SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 5-METHYLCARBAPENEMS

HIROSHI ONOUE and YUKITOSHI NARUKAWA

Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka 553, Japan

(Received for publication February 20, 1989)

Four possible racemic isomers of *N*-acetyl-5-methylthienamycin derivatives were synthesized and their antibacterial activities are discussed in relation to their physico-chemical properties. 5-Methylcarbapenems having various C-2 side chains were also prepared.

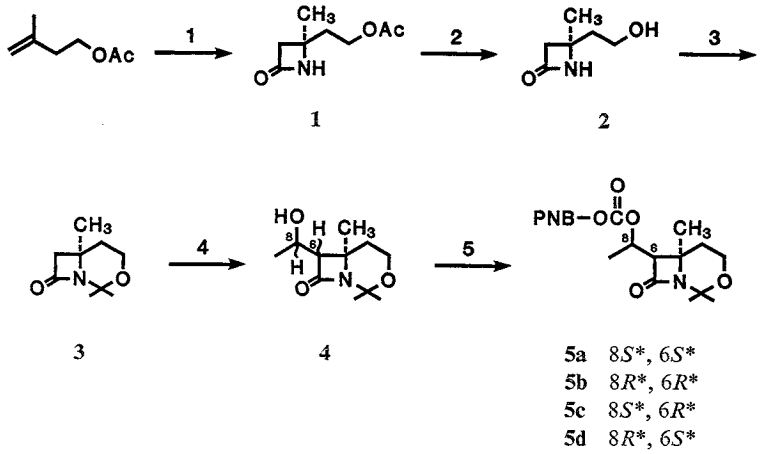
Although carbapenem antibiotics have excellent antibacterial potency and a wide range of activities, they are susceptible to renal dehydropeptidase-I (DHP-I), resulting in poor therapeutic efficacy *in vivo*[1]. Since the stability of cephem and oxacephem antibiotics to β-lactamase can be improved by the introduction of the 7α-methoxyl group[2], introducing an additional substituent into the carbapenem skeleton was tried to obtain metabolically stable derivatives. One of the most fruitful results was obtained with 1-β-methylcarbapenems, which showed improved biological stability with the retainment of antibacterial activities[3,4]. Recently, 6-methoxy-[5] or 6-methylcarbapenems[6] were synthesized, but they showed very weak activities. In an effort to find novel types of carbapenems with excellent chemical and biological stabilities, our recent interest was focused on C-5 substituted carbapenems, especially 5-methyl derivatives. Although the simple 5-methylcarbapenem was prepared previously[7], it lacked the hydroxyethyl side chain at its C-6 position, which is indispensable for high biological activity. This paper describes the syntheses of structurally unambiguous 5-methylcarbapenems and their antibacterial activities together with some physico-chemical properties.

We first decided to synthesize four possible isomers of racemic *N*-acetyl-5-methylthienamycin derivatives to examine the effect of the relative stereochemistry between C-6 and C-8 on the antibacterial activity. Our next target was to synthesize the C-2 modified derivative to search for 5-methylcarbapenems with improved activity.

Chemistry

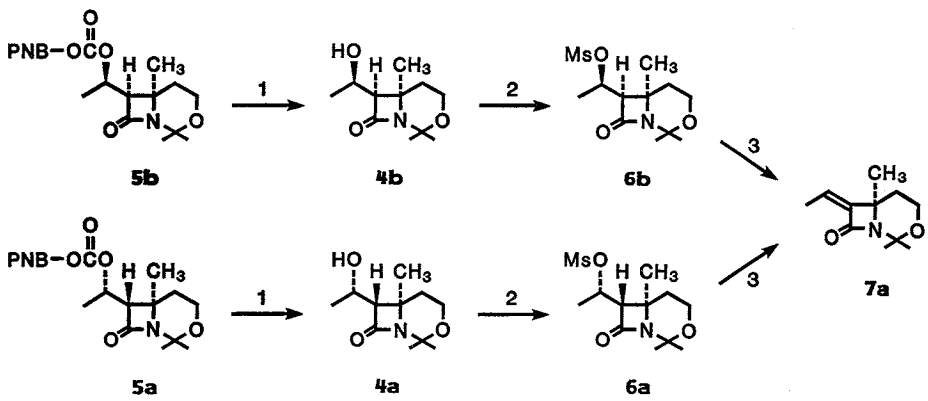
The reaction of chlorosulfonyl isocyanate with 3-methyl-3-butenyl acetate followed by reductive hydrolysis gave β-lactam **1** in 41% yield. Base-catalyzed deacetylation provided alcohol **2** in quantitative yield, which underwent protection with 2,2-dimethoxypropane to yield bicyclic acetonide **3** (92%). Treatment of **3** with lithium diisopropylamide (LDA) followed by acetaldehyde at −50°C gave aldol products **4** as a mixture of four isomers (89%). Each of the four isomers could be identified in the 400 MHz NMR spectrum of the product mixture, and the ratio was determined to be **4a** : **4b** : **4c** : **4d** = 47 : 36 : 8 : 9. Hydroxy-protection of this isomeric mixture **4** with *p*-nitrobenzyl (PNB) chloroformate provided a mixture of protected products, from which two of the major isomers **5a** and **5b** could be isolated as a crystalline material. One of the isolated isomers, **5b**, was subjected to X-ray crystallographic analysis and its structure was confirmed to be 8*R**,6*R** (carbapenem structure numbering). Chemical correlation of the structurally unambiguous isomer **5b** with another isomer **5a** was carried out by the

Scheme 1.



1) $ClSO_2NCO$, 2) $NaOCH_3$ - MeOH, 3) 2,2-dimethoxypropane, 4) LDA - CH_3CHO, 5) PNB chloroformate.

Scheme 2.

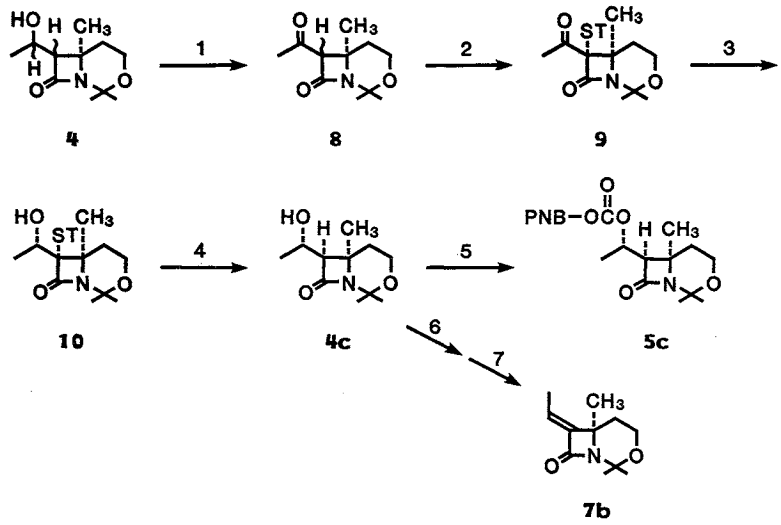


1) H_2 - Pd, 2) MsCl - Et_3N, 3) $NaHCO_3$ - MeOH.
Ms: Mesyl

well-known mesylation-elimination sequence[8] (Scheme 2). Both of the two isomers were subjected to deprotection of the PNB group, followed by mesylation and elimination to obtain the identical *Z*-ene lactam **7a**. Since this type of elimination is known to proceed *via* an anti coplanar pathway, the present result showed the structure of **5a** to be 8*S**,6*S**.

The third isomer (8*S**,6*R**) was synthesized in a stereoselective way[9] as shown in Scheme 3. Oxidation of an isomeric mixture of **4a**~**4d** gave ketone **8** as a mixture of 1 : 1 isomers (61%). Sulfenylation of **8** with *p*-tolyl *p*-toluenethiosulfonate in *N*,*N*-dimethylformamide (DMF) yielded **9** as a single isomer (60%). Reduction of **9** with sodium borohydride produced the alcohol **10** (61%) having the desired *S** configuration at the hydroxyethyl side chain as a crystalline solid. Reduction of **10** with tri-*n*-butyltin hydride provided the *cis* (6*R**) product **4c** in quantitative yield and the hydroxyl group of this product was protected as PNB carbonate to give the key intermediate **5c**. The structure of **4c** was confirmed by the mesylation-elimination sequence to give *E*-ene lactam **7b**.

