Fluoroprostaglandins: Synthesis of (±)-10β-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester

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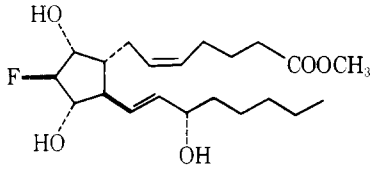
Received December 18, 1978

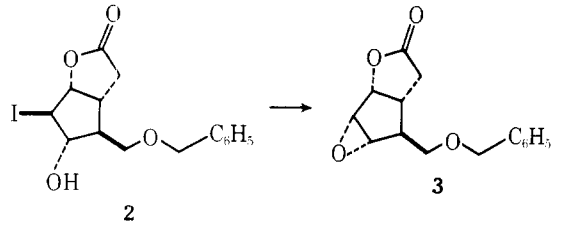
The total synthesis of 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (1) is described. Treatment of the 10α,11α-epoxyprostaglandin $F_{2\alpha}$ methyl ester (**24**) with potassium bifluoride in hot ethylene glycol gave rise to (±)-1 upon subsequent treatment with sodium hydroxide and reesterification. Epoxide **24** was synthesized from the known bicyclo[2.2.1]heptane derivative **10**. Attempted preparation of (±)-1 from the fluoro lactone **16** via the standard sequence [(a) reduction, (b) Wittig condensation, (c) CH_2N_2, and (d) cleavage of the tetrahydropyranyl ethers] gave none of the desired 10β-fluoroprostaglandin. A 70% yield of 9α,10α-epoxyprostaglandin $F_{2\alpha}$ methyl ester (**17**) was isolated.

Our continued interest in fluorinated prostaglandins[1] led us to prepare 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (1) in which the fluorine atom at C(10) bears an anti relationship to the two neighboring hydroxyls at C(9) and C(11). It was our belief that such fluorinated prostaglandins should possess interesting biological properties in view of the minor structural modification of the prostaglandin molecule and, more importantly, the electronegative nature of the fluorine atom. It has been demonstrated that fluorinated prostaglandins (e.g., 12-fluoroprostaglandin $F_{2\alpha}$,[2] 16,16-difluoroprostaglandin $F_{2\alpha}$,[3a] (15*R*,16*S*)-fluoro-13-dehydroprostaglandin $F_{2\alpha}$[3b]), while less prone to metabolic inactivation, possess interesting biological properties.[4]



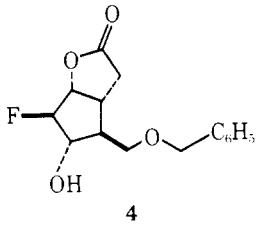
1

Our initial synthetic plan centered around the bicyclic epoxide **3** which was prepared in excellent yield by treatment of the known iodohydrin **2**[5] with silver oxide in dimethoxyethane at elevated temperatures. Despite the ready availability of **3**, all initial attempts to transform epoxide **3** into the



2 3

desired fluorohydrin **4** employing a variety of reagents and conditions (e.g., anhydrous hydrogen fluoride, HF·pyridine, potassium fluoride/dicyclohexyl-18-crown-6) failed. Not even the unwanted isomeric fluorohydrin **5** could be detected. It was our contention that had reaction occurred, the 10β-fluoro derivative (prostaglandin numbering) would have predominated due to the presence of the C(12) β-oriented benzyloxymethyl group. After numerous abortive attempts, success was finally achieved, albeit in only modest yield (40%), employing potassium bifluoride (KHF_2)[7] in hot ethylene glycol for a short reaction time. In addition to formation of the desired fluorohydrin, a 30% yield of the isomeric fluorohydrin **5** was isolated. With both fluorohydrins in hand, the task of deciding which isomer was the desired one was made easier. Preliminary evidence, obtained from the 60 MHz NMR spectra, led



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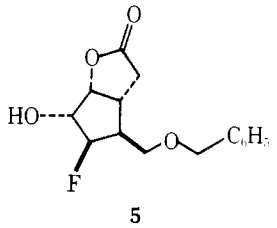
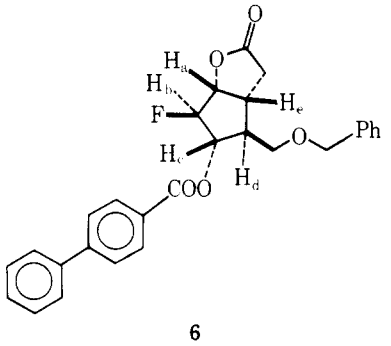


5

to the assignment of structure **4** to the more polar fluorohydrin and structure **5** to the less polar isomeric fluorohydrin. Additional evidence (vide infra) in support of structure **4** was obtained by detailed examination of the high-field ^1H NMR spectrum of the crystalline *p*-phenyl benzoate derivative **6**, mp 111–112 °C, obtained from fluorohydrin **4**.



6

The NMR spectrum of **6** revealed H_a as a doublet of doublets centered at δ 4.99 with J_{ae} = 8 Hz, J_{aF} = 14 Hz ($\theta_{H_aH_b}$ = 90°, J_{ab} = 0 Hz). A doublet of doublets located at δ 5.21 was assigned to H_b. The geminal fluorine–H_b coupling constant and J_{bc} were 54 and 5 Hz, respectively. Proton H_c at C(11) appeared as an octet centered at δ 5.60, with J_{cF} = 16 Hz, J_{bc} = 5 Hz, and J_{cd} = 7 Hz. Further evidence in support of structure **6** was obtained by extensive decoupling experiments.

Having established the β orientation of the fluorine atom at C(10), we proceeded to transform **6** into 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (1) employing standard prostaglandin methodology.[6] Debenzylation of **6** afforded the crystalline alcohol **7**[8] which upon Collins oxidation and subsequent treatment (without purification) of the resulting aldehyde with the sodium salt of dimethyl 2-oxoheptylphosphonate in dimethoxyethane gave rise to a 2:1 mixture of the desired enone **8** and the ε-fluoro dienone **9** in 60% isolated yield. All attempts to suppress the formation of **9** were unsuccessful.

