(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 ($CHCl_3$) 3600, 3400, 1780 cm^{-1}; NMR ($CDCl_3$, 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 $C_{15}H_{23}FO_4$–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 ($CHCl_3$) 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 $F_{2\alpha}$ Methyl Ester (1b) and (+)-15-*epi*-12-Fluoroprostaglandin $F_{2\alpha}$ 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 ($CHCl_3$) 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 ($CHCl_3$) 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-fluoro$PGF_{2\alpha}$ methyl ester (**1b**) and 15-*epi*-12-fluoro$PGF_{2\alpha}$ 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; $[\alpha]_D$ +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; $[\alpha]_D$ +16.7 (*c* 1.0, chloroform); IR ($CHCl_3$) 3610, 3450, 3010, 2960, 2940, 2865, 1731, 1460, 1445, 1410, 1370, 1320, 1220, 1160, 1120, 1060 cm^{-1}; NMR (250 MHz, $CDCl_3$) 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, $-CO_2CH_3$). Anal. Calcd for $C_{21}H_{35}FO_5$: C, 65.26; H, 9.10. Found: C, 65.11; H, 9.19.].

Acknowledgment. Generous support for this work by the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health (Grant HD 10725 to P.A.G.), and by a grant (CA 24487 to J.C.) from the National Cancer Institute is gratefully acknowledged. NMR (250 MHz) spectra were obtained in facilities supported by Public Health Service Grant RR-00292. Thanks are expressed to the National Science Foundation for funding (to J.C.) of a diffractometer at Cornell. We are indebted to Professor Jarabak, Department of Medicine, University of Chicago, for the 15-hydroxyprostaglandin dehydrogenase inhibition assays. Thanks are expressed to Professors J. Fried and N. Anderson and Drs. M. J. Karten and Richard P. Blye for useful discussions and comments. We thank Dr. T. K. Schaaf (Pfizer) for providing us with details for resolving racemic **2**.

Supplementary Material Available: Tables of fractional coordinates, temperature factors, bond distances and bond angles (4 pages). Ordering information is given on any current masthead page.

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 $F_{2\alpha}$

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The synthesis and biological evaluation of the methyl esters of (+)-14-fluoro$PGF_{2\alpha}$, (+)-15-*epi*-14-fluoro$PGF_{2\alpha}$, (+)-13(*E*)-14-fluoro$PGF_{2\alpha}$, and (+)-13(*E*)-15-*epi*-14-fluoro$PGF_{2\alpha}$ 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-fluoro$PGF_{2\alpha}$ methyl ester (**1a**) and (+)-15-*epi*-12-fluoro$PGF_{2\alpha}$ 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

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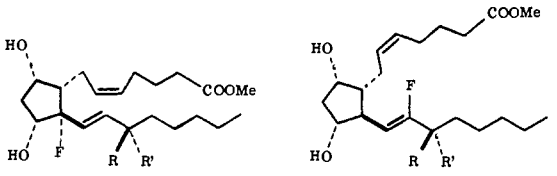
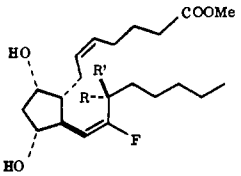


1a R = H, R' = OH
1b R = OH, R' = H

2a R = H, R' = OH
2b R = OH, R' = H

1a and **1b** were neither substrates for the human placental 15-hydroxyprostaglandin dehydrogenase nor inhibitors of the enzyme.[1] In light of the above data, we embarked on the synthesis of 14-fluoro$PGF_{2\alpha}$ methyl ester (**2a**) and 15-*epi*-14-fluoro$PGF_{2\alpha}$ methyl ester (**2b**) in which the fluorine atom is strategically placed adjacent to the metabolically unstable C(15) hydroxyl group of natural $PGF_{2\alpha}$.[2]

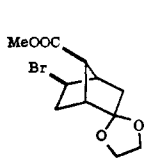
Reports detailing syntheses of prostaglandins possessing fluorinated ω side chains have been (a) limited in number and (b) focused exclusively on the C(16) position.[3] We detail below the synthesis of the two C(14) ω side chain fluorinated prostaglandins **2a** and **2b**. We also report the synthesis of (+)-13(*E*)-14-fluoro$PGF_{2\alpha}$ methyl ester (**3a**)



3a R = H, R' = OH
3b R = OH, R' = H

and (+)-13(*E*)-15-*epi*-14-fluoro$PGF_{2\alpha}$ methyl ester (**3b**) in which the C(13), C(14) olefin geometry has been inverted. In addition, we present the biological data on all four C(14)-fluorinated prostaglandins which have concentrated on pregnancy interruption in the hamster and smooth-muscle stimulating effects on gerbil colon and hamster uterine strips.

Chemistry. The synthetic route to the C(14) fluoro compounds **2** and **3** centered around the bicyclo[2.2.1]-heptane approach which we previously employed in conjunction with our efforts to prepare 12-fluoroprostaglandins.[1] The readily available (-)-bromo ketal ester **4**[1] was reduced to bromo alcohol **5** and subjected to



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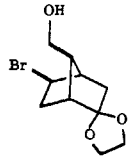
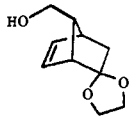


5



6

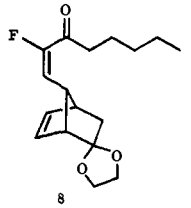
Table I. Biological Activities of Fluoroprostaglandins

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	12.5	0.28	0.001
1b	1	0.022	0.011
2a	<0.5[f]	0.263-0.288[i]	0.023-0.037[i]
2b	0.5	0.025	0.0034-0.0041[i]
3a	<0.1[g]	0.0002	0.002
3b	>1[h]	0.36-1.26[i]	0.15-0.26[i]

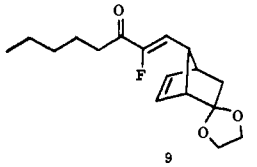
[a] Reference 11. [b] Derived by comparison of "minimum effective dose" of fluoroprostaglandins with that for natural $PGF_{2\alpha}$. The "minimum effective dose" is the minimum dose per hamster per day that will result in no pregnancies in a group of ten animals. For $PGF_{2\alpha}$, the "minimum effective dose" is 12.5 μg (subcutaneously). [c] Reference 14. [d] Potencies are calculated from dose-response curves for $PGF_{2\alpha}$ (three levels from 0.25 to 1.0 μg/mL) and test compounds. [e] Potencies are calculated from dose-response curves for $PGF_{2\alpha}$ (three levels from 60 to 120 ng/mL) and test compounds. [f] At 25 μg, 2 out of 10 animals had implants. [g] At 125 μg, 8 out of 10 animals had implants. [h] Whereas 3b was completely effective at a dose level of 12.5 μg, administration of 3.125 μg resulted in implants in only 1 out of 10 animals. [i] These are ranges and not confidence intervals because of the nonparallelism of the regression lines.

dehydrobromination with 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing toluene. The aldehyde derived from alcohol **6** permits, in principle, direct elaboration of the ω side chain upon treatment with the sodio derivative of dimethyl α-fluoro-β-oxoheptylphosphonate (**7**).

