Pergamon

BIOORGANIC & MEDICINAL CHEMISTRY

Bioorganic & Medicinal Chemistry 9 (2001) 961–982

Synthesis and Antibacterial Activity of Novel 4-Pyrrolidinylthio Carbapenems Part IV. 2-Alkyl Substituents Containing Cationic Heteroaromatics Linked Via a C–C Bond

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Received 13 September 2000; accepted 18 November 2000

Abstract—The synthesis and biological activity of a novel series of 2-alkyl-4-pyrrolidinylthio-β-methylcarbapenems containing a variety of cationic heteroaromatic substituents linked via a C–C bond is described. As a result of these studies, we selected FR21818 (**1n**) as a candidate compound for development. FR21818 exhibited a well balanced spectrum of antibacterial activity, including *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), excellent urinary recovery, good stability against renal dehydropeptidase-I (DHP-I), no antigenicity and mutagenicity, weak toxicities, and good efficacy and therapeutic effect on mice systemic infections. Affinities to PBP's, permeability of outer membrane, and plasma levels in mice, dog, and cynomolgous monkey of FR21818 are also reported.

Introduction

The acquisition of resistance by pathogens is becoming a serious problem in modern chemotherapy.[1–3] Since the discovery of penicillin, many researchers and pharmaceutical companies have researched and developed many kinds of antibacterial agent, including β-lactams, tetracyclines, macrolides, quinolones, aminoglycosides, etc. As a result of these efforts, for a while we seemed to be able to control all bacterial infections; however, this is now shown to be difficult due to the appearance of many resistant strains. Resistant bacteria have appeared for almost all types of antibiotic agent and for most bacterial strains, and have been often induced by the excessive and/or inappropriate usage of antibiotics. To overcome these resistance problems, the search for novel antibiotics represents an ongoing effort that has focused predominantly on established classes, due primarily to the paucity of novel structural lead compounds.

Presently, amongst resistant strains of bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), is one of the most critical strains that causes hospital infections.[1] Another is *Ps. aeruginosa*, a Gram negative bacteria, that possesses an outer membrane which acts as an impermeable barrier for antibiotics. Resistant strains of *Ps. aeruginosa* are also becoming a serious problem in the clinic. Certain antibiotics are intrinsically active against resistant bacteria; one successful example is vancomycin,[4] however, its activity is restricted to Gram positive bacteria, including MRSA. Furthermore, strains that are resistant to vancomycin[5] have recently been isolated. With the aim of solving this resistance problem in a broad range of bacteria, including Gram positive (especially MRSA) and negative bacteria (especially resistant strains of *Ps. aeruginosa*), we have been searching for novel antibiotics.

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0968-0896/01/$ - see front matter
PII: S0968-0896(00)00314-X

We selected the carbapenem skeleton[6–9] as the prototype for a new antibiotic for the following reasons: (1) good selective affinity for the target proteins, penicillin binding proteins (PBP's), which do not exist in humans, (2) the superior antibacterial efficacy profile. For example, the bactericidal activity of carbapenems is superior to the bacteriostatic activity of cephalosporins, and (3) the broad antibacterial spectrum associated with these compounds. A weak point of the carbapenem skeleton is instability to the renal enzyme dehydropeptidase-I (DHP-I); co-administration of a DHP-I inhibitor (cilastatin) with imipenem was the first approach taken to solve this problem, and more recently several approaches have been described to improve stability, bioavailability, and in vivo antibacterial activity.

From the literature of carbapenem antibiotics, especially the SAR related to meropenem[10,11] and panipenem,[12] the importance of a pyrrolidine ring for potent activity and high PBP affinity were noted. It was also reported that the good activity of biapenem[13,14] against *Ps. aeruginosa* was related to its good outer membrane permeability. The quaternary ammonium cationic center present in the side chain of biapenem is critical to impart good outer membrane permeability of *Ps. aeruginosa*, thus we postulated that a combination of these two factors in a single side chain might lead to agents with a broader spectrum of activity, including Gram positive bacteria (MRSA) and Gram negative bacteria, especially *Ps. aeruginosa*. As a result of these efforts we discovered FR21818[15] (**1n**) and FR21751[16] (**1j**) which both possessed excellent and broad spectrum of activity against Gram positive and Gram negative bacteria, good DHP-I stability, and good urinary recovery. The preliminary SAR and synthesis of a series of azoliomethyl substituted pyrrolidines containing heterocycles linked via a carbon–carbon bond to the spacer was described in earlier communications.[15–17] In this paper, we describe full details of the SAR and synthesis of this type of carbapenem compound, and also describe the in vivo activity, pharmacokinetics and toxicity evaluation of FR21818.

The carbapenems possessing cationic heteroaromatics and a carbon–nitrogen bond in the spacer moiety shown in Figure 1 (type A), were reported earlier by us.[9] With this series, we uncovered a relationship between in vitro antibacterial activity and the length of the alkyl spacer part and discovered FR20950,[9] containing a two methylene spacer moiety and an imidazolio group, which possesses a good balanced spectrum of antibacterial activities. Additionally, we found that a longer distance between the two nitrogen atoms than a two methylene length spacer was needed for optimal antibacterial activity. On the other hand, we were concerned that the carbon–cationic nitrogen bond, as in type A (Fig. 1) may be possibly chemically unstable and/or possess biological reactivity towards protein nucleophilic side chains, leading to the possibility that the complex of an unstable agent and proteins could act as an antigen and display antigenicity. To avoid this problem, we aimed to alter the substitution position on the heteroaromatic ring from a nitrogen atom to a carbon atom. With this alteration, the carbon–nitrogen bond on the spacer part was transformed to a carbon–carbon bond, which was expected to be chemically and biologically stable (Fig. 1, type B).

Results and Discussion

Chemistry

The general synthetic route to the target carbapenems (**1b–1u**) is based on the retrosynthesis shown in Figure 2. The target carbapenem can be retrosynthetically divided into two parts, the carbapenem skeleton and the thiol side chain. The side chain can also be divided into two parts, the pyrrolidine ring and heteroaromatic moiety. The total synthesis of our carbapenem compounds was achieved with two key steps. The first is carbon–carbon bond formation between a heteroaromatic anion and a 2-formyl pyrrolidine derivative, derived from 4-hydroxyproline. The obtained coupling compounds are then transformed to thiol derivatives as substrates for the next key step. The other key step is the coupling reaction of the obtained thiol derivatives and an activated carbapenem skeleton. Finally, the target carbapenems can be obtained from the coupled carbapenem derivatives by alkylation of the heteroaromatic ring and deprotection.

The first key step, the carbon-carbon bond forming reaction between a 2-formyl pyrrolidine derivative and a heteroaromatic anion and subsequent conversion is outlined in Scheme 1. The starting formyl derivatives

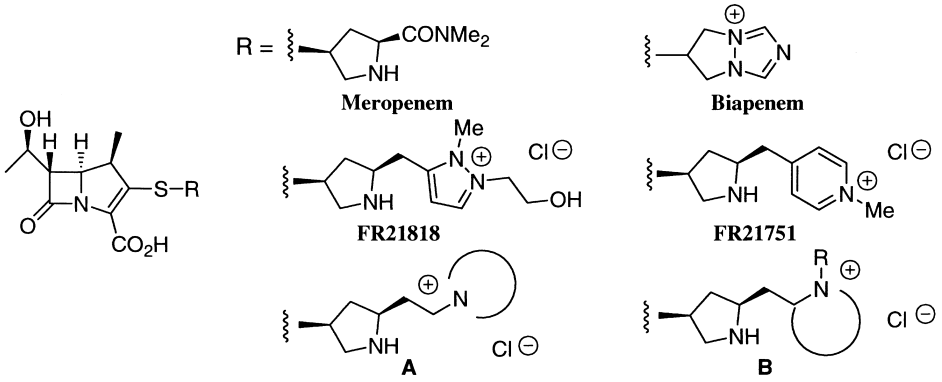


Figure 1. Carbapenem antibiotics.

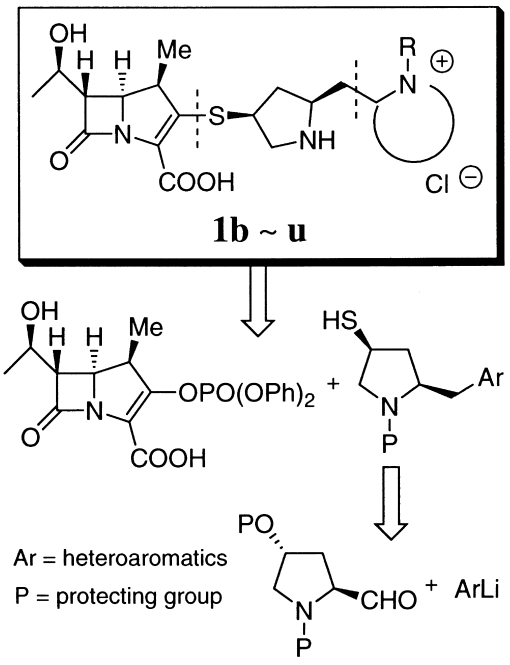
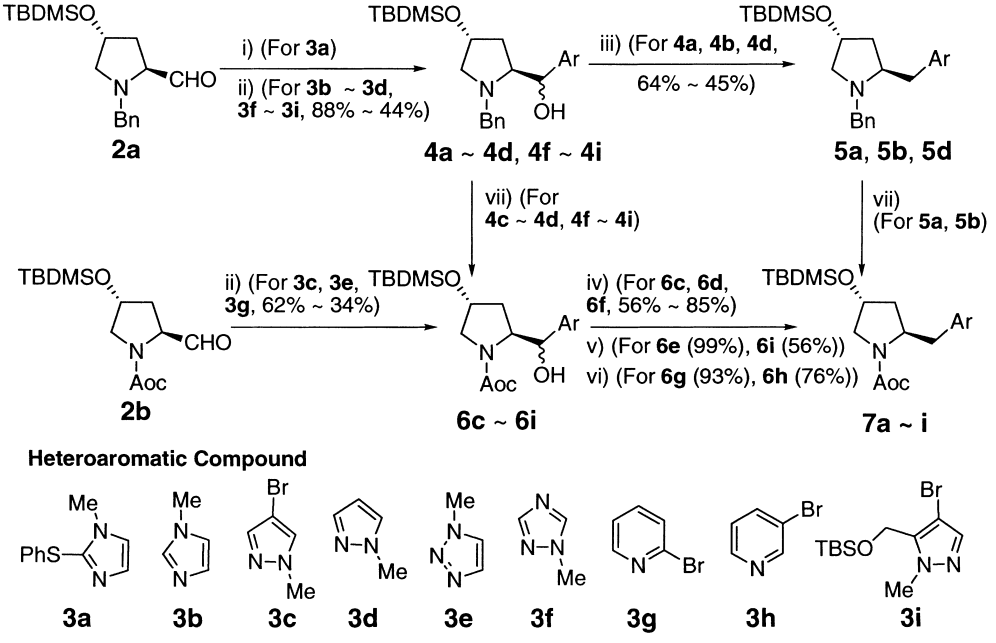


Figure 2. Retrosynthetic analysis of target compounds.

2a, **b** were easily synthesized by literature methods[9,18] from 4-hydroxyproline. The heteroaromatics (**3a–3h**) used in this coupling reaction were commercially available or easily synthesized by literature methods.[19] **3i** was synthesized from *N*-methylpyrazole by the method outlined in our previous Letter.[17] The heteroaromatic lithium anions were derived by halogen–lithium exchange reaction of bromo compounds (**3c**, **3g–3i**) with ^{n}BuLi, or regioselective α-lithiation of *N*-methyl heteroaromatics (**3a**, **3b**, **3d–3f**) with LDA or ^{n}BuLi.[19a,20] In the case of **3a**, a satisfactory result was obtained using the literature method, employing LDA for deprotonation and the reaction position (5-position) was assumed from the literature precedent.[19a] Subsequent to coupling reaction of **2a** and **3a**, the phenylthio protecting group on imidazole was removed by reduction. In the case of **3b**, **3d–3f**, regioselective deprotonation occurred at the adjacent position to the *N*-methyl group, which was assumed from literature.[20] The secondary alcohols **4a–4d**, **4f–4i** were obtained as stereoisomeric mixtures at the hydroxyl group (approximately 1:1–2:1, detected by NMR) in moderate to good yield. Similarly, the reactions of *N*-allyloxycarbonylprotected formyl derivative **2b** and heteroaromatic anions (**3c**, **3e**, **3g**) were readily performed to give **6c**, **6e**, **6g** in good to moderate yield. The alcohol derivatives (**4a–4d**, **4f–4i**) were converted to dehydroxylated compounds **7a–7d**, **7f–7i** by two different routes. In the case of **4a**, **4b**, **4d**, the secondary alcohol was removed in three steps (chlorination, phenylthio group introduction and reduction with ^{n}Bu$_3$SnH or Raney-Ni) to give **5a**, **5b**, **5d**. Exchange of the amino protecting group of **5a** and **5b** from benzyl to allyloxycarbonyl was achieved by the usual methods to give **7a** and **7b**. On the other hand, in the case of other pyrazole, triazole, and pyridine derivatives (**4c**, **4d**, **4f–4i**), exchange of the amino protecting group was achieved initially by ordinary methods to give **6c**, **6d**, **6f–6i**. The deoxygenation of the sterically blocked secondary alcohol group of **6c–6i** was then achieved by one of the methods described below. Deoxygenation was achieved in two steps. The first step was conversion of the alcohol to a leaving group, and the next step was reduction by radical reaction or heterogeneous reduction. In the case of **6c**, **6d**, **6f**, conversion of the alcohol to phenylthiocarbonyloxy group and radical reduction (^{n}Bu$_3$SnH, AIBN) afforded **7c**, **7d** and **7f** (56–85%).[21] In the case of **6e** and **6i**, the alcohol was converted to the xanthate and radical reduction



Scheme 1. C–C bond formation reactions of 2-formyl pyrrolidine with heteroaromatic anions. Reagents and conditions: (i) LDA, **3a**, DME-THF (56%), then Raney-Ni, EtOH (76%); (ii) ^{n}BuLi, **3b–3i**, THF; (iii) (1) $SOCl_2$, CH_2Cl_2; (2) PhSH, CH_2Cl_2; (3) ^{n}BuS_3nH, AIBN, toluene or Raney-Ni, Me_2CO; (iv) (1) PhOCSCl, pyridine, CH_2Cl_2; (2) ^{n}BuS_3nH, AIBN, toluene; (v) (1) CS_2, imidazole, NaH, MeI, THF; (2) ^{n}BuS_3nH, AIBN, toluene; (vi) CBr_4, PPh_3, THF, then Zn-powder, DMF, AcOH; (vii) Pd-C, $HCOONH_4$ then AocCl, THF-H_2O (53–98%).

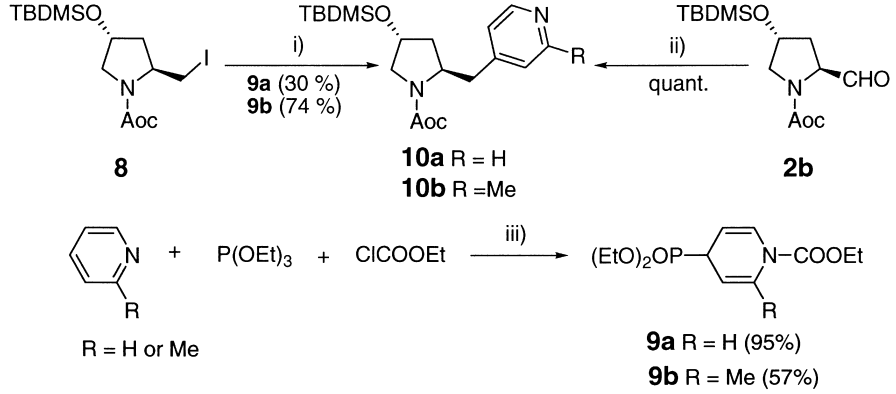
gave **7e** and **7i**. In the case of **6g** and **6h**, the alcohol was converted to the corresponding bromide and then reduced by Zn–metal to give **7g** and **7h**, respectively.

