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Discovery of Novel *trans*-3,5-Disubstituted Pyrrolidinylthio-1β-Methylcarbapenems

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Abstract—Novel *trans*-3,5-disubstituted pyrrolidinylthio-1β-methylcarbapenems were designed and synthesized to provide J-111,347 (**1a**) as the first example of an exceptionally broad-spectrum antibiotic, showing activity against methicillin-resistant *Staphyloccocus aureus* (MRSA) as well as *Pseudomonas aeruginosa*. Further derivation of **1a** afforded J-111,225 (**2a**), J-114,870 (**3a**), and J-114,871 (**3b**), which showed improved safety profiles and retained broad-spectrum antibacterial activities.

Introduction

Emergence of multidrug-resistant bacteria, especially MRSA, has caused serious concern in clinics worldwide. Since there is no better chemotherapeutic agent against MRSA, vancomycin has been used in spite of its significant adverse effect profile.[1] Recently, the emergence of vancomycin-resistant MRSA has raised an alarm for the overuse of vancomycin.[2] Therefore, development of new chemotherapeutic agents showing potent activity against MRSA and good safety profiles has been urgently demanded. Carbapenem antibiotics, such as imipenem, meropenem, panipenem, and biapenem, possess better safety profiles and superior activity against a broad range of pathogens including *Pseudomonas aeruginosa*, another important pathogen in the clinic. However, these carbapenems have no appreciable efficacy against MRSA.

In the course of our structure–activity relationship studies of carbapenems having pyrrolidinylthio side chains at the C-2 position, we found that introduction of an additional basic function onto the pyrrolidine ring was important for enhancing anti-pseudomonal activity. Consequently, we reported the development of the potent carbapenem BO-2727[3] which exhibited broad-spectrum activity with good efficacy against *P. aeruginosa*, and with significant but insufficient efficacy against MRSA.

On the other hand, we also reported BO-3482,[4] a dithiocarbamate carbapenem possessing potent anti-MRSA activity, and demonstrated that increased lipophilicity of the C-2 side chain enhanced anti-MRSA activity. Similarly, Sumitomo's structure–activity relationship studies of carbapenems having substituted-thiazol-2-ylthio side chains at the C-2 position indicated that more lipophilic phenyl-substituted thiazolthio analogues showed greater activity against MRSA than simple alkyl-substituted thiazolthio analogues.[5]

Based on these observations, we designed and synthesized new carbapenems with pyrrolidinylthio side chains which possessed well-balanced hydrophobicity and basicity, in order to obtain novel carbapenems exhibiting sufficient efficacy against MRSA as well as *P. aeruginosa*. That is, a phenyl ring was introduced as a hydrophobic site between the pyrrolidine ring and an aminoalkyl substituent, a basic site (Fig. 1).

Among the compounds with or without several kinds of spacers between the pyrrolidine ring and the phenyl ring, J-111,347 (**1a**), having a 4-(aminomethyl)phenyl group directly attached at C-5 of the pyrrolidine ring, was found to have excellent antibacterial activity against MRSA and *P. aeruginosa*. With regard to the structure

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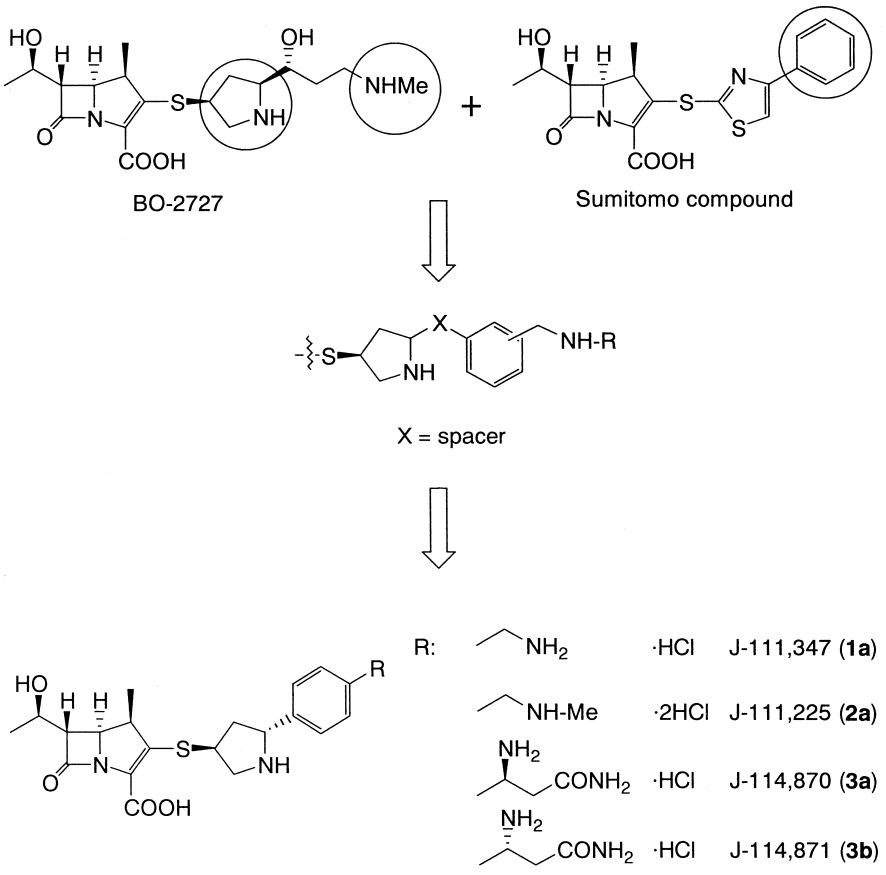


Figure 1.

of the pyrrolidine ring part, it should be noted that **1a** had an unusual *trans*-(3*S*,5*R*)-stereochemistry differing from the well-known 1β-methylcarbapenems such as meropenem,[6] S-4661,[7] MK-826 (L-749,345),[8] and BO-2727, which have a *cis*-(3*S*,5*S*)-disubstituted pyrrolidine ring as a C-2 side chain. Since **1a** showed epileptogenicity in the rat head assay (200 μg/rat-head), it should be modified for clinical use.

In order to eliminate the undesirable epileptogenic potency, the aminomethyl moiety of **1a** was modified by introducing various kinds of substituents, 1) onto the nitrogen of the primary amino function, or 2) onto the benzilic carbon adjacent to the amino function. These derivations afforded three analogues, J-111,225 (**2a**), J-114,870 (**3a**), and J-114,871 (**3b**), which maintained excellent antimicrobial activity similar to **1a** and showed no epileptogenicity in the rat-head assay. Following the preliminary account of this work presented previously,[9] we describe herein the details of the creation of **1a**, and the synthesis, structure–activity relationships, and some biological properties of the new carbapenems, **2a**, **3a**, **3b**, and their related compounds (Fig. 1).

Results and Discussion

Chemistry

We synthesized carbapenems having various spacers, such as methylene (**4a**, **4b**), thiomethylene (**5a**, **5b**), aminomethylene (**6b**), and oxymethylene (**7b**) functions, between the pyrrolidine and phenyl ring, by using the method described in our previous paper[10] (Fig. 2) or that used for FR21818.[11]

J-111,225 (**2a**), J-114,870 (**3a**), J-114,871 (**3b**), and their related compounds (**1a**, **1b**, **2b–j**, **3c–l**, **8a**, **8b**, **9a**, **9b**, **10a** and **10b**) were prepared as described for the preparation of **1a**[12] or according to our previous method.[13] We describe herein the synthetic process of J-111,347 (**1a**) as a representative example (Scheme 1).

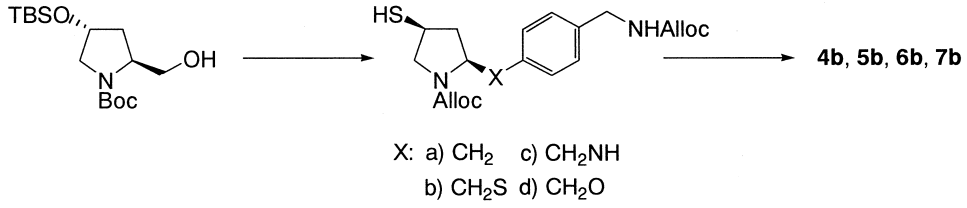
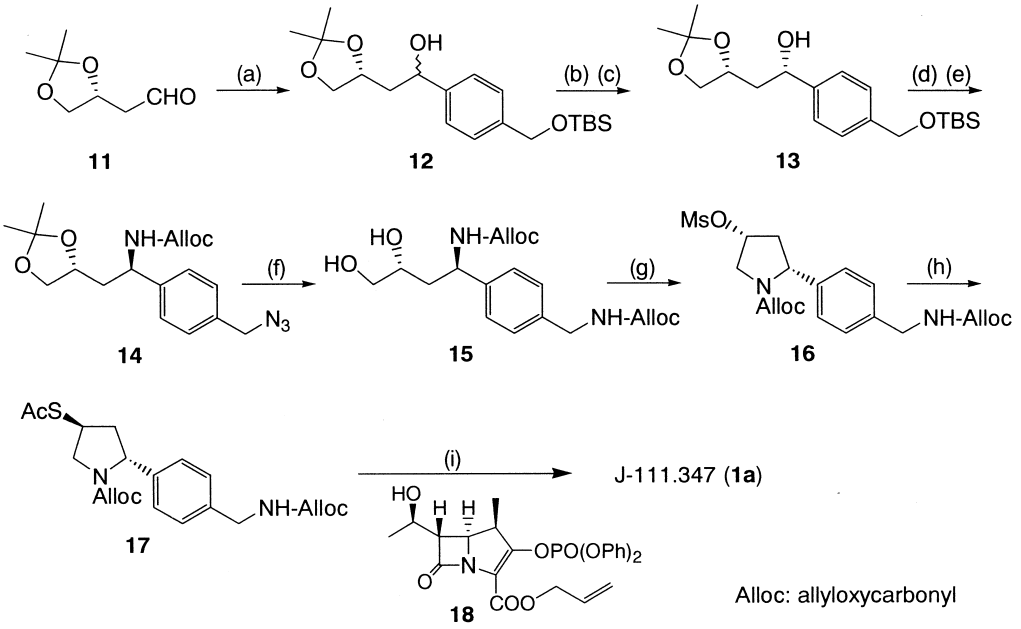


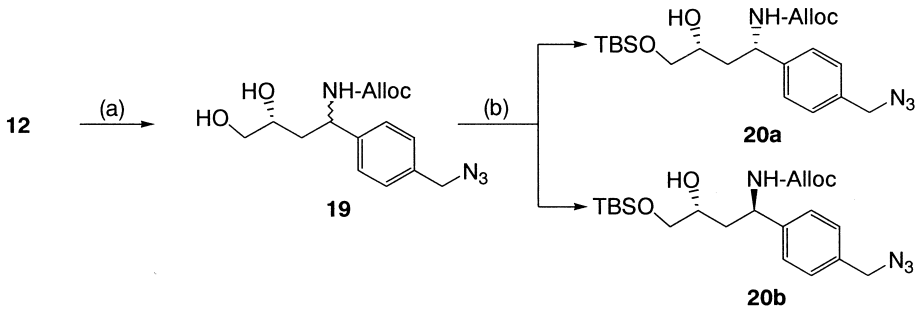
Figure 2.



