Synthesis and Antibacterial Activity of 1-Substituted-methyl Carbenamems

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The synthesis of the 1α- and the 1β-substituted (fluoro, cyano, hydroxy and acetoxyl)-methyl carbenamems 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 1α-methyl carbenamems together with imipenem. The synthesis and antibacterial activity of the 1β-substituted (fluoro and cyano)-methyl carbenamems having 2-(1-alkyl-4-pyridinio)thiomethyl side chains are also described.

Keywords β-lactam antibiotic; carbenamem antibiotic; 1α-substituted-methyl carbenamem; 1β-substituted-methyl carbenamem; 1-fluoromethyl carbenamem; 1-cyanomethyl carbenamem; 1-hydroxymethyl carbenamem; 1-acetoxyxymethyl carbenamem; antagonistic activity; methylcillin-resistant S. aureus (MRSA)

The 1β-methyl carbenamems 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 carbenem skeleton as well as their enhanced chemical and metabolic stability with high antibacterial potency.13 Since the first report on 1β-methyl carbenamems by a Meck group,1 a considerable number of carbenamems 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 methyl1b,3a by a substituent(s) other than alkyl group such as hydroxy,3b methoxy,1b,3b acetoxy,3b fluorne3b often resulted in reduced antibacterial activity or chemical instability.

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

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

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

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

As for the substituent at the 2-position for the 1β-substitued-methyl carbenamems 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 carbenamems 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.3 Therefore, we decided to synthesize the 1β-substitued (fluoro, cyano, hydroxy and acetoxyl)-methyl carbenamems (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-substitued-methyl carbenamems (6—8) with the corresponding 1β-methyl analogs (3—5) prepared in these laboratories is beneficial for the exact evaluation of these new 1β-substitued-methyl carbenamems.

On the other hand, it is now well recognized that 1β-methyl carbenamems showed higher antibacterial activity and metabolic stability than the corresponding 1α-counterparts.15,3b Some 1α-methyl carbenamem derivatives, however, showed more favorable biological property than the corresponding 1β-methyl counterparts.3b Taking these results into consideration, we decided to prepare both the

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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), 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) 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-phenylthiobutanoate 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 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-butylidimethylsilyl (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, through the following sequence. Conversion of the hydroxymethyl olefin (12c) to the corresponding iodide (12g) by a conventional procedure (1. MsCl–Et3N, 2. NaI in hexamethylphosphoramide (HMPA), 78%), and subsequent reduction of this iodide (12g) with sodium cyanoborohydride in HMPA 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.

The 1α-cyanomethyl olefin (12b) was prepared from the 1α-hydroxymethyl olefin (12c) by the conventional two steps procedure (1. MsCl–Et3N, 2. NaCN–tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) in HMPA, 88%).

Attempted fluorinations of the hydroxymethyl derivatives (18c, 12c) using diethylamino sulfinylfluoride (DAST) 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, was introduced to the acetoxyethyl 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-methylene 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
group proceeds much more cleanly than that of the corresponding hydroxy group in some cases.\textsuperscript{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 sulfinamides group of 20a by the literature method (2-mercaptopyridine-Et\textsubscript{3}N)\textsuperscript{13b} 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 (1S)-ester sulfide (16f) using the same reaction sequences as described above. DAST fluorination of the 1β-trimethylsilyl 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 (11a, 12a, 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-COPBA 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\textsuperscript{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 carbinal mixture (23e), and subsequent oxidation of the resulting carbinal mixture afforded the keto phosphorane (24e). Although intramolecular Wittig cyclization of 24e in refluxing benzene gave the carbapenem (29e) in good yield, deprotonation of the TBDMS group of 29e by tetrabutylammonium fluoride accompanied with β-lactam ring cleavage to give the desired diol (30e) 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$_3$N) 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-acetoxyethyl 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 carbinal 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 carbinal (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-position. As described previously, it has shown that the 1β-methyl carbapenems bearing (quaternary heteroatomic)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, 36a, 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-(quaternary 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](chart6.png)
methicillin-sensitive *S. aureus* and low-resistance groups of MRSA (L-MRSA)\(^3\) than imipenem, it showed higher activity against high-resistance groups of MRSA (H-MRSA)\(^3\) 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 substitutes 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 derivaties (7, 8, a, b), remained unchanged.

Contrary to our expectations, conversion of the thiazidazole 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 thiazidazoyliiethiomethyl 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 CDCl3) and in D2O or external (in D2O) standard. In
some cases, 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt (DSS) were used as an internal (in D₂O) standard. Ultraviolet (UV) spectra were measured on a Hitachi 240 spectrometer. Mass spectra (MS) were obtained on a Hitachi M-68 mass spectrometer. Specific optical rotation ([α]D) were taken at 24°C on a Perkin-Elmer 241 Polarimeter. Medium pressure liquid chromatography was performed with Merck prepared columns (Lobar column).

