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

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Abstract—The synthesis and biological activity of a novel series of 2-alkyl-4-pyrrolidinylthio-β-methylcarbapenems containing a variety of cationic heteroaromatic substituents is described. As a result of these studies, we uncovered a relationship between in vitro antibacterial activity and the length of the alkyl spacer part, and discovered FR20950 (**1c**), containing a two methylene spacer moiety and an imidazolio group, which possesses a balanced spectrum of antibacterial activity, including *Pseudomonas aeruginosa* and Methicillin-resistant *Staphylococcus aureus* (MRSA). Furthermore, FR20950 exhibited excellent urinary recovery, and comparable stability against renal dehydropeptidase-I (DHP-I) to Biapenem. DHP-I stability could be improved by introduction of a substituent on to the imidazole ring.

Introduction

To control bacterial infections, many researchers and pharmaceutical companies have researched and developed many kinds of antibacterial agents, including β-lactams, tetracyclines, macrolides, quinolones, aminoglycosides, etc. However, in modern chemotherapy the acquisition of resistance by pathogens is becoming a serious problem.[1–3] This problem has occurred for almost all types of antibiotic agent and for most bacterial strains, and is often induced by the excessive and/or inappropriate usage of antibiotics. The resistance mechanisms in Gram positive and negative bacteria can be classified in the following way: (1) mutation of the target protein for the antibiotic (for example, penicillin-binding proteins, ie PBP-2′), (2) poor outer membrane permeability in Gram negative bacteria (especially *Ps. aeruginosa*), (3) production of enzymes that destroy the antibiotic (for example β-lactamase), and (4) the active exclusion of antibiotics from bacteria cells (P-glycoprotein). To overcome these resistance problems, the search for novel antibiotics represents an enormous, and ongoing effort, that has focused predominantly on established classes.

Certain antibiotics are intrinsically active against resistant bacteria; one successful example is Vancomycin,[4] however, its activity is restricted to Gram positive bacteria, including Methicillin-resistant *S. aureus* (MRSA). Furthermore, strains that are resistant to Vancomycin[5] are now beginning to be 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. We selected the carbapenem skeleton[6] as the prototype for a new antibiotic for the following reasons; (1) good selective toxicity for the target proteins, penicillin binding proteins (PBP's), which do not exist in humans, (2) the superior efficacy profile of the antibacterial activity. Thus, the bactericidal activity of carbapenems is superior to the bacteriostatic activity of cephalosporins, and (3) broad antibacterial spectrum. Whilst the weak point of the carbapenem skeleton is instability to the renal enzyme dehydropeptidase-I (DHP-I), several approaches exist to improve stability and improve bioavailability and in vivo antibacterial activity.

Key words: Carbapenems; antibacterials; cationic heteroaromatics; DHP-I stability.

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From the literature of carbapenem antibiotics, especially the SAR related to Meropenem[7,8] and Panipenem,[9] 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[10,11] against *Ps. aeruginosa* was related to its good outer membrane permeability. The quaternary ammonium cationic center present in the side chain of Biapenem was critical to impart good outer membrane permeability. We postulated that a combination of these two factors in a single side chain might lead to agents with superior efficacy. We described in earlier communications a series of azoliomethyl substituted pyrrolidines containing heterocycles linked via a carbon–carbon bond to the spacer,[12–14] an effort that culminated in FR21818 (Fig. 1). In this report, we examine the relationship between the spacer length and activities in a related series to FR21818 that contains a carbon–nitrogen bond as the point of attachment of the heterocycle to the spacer moiety.

We have also reported various alkoxymethyl and thioalkylmethyl-substituted pyrrolidine derivatives[15,16] however, introduction of cationic centers, in the form of quaternary heterocyclic salts, did not lead to an improved spectrum of activity, indicating that the nature of the spacer group seems to be critical for good activity.

Results and Discussion

Chemistry

The general synthetic route to the target carbapenems (**1a**–**s**) was based on the retrosynthesis shown in Figure 2. The target carbapenems (**1a**–**s**) can be retrosynthetically divided into three parts: the carbapenem skeleton (**A**), a pyrrolidine structure which can be prepared from 4-hydroxyproline (**B**), and various heteroaromatics (**C**). Two different approaches were adapted in this work for preparation of these compounds. The first route involved as the key step, coupling of unit **A** and a preformed **BC** moiety, and the second involved coupling of an assembled **AB** unit with the appropriate heterocycle **C**. We predominantly employed the first route, because the carbapenem skeleton **A** is relatively unstable and as such it is recommended that the coupling reaction to afford this moiety occurs towards the final stage of the synthetic route. Various protected hydroxyproline derivatives, suitably activated with a leaving group, were coupled with appropriate heteroaromatics,

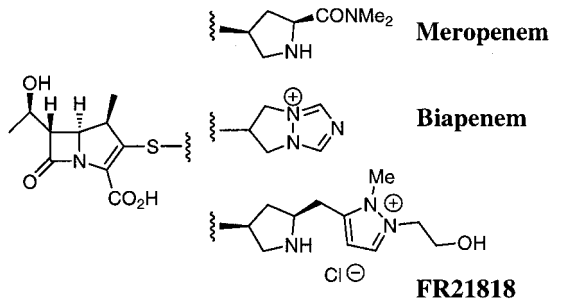


Figure 1. Carbapenem antibiotics.

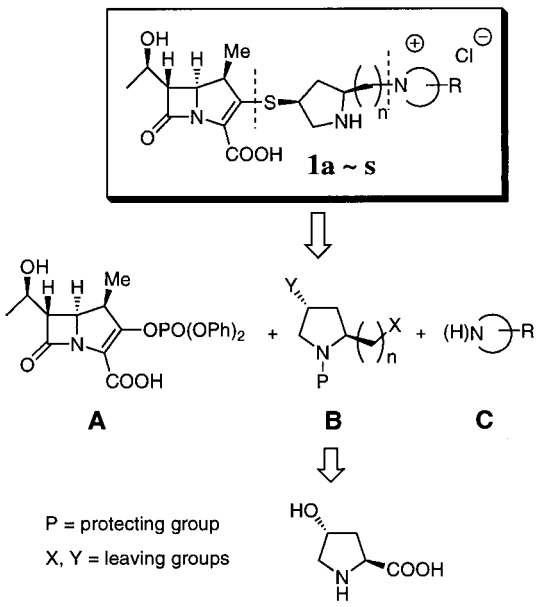
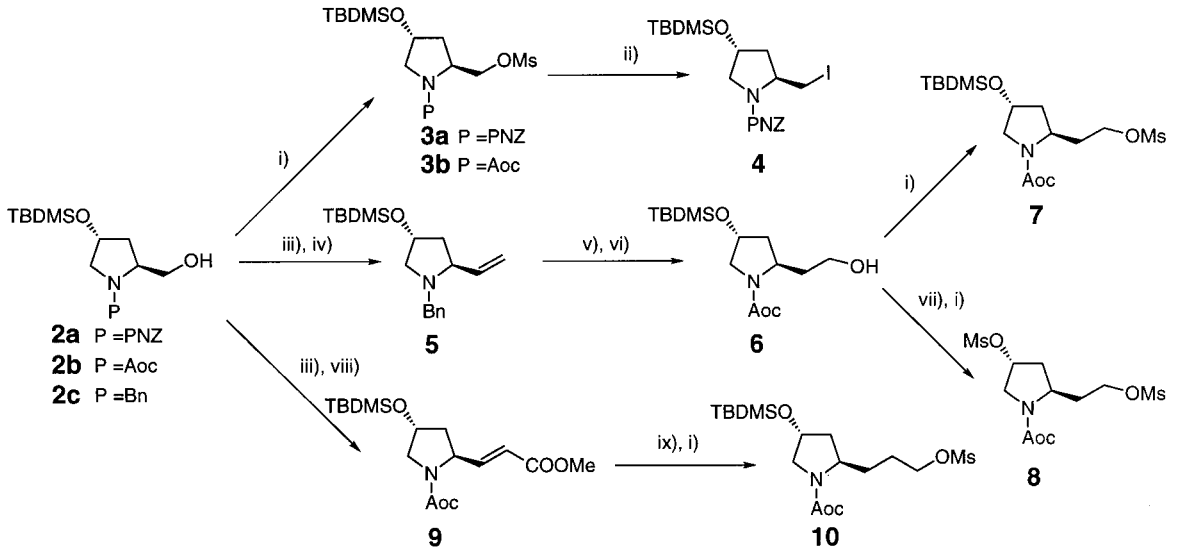


Figure 2. Retrosynthetic analysis of target compounds.

and the resulting products transformed to thiols by a variety of methods. Finally, construction of the target compounds (**1a**–**g**, **j**–**s**) was achieved by coupling of the thiol with an activated carbapenem, followed by global deprotection to remove protecting groups.

The preparation of pyrrolidine derivatives containing leaving groups (**4**, **7**, **8**, **10**) is outlined in Scheme 1. The starting materials, 2-hydroxymethylpyrrolidine derivatives **2a**–**c** were obtained by standard methods.[15,17,18] Mesyloxymethyl derivative **3b** and iodomethyl derivative **4** were obtained by mesylation of **2b** and subsequent reaction with NaI. The pyrrolidine derivatives required for preparation of one carbon homologated compounds (Fig. 2, $n=2$) were obtained from **2c**. The hydroxymethyl group of **2c** was transformed to a methylene (**5**) by Swern oxidation and subsequent Wittig reaction. The methylene compound **5** was transformed to the hydroxyethyl derivative **6** by standard hydroboration (9-BBN, $NaBO_3 \cdot 4H_2O$) and protecting group interconversion from benzyl to allyloxycarbonyl (Pd-C, H_2, AocCl). Compound **6** was then activated as the mesylate **7** by the same method used for **3a**–**b**. Dimesylate **8** was prepared by deprotection of the silyl group (c-HCl) of **6** and subsequent mesylation. The pyrrolidine intermediate (**10**) for two carbon homologated compounds (Fig. 2, $n=3$) was also obtained from **2b**. Hydroxymethyl compound (**2b**) was transformed to α,β-unsaturated ester (**9**) by Swern oxidation and Wittig reaction ($Ph_3P=CHCOOMe$) in a similar manner as for **5**. The α,β-unsaturated ester (**9**) was transformed to alcohol by one pot 1,4-reduction and ester reduction using sodium borohydride ($NaBH_4$) and lithium iodide (LiI) in THF as a solvent. The obtained alcohol was transformed to mesylate (**10**) by the usual method.

The coupling reactions of the pyrrolidine derivatives containing various leaving groups (**B**) with heteroaromatic derivatives (**C**), and subsequent transformation to the



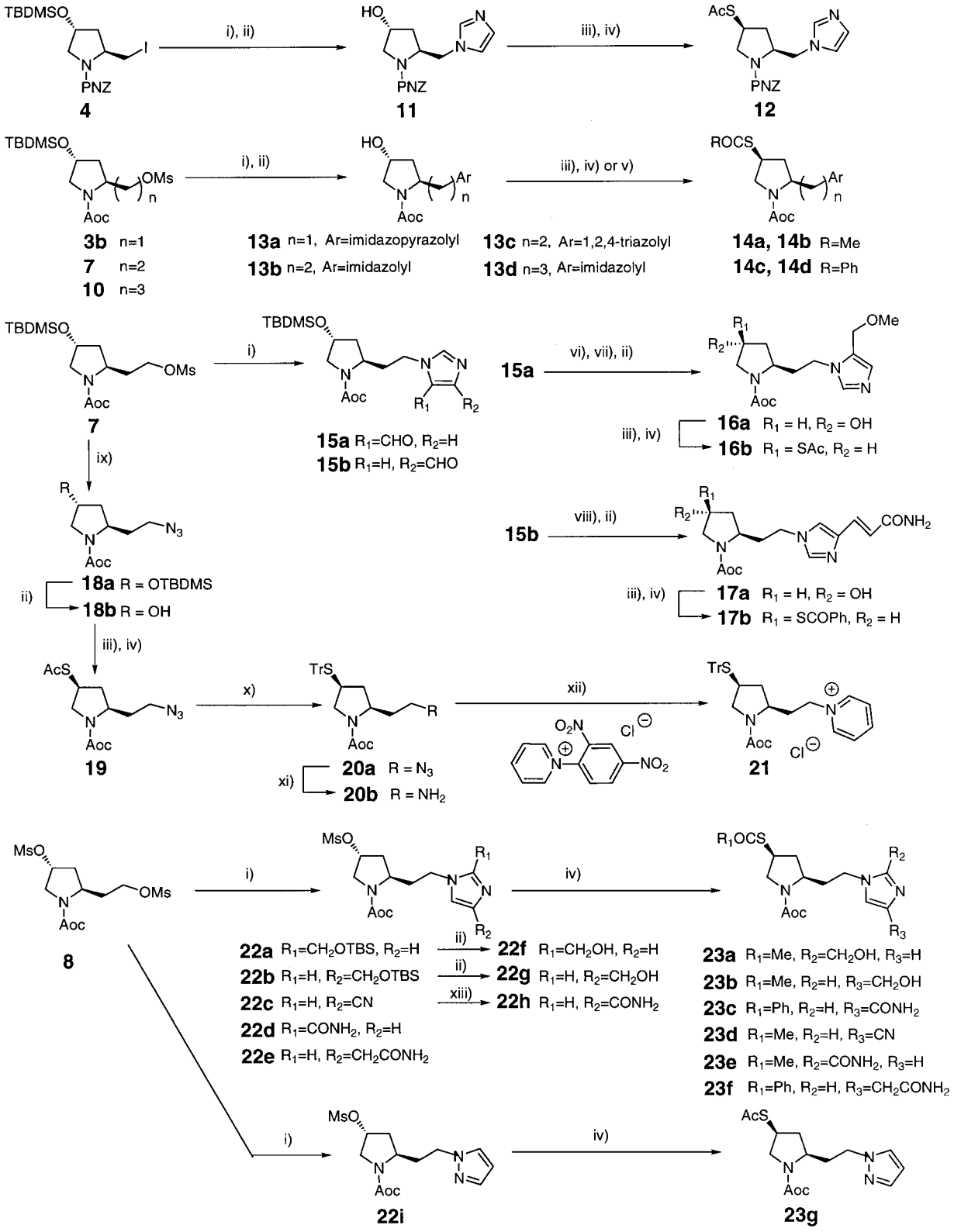
Scheme 1. Synthesis of key pyrrolidine intermediates. *Reagents and conditions:* (i) MsCl, Et_3N, CH_2Cl_2; (ii) NaI, DMF; (iii) DMSO, $(ClCO)_2$, Et_3N, CH_2Cl_2; (iv) $Ph_3P^+MeCl^-$, KO^{t}Bu, THF; (v) 9-BBN, THF then $NaBO_3{\cdot}4H_2O$; (vi) 10% Pd–C, H_2, MeOH, then AocCl, THF–H_2O; (vii) c-HCl, MeOH; (viii) $Ph_3P{=}CHCO_2Me$, THF; (ix) $NaBH_4$–LiI, THF, reflux.

