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Carbapenem and Penem Antibiotics. II. Synthesis and Antibacterial Activity of 2-Functionalized-methyl Carbapenems Related to Asparenomycins[1)]

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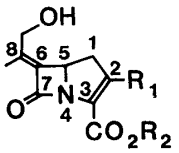
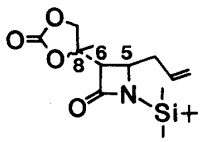
Racemic 2-acetoxymethyl and 2-(heteroaromatic)thiomethyl carbapenems having a 1-(hydroxymethyl)ethylidene or cyclic carbonate side-chain at C-6 (**5**, **25**, **38**, **40**, **42**, and **36b**, **23b**, **28b**, **30b**, **32b**, **34b**) were synthesized from the common intermediates **3a** and **3b**, and their antibacterial activities were determined.

Keywords——β-lactam antibiotic; carbapenem antibiotic; 2-functionalized-methyl carbapenem; asparenomycin; allylazetidinone; cyclic carbonate; intramolecular Wittig reaction; carbapenem antibiotic carboxy deprotection; antibacterial activity

In the preceding paper we reported the establishment of a convenient methodology for synthesizing carbapenems **1** having at C-6 the 1-(hydroxymethyl)ethylidene side-chain, characteristic of asparenomycins (**2**), starting from azetidinone-carbonates **3a**, **b**, as well as the successful synthesis of *dl*-asparenomycins and related derivatives.[2)] The antibacterial activity





3a : (5*R**, 6*S**, 8*R**)
3b : (5*R**, 6*S**, 8*S**)

1: R_1=H
2: R_1=(O)n S NHAc , R_2=Na
4: R_1=CH_2-S-heteroaromatic , R_2=Na
5: R_1=CH_2OAc , R_2=CH_2OC(=O)+ (POM)
6: R_1=CH_3 , R_2=Na

Chart 1

of the synthesized compounds was, however, found to be insufficient, especially against Gram-positive bacteria, to justify further effort.

In an attempt to discover more potent antibiotics with the same C-6 side-chain, we then modified the C-2 position of the parent asparenomycin structure by replacing the original alkylthio group with a methyl group with or without a functional group. As will be described in this paper, we eventually found that the 2-(heteroaromatic)thiomethyl derivatives **4** as well as the acetoxymethyl derivatives **5** possessed excellent antibacterial activity.

We report herein details of the synthesis and antibacterial activity of the synthesized compounds.

Chemistry

As a first step in the modification work, we prepared the 2-methyl derivative **6** starting from the common intermediate **3a**, as shown in Chart 2. Preparation of the carbapenem **10a**

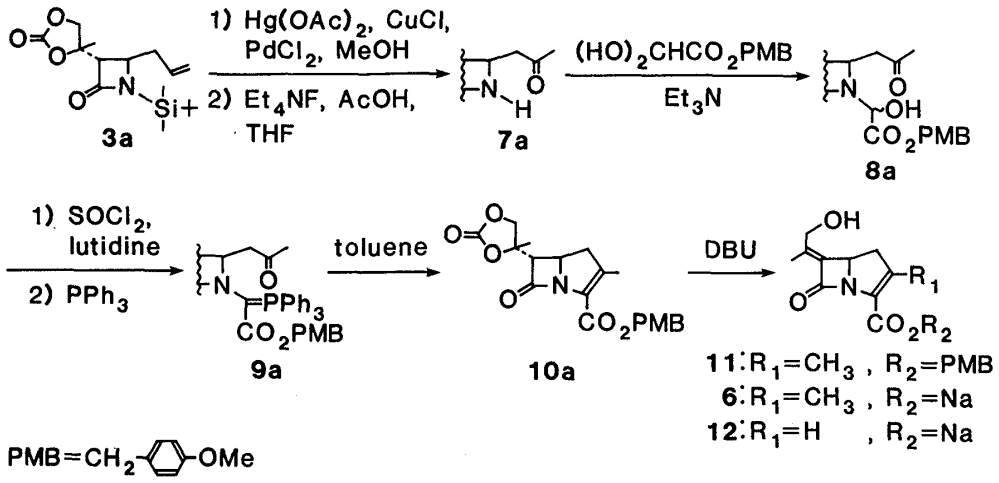


Chart 2

was easily achieved by an established method[3] using an intramolecular Wittig reaction of the ylid **9a**, which proceeded smoothly in refluxing toluene. Transformation of the carbonate-carbapenem **10a** into the sodium salt of the asparenomycin-type compound **6** was effected by brief treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene followed by deprotection of the carboxyl group with $AlCl_3$ and anisole as reported in the preceding paper.[2] The 2-methyl compound **6**, which turned out to be unexpectedly unstable and was obtained in only 18% yield from the ester **11**, showed greatly diminished antibacterial activity in comparison with the corresponding 2-unsubstituted carbapenem **12**.[4]

We then decided to synthesize novel carbapenems **4** having a functionalized methyl group at C-2, which could be viewed as a hybrid of the naturally occurring carbapenem and cephalosporin structures.

Although such compounds would, in principle, be accessible from the intermediates **3a** and **3b** by applying an intramolecular Wittig reaction as used for the preparation of the above 2-methyl compound **6**, the presence of a leaving group at the C-2 methyl group would make the carbapenem compounds very labile. Therefore we first tried to synthesize a pivaloyloxymethyl (POM) ester of the 2-acetoxymethyl derivative **5** which we expected to be one of the least unstable compounds.

The synthesis of **5** was carried out as shown in Chart 3. Epoxidation of the allylazetidinone **3a** with *m*-chloroperbenzoic acid (*m*-CPBA) gave an epimeric mixture of epoxides **13a**

