Acetylation of **16a** gave **16b**, an oil: MS, $m/e$ 416 (M$^+$); $[\alpha]_D$ -169° (EtOH); UV (EtOH) $\lambda_{max}$ 278 nm (sh, $\epsilon$ 2180), 284 (2390); IR (CCl$_4$) 1730 cm$^{-1}$; $^1$H NMR $\delta$ (CDCl$_3$) 0.88, 0.95, 1.01, 1.38 (methyl groups), 2.14, 2.28 (OAc groups), 4.6 (t, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 9 Hz, C-2 H), 6.31, 6.53 (d, $J$ = 2 Hz) (aromatic).

**6α-Hydroxyhexahydrocannabinol (23a).** Compound 25[16] (100 mg) in ethyl acetate (5 mL) was reduced with hydrogen at 3 atmospheric pressures over Adam's catalyst (20 mg). The solution was filtered and evaporated to dryness. The oil obtained (**23b**) showed one spot on TLC. It was reduced without prior purification with lithium aluminum hydride, following the procedure and workup described above. 6α-Hydroxyhexahydrocannabinol (C-1 methyl group $\alpha$, axial) (**23a**) was obtained as an oil: MS, $m/e$ 332 (M$^+$); $[\alpha]_D$ -85.4° (EtOH); $^1$H NMR $\delta$ (CDCl$_3$) 0.87, 1.09, 1.27, 1.36 (methyl groups), 3.92 (br s, 1, C-6 H), 6.05, 6.23 (d, $J$ = 2 Hz) (aromatic).

# Fluoroprostaglandins: Synthesis and Biological Evaluation of the Methyl Esters of (+)-12-Fluoro-, (-)-*ent*-12-Fluoro-, (+)-15-*epi*-Fluoro-, and (-)-*ent*-15-*epi*-12-Fluoroprostaglandin F$_{2\alpha}$

Paul A. Grieco,* William Owens, C.-L. J. Wang, Eric Williams, William J. Schillinger,

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

Ken Hirotsu, and Jon Clardy*

*Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853. Received January 9, 1980*

The synthesis and biological activity of the methyl esters of (+)-12-fluoroPGF$_{2\alpha}$, (+)-15-*epi*-12-fluoroPGF$_{2\alpha}$, (-)-*ent*-12-fluoroPGF$_{2\alpha}$, and (-)-*ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ are described. Each fluoroprostaglandin has been evaluated from pregnancy interruption in the hamster and smooth-muscle stimulating effects on gerbil colon and hamster uterine strips. All fluoroprostaglandins synthesized were shown to be neither substrates for the 15-hydroxyprostaglandin dehydrogenase nor inhibitors of the enzyme.
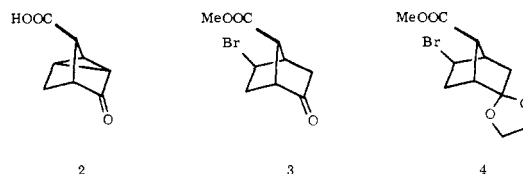
Our interest in developing luteolytic prostaglandins devoid of smooth-muscle stimulating activity led us some years ago to undertake the synthesis of ring-fluorinated derivatives of natural PGF$_{2\alpha}$.[1] The rationale behind incorporating fluorine atoms into the prostaglandin nucleus was, in part, based on the early observation by Fried and Sabo[2] who demonstrated that substantial enhancement of biological activity can be realized by substituting fluorine atoms for protons in biologically active substances. We were also cognizant of the possibility that analogues of natural PGF$_{2\alpha}$ possessing strategically placed fluorine atoms might not only exhibit prostaglandin-like activity but, more importantly, be more resistant to metabolic deactivation.

In order to probe the effect on biological activity of introducing a fluorine atom into the C(12) position of natural PGF$_{2\alpha}$, we set out to prepare and evaluate the methyl esters of 12-fluoroPGF$_{2\alpha}$ (**1a**), 15-*epi*-12-fluoroPGF$_{2\alpha}$ (**2a**), *ent*-12-fluoroPGF$_{2\alpha}$ (**3a**), and *ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ (**4a**). Despite numerous published reports during the last decade describing syntheses of prostaglandin analogues,[3] accounts detailing work relating to fluorinated prostaglandins have been few.[4] We detail below the synthetic routes to the four ring-fluorinated prostaglandins **1b-4b** and present the biological results which have primarily been concerned with pregnancy interruption in the hamster and smooth-muscle stimulating effect on gerbil colon and hamster uterine strips.

**Chemistry.** Fluoro analogues **1b** and **2b** were synthesized from (+)-*anti*-5-carboxytricyclo[2.2.1.0$^{2,6}$]heptan-3-one (**2**),[5] $[\alpha]_D$ +81.8° (dioxane), which was obtained



1a  R = H;  1b  R = Me

2a  R = H;  2b  R = Me

3a  R = H;  3b  R = Me

4a  R = H;  4b  R = Me
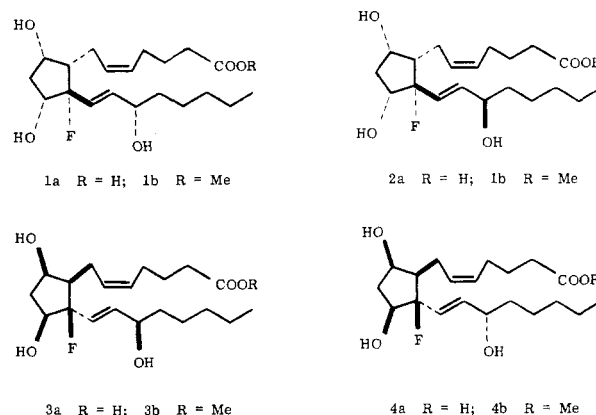
in optically pure form by resolution of racemic **2** with



2

3

4

(-)-α-methylbenzylamine. Addition of hydrobromic acid

*Corresponding address: Department of Chemistry, Indiana University, Bloomington, Indiana 47405.

