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From Penicillin to Penem and Carbapenem. VII.[1] Synthesis and Antibacterial Activity of Penem Derivatives

KATSUMI FUJIMOTO,[a] YUJI IWANO,[a] KOICHI HIRAI,*,[a] and SHINICHI SUGAWARA[b]

Chemical Research Laboratories[a] and Research Institute,[b] Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

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The azetidinone derivative (**6**), which has an (*R*)-hydroxyethyl substituent at the C-3 position, was prepared efficiently from 6-aminopenicillanic acid. From the dibromo *seco* derivative (**10**), compounds of the same type (**16** and **17**), but in *dl*-form, were obtained. Compounds **6** and **16** were reacted with various thiocarboxylic acids to obtain the penem derivatives (**23a**—**n**).

The minimum inhibitory concentration values of these penems against various microorganisms were determined, and the structure–activity relationship is discussed.

Keywords——penem; thienamycin; 4-acetoxyazetidin-2-one; thiocarboxylic acid; Wittig condensation; MIC; structure–activity relationship

Current interest in the structure–activity relationships of the potent β-lactam antibiotics, penem and carbapenem derivatives, has prompted chemists to synthesize various derivatives of these antibiotics. The pioneering work from the Woodward Research Institute on penems,[2] and from the Merck group on carbapenems[3] revealed that the *R* configuration of the hydroxyethyl substituent on the β-lactam ring together with a 5,6-*trans* relationship is optimal for both potency and stability to β-lactamase.

As a part of our research on the conversion of penicillin into penem and carbapenem derivatives we are especially interested in penem derivatives (such as **23b**) which have a propylamine side chain in lieu of the mercaptoethanolamine moiety in the thienamycin molecule. Thus we synthesized various types of derivatives which have the (*R*)-hydroxyethyl substituent on the β-lactam ring, and checked them for antibacterial activities.[4]

For the synthesis of the (*R*)-hydroxyethyl-substituted compounds, we utilized the readily available methyl dibromopenicillanate (**1**),[5] which is easily obtained from 6-aminopenicillanic acid (6-APA). Treatment of **1** with one equivalent of MeMgBr at −50 °C in tetrahydrofuran (THF), followed by reaction with acetaldehyde, gave the desired (*R*)-hydroxyethylated derivative **2a** as a crystalline product, mp 102 °C. After filtration, the mother liquor was further chromatographed on a silica gel column to separate **2a** and the (*S*)-hydroxyethylated derivative (**3a**), mp 78—80 °C. The ratio of *R* and *S* products was estimated from the nuclear magnetic resonance (NMR) spectrum to be *ca.* 5 : 1.

The absolute configurations of the above two compounds were determined by careful comparison with the results of the Merck group[6] and chemical degradation studies (*vide infra*). The hydroxy group in **2a** was protected by treatment with *tert*-butylchlorodimethylsilane and imidazole in dimethylformamide (DMF). Removal of the bromine atom of **2a** or **2b** was smoothly accomplished with zinc dust in methanol in the presence of two euivalents of acetic acid or zinc–silver couple in methanol.[6] The alcoholic compound **4a** was silylated to give the same compound **4b** that had been obtained from **2b** directly. After chromatographic purification the *trans* configuration of **4b** was easily deduced

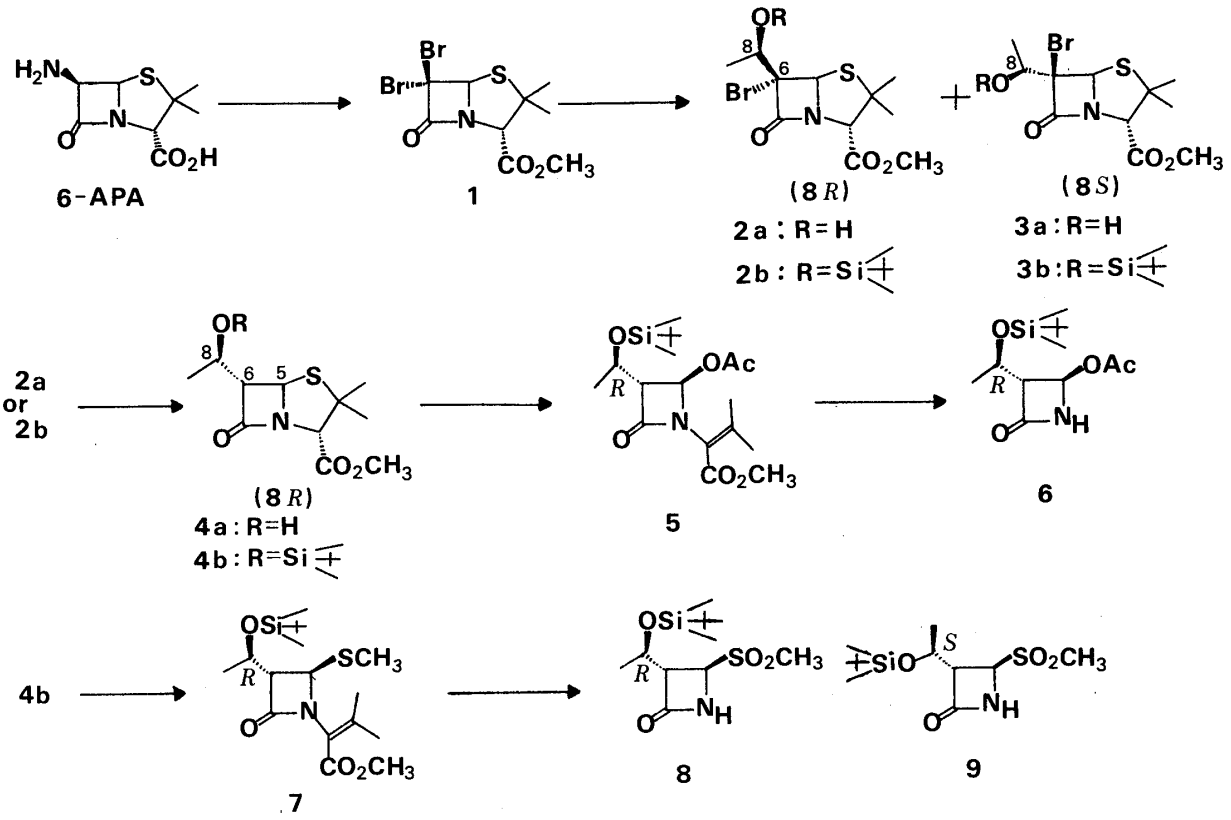


Chart 1

from the coupling constant of $J = 1.5$ Hz between the C_5 (δ 5.16) and C_6 (δ 3.80) protons. The conversion of **4b** into the monocyclic β-lactam (**5**) mp 65 °C, which has a 3,4-*trans* acetoxy group at the C-4 position of the azetidinone ring, was effectively achieved by heating **5** with two equivalents of $Hg(OAc)_2$ in acetic acid for 2 h. The side chain at the N-1 position was oxidatively removed (1.5 eq of $KMnO_4$ in aqueous acetone for 24 h at 25 °C) to afford the known crystalline monocyclic β-lactam (**6**), mp 104 °C $[\alpha]_D^{20}$ +48 °.[7] For the purpose of determining the absolute configuration of the hydroxyethyl moiety in **4a**, compound **4b** was treated with 7.5 eq of CH_3I and 2 eq of NaH in THF for 5 min to afford the *seco* derivative **7**. The N-1 substituent was oxidatively removed to provide the monocyclic β-lactam derivative **8**, mp 100 °C. This compound (**8**) was assigned as *R-trans* by comparison with an authentic sample of the standard *S-trans* compound (**9**), mp 85—87 °C, whose structure was unequivocally determined by X-ray crystallography.[8]

The synthesis of the racemic monocyclic β-lactams **16** and **17** was achieved by the route shown in Chart 2.[4,9] The *dl-seco* compound **10**[8] was hydroxylated to **11a** under the same conditions as used for the synthesis of **2a** from **1**, and after protection of the hydroxy group with a *tert*-butyldimethylsilyl group, compound **11b**, mp 68—69 °C, was debrominated to **12** (*trans*) and **13** (*cis*) in a ratio of 62 : 38 by using Zn in methanol in the presence of 2 eq of acetic acid. After separation of these products by chromatography, the SCH_3 groups in **12** and **13** were replaced by acetoxy groups by heating with $Hg(OAc)_2$ in acetic acid to give the 3,4-*trans*-4-acetoxy azetidinone derivatives **14** and **15**. The N-1 substituents in **14** and **15** were oxidatively removed by $KMnO_4$ treatment to afford the free NH compounds **16**, mp 72 °C, and **17**, mp 75 °C, respectively. Compound **17** showed the same NMR spectrum as compound **6**, but had no $[\alpha]_D^{20}$ value.[4]

With the required intermediates in hand, we concentrated our efforts upon the synthesis of various types of penem derivatives. First the displacement of the acetoxy group of **6** with a