C–C bond formation between the 4-position of pyridine[22–24] and 2-formyl pyrrolidine was readily achieved (Scheme 2). 4-Bromopyridine is commercially available as the hydrogen bromide salt, however, by analogy to 2- and 3-bromopyridine (Scheme 1), 4-bromopyridine could be coupled with aldehyde (**2a**) by neutralization of HBr salt and extraction with IPE, but the yield of the reaction was poor and unsatisfactory, primarily because free 4-bromopyridine is unstable and easily polymerized at ambient temperature. The Akiba group[22] has demonstrated a useful method to generate a stable anion at the 4-position of pyridine by using a phosphonate derivative. We adopted their method to our target compounds. Using iodide (**8**) and pyridine or picoline reagent (**9a, b**) as a reactant, the lithium anions of **9a** and **9b** were reacted with iodide **8** at −78 °C to give an intermediate phosphonate compound, that after isolation, was treated with 2.2 equivalent of ^{n}BuLi to give **10a**, **10b**. Since phosphonate (**9a**, **b**) is a kind of Horner-Wittig reagent, we expected that phosphonate **9a** and a carbonyl compound may directly react to give the desired product. The lithium anion of **9a** was reacted with formyl derivative **2b** at −78 °C to give the addition product (detected by TLC), and the elimination reaction proceeded by slow warming to give target compound **10a** in good yield in a one-pot procedure. Pyridine and picoline reagents (**9a**, **b**) were easily prepared by the literature method from pyridine or picoline and triethyl phosphite and ethyl chloroformate.[23]

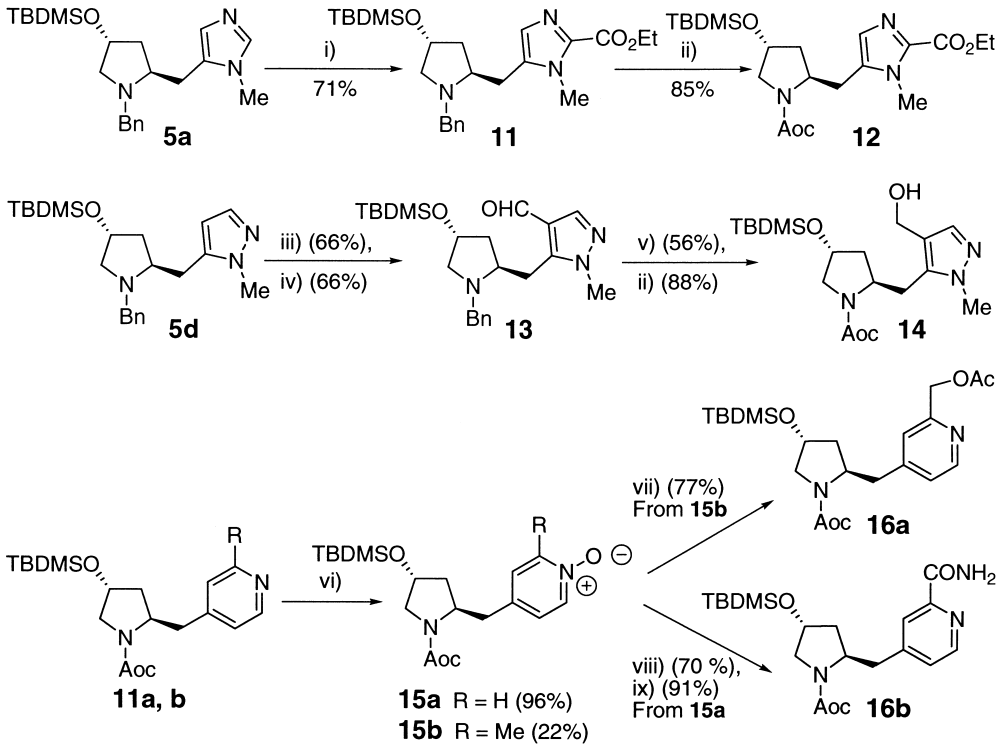
In several cases, the coupling products were next subjected to functional group introduction to the heteroaromatic nucleus (Scheme 3). An ethoxycarbonyl group was introduced to imidazole **5a** by regiospecific deprotonation of the 2-position of the imidazole ring (^{n}BuLi) and subsequent treatment with ClCOOEt to give **11** in 71% yield. The amino protecting group was then transformed from benzyl to allyloxycarbonyl to give **12**. In the case of pyrazole **5d**, direct selective deprotonation was not achieved with ^{n}BuLi, hence anion formation was achieved by two steps (bromination and halogen-metal exchange). Subsequent quench by DMF gave formyl compound **13**, which was reduced with $NaBH_4$ and the amino protecting group was transformed to give **14**. In the case of pyridine **11a** and picoline **11b**, introduction of functional groups at the 2-position of the pyridine ring via *N*-oxidation, was achieved with $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone) to give **15a** (96%) and **15b** (22%), followed by treatment with TMSCN and $ClCONMe_2$[25] and subsequent oxidative hydroxylation by H_2O_2 to give 2-carbamoylpyridine **16b** from **15a**. **15b** was converted to an acetoxy group by reaction with Ac_2O under reflux to give **16a** in 77% yield.[26]

The conversion of the *tert*-butyldimethylsilyloxy group to thiobenzoate is shown in Scheme 4. As a precursor of the side chains used in the coupling reactions with the carbapenem skeleton, thiobenzoates **17a–17k**, **19**, **21**, **23** were prepared. In the case of **17a–17k**, the TBDMS group of **7a–7h**, **10a**, **16a**, **16b** was removed under acidic conditions, and the obtained alcohols were converted to the thiobenzoate by Mitsunobu reaction (PhCOSH, DEAD, PPh_3) or mesylation (MsCl) and nucleophilic substitution reaction by thiobenzoate anion (PhCOSH, ^{t}BuOK). In the case of 2-hydroxymethyl-imidazole (**19**), the 2-ethoxycarbonyl imidazole (**12**) was converted to the mesylate (**18**) by acidic deprotection and subsequent mesylation. After reduction of ethoxycarbonyl, conversion of the mesylate function to thiobenzoate was achieved to give **19**. In the case of 4-hydroxymethylpyrazole (**21**), protection of the primary hydroxyl group in **14** as an acetate, followed by desilylation and mesylation of the obtained secondary alcohol, and removal of the acetyl group, gave **20**. The mesylate (**20**) was converted to thiobenzoate by the usual method to give **21**. In the case of **23**, after removal of both silyl protecting group from **7i**, selective protection of the primary alcohol was achieved to give **22**. The secondary alcohol of **22** was then converted to thiobenzoate by the usual method, and subsequent silyl deprotection gave **23**.

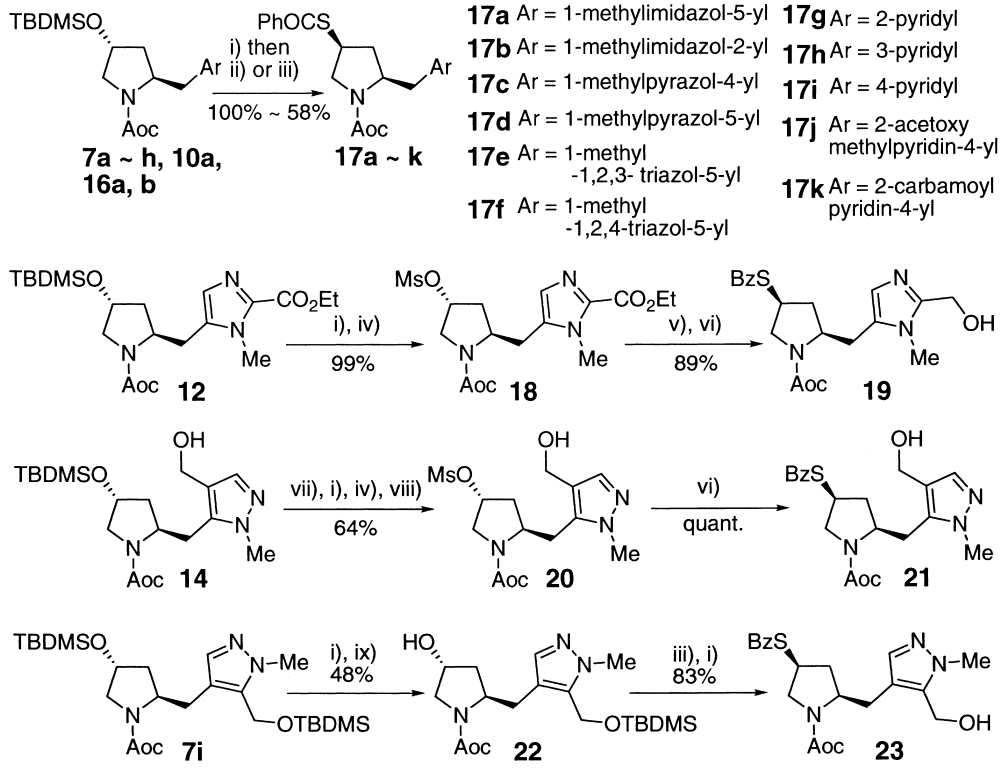
The coupling of thiol derivatives, which were obtained by benzoylthio group deprotection, with activated carbapenem **24**[18,27] and subsequent cationic salt formation and deprotection are summarized in Scheme 5. The thiobenzoates (**17a–k**, **19**, **21**, **23**) were smoothly deprotected by NaOMe to produce the thiols which were then immediately coupled with the activated carbapenem (**24**) in



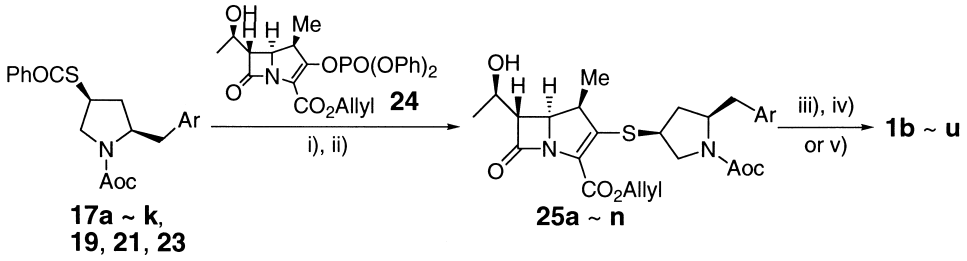
Scheme 2. C–C bond formation of pyridine at the 4-position and pyrrolidine ring. Reagents and conditions: (i) **9a** or **9b**, ^{n}BuLi (1.1 equiv), THF, then ^{n}BuLi (2.2 equiv); (ii) **9a**, ^{n}BuLi (1.3 equiv), THF; (iii) MeCN, −20–0 °C.



Scheme 3. Introduction of substituents to heteroaromatics. Reagents and conditions: (i) ^{n}BuLi, THF, then ClCOOEt; (ii) Pd-C, $HCOONH_4$, MeOH, then AocCl, THF-H_2O; (iii) Br_2, Na_2CO_3, CH_2Cl_2; (iv) ^{n}BuLi, Et_2O, then DMF; (v) $NaBH_4$, THF-MeOH; (vi) Oxone, $NaHCO_3$, MeOH-H_2O; (vii) Ac_2O, 150 °C; (viii) TMSCN, $ClCONMe_2$, CH_2Cl_2, rt; (ix) 30% H_2O_2, K_2CO_3, DMSO.

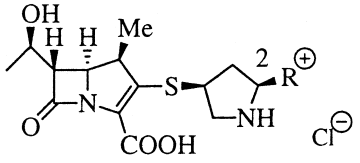


Scheme 4. Synthesis of thiobenzoates. Reagents and conditions: (i) HCl, MeOH or MeCN; (ii) PhCOSH, DEAD, PPh_3, THF; (iii) MsCl, Et_3N, CH_2Cl_2 then PhCOSH, KO^{t}Bu, DMF; (iv) MsCl, Et_3N, AcOEt; (v) $NaBH_4$, LiCl, THF, EtOH; (vi) PhCOSH, ^{t}BuOK, DMF; (vii) AcCl, Et_3N AcOEt; (viii) NaOMe, MeOH; (ix) TBDMSCl, imidazole, DMAP, CH_2Cl_2.



Scheme 5. Synthesis of novel carbapenems. Reagents and conditions: (i) NaOMe, MeCN, DMAC; (ii) EtN^iPr_2, DMAC, MeCN; (iii) MeI, Me_2CO (**1h, 1i, 1j, 1o, 1q, 1s, 1u**), MeOTf, CH_2Cl_2 (**1b–1g**, **1l**), ICH_2CONH_2 (**1m**, **1t**); (iv) $Pd(PPh_3)_4$, PPh_3, THF, EtOH, morpholine or $^nBu_3SnH$; (v) (**1k**, **1n**, **1p**, **1r**); (1) $TBDMSOCH_2CH_2OTf$, $ClCH_2CH_2Cl$; (2) TBAF, AcOH, THF; (3) $Pd(PPh_3)_4$, PPh_3, THF, EtOH, morpholine.

Table 1. Antibacterial activity (MIC)[a,b] of novel carbapenems



R	S.a.(1)	S.a.(2)	S.a.(3)	E.c.	P.v.	P.a.(1)	P.a.(2)	P.a.(3)	P.a.(4)	P.a.(5)
Meropenem	0.1	6.25	25	≤0.025	0.1	1.56	0.39	0.2	1.56	0.39
Biapenem	0.05	1.56	25	0.39	3.13	1.56	0.78	0.2	1.56	0.2
1a[c]	<0.025	1.56	12.5	0.1	0.78	0.78	0.78	0.39	1.56	0.39
1b	0.05	1.56	6.25	0.2	0.78	3.13	0.78	0.2	1.56	0.39
1c	0.1	3.13	6.25	0.1	0.78	12.5	1.56	0.39	6.25	0.78
1d	0.05	1.56	3.13	0.2	1.56	3.13	0.78	0.39	1.56	0.78
1e	0.05	1.56	6.25	0.2	0.78	1.56	0.39	0.2	1.56	0.39
1f	0.05	1.56	25	0.1	0.78	3.13	0.78	0.39	3.13	0.78
1g	0.1	3.13	12.5	0.2	0.78	12.5	3.13	1.56	12.5	1.56
1h[d]	0.05	3.13	12.5	0.2	0.39	1.56	0.78	0.2	1.56	0.78
1i	0.05	1.56	6.25	0.2	0.78	3.13	0.39	0.2	1.56	0.39
1j[d]	0.05	0.78	6.25	0.1	0.78	1.56	0.39	0.2	1.56	0.39

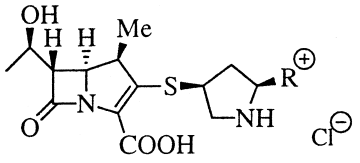
[a]MIC (μg/ml).
[b]S.a.(1), *S. aureus* 209P JC-1; S.a.(2), *S. aureus* 2538; S.a.(3), *S. aureus* 3004; E.c., *E. coli* NIHJ JC-2; P.v., *P. vulgaris* IAM 1025; P.a.(1), *Ps. aeruginosa* IAM 1095; P.a.(2), *Ps. aeruginosa* 2; P.a.(3), *Ps. aeruginosa* 26; P.a.(4), *Ps. aeruginosa* 175; P.a.(5), *Ps. aeruginosa* FP 1457.
[c]This compound was already shown in our previous report.
[d]Diastereomeric mixtures on the 2-position of pyrrolidine ring.

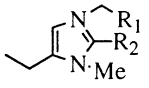
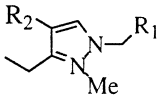
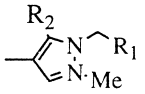
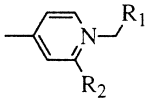
the presence of Hünig's base in MeCN-DMAC, to give coupling products **25a–n**. The protected carbapenems **25a–n** were then transformed to cationic salts by reaction with the appropriate alkylating reagents, then deprotected to give target compounds. In the case of methylation, MeI, and MeOTf were used as alkylation reagent, and the allyloxycarbonyl group and allyl ester moiety were then simultaneously deprotected by $Pd(Ph_3P)_4$, Ph_3P and an allyl trapping reagent (morpholine or $^nBu_3SnH$) to give **1b–1j**, **1l**, **1o**, **1q**, **1s** and **1u**.[28,29] In the case of carbamoylmethylation, ICH_2CONH_2 was used, and similarly deprotection gave **1m** and **1t**. In the case of hydroxyethylation, *tert*-butyldimethylsilyloxyethyl trifluoromethanesulfonate which was synthesized by the method outlined in our previous Letter,[15] was used and all protecting groups were removed by one-pot reaction to give **1k**, **1n**, **1p** and **1r**. The desilylation was achieved by treatment with TBAF in the presence of AcOH, and the reaction mixture was directly used in the next allyloxycarbonyl group and allylester deprotection. In the case of pyridine compound (**1h**, **1j**, **1r**, **1t**, **1u**), unusual epimerization on the 2-position of pyrrolidine ring was observed on deprotection step. We previously reported about this epimerization on FR21751 (**1j**).[16]

Biological activity

In vitro antibacterial activities of these novel carbapenems, possessing various five- and six-membered ring cationic heteroaromatics, and the reference compounds meropenem, biapenem and **1a** (previous publication),[9] are shown in Table 1. Concerning imidazole derivatives (**1a–c**), exchange of the spacer bond from carbon–nitrogen to carbon–carbon, led to superior activities against MRSA (S.a.(3)) for derivatives **1b** and **1c**, relative to **1a**. However, against some strains of resistant *Ps. aeruginosa*, activity was inferior. This change of activities is consistent with our final purpose, since a good balance of activity against both MRSA and *Ps. aeruginosa* is important. Moreover, upon comparing imidazole isomers (**1b**, **1c**), **1b** was slightly superior against both MRSA and *Ps. aeruginosa*, relative to **1c**. Similar to the imidazole derivatives, the pyrazole derivatives (**1d**, **1e**) displayed good activities against both MRSA and resistant *Ps. aeruginosa*. When comparing regioisomers for activity towards MRSA (S.a.(3)), **1d** was superior to **1e**. However, with respect to activity against most strains of *Ps. aeruginosa*, **1e** was superior to **1d**. For both triazole isomers (**1f**, **1g**), inferior activities against MRSA were

Table 2. Antibacterial activity (MIC)[a,b] of novel carbapenems



R		S.a.(1)	S.a.(2)	S.a.(3)	E.c.	P.v.	P.a.(1)	P.a.(2)	P.a.(3)	P.a.(4)	P.a.(5)
											
1k	$R_1 = CH_2OH$ $R_2 = H$	0.05	1.56	12.5	0.1	1.56	3.13	1.56	0.39	3.13	0.78
1l	$R_1 = H$ $R_2 = CH_2OH$	0.05	1.56	6.25	0.2	0.78	1.56	0.78	0.2	1.56	0.78
1m	$R_1 = CONH_2$ $R_2 = H$	0.05	3.13	12.5	0.1	0.78	3.13	0.78	0.2	1.56	0.39
											
1n	$R_1 = CH_2OH$ $R_2 = H$	0.05	1.56	6.25	0.2	1.56	6.25	0.78	0.2	3.13	0.78
1o	$R_1 = H$ $R_2 = CH_2OH$	0.1	3.13	25	0.2	0.78	3.13	0.78	0.39	3.13	0.78
											
1p	$R_1 = CH_2OH$ $R_2 = H$	0.05	1.56	12.5	0.39	1.56	1.56	0.78	0.39	3.13	0.78
1q	$R_1 = H$ $R_2 = CH_2OH$	0.05	1.56	6.25	0.39	1.56	6.25	0.78	0.39	3.13	0.78
											
1r[c]	$R_1 = CH_2OH$ $R_2 = H$	0.05	1.56	12.5	0.1	1.56	3.13	0.78	0.2	3.13	0.39
1s	$R_1 = H$ $R_2 = CH_2OH$	≤0.025	1.56	6.25	0.1	0.78	3.13	0.39	0.2	1.56	0.39
1t[c]	$R_1 = CONH_2$ $R_2 = H$	0.05	3.13	6.25	0.2	0.78	3.13	0.78	0.2	1.56	0.39
1u[c]	$R_1 = H$ $R_2 = CONH_2$	0.05	1.56	12.5	0.1	0.78	1.56	0.78	0.39	3.13	0.78

[a]MIC (μg/ml).
[b]S.a.(1), *S. aureus* 209P JC-1; S.a.(2), *S. aureus* 2538; S.a.(3), *S. aureus* 3004; E.c., *E. coli* NIHJ JC-2; P.v., *P. vulgaris* IAM 1025; P.a.(1), *Ps. aeruginosa* IAM 1095; P.a.(2), *Ps. aeruginosa* 2; P.a.(3), *Ps. aeruginosa* 26; P.a.(4), *Ps. aeruginosa* 175; P.a.(5), *Ps. aeruginosa* FP 1457.
[c]Diastereomeric mixtures on the 2-position of pyrrolidine ring.

