Tetrahedron Letters No. 19, pp 1761 - 1763, 1974. Pergamon Press. Printed in Great Britain.

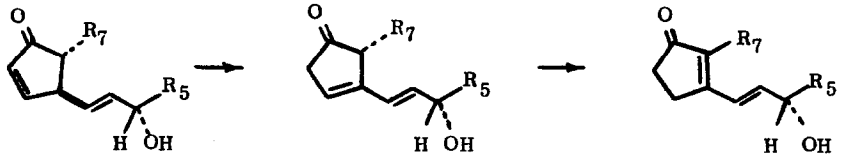
TRANSFORMATION OF PROSTAGLANDIN A_2 INTO PROSTAGLANDIN C_2

E. J. Corey and Clifford R. Cyr

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 28 February 1974; received in UK for publication 3 April 1974)

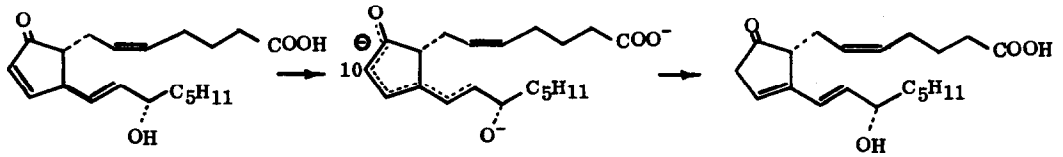
Prostaglandins of the C series have recently been identified as intermediates in the deactivating conversion of A prostaglandins to B prostaglandins in mammalian blood.[1] In addition, the C prostaglandins have been found to possess high biological activity. We have recently described[2] a stereocontrolled total synthesis of prostaglandin (PG) C_2 using the bicyclo[2.2.1]heptane approach[3] via



PGA PGC PGB

intermediates which also lead to PGA_2.[4,5] Another method for the synthesis of PGC_2(II), directly from PGA_2 (I), is described herein.

The method envisioned for conversion of PGA_2 to PGC_2 involves generation of a γ-extended enolate ion (III) by proton abstraction from C-12 followed by α-protonation (at C-10) under conditions which do not destroy the highly sensitive PGC_2 so formed. Such a deconjugation process finds precedent in earlier work, for example, the Δ^4-3-keto steroid $\rightarrow$ Δ^5-3-keto steroid transformation.[6] In practice it was found that the choice of basic reagent was unexpectedly critical. In all experiments the enolate-forming process was conducted for no more than a minute, the enolate was quenched at low temperatures with acetic acid-methanol and the product was recovered by rapid extraction at 0° from pH 4 buffer. PGC_2 is stable under the conditions used for isolation.



Best results were obtained with t-butoxide or t-amyloxide ion as base. The procedure using the former reagent is as follows: A solution of 0.65 ml of 1 M potassium t-butoxide in t-butyl alcohol was added to 2 ml of dry tetrahydrofuran (THF) at -23° (dry ice - CCl_4 bath) under argon. A precooled (-23°) solution of 40 mg (0.12 mmole) of PGA_2 in 2 ml of THF was then added at once with rapid stirring. After 1 min 1.0 ml of a cold (-23°) solution (1.75 M) of acetic acid in methanol was added at once and the resulting mixture was stirred rapidly at -23° for 15 sec and then poured into a cold (0°) mixture of pH 4 phosphate buffer (5%) and ether. After separation of phases and rapid extraction of the aqueous part with three 40-ml portions of ether, the ethereal extracts were washed with saturated sodium chloride solution, dried ($CaSO_4$), and concentrated in vacuo to give crude PGC_2 (II) (36 mg) as a pale yellow oil. Analysis of the reaction mixture by thin layer chromatography and ultraviolet absorption indicated contamination of the PGC_2 by variable amounts of PGA_2 and PGB_2. Pure PGC_2 was isolated (30% yield) by preparative thin layer chromatography on silica gel using benzene-THF-acetic acid (70:25:1); R_f values were: PGC_2 0.64; PGA_2 and PGB_2 0.55. Unambiguous identification of PGC_2 was made by (1) ultraviolet absorption[1] (λ max in CH_3OH 234 nm, $\epsilon = 17,000$), (2) infrared absorption[1] (carbonyl stretch at 1750 cm^{-1} due to cyclopentanone and 1715 cm^{-1} due to carboxyl, in $CHCl_3$), (3) nmr spectrum, (4) mass spectrum[1] of the methyl ester and (5) rapid and quantitative conversion to PGB_2 by a trace of base in methanol at 25°.

The use of the following strong bases in excess under conditions similar to those of the above-described experiment led only to the recovery of PGA_2: t-butyllithium, lithium bistrimethylsilylamide, sodium bistrimethylsilylamide, lithium N-isopropyl-N-cyclohexylamide, lithium diisopropylamide and lithium tetramethylpiperidide. These bases evidently deprotonate I selectively at C-8 rather than at C-12.[7] Tritylllithium reacted mainly to form the 1,4-addition product (cf. ref 7). Lithium methylsulfinylcarbanide in dimethylsulfoxide[8] afforded PGC_2 (ca. 25%), PGB_2 (ca. 30%) and a third unidentified product (ca. 45%).

Using the procedure given above, PGC_2 can now be prepared conveniently from the more stable (and more readily available) PGA_2.[9]

References

1. (a) R. L. Jones, J. Lipid Res., 13, 511 (1972); (b) R. L. Jones and S. Cammock, Advan. Biol. Sci., 9, 61 (1973).
2. E. J. Corey and G. Moinet, J. Amer. Chem. Soc., 95, 7185 (1973).
3. See, J. S. Bindra, A. Grodski, T. K. Schaaf and E. J. Corey, ibid., 95, 7522 (1973) and references cited therein.
4. E. J. Corey and G. Moinet, ibid., 95, 6831 (1973).
5. For a synthesis of 8-methylprostaglandin C_2 see, E. J. Corey and H. S. Sachdev, ibid., 95, 8484 (1973).
6. See, E. Shapiro, L. Weber, E. P. Oliveto, H. L. Herzog, R. Neri, S. Tolksdorf and M. Tanabe, Steroids, 8, 461 (1966).
7. See, R. A. Lee and W. Reusch, Tetrahedron Lett., 969 (1973), for an interesting study of enolate vs γ-extended enolate formation with various bases.
8. E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 87, 1345 (1965).

9. This work was supported by the U.S. Agency for International Development and the National Institutes of Health.