In order to circumvent the problem of β elimination encountered above, the ω side chain was elaborated prior to introduction of the fluorine atom at C(10) by condensation of the standard Horner–Emmons reagent with the 7-formylbi-

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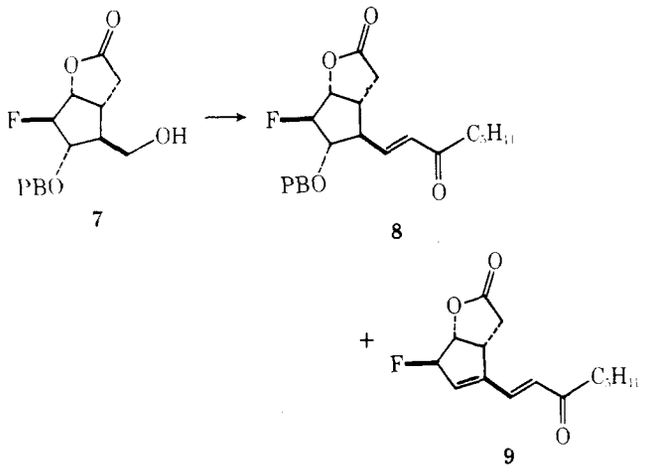
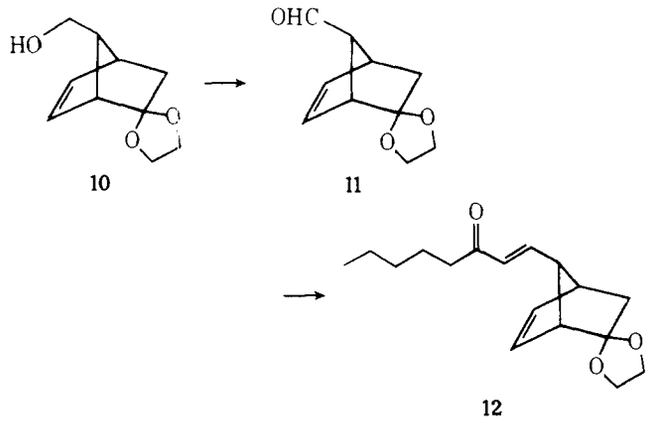


7 8 9

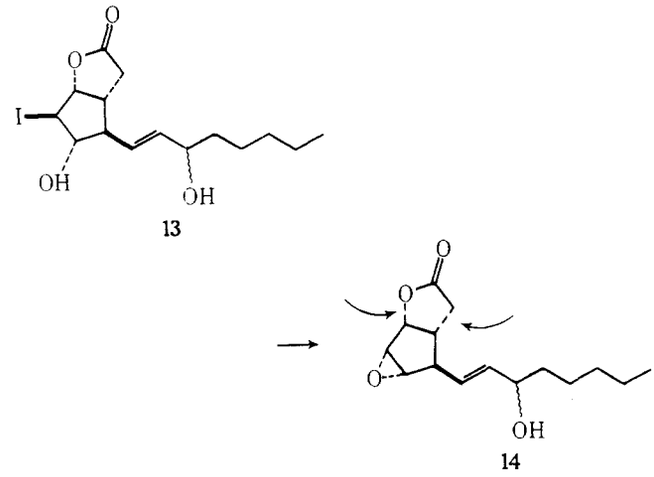
PB = *p*-phenylbenzoyl

cyclo[2.2.1]heptene derivative **11** which was readily available from the known alcohol **10**[1b] via Collins oxidation. Transfor-



10 11 12

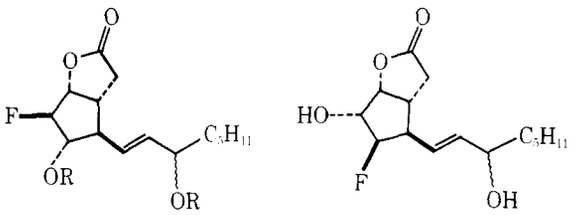
mation of 12 into the requisite α-epoxide **14** was accomplished in high overall yield via the intermediacy of iodohydrin **13**.[9] The preparation of **13** from enone **12** was carried out



13 14

employing the following sequence of reactions: (a) reduction at C(15); (b) deketalization; (c) Baeyer–Villiger oxidation; and (d) iodolactonization. Treatment of iodohydrin **13** with silver oxide in refluxing dimethoxyethane for 2.5 h gave in 94% yield epoxide **14**.

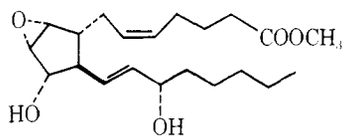
Treatment of **14** with potassium bifluoride as described above gave rise to fluorohydrin **15** which was shown to be identical in all respects with a sample of **15** prepared by reduction ($NaBH_4$, EtOH, −20 °C) of enone **8** and subsequent methanolysis with K_2CO_3/MeOH. The isomeric fluorohdyrin **15′** was isolated as a minor product which was in keeping with our results obtained from epoxide **3**. With the structure of **15**



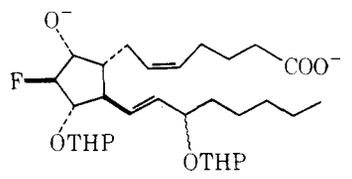
15, R = H
16, R = THP

15′

assured, the hydroxyl groups were protected as their tetrahydropyranyl ethers. Introduction of the α side chain was accomplished in the standard manner [(a) *i*-Bu_2AlH; (b) Ph_3P = $CH(CH_2)_3COO^-$, Me_2SO].[6] However, after esterification and cleavage of the tetrahydropyranyl ethers, none of the desired 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ether (**1**) could be detected. Much to our surprise a 34% overall yield of the 9α,10α-epoxyprostaglandin $F_{2\alpha}$ methyl ester (**17**) was isolated.[10]