thiol derivatives, are summarized in Scheme 2. The heteroaromatics used in these reactions were commercially available or synthesized by known methods.[19–23]

Iodide **4** and mesylates (**3b**, **7**, **10**) were coupled with heteroaromatic nucleophiles under basic conditions (NaH or ^{t}BuOK and imidazoles, imidazopyrazole, or 1,2,4-triazole) or using the heterocycle as base (coupling of iodide with imidazole). Subsequent deprotection of the silyl group afforded alcohols **11** and **13a–d**. The alcohols **11** and **13a**,**b** were transformed to a mesylate followed by a nucleophilic substitution reaction with thioacetate anion (AcSH, ^{t}BuOK or NaH) to afford thioacetates **12** and **14a**,**b**. The 4-hydroxyl group underwent clean inversion in the transformation from alcohol to a thioacetate group. One step conversion of alcohol to thiobenzoate was achieved by Mitsunobu reaction with thiobenzoic acid, triphenylphosphine and DEAD, to give **14c**,**d** in high yield. Various substituted imidazole derivatives were also synthesized. The intermediates **16b** and **17b** were prepared from the same mesylate (**7**) and commercially available 4-formylimidazole. Mesylate (**7**) was coupled with 4-formylimidazole by the usual basic conditions to afford a mixture of 5-formylimidazole (**15a**) and 4-formylimidazole (**15b**), that were separated by silica gel column chromatography (isolated yield, 24% for **15a** and 36% for **15b**). The 5-formylimidazole (**15a**) was reduced with $NaBH_4$, methylation of the obtained alcohol with MeI–^{t}BuOK, and then deprotection of the silyl group gave methoxymethylimidazole (**16a**). On the other hand, 4-formylimidazole (**15b**) was transformed to **17a** by Horner–Wittig reaction and silyl deprotection. The substituted imidazole derivatives **16a** and **17a** were similarly transformed to thioacetates **16b** and **17b** by the usual methods (mesylation and thioacetate substitution).

Introduction of a pyridine ring to pyrrolidine derivatives was not achieved by direct nucleophilic substitution reaction of the aromatic nucleophile, since we expected that a cationic salt of a pyridine ring produced by direct nucleophilic reaction of pyridine and substrate may have isolation and purification difficulties, and possibly instability in basic conditions. We adapted an indirect method via amine intermediate (**20b**) to obtain cationic pyridine salt (**21**). A triphenylmethyl group was selected as a thiol protecting group rather than acetate, due to facile deprotection under acidic conditions, as compared to the basic conditions used for thioester derivatives. To synthesize amine intermediate **20b**, introduction of an azide group to mesylate **7** was achieved under standard conditions (NaN_3, NH_4Cl, DMF). The obtained azide (**18a**) was then transformed to thioacetate (**19**) by the usual three steps. After protecting group transformation from a thioacetate (**19**) to a triphenylmethylthio group (**20a**), reduction of the azide group gave the amine **20b**. Construction of the cationic pyridine group was achieved by the coupling of Zincke's salt and amine[24] to give **21**.

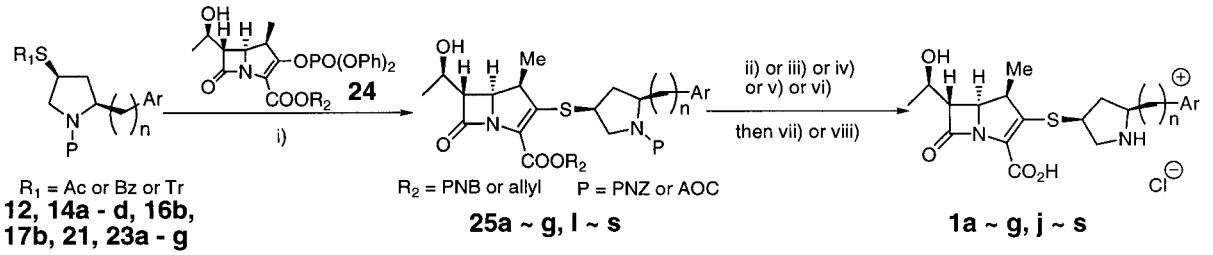
Various other substituted imidazole derivatives were constructed from the reaction of dimesylate **8** with the appropriate substituted imidazole nucleophile. Imidazoles were readily prepared by standard methods. Thus, dimesylate (**8**) reacted with the substituted imidazole to produce imidazole derivatives **22a–e**. Reactions occurred selectively at the primary mesylate, due to steric hindrance. Concerning the imidazole regioselectivity, the 5-substituted imidazole was not isolated in the reactions of 4-nitrile, 4-*tert*-butyldimethylsiloxymethyl, and 4-amidomethyl substituted imidazoles. After the appropriate transformation of **22a–c** (deprotection of the silyl group to give **22f**,**g**, and oxidation from nitrile to amide **22h**), the secondary mesylate group of **22c–e**, **f–h** was transformed by the usual substitution reaction with thioacetate or thiobenzoate to give thioesters **23a–f**. Using pyrazole as the nucleophile in the reaction with the dimesylate **8**, a selective nucleophilic reaction



Scheme 2. Preparation of thioester pyrrolidine derivatives. *Reagents and conditions:* (i) Heteroaromatics, base (NaH or ^{t}BuOK or no base); (ii) c-HCl, MeOH; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) AcSH, NaH, DMF, or AcSK, MeCN, or PhCOSH, ^{t}BuOK, DMF; (v) Ph_3P, DEAD, PhCOSH, THF; (vi) $NaBH_4$, THF–MeOH; (vii) ^{t}BuOK, MeI, THF; (viii) $(EtO)_2POCH_2CONH_2$, ^{t}BuOK, THF; (ix) NaN_3, NH_4Cl, DMF; (x) NaOMe, THF–MeOH, then TrCl; (xi) PPh_3, pyridine, NH_3 aq.; (xii) ^{n}BuOH; (xiii) 30% H_2O_2, K_2CO_3, DMSO.

occurred to give **22i** in good yield. Transformation of mesylate (**22i**) to thioacetate (**23g**) was achieved by nucleophilic substitution with the thioacetate salt.

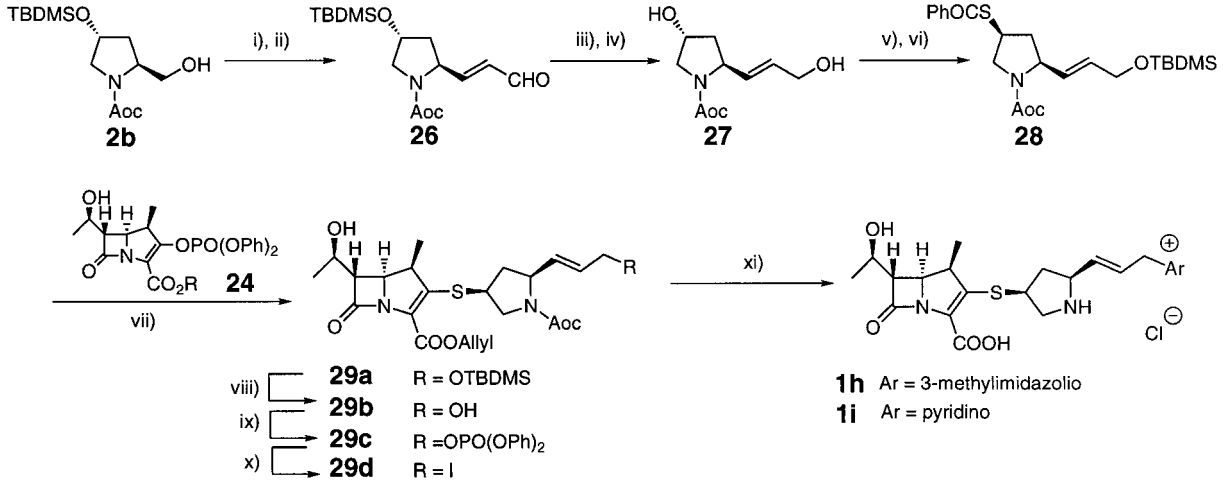
The coupling of thiol derivatives with an activated carbapenem **24**[18,25] and subsequent cationic salt formation and deprotection are summarized in Scheme 3. The



Scheme 3. Synthetic route to novel carbapenems. *Reagents and conditions:* (i) NaOMe, MeOH, (or TFA, Et_3SiH), then **24**, $^{i}Pr_2EtN$, DMAC, MeCN; (ii) MeI, Me_2CO or THF; (iii) ICH_2CONH_2, Me_2CO; (iv) $I(CH_2)_3NHAoc$, DMF; (v) MeOTf, CH_2Cl_2; (vi) FSO_3Me, CH_2Cl_2; (vii) $Pd(PPh_3)_4$, PPh_3, THF–EtOH, $^{n}Bu_3SnH$ or morpholine; (viii) $Pd(OH)_2$-C, H_2, THF–phosphate buffer (pH 6.5).

thioesters (**12**, **14a–d**, **16b**, **17b**, **21**, **23a–g**) were smoothly deprotected by NaOMe in MeOH or acetonitrile to produce the thiols which were then immediately coupled with the activated carbapenem (**24**) in the presence of Hünig's base in acetonitrile, to give coupling products **25a–g**, **l–s**. In the case of triphenylmethylthio derivative **21**, the trityl group was deprotected under acidic conditions using TFA and Et_3SiH to give the thiol derivative as a crude solution, and this solution was directly coupled with **24**, in a similar manner. The coupling products **25a–h**, **m–t** were transformed to cationic salts by reaction with the appropriate alkylating reagent, then deprotected to give target compounds. In the cationic salt formation step, carbamoylmethyliodide and allyloxycarbonylaminoethyliodide were used to produce derivatives **1j** and **1k**. Other salts usually used MeI, however, in the case of imidazole derivatives with poor reactivities, we used stronger methylation reagents (MeOTf or FSO_3Me for **25d**, **25o–p**, **25s**). After construction of the cationic center, deprotection was achieved by two procedures. The allyloxycarbonyl group and allyl ester moieties were simultaneously deprotected by $Pd(Ph_3P)_4$, Ph_3P, and an allyl trapping reagent (morpholine or $^{n}Bu_3SnH$),[26,27] and the *p*-nitrobenzyloxycarbonyl and *p*-nitrobenzyl groups were removed by hydrogenolysis ($Pd(OH)_2$-C, H_2) to give the target carbapenems.

In contrast to these synthetic routes (Fig. 2), we also employed another synthetic strategy for several derivatives. After coupling of carbapenem skeleton **A** and pyrrolidine **B**, the coupled compound **AB** and the heteroaromatic moiety **C** were coupled to give the target compound. These results are summarized in Scheme 4. The starting material (**2b**) was oxidized under Swern conditions followed by olefin formation with a Wittig reagent ($Ph_3P=CHCHO$), to give α,β-unsaturated aldehyde (**26**). This compound was reduced with $NaBH_4$ in a mixture of THF and EtOH, followed by deprotection of the silyl group under acidic conditions to give diol **27**. In this reduction step, 1,2-reduction of the α,β-unsaturated aldehyde occurred selectively to give allyl alcohol. The primary alcohol group of diol **27** was selectively protected with a *tert*-butyldimethylsilyl group, and the remaining secondary alcohol transformed to the thiobenzoate ester **28** under Mitsunobu conditions (DEAD, Ph_3P, PhCOSH). The thiobenzoate group of **28** was deprotected (NaOMe in MeOH), and coupled with carbapenem skeleton **24** to give **29a**. The *tert*-butyldimethylsilyl group of **29a** was deprotected to give alcohol **29b**, which was subsequently transformed to iodide by a two step transformation (activation of the alcohol by $(PhO)_2P(O)Cl$ and DMAP, and substitution reaction with iodide anion) to give iodide **29d**. This iodide



Scheme 4. Synthetic route to novel carbapenems **1h** and **1i**. *Reagents and conditions:* (i) DMSO, $(ClCO)_2$, Et_3N, CH_2Cl_2; (ii) $Ph_3P=CHCHO$, toluene; (iii) $NaBH_4$, THF–EtOH; (iv); c-HCl, MeCN; (v) TBDMSCl, imidazole, DMF; (vi) DEAD, PPh_3, PhCOSH, THF; (vii) NaOMe, MeOH, then **24**, $EtN^{i}Pr_2$, MeCN; (viii) TBAF, AcOH, THF; (ix) $(PhO)_2P(O)Cl$, DMAP, CH_2Cl_2; (x) NaI, Me_2CO; (xi) heteroaromatics (**1h**, 3-methylimidazole, **1i**, pyridine), CH_2Cl_2, then $Pd(PPh_3)_4$, PPh_3, THF–EtOH, $^{n}Bu_3SnH$.

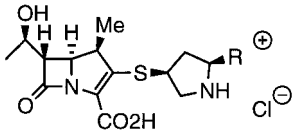
was then coupled with several heteroaromatics (3-methylimidazole or pyridine) by nucleophilic substitution. Subsequent deprotection of the allyloxycarbonyl groups by ordinary methods gave imidazolio derivative **1h** and pyridinio derivative **1i**, respectively.

