

## 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**).

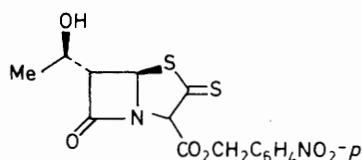
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We and others have described the synthesis of the 2-thioxopenam ring system<sup>1,2</sup> which is a versatile intermediate for the preparation of broad spectrum antibacterial penems. We have extended our studies on the synthesis of this system and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

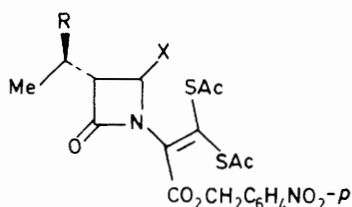
The *t*-butyldimethylsilyl protected† 3-hydroxyethyl-bis(acetylthio)-azetidinone (**2**) was synthesised according to pro-

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† 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 <sub>2</sub> Bu <sup>t</sup>	SEt	R
(3)	OSiMe <sub>2</sub> Bu <sup>t</sup>	Cl	R
(4)	OH	SEt	R
(5)	OH	Cl	R,S
(6)	OH	SCH <sub>2</sub> CH=CH <sub>2</sub>	R
(7)	H	SCH <sub>2</sub> CH=CH <sub>2</sub> ( <i>trans</i> )	(racemic)
(8)	H	Cl ( <i>cis-trans</i> )	(racemic)

cedures previously published.<sup>2,3</sup> Treatment of (2) with chlorine (CHCl<sub>3</sub>, 20 °C) gave cleanly and in good yield only the (4*R*)-4-chloroazetidinone (3) in accordance with the reported procedure.<sup>2</sup> 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),<sup>1</sup> proceeded with inversion at C-4, giving the (5*S*)-thioxopenam in 90% yield.<sup>2</sup>

In accordance with the procedure used for the synthesis of a (5*R*)-2-aryloxypenam,<sup>4</sup> 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<sub>2</sub>, CHCl<sub>3</sub>, -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<sub>2</sub>, 5–7 °C) with 4*S*:4*R* = 4–6:1. In comparison, the chlorinolysis (1.1 equiv. of Cl<sub>2</sub>, CHCl<sub>3</sub>, -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,  $\nu_{\max}$  (liquid film) 1791 and 1751 cm<sup>-1</sup>; <sup>1</sup>H n.m.r. (CDCl<sub>3</sub>)  $\delta$  1.41 (d, *J* 6.3 Hz, CHCH<sub>3</sub>), 3.71 (dd, *J*<sub>1</sub> 6.4, *J*<sub>2</sub> 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); [ $\alpha$ ]<sub>D</sub><sup>21.5</sup> +23.5° (*c* 1, CHCl<sub>3</sub>).

Tanaka<sup>2</sup> and we<sup>3</sup> 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

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