Communications to the Editor

[Chem. Pharm. Bull.]
30(3)1102-1105(1982)]

SYNTHESIS OF NEW SULFUR-CONTAINING PROSTAGLANDIN I₁¹⁾

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A synthesis of 4-thia-PGI₁ involving addition of alkylsulfenyl chloride to allylcyclopentanol and spontaneous intramolecular cyclization is described.

KEYWORDS—4-thia-prostaglandin I₁: 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 PGI₂ analogs have been synthesized, there are a few reports of PGI₁ (5,6-dihydro-PGI₂) analogs,²⁾ which are regarded as stable PGI₂ analogs. PGI₁ has a different biological profile from PGI₂; ³⁾ *e.g.*, 6 β -PGI₁ has strong anti-ulcer activity with weak vasodepressing and anti-aggregatory activities. Thus it is interesting to develop a new convenient synthesis of PGI₁ analogs aiming promising therapeutic agents free from side effects possibly derived from PGI₂. In the course of our synthetic studies of stable PGI₂ analogs using sulfenyl chloride,⁴⁾ we have paid attention to the unique reactivity of sulfenyl chloride⁵⁾ to help us synthesize new sulfur-containing PGI₁ analogs. We report here the efficient synthesis of 4-thia-PGI₁ which involves the addition of methoxycarbonylethylsulfenyl chloride to allylcyclopentanol **1** and spontaneous intramolecular cyclization.

For the synthesis of 4-thia-PGI₁, 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*-15⁸⁾-*epi*-**2** in 50% yield.⁹⁾ Stereoselective reduction of cyclopentanone **2'** was accomplished with L-Selectride¹⁰⁾ (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 chloride¹¹⁾ (1.2 eq. CH₂Cl₂, -60°C, 0.5 h) in the presence of K₂CO₃ (3 eq.) gave a diastereomeric mixture of protected 4-thia-PGI₁ methyl esters **4a**, **5a**, **6a**, and **7a** in 70% yield.⁹⁾ Deprotection with AcOH-THF-H₂O (3:2:2, r.t., 3 days) gave a diastereomeric mixture of four 4-thia-PGI₁ 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-PGI₁ methyl esters so obtained, two of them (**4** and **5**) were prepared from (R)-**1a**, which was

6β-PGI₁ 6α-PGI₁

1a: R=H

1b: R=Si^tBuMe₂

1c: R=Bz

2

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

3

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

4a

4b

4c

5a

5b

5c

6a

6b

6c

7a

7b

7c

a: R¹=Me, R = Si^tBuMe₂; b: R¹=Me, R²=H; c: R¹=R²=H

8

(R)-9

resolved using (1R,5S)-6,6-dimethyl-4-hydroxy-3-oxabicyclo[3.1.0]hexane-2-one 8¹²⁾ as a resolving agent.¹³⁾ The two 4-thia-PGI₁ 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 6 α - and 6 β -4-thia-PGI₁ methyl esters.¹⁴⁾ In the ¹H-NMR spectra of the two-4-thia-PGI₁ 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 6 β -4-thia-PGI₁ methyl ester 4b and the less polar isomer, to 6 α -4-thia-PGI₁ methyl ester 5b as in the case of PGI₁.¹⁵⁾ This assignment was further supported by the fact that 6 β -PGI₁ derivatives are more polar than their 6 α -isomers.¹⁶⁾ From these considerations the four stereoisomers of the 4-thia-PGI₁ methyl esters obtained as mentioned above were determined as 6 β -4-thia-PGI₁ methyl ester 4b, 6 α -4-thia-PGI₁ 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-PGI₁ 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.

ACKNOWLEDGEMENT The authors are grateful to Professor S. Ikegami, Teikyo Univ., for valuable suggestions on the reaction of sulfenyl chloride.

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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 g 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 ($[\theta]_{229} = +1.1 \times 10^5$ 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 $\text{C}_{25}\text{H}_{47}\text{O}_5\text{SSI}_2$, 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.

(Received January 29, 1982)