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# A NEW SYNTHESIS OF 6,9α-THIAPROSTACYCLIN

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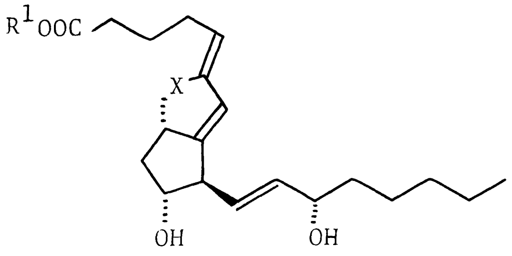
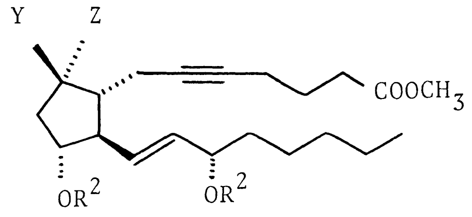
6,9α-Thiaprostacyclin (2a) and its methyl ester (2b) were synthesized using intramolecular cyclization of the acetylenic mercaptide 6 under the basic condition.

Since the discovery of prostacyclin (PGI$_2$, 1)[1] in 1976, several syntheses of 1[2] and its stable analogues[3,4] have been reported. Perhaps of greatest interest are those analogues which are stable enough without loss of any biological activities. We disclose herein our independent and highly efficient synthesis of 6,9α-thiaprostacyclin (2a and 2b), which have been reported to have high comparable potency to that of natural prostacyclin (1) in inhibiting platelet aggregation[4a] and to be fairly stable even under acidic conditions.





|  | X | R$^1$ |
|---|---|---|
| 1 | O | H or CH$_3$ |
| 2a | S | H |
| 2b | S | CH$_3$ |

|  | Y | Z | R$^2$ |
|---|---|---|---|
| 3 | OH | H | COPh |
| 4 | OSO$_2$CH$_3$ | H | COPh |
| 5 | H | SAc | COPh |
| 6 | H | S$^\ominus$ | H or COPh |

9β-Hydroxy-11α,15α-dibenzoyloxyprosta-5-yn-13(E)-enoic acid methyl ester (3), readily available by the procedure of Lin, et al.,[5] was treated with methanesulfonyl chloride (2 equiv) and triethylamine (2.5 equiv) in methylene chloride at -20°C for 1.5 h to give the mesylate 4 in quantitative yield. The crude mesylate 4 was converted to the 9α-thioacetate 5 by exposing to excess sodium thioacetate in dimethyl sulfoxide at 45°C for 18 h.[6]

The treatment of the crude thioacetate 5 with a small excess of potassium carbonate in degassed methanol at room temperature for 3 h directly afforded 6,9α-thiaprostacyclin methyl ester (2b)[7] in 50-60% yield (based on the mesylate 4). Hydrolysis of the methyl ester 2b in aqueous methanol containing sodium hydroxide

(2 equiv) produced 6,9α-thiaprostacyclin (2a) in 96% yield after purification by column chromatography on silics gel.

The Z-geometry of the thio-enol ether double bond in 2a and 2b was based on the mechanistic considerations[8] as well as their pmr spectra: Pmr ($CDCl_3$) of 2a, δ 5.47 (2H, olefinic), 5.30 (1H, thio-enolic); Pmr ($CDCl_3$) of 2b, δ 5.51(2H, olefinic), 5.31 (m, 1H, thio-enolic), 3.67 (s, 3H, $COOCH_3$).

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## References and Notes

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7. Ir ($CHCl_3$) ν 1640 $cm^{-1}$ (vinylic sulfide).
   MS $M^+=382$.
   U.V. (MeOH) $\nu_{max}$ 205 and 236 nm.
   TLC $R_f$ value (ethyl acetate:n-hexane 3:1) 0.37.
8. The addition reaction of mercaptan to acetylene under the basic conditions proceeds cleanly and gives Z-thio-enol ether in high stereo-selectivity: (a) W. E. Truce and J. A. Simms, J. Am. Chem. Soc., 78, 2756 (1956); (b) B. A. Trifimov, S. V. Amcsova, M. L. Alpert, and N. N. Skatova, Zh. Org. Khim., 13, 2229 (1977).

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