Scheme 1. Reagents; (a) 1-bromo-4-(*tert*-butyldimethylsilyloxy)methylbenzene, *n*-BuLi, THF, −70 °C, 88%, (b) TPAP, NMO, molecular sieve 4Å, CH_2Cl_2, 0 °C, 88%, (c) $LiAlH_4$, LiI, THF, −78 °C, 76%, (d) i: DEAD, PPh_3, DPPA, THF, 0 °C, 86%; ii: PPh_3, THF-H_2O, r.t.; iii: TEA, Alloc-Cl, THF, 0 °C, 90%, (e) i: *n*-Bu_4NF, THF, 0 °C, 98%; ii: TEA, MsCl, CH_2Cl_2, 0 °C; iii: NaN_3, DMF, r.t., 91%, (f) i: PPh_3, THF-H_2O, r.t.; ii: TEA, Alloc-Cl, 0 °C; iii: HCl-MeOH, 78%, (g) i: TEA, MsCl, CH_2Cl_2, 0 °C; ii: *t*-BuOK, THF, −20 °C, 97%, (h) AcSK, DMF, 65 °C, 86%, (i) i: NaOH, 0 °C; ii: *i*-Pr_2NEt, **18**, CH_3CN, 0 °C, 65%; iii: $(PPh_3)_2PdCl_2$, *n*-Bu_3SnH, H_2O, CH_2Cl_2, 72%.

Thioacetate **17**, a protected C-2 side chain of **1a**, was prepared starting from butanal **11** which was obtained from commercially available D-malic acid by a conventional method.[14] Condensation of the butanal **11** with substituted phenyl lithium generated from the corresponding bromide afforded a diastereomeric mixture of alcohol **12**. Formation of the chiral alcohol **13** was performed by the oxidation of **12** with a tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) combination and following diastereoselective reduction with the LAH-LiI system described by Mori and Suzuki.[15] The stereochemistry of the carbinol center of **13** was determined by ^1H NMR analysis[16] of the corresponding MTPA esters. The secondary hydroxyl group of **13** was transformed to an allyloxycarbonyl(Alloc)-protected amino group, and after subsequent desilylation, the other benzilic hydroxyl group was substituted with NaN_3 to afford an azide **14**. The azide **14** was reduced with triphenylphosphine and H_2O to provide an amino group which was protected with an Alloc group, and then the acetonide moiety was removed by acid treatment to furnish diol **15**. Mesylation of **15** gave dimesylate which was subjected to cyclization reaction by potassium *tert*-butoxide to provide the desired pyrrolidine **16** in excellent yield. Conversion to **1a** from thioacetate **17**, obtained by the substitution of **16** with AcSK, is as follows: Thioacetate **17** was hydrolized to the corresponding thiol which was in turn coupled with carbapenem diphenylphosphate **18**[17] in the presence of diisopropylethylamine in CH_3CN. Deprotection of the coupling adduct was accomplished according to the method of Guibe et al.,[18] and the resulting crude carbapenem was purified by reversed-phase column chromatography to furnish the final compound **1a** as an amorphous powder after lyophilization.

The *cis* isomer **1b** corresponding to the *trans* isomer **1a** was prepared as shown in Scheme 2. Selective monosilylation of a mixture of diol **19** gave a separable mixture of mono-silylated alcohol **20a** and **20b** (**20a**:**20b** = ca. 3:4). Then, the optically active alcohol **20a** was converted to **1b** as described above.



Scheme 2. Reagents; (a) i: DEAD, PPh_3, DPPA, THF, 0 °C; ii: PPh_3, THF-H_2O, r.t.; iii: TEA, Alloc-Cl, THF, 0 °C; v: TEA, MsCl, CH_2Cl_2, 0 °C; vi: NaN_3, DMF, r.t.; vii: *p*-TsOH, MeOH, r.t., (b) TBS-Cl, imidazole, CH_2Cl_2, r.t., **20a**: 29.8%, **20b**: 40.5%.

Biological properties

The carbapenems obtained above were evaluated for their in vitro antibacterial activity against *S. aureus*, including an MRSA strain (pMS520/Smith), a methicillin-resistant *Staphylococcus epidermidis* strain (MRSE, MB5181), *E. coli*, and *P. aeruginosa*, including a ceftazidime-resistant *Pseudomonas aeruginosa* strain (AKR17); their susceptibility to porcine renal dehydropeptidase-I (DHP-I); and their epileptogenicity (Tables 1–6). Standard serial dilution techniques were employed for MIC determinations. Both imipenem and vancomycin were used as reference drugs.

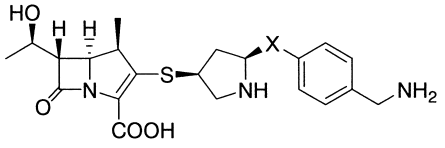
First, the 4-(aminomethyl)phenyl group was introduced on the pyrrolidine ring directly or by using several linkers. As expected, remarkable enhancement of the anti-MRSA activity was observed in the resulting carbapenems, **4b**, **5b**, **6b** and **7b**, compared with BO-2727 (Table 1). A thiomethylene analogue, **5b**, and no-spacer analogue, **1b**, in which an aminomethylphenyl structure was directly attached to the pyrrolidine ring, exhibited better antibacterial activities than other compounds. It was notable that only the methylene analogue **4b** did not show the undesirable epileptogenicity in the rat head assay at 200 μg/rat head.

Next, we evaluated diastereomers of **1b, 4b,** and **5b** which consist of *trans*-configurated pyrrolidine side chains (Table 2). *trans* Diastereomers (**4a**, **5a**) showed decreased potency against all strains compared with the potencies of the corresponding *cis* isomers (**4b**, **5b**). Interestingly, a *trans* diastereomer J-111,347 (**1a**) was two-fold more active than the corresponding *cis* isomer (**1b**) against the MRSA, MRSE, and *P. aeruginosa* strains. Such ambidextrous activity of **1a** was not seen in the *trans* isomers, **4a** and **5a**, which have methylene and thiomethylene spacers, respectively, between the pyrrolidine and aminomethylphenyl rings. In these studies, we discovered that a novel carbapenem consisting of a *trans*-configurated pyrrolidine side chain, J-111,347 (**1a**), showed antibacterial activities against both MRSA and *P. aeruginosa*.

Subsequently, several analogues of **1a** were synthesized to confirm the effect of *trans* stereochemistry of the pyrrolidine ring on antibacterial activity (Table 3). All the *trans* isomers showed better antibacterial activities than the corresponding *cis* isomers; however, the aminoethyl analogues, **8a** and **8b**, the naphthalene analogues, **9a** and **9b**, and the thiophene analogues, **10a** and **10b**, exhibited reduced antibacterial activities against both the MRSA and *P. aeruginosa* strains.

Thus, J-111,347 (**1a**) was the first example of an extremely broad-spectrum antibiotic which showed potent activity against MRSA as well as *P. aeruginosa*. However, **1a** and its analogues were found to be epileptogenic by the rat intracerebroventricular (ICV) assay. Such seizure potential often appeared as an adverse effect during the development of carbapenems. The relation between the epileptogenic potency of carbapenems and the stereochemical environment of the side chain as well as its basicity was investigated by Sunagawa et al.[19] The structure–activity relationship of BO-2727 derivatives also suggested this effect of the structure of the side chain, that is, introduction of substituent on the primary amino group of the side chain reduced the epileptogenicity. Based on these findings, we modified **1a** by introducing substituents onto the nitrogen of the primary amino group affording derivatives (**2a**–**j**), in order to eliminate the epileptogenicity of **1a** without losing its broad-spectrum antibacterial activities (Fig. 3 and Table 4). All of the *N*-alkylated analogues (**2a**, **2b**, **2d**, **2e** and **2h**) tested, showed no epileptogenic potency. J-111,225 (**2a**), an *N*-methyl analogue of **1a**, showed potency against MRSA and MRSE similar to that of vancomycin, and increased potency against *P. aeruginosa* compared with imipenem. The *N,N*-dimethyl analogue and trimethyl quarternary ammonium analogue (**2b** and **2c**) exhibited reduced

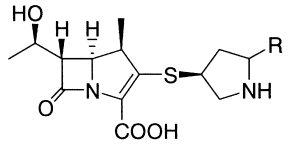
Table 1. In vitro activity[a] and biological properties of **1b**, **4b**, **5b**, **6b** and **7b**

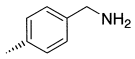
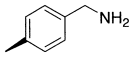
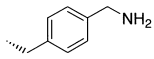
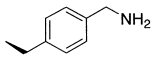


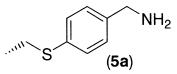
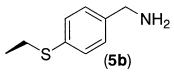
X Organism	(**1b**)	-CH_2- (**4b**)	-CH_2S- (**5b**)	-CH_2N- (**6b**)	-CH_2N- (**7b**)	BO-2727	VCM	IPM
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006	0.012	0.39	≤0.006
S. aureus pMS520/Smith[b]	1.56	3.13	1.56	3.13	3.13	12.5	0.78	50
S. epidermidis MB5181[b]	3.13	3.13	3.13	6.25	6.25	12.5	1.56	50
E. coli NlHJ JC2	0.025	0.025	0.025	0.025	0.025	0.05	>100	0.1
P. aeruginosa AK109	0.78	0.39	0.78	1.56	1.56	0.39	>100	1.56
P. aeruginosa AKR17[c]	6.25	6.25	3.13	12.5	12.5	1.56	>100	3.13
DHP-I susceptibility[d]	0.12	0.17	0.22	0.15	0.15	0.11	—	1.0
Epileptogenicity (200 μg/rat head, $n=5$)	4/5	0/5	2/5	2/5	3/5	0/5	—	5/5

[a]MIC(μg/ml) determined by agar dilution method.
[b]Methicillin-resistant.
[c]Ceftazidime-resistant.
[d]Relative rate of hydrolysis to imipenem, porcine renal DHP-I.

