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THE SYNTHESIS OF PROSTAGLANDIN ENDOPEROXIDE ANALOGS

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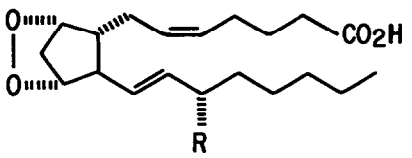
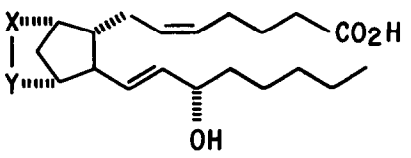
Several years ago, the suggestion was made that the biosynthesis of prostaglandins proceeds through endoperoxide intermediates,[1,2] a hypothesis strongly supported by an elegant oxygen labelling study.[2] More recently, Samuelsson and his coworkers,[3,4] and Nugteren and Hazelhof[5] have biosynthesized, isolated and characterized two endoperoxides designated as PGG_2 and PGH_2. These intermediates, despite their fairly short half-life in aqueous buffers (~5 min.), possess an interesting spectrum of biological activity.[3,4]



PGG_2 , R = OOH
PGH_2 , R = OH



1 , X = O , Y = CH_2
2 , X = CH_2, Y = O

We report herein the synthesis of two analogs of PGH_2[6] in which a methylene group has been substituted for each of the peroxide oxygens--namely the cyclic ethers 1 and 2 above. An ether linkage is more stable chemically than a peroxide unit, but the geometry of the rigid oxabicyclo[2.2.1] heptane ring system approximates that of PGH_2. We therefore undertook the synthesis of 1 and 2 to determine whether these had biological properties similar to or antagonistic to those of the natural endoperoxides.

The synthesis of cyclic ether 1 is outlined in Figure I. The introduction of a C-11 hydroxymethyl group into the prostaglandin carbon skeleton was accomplished utilizing a benzophenone-sensitized photo-addition of methanol [7,8] to PGA_2. Following irradiation (3500Å) of a solution of PGA_2 in methanol (containing a molar equivalent of benzophenone) for about five hours, 11-deoxy-11-hydroxymethyl-PGE_2 (a 4/1 mixture of epimers at C-11 favoring the 11α-isomer) was isolated in 80% yield. Chromatographic purification on silica gel afforded the pure 11α-isomer 4 ($\delta^{CDCl_3}_{TMS}$ 3.90-3.50; 2H; $\underline{CH_2}OH$; multiplet).[9,10] The configurational assignment at C-11 was based on relative tlc mobilities of the two isomers (11α more polar) and subsequent transformations of the more polar isomer.

Reduction of 11-deoxy-11α-hydroxymethyl-PGE_2 4 with lithium perhydro-9b-boraphenalyl hydride[11] afforded crystalline 11-deoxy-11α-hydroxymethyl-$PGF_{2\alpha}$ 5, mp 64-65°, in 94% yield.[9,10] There was no evidence for the formation of any of the 9β-isomer. The assignment of configuration at C-9 was based on literature precedent [12] and the chemical shift of the C-9 hydrogen in the nmr.[13]

