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SYNTHESIS OF 16,16-(2-FLUOROTRIMETHYLENE)-PROSTAGLANDINS AND 16,16-(2,2-DIFLUOROTRIMETHYLENE)-PROSTAGLANDINS

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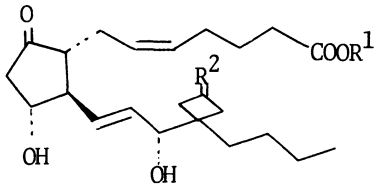
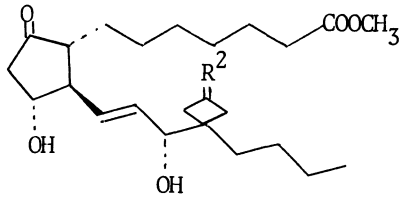
Synthesis of the new prostaglandin(PG) analogs, 16,16-(2-fluorotrimethylene)-PGE_2 and -PGE_1, 16,16-(2,2-difluorotrimethylene)-PGE_2 and -PGE_1 is reported. These new PG analogs have higher biological activities but lower side-effects than the natural PGs.

16,16-Trimethylene-prostaglandins show very strong activities[1], since these PG analogs block the action of 15-hydroxy-PG dehydrogenase[2]. Although the potential importance of these active PG analogs is becoming apparent, the side-effects, i.e. production of diarrhea, of such analogs are a serious problem. We now report the synthesis of 16,16-(2-fluorotrimethylene)-PGEs(1a, 2a and 3a) and 16,16-(2,2-difluorotrimethylene)-PGEs(1b, 2b and 3b) as fluorine containing 16,16-trimethylene-PGs possessing higher biological activities but lower side-effects.

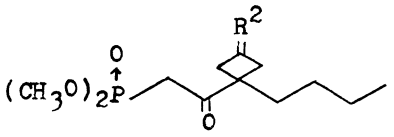




1a R^1=H, R^2=  2a R^1=CH_3, R^2=  3a R^2= 

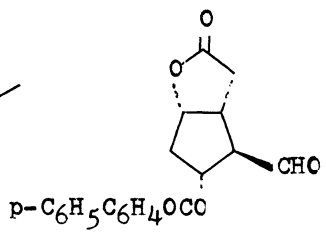
1b R^1=H, R^2=  2b R^1=CH_3, R^2=  3b R^2= 

Synthetic routes are as follows. The phosphonates 4a and 4b were prepared by the following series of reactions. Butylation of the known cyclobutane carboxylic acid 5[3] by the treatment with $(i\text{-}Pr)_2NLi$(2.1 equiv) in THF below 0°C followed by n-BuBr(2.1 equiv) gave 6[4] [MS m/e 262(M^+)] quantitatively. Treatment of the acid 6 with MeOH-HCl followed by catalytic hydrogenolysis over Pd



4a R^2= 

4b R^2= 



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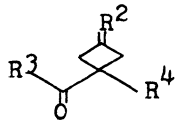


