vacuo, leaving 195 mg (31.5%) of light brown product: mp 125–126 °C; NMR (D_2O) δ 1.38 (d, J = 6 Hz, 6 H), 1.4–2.4 (m, 3 H), 2.5–4.8 (m, 7 H), 6.67 (s, 2 H). Anal. ($C_{13}H_{20}NO_2Br·0.5H_2O$) C, H, N.

2-(Isopropylamino)-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (12). The compound was synthesized as for **5** in 65% yield: mp 211–213 °C; NMR (D_2O) δ 1.38 (d, J = 6 Hz, 6 H), 1.4–2.4 (m, 3 H), 2.5–4.8 (m, 7 H), 6.6–6.7 (m, 2 H). Anal. ($C_{13}H_{20}NO_2Br·H_2O$) C, H, N.

2-[[2-(3,4-Dihydroxyphenyl)ethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxyphenyl glycidate[15] afforded MeO_4-**7** in 37% yield. Deblocking and workup as for **5** afforded **7** as an off-white solid: mp 183–185 °C; NMR (D_2O) δ 1.3–2.3 (m, 2 H), 2.3–3.0 (m, 6 H), 3.0–3.4 (m, 3 H), 6.3–6.9 (m, 5 H). Anal. ($C_{18}H_{22}NO_4Br·3H_2O$) C, H, N.

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (7). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxyphenylacetone (Aldrich) afforded a 35% yield of MeO_4-**7**. Deblocking and workup as for **5** afforded **7** as a dark solid: mp 145 °C; NMR (D_2O) δ 1.30 (d, J = 7 Hz), 1.5–2.3 (m, 2 H), 2.4–3.0 (m, 6 H), 3.3–3.9 (m, 2 H), 6.4–6.8 (m, 5 H). Anal. ($C_{19}H_{24}NO_4Br·1.5H_2O$) C, H, N.

2-[[3-(4-Hydroxyphenyl)-1-methylpropyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (8). The reductive amination of the protected A-6,7-DTN and 4-(*p*-hydroxyphenyl)-2-butanone (Aldrich) afforded MeO_2-**8** in 90% yield. Deblocking and workup as for **5** afforded **8** as an off-white powder: mp 236–237 °C; NMR (CD_3OD) δ 1.3–1.7 (m, 3 H), 1.7–3.8 (m, 12 H), 6.43 (s, 2 H), 6.65 (d, J = 7 Hz, 2 H), 7.00 (d, J = 7 Hz, 2 H). Anal. ($C_{20}H_{26}NO_3Br$) C, H, N.

2-[[3-(2,4-Dihydroxyphenyl)-1-methylpropyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (9). The reductive amination of the protected A-6,7-dTN and 4-(3,4-dimethoxyphenyl)-2-butanone[16] afforded MeO_4-**9** in 60% yield. Deblocking and workup as for **5** afforded **9** as a pale brown solid: mp 199–201 °C dec; NMR (CD_3OD) δ 1.40 (d, J = 6 Hz, 3 H), 1.6–2.4 (m, 4 H), 2.4–3.0 (m, 6 H), 3.0–3.7 (m, 2 H), 4.8 (6 s, 9 H), 6.3–6.8 (m, 5 H). Anal. ($C_{20}H_{26}NO_4Br·H_2O$) C, H, N.

2,2′-Iminobis[1,2,3,4-tetrahydro-6,7-naphthalenediol] (10). The reductive amination of the protected A-6,7-DTN and 3,4-dimethoxy-2-tetralone[11,12] afforded MeO_4-**7**·HCl in 90% yield. The dicatechol proved to be too unstable to afford a correct combustion analysis, so a correct C, H, N analysis was obtained on MeO_4-**10**·HCl: NMR (CD_3OD) δ 1.7–2.6 (m, 4 H), 2.7–3.2 (m, 8 H), 3.2–3.8 (m, 2 H), 3.77 (s, 12 H), 6.55 (2, 4 H). Deblocking and workup as for **5** afforded **10** as a pale brown solid: mp 244–246 °C; NMR (CD_3OD) δ 1.4–2.4 (m, 4 H), 2.6–3.2 (m, 8 H), 3.3–4.0 (m, 2 H), 6.47 (s, 4 H).

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (13). The reductive amination of the protected A-5,6-DTN and 3,4-dimethoxyphenylacetone (Aldrich) afforded a 37% yield of MeO_4-**13**. Deblocking and workup as for **5** afforded **13** as a yellow solid: mp 160–161 °C; NMR (D_2O) δ 1.35 (d, J = 7 Hz, 3 H), 1.8–2.4 (m, 2 H), 2.4–3.1 (m, 6 H), 3.3–3.8 (m, 2 H), 6.3–6.9 (m, 5 H). Anal. ($C_{19}H_{24.33}NO_4Br_{1.33}·3H_2O$) C, H, N, Br.