17

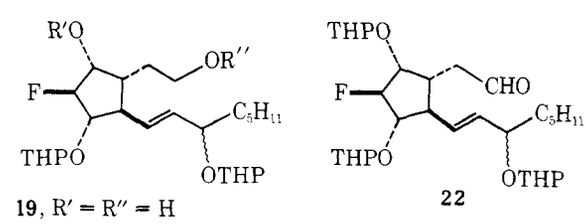


18

Fluorohydrins, unlike other halohydrins, are generally very stable and not prone to undergo rapid epoxide formation. Undoubtedly, the intermediate alkoxide **18** in the dimethyl sulfoxide medium rapidly displaces the trans-disposed fluorine atom. Our attempts to prevent the loss of fluoride ion by lowering the reaction temperature and reducing the reaction time were not successful.

With **17** in hand, we attempted to reintroduce the fluorine atom by reaction of **17** with potassium bifluoride. Despite the numerous products obtained from this reaction, no trace of the desired 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester could be isolated.

Intent on preparing a few milligrams of 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) for biological evaluation, we finally succeeded by employing a circuitous route. Reduction ($LiAlH_4$, −20 °C) of lactone **16** provided diol **19** which was

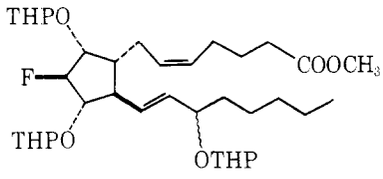


19, R′ = R″ = H
20, R′ = H; R″ = *t*-$BuMe_2Si$
21, R′ = THP; R″ = H

22

selectively silylated using *tert*-butyldimethylchlorosilane–imidazole.[11] Tetrahydropyranylation of **20** and subsequent desilyation using tetra-*n*-butylammonium fluoride[11] gave alcohol **21** in ca. 80% overall yield. Oxidation of **21** with Collins

reagent at −10 °C gave a 77% yield of aldehyde **22** which upon condensation with the Wittig reagent derived from 5-triphenylphosphonovaleric acid in dimethyl sulfoxide produced, after esterification with etheral diazomethane, a 78% yield of adduct **23.** Cleavage of the tetrahydropyranyl ethers gave in



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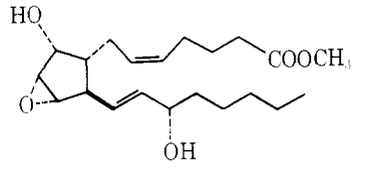
80% yield a 1:1 mixture of 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) and 15-epi-10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1′**) which were readily separated on a silica gel column. The more polar isomer has been tentatively assigned the (15*S*) natural configuration.[12]

Despite the fact that compound **1** was now in hand, we were concerned about the lengthy sequence of reactions employed. Undaunted by our failure to isolate even a trace of **1** from the attempted opening of epoxide **17** with potassium bifluoride, we prepared the isomeric epoxy alcohol **24** in hopes of being able to improve the synthesis of **1.** Epoxide **24** was made



24

available in three steps [(a) diisobutylaluminum hydride; (b) Wittig reaction; (c) CH_2N_2] from the unprotected hydroxy lactone **14.** Compound **24** (more polar) and the C(15) epimeric isomer **25** were readily separated chromatographically. Much to our surprise, treatment of **24** with potassium bifluoride in hot ethylene glycol (190–195 °C) for ca. 35 min gave rise, after treatment with 1.1 equiv of sodium hydroxide in methanol and re-esterification with diazomethane, to a 25% yield of pure 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) which was identical in all respects with the sample prepared above. Similarly, compound **25** was converted into 15-epi-10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester.

Experimental Section

Melting points were determined on a Fisher–Johns hot-stage melting-point apparatus. All melting points and boiling points are uncorrected. Infared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 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), hexamethylphosphramide (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. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GHLF (250 μm).

1aα,1bα,4,4aα,5α,5aα-Hexahydro-5-[(phenylmethoxy)methyl]-3*H*-oxireno[4,5]cyclopenta[1,2-*b*]furan-3-one (3). A solution of 620 mg (1.6 mmol) of iodohydrin **2** in 2.5 mL of dry dimethoxyethane containing 742 mg (3.2 mmol) of silver oxide was heated at 85 °C. After 3 h, TLC analysis (silica gel, ether) indicated the complete absence of starting material. The reaction mixture was filtered, and the precipitate was washed with 3 × 10 mL of warm dimethoxyethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified on 20 g of silica gel. Elution with ether–hexane, 1:1, gave 370 mg (89%) of pure **3** as an oil: R_f 0.56 (ether–benzene, 3:1); IR (film) 3025, 2965, 2930, 2865, 1778, 1500, 1455, 1415, 1381, 1336, 1305, 1275, 1221, 1169, 1105, 1078, 1050, 1040, 981, 911, 866, 855, 700 cm^{-1}; NMR (60 MHz) ($CDCl_3$) 7.35 (m, 5 H), 5.05 (bd, 1 H, J = 6 Hz, –CHOCO), 4.50 (s, 2 H, $-OCH_2C_6H_5$), 3.8–3.5 (m, 4 H), 3.0–2.2 (m, 4 H); mol wt calcd ($C_{15}H_{16}O_4$), 260.10486, and found, 260.10465.

