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# CONFIGURATION AT C-6 OF 6,9α-OXIDO-BRIDGED PROSTAGLANDINS

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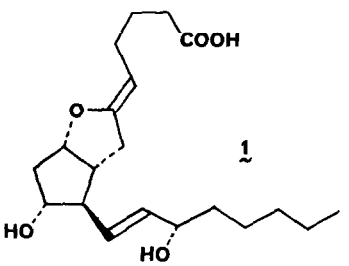
We have previously described syntheses of $PGI_2$ (Vane's PGX) (1)[1] and its biologically less active stereoisomer at the 5,6-double bond (2)[1,2] from $PGF_{2\alpha}$ and the 5,6-trans-isomer of $PGF_{2\alpha}$ respectively by a route involving internal halo ether formation and elimination of hydrogen halide.[3] Because of the mechanistically imposed trans nature of the addition and elimination steps, the stereospecific formation of 1 and 2 insured the assigned stereochemistry at the $\Delta^5$-double bond. The stereochemistry of the intermediate halo ethers was not established rigorously, although a surmise was offered.[1] This note reports the unambiguous determination of the stereochemistry of the intermediate halo ether and also the mercuric and seleno ethers previously reported.[1,4]

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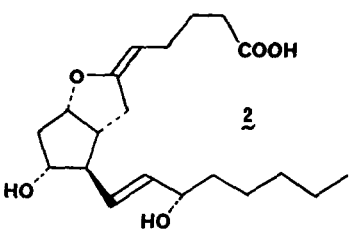


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As described earlier reaction of $PGF_{2\alpha}$-11,15-bistetrahydropyranyl ether with N-bromosuccinimide in THF-chloroform affords after cleavage of the pyranyl groups two threo bromo ethers, as more polar and less polar (ratio 3:1) diastereomers 3a and 4a, respectively.[5] Reaction of the more polar isomer 3a and the less polar isomer 4a separately with 3 equiv of tri-n-butyltin hydride in benzene for 1.5 hr at 70-75° (trace of azoisobutyronitrile added for initiation) afforded, respectively, the more polar and less polar C-6 epimers 3b and 4b, which had previously been obtained[1] from $PGF_{2\alpha}$ by an internal oxymercuration-borohydride demercuration sequence. Similarly, the previously prepared[1] isomeric phenylseleno ethers, more polar and less polar forms, were shown to correspond stereochemically to more polar and less polar bromo ethers 3a

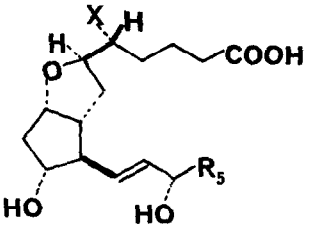
and 4a, respectively, by reaction with tributyltin hydride. The more polar phenylseleno ether 3c was converted to the more polar hydrogenolysis product 3b and the less polar phenylseleno ether afforded the less polar dehydrogenolysis product 4b. Thus a correlation was established showing that the more polar isomers in the bromo ether (a) ether (b) and seleno ether (c) series all correspond in orientation of the carboxyl side chain attached to C-6.

The more polar and less polar isomers were shown to have, respectively, exo and endo oriented carboxyl side chains at C-6 by the following experiments. The more polar seleno ether acid 3c was converted by treatment with excess hydrogen peroxide (30%) in THF at 0° for 15 min and 23° for 3.5 hr, dilution with water, ether extraction and isolation, to the dihydroxy acid 5 (95%) (methyl ester[6] $R_f$ 0.52 on silica gel plates using 20:10:1 benzene-dioxane-acetic acid). Similarly, the less polar seleno ether 4c was transformed into the unsaturated dihydroxy acid 6 (95%) (methyl ester[6] $R_f$ 0.59 using silica gel tlc plates with 20:10:1 benzene-dioxane-acetic acid).

Each of the acids 5 and 6 was then subjected to lactonization via the corresponding thiol esters with 1-isopropyl-2-mercapto-4-t-butyl imidazole[7] with the following results. The less polar acid 6 was stirred with 8 equiv of 2,2' (4-t-butyl-1-isopropylimidazolyl) disulfide and 8.8 equiv of triphenylphosphine in dry toluene at 23° for 1 hr to form the thiol ester[7] and then diluted with dry toluene and heated under argon at 110° for 24 hr. Evaporation of toluene and treatment of the residue with methyl iodide (excess) in acetonitrile at 23° for 40 min (to form water-soluble products from the various imidazole species present and to consume excess triphenylphosphine) followed by removal of acetonitrile and partitioning between ether and water, gave after evaporation of the ether phase a mixture which could be separated by chromatography on silica gel plates using methylene chloride-methanol (94:6) for development. There was obtained as major product ($>$ 50% yield) the hydroxy lactone 7[6] (infrared absorption due to carbonyl at 1736 $cm^{-1}$ in $CCl_4$), $R_f$ 0.19 on silica gel plates with 94:6 methylene chloride-methanol (as compared with $R_f$ values of 0.44 for triphenylphosphine oxide and 0.13 for the methyl ester of 6). Although the pmr and mass spectral data support structure 7 for this lactone, they do not exclude the isomeric 1 → 15 lactone structure. However, this latter possibility, intrinsically less likely because of a very high degree of strain in the 1 → 15 lactone ring, is definitely excluded by the observation that the hydroxy lactone is readily oxidized by manganese dioxide in methylene chloride (2 hr at 23°) to a conjugated enone ($\Delta^{13}$-15-one)-lactone, (infrared absorption in $CH_2Cl_2$ at 1738, 1673 and 1639 $cm^{-1}$) as expected for 7. Formation of a 1→11 lactone from the hydroxy acid 6 clearly indicates the endo orientation of the carboxyl chain attached to C-6 since such a bridge is not possible for an exo oriented sidechain.

