Total Synthesis of Prostaglandin D_2 Methyl Ester

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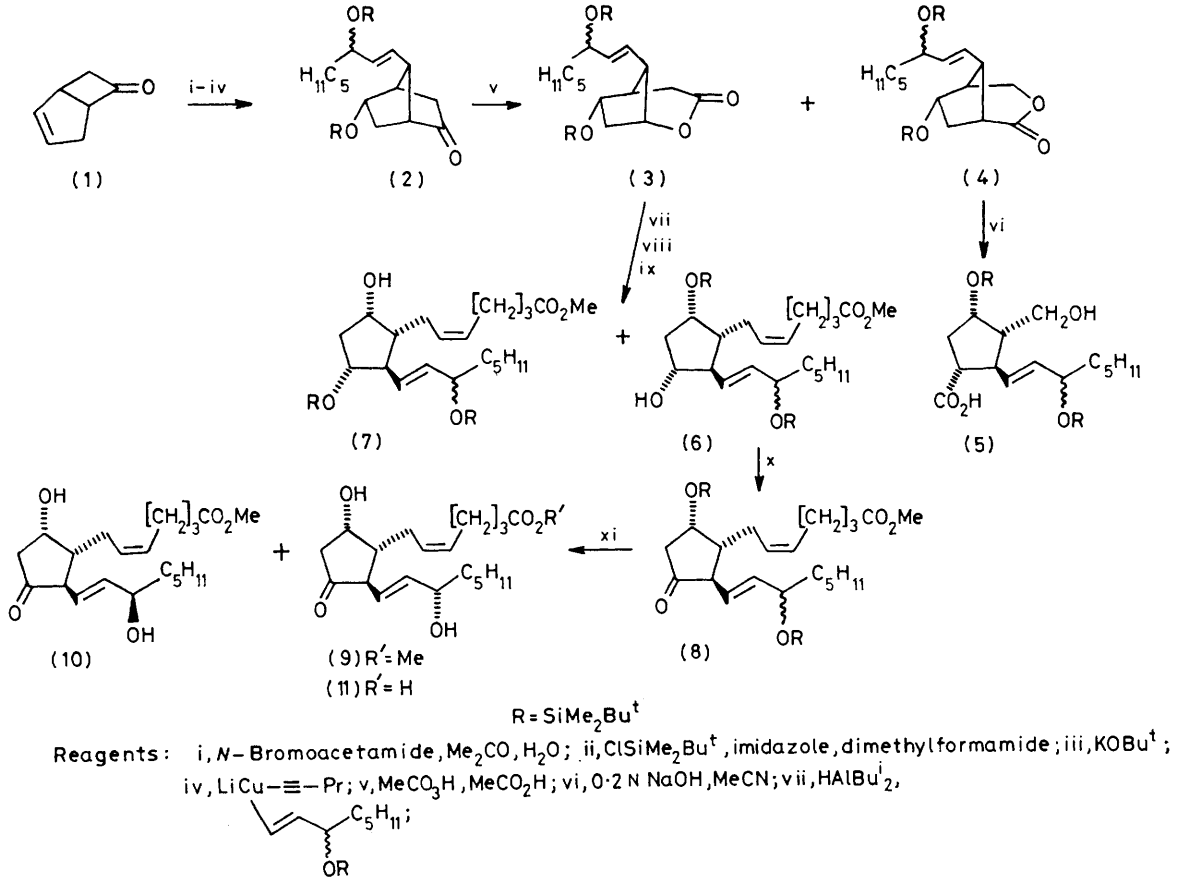
Summary The readily available norbornanone (**2**) gave a mixture of the lactones (**3**) and (**4**) on peracid oxidation, the minor component (**4**) being removed by treatment with aqueous alkali; conversion of (**3**) into (**6**) was performed so as to minimise silyl group scrambling, and the alcohol (**6**) was transformed into (±) prostaglandin D_2 methyl ester (**9**) by oxidation followed by deprotection using HF in acetonitrile.

PROSTAGLANDIN D_2 (**11**) is a primary prostaglandin that displays pronounced biological activity. Only four routes to prostaglandin D_2 have been described previously, one from prostaglandin $F_{2\alpha}$[1] and three protracted *de novo* syntheses.[2–4] Three of these documented processes[1–3] suffer from the concurrent production of quantities of an isomer (prostaglandin E_2) detracting from their efficiency and quality. The fourth involves a lengthy protection and deprotection sequence and gives only moderate yields of the desired product.

