Total Synthesis of Prostaglandin-A_2 through *SN'* Reaction of an Allylic Epoxide and a Heterocuprate Reagent

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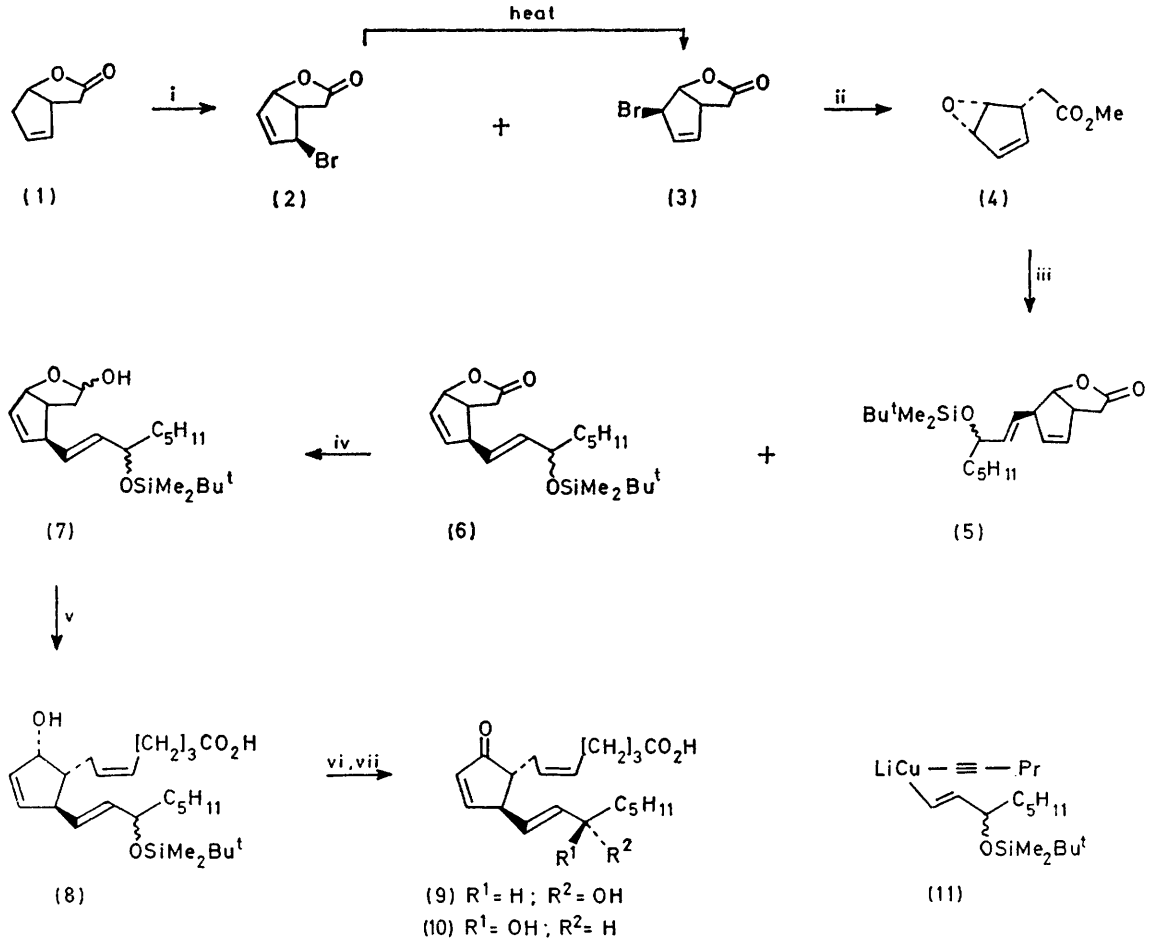
Summary The epoxyester (**4**) reacted with the cuprate reagent (**11**) in *SN'* fashion preferentially to give the lactone (**6**) which could be readlily converted into prostaglandin-A_2.

PROSTAGLANDIN-A_2 (**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 prostaglandin[2] 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-A_2 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, $Ph_3PCH[CH_2]_3CO^-$. vi, Collins oxidation. vii, H_2O $MeCO_2H$, 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 epoxide 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 prostanoid (**8**) (70%) and deprotection (70%) gave equal quantities of prostaglandin-A_2 (**9**) and the less polar 15 *epi*-prostaglandin-A_2 (**10**) after chromatography over silica. Biological and chromatographic data indicated that the sample of (±)-prostaglandin-A_2 prepared in the above manner was identical with authentic material.

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[1] W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, *J. Amer. Chem. Soc.*, 1977, **99**, 1222.
[2] J. R. Weeks, *Science*, 1973, **181**, 370; J. Buendia, M. Vivat, E. Toromanoff, and J. Martel, *Bull. Soc. chim. France* (II), 1978, 140 and references therein.
[3] E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95**, 6831; E. J. Corey and J. Mann, *ibid.*, p. 6832; G. Stork and S. Raucher, *ibid.*, 1976, **98**, 1583; D. F. Taber, *ibid.*, 1977, **99**, 3514; E. J. Corey, G. W. J. Fleet, and M. Kato, *Tetrahedron Letters*, 1973, 3963; J. Martel, E. Toromanoff, J. Mathieu, and G. Nomine, *ibid.*, 1972, 1491.
[4] P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
[5] See C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, preceding communication.