During the Emmons reaction, no isomerization of the aldehyde group was observed; however, we were surprised to find as the major product (64%) enone **8**, with less than



8

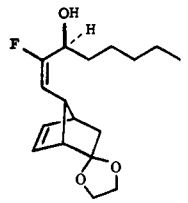


9

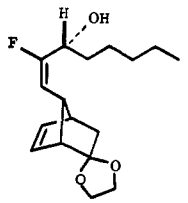
10% of the "desired" α-fluoro enone **9** present.[4] The NMR analysis of the C(13) (prostaglandin numbering) proton of compound **8** revealed a doublet of doublets centered at δ 5.70 with J_{HF} = 23 Hz and J_{HH} = 9 Hz. In contrast, the C(13) proton of **9** which was located at δ 5.94 possessed coupling constants of 36 (HF coupling) and 9 Hz. The NMR data are completely in accord with the structural assignments made above for enones **8** and **9**.

Enone **8** represents a direct precursor to 13(*E*)-14-fluoro$PGF_{2\alpha}$ methyl ester (**3a**) and the corresponding C(15) epimeric analogue **3b**. In addition, **8** can be used indirectly to prepare 14-fluoroprostaglandins **2a** and **2b** (vide infra). Reduction of enone **8** with sodium borohydride in ethanol containing cerium chloride[5] gave rise (>95%) to an ca. 1:1 mixture of allylic alcohol **10a** (R_f 0.55, ether-hexanes, 1:1) and the C(15) epimeric alcohol **10b** (R_f 0.50), which were readily separated by column chromatography on silica gel. The C(15) *S* configuration has been assigned to the isomer in the "a" series. This assignment is based on our observation that **10a** gives rise to the less polar 13(*E*)-14-fluoro$PGF_{2\alpha}$ methyl ester (**3a**), which has been assigned

(1) C.-L. J. Wang, P. A. Grieco, and F. Okuniewicz, *J. Chem. Soc., Chem. Commun.*, 468 (1976); P. A. Grieco, W. Owens, C.-L. J. Wang, E. Williams, W. J. Schillinger, K. Hirotsu, and J. Clardy, *J. Med. Chem.*, preceding paper in this issue.
(2) For a preliminary report of our work describing the synthesis of 14-fluoro$PGF_{2\alpha}$ methyl ester in racemic form, see P. A. Grieco, Y. Yokoyama, K. C. Nicolaou, W. E. Barnette, J. P. Smith, M. Ogletree, and A. M. Lefer, *Chem. Lett.*, 1001 (1978).
(3) B. J. Magerlein and W. L. Miller, *Prostaglandins*, **9**, 527 (1975); J. Fried, M.-S. Lee, B. Gaede, J. C. Sih, Y. Yoshikawa, and J. A. McCracken, *Adv. Prostaglandin Thromboxane Res.*, 1, 183 (1976); E. W. Yankee, D. E. Ayer, G. L. Bundy, F. H. Lincoln, W. L. Miller, Jr., and G. A. Youngdale, *ibid.*, 1, 195 (1976); P. A. Grieco, C.-L. J. Wang, W. H. Owens, T. Sugahara, Y. Yokoyama, F. Okuniewicz, and G. P. Withers, "Chemistry and Biochemistry of Prostanoids", Pergamon Press, Elmsford, N.Y., 1979, p 87.
(4) Cf. M. Schlosser, *Tetrahedron*, **34**, 3 (1978).
(5) J.-L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978).

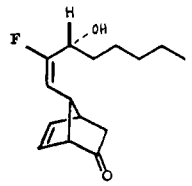


10a

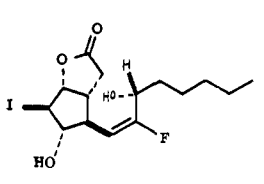


10b

the natural 15*S* configuration in keeping with the TLC behavior of 13(*E*),15(*S*)-prostaglandins and the 15*R* isomers.[6a,7] Deketalization of **10b** gave rise to bicyclo[2.2.1]heptanone derivative **11b**, which set the stage for elaboration of the five-membered ring of prostaglandin **3b**.

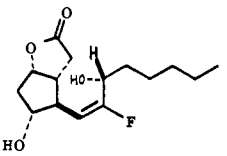


11b



12b

Baeyer–Villiger oxidation of ketone **11b**, employing basic hydrogen peroxide, gave the corresponding dihydroxycarboxylic acid, which was immediately subjected to treatment with iodine–potassium iodide. Deiodination of the resultant iodolactone **12b** (75% overall from **11b**) provided lactone **13b** as an enantiomerically pure substance. The transformation of **13b** into (+)-13(*E*)-15-



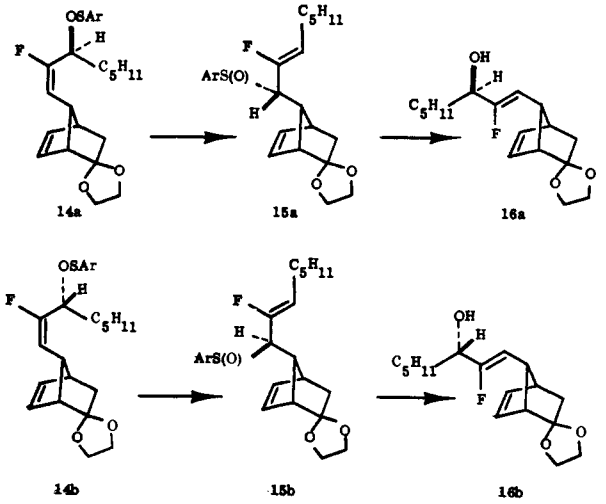
13b

epi-14-fluoroPGF$_{2\alpha}$ methyl ester **3b** proceeded in a straightforward manner via a five-step sequence of reactions as outlined below: (a) tetrahydropyranylation (DHP, PPTS,[16] CH_2Cl_2), (b) reduction (*i*-Bu_2AlH, $PhCH_3$, −78 °C), (c) Wittig reaction, (d) esterification, and (e) cleavage of protecting groups (60% acetic acid).

