

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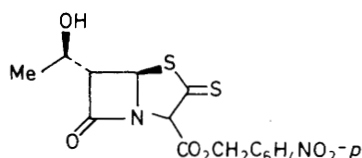
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Hydroxy group directed chlorinolysis of (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-ethylthioazetidin-2-one (**4**) gives predominantly the corresponding (4*S*)-4-chloroazetidinone (**5**) which is cyclised to the (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-thioxopenam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

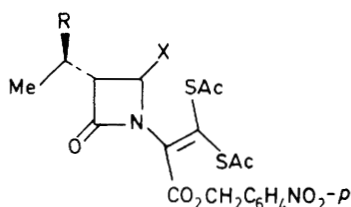
We and others have described the synthesis of the 2-thioxopenam ring system^{1,2} which is a versatile intermediate for the preparation of broad spectrum antibacterial penems. We have extended our studies on the synthesis of this system and now report a stereoselective synthesis of the (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-thioxopenam (**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 ₂ Bu ^t	SEt	<i>R</i>
(3)	OSiMe ₂ Bu ^t	Cl	<i>R</i>
(4)	OH	SEt	<i>R</i>
(5)	OH	Cl	<i>R,S</i>
(6)	OH	SCH ₂ CH=CH ₂	<i>R</i>
(7)	H	SCH ₂ CH=CH ₂ (<i>trans</i>)	(racemic)
(8)	H	Cl (<i>cis-trans</i>)	(racemic)

cedures previously published.^{2,3} Treatment of (2) with chlorine (CHCl₃, 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-aryloxypenam,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 Cl₂, CHCl₃, –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 Cl₂, 5–7 °C) with 4*S*:4*R* = 4–6:1. In comparison, the chlorinolysis (1.1 equiv. of Cl₂, CHCl₃, –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. (CDCl₃) δ 1.41 (d, *J* 6.3 Hz, CHCH₃), 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); [α]_D^{21.5} +23.5° (*c* 1, CHCl₃).

Tanaka² and we³ 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.