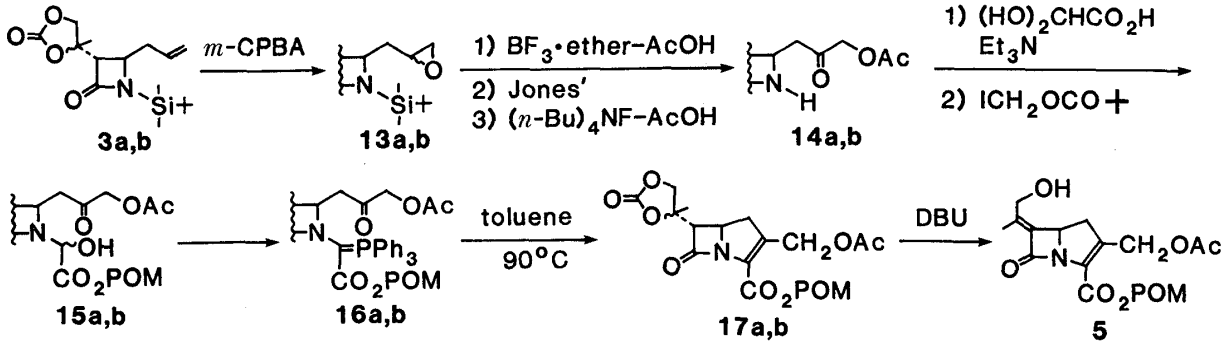
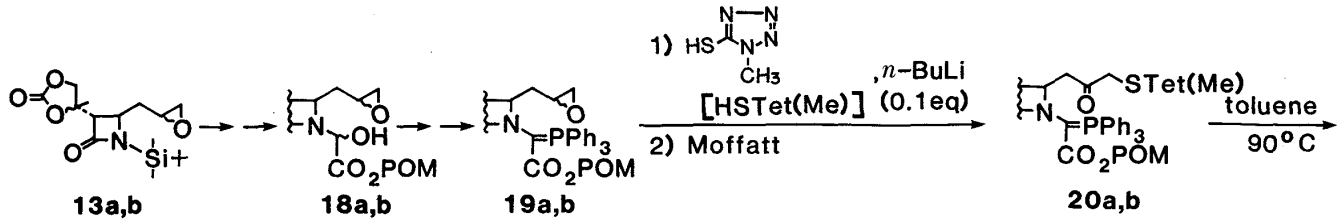
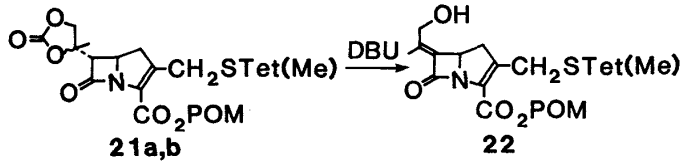
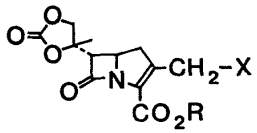
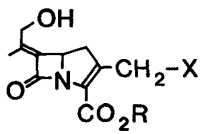


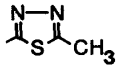
Chart 3



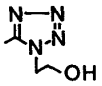


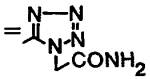




Tz(Me) = 

Tz(H) = 

Tet(CH_2CH_2OH) = 

Tet(CH_2CONH_2) = 

23b : R=Na , X=STet(Me)
24a,b : R=PMB , X=STet(Me)
27b : R=PMB , X=STz(Me)
28b : R=Na , X=STz(Me)
29b : R=PMB , X=STz(H)
30b : R=Na , X=STz(H)
31b : R=PMB , X=STet(CH_2CH_2OH)
32b : R=Na , X=STet(CH_2CH_2OH)
33b : R=allyl , X=STet(CH_2CONH_2)
34b : R=Na , X=STet(CH_2CONH_2)
35b : R=PMB , X=OAc
36b : R=Na , X=OAc

25 : R=Na , X=STet(Me)
26 : R=PMB , X=STet(Me)
37 : R=PMB , X=STz(Me)
38 : R=Na , X=STz(Me)
39 : R=PMB , X=STz(H)
40 : R=Na , X=STz(H)
41 : R=PMB , X=STet(CH_2CH_2OH)
42 : R=Na , X=STet(CH_2CH_2OH)
43 : R=Na , X=STet(CH_2CONH_2)

Chart 4

which were converted into the keto-acetate **14a** by epoxide cleavage with acetic acid and BF_3-etherate and subsequent oxidation followed by *N*-desilylation. The azetidinone **14a** was transformed to the ylid **16a** in the usual way *via* **15** without any difficulties, and on heating in toluene at 90 °C, **16a** cyclized cleanly to give the carbapenem **17a**. Preparation of the desired asparenomycin-type carbapenem **5** was achieved by brief treatment of **17a** in benzene with a catalytic amount of DBU. The POM ester **5** was found to be reasonably stable and showed excellent antibacterial activity when assayed in the presence of horse serum.

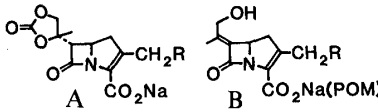
Since this result was encouraging, we then prepared a C-2 1-methyltetrazolylthiomethyl derivative **22**, which was expected to be biologically more active but chemically less stable because of the better leaving ability of the tetrazolylthio group.

Synthesis of **22** was achieved by a somewhat different sequence of reactions from that of the acetoxymethyl derivatives **5**, as shown in Chart 4. The epoxides **13a** and **13b** were converted into the epoxy-ylids **19a** and **19b** *via* **18a** and **18b** by the usual multi-step sequence. Epoxy-cleavage with thiol in the presence of a catalytic amount of a base followed by oxidation afforded the keto-ylids **20a** and **20b**, which were subjected to heating at 90 °C in toluene giving the carbapenems **21a** and **21b**. Both compounds were then transformed into the target compound **22**, which showed, as expected, more potent antibacterial activity than the acetoxy derivative.

Moreover, we were surprised to find that the corresponding carbonate **21b** having a 5*R**,6*S**,8*S** stereostructure possessed activity almost identical with that of **22**, whereas the isomeric carbonate **21a** had only a fraction of the activity. Because the chemical stability of the carbapenem **21b** with the less-vulnerable carbonate side-chain was expected to be higher than that of the asparenomycin-type counterpart **22**, we considered that sodium carboxylate **23** might be prepared safely from the *p*-methoxybenzyl (PMB) ester **24b** by using the $AlCl_3$–anisole carboxy deprotection method.[2] This assumption proved to be correct, and even the asparenomycin-type compound **25** could be produced by this method.

Thus, the PMB ester **24b**, prepared in the same way as **21**, was subjected to the deblocking reaction to afford the salt **23b** with a fairly good purity. Similarly, compound **26** prepared from **24a** was deprotected to give the salt **25**. By following the same sequence of reactions as described above, analogs **27**—**43** having other functional groups at C-2′ were

TABLE I. *In Vitro* Antibacterial Activity[a]



R	Structure		MIC (μg/ml)					
			S. aureus C-14(R)	*S. pyogenes* C-203	*E. coli* EC-14	*K. pneumoniae* SRL-1	*P. vulgaris* CN-329	*S. marcescens* A13880
OAc	A	**36b**	0.39	0.39	0.39	0.78	1.56	3.13
	B(POM)[b]	**5**	0.39	0.39	0.2	0.39	3.13	3.13
STet(Me)	A	**23b**	0.39	0.2	0.2	0.39	0.78	1.56
	B	**25**	0.39	0.39	0.39	0.39	0.78	1.56
STz(Me)	A	**28b**	0.39	0.39	0.78	0.78	1.56	12.5
	B	**38**	0.2	0.2	0.78	0.78	0.78	12.5
STz(H)	A	**30b**	0.2	0.2	0.39	0.78	0.78	3.13
	B	**40**	0.1	0.39	0.2	0.39	0.78	3.13
STet(CH_2CH_2OH)	A	**32b**	0.39	0.2	0.2	0.39	0.78	0.78
	B	**42**	0.39	0.39	0.2	0.39	0.78	1.56
STet(CH_2CONH_2)	A	**34b**	0.78	0.78	0.39	0.78	1.56	3.13
H	B	**6**	>100	>100	25	50	>100	>100

a) MICs (minimum inhibitory concentrations) were determined by the agar dilution method. Inoculation was performed with one loopful of 10^6 cells per ml. *b*) Assay medium was supplemented with 5% horse serum.

prepared. We also found that the carbapenem carboxylates A (Table I) with the 8*S**-carbonate side-chain can be transformed cleanly into the asparenemycin-type derivatives B when they are allowed to stand in a diluted sodium bicarbonate solution for several hours at room temperature.

