SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NEW 2-SUBSTITUTED PENEMS. II

TOSHIYUKI NISHI, KUNIO HIGASHI, TSUNEHIKO SOGA, MAKOTO TAKEMURA and MAKOTO SATO

Exploratory Research Laboratories I, Daiichi Pharmaceutical Co., Ltd., 1-16-13 Kitakasai, Edogawa-ku, Tokyo 134, Japan

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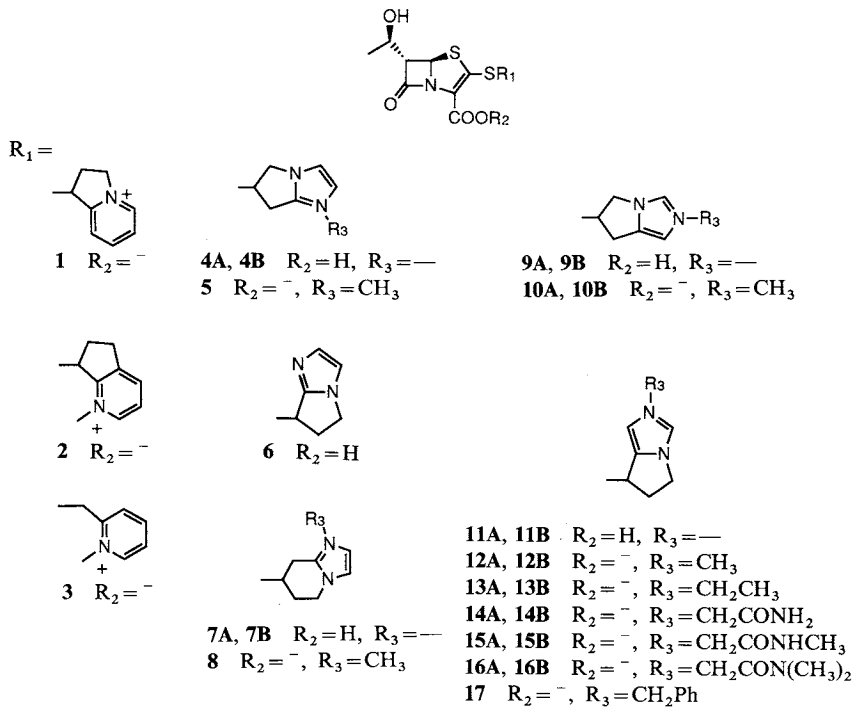
A series of new penems (**4**~**17**), having a bicyclic imidazole moiety as the C-2 substituent, has been synthesized. The antimicrobial activity of these compounds and their susceptibility to renal dehydropeptidase-I (DHP-1) are elucidated, and their structure-activity relationships are discussed.

We have reported that a new series of penem compounds (**1**, **2**) bearing a bicyclic pyridinium group showed fairly good resistance to hydrolysis by DHP-1, potent antimicrobial activities and a broad spectrum of activity[1]. It was also noteworthy that these compounds (**1**, **2**) revealed markedly superior antimicrobial activity againt Gram-negative bacteria, especially against *Pseudomonas aeruginosa*, to that of the pyridinium methyl thio derivative (**3**). These findings prompted us to investigate other penems with a heterobicyclic substituent. In the course of our studies, we found that a new series of penem derivatives (**4**~**17**) with bicyclic imidazole moiety at the C-2 position has better antimicrobial activities, with a broader spectrum than compounds **1**~**3**. The effect on antimicrobial activity of the introduction of a new bicyclic

Chart 1.

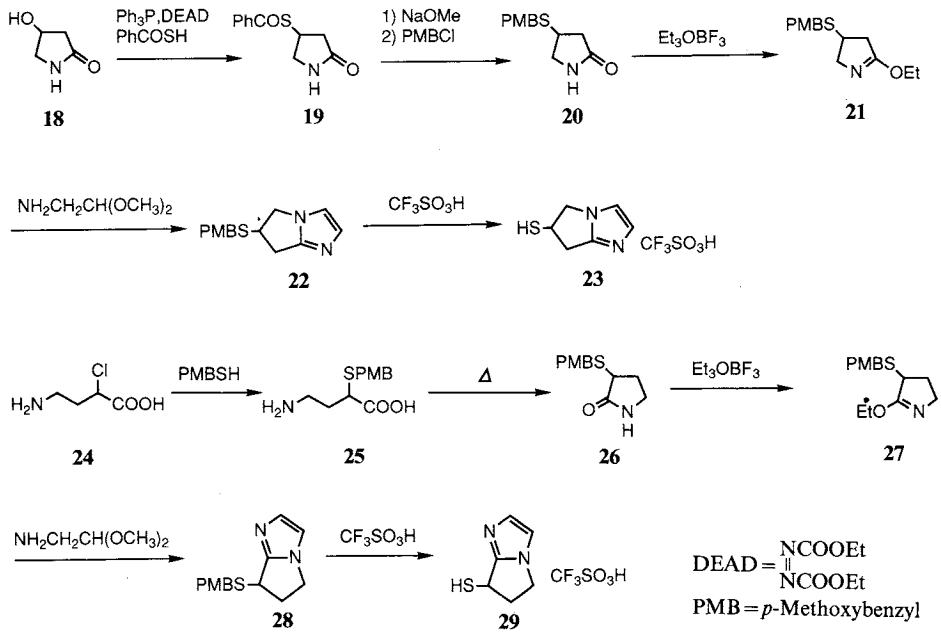


ring system, and structure-activity relationships between the unquaternary bicyclic derivatives (**4**, **6**, **7**, **9** and **11**) and the alkylated quaternary bicyclic derivatives (**5**, **8**, **10** and **12**~**17**) were investigated. The present paper deals with the synthesis and antimicrobial activity of new penem derivatives with a bicyclic imidazole substituent.

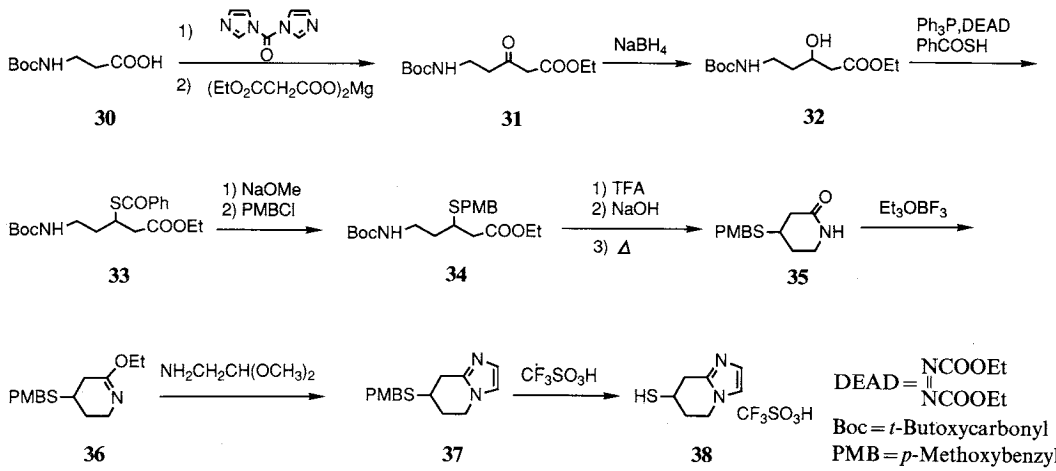
Chemistry

Bicyclic imidazoles **23**, **29** and **38**, which are cyclized between the 1- and 2-positions of imidazole, were prepared by imidazole ring closure of the corresponding cyclic imino ethers (**21**, **27** and **36**) having a the *p*-methoxybenzylthio group as a key intermediate, respectively, as shown in schemes 1 and 2. MITSUNOBU reaction[2] of alcohol **18**[3] with thiobenzoic acid gave **19**. The protective group of thiol de-

Scheme 1.



