deoxy sugar obtained was not a substrate for aldolase. Both ^{13}C and ^{1}H chemical shifts of compounds 6-deoxyF and 6-deoxyS are shown in Table I.

6,7-Dideoxyheptoses. DHAP (50 mmol) and D,L-α-hydroxybutyraldehyde (50 mmol) were subjected to aldolase-catalyzed condensation (200 U in 20 mL of gel) in a 1-L solution, pH 6.5, over 10 h, and a solution containing compounds **2** and **3** (45 mmol, determined by aldolase) was obtained. Unexceptional acid hydrolysis removed the phosphate moiety, and a mixture of 6,7-dideoxyheptoses was obtained (16 g, 82% overall yield).

Following the procedure described above for the Amberlite-catalyzed aldol condensation, dihydroxyacetone (4.5 g, 50 mmol) and D,L-α-hydroxybutyraldehyde (4.4 g, 50 mmol) were condensed to give a mixture of products (6.9 g) containing 6,7-dideoxyheptoses on the basis of HPLC analysis. The overall yield for the conversion was 78%.

Furaneol. To a solution containing 6-deoxyF or 6-deoxyS (2 g, 12.2 mmol) and ethanol (5 mL) in a glass tube were added piperidine (0.6 g) and glacial acetic acid (1 g). The tube was capped with a no-air stopper and the mixture was heated at 80 °C for 20 h. After removal of ethanol and acetic acid by concentration under reduced pressure, the residue was extracted into chloroform (160 mL) and washed three times with saturated NaCl solution (20 mL each time). The chloroform solution was concentrated under reduced pressure to an oily residue, which was dried in vacuo over concentrated H_2SO_4 and KOH pellets over night. The light brown material (1.2 g, 78% crude yield) obtained was recrystallized from petroleum ether, and pure Furaneol (1 g) was obtained: mp 79–80 °C dec (lit.[6] mp 78–80 °C dec); ^{1}H NMR (250 MHz) $CDCl_3$ containing Me_4Si internal standard) δ 1.40 (d, 3 H), 2.20 (s, 3 H), 4.50 (q, 1 H).

The following buffer components were tested (at 90 °C, 20 h) and no Furaneol was observed: acetic acid/ethanol, phosphate in H_2O (pH 3–4), phosphate in H_2O (pH 8.0), sodium bicarbonate in H_2O (pH 8.0), Dowex 1 acetate in H_2O, and ammonium acetate in ethanol.

Furaneol Analogues. A mixture of compounds **6** and **7** was prepared from 6,7-dideoxyheptoses with use of conditions similar to those for the preparation of Furaneol. Since **6** and **7** are not crystalline, isolation was accomplished by chromatography on silica gel column (2 × 50 cm) and eluted with organic solvent ($CHCl_3$/ethyl acetate = 10:1 v/v). Starting from a mixture of compounds **4** and **5** prepared via aldolase-catalyzed condensation, the yield of **6** and **7** was 50%. A 30% yield was obtained when starting from the compounds prepared via Amberlite-catalyzed condensation: ^{1}H NMR for **6** (270 MHz, $CDCl_3$) δ 0.99 (t, 3 H), 1.75 (m, 2 H), 4.37 (t, 1 H), 2.26 (s, 3 H); ^{1}H NMR for **7** (270 MHz, $CDCl_3$) δ 0.88 (t, 3 H), 2.63 (q, 2 H), 4.46 (q, 1 H), 1.45 (d, 3 H). The ratio of **6** to **7** is 7:2.

Hydrogenolysis of FDP. A 200-mL pressure bottle was charged with $FDPCa_2$ (75% pure, 18 mmol, 10 g), NaI (8.9 mmol, 1.34 g), MeOH (50 mL), and distilled water (50 mL). KOH (31.3 mmol, 1.76 g) was also introduced to the rapidly stirred mixture. With 1.0 g of KOH, the pH was 12. With 1.76 g, the pH was 14. Pd/C (10%, 200 mg) was added to the bottle, which was then closed, flushed, and pressurized at 60 psi with hydrogen. After 24 h at 90 °C, the pH was 7. The catalyst and insoluble inorganic phosphate were filtered, and the yellow solution was extracted. After workup, a yellow oil was obtained (660 mg, 28.7%). Most of the oil crystallized overnight on standing at 4 °C under argon. The crystalline solid was Furaneol (mp 77–79 °C); spectral characteristics were indistinguishable from those of an authentic sample.

When the reaction was done with a buffer and a lower pressure of hydrogen, a 20-mL pressure bottle was charged with piperidine (1.2 mmol, 102 mg), absolute MeOH (3 mL), glacial acetic acid (2.7 mmol, 162 mg), distilled water (3 mL), $FDP{\cdot}Na_3$ (98% pure, 2.09 mmol, 850 mg), and 10% Pd/C (10 mg). A magnetic stirring bar was placed in the container, which was closed, flushed with argon and hydrogen, and finally pressurized at 15 psi of hydrogen.

Furaneol from 6-Deoxy-D-glucose. A 5-mL round-bottomed flask was charged with 6-deoxy-D-glucose (0.913 mmol, 150 mg) and a 2-mL ethanolic solution of glacial acetic acid (1.25 mmol, 75 mg) and piperidine (0.53 mmol, 45 mg). A magnetic stirring bar was placed in the flask, and the flask was closed with a septum and flushed with argon. The reaction was carried out at 80 °C for 24 h. After the transformation was complete, the yellow solution was extracted with chloroform (four times) and NaCl-saturated water. The organic phase was dried over $MgSO_4$, the solution filtered, and the solvent removed at reduced pressure to give 110 mg of Furaneol (90% pure, 85% yield).

Registry No. **1**, 71075-63-3; **2**, 86943-33-1; **3**, 86943-34-2; **4**, 86953-24-4; **5**, 86953-25-5; **6**, 27538-10-9; **7**, 27538-09-6; I, 3658-77-3; aldolase, 9024-52-6; TPI, 9023-78-3; SDH, 9028-21-1; G-6-P, 56-73-5; G-1-P, 59-56-3; Gal-6-P, 6665-00-5; F-1-P, 15978-08-2; F-6-P, 643-13-0; 6-deoxy-F-1-P, 86992-64-5; 6-deoxy-S-1-P, 86992-65-6; 6-deoxy-F, 4429-06-5; 6-deoxy-S, 18545-94-3; FDP, 488-69-7; DHAP, 57-04-5; DL-α-hydroxybutyraldehyde, 86943-35-3; L-lactaldehyde, 3913-64-2; D-lactaldehyde, 3946-09-6; 6-deoxy-D-glucose, 7658-08-4; butyraldehyde, 123-72-8; α-chlorobutyraldehyde, 28832-55-5; DL-α-hydroxybutyraldehyde dimethyl acetal, 86943-36-4; DHA, 96-26-4; DL-lactaldehyde, 3913-65-3; Amberlite IRA-400, 9002-24-8; D-fucose, 3615-37-0; L-fucose, 2438-80-4.

