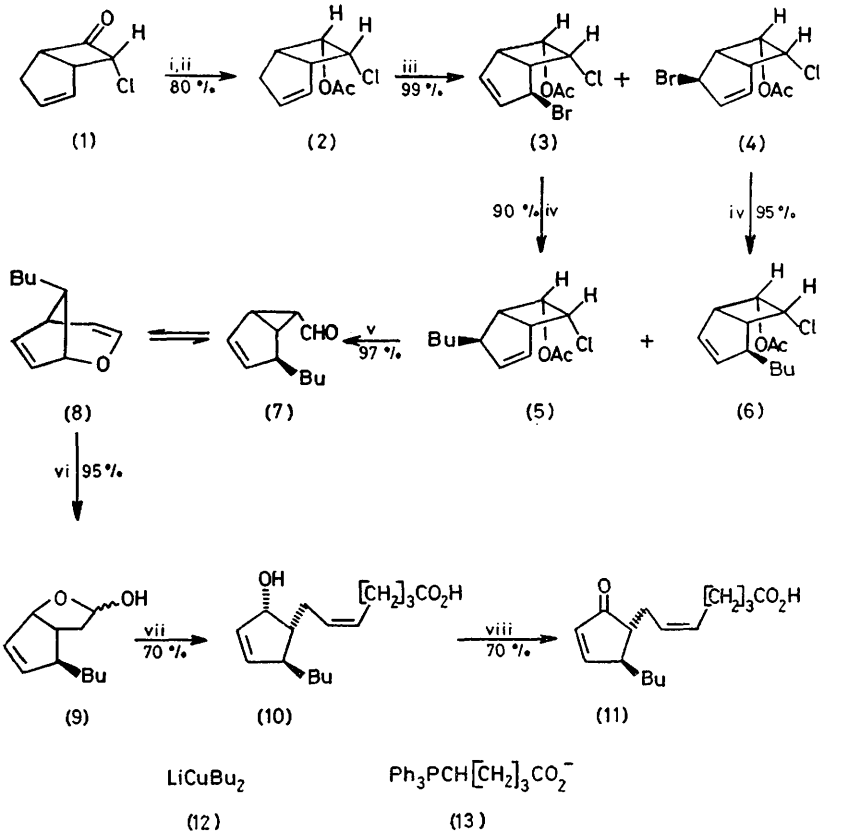
Synthesis of 12-Alkyl Analogues of Prostaglandin-A_2

By CHRISTOPHER B. CHAPLEO and STANLEY M. ROBERTS*
(The Ramage Laboratories, Department of Chemistry and Applied Chemistry, Salford University, Salford, Lancs. M5 4WT)
and ROGER F. NEWTON*
[Chemical Research Department, Glaxo-Allenburys Research (Ware) Ltd., Ware, Herts. SG12 0DJ]

Summary The prostaglandin-A_2 analogue (**11**) has been prepared *via* an *SN' syn* reaction involving the halogeno-esters (**3**) and (**4**) with a butyl cuprate reagent.

IN view of the biological interest in prostaglandin A congeners,[1] we required a synthetic route to prostaglandin A_2 analogues in which the octenol side chain was replaced by a simple alkyl group. Our new method of preparation of these compounds is illustrated by the synthesis of the butyl-compound (**11**) which involves eight steps from the readily available chloroketone (**1**)[2] and an overall yield of 35%.



(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13)

Reagents: i, $NaBH_4$, EtOH. ii, Ac_2O, C_5H_5N. iii, *N*-Bromo-succinimide, *hν*, CCl_4. iv, Reagent (**12**), −78 °C, tetrahydro-furan. v, NaOMe–MeOH. vi, $(CO_2H)_2$–H_2O. vii, Reagent (**13**). viii, Collins oxidation.

Regiospecific borohydride reduction of the ketone (**1**)[3,4] followed by acetylation furnished the ester (**2**) which on photon-induced bromination employing *N*-bromosuccinimide (NBS) in carbon tetrachloride gave a mixture of the dihalogenoacetates (**3**) and (**4**). This mixture reacted with the cuprate reagent (**12**) in tetrahydrofuran at −78 °C to give a mixture of the butylbicycloheptenones (**5**) and (**6**).[5] Sodium methoxide in methanol at room temperature converted this mixture into the cyclopropylaldehyde (**7**) which exists in equilibrium with the 2-oxabicyclo[3.2.1]-octa-3,6-diene (**8**) at ambient temperature.[6] An aqueous solution of oxalic acid effected hydrolysis of the cyclic enol (**8**) and furnished the lactol (**9**) in practically quantitative yields.[7] A Wittig reaction involving the lactol (**9**) and the reagent (**13**) gave the prostanoid (**10**) which was subjected to a Jones oxidation procedure to form the desired cyclopentenone derivative (**11**).

We observed that the compound (**11**) possesses potent analgaesic properties.

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[1] J. R. Weeks, *Science*, 1973, **181**, 370.
[2] For an alternative synthetic route to related prostaglandin-A_1 analogues see J. B. Wiel and F. Rouessac, *J.C.S. Chem. Comm.*, 1976, 446.
[3] M. Rey, S. M. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **53**, 417.
[4] P. R. Brook, A. J. Duke, and J. R. C. Duke, *J.C.S. Chem. Comm.*, 1970, 574.
[5] C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, preceding communication.
[6] *cf.* M. Rey and A. S. Dreiding, *Helv. Chim. Acta*, 1965, **48**, 1987; P. R. Brook, A. J. Duke, J. M. Harrison, M. Rey, S. M. Roberts, and A. S. Dreiding, *Helv. Chim. Acta*, 1977, **60**, 1528; see also K. Harding and J. M. Trotter, *J. Org. Chem.*, 1977, **42**, 4157.
[7] These reaction conditions were suggested by M. Rey and A. S. Dreiding from their unpublished work on related systems.