# STUDIES ON PENEM ANTIBIOTICS

## I. SYNTHESIS AND *IN VITRO* ACTIVITY OF NOVEL 2-CHIRAL SUBSTITUTED PENEMS†

MASAJI ISHIGURO, HIROMITSU IWATA, TAKASHI NAKATSUKA, RIE TANAKA, YOKO MAEDA, TATSURO NISHIHARA and TERUHISA NOGUCHI

Suntory Institute for Biomedical Research, 1-1-1 Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka, Japan

TAKESHI NISHINO

Kyoto Pharmaceutical University, 5 Nakauchi-machi, Misasagi, Yamashina, Kyoto, Japan

(Received for publication May 31, 1988)

Since the first disclosure of penem antibiotics by WOODWARD,[2] these compounds which have both broad antibacterial spectra, including Gram-positive and Gram-negative species and stability to various β-lactamases[3,4] have received much attention as potential therapeutic agents.

In recent years, we have been engaged in the development of new orally active 2-substituted penems and we find that the stereochemistry of the C-2 substituent of penems has a relationship to the biological activity. To investigate these relationships further and develop a new penem, we prepared several penems from the intermediate, (2*S*,3*R*)-3-phenylsulfonyl-2-((*R*)-*tert*-butyldimethylsilyloxyethyl)azetidinone (**1**)†† prepared from commercially available methyl (*R*)-3-hydroxybutyrate by the method described below (Scheme 1).[11]

In this paper we describe the synthesis of the important intermediate **1**, novel penems **13A**~**13S**, as well as their MICs against, aerobic, anaerobic, Gram-positive, and Gram-negative bacteria.

*tert*-Butyldimethylsilyl ether **2** was reduced with lithium aluminum hydride in diethyl ether at −78°C for 0.5 hour to alcohol **3** in quantitative yield. This alcohol was treated with *p*-toluenesulfonylchloride in 2,6-lutidine at room temperature for 3 hours to tosylate **4** in 94%, which was transformed into phenylsulfide **5** by treatment with sodium thiophenolate in refluxing THF for 1 hour in 97% yield.

The vinylsulfide **6** was then prepared in 72% yield by chlorination of sulfide **5** with *N*-chlorosuccinimide in carbon tetrachloride at room temperature for 1.5 hours, followed by dehydrochlorination by treatment with lithium carbonate and lithium chloride in dimethylformamide at 80°C for 2 hours. This vinylsulfide **6** was a mixture of *E* and *Z* isomers (**6A** and **6B**) in 2.5 : 1 ratio from its NMR spectrum.

Treatment of this vinylsulfide **6** with chlorosulfonyl isocyanate[12~14] in ether at room temperature for 4 hours, evaporation of solvent and subsequent treatment with thiophenol and pyridine in acetone at room temperature gave diastereomeric mixture of β-lactams **7** and **8** (2 : 1 ratio) in 45% yield. Recrystallization of this mixture from *n*-pentane gave the desired diastereoisomer **7** as colorless crystals and the pentane soluble isomer **8**. It is worthy to note that no 3,4-*cis* isomer was obtained in this reaction.

Phenylthioazetidinone **7** can be transformed to sulfonylazetidinone **1** by oxidation with *m*-chloroperbenzoic acid.[15]

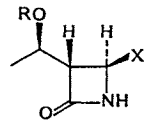
The (5*S*,6*R*)-6-((*R*)-hydroxyethyl)penem derivatives were prepared by seven steps from azetidinone **1**. Substitution of phenyl sulfonyl group of **1** with thiolcarboxylic acid, conversion to phosphorane **11** by a usual method,[16] cyclization to penem **12**, removal of *tert*-butyldimethylsilyl group and allyl group[17] of **12** gave the penem **13**, as described in the Scheme 2.

