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SELECTIVE PROTECTION OF HYDROXYLS IN NATURAL TYPE E AND F PROSTAGLANDINS

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Methods for selective protection of hydroxyls in natural type E and F prostaglandins were developed.

Keywords: prostaglandins, protecting groups.

Prostaglandins are polyfunctional compounds that characteristically exhibit broad spectra of physiological activity, e.g., a combination of dilatory (on smooth muscle of bronchi), constrictive (on smooth muscle of the gastro-intestinal tract), pro- or antiaggregation (on platelets), and hypo- or hypertensive activities [1]. Such a broad spectrum of biological activity prevents the broad application of natural prostaglandins as drugs because of the many side effects. Modification of natural prostaglandins in order to alter their spectra of biological activity, decrease the types of activity responsible for the appearance of undesired side effects, and increase simultaneously the desired types of biological activity would enable these limitations to be obviated [2]. Modification of natural prostaglandins recently became critical again because of the discovery of new natural prostanoids, prostamides (ethanolamides) and 2-glycerol esters, cyclo-oxygenase derivatives of the endocannabinoids anandamide and 2-arachidonylglycerol [3].

One direction of such modification is the change of a functionally significant prostaglandin structural element, in particular, a hydroxyl. The chemical properties of prostaglandin hydroxyls differ little. Regioselective modification of one of the hydroxyls, for example, adding a fluoride or acyl group, is usually not possible. However, the differences are adequate for selective protection of the hydroxyls that must be retained intact in the target compound. Modification of natural type E and F prostaglandins with two and three free hydroxyls, respectively, cause the greatest challenges for selective protection.

Protecting group strategies that are compatible with the prostaglandin chemical properties should be used to solve the problem of differentiating the hydroxyls. Thus, acetyls must be removed in basic solution. This is not compatible with type E prostaglandins whereas type F prostaglandins are stable under such conditions. Herein we describe the application of silyl and acetyl protecting groups for differentiating the hydroxyls. The resulting synthons with a single free hydroxyl could be converted into fluorodeoxyprostaglandins with unique biological properties through the action of reagents based on aminosulfurtrifluorides [4, 5].

Selective protection of hydroxyls can be effected either by selective addition of a blocking group or its selective removal. A combination of various protecting groups is possible where prostaglandin is converted in the first step into a partial silyl ether whereas the free hydroxyls are acetylated. Reagents that are sensitive to the steric environment of the hydroxyls must be used for such conversions. Thus, the C-9 hydroxyl of the methyl ether C atom of prostaglandin $F_{2\alpha}$, which is located in the *cis*-position to C-8 of the prostaglandin side chain, is not silylated even with a 100-fold excess of reagent if trimethylsilyldiethylamine is used for the silylation. The 11,15-disilyl derivative is formed exclusively [6].

We found that a mixture of monosilyl ethers at the 11- or 15-hydroxyls was formed with a slight excess of silylating reagent (less than 10-15-fold). These gave a mixture of diacetates **2a** and **2b** in a 7:1 ratio (Scheme 1) after acetylation by acetic anhydride in the presence of Py and removal of the TMS protection. The ratio of these acetates was reversed if the limited deacetylation of known triacetate **3** [7] was carried out using K_2CO_3 in MeOH. In this instance, diacetate **2b** made up 65% of the total diacetate fraction that was formed in 75% yield taking into account unreacted triacetate **3**. These diacetates could be converted into the corresponding methyl ethers of fluorodeoxyprostaglandins **4** and **5** by the action of MSTF and

