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SYNTHESIS OF PROSTAGLANDIN I_3 (PGI_3)

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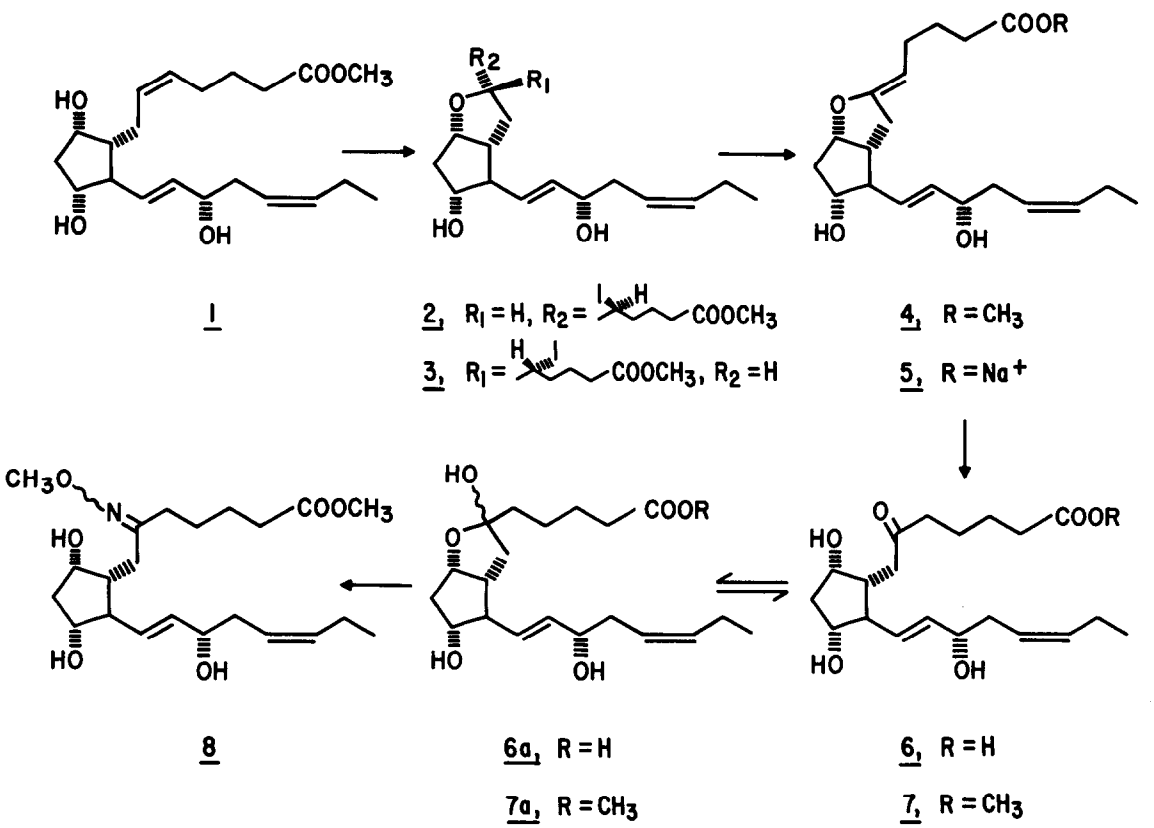
Prostacyclin (PGI_2) is a potent, naturally occurring inhibitor of platelet aggregation[1] that is generated enzymatically from arachidonic acid *via* the intermediate prostaglandin endoperoxide, PGH_2.[1,2] The existence of the analogous endoperoxide, PGH_3, is implied by the presence of prostaglandins of the "3-series" (e.g., PGE_3[3] and $PGF_{3\alpha}$[4]) in mammalian tissues. In fact, crude enzyme preparations capable of the biosynthesis of PGG_2 and PGH_2 can also produce PGH_3.[5] One may reasonably expect, therefore, that the enzymes producing PGI_2 from PGH_2 might also produce PGI_3 (prostaglandin I_3) from PGH_3. In anticipation of this possibility, we have prepared PGI_3 and its hydrolysis product, 17,18-didehydro-6-oxo-$PGF_{1\alpha}$, by chemical synthesis and report their properties here.