Scheme 2.



rivative **19** was converted into the *p*-methoxybenzyl group and then the lactam (**20**) was treated with triethyloxonium fluoroborate (Meerwein reagent) to give imino ether **21**, which was further converted into bicyclic imidazole **22** by treatment with aminoacetaldehyde dimethylacetal, followed by heating of resultant reaction product in the presence of *p*-toluenesulfonic acid. Deprotection of thioether **22** with trifluoromethanesulfonic acid[4] gave thiol **23**.

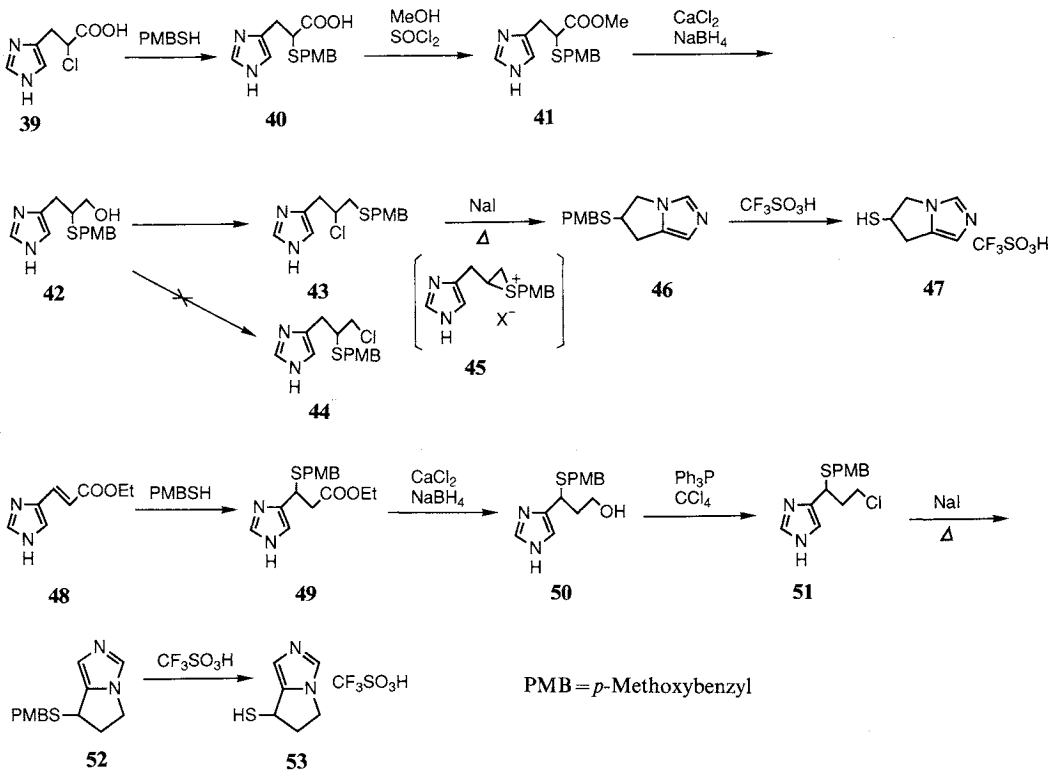
As for the preparation of the thiol (**29**), replacement of the chloro group of amino acid **24**[5] with *p*-methoxybenzylmercaptan using NaOH as a base gave **25** in good yield, and subsequent cyclization with heating gave lactam **26**. The lactam (**26**) was converted into bicyclic thiol **29** in a manner similar to that described above.

In the case of the preparation of the thiol (**38**), chain extension of Boc-*β*-alanine (**30**) was performed using MASAMUNE reaction[6] to give **31**, which was then converted into the bicyclic thiol (**38**), *via* the key intermediate (**34**) as shown in scheme 2.

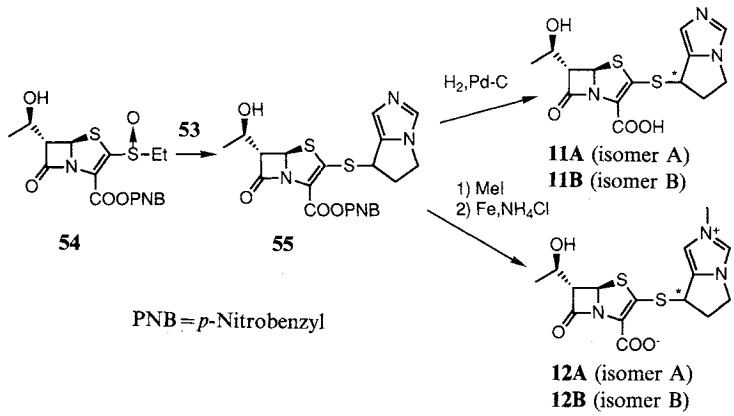
Bicyclic imidazoles **47** and **53**, which are cyclized between the 1- and 5-positions of imidazole, were derived from imidazole derivatives **39** and **48** as starting materials, respectively, as shown in Scheme 3. Chlorination[7] of **42** gave rearranged compound (**43**), instead of expected compound (**44**). However, treatment of **43** with sodium iodide under heating gave the target compound (**46**). The formation of **46** may well be accounted for by the ring closure of the sulfonium intermediate (**45**). Thioether **46** was deprotected with trifluoromethanesulfonic acid to give the thiol (**47**).

Michael addition of **48** with *p*-methoxybenzylmercaptan using tetramethylguanidine as a base gave **49**, which was converted into bicyclic thiol **53** in a manner similar to that described above.

Scheme 3.



Scheme 4.



Sulfoxide **54**[8] was used as a key intermediate[1] for the synthesis of new penems. The general synthetic pathway is shown in Scheme 4. Sulfoxide **54** was treated with thiol **53** in the presence of *N,N*-diisopropylethylamine to give the protected penem (**55**). Catalytic hydrogenation of **55** over Pd-C gave **11A** and **11B** after purification by HPLC. Compound **55** was quaternized with methyl iodide, followed by deprotection using Fe and NH_4Cl[9] to give compounds **12A** and **12B** after purification by HPLC. Compounds **13**~**17** were prepared in a similar manner by use of corresponding alkyl halides, respectively. Regioisomers **4**~**10** were derived similarly from thiols **23**, **29**, **38** and **47**, respectively. Since the absolute configurations of **11A** and **11B**, or **12A** and **12B** have not been confirmed, we define the epimer of each new penem derivative which has the shorter retention time in HPLC as isomer A, and the other as isomer B for convenience. However, compounds **5**, **6**, **8** and **17** could not be separated by HPLC under several conditions.

Biological Properties and Discussion

The minimum inhibitory concentrations (MICs) of the newly prepared penems are shown in Tables 1, 2 and 3. All of the compounds tested were highly active against Gram-positive bacteria.

The effects on the antimicrobial activity in the bicyclic ring system were investigated. As expected, these zwitterionic bicyclic compounds showed potent and broad antimicrobial activity, including activity against Gram-negative bacteria, although their MICs for *Pseudomonas aeruginosa* ranged from 25 to $>100\,\mu g/ml$ (see Table 1). As for ring systems adjacent to the sulfur atom of the C-2 substituent, a five-membered ring system was better than a six-membered one for activity against Gram-negative bacteria: **4A** and **4B** were roughly twice as active as **7A** and **7B**, but all four compounds had similarly high activity against Gram-positive bacteria. In the case of the five-membered bicyclic derivatives, the antimicrobial activities were almost equal; however, compound **6** was at least 4 to 8 times less active than the other five-membered bicyclic compounds against *Pseudomonas aeruginosa*, and compound **11A** had twice to 4 times the activity of compound **11B** against Gram-negative bacteria. These facts indicated that bicyclic ring system and difference in the absolute configuration affect the activity. However, no significant difference was observed between isomer A and isomer B in compounds **4**, **7** or **9**. Some bicyclic imidazole derivatives were found to be more active than indolizine derivative **1** reported previously[1], except against *Pseudomonas aeruginosa* (see Table 1).