As expected from this result, no lactone was produced from the more polar acid 5 under the same conditions which effectively lactonize the less polar isomer 6.[8]

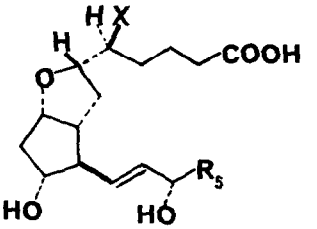
The above assignments of exo and endo orientations at C-6 to the more polar and less polar isomeric series are indicated also by carbon-13 chemical shift data obtained for the free acids of 3a and 4a. The carbon-13 spectra reveal upfield shifts for C-6 and C-9 (of 2.2 and 1.6 ppm, respectively) for the more polar isomer relative to the less polar isomer. Such an upfield shift may be attributed to a gamma effect by an exo-oriented bromo-alkyl sidechain at C-6.[10]




3a, X = Br

3b, X = H

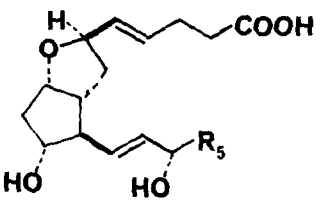
3c, X = $SeC_6H_5$




4a, X = Br

4b, X = H

4c, X = $SeC_6H_5$

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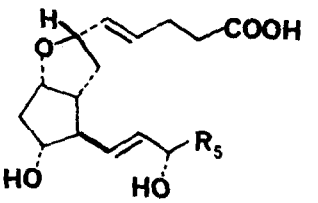


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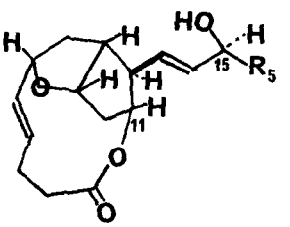


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## References and Notes


1. E. J. Corey, G. E. Keck and I. Székely, J. Am. Chem. Soc., 99, 2006 (1977).
2. E. J. Corey, I. Székely and C. S. Shiner, Tetrahedron Lett., 3529 (1977).
3. For other publications describing this same approach see, (a) J. Fried and J. Barton, Proc. Nat. Acad. Sci. U.S., 74, 2199 (1977); (b) R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizak, and U. Axen, J. Am. Chem. Soc., 99, 4182 (1977); (c) I. Tömösközi, G. Galambos, V. Simonidesz, and G. Kovacs, Tetrahedron Lett., 2627 (1977); (d) N. Whittaker, ibid., 2805 (1977); and (e) K. C. Nicolaou and W. E. Barnette, Chem. Comm., 331 (1977).
4. Submission of this letter follows the recent appearance of a note on the same subject by N. A. Nelson, J. Am. Chem. Soc., 99, 7362 (1977). The conclusions reached therein and in the present paper are identical, although the sequences used for determination of stereochemistry are different. The earliest correct assignment of stereochemistry of the halo ether intermediates was reported in reference 3a.
5. These stereochemical designations, which follow unambiguously from the information presented herein, are introduced at this point for clarity of presentation.
6. Satisfactory infrared, proton magnetic resonance and high resolution mass spectral data were obtained for all stable intermediates.
7. E. J. Corey and D. J. Brunelle, Tetrahedron Lett., 3409 (1976) and references therein cited; E. J. Corey and S. Bhattacharyya, ibid., 3919 (1977).
8. Although the exo carboxylic acid 5 might conceivably be subject to 1→15 lactonization, examination of models indicates that this ring system is very strained.
9. Assignments were made from wide-band proton noise decoupled and single-frequency, off-resonance decoupled spectra and by analogy with the previously reported spectrum of $PGF_{2\alpha}$ (see, G. F. Cooper and J. Fried, Proc. Nat. Acad. Sci., U.S., 70, 1579 (1973)).
10. This research was assisted financially by a grant from the National Science Foundation.