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SYNTHESIS OF 6,9α-OXIDO-11α,15α-DIHYDROXYPROSTA-(E)5, (E)13-DIENOIC ACID, AN ISOMER OF PGI_2 (VANE'S PGX)

E. J. Corey, Istvan Székely and Christopher S. Shiner

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

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A previous publication[1] from these laboratories has described the synthesis of 6,9α-oxido-11α,15α-dihydroxyprosta-(Z)5,(E)13-dienoic acid (1) from the 11,15-bistetrahydropyranyl (THP) ether of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) by a stereochemically unambiguous route. The biological properties of this substance (in the carboxylate form) were found to correspond to those reported for Vane's PGX[2,3] (now referred to as PGI_2[4]) by tests in two different laboratories.[5,6] As mentioned earlier,[1] the stereoisomer of 1 having the E configuration of the 5,6-olefinic linkage (2) was much less active biologically. For example in inhibition of human platelet aggregation 1 is on the order of 25 times as active as PGE_1 whereas 2 is only one-fifth to one-tenth as active. Although 2 does not appear to be as important biologically as is stereoisomer 1, it is nonetheless deserving of careful biological study. We describe here two different routes by which 2 has been synthesized in these laboratories.[7]

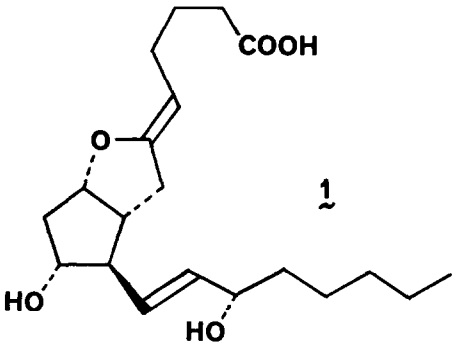
Reaction of the previously described mixture of two diastereomeric bromo ethers 3[1] (produced by the reaction of NBS with the 11,15-bis-THP ether of $PGF_{2\alpha}$; ratio ca. 3:1) with excess potassium superoxide and 18-crown-6 in dry dimethyl sulfoxide at 20° for 1 hr afforded a corresponding mixture of alcohols 4[8] by inversion at C-5[9] (85%). This product was esterified with excess diazomethane in ether and then converted to the mesylate 5[8] (84% yield) by reaction with methanesulfonyl chloride (6 equiv) and triethylamine (6 equiv) in dry methylene chloride at -20° for 2 hr.[10] Application of the same mesylation procedure to the free acid 4 produced only the corresponding 1,5-lactone.

Cleavage of the THP protecting groups in 5 in the usual way (acetic acid-THF-water 3:1:1 at 40° for 3 hr) gave after chromatographic separation two diastereomeric diol esters[8] (6) (ratio ca. 3:1) of R_f 0.32 (major) and 0.35 (minor) using silica gel plates with benzene-dioxane-acetic acid 20:10:1 for elution. The major isomer,[8] which arises from the predominating diastereomer in the bromo ether mixture 3, was saponified to the corresponding acid 7 (5 equiv lithium hydroxide in methanol-water 3:1 at 5° for 15 hr) and then treated with excess potassium t-butoxide in t-butyl alcohol at 60° for 10 hr under argon to effect elimination to form 2. Extractive separation of 2 was performed as previously described for 1[1] and the cold extract was promptly treated with diazomethane to form the methyl ester of 2.[8] The pmr spectrum of this methyl ester of 2 in C_6D_6 showed as reported earlier[1] a peak at 4.77 ppm due to the vinylic proton at C-5, as distinguished from PGI_2 (1) methyl ester which shows a pmr peak (in C_6D_6 solution) due to the C-5 proton at 4.15 ppm.[11] The methyl esters of 2 and 1 could be distinguished clearly by tlc analysis and showed respective R_f values of 0.41 and 0.45 (silica gel plates pre-treated with ethereal ammonia; two developments with ether-acetone 3:1 as solvent). For bioassay the salt of 2 was prepared in aqueous solution by alkaline hydrolysis of

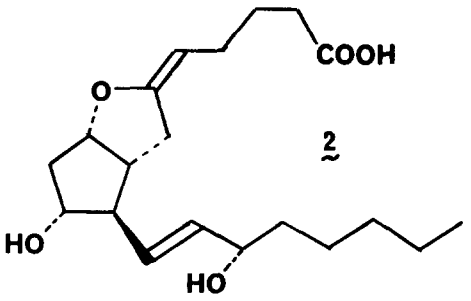
its methyl ester.

The E stereochemistry at the crucial 5,6-double bond of 2 is assigned on the basis that (1) the formation of bromo ether 3 from $PGF_{2\alpha}$ bis THP involves trans addition of bromine and the 9-α-oxygen to the 5,6-double bond, (2) the superoxide displacement of bromine in 3 proceeds with inversion and (3) the t-butoxide induced elimination of methanesulfonate from 7 occurs by a trans-coplanar E2-elimination process. It is noteworthy in this regard that the methyl ester of 2 prepared as described above was not appreciably contaminated by any PGI_2 methyl ester.

