Chem. Pharm. Bull.
29(11)3158—3172(1981)

2-(Alkylthio)penem-3-carboxylic Acids. V.[1] Synthesis and Antibacterial Activities of "1-Thiathienamycin" and Related Compounds

Teruo Hayashi, Akira Yoshida, Noriko Takeda, Sadao Oida,*
Shinichi Sugawara, and Eiji Ohki

*Central Research Laboratories, Sankyo Co., Ltd., Hiromachi,
Shinagawa-ku, Tokyo, 140, Japan*

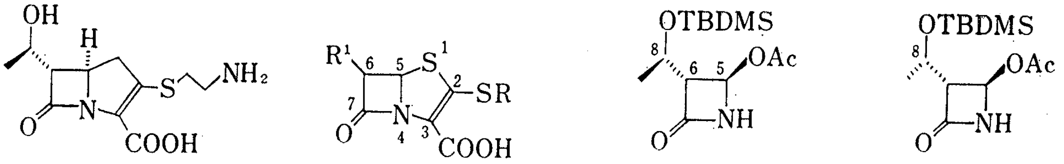
(Received April 25, 1981)

The synthesis of optically active "1-thiathienamycin" **13a** and other (hydroxyethyl)-penemcarboxylic acids from the 8*R* and 8*S* azetidinones **3** and **4** *via* an intramolecular Wittig reaction of the trithiocarbonatephosphoranes **7** is described. *Trans* and *cis* penem esters **8** and **9** were found to form an equilibrium mixture on heating. The antibacterial activities of these penemcarboxylic acids are discussed.

Keywords——antibiotics; β-lactam; 6-(hydroxyethyl)penem-3-carboxylic acid; thienamycin analog; thermal equilibration of penem nucleus; anti-*Pseudomonas* activity

Thienamycin is a highly potent β-lactam antibiotic having a novel 1-carbapenem structure (**1**).[2] Its activity is especially high against gram-positive bacteria, and extentds over the full range of gram-negative bacteria including *Pseudomonas* species.[3] Meanwhile, we reported recently the synthesis of 6-unsubstituted 2-(alkylthio)penem-3-carboxylic acids[4] **2a** and the 6-ethyl analogs[5] **2b** which were found to have marked broad-spectrum antibacterial activity.[5,6] Consequently, it seemed of interest to determine whether the hydroxyethyl group at the C-6 position, the natural side chain of thienamycin, would improve the antibacterial potency of the parent penems.

In the preceding paper,[1] we described the preparation of 8*R*[7] and 8*S* (hydroxyethyl)-azetidinones **3** and **4** in both racemic and optically active forms, functionalized for elaboration to (hydroxyethyl)penems. The optically active azetidinones were more efficiently obtained starting from 6-aminopenicillanic acid.



1

2a : $R^1=H$
2b : $R^1=C_2H_5$
2c : $R^1=CH(OH)CH_3$

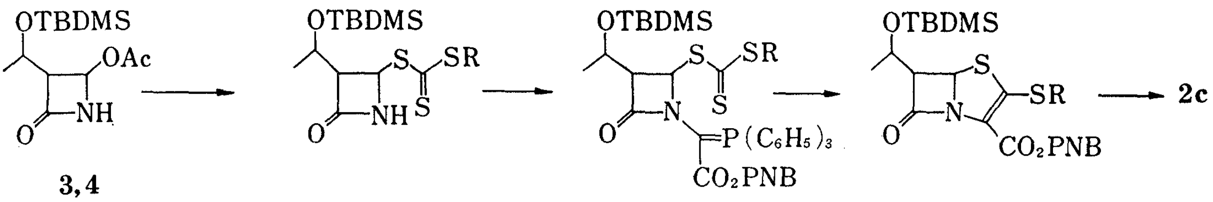
3 (8*R*)

4 (8*S*)

TBDMS: *tert*-butyldimethylsilyl

Chart 1

In this paper, we wish to describe the synthesis of 6-(hydroxyethyl)-2-(alkylthio)penem-3-carboxylic acid **2c**, by combining the chemistry of the preceding paper and our previous work on construction of the penem system from 4-acetoxy-2-azetidinone.[4,5] As will be shown later, we prepared numerous substituted penemcarboxylic acids **2c**, with the optically active azetidinones **3** and **4** as starting materials, according to the general reaction sequence as shown in Chart 2. We would like to mention here, as a typical example, the preparation of 2-(aminoethylthio) substituted penems **2c** ($R=CH_2CH_2NH_2$), of which the 5*R*, 6*S*, 8*R* diastereomer,



