Synthesis and Antibacterial Activity of 1-Substituted-methyl Carbapenems

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The synthesis of the 1α- and the 1β-substituted (fluoro, cyano, hydroxy and acetoxy)-methyl carbapenems having a 2-(1,3,4-thiadiazol-2-yl)thiomethyl side chain are described, and their *in vitro* antibacterial activities are compared with the corresponding 1β-methyl carbapenems together with imipenem. The synthesis and antibacterial activity of the 1β-substituted (fluoro and cyano)-methyl carbapenems having 2-(1-alkyl-4-pyridinio)thiomethyl side chains are also described.

Keywords β-lactam antibiotic; carbapenem antibiotic; 1α-substituted-methyl carbapenem; 1β-substituted-methyl carbapenem; 1-fluoromethyl carbapenem; 1-cyanomethyl carbapenem; 1-hydroxymethyl carbapenem; 1-acetoxymethyl carbapenem; antibacterial activity; methicillin-resistant *S. aureus* (MRSA)

The 1β-methyl carbapenems represented by L-646591 (**1**),[1] SM-7338 (**2**)[2] are of recent chemical and therapeutic interest in the field of β-lactam antibiotics because of the intriguing carbapenem skeleton as well as their enhanced chemical and metabolic stability with high antibacterial potency.[1] Since the first report on 1β-methyl carbapenems by a Merck group,[1] a considerable number of carbapenems containing a substituent(s) at the 1-position other than 1β-methyl group have been prepared so far.[1,3] However, substitution of the 1β-methyl group by a larger alkyl group than methyl[1b,3a] or by a substituent(s) other than alkyl group such as hydroxy,[1b] methoxy,[1b,3b] acetoxy,[3c] fluorine[3d] often resulted in reduced antibacterial activity or chemical instability.

These results seemed to indicate to us that the introduction of an appropriate substituted-methyl group at the 1β-position of the carbapenem nucleus might result in enhanced antibacterial activity and biological properties compared to the corresponding 1β-methyl carbapenem.

Since fluorine can be substituted for hydrogen with only minimal steric, but with considerable electronic effect, we reasoned that carbapenem derivatives having the 1β-fluoromethyl group might possess interesting biological properties.[4] In addition, 1β-cyanomethyl carbapenems were expected to have similar chemical and biological properties to the corresponding 1β-fluoromethyl carbapenems.

We were also interested in the difference of antibacterial activity between the 1β-fluoromethyl and the 1β-hydroxymethyl carbapenem derivatives, because there is a close physicochemical similarity between hydroxyl and fluorine.[4]

Preparation of the 1β-acetoxymethyl carbapenems was also planned, because an acetoxymethyl group has a similar electron-withdrawing effect to a fluoromethyl group and has a relatively large steric volume.

As for the substituents at the 2-position for the 1β-substituted-methyl carbapenems mentioned above, we planned to introduce a novel C-2 side chain which was expected to contribute to potent antibacterial activity. Very recently, the 1β-methyl carbapenems having (heteroaromatic)thiomethyl and (quaternary heteroaromatic)thiomethyl groups at the 2-position represented by **3**, **4**, and **5** were prepared in these laboratories, and showed potent and well-balanced antibacterial activity.[5] Therefore, we decided to synthesize the 1β-substituted (fluoro, cyano, hydroxy and acetoxy)-methyl carbapenems (**6**—**8**) having (1,3,4-thiadiazol-2-yl)thiomethyl and (1-alkyl-4-pyridinio)thiomethyl groups at the 2-position. Direct comparison of the antibacterial activities of these 1β-substituted-methyl carbapenems (**6**—**8**) with the corresponding 1β-methyl analogs (**3**—**5**) prepared in these laboratories is beneficial for the exact evaluation of these new 1β-substituted-methyl carbapenems.

On the other hand, it is now well recognized that 1β-methyl carbapenems showed higher antibacterial activity and metabolic stability than the corresponding 1α-counterparts.[1b,5a] Some 1α-methyl carbapenem derivatives, however, showed more favorable biological property than the corresponding 1β-methyl counterparts.[6] Taking these results into consideration, we decided to prepare both the

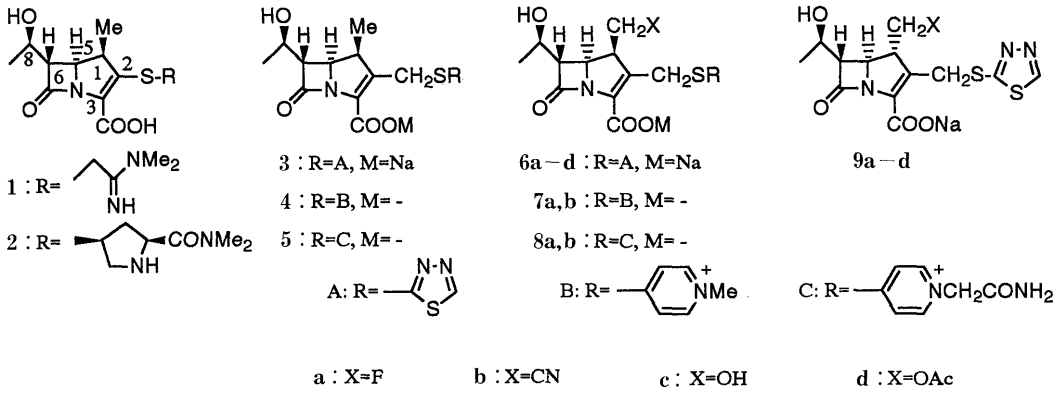

Chart 1

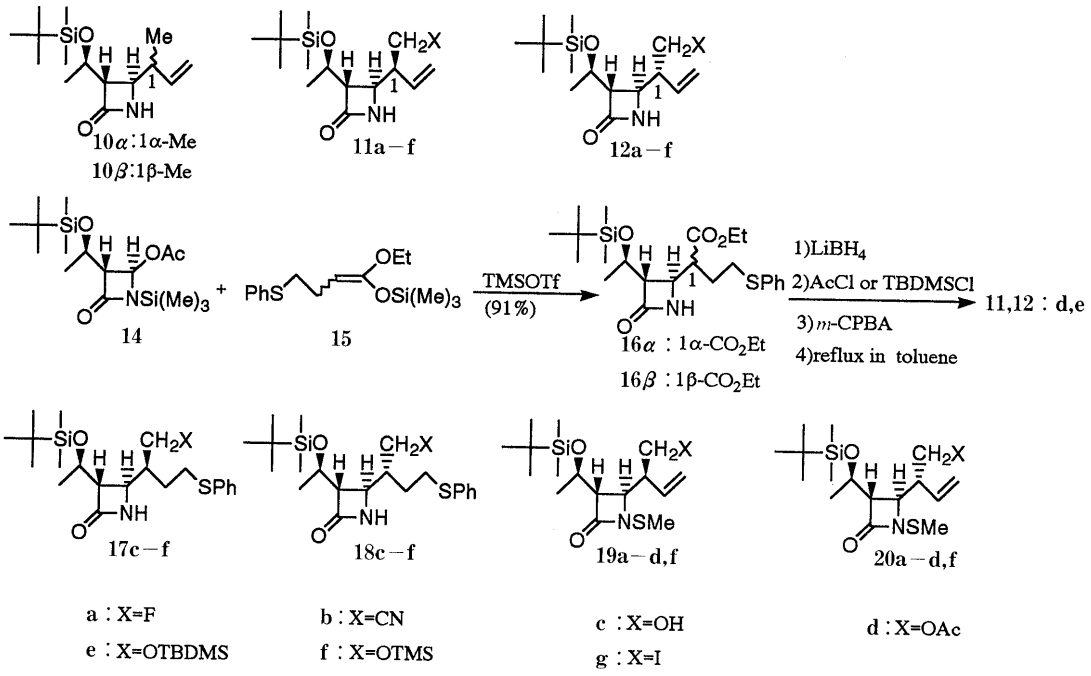

Chart 2

1α- and the 1β-substituted-methyl derivatives (**6**—**9**).

Here we report the synthesis and antibacterial activity of the 1α- and the 1β-substituted (fluoro, cyano, hydroxy and acetoxy)-methyl-2-(1,3,4-thiadiazol-2-yl)thiomethyl carbapenem derivatives (**9a**—**d**, **6a**—**d**) and the 1β-substituted (cyano and fluoro)-methyl-2-(1-alkyl-4-pyridinio)thiomethyl carbapenem derivatives (**7**, **8**; **a**, **b**).

Chemistry Earlier work by the Shionogi group in the synthesis of the 1β-methyl carbapenems (**3**—**5**),[5] in which the 1β-methyl olefin (**10β**; carbapenem structure numbering) was the key intermediate, had led us to believe that the 1-substituted-methyl olefins (**11**, **12**; **a**, **b**, **d**, **e**) would be transformed into the desired 1-substituted-methyl carbapenems (**6**—**9**; **a**—**d**). Consequently, our initial target compounds were the 1-hydroxymethyl olefins (**11c**, **12c**) considered to be derived from the ester sulfides (**16β**, **16α**), respectively.

Thus, ethyl 4-phenylthiobutyrate was converted to its silyl ketene acetal (**15**) using the standard procedure (lithium diisopropylamide (LDA)–trimethylchlorosilane (TMSCl)), which was then subjected to condensation with the azetidinone (**14**) in the presence of trimethylsilyl triflate[7] to give the diastereoisomeric mixture of the ester sulfides (**16α** and **16β**, 3:4) in 91% yield (Chart 2). The diastereoisomeric ester sulfides, thus prepared, were separated by silica gel column chromatography, and subsequent conversions to the corresponding 1-hydroxymethyl olefins (**12c**, **11c**) were carried out independently.