Table 2. In vitro activity[a] and biological properties of J-111,347 (**1a**) and related compounds



R Organism	 (**1a**)	 (**1b**)	 (**4a**)	 (**4b**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	0.05	≤0.006
S. aureus pMS520/Smith[b]	0.78	1.56	12.5	3.13
S. epidermidis MB5181[b]	1.56	3.13	12.5	3.13
E. coli NlHJ JC2	0.025	0.025	0.39	0.025
P. aeruginosa AK109	0.39	0.78	25	0.39
P. aeruginosa AKR17[c]	3.13	6.25	>100	6.25
DHP-I susceptibility[d]	0.29	0.12	0.28	0.17
Epiletogenicity (200 μg/rat head, $n=5$)	5/5	4/5	3/5	0/5

R Organism	 (**5a**)	 (**5b**)	VCM	IPM
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	0.39	≤0.006
S. aureus pMS520/Smith[b]	3.13	1.56	0.78	50
S. epidermidis MB5181[b]	3.13	3.13	1.56	50
E. coli NlHJ JC2	0.05	0.025	>100	0.1
P. aeruginosa AK109	1.56	0.78	>100	1.56
P. aeruginosa AKR17[c]	12.5	3.13	>100	3.13
DHP-I susceptibility[d]	0.14	0.22	NT[e]	1.0
Epiletogenicity (200 μg/rat head, $n=5$)	NT[e]	2/5	NT[e]	5/5

[a]MIC (μg/mL) determined by agar dilution method.
[b]Methicillin-resistant.
[c]Ceftazidime-resistant.
[d]Relative rate of hydrolysis to imipenem, porcine renal DHP-I.
[e]Not tested.

antibacterial activities against both MRSA and *P. aeruginosa*. Introduction of a substituent larger than the methyl group, such as ethyl (**2d**), *iso*-propyl (**2e**), carbamoylmethyl (**2f**), hydroxyethyl (**2g**) and sulfamoyl (**2h**), also reduced the antibacterial activities of **2a** against MRSA and *P. aeruginosa*. Only J-111,225 (**2a**) showed potent antibacterial activities against MRSA and *P. aeruginosa* comparable to those of **1a** with no epileptogenic potency.

Next, several substituents were introduced onto the benzilic carbon adjacent to the primary amino group of **1a**, in order to avoid the epileptogenic adverse effect (Fig. 4). Similar to the *N*-alkylated analogues described above (Table 4), all the substituents introduced so far were effective in eliminating epileptogenicity (200 μg/head, Table 5). Among these analogues, J-114,870 (**3a**) and J-114,871 (**3b**), which had a carbamoylmethyl group, exhibited excellent antibacterial activities comparable to those of **1a** and good stability to porcine renal DHP-I, while other analogues showed decreased antibacterial activities.

Three compounds, J-111,225 (**2a**), J-114,870 (**3a**), and J-114,871 (**3b**), were selected for further evaluation in view of their excellent antibacterial activities, reduced potential to cause seizures, and DHP-I stability. Preliminary in vivo studies of the selected compounds, **2a**, **3a**, and **3b**, demonstrated their significant efficacy against both MRSA and *P. aeruginosa*.[9] Subsequent evaluation of the candidates, **2a**, **3a** and **3b**, revealed good safety profiles with regard to epileptogenic potency (ED_{50}), acute toxicity (LD_{50}) in mice, and 48-h rabbit nephrotoxicity (Table 6).

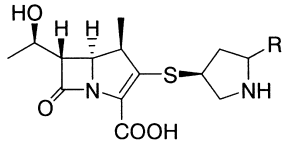
In summary, the novel carbapenems, J-111,225 (**2a**), J-114,870 (**3a**), and J-114,871 (**3b**), were designed, synthesized, and evaluated. These compounds were selected to be developed in view of an ultra-broad antimicrobial spectrum covering MRSA as well as *P. aeruginosa*, excellent safety profile including high stability to renal DHP-I and low epileptogenecity, and good physicochemical properties.

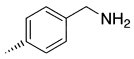
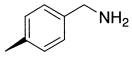
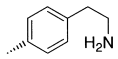
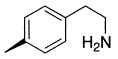
Experimental

Antibiotics and strains

Imipenem was a product of Banyu Pharmaceutical Co., Ltd., Japan. Vancomycin was purchased from Sigma Chemical Co., St. Louis, MO. The antibiotics were dissolved in

Table 3. In vitro activity[a] and biological properties of J-111,347 (**1a**) and related compounds



R Organism	 (**1a**)	 (**1b**)	 (**8a**)	 (**8b**)
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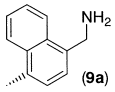
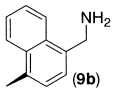
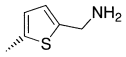
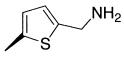
S. aureus pMS520/Smith[b]	0.78	1.56	1.56	3.13
S. epidermidis MB5181[b]	1.56	3.13	3.13	3.13
E. coli NlHJ JC2	0.025	0.025	0.025	0.05
P. aeruginosa AK109	0.39	0.78	0.78	0.78
P. aeruginosa AKR17[c]	3.13	6.25	6.25	>25
DHP-I susceptibility[d]	0.29	0.12	0.26	0.12
Epiletogenicity (200 μg/rat head, $n=5$)	5/5	4/5	3/5	5/5

R Organism	 (**9a**)	 (**9b**)	 (**10a**)	 (**10b**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]	1.56	1.56	1.56	3.13
S. epidermidis MB5181[b]	0.78	0.78	1.56	3.13
E. coli NlHJ JC2	0.05	0.2	0.025	0.05
P. aeruginosa AK109	6.25	6.25	0.78	1.56
P. aeruginosa AKR17[c]	>25	>25	3.13	6.25
DHP-I susceptibility[d]	0.16	<0.05	0.84	0.22
Epiletogenicity (200 μg/rat head, $n=5$)	5/5	5/5	5/5	NT[e]

[a]MIC (μg/mL) determined by agar dilution method.
[b]Methicillin-resistant.
[c]Ceftazidime-resistant.
[d]Relative rate of hydrolysis to imipenem, porcine renal DHP-I.
[e]Not tested.

Table 4. In vitro activity[a] and biological properties of J-111,225 (**2a**) and related compounds

Organism	(**2a**)	(**2b**)	(**2c**)	(**2d**)	(**2e**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]	0.78	1.56	3.13	1.56	1.56
S. epidermidis MB5181[b]	1.56	3.13	3.13	1.56	1.56
E. coli NlHJ JC2	0.025	0.05	0.10	0.025	0.05
P. aeruginosa AK109	0.39	0.78	0.78	1.56	0.78
P. aeruginosa AKR17[c]	1.56	6.25	6.25	6.25	6.25
DHP-I susceptibility[d]	0.25	0.22	0.27	0.44	0.46
Epiletogenicity (200 μg/rat head, $n=5$)	0/5	0/5	NT[e]	0/5	0/5
R Organism	(**2f**)	(**2g**)	(**2h**)	(**2i**)	(**2j**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]	3.13	1.56	1.56	1.56	1.56
S. epidermidis MB5181[b]	1.56	1.56	6.25	0.78	0.78
E. coli NlHJ JC2	0.025	0.05	0.025	0.05	0.012
P. aeruginosa AK109	1.56	0.78	1.56	1.56	0.78
P. aeruginosa AKR17[c]	6.25	6.25	3.13	6.25	3.13
DHP-I susceptibility[d]	0.31	0.31	0.12	0.25	NT[e]
Epiletogenicity (200 μg/rat head, $n=5$)	NT[e]	NT[e]	0/5	NT[e]	NT[e]

[a]MIC (μg/mL) determined by agar dilution method.
[b]Methicillin-resistant.
[c]Ceftazidime-resistant.
[d]Relative rate of hydrolysis to imipenem, porcine renal DHP-I.
[e]Not tested.

Table 5. In vitro activity[a] and biological properties of J-114,870 (**3a**), J-114,871 (**3b**), and related compounds

Organism	(**3a**)	(**3b**)	(**3c**)	(**3d**)	(**3e**)	(**3f**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]	1.56	1.56	3.13	1.56	3.13	0.39
S. epidermidis MB5181[b]	1.56	1.56	3.13	1.56	6.25	0.39
E. coli NlHJ JC2	0.025	0.025	0.025	0.025	0.05	0.025
P. aeruginosa AK109	0.78	1.56	1.56	1.56	1.56	3.13
P. aeruginosa AKR17[c]	1.56	1.56	6.25	6.25	12.5	6.25
DHP-I susceptibility[d]	0.27	0.27	0.32	0.41	0.46	0.22
Epiletogenicity (200 μg/rat head, $n=5$)	0/5	0/5	0/5	NT[e]	0/5	NT[e]
Organism	(**3g**)	(**3h**)	(**3i**)	(**3j**)	(**3k**)	(**3l**)
S. aureus 209P NlHJ JC1	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006	≤0.006
S. aureus pMS520/Smith[b]	1.56	1.56	1.56	1.56	1.56	1.56
S. epidermidis MB5181[b]	0.78	0.78	1.56	1.56	1.56	3.13
E. coli NlHJ JC2	0.025	0.025	0.10	0.05	0.025	0.025
P. aeruginosa AK109	3.13	0.78	3.13	1.56	3.13	1.56
P. aeruginosa AKR17[c]	12.5	3.13	25	6.25	6.25	12.5
DHP-I susceptibility[d]	0.27	0.55	0.20	0.37	0.32	0.29
Epiletogenicity (200 μg/rat head, $n=5$)	NT[e]	0/5	0/5	0/5	0/5	0/5

[a]MIC (μg/mL) determined by agar dilution method.
[b]Methicillin-resistant.
[c]Ceftazidime-resistant.
[d]Relative rate of hydrolysis to imipenem, porcine renal DHP-I.
[e]Not tested.

Table 6. Safety profile of selected compounds

Compound	(**1a**)	(**2a**)	(**3a**)	(**3b**)
Epiletogenicity[a] ED_{50} (μg/head, $n=5$)	ca. 76	>400	>400	>200
Acute toxicity in mice LD_{50} (mg/Kg, single i.v., $n=5$)	>1500	600∼700	ca. 1850	>1000
48-hour nephrotoxicity (225 mg/Kg, single i.v., $n=3$)	NT[b]	No change	No change	No change

[a]Injected intracerebroventricularly.
[b]Not tested.

10 mM 3-morpholino-propanesulfonate (MOPS) buffer/pH 7.0 on the day of use. The strains used in the study were from our collections; MRSA pMS520/Smith was a generous gift from M. Inoue, School of Medicine, Kitasato University, Japan.

Determination of MIC

MICs were determined by a two-fold serial agar dilution method using Mueller-Hinton medium (Difco Laboratories, Detroit, MI.). An overnight culture was diluted to give a final concentration of approximately 10^6 CFU/mL. A portion of the dilution was delivered onto a drug-containing agar surface with an inoculum apparatus (Microplanter: Sakuma Seisakusho, Co., Ltd, Tokyo, Japan). The final inoculum size was approximately 10^4 CFU per spot. The MIC was defined as the lowest concentration of antibiotics that completely prevented visible growth was inhibited.

