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TOTAL SYNTHESIS OF PROSTAGLANDINS E_2 AND $F_{2\alpha}$ (dl) VIA A TRICARBOCYCLIC INTERMEDIATE

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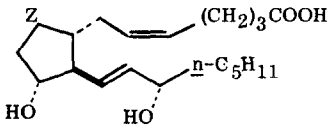
The total synthesis of the important hormonal substances prostaglandin $F_{2\alpha}$ (I) and prostaglandin E_2 (II) in both the racemic (1) and natural (2) forms has recently been achieved in these laboratories by a highly effective approach (3-5). This note describes a different synthetic pathway which also leads to I and II (in racemic form). This pathway merges in the last stage with that developed earlier (1).

The starting point for the present synthetic scheme (Chart 1) was 6-methoxy-bicyclo[3.1.0]hexene-2 (III), which was obtained as a 4 : 1 mixture of endo and exo forms from α,α-dichloromethyl methyl ether (6) and cyclopentadiene using a modified procedure (7). Treatment of a solution of III (4 : 1 endo--exo mixture) and dichloroacetyl chloride (2 equiv.) in pentane at reflux with excess triethylamine in pentane resulted in position-specific and stereospecific addition of the elements of dichloroketene (8) to form the tricyclic ketone IV (9) (80%). Dechlorination of IV was effected by treatment with excess zinc dust in glacial acetic acid at 40° for ca. 1 hr. to give the tricyclic ketone V (9) (78% from IV). Careful analysis of the total dechlorination product by gas chromatography indicated it to be a mixture of two isomers, the endo methoxy structure V and the stereoisomer having exo methoxy in a ratio of 97 : 3. This fact implies that the formation of tricyclic ketone takes place quite selectively from the endo form of III. The structure of V was shown by the chemical correlation which is described in a later section (and outlined in Chart 2).

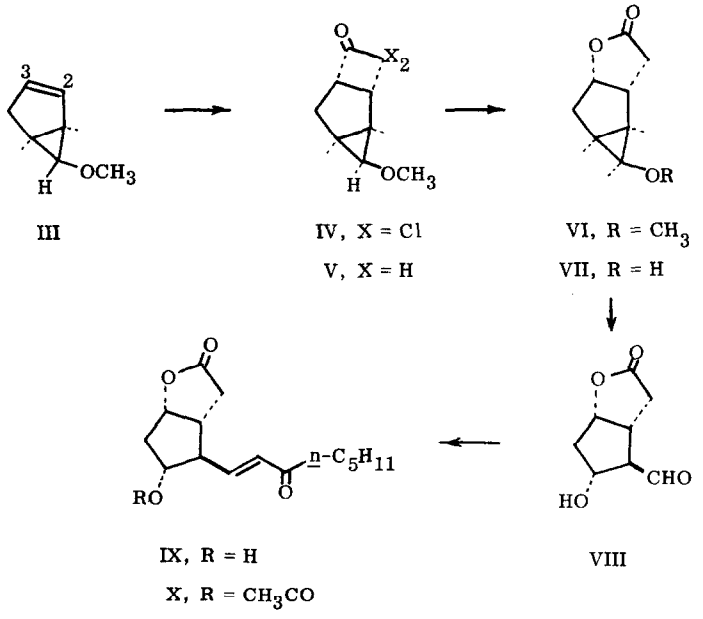
Treatment of a solution of V in glacial acetic acid with 3 equiv. of hydrogen peroxide (30% aqueous) in glacial acetic acid at ca. 5-10° for 16 hr. produced the methoxy γ-lactone VI (9), b.p. 114-116° (0.25 mm.) in >90% yield. Reaction of VI with a solution of boron tribromide (3 equiv.) (1, 10) in methylene chloride (initially at -65°, then at 0° for 15 min.) produced the endo cyclopropanol VII (9), m.p. 67°, in 77% yield. In order to obtain the hydroxy aldehyde VIII, a key intermediate in the synthesis, the cyclopropanol VII was subjected to oxidation by a number of reagents including mercuric, thallic, and lead IV acetates (11) and other oxidizing substances intended to induce electron deficiency at the cyclopropanol oxygen (12). The most useful of the reagents tried was found to be chromic acid (13). Treatment of the cyclopropanol VII in 2 M water--acetic acid (1 : 7) with 1 equiv. of chromic acid and 0.05 equiv. of ceric ammonium nitrate in water--acetic acid (1 : 7) at 20° for 1 hr. and evaporation in vacuo (<25°) followed by three cycles of addition of diglyme and evaporation in vacuo (<25°) gave a mixture of three products, one of which was the desired hydroxy aldehyde VIII (14). Since the product VIII was not sufficiently stable to survive chromatographic separation from the mixture, it was treated in dimethoxyethane solution (after filtration) directly with the sodio derivative of



