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SYNTHESIS OF 16-METHYLENE-PROSTAGLANDINS AND 16,16-ETHANO-PROSTAGLANDINS

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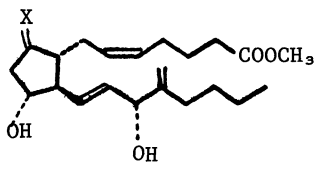
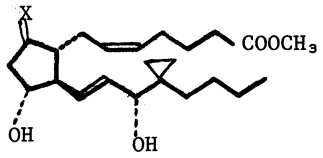
Synthesis of the new prostaglandin (PG) analogs sensitive to acid, 16-methylene-$PGF_2\alpha$ methyl ester, 16-methylene-PGE_2 methyl ester, 16,16-ethano-$PGF_2\alpha$ methyl ester, and 16,16-ethano-PGE_2 methyl ester, is reported. These PG analogs have higher biological activities but have fewer side-effects.

16-Methyl-prostaglandins (16-methyl-PGs), 15,16-dimethyl-PGs, and 16,16-dimethyl-PGs show higher biological activities than the natural PGs.[1] These PG analogs block the action of the prostaglandin-degrading enzyme, 15-hydroxyprostaglandin dehydrogenase,[2] thus increasing the biological activities of such analogs. Although the potential importance of these active PG analogs is becoming apparent, the side effects i.e. production of diarrhea, of such analogs is a serious problem. We now report the synthesis of 16-methylene-$PGF_2\alpha$ methyl ester (1a), 16-methylene-PGE_2 methyl ester (1b), 16,16-ethano-$PGF_2\alpha$ methyl ester (2a), and 16,16-ethano-PGE_2 methyl ester (2b), whose activities are comparable to 16-methyl-PGE but possessing fewer side-effects.



1a, X = $\overset{OH}{H}$

1b, X = O

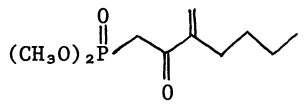


2a, X = $\overset{OH}{H}$

2b, X = O

Synthetic routes are straight-forward as follows. The phosphonate 3 and 4 were prepared by the reaction of α-lithio derivative of dimethyl-methylphosphonate[3] with the corresponding ethyl ester, ethyl 2-methylene-n-hexanoate[4] and ethyl 2,2-ethano-n-hexanoate,[5] respectively. The Wittig reaction of the readily available (-)-β-acetoxy-aldehyde 5[6] with the corresponding phosphonate reagents in THF for 2 hr at room temperature gave the enone 6a in 52% yield after column chromatography on silica gel: nmr ($CDCl_3$) δ 6.85-6.65 (2H, m), 5.98 (1H, s), 5.30-4.35 (2H, m), 2.02 (3H, s), 0.90 (3H, t); ir (liquid film) ν 1775, 1740, 1665, 1615, 980 cm^{-1}; homogeneous by tlc (benzene-AcOEt 4:1, R_f 0.49) and 6b in 51% yield after column chromatography on silica gel: nmr ($CDCl_3$) δ 6.75-6.45(1H, dd), 6.40-6.15 (1H, d), 5.06 (2H, m), 2.03 (3H,s), 0.95 (3H, t), 0.85-0.65 (2H, m); ir (liquid film) ν 3100, 1780, 1740, 1680, 1630, 980 cm^{-1}; homogeneous by tlc (benzene-AcOEt 4:1, R_f 0.50). Sodium borohydride (3 equiv) reduction in MeOH at -40° for 20 min of the resulting enone 6a and 6b afforded

