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

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

Recent publications on the effect of 6-substitution in the 2thiopenem series have shown that the (6S)-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 (5R,6S)-6-[(R)-1-hydroxyethyl]-2-aryloxypenem.

The t-butyldimethylsilyl protected (3S,4R)-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(SiMe₃)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) [Cl₂ (1.3 equiv.), CHCl₃, -40 °C] afforded the (4R)-4-chloroazetidinone§ (7) in 67% yield with no observable trace of the (4S)-isomer which is in accordance with an analogous procedure previously reported.² Treatment of (7) with imida zole (1 equiv.) (dioxane-water, 9:1, 5 °C) afforded as the sole β -lactam product the (5S)-penem (2), ν_{max} (CDCl₃) 1792 (β lactam) and 1717 (ester) cm⁻¹; δ(CDCl₃) 1.45 (3H, d, J 6 Hz, CH₃), 3.93 (dd, J 4 and 6 Hz, 6-H), 4.36-4.43 (1H, m, CHCH₃), and 5.70 (1H, d, J 4 Hz, 5-H); $[\alpha]_{D}^{25}$ -69.3° (c = 1, $CHCl_3$). Thermal equilibration of the (5S)-penem (2) to the corresponding (5R)-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 (5R)penem (5R:5S, 2:1). From the resulting mixture we were unable to effect easily complete separation of the (5R, 5S)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 (5R)-penems in a pure form.

A related chlorination reported³ for a series of various 3substituted 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.

 $[\]ddagger$ (5) may exist as the thioenol, thioester, or as an equilibrium mixture.

[§] δ (CDCl₃) *inter alia* 1.25 (3H, d, *J* 6 Hz, CHCH₃), 3.47 (1H, dd, *J* 1.5 and 3 Hz, 3-H), and 6.08 (1H, d, *J* 1.5 Hz, 4-H).



that chlorinolysis of the corresponding (3S)-3-hydroxyethyl azetidinone would provide some of the (4S)-4-chloroazetidinone (9), which would cyclise with inversion at C-4 to give the desired (5R)-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 (H₂O-tetrahydrofuran, 1:9, 25 °C) or 40% HF (H₂O-MeCN, 1:2, 25 °C) gave the alcohol (8) in 50% yield. Chlorinolysis of (8) [Cl₂ (1.0 equiv.), CHCl₃, -60 °C] gave the 4-chloroazetidinone (9) in 74% yield as a 9:1 mixture of (4S)- and (4R)-isomers. The more favourable than expected 4S:4R ratio obtained in this chlorinolysis can be ascribed to reagent approach control

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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} (CDCl₃) 1788 cm⁻¹; δ (CDCl₃) (mixture of *E*- and *Z*-isomers) 1.05 and 1.08 (9H, s, CMe₃), 1.39 and 1.46 (3H, 2d, *J* 6 Hz, CHCH₃), 2.20 (1H, br.s, OH), 3.50–3.60 (1H, m, 3-H), 4.30–4.42 (1H, m, CHCH₃), 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} (CDCl₃) 1787 and 1710 cm⁻¹; δ (CDCl₃) 1.37 (3H, d, *J* 6 Hz, CHCH₃), 1.56 (1H, br.s, OH), 3.76 (1H, dd, *J* 1.4 and 6 Hz, 6-H), 4.28–4.36 (1H, m, CHCH₃), and 5.64 (1H, d, *J* 1.4 Hz, 5-H); [α]_D²⁵ +49.5° (*c* = 1, CHCl₃).

The penem (3) was hydrogenolysed (H_2 , 10% Pd/C, KHCO₃, 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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¶ $\delta(D_2O)$ 1.30 (3H, d, J 6.2 Hz, CH₃), 3.91 (1H, dd, J 1.4 and 6.2 Hz, 6-H), 4.16–4.34 (1H, m, CHCH₃), 5.65 (1H, d, J 1.4 Hz, 5-H), and 7.21 and 7.43 (4H, AB, J 9 Hz, p-C₆H₄Cl); $[\alpha]_D^{25}$ +55.0° (c 0.5, H₂O).