Total Synthesis of (±)-Prostaglandin D_1: Use of Triethylsilyl Protecting Groups†

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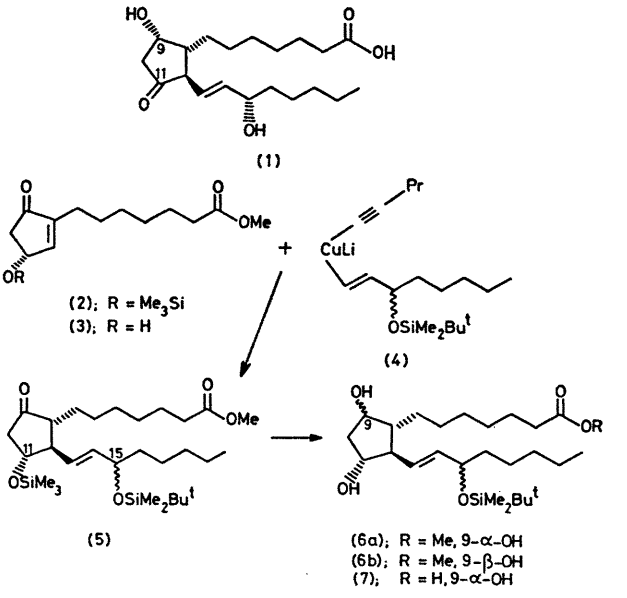
Summary (±)-Prostaglandin D_1 has been synthesised by oxidation of (±)-$PGF_{1\alpha}$ 15-t-butyldimethylsilyl ether and also of its 9-triethylsilyl ether; preparation and selective hydrolysis of triethylsilyl ethers are key steps in the sequence.

THE biosynthetic and structural studies associated with PGD_1 [(15*S*, 13*E*)-9α,15-dihydroxy-11-oxoprost-13-enoic acid] (**1**) were well described by 1972,[1] but since then there have been only a few reports on the chemistry and properties of this metabolite.[2] The total synthesis of PGD_1 is now described which involves oxidation studies on $PGF_{1\alpha}$ derivatives. The triethylsilyl group has been used to regioselectively protect and unmask hydroxy groups at C-9 and C-11. Previous work associated with the synthesis of PGD_2 involved non-selective oxidation of the C-9 and C-11 hydroxy groups of $PGF_{2\alpha}$ derivatives,[3] or lengthy sequences for protection at C-9 prior to oxidation at C-11.[4]

The synthesis of PGD_1 involves preparation of (±)-PGE_1 derivatives by conjugate addition of the organo-cuprate (**4**) to the trimethylsilyl ether (**2**) of the known 4-hydroxycyclopentenone (**3**).[5,6] Quenching the resulting enolate ion with

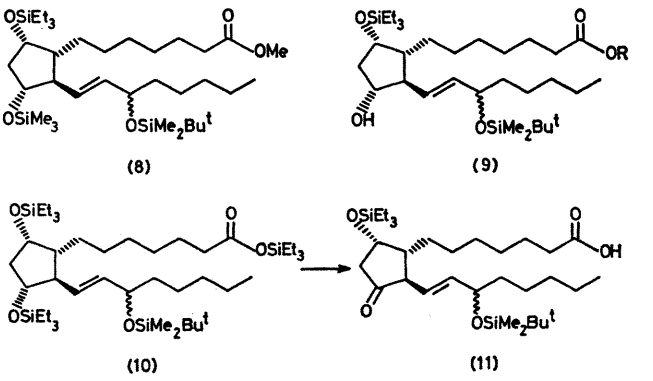


† The reactions were carried out with racemates to give (±)-prostaglandins and their (±)-15-epimers. However, since the starting materials (**2**) and (**3**) have been resolved, our sequence allows an asymmetric convergent synthesis of PGD_1.

ammonium sulphate in a two-phase ether–aqueous system allowed both silyl protecting groups at C-11 and C-15 to be retained. The PGE_1 derivative (**5**) was purified by dry column chromatography[7] (ethyl acetate–toluene, 1:3; R_F 0·64) and reduced with sodium borohydride[8] to give a 3:1 mixture of $PGF_{1\alpha}$ and $PGF_{1\beta}$ methyl esters protected only at C-15 (**6a** and **6b**). Isolation of the 9α-isomer (**6a**) by dry column chromatography (ethyl acetate–toluene, 1:1; R_F 0·29) followed by saponification (10% sodium hydroxide in 50% aqueous methanol at 20 °C for 2·5 h) gave $PGF_{1\alpha}$ 15-t-butyldimethylsilyl ether (**7**).

Regioselective oxidation at C-11 requires prior protection of the hydroxy group at C-9. Thus trimethylsilylation of the ester (**6a**) at C-11 with trimethylsilyldiethylamine[9] in acetone at −40 °C followed by triethylsilylation at C-9 with triethylsilyldiethylamine–triethylchlorosilane (10:1) at 20 °C for 20 h gives the fully protected $PGF_{1\alpha}$ derivative (**8**; 80%). Selective hydrolysis of the trimethylsilyl group using tetrahydrofuran (THF)–AcOH–H_2O (8:8:1) for 1·0 h at 20 °C gives the required intermediate (**9**; R = Me, 92%). Reaction with Jones reagent at −30 °C[3] followed by mild acid hydrolysis using AcOH–H_2O–THF (65:35:10) at 45 °C for 2·5 h gives the PGD_1 methyl ester (58%).

A more attractive and shorter route involves use of the same protecting group in the ring followed by selective hydrolysis. Thus (±)-$PGF_{1\alpha}$ 15-t-butyldimethylsilyl ether (**7**) was conveniently protected (see **10**) by triethylsilylation at C-1, C-9, and C-11 by treatment with triethylsilyl chloride in pyridine at 60 °C for 0·5 h (95%). Careful hydrolysis with THF–AcOH–H_2O (8:8:1) at 20 °C for 4 h cleaved the ester group and favoured hydrolysis (**9**; R = H) at C-11 (76%) over formation of the $PGF_{1\alpha}$ derivative (**7**; 21%). Oxidation with Jones reagent or better, buffered pyridinium chlorochromate, to give (**11**; 75%) followed by removal of both protecting groups at C-9 and C-15 with THF–AcOH–H_2O (10:65:35) at 45 °C for 3 h gives (±)-



PGD_1 (**1**; 75%), m.p. 75—77 °C, R_F 0·48, identical with an authentic material, and (±)-15-*epi*-PGD_1 (88%), R_F 0·52, which were separated by t.l.c. (ethyl acetate–formic acid, 80:1). Since the triethylsilyl group at C-11 is selectively removed under mild acidic conditions, hydrolysis in the presence of an oxidising agent will give the 11-oxo-derivative (**11**). Thus reaction of the (±)-$PGF_{1\alpha}$ 9,11-bistriethylsilyl ether (**10**) or its corresponding acid with a stoicheiometric two-fold excess of pyridinium chlorochromate and sodium acetate (2:1, w/w) in dichloromethane at 20 °C gives the PGD_1 derivative (**11**; 80%). The triethylsilyl protecting group has been similarly utilized in a synthesis of PGD_2.[10]

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