(1) (a) C.-L. J. Wang, P. A. Grieco, and F. A. Okuniewicz, *J. Chem. Soc., Chem. Commun.*, 468 (1976); (b) P. A. Grieco, T. Sugahara, Y. Yokoyama, E. Williams, *J. Org. Chem.*, **44**, 2189 (1979); (c) P. A. Grieco, E. Williams, and T. Sugarhara, *ibid.*, **44**, 2194 (1979); (d) P. A. Grieco, C.-L. J. Wang, W. Owens, E. Williams, T. Sugahara, Y. Yokoyama, F. J. Okuniewicz, G. Withers, "Chemistry and Biochemistry of Prostanoids", Pergamon Press, Elmsford, N.Y., 1979, p 87.

(2) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **76**, 1455 (1954).

(3) J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press, New York, 1977; A. Mitra, "The Synthesis of Prostaglandins", Wiley-Interscience, New York, 1977.
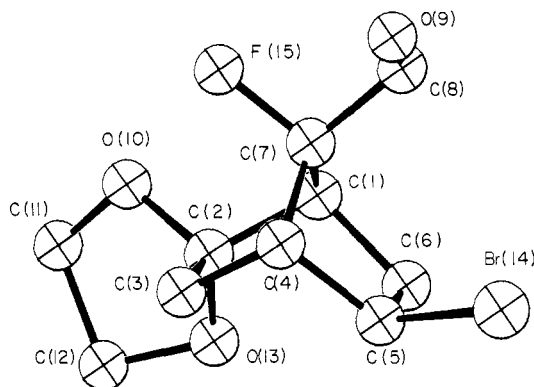
**Figure 1.** A computer-generated perspective drawing of the final X-ray model of racemic **7**. The enantiomer shown is an arbitrary choice, and hydrogens are omitted for clarity.
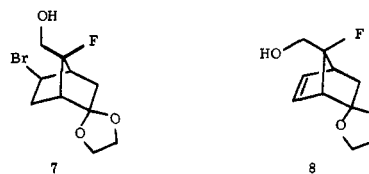
to cyclopropyl ketone **2**,[6] followed by esterification, afforded (+)-bromo keto ester **3**, $[\alpha]_D$ +11.0° (chloroform), as a crystalline compound, mp 110–111 °C. Ketalization of **3** using 2-methyl-2-ethyl-1,3-dioxolane in benzene containing p-toluenesulfonic acid generated ketal ester **4**, mp 36–37 °C, $[\alpha]_D$ –1.4° (chloroform).

Of prime importance to the success of our synthetic strategy was the ability at some stage in the synthesis to introduce a fluorine atom into the bicyclo[2.2.1]heptane system. The C(7) carbomethoxy substituent in compound **4** [note C(7) corresponds to the C(12) position in **1b**] provides, in principle, the necessary handle for introduction of the requisite fluorine atom. Whereas activated methylene groups in 1,3-dicarbonyl systems undergo smooth fluorination with perchloryl fluoride,[7] only limited success has been reported with ester enolates.[8] Fortunately, fluorination of the ester enolate derived from ester **4** with perchloryl fluoride in tetrahydrofuran at ca. –35 °C gave rise to an 86% yield of a 1:1 mixture of the desired fluoro ester **5** and the isomeric fluoro ester **6**. Chromatographic



separation on silica gel provided pure **5**, $[\alpha]_D$ +3.3° (chloroform), as a crystalline compound, mp 67–68 °C ($R_f$ 0.41, hexanes–ethyl acetate, 4:1), and pure **6**, $[\alpha]_D$ + 25.7° (methanol), mp 84.0–84.5 °C.

Confirmation of the stereochemical assignment of C(7) in fluoro ester **5** was arrived at by single-crystal X-ray analysis of racemic fluoro alcohol **7**, which was obtained by direct reduction [LiAlH$_4$, Et$_2$O] of racemic ester **5**.[1a] Figure 1 is a computer-generated perspective drawing of

(4) J. M. Muchowski and E. Verlade, *Prostaglandins*, 10, 297 (1975); C. E. Arroniz, J. Gallina, E. Martinez, J. M. Muchowski, E. Verlarde, W. H. Rooks, *ibid.*, 16, 47 (1978); B. J. Magerlein and W. L. Miller, *ibid.*, 9, 527 (1975); J. Fried, M.-S. Lee, B. Gaede, J. C. Sih, Y. Yoshikawa, J. A. McCracken, *Adv. Prostaglandin Thromboxane Res.*, 1, 183 (1976); D. A. van Dorp and E. J. Crist, *Recl. Trav. Chim. Pays-Bas.*, 94, 247 (1975).

(5) J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *J. Am. Chem. Soc.*, 95, 7522 (1973).

(6) See R. Peel and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 151, 1974.

(7) C. M. Sharts and W. A. Sheppard, *Org. React.*, 21, 225 (1974).

(8) W. J. Gensler, Q. A. Ahmed, and M. V. Leeding, *J. Org. Chem.*, 33, 4279 (1968).

the final X-ray model of racemic **7**. The object of the experiment was to confirm the stereochemical assignments, and these are clearly shown to be correct. All bond distances and angles generally agree well with anticipated values. The C(5)–C(6) bond is an exception and is too short. We attribute this to disorder caused by a torsional distortion about the C(5)–C(6) bond and application of the riding model yields a normal bond distance. There are no intermolecular contacts less than van der Waals' contacts save for an O(9)H···O(10) distance of 2.85 Å. Having unambiguously established the configuration about C(7) in compound **7**, we focused our attention on transforming (–)-**7** into (+)-fluoroPGF$_{2\alpha}$ methyl ester.

Dehydrohalogenation of (–)-**7** employing 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing toluene provided olefinic alcohol **8**, $[\alpha]_D$ –106.8° (chloroform). Alcohol **8** was subjected to Collins oxidation, followed by condensation with the sodium derivative of dimethyl 2-oxoheptylphosphonate in dry tetrahydrofuran at 50 °C. Pure *trans*-enone **9** was
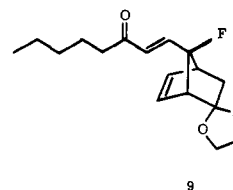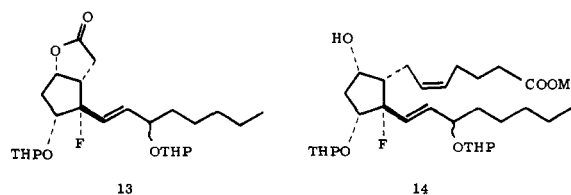


obtained in 51% overall yield. The NMR spectrum of **9** revealed the C(13) [prostaglandin numbering] proton at $\delta$ 7.08 as a doublet of doublets ($J_{\alpha,\beta}$ = 16 Hz, $J_{\beta,F}$ = 18 Hz) and the C(14) proton at $\delta$ 6.35 as a doublet ($J$ = 16 Hz) in agreement with the *trans*-enone system.

