Communications to the Editor

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SYNTHESIS OF NEW SULFUR-CONTAINING PROSTAGLANDIN I_1[1)]

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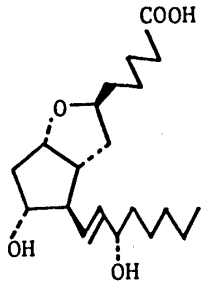
A synthesis of 4-thia-PGI_1 involving addition of alkylsulfenyl chloride to allylcyclopentanol and spontaneous intramolecular cyclization is described.

KEYWORDS——4-thia-prostaglandin I_1: intramolecular cyclization with sulfenyl chloride; 2-allyl-4-hydroxycyclopent-2-en-1-one; stereochemistry; (1R,5S)-6,6-dimethyl-4-hydroxy-3-oxabicyclo[3.1.0]hexan-2-one

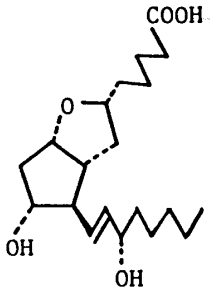
Although a number of PGI_2 analogs have been synthesized, there are a few reports of PGI_1 (5,6-dihydro-PGI_2) analogs,[2)] which are regarded as stable PGI_2 analogs. PGI_1 has a different biological profile from PGI_2;[3)] *e.g.*, 6β-PGI_1 has strong anti-ulcer activity with weak vasodepressing and anti-aggregatory activities. Thus it is interesting to develop a new convenient synthesis of PGI_1 analogs aiming promising therapeutic agents free from side effects possibly derived from PGI_2. In the course of our synthetic studies of stable PGI_2 analogs using sulfenyl chloride,[4)] we have paid attention to the unique reactivity of sulfenyl chloride[5)] to help us synthesize new sulfur-containing PGI_1 analogs. We report here the efficient synthesis of 4-thia-PGI_1 which involves the addition of methoxycarbonylethylsulfenyl chloride to allylcyclopentanol 3 and spontaneous intramolecular cyclization.

For the synthesis of 4-thia-PGI_1, 2-allyl-4-hydroxycyclopent-2-en-1-one (*dl*)-1a,[6)] prepared from furfural according to the modified Piancatelli's method,[7)] was selected as a key synthetic intermediate. The Michael addition of the protected allylcyclopentenone (*dl*)-1b with optically active mixed cuprate prepared from (1E,3S)-3-*t*-butyldimethylsilyloxy-1-lithio-octene and CuSPh gave a diastereomeric mixture 2' composed of allylcyclopentanone 2 and *ent*-15[8)]-*epi*-2 in 50% yield.[9)] Stereoselective reduction of cyclopentanone 2' was accomplished with L-Selectride[10)] (THF, -70°C, 15 min) to give a diastereomeric mixture 3' composed of allylcyclopentanol 3 and *ent*-15-*epi*-3 in 71% yield.[9)] Treatment of 3' with methoxycarbonylethylsulfenyl chloride[11)] (1.2 eq. CH_2Cl_2, -60°C, 0.5 h) in the presence of K_2CO_3 (3 eq.) gave a diastereomeric mixture of protected 4-thia-PGI_1 methyl esters 4a, 5a, 6a, and 7a in 70% yield.[9)] Deprotection with AcOH-THF-H_2O (3:2:2, r.t., 3 days) gave a diastereomeric mixture of four 4-thia-PGI_1 methyl esters 4b, 5b, 6b, and 7b in 22%, 16%, 17%, and 19% yields in decreasing order of polarity after isolation with silica gel column chromatography.

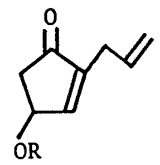
In order to determine the stereochemistry of the four 4-thia-PGI_1 methyl esters so obtained, two of them (4 and 5) were prepared from (R)-1a, which was



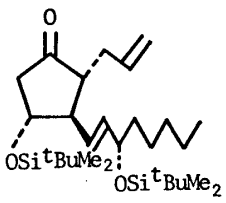
6β-PGI$_1$



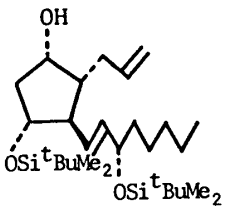
6α-PGI$_1$



1a: R=H
1b: R=Si^{t}BuMe$_2$
1c: R=Bz

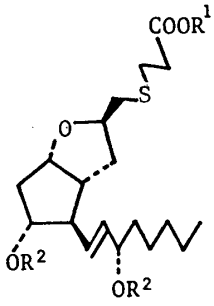


2

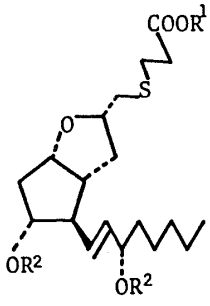


3

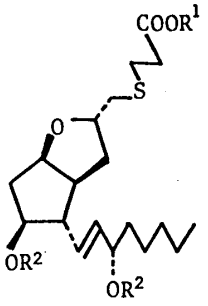
2': (2 and *ent*-15-*epi*-2) 3': (3 and *ent*-15-*epi*-3)