The methyl ester of 2 was also prepared by a different route which gave identical material. 5-trans-$PGF_{2\alpha}$ (10) which served as substrate for bromo ether formation in this approach was synthesized as follows. The methyl ester of $PGF_{2\alpha}$ was converted quantitatively to the 9,11,15-tris-t-butyldimethylsilyl ether (8) $[\alpha]_D^{25}$ + 16.0° (c 1.7, benzene) by treatment with t-butyldimethylsilyl chloride (5 equiv) and imidazole (12 equiv) in DMF at 25° for 18 hr.[12] Irradiation of a mixture of this silyl ether methyl ester and 0.5 equiv of diphenyl disulfide[13] in benzene under argon at 17° (external mercury spot lamp, Pyrex reactor, 12 hrs) afforded a mixture of the 5-trans and 5-cis isomers (9 and 8) which were cleanly separated by column chromatography on silica gel impregnated with silver nitrate (10% by weight) using benzene-methylene chloride mixtures for elution. Pure 5-trans isomer 9 was obtained as an oil $[\alpha]_D^{25}$ + 12.9° (c 1.33, methylene chloride) in 65% yield in addition to 10% of recovered 8. Desilylation[12] of 9 with tetra-n-butyl ammonium fluoride in THF at 25° and subsequent saponification (lithium hydroxide in methanol-water 2:1) afforded cleanly 5-trans-$PGF_{2\alpha}$ (10).[14] Exposure of 10 to 1.1 equiv of N-bromosuccinimide in dimethylformamide afforded quantitatively a mixture of two bromo ethers in a ratio of 2.3:1 (R_f values 0.32 and 0.36, respectively, on silica gel plates using benzene-THF-acetic acid (20:20:1)). The major isomer, an oil, $[\alpha]_D^{25}$ 10.2 (c 0.85, chloroform) was converted to the methyl ester of 2 using potassium t-butoxide for elimination essentially as described earlier[1] for PGI_2 methyl ester. The semi-solid product was spectroscopically and chromatographically identical to the methyl ester of 2 prepared by the superoxide displacement route outlined above. Obviously, trans addition of bromine and oxygen at C-9 to the trans-5,6-olefinic linkage of 10 followed by trans elimination of the elements of HBr is expected to form the enol ether double bond of 2 in the E configuration. Finally it should be mentioned that exposure of 2 methyl ester to 0.01 N hydrochloric acid in aqueous THF at 25°[1] very rapidly effects hydrolysis of the enol ether function to form the methyl ester of 6-keto-$PGF_{1\alpha}$, a property paralleling that of PGI_2 methyl ester.[1-3,15]



1



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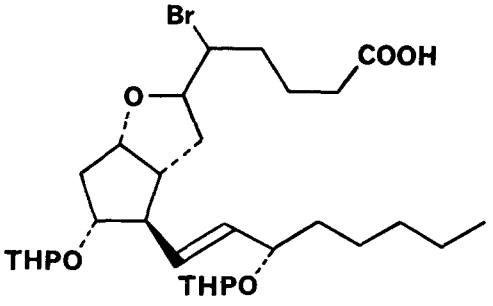

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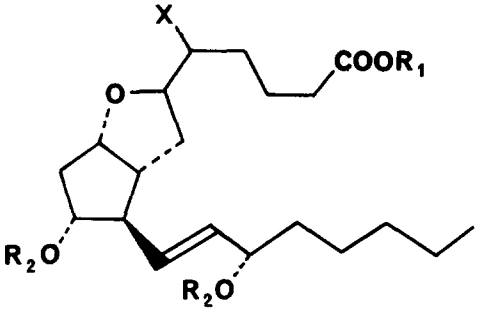
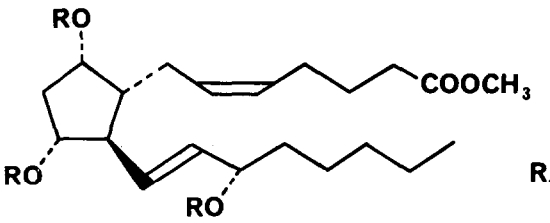


4, X = OH, R_1 = H, R_2 = THP

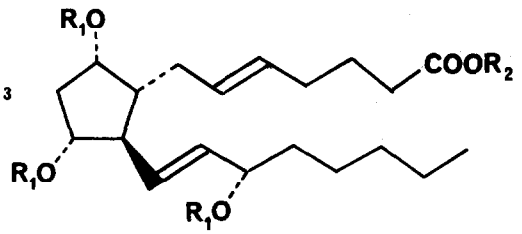
5, X = OSO_2CH_3, R_1 = CH_3, R_2 = THP

6, X = OSO_2CH_3, R_1 = CH_3, R_2 = H

7, X = OSO_2CH_3, R_1 = R_2 = H



8, R = t-$BuMe_2Si$



9, R_1 = t-$BuMe_2Si$, R_2 = CH_3

10, R_1 = R_2 = H

References and Notes

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7. After the completion of our work and publication of ref. 1, an account of similar work at the Upjohn laboratory appeared. See, R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axon, J. Am. Chem. Soc., 99, 4182 (1977).
8. Satisfactory (a) infrared, nmr and (b) mass spectral data were obtained for this intermediate using a chromatographically homogeneous sample.
9. E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida and C. S. Shiner, Tetrahedron Lett., 3183 (1975).
10. Relative R_f values of the methyl ester of 4 and the mesylate methyl ester 5 on silica gel plates using benzene-dioxane-acetic acid 20:10:1 were 0.63 and 0.74 respectively.
11. The position of this peak at 4.15 ppm was incorrectly given as 4.55 in our earlier[1] paper. Stretching frequencies for the 5,6 double bond in the methyl esters of 2 and 1 were found to occur (CCl_4 solution) at 1688 and 1696 cm^{-1} respectively.
12. E. J. Corey and A. Venkateswarlu, J. Am. Chem. Soc., 94, 6190 (1972).
13. E. J. Corey and E. Hamanaka, ibid., 89, 2758 (1967).
14. A similar but less efficient and convenient preparation of 5-trans-$PGF_{2\alpha}$ has been reported recently by an Upjohn group, W. P. Schneider, G. L. Bundy, F. H. Lincoln, E. G. Daniels, and J. E. Pike, ibid., 99, 1222 (1977).

15. This study was supported in part by the National Science Foundation and by an IREX fellowship to I. S.