Reduction of more polar ester sulfide (**16α**)with lithium borohydride gave the hydroxymethyl sulfide (**18c**) whose hydroxy group was protected by acetyl, *tert*-butyldimethylsilyl (TBDMS) and trimethylsilyl (TMS) groups using conventional conditions to give the corresponding protected alcohols (**18d**—**f**), respectively. Compounds **18d** and **18e** were then subjected to an oxidation–elimination procedure as described below. Treatment of the protected alcohols (**18d**, **e**) with *m*-chloroperbenzoic acid (*m*-CPBA) gave the corresponding sulfoxides, which were then refluxed in toluene to give the protected hydroxymethyl olefins (**12d**, **e**), respectively (Chart 2). Removal of the protecting group of the acetate (**12d**) by the conventional method gave the desired hydroxymethyl olefin (**12c**), and the absolute configuration at C-1 of this olefin was determined unequivocally to be (*R*) by leading to the authentic 1α-methyl olefin (**10α**), prepared in these laboratories,[5] through the following sequence. Conversion of the hydroxymethyl olefin (**12c**) to the corresponding iodide (**12g**) by a conventional procedure (1. $MsCl$–Et_3N, 2. NaI in hexamethylphosphoramide (HMPA), 78%), and subsequent reduction of this iodide (**12g**) with sodium cyanoborohydride in HMPA[8] gave the 1-methyl olefin (**10α**) (Chart 3) whose spectroscopic data and physical properties were in complete agreement with that obtained from the authentic 1α-methyl olefin.[5]

The 1α-cyanomethyl olefin (**12b**) was prepared from the 1α-hydroxymethyl olefin (**12c**) by the conventional two steps procedure (1. $MsCl$–Et_3N, 2. NaCN–tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in HMPA, 88%).

Attempted fluorinations of the hydroxymethyl derivatives (**18c**, **12c**) using diethylamino sulfurtrifluoride (DAST)[9] failed, giving complex mixtures. At this point, it became necessary to protect the azetidinone nitrogen of **18c** and **12c** by a group stable to the fluorination condition. Thus, the sulfenamide protecting group, successfully applied to protect an azetidinone nitrogen by Merck chemists,[3d] was introduced to the acetoxymethyl olefin (**12d**) according to the literature method. Treatment of **12d** with LDA and methyl methanethiosulfonate gave the sulfenamide (**20d**) in 95% yield, and subsequent saponification of its acetoxy group yielded the required *N*-methylthio hydroxymethyl olefin (**20c**) quantitatively. Direct fluorination of **20c** using DAST gave the desired fluoromethyl olefin (**20a**), albeit in low yield.

Since DAST-fluorination of a trimethylsilylated-hydroxy

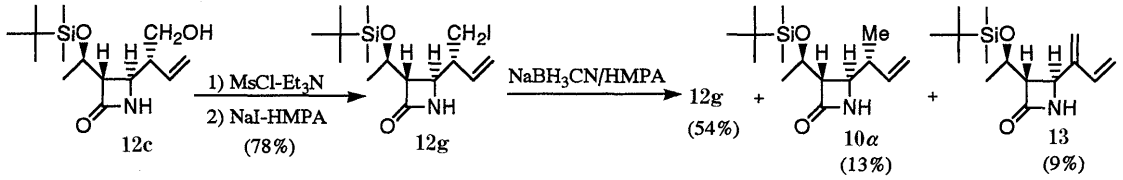

Chart 3

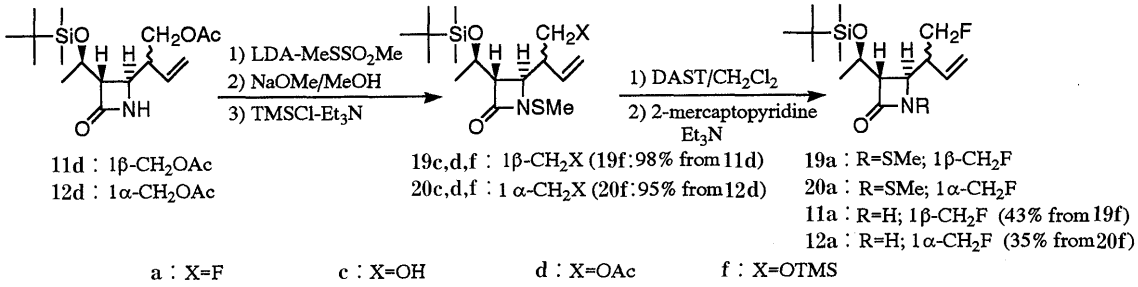

Chart 4

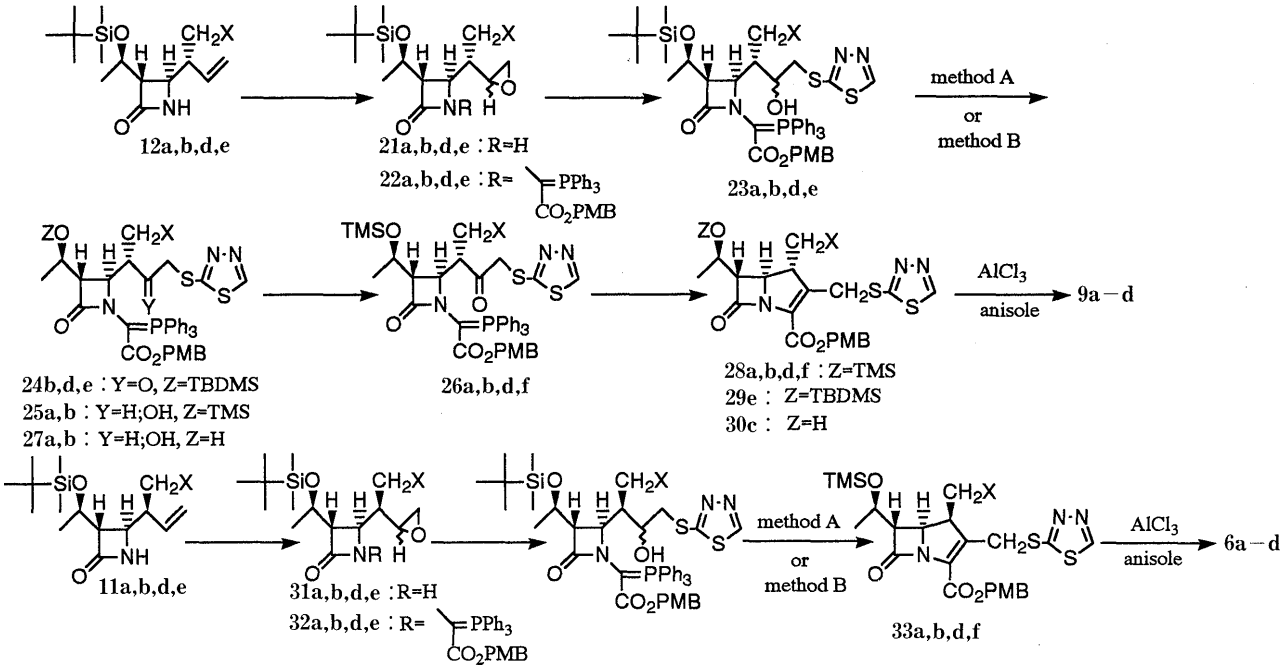

Chart 5

group proceeds much more cleanly than that of the corresponding hydroxy group in some cases,[10] we next tried DAST-fluorination of the trimethylsilyloxy olefin (**20f**). As we expected, DAST-fluorination of **20f**, prepared from **20c** in quantitative yield, gave a much more satisfactory result compared to that of the corresponding hydroxy olefin (**20c**). Deprotection of the sulfenamide group of **20a** by the literature method (2-mercaptopyridine–Et_3N)[3d] gave the desired fluoromethyl olefin (**12a**) in a 33% overall yield from the corresponding acetoxymethyl olefin (**12d**) (Chart 4).

Four 1β-isomers (**11a, b, d, e**) corresponding to the above 1α-methyl olefin (**12a, b, d, e**) were prepared from the (1*S*)-ester sulfide (**16β**) using the same reaction sequences as described above. DAST fluorination of the 1β-trimethylsily ether (**19f**) afforded a more satisfactory result (42% overall yield from **11d**) compared to that of the corresponding 1α-isomer (Chart 4).

With desired key intermediates (**11, 12; a, b, d, e**) in hand, our attention was next focused on the preparation of the title carbapenems (**6, 9**). Treatment of 1α-substituted-methyl olefins (**12a, b, d, e**) with *m*-CPBA gave the diastereoisomeric epoxides (**21a, b, d, e**), respectively, which were subsequently converted into the corresponding phosphoranes (**22a, b, d, e**) by the well established procedure developed by Woodward[11] (Chart 5). The base-catalyzed epoxy ring cleavage

of the epoxy phosphorane (**22e**) with the lithium salt of 2-mercapto-1,3,4-thiadiazole gave the carbinol mixture (**23e**), and subsequent oxidation of the resulting carbinol mixture afforded the keto phosphorane (**24e**). Although intramolecular Wittig cyclization of **24e** in refluxing benzene gave the carbapenem (**29e**) in good yield, deprotection of the TBDMS group of **29e** by tetrabutylammonium fluoride accompanied with β-lactam ring cleavage to give the desired diol (**30c**) only in a poor yield. Consequently, replacement of the TBDMS groups of the keto phosphorane (**24e**) to more easily cleavable TMS groups (**26f**) was carried out by the conventional method (1. AcOH–HCl, 2. TMSCl–Et_3N) prior to construction of the carbapenem skeleton. The keto phosphorane (**26f**), thus prepared, was subjected to intramolecular Wittig cyclization to give the desired 1α-trimethylsilyloxymethyl carbapenem (**28f**) (method A in Chart 5).

The 1β-isomer (**33f**) corresponding to **28f**, and the 1α- and the 1β-acetoxymethyl carbapenems (**28d, 33d**) were prepared by the same reaction sequence as described above, starting from the epoxy phosphoranes (**32e**, **22d**, and **32d**), respectively (method A in Chart 5).

An attempted preparation of the 1α-cyanomethyl carbapenem (**28b**) from the corresponding carbinol mixture (**23b**) using the same reaction sequence as described above failed, because oxidation of **23b** accompanied intramolecular Wittig cyclization of the oxidation product (**24b**) before replacing the TBDMS group.

Accordingly, an alternate route for the preparation of the carbapenem (**28b**) was examined. Treatment of the diol (**27b**) with trimethylchlorosilane and a hindered base gave the mono-TMS-protected carbinol (**25b**) selectively, which was subsequently oxidized to give a mixture of the keto phosphorane (**26b**) and the cyclized carbapenem (**28b**). Cyclization of the remaining **26b** in this mixture was smoothly accomplished in refluxing benzene (method B in Chart 5).