In certain cases (**32b** and **34b**), isolation of pure material was found to be difficult due to contamination with the asparenomycin-type compounds **42** and **43**, respectively, which were produced during HP-20AG chromatography. In order to avoid this problem, we employed a recently developed deprotection procedure which was used successfully for penem antibiotics.[5] The allyl ester **33b** could be transformed cleanly into the salt **34b** by treatment with a catalytic amount of $Pd(PPh_3)_4$ and sodium ethylhexanoate.

Antibacterial Activity

The above carbapenem derivatives having either the 1-(hydroxymethyl)ethylidene or the carbonate side-chain at C-6 were tested for antibacterial activity, and the results are shown in Table I.

The carbapenems with the carbonate side-chain of 5*R**,6*S**,8*S** stereochemistry showed the same antibacterial properties against both Gram-positive and -negative organisms as the corresponding asparenomycin-type counterparts. Most of the compounds having a 2-functionalized methyl group exhibited potent antibacterial activity against a broad range of microorganisms except *Pseudomonas aeruginosa*. The very poor antibacterial activity of the 2-methyl derivative **6** is probably due to chemical instability.

Experimental

All reactions were carried out under a nitrogen atmosphere using dry solvents under anhydrous conditions, unless otherwise stated. Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi 260-10 spectrophotometer in $CHCl_3$ as a solvent or a JASCO DS-403G spectrophotometer in KBr unless otherwise noted. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60A or a Varian EM-390 (90 MHz) spectrometer for ^{1}H-NMR in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard and a Varian XL-100A (100 MHz) in D_2O with TMS as an external standard unless otherwise stated. Ultraviolet (UV) spectra were obtained on a Hitachi EPS-3T or EPS-2 spectrometer. Mass spectra (MS) were obtained on a Hitachi RUM8-GN (FD-Mass) or M-68 (SIMS) mass spectrometer. Elemental analysis values obtained were within 0.3% of those calculated for the formula given. Medium-pressure liquid chromatographies were performed on Merck "Lobar®" prepacked columns packed with LiChroprep Si 60; size A (240—10 mm, 40—60 μm), size B (310—25 mm, 40—63 μm) and size C (440—37 mm, 63—125 μm). Organic solvents were dried with $MgSO_4$ and removed by evaporation under reduced pressure using a rotary evaporator.

(3*S,4*R**)-3-[(4*R**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-4-(2-oxopropyl)-2-azetidinone (7a)**——A solution of the allylazetidinone **3a** (1.73 g, 5.3 mmol) and mercuric acetate (1.92 g, 1.1 eq) in methanol (10 ml) was stirred at room temperature for 2 h and then added to a solution of cuprous chloride dihydrate (3.09 g) and palladium chloride (120 mg) in methanol (20 ml). The mixture was stirred at 60 °C for 1 h. After cooling, the reaction mixture was made basic with saturated $NaHCO_3$ solution, filtered and concentrated to remove most of the methanol. The product was extracted with EtOAc, washed with water and dried. Concentration of the extract and chromatography of the residue on a Lobar column (size B, benzene–EtOAc 1 : 1) gave the ketone (1.62 g, 86%).

A solution of the above ketone in tetrahydrofran (THF 10 ml) containing acetic acid (0.4 g) was treated with tetraethylammonium fluoride dihydrate (1.38 g, 1.2 eq), and the mixture was stirred at room temperature for 2 h, then diluted with EtOAc, washed with saturated brine, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 5) to give **7a** (895 mg, 83%); mp 131—132 °C (benzene). IR: 2900, 1805, 1760, 1715 cm^{-1}. ^{1}H-NMR δ: 1.60 (3H, s, C-8Me), 2.17 (3H, s, COMe), 2.83 (1H, d, J=4 Hz, C-6H), 3.00 (2H, m, $COCH_2$), 3.93 (1H, dd, J=4, 2 Hz, C-5H), 4.13 and 4.67 (2H, ABq, J=9 Hz, OCH_2), 6.67 (br, NH). *Anal.* Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.76; N, 6.16. Found: C, 52.64; H, 5.65; N, 6.11.

***p*-Methoxybenzyl (5*R**,6*S**)-2-Methyl-6-[(4*R**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (10a)**——A mixture of the azetidinone **7a** (1.00 g, 4.39 mmol), glyoxylic acid PMB ester (1.12 g, 1.2 eq) and triethylamine (61 μl, 0.1 eq) in THF (20 ml) was allowed to stand at room temperature overnight. The reaction mixture was concentrated, diluted with EtOAc, washed with water, dried, concentrated and chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 5) to give **8a** as an epimeric mixture. **8a**: IR: 3500, 1805, 1760, 1600 cm^{-1}. ^{1}H-NMR δ: 1.51 and 1.52 (3H, s, C-8Me), 2.05 and 2.09 (3H, s, COMe), 2.85 (2H, m, CH_2CO), 3.19 and 3.21 (1H, d,

$J=2$ Hz, C-6H), 3.80 (3H, s, OMe), 4.05 and 4.51 (2H, ABq, $J=8$ Hz, C-8CH_2), 4.10 (1H, m, C-5H), 5.15 (2H, s, CO_2CH_2), 5.20 and 5.22 (1H, s, CHOH), 6.80 and 7.30 (4H, A_2B_2q, $J=8$ Hz, Ar). MS (FD) *m/e*: 421 (M^+).

A solution of **8a** (1.52 g, 3.6 mmol) in THF (20 ml) was treated at −20 °C with 2,6-lutidine (1.0 ml, 1.3 eq) and thionyl chloride (337 μl, 1.3 eq) for 1.5 h. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ solution and brine, dried and concentrated to give the chlorides (1.55 g, 98%). IR: 1805, 1760, 1600 cm^{-1}. ^{1}H-NMR δ: 1.52 (3H, s, C-8Me), 2.14 (3H, s, COMe), 3.00 (2H, m, CH_2CO), 3.30 and 3.32 (1H, d, $J=2$ Hz, C-6H), 3.80 (3H, s, OMe), 4.05 and 4.52 (2H, ABq, $J=8$ Hz, C-8CH_2), 4.35 (1H, m, C-5H), 5.15 and 5.20 (2H, s, CO_2CH_2), 6.10 and 6.18 (1H, s, CHCl), 6.80 and 7.30 (4H, A_2B_2q, $J=8$ Hz, Ar). MS (FD) *m/e*: 439 (M^+).

