[Chem. Pharm. Bull. 33(10)4382—4394(1985)]

Carbapenem and Penem Antibiotics. IV. Synthesis and Antibacterial Activity of (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-functionalized-methyl Carbapenem and Penem Derivatives[1)]

Hisao Ona, Shoichiro Uyeo,* Takashi Fukao, Masayoshi Doi and Tadashi Yoshida

Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu, Fukushima-ku, Osaka 553, Japan

(Received January 10, 1985)

Racemic 2-acetoxymethyl and 2-(heteroaromatic)thiomethyl carbapenem and penem antibiotics having a 1-(*R**)-hydroxyethyl side-chain at C-6 (**6**, **7**, **8**, and **45**, **59**, **47**, **49**, **51**) were synthesized, and their antibacterial activities were determined.

Keywords——β-lactam antibiotic; penem antibiotic; allylazetidinone; tritylthioazetidinone; intramolecular Wittig reaction; carbapenem antibiotic carboxy deprotection; penem antibiotic carboxy deprotection; antibacterial activity

Among many natural and synthetic carbapenem and penem antibiotics so far reported, compounds having a (6*S*,8*R*)-1-hydroxyethyl side-chain show consistently potent antibacterial activity, as represented by the clinical candidates imipenem (**1**)[2)] and Sch29482 (**2**).[3)] At the time when we completed our syntheses of the 2-functionalized-methyl carbapenem and penem derivatives **3** described in the preceding papers,[4)] antibacterial activity of the 2-functionalized-methyl compounds **4** with the hydroxyethyl side-chain had not yet been reported. We therefore decided to prepare these compounds using the same reaction sequences as reported in the preceding papers[4)] and to compare the biological activities of derivatives with different C-6 side-chains. As described in this paper, we were unable to prepare 2-(1-methyltetrazol-5-yl)thiomethyl carbapenem **5**, which was anticipated to be very unstable owing to the good leaving ability of the tetrazolylthio group, even as a pivaloyloxymethyl (POM) ester. We were, however, able to synthesize the corresponding acetoxy and thiadiazolyl derivatives **6**, **7** and **8**, and we found that they possessed potent antibacterial activity. On the other hand, the 2-functionalized-methyl penems **9**, including 1-methyltetrazolylthio derivatives, could be prepared by the sequence of reactions as planned. These penem derivatives also exhibited potent antibacterial activity.

We describe herein details of the synthesis and the preliminary results of antibacterial activity tests. Syntheses and biological activities of recent clinical candidates, 2-acetoxymethyl and 2-carbamoyloxymethyl penems **10** and **11**, and 2-(heteroaromatic)thiomethyl penems **9** (from Farmitalia Carlo Erba),[5a-g)] as well as some 2-aminoacyloxymethyl carbapenems[6)] have been reported.

Chemistry

We carried out the synthesis of the carbapenems as shown in Chart 2. Since we had the azetidinone-α-glycol **12a** in quantity, we utilized this material for the preparation of a key starting material **16**. Oxidation of the α-glycol **12a** with sodium metaperiodate in aqueous tetrahydrofuran (THF) gave a ketone **13**, which was selectively reduced with K-selectride® in ether to the 1-(*R**)-hydroxyethyl-azetidinone **14**.[7)] The hydroxy group was protected with a

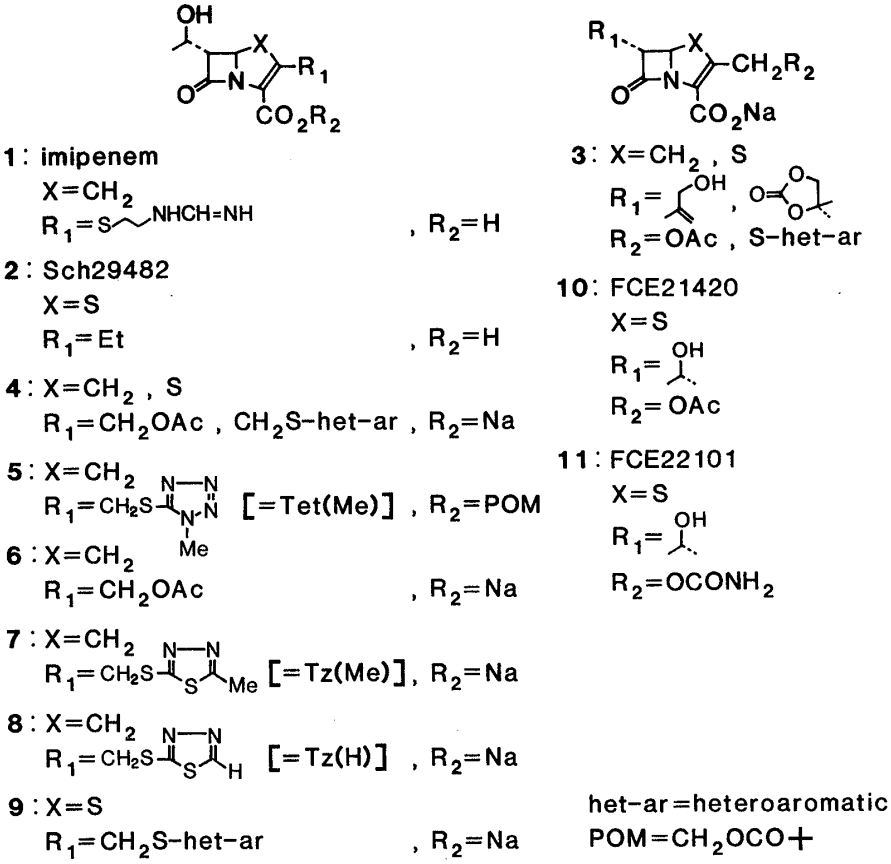


Chart 1

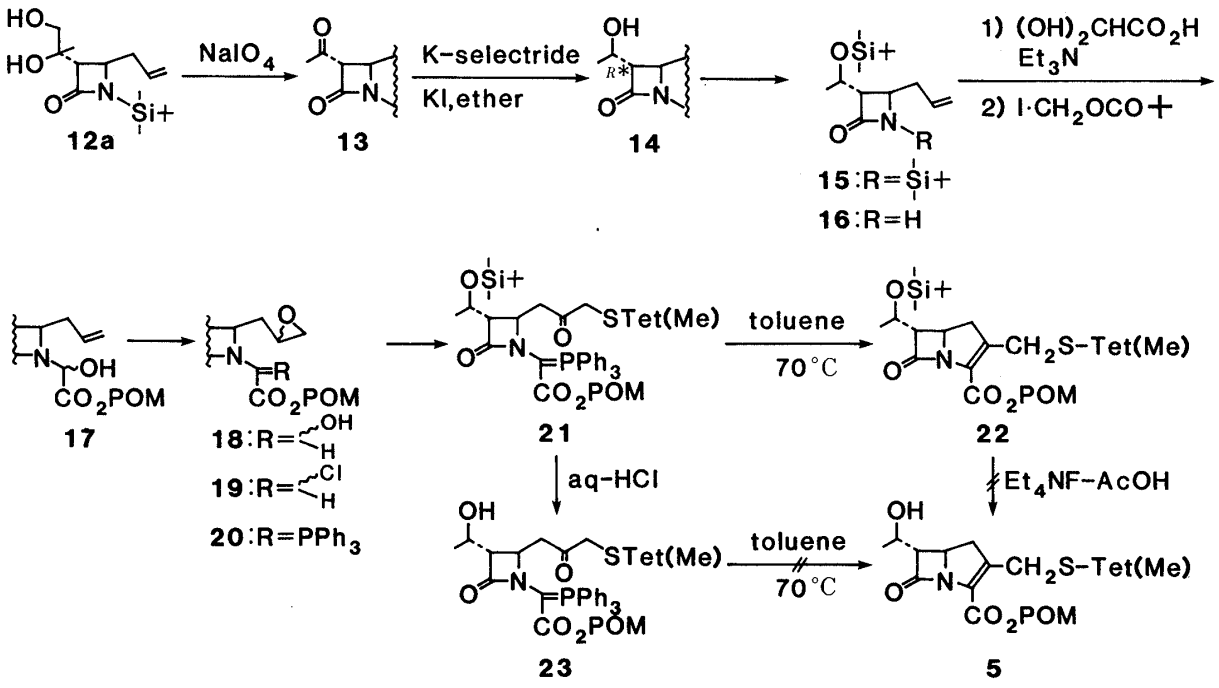


Chart 2

tert-butyldimethylsilyl group and the *N*-silyl group of the resulting *O*,*N*-disilyl compound **15** was then removed selectively with tetra-*n*-butylammonium fluoride in THF containing acetic acid to give the azetidinone **16**.

