Total Synthesis of (±)-6β-Prostaglandin I_1

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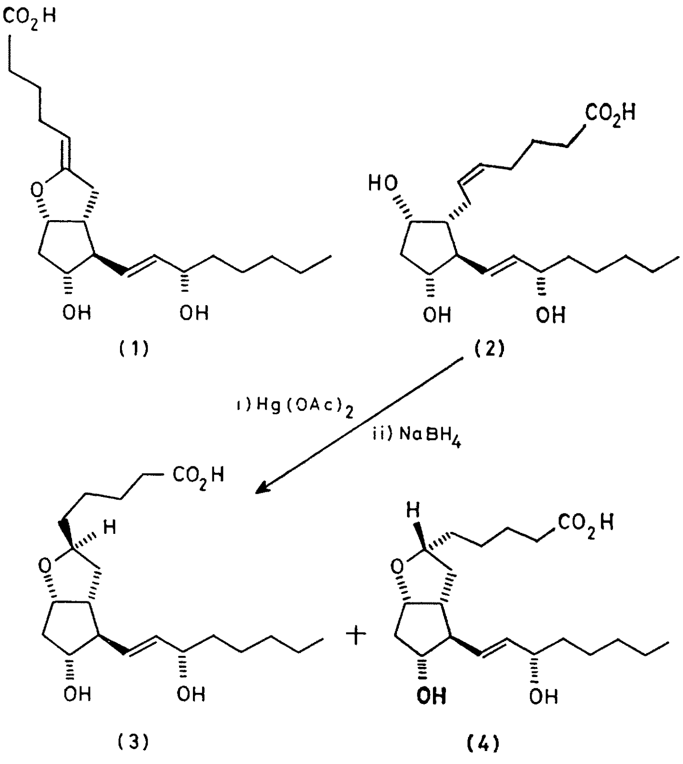
Summary (±)-6β-Prostaglandin I_1 (**3**) has been prepared from the readily available unsaturated aldehyde (**6**) in four steps.