The 1β-cyanomethyl carbapenem (**33b**), and the 1α- and the 1β-fluoromethyl carbapenems (**28a, 33a**) were prepared successfully using the same reaction sequence as described above (method B in Chart 5).

The intramolecular Wittig cyclization of the keto phosphorane (**26a, b, d, f**) having the 1α-substituted-methyl groups required much lower temperature or shorter reaction time than that of the corresponding 1β-counterparts, irrespective of the substituents at the 1-position, as observed in the case of the 1β-methyl carbapenems.[5]

The final deprotection step of the carbapenems (**28, 33**; **a, b, d, f**) were accomplished by treatment with $AlCl_3$ in the presence of anisole[12] to give the deprotected carbapenems, which were purified through Diaion HP-20 as their sodium salts (**9, 6**; **a—d**), respectively.

Encouraged by the activity of the 1β-fluoromethyl and the 1β-cyanomethyl carbapenems (**6a, b**) as shown in Table I, the modifications were extended to the substituent at the 2-poisiton. As described previously, it has shown that the 1β-methyl carbapenems bearing (quaternary heteroaromatic)thiomethyl groups at the 2-position such as **4** and **5** resulted in enhanced activity against both gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa* compared to the corresponding 2-thiadiazolylthiomethyl derivative (**3**). We therefore became interested in the synthesis of the 2-(quaternary pyridinium)thiomethyl carbapenem derivatives (**7, 8**; **a, b**) having the 1β-fluoromethyl and the 1β-cyanomethyl substituents to enhance the activity of the corresponding 2-thiadiazolylthiomethyl derivatives (**6a, b**) against gram-positive bacteria and *P. aeruginosa*.

The epoxy phosphoranes (**32a, b**) were converted to the 2-(4-pyridyl)thiomethyl carbapenems (**34a, b**), which were quaternized by the alkyl iodides (iodomethane and iodo acetamide) at the pyridine nitrogen to give the corresponding quaternary pyridinium derivatives (**35, 36**; **a, b**) in good yields (Chart 6).

The final deprotection step was carried out by the conventional $AlCl_3$–anisole method[12] to give the desired 2-(quaternized pyridinium)thiomethyl carbapenems (**7, 8**; **a, b**).

***In Vitro* Antibacterial Activity** The antibacterial activities (the minimum inhibitory concentration [MIC] values) of the 1α-substituted-methyl-2-(1,3,4-thiadiazol-2-yl)thiomethyl carbapenem derivatives (**9a—d**) and the corresponding 1β-counterparts (**6a—d**), together with the corresponding 1β-methyl analog (**3**) against selected strains of gram-positive and gram-negative bacteria, are given in Table I. As we expected, the 1β-substituted-methyl isomers (**6a—d**) are much more active against both gram-positive and gram-negative bacteria than the corresponding 1α-counterparts (**9a—d**) except for the 1β-hydroxymethyl derivative (**6c**) whose activity against some gram-negative bacteria are weaker than that of the corresponding 1α-counterpart (**9c**).

Among the 1β-substituted-methyl derivatives (**6a—d**), the fluoro and the cyano derivatives (**6a, b**) showed much higher activity against both gram-positive and gram-negative bacteria than the other derivatives (**6c, d**), and the fluoro derivative (**6a**) possessed the highest activity.

A specific feature of the 1β-fluoromethyl derivative (**6a**) is that it possesses a good activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. faecalis* which are recognized as recently increasing pathogens. Although the fluoro derivative (**6a**) is less active against

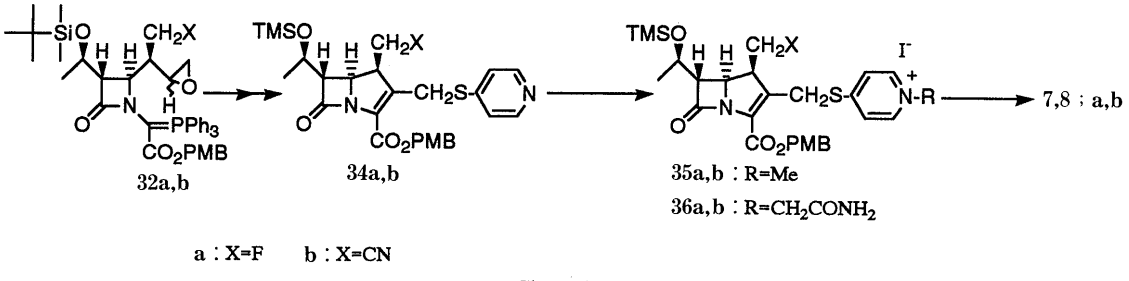

Chart 6

TABLE I. *In Vitro* Antibacterial Activities of Carbapenems (**6a—d**, **9a—d**). MIC (μg/ml)

Compound No.	*S.aureus* FDA JC-1	*S. aureus* SR3131(L)[a]	*S. aureus* SR3626(H)[b]	*E. faecalis* SR1004	*E. coli* NIHJ JC-2	*P. vulgaris* CN-329	*E. cloacae* ATCC13047	*S. marcescens* ATCC13880	*P. aeruginosa* SR24
6a	0.02	0.2	6.3	1.6	0.1	0.1	0.2	0.2	6.3
9a	0.4	3.1	100	50	1.6	3.1	12.5	6.3	>100
6b	0.05	0.2	6.3	1.6	0.1	0.2	0.2	0.2	50
9b	0.4	6.3	>100	50	3.1	3.1	12.5	12.5	>100
6c	0.2	0.8	50	6.3	0.1	0.4	12.5	1.6	>100
9c	0.8	6.3	100	100	0.8	3.1	1.6	1.6	100
6d	0.1	0.8	12.5	3.1	6.3	0.8	6.3	12.5	50
9d	0.8	12.5	>100	>100	100	>100	>100	>100	>100
3	0.0125	0.1	3.1	0.8	0.2	0.05	0.4	0.8	12.5
Imipenem	0.006	0.05	50	1.6	0.1	0.4	0.4	0.8	1.6

a) Low-resistance groups of methicillin-resistant *S. aureus*. *b*) High-resistance groups of methicillin-resistant *S. aureus*.

TABLE II. *In Vitro* Antibacterial Activities of Carbapenems (**7**, **8**; **a**, **b**). MIC (μg/ml)

Compound No.	*S.aureus* FDA JC-1	*S. aureus* SR3131(L)[a]	*S. aureus* SR3626(H)[b]	*E. faecalis* SR1004	*E. coli* NIHJ JC-2	*P. vulgaris* CN-329	*E. cloacae* ATCC13047	*S. marcescens* ATCC13880	*P. aeruginosa* SR24
7a	<0.01	0.05	12.5	0.8	0.1	0.4	0.2	0.4	6.3
7b	0.02	0.1	25	1.6	0.4	0.8	0.4	0.8	12.5
4	0.006	0.05	6.3	0.4	0.1	0.2	0.2	0.2	6.3
8a	0.01	0.05	25	0.8	0.1	0.4	0.2	0.4	6.3
8b	0.02	0.1	25	1.6	0.2	0.8	0.4	0.8	12.5
5	0.01	0.1	12.5	0.4	0.1	0.4	0.2	0.4	6.3
Imipenem	0.006	0.05	50	1.6	0.1	0.4	0.4	0.8	1.6

a) Low-resistance groups of methicillin-resistant *S. aureus*. *b*) High-resistance groups of methicillin-resistant *S. aureus*.

methicillin-sensitive *S. aureus* and low-resistance groups of MRSA (L-MRSA)[13] than imipenem, it showed higher activity against high-resistance groups of MRSA (H-MRSA)[13] than imipenem. In addition, the fluoro derivative (**6a**) showed higher activity against gram-negative bacteria than imipenem except for *P. aeruginosa*.

Upon comparison of the fluoro derivative (**6a**) with the corresponding 1β-methyl derivative (**3**), some characteristic features can be drawn. Contrary to our expectations, the fluoro derivative (**6a**) is less active against gram-positive bacteria, but is slightly more active against gram-negative bacteria including *P. aeruginosa* than the corresponding 1β-methyl carbapenem (**3**).

These results encouraged us to further study modification of the C-2 substituents for the selected 1β-substituted (cyano and fluoro)-methyl carbapenems (**6a, b**).

Since the 1β-methyl carbapenems possessing (4-alkyl pyridinio)thiomethyl side chains at the C-2 position (**4**, **5**) exhibited enhanced activity against most of the gram-positive and gram-negative bacteria including *P. aeruginosa* compared to the corresponding 2-(1,3,4-thiadiazol-2-yl)thiomethyl carbapenem (**3**) as described previously, we were interested in the antibacterial activity of the 1β-substituted (fluoro and cyano)-methyl carbapenems (**7**, **8**; **a, b**) having the 2-(4-alkyl pyridinio)thiomethyl side chains to improve the activity of **6a, b** against gram-positive bacteria and *P. aeruginosa*. Thus, the desired 1β-substituted-methyl carbapenems (**7**, **8**; **a, b**) were prepared and their antibacterial activities against selected gram-positive and gram-negative bacteria were tested.

Table II shows the antibacterial activities (MIC values) of **7a, b** and **8a, b**, together with the corresponding 1β-methyl analogs (**4**, **5**). The positive charge in the pyridinium ring at the 2-position of the cyano derivatives (**7b**, **8b**) resulted in enhanced activity against gram-positive bacteria and *P. aeruginosa* except for H-MRSA, while it resulted in decreased activity against gram-negative bacteria other than *P. aeruginosa* compared to **6b**. Similarly, the fluoro derivatives (**7a**, **8a**) showed enhanced activity against gram-positive bacteria except for H-MRSA, and showed reduced activity against some gram-negative bacteria compared to **6a**. Unfortunately, the anti-pseudomonal activity of the fluoro derivative (**7a**), which was the most active compound in these pyridinium derivatives (**7**, **8**; **a, b**), remained unchanged.

