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Synthesis and Antibacterial Activity of Novel 4-Pyrrolidinylthio Carbapenems—I. 2-Alkoxymethyl Derivatives

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Abstract—The synthesis and in vitro antibacterial activity of a novel series of 2-alkoxymethyl-4-pyrrolidinylthio-1β-methyl carbapenems are described. As a result of these studies, we discovered that FR27743 (**19j**) containing a novel 2-fluoroethoxymethyl substituent possesses a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa*. Furthermore, FR27743 exhibited excellent stability against renal dehydropeptidase-I (DHP-I), good urinary recovery, and superior in vivo activity compared to that for Meropenem against several systemic infections. © 1997 Elsevier Science Ltd.

Introduction

Thinking about the history of antibiotic research to date, we can see it as a struggle between resistant strains of bacteria and newly introduced, increasingly effective antibacterial agents. However, without exception, resistant bacteria have been induced when using novel types of antibiotics in a clinical setting, hence the continuing need for newer, novel, and ever more potent antibiotics that are especially active against these resistant bacteria.[1,2] Thus, there are new bacteria that are resistant to most of the major classes of antibiotics such as β-lactams, macrolides, tetracyclines, aminoglycosides, and quinolones. β-Lactams, a class of antibiotics that includes penicillins, cephems, monobactams, and carbapenems,[3] are in widespread use due principally to a spectrum of antibiotic activity, weak toxicities to the host and selective toxicity towards the pathogen. Among these β-lactams, carbapenems[4] show especially broad antibacterial activities against both Gram-positive and Gram-negative organisms, have strong bactericidal effects and represent the least developed of the major classes of β-lactams.

The earliest carbapenems to become available, namely Imipenem (**1**)[3] and Panipenem (**2**),[5] possess a non-1-substituted carbapenem skeleton, as in the original, prototype carbapenem natural product thienamycin.[6] Whilst these compounds have a broad, potent spectra of antibacterial activity, they are unstable to the renal enzyme dehydropeptidase-I (DHP-I) and have a low urinary recovery. Co-administration of a DHP-I inhibitor (cilastatin) with Imipenem was the first approach taken to solve this problem. However, the optimal solution to this problem would be to find a compound that is stable itself against DHP-I.

Efforts to improve the intrinsic DHP-I stability of the carbapenem skeleton by introduction of a 1β-methyl

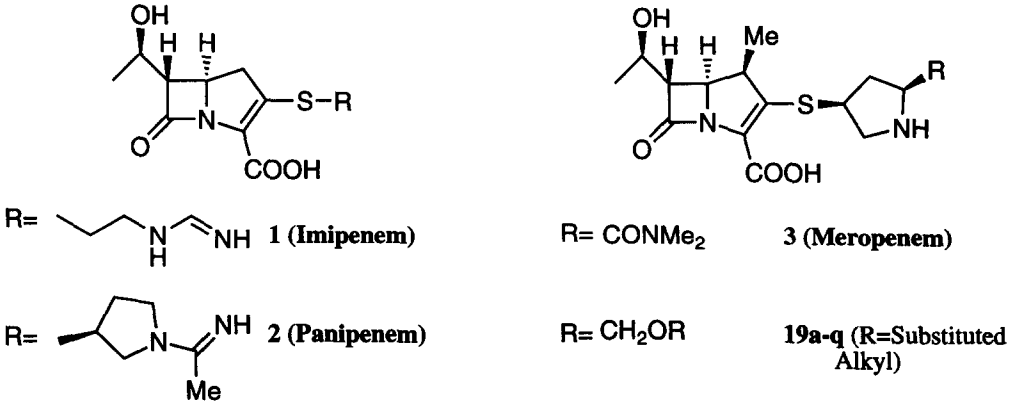


Figure 1. Carbapenem antibiotics.

substituent have been reported.[7,8] Recently, the first 1β-methyl carbapenem Meropenem (**3**)[7] was developed and is now in use clinically. Subsequent candidate compounds (e.g. Biapenem,[8,9] BO-2727,[10] and S-4661[11]) are currently in clinical trials. Other strategies for improving DHP-I stability have been disclosed. The main approach involves preparation of 2-carbon linked derivatives such as aryl-[12] or vinyl-[13] substituted analogues. An alternative approach involves preparation of a tricyclic skeleton as in the Glaxo compound GV104326,[14] or incorporation of a guanidinoethyl moiety at position 1 as in the Bristol-Myers Squibb compound BMS-181139.[15]

In this context, we decided to approach the discovery of new 1β-methyl carbapenem antibiotics by improving the Meropenem profile. In pyrrolidinylthio derivatives of carbapenems, acute toxicity and nephrotoxicity are problems that are postulated to be related to the basicity of the pyrrolidine amino group.[16] The low toxicity of Meropenem thus would be the result of the electron withdrawing effect of the amide group attached to pyrrolidine. Additionally, the same amide enhances antibacterial activity. Therefore, we designed new substituents for the pyrrolidine ring which possess an electron withdrawing effect to diminish the basicity of the pyrrolidine amine. In the course of our search for such substituents, we found that a 2-methoxymethyl-pyrrolidine derivative[17] possesses good antibacterial activity against Gram-positive and Gram-negative organisms, with the exception of *Ps. aeruginosa*, which is known to possess an outer membrane that acts as a protection against antibiotics. We thus used this compound as a seed for further studies.

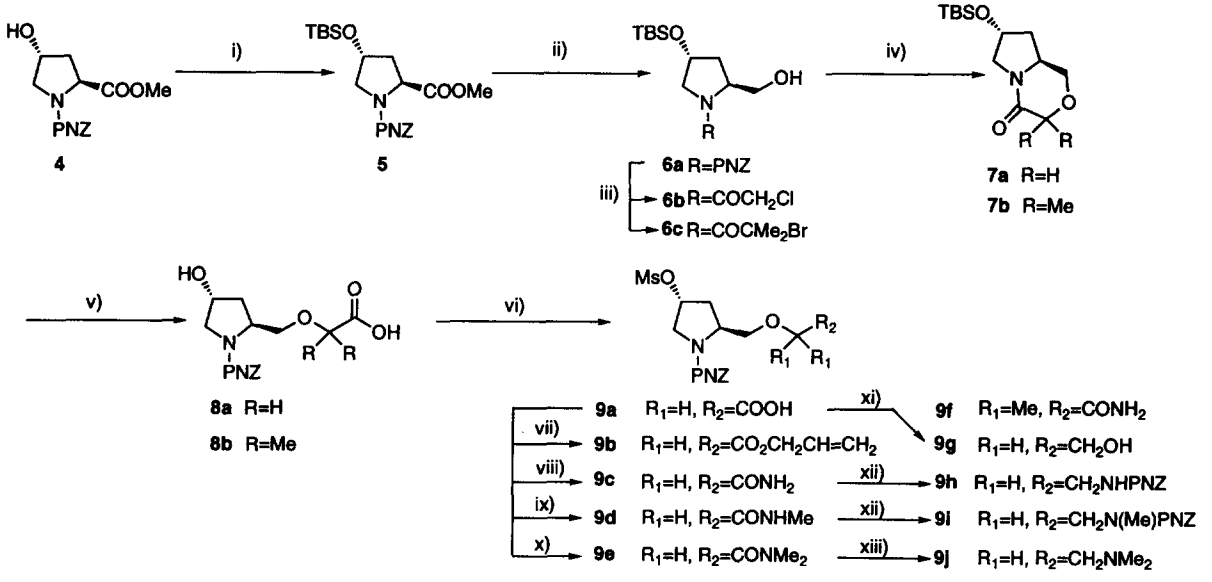
In this paper, we wish to report the synthesis, antibacterial activity, DHP-I stability and urinary recovery of novel 2-substituted methoxymethyl-4-pyrrolidinylthio-1β-methylcarbapenems as well as the in vivo protective effects against systemic infection, leading to the discovery of FR27743 as the best balanced compound from this series.

Results and Discussion

Chemistry

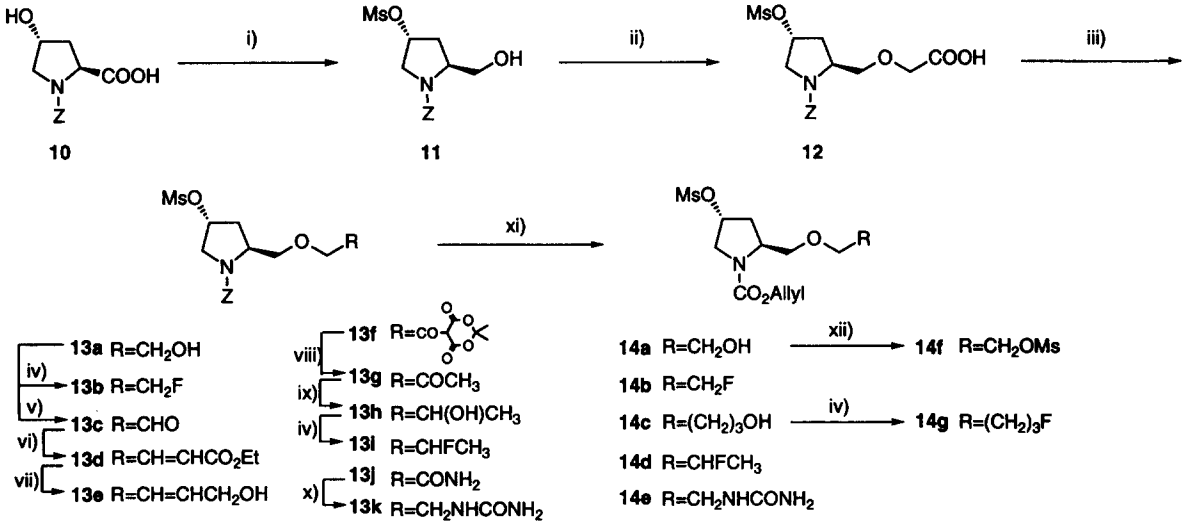
Synthetic routes for the novel carbapenems prepared in this work are shown in Schemes 1–4. In summary, a thioester derivative (**15a–o** or **20**) was converted to the free thiol and then immediately coupled with an activated carbapenem (**16**, **17**, or **21**) followed by various modifying steps and the removal of protecting groups to give the final antibacterial agents (Schemes 3–4).

As a key starting material for all thiol derivatives, we employed commercially available 4-hydroxyproline. All mesylate derivatives of the 2-alkoxymethyl substituted pyrrolidines were obtained by one of two routes. The first involved formation of the ether bond by intramolecular cyclization[18] to produce a bicyclic compound, that was ring opened and modified further. The second involved direct *O*-alkylation of a hydroxymethyl moiety (Schemes 1–2).



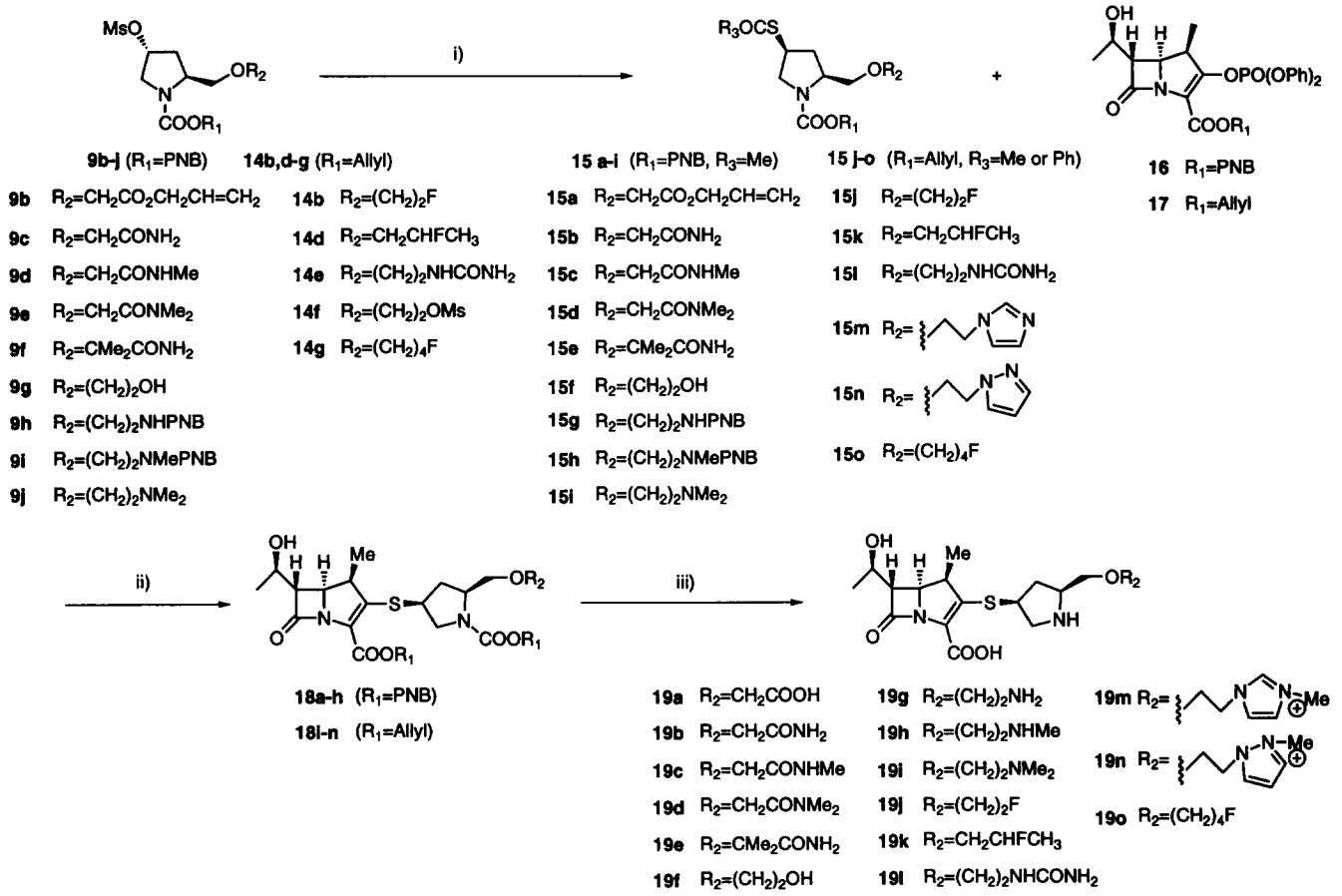
Reagents and Conditions: i) TBSCl, imidazole, DMF ii) $NaBH_4$, EtOH, iii) 1. $Pd(OH)_2$-C, H_2, MeOH, 2. $ClCOCH_2Cl$ or $BrCOC(Me)_2Br$, iv) NaH, THF, v) 1. 6N-HCl, reflux, 2. PNZCl, vi) MsCl, Et_3N, AcOEt (**9a**) or MsCl, Et_3N, THF, then 10%NH_3 / EtOH, (**9f**) vii) CH_2=$CHCH_2OH$, H_2SO_4, reflux, viii) 1. $ClCOO^tBu$, Et_3N, THF, 2. c-NH_3, ix) 1. $POCl_3$, DMF, THF, 2. 30%$MeNH_2$ / MeOH x) 1. $POCl_3$, DMF, THF, 2. Me_2NH•HCl, Et_3N, MeOH, xi) $ClCOO^tBu$, Et_3N, THF, then $NaBH_4$, xii) 1. $NaBH_4$, BF_3•OEt_2, 2. PNZCl, NaOH, xiii) $NaBH_4$, BF_3•OEt_2.