We reported previously[1] that quaternary penem derivatives with a bicyclic pyridinium moiety showed

Table 1. Antimicrobial activity (MIC μg/ml) of penems.

Organisms	4A	4B	9A	9B	6
Escherichia coli NIHJ	0.10	0.10	<0.10	0.10	0.10
Citrobacter freundii IID 976	0.20	0.10	0.10	0.10	0.20
Proteus vulgaris 08601	0.20	0.10	0.20	0.20	0.20
P. mirabilis IFO 3849	0.10	0.10	0.10	0.10	0.10
Klebsiella pneumoniae Type 1	0.20	0.10	0.10	0.20	0.20
Enterobacter cloacae 12005	0.39	0.20	0.39	0.39	1.56
Serratia marcescens 10100	0.78	0.20	0.39	0.78	0.78
Pseudomonas aeruginosa 32233	25	25	50	25	>100
Staphylococcus aureus 209P	<0.10	<0.10	<0.10	<0.10	0.10
S. epidermidis 56500	<0.10	<0.10	<0.10	<0.10	0.20
Streptococcus pyogenes G-36	<0.10	<0.10	<0.10	<0.10	<0.10
S. faecalis ATCC 19433	1.56	3.13	6.25	3.13	6.25

Organisms	11A	11B	7A	7B	1
Escherichia coli NIHJ	<0.10	0.39	0.20	0.20	0.20
Citrobacter freundii IID 976	<0.10	0.39	0.20	0.20	0.10
Proteus vulgaris 08601	0.20	0.39	0.20	0.20	0.20
P. mirabilis IFO 3849	<0.10	0.39	0.10	0.20	0.20
Klebsiella pneumoniae Type 1	0.39	0.39	0.10	0.20	0.10
Enterobacter cloacae 12005	0.39	0.78	0.39	0.78	0.39
Serratia marcescens 10100	0.39	0.78	0.78	0.39	0.39
Pseudomonas aeruginosa 32233	25	50	50	50	3.13
Staphylococcus aureus 209P	<0.10	<0.10	<0.10	<0.10	<0.10
S. epidermidis 56500	<0.10	<0.10	<0.10	<0.10	<0.10
Streptococcus pyogenes G-36	<0.10	<0.10	<0.10	<0.10	<0.10
S. faecalis ATCC 19433	1.56	3.13	3.13	3.13	3.13

Table 2. Antimicrobial activity (MIC μg/ml) of penems.

Organisms	5	10A	10B	12A	12B	8
Escherichia coli NIHJ	0.20	0.20	0.78	0.10	1.56	0.78
Citrobacter freundii IID 976	0.10	0.10	0.39	0.10	0.78	0.78
Proteus vulgaris 08601	0.20	0.39	0.78	0.20	1.56	3.13
P. mirabilis IFO 3849	0.20	0.20	0.39	0.10	1.56	1.56
Klebsiella pneumoniae Type 1	0.20	0.20	0.39	0.20	0.78	0.78
Enterobacter cloacae 12005	0.78	0.39	1.56	0.20	1.56	3.13
Serratia marcescens 10100	0.78	0.78	1.56	0.39	3.13	0.78
Pseudomonas aeruginosa 32233	6.25	3.13	1.56	0.78	6.25	12.5
Staphylococcus aureus 209P	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
S. epidermidis 56500	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
Streptococcus pyogenes G-36	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
S. faecalis ATCC 19433	3.13	1.56	1.56	0.78	3.13	1.56

high activity against *Pseudomonas aeruginosa*. In order to obtain improved anti-pseudomonal activity, we examined the bicyclic imidazolium compounds. As expected, these quaternary compounds showed markedly enhanced anti-pseudomonal activity, *i.e.* quaternary compounds **5**, **8**, **10A**, **10B**, **12A** and **12B**, all of which have a methyl group, exhibited activity against *Pseudomonas aeruginosa* 4 to 32 times higher than that of the corresponding unquaternary compounds (**4**, **7**, **9A**, **9B**, **11A** and **11B**), although their antimicrobial activities against other organisms were very similar to those of the latter compounds (see Tables 1 and 2). Compound **12A** was 4 to 16 times as active as **12B** against Gram-negative bacteria,

Table 3. Antimicrobial activity (MIC μg/ml) and DHP-1 stability of penems.

Organisms	12A	12B	13A	13B	14A	14B
Escherichia coli NIHJ	0.10	1.56	0.10	0.39	0.10	0.78
Citrobacter freundii IID 976	0.10	0.78	0.10	0.78	0.10	0.78
Proteus vulgaris 08601	0.20	1.56	0.20	0.78	0.20	1.56
P. mirabilis IFO 3849	0.10	1.56	0.10	0.78	0.10	1.56
Klebsiella pneumoniae Type 1	0.20	0.78	<0.10	0.78	0.10	0.78
Enterobacter cloacae 12005	0.20	1.56	0.20	3.13	0.20	3.13
Serratia marcescens 10100	0.39	3.13	0.20	1.56	0.20	3.13
Pseudomonas aeruginosa 32233	0.78	6.25	0.78	12.5	0.39	25
Staphylococcus aureus 209P	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
S. epidermidis 56500	<0.10	<0.10	<0.10	0.10	<0.10	0.10
Streptococcus pyogenes G-36	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
S. faecalis ATCC 19433	0.78	3.13	0.78	3.13	1.56	3.13
DHP-1 susceptibility[a]	<2		3.3		4.7	

Organisms	15A	15B	16A	16B	17	Imipenem
Escherichia coli NIHJ	0.10	3.13	0.10	0.78	0.20	0.20
Citrobacter freundii IID 976	0.20	1.56	0.20	0.78	0.20	0.10
Proteus vulgaris 08601	0.39	3.13	0.39	1.56	0.39	0.39
P. mirabilis IFO 3849	<0.10	0.78	0.10	0.78	0.39	0.10
Klebsiella pneumoniae Type 1	0.10	0.78	0.39	0.78	0.39	0.10
Enterobacter cloacae 12005	0.20	3.13	0.78	3.13	3.13	0.78
Serratia marcescens 10100	0.20	3.13	0.39	3.13	0.78	0.78
Pseudomonas aeruginosa 32233	0.39	25	0.78	12.5	50	1.56
Staphylococcus aureus 209P	<0.10	<0.10	<0.10	0.10	<0.10	<0.10
S. epidermidis 56500	<0.10	0.20	0.10	0.20	<0.10	0.10
Streptococcus pyogenes G-36	<0.10	<0.10	<0.10	<0.10	<0.10	<0.10
S. faecalis ATCC 19433	1.56	6.25	3.13	6.25	0.78	0.78
DHP-1 susceptibility[a]	6.2					100

[a] DHP-1 susceptibility is given relative to imipenem = 100.

indicating that the MICs of these compounds were influenced by a difference in the absolute configuration of the C-2 substituent, as in the case of **11A** and **11B**.

Since **12A** was the most active penem derivative of these compounds, including anti-pseudomonal activity, the influence of other groups substituted for the methyl group on quaternary compound **12** was investigated (see Table 3). The effect on the activity of the difference of the absolute configuration was similar in quaternary compounds tested. Introduction of a benzyl group as a lipophilic substituent did not improve the activity against *Pseudomonas aeruginosa*, although introduction of a hydrophilic substituent such as a carbamoylmethyl or *N*-methylcarbamoylmethyl group enhanced the activity against *Pseudomonas aeruginosa*, *i.e.* both compounds **14A** and **15A** were twice as active as methyl derivative **12A** against *Pseudomonas aeruginosa*. Compound **16A**, which has an *N*,*N*-dimethylcarbamoylmethyl group was, however, less active than compounds **14A** and **15A** against *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens* and *Pseudomonas aeruginosa*. Further, we compared the susceptibility to DHP-1 and the antimicrobial activity of these quaternary compounds with those of imipenem having clinically potent antimicrobial activity (see Table 3). The compounds (**12A**, **13A**, **14A** and **15A**), which were more active than the corresponding isomer B, were 16 to over 50 times more resistant than imipenem[10~12] to hydrolysis by DHP-1 of swine, and were more active than imipenem against Gram-negative bacteria, including *Pseudomonas aeruginosa*.

