) spectrometer or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

Methyl (1α,4α,5α,7*R)-5-Bromo-7-hydroxyspiro[bicyclo-[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-carboxylate (7).** A solution of bromo ester **6** (9.52 g, 32.7 mmol) in 40 mL of dry tetrahydrofuran was added over 30 min to a cooled (−78 °C) solution of lithium diisopropylamide, prepared from 5.09 g (50.4 mmol) of diisopropylamine in 130 mL of anhydrous tetrahydrofuran and 31.5 mL (50.4 mmol) of *n*-butyllithium (1.6 M in hexane) at −78 °C. After approximately 90 min, oxygen was gently bubbled into the reaction mixture at −78 °C. After an additional 20 min the temperature was raised to 0 °C at which time oxygen was passed into the reaction mixture for an additional 2 h. The reaction was quenched with 35 mL of a 20% aqueous solution of sodium sulfite. The reaction mixture was concentrated in vacuo and treated with saturated brine solution. The product was extracted with ethyl acetate (4 × 70 mL), and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 11.37 g of a clear oil which was chromatographed on 450 g of silica gel. Elution with hexane–ether (1:1) gave in order of elution 1.64 g (17%) of starting bromo ester **6**, 1.71 g (18%) of hydroxy ester **8**, mp 126 °C, and 5.52 g (58%) of hydroxy ester **7**, mp 102 °C: IR ($CHCl_3$) 3500, 3050, 2950, 2895, 1740, 1450, 1440, 1330, 1264, 1106, 1058, 1040, 950 cm^{-1}; NMR ($CDCl_3$) δ 4.17–3.80 (m, 5 H), 3.84 (s, 3 H, $-COOCH_3$), 2.85–2.25 (m, 5 H), 1.72 (d, 1 H, J = 14 Hz, 3-endo proton). An analytical sample was prepared by recrystallization from hexane–chloroform. Anal. Calcd for $C_{11}H_{15}BrO_5$: C, 43.01; H, 4.92. Found: C, 42.72; H, 4.78.

(1α,4α,5α,7*R)-5-Bromo-7-hydroxy-7-hydroxymethylbicyclo-[2.2.1]heptane-2,2′-[1,3]dioxolane (18).** To a stirred suspension of 1.80 g (47.3 mmol) of lithium aluminum hydride in 120 mL of anhydrous tetrahydrofuran cooled to 0 °C was slowly added 5.06 g (16.5 mmol) of bromo ester **7** in 65 mL of dry tetrahydrofuran. Upon completion of the addition, the reaction was heated to reflux. After 2 h, the reaction mixture was cooled to 0 °C and quenched with 90 mL of wet ether, followed by careful addition of water (15 mL). The reaction mixture was dried ($MgSO_4$) and filtered. The precipitate was washed exhaustively with ethyl acetate. The combined organic layers were concentrated in vacuo under high vacuum, yielding 4.43 g (96%) of diol **18** as a white solid, mp 82–83 °C. Recrystallization from ether–pentane gave analytically pure diol: mp 84.5–86.0 °C; IR ($CHCl_3$) 3525, 3000, 2895, 1380, 1332, 1120, 1100, 1054, 1020, 1000, 948, 896 cm^{-1}; NMR ($CDCl_3$) δ 4.4–3.6 (m, 7 H), 3.0–2.5 (m, 6 H); mass spectrum *m/e* (rel intensity) 263 (8), 262 (15, $M^+ - H_2O$), 261 (9), 260 (14, $M^+ - H_2O$), 249 (11), 247 (10), 199 (38), 181 (76), 180 (24), 163 (12), 145 (20), 137 (100), 136 (44), 93 (16), 91 (25), 87 (25), 86 (46). Anal. Calcd for $C_{10}H_{15}BrO_4$: C, 43.02; H, 5.42. Found: C, 43.20; H, 5.28.