Supplementary Material Available: Detailed experiments regarding the preparation of Furaneol from fucose and different hexose phosphates by hydrogenolysis (5 pages). Ordering information is given on any current masthead page.

C(12)-Substituted Prostaglandins. An Enantiospecific Total Synthesis of (+)-12-(Fluoromethyl)prostaglandin $F_{2\alpha}$ Methyl Ester

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Received April 8, 1983

(+)-12-(Fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester (**1**) was prepared from the readily available methyl (−)-(1α,4α,5α,7*S**)-5-bromospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-carboxylate (**2**). The synthesis proceeds via the intermediacy of aldehyde **10** (R = CH_2F), which upon reaction with 1-lithio-1-*cis*-heptene provides in an enantiospecific process access to adduct **11** (R = CH_2F). Exposure of the desired cis-allylic acetate **12** to $PdCl_2(CH_3CN)_2$ in tetrahydrofuran gives rise solely to enantiomerically pure trans-allylic acetate **14**, which is transformed into **1** via standard prostaglandin methodology. (+)-12-(Fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester was evaluated for pregnancy interruption in the hamster and smooth muscle stimulating properties on gerbil colon and hamster uterine strips.

Several years ago we embarked on a program to prepare a variety of C(12)-substituted prostaglandin derivatives for evaluation as potential luteolytic agents. At the time we initiated our program, synthetic routes to C(12)-substituted prostaglandins were lacking. Despite the development during the past 10 years of methodology for gaining access to the C(12) position in the prostaglandin nucleus,[1] C(12)-derivatized prostaglandins remain rela-

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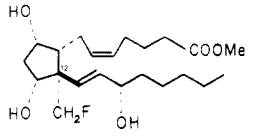
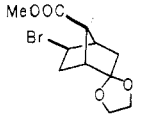
tively rare.[1,2] Our continued interest in fluoroprostaglandins[2a,d,3] and, more significantly, in 12-fluoroprostaglandins led us to undertake the total synthesis of 12-(fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester (1). We detail below an enantiospecific total synthesis of 1.



1

Success at achieving an enantiospecific synthesis of 1 was dependent on (1) the ability to introduce at some early stage in the synthesis a fluoromethyl group into a suitable chiral starting material and (2) elaboration of the C(15) configuration of 1 with complete stereochemical control. The readily available chiral bromo ketal ester 2[3a] possessing



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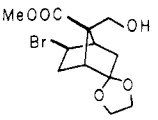

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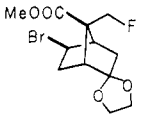
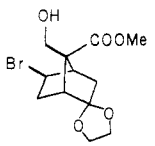


4

an activated proton at C(7) [the C(7) position in 2 corresponds to the C(12) position in 1] provided us with a means for incorporating a fluoromethyl group. In principle hydroxymethylation of 2 followed by replacement of the hydroxyl in 3 by a fluorine atom should give way to fluoromethylated ester 4. As anticipated, hydroxymethylation of the ester enolate derived from 2 (LDA, THF, −78 °C; HCHO; see Experimental Section) led in 91% yield to a mixture of 5 (mp 123–124 °C) and 3 (mp 112.5–113.5 °C)



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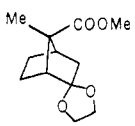
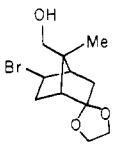


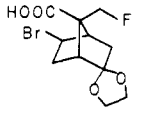
5a



6

in a ratio of 1.5:1.0. The structure of the major isomer 5 was unambiguously established by conversion [(1) MsCl, Py; (2) NaI, acetone; (3) Bu_3SnH, PhH] into the known bicyclo[2.2.1]heptane derivative 5a.[4] We were not dismayed by the results of the hydroxymethylation since both 3 and 5 can be employed in a synthesis of 1. Since the logical precursor to the fluoromethylated derivative 4 appeared to be alcohol 3, we proceeded by transforming alcohol 3 into its corresponding mesylate which was subjected to treatment with potassium fluoride in diethylene glycol at 100 °C. The desired fluoromethylated derivative 4 was obtained in 78% overall yield as a crystalline compound, mp 103–104 °C. Unfortunately all our attempts to reduce the ester function in 4 while maintaining the fluoromethyl group proved fruitless. For example, reduction of 4 with lithium aluminum hydride in ether at 0 °C provided alcohol 6 in 81% yield.

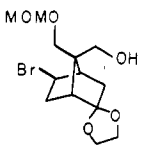
Attempts to convert ester 4 into its corresponding acid 4a, so as to examine reduction of the carboxylic acid res-



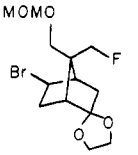
4a

idue, proved exceedingly difficult. Success was finally achieved by employing lithium *n*-propyl mercaptide.[5] Acid 4a was isolated in 92% yield. Once again all attempts to reduce 4a met with no success. Use of the acid chloride and mixed anhydrides of 4a also proved fruitless.

In view of the ready availability of the epimeric hydroxymethylated ester 5, our synthetic efforts to circumvent the above problems were abandoned. Protection of the hydroxyl function in 5 as its methoxymethyl ether (MOM) and subsequent reduction ($LiAlH_4$, Et_2O) of the ester provided alcohol 7: $[\alpha]_D$ +10.8° (*c* 5.66, $CHCl_3$); 95%



7



8

overall yield. Mesylation of 7 followed by exposure to anhydrous potassium fluoride in diethylene glycol (100 °C) afforded the desired C(7)-fluoromethylated bicyclo-[2.2.1]heptane derivative 8 in 43% isolated yield along with 21% recovered starting mesylate. That fluorine was present in compound 8 was clearly evident upon examination of the ^1H NMR spectrum of 8 which revealed that there were two diastereotopic protons coupled to fluorine (J_{HF} = 46.5 Hz). Several attempts were made to improve the moderate yield of 8. Use of tetra-*n*-butylammonium fluoride in tetrahydrofuran at 60 °C gave after 14 h only a trace of the desired 8. Similarly unsuccessful was the use of potassium fluoride in dimethyl sulfoxide.

