# Studies on Penem and Carbapenem. II. An Improved Synthesis of Orally Active Penem Antibiotic (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-Fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate[1)]

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**An orally active penem antibiotic (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate (1) was synthesized in 3 steps with a 50% yield from (3*S*,4*R*)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[[(2-fluoroethylthio)thiocarbonyl]thio]azetidin-2-one (4) and a new building block, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyloxyoxalyl chloride (3).**

**Keywords** penem; ester; prodrug; oral; synthesis; β-lactam

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate (**1**) is an orally active ester-type prodrug of a penem antibiotic **2**, which has broad and potent antimicrobial activities against both gram-positive and gram-negative organisms including β-lactamase-producing strains.[1,2)] When administered orally, the prodrug **1** gave a high and prolonged plasma level of its parent **2** and showed a good therapeutic effect, especially against infection by *Staphylococus aureus*.[1)] The practical synthesis of **1** was required for further biological evaluations.

This paper describes a short step synthesis of the prodrug **1** utilizing a new building block, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyloxyoxalyl chloride (**3**).

In the previous synthesis, the prodrug **1** was prepared in a 40% yield over 5 steps from (3*S*,4*R*)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[[(2-fluoroethylthio)thiocarbonyl]thio]azetidin-2-one (**4**) including the cyclization of allyloxalimide (**5**), as depicted in Chart 2.[1,3)] This route passing through the parent compound **2** was suited for derivatization at the ester moiety of the prodrug, but it was not preferable for the practical synthesis of the prodrug **1**. If the ester moiety of the prodrug **1**, the (5-methyl-2-oxo-1,3-