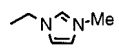
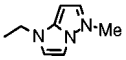
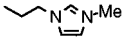
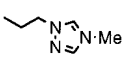
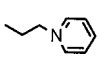
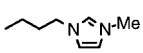
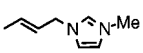
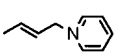
Biological activity

In vitro antibacterial activity, DHP-I stability,[28,29] and urinary recovery of the novel carbapenems prepared in this work are shown in Tables 1 and 2. We investigated the structure activity relationships of various lengths of methylene spacer, which connects the pyrrolidine ring and the heteroaromatic portion. The results are summarized in Table 1. We can separate compounds in Table 1 into three different groups: (1) compounds that possess one methylene unit as a spacer (**1a**,**b**), (2) compounds that possess a two methylene unit as a spacer (**1c**–**f**), and (3) compounds that possess a three methylene unit as a spacer, including a trans double bond (**1g**–**i**). In these groups, we compared the *N*-methylated imidazole rings as the cationic center (**1a**, **1c**, **1g**, **1h**), and compared in vitro activities. Regarding antibacterial activity against *S. aureus*, including MRSA (S.a.(2, 3)), as a representative Gram positive bacteria, it was shown that superior activity was achieved with the longer spacer groups. Relative to **1a** (group 1), compound **1c** (group 2) had fourfold higher activity against MSSA (Sa.(1)), and twofold higher activity against MRSA. Moreover, the three methylene linked compound **1g** (group 3) displayed fourfold higher MRSA activity, relative to **1a**. Compound **1h**, containing a double bond in the spacer part was roughly equal in activity relative to the saturated compound **1g**. As a result, regarding the activities against *S. aureus* including MRSA, compounds that possess a three methylene unit (**1g**, group 3) were the best compounds, and were two to fourfold more active than the reference compound Biapenem.

On the other hand, regarding the activities against *Ps. aeruginosa*, the compounds that possess two methylenes as a spacer (group 2) had the best profile. This was obvious from a comparison of activities against *Ps. aeruginosa* of compounds **1a**, **1h**, **1g**, **1c**, which increase in that order. As a result, the two methylene compound **1c** (group 2) displayed the best activity against *Ps. aeruginosa*, and this activity was comparable to the reference compounds. The *Ps. aeruginosa* activity of compound **1h**, containing a double bond in the spacer, was marginally improved relative to the saturated compound **1g**. Outer membrane permeability of *Ps. aeruginosa* is one of the important factors to determine antibacterial activities. Protein D2 of the *Ps. aeruginosa* outer membrane is known to facilitate the specific permeation of imipenem across this membrane barrier. Competitive inhibition of imipenem flux by basic amino acids has been reported (there is a similarity of structure between basic amino acids and the part of imipenem

Table 1. Antibacterial activity (MIC),[a] DHP-I stability and urinary recovery of novel carbapenems



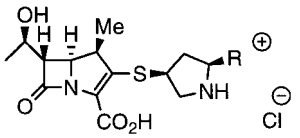
	R	S.a.(1)	S.a. (2)	S.a.(3)	E.c.	P.v.	P.a.(1)	P.a.(2)	P.a.(3)	P.a.(4)	P.a.(5)	DHP[b]	U.R.[c]
Meropenen		0.1	6.25	25	≤0.025	0.1	1.56	0.39	0.2	1.56	0.39	1	25%
Biapenem		0.05	1.56	25	0.39	3.13	1.56	0.78	0.2	1.56	0.2	0.19	71%
1a		0.1	3.13	25	0.1	0.2	6.25	3.13	0.78	6.25	1.56	0.46	76%
1b		0.05	1.56	12.5	0.1	0.39	12.5	1.56	0.39	6.25	0.78	0.69	NT
1c		< 0.025	1.56	12.5	0.1	0.78	0.78	0.78	0.39	1.56	0.39	0.48	84%
1d		0.05	3.13	12.5	0.2	1.56	3.13	0.39	0.2	1.56	0.39	0.17	75%
1e		≤0.025	1.56	6.25	0.2	0.78	1.56	0.78	0.2	1.56	0.39	0.25	69%
1f		≤0.025	1.56	6.25	0.1	0.78	1.56	0.78	0.2	3.13	0.78	0.92	74%
1g		≤0.025	0.78	6.25	0.2	3.13	3.13	1.56	0.39	3.13	0.78	0.56	66%
1h		≤0.025	0.78	12.5	0.2	1.56	1.56	0.78	0.39	3.13	0.78	0.56	76%
1i		≤0.025	1.56	6.25	0.2	0.78	3.13	1.56	0.39	3.13	0.78	0.64	62%

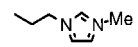
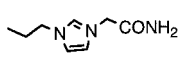
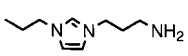
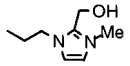
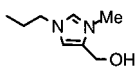
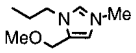
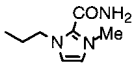
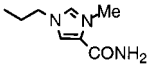
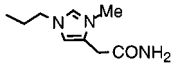
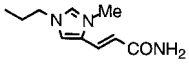
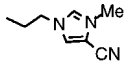
[a] S.a. (1), *S. aureus* 209P JC-1; S.a. (2), *S. aureus* 2538; S.a. (3), *S. aureus* 3004; E.c., *E. coli* NIHJ JC-2; P.v., *P. vulgaris* IAM 1025; P.a. (1), *Ps. aeruginosa* IAM 1095; P.a. (2), *Ps. aeruginosa* 2; P.a.(3), *Ps. aeruginosa* 26; P.a. (4), *Ps. aeruginosa* 175; P.a.(5), *Ps. aeruginosa* FP 1457; DHP, DHP-I stability; U.R., Urinary Recovery.

[b] Human DHP-I stability is given relative to meropenem.

[c] Recovery (%) in Mouse after s.c. administration (20 mg/kg).

Table 2. Antibacterial activity (MIC), DHP-I stability and urinary recovery of novel carbapenems[a]



	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)	DHP	U.R.
(**1c**)		≤0.025	1.56	12.5	0.1	0.78	0.78	0.78	0.39	1.56	0.39	0.48	84%
(**1j**)		0.05	1.56	12.5	0.2	1.56	3.13	0.78	0.2	3.13	0.78	0.62	76%
(**1k**)		≤0.025	1.56	6.25	0.39	3.13	3.13	0.78	0.39	1.56	0.78	0.24	56%
(**1l**)		≤0.025	3.13	12.5	0.2	1.56	3.13	0.78	0.39	3.13	0.78	1.28	60%
(**1m**)		≤0.025	1.56	6.25	0.2	0.78	1.56	0.78	0.2	3.13	0.78	0.28	64%
(**1n**)		0.05	1.56	12.5	0.2	1.56	3.13	1.56	0.78	6.25	0.78	0.45	67%
(**1o**)		≤0.025	1.56	6.25	0.2	1.56	6.25	0.78	0.2	1.56	0.39	0.50	61%
(**1p**)		0.05	0.78	6.25	0.39	1.56	1.56	0.78	0.2	3.13	0.78	0.10	72%
(**1q**)		0.05	3.13	12.5	0.39	1.56	1.56	0.78	0.39	3.13	0.39	0.19	73%
(**1r**)		≤0.025	1.56	6.25	0.1	1.56	6.25	0.78	0.39	3.13	0.78	0.74	70%
(**1s**)		0.05	1.56	6.25	0.39	1.56	3.13	0.78	0.39	3.13	0.78	0.12	66%

[a] 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; DHP, DHP-I stability; U.R., Urinary Recovery.

containing the carboxyl group and the substituent on C2).[30] As a result, it appears that superior outer membrene permeability on *Ps. aeruginosa* was observed with superior binding affinities of the carbapenems to D2 protein which was related to the proper distance and direction of the cationic center from carboxylate ion. Against other Gram negative bacteria, such as *E. coli* and *P. vulgaris*, there was a small tendency to lower activities by elongation of the spacer group. Considering the balance of antibacterial activities against all strains, **1c** was obviously the best compound in Table 1.

Next, to investigate the generality of these SAR observations on the relationship between the spacer length and activity, we evaluated other kinds of cationic heteroaromatic salts. We evaluated heteroaromatics that possessed the same spacer parts (**1b** versus **1a**, **1d**–**f** versus **1c**, and **1h** versus **1i**). As a result, compounds with different heteroaromatic groups (**1b**, **d**–**f**, **i**) displayed relatively similar activities compared to the imidazole compound with the same spacer moiety. Therefore, for antibacterial activity, we concluded that the length of the spacer part is a more important factor than the nature of the heteroaromatic ring in this type of carbapenem.

It is widely known that carbapenem antibiotics are relatively easily decomposed by a metabolic enzyme, DHP-I. The best compound in Table 1 (**1c**) possessed a satisfactory profile regarding antibacterial activity, however, its DHP-I stability was not optimum. All compounds in Table 1, especially **1c**, displayed superior stability against DHP-I compared to Meropenem, however, except for **1d**, most compounds displayed inferior stability to DHP-I, compared to Biapenem. For good bioavailabilty and in vivo antibacterial activity, improvement of DHP-I stability was needed in the imidazole compound **1c**. Thus we attempted to introduce substituents on to the imidazole ring.

The antibacterial activities, DHP-I stabilities, and urinary recoveries of substituted imidazole derivatives are summarized in Table 2. An obvious improvement in DHP-I stability was achieved by the introduction of an amido group (**1p**), amidomethyl group (**1q**), or nitrile group (**1s**). On the other hand, the antibacterial activity against MRSA (S.a.(3)) was improved by introduction of an amino group (**1k**), hydroxy group (**1m**), amido group (**1o**, **1p**, **1r**), or a nitrile group (**1s**), compared to **1c**. However, against some *Ps. aeruginosa* strains (P.a.(1)

or P.a.(4)) and a strain of Gram negative bacteria (P.v.) these compounds (**1j**–**1s**) showed a reduction in antibacterial activities. A compound possessing a desirable profile of activity comparable to that of **1c** was not discovered amongst these analogues. The urinary recoveries of all compounds in Tables 1 and 2, were good to excellent (60–80%). This is superior to that of Meropenem and almost equal to that of Biapenem.

From these results, we selected **1c** as a representative of this type of carbapenem antibiotic, and investigated further. Table 3 displays the in vivo protective effect against systemic infection in mice caused by a strain of *Ps. aeruginosa* in comparison to reference compounds. As a result, a comparable effect to reference compounds was observed.

Conclusions

We have designed and synthesized novel pyrrolidine carbapenems connected with cationic heteroaromatics and investigated their antibacterial activity, DHP-I stability, and urinary recovery. We found a relationship between in vitro antibacterial activities and the length of the spacer connecting the heteroaromatics to the pyrrolidine ring, and that a two methylene group was the best spacer length for a good balance of activity against Gram-positive (include MRSA) and Gram-negative bacteria (especially *Ps. aeruginosa*). The representative compound **1c** possessed relatively poor stability to DHP-I which was improved by the introduction of substituents to the imidazole ring, however, the good antibacterial spectrum of **1c** was weakened in these derivatives. As a result, the representative compound **1c** (FR20950) displayed comparable in vivo activity to reference compounds, and is undergoing further evaluation as a potential new carbapenem antibiotic.

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 R-90H spectrometer (^{1}H, 90 MHz) or 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 Hitachi Model M-80 mass spectrometer (EI-MS), 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 and analytical data for intermediates and final compounds are collected in Tables 4, 5, and 6.

Table 3. In vivo protective effect against infection in mouse[a]

	1c	IPM[b]	MPM[c]	Biapenem
ED_{50} (mg/kg)	0.289	0.289	0.289	0.219
MIC (μg/mL)	1.56	1.56	1.56	1.56

[a] *Ps. aeruginosa* 93, 8.0×10^8 Cells/head.
[b] IPM/CS, Imipenem + cilastatin.
[c] MPM/CS, Meropenem + cilastatin.

(2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-2-iodomethyl-1-(4-nitrobenzyloxycarbonyl) pyrrolidine (4). To a solution of **2a** (20 g) and Et_3N (8.85 mL) in CH_2Cl_2 (200 mL) was added dropwise a solution of methanesulfonylchloride (MsCl) (4.53 mL) in CH_2Cl_2 (20 mL) at 0°C. After stirring at 0°C for 30 min, the mixture was quenched with water and separated. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give (2*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (**3a**) as a oil. A mixture of this crude oil and NaI (10.95 g) in DMF (100 mL) was stirred at 70–75°C for 8 h. After pouring into ice-water (500 mL), the mixture was extracted with AcOEt (300 mL×3). The combined organic extract was dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 400 mL, $CHCl_3$ elution) to give **4** (15.0 g, 59%) as a solid. Mp 105–106°C; IR (Nujol) cm^{-1} 1690; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.87 (9H, s), 1.80–2.28 (2H, m), 3.41–4.00 (5H, m), 4.30–4.50 (1H, m), 5.27 (2H, s), 7.52 (2H, d, J = 8.1 Hz), 8.22 (H, d, J = 8.1 Hz).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-methanesulfonyloxymethylpyrrolidine (3b). 3b was prepared from **2b** (63.1 g) by a similar method to that described for preparation of **3a**. An orange oil (43.19 g, ~100%). IR (Neat) cm^{-1} 1699; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.78 (9H, s), 1.50–1.70 (1H, m), 1.95–2.10 (2H, m), 2.93 (3H, s), 3.38~3.50 (2H, m), 4.10–4.40 (3H, m), 4.50–4.60 (3H, m), 5.13–5.28 (2H, m), 5.79–6.00 (1H, m).