Treatment of the mesylate derived from alcohol 7 with tetra-*n*-butylammonium fluoride in dimethyl sulfoxide at 80 °C led to the completely dehydrobrominated derivative 9 in 94% yield. The loss of the exo bromine atom was unexpected and, more importantly, undesired, since the presence of the 5-exo bromine atom plays a critical role in elaborating the chirality at C(15) in 1 (vide infra). With intermediate 8 in hand, we focused our attention on ela-

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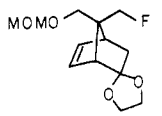
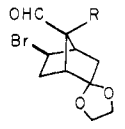


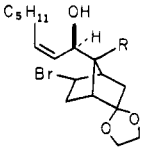
9

boration of the ω side chain of 1 bearing the C-15 *S* configuration.

We have previously shown that 1-lithio-1-*cis*-heptene adds in a highly stereoselective fashion to aldehydes of type **10** (R = H, Me, $OCH_2C_6H_5$) giving rise to adduct **11**.[6,7]



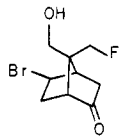
10



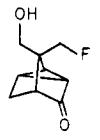
11

The availability of adduct **11** with its newly created chiral center suggested to us some time ago the possibility of developing a stereocontrolled method for elaborating the C-15 *S* configuration of the ω side chain of prostanoids via some type of chirality-transfer process.[6a] The palladium(II)-catalyzed [3,3]-sigmatropic rearrangement of allylic acetates appeared to be ideally suited to meet our specific requirements.[6,8] In this connection we have developed and communicated on a previous occassion an enantiospecific synthesis of prostaglandins possessing either the C-15 *S* or C-15 *R* configuration.[6]

We detail below the application of this methodology to the elaboration of the ω side chain of **1**. Toward this end, MOM ether **8** was treated with acid (HCl, THF, *i*-PrOH), resulting (87%) in complete deprotection, including loss of the ketal function. Attempts to find conditions so as to maintain the ketal group and avoid the formation of **12**

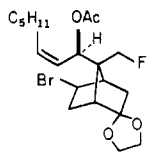


12

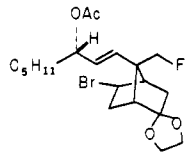


12a

were unsuccessful. It is of interest to note that on being allowed to stand for long periods of time, compound **12** undergoes dehydrobromination with formation of ketone **12a**. Reketalization of **12** followed by Collins oxidation provided (90%) aldehyde **10** (R = CH_2F). Condensation of **10** (R = CH_2F) with 1-lithio-1-*cis*-heptene in tetrahydrofuran at −78 °C provided after workup an 84% yield of allylic alcohol **11** (R = CH_2F) as the sole product. Conversion (Ac_2O, DMAP, Py, HC_2Cl_2) of **11** (R = CH_2F) into its corresponding acetate **13** followed by exposure to

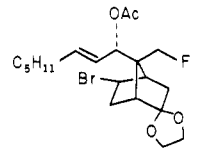


13



14

0.04 equiv of $Pd(CH_3CN)_2Cl_2$ in tetrahydrofuran for 14 h at room temperature provided in 88% isolated yield the rearranged allylic acetate **14**, $[\alpha]_D$ −94.1° (*c* 1.5, $CHCl_3$). The structure assigned to **14** is in keeping with the literature cited above. The NMR spectrum of **14** revealed the C(13) (prostaglandin numbering) proton as a doublet centered at δ 6.16 (*J* = 16 Hz) and the C(14) proton as a doublet of doublets centered at δ 5.47 (*J* = 16, 7 Hz) in agreement with the *trans*-double bond. No trace of the isomeric *trans*-allylic acetate **14a**, which ought to be in

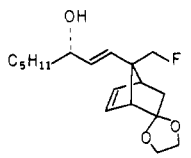


14a

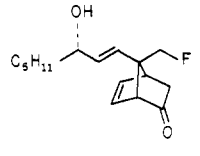
equilibrium under the conditions of the reaction with the desired trans-allylic acetate **14**, was noted. We attribute the exclusive formation of **14** to the severe steric crowding about "C(13)" due to the presence of the syn exo-oriented bromine atom and the fact that "C(13)" is neopentyl in nature.

The configuration about "C(15)" in structure **14** was unambiguously established by employing a procedure introduced by Just and Oh[10] for determining the absolute configuration at C(15) in prostaglandins. The method is based on the fact that (+)- and (−)-2-acetoxyheptanal react with *l*-ephedrin, giving rise to oxazolidines whose R_f values on TLC analysis are characteristic of the absolute configuration about the carbon bearing the acetoxy function. Allylic acetate **14** was subjected to ozonolysis (CH_2Cl_2, −78 °C, 10 min), and the 2-acetoxyheptanal obtained was directly treated with *l*-ephedrine. The resultant oxazolidines were shown to be identical (TLC) with the oxazolidines obtained from an authentic sample of 2(*S*)-acetoxyheptanal.[11]

With unambiguous confirmation of the absolute configuration about the newly created chiral center in **14**, we turned our attention to completion of the total synthesis of **1**. Cleavage of the acetate in **14** followed by dehydrobromination employing DBU in refluxing DMF led to olefinic alcohol **15** in 83% yield. Deketalization provided



15



16

access to the bicyclo[2.2.1]heptenone **16**. Subjection of **16** to Baeyer–Villiger oxidation afforded the corresponding dihydroxy carboxylic acid, which was directly transformed into iodolactone **17**. Deiodination employing tri-*n*-butyltin hydride in benzene led to **18** which was converted into **1** by using standard prostaglandin methodology (see Experimental Section).

Preliminary results obtained with (+)-12-(fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester demonstrated that **1** was ineffective in terminating pregnancy in hamsters

(6) (a) Grieco, P. A.; Takigawa, T.; Bongers, S.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7587. (b) Grieco, P. A.; Tuthill, P. A.; Sham, H.-L. *J. Org. Chem.* **1981**, *46*, 5005.

(7) Cf.: Majetich, G.; Grieco, P. A.; Bongers, S.; Erman, M. G.; Langs, D. A. *J. Org. Chem.* **1981**, *46*, 209.

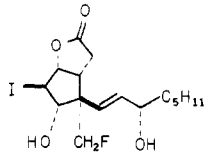
(8) Cf.: Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200. Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, 321.

(9) Prepared from the corresponding 1-iodo-1-*cis*-heptene (Dieck, H. A.; Heck, R.F. *J. Org. Chem.* **1975**, *40*, 1083).

