The Synthesis of (±)-Prostaglandins E_2, $F_{2\alpha}$, and $F_{2\beta}$

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PROSTAGLANDIN E_2 (PGE_2) (5; R = H) and $F_2\alpha$ ($PGF_2\alpha$) (6) are recognized as the most commonly occurring natural prostaglandins,[1] and show both qualitative and quantitative differences in biological activity[2] from their 5,6-dihydro-analogue, PGE_1 and $PGF_{1\alpha}$. Total syntheses of (±)-PGE_1 and (±)-$PGF_{1\alpha}$ have recently been reported.[3] This report details a synthesis of (±)-PGE_2, and $PGF_{2\alpha}$, and $PGF_{2\beta}$ based on 6-*endo*-substituted bicyclo[3,1,0]hexane intermediates described in an accompanying communication.[3f]

6-*endo*-(1′-Heptenyl)bicyclo[3,1,0]hexane-3-one[3f] (1) was hydroxylated with osmium tetroxide and the resulting *vic*-glycol was converted into its acetonide (2). This was alkylated with 1-bromo-7-tetrahydropyranyloxyhept-2-yne† by means of potassium t-butoxide in tetrahydrofuran. Selective hydrolysis of the tetrahydropyranyl ether with oxalic acid in methanol and oxidation of the resulting primary alcohol by Jones' reagent[4] gave the carboxylic acid (3). The triple bond was hydrogenated to a *cis*-double bond using palladium on barium sulphate catalyst in pyridine. Removal of the acetonide grouping in aqueous tetrahydrofuran containing hydrochloric acid, followed by esterification of the carboxy-group with trichloroethanol gave compound (4) as a mixture of two isomeric racemates. This was converted into the bis-mesylates which were solvolysed in aqueous acetone to produce the trichloroethyl esters of (±)-prostaglandin E_2 (5; R = $CH_2{\cdot}CCl_3$) and its 15-epimer, each in about 15% yield, easily separable by silica gel chromatography.‡ Treatment of the more polar of these with zinc in acetic acid removed the trichloroethyl ester group,[5] producing (±)-PGE_2 (5; R = H), which gave n.m.r. (in $CDCl_3$), i.r. (in CH_2Cl_2), and mass spectra identical with those of natural PGE_2. Treatment with base gave a material

† This was prepared by *C*-alkylation of the dilithium salt of prop-2-yn-1-ol with 1-bromo-4-tetrahydropyranyloxybutane, mesylation of the resulting propargylic alcohol and displacement of mesylate by lithium bromide. This sequence was previously carried out by G. Just and E. S. Ferdinandi, private communication to J. E. Pike.

‡ The above intermediates were all noncrystalline, and were characterized by n.m.r., i.r., and mass spectra, and by g.l.c. and t.l.c.

showing u.v. absorption at 278 nm. (ϵ 26,000) and t.l.c. mobility identical with that of authentic PGB_2. The mobility and colour reactions (with vanillin–phosphoric acid spray) of synthetic and natural PGE_2 were identical on both silica gel and silver nitrate-impregnated silica gel thin-layer plates (AIX system[6]), as was the g.l.c. analysis of the derived methoxime, trimethylsilyl derivatives.§ These g.l.c. peaks from both natural and synthetic PGE_2 were collected and showed the same mass-spectral fragmentation patterns and molecular-ion peaks (597). The synthetic (±)-PGE_2 showed at least 50% of the biological activity of natural PGE_2 in its effects on blood pressure in rats and on contraction of smooth muscle.¶

Reduction of (±)-PGE_2 with sodium borohydride gave (±)-$PGF_{2\alpha}$ (6) and its 9-epimer, (±)-$PGF_{2\beta}$, in about a 45 : 55 ratio. These were separated on acid-washed silica gel and the more polar (±)-$PGF_{2\beta}$ fractions easily crystallized, m.p. 90—92° after recrystallization from ethyl acetate These products were identical with those obtained from natural PGE_2 by t.l.c. on several systems, including silver nitrate-impregnated plates, by mass spectra, and by g.l.c. analysis of their trimethylsilyl derivatives. The (±)-$PGF_{2\alpha}$ had at least 50% the activity of natural $PGF_{2\alpha}$ in its affect on blood pressure and smooth muscle.¶

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¶ The biological assays were performed by Dr. J. R. Weeks and associates of the Experimental Biology Unit of the Upjohn Company.

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