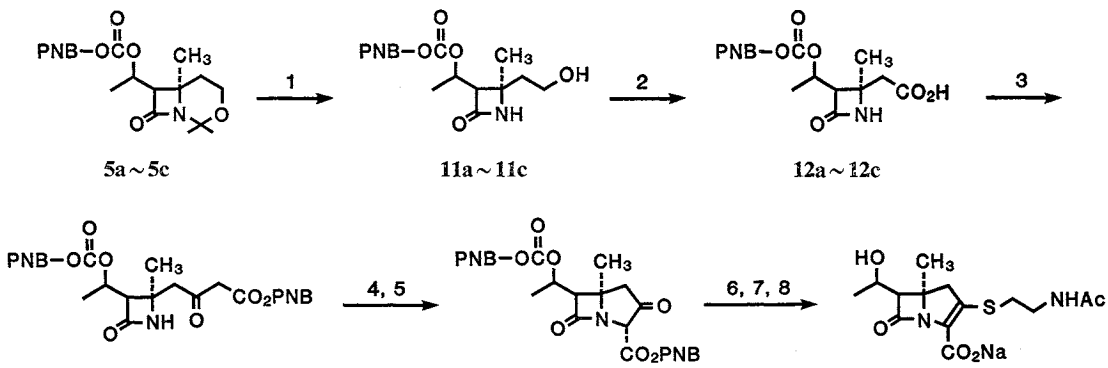
Scheme 3.



1) Jones reagent, 2) CH_3-⟨⟩-SSO_2-⟨⟩-CH_3 – Et_3N, 3) $NaBH_4$, 4) Bu_3SnH - AIBN, 5) *n*-BuLi - PNB chloroformate, 6) MsCl - Et_3N, 7) $NaHCO_3$ - MeOH.

ST= S-⟨⟩-CH_3

Scheme 4.

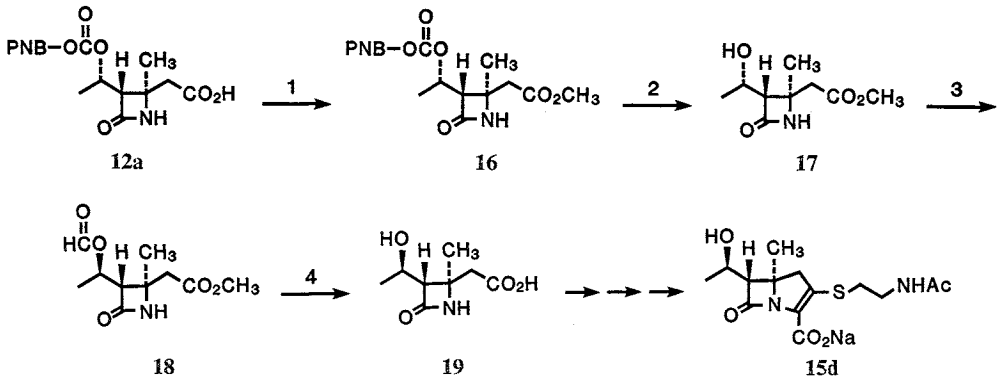


1) H^+, 2) Jones reagent, 3) carbonyldiimidazole, $(PNB\text{-}OOCCH_2COO)_2Mg$, 4) TsN_3, 5) $Rh_2(OAc)_4$, 6) $ClPO(OPh)_2$, (*iso*-Pr)$_2$NEt, 7) $HSCH_2CH_2NHAc$, (*iso*-Pr)$_2$NEt, 8) H_2 - Pd.
Ts: Tosyl

Each of the three bicyclic acetals **5a**~**5c** was hydrolyzed under acidic condition to give deprotected monocyclic azetidinones **11a**~**11c** in 32~80%. Jones oxidation of these alcohols gave acids **12a**~**12c** and these intermediates were subjected to the well-known carbapenem synthetic sequence[8] to give the stereoisomers of *N*-acetyl-5-methylthienamycin **15a**~**15c** (Scheme 4).

The final 8*R**,6*S** isomer, racemic *N*-acetyl-5-methylthienamycin, was synthesized as follows (Scheme 5). The carboxylic acid **12a** having 8*S**,6*S** configuration was converted to methyl ester **16** whose PNB group was removed by catalytic hydrogenation to give hydroxy ester **17**. Mitsunobu

Scheme 5.



1) CH_2N_2, 2) H_2 - Pd, 3) Ph_3P, *iso*-PrOOCN=NCOO *iso*-Pr, HCOOH, 4) OH^-.

Table 1. Physico-chemical properties of *N*-acetylthienamycin derivatives.

	N-Acetylthienamycin	**15d**
Hydrolysis rate[a] (half life time)	0.326 (2.1 hours)	0.126 (5.5 hours)
IR carbonyl absorption[b]	1761.1 (1778.9)[c]	1754.1 (1775.9)[c]

[a] $hour^{-1}$, 35°C, pH 9.24.
[b] cm^{-1}, DMSO solution.
[c] Data of PNB ester in $CHCl_3$ solution.

inversion reaction of **17** yielded formylated ester **18** and after alkaline hydrolysis, hydroxy acid **19** with 8*R**,6*S** configuration was obtained. This hydroxy acid **19** was converted to *N*-acetyl-5-methylthienamycin **15d** as described above except that the hydroxyl group was not protected in this case.

To shed light on the relationship between chemical reactivity and antibacterial activity of 5-methylcarbapenem, we examined their physico-chemical properties; the hydrolysis rate and IR carbonyl absorption frequency (Table 1). The data of optically active *N*-acetylthienamycin is included as a reference. The compound (**15d**) selected for this measurement had the highest antibacterial activity among the four isomers. Comparison of its data with those of *N*-acetylthienamycin revealed that for the 5-methyl derivative, the hydrolysis rate was reduced to about one-third, and the carbonyl absorption wave number was shifted to a lower frequency by about 7 cm^{-1}. These results suggest that the chemical reactivity of 5-methylcarbapenem is reduced by the electron-donating effect of the 5-methyl group.

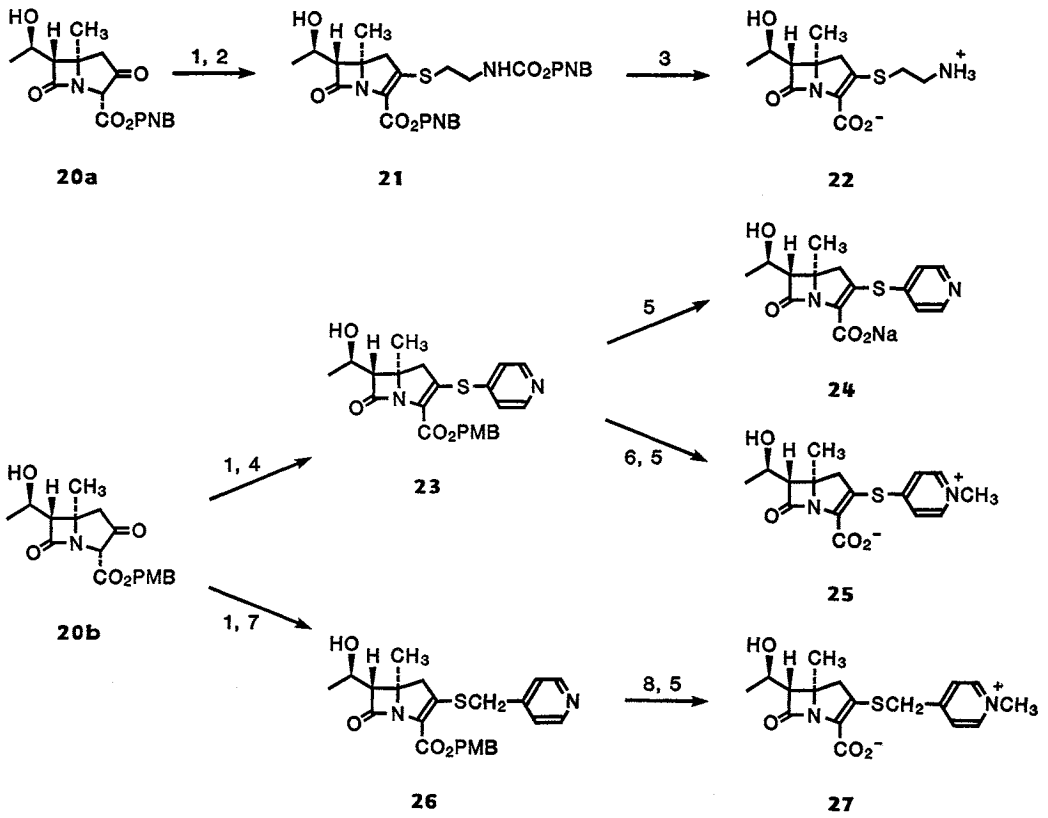
Having established the relative stereochemistry of the most active isomer to be 8*R**,6*S** (*vide infra*), we turned to the modification of the C-2 side chain to improve its potency and synthesized various C-2 substituted 5-methylcarbapenems (Scheme 6). The synthesis was carried out by introducing the appropriate thiol into the bicyclic keto ester intermediate **20a**. We also prepared *p*-methoxybenzyl ester intermediates **20b** which could be deprotected in the final step with the aluminum trichloride-anisole system[10]. This final deprotection step was superior to the conventional catalytic deprotection of PNB esters, especially for substrates with the pyridinium moiety at the C-2 side chain.