2-[[3-(4-Hydroxyphenyl)-1-methylpropyl]amino]-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (14). The reductive amination of the protected A-5,6-DTN and 4-(*p*-hydroxyphenyl)-2-butanone (Aldrich) afforded MeO_2-**14** in 86% yield. Deblocking and workup as for **5** afforded **14** as an off-white solid: mp 241–242 °C; NMR (D_2O) δ 1.43 (d, J = 7 Hz, 3 H), 1.5–2.4 (m, 4 H), 2.5–3.1 (m, 6 H), 3.1–3.8 (m, 2 H), 6.4–7.3 (m, 6 H). Anal. ($C_{20}H_{26}NO_3Br·H_2O$) C, H, N.

Acknowledgment. The excellent secretarial assistance of Ms. Chris Maier and Ms. Diane Lulofs in the preparation of this manuscript is greatly appreciated.

(15) W. Schneider and E. Kaemmerer, *Arch. Pharm. (Weinheim, Ger.)*, **299**, 817 (1966).

(16) M. Winn, R. Rasmussen, F. Minard, J. Kyncl, and N. Plotnikoff, *J. Med. Chem.*, **18**, 434 (1975).

Synthesis and Biological Evaluation of the Methyl Esters of (+)-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ and (+)-15-*epi*-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$

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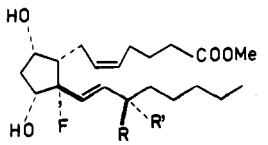
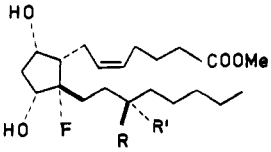
(+)-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ methyl ester (**2a**) and (+)-15-*epi*-12-fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ methyl ester (**2b**) were prepared from the readily available (−)-7-fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (**3**). Fluoroprostaglandins **2a** and **2b** possess truly significant separations of antifertility activity from smooth-muscle stimulating properties. In addition, our studies showed that **2a** and **2b** were totally inert toward the placental 15-hydroxyprostaglandin dehydrogenase.

The luteolytic effect associated with prostaglandin $F_{2\alpha}$ which enables man to control the reproductive cycle of animals[1] prompted us some years ago to synthesize novel fluoroprostaglandins in hopes of developing analogues of natural $PGF_{2\alpha}$ which possess enhanced luteolytic potency while being devoid of smooth-muscle stimulating activity. Our demonstration[2] that both (+)-12-fluoro$PGF_{2\alpha}$ methyl ester (**1a**) and (+)-15-*epi*-12-fluoro$PGF_{2\alpha}$ methyl ester (**1b**)



1a R = H, R′ = OH
1b R = OH, R = H



2a R = H, R′ = OH
2b R = OH, R′ = H

possess significant activity in the hamster antifertility assay while exhibiting lowered smooth-muscle stimulating properties (see Table I), coupled with similar observations by Andersen[3] with (+)-13,14-dihydro$PGF_{2\alpha}$ methyl ester

(1) Pharris, B. B.; Wyngarden, L. J. *Proc. Soc. Exp. Biol. Med.* **1969**, *130*, 92.
(2) Grieco, P. A.; Owens, W.; Wang, C.-L. J.; Williams, E.; Schillinger, W. J. *J. Med. Chem.* **1980**, *23*, 1072.

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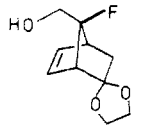
(1c), led us to prepare and examine the biological properties of the 13,14-dihydro derivatives of **1a** and **1b**. We had also previously established that both **1a** and **1b** were neither substrates for the human placental 15-hydroxyprostaglandin dehydrogenase nor inhibitors of the enzyme.[2]

We detail below the synthetic route to (+)-12-fluoro-13,14-dihydroPGF$_{2\alpha}$ methyl ester (**2a**) and (+)-15-*epi*-12-fluoro-13,14-dihydroPGF$_{2\alpha}$ methyl ester (**2b**) and present the biological data which concentrated primarily on pregnancy interruption in the hamster and smooth-muscle stimulating effects in gerbil colon and hamster uterine strips. In addition, both **2a** and **2b** were examined to see if they were substrates for the 15-hydroxyprostaglandin dehydrogenase or inhibitors of the enzyme.

Chemistry. Fluoroprostaglandins **2a** and **2b** were prepared from (−)-7-fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (**3**), $[\alpha]_D$ −106.8°(*c* 1.94, chloroform), which played a key role in our earlier synthesis of **1a** and **1b**.[2] The configuration at C(7) in the bicyclo[2.2.1]heptane derivative **3**, previously established by single-crystal X-ray analysis, guarantees the stereochemistry at C(12) in **2a** and **2b**. Elaboration of the ω side chain was achieved by mesylation of **3**, followed by treatment of the resultant mesylate with sodium iodide in refluxing acetone. Iodide **4**, $[\alpha]_D$ −61.0° (*c* 2.45, chloroform), was obtained in 77% overall yield from **3**. Al-



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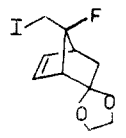

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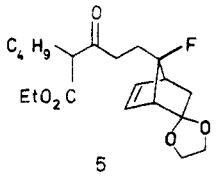
kylation of 4 with the dianion[4] derived from 3-carbethoxy-2-heptanone gave rise (89%) to β-keto ester **5**, which was smoothly decarboxylated [Ba(OH)$_2$, EtOH, HOH, 100 °C] to provide access (85%) to ketone **6**, $[\alpha]_D$ −79.0° (*c* 2.6, chloroform).



