Synthesis of (4*E*)-9-Deoxy-6,9α-epoxy-Δ^4-$PGF_{1\alpha}$, a Prostacyclin (PGX) Isomer

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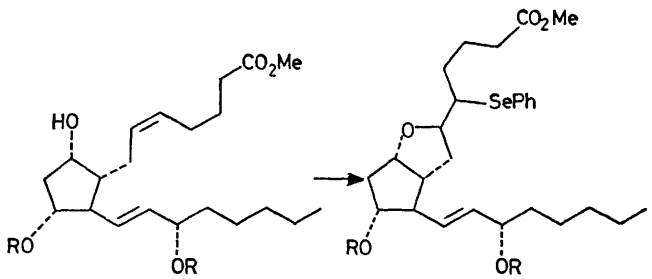
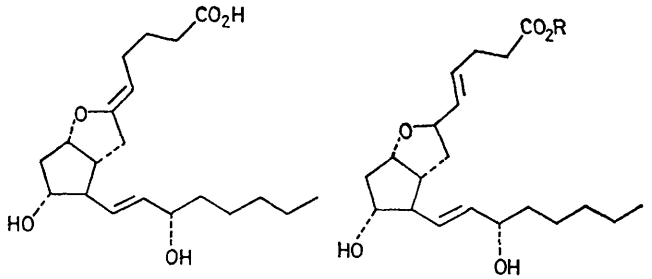
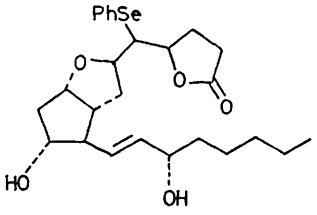
Summary (4*E*)-9-Deoxy-6,9α-epoxy-Δ^4-$PGF_{1\alpha}$, a prostacyclin (PGX) isomer, has been synthesized from $PGF_{2\alpha}$ methyl ester by a novel PhSeCl-induced cyclization.

PROSTACYCLIN (PGX) (**7**), a major factor in blood platelet aggregation, has recently been reported[1] as the newest and highly promising entry in the prostaglandin field. Because of its striking activities,[1] particularly its anti-thrombotic effects, this compound is a potential drug for treatment of thrombosis, stroke, and heart attack.[1] However, its relative instability (biological half life, $t_{\frac{1}{2}}$, *ca.* 2 min) and its important role in physiological processes has necessitated







the preparation of stable analogues. We report here the synthesis of the first analogue of prostacyclin, namely (4*E*)-9-deoxy-6,9α-epoxy-Δ^4-$PGF_{1\alpha}$ (**6**) by a novel and selective ring closure induced by PhSeCl.[2]

The natural form of $PGF_{2\alpha}$ methyl ester (**1**), on exposure to PhSeCl[2a] (1·1 equiv.) in CH_2Cl_2 at −78 °C, afforded the phenylselenoether (**2**)† (mixture of diastereoisomers) as the major product (75%).‡ This regio- and chemo-specific ring closure was expected on steric and proximity grounds. Conversion of (**2**) into the corresponding selenoxide (1·5 equiv. of H_2O_2, tetrahydrofuran, 0—25 °C) followed by *syn* elimination (25 °C), away from the oxygen to afford a *trans* double bond as expected,[2,3] furnished the methyl ester (**5**) in 81% yield. Saponification of (**5**) (10 equiv. of LiOH in 3 : 1 MeOH–H_2O at 25 °C) afforded (**6**) in quantitative yield.

Although the structures assigned to (**6**) and the intermediates leading to it were consistent with the ^1H n.m.r. data, a more rigorous proof of these assignments was sought. Thus, 11,15-diacetoxy-$PGF_{2\alpha}$ methyl ester (**3**),§ when treated with PhSeCl as described above, afforded the cyclic ether (**4**) as the major product which, on deacetylation (anhydrous K_2CO_3 in absolute MeOH at 25 °C), led to (**2**), identical with the material obtained directly from (**1**). Finally, the position of the newly generated double bond, and hence the five-membered nature of the ether species, was firmly established by phenylselenolactonization[2b] (PhSeCl, CH_2Cl_2, −78 °C) of (**6**) to the γ-lactone (**8**) [ν_{max} (neat) 1770 cm^{-1}].‡

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† Satisfactory spectral data were obtained for all new compounds.

‡ It is quite possible that at least some six-membered ring product is initially formed which rearranges upon workup and chromatography to the observed, thermodynamically more stable, oxacyclopentane system.

§ Obtained from 15-acetoxy-PGE_2 methyl ester (E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, 1975, **72**, 3355; G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Amer. Chem. Soc.*, 1972, **94**, 2123) by acetylation followed by K-Selectride reduction.

[1] *Chem. Eng. News*, December 20, 1976; Intra-Science Research Foundation Annual Symposium, Santa Monica, California, 1976; S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature*, 1976, **263**, 666; R. J. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, *Prostaglandins*, 1976, **12**, 685; S. Moncada, R. J. Gryglewski, S. Bunting, and J. R. Vane, *ibid.*, p. 715.

[2] For a systematic study of the use of this reagent in (a) cyclic ether formation see: K. C. Nicolaou and Z. Lysenko, *Tetrahedron Letters*, 1977, 1257: (b) lactone formation see: *J. Amer. Chem. Soc.*, in the press.

[3] H. J. Reich, J. M. Renga, and I. L. Reich, *J. Amer. Chem. Soc.*, 1975, **97**, 5437, and references cited therein; K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chemica Scripta*, 1975, **8A**, 9, and references cited therein.