Scheme 1.



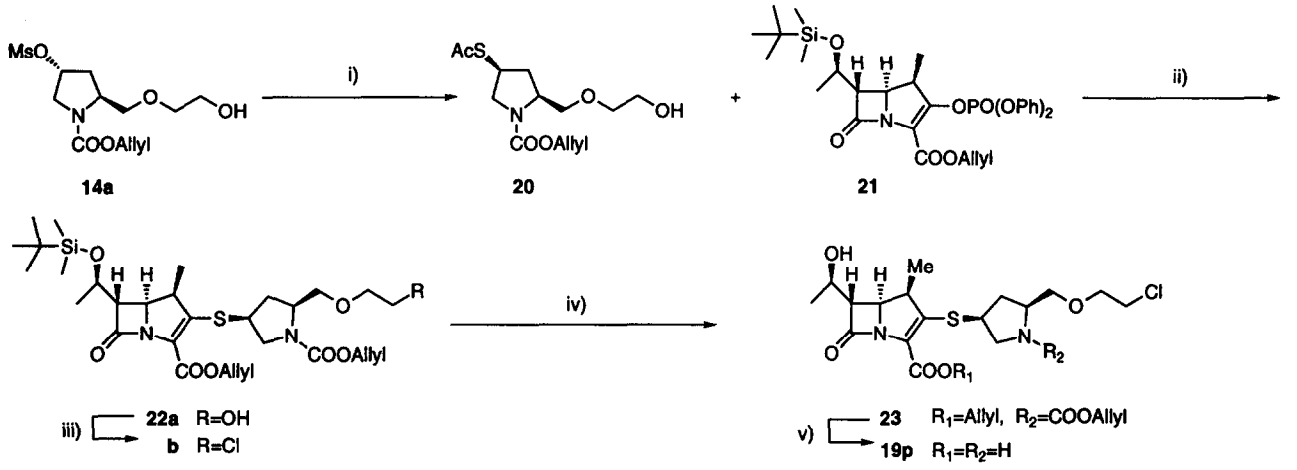
Reagents and conditions: i) 1. H_2SO_4, MeOH, 2. MsCl, Et_3N, 3. $NaBH_4$, ii) 1. $BrCH_2CO_2Et$, ^tBuOK, THF, 2. 2N-NaOH, iii) $NaBH_4$, $BF_3{\cdot}OEt_2$, THF (**13a**), or Meldrum's acid, DMAP, WSCD·HCl, CH_2Cl_2 (**13f**), or $ClCO_2{}^tBu$, Et_3N, THF, 2. c-NH_3, THF (**13j**), iv) $Et_2NCF_2CFHCF_3$, CH_2Cl_2, v) DMSO, $(ClCO)_2$ Et_3N, CH_2Cl_2, vi) Ph_3PCHCO_2Et, toluene, reflux, vii) DIBAH, THF, viii) AcOH-H_2O, reflux, ix) $NaBH_4$, EtOH, x) 1.$NaBH_4$, $BF_3{\cdot}OEt_2$, THF, then KOCN, THF-H_2O, xi) 1. Pd-C, H_2, HCl-MeOH, 2. $ClCO_2CH_2CH{=}CH_2$, THF-H_2O, xii) MsCl, Et_3N.

Scheme 2.



Reagents and Conditions: i) AcSH, ^tBuOK, DMF (**15a, c, d, h, l**), or AcSH, $Ca(OH)_2$, MIBK (**15j**), or AcSH, NaH, DMF (**15b, e, f, g, k, l, o**), or imidazole, ^tBuOK, DMF then PhCOSH, NaH, DMF (**15m**), or pyrazole, ^tBuOK, DMF then PhCOSH, NaH, DMF (**15n**), ii) 1. NaOMe, CH_3CN, 2. $^iPr_2EtN$, MeCN (or MeCN-DMAC), iii) $Pd(PPh_3)_4$, PPh_3, Sodium 2-ethylhexanoate, THF then $Pd(OH)_2$, H_2 (**19a**), or $Pd(OH)_2$, H_2 (**19b ~ l**), or $Pd(PPh_3)_4$, PPh_3, dimedone or morpholine, THF-EtOH (**19j ~ l, o**), or MeOTf then $Pd(PPh_3)_4$, PPh_3, morpholine (**19m ~ n**).

Scheme 3.



Reagents and Conditions: i) NaH, AcSH, DMF, ii) 1. **20**, NaOMe, CH_3CN, 2. iPr_2EtN, CH_3CN, iii) PPh_3, CCl_4, iv) TBAF, AcOH-THF, rt, v) $Pd(PPh_3)_4$, PPh_3, dimedone, THF-EtOH

Scheme 4.

To synthesize the alkoxy derivatives under mild conditions, we planned to use the nitrogen atom of pyrrolidine as an anchor for the substituent.[18] As shown in Scheme 1, this plan was achieved by the formation of haloacetyl derivatives of pyrrolidine (**6b, c**), followed by intramolecular cyclization to give the morpholine derivatives (**7a, b**) and hydrolytic cleavage of the amide leading to the acids (**8a, b**). The starting material **4**[19] was obtained by ordinary protection methods from 4-hydroxyproline. Next, silylation (TBDMSCl) and reduction of the ester **5** ($NaBH_4$) gave alcohol **6a**. Under ordinary conditions, ester groups are not reduced by $NaBH_4$, but in this case we presume an activating effect of the amino group. Deprotection of **6a** ($Pd(OH)_2$-C, H_2), followed by acylation of the resulting amine with α-haloacid halides gave the α-halogenomethylamides **6b, c**, which were cyclized by treatment with NaH to give the bicyclic compounds **7a, b**. After acid hydrolysis with hydrochloric acid, re-protection of the amine group as *p*-nitrobenzyl gave the carboxylates **8a, b**. Removal of the silyl protecting group also occurred using these conditions. After the free hydroxyl group of **8a, b** was converted to a mesylate (e.g. **9a**), the carbonyl group was converted to various acid derivatives (**9b–f**), alcohol (**9g**), and amines (**9h–j**).

Protection of the carboxylic acid **9a** was achieved with allyl chloride to give an allylester **9b**. The amides **9c–f** were obtained from carboxylic acid **9a** by several activating methods, including formation of an activated ester (**9c–e**), and a mesylate (**9f**). In particular, **9f** was obtained from **8b** by a one pot reaction involving double mesylation of the alcohol and carboxylic acid groups, followed by treatment with ammonia. The alcohol **9g** was obtained by $NaBH_4$ reduction of an intermediate mixed anhydride. The amides **9c–e** were converted to amines **9h–j** by reduction with $NaBH_4$–BF_3·Et_2O, and the resulting amine group protected as *p*-nitrobenzyloxycarbonyl.

The direct alkylation route, which required relatively fewer synthetic steps, is summarized in Scheme 2. The starting material **10** was transformed into the alcohol **11** by methyl ester formation, mesylation of the secondary alcohol and ester reduction with $NaBH_4$. Direct and mild ether bond formation was achieved using ^{t}BuOK–ethyl bromoacetate at −10 to −5 °C for 30 min; subsequent basic hydrolysis then gave the carboxylate **12**.

The carboxylate **12** was converted to many different kinds of derivatives. After conversion to alcohol **13a** by reduction ($NaBH_4$–BF_3·Et_2O), the fluoride **13b** was obtained by treatment with hexafluoropropane diethylamine complex. The alcohol **13a** was converted by Swern oxidation to aldehyde **13c**, which was converted to an α, β-unsaturated ester **13d** by the Wittig reaction. Chemoselective reduction of the ester function (DIBAL) gave the allyl alcohol **13e**. In this reduction, the olefin bond was left unchanged. The carboxylate **12** was converted to a cyclic diester **13f** by condensation with Meldrum's acid. Subsequent acid hydrolysis and decarboxylation in boiling acetic acid gave the ketone **13g**. After reduction of the ketone group, the obtained the secondary alcohol **13h** was converted to the 1-fluoro ethyl **13i** as a mixture of stereoisomers. Urea **13k** was obtained in 2 steps from the amide **13j**, which was obtained from the carboxylate **12**. Thus, amide **13j** was reduced ($NaBH_4$–BF_3·Et_2O) to give an amine which was converted to the urea **13k** with KOCN.

Carbobenzyloxy protecting groups of derivatives **13a,b,e,i,k**, were then transformed to allyloxycarbonyl protecting groups (**14a–e**) by deprotection and reprotection. During this conversion, the double bond of **13e** was saturated by the hydrogenolysis conditions employed in the deprotection step. The dimesylate **14f** was obtained from **14a** by treatment of MsCl. The fluoride **14g** was obtained from **14c** by fluorination.

Thiol formation, coupling with an activated carbapenem, and subsequent deprotection are shown in Scheme 3. The mesylates **9b–j**, **14b,d,e,g** were transformed to the thioesters **15a–o** by reaction with the sodium, potassium, or calcium salts of thioacetic acid. The dimesylate **14f** was transformed to **15m,n** by selective substitution at the primary mesylate with a heteroaromatic base, followed by transformation of the remaining secondary mesylate to thiobenzoate.

The deprotection reaction of the thioesters **15a–o** was achieved by treatment with NaOMe at low temperature. The resulting thiol or thiolate salts was used in the next reaction immediately. Coupling with activated carbapenem **16** or **17**[20] in the presence of Hünig's base gave protected carbapenems **18a–n**.

Simultaneous deprotection of the pyrrolidine amino group and 3-carboxylate of the carbapenem skeleton was achieved under various reaction conditions. The *p*-nitrobenzyl ester and carbamate were removed under hydrogenolysis conditions to give **19b–i**. On the other hand, the allyl ester and allyl carbamate groups were cleaved by treatment with $Pd(Ph_3P)_4$ in the presence of an appropriate trapping agent (dimedone or morpholine) to give **19j–o**. In the case of **18a**, the deprotection was achieved in two steps, involving hydrogenolysis of the *p*-nitrobenzylester and carbamate, and allyl ester cleavage. Derivatives **18m,n** containing heteroaromatic substituents were first converted to quaternary salts with methyl triflate and deprotected to give **19m,n**.

The chloroethyl compound **23** was synthesized by a different route (Scheme 4). The formation of a chloride from a hydroxy was achieved on protected carbapenem **22a**, since the chloroethyl group was expected to react easily with a thioacetate salt. The hydroxyethyl compound **14a** was thus converted to thioester **20** by treatment with sodium thioacetate and then converted to a thiol and coupled with activated carbapenem **21** to give protected carbapenem **22a**. The terminal hydroxy group of **22a** was transformed to the chloride **22b**, which was then deprotected by two steps. The first step was desilylation with TBAF to give **23**, and the second step was allyl ester cleavage with $Pd(Ph_3P)_4$ in the presence of dimedone to give **19p**.

Biological activity

We initially synthesized the known compound **19q**[17] and investigated its antibacterial activity, DHP-I stability,[21] and urinary recovery. As a result it became clear that compound **19q** possessed good activity against Gram positive and negative bacteria, except *Ps. aeruginosa*, and also had improved stability to DHP-I compared to Meropenem, and quite high ($\sim 2\times$) urinary recovery. Therefore, we selected this compound as a lead compound for further modification, with the goal of an overall improved profile. To improve the *Ps. aeruginosa* activity of this lead compound (**19q**), it is well known that higher outer membrane permeability is required in order to display good activity.[22] We thus designed new derivatives by the introduction of hydrophilic substituents, since we postulated that more polar compounds would be better equipped to cross the D2 porin, the main mediator of carbapenem diffusion, into *Ps. aeruginosa*.

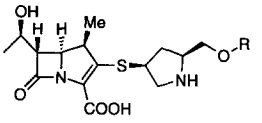
In vitro antibacterial activity of the new 2-alkoxy substituted pyrrolidine carbapenem derivatives prepared in this work are shown in Table 1. The carboxylate and amide compounds (**19a,c,d**) had higher activity against Gram-negative bacteria, including *P. vulgaris* and *P. mirabilis* compared to **19q**. Additionally **19b,e** had higher activity against *Ps. aeruginosa*. Amine-containing substituents (**19g–i**) were less active, since they have a tendency to display only moderate activity against both Gram-negative and positive bacteria. However, some of these amines (**19g,h**) did display improved activity against *Ps. aeruginosa* compared to **19q**. Compounds containing cationic heterorings (**19m, 19n**) were relatively weak compared to **19q**. The urea **19l** displayed excellent activity against *Ps. aeruginosa*, however it had lower activity against other clinically significant bacteria. These results indicate that good activity against *Ps. aeruginosa* can indeed be obtained by the introduction of a hydrophilic function to the 2-methoxymethyl derivative **19q**.

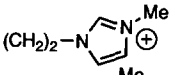
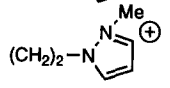
Amongst these compounds, the alcohol **19f** and the fluoride **19j** have especially good and well-balanced activity profiles, and indeed, the fluoride **19j** was a little better than alcohol **19f**. The antibacterial activity against *Ps. aeruginosa* of fluoride **19j** was unexpected, since a fluoroethyl group was not expected to be especially hydrophilic. One explanation may be that this could be due to a tendency of the fluoro group to form a hydrogen bond in aqueous solution. This would tend to explain the lower antibacterial activity against *Ps. aeruginosa* of the chloroethyl compound (**19p**) and the good activity of hydroxyethyl compound (**19f**). However, the homologated fluoroalkyl compound **19o** showed low *Ps. aeruginosa* activity, indicating that the distance of the hydrophilic center from the pyrrolidine ring is important for activity. The best compound obtained in this work, **19j**, possesses comparable antibacterial activity to the marketed reference compounds panipenem (**2**) and meropenem (**3**).