6-Fluoro-3,3aα,4α,5β,6α,6aα-hexahydro-2-oxo-4[(phenylmethoxy)methyl]-2*H*-cyclopenta[*b*]furan-5-yl [1,1′-Biphenyl]-4-carboxylate (6). A solution of 135 mg (0.52 mmol) of epoxide **3** in 13 mL of ethylene glycol containing 404 mg (5.2 mmol) of potassium bifluoride was refluxed for 1.5 h. The reaction mixture was cooled and treated with water. Extraction of the product with methylene chloride (5 × 25 mL) gave after drying over anhydrous magnesium sulfate and evaporation of the solvent in vacuo 114 mg of material. Chromatography of the crude product on 14 g of silica gel using hexane–ether, 2:1, provided in order of elution 44 mg (30%) of fluorohydrin **5** [R_f 0.52 (ether); IR ($CHCl_3$) 3600, 3380, 2940, 2860, 1785, 1500, 1458, 1419, 1368, 1350, 1320, 1280, 1170, 1080, 1048, 1020, 910, 890, 850, 700 cm^{-1}; NMR (60 MHz) ($CDCl_3$) 7.31 (s, 5 H), 4.97 (m, 1 H, –CHOCO), 4.91 (bd, 1 H, J_{HF} = 52 Hz, –CHF), 4.58 (s, 2 H, $-OCH_2C_6H_5$), 3.60 (m, 2 H, $-CH_2O$); MS *m/e* (70 eV) 280], 5.6 mg of a mixture of fluorohydrins **4** and **5**, and 58 mg (40%) of fluorohydrin **4** [R_f 0.48 (ether); IR ($CHCl_3$) 3610, 3540, 3410, 3025, 2960, 2940, 2870, 1785, 1501, 1458, 1365, 1280, 1235, 1170, 1095, 1035, 1010, 700 cm^{-1}; NMR (60 MHz) ($CDCl_3$) 7.32 (s, 5 H), 4.85 (octet, 1 H, J_{HF} = 52 Hz, J = 6 Hz, J = 3 Hz, –CHF), 4.55 (s, 2 H, $-OCH_2C_6H_5$), 3.58 (d, 2 H, J = 6 Hz, $-CH_2O$); MS *m/e* (70 eV) 280].

To a solution of 52 mg (0.18 mmol) of fluorohydrin **4** in 0.3 mL of dry pyridine was added 48 mg (0.25 mmol) of *p*-phenylbenzoyl chloride. After 1.5 h at room temperature, the reaction was quenched by the addition of 0.15 mL of water. After an additional 1 h, the pyridine was evaporated in vacuo and the product taken up in 10 mL of a 4:1 mixture of methylene chloride–cyclohexane. The organic layer was washed with 10% aqueous hydrochloric acid, saturated sodium bicarbonate solution, and brine and dried over anhydrous magnesium sulfate. The crude product upon recrystallization from methylene chloride–petroleum ether gave 68 mg (80%) of pure *p*-phenylbenzoate **6**: mp 110.5–111.5 °C: R_f 0.51 (ether–hexane, 2:1); IR ($CHCl_3$) 3030, 2960, 2940, 2865, 1785, 1725, 1618, 1568, 1495, 1458, 1410, 1370, 1318, 1272, 1210, 1165, 1100, 1040, 1025, 1014, 975, 860, 700 cm^{-1}; NMR (250 MHz) ($CDCl_3$) 7.87 (AB_q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 100 Hz), 7.63 (d, 2 H, J = 7 Hz), 7.46 (m, 3 H), 7.30 (s, 5 H), 5.60 (octet, 1 H, J_{H_cF} = 16 Hz, $J_{H_aH_b}$ = 5 Hz, $J_{H_cH_d}$ = 7 Hz, H_c), 5.21 (dd, 1 H, H_{H_bF} = 53 Hz, $J_{H_bH_c}$ = 5 Hz, H_b), 4.99 (dd, 1 H, $J_{H_aH_e}$ = 8 Hz, J_{H_aF} = 14 Hz, H_a), 4.54 (s, 2 H, $-OCH_2C_6H_5$), 3.60 (m, 2 H, $-CH_2O-$), 3.12 (m, 1 H, $-CHCH_2COO-$), 2.88 (dd, 1 H, J = 18 Hz, J = 10 Hz, –CHCOO–), 2.60 (dd, 1 H, J = 18 Hz, J = 2 Hz, –CHCOO–), 2.40 (m, 1 H, $-CHCH_2O-$); MS *m/e* (70 eV) 460. Anal. Calcd for $C_{28}H_{25}FO_5$: C, 73.03; H, 5.47. Found: C, 73.21; H, 5.36.

6-Fluoro-3,3aα,4α,5β,6α,6aα-hexahydro-4-(hydroxymethyl)-2-oxo-2*H*-cyclopenta[*b*]furan-5-yl [1,1′-Biphenyl]-4-carboxylate (7). A solution of 93 mg (0.20 mmol) of benzyl ether **6** in a mixture of 4 mL of ethyl acetate and 2 mL of ethanol containing 10 mg of 10% palladium on carbon and three drops of 1 N hydrochloric acid was shaken (Parr apparatus, 20 h) under hydrogen (45 psi). Filtration of the catalyst through Celite and evaporation of the solvent under reduced pressure gave crude crystalline alcohol **7.** Recrystallization from methylene chloride–hexane afforded 62 mg (83%) of pure alcohol **7**: mp 161–162 °C; R_f 0.78 (ether–ethyl acetate, 1:1); IR ($CHCl_3$) 3400 (broad), 1785, 1709, 1610, 1280 cm^{-1}; NMR (60 MHz) ($CDCl_3$) 7.85 (ABq, 4 H, J = 9 Hz, $\Delta\nu_{AB}$ = 24.3 Hz), 7.50 (m, 5 H), 5.7–4.8 (m, 3 H), 3.66 (m, 2 H), 3.4–3.0 (m, 2 H), 2.8–2.5 (m, 3 H); MS *m/e* 15 eV) 370. Anal. Calcd for $C_{21}H_{19}FO_5$: C, 68.10; H, 5.17. Found: C, 67.98; H, 5.10.

