The Norbornadiene Route to Prostaglandin I₂ and Other Prostaglandins: Preparation and Rearrangement of 7-Substituted Norbornadienes

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The cyclopentenylacetaldehyde (1) required for the synthesis of prostacyclin (prostaglandin l_2) and other prostanoids is now readily available from the preparation and rearrangement of 7-substituted norbornadienes.

The first de novo synthesis of prostacyclin (PGI₂) (2), a potent inhibitor of blood platelet aggregation, involves eighteen steps from cyclopentadiene and requires the cyclopentenylacetalde-

hyde (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-

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CHO
$$C_{5}H_{11}$$

$$OSiMe_{2}Bu^{t}$$

$$C_{5}H_{11}$$

$$OH$$

$$OH$$

$$C_{5}H_{11}$$

$$OSiMe_{2}Bu^{t}$$

Scheme 2. Reagents: i, HCl, diethyl ether; ii, (4); iii, Bu₄NF or HF; iv, LiAlH₄; v, ClSiMe₂Bu^t; vi, MeCO₃H, Na₂CO₃.

ŌSiMe 2But

bornadienes whereby the first ten stages of the first synthesis have been replaced by five steps to give the key aldehyde (1) in acceptable yields.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

$$\begin{array}{c} OSi\,Me_2Bu^t \\ \hline \\ C_5H_{11} \\ \hline \\ O \end{array}$$

with simple primary alkyl and aryl Grignard reagents3 it did not react with the alkynyl Grignard reagent (4). However, 7chloronorbornadiene 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(1) 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-formylnorbornadiene⁵ 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, 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 equilibrium8 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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