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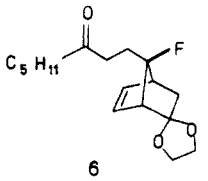

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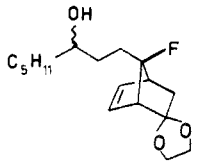
Reduction of **6** with sodium borohydride in ethanol generated a quantitative yield of two diastereomeric alcohols, **7**, which were pushed forward without attempting



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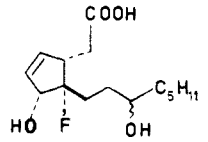


8

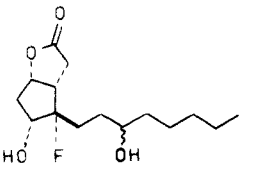
to separate them. Deketalization [10% HCl–THF, 1:1] of **7** and subsequent Baeyer–Villiger oxidation employing basic hydrogen peroxide in aqueous methanol at 5 °C afforded a near quantitative yield of the sensitive di-

Table I. Biological Activities of 12-Fluoroprostaglandins

compd	rel antifertility in hamster[a,b]	rel hamster uterine contraction[c,d]	rel gerbil colon contraction[a,c]
PGF$_{2\alpha}$	1	1	1
1a	12.5	0.28	0.001
1b	1	0.022	0.011
1c	9	0.95	0.11
2a	2	0.014–0.016[g,h]	0.004[i]
2b	<0.5[f]	0.005[j]	0.001[k]

[a] Reference 9. [b] Derived by comparison of "minimum effective dose" of prostaglandin analogue with that of 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 11. [d] Potencies are calculated from dose–response curves for PGF$_{2\alpha}$ (three dose levels: 0.25, 0.5, and 1.0 μg/mL) and test compounds. [e] Potencies are calculated from dose–response curves for PGF$_2$ (three dose levels: 60, 90, and 100 ng/mL) and test compounds. [f] At 25 μg, 5 out of 10 animals had implants. [g] This is a range and not a confidence interval because of the nonparallelism of the regression lines. [h] Six dose levels employed: 0.312, 0.781, 3.12, 6.25, 15.62, and 31.25 μg/mL. [i] Three dose levels: 12.5, 15.62, and 31.25 μg/mL. [j] Four dose levels: 3.75, 12.5, 31.25, and 62.5 μg/mL. [k] Three dose levels: 12.5, 31.25, and 62.5 μg/mL.

hydroxycarboxylic acid **8**. Subjection of **8** to iodolactonization–deiodination generated bicyclic lactone **9**



9

(70% overall), which was transformed into (+)-12-fluoro-13,14-dihydroPGF$_{2\alpha}$ methyl ester (**2a**) and (+)-15-*epi*-12-fluoro-13,14-dihydroPGF$_{2\alpha}$ methyl ester (**2b**) via a five-step sequence: (a) tetrahydropyranylation, (b) reduction of lactone with diisobutylaluminum hydride, (c) condensation of the resultant lactol with the Wittig reagent derived from 5-(triphenylphosphono)valeric acid, (d) esterification, and (e) cleavage of the protecting groups (EtOH, PPTS[5]). Analogues **2a** (less polar) and **2b** (more polar) were separated by column chromatography on silica gel. The less polar compound **2a** has been assigned the C(15) *S* configuration in agreement with published[6] and unpublished[7]

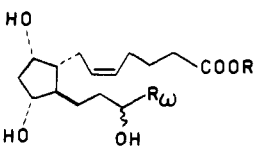
(3) We are grateful to Professor Niels Andersen for sharing with us the biological data on (+)-13,14-dihydroPGF$_{2\alpha}$ methyl ester (1c) prior to publication [Andersen, N. H.; Imamoto, S.; Subramanian, N.; Picker, D. H.; Ladner, D. W.; De, B.; Tynan, S. S.; Eggerman, T. L.; Harker, L. A.; Robertson, R. P.; Oien, H. G.; Rao, Ch. V. *Prostaglandins*, submitted].

(4) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

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

(6) De, B.; Andersen, N. H.; Ippolito, R. M.; Wilson, C. H.; Johnson, W. D. *Prostaglandins* **1980**, *19*, 221.

