CHEMISTRY LETTERS, pp. 1499-1502, 1979.

SYNTHESIS OF 5-FLUORO-PROSTAGLANDINS

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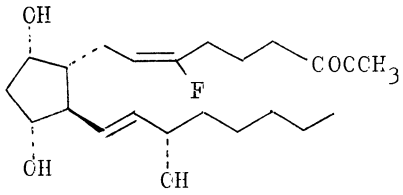
(5E)- And (5Z)-5-fluoro-prostaglandin(PG)$F_{2\alpha}$ methyl esters 1 and 2 were synthesized *via* decarboxylative elimination reaction from key intermediate α-fluoro-β-hydroxy ester 7. 5-Fluoro-6-keto-PGE_1 methyl ester 3 was also synthesized from the key intermediate 7. These 5-fluoro-PGs 1, 2 and 3 showed interesting biological properties.

Recent publications have described the syntheses of fluorinated PGs related to natural $PGF_{2\alpha}$[1] and modified PGs[2]. But few examples are known about PGs containing fluorinated α-chain[3]. In this paper we wish to report the synthesis of (5E)- and (5Z)-5-fluoro-$PGF_{2\alpha}$ methyl esters 1 and 2, and 5-fluoro-6-keto-PGE_1 methyl ester 3 which indicate interesting biological properties, using a new synthetic method concerned with the construction of fluoro-olefin moieties.

The α-fluoro ester 4 [ir ν 1770, 1750 cm^{-1}; nmr δ 3.65(3H,s), 3.15(6H,s)] was obtained by the treatment of methyl 2-fluoro-6-hydroxyhexanoate[4] with 2-methoxypropene in the presence of p-TsOH in CH_2Cl_2(25°C, 30 min). Treatment of 4 with lithium diisopropylamide in THF(-78°C, 10 min) followed by addition of aldehyde 6[5] in THF(-78°C warming to 25°C in 1 h) gave 7 [ir ν 3400, 1770, 1745, 980 cm^{-1}] as an inseparable mixture of diastereomers in 70% yield. Hydrolysis of 7 with 1N NaOH in MeOH(65°C, 30 min) followed by acidification with solid oxalic acid gave α-fluoro-β-hydroxy acid 8 [ir ν 3400, 3500-2400, 1760-1740 cm^{-1}] quantitatively. Decarboxylative elimination reaction of 8 by the treatment with DMF dimethyl acetal in $CHCl_3$(25°C, 1 h, then reflux for 1.5 h)[6] gave fluoro-olefin 10 [nmr δ 5.65-5.25(2H,m), 5.24-4.80(1H,m), 4.80-4.50(3H,m)] as an inseparable mixture of geometrical isomers(E:Z=1:3)[7] quantitatively. Treatment of 10 with 1N HCl in THF(0°C, 30 min) followed by Sarett



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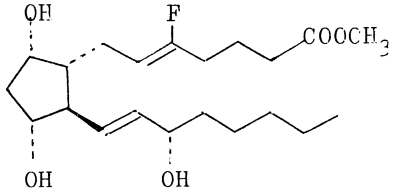

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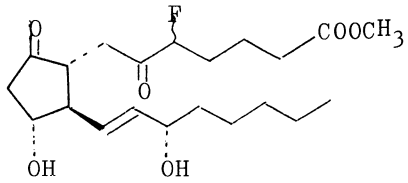

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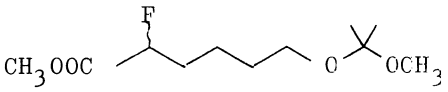

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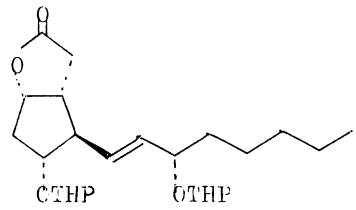

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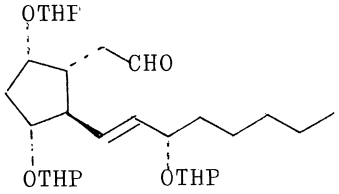