The DHP-I stability[21] and urinary recovery of selected carbapenems are displayed in Table 2. All compounds displayed good stability compared to the reference compounds (**2**,**3**). In particular, **19j** was the most stable of these compounds. All compounds showed high values of urinary recovery which can be correlated with the good DHP-I stability.

As a result of the broad spectrum of potent antibacterial activity, especially against *Ps. aeruginosa*, stability to DHP-I, and urinary recovery, FR27743 (**19j**) was selected as the best compound for further investigation. Table 3 displays the in vivo protective effect against systemic infection in mice caused by strains of *S. aureus*

Table 1. Antibacterial activity (MIC) of novel carbapenems



Compd	R	S.a.	S.a.(R)	E.c.	K.p.	E.cl.	P.m.	P.v.	P.a.1	P.a.2
19a	CH_2COOH	0.39	100	0.1	0.05	0.1	0.2	0.2	3.13	3.13
19b	CH_2CONH_2	0.1	50	0.1	0.1	0.2	0.78	0.78	0.39	0.78
19c	$CH_2CONHMe$	0.1	25	0.1	0.05	0.2	0.39	0.39	1.56	1.56
19d	CH_2CONMe_2	0.1	50	0.1	0.05	0.2	0.78	0.2	3.13	3.13
19e	CMe_2CONH_2	0.1	25	0.1	0.1	0.39	0.39	3.13	0.39	0.78
19f	CH_2CH_2OH	0.1	50	0.1	0.05	0.2	0.39	0.39	0.39	0.78
19g	$CH_2CH_2NH_2$	0.05	12.5	0.2	0.39	0.78	3.13	3.13	1.56	1.56
19h	CH_2CH_2NHMe	0.05	12.5	0.2	0.2	0.39	1.56	0.78	0.78	1.56
19i	$CH_2CH_2NMe_2$	0.2	50	0.78	0.39	1.56	12.5	1.56	3.13	6.25
19j	CH_2CH_2F	0.1	25	0.1	0.05	0.2	0.39	0.1	0.39	0.78
19k	CH_2CHFCH_3	0.39	100	0.39	0.78	0.39	1.56	0.78	3.13	12.5
19l	$(CH_2)_2NHCONH_2$	0.1	25	0.2	0.2	0.39	0.78	0.39	0.39	0.78
19m		0.05	12.5	0.39	0.39	0.78	3.13	3.13	6.25	1.56
19n		0.05	12.5	0.39	0.2	0.78	3.13	6.25	6.25	1.56
19o	$(CH_2)_4F$	0.05	25	0.2	0.1	0.2	0.78	0.39	25	6.25
19p	CH_2CH_2CI	0.05	25	0.05	0.1	0.1	0.39	0.2	1.56	3.13
19q	Me	0.025	6.25	0.1	0.05	0.2	0.78	0.78	3.13	1.56
2	Panipenem	0.025	50	0.2	0.1	0.39	1.56	1.56	0.36	0.39
3	Meropenem	0.1	25	0.025	0.025	0.05	0.05	0.1	0.2	0.39

S.a., *S. aureus* 209P JC-1, S.a.(R), *S. aureus* 3004; E.c., *E. coli* NIHJ JC-2; K. p., *K. pneumoniae* 12; E.cl., E. *cloacae* 60; P.m., *P. mirabilis* 1; P.v., *P. vulgaris* IAM 1025; P.a.1, *Ps. aeruginosa* IAM 1095; P.a.2, *Ps. aeruginosa* FP 1457.

and *Ps. aeruginosa*, in comparison to panipenem (**2**) and meropenem (**3**). Overall, a comparable effect to panipenem (DHP-I labile) and a clearly superior efficacy compared to meropenem (DHP-I improved stability) was observed.

Conclusions

We have designed and synthesized novel 5-alkoxymethylpyrrolidine carbapenems and investigated their antibacterial activity, DHP-I stability, and urinary recovery. The best compound FR27743 (**19j**) displayed comparable antibacterial activity to the reference compounds, but better stability to DHP-I and good urinary recovery. Furthermore, this compound displayed a good protective effect against several systemic infections in mice.

Experimental Section

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 (^{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.

Table 2. Urinary recovery and DHP-I Stability of selected novel carbapenems

Compound	19c	19e	19f	19h	19j	191	19q	2	3
DHP-I stability*1 (human)	<0.43	0.71	0.71	0.51	0.26	0.55	0.43	2.04	1.0
Urinary recovery*2	52	67	56	47	46	54	57	24	20

[a]DHP-I Stability is given relative to meropenem.
[b]Recovery (%) in rats after s.c. administration (10 mg/kg).

Table 3. In vivo protective effect against infection in mouse

	19j	Panipenem	Meropenem
S. aureus FP1469			
ED_{50} (mg/kg)	0.106	0.081	0.934
MIC (μ/ml)	0.05	0.05	0.1
Ps.aeruginosa 93			
ED_{50} (mg/kg)	0.537	0.610	1.05
MIC (μ/ml)	1.56	6.25	0.78

Methyl (2*S*,4*R*)-4-*tert*-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-2-carboxylate (5). To a solution of methyl (2*S*,4*R*)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-2-carboxylate (**4**) (178 g) in DMF (500 mL), imidazole (93.9 g) and *tert*-butyldimethylchlorosilane (TBSCl) (93.9 g) were added and the solution stirred at room temperature for 14 h. The reaction mixture was then diluted with AcOEt (2 L), washed thoroughly with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to give **5** (260 g, 100%) as a colorless oil. IR (CH_2Cl_2) cm^{-1} 1710, 1750; ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.8–2.4 (2H, m), 3.3–3.8 (2H, m), 3.61 and 3.76 (total 3H, each s), 4.3–4.5 (2H, m), 5.20 (1H, ABq, J =14 Hz), 5.23 (1H, s), 7.42 (2H, dd, J = 5.0, 9.0 Hz), 8.15 (2H, d, J = 9.0 Hz). $[\alpha]^{19}_D$ −36.2° (*c* 1.00; $CHCl_3$).

(2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-2-hydroxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (6a). To a solution of **5** (790 g) in EtOH (10 L) was added $NaBH_4$ (208 g) at room temperature, and the mixture was stirred for 16 h. The mixture was diluted with AcOEt (18 L), washed thoroughly with brine (× 4), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was triturated with hexane and the resulting precipitate was collected by filtration, washed with isopropylether:hexane (1:9), and dried under reduced pressure to give **6a** (354 g, 48%) as a pale yellow solid. Mp 49–51°C; IR (Nujol) cm^{-1} 1670, 1705, 3300, 3400; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 and 0.07 (total 6H, each s), 0.86 (9H, s), 1.60–1.80 (1H, m), 1.95–2.05 (1H, m), 3.43–3.53 (2H, m), 3.60 (1H, dd, J = 6.5, 11.6 Hz), 3.77 (1H, dd, J = 2.0, 11.6 Hz), 4.10–4.20 (1H, m), 4.36 (1H, brs), 5.23 and 5.28 (2H, ABq, J = 13.6 Hz), 7.51 (2H, d, J = 8.8 Hz), 8.22 (2H, d, J = 8.8 Hz); APCI-MS *m/z* 411 $(MH)^+$; $[\alpha]^{19}_D$ −40.2° (*c* 1.00; $CHCl_3$); anal. calcd for $C_{19}H_{30}N_2O_6Si$: C, 55.59%; H, 7.37%; N, 6.82%. Found: C, 56.07%; H, 7.56%; N, 6.77%.

(2*S*,4*R*)-4-*tert*-Butyldimethylsilyloxy-1-chloroacetyl-2-hydroxymethylpyrrolidine (6b). A mixture of **6a** (10.0 g) and 20% $Pd(OH)_2$–C (0.5 g) in MeOH (100 mL) was stirred at room temperature for 3 h under a hydrogen atmosphere (1 atm). After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure to give a syrupy oil. To a solution of the obtained oil in a mixture of THF (100 mL) and water (100 mL), was added dropwise a solution of chloroacetylchloride (5.0 mL) in THF (10 mL) at 0–5 °C. During the addition, the pH of the reaction mixture was maintained at 8–9 by addition of 4 N-NaOH. After stirring for 2 h, the mixture was extracted with THF:AcOEt (1:1) (100 mL×5), dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (400 mL, MeOH:CH_2Cl_2 (1:99) elution) to give **6b** (4.22 g, 56%) as a colorless oil. FT-IR (neat) cm^{-1} 3412, 2953, 2931, 2858, 1649, 1466, 1456; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.72 (1H, ddd, J = 4.3, 9.1, 13.3 Hz), 1.97–2.10 (1H, m), 3.49 (1H, td, J = 1.8, 11.0 Hz), 3.54–3.68 (2H, m), 3.77 (1H, dd, J = 2.2, 11.8 Hz), 4.04 (2H, s), 4.29–4.44 (2H, m); APCI-MS *m/z* 308 $(MH)^+$; anal. calcd for $C_{13}H_{26}ClNO_3Si{\cdot}0.8H_2O$: C, 48.48%; H, 8.41%; N, 4.33%. Found: C, 48.45%; H, 8.63%; N, 4.35%.

(2*S*,4*R*)-1-(2-Bromo-2-methylpropionyl)-4-*tert*-butyldimethylsilyloxy-2-hydroxymethylpyrrolidine (6c). **6c** was prepared as described for the preparation of **6b** using 2-bromo-2-methylpropionylbromide instead of chloroacetylchloride. White solid (56%); Mp 84–84.5 °C; FT-IR (KBr) cm^{-1} 3419, 3288, 2956, 2929, 2854, 1620, 1595, 1466, 1421; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 and 0.08 (total 6H, each s), 0.86 (9H, s), 1.62 (1H, ddd, J = 4.2, 9.4, 13.4 Hz), 1.97 (6H, s), 2.00–2.06 (1H, m), 3.50–3.63 (2H, m), 3.75 (1H, dd, J = 2.3, 11.7 Hz), 4.24 (1H, brd, J = 11.5 Hz), 4.35–4.53 (2H, m); APCI-MS *m/z* 380, 382 $(MH)^+$; anal. calcd for $C_{15}H_{30}BrNO_3Si$: C, 47.36%; H, 7.95%; N, 3.68%. Found: C, 47.42%; H, 8.17%; N, 3.64%.

(6*S*,8*R*)-8-*tert*-Butyldimethylsilyloxy-1-aza-4-oxabicyclo[4.3.0]nonan-2-one (7a). To a suspension of NaH (62.8% in oil) (0.55 g) in THF (60 mL) was added dropwise a solution of **6b** (4.20 g) in THF (20 mL) at 0–20°C. After stirring for 3 h at room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with AcOEt (80 mL), washed with water (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give a crude residue. This residue was purified by column chromatography (SiO_2 60 mL, MeOH:$CHCl_3$ (1:99) elution) and trituration with hexane to give **7a** (3.49 g, 94%) as a white solid. Mp 85–85.5 °C; FT-IR (KBr) cm^{-1} 2956, 2933, 2858, 1649, 1466, 1427; ^1H NMR (200 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 1.48 (1H, dt, J = 4.2, 11.7 Hz), 1.95 (1H, dd, J = 5.0, 12.4 Hz), 2.85 (2H, s), 3.24 (1H, t, J = 10.5 Hz), 3.35 (1H, d, J = 13.1 Hz), 3.85 (1H, dd, J = 4.8, 13.0 Hz), 3.96–4.30 (4H, m), 4.49 (1H, t, J = 4.5 Hz); APCI-MS *m/z* 272 $(MH)^+$; anal. calcd for $C_{13}H_{25}NO_3Si$: C, 57.53%; H, 9.28%; N, 5.16%. Found: C, 57.59%; H, 9.52%; N, 5.10%.

(6*S*,8*R*)-8-*tert*-Butyldimethylsilyloxy-3,3-dimethyl-1-aza-4-oxabicyclo[4.3.0]nonan-2-one (7b). **7b** was prepared from **6c** as described for the preparation of **7a**. White solid (41%); Mp 41–45°C; FT-IR (KBr) cm^{-1} 2956, 2933, 2858, 1643, 1470, 1441; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.42 (3H, s),

1.47 (3H, s), 1.38–1.52 (1H, m), 1.82 (1H, dd, J = 4.9, 12.3 Hz), 3.20–3.35 (2H, m), 3.73 (1H, dd, J = 4.8, 13.1 Hz), 3.89–4.09 (2H, m), 4.38 (1H, t, J = 4.4 Hz); APCI-MS m/z 300 $(MH)^+$; anal. calcd for $C_{15}H_{29}NO_3Si$: C, 60.16%; H, 9.76%; N, 4.68%. Found: C, 60.04%; H, 10.01%; N, 4.66%.

(2*S*,4*R*)-2-(Carboxymethoxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (8a). A suspension of **7a** (1.43 g) in 6 N HCl aqueous solution (14 mL) was heated at reflux for 3 h. The obtained solution was washed with AcOEt (7 mL×2), and the aqueous layer was evaporated under reduced pressure to give a crude residue. This residue was dissolved in a mixture of water (30 mL) and THF (30 mL), and treated dropwise with a solution of 4-nitrobenzyloxycarbonylchloride (1.36 g) in THF (6 mL) at 0–5 °C, adjusting pH to 8.5–9.5 with 4N-NaOH. After stirring for 2 h, the mixture was adjusted to pH 2.5 with 6 N HCl, and extracted with AcOEt (50 mL×2). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was chromatographed on silica gel (40 mL, MeOH:$CHCl_3$ (3:97) elution) to give **8a** (1.45 g, 78%) as a syrup. IR (neat) cm^{-1} 1680–1710, 3400; ^1H NMR (90 MHz, DMSO-d_6) δ 1.9–2.1 (2H, m), 3.2–3.5 (2H, m), 3.58 (2H, d, J = 3.6 Hz), 3.98 (2H, s), 3.9–4.1 (1H, m), 4.2–4.3 (1H, m), 5.21 (2H, s), 7.59 (2H, d, J = 9.0 Hz), 8.20 (2H, d, J = 9.0 Hz).

(2*S*,4*R*)-2-[(1-Carboxy-1-methyl)ethoxymethyl]-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (8b). **8b** was prepared from **7b** as described for the preparation of **8a**. Pale yellow oil (58%); IR (neat) cm^{-1} 1670–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.39 (3H, s), 1.42 (3H, s), 2.0–2.2 (2H, m), 3.4–3.7 (4H, m), 4.1–4.6 (2H, m), 5.22 (2H, s), 7.49 (2H, d, J = 9.0 Hz), 8.19 (2H, d, J = 9.0 Hz).