(2*S*,4*R*)-1-Benzyl-4-*tert*-butyldimethylsilyloxy-2-vinylpyrrolidine (5). To a solution of oxalyl chloride (20 mL) in CH_2Cl_2 (700 mL) was added, dropwise, DMSO (34.0 mL) at −40 to −50°C. After stirring for 5 min, a solution of **2c** (70.1 g) in CH_2Cl_2 (300 mL) was added to the mixture at −40 to −50°C. After stirring for 10 min, Et_3N (151.9 mL) was added, dropwise, to the solution and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into 1N HCl and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$, water and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give (2*S*,4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxy-2-formylpyrrolidine as a crude oil. This oil was used in the next reaction immediately because of its instability. To a suspension of methyltriphenylphosphonium chloride (62.67 g) in THF (300 mL) was added, portionwise, ^{t}BuOK (24.20 g) at 0−5°C. After stirring at room temperature for 2 h, the mixture was added, dropwise, to a solution of the above crude aldehyde in THF (200 mL) at 0−5°C, and then stirred at the same temperature for 1 h. The mixture was then poured into water and extracted with AcOEt. The organic layer was washed

Table 4. NMR data for thiols

No.	^{1}H NMR (200 MHz, $CDCl_3$) δ ppm	Yield
14b	1.45–1.80 (1H, m), 1.85–2.10 (1H, m) 2.26–2.60 (2H, m) 2.34 (3H, s), 2.34 (3H, s), 3.22 (1H, dd, J = 7.6 Hz, 3.9 Hz), 3.80–4.20 (5H, m), 4.59 (2H, d, J = 5.7 Hz), 5.21–5.36 (2H, m), 5.84–6.03 (1H, m), 6.96 (1H, brs), 7.06 (1H, s), 7.50 (1H, s).	40%
14c	1.65–1.85 (1H, m), 2.05–2.30 (1H, m), 2.40–2.75 (2H, m), 3.32 (1H, dd, J = 11.3Hz, 6.8Hz), 4.00–4.40 (5H, m), 4.61 (2H, dd, J = 4.3 Hz, 1.2 Hz), 5.21–5.36 (2H, m), 5.85–6.08 (1H, m), 7.40–7.75 (4H, m), 7.95 (1H, s), 7.90–7.95 (1H, m), 8.14–8.35 (1H, m).	94%
14d	1.40–2.20 (5H, m), 2.55–2.80 (1H, m), 3.26 (1H, dd, J = 11.1 Hz, 7.3 Hz), 3.95–4.25 (5H, m), 4.57–4.61 (2H, m), 5.20–5.35 (2H, m), 5.84–6.03 (1H, m), 6.93 (1H, s), 7.07 (1H, s), 7.39–7.64 (4H, m), 7.90–7.95 (2H, m).	86%
16b	1.50–1.75 (1H, m), 1.85–2.10 (1H, m), 2.34 (3H, s), 2.30–2.70 (2H, m), 3.21 (1H, dd, J = 11.4 Hz, 7.1 Hz), 3.30 (3H, s), 3.50–3.65 (1H, m), 3.90–4.15 (4H, m), 4.40 (2H, s), 4.62 (2H, d, J = 5.5 Hz), 5.15–5.36 (2H, m), 5.85–6.04 (1H, m), 7.01 (1H, s), 7.55 (1H, br.s).	52%
23a	1.55–1.75 (1H, m), 1.88–2.14 (1H, m), 2.34 (3H, s), 2.40–2.69 (2H.m), 3.22 (1H, dd, J = 10.9 Hz, 7.3 Hz), 3.80–4.20 (5H, m), 4.60 (2H, d, J = 6.2 Hz) 4.65 (2H,s) 5.10–5.40 (2H, m), 5.80–6.00 (1H, m), 6.80–7.10 (2H, m).	40%
23b	1.50–2.60 (4H, m), 2.34 (3H, s), 3.16–3.28 (1H, nm), 3.80–4.15 (5H, m), 4.58–4.65 (4H, m), 5.21–5.35 (2H, m), 5.84-6.00 (1H, m), 6.91–6.98 (1H, m), 7.46–7.50 (1H, m).	96%
23c	1.65–1.85 (1H, m), 1.95–2.15 (1H, m), 2.40–2.80 (2H, m), 3.34 (1H, dd, J = 11.1 Hz, 6.2 Hz), 3.95–4.26 (5H, m), 4.60 (2H, d, J = 5.6 Hz), 5.22–5.36 (2H, m), 5.85–6.10 (2H, m, $CONH_2$), 7.04 (1H, brs,$CONH_2$),7.30–7.64 (5H, m), 7.90–7.95 (2H, m).	49%
23d	1.50–1.80 (1H, m), 1.90–2.10 (1H, m), 2.30–2.60 (2H, m), 2.35 (3H, s), 3.22 (1H, dd, J = 11.6 Hz, 6.9 Hz), 3.80–4.30 (5H, m), 4.59 (2H, d, J = 5.6 Hz), 5.20–5.40 (2H, m), 5.80–6.00 (1H, m), 7.59 (2H, brs).	98%
23e	1.69–1.96 (1H, m), 2.04–2.18 (1H, m), 2.40–2.75 (2H, m), 3.31 (1H, dd, J = 11.1 Hz, 7.1 Hz), 3.90–4.26 (3H, m), 4.50–4.61 (4H, m), 5.20–5.35 (2H, m), 5.46 (1H, brs, $CONH_2$), 5.84–6.03 (1H, m), 7.00–8.00 (8H, m, $CONH_2$).	70%
23f	1.70–2.20 (2H, m), 2.40–2.70 (2H, m), 3.33 (1H, dd, J = 10.9 Hz, 6.3 Hz), 3.51 (2H, s), 3.90–4.30 (5H, m), 4.60 (2H, d, J = 5.4 Hz), 5.20–5.40 (3H, m, $CONH_2$), 5.90–6.10 (1H, m), 6.90–8.00 (8H, m).	76%
23g	1.40–1.70 (1H, m), 1.98–2.19 (1H, m), 2.32 (3H, s), 2.30–2.57 (2H, m), 3.17 (1H, dd, J = 11.4 Hz, 7.5 Hz), 3.77–3.99 (2H, m), 4.04–4.24 (3H, m), 4.58 (2H, d, J = 5.9 Hz), 5.18–5.34 (2H, m), 5.88–6.02 (1H, m), 6.24 (1H, t, J = 2.0 Hz), 7.30–7.50 (2H, m).	60%

with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, *n*-hexane:AcOEt (15:1) elution) to give **5** (35.10 g, 50.4%) as a yellow oil. IR (Neat) cm^{-1} 1467, 1371; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.85 (9H, s), 1.82–1.90 (2H, m), 2.11 (1H, dd, J = 9.7 Hz, 5.5 Hz), 3.09–3.22 (2H, m), 3.14 (1H, d, J = 13.1 Hz), 4.00 (1H, d, J = 13.0 Hz), 4.25–4.35 (1H, m), 5.12 (1H, dd, J = 10.0 Hz, 1.9 Hz), 5.22 (1H, dd, J = 17.2 Hz, 1.9 Hz), 5.72 (1H, ddd, J = 17.2 Hz, 9.9 Hz, 8.2 Hz), 7.20–7.30 (5H, m); APCI-MS m/z 318 $(MH)^+$.

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-(2-hydroxyethyl)pyrrolidine (6). To a solution of **5** (24.03 g) in THF (120 mL) was added 9-borabicyclo-[3.3.1]nonane (0.5 M in THF, 318 mL) at 0−5°C and the mixture stirred at room temperature for 4 h. The reaction mixture was quenched with a solution of $NaBO_3{\cdot}4H_2O$ (87 g) in water (200 mL) and at room temperature with vigorous stirring and then stirred for 12 h. After filtration of the mixture, the filtrate was separated. The organic layer was dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, *n*-hexane:AcOEt (1:1) elution) to give (2*R*,4*R*)-1-benzyl-4-*tert*-butyldimethylsilyloxy-2-(2-hydroxyethyl)pyrrolidine (20.89 g, 82.3%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.86 (9H, s), 1.52 (1H, ddt, J = 14.8 Hz, 3.1 Hz, 3.1 Hz), 1.84 (1H, ddd, J = 13.0 Hz, 8.4 Hz, 4.5 Hz), 1.99–2.22 (2H, m), 2.24 (1H, dd, J = 10.4 Hz, 5.4 Hz), 3.03 (1H, dd, J = 10.4 Hz, 5.5 Hz), 3.21–3.34 (1H, m), 3.31 (1H, d, J = 12.6 Hz), 3.73 (1H, dt, J = 11.0 Hz, 4.0 Hz), 4.00 (1H, td, J = 11.0 Hz, 2.8 Hz), 4.21 (1H, d, J = 12.6 Hz), 4.27–4.38 (1H, m), 7.22–7.36 (6H, m). A mixture of this oil (20.89 g) and 10% Pd/C (50% wet, 8 g) in MeOH (200 mL) was stirred vigorously for 3 h under an atmospheric pressure of hydrogen at room temperature. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure to give a crude residue. The obtained crude residue was dissolved in a mixture of THF (80 mL) and water (80 mL), and treated dropwise with a solution of allyl chloroformate (7.27 mL) in THF (20 mL) at 0–10°C adjusting pH (8–10) with 6 NNaOH. After stirring for 30 min, the mixture was extracted with AcOEt (×3). The combined organic layer was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, *n*-hexane:AcOEt (2:1) elution) to give **6** (18.52 g, 90.3%) as an oil. IR (Neat) cm^{-1} 1684; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.81 (9H, s), 1.40–1.80 (3H, m), 1.95–2.08 (1H, m), 3.35–3.40 (2H, m), 3.52–3.60 (2H, m), 4.10–4.30 (1H, m), 4.30–4.45 (1H, m), 4.54 (2H, d, J = 5.5 Hz), 5.13–5.30 (2H, m), 5.79–5.98 (1H, m); APCI-MS m/z 330 $(MH)^+$.

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-(2-methanesulfonyloxyethyl)pyrrolidine (7). 7 was prepared from **6** (18.52 g) by a similar method to that described for the preparation of **3a**. Oil (17.31 g, 75.6%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.80 (9H, s), 1.65–2.35 (4H, m), 2.96 (3H, s), 3.29–3.46 (1H, m), 3.33 (1H, dd, J = 11.4 Hz, 4.3 Hz), 4.00–4.15 (1H, m), 4.20–4.35 (3H, m), 4.50–4.60 (2H, m), 5.12–5.28 (2H, m), 5.78–5.94 (1H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(2-methanesulfonyloxyethyl)pyrrolidine (8). To a solution of **6** (5.0 g) in MeOH (25 mL) was added concentrated HCl (2.53 mL) at 0–5°C and the mixture stirred for 1 h. The mixture was quenched with NaOMe (28% in

Table 5. Physical data for carbapenems[a]

No.	^{1}H NMR (200 MHz, D_2O) δ ppm	MS	IR
1b	1.23 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.77–1.92 (1H,m), 2.75–2.91 (1H, m), 3.33–3.50 (3H, m), 3.68 (1H, dd J = 12.5 Hz, 6.7 Hz), 4.08 (3H, s), 4.00–4.30 (4H,m), 4.63–4.68 (2H, m), 6.54 (1H, d, J = 3.6 Hz), 7.61 (1H, dd, J = 2.4 Hz, 1.1 Hz), 7.93 (1H, d, J = 2.3 Hz), 7.99 (1H, d, J = 3.5 Hz).	446	1755–1740 1590–1580
1e	1.22 (3H, d, J = 7.2 Hz), 1.30 (3H, d J = 6.4 Hz), 1.72–1.87 (1H, m), 2.46–2.69 (2H, m), 2.78–2.90 (1H, m), 3.34–3.50 (3H, m), 3.70 (1H, dd, J = 12.4 Hz, 6.7 Hz), 3.79–3.95 (1H, m), 4.00 (3H, s), 4.00–4.15 (1H, m), 4.23–4.29 (2H, m), 4.57–4.66 (2H, m), 8.86 (1H, s).	422	1745, 1580
1g	1.20 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.59–2.08 (5H, m), 2.67–2.87 (1H, m), 3.35–3.48 (3H, m), 3.59–3.77 (2H, m), 3.89 (3H, s), 3.94–4.10 (1H, m), 4.19—4.30 (4H, m), 7.45 (1H, d, J = 1.7 Hz), 7.49 (1H, d, J = 1.8 Hz), 8.75 (1H, s).	NT	1724, 1570
1h	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.70–2.00 (1H, m), 2.60–2.90 (1H, m), 3.30–3.50 (3H, m), 3.63 (1H, dd, J = 12.4 Hz, 6.6 Hz), 3.92 (3H, s), 4.00–4.10 (1H, m), 4.10–4.40 (3H, m), 4.89 (2H, d, J = 5.7 Hz), 5.90–6.30 (2H, m), 7.48 (2H, s), 8.75 (1H, s).	NT	1740, 1570
1j	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.69–1.83 (1H, m), 2.40–2.70 (2H, m), 2.75–2.90 (1H, m), 3.35–3.55 (3H, m), 3.65–3.85 (2H, m), 4.00–4.15 (1H, m), 4.20–4.35 (2H, m), 4.43 (2H, t, J = 7.6 hz), 5.14 (2H, s), 7.57 (1H, s), 7.65 (1H, s), 8.98 (1H, s).	464	1740–1760 1660–1690
1k	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.70–1.90 (1H, m), 2.20–2.90 (5H, m), 3.00–3.10 (2H, m), 3.30–3.50 (3H, m), 3.60–3.90 (2H, m), 4.00–4.10 (1H, m), 4.20–4.50 (6H, m), 7.61 (2H, s), 8.97 (1H, s)	NT	1750, 1565
1l	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.70–1.85 (1H, m), 2.35–2.60 (2H, m), 2.70–2.90 (1H, m), 3.35–4.55 (10H, m), 3.92 (3H, s), 4.94 (2H, s), 7.49–7.57 (2H, m).	NT	1755, 1585
1m	1.22 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.70–1.85 (1H, m), 2.38–2.65 (2H, m), 2.70–2.90 (1H, m), 3.30–3.52 (3H, m), 3.63–3.85 (2H, m), 3.89 (3H, s), 4.00–4.10 (1H, m), 4.20–4.40 (4H, m), 4.73 (2H, br s), 7.48–7.58 (1H, m), 8.84 (1H, brs).	NT	1750, 1580
1n	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d,J = 6.4 Hz), 1.70–1.85 (1H, m), 2.35–2.58 (2H, m), 2.75–2.92 (1H, m), 3.42 (3H, s), 3.35–3.50 (3H, m), 3.64–3.86 (2H, m), 3.90 (3H, s), 4.00–4.15 (1H, m), 4.23–4.38 (4H, m), 4.63 (2H, s), 7.58 (1H, s), 8.90 (1H, s).	NT	1753, 1585
1o	1.23 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.65–1.83 (1H, m), 2.38–2.60 (2H, m) 2.72–2.90 (1H, m), 3.32–3.50 (3H, m), 3.63–3.81 (3H, m), 4.02 (3H, s), 4.20–4.30 (2H, m), 4.46 (2H, t, J = 8.6 Hz), 7.62 (1H, d, J = 2.0 Hz), 7.71 (1H, d, J = 2.0 Hz).	NT	1750, 1595
1q	1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.65–1.85 (1H, m), 2.35–2.60 (2H, m), 2.70–2.85 (1H, m), 3.30–3.50 (3H, m), 3.63–3.80 (2H, m), 3.80 (3H, s), 3.88 (2H, s), 3.95–4.10 (1H, m), 4.22–4.38 (4H, m), 7.53 (1H, s), 8.84 (1H, s).	NT	1750, 1675, 1575
1r	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.70–1.85 (1H, m), 2.35–2.65 (2H, m), 2.75–2.90 (1H, m), 3.30–3.55 (3H, m), 3.65–3.90 (2H, m), 3.95 (3H, s), 4.00–4.15 (1H, m), 4.20–4.35 (2H, m), 4.38 (2H, t, J = 7.7 Hz), 6.76 (1H, d, J = 15.9 Hz), 7.41 (1H, d, J = 16.3 Hz), 8.00 (1H, s), 8.92 (1H, s).	NT	1735, 1580–1510
1s	1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.70–1.90 (1H, m), 2.40–2.60 (2H, m), 2.80–2.90 (1H, m), 3.33–3.55 (3H, m), 3.64–3.85 (2H, m), 4.00–4.15 (1H, m), 4.06 (3H, s), 4.22–4.30 (2H, m), 4.46 (2H, t, J = 8.0 Hz), 8.46 (1H, s).	NT	1750, 1580