Reaction of $PGF_{3\alpha}$, methyl ester[6] (1, 3.40 mmol) with iodine (3.74 mmol) in methylene chloride in the presence of aqueous sodium bicarbonate gave two cyclic iodo-ethers, for which structures 2 and 3 were based upon the data given here and by analogy to results reported previously for the reaction of iodine with $PGF_2\alpha$ methyl ester.[7] The minor iodo-ether 2 (2%, less polar on silica gel tlc) was assigned the structure (5S,6S,17Z)-17,18-didehydro-5-iodo-PGI_1, methyl ester; ^{1}H nmr (δ, $CDCl_3$) 5.49 (m, 4H, two -CH=CH-), 4.49-3.33 (m, 5H, protons at C_5, C_6, C_9, C_{11} and C_{15}), 3.67 (s, 3H, $-OCH_3$), and 0.97 (5, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$); mass spectrum (bis TMS ether), calcd for $C_{26}H_{46}Si_2O_5I$ (M^+-CH_3): 621.1930, found: 621.1938. The major iodo-ether 3 (57%) was assigned the structure (5R,6R,17Z)-17,18-didehydro-5-iodo-PGI_1 methyl ester and was a viscous oil; ^{1}H nmr (δ, $CDCl_3$) 5.50 (m, 4H, two -CH=CH-), 4.54 (q, 1H, J = 5.5 Hz, C_9H), 4.25-3.47 (m, 4H, protons at C_5, C_6, C_{11} and C_{15}), 3.67 (s, 3H, $-OCH_3$), 0.97 (5, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$); ^{13}C nmr ($CDCl_3$, δ from TMS) 173.4, 135.1, 134.0, 132.4, 124.1, 80.9, 75.9, 72.4, 55.8, 51.5, 47.2, 41.0, 40.3, 35.8, 35.4, 35.0, 33.0, 25.1, 20.7 and 14.2; mass spectrum (bis TMS ether), found: 621.1907.

Dehydrohalogenation of the major iodo-ether (3) with 1,5-diazabicyclo[4.3.0]non-5-ene in benzene,[7] followed by chromatographic purification of the crude product over Florisil, gave PGI_3 methyl ester (4, 62%) as a viscous oil; infrared, ν_{OH} 3390, $\nu_{C=O}$ 1740, $\nu_{=C-O-}$ 1695 cm^{-1} (liquid film); ^{1}H nmr (δ, benzene-d_6, 100 MHz), 5.61 (m, 4H, olefinic protons), 4.22 (m, 3H), 3.75 (q, 1H, J = 7 Hz), 3.43 (s, 3H, $-OCH_3$), 0.99 (t, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$); mass spectrum (bis TMS ether), calcd. for $C_{27}H_{48}Si_2O_5$: 508.3040, found: 508.3025. Although the exact position of the C-5 vinyl ether proton in the nmr spectrum of 4 could not be determined because of other overlapping signals, this signal clearly was not between 4.5-5.0 δ, where it would be expected if the vinyl ether had the E-configuration.[7]



Prostaglandin I_3 sodium salt (5) was prepared by saponification of 4 with an equivalent of sodium hydroxide in methanol. Following lyophilization of the reaction solution, 5 was obtained as a white powder; infrared, $\nu_{=C-O-}$ 1690 cm^{-1} (nujol mull).

Detection of the hydrolysis product, 6-keto-$PGF_1\alpha$, in biological systems may be regarded as evidence that the unstable (at physiological pH) prostacyclin (PGI_2) molecule was present in that system.[8] Prostaglandin I_3 (5) is equally as sensitive to hydrolysis as is PGI_2, so we have characterized the hydrolysis product, (17Z)-17,18-didehydro-6-oxo-$PGF_1\alpha$ (6), in order that it may serve a similar role in the detection of PGI_3 in natural systems.