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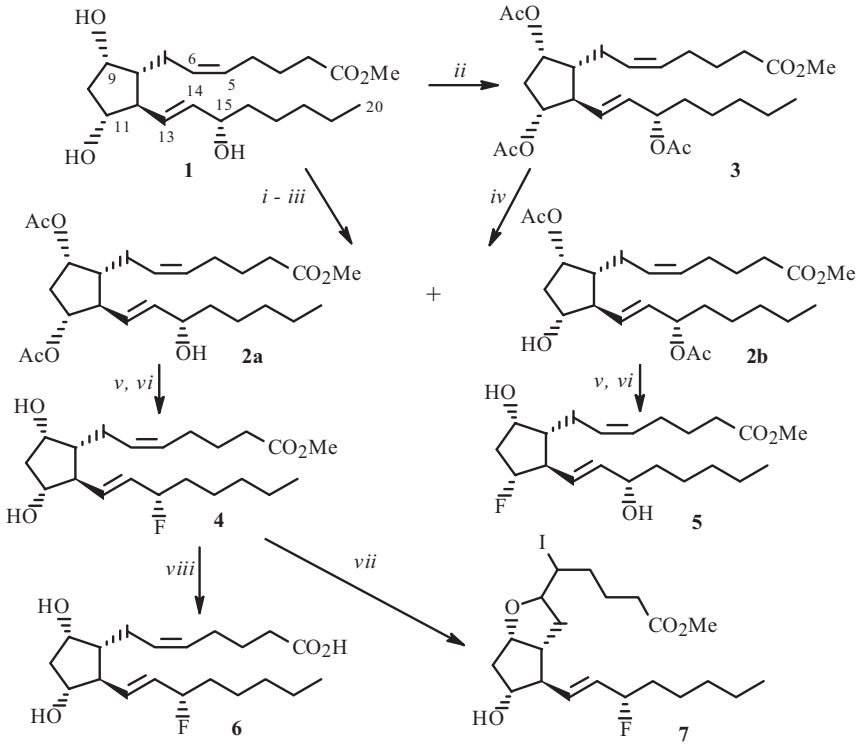
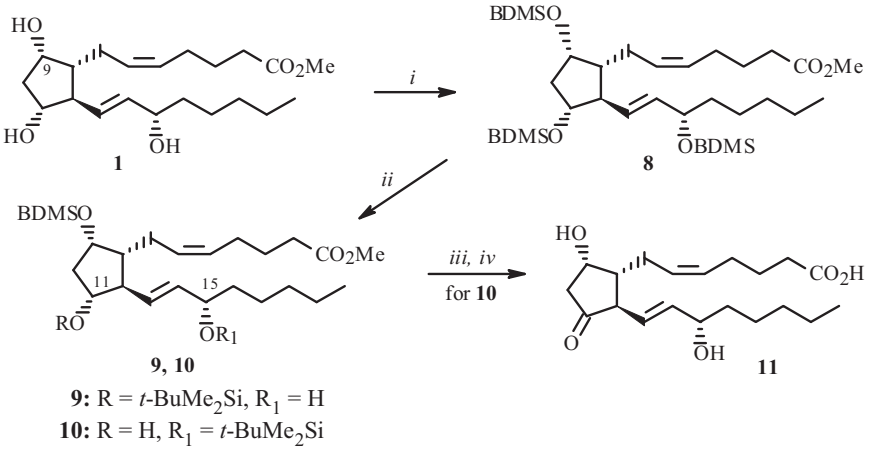
removal of the protective acetates. Then, fluorodeoxyprostaglandins could be obtained from them as the free acids, e.g., 15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (**6**) [4]; from prostanoid **4**, the methyl ether of 5-iodo-15-fluoro-15-deoxyprostaglandin I_1 (**7**) by iodine cyclization and then 15-fluoro-15-deoxyprostacyclin [8].



i. $TMSNEt_2$, acetone, –40°C, 1 h; *ii*. Ac_2O, Py, benzene, 23°C, 18 h; *iii*. 70% AcOH, 30°C, 2 h; *iv*. K_2CO_3, MeOH, 23°C, 30 min; *v*. MSTF, CH_2Cl_2, –78°C, 1 h; *vi*. MeOH, MeONa, 40°C, 2 h; *vii*. I_2, aq. $NaHCO_3$, Et_2O, 4°C, 18 h; *viii*. 40% KOH, MeOH–dioxane, 35°C, 3h

Scheme 1

The *tert*-butyldimethylsilyl (BDMS) group (Scheme 2) can also be used as a temporary protective group for differentiating the hydroxyls in type F prostaglandins. Limited desilylation of the tri-BDMS derivative of prostaglandin $F_{2\alpha}$ (**8**) by HF (50%) gave a mixture of di-BDMS ethers **9** and **10**, the ratio of which depended on the reaction time. However, prostanoid **9** dominated in all instances. Then, both silyl ethers **9** and **10** could be converted into the corresponding 15- and 11-fluoro derivatives. Difficultly accessible prostaglandin D_2 (**11**) could be synthesized from **10**.