The 1α-substituted methyl carbapenems (9a–d) were much more unstable than the corresponding 1β-isomers and were therefore separated by HPLC instead of by vacuum distillation. In contrast, the 1β-substituted methyl carbapenems (6a–d) had almost the same stability irrespective of the substituents at the 2-position. The stability of the 1-fluoromethyl carbapenems (6a–9a) under the condition (0.05 M 4-morpholino-1-propanesulfonic 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, 11%; 8a, 60%; impenem, 23%. On the other hand, the 1α-fluoromethyl carbapenem (9a) decreased its potency to half within 2.5 h.

(3S,4R)-3-(1R)-1-tert-Butylidimethylsilyloxytetrahydro-1H-imidazol-4-yl)-(1R)-1-ethoxy-carbonyl-3-phenylpropyl)-2-azetidinone (16a) and the Diasteroisomer (16b) To a solution of the N-chymotrypsin azetidinone (14) (62.6 g, 0.175 mol) and the crude ketone acetal (15), prepared from 0.26 mol of ethyl 4-penthylobutyrate and 0.26 mol of LDA, in CH₂Cl₂ (350 ml) was slowly added dimethyl 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 mixture was concentrated to 30 ml. The mixture was poured into ice water, and the organic layer was washed successively with aqueous NaHCO₃, and water, dried and concentrated. The residue was chromatographed on a Lobar column (toluene–AcOEt, 4:1) to give 16a (29.4 g, 57%), 16b (39.6 g, 50%) and the Diasteroisomer (16b) (26.2 g, 3%).

16a: [α]D +23.9º (c=1.014, CHCl₃). IR (CHCl₃): 3400, 1759, 1722 cm⁻¹. 1H-NMR (CDCl₃): δ: 0.84 (9H, s), 1.11 (3H, d, J=6.6 Hz), 1.25 (1H, t, J=7.4 Hz), 4.15–3.25 (6H, m), 3.81 (1H, dd, J=6, 2.6 Hz), 4.16 (2H, q, J=7.2 Hz), 4.18 (1H, m), 6.09 (1H, s), 7.15–7.45 (5H, m).

16b: [α]D +46.6º (c=1.099, CHCl₃). IR (CHCl₃): 3400, 1752, 1712 cm⁻¹. 1H-NMR (CDCl₃): δ: 0.88 (9H, s), 1.08 (3H, d, J=6.7 Hz), 1.26 (1H, t, J=7.5 Hz), 1.55–3.35 (6H, m), 3.68 (1H, dd, J=9, 2.2 Hz), 4.07 (1H, m), 4.19 (2H, q, J=7.2 Hz), 6.04 (1H, s), 7.15–7.45 (5H, m).

(3S,4R)-3-(1R)-1-tert-Butylidimethylsilyloxytetrahydro-1H-imidazol-4-yl)-(1R)-1-hydroxy-methyl-3-phenylpropyl)-2-azetidinone (18c) and the Diasteroisomer (17c) To a stirred solution of 16a (374 mg, 0.828 mmol) in dimethoxyethane (3.7 ml) was added LiH₂PO₄ (90 mg, 1.43 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 NaHCO₃ 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 was obtained by chromatographic purification (Lobar column, toluene–AcOEt, 1:1) and subsequent recrystallization from petroleum ether to give 86–88°C.

18c: IR (CHCl₃): 3400, 1755 cm⁻¹. 1H-NMR (CDCl₃): δ: 0.89 (9H, s), 1.29 (3H, d, J=6.8 Hz), 1.5–3.3 (3H, m), 3.43 (1H, dd, J=8, 2.2 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. Caled for C₂₃H₂₃NO₄S: C, 61.57; H, 8.61; N, 3.42. Found: C, 61.42; H, 8.76; N, 3.39.

The diasteroisomer (17c) was obtained by the same procedure, and an analytical sample was gave 117–119°C (petroleum ether). 18c: IR (CHCl₃): 3400, 1740 cm⁻¹. 1H-NMR (CDCl₃): δ: 0.85 (9H, s), 1.15 (3H, s), 1.15–3.6 (5H, m), 2.46 (1H, t, J=5.3 Hz), 3.52 (1H, dd, J=7, 2.5 Hz), 3.5–3.95 (2H, m), 4.07 (1H, dq, J=6.6 Hz), 6.38 (1H, s), 7.1–7.5 (5H, m). Anal. Caled for C₂₃H₂₃NO₄S: C, 61.57; H, 8.61; N, 3.42. Found: C, 61.42; H, 8.48; N, 3.44.