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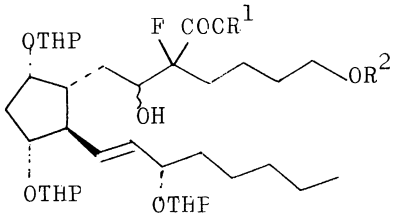
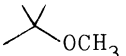
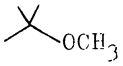
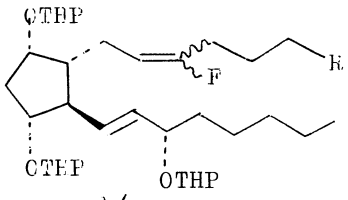


7 R^1=CH_3, R^2= 

8 R^1=H, R^2= 

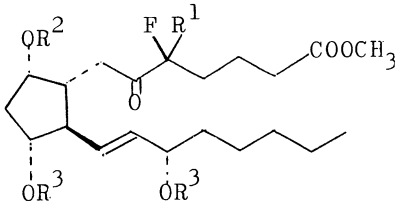
9 R^1=CH_3, R^2=H



10 R=CH_2O 

11 R=COOH

12 R=$COCH_3$

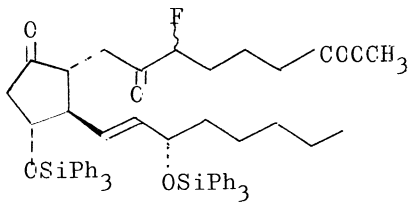


13 R^1=$COOCH_3$, R^2=R^3=THP

14 R^1=H, R^2=R^3=THP

15 R^1=H, R^2=R^3=H

16 R^1=H, R^2=H, R^3=Ph_3Si-



17

oxidation gave tri-THP ether of 5(E,Z)-5-fluoro-$PGF_{2\alpha}$ 11[ir ν 3500-2600, 1720 cm^{-1}] in 53% yield based on 10. Esterification of 11 with CH_2N_2 followed by deprotection in usual manner gave a separable mixture of (5E)- and (5Z)-fluoro-$PGF_{2\alpha}$ methyl esters in the ratio of 1:3[8]. Pure (5Z)-5-fluoro-$PGF_{2\alpha}$ methyl ester 2[mp 61-62°C; ir ν 3350, 1740, 1710 cm^{-1}; nmr δ 4.63(1H,dt,J=38,7.5 Hz); m/e 368.238(M^+-H_2O) (calcd for $C_{21}H_{33}O_4F$:368.236)] was obtained by fractional crystallization from diisopropyl ether. Further purification of mother liquor by column chromatography on silica gel impregnated with phosphomolybdic acid[9] gave (5E)-5-fluoro-$PGF_{2\alpha}$ methyl ester 1[ir ν 1740, 1700 cm^{-1}; nmr δ 5.60(1H,dt,J=22,7.5 Hz); m/e 368.234(M^+-H_2O) (calcd for $C_{21}H_{33}O_4F$: 368.236)] .

5-Fluoro-6-keto-PGE_1 methyl ester 3 was synthesized from 7 as follows. Treatment of 7 with 1N HCl in THF(0°C, 30 min) gave diol 9[ir ν 3450, 1770, 1745 cm^{-1}] quantitatively. Sarett oxidation of 9(50°C, 3 h) followed by the treatment with CH_2N_2 gave keto diester 13 [ir ν 1765, 1745 cm^{-1}] in 77% yield. Treatment of 13 with DMSO-NaCl-H_2O(50:2.8:1) at 150°C for 1 h[10] gave keto ester 14[ir ν 1745, 1735 cm^{-1}] in 77% yield. Deprotection of 14 in usual manner gave 5-fluoro-6-keto-$PGF_{1\alpha}$ methyl ester 15[ir ν 3450, 1735 cm^{-1}] in 77% yield. Selective protection of 11- and 15-hydroxy groups with triphenylsilyl group(2 equiv Ph_3SiBr in pyridine, -40°C, 15 min) followed by Collins oxidation gave 11,15-bis-triphenylsilyl ether of 5-fluoro-6-keto-PGE_1 methyl ester 17 [nmr δ 7.70-7.10(30H,m)] in 47% yield based on 15. Deprotection of 17 with AcOH-H_2O-THF(3:1:1) at 70°C for 2 h gave 5-fluoro-6-keto-PGE_1 methyl ester 3[ir ν 3400, 1740 cm^{-1}; m/e 382.214(M^+-H_2O) (calcd for $C_{21}H_{31}O_5F$:382.215)] as an inseparable mixture concerned with the configuration of 5-fluoro group in 70% yield.