Contrary to our expectations, conversion of the thiadiazole ring at the C-2 position of the fluoro derivative (**6a**) to the pyridinium ring (**7a**, **8a**) did not enhance the activity against gram-negative bacteria including *P. aeruginosa*.

Among the 1-substituted-methyl carbapenems prepared in this study, the 1β-fluoromethyl derivative (**6a**) having the thiadiazolylthiomethyl side chain at the 2-position showed the most potent and well-balanced activity as a whole. However, the fluoro derivative (**6a**) showed reduced activity against gram-positive bacteria compared to the 1β-methyl derivative (**4**) having the pyridinium side chain.

Experimental

General Procedures All reactions involving air-sensitive reactants or products were carried out under nitrogen using dry solvents. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi 260-10 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 (90 MHz) or a VXR 200 (200 MHz) spectrometer and are expressed in ppm downfield from tetramethylsilane as an internal (in $CDCl_3$ and in D_2O) or external (in D_2O) standard. In

some cases, 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt (DSS) were used as an internal (in D_2O) standard. Ultraviolet (UV) spectra were measured using a Hitachi EPS-3T spectrometer. Mass spectra (MS) were obtained on a Hitachi M-68 mass spectrometer. Specific optical rotations ($[\alpha]_D$) were taken at 24 °C on a Perkin–Elmer 241 Polarimeter. Medium pressure liquid chromatography was performed with Merck prepacked column (Lobar column).

The 1α-substituted-methyl carbapenems (**9a—d**) were much more unstable than the corresponding 1β-isomers (**6a—d**), and the 1β-substituted-methyl carbapenems (**6—8**) had almost the same stabilities irrespective of the substituents at the 2-position. The stabilities of the 1-fluoromethyl carbapenems (**6a—9a**) under the condition (0.05 M 4-morpholinepropanesulfonic acid (MOPS) buffer, pH 7.0, 37 °C) were measured using bioassay or the high performance liquid chromatography (HPLC) method, and are described below as representative. The residual potencies of the 1β-fluoromethyl carbapenems (**6a—8a**) after 24 h under the above condition were as follows. **6a**, 76%; **7a**, 71%; **8a**, 60%; imipenem, 23%. On the other hand, the 1α-fluoromethyl carbapenem (**9a**) decreased its potency to half within 2.5 h.

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-1-ethoxycarbonyl-3-phenylthiopropyl]-2-azetidinone (16α) and the Diastereoisomer (16β) To a solution of the *N*-trimethylsily azetidinone (**14**) (62.6 g, 0.175 mol) and the crude ketene acetal (**15**), prepared from 0.26 mol of ethyl 4-phenylthiobutyrate and 0.26 mol of LDA, in CH_2Cl_2 (350 ml) was slowly added trimethylsilyl triflate (12 ml, 0.062 mol) under ice-cooling, and the reaction mixture was stirred at room temperature for 3.5 h. To this mixture was added 4 N HCl (25 ml) and the stirring was continued for 30 min. The mixture was poured into ice water, and the organic layer was washed successively with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was chromatographed on a Lobar column (toluene–AcOEt, 4 : 1) to give **16α** (29.4 g, 37%), **16β** (39.6 g, 50%) and the mixture of **16α** and **16β** (2.6 g, 3%).

16α: $[\alpha]_D$ +23.9° (c=1.014, $CHCl_3$). IR ($CHCl_3$): 3400, 1759, 1722 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.84 (9H, s), 1.11 (3H, d, J=6 Hz), 1.25 (3H, t, J=7 Hz), 1.45—3.25 (6H, m), 3.81 (1H, dd, J=6, 2 Hz), 4.16 (2H, q, J=7 Hz), 4.18 (1H, m), 6.09 (1H, s), 7.15—7.45 (5H, m).

16β: $[\alpha]_D$ −46.1° (c=1.059, $CHCl_3$). IR ($CHCl_3$): 3400, 1752, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 1.08 (3H, d, J=7 Hz), 1.26 (3H, t, J=7 Hz), 1.55—3.35 (6H, m), 3.68 (1H, dd, J=9, 2 Hz), 4.07 (1H, m), 4.19 (2H, q, J=7 Hz), 6.0 (1H, s), 7.15—7.45 (5H, m).

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-1-hydroxymethyl-3-phenylthiopropyl]-2-azetidinone (18c) and the Diastereoisomer (17c) To a stirred solution of **16α** (374 mg, 0.828 mmol) in dimethoxyethane (3.7 ml) was added $LiBH_4$ (90 mg, 4.13 mmol) at 0 °C by portions, and the mixture was allowed to warm to room temperature. After stirring over-night at room temperature, the reaction was quenched by aqueous acetic acid under ice-cooling, and then extracted with AcOEt. The organic layer was washed with aqueous $NaHCO_3$ and water successively, dried and concentrated to give the crude **18c** (328 mg, 97%), which was subjected to the next reaction without further purification. An analytical sample obtained by chromatographic purification (Lobar column, toluene–AcOEt, 1 : 1) and subsequent recrystallization from petroleum ether showed mp 86—88 °C.

18c: IR ($CHCl_3$): 3400, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (9H, s), 1.29 (3H, d, J=6 Hz), 1.45—3,3 (7H, m), 3.43 (1H, dd, J=8, 2 Hz), 3.4—3.9 (2H, m), 4.11 (1H, dq, J=6, 2 Hz), 6.37 (1H, s), 7.05—7.45 (5H, m). *Anal.* Calcd for $C_{21}H_{35}NO_3SSi$: C, 61.57; H, 8.61; N, 3.42. Found: C, 61.42; H, 8.76; N, 3.39.

The diastereoisomer (**17c**) was obtained by the same procedure, and an analytical sample showed mp 117—119 °C (petroleum ether).

17c: IR ($CHCl_3$): 3400, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (9H, s), 1.15 (3H, d, J=6 Hz), 1.50—3.35 (6H, m), 2.46 (1H, t, J=5 Hz), 3.52 (1H, dd, J=7, 2 Hz), 3.5—3.95 (2H, m), 4.07 (1H, dq, J=6 Hz), 6.38 (1H, s), 7.1—7.5 (5H, m). *Anal.* Calcd for $C_{21}H_{35}NO_3SSi$: C, 61.57; H, 8.61; N, 3.42. Found: C, 61.62; H, 8.48; N, 3.44.

The following compounds (**18e, 17e; 18d, 17d**) were prepared from **18c** and/or **17c** by conventional methods (TBDMSCl–imidazole in *N*,*N*-dimethylformamide (DMF) and/or AcCl–pyridine in CH_2Cl_2).

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-1-*tert*-butyldimethylsilyloxymethyl-3-phenylthiopropyl]-2-azetidinone (18e) and the Diastereoisomer (17e) **18e**: IR ($CHCl_3$): 3400, 1748 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (18H, s), 1.18 (3H, d, J=6 Hz), 1.4—2.0 (3H, m), 3.72 and 3.56 (2H, ABq, J=32 Hz), 3.73 (1H, dd, J=5, 2 Hz), 4.15 (1H, dq, J=4, 6 Hz), 6.76 (1H, s), 7.05—7.5 (5H, m).

17e: IR ($CHCl_3$): 3400, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 0.87 (9H, s), 1.10 (3H, d, J=6 Hz), 1.45—3.85 (9H, m), 4.08 (1H, dq, J=6 Hz), 6.10 (1H, s), 7.1—7.45 (5H, m).

(3*S*,4*R*)-4-[(1*R*)-1-Acetoxymethyl-3-phenylthiopropyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (18d) and the Diastereoisomer (17d) **18d**: IR ($CHCl_3$): 3390, 1750, 1738 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (9H, s), 1.17 (3H, d, J=6 Hz), 1.45—1.86 (2H, m), 2.03 (3H, s), 1.95—2.3 (1H, m), 2.84 (1H, dd, J=5, 2 Hz), 2.63—3.30 (2H, m), 3.68 (1H, dd, J=6.5, 2 Hz), 3.99 and 4.25 (2H, ABX, J=11, 4.5, 5.4 Hz), 3.9—4.3 (1H, m), 6.0 (1H, s), 7.1—7.5 (5H, m).

17d: IR ($CHCl_3$): 3400, 1750, 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, s), 1.10 (3H, d, J=6 Hz), 1.50—2.15 (3H, m), 2.04 (3H, s), 2.68 (1H, dd, J=6, 2 Hz), 2.75—4.45 (5H, m), 3.44 (1H, dd, J=9, 2 Hz), 6.36 (1H, s), 7.05—7.45 (5H, m).

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-1-*tert*-butyl dimethylsilyloxymethyl-2-propenyl]-2-azetidinone (12e) and the Diastereoisomer (11e) To a solution of **18e** (1.63 g, 3.11 mmol) in CH_2Cl_2 (16 ml) was added dropwise a solution of *m*-CPBA (691 mg, 3.20 mmol) in CH_2Cl_2 (6 ml) under ice-cooling, and the mixture was stirred for 30 min at the same temperature. To this mixture was added dimethylsulfide (0.23 ml). It was stirred for 5 min, then poured into aqueous $NaHCO_3$ and washed with water, dried and concentrated. The residue was dissolved in toluene (35 ml) and the solution was refluxed for 19 h, then concentrated. The residue was chromatographed on a Lobar column (toluene–AcOEt, 4 : 1) to give **12e** (1.02 g, 79%) as a colorless powder, mp 87—89 °C.

12e: $[\alpha]_D$ −2.6° (c=1.003, $CHCl_3$). IR ($CHCl_3$): 3400, 1748, 1638 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (18H, s), 1.21 (3H, d, J=6 Hz), 2.1—2.45 (1H, m), 2.87 (1H, dd, J=4, 2 Hz), 3.66 (2H, d, J=6 Hz), 3.81 (1H, dd, J=6, 2 Hz), 4.19 (1H, dq, J=4, 6 Hz), 5.0—6.1 (4H, m). *Anal.* Calcd for $C_{21}H_{43}NO_3Si_2$: C, 60.96; H, 10.48; N, 3.39. Found: C, 60.81; H, 10.43; N, 3.58.

The diastereoisomer (**11e**) (colorless powder, mp 96—99 °C) was prepared by the same procedure.