The following compounds (18a, 18b, 18d, 18e) were prepared from 18c and/or 17c by conventional methods (TBDMSI–imidazole in N,N-dimethylformamide (DMF) and/or Ac₂O–pyridine in CH₂Cl₂).

(3S,4R)-3-(1R)-1-tert-Butylidimethylsilyloxytetrahydro-1H-imidazol-4-yl)-(1R)-1-tert-Butylidimethylsilyloxy-methyl-3-phenylpropyl)-2-azetidinone (18e) and the Diasteroisomer (17e) 18e: IR (CHCl₃): 3400, 1748 cm⁻¹. 1H-NMR (CDCl₃): δ: 0.88 (9H, s), 1.15 (3H, d, J=6.8 Hz), 2.15–2.80 (3H, m), 2.85 (1H, dd, J=6, 2.1 Hz), 3.61 (1H, dd, J=7, 2.1 Hz), 4.16 (1H, dq, J=6.6 Hz), 5.16–6.01 (3H, m), 6.47 (1H, s). Anal. Caled for C₂₃H₂₃NO₄S·0.4H₂O: C, 60.87; H, 9.20; N, 8.88. Found: C, 60.83; H, 8.97; N, 8.94.

The diasteroisomer (17e) mp 115–118°C was prepared by the same procedure.

11b: [α]D −34.7º (c=1.010, CHCl₃). IR (CHCl₃): 3400, 1762 cm⁻¹.
1H-NMR (CDCl3) δ 8.02 (9H, s), 1.19 (3H, d, J = 6.6 Hz), 2.54 (2H, d, J = 3.2 Hz), 2.4–2.8 (2H, m), 2.85 (1H, dd, J = 5, 2 Hz), 3.67 (1H, dd, J = 8, 2.8 Hz), 3.88 (1H, d, J = 2.8 Hz), 4.09 (1H, dd, J = 2.8, 8.8 Hz), 4.19 (1H, dq, J = 6.4, 4.4 Hz), 5.18–5.85 (3H, m), 5.2–5.9 (3H, m). Anal. Calc. for C12H13NO2SiS: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.51; H, 9.31; N, 3.38.

20f: IR (CHCl3): 1754 cm⁻¹. 1H-NMR (CDCl3) δ 0.88 (9H, s), 1.18 (3H, d, J = 6.4 Hz), 2.43 (2H, s), 2.46–2.58 (2H, m), 3.06 (1H, dd, J = 4.0, 2.8 Hz), 3.67 and 3.83 (2H, ABX), 5.12 (1H, d, J = 2.8 Hz), 5.45 (1H, d, J = 8.8 Hz), 5.67 (1H, dq, J = 6.4, 4.4 Hz), 5.78–5.85 (3H, m). Anal. Calc. for C12H13NO2SiS: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.59; H, 9.36; N, 3.34.

(35,4S)-3-[1R]-1-tert-Butylidimethylsilyloxyethyl]-4-[1(S)-1-fluoromethyl-2-propenyl]-1-methylthio-2-acetidinone (19a) The TMS ethers (19f, 20f) were prepared by a conventional method (TMSCl,pyridine in CH2Cl2) from the corresponding alcohols (19c, 20c), respectively.

19c: mp 36–37 °C. IR (CHCl3): 1740 cm⁻¹. 1H-NMR (CDCl3) 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), 4.10 (1H, d, J = 6.2 Hz), 4.31 (1H, d, J = 3.4, 6.2 Hz), 5.03–5.75 (3H, m). MS m/z: 417 [M⁺]. Anal. Calc. for C12H13NO2SiS: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.51; H, 9.31; N, 3.38.

20f: IR (CHCl3): 1754 cm⁻¹. 1H-NMR (CDCl3) δ 0.88 (9H, s), 1.18 (3H, d, J = 6.4 Hz), 2.43 (2H, s), 2.46–2.58 (2H, m), 3.06 (1H, dd, J = 4.0, 2.8 Hz), 3.67 and 3.83 (2H, ABX), 5.12 (1H, d, J = 2.8 Hz), 5.45 (1H, d, J = 8.8 Hz), 5.67 (1H, dq, J = 6.4, 4.4 Hz), 5.78–5.85 (3H, m). Anal. Calc. for C12H13NO2SiS: C, 54.62; H, 9.41; N, 3.35. Found: C, 54.59; H, 9.36; N, 3.34.
crude 245, thus obtained, was dissolved in CH2Cl2 (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 then diluted with AcOEt. After the usual work up, the residue was dissolved in CHCl3 (4 ml) and cooled to 0 °C. To this mixture was added Et2O (0.15 ml, 1.08 mmol) and TMSCl (0.137 ml, 0.87 mmol), and the whole was stirred for 20 min at the same temperature. The reaction mixture was poured into aqueous NaHCO3 and worked up in the usual way to give the crude 265. A solution of 258 (3.97 g 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 288 (32 mg, 99% from 238) as pale yellow oil.

