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A SYNTHESIS OF CRYSTALLINE THROMBOXANE B_2 FROM A DERIVATIVE OF PROSTAGLANDIN $F_2\alpha$[1]

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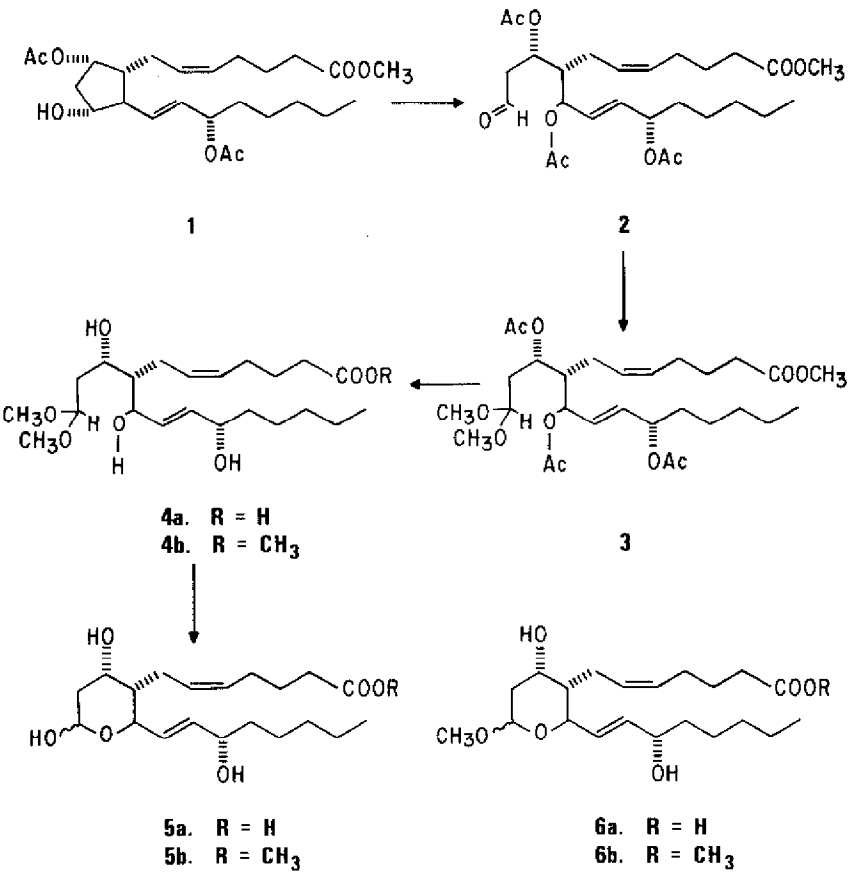
The recent recognition[2] that thromboxane B_2 (5a) is one of the major products of the biosynthetic system which converts arachidonic acid to prostaglandins has prompted efforts in these laboratories towards its synthesis.[1] The approach described here uses as starting material 9, 11-diacetoxy-$PGF_2\alpha$ methyl ester, 1, which is available from $PGF_2\alpha$-11,15-ditetrahydropyranyl ether.[3] The crucial step in this synthesis consists of a ring opening reaction initiated by the action of lead tetra-acetate on the 11α-hydroxyl group, a reaction which has precedence in the steroid area,[4] and which occurs with particular facility in the case of such homoallylic alcohols as 1.

Reaction of 1 with $Pb(OAc)_4$ in benzene at room temperature leads to the rather unstable acetoxy aldehyde 2[5] which was directly converted to its dimethyl acetal 3 using trimethyl orthoformate and pyridine hydrochloride in methanol. Compound 3 was obtained as an oil showing major ions in its mass spectrum at 556 (M^+), 525 ($M-OCH_3$), 497 ($M-CH_3CO_2$), 465, 404, 362, 344, 311, 139, 75 ($CH_3O-\overset{+}{C}H-OCH_3$), and 43. The IR, proton, and ^{13}C nmr spectra were also consistent with structure 3.

