Tetrahedron Letters No. 46, pp 4037 - 4040, 1977. Pergamon Press. Printed in Great Britain.

INTRAMOLECULAR SULFENYL BROMIDE ADDITION PROMISING A NEW SYNTHETIC ROUTE TO 9(O)-THIAPROSTACYCLIN

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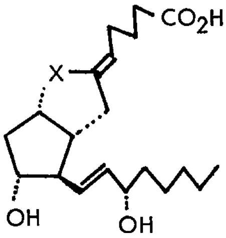
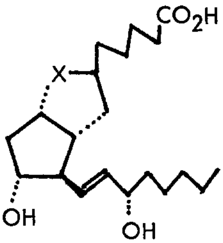
(Received in Japan 15 August 1977; received in UK for publication 26 September 1977)

Prostacyclin (1) exhibiting a potential anti-thrombotic activity has been recently discovered as the newest class of prostaglandins.[1] Its striking activities might promise to be a potential drug for treatment of thrombosis, stroke and heart attack. However, because of its relative instability, chemically modified analogs which possess increased metabolic stability and similar pharmacological potency have been desired. Synthetic works of prostacyclin[2-4] and its analogs[5,6] have prompted us to synthesize the thia analogs (2,4) to which increased stability is expected. Thus, we wish to report here a novel synthetic method designed for the synthesis of 9(O)-thiaprostacyclins (2,4)



