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PROSTAGLANDIN SYNTHESIS. III. AN IMPROVED OPENING OF BICYCLO[3.1.0]HEXANE INTERMEDIATES

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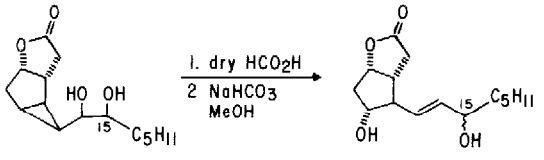
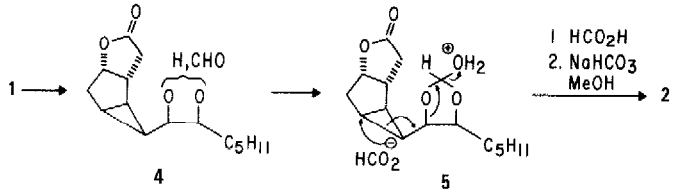
In previous papers (1) we described an efficient synthesis of prostaglandins which controls the stereochemistry at every position but C-15. In this communication we describe a new opening of a cyclopropyl carbinyl system through orthoester intermediates which improves the yield and, more importantly, retains in the products 11 and 13 the C-15 (prostaglandin numbering) stereochemistry of the cyclopropyl carbinyl precursors 8 and 9. This discovery paves the way for a total synthesis via bicyclo[3.1.0]hexane intermediates in which the stereochemistry at every position including 15 is stereocontrolled (2).

The new opening was found as a result of our inquiry into why anhydrous formic acid was required in the transformation of glycol 1 into diol 2 (1). Small concentrations of water were found to substantially reduce the yield of ring opened product resulting in the reisolation of



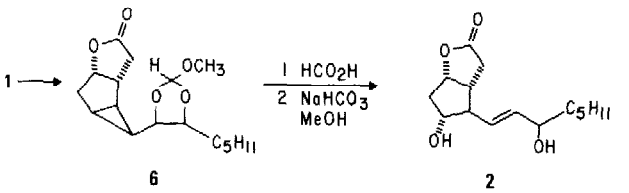
1 2

glycol 1 after methanolysis of the formates. It occurred to us that this observation was consistent with the formation of a monoformate 4 which cyclized to an orthoester intermediate 5.



4 5

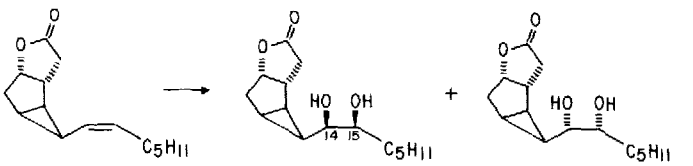
To test this hypothesis we synthesized orthoester 6 [$HC(OCH_3)_3$, benzene, pyridine hydrochloride, 25°C, 2-4 hours] and treated it with dry formic acid followed by methanol and $NaHCO_3$. Much to our delight the opening of 6 was complete in less than 5 minutes, whereas the openings of glycol 1



6 2

in formic acid required about 3 hours. Furthermore, the process was much cleaner, giving fewer side products and a higher overall yield of diol 2 (~70% as compared to ~60%).

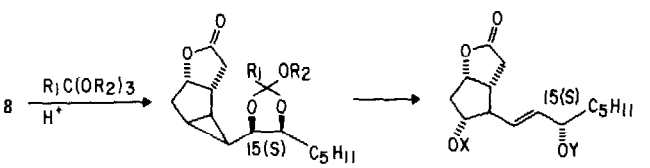
Our hypothesis of an orthoester intermediate also led to the conclusion that since the carbon-oxygen bond at 15 is not cleaved, the 15 stereochemistry (prostaglandin numbering, cf. 8) of the precursor should be retained in the opened product. To test this hypothesis we prepared the glycols 8 and 9 by osmium tetroxide oxidation of the alkene 7 (1, 3-5). The mixture of 8 and 9, so produced, was readily separated by silica gel chromatography (5). Each was converted to