(7) Professor Andersen (private communication) has informed us that the reversal in TLC polarities for C(15) epimers in the 13,14-dihydroPGF$_{2\alpha}$ series also holds for the following analogues:



R = H, Me

R_ω = $CH_2C(Me)_2C_3H_7$

$(CH_2)_2C(Me)_2C_3H_7$

$(CH_2)_2C_4F_9$

observations by Andersen who has shown that saturation of the 13,14-olefinic linkage in prostaglandins results in reversal of polarity for C(15) epimers.

Biological Results[8]

Fluoroprostaglandins **2a** and **2b** were evaluated for interruption of pregnancy in hamsters as an indication of the luteolytic effect of prostaglandins. The procedure employed was a minor modification of that described previously by Giannina.[9] The biological data are summarized in Table I. Unlike our experience with (+)-12-fluoro$PGF_{2\alpha}$ methyl ester (**1a**) and the observation recorded by Andersen for (+)-13,14-dihydro$PGF_{2\alpha}$ methyl ester (**1c**) which clearly demonstrated that both **1a** and **1c** possessed a substantial increase in antifertility activity over natural $PGF_{2\alpha}$, (+)-12-fluoro-13,14-dihydro$PGF_{2\alpha}$ methyl ester (**2a**) was only two times more potent than natural $PGF_{2\alpha}$.

In contrast, analogue **2b** was approximately one-half as potent as $PGF_{2\alpha}$; however, it is important to note that antifertility activity was present. The results with **2a**, **2b**, and Andersen's data on **1c** are indeed intriguing in view of the well-known fact that the Δ^{13}-olefin and the C-(15)-hydroxyl group play an important role in the biological properties of prostaglandins.

Both **2a** and **2b** were evaluated for smooth-muscle (in vitro) stimulating effects on gerbil colon and hamster uterine strips (Table I).[11] The most dramatic results observed with **2a** and **2b** can be found in their substantially lowered smooth-muscle stimulating properties relative to not only natural $PGF_{2\alpha}$ but to **1a** and **1c** as well.

We have also examined **2a** and **2b** to see if they were either substrates for the placental 15-hydroxyprostaglandin dehydrogenase or inhibitors of the enzyme. Our studies showed that **2a** and **2b** were totally inert toward the placental 15-hydroxyprostaglandin dehydrogenase.[13]

In summary, our results clearly demonstrate that the incorporation of a fluorine atom into the C(12) position of prostaglandins results in maintenance of antifertility activity while substantially diminishing smooth-muscle stimulating properties. In fact, Table I reveals that the specificity (ratio of hamster antifertility activity to hamster uterine contraction activity) observed for **2a**, as well as that for **2b**, is far superior to that observed for analogues **1a–c**.

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 298 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 60 (Varian T-60 spectrometer) or 220 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ 0.0) as an internal standard. Rotations were carried out at 25–28 °C on a Perkin-Elmer 241 polarimeter. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

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, 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).

(−)-7-(Iodomethyl)-7-fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane] (4). A solution of 1.35 g (6.74 mmol) of (−)-7-fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane]-7-methanol (**3**) in 5.0 mL of pyridine containing 1.16 g (10.13 mmol) of methanesulfonyl chloride was stirred at 5 °C for 22 h. After concentration in vacuo, the residue was treated with 200 mL of Et_2O and washed sequentially with H_2O, $CuSO_4$ solution, H_2O, and brine. The ether layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. There was obtained 1.98 g (100%) of crude mesylate [R_f 0.30 (hexane–Et_2O, 1:5); IR ($CHCl_3$) 1180 cm^{-1}; NMR (60 MHz; $CDCl_3$) δ 1.70 (dd, 1 H, J = 4 and 12 Hz), 2.41 (dt, 1 H, J = 5 and 12 Hz), 2.79 (m, 1 H), 2.99 (m, 1 H), 3.05 (s, 3 H), 3.6–4.2 (m, 4 H), 4.57 (d, 2 H, J = 24 Hz), 6.25 (m, 2 H)], which was used directly in the next reaction.

A solution of the above mesylate (1.98 g, 6.74 mmol) in 50 mL of acetone containing 10.11 g (67.4 mmol) of NaI was refluxed. After 23 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was treated with H_2O and the product was isolated by extraction with Et_2O. The combined Et_2O layers were washed with 10% $Na_2S_2O_3$ solution, saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified on 60 g of silica gel. Elution with hexane–Et_2O (2:1) provided 1.62 g (77%) of pure iodide **4**; $[\alpha]_D$ −61° (c 2.45, $CHCl_3$); R_f 0.43 (hexane–Et_2O, 1:1); IR (CCl_4) 1416, 1337, 1314, 1286, 1256, 1231, 1217, 1173, 1100, 1051, 1020, 1005, 968, 955, 927, 915, 842, 728 cm^{-1}; NMR (60 MHz; CCl_4) δ 1.60 (dd, 1 H, J = 4 and 12 Hz), 2.33 (dt, 1 H, J = 4 and 12 Hz), 2.67 (m, 1 H), 2.88 (m, 1 H), 3.60 (d, 2 H, J = 26 Hz), 3.6–4.1 (m, 4 H), 6.15 (m, 2 H). Anal. ($C_{10}H_{12}O_1FIO_2$) C, H.

