# Fluoroprostaglandins: Total Synthesis of (+)-13-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester

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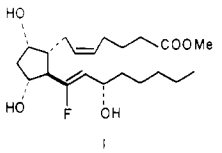
(+)-13-Fluoroprostaglandin $F_{2\alpha}$ methyl ester (1) was prepared from the readily available methyl (−)-(1α,4α,5α,7S*)-5-bromospiro[bicyclo[2.2.1]heptane-2,2′-[1,3]dioxolane]carboxylate (6). Construction of the 13-fluoro olefinic structural unit was achieved via a Schlosser–Wittig reaction employing chiral aldehyde 2 and chiral ylide 3. (+)-13-Fluoroprostaglandin $F_{2\alpha}$ methyl ester was evaluated for pregnancy interruption in the hamster and smooth muscle stimulating properties on hamster uterine strips.

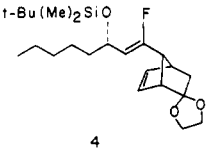
Since the report by Crabbé and co-workers in 1973 detailing the synthesis of 11,12-difluoromethanoprostaglandin $F_{2\alpha}$ methyl ester,[1] several fluorinated prostaglandins have been synthesized in an attempt to probe the effect on biological activity of introducing fluorine atoms into the carbon backbone of naturally occurring prostaglandins. In this regard fluorine atoms have been introduced into the C(5),[2] C(9),[3] C(10),[4] C(11),[3] C(12),[5] C(14),[6] and C(16)[7] positions of the prostaglandin skeleton. Reports describing the incorporation of a fluorine atom into the C(13) position are lacking. We detail below the total synthesis of (+)-13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (1).




1

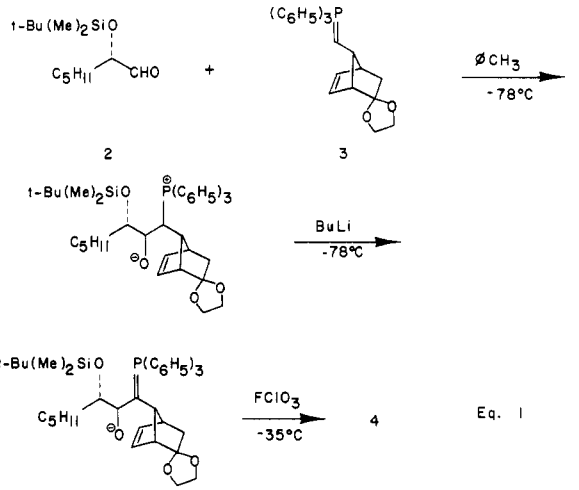
The primary purpose in synthesizing 1 stemmed from our longstanding interest in developing fluoro analogues of natural $PGF_{2\alpha}$ which possess enhanced luteolytic potency while being devoid of smooth muscle stimulating properties.[4-6,8] Interest in 1 was further enhanced by our previous observation[5,6] that analogues of natural prostaglandin $F_{2\alpha}$ bearing fluorine at either C(12) or C(14) possess increased luteolytic potency while exhibiting lowered smooth muscle stimulating activity relative to the natural compound. This advantageous separation of biological properties can, in part, be attributed to the reluctance shown by these fluorinated substances to undergo metabolic deactivation by the placental 15-hydroxyprostaglandin dehydrogenase.[5,6]

Our synthetic strategy centered around construction of fluoro olefin 4, which in principle can be transformed into 1 via standard prostaglandin methodology.[5] The formation of 4 was perceived as arising from a Schlosser modification

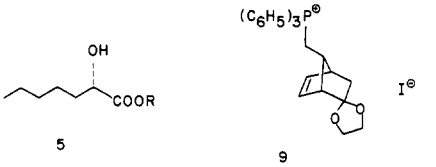



4

of the Wittig reaction wherein the initially formed mixture of betaines, derived from chiral aldehyde 2 and chiral ylide 3, is exposed to strong base (e.g., phenyllithium) and the in situ generated β-oxido ylide is treated with perchloryl fluoride (eq 1).[9]




Optically active α-silyloxy aldehyde 2, possessing the eventual C(15) chiral center, was secured in a straightforward manner from the known (+)-2(S)-hydroxyheptanoic acid (5)[10] (R = H) via a three-step sequence.




5 9

Esterification ($CH_2N_2$) of 5 (R = H) and subsequent silylation of the hydroxyl group provided the corresponding ester 5 (R = $CH_3$), which when submitted to reduction with diisobutylaluminum hydride afforded the desired aldehyde 2.

The precursor phosphonium salt 9 required for the formation of ylide 3 was prepared from the known (−)-bromo ketal ester 6[5] via a straightforward series of operations. Reduction of ester 6 followed by dehydrohalo-