Reduction of **9** with lithium aluminum hydride in ether at –15 °C afforded a near quantative yield of two diastereomeric alcohols **11**, which could not be readily separated.
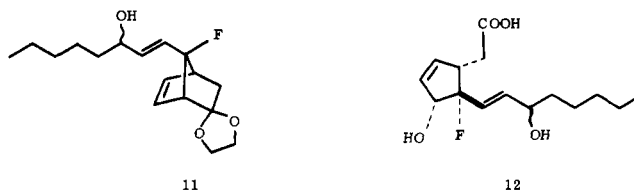


Deketalization (30% acetic acid–tetrahydrofuran) of **11** [epimeric at C(15)] and subsequent Baeyer–Villiger oxidation[9] employing 30% hydrogen peroxide and sodium hydroxide in aqueous methanol at 5 °C provided dihydroxycarboxylic acid **12**. Conversion of **12** into bicyclic lactone **13** was achieved via a standard series of reactions:



(a) iodolactonization, (b) deiodination, and (c) tetrahydropyranylation. Elaboration of the C(8) side chain of

(9) N. M. Weinshenker and R. Stephenson, *J. Org. Chem.*, 37, 3741 (1972).

12-fluoroPGF$_{2\alpha}$ was carried out using a three-step sequence: (a) reduction of lactone **13** with diisobutylaluminum hydride, (b) condensation of the resultant lactol with the Wittig reagent derived from 5-triphenylphosphonovaleric acid, and (c) esterification with diazomethane. Cleavage of the tetrahydropyranyl ethers in compound **14** afforded (+)-12-fluoroPGF$_{2\alpha}$ methyl ester **1b** (more polar) and (+)-15-*epi*-12-fluoroPGF$_{2\alpha}$ methyl ester **2b** (less polar), which were separated by column chromatography on silica gel. The more polar isomer has been tentatively assigned the 15*S* natural configuration in keeping with the relative mobilities on TLC of natural and 15-*epi*-prostaglandins.[10]

Resolution of racemic 3-oxobicyclo[2.2.1.0$^{2,6}$]heptane-5-carboxylic acid with (+)-2-methylbenzylamine provided cyclopropyl keto acid II$^{1d}$ of negative rotation which was



II
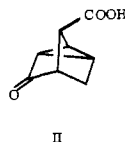
employed in the preparation of *ent*-12-fluoroPGF$_{2\alpha}$ methyl ester (**3b**) and *ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ methyl ester (**4b**) using the chemistry described above.[11]

**Biological Results.**[12]    Fluoroprostaglandins **1b–4b** were evaluated for interruption of pregnancy in hamsters (80–90 g of body weight) using a minor modification of the procedure of Giannina.[13] A single dose of each compound dissolved in ethanol was administered subcutaneously on day 5 of pregnancy. The biological data are summarized in Table I.    With the exception of (–)-*ent*-15-*epi*-12-fluoroPGF$_{2\alpha}$ methyl ester (**4b**), which was not examined at dose levels above 50 μg, all fluoroprostaglandins exhibited antifertility activity. Of special interest was the observation that (+)-15-*epi*-12-fluoroPGF$_{2\alpha}$ methyl ester (**2b**) was equipotent with natural PGF$_{2\alpha}$ and (+)-12-fluoroPGF$_{2\alpha}$ methyl ester (**1b**) was some 12.5 times more active than PGF$_{2\alpha}$. The significant antifertility activity associated with the enantiomeric fluoroprostaglandin **3b** and the diastereomer **2b** is, however, not totally unexpected. For example, it has been reported that *ent*-15-*epi*-13-dehydroPGF$_{2\alpha}$ possesses one-fourth the activity of natural PGF$_{2\alpha}$ in the hamster antifiertility assay.[15] Since all fluoroprostaglandins were analyzed as their methyl esters and the natural material (PGF$_{2\alpha}$) as the free acid,

**Table I.  Biological Activities of 12-Fluoroprostaglandins**

| compd | antifertility in hamster,$^{a,b}$ PGF$_{2\alpha}$ = 1 | hamster uterine contraction,$^{c,d}$ PGF$_{2\alpha}$ = 1 | gerbil colon contraction,$^{a,e}$ PGF$_{2\alpha}$ = 1 |
|---|---|---|---|
| **1a** | 25 | 0.65 | 0.23 |
| **1b** | 12.5 | 0.28 | 0.001 |
| **2b** | 1 | 0.022 | 0.011 |
| **3b** | 0.17 | 0.004 | 0.001 |
| **4b** | f | 0.0002 | 0.0002 |

$^a$ Reference 13.  $^b$ Derived by comparison of "minimum effective doses" of fluoroprostaglandins with that for natural PGF$_{2\alpha}$. The "minimum effective dose" is the minimum dose per hamster per day that will result in no pregnancies in a group of ten animals. For PGF$_{2\alpha}$, the "minimum effective dose" is 12.5 μg (subcutaneously). $^c$ Reference 16.  $^d$ Potencies calculated from dose-response curves for PGF$_{2\alpha}$ (three levels from 0.25 to 1.0 μg/mL) and test compounds.  $^e$ Potencies calculated from dose-response curves for PGF$_{2\alpha}$ (three levels from 60 to 120 ng/mL) and test compounds.  $^f$ No activity observed at 50 μg.

we prepared (+)-12-fluoroPGF$_{2\alpha}$ (**1a**) by treatment of **1b** with KOH in aqueous methanol (1:1) at 25 °C for 4 h and submitted it to biological evaluation for comparison purposes. Examination of Table I reveals that **1a** is 2 times more potent than **1b** and 25 times more active than natural PGF$_{2\alpha}$.

Fluoroprostaglandins **1b–4b** were also evaluated for smooth-muscle (in vitro) stimulating effects on gerbil colon and hamster uterine strips.[16] As indicated in the table, all test compounds exhibited only low level or negligible smooth-muscle stimulating properties.

