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

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Racemic and optically active 2-(heteroaromatic)thiomethyl penems having a 1-(hydroxymethyl)ethylidene or cyclic carbonate side-chain at C-6 (**24**, **51**, **63**, **65**, **37**, **40**, **69** and **21b**, **61b**, **26b**, **30b**, **64b**, **35b**, **66b**, **39b**, **68b**) were synthesized, and their antibacterial activities are determined.

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

In the preceding two papers[2)] we reported a convenient method for preparing carbapenems **1** having the 1-(hydroxymethyl)ethylidene C-6 side-chain which characterizes the novel-type carbapenem antibiotics, asparenomycins (**2**). We also reported that some 2-

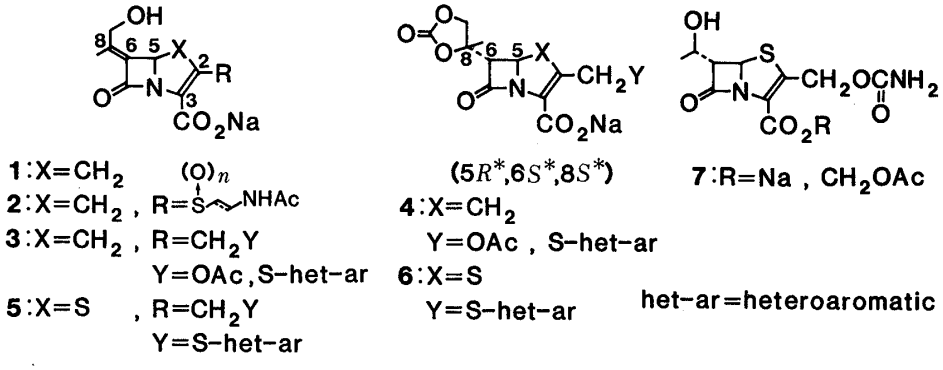


Chart 1

functionalized-methyl carbapenems with the asparenomycin C-6 side-chain **3** as well as those carbapenems with the cyclic carbonate side-chain **4** possess potent antibacterial activity against Gram-positive and Gram-negative bacteria (except *Pseudomonas aeruginosa*).

As it has been well recognized that penem antibiotics show similar but slightly less potent antibacterial activity when compared with the carbapenem counterparts, we carried out the synthesis of penem derivatives with these two side-chains in parallel with that of the carbapenems reported in the previous papers.[2)] In this paper we describe only the synthesis of 2-functionalized-methyl penems **5** and **6** in racemic and optically active forms. As will be shown in this paper, the *in vitro* antibacterial activities of these derivatives are very similar to those of the corresponding carbapenem congeners, as expected.

Recently, a Farmitalia group reported the development of the 2-functionalized-methyl penem antibiotics **7** as clinical candidates.[3)]

Chemistry

Since the chemical stability of penem derivatives is generally higher than that of the corresponding carbapenems, we hoped to apply the established synthetic methodology, which we reported in the preceding papers, for the penem synthesis without much difficulty. Our common intermediates **12a** and **12b**, which are equivalent to **8a** and **8b** in the carbapenem synthesis, were first prepared from a racemic trityltio-azetidinone **9**.[4] Deprotonation of **9** with lithium diisopropyl amide (LDA) in tetrahydrofuran (THF) followed by reaction with trimethylsilyloxyacetone gave an epimeric mixture of *O*-silyl compounds in good yield, from which a favorable product **10b**, having $5R^*$, $6S^*$ and $8S^*$ configurations, was isolated easily by silica gel chromatography. Compound **10b** was converted into the desired azetidinone **12b** by *O*-desilylation with acetic acid in methanol and subsequent carbonate formation with phosgene and pyridine in 30% overall yield from **9**. The diastereoisomer **12a** was similarly obtained in 43% yield. Formation of some C-5, 6 *cis* isomers was observed in this case. We assigned $5R^*,6S^*,8R^*$ (penem numbering) and $5R^*,6S^*,8S^*$ structures to **12a** and **12b**, respectively, based on a comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectra with those of the allylazetidinones **8a** and **8b**. The ^{1}H-NMR signals corresponding to the C-8 methylene protons of **12a** and **12b** appear as AB quartets at 4.02 and 4.45 ($J=8$ Hz),

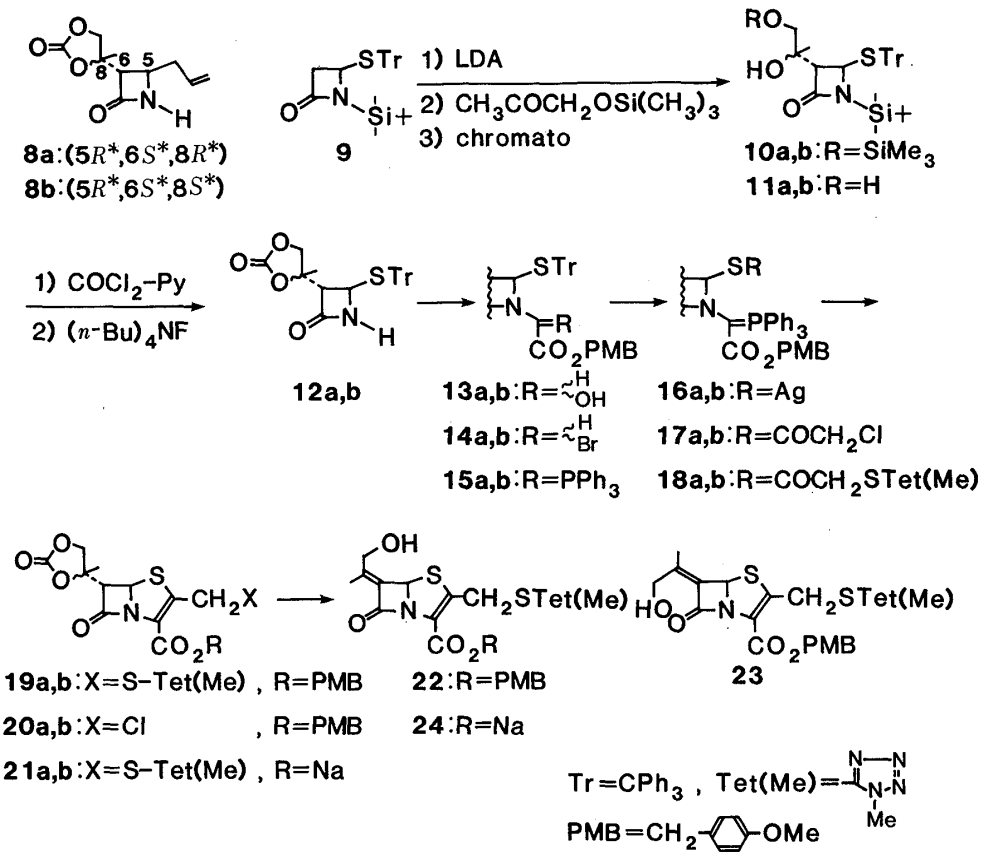


Chart 2

and 4.15 and 4.34 ppm ($J=8$ Hz), respectively. These signals are in good agreement with those of the allylazetidinones **8a** and **8b** at 4.14 and 4.68 (ABq, $J=8$ Hz), and 4.18 and 4.39 ppm (ABq, $J=9$ Hz), respectively. The chemical behavior of penems derived from the above intermediates was also consistent with the assigned structures, as described later. Preparation of the penems **5** and **6** was achieved by using the intramolecular Wittig reaction[5] and the $AlCl_3$–anisole carboxy-deprotection method as key reactions, as in the case of the carbapenem synthesis (Chart 1).