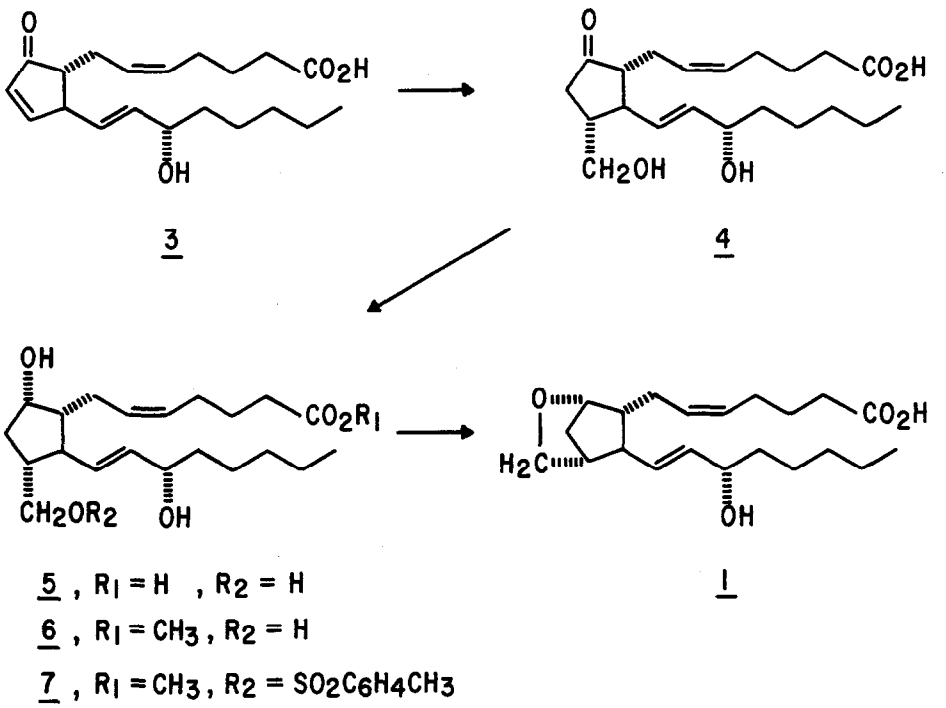


FIGURE I

Following esterification with diazomethane, the primary hydroxyl group of 11-deoxy-11α-hydroxymethyl-$PGF_2\alpha$ methyl ester 6 was converted selectively to the p-toluenesulfonate 7 in 45% yield (no attempt at optimization made) with p-toluenesulfonyl chloride in pyridine (12 hr., 0°). Treatment of 7 with aqueous methanolic potassium hydroxide at room temperature effected both the intramolecular displacement and ester hydrolysis affording (15S)-hydroxy-9α,11α-(epoxymethano) prosta-5Z,13E-dienoic acid 1 (isolated yield 78%). The nmr (3.36-3.85; six line pattern; 2H; $-C\underline{H}_2-O$) and the mass spectrum of 1 (M^+ observed at 350) are both consistent with the structure assigned.

The synthesis of (15S)-hydroxy-11α,9α-(epoxymethano)prosta-5Z,13E-dienoic acid 2 in which the C-9 oxygen of PGH_2 has been replaced by a methylene group is outlined in Figure II. PGE_2 methyl ester was first converted to 9-deoxy-9-methylene-PGE_2 methyl ester 10 in 75% overall yield. This was accomplished by the treatment of PGE_2 methyl ester, 11,15-bis(trimethylsilyl ether) 9 with three equivalents of N-methylphenylsulfonimidoylmethyl magnesium chloride[14] in tetrahydrofuran (-78°, 3 hr.), followed by reductive elimination[14] (aluminum amalgam, tetrahydrofuran, acetic acid, water; 25°, 60 min.) of a β-hydroxysulfoximine intermediate. The 9-methylene derivative 10 exhibited a broad singlet at 4.9 ppm (width at half-height, 8 Hz) in its nmr spectrum for the exo-methylene protons.