In conclusion, five-membered pyrrolo imidazol derivatives showed good activity against both Gram-positive and Gram-negative bacteria. The quaternized compounds possessed especially potent activity against *Pseudomonas aeruginosa*, and had good resistance to hydrolysis by DHP-1.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were obtained using Hitachi Models 260-30 and 270-30. ^{1}H NMR spectra were obtained on a Hitachi R-40 (90 MHz) or a JEOL FX-90Q (90 MHz) spectrometer, in the designated solvent, using tetramethylsilane or residual HOD (δ 4.80) as an internal reference. UV spectra were measured on a Hitachi 323 spectrometer. HPLC purification was performed using Sensyu-Pack Nucleosil 7C18 (Sensyu Kagaku Co., Ltd.).

Measurement of *In Vitro* Antibacterial Activity

Minimal inhibitory concentrations (MICs) were measured according to the 2-fold broth dilution method using Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.). The inoculum size was about 10^5 cfu/ml. The MIC was defined as the lowest concentration that prevented visual growth of bacteria after incubation at 37°C for 18 hours.

Test of Stability of Penem Compounds against Hydrolysis by DHP-1

The rate of hydrolysis of each derivative by swine DHP-1 was determined using the method described in the preceding paper[13]. Resistance of compounds to hydrolysis by the enzyme was represented in terms of the hydrolysis rate relative to that of the control compound, imipenem, represented as 100. The sample of DHP-1 used here was the same as that used in the preceding report.

4-Benzoylthio-2-pyrrolidone (**19**)

A solution of *N*,*N*-diethylazodicarboxylate (6.97 g, 40 mol) in THF (3 ml) was added to Ph_3P (10.5 g, 40 mmol) in THF (50 ml) and the mixture was stirred at 0~5°C for 30 minutes. To the reaction mixture was added a solution of **18** (2.02 g, 20 mmol) and thiobenzoic acid (5.53 g, 25 mmol) in THF (80 ml) at 0~5°C under argon. Then the mixture was stirred at room temperature for 1.5 hours under argon and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with aq NaCl, aq $NaHCO_3$ and aq NaCl and dried over Na_2SO_4. After evaporation of the solvent the residue was chromatographed on silica gel, eluting with benzene-EtOAc (1:9) to give **19** (3.47 g, 78%) as a yellow powder. MP 110~112°C; IR (KBr) 1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (1H, dd, J=6 and 18 Hz), 2.93 (1H, dd, J=9 and 18 Hz), 3.43 (1H, dd, J=5 and 10 Hz), 3.99 (1H, dd, J=8 and 10 Hz), 4.4 (1H, m), 6.8 (1H, br s), 7.4~8.0 (5H, m).

4-(*p*-Methoxybenzylthio)-2-pyrrolidone (**20**)

Sodium metal (0.37 g, 16 mmol) was dissolved in MeOH (30 ml) with ice cooling, then cooled to −10°C. A solution of **19** (3.43 g, 15.5 mmol) in MeOH (30 ml) was then added, and the mixture was stirred for 1 hour at that temperature under argon. After *p*-methoxybenzylchloride (2.51 g, 16 mmol) was added to this reaction mixture at the same temperature, the mixture was stirred for 1.5 hours at room temperature, and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with water, aq $NaHCO_3$ and aq NaCl and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel, eluting with benzene-EtOAc (1:1) to give **20** (2.69 g, 73%) as colorless crystals. MP 95~96°C; IR (KBr) 3240, 1670, 1610, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.16 (1H, dd, J=8 and 18 Hz), 3.2~3.6 (3H, m), 3.73 (2H, s), 3.80 (3H, s), 6.10 (1H, br s), 6.85 (2H, d, J=9 Hz), 7.27 (2H, d, J=9 Hz).

2-Ethoxy-4-(*p*-methoxybenzylthio)-1-pyrroline (**21**)

A solution of **20** (2.37 g, 10 mmol) and triethyloxonium fluorobolate, prepared from boron trifluoride etherate (6.63 g, 47 mmol) and epichlorohydrin (3.23 g, 35 mmol), in CH_2Cl_2 (30 ml) was stirred for 1 hour

at room temperature. A solution of $NaHCO_3$ (4 g) in water (20 ml) was added, and the reaction mixture was cooled with ice. The separated organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with benzene-EtOAc (1:1) to give **21** (1.97 g, 74%) as a pale brown oil. ^1H NMR ($CDCl_3$) δ 1.28 (3H, t, J=7 Hz), 2.6 (2H, m), 3.4~3.9 (5H, m), 3.77 (3H, s), 4.17 (2H, q, J=7 Hz), 6.82 (2H, d, J=9 Hz), 7.21 (2H, d, J=9 Hz).

6,7-Dihydro-6-*p*-methoxybenzylthio-5*H*-pyrrolo[1,2-*a*]imidazole (**22**)

A mixture of **21** (2.0 g, 7.5 mmol) and aminoacetaldehyde dimethylacetal (1.2 g, 11.3 mmol) in MeOH (100 ml) was refluxed with heating for 1 hour after the addition of acetic acid (0.68 g, 11.3 mmol). The mixture was concentrated under reduced pressure and the residue was dissolved in benzene (100 ml). To a solution of the mixture was added *p*-toluenesulfonic acid monohydrate (2.15 g, 11.3 mmol) and refluxed with heating for 3 hours. The mixture was concentrated under reduced pressure, then water and EtOAc were added to the residue and the solvent was made alkaline with aq $NaHCO_3$ before the distribution was carried out. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with $CHCl_3$-MeOH (19:1) to give **22** (1.34 g, 68%) as a brown oil. ^1H NMR ($CDCl_3$) δ 2.6~3.4 (2H, m), 3.5~4.2 (3H, m), 3.77 (2H, s), 3.80 (3H, s), 6.79 (1H, d, J=1 Hz), 6.85 (2H, d, J=9 Hz), 7.02 (1H, d, J=1 Hz), 7.24 (2H, d, J=9 Hz).

6,7-Dihydro-6-mercapto-5*H*-pyrrolo[1,2-*a*]imidazole Trifluoromethanesulfonate (**23**)

To a mixture of **22** (1.34 g, 5.2 mmol) and anisole (5 ml) in TFA (30 ml) was added trifluoromethanesulfonic acid (2.04 g, 13.6 mmol) in ice-cooled conditions. The reaction mixture was stirred at room temperature for 30 minutes and evaporated under reduced pressure. The residue was washed with petroleum ether, IPE and Et_2O to give **23** (1.48 g, 99%) as a brown oil. ^1H NMR (D_2O) δ 3.1~3.9 (3H, m), 4.1~4.6 (2H, m), 4.80 (HOD), 7.43 (2H, s).

4-Amino-2-(*p*-methoxybenzylthio)butyric Acid (**25**)

A mixture of **24** (13.75 g, 0.1 mol), water (100 ml), NaOH (8 g, 0.2 mol) and *p*-methoxybenzylmercaptan (17.2 g, 0.11 mol) was stirred for 24 hours at room temperature. The reaction mixture was washed with benzene and acidified to pH 4 with acetic acid under ice-cooled conditions to give a colorless precipitate, which was washed with cold water and then with acetone to yield **25** (23.23 g, 91%) as a colorless powder. MP 200~205°C; ^1H NMR (NaOD) δ 2.0~2.7 (2H, m), 3.10 (2H, t, J=7 Hz), 3.75 (1H, t, J=8 Hz), 4.08 (3H, s), 4.19 (2H, s), 7.25 (2H, d, J=9 Hz), 7.70 (2H, d, J=9 Hz).