The preparation of (+)-13(*E*)-14-fluoroPGF$_{2\alpha}$ methyl ester (**3a**) from allylic alcohol **10a** proceeded smoothly, employing the sequence of reactions described above for the conversion **10b** → **3b**.[8]

In contrast to the synthesis of (+)-13(*E*)-14-fluoroPGF$_{2\alpha}$ methyl ester, the elaboration of (+)-14-fluoroPGF$_{2\alpha}$ methyl ester (**2a**) constitutes a more serious problem in view of the very low yield of enone **9** which was obtained during the Emmons reaction. This problem was overcome by employing the sulfenate esters **14a** and **14b**, prepared directly from **10a** and **10b**, respectively, which underwent smooth [2,3] sigmatropic rearrangement to give rise to the allylic sulfoxides **15a** and **15b**.[6] It was found, as anticipated, that treatment of sulfoxides **15a** and **15b** with trimethyl phosphite[9] provided allylic alcohols **16a** and **16b**,

Scheme I

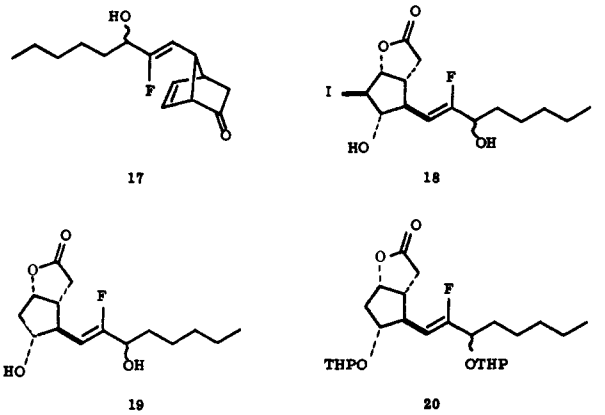


14a 15a 16a

14b 15b 16b

respectively, possessing the natural double-bond geometry. Note that during the rearrangement of allylic sulfenate **14a** → **16a** not only does the sequence proceed with inversion of the geometric center but also gives rise to inversion of configuration at C(15), both a consequence of the known stereospecific nature of the [2,3] sigmatropic rearrangement which proceeds through the thermodynamically more stable transition state.

In view of the observation in our laboratory that samples of racemic **2a** and **2b** could be very easily separated by column chromatography,[2] the experimental work leading to (+)-**2a** and (+)-**2b** was carried out on the mixture of **16a** and **16b**. Deketalization of **16a** and **16b** gave rise to bicyclo[2.2.1]heptenone **17**, which was subjected to Baeyer–Villiger oxidation and iodolactonization. Iodolactone **18** was deiodinated, and the resulting lactone diol **19** was tetrahydropyranylated. The conversion of **20** into (+)-**2a** and (+)-**2b** proceeded along standard lines (vide infra).



17 18 19 20

Biological Results.[10] Fluoroprostaglandins **2a**, **2b**, **3a**, and **3b** were evaluated for interruption of pregnancy in hamsters using a minor modification of the procedure of Giannina.[11] The biological data are summarized in Table

(6) (a) Cf. J. G. Miller, W. Kurz, K. Untch, and G. Stork, *J. Am. Chem. Soc.*, **96**, 6774 (1974); (b) for a review of the sulfenate–sulfoxide rearrangement, see D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

(7) E. W. Yankee, U.S. Patent 4 026 909 (May 31, 1977).

(8) The intermediates in the **3a** series possessed the following physical constants. **10a**: $[\alpha]_D$ −35.4° (*c* 1.13, $CHCl_3$). **12a**: $[\alpha]_D$ +52.9° (*c* 1.12, $CHCl_3$). **13a**: $[\alpha]_D$ −8.7° (*c* 0.44, $CHCl_3$). **3a**: $[\alpha]_D$ +11.8° (*c* 1.06, $CHCl_3$); R_f 0.35 (ether).

(9) D. J. Abbott and C. J. M. Stirling, *J. Chem. Soc. C*, 818 (1969); D. A. Evans and G. C. Andrews, *J. Am. Chem. Soc.*, **94**, 3672 (1974).

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

(11) The interruption of pregnancy test was carried out as described by Giannina and co-workers,[12] 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.

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

I. All C(14) fluoroprostaglandins examined, with the exception of (+)-13(*E*)-14-fluoroPGF$_{2\alpha}$ methyl ester (**3a**), which was not active at 125 μg, exhibited significant antifertility activity. Most surprising was the observation that (+)-13(*E*)-15-*epi*-14-fluoroPGF$_{2\alpha}$ methyl ester (**3b**), in which the olefin geometry about C(13), C(14) and the configuration at C(15) have been inverted, is at least as potent as PGF$_{2\alpha}$ in the hamster antifertility assay. Examination of Table I reveals that, whereas **3b** was fully effective at terminating pregnancy in hamsters at 12.5 μg, it was 90% effective at a dose of 3.125 μg. This suggests that **3b** may actually be three to four times more potent than PGF$_{2\alpha}$. Not unexpected was the finding that the diastereomeric fluoroprostaglandin **2b** was half as potent as natural PGF$_{2\alpha}$ and equipotent with **2a**.[13]

Fluoroprostaglandins **2a** and **3a**, along with the corresponding C(15) epimeric compounds **2b** and **3b**, were evaluated for smooth-muscle (in vitro) stimulating effects on gerbil colon and hamster uterine strips.[14] Table I reveals that all test compounds exhibited a reduction in smooth-muscle stimulating properties. It appears that, unlike our experience with (+)-12-fluoroPGF$_{2\alpha}$ methyl ester (**1a**) where we observed a significant increase in antifertility activity (some 12.5 times, see Table I), the introduction of a fluorine substituent into the C(14) position serves to primarily diminish smooth-muscle activity while maintaining antifertility activity.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded 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_4Si (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_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 GF (250 μm).

(−)-5-Bromospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol (5). To a suspension of 0.72 g (19 mmol) of lithium aluminum hydride in 30 mL of anhydrous ether cooled to 0 °C was added a solution of 5.5 g (19 mmol) of ester **4** in 20 mL of anhydrous ether. The reaction mixture was brought to reflux and after 1 h it was cooled to room temperature and quenched with "wet" ether. After drying over anhydrous magnesium sulfate and filtration, evaporation of the solvent in vacuo afforded 4.8 g (96%) of pure **5** as a crystalline solid: R_f 0.65 (hexanes–ether, 1:1); $[\alpha]_D$ −17.7° (*c* 1.01, chloroform); IR (CCl_4) 3625, 3400, 2975, 2880, 1475, 1438, 1370, 1325, 1245, 1230, 1208, 1160, 1100, 1065, 1041, 1020, 990, 975, 945, 910, 900, 840, 665 cm^{-1}; NMR (CCl_4) δ 1.50 (d, 1 H, *J* = 14 Hz, C(3) endo proton), 1.7–2.6 (m, 6 H), 3.6–4.0 (m, 8 H). Recrystallization from hexane–ether afforded an analytical sample, mp 68.0–68.5 °C. Anal. ($C_{10}H_{15}BrO_3$) C, H.