I, Z = H, OH

II, Z = =O

CHART 1



III

IV, X = Cl

V, X = H

VI, R = CH_3

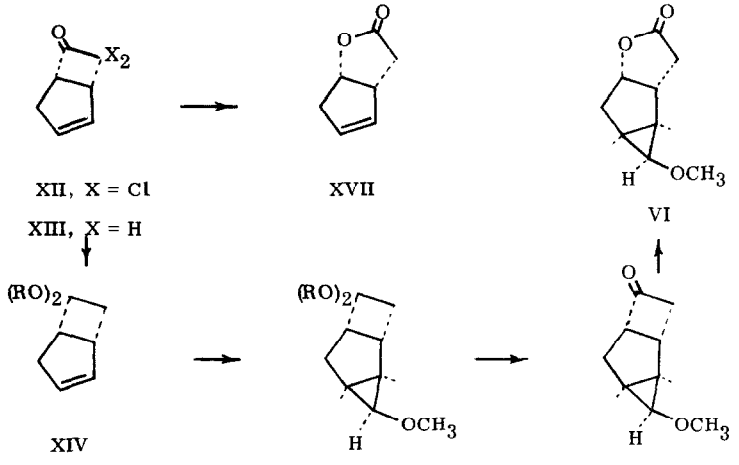
VII, R = H

VIII

IX, R = H

X, R = CH_3CO

CHART 2



XII, X = Cl

XIII, X = H

XIV

XV

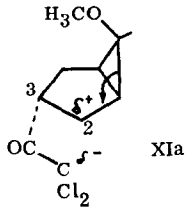
XVI

XVII

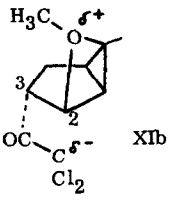
VI

2-oxoheptylphosphonate (1) at 25° for 3 hr. to give a mixture from which the hydroxy enone lactone IX was isolated chromatographically (silica gel--development with 20% ethyl acetate in benzene) in 12% yield based on the cyclopropanol VII. The lactone IX was identified by acetylation to X and comparison with authentic material which was synthesized by the previously described route (1, 2); the infrared and n. m. r. spectra and chromatographic behavior of the two samples of X were identical. The conversion of X to prostaglandins E_2 and $F_{2\alpha}$ has already been described (1), and so the sequence shown in Chart 1 represents another route to these substances. However, this approach must be regarded (at least for the present) as inferior to the earlier synthesis (1) because of the low efficiency and selectivity of the transformation VII → VIII.

The position-specific and stereospecific addition of dichloroketene to endo-6-methoxy-bicyclo[3. 1. 0]-hexene-2 (III) to produce the bicyclic ketone IV requires further discussion. The anti relationship of the three- and four-membered rings about the central five-membered ring in IV is to be expected and is easily explained on steric grounds. The orientational mode of the cycloaddition process, which is of greater novelty, can likewise be rationalized in a straightforward manner. If the electrophilic carbonyl carbon of dichloroketene is presumed to initiate the addition, attachment of this carbon to C-3 of III, rather than C-2, should be favored, since this leads to stabilization of the resulting transition state either by the electron-supplying cyclopropyl or endo methoxy group as shown for the extreme structures XIa and XIb, respectively:



XIa



XIb

Chart 2 outlines the chemical correlation which served to demonstrate the orientation of the addition of dichloroketene to III. The known bicyclo[3. 2. 0]heptenone XIII was prepared from the adduct of cyclopentadiene with dichloroketene (8) by dechlorination using zinc dust in acetic acid. The di-n-butyl ketal XIV was prepared from XIII using methyl orthoformate, n-butyl alcohol, p-toluenesulfonic acid mixture (98% yield), and converted to the tricyclic methoxy ketal XV (9) in fair yield by reaction with dichloromethyl methyl ether and methyllithium--lithium iodide in ether (7). Acid-catalyzed hydrolysis of XV yielded the corresponding ketone (XVI) (9) which was oxidized by 30% hydrogen peroxide in glacial acetic acid in excellent yield to the methoxy lactone VI, identical in all respects with the material obtained as shown in Chart 1.

Finally, it is noteworthy that the bicyclic ketone XIII could be converted in 90% yield to the unsaturated lactone XVII (9) by reaction with 30% aqueous hydrogen peroxide (2. 5 equiv.) in acetic acid--water (7 : 1) at 0° for 18 hr. The reaction proceeded selectively without detectible formation of epoxy ketone or epoxy lactone. The bicyclic lactone XVII is also of interest as an intermediate for the synthesis of prostaglandins. The note which follows describes one pathway for the conversion of XVII to prostaglandins $F_{2\alpha}$ and E_2 (15, 16).

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15. E. J. Corey and R. Noyori, Tetrahedron Letters, follows.
16. This work was assisted by a grant from the National Institutes of Health.