Determination of susceptibility to renal dehydropeptidase-1 (DHP-I)

Relative hydrolysis rates of carbapenems by porcine renal DHP-I were determined, taking the initial hydrolysis rate of imipenem as 1.0. Partially purified porcine DHP-I (final concentration, 0.3 U/mL) was incubated with 50 μM carbapenem at 35 °C in 50 mM MOPS buffer/pH 7.0. The initial hydrolysis rate was monitored by the spectrophotometric method. One unit of activity was defined as the amount of enzyme hydrolyzing 1 μM of glycyldehydrophenylalanine per minute when the substrate, 50 μM, was incubated at 35 C in 50 mM MOPS buffer/pH 7.0.

Determination of epileptogenicity

Male SD rats, 7 weeks of age, were cannulated into the right cerebroventricle 1 week before of drug administration. The carbapenems were dissolved in saline, adjusted to pH 7.0, and an aliquot of 10 μl/head was injected intracerebroventricularly ($n=5$). Convulsant behavior was monitored for 30 min after administration.

General methods

Melting points were measured on a Yanaco MP micro-melting point apparatus and were not corrected. The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer and a JEOL JNM-A500 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-A500. IR

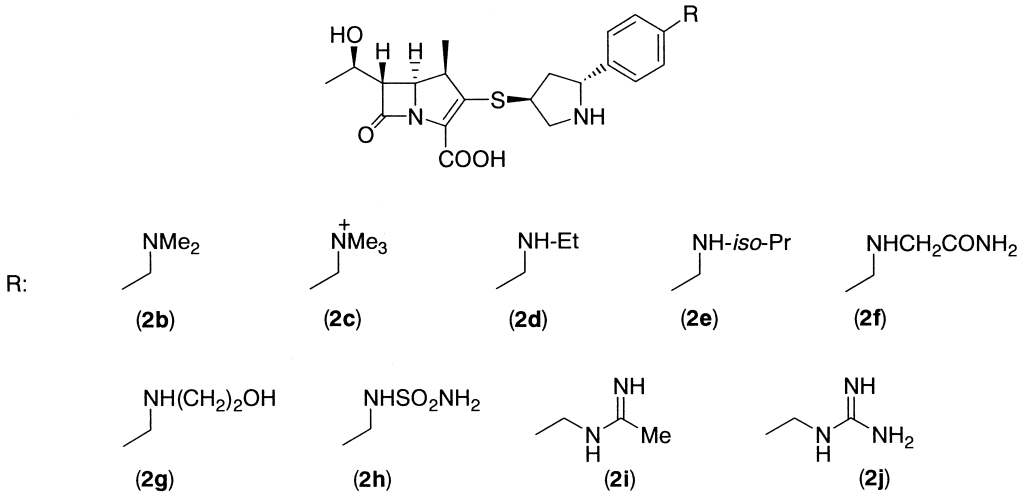


Figure 3.

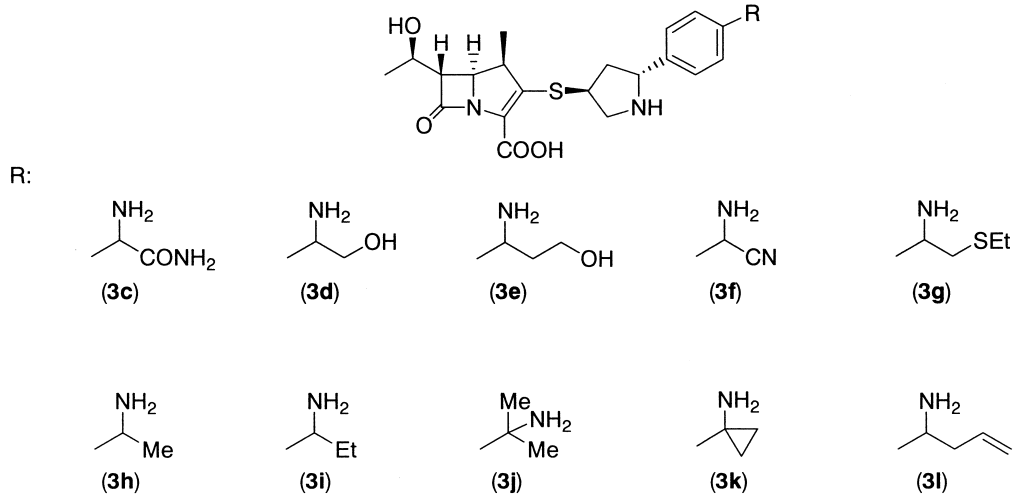


Figure 4.

absorption spectra were recorded with a Horiba FT-200 spectrometer. Specific rotations were measured with a Jasco DIP-370 polarimeter. UV spectra were taken on a SHIMAZU SPD-10A spectrometer in 0.1 M 3-morpholinopropanesulfonate buffer (pH 7.0). Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300. Reversed phase column chromatography was carried out on YMC-gel ODS-AQ 120-S50. All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques.

4a, **4b**, **5a**, **5b**, **6b** and **7b** were synthesized using a method described in the literature.[10,11]

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-(4-Aminomethylbenzyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 4a. IR ν_{max} (KBr) 3435, 1761, 1593, 1388 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.21 (3H, d, $J=7.8$ Hz), 1.37 (3H, d, $J=6.4$ Hz), 2.15 (1H, m), 2.44 (1H, m), 3.36 (5H, m), 3.87 (3H, m), 4.22 (2H, s), 4.30 (2H, m), 7.43 (4H, m); FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found: 432.1952.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(4-Aminomethylbenzyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 4b. IR ν_{max} (KBr) 3425, 1758, 1587, 1384 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.19 (3H, d, $J=7.2$ Hz), 1.28 (3H, d, $J=6.5$ Hz), 1.78 (1H, m), 2.71 (1H, m), 3.29 (5H, m), 3.83 (3H, m), 4.19 (2H, s), 4.22 (2H, m), 7.42 (4H, m); FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found: 432.1955; UV λ_{max}298 (ε 8410).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[(4-Aminomethylphenyl)thiomethyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 5a. IR ν_{max} (KBr) 1749, 1595, 1394, 1263 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.18 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=6.3$ Hz), 2.28 (2H, m), 3.35 (5H, m), 3.73 (1H, dd, $J=13.0$, 6.0 Hz), 4.03 (2H, m), 4.27 (4H, m), 7.45 (2H, d, $J=8.0$ Hz), 7.55 (2H, dd, $J=8.0$ Hz); FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_3O_4S_2$ $(M+H)^+$: 464.1678, Found: 464.1655; UV λ_{max} 297 (ε 7590).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-[(4-Aminomethylphenyl)thiomethyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 5b. IR ν_{max} (KBr) 3373, 1749, 1558, 1396, 1089 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.18 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.65 (1H, m), 2.64 (1H, m), 3.30 (3H, m), 3.46 (3H, m), 3.81 (2H, m), 4.16 (2H, s), 4.23 (2H, m), 7.43 (2H, d, J = 8.6 Hz), 7.54 (2H, d, J = 8.6 Hz); FAB-HRMS m/z calcd for $C_{22}H_{30}N_3O_4S_2$ $(M+H)^+$: 464.1678, Found: 464.1667; UV λ_{max}286 (ε 8290).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-[(4-Aminomethylphenyl)aminomethyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 6b. IR ν_{max} (KBr) 1749, 1595, 1394, 1263 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.17 (3H, d, J = 7.1 Hz), 1.24 (3H, d, J = 6.5 Hz), 1.71 (1H, m), 2.71 (1H, m), 3.30 (3H, m), 3.60 (3H, m), 4.01 (2H, m), 4.09 (2H, s), 4.18 (2H, m), 6.79 (2H, d, J = 8.6 Hz), 7.26 (2H, dd, J = 8.6 Hz); FAB-HRMS m/z calcd for $C_{22}H_{30}N_4O_4SNa$ $(M+Na)^+$: 469.1885, Found: 469.1874; UV λ_{max}300 (ε 10100).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-[(4-Aminomethylphenyl)oxymethyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 7b. IR ν_{max} (KBr) 3413, 1753, 1610, 1516, 1392, 1248 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.19 (3H, d, J = 7.2 Hz), 1.25 (3H, d, J = 6.5 Hz), 1.91 (1H, m), 2.76 (1H, m), 3.37 (3H, m), 3.68 (1H, dd, J = 12.2, 6.0 Hz), 4.10 (2H, s), 4.15 (5H, m), 4.38 (1H, m), 7.06 (2H, d, J = 8.7 Hz), 7.39 (2H, dd, J = 8.7 Hz); FAB-HRMS m/z calcd for $C_{22}H_{30}N_3O_5S$ $(M+H)^+$: 448.1906, Found: 448.1904; UV λ_{max}298 (ε 9220).

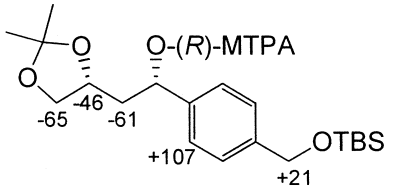
General procedure for the preparation of 5-aryl pyrrolidinylthio-1β-methylcarbapenems. The experimental procedure for **1a** was described as a representative example.

(3*R*)-1-(4-*tert*-Butyldimethylsiloxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutanol 12. To a solution of 4-(*tert*-butyldimethylsiloxymethyl)bromobenzene (14.6 g, 48.7 mmol) in THF (300 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 27.9 mL, 44.7 mmol) dropwise under a nitrogen atmosphere at −70 °C, and the mixture was stirred for 20 min at the same temperature. To this mixture was added a solution of **11** (5.86 g, 40.6 mmol) in THF (25 ml) dropwise under a nitrogen atmosphere at −70 °C. Work-up and purification in the usual manner gave **12** as a colorless oil (13.2 g, 88.8%): IR ν_{max} (KBr) 3518, 1516, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.92 (9H, s), 1.37 (3H, s), 1.46 (3H, s), 1.94 (2H, m), 3.57 (1H, m), 4.05 (1H, m), 4.26 (1H, m), 4.73 (2H, s), 4.92 (1H, m), 7.27 (2H, d, J = 9.3 Hz), 7.34 (2H, d, J = 9.3 Hz); FAB-HRMS m/z calcd for $C_{20}H_{34}O_4SiNa$ $(M+Na)^+$: 389.2124, Found: 389.2131.

