The Norbornadiene Route to Prostaglandin I_2 and Other Prostaglandins: Preparation and Rearrangement of 7-Substituted Norbornadienes

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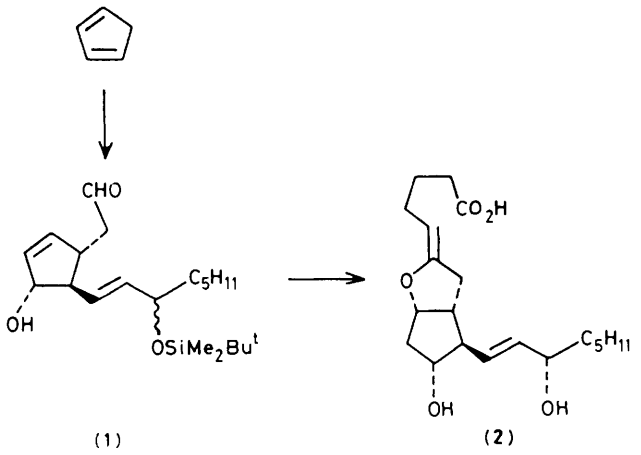
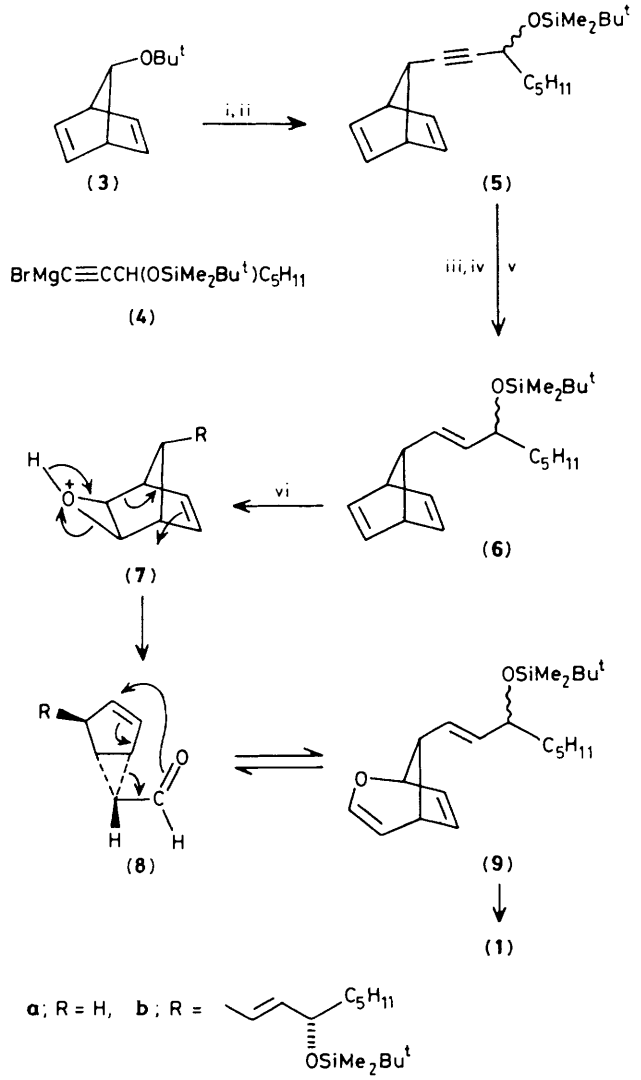
The cyclopentenylacetaldehyde (**1**) required for the synthesis of prostacyclin (prostaglandin I_2) and other prostanoids is now readily available from the preparation and rearrangement of 7-substituted norbornadienes.

The first *de novo* synthesis of prostacyclin (PGI_2) (**2**),[1] a potent inhibitor of blood platelet aggregation, involves eighteen steps from cyclopentadiene and requires the cyclopentenylacetaldehyde (**1**)[2] as the key intermediate (Scheme 1).[1] We have improved and simplified this synthesis by a study of the preparations and peracid oxidations of 7-substituted nor-



(1) (2)

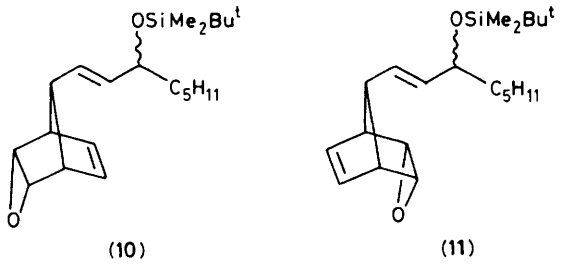
Scheme 1



Scheme 2. *Reagents:* i, HCl, diethyl ether; ii, (**4**); iii, Bu_4NF or HF; iv, $LiAlH_4$; v, $ClSiMe_2Bu^t$; vi, $MeCO_3H$, Na_2CO_3.

bornadienes whereby the first ten stages of the first synthesis have been replaced by five steps to give the key aldehyde (**1**) in acceptable yields. This approach also offers a feasible route to other prostanoids with a variety of lower side chains.

Although 7-t-butoxynorbornadiene (**3**) is known to react



(10) (11)

with simple primary alkyl and aryl Grignard reagents[3] it did not react with the alkynyl Grignard reagent (**4**). However, 7-chloronorbornadiene generated from 7-t-butoxynorbornadiene (**3**) by treatment with hydrogen chloride in diethyl ether,[4] reacted with reagent (**4**) in tetrahydrofuran in the presence of a catalytic amount of copper(I) chloride to give the 7-alkynylnorbornadiene (**5**) in 65% yield. That substitution had occurred at C-7 without rearrangement was confirmed by the ^1H n.m.r. spectrum which showed the four olefinic protons as two groups of signals centred at δ 6.75 and 6.68 and a singlet due to H-7 at δ 3.06. The 7-substituent was converted into the lower prostaglandin side chain prior to oxidative rearrangement. Thus deprotection of (**5**) by treatment with tetra-n-butylammonium fluoride or HF in acetonitrile followed by reduction with lithium aluminium hydride and reprotection with t-butyldimethylsilyl chloride afforded the corresponding allyl silyl ether (**6**) in 67% overall yield from (**5**). The first synthesis of this compound from 7-formylnorbornadiene[5] is a more difficult process and will be reported elsewhere.[6]

By analogy with norbornadiene which is known to give 6-formylbicyclo[3.1.0]hex-2-ene (**8a**) *via* the epoxide (**7a**) on peracid oxidation,[7] we hoped to obtain the bicyclic aldehyde (**8b**) from the *exo-anti*-epoxide (**7b**) intermediate. Treatment of the 7-alkenylnorbornadiene (**6**) with peracetic acid buffered with anhydrous sodium carbonate at 0 °C afforded the required aldehyde (**8b**)[2] which exists in equilibrium[8] with the less polar oxabicyclo[3.2.1]octa-3,6-diene (**9**). Hydrolysis of the latter gave the required hydroxycyclopentenylacetaldehyde (**1**), in 44% yield (Scheme 2). The *endo*-epoxides [(**10**) and (**11**), 22%] were also formed as minor products during the peracetic acid oxidation.

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