(2*S*,4*R*)-2-(Carboxymethoxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9a). To a solution of **8a** (1.42 g) and Et_3N (1.4 mL) in CH_2Cl_2 (14 mL) was added dropwise a solution of methanesulfonylchloride (0.62 mL) in CH_2Cl_2 (2 mL) at 0–5 °C. After stirring at 0–5 °C for 1 h, the mixture was poured into water (50 mL), adjusted to pH 2.5 with 6 N HCl and extracted with CH_2Cl_2 (50 mL×2). The combined extracts were washed with brine, dried over $MgSO_4$, evaporated under reduced pressure, and purified by silica gel chromatography (SiO_2 40 mL, MeOH:$CHCl_3$ (1:99) elution) to give **9a** (1.3 g, 75%) as an oil. IR ($CHCl_3$) cm^{-1} 1705; ^1H NMR (90 MHz, $CDCl_3$) δ 2.3–2.5 (2H, m), 3.03 (3H, s), 3.5–4.4 (5H, m), 4.08 (2H, s), 5.22 (2H, s), 5.2–5.4 (1H, m), 7.48 (2H, d, J = 8.5 Hz), 8.19 (2H, d, J = 8.5 Hz).

(2*S*,4*R*)-2-(Allyloxycarbonylmethoxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9b). A solution of **9a** (5.20 g) in allyl alcohol (52 mL) was treated with concentrated H_2SO_4 (0.5 mL) and stirred under reflux for 5 h. The obtained solution was then cooled, treated with Et_3N (3.14 mL) at 0–10°C, and evaporated under reduced pressure. The residue was dissolved in AcOEt (100 mL), washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give **9b** (6.05 g, 100%) as an oil. IR (neat) cm^{-1} 1705, 1755; ^1H NMR (90 MHz, $CDCl_3$) δ 2.3–2.7 (2H, m), 3.02 (3H, s), 3.5–4.3 (5H, m), 4.07 (2H, s), 4.62 (2H, d, J = 6.3 Hz), 5.1–5.4 (3H, m), 5.23 (2H, s), 5.7–6.1 (1H, m), 7.50 (2H, d, J = 8.6 Hz), 8.19 (2H, d, J = 8.6 Hz).

(2*S*,4*R*)-2-(Carbamoylmethoxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9c). To a solution of **9a** (1.28 g) and Et_3N (0.82 mL) in THF (13 mL) was added a solution of isobutylchloroformate (0.6 g) in THF (1 mL) at −10 to −5 °C and stirred for 30 min. The obtained mixture was poured into concentrated NH_3 (10 mL) at 0 °C, stirred for 30 min, and treated with a mixture of $CHCl_3$ (60 mL) and water (50 mL). The organic layer was separated, dried over $MgSO_4$, evaporated under reduced pressure, and purified by silica gel chromatography (SiO_2 50 mL, MeOH:$CHCl_3$ (1:99–2:98) elution) to give **9c** (1.0 g, 78%) as an oil. IR (neat) cm^{-1} 1670–1720; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.5 (2H, m), 3.07 (3H, s), 3.6–4.4 (5H, m), 4.00 (2H, s), 5.2–5.4 (1H, m), 5.29 (2H, s), 7.56 (1H, d, J = 9.5 Hz), 8.29 (1H, d, J = 9.5 Hz).

(2*S*,4*R*)-2-(*N*,*N*-Dimethylcarbamoyl)methoxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (9e). To a mixture of DMF (3.9 mL) and THF (30 mL) was added dropwise $POCl_3$ (3.75 mL) at 0–10 °C. After stirring at the same temperature for 30 min, to the mixture was added a solution of **9a** (14.50 g) in THF (15 mL) at 0–10 °C and the solution stirred at the same temperature for 30 min. This mixture was then added dropwise to a stirred solution of dimethylamine hydrochloride (50 g) and Et_3N (100 mL) in MeOH (200 mL) at room temperature. After stirring at the same temperature for 2 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in AcOEt (200 mL), washed with water (200 mL), 1 N HCl (200 mL), aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give **9e** (12.03 g, 78%) as an oil. IR (neat) cm^{-1} 1660, 1705; ^1H NMR (90 MHz, $CDCl_3$) δ 2.3–2.7 (2H m), 2.92 (6H, s), 3.02 (3H, s), 3.5–4.4 (5H, m), 4.12 (2H, s), 4.1–4.3 (1H, m), 5.23 (2H, s), 5.3–5.4 (1H, m), 7.50 (2H, d, J = 9.0 Hz), 8.20 (2H, d, J = 9.0 Hz).

(2*S*,4*R*)-4-Methanesulfonyloxy-2-(*N*-methylcarbamoyl)methoxymethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (9d). **9d** was prepared from **9a** as described for the preparation of **9e**, using methylamine instead of dimethylamine hydrochloride. Pale yellow oil (96%); IR (neat) cm^{-1} 1650–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.6 (2H, m), 2.80 (3H, d, J = 3.6 Hz), 3.03 (3H, s), 3.5–4.4 (5H, m), 3.93 (2H, s),

5.2–5.4 (1H, m), 5.24 (2H, s), 7.50 (2H, d, J = 7.2 Hz), 8.21 (2H, d, J = 7.2 Hz).

(2*S*,4*R*)-2-[(1-Carbamoyl-1-methyl)ethoxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (9f). A solution of **8b** (0.84 g) and Et_3N (1 mL) in THF (8 mL) was treated with a solution of MsCl (0.4 mL) in THF (2 mL) at −10 to −5 °C and stirred for 30 min. The obtained mixture was added to a solution of NH_3 (10%, 20 mL) in EtOH at 0°C, stirred for 1h, and evaporated under reduced pressure. The residue was treated with water (50 mL), extracted with AcOEt (50 mL), and the organic layer dried over $MgSO_4$, evaporated under reduced pressure and purified by silica gel chromatography (SiO_2 40 mL, MeOH:$CHCl_3$ (1:99) elution) to give **9f** (0.96 g, 95%) as an oil. IR ($CHCl_3$) cm^{-1} 1690, 1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (6H, s), 2.3–2.5 (2H, m), 3.05 (3H, s), 3.5–4.4 (5H, m), 5.2–5.6 (1H, m), 5.25 (2H, s), 7.51 (2H, d, J = 9.0 Hz), 8.23 (2H, d, J = 9.0 Hz).

(2*S*,4*R*)-2-(2-Hydroxyethoxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9g). To a solution of **9a** (2.4 g) and Et_3N (1.55 mL) in THF (50 mL) was added a solution of isobutylchloroformate (1.08 mL) in THF (3 mL) and stirred for 30 min at −5 to −10°C. The resulting insoluble precipitate was filtered off. To the filtrate was added $NaBH_4$ (700 mg) at 0°C. After the mixture was stirred (~1 h), the solution was quenched with water (30 mL) and AcOH (3 mL), and extracted with AcOEt. The obtained extract was washed with water, sat. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a residue which was purified by column chromatography (SiO_2 100 mL, MeOH:$CHCl_3$ (1:99) elution) to give **9g** (2.1 g, 90%) as an oil. IR (CH_2Cl_2) cm^{-1} 1680–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 2.3–2.5 (2H, m), 3.03 (3H, s), 3.5–4.5 (9H, m), 5.25 (2H, s), 5.3–5.4 (1H, m), 7.53 (2H, d, J = 8.4 Hz), 8.25 (2H, d, J = 8.4 Hz).

(2*S*,4*R*)-4-Methanesulfonyloxy-2-[2-[*N*-methyl-*N*-(4-nitrobenzyloxycarbonyl)amino]ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9i). To a suspension of $NaBH_4$ (1.87 g) in THF (75 mL) was added $BF_3{\cdot}Et_2O$ (18.7 mL) at 0–10 °C. After stirring at the same temperature for 30 min, a solution of **9d** (7.35 g) in THF (7.5 mL) was added at 0–10°C, and the mixture stirred at room temperature overnight (~15 h). The obtained mixture was treated with MeOH (5 mL) at 0–10°C, and followed by stirring for 2 h. The resulting insoluble precipitate was filtered off. The filtrate was evaporated under reduced pressure to give a residue. A solution of this residue in a mixture of concentrated HCl (7 mL) and MeOH (70 mL) was stirred at room temperature overnight then evaporated under reduced pressure. The obtained residue was dissolved in AcOEt (75 mL), washed with water (75 mL×2) and brine (75 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give a syrupy oil. To a solution of this syrupy oil in a mixture of water (30 mL) and THF (30 mL) was added a solution of 4-nitrobenzyloxycarbonylchloride (3.55 g) in THF (7 mL) at 0–10 °C, adjusting the pH to 8.5–9.5 with 4 N NaOH and stirred at 0–10 °C for 2 h. The mixture was evaporated under reduced pressure, dissolved in AcOEt, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give a syrupy oil, which was purified by silica gel chromatography (SiO_2 200 mL, MeOH:$CHCl_3$ (1:99) elution) to give **9i** (8.33 g, 83%) as an oil. IR (neat) cm^{-1} 1690–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.4 (2H, m), 2.95 (3H, s), 3.01 (3H, s), 3.4–4.3 (9H, m), 5.2–5.3 (1H, m), 5.17 (4H, brs), 7.43 (4H, brd, J = 9.0 Hz), 8.10 (4H, brd, J = 9.0 Hz).

(2*S*,4*R*)-4-Methanesulfonyloxy-2-[[*N*-(4-nitrobenzyloxycarbonyl)amino]ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9h). **9h** was prepared from **9c** as described for the preparation of **9i** (36%). IR ($CHCl_3$) cm^{-1} 1705. This compound was directly converted to thioacetate **15g**, further corroborating the structure.

(2*S*,4*R*)-2-[2-(*N*,*N*-Dimethylamino)ethoxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (9j). **9j** was prepared from **9e** as described for the preparation of **9i**, without the protection step with a 4-nitrobenzyl group. Oil (94%); IR (neat) cm^{-1} 1705; ^1H NMR (90 MHz, $CDCl_3$) δ 2.28 (6H, s), 2.3–2.6 (3H, m), 2.98 (3H, s), 3.4–4.3 (8H, m), 5.20 (2H, s), 5.2–5.3 (1H, m), 7.47 (2H, d, J = 8.1 Hz), 8.18 (2H, brd, J = 8.1 Hz).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-hydroxymethyl-4-methanesulfonyloxypyrrolidine (11). To a mixture of MeOH (500 mL) and concentrated H_2SO_4 (10 mL) was added **10** (100 g), and the mixture stirred under reflux for 4 h. The mixture was treated dropwise with Et_3N (63 mL) at 0–10 °C, and then evaporated under reduced pressure to give an oil. This oil was dissolved in THF (200 mL) and toluene (400 mL) and azeotropic evaporation of the mixture gave a crude oil. A solution of this obtained oil and Et_3N (63 mL) in AcOEt (1 L) was cooled to 0–5 °C, and treated with a solution of methanesulfonylchloride (35 mL) in AcOEt (100 mL) at 0–5 °C, stirred at same temperature for 30 min and quenched by ice–water (1 L). The organic layer was washed with 1 N HCl (1 L), saturated $NaHCO_3$ (1 L), and brine (1 L) and evaporated under reduced pressure to give methyl (2*S*,4*R*)-1-benzyloxycarbonyl-4-methanesulfonyloxy-pyrrolidine carboxylate as a crude oil. This oil was used in the next reaction without any purification. To a solution of this oil in THF (200 mL) and EtOH (300 mL) was added $NaBH_4$ (9.5 g × 3) at 0–10 °C and the mixture stirred at 25–30 °C for 2 h. The mixture was then poured into a mixture of concentrated HCl (92 mL) and ice–water (5 L) and stirred at 5–10 °C for 2 h to give a precipitate. The precipitate was filtered, washed with ice–water (500 mL×3), and dried under reduced pressure at 40 °C to give **11** as a solid (95. 2 g,

77%). IR (Nujol) 1690 cm^{-1}; ^1H NMR (90 Hz, $CDCl_3$) δ 2.0–2.6 (2H, m), 3.04 (3H, s), 3.5–4.4 (5H, m), 5.2 (2H, s), 5.2–5.4 (1H, m), 7.40 (5H, s).