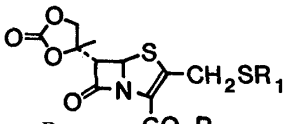
The ylids **15a** and **15b**, easily prepared from **12a** and **12b** *via* **13a** and **13b**, and the bromides **14a** and **14b**, were converted into *S*-chloroacetates **17a** and **17b** by way of the silver thiolate **16a** and **16b**. These versatile intermediates were first transformed to 1-methyltetrazolylthioacetates **18a** and **18b** by treatment with sodium thiolate in dimethylformamide (DMF) and then allowed to cyclize by heating them at 110 °C in toluene to produce the penems **19a** and **19b**. As is often observed in penem syntheses, owing to a partial epimerization at C-5, some C-5, 6 *cis* isomers were produced during this Wittig reaction at high temperature. However, this unfavorable formation of the isomer could be avoided by either controlling the reaction temperature carefully (90 °C in the case of **19b**) or changing the sequence of reactions as follows. Thus, the chloroacetyl-ylids **17a** and **17b** were cyclized on heating at lower temperature (60 °C) in toluene to afford the chloromethyl penems **20a** and **20b** without epimerization at C-5. Displacement of the chlorine atom with the sodium thiolate either in DMF or in methylene dichloride under phase-transfer conditions produced **19a** and **19b**. The carbonate **19a** was then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene to give **22** and its *Z*-isomer **23** in a ratio of 7 to 1. In contrast with carbapenems, the *Z*-isomer **23** could be isolated intact after aqueous work-up and silica gel chromatography. Deprotection of **19b** and **22** with $AlCl_3$ and anisole followed by HP-20AG chromatography and subsequent freeze–drying provided the sodium salts **21b** and **24** in a pure state. Slow transformation of **21b** into **24** in aqueous $NaHCO_3$ solution was observed.

By following the above sequence of reactions, we prepared several derivatives **25b**—**40** (Table I). As was the case in the carbapenem counterpart, a carbonate such as **33b** with the 1-hydroxyethyltetrazolyl group was prone to transformation into **36** during HP-20AG chromatography, thereby making the preparation of pure **33b** difficult. This problem could again be solved by use of the allyl protective group and Pd catalyst for deprotection.[6]

It has been believed that only penem derivatives having 5*R* stereochemistry possess antibacterial activity.[7] We performed the chiral synthesis of the aforementioned penems starting from penicillin by two approaches.

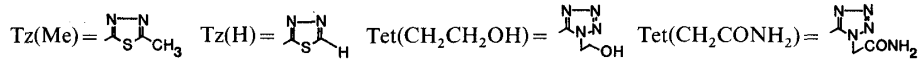
6α-Iodopenicillanic acid *p*-methoxybenzyl (PMB) ester (**42**), prepared from penicillin V

TABLE I. Penem Derivatives



Compound	R_1	R_2	Compound	R_1	R_2
25b	Tz(Me)	PMB	**27**	Tz(Me)	PMB
26b	Tz(Me)	Na	**28**	Tz(Me)	Na
62b (5*R*)[a]	Tz(Me)	Na	**63** (5*R*)	Tz(Me)	Na
29b	Tz(H)	PMB	**31**	Tz(H)	PMB
30b	Tz(H)	Na	**32**	Tz(H)	Na
64b (5*R*)	Tz(H)	Na	**65** (5*R*)	Tz(H)	Na
33b	Tet(CH_2CH_2OH)	PMB	**36**	Tet(CH_2CH_2OH)	PMB
34b	Tet(CH_2CH_2OH)	Allyl	**37**	Tet(CH_2CH_2OH)	Na
35b	Tet(CH_2CH_2OH)	Na	**67** (5*R*)	Tet(CH_2CH_2OH)	Na
66b (5*R*)	Tet(CH_2CH_2OH)	Na	**40**	Tet(CH_2CONH_2)	Na
38b	Tet(CH_2CONH_2)	PMB	**69** (5*R*)	Tet(CH_2CONH_2)	Na
39b	Tet(CH_2CONH_2)	Na			
68b (5*R*)	Tet(CH_2CONH_2)	Na			

a) The compounds denoted by (5*R*) are optically active.



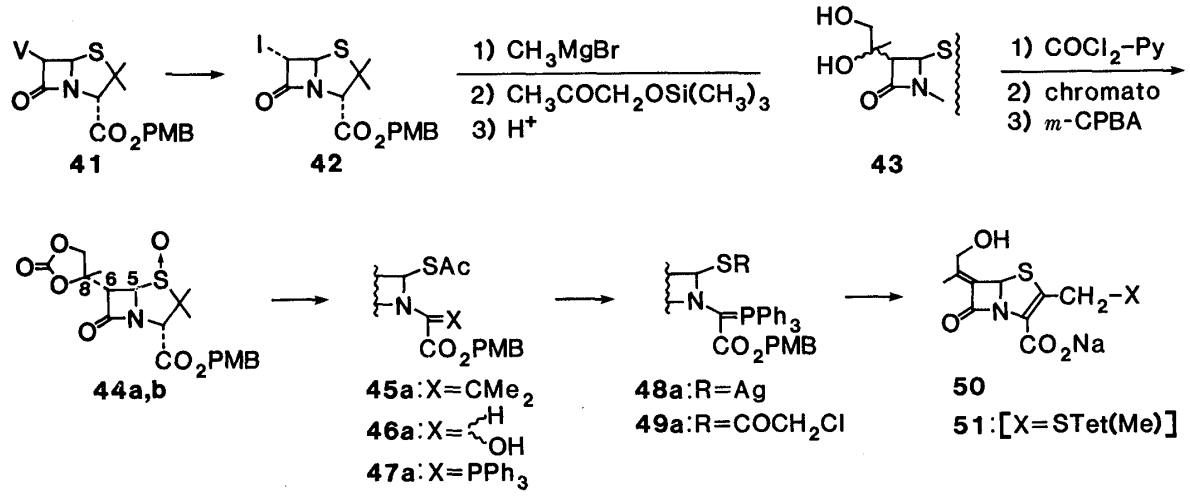


Chart 3

PMB ester (**41**) *via* an *N*-nitroso and a 6-diazo derivative,[8] was treated with methyl magnesium bromide in THF[9] and reacted with trimethylsilyloxyacetone to give, after acid work-up, a mixture of glycols **43**, which were converted into carbonates and separated by silica gel chromatography into C-5,6 *trans* and *cis* compounds. The *trans* compounds, obtained as major products, were oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to sulfoxides. The major product **44a**, which crystallized out in a pure state, was found to have a 6*S*,8*R* structure by ^{1}H-NMR analysis. The corresponding 8*S* isomer **44b** could be isolated in pure form from the mother liquor by careful chromatography on silica gel. Conversion of the penam sulfoxide **44a** to an *S*-acetyl-ylid **47a** proceeded in the usual manner without loss of the PMB ester moiety, *via* **45a** and **46a**.[10] The *S*-acetate **47a**, on treatment with silver perchlorate, gave the silver thiolate **48a**, which was then transformed to the penems with the asparenomycin-type side-chain **50** *via* the chloroacetate **49a** by a procedure identical to that used for the racemates (Chart 2).

