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# A TOTAL SYNTHESIS OF PROSTAGLANDIN $F_{2\alpha}$ (dl) FROM 2-OXABICYCLO[3.3.0]OCT-6-EN-3-ONE

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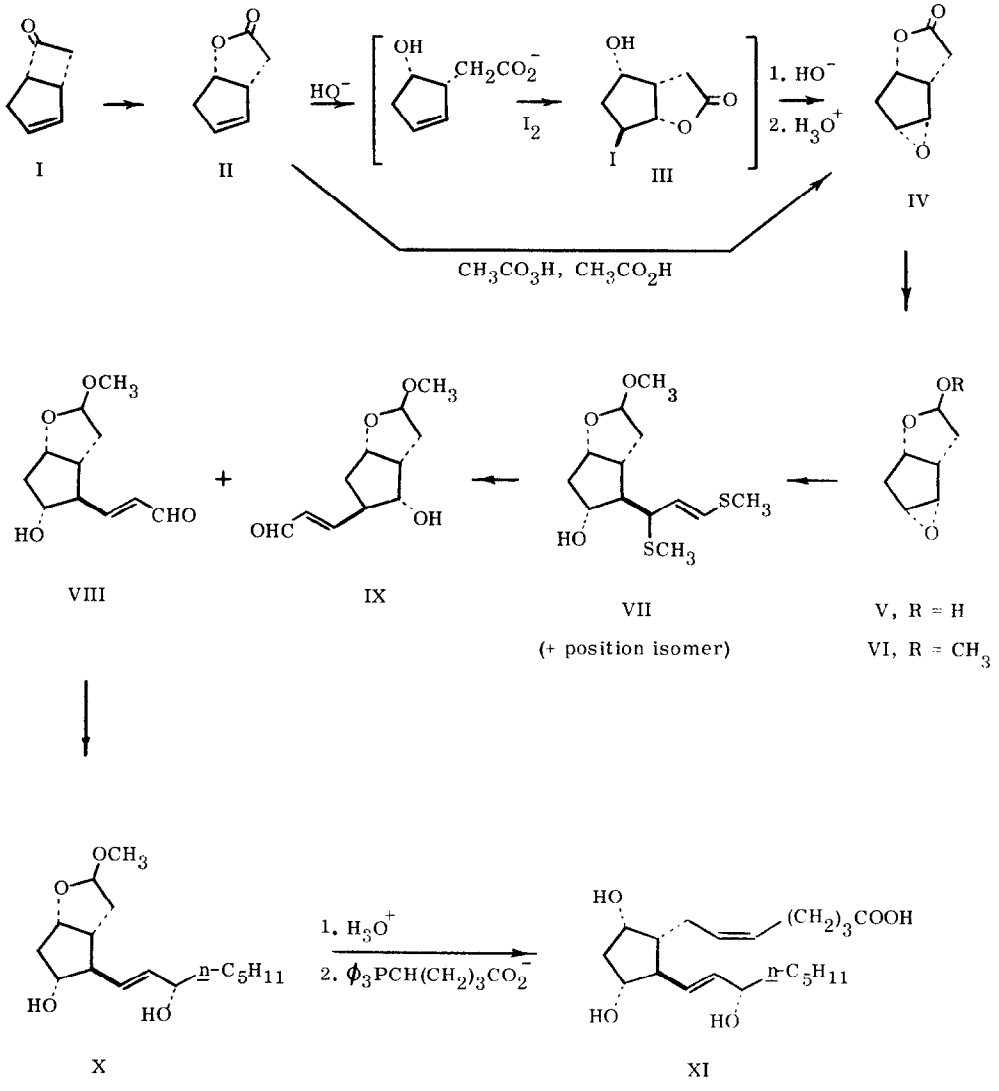
The preceding paper describes a simple and efficient conversion of bicyclo[3.2.0]hept-5-en-2-one (I) into 2-oxabicyclo[3.3.0]oct-6-en-3-one (II) by reaction with 30% hydrogen peroxide in acetic acid. The unsaturated lactone II is a possible starting point for the synthesis of prostaglandins by a number of reasonable pathways. In this note we describe one such synthetic approach which has been applied to the synthesis of racemic prostaglandin $F_{2\alpha}$.