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

Table 6. Elemental analysis data for selected carbapenems

No.	Found			Calcd			Molecular formula
	C(%)	H(%)	N(%)	C(%)	H(%)	N(%)	
1b	46.19	6.61	12.75	46.12	6.49	12.81	$C_{21}H_{28}ClN_5O_4S{\cdot}3.6H_2O$
1c	45.63	6.84	10.68	45.72	7.02	10.66	$C_{20}H_{29}ClN_4O_4S{\cdot}3.8H_2O$
1e	44.34	6.78	13.57	44.26	6.72	13.58	$C_{19}H_{28}ClN_5O_4S{\cdot}3.2H_2O$
1g	45.09	7.14	10.00	45.10	7.35	10.02	$C_{21}H_{31}ClN_4O_4S{\cdot}4.9H_2O$
1j	45.61	6.51	12.62	45.67	6.53	12.68	$C_{21}H_{30}ClN_5O_4S{\cdot}2.9H_2O$
1m	46.13	6.87	10.05	46.16	6.93	10.25	$C_{21}H_{31}ClN_4O_5S{\cdot}3.3H_2O$

MeOH, 5.84 mL) at 0°C and the resulting precipitates were filtered off. The filtrate was evaporated under reduced pressure to give a residue which was dissolved in CH_2Cl_2 (15 mL). The solution was dried over $MgSO_4$ and evaporated under reduced pressure to give a crude oily residue. This residue was washed with *n*-hexane and dried under reduced pressure to give (2*R*,4*R*)-1-allyloxycarbonyl-4-hydroxy-2-(2-hydroxyethyl)pyrrolidine (3.10 g, 94.9%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.60–1.80 (2H, m), 1.80–1.95 (1H, m), 2.10–2.25 (1H, m), 3.45 (1H, dd, J = 11.7 Hz, 4.9 Hz), 3.55–3.75 (3H, m), 4.20–4.40 (1H, m), 4.40–4.55 (1H, m), 4.60 (2H, d, J = 5.4 Hz), 5.19–5.36 (2H, m), 5.84–6.04 (1H, m). Mesylation of this diol (8.28 g) was achieved by a similar method to that described for the preparation of **3b**, using MsCl (6.26 mL, 2.1 eq.) and Et_3N (11.26 mL, 2.1 eq.). Oil (10.32 g, 72.2%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85–2.15 (2H, m), 2.30–2.65 (2H, m), 3.04 (3H, s), 3.05 (3H, s), 3.50–3.65 (1H, m), 3.92–4.45 (4H, m), 4.61 (2H, d, J = 4.4 Hz), 5.21–5.36 (3H, m), 5.85–6.05 (1H, m).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(*E*)-3-methoxy-3-oxo-1-propenyl]pyrrolidine (9). Swern oxidation of **2b** (200 g) was achieved by the same

method as described for the preparation of **5**, to give (*2S,4R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-formylpyrrolidine (202.7 g, ~100%) as a crude brown oil. IR (Neat) cm^{-1} 1710, 1696; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.87 (9H, s), 1.90–2.09 (2H, m), 3.42–3.64 (2H, m), 4.30–4.41 (2H, m), 4.59–4.64 (2H, m), 5.17–5.37 (2H, m), 5.81–5.97 (1H, m), 9.50 (0.5H, d, J = 3.3 Hz), 9.58 (0.5H, d, J = 2.6 Hz), two conformational isomers. To a solution of the obtained crude aldehyde (30 g) in THF (300 mL) was added methyl (triphenylphosphoranylidene)acetate (Ph_3P=CHCOOMe) (35.2 g). After stirring at room temperature overnight, the mixture was evaporated and purified by column chromatography (SiO_2 600 mL) to give **9** (29.8 g, 84.2%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.74–1.95 (1H, m), 2.01–2.22 (1H, m), 3.40–3.60 (2H, m), 3.73 (3H, s), 4.30–4.43 (1H, m), 4.49–4.68 (3H, m), 5.10–5.39 (2H, m), 5.75–6.00 (2H, m), 6.85 (1H, dd, J = 15.6 Hz, 6.4 Hz).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-(3-methanesulfonyloxypropyl)pyrrolidine (10). To a solution of **9** (18.7 g) in THF (190 mL) were added successively $NaBH_4$ (3.83 g) and LiI (13.5 g) at room temperature and the mixture was stirred under reflux for 4 h. After cooling to room temperature, the mixture was diluted with water (200 mL) and extracted with AcOEt (200 mL×3). The combined extracts were washed with brine (400 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give (2*S*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-(3-hydroxypropyl)pyrrolidine (17.2 g, 98.9%) as a pale yellow paste. ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.22–2.34 (6H, m), 3.36–3.37 (2H, m), 3.61 (2H, br t, J = 6.7 Hz), 3.95–4.11 (1H, m), 4.26–4.35 (1H, m), 4.52–4.54 (2H, m), 5.10–5.29 (2H, m), 5.79–5.98 (1H, m). The mesylation of the alcohol (17.1 g) was achieved by a similar method to that described for preparation of **3a** to give **10** (21.2 g, ~100%) as a yellow paste. ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.43–2.04 (6H, m), 3.01 (3H, s), 3.39 (1H, dd, J = 11.4 Hz, 4.5 Hz), 3.35–3.67 (1H, m), 3.91–4.11 (1H, m), 4.24 (2H, t, J = 6.0 Hz), 4.30–4.40 (1H, m), 4.49–4.69 (2H, m), 5.17–5.35 (2H, m), 5.84–6.03 (1H, m).

(2*S*,4*R*)-4-Hydroxy-2-(imidazol-1-yl)methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (11). A mixture of **4** (3 g) and imidazole (15 g) was melted at 100–110°C under stirring for 5 h. The mixture was poured into water (150 mL) and extracted with $CHCl_3$ (50 mL×3). The combined organic extracts were washed with water, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 60 mL, MeOH:$CHCl_3$ (1:99) elution) to give (2*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-2-(imidazol-1-yl)methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.57 g, 59.2%) as a syrup. IR (Neat) cm^{-1} 1705, 1525; ^1H NMR (90 MHz, $CDCl_3$) δ 0.01 (6H, s), 0.82 (9H, s), 1.50–2.20 (2H, m), 3.21 (1H, dd, J = 10.8 Hz, 4.5 Hz), 3.20–3.50 (1H, m), 3.75–4.60 (4H, m), 5.24–5.28 (2H, m), 6.78 (1H, s), 7.01 (1H, s), 7.33 (1H, s), 7.48 (2H, d, J = 8.1 Hz), 8.20 (2H, d, J = 8.1 Hz). Desilylation of the syrup (1.55 g) was achieved by a similar method to that described for preparation of **8** to give **11** (0.8 g, 69%) as a solid. Mp. 147–148°C; IR ($CHCl_3$) cm^{-1} 1710–1690; ^1H NMR (90 MHz, $CDCl_3$) δ 1.50–2.20 (2H, m), 3.29 (1H, dd, J = 10.8 Hz, 4.5 Hz), 3.40–3.70 (1H, m), 3.90–4.50 (4H, m), 5.26 (2H, s), 6.78 (1H, br s), 6.97 (1H, br s), 7.32 (1H, br s), 7.50 (2H, d, J = 8.1 Hz), 8.20 (2H, d, J = 8.1 Hz).

(2*S*,4*S*)-4-Acetylthio-2-(imidazol-1-yl)methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (12). Mesylation of **11** (0.79 g) was achieved by a similar method to that described for preparation of **3a** to give (2*S*,4*R*)-2-(imidazol-1-yl)methyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.78 g, 80.4%) as an oil. IR ($CHCl_3$) cm^{-1} 1710, 1525; ^1H NMR (90 MHz, $CDCl_3$) δ 1.75–2.62 (2H, m), 3.00 (3H, s), 3.00–3.40 (1H, m), 3.88–4.60 (4H, m), 4.80–4.98 (1H, m), 5.38 (2H, s), 6.80 (1H, br s), 7.04 (1H, br s), 7.39 (1H, br s), 7.51 (2H, d, J = 9.0 Hz), 8.22 (2H, d, J = 9.0 Hz). To a suspension of NaH (62.8% in oil, 0.08 g) in DMF (5 mL) was added *S*-thioacetic acid (0.16 mL) at 0°C. After stirring at room temperature for 10 min, a solution of the above mesylate (0.76 g) in DMF (2 mL) was added to the suspension, and the mixture stirred at 70–75°C for 5 h. The mixture was then quenched with water (70 mL) and extracted with AcOEt (70 mL). The organic extract was dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 40 mL, MeOH:$CHCl_3$ (2:98) elution) to afford **12** (0.38 g, 52.8%) as an oil. IR (Neat) cm^{-1} 1710, 1685; ^1H NMR (90 MHz, $CDCl_3$) δ 1.50–1.90 (1H, m), 2.32 (3H, s), 2.07–2.60 (1H, m), 2.93–3.12 (1H, m), 3.68–4.30 (5H, m), 5.21 (2H, s), 6.81 (1H, br s), 7.02 (1H, br s), 7.37 (1H, br s), 7.47 (2H, d, J = 8.1 Hz), 8.19 (2H, d, J = 8.1 Hz).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2-(imidazo[1,2-*b*]-pyrazol-1-ylmethyl)pyrrolidine (13a). To a solution of imidazo[1,2-*b*]pyrazole (1.75 g) in DMF (20 mL) was added NaH (60% in oil, 686 mg) at 0°C, and the mixture stirred for 30 min at the same temperature. The mixture was then added to a solution of **3b** (5 g) in DMF (50 mL) and stirred at 80–90°C for 2 h. The mixture was poured into ice-water (100 mL) and extracted with AcOEt (150 mL×2). The combined extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 200 mL, CH_2Cl_2:Me_2CO (3:1) elution) to give (2*S*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-(imidazo[1,2-*b*]pyrazol-1-ylmethyl)-pyrrolidine (4.24 g, 82.5%) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.80 (9H, s), 1.78–2.05 (2H, m), 3.15–3.50 (2H, m), 3.85–4.45 (4H, m), 4.67 (2H, d, J = 5.4 Hz), 5.20–5.39 (2H, m), 5.61 (1H, d, J = 1.8 Hz), 5.87–6.07 (1H, m), 6.64 (1H, br s), 7.30–7.31 (1H. m), 7.61 (1H, br s). Desilylation of this oil (4.23 g) was achieved by a similar method to that described for preparation of **8** to give **13a** (3.18 g, ~100%) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–2.15 (2H, m), 3.24 (1H, dd, J = 11.8 Hz, 4.5 Hz), 3.45–3.65 (1H, m), 4.00–4.20 (2H, m), 4.30–4.50 (2H, m), 4.65 (2H, d, J = 5.6 Hz), 5.24–5.39 (2H, m), 5.61 (1H, d, J = 2 Hz), 5.90–6.04 (1H, m), 6.65 (1H, br s), 7.28 (1H. br s), 7.58 (1H, br s).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2-[2-(imidazol-1-yl)ethyl]pyrrolidine (13b). To a solution of imidazole (1.52 g) in DMF (83 mL) was added successively ^{t}BuOK (2.51 g) and **7** (8.3 g) at room temperature. After stirring for 1 h at ~60°C, the mixture was quenched with water and extracted with AcOEt. The organic extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, $CHCl_3$:Me_2CO (100:0–97:3) elution) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-(imidazol-1-yl)ethyl]pyrrolidine (11.11 g, ~100%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.81 (9H, s), 1.45–1.70 (1H, m), 1.77–2.10 (2H, m), 2.15–2.40 (1H, m), 3.34 (1H, dd, J = 11.4 Hz, 4.4 Hz), 3.30–3.47 (1H, m), 3.85–4.05 (1H, m), 4.25–4.40 (1H, m), 4.50–4.60 (2H, m), 5.10–5.30 (2H, m), 5.80–6.00 (1H, m), 6.86–6.92 (1H, m), 7.01 (1H, m), 7.45–7.50 (1H, m): FAB-MS m/z 380.2 $(MH)^+$. Desilylation of the oil (11.11 g) was achieved by a similar method to that described for preparation of **8** to give **13b** (9.19 g, ~100%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.68–2.00 (2H, m), 2.15–2.23 (1H, m), 2.35–2.60 (1H, m), 3.43 (1H, dd, J = 11.9 Hz, 4.1 Hz), 3.60–3.75 (1H, m), 3.95–4.30 (3H, m), 4.40–4.45 (1H, m), 4.56 (2H, d, J = 5.4 Hz), 5.19–5.34 (2H, m), 5.83–6.02 (1H, m), 7.17 (2H, br s), 8.01 (1H, br s).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2-[2-(1,2,4-triazol-1-yl)ethyl]pyrrolidine (13c). The preparation of **13c** was achieved from **7** by a similar method to that described for preparation of **13a** using 1,2,4-triazole sodium salt. A yellow paste, 91%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–1.82 (1H, m), 2.00–2.20 (2H, m), 2.32–2.50 (1H, m), 3.35–3.50 (1H, m), 3.60–3.80 (1H, m), 4.00–4.13 (1H, m), 4.20–4.50 (3H, m), 4.58 (2H, d, J = 5.5 Hz), 5.20–5.35 (2H, m), 5.84–6.03 (1H, m), 7.93 (1H, s), 8.05–8.23 (1H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2-[3-(imidazol-1-yl)propyl)pyrrolidine (13d). The preparation of **13d** was achieved from **10** by a similar method to that described for preparation of **13b**. A yellow paste, 94%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29–1.50 (1H, m), 1.65–2.20 (5H, m), 3.27–3.74 (2H, m), 3.85–4.12 (3H, m), 4.33–4.46 (1H, m), 4.58 (2H, d, J = 5.6 Hz), 5.18–5.33 (2H, m), 5.78–6.06 (1H, m), 6.90 (1H, s), 7.04 (1H, s), 7.46 (1H, s).