(1α,4α,5α,7*R)-5-Bromo-2″, 2″-dimethylspiro[bicyclo[2.2.1]-heptane-2,2′-[1,3]dioxolane]-7,4″-[1,3]dioxolane (19).** To a stirred solution of 7.01 g (25.1 mmol) of crystalline diol 18 in 250 mL of acetone was added 8.14 g (51.2 mmol) of anhydrous copper sulfate and a catalytic amount of anhydrous *p*-toluenesulfonic acid. After 12 h at room temperature, the reaction mixture was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent in vacuo gave 7.73 g (96%) of acetonide **19** as a solid, mp 98–99 °C. Recrystallization of **19** from ether–pentane gave analytically pure acetonide: mp 103.0–103.5 °C; IR ($CHCl_3$) 2996, 2950, 2880, 1384, 1372, 1336, 1244, 1160, 1115, 1090, 1070, 1060, 862 cm^{-1}; NMR ($CDCl_3$) δ 4.22 (ABq, 2 H, J = 9 Hz, $\Delta\nu$ = 15.6 Hz, $-CH_2OC(Me)_2-$), 4.1–3.6 (m, 5 H), 2.9–1.7 (m, 6 H), 1.42 (s, 6 H); mass spectrum *m/e* (rel intensity) 305 (22, $M^+ - CH_3$), 303 (22, $M^+ - CH_3$), 261 (23), 239 (43), 238 (16), 182 (100), 125 (35). Anal. Calcd for $C_{13}H_{19}BrO_4$: C, 48.92; H, 6.00. Found: C, 49.04; H, 6.12.

(1α,4α,7*S)-2″,2″-Dimethylspiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]-dioxolane]-7,4″-[1,3]dioxolane (20).** A solution of 8.71 g (27.3 mmol) of acetonide **19** and 81.0 g (533 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 300 mL of toluene was heated at reflux for

80 h. The reaction mixture was concentrated under reduced pressure and the resulting crude product was dissolved in ethyl acetate. The organic layer was washed repeatedly with cold 1% hydrochloric acid until the aqueous layer was clear. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated under high-vacuum pump, yielding 5.54 g (98%) of olefin **20** as a light-yellow solid. An analytical sample of **20**, mp 33.0–33.5 °C, was prepared by column chromatography on silica gel using hexane–ether (1:1): IR ($CHCl_3$) 3075, 3000, 2955, 2885, 1475, 1455, 1430, 1380, 1370, 1330, 1310, 1165, 1150, 1105, 1075, 1060, 1040, 1009, 966, 948, 905, 878, 860, 835 cm^{-1}; NMR ($CDCl_3$) δ 6.29 (m, 2 H, –CH=CH–), 4.10–3.80 (m, 6 H), 2.82–2.55 (m, 2 H), 2.32 (dd, 1 H, J = 12 Hz, 4 H, 3-exo proton), 1.62 (d, 1 H, J = 12 Hz, 3-endo proton), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 238 (3, M^+), 223 (4, $M^+ - CH_3$), 180 (9), 162 (10), 91 (10), 86 (100), 79 (11), 66 (19), 44 (27), 43 (20). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.37; H, 7.65.

(1α,4α,7S*)-2′,2′-Dimethylspiro[bicyclo[2.2.1]hept-5-ene-7,4′-[1,3]dioxolan]-2-one (21). A solution of 3.49 g (14.7 mmol) of ketal **20** in 250 mL of tetrahydrofuran was cooled to 0 °C and treated with 40 mL of 1 M hydrochloric acid. The reaction was warmed to room temperature and stirring was continued for 13 h. The reaction mixture was neutralized with 2 N sodium hydroxide solution and the product was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated, and evaporated in vacuo leaving 2.72 g of a yellow oil which was purified on 260 g of silica gel. Elution with hexane–ether (3:2) gave 2.02 (71%) of pure crystalline ketone: mp 52.5–53.0 °C; IR ($CHCl_3$) 2990, 2940, 2875, 1742, 1391, 1374, 1252, 1225, 1201, 1098, 1075, 1060, 1041, 862 cm^{-1}; NMR ($CDCl_3$) δ 6.51 (m, 1 H, –C=CH), 6.06 (m, 1 H, –C=CH), 4.15 (s, 2 H, $-OCH_2-$), 3.00 (m, 2 H), 2.45 (dd, 1 H, J = 16 Hz, 4 Hz, 3-exo proton), 2.00 (d, 1 H, J = 16 Hz, 3-endo proton), 1.28 (s, 6 H); mass spectrum m/e (rel intensity) 194 (1, M^+), 179 (24, $M^+ - CH_3$), 137 (34), 136 (100), 108 (67), 95 (31), 94 (86), 92 (20), 91 (26), 66 (27), 59 (12). An analytical sample was prepared by recrystallization from cold hexane. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.06; H, 7.27. Found: C, 67.96; H, 7.41.