(1) Crabbé, P.; Cervantes, A. *Tetrahedron Lett.* **1973**, 1319.
(2) Nakai, H.; Hamanaka, N.; Miyake, H.; Hayashi, M. *Chem. Lett.* **1979**, 1499.
(3) Arroniz, C. E.; Gallina, J.; Martinez, E.; Muchowski, J. M.; Verarde, E.; Rooks, W. H. *Prostaglandins* **1978**, *16*, 47.
(4) Grieco, P. A.; Sugahara, T.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1979**, *44*, 2189. Grieco, P. A.; Williams, E.; Sugahara, T. *Ibid.* **1979**, *44*, 2194. Fried, J.; Mitra, D. K.; Nagarajan, M.; Mehrotra, M. M. *J. Med. Chem.* **1980**, *23*, 234.
(5) Wang, C.-L. J.; Grieco, P. A.; Okuniewicz, F. *J. Chem. Soc., Chem. Commun.* **1976**, 468. Grieco, P. A.; Owens, W.; Wang, C.-L. J.; Williams, E.; Schillinger, W. J.; Hirotsu, K.; Clardy, J. *J. Med. Chem.* **1980**, *23*, 1072.
(6) Grieco, P. A.; Schillinger, W. J.; Yokoyama, Y. *J. Med. Chem.* **1980**, *23*, 1077.
(7) Magerlein, B. J.; Miller, W. L. *Prostaglandins* **1975**, *9*, 527. Fried, J.; Lee, M.-S.; Gaede, B.; Sih, J. C.; Yoshikawa, Y.; McCracken, J. A. *Adv. Prostaglandin Thromboxane Res.* **1976**, *1*, 183.
(8) Grieco, P. A.; Vedananda, T. R. *J. Org. Chem.* **1983**, *48*, 3497. Grieco, P. A.; Takigawa, T. *J. Med. Chem.* **1981**, *24*, 839.
(9) Cf.: Schlosser, M. *Tetrahedron* **1978**, *34*, 3.
(10) Hauser, F. M.; Coleman, M. L.; Huffman, R. C.; Carrol, F. I. *J. Org. Chem.* **1974**, *39*, 3426.

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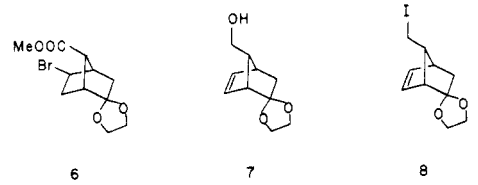
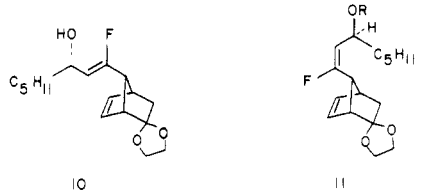


6 7 8

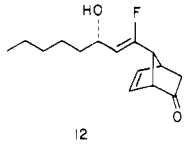
genation gave in 87% overall yield alcohol **7**. Tosylation of alcohol **7** and subsequent treatment with sodium iodide in refluxing acetone furnished the corresponding iodo derivative **8** (94%). Prolonged reaction of iodide **8** with 1.5 equiv of triphenylphosphine in refluxing xylene generated the required phosphonium iodide as a white foamy solid which, upon crystallization, afforded pure (-)-phosphonium iodide **9**, mp 180.5–181.5 °C, in 89% yield.

The stage was now set for the coupling of ylide **3** with aldehyde **2**. Ylide **3**, generated in toluene at −78 °C with freshly prepared phenyllithium in ether, was condensed at −78 °C with aldehyde **2**, and the resulting mixture of betaines was further treated with phenyllithium, giving rise to the corresponding β-oxido ylide, which was trapped at −35 °C with gaseous perchloryl fluoride.[11] Analysis of the reaction products after workup gave rise to a 12% yield of the desired fluorinated olefin **4**, often contaminated with a few percent of the corresponding unfluorinated material, and 41% of the undesired (*E*)-olefin **11** (R = $Si(Me)_2$-*t*-Bu).



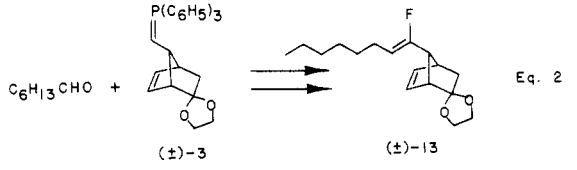
10 11

Assignment of the olefinic geometry in structures **4** and **11** (R = $Si(Me)_2$-*t*-Bu) follows from their respective $^1H$ NMR spectra. The olefinic proton in compound **4** appeared as a doublet of doublets centered at δ 4.32 with $J_{HF}$ = 39 Hz. In contrast, the olefinic proton in **11** (R = $Si(Me)_2$-*t*-Bu) appeared at δ 4.90 with $J_{HF}$ = 22 Hz. After chromatographic separation, the desired fluoro olefin **4** was subjected to desilylation giving rise to alcohol **10**. Deketalization afforded enantiomerically pure fluoro olefin 12.



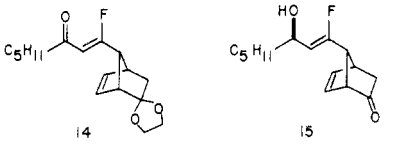
12

We were particularly disappointed with the low yield of **4** obtained from the Schlosser–Wittig reaction, since we had previously prepared (eq 2) in 55% yield via the



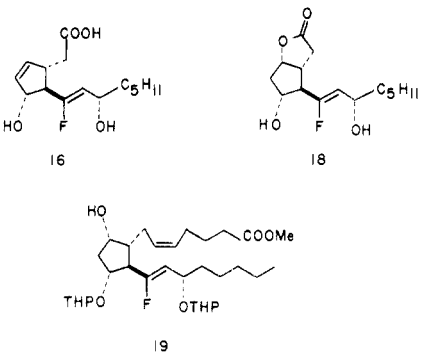
(±)-3 (±)-13 Eq. 2

Schlosser method, racemic fluoro olefin **13** with no trace of the (*E*)-olefin being present. Attempts to convert **13** into racemic **12** met with only modest success. Allylic oxidation ($CrO_3$·2Py, $CH_2Cl_2$) of **13** gave rise to only a 33% yield of enone **14**, which upon reduction ($NaBH_4$, $CeCl_3$·$6H_2O$, MeOH) and deketalization (10% 1:3 HCl/THF) provided (82% overall yield) a 1:1 mixture of (±)-**12** and (±)-**15**, which were readily separated by silica gel chromatography. The overall yield of pure (±)-12 from racemic phosphonium iodide **9** was only 7.4%. The unimpressive overall yield, coupled with the fact that we were working in the racemic series and that we already had **12** available in chiral form, led us to proceed with the transformation of **12** into 13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**).