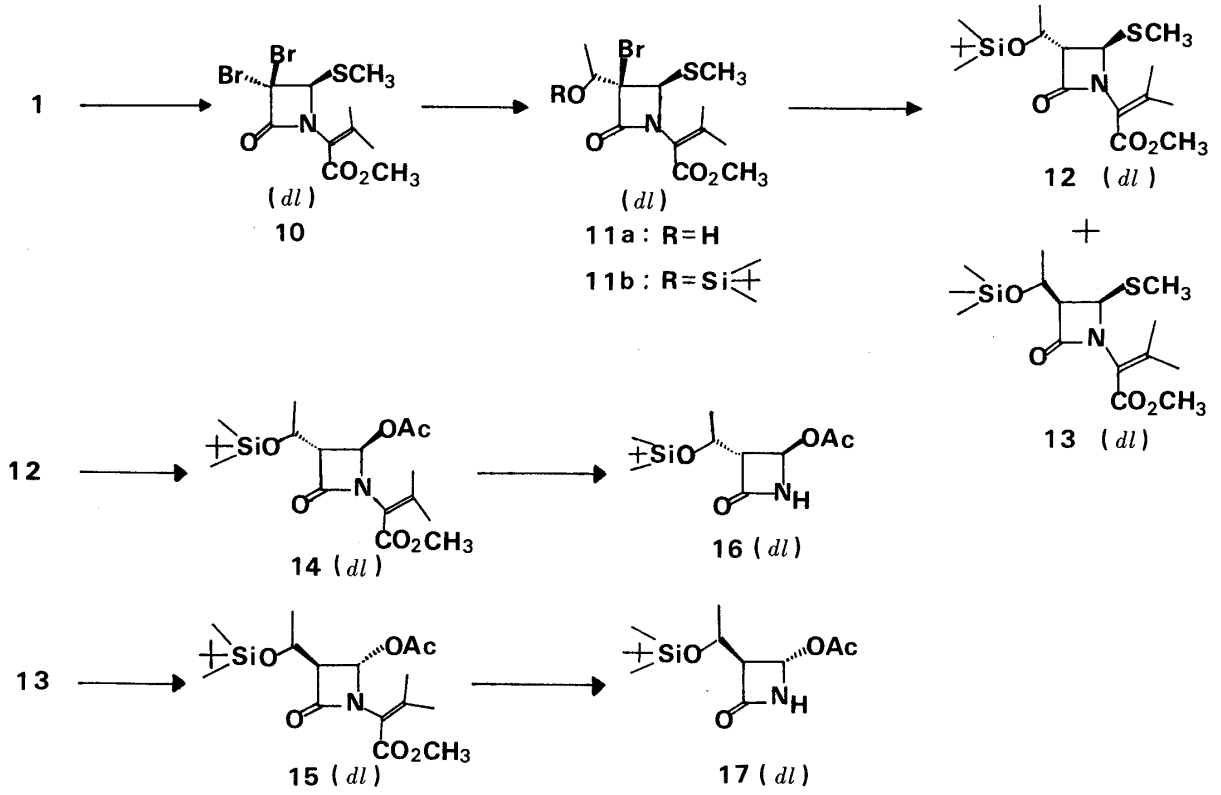


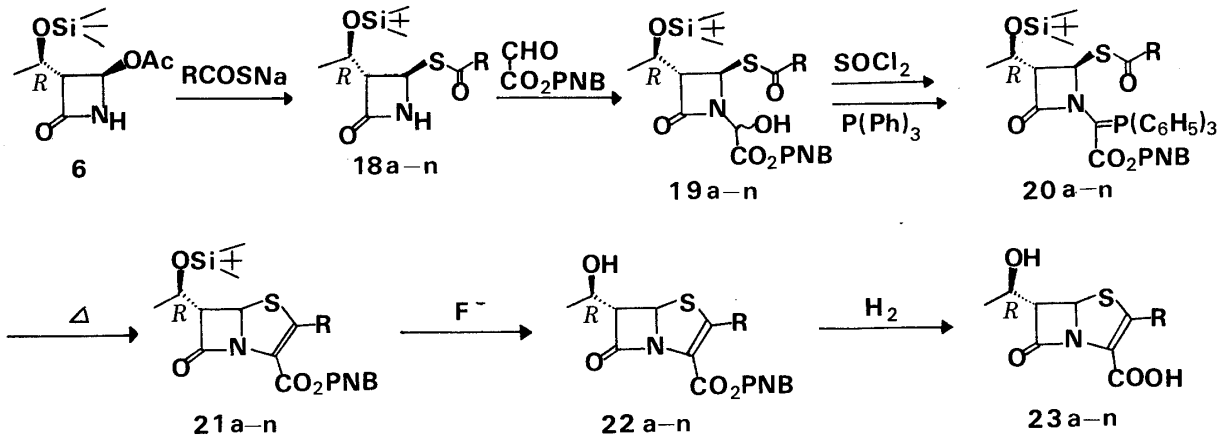
Chart 2

thioacyl group was effected by reaction with 1.1 eq of the sodium salts of various thioacid derivatives (RCOSNa).[10] The azetidinone derivatives **18a**—**g** were then coupled with *p*-nitrobenzyl (PNB) glyoxylate in refluxing benzene to give the aminals (**19a**—**g**).

The aminals (**19a**—**g**) were chlorinated with thionyl chloride and 2,6-lutidine, and then the ylides (**20a**—**g**) were formed with triphenylphosphine and pyridine or 2,6-lutidine. All the compounds so far synthesized gave the ylides successfully in the above general procedure, but the next step of cyclization (90—100 °C, in toluene in the presence of a catalytic amount of hydroquinone) by means of the intramolecular Wittig reaction was troublesome with some of the compounds. The reaction proceeded smoothly with the ylides having straight-chain thioacid moieties to generate the penem derivatives (**21a**—**g**), but no cyclization occurred in the case of the glycine-type moiety (R = CH_2NHPNZ in **20**). The silyl protective group in **21a**—**g** was removed by treatment with tetrabutylammonium fluoride and acetic acid in THF to give the free hydroxy compounds **22a**—**g**, and finally the PNB and *p*-nitrobenzyloxycarbonyl (PNZ) protective groups were removed hydrogenolytically to afford the desired penem derivatives **23a**—**g**, which were purified on CHP 20P (75—150 μ).[11] The 6-unsubstituted penems[2b] and the *dl*-type penem derivatives (entries 3, 5, and 8 in Table I) were synthesized analogously from 4-acetoxyazetidinone[12] and compound **16**. The antibacterial activities of the penem derivatives thus obtained are shown in Table I.

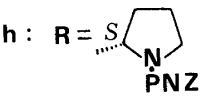
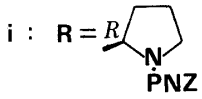
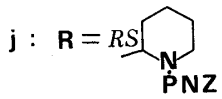
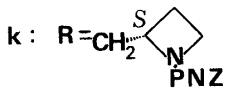
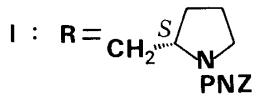
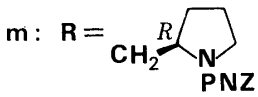
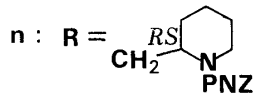
From Table I it is clear that compared to the racemic 6-unsubstituted penems,[2b] the *R*-hydroxyethyl substituted penems show enhanced antibacterial activities (entry 2 *vs.* 3, and 7 *vs.* 8), and the side chain length of the alkylamino moiety at C-2 in the penem nucleus does not greatly influence the antibacterial activities. It is of particular interest to note that hydrophilic substituents (OH or NH) are necessary for anti-*Pseudomonas* activity.

Next, in an attempt to obtain more active penem derivatives we synthesized penems having cyclic secondary amine side chains at the C-2 position. We chose L-azetidine carboxylic acid, D- and L-proline, and *dl*-piperidine carboxylic acid as starting materials. The homo acids



18—22

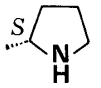
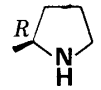
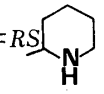
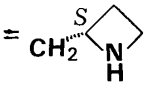
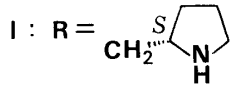
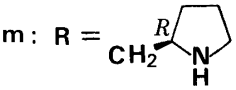
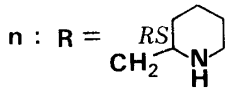
a : R = $(CH_2)_2NHPNZ$
b : R = $(CH_2)_3NHPNZ$
c : R = $(CH_2)_4NHPNZ$
d : R = CH_2CH_3
e : R = CH_2OSi (except 22)
f : R = $CH_2OCH_2CH_3$
g : R = $CH_2\overset{*}{C}H(CH_3)NHPNZ$ (* *R*,*S*)

h : R = 
i : R = 
j : R = 
k : R = 
l : R = 
m : R = 
n : R = 

22e : R = CH_2OH

23

a : R = $(CH_2)_2NH_2$
b : R = $(CH_2)_3NH_2$
c : R = $(CH_2)_4NH_2$
d : R = CH_2CH_3
e : R = CH_2OH
f : R = $CH_2OCH_2CH_3$
g : R = $CH_2\overset{*}{C}H(CH_3)NH_2$ (* *R*,*S*)

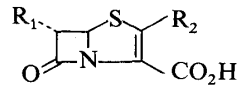
h : R = 
i : R = 
j : R = 
k : R = 
l : R = 
m : R = 
n : R = 

PNB = *p*-nitrobenzyl
PNZ = *p*-nitrobenzyloxycarbonyl

Chart 3

of these amino acids (*e.g.*, homoproline) were synthesized by the known method.[13] All the thioacids were prepared by the reaction of the corresponding mixed acid anhydrides with H_2S/Et_3N, and then were reacted with **6** in the same way as used for preparing the penem derivatives (**22a—g**) in Chart 3. The interesting point is the intramolecular Wittig type cyclization step: the α-amino acid type of compounds (**22h—j**) were far more difficult to cyclize than that of homo type ones (**22k—n**), because of the steric interaction (see Experimental). Among the results in Table II, it is noteworthy that the penem derivative with the *R*-pyrrolidinyl substituent (**23i**, prepared from D-proline) is about four times more active than that with the *S*-substituent (**23h**, prepared from L-proline).

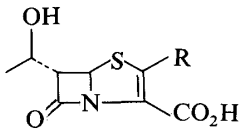
TABLE I. *In Vitro* Antibacterial Activities of Penem Derivatives

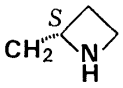
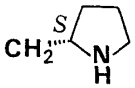
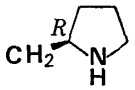
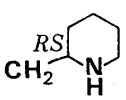


	R_1	R_2	*S.a* $(S)^{a)}$	*S.a* $(R)^{b)}$	*E.c* $(S)^{c)}$	*E.c* $(R)^{d)}$	*S.f*$^{e)}$	*P.a*$^{f)}$	*K.p*$^{g)}$	*K.*$^{h)}$	*P.v*$^{i)}$	*S.e*$^{j)}$
23a	$(R)^{k)}$	$(CH_2)_2NH_2$	0.02	0.05	1.5	1.5	3.1	12.5	1.5	1.5	12.5	3.1
23b	$(R)^{k)}$	$(CH_2)_3NH_2$	0.01	0.05	3.1	3.1	3.1	50	3.1	3.1	12.5	6.5
dl	H	$(CH_2)_3NH_2$	0.02	0.2	12.5	50	12.5	200	12.5	6.2	50	12.5
23c	$(R)^{k)}$	$(CH_2)_4NH_2$	0.1	0.1	3.1	3.1	3.1	50	3.1	3.1	12.5	3.1
dl	$(S^*)^{l)}$	$(CH_2)_4NH_2$	0.2	0.4	25	25	25	100	25	25	50	25
23d	$(R)^{k)}$	CH_2CH_3, Na salt	0.05	0.2	11.5	1.5	1.5	200	1.5	6.2	3.1	1.5
23e	$(R)^{k)}$	CH_2OH, Na salt	0.1	0.4	3.1	6.2	6.2	100	3.1	3.1	12.5	3.1
dl	H	CH_2OH, Na salt	12.5	25	25	>25	>25	(>25)	>25	>25	>25	>25
23f	$(R)^{k)}$	$CH_2OCH_2CH_3$, Na salt	0.1	0.1	1.5	3.1	0.8	200	1.5	12.5	6.2	0.8
23g	$(R)^{k)}$	$CH_2CH(CH_3)NH_2$	0.05	0.1	0.8	0.8	0.8	50	50	0.8	100	3.1

MIC values are in mcg/ml, and were determined in nutrient agar. *a*) *Staphylococcus aureus* FDA 209P JC. *b*) *Staphylococcus aureus* 56 (PCase$^+$). *c*) *Escherichia coli* NIHJ JC-2. *d*) *Escherichia coli* 609 (PSase$^+$). *e*) *Shigella flexneri* IID 642. *f*) *Pseudomonas aeruginosa* 1001. *g*) *Klebsiela pneumoniae* 806. *h*) *Klebsiella* sp. 846. *i*) *Proteus vulgaris* 1430. *j*) *Salmonella eteritidis* G. *k*) (1*R*)-hydroxyethyl. *l*) (1*S**)-hydroxyethyl.

TABLE II. *In Vitro* Antibacterial Activities of Penem Derivatives



	R	*S.a* $(S)^{a)}$	*S.a* $(R)^{b)}$	*E.c* $(S)^{c)}$	*E.c* $(R)^{d)}$	*S.f*$^{e)}$	*P.a*$^{f)}$	*K.p*$^{g)}$	*K.*$^{h)}$	*P.v*$^{i)}$	*S.e*$^{j)}$
23h		0.02	0.02	6.2	12.5	6.2	50	12.5	6.2	50	12.5
23i		0.01	0.01	0.8	0.8	0.8	100	0.8	0.8	200	1.5
23j		0.02	0.05	6.2	6.2	6.2	100	6.2	12.5	100	12.5
23k		0.05	0.1	3.1	6.2	3.1	100	3.1	6.2	25	6.2
23l		0.01	0.02	0.2	0.4	0.2	50	0.4	0.4	100	0.4
23m		0.01	0.01	6.2	6.2	6.2	200	12.5	12.5	200	6.2
23n		0.02	0.05	0.8	1.5	0.4	200	1.5	3.1	200	0.8
Thienamycin		0.01	0.01	0.1	0.1	0.2	6.2	0.1	0.1	3.1	0.2

MIC values are in mcg/ml, and were determined in nutrient agar. *a*) *Staphylococcus aureus* FDA 209P JC. *b*) *Staphylococcus aureus* 56 (PCase$^+$). *c*) *Escherichia coli* NIHJ JC-2. *d*) *Escherichia coli* 609 (PSase$^+$). *e*) *Shigella flexneri* IID 642. *f*) *Pseudomonas aeruginosa* 1001. *g*) *Klebsiela pneumoniae* 806. *h*) *Klebsiella* sp. 846. *i*) *Proteus vulgaris* 1430. *j*) *Salmonella eteritidis* G.