(−)-(1α,4α,7S*)-7-Fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl-3-octanone (6). To a suspension of 315 mg (7.45 mmol) of 56.8% NaH dispersion in 6.0 mL of dry THF was added a solution of 1.26 g (6.77 mmol) of 3-carbethoxy-2-heptanone in 8.0 mL of THF. After 10 min the reaction mixture was cooled to 0 °C and was treated with 4.44 mL (7.11 mmol) of a 1.6 M solution of n-butyllithium in hexane. After an additional 10 min, 1.18 mL (6.77 mmol) of HMPA was added, followed by the addition of a solution of 1.40 g (4.51 mmol) of iodide **4** in 8.0

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

(9) The interruption of pregnancy test was carried out as described by Giannina and co-workers[10] 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 dose level (3.12, 6.25, 12.5, and 25.0 μg). The compounds including $PGF_{2\alpha}$ were dissolved in ethanol, and a single dose of each compound was administered subcutaneously on day 5 of pregnancy.

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

(11) The oxytocin-like activity was determined using the assay as described by Holton[12] 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.

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

(13) 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.[14] 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 (0.02 mL), the substrate (40 μg), and NAD (1 mg) in 2.9 mL of 0.1 M phosphate buffer at pH 7.0. For $PGF_{2\alpha}$, the $\Delta OD_{340nm/10min}$ [enzyme (0.001 mL), $PGF_{2\alpha}$ (40 μg), NAD (1 mg), and 2.9 mL of 0.1 M phosphate buffer at pH 7.0] was 0.057. Inhibition studies were conducted by measuring the ΔOD_{340nm}, after a 10-min incubation at 25 °C, of placental enzyme (0.001 mL), $PGF_{2\alpha}$ (4 μg), test compound (40 μg), and NAD (1 mg) in 2.9 mL of 0.1 M phosphate buffer at pH 7.0. In the absence of test compound, there was no observable difference in ΔOD_{340nm}.

(14) Jarabak, J.; Braithwaite, S. S. *Arch. Biochem. Biophys.* **1976**, *177*, 245.

mL of THF. The reaction was stirred at 25 °C for 15 h and was quenched at 0 °C with H_2O. After evaporation of the solvent under reduced pressure, the residue was dissolved in 200 mL of Et_2O and washed with brine. After drying ($MgSO_4$), the solvent was removed in vacuo, leaving 2.66 g of residue. Chromatography on 50 g of SilicAR CC-7 using hexane–Et_2O, (5:1) provided 1.48 g (89%) of β-keto ester **5**: R_f 0.37 (hexane–Et_2O, 1:1); IR (CCl_4) 1741, 1715 cm^{-1}; NMR (60 MHz; CCl_4) δ 0.91 (br t, 3 H), 1.25 (t, 3 H, J = 7 Hz), 3.25 (t, 1 H, J = 7 Hz), 3.6–4.1 (m, 4 H), 4.12 (q, 2 H, J = 7 Hz), 6.02 (m, 2 H).

A solution of 1.03 g (2.80 mmol) of the above β-keto ester and 1.15 g (3.64 mmol) of $Ba(OH)_2 \cdot 8H_2O$ in 16 mL of 95% EtOH and 28 mL of H_2O was heated at 95–100 °C for 15 h. After cooling to room temperature, the reaction mixture was filtered and the EtOH was removed in vacuo. To the remaining aqueous solution was added solid NaCl and the product was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product (790 mg) was purified on 80 g of silica gel. Elution with hexane–Et_2O (3:1) gave 701 mg (85%) of pure ketone **6**: $[\alpha]_D$ −79° (c 2.60, $CHCl_3$); R_f 0.35 (hexane–Et_2O, 1:1); IR (CCl_4) 1718 cm^{-1}; NMR (60 MHz; CCl_4) δ 0.91 (br t, 3 H), 3.60–4.05 (m, 4 H), 6.08 (m, 2 H). Anal. ($C_{17}H_{25}FO_3$) C, H.

(1α,4α,7*R)-7-Fluorospiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]-dioxolan]-7-yl-3-octanol (7).** To a solution of 800 mg (2.7 mmol) of ketone **6** in 20 mL of EtOH was added at 0 °C 103 mg (2.7 mmol) of $NaBH_4$. The reaction mixture was stirred at room temperature for 2 h and quenched with 3 drops of HOAc. The solvent was removed under reduced pressure and the residue was dissolved in 50 mL of Et_2O. The Et_2O layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated in vacuo. The crude product was chromatographed on 50 g of silica gel. Elution with hexane–Et_2O (1:1) provided 803 mg (100%) of alcohol **7**: R_f 0.34 (hexane–Et_2O, 1:2); IR (CCl_4) 3610, 3400 cm^{-1}; NMR (60 MHz; CCl_4) δ 0.97 (br t, 3 H), 2.53 (m, 1 H), 2.73 (m, 1 H), 3.50 (m, 1 H), 3.7–4.1 (m, 4 H), 6.09 (m, 2 H). Anal. ($C_{17}H_{27}FO_3$) C, H.