(1*S*,3*R*)-1-(4-*tert*-Butyldimethylsiloxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutanol 13. To a solution of **12** (11.3 g, 30.8 mmol) and molecular sieve 4Å (15.4 g) in CH_2Cl_2 (100 mL) were added *N*-methylmorpholine *N*-oxide (5.4l g, 46.2 mmol) and tetrapropylammonium perruthenate (541 mg, 1.54 mmol) under a nitrogen atmosphere at 0 °C, and the mixture was stirred for 20 min at the same temperature. Work-up and purification in the usual manner gave (3*R*)-1-(4-*tert*-butyldimethylsiloxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutanone as a colorless oil (9.9 g, 88.0%): $[\alpha]_D^{20}$ −29.0 (c 1.0, $CHCl_3$); IR ν_{max} (KBr) 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.84 (9H, s), 1.29 (3H, s), 1.34 (3H, s), 2.99 (1H, dd, J = 17.3, 7.1 Hz), 3.44 (1H, dd, J = 17.3, 5.0 Hz), 3.53 (1H, dd, J = 8.4, 6.6 Hz), 4.20 (1H, dd, J = 8.4, 6.1 Hz), 4.53 (1H, m), 4.69 (2H, s), 7.31 (2H, d, J = 8.3 Hz), 7.82 (2H, d, J = 8.3 Hz); FAB-HRMS m/z calcd for $C_{20}H_{32}O_4SiNa$ $(M+Na)^+$: 387.1968, Found: 387.1967. **13** was obtained by reduction with the $LiAlH_4$-LiI system described by Mori and Suzuki.[15]

To a solution of the butanone described above (2.80 g, 7.69 mmol) in Et_2O (50 mL) was added LiI (10.29 g, 76.9 mmol) under a nitrogen atmosphere at −40 °C and the mixture was stirred for 5 min at the same temperature. The resulting mixture was then cooled to −78 °C and $LiAlH_4$ (2.91 g, 76.9 mmol) 5w > was added. The mixture was stirred for 30 min. Work-up and purification in the usual manner gave **13** as a colorless oil (2.14 g, 76.2%): [HPLC analysis: column, DAICEL CHIRALPAK AS (250×4.6 mm); detection, 254 nM; eluent, *n*-hexane/isopropanol = 90:10; flow rate, 0.5 mL/min; t_R of **13**, 9.1 min; t_R of corresponding 1*R* isomer, 8.6 min]. 90% de, $[\alpha]_D^{20}$ −27.4 (c 1.0, $CHCl_3$); IR ν_{max} (KBr) 3518, 1518, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.92 (9H, s), 1.37 (3H, s), 1.46 (3H, s), 1.89 (1H, m), 1.98 (1H, m), 3.53 (1H, dd, J = 8.1, 8.1 Hz), 4.03 (1H, dd, J = 8.1, 5.9 Hz), 4.23 (1H, m), 4.72 (2H, s), 4.89 (1H, dd, J = 8.5, 4.2 Hz), 7.27 (2H, d, J = 8.5 Hz), 7.32 (2H, d, J = 8.5 Hz); FAB-HRMS m/z calcd for $C_{20}H_{34}O_4SiNa$ $(M+Na)^+$: 389.2124, Found: 389.2112.

The stereochemical structure of **13** is shown below ($\Delta\delta\times10^{-3}$ ppm), which was determined by the advanced Mosher method with the corresponding MTPA esters.[16]



(1*R*,3*R*)-*N*-Allyloxycarbonyl-1-(4-azidomethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutylamine 14. To a solution of **13** (1.31 g, 3.56 mmol) in THF (30 mL) were added triphenylphosphine (1.97 g, 7.5 mmol), diethyl azodicarboxylate (1.12 ml, 7.14 mmol) and diphenylphosphoryl azide (1.54 mL, 7.14 mmol) dropwise under a nitrogen atmosphere at 0 °C, and the mixture was stirred for 20 min at the same temperature. Work-up and purification in the usual manner gave (1*R*,3*R*)-1-(4-*tert*-butyldimethylsiloxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutylazide as a colorless oil (1.21 g, 86.4%): ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.93 (9H, s), 1.31 (1H, s), 1.36 (2H, s), 1.41 (3H, s), 1.93 (2H, m), 3.54 (1H, m), 4.09 (1H, m), 4.34 (1H, m), 4.64 (1H, m), 4.72 (2H, s), 7.34 (4H, m); FAB–MS m/z 392 $(M+H)^+$. To a solution of the azide described above (1.03 g, 2.62 mmol) in THF (30 mL) and H_2O (6 mL)

was added triphenylphosphine (1.38 g, 5.26 mmol), and the mixture was stirred for 5 h at 50 °C. After evaporation under reduced pressure, to a solution of the residue in THF (60 mL) were added triethylamine (1.32 g, 13.1 mmol) and allyl chloroformate (420 μL, 3.94 mmol) at 0 °C. Work-up and purification in the usual manner gave (1*R*,3*R*)-*N*-allyloxycarbonyl-1-(4-*tert*-butyldimethylsiloxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutylamine as a colorless oil (1.019 g, 90.8%): $[\alpha]_D^{20}$ +44.1 (c 1.0, $CHCl_3$); IR ν_{max} (KBr) 1733, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.96 (9H, s), 1.33 (3H, s), 1.44 (3H, s), 1.94 (1H, m), 2.08 (1H, m), 3.46 (1H, m), 3.87 (1H, m), 4.50 (2H, m), 4.69 (2H, s), 4.96 (1H, m), 5.22 (2H, m), 5.79 (1H, m), 7.24 (2H, d, J = 7.5 Hz), 7.27 (2H, d, J = 7.5 Hz); FAB-HRMS m/z calcd for $C_{24}H_{39}NO_5SiNa$ $(M+Na)^+$: 472.2495, Found: 472.2500. To a solution of above (1.25 g, 2.75 mmol) in THF (30 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 3.75 mL, 3.75 mmol) dropwise under a nitrogen atmosphere at 0 °C, and the mixture was stirred for 30 min at the same temperature. Work-up and purification in the usual manner gave (1*R*,3*R*)-*N*-allyloxycarbonyl-1-(4-hydroxymethylphenyl)-3,4-*O*-isopropylidene-3,4-dihydroxybutylamine as a colorless oil (917 mg, 98.3%): IR ν_{max} (KBr) 3543, 1708, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s), 1.44 (3H, s), 1.95(1H, m), 2.07 (1H, m), 3.50 (1H, m), 3.98 (2H, m), 4.55 (2H, m), 4.64 (2H, s), 4.99 (1H, m), 5.22 (2H, m), 5.90 (1H, m), 7.27 (4H, m); FAB-HRMS m/z calcd for $C_{18}H_{25}NO_5Na$ $(M+Na)^+$: 358.1630, Found: 358.1631. To a solution of above (835 mg, 2.49 mmol) in CH_2Cl_2 (30 mL) were added triethylamine (1.74 mL, 12.5 mmol) and methanesulfonyl chloride (290 μL, 3.75 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and the mixture was evaporated under reduced pressure. To a solution of the residue in DMF (50 mL) was added sodium azide (485 mg, 7.45 mmol), and the mixture was stirred for 5 h at room temperature. Work-up and purification in the usual manner gave **14** as a colorless oil (818 mg, 91.3%): $[\alpha]_D^{20}$ +23.5 (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 1760, 1703, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (3H, s), 1.44 (3H, s), 1.87 (1H, m), 2.02 (1H, m), 3.47 (1H, m), 3.92 (2H, m), 4.32 (2H, s), 4.56(2H, m), 4.50 (1H, m), 5.22 (2H, m), 5.90 (1H, m), 7.29 (4H, s); FAB-HRMS m/z calcd for $C_{18}H_{24}N_4O_4Na$ $(M+Na)^+$: 383.1695, Found: 383.1683.

(1*R*,3*R*)-*N*-Allyloxycarbonyl-1-(4-*N*-allyloxycarbonylaminomethyl)phenyl-3,4-dihydroxybutylamine 15. To a solution of **14** (1.14 g, 3.17 mmol) in THF (40 mL) and H_2O (8 mL) was added triphenylphosphine (1.25 g, 4.76 mmol), and the mixture was stirred for 2 h at room temperature. After evaporation under reduced pressure, to a solution of the residue in THF (70 mL) were added triethylamine (2.23 mL, 16.0 mmol) and allyl chloroformate (507 μL, 4.76 mmol) at 0 °C. The reaction mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a solution of the residue in MeOH (20 mL) was added 10% HCl/MeOH (10 mL), and the mixture was stirred for 1 h at room temperature. Work-up and purification in the usual manner gave **15** as a colorless oil (941 mg, 78.6%): $[\alpha]_D^{20}$ +56.0 (*c* 0.5, $CHCl_3$); IR ν_{max} (Nujol) 3413, 1732, 1695, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.80 (1H, m), 2,36 (1H, m), 3.46 (1H, m), 3.54 (1H, m), 3.77 (2H, m), 4.32 (2H, s), 4.58 (4H, m), 4.97 (1H, m), 5.22 (4H, m), 5.53 (1H, m), 5.88 (2H, m), 7.27 (4H, s); FAB-HRMS m/z calcd for $C_{19}H_{26}N_2O_6Na$ $(M+Na)^+$: 401.1689, Found: 401.1676.

(2*R*,4*R*)-2-[4-(*N*-Allyloxycarbonylanimomethyl)phenyl]-1-allyloxycarbonyl-4-mesyloxypyrrolidine 16. To a solution of **15** (243 mg, 0.64 mmol) in CH_2Cl_2 (8 mL) were added triethylamine (259 mg, 2.56 mmol) and methanesulfonyl chloride (150 μL, 1.93 mmol) under a nitrogen atmosphere at 0 °C. The reaction mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and the mixture was evaporated under reduced pressure. To a solution of the residue in THF (10 mL) was added potassium *tert*-butoxide (160 mg, 1.42 mmol) under a nitrogen atmosphere at −20 °C. Work-up and purification in the usual manner gave **16** as a colorless oil (274 mg, 97.3%): $[\alpha]_D^{20}$ +29.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (Nujol) 1693, 1248, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (1H, m), 2.69 (3H, s), 2.71 (1H, m), 3.90 (1H, m), 4.02 (1H, m), 4.29 (2H, m), 4.53 (4H, m), 5.02 (3H, m), 5.23 (3H, m), 5.90 (2H, m), 7.22 (4H, s); FAB-HRMS m/z calcd for $C_{20}H_{26}N_2O_7SNa$ $(M+Na)^+$: 461.1358, Found: 461.1367.