Antibacterial Activity†

Table 2 summarizes the antibacterial activities of four isomers of racemic *N*-acetyl-5-methylthiena-

† MICs were determined by the agar dilution method.

Scheme 6.



1) $ClPO(OPh)_2$, (*iso*-Pr)$_2$NEt, 2) $HSCH_2CH_2NHCOOPNB$, (*iso*-Pr)$_2$NEt, 3) H_2-Pd, 4) HS-  , (*iso*-Pr)$_2$NEt, 5) $AlCl_3$, anisole, 6) CH_3OTf, 7) $HSCH_2$-  , (*iso*-Pr)$_2$NEt, 8) CH_3I.

PMB: *p*-Methoxybenzyl

mycin **15a**~**15d** together with the data of optically active *N*-acetylthienamycin. Clearly, the relative stereochemistry between C-6 and C-8 had a large effect on the activity, with almost one hundred difference between the most potent and the least potent isomers. The activity decreased in the following order: 8*R**,6*S**>8*S**,6*R**>8*S**,6*S**>8*R**,6*R**. This order is the same as that found for the parent 5-unsubstituted thienamycin isomers[11]. Therefore, the isomer with most potent activity has the same relative stereochemistry, 8*R**,6*S**, irrespective of the presence or absence of the 5-methyl group.

Comparison of chiral *N*-acetylthienamycin with **15d** having the same relative stereochemistry shows that introduction of the 5-methyl substituent resulted in decreased activities against both Gram-positive and Gram-negative strains except for *Pseudomonas aeruginosa*.

The results of the physico-chemical experiment of **15d** and *N*-acetylthienamycin suggested that the chemical reactivity of 5-methylated carbapenem was reduced by the electron-donating effect of the 5-methyl group. Therefore, the decreased antibacterial activity of 5-methylcarbapenem can be attributed to the reduced chemical reactivity.

Table 3 summarizes the antibacterial activities of various C-2 modified racemic 5-methylcar-

Table 2. Comparative activity (MIC; μg/ml) of *N*-acetylthienamycin derivatives.

Organism	*N*-Acetylthienamycin	**15 d**	**15 c**	**15 a**	**15 b**
Staphylococcus aureus JC-1	0.1	1.6	3.1	50	100
S. aureus Smith	0.1	3.1	6.3	100	100
Streptococcus pyogenes C-203	0.02	0.8	0.8	25	100
S. pneumoniae I	0.01	0.4	1.6	50	100
Escherichia coli JC-2	0.1	6.3	12.5	>100	>100
E. coli 73 (R)	0.2	6.3	25	>100	>100
Klebsiella pneumoniae SRL-1	0.2	6.3	6.3	>100	>100
Proteus mirabilis PR-4	0.4	12.5	25	>100	>100
Pseudomonas aeruginosa 25619	100	25	100	>100	>100
P. aeruginosa PS-24	100	>100	>100	>100	>100

Table 3. Comparative activity (MIC; μg/ml) of 5-methylcarbapenem derivatives and thienamycin.

Organism	Thienamycin	**22**	**27**	**24**	**25**
Staphylococcus aureus JC-1	0.025	0.4	0.4	0.2	0.1
S. aureus Smith	0.05	0.4	0.4	0.2	0.1
Streptococcus pyogenes C-203	—	0.4	0.1	0.2	0.05
S. pneumoniae I	—	0.4	0.1	0.1	0.1
Escherichia coli JC-2	0.4	25	12.5	3.1	3.1
E. coli 73 (R)	0.8	25	12.5	0.8	3.1
Klebsiella pneumoniae SRL-1	0.8	25	12.5	0.8	3.1
Proteus mirabilis PR-4	0.4	50	25	1.6	3.1
Pseudomonas aeruginosa 25619	3.1	6.3	6.3	12.5	12.5
P. aeruginosa PS-24	12.5	12.5	12.5	100	12.5

bapenems including optically active thienamycin. Data for **22** indicate that the introduction of 5-methyl substituent resulted in a decrease in activities against most of the strains. However, 5-methylcarbapenems such as **24** and **25** having C-2 substituents which activate β-lactam carbonyl group by π conjugation showed relatively good results. It should be pointed out that activity against *P. aeruginosa* is retained. This result could be explained by the improved permeability of 5-methylcarbapenems through the outer membrane of *P. aeruginosa*. A preliminary experiment in our laboratories disclosed that the stability of 5-methylcarbapenem in mouse kidney homogenate was much greater than that of the 5-unsubstituted one.

Experimental

General Methods

MP's were determined on a Yanagimoto apparatus and were not corrected. IR spectra were obtained on a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390, VXR-200, XL-200, and VXR-400 with TMS as an internal standard. In the case of spectra taken in D_2O, internal (3-trimethylsilyl)-1-propanesulfonic acid sodium salt (DSS) or external TMS was used. UV spectra were obtained on a Hitachi 320 spectrometer. Column chromatography was performed on Merck Silica gel 60 (230~400 mesh or 70~230 mesh). Elemental analyses were performed with crystalline compounds ($\pm$0.4% accuracy).

(4*R**)-4-(2-Acetoxyethyl)-4-methyl-2-azetidinone (**1**)

To a cooled (−15°C) solution of 41.78 g (0.33 mol) of 3-methyl-3-butenyl acetate in 100 ml of diethyl ether was added over 50 minutes, 27 ml (0.31 mol) of chlorosulfonyl isocyanate. After stirring in an ice-bath for 1 hour, the mixture was allowed to stand at 5°C overnight. The mixture was then

added dropwise over 20 minutes to an ice-cooled mixture of 59 g (0.47 mol) of sodium sulfite, 135 g (0.78 mol) of dipotassium hydrogen phosphate, 300 ml of water and 200 ml of diethyl ether. The resulting mixture was stirred at room temperature for additional 1 hour. Extractive work-up with diethyl ether and crystallization from diethyl ether gave 21.30 g (41%) of **1** as a colorless crystalline solid: MP 75.5~76.5°C; IR ($CHCl_3$) cm^{-1} 3400 (NH), 1750 (β-lactam C=O), 1730 (ester C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.45 (3H, s, CH_3), 2.05 (3H, s, CH_3COO), 2.03 (2H, t, J=7 Hz, CH_2), 2.79 (2H, ABq, d, J=2 and 15 Hz, $COCH_2$), 4.21 (2H, t, J=7 Hz, CH_2), 6.55 (1H, br, NHCO).

(4*R**)-4-(2-Hydroxyethyl)-4-methyl-2-azetidinone (**2**)

To a solution of 23.70 g (0.138 mol) of **1** in 250 ml of methanol was added with ice-cooling 3.0 ml of sodium methoxide (4.6 M solution in methanol, 0.014 mol). After stirring at 0°C for 2 hours, 0.96 ml of acetic acid was added and the mixture was concentrated *in vacuo*. The resulting oil was passed through a short column of silica gel using EtOAc - acetone (1 : 1). Concentration of the eluent gave 18.83 g (quantitative yield) of **2** as a colorless oil: IR ($CHCl_3$) cm^{-1} 3400 (NH), 1750 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.44 (3H, s, CH_3), 1.92 (2H, t, J=7 Hz, CH_2), 2.69 (2H, ABq, d, J=2 and 13 Hz, CH_2CO), 3.57 (1H, br, HO), 3.79 (2H, t, J=7 Hz, CH_2O), 6.95 (1H, br, NHCO).

(6*R**)-2,2,6-Trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**3**)

To a solution of 15.89 g (0.117 mol) of **2** and 22 ml (0.18 mol) of 2,2-dimethoxypropane in 160 ml of CH_2Cl_2 was added at room temperature 2.8 ml (0.023 mol) of boron trifluoride etherate. After stirring at room temperature for 2 hours, the mixture was washed with phosphate buffer solution (1 M, pH 7) and then with brine. The organic layer was dried and concentrated *in vacuo* to give an oil which was crystallized from hexane - diethyl ether to afford 18.14 g (92%) of **3**: MP 47.5~48.5°C; IR ($CHCl_3$) cm^{-1} 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.74 (3H, s, CH_3), 1.64~1.98 (2H, m, CH_2), 2.75 (2H, s, CH_2CO), 3.63~4.12 (2H, m, CH_2O).