3-(*p*-Methoxybenzylthio)pyrrolidin-2-one (**26**)

Amino acid **25** (15.3 g, 60 mmol) was heated at 200~205°C for 18 minutes to give a caramel, which was chromatographed on silica gel (35 g) using $CHCl_3$ (300 ml) and EtOAc (400 ml) as eluents. The fractions were combined and concentrated under reduced pressure to give an oil, which was crystallized from $CHCl_3$-isopropylether to give **26** (12.99 g, 91%) as crystals. MP 106~107°C; IR (KBr) 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7~2.2 (1H, m), 2.2~2.6 (1H, m), 3.1~3.6 (3H, m), 3.78 (3H, s), 3.95 (2H, ABq, J=13 Hz), 6.47 (1H, m), 6.82 (2H, d, J=8 Hz), 7.30 (2H, d, J=8 Hz).

Anal Calcd for $C_{12}H_{15}NO_2S$: C 60.73, H 6.73, N 5.90.
Found: C 60.53, H 6.43, N 5.86.

Thiol **29** was prepared from **26** as **23** was prepared from **20**. The spectroscopic data of **27**~**29** were as follows:

27: ^1H NMR ($CDCl_3$) δ 1.36 (3H, t, J=7 Hz), 1.7~2.1 (1H, m), 2.1~2.8 (1H, m), 3.4~4.0 (5H, m), 3.79 (3H, s), 4.24 (2H, q, J=7 Hz), 6.82 (2H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz).

28: ^1H NMR ($CDCl_3$) δ: 2.2~2.5 (1H, m), 2.6~3.0 (1H, m), 3.76 (3H, s), 3.7~4.2 (5H, m), 6.79 (2H, d, J=9 Hz), 6.83 (1H, d, J=2 Hz), 7.05 (1H, d, J=2 Hz), 7.29 (2H, d, J=9 Hz).

29: ^1H NMR (DMSO+D_2O) δ 2.0~2.7 (1H, m), 3.0~3.6 (1H, m), 4.24 (2H, m), 4.70 (1H, dd, J=4 and 7 Hz), 4,80 (HOD), 7.65 (2H, br s).

Ethyl 5-*tert*-Butoxycarbonylamino-3-oxovalerate (**31**)

Magnesium powder (0.88 g, 36.2 mmol) was added to EtOH (15 ml), and then CCl_4 (2.5 ml) was added dropwise to the mixture. After stirring at room temperature for 2 hours, a solution of ethyl malonate half ester (10.42 g, 78.9 mmol) in THF (45 ml) was added dropwise to the mixture and stirred at room temperature for 15 minutes, then concentrated under reduced pressure to give the magnesium slat. To a solution of **30** (8.76 g, 46.3 mmol) in THF (100 ml) was added carbonyldiimidazole (7.53 g, 46.4 mmol), and the mixture was stirred at room temperature for 30 minutes, after which a solution of the magnesium salt prepared above was added. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure. The residue was diluted with EtOAc, and then washed with 0.5 M aq HCl, water aq $NaHCO_3$. The organic layer was dried over Na_2SO_4, then evaporated under reduced pressure to give **31** (9.6 g, 80%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.27 (3H, t, J=7 Hz), 1.43 (9H, s), 2.76 (2H, t, J=6 Hz), 3.40 (2H, q, J=6 Hz), 3.42 (2H, s), 4.18 (2H, q, J=7 Hz), 5.90 (1H, br s).

Ethyl 5-*tert*-Butoxycarbonylamino-3-hydroxyvalerate (**32**)

To a solution of **31** (12.3 g, 47.4 mmol) in EtOH (200 ml) was added sodium borohydride (0.59 g, 15.6 mmol) at 0~5°C, and the mixture was stirred for 2 hours at the same temperature, then neutralized using 0.5 M aq HCl. After evaporation of the solvent, the residue was diluted with EtOAc, then washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel, eluting with benzene-EtOAc (1 : 1) to give **32** (8.2 g, 66%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.26 (3H, t, J=7 Hz), 1.44 (9H, s), 1.65 (2H, m), 2.46 (2H, d, J=6 Hz), 3.2 (3H, m), 4.13 (2H, q, J=7 Hz), 4.0~4.2 (1H, m).

p-Methoxybenzylthioether (**34**) was prepared from **32** as described for the preparation of **20** from **18**. The spectroscopic data of **33** and **34** were as follows:

33: ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, J=7 Hz), 1.46 (9H, s), 1.7~2.1 (2H, m), 2.77 (2H, d, J=6 Hz), 2.8~3.6 (2H, m), 4.16 (2H, q, J=7 Hz), 4.0~4.2 (1H, m), 7.2~7.6 (3H, m), 7.9~8.0 (2H, m).

34: ^1H NMR ($CDCl_3$) δ 1.24 (3H, t, J=7 Hz), 1.42 (9H, s), 1.5~1.8 (2H, m), 2.56 (2H, d, J=7 Hz), 2.8~3.3 (3H, m), 3.67 (2H, s), 3.76 (3H, s), 4.17 (2H, q, J=7 Hz), 6.83 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz).

4-*p*-Methoxybenzylthiopiperidin-2-one (**35**)

A mixture of **34** (4.3 g, 11 mmol), anisole (12.1 g, 110 mmol) and TFA (50 ml) was stirred at 0~5°C for 30 minutes, then concentrated under reduced pressure. To the residue dissolved in water (10 ml) was added 1 M aq NaOH (28 ml), and after being stirred at room temperature for 30 minutes, the mixture was extracted with $CHCl_3$. The organic layer was washed with aq NaCl and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in toluene (50 ml), and then refluxed with heating for 30 minutes. The solvent was removed under reduced pressure, and the resulting crystals were washed with Et_2O to give **35** (2.0 g, 72%). MP 141~142°C; IR (KBr) 1670, 1625, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6~2.1 (1H, m), 2.34 (1H, dd, J=7 and 16 Hz), 2.72 (1H, dd, J=4 and 16 Hz), 2.9~3.6 (3H, m), 3.76 (2H, s), 3.80 (2H, ABq, J=13 Hz), 6.85 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz).

Anal Calcd for $C_{13}H_{17}NO_2S$: C 62.12, H 6.82, N 5.57.
Found: C 62.09, H 6.76, N 5.58.

Thiol **38** was prepared from **35** as **23** was prepared from **20**. The spectroscopic data of **36**~**38** were as follows:

36: ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, J=6 Hz), 1.7~2.0 (1H, m), 2.08 (1H, dd, J=8 and 15 Hz), 2.56 (1H, dd, J=5 and 15 Hz), 2.8~3.1 (1H, m), 3.2~3.7 (2H, m), 3.70 (2H, s), 3.77 (3H, s), 4.02 (2H, q, J=6 Hz), 6.79 (2H, d, J=9 Hz), 7.18 (2H, d, J=9 Hz).

37: MP 75~77°C; IR (KBr) 1610, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8~2.4 (2H, m), 2.8~3.5 (3H, m), 3.80 (2H, s), 3.84 (3H, s), 3.8~4.2 (2H, m), 6.83 (1H, d, J=2 Hz), 6.90 (2H, d, J=9 Hz), 7.04 (1H, d, J=2 Hz), 7.31 (2H, d, J=9 Hz).