However, in the case of the homo compounds the activities are reversed; the *S*-derivative (**23l**) is about four times more active than the *R*-derivative (**23m**). In the *dl*-piperidinyl series the homo derivative (**23n**) is more active than the parent derivative (**23j**). Among the penem derivatives we have so far synthesized, the 2-(*S*)-pyrrolidinomethyl substituted one (**23l**) is the most active. This compound (**23l**) is about one-fourth as active as thienamycin, except against *Pseudomonas aeruginosa*.

The urinary recoveries of the penem derivatives **23a** and **23l** parenterally administered to mice were 49.7% and 57.4%, respectively, during 0—24 h.

Experimental

General——All melting points are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer model 137 spectrometer. Nuclear magnetic resonance (NMR) spectra were taken with Hitachi R-24 and Varian EM-360L spectrometers (60 MHz) and the chemical shifts are expressed in ppm unit from tetramethylsilane (TMS) as an internal standard; s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dq, doublet of quartets; m, multiplet; br, broad. Mass spectra (MS) were measured on a JEOL-01SG mass spectrometer. The (preparative) thin layer chromatography (TLC) was carried out on Merck Silica gel F_{254} pre-coated TLC plates, layer thickness (2 mm) 0.25 mm, and spots were visualized by ultraviolet (UV) irradiation or by spraying with vanadic acid–sulfuric acid followed by heating, or with iodine. Ordinary chromatography was performed by the rapid chromatography method[14] using Merck silica gel (Kieselgel 60 Art. 9385).

Methyl (3*S*,5*R*,6*S*)-6-Bromo-6-{(1*R*)-hydroxyethyl}penicillanate (2a) and Methyl (3*S*,5*R*,6*R*)-6-Bromo-6-{(1*S*)-hydroxyethyl}penicillanate (3a)——A solution of 25 g of methyl 6,6-dibromopenicillanate in 250 ml of absolute THF was treated with 80 ml of methylmagnesium bromide in THF (1 M, Tokyo Kasei) at below −50 °C. The mixture was stirred for 20 min at −70 °C, then 20 ml of acetaldehyde was added directly and the whole was stirred for 30 min. The reaction was quenched at −70 °C with 250 ml of saturated aqueous NH_4Cl. The dry-ice acetone bath was removed, and the mixture was stirred, giving two phases at ambient temperature. The organic phase was separated and the aqueous phase was extracted with ethyl acetate twice. The extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure the crude product (27 g) was taken up in a minimum amount of ethyl acetate, and the solution was left standing overnight to afford 14 g of crystal (mp 84 °C, washed with cold ether) of the desired (*R*)-hydroxyethylated compound (**2a**). The mother liquor was chromatographed on silica gel (dry column) with benzene : ethyl acetate = 5 : 1. The parts which showed $Rf = 0.25$ (benzene : ethyl acetate = 5 : 1) were gathered and extracted to give 3 g of the desired (*R*)-hydroxyethylated compound (**2a**) (total 17 g, 75%).

From the remaining solution, the (*S*)-hydroxyethylated product (**3a**) was obtained and purified by recrystallization several times.

(*R*)-Hydroxyethylated Product (**2a**): mp 102 °C (recrystallized from ethyl ether). *Anal.* Calcd for $C_{11}H_{16}BrNO_4S$: C, 39.06; H, 4.77; N, 4.14; S, 9.48. Found: C, 39.04; H, 4.75; N, 3.85; S, 9.81. NMR ($CDCl_3$) δ: 1.27 (3H, d, $J = 6$ Hz), 1.48 (3H, s), 1.65 (3H, s), 2.52 (3H, s), 3.79 (3H, s), 4.22 (1H, m), 4.52 (1H, s), 5.59 (1H, s). IR (Nujol): 3400, 1780, 1742 cm^{-1}.

(*S*)-Hydroxyethylated Product (**3a**): mp 78—80 °C (recrystallized from benzene : petroleum ether). *Anal.* Calcd for $C_{11}H_{16}BrNO_4S$: C, 39.06; H, 4.77; N, 4.14. Found: C, 39.11; H, 4.83; N, 4.23. NMR ($CDCl_3$) δ: 1.45 (3H, d, $J =$ 6 Hz), 1.47 (3H, s), 1.67 (3H, s), 2.4—2.9 (1H, br s), 3.72 (3H, s), 4.0—4.5 (1H, m), 4.50 (1H, s), 5.43 (1H, s). IR ($CHCl_3$): 3550, 1780, 1740 cm^{-1}.

Methyl (3*S*,5*R*,6*S*)-6-Bromo-6-{(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl}penicillanate (2b)——A mixture of a solution of 16 g of **2a** in DMF, 23.5 g of imidazole and 26 g of *tert*-butylchlorodimethylsilane was warmed to 55 °C and stirred for 5 h. The mixture was allowed to cool, ethyl acetate was added, and the solution was washed with water three times then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the products were chromatographed on silica gel (rapid, cyclohexane : ethyl acetate = 20 : 1) to give 20 g (93.5%) of the desired product (**2b**). $Rf = 0.8$ (cyclohexane : ethyl acetate = 5 : 1). NMR ($CDCl_3$), δ: 0.09 (6H, s), 0.85 (9H, s), 1.14 (3H, d, $J = 7$ Hz), 1.39 (3H, s), 1.55 (3H, s), 3.73 (3H, s), 4.20 (1H, q, $J = 7$ Hz), 4.48 (1H, s), 5.51 (1H, s).

Methyl (3*S*,5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}penicillanate (4a)——A suspension of 600 mg of silver acetate in 80 ml of acetic acid was warmed to 110—120 °C, then 20 g of activated zinc powder was added. The mixture was stirred for 1 min, then the solvent was decanted off and the residue was washed with 80 ml of acetic acid, 80 ml of ether, and 80 ml of methanol. The solid was suspended in 100 ml of methanol and cooled to −20 °C. A catalytic amount of allyl bromide and 20 g of methyl 6-bromo-6-hydroxyethylpenicillanate (**2a**) were added, and the reaction mixture was stirred for 20 min at −20 °C, then filtered through Celite. The Celite was washed with 20 ml of 25% hexane in ethyl acetate. Water was added to the filtrate and the mixture was filtered through Celite. The filtrate was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue

was chromatographed on silica gel (rapid chromatography, CH_2Cl_2) to give 13.2 g of the desired compound (**4a**, 86%).

Methyl (3*S*,5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}penicillanate (4b)——i) Acetic acid (1.85 g) and zinc powder (12.6 g) were added successively to a solution of 16 g of the 6-bromo-6-(*tert*-butyldimethylsilyloxy)ethyl derivative (**2b**) in 160 ml of methanol. The reaction was exothermic and the completion of the reaction was checked by TLC (about 10 min). The zinc powder was filtered off and the filtrate was concentrated. Ethyl acetate was added to the residue and the solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (rapid chromatography, benzene) to give 6.43 g of the desired product (**4b**, 49%).

ii) A mixture of a solution of 13.2 g of the methyl 6-(*R*)-hydroxyethylated derivative (**4a**) in DMF, 17.1 g of imidazole and 18.9 g of *tert*-butylchlorodimethylsilane was stirred overnight, then ethyl acetate was added. The organic layer was washed with water 4 times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (rapid chromatography, benzene) to give 14 g of the desired product (**4b**, 51%). MS *m/e*: 358 $(M-15)^+$. NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.82 (9H, s), 1.14 (3H, d, $J=6$ Hz), 1.37 (3H, s), 1.53 (3H, s), 3.60 (3H, s), 3.80 (1H, dd, $J=5$, 1.5 Hz), 3.6—4.2 (1H, m), 4.30 (1H, s), 5.16 (1H, d, $J=1.5$ Hz). IR (neat): 1780, 1752 cm^{-1}.

(3*R*,4*R*)-4-Acetoxy-3-{(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methylpropen-1-yl)-azetidin-2-one (5)——Mercuric acetate (9.83 g) was added to a solution of 5.2 g of the 6-hydroxyethyl derivative (**4b**) in 22 ml of acetic acid. The mixture was warmed to 90 °C and stirred for 1.5 h. The mercuric acetate was gradually dissolved and a white precipitate was observed. The precipitate was filtered off and washed with dichloromethane. Water was added to the filtrate and the mixture was neutralized with sodium bicarbonate powder. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 5 g of the desired product (**5**, 90%). mp 65 °C. *Anal.* Calcd for $C_{19}H_{33}NO_6Si$: C, 57.12; H, 8.32; N, 3.51. Found: C, 56.95; H, 8.36; N, 3.45. NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.84 (9H, s), 1.22 (3H, d, $J=6$ Hz), 1.83 (3H, s), 1.95 (3H, s), 2.12 (3H, s), 3.12 (1H, dd, $J=6$, 1.5 Hz), 3.70 (3H, s), 4.15 (1H, m), 6.24 (1H, d, $J=1.5$ Hz). IR (neat): 1782, 1765, 1730, 1640 cm^{-1}.

(3*R*,4*R*)-4-Acetoxy-3-{(1*R*)-(*tert*-butyldimethylsilyloxy)ethyl}azetidin-2-one (6)——To a cooled solution of 5 g of the azetidinone (**5**) and 3 ml of acetic acid in 250 ml of acetone was added 2.8 g of potassium permanganate in 100 ml of water. During the addition, the reaction temperature was kept between 5—10 °C. The reaction mixture was stirred for 3—5 h at room temperature, then excess potassium permanganate was destroyed with sodium sulfite (the color of permanganate faded). The mixture was neutralized with sodium bicarbonate and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by rapid chromatography (benzene : ethyl acetate = 5 : 1) to give 3 g of the azetidinone (**6**, 83%), as crystals. mp 104 °C (recrystallized from petroleum ether). *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 53.76; H, 8.62; N, 4.50. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.84 (9H, s), 1.19 (3H, d, $J=6$ Hz), 2.01 (3H, s), 3.04 (1H, dd, $J=4$, 1.5 Hz), 4.12 (1H, m), 5.75 (1H, d, $J=1.5$ Hz), 6.73 (1H, br s). IR (Nujol): 3200, 1780, 1740 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-methylthio-1-(1-methoxycarbonyl-2-methylpropen-1-yl)-azetidin-2-one (7)——A solution of 80 mg of the (*R*)-hydroxyethyl derivative (**4b**) and 0.3 ml of methyl iodide in THF was treated with 75 mg (3.5 eq) of potassium *tert*-butoxide (or 30 mg of 50% sodium hydride in mineral oil) at room temperature. The completion of the reaction was confirmed by TLC (about 5 min) and then ethyl acetate was added. The organic layer was washed with water 3 times and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 77 mg (99%) of the desired product (**7**). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.84 (9H, s), 1.20 (3H, d, $J=6$ Hz), 1.88 (3H, s), 2.03 (3H, s), 2.13 (3H, s), 3.00 (1H, dd, $J=5$, 2.5 Hz), 3.68 (3H, s), 4.20 (1H, m), 5.10 (1H, d, $J=2.5$ Hz). IR (neat): 1780, 1730, 1640 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-methylsulfonylazetidin-2-one (8)——To a solution of 3.84 g of the (*R*)-methylthio derivative (**7**) in 200 ml of acetone and 4.88 ml of acetic acid was added a solution of 4.68 g of potassium permanganate in 150 ml of water at 5—10 °C in ice bath over 30 min, and the mixture was stirred for 3 h at room temperature. The excess potassium permanganate was destroyed with aqueous sodium sulfite (the color of permanganate faded). The mixture was neutralized with sodium bicarbonate and filtered through Celite. The filtrate was concentrated under reduced pressure. Ethyl acetate was added to this residue, the organic layer was extracted with ethyl acetate and the extracts were combined. The combined extract was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give the desired product (**8**) in quantitative yield. $Rf=0.4$ (benzene : ethyl acetate = 1 : 1). mp 100 °C. $[\alpha]_D^{22} = -12.8°$ ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{25}NO_4SSi$: C, 46.87; H, 8.20; N, 4.56; S, 10.43. Found: C, 46.66; H, 8.18; N, 4.33; S, 10.57. NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.88 (9H, s), 1.28 (3H, d, $J=6$ Hz), 2.94 (3H, s), 3.54 (1H, t, $J=2$ Hz), 4.1—4.5 (1H, m), 4.70 (1H, d, $J=2$ Hz), 6.95 (1H, br s). IR (Nujol): 3350, 1795, 1780, 1737 cm^{-1}.