7-(1-Hydroxyethyl)-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**4**)

To a solution of 22 ml of diisopropylamine (0.157 mol) in 230 ml of THF was added at −50°C 95 ml (1.5 M in hexane) of *n*-butyllithium. After stirring for 10 minutes, a solution of 20.13 g (0.119 mol) of **3** in 50 ml of THF was added slowly so that the temperature of the mixture did not exceed −50°C. Stirring was continued for additional 15 minutes and 11 ml (0.197 mol) of acetaldehyde was added in one portion. After 15 minutes at −50°C, the mixture was partitioned between saturated ammonium chloride and EtOAc. Usual work-up followed by chromatography on silica gel afforded 22.48 g (89%) of **4** as a mixture of four isomers.

(6*R**,7*S**)-7-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**5a**) and (6*R**,7*R**)-7-[(1*R**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**5b**)

To a solution of 7.48 g (35.1 mmol) of **4** in 300 ml of CH_2Cl_2 was added with ice-cooling 15.30 g (71.0 mmol) of PNB chloroformate in 50 ml of CH_2Cl_2 and 8.59 g (70.3 mmol) of 4-(*N*,*N*-dimethylamino)pyridine successively. After 2.5 hours at room temperature, the mixture was poured into 10% phosphoric acid and extracted with CH_2Cl_2. The organic layer was dried, concentrated, and chromatographed (Lobar column, C-type) to give 4.18 g (30%) of 8*S**,6*S** isomer **5a** and 3.68 g (27%) of 8*R**,6*R** isomer **5b**. Both isomers were crystallized from hexane - diethyl ether.

8*S*,*6*S** Isomer (**5a**): MP 129.5~130°C; IR ($CHCl_3$) cm^{-1} 1740 (β-lactam C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.43 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.44 (3H, d, J=6 Hz, CH_3), 1.73 (3H, s, CH_3), 1.60~1.90 (2H, m, CH_2), 2.94 (1H, d, J=6 Hz, CHCO), 3.66~4.16 (2H, m, CH_2O), 5.10 (1H, quintet, J=6 Hz, CH), 5.26 (2H, s, $ArCH_2OCO$), 7.56 (2H, d, J=8 Hz, aromatic), 8.23 (2H, d, J=8 Hz, aromatic).

8*R**,6*R** Isomer (**5b**): MP 114~116°C; IR ($CHCl_3$) cm^{-1} 1740 (β-lactam C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (3H, d, J=7 Hz, CH_3), 1.40 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.5~2.2 (2H, m, CH_2), 2.95 (1H, d, J=9 Hz, CHCO), 3.8~4.1 (2H, m, CH_2O), 5.06~5.42 (1H, m, CH), 5.28 (2H, s, $ArCH_2OCO$), 7.56 (2H, d, J=8 Hz, aromatic), 8.26 (2H, d, J=8 Hz, aromatic).

(6*R**,7*R**)-7-[(1*R**)-1-Hydroxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**4b**)

A mixture of **5b** (504 mg, 1.28 mmol) and 15% palladium hydroxide on carbon (141 mg) in ethanol (15 ml) and THF (15 ml) was hydrogenated under 1 atm at room temperature for 1 hour. Filtration and evaporation followed by chromatography on silica gel afforded 245 mg (89%) of **4b** as a colorless oil: IR ($CHCl_3$) cm^{-1} 3500 (OH), 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (3H, d, J= 6 Hz, CH_3), 1.40 (3H, s, CH_3), 1.52 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.9~2.3 (2H, m, CH_2O), 2.72 (1H, d, J=9 Hz, C*H*OH), 2.76 (1H, br, HO), 3.7~4.0 (2H, m, CH_2), 4.1~4.4 (1H, m, CH).

(6*R**,7*R**)-7-[(1*R**)-1-Methanesulfonyloxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]-octane (**6b**)

To a mixture of **4b** (110 mg, 0.52 mmol) and triethylamine (108 μl, 0.78 mmol) in CH_2Cl_2 (2 ml) was added with ice-cooling mesyl chloride (48 μl, 0.62 mmol) and the mixture was stirred at 0°C for 10 minutes and at room temperature for 35 minutes. The mixture was then partitioned between EtOAc and 10% phosphoric acid, extracted with EtOAc, washed with 5% $NaHCO_3$ solution and with brine, dried, and concentrated to give **6b** (139 mg, 93%) as a colorless crystal: MP 138~139°C; IR ($CHCl_3$) cm^{-1} 1750 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.47 (3H, d, J=6 Hz, CH_3), 1.55 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.8~2.2 (2H, m, CH_2O), 2.98 (1H, d, J=10 Hz, CH), 3.14 (3H, s, CH_3), 3.7~4.2 (2H, m, CH_2), 5.05 (1H, qd, J=6 and 10 Hz, CH).

(*Z*)-7-Ethylidene-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**7a**)

A mixture of **6b** (102 mg, 0.35 mmol) and $NaHCO_3$ (64 mg, 0.76 mmol) in methanol (5 ml) was heated to reflux for 1.5 hours. The mixture was filtered and concentrated, and the residue was partitioned between EtOAc and water. Extractive work-up followed by crystallization from hexane gave **7a** (68 mg, 96%) as a colorless crystal: MP 138~139°C; IR ($CHCl_3$) cm^{-1} 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.42 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.99 (3H, d, J= 7 Hz, CH_3), 1.7~2.2 (2H, m, CH_2O), 3.6~4.1 (2H, m, CH_2), 5.64 (1H, q, J=7 Hz, CH=C).

(6*R**,7*S**)-7-[(1*S**)-1-Hydroxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**4a**)

4a was prepared from **5a** as described for **4b**; 95% yield, colorless crystal: MP 78~78.5°C; IR ($CHCl_3$) cm^{-1} 3500 (OH), 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (3H, d, J=6 Hz, CH_3), 1.42 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.7~1.9 (2H, m, CH_2O), 2.45 (1H, br, OH), 2.79 (1H, d, J=7 Hz, C*H*OH), 3.7~4.3 (3H, m, CH_2, CH).

(6*R**,7*S**)-7-[(1*S**)-1-Methanesulfonyloxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]-octane (**6a**)

6a was prepared from **4a** as described for **6b**; 97% yield, colorless crystal: MP 137.5~139.5°C; IR ($CHCl_3$) cm^{-1} 1750 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.43 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.58 (3H, d, J=6 Hz, CH_3), 1.72 (3H, s, CH_3), 1.7~1.9 (2H, m, CH_2O), 2.99 (1H, d, J=6 Hz, CH), 3.09 (3H, s, CH_3), 3.7~4.2 (2H, m, CH_2), 5.09 (1H, q, J=6 Hz, CH).

(*Z*)-7-Ethylidene-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**7a**)

7a was also derived from **6a** as described for **6b** in 95% yield.

(4*R**,3*S**)-3-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-(2-hydroxyethyl)-4-methyl-2-azetidinone (**11a**)

A solution of 3.98 g (10.1 mmol) of **5a** and 2.31 g (12.1 mmol) of *p*-toluenesulfonic acid in 60 ml of dioxane and 30 ml of water was heated to 80°C for 3 hours. After cooling to room temperature the mixture was partitioned between 5% $NaHCO_3$ solution and EtOAc. The organic solution was washed with aq $NaHCO_3$ and brine, dried, concentrated, and crystallized from ethanol - diethyl ether to give 2.87 g (80%) of **11a** as a colorless crystalline solid: MP 103.5~104.5°C; IR ($CHCl_3$) cm^{-1} 3400 (NH), 3600~3200 (OH), 1750 (β-lactam C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (3H, s, CH_3), 1.39 (3H, d, J=6 Hz, CH_3), 1.88 (2H, t, J=6 Hz, CH_2), 2.65 (1H, br, OH), 3.06 (1H, d, J=7 Hz, CHCO), 3.76 (2H, br q, J=6 Hz, CH_2O), 5.11 (1H, quintet, J=6 Hz, CHO), 5.25 (2H, s, CH_2OCO), 6.71 (1H, br, NH), 7.55 (2H, d, J=8 Hz, aromatic), 8.21 (2H, d, J=8 Hz, aromatic).