6-Fluoro-3,3aα,4α,5β,6α,6aα-hexahydro-2-oxo-4-(3-oxo-1(*E*)-octenyl)-2*H*-cyclopenta[*b*]furan-5-yl [1,1′-Biphenyl]-4-carboxylate (8). To a rigorously stirred solution of 200 mg (2.5 mmol) of dry pyridine in 3.2 mL of dry methylene chloride cooled to 0 °C was added 126 mg (1.26 mmol) of chromium trioxide. After 1 h, 652 mg of Celite was added and the reaction flask was cooled to 0 °C. A solution of 52 mg (0.14 mmol) of alcohol **7** in 0.3 mL of dry methylene chloride was added to the cooled flask containing the Collins reagent. After 10 min at 0 °C, 652 mg of sodium hydrogen sulfate monohydrate was added. Stirring was continued for an additional 10 min followed by filtration of the reaction mixture through a pad of magnesium sulfate. The precipitate was thoroughly washed with methylene

chloride. The combined organic washings were concentrated in vacuo (<0 °C) on a rotary evaporator. The crude aldehyde was used immediately in the next reaction.

To a stirred suspension of 7.0 mg (0.15 mmol) of 50% sodium hydride dispersion in 1.6 mL of dimethoxyethane (freshly distilled from lithium aluminum hydride) cooled to 0 °C under nitrogen was added dropwise a solution of 31 mg (0.14 mmol) of dimethyl (2-oxoheptyl)-phosphonate in 0.7 mL of dry dimethoxyethane. Upon completion of addition, the reaction mixture was warmed to 25 °C. After ca. 1 h, the phosphonate anion was cooled to 0 °C and treated with the aldehyde from above in 0.3 mL of dimethoxyethane. The reaction was quenched after 1.15 h by the addition of water. The product was isolated by extraction with ether. The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The crude enone was purified by chromatography on silica gel. Elution with ether–hexane, 2:1, gave in order of elution 8 mg (20%) of dienone **9** [R_f 0.57 (ether–hexane, 5:1); IR ($CHCl_3$) 2955, 2930, 2855, 1786, 1670, 1625, 1595, 1460, 1355, 1328, 1300, 1170, 1050, 903 cm^{-1}; NMR (250 MHz) 7.26 (dd, 1 H, J = 16.5 Hz, J = 1.5 Hz), 6.23 (bs, 1 H), 6.17 (dd, 1 H, J = 16.5 Hz, J = 2.5 Hz), 5.61 (d, 1 H, J = 52 Hz, –C**H**F), 5.16 (dd, 1 H, J_{HF} = 16 Hz, J = 6 Hz, –C**H**OCO), 3.88 (bs, 1 H), 2.93 (dd, 1 H, J = 18 Hz, J = 11 Hz, –C**H**COO), 2.62 (t, 2 H, J = 7 Hz, –COC**H**$_2$–), 2.45 (dd, 1 H, J = 18 Hz, J = 3 Hz, –C**H**COO), 1.6–1.3 (m, 6 H), 0.92 (t, 3 H, J = 7 Hz); UV (EtOH) 262 nm (ϵ 21 500); MS m/e (15 eV) 266], 26 mg (40%) of enone **8** [R_f 0.47 (ether–hexane, 5:1); IR ($CHCl_3$) 2960, 2925, 2850, 1785, 1723, 1698, 1670, 1628, 1610, 1491, 1460, 1409, 1375, 1270, 1210, 1160, 1115, 1098, 1005, 978, 858 cm^{-1}; NMR (60 MHz) $CDCl_3$ 7.83 (ABq, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 22.6 Hz), 7.50 (m, 5 H), 6.71 (dd, 1 H, J = 16 Hz, J = 7 Hz, –CHC**H**=C), 6.18 (d, 1 H, J = 16 Hz, –C=C**H**CO), 5.25 (dm, 1 H, J = 50 Hz, –C**H**F)], and 2.5 mg of starting alcohol.

[1α,4α,7*R(*E*)]-1-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl-1-octen-3-one (12).** To a solution of 12 mL (0.15 mol) of dry pyridine in 190 mL of dry methylene chloride at room temperature was carefully added in small portions 7.47 g (74.7 mmol) of chromium trioxide. The reaction mixture was mechanically stirred for 45 min prior to addition of 39 g of Celite (predried, 24 h at 120 °C) and cooled to 0 °C. A solution of 1.36 g (7.47 mmol) of ketal alcohol **10** in 20 mL of dry methylene chloride was added in one portion to the solution of Collins reagent generated above. After a total of 15 min, the reaction was quenched by the addition of 38.6 g of sodium bisulfate and filtered through a pad of anhydrous magnesium sulfate. The Celite was washed exhaustively with anhydrous ether. The combined organic layers were filtered through a second pad of magnesium sulfate to remove traces of chromium trioxide and evaporated in vacuo leaving the crude aldehyde [R_f 0.50 (ether–hexane, 2:1)] which was used directly in the next reaction.

To a stirred suspension of 359 mg (7.47 mmol) of 50% sodium hydride dispersion in 80 mL of dry tetrahydrofuran was added dropwise a solution of 1.68 g (7.54 mmol) of dimethyl (2-oxoheptyl)phosphonate in 35 mL of anhydrous tetrahydrofuran.

After 45 min at room temperature, the phosphonate anion was cooled to 0 °C and treated with a solution of aldehyde **11** in 35 mL of dry tetrahydrofuran. After a total of 30 min, the reaction was quenched by the addition of water, and the solvent was removed under reduced pressure leaving an oily residue which was dissolved in ether and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed on 80 g of silica gel. Elution with ether–hexane, 1:2, gave 1.64 g (80%) of pure enone **12** as a pale yellow oil: R_f 0.71 (ether–hexane, 2:1); IR (film) 3080, 3045, 2980, 2960, 2940, 2895, 2878, 1695, 1680, 1635, 1580, 1470, 1458, 1445, 1418, 1381, 1338, 1310, 1278, 1250, 1230, 1218, 1205, 1190, 1165, 1110, 1058, 1010, 1000, 980, 955, 940, 920, 895, 870, 854, 840, 800, 780, 720 cm^{-1}; NMR (60 MHz) (CCl_4) 6.60 (dd, 1 H, J = 15 Hz, J = 8 Hz, –CHC**H**=CHCO), 6.15 (m, 1 H, –C**H**=CH), 5.98 (d, 1 H, J = 15 Hz, –CH=C**H**CO), 5.91 (m, 1 H, –CH=C**H**), 3.80 (s, 4 H, –OCH_2CH_2O–), 0.92 (t, 3H); mol wt calcd ($C_{17}H_{24}O_3$), 276.1725, and found, 276.1772.