A mixture of the above chlorides (1.55 g, 3.53 mmol), PPh_3 (1.13 g, 1.2 eq) and 2,6-lutidine in dioxane (10 ml) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ solution and brine, dried, concentrated and chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 1) to give the ylid **9a** (1.60 g, 68%). IR: 1805, 1740, 1650, 1600 cm^{-1}. ^{1}H-NMR δ: 1.49 (3H, s, C-8Me), 2.12 (3H, s, COMe), 3.00 (2H, d, $J=8$ Hz, CH_2CO), 3.50 (1H, d, $J=2$ Hz, C-6H), 3.80 (3H, s, OMe), 4.00—5.20 (3H, m, C-5H, C-8CH_2), 6.60 (2H, s, CO_2CH_2), 6.80 and 7.30 (4H, A_2B_2q, $J=8$ Hz, Ar), 7.40—7.80 (15H, m, Ar).

A solution of the ylid **9a** (1.60 g, 2.4 mmol) in toluene (30 ml) was refluxed for 3.5 h. Evaporation of the solvent and chromatography of the residue on a Lobar column (size B, benzene–EtOAc 1 : 3) gave the title compound **10a** (639 mg, 69%) as an amorphous powder. IR: 1805, 1790, 1720 cm^{-1}. ^{1}H-NMR δ: 1.62 (3H, s, C-8Me), 2.10 (3H, s, C-2Me), 2.85 (2H, d, $J=6$ Hz, C-1H_2), 3.43 (1H, d, $J=2$ Hz, C-6H), 3.80 (3H, s, OMe), 4.10 (1H, m, C-5H), 4.15 and 4.60 (2H, ABq, $J=8$ Hz, C-8CH_2), 5.20 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, $J=8$ Hz, Ar). MS (FD) *m/e*: 387 (M^+).

***p*-Methoxybenzyl 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-methylcarbapen-2-em-3-carboxylate (11)**——A solution of DBU in toluene (1 M, 300 μl) was added to a solution of **10a** (477 mg, 1.23 mmol) in benzene-d_6 (5 ml), and the mixture was stirred under ice cooling until the reaction was complete (checked by NMR, 1 h). The reaction mixture was diluted with EtOAc, washed with diluted hydrochloric acid (1 N) and water, dried, concentrated and chromatographed on a Lobar column (size B, hexane–CH_2Cl_2–EtOAc 1 : 1 : 2) to give the title compound **11** (341 mg, 81%) as an amorphous powder. IR: 3400, 1750, 1710 cm^{-1}. ^{1}H-NMR δ: 1.98 (3H, s, C-8Me), 2.07 (3H, s, C-2Me), 2.80 (2H, d, $J=8$ Hz, C-1H_2), 3.79 (3H, s, OMe), 4.20 (2H, s, C-8CH_2), 4.70, (1H, m, C-5H), 5.20 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, $J=8$ Hz, Ar). MS (FD) *m/e*: 343 (M^+).

Sodium 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-methylcarbapen-2-em-3-carboxylate (6)——Compound **11** (310 mg, 0.90 mmol) was added to a solution of $AlCl_3$ (482 mg, 3.62 mmol, 4.0 eq) in a mixture of anisole (5 ml) and CH_2Cl_2 (1 ml) at −40 °C, and the mixture was stirred at the same temperature for 1.5 h. A solution of $NaHCO_3$ (1.1 g, 4.2 eq) in phosphate buffer (0.01 M, pH 7, 5 ml) was added to the reaction mixture at −40 °C and the whole was stirred for 30 min under ice cooling, then filtered. The aqueous filtrate was washed with CH_2Cl_2 and chromatographed on a Diaion HP-20AG column (2 × 30 cm, water). Fractions containing the product (checked by HPLC, Nucleosil 10C_{18}, 0.02 M pH 7 phosphate buffer–10% MeOH) were combined, concentrated and freeze-dried to give the title compound **6** (38 mg, 18%) as a pale yellow powder. ^{1}H-NMR (90 MHz D_2O, ext. TMS) δ: 2.43 (3H, s, C-8Me), 2.58 (3H, s, C-2Me), 3.35 (2H, d, $J=6$ Hz, C-1H_2), 4.65 (2H, s, C-8CH_2), 4.95 (1H, m, C-5H). UV (H_2O): 218, 295 nm. MS (SIMS, glycerol) *m/e*: 268 $(M+Na)^+$.

(3*S,4*R**)-1-*tert*-Butyldimethylsilyl-4-(2,3-epoxypropyl)-3-[(4*R**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]-2-azetidinone (13a)**——A mixture of **3a** (1.40 g, 4.29 mmol) in CH_2Cl_2 (20 ml) was treated with *m*-CPBA (85%, 2.30 g, 1.5 eq) under ice cooling and the mixture was stirred at room temperature for 2 d. The reaction mixture was washed with aqueous $NaHSO_3$ solution, aqueous $NaHCO_3$ solution and water, then dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 2 : 1) to give a less polar epoxide (564 mg, 38%) and a more polar epoxide (780 mg, 53%). ^{1}H-NMR (less polar epoxide) δ: 0.23 (3H, s, SiMe), 0.27 (3H, s, SiMe), 0.97 (9H, s, *tert*-Bu), 1.60 (3H, s, Me), 1.50—3.00 (5H, m, C-1H_2, epoxide-H_3), 3.33 (1H, d, $J=3$ Hz, C-6H), 3.85 (1H, m, C-5H), 4.16 and 4.77 (2H, ABq, $J=8$ Hz, C-8CH_2). (Polar epoxide) δ: 0.23 (3H, s, SiMe), 0.27 (3H, s, SiMe), 0.97 (9H, s, *tert*-Bu), 1.57 (3H, s, Me), 1.50—3.00 (5H, m, C-1H_2, epoxide-H_3), 3.30 (1H, d, $J=2$ Hz, C-6H), 3.83 (1H, m, C-5H), 4.10 and 4.73 (2H, ABq, $J=8$ Hz, C-8CH_2).

(3*S,4*R**)-4-(3-Acetoxy-2-oxopropyl)-3-[(4*R**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]-2-azetidinone (14a)**——BF_3-etherate (360 μl) was added to a solution of **13a** (6.00 g, 18.4 mmol, mixture of isomers) in a mixture of CH_2Cl_2 (30 ml) and acetic acid (20 ml) under ice cooling, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2, washed with water and aqueous $NaHCO_3$ solution, dried and concentrated.