The total yield by this procedure is rather low, and we found the following procedure to be more convenient for preparation of many types of penems (Scheme 3); substitution of phenyl sulfonyl group of **1** by tritylmercaptan (1.8 equiv, acetone - $H_2O$, room temp) in the basic condition (NaOH, pH 10.5) to give **14** in 90% yield. Acylation of NH group of **14** by allyl oxalyl chloride (1.5 equiv, $CH_2Cl_2$, 0°C) in the presence of *iso*-$Pr_2NEt$ (4 equiv) gave oxalimide **15**. Oxalimide **15** was used without purification and trityl group of **15** was converted to silver mercaptide **16** by $AgNO_3$ - pyridine ($AgNO_3$ 1.5 equiv, pyridine 1.5 equiv, $CH_3CN$, 0°C). The various acyl groups were attached by reaction

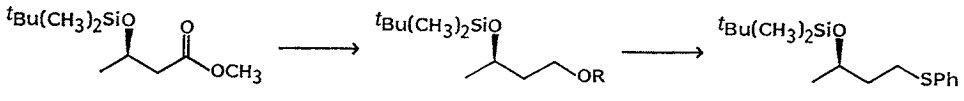
† See ref 1.

†† Other preparative methods of the intermediate **1** or its equivalents were reported. (ref 5~10).

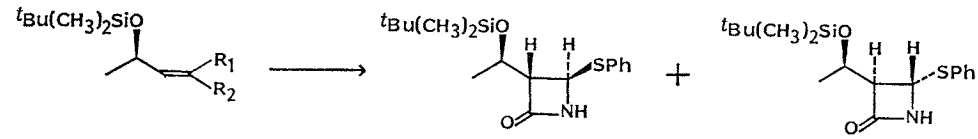
Scheme 1.