(2*R*,4*S*)-4-Acetylthio-2-[4-(*N*-allyloxycarbonylanimomethyl)phenyl]-1-allyloxycarbonylpyrrolidine 17. To a solution of **16** (274 mg, 0.62 mmol) in DMF (10 mL) was added potassium thioacetate (215 mg, 1.88 mmol) under a nitrogen atmosphere at room temperature, and the mixture was sttired for 3 h at 65 °C. Work-up and purification in the usual manner gave **17** as a colorless oil (227 mg, 86.8%): $[\alpha]_D^{20}$ +36.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (Nujol) 1699, 1249, 769, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22 (1H, m), 2.34 (3H, s), 3.60 (1H, m), 4.03 (2H, m), 4.34 (2H, m), 4.56 (4H, m), 5.02 (3H, m), 5.26 (3H, m), 5.90 (2H, m), 719 (4H, m) ; FAB-HRMS m/z calcd for $C_{22}H_{28}N_2O_5SNa$ $(M+Na)^+$: 455.1617, Found: 455.1619.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-(4-Aminomethylphenyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 1a (J-111,347). To an ice-cooled solution of **17** (227 mg, 0.54 mmol) in MeOH (8 mL) was added 1 M aqueous NaOH (540 μL) under a nitrogen atmosphere. After being stirred for 20 min at 0 °C, the reaction mixture was adjusted to pH 7.0 with 1 M aqueous HCl and concentrated under reduced pressure. The mixture was poured into H_2O, and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a stirred solution of the residue and allyl (1*R*,5*S*,6*S*)-2-diphenylphosphoryloxy-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate (**18**, 271 mg, 0.54 mmol) in CH_3CN (10 mL) was added diisopropylethylamine (153 μL, 0.87 mmol) dropwise at 0 °C. After being stirred overnight at 4 °C, the mixture was poured into H_2O, and the whole was extracted with EtOAc. Work-up and purification in the

usual manner gave the adduct, allyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-1-allyloxycarbonyl-5-[4-(*N*-allyloxycarbonylaminomethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate as a foam (222 mg, 65.4%): IR ν_{max} (KBr) 3373, 2966, 1751, 1587, 1392, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, $J=7.0$ Hz), 1.36 (3H, d, $J=6.2$ Hz), 2.24 (1H, m), 2.41 (1H, m), 3.21 (1H, dd, $J=7.2$, 2.4 Hz), 3.30 (1H, m), 3.78 (2H, m), 4.03 (1H, m), 4.24 (2H, m), 4.49 (5H, m), 4.63 (2H, m), 4.64 (1H, m), 4.75 (1H, m), 5.04 (2H, m), 5.26 (4H, m), 5.43 (1H, m), 5.94 (2H, m), 7.20 (4H, m); FAB-HRMS *m/z* calcd for $C_{32}H_{40}N_3O_8S$ $(M+H)^+$: 626.2536, Found: 626.2534. To an ice-cooled solution of above (210 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) were successively added H_2O (30 μL), bis(triphenylphosphine) palladium(II) dichloride (11.8 mg, 0.017 mmol), and tributyltin hydride (329 μL, 1.22 mmol) under a nitrogen atmosphere. Work-up and purification in the usual manner gave **1a** as an amorphous powder (110 mg, 72.9%): IR ν_{max} (KBr) 3421, 1749, 1646, 1558 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.0$ Hz), 1.27 (3H, d, $J=6.5$ Hz), 2.51 (1H, m), 2.73 (1H, m), 3.40 (3H, m), 3.86 (1H, dd, $J=12.5$, 6.0 Hz), 4.25 (5H, m), 5.03 (1H, dd, $J=10.5$, 7.0 Hz), 7.20 (4H, m); FAB-HRMS *m/z* calcd for $C_{21}H_{28}N_3O_4S$ $(M+H)^+$: 418.1801, Found: 418.1800; UV λ_{max}298 (ε 9520).

(1*S*,3*R*)-*N*-Allyloxycarbonyl-1-(4-azidomethylphenyl)-4-*tert*-butyldimethylsiloxy-3-hydroxybutylamine 20a and (1*R*,3*R*)-*N*-Allyloxycarbonyl-1-(4-azidomethylphenyl)-4-*tert*-butyldimethylsiloxy-3-hydroxybutylamine 20b. To a solution of **19** (650 mg, 2.03 mmol) in CH_2Cl_2 (15 mL) were added imidazole (208 mg, 3.05 mmol) and *tert*-butyldimethylchlorosilane (368 mg, 2.44 mmol) and the mixture was stirred overnight at room temperature. Work-up and purification in the usual manner gave **20a** as a colorless oil (263 mg, 29.8%) and **20b** as colorless oil (358 mg, 40.5%). **20a**: $[\alpha]_D^{20}$ −21.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 3524, 1703, 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.86 (1H, m), 2.49 (1H, m), 3.39 (1H, dd, $J=9.8$, 5.7 Hz), 3.54 (1H, dd, $J=9.8$, 3.5 Hz), 3.60 (1H, m), 4.22 (2H, s), 4.59 (2H, m), 4.76 (1H, m), 5.22 (2H, m), 5.89 (1H, m), 7.27 (4H, s); FAB-HRMS *m/z* calcd for $C_{21}H_{34}N_4O_4SiNa$ $(M+Na)^+$: 457.2247, Found: 457.2247. **20b**; $[\alpha]_D^{20}$ +39.4 (*c* 1.0, $CHCl_3$); IR ν_{max} (KBr) 3525, 1709, 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.84 (9H, s), 1.78 (1H, m), 2.92 (1H, m), 3.41 (2H, m), 3.74 (1H, m), 4.38 (2H, s), 4.53 (2H, m), 5.03 (2H, m), 5.21 (1H, m), 5.79 (1H, m), 7.27 (4H, s); FAB-HRMS *m/z* calcd for $C_{21}H_{34}N_4O_4SiNa$ $(M+Na)^+$: 457.2247, Found: 457.2233.

The following compounds (**1b**, **2a**–**j**, **3a**–**l**, **8a**, **8b**, **9a**, **9b**, **10a** and **10b**) were prepared as described for the preparation of **1a** or according to the method described in the literature.[13]

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(4-Aminomethylphenyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 1b. IR ν_{max} (KBr) 3421, 1749, 1652, 1558 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.0$ Hz), 1.27 (3H, d, $J=6.0$ Hz), 2.14 (1H, m), 3.00 (1H, m), 3.37 (1H, m), 3.46 (2H, m), 3.80 (1H, m), 4.14 (1H, m), 4.20 (2H, s), 4.24 (1H, m), 7.52 (2H, d, $J=8.0$ Hz), 7.55 (2H, d, $J=8.0$ Hz); FAB-HRMS *m/z* calcd for $C_{21}H_{28}N_3O_4S$ $(M+H)^+$: 418.1801, Found: 418.1793; UV λ_{max}298 (ε 9910).

(1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(3*S*,5*R*)-5-[4-(*N*-methylaminomethyl)phenyl]pyrrolidin-3-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid dihydrochloride 2a (J-111,225). $[\alpha]_D^{20}$ +9.0 (*c* 1.0, H_2O); IR (KBr) ν_{max} 3373, 1751, 1587, 1392, 1086 cm^{-1}; ^1H NMR (500 MHz, D_2O, as a hydrochloride) δ 1.02 (3H, d, $J=7.3$ Hz), 1.08 (3H, d, $J=6.4$ Hz), 2.33 (1H, dd, $J=14.0$, 6.7 Hz), 2.52 (3H, s), 2.57 (1H, m), 3.17 (1H, dq, $J=9.1$, 7.3 Hz), 3.27 (2H, m), 3.70 (1H, dd, $J=12.8$, 5.8 Hz), 4.04 (5H, m), 4.88 (1H, dd, $J=11.0$, 6.7 Hz), 7.35 (4H, m); ^{13}C NMR (125 MHz, D_2O, as a hydrochloride) δ 15.4, 19.7, 31.9, 35.9, 40.7, 42.1, 51.4, 51.9, 55.6, 58.5, 61.2, 64.7, 128.1, 130.2, 131.8, 134.2, 135.2, 136.7, 167.3, 176.3; FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found 432.1950. Anal. calcd for $C_{22}H_{29}N_3O_4S{\cdot}2HCl{\cdot}H_2O$: C,50.57; H, 6.37; N, 8.04; S, 6.14; Found: C, 50.87; H, 6.45; N, 7.83; S, 6.02.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(*N*,*N*-Dimethylaminomethyl)-phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2b. IR ν_{max} (KBr) 3371, 2968, 1755, 1589, 1390, 1286, 1263, 1074 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=6.6$ Hz), 2.55 (1H, m), 2.74 (1H, m), 2.83 (6H, s), 3.37 (1H, m), 3.50 (2H, m), 3.88 (1H, m), 4.22 (3H, m), 4.32 (2H, s), 5.08 (1H, m), 7.56 (4H, m); FAB-HRMS *m/z* calcd for $C_{23}H_{32}N_3O_4S$ $(M+H)^+$: 446.2114, Found: 446.2109; UV λ_{max}298 (ε 10940).

(1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(3*S*,5*R*)-5-[4-(*N*,*N*,*N*-trimethylammoniomethyl)phenyl]pyrrolidin-3-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylate hydrochloride 2c. IR ν_{max} (KBr) 3402, 2968, 1751, 1589, 1389, 1288, 1263, 1074 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=6.3$ Hz), 2.55 (1H, m), 2.78 (1H, m), 3.08 (9H, s), 3.38 (1H, m), 3.52 (2H, m), 3.85 (1H, m), 4.22 (3H, m), 4.51 (2H, s), 5.14 (1H, m), 7.63 (4H, m); FAB-HRMS *m/z* calcd for $C_{24}H_{34}N_3O_4S$ $(M+H)^+$: 460.2270, Found: 460.2266; UV λ_{max}298 (ε 8930).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(*N*-Ethylaminomethyl)phenyl]-pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2d. IR ν_{max} (KBr) 1749, 1558, 1394 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.24 (9H, m), 2.52 (1H, m), 2.75 (1H, m), 3.11 (2H, q, $J=7.3$ Hz), 3.36 (1H, m), 3.47 (2H, m), 3.88 (1H, m), 4.24 (5H, m), 5.08 (1H, m), 7.55 (4H, m); FAB-HRMS *m/z* calcd for $C_{23}H_{32}N_3O_4S$ $(M+H)^+$: 446.2114, Found: 446.2113; UV λ_{max}298 (ε 9190).

(1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(3*S*,5*R*)-5-[4-(*N*-isopropylaminomethyl)phenyl]pyrrolidin-3-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2e. IR ν_{max} (KBr) 1751,1650, 1618, 1394 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.3$ Hz), 1.26 (3H, d, $J=6.3$ Hz), 1.35 (6H, d, $J=6.6$ Hz), 2.52 (1H, m), 2.75 (1H, m), 3.38 (4H, m), 3.88 (1H, m), 4.20 (5H, m), 5.08 (1H, m), 7.54 (4H, m); FAB-HRMS *m/z* calcd for

$C_{24}H_{34}N_3O_4S$ $(M+H)^+$: 460.2270, Found: 460.2265; UV λ_{max}298 (ε 8640).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[*N*-(Carbamoylmethyl)aminomethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2f. IR ν_{max} (KBr) 1751, 1677, 1587, 1392 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.21 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=6.5$ Hz), 2.47 (1H, m), 2.74 (1H, m), 3.39 (3H, m), 3.52 (2H, s), 3.86 (1H, dd, $J=12.5$, 5.9 Hz), 3.96 (2H, s), 4.22 (3H, m), 5.00 (1H, m), 7.47 (4H, s); FAB-HRMS *m/z* calcd for $C_{23}H_{31}N_4O_5S$ $(M+H)^+$: 475.2015, Found: 475.2033; UV λ_{max}298 (ε 10700).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[*N*-(2-Hydroxyethyl)aminomethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2g. IR ν_{max} (KBr) 1749, 1558, 1394, 1081 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.0$ Hz), 1.27 (3H, d, $J=6.3$ Hz), 2.51 (1H, m), 2.72 (1H, m), 3.17 (2H, m), 3.40 (3H, m), 3.84 (3H, m), 4.24 (5H, m), 5.03 (1H, m), 7.53 (4H, m); FAB-HRMS *m/z* calcd for $C_{23}H_{32}N_3O_5S$ $(M+H)^+$: 462.2063, Found: 462.2048; UV λ_{max}298 (ε 9600).