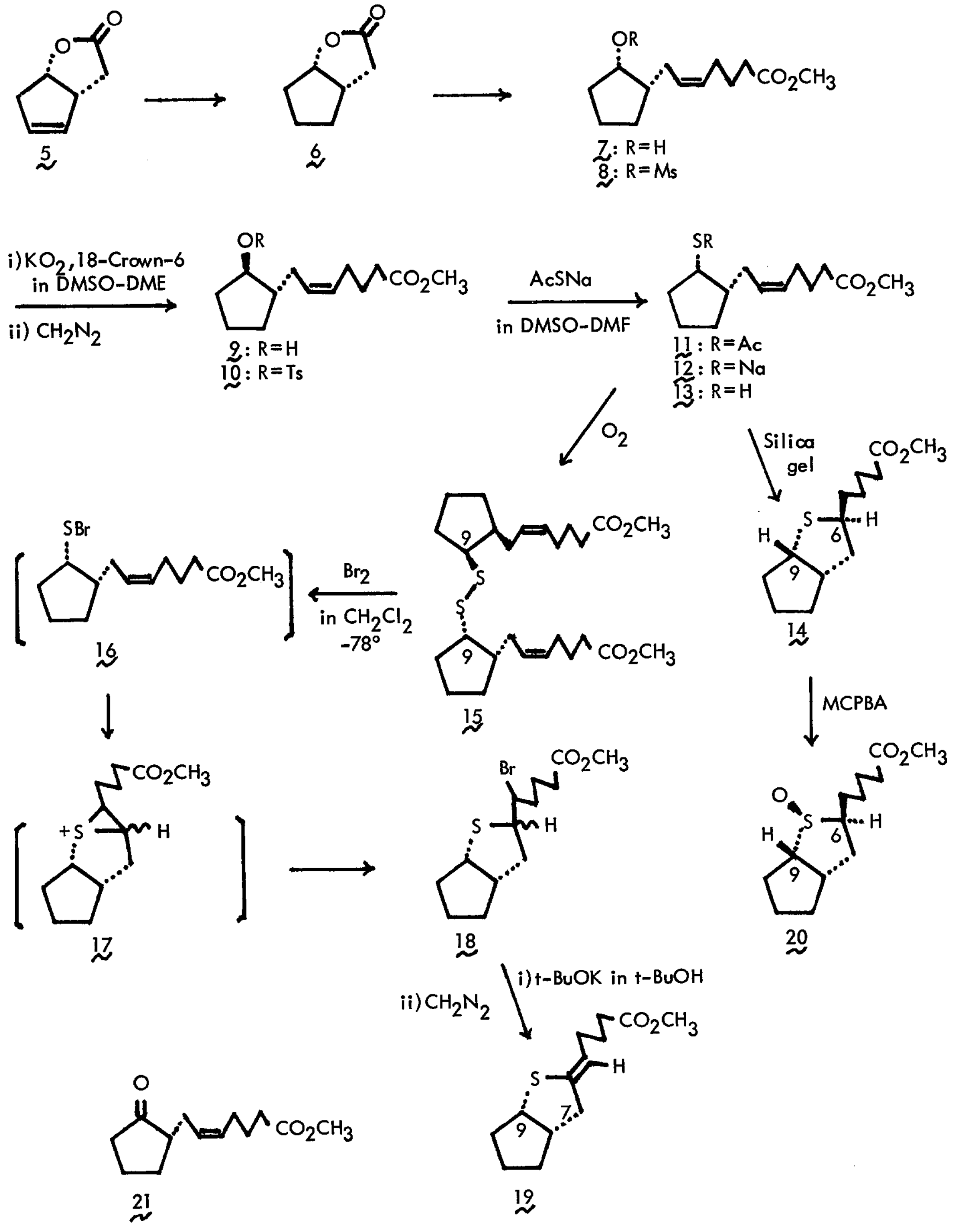
1: X=O
2: X=S



3: X=O
4: X=S

As synthetic sequences shown in Scheme 1, the known ene-lactone (5)[7] was catalytically hydrogenated in methanol at -25° to give the saturated lactone (6) quantitatively, which was derived to the hydroxy-ester (7) in 78-80% yield according to the Corey's method[8]; mass (m/e): 227 $[M^+ + 1]$, 226 $[M^+]$, 209 $[M^+ - OH]$, pmr ($CDCl_3$,ppm): 4.16 (1H,m,=CH-O). In order to inverse the configuration of the hydroxy group, 7 was converted into the corresponding mesylate (8) in the usual manner (3 equiv. of mesyl chloride and triethylamine in methylene chloride at -10° for 1.5 hr) and then 8, without purification, was reacted with potassium superoxide (8 equiv.)-18-crown-6 (3 equiv.) in DMSO-DME (2:1) at 25° for 4.5 hrs,[9] followed by esterification with diazomethane, to afford the trans-alcohol(9) in 65-70% yield; mass (m/e): 208 $[M^+ - H_2O]$, pmr ($CDCl_3$,ppm): 3.80 (1H,m,=CH-O). Alternative preparation from 7 also supplied 9 in 69% yield; oxidation of 7 with pyridinium chlorochromate[10] in methylene chloride at 25° overnight, then sodium borohydride reduction of the ketone

SCHEME I.


5
6
OR
CO_2CH_3
7: R=H
8: R=Ms
i) KO_2, 18-Crown-6 in DMSO-DME
ii) CH_2N_2
OR
CO_2CH_3
9: R=H
10: R=Ts
AcSNa
in DMSO-DMF
SR
CO_2CH_3
11: R=Ac
12: R=Na
13: R=H
O_2
Silica gel
CO_2CH_3
S
H
6
H
9
14
CO_2CH_3
9
S
S
9
CO_2CH_3
15
SBr
CO_2CH_3
16
Br_2
in CH_2Cl_2
-78°
MCPBA
CO_2CH_3
+S
H
17
Br
CO_2CH_3
S
H
18
O
S
H
6
H
9
CO_2CH_3
20
i) t-BuOK in t-BuOH
ii) CH_2N_2
CO_2CH_3
S
H
7
9
19
O
CO_2CH_3
21

(**21**) at -25°. In this reduction, there was obtained **7** in 18% yield. Both isomers were easily separable by column or thin layer chromatographic technique. The tosylate (**10**) converted quantitatively from **9** with tosyl chloride in pyridine at 0° for 15 hrs was thioacetylated[11] with sodium thioacetate in DMSO-DMF (1:1) at 50° for 20 hrs to give the cis-acetylthio derivative (**11**) in 69% yield. The inversion of the configuration of the substituent in this displacement reaction has been also observed by Hayashi and co-workers.[11]