Moreover, an alternative method was developed in order to prepare more easily the penems with a 6*S*,8*S* carbonate side-chain. 6α-Bromopenicillanic acid methyl ester (**53**), prepared easily from 6-aminopenicillanic acid (6-APA) (**52**), was degraded to the acetoxy-

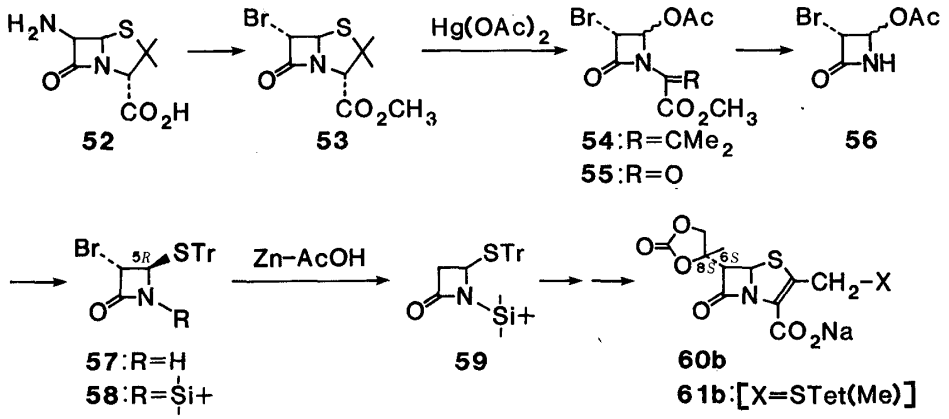


Chart 4

azetidinones **56** (*ca.* 1 : 1 mixture) by the known method[11] *via* **54** and **55**, and **56** gave a 5*R* tritylthio-azetidinone **57** on treatment with tritylmercaptan and sodium methoxide in methanol–THF.[12] After *N*-silylation, the bromine atom of the *N*-silyl-azetidinone **58** was

TABLE II. *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
Tet(Me)	A (5*R*)[b]	**61b**	0.1	0.2	0.39	0.2	0.2	6.25
Tet(Me)	B (5*R*)	**51**	0.1	0.2	0.39	0.2	0.39	3.13
Tet(Me)	A	**21b**	0.2	0.2	0.78	0.39	0.39	6.25
Tet(Me)	B	**24**	0.39	0.39	0.39	0.39	0.78	1.56
Tz(Me)	A	**26b**	0.2	0.2	6.25	3.13	3.13	100
Tz(Me)	B (5*R*)	**63**	0.1	0.1	3.13	0.78	0.78	25
Tz(H)	A (5*R*)	**64b**	0.05	0.1	0.78	0.39	0.78	12.5
Tz(H)	B (5*R*)	**65**	0.05	0.1	0.39	0.39	0.39	6.25
Tz(H)	A	**30b**	0.05	0.2	0.78	0.78	0.78	12.5
Tet(CH_2CH_2OH)	A (5*R*)	**66b**	0.2	0.2	0.39	0.2	0.39	3.13
Tet(CH_2CH_2OH)	A	**35b**	0.2	0.39	0.39	0.39	0.39	3.13
Tet(CH_2CH_2OH)	B	**37**	0.39	0.78	0.39	0.39	0.78	3.13
Tet(CH_2CONH_2)	A (5*R*)	**68b**	0.2	0.2	0.2	0.2	0.39	0.78
Tet(CH_2CONH_2)	B (5*R*)	**69**	0.1	0.1	0.1	0.1	0.2	0.78
Tet(CH_2CONH_2)	A	**39b**	0.2	0.39	0.2	0.2	0.39	1.56
Tet(CH_2CONH_2)	B	**40**	0.2	0.39	0.2	0.2	0.39	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. *b*) The compounds denoted by (5*R*) are optically active.

reductively removed with zinc and acetic acid to afford **59** having a sharp melting point (mp 121.5—122.5 °C, $[\alpha]_D$ −55.7° ($CHCl_3$)). Starting from this optically active material, the 5(*R*)-penems **60** with the 8*S* carbonate side-chain were prepared as listed in Table I.

Antibacterial Activity

As shown in Table II, the 2-functionalized-methyl penems exhibited potent *in vitro* antibacterial activity. They are comparable in activity with the carbapenem counterparts reported in the preceding paper, although better activity against *S. marcescens* was observed in the carbapenems.

The optically active 5*R* derivatives were about twice as active as the corresponding racemates. The penems having the carbonate C-6 side-chain showed almost identical activity to the corresponding penems having the 1-(hydroxymethyl)ethylidene side-chain, as in the case of the carbapenems.

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. 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®" pre-packed 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**)-1-*tert*-Butyldimethylsilyl-3-(1,2-dihydroxy-2-propyl)-4-triphenylmethylthio-2-azetidinone (11a, b)**—A solution of **9** (20.0 g, 43.6 mmol) in THF (50 ml) was added dropwise to a solution of LDA in THF [prepared

from diisopropylamine (5.6 g, 1.27 eq) and *n*-butyllithium (1.6 N solution in hexane, 35 ml, 1.3 eq) in THF (100 ml)] at −70 °C, and the mixture was stirred for 30 min. Then trimethylsilyloxyacetone (10.0 g, 1.6 eq) in THF (10 ml) was added and the reaction mixture was stirred for 1 h at −70 °C, diluted with brine and extracted with EtOAc. The organic extracts were dried and concentrated to give a residue, which was chromatographed on Lobar columns (size C × 2, benzene and benzene–EtOAc 9 : 1) to give **10b** (8.7 g, 37%) and **10a** containing *ca.* 10% of C-5, 6 *cis* products (13.6 g, 60%). **10b**: IR: 3500, 1740 cm^{-1}. ^{1}H-NMR δ: 0.10 (6H, s, $SiMe_2$), 0.27 (9H, s, $SiMe_3$), 0.92 (9H, s, *tert*-Bu), 1.05 (3H, s, Me), 3.17 and 3.69 (2H, ABq, J=10 Hz, OCH_2), 3.90 (1H, d, J=2 Hz, C-6H), 4.23 (1H, d, J=2 Hz, C-5H), 7.20—7.70 (15H, m, Ar).

The above crude **10b** was dissolved in a mixture of methanol (100 ml) and acetic acid (10 ml) and the mixture was stirred at 50 °C for 1 h. Evaporation of the solvent and recrystallization of the residue from hexane gave **11b** (7.6 g, 33%) as colorless crystals; mp 184—185 °C. IR: 3500, 3450, 1740 cm^{-1}. ^{1}H-NMR δ: 0.10 (6H, s, $SiMe_2$), 0.90 (9H, s, *tert*-Bu), 0.94 (3H, s, Me), 2.50 (2H, br s, OH), 3.21 and 3.49 (2H, ABq, J=8 Hz, OCH_2), 3.79 (1H, d, J=2 Hz, C-6H), 4.19 (1H, d, J=2 Hz, C-5H), 7.20—7.70 (15H, m, Ar). *Anal.* Calcd for $C_{31}H_{39}NO_3SSi$: C, 69.75; H, 7.36; N, 2.62. Found: C, 70.58; H, 7.17; N, 2.38.

Similarly **10a** was converted into **11a**. IR: 3550—3300, 1720 cm^{-1}. ^{1}H-NMR δ: 0.03 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.60 (3H, s, Me), 0.85 (9H, s, *tert*-Bu), 3.13 and 3.50 (2H, ABq, J=11 Hz, OCH_2), 3.47 (1H, d, J=2 Hz, C-6H), 4.25 (1H, d, J=2 Hz, C-5H), 3.0—5.9 (2H, br s, OH), 7.00—7.63 (15H, m, Ar).

(3*S,4*R**)-3-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-4-triphenylmethylthio-2-azetidinone (12a, b)**——Pyridine (5.78 ml, 5 eq) and a solution of phosgene in toluene (3.33 N, 8.56 ml, 2.0 eq) were added to a solution of **11b** (7.6 g, 14.26 mmol) in CH_2Cl_2 (100 ml) under ice cooling. The reaction mixture was stirred for 1 h under ice cooling, washed with water, dried and concentrated to give the crude carbonate (8.06 g, 98%). IR: 1805, 1750 cm^{-1}. ^{1}H-NMR δ: 0.10 (6H, s, $SiMe_2$), 0.92 (9H, s, *tert*-Bu), 1.47 (3H, s, C-8Me), 3.50 and 3.75 (2H, ABq, J=8 Hz, C-8CH_2), 3.77 (1H, d, J=2 Hz, C-6H), 4.10 (1H, d, J=2 Hz, C-5H), 7.20—7.70 (15H, m, Ar).

