Ring-Fluorinated Prostaglandins: Total Synthesis of (±)-10α-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester

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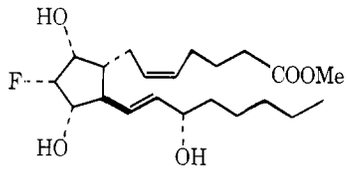
The total synthesis of 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) is described. Introduction of fluorine at C(10) involved treatment of triflate **15** with tetra-*n*-butylammonium fluoride in refluxing tetrahydrofuran.

Ring-fluorinated prostaglandins are relatively rare. Despite the vast number of prostaglandin analogues which have been synthesized during the last 10 years, only four reports have appeared in the literature which deal directly with the introduction of fluorine into the prostaglandin five-membered ring.[2,3] In general, fluorinated prostaglandins have received only scant attention.[4]

In an attempt to probe further the effect on biological activity of introducing fluorine atoms into the five-membered ring of natural prostaglandins, we set out to synthesize the two C(10) ring-fluorinated derivatives, 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) and 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**2**). The preparation of compound **2** was recently reported from our laboratories.[2c] We detail below the synthesis of pure crystalline 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**).



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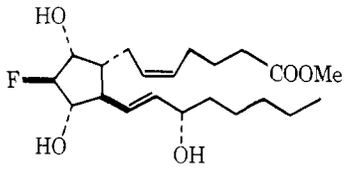

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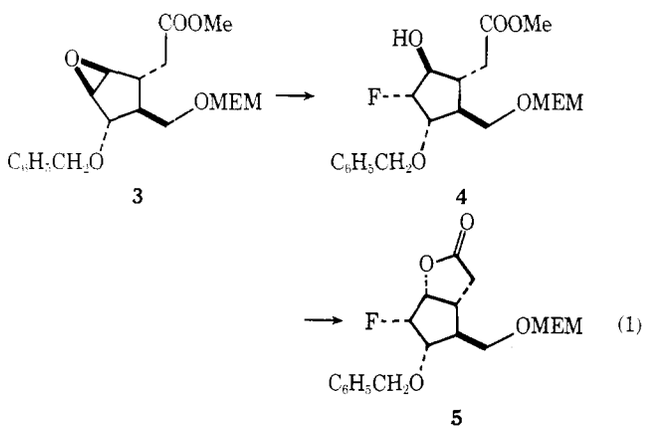
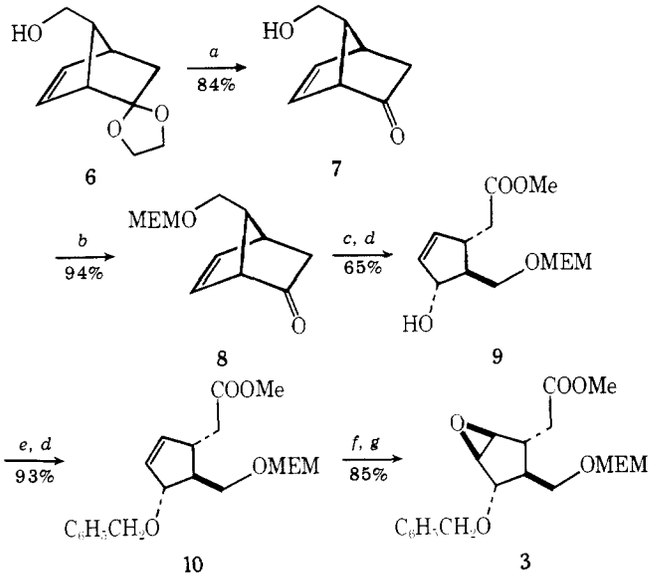
A survey of the literature[5] revealed very few examples of monofluorosubstitution on five-membered carbocyclic rings via S_N2 displacement of a halide, mesylate, or tosylate. Numerous cases involving six-membered carbocyclic rings or five-membered rings containing a heteroatom (e.g., oxygen) directly adjacent to the carbon atom undergoing substitution are known.[5] In light of the above, we set out to prepare epoxide **3** with the hope of being able to convert **3** into the fluorobicyclic lactone **5** via the intermediacy of fluorohydrin **4**. We had



3 **4** **5** (1)

anticipated that once **4** was in hand, acid catalysis or mesylation followed by treatment with aqueous base would lead to lactone **5** without any complications.[6]

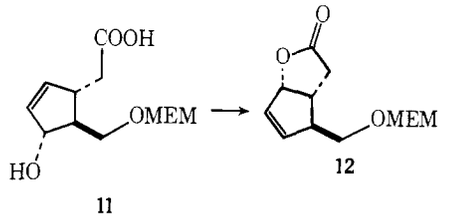
Chart I. Synthesis of Epoxide 3



[a] HOAc–HOH (3:2), 19 h. [b] MEMCl, *i*-Pr_2NEt, CH_2Cl_2. [c] H_2O_2, HOH, MeOH, NaOH, 5 °C. [d] CH_2N_2. [e] NaH, THF, $C_6H_5CH_2Br$. [f] NBA, acetone–HOH (2:1), *hν*. [g] Ag_2O, DME, reflux, 18 h.

Epoxide **3** was readily prepared from the known bicyclo[2.2.1]heptane derivative **6**[4d] by the sequence of reactions outlined in Chart I. Cleavage of ketal **6** with aqueous acetic acid followed by protection of the C(7) hydroxymethyl group as its β-methoxyethoxymethyl (MEM) ether[7] gave compound **8** in 79% overall yield. The reported stability under a wide variety of reaction conditions (e.g., strong bases, mild acids) of MEM ethers, coupled with the fact that they can be selectively cleaved in the presence of other functional groups (e.g., benzyl, allyl, THP ethers), was the prime reason for using this protecting group.