***dl*-3,3-Dibromo-4-methylthio-1-(1-methoxycarbonyl-2-methylpropen-1-yl)azetidin-2-one (10)**——To a solution of 9.5 g of methyl dibromopenicillanate (**1**) and 10 ml of methyl iodide in 100 ml of THF was added 6 g of potassium *tert*-

butoxide or 3 g of sodium hydride (50% in mineral oil). The progress of the reaction was checked by TLC (benzene). If necessary, potassium *tert*-butoxide or sodium hydride was added. After the termination of the reaction (about 24 h) water was added and the organic layer was extracted with ethyl acetate. The combined extract was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (dry chromatography, benzene) to give the desired product (**10**). $[\alpha]_D^{22} = 0°$ ($c = 1$, $CHCl_3$). NMR ($CDCl_3$) δ: 1.95 (3H, s), 2.17 (3H, s), 2.26 (3H, s), 3.79 (3H, s), 5.49 (1H, s). The benzyl dibromopenicillanate gave the corresponding benzyl ester when subjected to the same procedure.

***dl*-(3*R**,4*R**)-3-Bromo-3-{(1*S**)-hydroxyethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)-4-methylthioazetidin-2-one (11a)**——A solution of 4.5 g of the dibromo derivative (**10**) in 70 ml of absolute THF was cooled to −78 °C, and 11.5 ml of 1 M methylmagnesium bromide in THF was added. The mixture was stirred for 20 min, then 4 ml of acetaldehyde was added and the mixture was stirred for 20 min. Saturated aqueous ammonium chloride solution was added to this mixture. The organic layer was extracted with ethyl acetate and the extracts were combined. The combined extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (dry, benzene : ethyl acetate = 5 : 1) to give 2.65 g of the desired product (**11a**, 65%). NMR ($CDCl_3$) δ: 1.35 (3H, d, $J = 6$ Hz), 1.96 (3H, s), 2.08 (3H, s), 2.22 (3H, s), 3.15 (1H, d, $J = 6$ Hz), 3.75 (3H, s), 4.20 (1H, m), 5.29 (1H, s). IR (neat): 3450, 1780, 1760, 1725, 1630 cm^{-1}.

***dl*-(3*R**,4*R**)-3-Bromo-3-{(1*S**)-(*tert*-butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)-4-methylthioazetidin-2-one (11b)**——A mixture of a solution of 14.7 g of the *dl*-(1*S**)-hydroxyethyl derivative (**11a**), 15.46 g of *tert*-butylchlorodimethylsilane, and 8.5 g of imidazole in 150 ml of DMF was stirred overnight. Ice water was added to the reaction mixture and the products were extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (dry, benzene) to give 17 g of the desired product (**11b**, 87%). mp 68—69 °C (recrystallized from petroleum ether). *Anal.* Calcd for $C_{18}H_{32}BrNO_4SSi$: C, 46.34; H, 6.91; N, 3.00. Found: C, 46.36; H, 6.93; N, 2.64. NMR ($CDCl_3$) δ: 0.09 (3H, s), 0.12 (3H, s), 0.85 (9H, s), 1.35 (3H, d, $J = 6$ Hz), 1.96 (3H, s), 2.08 (3H, s), 2.23 (3H, s), 3.76 (3H, s), 4.30 (1H, q, $J = 6.5$ Hz), 5.30 (1H, s). IR (neat): 1780, 1725 cm^{-1}.

***dl*-(3*R**,4S*)-3-{(1*R**)-(*tert*-Butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)-4-methylthioazetidin-2-one (12) and *dl*-(3*R**,4*R**)-3-{(1*S**)-(*tert*-Butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)-4-methylthioazetidin-2-one (13)**——Zinc dust (7g) was added to a solution of 10 g of bromoazetidinone (**11b**) and 1 g of acetic acid in 60 ml of methanol at room temperature. The progress of the reaction was checked by TLC (benzene : ethyl acetate = 10 : 1). After 15 min the mixture was filtered and the filtrate was concentrated. Ethyl acetate was added to the residue and the solution was washed with water 3 times. The solvent was removed under reduced pressure and the crude product was purified by rapid chromatography to give 2.5 g of the *trans* derivative (**12**, 30%) and 2.2 g of the *cis* derivative (**13**, 26%).

The *trans* derivative (**12**): $Rf = 0.48$ (benzene : ethyl acetate = 10 : 1). NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.87 (9H, s), 1.29 (3H, d, $J = 6.5$ Hz), 1.94 (3H, s), 2.07 (3H, s), 2.17 (3H, s), 3.21 (1H, dd, $J = 5, 7$ Hz), 3.74 (3H, s), 4.27 (1H, q-like, $J = 6$ Hz), 4.98 (1H, d, $J = 3$ Hz).

The *cis* derivative (**13**): $Rf = 0.32$ (benzene : ethyl acetate = 10 : 1). MS *m/e*: 387 (M^+). *Anal.* Calcd for $C_{18}H_{33}NO_4SSi$: C, 55.78; H, 8.58; N, 3.61. Found: C, 56.02; H, 8.66; N, 3.74. NMR ($CDCl_3$) δ: 0.1 (6H, s), 0.86 (9H, s), 1.35 (3H, d, $J = 6.5$ Hz), 2.00 (3H, s), 2.04 (3H, s), 2.20 (3H, s), 3.40 (1H, dd, $J = 6.5, 5.5$ Hz), 3.72 (3H, s), 4.36 (1H, m), 5.05 (1H, d, $J = 5.5$ Hz).

***dl*-(3*R**,4*R**)-4-Acetoxy-3-{(1*S**)-(*tert*-butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)azetidin-2-one (14)**——A solution of 4 g of azetidinone (**12**) and 6.2 g of mercuric acetate in 20 ml of acetic acid was warmed to 90 °C and stirred for 1.5 h. The mixture was filtered, and the filtrate was cooled to room temperature, then neutralized with sodium bicarbonate. The organic layer was extracted with dichloromethane and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (TLC, benzene : ethyl acetate = 10 : 1) to give 3.5 g (85%) of the desired product (**14**). MS *m/e*: 399 (M^+). NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.84 (9H, s), 1.23 (3H, d, $J = 7$ Hz), 1.81 (3H, s), 1.91 (3H, s), 2.06 (3H, s), 3.14 (1H, dd, $J = 2, 6$ Hz), 3.61 (3H, s), 4.14 (1H, m), 6.02 (1H, d, $J = 2$ Hz). IR (neat): 1780, 1760, 1630 cm^{-1}.

***dl*-(3*R**,4*R**)-4-Acetoxy-3-{(1*R**)-(*tert*-butyldimethylsilyloxy)ethyl}-1-(1-methoxycarbonyl-2-methyl-1-propen-1-yl)azetidin-2-one (15)**——By the same procedure as described for **14**, a solution of 1.8 g of the *cis*-methylthio derivative (**13**) and 3 g of mercuric acetate in 20 ml of acetic acid was warmed up to 90 °C and stirred for 1.5 h to give 1.5 g (81%) of the desired product (**15**). NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.82 (9H, s), 1.24 (3H, d, $J = 7$ Hz), 1.87 (3H, s), 1.99 (3H, s), 2.14 (3H, s), 3.14 (1H, dd, $J = 2, 6$ Hz), 3.70 (3H, s), 4.21 (1H, m), 6.29 (1H, d, $J = 2$ Hz). IR (neat): 1782, 1765, 1730, 1640 cm^{-1}.

***dl*-(3*R**,4*R**)-4-Acetoxy-3-{(1*S**)-(*tert*-butyldimethylsilyloxy)ethyl}-azetidin-2-one (16)**——To a solution of 1.6 g of **14** in 100 ml of acetone was added a solution of 0.8 g of potassium permanganate in 30 ml of water. By the same procedure as used for the synthesis of **6**, the desired product (**16**) was obtained in 78% yield (900 mg). mp 72 °C. *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.47; H, 8.71; N, 4.87. NMR ($CDCl_3$) δ: 0.08 (6H, s),

0.84 (9H, s), 1.26 (3H, d, J=6.5 Hz), 2.02 (3H, s), 3.07 (1H, dd, J=4, 1.5 Hz), 4.13 (1H, m), 5.61 (1H, d, J=1.5 Hz), 6.9 (1H, br s). IR (Nujol): 3200, 1780, 1740 cm^{-1}.

***dl*-(3*R**,4*R**)-4-Acetoxy-3-{(1*R**)-(*tert*-butyldimethylsilyloxy)ethyl}azetidin-2-one (17)**——Starting with **15**, the above procedure gave the desired product (**17**). Yield 78%. mp 75 °C. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.84 (9H, s), 1.19 (3H, d, J=6 Hz), 2.01 (3H, s), 3.04 (1H, dd, J=5, 4 Hz), 4.12 (1H, m), 5.75 (1H, d, J=1.5 Hz), 6.73 (1H, br s). IR (Nujol): 3200, 1780, 1740 cm^{-1}.

***l*(−)-(*N*-*p*-Nitrobenzyloxycarbonylpyrrolidin-2-yl)carbothioic *S*-Acid**——Triethylamine (0.98 ml) and isobutyl chloroformate (0.47 ml) were added to a solution of 1 g of *l*(−)-*N*-*p*-nitrobenzyloxycarbonylproline in 20 ml of anhydrous dichloromethane at −10 °C, and the mixture was stirred for 40 min at the same temperature. Hydrogen sulfide was bubbled into the above mixture for 1 h at −10 °C. The reaction mixture was acidified with 2.5 N sulfuric acid and the organic layer was extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 1 g (95%) of the desired thioacid.

The same procedure was used to prepare all thiocarboxylic acids, and the products were used in the reaction with the acetoxyazetidinone derivative without purification.

{(2*S*)-*N*-*p*-Nitrobenzyloxycarbonylpyrrolidin-2-yl}thioacetic *S*-Acid——Triethylamine (1.13 ml) and isobutyl chloroformate (1.11 ml) were added successively to a solution of 1.6 g of *l*(−)-*N*-*p*-nitrobenzyloxycarbonylproline in 60 ml of ether at −15 °C. The mixture was stirred for 1 h at −20 °C, then the precipitate was filtered off rapidly and excess (about 4 eq) diazomethane was added. The reaction mixture was stirred for 3 h in an ice bath and allowed to stand overnight at 5 °C. The solution was washed with water and 5% aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 1.65 g (95%) of the diazoketone.