Removal of the acetates from 3 with methanolic sodium methoxide gave 4b, while aqueous basic hydrolysis of 3 gave the acid 4a, each characterized spectrally as above, the methyl ester 4b showing ions at 380 ($M-H_2O-CH_3OH$), 362 ($M-2\ H_2O-CH_3OH$), 349, 276, 251, 249, 224, 207, 195, 184, 99, and 75 mass units.

Hydrolysis of the dimethyl acetal 4b with a mixture of acetic acid, water and tetrahydrofuran (40:20:10) at room temperature gave a mixture of thromboxane B_2 methyl ester 5b and its cyclic methyl acetal 6b,[6] the former having thin-layer mobility, and as its TMS derivative, a gas chromatographic retention time and mass spectrum identical to the same derivative of natural thromboxane B_2,[7] and to samples prepared by syntheses as described in the accompanying communications.[1]

Hydrolysis of 4a with a mixture of tetrahydrofuran, water, and 85% phosphoric acid (12:10:1) gave largely thromboxane B_2 (5a) and a small amount of its methyl acetal (6a) which were separated by silica gel chromatography. The thromboxane B_2 fractions crystallized, and were recrystallized from ethyl acetate, m.p. 92–94°, Anal. Calcd. for $C_{20}H_{34}O_6$: C, 64.83; H, 9.25. Found: C, 64.70; H, 9.48. The mass spectrum, as the methyl ester, TMS derivative, gave ions at 600 (M^+), 585 (M-15), 510, 495, 325, 301, 296, 257, 225, 217, 199, 191, 173, 155, 147, 129 and 73, consistent with the mass spectrum reported by Hamberg and Samuelsson.[2a] Its thin-layer mobility, both as the acid and as its methyl ester, was also the same as that of an authentic sample.[7] The overall yield of 5a from 1 was about 25%.



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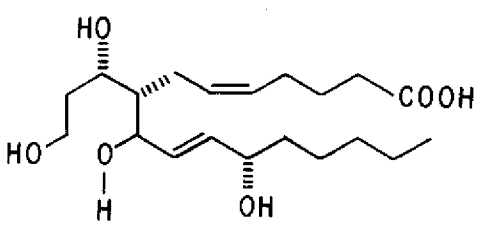
1. See accompanying manuscripts by N.A. Nelson and R.W. Jackson, and by R.C. Kelly, I. Schletter, and S. Stein on thromboxane B_2 synthesis.

2. a. M. Hamberg and B. Samuelsson, Proc. Nat. Acad. Sci. USA, 71, 3400 (1974); b. M. Hamberg, J. Svensson, and B. Samuelsson, ibid. 72, 2994 (1975).

3. E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker, and Ned. M. Weinshenker, J. Am. Chem. Soc. 92, 397 (1970). The $F_2\alpha$-11,15-di-THP derivative was esterified with diazomethane, the free 9α-hydroxyl group was acetylated, the 11,15-tetrahydropyranyl ethers were removed, and a second mild acetylation gave a separable (silica gel) mixture of the 9,11- and the 9,15-diacetates, of which the latter was the more polar.

4. See for example, M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, Helv. Chim. Acta 45, 2674 (1972); G.B. Spero, J.L. Thompson, W.P. Schneider and F. Kagan, J. Org. Chem. 28, 2225 (1963); K. Heusler and J. Kalvoda, Angew. Chem. 76, 518 (1964).

5. Compound 2 was also converted by several steps to the tetrol acid which gave, as its methyl



ester TMS derivative, a mass spectrum identical to that reproduced by Hamberg and Samuelsson[2a] for the compound derived by borohydride reduction of natural TxB_2.

6. The methyl acetal 6b was found by nmr to be a mixture of α and β isomers (at the acetal carbon) in the ratio of 1:2 (α:β).[1]

7. We are indebted to B. Samuelsson and E. Granström and also to R. Gorman, F. Sun, and R. C. Kelly of these laboratories for samples of natural thromboxane B_2 and to F. Sun for carrying out the GC-mass spectral comparisons of synthetic with natural materials.