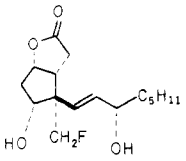
(10) Just, G.; Oh, H. *Tetrahedron Lett.* **1980**, *21*, 3667.

(11) The sample of 2(*S*)-acetoxyheptanal was prepared in a straightforward fashion from 2(*S*)-hydroxyheptanoic acid (Hauser, F. M.; Coleman, M. L.; Huffman, R. C.; Carrol, F. I. *J. Org. Chem.* **1974**, *39*, 3426).

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



17



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when dosed (25 μg) subcutaneously on day 5 of pregnancy.[13] (+)-12-(Fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester was devoid of any activity in both the gerbil colon and hamster uterine strip smooth muscle assays.[15]

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 220 MHz (Varian HR-220) or at 90 MHz (EM 390) 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 sodium–benzophenone. Pyridine, triethylamine, dimethylformamide, dimethyl sulfoxide, and diisopropylamine were distilled from calcium hydride. 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 GF (250 μm).

Hydroxymethylation of Methyl (−)-(1α,4α,5α,7S*)-5-Bromospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-carboxylate (2). To a solution of diisopropylamine (2.58 g, 25.5 mmol) in 40 mL of dry tetrahydrofuran cooled to −78 °C was added 17.0 mL of *n*-butyllithium (1.5 M in hexane). After 15 min, a solution of 5.0 g (17 mmol) of ester **2** in 10 mL of dry tetrahydrofuran was added dropwise over a period of 20 min. After an additional 30 min at −78 °C, the reaction mixture was warmed to 0 °C where it was kept for another 10 min before being cooled to −78 °C. Formaldehyde, generated from 10.2 g (340 mmol) of paraformaldehyde at 153 °C, was passed into the reaction mixture with the aid of a stream of nitrogen. After complete depolymerization the reaction mixture was stirred for an additional 30 min at −78 °C. The reaction was quenched by the addition of a saturated solution of ammonium chloride. The tetrahydrofuran was removed in vacuo and the product isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 6.20 g of residue which was purified on 250 g of silica gel. Elution with ether–hexane (1:2) provided 3.05 g (56%) of hydroxymethylated ester **5**: mp 123–124 °C; R_f 0.49 (ether); $[\alpha]^{23}_D$ +34.7° (*c* 1.37, $CHCl_3$); IR ($CHCl_3$) 3570, 3020, 2980, 2950, 2880, 1735, 1485, 1468, 1455, 1435, 1375, 1360, 1335, 1315, 1291, 1190, 1130, 1080, 1018, 995, 962, 942, 925, 895, 890, 855, 835 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.51 (d, 1 H, *J* = 15 Hz), 2.0–3.0 (m, 6 H), 3.74 (s, 3 H), 3.85 (m, 4 H), 4.10 (dd, 1 H, *J* = 5, 9 Hz), 4.35 (m, 2 H). Anal. Calcd for $C_{12}H_{17}BrO_5$: C, 44.87; H, 5.34. Found: C, 44.91; H, 5.28. Continued elution afforded 1.90 g (35%) of hydroxymethylated ester **3**: mp 112.5–113.5 °C; R_f 0.32; $[\alpha]^{23}_D$ −1.33° (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 3560, 3020, 2980, 2940, 2880, 1725, 1440, 1430, 1315, 1290, 1240, 1170, 1125, 1100, 1060, 1010, 995, 970, 960, 945, 915, 890, 855, 825 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.58 (d, 1 H, *J* = 15 Hz), 2.1–2.9 (m, 6 H), 3.77 (s, 3 H), 3.90 (m, 4 H), 4.0–4.2 (m, 3 H). Anal. Calcd for $C_{12}H_{17}BrO_5$: C, 44.87; H, 5.34. Found: C, 44.80; H, 5.41.

(+)-[1α,4α,5α,7S*]-5-Bromo-7-[(methoxymethoxy)methyl]spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]-7-methanol (7). A solution of 6.2 g (19.3 mmol) of alcohol **5** in 40 mL of dry chloroform containing 4.4 mL (57.9 mmol) of chloromethyl methyl ether and 13.4 mL (95.6 mmol) of diisopropylethylamine was stirred at room temperature for 14 h. The solvent was removed under reduced pressure, and the residue was chromatographed on 250 g of silica gel. Elution with ether–hexane (1:2) gave 6.9 g (98%) of pure MOM ether [R_f 0.75 (ether); $[\alpha]^{23}_D$ +50.6° (*c* 0.95, $CHCl_3$); IR (CCl_4) 2990, 2950, 2890, 2840, 2820, 1745, 1440, 1430, 1380, 1330, 1315, 1290, 1225, 1210, 1155, 1140, 1110, 1070, 1042, 1018, 970, 945, 928, 918, 890 cm^{-1}; NMR (90 MHz, CCl_4) 1.45 (d, 1 H, *J* = 14 Hz), 1.9–3.0 (m, 5 H), 3.26 (s, 3 H), 3.62 (s, 3 H), 3.80 (m, 4 H), 4.00 (dd, 1 H, *J* = 9.0, 5.0 Hz), 4.10 (AB q, 2 H, *J* = 9.5 Hz, $\Delta\nu_{AB}$ = 37.8 Hz), 4.54 (AB q, 2 H, *J* = 6.0 Hz, $\Delta\nu_{AB}$ = 6.7 Hz)] which was used directly in the next reaction.

To a suspension of 1.07 g (28.4 mmol) of lithium aluminum hydride in 60 mL of anhydrous ether under nitrogen at 0 °C was added a solution of 6.9 g (18.9 mmol) of the above ester in 30 mL of anhydrous ether. This mixture was stirred for 30 min at 0 °C followed by 1.5 h at room temperature. The reaction was quenched with methanol followed by the addition of water. The quenched reaction mixture was dried over anhydrous magnesium sulfate and filtered. Evaporation of the ether in vacuo left 6.5 g of crude product which was purified on 300 g of silica gel. Elution with ether gave 6.2 g (97%) of pure alcohol **7** as an oil: R_f 0.51 (ether); $[\alpha]^{23}_D$ +10.8° (*c* 5.66, $CHCl_3$); IR ($CHCl_3$) 3520, 2990, 2950, 2880, 1460, 1440, 1385, 1380, 1330, 1315, 1240, 1180, 1155, 1140, 1100, 1040, 1020, 1000, 975, 950, 925, 890, 860, 835 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.53 (d, 1 H, *J* = 14 Hz), 2.0–2.8 (m, 6 H), 3.41 (s, 3 H), 3.7–4.3 (m, 9 H), 4.74 (s, 2 H).