We first tried to prepare the POM ester of the (1-methyltetrazol-5-yl)thiomethyl

derivative **5**. The allylazetidinone **16** was converted to the POM ester **17** and oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to a mixture of epoxides **18**, which were then transformed into the ylids **20** in the usual manner *via* **19**. The epoxides of the ylids **20** were opened with the tetrazolethiolate and the resulting alcohols were oxidized to the keto-ylid **21** which cyclized smoothly on heating at 70 °C in toluene, giving the *O*-silyl carbapenem **22** in 60% yield. Attempted *O*-desilylation of the carbapenem **22**, however, was unsuccessful.[8] Preparation of the carbapenem POM ester **5** directly from the hydroxy-ylid **23**, which was prepared by *O*-desilylation of the monocyclic β-lactam **21** with hydrochloric acid in acetonitrile, was also unsuccessful. We therefore concluded that the originally designed compound **5** may be too unstable to be synthesized even in an ester form. We assumed, however, that the carbapenems **26** and **27**, having thiadiazolylthio groups with less leaving ability, might be stable enough to

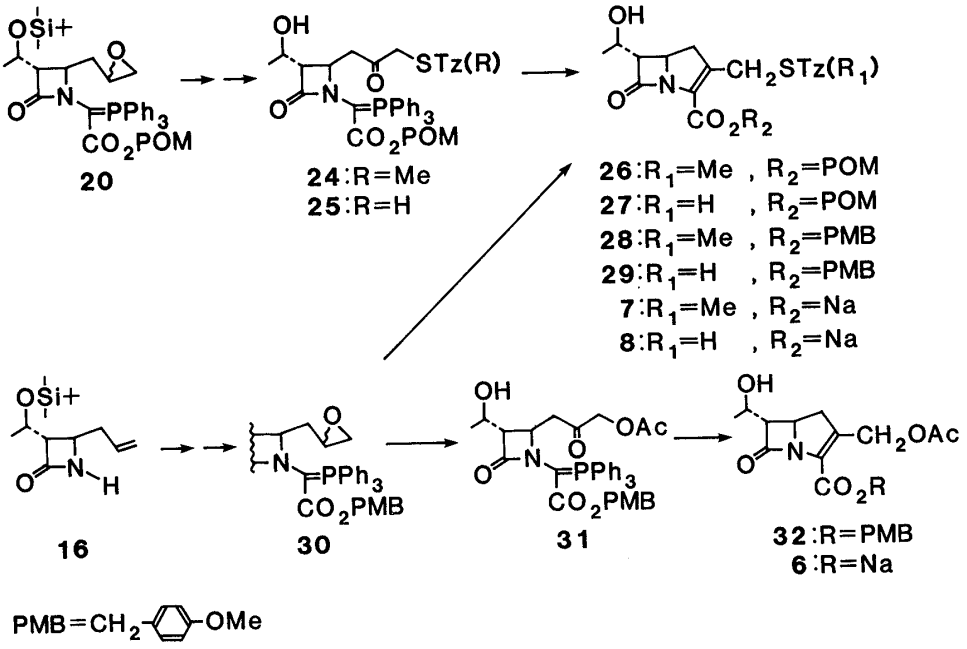


Chart 3

be synthesized by the planned procedure. In fact, we found that both compounds could be produced by the intramolecular Wittig reaction of the hydroxy-ylids **24** and **25**, respectively. Moreover, the corresponding *p*-methoxybenzyl (PMB) esters **28** and **29** could be deprotected by the $AlCl_3$–anisole method to provide the sodium salts **7** and **8** in 20—30% overall yields from the hydroxy-ylids. On the other hand, the epoxy-ylids **30** were treated with 1.3 mol equivalent of BF_3-etherate in methylene dichloride in the presence of acetic acid to provide hydroxyacetates, which, on oxidation and desilylation, gave the keto-ylid **31**. Subsequent cyclization to the carbapenem **32** and carboxy deprotection then afforded the 2-acetoxymethyl carbapenem **6** in 32% overall yield from the ylid **31**.

We think that the low yields in the above cyclization and deprotection reactions reflect the chemical instability of these carbapenems.

In parallel with the above carbapenem synthesis, we carried out the synthesis of the penem congeners, as shown in Chart 4. Because of the better chemical stability of penems, no particular difficulty was anticipated in the preparation of these penem compounds.

The starting material **37** was again prepared from the α-glycolazetidinone **33a** *via* the methylketone **34**. No selective reduction of the ketone **34** to the 1-(*R**)-hydroxyethyl derivative **35** has been reported so far.[9] Reduction of **34** with sodium borohydride produced a mixture of the *S**- and *R**-alcohols, from which the minor *R**-isomer **35** was isolated by recrystallization and chromatography on silica gel. *O*-Silylation to **36** and selective *N*-

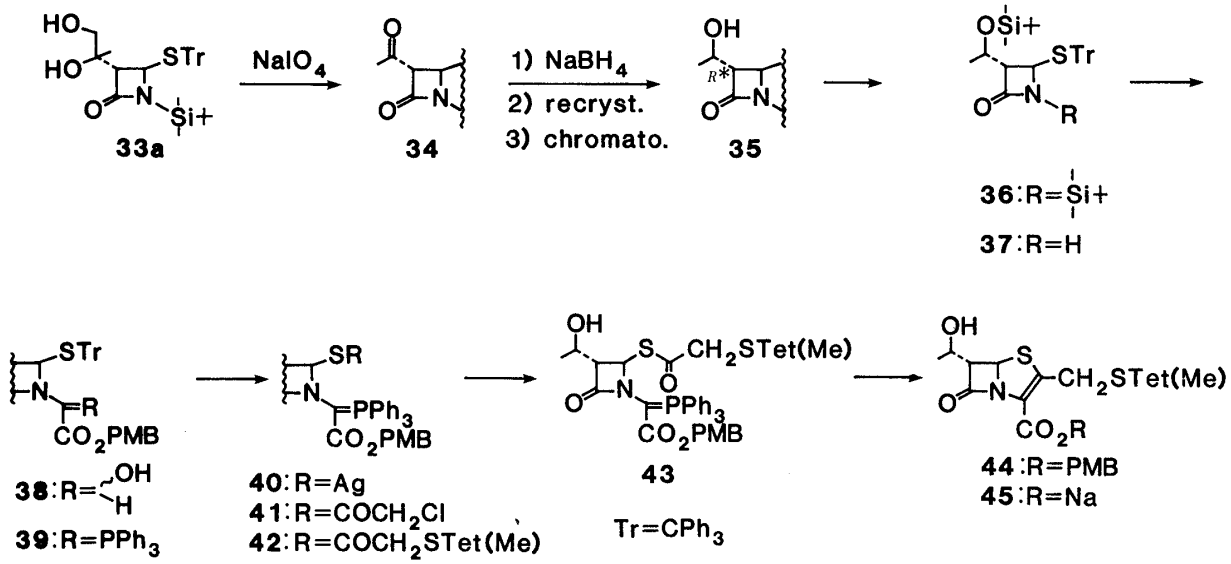
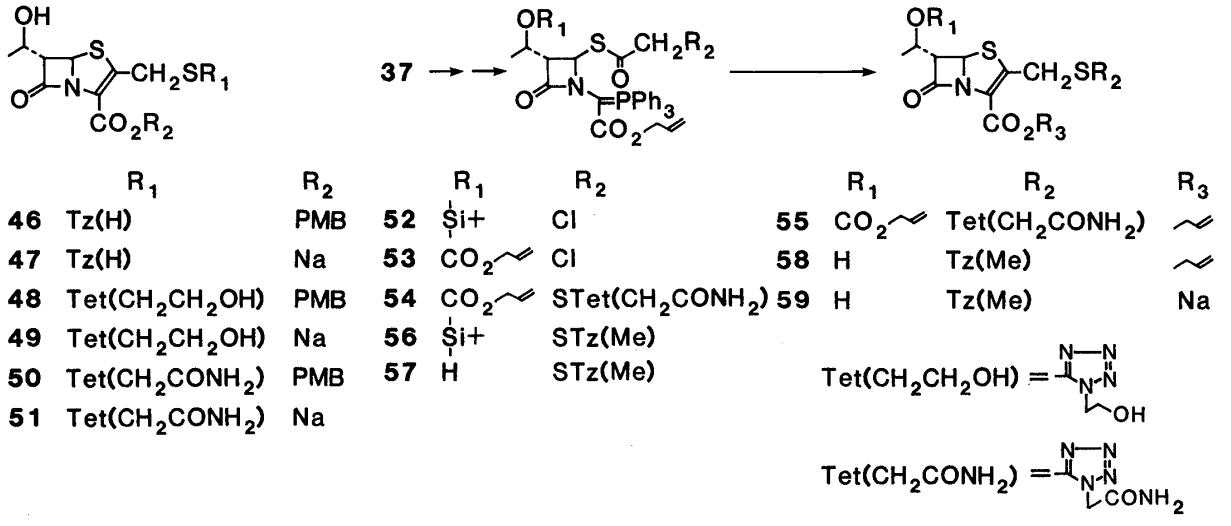


Chart 4

desilylation as described for **14** gave the starting tritylthioazetidinone **37**, which was converted into the ylid **39** *via* **38** in the usual way. The *S*-trityl-ylid **39** was transformed to the *S*-chloroacetate **41** by way of the Ag-salt **40** and then to the tetrazolylthio derivative **42**. After *O*-desilylation with hydrochloric acid, the hydroxy-ylid **43** was heated at 75 °C in benzene to produce the penem **44** in 76% yield, and carboxy deblocking with $AlCl_3$ and anisole provided the sodium salt **45**.



	R_1	R_2
46	Tz(H)	PMB
47	Tz(H)	Na
48	$Tet(CH_2CH_2OH)$	PMB
49	$Tet(CH_2CH_2OH)$	Na
50	$Tet(CH_2CONH_2)$	PMB
51	$Tet(CH_2CONH_2)$	Na

	R_1	R_2
52	Si+	Cl
53	CO_2~	Cl
54	CO_2~	$STet(CH_2CONH_2)$
56	Si+	STz(Me)
57	H	STz(Me)

	R_1	R_2	R_3
55	CO_2~	$Tet(CH_2CONH_2)$	~
58	H	Tz(Me)	~
59	H	Tz(Me)	Na

Chart 5

By following this procedure, the penems **47**, **49** and **51** having different 2-functional groups were prepared from the corresponding PMB esters **46**, **48** and **50**, respectively.