The residue (6.2 g, *ca.* 88%, hydroxy-acetates) was dissolved in CH_2Cl_2 (100 ml) and added dropwise to ice-cooled Collins' reagent which had been prepared by mixing CrO_3 (3.0 g) and pyridine (4.8 ml) in CH_2Cl_2 (20 ml). The whole was stirred for 30 min under ice cooling and at room temperature for 2 h. The reaction mixture was filtered, washed with water, dried and concentrated to give a residue, which was chromatographed on a Lobar column (size C, benzene–EtOAc 1 : 1) to give the acetoxy-*N*-silyl compound (5.38 g, 77%). IR: 1805, 1760 cm^{-1}; ^{1}H-NMR δ: 0.20 (3H, s, SiMe), 0.23 (3H, s, SiMe). 0.97 (9H, s, *tert*-Bu), 1.53 (3H, s, Me), 2.12 (3H, s, Ac), 2.87 (2H, m, $COCH_2$), 3.12 (1H, d, $J=2$ Hz, C-6H), 3.97 (1H, m, C-5H), 4.06 and 4.65 (2H, ABq, $J=8$ Hz, C-8CH_2).

Tetraethylammonium fluoride dihydrate (693 mg, 1.5 eq) was added to a solution of the above *N*-silyl compound

(1.0 g, 2.5 mmol) in THF (10 ml) containing acetic acid (220 μl) under ice cooling, and the mixture was stirred for 1 h at room temperature, then diluted with EtOAc, washed with saturated brine (*ca.* 10 ml), dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 2) to give **14a** (573 mg, 80%). IR: 2850, 1805, 1760, 1720 cm^{-1}. ^{1}H-NMR δ: 1.60 (3H, s, C-8Me), 2.12 (3H, s, Ac), 2.92 (2H, m, $COCH_2$), 3.20 (1H, d, J= 2 Hz, C-6H), 3.97 (1H, m, C-5H), 4.00 and 4.27 (2H, ABq, J=8 Hz, C-8CH_2), 4.73 (2H, s, $COCH_2O$), 7.12 (1H, br s, NH).

Pivaloyloxymethyl (5*R,6*S**)-2-Acetoxymethyl-6-[(4*R**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (17a)**——A mixture of **14a** (359 mg, 1.26 mmol), glycolic acid hydrate (116 mg, 1.0 eq) and triethylamine (263 μl, 1.5 eq) in THF (5 ml) was stirred with Molecular Sieves 4A at room temperature overnight. The reaction mixture was filtered and concentrated to give a residue, which was dissolved in dimethylformamide (DMF 2 ml). This solution was treated with iodomethyl pivalate (312 μl, 1.5 eq), and the reaction mixture was stirred for 10 min under ice cooling and for 5 min at room temperature, then diluted with EtOAc, washed with water, dried and concentrated to give a residue, which was chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 2) to give the POM ester **15a** (558 mg, 93%) as a mixture of stereoisomers. ^{1}H-NMR δ: 1.27 (9H, s, *tert*-Bu), 1.63 (3H, s, C-8Me), 2.17 (3H, s, Ac), 3.00 (2H, d, J=9 Hz, C-1H_2), 3.37 (1H, d, J=2 Hz, C-6H), 4.13 and 4.60 (2H, ABq, J=8 Hz, C-8CH_2), 4.17 (1H, m, C-5H), 4.70 (2H, s, $COCH_2O$), 5.33 (1H, br s, OH), 5.63 (1H, s, NCH), 5.87 (2H, d, J=6 Hz, CO_2CH_2).

2,6-Lutidine (135 μl, 1.5 eq) and thionyl chloride (85 μl, 1.5 eq) were added to a solution of the above POM ester **15a** (558 mg, 1.18 mmol) in THF (10 ml) cooled at −20 °C, and the mixture was stirred at −20 °C for 30 min and under ice cooling for 30 min, then diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried and concentrated. A mixture of the residue, triphenylphosphine (616 mg, 2 eq) and 2,6-lutidine (203 μl, 1.5 eq) in dioxane (5 ml) was stirred at room temperature overnight. The reaction mixture was concentrated, diluted with EtOAc, washed with water, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 2) to give the ylid **16a** (451 mg, 54% from **15a**). IR: 1805, 1740 cm^{-1}.

A solution of the above ylid **16a** (451 mg, 0.63 mmol) in toluene (20 ml) was heated at 90 °C (bath temperature) for 4 h. The reaction mixture was concentrated and the residue was chromatographed on a Lobar column (size A, benzene–EtOAc 1 : 1) to give the title compound **17a** (130 mg, 48%). IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.25 (9H, s, *tert*-Bu), 1.63 (3H, s, C-8Me), 2.07 (3H, s, Ac), 3.07 (2H, d, J=10 Hz, C-1H_2), 3.57 (1H, d, J=2 Hz, C-6H), 4.17 (1H, m, C-5H), 4.20 and 4.60 (2H, ABq, J=8 Hz, C-8CH_2), 5.10 (2H, d, J=8 Hz, C-2CH_2), 5.87 (2H, d, J=6 Hz, CO_2CH_2).

Pivaloyloxymethyl 2-Acetoxymethyl-6-[(*E*)-1-(hydroxymethyl)ethylidene]carbapen-2-em-3-carboxylate (5)——A solution of DBU in toluene (1 M, 20 μl) was added to a solution of **17a** (120 mg, 0.28 mmol) in C_6D_6 (0.5 ml), and the reaction mixture was stirred for 10 min at room temperature, then diluted with EtOAc, washed with water,dried and concentrated. The residue was purified by preparative high performance liquid chromatography (HPLC) (Nucleosil 30C_{18}, 20 × 250 mm, MeOH–H_2O 6 : 4) to give pure **5** (42 mg, 39%) as an oily compound. IR: 3500, 1760, 1610 cm^{-1}. ^{1}H-NMR δ: 1.27 (9H, s, *tert*-Bu), 2.02 (3H, s, C-8Me), 2.07 (3H, s, Ac), 2.98 (2H, d, J=9 Hz, C-1H_2), 4.29 (2H, s, C-8CH_2), 4.74 (1H, m, C-5H), 5.05 (2H, d, J=6 Hz, C-2CH_2), 5.90 (2H, d, J=6 Hz, CO_2CH_2).