(−)-[1α,4α,5α,7R*]-5-Bromo-7-[(methoxymethoxy)methyl]-7-(fluoromethyl)spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane] (8). A solution of 6.2 g (18.4 mmol) of alcohol **7**, 2.83 mL (36.8 mmol) of methanesulfonyl chloride, and 5.9 mL (73.6 mmol) of pyridine in 35 mL of methylene chloride was stirred under nitrogen at 0 °C for 30 min and at room temperature for 14 h. The reaction mixture was diluted with ethyl acetate and washed successively with water, aqueous copper sulfate, saturated sodium bicarbonate, water and brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on 150 g of silica gel. Elution with hexane–ether (1:4) provided 7.36 g (96%) of pure mesylate which was used directly in the next reaction.

The above mesylate (7.2 g, 17.5 mmol) was treated with 10.1 g (175 mmol) of anhydrous potassium fluoride in 40.0 mL of diethylene glycol at 100 °C for 48 h under nitrogen. The reaction mixture was cooled to 25 °C and quenched with water. The product was isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. The crude product was directly chromatographed on 200 g of silica gel. Elution with hexane–ether (3:1) gave 2.55 g (43%) of fluoromethylated product **8** as an oil: R_f 0.65 (hexane–ether, 1:1); $[\alpha]^{27}_D$ −21.7° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 2980, 2950, 2890, 2820, 2770, 1485, 1465, 1445, 1330, 1315, 1230, 1195, 1135, 1100, 1085, 1040, 1015, 1005, 975, 950, 940, 910, 890, 865, 835 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.56 (d, 1 H, *J* = 14 Hz), 2.1–2.9 (m, 5 H), 3.39 (s, 3 H), 3.7–4.4 (m, 7 H), 4.68 (s, 2 H), 4.72 (dd, 1 H, *J* = 46.5, 9.0 Hz), 4.93 (dd, 1 H, *J* = 46.5, 9.0 Hz). Anal. Calcd for $C_{13}H_{20}BrFO_4$: C, 46.03; H, 5.94. Found: C, 46.24; H, 6.10.

(−)-(1α,4α,5α,7R*)-2-Oxo-5-bromo-7-(fluoromethyl)bicyclo[2.2.1]heptane-7-methanol (12). A solution of 2.42 g (7.1 mmol) of MOM ether **8** in 10 mL of a 1:1 mixture of tetrahydrofuran–2-propanol was treated with 4.5 mL of 10% hydrochloric acid solution. The reaction mixture was stirred at 45 °C for 14 h. The cooled reaction mixture was diluted with ethyl acetate and was washed with sodium bicarbonate solution and brine. The crude product obtained after drying over anhydrous

(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 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 five of pregnancy.

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

(15) The oxytocin-like activity was determined by using the assay as described by Holton[16] with the exception that hamsters were used in place of rats.

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

magnesium sulfate was purified on 40 g of silica gel. Elution with ether–hexane (1:2) provided 1.56 g (87%) of keto alcohol **12**: mp 134–135 °C; $[\alpha]^{25}_D$ −2.4° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3620, 3460, 3020, 2980, 2925, 2895, 2870, 1750, 1475, 1446, 1418, 1380, 1360, 1295, 1260, 1225, 1150, 1105, 1090, 1020, 995, 975, 955, 920, 905, 885, 875, 835 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.70 (d, 1 H, *J* = 14 Hz), 1.92 (dd, 1 H, *J* = 14, 5 Hz), 2.3–2.7 (m, 4 H), 2.88 (br d, 1 H, *J* = 5 Hz), 4.18 (m, 5 H), 4.50 (dd, 1 H, *J* = 47, 11 Hz), 4.62 (dd, 1 H, *J* = 47, 11 Hz). Anal. Calcd for $C_9H_{12}BrFO_2$: C, 43.05; H, 4.81. Found: C, 43.23; H, 4.86.

(1α,4α,5α,7*R)-5-Bromo-7-(fluoromethyl)-7-formylspiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane] (10, R = CH_2F).** To a solution of 747 mg (2.97 mmol) of keto alcohol **12** in 10 mL of benzene containing 3.48 g (29.7 mmol) of 2-methyl-2-ethyl-1,3-dioxolane was added 100 mg of *p*-toluenesulfonic acid. After 15 h at room temperature the reaction mixture was diluted with ethyl acetate and was washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo provided crude ketal which was chromatographed on 40 g of silica gel. Elution with ether–hexane (1:2) gave 762 mg (87%) of pure hydroxy ketal: R_f 0.47 (hexane–ether, 1:3); $[\alpha]^{26}_D$ −30.6° (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 3620, 3460, 3030, 2980, 2890, 1472, 1445, 1380, 1360, 1330, 1315, 1225, 1188, 1165, 1130, 1118, 1080, 1050, 1015, 995, 965, 945, 935, 890, 860, 830 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 1.54 (d, 1 H, *J* = 14 Hz), 1.83 (br t, 1 H, *J* = 6.0 Hz), 2.0–2.9 (m, 5 H), 3.80 (m, 4 H), 4.02 (m, 1 H), 4.15 (m, 2 H), 4.90 (d, 2 H, *J* = 46.5 Hz).

To a mixture of 2.20 g (22.0 mmol) of chromium trioxide in 30 mL of dry methylene chloride at 0 °C under nitrogen was added dropwise 3.56 mL (44.1 mmol) of dry pyridine. After 45 min at room temperature the reaction flask was cooled to 0 °C, and 10 g of Celite (predried) was added followed by a solution of 435 mg (1.47 mmol) of the above alcohol in 8 mL of methylene chloride. Stirring was continued for another 30 min at 0 °C, and the reaction was quenched with anhydrous sodium bisulfate and the mixture filtered through a pad of anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on 30 g of silica gel. Elution with hexane–ether, (3:1) provided 387 mg (90%) of chiral aldehyde **10** (R = CH_2F) as an oil [IR ($CHCl_3$) 3025, 2980, 2885, 2725, 1715, 1445, 1375, 1330, 1318, 1313, 1190, 1170, 1148, 1100, 1085, 1070, 1055, 1015, 1005, 975, 945, 935, 900, 890, 865, 830 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.68 (d, 1 H, *J* = 15 Hz), 2.0–2.8 (m, 4 H), 3.0 (br d, 1 H), 3.7–4.2 (m, 5 H), 4.68 (dd, 1 H, *J* = 46.5, 10.0 Hz)] which was used directly in the next reaction.