The sensitive hydroxy acid **11**, produced during the Baeyer–Villiger oxidation of ketone **8**, was directly esterified with ethereal diazomethane in order to avoid rearrangement to the bicyclic lactone **12**. Benzylation of hydroxy ester **9** was



11 **12**

accompanied by some cleavage of the methyl ester which we were unable to avoid. Use of fresh sodium hydride and rigorously anhydrous conditions still led to cleavage of the methyl

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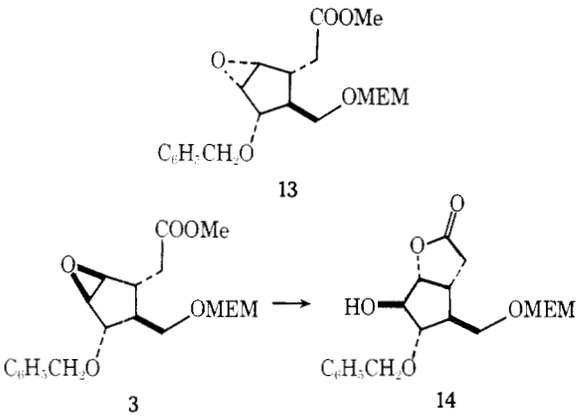
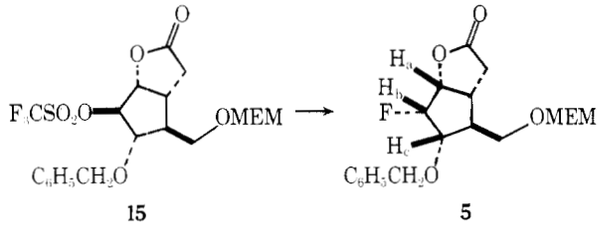
ester in approximately 30–35% yield. Reesterification of the crude benzylated product gave, however, a >90% yield of benzyl ester **10**.

Epoxidation of **10** with *m*-chloroperbenzoic acid in methylene chloride containing sodium bicarbonate gave a 3:1 mixture respectively of epoxides **13**[8] and **3**. Epoxide **3** was extremely sensitive to acid and rearranged to the bicyclic lactone **14**. The conversion of **3** into lactone **14** could be facilitated by treatment of a methylene chloride solution of **3** with boron trifluoride etherate at 0 °C. The yields of **14** ranged from a low of 45% to a high of 68%. During the course of this investigation, we observed that commercially available alumina (Woelm 200 neutral)[9] catalyzed the intramolecular opening of epoxide **3** under extremely mild conditions in reproducible yields on the order of 60%.



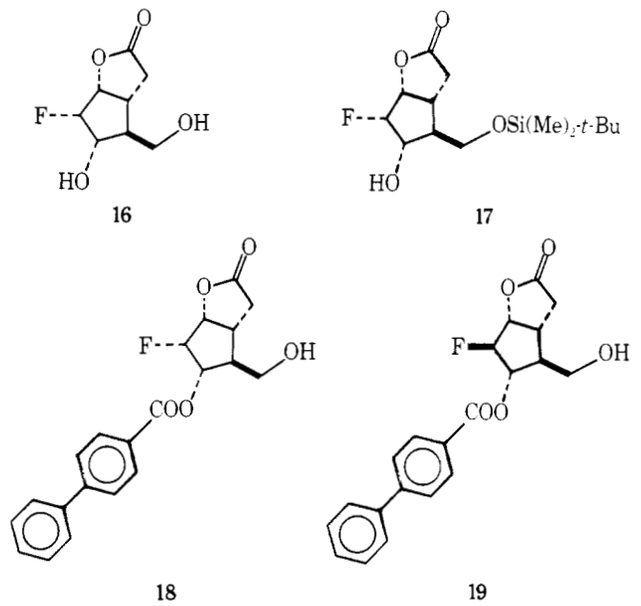
Exclusive formation of the desired β-oriented epoxide **3** was achieved via a two-step process. Submission of olefin **10** to bromohydrin formation ($CH_3CONHBr$, $h\nu$, aqueous acetone, −15 °C) followed by treatment with silver oxide in dimethoxyethane afforded an 85% yield of epoxide **3** as the sole product. Our efforts to generate fluoro lactone **5** from epoxide **3** via fluorohydrin **4** were unsuccessful. During one attempt, treatment of epoxide **3** with potassium bifluoride in hot ethylene glycol as described previously[2c] led not to the expected fluorohydrin but instead gave rise (56%) to an hydroxy lactone which was shown to be identical in all respects with the hydroxy lactone **14** prepared above.

Despite the limited amount of data on monofluorosubstitution of five-membered carbocyclic rings,[5] the availability of alcohol **14** raised the possibility of introducing a fluorine atom on the five-membered ring of **14** by direct S_N2 displacement of either the mesylate or tosylate derived from alcohol **14**. The use of triflates to facilitate nucleophilic displacement reaction on five-membered rings[10] prompted us to prepare the trifluoromethane sulfonate derivative **15**. Reaction of **15** with potassium fluoride in acetonitrile containing 18-crown-6[11] led to a disappointingly low yield (2%) of fluoro lactone **5**. Treatment of **15** with excess cesium fluoride[12] in refluxing dimethylformamide for 30 min produced a 13% yield of fluoro lactone **5**. An almost insignificant improvement in yield could be realized by changing solvents. For example, excess cesium fluoride in hexamethylphosphoramide heated at 140–145 °C for ca. 25 min gave a 16% yield of compound **5**. Use of much milder reaction conditions [tetra-*n*-butylammonium fluoride (TBAF), refluxing tetrahydrofuran, 15 min][10] afforded a 55% reproducible yield of the desired fluoro lactone **5**.[13]

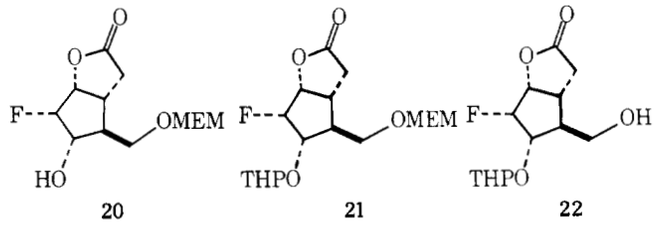


Preliminary evidence, obtained from the 250-MHz NMR spectrum, indicated that the fluorine atom was located at C(10) [prostaglandin numbering] and possessed the α orientation. The NMR spectrum revealed H_b as a doublet of triplets centered at δ 4.98 with an observed geminal fluorine–H_b coupling constant of 55 Hz. J_{ab} and J_{cb} were both 3 Hz. Further evidence in support of our structural assignment was arrived at by conversion of fluoro lactone **5** into the crystalline fluoro alcohol **18** which was shown to be isomeric at C(10) with the known crystalline fluoro alcohol **19**.[2c] Fluoro alcohol **19** was a key intermediate in the synthesis of 10β-fluoroprostaglandin $F_{2\alpha}$ methyl ester.[2c]

Cleavage of MEM ether **5** with aqueous hydrobromic acid in tetrahydrofuran followed by hydrogenolysis afforded (94%) the crystalline diol **16**, mp 102–103 °C. Selective silylation of the primary hydroxyl with *tert*-butyldimethylchlorosilane[14] provided (88%) bicyclic lactone **17**. Conversion of the secondary hydroxyl of **17** into its *p*-phenylbenzoate followed by desilylation[14] generated (63%) crystalline alcohol **18**, mp 180–181 °C [R_f 0.61 (ether–ethyl acetate, 1:1)]. The C(10) isomeric fluoro *p*-phenylbenzoate **19**[2c] melted at 161–162 °C and exhibited an R_f value of 0.78 (ether–ethyl acetate, 1:1).

