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STEREOCONTROLLED SYNTHESIS OF 7-HYDROXY- AND 7-ACETOXY-PGI_2: NEW STABLE PGI_2 ANALOGUES†

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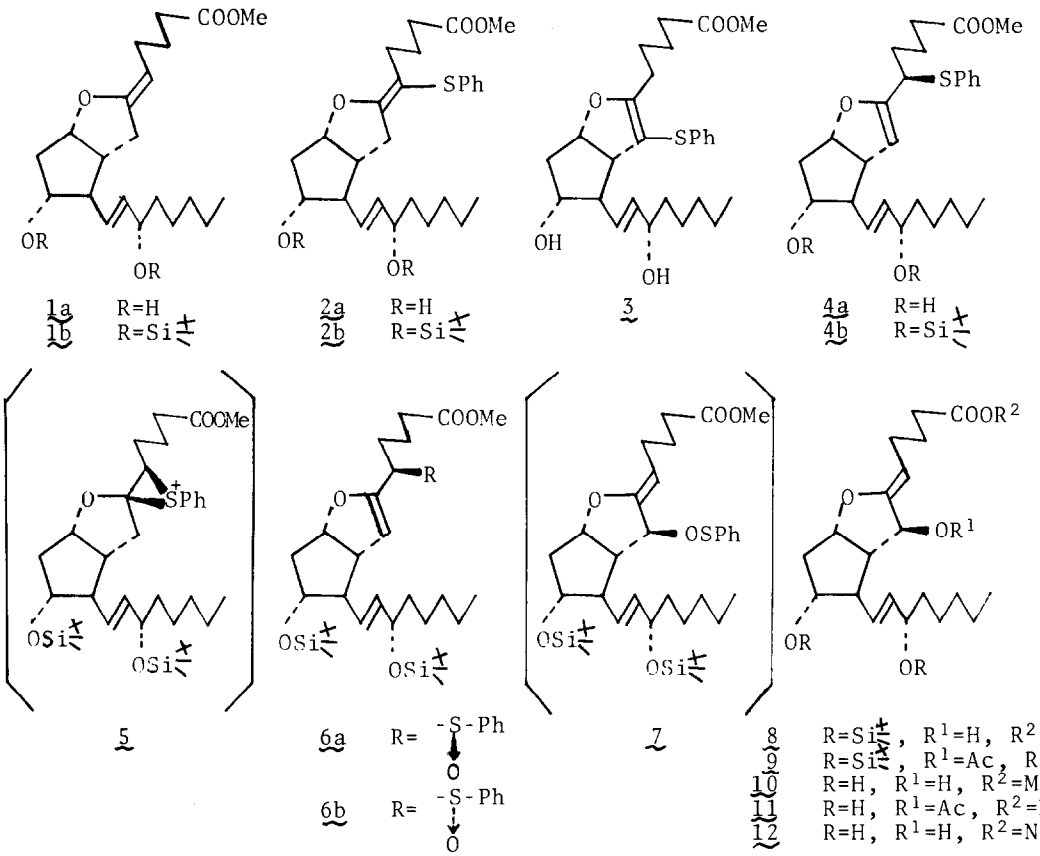
Stable analogues of PGI_2, 7-hydroxy- and 7-acetoxy-PGI_2, were synthesized from protected PGI_2 methyl ester 1b *via* sulfoxides 6a, 6b through stereocontrolled sulfoxide-sulfenate rearrangement.

Since a part of limitations of PGI_2 for clinical use is the hydrolysis-sensitive property due to its vinyl ether moiety,[1] stable PGI_2 analogues have been attractive target molecules to be synthesized.[2,3,4] One of the efficient approaches to this end is to introduce an electron withdrawing group around the vinyl ether function. To date there exist a few reports concerning the synthesis of stable PGI_2 analogues in this respect.[3] Previously we synthesized 5-PhS-PGI_2 2a and 7-PhS-Δ^6-PGI_1 3 and, in fact, introduction of the PhS-function in the vinyl ether double bond stabilized the vinyl ether linkage but lowered the biological activities as well.[4] To obtain chemically stable PGI_2 analogues retaining biological activity, we have explored another entry of stable PGI_2 analogues. We report here the stereocontrolled synthesis of 7-hydroxy- and 7-acetoxy-PGI_2 derivatives which were found to be more stable than PGI_2.

