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HALOGENATION OF PGI_2-ENOL ETHER WITH N-HALOSUCCINIMIDE SYNTHESIS OF NEW STABLE PGI_2 ANALOGS, 5-CHLORO- AND 5,7-DICHLORO-PGI_2[+]

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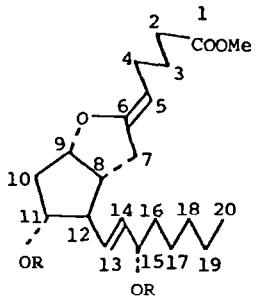
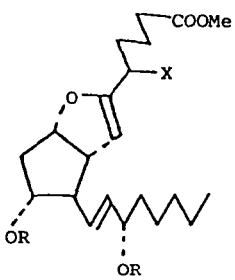
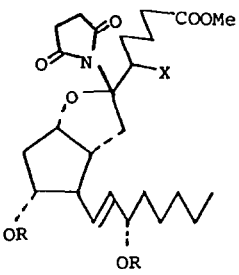
Reaction of the enol ether of PGI_2 with N-halosuccinimide and subsequent isomerization or halogenation gave new stable PGI_2 analogs, 5-chloro- and 5,7-dichloro-PGI_2

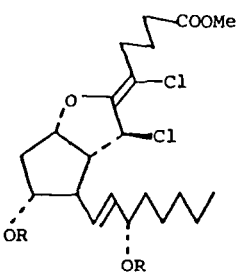
Many efforts have been made to obtain stable PGI_2 analogs which would be expected to be promising therapeutic agents [1] One of the efficient methods to stabilize PGI_2 is to introduce (an) electron-withdrawing group(s) around the enol ether function in the molecule [2] In this respect, we reported the syntheses of 5-PhS-,[3] 7-OH and 7-OAC-PGI_2,[4] which were stable, however, unfortunately with weak biological activities This time we chose (a) halogen atom(s) as (an) electron-withdrawing group(s), which would be introduced in the molecule of PGI_2 by the electrophilic halogenation It is well documented that the electrophilic halogenation of silyl enol ethers with N-halosuccinimide gives α-haloketones,[5] whereas the reaction of alkyl enol ethers has not been much studied [6] We report here that the reaction of PGI_2 with N-halosuccinimide and subsequent isomerization or halogenation led to new stable PGI_2 analogs of 5-chloro- and 5,7-dichloro-PGI_2

Halogenation of *t*-butyldimethylsilyl-protected PGI_2 methyl ester 1a[7] with N-chloro- or N-bromosuccinimide (1 05 equiv , CCl_4 , r t , 1 h) proceeded stereoselectively to afford silyl-protected (5*R*)-5-chloro-Δ^6-PGI_1 methyl ester 2a[8] or (5*R*)-5-bromo-Δ^6-PGI_1 methyl ester 2b in 60% or 57% yields accompanied with the formation of succinimido-adduct 4a (20%) or 4b (20%) Both compounds 2a and 2b were found homogeneous by their ^{13}C-NMR spectra and their 5*R*-configuration was tentatively assigned on the basis of the mechanistic consideration (*vide infra*) On the other hand, the similar halogenations of acetyl-protected PGI_2 methyl ester 1b gave a diastereomeric mixture of 5-chloro-Δ^6-PGI_1 methyl ester 3a (58%) (5*R* 5*S* = *ca* 5 3)[9] or 5-bromo-Δ^6-PGI_1 methyl ester 3b (60%) (5*R* 5*S* = *ca* 7 3)[9] besides respective succinimido-adduct 4c (20%) or 4d (13%) The selective formation of the 5*R*-isomers from protected PGI_2 methyl ester 1 could be accounted for the bulkiness of the C-11 substituent, which is close to the enol ether double bond as depicted in Fig 1,[10] where the halogenating agent could approach the enol ether double bond more easily from its less hindered upper side than from the lower side resulting in the selective formation of 5*R*-isomer Further chlorination of silyl-protected-(5*R*)-allyl chloride 2a was accomplished by treatment with N-chlorosuccinimide (10 equiv CCl_4, 60°C, 3 h)







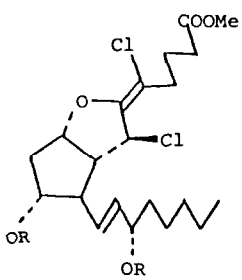


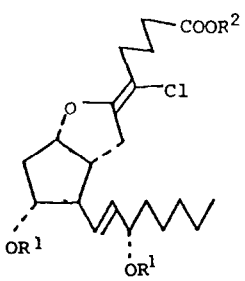
1a R=SiMe$_2$^{t}Bu
1b R=Ac

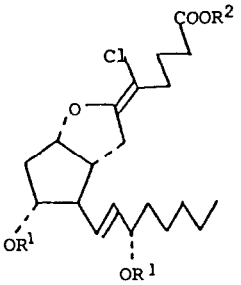
2a X=Cl(5R), R=SiMe$_2$^{t}Bu
2b X=Br(5R), R=SiMe$_2$^{t}Bu
3a X=Cl, R=Ac
3b X=Br, R=Ac