A solution of the diazoketone thus obtained in 30 ml of methanol was treated with 237 mg of silver oxide. After confirmation of completion of the reaction by TLC, the mixture was filtered and the filtrate was concentrated under reduced pressure. The crude products were purified by rapid chromatography (benzene : ethyl acetate = 5 : 1) to give 1.2 g of the homo-acid (92%). Triethylamine (0.97 ml) and isobutyl chloroformate (0.47 ml) were added to a solution of 1.0 g of the homo-acid in 20 ml of dichloromethane at −15 °C. The mixture was stirred for 1 h at −15 °C, then hydrogen sulfide was bubbled through the solution at the same temperature for 1 h. The solution was acidified with 2 N sulfuric acid, then the thioacid was extracted with dichloromethane, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 1.0 g of homo-thiocarboxylic acid.

The same procedure was used to prepare the other homothiocarboxylic acids, and the products were used in the next step without purification.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)acetylthio}-azetidin-2-one (18l) (General Procedure for the Reaction of Thiocarboxylic Acids with 6)——A solution of 900 mg of {(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}thioacetic *S*-acid in 2.77 ml of 1 N sodium hydroxide was stirred for 20 min in an ice bath, then 600 mg of the acetoxyazetidinone derivative (**6**) in 20 ml of dioxane was added slowly. The reaction mixture was stirred in an ice bath for 1.5 h and extracted with dichloromethane. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the product was purified by rapid chromatography (cyclohexane : ethyl acetate = 2 : 1) to give 1.0 g of the desired product (**18l**). NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.83 (9H, s), 1.18 (3H, d, J=6 Hz), 1.7—2.1 (4H, m), 2.9—3.6 (3H, m), 4.0—4.4 (2H, m), 5.18 (2H, s), 5.27 (1H, d, J=2.5 Hz), 6.84 (1H, br s), 7.38—8.30 (4H, A_2B_2).

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{3-(*p*-nitrobenzyloxycarbonylamino)propionylthio}azetidin-2-one (18a)——Starting with 3-(*p*-nitrobenzyloxycarbonylamino)propanethioic *S*-acid and **6**, the above procedure gave the desired product (**18a**). Reaction time 1 h. Yield 60%. Rf=0.2 (benzene : ethyl acetate = 3 : 1). *Anal.* Calcd for $C_{21}H_{33}N_3O_6SSi$: C, 52.15; H, 6.88; N, 8.69, S, 6.63. Found: C, 51.77; H, 6.48; N, 8.45; S, 6.54. NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=7 Hz), 2.7—3.8 (5H, m), 4.25 (1H, m), 5.30 (2H, s), 5.45 (1H, d, J=2.5 Hz), 5.8 (1H, br s), 7.2 (1H, br s), 7.4—8.5 (4H, A_2B_2). IR ($CHCl_3$): 3400, 1770, 1730 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{4-(*p*-nitrobenzyloxycarbonylamino)butyrylthio}azetidin-2-one (18b)——Starting with 4-(*p*-nitrobenzyloxycarbonylamino)butanethioic *S*-acid and **6**, the above procedure gave the desired product (**18b**). Reaction time 2 h. Yield 22.5%, recovered starting material 45%. Rf=0.2 (benzene : ethyl acetate = 3 : 1). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.83 (9H, s), 1.13 (3H, d, J=7 Hz), 1.6—2.1 (2H, m), 2.62 (2H, t, J=7 Hz), 3.0—3.4 (3H, m), 4.0—4.4 (1H, m), 5.22 (2H, s), 5.34 (1H, d, J=2.5 Hz), 6.9 (1H, br s), 7.4—8.4 (4H, m). IR (neat): 3400, 1770, 1730 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{5-(*p*-nitrobenzyloxycarbonylamino)pentanoylthio)azetidin-2-one (18c)——Starting with 5-(*p*-nitrobenzyloxycarbonylamino)pentanethioic *S*-acid and **6**, the above procedure gave the desired product (**18c**). Reaction time 1.5 h. Yield 99%. mp 98 °C (recrystallized from ether and petroleum ether). *Anal.* Calcd for $C_{24}H_{37}N_3O_7SSi$: 53.41; H, 6.91; N, 7.99; S, 5.94. Found: C, 53.23; H, 7.04; N, 7.97; S, 6.13. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.85 (9H, s), 1.13 (3H, d, J=7 Hz), 1.4—1.8 (4H, m), 2.55 (2H, t, J=7.5 Hz), 2.95—3.35 (4H, m), 4.10 (1H, m), 5.05 (2H, s), 5.20 (1H, d, J=2.5 Hz), 7.35—8.30 (4H, m). IR ($CHCl_3$): 3400, 1770, 1730, 1610 cm^{-1}.

***dl*-(3*R**,4*S**)-3-{(1*R**)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{5-(*p*-nitrobenzyloxycarbonylamino)pentanoylthio}-**

azetidin-2-one {(±)18(*S)c}**——Starting with 5-(*p*-nitrobenzyloxycarbonylamino)pentanethioic *S*-acid and **16**, the above procedure gave the desired product **{(±)18(*S**)c}**. Reaction time 1.5 h. Yield 98%. IR (neat): 3400, 1770, 1730 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(propionylthio)azetidin-2-one (18d)——Starting with propanethioic *S*-acid and **6**, the above procedure gave the desired product (**18d**). Reaction time 1 h. Yield 52%. mp 81—84 °C (recrystallized from petroleum ether). *Anal.* Calcd for $C_{14}H_{27}NO_3SSi$: S, 10.10. Found: S, 9.75. NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.91 (9H, s), 1.20 (3H, d, J=8 Hz), 1.25 (3H, d, J=7 Hz), 2.63 (2H, q, J=8 Hz), 3.16 (1H, dd, J=2, 4 Hz), 4.0—4.5 (1H, m), 5.31 (1H, d, J=2 Hz), 6.92 (1H, br s). IR (Nujol): 1775, 1705 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-((*tert*-(butyldimethylsilyloxy)acetylthio)azetidin-2-one (18e)——Starting with (*tert*-butyldimethylsilyloxy)thioacetic *S*-acid and **6**, the above procedure gave the desired product (**18e**). Reaction time 1 h. Yield 45%. Rf=0.5 (benzene : ethyl acetate = 5 : 1). mp 112 °C. *Anal.* Calcd for $C_{19}H_{39}NO_4SSi_2$: C, 52.61; H, 9.06; N, 3.23; S, 7.39. Found: C, 52.42; H, 8.95; N, 3.08; S, 7.43. NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.15 (6H, s), 0.85 (9H, s), 0.95 (9H, s), 1.20 (3H, d, J=7 Hz), 3.20 (1H, dd, J=2.5, 4.5 Hz), 4.25 (2H, s), 4.15—4.45 (1H, m), 5.23 (1H, d, J=2.5 Hz), 6.40 (1H, br s). IR (KBr): 3400, 1770, 1730, 1700 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(ethoxyacetylthio)azetidin-2-one (18f)——Startig with ethoxythioacetic *S*-acid and **6**, the above procedure gave the desired product (**18f**). Reaction time 2 h. Yield quant. Rf=0.5 (cyclohexane : ethyl acetate = 2 : 1). NMR ($CDCl_3$) δ: 0.10 (6H, s), 0.89 (9H, s), 1.0—1.5 (6H, m), 3.18 (1H, dd, J=2, 4 Hz), 3.61 (2H, q, J=7 Hz), 4.09 (2H, s), 3.9—4.5 (1H, m), 5.23 (1H, d, J=2 Hz), 7.09 (1H, br s).

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{*RS*-3-(*p*-nitrobenzyloxycarbonylamino)butyrylthio}-azetidin-2-one (18g)——Starting with 3-(*p*-nitrobenzyloxycarbonylamino)butanethioic *S*-acid and **6**, the above procedure gave the desired product (**18g**). Reaction time 1.5 h. Rf=0.2 (benzene : ethyl acetate = 3 : 1). Yield 24%. NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.87 (9H, s), 1.18 (3H, d, J=6 Hz), 1.27 (3H, d, J=8 Hz), 1.6—2.2 (1H, m), 2.77 (2H, d, J=6 Hz), 2.9—3.5 (1H, m), 3.6—4.6 (2H, m), 5.13 (2H, s), 5.40 (1H, d, J=2 Hz), 6.2—6.7 (1H, br s), 7.1—8.5 (5H, m). IR (neat): 3300, 1760, 1700 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}carbonylthioazetidin-2-one (18h)——Starting with {(*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}carbothioic *S*-acid and **6**, the above procedure gave the desired product (**18h**). Reaction time 1 h. Rf=0.45 (cyclohexane : ethyl acetate = 1 : 1). Yield 76%.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-carbonylthioazetidin-2-one (18i)——Starting with {(*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}carbothioic *S*-acid and **6**, the above procedure gave the desired product (**18i**). Reaction time 1 h. Yield 90%. Rf=0.45 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.86 (9H, s), 1.17 (3H, d, J=6 Hz), 1.6—2.4 (4H, m), 3.12 (1H, dd, J=2, 5 Hz), 3.3—3.9 (1H, m), 4.0—4.7 (2H, m), 5.0—5.4 (3H, s like), 6.85 (1H, br s), 7.2—8.3 (4H, m).

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)carbonylthioazetidin-2-one (18j)——Starting with *dl*-(*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)carbothioic *S*-acid and **6**, the above procedure gave the desired product (**18j**). Reaction time 1.5 h. Yield 63%. Rf=0.6 (cyclohexane : ethyl acetate = 1 : 1).

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl}acetylthio}azetidin-2-one (18k)——Starting with {(2*R*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl}thioacetic *S*-acid and **6**, the above procedure gave the desired product (**18k**). Reaction time 1.5 h. Yield 47%. Rf=0.5 (cyclohexane : ethyl acetate = 1 : 1). mp 143 °C. *Anal.* Calcd for $C_{24}H_{35}N_3O_7SSi$: C, 53.61; H, 6.56; N, 7.81. Found: C, 54.08; H, 6.58; N, 7.76. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.88 (9H, s), 1.19 (3H, d, J=7 Hz), 1.5—4.5 (8H, m), 3.18 (1H, d, J=2, 5 Hz), 5.18 (2H, s), 5.33 (1H, d, J=2 Hz), 6.6—7.1 (1H, m), 7.2—8.4 (4H, m). IR (Nujol): 1760, 1715 cm^{-1}.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}acetylthio}azetidin-2-one (18m)——Starting with {(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}thioacetic *S*-acid and **6**, the above procedure gave the desired product (**18m**). Reaction time 1.5 h. Rf=0.45 (cyclohexane : ethyl acetate = 1 : 1). Yield 80%.

(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)acetylthio}-azetidin-2-one (18n)——Starting with *dl*-(*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)thioacetic *S*-acid and **6**, the above procedure gave the desired product (**18n**). Reaction time 1.5 h. Yield 85%. Rf=0.5 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.83 (9H, s), 1.19 (3H, d, J=7 Hz), 1.2—1.9 (6H, m), 2.5—3.3 (3H, m), 3.7—5.1 (4H, m), 5.14 (2H, s), 5.22 (1H, d, J=2 Hz), 6.39 (1H, br s), 7.3—8.4 (4H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxyethyl}-4-{{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}acetylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19l) (General Procedure for the Synthesis of Hydroxyacetates)**——A solution of 1 g of the azetidinone (**18l**), 823 mg of *p*-nitrobenzyl glyoxylate, and 1 drop of triethylamine in 70 ml of benzene was refluxed for 2 h with continuous removal of water azeotropically. After removal of the solvent under reduced pressure the residue was chromatographed on silica gel (rapid chromatography, cyclohexane : ethyl acetate = 1 : 1) to give the desired product (**19l**, 51%). Rf=0.2 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.87 (9H, s), 1.20 (3H, d, J=6 Hz), 1.7—2.2 (4H, m), 2.9—3.65 (3H, m), 4.0—4.4 (2H,

m), 5.19 (2H, s), 5.25 (2H, s), 5.55 (1H, d, J=2.5 Hz), 7.4—8.4 (4H, m), 5.3 (1H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(3-*p*-nitrobenzyloxycarbonylaminopropionylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19a)**——Starting with **18a** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19a**). Reaction time, 10 h. Rf=0.5 (dichloromethane : ethyl acetate=2 : 1). Yield 83%. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.80 (9H, s), 1.12 (3H, d, J=7 Hz), 2.5—3.0 (2H, m), 3.0—3.6 (3H, m), 4.1 (1H, m), 5.1 (2H, s), 5.16 (2H, s), 5.25 (1H, d, J=2 Hz), 5.5 (2H, m), 7.3—8.3 (8H, m). IR (neat): 3400, 1780, 1760, 1710, 1604 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(4-*p*-nitrobenzyloxycarbonylaminobutyrylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19b)**——Starting with **18b** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19b**). Yield 68%. Rf=0.5 (dichloromethane : ethyl acetate=2 : 1). NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.80 (9H, s), 1.12 (3H, d, J=7 Hz), 2.4—2.7 (2H, m), 3.0—3.4 (2H, m), 4.1 (1H, m), 5.1—5.6 (5H, m), 7.3—8.3 (8H, m). IR (neat): 3400, 1775, 1750, 1730, 1605 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(5-*p*-nitrobenzyloxycarbonylaminopentanoylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19c)**——Starting with **18c** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19c**). Yield 87%. Rf=0.5 (dichloromethane : ethyl acetate=2 : 1). IR (neat): 3400, 1780, 1760, 1710, 1604 cm^{-1}.