38: ^1H NMR (DMSO+D_2O) δ 2.1~2.8 (2H, m), 3.30 (1H, dd, J=7 and 8 Hz), 3.81 (1H, dd, J=7 and 18 Hz), 3.6~3.9 (1H, m), 4.3~4.6 (2H, m), 7.45 (2H, s).

3-(Imidazol-4-yl)-2-(*p*-methoxybenzylthio)propionic Acid (**40**)

To a solution of **39**[14] (5.41 g, 31.0 mmol) and 1.5 N aq NaOH (50 ml) was added *p*-methoxybenzylmercaptan (5.3 g, 34.4 mmol), and the mixture was stirred for 3 days at room temperature. The reaction mixture was washed with benzene and acidified to pH 4 with acetic acid with ice cooling to give a colorless precipitate, which was washed with cold water and then with EtOH and Et_2O to give **40** (5.8 g, 64%) as colorless needles. MP 85~88°C; IR (KBr) 3500~2500 (broad), 1580, 1510 cm^{-1}; ^1H NMR (NaOD) δ 2.92 (2H, m), 3.43 (1H, dd, J=7 and 8 Hz), 3.70 (2H, s), 3.81 (3H, s), 6.82 (1H, d, J=1 Hz), 6.93 (2H, d, J=9 Hz), 7.27 (2H, d, J=9 Hz), 7.58 (1H, d, J=1 Hz).

Methyl 3-(Imidazol-4-yl)-2-(*p*-methoxybenzylthio)propionate (**41**)

Thionylchloride (0.47 ml, 5.0 mmol) was added dropwise to MeOH (30 ml) cooled to −10°C, and the solution and was stirred for 10 minutes at the same temperature. To the solution was added **40** (1.46 g, 5.0 mmol) and stirred at room temperature for 1 hour. The solution was concentrated under reduced pressure. After the addition of benzene to the residue, the solvent was distilled off under reduced pressure, and the residue was partitioned between $CHCl_3$ and aq $NaHCO_3$. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give **41** (0.98 g, 64%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 3.03 (2H, m), 3.54 (1H, dd, J=6 and 8 Hz), 3.70 (2H, s), 3.79 (3H, s), 6.82 (3H, m), 7.22 (2H, d, J=9 Hz), 7.51 (1H, d, J=1 Hz).

3-(Imidazol-4-yl)-2-(*p*-methoxybenzylthio)propanol (**42**)

To a solution of **41** (0.27 g, 2.4 mmol) and isopropanol (15 ml), calcium chloride (0.78 g, 7.1 mmol) and sodium borohydride (0.18 g, 4.7 mmol) were added, and the mixture was stirred at room temperature for 5 hours. It was diluted with EtOAc, washed with water and aq NaCl and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel, eluting with $CHCl_3$-MeOH (19:1) to give **42** (0.566 g, 87%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.93 (3H, m, CHSPMB, imidazole-CH_2), 3.64 (2H, m, OCH_2), 3.68 (2H, s, SCH_2Ar), 3.77 (3H, s, $ArOCH_3$), 6.76 (1H, d, J=1 Hz), 6.81 (2H, d, J=9 Hz), 7.20 (2H, d, J=9 Hz), 7.50 (1H, d, J=9 Hz); FD-MS m/z 279 (M^+).

4-[2-Chloro-3-(*p*-metoxybenzylthio)propyl]imidazole (**43**)

To a solution of the alcohol **42** (0.56 g, 2.0 mmol) in CCl_4 (10 ml) was added triphenylphosphine (0.63 g, 2.4 mmol), and the reaction mixture was refluxed for 2.5 hours. After cooling, the reactant was neutralized with triethylamine and the solvent was evaporated. The residue was chromatographed on silica gel, eluting with $CHCl_3$-MeOH (9:1) to give **43** (0.234 g, 39%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.79 (2H, d, J=6 Hz, CH_2SPMB), 3.14 (2H, m, imidazole-CH_2), 3.72 (2H, s, SCH_2Ar), 3.78 (3H, s, $ArOCH_3$), 4.22 (1H, m, CHCl), 6.82 (2H, d, J=9 Hz), 6.87 (1H, d, J=1 Hz), 7.21 (2H, d, J=9 Hz), 7.56 (1H, d, J=1 Hz).

6,7-Dihydro-6-*p*-methoxybenzylthio-5*H*-pyrrolo[1,2-*c*]imidazole (**46**)

To a solution of **43** (2.21 g, 7.4 mmol) in acetone (40 ml) was added sodium iodide (11.1 g, 74 mmol) and the mixture was refluxed under heating for 24 hours, then concentrated under reduced pressure. The residue was diluted with $CHCl_3$ and washed with aq NaOH and aq NaCl and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel, eluting with $CHCl_3$-MeOH (19:1) to give **46** (0.89 g, 46%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.6~3.4 (2H, m), 3.77 (2H, s), 3.81 (3H, s), 4.7~5.2 (3H, m), 6.70 (1H, br s), 6.86 (2H, d, J=9 Hz), 7.25 (2H, d, J=9 Hz), 7.42 (1H, br s).

Thiol **47** was prepared as described for the preparation of **22**, and the spectroscopic data of **47** is as follows:

47: ^1H NMR (D_2O) δ 2.9~3.9 (3H, m), 4.2~4.6 (2H, m), 4.80 (HOD), 7.24 (1H, s), 8.65 (1H, s); FD-MS m/z 260 (M^+).

Ethyl 3-(Imidazol-4-yl)-3-(*p*-methoxybenzylthio)propionate (**49**)

Ethyl urocanate hydrochloride (**48**) (3.0 g, 15 mmol) was made free base with aq $NaHCO_3$, extracted with $CHCl_3$ by salting-out, and then dried over Na_2SO_4. The solution was concentrated to 50 ml, and to

it were added *p*-methoxybenzylmercaptan (3.1 g, 20 mmol) and tetramethylguanidine (2.6 g, 22.5 mmol). The mixture was stirred for 24 hours at room temperature under argon. The solvent was concentrated under reduced pressure, and the residue was chromatographed on silica gel, eluting with benzene - EtOAc (1 : 1) to give **49** (0.89 g, 46%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, J=6 Hz), 2.8~3.0 (2H, m), 3.60 (2H, s), 3.76 (3H, s), 4.07 (2H, q, J=6 Hz), 4.23 (1H, t, J=6 Hz), 6.75 (2H, d, J=9 Hz), 6.86 (1H, s), 7.13 (2H, d, J=9 Hz), 7.53 (1H, s).

Thiol **53** was prepared from **49** in the same manner as **47** was obtained from **41**. The spectroscopic data of **50**~**53** were as follows:

50: ^{1}H NMR ($CDCl_3$) δ 1.9~2.3 (2H, m), 3.4~3.9 (2H, m), 3.50 (2H, s), 3.69 (3H, s), 3.94 (1H, t, J=6 Hz), 6.69 (2H, d, J=9 Hz), 6.81 (1H, s), 7.06 (2H, d, J=9 Hz), 7.49 (1H, s).

51: ^{1}H NMR ($CDCl_3$) δ 2.15~2.50 (2H, m), 3.3~3.8 (2H, m), 3.55 (2H, s), 3.74 (3H, s), 4.00 (1H, t, J=6 Hz), 6.74 (2H, d, J=9 Hz), 6.86 (1H, s), 7.12 (2H, d, J=9 Hz), 7.57 (1H, s).

52: ^{1}H NMR ($CDCl_3$) δ 2.3~2.6 (1H, m), 2.65~3.15 (1H, m), 3.70 (2H, s), 3.75 (3H, s), 3.8~4.2 (3H, m), 6.76 (1H, s), 6.78 (2H, d, J=9 Hz), 7.18 (2H, d, J=9 Hz), 7.34 (1H, s).