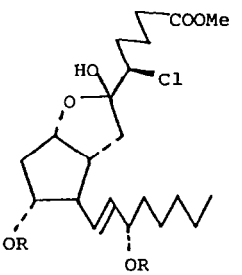
4a X=Cl, R=SiMe$_2$^{t}Bu
4b X=Br, R=SiMe$_2$^{t}Bu
4c X=Cl, R=Ac
4d X=Br, R=Ac

5 R=SiMe$_2$^{t}Bu









6 R=SiMe$_2$^{t}Bu

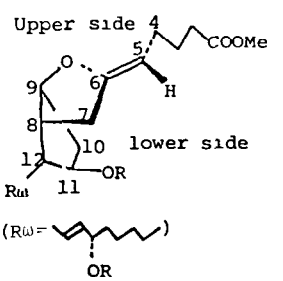
7a R^1=SiMe$_2$^{t}Bu, R^2=Me
7b R^1=H, R^2=Me
7c R^1=H, R^2=Na

8a R^1=SiMe$_2$^{t}Bu, R^2=Me
8b R^1=H, R^2=Me
8c R^1=H, R^2=Na

9 R=SiMe$_2$^{t}Bu

to afford a geometric mixture of (5*E*,7*S*)- and (5*Z*,7*S*)-5,7-dichloro PGI$_2$ methyl esters 5 and 6 in 15% and 20% yields, respectively [11]

In order to obtain 5-chloro-PGI$_2$ derivative 7, in the hope that 7 would be one of the promising stable PGI$_2$ analogs, isomerization of the endo-double bond (Δ^6) of above obtained 5-Cl-Δ^6-PGI$_1$ 2a to exo-double bond (Δ^5) was examined Previously we achieved to isomerize 5-PhS-Δ^6-PGI$_1$ 10 stereospecifically into 5-PhS-PGI$_2$ 11 in excellent yield[4] by treatment with trace conc H_2SO_4 However, the similar treatment of 5-Cl-Δ^6-PGI$_1$ 2a with trace conc H_2SO_4 gave isomerized 7a and 8a only in low yield After several examinations, the isomerization of 2a was effected as follows Treatment of a moistured benzene solution of allyl chloride 2a with a catalytic amount of pyridinium *p*-toluenesulfonate (r t , 16 h) gave hemiacetal 9 Subsequent dehydration of 9 with excess anhydrous $MgSO_4$ in refluxing benzene (1 5 h)[12] afforded



1a R=SiMe$_2$^{t}Bu
1b R=Ac

Fig. 1

5*E*-vinyl chloride 7a (20%) and 5*Z*-vinyl chloride 8a (28%) along with the starting allyl chloride 2a (18%) The silyl protecting groups of vinyl chlorides 7a and 8a were removed with n-Bu_4NF-Et_3N (15 equiv) in THF (r t , 5 h) to afford 5-chloro-PGI_2 methyl ester 7b (95%) and (5Z)-5-chloro-PGI_2 methyl ester 8b (80%) Solutions of sodium salts 7c and 8c were prepared by hydrolysis of 7b and 8b with NaOH-EtOH-H_2O (r t , 3 h) The Δ^5-olefin geometry of 5-chloro-PGI_2 methyl esters 7b and 8b, was determined on the basis of the ^{1}H-NMR (400 MHz) study with the aid of precise decoupling studies The chemical shifts of the C-4 methylene protons of 7b were found to be 2 38 ppm (1H) and 2 48 ppm (1H), while those of 8b, 2 27 ppm (2H) Moreover, the C-7 methylene protons of 7b (7α-H, 2 63 ppm, 7β-H, 2 70 ppm) appeared in a field lower than that of 8b (7α-H, 2 52 ppm, 7β-H, 2 67 ppm) Considering the deshielding effect[13] of oxygen and chlorine atoms on *cis*-related allylic protons, the Δ^5-olefin geometry of 7b and 8b were assigned to *E* and *Z*, respectively

These PGI_2 analogs described here were found to be much more stable than PGI_2 The half life of 7c and 8c in a pH 4 7 buffer solution were 1 5 h and 8 h, respectively,[14] while that of PGI_2 in a pH 5 98 buffer solution is only 22 4 seconds[15] Analog 7c showed an inhibitory activity on platelet aggregation (IC_{50}, 0 14 μg/ml), while 8c was less active The activity of 7c was retained after standing for 4 h at 0°C in a pH 7 4 buffer solution, whereas that of PGI_2 diminished to about 1/100 under the same condition