***dl*-*p*-Nitrobenzyl 2-{(3*R**,4*S**)-3-{(1*R**)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{5-(*p*-nitrobenzyloxycarbonylamino)pentanoylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate{(±)19(*S**)c}**——Starting with (±)-18(*S**)c and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product {(±)-19(*S**)c}. Yield 86%. Rf=0.5 (dichloromethane : ethyl acetate=2 : 1). IR (neat): 3400, 1780, 1760, 1710, 1605 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-propionylthio-2-oxoazetidin-1-yl}-2-hydroxyacetate (19d)**——Starting with **18d** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19d**). Yield 89%. Less polar diastereomer: NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.88 (9H, s), 1.16 (3H, t, J=7 Hz), 1.22 (3H, d, J=6 Hz), 2.55 (2H, q, J=7 Hz), 3.23 (1H, dd, J=3, 4 Hz), 3.9—4.7 (3H, m), 5.26 (2H, s), 5.2—5.6 (1H, m), 5.53 (1H, d, J=3 Hz), 7.4—8.4 (4H, m). More polar diastereomer: NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.84 (9H, s), 1.16 (3H, t, J=7 Hz), 1.20 (3H, d, J=6 Hz), 2.62 (2H, q, J=7 Hz), 3.18 (1H, dd, J=2, 4 Hz), 3.9—4.5 (2H, m), 5.20 (1H, s), 5.36 (2H, s), 5.55 (1H, d, J=2 Hz), 7.35—8.5 (4H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(*tert*-butyldimethylsilyloxyacetylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19e)**——Starting with **18e** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19e**). Reaction time 5 h. Yield 98%. Rf=0.3 (benzene : ethyl acetate=5 : 1). NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.11 (6H, s), 0.87 (9H, s), 0.94 (9H, s), 1.22 (3H, d, J=6 Hz), 3.1—3.5 (2H, m), 4.26 (1H, s), 3.8—4.7 (2H, m), 5.1—5.8 (2H, m), 7.2—8.5 (4H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(ethoxyacetylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19f)**——Starting with **18f** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19f**). Reaction time 2 h. Yield 70%. Rf=0.3 (cyclohexane : ethyl acetate=2 : 1). NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.88 (9H, s), 1.0—1.5 (6H, m), 5.20 (2H, s), 6.58 (1H, br s), 7.3—8.4 (4H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(*RS*-3-(*p*-nitrobenzyloxycarbonylamino)-butyrylthio)-2-oxoazetidin-1-yl}-2-hydroxyacetate (19g)**——Starting with **18g** and *p*-nitrobenzyl glyoxylate without triethylamine, the above procedure gave the desired product (**19g**). Reaction time 2 h. Yield 81%. One diastereomer: NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.87 (9H, s), 1.18 (3H, d, J=6 Hz), 1.27 (3H, d, J=8 Hz), 2.0—2.3 (1H, m), 2.78 (2H, d, J=6 Hz), 2.9—3.4 (1H, m), 3.6—4.9 (3H, m), 5.10 (2H, s), 5.1—5.6 (3H, m), 6.63 (1H, br s), 7.1—8.3 (8H, m). The other diastereomer: NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.86 (9H, s), 1.17 (3H, d, J=7 Hz), 1.62 (1H, s), 2.70 (2H, d, J=6 Hz), 3.15 (1H, dd, J=2, 4 Hz), 3.5—4.8 (3H, m), 5.10 (2H, s), 5.17 (2H, s), 5.1—5.6 (2H, m), 7.1—8.3 (8H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}carbonylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19h)**——Starting with **18h**, the above procedure gave the desired product (**19h**). Reaction time 2 h. Yield 65%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}carbonylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19i)**——Starting with **18i**, the above procedure gave the desired product (**19i**). Reaction time 2 h. Yield 82%. Rf=0.5 (cyclohexane : ethyl acetate=1 : 1). NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.85 (9H, s), 1.12—1.27 (4H, m), 2.02—2.25 (4H, m), 3.21 (1H, dd, J=3, 5 Hz), 3.35—3.8 (2H, m), 4.06—4.66 (3H, m), 5.16—5.46 (4H, m), 5.51 (1H, d, J=3 Hz), 7.26—7.64 (4H, m), 8.06—8.2 (4H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)carbonylthio}-2-oxoazetidin-2-on-1-yl}-2-hydroxyacetate (19j)**——Starting with **18j**, the above procedure gave the desired product (**19j**). Reaction time 2 h. Yield 76%. Rf=0.2 (cyclohexane : ethyl acetate=1 : 1).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl)acetylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19k)**——Starting with **18k**, the above procedure gave the desired product (**19k**). Reaction time 2 h. Yield 64%. Rf=0.3 and 0.4 (cyclohexane : ethyl acetate=1 : 1).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)acetylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19m)**——Starting with **18m**, the above procedure gave the desired product (**19m**). Reaction time, 2 h. Yield 72%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)acetylthio}-2-oxoazetidin-1-yl}-2-hydroxyacetate (19n)**——Starting with **18n**, the above procedure gave the desired product (**19n**). Reaction time 2 h. Yield 72%. *Rf*=0.5 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.84 (9H, s), 1.20 (3H, d, *J*=6 Hz), 1.3—2.2 (6H, m), 2.5—3.5 (4H, m), 3.19 (1H, dd, *J*=2, 4 Hz), 4.0—5.2 (3H, m), 5.14 (2H, s), 5.0—5.8 (3H, m), 7.2—8.5 (8H, m).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-acetylthio}-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20l) (General Procedure for Ylide Formation)**——To a solution of 1 g of the aminal derivative (**19l**) in 15 ml of THF was added 0.23 ml of 2,6-lutidine. The mixture was cooled to −20 °C and 0.14 ml of thionyl chloride was added. The reaction mixture was stirred for 1 h and the precipitate formed was filtered off. The solvent was removed under reduced pressure to give the crude chloro derivative.

The chloro derivative was dissolved in 20 ml of absolute dioxane, and 514 mg of triphenylphosphine and 0.28 ml of 2,6-lutidine was added to this solution. The reaction mixture was warmed to 50—60 °C and stirred for 20 h, then allowed to cool. Ethyl acetate was added to the mixture and the organic layer was washed with 5% hydrochloric acid and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on silica gel (rapid chromatography, cyclohexane : ethyl acetate = 1 : 1) to give 1.2 g (59%) of the desired product (**20l**).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(3-*N*-*p*-nitrobenzyloxycarbonylaminopropionylthio)-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20a)**——Starting with **19a**, the above procedure gave the desired product (**20a**). Chlorination, reaction time 1 h. Ylide formation, reaction time 3 h. Yield 24%. IR ($CHCl_3$): 1745, 1720, 1680, 1520 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(4-(*N*-*p*-nitrobenzyloxycarbonylamino)-butyrylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20b)**——Starting with **19b**, the above procedure gave the desired product (**20b**). *Rf*=0.35 (benzene : ethyl acetate = 1 : 1). Yield 38%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(5-*N*-*p*-nitrobezenzyloxycarbonylaminopentanoylthio)-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20c)**——Starting with **19c**, the above procedure gave the desired product (**20c**). *Rf*=0.2 (dichloromethane : ethyl acetate = 10 : 1). Yield 40%. IR ($CHCl_3$): 1745, 1720, 1680, 1520 cm^{-1}.

***dl*-*p*-Nitrobenzyl 2-{(3*R**,4*S**)-3-{(1*R**)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(5-*N*-*p*-nitrobenzyloxycarbonylamino)pentanoylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate {(±)20(*S**)c}**——Starting with (±)**19(*S**)c**, the above procedure gave the desired product {(±)**20(*S**)c**}. *Rf*=0.2 (benzene : ethyl acetate = 2 : 1). IR ($CHCl_3$): 1745, 1720, 1680, 1520 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxyethyl}-4-(propionylthio)-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20d)**——Starting from **19d**, the above procedure gave the desired product (**20d**). *Rf*=0.1 (benzene : ethyl acetate = 3 : 1). Yield 47%. IR (neat): 1745 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-(*tert*-butyldimethylsilyloxy)acetylthio)-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20e)**——Starting with **19e**, the above procedure gave the desired product (**20e**). Chlorination, reaction time 1 h. Ylide formation, reaction time 12 h. *Rf*=0.2 (cyclohexane : ethyl acetate = 2 : 1).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-ethoxyacetylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20f)**——Starting with **19f**, the above procedure gave the desired product (**20f**). Chlorination reaction time 30 min. Ylide formation, reaction time overnight. *Rf*=0.3 (cyclohexane : ethyl acetate = 2 : 1).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(*RS*-3-*p*-nitrobenzyloxycarbonylamino)-butyrylthio-2-oxoazetidin-1-yl}-2-triphenylphosphonylideneacetate (20g)**——Starting with **19g**, the above procedure gave the desired product (**20g**). *Rf*=0.2 (benzene : ethyl acetate = 3 : 1). IR (neat): 3300, 1765, 1725, 1700 cm^{-1}.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)carbonylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20h)**——Starting with **19h**, the above procedure gave the desired product (**20h**). Chlorination, reaction time 30 min. Ylide formation, reaction time 48 h. Yield 59%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)carbonylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20i)**——Starting with **19i**, the above procedure gave the desired product (**20i**). *Rf*=0.2 (cyclohexane : ethyl acetate = 1 : 1). Yield 39%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{*RS*-{*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl}carbonylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20j)**——Starting with **19j**, the above procedure gave the desired product (**20j**). *Rf*=0.3 (cyclohexane : ethyl acetate = 2 : 1). Yield 68%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl)acetylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20k)**——Starting with **19k**, the above procedure gave the desired product (**20k**). *Rf*=0.35 (cyclohexane : ethyl acetate = 1 : 1). Yield 32%.

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)methylcarbonylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20m)**——Starting with **19m**,

the above procedure gave the desired product (**20m**).