3,3aα,4α,5β,6α,6aα-Hexahydro-5-hydroxy-6-iodo-4-(3-hydroxy-1(*E*)-octenyl)-2*H*-cyclopenta[*b*]furan-2-one (13). To a suspension of 165 mg (4.35 mmol) of lithium aluminum hydride in 25 mL of anhydrous ether cooled to −25 °C was added dropwise over 5 min a solution of 1.20 g (4.35 mmol) of enone **12** in 10 mL of dry ether. After 20 min, the reaction was quenched by the careful addition of brine. The organic layer was dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo left 1.16 g (96%) of essentially pure ketal alcohol [R_f 0.57 (ether–hexane, 2:1); IR (CCl_4) 3625, 3470 cm^{-1}; NMR (60 MHz) (CCl_4) δ 6.01 (m, 1 H, olefinic proton), 5.80 (m, 1 H, olefinic proton), 5.42 (m, 2 H, trans olefinic protons), 3.78 (br s, 5 H)] which was used directly in the next reaction.

A solution of 1.16 g (4.17 mmol) of the above ketal in 25 mL of 60% acetic acid was stirred for 44 h at room temperature. The acetic acid was neutralized initially to pH 6 with 10% sodium hydroxide solution followed by addition of solid sodium bicarbonate. The product was isolated by ether extraction. Standard workup provided 957 mg (98%) of a ketone [IR (film) 3450, 1748 cm^{-1}; NMR (60 MHz) (CCl_4) δ 6.38 (m, 1 H, –CH=), 5.94 (m, 1 H, –CH=), 5.58 (m, 2 H, trans olefinic protons), 3.90 (m, 1 H, –C**H**OH–)] which was homogeneous by TLC analysis [R_f 0.46 (ether–hexane, 2:1)].

To a solution of 957 mg (4.09 mmol) of the above ketone in 23 mL of methanol and 20 mL of water cooled to 0 °C was added 5.0 mL (12.3 mmol) of a 10% aqueous sodium hydroxide solution followed by the slow dropwise addition of 3.43 mL (30.3 mmol) of 30% aqueous hydrogen peroxide. After 32 h at ca. 5 °C, the reaction mixture was washed with two portions of ether and acidified to pH 5.5 with concentrated hydrochloric acid. Excess hydrogen peroxide was destroyed by the addition of 3.3 g of sodium sulfite and the pH was adjusted to pH 5.5 with hydrochloric acid. Isolation of the product by extraction with ethyl acetate gave 1.05 g (96%) of an hydroxy acid [IR (film) 3700–2200, 1710 cm^{-1}] as a viscous oil which was submitted directly to iodolactonization.

The 1.05 g (3.92 mmol) of hydroxy carboxylic acid from above was treated at 0 °C with 172 mg (4.31 mmol) of sodium hydroxide in 7.0 mL of water. After the solution was carefully neutralized to pH 7 with carbon dioxide, a solution of 7.16 g (43.1 mmol) of potassium iodide and 3.48 g (13.7 mmol) of iodine in 7.0 mL of water was added. After a total of 34 h at 5 °C, the reaction was diluted with methylene chloride and decolorized by the addition of sodium sulfite. The product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure yielding 1.5 g of crude product. The iodolactone was purified on 75 g of silica gel. Elution with ether–hexane (2:1) gave 1.1 g (70%) of pure iodolactone **13** [R_f 0.33 (ether); IR ($CHCl_3$) 3610, 3400, 3020, 2970, 2940, 2870, 1785, 1475, 1460, 1420, 1381, 1358, 1296, 1240, 1165, 1058, 1010, 978, 910, 850 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 5.59 (m, 2 H, –C**H**=C**H**–), 5.07 (m, 1 H, –C**H**OCO–); mol wt calcd ($C_{15}H_{21}IO_3$–H_2O), 376.0535, and found, 376.0537].

Hexahydro-5-(3-hydroxy-1-octenyl)-3*H*-oxireno[4,5]cyclopenta[1,2-*b*]furan-3-one (14). A solution of 2.64 g (6.70 mmol) of iodohydrin **13** in 15 mL of anhydrous dimethoxyethane containing 3.11 g (13.4 mmol) of silver oxide was refluxed. After 2.5 h, TLC analysis (ether–ethyl acetate, 10:1) indicated the absence of starting material. The reaction mixture was filtered through a pad of Celite–magnesium sulfate (anhydrous) and washed with hot dimethoxyethane. Evaporation of the solvent in vacuo gave 1.80 g of crude epoxide which was chromatographed on 100 g of silica gel. Elution with ether–ethyl acetate (20:1) gave rise to 1.68 g (94%) of pure epoxide **14** as a clear oil [R_f 0.41 (ether–ethyl acetate, 10:1); IR ($CHCl_3$) 3615, 3040, 3020, 2960, 2860, 1780, 1470, 1460, 1418, 1380, 1365, 1325, 1295, 1260, 1235, 1215, 1170, 1055, 1030, 975, 917, 872, 860 cm^{-1}; NMR (60 MHz) ($CDCl_3$) 5.58 (m, 2 H, –CH=CH–), 5.09 (dd, 1 H, J = 8 and 2 Hz, –C**H**OCO), 4.05 (m, 1 H, –C**H**OH–), 3.8–3.3 (m, 3 H), 3.1–2.1 (m, 4 H), 1.7–1.1 (m, 8 H), 0.90 (t, 3 H); mol wt calcd ($C_{15}H_{22}O_4$–C_5H_{11}), 195.0657, and found, 195.0654].