5 R^2= , R^3=OH, R^4=H

6 R^2= , R^3=OH, R^4=n-Bu

7 R^2= , R^3=OCH_3, R^4=n-Bu

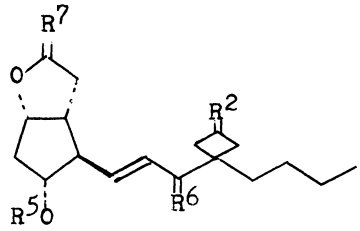
8 R^2= , R^3=OCH_3, R^4=n-Bu

9 R^2= , R^3=OCH_3, R^4=n-Bu

10 R^2=O, R^3=OCH_3, R^4=n-Bu

11 R^2= , R^3=OCH_3, R^4=n-Bu

12 R^2= , R^3=OCH_3, R^4=n-Bu



14a R^2= , R^5=p-$C_6H_5C_6H_4CO$, R^6=O, R^7=O

14b R^2= , R^5=p-$C_6H_5C_6H_4CO$, R^6=O, R^7=O

15a R^2= , R^5=p-$C_6H_5C_6H_4CO$, R^6= , R^7=O

15b R^2= , R^5=p-$C_6H_5C_6H_4CO$, R^6= , R^7=O

16a R^2= , R^5=H, R^6= , R^7=O

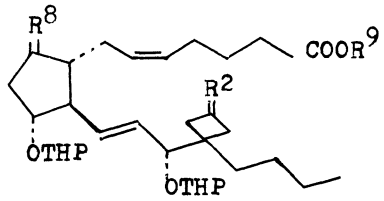
16b R^2= , R^5=H, R^6= , R^7=O

17a R^2= , R^5=THP, R^6= , R^7=O

17b R^2= , R^5=THP, R^6= , R^7=O

18a R^2= , R^5=THP, R^6= , R^7=

18b R^2= , R^5=THP, R^6= , R^7=



19a R^2= , R^8= , R^9=H

19b R^2= , R^8= , R^9=H

20a R^2= , R^8=O, R^9=H

20b R^2= , R^8=O, R^9=H

21a R^2= , R^8=O, R^9=CH_3

21b R^2= , R^8=O, R^9=CH_3

22a R^2= , R^8= , R^9=CH_3

22b R^2= , R^8= , R^9=CH_3

23a R^2= , R^8=O, R^9=CH_3

23b R^2= , R^8=O, R^9=CH_3

in AcOH at 25°C and then hydrolysis in MeOH with 1N aq NaOH(1.3 equiv) at 25°C for 2 h[5] gave a hydroxy ester 9 quantitatively[bp 97-103°C/1 Torr; MS m/e 168(M^+-H_2O)]. The hydroxy ester 9 was oxidized with $(CH_3)_2S$-Cl_2 in CCl_4-CH_2Cl_2 at -25°C for 2 h followed by treatment with Et_3N[6] to give a keto ester 10[MS m/e 185(M^++1)] quantitatively. Fluorination of 9 and 10 with SF_4 in $CHCl_3$ using a trace of EtOH as a catalyst[7] gave 11[3] [MS m/e 188(M^+)] and 12[MS m/e 207(M^++1)] in 34% and 87% yields respectively. Treatment of 11 and 12 with $(MeO)_2POCH_2Li$(2.4 equiv) in THF at -78°C for 30 min and then at 20°C for 1 h gave the desired fluorophosphonates 4a[bp 60-65°C/2-3 Torr; MS m/e 280(M^+)] and 4b[MS m/e 299(M^++1), 298(M^+)] in 67% and 70% yields respectively. Condensation of 4a and 4b with (-)β-p-phenylbenzoyloxyaldehyde 13[8] in DME for 40 min at 20°C gave the enones 14a[mp 126-127°C; MS m/e 504(M^+)] and 14b[mp 119-120°C; MS m/e 522(M^+)] in 68% and 73% yields respectively. Reduction with $NaBH_4$ in MeOH-THF at -30°C for 15 min of enones 14a and 14b afforded epimeric mixtures(the ratio of 15α to 15β=70:30[9]) of enols 15a and 15b in quantitatively. Pure 15α-15a and 15α-15b were isolated by fractional crystallization from CCl_4 followed by EtOH in 53% and 67% yields respectively[10]: 15α-15a[mp 161-162°C; MS m/e 290(M^+-216); $[\alpha]_D^{21}$ -77.5°(c 2.72, $CHCl_3$)] and 15α-15b[mp 162-163°C; MS m/e 524(M^+); $[\alpha]_D^{25}$ -88.6°(c 1.63, $CHCl_3$)]. Deacylation of 15α-15a and 15α-15b with K_2CO_3(1.0 equiv) in MeOH-THF at 20°C for 15 min gave diols 16a[MS m/e 326(M^+)] and 16b[MS m/e 345(M^++1)] in 99% and 90% yields respectively. Treatment of 16a and 16b with DHP in CH_2Cl_2 at 20°C for 15 min in the presence of p-TsOH gave bis-THP ethers 17a[MS m/e 392(M^+-THPOH)] and 17b[MS m/e 428(M^+-DHP)] quantitatively. Reduction of 17a and 17b with $(i\text{-}Bu)_2AlH$(4.0 equiv) in toluene at -78°C for 30 min gave hemiacetals 18a and 18b which were immediately used for the Wittig reaction without purification. Condensation of 18a and 18b with $\phi_3P{=}CH(CH_2)_3COONa$ in DMSO for 4 h at 20°C gave bis-THP ethers 19a [MS m/e 406(M^+-184)] and 19b[MS m/e 394(M^+-2xTHPOH)] in 88%(from 16a) and 91%(from 16b) yields respectively. Oxidation of 19a and 19b with CrO_3 reagent[11] followed by removal of THP groups with AcOH-H_2O-THF at 37°C for 2.5 h afforded 16,16-(2-fluorotrimethylene)-PGE_2 1a and 16,16-(2,2-difluorotrimethylene)-PGE_2 1b in 22% and 30% over-all yields from 19a and 19b respectively: 1a[MS m/e 392 (M^+-H_2O); $[\alpha]_D^{26}$ -67.5°(c 1.38, $CHCl_3$)] and 1b[MS m/e 410(M^+-H_2O); $[\alpha]_D^{26}$ -52.7°(c 1.47, $CHCl_3$)]. Methylation of 20a and 20b with CH_2N_2 followed by removal of THP groups with AcOH-H_2O-THF gave 16,16-(2-fluorotrimethylene)-PGE_2 methyl ester 2a and 16,16-(2,2-difluorotrimethylene)-PGE_2 methyl ester 2b in 71% and 52% over-all yields from 20a and 20b respectively: 2a[MS calcd m/e 406.2519(M^+-H_2O),found m/e 406.2507; $[\alpha]_D^{16}$ -84.0°(c 2.00, $CHCl_3$)] and 2b[MS calcd m/e 424.2424(M^+-H_2O), found m/e 424.2442; $[\alpha]_D^{26}$ -63.0°(c 1.56, $CHCl_3$)]. Selective reduction of the cis-Δ^5 bond of methyl esters 19a and 19b followed by the essentially same procedures as applied to 1a and 1b gave 16,16-(2-fluorotrimethylene)-PGE_1 methyl ester 3a and 16,16-(2,2-difluorotrimethylene)-PGE_1 methyl ester 3b in 56% and 80% over-all yields from 19a and 19b respectively: 3a[MS calcd m/e 408.2675(M^+-H_2O), found m/e 408.2663] and 3b[MS calcd m/e 426.2581(M^+-H_2O), found m/e 426.2596].