We also prepared an allyl ester of the penem **55**, in which the hydroxy group at C-8 was protected with an allyloxycarbonyl group, from the ylid **54** and converted it into the sodium salt **51** by the recently developed procedure using Pd catalyst and sodium ethylhexanoate.[10] Alternatively, deprotection of an allyl ester of the penem **58**, which was prepared by the same sequence of reactions as used for **44**, gave the antibiotic **59**.

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

R	X		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
CH_2OAc	CH_2	**6**	0.2	0.05	0.39	0.78	0.78	3.13
$CH_2STet(Me)$	S	**45**	0.1	0.1	0.78	0.78	0.78	3.13
$CH_2STz(Me)$	CH_2	**7**	0.1	0.025	0.39	0.39	0.39	3.13
$CH_2STz(Me)$	S	**59**	0.1	0.1	12.5	3.13	3.13	25
$CH_2STz(H)$	CH_2	**8**	0.05	0.025	0.1	0.2	0.39	0.78
$CH_2STz(H)$	S	**47**	0.05	0.05	1.56	0.78	1.56	6.25
$CH_2STet(CH_2CH_2OH)$	S	**49**	0.2	0.1	0.78	0.78	0.78	3.13
$CH_2STet(CH_2CONH_2)$	S	**51**	0.2	0.1	0.78	0.78	1.56	3.13
$SCH_2CH_2NHCH=NH$ (imipenem)	CH_2(H)	**1**	0.025	0.013	0.1	0.2	0.78	0.39
SCH_2CH_3(Sch29482)	S (H)	**2**	0.1	0.05	0.39	0.39	0.78	1.56

a) MICs (minimum inhibitory concentrations) were determined by the agar dilution method. Inoculation was performed with one loopful of 10^6 cells per ml.

Antibacterial Activity

The antibacterial activities of the carbapenem derivatives reported in this paper are listed in Table I and compared with those of imipenem (**1**) and Sch29482 (**2**). The former compounds showed potent activity with an expanded antibacterial spectrum (except against *Pseudomonas aeruginosa*).

As shown in the preceding paper, the optically active (5*R*) forms are twice as active as the corresponding racemates. Therefore, the compounds such as **7** and **8** may deserve further evaluation in comparison with Sch29482 (**2**).

It is too early as yet to conclude that the carbapenem or penem antibiotics **4** having the 1-hydroxyethyl side-chain described in this paper are superior in terms of biological activity to the corresponding antibiotics **3** having the asparenomycin-type or the cyclic carbonate side-chain reported in the preceding papers.

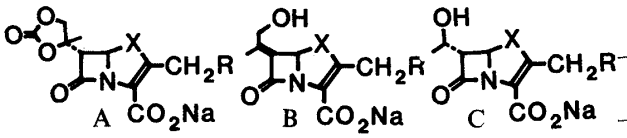
Stability in Tissue Homogenates

It is now well recognized that both carbapenem and penem antibiotics are metabolized by certain peptidases in living organs.[11)] Therefore, evaluations of several carbapenem and penem derivatives reported in this and the preceding papers for biological stability in mouse tissue homogenates were performed (Table II). The stability of the carbapenems with a thiadiazolylthiomethyl group can be compared in terms of the side-chain at C-6. The B-type compound **61** having the 1-(hydroxymethyl)ethylidene group was most labile in liver and kidney homogenates, and was almost completely degraded after a 2-h incubation. The A-type compound **60b**, having the carbonate side-chain was most stable among the three compounds, and was even more stable than imipenem (**1**), whereas the C-type compound **8**, having the 1-hydroxyethyl group was somewhat less stable than the A-type compound. Inactivation of the β-lactam compounds by kidney homogenate appeared to be greater than that by liver homogenate. Comparison of stability between A-type compounds **62b** and **63b** indicated that the carbapenem was more stable than the penem counterpart.

The high lability of A- and C-type carbapenems, **66b** and **6**, with the acetoxymethyl group at C-2, in the kidney homogenate may be due to hydrolytic inactivation by non-specific esterase at the 2-substituent.

Some of these compounds were also tested for stability in monkey kidney homogenate.

TABLE II. Stability in Tissue Homogenate (Mouse)



R	Structure	X		Remaining activity %[a] in tissue homogenate: Kidney 1 h	Kidney 2 h	Liver 1 h	Liver 2 h	Plasma 1 h	Plasma 2 h
STz(H)	A	CH_2	**60b**	70	59	96	78	100	94
STz(H)	B	CH_2	**61**	27	13	13	12	99	90
STz(H)	C	CH_2	**8**	45	37	87	80	77	76
STet(Me)	A	CH_2	**62b**	73	68	66	67	—	—
STet(Me)	A	S	**63b**	47	34	34	26	—	—
STet(CH_2CONH_2)	A	S	**64b**	33	17	—	—	—	—
STet(CH_2CONH_2)	B	S	**65**	10	<2	—	—	—	—
STet(CH_2CONH_2)	C	S	**51**	55	39	—	—	—	—
OAc	A	CH_2	**66b**	13	10	20	13	—	—
OAc	C	CH_2	**6**	18	14	33	27	—	—
Imipenem			**1**	48	41	71	65	—	—

a) Each compound was tested at a final concentration of 100 μg/ml and remaining activity % was determined after 1- and 2-h incubation at 37 °C.

The trend of stability of the three types of compounds was found to be parallel in the two animal species, although less enzyme activity was observed in the monkeys.

The observed intrinsic biological stability of **60b** and **62b** encouraged us to proceed with further studies of the carbapenems with a cyclic carbonate side-chain reported in the preceding papers. Our work along these lines will be reported elsewhere.

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**)-4-Allyl-1-*tert*-butyldimethylsilyl-3-[(*R**)-1-hydroxyethyl]-2-azetidinone (14)**——A solution of $NaIO_4$ (22 g, 1.3 eq) in water (220 ml) was added to a solution of the azetidinone-glycol **12a** (crude, 23.7 g, 79 mmol) in THF (330 ml) under ice cooling, and the mixture was stirred at room temperature for 15 min, then filtered, concentrated, diluted with EtOAc, washed with water, dried and concentrated to give **13**.

A solution of the above residue (**13**, 18 g) in ether (680 ml) was treated with K-selectride (0.5 N solution in THF, 320 ml, 2.38 eq) at room temperature for 0.5 h. The reaction mixture was treated with acetic acid (18 ml), then diluted with EtOAc (3 l), filtered, dried and concentrated. Chromatography on Lobar columns (size B+C, benzene–EtOAc 9 : 1—1 : 1) followed by crystallization of the product from *n*-hexane gave the title compound **14** (8.55 g, 47% from **13**).

(3*S,4*R**)-4-Allyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (16)**——A mixture of **14** (2.0 g, 7.42 mmol), *tert*-butyldimethylchlorosilane (1.29 g, 1.2 eq) and imidazole (1.39 g, 2.8 eq) in dimethylformamide (DMF) (15 ml) was stirred at room temperature overnight, then diluted with EtOAc, washed with water, dried and concentrated to give the crude *O*,*N*-disilyl compound **15** (3.08 g).

A mixture of the above crude product, acetic acid (0.47 ml, 1.1 eq) and tetraethylammonium fluoride dihydrate

(1.51 g, 1.1 eq) in THF (19 ml) was stirred at room temperature for 1 h, then concentrated, diluted with EtOAc, washed with saturated brine, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 2 : 1) to give **16** (2.0 g, 100%); mp 53—53.5 °C (*n*-hexane). IR: 3400, 1750 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.06 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 1.19 (3H, d, J=6.4 Hz, Me), 2.35 (2H, br t, J=6 Hz, C=CCH_2), 2.74 (1H, m, C-6H), 3.65 (1H, dt, J=1.8, 6.4 Hz, C-5H), 4.14 (1H, br quint, J=6 Hz, CHO), 5.0—6.0 (3H, m, CH=CH_2), 6.7 (1H, br, NH). *Anal.* Calcd for $C_{14}H_{27}NO_2Si$: C, 62.40; H, 10.10; N, 5.20. Found: C, 62.24; H, 10.01; N, 5.18.

(3*S,4*R**)-4-Allyl-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-1-[(pivaloyloxymethyloxycarbonyl)hydroxymethyl]-2-azetidinone (17)**——A mixture of the azetidinone **16** (1.78 g, 6.6 mmol), glyoxylic acid hydrate (0.70 g, 1.1 eq) and triethylamine (1.39 ml, 1.5 eq) in THF (27 ml) was stirred in the presence of Molecular Sieves 4A (5 g) at room temperature overnight, then filtered and concentrated. The residue was dissolved in DMF (4 ml) and treated with pivaloyloxymethyliodide (2.2 ml, 2 eq) under ice cooling for 50 min. The reaction mixture was diluted with EtOAc, washed with water, dried, concentrated and chromatographed on a Lobar column (size B, benzene–EtOAc 10 : 1, 4 : 1, 2 : 1) to give the title compound **17** (2.18 g, 72%) as a mixture of diastereoisomers and the starting material **16** (0.09 g, 5%). **17**: ^{1}H-NMR δ: 0.07 (6H, s, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.20 (12H, s, *tert*-BuCO_2, Me), 2.52 (2H, br t, J=6 Hz, C=CCH_2), 2.8—3.0 (1H, m, C-6H), 3.7—4.3 (3H, m, C-8H, C-5H, HO), 4.9—6.1 (4H, m, $NCHCO_2$, CH=CH_2), 5.83 (2H, br s, CO_2CH_2).