**1** R = $^t$Bu(CH$_3$)$_2$Si- X = $SO_2Ph$



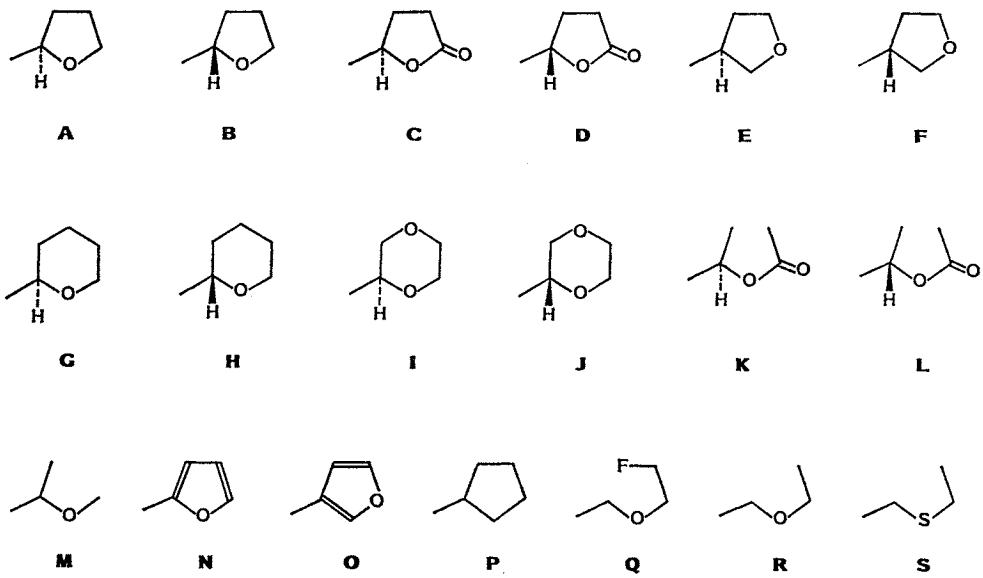
**2** **3** R = H **4** R = Ts **5**



**6A** $R_1$ = H $R_2$ = SPh
**6B** $R_1$ = SPh $R_2$ = H

**7** **8**

**7** ⟶ **1**

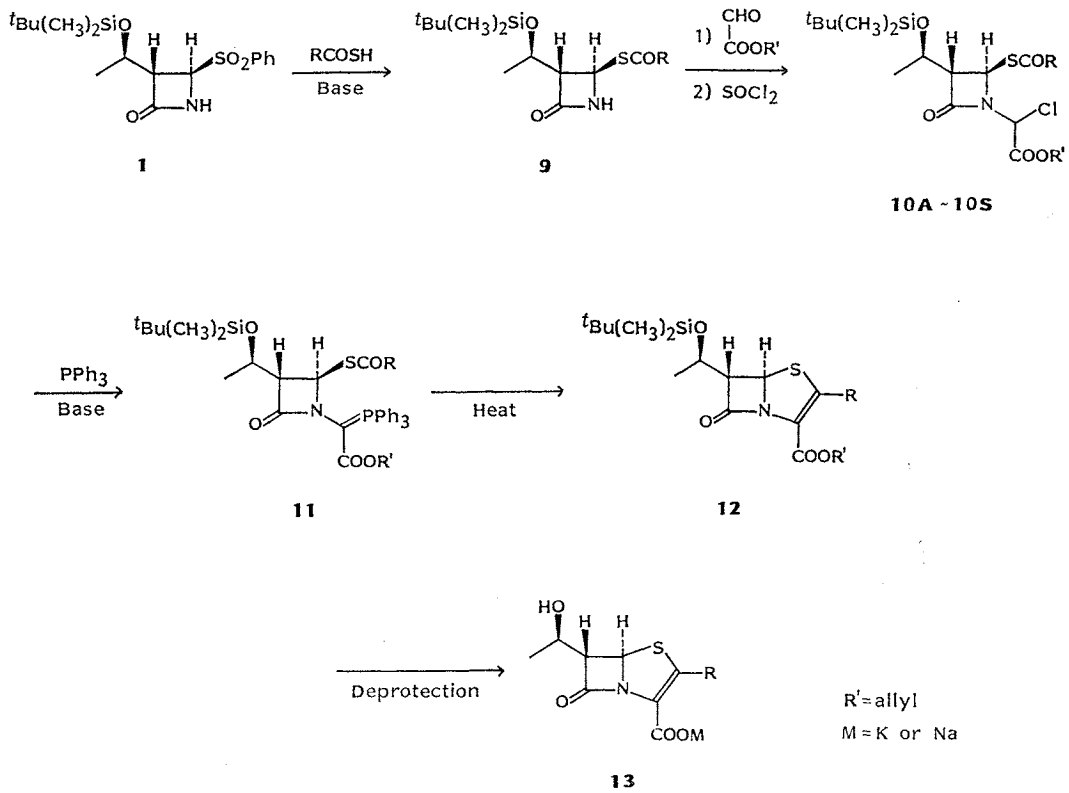


**A** **B** **C** **D** **E** **F**

**G** **H** **I** **J** **K** **L**

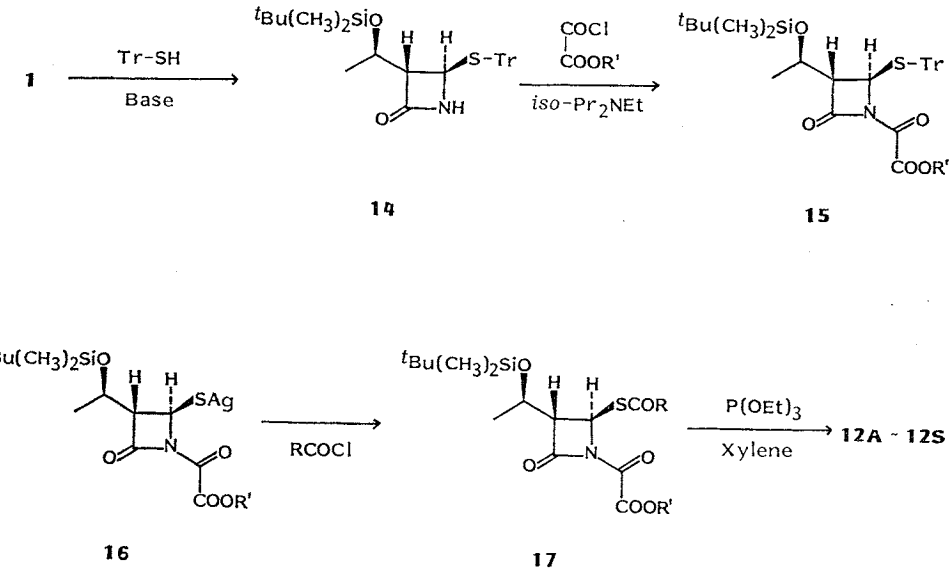
**M** **N** **O** **P** **Q** **R** **S**

Scheme 2.




1 9 10A~10S 11 12 13

Scheme 3.