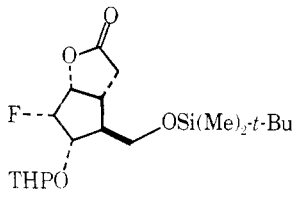


Having previously encountered in the 10β-fluoro series substantial (ca. 20%) β elimination of the C(11) *p*-phenylbenzoate unit during elaboration of the ω side chain via the Emmons reaction, we set out to prepare directly from **5** the C(11) tetrahydropyranyloxy derivative **22**. Hydrogenolysis (H_2, 10% Pd/C, EtOH) of **5** proceeded in near quantitative yield to alcohol **20**. Tetrahydropyranylation (DHP, CH_2Cl_2, TsOH) of **20** gave in very high yield compound **21**. The synthetic sequence to the key intermediate alcohol **22** was based on the ability to cleave the MEM ether in the presence of the THP ether for which there was ample precedent.[7] Attempted cleavage of MEM ether **21** with Lewis acids at low temperature for short reaction periods resulted in formation of alcohol



20 with no trace of the desired material **22.** Long reaction periods resulted in cleavage of both the THP ether and the MEM ether giving rise to diol **16.**

Unable to prepare alcohol **22** by the above sequence, we turned our attention to compound **17.** Tetrahydropyranylation of **17** using pyridinium *p*-toluenesulfonate (PPTS)[15] provided in 95% yield THP ether **23.** The *tert*-butyldimethylsilyl ether was efficiently cleaved with tetra-*n*-butylammonium fluoride in near quantitative yield. With the ready availability of the desired alcohol **22,** we transformed it into 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester employing, for the most part, well-established synthetic methodology[16] (Chart II). 10α-Fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) and 15-*epi*-10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1'**) were easily separated on silica gel. The more polar isomer has been assigned the (15*S*) natural configuration.[17]



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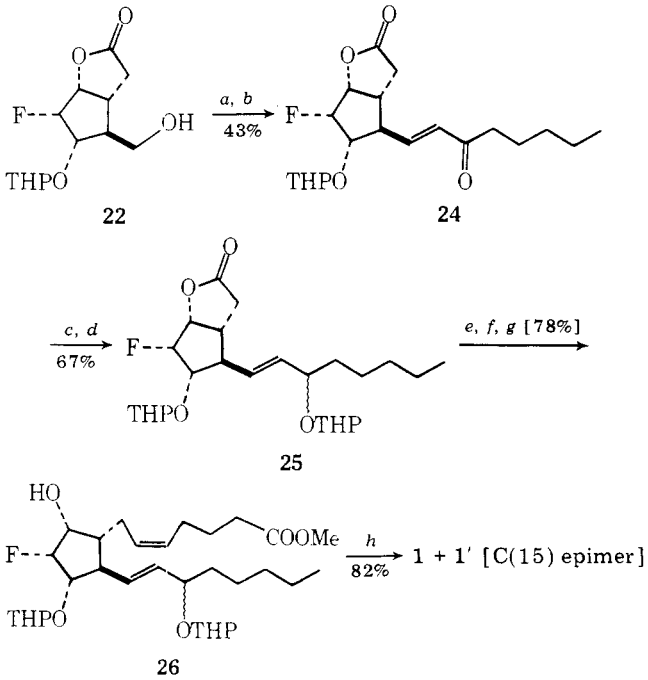
Experimental Section

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 at either 60 MHz (Varian A-60A or T-60 spectrometer), 100 MHz (Jeolco), or 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. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GHLF (250 μm).

Chart II. 10α-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester



[a] PCC, NaOAc, CH_2Cl_2. [b] NaH, THF, $(MeO)_2P(O)CH_2COC_5H_{11}$, 0 °C. [c] $NaBH_4$, $CeCl_3$, MeOH. [d] DHP, PPTS, CH_2Cl_2. [e] *i*-Bu_2AlH, toluene, −60 °C. [f] $(C_6H_5)_3P{=}CH(CH_2)_3COONa$, Me_2SO. [g] CH_2N_2. [h] PPTS, EtOH.

***anti*-7-Hydroxymethylbicyclo[2.2.1]hept-5-en-2-one (7).** A solution of 7.20 g (39.6 mmol) of ketal **6** in 240 mL of aqueous acetic acid [prepared from glacial acetic acid–water, 3:2 (v/v)] was stirred at room temperature for 19 h. The reaction was cooled to 0 °C and quenched with a cold solution of sodium hydroxide (96 g) in water (240 mL) followed by the addition of solid sodium bicarbonate until solution was pH 8. The product was isolated by exhaustive extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The crude product (5.10 g) was chromatographed on 200 g of silica gel. Elution with ether–hexane (3:1) provided 4.58 g (84%) of pure ketone **7** as a colorless oil: bp 125 °C (1.2 mmHg); R_f 0.29 (ether); IR (film) 3400, 2975, 2925, 2880, 1742, 1420, 1352, 1325, 1285, 1238, 1200, 1165, 1146, 1095, 1065, 1042, 1024, 995, 965, 940, 923, 880, 868, 830, 790, 755, 725 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 6.4 (m, 1 H, olefinic proton), 5.91 (m, 1 H, olefinic proton), 3.62 (d, 2 H, J = 6.5 Hz, $-CH_2OH$), 3.50 (s, 1 H, –OH), 3.2–2.9 (m, 2 H, C(1) and C(4) protons), 2.60 (t, 1 H, J = 6.5 Hz, C(7)H), 2.2–1.9 (m, 2 H, C(3) protons); mol wt calcd ($C_8H_{10}O_2$), 138.0681, and found, 138.0661. Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.63; H, 7.32.