(2*S*,4*R*)-2-Carboxymethoxymethyl-1-benzyloxycarbonyl-4-methanesulfonyloxypyrrolidine (12). To a solution of **11** (1.0 kg) and ethyl bromoacetate (0.5 L) in THF (4.0 L) was added dropwise a solution of ^{t}BuOK (340 g) in THF (1.0 L) at −10 to −5 °C. After stirring for 30 min, to the mixture was added ethyl bromoacetate (0.5 L) and then, dropwise, a solution of ^{t}BuOK (660 g) in THF (2.0 L). After stirring at the same temperature for 30 min, to the mixture was added 2 N NaOH (5.0 L), and the resulting mixture was stirred at 20–25 °C overnight. After evaporation of THF, the obtained aqueous solution was washed with AcOEt (2.0 L×3). To the aqueous layer was added AcOEt (4.0 L) and the stirred mixture adjusted to pH 4.5 using concentrated HCl (0.5 L). The organic layer was separated and the aqueous layer was then extracted with AcOEt (2.0 L). The combined organic layers were washed with brine (2.0 L×3), dried over $MgSO_4$, and evaporated under reduced pressure to give **12** as a syrupy oil (821 g, 70%). ^1H NMR (90 Hz, $CDCl_3$) δ 2.3–2.5 (2H, m), 3.00 (3H, s), 3.5–4.4 (7H, m), 5.16 (2H, s), 5.2–5.4 (1H, m), 7.37 (5H, s), 8.00 (1H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-(2-hydroxyethoxymethyl)-4-methanesulfonyloxypyrrolidine (13a). To a solution of $NaBH_4$ (95.5 g) in THF (4.89 L) was added dropwise $BF_3{\cdot}OEt_2$ (425 mL) at −10 to −5°C, stirred for 30 min at the same temperature, and treated dropwise with a solution of **12** (815 g) in THF (815 mL) at −10 to −5 °C. After stirring for 30 min, the solution was stirred at 10 °C for 1 h. The solution was then treated dropwise with MeOH (~200 mL), and the insoluble solid removed by filtration. The filtrate was then evaporated under reduced pressure. To the residue was added AcOEt (4.1 L) and water (2.4 L), and the stirred mixture adjusted to pH 6.0 using 4 N NaOH (300 mL). The organic layer was separated, washed with brine (2 L), dried over $MgSO_4$, and evaporated under reduced pressure to give **13a** (675.5 g, 86%) as a syrupy oil. IR (neat) 1665–1710 cm^{-1}; ^1H NMR (200 Hz, $CDCl_3$) δ 2.3–2.5 (2H, m), 2.98 (3H, s), 3.5–4.3 (10H, m), 5.13 (2H, s), 5.1–5.3 (1H, m), 7.35 (5H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-(2-fluoroethoxymethyl)-4-methanesulfonyloxypyrrolidine (13b). To a solution of **13a** (667 g) in CH_2Cl_2 (1.67 L) was added dropwise a solution of hexafluoropropene-diethylamine complex (403 mL) in CH_2Cl_2 (667 mL) at −10 to −5 °C and the solution stirred for 30 min at the same temperature, followed by 21 h at 30–35°C. The reaction mixture was poured into ice–water (2.0 L) and CH_2Cl_2 (1.0 L), adjusted to pH 7.0 with 4 N NaOH (~100 mL), and the organic layer separated. To the combined organic layer was added MeOH (667 mL), then NaOMe in MeOH (28%, 66.7 mL) at 15–20 °C, and the mixture stirred for 30 min. The mixture was quenched with AcOH (22.3 mL), and brine (1 L), and then adjusted to pH 6.0 using 4 N NaOH. The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure to give an oil (1030 g). The obtained oil was purified by column chromatography (SiO_2 6.66 L, hexane:AcOEt (2:1–0:1) elution) to give **13b** (495.7 g, 74%) as a syrupy oil. IR (neat) cm^{-1} 1685; ^1H NMR (90 Hz, $CDCl_3$) δ 2.2–2.4 (2H, m), 2.95 (3H, s), 3.4–4.7 (9H, m), 5.12 (2H, s), 5.2–5.3 (1H, m), 7.31 (5H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-(formylmethoxymethyl)-4-methanesulfonyloxypyrrolidine (13c). To a solution of oxalyl chloride (4.31 mL) in CH_2Cl_2 (200 mL) was added dropwise DMSO (7.01 mL) at −70 °C, and the solution stirred 10 min at the same temperature. To this solution was added dropwise a solution of **13a** (17.57 g) in CH_2Cl_2 (50 mL), followed by stirring for 15 min. Et_3N (37.8 mL) was then added dropwise at −70 °C. The reaction mixture was stirred at the same temperature for 2 h, then warmed to room temperature. After the precipitate was filtered off, the filtrate was quenched with water (100 mL) and extracted with AcOEt (200 mL). The organic layer was then washed with brine (100 mL), dried over $MgSO_4$ and treated with charcoal. After filtration, the solution was evaporated to give a residue which was purified by column chromatography (SiO_2 500 mL, MeOH:CH_2Cl_2 (1:9) elution) to give **13c** (15.7 g, 90%) as an amorphous solid. IR (Nujol) cm^{-1} 1670–1710; ^1H NMR (200 MHz, $CDCl_3$) δ 2.18–2.45 (2H, m), 3.01 (3H, s), 3.50–4.20 (7H, m), 5.14 (2H, brs), 5.20–5.40 (1H, m), 7.36 (5H, s), 9.60–9.70 (1H, m).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-[(3-ethoxycarbonyl-2-propenyl)oxymethyl]-4-methanesulfonyloxypyrrolidine (13d). A solution of **13c** (15.7 g) and (carbethoxymethylene)triphenylphosphorane (16.2 g) in toluene (150 mL) was refluxed for 3 h. After evaporation under reduced pressure, the residue was purified by column chromatography (SiO_2 700 mL, hexane:AcOEt (2:1–1:1, elution, give **13d** (12.9 g, 69%) as an amorphous solid. IR (Nujol) cm $^{-1}$1695, 1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (3H, t, J = 7.1 Hz), 2.30–2.50 (2H, m), 3.00 (3H, s), 3.43–4.26 (7H, m), 4.20 (2H, q, J = 7.1 Hz), 5.14 (2H, brs), 5.20–5.35 (1H, m), 5.76–6.01 (1H, m), 6.80–7.00 (1H, m), 7.35 (5H, brs).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-(4-hydroxy-2-butenyl)-oxymethyl-4-methanesulfonyloxypyrrolidine (13e). To a solution of **13d** (10 g) in THF (120 mL) was added dropwise a solution of DIBAH in toluene (1.0 M., 56.6 mL) at −40 °C, and then stirred at 0°C over night. The mixture was quenched with 1 N HCl (50 mL), and the resulting precipitate filtered off. To the filtrate was added water (100 mL), and the mixture was extracted with AcOEt (200 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and treated with charcoal. After filtration and evaporation of solvent, the residue was purified by

column chromatography (SiO_2 200 mL, hexane: AcOEt (1:4) elution) to give **13e** (5.07 g, 56%) as an amorphous solid. IR (Nujol) cm^{-1} 1690; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.4 (2H, m), 2.97 (3H, s), 3.4–4.2 (9H, m), 5.11 (2H, brs), 5.2–5.3 (1H, m), 5.6–5.8 (2H, m), 7.28 (5H, brs).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-[2-(2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-yl)-2-oxoethyl]oxymethyl-4-methanesulfonyloxypyrrolidine (13f). To a solution of **12** (79.4 g), 2,2-dimethyl-1,3-dioxane-4,6-dione (29.55 g) and 4-(*N*,*N*-dimethylamino)pyridine (25.05 g) in CH_2Cl_2 (635 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (39.3 g) at 5–10 °C, and the solution stirred at the same temperature for 1h and at room temperature for 18 h. The reaction mixture was then washed with water (650 mL), 1 N HCl (650 mL), saturated $NaHCO_3$ (650 mL) and brine (650 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2 1.6 L, MeOH:CH_2Cl_2 (2:98) elution) to give **13f** (81 g, 77%) as an oil. IR ($CHCl_3$) cm^{-1} 1640, 1690; ^1H NMR (90 MHz, $CDCl_3$) δ 1.60 (6H, s), 2.2–2.5 (2H, m), 2.99 (3H, s), 3.2–5.4 (10H, m), 7.32 (5H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-methanesulfonyloxy-2-(2-oxopropoxymethyl)pyrrolidine (13g). A solution of **13f** (20 g) in a mixture of AcOH (40 mL) and water (60 mL) was stirred under reflux for 40 h. The reaction mixture was poured into a mixture of AcOEt (400 mL) and water (400 mL). The organic layer was separated, washed with water (400 mL), saturated $NaHCO_3$ (400 mL×2), and brine (400 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2 600 mL, MeOH:CH_2Cl_2 (5:95) elution) to give **13g** (12.3 g, 82%) as an amorphous solid. IR (Nujol) cm^{-1} 1670–1730; ^1H NMR (200 MHz, $CDCl_3$) δ 2.08 (3H, brs), 2.24–2.58 (2H, m), 3.06 (3H, s), 3.30–4.25 (7H, m), 5.14 (2H, s), 5.30–5.40 (1H, m), 7.36 (5H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-[(2*RS*)-2-hydroxypropoxymethyl]-4-methanesulfonyloxypyrrolidine (13h). To a solution of **13g** (12 g) in ethanol (120 mL) was added $NaBH_4$ (2.4 g) at 0 °C, and the solution stirred for 7 h. The reaction mixture was quenched with acetone (20 mL) slowly at 0 °C and evaporated under reduced pressure. To the obtained residue was added water (100 mL) and extracted with AcOEt (200 mL). The organic layer was then washed with brine (100 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2 500 mL, MeOH:CH_2Cl_2 (5:95) elution) to give **13h** (7.3 g, 61%, a mixture of diastereomers) as an amorphous solid. IR (Nujol) cm^{-1} 1670–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.15 (3H, d, J = 6.3 Hz), 2.3–2.4 (2H, m), 3.02 (3H, s), 3.3–4.3 (8H, m), 5.14 (2H, s), 5.2–5.4 (1H, m), 7.33 (5H, brs).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-[(2*RS*)-2-fluoropropoxymethyl]-4-methanesulfonyloxypyrrolidine (13i). **13i** was obtained from **13h** by a similar method as described for **13b**. Amorphous solid (82%); IR (Nujol) cm^{-1} 1685–1710; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, dd, J = 6.3 Hz, 23.5 Hz), 2.30–2.42 (2H, m), 2.99 (3H, s), 3.30–4.00 (6H, m), 4.10–4.23 (1H, m), 4.55–4.95 (1H, m), 5.14 (2H, s), 5.25–5.35 (1H, m), 7.36 (5H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-2-amidomethoxymethyl-4-methanesulfonyloxypyrrolidine (13j). To a solution of **12** (2.65 kg) and Et_3N (1.24 L) in THF (13 L) was added dropwise a solution of isobutylchloroformate (1.77 mL) in THF (2 L) at −10 to −5°C for 1.5 h. The obtained activated ester solution was added dropwise to stirring concentrated NH_3 (18 kg) at −10 °C. The reaction mixture was then extracted with AcOEt (15 L, 5 L×2). The combined organic extracts were washed with water, 2 N HCl (10 L×2), saturated $NaHCO_3$ aqueous solution (5 L), and brine (10 L), and evaporated under reduced pressure to give **13j** (1.80 kg, 68%) as an oil. IR (neat) cm^{-1} 1670–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.6 (2H, m), 2.96 (3H, s), 3.5–4.3 (7H, m), 5.13 (2H, m), 5.1–5.4 (1H, m), 7.35 (1H, s).

(2*S*,4*R*)-1-Benzyloxycarbonyl-4-methanesulfonyloxy-2-(2-ureidoethoxymethyl)pyrrolidine (13k). To a suspension of $NaBH_4$ (440 g) in THF (14.5 L) was added dropwise $BF_3{\cdot}OEt_2$ (1.4 L) at 0 to −5°C over 1 h and the mixture stirred at the same temperature for a further 30 min. To the reaction mixture was then added dropwise a solution of **13j** (1.8 kg) in THF (3.6 L) over 2 h and the solution then stirred at room temperature for a further 2 h. The obtained mixture was quenched with EtOH (7.2 L) at 5–10 °C, stirred at room temperature for 3 h, and the resulting precipitate was filtered off. The filtrate was concentrated to give (2*S*,4*R*)-1-benzyloxycarbonyl-2-(2-aminoethoxymethyl)-4-methanesulfonyloxy pyrrolidine as a syrupy oil. To a solution of the obtained syrupy oil in a mixture of THF (9.0 L) and water (4.0 L) was added dropwise a solution of KOCN (1890 g) in water (4.0 L) at 40–50 °C at pH 4–5 over 5 h and then stirred for 1 h. The mixture was separated and the aqueous layer was extracted with AcOEt (5 L×2). The combined organic layers were washed with brine (5 L×2), dried over $MgSO_4$, treated with activated charcoal, filtered, and evaporated under reduced pressure to give **13k** (1.5 kg, 78%). IR (neat) cm^{-1} 1650–1700; ^1H NMR (90 MHz, $CDCl_3$) δ 2.2–2.5 (2H, m), 3.03 (3H, s), 3.2–4.7 (9H, m), 5.16 (2H, s), 5.0–5.4 (1H, m), 7.40 (5H, s).

(2*S*,4*R*)-1-Allyloxycarbonyl-2-(2-fluoroethoxymethyl)-4-methanesulfonyloxypyrrolidine (14b). To a solution of **13b** (490 g) in MeOH (4.9 L) and concentrated HCl (109 mL) was added 10% Pd–C (50%wet) (49 g) as a catalyst, and hydrogen was bubbled into the stirring mixture at room temperature for 2 h. After filtration of the catalyst, the catalyst was washed with

MeOH (0.5 L), and the combined organic layer was evaporated under reduced pressure to give an oil (412 g). The obtained oil was dissolved in a mixture of water (1.96 L) and THF (1.96 L), and treated dropwise with a solution of allylchloroformate (152 mL) in THF (160 mL) at 0–10 °C adjusting pH (9.09–9.5) with 4 N NaOH, and then stirred for 1 h at pH 9.0. The mixture was extracted with AcOEt (2.94 L). The organic layer was then washed with water (1.96 L) and brine (1.96 L), dried over $MgSO_4$, and evaporated under reduced pressure to give **14b** (434 g, ~100%) as a syrupy oil. IR (neat) cm^{-1} 1680–1710; ^1H NMR (200 MHz, $CDCl_3$) δ 2.35–2.45 (2H, m), 3.04 (3H, s), 3.56–4.00 (6H, m), 4.13–4.30 (1H, m), 4.38–4.60 (2H, m), 4.60–4.66 (2H, m), 5.19–5.35 (3H, m), 5.87–6.05 (1H, m).

Preparation of **14a**, **14c–e** was carried out by a method similar to that described for **14b** from the appropriate starting materials.

(2*S*,4*R*)-1-Allyloxycarbonyl-2-(2-hydroxyethoxymethyl)-4-methanesulfonyloxypyrrolidine (14a). (61%): IR (neat) cm^{-1} 1690; ^1H NMR (200 MHz, $CDCl_3$) δ 2.30–2.45 (2H, m), 2.50–2.70 (1H, m), 3.05 (3H, s), 3.54–3.95 (8H, m), 4.15–4.25 (1H, m), 4.60 (2H, d, J = 4.9 Hz), 5.20–5.38 (3H, m), 5.84–6.04 (1H, m).

(2*S*,4*R*)-1-Allyloxycarbonyl-2-[(4-hydroxybutan-1-yl)oxymethyl]-4-methanesulfonyloxypyrrolidine (14c). (72%): IR (Nujol) cm^{-1} 1670–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.6–2.0 (4H, m), 2.3–2.4 (2H, m), 3.05 (3H, s), 3.4–4.3 (9H, m), 4.61 (2H, d, J = 5.4 Hz), 5.2–5.4 (3H, m), 5.7–6.2 (1H, m).

(2*S*,4*R*)-1-Allyloxycarbonyl-2-[(2*RS*)-(2-fluoropropoxy)methyl]-4-methanesulfonyloxypyrrolidine (14d). (44%): IR (Nujol) cm^{-1} 1700; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (3H, dd, J = 6.4 Hz, 23.7 Hz), 2.30–2.50 (2H, m), 3.03 (3H, s) 3.44–3.98 (6H, m), 4.10–4.27 (1H, m), 4.61 (2H, brd, J = 4.8 Hz), 4.55–4.97 (1H, m), 5.20–5.34 (3H, m), 5.85–6.04 (1H, m).