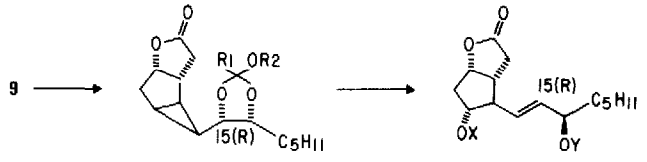
7 8 9

its orthoformate (10a and 12a) which was treated with formic acid and then methanolized. The hypothesis was confirmed in that the major isomer from 8 was 11d and from 9 was 13d. However, VPC analysis showed that some epimerization had occurred in each case (6). This epimerization was ascribed to the solvolysis of the allylic formate since reintroduction of 11a or 13a to formic acid resulted in increasing loss of stereochemical integrity with time.

We were unable to find conditions which allowed us to fully retain the 15 stereochemistry via the orthoformates. Thus, we turned to the preparation of orthoesters which would generate allylic esters less labile than formates to solvolysis. The orthoacetates (10b and 12b) and the orthopropionates (10c and 12c) were prepared and solvolyzed. The acetate, while giving a higher percentage of retained configuration than formate, still showed some epimerization. The propionate, on the other hand, showed complete retention of the 15 stereochemistry of its precursors (6).



10 11



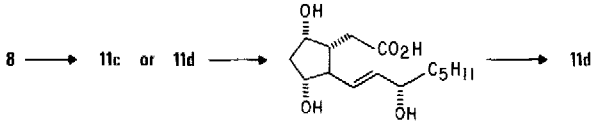
12

a $R_1 = H, R_2 = CH_3$
b $R_1 = CH_3, R_2 = C_2H_5$
c $R_1 = C_2H_5, R_2 = C_2H_5$

13

a X = Y = CHO
b X = CHO, Y = $COCH_3$
c X = CHO, Y = COC_2H_5
d X = Y = H

An additional important discovery was a method for obtaining the desired diol 11d in a pure state without resort to chromatography. Hydrolysis (NaOH, H_2O) of the crude product from the orthoester opening of glycol 8 led to a mixture containing triol acid 14 (m.p. 100°, 8).



14

This was purified by crystallization from ethyl acetate. The epimerically pure diol 11d was then obtained from 14 simply by heating under reflux in CH_2Cl_2 or $CHCl_3$. In this way an overall yield from glycol 8 to diol 11d of 50-55% was obtained (9).

ACKNOWLEDGMENT

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REFERENCES

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2. A communication describing the successful control of the 15 stereochemistry is in preparation.
3. For a new superior method for the catalytic oxidation of alkenes to glycols with osmium tetroxide see V. VanRheenen, D. Y. Cha and R. C. Kelly, Tetrahedron Lett. submitted for publication.
4. The stereochemistry of the glycols 8 and 9 were not known until their conversion to the known diols 11d and 13d, respectively. This stereochemistry is demanded by the known formation of cis-glycols on oxidation with osmium tetroxide and by the mechanism described for the orthoester opening. Particularly compelling is the fact that inversion at C-15 would require the acetates 11b and 13b and the propionates 11c and 13c (which completely retain their respective esters in formolysis) to epimerize 100% without substitution by formate. We consider this highly improbable.
5. It was found by VPC analysis on the cyclic butyl boronates that each erythro isomer contained 5-8% of a threo isomer. The threo contaminants arise from a corresponding amount of trans

olefin in cis olefin 7. By an unequivocal process, the threo isomers were synthesized from the erythro isomers. It was then shown that the 15(S)-erythro isomer is chromatographed on silica gel with the 15(R)-threo and the 15(R)-erythro with the 15(S)-threo.

6. Since, as noted in footnote 5, each erythro glycol contained 5-8% threo glycol with the opposite configuration at C-15, 100% retention of configuration would give diols 11d and 13d contaminated to the same extent. A greater per cent contamination meant that some epimerization had occurred during the reaction sequence.

7. The crude reaction mixture after orthoester opening and methanolysis of the esters was found to contain 70-75% diols (11d and 13d), 20-25% glycols 1 and small amounts of other materials.

8. This compound was first prepared in our laboratories by F. H. Lincoln.

9. Another 15-20% of pure diol 11d may be obtained from the mother liquors by silica gel chromatography.