Mild hydrolysis of **11** in methanol suspended with 1 equiv. of potassium carbonate at 25° for 30 min followed by acidification with 10% hydrochloric acid (to pH 3-4) was expected to afford the thiol derivative (**13**). Although the ir spectrum of the crude product exhibited a band at 2560 cm-1 assignable to a thiol group, this band could not be observed in two compounds separated by TLC technique. This observation reveals that the thiol (**13**) must be changed structurally during developing on a TLC plate (silica gel). A less polar component was found to be the cyclized product (**14**) by instrumental analysis; mass (m/e): 242 $[M^+]$, 127 $[M^+-(CH_2)_4CO_2CH_3]$, pmr ($CDCl_3$,ppm): 3.35 (1H,m, H-6), 2.75 (1H,m,H-9).[13] The stereochemical assignment was determined by comparison of an anisotropic shift of the neighboring protons by the thionyl oxygen of the sulfoxide (**20**) obtained by oxidation with m-chloroperbenzoic acid; pmr ($CDCl_3$,ppm): 3.35 (1H,m,H-6), 3.10 (1H,m,H-9). The structure of the other component was determined spectroscopically to be the disulfide (**15**),[12] which must be resulted from air oxidation; mass (m/e): 482 $[M^+]$, 241 $[M^+/2]$, pmr ($CDCl_3$,ppm): 5.40 (2H,m,olefinic H), 3.35 (1H,m,H-9). The best yield (~75%) of **15** from **11** was achieved by an oxygen-exposure over a reaction mixture of the sodium mercaptide (**12**) obtained by hydrolysis of **11** in methanol-sodium methoxide.

The well-known trans addition of sulfenyl halides to olefins[14] offers an advantage for the stereo-controlled synthesis of a Z-isomer (**19**). The reaction of the disulfide (**15**) with a molar equiv. of bromine in methylene chloride at -78°[15] gave the bromo sulfide (**18**). Because of instability of the sulfenyl bromide (**16**) formed initially from a S-S bond cleavage by bromine, immediate cyclization took place via the episulfonium ion (**17**)[15] and then resulted in **18**; mass spectrum (m/e: 318, 316 $[M^+-4H]$, 291, 289 $[M^+-OCH_3]$, 241 $[M^+-Br]$, 127 $[M^+-CHBr(CH_2)_3CO_2CH_3]$) shows that **18** is a 5-5-membered bicyclo compound.[16]

For the stereospecific trans elimination of hydrogen bromide from **18**, the unpurified bromide (**18**) was treated with potassium t-butoxide (20 equiv.) in t-butanol at 45° for 30 min and after usual work-up followed by esterification with diazomethane, the vinyl sulfide (**19**) was given in 40-50% yield from the disulfide (**15**). Mass (m/e: 240 $[M^+]$, 209 $[M^+-OCH_3]$, 181 $[M^+-CO_2CH_3]$, 153 $[M^+-CH_2CH_2CO_2CH_3]$), pmr ($CDCl_3$,ppm: 5.26 (1H,bt, olefinic H), 3.96 (1H ,m,H-9))[17] and ir spectra ($\nu^{c=c}_{max}$: 1639 cm-1) substantiated clearly the structure of **19**. The purification of **19** was carried out with Florisil column chromatography.

Application of the similar procedure to the synthesis of 9(O)-thiaprostacyclins (**2**,**4**) is now in progress.

Acknowledgment. We are grateful to Professor T.Hino, Faculty of Pharmaceutical Sciences, Chiba University, for measurements of mass spectra.

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12. Alternative preparation of **15** was carried out on the reaction of **10** with sodium disulfide in modest yield, in which the formation of tri- and tetra-sulfides was observed as minor products.

13. A single isomer could be detected on TLC analysis using several different solvent systems.

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16. Although the formation of two *threo*-diastereoisomers is possible in this reaction, there is observed a nearly single spot on TLC analysis. The stereochemistry of **18** is still not determined directly at the present time. However, based on stereochemistry in the cyclization of the thiol (**13**) to **14**, the configuration of **18** should be similar to **14**.

17. There was observed 25% NOE effect for the olefinic proton when the 7-methylene protons were irradiated.