(2*S*,4*R*)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-(2-ureidoethoxymethyl)pyrrolidine (14e). (95%): IR ($CHCl_3$) cm^{-1} 1670–1690; ^1H NMR (90 MHz, $CDCl_3$) δ 2.3–2.4 (2H, m), 3.05 (3H, s), 3.3–3.8 (7H, m), 4.0–4.3 (1H, m), 4.60 (2H, d, J = 3.6 Hz), 4.6–4.8 (1H, m), 5.2–5.4 (3H, m), 5.7–6.2 (1H, m).

(2*S*,4*R*)-1-Allyloxycarbonyl-2-[(2-methanesulfonyloxy)ethoxymethyl]-4-methanesulfonyloxypyrrolidine (14f). **14f** was obtained from **14a** by the same method as described for the mesylation step in the preparation of **11**. Yellow oil, (~100%); ^1H NMR (200 MHz, $CDCl_3$) δ 2.30–2.50 (2H, m), 3.05 (6H, s), 3.56–3.90 (6H, m), 4.15–4.30 (1H, m), 4.34 (2H, t, J = 4.2 Hz), 4.60 (2H, brd, J = 3.4 Hz), 5.20–5.36 (3H, m), 5.85–6.04 (1H, m), MS m/z 402 $(MH)^+$.

(2*S*,4*R*)-1-Allyloxycarbonyl-2-[(4-fluorobutan-1-yl)oxymethyl]-4-methanesulfonyloxypyrrolidine (14g). **14g** was obtained from **14c** by the same method described for preparation of **13b**. Yellow oil (50%); IR (neat) cm^{-1} 1690; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.0 (4H, m), 2.3–2.4 (2H, m), 3.03 (3H, s), 3.4–3.8 (6H, m), 4.0–4.3 (1H, m), 4.0–4.8 (2H, m), 4.60 (2H, d, J = 5.4 Hz), 5.1–5.4 (3H, m), 5.7–6.1 (1H, m).

Preparation of thioesters

(2*S*,4*S*)-4-Acetylthio-2-[(*N*-methylamido)methoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15c). To a solution of ^{t}BuOK (2.5 g) in DMF (33 mL) was added thioacetic acid (1.59 mL) at 0–10 °C and stirred. To the mixture was added a solution of **9d** (6.60 g) in DMF (6.6 mL) and the solution stirred at 75–80 °C for 3 h. The mixture was then poured into AcOEt (150 mL), washed with water (150 mL×3) and brine (150 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The obtained residue was purified by column chromatography (SiO_2 140 mL, MeOH:$CHCl_3$ (1:99) elution) to give **15c** (4.44 g, 71%) as a syrupy oil. IR (neat) cm^{-1} 1650–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.8–2.1 (1H, m), 2.33 (3H, s), 2.4–2.7 (1H, m), 2.80 (3H, d, J = 5.4 Hz), 3.1–3.3 (1H, m), 3.68 (2H, d, J = 4.5 Hz) 3.8–4.2 (3H, m), 3.94 (2H, s), 5.20 (2H, s), 7.49 (2H, d, J = 9.0 Hz), 8.21 (2H, d, J = 9.0 Hz).

Using the same procedure **15a**, **15d**, and **15h–i** were also prepared as described for **15c** from the appropriate mesylate.

(2*S*,4*S*)-4-Acetylthio-2-(allyloxycarbonylmethoxymethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15a). (74%): IR (neat) cm^{-1} 1690–1710, 1755; ^1H NMR (90 MHz, $CDCl_3$) δ 1.9–2.6 (2H, m), 2.27 (3H, s), 3.15 (1H, m), 3.5–4.2 (5H, m), 4.03 (2H, s), 4.58 (2H, d, J = 6.3 Hz), 5.14 (2H, s), 5.0–5.3 (2H, m), 5.7–6.1 (1H, m), 7.45 (2H, d, J = 8.6 Hz), 8.15 (2H, d, J = 8.6 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[(*N*,*N*-dimethylcarbamoyl)methoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15d). (72%): IR (neat) cm^{-1} 1660, 1690–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.9-2.7 (2H, m), 2.30 (3H, s), 2.93 (6H, s), 3.18 (1H, m). 3.7–4.2 (5H, m), 4.11 (2H, s), 5.19 (2H, s), 7.49 (2H, d, J = 8.1 Hz), 8.21 (2H, d, J = 8.1 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[2-[*N*-methyl-*N*-(4-nitrobenzyloxycarbonyl)amino]ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15h). (59%): IR (neat) cm^{-1} 1680–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.7–2.6 (2H, m), 2.27 (3H, s), 2.94 (3H, s), 3.0–3.2 (1H, m), 3.4–4.2 (9H, m), 5.16 (4H, s), 7.46 (4H, d, J = 9.0 Hz), 8.15 (4H, d, J = 9.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[2-(*N*,*N*-dimethylamino)ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15i). (48%): IR (neat) cm^{-1} 1680–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.7–2.6 (2H, m), 2.23 (6H, s), 2.28

(3H, s), 2.4–2.6 (2H, m), 3.0–3.3 (1H, m), 3.4–4.2 (7H, m), 5.16 (2H, s), 7.46 (2H, d, J = 9.0 Hz), 8.17 (2H, d, J = 9.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-(2-fluoroethoxymethyl)-1-(4-allyloxycarbonyl)pyrrolidine (15j). To a solution of **14b** (17.3 g) in methylisobutylketone (120 mL) was added thioacetic acid (5.88 mL) and $Ca(OH)_2$ (3.05 g) at ~45 °C. After stirring at 80–85 °C (exothermic reaction) for 5 h, the mixture was quenched by water (30 mL), and stirred. The insoluble residue was filtered off and washed with AcOEt (50 mL). The organic layer of the filtrate was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The obtained oil was purified by column chromatography (SiO_2 340 mL, hexane:AcOEt (1:9–2:8) elution) to give **15j** (13.8 g, ~85%) as an orange oil. IR (neat) cm^{-1} 1685–1715; ^1H NMR (90 MHz, $CDCl_3$) δ 1.8–2.5 (1H, m), 2.32 (3H, m), 2.3–2.7 (1H, m), 3.0–3.3 (1H, m), 3.5–4.3 (8H, m), 4.57 (2H, d, J = 6.0 Hz), 4.52 (2H, dt, J = 48.0, 4.5 Hz), 5.1–5.4 (2H, m), 5.7–6.2 (1H, m); APCI-MS m/z 305 (M^+).

(2*S*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-[(2*RS*)-(2-fluoropropoxy)methyl]pyrrolidine (15k). To a suspension of NaH (200 mg, suspension in oil 62.8%) in DMF (20 mL) was added thioacetic acid (0.39 mL) at ~10 °C. After stirring for 30 min, The mixture was treated dropwise with a solution of **14d** (1.46 g) in DMF (5 mL) and stirred at 90 °C for 3 h. The reaction mixture was poured into a mixture of AcOEt (60 mL), water (20 mL) and brine (10 mL). The organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give a residue which was purified by column chromatography (SiO_2 100 mL, hexane:AcOEt (2:1) elution) to give **15k** (59%) as a foam. IR (Nujol) cm^{-1} 1705; ^1H NMR (90 MHz, $CDCl_3$) δ 1.22 (d, J = 7.2 Hz), 1.48 (d, J = 8.1 Hz), total 3H, 1.35 (3H, dd, J = 16.0 Hz, 23.4 Hz), 1.9–2.2 (1H, m), 2.4–2.8 (1H, m), 2.36 (3H, s), 3.19 (1H, dd, J = 6.3 Hz, 10.0 Hz), 3.4–4.2 (7H, m), 4.59 (2H, brd, J = 4.5 Hz), 5.1–5.4 (2H, m), 5.7–6.1 (1H, m).

Using the same procedure **15b**, **15e–g**, **15l**, and **15o** were prepared as described for **15k** from the appropriate starting material.

(2*S*,4*S*)-4-Acetylthio-2-carbamoylmethyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15b). (77%): IR (neat) cm^{-1} 1670–1720; ^1H NMR (90 MHz, $CDCl_3$) δ 1.8–2.1 (1H, m), 2.37 (3H, s), 2.5–2.9 (1H, m), 2.8–3.0 (1H, m), 3.2–3.4 (1H, m), 3.72 (2H, d, J = 5.4 Hz), 3.98 (2H, s), 3.8–4.3 (2H, m), 5.22 (2H, s) 7.49 (2H, d, J = 9.0 Hz), 8.22 (2H, d, J = 9.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[(1-carbamoyl-1-methyl)ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15e). (92%): IR (neat) cm^{-1} 1670–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.42 (6H, s), 1.8–2.1 (1H, m), 2.37 (3H, s), 2.5–2.7 (1H, m), 2.8–3.0 (1H, m), 3.2–3.3 (1H, m), 3.4–3.6 (2H, m), 3.9–4.3 (2H, m), 5.23 (2H, s), 7.52 (2H, d, J = 9.0 Hz), 8.24 (2H, d, J = 9.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[2-hydroxyethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (15f). (88%): IR (neat) cm^{-1} 1675–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.6 (2H, m), 2.35 (3H, s), 2.8–3.0 (1H, m), 3.2–3.4 (1H, m), 3.5–4.3 (8H, m), 5.25 (2H, s), 7.56 (2H, d, J = 9.0 Hz), 8.28 (2H, d, J = 9.0 Hz).

(2*S*,4*S*)-4-Acetylthio-2-[*N*-(4-nitrobenzyloxycarbonyl)-aminoethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (15g). (73%): IR (neat) cm^{-1} 1685–1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.7–2.1 (1H, m), 2.31 (3H, s), 2.4–2.7 (1H, m), 3.1–4.2 (10H, m), 5.16 (4H, s), 7.43 (4H, brd, J = 8.1 Hz), 8.14 (4H, d, J = 8.1 Hz).

(2*S*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-[(2-ureidoethoxy)methyl]pyrrolidine (15l). (79%): IR (neat) cm^{-1} 1690; ^1H NMR (90 MHz, $CDCl_3$) δ 1.8–2.0 (1H, m), 2.30 (3H, m), 2.2–2.8 (1H, m), 3.1–4.2 (9H, m), 4.5–4.8 (1H, m), 4.58 (2H, d, J = 5.4 Hz), 5.1–5.4 (2H, m), 5.7–6.2 (1H, m).

(2*S*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-[(4-fluorobutan-1-yl)oxymethyl]pyrrolidine (15o). (71%): IR (Nujol) cm^{-1} 1710; ^1H NMR (90 MHz, $CDCl_3$) δ 1.6–2.0 (4H, m), 1.8–2.1 (1H, m), 2.35 (3H, s), 2.3–2.6 (1H, m), 3.1–3.3 (1H, m), 3.4–4.8 (9H, m), 4.58 (2H, d, J = 5.4 Hz), 5.1–5.4 (2H, m), 5.7–6.1 (1H, m).

(2*S*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-(2-imidazolylethyl)oxymethylpyrrolidine (15m). To a solution of imidazole (860 mg) in DMF (35 mL) was added ^{t}BuOK (1.31 g) at room temperature and the solution stirred for 10 min then treated with a solution of **14f** (3.9 g) in DMF (5 mL). After stirring for 10 min at room temperature, the mixture was stirred at 45 °C for 3 h to give a solution containing (2*S*,4*S*)-4-methanesulfonyl-1-allyloxycarbonyl-2-(2-imidazoylethyl)oxymethylpyrrolidine. To an ice-cold solution of ^{t}BuOK (1.31 g) in DMF (40 mL) was added dropwise thiobenzoic acid (1.49 mL) over 5 min, and the yellow solution stirred for 10 min at 0 °C and added to the solution containing the 2-imidazoylethyl derivative, followed by stirring at 95 °C for 20 h. The reaction mixture was cooled, diluted with brine and extracted with CH_2Cl_2 (×3). The organic layer was washed with water (×6), dried over $MgSO_4$, and evaporated under reduced pressure to give a residue which was purified with column chromatography (SiO_2, 200 mL, CH_2Cl_2:MeOH (20:1) elution) to give **15m** (3.76 g, 93%) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.97–2.08 (1H, m), 2.40–2.70 (1H, m), 3.20–3.30 (1H, m), 3.70–3.75 (4H, m), 4.03–4.30 (5H, m), 4.59 (2H, d, J = 5.3 Hz), 5.19–5.35 (2H, m), 5.84–6.04 (1H, m), 6.96 (1H, s), 7.05 (1H, s), 7.41–8.16 (6H, m); MS m/z 416 $(MH)^+$.

(2*S*,4*S*)-1-Allyloxycarbonyl-4-benzoylthio-2-[(2-pyrazolylethyl)oxymethyl]pyrrolidine (15n). **15n** was obtained from **14f** using pyrazole instead of imidazole by the same method as for **15m**. Yellow oil (73%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89–2.05 (1H, m), 2.35–2.60 (1H, m), 3.10–3.30 (1H, m), 3.64 (2H, brs), 3.82 (2H, t, J = 5.2 Hz), 4.01–4.30 (3H, m), 4.30 (2H, t, J = 5.2 Hz), 4.59 (2H, d, J = 5.5 Hz), 5.19–5.35 (2H, m), 5.84–6.03 (1H, m), 6.23 (1H, s), 7.41–7.70 (5H, m), 7.92 (1H, s), 7.95 (1H, s); MS m/z 416 $(MH)^+$.

Preparation of protected carbapenems 18

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-(2-fluoroethoxymethyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (18j). To a solution of **15j** (386 g) in MeOH (3.2 L) was added dropwise a solution of NaOMe in MeOH (28%, 380 mL) at −10 to −5 °C and the solution stirred for 1 h. The mixture was quenched with AcOH (121 mL) at −10 to −5 °C and evaporated under reduced pressure. To the obtained residue water (0.5 L) and AcOEt (1.6 L) were added and the organic layer separated. The organic layer was treated with $MgSO_4$ and charcoal filtered, evaporated under reduced pressure and purified by column chromatography (SiO_2 7.2 L, AcOEt:hexane (1:9–1:4) elution) to give (2*S*,4*S*)-1-allyloxycarbonyl-2-(2-fluoroethyl)oxymethyl-4-mercaptopyrrolidine (200 g) as an oil. This oil was used immediately in the next reaction because of instability of the thiol function. To a solution of activated carbapenem (**17**) (610 mmol) in MeCN (900 mL) was added a solution of the 4-mercapto derivative (161 g) in MeCN (180 mL), followed by ^{i}Pr$_2$EtN (127 mL) dropwise. After stirring at −10 to −5 °C for 1 h, and at 20–25 °C for 4 h, the reaction mixture was diluted with AcOEt (4.5 L), washed with water (1.5 L×3), 0.1 N HCl (1.5 L×2), water (1.5 L), and brine (1.5 L). The organic layer was dried over $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (SiO_2 6.4 L, AcOEt:hexane (3:7–3:2) elution) to give **18j** (69.5 g, 14%) as a syrup. IR (neat) cm^{-1} 1685–1710, 1750; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.3 Hz), 1.39 (3H, d, J = 5.4 Hz), 1.9–2.8 (2H, m), 3.2–4.8 (14H, m), 4.56 (2H, d, J = 4.5 Hz), 4.7–4.8 (2H, m), 5.2–5.5 (4H, m), 5.7–6.2 (2H, m).