3,4

2c

TBDMS: *tert*-butyldimethylsilyl
PNB: *p*-nitrobenzyl

Chart 2

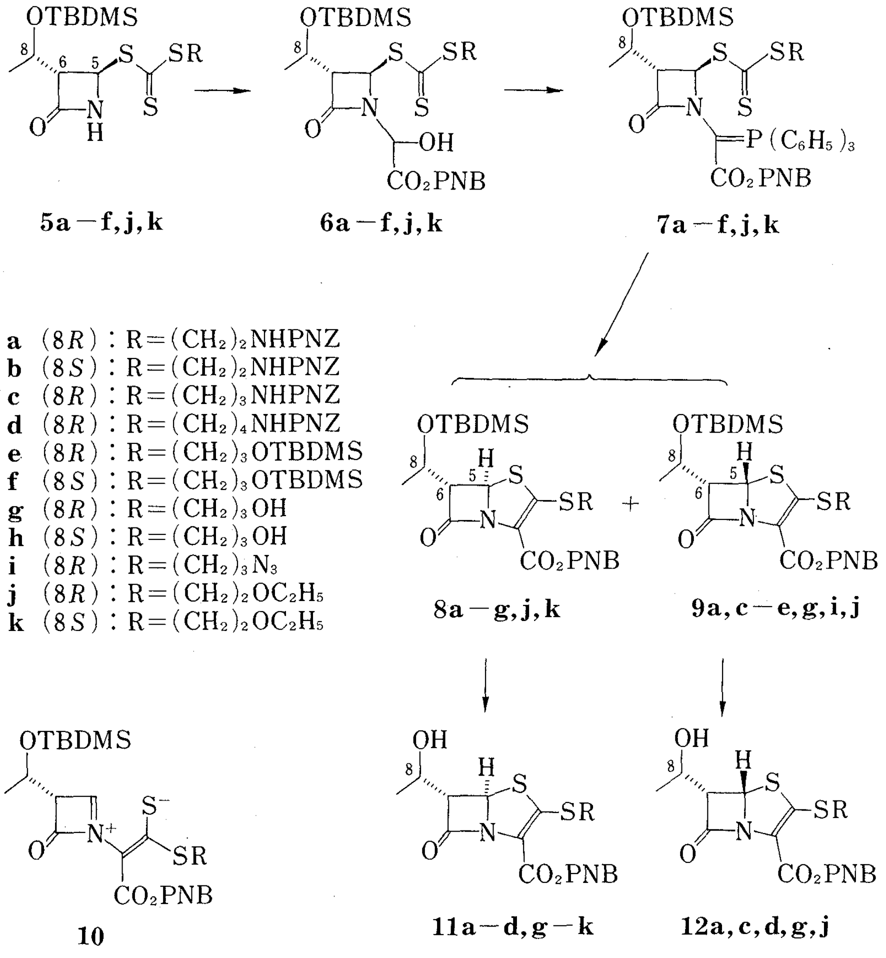
"1-thiathienamycin," with the same stereochemistry as thienamycin seemed to be the most interesting because of its close structural resemblance to the natural antibiotic.

The 8*R* azetidinone **3** was treated with sodium trithiocarbonate, prepared *in situ* by mixing equimolar amounts of sodium methoxide, 2-[[(*p*-nitrobenzyl)oxycarbonyl]amino]-ethanethiol and carbon disulfide, in methanol at −10°C to give the *trans* azetidinone trithiocarbonate **5a** in 87% yield. Assignment of *trans* stereochemistry for **5a** was based on a small coupling constant ($J_{5,6}=2.5$ Hz) in its nuclear magnetic resonance (NMR) spectrum. Conversion of **5a** thus obtained into the azetidinone phosphorane **7a** was carried out following the conventional procedure developed by Woodward *et al.*[8] Reflux of the trithiocarbonate **5a** with *p*-nitrobenzyl glyoxylate in benzene for 5 h gave a 1: 1 diasteromeric mixture of the hemiaminal **6a** in 78% yield. The hemiaminal **6a** was treated with thionyl chloride in the presence of 2,6-lutidine in tetrahydrodrofuran (THF) to give the α-chloroacetate, which was then, without isolation, warmed under gentle reflux for 42 h with triphenylphosphine and 2,6-lutidine to provide the phosphorane **7a** in 62% yield.