Hydrolysis of sodium salt 5 in 1:1 tetrahydrofuran - pH 1.5 buffer (3 hr) and isolation of the product[7] resulted in the formation of (17Z)-17,18-didehydro-6-oxo-$PGF_1\alpha$ (6) as a viscous oil; infrared, ν_{OH} 3375, $\nu_{C=O}$ 1710 cm^{-1} on a liquid film; ^1H nmr (δ, acetone-d_6) 5.48 (m, 4H, olefinic protons), 4.80-3.50 (m, 3H, C_9H, $C_{11}H$, $C_{15}H$), 0.95 (t, 3H, J = 7 Hz, $-CH_3$); mass spectrum (tetra TMS ether, methoxime) calcd for $C_{32}H_{64}Si_4NO_6$ ($M^+ - CH_3$): 670.3810, found: 670.3796. Hydrolysis of methyl ester 4 in the same way gave (17Z)-17,18-didehydro-6-oxo-$PGF_1\alpha$, methyl ester (7), also a viscous oil. Methyl ester 7, either neat or in solution, was subject to a mobile equilibrium that gave many spots on tlc. One of the new compounds undoubtedly is the hemi-ketal,

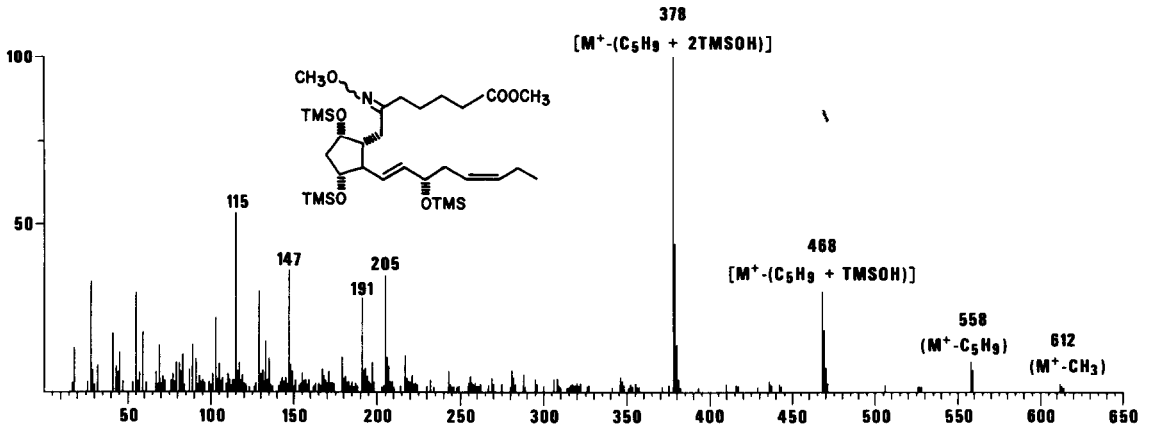


Figure 1. Mass spectrum of (17Z)-17,18-didehydro-6-oxo-$PGF_{1\alpha}$ methoxime methyl ester tris TMS ether.

7a. Exposure of such an equilibrium mixture to the preceding hydrolysis conditions forces the equilibrium to favor essentially pure 7. Because of this equilibrium, 7 was characterized as the methoxime derivative 8 (syn and anti forms are detected by tlc on silica gel with 1:1 acetone-hexane); infrared ν_{OH} 3320, $\nu_{C=O}$ 1730 cm^{-1} in $CHCl_3$ solution; ^1H nmr (δ, $CDCl_3$), 5.54 (4H, m, olefinic protons), 4.37-3.62 (m, 3H, C_9H, $C_{11}H$, $C_{15}H$), 3.85 and 3.79 (two s, syn and anti $-NOCH_3$), 3.67 (s, 3H, $-OCH_3$), 0.97 (5, 3H, J = 7 Hz, $-CH_2\underline{CH_3}$); mass spectrum (tris TMS ether) calcd for $C_{30}H_{58}Si_3NO_6$ ($M^+ - CH_3$): 612.3541, found: 612.3572. A mass spectrum obtained when compound 8 (as the tris TMS ether) was analyzed by gas chromatography - mass spectrometry is shown in Figure 1.

PGI_3, sodium salt (5), is equal to prostacyclin, sodium salt, in its ability to inhibit either PGH_2-[9] or ADP-induced[10] platelet aggregation.

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10. We thank E. E. Nishizawa and Thomas Honohan for measuring the ability of 5 to inhibit the ADP-induced aggregation of human platelet-rich plasma.