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SYNTHESIS OF THE SULFUR ANALOG OF Δ^6-PGI_1

Masakatsu SHIBASAKI, Yasuhiro TORISAWA, and Shiro IKEGAMI*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01

A synthesis of the sulfur analog of Δ^6-PGI_1 with potent inhibitory activity in platelet aggregation is described. The synthesis starting from the suitably protected Corey lactone includes the hydroxylation of the lactone and the novel intramolecular addition of the sulfenyl bromide.

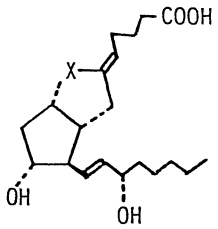
In the course of our synthetic studies on the chemically stable and biologically potent analogs of prostacyclin (PGI_2) with the aim of developing drugs, the carbon analog (4) of Δ^6-PGI_1 was previously synthesized. Unlike the high inhibitory activity of Δ^6-PGI_1 (2) to platelet aggregation,[1] the biological behaviors of the carbon analog (4) were unexpectedly weak.[2] Accordingly, in order to clarify the structure-activity relationship in the Δ^6-PGI_1 series, the sulfur analog (3) was chosen as an attractive target. In this communication we wish to report an efficient synthesis of the sulfur analog (3) of Δ^6-PGI_1.

In the synthetic plan of the sulfur analog (3), the *trans*-hydroxy-aldehyde (5) was selected as a key synthetic intermediate. However, methodology for the stereo and regiocontrolled synthesis of 5 seems to remain undeveloped. After many synthetic attempts, we finally found that the suitably protected Corey lactone (6) is a reasonable starting material for the present purpose.

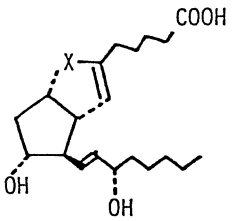
Thus, the formation of the enolate of 6 (1.2 equiv of LDA, THF, -78°) and subsequent treatment with 1.5 equiv of MoO_5.pyridine.HMPA complex[3] (-78°~r.t.) afforded the desired hydroxy-lactone (7) up to 80% yield as a mixture of diastereoisomers[4] [IR(neat) 3400, 1770 cm-1]. Reduction of 7 with 3 equiv of LAH (ether, reflux, 2 h) provided the triol (8) [MS(EI) 359(M^+-CH_2OH)] in 80% yield. The selective protection of the glycol moiety of the triol (8) was accomplished by treatment of 8 with 5 equiv of 2,2-dimethoxypropane and a catalytic amount of anhydrous *p*-toluenesulfonic acid in dry benzene at room temperature for 0.5 h, giving the hydroxy-acetonide (9) [IR(neat) 3500 cm-1; PMR($CDCl_3$,TMS) δ1.40, 1.45 (two singlets, $2CH_3$)] in 60% yield.[5] The structure of 9 was securely confirmed by the following transformation. The oxidation of 9 with PCC in the presence of sodium acetate afforded the 5-membered ketone (10) [IR(neat) 1740 cm-1] as a single product in 70% yield.

The next stage of the synthesis required the protection of the remaining hydroxy group with the inversion of its configuration. This was easily achieved by stirring 9 with triphenylphosphine (2 equiv), benzoic acid (1.5 equiv) and diethyl azodicarboxylate (2 equiv) at room temperature for 0.5 h,[6] affording the inverted benzoate (11) [MS(EI) 519(M^+-CH_3)] in nearly quantitative yield. The stereochemistry of the benzoate (11) was determined by the fact that treatment of 11 with potassium carbonate in methanol gave the alcohol (12), definitely different from the starting alcohol (9) [*Rf* values on silica gel TLC plate eluted with ether-petr.ether (1:1), 0.24 for 9 and 0.15 for 12].

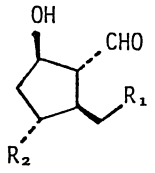
The extension of the lower side-chain was carried out by the standard method as follows; (i) desilylation of 11 with tetra-*n*-butylammonium fluoride in THF at room temperature for 5 h



1a: X=O
1b: X=S
1c: X=CH_2



2: X=O
3: X=S
4: X=CH_2



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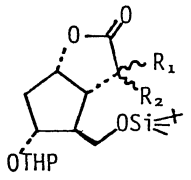
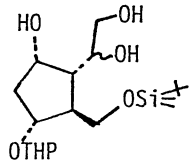


6: R_1=R_2=H
7: R_1=OH, R_2=H



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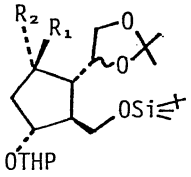
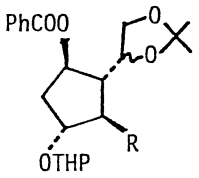
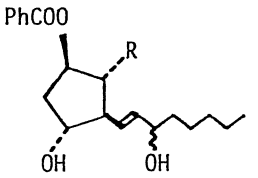