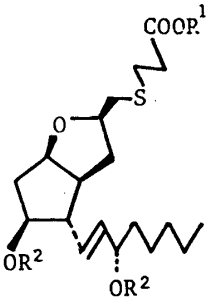
4a
4b
4c



5a
5b
5c

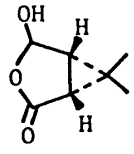


6a
6b
6c



7a
7b
7c

a: R^1=Me, R =Si^{t}BuMe$_2$; b: R^1=Me, R^2=H; c: R^1=R^2=H



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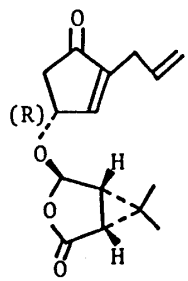

(R)-9

resolved using (1R,5S)-6,6-dimethyl-4-hydroxy-3-oxabicyclo[3.1.0]hexane-2-one 8[12] as a resolving agent.[13] The two 4-thia-PGI_1 methyl esters (4b and 5b) thus obtained were identical with two of the more polar components of the four isomers. Thus the two more polar components were assigned as 6α- and 6β-4-thia-PGI_1 methyl esters.[14] In the ^{1}H-NMR spectra of the two-4-thia-PGI_1 methyl esters (4b and 5b), the C-9 proton of the more polar isomer (4.48 ppm) appeared in a field lower than that of the less polar isomer (4.32 ppm). From these observations the more polar isomer was assigned to 6β-4-thia-PGI_1 methyl ester 4b and the less polar isomer, to 6α-4-thia-PGI_1 methyl ester 5b as in the case of PGI_1.[15] This assignment was further supported by the fact that 6β-PGI_1 derivatives are more polar than their 6α-isomers.[16] From these considerations the four stereoisomers of the 4-thia-PGI_1 methyl esters obtained as mentioned above were determined as 6β-4-thia-PGI_1 methyl ester 4b, 6α-4-thia-PGI_1 methyl ester 5b, *ent*-15-*epi*-4b (6b) and *ent*-15-*epi*-5b (7b)[17] in decreasing order of polarity. Conversion of methyl esters 4b, 5b, 6b, and 7b to the corresponding acids 4c, 5c, 6c, and 7c was accomplished by the usual hydrolysis.

This synthetic method using the new key intermediate 1 enables us to prepare various chemically stable 4-thia-PGI_1 analogs. Preliminary tests showed that analog 5b had preventive activity on ethanol elicited gastric lesions, while 4b had weaker activity. Both compounds did not show inhibitory activity on platelet aggregation.

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8) PG-numbering.
9) Each diastereomer could not be separated by silica gel column chromatography.
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11) This reagent was prepared from the corresponding thiol and N-chlorosuccinimide in CH_2Cl_2 or benzene.
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13) A benzene solution of (*dl*)-1a and the resolving agent 8 was refluxed azeotropically (3h) in the presence of pyridinium *p*-toluenesulfonate (catalytic amount) to give adducts (R)-9 and (S)-9 in 40% and 42% yield, respectively, after separation by silica gel column chromatography. The resolving agent moiety of (R)-9 was removed by refluxing its dioxane-water solution (3h) to obtain (R)-1a in 90% yield. The absolute configuration of (R)-1a was determined from the CD spectrum study of the corresponding benzoate 1c ($[\theta]_{229}=+1.1\times10^5$ in cyclohexane); see N. Harada and K. Nakanishi, Acc. Chem. Res., 5, 257 (1972).
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17) 4b NMR ($CDCl_3$) δ 3.70 (3H, s), 3.98–4.30 (3H, m), 4.48 (1H, m), 5.54 (2H, m); MS (20 eV) (bis-TMS derivative) m/e 515.2675 (M-CH_3, calcd for $C_{25}H_{47}O_5SSI_2$, 551.2685) 530 (M^+), 515, 499, 440; 5b NMR ($CDCl_3$) δ 3.70 (3H, s), 3.76–4.16 (3H, m), 4.32 (1H, m), 5.54 (2H, m); MS (20 eV) (bis-TMS derivative) m/e 530 (M^+), 515, 499, 440; 6b NMR ($CDCl_3$) δ 3.70 (3H, s), 3.98–4.34 (3H, m), 4.48 (1H, m), 5.60 (2H, m); MS (20 eV) (bis-TMS derivative) m/e 530 (M^+), 515, 499, 440; 7b NMR ($CDCl_3$) δ 3.70 (3H, s), 3.79–4.20 (3H, m), 4.32 (1H, m), 5.54 (2H, m); MS (20 eV) (bis-TMS derivative) m/e 530 (M^+), 515, 499, 440.

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