1-[(+)-[1α,4α,5α,7*R(*Z*)]-5-Bromo-7-(fluoromethyl)spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolan]-7-yl]-1(*R**)-acetoxy-2-octene (13).** To a solution of 0.89 g (3.9 mmol) of *cis*-1-iodo-1-heptene in 8 mL of dry heptane under nitrogen at −78 °C was added 2.5 mL (3.9 mmol) of a 1.55 M solution of *n*-butyllithium in hexane over 10 min. After 30 min, a solution of 357 mg (1.3 mmol) of aldehyde **10** (R = CH_2F) in 8 mL of dry tetrahydrofuran was added dropwise. After 45 min the reaction mixture was warmed to 0 °C and was quenched with a saturated ammonium chloride solution. The product was isolated by ether extraction. The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude allylic alcohol **11** (R = CH_2F) was purified on 20 g of silica gel. Elution with hexane–ether (1:4) afforded 425 mg (84%) of pure cis-allylic alcohol **11** (R = CH_2F) as an oil: R_f 0.43 (hexane–ether, 1:1); $[\alpha]^{25}_D$ −23.8° (*c* 2.7, $CHCl_3$); IR ($CHCl_3$) 3600, 2960, 2930, 2890, 2870, 2850, 1460, 1322, 1190, 1130, 1112, 1085, 1050, 1012, 1000, 980, 960, 945, 940, 905, 860 cm^{-1}; NMR (90 MHz $CDCl_3$) δ 0.9 (br t, 3 H, *J* = 6.5 Hz), 1.32 (m, 6 H), 1.58 (d, 1 H, *J* = 14.5 Hz), 1.9–2.9 (m, 7 H), 3.80 (m, 4 H), 4.17 (m, 1 H), 4.85 (dd, 1 H, *J* = 46.5, 10.0 Hz), 5.19 (dd, 1 H, *J* = 46.5, 10.0 Hz), 5.64 (m, 3 H).

A solution of 362 mg (0.9 mmol) of the above alcohol **11** (R = CH_2F) in 7 mL of methylene chloride containing 0.26 mL (2.7 mmol) of acetic anhydride, 0.43 mL (5.4 mmol) of dry pyridine, and 10 mg of 4-(dimethylamino)pyridine was allowed to stir under nitrogen for 40 h at room temperature. The reaction mixture was diluted with ether and washed successively with water, saturated copper sulfate solution, saturated sodium bicarbonate, and brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The crude acetate was purified on 20 g of silica gel. Elution with hexane–ether (5:1) provided 350 mg (90%) of acetate **13** as a colorless oil: R_f 0.52 (hexane–ether, 1:1); $[\alpha]^{25}_D$ +35.1° (*c* 1.2, $CHCl_3$); IR (CCl_4) 2955, 2925, 2880, 2870, 2855, 1744, 1456, 1367, 1325, 1248, 1235, 1196, 1167, 1138, 1115, 1080, 1050, 1015, 982, 960, 942, 925, 904, 892, 865 cm^{-1}; NMR (220 MHz, CCl_4) δ 0.91 (t, 3 H, *J* = 6.5 Hz), 1.36 (m, 6 H), 1.57 (d, 1 H, *J* = 14.0 Hz), 1.97 (s, 3 H), 1.8–2.2 (m, 3 H), 2.23 (dd, 1 H, *J* = 14.0, 6.0 Hz), 2.3–2.7 (m, 3 H), 3.7–4.1 (m, 5 H), 4.75 (dd, 1 H, *J* = 47.0, 11.0 Hz), 5.02 (dd, 1 H, *J* = 47.0, 11.0 Hz), 5.50 (m, 2 H), 6.23 (d, 1 H, J = 10 Hz). Anal. Calcd for $C_{20}H_{30}BrFO_4$: C, 55.40; H, 6.97. Found: C, 55.10; H, 6.73.

1-[(−)-[1α,4α,5α,7*R(*E*)]-5-Bromo-7-(fluoromethyl)spiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolan]-7-yl]-3(*S**)-acetoxy-1-octene (14).** To a solution of 814 mg (1.88 mmol) of *cis*-acetate **13** in 23 mL of dry tetrahydrofuran at room temperature under nitrogen was added 20 mg (0.075 mmol) of bis(acetonitrile)palladium(II) chloride. This mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with ethyl acetate and was washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude product was chromatographed on 40 g of silica gel. Elution with hexane–ether (5:1) afforded 719 mg (88%) of pure trans-allylic acetate **14** as an oil: R_f 0.43 (hexane–ether, 1:1); $[\alpha]^{25}_D$ −94.1° (*c* 1.5, $CHCl_3$); IR (CCl_4) 2950, 2928, 2870, 2855, 1737, 1460, 1440, 1366, 1330, 1238, 1200, 1148, 1118, 1080, 1050, 1015, 1005, 987, 968, 945, 920, 890 cm^{-1}; NMR (220 MHz, CCl_4) δ 0.88 (br t, 3 H, *J* = 6.5 Hz), 1.2–1.8 (m, 8 H), 1.56 (d, 1 H, *J* = 14 Hz), 1.95 (s, 3 H), 2.22 (dd, 1 H, *J* = 14, 5 Hz), 2.0–2.2 (m, 2 H), 2.48 (m, 1 H), 2.59 (m, 1 H), 3.7–4.0 (m, 5 H), 4.43 (dd, 1 H, *J* = 46.5, 10.0 Hz), 4.77 (dd, 1 H, *J* = 46.5, 10.0 Hz), 5.23 (m, 1 H), 5.47 (dd, 1 H, *J* = 16, 7 Hz), 6.16 (d, 1 H, *J* = 16 Hz).

1-[(−)-[1α,4α,7*R(*E*)]-7-(Fluoromethyl)spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolan]-7-yl]-3(*S**)-hydroxy-1-octene (15).** A solution of 700 mg (1.62 mmol) of trans-allylic acetate **14** in 20 mL of methanol was treated at room temperature for 14 h with 332 mg of potassium carbonate. The methanol was removed under reduced pressure, and the residue was taken up in ethyl acetate. After the mixture was washed with water and brine, the organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was purified on 40 g of silica gel. Elution with hexane–ether (1:1) provided 628 mg (99%) of pure trans-allylic alcohol as a colorless oil: R_f 0.30 (hexane–ether, 1:1); $[\alpha]^{27}_D$ −62.2° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3590, 3450, 2970, 2960, 2860, 1460, 1435, 1375, 1325, 1305, 1285, 1225, 1190, 1165, 1141, 1095, 1050, 1010, 1000, 980, 940, 905, 890, 860, 830 cm^{-1}; NMR (90 MHz $CDCl_3$) δ 0.90 (br t, 3 H, *J* = 6.5 Hz), 1.1–1.7 (m, 10 H), 2.2–2.7 (m, 5 H), 3.6–4.2 (m, 6 H), 4.51 (dd, 1 H, *J* = 46.5, 9.0 Hz), 4.81 (dd, 1 H, *J* = 46.5, 9.0 Hz), 5.54 (dd, 1 H, *J* = 16.5, 7.0 Hz), 6.10 (dd, 1 H, *J* = 16.5 Hz).