These new 16,16-(fluorotrimethylene)-PGs have a higher biological activities but lower side-effects than natural PGs: e.g. 16,16-(2-fluorotrimethylene)-PGE_1 methyl ester 3a is 5 times more potent in uterine contractile activity in the pregnant rats, but less potent(ca. 1/2) in diarrhea-producing activity in mice after oral administration than natural PGE_1.

References and Notes

1) (a) M. Kurono, H. Nakai, and T. Muryobayashi, Ger. Offen. 2510818(1975), Japan. Appl. 74-28544, 14 Mar 1974; Chem. Abstr., 84, 58751w(1976). (b) J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, J. Med. Chem., 20, 1042(1977).

2) (a) E. Änggård, and B. Samuelsson, Ark. Kem., 25, 293(1966). (b) J. Nakano, E. Änggård, and B. Samuelsson, Eur. J. Biochem., 11, 386(1969).

3) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Shertler, and J. Lavanish, Tetrahedron, 21, 2749(1965). Although the compound 5 was separable mixture of cis- and trans-isomer(ca. 1:1), the compound 11 was a single product from ^{19}F nmr spectrum:
^{19}F nmr(δ from CF_3COOH): 86.5-88.3(1F, J=10.0, 10.0, 23.0, 23.0 and 56.0 Hz).

4) Satisfactory analytical data(ir, pmr and mass spectra) were obtained for all new compounds.

5) After hydrogenolysis isolated products were the mixture of 8 and 9.

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7) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, J. Am. Chem. Soc., 82, 543(1960).

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9) The product ratio was estimated by isolated yields after chromatography on silica gel.

10) Pmr, ir and mass spectra of 15β-15a and 15β-15b are identical with those of 15α-15a and 15α-15b but R_f value of tlc and specific rotation are different: R_f(15β-15a and 15β-15b) 0.37(Et_2O), R_f(15α-15a and 15α-15b) 0.47(Et_2O); $[\alpha]_D^{19}$(15β-15a) -56.4°(c 3.75, $CHCl_3$); $[\alpha]_D^{25}$(15β-15b) -72.8° (c 1.30, $CHCl_3$).

11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Willy & Sons, Inc., New York, N. Y., 1967, p143.

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