It appears that incorporation of a fluorine atom into the C(12) position of natural PGF$_{2\alpha}$ enhances "luteolytic" potency while diminishing smooth-muscle effects. The enhancement in "luteolytic" activity associated with (+)-12-fluoroPGF$_{2\alpha}$ methyl ester (**1b**) is undoubtedly due, in part, to the fact that **1b** was not a substrate for the placental 15-hydroxyprostaglandin dehydrogenase. (+)-12-FluoroPGF$_{2\alpha}$ (**1a**) and the four prostaglandins (**1b–4b**) proved to be neither substrates for the 15-hydroxyprostaglandin dehydrogenase nor inhibitors of the enzyme.[20]

(10) N. H. Anderson, *J. Lipid Res.*, **10**, 316 (1969).

(11) Compounds in the ent series are designated by the corresponding roman numeral with the exception of **3b** and **4b**. The enantiomerically pure intermediates in the ent series possessed the following physical constants. II: mp 135–137 °C; [α]$_D$ –85.0° (c 0.5, dioxane). III: mp 108–109 °C; [α]$_D$ –10.1° (c 0.36, CHCl$_3$). IV: mp 33–35 °C; [α]$_D$ +1.4° (c 2.23, CHCl$_3$). V: mp 67.5–68.5 °C; [α]$_D$ –3.6° (c 1.01, CHCl$_3$). VII: mp 111.5–112.0 °C; [α]$_D$ +26.1° (c 1.01, CHCl$_3$). VIII: [α]$_D$ +106.6° (c 1.09, CHCl$_3$). IX: [α]$_D$ +68° (c 1.45, CHCl$_3$). **3b**: mp 103–105 °C; [α]$_D$ –16.7° (c 1.26, CHCl$_3$). **4b**: [α]$_D$ –5.1° (c 1.2, CHCl$_3$).

(12) The biological assays were provided by the Contraceptive Development Branch, National Institute of Child Health and Human Development, National Institutes of Health.

(13) The interruption of pregnancy test was carried out as described by Giannina and co-workers,[14] with the exception that one male per female was used instead of one male per three females. Ten hamsters (80–90 g of body weight) were used for each compound. The compounds were dissolved in ethanol and a single dose of each compound was administered subcutaneously on day 5 of pregnancy.

(14) T. Giannina, M. Butler, W. K. Sawyer, and B. G. Steinetz, *Contraception*, **9**, 507 (1974).

(15) J. Fried and C. H. Lin, *J. Med. Chem.*, **16**, 429 (1973).

(16) The oxytocin-like activity was determined using the assay as described by Holton,[17] with the exception that hamsters were used in place of rats. The data expressing agonist activity on the hamster uterus and gerbil colon are potency estimates based upon a comparison of regression lines derived from responses to six dose levels on a single strip. The use of a single strip precludes any analysis of variants.

(17) P. Holton, *Br. J. Pharmacol.*, **3**, 328 (1948).

(18) P. A. Grieco, C. S. Pognowski, S. D. Burke, M. Nishizawa, M. Miyashita, Y. Masaki, C.-L. J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 4111 (1977).

(19) All crystallographic calculations were done on a Prime 400 computer, operated by the Materials Science Center, Cornell University. The principal programs used were REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block diagonal least squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge, ORNL-TM305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL-3794; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast Fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

## 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 (Varian A-60A or T-60 spectrometer), 100 (Jeolco), or 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me$_4$Si (δ 0.0) 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. Rotations were carried out at 25–28 °C on a Perkin-Elmer 241 polarimeter. 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$_2$SO), 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 GF (250 μm).

**(+)-anti-5-Carboxytricyclo[2.2.1.0$^{2,6}$]heptan-3-one (2).** A solution containing 27.4 g (0.18 mol) of racemic 5-carboxytricyclo[2.2.1.0$^{2,6}$]heptan-3-one[18] in 1.1 L of acetone was heated to 50 °C and 21.9 g (0.18 mol) of *l*-(−)-α-methylbenzylamine was added. The hot solution was swirled while 1.1 L of warm hexanes was added at such a rate so as to prevent premature crystallization. The homogeneous solution was allowed to cool to room temperature slowly. After 20 h, the ammonium salt was collected by filtration, giving 39.0 g: mp 103–107 °C (130–135 °C, evacuated sealed tube); [α]$_D$ +3.5° (c 1.0, CH$_3$OH).

The above salt was dissolved in 1.5 L of acetone and heated to 50 °C. The solution was filtered hot, if necessary, prior to the slow addition of 1.5 L of warm hexanes so as to avoid crystallization. After cooling to room temperature, the homogeneous solution was allowed to stand for 20 h. Filtration provided 20.3 g of ammonium salt: mp 105–110 °C (137–141 °C, sealed tube); [α]$_D$ +23.6° (c 1.0, CH$_3$OH). Recrystallization of this material from 800 mL of acetone and 800 mL of hexanes using the above techniques afforded 11.5 g of salt: mp 107–110 °C (140–143 °C, sealed tube); [α]$_D$ +42.5° (c 1.0, CH$_3$OH). Further recrystallization from 470 mL of acetone and 470 mL of hexanes gave 8.2 g of salt: mp 110–112 °C (143–146 °C, sealed tube); [α]$_D$ +53.2° (c 1.0, methanol). Optical purity was achieved by a fourth recrystallization from 350 mL of acetone and 350 mL of hexanes. There was obtained 6.1 g of pure salt: mp 114–116 °C (149.0–151.5 °C, sealed tube); [α]$_D$ +58.9° (c 1.0, CH$_3$OH).

The above salt (6.1 g) was dissolved in 30 mL of 20% hydrochloric acid. After dissolution, solid sodium chloride was added to the aqueous acidic solution. The product was extracted with ethyl acetate (4 × 40 mL). The combined organic layers were washed with saturated brine solution and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gave

3.2 g of pure 2: mp 142.5–143.5 °C; [α]$_D$ +76° (c 1.0, CH$_3$OH) [lit.[5] mp 137–138 °C; [α]$^{25}$$_D$ +74.0° (c 1.0, CH$_3$OH)]. Our [α]$_D$ for optically pure 2 in methanol rapidly drops to +60°. Use of dioxane as solvent gave [α]$_D$ +81.8° (c 1.0) consistently.