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Spectral Data

2a ^{1}H-NMR($CDCl_3$) δ 2 85-3 2(1H, br), 3 66(3H, s), 3 7-4 2(2H, m), 4 38(1H, t, J=7 Hz), 4 7-5 0 (1H, br), 5 00(1H, d, J=3 Hz), 5 52(2H, m), MS(70 eV) m/e 630, 628(M^+), ^{13}C-NMR($CDCl_3$) δ 22 0(C 55 4(C_5), 76 1(C_{11}), 83 3(C_9), 101 6(C_7), 154 8(C_6) 3a MS(20 eV) m/e 486, 484 (M^+), ^{13}C-NMR($CDCl_3$) δ 22 1 and 22 0(C_3), 54 9(C_5), 78 03 and 77 79(C_{11}), 84 9 and 84 6(C_9), 101 3 and 101 0(C_7), 155 0 and 155 4(C_6) 5 ^{1}H-NMR($CDCl_3$) δ 3 67(3H, s), 3 85(1H, q, J=8 Hz), 4 05-4 3 (1H, br), 4 79(1H, s), 4 8-5 1(1H, br), 5 53(2H, m), MS(70 eV) m/e 607, 605(M-57) 6 ^{1}H-NMR ($CDCl_3$) δ 3 67(3H, s), 3 86(1H, q, J=7 Hz), 3 9-4 2(1H, br), 4 69(1H, s), 4 85-5 1(1H, br), 5 53(2H, m), MS(70 eV) m/e 607, 605(M-57) 7b ^{1}H-NMR($CDCl_3$) δ 2 16(1H, q, J=8 Hz, C_{12}-H), 2 325(2H, t, J=7 Hz, C_2-H_2), 2 37(1H, q, J=8 Hz, C_8-H), 2 38(1H, dt, J=14 Hz, 7 Hz, C_4-H), 2 48 (1H, dt, J=14 Hz, 7 Hz, C_4-H), 2 48(1H, dt, J=14 Hz, 7 Hz, $C_{10\alpha}$-H), 2 63(1H, d, J=17 Hz, $C_{7\alpha}$-H), 2 70(1H, dd, J=17 Hz, 8 Hz, $C_{7\beta}$-H), 3 68(3H, s), 3 90(1H, br, C_{11}-H), 4 10(1H, q, J=7 Hz, C_{15}-H), 4 66(1H, dt, J=3 Hz, 8 Hz, C_9-H), 5 53(1H, dd, J=8 Hz, 15 Hz, C_{13}-H), 5 64(1H, dd, J=6 Hz, 15 Hz, C_{14}-H), MS(20 eV) m/e 402, 400(M^+) 8b ^{1}H-NMR($CDCl_3$) δ 2 17(1H, q, J=8 Hz, C_{12}-H), 2 27(2H, t, J=7 Hz, C_4-H_2), 2 33(2H, t, J=7 Hz, C_2-H_2), 2 44(1H, q, J=8 Hz, C_8-H) 2 52 (1H, d, J=16 Hz, $C_{7\alpha}$-H), 2 53(1H, dt, J=14 Hz, 8 Hz, C_{10}-H), 2 67(1H, dd, J=16 Hz, 8 Hz, $C_{7\beta}$-H), 3 67(3H, s), 3 91(1H, q, J=8 Hz, C_{11}-H), 4 10(1H, q, J=7 Hz, C_{15}-H), 4 74(1H, dt, J=3 Hz, 8 Hz, C_9-H), 5 52(1H, dd, J=8 Hz, 16 Hz, C_{13}-H), 5 64(1H, dd, J=6 Hz, 16 Hz, C_{14}-H), MS(20 eV) m/e 402, 400(M^+)

References and Notes

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7. The starting PGI_2 derivatives 1a and 1b were prepared according to the procedure of Johnson et al (see ref 12), and used without purification in the presence of trace amount of triethylamine

8 Allyl chloride 2a was also obtained in 55% yield by treatment of 1a with *t*-butylhypochlorite (1 25 equiv , CH_2Cl_2, -70°C, 30 min)

9 The isomer ratio was estimated by the relative intensity of their ^{13}C-NMR signals and their C-5 configuration was tentatively determined by the mechanistic consideration

10 The crowded concave of this bicyclo[3 3 0] system has been shown by the facile formation of 6(9α), 6(11α)-dioxido-15S-hydroxyprost-13E-enoic acid methyl ester from PGI_2 methyl ester, see K Shimoji, Y Konishi, Y Arai, M Hayashi, and H Yamamoto, J Am Chem Soc , 100, 2547 (1978), J Ueda, T Yanagisawa, M Shibasaki, and S Ikegami, Tetrahedron Lett , 1978, 2511

11 The C-7 configuration was assigned to *S* since the C-7 proton of 5 and 6 appeared as a singlet at 4 79 ppm and 4 69 ppm, respectively, we have observed the coupling constant between 7α- and 8β-proton was less than 1 Hz (see ref 4) The Δ^5-olefin geometry of 5 and 6 was tentatively assigned to *E* and *Z*, respectively, based on the difference of the C-7 proton chemical shift caused by the deshielding effect of C-5 chlorine atom (see ref 13)

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14 The half life was measured by monitoring the intensity of their UV absorption (λ=210 nm)

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