Thiazoline ring formation of the phosphorane **7a** by an intramolecular Wittig reaction to provide the corresponding penem ester **8a** was achieved by heating in xylene at 125—130°C for 15 h in the presence of a small amount of hydroquinone, which effectively suppressed decomposition of both the starting material **7a** and the cyclization product. Chromatography of the reaction product gave a 76% yield of **8a** and a 17% yield of the less polar 5,6-*cis* isomer **9a**. 5,6-Stereochemistries of both isomers were assigned based on coupling constants ($J_{5,6}$) in their NMR spectra. The *trans* isomer **8a** revealed a doublet absorption, assignable to H-5, at δ 5.57 with a smaller coupling constant ($J_{5,6}=1.5$ Hz), while the *cis* isomer **9a** exhibited a doublet absorption at δ 5.60 with a larger coupling constant ($J_{5,6}=4$ Hz). Ultraviolet spectra of these penem esters display wavelength maxima *ca.* 340 nm, characteristic of 2-(alkylthio)-penem esters. Formation of the *cis* penem **9a** from the *trans* azetidinonephosphorane **7a** was unexpected. The *trans* isomer **8a** was heated in xylene at 125°C for several hours to give a mixture of **8a** and **9a** in approximately a 4: 1 ratio. Heating the *cis* isomer **9a** also gave the same mixture. Thus, the *cis*, *trans* interconversion was inevitable under the cyclization conditions of the phosphorane **7a**. This interconversion between **8a** and **9a** can be explained by considering the intermediate of the conjugated betaine as depicted by **10**.[9] More reliable experimental evidence for the epimerization which occurred at the C-5 position, not at the other possible position, C-6, will be given in the forthcoming paper. The *trans* penem ester **8a** was desilylated to hydroxyethylpenem **11a** in 92% yield by treatment with tetrabutylammonium fluoride in THF in the presence of acetic acid.[10] Hydrogenolysis of **11a** with 10% palladium-charcoal in a mixture of THF/phosphate buffer solution (pH 7.1) followed by purification on Diaion HP20AG, eluting with 2—5% aceton–ewater, afforded a 60% yield of the desired 5*R*, 6*S*, 8*R* amino acid **13a**, "1-thiathienamycin." UV $\lambda_{\max}^{H_2O}$ nm (ε): 253 (4790), 321 (6130); $[\alpha]_D$ +175° (H_2O). Analogously, deblocking of the *cis* penem ester **12a** afforded the 5*S*, 6*S*, 8*R* amino acid **14a**, having the unnatural C-5 configuration, UV $\lambda_{\max}^{H_2O}$ nm (ε): 252 (5010), 318 (6480); $[\alpha]_D$ −205° (H_2O).

Following the same procedure as described above, the 8*S* azetidinone **4** was transformed to the 8*S* phosphorane **7b** *via* **5b** and **6b**, and subjected to the cyclization reaction to give the 8*S* *trans* penem ester **8b** accompanied by a trace amount of the 5,6-*cis* penem. Desilylation of **8b** to **11b** and subsequent hydrogenolysis afforded the 8*S* amino acid **13b**, UV $\lambda_{\max}^{H_2O}$ nm (ε): 252 (4700), 320 (5700); $[\alpha]_D$ +198° (H_2O).

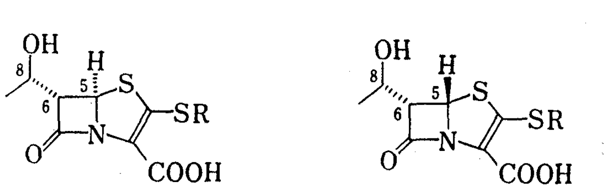
The 8*R* and 8*S* amino acids **13a** and **13b** thus obtained were acetylated with acetic anhydride in a mixture of THF/aqueous sodium bicarbonate solution to give the sodium salts of the corresponding acetamido acids **13e** and **13f**, respectively.



a (8*R*) : R=$(CH_2)_2NHPNZ$
b (8*S*) : R=$(CH_2)_2NHPNZ$
c (8*R*) : R=$(CH_2)_3NHPNZ$
d (8*R*) : R=$(CH_2)_4NHPNZ$
e (8*R*) : R=$(CH_2)_3OTBDMS$
f (8*S*) : R=$(CH_2)_3OTBDMS$
g (8*R*) : R=$(CH_2)_3OH$
h (8*S*) : R=$(CH_2)_3OH$
i (8*R*) : R=$(CH_2)_3N_3$
j (8*R*) : R=$(CH_2)_2OC_2H_5$
k (8*S*) : R=$(CH_2)_2OC_2H_5$

TBDMS: *tert*-butyldimethylsilyl
PNB: *p*-nitrobenzyl
PNZ: (*p*-nitrobenzyl)oxycarbonyl

Chart 3



a (8*R*): R=$(CH_2)_2NH_2$
b (8*S*): R=$(CH_2)_2NH_2$
c (8*R*): R=$(CH_2)_3NH_2$
d (8*R*): R=$(CH_2)_4NH_2$
e (8*R*): R=$(CH_2)_2NHCOCH_3$
f (8*S*): R=$(CH_2)_2NHCOCH_3$
g (8*R*): R=$(CH_2)_3OH$
h (8*S*): R=$(CH_2)_3OH$
i (8*R*): R=$(CH_2)_2OC_2H_5$
j (8*S*): R=$(CH_2)_2OC_2H_5$