(−)-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (6). A solution of 1.70 g (6.46 mmol) of bromide **5** and 10 g (66 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 30 mL of toluene was refluxed for 40 h. The reaction mixture was cooled, washed with water, and treated with a solution of 2.1 g of citric acid in 50 mL of water. The combined aqueous washings were extracted five times with 50-mL portions of ethyl acetate. The combined organic extracts were dried over anhydrous potassium carbonate and concentrated under reduced pressure. Chromatography of the crude product on 85 g of silica gel (elution with hexanes–ether, 1:1) yielded 1.03 g (87%) of pure **6** as a colorless oil: R_f 0.50 (ether); $[\alpha]_D$ −106.3° (*c* 1.02, chloroform); IR (CCl_4) 3640, 3425, 3075, 2975, 2950, 2880, 1630, 1475, 1440, 1335, 1305, 1280, 1220, 1175, 1110, 1090, 1058, 1025, 950, 938, 920, 895, 848, 830, 718 cm^{-1}; NMR (CCl_4) δ 1.45 (d, 1 H, *J* = 12 Hz, C(3) endo proton), 1.80 (dd, 1 H, *J* = 3.5 and 12 Hz, C(3) exo proton), 2.2–2.8 (m, 4 H), 3.40 (d, 2 H, *J* = 7 Hz, $-CH_2OH$), 3.79 (br s, 4 H), 5.6–6.2 (m, 2 H). Anal. ($C_{10}H_{14}O_3$) C, H.

Dimethyl α-Fluoro-β-oxoheptylphosphonate (7). To a three-necked round-bottom flask equipped with a mechanical stirrer containing a suspension of 150 mg (3.3 mmol) of sodium (50% paraffin dispersion) in 90 mL of dry toluene cooled to 0 °C was added 658 mg (2.9 mmol) of dimethyl β-oxoheptylphosphonate. After 1 h at room temperature, the reaction mixture was cooled to −35 °C. Perchloryl fluoride was slowly passed through the reaction mixture for 30 min. **Extreme caution should be exercised when employing perchloryl fluoride!** Prior to workup, nitrogen was bubbled through the reaction mixture for 1 h and the temperature was allowed to warm to room temperature. The reaction was quenched by the addition of "wet" ether and washed with brine. The solvent was removed under reduced pressure and the residue was chromatographed on 30 g of silica gel. Elution with chloroform–ether (2:1) gave 200 mg (29%) of pure **7** as a colorless oil: R_f 0.65 (ether–hexanes, 3:1); IR (CCl_4) 3025, 2990, 2950, 2930, 2870, 2850, 2825, 1720, 1465, 1455, 1445, 1395, 1375, 1260, 1180, 1142, 1050, 1030, 850, 838, 790 cm^{-1}; NMR (CCl_4) δ 5.0 (dd, 1 H, J_{HF} = 48 Hz, J_{HP} = 14 Hz), 3.78 (d, 6 H, *J* = 11 Hz), 2.60 (m, 2 H, $-COCH_2-$), 1.8 (m, 6 H), 0.90 (br t, 3 H). Anal. Calcd. for $C_9H_{18}FO_4P$: *m/e* 240.0927. Found: *m/e* 240.0929.

(−)-[1α,4α,7*R(*E*)]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl-2-fluoro-1-octen-3-one (8).** To 30 mL of dichloromethane containing 1.45 mL of dry pyridine, cooled to 0 °C, was added 0.90 g (9.0 mmol) of chromium trioxide. After 1 h at ambient temperature, the solution of Collins reagent was transferred under nitrogen to another flask and cooled to 0 °C. To this cooled homogeneous solution was added 124 mg (0.68 mmol) of alcohol **6** in 5 mL of dichloromethane. After approximately 15 min the reaction was quenched with ether and treated with ca. 4 g of anhydrous magnesium sulfate. The mixture was stirred 30 min and filtered through a pad of anhydrous magnesium sulfate. Removal of the solvent in vacuo gave the desired aldehyde as a light yellow oil, homogeneous by TLC (R_f 0.61, ether–hexanes, 1:1), which was used immediately in the next reaction.

To a stirred suspension of 40 mg of 50% sodium hydride oil dispersion in 6 mL of dry tetrahydrofuran, cooled to −20 °C, was carefully added 200 mg (0.83 mmol) of dimethyl α-fluoro-β-oxoheptylphosphonate in 5 mL of dry tetrahydrofuran. After addition was complete, the reaction mixture was allowed to stir for 1 h at ambient temperature. A solution of the above aldehyde in 2 mL of dry tetrahydrofuran was added to the phosphonate anion cooled to 0 °C. The resulting solution was allowed to stir for 0.5 h at 0 °C prior to quenching with saturated aqueous ammonium chloride solution. After removal of solvent under reduced pressure, the residue was dissolved in ether and washed with brine. The aqueous portion was backwashed twice with ether, and the combined organic portions were dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was chromatographed on 15 g of silica gel. Elution with ether–hexanes (1:1) gave 130 mg (64% from alcohol **6**) of enone **8** as a colorless liquid: R_f 0.62 (hexane–ether, 1:1); $[\alpha]_D$ −1.8° (*c* 1.09,

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

(14) The oxytocin-like activity was determined using the assay as described by Holton,[15] 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.

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

$CHCl_3$); IR (CCl_4) 3075, 2960, 2940, 2876, 1706, 1640, 1468, 1460, 1440, 1408, 1384, 1335, 1305, 1225, 1215, 1170, 1158, 1110, 1060, 1048, 1020, 985, 950, 940, 920, 895, 720 cm^{-1}; NMR (CCl_4) δ 6.19 (m, 1 H, -C*H*=CH-), 5.90 (m, 1 H, -CH=C*H*-), 5.70 (dd, 1 H, J = 23 and 9 Hz, -C*H*=CF-), 4.0-3.6 (m, 4 H), 2.9-2.3 (m, 5 H), 1.98 (dd, 1 H, J = 12 and 4 Hz, C(3) exo proton), 1.7-1.1 (m, 7 H), 0.90 (br t, 3 H), 0.90 (br t, 3 H); mass spectrum, m/e 294.1649 (calcd., 294.1632). Anal. ($C_{17}H_{23}FO_3$) C, H. Continued elution provided 18 mg (9%) of enone **9**: R_f 0.56 (hexane-ether, 1:1); IR (CCl_4) 3075, 2980, 2960, 2940, 2880, 1710, 1650, 1470, 1460, 1440, 1405, 1380, 1370, 1338, 1308, 1280, 1225, 1218, 1180, 1170, 1110, 1060, 1020, 980, 940, 918, 898, 720 cm^{-1}; NMR (CCl_4) δ 6.19 (m, 1 H, -C*H*=CH), 5.95 (m, 1 H, -CH=C*H*-), 5.93 (dd, 1 H, J = 36 and 9 Hz, -C*H*=CF-), 3.80 (br s, 4 H), 3.3-2.2 (m, 5 H), 1.90 (dd, 1 H, J = 12 and 4 Hz, C(3) exo proton), 1.7-1.0 (m, 7 H), 0.91 (br t, 3 H).