Table 3. DHP-I stability and urinary recovery of selected carbapenems

	Meropenem	Biapenem	**1b**	**1c**	**1d**	**1e**	**1g**	**1h**	**1j**	**1k**	**1n**	**1p**
DHP-I[a]	5.3	1	2.2	16.	1.5	2.2	1.2	2.1	1.6	1.3	1.4	1.1
U.R.[b] (%)	25	71	76	84	61	74	73	66	64	64	69	86

[a]DHP-I, DHP-I stability; human DHP-I stability is given relative to biapenem.
[b]U.R., urinary recovery; recovery (%) in mouse after sc administration (20 mg/kg).

displayed. The 1,2,4-triazole derivative (**1g**) displayed inferior activities against *Ps. aeruginosa*, relative to **1f**. For pyridine derivatives (**1h–1j**), of similar levels of activity against both MRSA and *Ps. aeruginosa* were displayed, and they showed a small tendency to have improved MRSA activity in the order **1h** < **1i** < **1j**. As a result, imidazole **1b**, pyrazole **1d** and **1e**, and pyridine **1j** displayed good balanced activities against both resistant *Ps. aeruginosa* and MRSA, and also compared to the reference compounds (meropenem, Biapenem), they displayed a superior balance of activities. Especially against MRSA, these novel compound (**1b**, **1d**, **1e**, **1j**) displayed the best activities.

In vitro antibacterial activities of novel carbapenems with substituted heteroaromatics are shown in Table 2. We evaluated the effect of antibacterial activities by introduction of hydrophilic functional groups to the most balanced compounds (**1b**, **1d**, **1e**, **1j**). The imidazoles, pyrazoles, and pyridines with a hydroxyalkyl substitution (**1k–1l**, **1p–1s**) displayed similar activities compared to the nonsubstituted compound, with several exceptions. The pyrazoles with a hydroxyalkyl substitution (**1n**, **1o**) displayed weak activities toward some strains (S.a.(3) and P.a.(1)). The imidazoles and pyridines with carbamoyl substitution (**1m**, **1t**, **1u**) also displayed comparable activities compared to the nonsubstituted compounds. From these results, it was concluded that the antibacterial activity was maintained by introduction of functional groups to the heteroaromatic.

The DHP-I stabilities and urinary recoveries of selected carbapenems are summarized in Table 3. It is well known that carbapenem antibiotics are relatively easily decomposed by the metabolic enzyme, DHP-I.[30,31] Good DHP-I stabilities are desirable for good bioavailability and in vivo activities. All compounds in Table 3 displayed superior stabilities against DHP-I, compared to meropenem, and most compounds (**1c**, **1d**, **1g**, **1j–1p**) displayed comparable results to biapenem. Concerning urinary recovery, it is also assumed that DHP-I stability influences recovery, hence the urinary recoveries of these compounds were superior to meropenem, and comparable to biapenem. These results showed that DHP-I stability and urinary recovery are improved by the presence of a cationic center in the side chain.

Amongst these novel compounds shown in Tables 1 and 2, we selected **1n** (FR21818) as a candidate compound for development after further evaluation of several toxicities, and due to the ease of isomerization for the potent pyridine compound FR21751.[16] FR21818 possessed weak acute toxicity in rats (> 1000 mg/kg i.v.), no antigenicity, no mutagenicity, weak renal toxicity in rabbits (negative at a concentration of 1000 mg/kg, i.v.), and weak subacute toxicity (2 weeks) in rats (no-effect level > 320 mg/kg, i.v.).[32]

The therapeutic effects of FR21818 on mice systemic infection caused by strains of *S. aureus* (MRSA) and *Ps. aeruginosa*, are shown in Table 4.[32] Against *S. aureus* 4066 (MRSA), a comparable effect to the reference carbapenems and a superior effect to Vancomycin was observed. Especially against *S. aureus* 8008, a superior effect to the reference carbapenems was observed. Against strains of *Ps. aeruginosa*, comparable effects to the reference compounds were observed. As a result, we could find that FR21818 possessed a similar therapeutic effect to reference compounds against these bacteria and especially possessed a superior therapeutic effect against a strain of *S. aureus*.

The affinities of FR21818 to various PBP's relative to Imipenem are summarized in Table 5.[32] FR21818 had high affinity to PBP's 1–4 of *S. aureus*, to PBP2 of *E. coli* and to PBP's 1–4 of *Ps. aeruginosa*, respectively. Additionally, FR21818 showed superior affinity (IC_{50}:

Table 4. Therapeutic effect of FR21818 on mice systemic infections

Organism (CFU/mouse)[a]	Drug	ED_{50} (mg/kg)[b]	MIC (μm/mL)
S. aureus 4066	FR21818	2.18	1.56
(MRSA)	Biapenem	2.11	3.13
(1.0×10^8)	Meropenem[c]	2.63	3.13
	Imipenem[d]	1.40	0.78
	Vancomycin	4.01	1.56
S. aureus 8008	FR21818	5.46	12.5
(MRSA)	Biapenem	35.2	25
(3.0×10^8)	Meropenem[c]	7.88	25
	Imipenem[d]	7.02	50
	Vancomycin	2.73	1.56
P. aeruginosa 93	FR21818	0.38	1.56
(6.0×10^5)	Biapenem	0.29	0.78
	Meropenem[c]	0.29	0.78
	Imipenem[d]	0.38	0.78
P. aeruginosa 7001	FR21818	0.32	0.39
(1.0×10^5)	Biapenem	0.28	0.39
	Meropenem[c]	0.28	0.39
	Imipenem[d]	0.58	1.56

[a]Mouse; ICR, 4 weeks old, male, $n=8$. Challenge dose; IP, with 5% mucin.
[b]Treatment; SC, 1 h after challenge.
[c]Meropenem/cilastatin = 1:1.
[d]Imipenem/cilastatin = 1:1.

Table 5. Affinity of FR21818 to PBPs[a]

S. aureus 2562	1	2	2′	3	4		
FR21818 (6.25)[b]	0.125	0.22	4.2	0.15	0.042		
Imipenem (12.5)[b]	0.13	0.094	> 12.5	0.63	< 0.02		
E. coli DH10B	1A	1Bs	2	3	4	5	6
FR21818 (0.05)[b]	1.90	1.10	0.048	11.0	0.75	5.6	> 12.5
Imipenem (0.1)[b]	0.32	0.39	0.036	> 12.5	< 0.02	0.30	1.15
P. aeruginosa PAO4096	1A	1B	2	3	4	5/6	
FR21818 (0.2)[b]	0.19	0.80	0.052	0.21	0.021	> 12.5	
Imipenem (0.2)[b]	0.06	0.20	0.25	0.15	0.15	0.65	

[a]IC_{50} to various PBP's (mg/mg).
[b]MIC (μg/ml).

4.2 μg/mL) to PBP2′ of MRSA relative to imipenem. One of the critical factors in resistance of MRSA, is the mutation of PBP2. We assume that the superior efficacy of FR21818 to MRSA relative to imipenem, is due to the superior PBP2′ affinity of FR21818.

The outer membrane permeability of FR21818 and reference compounds is shown in Table 6.[32] The outer membrane of Gram negative bacteria is effective as a barrier which protects the inside from antibiotics. Thus, high permeability of the outer membrane is needed for high antibacterial activity. From the results shown in Table 6, the outer membrane permeability of antibiotics is presented in the order: meropenem < FR21818 < biapenem < imipenem. We believe that we have obtained superior permeability relative to meropenem by introduction of cationic center to side chain in FR21818, in accord with our original hypothesis.

Plasma levels of FR21818 and reference compound in mice, dogs, and cynomolgus monkeys are shown in Figures 3–5.[32] In mouse, plasma levels of FR21818 were similar to biapenem, slightly higher than imipenem/cilastatin, and slightly lower than meropenem/cilastatin (Fig. 3). In dog, plasma levels of FR21818 were slightly higher than biapenem, and T1/2 was 0.82 h for FR21818 and 0.62 h for biapenem (Fig. 4). In monkey, plasma levels for FR21818 were slightly higher than for biapenem (Fig. 5).

Table 6. Outer membrane permeability of FR21818

	E. coli 5α/pFIP110		*P. aeruginosa* PAO4263/pJIP120	
	p (nm/s)	ratio[a]	p (nm/s)	ratio[a]
FR21818	405	0.33	10.2	0.114
Biapenem	837	0.69	29	0.33
Meropenem	231	0.19	7.9	0.089
Imipenem	1214	1	89	1

[a]Permeability ratio is given relative to imipenem.

Conclusions

We have designed and synthesized a novel series of 2-alkyl-4-pyrrolidinylthio-β-methylcarbapenems containing a variety of cationic heteroaromatic substituents linked via a C–C bond. As a result of these studies, we selected FR21818 (**1n**) as a candidate compound for development. FR21818 containing a functionalized pyrazolio group, exhibited a well balanced spectrum of antibacterial activity, including *Ps. aeruginosa* and MRSA, excellent urinary recovery, good stability against DHP-I, no antigenicity and mutagenicity, weak several toxicities, and good efficacy and therapeutic effect on mouse systemic infections. Also good affinities to PBP's, good permeability of outer membrane, and plasma levels in mouse, dog, and cynomolgous monkey, of FR21818 are displayed.

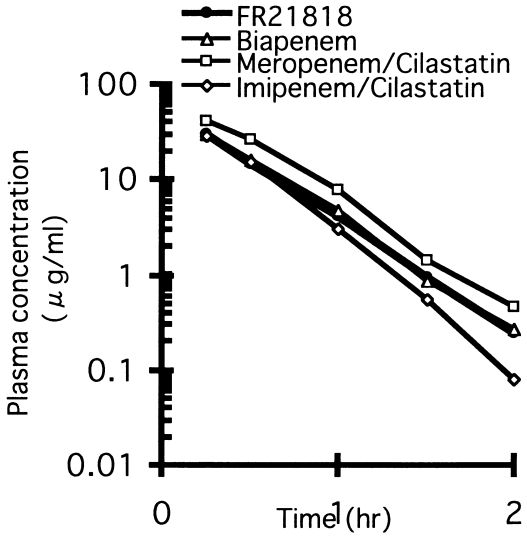
Experimental

General procedures

IR spectra were recorded on a Horiba Spectradesk FT-210 (FT-IR) or a Hitachi 260-10 spectrometer. NMR spectra were measured on a Bruker AC200P spectrometer (^{1}H, 200 MHz). Chemical shifts are given in parts per million, and TMS was used as the internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. DSS was used for spectra run in D_2O. MS spectra were measured on a Finnigan MAT TSQ-70 (FAB–MS) and a Hitachi M-1000 LC/9MS (APCI–MS). Reagents used in this study were obtained from commercial sources and used without further purification. Reaction solvents were the highest grade available. Selected spectroscopic data for intermediates and final compounds are collected in Tables 7–9.

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylimidazol-5-yl)methanol (4a). To a solution of **3a**[19a] (148.3 g) in a mixture of THF (1500 mL) and dimethoxyethane (DME, 950 mL) was added dropwise LDA (1.55 N in hexane) (664 mL) at −65 to −70 °C over 20 min, and the mixture was stirred at −60 to −65 °C for 50 min. To the mixture was added

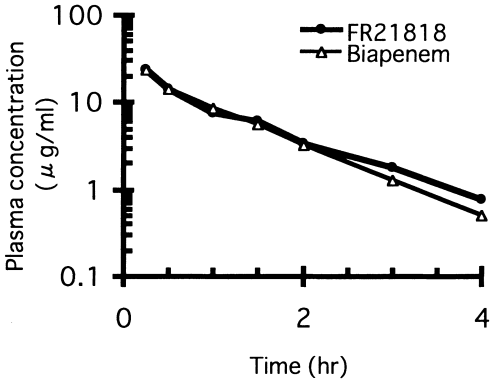
Drug	$T_{1/2}$ (hr)	$AUC_{(0-\infty)}$ (mg · hr / ml)	U.R.[1] (%) (0 - 6 hr)
FR21818	0.24	21.0	68.9
Biapenem	0.26	20.7	70.7
Meropenem[2]	0.27	31.3	56.3
Imipenem[3]	0.22	22.3	70.0



Drug; 20 mg / kg, s.c.
Mouse; ICR, male, n=4-8, 5 weeks old
Assay; Bioassay
1); Urinary excretion
2); Meropenem / Cilastatin = 1:1
3); Imipenem / Cilastatin = 1:1

Figure 3. Plasma levels of FR21818 in mice.

Drug	$T_{1/2}\ \beta$ (hr)	$AUC_{(0-\infty)}$ (mg · hr / ml)	U.R.[1] (%) (0 - 6 hr)
FR21818	0.82	29.3	57.8
Biapenem	0.62	24.7	41.2



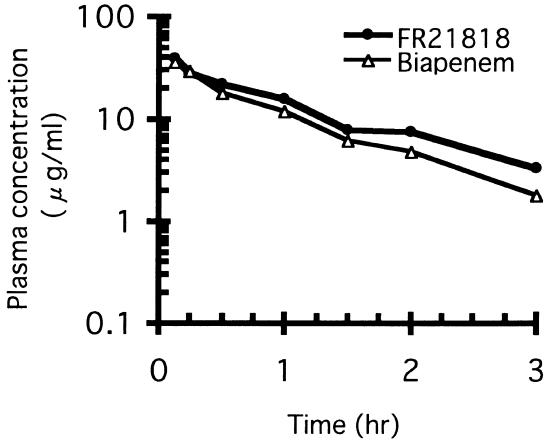
Drug; 10 mg / kg, i.v.
Dog;Beagle, male, n=3, 10 ~ 11.5 kg, cross over
Assay; Bioassay
1); Urinary excretion

Figure 4. Plasma levels of FR21818 in dogs.

