

Total Synthesis of Prostaglandin-A₂ through SN' Reaction of an Allylic Epoxide and a Heterocuprate Reagent

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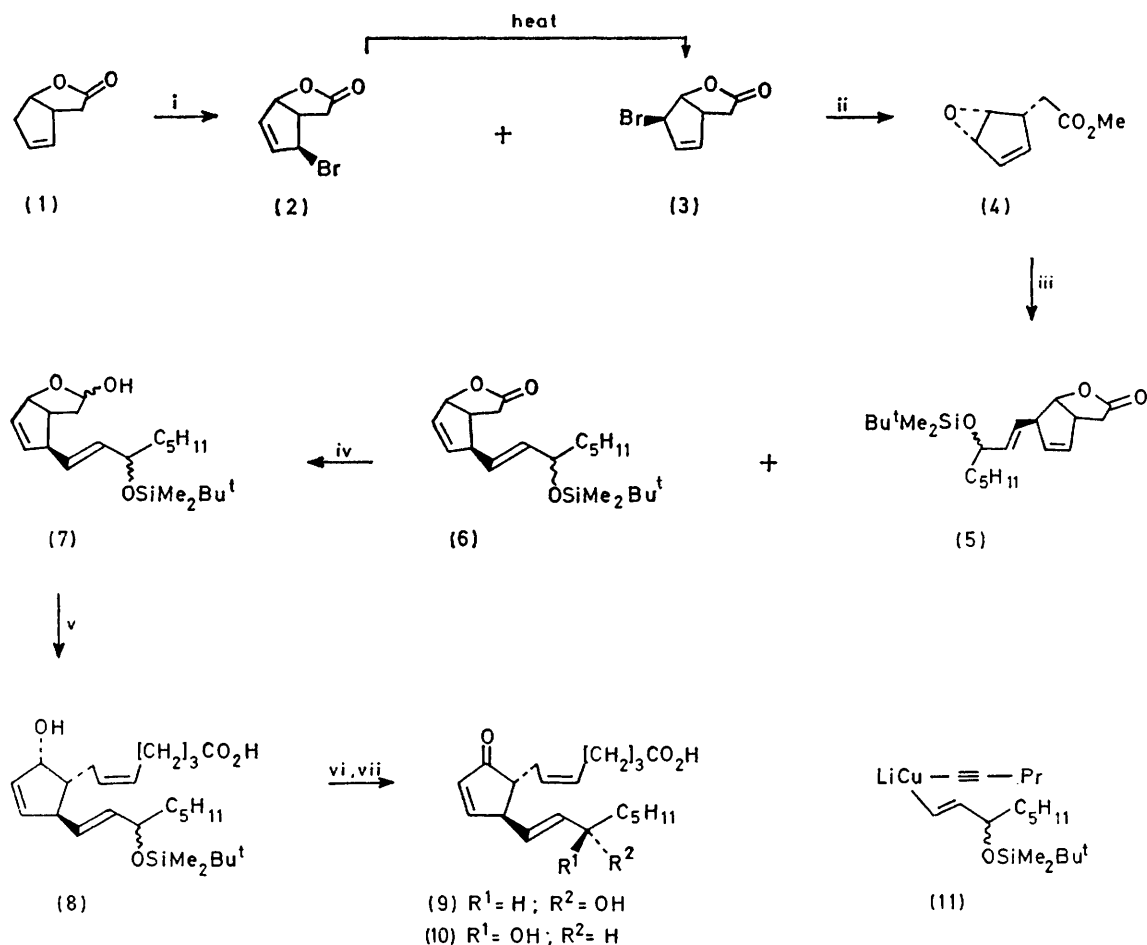
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Summary The epoxyester (4) reacted with the cuprate reagent (11) in SN' fashion preferentially to give the lactone (6) which could be readily converted into prostaglandin-A₂.

PROSTAGLANDIN-A₂ (9) is a naturally occurring material and is particularly abundant, as an ester, in the Caribbean coral *Plexaura homomalla* (Var.S).¹ The observed biological activity of this prostaglandin² has prompted a

search for *de novo* syntheses and a number of successful pathways have been described.³ We report a new high yield route to prostaglandin-A₂ which involves seven steps from the readily available bicyclic lactone (1).⁴

Allylic bromination of (1) using *N*-bromosuccinimide in boiling carbon tetrachloride containing a catalytic amount of benzoyl peroxide gave a mixture of the allyl bromides (2) and (3) as well as trace amounts of other bromolactones. From this mixture, the bromolactone (3) crystallized in 35%



Reagents: i, *N*-Bromosuccinimide, *hν*, CCl_4 . ii, K_2CO_3 , MeOH, Et_2O . iii, Reagent (11), -78°C . iv, Di-isobutylaluminium hydride. v, $\text{Ph}_2\text{PCH}[\text{CH}_2]_3\text{CO}^-$. vi, Collins oxidation. vii, H_2O MeCO₂H, tetrahydrofuran.

yield; further quantities of the lactone (3) could be obtained on heating the oily residue from the crystallization that was rich in the lactone (2). Anionotropy furnished a mixture of the lactones (2) and (3) in the ratio 1:4 from which (3) could be crystallized. Repetition of this process enabled the bromolactone (3) to be obtained from (1) in 50% yield.

On reaction with potassium carbonate in ether-methanol the bromolactone (3) gave, as the key intermediate, the epoxyester (4) in 85% yield and reaction of this epoxyester with the heterocuprate reagent (11) in ether at -78°C gave, after chromatography, the lactone (6) (43%) (the product of an SN' reaction) and the lactone (5) (14%).⁵ Partial reduction of the lactone (6) using di-isobutylaluminium

hydride produced the lactol (7) in quantitative yield and reaction of this lactol with the appropriate Wittig reagent gave the cyclopentenol (8) (70%). Collins oxidation of the prostanoic acid (8) (70%) and deprotection (70%) gave equal quantities of prostaglandin-A₂ (9) and the less polar 15 *epi*-prostaglandin-A₂ (10) after chromatography over silica. Biological and chromatographic data indicated that the sample of (\pm)-prostaglandin-A₂ prepared in the above manner was identical with authentic material.

We thank the S.R.C. and Glaxo-Allenburys Ltd. (C.A.S.E. awards to M. A. W. F. and T. V. L.) for financial support.

(Received, 30th March 1979, Com. 342.)

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⁵ See C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, preceding communication.