(4*R**,3*S**)-3-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-carboxymethyl-4-methyl-2-azetidinone (**12a**)

To a solution of 11.73 g (33.3 mmol) of **11a** in 200 ml of acetone was added with ice-cooling 18.5 ml of Jones reagent (50 mmol). After stirring at room temperature for 1 hour, the reaction was quenched with 2-propanol and precipitate formed was collected by filtration. The precipitate was thoroughly washed with water and dried to give 7.96 g (65%) of **12a** as a white solid. The acetone filtrate was concentrated and partitioned between $NaHCO_3$ solution and EtOAc. The aqueous layer was separated, washed with EtOAc, and acidified with 2 N HCl. The precipitate was collected by filtration, washed with water to give 1.90 g (16%) of **12a**. Total yield 81%: IR (KBr) cm^{-1} 3350 (NH), 3600~2400 (COOH), 1750 (β-lactam C=O), 1730 (C=O), 1520 (NO_2); ^1H NMR (200 MHz, DMSO-d_6) δ 1.28 (3H, s, CH_3), 1.34 (3H, d, J=6.5 Hz, CH_3), 2.61 (2H, s, CH_2COO), 3.14 (1H, d, J=4.1 Hz, CHCO), 5.03 (1H, qd, J=6.5 and 4.1 Hz, CH), 5.30 (2H, s, CH_2OCO), 7.65 (2H, d, J=8.8 Hz, aromatic), 8.25 (2H, d, J=8.8 Hz, aromatic).

p-Nitrobenzyl (5*R**,6*S**)-6-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate

Yellow foam: IR ($CHCl_3$) cm^{-1} 3450 (NH), 1785 (β-lactam C=O), 1745 (ester C=O), 1680 (amide C=O), 1530 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.46 (3H, d, J=6 Hz, CH_3), 1.50 (3H, s, CH_3), 1.96 (3H, s, CH_3CO), 2.8~3.0 (2H, m, CH_2), 3.2~3.5 (5H, m, CH_2, CHCO), 5.13 (1H, quintet, J=6 Hz, CHO), 5.26 (2H, s, CH_2OCO), 5.34 (2H, ABq, J=14 Hz, CH_2OCO), 6.38 (1H, br t, J=5 Hz, NH), 7.54 (2H, d, J=8 Hz, aromatic), 7.63 (2H, d, J=8 Hz, aromatic), 8.16 (2H, d, J=8 Hz, aromatic), 8.18 (4H, d, J=8 Hz, aromatic).

Sodium (5*R**,6*S**)-6-[(1*S**)-1-Hydroxyethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate (**15a**)

Pale yellow powder: IR (KBr) cm^{-1} 1750 (β-lactam C=O), 1650 (amide C=O), 1600 (carboxylate C=O); ^1H NMR (90 MHz, D_2O, external TMS) δ 1.76 (3H, d, J=6 Hz, CH_3), 1.95 (3H, s, CH_3), 2.46 (3H, s, CH_3CO), 3.3~3.5 and 3.8~4.0 (7H, m, CH_2CH_2, CH_2, CHCO), 4.70 (1H, quintet, J=6 Hz, C*H*OH); UV $\lambda_{max}^{H_2O}$ nm 300.

8*R**,6*R** isomer (**5b**) was converted to the corresponding 5-methylcarbapenem (**15b**) as described above.

(4*R**,3*R**)-3-[(1*R**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-(2-hydroxyethyl)-4-methyl-2-azetidinone (**11b**)

Yield 67%, colorless crystal: MP 84~84.5°C; IR ($CHCl_3$) cm^{-1} 3400 (NH), 3600~3200 (OH), 1750 (β-lactam C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (3H, d, J=6 Hz, CH_3), 1.43 (3H, s, CH_3), 1.6~2.2 (2H, m, CH_2), 2.78 (1H, br, OH), 2.92 (1H, d, J=7 Hz, CHCO), 3.7~3.9 (2H, m, CH_2O), 5.17 (1H, quintet, J=7 Hz, CH), 5.26 (2H, s, CH_2OCO), 6.76 (1H, br, NH), 7.55 (2H, d, J=8 Hz, aromatic), 8.22 (2H, d, J=8 Hz, aromatic).

(4*R**,3*R**)-3-[(1*R**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-carboxymethyl-4-methyl-2-azetidinone (**12b**)

Yield 77%, colorless crystal: MP 74°C (dec); IR ($CHCl_3$) cm^{-1} 3400 (NH), 3300 (OH), 1735 (β-lactam C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.44 (3H, d, J=6 Hz, CH_3), 1.52 (3H, s, CH_3), 2.68 (2H, ABq, J=15 Hz, CH_2COO), 3.04 (1H, d, J=6 Hz, CHCO), 5.0~5.3 (1H, m, CH), 5.24 (2H, ABq, J=14 Hz, CH_2OCO), 7.54 (2H, d, J=8 Hz, aromatic), 7.66 (1H, br, NH), 8.20 (2H, d, J=8 Hz, aromatic), 8.70 (1H, br, COOH).

p-Nitrobenzyl (5*R**,6*R**)-6-[(1*R**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate

Pale yellow foam: IR ($CHCl_3$) cm^{-1} 3450 (NH), 1785 (β-lactam C=O), 1750 (ester C=O), 1675 (amide C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.41 (3H, d, J=6 Hz, CH_3), 1.57 (3H, s, CH_3), 1.96 (3H, s, CH_3CO), 2.8~3.6 (7H, m, SCH_2CH_2N, CH_2, CHCO), 5.0~5.3 (1H, m, CHO), 5.29 (2H, s, CH_2OCO), 5.31 (2H, ABq, J=14 Hz, CH_2OCO), 6.47 (1H, br t, NH), 7.55 (2H, d, J=8 Hz, aro-

matic), 7.64 (2H, d, J=8 Hz, aromatic), 8.20 (4H, d, J=8 Hz, aromatic).

Sodium (5*R**,6*R**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate (**15b**)

White powder: IR (KBr) cm^{-1} 1740 (β-lactam C=O), 1650 (amide C=O), 1595 (carboxylate C=O); ^1H NMR (90 MHz, D_2O, external TMS) δ 1.59 (3H, d, J=7 Hz, CH_3), 1.90 (3H, s, CH_3), 2.44 (3H, s, CH_3CO), 3.3~3.5 (2H, m, CH_2), 3.47 (2H, ABq, J=17 Hz, CH_2), 3.6~4.0 (3H, m, CH_2, CH), 4.08 (1H, dq, J=7 and 10 Hz, C*H*OH); UV $\lambda_{max}^{H_2O}$ nm 300.

(6*R**)-7-Acetyl-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**8**)

To a solution of 11.88 g (55.7 mmol) of isomeric mixture of **4** in 240 ml of acetone was added with ice-cooling 31 ml of Jones reagent (84 mmol). After stirring at room temperature for 50 minutes, the reaction was quenched with 2-propanol and precipitate was removed by filtration. The precipitate was dissolved in dilute HCl and extracted with EtOAc. The acetone filtrate was concentrated and poured into 10% phosphoric acid, and extracted with EtOAc. Both extracts were combined, dried, concentrated, and chromatographed on silica gel to give 7.18 g (61%) of **8** as a mixture of two isomers (*ca.* 1 : 1 ratio); pale yellow oil: IR ($CHCl_3$) cm^{-1} 1755 (β-lactam C=O), 1715 (ketone C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 and 1.43 (3H, two s, CH_3), 1.50 and 1.61 (3H, two s, CH_3), 1.74 (3H, s, CH_3), 2.29 (3H, s, CH_3CO), 1.5~2.1 (2H, m, CH_2O), 3.7~4.2 (3H, m, CH_2, CH).

(6*R**,7*S**)-7-Acetyl-7-(4-toluenesulfenyl)-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**9**)

To a solution of 7.18 g (34.0 mmol) of **8** and 11.80 g (42.4 mmol) of *p*-tolyl *p*-toluenethiosulfonate in 70 ml of DMF was added at room temperature 14.3 ml (103 mmol) of triethylamine. After 2 hours, the mixture was poured into 10% phosphoric acid and extracted with EtOAc. The extract was washed with 5% $NaHCO_3$ solution and with brine, and dried. Concentration and chromatography on silica gel yielded 6.75 g (60%) of **9** as a pale yellow oil: IR ($CHCl_3$) cm^{-1} 1760 (β-lactam C=O), 1700 (ketone C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.44 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.6~1.9 (2H, m, CH_2O), 2.14 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.7~4.2 (3H, m, CH_2, CH), 7.0~7.2 (2H, m, aromatic), 7.4~7.6 (2H, m, aromatic).

