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A SIMPLE ROUTE TO A KEY INTERMEDIATE FOR THE SYNTHESIS OF 11-DESOXYPROSTAGLANDINS

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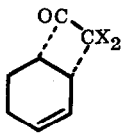
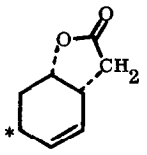
11-Desoxyprostaglandins are of considerable current interest as possible substrates for microbiological hydroxylation at C(11) (prostanoid numbering) and elsewhere, as possible antagonists of the prostaglandins in the E and F series, and as hypotensive agents (1). We record here an especially simple and effective synthetic approach to these substances.

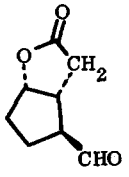
Bicyclo[4.2.0]oct-2-en-7-one (I) was prepared from 1,3-cyclohexadiene following a previously developed procedure for the conversion of cyclopentadiene to bicyclo[3.2.0]hept-2-en-6-one (2,3). The 1:1 adduct from 1,3-cyclohexadiene and dichloroketene (II) was obtained in 78% yield by the simultaneous addition over 4 hr. of hexane solutions of dichloroacetyl chloride (2.1 equiv.) and triethylamine (2 equiv.) to 1,3-cyclohexadiene at 22-28° with a further 4-hr. reaction period at 26°. Dechlorination of II was effected by treatment with 5 equiv. of zinc in acetic acid at 45-50° (1.5 hr.) followed by another equiv. of zinc at 70-75° (10 min.) to afford I as a colorless liquid, b.p. 85-90° (22 mm.), infrared max. 1775 $cm.^{-1}$ (C=O) and 1640 $cm.^{-1}$ (C=C), in 95% yield (4,5). Selective oxidation of I to the unsaturated γ-lactone III (4) could be carried out in ca. 95% yield either by the previously described technique (2) (dropwise addition of 2.4 equiv. of 30% hydrogen peroxide over 45 min. to I in 9:1 acetic acid--water at 0° and further reaction of the homogeneous solution for 16 hr. at 0-5°) or by reaction with excess (10 equiv.) hydrogen peroxide in basic (pH ca. 10) 1:1 methanol--water solution at 0° for 25 min. The lactone III was obtained as a colorless oil, infrared max. at 1775 $cm.^{-1}$ ($CHCl_3$), showing a single peak by gas chromatographic analysis on a 3% OV-7 column at 150° and only a single spot by thin-layer chromatographic analysis (R_f 0.45 on silica gel using 5% ether in benzene). Reaction of III with thallium(III) nitrate in methanol under conditions previously described (6) for the conversion of cyclohexene to cyclopentane carboxaldehyde afforded complex mixtures containing only moderate amounts of the desired aldehyde IV. However, after considerable experimentation it was discovered that the desired rearrangement of III to IV could be conducted effectively using 1.6 equiv. of thallium(III) nitrate in water which was 0.5 M in perchloric acid and 4.0 M in sodium perchlorate at 25-28° for 0.5 hr. The lactone--aldehyde IV (4b) so obtained was unaffected under acidic conditions which cause enolization and hence the formyl group must be in the more stable trans relationship



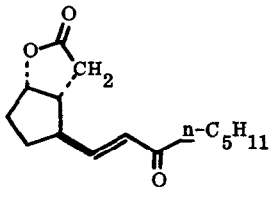
I, X = H
II, X = Cl



III



IV



V

to the lactone ring. Treatment of IV with the sodio derivative (from NaH) of dimethyl 2-oxoheptylphosphonate (7-10) (1.12 equiv.) in dimethoxyethane at 0° for 1.5 hr. and 25° for 0.5 hr. afforded after purification by simple chromatography the enone V as a colorless oil (4) in 70% overall yield from III. The infrared spectrum of V (in $CHCl_3$) as expected showed bands due to s-trans (1670 and 1655 $cm.^{-1}$) and s-cis (1690 and 1630 $cm.^{-1}$) conformational forms (11); an ultraviolet absorption max. (CH_3OH) occurred at 225 nm. (log ϵ 4.16).

The intermediate V can be converted by the methods previously described (9) to 11-desoxy analogs of the F_α and E primary prostaglandins (in 3 and 6 steps, respectively, for $F_{2\alpha}$ and E_2). Consequently, 11-desoxy prostaglandins are now accessible by a short and efficient synthetic approach through a common intermediate. The enone V is an especially promising substrate for the microbiological hydroxylation approach. Finally, adaptation of this synthesis to provide another purely chemical route to natural prostaglandins is possible, and to this end we are now studying the conversion of the unsaturated lactone III to the requisite allylically hydroxylated derivative (III, OH at C*) (12).

References

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4. Satisfactory (a) analytical and (b) spectroscopic data were obtained for this intermediate.

5. An alternative but less efficient procedure for the preparation of I has recently been described by L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, Tetrahedron, 27, 615 (1971).

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