In our previous study,[4] PGI_2 methyl ester 1a was subjected to react with PhSCl to give vinyl sulfides 2a and 3, which would be formed partly *via* allyl sulfide intermediate 4a by way of the acid catalyzed rearrangement by HCl produced during the reaction. When, in the presence of Et_3N (3 eq.) to scavenge HCl, PhSCl (1.5 eq.) was added to 1b in benzene at r. t., allyl sulfide 4b[5] could be obtained in 86% yield.[6] From the steric consideration of the *cis*-bicyclo[3.3.0] system, it is reasonable that the phenylthio group approached from the less hindered β-side of the Δ^5-double bond to form the episulfonium ion intermediate 5, whose C-7 proton was then eliminated to form allyl sulfide 4b. Thus, the configuration at C-5 of 4b was assigned to R. Interestingly, when a chloroform solution of 4b was treated with a catalytic amount of conc. H_2SO_4 at r. t., the Δ^6-double bond rapidly isomerized to give (5E)-sulfide 2b[7] in 83% yield without formation of the (5Z)-isomer. This fact further supports the 5R-configuration of 4b considering the acid catalyzed concerted allyl proton rearrangement initiated by the proton addition to C-7 from the less hindered



β-side. Oxidation of allyl sulfide 4b with m-chloroperbenzoic acid (1.2 eq.) in CH_2Cl_2-aqueous 0.05M $NaHCO_3$ gave an isomeric mixture of sulfoxides 6a and 6b in 53% yield, which could not be isolated as single isomers because of the rapid epimerization of the allyl sulfoxides *via* sulfenate ester 7, *i.e.* 6a ⇌ 7 ⇌ 6b.[8] Treatment of the mixture of 6a and 6b with Et_2NH or $(Me_2N)_3P$ (15 eq.) in THF (r. t., 12 h) gave rearranged alcohol 8[9] in 68% yield. The silyl protecting groups of 8 were removed with n-Bu_4NF-Et_3N (8 eq.) in THF (r. t., 2 h) to give (7S)-hydroxy-PGI_2 methyl ester 10 in 87% yield, which was hydrolyzed with NaOH-MeOH-H_2O to give (7S)-hydroxy-PGI_2 sodium salt solution 12.

The stereochemistry of alcohol 8 was determined as follows. In the ^{1}H-nmr spectrum the C-5 vinyl proton of 8 appeared at 4.38 ppm, while those of PGI_2 methyl ester 1a and its (5E)-isomer 13 have been reported to appear at 4.16 and 4.67 ppm, respectively.[10] Considering that the downfield shift by 0.22 ppm from PGI_2 methyl ester 1a was caused by the C-7 hydroxyl group,[11] the geometry of the

Δ^5-olefin was assigned to Z. Furthermore, the Z-geometry of the Δ^5-double bond was unambiguously determined on the basis of the assumption that (5R)-phenylsulfinyl group concertedly[8] migrated to the less hindered β-side of 7-position to form sulfenate ester 7 which lead to alcohol 8.[12] Thus in order to form the (5Z)-isomer from sulfoxides 6a and 6b, the C-7 configuration of 8 must be S.

Treatment of 6a and 6b with Ac_2O-pyridine (60°C, 2 h) gave acetate 9[13] in 62% yield. Deprotection with n-Bu_4NF-Et_3N (10 eq.) in THF (r. t., 30 min) gave (7S)-acetoxy-PGI_2 methyl ester 11 which was hydrolyzed to give 12. The Δ^5-olefin geometry was assigned to Z as above from the ^{1}H-nmr study in which the C-5 vinyl proton of 9 appeared at 4.56 ppm, shifted downfield by 0.40 ppm from that of 1a. Since this rearrangement possibly proceeded *via* sulfenate ester 7,[14] the C-7 configuration was assigned to S as in the case of 8.