Preparation of Dihydroxycarboxylic Acid 8. A solution of 800 mg (2.68 mmol) of ketal **7** in 15 mL of THF and 5 mL of 10% HCl solution was stirred at room temperature. After 5 h the solvent was concentrated in vacuo. The residue was diluted with H_2O and the product extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure, leaving 680 mg (100%) of ketone [IR (CCl_4) 3610, 3480, 1762 cm^{-1}; NMR (60 MHz; CCl_4) δ 0.90 (br t, 3 H), 3.43 (m, 1 H), 6.00 (m, 1 H), 6.40 (m, 1 H)] which was homogeneous by TLC analysis [R_f 0.43 (hexane–Et_2O, 1:2)] and used directly in the next reaction.

To a solution of 680 mg (2.67 mmol) of the above ketone in 15 mL of MeOH and 8 mL of H_2O was added 3.2 mL of a 10% NaOH solution and 1.34 mL of an aqueous 30% H_2O_2 solution. The reaction was stirred at 0 °C for 3 h and at room temperature for 9 h. After cooling to 0 °C, the reaction was quenched by the addition of $Na_2S_2O_3$ solution. The reaction mixture was carefully acidified with 10% HCl and the product was extracted with EtOAc (8 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure provided 771 mg (100%) of the crude sensitive dihydroxycarboxylic acid **8** [IR ($CHCl_3$) 3575, 3500–2500, 1709 cm^{-1}], which was employed directly in the next reaction.

(3aα,4α,5β,6α,6aα)-Hexahydro-5-hydroxy-6-iodo-4-(3-hydroxyoctanyl)-4-fluoro-2*H*-cyclopenta[*b*]furan-2-one. Dihydroxycarboxylic acid **8** (771 mg, 2.67 mmol) was dissolved at 0 °C in 6.0 mL of H_2O containing 117 mg (2.93 mmol) of NaOH. The cooled homogeneous solution was neutralized to pH 7 with CO_2 and was subsequently treated with a solution of 4.9 g (29.4 mmol) of KI and 2.52 g (9.8 mmol) of I_2 in 6.0 mL of H_2O. The resultant black reaction mixture was stirred at 5 °C for 60 h. The reaction was quenched by the addition of an aqueous $Na_2S_2O_3$ solution. The product was isolated by extraction with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered. Evaporation of the solvent under reduced pressure afforded 912 mg (82%) of the desired iodolactone [R_f 0.50 (ether); IR ($CHCl_3$) 3590, 3450, 1785 cm^{-1}] which was homogeneous by TLC analysis. Anal. ($C_{15}H_{24}FIO_4$) C, H.

(3aα,4α,5β,6aα)-Hexahydro-5-hydroxy-4-(3-hydroxyoctanyl)-4-fluoro-2*H*-cyclopenta[*b*]furan-2-one (9). To a solution of 912 mg (2.20 mmol) of (3aα,4α,5β,6α,6aα)-hexahydro-5-hydroxy-6-iodo-4-(3-hydroxyoctanyl)-2*H*-cyclopenta[*b*]furan-2-one in 60 mL of benzene containing 50 mg of azobisisobutyronitrile was added 1.92 g (6.60 mmol) of Bu_3SnH. After 5 h at 60 °C the reaction mixture was concentrated in vacuo. The resultant residue was allowed to stand on 80 g of silica gel for 2 h prior to elution with Et_2O–EtOAc (10:1). There was obtained 542 mg (85%) of pure lactone **9**: R_f 0.17 (Et_2O); IR ($CHCl_3$) 3570, 3410, 1758 cm^{-1}; NMR (60 MHz; $CDCl_3$) δ 0.7–3.3 (m, 2 H), 3.4–4.2 (m, 2 H), 4.89 (m, 1 H). Anal. ($C_{15}H_{25}FO_4$) C, H.

(3aα,4α,5β,6aα)-Hexahydro-5-[(tetrahydropyranyl)oxy]-4-fluoro-4-[[(3-tetrahydropyranyl)oxy]octanyl]-2*H*-cyclopenta[*b*]furan-2-one. A solution of 490 mg (1.7 mmol) of diol **9** in 20 mL of dry CH_2Cl_2 containing 429 mg (5.1 mmol) of DHP and a catalytic amount (~10 mg) of TsOH was stirred at 0 °C for 1 h. After an additional 1 h at room temperature, the reaction mixture was diluted with Et_2O (100 mL) and was washed with a saturated solution of $NaHCO_3$ and brine. After drying over anhydrous $MgSO_4$, the solvent was evaporated in vacuo. The residue was chromatographed on 50 g of silica gel. Elution with hexane–Et_2O (1:1) provided 605 mg (78%) of product as a colorless oil, which was used directly in the next reaction.