enols, 7a and 7b, respectively, in almost quantitative yield[6]. The pure 15α-7a was isolated by column chromatography on silica gel in 33% yield,[7] but 15α-7b could not be isolated by column chromatography on silica gel.[8] Reduction and deacetylation of 15α-7a or 7b with diisobutylaluminum hydride (4 equiv) in toluene at -78° for 30 min gave quantitatively the triol 8a: nmr ($CDCl_3$) δ 5.80-5.35 (2H, m), 5.10 (1H, s), 4.85 (1H, s), 4.75-4.30 (2H, m), 4.30-3.55 (2H, m), 0.90 (3H, t); ir (liquid film) ν 3350, 1650, 975 cm^{-1}; homogeneous by tlc (CH_2Cl_2-MeOH 19:1, R_f 0.27), or 8b: nmr ($CDCl_3$) δ 5.75-5.40 (3H, m), 4.75-4.40 (1H, m), 4.10-3.75 (2H, m), 0.95 (3H, t), 0.35-0.05 (4H, m); ir (liquid film) ν 3450, 1450, 982 cm^{-1}; homogeneous by tlc (AcOEt, R_f 0.35). Triol 8a or 8b was condensed with 4-carboxy-n-butylidene-triphenylphosphorane in DMSO for 2 hr at room temperature to form 16-methylene-$PGF_2\alpha$ (9a) in 59% yield: nmr ($CDCl_3$) δ 5.72-5.50 (2H, m), 5.50-5.25 (2H, m), 5.13 (1H, s), 4.95 (4H, bs), 4.89 (1H, s), 4.65-4.47 (1H, m), 4.30-4.08 (1H, m), 4.07-3.80 (1H, m), 0.92 (3H, t); ir (liquid film) ν 3450, 1710, 1650, 975 cm^{-1}; specific rotation (EtOH solution, c 1.06) $[\alpha]_D^{23}$ -11.3°; homogeneous by tlc ($CHCl_3$-THF-AcOH 10:2:1, R_f 0.16) or 16,16-ethano-15ξ-$PGF_2\alpha$ (9b) in 55% yield. 16,16-Ethano-$PGF_2\alpha$ (15α-9b) was isolated by column chromatography on silica gel in 44% yield: nmr ($CDCl_3$) δ 5.65-5.20 (4H, m), 5.20-4.80 (4H, m), 4.25-3.75 (3H, m), 0.95 (3H, t), 0.65-0.15 (4H, m); ir (liquid film) ν 3350, 3100, 1710, 980 cm^{-1}; specific rotation (EtOH solution, c 1.00) $[\alpha]_D^{24}$ +22.4°; homogeneous by tlc ($CHCl_3$-THF-AcOH 10:2:1, R_f 0.18).[9]



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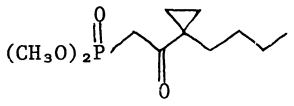

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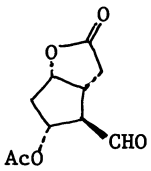

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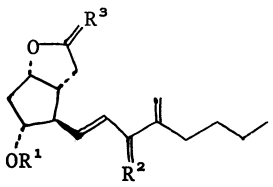
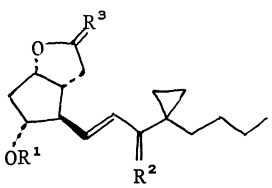


6a R¹=Ac, R²=R³=0

7a R¹=Ac, R²=  , R³=0

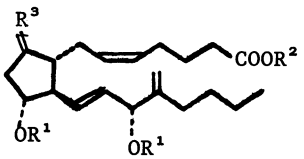
8a R¹=H, R²=  , R³= 



6b R¹=Ac, R²=R³=0

7b R¹=Ac, R²=, R³=0

8b R¹=H, R²=R³=

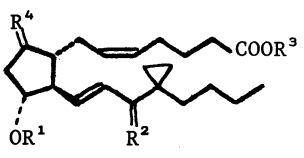


9a R¹=R²=H, R³= 

10a R¹=TMS, R²=CH₃, R³= 

11a R¹=TMS, R²=CH₃, R³=0

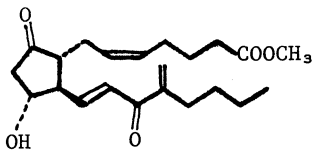
(TMS = trimethylsilyl)