Pivaloyloxymethyl (3*S,4*R**)-α-[4-(2,3-Epoxypropyl)-3-(4-methyl-2-oxo-1,3-dioxolan-4-yl)-2-azetidinone-1-yl]-α-triphenylphosphoranilideneacetate (19a, b)**——The epoxy-azetidinone **13b** (1.4 g, 4.3 mmol, mixture of isomers) was desilylated by the same method as used for **7** and **14** and then converted into the POM esters **18b** (720 mg, 42%, mixture of four isomers) by the same procedure as described for **15**. **18b**: ^{1}H-NMR (one of the isomers) δ: 1.23 (9H, s, *tert*-Bu), 1.65 (3H, s, C-8Me), 1.5—3.0 (5H, m, C-1H_2, epoxide-H_3), 3.37 (1H, d, J=2 Hz, C-6H), 4.00 (1H, m, C-5H), 4.17 and 4.43 (2H, ABq, J=8 Hz, C-8CH_2), 5.36 (1H, s, NCH), 5.53 (1H, br s, OH), 5.82 (2H, s, CO_2CH_2).

The POM ester **18b** (600 mg, 1.5 mmol) was converted to the ylid **19b** (680 mg, 72%) by the same method as used for **16**. **19b**: IR: 1805, 1740 cm^{-1}.

Pivaloyloxymethyl (5*R,6*S**)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-carbapen-2-em-3-carboxylate (21a, b)**——A solution of *n*-butyllithium in hexane (1.6 N, 265 μl, 0.5 eq) was added to a solution of 1-methyltetrazolethiol (328 mg, 4.0 eq) in THF (5 ml) under ice cooling. To this mixture was added a solution of the ylid **19b** (455 mg, 0.71 mmol), and the reaction mixture was stirred at room temperature overnight, then diluted with EtOAc, washed with aqueous $NaHCO_3$ solution and brine, dried and concentrated to give a residue (400 mg). IR: 3500, 1805, 1740 cm^{-1}.

The residue was dissolved in acetone (3 ml) and treated with a slight excess of Jones' reagent under ice cooling for 1 h. Excess reagent was decomposed with methanol. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ solution and brine, dried and concentrated. The residue was chromatographed on a Lobar column (size A, benzene–EtOAc 1 : 1) to give **20b** (320 mg, 60%). IR: 1805, 1740 cm^{-1}.

A solution of the above ylid **20b** (320 mg, 0.42 mmol) in toluene (20 ml) was heated at 90 °C (bath temperature) for 4 h then concentrated. The residue was chromatographed on a Lobar column (size A, EtOAc–CH_2Cl_2 1 : 3) to give **21b** contaminated with triphenylphosphine oxide. This mixture was separated by preparative HPLC (Nucleosil 30C_{18}, 20 × 250 mm, MeOH–H_2O 7 : 3) to give pure **21b** (66 mg, 32%) as oil. IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.20 (9H, s, *tert*-Bu), 1.67 (3H, s, C-8Me), 3.23 (2H, d, J=8 Hz, C-1H_2), 3.60 (1H, d, J=2 Hz, C-6H), 3.93 (3H, s, NMe), 4.13 (1H, m, C-5H), 4.20 and 4.37 (2H, ABq, J=8 Hz, C-8CH_2), 4.40 (2H, s, C-2CH_2), 5.83 (2H, s,

CO_2CH_2).

Following the same procedure as described above, **21a** was synthesized from **13a**. **21a**: IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.20 (9H, s, *tert*-Bu), 1.60 (3H, s, C-8Me), 3.17 (2H, d, J=8 Hz, C-1H_2), 3.50 (1H, d, J=2 Hz, C-6H), 3.92 (3H, s, NMe), 4.10 and 4.57 (2H, ABq, J=8 Hz, C-8CH_2), 4.40 (2H, s, C-2CH_2), 4.13 (1H, m, C-5H), 5.82 (2H, s, CO_2CH_2).

Pivaloyloxymethyl 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylcarbapen-2-em-3-carboxylate (22)——A solution of DBU in toluene (1 M, 22 μl) was added to a solution of **21b** (50 mg, 0.1 mmol) in CD_3CN (0.5 ml), and the mixture was stirred at room temperature for 10 min. The same work-up as for **5** gave a crude product, which was purified by preparative HPLC (Nucleosil 30C_{18}, 20×250 mm, MeOH–H_2O 6:4) to give pure **22** (23 mg, 51%). IR: 3490, 1760, 1610 cm^{-1}. ^{1}H-NMR δ: 1.20 (9H, s, *tert*-Bu), 2.00 (3H, s, C-8Me), 3.07 (2H, d, J=8 Hz, C-1H_2), 3.90 (3H, s, NMe), 4.23 (2H, s, C-8CH_2), 4.34 (2H, d, J=6 Hz, C-2CH_2), 4.75 (1H, m, C-5H), 5.90 (2H, s, CO_2CH_2).

The following compounds were prepared by the methods described above.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(1-methyl-1*H*-tetrazol-5-yl)-thiomethylcarbapen-2-em-3-carboxylate (24b)**——**24b**: IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 3.10 (2H, d, J=9 Hz, C-1H_2), 3.55 (1H, d, J=2 Hz, C-6H), 3.75 (3H, s, NMe), 3.80 (3H, s, OMe), 4.10 (1H, m, C-5H), 4.15 and 4.32 (2H, ABq, J=8 Hz, C-8CH_2), 4.41 (2H, s, C-2CH_2), 5.17 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)-thiomethylcarbapen-2-em-3-carboxylate (27b)**——**27b**: IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 2.67 (3H, s, Me), 3.10 (2H, d, J=9 Hz, C-1H_2), 3.50 (1H, d, J=2 Hz, C-6H), 3.80 (3H, s, OMe), 4.03 (1H, m, C-5H), 4.17 and 4.40 (2H, ABq, J=8 Hz, C-8CH_2), 4.48 (2H, s, C-2CH_2), 5.17 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(1,3,4-thiadiazol-2-yl)thiomethyl-carbapen-2-em-3-carbaxylate (29b)**——**29b**: IR: 1805, 1790, 1715, 1610 cm^{-1}. ^{1}H-NMR δ: 1.61 (3H, s, C-8Me), 3.10 (2H, d, J=9 Hz, C-1H_2), 3.55 (1H, d, J=2 Hz, C-6H), 3.80 (3H, s, OMe), 4.04 (1H, m, C-5H), 4.14 and 4.41 (2H, ABq, J=8 Hz, C-8CH_2), 4.50 (2H, s, C-2CH_2), 5.20 (2H, s, CO_2CH_2), 6.81 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar), 9.06 (1H, s, SCH=).