**Methyl (+)-(1α,4α,5α,7S*)-5-Bromo-2-oxobicyclo[2.2.1]-heptane-7-carboxylate (3).** A solution of 21.5 g (0.14 mol) of keto acid 2 in 225 mL of glacial acetic acid was treated at reflux for 3 h with 225 mL of 48% hydrobromic acid. Air was passed through the reaction mixture prior to evaporation of the solvent under reduced pressure. The solid residue was dissolved in ethyl acetate (1.0 L), washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. After pumping overnight under high vacuum, the crude bromo keto acid (35 g) was recrystallized from water to give 29.5 g (90%) of pure keto acid: mp 170–171 °C; [α]$_D$ −10.1° (c 1.05, chloroform). Direct esterification of 28.0 g of the above bromo keto acid was accomplished with an ethereal solution of diazomethane (500 mL), prepared from 25 g of N-methyl-N-nitrosourea. The reaction was quenched with acetic acid, extracted with sodium bicarbonate solution, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 29.6 g (100%) of crystalline bromo keto ester 3: mp 108–109 °C; IR (CHCl$_3$) 3020, 2950, 2920, 1755, 1735, 1440, 1405, 1370, 1315, 1295, 1268, 1225, 1180, 1170, 1145, 1118, 1040, 1025, 975, 950, 920, 900, 882, 820 cm$^{-1}$; NMR (CCl$_4$) δ 2.0–3.4 (m, 7 H), 3.75 (s, 3 H), 4.10 (m, 1 H). Recrystallization from ethanol gave analytically pure 3: mp 110–111 °C; [α]$_D$ +11.0° (c 1.04, chloroform). Anal. Calcd for C$_9$H$_{11}$BrO$_3$: C, 43,75; H, 4.49. Found: C, 43.88; H, 4.52.

**Methyl (−)-(1α,4α,5α,7S*)-5-Bromospiro[bicyclo[2.2.1]-heptane-2,2′-[1,3]dioxolane]-7-carboxylate (4).** A solution of 16.1 g (65 mmol) of bromo keto ester 3 and 35.8 g (0.3 mol) of 2-methyl-2-ethyl-1,3-dioxolane in 150 mL of benzene containing 2.75 g of p-toluenesulfonic acid was stirred at room temperature for 20 h. The reaction mixture was washed with saturated sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 19 g of crude crystalline material. Recrystallization from ether-pentane gave 17.0 g (90%) of pure ketal 4: mp 40–41 °C; [α]$_D$ −1.4° (c 2.0, chloroform); IR (CHCl$_3$) 3000, 2955, 2890, 1729, 1435, 1370, 1329, 1310, 1251, 1231, 1210, 1190, 1155, 1105, 1070, 1040, 1021, 995, 950, 910, 898, 842 cm$^{-1}$; NMR (CDCl$_3$) δ 1.52 (d, 1 H, J = 14 Hz), 2.01 (dd, 1 H, J = 14 and 5.5 Hz), 2.48 (m, 3 H), 2.92 (m, 2 H), 3.70 (s, 3 H), 3.90 (m, 5 H). Anal. Calcd for C$_{11}$H$_{15}$BrO$_4$: C, 45.38; H, 5.19. Found: C, 45.54; H, 5.20.

**Methyl (+)-(1α,4α,5α,7R*)-5-Bromo-7-fluorospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-carboxylate (5).** To a solution of lithium diisopropylamide prepared from 1.94 g (19.2 mmol) of diisopropylamine in 40 mL of tetrahydrofuran and 11.6 mL of n-butyllithium (1.65 M in hexene) at −78 °C was added a solution of 4.66 g (16 mmol) of bromo ketal ester 4 in 20 mL of anhydrous tetrahydrofuran over 20 min. After an additional 30 min at −78 °C, the temperature of the bath was raised to −35 °C and perchloryl fluoride (FClO$_3$) was slowly passed into the reaction vessel over a 3-h period. Prior to workup, nitrogen was passed through the reaction medium (ca. 1 h) to remove excess perchloryl fluoride. During this time the temperature was raised to 0 °C. **Extreme caution must be exercised when employing perchloryl fluoride!** The reaction mixture was quenched with water. The tetrahydrofuran was removed on the rotary and the resulting residue was extracted with ether. The ether layer was dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave 5.14 g of crude product which was purified on 250 g of silica gel. Elution with hexanes–ethyl acetate (6:1) gave 2.13 g (43%) of fluoro ester 5 [R$_f$ 0.41 (hexanes–ethyl acetate, 4:1); mp 67–68 °C; [α]$_D$ +3.3° (c 1.04, chloroform); IR (CHCl$_3$) 3030, 3000, 2950, 2895, 1745, 1450, 1440, 1320, 1300, 1270, 1250, 1220, 1150, 1105, 1070, 1060, 1050, 1010, 950, 930, 890, 870, 840 cm$^{-1}$; NMR (CCl$_4$) δ 1.65 (dd, 1 H, J = 14 and 4 Hz), 2.30–3.00 (m, 5 H), 3.83 (s, 3 H), 3.60–4.10 (m, 5 H). Anal. Calcd for C$_{11}$H$_{14}$O$_4$FBr: C, 42.74; H, 4.56. Found: C, 42.66; H, 4.61.] and 2.12 g (43%) of the C(7) isomeric fluoro ester 6 [R$_f$ 0.33; mp 84.0–84.5 °C; [α]$_D$ +25.7° (c 1.0, methanol); IR (CHCl$_3$) 3030, 3000, 2960, 2900, 2860, 1755, 1440, 1340, 1330, 1035, 1200, 1160, 1105, 1080, 1055, 1020, 950, 930, 900, 870, 840 cm$^{-1}$; NMR (CCl$_4$) δ 1.58 (dd, 1 H, J = 14 and 5 Hz)].

(20) These studies were conducted in the laboratory of Professor Jarabak in the Department of Medicine at the University of Chicago using procedures described by him previously.[21] All fluoroprostaglandins were examined to see if they were substrates for the placental 15-hydroxyprostaglandin dehydrogenase by measuring the ΔOD$_{340nm}$ after a 10-min incubation at 25 °C, of placental enzyme (0.002, 0.01, and 0.25 mL), the substrate (40, 40, and 100 μg, respectively), and NAD (1 mg) in 2.9 mL of phosphate buffer at pH 7.0. For PGE$_2$, ΔOD$_{340nm/10min}$ [enzyme (0.002 mL), PGE$_2$ (40 μg), NAD (1 mg), and 2.9 mL of phosphate buffer at pH 7.0] was 0.019. Inhibition studies were conducted by measuring the ΔOD$_{340nm}$, after a 10-min incubation at 25 °C, of placental enzyme (0.002 mL), PGE$_2$ (8.0 μg), test compound (40 and 100 μg), and NAD (1 mg added after 5 min) in 2.9 mL of phosphate buffer at pH 7.0. In the absence of test compound, there was not observable difference in ΔOD$_{340nm}$.