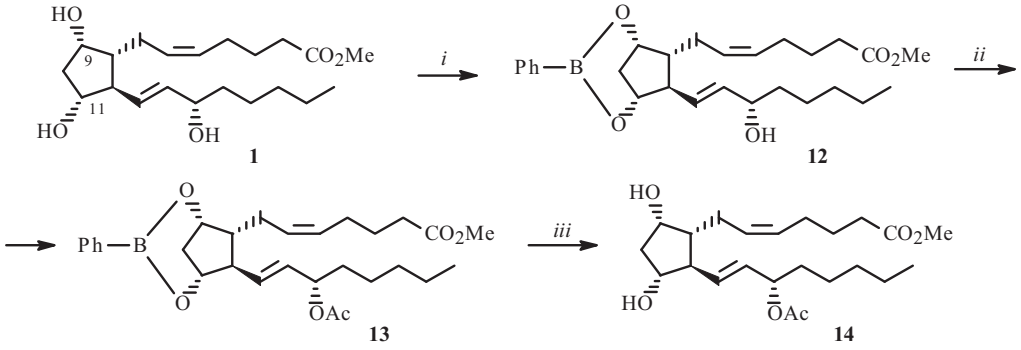
9: R = *t*-$BuMe_2Si$, R_1 = H
10: R = H, R_1 = *t*-$BuMe_2Si$

i. DMF, BDMSCl, imidazole, 25°C, 18 h; *ii*. 50% HF, 25°C, 5 min; *iii*. CrO_3, acetone, 4°C, 2 min; *iv*. THF, 50% HF, 25°C, 4 h

Scheme 2

As noted above, the 9-OH of prostaglandin $F_{2\alpha}$ was less reactive in the aforementioned blocking–deblocking reactions because of steric hindrance. This allowed the corresponding C-9 monosilyl or monoacetyl derivatives of prostaglandin $F_{2\alpha}$ and also protected derivatives of prostaglandin $F_{2\alpha}$ with a free C-9 hydroxyl to be prepared in high yield. These served as starting materials for synthesizing modified prostaglandins, e.g., 11,15-difluorodideoxy- and 9-fluorodeoxyprostaglandins $F_{2\alpha}$.

Temporary protection of the hydroxyl of the cyclopentane ring by conversion to the phenylboronate ester **12** using phenylboronic acid in dioxane could be used to synthesize the methyl ether of prostaglandin $F_{2\alpha}$ 15-acetate (**14**). Ester **12** was not isolated but worked up with acetic anhydride and Py in benzene to obtain the prostaglandin (**13**). Removal of the phenylboronate protection by treatment with H_2O_2 produced the desired acetate **14** (Scheme 3).

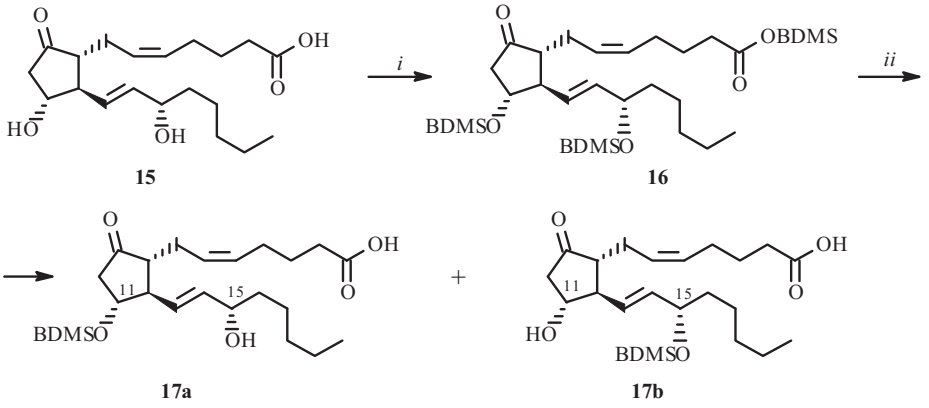


i. $PhB(OH)_2$, dioxane; *ii*. Ac_2O, Py, DMAP, benzene, 23°C, 18 h; *iii*. H_2O_2, acetone, 60°C, 3 h

Scheme 3

Temporary silyl protection, e.g., BDMS ethers, must be used to differentiate hydroxyls in base-labile type E prostaglandins containing a free carboxyl group.

