A Total Synthesis of (±)-Prostaglandin E_3 Methyl Ester *via* *endo*-Bicyclohexane Intermediates

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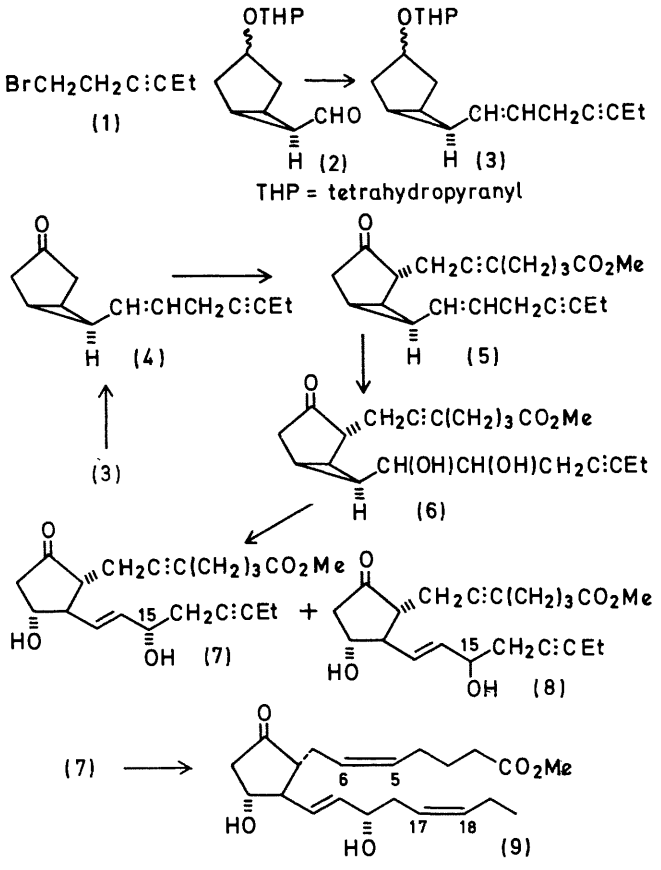
Summary (±)-Prostaglandin E_3 methyl ester has been synthesized *via* *endo*-bicyclohexane intermediates.

SEVERAL syntheses of prostaglandins E_1 (PGE_1) and E_2 (PGE_2) have recently been reported.[1] We describe a total synthesis of prostaglandin E_3 (PGE_3) methyl ester (**9**) which is distinguished from PGE_2 by an additional *cis*-double bond between C-17 and C-18. PGE_3[2] has been obtained from natural sources in only limited quantities and was therefore not as available for broad biological testing as other prostaglandins.

Hex-3-yn-1-ol on treatment with triphenylphosphine and *N*-bromosuccinimide gave 1-bromohex-3-yne (**1**). This modification of the method first described by Trippett[3] produced (**1**) in about five times higher yield than the procedure described[4] for the preparation of (**1**). Wittig reaction of the phosphonium salt of (**1**) with aldehyde (**2**)[5] resulted in olefin (**3**) which was converted into ketone (**4**) by standard procedures.[5] Alkylation of the potassium enolate of (**4**) with methyl 7-bromo-hept-5-ynoate[6] gave compound (**5**).† Treatment with osmium tetroxide resulted in the selective hydroxylation of the double bond. Mesylation of the glycol followed by solvolysis in acetone–water[5] yielded (±)-5(6);17(18)-bisdehydro-PGE_3 methyl ester (**7**) (m.p. 92—94°), and its 15-epimer (**8**). Hydrogenation of (**7**) over Lindlar catalyst in the presence of quinoline produced (±)-PGE_3 methyl ester (**9**). The synthetic material was shown to be identical with the methyl ester of natural PGE_3 using t.l.c. with silica gel–silver nitrate plates.[7] The methoxime ditrimethylsilyl ether derivative,[8] and the methoxime diacetate derivative of (**9**) were prepared and found identical with the same derivative of the methyl ester of natural PGE_3 in two g.l.c. systems‡ and by comparison of their mass spectra.§



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† Satisfactory analyses were obtained for all the new compounds described in this communication.

‡ The two g.l.c. systems used were (a) 1% Se30-230°, MOAc retention time 25·0, 25·5; MOTMSI retention time 24·0, 24·5, and (b) 2% Epon-230°, MOTMSi retention time 23·7, 24·2.

§ The mass spectra were obtained on an LKB 9000 mass spectrometer (electron energy 22·5 ev, trap current 60 μA).

[1] (a) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Amer. Chem. Soc.*, 1969, **91**, 5372; (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, p. 5675; and references cited therein.

[2] (a) S. Bergstrom, *Science*, 1967, **157**, 382; (b) B. Samuelsson, *J. Amer. Chem. Soc.*, 1963, **85**, 1878.

[3] S. Trippett, *J. Chem. Soc.*, 1962, 2337.

[4] F. Sondheimer, *J. Chem. Soc.*, 1950, 877.

[5] U. Axen, F. H. Lincoln, and J. L. Thompson, *Chem. Comm.*, 1969, 303.

[6] This reagent was prepared by methods described in connection with the total synthesis of PGE_2; W. P. Schneider, *Chem. Comm.*, 1969, 304.

[7] For a general review of t.l.c. of prostaglandins see K. Gréen and B. Samuelsson, *J. Lipid Res.*, 1964, **5**, 117. In this case the organic phase of ethyl acetate–methanol-water (160/50/100) was used as the mobile phase. The R_F of both natural and synthetic methyl esters was 0·4.

[8] (a) K. Gréen, *Chem. Phys. Lipids*, 1969, **3**, 254; (b) F. Vane and M. G. Horning, *Analyt. Letters*, 1969, **2**, 357.