A mixture of the above crude carbonate (8.06 g, 13.5 mmol), $(n\text{-Bu})_4NF$ (4.7 g, 1.2 eq) and acetic acid (1.72 ml, 2 eq) in THF (60 ml) was stirred under ice cooling for 1 h. The reaction mixture was diluted with EtOAc (200 ml), washed with saturated brine (20 ml), dried and concentrated. The residue was chromatographed on a Lobar column (size C, benzene–EtOAc 1 : 2) and the product was crystallized to give **12b** (5.66 g, 87%); mp 129—130 °C (ether–hexane). IR: 1810, 1760 cm^{-1}. ^{1}H-NMR δ: 1.54 (3H, s, Me), 3.40 (1H, d, J=2 Hz, C-6H), 4.15 and 4.34 (2H, ABq, J=8 Hz, OCH_2), 4.70 (1H, br s, NH), 7.20—7.50 (15H, m, Ar). *Anal.* Calcd for $C_{26}H_{23}NO_4S$: C, 69.26; H, 5.90; N, 3.31. Found: C, 70.13; H, 5.17; N, 3.14.

Similarly **11a** was transformed into **12a**. IR: 1810, 1770 cm^{-1}. ^{1}H-NMR δ: 1.58 (3H, s, Me), 3.28 (1H, d, J=2 Hz, C-6H), 4.02 and 4.50 (2H, ABq, J=8 Hz, OCH_2), 4.47 (1H, d, J=2 Hz, C-5H), 7.00—7.57 (15H, m, Ar).

***p*-Methoxybenzyl α-[(3*S**,4*R**) and (3*S*,4*R*)-4-Chloroacetylthio-3-(4-methyl-2-oxo-1,3-dioxolan-4-yl)-2-azetidinon-1-yl]-α-triphenylphosphoranylideneacetate (17a, b) and (49a). (A) Preparation of Racemic Compounds 17a, b from 12a, b**——A mixture of the azetidinone **12b** (6.0 g, 13.5 mmol), PMB glycolate hydrate (3.18 g, 1.11 eq) and triethylamine (0.5 ml) in THF (50 ml) was stirred at room temperature for 2 h in the presence of Molecular Sieves 4A. The reaction mixture was diluted with EtOAc, filtered, washed with water, dried and concentrated to yield **13b** (8.90 g). IR: 3500, 1810, 1760 cm^{-1}.

2,6-Lutidine (3.45 ml, 2.0 eq) and thionyl bromide (1.7 ml, 1.5 eq) were added to a solution of the above residue in THF (50 ml) at −30 °C, and the mixture was stirred at the same temperature 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 to give crude bromides **14b** (8.70 g). IR: 1810, 1760 cm^{-1}.

A mixture of the above bromides **14b**, triphenylphosphine (4.72 g, 1.2 eq) and 2,6-lutidine (2.41 ml, 1.4 eq) in dioxane (30 ml) was stirred at room temperature for 10 h. The reaction mixture was diluted with EtOAc, washed with brine, dried and concentrated to give a residue, which was chromatographed on Lobar columns (size C × 2, benzene–EtOAc 1 : 1) to give the ylid **15b** (8.20 g, 69%). IR: 1805, 1750 cm^{-1}.

A solution of the the above ylid **15b** (8.0 g, 9.07 mmol) in a mixture of THF (50 ml) and water (5 ml) was treated with $AgNO_3$ (2.31 g, 1.5 eq) under ice cooling, and the mixture was stirred for 3 h, then diluted with CH_2Cl_2, washed with water, dried and concentrated to give the silver salt **16b** (7.1 g).

This crude **16b** was dissolved in CH_2Cl_2 (50 ml) and treated with pyridine (6.8 ml, 4.0 eq) and chloroacetyl chloride (6.90 ml, 3.0 eq) at −40 °C for 1 h. The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$ solution and brine, dried and concentrated. The residue was chromatographed on a Lobar column (size C, CH_2Cl_2–EtOAc 1 : 1) to give the title compound **17b** as a foam (4.2 g, 65%). IR: 1805, 1755 cm^{-1}.

(B) Preparation of the Optically Active Compound 49a from Penicillin V. *p*-Methoxybenzyl 6α-Iodopenicillanate (42)——Dinitrogen tetroxide (31 ml) was added to a mixture of penicillin V PMB ester (**41**) (98 g, 0.208 mol) and anhydrous NaOAc (114 g, 8.3 eq) in CH_2Cl_2 (400 ml) at −15 °C. The reaction mixture was stirred under ice cooling for 1 h and poured into a mixture of aqueous $NaHCO_3$ solution (1 l, containing 100 g of $NaHCO_3$) and CH_2Cl_2 (500 ml) under vigorous stirring. After 30 min of stirring under ice cooling, the organic phase was separated, dried and concentrated to *ca.* 1 l (*N*-NO compound).

Pyridine (21 ml) was added to the solution and the mixture was refluxed for 2 h, then washed with aqueous

$NaHCO_3$ solution and brine, dried and concentrated to *ca.* 600 ml (6-diazo compound).

A solution of NaI (187 g, 7.0 eq) in water (200 ml) was added to the above mixture, followed by dropwise addition of 50% H_2SO_4 (40 ml) under ice cooling. The organic phase was separated, washed with saturated $NaHSO_3$ solution and brine, dried and concentrated. The residue was chromatographed on a silica gel column in benzene to give the title compound **42** (60 g, 65%) as a pale yellow oil. ^{1}H-NMR δ: 1.36 (3H, s, Me), 1.60 (3H, s, Me), 3.77 (3H, s, OMe), 4.50 (1H, s, C-3H), 4.97 (1H, d, J=2 Hz, C-6H), 5.10 (2H, s, CO_2CH_2), 5.47 (1H, d, J=2 Hz, C-5H), 6.80 and 7.27 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R*,6*S*)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)penicillanate *S*-Oxide (44a, b)**——A solution of MeMgBr in ether (1.85 N, 24.2 ml, 1.0 eq) was added to a solution of the iodopenicillin **42** (20 g, 44.8 mmol) in THF (500 ml) at −70 °C, and the mixture was stirred for 15 min. Trimethylsilyloxyacetone (25 ml, 3.5 eq) was added, and the reaction mixture was stirred for 1 h. Then 0.5 N hydrochloric acid (280 ml) and EtOAc (400 ml) were added, and the whole was stirred for 1 h under ice cooling. The organic phase was separated, washed with saturated brine, dried and concentrated to give a mixture of glycols **43** (*ca.* 18 g).

The above mixture of glycols **43** was dissolved in CH_2Cl_2 (200 ml) and treated with pyridine (10.88 ml, 3.0 eq) and phosgene in toluene (3.33 N, 13.5 ml, 1.0 eq) at −30 to −10 °C for 1 h. The reaction mixture was washed with brine, dried and concentrated to give a residue, which was chromatographed on a Lobar column (size C, benzene–EtOAc 4 : 1) to give the C-5, 6 *trans* product (9.8 g, 52%) as a mixture of the C-8 epimers and the C-5, 6 *cis* product (2.2 g, 11%) as a single product. The major *trans* product. IR: 1810, 1780 cm^{-1}. ^{1}H-NMR δ: 1.33 (3H, s, C-2Me), 1.53 (6H, s, C-2Me, C-8Me), 3.50 (1H, d, J=2 Hz, C-6H), 3.72 (3H, s, OMe), 4.43 (1H, s, C-3H), 4.07 and 4.50 (2H, ABq, J=8 Hz, C-8CH_2), 5.07 (2H, s, CO_2CH_2), 5.23 (1H, d, J=2 Hz, C-5H), 6.80 and 7.20 (4H, A_2B_2q, J=8 Hz, Ar).