***p*-Methoxybenzyl (5*R**,6*S**)-2-[1-(2-Hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (31b)**——**31b**: IR: 3450, 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.61 (3H, s, C-8Me), 3.10 (2H, d, J=6 Hz, C-1H_2), 3.30 (1H, br s, OH), 3.54 (1H, d, J=2 Hz, C-6H), 3.80 (3H, s, OMe), 4.02 (1H, m, C-5H), 4.00—4.40 (4H, m, C_2H_4), 4.15 and 4.32 (2H, ABq, J=8 Hz, C-8CH_2), 4.35 (2H, s, C-2CH_2), 5.18 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**,6*S**)-2-Acetoxymethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (35b)**——**35b**: IR: 1805, 1790 cm^{-1}. ^{1}H-NMR δ: 1.60 (3H, s, C-8Me), 2.09 (3H, s, Ac), 3.10 (2H, d, J=9 Hz, C-1H_2), 3.32 (1H, d, J=2 Hz, C-6H), 3.90 (3H, s, OMe), 4.20 (1H, m, C-5H), 4.10 and 4.39 (2H, ABq, J=8 Hz, C-8CH_2), 5.15 (2H, d, J=6 Hz, C-2CH_2), 5.30 (2H, s, CO_2CH_2), 6.83 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylcarbapen-2-em-3-carboxylate (26)**——**26**: ^{1}H-NMR δ: 1.97 (3H, s, C-8Me), 3.07 (2H, d, J=7 Hz, C-1H_2), 3.80 (3H, s, OMe), 3.88 (3H, s, NMe), 4.20 (2H, s, CH_2OH), 4.25 and 4.57 (2H, ABq, J=8 Hz, C-2CH_2), 4.75 (1H, m, C-5H), 5.20 (2H, s, CO_2CH_2), 6.84 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (37)**——**37**: IR: 3400, 1750, 1710 cm^{-1}. ^{1}H-NMR δ: 1.98 (3H, s, C-8Me), 2.68 (3H, s, Me), 3.05 (2H, d, J=8 Hz, C-1H_2), 3.79 (3H, s, OMe), 4.20 (2H, s, C-8CH_2), 4.25 and 4.55 (2H, ABq, J=8 Hz, C-2CH_2), 4.80 (1H, m, C-5H), 5.20 (2H, s, CO_2CH_2), 6.85 and 7.30 (4H, A_2B_2q, J=8 Hz, Ar).

Sodium (5*R,6*S**)-6-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-carbapen-2-em-3-carboxylate (23b)**——A solution of **24b** (1.1 g, 2.18 mmol) in CH_2Cl_2 (1 ml) was added to a solution of $AlCl_3$ (1.16 g, 4 eq) in a mixture of CH_2Cl_2 (1 ml) and anisole (10 ml) cooled at −40 °C, and the mixture was stirred at the same temperature for 1.5 h. A solution of $NaHCO_3$ (3.3 g, 4.5 eq) in phosphate buffer (0.01 M, pH 7, 10 ml) and CH_2Cl_2 (20 ml) were added to the reaction mixture and the whole was stirred for 30 min under ice cooling. The reaction mixture was filtered and the aqueous phase of the filtrate was washed with CH_2Cl_2 and poured into a column filled with Diaion HP-20AG (2.5×35 cm). The column was eluted with deionized water and fractions were analyzed by HPLC (Nucleosil 10C_{18}, 0.02 M pH 7 phosphate buffer). Fractions containing the product but no chlorine ion ($AgNO_3$ test) were combined and concentrated to a small volume under reduced pressure. Freeze-drying of the solution gave **23b** (240 mg, 27%) as a colorless powder. ^{1}H-NMR (100 MHz, D_2O, from DSS) δ: 1.02 (3H, s, C-8Me), 2.44 (2H, d, J=6 Hz, C-1H_2), 3.24 (1H, d, J=2 Hz, C-6H), 3.44 (3H, s, NMe), 3.50 (1H, m, C-5H), 3.51 and 3.69 (2H, ABq, J=6 Hz, C-8CH_2), 3.78 and 3.91 (2H, ABq, J=6 Hz, C-2CH_2). MS (SIMS, glycerol) *m/e*: 426 $(M+Na)^+$. The following compounds were prepared using the procedure described for **23b**.

Sodium (5*R,6*S**)-6-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethyl-carbapen-2-em-3-carboxylate (28b)**——**28b**: ^{1}H-NMR (100 MHz, D_2O, from DSS) δ: 1.03 (3H, s, C-8Me), 2.10 (3H,

s, Me), 2.45 (2H, d, J=2 Hz, C-1H_2), 3.21 (1H, d, J=2 Hz, C-6H), 3.50 (1H, m, C-5H), 3.52 and 3.80 (2H, ABq, J=6 Hz, C-8CH_2), 3.81 and 3.97 (2H, ABq, J=6 Hz, C-2CH_2). UV (H_2O): 235, 276 nm. MS (SIMS, glycerol) *m/e*: 442 $(M+Na)^+$.

Sodium (5*R,6*S**)-[(4*S**)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (30b)**——**30b**: IR (KBr): 3420, 1805, 1795, 1760 cm^{-1}. ^{1}H-NMR (100 MHz, D_2O, from DSS) δ: 1.66 (3H, s, C-8Me), 3.08 (2H, d, J=10 Hz, C-1H_2), 3.82 (1H, d, J=2 Hz, C-6H), 4.10 (1H, m, C-5H), 4.23 (2H, d, J=8 Hz, C-2CH_2), 4.42 and 4.54 (2H, ABq, J=7 Hz, C-8CH_2), 9.44 (1H, s, SCH=). UV (H_2O): 237, 275 nm. MS (SIMS, glycerol) *m/e*: 428 $(M+Na)^+$.

Sodium (5*R,6*S**)-2-[1-(2-Hydroxyethyl)-1*H*-tetrazol-5-yl]-thiomethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (32b)**——**32b**: ^{1}H-NMR (D_2O) δ: 2.10 (3H, s, C-8Me), 3.47 (2H, d, J=7 Hz, C-1H_2), 4.28 (1H, d, J=2 Hz, C-6H), 4.40 and 4.55 (2H, ABq, J=8 Hz, C-8CH_2), 4.50 (1H, m, C-5H), 4.30—4.70 (4H, m, NC_2H_4), 4.65 and 4.84 (2H, ABq, J=8 Hz, C-2CH_2). UV (H_2O): 235, 278 nm. MS (SIMS, glycerol) *m/e*: 456 $(M+Na)^+$.

Sodium (5*R,6*S**)-2-Acetoxymethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (36b)**——**36b**: ^{1}H-NMR (100 MHz, D_2O, from DSS) δ: 1.03 (3H, s, C-8Me), 1.46 (3H, s, Ac), 2.35 (2H, d, J=4 Hz, C-1H_2), 3.24 (1H, d, J=2 Hz, C-6H), 3.56 (1H, m, C-5H), 3.79 and 3.85 (2H, ABq, J=6 Hz, C-8CH_2), 4.26 and 4.52 (2H, ABq, J=6 Hz, C-2CH_2). UV (H_2O): 238, 270 nm. MS (SIMS, glycerol) *m/e*: 370 $(M+Na)^+$.