Thus, prostaglandin E_2 (**15**) was fully silylated by BDMS-Cl in the presence of imidazole to produce the *tert*-butyldimethylsilyl ether of 11,15-di(*tert*-butyldimethylsilyl)prostaglandin E_2 (**16**). The latter was worked up with HCl solution (1 M) in THF for 5 min. This removed the silyl protection from the carboxylic group and also one of the hydroxyls and formed a mixture of monosilyl derivatives of prostaglandin E_2, i.e., 11-*tert*-butyldimethylsilylprostaglandin E_2 (**17a**) and 15-*tert*-butyldimethylsilylprostaglandin E_2 (**17b**) with the 15-OH regio-isomer dominating. These were separated by column chromatography over silica gel (Scheme 4). Then, prostanoids **17a** and **17b** could be converted into the corresponding fluorodeoxyprostaglandins [9].



i. DMF, BDMSCl, imidazole, 25°C, 18 h; *ii*. THF, 1 M HCl, 5 min

Scheme 4

The presented examples are just some of the possibilities for differentiating the hydroxyls and represent convenient methods for preparing synthons from natural prostaglandins. Type F prostaglandins are the most versatile for preparing both natural and modified prostaglandins of other types. Protected prostanoids with one free hydroxyl and orthogonal protecting groups on the others can be synthesized by using a combination of protecting groups that are selectively introduced or removed. This can allow conversion to modified type E, D, and I prostaglandins. Type E modified prostaglandins in several instances

were more conveniently synthesized from commercially available natural prostaglandins E_1 and E_2 using acid-labile silyl ethers. Thus, the synthetic schemes presented above allow protecting groups to be introduced at any hydroxyls of type E and F prostaglandins.

EXPERIMENTAL

Natural prostaglandins were obtained from the pilot plant of the Institute of Chemistry (Tallin, Estonia). Morpholinosulfurtrifluoride (MSTF) was synthesized from SF_4 and trimethylsilylmorpholine as described earlier [5]. UV spectra were recorded on a Specord UV–Vis instrument (Germany). Fast-atom bombardment (FAB) mass spectra were recorded on an MS-50TS instrument (Kratos, Great Britain). PMR spectra were taken from $CDCl_3$ solutions with chemical shifts (δ, ppm) relative to Me_4Si on a Bruker CPX200 spectrometer (Bruker, Germany) at operating frequency 200 MHz. Rotation angles were determined on a Jasco DIP-360 polarimeter (Japan Spectroscopica Co., Japan). HPLC was performed on a DuPont 8800 gradient liquid chromatograph (DuPont, USA) equipped with SPD 2A spectrophotometric (Shimadzu, Japan) and refractive-index (DuPont, USA) detectors connected in series. TLC was carried out on Silufol UV-254 plates (Kavalier, Czech. Rep.) with detection by phosphomolybdic acid (5%) in alcohol. Column chromatography was performed using silica gel L (40–100 μm) (Chemapol, Czech. Rep.). The course of the separation was monitored by TLC. Solutions were evaporated in a rotary evaporator *in vacuo* (water aspirator) at <30°C (water bath).

General Method for Preparing *tert*-Butyldimethylsilyl Prostaglandin Derivatives. A solution of silylated prostaglandin (100 mg) in DMF (1 mL) was stirred, treated with *tert*-butyldimethylchlorosilane and imidazole calculated for 1.5 equivalents per single silylated group. The mixture was stirred for 18 h at room temperature and diluted with H_2O (5 mL) and Et_2O (5 mL). The Et_2O layer was separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were washed with H_2O and saturated NaCl solution and dried over anhydrous Na_2SO_4. The desiccant was filtered off. The filtrate was evaporated.