dropwise a solution of **2a**[9] (272 g) in a mixture of THF (500 mL) and DME (250 mL) at −65 to −68 °C over 60 min. After stirring at the same temperature for 30 min, the mixture was warmed to −5 °C over 2 h, poured into a mixture of EtOAc (3000 mL) and ice-water (4000 mL), and separated. The aqueous layer was extracted with EtOAc (1000 mL). The combined organic layers was washed with H_2O (3000 mL) and brine, dried over $MgSO_4$, evaporated under reduced pressure to dryness, and treated with IPE (1500 mL). The precipitate was collected by filtration, washed with IPE and hexane, and dried at room temperature under atmospheric pressure to give (*RS*)-[(2*S*, 4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methyl-2-phenylthioimidazol-5-yl)methanol (222.4 g, 56.0%, as a mixture of diastereomers (2:1)) as a white powder. ^{1}H NMR ($CDCl_3$) δ −0.05–0.13 (6H, m), 0.83 and 0.86 (9H, s), 1.66–1.85 (1H, m), 1.92–2.29 (1H, m), 2.42 (dd, J = 9.7 Hz, 6.1 Hz) and 2.62 (dd, J = 11.7 Hz, 2.3 Hz) Total 1H, 2.97 (dd, J = 11.7 Hz, 4.4 Hz) and 3.15 (dd, J = 9.7 Hz, 5.4 Hz) total 1H, 3.23–3.57 (1H, m), 3.55 (3H, s), 3.84 (d, J = 13.0 Hz) and 3.58 (d, J = 13.0 Hz) total 1H, 3.99 (d, J = 13.0 Hz) and 3.96 (d, J = 13.0 Hz) total 1H, 4.18–4.40 (1H, m), 4.25 (d, J = 8.5 Hz) and 4.58 (d, J = 2.3 Hz) total 1H, 7.00–7.35 (11H, m); MS (APCI$^+$) 510 (MH^+). Raney-Ni in water (1400 mL) was washed with EtOH (1700 mL×3) under nitrogen. After removal of the solvent, to the solid was added EtOH (4400 mL), and the white powder (222 g) obtained in the first step, and stirred at room temperature for 2.5 h. After filtration, the filtrate was evaporated, dissolved in CH_2Cl_2 (1200 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was then dissolved in hexane (500 mL) and evaporated under reduced pressure to give **4a** (133.4 g, 76.4%, as a mixture of diastereomers (2:1)) as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ −0.03–0.03 (6H, m), 0.83 and 0.87 (9H, s), 1.69–1.90 (1H, m), 1.90–2.30 (1H, m), 2.40 (dd, J = 9.6 Hz, 6.4 Hz) and 2.62 (dd, J = 11.6 Hz, 2.4 Hz) total 1H, 2.98 (dd, J = 11.6 Hz, 4.5 Hz) and 3.15 (dd, J = 9.6 Hz, 5.4 Hz) total 1H, 3.25–3.50 (1H, m), 3.53 (3H, s), 3.86 (d, J = 13.0 Hz) and 3.55 (d, J = 13.1 Hz) total 1H, 4.05 (d, J = 13.0 Hz) and 3.97 (d, J = 13.1 Hz) total 1H, 4.23–4.41 (1H, m), 4.25 (d, J = 7.7 Hz) and 4.62 (d, J = 2.2 Hz) total 1H, 6.90 and 6.94 (1H, s), 7.19–7.42 (6H, m); MS (APCI$^+$) 402 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylpyrazol-5-yl)methanol (4d). To a solution of **3d** (30.5 g) in THF (460 mL) was added dropwise ^{n}BuLi (1.6 N in hexane) (250 mL) at −60 to −70 °C. After

Drug	$T_{1/2}\ \alpha$ (hr)	$T_{1/2}\ \beta$ (hr)	$AUC_{(0-\infty)}$ (mg · hr / ml)
FR21818	0.048	0.89	44.4
Biapenem	0.17	0.81	33.4



Drug; 10 mg / kg, i.v.
Monkey;Cynomolgus, male, n=3, 4.1 ~ 5.5 kg, cross over
Assay; Bioassay

Figure 5. Plasma levels of FR21818 in cynomolgus monkeys.

stirring at 0 to 5 °C for 30 min, a solution of **2a** (91.4 g) in THF (90 mL) was added to the mixture at −60 to −70 °C. The mixture was warmed to 0 to 5 °C over 40 min, stirred at the same temperature for 2 h, and then quenched with ice-water (300 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (×2). The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 6 L, EtOAc/hexane (1:1–5:1)) to give **4d** (101 g, 87.9%, as a mixture of diastereomers (2:1)) as an oil. IR (Neat) cm^{-1} 3200, 1240; ^1H NMR ($CDCl_3$) δ 0.01 and 0.05 (6H, s), 0.86 and 0.89 (9H, s), 1.56–1.85 (1H, m), 1.93–2.20 (1H, m), 2.48 (dd, $J=9.9$ Hz, 5.8 Hz) and 2.61 (dd, $J=11.5$ Hz, 2.9 Hz) total 1H, 3.02 (dd, $J=11.5$ Hz, 4.5 Hz) and 3.20 (dd $J=9.9$ Hz, 5.2 Hz) total 1H, 3.24–3.51 (1H, m), 3.82 and 3.86 (3H, s), 3.66 (d, $J=12.9$ Hz) and 3.79 (d, $J=13.1$ Hz) and 3.93 (d, $J=13.1$ Hz) and 4.02 (d, $J=12.9$ Hz) total 2H, 4.18–4.39 (1H, m), 4.41 (d, $J=6.1$ Hz) and 4.69 (d, $J=2.7$ Hz) total 1H, 6.14 (d, $J=1.9$ Hz) and 6.18 (d, $J=1.9$ Hz) total 1H, 7.20–7.38 (5H, m), 7.38 (d, $J=1.9$ Hz) and 7.40 (d, $J=1.9$ Hz) total 1H; MS (APCI$^+$) 402 (MH^+).

Using the same procedure, **4b**, **4c**, **4f–4i** were also prepared by the coupling reaction of aldehyde **2a** and the appropriate heteroaromatics.

Table 7. Physical data for pyrrolidine derivatives **7a–i**[a]

No.	^1H NMR (200 MHz, D_2O) δ ppm	MS	IR
7a	0.00 (6H s), 0.81 (9H, s), 1.78–2.05 (2H, m), 2.54–2.74 (1H, m), 3.12~3.27 (1H, m), 3.36–3.61 (2H, m), 3.60 (3H, s), 4.04–4.35 (2H, m), 4.54–4.71 (2H, m), 5.12–5.37 (2H, m), 5.86–6.06 (1H, m), 6.79 (1H, s), 7.40 (1H, s).	380	NT
7b	0.02 (6H, s), 0.83 (9H, s), 1.82–1.95 (1H, m), 2.16–2.28 (1H, dd, $J=14.3$ Hz, 8.8 Hz), 3.28–3.34 (2H, m), 3.63 (3H, s), 4.08–4.21 (2H, m), 4.62 (2H, m), 5.17–5.33 (2H, m), 5.85–5.99 (1H, m), 6.78 (1H, s), 6.89 (1H, s).	380	NT
7c	0.01 (6H, s), 0.83 (9H, s), 1.65–2.00 (2H, m), 2.70–2.95 (2H, m), 3.26 (1H, dd, $J=11.2$ Hz, 4.7 Hz), 3.28–3.45 (1H, m), 3.84 (3H, s), 4.03–4.22 (2H, m), 4.58–4.70 (2H, m), 5.17–5.40 (2H, m), 5.86–6.06 (1H, m), 7.12 (1H, s), 7.25 (1H, s)	380	1680, 1395, 1090
7d	0.03 (6H, s), 0.84 (9H, s), 1.73–2.00 (2H, m), 2.65–2.83 (1H, m), 3.03–3.50 (3H, m), 3.75–3.90 (3H, m), 4.08–4.28 (2H, m), 4.55–4.68 (2H, m), 5.18–5.38 (2H, m), 5.86–6.06 (1H, m), 6.01 (1H, d, $J=1.8$ Hz), 7.39 (1H, d, $J=1.8$ Hz)	380	1680, 1395, 1090
7e	0.03 (6H, s), 0.84 (9H, s), 1.62–2.06 (2H, m), 2.80–2.95 (1H, m), 3.20–3.56 (3H, m), 3.94–4.30 (5H, m), 4.57–4.68 (2H, m), 5.18–5.38 (2H, m), 5.85–6.05 (1H, m), 7.45 (1H, s)	381	1701, 1404, 1111
7f	0.03 (6H, s), 0.84 (9H, s), 1.89–2.28 (2H, m), 2.97–3.09 (1H, m), 3.23–3.55 (3H, m), 3.78–3.88 (3H, m), 4.15–4.30 (2H, m), 4.62–4.66 (2H, m), 5.19–5.34 (2H, m), 5.84–6.01 (1H, m), 7.75 (1H, s)	381	NT
7g	0.00 (6H, m), 0.83 (9H, m), 1.60–2.20 (2H, m), 2.83–3.10 (1H, m), 3.10–3.60 (3H, m), 4.00–4.10 (1H, m), 4.10–4.48 (1H, m), 4.48–4.78 (2H, m), 5.10–5.40 (2H, m), 5.80–6.08 (1H, m), 7.00–7.40 (2H, m), 7.50–7.90 (1H, m), 8.48–8.72 (1H, m)	NT	1680, 1400, 1100
7h	0.00 (6H, s), 0.84 (9H, s), 1.70–2.20 (2H, m), 2.70–3.60 (4H, m), 4.00–4.40 (2H, m), 4.60–4.80 (2H, m), 5.20–5.40 (2H, m), 5.90–6.10 (1H, m), 7.20–7.40 (1H, m), 7.40–7.60 (1H, m), 8.40–8.70 (1H, m), 8.40–8.70 (2H, m)	NT	NT
7i	0.00 (6H, s), 0.07 (6H, s), 0.83 (9H, s), 0.88 (9H, s), 1.60–1.95 (2H, m), 2.50–2.75 (1H, m), 2.80–2.95 (1H, m), 3.20–3.50 (2H, m), 3.87 (3H, s), 4.00–4.20 (2H, m), 4.55–4.70 (4H, m), 5.19–5.35 (2H, m), 5.87–6.03 (1H, m), 7.20 (1H, s)	524	NT

[a]MS, APCI–MS (NH^+), m/z; IR, IR (neat), cm^{-1}.

Table 8. Physical data for benzoylthio compounds[a]

No.	^{1}H NMR (200 MHz, D_2O) δ ppm	MS	IR
17a	1.82–2.02 (1H, m), 2.41 ~2.72 (1H, m), 2.70–2.98 (1H, m), 3.20–3.67 (2H, m), 3.67 (3H, brs), 3.92–4.30 (3H, m), 4.49–4.73 (2H, m), 5.15–5.42 (2H, m), 5.82–6.16 (1H, m), 6.82 (1H, s), 7.30–7.70 (4H, m), 7.80–8.22 (2H, m)	386	NT
17b	2.10–2.39 (1H, m), 2.43–2.73 (1H, m), 2.92 (1H, dd, J = 15.6 Hz, 10.1 Hz), 3.32 (1H, dd, J = 10.8 Hz, 6.3 Hz), 3.36–3.70 (1H, m), 3.68 (3H, s), 4.03–4.38 (3H, m), 4.57–4.71 (2H, m), 5.21–5.37 (2H, m), 5.86–5.97 (1H, m), 6.81 (1H, d, J = 1.2 Hz), 6.93 (1H, d, J = 1.2 Hz), 7.40–7.69 (5H, m)	386	NT
17c	1.74–1.88 (1H, m), 2.40–2.60 (1H, m), 2.79 (1H, dd, J = 14.2 Hz, 8.9 Hz), 2.90–3.15 (1H, m), 3.19 (1H, dd, J = 10.8 Hz, 7.3 Hz), 3.86 (3H, s), 3.95–4.25 (3H, m), 4.58–4.74 (2H, m), 5.19–5.42 (2H, m), 5.87–6.08 (1H, m), 7.17 (1H, s), 7.31 (1H, s), 7.37–7.74 (3H, m), 7.88–7.98 (2H, m)	386	1680, 1655, 1400
17d	1.80–2.00 (1H, m), 2.42–2.68 (1H, m), 2.75–3.00 (1H, m), 3.20–3.55 (2H, m), 3.75–3.98 (3H, brs), 4.00–4.30 (3H, m), 4.52–4.70 (2H, m), 5.18–5.40 (2H, m), 5.86–6.06 (1H, m), 6.04 (1H, d, J = 1.8 Hz), 7.40 (1H, d, J = 1.8 Hz), 7.30–8.20 (5H, m)	386	1680, 1650, 1390
17e	1.73–1.93 (1H, m), 2.48–2.70 (1H, m), 2.99 (1H, dd, J = 14.7 Hz, 9.7 Hz), 3.20–3.55 (2H, m), 3.85–4.30 (6H, m), 4.55–4.70 (2H, m), 5.18–5.40 (2H, m), 5.85–6.05 (1H, m), 7.35–8.18 (6H, m)	387	1701, 1664
17f	2.10–2.32 (1H, m), 2.52–2.95 (1H, m), 3.08 (1H, dd, J = 14.5 Hz, 9.5 Hz), 3.25–3.60 (2H, m), 3.90 (3H, brs), 4.05–4.40 (3H, m), 4.61–4.64 (2H, m), 5.22–5.36 (2H, m), 5.85–6.05 (1H, m), 7.80 (1H, s), 7.40–8.30 (5H, m)	387	NT
17g	1.67–2.13 (2H, m), 2.30–2.60 (1H, m), 2.98 (1H, dd, J = 13.2 Hz, 9.3 Hz), 3.15–3.35 (1H, m), 3.40–3.65 (1H, m), 4.00–4.40 (2H, m), 4.61–4.64 (2H, m), 5.20–6.03 (2H, m), 5.89–6.12 (1H, m), 7.10–7.20 (2H, m), 7.40–7.65 (4H, m), 7.90–7.95 (2H, m), 8.53–8.55 (1H, m)	NT	1685, 1650
17h	1.70–1.90 (2H, m), 2.20–2.60 (1H, m), 2.84 (1H, dd, J = 13.3 Hz, 9.4 Hz), 3.20–3.40 (2H, m), 4.03–4.26 (2H, m), 4.63–4.66 (2H, m), 5.23–5.39 (2H, m), 5.88–6.07 (1H, m), 7.20–7.73 (6H, m), 7.91–7.94 (2H, m), 8.47–5.50 (4H, m)	NT	NT
17i	1.65–1.85 (1H, m), 2.30–2.65 (1H, m), 2.80 (1H, dd, J = 13.1 Hz, 9.6 Hz), 3.20–3.60 (2H, m), 3.90–4.35 (3H, m), 4.62–4.66 (2H, m), 5.23–5.39 (2H, m), 5.87–6.07 (1H, m), 7.14–7.73 (5H, m), 7.90–7.95 (2H, m), 8.47–8.53 (2H, m)	NT	NT
21	1.60–2.70 (3H, m), 2.90–3.55 (3H, m), 3.75–4.70 (10H, m), 5.20–5.45 (2H, m), 5.85–6.05 (1H, m), 7.35–8.10 (6H, m)	416	NT
23	1.84–1.96 (1H, m), 2.50–2.63 (1H, m), 2.73 (1H, dd, J = 14.2 Hz, 9.0 Hz), 3.00–3.10 (1H, m), 3.20–3.60 (2H, m), 3.90 (3H, s), 4.00–4.21 (2H, m), 4.58–4.69 (4H, m), 5.21–5.35 (2H, m), 5.85–6.15 (1H, m), 7.27 (1H, s), 7.40–8.01 (5H, m)	416	NT
17j	1.70–2.00 (2H, m), 2.15 (3H, s), 2.30–2.65 (1H, m), 2.70–2.90 (1H, m), 3.20–3.60 (2H, m), 4.00–4.40 (2H, m), 4.55–4.75 (2H, m), 5.15–5.20 (2H, s), 5.85–6.15 (1H, m), 7.00–7.30 (2H, m), 7.40–8.00 (5H, m), 8.50 (1H, d, J = 5.0 Hz)	NT	1747, 1701, 1662
17k	1.65–2.10 (2H, m), 2.35–2.65 (1H, m), 2.87 (1H, dd, J = 13.1 Hz, 9.5 Hz), 3.20–3.80 (2H, m), 3.85–4.50 (2H, m), 4.62–4.66 (2H, m), 5.23–5.39 (2H, m), 5.75–6.15 (2H, m), 7.27–8.20 (5H, m), 8.08 (1H, s), 8.48 (1H, d, J = 4.9 Hz)	426	1693
19	1.85–2.05 (1H, m), 2.40–2.65 (1H, m), 2.69–2.90 (1H, m), 3.10–4.00 (3H, m), 3.70 (3H, brs), 4.00–4.30 (3H, m), 4.60–4.75 (4H, m), 5.22–5.37 (2H, m), 5.86–6.05 (1H, m), 6.68 (1H, s), 7.43–7.64 (3H, m), 7.91–7.95 (2H, m)	NT	NT

[a]MS, APCI (NH^+), m/z; IR, IR (neat), cm^{-1}.