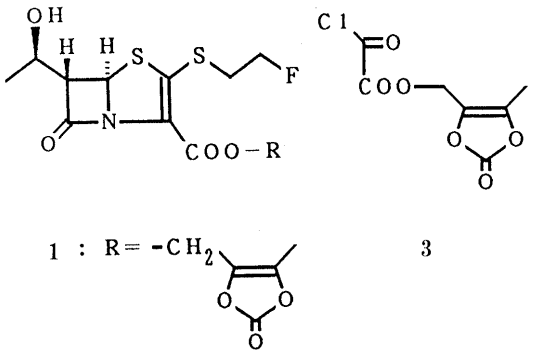


Chart 1

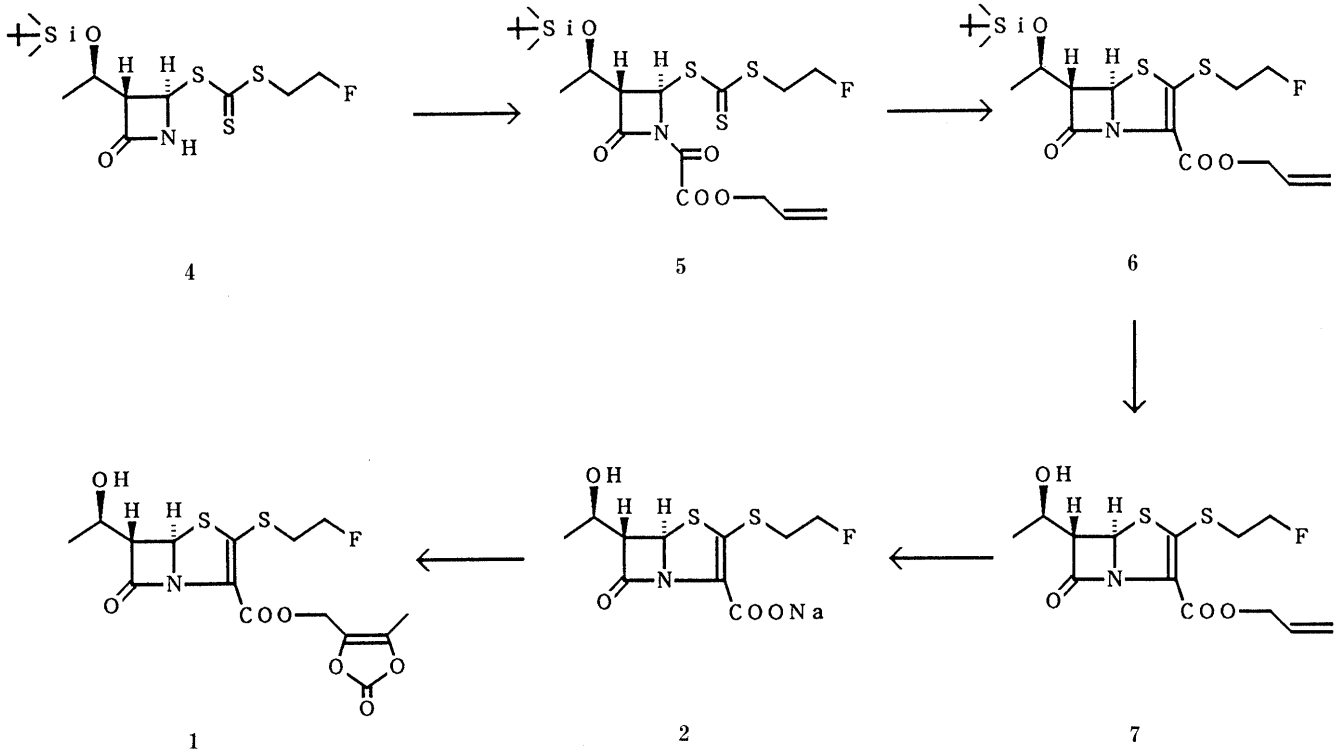


Chart 2

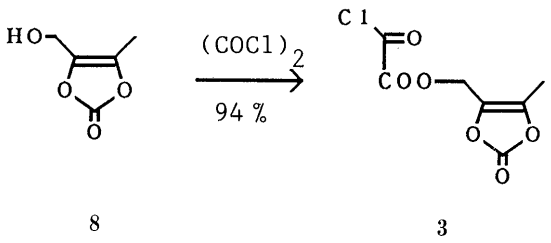

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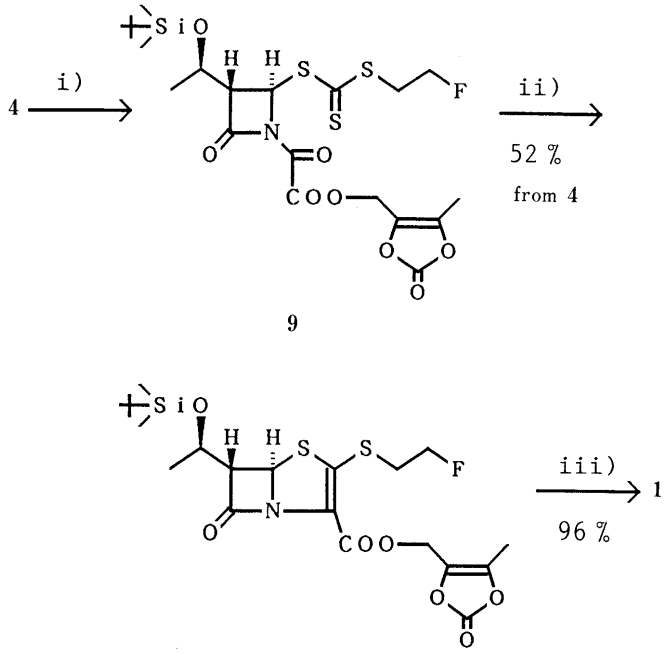
Chart 3



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i) **3**, iso-$Pr_2NEt$, $CaCO_3/CH_2Cl_2$; ii) $(EtO)_3P/CHCl_3$, reflux; iii) $Bu_4NF$, AcOH/THF

Chart 4

dioxol-4-yl)methyl group, could be used in place of the allyl group in **5**, **6** and **7** as the protecting group, the deallylation process (**7**→**2**) and the esterification process (**2**→**1**) would be excluded.

For this purpose, the synthesis of a new building block (5-methyl-2-oxo-1,3-dioxol-4-yl)methyloxyoxalyl chloride (**3**) was necessary. The desired chloride (**3**) was obtained in a 94% yield by the reaction of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol (**8**)[4] with oxalyl chloride.