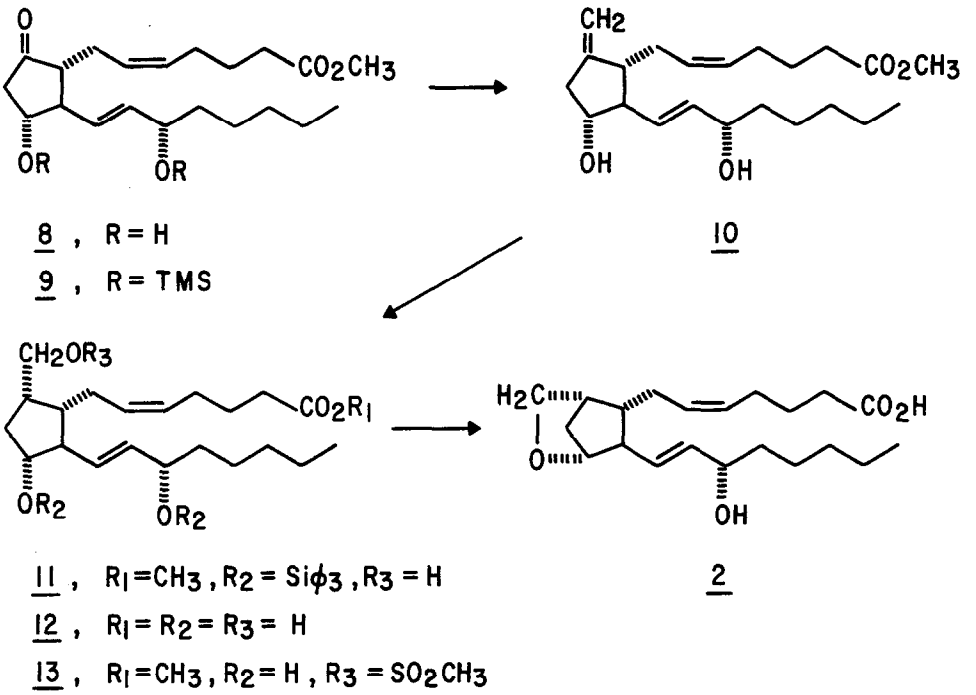


FIGURE II

After protection of the C-11 and C-15 hydroxyls of 10 as triphenylsilyl ethers (97% yield), selective hydroboration of the exo-methylene at C-9 proceeded cleanly with 9-borabicyclo[3.3.1] nonane[15] (9-BBN) (3 equivalents, 0°, 4 hr.) and afforded the primary alcohol 11 in 67% isolated yield. For purposes of characterization, removal of the silyl protecting groups followed by methyl ester hydrolysis afforded 9-deoxy-9α-hydroxymethyl-$PGF_2\alpha$ 12 [ν_{max} 3540, 3000, 2920, 2850, 2640, 1709 cm^{-1}; mass spectrum--no M^+ observed--peaks present at m/e 350 (M-18) and 332 (M-36)]. No other hydroboration product was isolated in larger than trace amounts. The only by-product identified was the C-1 primary alcohol corresponding to 11, the result of ester reduction by 9-BBN (10-15%). The stereochemistry at C-9 of primary alcohol 11 was assigned initially on mechanistic grounds (attack by a hindered reagent on the less crowded β-face of the molecule) and was readily confirmed by the subsequent cyclization with the 11α-hydroxyl. Conversion of primary alcohol 11 to the mesylate (methanesulfonyl chloride, triethylamine, methylene chloride, 0°, 10 min.), followed by silyl ether hydrolysis (phosphoric acid, aqueous tetrahydrofuran, 18 hr., 25°) afforded monomesylate 13 purification of which was unnecessary. Treatment of crude 13 with aqueous methanolic potassium hydroxide (2 hr., 25°) afforded (15S)-hydroxy-11α,9α-(epoxymethano)prosta-5Z,13E-dienoic

acid 2 in 75% overall yield from 11. The absence of any significant by-product in this cyclization constitutes further evidence for the stereospecificity of the hydroboration step (10→11).

The structure of cyclic ether 2 was confirmed by ir (no mesylate, no exo-methylene), nmr (3.48-3.9 ppm; 4-line pattern; 2H; $-CH_2O-$) and high resolution mass spectroscopy (M^+ for TMS derivative observed at 494.3244; theory for $C_{27}H_{50}Si_2O_4$, 494.3248).

Like PGH_2, cyclic ethers 1 and 2 are potent bronchoconstrictors in laboratory animals.[16] Their other biological effects are under investigation.

ACKNOWLEDGMENT

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