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SYNTHESIS OF BIS-OXA-PROSTAGLANDINS[1]

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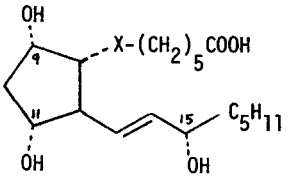
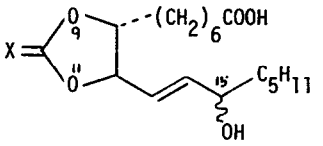
The oxaprostaglandin analog (1a)[2], in which an oxygen heteroatom replaces a methylene group in the side chain of the natural substance (1b), has interesting biological properties. We describe here the preparation of the prostaglandin analogs (2a)[3] and (2b) in which oxygen heteroatoms replace hydroxymethine groups of the cyclopentane ring.

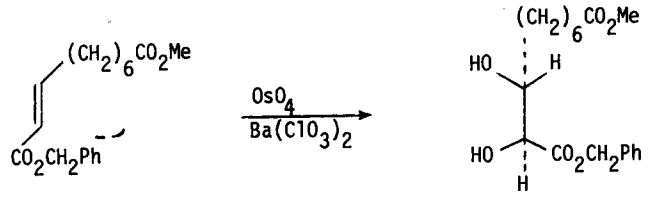


(1) a, X = O
b, X = CH_2

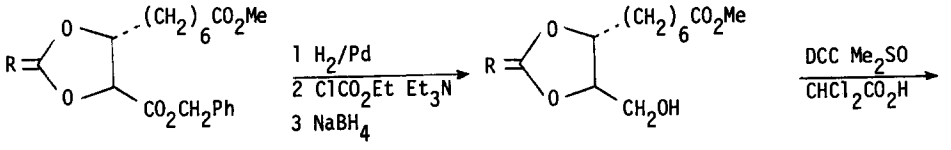


(2) a, X = H,H
b, X = O

Hydroxylation[4] of the trans-olefinic ester (3)[5] with osmium tetroxide-barium chlorate in aqueous tetrahydrofuran gave the diol (4) [68%; m.p. 37-38°;



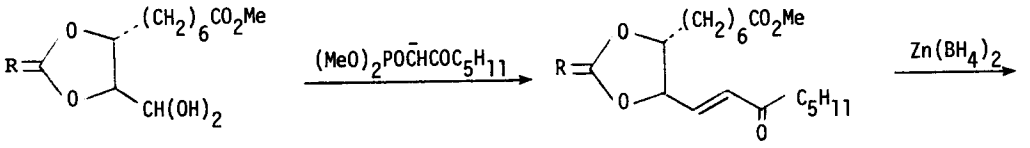
(3) (4)



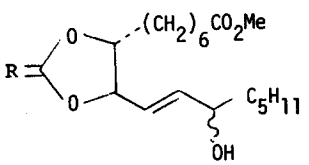
(5) (6)

a, R = H,H

b, R = O



(7) (8)



(9)

Hydrolysis → (2)

m/e 173, 338 (M^+)][6], which was converted to the cyclic acetal (5a) [81%; oil; m/e 291, 350 (M^+)] by heating under reflux (water separator) with paraformaldehyde in benzene containing perchloric acid. The benzyl group of the ester (5a) was hydrogenolyzed (Pd-C, methanol) and the resulting acid reduced[7] by conversion to the mixed ethyl carbonic anhydride (ethyl chloroformate, triethylamine) and treatment with sodium borohydride forming the alcohol (6a) [71%; oil; m/e 215 ($M-CH_2OH$). Oxidation[8] of (6a) [dicyclohexylcarbodiimide, dichloroacetic acid, dimethylsulfoxide) gave the aldehyde hydrate (7a) [66%; oil; ν_{max} 3310 (OH), 1715 cm^{-1} (COOMe)]. Construction of the remaining side chain from (7a) via the enone (8a) [oil; ν_{max} 1730, 1670, 1630 cm^{-1}] followed well established procedures[9] forming a mixture of the 15-epimers (9a) [oils; m/e 271, 342 (M^+)] which were separated by column chromatography on silica gel. Hydrolysis of the esters (9a) with sodium hydroxide in 80% methanol gave the required 15α-hydroxy-9,11-bisoxaprost-13-enoic acid (2a) and the 15β-epimer [10% each from (7a); gums; ν_{max} 3290, 1700 cm^{-1}; m/e 170, 209, 239, 280, 310 ($M-H_2O$)].

The cyclic carbonate (5b) [oil; ν_{max} 1805 (carbonate), 1730 cm^{-1}; m/e 258, 332, 364 (M^+)] was prepared by reaction of the diol (4) with phosgene (benzene solution) in tetrahydrofuran containing pyridine. Reactions analogous to those described above converted (5b) to the alcohol (6b) [oil; m/e 229, 260 (M^+)], the aldehyde hydrate (7b) [oil; ν_{max} 3320, 1795, 1730 cm^{-1}], the enone (8b) [oil; ν_{max} 1795, 1730, 1675, 1635 cm^{-1}; m/e 298, 322 ($M-CH_3OH$)] and an inseparable mixture of the 15α and 15β-epimers (9b) [oil; ν_{max} 3350, 1790, 1730 cm^{-1}; m/e 253, 285 ($M-C_5H_{11}$)]. Hydrolysis[10] of the esters (9b) with yeast gave 15(α + β)-hydroxy-10-oxo-9,11-bisoxaprost-13-enoic acid (2b) [12% from (4); gum; ν_{max} 3320, 1785, 1705 cm^{-1}, m/e 253, 271 ($M-C_5H_{11}$).

Compounds (2a, 15α and 15β) and (2b) showed weak activity (ca. 0.005 x PGE_2) in the gerbil colon smooth muscle contraction assay[11].

REFERENCES AND FOOTNOTES

1. Contribution No. 439 from the Syntex Institute of Organic Chemistry and No. 34 in the series Studies in Prostaglandins.

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3. Synthetic products are racemic, only one enantiomer is shown in the diagrams.

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6. N.m.r. spectra of all compounds were consistent with the assigned structures. I.r. spectra refer to liquid films.

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11. We thank W. Rooks and S. Jubb for this assay.