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylimidazol-2-yl)methanol (4b). The isomer A of **4b** was isolated by precipitation with hexane from crude oil (48 g, 14.7%). The filtrate was evaporated and purified with column chromatography (SiO_2 5200 mL, EtOAc/hexane (3:2–1:0)) to give the isomer B of **4b** (147.4 g, 45%) containing 17% of isomer A, as a solid. Isomer B: brown oil; ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.86 (9H, s), 1.84–2.04 (2H, m), 2.57 (1H, dd, J = 11.1 Hz, 3.3 Hz), 2.97 (1H, dd, J = 11.1 Hz, 4.7 Hz), 3.66 (3H, s), 3.80 (1H, d, J = 13.0 Hz), 3.81–3.91 (1H, m), 4.10 (1H, d, J = 13.0 Hz), 4.18–4.25 (1H, m), 4.41 (1H, d, J = 5.6 Hz), 6.79 (1H, d, J = 1.2 Hz), 6.93 (1H, d, J = 1.2 Hz), 7.20–7.30 (5H, m); MS (APCI$^+$) 402 (MH^+). Isomer A: amorphous solid; ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 1.89–2.03 (1H, m), 2.17–2.31 (1H, m), 2.42 (1H, dd, J = 9.6 Hz, 6.3 Hz), 3.13 (1H, dd, J = 9.6 Hz, 5.4 Hz), 3.44–3.51 (2H, m), 3.57 (1H, d, J = 13.1 Hz), 3.67 (3H, s), 3.88 (1H, d, J = 13.1 Hz), 4.22–4.34 (1H, m), 4.70 (1H, d, J = 3.6 Hz), 6.79 (1H, d, J = 1.2 Hz), 6.96 (1H, d, J = 1.2 Hz), 7.22–7.37 (5H, m); MS (APCI$^+$) 402 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylpyrazol-4-yl)methanol (4c). Oil (65% as a mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$) δ 0.01 (s) and 0.02 (s) and 0.04 (s) total 6H, 0.85 (s) and 0.89 (s) total 9H, 1.46–1.62 (m) and 1.80–2.13 (m) total 2H, 2.41 (dd, J = 9.7 Hz, 5.6 Hz) and 2.52 (dd, J = 10.2 Hz, 3.5 Hz) total 1H, 3.00 (dd, J = 11.0 Hz, 4.7 Hz) and 3.12–3.25 (m) and 3.27–3.38 (m) total 2H, 3.54 (d, J = 13.0 Hz) and 3.72 (d, J = 13.1 Hz) and 3.91 (d, J = 13.1 Hz) and 4.11 (d, J = 13.0 Hz) total 2H, 3.88 (s) and 3.95 (s) total 3H, 4.15–4.35 (1H, m), 4.41 (d, J = 5.4 Hz) and 4.85 (d, J = 2.7 Hz) total 1H, 7.23–7.40 (6H, m), 7.41 (s) and 7.45 (s) total 1H; MS (APCI$^+$) 402 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methyl-1,2,4-triazol-5-yl)methanol (4f). Oil (75% as 1.6:1 mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$) δ 0.00–0.04 (6H, m), 0.85–0.88 (9H, m), 1.70–2.20 (2H, m), 2.49 (dd, J = 9.9 Hz, 5.6 Hz) and 2.63 (dd, J = 11.3 Hz, 3.8 Hz) total 1H, 3.02 (dd, J = 11.3 Hz, 4.6 Hz) and 3.17 (dd, J = 9.9 Hz, 5.2 Hz) total 1H, 3.40–4.01 (6H, m), 4.20–4.35 (1H, m), 4.53 (d, J = 4.7 Hz) and

Table 9. Physical data for carbapenems[a]

No.	^{1}H NMR (200 MHz, D_2O) δ ppm	MS	IR
1b	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.73–1.94 (1H, m), 2.71–2.97 (1H, m), 3.22–3.56 (5H, m), 3.72 (1H, dd, J = 12.4 Hz, 6.6 Hz), 3.83 (3H, s), 3.86 (3H, s), 4.00–4.33 (4H, m), 7.43 (1H, s), 8.69 (1H, s).	421	1750–1710, 1580–1530
1c	1.22 (3H, d, J = 7.1 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.30–1.54 (1H, m), 2.49–2.70 (1H, m), 2.94–3.12 (1H, m), 3.12–3.60 (6H, m), 3.70–3.94 (1H, m), 3.86 (6H, s), 4.12–4.37 (2H, m), 7.37 (2H, s)	421	1720, 1570, 1440
1d	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.70–1.88 (1H, m), 2.67–2.84 (1H, m), 3.05–3.20 (2H, m), 3.28–3.83 (2H, m), 3.85–4.15 (2H, m), 4.10 (6H, s), 4.18–4.32 (2H, m), 8.19 (2H, s)	421	NT
1e	1.21 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.78–1.93 (1H, m), 2.78–2.94 (1H, m), 3.30–3.55 (5H, m), 3.73 (1H, dd, J = 12.5 Hz, 6.6 Hz), 4.02 (3H, s), 4.10 (3H, s), 4.00–4.30 (4H, m), 6.76 (1H, d, J = 3.0 Hz), 8.16 (1H, d, J = 3.0 Hz)	421	1760, 1605
1f	1.22 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.75–1.95 (1H, m), 2.75–2.95 (1H, m), 3.25–3.60 (5H, m), 3.74 (1H, dd, J = 12.5 Hz, 6.6 Hz), 4.00–4.33 (4H, m), 4.27 (3H, s), 4.31 (3H, s), 8.56 (1H, s)	422	1757, 1585
1g	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.58 (1H, m), 2.64–2.79 (1H, m), 3.18–4.00 (8H, m), 3.96 (3H, s), 4.13 (3H, s), 4.18–4.35 (2H, m), 8.79 (1H, s)	422	1725
1h	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.35–1.60 (0.5H, m), 2.05–2.20 (1H, m), 2.55–2.85 (0.5H, m), 2.90–3.10 (1H, m), 3.20–4.05 (7H, m), 4.20–4.30 (2H, m), 4.33 (3H, s), 7.90 (1H, dd, J = 7.9 Hz, 5.9 Hz), 8.02 (1H, d, J = 7.5 Hz), 8.47 (1H, dd, J = 7.9 Hz, 7.5 Hz), 8.75 (1H, d, J = 5.9 Hz)	418	1725, 1570, 1445
1i	1.21 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.50–1.70 (1H, m), 2.50–2.70 (1H, m), 3.20–3.60 (5H, m), 3.70–4.00 (2H, m), 4.10–4.30 (2H, m), 4.39 (3H, m), 8.02 (1H, dd, J = 8.0 Hz, 6.0 Hz), 8.49 (1H, d, J = 8.0 Hz), 8.72 (1H, d, J = 6.0 Hz), 8.80 (1H, s)	NT	1740
1k	1.22 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.75–1.97 (1H, m), 2.77–2.98 (1H, m), 3.24–3.60 (5H, m), 3.74 (1H, dd, J = 12.5 Hz, 6.6 Hz), 3.85 (3H, s), 3.88–4.02 (2H, m), 4.02–4.40 (4H, m), 7.54 (1H, s), 8.81 (1H, s)	NT	1750, 1570
1l	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.75–1.90 (1H, m), 2.75–2.95 (1H, m), 3.25–3.50 (5H, m), 3.66–3.76 (1H, m), 3.84 (3H, s), 3.89 (3H, s), 4.05–4.30 (4H, m), 4.93 (2H, s), 7.45 (1H, s)	451	1730
1m	1.22 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.72–1.95 (1H, m), 2.79–2.98 (1H, m), 3.23–3.55 (5H, m), 3.71 (1H, dd, J = 12.5 Hz, 6.6 Hz), 3.88 (3H, s), 4.02–4.35 (4H, m), 5.08 (2H, s), 7.50 (1H, s) 8.84 (1H, s)	NT	1750, 1680, 1570
1n	1.21 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.79–1.94 (1H, m), 3.25–3.55 (5H, m), 3.73 (1H, dd, J = 12.5 Hz, 6.5 Hz), 3.90–4.32 (6H, m), 4.07 (6H, s), 4.64 (2H, t, J = 4.9 Hz), 6.83 (1H, d, J = 3.0 Hz), 8.27 (1H, d, J = 3.0 Hz	451	1759, 1590
1o	1.22 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.70–2.00 (1H, m), 2.65–2.85 (1H, m), 3.30–3.90 (7H, m), 3.95–4.05 (1H, m), 4.07 (3H, s), 4.11 (3H, s), 4.15–4.35 (2H, m), 4.67 (2H, s), 8.24 (1H, s)	451	1755, 1460
1p	1.21 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.72–1.90 (1H, m), 3.10–3.25 (2H, m), 3.26–3.55 (3H, m), 3.69 (1H, dd, J = 12.5 Hz, 6.7 Hz), 3.90–4.14 (4H, m), 4.15 (3H, s), 4.16–4.33 (2H, m), 4.61 (2H, t, J = 4.9 Hz), 8.25 (1H, s), 8.31 (1H, s)	451	1750, 1590
1q	1.21 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.65–1.90 (1H, m), 2.60–2.85 (1H, m), 3.10–3.55 (5H, m), 3.60–4.05 (3H, m), 4.11 (3H, s), 4.20 (3H, s), 4.25–4.30 (2H, m), 4.85 (2H, s), 8.22 (1H, s)	451	1749, 1652, 1578
1r	1.21 (3H, d, J = 7.1 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.80–2.90 (2H, m), 3.30–4.80 (14H, m), 8.07 (2H, d, J = 6.5 Hz), 8.83 (2H, d, J = 6.6 Hz)	448	1740
1s	1.21 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.75–1.95 (1H, m), 2.65–2.90 (1H, m), 3.30–3.65 (5H, m), 3.72 (1H, dd, J = 12.5 Hz, 6.9 Hz), 4.00–4.15 (1H, m), 4.15–4.35 (6H, m), 4.22 (3H, s), 5.02 (2H, s), 7.85–7.95 (1H, m), 8.15–8.20 (1H, m), 8.72 (1H, d, J = 6.5 Hz)	448	1760, 1645, 1580
1t	1.21 (3H, d, J = 7.1 Hz), 1.28 (3H, d, J = 6.8 Hz), 1.80–2.90 (2H, m), 3.30–4.50 (10H, m), 5.50 (2H, s), 8.09 (1H, d, J = 6.7 Hz), 8.78 (2H, d, J = 6.8 Hz)	461	1750, 1690
1u	1.21 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.80–1.95, 2.30–2.45 and 2.70–2.90 (2H, m), 3.30–3.60 (5H, m), 3.60–3.95 (1H, m), 4.00–4.30 (4H, m), 4.39 (3H, s), 8.12 (1H, d, J = 6.4 Hz), 8.24 (1H, d, J = 1.9 Hz), 8.88 (1H, d, J = 6.4 Hz)	NT	1755, 1700, 1635, 1580

[a]MS FAB–MS (NH^+), m/z; IR, IR (Nujol), cm^{-1}.

4.82 (d, J = 3.4 Hz) total 1H, 7.23–7.35 (5H, m), 7.78 (s) and 7.80 (s) total 1H; MS (APCI$^+$) 403 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(pyridin-2-yl)methanol (4g). Oil (76% as 1.2/1 mixture of diastereoisomers): IR (neat) cm^{-1} 3250, 2920, 1580, 1430; ^{1}H NMR ($CDCl_3$) δ 0.00–0.03 (6H, m), 0.81 (s) and 0.84 (s) total 9H, 1.13–1.31 (m) and 1.78–1.90 (m) total 1H, 2.03 (1H, dd, J = 7.5 Hz, 5.8 Hz), 2.39 (1H, dd, J = 10.1 Hz, 5.4 Hz), 2.97 (dd, J = 10.3 Hz, 4.9 Hz) and 3.17 (dd, J = 9.6 Hz, 5.4 Hz) total 1H, 3.40–4.22 (3H, m), 4.10–4.30 (1H, m), 4.60 (d, J = 2.4 Hz) and 4.93 (d, J = 3.3 Hz) total 1H, 7.05–7.75 (8H, m), 8.53–8.58 (1H, m).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(pyridin-3-yl)methanol (4h). Oil (74% as 1:1 mixture of diastereoisomers): ^{1}H NMR ($CDCl_3$) δ −0.08–0.00 (6H, m), 0.78 (s) and 0.84 (s) total 9H, 1.10–1.30 (m) and 1.80–1.95 (m) total 1H, 1.90–2.05 (1H, m), 2.41–2.54 (1H, m), 2.99 (dd, J = 11.1 Hz, 4.5 Hz) and 3.19 (dd, J = 10.2 Hz, 5.2 Hz) total 1H, 3.20–3.45 (1H, m), 3.63 (s) and 3.63 (d, J = 13.0 Hz) and 4.13 (d, J = 13.0 Hz) total 2H, 4.16–4.28 (1H, m), 4.46 (d, J = 4.4 Hz) and 4.82 (d, J = 3.0 Hz) total 1H, 7.19–7.34 (6H, m), 7.64–7.72 (1H, m), 8.46–8.60 (2H, m).

(*RS*)-[(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(5-*tert*-butyldimethylsilyloxymethyl-1-methylpyrazol-4-yl)methanol (4i). Oil (0.75 g, 44% as a mixture of diastereoisomers). ^{1}H NMR ($CDCl_3$) δ −0.11–0.04 (12H, m), 0.77 (9H, m), 0.80 (9H, s), 1.00–4.80 (9H, m), 3.76–3.77 (3H, m), 4.58–4.60 (2H, m), 7.16–7.28 (6H, m); MS (APCI$^+$) 546 (MH^+).

6c, **6e**, **6g** were also prepared probably as a diastereomeric mixture, by the coupling reaction of aldehyde **2b**[9] and the appropriate heteroaromatics by the same method as described for **4d**. The NMR spectrum of the coupling product **6c**, **6g** were identical to the products obtained from diastereomeric mixtures **4c**, **4g**. However, we could not obtain further information about diastereomers from NMR signal and also not separate diastereomers by TLC.

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylpyrazol-4-yl)methanol (6c). Brown oil (39%). IR (neat) cm^{-1} 3300, 1670, 1400, 1100; ^{1}H NMR ($CDCl_3$) δ 0.01 and 0.02 (6H, s), 0.83 and 0.84 (9H, s), 1.50–2.00 (3H, m), 3.08–3.70 (2H, m), 4.10–4.50 (2H, m), 3.87 and 3.88 (3H, s), 4.58–4.70 (2H, m), 4.72–5.00 (1H, m), 5.19–5.45 (2H, m), 5.86–6.05 (1H, m), 7.26 (s) and 7.37 (s) and 7.41 (s) total 2H; MS (APCI$^+$) 396 (MH^+), 378 ($MH^+ - H_2O$).

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methyl-1,2,3-triazol-5-yl)methanol (6e). Oil (62%). IR (Nujol) cm^{-1} 3197, 1699; ^{1}H NMR ($CDCl_3$) δ 0.02 and 0.03 and 0.05 (6H, s), 0.84 and 0.85 (9H, s), 1.43–1.95 (2H, m), 3.27–3.73 (2H, m), 4.63–4.90 (8H, m), 5.19–5.40 (2H, m), 5.85–6.05 (1H, m), 7.50 and 7.53 (1H, s); MS (APCI$^+$) 397 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(pyridin-2-yl)methanol (6g). Oil (34%). IR (Nujol) cm^{-1} 3350, 1690; ^{1}H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 1.50–2.20 (2H, m), 3.40–3.60 (2H, m), 4.32–4.45 (1H, m), 4.50–4.70 (3H, m), 5.20–5.45 (3H, m), 5.86–6.03 (1H, m), 7.18–7.42 (2H, m), 7.66–7.74 (1H, m), 8.50–8.60 (1H, m).

6c was also prepared from **4c** by exchange of the *N*-protecting group. To a solution of **4c** (70 g) in MeOH (700 mL) was added $HCOONH_4$ (44 g) and 10% Pd/C (wet, 20 g). The mixture was stirred under reflux for 40 min, and then cooled to room temperature. After filtration, the mixture was evaporated and treated with $CHCl_3$ (500 mL). The precipitated excess ammonium formate was filtered off with Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of THF and water (1:1, 1000 mL) and a solution of allyl chloroformate (22.3 mL) in THF (60 mL) was added, adjusting pH (8.5–10) with 4 N NaOH, at 0–5 °C. The mixture was stirred for 30 min at the same temperature. The organic layer was separated and the aqueous layer extracted with EtOAc (×2). The combined organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give **6c** (66.2 g, 96%) maybe as a diastereomeric mixture. The physical data of this oil were identical with the data obtained earlier.

The preparation of **6d**, **6f–6i** by exchange of the *N*-protecting group from **4d**, **4f–4i** was achieved by the same method as that of **6c**.

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methylpyrazol-5-yl)methanol (6d). Oil (103.6 g, 97.1%). IR (neat) cm^{-1} 3220, 1665, 1395; ^{1}H NMR ($CDCl_3$) δ 0.01 and 0.03 (6H, s), 0.84 and 0.85 (9H, s), 1.42–2.08 (2H, m), 3.28–3.70 (2H, m), 3.85–4.00 (3H, m), 4.10–4.80 and 5.18–5.38 (7H, m), 5.85–6.06 (1H, m), 6.12–6.18 (1H, m), 7.35–7.41 (1H, m); MS (APCI$^+$) 396 (MH^+).

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(1-methyl-1,2,4-triazol-5-yl)methanol (6f). Colorless oil (5.96 g, 98%). ^{1}H NMR ($CDCl_3$) δ 0.02–0.06 (6H, m), 0.84–0.89 (9H, m), 1.60–2.40 (2H, m), 3.25–3.70 (2H, m), 3.98–4.01 (3H, m), 4.00–5.90 (3H, m), 4.55–4.65 (2H, m), 4.95–5.40 (2H, m), 5.87–6.05 (1H, m), 7.74–7.75 (1H, m); MS (APCI$^+$) 397 (MH^+).

The physical data of **6g** obtained by exchange of the *N*-protecting group was identical with the data obtained by coupling of **2b** with the heteroaromatic (184.11 g, 94%).

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(pyridin-3-yl)methanol (6h). Oil (0.41 g, 53%). ^{1}H NMR ($CDCl_3$) δ 0.00–0.05 (6H, m), 0.83 and 0.88 (9H, s), 1.50–2.10 (2H, m), 2.54 (dd, J = 11.2 Hz, 4.3 Hz) and 3.03 (dd, J = 11.1 Hz, 4.5 Hz) total 1H, 3.35–3.55 (1H, m), 3.60–4.50 (3H, m), 4.60–4.75 (2H, m), 5.23–5.39 (2H, m), 5.88–6.07 (1H, m), 7.23–7.35 (1H, m), 7.66–7.80 (1H, m), 8.48–8.64 (2H, m).

(*RS*)-[(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]-(5-*tert*-butyldimethylsilyloxymethyl-1-methylpyrazol-4-yl)methanol (6i). Oil (6.39 g, 80%). ^{1}H NMR ($CDCl_3$) δ −0.11 (6H, s), −0.05 (6H, s), 0.70 (9H, s), 0.77 (9H, s), 1.70–1.80 (2H, m), 3.00–3.60 (2H, m), 3.74–4.75 (3H, m), 3.96–4.46 (2H, m), 4.55–4.90 (4H, m), 5.10–5.48 (3H, m), 5.75–6.00 (1H, m), 7.22–7.29 (1H, m); MS (APCI$^+$) 540 (MH^+).