Saponification of the unsaturated lactone II with 2 equiv. of aqueous alkali followed by neutralization ($CO_2$) and iodination at 0° (16 hr.) using excess potassium triiodide (3 equiv.) afforded the iodo lactone III. This intermediate was treated directly with aqueous alkali (to effect hydrolysis of the lactone and cyclization of the resulting iodohydrin) followed by dilute hydrochloric acid (for relactonization) to produce the pure oxido lactone IV (1), m.p. 87-88° (from benzene), in fair yield. The sequence of stereo-controlled operations used for the generation of IV from II insures that the stereochemistry of the oxido lactone IV is cis-syn-cis as shown. Interestingly, the same oxido lactone could be obtained in good yield from II simply by reaction with commercial 40% peracetic acid (1.5 equiv.) in acetic acid at 25° for 16 hr. followed by a standard work-up and recrystallization from benzene. The epoxidation of II under these conditions produced in 96% yield a mixture containing mainly II (89%) with only a minor amount (11%) of the cis-anti-cis stereoisomer. The desired stereoselective epoxidation reaction was observed only in acetic acid medium. The use of peracid (m-chloroperbenzoic acid) in a variety of other solvents gave results as follows (solvent, ratio of syn to anti oxido lactone): n-hexane, 4; cyclohexane, 2.7; benzene, 0.89; carbon tetrachloride, 0.67; methylene chloride, 2.3; chloroform, 1.3; ether, 0.93; ethyl acetate, 1.0; t-butyl alcohol, 1.1.

Reduction of the cis-syn-cis-oxido lactone IV with 1 equiv. of diisobutylaluminum hydride in toluene at -78° for 3 hr. proceeded smoothly to give the oily oxido lactol V (1) in 98% yield (2). Treatment of V with excess methanol containing a catalytic amount (ca. 0.015 equiv.) of boron trifluoride etherate at -20° for 1.5 hr. and then at 0° for 1 hr. produced the cyclic acetal VI (1), m.p. 53-54° (from cyclohexane), in 70% yield without damage to the oxide function. The oxido acetal VI was next subjected to reaction with 1.05 equiv. of 1,3-bis(methylthio)allyllithium (3) in tetrahydrofuran under argon at -78° for 4 hr. (at which time the dark red color of the reagent had been discharged) to give a mixture of isomeric products containing the desired coupling product VII. This mixture was hydrolyzed without separation using


I
II
HO⁻
OH
CH2CO2⁻
I2
OH
O
O
I
III
1. HO⁻
2. H3O⁺
IV
CH3CO3H, CH3CO2H
OCH3
O
HO
CHO
VIII
+
OCH3
O
OHC
OH
IX
OCH3
O
HO
SCH3
SCH3
VII
(+ position isomer)
OR
O
O
V, R = H
VI, R = CH3
OCH3
O
HO
n-C5H11
HO
X
1. H3O⁺
2. ϕ3PCH(CH2)3CO2⁻
HO
(CH2)3COOH
n-C5H11
HO
HO
XI

mercuric chloride--calcium carbonate in acetonitrile--water (4 : 1) under argon at 50° for 3 hr. to give a mixture of two unsaturated aldehydes which were separated by preparative layer chromatography on silica gel using ether for development. The more polar component ($R_f$ 0.45), obtained in 30% yield, proved to be the desired hydroxy aldehyde VIII (1), m.p. 100-102° (from benzene), whereas the less polar component ($R_f$ 0.58) (40% yield) could be assigned the position-isomeric structure IX (1). Reaction of the aldehyde VIII with n-amyllithium led quantitatively to a mixture of epimeric secondary alcohols in approximately equal amounts. The more polar component ($R_f$ 0.23) (X) (1) was converted to prostaglandin $F_{2\alpha}$ by hydrolysis using 0.03 N hydrogen chloride in 2 : 1 acetonitrile--water at 25° for 2 hr. followed by isolation of the resulting lactol and reaction with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid in dimethyl sulfoxide (2). The product so obtained was identical spectroscopically and chromatographically with an authentic sample of dl-prostaglandin $F_{2\alpha}$ (2). In the same way the epimer of X ($R_f$ 0.31) was converted in two steps to dl-15-epi-prostaglandin $F_{2\alpha}$.

The synthetic route from II to prostaglandin $F_{2\alpha}$ which is outlined above is attractive because of its directness. Its utility is diminished, however, by the occurrence of ring opening in both possible directions in the reaction of the oxide VI with 1,3-bis(methylthio)allyllithium. If this difficulty could be removed, the synthesis might be made competitive with that described earlier (2, 4).

## REFERENCES

1. Satisfactory analytical (or mass spectral), infrared, and nuclear magnetic resonance data were obtained for this intermediate.
2. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, J. Am. Chem. Soc. 91, 5675 (1969).
3. The preparation and reactions of this new reagent will be described in a subsequent publication, E. J. Corey and B. W. Erickson, in preparation. The reagent functions as a nucleophilic equivalent of the synthon -CH=CHCHO.
4. This work was supported by a grant from the National Institutes of Health.