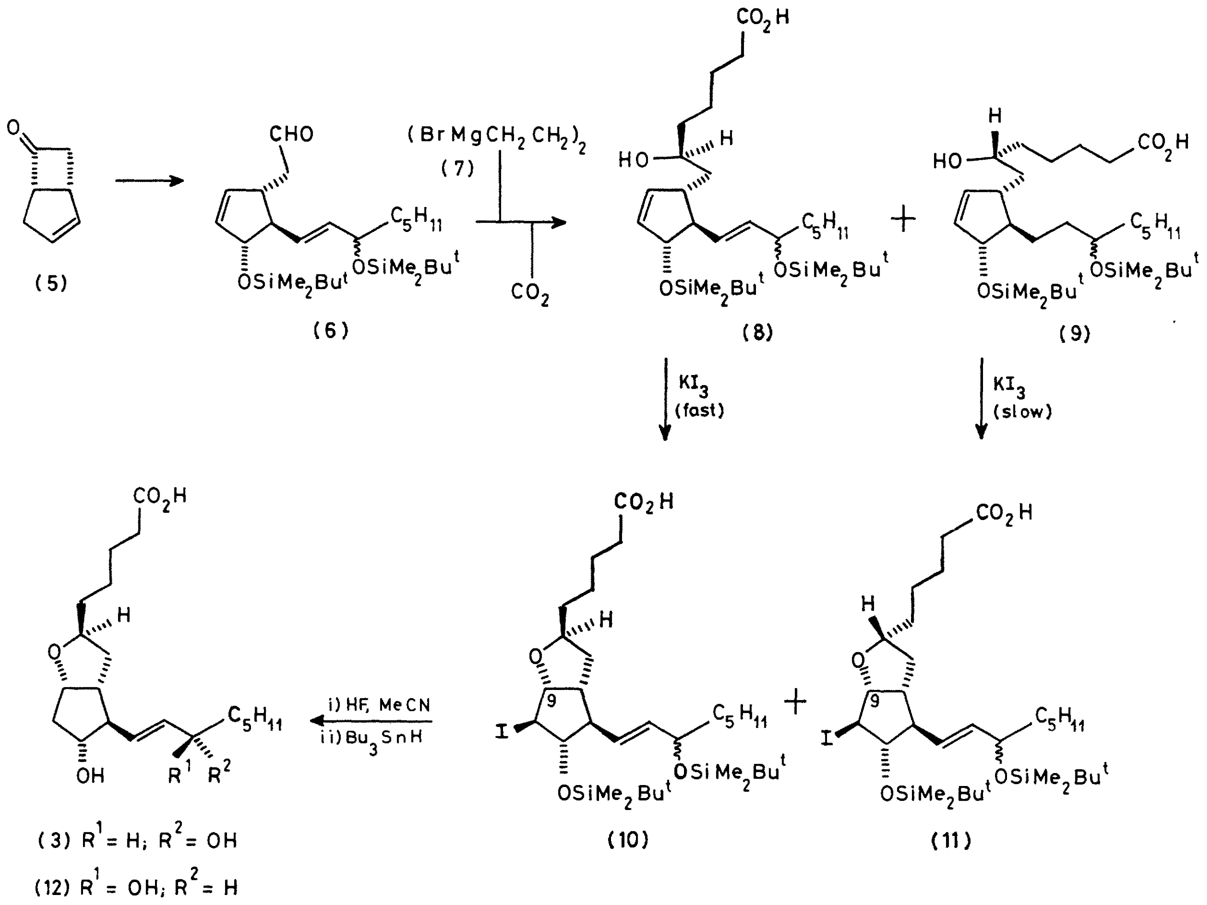
THE isolation and identification of prostaglandin I_2 (**1**) by Vane *et al.*[1] caused a resurgence of interest in prostaglandin chemistry since this compound was shown to be a very potent inhibitor of human blood platelet aggregation and a powerful vasodilator. Under neutral or acidic conditions prostaglandin I_2 is rapidly converted into 6-oxoprostaglandin $F_{1\alpha}$, a compound of greatly reduced biological activity. Various analogues of prostaglandin I_2 have been synthesised in an effort to discover a stable compound that retains the desirable biological properties of the natural material. For example, the two epimers of prostaglandin I_1 (**3**) and (**4**) have been prepared from prostaglandin $F_{2\alpha}$ (**2**) (Scheme 1)[2] and they have been shown to possess considerable biological activity.[3] We report a short, stereoselective, *de novo* synthesis of (±)-6β-prostaglandin I_1 (**3**) which is flexible enough to provide access to a wide range of analogues.

The unsaturated aldehyde (**6**) may be prepared from the ketone (**5**) (Scheme 2) in large quantities.[4] The aldehyde (**6**) was treated with an excess of the Grignard reagent (**7**)[5] in ether; after (**6**) had been completely consumed, dried carbon dioxide gas was passed through the reaction mixture. Adipic acid was removed from the resulting solution by washing with an aqueous solution of sodium hydrogen carbonate. Evaporation and short path column chromatography furnished a mixture of the diastereoisomeric alcohols (**8**) and (**9**) in 50% yield.



Ratio (3) : (4) *ca.* 2 : 1

SCHEME 1



SCHEME 2

Treatment of the mixture of (**8**) and (**9**) with potassium tri-iodide in tetrahydrofuran gave unchanged alcohol (**9**) (40%) and the iodo-ether (**10**) (34%) contaminated with a small amount (*ca.* 6%) of the isomeric iodo-ether (**11**). The ether (**10**) was purified by chromatography. The isomeric ethers were identified by n.m.r. spectroscopy, in particular by the chemical shift of 9-H.[3] Further quantities of the ethers (**10**) and (**11**) were obtained by recycling the alcohol (**9**) through a series of reactions involving Collins' oxidation, sodium borohydride reduction, and cyclization.

Presumably the degree of interaction of the acid side-chain and the five-membered ring dictates the relative rate of cyclization for the iodonium ions derived from the unsaturated alcohols (**8**) and (**9**) leading to the observed predominance of (**10**) over (**11**) if the reaction is curtailed before completion.

Deprotection and hydrodeiodination of the ether (**10**) gave (±)-6β-prostaglandin I_1 (**3**) and (±)-15-*epi*-6β-prostaglandin I_1 (**12**).

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