14 15 16 17

of the acyl chlorides (1.6 equiv, $CH_3CN$, 0°C) to give **17**. Cyclization of **17** by $P(OEt)_3$ at 130°C in xylene[18,19] gave the same synthetic intermediate **12A~12S** in 34% yield in the case of **12A** based on **1** as described in the Scheme 3.

This procedure has an advantage over the

Table 1. MICs against aerobic bacteria.

| Organism | MIC ($\mu$g/ml) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **13A** | **13B** | **13C** | **13D** | **13E** | **13F** | **13G** | **13H** | **13I** |
| *Staphylococcus aureus* 209P JC-1 | 0.05 | 0.05 | 0.1 | 0.2 | 0.05 | 0.05 | 0.1 | 0.1 | 0.05 |
| *Bacillus subtilis* ATCC 6633 | <0.025 | 0.2 | 0.1 | 0.2 | 0.05 | 0.05 | 0.05 | 0.39 | 0.05 |
| *Micrococcus luteus* ATCC 9341 | 0.05 | <0.025 | 0.1 | 0.2 | 0.05 | 0.1 | 0.1 | 0.05 | 0.1 |
| *Comamonas terrigena* IFO 13299 | <0.025 | 0.2 | 0.1 | 0.39 | | | | | |
| *Escherichia coli* NIHJ JC-2 | 0.78 | 6.25 | 1.56 | 3.13 | 1.56 | 1.56 | 6.25 | >50 | 1.56 |
| *Salmonella typhi* O-901 | 0.1 | 3.13 | 1.56 | 6.25 | 1.56 | 0.78 | 3.13 | 50 | 0.39 |
| *Klebsiella pneumoniae* PCI 602 | 0.39 | 1.56 | 0.39 | 1.56 | 0.05 | 0.1 | 0.1 | 3.13 | 0.05 |
| *Serratia marcescens* IAM 1136 | 1.56 | 25 | 3.13 | 12.5 | 12.5 | 6.25 | 25 | >50 | 6.25 |
| *Proteus mirabilis* IFO 3849 | 1.56 | 6.25 | 6.25 | 3.13 | 6.25 | 6.25 | 6.25 | 50 | 6.25 |
| *P. morganii* IFO 3848 | 0.78 | 6.25 | 3.13 | 12.5 | 12.5 | 12.5 | 3.13 | 25 | 6.25 |
| *Enterobacter cloacae* 963 | 0.2 | 12.5 | 3.13 | 12.5 | 6.25 | 6.25 | 25 | >50 | 3.13 |
| *Pseudomonas aeruginosa* No. 12 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *P. cepacia* 527 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *Acinetobacter calcoaceticus* AC54 | 6.25 | 25 | 25 | 50 | 12.5 | 3.13 | 50 | >50 | 12.5 |
| *Alcaligenes faecalis* IFO 13111 | 0.78 | 3.13 | 1.56 | 3.13 | 1.56 | 0.78 | 0.78 | 6.25 | 0.78 |
| *E. coli* W3630/Rms212 | 0.78 | 12.5 | 1.56 | 3.13 | 3.13 | 3.13 | 12.5 | >50 | 1.56 |
| *E. coli* W3630/Rms213 | 0.78 | 6.25 | 0.78 | 3.13 | 1.56 | 1.56 | 6.25 | >50 | 0.78 |
| *E. coli* W3630/Rte16 | 1.56 | 12.5 | 6.25 | 12.5 | 12.5 | 12.5 | 25 | >50 | 12.5 |
| *Proteus vulgaris* GN 7919 | 0.78 | 0.78 | 0.78 | 3.13 | 1.56 | 0.78 | 3.13 | 12.5 | 0.78 |
| *Citrobacter freundii* GN 7391 | 25 | >50 | 25 | >50 | 50 | 50 | >50 | >50 | 25 |
| *P. aeruginosa* GN 10369 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *S. marcescens* GN 10857 | 25 | >50 | 50 | >50 | 50 | 50 | >50 | >50 | 50 |