A solution of 628 mg (1.61 mmol) of the above bromide in 13 mL of dimethylformamide was treated at reflux for 18 h with 2.45 mL (16.1 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed sequentially with aqueous citric acid, a saturated sodium bicarbonate solution, and brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was chromatographed on 20 g of silica gel. Elution with hexane–ether (2:1) gave 415 mg (83%) of alcohol **15** as a colorless oil: R_f 0.36 (hexane–ether, 1:2); $[\alpha]^{25}_D$ −86.8° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 3590, 3430, 2950, 2920, 1460, 1375, 1320, 1215, 1100, 1080, 1035, 1004, 978, 940, 895, 860 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.88 (br t, 3 H, *J* = 6.5 Hz), 1.1–1.6 (m, 9 H), 1.63 (d, 1 H, *J* = 14 Hz), 2.15 (dd, 1 H, *J* = 14, 4 Hz), 2.64 (br s, 1 H), 2.89 (br s, 1 H), 3.7–4.2 (m, 5 H), 4.57 (dd, 1 H, *J* = 46.5, 9 Hz), 4.90 (dd, 1 H, *J* = 46.5, 9 Hz), 5.38 (dd, 1 H, *J* = 16.5, 6.0 Hz), 5.70 (d, 1 H, *J* = 16.5 Hz), 6.04 (m, 1 H), 6.20 (m, 1 H). Anal. Calcd for $C_{18}H_{27}FO_3$: C, 69.64; H, 8.76. Found: C, 69.66; H, 8.88.

(−)-[1α,4α]-7(*R)-[3(*S**)-hydroxy-1(*E*)-octenyl]-7-(fluoromethyl)bicyclo[2.2.1]hept-5-en-3-one (16).** A solution of 415 mg (1.33 mmol) of ketal **15** in 13.5 mL of tetrahydrofuran was treated at room temperature with 4.5 mL of 10% hydrochloric acid. After 13 h, the reaction mixture was diluted with ethyl acetate and was washed with a sodium bicarbonate solution and brine. The organic layer was dried over anhydrous magnesium

sulfate and concentrated in vacuo. The crude product was chromatographed on 20 g of silica gel. Elution with hexane–ether (1:1) gave 346 mg (97%) of pure ketone **16** as a colorless oil: R_f 0.30 (hexane–ether, 1:2); $[\alpha]^{26}_D$ −396° (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) 3600, 3460, 2990, 2950, 2920, 2850, 1735, 1635, 1462, 1456, 1420, 1375, 1310, 1262, 1220, 1120, 1045, 1000, 975, 965, 935, 905, 870 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.88 (br t, 3 H, *J* = 6.5 Hz), 1.1–1.8 (m, 8 H), 1.7 (s, 1 H), 1.97 (d, 1 H, *J* = 16.5 Hz), 2.32 (dd, 1 H, *J* = 16.5, 3.0 Hz), 2.94 (br s, 1 H), 3.2 (br s, 1 H), 4.08 (m, 1 H), 4.45 (d, 2 H, *J* = 46.5 Hz), 5.60 (m, 2 H), 5.90 (m, 1 H), 6.5 (m, 1 H). Anal. Calcd for $C_{16}H_{23}FO_2$: C, 72.14; H, 8.70. Found: C, 71.97; H, 8.73.

(−)-[3,3aα,4*R,5β,6α,6aα]-Hexahydro-4-(fluoromethyl)-4-[3(*S**)-hydroxy-1(*E*)-octenyl]-5-hydroxy-6-iodo-2*H*-cyclopenta[*b*]furan-2-one (17).** To a solution of 346 mg (1.3 mmol) of ketone **16** in 7.4 mL of methanol was added 6.3 mL of H_2O. This mixture was cooled to 0 °C, and 1.5 mL of a 10% sodium hydroxide solution was added followed by 1.1 mL of 30% hydrogen peroxide. After 36 h at 5 °C, the reaction mixture was washed with ether, and 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. The product was isolated with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The crude acid thus obtained was dissolved in 3.2 mL of water containing 63.5 mg (1.6 mmol) of sodium hydroxide at 0 °C. The cooled homogeneous solution was neutralized to pH 7 with gaseous carbon dioxide and was treated with a solution of 2.4 g (14.5 mmol) of potassium iodide and 1.2 g (5 mmol) of iodine in 3.2 mL of water. This solution was then stirred for 48 h at 5 °C. Ethyl acetate was added followed by the addition of saturated sodium thiosulfate to decolorize the solution. The product was isolated by extraction with ethyl acetate. Organic extracts were combined and dried over anhydrous magnesium sulfate and concentrated in vacuo to yield 450 mg (81% overall) of pure iodo lactone **17**: R_f 0.37 (ether); $[\alpha]^{25}_D$ −13.8° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3590, 2990, 2950, 2920, 2840, 1775, 1460, 1450, 1360, 1293, 1165, 1035, 990, 970, 900, 840, cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 6.5 Hz), 1.1–1.7 (m, 8 H), 1.70 (s, 1 H), 1.84 (m, 1 H), 2.7–3.2 (m, 3 H), 4.0–5.2 (m, 6 H), 5.61 (m, 2 H).