(6*R**,7*S**)-7-[(1*S**)-1-Hydroxyethyl]-7-(4-toluenesulfenyl)-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo-[4.2.0]octane (**10**)

To a solution of 6.75 g (20.2 mmol) of **9** in 70 ml of THF and 70 ml of ethanol was added with ice-cooling 923 mg (24.4 mmol) of sodium borohydride. The mixture was stirred in an ice-bath for 0.5 hour and at room temperature for 0.5 hour and quenched with acetone. Most of the solvent was removed *in vacuo*, partitioned between 10% phosphoric acid and EtOAc. The organic layer was washed with 5% $NaHCO_3$ solution and with brine, dried, and concentrated. The residue was crystallized from hexane and CH_2Cl_2 to give 3.03 g (45%) of **10** as a colorless crystalline solid. The mother liquor was concentrated and chromatographed to afford 1.09 g (16%) of the additional product. Total yield was 61%: MP 132~133°C; IR ($CHCl_3$) cm^{-1} 3600~3300 (OH), 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.46 (3H, d, J=7 Hz, CH_3), 1.70 (6H, s, CH_3), 2.22 (1H, br, OH), 2.33 (3H, s, CH_3), 2.8~3.2 (2H, m, CH_2O), 3.7~4.3 (3H, m, CH_2, CH), 7.0~7.2 (2H, m, aromatic), 7.5~7.7 (2H, m, aromatic).

(6*R**,7*R**)-7-[(1*S**)-1-Hydroxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**4c**)

A mixture of **10** (4.12 g, 12.3 mmol), 13.0 ml (49 mmol) of tri-*n*-butyltin hydride, and 0.20 g (1.22 mmol) of azobisisobutyronitrile (AIBN) in 150 ml of acetone was refluxed under argon for 3.3 hours. Concentration and chromatography on silica gel gave quantitatively 2.73 g of **4c** as a colorless oil: IR ($CHCl_3$) cm^{-1} 3600~3300 (OH), 1740 (β-lactam C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (3H, d, J=7 Hz, CH_3), 1.40 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.9~2.6 (2H, m, CH_2O), 1.96 (1H, br, OH), 2.78 (1H, d, J=10 Hz, C*H*OH), 3.7~4.4 (3H, m, CH_2, CH).

(6*R**,7*R**)-7-[(1*S**)-1-Methanesulfonyloxyethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]-octane (**6c**)

6c was prepared from **4c** as described for **6b**; 94% yield, colorless oil: IR ($CHCl_3$) cm^{-1} 1750

(β-lactam C=O); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.42 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.63 (3H, d, J=6 Hz, CH_3), 1.71 (3H, s, CH_3), 2.0~2.4 (2H, m, CH_2O), 3.06 (1H, d, J=10 Hz, CH), 3.02 (3H, s, CH_3), 3.8~4.1 (2H, m, CH_2), 5.18 (1H, dq, J=6 and 10 Hz, CH).

(*E*)-7-Ethylidene-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**7b**)

7b was prepared from **6c** as described for **7a**; 90% yield, colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.45 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.74 (3H, d, J=7 Hz, CH_3), 1.75 (3H, s, CH_3), 1.8~2.2 (2H, m, CH_2O), 3.6~4.1 (2H, m, CH_2), 6.04 (1H, q, J=7 Hz, CH=C).

(6*R**,7*R**)-7-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-2,2,6-trimethyl-8-oxo-3-oxa-1-azabicyclo[4.2.0]octane (**5c**)

To a solution of 1.050 g (4.92 mmol) of **4c** in 25 ml of dry THF was added 3.9 ml (1.5 M in hexane, 5.9 mmol) of *n*-butyllithium at −78°C. To this was added after 10 minutes, a solution of 1.612 g (7.48 mmol) of *p*-nitrobenzyl chloroformate in 4 ml of dry THF, stirred at −78°C for 10 minutes, and warmed to room temperature over 30 minutes. The mixture was poured into water, extracted with EtOAc, and dried. Concentration and chromatography on silica gel gave 1.287 g (67%) of **5c** as a colorless oil: IR ($CHCl_3$) cm^{-1} 1750 (β-lactam C=O), 1520 (NO_2); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.47 (3H, d, J=6 Hz, CH_3), 1.53 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.8~2.2 (2H, m, CH_2), 3.01 (1H, d, J=11 Hz, CHCO), 3.7~4.2 (2H, m, CH_2O), 5.15 (1H, dq, J=6 and 11 Hz, CH), 5.23 (2H, s, CH_2OCO), 7.51 (2H, d, J=8 Hz, aromatic), 8.22 (2H, d, J=8 Hz, aromatic).

8*S**,6*R** isomer (**5c**) was converted to the corresponding 5-methylcarbapenem (**15c**) as described for **15a**.

(4*R**,3*R**)-3-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-(2-hydroxyethyl)-4-methyl-2-azetidinone (**11c**)

Yield 32%, colorless oil: IR ($CHCl_3$) cm^{-1} 3400 (NH), 3600~3200 (OH), 1750 (β-lactam C=O), 1520 (NO_2); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.48 (3H, s, CH_3), 1.49 (3H, d, J=6 Hz, CH_3), 1.7~2.2 (2H, m, CH_2), 1.80 (1H, br, OH), 3.11 (1H, d, J=11 Hz, CHCO), 3.87 (2H, dd, J=5 and 8 Hz, CH_2O), 5.15 (1H, dq, J=6 and 11 Hz, CH), 5.26 (2H, s, CH_2OCO), 6.43 (1H, br, NH), 7.55 (2H, d, J=8 Hz, aromatic), 8.26 (2H, d, J=8 Hz, aromatic).

(4*R**,3*R**)-3-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-carboxymethyl-4-methyl-2-azetidinone (**12c**)

64% Yield, white powder: MP 76°C (dec); IR ($CHCl_3$) cm^{-1} 3400 (NH), 3400~3200 (OH), 1760 (lactam C=O), 1740 (carboxylic acid C=O), 1520 (NO_2); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.50 (3H, d, J=6 Hz, CH_3), 1.53 (3H, s, CH_3), 2.63 (2H, ABq, J=16 Hz, CH_2COO), 3.14 (1H, d, J=11 Hz, CHCO), 4.9~5.2 (1H, m, CH), 5.28 (2H, s, CH_2OCO), 7.27 (2H, br, NH, COOH), 7.56 (2H, d, J=8 Hz, aromatic), 8.26 (2H, d, J=8 Hz, aromatic).

p-Nitrobenzyl (5*R**,6*R**)-6-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate

Pale yellow foam: IR ($CHCl_3$) cm^{-1} 3450 (NH), 1780 (β-lactam C=O), 1750 (ester C=O), 1675 (amide C=O), 1520 (NO_2); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.51 (3H, d, J=6 Hz, CH_3), 1.53 (3H, s, CH_3), 1.95 (3H, s, CH_3CO), 2.8~3.1 and 3.3~3.6 (7H, m, SCH_2CH_2N, CH_2, CHCO), 5.07 (1H, dq, J=6 and 10 Hz, CHO), 5.28 (2H, s, CH_2OCO), 5.37 (2H, ABq, J=14 Hz, CH_2OCO), 6.00 (1H, br t, NH), 7.56 (2H, d, J=8 Hz, aromatic), 7.66 (2H, d, J=8 Hz, aromatic), 8.23 (2H, d, J=8 Hz, aromatic), 8.25 (2H, d, J=8 Hz, aromatic).

Sodium (5*R**,6*R**)-6-[(1*S**)-1-Hydroxyethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate (**15c**)

Pale yellow powder: IR (KBr) cm^{-1} 1750 (β-lactam C=O), 1650 (amide C=O), 1595 (carboxylate C=O); ^{1}H NMR (90 MHz, D_2O, external TMS) δ 1.78 (3H, d, J=6 Hz, CH_3), 1.93 (3H, s, CH_3), 2.44 (3H, s, CH_3CO), 3.3~3.5 and 3.7~4.0 (7H, m, SCH_2CH_2N, CH_2, CHCO), 4.52 (1H, m, C*H*OH); UV $\lambda_{max}^{H_2O}$ nm 300.