***anti*-7-[(β-Methoxyethoxymethoxy)methyl]bicyclo[2.2.1]-hept-5-en-2-one (8).** A solution of 4.58 g (33.2 mmol) of keto alcohol **7** in 60 mL of anhydrous methylene chloride containing 8.7 mL (49.8 mmol) of diisopropylethylamine under nitrogen was treated dropwise with 5.7 mL (49.8 mmol) of methoxyethoxymethyl chloride. After the mixture was stirred for 4 h, the reaction was diluted with 100 mL of methylene chloride and washed with 50% brine solution. The aqueous layer was washed with methylene chloride, and the combined organic layers were dried ($MgSO_4$) prior to filtration with evaporation of the solvent under reduced pressure. There was obtained 7.40 g of crude product which was purified directly on 200 g of silica gel. Elution with ether–hexane (1:1) provided 7.02 g (94%) of pure MEM ether (**8**) as a colorless oil: bp 125–127 °C (0.35 mmHg); R_f 0.68 (ether); IR (film) 2940, 2890, 2820, 1746, 1455, 1420, 1398, 1370, 1352, 1322, 1310, 1280, 1265, 1249, 1205, 1175, 1160, 1111, 1095, 1065, 1045, 990, 971, 960, 875, 855, 820, 780, 770, 755, 740, 720 cm^{-1}; NMR (60 MHz) (CCl_4) δ 6.36 (m, 1 H, olefinic proton), 5.92 (m, 1 H, olefinic proton), 4.50 (s, 2 H, $-OCH_2O-$), 3.63–3.35 (m, 6 H, $-OCH_2CH_2OCH_2OCH_2-$), 3.28 (s, 3 H, $-OCH_3$), 3.20–2.50 (m, 3 H), 1.86 (m, 2 H, C(3) protons). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.40; H, 8.21.

Methyl 4-Hydroxy-5-[(β-methoxyethoxymethoxy)methyl]-2-cyclopentene-1-acetate (9). A solution of 8.40 g (37.2 mmol) of ketone **8** in 200 mL of methanol and 175 mL of water was cooled to 0 °C and treated with 45 mL of a 2.5 M sodium hydroxide solution followed by 31 mL of 30% hydrogen peroxide. After 19 h at 0–5 °C, the reaction mixture was extracted with ether and the aqueous layer was treated with 37 g of solid sodium sulfite. The pH of the aqueous layer was adjusted to pH 4 with concentrated hydrochloric acid. Exhaustive extraction with ethyl acetate gave, after drying ($MgSO_4$) and removal of the solvent in vacuo, a viscous oil which was treated at 0 °C directly with an ethereal solution of diazomethane. Removal of the ether under reduced pressure yielded the crude ester **9** which was chromatographed on 300 g of silica gel. Elution with ether–hexane (2:1) provided 6.61 g (65%) of pure **9** as a colorless oil: bp 95–100 °C (bath temperature, 0.16 mmHg); R_f 0.35 (ether); IR (film) 3450, 3060, 2960, 2935, 2895, 2820, 1738, 1441, 1418, 1375, 1355, 1310, 1255, 1205, 1180, 1170, 1140, 1110, 1050, 930, 880, 851, 780, 740 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 5.76 (b s, 2 H, $-CH{=}CH-$), 4.65 (m, 3 H, C(4)H, $-OCH_2O-$), 3.80–3.50 (m, 6 H), 3.61 (s, 3 H, $-COOCH_3$), 3.27 (s, 3 H, $-OCH_3$), 3.10–2.10 (m, 4 H). Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 57.00; H, 8.19.

Methyl 4-(Phenylmethoxy)-5-[(β-methoxyethoxymethoxy)-methyl]-2-cyclopentene-1-acetate (10). To a stirred suspension of 1.43 g (29.7 mmol) of sodium hydride (50% oil dispersion) in 80 mL of anhydrous tetrahydrofuran under an atmosphere of nitrogen was added, in one portion, 3.70 g (13.5 mmol) of cyclopentenol **9** dissolved in 40 mL of dry tetrahydrofuran. The reaction was heated to 50 °C and treated with 3.5 mL (29.7 mmol) of benzyl bromide. Upon completion of the addition, the reaction was refluxed. After 12 h, the reaction was quenched by the addition of water and the solvent was evaporated in vacuo. The resulting aqueous residue was acidified to pH 4 with a 2 M solution of sodium bisulfate, and the product (mixture of ester and acid) was isolated by extraction with ethyl acetate. After washing the combined organic layers with brine and drying them over anhydrous magnesium sulfate, the solvent was removed under

reduced pressure. The crude product was treated with ethereal diazomethane. Usual workup gave the desired product **10** in near quantitative yield. Chromatography of the resulting oil on 150 g of silica gel employing ether–hexane (1:3) provided 4.56 g (93%) of pure benzyl ether **10** as a pale yellow oil: R_f 0.84 (ether). Distillation of **10** yielded an analytical sample: bp 125–130 °C (bath temperature) (0.016 mmHg); IR (film) 3070, 3040, 2955, 2935, 2890, 1740, 1500, 1457, 1440, 1415, 1368, 1315, 1260, 1208, 1175, 1135, 1117, 1095, 1070, 1050, 1027, 990, 880, 780, 740, 700 cm^{-1}; NMR (60 MHz) (CCl_4) δ 7.20 (b s, 5 H, C_6H_5), 5.78 (b s, 2 H, -C**H**=C**H**–), 4.58 (s, 2 H), 4.50 (s, 2 H), 4.28 (d, 1 H, C(4)H), 3.60 (s, 3 H, -COOC**H**$_3$), 3.48 (m, 6 H), 3.30 (s, 3 H, -OC**H**$_3$), 3.00–2.00 (m, 4 H). Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.78; H, 7.89.

Epoxidation of Methyl 4-(Phenylmethoxy)-5-[(β-methoxyethoxymethoxy)methyl]-2-cyclopentene-1-acetate (10). A solution of 3.93 g (28.5 mmol) of *N*-bromoacetamide in 80 mL of acetone and 40 mL of water at 0 °C was irradiated for 45 min with a 275-W sunlamp. The resulting yellow solution was cooled to −10 °C and 5.18 g (14.2 mmol) of cyclopentene **10** in 27 mL of acetone was added in one portion. After 3.5 h (−10 °C), the reaction was quenched by the addition of a 10% aqueous sodium thiosulfate solution. The reaction mixture was made basic by the addition of solid sodium bicarbonate and the solvent was removed in vacuo. The resulting residue was taken up in ether and washed with 50% brine solution. The aqueous layer was backwashed with ether. The combined ether layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. There was obtained 7.08 g of crude bromohydrin which was used immediately in the next reaction.