10α,11α-Epoxyprostaglandin $F_{2\alpha}$ Methyl Ester (24). A solution of 122 mg (0.46 mmol) of lactone **14** in 2.5 mL of dry toluene was treated dropwise at −78 °C with 1.2 mL (1.4 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 ether, warmed to room temperature, and treated with water. Isolation of the product by extraction with ether gave in quantitative yield the crude lactol [R_f 0.42 (ether)] which was used directly in the next reaction.

A suspension of 220 mg (4.59 mmol) of 50% sodium hydride dispersion in 1.5 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 1.02 g (2.3 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 1.4 mL of dry dimethyl sulfoxide. A solution of 123 mg of the above lactol in 1.1 mL of dry dimethyl sulfoxide was added to the dark red ylid solution. After 2 h at 25 °C, the reaction was quenched by the addition 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 residue was esterified with ethereal diazomethane. The crude product was chromatographed on 17 g of silica gel. Elution with ether gave 109 mg (65% overall yield) of dihydroxy ester **24** as a mixture of epimers at C(15). Dihydroxy ester **24** was readily separated from the C(15) isomeric compound **25** by chromatography on 20 g of silica gel. Elution with ether gave 32 mg of pure **25** [less polar R_f 0.29 (ether)], 50 mg of a mixture of **24** and **25**,

and 27 mg (more polar) of pure dihydroxy ester **24** [R_f 0.21 (ether); IR ($CHCl_3$) 3600, 3400, 3000, 2955, 2940, 2860, 1730, 1460, 1440, 1402, 1381, 1370, 1320, 1260, 1210, 1180, 1158, 1080, 861 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 5.64–5.22 (m, 4 H, olefinic), 4.65–3.80 (m, 2 H), 3.70 (s, 3 H), 3.38 (d, 1 H, J = 3 Hz), 0.90 (t, 3 H); mol wt calcd ($C_{21}H_{34}O_5$–H_2O), 348.2300, and found, 348.2304].

10β-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (1). A solution of 25 mg (0.068 mmol) of epoxide **24** in 0.4 mL of ethylene glycol containing 80 mg (1.02 mmol) of potassium bifluoride was heated at 185 °C for 35 min. After cooling, 1.0 mL of water was added, and the product was extracted with 5 × 10 mL of ethyl acetate. The crude product obtained after combining the organic extracts and removing the solvent in vacuo was treated with 0.08 mmol of sodium hydroxide in 0.2 mL of water and 0.3 mL of methanol. After 18 h, the crude 10β-fluoroprostaglandin $F_{2\alpha}$ was isolated and directly esterified with an ethereal solution of diazomethane. Chromatography of the crude product on 6.02 g of silica gel using hexane–ether (1:1) gave 10 mg (25%) of pure 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**): R_f 0.38 (ether, two developments); IR ($CHCl_3$) 3610, 3400, 3010, 2960, 2930, 2860, 1728, 1460, 1440, 1371, 1230, 1210, 1015, 978 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.61–5.37 (m, 4 H, olefinic protons), 4.71 (d, J = 51 Hz, –CHF–), 4.15–3.81 (m, 3 H), 3.68 (s, 3 H), 3.04 (br s, 1 H). Anal. Calcd for $C_{21}H_{35}O_5F$: C, 65.25; H, 9.10. Found: C, 65.09; H, 9.18.

6-Fluoro-3,3aα,4α,5β,6α,6aα-Hexahydro-5-hydroxy-4-(3-hydroxy-1(*E*)-octenyl)-2*H*-cyclopenta[*b*]furan-2-one (15). A solution of 67 mg (0.23 mmol) of epoxide **14** in 1.0 mL of ethylene glycol containg 183 mg (4.6 mmol) of potassium bifluoride was heated at 170–180 °C for 40 min. The reaction was cooled and then quenched by the addition of 2.0 mL of water. The crude product was isolated by extraction with chloroform (3 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude product was chromatographed on 20 g of silica gel. Elution with chloroform–ethyl acetate (2:1) gave in order of elution 13 mg (19%) of the isomeric fluorohydrin **15′** and 19 mg (29%) of pure fluorohydrin **15** [IR($CHCl_3$) 3600, 3400, 3000, 2955, 2925, 2850, 1782, 1460, 1412, 1380, 1388, 1230, 1209, 1160, 1080, 1020, 975, 900 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.76–5.44 (m, 2 H, –CH=CH–), 4.88 (dd, 1 H, J = 7, 48 Hz, –CHF–), 4.85 (dd, 1 H, J = 5, 17 Hz, –CHOCO), 4.20–3.91 (m, 2 H), 0.92 (t, 3 H)] which was identical in all respects with a sample of **15** prepared from enone **8** via reduction ($NaBH_4$) and hydrolysis (K_2CO_3/MeOH).

6-Fluoro-3,3aα,4α,5β,6α,6aα-Hexahydro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[3-(tetrahydro-2*H*-pyran-2-yl)oxy]-1-(*E*)-octenyl]-2*H*-cyclopenta[*b*]furan-2-one (16). A solution of 84 mg (0.29 mmol) of diol **15** in 3 mL of dry methylene chloride containing 123 mg (1.45 mmol) of dihydropyran and a catalytic amount of *p*-toluenesulfonic acid was stirred at 0 °C for 30 min. The reaction was quenched by the addition of solid sodium bicarbonate. Filtration followed by evaporation of the solvent in vacuo gave crude **16** which was chromatographed on 15 g of silica gel. Elution with hexane–ether (1:1) provided 135 mg (87%) of bis(tetrahydropyranyloxy) lactone **16** as a colorless oil [IR (CCl_4) 2950, 2865, 1791, 1690, 1470, 1455, 1442, 1420, 1390, 1358, 1345, 1322, 1290, 1265, 1204, 1185, 1155, 1131, 1112, 1080, 1060, 1025, 975, 918, 875 cm^{-1}] which was used directly in the next reaction.