14 15

Baeyer–Villiger oxidation of **12** employing basic hydrogen peroxide in aqueous methanol at 5 °C gave rise to the sensitive dihydroxy carboxylic acid **16**. Carboxylic acid



16 18 19

**16** was converted into the corresponding iodo lactone **17** and subsequently into bicyclic lactone **18** via iodo lactonization–deiodination. The hydroxyl functions in **18** were protected as their tetrahydropyranyl ethers prior to reduction of the γ-lactone with diisobutylaluminum hydride. Condensation of the resultant lactol with the Wittig reagent derived from 5-(triphenylphosphonio)valeric acid generated a hydroxy carboxylic acid which was esterified with ethereal diazomethane giving rise to **19** in 83% yield. Removal of the tetrahydropyranyl ethers (EtOH, PPTS)[12] furnished pure (+)-13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) ($[\alpha]^{26}_D$ +30° (*c* 2.8, $CHCl_3$)) in 91% yield.

(+)-13-Fluoroprostaglandin $F_{2\alpha}$ methyl ester was evaluated for interruption of pregnancy in hamsters[13] and examined for smooth muscle (in vitro) stimulating effects on hamster uterine strips.[15] The antifertility assay revealed that (+)-13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) was 4.2 times more effective in terminating pregnancy in hamsters than natural prostaglandin $F_{2\alpha}$. Somewhat disappointing were the results from the smooth muscle assay which revealed that (+)-**1** was equipotent with natural $PGF_{2\alpha}$.

## Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded at 360 MHz (Nicolet NT-360 spectrometer), 220 MHz (Varian

(11) Extreme caution should be exercised when carrying out fluorinations with perchloryl fluoride.

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

(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 adminstered 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.

HR-220 spectrometer), 90 MHz (Varian EM-390 spectrometer), and 60 MHz (Varian T-60A) as indicated. Spectra were recorded in $CDCl_3$ or $CCl_4$, and the chemical shifts are reported in parts per million ($\delta$) relative to $Me_4Si$ ($Me_4Si$, $\delta$ 0.00) as an internal standard. Coupling constants are reported in hertz (Hz). Infrared (IR) spectra were recorded on a Perkin-Elmer 298 grating infrared spectrometer and are reported in wave numbers ($cm^{-1}$). Rotations were measured at 23–28 °C on a Perkin-Elmer 241 polarimeter. Specific rotations $[\alpha]_D$ are reported in degree per decimeter and the concentration ($c$) is given in grams per 100 mL of specified solvent. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. All melting points and boiling points are uncorrected. High-resolution mass spectra were recorded on a Varian MAT CH-5 spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reactions were run under an atmosphere of argon or nitrogen. "Dry" solvents were distilled over a drying agent prior to use and stored as indicated: tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium–benzophenone ketyl in a recycling still; diethyl ether (ether) was distilled from lithium aluminum hydride and was stored over sodium metal; pyridine, triethylamine, and diisopropylamine were distilled from calcium hydride and were stored over potassium hydroxide pellets; dimethylsulfoxide was distilled from calcium hydride; methylene chloride was passed through a column of alumina prior to use; toluene and benzene were distilled from sodium under argon and stored over sodium metal; chromium trioxide was dried over anhydrous phosphorus pentoxide under reduced pressure(<0.1 mmHg); dimethylformamide was distilled from calcium hydride under reduced pressure and stored over 3-Å molecular sieves. *n*-Butyllithium (Aldrich Chemical Co.) was titrated (with a 1 M isopropyl alcohol–benzene solution with *o*-phenanthroline as an indicator) to a constant molarity prior to use.

Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel glass plate precoated with silica gel GF (250 $\mu$m). Column chromatography was performed with Merck 80–270 mesh silica gel.

**Methyl (−)-2-[(*tert*-Butyldimethylsilyl)oxy]heptanoate (5, R = $CH_3$).** To a solution of (+)-2(*S*)-hydroxyheptanoic acid **5** (R = H) (750 mg, 51 mmol) in ether at room temperature was added an ethereal solution of diazomethane. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on 50 g of silica gel. Elution with hexane–ether (2:1) gave 725 mg (87%) of methyl (+)-2(*S*)-hydroxyheptanoate, $[\alpha]^{23}_D$ +10.7° (*c* 4.57, $CHCl_3$) [IR ($CHCl_3$) 3530, 1732 $cm^{-1}$], which was employed directly in the next reaction.

A solution of the above ester (617 mg, 3.86 mmol) in 20 mL of methylene chloride was treated with 0.85 mL (6.18 mmol) of triethylamine, 870 mg (4.79 mmol) of *tert*-butyldimethylsilyl chloride, and a catalytic amount (30 mg) of 4-(dimethylamino)-pyridine at room temperature. After 96 h an aqueous solution of sodium bicarbonate was added, and the product was extracted with methylene chloride. The combined organic extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The resulting residue was purified on 50 g of siliCAR CC-7. Elution with hexane–ether (10:1) provided 906 mg (86%) of methyl (−)-2-[(*tert*-butyldimethylsilyl)oxy]heptanoate **5** (R = $CH_3$): $[\alpha]^{23}_D$ −31.2° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 2940, 2910, 2840, 1730, 1450, 1430, 1245, 1165, 1130, 1100, 1000, 825 $cm^{-1}$; NMR (60 MHz, $CCl_4$) $\delta$ 4.1 (t, 1 H, $J$ = 6 Hz), 3.66 (s, 3 H), 1.15 (m, 8 H), 0.88 (s, 12 H).