(2*R*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylimidazol-5-yl) methyl]pyrrolidine (5a). To a solution of **4a** (234 g) in CH_2Cl_2 (4900 mL) was added dropwise a solution of $SOCl_2$ (46.8 mL) in CH_2Cl_2 (50 mL) at −20 to −15 °C, and the mixture was stirred at −20 °C for

60 min. To the mixture was added dropwise a solution of PhSH (65.7 mL) in CH_2Cl_2 (120 mL) at −20 to −15 °C, and the mixture was stirred at −20 to −15 °C for 30 min. To the mixture was added dropwise Et_3N (89.2 mL) at −20 to −15 °C. After stirring at −15 to −5 °C for 60 min. The mixture was poured into ice-water (4000 mL), added NaCl, and separated. The organic layer was washed with saturated $NaHCO_3$ solution (2000 mL×2), dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 6000 mL, $CHCl_3$/MeOH (100:1–5:1)) to give (2*S*,4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylimidazol-5-yl)-phenylthiomethyl]pyrrolidine as a brown oil (211.7 g, 73.5%). To a solution of the oil (211 g) in toluene (2500 mL) was added $^nBu_3SnH$ (173 mL) and AIBN (10.5 g) at rt, and the mixture was stirred under reflux for 1.5 h. To the mixture was added $^nBu_3SnH$ (58 mL) and AIBN (3.5 g) at rt. After stirring under reflux for 15 min, the mixture was cooled to rt and evaporated under reduced pressure to give oil (473 g). The oil was purified with column chromatography (SiO_2 12000 mL, EtOAc then $CHCl_3$/MeOH (30:1) to give **5a** (130.7 g, 79.4% (two steps total 58.4%)) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.86 (9H, s), 1.74–1.92 (2H, m), 2.27 (1H, dd, *J* = 9.8 Hz, 5.9 Hz), 2.52 (1H, dd, *J* = 15.2 Hz, 9.0 Hz), 2.84 (1H, dd, *J* = 15.2 Hz, 3.9 Hz), 2.99–3.20 (2H, m), 3.44 (1H, d, *J* = 13 Hz), 4.01 (1H, d, *J* = 13 Hz), 3.51 (3H, s), 4.03–4.35 (1H, m), 6.83 (1H, d, *J* = 0.8 Hz), 7.21–7.42 (6H, m); MS (APCI$^+$) 386 (MH^+).

Using the same procedure, **5d** was also prepared from **4d**.

(2*R*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylimidazol-2-yl) methyl]pyrrolidine (5b). Using the same procedure as that of **5a**, (2*R*,4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylimidazol-2-yl)-phenylthiomethyl]pyrrolidine was prepared from the isomer B of **4b** as an amorphous solid (48.6 g, 100%). To a suspension of Raney-Ni (NDT-90, 710 mL) and Me_2CO (300 mL) was added the amorphous solid (47.8 g) in Me_2CO (500 mL) under an atmosphere of nitrogen. The mixture was stirred under reflux for 1.5 h. After cooling, the Raney-Ni was removed by filtration, and washed with Me_2CO (500 mL×5). The filtrate and the washings were combined, evaporated, and purified with column chromatography (SiO_2 2400 mL, $CHCl_3$/MeOH (30:1) to give **5b** (23.8 g, 64%) as a pale yellow oil; ^1H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.86 (9H, s), 1.88–1.95 (2H, m), 2.28 (1H, dd, *J* = 9.8 Hz, 5.7 Hz), 2.68 (1H, dd, *J* = 14.1 Hz, 8.4 Hz), 2.94 (1H, dd, *J* = 14.6 Hz, 4.8 Hz), 3.13 (1H, dd, *J* = 9.8 Hz, 5.7 Hz), 3.21–3.36 (1H, m), 3.44 (1H, d, *J* = 13.1 Hz), 3.92 (1H, d, *J* = 13.1 Hz), 3.55 (3H, s), 4.25–4.34 (1H, m), 6.77 (1H, d, *J* = 1.2 Hz), 6.94 (1H, d, *J* = 1.2 Hz), 7.21–7.33 (5H, m); MS (APCI$^+$) 386 (MH^+). Using the same procedure, **5b** was obtained from the isomer A of **4b** (62%)

(2*R*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylpyrazol-5-yl) methyl]pyrrolidine (5d). An oil (47.36 g, 45%); ^1H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.85 (9H, s), 1.68–1.92 (2H, m), 2.28 (1H, dd, *J* = 9.8 Hz, 5.6 Hz), 2.58 (1H, dd, *J* = 15.0 Hz, 8.9 Hz), 2.91 (1H, dd, *J* = 15.0 Hz, 4.1 Hz), 3.02–3.20 (1H, m), 3.16 (1H, dd, *J* = 9.8 Hz, 5.8 Hz), 3.44 (1H, d, *J* = 13.0 Hz), 3.77 (3H, s), 4.00 (1H, d, *J* = 13.0 Hz), 4.18–4.30 (1H, m), 6.07 (1H, d, *J* = 1.8 Hz), 7.22–7.34 (5H, m), 7.39 (1H, d, *J* = 1.8 Hz).

7a and **7b** were prepared from **5a** and **5b** by the same method as described for **6c**. The physical data for **7a–7i** are collected in Table 7.

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylpyrazol-4-yl)methyl]pyrrolidine (7c). To a ice-cooling solution of **6c** (71.2 g) in CH_2Cl_2 (700 mL) was added pyridine (54 mL) and PhOCSCl (34.3 g). The mixture was stirred for 30 min at 0 °C, then stirred for 3 h at room temperature. After the evaporation of CH_2Cl_2, the residue was poured into saturated $NaHCO_3$, then extracted with EtOAc. The organic layer was washed H_2O and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 2000 mL, EtOAc/hexane (3:5–4:5)) to give (2*S*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methylpyrazol-4-yl)-(phenoxythiocarbonyloxy)methyl]pyrrolidine (46.2 g, 48.3%) as an oil. IR (neat) cm^{-1} 1685, 1400, 1090; ^1H NMR ($CDCl_3$) δ 0.02 and 0.04 (6H, s), 0.84 (9H, s), 1.86–2.16 (2H, m), 2.95–3.18 and 3.35–3.80 (2H, m), 3.80–3.92 (3H, m), 3.92–4.10 and 4.32–4.42 (1H, m), 4.42–4.73 (3H, m), 5.08–5.43 (3H, m), 5.82–6.10 (1H, m), 7.05–7.51 (7H, m); MS (APCI$^+$) 532 (MH^+). To a solution of the oil (42.9 g) in toluene (600 mL) was added $^nBu_3SnH$ (43.5 mL) and AIBN (2.65 g) at room temperature. The mixture was refluxed for 3.5 h. To the mixture was added $^nBu_3SnH$ (10.9 mL) and AIBN (1.33 g), then refluxed again for 3.5 h. After cooling, the mixture was concentrated under reduced pressure and purified with column chromatography (SiO_2 2400 mL, EtOAc/hexane (4:5)) to give **7c** (22.3 g, 72.9%) as an oil.

7d and **7f** was prepared from **6d** and **6f** by the same method as described for **7c**. **7d** (55.5 g, two steps total 55.9%); **7f** (2.69 g, two steps total 84.8%).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methyl-1,2,3-triazol-5-yl)methyl]pyrrolidine (7e). To a solution of **6e** (70 g), imidazole (140 mg) and CS_2 (32 mL) in THF (700 mL) was added NaH (60% oil suspension, 7.79 g) at 0 to 8 °C and the mixture was stirred for 30 min at the same temperature. After addition of MeI (22 mL), the mixture was stirred at 0 to 8 °C for 1 h and at room temperature for 4 h. The mixture was quenched with ice-water (200 mL) and extracted with EtOAc (150 mL×2). The combined organic layer was washed with brine (×3), dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 2000 mL, EtOAc/hexane (1:2)) to give 85 g (99%) of (2*S*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(1-methyl-1,2,3-triazol-5-yl)-1-(methylthiothiocarbonyloxy)methyl] pyrrolidine as an oil. A diastereomeric mixture; IR (neat) cm^{-1} 1703, 1404, 1201; ^1H NMR ($CDCl_3$) δ 0.02–0.08 (6H, m), 0.84 and 0.87 (9H, s), 1.82–2.50 (2H, m), 2.56 and 2.58 (3H, s), 2.85–3.00 and 3.30–3.60 (2H, m), 3.95–4.30 (2H, m), 4.03 (3H, s), 4.48–4.70 (3H, m), 5.15–5.38 (2H, m), 5.80–6.05 (1H, m), 7.59 and 7.60 (1H, s); MS (APCI$^+$) 487 (MH^+). To a solution of the oil (84 g) in toluene (850 mL) was added $^nBu_3SnH$ (56 mL) and AIBN (2 g),

and the mixture was refluxed for 30 min. After cooling to room temperature, the mixture was filtered with Celite and evaporated to give residue (150 g) which was purified with column chromatography (SiO_2 6000 mL, EtOAc/hexane (2:1)) to give **7e** (65.7 g, 100%) as an oil.

7i was prepared from **6i** by the same method as described for **7e**. **7i** (3.47 g, two steps total 56.2%).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(pyridin-2-yl)methyl]pyrrolidine (7g). To a solution of **6g** (19.8 g) and Ph_3P (21.2 g) in THF (400 mL) was added CBr_4 (25.1 g) at room temperature. After stirring at room temperature for 2 h and allowed to stand overnight, the mixture was filtered. The filtrate was evaporated under reduced pressure to give residue which was dissolved in a mixture of DMF (200 mL) and AcOH (60 mL). To the solution was added portionwise Zn-powder (16.5 g) under 30 °C. After stirring at room temperature for 1 h, the mixture was neutralized with $NaHCO_3$ (84 g) in water and extracted with EtOAc (×3). The combined extracts was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give **7g** (17.7 g, 93.1%).

7h was prepared from **6h** by the same method as described for **7g**. **7h** (Oil, 11.4 g, 75.7%).

Diethyl 1-ethoxycarbonyl-1,4-dihydroxypyridine-4-phosphonate (9a). To a solution of pyridine (158.2 g) in MeCN (950 mL) was added ClCOOEt (191.2 mL) at −20 °C over 20 min, and the mixture was stirred at 0 °C for 40 min. To the mixture was added triethyl phosphite (343 mL) at −20 °C over 20 min. After stirring at room temperature for 20 h, the mixture was evaporated under reduced pressure and azeotropically concentrated with toluene to give **9a** (550 g, 95%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.20–1.40 (9H, m), 3.39–3.58 (1H, m), 4.06–4.31 (6H, m), 4.80–5.10 (2H, m), 6.70–7.00 (2H, m).

Diethyl 1-ethoxycarbonyl-1,4-dihydroxy-2-methylpyridine-4-phosphonate (9b). Using the same procedure as described for **9a** and additional purification with column chromatography (SiO_2), **9b** was also prepared from 2-picoline (229.1 g). **9b** (428.42 g, 57.4%): IR (neat) cm^{-1} 2983, 1724; ^{1}H NMR ($CDCl_3$) δ 1.22–1.40 (9H, m), 2.18–2.21 (3H, m), 3.25–3.50 (1H, m), 4.04–4.27 (6H, m), 4.80–4.90 (1H, m), 5.00–5.10 (1H, m), 6.94 (1H, dd, J = 7.9 Hz, 5.2 Hz).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(pyridin-4-yl)methyl]pyrrolidine (10a). Preparation from iodide (**8**). To a solution **9a** (0.75 g) in THF (10 mL) was added to dropwise ^{n}BuLi (1.66 N in hexane) (1.56 mL) at −60 to −70 °C, and the mixture was stirred at −70 °C for 1 h. To the mixture was added dropwise a solution of **8** (1.0 g) in THF (2 mL) at −60 to −70 °C. The mixture was stirred at −70 °C for 30 min and then at 0 °C for 20 min. To the mixture was added ^{n}BuLi (1.66 N in hexane) (3.12 mL) at −70 °C. After warming to 0 °C, the mixture was quenched with water and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 70 mL, eluted by EtOAc/hexane (4:6–5:5)) to give **10a** (0.27 g, 30%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.81 (9H, s), 1.60–2.00 (2H, m), 2.75–3.50 (4H, m), 4.05–4.30 (2H, m), 4.64 (2H, dd, J = 5.4 Hz, 1.5 Hz), 5.21–5.37 (2H, m), 5.87–6.06 (1H, m), 7.05–7.10 (2H, m), 8.52 (2H, d, J = 6.0 Hz); MS (APCI$^+$) 377 (MH^+).

Preparation from aldehyde (2b). To a solution of **9a** (24 g) in THF (200 mL) was added dropwise ^{n}BuLi (1.66 N in hexane) (50 mL) at −50 to −70 °C, and the mixture was stirred at −70 °C for 30 min. To the mixture was added dropwise a solution of **2b** (20 g) in THF (40 mL) at −50 to −70 °C. After stirring at −70 °C for 30 min, the mixture was warmed to room temperature and stirred at room temperature overnight. The mixture was quenched with water (200 mL), and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 880 mL, eluted by EtOAc/hexane (4:6–6:4)) to give **10a** (25.44 g, 106%).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(2-methylpyridin-4-yl)methyl]pyrrolidine (10b). 10b was obtained from **9b** (75.6 g) and **8** (64.84 g) using the similar procedure as described for **10a**. **10b** an orange oil (43.96 g, 74%): IR (neat) cm^{-1} 2929, 1714; ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 1.22–1.45 (1H, m), 1.60–1.95 (1H, m), 2.53 (3H, s), 2.55–2.82 (1H, m), 3.00–3.25 (1H, m), 3.30–3.50 (2H, m), 4.05–4.30 (2H, m), 4.65–4.70 (2H, m), 5.21–5.37 (2H. m), 5.88–6.12 (1H, m), 6.88–7.03 (2H, m), 8.39 (1H, d, J = 5.0 Hz); MS (APCI$^+$) 391 (MH^+).

(2*R*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-[(2-ethoxycarbonyl-1-methylimidazol-5-yl)methyl]pyrrolidine (11). To a solution of **5a** (46.05 g) in THF (468 mL) was added dropwise ^{n}BuLi (1.64M in hexane) (88.26 mL) at −60 to −75 °C. After stirring for 50 min at the same temperature, the mixture was added to a solution of ClCOOEt (13.84 mL) in THF (234 mL) at −60 to −75 °C over 30–40 min. After stirring at the same temperature for 30–40 min, the mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:50–1:20) to give **11** (39.23 g, 71.1%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.84 (9H, s), 1.43 (3H, t, J = 7.1 Hz), 1.67–1.92 (2H, m), 2.57 (1H, dd, J = 15.4 Hz, 8.8 Hz), 2.86 (1H, dd, J = 15.4 Hz, 4.1 Hz), 2.30 (1H, dd, J = 9.9 Hz, 5.4 Hz), 3.07–3.22 (1H, m), 3.18 (1H, dd, J = 9.9 Hz, 5.7 Hz), 3.47 (1H, d, J = 13.0 Hz), 3.86 (3H, s), 4.00 (1H, d, J = 13.0 Hz), 4.22–4.34 (1H, m), 4.40 (2H, q, J = 7.1 Hz), 7.16–7.33 (6H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(2-ethoxycarbonyl-1-methylimidazol-5-yl)methyl]pyrrolidine (12). 12 (15.11 g, 85.3%) was obtained in substantially the same manner as the exchange of the *N*-protecting group of **4c**. Oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (9H, s), 1.39 (3H, t, J = 7.1 Hz), 1.68–1.88 (2H, m), 2.65 (1H, dd, J = 14.6 Hz, 9.6 Hz), 3.00–3.60

(3H, m), 3.89–3.96 (3H, m), 4.00–4.20 (1H, m), 4.20–4.31 (1H, m), 4.37 (2H, q, $J = 7.1$ Hz), 4.60–4.70 (2H, m), 5.18–5.33 (2H, m), 5.82–6.02 (1H, m), 6.90 (1H, s).

