A General Method for the Conversion of F into E Prostaglandins[†]

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Summary A simple general method for the conversion of F into E prostaglandins involving selective silylation of the 11- and 15-hydroxy-groups is reported.

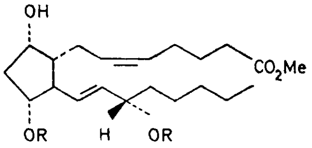
IN spite of intense interest in the synthesis of the prostaglandins[1] no general method has as yet been reported for the conversion of PGF into PGE compounds. A simple general method of this type appeared to offer attractive possibilities, particularly so for the Chicago group in connection with a recently reported synthesis.[2,3] We report such a method involving selective silylation of the 11- and 15-hydroxy-groups, followed by oxidation of the free 9-hydroxy-group.

Yankee and Bundy[4] reported recently that 15-methyl-$PGF_{2\alpha}$ methyl ester could be silylated preferentially at the 11-position using the selective silylating agent *N*-trimethylsilyldiethylamine.[5] Subsequent oxidation of this mono-trimethylsilyl ether with Collins reagent[6,7] followed by hydrolysis led to 15-methyl-PGE_2 methyl ester.[‡] On the basis of this work, it appeared of interest to investigate whether prostaglandins possessing a secondary 15-hydroxy-group might be silylated at both C-11 and C-15, leaving C-9

[†] The work reported in this communication was carried out independently in the laboratories of The Upjohn Company [compound (**1**)] (*Received*, 5*th June* 1972; *Com.* 946) and at the University of Chicago [compounds (**1**) and (**2**)] (*Received*, 12*th June* 1972; *Com.* 1027.) At the suggestion of the Editors the contents of the two manuscripts originally submitted separately have been combined in the present communication. Reprint requests may be directed to either laboratory.

[‡] This procedure was first described by Dr. G. L. Bundy at the Middle Atlantic Regional Meeting, American Chemical Society, Philadelphia, Feb. 16, 1972.

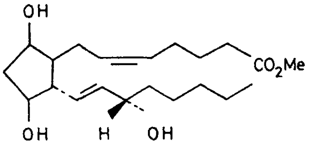
unprotected for oxidation. This was indeed found to be the case and the methyl esters of PGF$_{2\alpha}$ (**1a**) and *ent*-15-*epi*-PGF$_{2\alpha}$ (**2**) have been converted into the corresponding PGE$_2$ derivatives (**3**) and (**4**) in 35—50% yield. In addition,



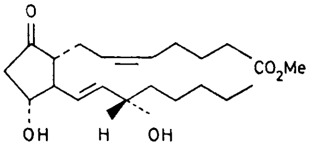
(1)

a ; R = H

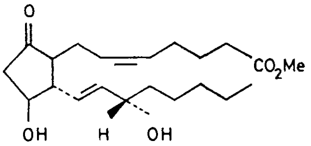
b ; R = Me$_3$Si



(2)



(3)



(4)

there was obtained recovered starting material (10—20%) and in the case of the Chicago group the corresponding 15-dehydro-PGE derivatives. Identity of (**3**) and (**4**) with authentic materials was established by t.l.c. (several solvent systems), i.r., n.m.r., and mass spectra.

The following conditions are representative:§ a solution of PGF$_{2\alpha}$ methyl ester (**1a**) (20 mg) in dry acetone (0·4 ml) was stirred at −40° under nitrogen. *N*-Trimethylsilyldiethylamine (0·8 ml) was then added, and after 1 h the reaction was quenched with dry methanol (0·6 ml) and the mixture allowed to warm to 25°. Evaporation to dryness under reduced pressure yielded as the major product the bis-trimethylsilyl derivative (**1b**), which was oxidized with Collins reagent ***in situ*** (prepared from 36 mg of CrO$_3$ and 55 μl of pyridine in 0·8 ml of CH$_2$Cl$_2$) for 5 min at 25°, followed by desilylation with a mixture of 1 ml of methanol, 0·1 ml of water and 0·05 ml of acetic acid for 1 h. High pressure chromatography on silica gel afforded on elution with varying ratios of hexane–ethyl acetate 10 mg of PGE$_2$ methyl ester (**3**) [45% from (**1a**)], 4·4 mg of recovered PGF$_{2\alpha}$ methyl ester (20%) and 3·2 mg of 15-dehydro-PGE$_2$ methyl ester, (15%), $[\alpha]_D$ (EtOH) −25·6° (*c*, 0·8); λ_{max} (EtOH) 228 nm (13,000); n.m.r. spectrum identical with that reported by Miyano *et al.*[8] Similarly, *ent*-15-*epi*-PGF$_{2\alpha}$ methyl ester furnished *ent*-15-*epi*-PGE$_2$ methyl ester (**4**), $[\alpha]_D$ (EtOH) +43° (*c*, 0·23), in 44% yield.

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§ These conditions were the ones arrived at by the Chicago group. The Upjohn work differed in the method of quenching of the silylation reaction, which was accomplished by dilution with cold ether followed by extraction with cold 50% saturated aqueous NaHCO$_3$. No 15-oxo-derivative was isolated in this case.

[1] For a recent review, see U. Axen, J. E. Pike, and W. P. Schneider, in 'The Total Synthesis of Natural Products,' vol. I, ed., J. W. ApSimon, Wiley, New York, 1972, in the press.

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[6] J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 1968, 3363.

[7] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.

[8] M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, 1972, **37**, 1810.