***p*-Nitrobenzyl 2-{(3*S*,4*R*)-3-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-4-{(*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)methylcarbonylthio-2-oxoazetidin-1-yl}-2-triphenylphosphoranylideneacetate (20n)**——Starting with **19n**, the above procedure gave the desired product (**20n**). *Rf*=0.4 (cyclohexane : ethyl acetate = 1 : 1). Yield 77%.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl-methyl}-2-penem-3-carboxylate (21l) (General Procedure for the Intramolecular Wittig Cyclization Reaction)**——To a solution of 1.2 g of the ylide (**20l**) in 80 ml of absolute toluene was added catalytic amount of hydroquinone. The mixture was stirred for 20 h at 90—100 °C, then allowed to cool. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (rapid chromatography, cyclohexane : ethyl acetate = 2 : 1) to give 390 mg of the desired product (**21l**): NMR ($CDCl_3$) δ : 0.04 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.23 (3H, d, J=6.5 Hz), 1.8—2.1 (4H, m), 3.1—3.8 (5H, m), 4.0—4.4 (2H, m), 5.17 (2H, s), 5.23 (2H, AB type, J=14 Hz), 5.58 (1H, d, J=2 Hz), 7.3—8.3 (8H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(2-*p*-nitrobenzyloxycarbonylaminoethyl)-2-penem-3-carboxylate (21a)**——Reaction time 17 h. *Rf*=0.6 (benzene : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.8 (9H, s), 1.16 (3H, d, J=6.5 Hz), 2.8—3.5 (4H, m), 3.7 (1H, dd, J=1.5, 4 Hz), 4.2 (1H, m), 5.18 (2H, s), 5.14 (1H, d, J=15 Hz), 5.38 (1H, J=15 Hz), 5.60 (1H, d, J=1.5 Hz), 7.3—8.4 (8H, m). IR (neat): 3400, 1797, 1700—1740, 1610, 1580 cm^{-1}. UV λ_{max}^{EtOH} nm: 264, 320.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(3-*p*-nitrobenzyloxycarbonylaminopropan-1-yl)-2-penem-3-carboxylate (21b)**——Reaction time 16 h. Yield 37%. *Rf*=0.6 (benzene : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.80 (9H, s), 1.20 (3H, d, J=7 Hz), 1.80 (2H, m), 2.6—3.3 (4H, m), 3.57 (1H, dd, J=2, 5 Hz), 4.10 (1H, m), 5.12 (2H, s), 5.10 and 5.33 (2H, AB type, J=15 Hz), 5.51 (1H, d, J=2 Hz), 7.3—8.3 (8H, m). IR (neat): 3400, 1798, 1700—1740, 1610, 1580 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(4-*p*-nitrobenzyloxycarbonylaminobutan-1-yl)-2-penem-3-carboxylate (21c)**——Reaction time 18 h. Yield 46%. *Rf*=0.5 (benzene : ethyl acetate = 2 : 1). NMR ($CDCl_3$) δ: 0.05 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.25 (3H, d, J=7 Hz), 1.35—1.80 (4H, m), 2.65—2.90 (2H, m), 3.0—3.35 (2H, m), 3.66 (1H, dd, J=1.5, 5 Hz), 4.20 (1H, m), 5.14 (2H, s), 5.10 and 5.40 (2H, AB type, J=15 Hz), 5.5 (1H, d, J=1.5 Hz), 7.3—8.2 (8H, m). IR (neat): 3350, 1775, 1700, 1595 cm^{-1}.

***dl*-*p*-Nitrobenzyl (5*R**,6*S**)-6-{(1*S**)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(4-*p*-nitrobenzyloxycarbonylaminobutan-1-yl)-2-penem-3-carboxylate {(±)21(*S**)c}**——Yield 46%. NMR ($CDCl_3$) δ: 0.09 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=7 Hz), 1.35—1.8 (4H, m), 2.65—2.90 (2H, m), 3.0—3.35 (2H, m), 3.71 (1H, dd, J=1.5, 5 Hz), 4.20 (1H, m), 5.14 (2H, s), 5.10 and 5.40 (2H, AB type, J=15 Hz), 5.4 (1H, d, J=1.5 Hz), 7.3—8.2 (8H, m). IR (neat): 3350, 1780, 1710, 1610 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-ethyl-2-penem-3-carboxylate (21d)**——Reaction time 18 h. Yield 16%. Recovered starting material (**20d**), 37%. *Rf*=0.5 (benzene : ethyl acetate = 3 : 1). NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.07 (3H, s), 0.83 (9H, s), 1.13 (3H, t, J=7 Hz), 1.25 (3H, d, J=6 Hz), 2.86 (2H, dd, J=2, 7 Hz), 3.65 (1H, dd, J=2, 4 Hz), 3.9—4.5 (1H, m), 5.1—5.5 (2H, m), 5.51 (1H, d, J=1 Hz), 7.3—8.4 (4H, m). IR (neat): 1785, 1710 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(*tert*-butyldimethylsilyloxymethyl)-2-penem-3-carboxylate (21e)**——Reaction time 3.5 h. Yield 91%. mp 105 °C (recrystallized from ether : hexane). *Anal.* Calcd for $C_{28}H_{44}N_2O_7SSi_2$: C, 55.23; H, 7.28; N, 4.60. Found: C, 55.39; H, 7.32; N, 4.54. NMR ($CDCl_3$) δ : 0.05—1.0 (12H, m), 0.84 (9H, s), 0.90 (9H, s), 1.24 (3H, d, J=7 Hz), 3.71 (1H, dd, J=2.5, 4 Hz), 4.05—4.40 (1H, m), 4.83 (2H, s), 5.16 and 5.37 (2H, AB type, J=14 Hz), 5.55 (1H, d, J=2.5 Hz), 7.5—8.2 (4H, m). IR (Nujol): 1792, 1712, 1615, 1590 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-ethoxymethyl-2-penem-3-carboxylate (21f)**——Reaction time 8 h. Yield 98%. *Rf*=0.5 (cyclohexane : ethyl acetate = 2 : 1). NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.08 (3H, s), 0.82 (9H, s), 1.0—1.5 (6H, m), 3.53 (2H, q, J=7 Hz), 3.71 (1H, dd, J=2, 5 Hz), 3.9—4.5 (2H, m), 4.60 and 4.65 (2H, AB type, J=15 Hz), 5.21 and 5.30 (2H, AB type, J=13 Hz), 7.15 (1H, br s), 7.4—8.4 (4H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-(*RS*-2-*p*-nitrobenzyloxycarbonylaminopropan-1-yl)-2-penem-3-carboxylate (21g)**——Reaction time 16 h. Yield 49%. Recovered starting material (**20g**), 26%. *Rf*=0.55 (benzene : ethyl acetate = 3 : 1). NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.82 (9H, s), 1.17 (6H, d like, J=7 Hz), 2.4—4.4 (5H, m), 5.15 (2H, s), 4.8—5.7 (3H, m), 7.39 (1H, br s), 7.3—8.4 (8H, m). IR (neat): 1795, 1720 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-2-penem-3-carboxylate (21h)**——Reaction solvent xylene. Reaction temp. 150 °C. Reaction time 40 h. Yield 18%. NMR ($CDCl_3$) δ: 0.08 (6H, s), 0.80 (9H, s), 1.25 (3H, d, J=6.5 Hz), 1.8—2.2 (4H, m), 3.3—3.8 (4H, m), 4.0—4.4 (1H, m), 5.18 (2H, s), 5.1—5.5 (2H, m), 5.78 (1H, d, J=3 Hz), 7.4—8.3 (4H, m). IR (neat): 1790, 1710 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-2-penem-3-carboxylate (21i)**——Reaction time 40 h. Yield 40%. NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.06 (3H, s), 0.81 (9H, s), 1.20 (3H, d, J=6 Hz), 1.6—2.4 (4H, m), 3.3—3.8 (4H, m), 3.9—4.4 (1H, m), 5.0—5.4 (4H, m), 5.51 (1H, d, J=2 Hz), 7.3—8.4 (8H, m), IR (neat): 1790, 1710 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-**

2-yl}-2-penem-3-carboxylate (21j)——Yield 25%. *Rf*=0.5 (cyclohexane : ethyl acetate = 2 : 1). NMR ($CDCl_3$) δ: 0.03 (3H, s), 0.05 (3H, s), 0.80 (9H, s), 1.19 (3H, d, *J*=6 Hz), 1.2—2.2 (6H, m), 3.55 (1H, dd, *J*=2, 5 Hz), 3.8—5.4 (7H, m), 5.51 (1H, d, *J*=2 Hz), 6.8—8.4 (8H, m). IR (neat): 1790, 1705 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)-ethyl}-2-{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl}methyl-2-penem-3-carboxylate (21k)**——Reaction time 40 h. Yield 44%. *Rf*=0.6 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.04 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 1.27 (3H, d, *J*=7 Hz), 2.1—2.5 (2H, m), 2.51 (2H, t, *J*=7 Hz), 3.36 (2H, t, *J*=7 Hz), 3.70 (1H, dd, *J*=2, 5 Hz), 3.8—4.5 (2H, m), 7.1—8.4 (8H, m). IR ($CHCl_3$): 1785, 1710 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}methyl-2-penem-3-carboxylate (21m)**——Reaction time 20 h. Yield 43%. *Rf*=0.6 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 0.02 (3H, s), 0.08 (3H, s), 0.82 (9H, s), 1.26 (3H, d, *J*=6 Hz), 1.6—2.4 (4H, m), 3.0—3.7 (4H, m), 3.69 (1H, dd, *J*=2, 4 Hz), 3.9—4.4 (2H, m), 5.23 (2H, m), 5.1—5.5 (2H, m), 5.59 (1H, d, *J*=2 Hz), 7.3—8.5 (8H, m). IR (neat): 1785, 1705 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-(*tert*-Butyldimethylsilyloxy)ethyl}-2-{((*RS*)-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl)methyl}-2-penem-3-carboxylate (21n)**——Reaction time 15 h. Yield 55%. *Rf*=0.4 (cyclohexane : ethyl acetate = 2 : 1). NMR ($CDCl_3$) δ: 0.02 (3H, s), 0.06 (3H, s), 0.82 (9H, s), 1.21 (3H, d, *J*=6 Hz), 1.3—2.1 (6H, m), 2.6—3.5 (2H, m), 3.64 (1H, dd, *J*=2, 5 Hz), 3.8—4.9 (4H, m), 4.9—5.5 (4H, m), 5.49 (1H, d, *J*=2 Hz), 7.2—8.4 (8H, m). IR ($CHCl_3$): 1795, 1705 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{((2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl)methyl}-2-penem-3-carboxylate (22l) (General Procedure for the Desilylation)**——A solution of 370 mg of carbapenem (**21l**) in 20 ml of THF was treated with 0.3 ml of acetic acid and 883 mg of tetrabutylammonium fluoride trihydrate in an ice bath. The mixture was warmed to room temperature and stirred for 16 h. Ethyl acetate was added to the reaction mixture, and the organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (rapid chromatography, cyclohexane : ethyl acetate = 1 : 2) to give 282 mg (92%) of the desired product (**22l**). NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=6.5 Hz), 1.7—2.1 (4H, m), 3.42 (2H, t, *J*=7 Hz), 3.2—3.8 (2H, m), 4.0—4.4 (2H, m), 5.17 (2H, m), 5.25 (4H, AB type, *J*=14 Hz), 5.50 (1H, d, *J*=2 Hz), 7.35—8.3 (4H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(2-*p*-nitrobenzyloxycarbonylaminoethyl)-2-penem-3-carboxylate (22a)**——*Rf*=0.3 (benzene : ethyl acetate = 1 : 1). mp 169—171 °C (recrystallized from THF–methanol). *Anal.* Calcd for $C_{25}H_{24}N_4O_{10}S$: C, 52.45; H, 4.23; N, 9.79. Found: C, 52.19; H, 4.20; N, 9.56. NMR ($CDCl_3$) δ: 1.19 (3H, d, *J*=6 Hz), 2.8—3.8 (4H, m), 4.3 (1H, m), 5.20 (1H, s), 5.20 and 5.45 (2H, AB type, *J*=14.5 Hz), 5.60 (1H, d, *J*=1.5 Hz), 7.5—8.4 (4H, m). IR (Nujol): 3420, 1780, 1719, 1610 cm^{-1}. UV λ_{max}^{EtOH} nm: 264, 318.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(3-*p*-nitrobenzyloxycarbonylaminopropan-1-yl)-2-penem-3-carboxylate (22b)**——Yield 45%. IR (Nujol): 3420, 1780, 1719, 1610 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(4-*p*-nitrobenzyloxycarbonylaminobutan-1-yl)-2-penem-3-carboxylate (22c)**——mp 112—116 °C (recrystallized from ether–ethyl acetate). *Anal.* Calcd for $C_{27}H_{28}N_4O_{10}S$: C, 53.99; H, 4.70; N, 9.33. Found: C, 53.21; H, 4.62; N, 9.04.