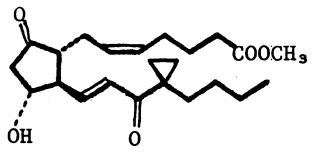
9b R¹=R³=H, R²=, R⁴=

10b R¹=TMS, R²=, R³=CH₃, R⁴= 

11b R¹=TMS, R²=, R³=CH₃, R⁴=0



12a



12b

The structures between the C-13 and C-16 positions of ω-chain in 9a and 9b are rather sensitive to acid. Thus, the carboxyl functions of 9a and 15α-9b were converted to the methyl ester 1a and 2a, respectively, by diazomethane. The esters 1a and 2a were transformed into 1b and 2b by the following sequence: (1) silylation of the hydroxyl functions (C-11 and C-15) by N-trimethylsilyl-diethylamine[10,11] (2) oxidation of the C-9 hydroxyl function (3) desilylation. The selective silylation of 1a was the same as that of the natural $PGF_2\alpha$,[10,11] but in the case of 2a the selectivity was slight lower than in 1a; the 9,11-bis-trimethylsilyl compound was produced as a by-product in this reaction (ca. 30% yield) probably due to the steric hindrance of the cyclopropyl function at the C-16 position. Oxidation of 10a and 10b using Collins reagent[12] or N-chlorosuccin-imide-dimethyl sulfide[13] gave 11a and 11b, respectively. To quench the Collins reaction, the sequential addition of allyl alcohol or benzyl alcohol and sodium bisulfate was important process in our reaction, otherwise the fairly large amounts of 15-oxo-compounds 12a and 12b were produced as by-products (ca. 30% yield).[14] Desilylation of 11a and 11b with aqueous oxalic acid-ethyl acetate (1:1) at room temperature gave 16-methylene-PGE_2 methyl ester (1b): nmr ($CDCl_3$) δ 5.70-5.56 (2H, m), 5.48-5.26 (2H, m), 5.12 (1H, s), 4.88 (1H, s), 4.60-4.47 (1H, m), 4.22-3.86 (1H, m), 3.66 (3H, s), 2.90-2.57 (1H, dd), 0.93 (3H, t); ir (liquid film) ν 3400, 1740, 1650, 1440, 980 cm^{-1}; specific rotation (EtOH solution, c 1.1) $[\alpha]_D^{24}$ -101.9°; homogeneous by tlc ($CHCl_3$-THF-AcOH 10:2:1, R_f 0.41) in 53% over-all yield from 1a, and 16,16-ethano-PGE_2 methyl ester (2b): nmr ($CDCl_3$) δ 5.71-5.52 (2H, m), 5.48-5.28 (2H, m), 4.30-3.25 (2H, m), 3.66 (3H, s), 2.89-2.58 (1H, dd), 0.89 (3H, t), 0.55-0.30 (4H, m); ir (liquid film) ν 3400, 3060, 1740, 980 cm^{-1}; specific rotation (AcOEt solution, c 0.375) $[\alpha]_D^{24}$ -39.2°; homogeneous by tlc (AcOEt-benzene 2:1, R_f 0.33) in 33% over-all yield from 2a, respectively.

Our method for the total synthesis of 1a, 1b, 2a and 2b is characterized by the following features. (a) Introducing ω-chain with the Wittig reagent without the protection of the hydroxyl functions at the C-11 and C-15 positions. (b) Making the product stable by esterification of the carboxyl function after introducing ω-chain. (c) Conversion of PGF analogs to PGE analogs by selective silylation, oxidation and desilylation. This method can be applied generally to the synthesis of PG analogs which are sensitive to acid.

All of 1a, 1b, 2a, and 2b showed higher PG-like biological activities than the natural PGs. For example, 16-methylene-PGE_2 methyl ester (1b) and 16,16-ethano-PGE_2 methyl ester (2b) were ca. 35 times and ca. 80 times more active than PGE_2 in the inhibitory action on pentagastrin-induced gastric acid secretion in rats, while diarrhea-producing activity in mice after oral administration of 1b and 2b was only ca. 1/30 and ca. 1/9 that of 16(R)-methyl-PGE_2, respectively.

References and Notes

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(7) Nmr and ir spectra of 15β-7a are identical as those of 15α-7a but R_f value of tlc is different; R_f 0.48 (CH_2Cl_2-MeOH 19:1). R_f value of 15α-7a is 0.57 (CH_2Cl_2-MeOH 19:1).

(8) The isolation of C-15 epimer was accomplished at the compound 9b.

(9) Nmr and ir spectra of the C-15 epimer are identical as those of 16,16-ethano-$PGF_2\alpha$ but R_f value of tlc is different; R_f 0.28 ($CHCl_3$-THF-AcOH 10:2:1).

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(11) Selectivity of 2a with N,O-bis-(trimethylsilyl)-acetamide was the same as that with N-methyl-silyldiethylamine.

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(14) Probably desilylation followed by oxidation occurred in part on adding sodium bisulfate in the absence of allyl alcohol or benzyl alcohol.

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