(21) J. Jarabak and S. S. Braithwaite, *Arch. Biochem. Biophys.*, **177**, 245 (1976).

(−)-5-Bromo-7-fluorospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol (7). To a suspension of 0.57 g (15 mmol) of lithium aluminum hydride in 20 mL of anhydrous ether at 0 °C was added a solution of 3.05 g (10 mmol) of fluoro ester 5 in 10 mL of anhydrous ether. The reaction was stirred at room temperature for 2 h. The reaction was quenched with wet ether. Filtration, followed by removal of the solvent under reduced pressure, gave 2.74 g of crystalline product. Recrystallization from hexanes–chloroform gave 2.53 g (90%) of pure 7: mp 111–112 °C; $[\alpha]_D$ −25.5° (c 1.04, chloroform); IR (CHCl₃) 3605, 3500, 3005, 3000, 2950, 2890, 1470, 1460, 1440, 1400, 1340, 1320, 1240, 1200, 1150, 1110, 1090, 1060, 1040, 1005, 980, 950, 940, 920, 890, 870, 840 cm⁻¹; NMR (CDCl₃) δ 1.5–3.0 (m, 7 H), 3.6–4.6 (m, 7 H). Anal. Calcd for C₁₀H₁₄BrFO₃: C, 42.72; H, 5.02. Found: C, 42.70; H, 5.10.

**Single Crystal X-ray Diffraction Analysis of Racemic 5-Bromo-7-fluorospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol (7).** Crystals suitable for a single-crystal X-ray analysis were grown from hexanes–chloroform. Preliminary X-ray photographs which showed orthorhombic symmetry and accurate lattice parameters of a = 6.335 (2), b = 7.460 (2), and c = 22.496 (4) Å were detained from a least-squares fit of 15 accurately measured 2θ values. Systematic extinctions and density measurement indicate space group $P2_12_12_1$ with one molecule of C₁₀H₁₄BrFO₃ per asymmetric unit. All unique diffraction maxima with 2θ ≤ 114° were recorded on a computer-controlled four-circle diffractor using a variable speed, 1° ω-scan technique and graphic monochromated Cu Kα (1.54178 Å) radiation. Of the 750 reflections surveyed in this manner, 735 (98%) were judged observed [I ≥ 3σ(I)] after correction for Lorentz polarization and background effects.

The structure was solved by standard heavy atom techniques.[19] Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and fixed isotropic temperature factors for the hydrogens have converged to a current crystallographic residual of 0.04 for the observed reflections. The crystal used was obtained from a racemic sample of 7 but, nevertheless, crystallized in a chiral space group. In order to determine whether 7 spontaneously resolved on a microscopic or macroscopic scale, we introduced anomalous scattering corrections for Br. We were unable to find a significant enantiomeric discrimination and thus conclude that our sample resolved only in microscopic domains. The enantiomer shown in Figure 1 represents an arbitrary choice. Please see the paragraph at the end of this paper on supplementary material which gives additional crystallographic details.

(−)-7-Fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (8). A solution of 1.70 g (6 mmol) of bromide 7 and 9.12 g (60 mol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 20 mL of toluene was refluxed (bath temperature 130 °C) for 40 h. The reaction was cooled and chromatographed on silica gel (ether–hexanes, 5:1) to afford 1.12 g (93%) of olefin 8: $[\alpha]_D$ −106.8° (c 1.94, chloroform); IR (CHCl₃) 3600, 3450, 3000, 2950, 2905, 2870, 1450, 1430, 1390, 1325, 1305, 1280, 1220, 1200, 1135, 1105, 1100, 1050, 1020, 1005, 950, 905, 840 cm⁻¹; NMR (CCl₄) δ 1.51 (dd, 1 H, J = 12 and 4 Hz), 2.22 (dt, 1 H, J = 4 and 12 Hz), 2.5–2.9 (m, 2 H), 3.4–4.0 (m, 7 H), 6.10 (m, 2 H). Anal. Calcd for C₁₀H₁₃FO₃: M⁺ 200.0849. Found: 200.0850.

(−)-[1α,4α,7S*(E)]-7-Fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl-1-octen-3-one (9). To a solution of 6.1 mL (75 mmol) of dry pyridine in 70 mL of dry methylene chloride at room temperature was added in small portions 3.75 g (37.5 mmol) of chromium trioxide. The reaction mixture was stirred for an additional 15 min and a solution of alcohol 8 (500 mg, 2.5 mmol) in 2 mL of dry methylene chloride was added in one portion. After 15 min the reaction was quenched by the addition of benzene and filtered through Celite. The Celite was washed exhaustively with benzene. The combined organic washings were filtered through a second pad of Celite to remove the last traces of chromium salts and concentrated under reduced pressure. The crude aldehyde was directly condensed with the Emmons reagent prepared from 120 mg (2.5 mmol) of 50% sodium hydride dispersion and 555 mg (2.5 mmol) of dimethyl (2-oxoheptyl)phosphonate in 12 mL of tetrahydrofuran. After adding the aldehyde, the resulting mixture was warmed to 52 °C. After 20 h, the reaction was quenched by the addition of water. The

solvent was removed under reduced pressure. The residue was dissolved in ether and was washed with brine. The ether layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude enone was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:4) provided 375 mg (51%) of pure enone 9 as a colorless oil: $[\alpha]_D$ −72.3° (c 1.24, methanol); IR (CHCl₃) 3025, 3000, 2955, 2930, 2895, 1695, 1680, 1635, 1470, 1460, 1440, 1405, 1370, 1335, 1315, 1230, 1160, 1130, 1090, 1055, 1005, 985, 955, 910, 840 cm⁻¹; NMR (CCl₄) δ 0.90 (br t, 3 H), 1.1–1.9 (m, 7 H), 2.2–2.9 (m, 5 H), 3.6–4.2 (m, 4 H), 6.20 (m, 2 H), 6.40 (d, 1 H, J = 16 Hz), 7.01 (dd, 1 H, J = 16 and 18 Hz). Anal. Calcd for C₁₇H₂₃FO₃: m/e 294.1631. Found: m/e 294.1629.

