Stereoselective Synthesis of a (5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-aryloxypenem

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(5*R*,6*S*)-[(*R*)-1-Hydroxyethyl]-2-aryloxypenems can be synthesised through hydroxy group directed chlorinolysis of the (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-ethylthioazetidinone (**8**) to the (4*S*)-4-chloroazetidinone (**9**) with subsequent cyclisation.

Recent publications on the effect of 6-substitution in the 2-thiopenem series have shown that the (6*S*)-6-[(*R*)-1-hydroxyethyl] group is optimally effective for β-lactamase stability and antibacterial activity.[1] We now report the stereoselective synthesis of the first example of a (5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-2-aryloxypenem.

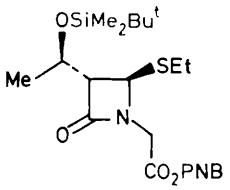
The t-butyldimethylsilyl protected (3*S*,4*R*)-3-[(*R*)-1-hydroxyethyl]-4-ethylthio-2-oxoazetidin-1-ylacetate (**1**), which was synthesised by a route similar to that previously published,[2] was treated with base followed by *O*-4-chlorophenyl chlorothioformate (1.5 equiv.) [$LiN(SiMe_3)_2$(2.25 equiv.), −78 °C to room temperature]. The resulting lithium salt (**4**) after protonation with acetic acid gave the thioenol (**5**),†‡ which was found to be somewhat unstable and difficult to purify. In order to overcome this the salt (**4**) was treated *in situ* (−40 to 20 °C) with pivaloyl chloride and the resulting *S*-pivalate (**6**) isolated in 50% yield after chromatography as the partially separable *E*–*Z* mixture. Previous attempts to isolate the thioenol as the *S*-acetate gave (**5**) as the only isolable compound, indicating high lability of the *S*-acetate. Chlorinolysis of (**6**) [Cl_2 (1.3 equiv.), $CHCl_3$, −40 °C] afforded the (4*R*)-4-chloroazetidinone§ (**7**) in 67% yield with no observable trace of the (4*S*)-isomer which is in accordance with an analogous procedure previously reported.[2] Treatment of (**7**) with imidazole (1 equiv.) (dioxane–water, 9:1, 5 °C) afforded as the sole β-lactam product the (5*S*)-penem (**2**), ν_{max} ($CDCl_3$) 1792 (β-lactam) and 1717 (ester) cm^{-1}; δ($CDCl_3$) 1.45 (3H, d, *J* 6 Hz, CH_3), 3.93 (dd, *J* 4 and 6 Hz, 6-H), 4.36—4.43 (1H, m, $CHCH_3$), and 5.70 (1H, d, *J* 4 Hz, 5-H); $[\alpha]_D^{25}$ −69.3° (*c* = 1, $CHCl_3$). Thermal equilibration of the (5*S*)-penem (**2**) to the corresponding (5*R*)-penem according to procedures found effective in the 2-thiopenem series[2a,4] (xylene, 90—100 °C, 1.5 h) gave only incomplete conversion into the desired (5*R*)-penem (5*R*:5*S*, 2:1). From the resulting mixture we were unable to effect easily complete separation of the (5*R*,5*S*)-penem mixture. Changing solvents (*viz.* dioxane, dimethylformamide, or nitromethane), or temperature (over the range 40—120 °C) gave no indication that a satisfactory thermal conversion was possible. We sought consequently a new procedure for the synthesis of the desired (5*R*)-penems in a pure form.

A related chlorination reported[3] for a series of various 3-substituted azetidinones showed *cis*:*trans* ratios of between 1:8 and 2:3. It was expected, therefore, on steric grounds,

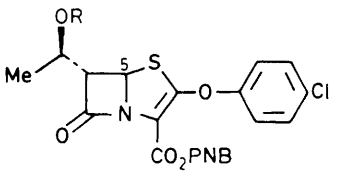
† All new compounds gave satisfactory combustion analysis and/or accurate mass measurement.

‡ (**5**) may exist as the thioenol, thioester, or as an equilibrium mixture.