**(−)-[1$\alpha$,4$\alpha$,7*R**]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]-dioxolane]-7-methanol (7).** To a suspension of 1.03 g (25.7 mmol) of lithium aluminum hydride in 70 mL of anhydrous ether cooled to 0 °C was slowly added 5.00 g (17.0 mmol) of (−)-bromo ketal ester **6** in 35 mL of dry ether. After addition was complete, the reaction mixture was stirred for an additional 0.5 h, at which time it was quenched at 0 °C by sequential addition of 1.03 mL of water, 1.03 mL of 15% aqueous sodium hydroxide solution, and 3.09 mL of water. Anhydrous magnesium sulfate was added, and the resulting mixture was filtered through a sintered-glass funnel. The aluminum salts were washed exhaustively with ethyl acetate. The combined organic layers were concentrated in vacuo, yielding 4.29 g of a crude alcohol as a white solid. Chromatography on 200 g of silica gel (elution with 1:2 hexane–ether) provided 4.26 (94%) of pure alcohol as a crystalline substance; mp 68–68.5 °C; $R_f$ 0.13 (1:1 hexane–ether); $[\alpha]^{23}_D$ −17.5° (*c* 1.03, $CHCl_3$); IR ($CCl_4$) 3625, 3400, 2975, 2880, 1475, 1438, 1370, 1325, 1245, 1230, 1208, 1160, 1100, 1065, 1041, 1020, 990, 975, 945, 910, 900, 845, 665 $cm^{-1}$; NMR (90 MHz, $CCl_4$) $\delta$ 1.50 (d, 1 H, $J$ = 14 Hz, C-3 endo H), 1.7–2.6 (m, 6 H), 3.6–4.0 (m, 8 H). Anal. Calcd for $C_{10}H_{15}BrO_3$: 264.0184. Found: 264.0182.

A solution of 4.24 g (16.1 mmol) of the above bromo ketal and 24.5 g (161 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 50 mL of toluene was heated at reflux for 36 h. The cooled (25 °C) reaction mixture was directly applied to a column containing 400 g of silica gel. Elution with ether–hexane (3:1) afforded 2.92 g (100%) of pure olefinic alcohol **7**: $R_f$ 0.2 (1:3 hexane–ether); $[\alpha]^{23}_D$ −103° (*c* 1.11, $CHCl_3$); IR ($CHCl_3$) 3620, 3460, 2980, 2940, 2890, 1630, 1475, 1445, 1335, 1300, 1230, 1210, 1170, 1105, 1085, 1050, 1015, 950, 890, 850, 830 $cm^{-1}$; NMR (60 MHz, $CDCl_3$) $\delta$ 1.6 (d, 1 H, $J$ = 12 Hz, C-3 endo H), 1.4 (m, 1 H, OH), 2.0 (dd, 1 H, $J$ = 12 and 4 Hz, C-3 exo H), 2.3–2.93 (m, 3 H), 3.3–3.8 (m, 2 H, $CH_2OH$), 3.92 (m, 4 H, $OCH_2CH_2O$), 5.86–6.1 (m, 1 H, C*H*=CH), 6.1–6.3 (m, 1 H, CH=C*H*). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.82; H, 7.70.

**(−)-[1$\alpha$,4$\alpha$,7*R**]-7-(Iodomethyl)spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxolane] (8).** A solution of 3.78 g (20.8 mmol) of alcohol **7** in 25 mL of pyridine containing 5.14 g (27 mmol) of toluenesulfonyl chloride was stirred at 0 °C for 0.5 h, followed by 14 h at room temperature. The reaction was quenched with ice water. The resulting solution was extracted with ether. The combined ether extracts were washed sequentially with water, aqueous copper sulfate solution, water, aqueous sodium bicarbonate solution, and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified on 200 g of silica gel. Elution with hexane–ether (3:1) provided 6.32 g (91%) of the corresponding tosylate: $R_f$ 0.32 (1:2 hexane-ether); IR ($CHCl_3$) 3070, 2980, 2960, 2890, 1600, 1495, 1460, 1400, 1360, 1330, 1305, 1210, 1190, 1175, 1105, 1095, 1065, 1050, 1025, 965, 950, 900, 855, 835, 815, 780, 755, 720, 665 $cm^{-1}$; NMR (90 MHz, $CDCl_3$) $\delta$ 1.4 (d, 1 H, $J$ = 13 Hz, C-3 endo H), 1.83 (dd, 1 H, $J$ = 13 and 4 Hz, C-3 exo H), 2.33–2.76 (m, 3 H), 2.45 (s, 3 H, $CH_3$), 3.82 (m, 4 H, $OCH_2CH_2O$), 3.9 (d, 2 H, $J$ = 7 Hz, $CH_2OTs$), 5.7–5.9 (m, 1 H, C*H*=CH), 5.9–6.1 (m, 1 H, CH=C*H*), 7.26 (d, 2 H, $J$ = 9 Hz), 7.68 (d, 2 H, $J$ = 9 Hz).

A solution of the above tosylate (6.32 g, 18.8 mmol) in 130 mL of acetone containing 11.28 g (75.23 mmol) of sodium iodide was refluxed. After 14 h the solvent was removed under reduced pressure. The residue was treated with water, and the product was isolated by extraction with ether. The combined ether extracts were washed with 10% aqueous sodium thiosulfate solution, saturated aqueous sodium bicarbonate solution, and brine. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified on 200 g of silica gel. Elution with hexane–ether (3:1) gave 5.07 g (92%) of pure iodide **8**: $R_f$ 0.59 (1:1) hexane–ether); $[\alpha]^{23}_D$ −48.5° (*c* 3.6, $CHCl_3$); IR (neat) 3080, 2990, 2960, 2390, 1480, 1445, 1435, 1335, 1310, 1280, 1260, 1230, 1190, 1170, 1110, 1075, 1060, 1050, 1020, 990, 955, 945, 920, 900, 865, 850, 835, 790, 750, 735, 715 $cm^{-1}$; NMR (90 MHz, $CCl_4$) $\delta$ 1.48 (d, 1 H, $J$ = 12 Hz, C-3 endo H), 1.9 (dd, 1 H, $J$ = 12 and 4 Hz, C-3 exo H), 2.46–2.86 (m, 3 H), 3.13 (d, 2 H, $J$ = 8 Hz, $CH_2I$), 3.83 (m, 4 H, $OCH_2CH_2O$), 5.9 (m, 1 H, C*H*=CH), 6.13 (m, 1 H, CH=C*H*). Anal. Calcd for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.48. Found: C, 40.95; H, 4.45.