A mixture of the above *trans* product (9.8 g, 23.2 mmol) and *m*-CPBA (85%, 5.69 g, 1.2 eq) in CH_2Cl_2 (250 ml) was stirred under ice cooling for 1 h. The reaction mixrure was washed with aqueous $NaHSO_3$ solution, aqueous $NaHCO_3$ solution and water, dried and concentrated to give a residue, which was crystallized from EtOH to afford **44a** (7.1 g, 70%). Careful chromatography of the mother liquid on a Lobar column (size B, benzene–EtOAc 1 : 3) gave the C-8*S* isomer **44b** (1.85 g, 18%) as oil. **44a**: mp 176—178 °C (EtOH). IR: 1810, 1785, 1740 cm^{-1}. ^{1}H-NMR δ: 1.08 (3H, s, Me), 1.63 (3H, s, Me), 1.67 (3H, s, Me), 3.82 (3H, s, OMe), 3.85 (1H, d, J=2 Hz, C-6H), 4.47 (1H, s, C-3H), 4.20 and 4.73 (2H, ABq, J=8 Hz, C-8CH_2), 4.98 (1H, d, J=2 Hz, C-5H), 5.17 (2H, s, CO_2CH_2), 6.87 and 7.34 (4H, A_2B_2q, J=8 Hz, Ar). **44b**: IR: 1810, 1785, 1740 cm^{-1}. ^{1}H-NMR δ: 1.07 (3H, s, Me), 1.60 (3H, s, Me), 1.70 (3H, s, Me), 3.80 (3H, s, OMe), 3.93 (1H, d, J=2 Hz, C-6H), 4.48 (1H, s, C-3H), 4.23 and 4.73 (2H, ABq, J=8 Hz, C-8CH_2) 4.98 (1H, d, J=2 Hz, C-5H), 5.15 (2H, s, CO_2CH_2), 6.89 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

(3*S*,4*R*)-4-Acetylthio-1-(1-*p*-methoxybenzyloxycarbonyl-2-methyl-1-propenyl)-3-[(4*R*)-4-methyl-2-oxo-1,3-dioxolan-4-yl]-2-azetidinone (45a)——A mixture of the sulfoxide **44a** (6.90 g, 15.2 mmol), trimethyl phosphite (1.97 g, 1.2 eq) and acetic anhydride (6.06 ml, 4.0 eq) in toluene (150 ml) was heated under reflux for 1 h. The reaction mixture was diluted with benzene, washed with saturated $NaHCO_3$ solution, dried and concentrated (isopropenyl derivative).

The residue was dissolved in CH_2Cl_2 (200 ml) and treated with triethylamine (1 ml) at room temperature for 30 min. The reaction mixture was concentrated and the residue was chromatographed on a Lobar column (size C, benzene–EtOAc 2 : 1) to give the *S*-acetate **45a** (5.7 g, 78%) as oil. IR: 1810, 1765 cm^{-1}. ^{1}H-NMR δ: 1.50 (3H, s, Me), 1.92 (3H, s, Me), 2.23 (3H, s, Me), 2.67 (3H, s, Ac), 3.50 (1H, d, J=2 Hz, C-6H), 3.75 (3H, s, OMe), 3.97 and 4.45 (2H, ABq, J=8 Hz, C-8CH_2), 5.17 (2H, s, CO_2CH_2), 5.63 (1H, d, J=2 Hz, C-5H), 6.77 and 7.30 (4H, A_2B_2q, J= 8 Hz, Ar).

***p*-Methoxybenzyl α-[(3*S*,4*R*)-4-Chloroacetylthio-3-[(4*R*)-4-methyl-2-oxo-1,3-dioxolan-4-yl]-2-azetidinon-1-yl]-α-triphenylphosphoranylideneacetate (49a)**——Ozone was passed through a solution of the *S*-acetate **45a** (5.0 g, 10.8 mmol) in CH_2Cl_2 (250 ml) and MeOH (25 ml) at −70 °C and the reaction was continued for 30 min after a blue color persisted. Excess ozone was removed by nitrogen gas bubbling and acetic acid (50 ml) and Zn powder (12 g) were added to the reaction mixture. The whole was stirred for 30 min under ice cooling, then filtered, washed with water, dried and concentrated to give a epimeric mixture of alcohols **46a** (*ca.* 4.59 g). IR: 3500, 1810, 1765 cm^{-1}.

The crude products were dissolved in THF (20 ml) and treated with 2,6-lutidine (1.68 ml, 1.4 eq) and thionyl bromide (0.94 ml, 1.2 eq) at −30 °C for 30 min. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried and concentrated to give the crude bromides (4.38 g). IR: 1810, 1765 cm^{-1}.

A mixture of the above crude bromides, triphenylphosphine (3.29 g, 1.2 eq) and 2,6-lutidine (1.68 ml, 1.4 eq) in dioxane (20 ml) was stirred for 10 h, then diluted with EtOAc, washed with water, dried and concentrated. The residue was chromatographed on a Lobar column (size C, benzene–EtOAc 2 : 1) to give the ylid **47a** (3.47 g, 60%). IR: 1805, 1755 cm^{-1}.

A solution of the ylid **47a** (1.7 g, 2.5 mmol) in a mixture of dioxane (50 ml) and H_2O (10 ml) was treated with $AgClO_4$ (2.0 g, 3.0 eq), and the mixture was stirred under ice cooling for 3 h, then diluted with CH_2Cl_2, washed with water, dried and concentrated to give the crude silver salt **48a** (1.5 g).

The above salt **48a** was dissolved in CH_2Cl_2 (15 ml) and treated with chloroacetyl chloride (1.46 ml, 3.0 eq) and pyridine (1.95 ml, 4.0 eq) at −40 °C for 1 h. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried and concentrated to give the crude chloroacetyl-ylid **49a** (*ca.* 1.1 g, 62%), which was used as such for further reactions. **49a**: IR: 1805, 1755 cm^{-1}.

***p*-Methoxybenzyl (5*R**,6*S**)-2-Chloromethyl-6-(4-methyl-2-oxo-1,3-dioxolan-4-yl)penem-3-carboxylate (20a, b)**——A solution of the chloroacetate **17b** (710 mg, 1.0 mmol) in toluene (10 ml) was heated at 60 °C for 1.5 h, then concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 4 : 1) to give **20b** (328 mg, 76%). IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.66 (3H, s, C-8Me), 3.80 (3H, s, OMe), 4.10 (1H, d, J=2 Hz, C-6H), 4.13 and 4.40 (2H, ABq, J=9 Hz, C-8CH_2), 4.58 and 4.80 (2H, ABq, J=9 Hz, C-2CH_2), 5.19 (2H, s, CO_2CH_2), 5.61 (1H, d, J=2 Hz, C-5H), 6.87 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

Similarly, **20a** was prepared from **17a**. **20a**: IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 3.80 (3H, s, OMe), 4.03 (1H, d, J=2 Hz, C-6H), 4.20 and 4.60 (2H, ABq, J=9 Hz, C-8CH_2), 4.64 and 4.80 (2H, ABq, J=8 Hz, C-2CH_2), 5.20 (2H, s, CO_2CH_2), 5.64 (1H, d, J=2 Hz, C-5H), 6.87 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**,6*S**)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-2-(1-methyl-1*H*-tetrazol-5-yl)-thiomethyl-penem-3-carboxylate (19a, b). (A) Preparation from 20a, b**——A mixture of **20a** (40 mg, 0.092 mmol), the sodium salt of 5-mercapto-1-methyltetrazole (19 mg, 1.5 eq) and tetra-*n*-butylammonium bromide (3 mg) in CH_2Cl_2 (2 ml) and water (0.5 ml) was stirred at room temperature for 2 h, then diluted with CH_2Cl_2, washed with $NaHCO_3$ solution, dried and concentrated. The residue was chromatographed on a Lobar column (size A, benzene–EtOAc 2 : 1) to give **19a** (38 mg, 81%) as foam. IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.56 (3H, s, C-8Me), 3.79 (3H, s, NMe), 3.90 (3H, s, OMe), 3.99 (1H, d, J=2 Hz, C-6H), 4.15 and 4.60 (2H, ABq, J=9 Hz, C-8CH_2), 4.54 and 4.78 (2H, ABq, J=8 Hz, C-2CH_2), 5.18 (2H, s, CO_2CH_2), 5.57 (1H, d, J=2 Hz, C-5H), 6.85 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar). UV (EtOH): 227, 328 nm.