9α,10α-Epoxyprostaglandin $F_{2\alpha}$ Methyl Ester (17). To a solution of 44 mg (0.097 mmol) of lactone **16** in 4 mL of dry toluene cooled to −78 °C under nitrogen was added dropwise via syringe 206 μL (0.29 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 100 μL of methanol. The reaction was diluted with 20 mL of ether and warmed to room temperature. Aqueous ammonium chloride (10%; 0.1 mL) was added and stirring was continued for 40 min. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuo. There was obtained 44 mg of lactol which was used directly in the next reaction.

A suspension of 84 mg (1.75 mmol) of 50% sodium hydride dispersion in 3.0 mL of anhydrous dimethyl sulfoxide was heated at ~70 °C for 50 min under nitrogen. To the cooled solution (25 °C) of dimsylsodium was added 430 mg (0.97 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 1.0 mL of dry Me_2SO. To the dark ylid solution was added 44 mg of the lactol prepared above in 0.5 mL of Me_2SO. After 1 h at 25 °C, the reaction was quenched by the addition of 10% aqueous ammonium chloride solution and carefully acidified to pH 5 with 5% aqueous sodium hydrogen sulfate solution. The product was isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was esterified with a solution of ethereal diazomethane. The crude product was chromatographed on 10 g of silica gel using hexane–ether (1:2). There was obtained 36 mg (70%) of a material which exhibited no hydroxyl absorption in the infrared spectrum [IR ($CHCl_3$) 3015, 2950, 2865, 1730, 1468, 1450, 1440, 1385, 1378, 1355, 1339, 1320, 1215, 1205, 1180, 1158, 1128, 1112, 1078, 1034, 1020, 974, 929, 905, 885, 868, 845 cm^{-1}].

A solution of the above product (36 mg) in 2.0 mL of 60% acetic acid was heated at 40 °C for 3.5 h. Removal of the solvent under reduced pressure (<0.1 mm) gave 25 mg of crude product which was chromatographed on 20 g of silica gel. Elution with ether gave (48% overall yield) in order of elution 5 mg (14%) of 15-epi-9α,10α-epoxyprostaglandin $F_{2\alpha}$ methyl ester and 12 mg (34%) of pure 9α,10α-epoxyprostaglandin $F_{2\alpha}$ methyl ester (**17**) as a colorless oil: NMR (250 MHz) ($CDCl_3$) δ 5.60–5.32 (m, 4 H, olefinic protons), 4.06 (m, 1 H, C(15) proton), 3.89 (br s, 1 H, C(11) proton), 3.67 (s, 3 H, –$COOCH_3$), 3.53 (d, 1 H, J ~ 5 Hz, C(9) or C(10) proton), 3.40 (d, 1 H, J ~ 4 Hz, C(9) or (C(10) proton).

Acknowledgments. Support for this work by the National Institute of Child Health and Human Development (HD 10725) is gratefully acknowledged. NMR (250 MHz) spectra were obtained on facilities supported by PHS Grant RR-00292.

Registry No.—**1**, 69927-57-7; **1′**, 69927-58-8; 1 free acid, 69943-45-9; **2**, 37053-18-2; **3**, 69927-59-9; **4**, 69927-60-2; **5**, 69927-61-3; **6**, 69927-62-4; **7**, 69927-63-5; **8**, 69927-64-6; **9**, 69927-65-7; **10**, 50703,29-2; **11**, 68372-72-5; **12**, 69927-66-8; **13**, 50890-03-4; **14**, 69927-67-9; **15**, 69927-68-0; **15′**, 69927-69-1; **16**, 69927-70-4; **17** bis(THP) ether, 69927-84-0; **17** free acid bis(THP) ether, 69927-85-1; **17**, 69941-92-0; **19**, 69927-71-5; **20**, 69927-72-6; **21**, 69927-73-7; **22**, 69927-74-8; **23**, 69927-75-9; **24**, 69927-76-0; **25**, 69927-77-1; i, 69979-95-9; 1-spiro-[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl-1-octen-3-ol, 69927-78-2; 7-(3-hydroxy-1-octen-1-yl) bicyclo[2.2.1]hept-5-en-2-one, 50890-06-7; 2(3-hydroxy-1-octene-1-yl)-3-hydroxycyclopent-4-en-1-yl acetic acid, 69927-79-3; hexahydro-5-(3-hydroxy-1-octenyl)-3*H*-oxiren[4,5]cyclopenta[1,2-*b*]furan-3-ol, 69927-80-6; dimethyl (2-oxoheptyl)phosphonate, 36969-89-8; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6; hexahydro-6-fluoro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-octenyl]-2*H*-cyclopenta[*b*]furan-2-ol, 69927-81-7; 15-epi-9α,10α-epoxyprostaglandin $F_{2\alpha}$ methyl ester 69927-82-8; 6-fluoro-3,(+−)3aα,4α,5β,6α,6aα-hexahydro-4-formyl-2-oxo-2*H*-cyclopenta[*b*]-furan-5-yl [1,1′-biphenyl]-4-carboxylate, 69927-83-9; dimethyl (2-oxoheptyl)phosphonate, sodium salt, 32021-35-5; sodium 5-(triphenylphosphoranylidene)pentanoate, 41723-91-5.

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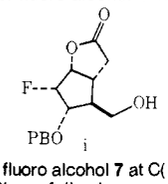
(8) We have prepared the 10α-fluoro alcohol i, mp 180–181 °C, which was



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shown to be isomeric with fluoro alcohol **7** at C(10) [Grieco, P. A.; Williams, E.; Sugahara, T. *J. Org. Chem.* following paper in this issue.

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