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A BIOGENETIC APPROACH TO THE SYNTHESIS OF A PROSTANOID PRECURSOR.

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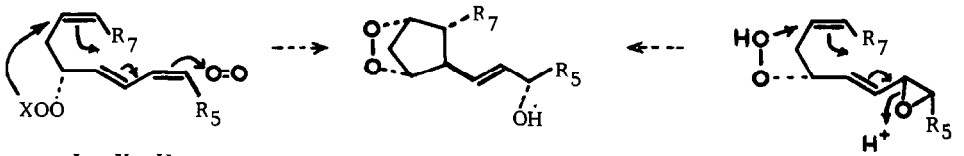
The endoperoxide II has been shown to be a key intermediate in the synthesis of primary (E and F) prostaglandins from C_{20} unsaturated fatty acids such as all cis-eicosa-8, 11, 14-trienoic acid.[1] The first step in the process appears to be hydroperoxidation of the starting fatty acid to Ia or Ib, however details of the cyclization to form II are lacking. The biosynthesis of II is most commonly considered to proceed from Ib by the radical induced cyclization which is depicted in expression I. Another possibility, which to our knowledge has not received consideration previously and which in principle also appears plausible, is the cationic cyclization of the 14, 15-epoxy-11-hydroperoxide III, as shown. This note describes a synthetic approach to prostaglandins which contains some of the elements implicit in scheme III.

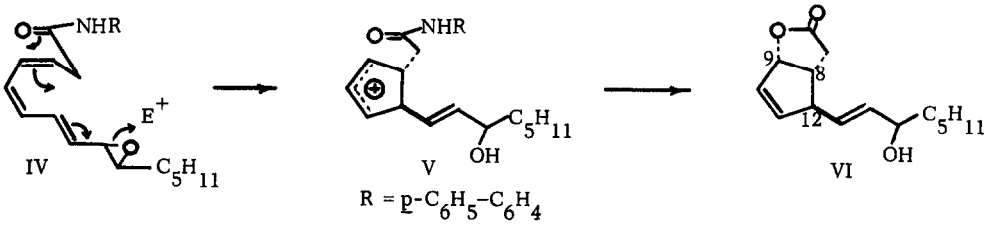


Ia, X = H
Ib, X = •

II

III

The lactone VI is a key intermediate in recently developed syntheses of prostaglandins.[2,3] It is evident that this structure could result from a cationic cyclization process starting from the triene-amide-oxide IV as illustrated. Such a cyclization can be regarded as an example of the familiar pentadienyl cation → cyclopentenyl cation type,[4,5] which is an especially facile ring closure reaction. The acetyl amide side chain in the intermediate allylic cation V is a potential neighboring group which can deliver an oxygen substituent specifically to C(9) and simultaneously control the cis arrangement of substituents at C(9) and C(8). The trans orientation of substituents at C(8) and C(12) would be expected on thermodynamic and kinetic grounds. The triene IV was synthesized by the route indicated in the chart.



R = p-C_6H_5-C_6H_4

Oct-2-yn-1-ol was reduced[6] to trans-oct-2-en-1-ol by lithium aluminum hydride in 94% yield. Treatment with m-chloroperbenzoic acid in methylene chloride at room temperature for forty hours gave the epoxyoctanol VII, m.p. 33-34°, (64% yield) which was quantitatively oxidized to the epoxyaldehyde VIII, m.p. -8°, using Collins reagent. The overall yield of the epoxyaldehyde from oct-2-yn-1-ol was 61%.

Treatment of propargyl alcohol with 2 equiv. of n-butyllithium followed by 2 equiv. of trimethylchlorosilane gave the trimethylsilyl ether IX which was hydrolyzed by dilute hydrochloric acid to the trimethylsilyl alcohol X, b.p. 45-48° (1.5 mm), (80% from propargyl alcohol). The alcohol X with triphenylphosphite-bromine complex in the presence of pyridine gave the acetylenic bromide XI, b.p. 48-50° (6 mm), (52% yield) which was converted to the phosphonium salt XII, m.p. 178-180°, by treatment with triphenylphosphine in dioxane in the presence of 48% hydrobromic acid in 55% yield. The phosphonium salt XII was obtained from propargyl alcohol without purifying any of the intermediates in an overall yield of 34%.

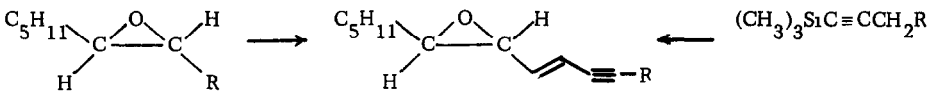
A Wittig reaction between the epoxyaldehyde VIII and the ylid from the phosphonium salt XII gave the trans-trimethylsilyleneyne XIII from which the trimethylsilyl group was quantitatively cleaved by exposure to a suspension of potassium fluoride hydrate in dimethylformamide at 5° to give the eneyne XIV in 69% yield based on the epoxyaldehyde VIII (42% based on oct-2-yn-1-ol).

