Tetrahedron Letters No. 6, pp 559 - 562, 1978. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 9(O)-THIAPROSTACYCLIN

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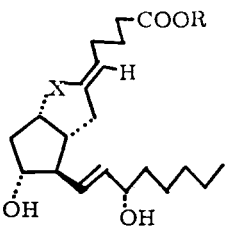
(Received in Japan 12 November 1977; received in UK for publication 15 December 1977)

Much attention in the recent progress of prostaglandin field has been focused on prostacyclin (PGI_2) (1) which exhibits highly potent activity in inhibiting blood platelet aggregation.[1] Although chemical synthesis of 1 has been succeeded by various groups,[2] its remarkable instability makes it undesirable as a potential drug for treatment of thrombosis, stroke and heart attack.[3] Since our previous examination, a chemical modification in replacing the oxygen by a sulfur atom (3), provided significant information on the stability of 3,[4] we directed this minor modification to prostacyclin. Thus, we wish to report here a successful synthesis of 9(O)-thiaprostacyclin (2g) to which striking activities are expected.[5]

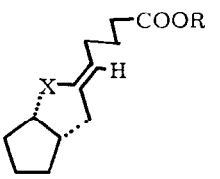
The syntheis of 9(O)-thiaPGI_2 methyl ester (2b) was started from well-known bis(THP)PGE_2 methyl ester (4)[6] obtainable from PGE_2 in two steps. Reduction of 4 with $NaBH_4$ yielded a 1:1 mixture of the alcohols (5 and 7). In order to inverse the configuration of the 9α-hydroxy group, 5 was treated with methanesulfonyl chloride (1.5 mequiv) and triethylamine (1.5 mequiv) in methylene chloride at -10° for 1.5 hr, and then the resulting mesylate (6), without purification, was reacted with potassium superoxide (8 mequiv)-18-crown-6 (3 mequiv) in DMSO-DME (2:1)[7] at 25° for 4.5 hrs, followed by esterification with diazomethane, to afford the 9β-alcohol (7) in 50-60% yield[8] (observed Rf values on silica gel TLC plate eluted with ether-petr.ether (2:1); 0.22 for 7 and 0.26 for 5).

The introduction of a sulfur atom accompaning the inversion of the 9β-OH configuration was carried out by treatment of the tosylate (8), readily derived from 7 with tosyl chloride in pyridine at 0° for 15 hrs, with excess sodium thioacetate in DMSO-DMF (1:1) at 50° for 20 hrs. The reaction gave the corresponding 9α-acetylthio derivative (9) (ir, $\nu_{max}^{C=O}$: 1690 cm-1 (CH_3COS-); mass (m/e), EI: 551 [M^+-$COCH_3$], CI (NH_3): 612 [M^++ NH_4]) in ~55% yield from 7.[9]

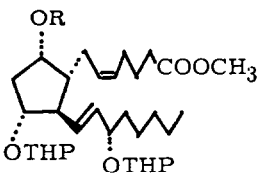
Mild hydrolysis of 9 in methanol suspended with 1 mequiv of potassium carbonate at 25° for 30 min, followed by acidification with 10% hydrochloric acid (to pH 3-4), and then, purification by preparative TLC (silica gel) afforded the cyclic sulfide (11)[10] (mass (m/e), EI: 552 [M^+], 521 [M^+-OCH_3], 366 [M^+-$(CH_2)_4COOCH_3$-C_5H_{11}], CI (NH_3): 570 [M^++NH_4]) in 60% yield, along with a small amount of the disulfide (12) resulted from air oxidation. This facile catalytic cyclization is characteristic of a thiol group in this system and also observed in the previous study.[4] Its stereochemistry was tentatively assigned as shown in the structure of 11. The disulfide (12) was satisfactorily obtained in 80% yield by oxygen-



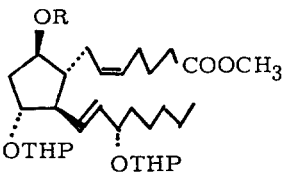
1: X = O, R = H
2a: X = S, R = H
2b: X = S, R = CH_3