Table 1. (Continued)

| Organism | MIC (μg/ml) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **13J** | **13K** | **13L** | **13M** | **13N** | **13O** | **13P** | **13Q** | **13R** | **13S** |
| *Staphylococcus aureus* 209P JC-1 | 0.2 | 3.13 | 3.13 | 0.78 | 0.39 | 0.2 | 0.025 | 0.1 | 0.2 | 0.1 |
| *Bacillus subtilis* ATCC 6633 | 0.2 | 3.13 | 3.13 | 0.39 | 0.78 | 0.39 | 0.05 | 0.1 | 0.2 | 0.2 |
| *Micrococcus luteus* ATCC 9341 | 0.1 | 0.78 | 0.78 | 0.78 | 0.2 | 0.2 | 0.05 | 0.1 | 0.2 | 0.2 |
| *Comamonas terrigena* IFO 13299 | | 3.13 | 3.13 | 0.39 | 0.78 | 0.78 | | 0.05 | 0.1 | 0.1 |
| *Escherichia coli* NIHJ JC-2 | 12.5 | >50 | 50 | 25 | 25 | 12.5 | 50 | 0.78 | 6.25 | 25 |
| *Salmonella typhi* O-901 | 6.25 | >50 | 25 | 12.5 | 6.25 | 6.25 | 12.5 | 0.78 | 1.56 | 3.13 |
| *Klebsiella pneumoniae* PCI 602 | 0.78 | 25 | 6.25 | 3.13 | 3.13 | 3.13 | 0.2 | 0.39 | 1.56 | 0.78 |
| *Serratia marcescens* IAM 1136 | 50 | >50 | >50 | >50 | 25 | 25 | 25 | 6.25 | 12.5 | 25 |
| *Proteus mirabilis* IFO 3849 | 25 | >50 | 25 | 50 | 12.5 | 12.5 | 6.25 | 3.13 | 12.5 | 6.25 |
| *P. morganii* IFO 3848 | 25 | >50 | 50 | 50 | 12.5 | 12.5 | 6.25 | 6.25 | 6.25 | 3.13 |
| *Enterobacter cloacae* 963 | 25 | >50 | >50 | >50 | 25 | 25 | 50 | 3.13 | 12.5 | 50 |
| *Pseudomonas aeruginosa* No. 12 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *P. cepacia* 527 | >50 | >50 | >50 | >50 | >50 | >50 | | >50 | >50 | >50 |
| *Acinetobacter calcoaceticus* AC54 | 25 | >50 | >50 | >50 | >50 | >50 | | 25 | 25 | >50 |
| *Alcaligenes faecalis* IFO 13111 | 6.25 | >50 | 25 | 12.5 | 6.25 | 12.5 | 0.78 | 0.78 | 1.56 | 0.78 |
| *E. coli* W3630/Rms212 | 12.5 | >50 | >50 | 50 | 25 | 25 | 50 | 1.56 | 6.25 | 25 |
| *E. coli* W3630/Rms213 | 12.5 | >50 | 50 | 25 | 25 | 25 | 50 | 0.78 | 6.25 | 12.5 |
| *E. coli* W3630/Rte16 | 25 | >50 | >50 | 50 | 12.5 | 12.5 | >50 | 3.13 | 6.25 | 12.5 |
| *Proteus vulgaris* GN 7919 | 6.25 | 50 | 12.5 | 25 | 3.13 | 3.13 | 3.13 | 0.78 | 1.56 | 1.56 |
| *Citrobacter freundii* GN 7391 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 12.5 | >50 | >50 |
| *P. aeruginosa* GN 10369 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | >50 |
| *S. marcescens* GN 10857 | >50 | >50 | >50 | >50 | >50 | >50 | >50 | 25 | >50 | >50 |

Medium: Heart infusion agar, inoculum size: $10^6$ cfu.

Table 2. MICs against anaerobic bacteria.