Condensation of but-3-ynoic acid[7] and 4-aminobiphenyl with ethoxyacetylene gave the acetylenic amide XV, m.p. 152°, (81% yield) which was converted into the corresponding cuprous acetylide XVI by treatment with ammoniacal cuprous chloride. Other methods of preparing the acetylenic amide XV led to significant proportions of the tautomeric allenic amide. 4-aminobiphenyl enchanced crystallinity.

The cuprous acetylide XVI solubilized by hexamethylphosphorus triamide in tetrahydrofuran was treated with the lithium salt of the acetylene XIV and subsequently with 2 equiv. of iodine to give the enediyne XVII, m.p. 106-108°, in 44% yield. Reduction of the diyne XVII at 5° with hydrogen in tetrahydrofuran in the presence of a catalyst of 5% rhodium on alumina treated with synthetic quinoline gave the triene IV, m.p. 118° (39% yield) together with a more polar product, derived from hydrogenolysis of the epoxide. Other palladium and rhodium catalysts, and more polar solvents, gave lower yields of the required triene. The overall yield of the triene from oct-2-yn-1-ol was 7.3%.

The trieneamide IV in a 2-nitropropane-1-nitropropane mixture (3:2) at -104° (cyclohexene - liquid nitrogen) was treated with 1 equiv. of boron trifluoride etherate. After thirty hours, the intermediate imidate ester was hydrolyzed (potassium biphthalate, pH 4, 10 min. at 0°) to the lactone VI which was isolated by

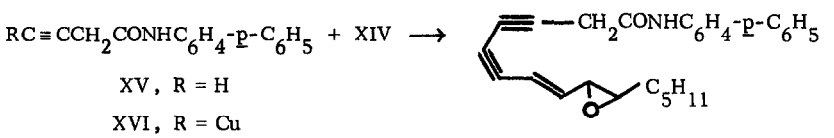
preparative tlc (silica plates, benzene-ethyl acetate, 3 1) in 15% yield from the triene IV. Equal amounts of the C(15)-epimeric lactones VI were formed; the two epimers were separated by preparative tlc (silica plates developed eight times with benzene-ethylacetate, 4 : 1) and were shown to be identical with authentic C(15)-α and C(15)-β lactones VI[2, 3] (n.m.r., i.r. and tlc behavior in benzene-ethyl acetate 4 : 1, pentane-acetone 3 . 1, methylene chloride-methanol 19 : 1). The epimeric mixture of the lactones VI was oxidized by activated manganese dioxide to the corresponding C(15) ketone which was shown to be spectroscopically and chromatographically identical with authentic material.[2, 3] Several acid catalysts (e.g. stannic chloride, titanium tetrachloride, lithium hexafluorophosphate, magnesium perchlorate, and toluenesulphonic acid) were studied in different solvents (1-nitropropane, tetrahydrofuran, methylene chloride, methanol); the most satisfactory yields of the lactone VI were obtained under conditions which would favor relatively long lifetimes of the various cationic intermediates (low temperatures and the absence of nucleophiles). Under all the conditions, equal amounts of the two C(15) epimeric lactones VI were formed.



VII, R = CH_2OH
VIII, R = CHO

XIII, R = $Si(CH_3)_3$
XIV, R = H

X, R = OH
XI, R = Br
XII, R = $Ph_3P^+Br^-$



XV, R = H
XVI, R = Cu

The synthetic approach to prostaglandins outlined above is primarily of interest in connection with the cyclization step. To our knowledge it represents the first application of the pentadienyl $\longrightarrow$ cyclopentenyl cation process to the synthesis of a moderately complex substance. Clearly, a greater measure of efficiency and control in the cyclization would be desirable.[8]

Of the various published routes to prostaglandins the scheme of the Roussel-Uclaf group[9] is most closely related to that described above.[10]

References.

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6. E. B. Bates, E. R. H. Jones and M. C. Whiting, J. Chem. Soc., 1854 (1954).
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8. Preliminary experiments have also been carried out on the cyclization of the acid corresponding to IV. Treatment of IV with 1 eq. of BuLi at -78° in tetrahydrofuran followed by nitrosyl chloride afforded an N-nitroso derivative which was allowed to decompose in the presence of water at -25° to +25°. The acid fraction so obtained (ca. 35%) was then exposed to boron trifluoride etherate in 1-nitropropane at -78°. Although the lactone VI was formed, the yield overall from IV was somewhat lower than for the direct cyclization IV → VI.
9. J. Martel, E. Toromanoff, J. Mathieu and G. Nomine, Tetrahedron Lett., 1491 (1972).

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