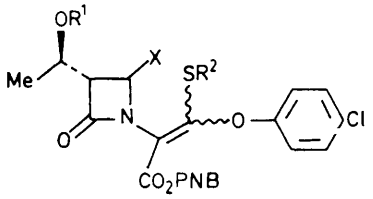
§ δ($CDCl_3$) *inter alia* 1.25 (3H, d, *J* 6 Hz, $CHCH_3$), 3.47 (1H, dd, *J* 1.5 and 3 Hz, 3-H), and 6.08 (1H, d, *J* 1.5 Hz, 4-H).



(1)



(2) R = $SiMe_2Bu^t$
(3) R = H (5*R*)



	R^1	R^2	X	Config. at C-4
(4)	$SiMe_2Bu^t$	Li	SEt	*R*
(5)	$SiMe_2Bu^t$	H	SEt	*R*
(6)	$SiMe_2Bu^t$	$COBu^t$	SEt	*R*
(7)	$SiMe_2Bu^t$	$COBu^t$	Cl	*R*
(8)	H	$COBu^t$	SEt	*R*
(9)	H	$COBu^t$	Cl	*R,S*

PNB = 4-$O_2NC_6H_4CH_2$

that chlorinolysis of the corresponding (3*S*)-3-hydroxyethyl azetidinone would provide some of the (4*S*)-4-chloroazetidinone (**9**), which would cyclise with inversion at C-4 to give the desired (5*R*)-penem.

The predisposition of the pivaloyl derivative (**6**) to nucleophilic attack precluded the use of fluoride salts to remove the t-butyldimethylsilyl group. However, acid-catalysed desilylation proved to be effective and 0.6 M HCl (H_2O–tetrahydrofuran, 1:9, 25 °C) or 40% HF (H_2O–MeCN, 1:2, 25 °C) gave the alcohol (**8**) in 50% yield. Chlorinolysis of (**8**) [Cl_2 (1.0 equiv.), $CHCl_3$, −60 °C] gave the 4-chloroazetidinone (**9**) in 74% yield as a 9:1 mixture of (4*S*)- and (4*R*)-isomers. The more favourable than expected 4*S*:4*R* ratio obtained in this chlorinolysis can be ascribed to reagent approach control through hydrogen bonding between chloride anion and the (3*S*)-hydroxyethyl group. Related to this, intramolecular hydrogen bonding has been observed in *o*-chlorophenols and β-chloroalcohols.[5] The (4*S*)-isomer was readily purified by chromatography (silica, ethyl acetate–hexane, 1:4), ν_{max} ($CDCl_3$) 1788 cm^{-1}; δ($CDCl_3$) (mixture of *E*- and *Z*-isomers) 1.05 and 1.08 (9H, s, CMe_3), 1.39 and 1.46 (3H, 2d, *J* 6 Hz, $CHCH_3$), 2.20 (1H, br.s, OH), 3.50—3.60 (1H, m, 3-H), 4.30—4.42 (1H, m, $CHCH_3$), and 6.14 and 6.17 (1H, 2d, *J* 4.3 Hz, 4-H). Cyclisation of (**9**) (imidazole, dioxane–water, 9:1, 5 °C) gave only the (5*R*)-penem (**3**), ν_{max} ($CDCl_3$) 1787 and 1710 cm^{-1}; δ($CDCl_3$) 1.37 (3H, d, *J* 6 Hz, $CHCH_3$), 1.56 (1H, br.s, OH), 3.76 (1H, dd, *J* 1.4 and 6 Hz, 6-H), 4.28—4.36 (1H, m, $CHCH_3$), and 5.64 (1H, d, *J* 1.4 Hz, 5-H); $[\alpha]_D^{25}$ +49.5° (*c* = 1, $CHCl_3$).

The penem (**3**) was hydrogenolysed (H_2, 10% Pd/C, $KHCO_3$, H_2O–dioxane, 1:1, 20 °C) and the resulting potassium salt,¶ isolated by lyophilisation after filtration, exhibited broad spectrum antibacterial activity.

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¶ δ(D_2O) 1.30 (3H, d, *J* 6.2 Hz, CH_3), 3.91 (1H, dd, *J* 1.4 and 6.2 Hz, 6-H), 4.16—4.34 (1H, m, $CHCH_3$), 5.65 (1H, d, *J* 1.4 Hz, 5-H), and 7.21 and 7.43 (4H, AB, *J* 9 Hz, *p*-C_6H_4Cl); $[\alpha]_D^{25}$ +55.0° (*c* 0.5, H_2O).