[1α,4α,7S*(E)]-7-Fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-3-hydroxy-1-octenol (11). To a suspension of 130 mg (3.42 mmol) of lithium aluminum hydride in 45 mL of anhydrous ether cooled to −15 °C was added 1.0 g (3.40 mmol) of enone 9 in 5 mL of dry ether. After 15 min at −15 °C, the reaction was quenched by the addition of "wet" ether. Usual workup, followed by chromatography on silica gel (elution with ether–hexane, 1:1), gave 960 mg (96%) of allylic alcohol 11 as a mixture of diastereomers: IR (CHCl₃) 3600, 3005, 2995, 2965, 2945, 2860, 1470, 1460, 1440, 1380, 1335, 1318, 1290, 1220, 1120, 1090, 1050, 1020, 1005, 980, 950, 910, 840 cm⁻¹; NMR (CDCl₃) δ 0.89 (br t, 3 H), 1.1–1.8 (m, 9 H), 2.38 (dt, 1 H), 2.5–2.9 (m, 2 H), 3.8–4.2 (m, 5 H), 5.7–6.4 (m, 4 H). Anal. Calcd for C₁₇H₂₅FO₃: m/e 296.1788. Found: 296.1789.

**Preparation of Hydroxycarboxylic Acid 12.** A solution of 360 mg (1.19 mmol) of ketal 11 in 3 mL of tetrahydrofuran containing 6.3 mL of acetic acid and 14.7 mL of water was allowed to stir for 48 h at room temperature. The acetic acid was neutralized with a saturated solution of sodium bicarbonate, and the product was isolated by extraction with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo afforded 368 mg of crude ketone, which was used directly in the next reaction.

To a cooled (0 °C) solution of the above ketone (368 mg) in 5 mL of methanol containing 2 mL of water was added 3 mL of an aqueous sodium hydroxide solution (prepared from 143 mg of NaOH and 3 mL of H₂O), followed by 0.89 mL (8.9 mmol) of 30% hydrogen peroxide. After 40 h at 5 °C, the reaction mixture was extracted with ether (2 × 5 mL). The combined ether layers were dried (anhydrous magnesium sulfate) and evaporated in vacuo to afford 100 mg (20%) of recovered ketal 11. Excess hydrogen peroxide was destroyed with saturated sodium thiosulfate solution. The pH of the aqueous portion was adjusted to ca. 5.0 with 5% hydrochloric acid and extracted with 5 × 10 mL portions of ethyl acetate. The combined ethyl acetate layers were dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure, affording 223 mg (70%) of desired hydroxy acid 12 which was used without further purification: IR (CHCl₃) 3600, 3550–2500, 3000, 2960, 2930, 2870, 2860, 1715, 1470, 1460, 1410, 1290, 1260, 1220, 1130, 1100, 1040, 975, 805 cm⁻¹; NMR (CDCl₃) δ 0.60–1.80 (m, 12 H), 2.20–2.70 (m, 2 H), 4.00–4.80 (m, 2 H), 5.60–6.50 (m, 7 H).

(3,3aα,4R*,5β,6α,6aα)-Hexahydro-4-fluoro-4-[3-hydroxy-1(E)-octenyl]-5-hydroxy-6-iodo-2H-cyclopenta[b]furan-2-one. The above hydroxy acid (223 mg, 0.78 mmol) was dissolved in 5 mL of water (0 °C) containing 33 mg (0.84 mmol) of sodium hydroxide. The cooled solution was neutralized to pH 7 with carbon dioxide and treated with 1.25 g (7.52 mmol) of potassium iodide and 636 mg (2.50 mmol) of iodine in 15 mL of water. The resulting black solution was stirred for 48 h at 5 °C, at which time methylene chloride was added followed by the addition of a saturated sodium thiosulfate solution to decolorize the solution. The product was isolated by extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. There was obtained 160 mg (50%) of iodolactone which was homogeneous by TLC analysis (ether): $R_f$ 0.52; IR (CHCl₃) 3600, 3400, 1785 cm⁻¹; NMR (250 MHz) (CDCl₃) δ 0.92 (m, 3 H), 1.2–1.8 (m, 10 H), 2.6 (m, 2 H), 4.0–4.2 (m, 2 H), 5.1 (dd, 1 H, J = 9 and 4 Hz), 5.5–5.7 (m, 1 H), 5.9–6.0 (m, 1 H). Anal. Calcd for C₁₅H₂₀FIO₃·H₂O: m/e 394.0441. Found: m/e 394.0442. Acidification of the aqueous layer with 5% hydrochloric acid, followed by extraction with ethyl acetate, provided 75 mg (34%) of recovered 12.

**(3,3aα,4R*,5β,6aα)-Hexahydro-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-fluoro-4-[3-[(tetrahydro-2H-pyranyl-2-yl)oxy]-1(E)-octenyl]-2H-cyclopenta[b]furan-2-one (13).** To a solution of 241 mg (0.58 mmol) of the above iodolactone in 5 mL of benzene containing 15 mg of azobis(isobutyronitrile) was added 350 mg (1.2 mmol) of tri-*n*-butyltin hydride. After ca. 2 h at 50 °C, the benzene was removed in vacuo and the residue was allowed to stand on a column of silica gel (15 g) for 1 h prior to elution with ether. There was obtained 145 mg (86%) of the desired lactone: IR (CHCl₃) 3600, 3400, 1780 cm⁻¹; NMR (CDCl₃, 250 MHz) δ 0.92 (m, 3 H), 1.2–2.1 (m, 11 H), 2.5–2.9 (m, 4 H), 3.3–4.2 (m, 2 H), 4.7–5.0 (m, 1 H), 5.0–5.7 (m, 1 H), 5.8–6.0 (m, 1 H). Anal. Calcd for $C_{15}H_{23}FO_4 \cdot H_2O$: *m/e* 268.1475. Found: *m/e* 268.1477.