(3aβ,4α,5α,6β,6aβ)-Tetrahydro-5-hydroxy-6-iodo-2′,2′-dimethylspiro[4*H*-cyclopenta[*b*]furan-4,4′-[1,3]-dioxolan]-2(3*H*)-one (22). To a solution of 1.02 g (5.27 mmol) of ketone **21** in 22.5 mL of methanol and 1.4 mL of water cooled in an ice–water bath was added 16.7 mL (41.8 mmol) of 10% aqueous sodium hydroxide solution, followed by the slow dropwise addition of 5.03 mL (74.0 mmol) of 50% aqueous hydrogen peroxide. After stirring at ca. 5 °C for 17 h the reaction was quenched by the addition of sodium thiosulfate. The reaction mixture was concentrated in vacuo and acidified to pH 5.5 with 2 M hydrochloric acid. The aqueous layer was extracted exhaustively with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure leaving 1.17 g (97%) of crude hydroxy acid **25** which was not purified further, but used directly in the next reaction.

To a solution of 1.30 g (15.5 mmol) of sodium bicarbonate in 18.5 mL of water cooled in an ice–water bath was added 1.17 g (5.11 mmol) of hydroxy acid **25** (from above), and a solution of 5.07 g (30.6 mmol) of potassium iodide and 2.58 g (10.2 mmol) of iodine in 13 mL of water. The reaction was quenched after 48 h at 5 °C with sodium thiosulfate. The aqueous layer was saturated with sodium chloride and was extracted with ethyl acetate (6 × 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo yielding 1.56 g of a white solid. The iodolactone was purified on 200 g of silica gel. Elution with hexane–ethyl acetate (2:3) gave 1.19 g (66%) (60% overall from ketone **21**) of pure iodolactone as a crystalline substance. Recrystallization from ether gave analytically pure iodolactone **22**: mp 133.5–134.5 °C; IR ($CHCl_3$) 3560, 3000, 2950, 2880, 1790, 1390, 1379, 1163, 1140, 1116, 1066, 1060, 1030, 1000, 982, 910, 895, 871, 855 cm^{-1}; NMR ($CDCl_3$) δ 5.1 (m, 1 H), 4.3–3.9 (m, 4 H), 3.2–2.4 (m, 4 H), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 327 (16, $M^+ - OH$), 227 (13, $M^+ - I$), 154 (100), 127 (52), 97 (55), 84 (11), 68 (40), 59 (45), 57 (23), 55 (19), 44 (98). Anal. Calcd for $C_{11}H_{15}IO_5$: C, 37.31; H, 4.27. Found: C, 37.51; H, 4.31.

(3aα,4β,5β,6aα)-Tetrahydro-5-hydroxy-2′2′-dimethylspiro[4*H*-cyclopenta[*b*]furan-4,4′-[1,3]dioxolan]-2[3*H*]-one (23). A solution of 1.21 g (3.42 mmol) of iodolactone **22** in 40 mL of absolute ethanol cooled to 0 °C was treated with 0.32 mL (1.18 mmol) of tri-*n*-butyltin chloride and 0.17 g (4.50 mmol) of sodium borohydride. The solution was irradiated with a sunlamp for 15 min. After an additional 20 min the reaction was quenched with oxalic acid and the product was extracted with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 1.08 g of an oil which was purified by column chromatography using 40 g of silica gel. Elution with hexane–ethyl acetate (1:2) yielded 368 mg (47%) of crystalline hydroxy lactone **23**: mp 129.0–129.5 °C; IR ($CHCl_3$) 3580, 3030, 2998, 2948, 2880, 1772, 1390, 1380, 1306, 1255, 1230, 1184, 1155, 1118, 1090, 1065, 1030, 982, 864 cm^{-1}; NMR ($CDCl_3$) δ 4.95 (m, 1 H, –CHOCO), 4.01–3.70 (m, 3 H, $-CH_2O$, –CHOH), 2.87–2.65 (m, 3 H), 2.30–2.01 (m, 3 H), 1.45 (s, 6 H); mass spectrum m/e (rel intensity) 213 (100, M^+ – Me), 172 (11), 153 (15), 142 (12), 98 (17), 59 (10). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.90; H, 7.18.