**[[(−)-[1$\alpha$,4$\alpha$,7*R**]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]dioxalan]-7-yl]methyl]triphenylphosphonium Iodide (9).** A solution of 5.07 g (17.4 mmol) of iodide (8) in 25 mL of dry xylene containing 6.83 g (26.0 mmol) of triphenylphosphine was refluxed for 24 h. After the reaction was complete, the solvent was removed under reduced pressure. The gummy residue was crystallized from acetonitrile–ethyl acetate. There was obtained 8.8 g (91%) of pure phosphonium iodide **9**: mp 180.0–181.5 °C; $[\alpha]^{23}_D$ −24.1° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2920, 1585, 1475, 1430, 1375, 1325, 1300, 1220, 1200, 1175, 1100, 1060, 1050, 1000, 990, 940, 910, 885, 825, 675, 650 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) $\delta$ 1.45 (d, 1 H, $J$ = 13 Hz, C-3 endo H), 1.83 (dd, 1 H, $J$ = 13 and 4 Hz, C-3 exo H), 2.23 (br s, 1 H, C-1 H), 2.60 (m, 1 H, C-7 H), 2.95 (br s, 1 H, C-4 H), 3.38–4.02 (m, 6 H), 5.93 (m, 1 H, C*H*=CH), 6.30 (m, 1 H, CH=C*H*), 7.68–7.98 (m, 15 H). Anal. Calcd for $C_{28}H_{28}IO_2P$: C, 60.66; H, 5.09. Found: C, 60.50; H, 4.89.

**2-[(*tert*-Butyldimethylsilyl)oxy]heptan-1-al (2).** A solution of 894 mg (3.26 mmol) of ester **5** (R = $CH_3$) in 20 mL of toluene at −78 °C was treated with 2.45 mL (3.92 mmol) of diisobutylaluminum hydride (1.6 M in toluene). After 30 min the reaction was quenched by careful addition of methanol. The reaction mixture was warmed to room temperature, and excess water was added. Ether was added and stirring was continued for an additional hour. After drying over anhydrous magnesium sulfate the solvent was concentrated under reduced pressure. The crude aldehyde was chromatographed on 8 g of silica gel. Elution with hexane–ether (20:1) gave 785 mg (87%) of pure aldehyde **2**, which was used directly in the next reaction: $[\alpha]_D$ −34.1° (*c* 1.02, $CHCl_3$); IR ($CCl_4$) 2960, 2930, 2860, 2800, 1735, 1460, 1375, 1360, 1250, 1135, 1100, 1055, 1005, 960, 940, 900, 870, 835 $cm^{-1}$; NMR (60 MHz, $CCl_4$) δ 9.78 (d, 1 H, *J* = 3 Hz, CHO), 3.80 (m, 1 H), 1.2 (m, 8 H), 0.80 (s, 12 H, $CH_2CH_3$ and $C(CH_3)_3$)).

**(−)-1-[[1α,4α,7*R**]-Spiro[bicyclo[2.2.1]hept-5-ene-2,2′-[1,3]-dioxolan]-7-yl]-3(*S**)-hydroxy-1-fluoro-1(*Z*)-octene (10).** To a suspension of 1.37 g (2.47 mmol) of predried phosphonium salt **9** in 30 mL of dry toluene was added 4.07 mL (3.45 mmol) of freshly prepared phenyllithium–lithium bromide (0.85 M in ether) at room temperature. After 2 h the reaction mixture was cooled to −78 °C and 710 mg (2.91 mmol) of aldehyde **2** was added. The decolorized reaction mixture was treated with 6 mL (5.1 mmol) of phenyllithium–lithium bromide (0.85 M in ether) at −78 °C followed by warming to −20 °C. After 3 h the resulting dark red solution was cooled to −35 °C, and gaseous perchloryl fluoride was passed into the reaction flask until decolorization was complete. Excess perchloryl fluoride was expelled by bubbling nitrogen through the solution for ca. 30 min. The reaction mixture was stirred at room temperature for 14 h, at which time it was filtered, the precipitate was washed with ether, and the combined organic extracts were concentrated under reduced pressure. The residue thus obtained was dissolved in a minimum amount of methanol. The product was isolated by extraction with ether–hexane (1:1). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was chromatographed on 80 g of silica gel. Elution with ether–hexane (1:20) afforded in order of elution 122 mg (12%) of *Z* fluoro olefin **4** ($R_f$ 0.58, (3:1 hexane–ether) and 460 mg (45%) of fluoro olefin **11** (R = $Si(Me)_2$-*t*-Bu) ($R_f$ 0.51).