(3*S,4*R**)-4-(2,3-Epoxypropyl)-3-[(*R**)-1-*tert*-butyldimethylsilyloxyethyl]-1-[(pivaloyloxymethyloxycarbonyl)-hydroxymethyl]-2-azetidinone (18)**——A mixture of the allylazetidinone **17** (2.18 g, 4.76 mmol), *m*-CPBA (85%, 1.93 g, 2.0 eq) and $NaHCO_3$ (0.64 g, 1.6 eq) in CH_2Cl_2 (29 ml) was stirred at room temperature for 2 d, then diluted with EtOAc, washed with aqueous $Na_2S_2O_3$ solution and Na_2CO_3 solution, dried and concentrated to give crude **18** (2.2 g, 98%) as a mixture of four isomers. IR: 3600—3300, 2950, 2925, 2850, 1775 cm^{-1}. ^{1}H-NMR δ: 0.07 (6H, s, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.22 (9H, s, *tert*-BuCO_2), 1.28 (3H, d, J=6 Hz, Me), 3.8—4.5 (3H, m, C-8H, C-5H, OH), 5.50 and 5.82 (2H, s×2, CO_2CH_2), other signals could not be assigned.

(3*S,4*R**)-3-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-4-(2,3-epoxypropyl)-1-(pivaloyloxymethyloxycarbonyl)-triphenylphosphoranylidenemethyl-2-azetidinone (20)**——2,6-Lutidine (1.34 ml, 2.5 eq) and $SOCl_2$ (0.51 ml, 1.5 eq) were added to a solution of the crude **18** (2.2 g, 4.64 mmol) in THF (9.3 ml) at −30 °C, and the reaction mixture was stirred at the same temperature for 30 min, then diluted with EtOAc, washed with water, dried and concentrated to give **19**.

The residue (**19**, mixture of chlorides) was dissolved in THF (9.3 ml) and treated with PPh_3 (2.4 g, 2 eq) and 2,6-lutidine (1.1 ml, 2 eq) at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with water, dried, concentrated and chromatographed on a Lobar column (size B, benzene–EtOAc 2 : 1) to give the ylids **20** (2.22 g, 65% from **17**). IR: 2950, 2925, 2850, 1740, 1630 cm^{-1}. ^{1}H-NMR δ: 0.80 and 0.83 (9H, s×2, *tert*-Bu), 1.03 and 1.22 (9H, s×2, *tert*-BuCO_2), 5.35 and 5.75 (2H, br s, CO_2CH_2), 7.2—8.0 (15H, m, Ar), other signals could not be assigned.

(3*S,4*R**)-3-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-4-[3-(1-methyl-1*H*-tetrazol-5-ylthio)-2-oxopropyl]-1-(pivaloyloxymethyloxycarbonyl)triphenylphosphoranylidenemethyl-2-azetidinone (21)**——A solution of *n*-butyllithium in hexane (1.68 N, 0.24 ml, 0.5 eq) was added to a solution of 1-methyltetrazole-5-thiol (233 mg, 2.5 eq) in THF (2.4 ml) under ice cooling, and the mixture was stirred at room temperature for 10 min. Then a solution of the epoxy-ylids **20** (574 mg, 0.80 mmol) in THF (2.4 ml) was added and the whole was stirred at room temperature overnight, diluted with EtOAc, washed with water, dried and concentrated to give the crude hydroxy-ylids (610 mg, 91%).

The above crude product was dissolved in acetone (6.9 ml) and treated with Jones' reagent (4 M, 0.26 ml, 1.5 eq) under ice cooling for 30 min. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried, concentrated and chromatographed on a Lobar column (size B, benzene–EtOAc 2 : 1, 1 : 1) to give the keto-ylid **21** (376 mg, 60%). IR: 1740, 1630 cm^{-1}. ^{1}H-NMR δ: 0.13 (6H, s, $SiMe_2$), 0.90 (9H, s, *tert*-Bu), 1.17 and 1.35 (9H, s×2, *tert*-BuCO_2), 4.10 and 4.13 (3H, s×2, NMe), 4.60 (2H, br s, $COCH_2S$), 5.45 and 5.87 (2H, s×2, CO_2CH_2), 7.5—8.1 (15H, br, Ar), other signals could not be assigned.

Pivaloyloxymethyl (5*R,6*S**)-6-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-2-(1-methyl-1*H*-tetrazol-5-yl)-thiomethylcarbapen-2-em-3-carboxylate (22)**——A solution of the ylid **21** (142 mg, 0.11 mmol) in toluene (7.5 ml) was heated at 70 °C (bath temperarure) for 4 h, then concentrated and chromatographed on a Lobar column (size A, benzene–EtOAc 4 : 1, 2 : 1) to give the carbapenem **22** (22 mg, 61%). IR: 2950 (sh), 2925, 2860, 1780 (sh), 1750 cm^{-1}. ^{1}H-NMR δ: 0.07 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 1.23 (12H, s, *tert*-BuCO_2, Me), 3.0—3.2 (1H, m, C-6H), 3.08 (2H, br d, J=9 Hz, C-1H_2), 3.95 (3H, s, NMe), 3.9—4.4 (2H, m, C-5H, C-8H), 4.48 (2H, br, C-2CH_2), 5.88 (2H, br s, CO_2CH_2). UV (EtOH): 294 nm.

Pivaloyloxymethyl (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (26)**——The hydroxy-ylid **24** was prepared from **20** using the same method as described for **23**. **24**: IR: 3500 (br), 1745, 1640 cm^{-1}. ^{1}H-NMR δ: 1.07 and 1.23 (9H, s×2, *tert*-BuCO_2), 2.70 (3H, s, N=CMe), 5.35 and 5.70 (2H, br s×2, CO_2CH_2), 7.4—8.0 (15H, m, Ar), other signals could not be assigned.

A solution of the above ylid **24** (84 mg, 0.11 mmol) in toluene (5.5 ml) was heated at 80 °C for 4 h, then concentrated and chromatographed on a Lobar column (size A, hexane–CH_2Cl_2–EtOAc–MeCN 1 : 1 : 1 : 1, MeCN) to give the carbapenem **26** (17 mg, 32%) and the starting material **24** (20 mg, 24%). **26**: IR: 3600—3000, 1775,

1750 cm^{-1}. ^{1}H-NMR δ: 1.22 (9H, s, *tert*-Bu), 1.30 (3H, d, J=6 Hz, Me), 2.72 (3H, s, N=CMe), 3.0—3.3 (1H, m, C-6H), 3.10 (2H, br d, J=10 Hz, C-1H_2), 4.0—4.4 (2H, m, C-5H, C-8H), 4.42 and 4.54 (2H, ABq, J=14 Hz, C-2CH_2), 5.82 and 5.91 (2H, ABq, J=6 Hz, CO_2CH_2). UV (EtOH): 268, 308 nm.

Pivaloyloxymethyl (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (27)**——This compound was prepared from the hydroxy-ylid **25** as described for **26**. **27**: IR: 3600—3300, 1780, 1750 cm^{-1}. ^{1}H-NMR δ: 1.23 (9H, s, *tert*-Bu), 1.32 (3H, d, J=6 Hz, Me), 3.0—3.3 (3H, m, C-1H_2, C-6H), 4.0—4.5 (2H, m, C-5H, C-8H), 4.52 and 4.68 (2H, ABq, J=13.5 Hz, C-2CH_2), 5.87 and 6.96 (2H, ABq, J=6 Hz, CO_2CH_2), 7.23 (1H, s, N=CH).

(3*S,4*R**)-3-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-4-(2,3-epoxypropyl)-1-(*p*-methoxybenzyloxycarbonyl)-triphenylphosphoranylidenemethyl-2-azetidinone (30)**——A mixture of the azetidinone **16** (4.8 g, 17.1 mmol), glyoxylic acid PMB ester (5.1 g, 1.4 eq) and triethylamine (1.9 ml, 0.8 eq) in THF (120 ml) was stirred at room temperature for 2 d, then concentrated, diluted with EtOAc, washed with water, dried and concentrated to give the hydroxy-esters (8.7 g).