(+)-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ Methyl Ester (2a) and (+)-15-*epi*-12-Fluoro-13,14-dihydroprostaglandin $F_{2\alpha}$ Methyl Ester (2b). To a solution of 605 mg (1.33 mmol) of the above lactone in 14 mL of toluene cooled to −78 °C was added 4.0 mL (4.0 mmol) of a 1 M solution of *i*-Bu_2AlH in hexane. The reaction was stirred at −60 °C for 2 h and was quenched by the careful addition of MeOH. The reaction mixture was warmed to room temperature and diluted with 30 mL of EtOAc. Addition of water, followed by isolation of the product by extraction with EtOAc, gave a quantitative yield of crude lactol. Purification on 50 g of silica gel using hexane–Et_2O (1:2) afforded 575 mg (95%) of pure lactol [R_f 0.28 (hexane–Et_2O, 1:3); IR ($CHCl_3$) 3580, 3410 cm^{-1}], which was used directly in the next reaction.

A suspension of 562 mg (13.3 mmol) of NaH (56.8% oil dispersion) in 5.7 mL of freshly distilled Me_2SO was sitrred at 50–55 °C for 2.5 h under nitrogen. To the above solution of dimsyl sodium, cooled to room temperature, was added 2.95 g (6.65 mmol) of 4-carboxybutyltriphenylphosphonium bromide [dried for 2 h at 100 °C (0.2 mmHg) prior to use] in 7.1 mL of Me_2SO. After 30 min, 575 mg (1.25 mmol) of lactol in 4.3 mL of Me_2SO was added. After 14 h at room temperature, the reaction was quenched by the addition of H_2O and acidified to pH 4 with 2 N $NaHSO_4$ solution. This mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered. The solvent was removed under pressure. The residual crude acid was esterified with an ethereal solution of diazomethane. After concentration in vacuo, the crude product was chromatographed on 80 g of silica gel. Elution with hexane–Et_2O (1:1) gave 624 mg (89%) of the bis(tetrahydropyranyl ether) of **2a** and **2b**, which were used directly in the next reaction.

A solution of 624 mg (1.12 mmol) of the above bis(tetrahedropyranyl ether) in 15 mL of EtOH containing 50 mg of pyridinium *p*-toluenesulfonate (PPTS)[5] was stirred at 45 °C for 12 h and at 65 °C for 2 h prior to workup. The reaction was quenched by the addition of solid $NaHCO_3$, and the solvent was removed under reduced pressure. The residue was purified on 30 g of silica gel. Elution with Et_2O provided 386 mg (89%) of a mixture of **2a** and **2b**. Careful chromatography using benzene–EtOAc–HCOOH (50:50:1) as eluent gave, in order of elution, 54 mg of (+)-12-fluoro-13,14-dihydro$PGF_{2\alpha}$ methyl ester (**2a**) [R_f 0.32 (benzene–THF–HCOOH, 15:5:1); $[\alpha]_D$ +22.0° (c 4.0, $CHCl_3$); IR ($CHCl_3$) 3580, 3420, 3000, 2955, 2930, 2870, 2860, 1730, 1460, 1452, 1436, 1404, 1364, 1315, 1230, 1182, 1174, 1152, 1112, 1062, 1048 cm^{-1}; NMR (220 MHz; $CDCl_3$) δ 5.43 (m, 2 H, CH=CH), 4.11 (m, 1 H), 3.95 (m, 1 H), 3.66 (s, 3 H), 3.59 (m, 1 H). Anal. ($C_{21}H_{37}FO_5$) C, H], 228 mg of a mixture of **2a** and **2b**, and 28 mg of (+)-15-*epi*-12-fluoro-13,14-dihydro$PGF_{2\alpha}$ methyl ester (**2b**) [R_f 0.36 $[\alpha]_D$ +17.0° (c 1.40, $CHCl_3$). Anal. ($C_{21}H_{37}FO_5$) C, H].

