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NUCLEOPHILIC INVERSION AT C_{11} OF PROSTAGLANDIN INTERMEDIATES

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The inversion of selected asymmetric centers in intermediates related to those in the Corey synthesis[1] provides a route for the preparation of prostaglandin stereoisomers[2]. We report here our studies related to the inversion of the C_{11}-hydroxyl group[3] in the optically active intermediates 1a and 2a. The application of these results to the synthesis of 11-epi-$PGF_{2\alpha}$ and 11-epi-PGE_2 is described in the following communication.

The reaction of tetraethylammonium formate or acetate with the tosylates 1b or 2b in dry acetone resulted in formation of the corresponding inverted formates (3d and 5d) or acetates (3c and 5c) contaminated only with the respective elimination products (4 and 6). A summary of these results is presented in Table I below.

Table I

Selectivity of Nucleophilic Displacement

Substrate	Nucleophile	% Nucleophilic Displacement[a]	Crude Yield of Products
1a	OAc	65-70	90[b]
1a	OCHO	85-87	90[b]
2a	OAc	50-55	∿100%
2a	OCHO	60-63	∿100%

(a) The displacement percentages were determined by NMR and elimination products accounted for the remaining material.

(b) The lower yields relative to substrate 2b were caused by greater water solubility of 3c and 3d.

In general, a solution of 100 mg of the substrate was heated under reflux for 30 minutes in 15 ml of dry acetone saturated with the recrystallized quaternary ammonium salt. Percentages of nucleophilic displacement and elimination products were easily obtained by NMR ($CDCl_3$) analysis of the crude product mixtures after removal of water soluble materials. It is evident from the results that formate anion is the superior nucleophile and that elimination occurs to a greater extent in substrate **2b**. Other influencing factors not evident in Table I were inferred from individual experiments performed with the above substrates. Thus, the use of mesylate as a leaving group gave a 2:1 ratio of elimination to displacement using tetraethylammonium acetate with compound **1a**. The purity of the starting tosylate also had a significant effect on this ratio, resulting in more elimination with impure material. Addition of 5-10% of a polar solvent (DMF, HMPA) resulted in a 15-20% increase in elimination for both formate and acetate, again using the methyl ether substrate.

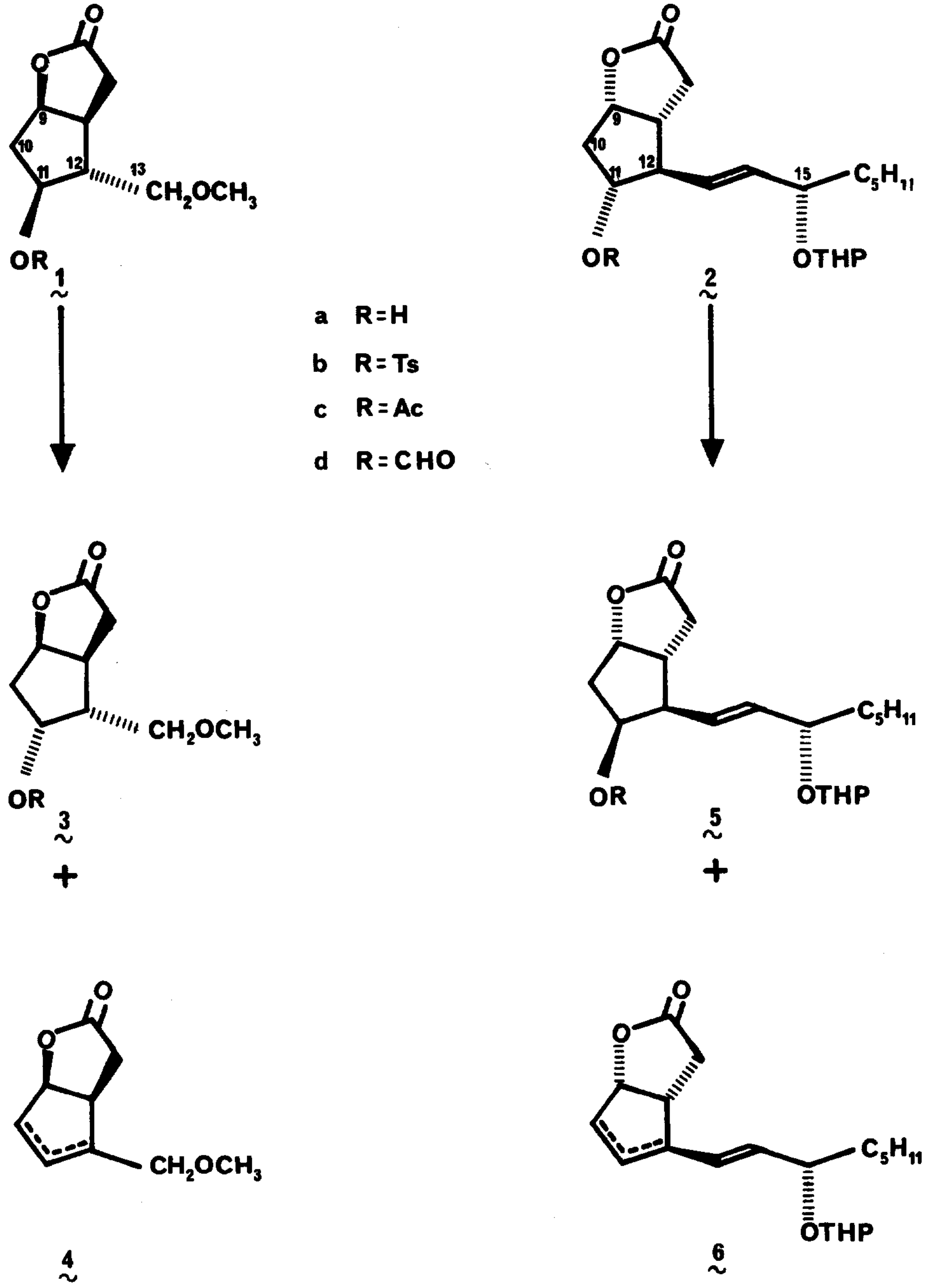
Evidence for the stereoselectivity of displacement was obtained by NMR analysis for each example listed in Table I. A downfield shift ($\sim$20 cps) of the C_9-proton was noted in deuteriochloroform for all inverted isomers relative to the authentic acetates (**1c** and **2c**) and formates (**1d** and **2d**). Use of deuteriobenzene also resulted in a significant difference in chemical shifts of the isomeric acetate and formate protons except for the formates **2d** and **5d**, where the difference was too small even at 220 Mc for quantitative purposes. Integration of the NMR spectra ($CDCl_3$ and C_6D_6) of the crude reaction mixtures after removal of water-soluble materials demonstrated that complete inversion had occurred to within the limits of detection by the NMR method (±5%).

References

1) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, V. Koelliker and N. M. Weinshenker, ibid., 92, 397 (1970).

2) See also E. J. Corey and S. Terashima, Tetrahedron Letters, 111 (1972).

3) The numbering refers to that used for the prostanoic acid ring system; see U. S. Von Euler and R. Eliasson, "Prostaglandins," Academic Press, New York, 1967, p. 14.



a R=H

b R=Ts

c R=Ac

d R=CHO