(4*R**,3*S**)-3-[(1*S**)-1-(*p*-Nitrobenzyloxycarbonyloxy)ethyl]-4-methoxycarbonylmethyl-4-methyl-2-azetidinone (**16**)

To an ice-cooled solution of excess diazomethane in diethylether was added 5.03 g (13.7 mmol) of **12a** in THF (50 ml) and 50 ml of DMF was then added. After being stirred with ice-cooling for 30 minutes, the mixture was quenched by acetic acid and poured into 10% phosphoric acid and EtOAc. Extractive work-up followed by crystallization from hexane - CH_2Cl_2 gave 4.99 g (96%) of **16** as a colorless crystal: MP 111~112°C; IR ($CHCl_3$) cm^{-1} 3400 (NH), 1760 (lactam C=O), 1740 (ester C=O), 1520 (NO_2); ^1H NMR (90 MHz, $CDCl_3$) δ 1.41 (3H, s, CH_3), 1.46 (3H, d, J=6 Hz, CH_3), 2.67 (2H, s, CH_2COO), 3.07 (1H, d, J=6 Hz, CHCO), 3.69 (3H, s, CH_3OCO), 5.14 (1H, quintet, J=6 Hz, CH), 5.25 (2H, s, CH_2OCO), 6.52 (1H, br, NH), 7.53 (2H, d, J=8 Hz, aromatic), 8.19 (2H, d, J=8 Hz, aromatic).

(4*R**,3*S**)-3-[(1*S**)-1-Hydroxyethyl]-4-methoxycarbonylmethyl-4-methyl-2-azetidinone (**17**)

A mixture of **16** (4.99 g, 13.1 mmol) and 15% palladium hydroxide on carbon (1.14 g) in ethanol (70 ml) and THF (50 ml) was hydrogenated at room temperature under 1 atm for 1 hour. Filtration and evaporation followed by chromatography afforded 2.41 g (91%) of **17** as a colorless crystal: MP 91~92.5°C; IR ($CHCl_3$) cm^{-1} 3400 (NH), 3600~3200 (OH), 1740 (C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, d, J=6 Hz, CH_3), 1.48 (3H, s, CH_3), 2.63 (1H, br, OH), 2.66 (2H, s, CH_2COO), 2.86 (1H, d, J=6 Hz, CHCO), 3.70 (3H, s, CH_3OCO), 4.0~4.2 (1H, m, CH), 6.60 (1H, br, NH).

(4*R**,3*S**)-3-[(1*R**)-1-Formyloxyethyl]-4-methoxycarbonylmethyl-4-methyl-2-azetidinone (**18**)

To an ice-cooled solution of **17** (2.41 g, 12.0 mmol) and triphenylphosphine (3.81 g, 14.5 mmol) in THF (50 ml) were added formic acid (0.68 ml, 18 mmol) and diisopropyl azodicarboxylate (2.8 ml, 14 mmol). After being stirred with ice-cooling for 10 minutes and at room temperature for 3 hours, solid $NaHCO_3$ (0.38 g, 4.5 mmol) was added. Filtration and evaporation followed by chromatography gave **18** (2.78 g, quantitative yield) as a colorless oil: IR ($CHCl_3$) cm^{-1} 3400 (NH), 1765 (β-lactam C=O), 1725 (ester C=O); ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.46 (3H, d, J=6 Hz, CH_3), 2.68 (2H, ABq, J=15 Hz, CH_2COO), 3.12 (1H, d, J=11 Hz, CHCO), 3.70 (3H, s, CH_3OCO), 5.35 (1H, dq, J=6 and 11 Hz, CH), 6.70 (1H, br, NH), 8.00 (1H, s, CHO).

(4*R**,3*S**)-3-[(1*R**)-1-Hydroxyethyl]-4-carboxymethyl-4-methyl-2-azetidinone (**19**)

To an ice-cooled solution of **18** (381 mg, 1.66 mmol) in methanol (8 ml) and water (2 ml) was added dropwise 2.4 N NaOH aqueous solution (1.52 ml, 3.65 mmol). After being stirred at 0°C for 45 minutes and at room temperature for 3 hours, the mixture was concentrated *in vacuo* and partitioned between water and diethyl ether. The organic layer was removed and the aqueous layer was acidified with 2 N HCl. After saturation with NaCl, the aqueous layer was extracted with methyl ethyl ketone, dried, and concentrated to give **19** as a colorless solid (205 mg, 66%): IR (KBr) cm^{-1} 3600~2400 (OH), 1720 (C=O); ^1H NMR (90 MHz, CD_3OD) δ 1.33 (3H, d, J=6 Hz, CH_3), 1.51 (3H, s, CH_3), 2.72 (2H, s, CH_2COO), 2.93 (1H, d, J=11 Hz, CHCO), 4.09 (1H, dq, J=6 and 11 Hz, CH).

8*R**,6*S** isomer (**19**) was converted to the corresponding 5-methylcarbapenem (**15d**) as described above.

p-Nitrobenzyl (5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate

Pale yellow solid: MP 189~191°C; IR (KBr) cm^{-1} 1770 (β-lactam C=O), 1690 (ester C=O), 1650 (amide C=O), 1510 (NO_2); ^1H NMR (90 MHz, DMSO-d_6) δ 1.20 (3H, d, J=6 Hz, CH_3), 1.47 (3H, s, CH_3), 1.80 (3H, s, CH_3CO), 2.8~3.4 (7H, m, SCH_2CH_2N, CH_2, CHCO), 3.8~4.3 (1H, m, CH), 4.91 (1H, d, J=6 Hz, OH), 5.36 (2H, ABq, J=13 Hz, CH_2OCO), 7.72 (2H, d, J=8 Hz, aromatic), 8.15 (1H, br, NH), 8.24 (2H, d, J=8 Hz, aromatic).

Sodium (5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(2-acetamidoethylthio)carbapen-2-em-3-carboxylate (**15d**)

White solid: IR (KBr) cm^{-1} 1740 (β-lactam C=O), 1650 (amide C=O), 1590 (carboxylate C=O); ^1H NMR (90 MHz, D_2O, external TMS) δ 1.79 (3H, d, J=6 Hz, CH_3), 2.00 (3H, s, CH_3), 2.46 (3H,

s, CH_3CO), 3.2~4.0 (7H, m, CH_2, SCH_2CH_2N, CH), 4.71 (1H, dq, J=6 and 10 Hz, C*H*OH); UV $\lambda_{max}^{H_2O}$ nm 300.

Determination of Hydrolysis Rate Constants

Hydrolysis rate constants of chiral *N*-acetylthienamycin and **15d** were determined according to the literature method[12] with 10^{-4} M of substrate in $NaHCO_3$ - Na_2CO_3 - NaCl buffer solution (0.1 M, μ=0.5, pH 9.24) at 35.0±0.1°C. UV-absorption at 300 or 320 nm was observed and no new band appeared around here.

p-Nitrobenzyl ((5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-[2-(*p*-nitrobenzyloxycarbonylamino)ethylthio]carbapen-2-em-3-carboxylate (**21**)

21 was prepared as described above; pale yellow foam: IR ($CHCl_3$) cm^{-1} 3450 (NH), 1780 (β-lactam C=O), 1730 (ester C=O), 1520 (NO_2); ^1H NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, J=6.2 Hz, CH_3), 1.60 (3H, s, CH_3), 2.91~3.30 (5H, m, CH_2, CHCO), 3.43 (2H, q, J=6.5 Hz, CH_2N), 4.28 (1H, qd, J=6.4 and 9.6 Hz, CH), 5.20 (2H, s, CH_2OCO), 5.38 (2H, ABq, J=13.8 Hz, CH_2OCO), 7.50 (2H, d, J=8.6 Hz, aromatic), 7.66 (2H, d, J=8.9 Hz, aromatic), 8.22 (4H, d, J=8.2 Hz, aromatic).

(5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(2-aminoethylthio)carbapen-2-em-3-carboxylic acid (**22**)

Colorless solid: IR (KBr) cm^{-1} 1750 (β-lactam C=O), 1580 (carboxylate C=O); ^1H NMR (200 MHz, D_2O, DSS) δ 1.23 (3H, d, J=6.3 Hz, CH_3), 1.53 (3H, s, CH_3), 3.09 (2H, ABq, J=17.4 Hz, CH_2CO), 3.05~3.27 (4H, m, SCH_2CH_2N), 3.32 (1H, d, J=9.7 Hz, CHCO), 4.28 (1H, dq, J=6.3 and 9.7 Hz, C*H*OH); UV $\lambda_{max}^{H_2O}$ nm 298.

p-Methoxybenzyl (5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(4-pyridylthio)carbapen-2-em-3-carboxylate (**23**)

23 was prepared as described above; pale yellow foam: IR ($CHCl_3$) cm^{-1} 3300 (OH), 1775 (β-lactam C=O), 1710 (ester C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (3H, d, J=6.1 Hz, CH_3), 1.52 (3H, s, CH_3), 2.68 (2H, ABq, J=18.0 Hz, CH_2), 3.07 (1H, d, J=10.0 Hz, CHCO), 3.80 (3H, s, CH_3O), 4.22 (1H, dq, J=6.1 and 10.0 Hz, C*H*OH), 5.27 (2H, ABq, J=12.2 Hz, CH_2OCO), 6.85~6.93 (2H, m, aromatic), 7.35~7.44 (4H, m, aromatic), 8.57~8.62 (2H, m, aromatic).