(3aα,4aα,7aα,7bα)-Hexahydro-7b-(hydroxymethyl)-2,2′-dimethyl-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (24). To a stirred solution of 682 mg (2.99 mmol) of spiroacetonide **23** in 40 mL of acetone was added 690 mg (4.33 mmol) of anhydrous copper sulfate and four crystals of *p*-toluenesulfonic acid. After a total of 13 h at 60 °C, the reaction mixture was diluted with ethyl acetate and filtered. Removal of the solvent afforded 791 mg of a light-brown oil. The product was purified on 40 g of silica gel. Elution with hexane–ethyl acetate (1:5) provided 525 mg (77%) of pure alcohol **24** as a clear oil: IR ($CHCl_3$) 3600, 3500, 3030, 3010, 2990, 2940, 2875, 1770, 1460, 1421, 1415, 1390, 1380, 1370, 1355, 1334, 1301, 1240, 1198, 1170, 1148, 1120, 1090, 1040, 1020, 996, 970, 960, 900 cm^{-1}; NMR ($CDCl_3$) δ 5.02 (t, 1 H, J = 5 Hz, –CHOCO), 4.67 (d, 1 H, J = 5 Hz, –CHO-C), 3.66 (s, 2 H, $-CH_2OH$), 3.10 (s broad, 1 H, OH), 3.00–2.00 (m, 5 H), 1.45 (s, 3 H), 1.40 (s, 3 H); mass spectrum m/e (rel intensity) 213 (100, M^+ – Me), 197 (6), 171 (5), 135 (4), 107 (3), 59 (3), 58 (10), 43 (10). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.81; H, 7.20.

[3aα,4aα,7aα,7bα(*E*)]-Hexahydro-2,2-dimethyl-7b-(3-oxo-1-octenyl)-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (28). To a solution of 328 mg (1.44 mmol) of alcohol **24** in 12 mL of dry dimethyl sulfoxide was added 978 mg (4.75 mmol) of *N,N′*-dicyclohexylcarbodiimide and 75 μL (0.91 mmol) of dichloroacetic acid. The reaction was stirred at room temperature for 20 h. The reaction was diluted with methylene chloride and the precipitated urea was removed by filtration. The filtrate was concentrated in vacuo and the residue was once again washed with methylene chloride and filtered. This procedure was repeated several times. The product was purified by column chromatography on 50 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 268 mg (82%) of pure aldehyde **27** which was used directly in the next reaction.

To a stirred suspension of 62 mg (1.29 mmol) of 50% sodium hydride dispersion in 15 mL of anhydrous tetrahydrofuran cooled to 0 °C under nitrogen was added dropwise a solution of 350 mg (1.58 mmol) of dimethyl (2-oxoheptylphosphonate in 5 mL of dry tetrahydrofuran. Upon completion of the addition, the reaction was warmed to 25 °C (1 h). The phosphonate anion was cooled to 0 °C and treated with a solution of 254 mg (1.12 mmol) of aldehyde **27** in 2 mL of dry tetrahydrofuran. The reaction was quenched at 0 °C after 1 h with saturated aqueous ammonium chloride solution. The product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product (474 mg) was purified on 50 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 318 mg (88%) of pure crystalline enone **28**: mp 89–90 °C: IR ($CHCl_3$) 1780, 1698, 1680, 1632 cm^{-1}; NMR ($CDCl_3$) δ 6.58 (ABq, 2 H, J = 15 Hz, $\Delta\nu_{AB}$ = 23.6 Hz, –CH=CH), 4.95 (t, 1 H, J = 5 Hz, –CHOCO), 4.60 (d, 1 H, J = 5 Hz, $-CHOC(CH_3)_2$), 1.47 (s, 3 H), 1.29 (s, 3 H), 0.88 (t, 3 H); mass spectrum m/e (rel intensity) 307 (60, M^+ – Me), 265 (29), 205 (9), 193 (25), 167 (15), 165 (11), 164 (12), 121 (10), 107 (15), 99 (97), 95 (10), 91 (11), 81 (15), 79 (12), 71 (29), 69 (15), 60 (17), 56 (15), 55 (45), 44 (35), 43 (100). A sample was prepared by recrystallization from hexane–ether, mp 90–91 °C. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.10; H, 8.08. Found: C, 67.36; H, 8.22.