Using the same procedure **18b–i** were also prepared as described for **18j** from **16** and the appropriate starting material.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-carbamoylmethoxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18b). (55%): IR (Nujol) cm^{-1} 1670–1710, 1765; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.30 (3H, d, J = 6.3 Hz), 1.36 (3H, d, J = 5.4 Hz), 1.8–2.3 (1H, m), 2.4–2.8 (1H, m), 3.2–3.4 (3H, m), 3.6–3.8 (3H, m), 4.1–4.3 (4H, m), 4.94 (2H, s), 5.20 (2H, s), 5.15 (1H, d, J = 13.1 Hz), 5.50 (1H, d, J = 13.1 Hz), 7.46 (2H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.1 Hz), 8.19 (4H, d, J = 8.1 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(*N*-methylcarbamoyl)methoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18c). (64%): IR ($CHCl_3$) cm^{-1} 1680–1710, 1765; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.24 (3H, d, J = 5.4 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.8–2.1 (1H, m), 2.4–2.9 (1H, m), 2.77 (3H, d, J = 5.4 Hz), 3.1–4.3 (8H, m), 3.68 (2H, d, J = 4.5 Hz), 3.90 (2H, s), 5.15 (2H, s), 5.15 (1H, d, J = 11.7 Hz), 5.46 (1H, d, J = 11.7 Hz), 7.44 (1H, d, J = 9.0 Hz), 7.58 (1H, d, J = 9.0 Hz), 8.13 (2H, d, J = 9.0 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(*N*,*N*-dimethylcarbamoyl)methoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18d). (62%): IR ($CHCl_3$) cm^{-1} 1690–1710, 1765; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 7.2 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.0–2.7 (2H, m), 2.95 (6H, s), 3.2–4.3 (10H, m), 4.13 (2H, s), 5.21 (2H, s), 5.23 (1H, d, J = 13.5 Hz), 5.48 (1H, d, J = 13.5 Hz), 7.53 (2H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.2 Hz), 8.22 (4H, d, J = 8.2 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(1-carbamoyl-1-methyl)ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18e). (49%): IR ($CHCl_3$) cm^{-1} 1690–1710, 1765; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.31 (3H, d, J = 7.2 Hz), 1.38 (3H, d, J = 5.4 Hz), 1.38 (6H, s), 1.7–2.2 (1H, m), 2.4–2.8 (1H, m), 3.2–4.4 (8H, m), 3.64 (2H, d, J = 4.5 Hz), 5.20 (1H, d, J = 14.4 Hz), 5.21 (2H, s), 5.53 (1H, d, J = 14.4 Hz), 7.51 (2H, d, J = 9.0 Hz), 7.63 (2H, d, J = 9.0 Hz), 8.23 (4H, d, J = 9.0 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(2-hydroxyethyl)oxy-methyl]-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18f). (68%): IR (Nujol) cm^{-1} 1680–1780; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 5.4 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.8–2.2 (1H, m), 2.3–2.8 (1H, m), 2.3–4.3 (14H, m), 5.22 (2H, s), 5.32 (2H, ABq, J = 13.5 Hz), 7.51 (2H, d, J = 9.0 Hz), 7.63 (2H, d, J = 9.0 Hz), 8.22 (4H, d, J = 9.0 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-[*N*-(4-nitrobenzyloxycarbonyl)amino]ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (18g). (60%) This compound was directly converted to **19g**, further corroborating the structure.

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-[*N*-methyl-*N*-(4-nitrobenzyloxycarbonyl)amino]ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18h). (26%): IR ($CHCl_3$) cm^{-1} 1690–1710, 1765; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 8.1 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.8–2.1 (1H, m), 2.3–2.6 (1H, m), 2.91 (3H, s), 3.1–4.2 (14H, m), 5.14 (4H, s), 5.14 (1H, d, J = 12.2 Hz), 5.40 (1H, d, J = 12.2 Hz), 7.41 (4H, d, J = 9.0 Hz), 7.55 (2H, d, J = 8.1 Hz), 8.13 (6H, d, J = 8.1 Hz).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-(*N*,*N*-dimethylamino)ethoxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18i). (43%) This compound was directly converted to **19i**, further corroborating the structure.

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(2-ureidoethoxy)methyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (18l). **18l** was prepared from **17** and **15l** by the similar method as described for **18j**. Yellow foam (36%); IR (CH_2Cl_2) cm^{-1} 1650–1695, 1770; ^1H NMR (90 MHz, $CDCl_3$) δ 1.28 (3H, d, J = 7.2 Hz), 1.33 (3H, d, J = 7.2 Hz), 1.8–2.1 (1H, m), 2.4–2.7 (1H, m), 3.2–4.3 (14H, m), 4.62 (2H, d, J = 4.5 Hz), 4.6–4.8 (2H, m), 5.2–5.5 (4H, m), 5.8–6.2 (2H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[[(2*RS*)-2-fluoropropyl]oxymethyl]pyrrolidine-4-yl]-thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18k). To a solution of **15k** (790 mg) in MeCN (5 mL) was added dropwise NaOMe (28% in MeOH, 0.49 mL) at −20 °C, and the solution stirred for 15 min to give the thiolate salt as a MeCN solution. To a solution of activated carbapenem **17** (2.1 mmol) in a mixture of MeCN (10 mL) and DMAC (5 mL) was added the thiolate solution at 0 °C. After stirring at room temperature for 5 h. the reaction mixture was quenched with water (20 mL) and extracted with AcOEt (50 mL). The organic extract was then washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2 100 mL, AcOEt:hexane (1:1–1:2) elution) to give **18k** (300 mg, 30%) as a foam. IR (Nujol) cm^{-1} 1690–1710, 1765; ^1H NMR (90 MHz, $CDCl_3$) δ 1.31 (3H, d, J = 9.0 Hz), 1.34 (3H, dd, J = 7.7 Hz, 23.0 Hz), 1.40 (3H, d, J = 6.3 Hz), 1.5–2.2 (1H, m), 2.4–2.7 (1H, m), 3.1–5.8 (13H, m), 4.62 (2H, d, J = 4.5 Hz), 4.6–4.8 (2H, m), 5.2–5.5 (4H, m), 5.7–6.1 (2H, m).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(4-fluorobutane-1-yl)oxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (18o). **18o** was prepared from **17** and **15o** by the similar method as described for **18k** from **17** and **15o**. Yellow foam (33%); IR (Nujol) cm^{-1} 1685–1710, 1750; ^1H NMR (90 MHz, $CDCl_3$) δ 1.33 (3H, d, J = 6.3 Hz), 1.39 (3H, d, J = 5.4 Hz), 1.5–1.9 (5H, m), 2.3–2.8 (1H, m), 3.2–4.8 (14H, m), 4.5–4.8 (4H, m), 5.2–5.5 (4H, m), 5.7–6.2 (2H, m).

4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(allyloxycarbonylmethoxymethyl)-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (18a). To a solution of **15a** (4.25 g) in allyl alcohol (40 mL) was added NaH in mineral oil (62%, 0.5 g) at −5 to −0 °C. After stirring for 1 h, the mixture was quenched with AcOH (1 mL) and evaporated under reduced pressure. To the residue was added water (50 mL) and AcOEt (50 mL) and the organic layer separated, dried over $MgSO_4$, evaporated under reduced pressure, and purified by column chromatography (SiO_2 60 mL) to give (2*S*,4*S*)-1-allyloxycarbonyl-2-allyloxycarbonylmethoxymethyl-4-mercapto pyrrolidine (2.29 g). **18a** was prepared from **17** and this 4-mercapto derivative by using the same procedure as described for **18j**. Yellow foam (1.36 g, 23%); IR ($CHCl_3$) cm^{-1} 1705, 1755; ^1H NMR (90 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 8.1 Hz), 1.37 (3H, d, J = 7.2 Hz), 2.0–2.8 (2H, m), 3.2–4.3 (10H, m), 4.10 (2H, s) 4.6–4.8 (4H, m), 5.23 (2H, s), 5.2–5.5 (4H, m), 5.7–6.2 (2H, m), 7.52 (2H, d, J = 9.0 Hz), 8.22 (2H, d, J = 9.0 Hz).

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-(2-pyrazolylethyl)oxymethylpyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (18n). To a solution of **15n** (2.93 g) in MeCN (29 mL) was added dropwise a solution of NaOMe in MeOH (5.2 N, 1.30 mL) at 0–5 °C and stirred for 5 min. The mixture was quenched by the addition of AcOH (0.386 mL) and stirred for 5 min to give the thiol in solution. To a solution of activated carbapenem (**17**) (5.88 mmol) in MeCN (17 mL) was added the solution of thiol, DMAC (30 mL) and $^iPr_2EtN$ (1.23 mL), and stirred, at 0–5 °C for 6 h. The reaction mixture was quenched with AcOEt (300 mL), washed with brine (150 mL×5) and water (150 mL×3), dried over $MgSO_4$, and evaporated under reduced pressure to give an orange oil. The obtained oil was purified by column chromatography (SiO_2 200 mL, CH_2Cl_2:MeOH (30:1) elution) to give **18n** (1.39 g, 42%) as an orange oil. ^1H NMR (200 MHz, $CDCl_3$) 1.26 (3H, d, J = 7.2 Hz), 1.36 (3H, d, J = 6.2 Hz), 1.90–2.50 (2H, m), 3.12–4.30 (13H, m), 4.58 (2H, d, J = 4.6 Hz), 4.70 (1H, dd, J = 5.5 Hz, 13.5 Hz), 4.83 (1H, dd, J = 5.4 Hz, 13.5 Hz), 5.20–5.49 (5H, m), 5.85–6.05 (2H, m), 6.24 (1H, brs), 7.43–7.51 (2H, m); MS m/z 561 $(MH)^+$.

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-(2-imidazolylethyl)oxymethylpyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (18m). **18m** was obtained from **15m** by the same method as described for **18n**. Orange oil (36%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, d, J = 7.2 Hz), 1.37 (3H, d, J = 6.3

Hz), 1.80–2.50 (2H, m), 3.18–4.30 (14H, m), 4.58 (2H, d, J = 5.4 Hz), 4.69 (1H, dd, J = 5.5 Hz, 13.0 Hz), 4.82 (1H, dd, J = 5.4 Hz, 13.0 Hz), 5.20–5.49 (4H, m), 5.82–6.05 (2H, m), 6.96 (1H, s), 7.05 (1H, s), 7.51 (1H, s); MS m/z 561 $(MH)^+$.

Preparation of final carbapenem antibacterial agents

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(Carboxymethoxymethyl)-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19a). To a solution of **18a** (1.33 g), sodium 2-ethylhexanoate (0.75 g), and triphenylphosphine (0.21 g) in THF (60 mL) was added tetrakistriphenylphosphinepalladium(0) (0.25 g) and the resulting mixture stirred at room temperature for 1h. To this mixture was then added 0.3 M acetic acid buffer (pH=5.8) (60 mL), 20% $Pd(OH)_2$ on carbon (0.5 g), and the mixture stirred at room temperature under an atmosphere of hydrogen (1 atm) for 6 h. The mixture was then filtered and evaporated. The residual aqueous solution was washed with AcOEt (60 mL×3), evaporated again to remove organic solvent, adjusted pH (6.0), and purified by column chromatography (HP-20, 60 mL, Me_2CO:water (2:98) elution). The product-containing eluate (pH = 6.0) was lyophilized to give **19a** (0.37 g, 46%) as a white, amorphous, hygroscopic solid. Mp 175 °C (decomp.); IR (KBr) cm^{-1} 1740; ^1H NMR (90 MHz, D_2O) δ 1.20 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.5–2.0 (1H, m), 2.3 –2.9 (1H, m), 3.2–4.3 (12H, m); FAB-MS m/z 423 $(M+Na)^+$, 401 $(MH)^+$.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(Carbamoyl)methoxymethyl-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19b). To a solution of **18b** (0.73 g) in a mixture of THF (40 mL) and 0.1 M phosphate buffer solution (pH=6.5) (40 mL) was added 20% $Pd(OH)_2$–C (0.2 g) and the mixture stirred vigorously at room temperature under an atmosphere of hydrogen (1 atm) for 4 h. The mixture was filtered and evaporated. The residual aqueous solution was washed with AcOEt (40 mL×2), evaporated again to remove organic solvent and purified by column chromatography (HP-20, 40 mL, Me_2CO:water (5:95) elution). The eluate was lyophilized to give **19b** (0.33 g, 81%) as a white, amorphous, hygroscopic solid. Mp 165 °C (decomp.); IR (KBr) cm^{-1} 1670, 1730–1750; ^1H NMR (90 MHz, D_2O) δ 1.20 (3H, d, J = 7.2 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.5–2.0 (1H, m), 2.5–2.9 (1H, m), 4.12 (2H, s), 3.2–4.3 (10H, m); EI-MS m/z 185, 400 $(M)^+$; anal. calcd for $C_{17}H_{25}N_3O_6S{\cdot}3.4H_2O$: C, 44.32%; H, 6.96%; N, 9.12%. Found: C, 44.00%; H, 6.65%; N, 8.91%.