(-)-[1α,4α,7*R(*E*)]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2'-[1,3]dioxolan]-7-yl-2-fluoro-1-octen-3-ol (10b).** A cooled (0 °C) solution of 162 mg (0.55 mmol) of enone **8** in 2 mL of absolute ethanol containing 340 mg (0.96 mmol) of cerium chloride hexahydrate was treated with 41 mg (1.05 mmol) of sodium borohydride in 3 mL of absolute ethanol. After 15 min the reaction was quenched by the careful addition of saturated aqueous ammonium chloride solution. The solvent was removed in vacuo, and the residue was dissolved in ether and washed with brine. The aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on 25 g of silica gel. There was obtained, in order of elution (hexanes-ether, 5:1), 72 mg of allylic alcohol **10a** [R_f 0.55 (hexanes-ether, 1:1); $[\alpha]_D$ -35.37° (c 1.13, $CHCl_3$)] and 83 mg of allylic alcohol **10b** [R_f 0.50; $[\alpha]_D$ -18.8° (c 1.01, $CHCl_3$)]. The spectral properties for isomer **10b** were as follows: IR (CCl_4) 3620, 3475, 3075, 2955, 2875, 1690, 1470, 1445, 1380, 1335, 1300, 1221, 1155, 1110, 1058, 1020, 990, 950, 940, 920, 895, 870, 855, 720 cm^{-1}; NMR (CCl_4) δ 6.05 (m, 1 H, -C*H*=CH-), 5.81 (m, 1 H, -CH=C*H*-), 5.10 (dd, 1 H, J = 22 and 10 Hz, -C*H*=CF-), 4.20 (d br t, 1 H, J = 26 and 7 Hz, C(15) proton), 3.80 (br s, 4 H), 2.2-3.0 (m, 3 H), 1.85 (dd, 1 H, J = 12 and 4 Hz, C(3) exo proton), 1.1-1.8 (m, 8 H), 0.90 (br t, 3 H); mass spectrum, m/e 296.1772 (calcd., 296.1787). Anal. ($C_{17}H_{25}FO_3$) C, H.

7(*R)-[3(*S**)-Hydroxy-2-fluoro-1(*E*)-octenyl]bicyclo[2.2.1]hept-5-en-2-one (11b).** A solution of 75 mg (0.25 mmol) of allylic alcohol **10b** in 4 mL of 60% aqueous acetic acid was stirred at ambient temperature for 16 h. The reaction was quenched by the addition of an aqueous sodium bicarbonate solution. The aqueous layer was washed with ether (4 × 25 mL), and the combined organic layers were dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo provided 59 mg (92%) of ketone **11b** as a light yellow oil: IR (CCl_4) 3615, 3450, 3080, 2970, 2940, 2875, 2860, 1750, 1695, 1475, 1463, 1425, 1386, 1325, 1304, 1160, 1130, 1100, 1060, 940, 930, 909, 880, 859, 721 cm^{-1}; NMR (CCl_4) δ 6.40 (m, 1 H, -C*H*=CH-), 5.95 (m, 1 H, -CH=C*H*-), 5.23 (dd, 1 H, J = 24 and 10 Hz, -CH=CF), 4.22 (dm, 1 H, J_{HF} = 25 Hz, -CFC*H*OH-), 1.0-3.3 (m, 14 H), 0.90 (br t, 3 H). Anal. Calcd. for $C_{15}H_{21}FO_2$: m/e 256.1526. Found: m/e 256.1525, which was used directly in the next reaction.

(+)-[3aα,4α(*E*),5β,6α,6aα]-Hexahydro-5-hydroxy-6-iodo-4-[2-fluoro-3(*S)-hydroxy-1-octenyl]-2*H*-cyclopenta[*b*]furan-2-one (12b).** To a solution of 91 mg (0.36 mmol) of ketone **11b** in 3.0 mL of methanol cooled to 0 °C was added 60 mg (1.07 mmol) of potassium hydroxide in 0.5 mL of water and 0.29 mL of 30% hydrogen peroxide. After 20 h at 0-5 °C, the reaction was quenched with aqueous sodium thiosulfate solution. The aqueous solution was washed with ether, and the aqueous portion was carefully acidified to pH 5.0 with 5% hydrochloric acid. The product was isolated by extraction with ethyl acetate (5 × 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 85 mg of sensitive dihydroxycarboxylic acid, which was used immediately without any further purification.

The above acid (85 mg) was dissolved in 1.0 mL of water (0 °C) containing 12 mg of sodium hydroxide. The cooled solution was neutralized to pH 7 with carbon dioxide and treated with 345 mg (2.09 mmol) of potassium iodide and 263 mg (1.04 mmol) of iodine in 2.0 mL of water. The resultant black solution was stirred for 3 days at 0-5 °C. The reaction was quenched by the sequential addition of 10 mL of methylene chloride and an aqueous solution of sodium thiosulfate. The product was isolated by extraction with chloroform (3 × 25 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on 15 g of silica gel. Elution with ether-hexanes, 1:1, gave 104 mg (75% overall) of pure iodolactone **12b**: R_f 0.87 (ether); $[\alpha]_D$ +37.2° (c 1.09, $CHCl_3$); IR ($CHCl_3$) 3600, 3400, 1780, 1685 cm^{-1}. Anal. Calcd. for $C_{15}H_{22}FIO_4$-H_2O: m/e 394.0441. Found: m/e 394.0446.

(-)-[3aα,4α(*E*),5β,6aα]-Hexahydro-5-hydroxy-4-[2-fluoro-3(*S)-hydroxy-1-octenyl]-2*H*-cyclopenta[*b*]furan-2-one (13b).** To a solution of 100 mg (0.24 mmol) of iodolactone **12b** in 3.0 mL of benzene containing 3 mg of azobis(isobutyronitrile) was added 212 mg (0.73 mmol) of tri-*n*-butyltin hydride. After ca. 3 h at 60 °C, the benzene was removed in vacuo and the residue was allowed to stand on a column of silica gel (11 g) for 1 h prior to elution with hexanes-ether, 1:1. There was obtained 66 mg (95%) of pure lactone **13b** as a colorless oil: R_f 0.42 (ether); $[\alpha]_D$ -37.8° (c 1.02, $CHCl_3$); IR ($CHCl_3$) 3375, 2995, 2970, 2925, 2860, 1762, 1690, 1490, 1465, 1441, 1415, 1382, 1350, 1280, 1220, 1150, 1110, 1075, 1040, 970, 930, 910, 840 cm^{-1}; NMR ($CDCl_3$) δ 3.7-5.2 (m, 6 H), 2.3-3.5 (m, 4 H), 1.2-2.2 (m, 10 H), 0.90 (br t, 3 H); mass spectrum, m/e 268.1488 (calcd., 268.1475). Anal. ($C_{15}H_{23}FO_4$) C, H.