Similarly, **19b** was prepared from **20b**. **19b**: IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.62 (3H, s, C-8Me), 3.79 (3H, s, NMe), 3.90 (3H, s, OMe), 4.10 (1H, d, J=2 Hz, C-6H), 4.13 and 4.74 (2H, ABq, J=8 Hz, C-8CH_2), 4.25 and 4.62 (2H, ABq, J=9 Hz, C-2CH_2), 5.19 (2H, s, CO_2CH_2), 5.59 (1H, d, J=2 Hz, C-5H), 6.85 and 7.34 (4H, A_2B_2q, J=8 Hz, Ar).

(B) Preparation from the Chloroacetyl-ylids 17a, b——A mixture of **17b** (248 mg, 0.35 mmol), sodium 1-methyltetrazole-5-thiolate (200 mg, 4.1 eq) and tetra-*n*-butylammonium bromide (20 mg) in CH_2Cl_2 (10 ml) and water (1 ml) was stirred at room temperature for 2 h, then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 1 : 3) to give the tetrazole-ylid **18b** (260 mg, 95%). IR: 1805, 1755 cm^{-1}.

A solution of the above ylid **18b** in toluene (20 ml) was heated at 90 °C (inner temperature) for 2 h and concentrated. The residue was chromatographed on a Lobar column (size A, benzene–EtOAc 2 : 1) to give **19b** (130 mg, 77%) as a foam. When this reaction was carried out at reflux temperature, formation of some C-5, 6 *cis* penem was detected by thin layer chromatography (TLC). The *cis* compound, isolated by chromatography on a Lobar column (size A, benzene–EtOAc 1 : 1), gave the following NMR signals. ^{1}H-NMR δ: 1.65 (3H, s, C-8Me), 3.79 (3H, s, NMe), 3.90 (3H, s, OMe), 4.00 (1H, d, J=4 Hz, C-6H), 4.10 and 4.30 (2H, ABq, J=7 Hz, C-8CH_2), 4.60 and 4.75 (2H, ABq, J=8 Hz, C-2CH_2), 5.19 (2H, s, CO_2CH_2), 5.50 (1H, d, J=4 Hz, C-5H), 6.85 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar). The following compounds were prepared by the same methods as used for **19a, b**.

***p*-Methoxybenzyl (5*R**,6*S**)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-2-[(5-methyl-1,3,4-thiadiazol-2-yl)-thiomethyl]penem-3-carboxylate (25a, b)——25a**: IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.59 (3H, s, C-8Me), 2.73 (3H, s, Me), 3.80 (3H, s, OMe), 4.00 (1H, d, J=2 Hz, C-6H), 4.17 and 4.60 (2H, ABq, J=9 Hz, C-8CH_2), 4.62 and 4.79 (2H, ABq, J=8 Hz, C-2CH_2), 5.20 (2H, s, CO_2CH_2), 5.58 (1H, d, J=2 Hz, C-5H), 6.87 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar). **25b**: IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.61 (3H, s, C-8Me), 2.72 (3H, s, Me), 3.79 (3H, s, OMe), 4.06 (1H, d, J=2 Hz, C-6H), 4.15 and 4.39 (2H, ABq, J=9 Hz, J=9 Hz, C-8CH_2), 4.61 and 4.80 (2H, ABq, J=8 Hz, C-2CH_2), 5.19 (2H, s, CO_2CH_2), 5.59 (1H, d, J=2 Hz, C-5H), 6.87 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**,6*S**)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-2-[(1,3,4-thiadiazol-2-yl)thiomethyl]penem-3-carboxylate (29a, b)——29a**: IR: 1815, 1790 cm^{-1}. ^{1}H-NMR δ: 1.58 (3H, s, C-8Me), 3.80 (3H, s, OMe), 4.00 (1H, d, J=2 Hz, C-6H), 4.19 and 4.60 (2H, ABq, J=9 Hz, C-8CH_2), 4.68 and 4.82 (2H, ABq, J=8 Hz, C-2CH_2), 5.20 (2H, s, CO_2CH_2), 5.60 (1H, d, J=2 Hz, C-5H), 6.89 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar), 9.07 (1H, s, N=CHS). **29b**: IR: 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.62 (3H, s, C-8Me), 3.79 (3H, s, OMe), 4.08 (1H, d, J=2 Hz, C-6H), 4.16 and 4.38 (2H, ABq, J=8 Hz, C-8CH_2), 4.61 and 4.81 (2H, ABq, J=8 Hz, C-2CH_2), 5.20 (2H, s, CO_2CH_2), 5.59 (1H, d, J=2 Hz, C-5H), 6.89 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar), 9.05 (1H, s, N=CHS).

***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]penem-3-carboxylate (33b)——33b**: IR: 3500, 1815, 1795 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 3.79 (3H, s, OMe), 4.06 (2H, t, J=4 Hz, N$\underline{CH_2}CH_2O$), 4.20 (1H, d, J=2 Hz, C-6H), 4.00—4.40 (2H, m, C-2H_2), 4.35 (2H, t, J=4 Hz, N$CH_2\underline{CH_2}O$), 4.42 and 4.72 (2H, ABq, J=8 Hz, C-8CH_2), 5.17 (2H, s, CO_2CH_2), 5.59 (1H, d, J=2 Hz, C-5H), 6.85 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (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]penem-3-carboxylate (38b)——38b**: IR: 1810, 1790, 1700 cm^{-1}. ^{1}H-NMR δ: 1.63 (3H, s, C-8Me), 3.80 (3H, s, OMe), 4.11 (1H, d, J=2 Hz, C-6H), 4.16 and 4.43 (2H, ABq, J=7 Hz, C-8CH_2), 4.48 and 4.72 (2H, ABq, J=8 Hz, C-2CH_2), 4.96 (2H, s, $C\underline{H_2}CONH_2$), 5.19 (2H, s, CO_2CH_2), 5.57 (1H, d, J=2 Hz, C-5H), 6.85 and 7.35 (4H, A_2B_2q, J=8 Hz, Ar).

Allyl (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]penem-3-carboxylate (34b)——The allyl ester **34b** was prepared from the azetidinone **12b** by the same method as described for **19a, b**. **34b**: IR: 3500, 1810, 1790 cm^{-1}. ^{1}H-NMR δ: 1.66 (3H, s, C-8Me), 3.00 (1H, br s, OH), 4.07 (2H, t, J=4 Hz, $NC\underline{H}_2C\underline{H}_2O$), 4.20 (1H, d, J=2 Hz, C-6H), 4.00—4.70 (6H, m), 4.50 and 4.75 (2H, ABq, J=8 Hz, C-$2CH_2$), 5.20—5.50 (2H, m, $C=CH_2$), 5.65 (1H, d, J=2 Hz, C-5H), 5.70—6.15 (1H, m, CH=C).

***p*-Methoxybenzyl (5*R**)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (22)**——A solution of DBU in toluene (1 M, 10 μl) was added to a solution of **19a** (10 mg, 0.019 mmol) in $CDCl_3$ (0.4 ml), and the mixture was stirred at room temperature for 10 min, then diluted with EtOAc, washed with water, dried and concentrated to give a mixture of **22** and the *Z*-isomer **23** in 3 : 1 ratio (determined by NMR) (8 mg). When this reaction was done in C_6D_6 the ratio of **22** to **23** was 7 : 1. **22**: ^{1}H-NMR δ: 1.97 (3H, s, C-8Me), 3.40 (1H, br s, OH), 3.80 (3H, s, NMe), 3.89 (3H, s, OMe), 4.28 (2H, s, C-$8CH_2$), 4.49 and 4.80 (2H, ABq, J=9 Hz, C-$2CH_2$), 5.20 (2H, s, CO_2CH_2), 6.31 (1H, s, C-5H), 6.85 and 7.40 (A_2B_2q, J=8 Hz, 4H, Ar). **23**: ^{1}H-NMR δ: 1.76 (3H, s, C-8Me), 3.40 (1H, br s, OH), 3.80 (3H, s, NMe), 3.90 (3H, s, OMe), 4.39 (2H, s, C-$8CH_2$), 4.52 and 4.81 (2H, ABq, J=9 Hz, C-$2CH_2$), 5.15 (2H, s, CO_2CH_2), 6.03 (1H, s, C-5H), 6.85 and 7.40 (4H, A_2B_2q, J=8 Hz, Ar). The following compounds were prepared by the same method as used for **22**.