A mixture of the above hydroxy-esters, *m*-CPBA (85%, 8.7 g, 2.5 eq) and $NaHCO_3$ (3.6 g, 2.5 eq) in CH_2Cl_2 (150 ml) was stirred at room temperature for 3 d, then was washed with aqueous $Na_2S_2O_3$ solution and $NaHCO_3$ solution, dried and concentrated. The residue was chromatographed on Lobar columns (size B × 2, benzene–EtOAc 2:1) to give less polar epoxides (3.7 g, 45%) and more polar epoxides (4.2 g, 49%) as mixtures of the epimeric alcohols. (Less polar isomers): IR: 3520, 2965, 2935, 1760, 1618 cm^{-1}. ^{1}H-NMR δ: 0.05 (6H, s, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.23 (3H, d, J=6 Hz, Me), 1.3—2.5 (3H, m, epoxide), 2.6—3.1 (3H, m, C-1H_2, C-6H), 3.80 (3H, s, OMe), 3.8—4.3 (2H, m, C-5H, C-6CH), 5.19 (2H, s, CO_2CH_2), 5.40 (1H, br s, $CHCO_2$), 6.89 and 7.32 (4H, A_2B_2q, J=9 Hz, Ar). (Polar isomers): IR: 3500 (br), 3375 (br), 2950, 2925, 1750, 1615 cm^{-1}. ^{1}H-NMR δ: 0.07 (6H, s, $SiMe_2$), 0.87 (9H, s, *tert*-Bu), 1.24 (2H, d, J=6 Hz, Me), 1.4—2.6 (3H, m, epoxide), 2.6—3.1 (3H, m, C-6H, C-1H_2), 3.81 (3H, s, OMe), 3.8—4.2 (2H, m, C-5H, C-8H), 5.22 (2H, s, CO_2CH_2), 5.43 and 5.56 (1H, m, $CHCO_2$), 6.90 and 7.25 (4H, A_2B_2q, J=9 Hz, Ar).

A solution of the epoxy-alcohols (mixture of four isomers, 7.7 g, 16.1 mmol) in THF (63 ml) was treated with 2,6-lutidine (4.8 ml, 2.5 eq) and thionyl chloride (1.76 ml, 1.5 eq) at −40 °C for 30 min to give, after usual work up, the chlorides.

A mixture of the above crude chlorides, triphenylphosphine (4.2 g, 1.0 eq) and 2,6-lutidine (2.9 ml, 1.5 eq) in THF (60 ml) was stirred at room temperature overnight. Usual work up and chromatography on Lobar columns (size B × 2, benzene–EtOAc 4:1, 2:1) gave the title ylids **30** (9.0 g, 73% from **16**). IR: 2930, 1735, 1610 cm^{-1}.

(3*S,4*R**)-3-[(*R**)-1-Hydroxyethyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranylidenemethyl-4-[3-(5-methyl-1,3,4-thiadiazol-2-ylthio)-2-oxopropyl]-2-azetidinone**——A solution of *n*-butyllithium in hexane (1.6 M, 2.7 ml, 0.5 eq) was added to a solution of 5-methyl-1,3,4-thiadiazole-2-thiol (2.25 g, 2.0 eq) in THF (26 ml) under ice cooling. This solution was added to a solution of the ylids **30** (6.2 g, 8.5 mmol) in THF (38 ml) and the mixture was stirred at room temperature overnight, then concentrated, diluted with EtOAc, washed with water, dried, concentrated and chromatographed on a Lobar column (size C, benzene–EtOAc 1:1) to give alcohols (6.4 g, 82%). IR: 3370 (br), 2925, 1735, 1610 cm^{-1}.

Trifluoroacetic anhydride (2 ml, 2 eq) was added to a solution of dimethylsulfoxide (DMSO 1.5 ml, 3 eq) in CH_2Cl_2 (19 ml) at −70 °C and the mixture was stirred for 20 min. To this mixture was added a solution of the above ylids (6.0 g, 7 mmol) in CH_2Cl_2 (30 ml), and the whole was stirred at −70 °C for 30 min. Triethylamine (4.1 ml, 4.2 eq) was then added, and the reaction mixture was stirred for 30 min at the same temperature, then diluted with water, and extracted with EtOAc. The extract was washed with water, dried and concentrated to give the keto-ylid (5.7 g, 95%). IR: 3400 (br), 2945, 1740, 1630 (sh), 1615 cm^{-1}.

A solution of the above keto-ylid (5.6 g, 6.56 mmol) in a mixture of MeOH (53 ml) and MeCN (21 ml) was treated with hydrochloric acid (1 N, 65 ml) at room temperature for 1 h. The reaction mixture was made basic with excess K_2CO_3, saturated with NaCl, extracted with EtOAc, washed with saturated brine, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 1:1, EtOAc, MeCN, MeCN–isoPrOH 9:1) to give the carbapenem **26** (192 mg, *ca.* 3%, containing $P(O)Ph_3$) and the title ylid (3.86 g, 79%). IR: 3420 (br), 2980, 1740, 1610 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 1.1 (3H, br, Me), 2.69 (3H, s, =CMe), 3.76 (3H, s, OMe), 7.2—7.9 (Ar), other signals could not be assigned.

(3*S,4*R**)-4-(3-Acetoxy-2-oxopropyl)-3-[(*R**)-1-hydroxyethyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranylidenemethyl-2-azetidinone (31)**——A mixture of the epoxy-ylids **30** (3.07 g, 4.24 mmol), acetic acid (4.85 ml, 20 eq) and BF_3-etherate (0.68 ml, 1.3 eq) in CH_2Cl_2 (21 ml) was stirred under ice cooling for 30 min and at room temperature for 2 h, then diluted with EtOAc, washed with water and aqueous $NaHCO_3$ solution, dried and concentrated to give the hydroxy-ylids (crude, 3.56 g).

A solution of DMSO (1.2 ml, 4 eq) in CH_2Cl_2 (10 ml) was treated with trifluoroacetic anhydride (1.6 ml, 2.7 eq) at −70 °C for 30 min. To this mixture was added a solution of the above hydroxy-ylids in CH_2Cl_2 (8 ml), and the whole was stirred at −70 °C for 1 h. Triethylamine (3.2 ml, 5.4 eq) was added, and the reaction mixture was stirred at the same temperature for 10 min, then diluted with EtOAc, washed with water, dried and concentrated to give the keto-ylid (crude, 3.31 g). ^{1}H-NMR δ: 0.85 (9H, s, *tert*-Bu), 3.73 (3H, s, OMe), 6.6—7.8 (m, Ar), other signals could not be

assigned.

A solution of the above *O*-silyl-ylid (crude, 3.31 g, 4.24 mmol) in a mixture of MeCN (21 ml) and MeOH (21 ml) was treated with 1 N HCl (21 ml), and the mixture was stirred at room temperature for 2 h, then diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried, concentrated and chromatographed on a Lobar column (size B, hexane–CH_2Cl_2–EtOAc–MeCN 1 : 1 : 1 : 1) to give the ylid **31** (0.97 g, 34% from the epoxy-ylids **30**). IR: 3360 (br), 2960, 1735, 1610, 1575 cm^{-1}.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (28)**——The hydroxy-ylid (1.10 g, 1.49 mmol) in benzene (76 ml) was heated at 70 °C for 4 h. Evaporation of the solvent gave a mixture of the crude carbapenem **28** and $P(O)Ph_3$, which was used as such for the next deprotection reaction. A small amount of the mixture was chromatographed on a Lobar column (size A, benzene–EtOAc 2 : 1, hexane–CH_2Cl_2–EtOAc–MeCN 1 : 1 : 1 : 1) to give the title compound **28** in a pure state. IR: 3300 (br), 2950 (br), 1775, 1715, 1610 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 1.29 (3H, d, J=6 Hz, Me), 1.63 (1H, br s, OH), 2.70 (3H, s, =CMe), 3.05 (2H, br d, J=9 Hz, C-1H_2), 3.16 (1H, dd, J=3, 9 Hz, C-6H), 3.80 (3H, s, OMe), 4.0—4.35 (2H, m, C-5H, C-8H), 4.40 and 4.56 (2H, ABq, J=14 Hz, C-2CH_2), 5.23 (2H, s, CO_2CH_2), 6.89 and 7.31 (4H, A_2B_2q, J=9 Hz, Ar). UV (MeCN): 227, 275, 281, 290 nm. The following compounds were prepared by the same method as described for **28**.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (29)**——**29** (40%, 13% recovery of the starting ylid). IR: 3600—3300, 1780, 1720, 1615 cm^{-1}. ^{1}H-NMR δ: 1.28 (3H, d, J=6 Hz, Me), 2.7 (1H, br, OH), 3.04 (2H, br d, J=9 Hz, C-1H_2), 3.15 (1H, m, C-6H), 3.77 (3H, s, OMe), 3.9—4.4 (2H, m, C-5H, C-8H), 4.41 and 4.57 (2H, ABq, J=14 Hz, C-2CH_2), 5.18 (2H, s, CO_2CH_2), 6.80 and 7.28 (4H, A_2B_2q, J=9 Hz, Ar), 8.97 (1H, s, =CH). UV (MeCN): 224 (15000), 275 (7000), 281 (6900), 290 (6000) nm.

***p*-Methoxybenzyl (5*R**,6*S**)-2-Acetoxymethyl-6-[(*R**)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (32)**——**32**: ^{1}H-NMR (90 MHz) δ: 1.27 (3H, d, J=6 Hz, Me), 1.95 (3H, s, Ac), 2.82 (2H, br d, J=10 Hz, C-1H_2), 3.14 (1H, dd, J=3, 9 Hz, C-6H), 3.67 (3H, s, OMe), 3.9—4.3 (2H, m, C-5H, C-8H), 4.97 and 5.22 (2H, ABq, J=14 Hz, C-2CH_2), 5.18 (2H, s, CO_2CH_2), 6.8—7.9 (Ar).