| Organism | MIC ($\mu$g/ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **13A** | **13B** | **13D** | **13E** | **13F** | **13G** | **13H** | **13I** |
| *Bacteroides fragilis* GM7000 | <0.025 | 0.1 | 0.2 | <0.025 | 0.05 | 0.1 | 0.78 | 0.025 |
| *B. fragilis* ATCC 25285 | <0.025 | 0.1 | 0.39 | <0.025 | | | | |
| *B. fragilis* R-1-23 | <0.025 | 0.1 | 0.78 | 0.05 | 0.05 | 0.2 | 0.78 | 0.05 |
| *B. fragilis* R-2-8 | <0.025 | 0.1 | 0.39 | 0.05 | 0.05 | 0.2 | 0.78 | 0.2 |
| *B. fragilis* V-224-1 | 0.78 | 0.2 | 6.25 | 0.78 | 1.56 | 3.13 | 1.56 | 3.13 |
| *B. fragilis* V-240-2 | 0.78 | 0.2 | 1.56 | 0.39 | 0.39 | 0.78 | 1.56 | 0.39 |
| *B. fragilis* V-271-1 | 0.39 | 0.2 | 3.13 | 0.2 | 0.2 | 0.39 | 0.78 | 0.2 |
| *B. fragilis* V-280-1 | <0.025 | 0.1 | 3.13 | 0.05 | 0.05 | 0.1 | 0.78 | 0.05 |
| *B. fragilis* V-288 | 0.1 | 0.2 | 0.39 | 0.2 | 0.39 | 1.56 | 3.13 | 1.56 |
| *B. fragilis* V-307-2 | 0.1 | 0.2 | 0.78 | 0.39 | 0.39 | 0.78 | 1.56 | 0.39 |
| *B. thetaiotaomicron* WAL2926 | 0.1 | 0.39 | 1.56 | 0.2 | 0.2 | 1.56 | 3.13 | 0.39 |
| *B. thetaiotaomicron* WAL3304 | 0.2 | | 1.56 | | 3.13 | 25 | 6.25 | 6.25 |
| *B. distasonis* Ju-11-1 | <0.025 | <0.025 | 0.2 | <0.025 | 0.025 | 0.1 | 0.2 | 0.025 |
| *B. vulgatus* ES-14 | 0.2 | 0.1 | 0.78 | <0.025 | 0.05 | 0.05 | 0.39 | 0.05 |
| *B. vulgatus* ES-21 | 0.1 | 0.1 | 0.39 | <0.025 | 0.05 | 0.2 | 0.39 | 0.1 |
| *B. ovatus* Ju-6-1 | 0.39 | 0.78 | 3.13 | 0.78 | | | | |
| *Fusobacterium varium* ATCC 8501 | 0.2 | 0.78 | 3.13 | 0.2 | 0.39 | 0.39 | 6.25 | 0.78 |
| *F. varium* B-1083 | 0.2 | 0.78 | 3.13 | 0.2 | 0.39 | 0.39 | 6.25 | 0.39 |
| *F. varium* 1482 | 0.2 | 0.78 | 3.13 | 0.2 | 0.39 | 0.78 | 6.25 | 0.78 |
| *F. necrophorum* S-45 | | | 0.025 | | | | | |
| *F. mortiferum* F-1-9 | 0.2 | 0.39 | 0.78 | 0.1 | 0.2 | 0.2 | 0.78 | 0.2 |

Table 2. (Continued)