Compounds (**19c–f**) were also prepared as described for **19b** from the appropriate starting materials.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(*N*-Methylcarbamoyl)-methoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19c). (61%): Mp 150 °C (decomp.); IR (KBr) cm^{-1} 1720–1760; ^1H NMR (200 MHz, D_2O) δ 1.23 (3H, d, J = 7.2 Hz), 1.30 (3H, d, J = 6.4 Hz), 1.72–1.87 (1H, m), 2.64–2.80 (1H, m), 2.80 (3H, s), 3.34–3.50 (3H, m), 3.66–4.06 (5H, m), 4.13 (2H, s), 4.21–4.29 (2H, m); FAB-MS m/z 173, 414 $(MH)^+$; anal. calcd for $C_{18}H_{27}N_3O_6S{\cdot}2H_2O$: C, 48.10%; H, 6.95%; N, 9.35%. Found: C, 48.25%; H, 6.99%; N, 9.16%.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(*N*,*N*-Dimethylcarbamoyl)-methoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19d). (72%): Mp 150 °C (decomp.); IR (KBr) cm^{-1} 1730–1750; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.4 Hz), 1.71–1.86 (1H, m), 2.60–2.75 (1H, m), 2.93 and 2.95 (total 6H, each s), 3.33–3.47 (3H, m), 3.67–4.27 (7H, m), 4.39 (2H, s); FAB-MS m/z 187, 428 $(MH)^+$; Anal. calcd for $C_{19}H_{29}N_3O_6S{\cdot}1.8H_2O$: C, 49.62%; H, 7.14%; N, 9.14%. Found: C, 49.61%; H, 7.20%; N, 9.02%.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(1-Carbamoyl-1-methyl)-ethoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19e). (62%): Mp 175 °C (decomp.); IR (KBr) cm^{-1} 1730–1750; ^1H NMR (90 MHz, D_2O) δ 1.20 (3H, d, J = 8.1 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.43 (6H, s), 1.5–2.0 (1H, m), 2.5–2.9 (1H, m), 3.3–4.3 (10H, m); EI-MS m/z 185, 428 $(M)^+$.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(2-Hydroxyethoxymethyl)-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19f). (38%): Mp 170–175 °C; IR (KBr) cm^{-1} 1730–1760; ^1H NMR (90 MHz, D_2O) δ 1.21 (3H, d, J = 8.1 Hz), 1.28 (3H, d, J = 5.4 Hz), 1.5–2.0 (1H, m), 2.5–2.9 (1H, m), 3.2–4.3 (14H, m).

The following compounds (**19g–i**) were obtained as the acetate salts by addition of acetic acid before lyophilization.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(2-Aminoethoxymethyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19g). (51%): IR (KBr) cm^{-1} 1730–1760; ^1H NMR (90 MHz, D_2O) δ 1.20 (3H, d, J = 6.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 1.6–2.0 (1H, m), 1.92 (3H, s), 2.5–2.9 (1H, m), 3.2–3.4 (14H, m); APCI-MS m/z 304 $(MH)^+$.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-(*N*-Methylamino)ethoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate (19h). (13%): Mp 80 °C (decomp.); IR (KBr) cm^{-1} 1735–1755; ^1H NMR (90 MHz, D_2O) δ 1.22 (3H, d, J = 8.1 Hz), 1.29 (3H, d, J = 5.4 Hz), 1.6–2.0 (1H, m), 1.92 (3H, s), 2.4–2.9 (1H, m), 2.77 (3H, s), 3.3–4.3 (14H, m); FAB-MS m/z 400 $(MH–AcOH)^+$.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-(*N*,*N*-Dimethylamino)-ethoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate (19i). (15%): Mp 90 °C (decomp.); IR (KBr) cm^{-1} 1720; ^1H NMR (90 MHz, D_2O) δ 1.27 (3H, d, *J* = 4.5 Hz), 1.33 (3H, d, *J* = 6.3 Hz), 1.5–1.9 (1H, m), 1.97 (3H, s), 2.3–2.9 (1H, m), 2.94 (6H, s), 3.0–4.3 (14H, m); FAB-MS *m/z* 414 $(MH-AcOH)^+$.

(4*R*,5*S*,6*S*)-3-[(2S,4*S*)-2-(2-Fluoroethyloxymethyl)-pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19j). To a solution of **18j** (2.35 g), morpholine (0.84 mL), and triphenylphosphine (0.24 g) in a mixture of water (3 mL), EtOH (12 mL) and THF (35 mL) was added tetrakistriphenylphosphinepalladium(0) (0.32 g) at room temperature and the mixture stirred for 2 h to give a precipitate. This precipitate was filtered, washed with THF and dried under reduced pressure to give **19j** (0.67 g, 38%) as a white, amorphous, hygroscopic solid. Mp 155 °C (decomp.); IR (KBr) cm^{-1} 1735, 1760; ^1H NMR (200 MHz, D_2O) δ 1.23 (3H, d, *J* = 7.2 Hz), 1.30 (3H, d, *J* = 6.4 Hz), 1.71–1.85 (1H, m), 2.63–2.79 (1H, m), 3.35–3.49 (3H, m), 3.66–4.04 (7H, m), 4.21–4.27 (2H, m), 4.52–4.79 (2H, m); APCI-MS *m/z* 377, 389 $(MH)^+$; anal. calcd for $C_{17}H_{25}FN_2O_5S \cdot 1.7H_2O$: C, 48.72%; H, 6.83%; N, 6.68%. Found: C, 48.67%; H, 6.84%; N, 6.66%.

Using dimedone as the allyl trapping reagent instead of morpholine and purifying the compounds by using HP-20 as a column medium, the following compounds **19k–l**, **19o** were prepared as described for **19j** from the appropriate starting material.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[[(2*RS*)-2-Fluoropropoxy]-methyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid (19k). (100%): IR (Nujol) cm^{-1} 1755; ^1H NMR (90 MHz, D_2O) δ 1.05 (d, *J* = 6.3 Hz), 1.49 (d, *J* = 6.3 Hz), total 3H, 1.21 (3H, d, *J* = 5.4 Hz), 1.32 (3H, d, *J* = 6.3 Hz), 1.5–1.9 (1H, m), 2.4–3.0 (1H, m), 3.2–5.0 (13H, m); FAB-MS *m/z* 160, 194, 403 $(MH)^+$.

(4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-3-[(2*S*,4*S*)-2-[(2-ureidoethoxy)methyl]pyrrolidine-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19l). (75%): IR (Nujol) cm^{-1} 1755; ^1H NMR (200 MHz, D_2O) δ 1.22 (3H, d, *J* = 7.2 Hz), 1.29 (3H, d, *J* = 6.4 Hz), 1.73–1.87 (1H, m), 2.62–2.77 (1H, m), 3.30–4.02 (12H, m), 4.20–4.28 (2H, m); APCI-MS *m/z* 417, 429 $(MH)^+$; anal. calcd for $C_{18}H_{28}N_4O_6S \cdot 2.4H_2O$: C, 45.83%; H, 7.01%; N, 11.88%. Found: C, 45.81%; H, 6.94%; N, 11.84%.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[(4-Fluorobutan-1-yl)oxy-methyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19o). (31%): IR (Nujol) cm^{-1} 1750; ^1H NMR (90 MHz, D_2O) δ 1.24 (3H, d, *J* = 8.1 Hz), 1.31 (3H, d, *J* = 5.4 Hz), 1.5–2.0 (5H, m), 2.4–2.9 (1H, m), 3.3–5.0 (14H, m); APCI-MS *m/z* 405, 417 $(MH)^+$; anal. calcd for $C_{19}H_{29}FN_2O_5S \cdot 2.2H_2O$: C, 50.03%; H, 7.38%; N, 6.14%. Found: C, 50.05%; H, 7.14%; N, 6.05%.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-(3-Methylimidazolio)-ethoxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride (19m). To a solution of **18m** (1.507 g) in CH_2Cl_2 (15 mL) was added dropwise methyltrifluoromethanesulfonate (485 mg) at 0 °C, then stirred for 10 min, and evaporated under reduced pressure to give the crude salt as an amorphous powder. To a solution of this salt in a mixture of THF:EtOH (1:1) (15 mL) was added triphenylphosphine (282 mg), morpholine (0.59 mL), and tetrakistriphenylphosphinepalladium(0) (124 mg) at room temperature, and the mixture stirred for 1 h. The obtained mixture was diluted by AcOEt and extracted with water (×2). The aqueous layer was washed with CH_2Cl_2 (×3), evaporated, and adjusted to pH 6.0. The obtained solution was loaded onto a SP column (140 mL), washed with water, then eluted with Me_2CO:water (5:95). The combined product-containing fractions were evaporated to ~150 mL of solution, then adjusted to pH ~4.2, passed through a short column of Amberlyst A-26 (10 mL), evaporated to ~100 mL, and lyophilized. The obtained powder was purified by ODS column (50 mL) (1–5% MeCN in phosphate buffer (pH=7.0) elution). The combined product-containing fractions were evaporated to remove MeCN, then re-loaded onto the ODS column (50 mL), washed with water (10 resins), and eluted with MeCN:water (6:4). The eluate was evaporated, passed through an Amberlyst A-26 column (5 mL), and lyophilized to give **19m** (163 mg, 12%) as a white powder: IR (KBr) cm^{-1} 1755; ^1H NMR (200 MHz, D_2O) δ 1.21 (3H, d, *J* = 7.2 Hz), 1.28 (3H, d, *J* = 6.4 Hz), 1.60–1.74 (1H, m), 2.58–2.74 (1H, m), 3.28–3.49 (3H, m), 3.60–4.05 (7H, m), 3.89 (3H, s), 4.20–4.28 (2H, m), 4.42–4.47 (2H, m), 7.46 (1H, d, *J* = 1.8 Hz), 7.55 (1H, d, *J* = 1.8 Hz), 8.81 (1H, s); FAB-MS *m/z* 308, 451 $(M-Cl)^+$; Anal. calcd for $C_{21}H_{31}ClN_4O_5S \cdot 4.0H_2O$: C, 45.12%; H, 7.03%; N, 10.02%. Found: C, 45.01%; H, 6.96%; N, 9.97%.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-[2-(3-Methylpyrazolio)ethyl-oxymethyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid chloride (19n). **19n** was obtained from **18n** by the same method as described for **19m**. White powder (2.7%); ^1H NMR (200 MHz, D_2O) δ 1.22 (3H, d, *J* = 7.2 Hz), 1.30 (3H, d, *J* = 6.4 Hz), 1.65–1.80 (1H, m), 2.65–2.75 (1H, m), 3.20–3.55 (3H, m), 3.20–4.05 (7H, m), 4.17 (3H, s), 4.20–4.30 (2H, m), 4.71–4.82 (2H, m), 6.80 (1H, t, *J* = 3.0 Hz), 8.21 (1H, d, *J* = 3.0 Hz), 8.31 (1H, d, *J* = 3.0 Hz); FAB-MS *m/z* 451 $(M-Cl)^+$.

Preparation of chloroethoxy derivative

(2*S*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-(2-hydroxyethoxymethyl)pyrrolidine (20). **20** was prepared from **14a** by the same method as described for **15j**. Yellow oil (41%); IR (neat) cm^{-1} 1670–1690; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80–2.08 (1H, m), 2.34 (3H, s), 2.40–2.70 (1H, m), 3.20 (1H, dd, J = 7.2 Hz, 11.1 Hz), 3.56–3.80 (6H, m), 3.84–4.00 (1H, m), 4.05–4.22 (2H, m) 4.59 (2H, d, J = 5.5 Hz), 5.20–5.36 (2H, m), 5.84–6.03 (1H, m); APCI-MS m/z 304 $(MH)^+$.

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-(2-hydroxyethoxymethyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (22a). **22a** was prepared from **20** and silyl protected carbapenem **21** by the same method as described for **18k**. Yellow oil (8.8 g, 43%); IR (neat) cm^{-1} 1680, 1700–1710, 1765–1780; ^1H NMR (200 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.80 (9H, s), 1.14–1.21 (6H, m), 1.82–2.00 (1H, m), 2.30–2.60 (1H, m), 3.05–3.27 (2H, m), 3.47–3.63 (6H, m), 3.80–4.19 (4H, m), 4.50–4.82 (4H, m), 5.12–5.40 (4H, m), 5.76–6.00 (2H, m); FAB-MS m/z 625 $(MH)^+$.

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(2-chloroethoxy)methyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (22b). A solution of **22a** (4.5 g) and triphenylphosphine (3.78 g) in CCl_4 (90 mL) was stirred under reflux for 14 h. After the insoluble precipitate was filtered off, the filtrate was evaporated under reduced pressure and purified by column chromatography (SiO_2 180 mL, hexane:AcOEt (4:1) elution) to give **22b** (2.42 g, 52%) as a yellow oil. IR (neat) cm^{-1} 1690–1710, 1770; ^1H NMR (90 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.91 (9H, s), 1.2–1.3 (6H, m), 1.8–2.2 (1H, m), 2.3–2.6 (1H, m), 3.2–4.2 (14H, m), 4.56 (2H, d, J = 5.4 Hz), 4.7–4.8 (2H, m), 5.1–5.5 (4H, m), 5.7–6.1 (2H, m); FAB-MS m/z 643 $(MH)^+$.

Allyl (4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-1-allyloxycarbonyl-2-[(2-chloroethoxy)methyl]pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (23). To a solution of **22b** (0.72 g) and AcOH (0.65 mL) in THF (7.2 mL) was added tetrabutylammonium fluoride (5.6 mL, 1 M solution in THF) and the solution was stirred at room temperature for 10 h. The obtained solution was diluted with AcOEt (50 mL), washed with water (50 mL×3), dried over $MgSO_4$, and purified by column chromatography (SiO_2 20 mL, hexane:AcOEt (4:1) elution) to give **23** (0.3 g, 51%) as an oil. IR (neat) cm^{-1} 1680–1710, 1770; ^1H NMR (90 MHz, $CDCl_3$) δ 1.28 (3H, d, J = 7.2 Hz), 1.38 (3H, d, J = 6.3 Hz) 1.8–2.7 (2H, m), 3.2–4.3 (14H, m), 4.58 (2H, d, J = 5.4 Hz), 4.7–4.8 (2H, m), 5.2–5.5 (4H, m), 5.7–6.2 (2H, m); FAB-MS m/z 529 $(MH)^+$.

(4*R*,5*S*,6*S*)-3-[(2*S*,4*S*)-2-(2-Chloroethoxymethyl)pyrrolidine-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (19p). **19p** was obtained from **23** by the same method as described for **19j** using dimedone as a trapping agent. Brown, amorphous, hygroscopic solid (26%); Mp 170 °C (decomp.); IR (Nujol) cm^{-1} 1720–1760; ^1H NMR (90 MHz, D_2O) δ 1.25 (3H, d, J = 7.2 Hz), 1.33 (3H, d, J = 6.3 Hz), 1.6–2.0 (1H, m), 2.5–2.9 (1H, m), 3.3–4.3 (14H, m); FAB-MS m/z 303, 405 $(MH)^+$.

Measurement of in vitro antibacterial activity

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

Stability to DHP-I

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

Efficacy in lethal systemic infection

Strains were intraperitoneally inoculated in groups of eight male ICR mice aged 4 wks with 0.5 mL of bacterial suspension in 5% gastric mucin, given at one to five 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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