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (7)**——A solution of the above residue containing the carbapenem **28** (*ca.* 2.1 mmol, contaminated with $P(O)Ph_3$) was added to a solution of $AlCl_3$ (1.24 g, 4 eq) in a mixture of anisole (32 ml) and CH_2Cl_2 (4.2 ml) at −60 °C, and the whole was stirred at −60 to −40 °C for 1.5 h. A solution of $NaHCO_3$ (3.5 g, 18 eq) in phosphate buffer (0.05 M, pH 7, 140 ml) was added, and the reaction mixture 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 (25 × 310 mm, H_2O, H_2O–8% MeOH). Fractions containing the product [high performance liquid chromatography (HPLC), Nucleosil $10C_{18}$, 0.02 M pH 7 phosphate buffer–5% MeOH] were combined (285 ml), concentrated under reduced pressure at 20 °C and freeze-dried to give the title compound **7** (168 mg, 20% from the hydroxy-ylid) as an amorphous powder. IR (KBr): 3440 (br), 1755, 1630, 1595 cm^{-1}. ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.71 (3H, d, J=6 Hz, Me), 3.18 (3H, s, =CMe), 3.47 (2H, d, J=9 Hz, C-1H_2), 3.78 (1H, dd, J=3, 6 Hz, C-6H), 4.4—4.8 (2H, m, C-5H, C-8H), 4.64 and 4.92 (2H, ABq, J=13.5 Hz, C-2CH_2). UV (H_2O): 225, 279 nm. The following compounds were prepared by the same method as described for **7**.

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylcarbapen-2-em-3-carboxylate (8)**——**8** (30%): IR (KBr): 3400 (br), 1750, 1600 cm^{-1}. UV (H_2O): 275 (*ca.* 12000).

Sodium (5*R,6*S**)-2-Acetoxymethyl-6-[(*R**)-1-hydroxyethyl]carbapen-2-em-3-carboxylate (6)**——**6** (32% from the hydroxy-ylid): ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.73 (3H, d, J=7 Hz, Me), 2.57 (3H, s, Ac), 3.41 (2H, d, J=9 Hz, C-1H_2), 3.86 (1H, dd, J=3, 6 Hz, C-6H), 4.5—5.0 (2H, m, C-5H, C-8H), 5.34 and 5.67 (2H, ABq, J=14 Hz, C-2CH_2). UV (H_2O): 233, 269 nm.

(3*S,4*R**)-3-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-4-triphenylmethylthio-2-azetidinone (37)**——A solution of $NaIO_4$ (8.84 g, 1.1 eq) in water (94 ml) was added to a solution of the azetidinone-diol **33a** (20.0 g, 37.5 mmol) in a mixture of THF (375 ml) and water (94 ml) under ice cooling, and the whole was stirred at room temperature overnight, concentrated under reduced pressure, diluted with EtOAc, washed with brine, dried and concentrated to give the crude methylketone **34** (18.3 g, 97%).

A solution of $NaBH_4$ (4.38 g, 1.5 eq) in MeOH (90 ml) was added to a solution of the above keto-azetidinone **34** (38.5 g, 76.8 mmol) in a mixture of THF (250 ml) and MeOH (140 ml) under ice cooling, and the reaction mixture was stirred for 10 min at the same temperature, diluted with EtOAc, washed with brine, dried and concentrated. The residue was crystallized from a mixture of hexane and EtOAc to give the C-8*S** isomer (9.18 g). The mother liquid was chromatographed on Lobar columns (size B × 4, benzene–EtOAc 9 : 1, 4 : 1). The late fractions containing mostly the C-8*R** isomer were combined and the product was recrystallized from EtOAc–hexane (1 : 10) to give the C-8*R** isomer **35** (9.68 g, 25%) as crystals.

A mixture of the above azetidinone-alcohol **35** (9.68 g, 19.25 mmol), *tert*-butyldimethylchlorosilane (3.51 g, 1.2 eq) and imidazole (3.74 g, 2.9 eq) in DMF (39 ml) was stirred at room temperature overnight, then diluted with EtOAc, washed with water, dried and concentrated to give the *O*-silyl product **36**.

The above crude *O*,*N*-disilyl compound **36** was dissolved in a mixture of THF (96 ml) and acetic acid (1.33 ml,

1.2 eq) and treated with $Et_4NF \cdot 2H_2O$ (4.3 g, 1.2 eq) at room temperature for 30 min. The reaction mixture was concentrated, diluted with EtOAc, washed with brine, dried and concentrated to give the title compound **37** (10 g, 100%); mp 84—86 °C. IR: 3390, 2950, 2925, 1760 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.07 (6H, s, $SiMe_2$), 0.72 (9H, s, *tert*-Bu), 1.25 (3H, d, J=7 Hz, Me), 3.11 (1H, t, J=2.5 Hz, C-6H), 4.23 (1H, dq, J=2.5, 7 Hz, C-8H), 4.43 (1H, br s, NH), 4.55 (1H, d, J=2.5 Hz, C-5H), 7.2—7.7 (15H, m, Ar). *Anal.* Calcd for $C_{30}H_{37}NO_2SSi$: C, 71.52; H, 7.40; N, 2.78. Found: C, 71.49; H, 7.71; N, 2.78.

(3*S,4*R**)-3-[(*R**)-1-Hydroxyethyl]-1-(*p*-methoxybenzyloxycarbonyl)triphenylphosphoranylidenemethyl-4-triphenylmethylthio-2-azetidinone (39)**——A mixture of the azetidinone **37** (10.0 g, 19.2 mmol), glyoxylic acid PMB ester (4.9 g, 1.2 eq) and triethylamine (1.34 ml, 0.5 eq) in THF (96 ml) was stirred at room temperature overnight. Evaporation of the solvent and chromatography of the residue on Lobar columns (size B × 2, benzene–EtOAc 9 : 1) gave the alcohols **38** (11.3 g, 84%). IR: 3400 (br), 2950, 2925, 1765, 1750 (sh) cm^{-1}.

A solution of the above alcohols **38** (11.3 g, 16.2 mmol) in THF (162 ml) was treated with 2,6-lutidine (3.75 ml, 2 eq) and thionyl bromide (1.8 ml, 1.5 eq) at −35 °C for 30 min. The reaction mixture was diluted with EtOAc, washed with water, dried and concentrated to give the bromides.

A mixture of the above bromides, PPh_3 (6.37 g, 1.5 eq) and 2,6-lutidine (2.8 ml, 1.5 eq) in THF (162 ml) was stirred at room temperature overnight, then concentrated, diluted with EtOAc, washed with water, dried, concentrated and chromatographed on Lobar columns (size B × 3, benzene–EtOAc 9 : 1) to give the title compound **39** (9.84 g, 65%); mp 176—177 °C (ether–hexane). IR: 2950, 2925, 1745, 1610 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.07 (6H, s, $SiMe_2$), 0.74 and 0.80 (9H, s × 2, *tert*-Bu), 3.75 and 3.77 (3H, s × 2, OMe), 6.6—8.0 (m, Ar), other signals could not be assigned. *Anal.* Calcd for $C_{58}H_{60}NO_5PSSi$: C, 73.93; H, 6.42; N, 1.49. Found: C, 73.75; H, 6.39; N, 1.56.

(3*S,4*R**)-3-[(*R**)-1-*tert*-Butyldimethylsilyloxyethyl]-4-chloroacetoxythio-1-(*p*-methoxybenzyloxycarbonyl)-triphenylphosphoranylidenemethyl-2-azetidinone (41)**——A solution of $AgNO_3$ (1.22 g, 1.2 eq) in MeOH (36 ml) was added to a solution of the S-Tr compound **39** (5.65 g, 6.0 mmol) in THF (60 ml) containing pyridine (0.58 ml, 1.2 eq) under ice cooling, and the mixture was stirred at room temperature for 30 min, then diluted with CH_2Cl_2, washed with water, dried and concentrated to give the Ag salt **40** as an amorphous black powder. IR: 3410, 2950 (sh), 2925, 1740, 1615 cm^{-1}.

Pyridine (1.93 ml, 4 eq) and chloroacetyl chloride (1.43 ml, 3 eq) were added to a solution of the above residue in CH_2Cl_2 (90 ml) at −45 °C, and the reaction mixture was stirred for 1 h during which time the temperature reached 0 °C. The reaction mixture was diluted with EtOAc, washed with water, dried, concentrated and chromatographed on Lobar columns (size B × 3, benzene–EtOAc 4 : 1, 2 : 1) to give the chloroacetyl-ylid **41** (4.23 g, 91% from **39**). IR: 2950, 2925, 1750, 1690, 1610 cm^{-1}.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (44)**——A mixture of the chloroacetyl-ylid **41** (155 mg, 0.2 mmol), sodium 1-methyltetrazolylethiolate dihydrate (105 mg, 3 eq) and *tert*-Bu_4NBr (33 mg, 0.5 eq) in CH_2Cl_2 (3 ml) and water (0.2 ml) was agitated vigorously at room temperature for 2 h, then diluted with EtOAc, washed with water and aqueous $NaHCO_3$ solution, dried, concentrated and chromatographed on a Lobar column (size A, benzene–EtOAc 4 : 1, 2 : 1) to give the *O*-silyl-penem (26 mg, 22%) and the ylid **42** (108 mg, 63%). IR: 2950, 1755, 1690, 1610 cm^{-1}.

