Stereoselective Synthesis of a (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-thioxopenam Ester through a Hydroxy Group Directed Chlorinolysis

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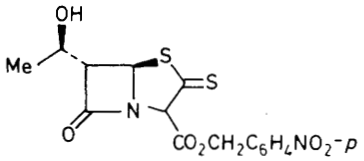
Hydroxy group directed chlorinolysis of (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-ethylthioazetidin-2-one (**4**) gives predominantly the corresponding (4*S*)-4-chloroazetidinone (**5**) which is cyclised to the (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-thioxopenam (**1**).

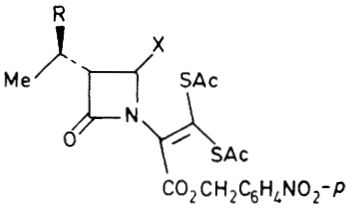
We and others have described the synthesis of the 2-thioxopenam ring system[1,2] which is a versatile intermediate for the preparation of broad spectrum antibacterial penems. We have extended our studies on the synthesis of this system and now report a stereoselective synthesis of the (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-thioxopenam (**1**).

The t-butyldimethylsilyl protected† 3-hydroxyethyl-bis-(acetylthio)-azetidinone (**2**) was synthesised according to pro-

† The protection of the hydroxyethyl group is required during the generation of the bis(acetyl) ketene dithioacetal.



(1)



	R	X	Config. at C-4
(2)	$OSiMe_2Bu^t$	SEt	*R*
(3)	$OSiMe_2Bu^t$	Cl	*R*
(4)	OH	SEt	*R*
(5)	OH	Cl	*R*,*S*
(6)	OH	$SCH_2CH{=}CH_2$	*R*
(7)	H	$SCH_2CH{=}CH_2$ (*trans*)	(racemic)
(8)	H	Cl (*cis*–*trans*)	(racemic)

cedures previously published.[2,3] Treatment of (**2**) with chlorine ($CHCl_3$, 20 °C) gave cleanly and in good yield only the (4*R*)-4-chloroazetidinone (**3**) in accordance with the reported procedure.[2] The absence of the corresponding (4*S*)-isomer presumably reflects the high level of steric crowding afforded by the proximal silylated side-chain. Cyclisation of (**3**), through deacetylation with imidazole (dioxane–water, 9:1, 20 °C),[1] proceeded with inversion at C-4, giving the (5*S*)-thioxopenam in 90% yield.[2]

In accordance with the procedure used for the synthesis of a (5*R*)-2-aryloxypenem,[4] desilylation using a 1 M solution of anhydrous hydrogen chloride in dimethylformamide (room temp.) afforded the hydroxy derivative (**4**) in 70% yield. Subsequent chlorination of (**4**) (1.5 equiv. of Cl_2, $CHCl_3$, −40 °C) gave the isomeric chloroazetidinones‡ (**5**) in 34% yield with 4*S*:4*R* >4:1. Similar chlorinolysis of the allylthio azetidinone (**6**) gave (**5**) in the ratio 4*S*:4*R* = 4:1. The yield of (**5**) could be improved to 60—80% by conducting the chlorinolysis of (**4**) in anhydrous benzene (1.5 equiv. of Cl_2, 5—7 °C) with 4*S*:4*R* = 4—6:1. In comparison, the chlorinolysis (1.1 equiv. of Cl_2, $CHCl_3$, −20 °C) of the 3-ethylazetidinone (**7**) gave a 1:1 mixture of *cis*- and *trans*-4-chloro-derivatives (**8**) in *ca.* 80% yield, indicating the directing influence of the hydroxy group as previously proposed. The (4*R*)- and (4*S*)-isomers of the 4-chloro-compound (**5**) were readily separated by column chromatography (silica gel, ethyl acetate–hexane). Cyclisation of the (4*S*)-chloroazetidinone (**5**) (imidazole, dioxane–water, 9:1, room temp.) gave only the (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-thioxopenam (**1**) in quantitative yield, ν_{max} (liquid film) 1791 and 1751 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.41 (d, *J* 6.3 Hz, $CHCH_3$), 3.71 (dd, J_1 6.4, J_2 1.46 Hz, 6-H), 4.30—4.45 (m, 8-H), 5.41 (s, 3-H), and 5.89 (d, *J* 1.46 Hz, 5-H); $[\alpha]_D^{21.5}$ +23.5° (*c* 1, $CHCl_3$).

Tanaka[2] and we[3] have shown that the thioxopenam can be readily alkylated, for example with an alkyl bromide in the presence of base (*e.g.* di-isopropylethylamine) to give directly the corresponding (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]penems.

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References

1 N. J. Daniels, G. Johnson, B. C. Ross, and M. A. Yeomans, *J. Chem. Soc., Chem. Commun.*, 1982, 1119.
2 T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura, and T. Miyadera, *J. Chem. Soc., Chem. Commun.*, 1982, 713.
3 G.B. Pat. 2 087 880.
4 M. D. Cooke, K. W. Moore, B. C. Ross, and S. E. Turner, preceding communication.

‡ All new compounds gave satisfactory combustion analysis and/or accurate mass measurement.