53: ^{1}H NMR (D_2O) δ 2.5~2.8 (1H, m), 3.0~3.4 (1H, m), 4.2~4.7 (3H, m), 4.80 (HOD), 7.33 (1H, s), 8.62 (1H, s).

p-Nitrobenzyl (5*R*,6*S*,8*R*)-2-[(6,7-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)thio]-6-(1-hydroxyethyl)-2-penem-3-carboxylate (**55**)

To a solution of **54** (0.256 g, 0.6 mmol) and **53** (0.44 g, 1.5 mmol) in DMF (3 ml) was added *N*,*N*-diisopropylethylamine (0.54 ml, 3.1 mmol) at −40°C under argon. After stirring at the same temperature for 30 minutes, the reaction mixture was diluted with EtOAc, washed with water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with $CHCl_3$ - MeOH (24 : 1) to give **55** (0.29 g, 99%) as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, d, J=6 Hz), 2.5~3.0 (1H, m), 3.0~3.5 (1H, m), 3.7~3.9 (1H, m), 4.0~4.4 (3H, m), 4.7~4.9 (1H, m), 5.15 and 5.44 (2H, each d, J=15 Hz), 5.77 (1H, s), 6.96 and 6.99 (1H, each s), 7.48 (1H, s), 7.58 and 8.17 (each 2H, each d, J=9 Hz).

(5*R*,6*S*,8*R*)-2-[(6,7-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)thio]-6-(1-hydroxyethyl)-2-penem-3-carboxylic acid (**11**)

A solution of **55** (0.146 g, 0.3 mmol) in THF (10 ml) and 1/15 M phosphate buffer (pH 7.0, 10 ml) was subjected to catalytic hydrogenation under atmospheric pressure for 2 hours at room temperature in the presence of 10% Pd-C (0.15 g). The catalyst was removed by filtration and washed with water. The combined filtrate and washings were concentrated under reduced pressure to remove organic solvents. The resultant aqueous solution was washed with EtOAc, concentrated under reduced pressure, and chromatographed on a column of Diaion HP-20. Fractions eluted with 5% aq THF were concentrated under reduced pressure and were purified by HPLC, eluting with 5% aq acetonitrile. Fractions having UV absorption at 325 nm were combined and lyophilized to give **11A** (0.019 g, 18%) and **11B** (0.022 g, 21%) as a colorless powder. **11A**: IR (KBr) 1770, 1580 cm^{-1}; ^{1}H NMR (D_2O) δ 1.39 (3H, d, J=6 Hz), 2.6~3.1 (1H, m), 3.1~3.6 (1H, m), 4.05 (1H, dd, J=2 and 6 Hz), 4.2~4.7 (3H, m), 5.80 (1H, d, J=2 Hz), 7.44 (1H, s), 8.61 (1H, s); UV λmax (H_2O) 250, 324 nm. **11B**: IR (KBr) 1770, 1580 cm^{-1}; ^{1}H NMR (D_2O) δ 1.38 (3H, d, J=6 Hz), 2.6~3.0 (1H, m), 3.1~3.5 (1H, m), 4.02 (1H, dd, J=2 and 6 Hz), 4.2~4.6 (3H, m), 5.81 (1H, d, J=2 Hz), 7.49 (1H, s), 8.64 (1H, s); UV λmax (H_2O) 258, 323 nm.

The compounds **4A**, **4B**, **6**, **7A**, **7B**, **9A** and **9B** were prepared from **23**, **29**, **38** and **47** as **11** was prepared from **53**. The spectroscopic data of **4A**, **4B**, **6**, **7A**, **7B**, **9A** and **9B** were as follows:

4A: IR (KBr) 1765, 1585 cm^{-1}; ^{1}H NMR (D_2O) δ 1.36 (3H, d, J=6 Hz), 2.9~3.2 (1H, m), 3.4~3.8 (1H, m), 4.00 (1H, dd, J=2 and 6 Hz), 4.1~4.5 (2H, m), 4.5~4.8 (2H, m), 5.80 (1H, d, J=2 Hz), 7.30 (2H, s); UV λmax (H_2O) 253, 323 nm.

4B: IR (KBr) 1765, 1585 cm^{-1}; ^{1}H NMR (D_2O) δ 1.36 (3H, d, J=6 Hz), 3.1~3.5 (1H, m), 3.6~3.9 (1H, m), 3.99 (1H, dd, J=2 and 6 Hz), 4.1~4.5 (2H, m), 4.5~4.8 (2H, m), 5.78 (1H, d, J=2 Hz), 7.35 (2H, s); UV λmax (H_2O) 253, 323 nm.

6: IR (KBr) 1760, 1580 cm^{-1}; ^{1}H NMR (D_2O) δ 1.33 (3/2H, d, J=6 Hz), 1.36 (3/2H, d, J=6 Hz), 2.8~3.1 (1/2H, m), 3.1~3.5 (1/2H, m), 4.0~4.6 (4H, m), 5.66 (1/2H, d, J=2 Hz), 5.73 (1/2H, d, J=2 Hz),

7.2~7.4 (2H, m); UV λmax (H_2O) 253, 325 nm.

7A: IR (KBr) 1770, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.38 (3H, d, J=6 Hz), 2.1~2.6 (2H, m), 3.13 (1H, dd, J=7 and 18 Hz), 3.60 (1H, dd, J=5 and 18 Hz), 4.01 (1H, dd, J=2 and 7 Hz), 4.0~4.5 (4H, m), 5.78 (1H, d, J=2 Hz), 7.35 (2H, s); UV λmax (H_2O) 260, 322 nm.

7B: IR (KBr) 1770, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.38 (3H, d, J=6 Hz), 2.1~2.6 (2H, m), 3.17 (1H, dd, J=7 and 18 Hz), 3.63 (1H, dd, J=6 and 18 Hz), 4.00 (1H, dd, J=2 and 7 Hz), 4.0~4.5 (4H, m), 5.78 (1H, d, J=2 Hz), 7.35 (2H, s); UV λmax (H_2O) 258, 322 nm.

9A: IR (KBr) 1765, 1580 cm^{-1}; ^1H NMR (D_2O) δ 1.37 (3H, d, J=6 Hz), 3.2~3.6 (2H, m), 4.01 (1H, dd, J=2 and 6 Hz), 4.2~4.5 (4H, m), 5.79 (1H, d, J=2 Hz), 7.11 (1H, br s), 8.37 (1H, br s); UV λmax (H_2O) 253, 323 nm.

9B: IR (KBr) 1765, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.37 (3H, d, J=6 Hz), 3.0~3.8 (2H, m), 4.01 (1H, dd, J=2 and 6 Hz), 4.2~4.6 (4H, m), 5.78 (1H, d, J=2 Hz), 7.11 (1H, br s), 8.36 (1H, br s); UV λmax (H_2O) 253, 323 nm.

(5*R*,6*S*,8*R*)-2-[(6,7-Dihydro-2-methyl-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl)thio]-6-(1-hydroxyethyl)-2-penem-3-carboxylate (**12**)

To a solution of compound **55** (0.146 g, 0.3 mmol) in THF (3 ml) and acetone (10 ml) was added MeI (0.37 ml, 6.0 mmol), and the reaction mixture was stirred at 5°C for 30 hours under argon. After evaporation of the solvent, the residue was washed with petroleum ether, and then dissolved in a mixture of THF (11 ml) and water (11 ml). To the solution was added NH_4Cl (2.48 g) and Fe powder (1.24 g, 100 mesh), and the mixture was stirred vigorously at 5~10°C for 2 hours. The mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and chromatographed on a column of Diaion HP-20. Fractions eluted with 5% aq THF were concentrated under reduced pressure and were purified by HPLC, eluting with 7% aq acetonitrile. Fractions having UV absorption at 325 nm were combined and lyophilized to give **12A** (0.014 g, 13%) and **12B** (0.017 g, 15%) as colorless powders. **12A**: IR (KBr) 1760, 1580 cm^{-1}; ^1H NMR (D_2O) δ 1.38 (3H, d, J=6 Hz), 2.6~3.0 (1H, m), 3.1~3.5 (1H, m), 3.96 (1H, s), 4.04 (1H, dd, J=2 and 6 Hz), 4.1~4.6 (3H, m), 4.9~5.1 (1H, m), 5.79 (1H, d, J=2 Hz), 7.46 (1H, s), 8.69 (1H, s); UV λmax (H_2O) 250, 325 nm. **12B**: IR (KBr) 1765, 1595 cm^{-1}; ^1H NMR (D_2O) δ 1.38 (3H, d, J=6 Hz), 2.5~2.9 (1H, m), 3.0~3.5 (1H, m), 3.96 (3H, s), 4.02 (1H, dd, J=2 and 6 Hz), 4.1~4.6 (3H, m), 5.80 (1H, d, J=2 Hz), 7.52 (1H, s), 8.69 (1H, s); UV λmax (H_2O) 260, 325 nm.

