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TOTAL SYNTHESIS OF 14-FLUOROPROSTAGLANDIN $F_{2\alpha}$ AND 14-FLUOROPROSTACYCLIN

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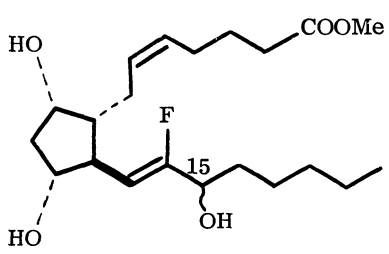
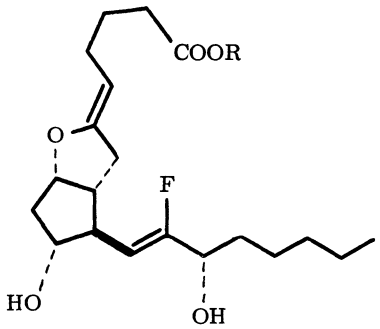
The synthesis of (±)-14-fluoro$PGF_{2\alpha}$ methyl ester (1), (±)-15-epi-14-fluoro$PGF_{2\alpha}$ methyl ester (12), and (±)-14-fluoroprostacyclin (2) is detailed. Prostaglandins 1 and 12 have been evaluated for pregnancy interruption in the hamster and smooth muscle stimulating effects on gerbil colon and hamster uterine strips. Prostacyclin 2 was evaluated for inhibition of human blood platelet aggregation and dilation of the isolated perfused cat coronary artery.

Recent reports have described the synthesis of C-12[1] and C-16[2] fluorinated prostaglandins related to natural $PGF_{2\alpha}$. These fluorinated prostaglandin analogs have been shown to possess activity in the hamster antifertility assay while at the same time maintaining low smooth muscle stimulating activity. Our interest in derivatives of natural $PGF_{2\alpha}$ which possess a significant separation of antifertility and smooth muscle stimulating activity as well as the biology of prostacyclins led us to introduce a fluorine atom into the C-14 position of $PGF_{2\alpha}$ and prostacyclin (PGI_2). We report below the synthesis and evaluation of (±)-14-fluoro-$PGF_{2\alpha}$ methyl ester (1) and (±)-14-fluoroprostacyclin (2).



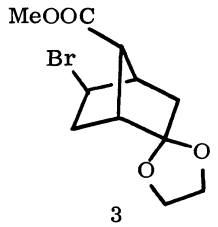
1: 15(S)-OH

12: 15(R)-OH



2(R = Me or Na)

The intermediate alcohol 4 was prepared in 75% overall yield by a two-step sequence involving reduction ($LiAlH_4$, ether, reflux, 5h) and dehydrohalogenation (DBU, toluene, reflux, 20h) from the known bromo ester 3.[3] Collins oxidation of 4 followed by condensation with the sodio derivative of dimethyl α-fluoro-β-oxoheptylphosphonate[4] in tetrahydrofuran (reflux 5h) gave enone 5 [ir(CCl_4) 1707, 1648 cm^{-1}; nmr(CCl_4) δ 5.94 (dd, 1H, $J_{H_aH_b}$ = 9 Hz, J_{H_aF} = 36 Hz)] as a minor product (9%). Infrared analysis of the major



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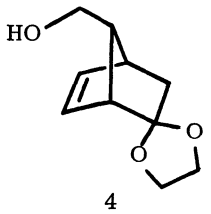

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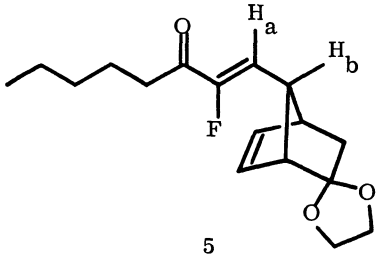
product 6 (43% overall) revealed absorptions at 1705 and 1640 cm^{-1} in keeping with an α-fluoro substituted enone. NMR analysis revealed a proton located at δ 5.70 with J_{H_aF} = 23 Hz and $J_{H_aH_b}$ = 9 Hz also indicative of the assigned structure. Reduction of enone 6 ($NaBH_4$, 95% ethanol, -10°, 30 min) provided in 95% yield alcohol 7: nmr(CCl_4) δ 5.18 (dd, 1H, $J_{H_aH_b}$ = 10 Hz, J_{H_aF} = 22 Hz).