(2*R*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-[(4-formyl-1-methylpyrazol-5-yl)methyl]pyrrolidine (13). To a solution of Br_2 (0.14 mL) and Na_2CO_3 (0.55 g) in CH_2Cl_2 (10 mL) was added dropwise a solution of **5d** (1.0 g) in CH_2Cl_2 (2 mL) at 0 °C. After stirring at room temperature for 30 min, the mixture was quenched with a mixture of saturated $Na_2S_2O_3$ aqueous solution (5 mL) and CH_2Cl_2 (20 mL). The organic layer was separated, washed successively with saturated $Na_2S_2O_3$ aqueous solution and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 100 mL, EtOAc/hexane = 1:2) to give (2*R*,4*R*)-1-benzyl-2-[(4-bromo-1-methylpyrazol-5-yl)methyl]-4-*tert*-butyldimethylsilyloxypyrrolidine (791 mg, 66%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.85 (9H, s), 1.65–1.88 (2H, m), 2.27–2.40 (1H, m), 2.60–3.22 (4H, m), 3.50 (1H, d, $J = 13.0$ Hz), 3.79 (3H, s), 3.96 (1H, d, $J = 13.0$ Hz), 4.20–4.35 (1H, m), 7.20–7.33 (5H, m), 7.39 (1H, s); MS (APCI$^+$) 466, 464 (MH^+). To a solution of the oil (1.0 g) in Et_2O (15 mL) was added dropwise ^{n}BuLi (1.62 M in hexane) (1.86 mL) at −10 °C, and the mixture was stirred at −10 °C for 30 min and at room temperature for 1 h. To the mixture was added dropwise DMF (0.5 mL) at −30 °C. After stirring at −20 to 0 °C for 1 h, the mixture was quenched with a mixture of saturated NH_4Cl solution (10 mL) and EtOAc (50 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 100 mL, EtOAc/hexane = 1:2) to give **13** (591 mg, 66%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.85 (9H, s), 1.70–1.81 (2H, m), 2.32 (1H, dd, $J = 10.3$ Hz, 4.8 Hz), 3.00–3.35 (4H, m), 3.53 (1H, d, $J = 13.1$ Hz), 3.83 (3H, s), 3.93 (1H, d, $J = 13.1$ Hz), 4.20–4.35 (1H, m), 7.20–7.40 (5H, m), 7.88 (1H, s), 9.86 (1H, s); MS (APCI$^+$) 414 (MH^+).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(4-hydroxymethyl-1-methylpyrazol-5-yl)methyl]pyrrolidine (14). To a solution of **13** (14.0 g) in a mixture of THF (140 mL) and MeOH (140 mL) was added $NaBH_4$ (1.28 g) under 0 to 5 °C. After stirring at the same temperature for 1 h, the solution was quenched with 1 N HCl (33 mL) and evaporated under reduced pressure. The residue was dissolved in EtOAc (300 mL), washed with H_2O, saturated $NaHCO_3$, and brine successively. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 800 mL, EtOAc/hexane = 2:1) to give (2*R*,4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxy-2-[(4-hydroxymethyl-1-methylpyrazol-5-yl)methyl]pyrrolidine (7.91 g, 56%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.86 (9H, s), 1.45–1.60 (1H, m), 1.80–1.95 (1H, m), 2.45–2.85 (3H, m), 2.97 (1H, dd, $J = 11.2$ Hz, 4.7 Hz), 3.56 (1H, d, $J = 12.2$ Hz), 3.69 (3H, s), 3.73 (1H, d, $J = 12.2$ Hz), 4.15–4.30 (1H, m), 4.41 (2H, s), 5.05–5.50 (1H, m), 7.19–7.33 (5H, m), 7.38 (1H, s); MS (APCI$^+$) 416 (MH^+). **14** was obtained from the oil (7.91 g) in substantially the same manner as described in the exchange of *N*-protecting group of **4c**. **14** (6.89 g, 88%); ^{1}H NMR ($CDCl_3$) δ 0.01 (6H, s), 0.81 (9H, s), 1.75–1.90 (2H, m), 2.60–2.80 (1H, m), 3.10–3.55 (3H, m), 3.85 (3H, s), 4.05–4.65 (6H, m), 5.15–5.35 (2H, m), 5.80–6.05 (1H, m), 7.41 (1H, s); MS (APCI$^+$) 410 (MH^+).

4-[(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]methyl-2-methylpyridine *N*-oxide (15b). To a cooled solution of **11b** (43.96 g) in MeOH (440 mL) was added a solution of $NaHCO_3$ (20.14 g) in H_2O (250 mL), followed by addition of a solution of oxone (52.10 g) in H_2O (250 mL). The resulting suspension was stirred at room temperature for 3.5 h. To the mixture was added $CHCl_3$ (1200 mL) and the insoluble materials were filtered off. The filtrate was separated and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, EtOAc/MeOH = 10:1) to give **15b** (9.95 g, 21.7%) as an orange oil. IR (neat) cm^{-1} 2951, 1701; ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 1.58–1.75 (1H, m), 1.80–2.00 (1H, m), 2.48 (3H, s), 2.65–2.88 (1H, m), 2.90–3.60 (2H, m), 3.27 (1H, dd, $J = 11.3$ Hz, 4.4 Hz), 4.10–4.25 (2H, m), 4.61 (2H, d, $J = 5.1$ Hz), 5.19–5.34 (2H, m), 5.84–6.03 (1H, m), 6.90–7.10 (2H, m), 8.15 (1H, d, $J = 6.6$ Hz); MS (APCI$^+$) 407 (MH^+).

4-[(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidin-2-yl]methylpyridine *N*-oxide (15a). 15a was obtained from **11a** (359.7 g) using the similar procedure as described for **15b**. **15a** an orange oil. (359,9 g, 96%): IR (neat) cm^{-1} 2954, 1699; ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (9H, s), 1.52–2.00 (2H, m), 2.70–3.00 (1H, m), 3.00–3.65 (2H, m), 3.25 (1H, dd, $J = 11.3$ Hz, 4.4 Hz), 4.05–4.28 (2H, m), 4.55–4.70 (2H, m), 5.19–5.34 (2H. m), 5.83–6.03 (1H, m), 7.05–7.15 (2H, m), 8.11 (2H, d, $J = 6.9$ Hz); MS (FAB$^+$) 393.2 (MH^+).

(2*R*,4*R*)-2-(2-Acetoxymethylpyridin-4-yl)methyl-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxypyrrolidine (16a). A solution of **15b** (8.56 g) in Ac_2O (6.43 g) was stirred at 150 °C for 30 min. After cooling to 5 °C, the mixture was poured into a mixture of EtOAc and ice-water, and then adjusted pH (7) by addition of saturated $NaHCO_3$ solution. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, EtOAc/IPE = 2:1) to give **16a** (7.23 g, 76.7%) as an orange oil. IR (neat) cm^{-1} 2954, 1749, 1699; ^{1}H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.83 (9H, s), 1.58–1.99 (2H, m), 2.10 (3H, s), 2.68–2.93 (1H, m), 3.00–3.58 (3H, m), 4.05–4.34 (2H, m), 4.59–4.72 (2H, m), 5.20 (2H, s), 5.20–5.37 (2H, m), 5.85–6.05 (1H, m), 7.00–7.20 (2H, m), 8.51 (1H, d, $J = 5.0$ Hz); MS (APCI$^+$) 449 (MH^+).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(2-carbamoylpyridin-4-yl)methyl]pyrrolidine (16b). To a solution of **15a** (359.9 g) in CH_2Cl_2 (1000 mL) was added TMSCN (102.7 g) at room temperature and then *N*,*N*-dimethylcarbamoyl chloride (111.3 g) over 1 h. After stirring at room temperature for 16 h, the mixture was poured into a mixture of ice-water (1000 mL) and 5 N NaOH (100 mL), and adjusted pH (7) by addition of 5 N NaOH. The organic layer was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure,

and purified by column chromatography (SiO_2, EtOAc/hexane = 1:2–1:1) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(2-cyanopyridin-4-yl)methyl] pyrrolidine (263.26 g, 69.7%) as a yellow oil. IR (neat) cm^{-1} 2930, 2230, 1680; ^1H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (9H, s), 1.58–2.00 (2H, m), 2.75–3.00 (1H, m), 3.15–3.60 (3H, m), 4.10–4.30 (2H, m), 4.55–4.70 (2H, m), 5.20–5.35 (2H, m), 5.80–6.10 (1H, m), 7.25–7.40 (1H, m), 7.50 (1H, s), 8.59 (1H, d, J = 5.1 Hz); MS (APCI$^+$) 402 (MH^+). To a solution of the oil (140× g) in DMSO (560 mL) was added powder K_2CO_3 (24.1 g) at 10 °C and dropwise 30% H_2O_2 (47.5 mL) over 25 min. After stirring at room temperature for 3.5 h, the mixture was cooled to 5 °C, quenched with a mixture of EtOAc (500 mL) and 10% $Na_2S_2O_3$ solution (200 mL), and stirred at 5 °C for 1 h. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give **16b** (132.78 g, 90.7%) as a yellow oil. IR (neat) cm^{-1} 1693, 1697; ^1H NMR ($CDCl_3$) δ 0.00 (6H, s), 0.82 (9H, s), 1.60–2.00 (2H, m), 2.79–3.01 (1H, m), 3.15–3.60 (3H, m), 4.07–4.38 (2H, m), 4.62–4.66 (2H, m), 5.21–5.37 (2H, m), 5.87–6.10 (1H, m), 5.63–5.78 (1H, m, $CONH_2$), 7.20–7.38 (1H, m, $CONH_2$), 7.83–7.95 (1H, m), 8.03 (1H, s), 8.47 (1H, d, J = 4.9 Hz); MS (APCI$^+$) 420 (MH^+).

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(1-methylpyrazo-4-yl)methyl]pyrrolidine (17c). To a solution of **7c** (22.3 g) in MeOH (220 mL) was added 1 N HCl (118 mL) at 0 °C, and then the mixture was stirred at 0 °C for 15 min and at room temperature for 1.5 h. After cooling to 0 °C, the mixture was quenched with $NaHCO_3$ (10.4 g) and evaporated under reduced pressure. The resulting aqueous residue was extracted with $CHCl_3$ (×3). The combined extracts was washed with water and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, 1200 mL, $CHCl_3$/MeOH = 10:1) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-hydroxy-2-[(1-methylpyrazo-4-yl) methyl]prrolidine (15.3 g, 98%) as an oil. IR (neat) cm^{-1} 3350, 1670, 1410; ^1H NMR ($CDCl_3$) δ 1.75–2.10 (2H, m), 2.70–3.00 (2H, m), 3.20–3.38 (1H, m), 3.45–3.70 (1H, m), 3.85 (3H, s), 4.10–4.33 (2H, m), 4.55–4.75 (2H, m), 5.20–5.40 (2H, m), 5.87–6.08 (1H, m), 7.13 (1H, s), 7.27 (1H, s); MS (APCI$^+$) 266 (MH^+). To a solution of the oil (15.3 g) and Ph_3P (19.67 g) in THF (180 mL) was added DEAD (13.06 g) at −30 °C. After stirring at the same temperature for 15 min, the mixture was treated with PhCSOH (9.5 mL) for 2 h at room temperature, evaporated under reduced pressure, and diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ (×3), water, brine, dried over $MgSO_4$, evaporated under reduced pressure, and treated with a mixture of IPE (50 mL) and ether (50 mL). The precipitate was removed by filtration and the filtrate was evaporated under reduced pressure and purified by column chromatography (SiO_2, 2200 mL, EtOAc/IPE = 2:3–1:1) to give **17c** (21.8 g, 98%, two steps 96%) as an oil.

Using a similar procedure, **17a**, **17b**, **17d–j** were also prepared from the appropriate silyloxy derivatives (**7a**, **7b**, **7d–7h**, **10a**, **16a**). **17a** (58%), **17b** (84%), **17d** (98%), **17e** (81%), **17f** (100%), **17g** (67%), **17h** (63%), **17i** (68%), **17j** (67%). Physical data for products are shown in Table 8.

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(2-carbamoylpyridin-4-yl)methyl]pyrrolidine (17k). To a solution of **16b** (132.7 g) in MeOH (660 mL) was added dropwise concentrated HCl (52.7 mL) at 5 °C. After stirring at room temperature for 2 h, the mixture was quenched with $NaHCO_3$ (53.09 g) at 5 °C and stirring at room temperature for 1 h, concentrated in vacuo, and azeotropically removed water with toluene (600 mL). The residue was dissolved in CH_2Cl_2 (600 mL), stirred for 20 min, and then filtered. The filtrate was evaporated under reduced pressure and purified by column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:10) to give (2*R*,4*R*)-1-allyloxycarbonyl-2-(2-carbamoylpyridin-4-yl)methyl-4-hydroxypyrrolidine (108.32 g) as an oil. IR (neat) cm^{-1} 1685, 1635; ^1H NMR (DMSO-d_6) δ 1.60–1.90 (2H, m), 2.83 (1H, dd, J = 12.8 Hz, 8.6 Hz), 3.18–3.43 (3H, m), 4.00–4.22 (2H, m), 4.42–4.61 (2H, m), 5.17–5.36 (2H, m), 5.80–6.15 (1H, m), 7.37 (1H, d, J = 4.8 Hz), 7.64 (1H, s, $CONH_2$), 7.88 (1H, s), 8.10 (1H, s, $CONH_2$), 8.53 (1H, d, J = 4.8 Hz); MS (APCI$^+$) 306 (MH^+). To a solution of the oil (108.32 g) in CH_2Cl_2 (500 mL) was added Et_3N (43.1 g) and MsCl (44.73 g) over 30 min at 5 °C. After stirring at 5 °C for 2 h, the mixture was poured into ice water (300 mL) and separated. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated under reduced pressure to give (2*R*,4*R*)-1-allyloxycarbonyl-2-(2-carbamoylpyridin-4-yl)methyl-4-methylsulfonyloxypyrrolidine (129.58 g) as an oil. IR (neat) cm^{-1} 1689; ^1H NMR ($CDCl_3$) δ 1.80–2.05 (1H, m), 2.20–2.40 (1H, m), 2.75–3.00 (1H, m), 3.01 (3H, s), 3.25–3.55 (2H, m), 3.85–4.45 (2H, m), 4.64–4.67 (2H, m), 5.24–5.39 (2H, m), 5.31 (1H, s), 5.85–6.10 (2H, m, $CONH_2$), 7.20–7.40 (1H, m, $CONH_2$), 7.85–7.95 (1H, m), 8.03 (1H, s), 8.53 (1H, d, J = 4.9 Hz); MS (APCI$^+$) 384 (MH^+). To a solution of KO^{t}Bu (45.48 g) in DMF (500 mL) was added dropwise PhCSOH (56.01 g) at room temperature and the mixture was stirred for 30 min. To the mixture was added dropwise a solution of the mesylate (129.5 g) in DMF (400 mL) over 25 min at room temperature. After stirring at 80 °C for 2.3 h, the mixture was cooled and poured into a mixture of EtOAc (1200 mL) and ice water (2700 mL). The organic layer was separated, washed with water and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, EtOAc/hexane = 1:1–2:1–EtOAc only) to give **17k** (52.97 g, 3 steps 39.4%) as a red amorphous solid.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-(2-ethoxycarbonyl-1-methylimidazol-5-yl)methyl-4-methanesulfonyloxypyrrolidine (18). Silyl deprotection and subsequent mesylation of **12** (15.11 g) was achieved using the same procedure as described in the preparation of **17k** to give mesylate **18** (13.70 g, 98.6%) as an oil. ^1H NMR ($CDCl_3$) δ 1.39 (3H, t, J = 7.1 Hz), 1.95–2.15 (1H, m), 2.25–2.50 (1H, m), 2.76 (1H, dd, J = 14.9 Hz, 9.2 Hz), 3.00–4.00 (3H, m), 3.02 (3H, s), 3.99 (3H, brs), 4.05–4.30 (1H, m), 4.40 (2H, q, J = 7.1 Hz), 4.63–4.66 (2H, m), 5.14–5.37 (3H, m), 5.86–6.05 (1H, m), 6.95 (1H, s).

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(2-hydroxymethyl-1-methylimidazol-5-yl)methyl]pyrrolidine (19). To a solution of **18** (13.7 g) in EtOH (137 mL) and THF (67 mL) was added LiCl (2.79 g) and $NaBH_4$ (2.49 g) at room temperature. After stirring at 50 to 55 °C for 2 h, the mixture was poured into a mixture of ice-water and EtOAc, and adjusted to pH 2.6 with 6 N HCl. After stirring for several min, the mixture was again adjusted to pH 9.5–10 with 6 N NaOH, and separated. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, purified by column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:9) to give (2*R*,4*R*)-1-allyloxycarbonyl-2-(2-hydroxymethyl-1-methylimidazol-5-yl) methyl-4-methanesulfonyloxypyrrolidine (11.04 g, 89.7%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.90–2.15 (1H, m), 2.30–2.50 (1H, m), 2.65 (1H, dd, *J* = 14.7 Hz, 9.8 Hz), 3.00–3.80 (2H, m), 3.01 (3H, s), 3.56 (3H, brs), 3.88–4.25 (2H, m), 4.55–4.65 (4H, m), 5.10–5.37 (3H, m), 5.86–6.05 (1H, m), 6.63 (1H, s). Thiobenzoylation of the oil (11.04 g) was achieved using the same procedure as described in the preparation of **17k** to give **19** (8.94 g, 72.8%) as an oil.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-(4-hydroxymethyl-1-methylpyrazol-5-yl)methyl-4-methanesulfonyloxypyrrolidine (20). To a solution of **14** (6.89 g) and Et_3N (3.28 mL) in EtOAc (3.28 mL) was added dropwise AcCl (1.44 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was quenched with water (40 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in MeCN (70 mL). Then, concentrated HCl (2.8 mL) was added to the solution. After stirring at room temperature for 1.5 h, the mixture was quenched with a mixture of EtOAc (140 mL) and saturated $NaHCO_3$ (50 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give an oil. To the solution of the oil in EtOAc (70 mL) was added Et_3N (3.28 mL) and MsCl (1.56 mL) at 0 °C. After stirring at room temperature for 1 h, the mixture was washed successively with water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give (2*R*,4*R*)-2-(4-acetoxymethyl-1-methylpyrazol-5-yl)methyl-1-allyloxycarbonyl-4-methanesulfonyloxypyrrolidine (7.33 g, 105%) as an oil. To a solution of the oil (7.6 g) in MeOH (73 mL) was added dropwise 28% NaOMe in MeOH (3.51 mL) at 0 °C. After stirring for 15 min, the mixture was quenched with concentrated HCl (1.46 mL) and evaporated under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 500 mL, MeOH/CH_2Cl_2 = 1:20) to give **20** (4.32 g, 63.5%) as an oil. ^{1}H NMR ($CDCl_3$) δ 2.00–2.50 (3H, m), 2.70–2.90 (1H, m), 3.01 (3H, m), 3.30–4.75 (11H, m), 5.10–5.45 (3H, m), 5.80–6.10 (1H, m), 7.42 (1H, s); MS (APCI$^+$) 374 (MH^+).