The crude bromohydrin from above was dissolved in 80 mL of dry dimethoxyethane and treated with 16.5 g (71.2 mmol) of silver oxide. The vigorously stirred solution was refluxed (bath temperature 105–115 °C) under an atmosphere of nitrogen for 22 h. The reaction mixture was cooled to room temperature and filtered through a pad of anhydrous magnesium sulfate. The filtrate was concentrated in vacuo leaving 5.03 g of an oil which was chromatographed on 200 g of silica gel. Elution with ether–hexane (1:2) gave 4.62 g (85%) of pure β-epoxide **3** as an oil: R_f 0.69 (ether); IR (film) 3080, 3060, 3025, 2945, 2920, 2875, 2810, 1740, 1498, 1450, 1435, 1410, 1363, 1263, 1200, 1170, 1090, 1040, 986, 940, 915, 882, 840, 738, 700 cm^{-1}; NMR (60 MHz) (CCl_4) δ 7.24 (s, 5 H), 4.73 (m, 4 H, -OC**H**$_2$O–, -OC**H**$_2$C$_6$H$_5$), 3.80 (s, 1 H), 3.62 (s, 3 H, -COOC**H**$_3$), 3.56–3.35 (m, 8 H), 3.31 (s, 3 H, -OC**H**$_3$), 2.70–1.90 (m, 4 H). Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.15; H, 7.57.

3,3aα,4aα,5β,6α,6aα-Hexahydro-6-hydroxy-5-(phenylmethoxy)-4-[(β-methoxyethoxymethoxy)methyl]-2*H*-cyclopenta[*b*]furan-2-one (14) To a suspension of 80 g of alumina (Woelm 200 neutral super activity grade I) in 100 mL of anhydrous ether was added 4.04 g (10.6 mmol) of epoxide **3** dissolved in 50 mL of anhydrous ether. After the solution was stirred for 31 h, the reaction was treated with 200 mL of methanol and stirring was continued for an additional 4 h. The heterogeneous reaction mixture was filtered through Celite. The precipitate was washed with methanol. The filtrate was evaporated under reduced pressure, and the resulting oil was chromatographed on 200 g of silica gel. Elution with ether–hexane (3:1) gave 2.24 g (58%) of pure alcohol **14** as a colorless oil: R_f 0.33 (ether); IR (film) 3430, 3060, 3022, 2720, 2875, 1779, 1495, 1465, 1451, 1435, 1411, 1365, 1288, 1240, 1200, 1165, 1130, 1115, 1090, 1040, 955, 847, 741, 697 cm^{-1}; NMR (60 MHz) ($CDCl_3$) δ 7.20 (s, 5 H), 4.58 (m, 5 H), -OC**H**$_2$C$_6$H$_5$, -OC**H**$_2$O–, -C**H**OCO), 4.11 (m, 2 H), 3.84–3.41 (m, 7 H), 3.31 (s, 3 H, -OC**H**$_3$), 3.0–2.0 (m, 4 H).

6-Fluoro-3,3aα,4aα,5β,6β,6aα-Hexahydro-5-(phenylmethoxy)-4-[(β-methoxyethoxymethoxy)methyl]-2*H*-cyclopenta[*b*]furan-2-one (5). A solution of 3.10 mg (0.85 mmol) of bicyclic alcohol **14** in 4.8 mL of dry methylene chloride containing 0.12 mL (1.48 mmol) of anhydrous pyridine cooled to 0 °C was treated dropwise over a 30-min period with a solution of 0.21 mL (1.27 mmol) of trifluoromethanesulfonic anhydride in 1.6 mL of dry methylene chloride. After an additional 30 min at 0 °C, the reaction was diluted with 50 mL of methylene chloride and washed with a saturated sodium bicarbonate solution. The organic phase was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent in vacuo (30 °C) provided the crude triflate as reddish crystals which were used immediately in the next reaction.

The crude triflate from above in 5.5 mL of anhydrous tetrahydrofuran was added in one portion to 1.11 g (4.27 mmol) of tetra-*n*-butylammonium fluoride (weighed in an inert atmosphere). The reaction mixture was refluxed for 15 min. After the solution was cooled to 25 °C, the reaction was diluted with 75 mL of ether and washed with a 50% brine solution. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with ether–hexane (2:1) gave 172 mg (55%) of pure fluoro lactone **5** as an oil: R_f 0.45 (ether); IR (film) 3060, 3030, 2925, 2875, 2810, 1780, 1500, 1470, 1457, 1410, 1366, 1310, 1285, 1210, 1168, 1110, 1068, 990, 964, 911, 852, 800, 751, 700 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 7.34 (s, 5 H), 4.98 (dt, 1 H, J_{FH} = 55 Hz, J = 3 Hz, C(6)H), 4.83–4.70 (m, 1 H, C(6a)H), 4.65 (ABq, 2 H, J = 8 Hz, $\Delta\nu_{AB}$ = 4.1 Hz), 4.61 (ABq, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 44.4 Hz), 3.88–3.51 (m, 7 H), 3.37 (s, 3 H, OCH$_3$), 2.80 (m, 2 H), 2.40 (m, 2 H). Anal. Calcd for $C_{19}H_{25}FO_6$: C, 61.95; H, 6.84. Found: C, 62.17; H, 7.09.

6-Fluoro-3,3aα,4aα,5β,6β,6aα-Hexahydro-5-hydroxy-4-(hydroxymethyl)-2*H*-cyclopenta[*b*]furan-2-one (16). A solution of 210 mg (0.57 mmol) of fluoro MEM ether **5** in 3.0 mL of tetrahydrofuran was treated with 3.0 mL of 48% aqueous hydrobromic acid. After the solution was stirred at room temperature for 2 h, the acid was neutralized with 7.0 mL of 10% sodium hydroxide solution. Solid sodium bicarbonate was added until the mixture was basic. The product was extracted with 2 × 70 mL portions of ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was chromatographed on 8.0 g of silica gel. Elution with ether gave 149 mg (93%) of the desired alcohol as a colorless oil: R_f 0.49 (ethyl acetate); IR (film) 3425, 3060, 3040, 2935, 2880, 1778, 1500, 1473, 1458, 1420, 1364, 1310, 1285, 1208, 1171, 1138, 1118, 1084, 1062, 1031, 951, 918, 895, 850, 805, 740, 700 cm^{-1}; NMR (100 MHz) ($CDCl_3$) δ 7.35 (s, 5 H), 4.98 (dt, 1 H, J_{HF} = 56 Hz, J = 3.0 Hz, -C**H**F–), 4.81 (m, 1 H, -C**H**OCO–), 4.60 (ABq, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 8.1 Hz, -OC**H**$_2$C$_6$H$_5$), 4.1–3.4 (m, 3 H), 3.0–2.0 (m, 4 H); mol wt calcd ($C_{15}H_{17}FO_4$), 280.1119, and found, 280.1111. A solution of 305 mg (1.09 mmol) of the above alcohol in 9.5 mL of absolute ethanol was added to 140 mg of 10% palladium on carbon under an atmosphere of hydrogen. The reaction was stirred for 6 h. The reaction mixture was filtered through Celite to remove the catalyst. The filtrate was concentrated in vacuo, and the residue was chromatographed on 14 g of silica gel. Elution with ether–methanol (10:1) gave 195 mg (94%) of the fluoro diol **16** as a white crystalline compound: R_f 0.46 [ether–methanol, 5:1]; IR (KBr) 3370, 3200, 2975, 2970, 2880, 1780, 1471, 1425, 1419, 1380, 1370, 1349, 1318, 1305, 1290, 1270, 1224, 1219, 1170, 1120, 1079, 1075, 1055, 1041, 1025, 975, 945, 938, 905, 873, 850, 835, 795, 788, 725, 695, 680 cm^{-1}; NMR (100 MHz) (CF_3COOH) δ 5.02 (dm, 1 H, J_{HF} = 18 Hz, -C**H**OCO–), 4.98 (dt, 1 H, J_{HF} = 54 Hz, J = 3 Hz, -C**H**F–), 4.53 (m, 1 H), 4.40–4.05 (m, 1 H), 3.96 (d, 2 H, J = 6 Hz, -C**H**$_2$OH), 3.2–2.3 (m, 5 H). Recrystallization from acetone–hexane afforded an analytical sample of diol **16**, mp 102–103 °C. Anal. Calcd for $C_8H_{11}FO_4$: C, 50.53; H, 5.83. Found: C, 50.55; H, 5.95.