[3aα,4aα,7aα,7bα(*E*)]-Hexahydro-2,2-dimethyl-7b-[3(*RS*)-*tert*-butyldimethylsilyloxy-1-octenyl]-6*H*-furo[3′,2′:3,4]cyclopenta[1,2-*d*]-1,3-dioxol-6-one (30). Sodium borohydride (139 mg, 3.7 mmol) was added to a solution of 590 mg (1.8 mmol) of trans-enone **28** in 15 mL of 95% ethanol cooled to −10 °C. The reaction was quenched at −10 °C after 1 h with 60% aqueous acetic acid and neutralized with solid sodium bicarbonate. The solvent was concentrated under reduced pressure and the residue was taken up in water (5 mL). The product was isolated by extraction with ether (3 × 100 mL). The combined ethereal extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The crude product was subjected to column chromatography on 30 g of silica gel prior to silylation. Elution with ether–ethyl acetate (10:1) gave 592 mg (96%) of alcohol **29** as a colorless oil which was a mixture of epimers at C-15. Alcohol **29** was used directly in the next reaction.

A solution of the above alcohol (592 mg, 1.8 mmol) in 4.8 mL of dry dimethyl formamide was treated at room temperature with 554 mg (3.6 mmol) of *tert*-butyldimethylsilyl chloride and 245 mg (3.6 mmol) of imidazole. After 2 h the reaction mixture was diluted with benzene

and washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. The crude product was purified on 40 g of neutral silica gel (SilicAR CC-7). Elution with hexane–ether (1:1) gave 680 mg (86%) of pure silyl ether **30** as a colorless solid: IR (CCl_4) 2960, 2940, 2900, 2855, 1795, 1695, 1472, 1460, 1415, 1385, 1375, 1362, 1350, 1340, 1328, 1295, 1260, 1215, 1192, 1155, 1090, 1060, 1044, 1009, 990, 974, 954, 940, 895, 876, 838 cm^{-1}; NMR (CCl_4) δ 5.72 (m, 2 H), 4.80 (t, broad, 1 H, J = 5 Hz), 4.44 (d, broad), 1 H, J = 6 Hz), 4.15 (m, 1 H), 1.41 (s, 3 H), 1.24 (s, 3 H), 0.90 (s, 9 H), 0.00 (s, 6 H).

Wittig Reaction on Lactol 31. To a solution of 145 mg (0.33 mmol) of lactone **30** in 5 mL of dry toluene cooled to −78 °C under nitrogen was added dropwise via syringe 0.71 mL (0.99 mmol) of a 20% solution of diisobutylaluminum hydride in toluene. The reaction was quenched at −78 °C after 30 min by the careful dropwise addition of methanol. The reaction was diluted with 40 mL of ether and was warmed to room temperature. Water (0.5 mL) was added and stirring was continued for 40 min, followed by direct drying over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo provided 136 mg of hemiacetal **31** which was used directly in the next reaction.