288 IR (CHCl3) 1775, 1710 cm−1. 1H-NMR (CDCl3) δ = 1.11 (3H, d, J = 6.6 Hz), 3.03 (3H, s, J = 6.6 Hz), 3.36 (3H, s, J = 8.5 Hz), 3.68 (3H, s), 3.75 (2H, d, J = 5.5 Hz), 3.85 (1H, d, J = 8.5 Hz), 4.08 (1H, q, J = 6.2 Hz), 4.13 and 4.63 (2H, ABq, J = 12.5 Hz), 5.20 (2H, s), 6.76 and 7.29 (2H × 2, d, J = 8.9 Hz), 8.89 (1H, s). MS (LSIMS, glycerol) m/z = 622 (M + H•)

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

II.B.1.3.4-Thiazolid-2-yl)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-2-trimethylsilyloxyethylcarbenap-2-em-carboxylate (33B) IR (CHCl3) 2400, 1785, 1720 cm−1. 1H-NMR (CDCl3) δ = 1.25 (3H, d, J = 6.0 Hz), 2.69 and 2.95 (2H, ABX, J = 11, 9, 3.6 Hz), 3.40 (1H, dd, J = 4.5, 3.5 Hz), 3.3–3.9 (1H, m), 3.78 (3H, s), 4.30 (1H, dd, J = 11, 3.6 Hz), 4.26 and 4.94 (2H, ABq, J = 14.5 Hz), 5.24 (2H, s), 6.86 and 7.38 (2H × 2, d, J = 8.9 Hz), 9.03 (1H, s). MS (LSIMS, glycerol) m/z = 559 (M + H•)•

II.B.2.1-(3,4-Thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (28a) IR (CHCl3) 1777, 1713 cm−1. 1H-NMR (CDCl3) δ = 1.25 (3H, d, J = 6.0 Hz), 3.58 (1H, dd, J = 6.6, 3.2 Hz), 3.5–3.8 (1H, m), 3.80 (1H, s), 4.06 (1H, dd, J = 8.2, 3.4 Hz), 1.78 (1H, q, J = 6.2 Hz), 5.0–5.1 (4H, m), 5.19 and 5.26 (2H, ABq, J = 12.2 Hz), 6.88 and 7.38 (2H × 2, d, J = 8.6 Hz), 9.00 (1H, s). MS (LSIMS, glycerol) m/z = 552 (M + H•)

II.B.3.1-(3,4-Thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (33a) IR (CHCl3) 1782, 1715 cm−1. 1H-NMR (CDCl3) δ = 1.24 (3H, d, J = 6.0 Hz), 3.3–3.6 (1H, m), 3.81 (3H, s), 3.47 (1H, dd, J = 5.4, 2.6 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, ABX, J = 10, 4.2, 2.8 Hz), 5.22 and 5.28 (2H, ABq, J = 12.2 Hz), 6.88 and 7.39 (2H × 2, d, J = 8.8 Hz), 9.00 (1H, s). MS (LSIMS, glycerol) m/z = 552 (M + H•)

II.C.1.(3,4-Thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (36c)

Sodium (15,5,6,6)-(6-[(1R)-1-Hydroxyethyl]-1-hydroxy-2-[(1,3,4-thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (6c) (6c) (6c)

Sodium (15,5,6,6)-(6-[(1R)-1-Hydroxyethyl]-1-hydroxy-2-[(1,3,4-thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (6d) (6d) (6d)

Sodium (15,5,6,6)-(6-[(1R)-1-Hydroxyethyl]-1-hydroxy-2-[(1,3,4-thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (9a) (9a) (9a)

Sodium (15,5,6,6)-(6-[(1R)-1-Hydroxyethyl]-1-hydroxy-2-[(1,3,4-thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (6a) (6a) (6a)

Sodium (15,5,6,6)-(6-[(1R)-1-Hydroxyethyl]-1-hydroxy-2-[(1,3,4-thiazolid-2-y1)-thioimethyl-6-[(1R)-1-trimethylsilyloxyethyl]-carbenap-2-em-carboxylate (9b) (9b) (9b)

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p-Methoxybenzyl (1S,5S,5S)-1-Fluoromethyl-6-[(1R)-1-hydroxyethyl]-2-(1-methyl-4- pyridinio)thiobenzylcarbapen-2-3-carboxylate (7a) R (CHCl₃): 1871, 1715, 1651 cm⁻¹. IR (KBr): 3400, 1740, 1652, 1254 cm⁻¹. FAB mass spectrum (m/z): 792 [M+H⁺]⁺.

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References and Notes