A solution of the above *O*-silyl-ylid **42** (105 mg, 0.12 mmol) in a mixture of MeOH (1.2 ml) and MeCN (0.2 ml) was treated with 1 N HCl (1.2 ml), and the whole was stirred at room temperature for 1.5 h, then diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried, concentrated and chromatographed on a Lobar column (size A, hexane–CH_2Cl_2–EtOAc–MeCN 1 : 1 : 1 : 1) to give the hydroxy-ylid **43** (77 mg, 88%). IR: 3500 (br), 1760, 1610 cm^{-1}. ^{1}H-NMR δ: 3.78 (3H, br s, OMe), 3.95 (3H, s, NMe), 7.3—7.9 (19H, m, Ar), other signals could not be assigned.

The hydroxy-ylid **43** (158 mg, 0.21 mmol) was dissolved in benzene (11 ml) containing a small amount of CH_2Cl_2 and the solution was heated at 75 °C for 4.5 h, then concentrated. The residue was chromatographed on a Lobar column (size A, hexane–CH_2Cl_2–EtOAc–MeCN 1 : 1 : 1 : 1) to give the penem **44** (75 mg, 76%). IR: 3375 (br), 1790, 1705, 1610, 1580 cm^{-1}. ^{1}H-NMR δ: 1.29 (3H, d, J=6 Hz, Me), 2.72 (1H, br, OH), 3.72 (1H, dd, J=1.5, 6.8 Hz, C-6H), 3.78 (3H, s, OMe), 3.90 (3H, s, NMe), 4.0—4.4 (1H, m, C-8H), 4.51 and 4.75 (2H, ABq, J=15 Hz, C-2CH_2), 5.18 (2H, s, CO_2CH_2), 5.57 (1H, d, J=1.5 Hz, C-5H), 6.87 and 7.34 (4H, A_2B_2q, J=9 Hz, Ar). UV (EtOH): 227, 259, 280 (sh), 331 nm. The following compounds were prepared by a method similar to that described for **44**.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (46)**——**46**: IR: 3400, 2950, 1780, 1700, 1605 cm^{-1}. ^{1}H-NMR δ: 1.29 (3H, d, J=6 Hz, Me), 2.4—3.0 (1H, br, OH), 3.72 (1H, dd, J=1.5, 7 Hz, C-6H), 3.79 (3H, s, OMe), 4.17 (1H, br quint, J=6.5 Hz, C-8H), 4.64 and 4.79 (2H, ABq, J=14 Hz, C-2CH_2), 5.19 (2H, s, CO_2CH_2), 5.56 (1H, d, J=1.5 Hz, C-5H), 6.87 and 7.36 (4H, A_2B_2q, J=9 Hz, Ar), 9.04 (1H, s, N=CHS). UV (EtOH): 227, 261, 280 (sh), 328 nm.

***p*-Methoxybenzyl (5*R**,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethylpenem-3-carboxylate (48)**——**48**: IR: 3400 (br), 2950, 1790, 1700, 1610, 1575 cm^{-1}. ^{1}H-NMR δ: 1.28 (3H, d, J=6 Hz, Me), 2.6—3.3 (2H, br, OH × 2), 3.72 (1H, dd, J=7, 1 Hz, C-6H), 3.78 (3H, s, OMe), 3.9—4.5 (5H, m, C-8H, NCH_2CH_2O), 4.44 and 4.71 (2H, ABq, J=14 Hz, C-2CH_2), 5.16 (2H, s, CO_2CH_2), 5.56 (1H, d, J=1 Hz, C-5H), 6.87 and 7.34 (4H, A_2B_2q, J=9 Hz, Ar). UV (EtOH): 228, 260 (sh), 280 (sh), 330 nm.

***p*-Methoxybenzyl (5*R**,6*S**)-2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(*R**)-1-hydroxyethyl]-**

penem-3-carboxylate (50)——**50**: IR (Nujol): 3515, 1790, 1695, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3+CD_3CN$) δ: 1.21 (3H, d, J=6 Hz, Me), 2.5—3.2 (1H, m, OH), 3.68 (1H, dd, J=6, 1.5 Hz, C-6H), 3.76 (3H, s, OMe), 4.07 (1H, quint, J=6 Hz, C-8H), 4.42 and 4.68 (2H, ABq, J=15 Hz, C-2CH_2), 4.98 (2H, s, NCH_2CO), 5.14 (2H, s, CO_2CH_2), 5.54 (1H, d, J=1.5 Hz, C-5H), 5.9—6.3 and 6.5—6.9 (2H, m, $CONH_2$), 6.86 and 7.32 (4H, A_2B_2q, J=9 Hz, Ar).

(3*S,5*R**)-3-[(*R**)-1-Allyloxycarbonyloxyethyl]-1-(allyloxycarbonyl)triphenylphosphoranylidenemethyl-4-chloroacetylthio-2-azetidinone (53)**——The allyl ester **52** was prepared by the same procedure as used for the corresponding PMB ester **41**. **52**: IR: 3370 (br), 2950, 1755, 1620 cm^{-1}.

A mixture of the *O*-silyl-ylid **52** (5.8 g, 8.34 mmol), acetic acid (8.3 ml) and conc. HCl (6.7 ml) in MeCN (83 ml) was stirred under ice cooling for 1 h, then diluted with EtOAc, washed with water and aqueous $NaHCO_3$ solution, dried and concentrated to give the hydroxy-ylid (5.77 g). IR: 3300 (br), 2950, 1755, 1620 cm^{-1}.

The above crude ylid (5.48 g, 7.92 mmol) in CH_2Cl_2 (79 ml) was treated with pyridine (4.6 ml, 7.2 eq) and allylchlorocarbonate (2.6 ml, 6.0 eq) under ice cooling for 2 h. The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried, concentrated and chromatographed on Lobar columns (size B × 3, benzene–EtOAc 4:1, 2:1) to give the title compound **53** (3.93 g, 72%).

Allyl (5*R,6*S**)-6-[(*R**)-1-Allyloxycarbonyloxyethyl]-2-(1-carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (55)**——A mixture of the chloroacetyl-ylid **53** (0.96 g, 1.41 mmol), 1-carbamoylmethyltetrazole-5-thiol (0.37 g, 1.6 eq) and triethylamine (0.29 ml, 1.5 eq) in MeCN (5.7 ml) was stirred at room temperature for 1 h, then diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried and concentrated to give the crude *S*-tetrazolyl-ylid **54** (1.19 g).

A solution of the above ylid **54** in benzene (71 ml) was refluxed for 3 h, then concentrated and chromatographed on a Lobar column (size B, hexane–CH_2Cl_2–EtOAc–MeCN 2:1:1:1, 1:1:1:1) to give the penem derivatives **55** (494 mg, 69% from the chloroacetate **53**). ^{1}H-NMR δ: 1.41 (3H, d, J=6 Hz, Me), 3.92 (1H, dd, J=1.5, 7 Hz, C-6H), 4.4—4.8 (5H, m, C-8H, CO_2CH_2 × 2), 4.8—5.2 (2H, m, C-2CH_2), 5.02 (2H, s, NCH_2CO), 5.1—5.3, 5.3—5.5 and 5.7—6.2 (6H, m, CH=CH_2 × 2), 5.59 (1H, d, J=1.5 Hz, C-5H), 6.2—6.9 (3H, m, $NHCONH_2$).

(3*S,4*R**)-1-(Allyloxycarbonyl)triphenylphosphoranylidenemethyl-3-[(*R**)-1-hydroxyethyl]-4-(5-methyl-1,3,4-thiadiazol-2-yl)acetylthio-2-azetidinone (57)**——A mixture of the crude *O*-silyl-ylid **52** (4.09 g, 5.88 mmol), 5-methylthiadiazole-2-thiol (1.01 g, 1.3 eq) and triethylamine (1.06 ml, 1.3 eq) in a mixture of MeCN (24 ml) and DMF (6.5 ml) was stirred at room temperature for 1 h, then diluted with EtOAc, washed with water, dried and concentrated to give the *O*-silyl-ylid **56** (4.60 g, 99%). IR: 2950, 2925, 2850, 1750, 1690, 1610 cm^{-1}.

A solution of the above ylid **56** (4.60 g, 5.82 mmol) in a mixture of MeCN (58 ml) and acetic acid (5.9 ml) was treated with conc. HCl (3.5 ml), and the mixture was stirred under ice cooling for 1.5 h, then diluted with EtOAc, washed with aqueous $NaHCO_3$ solution, dried and concentrated to give the hydroxy-ylid **57** (3.95 g, 100%). IR: 3450, 3000, 1760, 1610 cm^{-1}.

Allyl (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (58)**——A solution of the hydroxy-ylid **57** (crude, 3.94 g, 5.8 mmol) in benzene (293 ml) was refluxed for 4 h, then concentrated and chromatographed on Lobar columns (size B × 2, hexane–CH_2Cl_2–EtOAc–MeCN 1:1:1:1) to give the hydroxy-penem **58** (1.70 g, 73%). ^{1}H-NMR δ: 1.28 (3H, d, J=6 Hz, Me), 2.72 (3H, s, N=CMe), 3.69 (1H, dd, J=1.5, 7 Hz, C-6H), 4.14 (1H, quint, J=7 Hz, C-8H), 4.6—4.8 (2H, m, CO_2CH_2), 4.62 and 4.75 (2H, ABq, J=14 Hz, C-2CH_2), 5.1—5.6 and 5.7—6.2 (3H, m, CH=CH_2), 5.59 (1H, d, J=1.5 Hz, C-5H). UV (EtOH): 258, 329.5 nm.