(+)-[3,3aα,4*R,5β,6α,6aα]-Hexahydro-4-(fluoromethyl)-4-[3(*S**)-hydroxy-1(*E*)-octenyl]-5-hydroxy-2*H*-cyclopenta-[*b*]furan-2-one (18).** To a solution of 140 mg (0.33 mmol) of iodo lactone **17** in 7 mL of benzene containing 4 mg of azobis-[isobutyronitrile] under nitrogen was added 288 mg (~1.0 mmol) of tri-*n*-butyltin hydride. After 2 h at 56 °C, the reaction mixture was cooled to room temperature and applied directly to a column of silica gel (15.0 g) where it was allowed to stand for 1.5 h prior to elution with ether. Pure lactone **18** was isolated (89 mg) in 90% yield as a colorless oil: R_f 0.24 (ether); $[\alpha]^{27}_D$ +11.0° (*c* 1.70, $CHCl_3$); IR ($CHCl_3$) 3600, 3410, 2930, 2860, 1765, 1465, 1370, 1335, 1188, 1075, 1025, 1010, 990, 980, 890 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 0.88 (br t, 3 H, *J* = 6.5 Hz), 1.1–1.7 (m, 8 H), 1.9–3.2 (m, 7 H), 4.15 (m, 2 H), 4.70 (d, 2 H, *J* = 46.5 Hz), 5.10 (m, 1 H), 5.58 (d, 2 H, *J* = 3.0 Hz). Anal. Calcd for $C_{16}H_{25}FO_4$: C, 63.98; H, 8.39. Found: C, 63.96; H, 8.39.

(+)-12-(Fluoromethyl)prostaglandin $F_{2\alpha}$ Methyl Ester (1). A solution of 72 mg (0.24 mmol) of diol **18**, 67 μL (0.72 mmol) of dihydropyran, and a catalytic amount of pyridinium *p*-toluenesulfonate[12] in 4 mL of dry methylene chloride under nitrogen was stirred for 3.5 h at room temperature. The reaction mixture was diluted with ether, was washed with saturated sodium bicarbonate and brine, and was dried over anhydrous magnesium sulfate. Concentration under reduced pressure afforded 102 mg (91%) of pure bis(tetrahydropyranyl) ether [R_f 0.39 (hexane–ether, 1:2); IR (CCl_4) 1780 cm^{-1}] which was used directly in the next reaction.

To a solution of the above lactone (65 mg, 0.13 mmol) in 1.5 mL of dry toluene cooled to −78 °C under nitrogen was added dropwise 0.24 mL (0.39 mmol) of a 1.6 M solution of diisobutylaluminum hydride in toluene. After 1 h at −78 °C, the reaction mixture was warmed to −60 °C. The reaction was quenched at −60 °C after 1 h by the careful addition of methanol followed by water. The product was isolated by extraction with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was passed through a column of silica gel (10 g). Elution with ether–hexane (1:1) provided 62 mg (95%) of pure lactol [R_f 0.35 (hexane–ether, 1:2); IR ($CHCl_3$) 3590, 3400 (br) cm^{-1}] which was employed directly in the next reaction.

A suspension of 168 mg (3.9 mmol) of sodium hydride (50% oil dispersion) in 1.7 mL of dry dimethyl sulfoxide was stirred at 50–55 °C for 3 h under nitrogen. To this solution, at room temperature, was added 875 mg (1.95 mmol) of (4-carboxybutyl)triphenylphosphonium bromide (dried at ca. 100 °C for 2 h prior to use) in 2.0 mL of dry dimethyl sulfoxide. After 30 min, a solution of 62 mg (0.13 mmol) of the above lactol in 1.5 mL of dry dimethyl sulfoxide was added to the deep red ylide solution. The reaction was quenched after 1 h with ice–water, and the reaction mixture was carefully acidified to pH 4.0 with a 2 N sodium bisulfate solution. The product was isolated by exahustive extraction with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude 12-(fluoromethyl)prostaglandin $F_{2\alpha}$ bis(tetrahydropyranyl) ether was directly esterified with ethereal diazomethane. The crude ester was chromatographed on 20 g of silica gel. Elution with ether–hexane (1:4, 1:2, 2:1) afforded 44 mg (59%) of bis(tetrahydropyranyl) ester which was used in the next reaction.

A solution of 16 mg (0.028 mmol) of the above bis(tetrahydropyranyl) ester in 2.0 mL of ethanol containing 7 mg of pyridinium *p*-toluenesulfonate[12] was stirred for 7.5 h at ca. 50 °C. The reaction was quenched by the addition of solid sodium bicarbonate. The solvent was removed under reduced pressure. The residue was taken up in ethyl acetate, washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, leaving crude 12-(fluoromethyl)prostaglandin $F_{2\alpha}$ methyl ester which was purified on 10 g of silica gel. Elution with ether–ethyl acetate (5:1) gave 7.9 mg (71%) of pure **1**: R_f 0.33 (ether–ethyl acetate, 2:1); $[\alpha]^{25}_D$ +27.2° (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3590, 3410 (br), 2990, 2950, 2920, 2850, 1719, 1455, 1445, 1435, 1410, 1360, 1312, 1230, 1210, 1150, 1110, 1000, 970, 910, 880, 865, 830 cm^{-1}; NMR (220 MHz, $CDCl_3$) δ 0.87 (br t, 3 H, *J* = 6.5 Hz), 1.2–2.5 (m, 21 H), 2.91 (br s, 1 H), 3.66 (s, 3 H), 4.07 (m, 2 H), 4.23 (m, 1 H), 4.79 (d, 2 H, *J* = 46.5 Hz), 5.42 (m, 2 H), 5.59 (m, 2 H). Anal. for $C_{22}H_{37}FO_5$: C, 65.95; H, 9.32. Found: C, 65.87; H, 9.28.

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Registry No. **1**, 87011-98-1; **1** (11,15-ditetrahydropyranyl ether), 87011-93-6; **1** (acid, 11,15-ditetrahydropyranyl ether), 87011-96-9; **2**, 71155-12-9; **3**, 87068-08-4; **3** (mesylate), 87011-74-3; **4**, 87011-75-4; **4a**, 87011-76-5; **4a** (acid chloride), 87011-77-6; **5**, 87068-09-5; **5** (mesylate), 87068-11-9; **5** (iodide), 87011-94-7; **5** (MOM ether), 87011-78-7; **5a**, 87068-10-8; **6**, 71485-89-7; **7**, 87011-79-8; **7** (mesylate), 87011-80-1; **8**, 87011-81-2; **9**, 87011-82-3; **10** (R = CH_2F), 87039-12-1; **11** (R = CH_2F), 87011-83-4; **12**, 87011-84-5; **12** (ethylene ketal), 87011-97-0; **12a**, 87011-85-6; **13**, 87011-86-7; **14**, 87011-87-8; **14**-ol, 87011-95-8; **15**, 87011-88-9; **16**, 87039-13-2; **17**, 87011-89-0; **18**, 87011-90-3; **18** (ditetrahydropyranyl ether), 87011-91-4; **18** lactol (ditetrahydropyranyl ether), 87011-92-5; 1-lithio-1-*cis*-heptene, 69556-80-5; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.