(+)-13(*E*)-15-*epi*-14-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (3b). A solution of 85 mg (0.30 mmol) of lactonediol **13b** in 2.0 mL of methylene chloride containing 0.11 mL of dihydropyran and 15 mg of pyridinium p-toluenesulfonate[16] was stirred at ambient temperature for 4 h. The reaction mixture was quenched by the addition of solid sodium bicarbonate and 20 mL of ether. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was chromatographed on 11 g of silica gel. Elution with hexanes-ether, 2:1, gave 120 mg (88%) of the corresponding bis(tetrahydropyranyl) lactone [R_f 0.85 (ether); IR ($CHCl_3$) 1770, 1690 cm^{-1}], which was used directly in the next reaction.

To a solution of 41 mg (0.09 mmol) of the above tetrahydropyranylated lactone in 3 mL of toluene, cooled to -78 °C, was added dropwise 0.27 mL of diisobutylaluminum hydride solution (1 M in hexane). After 30 min, the reaction was quenched by the careful addition of methanol. The reaction mixture was warmed to room temperature and diluted with 20 mL of ether. Addition of water, followed by isolation of the product in the usual manner by extraction with ether, gave 42 mg (99%) of the corresponding lactol [R_f 0.55 (ether); IR ($CHCl_3$) 3600, 3395 cm^{-1}], which was used directly in the next reaction.

A suspension of 82 mg of sodium hydride, 50% oil dispersion, in 1.0 mL of dry dimethyl sulfoxide was stirred at 65 °C for 1.5 h. To the above solution of dimsyl sodium, cooled to room temperature, was added 399 mg (0.90 mmol) of (4-carboxybutyl)-triphenylphosphonium bromide [dried for 3 h at 75 °C (0.25 mm) prior to use] in 1.50 mL of dry dimethyl sulfoxide. After ca. 15 min, a solution of 42 mg (0.09 mmol) of the above lactol in 3 mL of dry dimethyl sulfoxide was added to the red ylide solution. After 30 min the reaction was quenched with ice and acidified with sodium bisulfate solution (pH 4.5-5). The resulting solution was extracted exhaustively with ethyl acetate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in ether (2 mL) and esterified with diazomethane. The crude product was chromatographed on 6 g of silica gel. Elution with hexanes-ether (2:1) yielded 40 mg (78%) of the bis(tetrahydropyranyl ether) of **3b** [R_f 0.29, ether-hexanes (1:1); IR ($CHCl_3$) 3500, 1735 cm^{-1}].

A solution of the above bis(tetrahydropyranyl ether) derivative of **3b** (40 mg, 0.07 mmol) in 2.0 mL of 60% acetic acid was stirred at ambient temperature. After 2.5 h the solvent was removed in vacuo and the residue was applied to a column of silica gel (10 g). Elution of ether-hexanes, 1:1, afforded 14.7 mg (56%) of **3b** as a colorless oil: R_f 0.25 (ether); $[\alpha]_D$ +12.5° (c 1.06, $CHCl_3$); IR ($CHCl_3$) 3600, 3395, 3005, 2955, 2940, 2855, 1728, 1470, 1460, 1440, 1420, 1380, 1370, 1318, 1235, 1210, 1178, 1149, 1120, 1100, 1080,

(16) M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, 42, 3772 (1977).

1050, 1020, 925, 870, 770, 720 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.46–5.29 (m, 2 H, -C*H*=C*H*-), 4.97 (dd, 1 H, J_{HF} = 21.1 Hz, J_{HH} = 10.8 Hz, -C*H*=CF-), 4.46 (dt, 1 H, J_{HF} = 27.8 Hz, J_{HH} = 7.2 Hz, =CFC*H*(OH)-), 4.12 (br t, 1 H), 3.87 (br s, 1 H), 3.65 (s, 3 H, -$COOCH_3$), 0.88 (t, 3 H). Anal. ($C_{21}H_{35}FO_5$) C, H.

[1α,4α,7*R(*Z*)]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2'-[1,3]-dioxolan]-7-yl-2-fluoro-1-octen-3-ol (16).** To a solution of 180 mg (61 mmol) of a 1:1 mixture of allylic alcohols **10a** and **10b** in 2.0 mL of dry tetrahydrofuran cooled to -65 °C was added 0.41 mL (0.62 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 5 min, 96 mg (0.61 mmol) of *p*-toluenesulfenyl chloride was added. The reaction mixture was stirred for 15 min at -65 °C and 1 h at ambient temperature before quenching with saturated aqueous ammonium chloride solution. The reaction mixture was diluted with brine and the product isolated by extraction with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude allylic sulfoxide **15** (R_f 0.12, ether–hexanes, 1:1) was dissolved in 2.0 mL of absolute methanol and treated with 3.0 mL of freshly distilled trimethyl phosphite. After a total of 3 h at ambient temperature, the solvent was removed in vacuo. The residue was chromatographed on 20 g of silica gel. Elution with hexanes–ether (3:1) afforded 127 mg (71%) of allylic alcohol **16** as a colorless liquid: R_f 0.50 (ether–hexanes, 1:1); IR (CCl_4) 3620, 3490, 3075, 2955, 2930, 2875, 1701, 1638, 1470, 1460, 1440, 1380, 1335, 1308, 1270, 1250, 1225, 1215, 1169, 1110, 1095, 1035, 1020, 985, 950, 940, 920, 895, 855, 720 cm^{-1}; NMR (CCl_4) δ 6.11 (m, 1 H, -C*H*=CH-), 5.90 (m, 1 H, -CH=C*H*-), 4.81 (dd, 1 H, J_{HF} = 38 Hz, J_{HH} = 9 Hz, -C*H*=CF-), 3.55–4.10 (m, 5 H), 3.15 (dm, 1 H), 2.71 (m, 1 H), 2.52 (m, 1 H), 1.08–2.11 (m, 10 H), 0.90 (br t, 3 H); mass spectrum, *m/e* 296.1779 (calcd., 296.1788). Anal. ($C_{17}H_{25}FO_3$) C, H.

7(*R)-[3-Hydroxy-2-fluoro-1(*Z*)-octenyl]bicyclo[2.2.1]-hept-5-en-2-one (17).** A solution of 167 mg (0.56 mmol) of ketal **16** in 5.0 mL of 60% acetic acid was stirred for 18 h. The reaction was quenched by the addition of a saturated sodium bicarbonate solution. The product was isolated by extraction with ether. The combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure. There was obtained 140 mg (98%) of ketone **17** as a colorless oil, which was homogeneous by TLC analysis: R_f 0.45 (ether–hexanes, 1:1); IR (CCl_4) 3620, 3475, 3075, 2960, 2940, 2865, 1755, 1702, 1470, 1460, 1440, 1420, 1380, 1370, 1320, 1295, 1266, 1240, 1155, 1139, 1120, 1055, 1040, 1010, 958, 935, 908, 870, 720 cm^{-1}; NMR (CCl_4) δ 6.40 (m, 1 H, -C*H*=CH-), 5.99 (m, 1 H, -CH=C*H*-), 4.97 (dd, 1 H, J_{HF} = 38 Hz, J_{HH} = 8 Hz, -C*H*=CF-), 3.5–4.2 (m, 1 H, C(15) proton), 3.35 (br d, 1 H), 3.08 (br s, 1 H), 2.93 (br s, 1 H), 2.50 (br s, 1 H), 1.95 (m, 2 H), 1.51–1.72 (m, 8 H), 0.90 (br t, 3 H); mass spectrum, *m/e* 252.1524 (calcd., 252.1526). Anal. ($C_{15}H_{21}FO_2$) C, H.