11e: $[\alpha]_D$ −16.3° (c=1.010, $CHCl_3$). IR ($CHCl_3$): 3410, 1745, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (18H, s), 1.13 (3H, d, J=6 Hz), 2.15—2.55 (1H, m), 2.84 (1H, dd, J=4, 2 Hz), 3.5—3.9 (3H, m), 4.18 (1H, dq, J=4, 6 Hz), 5.0—5.9 (3H, m), 6.02 (1H, s). *Anal.* Calcd for $C_{21}H_{43}NO_3Si_2$: C, 60.96; H, 10.48; N, 3.39. Found: C, 60.74; H, 10.35; N, 3.39.

The following compounds (**12d, 11d**) were prepared by the same procedure.

(3*S*,4*R*)-4-[(1*R*)-1-Acetoxymethyl-2-propenyl]-3-[(1*R*)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (12d) and the Diastereoisomer (11d) **12d**: mp 61—62 °C (hexane), $[\alpha]_D$ −14.6° (c=1.015, $CHCl_3$). IR ($CHCl_3$): 3400, 1750, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.22 (3H, d, J=6 Hz), 2.06 (3H, s), 2.3—2.7 (1H, m), 2.91 (1H, dd, J=5, 2 Hz), 3.64 (1H, dd, J=6, 2 Hz), 3.9—5.95 (6H, m), 5.99 (1H, s). *Anal.* Calcd for $C_{17}H_{31}NO_4Si$: C, 59.78; H, 9.15; N, 4.10. Found: C, 59.65; H, 9.23; N, 4.00.

11d: mp 78—80 °C (hexane), $[\alpha]_D$ −35.8° (c=1.020, $CHCl_3$). IR ($CHCl_3$): 3400, 1750, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (9H, s), 1.17 (3H, d, J=6 Hz), 2.06 (3H, s), 2.32—2.7 (1H, m), 2.84 (1H, dd, J=4, 2 Hz), 3.62 (1H, dd, J=9, 2 Hz), 4.01 and 4.31 (2H, ABX, J=11, 6.5, 5.5 Hz), 4.0—4.4 (1H, m), 5.09—5.95 (3H, m), 6.46 (1H, s). *Anal.* Calcd for $C_{17}H_{31}NO_4Si$: C, 59.78; H, 9.15; N, 4.10. Found: C, 59.54, H, 9.21; N, 4.05.

(3*S*,4*R*)-3-[(1R)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-cyanomethyl-2-propenyl]-2-azetidinone (12b) To a stirred solution of **12c** (2.03 g, 6.78 mmol), prepared from **12d** by a conventional method (NaOMe in methanol), in CH_2Cl_2 (20 ml) was added Et_3N (1.89 ml, 13.6 mmol) followed by methanesulfonyl chloride (MsCl: 0.63 ml, 8.14 mmol) at −20 °C, and the mixture was stirred for 30 min at the same temperature. The reaction mixture was poured into dil. HCl, then washed, dried and concentrated. To the residue dissolved in HMPA (15 ml) was added NaCN (532 mg, 10.9 mmol) and TDA-1 (0.22 ml), and the mixture was stirred for 24 h at room temperature. After the usual work up, the residue was chromatographed on a Lobar column to give **12b** (1.84 g, 88%), mp 85—86 °C.

12b: $[\alpha]_D$ −20.0° (c=0.792, $CHCl_3$). IR ($CHCl_3$): 3400, 3390, 2225, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.25 (3H, d, J=6 Hz), 2.15—2.80 (3H, m), 2.85 (1H, dd, J=6, 2 Hz), 3.61 (1H, dd, J=7, 2 Hz), 4.16 (1H, dq, J=6 Hz), 5.16—6.01 (3H, m), 6.47 (1H, s). *Anal.* Calcd for $C_{16}H_{28}N_2O_2Si \cdot 0.4H_2O$: C, 60.87; H, 9.20; N, 8.88. Found: C, 60.83; H, 8.97; N, 8.94.

The diastereoisomer (**11b**, mp 115—118 °C) was prepared by the same procedure.

11b: $[\alpha]_D$ −34.7° (c=1.010, $CHCl_3$). IR ($CHCl_3$): 3400, 1762 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 0.92 (9H, s), 1.19 (3H, d, J=6 Hz), 2.54 (2H, d, J=3 Hz), 2.4—2.8 (1H, m), 2.85 (1H, dd, J=5, 2 Hz), 3.67 (1H, dd, J=8, 2 Hz), 4.0—6.0 (4H, m), 6.58 (1H, s). *Anal.* Calcd for $C_{16}H_{28}N_2O_2Si$: C, 62.29; H, 9.15; N, 9.08. Found: C, 62.19; H, 8.97; N, 8.94.

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*R*)-1-methylallyl]-2-azetidinone (10α) To a solution of **12c** (410 mg, 1.37 mmol) in CH_2Cl_2 (4 ml) was added Et_3N (0.38 ml, 2.74 mmol) and MsCl (0.13 ml, 1.64 mmol) at −20 °C, and the mixture was stirred for 15 min. After the usual work up, the residue was dissolved in HMPA (4.7 ml), and NaI (555 mg, 3.7 mmol) was added to the solution. The reaction mixture was stirred for 3 h at 60 °C, and then worked up in the usual way. The residue was chromatographed on a Lobar column to give **12g** (401 mg, 78%), mp 112—114 °C. IR ($CHCl_3$): 3405, 1757 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (9H, s), 1.25 (3H, d, J=6 Hz), 2.2—3.45 (3H, m), 3.64 (1H, dd, J=6, 2 Hz), 4.19 (1H, dq, J=6 Hz), 5.1—6.1 (3H, m). *Anal.* Calcd for $C_{15}H_{28}INO_2Si$: C, 44.00; H, 6.89; N, 3.42. Found: C, 44.19; H, 6.92; N, 3.50. To a solution of **12g** (100 mg, 0.244 mmol) in HMPA (1.2 ml) was added $NaBH_3CN$ (61 mg, 0.976 mmol) at room temperature, and the reaction mixture was stirred for 2 h at 50 °C. After the usual work up, the residue was chromatographed on a Lobar column to give **10α** (9 mg, 13%, mp 123—125 °C, lit. mp 124.5—126 °C), along with **13** (6 mg, 9%) and **12g** (54 mg, 54%). The spectroscopic data of **10α** were completely identical to that of the authentic **10α** prepared in these laboratories.[5] **13**: mp 91—93 °C. IR ($CHCl_3$): 3405, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (9H, s), 1.21 (3H, d, J=6 Hz), 2.9—3.05 (1H, m), 4.1—4.6 (2H, m), 5.1—6.6 (6H, m). *Anal.* Calcd for $C_{15}H_{27}NO_2Si\cdot 0.2H_2O$: C, 63.20; H, 9.69; N, 4.91. Found: C, 63.17; H, 9.49; N, 4.96.

(3*S*,4*R*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-hydroxymethyl-2-propenyl]-1-methylthio-2-azetidinone (19c) To a solution of **11d** (2.0 g, 5.85 mmol) in tetrahydrofuran (THF, 30 ml) was added successively an ice-cold THF solution of LDA (prepared from diisopropylamine (0.77 ml, 5.85 mmol) and *n*-BuLi (1.54 M hexane solution, 3.8 ml, 5.85 mmol) in THF (11 ml)), HMPA (1.02 ml, 5.85 mmol), and methyl methanethiosulfonate (1.5 ml, 14.6 mmol) at −78 °C, and the reaction mixture was stirred for 40 min at the same temperature. After the temperature was raised gradually to 0 °C, the mixture was diluted with AcOEt and washed successively with dil. HCl, aqueous $NaHCO_3$, and water, and then dried and concentrated. The residue was dissolved in MeOH (28 ml) and the solution was treated with NaOMe (5.18 M MeOH solution: 1.33 ml, 6.9 mmol) at −25 °C. After being stirred for 1.5 h at −25 °C, the mixture was poured into dil. HCl, and extracted with AcOEt. The organic layer was washed, dried, and concentrated, and the residue was chromatographed on a Lobar column (toluene–AcOEt, 2:1) to give **19c** (1.99 g, 98%).

19c: IR ($CHCl_3$): 3440, 1755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (9H, s), 1.24 (3H, d, J=6.2 Hz), 2.3 (1H, s), 2.44 (3H, s), 2.6—2.8 (1H, m), 3.12 (1H, dd, J=6.2, 2.6 Hz), 3.75—3.93 (3H, m), 4.16 (1H, dq, J=6.2 Hz), 5.2—5.9 (3H, m).

The diastereoisomer (**20c**) was prepared from **12d** by the same procedure as above.

20c: IR ($CHCl_3$): 3440, 1757 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (9H, s), 1.27 (3H, d, J=6 Hz), 2.42 (3H, s), 2.45—2.62 (1H, m), 3.18 (1H, dd, J=6.6, 2.8 Hz), 3.6—3.8 (3H, m), 4.14 (1H, dq, J=6.2 Hz), 5.2—5.9 (3H, m).

The TMS ethers (**19f**, **20f**) were prepared by a conventional method (TMSCl–pyridine in CH_2Cl_2) from the corresponding alcohols (**19c**, **20c**), respectively.

19f: mp 36—37 °C. IR ($CHCl_3$): 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (9H, s), 1.10 (3H, d, J=6.2 Hz), 2.37 (3H, s), 2.55—2.7 (1H, m), 2.95 (1H, dd, J=3.4, 2.6 Hz), 3.65 and 3.74 (2H, ABX, J=10.2, 6.4, 5.6 Hz), 3.98 (1H, dd, J=5.0, 2.6 Hz), 4.15 (1H, dq, J=3.4, 6.2 Hz), 5.03—5.75 (3H, m). MS *m/z*: 417 ([M]$^+$). *Anal.* Calcd for $C_{19}H_{39}NO_3SSi_2$: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.51; H, 9.31; N, 3.38.

20f: IR ($CHCl_3$): 1754 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.18 (3H, d, J=6.4 Hz), 2.43 (3H, s), 2.46—2.58 (1H, m), 3.06 (1H, dd, J=4.0, 2.8 Hz), 3.67 and 3.83 (2H, ABX, J=10.2, 7.4, 5.8 Hz), 4.09 (1H, dd, J=3.6, 2.8 Hz), 4.19 (1H, dq, J=6.4, 4.4 Hz), 5.18—5.85 (3H, m). *Anal.* Calcd for $C_{19}H_{39}NO_3SSi_2$: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.59; H, 9.26; N, 3.44.