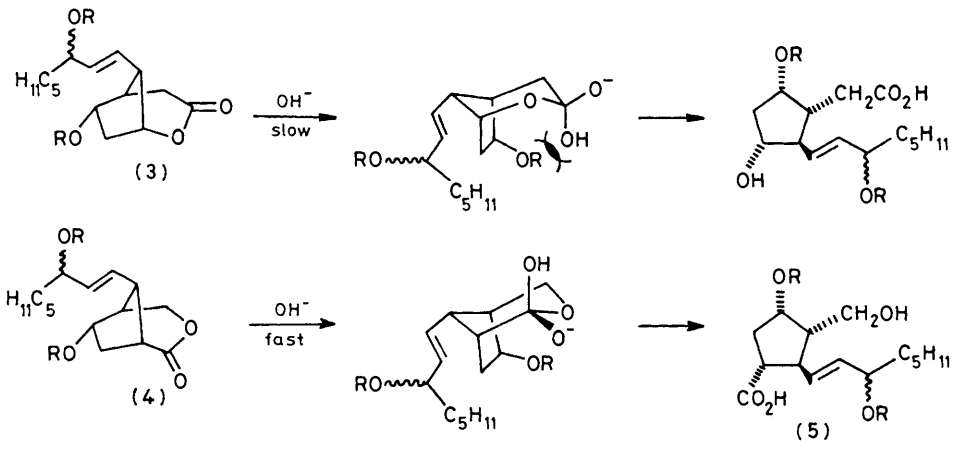
We have shown previously that the bicycloheptenone (**1**) is readily converted into the disubstituted norbornanone (**2**) in four steps with an overall yield of 65%.[5,6] Baeyer–Villiger oxidation of the ketone (**2**) using peracetic acid gave a mixture of the 2-oxabicyclo-octanone (**3**) and the unwanted isomer (**4**) in the ratio 71 : 29. The necessity to perform a difficult chromatographic separation at this stage[6] was avoided when it was found that the minor component (**4**) was preferentially hydrolysed on treatment of the lactone mixture with aqueous hydroxide ion. Hence 0·2 N sodium hydroxide solution was added to the lactones (**3**) and (**4**) in acetonitrile. After 7·5 h the ether soluble products were filtered through a column of silica gel to give the pure lactone (**3**) (70%) and the hydroxy acid (**5**) (14%). The more rapid rate of hydrolysis of the lactone (**4**) compared to the lactone (**3**) is probably due to the differences in transannular steric interactions within the two transition states (Scheme).[7]

The lactone (**3**) was reduced with di-isobutyl aluminium hydride to form the corresponding lactol which was treated with the requisite Wittig reagent in benzene for 10 min. In this way, 9,15-bis(t-butyldimethylsilyl)prostaglandin $F_{2\alpha}$ methyl ester (**6**) was obtained in 79% yield from the lactone (**3**), together with a trace amount ($\leqslant$2%) of the isomer (**7**) after methylation and chromatography. The short reaction time is crucial: in agreement with a recent report[8] we found that, if the Wittig reaction was allowed to proceed for a substantially longer period of time, extensive scrambling of the silyl protecting group between O–C (9) and O–C (11) occurred.†

Pyridinium chlorochromate oxidation of the alcohol (**6**) gave the ketone (**8**) (89%). Attempts to desilylate the protected prostaglandin (**8**) using conventional reagents (*e.g.*



† Under the same Wittig conditions but with a reaction time of 24 h, the overall yield was unaffected, but the ratio (**6**) : (**7**) was 2 : 1.



SCHEME

aqueous $MeCO_2H$ or Bu_4NF) gave multicomponent mixtures of products but aqueous HF in acetonitrile[9] effected smooth desilylation to give (±)-prostaglandin D_2 methyl ester (**9**) (38%) and (±)-15-*epi*-prostaglandin D_2 methyl ester (**10**) (32%).

Thus (±)-prostaglandin D_2 methyl ester (**9**) is now available from the ketone (**1**) in eleven steps, and this represents the shortest and most practical route to this simple derivative of an important natural product.

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[1] E. E. Nishizawa, W. L. Miller, R. R. Gorman, and G. L. Bundy, *Prostaglandins*, 1975, **9**, 109.
[2] M. Hayashi and T. Tanouchi, *J. Org. Chem.*, 1973, **28**, 2115.
[3] E. F. Jenny, P. Schaublin, H. Fritz, and H. Fuhrer, *Tetrahedron Letters*, 1974, 2235.
[4] N. H. Anderson, S. C. Imamoto, and D. H. Picker, *Prostaglandins*, 1977, **14**, 61.
[5] Z. Grudzinski and S. M. Roberts, *J.C.S. Perkin I*, 1975, 1767.
[6] T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J.C.S. Perkin I*, 1978, 1176.
[7] P. Deslongchamps, *Tetrahedron*, 1975, **31**, 2463.
[8] Y. Torisawa, M. Shibasaki, and S. Ikegami, *Tetrahedron Letters*, 1979, 1865.
[9] D. P. Reynolds, R. F. Newton, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Letters*, 1979, 3981.