A suspension of 313 mg (6.27 mmol) of 50% sodium hydride dispersion (washed with hexane prior to use) in 3.0 mL of freshly distilled dimethyl sulfoxide was heated at 75 °C for 1 h under nitrogen. To the above solution cooled to room temperature was added 1.46 g (3.3 mmol) of (4-carboxybutyl)triphenyl phosphonium bromide in 4.0 mL of dry dimethyl sulfoxide. A 4.0-mL aliquot of the dark-red ylid solution was added to a solution of 136 mg of hemiacetal **31** in 1.0 mL of dry dimethyl sulfoxide. After 18 h at 25 °C, the reaction mixture was heated at 60 °C for 20 min. The reaction was quenched by the addition of 10 mL of ice–water and carefully acidified to pH 5 with 0.5 N sodium hydrogen sulfate. The product was isolated by extraction with ether (4 × 150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The yellow residue was esterified with ethereal diazomethane. The crude product was chromatographed on 20 g of silica gel. Elution with hexane–ether (1:1) gave 85 mg (48% overall yield from 30) of hydroxy ester **32** as a colorless oil: IR (CCl_4) 3555, 2990, 2950, 2930, 2855, 1740, 1460, 1439, 1385, 1375, 1365, 1258, 1217, 1175, 1060 cm^{-1}; NMR ($CDCl_3$) 5.60 (m, 2 H), 5.38 (m, 2 H), 4.41 (m, 1 H), 4.10 (m, 2 H), 3.61 (s, 3 H), 1.47 (s, 3 H), 1.25 (s, 3 H), 0.87 (s, 9 H).

(±)-12-Hydroxy-PGF$_{2\alpha}$-(11,12-*O*-isopropylidene) Methyl Ester (33). A solution of 50 mg (0.09 mmol) of silyl ether **32** in 3.0 mL of tetrahydrofuran was treated at 25 °C for 4 h with 70 mg (0.27 mmol) of tetra-*n*-butylammonium fluoride. The reaction mixture was diluted with 50 mL of ether and washed with a saturated solution of sodium bicarbonate. The ether layer was dried over anhydrous magnesium sulfate and evaporated, leaving 35 mg of crude product as a mixture of epimers at C-15 which was purified on 15 g of silica gel. Elution with ether–ethyl acetate (10:1) gave 29 mg (76%) of a colorless oil. The product (20 mg) was separated into the C-15 α and β epimers 33 (more polar) and 34 (less polar) on 10 g of silica gel using benzene–ethyl acetate (3:1). There was obtained in order of elution, 5 mg of pure **34**, a mixture (10 mg) of **33** and **34**, and 3 mg of pure **33**: IR ($CHCl_3$) 3540, 3005, 2960, 2935, 2865, 1730, 1470, 1460, 1440, 1418, 1386, 1378, 1365, 1335, 1315, 1260, 1235, 1205, 1171, 1138, 1105, 1059, 1021, 985 cm^{-1}; NMR ($CDCl_3$) δ 5.75 (m, 2 H), 5.40 (m, 2 H), 4.48 (m, 1 H), 4.08 (m, 2 H), 3.67 (s, 3 H), 1.52 (s, 3 H), 1.35 (s, 3 H), 0.90 (t, 3 H).

(±)-12-Hydroxy-PGF$_{2\alpha}$ Methyl Ester (5). A 1:1 mixture of acetonides **33** and **34** (48 mg, 0.11 mmol) in 2.0 mL of methanol was treated at room temperature with a catalytic amount of *p*-toluenesulfonic acid for 24 h. The reaction mixture was diluted with 50 mL of chloroform and washed with a saturated solution of sodium bicarbonate. After drying over anhydrous magnesium sulfate and evaporation of the solvent in vacuo, the crude product was chromatographed on 15 g of neutral silica gel (SilicAR CC-7). Elution with ether–ethyl acetate–methanol (10:10:1) provided 11 mg (26%) of a mixture of (±)-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**5**) and (±)-15-*epi*-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**35**). The mixture of **5** and **35** was separated on SilicAR CC-7 employing ether–ethyl acetate (1:1). There was obtained in order of elution 5 mg of **35**, 6 mg of a mixture of **35** and **5**, and 3 mg of (±)-12-hydroxy-PGF$_{2\alpha}$ methyl ester (**5**) as a solid. Recrystallization of **5** from ether–pentane gave pure **5**: mp 65–67 °C; IR ($CHCl_3$) 3620, 3425, 3030, 2960, 2945, 2865, 1738, 1463, 1420, 1241, 1210, 1165, 1110, 1055, 982, 938 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.78 (dd, 1 H, J = 15 Hz, 7 Hz), 5.50 (d, 1 H, J = 15 Hz), 5.38 (m, 2 H, *cis*-CH=CH–), 4.12 (m, 2 H), 3.92 (m, 1 H), 3.66 (s, 3 H), 0.88 (t, 3 H).

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