6-Fluoro-3,3aα,4aα,5β,6β,6aα-Hexahydro-5-hydroxy-4-[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-cyclopenta[*b*]furan-2-one (17). A mixture of 174 mg (0.92 mmol) of fluoro diol **16**, 152 mg (1.01 mmol) of *tert*-butyldimethylchlorosilane, and 143 mg (2.11 mmol) of imidazole in 1.3 mL of anhydrous dimethylformamide was stirred at 0 °C under an atmosphere of nitrogen for 3 h followed by warming to room temperature. After a total of 6 h, the reaction was diluted with 30 mL of ether and washed with a 50% solution of brine. The aqueous layer was backwashed with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed on 12 g of silica gel. Elution with ether–hexane (1:1) provided 246 mg (88%) of pure silyl ether **17** as a colorless oil: R_f 0.78 (ether); IR (film) 3420, 2960, 2940, 2890, 2860, 1780, 1475, 1461, 1418, 1385, 1360, 1350, 1320, 1260, 1211, 1165, 1103, 1075, 1050, 1008, 990, 972, 960, 940, 915, 895, 838, 812, 780 cm^{-1}; NMR (100 MHz) ($CDCl_3$) δ 5.04 (dt, 1 H, J_{HF} = 55 Hz, J = 3 Hz, -C**H**F–), 4.90 (ddd, 1 H, J = 20, 8, 4 Hz, -C**H**OCO–), 4.08 (dm, 1 H, J = 20 Hz, -C**H**OH–), 3.78 (d, 2 H, J = 6 Hz, -C**H**$_2$OSi); mol wt calcd ($C_{14}H_{25}FO_4Si$–H_2O), 286.1401, and found, 286.1368.

6-Fluoro-3,3aα,4aα,5β,6β,6aα-hexahydro-4-(hydroxymethyl)-2-oxo-2*H*-cyclopenta[*b*]furan-5-yl[1,1′-biphenyl]-4-carboxylate (18). A solution of 19 mg (0.063 mmol) of fluorohydrin **17** in 0.08 mL of dry pyridine was treated with 16 mg (0.75 mmol) of *p*-phenylbenzoyl chloride. The reaction was stirred at room temperature for 3 h. The reaction was quenched by the addition of three drops of water. Stirring was continued for an additional 15 min. After dilution with 20 mL of ether, the reaction mixture was washed with a saturated brine solution. The organic phase was dried ($MgSO_4$) and concentrated in vacuo leaving 30 mg of crude *p*-phenylbenzoate.

The above *p*-phenylbenzoate (30 mg, 0.06 mmol) in 0.25 mL of anhydrous tetrahydrofuran was treated with 49 mg (0.19 mmol) of tetra-*n*-butylammonium fluoride. After 1 h, the reaction mixture was diluted with 20 mL of ethyl acetate and washed with a 50% brine solution. The aqueous layer was backwashed with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on 2.0 g of silica gel. Elution with ether–ethyl acetate (1:1) gave 14 mg (63%) of pure alcohol **18** as a crystalline compound: R_f 0.61 (ether–ethyl acetate, 1:1); IR ($CHCl_3$) 1785, 1717 cm^{-1}; NMR (250 MHz) (CD_3COCD_3) δ

7.84–7.70 (m, 4 H), 7.56–7.37 (m, 5 H), 5.48–5.37 (m, 1.5 H), 5.22–5.10 (m, 1.5 H). Recrystallization from methylene chloride–hexane provided an analytical sample of **18**, mp 180–181 °C. Anal. Calcd for $C_{21}H_{19}FO_5$: C, 68.10; H, 5.17. Found: C, 67.74; H, 5.30.

6-Fluoro-3,3aα,4α,5β,6β,6aα-Hexahydro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-[(*tert*-butyldimethylsilyloxy)methyl]-2*H*-cyclopenta[*b*]furan-2-one (23). A solution of 245 mg (0.81 mmol) of fluorohydrin **17** in 6.8 mL of anhydrous methylene chloride containing 0.15 mL (1.61 mmol) of dihydropyran and 40 mg (0.16 mmol) of pyridinium *p*-toluenesulfonate[15] was stirred at room temperature for 4 h. The reaction was diluted with 70 mL of ether and washed with a saturated sodium bicarbonate solution. The ether layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude oil was chromatographed on 13 g of silica gel. Elution with ether–hexane (1:2) provided 297 mg (95%) of pure tetrahydropyranyl ether **23** as a colorless oil: R_f 0.55 (ether–hexane, 2:1); IR ($CHCl_3$) 2960, 2930, 2900, 2860, 1782, 1478, 1468, 1448, 1420, 1394, 1380, 1328, 1315, 1263, 1170, 1120, 1098, 1078, 1062, 1038, 990, 975, 940, 919, 875, 840, 810 cm^{-1}. Anal. Calcd for $C_{19}H_{33}FO_5Si$: C, 58.73; H, 8.56. Found: C, 59.01; H, 8.76.