Acylation of the trithiocarbonate (**4**) with the chloride (**3**) gave the oxalimide (**9**). The cyclization of the oxalimide (**9**) to the penem **10**, which was the key reaction in this synthesis, was successfully performed in a 52% yield by treating **9** with triethyl phosphite in refluxing chloroform for 16 h. The conversion of **10** to **1** was achieved in a high yield (96%) by removal of the *tert*-butyldimethylsilyl group.

Thus, a facile synthesis of the penem prodrug **1** was accomplished in 3 steps from the trithiocarbonate (**4**) with a good overall yield (50%).

## Experimental

**General** Melting point was determined with a Yanaco melting point apparatus and was uncorrected. Proton nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a Varian EM-360L or a JEOL GX-270 spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Nicolet FT-IR (5SXC) spectrometer.

**(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyloxyoxalyl Chloride (3)** A solution of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl alcohol (**8**) (1.38 g) in tetrahydrofuran (3.2 ml) was added to a stirred solution of oxalyl chloride (1.15 ml) in tetrahydrofuran (6.4 ml) cooled to −10 °C. The mixture was stirred at room temperature for 2 h. Evaporation of the solvent and excess reagent gave the title compound **3** as an oil (2.2 g). $^1$H-NMR (60 MHz, $CDCl_3$) $\delta$ (ppm): 2.21 (3H, s, $CH_3$), 5.09 (2H, s, $CH_2$). IR $\nu_{CHCl_3}$ $cm^{-1}$: 1817, 1765, 1745.

**(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-Fluoroethylthio)-6-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]penem-3-carboxylate (10)** Diisopropylethylamine (1.69 ml) was added to a mixture of (3*S*,4*R*)-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-4-[[(2-fluoroethylthio)thiocarbonyl]-thio]azetidin-2-one (**4**) (3.104 g), calcium carbonate (3.26 g) and (5-methyl-2-oxo-1,3-dioxol-4-yl)methyloxyoxalyl chloride (**3**) (2.14 g) in dichloromethane (38 ml) cooled to 0—5 °C. After being stirred for 1 h under the same conditions, the reaction mixture was diluted with dry chloroform (32 ml) and filtered through silica gel (16 g). The silica gel layer was washed with dry chloroform (32 ml). The filtrate and washings were combined and diluted with dry chloroform to 243 ml. To the solution was added, dropwise over 3.5 h, triethylphosphite (2.8 ml) in chloroform (64 ml). The mixture was refluxed under a nitrogen atmosphere for 16 h. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel using a mixture of benzene–EtOAc (5 : 1) to give the title compound **10** as an oil (2.18 g). $^1$H-NMR (60 MHz, $CDCl_3$) $\delta$ (ppm): 0.89 (9H, s, *tert*-butyl), 1.24 (3H, d, $J$=6.0 Hz, $CH_3$), 2.15 (3H, s, $CH_3$), 3.23 (2H, dt, $J$=19.0, 6.0 Hz, $SCH_2$), 3.68 (1H, dd, $J$=4.0, 2.0 Hz, CH), 3.95—4.45 (1H, m, CH), 4.65 (2H, dt, $J$=47.0, 6.0 Hz, $CH_2F$), 4.80 and 5.08 (2H, ABq, $J$=14.0 Hz, $COOCH_2$), 5.62 (1H, d, $J$=2.0 Hz, CH). IR $\nu_{CHCl_3}$ $cm^{-1}$: 1815, 1780, 1730, 1685.

**(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-Fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate (1)** To a solution of (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-2-(2-fluoroethylthio)-6-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]penem-3-carboxylate (**10**) (2.14 g) in tetrahydrofuran (43 ml) was added acetic acid (2.4 ml) and 1 M tetrabutylammonium fluoride in tetrahydrofuran (16.5 ml), and the mixture was stirred at room temperature for 3 d. The mixture was diluted with ethyl acetate and washed successively with aq. NaCl, 5% $NaHCO_3$ and aq. NaCl, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a Lobar column (LiChroprep Si 60, size B). Fractions eluted with benzene–ethyl acetate (2 : 1) were concentrated *in vacuo* to give the title compound **1** as colorless needles (1.60 g), mp 138—140 °C. $^1$H-NMR and IR spectra of this compound were identical to those reported previously.[1]

## References


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