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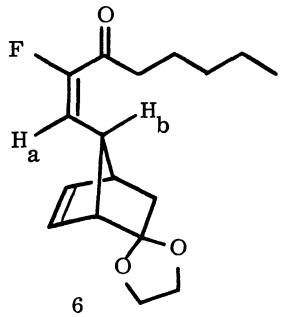

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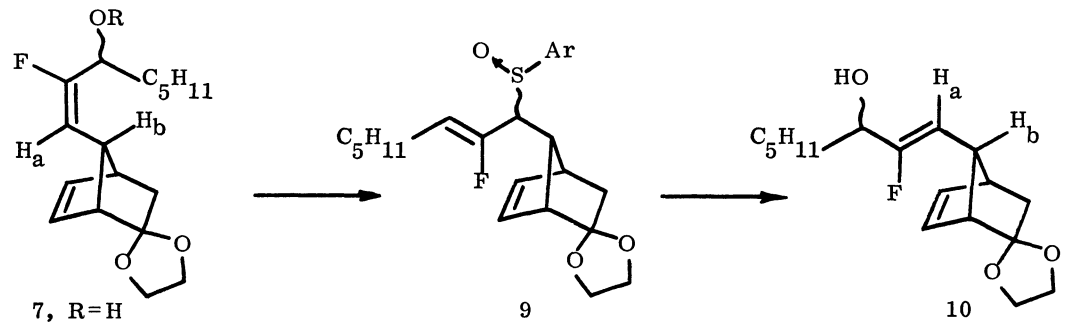
Treatment of allylic alcohol 7 at -78° with n-butyllithium (1.0 equiv) in tetrahydrofuran, followed by addition of p-toluenesulfenyl chloride and warming to room temperature (1 h) gave allylic sulfoxide 9.[5] Compound 9 upon treatment with excess trimethylphosphite in methanol[7] (room temperature, 3 hr) provided (84% overall) exclusively the desired allylic alcohol 10: nmr(CCl_4) δ 3.14 (d, 1H, J = 9 Hz, H_b), 4.80 (dd, 1H, $J_{H_aH_b}$ = 9 Hz, J_{H_aF} = 38 Hz).[8]

With the geometry of the olefinic linkage established attention was focussed on elaboration of intermediate 10 into 14-fluoro$PGF_{2\alpha}$. Deketalization (60% aq acetic acid, 25°, 20 h) of 10 followed by Baeyer-Villiger

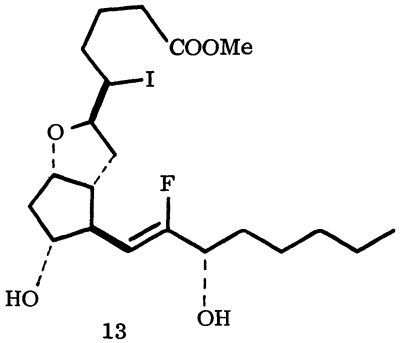


7, R=H

8, R=SAr

9

10



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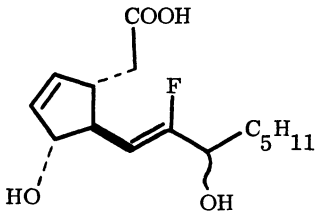

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oxidation [30% H_2O_2 (7.0 equiv), KOH (3.5 equiv), methanol, water] provided hydroxy carboxylic acid 11 in 84% overall yield. Hydroxy carboxylic acid 11 was elaborated into (±)-14-fluoro$PGF_{2\alpha}$ methyl ester (1) and (±)-15-epi-14-fluoro$PGF_{2\alpha}$ methyl ester (12) by conventional methods.[9] (±)-1 and (±)-12 were readily separated on a silica gel column using ether-methanol (50:1). The more polar isomer has been tentatively assigned the (15S) natural configuration in keeping with the tlc behavior of natural prostaglandins and the (15R) unnatural isomers.[10]