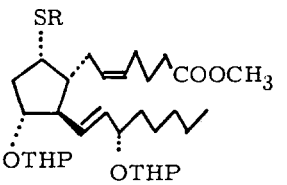
3: X = O, S



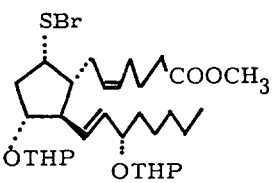
5: R = H
6: R = Ms



7: R = H
8: R = Ts



9: R = Ac
10: R = Na



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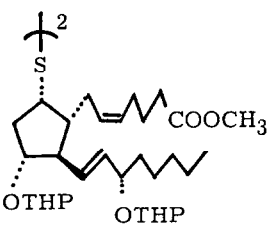

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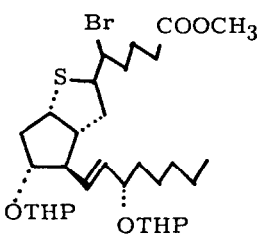

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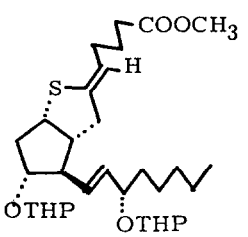

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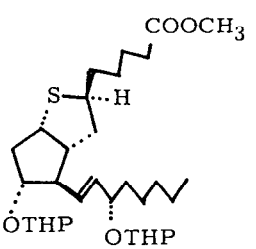

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exposure over the reaction mixture of the mercaptide (10) prepared from 9 by hydrolysis in methanol-sodium methoxide (2 mequiv); mass (m/e), EI: 551 [M^+/21].

The application of the exclusive trans addition of sulfenyl halide to olefin,[11] intramolecular additions giving S-containing heterocycles,[12] is the best way for the stereo-controlled synthesis of a Z-isomer in the present subject.

The formation of the sulfenyl bromide (13) from the disulfide (12) is the most fitted and important step in this whole synthetic process since it is well-known that the reaction of disulfide with bromine proceeds cleanly and quantitatively. Thus, treatment of 12 with an equimolar amount of bromine in methylene chloride at 0° for 10 min yielded the bromosulfide (14),[13] the reaction proceeding via intramolecular cyclization of the initially formed sulfenyl bromide (13). Then, 14, without purification, was treated with excess DBU in toluene at 70° for 2.5 hrs to give the vinyl sulfide (15) with Z geometry attributable to the trans-coplanar E_2 elimination of hydrogen bromide. Purification of the product by silica gel column chromatography gave the pure material (15) in 50-60% yield from the disulfide (12); ir, $\nu_{max}^{c=c}$: 1637 cm-1 (vinylic sulfide); mass (m/e), EI: 550 [M^+], CI (NH_3): 568 [M^++NH_4].

Crucial hydrolysis of the tetrahydropyranyl ether of 15 was successfully carried out in AcOH-H_2O-THF (3:1:1) at 45° for 1 hr,[4] resulting 9(O)-thiaprostacyclin methyl ester (2b) (ir, $\nu_{max}^{c=c}$: 1640 cm-1 (vinylic sulfide); pmr ($CDCl_3$, ppm): 5.80-5.05 (three olefinic protons); mass (m/e), EI: 382 [M^+], 364 [M^+-H_2O], 346 [M^+-$2H_2O$], 277 [M^+-H_2O-$(CH_2)_2COOCH_3$], 259 [M^+-$2H_2O$-$(CH_2)_2COOCH_3$], CI (NH_3): 400 [M^++NH_4]) in 40-50% yield after purification by Florisil column chromatography.

It is considered that relatively low yield in the step of THP-cleavage is attributed to the partial decomposition of the final product (2b) under the condition used,[14] indicating that 2b is less stable than the model compound (3, X=S).[4] The conversion of 2b into 2a was accomplished by usual saponification technique.

Considering high inhibitory activity of platelet aggregation observed recently for 2a,[5] 9(O)-thiaprostacyclins (2) and their analogs could be warranted as a potential drug.

Acknowledgment. We thank JEOL Ltd. for his kind measurements of mass and pmr spectra.

References and Notes

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8. The yield was calculated based on the recovery of 6 (~15%).

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13. Our attempt of the direct cyclization of the mercaptide (10) with NBS in a 1:1 mixture of carbon tetrachloride and THF gave an unsatisfactory result.

14. In order to avoid a loss of material, the use of a t-butyldimethylsilyl(BDMS) group for protection of hydroxy groups is under examination.