6-Fluoro-3,3aα,4α,5β,6β,6aα-Hexahydro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-(hydroxymethyl)-2*H*-cyclopenta[*b*]-furan-2-one (22). To 630 mg (2.41 mmol, weighed under nitrogen) of tetra-*n*-butylammonium fluoride cooled to 0 °C was added, in one portion, a solution of 255 mg (0.66 mmol) of silyl ether **23** in 2.8 mL of anhydrous tetrahydrofuran. The reaction was warmed to room temperature after 5 min, and stirring was continued for 15 min. The reaction mixture was treated with 50% brine solution, and the product was isolated by extraction with ethyl acetate. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude oil was purified in 10 g of silica gel. Elution with ether–ethyl acetate (1:2) gave 177 mg (98%) of pure alcohol **22** as a colorless oil: R_f 0.38 (ethyl acetate); IR (film) 3450, 2950, 2875, 1782, 1472, 1455, 1445, 1435, 1420, 1360, 1325, 1315, 1285, 1265, 1215, 1204, 1195, 1185, 1173, 1145, 1120, 1080, 1061, 1048, 1040, 1035, 975, 950, 915, 875, 850, 815, 798, 790, 763 cm^{-1}; mol wt calcd ($C_{13}H_{19}FO_5$–H_2O), 256.1111, and found, 256.1119.

6-Fluoro-3,3aα,4α,5β,6β,6aα-Hexahydro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-(3-oxo-1(*E*)-octenyl)-2*H*-cyclopenta-[*b*]furan-2-one (24). To a mixture of 190 mg (0.88 mmol) of pyridinium chlorochromate,[18] 14 mg (0.18 mmol) of sodium acetate, and 0.5 g of Celite in 2.0 mL of anhydrous methylene chloride under a nitrogen atmosphere was added 60 mg (0.22 mmol) of alcohol **22** dissolved in 1.0 mL of methylene chloride. The reaction was stirred for 3 h at room temperature followed by dilution with 30 mL of ethyl acetate. Filtration through a pad of fluorisil and anhydrous magnesium sulfate followed by washing of the pad with ethyl acetate and evaporation of the solvent in vacuo provided 45 mg of the desired fluoro aldehyde which was used immediately in the next reaction.

To a stirred suspension of 10.5 mg (0.22 mmol) of 50% sodium hydride dispersion in 3.0 mL of tetrahydrofuran (freshly distilled from lithium aluminum hydride) cooled to 0 °C under nitrogen was added dropwise 0.05 mL of dimethyl (2-oxoheptyl)phosphonate. After the solution was stirred at room temperature for 2 h, the mixture was cooled to 0 °C and treated with the above aldehyde in 1.8 mL of anhydrous tetrahydrofuran. After 20 min, the reaction was quenched with a few drops of saturated ammonium chloride solution. The reaction mixture was diluted with 30 mL of ether and washed with 50% brine solution. The aqueous layer was backwashed with ether, and the combined ether phases were dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent provided crude enone which was chromatographed on 3 g of silica gel. Elution with ether–hexane (2:1) gave 35 mg (43% overall) of pure crystalline enone **24**: mp 62–65 °C; R_f 0.40 (ether); IR (KBr) 2945, 2870, 1768, 1691, 1629, 1470, 1408, 1380, 1352, 1325, 1283, 1280, 1232, 1205, 1175, 1131, 1116, 1095, 1060, 1025, 968, 912, 895, 870, 851, 816, 800, 738, 720 cm^{-1}.

6-Fluoro-3,3aα,4α,5β,6β,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 (25). A solution of 52 mg (0.14 mmol) of enone **24** in 1.0 mL of methanol containing 50 mg of cerium(III) chloride[19] was treated over a 2-min period with 5.4 mg (0.14 mmol) of sodium borohydride. After 15 min at room temperature, the reaction was quenched with a few drops of saturated ammonium chloride solution and 30 mL of ethyl acetate. The mixture was washed with 50% brine solution, and the organic layer was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave 53 mg of the desired allylic alcohol which was homogeneous by TLC analysis: R_f 0.53 (ether–ethyl acetate, 1:1).

The above allylic alcohol (53 mg) in 1.5 mL of anhydrous methylene chloride containing 7 mg (0.028 mmol) of pyridinium *p*-toluenesulfonate[15] was treated with 0.026 mL (0.28 mmol) of dihydropyran. After 6 h at room temperature, the reaction mixture was diluted with 30 mL of ether. Subsequent washing with saturated sodium bicarbonate solution, drying over anhydrous magnesium sulfate, filtration, and removal of the solvent in vacuo afforded an oil which was chromatographed on 3 g of silica gel. Elution with ether–hexane (3:1) provided 43 mg (67% overall) of pure **25** as a white solid: R_f 0.85 (ether–ethyl acetate, 1:1); IR (KBr) 2935, 2850, 1780, 1470, 1456, 1441, 1359, 1206, 1185, 1137, 1112, 1095, 1078, 1058, 1025, 975, 912, 891, 869, 818, 800 cm^{-1}.

10α-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (1). A solution of 42 mg (0.09 mmol) of lactone **25** in 0.8 mL of dry toluene cooled to −60 °C under nitrogen was treated dropwise with 0.28 mL (0.28 mmol) of a 1 M solution of diisobutylaluminum hydride in toluene. After 1 h, the reaction was quenched at −60 °C by the careful addition of methanol. The mixture was diluted with 35 mL of ethyl acetate, warmed to room temperature, and washed with water. Several drops of a 2 M sodium bisulfate solution were necessary to break up the gelatinous precipitate. The aqueous layer was backwashed with ethyl acetate, and the combined organic layers were dried over anhydrous magnesium sulfate. Following evaporation of the solvent in vacuo and azeotropic removal of water with benzene to remove the last traces of moisture, there was obtained 44 mg of the desired hemiacetal which was used immediately in the next reaction.

A suspension of 45 mg (0.93 mmol) of 50% sodium hydride dispersion in 0.5 mL of dry dimethyl sulfoxide was heated with stirring at 50–55 °C for 2 h under a nitrogen atmosphere. To the above solution of dimsylsodium cooled to room temperature was added 205 mg (0.46 mmol) of (4-carboxybutyl)triphenylphosphonium bromide [dried for 2 h at 100 °C (0.1 mmHg) prior to use] in 0.4 mL of dry dimethyl sulfoxide. After 30 min, a solution of the above hemiacetal (44 mg) in 0.3 mL of dry dimethyl sulfoxide was added to the red-orange ylid solution. After 2 h, the reaction was quenched with ice and diluted with 30 mL of ethyl acetate. The pH was adjusted to ca. 4 with 2 M sodium bisulfate prior to washing with water. The aqueous layers were exhaustively extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was treated with an ethereal solution of diazomethane. The crude bis(tetrahydropyranyl) derivative **26** of 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester was purified on 3 g of silica gel. Elution with ether gave 40 mg (78%) of a mixture consisting of approximately equal amounts of pure **26** and the corresponding C(15) β-isomer.