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A Nonmetabolized Analogue of Phenytoin[1]

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Nine novel analogues of 5,5-diphenylhydantoin bearing a CF_3 groups(s) in the meta or para position of one or both rings were synthesized. Preliminary evaluation of all the analogues (performed by the ADD Program, NIH) indicated no significant anticonvulsant activity against electrical or chemical shock in mice at doses of ≤100 mg/kg. The analogue 5,5-bis[4-(trifluoromethyl)phenyl]hydantoin (1) was synthesized labeled with ^{14}C in the 4 position of the hydantoin ring. Certain physicochemical properties (pK_a, partition ratio, protein binding, etc.) and the LD_{50} of 1 in mice (40 mg/kg, ip; 100 mg/kg, po) were determined. The disposition of [^{14}C]1 was determined in rodents. The compound was excreted unchanged in rat feces (94% in 18 days), urinary excretion <0.5%. The half-life of elimination of [^{14}C]1 from plasma was 67–72 h (ip and iv) in rats and 115 h (ip) in mice. Studies of tissue distribution and biliary excretion of [^{14}C]1 indicate low tissue/plasma ratios (due to high plasma binding, 97%) and low biliary excretion. The lack of metabolism of [^{14}C]1 may possibly be explained by (1) the strong electron-withdrawing effects of CF_3 substituents, (2) the preemption of the primary metabolic sites, (3) the accompanying steric hindrance, and (4) the apparent inability of the CF_3 group to undergo the NIH shift.

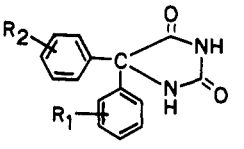
It has been proposed that electron-withdrawing groups on aromatic rings inhibit in vivo and in vitro oxidation of the aromatic nucleus of a number of drugs.[2-5] As a further test of this hypothesis, we synthesized and studied the biological fate of a bis(trifluoromethyl) analogue of phenytoin (Dilantin, diphenylhydantoin, DPH), i.e., 5,5-bis-[4-(trifluoromethyl)phenyl]hydantoin (1). Strong deactivation toward electrophilic substitution in 1 should markedly reduce aromatic hydroxylation (the major route of biotransformation of DPH). The combination of electronic and steric factors was expected to result in a more slowly metabolized and eliminated compound compared to DPH. Further, increased activity of 1 was anticipated, since CF_3 or F substitution of the aromatic rings has resulted in increased activity for certain other molecules.[6,7] Fluorinated phenytoins are active[8] as anticonvulsant agents but cause more gingival hyperplasia than DPH.[9] To facilitate measurement of physicochemical properties and studies of the diposition of 1 in rodents, [^{14}C]1 was synthesized. Besides compound 1, eight other novel analogues of DPH were synthesized; all were screened for anticonvulsant activity.[10,11]

Chemistry. The trifluoromethyl-substituted analogues of DPH 1–9 (Table I) were synthesized by the procedure of Bucherer and Berg, as modified by Henze and Isbell.[12] Grignard reagents were condensed with the appropriate aldehydes to give substituted benzhydrols, which were oxidized with pyridinium chlorochromate[13] to the corresponding benzophenones. The latter were converted to the hydantoins by heating with KCN and ammonium carbonate in acetamide in a sealed tube. The labeled analogue, [^{14}C]1, was obtained by the same procedure.

Results

Physicochemical Properties. Physicochemical properties for 1 were determined; these data and the corresponding values for DPH are given in Table II. The K_p for 1 was ten times that reported for DPH[14]. Previously reported vaues for the pK_a of DPH range from 8.1 to 8.3 under different experimental conditions.[15-23]

Table I. Substituted Diphenylhydantoins[a]



compd	R_1	R_2	mp, °C	% yield	activity,[b] mmol/kg MES	scMET
3	3-CF_3	3-CF_3	225–226	45	*c*	2.6
4	4-CF_3	H	207–209	88	0.94	*c*
5	3-CF_3	H	216–218	74	0.31	*c*
DPH	H	H			0.038	inact

[a] The following compounds were inactive against either maximal electroshock (MES) or subcutaneous pentylenetetrazol (scMET) induced seizures in mice at 0.5 or 4 h after ip administration at doses ≤0.77–0.90 mmol/kg: 1, R_1 = 4-CF_3, R_2 = 4-CF_3, mp 280–282 °C (an independent synthesis has also been reported[11]); 2, R_1 = 3-CF_3, R_2 = 4-CF_3, mp 240–241; 6, R_1 = 4-CF_3, R_2 = 4-CH_3, mp 226–228; 7, R_1 = 3-CF_3, R_2 = 4-CH_3, mp 219–220; 8, R_1 = 4-CF_3, R_2 = 3-CH_3, mp 203–204; 9, R_1 = 3-CF_3, R_2 = 4-CH_3, mp 194–195. Yields were between 52 and 90%. Satisfactory spectra (IR, NMR, and mass) were obtained for all compounds. All compounds were analyzed for C, H, F, and N (Midwest Microlabs, Ltd., Indianapolis, IN); analyses were found to be within ±0.4% of theoretical values. [b] Dose required for protection against MES- or scMET-induced seizures 4 h after ip administration. [c] Inactive in this test at 0.5 or 4 h after ip administration at doses ≤0.77–0.90 mmol/kg.

Plasma Half-life. The values for plasma $t_{1/2}$ (β phase) of [^{14}C]1 in rats, after a dose of 5 mg/kg given ip (group

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