Fluorination of Prostaglandins. MSTF calculated for 1.5 equivalents per single fluorinated group was dissolved in CH_2Cl_2 (3 mL) under an Ar atmosphere, stirred, cooled to –70°C, treated dropwise with a solution of fluorinated prostaglandin in CH_2Cl_2, stirred until the reaction was finished (TLC monitoring), treated with saturated aqueous NH_4Cl solution (3 mL), left to self-heat to room temperature, and diluted with H_2O (5 mL). The organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The organic extracts were combined, washed with H_2O and saturated NaCl solution, and dried over anhydrous Na_2SO_4. The desiccant was filtered off. The filtrate was evaporated. The solid was purified by column chromatography over silica gel.

Methyl Ester of 9,11-Diacetylprostaglandin $F_{2\alpha}$ (2a) and Methyl Ester of 9,15-Diacetylhydroxyprostaglandin $F_{2\alpha}$ (2b) from the Methyl Ester of Prostaglandin $F_{2\alpha}$. A solution of the methyl ester of prostaglandin $F_{2\alpha}$ (**1**, 80 mg) in anhydrous acetone (1.6 mL) was stirred vigorously at –40°C, treated with trimethylsilyldiethylamine (300 μL), stirred for 40 min at the same temperature, and evaporated to dryness. The residue was evaporated twice with benzene. The light-yellow oily residue was dissolved in benzene (1 mL), treated with Py (300 μL) and acetic anhydride (600 μL), stirred at room temperature for 18 h, diluted with cold MeOH, and evaporated to dryness. The solid was dissolved in acetone (1 mL), diluted with aqueous acetic acid (1 mL, 67%), stirred for 2 h at 40°C, and evaporated. The solid was dissolved in benzene and chromatographed over silica gel using a benzene:acetone gradient to afford the methyl ester of 9,11,15-triacetylprostaglandin $F_{2\alpha}$ (**3**, 9 mg), yield 8%; the methyl ester of 9,15-diacetylprostaglandin $F_{2\alpha}$ (**2b**, 6 mg), yield 6%, colorless oil, R_f 0.32 ($CHCl_3$:EtOAc, 5:1). PMR spectrum: 5.48 (2H, m, H-13, H-14), 5.25 (2H, m, H-5, H-6), 5.02 (1H, m, H-9), 4.75 (1H, m, H-15), 4.05 (1H, m, H-11), 3.58 (3H, s, CO_2CH_3), 1.92 [3H, s, C(9)$OCOCH_3$], 1.88 [3H, s, C(15)$OCOCH_3$], 0.82 (3H, t, H-20); and the methyl ester of 9,11-diacetylprostaglandin $F_{2\alpha}$ (**2a**), 38 mg (39%), colorless oil, R_f 0.12 ($CHCl_3$:EtOAc, 5:1), $[\alpha]_D^{22}$+11.4° (*c* 1.04, $CHCl_3$). PMR spectrum: 5.52 (2H, m, H-13, H-14), 5.25 (2H, m, H-5, H-6), 5.08 (2H, m, H-9, H-11), 3.85 (1H, m, H-15), 3.58 (3H, s, CO_2CH_3), 1.92 [6H, s, C(9)$OCOCH_3$, C(11)$OCOCH_3$], 0.80 (3H, t, H-20).

From the Methyl Ester of 9,11,15-Triacetylprostaglandin $F_{2\alpha}$. A solution of the methyl ester of 9,11,15-triacetylprostaglandin $F_{2\alpha}$ (200 mg) [7] in MeOH (5 mL) was treated with K_2CO_3 (100 mg), stirred for 30 min at room temperature, diluted with H_2O (10 mL), acidified with HCl solution (1 M), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were worked up as described above. The solid was dissolved in benzene and purified by chromatography over silica gel using a benzene:acetone gradient to afford the methyl ester of 9,11,15-triacetylprostaglandin

$F_{2\alpha}$ (**3**, 50 mg, 25%); the methyl ester of 9,11-diacetylprostaglandin $F_{2\alpha}$ (**2a**, 48 mg, 26%); and the methyl ester of 9,15-diacetylprostaglandin $F_{2\alpha}$ (**2b**, 89 mg, 49%).

