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RING EXPANSION REACTIONS OF 11-NOR PGE_2. SYNTHESIS OF NEW LACTONE, LACTAM AND CYCLOPENTANONE PROSTANOIDS[1]

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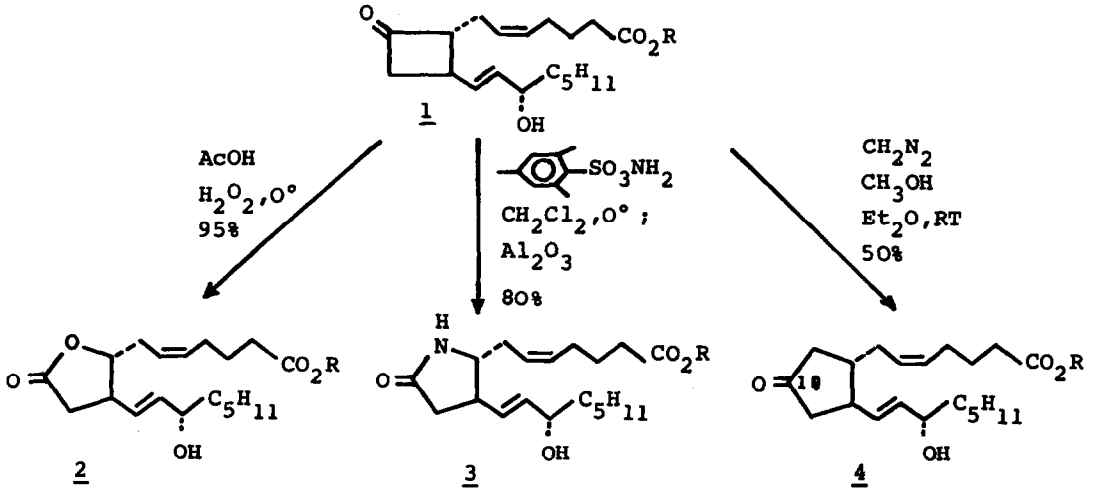
Recently we described an efficient synthesis of 11-nor PGE_2 (1) from the readily available adduct of cyclopentadiene and dichloroketene[3]. In developing this synthesis we had in mind the possibility of subsequently taking advantage of the reactive nature of (1) to effect certain transformations that would lead to novel modified prostaglandins. We now wish to report three regioselective ring expansion reactions of this cyclobutanone (1) that are carried out under exceedingly mild conditions and give rise directly to new lactone, lactam, and cyclopentanone prostanoids in high yield.



11-Nor PGE_2 (1a) in aqueous acetic acid at 0° was treated with an excess of 30% aqueous hydrogen peroxide[4] to smoothly afford a single product[5], 15α-hydroxy-10-oxo-9-oxaprosta-5,13-dienoic acid (2a), in 95% yield[6,7]. Esterification of this novel lactone prostaglandin (2a) with ethereal diazomethane gave the ester-lactone (2b) [I.R. : ν_{max} (film) 3450, 1775, 1740 cm^{-1} ; N.M.R.: $\delta(CCl_4)$ 3.70 (s, 3-H), 4.05 (m, 2-H), 5.60 ppm (m, 4-H) ; m/e = 352 (M^+)].

Similarly, treatment of (1b) in methylene chloride at 0° with an excess of O-mesitylenesulfonylhydroxylamine followed by adsorption on basic alumina and elution with methanol[8], readily gave the new lactam prostaglandin, methyl 15α-hydroxy-10-oxo-9-azaprosta-5,13-dienoate (3b)[5] [mp 76-77°; I.R. : ν(film) 3300, 1735, 1690 cm^{-1} ; N.M.R. : $\delta(CDCl_3)$ 3.40 (m, 1-H), 3.70 (s, 3-H), 4.12 (m, 1-H), 5.55 ppm (m, 4-H) ; m/e = 351 (M^+)] in 80% yield[7,9,10].

In addition, the previously unreported methyl 15α-hydroxy-10-oxoprosta-5,13-dienoate (4b)[5] [I.R. : ν_{max} (CCl_4) 3500, 1740 cm^{-1} ; N.M.R. : $\delta(CCl_4)$ 3.60 (s, 3-H), 4.00 (m, 1-H), 5.40 ppm (m, 4-H) ; m/e = 350 (M^+)] was obtained in 50% isolated yield, together with 11-desoxy PGE_2 methyl ester (25% yield), by carefully controlled treatment of (1b) at room temperature with diazomethane in 5:1 diethyl ether-methanol solution, followed by chromatographic separation on silica gel[7,11]. The ester (4b) was then hydrolysed to the corresponding acid (4a) quantitatively with aqueous MeOH-K_2CO_3. Surprisingly, this represents one of the first examples of a cyclobutanone ring enlargement with diazomethane.

The above transformations illustrate the flexibility of 11-nor PGE_2 (1) as a common intermediate in the facile synthesis of novel prostaglandins. We are currently pursuing additional modifications of this compound.

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5. This product was judged to be free of isomeric impurities by NMR and TLC analysis.
6. For examples of other oxa-prostaglandins, see : J.F. Fried, M.M. Mehra, and W.L. Kao, J. Amer. Chem. Soc., 93, 5594 (1971) ; F.M. Hauser and R.C. Huffman, Tetrahedron Lett., 905 (1974) ; G.J. Laurens and J.M. Koekemoer, ibid., 3715, 3719 (1975) and references cited.
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