(3*S*,4*S*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-fluoromethyl-2-propenyl]-1-methylthio-2-azetidinone (19a) The TMS ether **19f** (4.3 g, 10.3 mmol) was dissolved in CH_2Cl_2 (45 ml) and cooled to −60 °C, and to this solution was added DAST (1.69 ml, 12.8 mmol). The resulting solution was allowed to warm to 0 °C, stirred for 19 h at the same temperature, and then poured into sat. $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed successively with aqueous $NaHCO_3$ and water, and then dried and concentrated. The residue was purified by chromatography (Lobar column, toluene–AcOEt, 2:1) to give **19a** (1.77 g, 49%). mp 35—35.5 °C.

19a: IR ($CHCl_3$): 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.17 (3H, d, J=6.2 Hz), 2.44 (3H, s), 2.75—3.0 (1H, m), 3.02 (1H, dd, J=3.8, 2.6 Hz), 3.98 (1H, dd, J=5.4, 2.6 Hz), 4.22 (1H, dq, J=3.8, 6.2 Hz), 4.59 and 4.69 (2H, dABX, J=47, 9.0, 5.0, 5.8 Hz), 5.2—5.8 (3H, m). *Anal.* Calcd for $C_{16}H_{30}FNO_2SSi$: C, 55.29; H, 8.70; N, 4.03. Found: C, 55.16; H, 8.65; N, 4.16.

The following diastereoisomer (**20a**) was prepared by the same procedure.

20a: IR ($CHCl_3$): 1756 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.19 (3H, d, J=6.2 Hz), 2.44 (3H, s), 2.6—2.9 (1H, m), 3.07 (1H, dd, J=4.0, 2.8 Hz), 4.01 (1H, dd, J=4.8, 2.8 Hz), 4.21 (1H, dq, J=6.4, 4.2 Hz), 4.54 and 4.64 (2H, dABX, J=47, 9.2, 7.0, 5.8 Hz), 5.2—5.9 (3H, m).

(3*S*,4*S*)-3-[(1*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[(1*S*)-1-fluoromethyl-2-propenyl]-2-azetidinone (11a) To a solution of **19a** (1.74 g, 5.0 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (0.77 ml) followed by 2-mercaptopyridine (0.61 g, 5.5 mmol) at −20 °C. After stirring for 1.5 h at the same temperature, the mixture was poured into dil. HCl. The organic layer was washed, dried, and then concentrated. The residue was purified by chromatography (Lobar column, toluene–AcOEt, 2:1) to give **11a** (1.34 g, 88%) as colorless crystals (mp 136—137.5 °C).

11a: $[\alpha]_D$ −25.4° (c=1.009, $CHCl_3$). IR ($CHCl_3$): 3410, 1758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.16 (3H, d, J=6.2 Hz), 2.48—2.73 (1H, m), 2.89 (1H, ddd, J=4.2, 2.2, 1.4 Hz), 3.73 (1H, dd, J=8.8, 2.2 Hz), 4.20 (1H, dq, J=4.2, 6.2 Hz), 4.47 and 4.55 (2H, dABX, J=47.2, 9.4, 4.7, 7.8 Hz), 5.2—5.7 (3H, m), 5.99 (1H, s). *Anal.* Calcd for $C_{15}H_{28}FNO_2Si\cdot 0.1H_2O$: C, 59.40; H, 9.37; N, 4.62. Found: C, 59.44; H, 9.34; N, 4.78.

The diastereoisomer (**12a**) was prepared by the same procedure. **12a**: mp 116—117 °C, $[\alpha]_D$ −22.4° (c=1.001, $CHCl_3$). IR ($CHCl_3$): 3400, 1757 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s), 1.24 (3H, d, J=6.2 Hz), 2.3—2.6 (1H, m), 2.91 (1H, ddd, J=4.8, 2.0, 1.0 Hz), 3.73 (1H, dd, J=7.4, 2.0 Hz), 4.20 (1H, dq, J=5.2, 6.2 Hz), 4.45 and 4.54 (2H, dABX, J=47, 9.2, 4.6, 5.4 Hz), 5.2—5.9 (3H, m), 5.8 (1H, s). *Anal.* Calcd for $C_{15}H_{28}FNO_2Si$: C, 59.76; H, 9.36; N, 4.65. Found: C, 59.65; H, 9.26; N, 4.76.

The epoxides (**21a, b, d, e**, **31a, b, d, e**) and the epoxy phosphoranes (**22a, b, d, e**, **32a, b, d, e**) were prepared by the procedure previously established in these laboratories.[5] All the spectroscopic data of the compounds are in good agreement with the corresponding structures. The spectroscopic data of the epoxide (**31b**) and the epoxy phosphorane (**32b**) are described below as representatives.

31b (Mixture of Two Diastereoisomers, 1:1): mp 95—97 °C, $[\alpha]_D$ −32.2° (c=1.013, $CHCl_3$). IR ($CHCl_3$): 3410, 2400, 1770 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (9H, s), 1.13 and 1.16 (3H, 2d, J=6 Hz), 1.5—3.2 (7H, m), 3.76 (1H, dd, J=6, 2 Hz), 3.95—4.3 (1H, m), 6.52 (1H, s). *Anal.* Calcd for $C_{16}H_{28}N_2O_3Si$: C, 59.21; H, 8.70; N, 8.63. Found: C, 59.02; H, 8.57; N, 8.61.

32b (Mixture of Two Diastereoisomers, 1:1): $[\alpha]_D$ −9.8° (c=1.016, $CHCl_3$). IR ($CHCl_3$): 1740, 1635, 1610 cm^{-1}. *Anal.* Calcd for $C_{44}H_{51}N_2O_6PSi\cdot 0.7CH_2Cl_2$: C, 65.28; H, 6.42; N, 3.41. Found: C, 65.29; H, 6.45; N, 3.48.

***p*-Methoxybenzyl (1*R*,5*R*,6*S*)-2-(1,3,4-Thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]-1-trimethylsilyloxymethylcarbapen-2-em-3-carboxylate (28f)** To a mixture of **22e** (1.00 g, 1.15 mmol) and 2-mercapto-1,3,4-thiadiazole (231 mg, 1.96 mmol) in THF (8 ml) at −40 °C was added a solution of *n*-BuLi (1.5 M solution in hexane: 0.38 ml, 0.575 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 20 h at the same temperature. The reaction was diluted with AcOEt, washed with aqueous $NaHCO_3$ and water, and then dried and concentrated. The residue was purified by chromatography (Lobar column, toluene–AcOEt, 1:1) to give the diastereoisomeric mixture of the carbinols (**23e**: 776 mg, 68%). IR ($CHCl_3$): 3400, 1727, 1605 cm^{-1}. The carbinol mixture (**23e**: 355 mg, 0.36 mmol) obtained above was dissolved in CH_2Cl_2 (3.7 ml) and cooled to −70 °C, and to this solution was added dimethyl sulfoxide (DMSO, 77 μl, 1.076 mmol) followed by a dropwise addition of trifluoroacetic anhydride (77 μl, 0.538 mmol). After maintaining the reaction at −70 °C for 1.5 h, Et_3N (201 μl, 1.438 mmol) was added dropwise and the mixture was stirred for 1.5 h at the same temperature. After the addition of water (2.5 ml) to quench the reaction, the mixture was stirred for 5 min and poured into aqueous $NaHCO_3$, and then extracted with AcOEt. The organic layer was washed with water, dried, and concentrated to give the crude keto phosphorane (**24f**). The

crude **24f**, thus obtained, was dissolved in CH_3CN (3.7 ml), and to this was added AcOH (0.31 ml, 5.4 mmol) and conc. HCl (0.23 ml, 2.7 mmol) at −10 °C. The resulting solution was stirred for 1.5 h at the same temperature, and poured into aqueous $NaHCO_3$, and then diluted with AcOEt. After the usual work up, the residue was dissolved in CH_2Cl_2 (4 ml) and cooled to 0 °C. To this mixture was added Et_3N (0.15 ml, 1.08 mmol) and TMSCl (0.137 ml, 1.08 mmol), and the whole was stirred for 20 min at the same temperature. The reaction mixture was poured into aqueous $NaHCO_3$ and worked up in the usual way to give the crude **26f**.

A solution of crude **26f** in benzene (5 ml) was heated to reflux for 25 min and the solvent was removed under reduced pressure. The residue was chromatographed on a Lobar column (toluene–AcOEt, 4 : 1) to give **28f** (132 mg, 59% from **23e**) as pale yellow oil.

28f: IR ($CHCl_3$): 1775, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6 Hz), 3.03 (1H, dd, J=6, 3 Hz), 3.36 (1H, dt, J=8, 5 Hz), 3.68 (3H, s), 3.75 (2H, d, J=5 Hz), 3.89 (1H, dd, J=8, 3 Hz), 4.08 (1H, dq, J=6 Hz), 4.13 and 4.63 (2H, ABq, J=12 Hz), 5.10 (2H, s), 6.76 and 7.29 (2H × 2, 2d, J=9 Hz), 8.89 (1H, s). MS (LSIMS, glycerol) m/z: 622 ($[M+H]^+$).

The following compounds (**33f, 28d, 33d**) were prepared by the same procedure.

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-2-(1,3,4-Thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]-1-trimethylsilyloxymethylcarbapen-2-em-3-carboxylate (33f)** IR ($CHCl_3$): 1770, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J=5 Hz), 3.31 (1H, dt, J=10.5, 5 Hz), 3.49 (1H, dd, J=5, 3 Hz), 3.80 (3H, s), 3.81 (2H, d, J=5 Hz), 4.16 (1H, dd, J=10.5, 3 Hz), 4.18 (1H, dq, J=5 Hz), 4.20 and 4.94 (2H, ABq, J=14 Hz), 5.24 (2H, s), 6.78 and 7.31 (2H × 2, 2d, J=9 Hz), 8.99 (1H, s). MS (LSIMS, glycerol) m/z: 622 ($[M+H]^+$).