Treatment of (±)-14-fluoro$PGF_{2\alpha}$ methyl ester (1) with iodine (1.2 equiv) in methylene chloride at -10°C in the presence of anhydrous potassium carbonate (2.0 equiv) for 24 h furnished (78%) iodoether 13: nmr ($CDCl_3$) δ 3.80 (m, 1H), 4.00 (m, 1H), 4.52 (m, 1H), 4.66 (m, 1H). Exposure of iodoether 13 to excess sodium methoxide in absolute methanol at 75°C for 1 h led cleanly and essentially in quantitative yield to (±)-14-fluoroprostacyclin methyl ester 2 (R=Me): nmr(CD_3OD) δ 3.80 (m, 1H), 3.98 (m, 1H), 4.09 (m, 1H), 4.53 (m, 1H), 4.73 (dd, 1H, J_{HF} = 37.5 Hz, J_{HH} = 10 Hz). Addition of 10% water to the above solution afforded (1h at 75°C or 24 h at 25°C) quantitatively (±)-14-fluoroprostacyclin as its sodium salt 2 (R=Na).[11]

Preliminary results with racemic 14-fluoro$PGF_{2\alpha}$ methyl ester (1) and racemic 15-epi-14-fluoro$PGF_{2\alpha}$ methyl ester (12) indicate that both compounds are completely effective at terminating pregnancy in hamsters at a subcutaneous dose level of 50 μg/hamster. Our data would suggest that the enantiomerically pure 14-fluoro$PGF_{2\alpha}$ methyl ester is at least as potent as natural $PGF_{2\alpha}$. Of interest was the unexpectedly high activity of racemic 12 in the hamster antifertility assay.[12] Testing of both 1 and 12 in the gerbil colon and hamster uterine strip smooth muscle stimulating assays revealed that they are only very weakly effective. For example, compound 1 possessed 10% the potency of natural $PGF_{2\alpha}$ in the hamster uterine strip assay and only 0.7% the potency of $PGF_{2\alpha}$ in the isolated gerbil colon assay. Similarly, racemic 12 demonstrated only 1.0% and 0.2% the potency of $PGF_{2\alpha}$ in the hamster uterine strip and the isolated gerbil colon assay respectively. Further studies in the fluoroprostaglandin area are in progress to improve upon the antifertility/uterine contraction (hamster) ratio.

(±)-14-Fluoroprostacyclin 2 (R=Na) was found to be an equipotent biological mimic of natural PGI_2 with regard to both inhibition of human blood platelet aggregation and dilation of the isolated perfused cat coronary artery. Considering the racemic nature of 2, the observed potency is remarkable and suggests that the 14-fluoroprostacyclin in its optically active form could be the first significantly more potent analog of PGI_2 than the natural compound itself.

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4. Dimethyl α-fluoro-β-oxoheptylphosphonate [ir(CCl_4) 1728 cm^{-1}; nmr(CCl_4) δ 4.95 (dd, 1H, J_{HF}=15 Hz, J_{HP}=48 Hz, -PC<u>H</u>F-), 3.80 (d, 6H, J=11 Hz), 2.58 (m, 2H, -$COCH_2$-)] was prepared by fluorination of the sodio derivative of dimethyl β-oxoheptylphosphonate in toluene at -35° using perchloryl fluoride. <u>EXTREME CAUTION SHOULD BE EXERCISED WHEN USING PERCHLORYL FLUORIDE.</u>
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8. Enones 5 and 6 obtained from the Emmons reaction need not be separated. Reduction of the mixture with sodium borohydride followed by application of the sulfenate-sulfoxide rearrangement as described above leads exclusively to allylic alcohol 10.
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