A solution of 81 mg (0.20 mmol) of the above *Z* fluoro olefin **4** in 5.0 mL of tetrahydrofuran was treated with 125 mg (0.39 mmol) of tetra-*n*-butylammonium fluoride trihydrate at room temperature. After 14 h the solvent was removed under reduced pressure, and the residue was diluted with ether and washed with water and brine. The ether 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) yielded 43.8 mg of (*Z*)-allylic alcohol **10**: $R_f$ 0.40 (1:2 hexane–ether); $[\alpha]^{23}_D$ −91° (*c* 2.17, $CHCl_3$); IR ($CCl_4$) 3615, 3480, 3030, 2980, 2950, 2920, 2865, 1700, 1460, 1435, 1370, 1325, 1300, 1245, 1215, 1175, 1155, 1100, 1050, 1010, 940, 920, 910, 885, 840, 710, 690 $cm^{-1}$; NMR (220 MHz, $CCl_4$) δ 0.88 (t, 3 H, *J* = 6 Hz, $CH_2CH_3$), 1.16–1.59 (m, 8 H), 1.51 (d, 1 H, *J* = 13 Hz, C-3 endo H), 1.62 (s, 1 H, C-1 OH), 1.93 (dd, 1 H, *J* = 13 and 3 Hz, C-3 exo H), 2.68 (m, 1 H, C-1 H), 2.84–2.97 (m, 2 H, C-4 H and C-7 H), 3.75–4.0 (m, 4 H), 4.31–4.48 (m, 1 H, C*H*(OH)), 4.34 (dd, 1 H, $J_{HF}$ = 40 Hz, *J* = 7 Hz, CH=CF), 5.88 (dd, 1 H, *J* = 6 and 3 Hz, C*H*=CH), 6.13 (dd, 1 H, *J* = 6 and 3 Hz, CH=C*H*). Anal. Calcd for $C_{17}H_{25}FO_3$: C, 68.89; H, 8.50. Found: C, 68.70; H, 8.45.

A solution of 460 mg (1.12 mmol) of the above *E* fluoro olefin **11** (R = $Si(Me)_2$-*t*-Bu) in 10 mL of tetrahydrofuran was treated with 880 mg (2.78 mmol) of tetra-*n*-butylammonium fluoride trihydrate at room temperature. After 14 h the solvent was removed under reduced pressure, and the residue was diluted with ether. The resulting ethereal solution was washed with water and brine. The ether layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on 80 g of silica gel. Elution with hexane–ether (1:1) yielded 305 mg of (*E*)-allylic alcohol **11** (R = H): $R_f$ 0.46 1:2 hexane–ether); $[\alpha]^{23}_D$ −60° (*c* 5.85, $CHCl_3$); IR ($CCl_4$) 3610, 3480, 3070, 2980, 2950, 2920, 2860, 2850, 1680, 1465, 1455, 1435, 1375, 1325, 1305, 1265, 1250, 1215, 1200, 1160, 1150, 1100, 1050, 1010, 990, 940, 910, 885, 830, 710, 620 $cm^{-1}$; NMR (220 MHz, $CCl_4$) δ 0.91 (t, 3 H, *J* = 6 Hz, $CH_2CH_3$), 1.28 (m, 8 H), 1.49 (d, 1 H, *J* = 13 Hz, C-3 endo H), 1.92 (s, 1 H, OH), 1.92 (dd, 1 H, *J* = 13 and 3 Hz, C-3 exo H), 2.76 (m, 1 H, C-1 H), 3.06 (m, 2 H, C-4 H and C-7 H), 3.78–3.98 (m, 4 H, $OCH_2CH_2O$), 4.09 (m, 1 H, C*H*(OH)), 4.98 (dd, 1 H, $J_{HF}$ = 22 Hz, *J* = 9 Hz, CH=CF), 5.93 (dd, 1 H, *J* = 6 and 3 Hz, C*H*=CH), 6.20 (dd, 1 H, *J* = 6 and 3 Hz, CH=C*H*).

**(−)-[1α,4α]-7(*R**)-[3(*S**)-Hydroxy-1-fluoro-1(*Z*)-octen-1-yl]bicyclo[2.2.1]hept-5-en-3-one (12).** A solution of 36 mg (0.12 mmol) of ketal **10** in 2 mL of tetrahydrofuran containing 0.67 mL of 10% hydrochloric acid was stirred at room temperature. After 13 h the reaction mixture was diluted with water, and the resulting solution was extracted with ether. The combined ether layers were washed with a saturated solution of sodium bicarbonate, water, and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on 8 g of silica gel. Elution with hexane–ether (2:1) gave 20 mg (67%) of pure ketone **12**: $R_f$ 0.28 (1:2 hexane-ether); $[\alpha]^{25}_D$ −432° (*c* 1.46, $CHCl_3$); IR ($CCl_4$) 3620, 3490, 2950, 2920, 2350, 1745, 1700, 1460, 1410, 1375, 1355, 1315, 1255, 1225, 1160, 1115, 1100, 1060, 1010, 955, 970, 905, 880, 715, 695 $cm^{-1}$; NMR (90 MHz, $CCl_4$) δ 0.88 (t, 3 H, *J* = 6 Hz, $CH_3$), 1.11–1.75 (m, 9 H), 1.97 (m, 2 H), 3.10 (m, 2 H), 3.26 (m, 1 H, C-1 H), 4.50 (dd, 1 H, $J_{HF}$ = 40 Hz, *J* = 7 Hz, CH=CF), 4.45 (m, 1 H, C*H*(OH)), 6.00 (m, 1 H, CH=CH), 6.4 (dd, 1 H, *J* = 6 and 3 Hz, CH=CH). Anal. Calcd for $C_{15}H_{21}FO_2$: C, 71.40; H, 8.39. Found: C, 71.15; H, 8.30.