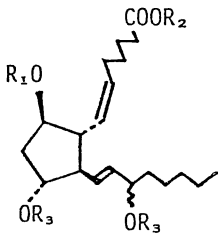
9: R_1=H, R_2=OH
10: R_1-R_2=O
11: R_1=OCOPh, R_2=H
12: R_1=OH, R_2=H



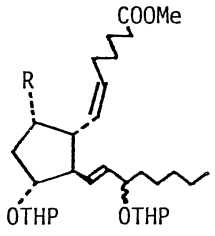
13: R=CH_2OH
14: R=



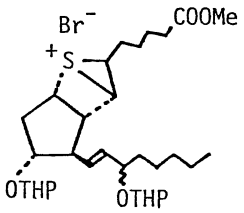
15: R=CH(OH)CH_2OH
16: R=CHO



17: R_1=COPh, R_2=R_3=H
18: R_1=COPh, R_2=Me, R_3=H
19: R_1=H, R_2=Me, R_3=THP
20: R_1=Ts, R_2=Me, R_3=THP



21: R=SAc
22: R=S



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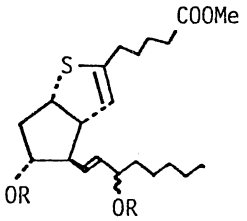

24: R=THP
25: R=H

to the alcohol (13) (85% yield), (ii) oxidation of 13 with 10 equiv of Collins reagent and then the Emmons-Horner reaction using dimethyl (2-oxoheptyl)phosphonate to the enone (14) [IR(neat) 1720, 1665, 1620 cm-1; MS(EI) 499(M^+-CH_3)] (85% yield). Reduction of 14 with $NaBH_4$ in methanol at -25° for 0.5 h, followed by acidification by the addition of excess oxalic acid and continued stirring at room temperature for 24 h gave the crystalline tetraol (15) [MS(EI) 374(M^+-H_2O)] as a mixture of the diastereoisomers at the C-15 position (PG numbering) in nearly quantitative yield.

Construction of the upper side-chain from 15 proved to be unexpectedly so difficult that the careful selection of reaction conditions was required. Oxidation with excess $NaIO_4$ in dioxane-water (3:1) cleanly converted 15 to the aldehyde (16). Since the aldehyde (16) was surprisingly unstable, it was immediately treated with Wittig ylid (5 equiv) prepared from (5-carboxypentyl)triphenylphosphonium bromide[7] and sodium methylsulfinylmethanide in DMSO at room temperature for 0.5 h. The crude acid (17) was then esterified with CH_2N_2 and purified by

silica gel column chromatography to afford the benzoate methyl ester (18), which was subsequently protected as THP ether, followed by deprotection of the benzoate group (K_2CO_3 in methanol). Through this sequence, the desired hydroxy-ester (19) was securely separated from the unwanted side product[8] and obtained in *ca.* 20% overall yield from the tetraol (15) [IR(neat) 3450, 1740 cm-1; PMR($CDCl_3$,TMS) δ5.10-5.70 (multiplet, 4H, olefinic protons); MS(CI,NH_3) 554(M^++NH_4)]. The stereochemistry of the newly formed double bond in 19, one of the most important points,[9] was tentatively assigned as *cis*-configuration from much literature precedent.[10]

Introduction of a sulfur atom with the concomitant inversion of 9-hydroxy configuration was easily achieved by our previously reported method.[12] Thus, treatment of the alcohol (19) with 10 equiv of tosyl chloride in pyridine at room temperature afforded the tosylate (20) in 80% yield, which was converted to the corresponding thioacetate (21) [IR(neat) 1740, 1690 cm-1; MS(CI,NH_3) 612(M^++NH_4)] in nearly quantitative yield by reaction with sodium thioacetate in DMSO-DMF (1:1) at 50~60° for 5 h. Then the thioacetate (21) was directly oxidized to the disulfide (22)[12] in 95% yield by treatment with 2.5 equiv of sodium methoxide in methanol under oxygen atmosphere at room temperature for 10 h, followed by esterification with CH_2N_2 [*Rf* values on silica gel TLC plate eluted with ether-petr.ether (2:1), 0.45 for 21 and 0.35 for 22].