[3aα,4α(*Z*),5β,6α,6aα]-Hexahydro-5-hydroxy-6-iodo-4-(2-fluoro-3-hydroxy-1-octenyl)-2*H*-cyclopenta[*b*]furan-2-one (18). A solution of 178 mg (0.70 mmol) of ketone **17** in 4.0 mL of methanol containing 0.8 mL of water cooled to 0 °C was treated with 138 mg (2.46 mmol) of potassium hydroxide in 0.9 mL of water and 0.56 mL of 30% hydrogen peroxide. After 20 h at ca. 5 °C, water was added and the mixture was washed with ether. The aqueous layer was treated with sodium thiosulfate and carefully acidified to pH 5.0 with 5% hydrochloric acid. The product was isolated by extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, yielding 158 mg (79%) of the corresponding sensitive dihydroxycarboxylic acid, which was used directly in the next reaction.

The above acid (140 mg, 0.48 mmol) was dissolved in 1.5 mL of water (0 °C) containing 20 mg (0.48 mmol) of sodium hydroxide. The cooled solution was neutralized to pH 7 with carbon dioxide and treated with 523 mg (3.36 mmol) of potassium iodide and 432 mg (1.68 mmol) of iodine in 3.0 mL of water. The black reaction mixture was stirred for 4 days at 5 °C. The reaction was quenched by the addition of 15 mL of methylene chloride and an aqueous solution of sodium thiosulfate. The product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude iodolactone was chromatographed on 12 g of silica gel. Elution with hexanes–ether, 1:2, gave 146 mg (74%) of iodolactone **18** as a colorless glass: R_f 0.70 (ether); IR ($CHCl_3$) 3610, 3400, 3025, 2960, 2945, 2870, 1785, 1710, 1470, 1460, 1420, 1380, 1350, 1320, 1295, 1225, 1165, 1050, 915, 891, 850, 720 cm^{-1}; NMR ($CDCl_3$) 4.9–5.3 (m, 1.5 H), 3.7–4.6 (m, 3.5 H), 2.3–3.2 (m, 4 H), 1.1–2.0 (m, 8 H), 0.92 (br t, 3 H). Anal. Calcd. for $C_{15}H_{22}FIO_4$–H_2O: *m/e* 394.0441. Found: *m/e* 394.0496.

[3aα,4α(*Z*),5β,6aα]-Hexahydro-5-hydroxy-4-(2-fluoro-3-hydroxy-1-octenyl)-2*H*-cyclopenta[*b*]furan-2-one (19). To a solution of 123 mg (0.30 mmol) of iodolactone **18** in 5.0 mL of benzene was added 260 mg (0.90 mmol) of tri-*n*-butyltin hydride and 2.0 mg of azobis(isobutyronitrile). The mixture was heated at 65 °C for 2 h. The reaction mixture was applied directly to a column of silica gel (12 g) and allowed to stand for approximately 1 h before elution with hexanes, followed by hexanes–ether, 1:1. Elution with ethyl acetate provided 80 mg (93%) of lactone **19** as a colorless oil: R_f 0.23 (ether); IR ($CHCl_3$) 3610, 3420, 3015, 2965, 2940, 2910, 2870, 1775, 1710, 1475, 1460, 1418, 1380, 1350, 1295, 1220, 1170, 1085, 1078, 1040, 980, 930, 915, 720 cm^{-1}; NMR ($CDCl_3$) δ 4.78–5.15 (m, 1.5 H), 3.71–4.52 (m, 2.5 H), 0.90 (br t, 3 H). Anal. ($C_{15}H_{23}FO_4$) C, H.

[3aα,4α(*Z*),5β,6aα]-Hexahydro-5-[(tetrahydropyranyl)-oxy]-4-[[(2-fluoro-3-tetrahydropyranyl)oxy]-1-octenyl]-2*H*-cyclopenta[*b*]furan-2-one (20). A solution of 78 mg (0.27 mmol) of lactone **19** in 3.0 mL of methylene chloride was treated with 90 mg of dihydropyran and 13 mg of pyridinium *p*-toluenesulfonate.[16] After 4 h, the reaction was quenched by the addition of solid sodium bicarbonate and 10 mL of ether. The reaction mixture was concentrated and the residue applied to a column of silica gel (6 g). Elution with ether–hexanes, 1:1, gave 114 mg (92%) of lactone **20** as a colorless oil, which was used directly in the next reaction.

(+)-14-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (2a) and (+)-15-*epi*-14-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (2b). To a solution of 61 mg (0.13 mmol) of bis(tetrahydropyranyl) lactone **20** in 2.0 mL of toluene cooled to -78 °C was added dropwise 400 μL of a 1 M solution of diisobutylaluminum hydride in hexane. After stirring for 30 min, the reaction was quenched at -78 °C by the careful addition of methanol and warmed to room temperature. The product was isolated by extraction with ether. There was obtained 60 mg (99%) of the corresponding lactol as a colorless oil, which was used directly in the next reaction.

To 1.0 mL of dimethyl sulfoxide, freshly distilled from calcium hydride, was added 108 mg (4.5 mmol) of sodium hydride. After 2.5 h at 50 °C, the solution of dimsyl sodium was cooled to 0 °C before the addition of 589 mg (2.65 mmol) of (4-carboxybutyl)-triphenylphosphonium bromide (dried before use at 65 °C under high vacuum for 3 h) in 3 mL of dry dimethyl sulfoxide. The resulting ylide solution was stirred at ambient temperature for 15 min, prior to the addition of the above lactol in 2.0 mL of dimethyl sulfoxide. After 40 min the reaction was quenched with a saturated ammonium chloride solution and acidified to pH 4.5 with a 1 M solution of sodium bisulfate. The product was isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in ether and treated with an ethereal solution of diazomethane. Removal of the solvent in vacuo gave an oil, which was chromatographed on 8 g of silica gel. Elution with hexanes–ether (2:1, followed by 1:2) gave 39 mg (52% overall) of the bis(tetrahydropyranyl) derivatives of **2a** and **2b**, which were directly subjected to hydrolysis.