**(+)-3,3aα,4α,5β,6α,6aα-Hexahydro-5-hydroxy-6-iodo-4-[1-fluoro-3(*S**)-hydroxy-1(*Z*)-octen-1-yl]-2*H*-cyclopenta[*b*]-furan-2-one (17).** To a cooled (0 °C) solution of 82 mg (0.32 mmol) of ketone **12** in 1.8 mL of methanol containing 16 mL of water was added 0.39 mL of a 10% sodium hydroxide solution followed by 0.17 mL of 30% hydrogen peroxide. After 20 h at 5 °C and 6 h at room temperature, the reaction mixture was treated with an aqueous saturated solution of sodium metabisulfite to quench excess hydrogen peroxide. The pH of the aqueous portion was adjusted to ca. 6 with 5% hydrochloric acid. The product was extracted with ethyl acetate. The combined organic extracts were washed with a small portion of brine and dried over anhydrous magnesium sulfate. The crude hydroxy acid **16** [IR ($CHCl_3$) 3690, 3560–2400, 2950, 2920, 2850, 1705, 1450, 1400, 1375, 1335, 1285, 1225, 1160, 1125, 1075, 1005, 960, 900, 870, 830, 820 $cm^{-1}$] was dissolved at 0 °C in 0.7 mL of water containing 13 mg (0.33 mmol) of sodium hydroxide. The resulting homogeneous solution was neutralized to pH 7 with gaseous carbon dioxide and treated with a solution of 0.55 g (3.3 mmol) of potassium iodide and 0.28 g (1.1 mmol) of iodine in 0.7 mL of water. After 64 h at ∼0 °C, ethyl acetate was added followed by the addition of an aqueous saturated solution of sodium thiosulfate to decolorize the solution. The product was isolated by extraction with ethyl acetate. The organic extracts were combined, washed with water and brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded 95 mg of crude product, which upon purification (8 g of silica gel; eluent, ether) provided 71 mg (53% overall yield from ketone **12**) of pure iodo lactone **17**: $R_f$ 0.61 (ether); $[\alpha]^{27}_D$ +28.5° (*c* 3.45, $CHCl_3$); IR ($CHCl_3$) 3590, 3380 (br), 2980, 2940, 2915, 2840, 1775, 1695, 1450, 1410, 1370, 1345, 1280, 1150, 1100, 1040, 1000, 900, 875, 835 $cm^{-1}$; NMR (90 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6 Hz, $CH_2CH_3$), 1.1–1.8 (m, 9 H), 1.9–3.3 (m, 5 H), 3.9–4.8 (m, 3 H), 4.96–5.2 (m, 1 H, CHOCO), 4.86 (dd, 1 H, $J_{HF}$ = 34 Hz, *J* = 8 Hz, CH=CF).

**(−)-3,3aα,4α,5β,6,6aα-Hexahydro-5-hydroxy-4-[1-fluoro-3-(*S**)-hydroxy-1(*Z*)-octen-1-yl]-2*H*-cyclopenta[*b*]furan-2-one (18).** To a solution of 71 mg (0.17 mmol) of iodo lactone **17** in 4 mL of dry benzene containing 1.5 mg of azobis(isobutyronitrile) was added 150 mg (0.51 mmol) of tri-*n*-butyltin hydride. After ca. 4 h at 60 °C and 1 h at 70 °C, the cooled reaction mixture was allowed to stand on a column of 8 g of silica gel for 2 h. Elution with ether–ethyl acetate (5:1) afforded 29 mg (59%) of pure lactone **18**: $R_f$ 0.10 (ether); $[\alpha]^{27}_D$ −0.36° (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3600, 3400 (br), 3000, 2955, 2930, 2850, 1765, 1700, 1455, 1415, 1375, 1345, 1310, 1285, 1220, 1160, 1085, 1040, 970, 905, 865 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6 Hz, $CH_2CH_3$), 1.09–1.72 (m, 8 H), 1.84–3.01 (m, 6 H), 3.25 (m, 1 H, OH), 4.25 (m, 2 H, C*H*OH; OH), 4.59 (m, 1 H, C*H*(OH)), 4.80 (dd, 1 H, $J_{HF}$ = 37 Hz, *J* = 8 Hz, CH=CF), 4.91 (m, 1 H, CHOCO). Anal. Calcd for $C_{15}H_{23}FO_4$: C, 62.92; H, 8.09. Found: C, 62.81; H, 7.92.

**(+)-13-Fluoroprostaglandin $F_{2\alpha}$ Methyl Ester (1).** A solution of 29 mg (0.1 mmol) of diol **18** in 3 mL of dry methylene chloride containing 30 μL (0.30 mmol) of dihydropyran and 2 mg of pyridinium *p*-toluenesulfonate was stirred at room temperature for 1 h. The reaction mixture was quenched by addition of an aqueous sodium bicarbonate solution. The reaction mixture was extracted with ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:1) gave 45 mg (98%) of the corresponding bis(tetrahydropyranyl) ether [$R_f$ 0.46 (1:3 hexane-ether); IR ($CHCl_3$) 2920, 2850, 2830, 1750, 1695, 1455, 1445, 1430, 1370, 1340, 1315, 1275, 1250, 1215, 1190, 1175, 1160, 1145, 1120, 1105, 1065, 1025, 1010, 965, 905, 900, 860 $cm^{-1}$], which was employed directly in the next reaction.

To a solution of 45 mg (0.099 mmol) of the above tetrahydropyranylated lactone in 1.0 mL of dry toluene, cooled to −78 °C, was added dropwise 0.19 mL (0.30 mmol) of diisobutylaluminum hydride (1.6 M in toluene). After 1 h at −78 °C and 1 h at −60 °C, the reaction was quenched by the careful addition of methanol. The reaction mixture was warmed to room temperature and diluted with ethyl acetate and water. After 1.5 h at room temperature anhydrous magnesium sulfate was added. The resulting mixture was filtered and concentrated under reduced pressure. The crude lactol was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:2) provided 43.5 mg (96%) of pure lactol [$R_f$ 0.34 (1:3 hexane-ether); IR ($CHCl_3$) 3590, 3380 (br), 2990, 2920, 2840, 1695, 1460, 1445, 1435, 1370, 1340, 1315, 1270, 1225, 1170, 1145, 1120, 1065, 1010, 970, 905, 895, 840 $cm^{-1}$], which was used directly in the next reaction.

