

A HIGHLY EFFICIENT ROUTE TO A KEY INTERMEDIATE
FOR THE SYNTHESIS OF A PROSTAGLANDINS

E. J. Corey and Paul A. Grieco

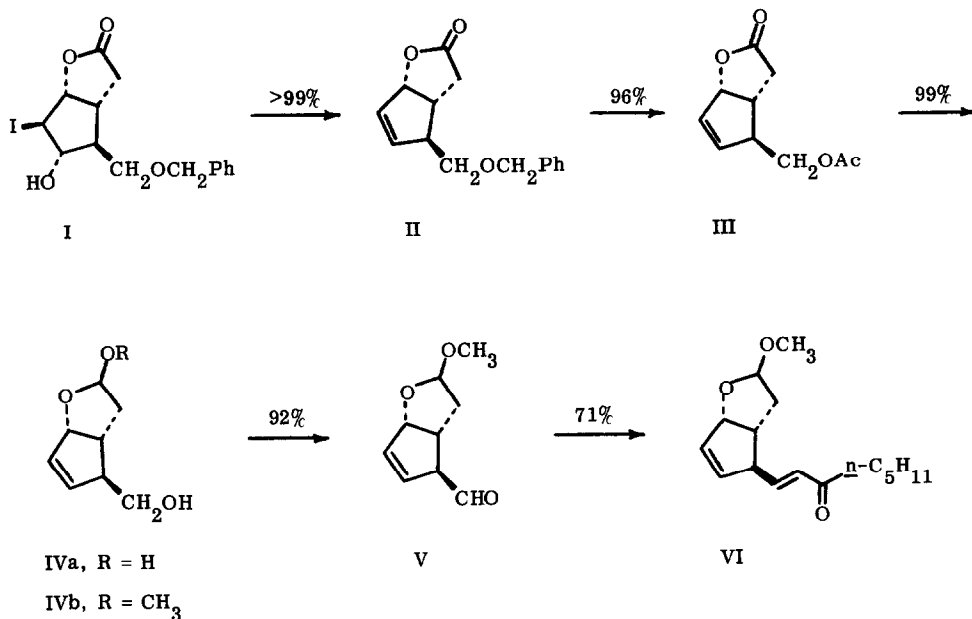
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

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The iodo lactone I, which has been used as a key intermediate for the synthesis of the six natural primary prostaglandins, is readily available by a synthetic process in which the average yield per step is 95% (1-4). Although the A prostaglandins can be derived from the primary E prostaglandins by dehydration of the β -ketol unit of the latter, it has also been of interest to effect a more direct synthesis of the A series. In this note we describe a synthesis of the key intermediate VI from which A prostaglandins are available directly using the transformations developed previously in these laboratories for elaboration of the carboxylic side chain. The average yield per step for the synthesis of VI from I is 94% and in consequence the prostaglandin A precursor VI is now also very readily available.

The first step in the process leading to VI involves a novel elimination reaction. Treatment of the iodo lactone I (4), $[\alpha]_D^{28} -39.3^\circ$ ($c = 0.975$ in CH_3OH), in dry pyridine (6 ml./g. of I) with 1.3 equiv. of methanesulfonyl chloride at -20° for 2 hr. and then 0° for 1.5 hr. afforded after quenching with ice-cold saturated sodium thiosulfate solution and extractive isolation with ether, the unsaturated lactone II (5) in >99% yield as a colorless oil, $[\alpha]_D^{28} +205.3^\circ$ ($c = 1.0$ in CHCl_3), which was homogeneous by thin layer chromatographic (t. l. c.) analysis. This conversion of I to II is noteworthy because of its high efficiency and the fact that with methanesulfonyl chloride activation the elimination of the iodo hydrin is effected under extremely mild conditions without need for the customary reducing agent (e. g., Zn or SnCl_2).

The unsaturated lactone II was transformed into the acetate III in one step using excess acetic anhydride and a boron trifluoride etherate (0.1 ml./g. of II) at 0° for 20 min. Evaporation of excess acetic anhydride, extractive work-up, and filtration through silica gel using benzene--ether, gave III (5) as a colorless oil, $[\alpha]_D^{24} +226.7^\circ$ ($c = 1.73$ in CHCl_3), which was homogeneous by t. l. c. analysis in 94-98% yield. Treatment of the acetoxy lactone III with 4 mole equiv. of diisobutylaluminum hydride in toluene at -78° for 2.5 hr. yielded the oily hemiacetal IVa (5a) after addition of methanol and extractive work-up using ethyl acetate as solvent, and this was converted to the cyclic methyl acetal IVb (5a) by reaction with a catalytic amount of boron trifluoride in methanol at -20° for 1.5 hr. and 0° for 1 hr. Oxidation of IVb with



the Collins reagent (6) gave the aldehyde V (92%) (5a) which was directly transformed into the liquid enone VI (5) in 71% yield by reaction with the sodio derivative of dimethyl 2-oxoheptylphosphonate in dry dimethoxyethane at 0° for 45 min. (7).

The elimination employed here for the one-step conversion of I to II may be mechanistically related to the Cornforth procedure (8) for the conversion of epoxides to olefins by reaction of iodide ion in acetic acid to form iodohydrin and subsequent reaction with a reagent prepared from stannous chloride and phosphorus oxychloride in pyridine. It is not clear whether in the Cornforth process the stannous chloride is involved in the elimination or whether it merely functions to reduce the iodine formed by elimination. Our results imply the latter possibility and suggest that the function of phosphorus oxychloride may be analogous to that of methanesulfonyl chloride in the conversion of I to II (9, 10).

References

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5. Satisfactory (a) nuclear magnetic resonance and infrared spectra and (b) high resolution mass spectra were obtained for a sample of this intermediate which was homogeneous by t.l.c. analysis.
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9. Subsequent to the completion of our work, we have learned of a similar transformation of the methyl ether analog of I to that of II by a process similar to that recorded here (Dr. Pierre Crabbé, Syntex Corp., personal communication).
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