***p*-Methoxybenzyl (5*R**)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (27)**——**27**: ^{1}H-NMR δ: 1.96 (3H, s, C-8Me), 2.69 (3H, s, Me), 3.79 (3H, s, OMe), 4.28 (2H, s, C-$8CH_2$), 4.50 and 4.79 (2H, ABq, J=9 Hz, C-$2CH_2$), 5.20 (2H, s, CO_2CH_2), 6.30 (1H, s, C-5H), 6.85 and 7.40 (4H, A_2B_2q, J=8 Hz, Ar).

***p*-Methoxybenzyl (5*R**)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carbonate (31)**——**31**: ^{1}H-NMR δ: 1.79 (3H, s, C-8Me), 3.80 (3H, s, OMe), 4.29 (2H, s, C-$8CH_2$), 4.61 and 4.83 (2H, ABq, J=9 Hz, C-$2CH_2$), 5.21 (2H, s, CO_2CH_2), 6.31 (1H, s, C-5H), 6.85 and 7.40 (4H, A_2B_2q, J=8 Hz, Ar).

Sodium (5*R,6*S**) and (5*R*,6*S*)-6-(4-Methyl-2-oxo-1,3-dioxolan-4-yl)-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (21a, b) and (61b)**——The PMB ester **19a** (100 mg, 0.20 mmol) was added to a solution of $AlCl_3$ (104mg, 4.0 eq) in a mixture of anisole (2 ml) and CH_2Cl_2 (0.2 ml) at −40 °C, and the mixture was stirred for 1 h at the same temperature. A solution of $NaHCO_3$ (295 mg, 4.8 eq) in pH 7 phosphate buffer (0.01 M, 10 ml) and CH_2Cl_2 (20 ml) were added, and the reaction mixture was stirred under ice cooling for 30 min and filtered. The aqueous filtrate was chromatographed on a HP-20AG column (10 mm × 240 mm, H_2O) and the fractions containing the product [high performance liquid chromatography (HPLC), Nucleosil $10C_{18}$, 0.02 M pH 7 phosphate buffer–15% MeOH] were concentrated and freeze-dried to give **21a** (35 mg, 43%) as a colorless powder. ^{1}H-NMR (D_2O, from DSS) δ: 1.62 (3H, s, C-8Me), 4.10 (3H, s, NMe), 4.36 (1H, d, J=2 Hz, C-6H), 4.44 and 4.65 (2H, ABq, J=9Hz, C-$8CH_2$), 4.50 and 4.74 (2H, ABq, J=8 Hz, C-$2CH_2$), 5.74 (1H, d, J=2 Hz, C-5H). UV (H_2O): 312 nm.

Similarly, **19b** (100 mg, 0.20 mmol) gave **21b** (38 mg, 47%). ^{1}H-NMR (D_2O, from DSS) δ: 1.68 (3H, s, C-8Me), 4.09 (3H, s, NMe), 4.36 (1H, d, J=2 Hz, C-6H), 4.41 and 4.58 (2H, ABq, J=8 Hz, C-$8CH_2$), 4.44 and 4.52 (2H, ABq, J=8 Hz, C-$2CH_2$), 5.70 (1H, d, J=2 Hz, C-5H). UV (H_2O): 312 nm. The following compounds were prepared by the same procedure as used for **21a**.

Sodium (5*R,6*S**) and (5*R*,6*S*)-6-[(4*S**) and (4*S*)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (26b) and (62b)**——**26b** and **62b**: ^{1}H-NMR (D_2O) δ: 2.12 (3H, s, C-8Me), 3.18 (3H, s, Me), 4.40 (1H, d, J=2 Hz, C-6H), 4.70 and 4.85 (2H, ABq, J=8 Hz, C-$8CH_2$), 4.95 and 5.10 (2H, ABq, J=8 Hz, C-$2CH_2$), 6.10 (1H, d, J=2 Hz, C-5H). UV (H_2O) 310 nm.

Sodium (5*R,6*S**) and (5*R*,6*S*)-6-[(4*S**) and (4*S*)-4-Methyl-2-oxo-1,3-dioxolan-4-yl]-2-(1,3,4-thiadiazol-2-yl)-thiomethylpenem-3-carboxylate (30b) and (64b)**——**30b** and **64b**: ^{1}H-NMR (D_2O, from DSS) δ: 1.67 (3H, s, C-8Me), 4.34 (1H, d, J=2 Hz, C-6H), 4.38 and 4.58 (2H, ABq, J=7 Hz, C-$8CH_2$), 4.59 and 4.70 (2H, ABq, J=8 Hz, C-$2CH_2$), 5.68 (1H, d, J=2 Hz, C-5H), 9.43 (1H, s, N=CHS). UV (H_2O): 309 nm.

Sodium (5*R) and (5*R*)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1-methyl-1*H*-tetrazol-5-yl)thiomethylpenem-3-carboxylate (24) and (51)**——**24** and **51**: ^{1}H-NMR (D_2O, from DSS) δ: 1.95 (3H, s, C-8Me), 4.08 (3H, s, NMe), 4.16 and 4.30 (2H, ABq, J=8 Hz, C-$8CH_2$), 4.35 and 4.50 (2H, ABq, J=8 Hz, C-$2CH_2$), 6.29 (1H, s, C-5H). UV (H_2O): 295, 340 nm.

Sodium (5*R) and (5*R*)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(5-methyl-1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (28) and (63)**——**28** and **63**: ^{1}H-NMR (D_2O, from DSS) δ: 1.94 (3H, s, C-8Me), 2.73 (3H, s, Me), 4.18 and 4.30 (2H, ABq, J=8 Hz, C-$8CH_2$), 4.46 and 4.59 (2H, ABq, J=8 Hz, C-$2CH_2$), 6.28 (1H, s, C-5H). UV (H_2O): 295, 340 nm.

Sodium (5*R) and (5*R*)-6-[(*E*)-1-(Hydroxymethyl)ethylidene]-2-(1,3,4-thiadiazol-2-yl)thiomethylpenem-3-carboxylate (32) and (65)**——**32** and **65**: ^{1}H-NMR (D_2O, from DSS) δ: 1.94 (3H, s, C-8Me), 4.17 and 4.30 (2H, ABq, J=7 Hz, C-$8CH_2$), 4.56 and 4.68 (2H, ABq, J=8 Hz, C-$2CH_2$), 6.28 (1H, s, C-5H), 9.42 (1H, s, N=CHS). UV (H_2O): 295, 340 nm.

Sodium (5*R) and (5*R*)-2-[1-(2-Hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethyl-6-[(*E*)-1-(hydroxymethyl)ethylidene]-penem-3-carboxylate (37) and (67)**——**37** and **67**: ^{1}H-NMR (D_2O, from DSS) δ: 1.97 (3H, s, C-8Me), 4.00 (2H, t, J=4 Hz, $NC\underline{H}_2C\underline{H}_2O$), 4.17 and 4.30 (2H, ABq, J=8 Hz, C-$2CH_2$), 4.40—4.70 (4H, m, C-$8CH_2$, $NCH_2C\underline{H}_2O$), 6.30 (1H, s, C-5H). UV (H_2O): 297, 340 nm.