In a similar manner, **5**, **8**, **10A**, **10B** were prepared from **23**, **38** and **47** as described for the preparation of **12** from **53**. The spectroscopic data were as follows:

5: IR (KBr) 1770, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.36 (3H, d, J=6 Hz), 3.40 (2H, m), 3.83 (3H, s), 4.01 (1H, dd, J=2 and 6 Hz), 4.2~4.5 (4H, m), 5.79 (1H, d, J=2 Hz), 7.43 (2H, s); UV λmax (H_2O) 253, 324 nm.

8: IR (KBr) 1770, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.36 (3H, d, J=6 Hz), 2.1~2.7 (2H, m), 3.0~3.6 (2H, m), 3.80 (3H, s), 3.9~4.1 (2H, m), 4.2~4.5 (3H, m), 5.80 (1H, s), 7.42 (2H, s); UV λmax (H_2O) 260, 323 nm.

10A: IR (KBr) 1760, 1580 cm^{-1}; ^1H NMR (D_2O) δ 1.37 (3H, d, J=6 Hz), 3.22 (1H, dd, J=4 and 18 Hz), 3.68 (1H, dd, J=7 and 18 Hz), 3.94 (3H, s), 4.01 (1H, dd, J=2 and 7 Hz), 4.2~4.7 (4H, m), 5.78 (1H, d, J=2 Hz), 7.23 (1H, s), 8.64 (1H, s); UV λmax (H_2O) 253, 323 nm.

10B: IR (KBr) 1765, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.37 (3H, d, J=6 Hz), 3.12 (1H, dd, J=4 and 18 Hz), 3.64 (1H, dd, J=7 and 18 Hz), 3.94 (3H, s), 4.01 (1H, d, J=2 and 7 Hz), 4.2~4.7 (4H, m), 5.78 (1H, d, J=2 Hz), 7.24 (1H, s), 8.64 (1H, s); UV λmax (H_2O) 253, 323 nm.

The compounds **13A**, **13B**, **14A**, **14B**, **15A**, **15B**, **16A**, **16B** and **17** were prepared from **55** and the corresponding alkyl halides as described for the preparation of **12**.

13A: IR (KBr) 1765, 1580 cm^{-1}; ^1H NMR (D_2O) δ 1.34 (3H, d, J=6 Hz), 1.52 (3H, t, J=7 Hz), 2.6~3.0 (1H, m), 3.0~3.5 (1H, m), 4.00 (1H, d, J=6 Hz), 4.1~4.7 (3H, m), 4.26 (2H, q, J=7 Hz), 4.9~5.1 (1H, m), 5.75 (1H, s), 7.50 (1H, s), 8.71 (1H, s); UV λmax (H_2O) 248, 324 nm.

13B: IR (KBr) 1765, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.33 (3H, d, J=6 Hz), 1.52 (3H, t, J=7 Hz), 2.5~2.9 (1H, m), 2.9~3.5 (1H, m), 3.97 (1H, d, J=6 Hz), 4.1~4.7 (3H, m), 4.26 (2H, q, J=7 Hz), 4.9~5.1 (1H, m), 5.77 (1H, s), 7.54 (1H, s), 8.71 (1H, s); UV λmax (H_2O) 258, 324 nm.

14A: IR (KBr) 1760, 1680, 1580 cm^{-1}; ^1H NMR (D_2O) δ 1.31 (3H, d, J=6 Hz), 2.5~3.0 (1H, m),

3.0~3.6 (1H, m), 3.99 (1H, dd, J=1 and 6 Hz), 4.1~4.6 (3H, m), 4.9~5.2 (1H, m), 5.08 (2H, s), 5.72 (1H, d, J=1 Hz), 7.46 (1H, s), 8.77 (1H, s); UV λmax (H_2O) 248, 326 nm.

14B: IR (KBr) 1765, 1695, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.30 (3H, d, J=6 Hz), 2.4~2.9 (1H, m), 2.9~3.5 (1H, m), 3.95 (1H, dd, J=2 and 6 Hz), 4.1~4.6 (3H, m), 4.9~5.2 (1H, m), 5.09 (2H, s), 5.71 (1H, d, J=2 Hz), 7.50 (1H, s), 8.78 (1H, s); UV λmax (H_2O) 256, 324 nm.

15A: IR (KBr) 1765, 1680, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.27 (3H, d, J=6 Hz), 2.5~3.0 (4H, m), 3.0~3.6 (1H, m), 3.95 (1H, dd, J=1 and 6 Hz), 4.23 (1H, t, J=6 Hz), 4.3~4.6 (2H, m), 4.9~5.1 (1H, m), 4.99 (2H, s), 5.67 (1H, d, J=1 Hz), 7.42 (1H, s), 8.74 (1H, s); UV λmax (H_2O) 248, 324 nm.

15B: IR (KBr) 1775, 1685, 1595 cm^{-1}; ^1H NMR (D_2O) δ 1.27 (3H, d, J=6 Hz), 2.4~2.9 (4H, m), 2.9~3.4 (1H, m), 3.95 (1H, dd, J=2 and 6 Hz), 4.27 (1H, t, J=6 Hz), 4.3~4.6 (2H, m), 4.9~5.1 (1H, m), 5.00 (2H, s), 5.68 (1H, d, J=2 Hz), 7.44 (1H, s), 8.75 (1H, s); UV λmax (H_2O) 258, 325 nm.

16A: IR (KBr) 1775, 1660, 1585 cm^{-1}; ^1H NMR (D_2O) δ 1.34 (3H, d, J=6 Hz), 2.5~3.5 (8H, m), 4.00 (1H, d, J=6 Hz), 4.1~4.6 (3H, m), 4.9~5.1 (1H, m), 5.31 (2H, s), 5.74 (1H, br s), 7.42 (1H, s), 8.73 (1H, s); UV λmax (H_2O) 247, 325 nm.

16B: IR (KBr) 1775, 1660, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.32 (3H, d, J=6 Hz), 2.5~3.5 (8H, m), 3.97 (1H, d, J=6 Hz), 4.1~4.6 (3H, m), 4.9~5.1 (1H, m), 5.30 (2H, s), 5.73 (1H, d, J=2 Hz), 7.43 (1H, s), 8.72 (1H, s); UV λmax (H_2O) 256, 325 nm.

17: IR (KBr) 1770, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.31 (3H, d, J=6 Hz), 2.5~3.0 (1H, m), 3.0~3.5 (1H, m), 3.73 and 3.89 (each 1/2H, each d, J=6 Hz), 4.1~4.6 (3H, m), 4.9~5.1 (1H, m), 5.41 (2H, s), 5.49 and 5.60 (each 1/2H, each br s), 7.48 (6H, s), 8.78 and 8.82 (each 1/2H, each s); UV λmax (H_2O) 253, 325 nm.

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