(1*R*,5*S*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(3*S*,5*R*)-5-[4-(sulfamoylaminomethyl)phenyl]pyrrolidin-3-ylthio]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2h. IR ν_{max} (KBr) 1753, 1589, 1394, 1152 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.24 (3H, d, $J=7.0$ Hz), 1.29 (3H, d, $J=6.5$ Hz), 2.49 (1H, m), 2.74 (1H, m), 3.40 (3H, m), 3.76 (1H, m), 4.22 (3H, m), 5.02 (1H, m), 7.48 (4H, m); FAB–MS *m/z* 497 $(M+H)^+$; UV λ_{max}298 (ε 10200).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[*N*-(Acetimidoyl)aminomethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2i. IR ν_{max} (KBr) 1749, 1681, 1648, 1560, 1394 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.21 (3H, d, $J=7.1$ Hz), 1.26 (3H, d, $J=6.3$ Hz), 2.26 (3H, s), 2.48 (1H, m), 2.78 (1H, m), 3.36 (1H, m), 3.48 (2H, m), 3.87 (1H, dd, $J=12.5$, 5.9 Hz), 4.21 (3H, m), 4.51 (2H, s), 5.05 (1H, m), 7.42 (2H, d, $J=8.3$ Hz), 7.49 (2H, d, $J=8.3$ Hz); FAB-HRMS *m/z* calcd for $C_{23}H_{31}N_4O_4S$ $(M+H)^+$: 459.2066, Found: 459.2094; UV λ_{max}298 (ε 7590).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(Guanidinoaminomethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 2j. IR ν_{max} (KBr) 1749, 1653, 1558, 1396, 804 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.3$ Hz), 1.26 (3H, d, $J=6.6$ Hz), 2.48 (1H, m), 2.79 (1H, m), 3.38 (1H, m), 3.43 (2H, m), 3.87 (1H, m), 4.21 (3H, m), 4.51 (2H, s), 5.02 (1H, m), 7.46 (4H. m); FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_5O_4S$ $(M+H)^+$: 460.2019, Found: 460.2045; UV λ_{max}298 (ε 8640).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[(*S*)-1-Amino-2-carbamoylethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3a (J-114,870). $[\alpha]_D^{20}$ +1.2 (*c* 1.0, H_2O); IR (KBr) ν_{max} 1751, 1672, 1585, 1388, 1259, 1147, 773, 665 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.04 (3H, d, $J=7.0$ Hz), 1.08 (3H, d, $J=6.4$ Hz), 2.36 (1H, dd, $J=14.0$, 7.0 Hz), 2.61 (1H, m), 2.81 (1H, dd, $J=15.6$, 7.3 Hz), 2.88 (1H, dd, $J=15.6$, 7.3), 3.18 (1H, dq, $J=8.8$, 7.0 Hz), 3.28 (1H, dd, $J=5.8$, 2.8 Hz), 3.31 (1H, br d, $J=12.8$ Hz), 3.72 (1H, dd, $J=12.8$, 5.8 Hz), 4.05 (3H, m), 4.59 (1H, t, $J=7.3$ Hz), 4.92 (1H, dd, $J=11.0$, 7.0 Hz), 7.36 (4H, m); ^{13}C NMR (125 MHz, D_2O) δ 15.3, 19.7, 35.7, 37.8, 40.7, 42.0, 51.2, 51.8, 55.6, 58.5, 61.2, 64.7, 127.6, 128.2, 134.3, 134.7, 136.3, 136.5, 167.3, 173.3, 176.3; FAB-HRMS *m/z* calcd for $C_{23}H_{31}N_4O_5S$ $(M+H)^+$: 475.2015, Found 475.2011. Anal. calcd for $C_{22}H_{30}N_4O_5S{\cdot}HCl{\cdot}2H_2O$: C, 50.50; H, 6.45; N, 10.24; S, 5.86; Found: C, 50.61; H, 6.55; N, 10.32; S, 5.60.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[(*R*)-1-Amino-2-carbamoylethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3b (J-114,871). $[\alpha]_D^{20}$ −12.6 (*c* 1.0, H_2O); IR (KBr) ν_{max} 3417, 1751, 1673, 1583, 1390, 1261, 1147, 572 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.04 (3H, d, $J=7.3$ Hz), 1.08 (3H, d, $J=6.4$ Hz), 2.36 (1H, dd, $J=14.0$, 6.7 Hz), 2.60 (1H, m), 2.81 (1H, dd, $J=15.8$, 7.3 Hz), 2.88 (1H, dd, $J=15.8$, 7.3), 3.18 (1H, dq, $J=9.4$, 7.3 Hz), 3.28 (1H, dd, $J=6.1$, 2.8 Hz), 3.31 (1H, br d, $J=12.8$ Hz), 3.72 (1H, dd, $J=12.8$, 5.8 Hz), 4.05 (3H, m), 4.59 (1H, t, $J=7.3$ Hz), 4.92 (1H, dd, $J=11.0$, 6.7 Hz), 7.36 (4H, m); ^{13}C NMR (125 MHz, D_2O) δ 15.3, 19.7, 35.7, 37.8, 40.7, 42.0, 51.2, 51.8, 55.6, 58.5, 61.2, 64.7, 127.6, 128.2, 134.3, 134.7, 136.3, 136.5, 167.3, 173.3, 176.3; FAB-HRMS *m/z* calcd for $C_{23}H_{31}N_4O_5S$ $(M+H)^+$: 475.2015, Found 475.2042. Anal. calcd for $C_{22}H_{30}N_4O_5S{\cdot}HCl{\cdot}2H_2O$: C, 50.50; H, 6.45; N, 10.24; S, 5.86; Found: C, 50.80; H, 6.66; N, 10.18; S, 5.65.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-1-carbamoylmethyl)-phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3c. IRν_{max} (KBr) 1749, 1697, 1394 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, $J=7.3$ Hz), 1.26 (3H, d, $J=6.3$ Hz), 2.55 (1H, m), 2.78 (1H, m), 3.36 (1H, m), 3.50 (2H, m), 3.90 (1H, m), 4.23 (3H, m), 5.14 (2H, m), 7.57 (4H, m); FAB-HRMS *m/z* calcd for $C_{22}H_{29}N_4O_5S$ $(M+H)^+$: 461.1859, Found: 461.1847; UV λ_{max}299 (ε 8940).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-2-hydroxyethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3d. IR ν_{max} (KBr) 1745, 1650, 1540, 1396 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=7.0$ Hz), 2.54 (1H, m), 2.78 (1H, m), 3.38 (1H, m), 3.44 (2H, m), 3.90 (3H, m), 4.23 (3H, m), 4.51 (1H, m), 5.10 (1H, m), 7.53 (4H, m); FAB-HRMS *m/z* calcd for $C_{22}H_{30}N_3O_5S$ $(M+H)^+$: 448.1906, Found: 448.1902; UV λ_{max}299 (ε 9420).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-3-hydroxypropyl)-phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3e. IR ν_{max} (KBr) 1743, 1650, 1560, 1540 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23 (3H, d, $J=7.3$ Hz), 1.27 (3H, d, $J=6.5$ Hz), 2.20 (2H, m), 2.52 (1H, m), 2.73 (1H, m), 3.40 (4H, m), 3.60 (1H, m), 3.85 (1H, m), 4.24 (3H, m), 4.52 (1H, m), 5.03 (1H, m), 7.51 (2H, d, $J=8.6$ Hz), 7.55 (2H, d, $J=8.6$ Hz); FAB-HRMS *m/z* calcd for $C_{23}H_{32}N_3O_5S$