***p*-Methoxybenzyl (1*R*,5*R*,6*S*)-1-Acetoxymethyl-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (28d)** IR ($CHCl_3$): 1780, 1735, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6 Hz), 2.03 (3H, s), 3.19 (1H, dd, J=5, 2 Hz), 3.55—3.9 (1H, m), 3.80 (3H, s), 3.97 (1H, dd, J=8, 2 Hz), 4.20 (1H, dq, J=6 Hz), 4.26 and 4.74 (2H, ABq, J=13 Hz), 4.41 (2H, d, J=5 Hz), 5.22 (2H, s), 6.87 and 7.41 (2H × 2, 2d, J=8 Hz), 9.00 (1H, s). MS (LSIMS, glycerol) m/z: 592 ($[M+H]^+$).

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-1-Acetoxymethyl-2-(1,3,4-thiadiazol-2-yl)thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (33d)** IR ($CHCl_3$): 1775, 1733, 1715, 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6 Hz), 3.25 (1H, dd, J=6, 3 Hz), 3.4—4.7 (5H, m), 3.79 (3H, s), 4.18 and 4.87 (2H, ABq, J=14.4 Hz), 5.23 (2H, s), 6.86 and 7.37 (2H × 2, 2d, J=9 Hz), 8.98 (1H, s). MS (LSIMS, glycerol) m/z: 592 ($[M+H]^+$).

***p*-Methoxybenzyl (1*R*,5*R*,6*S*)-1-Cyanomethyl-2-(1,3,4-thiadiazol-2-yl)-thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (28b)** The alcohol (**23b**, 1.59 g, 1.81 mmol) was dissolved in CH_3CN (17 ml) and cooled to −10 °C, and to this solution was added AcOH (1.55 ml) and conc. HCl (1.16 ml). After stirring for 2.5 h at −10 °C, the mixture was poured into cold AcOEt and worked up in the usual way. The residue was dissolved in CH_2Cl_2 (25 ml) and cooled to −10 °C, and to this solution was added 2,6-lutidine (0.63 ml, 5.42 mmol) followed by TMSCl (0.46 ml, 3.61 mmol). After stirring for 1.25 h at −10 °C, the reaction was quenched by water (10 ml), and the mixture was poured into aqueous $NaHCO_3$. After the usual work up, the residue was purified by chromatography (silica gel) to give the mono-silylated phosphorane (**25b**, 1.35 g, 89% from **22b**).

To a solution of **25b** (205 mg, 0.243 mmol) in CH_2Cl_2 (3.5 ml) was added DMSO (52 μl, 0.729 mmol) followed by trifluoroacetic anhydride (51 μl, 0.365 mmol) at −70 °C. After stirring for 0.5 h at −70 °C, Et_3N (136 μl, 0.97 mmol) was added to this mixture and stirring continued for 30 min at the same temperature. The reaction was quenched by water (2 ml) and the mixture was stirred for 5 min, and then poured into aqueous $NaHCO_3$. After the usual work up, the residue was dissolved in benzene (3 ml) and heated to reflux for 20 min and then concentrated. The residue was purified by chromatography (Lobar column, toluene–AcOEt, 2 : 1) to give **28b** (102 mg, 67% from **23b**) as pale yellow oil.

28b: IR ($CHCl_3$): 1773, 1705, 1603 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=6 Hz), 2.9—3.9 (3H, m), 3.20 (1H, dd, J=6, 3 Hz), 3.80 (3H, s), 3.97 (1H, dd, J=8, 3 Hz), 4.13 (1H, dq, J=6 Hz), 4.22 and 4.70 (2H, ABq, J=12.6 Hz), 5.23 (2H, s), 6.88 and 7.38 (2H × 2, 2d, J=9 Hz), 9.01 (1H, s). MS (LSIMS, glycerol) m/z: 559 ($[M+H]^+$).

The following compounds (**33b, 28a, 33a**) were prepared by the same procedure.

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-1-Cyanomethyl-2-(1,3,4-thiadiazol-2-yl)-thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (33b)** IR ($CHCl_3$): 2400, 1785, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6 Hz), 2.69 and 2.95 (2H, ABX, J=11, 9, 3.6 Hz), 3.40 (1H, dd, J=4.5, 3 Hz), 3.3—3.9 (1H, m), 3.78 (3H, s), 4.30 (1H, dd, J=11, 3 Hz), 4.26 and 4.94 (2H, ABq, J=14.5 Hz), 5.24 (2H, s), 6.86 and 7.38 (2H × 2, 2d, J=9 Hz), 9.03 (1H, s). MS (LSIMS, glycerol) m/z: 559 ($[M+H]^+$).

***p*-Methoxybenzyl (1*R*,5*S*,6*S*)-1-Fluoromethyl-2-(1,3,4-thiadiazol-2-yl)-thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (28a)** IR ($CHCl_3$): 1777, 1713 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=5.8 Hz), 3.19 (1H, dd, J=6.6, 3.2 Hz), 3.5—3.8 (1H, m), 3.80 (3H, s), 4.06 (1H, dd, J=8.2, 3.2 Hz), 4.18 (1H, dq, J=6.2 Hz), 4.2—5.1 (4H, m), 5.19 and 5.26 (2H, ABq, J=12.2 Hz), 6.88 and 7.38 (2H × 2, 2d, J=8.6 Hz), 9.00 (1H, s). MS (LSIMS, glycerol) m/z: 552 ($[M+H]^+$).

***p*-Methoxybenzyl (1*S*,5*S*,6*S*)-1-Fluoromethyl-2-(1,3,4-thiadiazol-2-yl)-thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (33a)** IR ($CHCl_3$): 1782, 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6 Hz), 3.3—3.6 (1H, m), 3.81 (3H, s), 3.47 (1H, dd, J=5.4, 3.6 Hz), 4.22 (1H, dd, J=5.4, 2.6 Hz), 4.25 and 4.94 (2H, ABq, J=14.2 Hz), 4.67 and 4.85 (2H, dABX, J=47, 10, 4.2, 2.8 Hz), 5.22 and 5.28 (2H, ABq, J=12.2 Hz), 6.88 and 7.39 (2H × 2, 2d, J=8.8 Hz), 9.00 (1H, s). MS (LSIMS, glycerol) m/z: 552 ($[M+H]^+$).

Sodium (1*R*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-hydroxymethyl-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (9c) To a mixture of **28c** (121 mg, 0.195 mmol), CH_2Cl_2 (1.3 ml), and anisole (1.3 ml) was added a solution of $AlCl_3$ (78 mg, 0.584 mmol) in anisole (1 ml) at −50 °C, and the reaction mixture was stirred for 40 min at the same temperature. Aqueous solution of $NaHCO_3$ (221 mg, 2.63 mmol/3.5 ml) was added and the mixture was stirred for 15 min at the same temperature, then aqueous NaF (16 mg, 0.39 mmol/0.2 ml) was added and the whole was stirred under ice-cooling for 15 min. The mixture was filtered and the aqueous filtrate was chromatographed on a HP-20AG column (H_2O). The fractions containing the product were concentrated and freeze-dried to give **9c** (18 mg, 24%) as a white powder.

9c: IR (KBr): 3400, 1760, 1754, 1593 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.91 (3H, d, J=6 Hz), 3.98 (1H, dd, J=5, 3 Hz), 4.1—4.35 (1H, m), 4.49 and 4.57 (2H, ABX, J=11, 6, 4.5 Hz), 4.63 (1H, dd, J=7.5, 3 Hz), 4.88 (1H, dq, J=6 Hz), 4.56 and 5.55 (2H, ABq, J=14 Hz), 10.07 (1H, s). UV $\lambda_{max}^{H_2O}$ nm (ε): 275 (7500).

The following compounds (**6c, 9d, 6d, 9a, 6a, 9b, 6b**) were also prepared by the same method used for **9c**.

Sodium (1*S*,5*R*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-1-hydroxymethyl-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (6c) IR (KBr): 3420, 1745, 1595 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.91 (3H, d, J=6 Hz), 4.05 (1H, dt, J=9.5, 4.5 Hz), 4.20 (1H, dd, J=6.0, 2.7 Hz), 4.46 (2H, d, J=4.5 Hz), 4.77 (1H, dd, J=9.5, 2.7 Hz), 4.84 (1H, dq, J=6.0 Hz), 4.48 and 5.57 (2H, ABq, J=14.0 Hz), 10.05 (1H, s). UV $\lambda_{max}^{H_2O}$ nm (ε): 277 (8000).

Sodium (1*R*,5*R*,6*S*)-1-Acetoxymethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (9d) IR (KBr): 3420, 1740, 1598 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, J=6.4 Hz), 2.06 (3H, s), 3.39 (1H, dd, J=6, 3 Hz), 3.68—3.84 (1H, m), 3.98 (1H, dd, J=7.5, 3 Hz), 4.10 and 4.73 (2H, ABq, J=14 Hz), 4.21 (1H, dq, J=6.5, 6 Hz), 4.34 and 4.44 (2H, ABX, J=11, 6, 5 Hz), 9.40 (1H, s). UV $\lambda_{max}^{ethanol}$ nm (ε): 277 (9500).

Sodium (1*S*,5*R*,6*S*)-1-Acetoxymethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (6d) IR (KBr): 3420, 1743, 1598 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, J=6 Hz), 3.41 (1H, dd, J=9, 2.5 Hz), 3.54—3.66 (1H, m), 3.92 and 4.86 (2H, ABq, J=14 Hz), 4.1—4.65 (4H, m), 9.40 (1H, s). UV $\lambda_{max}^{ethanol}$ nm (ε): 277 (11000).

Sodium (1*R*,5*S*,6*S*)-1-Fluoromethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (9a) IR (KBr): 3420, 1755, 1595 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.26 (3H, d, J=6.2 Hz), 3.40 (1H, dd, J=5.6, 2.8 Hz), 3.65—3.95 (1H, m), 4.04 (1H, dd, J=7.8, 2.8 Hz), 4.23 (1H, dq, J=6 Hz), 4.04 and 4.83 (2H, ABq, J=13.2 Hz), 4.80 (2H, dd, J=47, 4.6 Hz), 9.42 (1H, s). UV $\lambda_{max}^{H_2O}$ nm (ε) 274 (8000).