Interestingly, 7-oxygenated PGI_2 derivatives 10 and 11 thus obtained were stable enough to be purified with normal silica gel preparative TLC without using base.[15] Moreover, the potency of the inhibition of platelet aggregation of 11 was maintained in a PH7.4 buffer solution for at least 4 h at r. t., while that of PGI_2 methyl ester 1a fell down to less than one tenth even at 0°C (4 h). The stability of these 7-oxygenated PGI_2 derivatives 10 and 11 are probably ascribed to the inductive effect[16] of the C-7 hydroxyl or acetoxy group. Analogue 11 had weak inhibitory activity on platelet aggregation and relatively higher hypotensive activity, but 10 and 12 did not show any of these activities.[17]

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References and Notes

+ Prostaglandin Chemistry XV. For part XIV; see ref. 4.

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2. For example, M. Shibasaki, Y. Torisawa, and S. Ikegami, Chem. Lett., 1247 (1980); W. Skuballa, Tetrahedron Lett., 21, 3261 (1980); R. A. Johnson and E. G. Nidy, J. Org. Chem., 45, 3802 (1980); and references cited therein.
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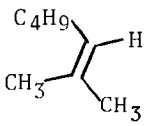
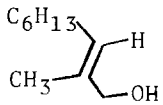
5. ^{1}H-nmr (CCl_4) δ 3.65 (3H, s), 3.5-4.2 (3H, br), 4.6-4.9 (1H, br), 4.65 (1H, d, J=3Hz), 5.45 (2H, m); MS m/e 702 (M^+).
6. All the yields indicated in this paper are isolated yields by preparative silica gel TLC or silica gel column chromatography.
7. Its ^{1}H-nmr spectrum and TLC behavior completely coincided with those of (5E)-sulfide 2b obtained previously.[4]
8. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, J. Am. Chem. Soc., 90, 4869 (1968).
9. ^{1}H-nmr (CCl_4) δ 3.66 (3H, s), 3.6-4.2 (2H, br), 4.14 (1H, s), 4.38 (1H, t, J=7Hz), 4.5-4.9 (1H, m), 5.5 (2H, m); MS m/e 610 (M^+).
10. R. A. Johnson, F. H. Lincoln, E. G. Nidy, W. P. Schnider, J. L. Thompson, and U. Axen, J. Am. Chem. Soc., 100, 7690 (1978).
11. The following allyl hydroxyl group is known to cause the downfield shift of the *cis*- and *trans*-vinyl proton by 0.26 and 0.14 ppm, respectively; see Standard Proton Nmr Spectra Collection, No. 7926, Sadtler Research Laboratories, and E. J. Corey and H. Yamamoto, J. Am. Chem. Soc., 92, 226 (1970).

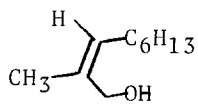
5.05 ppm



5.31 ppm



5.19 ppm



12. D. A. Evans, and G. C. Andrews, Acc. Chem. Res., 7, 147 (1974).
13. ^{1}H-nmr (CCl_4) δ 2.01 (3H, s), 3.63 (3H, s), 3.6-3.9 (1H, m), 3.9-4.2 (1H, m), 4.56 (1H, t, J=7Hz), 4.5-4.8 (1H, m), 5.25 (1H, d, J=1Hz), 5.5 (2H, m); MS m/e 652 (M^+).
14. S. Yamagiwa, H. Sato, N. Hoshi, H. Kosugi, and U. Uda, J. Chem. Soc. Perkin I, 570 (1979).
15. PGI_2 methyl ester 1a is usually purified by Florisil column chromatography using an eluent containing Et_3N.[10]
16. In the ^{13}C-nmr C-5 of acetate 11 (102.5 ppm) shifted downfield by 5.6 ppm from that of PGI_2 methyl ester 1a (96.9 ppm)[10], showing that the electron density of the Δ^5-double bond of 11 is lower than that of 1a.
17. Inhibitory activity on ADP-induced rabbit platelet aggregation of 11 was about one thousand times weaker (IC_{50} = 8.2 μg/ml) than that of PGI_2 sodium salt, and 11 showed a transient fall of blood pressure at doses more than 1 μg/Kg which was about one hundred times weaker than that of PGI_2 sodium salt; submitted to J. Pharm-bio. Dyn.

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