| Organism | MIC (μg/ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **13J** | **13K** | **13M** | **13N** | **13O** | **13Q** | **13R** | **13S** |
| *Bacteroides fragilis* GM7000 | 0.39 | 6.25 | 0.78 | 0.39 | 0.39 | 0.05 | 0.1 | 0.1 |
| *B. fragilis* ATCC 25285 | | | 1.56 | 0.78 | 0.39 | 0.05 | 0.2 | 0.2 |
| *B. fragilis* R-1-23 | 0.39 | | 1.56 | 0.78 | 0.78 | 0.05 | 0.2 | 0.78 |
| *B. fragilis* R-2-8 | 3.13 | 6.25 | 1.56 | 0.78 | 0.39 | 0.1 | 0.1 | 0.2 |
| *B. fragilis* V-224-1 | 6.25 | >50 | 6.25 | 6.25 | 6.25 | 0.78 | 1.56 | 1.56 |
| *B. fragilis* V-240-2 | 1.56 | | 6.25 | 1.56 | 0.78 | 0.2 | 0.39 | 0.39 |
| *B. fragilis* V-271-1 | 0.78 | | 1.56 | 0.78 | 0.39 | 0.1 | 0.2 | 0.2 |
| *B. fragilis* V-280-1 | 0.39 | 25 | 1.56 | 6.25 | 6.25 | 0.05 | 0.1 | 0.2 |
| *B. fragilis* V-288 | 3.13 | 50 | 1.56 | 0.78 | 0.78 | 0.2 | 0.2 | 0.2 |
| *B. fragilis* V-307-2 | 1.56 | 25 | 3.13 | 0.78 | 0.78 | 0.2 | 0.39 | 0.39 |
| *B. thetaiotaomicron* WAL2926 | 1.56 | 50 | 3.13 | 3.13 | 1.56 | 0.2 | 0.39 | 1.56 |
| *B. thetaiotaomicron* WAL3304 | 12.5 | 25 | 3.13 | | | 0.2 | 0.39 | 1.56 |
| *B. distasonis* Ju-11-1 | 0.1 | 3.13 | 0.78 | 0.39 | 0.2 | 0.05 | 0.2 | 0.39 |
| *B. vulgatus* ES-14 | 0.2 | 12.5 | 1.56 | 0.78 | 0.78 | 0.05 | 0.2 | 0.39 |
| *B. vulgatus* ES-21 | 0.39 | 6.25 | 3.13 | 6.25 | 6.25 | 0.1 | 1.56 | 0.39 |
| *B. ovatus* Ju-6-1 | | | 6.25 | | | 0.39 | 3.13 | 3.13 |
| *Fusobacterium varium* ATCC 8501 | 3.13 | 25 | 3.13 | 6.25 | 6.25 | 0.39 | 0.39 | 0.39 |
| *F. varium* B-1083 | 3.13 | 12.5 | 3.13 | 6.25 | 6.25 | 0.39 | 0.78 | 0.39 |
| *F. varium* 1482 | 6.25 | 12.5 | 6.25 | 6.25 | 6.25 | 0.39 | 0.78 | 0.39 |
| *F. necrophorum* S-45 | | 0.78 | 0.05 | | | | 0.39 | 0.2 |
| *F. mortiferum* F-1-9 | 1.56 | 6.25 | 3.13 | 1.56 | 1.56 | 0.39 | | |

Medium: GAM agar, inoculum size: $10^6$ cfu.

previous method in that the various penem derivatives are more easily prepared in short steps without use of thiolcarboxylic acid.

By the methods described, we synthesized the following penems **13A**~**13S**. Diastereomers which had an asymmetric carbon on the C-2 substituent were separated by silica gel chromatography at several stages, or prepared from optically active starting materials.[20~23] *In vitro* antibacterial activity of the new penems against a selection of representative Gram-positive, Gram-negative and anaerobic bacteria is listed in Tables 1 and 2.

From these data, it is seen that; 1) the stereochemistry of the C-2 substituent has a great influence on the antimicrobial activity; 2) penems which have an oxygen containing unsaturated ring at C-2 position like **13N** and **13O** are less potent than the corresponding saturated ring compounds; 3) penems which have cyclic side chains are much more potent than those have non-cyclic side chains (**13C** and **13K**).