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(4-hydroxymethyl-1-methylpyrazol-5-yl)methyl]pyrrolidine (21). To a solution of KO^{t}Bu (1.69 g) in DMF (20 mL) was added dropwise PhCSOH (1.91 mL) at −10 to −20 °C and the mixture was stirred for 30 min. To the mixture was added dropwise a solution of **20** (4.32 g) in DMF (45 mL). After stirring at 85–90 °C for 3 h, the mixture was poured into a mixture of EtOAc (100 mL) and ice water (50 mL). The organic layer was separated, washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 300 mL, MeOH/CH_2Cl_2 = 1:19) to give **21** (5.38 g, 112%) as an oil.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-(5-*tert*-butyldimethylsilyloxymethyl-1-methylpyrazol-4-yl)methyl-4-hydroxypyrrolidine (22). A solution of **7i** (3.47 g) in MeCN (30 mL) was treated concentrated HCl (1.7 mL) at room temperature for 2 h. The mixture was quenched with a solution of 28% NaOMe in MeOH (2.07 mL) at 0 °C, and insoluble material was filtered off. The filtrate was evaporated under reduced pressure and purified by column chromatography (SiO_2 300 mL, MeOH/CH_2Cl_2 = 1:10) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-hydroxy-2-[(5-hydroxymethyl-1-methylpyrazol-4-yl)methyl]pyrrolidine (1.63 g, 83%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.85–2.05 (2H, m), 2.45–3.10 (2H, m), 3.40–3.60 (2H, m), 3.86 (3H, s), 3.90–4.75 (6H, m), 5.10–5.40 (2H, m), 5.80–6.05 (1H, m), 7.19 (1H, m); MS (APCI$^+$) 296 (MH^+). To a solution of the oil (1.62 g) in CH_2Cl_2 (20 mL) were added successively Et_3N (0.92 mL), DMAP (34 mg), and TBDMSCl (0.91 g) at 0 °C. After stirring at 0 °C overnight, the mixture was quenched with a mixture of CH_2Cl_2 (50 mL) and water (20 mL). The organic layer was separated, washed in turn with water and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 200 mL, MeOH/CH_2Cl_2 = 1:19) to give **22** (1.29 g, 58%). ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, m), 0.84 (9H, s), 1.65–2.00 (2H, m), 2.45–2.90 (2H, m), 3.22 (1H, dd, *J* = 11.8 Hz, 4.4 Hz), 3.25–3.55 (1H, m), 3.79 (3H, s), 3.90–4.20 (2H, m), 4.40–4.60 (4H, m), 5.05–5.30 (2H, m), 5.75–6.00 (1H, m), 7.12 (1H, s).

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(5-hydroxymethyl-1-methylpyrazol-4-yl)methyl]pyrrolidine (23). Mesylation of **22** (1.29 g) was achieved using the same procedure as described in the preparation of **17k** and subsequent desilylation was achieved using the same procedure as described in the preparation of **22** to give (2*R*,4*R*)-1-allyloxycarbonyl-2-(5-hydoxymethyl-1-methylpyrazol-4-yl)methyl-4-methanesulfonyloxypyrrolidine (1.10 g, 93%) as an oil. ^{1}H NMR ($CDCl_3$) δ 2.00–2.40 (2H, m), 2.60–3.00 (2H, m), 3.01 (3H, s), 3.30–3.90 (2H, m), 3.91 (3H, s), 4.00–4.30 (1H, m), 4.55–4.70 (4H, m), 4.90–5.45 (3H, m), 5.80–6.10 (1H, m), 7.22 (1H, m); MS (APCI$^+$) 374 (MH^+). Using the similar procedure as described in the preparation of **17k**, **23** was obtained from the oil (1.10 g). **23** (1.08 g, 89%).

Allyl (4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-1-allyloxycarbonyl-2-[(1-methylpyrazol-5-yl)methyl]pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (25d). To a solution of **17d** (80 g) in MeCN (800 mL) was added dropwise a solution of 28% NaOMe in MeOH (38.2 mL) at 0 to 5 °C, and then the mixture was stirred at 0 °C for 10 min. After quenched with AcOH, the mixture was diluted with EtOAc (4000 mL), washed with water (×2) and brine (×2),

dried over $MgSO_4$, and evaporated under reduced pressure. The residue was immediately dissolved in dimethylacetamide (DMAC) (400 mL) and used in the next reaction because of instability of the thiol function. To the solution of activated carbapenem (**24**) (172.9 mmol) in MeCN (520 mL) was added the above solution and $^{i}Pr_2NEt$ (36.1 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. To the mixture was added $^{i}Pr_2NEt$ (9 mL) at 0 °C. After stirring at 0 °C for overnight, the mixture was diluted with EtOAc (8000 mL), washed with H_2O (2000 mL×6) and brine (2000 mL×2), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/Me_2CO = 5:2, then $CHCl_3$/EtOAc/MeOH = 40:5:2) to give **25d** (59.0 g, 64.3%) as a pale yellow oil. This oil was used immediately in the next reaction because of instability.

Using the similar procedure, **25a–25c**, **25e–25h**, **25k–25n** were also prepared from activated carbapenem (**24**) and the appropriate benzoylthio derivatives (**17a–17c**, **17e–17h**, **17k**, **19**, **21**, **23**). **25a** (53%), **25b** (58%), **25c** (59%), **25e** (64%), **25f** (45%), **25g** (19%), **25h** (49%), **25k** (56%), **25l** (38%), **25m** (42%), **25n** (35%). A longer treatment of NaOMe (20 min) at thiobenzoate (**17j**) using the similar procedure for coupling reaction with **24** to give deacetyl product **25j** (21%).

(4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-2-[(1-methyl-3-pyridinio)methyl]-pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1i). To a solution of **25h** (3.76 g) in Me_2CO (17 mL) was added MeI (4.44 mL) at 0 °C. After stirring at room temperature overnight, the mixture was concentrated to give allyl (4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-2-[(1-methyl-3-pyridinio)methyl]pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydroiodide as an oil (4.76 g). To the solution of the oil (4.67 g) in a mixture of THF (55 mL) and EtOH (18.5 mL) was added successively PPh_3 (0.37 g), AcOH (1.21 mL), $Pd(PPh_3)_4$ (0.33 g), and $^{n}BuSnH$ (5.7 mL) at room temperature. The mixture was stirred at room temperature for 20 min, evaporated (total 40 mL), and poured into water. The solution was washed with EtOAc (×2) and CH_2Cl_2 (×3), and purified by column chromatography (nonionic adsorption resin, Diaion HP-20, 400 mL) After washing with H_2O (800 mL), the product was eluted with a mixture of H_2O/MeCN (98:2–86:14). The solution was treated with ion exchange resin (Amberlyst A-26 (Cl^-)) to give an aqueous solution which was lyophilization to give **1i** (250 mg, 7.8%) as an amorphous powder.

Using the similar procedure, **1h**, **1o**, **1q**, **1s** and **1u** were also prepared from protected carbapenems **25g**, **25m**, **25n**, **25j** and **25k**. **1h** (126 mg, 16%), **1o** (140 mg, 13%), **1q** (103 mg, 30%), **1s** (180 mg, 21%), **1u** (30 mg, 2.3%). And the experimentals of 4-pyridinio compound **25i** and **1j** from **24** and **17i** were reported in ref 16. The physical data of carbapenems **1b–1u** were shown in Table 9.

(4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-2-(1,2-dimethyl-5-pyrazoliomethyl) pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1e). To a solution of **25d** (6.0 g) in CH_2Cl_2 (120 mL) was added methyl tirfluoromethanesulfonate (1.54 mL) at room temperature. After stirring for 2 h, the mixture was evaporated under reduced pressure to give allyl (4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-1-allyloxycarbonyl-2-[(1,2-dimethyl-5-pyrazolio)methyl]pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylate hydrogentrifluoromethanesulfonate as an oil. To the solution of the oil in a mixture of THF (30 mL) and EtOH (60 mL) was added successively Ph_3P (1.19 g), morpholine (2.48 mL), and $Pd(Ph_3P)_4$ (660 mg) at room temperature. After stirring for 1 h, the mixture was treated with THF (100 mL). The precipitate was collected by filtration, dissolved in H_2O (200 mL), washed with CH_2Cl_2 (×2), adjusted pH (6.0) with 1 N HCl, and purified by column chromatography (HP-20, 600 mL). After washing with H_2O, the product was eluted with a mixture of Me_2CO and H_2O (5:95). The fractions containing the desired product were collected and concentrated under reduced pressure. The residual aqueous solution was treated with ion exchange resin (Amberlyst A-26 (Cl^-)) (60 mL) and lyophilized to give **1e** (2.7 g, 52%) as an amorphous powder.

Using the similar procedure, **1b–1d**, **1f**, **1g** and **1l** were also prepared from protected carbapenems **25a–25c**, **25e**, **25f** and **25l**. **1b** (532 mg, 35%), **1c** (194 mg, 18%), **1d** (638 mg, 74%), **1f** (429 mg, 48%), **1g** (510 mg, 59%), **1l** (485 mg, 15%).

Using iodoacetamide as a alkylation reagent, **1m** and **1t** were prepared from protected carbapenems **25a** and **25i**, by the similar methods as described for the preparation of **1i**. **1m** (590 mg, 13%), **1t** (260 mg, 9.2%).

(4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-2-[(1-hydroxyethyl-2-methyl-4-pyrazolio)methyl]pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1p). To a solution of **25c** (6.2 g) in 1,2-dichloroethane (120 mL) was added *tert*-butyldimethylsilyloxyethyl trifluoromethanesulfonate (4.32 g) at room temperature. After stirring for 4 days, the mixture was concentrated under reduced pressure. The residue was dissolved in THF (60 mL) and treated with AcOH (0.702 mL) and TBAF (1.0 M in THF, 11.7 mL) for 1 h at room temperature. Then to the mixture was added EtOH (60 mL), Ph_3P (1.23 g), morpholine (2.56 mL), and $Pd(Ph_3P)_4$ (676 mg) at room temperature. After stirring 1 h, the mixture was treated with THF (90 mL). The precipitate was collected by filtration, dissolved in H_2O (250 mL), and washed with CH_2Cl_2 (×2). The aqueous layer was adjusted to pH 6 with 1 N HCl and purified by column chromatography (nonionic adsorption resin, Diaion SP-205, 620 mL). After washing with H_2O, the product was eluted with a mixture of Me_2CO and H_2O (1:9). The fractions containing the product were collected and concentrated under reduced pressure. The residual aqueous solution was treated with ion exchange resin (Amberlyst A-26 (Cl^-)) (60 mL) and lyophilized to give **1p** (2.2 g, 39%) as an amorphous powder.

Using the similar procedure, **1k**, **1n** and **1r** were also prepared from protected carbapenems **25a**, **25d** and **25i**.

1k (2.48 g, 28%), **1n** (2.6 g, 46%, elemental analysis calcd for $C_{21}H_{31}ClN_4O_5S \cdot 2H_2O$: C, 48.22%; H, 6.74%; N, 10.71%. Found: C, 47.91%; H, 6.58%; N, 10.58%), **1r** (4.38 g, 24%).

4-Bromo-5-*tert*-butylydimethylsilyloxymethyl-1-methylpyrazole (3i). To a solution of *N*-methylpyrazole (20.45 g) in THF (400 mL) was added ^{n}BuLi (1.62 M solution in hexane, 170 mL) at −60 to −55 °C. After stirring at 0 °C for 1 h, the solution was treated with DMF (73 mL) by dropwise addition at −60 to −50 °C. After stirred at 0 °C for 1 h, the mixture was quenched with water and extracted with EtOAc (×4). The combined extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified with column chromatography (SiO_2 500 mL, eluted by EtOAc/hexane (15:85)) to give a pale yellow oil (24.35 g). To a solution of the oil (14.35 g) in a mixture of THF (100 mL) and MeOH (100 mL) was added $NaBH_4$ (4.93 g) at 0 to 30 °C. After stirring at 0 °C for 30 min, the mixture was quenched with 6 N HCl (21 mL), evaporated, and purified with column chromatography (SiO_2 400 mL, eluted by MeOH/CH_2Cl_2 (5:95)) to give a fraction of regioisomeric mixture (2.83 g) and 5-hydroxymethyl-1-methylpyrazole (7.91 g, 54%). The fraction of regioisomeric mixture was separated by column chromatography (SiO_2 200 mL, eluted by MeOH/CH_2Cl_3 (2.5:97.5–10:90)) to give 3-hydroxymethyl-1-methylpyrazole (0.439 g, 3%) as a former fraction and 5-hydroxymethyl-1-methylpyrazole (2.33 g, 16%) as a latter fraction. 3-hydroxymethyl-1-methylpyrazole (0.439 g, 3%); Oil, ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.83 (3H, s), 4.55 (2H, d, J = 5.6 Hz), 5.55 (1H, t, J = 5.6 Hz), 6.37 (1H, d, J = 2.4 Hz), 7.72 (1H, d, J = 2.4 Hz); MS (APCI$^+$) 113 (MH^+). 5-hydroxymethyl-1-methylpyrazole (10.24 g, 70%); A solid, IR (KBr) cm^{-1} 3260–3090, 1487; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.77 (3H, s), 4.48 (2H, d, J = 5.5 Hz), 5.23 (1H, t, J = 5.5 Hz), 6.14 (1H, d, J = 1.7 Hz), 7.28 (1H, d, J = 1.7 Hz); MS (APCI$^+$) 113 (MH^+). Anal. calcd for $C_5H_8N_2O_1 \cdot 0.15H_2O$: C, 52.30%; H, 7.28%; N, 24.39%. Found: C, 52.04%; H, 6.95%; N, 24.27%. To a solution of 5-hydroxymethyl-1-methylpyrazole (10.24 g) and imidazole (8.08 g) in DMF (50 mL) was added TBDMSCl (17.9 mL) at 0 °C. After stirring at room temperature overnight, the mixture was quenched with ice-water (1 L) and extracted with EtOAc (200 mL×3). The combined organic extracts were washed with water (100 mL×2) and brine, dried over MgSO4, filtered, evaporated, and purified by column chromatography (SiO_2 500 mL, eluted by EtOAc/hexane (20:80–30:70)) to give 5-*tert*-butylydimethylsilyloxymethyl-1-methylpyrazole (22.26 g, 107%) as an oil. IR (neat) cm^{-1} 2954, 2933, 1468; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 3.88 (3H, s), 4.68 (2H, s), 6.12 (1H, d, J = 1.9 Hz), 7.37 (1H, d, J = 1.9 Hz); MS (APCI$^+$) 227 (MH^+). A solution of the oil (10 g) in CH_2Cl_2 (10 mL) was added to a mixture of Br_2 (2.5 mL) and Na_2CO_3 (9.4 g) in CH_2Cl_2 (25 mL) at 0 to 5 °C. After stirring at 0 to 5 °C for 1 h and then at room temperature for 1 h, the mixture was quenched with water (50 mL) and extracted with CH_2Cl_2. The combined extracts were washed with water, saturated $NaHSO_3$ aqueous solution, and brine successively, and dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil. The oil was purified with column chromatography (SiO_2 300 mL, eluted by EtOAc/hexane (15:85)) to give **3i** (10.81 g, 80.2%) as a brown oil. IR (neat) cm^{-1} 2952, 2933, 2858; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 3.93 (3H, s), 4.69 (2H, s), 7.38 (1H, s); MS (APCI$^+$) 305, 307 (MH^+).

Measurement of in vitro antibacterial activity

According to the method of the Japan Society of Chemotherapy, the MICs of compound were determined by the 2-fold agar dilution method using heart infusion agar (Eiken). The inoculum size was adjusted to 10^6 cfu/mL, and incubation was carried out at 37 °C for 20 h.

Stability to DHP-I

The stability of carbapenems against recombinant human renal DHP-I was determined spectrophotomerically and expressed as the ratio of hydrolysis to that of Biapenem at 50 μg/mL.

Urinary recovery

Rats were used in groups of nine to 10. The animals were housed individually in a metabolism cage and urine was collected 0–24 h after dosing from each animal.

Efficacy in lethal systemic infection

A strain were intraperitoneally inculated in groups of 8 male ICR mice aged 4 weeks with 0.5 mL of bacterial suspension in 5% gastric mucin, given at 1 to 5 minimum lethal dose (MLD). The infected mice were treated subcutaneously with serially diluted drugs 1 h after infection. The survival of the infected mice was observed for 3–5 days, and the 50% effective dose (ED50) was determined after 4 days by the Probit method.

Affinity to PBP's

Assay were performed by a modification of SPRATT's method. Affinity was calculated from BAS2000 image data after radioluminography.

Outer membrane permeability

Permeability coefficients were determined by the method of Zimmermann and Rosselet by using transformed *E. coli* and *Ps. aeruginosa* producing *S. marcescens*-derived recombinant carbapenemase.

Pharmacokinetic parameters

20 mg/kg (mice) or 10 mg (dogs and monkeys) of carbapenems were administered subcutaneously for mice, intravenously for dogs and monkeys. Concentrations were determined by the ager diffusion method using *Bacillus subtills* ATCC6633. A one-compartment model

was used for mice, and a two-compartment model was employed for analytical studies in dogs and monkeys with the NONLIN computer program.

Acknowledgements

The authors are grateful to Dr. Kazuo Sakane for useful suggestions and encouragement during the preparation of this paper.

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