Methyl Ester of 15-Fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (4). The methyl ester of 9,11-diacetylprostaglandin $F_{2\alpha}$ (**2a**, 80 mg) was fluorinated by MSTF. The resulting fluoride was purified by column chromatography over silica gel using a benzene:EtOAc gradient to afford the methyl ester of 15-fluoro-15-deoxy-9,11-diacetylprostaglandin $F_{2\alpha}$ (56 mg, 70%), colorless viscous oil, R_f 0.32 (hexane:Et_2O, 1:1). Mass spectrum (*m*/*z*, *I*, %): 454 (0.1) [M], 423 (0.3) [M – OMe], 411 (0.5) [M – Ac], 394 (2) [M – AcOH], 374 (3) [M – AcOH – HF], 334 (31) [M – 2×AcOH], 314 (100) [M – 2×AcOH – HF]. The resulting fluoroprostaglandin was dissolved in MeOH (10 mL), treated with NaOMe (27 mg) in MeOH, and stirred for 1 h at 40°C. The excess of NaOMe was decomposed by glacial AcOH. The mixture was evaporated. The solid was suspended in H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were worked up as described above. Fluoride **4** was purified by column chromatography using a benzene:EtOAc gradient to afford the methyl ester of 15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (**4**, 41 mg, 63% calculated for **2a**), thick colorless oil, R_f 0.62 ($CHCl_3$:MeOH, 10:1). PMR spectrum: 5.65 (2H, m, H-13, H-14), 5.42 (2H, m, H-5, H-6), 5.03 (1H, dm, J_{HF} = 51 Hz, H-15), 4.37 (1H, m, H-9), 4.12 (1H, m, H-11), 3.67 (3H, s, CO_2CH_3), 0.90 (3H, t, H-20). Mass spectrum (*m*/*z*, *I*, %): (*bis*-trimethylsilyl derivative): 514 (6) [M], 499 (6) [M – Me], 443 (29), [M – C_5H_{11}], 423 (20) [M – C_5H_{11} –HF], 373 (41), [M – 141], 371 (70) [M – 143], 353 (15) [M – C_5H_{11} – MeSiOH], 333 (47) [M – C_5H_{11} – Me_3SiOH – HF], 129 (100).

Methyl Ester of 11-Fluoro-11-deoxyprostaglandin $F_{2\alpha}$ (5). The methyl ester of 9,15-diacetylprostaglandin $F_{2\alpha}$ (**2b**, 30 mg) was fluorinated by MSTF. The resulting fluoride was separated as described above to afford the methyl ester of 11-fluoro-11-deoxy-9,15-diacetylprostaglandin $F_{2\alpha}$ (20 mg, 67%), colorless viscous oil, R_f 0.23 (hexane:Et_2O, 1:1). Mass spectrum (*m*/*z*, *I*, %): 423 (0.2) [M – OMe], 396 (2) [M – 58], 394 (1) [M – AcOH], 374 (9) [M – AcOH – HF], 334 (9) [M – 2×AcOH], 314 (81) [M – 2×AcOH – HF], 117 (100). The resulting fluoroprostanoid was dissolved in MeOH (3 mL), treated with NaOMe (10 mg) in MeOH, and stirred for 2 h at 40°C. The excess of NaOMe was decomposed by glacial AcOH. The mixture was evaporated. The solid was suspended in H_2O (3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were worked up as described above. The product was isolated by column chromatography over silica gel using a benzene:EtOAc gradient to afford the methyl ester of 11-fluoro-11-deoxyprostaglandin $F_{2\alpha}$ (**5**, 13.8 mg, 85%), thick oil, R_f 0.34 ($CHCl_3$:EtOAc, 5:1), $[\alpha]_D^{23}$ +31.5° (*c* 0.92, $CHCl_3$), lit. [10] $[\alpha]_D$ +32.3°.