(2*R*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-(imidazo-[1,2-*b*]pyrazol-1-yl)methylpyrrolidine (14a). Mesylation of **13a** (3.16 g) was achieved by a similar method to that described for the preparation of **3a** to give (2*R*,4*R*)-1-allyloxycarbonyl-2-(imidazo[1,2-*b*]pyrazol-1-yl)methyl-4-methanesulfonyloxypyrrolidine (3.06 g, 76.3%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.99–2.13 (1H, m), 2.35–2.50 (1H, m), 2.98 (3H, s), 3.24–3.36 (1H, m), 3.83–4.52 (4H, m), 4.66–4.70 (2H, m), 4.85–5.00 (1H, m), 5.20–5.40 (2H, m), 5.61 (1H, d, J = 1.9 Hz), 5.88–6.07 (1H, m), 6.64 (1H, br s), 7.31–7.32 (1H. m), 7.60–7.62 (1H, m). To a solution of this oil (3.04 g) in MeCN (60 mL) was added potassium *S*-thioacetate (1.41 g) and the solution stirred at 80–90°C for 4 h. The mixture was quenched with a mixture of water and brine (1:1, 50 mL) and extracted with AcOEt (100 mL). The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 200 mL, CH_2Cl_2:Me_2CO (5:1) elution) to give **14a** (2.33 g, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71–1.85 (1H, m), 2.33 (3H, s), 2.30–2.60 (1H, m), 3.00–3.30 (1H, m), 3.80–4.30 (5H, m), 4.63 (2H, d, J = 5.5 Hz), 5.24–5.38 (2H, m), 5.66 (1H, br s), 5.85–6.10 (1H, m), 6.67 (1H, br s), 7.30–7.31 (1H. m), 7.60–7.62 (1H, m).

The preparation of **14b** (40%) was achieved from **13b** by a similar method to that described for preparation of **14a**.

Mitsunobu reaction of **13c** and **13d** was respectively achieved by a similar method to that described for preparation of **28** to give **14c** (94%) and **14d** (86%).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-(5-formylimidazol-1-yl)ethyl]pyrrolidine (15a) and (2*R*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-(4-formylimidazol-1-yl)ethyl]pyrrolidine (15b). To a solution of **7** (63 g) and 4-formylimidazole (17.8 g) in DMF (300 mL) was added ^{t}BuOK (20.8 g) and the mixture stirred at 45°C for 2 h. After evaporation of the solvent, the residue was dissolved in a mixture of AcOEt (1.5 L) and water (200 mL). The organic layer was separated, washed in turn with 1N HCl (100 mL) and brine (300 mL×3), dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 2000 L, hexane:AcOEt (1:1–1:2–0:1) elution). The former fractions were collected and evaporated to give **15a** (14.9 g, 24%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.80 (9H, s), 1.70–2.30 (4H, m), 3.36 (1H, dd, J = 11.4 Hz, 4.5 Hz), 3.30–3.60 (1H, m), 3.95–4.10 (1H, m), 4.20–4.40 (3H, m), 4.50–4.55 (2H, m), 5.10–5.30 (2H, m), 5.78–6.27 (1H, m), 7.61–7.78 (2H, m), 9.68 (1H, s). The latter fractions were collected and evaporated to give **15b** (22.4 g, 36%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.80 (9H, s), 1.50–1.70 (1H, m), 1.79–2.00 (2H, m), 2.10–2.30 (1H, m), 3.33 (1H, dd, J = 11.5 Hz, 4.4 Hz), 3.28–3.55 (1H, m), 3.90–4.10 (3H, m), 4.25–4.36 (1H, m), 4.55 (2H, d, J = 5.3 Hz), 5.15–5.30 (2H, m), 5.79–6.00 (1H, m), 7.50–7.75 (2H, m), 9.81 (1H, s).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2-[2-(5-methoxymethylimidazol-1-yl)ethyl]pyrrolidine (16a). To a solution of **15a** (12.65 g) in a mixture of THF (60 mL) and MeOH (60 mL) was added $NaBH_4$ (1.17 g) at 0°C. After stirring for 1 h, the mixture was adjusted to pH 8 with 6N HCl. The resulting precipitates were filtered off and the filtrate was evaporated under reduced pressure to give a residue which was purified by column chromatography (SiO_2 500 mL, $CHCl_3$:MeOH (9:1) elution) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-(5-hydroxymethylimidazol-1-yl)ethyl]pyrrolidine (10.23 g, 81%) as an amorphous solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.86 (9H, s), 1.65–2.50 (4H, m), 3.30–3.50 (2H, m), 3.95–4.15 (3H, m), 4.30–4.45 (1H, m), 4.55–4.65 (2H, m), 4.60 (2H, s), 5.18–5.35 (2H, m), 5.84–6.03 (1H, m), 6.87 (1H, s), 7.45

(1H, br s). To a solution of the above alcohol (9.22 g) in THF (100 mL) was added ^{t}BuOK (3.54 g) at 0°C. After stirring for 10 min, MeI (2.80 mL) was added to the mixture, which was then stirred for 1 h at 0°C. The mixture was dissolved in AcOEt (100 mL), washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (SiO_2 400 mL, $CHCl_3$:MeOH (19:1) elution). Fractions containing the desired compound were collected and evaporated to give (2*R*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-(5-methoxymethylimidazol-1-yl)ethyl]pyrrolidine as a residue (7.79 g). Desilylation of this residue (7.79 g) was achieved by a similar method to that described for preparation of **8** to give **16a** (3.63 g, 52%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50–2.50 (4H, m), 3.29 (3H, s), 3.40–3.50 (1H, m), 3.55–3.80 (1H, m), 3.95–4.15 (3H, m), 4.35–4.50 (1H, m), 4.38 (2H, s), 4.59 (2H, d, J = 5.4 Hz), 5.19–5.35 (2H, m), 5.84–6.01 (1H, m), 6.98 (1H, s), 7.55 (1H, br s). **16b** (52%) was prepared from **16a** by a similar method to that described for preparation of **14a**.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-[4-[(*E*)-2-carbamoylethenyl]imidazol-1-yl]ethyl]-4-hydroxypyrrolidine (17a). To a solution of diethyl carbamoylmethylphosphonate (12.7 g) and ^{t}BuOK (13.9 g) in THF (400 mL) was added a solution of **15b** (24 g) in THF (50 mL) at 45°C. After stirring for 1 h, the mixture was quenched with water (3 mL) and evaporated under reduced pressure. The residue was dissolved in a mixture of AcOEt (500 mL) and water (50 mL). The organic layer was separated, washed with water (50 mL×2) and brine (50 mL×2), dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 500 mL, CH_2Cl_2:MeOH (10:1)) to give (2*R*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[2-[4-[(E)-2-carbamoylethenyl]imidazol-1-yl]ethyl]pyrrolidine (13.87 g, 53%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.84 (9H, s), 1.50–1.75 (1H, m), 1.75–2.10 (2H, m), 2.16–2.40 (1H, m), 3.36 (1H, dd, J = 11.5 Hz, 4.4 Hz), 3.33–3.65 (1H, m), 3.90–4.15 (3H, m), 4.30–4.45 (1H, m), 4.59 (2H, d, J = 5.3 Hz), 5.19–5.34 (2H, m), 5.57 (2H, br s, $CONH_2$), 5.83–6.02 (1H, m), 6.61 (1H, d, J = 15.0 Hz), 7.11 (1H, m), 7.50 (1H, d, J = 15.0 Hz), 7.51 (1H, br s). Desilylation of the oil (13.87 g) was achieved as described for **8** to give **17a** (9.92 g, 96%) as a pale yellow foam. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63–2.18 (3H, m), 2.30–2.50 (1H, m), 3.35–3.70 (2H, m), 3.90–4.15 (3H, m), 4.35–4.43 (1H, m), 4.58 (2H, d, J = 5.6 Hz), 5.20–5.35 (2H, m), 5.83–6.03 (1H, m), 6.57 (1H, d, J = 15.4 Hz), 7.16 (1H, br s), 7.34 (1H, d, J = 15.9 Hz), 7.57 (1H, br s).

(2*R*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[2-[4-[(*E*)-2-carbamoylethenyl]imidazol-1-yl]ethyl]pyrrolidine (17b). Mesylation of **17a** (9.9 g) was achieved by a similar method to that described for preparation of **3a** to give (2*R*,4*R*)-1-allyloxycarbonyl-2-[2-[4-[(*E*)-2-carbamoylethenyl]imidazol-1-yl]ethyl]-4-methanesulfonyloxypyrrolidine (8.84 g, 72%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80–2.05 (2H, m), 2.30–2.70 (2H, m), 3.04 (3H, s), 3.49–3.65 (1H, m), 3.95–4.20 (4H, m), 4.61 (2H, d, J = 6.8 Hz), 5.22–5.36 (3H, m), 5.83–6.03 (1H, m), 6.65 (1H, d, J = 15.3 Hz), 7.14 (1H, br s), 7.47 (1H, d, J = 15.3 Hz), 7.54 (1H, br s). To a mixture of ^{t}BuOK (1.8 g) in DMF (50 mL) was added dropwise PhCOSH (1.9 mL) at 0°C. After stirring for 30 min, a solution of the obtained mesylate (5.5 g) in DMF (20 mL) was added to the mixture and stirred at 80°C for 4 h. The mixture was evaporated under reduced pressure and purified by column chromatography (SiO_2 300 mL, CH_2Cl_2:MeOH (9:1)) to give **17b** (5.33 g, 88%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–2.70 (4H, m), 3.34 (1H, dd, J = 11.1 Hz, 6.3 Hz), 3.90–4.30 (5H, m), 4.60 (2H, d, J = 5.6 Hz), 5.22–5.37 (2H, m), 5.65 (2H, br s, $CONH_2$), 5.85–6.04 (1H, m), 6.63 (1H, d, J = 6.6 Hz), 7.14 (1H, br s), 7.40–7.65 (5H, m), 7.90–7.95 (2H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-(2-azidoethyl)-4-*tert*-butyldimethylsilyloxy pyrrolidine (18a). To a solution **7** (37 g) in DMF (185 mL) was added NH_4Cl (5.84 g) and NaN_3 (7.1 g). After stirring at 70°C for 3 h, the mixture was quenched with water and extracted with AcOEt (×3). The organic layer was washed with water (×2) and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give **18a** (29.65 g, 92%) as an oil. IR (Neat) cm^{-1} 2925, 2080, 1665, 1400; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.86 (9H, s), 1.50–2.35 (4H, m), 3.30–3.50 (3H, m), 3.75–4.45 (3H, m), 4.60–4.70 (2H, m), 5.18–5.85 (2H, m), 5.85–6.01 (1H, m).

(2*R*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-(2-azidoethyl)-pyrrolidine (19). Desilylation of **18a** (29.65 g) was achieved as described for the preparation of **8** to give **18b** (20 g, 100%) as an oil. Mesylation and subsequent thioacetylation of **18b** (20 g) was achieved as described for the preparation of **14a**, to give **19** (14.68 g, 58%) as an oil. IR (Neat) cm^{-1} 2925, 2080, 1665, 1395; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65–1.90 (2H, m), 2.15–2.35 (1H, m), 2.35 (3H, s), 2.50–2.70 (1H, m), 3.18 (1H, dd, J = 11.4 Hz, 7.4 Hz), 3.30–3.45 (2H, m), 3.81–4.14 (3H, m), 4.59 (2H, d, J = 4.9 Hz), 5.21–5.36 (2H, m), 5.84–6.04 (1H, m).

(2*R*,4*S*)-1-Allyloxycarbonyl-2-(2-azidoethyl)-4-triphenylmethylthiopyrrolidine (20a). A solution of **19** (14.68 g) in a mixture of THF (74 mL) and MeOH (74 mL) was treated with NaOMe (28% in MeOH, 11.3 mL) at 0°C for 1 h. To the mixture was added triphenylmethyl chloride (14.4 g), followed by stirring for 5 h at 0°C. The mixture was quenched with water and extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, hexane: AcOEt (10:1–5:1) elution) to give **20a** (16.48 g, 67%) as an oil. IR (Neat) cm^{-1} 2925, 2080, 1665, 1395; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35–1.71 (2H, m), 1.90–2.25 (2H, m), 2.70–3.40 (5H, m), 3.62–3.75 (1H, m), 4.40–4.60 (2H, m), 5.19–5.29 (2H, m), 5.78–5.97 (1H, m), 7.18–7.49 (15H, m).