Sodium 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylcarbapen-2-em-3-carboxylate (25)——Compound **26** (200 mg, 0.44 mmol) was added to a solution of $AlCl_3$ (213 mg, 1.6 eq) in a mixture of anisole (8 ml) and CH_2Cl_2 (2 ml) cooled at −40 °C, and the mixture was stirred for 1.5 h at the temperature. A solution of $NaHCO_3$ (7.19 mmol) in 0.01 M pH 7 phosphate buffer (5 ml) and CH_2Cl_2 (10 ml) were added, and the reaction mixture was stirred for 30 min under ice cooling, then worked-up as for **23** to give **25** (79 mg, 51%) as a yellow powder. ^{1}H-NMR (D_2O) δ: 2.41 (3H, s, C-8Me), 3.40 (2H, d, J=8 Hz, C-1H_2), 4.30 (3H, s, NMe), 4.52 (2H, s, C-8CH_2), 4.55 and 4.72 (2H, ABq, J=8 Hz, C-2CH_2), 4.90 (1H, m, C-5H). UV (H_2O): 228, 300 nm. MS (SIMS, glycerol) *m/e*: 382 $(M+Na)^+$. The following compound was prepared by the same procedure as used for **25**.

Sodium 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (38)——**38**: ^{1}H-NMR (D_2O) δ: 2.40 (3H, s, C-8Me), 3.18 (3H, s, Me), 3.40 (2H, d, J=8 Hz, C-1H_2), 4.62 (2H, s, C-8CH_2), 4.64 and 4.80 (2H, ABq, J=8 Hz, C-2CH_2), 4.90 (1H, m, C-5H). UV (H_2O): 230, 295 nm. MS (SIMS, glycerol) *m/e*: 398 $(M+Na)^+$.

Sodium 6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (40)——The carbonate-PMB ester **29b** (410 mg, 0.84 mmol) was deprotected by the same method as used for **23b**. Chromatography on a HP-20AG column followed by freeze-drying gave the carbonate **30b** (300 mg, 32%) and the title compound **40** (30 mg, 11%). IR (KBr): 3410, 1790, 1740, 1600 cm^{-1}. ^{1}H-NMR (D_2O) δ: 2.39 (3H, s, C-8Me), 3.40 (2H, d, J=10 Hz, C-1H_2), 4.63 (2H, s, C-8Me), 4.79 (2H, d, J=8 Hz, C-2CH_2), 4.90 (1H, m, C-5H), 9.84 (1H, s, SCH=). UV (H_2O): 238, 290 nm. MS (SIMS, glycerol) *m/e*: 384 $(M+Na)^+$. The following compound was also prepared by the method used for **40**.

Sodium 2-[1-(2-Hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethyl-6-[(*E*)-1-(hydroxymethyl)ethylidene]carbapen-2-em-3-carboxylate (42)——**42**: ^{1}H-NMR (D_2O) δ: 2.46 (3H, s, C-8Me), 3.45 (2H, d, J=7 Hz, C-1CH_2), 4.30—4.80 (4H, m, NC_2H_4), 4.65 (2H, s, C-8CH_2), 4.69 and 4.95 (2H, ABq, J=8 Hz, C-2CH_2), 4.90 (1H, m, C-5H). UV (H_2O): 245, 300 nm. MS (SIMS, glycerol) *m/e*: 412 $(M+Na)^+$.

Allyl (5*E,6*S**)-2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (33b)**——The allyl ester **33b** was prepared from **13b** by a similar method to that used for **24b**. **33b**: IR: 2900, 1805, 1790, 1700 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 3.10 (2H, d, J=7 Hz, C-1H_2), 3.63 (1H, d, J=2 Hz, C-6H), 4.00 (1H, m, C-5H), 4.15 and 4.29 (2H, ABq, J=8 Hz, C-8CH_2), 4.50 (2H, s, C-2CH_2), 4.70 (2H, d, J=6 Hz, C-2CH_2), 5.00 (2H, s, NCH_2), 5.20—5.50 (2H, m, C=CH_2), 5.70—6.15 (1H, m,CH=), 6.80 (2H, br s, NH_2).

Sodium (5*R,6*S**)-2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(4*S**)-4-methyl-2-oxo-1,3-dioxolan-4-yl]carbapen-2-em-3-carboxylate (34b)**——$Pd(PPh_3)_4$ (52 mg, 0.1 eq) and PPh_3 (10 mg, 0.08 eq) were added to a solution of the allyl ester **33b** (210 mg, 0.45 mmol) in a mixture of benzene (35 ml) and MeCN (5 ml), and the mixture was stirred at room temperature for 10 min. Sodium 2-ethylhexanoate (75 mg, 1.0 eq) was added to the above mixture and the whole was stirred for 30 min. The reaction mixture was then stirred vigorously with H_2O (30 ml) and the aqueous phase was washed several times with benzene. Concentration and freeze-drying of the aqueous phase gave **34b** (163 mg, 81%) as a powder. ^{1}H-NMR (D_2O) δ: 2.10 (3, s, C-8Me), 3.45 (2H, d, J=6 Hz, C-1H_2), 4.29 (1H, d, J=2 Hz, C-6H), 4.50 (1H, m, C-5H), 4.65 and 4.82 (2H, ABq, J=8 Hz, C-8CH_2), 4.75 (2H, s, NCH_2CO), 4.79 and 4.90 (2H, ABq, J=8 Hz, C-2CH_2). UV (H_2O): 235, 276 nm. MS (SIMS, glycerol) *m/e*: 469 $(M+Na)^+$.

Sodium 2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(*E*)-1-(hydroxymethyl)ethylidene]carbapen-2-em-3-carboxylate (43)——A solution of the carbonate **34b** (50 mg, 0.11 mmol) in H_2O (5 ml) containing $NaHCO_3$ (100 mg) was allowed to stand at room temperature for 3 h. The reaction mixture was chromatographed on HP-20AG to give the title compound **43** (19 mg, 47%). ^{1}H-NMR (D_2O) δ: 2.46 (3H, s, C-8Me), 3.41 (2H, d, J=7 Hz, C-1H_2), 4.70 (2H, s, C-8CH_2), 4.71 and 4.98 (2H, ABq, J=8 Hz, C-2CH_2), 4.80 (2H, s, NCH_2CO), 4.90 (1H, m, C-5H). UV

(H_2O): 240, 300 nm.

Determination of Minimum Inhibitory Concentrations (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 compound. Organisms were incubated at 37 °C for 18—20 h. The MIC of the compound was defined as the lowest concentration that visibly inhibited growth.

Some of the POM ester compounds were also tested in assay medium supplemented with 5% horse serum for the hydrolysis of ester.

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References and Notes

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