Tetrahedron Letters No. 28, pp 2439 - 2440, 1974. Pergamon Press. Printed in Great Britain.

A SHORT SYNTHETIC ROUTE TO PROSTAGLANDINS UTILIZING POSITION-SELECTIVE EPOXIDE OPENING BY THE VINYL GILMAN REAGENT

E. J. Corey, Kyriacos C. Nicolaou and David J. Beames

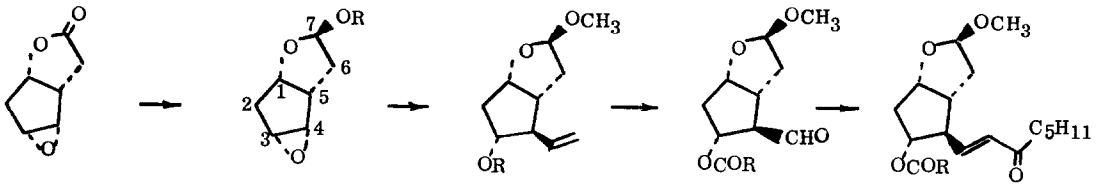
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

(Received in USA 6 May 1974; received in UK for publication 31 May 1974)

The epoxy lactone I, which is readily available from cyclopentadiene,[1,2] was used some time ago as a key intermediate in an early total synthesis[1a] of prostaglandins. Although the route which was followed was quite short, it suffered from unfavorable position ("regio") selectivity in one step which involved attachment of the omega chain to the five-membered ring [at C(12)] by epoxide displacement. It has now been discovered that this problem can be overcome by use of divinylcopperlithium (vinyl Gilman reagent) in the epoxide opening step.

Reduction of the oxido lactone I with diisobutylaluminum hydride in toluene at -78° for 3 hr. yields quantitatively the oxido lactol II, R=H (mixture of epimers about C-7), from which the oxido lactol methyl ether II, R=CH_3, mp 53-54°, is obtained quantitatively using 0.04 equiv. of boron fluoride etherate in excess methanol at -20° for 24 hr. The exo orientation of methoxy at C(7) in this product was established by pmr studies using shift reagents.[3,4] Use of shorter reaction times or more mild conditions afforded not only II, R=CH_3, but also the C(7) epimeric methyl ether (endo orientation of OCH_3). Reaction of II with 7 equiv. of vinyl Gilman reagent in ether at -20° for 15 hr. resulted in the formation of III, R=H, as the major product together with a minor amount of the position isomer resulting from attack of vinyl at C(3) [ratio of attack at C(4) to attack at C(3), 81:19 by pmr and vpc analyses; total yield 94%]. Treatment of III, R=H, with p-phenylphenylisocyanate and triethylamine in tetrahydrofuran at 25° for 15 hr., followed by chromatographic separation and recrystallization, gave the vinyl urethane III, R=p-$C_6H_5C_6H_4NHCO$, mp 161-163°, in 72% overall yield from II. Oxidation of III, R=p-$C_6H_5C_6H_4NHCO$, with sodium metaperiodate in the presence of a catalytic amount of osmium tetroxide in water-tetrahydrofuran-t-butyl alcohol at 25° and ca. pH 5 afforded the aldehyde IV, R=p-$C_6H_5C_6H_4NH$, as a colorless solid which was further converted by reaction with the sodio derivative of dimethyl-2-oxoheptylphosphonate[5] in dimethoxyethane at 0° to the enone V (60% overall from the urethane III). The pathway from V to various prostaglandins is well established.[6,7]

We have also studied the crucial oxide displacement process with the t-butyldimethylsilyl and tribenzylsilyl ether analogs of the intermediate II and vinyl Gilman reagent and have obtained almost identical results in all three cases. In our earlier studies[1a] reagents such as diisobutylaluminum cyanide, alkali cyanides, hydrogen cyanide, salts of nitromethane and vinylic lithium compounds were found to be unsatisfactory with regard to position selectivity (and in some cases also total yield) in oxide displacement.



I II III IV V

The synthetic route to prostaglandins described herein is convenient and direct.[8,9]

REFERENCES

1. See (a) E. J. Corey, Z. Arnold and J. Hutton, Tetrahedron Letters, 307 (1970) and E. J. Corey and R. Noyori, ibid., 311 (1970); and (b) E. J. Corey and J. Mann, J. Amer. Chem. Soc., 95, 6832 (1973), for optical resolution.
2. J. J. Partridge, N. K. Chadha and M. R. Uskoković, J. Amer. Chem. Soc., 95, 7171 (1973).
3. The downfield shifts in the pmr spectra induced by Eu(fod)$_3$ of the proton at C(1) and the CH_3O protons were much smaller for II than for the corresponding protons of the endo C(7) epimer whereas the shift of the proton at C(7) in II was greater than for the C(7) proton of the epimer with 7-endo methoxy.
4. Satisfactory infrared, pmr and high resolution mass spectra were obtained on intermediates II-V reported herein. All intermediates used in the present study were racemic.
5. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker and N. M. Weinshenker, J. Amer. Chem. Soc., 92, 397 (1970).
6. See (a) E. J. Corey, K. B. Becker and R. K. Varma, ibid., 94, 8616 (1972); (b) E. J. Corey and G. Moinet, ibid., 95, 6831 (1973), and other references cited therein.
7. We have also prepared the p-phenylbenzoate esters of the series III-V and have correlated these derivatives with substances prepared in earlier studies; see, E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, ibid., 93, 1491 (1971).
8. A related synthesis in which an oxido cyclopentane is cleaved by an ethynyl-alane reagent with position selectivity has been described by the Chicago group; see, J. Fried et al., J. Amer. Chem. Soc., 94, 4342, 4343 (1972) and J. Fried and J. C. Sih, Tetrahedron Letters, 3899 (1973).

9. This work was assisted financially by grants from the National Institutes of Health and the U.S. Agency for International Development.