$(M+H)^+$: 462.2063, Found: 462.2064; UV λ_{max}298 (ε 9750).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-1-cyanomethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3f. IR ν_{max} (KBr) 2240, 1749, 1648, 1560, 1394 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.52 (1H, m), 2.73 (1H, m), 3.40 (3H, m), 3.78 (1H, m), 4.24 (2H, m), 5.08 (2H, m), 7.57 (4H, m); FAB–MS m/z 443 $(M+H)^+$; UV λ_{max}298 (ε 10300).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-2-ethylthioethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3g. IR ν_{max} (KBr) 1743, 1650, 1558, 1540 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.17 (3H, d, J = 7.4 Hz), 1.23 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.3 Hz), 2.51 (2H, q, J = 7.3 Hz), 2.55 (1H, m), 2.78 (1H, m), 3.13 (2H, m), 3.36 (1H, m), 3.47 (2H, m), 3.88 (1H, m), 4.24 (3H, m), 4.55 (1H, m), 5.06 (1H, m), 7.55 (4H, m); FAB-HRMS m/z calcd for $C_{24}H_{34}N_3O_4S_2$ $(M+H)^+$: 492.1991, Found: 492.1973; UV λ_{max}300 (ε 9810).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Aminoethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3h. IR ν_{max} (KBr) 1751, 1576, 1456, 1389, 1286, 1261, 1146 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.2 Hz), 1.62 (3H, d, J = 6.9 Hz), 2.51 (1H, dd, J = 14.1, 6.1 Hz), 2.75 (1H, m), 3.36 (1H, m), 3.46 (2H, m), 3.87 (1H, dd, J = 12.5, 6.0 Hz), 4.22 (3H, m), 4.55 (1H, q, J = 6.9 Hz), 5.05 (1H, dd, J = 11.1, 6.7 Hz), 7.52 (4H, s); FAB-HRMS m/z calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found: 432.1955; UV λ_{max}298 (ε 9580).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Aminopropyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3i. IR ν_{max} (KBr) 1751, 1626, 1568, 1392, 1267 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.83 (3H, t, J = 7.4 Hz), 1.21 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.99 (2H, m), 2.47 (1H, m), 2.71 (1H, m), 3.38 (3H, m), 3.84 (1H, dd, J = 12.6, 5.9 Hz), 4.22 (4H, m), 5.00 (1H, dd, J = 10.8, 6.7 Hz), 7.48 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.6 Hz); FAB-HRMS m/z calcd for $C_{23}H_{32}N_3O_4S$ $(M+H)^+$: 446.2114, Found: 446.2114; UV λ_{max}298 (ε 8210).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-1-methylethyl)phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3j. IR ν_{max} (KBr) 2972, 1753, 1626, 1583, 1394, 1302, 579 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.5 Hz), 1.74 (6H, s), 2.54 (1H, m), 2.80 (1H, m), 3.39 (1H, m), 3.50 (2H, m), 3.91 (1H, m), 4.24 (3H, m), 5.11 (1H, m), 7.58 (4H, m); FAB-HRMS m/z calcd for $C_{23}H_{32}N_3O_4S$ $(M+H)^+$: 446.2114, Found: 446.2089; UV λ_{max}298 (ε 8170).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Aminocyclopropyl)phenyl]-pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3k. IR ν_{max} (KBr) 1749, 1558, 1394, 1261 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.27 (8H, m), 1.36 (2H, m), 2.49 (1H, m), 2.72 (1H, m), 3.46 (3H, m), 3.84 (1H, dd, J = 13.0, 6.0 Hz), 4.20 (3H, m), 5.03 (1H, dd, J = 11.0, 7.0 Hz), 7.49 (4H, s); FAB-HRMS m/z calcd for $C_{23}H_{30}N_3O_4S$ $(M+H)^+$: 444.1957, Found: 444.1954; UV λ_{max}298 (ε 9650).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-(1-Amino-3-butenyl)phenyl]-pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 3l. IR ν_{max} (KBr) 1749, 1616, 1396, 1288 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.54 (1H, m), 2.75 (2H, dd, J = 7.1, 7.1 Hz), 2.80 (1H, m), 3.37 (1H, m), 3.49 (2H, m), 3.91 (1H, m), 4.23 (3H, m), 4.48 (1H, t, J = 7.4 Hz), 5.10 (1H, m), 5.18 (2H, m), 5.69 (1H, m), 7.53 (4H, m); FAB-HRMS m/z calcd for $C_{24}H_{32}N_3O_4S$ $(M+H)^+$: 458.2114, Found: 458.2104; UV λ_{max}298 (ε 9030).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-(4-Aminoethylphenyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 8a. IR ν_{max} (KBr) 1747, 1583, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.21 (3H, d, J = 7.1 Hz), 1.25 (3H, d, J = 6.3 Hz), 2.47 (1H, m), 2.74 (1H, m), 3.01 (2H, t, J = 7.2 Hz), 3.26 (2H, t, J = 7.2 Hz), 3.35 (1H, m), 3.46 (2H, m), 3.83 (1H, m), 4.22 (3H, m), 5.03 (1H, m), 7.37 (2H, d, J = 8.3 Hz), 7.45 (2H, d, J = 8.3 Hz); FAB-HRMS m/z calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found: 432.1947; UV λ_{max}298 (ε 9190).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(4-Aminoethylphenyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 8b. IR ν_{max} (KBr) 1747, 1621, 1153, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.22 (3H, d, J = 6.9 Hz), 1.27 (3H, d, J = 6.6 Hz), 2.19 (1H, m), 3.00 (3H, m), 3.27 (2H, t, J = 7.7 Hz), 3.46 (1H, m), 3.49 (2H, m), 3.77 (1H, m), 4.13 (1H, m), 4.22 (2H, m), 4.81 (1H, m), 7.39 (2H, d, J = 7.7 Hz), 7.50 (2H, d, J = 7.7 Hz); FAB-HRMS m/z calcd for $C_{22}H_{30}N_3O_4S$ $(M+H)^+$: 432.1957, Found: 432.1967; UV λ_{max}298 (ε 9440).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-(4-Aminomethyl-1-naphtyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 9a. IR ν_{max} (KBr) 1754, 1575, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.23 (3H, d, J = 7.0 Hz), 1.26 (3H, d, J = 6.3 Hz), 2.61 (1H, m), 3.02 (1H, m), 3.40 (1H, m), 3.47 (1H, m), 3.53 (1H, m), 3.87 (1H, m), 4.23 (2H, m), 4.29 (1H, m), 4.70 (2H, m), 5.86 (1H, m), 7.64 (1H, m), 7.73 (3H, m), 8.16 (1H, m), 8.22 (1H, m); FAB-HRMS m/z calcd for $C_{25}H_{30}N_3O_4S$ $(M+H)^+$: 468.1957, Found: 468.1961; UV λ_{max}297 (ε 10900).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(4-Aminomethyl-1-naphtyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 9b. IR ν_{max} (KBr) 1747, 1583, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.20 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.5 Hz), 2.33 (1H, m), 3.12 (1H, m), 3.41 (2H, m), 3.52 (1H, m), 3.89 (1H, m), 4.20 (3H, m), 4.70 (2H, m), 5.68 (1H, m), 7.68 (1H, m), 7.73 (2H, m), 7.80 (1H, m), 8.18 (2H, m); FAB-HRMS m/z calcd for $C_{25}H_{30}N_3O_4S$ $(M+H)^+$: 468.1957, Found: 468.1961; UV λ_{max}296 (ε 16100).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-(5-Aminomethyl-2-thienyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 10a. IR ν_{max} (KBr) 1754, 1579, 721 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.21 (3H, d, $J=7.2$ Hz), 1.25 (3H, d, $J=6.3$ Hz), 2.51 (1H, m), 2.73 (1H, m), 3.32 (2H, m), 3.42 (1H, m), 3.74 (1H, m), 4.19 (3H, m), 4.34 (2H, s), 5.20 (1H, m), 7.16 (2H, m); FAB-HRMS *m/z* calcd for $C_{19}H_{26}N_3O_4S_2$ $(M+H)^+$: 424.1365, Found: 424.1356; UV λ_{max}298 (ε 10300).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-(5-Aminomethyl-2-thienyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 10b. IR ν_{max} (KBr) 1754, 1575 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 1.20 (3H, d, $J=7.0$ Hz), 1.26 (3H, d, $J=6.2$ Hz), 2.04 (1H, m), 2.96 (1H, m), 3.37 (3H, m), 3.58 (1H, m), 4.03 (1H, m), 4.20 (2H, m), 4.34 (2H, s), 7.12 (2H, m); FAB-HRMS *m/z* calcd for $C_{19}H_{26}N_3O_4S_2$ $(M+H)^+$: 424.1365, Found: 424.1362; UV λ_{max}300 (ε 10500).

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References and Notes

1. Farber, B. E.; Moellering, R. C. Jr. *Antimicrob. Agents Chemother*. **1983**, *23*, 138.
2. McCormick, M. H.; Stark, W. M.; Pittinger, G. E.; Pittinger, R. C.; Mcguire, G. M. *Antibiot. Ann*. **1995**, 606.
3. (a) Ohtake, N.; Okamoto, O.; Mitomo, R.; Kato, Y.; Yamamoto, K.; Haga, Y.; Fukatsu, H.; Nakagawa, S. J. *Antibiotics* **1997**, *50*, 598. (b) Nakagawa, S.; Hashizume, T.; Matsuda, K.; Sanada, M.; Okamoto, O.; Fukatsu, H.; Tanaka, N. *Antimicrob. Agents Chemother*. **1993**, *37*, 2756.
4. (a) Nagano, R.; Shibata, K.; Naito, T.; Fuse, A.; Asano, K.; Hashizume, T.; Nakagawa, S. *Antimicrob. Agents Chemother*. **1997**, *41*, 2278. (b) Adachi, Y.; Nakamura, K.; Kato, Y.; Hazumi, N.; Hashizume, T.; Nakagawa, S. *Antimicrob. Agents Chemother*. **1997**, *41*, 2282. (c) Ohtake, N.; Imamura, H.; Jona, H.; Kiyonaga, H.; Shimizu, A.; Moriya, M.; Sato, H.; Nakano, M.; Ushijima, R.; Nakagawa, S. *Bioorg. Med. Chem*. **1998**, *6*, 1089.
5. Shinagawa, H.; Yamaga, H.; Houchigai, H.; Sumita, Y.; Sunagawa, M. *Bioorg. Med. Chem*. **1997**, *5*, 601.
6. (a) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519. (b) Sumita, Y.; Inoue, M.; Mitsuhashi, M. *Eur. J. Clin. Microbiol. Infect. Dis*. **1989**, *8*, 362.
7. Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiotics* **1996**, *49*, 199.
8. Gill, C. J.; Jackson, J. J.; Gerckens, L. S.; Pelak, B. A.; Thompson, R. K.; Sundelof, J. G.; Kropp, H.; Rosen, H. *Antimicrob. Agents Chemother*. **1998**, *42*, 1996.
9. (a) Imamura, H.; Ohtake, N.; Shimizu, A.; Jona, H.; Sato, H.; Nagano, R.; Ushijima, R.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 109. (b) Imamura, H.; Ohtake, N.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Kiyonaga, H.; Suzuki-Sato, C.; Nakano, M.; Nagano, R.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 115. (c) Nagano, R.; Shibata, K.; Adachi, Y.; Imamura, H.; Hashizume, T.; Morishima, H. *Antimicrob. Agents Chemother*. **2000**, *44*, 489. (d) Shibata, K.; Nagano, R.; Hashizume, T.; Morishima, H. *Program and Abstracts of the 38th Intersci. Conf. on Antimicrob. Agents Chemother*. **1998**, F057. (e) Shibata, K.; Nagano, R.; Hashizume, T.; Morishima, H. *J. Antimicrob. Chemother*. **2000**, *45*, 379.
10. Ohtake, N.; Okamoto, O.; Kato, S.; Ushijima, R.; Fukatsu, H.; Nakagawa, S. *J. Antibiotics* **1997**, *50*, 586.
11. Azami, H.; Barrett, D.; Matsuda, K.; Tsutsumi, H.; Washizuka, K.; Sakurai, M.; Kuroda, S.; Shirai, F.; Chiba, T.; Kamimura, T.; Murata, M. *Bioorg. Med. Chem*. **1999**, *7*, 1665.
12. Imamura, H.; Ohtake, N.; Sakuraba, S.; Shimizu, A.; Yamada, K.; Morishima, H. *Chem. Pharm. Bull*. **2000**, *48*, 310.
13. Imamura, H.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Nagano, R.; Yamada, K.; Hashizume, T.; Morishima, H. *J. Antibiotics* **2000**, *53*, 314.
14. Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
15. Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett*. **1988**, *29*, 5423.
16. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.
17. (a) Deziel, R.; Endo, M. *Tetrahedron Lett*. **1988**, *29*, 61. (b) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29. (c) Berks, A. H., *Tetrahedron* **1996**, *52*, 331.
18. Dangles, O.; Guibe, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem*. **1987**, *52*, 4984.
19. Sunagawa, M.; Nouda, H. *Jap. J. Antibiotics* **1996**, *49*, 1.