***dl*-*p*-Nitrobenzyl (5*R**,6*S**)-6-{(1*S**)-Hydroxyethyl}-2-(4-*p*-nitrobenzyloxycarbonylaminobutan-1-yl)-2-penem-3-carboxylate {(±)22(*S**)c}**——Yield 95%. *Rf*=0.3 (benzene : ethyl acetate = 1 : 1).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-ethyl-2-penem-3-carboxylate (22d)**——Yield 95%. *Rf*=0.38 (benzene : ethyl acetate = 3 : 1). mp 148—149 °C. NMR ($CDCl_3$) δ: 1.20 (3H, t, *J*=8 Hz), 1.34 (3H, d, *J*=6 Hz), 2.03 (1H, br s), 2.85 (2H, dq, *J*=2, 8 Hz), 3.70 (1H, dd, *J*=2, 6 Hz), 4.19 (1H, q, *J*=6 Hz), 5.20 and 5.45 (2H, AB type, *J*=20 Hz), 5.58 (1H, d, *J*=2 Hz), 7.3—8.5 (4H, m). IR (Nujol): 1780, 1705 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-hydroxymethyl-2-penem-3-carboxylate (22e)**——Yield 64%. mp 158 °C. *Anal.* Calcd for $C_{16}H_{16}N_2O_7S$: C, 50.52; H, 4.24; N, 7.36. Found: C, 50.40; H, 4.25; N, 7.31. IR (Nujol): 3360, 1782, 1760, 1685 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-ethoxymethyl-2-penem-3-carboxylate (22f)**——Yield 64%. *Rf*=0.37 (benzene : ethyl acetate = 3 : 1). mp 121 °C. NMR ($CDCl_3$) δ: 1.19 (3H, t, *J*=6 Hz), 1.34 (3H, d, *J*=6 Hz), 2.85 (1H, br s), 3.50 (2H, q, *J*=6 Hz), 3.72 (1H, dd, *J*=2, 6 Hz), 3.8—4.5 (2H, m), 4.60 and 4.62 (2H, AB type, *J*=15 Hz), 5.22 and 5.30 (2H, AB type, *J*=14 Hz), 5.54 (1H, d, *J*=2 Hz), 7.2—8.3 (4H, m). IR (Nujol): 3350, 1770, 1705 cm^{-1}.

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(*RS*-2-*p*-nitrobenzyloxycarbonylaminopropan-1-yl)-2-penem-3-carboxylate (22g)**——Yield 71%. recovered starting material 19%. NMR ($CDCl_3$) δ: 1.24 (3H, d, *J*=7 Hz), 1.29 (3H, d, *J*=6 Hz), 5.20 (2H, s), 5.0—5.8 (3H, m), 7.51 (1H, br s), 7.5—8.4 (4H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-2-penem-3-carboxylate (22h)**——Yield 49%. *Rf*=0.2 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 1.30 (3H, d, *J*=6 Hz), 1.7—2.2 (4H, m), 3.3—3.9 (4H, m), 4.0—4.3 (1H, m), 5.2 (2H, s), 5.1—5.5 (3H, m), 7.4—8.3 (4H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-yl}-2-penem-3-carboxylate (22i)**——Yield 66%. NMR ($CDCl_3$) δ: 1.29 (3H, d, *J*=6 Hz), 1.5—2.4 (4H, m), 2.94 (1H, br s), 3.2—3.9 (4H, m), 3.9—4.2 (1H, m), 4.9—5.7 (4H, m), 5.54 (1H, d, *J*=2 Hz), 7.1—8.4 (8H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl}-2-penem-3-carboxylate (22j)**——Yield 38%. *Rf*=0.3 (cyclohexane : ethyl acetate = 1 : 1). NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6 Hz), 1.3—2.7 (6H, m), 3.4—4.7 (5H, m), 5.0—5.7 (4H, m), 5.51 (1H, d, J=2 Hz), 5.6—6.2 (1H, m).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{(2*S*)-*N*-*p*-nitrobenzyloxycarbonylazetidin-2-yl}methyl}-2-penem-3-carboxylate (22k)**——Yield 22%. *Rf*=0.2 (cyclohexane : ethyl acetate = 1 : 1).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{(2*R*)-*N*-*p*-nitrobenzyloxycarbonylpyrrolidin-2-ylmethyl}-2-penem-3-carboxylate (22m)**——Yield 92%. *Rf*=0.2 (cyclohexane : ethyl acetate = 1 : 1).

***p*-Nitrobenzyl (5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{*RS*-*N*-*p*-nitrobenzyloxycarbonylpiperidin-2-yl}methyl}-2-penem-3-carboxylate (22n)**——Yield 78%. *Rf*=0.3 (cyclohexane : ethyl acetate = 1 : 1. NMR ($CDCl_3$) δ: 1.30 (3H, d, J=7 Hz), 1.3—2.1 (6H, m), 2.5—3.4 (3H, m), 3.5—3.8 (1H, m), 3.8—4.9 (4H, m), 4.9—5.6 (5H, m), 7.2—8.3 (8H, m). IR (neat): 3425, 1775, 1690 cm^{-1}.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{(2*S*)-pyrrolidin-2-yl}methyl}-2-penem-3-carboxylic Acid (23l) (General Procedure for the Syntheses of Penems (23))——A 10% Pd/C catalyst was added to a solution of 282 mg of the hydroxypenem in 12 ml of THF and 12 ml of 0.1 M phosphate buffer, (pH 7.04). The mixture was stirred for 5 h under a hydrogen atmosphere (1 atm), then the catalyst was filtered off and washed with the same buffer. The filtrate was washed with ethyl acetate twice and the aqueous layer was concentrated to 2 ml under reduced pressure. The solution was chromatographed on CHP 20P (75—150 μ). Elution was performed first with water, followed by 2% acetone in water and then 5% acetone in water. The penem (**23l**) (80 mg) was obtained from the 5% acetone elute. NMR (D_2O, DSS) δ: 1.31 (3H, d, J=6.5 Hz), 1.8—2.3 (4H, m), 2.9—3.5 (4H, m), 3.6—4.4 (2H, m), 5.68 (1H, d, J=1.5 Hz).

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(2-aminoethyl)-2-penem-3-carboxylic Acid (23a)——Yield 33%. *Rf*=0.3 (Eastman 6065 cellulose, isopropanol : *n*-butanol : water = 7 : 7 : 6). NMR (D_2O, DSS) δ: 1.37 (3H, d, J=6 Hz), 3.0—3.4 (2H, m), 3.9 (1H, dd, J=6, 1.5 Hz), 4.1—4.5 (3H, m), 5.75 (1H, d, J=1.5 Hz). IR (Nujol): 2400—3400, 1770, 1540—1640 cm^{-1}. UV λ_{max}^{water} nm: 260, 305. $[\alpha]_D^{22}=+106°$ (c=0.54, water).

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(3-aminopropan-1-yl)-2-penem-3-carboxylic Acid (23b)——Yield 50%. IR (Nujol): 2300—3400, 1770, 1540—1630 cm^{-1}. UV λ_{max}^{water} nm: 258, 304.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(4-aminobutan-1-yl)-2-penem-3-carboxylic Acid (23c)——Yield 33%. IR (Nujol): 2500—3600, 1770, 1540—1640 cm^{-1}. UV λ_{max}^{water} nm: 259, 303. $[\alpha]_D^{22}=+106°$ (c=0.6, water).

***dl*-(5*R**,6*S**)-6-{(1*S**)-Hydroxyethyl}-2-(4-aminobutan-1-yl)-2-penem-3-carboxylic Acid {(±)23(*S**)c}**——IR (Nujol): 2500—3600, 1770, 1540—1640 cm^{-1}. UV λ_{max}^{water} nm: 259, 303.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-ethyl-2-penem-3-carboxylic Acid Sodium Salt (23d)——Starting with **22d**, the above procedure (using 1 eq of sodium bicarbonate instead of phosphate buffer) gave the desired product (**23d**). Yield 44%. UV λ_{max}^{water} nm: 260, 303.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-hydroxymethyl-2-penem-3-carboxylic Acid Sodium Salt (23e)——Starting with **22e**, the above procedure (using 1 eq of sodium bicarbonate instead of phosphate buffer) gave the desired product (**23e**). UV λ_{max}^{water} nm: 260, 304.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-ethoxymethyl-2-penem-3-carboxylic Acid Sodium Salt (23f)——Starting with **22f**, the above procedure (using 1 eq of sodium bicarbonate instead of phosphate buffer) gave the desired product (**23f**). Yield 3%. NMR (D_2O, DSS) δ: 1.23 (3H, t, J=6 Hz), 1.35 (3H, d, J=6 Hz), 3.62 (2H, q, J=6 Hz), 3.90 (1H, dd, J=5, 2 Hz), 5.62 (1H, d, J=2 Hz). UV λ_{max}^{water} nm: 260, 304.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-(2-aminopropyl)-2-penem-3-carboxylic Acid (23g)——Yield 49%. UV λ_{max}^{water} nm: 259, 303.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl)}-2-{(2*S*)-pyrrolidin-2-yl}-2-penem-3-carboxylic Acid (23h)——Yield 42%. UV λ_{max}^{water} nm: 260, 303.

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{(2*R*)-pyrrolidin-2-yl}-2-penem-3-carboxylic Acid (23i)——Yield 19%. NMR (D_2O, DSS) δ: 1.25 (3H, d, J=6.5 Hz), 1.8—2.3 (4H, m), 3.32 (2H, t, J=7 Hz), 3.8—4.4 (2H, m), 5.65 (1H, d, J=2 Hz).

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{*RS*-piperidin-2-yl}-2-penem-3-carboxylic Acid (23j)——Yield 24%. NMR (D_2O, DSS) δ: 1.25 (3H, d, J=6.5 Hz), 1.7—2.2 (6H, m), 3.3—4.4 (4H, m), 5.7 (1H, d, J=1.5 Hz).

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{(2*S*)-azetidin-2-yl}-methyl}-2-penem-3-carboxylic Acid (23k)——Yield 38%. NMR (D_2O, DSS) δ: 1.40 (3H, d, J=6.5 Hz), 1.8—2.2 (2H, m), 2.9—3.5 (4H, m), 3.6—4.4 (2H, m), 5.68 (1H, d, J=1.5 Hz).

(5*R*,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{(2*R*)-pyrrolidin-2-yl}-methyl}-2-penem-3-carboxylic Acid (23m)——NMR (D_2O, DSS) δ: 1.33 (3H, d, J=6.5 Hz), 1.8—2.3 (4H, m), 2.9—3.5 (4H, m), 5.64 (1H, d, J=1.5 Hz).

(5R,6*S*)-6-{(1*R*)-Hydroxyethyl}-2-{{*RS*-piperidin-2-yl}methyl}-2-penem-3-carboxylic Acid (23n)——NMR (D_2O, DSS) δ: 1.25 (3H, d, J=6.5 Hz), 1.5—2.2 (6H, m), 2.9—3.4 (4H, m), 3.6—4.4 (2H, m), 5.60 (1H, d, J=1.5 Hz).

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