(2*R*,4*S*)-1-Allyloxycarbonyl-2-(2-aminoethyl)-4-triphenylmethylthiopyrrolidine (20b). To a solution of **20a** (10.1 g) in pyridine (30 mL) was added Ph_3P (8.5 g) at room temperature. After stirring for 1 h, aqueous NH_3 (28%,

2.7 mL) was added to the mixture, followed by stirring at room temperature overnight. The mixture was evaporated under reduced pressure and purified by column chromatography (SiO_2) to give **20b** (9.03 g, 94%) as an oil. IR (Neat) cm^{-1} 1660, 1390; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35–2.15 (4H, m), 2.60–3.00 (5H, m), 3.60–3.80 (1H, m), 4.40–4.60 (2H, m), 5.20–5.30 (2H, m), 5.77–5.96 (1H, m), 7.15–7.50 (15H, m).

(2*R*,4*S*)-1-Allyloxycarbonyl-2-[2-(1-pyridinio)ethyl]-4-(triphenylmethylthio)pyrrolidine chloride. (21) A solution of **20b** (5.78 g) and 1-(2,4-dinitrophenyl)pyridinium chloride (4.19 g) in *n*-butanol (60 mL) was stirred under reflux for 4 h, then evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, $CHCl_3$:MeOH (5:1–4:1) elution) to give **21** (5.88 g, 84%) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–1.75 (1H, m), 2.30–2.90 (6H, m), 3.55–3.75 (1H, m), 4.43 (2H, d, J = 5.4 Hz), 4.85–5.05 (1H, m), 5.20–5.30 (3H, m), 5.75–5.94 (1H, m), 7.17–7.45 (15H, m), 8.07 (2H, t, J = 7.0 Hz), 8.44 (1H, t, J = 7.8 Hz), 9.66 (2H, d, J = 5.5 Hz).

(2*R*,4*R*)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-[2-(pyrazol-1-yl)ethyl]pyrrolidine (22i). To a solution of **8** (27.14 g) in DMF (270 mL) was added pyrazole (5.47 g) and ^{t}BuOK (9.02 g). The mixture was stirred at 50–60°C for 2 h, poured into water, and extracted with AcOEt (×3). The combined organic extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2, hexane: AcOEt (1:1–1:3) elution) to give **22i** (14.85 g, 59%) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.70–1.90 (1H, m), 1.95–2.15 (1H, m), 2.20–2.60 (2H, m), 3.04 (3H, s), 3.45–3.60 (1H, m), 3.90–4.35 (4H, m), 4.60 (2H, d, J = 5.5 Hz), 5.14–5.35 (3H, m), 5.84–6.03 (1H, m), 6.25 (1H, t, J = 1.9 Hz), 7.41–7.53 (2H, m).

Using a similar procedure **22a–e** were also prepared by the same method as described for **22i** from the dimesylate 8 and the appropriate substituted imidazole.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-[2-(*tert*-butyldimethylsilyloxymethyl)imidazol-1-yl]ethyl]-4-methanesulfonyloxypyrrolidine (22a). A yellow paste (91%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.75–2.10 (2H, m), 2.31–2.57 (2H, m), 3.04 (3H, s), 3.43–3.62 (1H, m), 3.92–4.22 (4H, m), 4.51 (2H, d, J = 8.0 Hz), 4.77 (2H, s), 5.13–5.39 (3H, m), 5.74–5.93 (1H, m), 6.82–7.07 (2H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-[4-(*tert*-butyldimethylsilyloxymethyl)imidazol-1-yl]ethyl]-4-methanesulfonyloxypyrrolidine. (22b) A brown paste (~100%); ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (6H, s), 0.93 (9H, s), 1.65–1.96 (2H, m), 2.20–2.40 (2H, m), 2.94 (3H, s), 3.35–3.55 (1H, m), 3.80–4.09 (4H, m), 4.50–4.60 (2H, m), 4.64 (2H, s), 5.13–5.27 (3H, m), 5.76–6.00 (1H, m), 6.85 (1H, s), 7.50 (1H, s).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(4-cyanoimidazol-1-yl)-ethyl]-4-methanesulfonyloxypyrrolidine (22c). A yellow paste (39%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–2.00 (2H, m), 2.20–2.60 (2H, m), 3.05 (3H, s), 3.50–3.60 (1H, m), 3.90–4.20 (4H, m), 4.62 (2H, d, J = 5.7 Hz), 5.20–5.40 (3H, m), 5.80–6.00 (1H, m), 7.50–7.70 (2H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(2-carbamoylimidazol-1-yl)ethyl]-4-methanesulfonyloxypyrrolidine (22d). A yellow solid (80%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.92–2.21 (2H, m), 2.40–2.60 (2H, m), 3.04 (3H, s), 3.50–3.65 (1H, m), 3.94–4.20 (2H, m), 4.49 (2H, t, J = 7.7 Hz), 4.60 (2H, d, J = 5.5 Hz), 5.15–5.34 (3H, m), 5.63 (1H, br s, $CONH_2$), 5.84–6.03 (1H, m), 7.03–7.28 (2H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(4-carbamoylmethylimidazol-1-yl)ethyl]-4-methanesulfonyloxypyrrolidine (22e). A yellow paste (13%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.75–2.00 (2H, m), 2.30–2.55 (2H, m), 3.04 (3H, s), 3.51 (2H, s), 3.51–3.65 (1H, m), 3.85–4.15 (4H, m), 4.61 (2H, d, J = 5.5 Hz), 5.20–5.36 (3H, m), 5.84–6.04 (1H, m), 6.85 (1H, br s), 7.06 (1H, br s, $CONH_2$), 7.49 (1H, br s).

22f and **22g** were prepared from **22a**, and **22b**, respectively, by a similar deprotection method as described for preparation of **8**.

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(2-hydroxymethyl)imidazol-1-yl]ethyl]-4-methanesulfonyloxypyrrolidine (22f). A light brown paste (60%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–2.10 (2H, m), 2.30–2.60 (2H, m), 3.02 (3H, s), 3.50–3.70 (1H, m), 3.90–4.20 (4H, m), 4.50–4.70 (4H, m), 5.10–5.40 (3H, m), 5.80–6.00 (1H, m), 6.80–7.00 (2H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(4-hydroxymethyl)imidazol-1-yl]ethyl]-4-methanesulfonyloxypyrrolidine. (22g) A yellow paste (33%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.75–2.15 (2H, m), 2.20–2.60 (2H, m), 3.03 (3H, s), 3.50–3.70 (1H, m), 3.90–4.20 (4H, m), 4.50–4.70 (4H, m), 5.20–5.40 (3H, m), 5.85–6.04 (1H, m), 6.90–7.00 (1H, m), 7.40–7.60 (1H, m).

(2*R*,4*R*)-1-Allyloxycarbonyl-2-[2-(4-carbamoylimidazol-1-yl)ethyl]-4-methanesulfonyloxypyrrolidine (22h). To a solution of **22c** (24.8 g) in DMSO (100 mL) was added K_2CO_3 (1.86 g) and H_2O_2 (30% aqueous solution, 9.92 mL) at room temperature. After stirring at 60°C for 5 h, the mixture was poured into brine (400 mL) and extracted with a mixture of AcOEt and THF (1:1, 200 mL×4). The combined extracts were dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 600 mL, $CHCl_3$: MeOH (14:1) elution) to give **22h** (11.54 g, 44%) as an oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–2.10 (2H, m), 2.30–2.50 (2H, m), 3.05 (3H, s), 3.50–3.62 (1H, m), 3.95–4.20 (4H, m), 4.61 (2H, d, J = 5.6 Hz), 5.22–5.36 (3H, m), 5.84–6.04 (2H, m, $CONH_2$), 7.05–7.60 (2H, m, $CONH_2$), 7.65 (1H, br s); APCI-MS m/z 387 $(MH)^+$.

23a–g were prepared from **22c–i**, respectively, by a similar method as described for the preparation of **14a** (as a thioacetate) or **17b** (as a thiobenzoate).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(2*R*,4*S*)-2-[2-(3-methyl-1-imidazolio)ethyl]pyrrolidine-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

hydrochloride (1c). To a solution of **14b** (4.54 g) in a mixture of THF (45 mL) and MeOH (45 mL) was added dropwise a solution of NaOMe in MeOH (28%, 2.97 mL) at 0°C. After stirring for 30 min at 0°C, the mixture was quenched with AcOH (0.8 mL) at 0°C and evaporated under reduced pressure. The obtained residue was diluted with AcOEt (200 mL), washed water (50 mL) and brine (50 mL), dried over $MgSO_4$, and filtered. To the obtained filtrate dimethylaminopyridine (DMAC) was added and the solution was evaporated under reduced pressure to give a solution of (2*S*,4*S*)-1-allyloxycarbonyl-2-(2-imidazoylethyl)-4-mercaptopyrrolidine in DMAC. This solution was used immediately in the next reaction because of instability of the thiol function. To a solution of activated carbapenem (**24**) (12.8 mmol) in MeCN (38 mL) was added the above solution and $^{i}Pr_2EtN$ (2.7 mL). After stirring at 0°C overnight, the mixture was poured into water (200 mL) and extracted with a mixture of AcOEt and THF (1:1) (200 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure, and purified by column chromatography (SiO_2 200 mL, $CHCl_3$:MeOH (20:1) elution) to give **25c** (4.74 g, 70%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 6.2 Hz), 1.50–1.75 (1H, m), 1.90–2.10 (1H, m), 2.30–2.60 (3H, m), 3.20–3.40 (3H, m), 3.50–3.65 (1H, m), 3.95–4.15 (4H, m), 4.18–4.30 (2H, m), 4.59 (2H, d, J = 4.9 Hz), 4.68 (1H, dd, J = 12.8 Hz, 5.5 Hz), 4.83 (1H, dd, J = 12.8 Hz, 5.5 Hz), 5.23–5.49 (4H, m), 5.88–6.04 (2H, m), 6.98 (1H, br s), 7.07 (1H, s), 7.52 (1H, br s). The oil was used immediately in the next reaction because of instability of the β-lactam function. To a solution of the above oil (6.94 g) in Me_2CO (35 mL) was added MeI (8.14 mL) at room temperature. After stirring at room temperature overnight, the mixture was evaporated to give a crude salt. To a solution of this salt in a mixture of THF (88 mL) and EtOH (88 mL) was added Ph_3P (0.69 g), $Pd(Ph_3P)_4$ (0.6 g), and n-Bu_3SnH (14.1 mL) at room temperature, and then the mixture was stirred for 30 min at room temperature. The resulting precipitate was filtered, washed with THF and EtOH, and dried under reduced pressure to give a crude powder. A solution of the powder in water (45 mL) was loaded onto a HP-20 column (440 mL), washed with water, then eluted with a mixture of Me_2CO and water (5:95). The combined product-containing fractions were evaporated and lyophilized to give a powder (4 g). The powder was purified by column chromatography (ODS 400 mL, phosphate buffer (pH = 6.86):MeCN (5:1) elution). The combined product-containing fraction was evaporated to remove MeCN, adjusted to pH (6.0), then re-loaded onto a HP-20 column (200 mL), washed with water, then eluted with a mixture of Me_2CO and water (5:95). The eluate was evaporated, passed through a Amberlyst A-26 column (200 mL) and then treated with charcoal, filtered, and lyophilized to give **1c** (3.49 g, 58%) as a white powder. IR (Nujol) cm^{-1} 1750; ^{1}H NMR (200 MHz, D_2O) δ 1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.65–1.80 (1H, m), 2.35–2.60 (2H, m), 2.70–2.85 (1H, m), 3.34–3.50 (3H, m), 3.57–3.74 (2H, m), 3.91 (3H, s), 3.90–4.10 (1H, m), 4.21–4.40 (4H, m), 7.49 (1H, d, J = 1.7 Hz), 7.55 (1H, d, J = 1.8 Hz), 8.81 (1H, br s).

Compounds **1b**, **1e**, **1g**, **1l**–**1n**, **1q**, **1r** were all prepared using the same methodology as described for preparation of **1c** from the appropriate thioacetate or thiobenzoate. Compound **1j** and **1k** were prepared similarly from **25c** using iodoacetamide or *N*-allyloxycarbonyl-3-iodopropylamine as the alkylating agent.

(4*R*,5S,6S)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(2*S*,4*S*)-2-(3-methylimidazoliomethyl)pyrrolidine-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1a). The coupling reaction of activated carbapenem (**24**) and thioacetate (**12**) was achieved by a similar method as described for the preparation of **25c** to give **25a** (37%) as an oil. A solution of **25a** (610 mg) and MeI (2 mL) in THF (3 mL) was stirred at room temperature for 15 h and the solution was evaporated under reduced pressure to give a crude oil (0.8 g, ~100%). The obtained crude oil was dissolved in a mixture of THF (50 mL) and phosphate buffer (0.1 M, pH 6.5), and to the mixture was added $Pd(OH)_2$–C (20%, 0.3 g). After stirring at room temperature under hydrogen for 5 h, the mixture was filtered and THF was evaporated under reduced pressure. The residual solution was washed with AcOEt (50 mL×2), organic solvent removed from the aqueous layer by evaporation under reduced pressure, loaded onto a HP-20 column (50 mL), washed with water, and then eluted with a mixture of Me_2CO and water (1:99). The eluate was evaporated and lyophilized to give **1a** (0.25 g, 65%) as a white powder. ^{1}H NMR (90 MHz, D_2O) δ 1.21 (3H, d, J = 6.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.60–2.05 (1H, m), 2.65–3.00 (1H, m), 3.24–4.80 (10H, m), 3.93 (3H, s), 7.52 (1H, br s), 7.60 (1H, br s), 8.88 (1H, br s).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(2*R*,4*S*)-2-[2-(1-pyridinio)ethyl]pyrrolidine-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1f). To a solution of **21** (2.5 g) in CH_2Cl_2 (8.8 mL) was added dropwise Et_3SiH (0.84 mL) at 5°C, and then TFA (8.75 mL). After stirring for 1 h at room temperature, the mixture was evaporated under reduced pressure. The residue was washed with hexane, and treated with DMAC (10 mL) and MeCN (10 mL) to give a solution of **25f**. This solution was used immediately in the next reaction because of instability of thiol function. Coupling this solution and activated carbapenem **24** by a similar method as described for the preparation of **1c** gave **1f** (0.42 g, 21%) as a white powder. IR (Nujol) cm^{-1} 1730, 1540–1580; ^{1}H NMR (200 MHz, D_2O) δ 1.22 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.72–1.88 (1H, m), 2.55–2.91 (3H, m), 3.34–3.50 (3H, m), 3.66–3.95 (4H, m), 4.00–4.15 (1H, m), 4.20–4.35 (2H, m), 8.13 (2H, t, J = 7.3 Hz), 8.61 (1H, t, J = 7.9 Hz), 8.92 (1H, d, J = 6.9 Hz). MS(FAB+) 418(MH+) (Free).