Sodium (5*R,6*S**) and (5*R*,6*S*)-2-[(2-Hydroxyethyl)-1*H*-tetrazol-5-yl]thiomethyl-6-[(4*S**) and (4*S*)-4-methyl-2-**

oxo-1,3-dioxolan-4-yl]penem-3-carboxylate (35b) and (66b). (A) From the PMB Ester 33b——Following the same procedure as for **21a**, the PMB ester **33b** (100 mg, 0.18 mmol) was converted into the salt **35b** (27 mg, 33%). ^{1}H-NMR (D_2O, from DSS) δ: 1.68 (3H, s, C-8Me), 4.00 (2H, t, J=4 Hz, NCH_2CH_2O), 4.35—4.70 (4H, m, C-8CH_2, NCH_2CH_2O), 4.36 (1H, d, J=2 Hz, C-6H), 4.38 and 4.50 (2H, ABq, J=8 Hz, C-8CH_2), 5.72 (1H, d, J=2 Hz, C-5H). UV (H_2O): 310 nm.

(B) From the Allyl Ester 34b——$Pd(PPh_3)_4$ (5 mg) and PPh_3 (3 mg) were added to a solution of the allyl ester **34b** (30 mg, 0.064 mmol) and acetic acid (5.8 mg, 1.5 eq) in CH_2Cl_2 (0.2 ml) under ice cooling, and the mixture was stirred for 30 min under ice cooling. A solution of $NaHCO_3$ (11 mg, 2.0 eq) in water (1 ml) was added, and the reaction mixture was stirred for several min. The aqueous phase was separated and purified by preparative HPLC (Nucleosil 10C_{18}, 0.5 cm × 15 cm, H_2O–MeOH 93 : 3). Fractions containing the product were concentrated and freeze-dried to give **35b** (15 mg, 52%) as a colorless powder: the ^{1}H-NMR (D_2O) and UV (H_2O) spectra were identical with those of **35b** obtained from the PMB ester **33b**.

Sodium (5*R)-2-(1-Carbamoylmethyl-1*H*-tetrazol-5-yl)thiomethyl-6-[(*E*)-1-(hydroxymethyl)ethylidene]penem-3-carboxylate (40)**——A solution of the carbonate-sodium salt **39b** (30 mg, 0.065 mmol) in water (5 ml) containing $NaHCO_3$ (20 mg) was allowed to stand at room temperature for 3 h, then chromatographed on an HP-20AG column (10 mm × 240 mm, H_2O) and freeze-dried to give **40** (19 mg, 71%) as a pale yellow powder. ^{1}H-NMR (D_2O, from DSS) δ: 1.95 (3H, s, C-8Me), 4.18 and 4.30 (2H, ABq, J=8 Hz, 2H, C-8CH_2), 4.43 and 4.62 (2H, ABq, J=8 Hz, C-2CH_2), 5.36 (2H, s, NCH_2), 6.29 (1H, s, C-5H). UV (H_2O): 298, 340 nm.

Preparation of the Optically Active Azetidinone 59 from Penicillin. (3*S*,4*R*)-3-Bromo-4-triphenylmethylthio-2-azetidinone (57)——A mixture of 6α-bromopenicillanic acid methyl ester (**53**) (73 g, 248 mmol) and $Hg(OAc)_2$ (294 g, 3.7 eq) in acetic acid (300 ml) was heated at 90 °C for 4 h. Most of the solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated. Chromatography of the residue on Lobar columns (size C × 2, benzene–EtOAc 9 : 1) gave the *O*-acetate **54** (50 g, 87%) as an epimeric mixture (*ca.* 1 : 1). ^{1}H-NMR δ: 2.22 and 2.27 (6H, d, J=8 Hz, C=CMe_2), 2.43 (3H, s, OAc), 3.93 (3H, s, OMe), 4.90 (s) and 5.30 (1H, d, J=3 Hz, C-6H), 6.30 (s) and 6.42 (1H, d, J=3 Hz, C-5H).

Ozone was passed through a solution of **54** (50 g, 156 mmol) in CH_2Cl_2 (400 ml) at −70 °C until a blue color persisted. Excess ozone was removed by nitrogen bubbling and the reaction mixture was treated with dimethylsulfide (25 ml) at room temperature for 30 min, then concentrated.

The residue was dissolved in methanol (300 ml) and the solution was allowed to stand at room temperature overnight, then concentrated and chromatographed on Lobar columns (size C × 2, benzene–EtOAc 2 : 1) to give **56** (33.2 g, 100%) as an epimeric mixture. IR: 3410, 1810, 1750 cm^{-1}. ^{1}H-NMR δ: 2.23 and 2.28 (3H, s, Ac), 4.80 (1H, br s) and 5.20 (1H, t, J=2 Hz, C-6H), 5.85 and 6.07 (1H, s, and d, J=2 Hz, C-5H), 7.40 (1H, br, OH).

A solution of NaOMe in MeOH (5.2 N, 0.55 ml, 1 eq) was added dropwise to a solution of the *O*-acetate **56** (0.60 g, 2.88 mmol) and triphenylmethylmercaptan (0.80 g, 1 eq) in a mixture of EtOH (20 ml) and THF (10 ml) at −20 °C, and the mixture was stirred at −10 °C for 30 min, then diluted with CH_2Cl_2, washed with water, dried and concentrated. The residue was chromatographed on a Lobar column (size B, benzene–EtOAc 9 : 1) to give the title compound **57** (0.73 g, 60%). IR: 3390, 1785 cm^{-1}. ^{1}H-NMR δ: 4.67 (1H, m, C-6H), 4.83 (1H, m, C-5H), 5.03 (1H, br, NH), 7.47 (15H, s, Ar).

(4*R*)-1-*tert*-Butyldimethylsilyl-4-triphenylmethylthio-2-azetidinone (59)——A mixture of the azetidinone **57** (17.5 g, 41.3 mmol), *tert*-butyldimethylsilyl chloride (9.35 g, 1.5 eq) and triethylamine (7.5 g, 1.8 eq) in CH_2Cl_2 (200 ml) was stirred at room temperature overnight, then washed with water, dried and concentrated to give crude **58**. ^{1}H-NMR δ: 0.25 (6H, s, $SiMe_2$), 0.92 (9H, s, *tert*-Bu), 4.28 (2H, d, J=2 Hz, C-5H, C-6H), 7.27 (15H, s, Ar).

Zn powder (18 g, 6.7 eq) was added in small portions to the above crude **58** in a mixture of CH_2Cl_2 (150 ml), MeOH (100 ml) and AcOH (20 ml) under vigorous stirring. After 1 h of stirring at room temperature, the reaction mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2, and the solution was washed with water, dried, concentrated and chromatographed on Lobar columns (size C × 2, benzene–EtOAc 9 : 1) to give the title compound **59** (13.9 g, 73%). Recrystallization from *n*-pentane gave the pure material (10.3 g); mp 121.5—122.5 °C. $[\alpha]_D$ −55.7 ± 1.0° ($CHCl_3$, c=1.00). NMR (identical with that of the racemate **9**).

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.

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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) 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).
3) *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).
4) A. Martel, J. Collerette, J. Banville, J.-P. Daris, P. Lapointe, B. Belleau and M. Menard, *Can. J. Chem.*, **61**, 613 (1983).
5) I. Ernest, J. Gosteli, W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978).
6) P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, **47**, 587 (1982).
7) I. Ernest, J. Gosteli and R. B. Woodward, *J. Am. Chem. Soc.*, **101**, 6301 (1979).
8) J. C. Sheehan, Y. S. Lo, J. Löliger and C. C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974).
9) F. DiNinno, T. R. Beattie and B. G. Christensen, *J. Org. Chem.*, **42**, 2960 (1977).
10) S. Uyeo and H. Ona, *Chem. Pharm. Bull.*, **28**, 1563 (1980).
11) A. Yoshida, T. Hayashi, N. Takeda, S. Oida and E. Ohki, *Chem. Pharm. Bull.*, **29**, 2899 (1981).
12) I. Ernest, "Chemistry and Biology of β-Lactam Antibiotics," Vol. 2, ed. by R. B. Morin and M. Gorman, Academic Press, New York, 1982, p. 345.