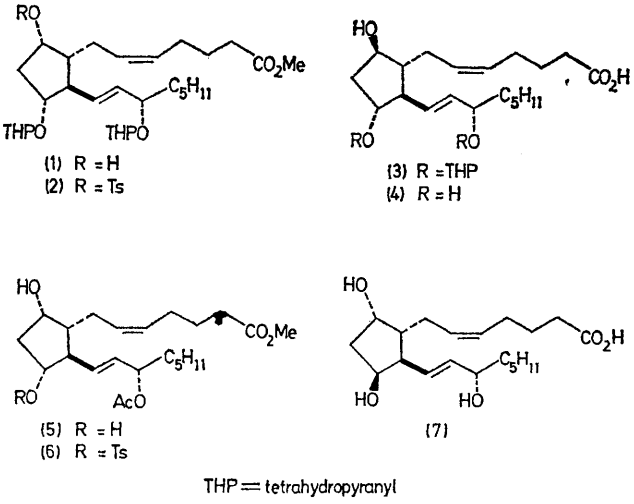
# Simple Stereospecific Routes to 9-*epi*-Prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$) and 11-*epi*-Prostaglandin $F_{2\alpha}$

By E. J. COREY,* KYRIACOS C. NICOLAOU, and MASAKATSU SHIBASAKI
(*Department of Chemistry, Harvard University, Cambridge, Massachusetts* 02138)

*Summary* Prostaglandin $F_{2\beta}$ and 11-*epi*-prostaglandin $F_{2\alpha}$ have been prepared stereospecifically from intermediates which are readily available by total synthesis.

PROSTAGLANDIN $F_{2\beta}$ ($PGF_{2\beta}$) (**4**), though not known to occur naturally, is of special interest as a powerful bronchodilator.[1] The only reported synthetic route to this compound (or its analogues) is the wasteful reduction of $PGE_2$ (or analogues) by sodium borohydride which affords approximately equal amounts of $PGF_{2\beta}$ and its 9-epimer, $PGF_{2\alpha}$.[2] Because of the need for an efficient route to $PGF_{2\beta}$ which would also be applicable to its analogues, we have developed a method which depends on the recently discovered use of the superoxide ion ($O_2^{-}\cdot$) as a potent reagent for $S_N2$ displacement leading from halides or sulphonates directly to alcohols with inversion of configuration.[3]

The 11,15-bistetrahydropyranyl (THP) ether of $PGE_{2\alpha}$, a general synthetic intermediate for prostaglandins of the first and second series,[4] was converted (by $CH_2N_2$) into the oily methyl ester (**1**), $[\alpha]_D^{25}$ — 16·0° ($CHCl_3$),† and thence into the 9-tosyl derivative (**2**) by reaction with toluene-*p*-sulphonyl chloride (3 equiv.) in pyridine (24 equiv.) at 25 °C for 36 h. Treatment of (**2**) with $KO_2$ (several equiv.) and 18-crown-6 (3 equiv.) in dimethyl sulphoxide–dimethoxyethane[5] (DMSO–DME) (2 : 1) at 25 °C for 4·5 h afforded a mixture of the acid (**3**) and the corresponding methyl ester which was saponified (10 equiv. of LiOH in 3 : 1 methanol–water, 0 °C, 3·5 h) and freed of the THP protecting groups by exposure to acetic acid–water–tetrahydrofuran (3 : 1 : 1) at 45 °C for 3 h to provide $PGF_{2\beta}$ (**4**) in pure form after column chromatography on silica gel (45% overall yield from **1**); m.p. 94—95 °C; $[\alpha]_{365}^{25}$ + 12·7° (in MeOH); i.r. and $^1$H n.m.r. spectra identical with those reported.[6] The relative $R_f$ values found for $PGF_{2\beta}$ and $PGF_{2\alpha}$ on silica gel plates using benzene–formic acid–tetrahydrofuran (15 : 2 : 5) for development were 0·38 and 0·46, respectively, after two developments. The methyl ester of (**4**) could be prepared by $KO_2$ displacement with (**2**) as substrate followed by esterification ($CH_2N_2$) and THP ether cleavage as above, m.p. 84—85·5°, $[\alpha]_{365}^{25}$ + 10·1° (in MeOH); $R_f$ 0·17 on silica gel plates with $CH_2Cl_2$–MeOH (9 : 1) for development as compared to 0·36 for $PGF_{2\alpha}$ methyl ester.




11-*epi*-$PGF_{2\alpha}$ (**7**), hitherto available with difficulty,[7] can also be made in a similar way starting from $PGF_{2\alpha}$ methyl

† The structures assigned to al lintermediates for which rotations are given have been verified by spectroscopic and mass spectrometric data.

ester. The ester was heated at reflux with benzeneboronic acid (1·2 equiv.) in $CH_2Cl_2$ with water removal by Molecular Sieves (Linde 4A) to form the 9α, 11α-boronate–carboxylate methyl ester. Treatment of the boronate ester with acetic anhydride (5 equiv.)–pyridine (10 equiv.) containing a catalytic amount of 4-dimethylaminopyridine for 2 h at 25 °C furnished the corresponding 15-acetate which was deprotected to (**5**) ($[\alpha]_D^{25}$ − 5·43° in $CHCl_3$) by stirring in 95% ethanol at 25 °C with $H_2O_2$-$NaHCO_3$ (overall yield 85%). Reaction of (**5**) with toluene-*p*-sulphonyl chloride (1·5 equiv.) in pyridine at 25 °C for 6 h gave (**6**), $[\alpha]_D^{25}$ + 9·82° in $CHCl_3$, 72% yield. The tosylate (**6**) was converted into 11-*epi*-$PGF_{2\alpha}$ (**7**) by reaction with $KO_2$ (10 equiv.) and 18-crown-6 (5 equiv.) in DMSO–DME (2 : 1) at 25 °C for 2 h followed by saponification with 0·25-N LiOH in 1 : 1 methanol–water at 25 °C for 20 h. Pure (**7**), $[\alpha]_D^{25}$ + 89·6° in MeOH, m.p. 117—119 °C, was obtained in 78% yield from (**6**).

Thus the C-9 and C-11 epimers of $PGF_{2\alpha}$ and biologically interesting analogues are now readily available by stereocontrolled total synthesis.

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