A solution of 40 mg (0.072 mmol) of the bis(tetrahydropyranyl) derivative **26** and the corresponding C(15) epimeric compound in 0.6 mL of absolute ethanol was treated with 3.6 mg (0.014 mmol) of pyridinium *p*-toluenesulfonate.[15] After 20 h at room temperature, the reaction mixture was concentrated in vacuo and the residue was chromatographed on 2.0 g of silica gel. Elution with ether gave, in order of elution, 6.9 mg of pure 15-epi-10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1'**) (less polar) as a crystalline compound, mp 52.0–52.5 °C (from ether–hexane); 4.1 mg of a mixture of **1** and **1'**; and 11.7 mg of pure 10α-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) (more polar) as a crystalline compound, mp 86–87 °C (from ether–hexane): IR ($CHCl_3$) 3615, 3400, 3010, 2960, 2940, 2865, 1730, 1460, 1440, 1421, 1385, 1368, 1230, 1110, 975 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.68–5.51 (m, 2 H, olefinic protons), 5.48–5.27 (m, 2 H, olefinic protons), 4.73 (dt, 1 H, J_{HF} = 51 Hz, J = 4 Hz, –C**H**F–), 4.22 (bs, 1 H), 4.07 (m, 1 H), 3.88 (m, 1 H), 3.68 (s, 3 H, $-COOCH_3$), 0.88 (t, 3 H, J = 7 Hz).

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Registry No.—**1**, 69927-86-2; **1'**, 69927-87-3; **3**, 69927-88-4; **5**, 69927-89-5; **6**, 50703-29-2; **7**, 62447-87-4; **8**, 69927-90-8; **9**, 69927-91-9; **10**, 69927-92-0; **10** bromohydrin, 69927-39-5; **10** free acid, 69928-07-0; **11**, 69928-08-1; **13**, 69979-96-0; **14**, 69927-93-1; **15**, 69927-94-2; **16**, 69927-95-3; **17**, 69927-96-4; **17** *p*-phenylbenzoate, 69928-09-2; **18**, 69979-95-9; **22**, 69927-97-5; **23**, 69927-98-6; **24**, 69927-99-7; **25**, 69927-70-4; **26** α-isomer, 69928-00-3; **26** β-isomer, 69928-01-4; methoxyethoxymethyl chloride 3970-21-6; 3aα,4α,5β,6β,6aα-hexahydro-6-fluoro-5-(phenylmethoxy)-4-hydroxymethyl-2*H*-cyclopenta[*b*]foran-2-one, 69928-02-5; 3aα,4α,5β,6β,6aα-hexahydro-6-fluoro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-formyl-2*H*-cyclopenta[*b*]furan-2-one, 69928-03-6; dimethyl-2-oxoheptylphosphonate, 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-methoxy-2*H*-cyclopenta[*b*]furan-2-ol, 69928-04-7; hexahydro-6-fluoro-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-(3-hydroxy-1-octenyl)-2*H*-cyclopenta[*b*]furan-2-one, 69928-05-8; sodium 5-(triphenylphosphoranylidene)pentanoate, 41723-91-5; i, 69928-06-9.

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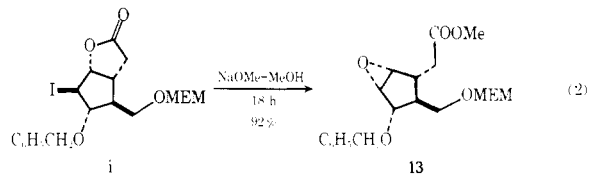

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Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 10.[1] NaH–RONa–$Co(OAc)_2$–CO, a New Reagent for the Carbonylation of Aryl Halides at Atmospheric Pressure

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The preparation of CoCRA (NaH–RONa–$Co(OAc)_2$) under carbon monoxide at atmospheric pressure led to cobalt carbonyl species of unprecedented reactivity. These new reagents, designated as CoCRACO, were found to be very efficient for the carbonylation of aryl halides at *atmospheric pressure.* Mixtures of aromatic acids and esters were obtained in good yields. Carbonylation of aryl halides in the presence of amines led to benzamides. Furthermore, it was demonstrated that all these reactions were catalytic with respect to cobalt.

It is well known that the preparation of cobalt carbonyl species from cobalt salts in aprotic media requires rather drastic conditions.[2] To our knowledge, only the use of iron–manganese alloy allows the preparation of active carbonyl species from cobalt salts at atmospheric pressure.[3]

Current literature also indicates that extreme conditions of reaction temperature and pressure are required for the carbonylation of aryl halides by cobalt carbonyl species.[4] The carbonylation of such halides is generally best achieved by nickel carbonyl species. Note that the presence of bases is often reported as favoring this kind of reaction; it is generally assumed that anionic carbonyl species react more easily with aryl halides than do neutral species.[5,6]

If we now consider the preparation and properties of complex reducing agents "NaH–RONa–MX_n" (abbreviated MCRA),[7] it could be thought that a preliminary reduction of metallic salts by NaH–RONa occurs and that, during the formation of MCRA, low oxidation state metal species and bases are simultaneously present. Thus, if some efficient ligands (like phosphines, dienes, or carbon monoxide) were simultaneously present, a stabilized low oxidation state complex should result instead of a reducing species.[8] Moreover, with carbon monoxide as ligand, anionic species should be reasonably expected.[9]

Some preliminary results verified these hypotheses.[10] Indeed, it was shown that preparation of CoCRA (NaH–*t*AmONa–$Co(OAc)_2$) under a slow stream of carbon monoxide led to cobalt carbonyl species (abbreviated here as CoCRACO for convenience) which were able to carbonylate aryl bromides at atmospheric pressure. However, subsequent studies showed that these reactions were of poor reproducibility. As a matter of fact, without apparent reason, reduction sometimes exceeded carbonylation. We therefore reinvestigated these reactions, and we can now report a highly reproducible method for the carbonylation of aryl halides at atmospheric pressure.

Results and Discussion

The Carbonylating Medium: NaH–RONa–$Co(OAc)_2$–CO (CoCRACO). In our previous work,[10] the cobalt carbonyl species were prepared by adding $Co(OAc)_2$, at 25 °C, to a suspension of NaH–*t*-AmONa in THF under a slow stream of carbon monoxide. The reaction medium was then warmed to 63 °C and stirred for 4 h before adding the aryl halide. Taking into account the poor reproducibility of the carbonylation reaction vs. reduction with the reagents thus obtained, a systematic study of reaction conditions was undertaken using bromobenzene as a test substrate.

This study led us to the following general procedure (more details are given in the Experimental Section): At room tem-

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