Sodium (1*S*,5*S*,6*S*)-1-Fluoromethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (6a) $[\alpha]_D$ −59.5° (c=1.012, H_2O). IR (KBr): 3420, 1755, 1596 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, J=6.6 Hz), 3.52 (1H, dd, J=6.2, 2.8 Hz), 3.45—3.8 (1H, m), 4.21 (1H, dd, J=6.2, 2.8 Hz), 4.24 (1H, dq, J=6 Hz), 3.91 and 4.94 (2H, ABq, J=14.6 Hz), 4.6—4.9 (2H, m), 9.43 (1H, s). UV $\lambda_{max}^{H_2O}$ nm (ε): 276(9300).

Sodium (1*R*,5*R*,6*S*)-1-Cyanomethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (9b) IR (KBr): 3410, 3085, 2245, 1758, 1598 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.94 (3H, d, J=6.3 Hz), 3.61 and 3.72 (2H, ABX, J=17.0, 7.5, 4.7 Hz), 4.09 (1H, dd, J=5.4, 2.8 Hz), 4.4—4.6 (1H, m), 4.62 (1H, dd, J=7.5, 2.8 Hz), 4.88 (1H,

dq, $J=5.4$, 6.3 Hz), 4.66 and 5.48 (2H, ABq, $J=14.0$ Hz), 10.05 (1H, s). UV $\lambda_{max}^{H_2O}$ nm (ε): 275 (7900).

Sodium (1*S*,5*R*,6*S*)-1-Cyanomethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (6b) IR (KBr): 3400, 2240, 1752, 1595 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, $J=6$ Hz), 2.91 (2H, d, $J=6$ Hz), 3.54 (1H, dd, $J=5$, 2.5 Hz), 3.74 (1H, dt, $J=10$, 6 Hz), 4.24 (1H, dd, $J=10$, 2.5 Hz), 4.18—4.35 (1H, m), 3.89 and 4.93 (2H, ABq, $J=15$ Hz), 9.41 (1H, s). UV $\lambda_{max}^{ethanol}$ nm (ε): 278 (10600).

The epoxy phosphoranes (**32a, b**) were converted to the corresponding cyclized carbapenems (**34a, b**) by a similar reaction sequence as described for the 2-thiadiazolylthiomethyl analog (**28f**).

***p*-Methoxybenzyl (1*S*,5*S*,6*S*)-1-Fluoromethyl-2-(4-pyridyl)thiomethyl-6-[(1*R*)-1-trimethysilyloxyethyl]carbapen-2-em-3-carboxylate (34a)** IR ($CHCl_3$): 1782, 1715, 1615, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, $J=6.2$ Hz), 3.42 (1H, ddd, $J=6.2$, 3.2, 1.0 Hz), 3.25—3.45 (1H, m), 3.50 and 3.58 (2H, ABq, $J=14.6$ Hz), 3.80 (3H, s), 4.15 (1H, dd, $J=10.8$, 3.2 Hz), 4.1—4.3 (1H, m), 4.62 and 4.68 (1H, dABX, $J=47.4$, 10.4, 4.8, 3.0 Hz), 5.26 (2H, s), 6.88 and 7.40 (2H×2, 2d, $J=8.8$ Hz), 7.07 (2H, d, $J=5.4$ Hz), 8.33 (2H, m). MS (LSIMS, glycerol) *m/z*: 545 ([M+H]$^+$).

***p*-Methoxybenzyl (1*S*,5*R*,6*S*)-1-Cyanomethyl-2-(4-pyridyl)thiomethyl-6-[(1*R*)-1-trimethylsilyloxyethyl]carbapen-2-em-3-carboxylate (34b)** IR ($CHCl_3$): 1781, 1718, 1608, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=6.2$ Hz), 2.52 and 2.68 (2H, ABX, $J=17.2$, 9, 5 Hz), 3.34 (1H, dd, $J=5$, 3.2 Hz), 3.5—3.7 (1H, m), 3.80 (3H, s), 4.21 (1H, dd, $J=10.2$, 3.2 Hz), 4.25 (1H, dq, $J=5$, 6.2 Hz), 3.56 and 4.98 (2H, ABq, $J=15.2$ Hz), 5.26 (2H, s), 6.88 and 7.39 (2H×2, 2d, $J=8.8$ Hz), 7.07 (2H, d, $J=6.0$ Hz), 8.25—8.55 (2H, m). MS (LSIMS, glycerol) *m/z*: 552 ([M+H]$^+$).

(1*S*,5*R*,6*S*)-1-Cyanomethyl-2-(1-methyl-4-pyridinio)thiomethyl-6-[(1*R*)-1-trimethysilyloxyethyl]carbapen-2-em-3-carboxylate (7b) A solution of **34b** (125 mg, 0.227 mmol) and iodomethane (1.25 ml) in acetone (2.5 ml) was stirred at room temperature for 100 min and then concentrated. The residue was triturated with hexane to give **35b** as a yellow powder (139 mg, 89%). IR (Nujol): 3400, 2225, 1770, 1703, 1623 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=6.0$ Hz), 2.84 and 2.90 (2H, ABX, $J=17.2$, 7.8, 5.4 Hz), 3.43 (1H, dd, $J=5$, 3.4 Hz), 3.55—3.85 (1H, m), 3.82 (3H, s), 4.2—4.5 (2H, m), 4.31 (3H, s), 4.25 and 4.94 (2H, ABq, $J=13.2$ Hz), 5.26 (2H, s), 6.87 and 7.39 (2H×2, 2d, $J=8.8$ Hz), 7.75 and 8.46 (2H×2, 2d, $J=7.2$ Hz). The PMB ester **35b** (187 mg, 0.27 mmol) was dissolved in a mixture of CH_2Cl_2 (1.8 ml) and anisole (1.8 ml), and cooled to −50 °C. To this mixture was added dropwise a solution of $AlCl_3$ (108 mg, 0.81 mmol) in anisole (1.2 ml), and the whole was stirred for 20 min at the same temperature. A solution of $NaHCO_3$ (305 mg, 3.65 mmol) in water (5 ml) was added, and the reaction mixture was stirred for 30 min under ice-cooling and filtered. The aqueous filtrate was chromatographed on a HP-20AG column, and the fractions containing the product were concentrated and freeze-dried to give **7b** as a yellow powder (67 mg, 66%).

7b: $[\alpha]_D$ −61.0° ($c=0.702$, H_2O). IR (KBr): 3400, 2240, 1758, 1632, 1597 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, $J=6.4$ Hz), 2.8—3.1 (2H, m), 3.55 (1H, dd, $J=5.6$, 3.0 Hz), 3.6—3.8 (1H, m), 4.19 (1H, dd, $J=10.0$, 3.0 Hz), 4.19 (3H, s), 4.25 (1H, dq, $J=5.6$, 6.4 Hz), 4.00 and 5.06 (2H, ABq, $J=15$ Hz), 7.81 and 8.40 (2H×2, 2d, $J=7.2$ Hz). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (10900), 303 (17300).

The following compounds (**7a, 8a, 8b**) were prepared by the same or a slightly modified procedure.

(1*S*,5*S*,6*S*)-1-Fluoromethyl-6-[(1*R*)-1-hydroxyethyl]-2-(1-methyl-4-pyridinio)thiomethylcarbapen-2-em-3-carboxylate (7a) $[\alpha]_D$ −47.1° ($c=0.577$, H_2O). IR (KBr): 3400, 1758, 1633, 1595 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.27 (3H, d, $J=6.4$ Hz), 3.4—3.7 (2H, m), 3.99 and 5.08 (2H, ABq, $J=15.0$ Hz), 4.1—4.35 (2H, m), 4.19 (3H, s), 4.55—5.0 (2H, m), 7.80 and 8.40 (2H×2, 2d, $J=7.0$ Hz). UV $\lambda_{max}^{H_2O}$ nm (ε): 229 (11200), 303 (19600).

(1*S*,5*S*,6*S*)-2-(1-Carbamoylmethyl-4-pyridinio)thiomethyl-1-fluoromethyl-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (8a) $[\alpha]_D$ −48.9° ($c=1.012$, H_2O). IR (KBr): 3400, 1760, 1697, 1633, 1592 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.28 (3H, d, $J=6.2$ Hz), 3.4—3.75 (2H, m), 4.02 and 5.12 (2H, ABq, $J=14.8$ Hz), 4.12—4.32 (1H, m), 4.5—5.1 (2H, m), 5.31 (2H, s), 7.86 and 8.40 (2H×2, 2d, $J=6.6$ Hz). UV $\lambda_{max}^{H_2O}$ nm (ε): 232 (10800), 309 (20700).

(1*S*,5*R*,6*S*)-2-(1-Carbamoylmethyl-4-pyridinio)thiomethyl-1-cyanomethyl-6-[(1*R*)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (8b) $[\alpha]_D$ −61.3° ($c=0.906$, H_2O). IR (KBr): 3400, 1755, 1692, 1631, 1593 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.29 (3H, d, $J=6.4$ Hz), 2.95 (2H, d, $J=5.6$ Hz), 3.55 (1H, dd, $J=5.4$, 2.8 Hz), 3.69 (1H, dt, $J=10.0$, 5.6 Hz), 4.21 (1H, dd, $J=10.0$, 2.8 Hz), 4.25 (1H, dq, $J=5.4$, 6.4 Hz), 4.03 and 5.11 (2H, ABq, $J=15.2$ Hz), 5.31 (2H, s), 7.87 and 8.41 (2H×2, 2d, $J=7.2$ Hz). UV $\lambda_{max}^{H_2O}$ nm (ε): 231 (10600), 308 (20500).

Determination of MICs MICs were determined by the agar dilution method using sensitivity test agar (Eiken, Japan). An overnight culture of bacteria in tryptosoy broth (Eiken, Japan) was diluted to about 10^6 cells/ml with the same broth and inoculated with an inoculating device onto agar containing serial twofold dilutions of the test compounds. Organisms were incubated at 37 °C for 18—20 h. The MIC of a compound was defined as the lowest concentration that visibly inhibited growth.

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