Sodium (5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(4-pyridylthio)carbapen-2-em-3-carboxylate (**24**)

24 was prepared according to the literature method[10]; pale yellow solid: IR (KBr) cm^{-1} 1750 (β-lactam C=O), 1600 (carboxylate C=O); ^1H NMR (200 MHz, D_2O, DSS) δ 1.31 (3H, d, J=6.4 Hz, CH_3), 1.53 (3H, s, CH_3), 2.82 (2H, ABq, J=17.6 Hz, CH_2), 3.32 (1H, d, J=9.7 Hz, CHCO), 4.27 (1H, (dq, J=6.4 and 9.7 Hz, C*H*OH), 7.45~7.49 (2H, m, aromatic), 8.42~8.47 (2H, m, aromatic).

(5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(1-methyl-4-pyridiniothio)carbapen-2-em-3-carboxylate (**25**)

To a solution of **23** (294 mg, 0.67 mmol) in CH_2Cl_2 (10 ml) was added methyl trifluoromethanesulfonate (CH_3OTf) (0.083 ml, 0.73 mmol) at −40°C. After being stirred for 10 minutes the mixture was slowly warmed to room temperature over 30 minutes and evaporated to give a pale yellow foam (416 mg). This pyridinium salt was deprotected as for **24** to give **25** (14% yield) as a yellow solid: IR (KBr) cm^{-1} 1760 (β-lactam C=O), 1620 (carboxylate C=O); ^1H NMR (200 MHz, D_2O, DSS) δ 1.34 (3H, d, J=6.3 Hz, CH_3), 1.64 (3H, s, CH_3), 3.03 (2H, ABq, J=17.6 Hz, CH_2), 3.49 (1H, d, J=9.6 Hz, CHCO), 4.23 (3H, s, CH_3N), 4.32 (1H, dq, J=6.3 and 9.6 Hz, C*H*OH), 7.73~7.78 (2H, m, aromatic), 8.44~8.49 (2H, m, aromatic).

p-Methoxybenzyl (5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(4-pyridylmethylthio)carbapen-2-em-3-carboxylate (**26**)

26 was prepared as described above; pale yellow foam: IR ($CHCl_3$) cm^{-1} 1775 (β-lactam C=O), 1700 (ester C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (3H, d, J=6.2 Hz, CH_3), 1.45 (3H, s, CH_3), 1.77 (1H, br, OH), 2.90 (2H, ABq, J=17.4 Hz, CH_2), 3.03 (1H, d, J=10.2 Hz, CHCO), 3.80 (3H, s, CH_3O),

4.00 (2H, ABq, J=14.3 Hz, CH_2S), 4.22 (1H, dq, J=6.2 and 10.2 Hz, C*H*OH), 5.24 (2H, ABq, J=12.3 Hz, CH_2OCO), 6.85~6.91 (2H, m, aromatic), 7.26~7.34 (2H, m, aromatic), 7.37~7.43 (2H, m, aromatic), 8.53~8.66 (2H, m, aromatic).

(5*R**,6*S**)-6-[(1*R**)-1-Hydroxyethyl]-5-methyl-2-(1-methyl-4-pyridiniomethylthio)carbapen-2-em-3-carboxylate (**27**)

To a solution of **26** (208 mg, 0.46 mmol) in acetone (15 ml) was added iodomethane (1.5 ml) and the mixture was allowed to stand at room temperature overnight. After concentration, the residue was triturated with diethyl ether to give a yellow solid (257 mg). This pyridinium salt was deprotected as for **24** to give **27** as a pale yellow solid, 12% yield: IR (KBr) cm^{-1} 1750 (β-lactam C=O), 1600 (carboxylate C=O); ^1H NMR (200 MHz, D_2O, DSS) δ 1.29 (3H, d, J=6.3 Hz, CH_3), 1.35 (3H, s, CH_3), 2.92 (2H, ABq, J=17.3 Hz, CH_2), 3.23 (2H, d, J=9.8 Hz, CHCO), 4.23 (1H, dq, J=6.3 and 9.8 Hz, C*H*OH), 4.32 (2H, ABq, J=16.4 Hz, CH_2S), 4.34 (3H, s, CH_3N), 8.04~8.08 (2H, m, aromatic), 8.68~8.72 (2H, m, aromatic).

Acknowledgment

The authors thank Dr. Y. KOMATSU, Dr. T. YOSHIDA, and their associates for the antibacterial assays, Dr. M. SHIRO for X-ray crystallographic analysis, Dr. Y. TERUI for NMR measurement, and Dr. M. TAKASUKA for IR measurement.

References

1) KROPP, H.; J. G. SUNDELOF, R. HAJDU & F. M. KAHAN: Metabolism of thienamycin and related carbapenem antibiotics by the renal dipeptidase, dehydropeptidase-I. Antimicrob. Agents Chemother. 22: 62~70, 1982
2) NAGATA, W.; M. NARISADA & T. YOSHIDA: Partial synthesis of nuclear analogs of cephalosporins. *In* Chemistry and Biology of β-Lactam Antibiotics. Vol 2. Nontraditional β-Lactam Antibiotics. *Eds.*, R. B. MORIN & M. GORMAN, pp. 1~98, Academic Press, New York, 1982
3) SHIH, D. H.; F. BAKER, L. CAMA & B. G. CHRISTENSEN: Synthetic carbapenem antibiotics I. 1-β-Methylcarbapenem. Heterocycles 21: 29~40, 1984
4) SUNAGAWA, M.; H. MATSUMURA, T. INOUE, M. FUKASAWA & M. KATO: SM-7338, a new carbapenem antibiotics: Structure-activity relations and physicochemical properties. Program and Abstracts of the 27th Intersci. Conf. on Antimicrob. Agents Chemother., No. 752, p. 228, New York, Oct. 4~7, 1987
5) WATANABE, A.; Y. FUKAGAWA, T. ISHIKURA & T. YOSHIOKA: Total synthesis of 6-hydroxy-*epi*-PS 5 and 6-methoxy-*epi*-PS 5. Bull. Chem. Soc. Jpn. 60: 2091~2099, 1987
6) SATOH, H. & T. TSUJI: Synthesis of racemic carbapenems with a 6β-methyl group. Heterocycles 27: 2803~2806, 1988
7) PONSFORD, R. J.; P. M. ROBERTS & R. SOUTHGATE: Intramolecular Wittig reactions with thioesters: The synthesis of 7-oxo-3-phenylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates. J. Chem. Soc. Chem. Commun. 1979: 847~848, 1979
8) BOUFFARD, F. A.; D. B. R. JOHNSTON & B. G. CHRISTENSEN: Thienamycin total synthesis. 1. Synthesis of azeditinone precursors of (±)-thienamycin and its stereoisomers. J. Org. Chem. 45: 1130~1135, 1980
9) BATESON, J. H.; A. M. QUIN & R. SOUTHGATE: Sulphenylation and halogenation reactions leading selectively to cis-carbapenem precursors; Stereospecific synthesis of (±)-6-epithienamycin. J. Chem. Soc. Chem. Commun. 1986: 1151~1152, 1986
10) OHTANI, M.; F. WATANABE & M. NARISADA: Mild deprotection of carbapenem esters with aluminum trichloride. J. Org. Chem. 49: 5271~5272, 1984
11) LEANZA, W. J.; K. J. WILDONGER, J. HANNAH, D. H. SHIH, R. W. RATCLIFFE, L. BARASH, E. WALTON, R. A. FIRESTONE, G. F. PATEL, F. M. KAHAN, J. S. KAHAN & B. G. CHRISTENSEN: Structure-activity relationships in the thienamycin series. *In* Recent Advances in the Chemistry of β-Lactam Antibiotics. *Ed.*, G. I. GREGORY, pp. 240~254, The Royal Society of Chemistry, London, 1981
12) NARISADA, M.; T. YOSHIDA, M. OHTANI, K. EZUMI & M. TAKASUKA: Synthesis and substituent effects on antibacterial activity, alkaline hydrolysis rates, and infrared absorption frequencies of some cephem analogues related to latamoxef (moxalactam). J. Med. Chem. 26: 1577~1582, 1983