These 5-fluoro-PGs showed interesting biological properties. For example 5-fluoro-6-keto-PGE_1 methyl ester 3 was 10 times more potent than PGE_1 in uterine contractile activity(rat) and 10 times more potent than PGE_1 in inhibition of stress ulcer(rat).

References and Notes

1) (a) P. A. Grieco, T. Sugahara, Y. Yokoyama, and E. Williams, J. Org. Chem., 44, 2189(1979) and references cited. (b) P. A. Grieco, E. Williams, and T. Sugahara, J. Org. Chem., 44, 2194(1979).

2) H. Nakai, N. Hamanaka, and M. Kurono, Chem. Lett., 1979, 63.

3) J. Nakano, E. Änggärd, and B. Samuelsson, Eur. J. Biochem., 11, 386(1969).

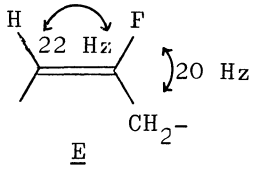
4) Methyl 2-fluoro-6-hydroxyhexanoate was prepared from 4-chlorobutanol by sequential reactions: i) DHP, p-TsOH/CH_2Cl_2(0°C, 30 min, 100%), ii) NaCN/DMSO(110°C, 3 h, 100%), iii) DIBAL/toluene(-70°C, 2 h), iv) 5% H_2SO_4(0°C, 1 h, 78%), v) NaCN-$NaHSO_3$ /H_2O(0°C, 30 min, 100%), vi) TsCl/Et_3N(0°C, 30 min, 100%), vii) KF/diethylene glycol(130°C, 1.5 h, 62%), viii) 30% H_2O_2-1N NaOH/aqueous MeOH(25°C, 30 min, 53%), ix) KOH/aqueous EtOH(90°C, 1 h, 83%), x) CH_2N_2/MeOH-Et_2O(25°C, 5 min, 100%), xi) aqueous AcOH/THF(65°C, 2 h, 97%).

5) The aldehyde 6 was obtained from the known compound 5 [E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Am. Chem. Soc., 91, 5675(1969)] in 63% over-all yield by the sequential reactions: i) 2N NaOH/MeOH(25°C, 30 min), ii) CH_2N_2/MeOH-Et_2O, iii) DHP, p-TsOH/CH_2Cl_2(0°C, 10 min), iv) DIBAL/toluene (-78°C, 30 min).

6) S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki, Tetrahedron Lett., 1975, 1545.

7) Decarboxylative elimination reaction of α-fluoro-β-hydroxy carboxylic acid 8 with Ph_3P and EtO_2C-N=N-CO_2Et in THF(J. Mulzer, A. Pointner, A. Chucholowski, and G. Brüntrup, Chem. Comm., 1979, 52) gave the same result as DMF acetal method concerned with the ratio of 5E- and 5Z-isomers. Based on the above results, both methods for decarboxylative elimination reaction appear to pass through trans-elimination[6].

8) The ratio of products was determined by integration of area intensities of ^{19}F nmr. Chemical shift of ^{19}F from CF_3CCH: 1 20.6 $_{ppm}$(1F,dt,J=22,20 Hz); 2 30.4 $_{ppm}$(1F,dt,J=38,18 Hz).
The stereochemistry of newly formed double bond was determined by the coupling constant.



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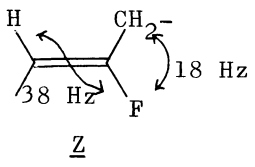

Z

9) Silica gel(50 g) and 200 ml of 15% EtOH solution of phosphomolybdic acid(pH 3-4, adjusted with powdered $NaHCO_3$) was well mixed and dried up in vaccuo at room temperature for 12 h.

10) G. Stork, Y. Nakahara, Y. Nakahara, and W. J. Greenlee, J. Am. Chem. Soc., 100, 7775(1978).

(Received September 25, 1979)