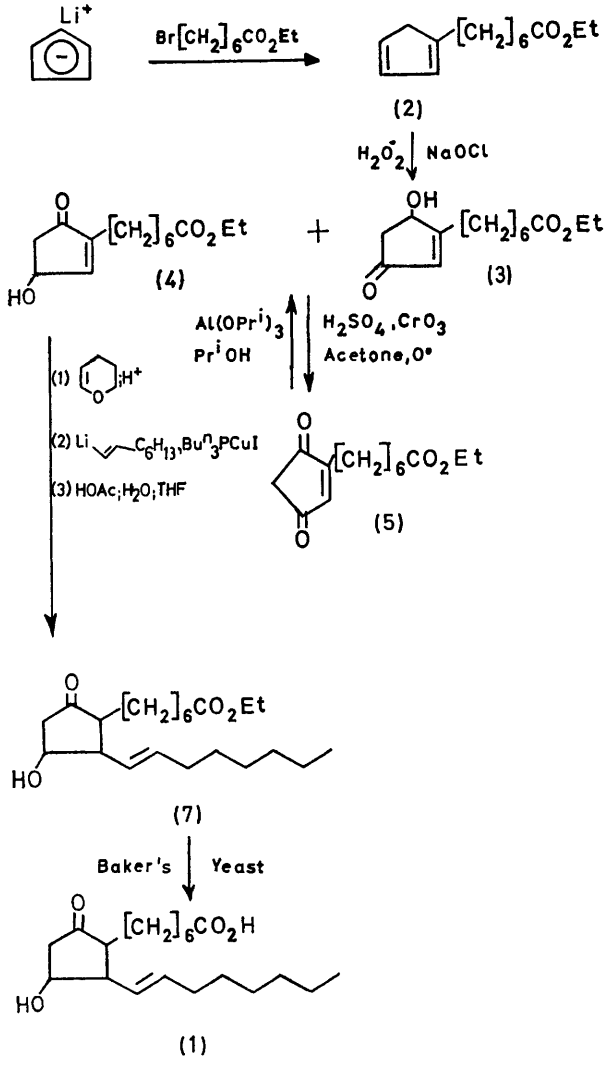
Total Synthesis of (±)-15-Deoxyprostaglandin E_1

By CHARLES J. SIH,* ROBERT G. SALOMON, PHILIP PRICE, GEORGE PERUZZOTI, and RATTAN SOOD
(*School of Pharmacy, University of Wisconsin, Madison, Wisconsin* 53706)

Summary A method for the preparation of (±)-15-deoxyprostaglandin E_1 (**1**) is described.

WE report the first synthesis of (±)-15-deoxyprostaglandin E_1 (**1**), a potential penultimate intermediate for micro-



SCHEME.

biological transformation into the naturally occurring prostaglandin E_1 (PGE_1).

The synthetic sequence is outlined in the Scheme. Alkylation of lithium cyclopentadienide with ethyl 7-bromoheptanoate[1] in tetrahydrofuran at 25° afforded the alkylated cyclopentadiene (**2**) in essentially quantitative yield. The diene (**2**) was used immediately in a 1,4-cycloaddition to chemically-generated singlet oxygen by the reaction of sodium hypochlorite and hydrogen peroxide[2] at −10° in ethanol† to give a mixture of hydroxycyclopentenones (**3**) and (**4**)[3] which were characterised by n.m.r. and u.v. spectroscopy. These positional isomers were separated by column chromatography on silicic acid using benzene–ethyl acetate. Alternatively, this mixture was oxidized with Jones reagent at 0° to yield (**5**),‡ m.p. 43—45°, which was then reduced with aluminum isopropoxide[4] back to (**3**) and (**4**) in a ratio of 1:2. Treatment of (**4**) with an excess of dihydropyran at 25° in the presence of an acid catalyst gave the tetrahydropyranyl ether (**6**).‡ (**6**) was then treated with two molar equivalents of 1-lithio-*trans*-oct-1-ene,[5] in the presence of a molar equivalent of tri-n-butylphosphine–copper(I) iodide complex[6] at 0° in ether. After removing the tetrahydropyranyl protecting group,[7] (±)-15-deoxyprostaglandin E_1 ethyl ester (**7**)‡ [60% yield from (**4**)] was obtained. The *trans*-stereochemistry of the double bond remains unchanged during the 1,4-addition on the basis of the n.m.r. and i.r. spectral data. Furthermore, it has been shown by Casey and Boggs[8] that the addition of both lithium di-*cis*- and di-*trans*-prop-1-enylcuprate to cyclohex-2-enone is completely stereospecific. The synthetic sequence was completed by exposure of (**7**) to baker's yeast yielding (±)-15-deoxyprostaglandin E_1§ (**1**)‡ (52%, not optimized).

The application of 1,4-addition of nucleophilic C_8 synthons for the efficient elaboration of the prostanoic acid skeleton is in progress.

We thank Professor Charles Casey for bringing the vinylcopper reaction to our attention, Professor Howard Whitlock for helpful suggestions, and Professor Carl Buckner for the pharmacological assays. This investigation was supported by research grants from the National Institutes of Health and the Wisconsin Alumni Research Foundation.

(*Received*, 26*th November* 1971; *Com.* 2035.)

† The yield varied from 20—40%. Reaction of the corresponding methyl ester in methanol at −10° improved the yield to 55%; the ratio of the positional isomers (**3**) and (**4**) varied from 1—**4**:1, respectively, depending on the reaction conditions.

‡ Characterised by n.m.r. and u.v. data.

§ In the guinea pig tracheal strip assay, (±)-15-deoxyPGE_1 (**1**) has 10% of the activity of PGE_1.

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