15-Fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (6). A solution of the methyl ester of 15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (**4**, 30 mg) in dioxane:MeOH (7 mL, 1:5) was treated with aqueous KOH (5 mL, 40%), stirred for 2 h at room temperature, acidified with HCl (1 M), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were worked up as described above to afford 15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ (**6**, 30.7 mg, 69%), thick oil solidifying at <3°C, R_f 0.44 (toluene:dioxane:AcOH, 40:10:1), $[\alpha]_D^{22}$ +26.3° (*c* 0.75, EtOH), mp 130–131°C (*tris*-hydroxymethylaminomethane salt). IR spectrum (KBr, film, cm^{-1}): 3500, 2960, 2930, 2870, 1740, 1725, 1460, 1440, 1370, 1250, 1170, 1040, 970, 950. PMR spectrum: 5.65 (2H, m, H-13, H-14), 5.42 (2H, m, H-5, H-6), 5.03 (1H, dm, J_{HF} = 51 Hz, H-15), 4.37 (1H, m, H-9), 4.12 (1H, m, H-11), 0.90 (3H, t, H-20).

Methyl Ester of Prostaglandin $F_{2\alpha}$ 15-Acetate (14). A solution of the methyl ester of prostaglandin $F_{2\alpha}$ that was prepared from prostaglandin $F_{2\alpha}$ (168 mg) in dioxane (10 mL) was treated with phenylboronic acid (170 mg), held for 18 h at room temperature and 2 h at 50°C, evaporated, and thoroughly dried *in vacuo* with an oil pump. The resulting purified prostanoid **12** was dissolved in benzene (20 mL); treated with acetic anhydride (1 mL), Py (0.5 mL), and *N*,*N*-dimethylaminopyridine (0.5 mg); held for 18 h at room temperature; carefully diluted with MeOH (3 mL); and evaporated to dryness. The solid was suspended in H_2O and extracted with EtOAc (3 × 20 mL). The combined organic extracts were worked up as described above. The resulting acetyl derivative (**13**) was dissolved in acetone (15 mL) and worked up with aqueous H_2O_2 (10 mL, 30%). The mixture was incubated for 3 h at 60°C. The acetone was evaporated. The solid was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The combined organic extracts were worked up as described above. The mixture of products was separated by column chromatography over silica gel using a $CHCl_3$:EtOAc gradient to afford the methyl ester of $F_{2\alpha}$ (**1**, 50 mg) and the methyl ester of prostaglandin $F_{2\alpha}$ 15-acetate (**14**, 109 mg, 83% considering the isolated methyl ester of prostaglandin $F_{2\alpha}$, light-yellow oil, R_f 0.55 ($CHCl_3$:MeOH, 10:1), $[\alpha]_D^{22}$ –4.7° (*c* 0.875, EtOH), lit. [11] $[\alpha]_D$ –5.3°.

11-*tert*-Butyldimethylsilylprostaglandin E_2 (17a) and 15-*tert*-Butyldimethylsilylprostaglandin E_2 (17b). Prostaglandin E_2 (**15**, 100 mg) was fully silylated by BDMS-Cl as described above. The resulting trisilyl derivative (**16**) was dissolved in THF (2 mL), treated with HCl solution (500 μL, 1 M), stirred at room temperature for 5 min, diluted with HCl (500 μL, 1 M), stirred at room temperature for 5 min, treated with $CHCl_3$ (5 mL), and poured into saturated aqueous $NaHCO_3$

solution. The organic layer was separated. The aqueous layer was acidified by HCl (1 M) until the pH was 3 and extracted with EtOAc (3 × 10 mL). The combined organic extracts were worked up as described above. The mixture of 11- and 15-monosilyl derivatives of prostaglandin E_2 was separated by column chromatography over silica gel using a benzene:EtOAc gradient to afford 15-*tert*-butyldimethylsilylprostaglandin E_2 (**17b**, 33.2 mg, 49%), colorless viscous oil, R_f 0.45 (benzene:EtOAc, 2:1), mass spectrum (*m*/*z*, *I*, %) (mass spectrum taken as the methyl ester): 480 (0.1) [M], 449 (2.3) [M – OMe], 431 (3.4) [M – OMe – H_2O], 423 (100) [M – C_4H_9], 409 (13) [M – C_5H_{11}] and 11-*tert*-butyldimethylsilylprostaglandin E_2 (**17a**, 21.4 mg, 32%), colorless viscous oil, R_f 0.61 (benzene:EtOAc, 2:1), mass spectrum (*m*/*z*, *I*, %): 480 (0.2) [M], 449 (1.5) [M – OMe], 431 (5.3) [M – OMe – H_2O], 423 (100) [M – C_4H_9], 409 (20) [M – C_5H_{11}].

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