To a solution of 39 mg (0.07 mmol) of the above bis(tetrahydropyranyl) derivatives of **2a** and **2b** in 1.5 mL of ethanol was added 10 mg of pyridinium *p*-toluenesulfonate.[16] After 16 h at ambient temperature, the temperature was raised to 40 °C. After 3 h the reaction was quenched by the addition of solid sodium bicarbonate and 15 mL of ether. Filtration, followed by removal of the solvent in vacuo, left a residue which was chromatographed on 8.0 g of silica gel. Elution with ether–methanol, 100:1, gave, in order of elution, 7.1 mg (27%) of 15-*epi*-14-fluoro$PGF_{2\alpha}$ methyl ester (**2b**)[17] [R_f 0.34 (ether), $[\alpha]_D$ +17.3° (*c* 0.71, $CHCl_3$)] and 7.7 mg (29%) of 14-fluoro$PGF_{2\alpha}$ methyl ester (**2a**)[17] [R_f 0.23, $[\alpha]_D$ +22.6° (*c* 0.77, $CHCl_3$)]: IR ($CHCl_3$) 3600, 3420, 3005, 2955, 2930,

(17) By anology to the TLC behavior of natural and 15-*epi*-prostaglandins reported by Anderson [N. H. Anderson, *J. Lipid Res.*, 10, 316 (1969)], the more polar isomer has been assigned the natural 15*S* configuration.

2860, 1726, 1458, 1435, 1410, 1380, 1365, 1315, 1225, 1210, 1170, 1155, 1118, 1100, 1048, 1028, 975, 925, 860, 825 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.42 (m, 2 H, -CH=CH-), 4.71 (dd, 1 H, J_{HF} = 37 Hz, J_{HH} = 10 Hz, -CH=CF-), 4.18 (m, 1 H), 4.09 (dt, 1 H, J_{HF} = 17 Hz, J_{HH} = 7 Hz, =CFCHOH-), 3.96 (m, 1 H), 3.68 (s, 3 H), 2.82 (td, 1 H), 2.00-2.60 (m, 7 H), 1.20-1.80 (m, 12 H), 0.88 (br t, 3 H). Anal. ($C_{21}H_{35}FO_5$) C, H.

Acknowledgment. Support for this work by the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health (N01 HD-8-2809), is gratefully acknowledged. NMR (250 MHz) spectra were obtained on facilities supported by Public Health Service Grant RR-00292. Thanks are expressed to Drs. Marvin J. Karten and Richard P. Blye for useful discussions.

Anticoccidial Derivatives of 6-Azauracil. 3. Synthesis, High Activity, and Short Plasma Half-life of 1-Phenyl-6-azauracils Containing Sulfonamide Substituents[1]

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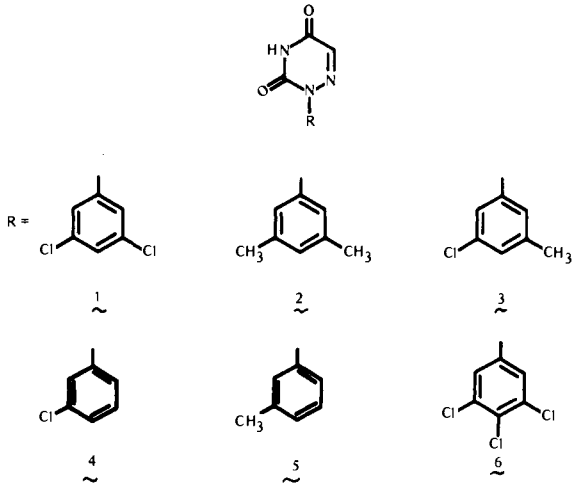
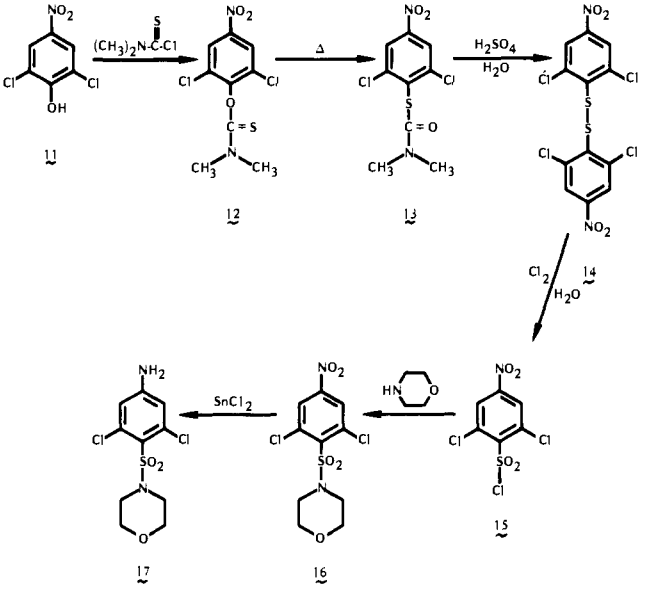
A series of 1-phenyl-6-azauracils containing sulfonamide substituents was prepared. In contrast to previous 1-phenyl-6-azauracils, some of these sulfonamides combine high activity against *Eimeria tenella* infections in chickens with a very rapid rate of clearance from plasma. Most active was 1-[3'-chloro-5'-methyl-4'-(morpholinylsulfonyl)phenyl]-6-azauracil, with a minimum effective concentration in feed of about 10 ppm.

We had previously discovered that the attachment of suitably substituted phenyl rings to the 1 position of 6-azauracil produces potent anticoccidial agents, for example 1.[2] As activity increased among these 1-phenyl-6-azauracils, so did the plasma half-life in chickens, but persistence of the drug in the body of food animals is obviously undesirable. The very potent compound 1 had an extremely long plasma half-life (160 h). Retention of the substitution pattern but replacement of the chlorine atoms by methyl groups gave 2, which was cleared more rapidly from plasma. Rapid clearance was, however, achieved at a considerable sacrifice of potency. To a degree, a combination of the two desirable properties was accomplished in 3, which was intermediate in both potency and plasma clearance time. Monosubstituted compounds 4 and 5 were markedly less potent.



It was suspected that the electronegative character of the chloro substituents made an important contribution to the potency of 1, while their lipophilicity contributed to its slow clearance. The 3,5-substitution pattern in the phenyl ring was critical to maximum activity, yet in certain compounds, e.g., 6, a 4-substituent could be added without loss of potency; it seemed reasonable, then, to seek an electron-withdrawing 4-substituent with a low degree of hydrophobic character. Attached to 1, such a group might facilitate clearance, or incorporated into 2, it might enhance potency.

Scheme I



The sulfonamide group seemed like an attractive possibility, since it has one of the lowest recorded π values,[3]

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(1) This work was presented in part at the 179th National Meeting of the American Chemical Society. See "Abstracts of Papers", 179th Meeting of the American Chemical Society, Houston, Texas, March 1980, American Chemical Society, Washington, D.C., 1980, Abstract MEDI 050.

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0022-2623/80/1823-1083$01.00/0