Generation of the sulfenyl bromide and its intramolecular addition to the *cis* double bond is a specutacular feature of the present synthesis. Inspection of a molecular model suggests that this intramolecular addition must proceed *via* energetically unfavorable transition state such as 23 and consequently the intermolecular path might be preferable. In contrast to this speculation, the intramolecular addition of the sulfenyl bromide proved to proceed preferencially, rather than the intermolecular process.[9] The addition of an equimolar amount of bromine in carbon tetrachloride to a diluted solution of the disulfide (22) in carbon tetrachloride (5 mg/ml) at 0° for 0.25 h, followed by removal of the solvent and immediate treatment with excess DBU in toluene at 55~65° for 2.5 h to yield the desired *endo*-vinyl sulfide (24). Purification through silica gel column chromatography (ether-petr.ether, 1:1) gave the pure material [IR(neat) 1740 cm-1; PMR($CDCl_3$,TMS) δ5.20-5.70 (multiplet, 2H, olefinic protons), 5.10 (multiplet, 1H, vinyl sulfide proton); MS(CI,NH_3) 568(M^++NH_4)] in *ca.*40% yield from the disulfide (22). Careful hydrolysis of two THP groups in 24 in AcOH-H_2O-THF (3:1:1) at 45~55° for 1.5 h provided the desired new sulfur analog (25) as a mixture of the diastereoisomers at the C-15 position (PG numbering) in nearly equal amount.. The more polar isomer was tentatively assigned the structure of the 15α-isomer[11] [*Rf* 0.30 on silica gel TLC plate eluted with ether-petr.ether (9:1) for two times; MS(EI) 382(M^+), 364(M^+-H_2O), 346(M^+-2H_2O)], while the less polar isomer [*Rf* 0.35] as the 15β.

The chemical stability of the both isomers is nearly the same as that of the previously synthesized 9(O)-thiaprostacyclin methyl ester.[12] The conversion of the more polar isomer of 25 to 3 was accomplished by usual saponification technique.

Preliminary biological results obtained with the sulfur analogs (3) indicated high inhibitory activity in platelet aggregation of rabbit induced by ADP, which was comparable to that of 9(O)-thiaprostacyclin.[13] Biological details will be published elsewhere.

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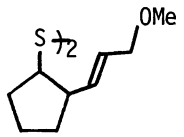
References and Notes

1) K.Shimoji, Y.Konishi, Y.Arai, M.Hayashi, and H.Yamamoto, *J. Am. Chem. Soc.*, 100, 2547 (1978). In the prostacyclin series, the stable analogs (1b,1c) showed high biological activities comparable to 1a.
2) M.Shibasaki, K.Iseki, and S.Ikegami, *Tetrahedron Lett.*, 1980, 169.
3) E.Vedejs, D.A.Engler, and J.E.Telschow, *J. Org. Chem.*, 43, 188 (1978).
4) Diastereoisomers were present in a ratio of *ca.* 2:1.
5) Even under these conditions, the partial cleavage of the alcohol protecting groups took place.
6) A.K.Bose, B.Lal, W.A.Hoffman III, and M.S.Manhas, *Tetrahedron Lett.*, 1973, 1619.
7) The phosphonium bromide was prepared from cyclohexanone as follows; (i) H_2O_2/NaOH, (ii) HBr-H_2SO_4, (iii) Ph_3P in toluene.
8) The elimination product (conjugate diene) was obtained as a major side product.
9) In the case of the *cis*-olefin, a mixture of the *threo*-cyclic bromo-sulfides should be obtained *via* intramolecular *trans*-addition of the sulfenyl bromide, which should give the *endo*-vinyl sulfide so easily *via trans*-elimination of HBr.

   These assumptions were strongly supported by the following evidences. The *erythro*-cyclic bromo-sulfides (27) [MS(EI) 252 and 250 (M^+), 207 and 205 (M^+-CH_2OCH_3)] derived from the *trans*-olefin (26) was found to remain intact under usual elimination conditions, while the *threo*-cyclic bromo-sulfides (29) prepared from the *cis*-olefin (28) provided the *endo*-vinyl sulfide (30) [PMR($CDCl_3$,TMS) δ5.03 (m,1H,H_A)] in good yield.



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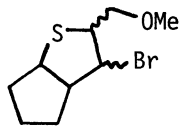

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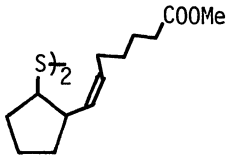

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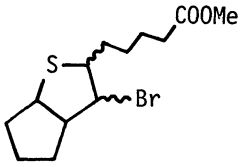

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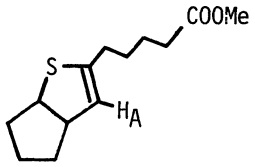

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10) For example, see E.J.Corey, N.M.Weinshenker, T.K.Schaaf, and W.Huber, *J. Am. Chem. Soc.*, 91, 5675 (1969).
11) Configurational assignments were based on the known chromatographic behaviors of the natural PGs; N.H.Andersen, *J. Lipid Res.*, 40, 316 (1969).
12) M.Shibasaki and S.Ikegami, *Tetrahedron Lett.*, 1977, 4037; Idem, *ibid.*, 1978, 559.
13) Test of biological activity was carried out by Dr.S.Kurozumi and coworkers, Teijin Institute for Biomedical Research.

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