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (45)**——A solution of the PMB ester **44** (35 mg, 0.76 mmol) in a mixture of CH_2Cl_2 (0.1 ml) and anisole (0.5 ml) was added to a solution of $AlCl_3$ (53 mg, 4 eq) in a mixture of anisole (1 ml) and CH_2Cl_2 (0.1 ml) at −50 °C, and the mixture was stirred for 1 h at the same temperature, then a solution of $NaHCO_3$ (151 mg, 18 eq) in phosphate buffer (pH 7, 0.06 M, 3 ml) and CH_2Cl_2 (10 ml) were added. The whole was stirred vigorously 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 (2.2 × 10 cm, deionized water). Fractions eluted with water containing MeOH (5%) were collected concentrated under reduced pressure and freeze-dried to give the title compound **45** (13 mg, 47%). ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.73 (3H, d, J=6 Hz, Me), 4.27 (1H, dd, J=1.5, 6 Hz, C-6H), 4.53 (3H, s, NMe), 4.65 (1H, quint, J=6 Hz, C-8H), 4.88 and 5.00 (2H, ABq, J=14 Hz, C-2CH_2), 6.02 (1H, d, J=1, 5 Hz, C-5H). UV (H_2O): 255, 314 nm. The following compounds were prepared by the same method as described for **45**.

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (47)**——**47**: ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.72 (3H, d, J=6 Hz, Me), 4.28 (1H, dd, J=1.5, 6 Hz, C-6H), 4.67 (1H, quint, J=6 Hz, C-8H), 5.10 (2H, s, C-2CH_2), 6.02 (1H, d, J=1.5 Hz, C-5H), 9.92 (1H, s, N=CHS). UV (H_2O): 264, 312 nm.

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-[1-(2-hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethylpenem-3-carbonate (49)**——**49**: ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.73 (3H, d, J=6 Hz, Me), 4.32 (1H, dd, J=1.5, 6 Hz, C-6H), 4.47 (2H, br t, J=6 Hz, NCH_2), 4.67 (1H, quint, J=6 Hz, C-8H), 5.0—5.2 (2H, m, CH_2O), 5.06 (2H, s, C-2CH_2), 6.04 (1H, d, J=1.5 Hz, C-5H). UV (H_2O): 257, 314.5 nm.

Sodium (5*R,6*S**)-2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(*R**)-1-hydroxyethyl]penem-3-carboxylate (51). (A) From the PMB Ester 50**——The PMB ester **50** (181 mg, 0.27 mmol) was deprotected as

described for **44** to give the title compound **51** (62 mg, 57%). ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.73 (3H, d, J= 6 Hz, Me), 4.31 (1H, dd, J=1.5, 6 Hz, C-6H), 4.67 (1H, quint, J=6 Hz, C-8H), 4.94 and 5.10 (2H, ABq, J=14 Hz, C-2CH_2), 5.82 (2H, s, NCH_2CO), 6.04 (1H, d, J=1.5 Hz, C-5H). UV (H_2O): 260 (2400), 315 (1700) nm.

(B) From the Allyl Ester 55——A solution of sodium ethylhexanoate (0.3 M) and ethylhexanoic acid (0.1 M) in EtOAc (8.6 ml, 3 and 1 eq) was added to a solution of the allyl ester **55** (440 mg, 0.86 mmol) and PPh_3 (8 mg, 0.02 eq) in benzene (34 ml), followed by the addition of $Pd(PPh_3)_4$ (151 mg, 0.1 eq), all under ice cooling, and the mixture was stirred at room temperature for 10 min. The precipitate was collected by filtration, washed with benzene and CH_2Cl_2, and dissolved in water. The solution was filtered and chromatographed on an HP-20AG column (25 × 300 mm, deionized water). Fractions containing the product were collected, concentrated and freeze-dried to give the title compound **51** (240 mg, 90% purity by HPLC, 68%). ^{1}H-NMR (D_2O), identical with **51** obtained from the PMB ester **50**.

Sodium (5*R,6*S**)-6-[(*R**)-1-Hydroxyethyl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (59)**——A solution of the allyl ester **58** (400 mg, 1.0 mmol), sodium ethylhexanoate (185 mg, 1.1 eq), PPh_3 (13 mg, 0.05 eq) and $Pd(PPh_3)_4$ (116 mg, 0.1 eq) in a mixture of benzene (6 ml) and CH_2Cl_2 (2 ml) was stirred at room temperature for 30 min. No precipitation occurred. The product was extracted with water, washed with CH_2Cl_2 and ether, concentrated under reduced pressure and chromatographed on an HP-20AG column (25 × 300 mm, deionized water containing 5% MeOH). Fractions containing the product were combined, concentrated and freeze-dried to give the title compound **59** (285 mg, 82% purity by HPLC, 75%) as an amorphous powder. ^{1}H-NMR (90 MHz, D_2O, ext. TMS) δ: 1.74 (3H, d, J=6 Hz, Me), 3.19 (3H, s, N=CMe), 4.26 (1H, dd, J=1.5, 6 Hz, C-6H), 4.67 (1H, quint, J=6 Hz, C-8H), 5.02 (2H, s, C-2CH_2), 6.02 (1H, d, J=1.5 Hz, C-5H). UV (H_2O): 265, 308 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 a compound was defined as the lowest concentration that visibly inhibited growth.

Stability Test——Jcl-ICr male mice weighing 25 g were used. Under ether anaethesia, the blood was collected in a heparinized capillary tube from the orbital sinus. The kidneys and liver were dissected out and each tissue homogenate was prepared at 10% final concentration with phosphate buffer solution (pH 7.0, 0.1 M).

A mixture of 100 μg of the test compound and 1.0 ml of tissue homogenate was incubated at 37 °C. Aliquots were collected at intervals, and after centrifugation the supernatant was subjected to bioassay.

The tissues of female cynomolgus monkeys were also used similarly.

Acknowledgement The authors wish to thank Drs. M. Imuta, W. Nagata, M. Yoshioka and M. Narisada (discussions), Y. Terui (NMR) and Y. Nakagawa (mass spectroscopy) for their contributions to this work.

References and Notes

1) This work was presented at The Third International Symposium on Recent Advances in The Chemistry of β-Lactam Antibiotics, Cambridge, U.K., July 1984.
2) *a*) W. J. Leanza, K. J. Wildonger, T. W. Miller and B. G. Christensen, *J. Med. Chem.*, **22**, 1435 (1979); *b*) H. Kropp, J. G. Sundelof, J. S. Kahan, F. M. Kahan and J. Birnbaum, *Antimicrob. Agents Chemother.*, **17**, 993 (1980).
3) *a*) A. K. Ganguly, V. M. Girijavallabhan, S. McCombie, P. Pinto, R. Rizvi, P. D. Jeffrey and S. Lin, *J. Antimicrob. Chemother.*, **9c**, 1 (1982); *b*) R. M. Brown, R. Wise and J. M. Andrews, *ibid.*, **9c**, 17 (1982).
4) H. Ona, S. Uyeo, K. Motokawa and T. Yoshida, *Chem. Pharm. Bull.*, **33**, 4346 (1985); M. Imuta, H. Ona, S. Uyeo, K. Motokawa and T. Yoshida, *ibid.*, **33**, 4361 (1985); M. Imuta, S. Uyeo, M. Nakano and T. Yoshida, *ibid.*, **33**, 4371 (1985).
5) *a*) M. Foglio, C. Battistini, F. Zarini and G. Franceschi, *Heterocycles*, **19**, 485 (1982); *b*) A. Sanfilippo, C. D. Bruna, D. Jabes, E. Morvillo, G. Schioppacassi, G. Franceschi, F. Arcamone, C. Battistini, M. Foglio and F. Zarini, *J. Antibiot.*, **35**, 1248 (1982); *c*) G. Franceschi, M. Foglio, M. Alpegiani, C. Battistini, A. Bedeschi, E. Perrone, F. Zarini, F. Arcamone, C. D. Bruna and A. Sanfilippo, *ibid.*, **36**, 938 (1983); *d*) R. Wise, J. M. Andrews and G. Danks, *Antimicrob. Agents Chemother.*, **24**, 909 (1983); *e*) C. Battistini, C. Scarafile, M. Foglio and G. Franceschi, *Tetrahedron Lett.*, **25**, 2395 (1984); *f*) E. Perrone, M. Alpegiani, A. Bedeschi, F. Giudici and G. Franceschi, *ibid.*, **25**, 2399 (1984); *g*) M. Alpegiani, A. Bedeschi, E. Perrone and G. Franceschi, *ibid.*, **25**, 4167, 4171 (1984); *h*) G. Franceschi, M. Alpegiani, A. Bedeschi, M. Foglio, E. Perrone, G. Meinadi, S. Grasso and I. De Carneri, *J. Antibiot.*, **37**, 685 (1984).
6) M. Shiozaki, N. Ishida, H. Maruyama, T. Hiraoka and S. Sugawara, *J. Antibiot.*, **37**, 57 (1984).
7) T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, **102**, 6161 (1980).

8) Attempted *O*-desilylation of the corresponding 5-methylthiadiazol-2-yl-thiomethyl derivative was also unsuccessful.
9) Bristol Myers Co., Japan. Patent Kokai 8125110.
10) P. J. Jeffrey and S. W. McCombie, *J. Org. Chem.*, **47**, 587 (1982).
11) H. Kropp, J. G. Sundelof, R. Hajdu and F. M. Kahan, *Antimicrob. Agents Chemother.*, **22**, 62 (1982).