## References


1) ISHIGURO, M.; H. IWATA, T. NAKATSUKA, R. TANAKA, Y. MAEDA, T. NISHIHARA, T. NOGUCHI & T. NISHINO: Novel 2-chiral substituted penems: Synthesis and activity of a new orally active penem SUN5555. Program and Abstracts of the 26th Intersci. Conf. on Antimicrob. Agents Chemother., No. 1284, p. 329, New Orleans, Sept. 28~Oct. 1, 1986
2) WOODWARD, R. B.: Recent advances in the chemistry of β-lactam antibiotics. *In* Recent Advances in the Chemistry of β-Lactam Antibiotics. Spec. Publ. No. 28, *Ed.*, J. ELKS, pp. 167~180, The Chemical Society, London, 1977
3) ERNEST, I.: The penems. *In* Chemistry and Biology of β-Lactam Antibiotics. Non Traditional β-Lactam Antibiotics. Vol. 2. *Eds.*, R. B. MORIN & M. GORMAN, pp. 315~360, Academic Press, New York, 1982
4) AFONSO, A.; A.K. GANGLY, V. GIBIJAVALLABHAN & S. MCCOMBIE: Synthesis of penem antibiotics. *In* Recent Advances in the Chemistry of β-Lactam Antibiotics. Spec. Publ. No. 52, *Eds.*, A. G. BROWN & S. M. ROBERTS, pp. 226~279, The Chemical Society, London, 1985
5) DININNO, F.; T.R. BEATTIE & B.G. CHRISTENSEN: Aldol condensations of regiospecific penicillanate and cephalosporanate enolates. Hydroxyethylation at C-6 and C-7. J. Org. Chem. 42: 2960~2965, 1977
6) SHIOZAKI, M.; N. ISHIDA, T. HIRAOKA & H. YANAGISAWA: Stereocontrolled synthesis of chiral intermediates of thienamycin from threonines. Tetrahedron Lett. 22: 5205~5208, 1981
7) SALZMANN, T. N.; R. W. RATCLIFFE, B. G. CHRISTENSEN & F. A. BOUFFARD: A stereocontrolled synthesis of (+)-thienamycin. J. Am. Chem. Soc. 102: 6161~6163, 1980
8) ITO, Y.; T. KAWABATA & S. TERASHIMA: A novel synthesis of (3R,4R)-4-acetoxy-3-[(R)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone, the versatile key intermediate of carbapenem synthesis, from (S)-ethyl lactate. Tetrahedron Lett. 27: 5751~5754, 1986
9) CHIBA, T.; M. NAGATSUMA & T. NAKAI: A facile, stereocontrolled entry to key intermediates for thienamycin synthesis from ethyl (*S*)-3-hydroxybutanoate. Chem. Lett. 1985: 1343~1346, 1985
10) OHASHI, T.; K. SUGA, I. SADA, T. MIYAMA & K. WATANABE (Kanegafuchi Chemical): Novel β-lactams and its preparative method. Jpn. Kokai 18791('84), July 5, 1984
11) ISHIGURO, M.; H. IWATA, T. NAKATSUKA & M. OKITSU (Suntory): Novel method for preparation of 2-azetidinone. Jpn. Kokai 207373('85), Mar. 9, 1985
12) KAMAL, A. & P. B. SATTUR: Chlorosulfonyl isocyanate: a novel reagent for the synthesis of heterocycles. Heterocycles 26: 1051~1076, 1987
13) HIRAI, K.; H. MATSUDA & Y. KISHIDA: Synthesis of 2-azetidinone (β-lactam) ring by chlorosulfonyl isocyanate (CSI). Chem. Pharm. Bull. 21: 1090~1095, 1973
14) SCHMIDT, J. (H-La Roche, und Co. A.-G.): Sterically uniform 2-azetidinone. Jpn. Kokai 97260('85), Oct. 17, 1985
15) CLAUSS, K.; D. GRIMM & G. PROSSEL: β-Lactame mit über Heteroatome gebundenen Substituenten. Liebigs Ann. Chem. 1974: 539, 1974
16) LANG, M.; K. PRASAD, W. HOLICK, J. GOSTELI, I. ERNEST & R. B. WOODWARD: The penems, a new class of β-lactam antibiotics. 2. Total synthesis of racemic 6-unsubstituted representatives. J. Am. Chem. Soc. 101: 6296~6301, 1979
17) JEFFREY, P. D. & S. W. MCCOMBIE: Homogeneous, palladium(0) catalized exchange deprotection of allyl esters, carbonates, and carbamates. J. Org. Chem. 47: 587, 1982
18) YOSHIDA, A.; Y. TAJIMA, N. TAKEDA & S. OIDA: An efficient carbapenem synthesis *via* an intramolecular Wittig reaction of new trialkoxyphosphorane-thiolesters. Tetrahedron Lett. 25: 2793~2796, 1984
19) BATTISTINI, C.; C. SCARAFILE, M. FOGLIO &

G. FRANCESCHI: A new route to penems and carbapenems. Tetrahedron Lett. 25: 2395~2398, 1984

20) BELANGER, P. C. & H. W. R. WILLIAMS: Synthesis of optically active 2-tetrahydrofuran derivatives. Can. J. Chem. 61: 1383, 1982

21) TANIGUCHI, M.; K. KOGA & S. YAMADA: Stereochemical studies-XXX stereoselective synthesis of D-ribose from L-glutamic acid. Tetrahedron 30: 3547, 1974

22) HILL, R. K. & W. R. SCHEARER: The absolute configuration at C-12 of $\alpha$-erythroidine. J. Org. Chem. 27: 921, 1962

23) TANIGUCHI, M.; K. KOGA & S. YAMADA: Stereochemical studies XVI. Deaminative acetolyses of L-valine and L-valine benzylester. Chem. Pharm. Bull. 20: 1438~1444, 1972