A solution of the above diol (145 mg, 0.5 mmol) in 10 mL of dry methylene chloride containing 130 mg (1.52 mmol) of dihydropyran and a catalytic amount (15 mg) of *p*-toluenesulfonic acid was stirred at 0 °C for 3 h. The reaction mixture was diluted with 20 mL of ether, washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product (210 mg) was chromatographed on 15 g of silica gel. Elution with ether–hexanes (1:1) gave 160 mg (70%) of pure 13 as a colorless oil: IR (CHCl₃) 3010, 2950, 2875, 2855, 1780, 1470, 1458, 1445, 1415, 1390, 1380, 1368, 1360, 1350, 1325, 1300, 1290, 1278, 1265, 1240, 1180, 1145, 1134, 1080, 1040, 1020, 988, 950, 910, 900, 882, 870, 815 cm⁻¹.

**(+)-12-Fluoroprostaglandin F₂α Methyl Ester (1b) and (+)-15-*epi*-12-Fluoroprostaglandin F₂α Methyl Ester (2b).** To a solution of 105 mg (0.23 mmol) of lactone 13 in 3 mL of toluene cooled to −78 °C under nitrogen was added dropwise 0.69 mL (0.69 mmol) of diisobutylaluminum hydride (20% in hexane). After 1 h, the reaction was cautiously quenched at −78 °C with methanol. The reaction mixture was diluted with 10 mL of ether and was warmed to room temperature. Addition of water, followed by isolation of the product in the usual manner by extraction with ether, gave 108 mg (quantitative) of the corresponding hemiacetal [$R_f$ 0.55 (ether); IR (CHCl₃) 3600, 3400 cm⁻¹], which was used directly in the next reaction.

A suspension of 199 mg (4.14 mmol) of 50% sodium hydride dispersion in 2.0 mL of dry dimethyl sulfoxide was heated at ca. 70 °C for 50 min under nitrogen. To 1.0 mL of the above solution of dimsyl sodium cooled to 25 °C was added 458 mg (1.04 mmol) of (4-carboxybutyl)triphenylphosphonium bromide [dried for 1.5 h at ca. 90 °C (0.2 mmHg) prior to use] in 1.0 mL of dry dimethyl sulfoxide. After 5 min, a solution of 108 mg (0.23 mmol) of the above hemiacetal in 1.0 mL of dry dimethyl sulfoxide was added to the dark ylide solution. The reaction was quenched after 20 h by the addition of ice and carefully acidified to pH 5 with 2 N sodium hydrogen sulfate solution. The product was isolated by extraction with ether (5 × 10 mL). The combined ether layers

were washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was esterified with a solution of ethereal diazomethane. The crude product (14) was purified on 15 g of silica gel. Elution with ether–hexanes (1:1) gave 87 mg (70%) of 14 as a colorless oil: IR (CHCl₃) 3600, 3475, 3010, 2950, 2870, 1730, 1470, 1458, 1445, 1410, 1380, 1370, 1360, 1345, 1325, 1290, 1268, 1240, 1205, 1160, 1135, 1115, 1080, 1038, 1025, 980, 940, 915, 885, 875, 815 cm⁻¹.

A solution of 87 mg (0.16 mmol) of bis(tetrahydropyranyl ether) 14 in 0.2 mL of tetrahydrofuran was treated with 1.0 mL of glacial acetic acid–water (2:1) and heated at 45 °C for 6 h. Removal of solvent under reduced pressure (<0.22 mmHg) gave 70 mg of a mixture of 12-fluoroPGF₂α methyl ester (1b) and 15-*epi*-12-fluoroPGF₂α methyl ester (2b). Chromatography on 10 g of silica gel (elution with benzene–tetrahydrofuran–formic acid, 15:5:2) gave, in order of elution, 20 mg (35%) of 2b [$R_f$ 0.38; mp 55–57 °C; [α]_D +6.1° (*c* 1.62, chloroform). Anal. Calcd for $C_{21}H_{35}FO_5$: C, 65.26; H, 9.10. Found: 65.01; H, 9.07.] and 20 mg (35%) of 1b [$R_f$ 0.31; mp 107–108 °C; [α]_D +16.7 (*c* 1.0, chloroform); IR (CHCl₃) 3610, 3450, 3010, 2960, 2940, 2865, 1731, 1460, 1445, 1410, 1370, 1320, 1220, 1160, 1120, 1060 cm⁻¹; NMR (250 MHz, CDCl₃) δ 5.89 (dd, 1 H, *J* = 6 and 15 Hz, C(14) proton), 5.57 (dd, 1 H, *J* = 15 and 21 Hz, C(13) proton), 5.43 (m, 2 H, C(5), C(6) protons), 4.14 (m, 2 H, C(9), C(15) protons), 3.89 (m, 1 H, C(11) proton, 3.61 (s, 3 H, –CO₂CH₃). Anal. Calcd for $C_{21}H_{35}FO_5$: C, 65.26; H, 9.10. Found: C, 65.11; H, 9.19.].

# C(14)-Fluorinated Prostaglandins: Synthesis and Biological Evaluation of the Methyl Esters of (+)-14-Fluoro-, (+)-15-*epi*-14-Fluoro-, (+)-13(*E*)-14-Fluoro-, and (+)-13(*E*)-15-*epi*-14-Fluoroprostaglandin F₂α

Paul A. Grieco,* William J. Schillinger, and Yuusaku Yokoyama

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. Received January 28, 1980*

The synthesis and biological evaluation of the methyl esters of (+)-14-fluoroPGF₂α, (+)-15-*epi*-14-fluoroPGF₂α, (+)-13(*E*)-14-fluoroPGF₂α, and (+)-13(*E*)-15-*epi*-14-fluoroPGF₂α are described. Each fluoroprostaglandin has been evaluated for pregnancy interruption in the hamster and smooth-muscle stimulating effects on gerbil colon and hamster uterine strips.

A few years ago, we initiated a program which had as its goal the synthesis of ring-fluorinated prostaglandins

possessing luteolytic properties with minimal smooth-muscle contracting activity. We have been encouraged by our finding that both (+)-12-fluoroPGF₂α methyl ester (1a) and (+)-15-*epi*-12-fluoroPGF₂α methyl ester (1b) possessed significant activity in the hamster antifertility assay while exhibiting very low smooth-muscle stimulating activity (see Table I).[1] In addition, we have demonstrated that both

* Corresponding address: Department of Chemistry, Indiana University, Bloomington, Indiana 47405