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SYNTHESIS OF A TETRAHYDROFURANONE PROSTAGLANDIN ANALOG[1]

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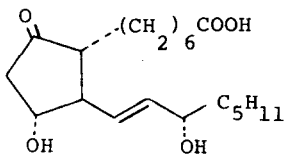
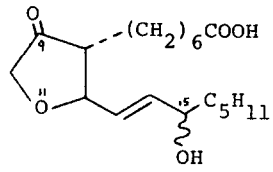
We have recently described[2] the preparation of prostaglandin analogs containing two oxygen heteroatoms in the five-membered ring. In this paper we describe the synthesis of the oxaprostaglandin analog (2)[3] in which a tetrahydrofuranone[4] system, containing one oxygen heteroatom, replaces the hydroxycyclopentanone ring of the natural prostaglandin (1).

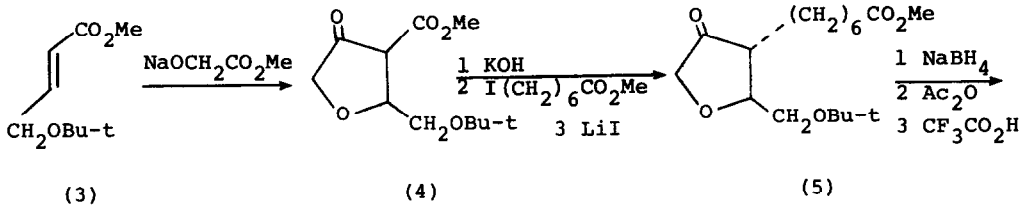


(1)

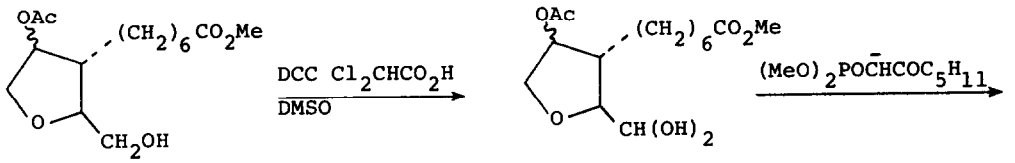


(2)

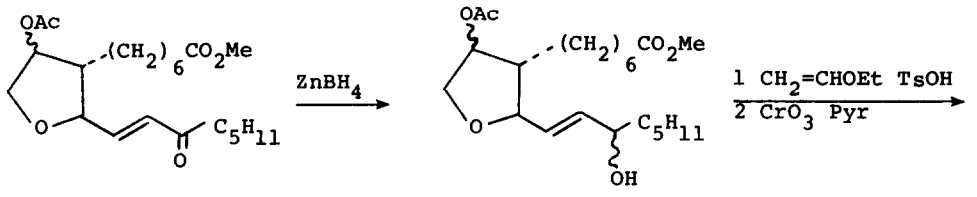
Methyl 4-t-butoxybut-2-enoate (3) [b.p. 32-34°/1 mm][5] was prepared by hydrogenation of the corresponding acetylenic ester[6] and converted to the tetra-



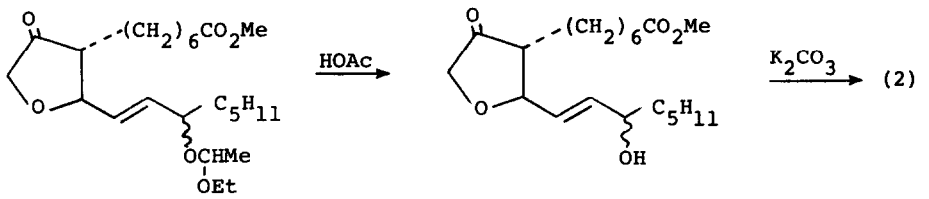
(3) (4) (5)



(6) (7)



(8) (9)



(10) (11) (2)

hydrofuranone derivative (4) [26%; oil; b.p. 92-100°/1 mm; ν_{max} 1775, 1730 cm^{-1}] by reaction[7] with the anion of methyl glycolate. Treatment of this β-ketoester with potassium hydroxide in methanol gave a crystalline potassium salt which was alkylated with methyl 7-iodoheptanoate in DMSO and decarboxylated[8] with lithium iodide in DMF forming the ketoester (5) [45%; oil; ν_{max} 1745 (sh), 1730 cm^{-1}], the two side chains are assumed to have the more stable trans relationship. Reduction of (5) (sodium borohydride in methanol), acetylation (acetic anhydride, pyridine in benzene) and cleavage of the t-butyl protecting group (trifluoroacetic acid) gave the alcohol (6) [92%; oil; ν_{max} 3380, 1730 cm^{-1}]. Oxidation of (6) (DCC, DMSO, dichloroacetic acid)[9] led to the aldehyde hydrate (7) [55%; oil; ν_{max} 3340, 1730 cm^{-1}; semicarbazone m.p. 123-125°].

The remaining side chain was constructed by methods previously applied[10] in the prostaglandin field, via the enone (8) [89%; oil, ν_{max} 1730, 1670, 1630 cm^{-1}; m/e 325 ($M-C_5H_{11}$), 336 (M-HOAc), 396 (M+)], and the 15(α + β) alcohols (9). Protection[11] of the 15-hydroxyl group of (9) with ethyl vinyl ether, cleavage of the 9-acetate function with sodium methoxide in methanol and oxidation[12] with chromium trioxide-pyridine complex gave the ketone (10) [52%, ν_{max} 1750, 1735 cm^{-1}]. Cleavage of the ether protecting group with aqueous acetic acid gave the 15-epimeric alcohols (11) [42 and 48%; oils; ν_{max} 3340, 1745, 1730 cm^{-1}; m/e 283 ($M-C_5H_{11}$), 354 (M+)] which were separated by column chromatography on silica gel. Hydrolysis of the methyl ester of (11) with potassium carbonate in aqueous methanol led to the required epimers of 15-hydroxy-9-oxo-11-oxaprost-13-enoic acid (2) [92 and 96%; ν_{max} 3310, 1745, 1710 cm^{-1}; m/e 269 ($M-C_5H_{11}$), 340 (M+)].

Both 15-epimers (2) showed weak (0.05 - 0.005 x PGE_2) activity in the *in vitro* gerbil colon assay for smooth muscle contracting activity[13].

REFERENCES AND FOOTNOTES

1. Contribution No. 440 from the Syntex Institute of Organic Chemistry and No. 35 in the series Studies in Prostaglandins.
2. Preceding paper.
3. Synthetic products are racemic, only one enantiomer is shown in the diagrams.

4. Some related lactone analogs have been described recently: F. M. Hauser and R. C. Huffman, Tetrahedron Letters, 905 (1974).

5. Satisfactory elemental analyses were obtained for (3), (4) and the semicarbazone derived from (7). N.m.r. spectra of all compounds were consistent with the assigned structures. I.r. spectra refer to liquid films.

6. R. Mantione, Bull. Soc. Chim. Fr., 4523 (1969).

7. M. A. Gianturco, P. Friedel and A. S. Giammarino, Tetrahedron, 20, 1763 (1964).

8. Organic Syntheses, 45, 7 (1965).

9. K. E. Pfitzner and J. G. Moffatt, J. Amer. Chem. Soc., 87, 5670 (1965).

10. E. J. Corey, N. M. Weinshenker, T. K. Schaaf and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969).

11. C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti and M. Casey, J. Amer. Chem. Soc., 94, 3643 (1972).

12. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).

13. We wish to thank W. Rooks, K. Neiger and S. Jubb for this assay.