A suspension of 59 mg (1.39 mmol) of 56.9 sodium hydride dispersion in 0.65 mL of dry dimethyl sulfoxide was stirred at 50–55 °C for ca. 3 h. To the above solution of dimsyl sodium, cooled to room temperature, was added 308 mg (0.695 mmol) of (4-carboxylbutyl)triphenylphosphonium bromide [dried for 2 h at 100 °C under vacuum prior to use] in 0.8 mL of dry dimethyl sulfoxide. After 30 min, a solution of 43.5 mg (0.095 mmol) of the above lactol in 0.65 mL of dry dimethyl sulfoxide was added to the red ylide solution in one portion. After 20 min at room temperature, the reaction was quenched with water and acidified to pH 4.5–5.0 with a sodium bisulfate solution. The resulting solution was extracted exhaustively with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was esterified with ethereal diazomethane. The crude product was chromatographed on 8 g of silica gel. Elution with hexane–ether (1:3) yielded 47 mg (89%) of ester **19** [$R_f$ 0.46 (1:3 hexane–ether); IR ($CHCl_3$) 3520 (br), 2995, 2940, 2825, 1720, 1700, 1450, 1430, 1375, 1350, 1335, 1315, 1270, 1220, 1195, 1165, 1145, 1125, 1070, 1030, 1015, 990, 900, 875, 865, 710, 655 $cm^{-1}$], which was used in the next reaction.

A solution of 28 mg (0.051 mmol) of ester **19** in 3 mL of absolute ethanol containing 8 mg of pyridinium *p*-toluenesulfonate was heated at 50–55 °C under argon. After ca. 5 h the cooled (25 °C) reaction mixture was quenched with solid sodium bicarbonate and concentrated under reduced pressure. The residue was chromatographed on 8 g of silica gel. Elution with ether–ethyl acetate (2:1) afforded 17.8 mg (91%) of pure 13-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**): $R_f$ 0.24 (ethyl acetate); $[\alpha]^{26}_D$ +30° (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 3600, 3400 (br), 2990, 2940, 2920, 2850, 1720, 1700, 1450, 1430, 1360, 1310, 1275, 1220, 1160, 1150, 1105, 1090, 1080, 1040, 1020, 1000, 960, 880 $cm^{-1}$; NMR (220 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J$ = 6.5 Hz, $CH_2CH_3$), 1.2–1.9 (m, 12 H), 2.0–2.4 (m, 5.5 H), 2.31 (t, 2 H, $J$ = 7 Hz, $CH_2CO_2CH_3$), 2.47 (m, 0.5 H, C-12 H), 3.01 (d, 1 H, $J$ = 4 Hz, OH), 3.30 (br s, 1 H, OH), 3.63 (s, 3H, $CO_2CH_3$), 4.20 (3 H, 2CHOH, OH), 4.57 (m, 1 H, CHOH), 4.74 (dd, 1 H, $J_{HF}$ = 36 Hz, $J$ = 9 Hz, CH=CF), 5.39 (m, 2 H, CH=CH). Anal. Calcd for $C_{21}H_{35}FO_5$: C, 65.26; H, 9.13. Found: C, 65.01; H, 9.21.

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**Registry No.** **1**, 97211-24-0; **2**, 97211-25-1; **3**, 97211-26-2; **4**, 97211-27-3; **4** (phosphonium intermediate), 97211-40-0; **4** (phosphoranylidene intermediate), 97211-41-1; **5** (R = H), 52437-21-5; **5** (R = $CH_3$), 97211-28-4; **5** (R = $CH_3$) (*t*-$BuMe_2Si$), 97211-29-5; **6**, 71155-12-9; **6**-o1, 74778-89-5; **7**, 57820-77-6; **7** (tosylate), 97211-39-7; **8**, 97211-30-8; **9**, 97211-31-9; **10**, 97211-32-0; **11** (R = *t*-$BuMe_2Si$), 97275-90-6; **11** (R = H), 97275-91-7; **12**, 97211-33-1; (±)-**13**, 97211-34-2; (±)-**14**, 97211-35-3; (±)-**15**, 97275-93-9; (±)-**15** ethylene ketal), 97275-94-0; **16**, 97211-36-4; (±)-**16**, 97275-92-8; **17**, 97234-63-4; **18**, 97211-37-5; **18** (2THP), 97211-42-2; **19**, 97211-38-6; **19** (lactol), 97211-43-3; **19** (acid), 97211-44-4; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

# Diastereofacial Selectivity in the Reaction of Allylic Organometallic Compounds with Imines. Stereoelectronic Effect of Imine Group

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The diasterofacial selectivity in the reaction of crotyl organometallic compounds (**4**) (M = $Li^+$, Mg, B, and Sn) with imines (**3**) is investigated. The reaction of ordinary imines produces the erythro isomer (**5**) predominantly regardless of the metal (M). With increase of the steric bulk of the R group or with aryl substituent in the R′ group, the threo isomer (**6**) predominates in the reaction of crotyl-9-BBN. The ratio of erythro (**11**)/threo (**12**) in the reaction of pent-3-en-2-yl-9-BBN (**9**) is higher than the ratio of erythro (**5**)/threo (**6**) in the reaction of crotyl-9-BBN itself. On the basis of these observations, the transition-state geometry is discussed.

Although the diastereofacial selectivity in the reaction of allylic organometallic compounds with aldehydes has been intensely investigated during the last few years,[1] no attempts have yet been made to elucidate such selectivity with imines.[2] If high diastereofacial selectivity is realized with imines, such reactions may be practically useful for the synthesis of nitrogen-containing natural products, e.g., amino sugars,[3] sphingolipid bases, amino acids,[4] and β-

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