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SYNTHESIS OF PROSTAGLANDIN I_3 (PGI_3)

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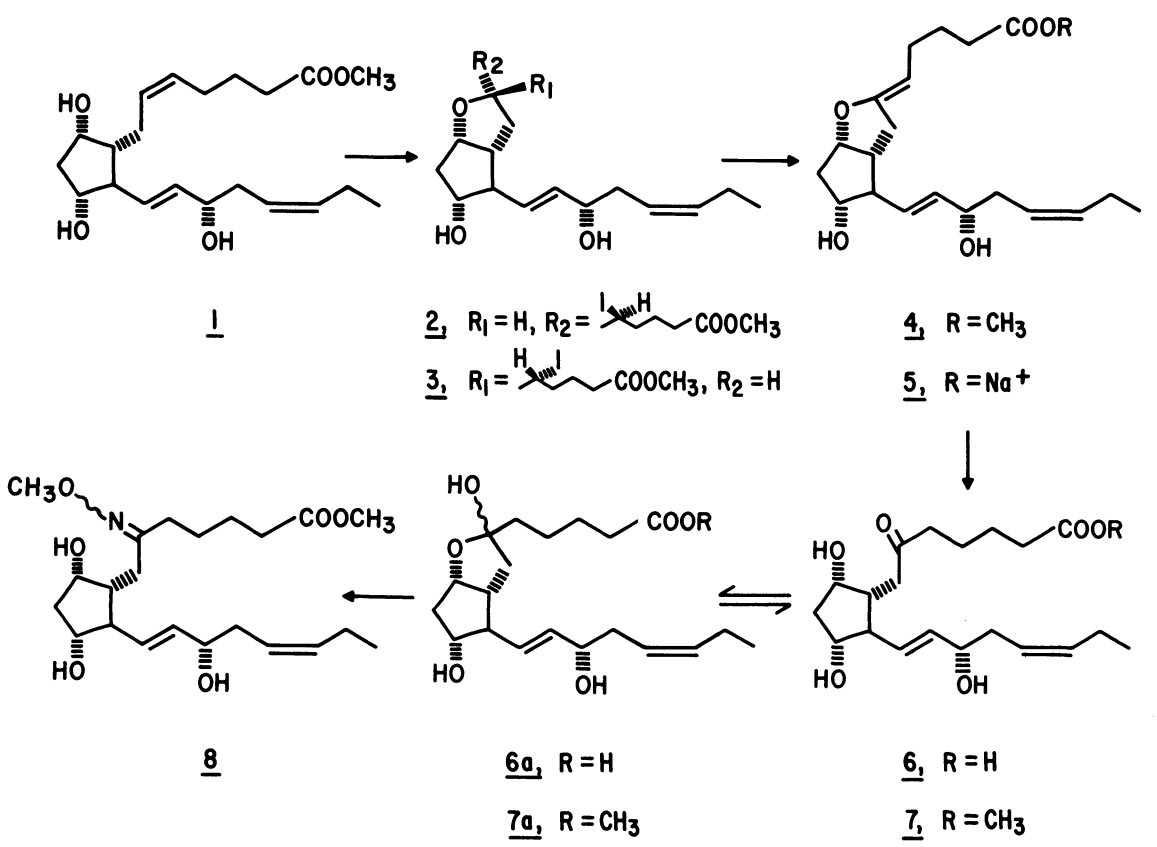
Prostacyclin (PGI_2) is a potent, naturally occurring inhibitor of platelet aggregation[1] that is generated enzymatically from arachidonic acid via the intermediate prostaglandin endoperoxide, PGH_2.[1,2] The existence of the analogous endoperoxide, PGH_3, is implied by the presence of prostaglandins 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,

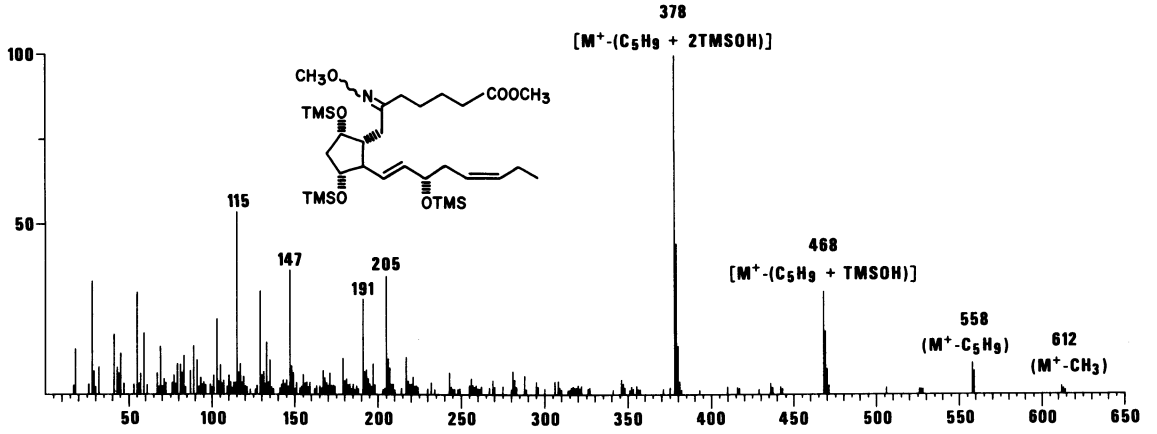


Figure 1. Mass spectrum of (17Z)-17,18-didehydro-6-oxo-PGF$_1\alpha$ methoxime methyl ester tris TMS ether.

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.

REFERENCES AND NOTES

1. (a) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, Nature, 263, 663 (1976); (b) R. J. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, Prostaglandins, 12, 685 (1976); (c) S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, Prostaglandins, 12, 897 (1976).
2. R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, Prostaglandins, 12, 915 (1976).
3. (a) S. Bergstrom, F. Dressler, R. Rymage, B. Samuelsson, and J. Sjovall, Arkiv Kemi, 19, 563 (1962); (b) B. Samuelsson, J. Am. Chem. Soc., 85, 1878 (1963).
4. B. Samuelsson, Biochim. Biophys. Acta, 84, 707 (1964).

5. (a) P. Needleman, M. Minkes, and A. Raz, Science, 193, 163 (1976); (b) A. Raz, M. Minkes, and P. Needleman, Biochim. Biophys. Acta, 488, 305 (1977).
6. We thank R. C. Kelly and I. Schletter for providing us with $PGF_{3\alpha}$ methyl ester prepared by total synthesis (unpublished results, The Upjohn Company).
7. R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, J. Am. Chem. Soc., 99, 4182 (1977).
8. Cf., F. Cottee, R. J. Flower, S. Moncada, J. A. Salmon, and J. R. Vane, Prostaglandins, 14, 413 (1977).
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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.