(4*R*,5*S*,6*S*)-3-[(2*R*,4*S*)-2-[2-(4-Carbamoyl-3-methyl-1-imidazolio)ethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1p). The coupling reaction of **23c** (6.37 g) and activated carbapenem **24** was achieved by a similar method to that of the preparation of **25c** to give **25p** (2.23 g, 38%) as an oil. To a solution of **25p** (2.07 g) in CH_2Cl_2 (20 mL) was added CF_3SO_3Me

(1.16 mL) at 0°C, and the solution was stirred for 30 min. The obtained mixture was treated with a suspension of ion exchange resin (Amberlyst A-26, Cl-type) (10 mL) in CH_2Cl_2 (10 mL) for 5 min. After filtration to remove the resin, the resin was washed with a mixture of CH_2Cl_2 and MeOH (4:1). The filtrate and the washings were collected and concentrated under reduced pressure to give imidzolio salt as a pale yellow solid (2.75 g, ~100%). Deprotection of this carbapenem compound was achieved by a similar method as shown in the preparation of **1d** to give **1p** (421 mg, 19.2%) as a white power. ^{1}H NMR (200 MHz, D_2O) δ 1.22 (3H, d, J = 7.7 Hz), 1.29 (3H, d, J = 6.2 Hz), 1.70–1.90 (1H, m), 2.40–2.60 (2H, m), 2.70–2.90 (1H, m), 3.30–3.80 (6H, m), 4.04 (3H, s), 4.20–4.50 (4H, m), 8.15 (1H, s), 9.01 (1H, s).

1o, **1s** were prepared from **23d** and **23c**, respectively, by a similar method as described for the preparation of **1p**.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-3-[(2*R*,4*S*)-2-[2-(2-methyl-1-pyrazolio)ethyl]pyrrolidine-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1d). The coupling reaction of **23g** and activated carbapenem (**24**) was achieved by a similar method to that of the preparation of **25c** to give **25d** (10.49 g, 98%) as an oil. To a solution of **25d** in CH_2Cl_2 (150 mL) was added FSO_3Me (2.33 mL) at 5°C. After stirring at room temperature for 1.5 h, the mixture was evaporated under reduced pressure to give pyrazolio salt (12.75 g, ~100%) as an oil. Deprotection of this carbapenem compound was achieved by similar method as shown in the preparation of **1c** to give **1d** (2.34 g, 25.9%) as a white powder. IR (Nujol) cm^{-1} 1765--1740, 1580--1570; ^{1}H NMR (200 MHz, D_2O) δ 1.22 (3H, d, J = 7.2 Hz), 1.29 (3H, d, J = 6.4 Hz), 1.71--1.86 (1H, m), 2.42--2.64 (2H, m), 2.76--2.91 (1H, m), 3.30--3.49 (3H, m), 3.67--3.95 (2H, m), 4.03--4.17 (1H, m) , 4.17 (3H, s), 4.17--4.28 (2H, m), 4.62 (2H, t, J = 8.0 Hz), 6.80 (1H, t, J = 3.0 Hz), 8.22 (1H, d, J = 2.8 Hz), 8.29 (1H, d, J = 2.3 Hz); MS (FAB+) 421.2 (MH+).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(*E*)-2-formylethenyl) pyrrolidine (26). 26 was obtained from **2b** (79.5 g) using (triphenylphosphoranylidene)-acetaldehyde (107 g) instead of Ph_3P=CHCOOMe by a similar method as for **9**. Brown oil (59.7 g, 69.3%); IR (Neat) cm^{-1} 1682, 1400; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (6H, s), 0.87 (9H, s), 1.80–2.00 (1H, m), 2.05–2.30 (1H, m), 3.40–3.60 (2H, m), 4.34–4.42 (1H, m), 4.50–4.80 (3H, m), 5.20–5.30 (2H, m), 5.70–6.10 (1H, m), 6.16 (1H, dd, J = 15.7 Hz, 7.7 Hz), 6.60–6.90 (1H, m), 9.56 (1H, d, J = 7.7 Hz).

(2*S*,4*R*)-1-Allyloxycarbonyl-2-[(*E*)-3-hydroxy-1-propen-1-yl]-4-hydroxypyrrolidine (27). To a solution of **26** (59.8 g) in a mixture of EtOH (300 mL) and THF (300 mL) was added $NaBH_4$ (6.66 g) at room temperature. After stirring for 1 h, brine (600 mL) was added to the mixture which was then extracted with AcOEt (300 mL×3). The combined extracts were washed with water (500 mL×5) and brine (500 mL×2), dried over $MgSO_4$, and evaporated under reduced pressure to give (2*S*,4*R*)-1-allyloxycarbonyl-4-*tert*-butyldimethylsilyloxy-2-[(*E*)-3-hydroxy-1-propen-1-yl]pyrrolidine (59.4 g, 98.8%) as a light brown oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.80 (1H, m), 1.90–2.20 (1H, m), 3.30–3.60 (2H, m), 4.16 (2H, m), 4.30–4.70 (4H, m), 5.20–5.29 (2H, m), 5.50–6.10 (3H, m). Desilylation of this oil (9.59 g) was achieved by a similar method to that described for preparation of **8** to give crude **27** (7.04 g, ~100%) as a pale yellow oil that was used directly in the next step. IR (Neat) cm^{-1} 1670, 1405; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00–2.30 (2H, m), 3.63 (2H, m), 4.12 (2H, d, J = 5.1 Hz), 4.40–4.70 (4H, m), 5.10–5.50 (2H, m), 5.50–6.10 (3H, m).

(2*S*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(*E*)-3-*tert*-butyldimethylsilyloxy-1-propen-1-yl]pyrrolidine (28). To a solution of **27** (7.04 g) in DMF (30 mL) was added *t*-$BuMe_2SiCl$ (5.0 g) and imidazole (2.5 g). After stirring for 2 h, the mixture was quenched with water and extracted with AcOEt (100 mL×2). The combined organic layer was washed with brine (50 mL×2), dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2) to give (2*S*,4*R*)-1-allyloxycarbonyl-2-[(*E*)-3-*tert*-butyldimethylsilyloxy-1-propen-1-yl]-4-hydroxypyrrolidine (4.53 g, 44.3%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.91 (9H, s), 1.80–2.00 (1H, m), 2.00–2.20 (1H, m), 3.57 (2H, m), 4.16 (2H, d, J = 2.9 Hz), 4.30–4.70 (4H, m), 5.10–5.40 (2H, m), 5.50–5.70 (2H, m), 5.89 (1H, m). To a solution of the above mono-silyl derivative (4.53 g) in THF (40 mL) was added Ph_3P (5.25 g), followed by diethyl azodicarboxylate (3.1 mL) dropwise at 0°C. After stirring for 30 min, PhCOSH (2.8 mL) was then added dropwise at 0°C, and the mixture stirred for 30 min at 0°C. The mixture was poured into saturated $NaHCO_3$ (40 mL) and extracted with AcOEt (100 mL×2). The combined extracts were washed with brine (50 mL×2), dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2) to give **28** (5.92 g, 93.2%) as a pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 1.90–2.70 (2H, m), 3.41–4.40 (5H, m), 4.50–4.70 (3H, m), 5.10–5.40 (2H, m), 5.60–6.20 (3H, m), 7.30–7.80 (3H, m), 8.10 (2H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(*E*)-3-*tert*-butyldimethylsilyloxy-1-propen-1-yl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (29a). The preparation of **29a** (1.65 g, 22%) was achieved from **28** (5.9 g) by a similar method as described for preparation of **25c**. A pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.26 (3H, d, J = 7.2 Hz), 1.35 (3H, d, J = 6.2 Hz), 2.00–2.70 (2H, m), 3.10–3.57 (4H, m), 4.00–4.30 (5H, m), 4.49 (1H, m), 4.68 (2H, d, J = 12.0 Hz), 4.68–4.84 (2H, m), 5.10–5.44 (4H, m), 5.50–6.10 (4H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(*E*)-3-hydroxy-1-propen-1-yl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (29b). To a solution of **29a** (1.65 g) in THF (10 mL) was added AcOH (0.54 mL) at room

temperature. After a short stirring, a solution of TBAF (70% aqueous solution, 3.0 g) in THF (5 mL) was added to the mixture. After stirring for 4 h, the mixture was poured into a mixture of AcOEt (100 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with AcOEt (100 mL). The combined organic layer was washed with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL×2), dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography to give **29b** (0.77 g, 57%) as a pale yellow oil. IR (CH_2Cl_2) cm^{-1} 1765, 1695; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, d, $J=7.2$ Hz), 1.36 (3H, d, $J=6.2$ Hz), 1.60–2.00 (2H, m), 2.59 (1H, dt, $J=6.4$ Hz, 13.3 Hz), 3.20–3.50 (3H, m) 3.64 (1H, m), 4.00–4.40 (5H, m), 4.40–4.90 (4H, m), 5.10–5.60 (4H, m), 5.60–6.10 (4H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(*E*)-3-diphenoxyphosphoryloxy-1-propen-1-yl]pyrrolidine-4-yl]-thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (29c). To a solution of **29b** (370 mg) in CH_2Cl_2 (1.9 mL) was added successively DMAP (106 mg) and diphenylchlorophosphate (0.159 mL) at −50°C. After stirring at −50°C for 40 min, the mixture was quenched with saturated $NaHCO_3$ (2 mL) and extracted with AcOEt (12 mL). The organic extract was washed with aqueous HCl (0.1N, 5 mL), water (10 mL), and brine (10 mL), then dried over $MgSO_4$, and evaporated under reduced pressure to give **29c** (536 mg, 99%) as a light brown paste. IR (CH_2Cl_2) cm^{-1} 1764, 1692, 1592; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, d, $J=7.2$ Hz), 1.36 (3H, d, $J=6.3$ Hz), 1.61–1.93 (1H, m), 2.43–2.66 (1H, m), 3.14–3.48 (3H, m), 3.48–3.76 (1H, m), 3.88–4.50 (4H, m), 4.50–4.95 (6H, m), 5.09–5.58 (4H, m), 5.60–6.14 (4H, m), 7.20–7.40 (10H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(*E*)-3-iodopropen-1-yl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (29d). To a solution of **29c** (431 mg) in Me_2CO (3 mL) was added NaI (178 mg), and the mixture was stirred at 50°C for 30 min. The mixture was quenched with water (5 mL) and extracted with AcOEt (15 mL). The organic layer was washed with water (10 mL), saturated sodium thiosulfate (10 mL) and brine (10 mL×2), dried over $MgSO_4$, and evaporated under reduced pressure to give **29d** (451 mg, 100%) as a yellow solid. IR ($CHCl_3$) cm^{-1} 1762, 1682; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, d, $J=7.3$ Hz), 1.36 (3H, d, $J=6.3$ Hz), 1.64–2.70 (2H, m), 3.17–3.45 (3H, m), 3.45–3.71 (1H, m), 3.70–4.50 (6H, m), 4.50–4.92 (4H, m), 5.10–5.60 (4H, m), 5.60–6.10 (4H, m).

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2*S*,4*S*)-2-[(*E*)-3-(1-pyridinio)-1-propen-1-yl]pyrrolidine-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate hydrochloride (1i). To a solution of **29d** (441 mg) in CH_2Cl_2 (4.4 mL) was added pyridine (0.594 mL) at room temperature. After stirring for 1.5 h, the mixture was evaporated and then triturated with ether to give a crude yellow powder (468 mg). To the solution of this powder (453 mg), Ph_3P (17 mg), AcOH (0.1 mL), and $Pd(Ph_3P)_4$ (23 mg) in a mixture of EtOH (4.5 mL) and THF (4.5 mL) was added dropwise nBu_3SnH (0.43 mL) at room temperature. After stirring for 30 min, the mixture was diluted with THF (4.5 mL). The resultant precipitate was collected by decantation, washed with THF (4.5 mL×4), and then dissolved in water (9 mL). The solution was washed with AcOEt (9.0 mL×2), concentrated to ca. 5 mL, and the obtained solution loaded onto nonionic adsorption resin (Dianion HP-20 = 45 mL, water:Me_2CO (100:0–96:4) elution). The combined product-containing fractions were concentrated to ca. 10 mL, then passed through ion exchange resin (Amberlyst A-26 = 1.4 mL, water (10 mL) elution), and lyophilized to give **1i** (51 mg, 15%) as a white solid. IR (Nujol) cm^{-1} 1730; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (3H, d, $J=7.2$ Hz), 1.28 (3H, d, $J=6.4$ Hz), 1.83–1.96 (1H, m), 2.74–2.95 (1H, m), 3.30–3.50 (3H, m), 3.71 (1H, dd, $J=12.5$ Hz, 6.8 Hz), 4.00–4.15 (1H, m), 4.20–4.46 (3H, m), 5.32 (2H, d, $J=5.8$ Hz), 6.07–6.38 (2H, m), 8.11 (2H, t, $J=7.2$ Hz), 8.60 (1H, t, $J=7.9$ Hz), 8.85 (2H, d, $J=5.5$ Hz).

The preparation of **1h** (1.18 g, 30%) was achieved from **29d** (5.0 g) and 1-methylimidazole (1.98 mL) by a similar method as described for preparation of **1i**.

Measurement of in vitro antibacterial activity

According to the method of the Japan Society of Chemotherapy, the MICs of compound were determined by the twofold 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 meropenem at 50 μg/mL.

Efficacy in lethal systemic infection

A strain was intraperitoneally inoculated in groups of eight male ICR mice aged 4 weeks with 0.5 mL of bacterial suspension in 5% gastric mucin, given at one to five times 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 (ED_{50}) was determined from the final survival rates by the Probit method.

Urinary recovery

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

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