Chart 4

TABLE I. Antibacterial *in Vitro* Activities of 2-(Alkylthio)-6-(1-hydroxyethyl)penem-3-carboxylic Acids (13 and 14)

Compd.	R	Stereo-chemistry	*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]
13a	$(CH_2)_2NH_2$	8*R* *trans*	≤0.01	≤0.01	0.4	0.8	0.8	6.2	0.8	0.8	6.2	1.5
13b	$(CH_2)_2NH_2$	8*S* *trans*	0.4	1.5	12.5	25	25	100	25	25	25	25
13c	$(CH_2)_3NH_2$	8*R* *trans*	≤0.01	≤0.01	0.4	0.8	0.8	6.2	0.8	0.8	6.2	0.8
13d	$(CH_2)_4NH_2$	8*R* *trans*	≤0.02	≤0.02	0.4	0.8	0.8	12.5	0.8	0.8	6.2	1.5
13e	$(CH_2)_2NHCOCH_3$ Na slat	8*R* *trans*	0.05	0.1	0.4	0.8	0.8	200	0.4	0.8	1.5	0.8
13f	$(CH_2)_2NHCOCH_3$ Na salt	8*S* *trans*	3.1	12.5	12.5	12.5	12.5	>50	12.5	12.5	25	12.5
13g	$(CH_2)_3OH$ Na salt	8*R* *trans*	≤0.01	0.05	0.2	0.4	0.4	>100	0.4	1.5	0.8	0.4
13h	$(CH_2)_3OH$ Na salt	8*S* *trans*	0.4	0.8	6.2	6.2	6.2	>50	6.2	12.5	6.2	3.1
13i	$(CH_2)_2OC_2H_5$ Na salt	8*R* *trans*	0.05	0.1	1.5	1.5	0.4	>100	0.8	6.2	0.4	0.8
13j	$(CH_2)_2OC_2H_5$ Na salt	8*S* *trans*	0.8	1.5	12.5	12.5	3.1	>200	6.2	100	12.5	6.2
14a	$(CH_2)_2NH_2$	8*R* *cis*	6.2	25	>100	>100	>100	>100	>100	>100	>100	>100
14c	$(CH_2)_3NH_2$	8*R* *cis*	6.2	25	>200	>200	>200	>200	>200	>200	>200	>200
14d	$(CH_2)_4NH_2$	8*R* *cis*	3.1	12.5	>100	>100	>100	>100	>100	>100	>100	>100
14i	$(CH_2)_2OC_2H_5$ Na salt	8*R* *cis*	6.2	12.5	>200	>200	100	>200	200	>200	100	100

MIC values are given in μg/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 (CSase⁺).
e) *Shigella flexneri* IID 642.
f) *Pseudomonas aeruginosa* 1001.
g) *Klebsiella pneumoniae* 806.
h) *Klebsiella* sp. 846.
i) *Proteus vulgaris* 1430.
j) *Salmonella enteritidis* G.

Homologs of amino acids with a longer side chain at the C-2 position (**13c**, **d** and **14c**, **d**) were similarly prepared by the reaction sequence described above, starting from the 8*R* azetidinone **3** and, as components of the C-2 substituents, the corresponding [[(*p*-nitrobenzyl)oxycarbonyl]amino]alkanethiols.

Penem acids (**13g**, **h**) with a hydroxy function in the C-2 side chain were also prepared starting from the azetidinones **3** and **4** and 3-(*tert*-butyldimethylsilyloxy)propanethiol. An intramolecular Wittig reaction of the phosphorane **7e** obtained from the 8*R* azetidinone **3** *via* **5e** and **6e** afforded an inseparable mixture (4: 1 by NMR) of the *trans* and *cis* penem esters **8e** and **9e** in 66% yield. Selective deprotection of the primary alcohol group in **8e** and **9e** was attempted by treatment of the mixture with two equivalents of tetrabutylammonium fluoride in THF in the presence of acetic acid at room temperature for 3 h. The product was separated by preparative thin layer chromatography to give the *trans* isomer **8g** (43%) and the *cis* isomer **9g** (12%) along with a mixture of dihydroxypenem esters **11g** and **12g** (12%) and the starting material (24%). On the other hand, an intramolecular Wittig reaction of the 8*S* phosphorane **7f** derived from **4** afforded the *trans* penem ester **8f** exclusively. Desilylation of **8g** and **8f** to the corresponding 8*R* and 8*S* dihydroxy penems **11g** and **11h** by longer treatment with tetrabutylammonium fluoride and subsequent hydrogenolysis in phosphate buffer solution afforded the dihydroxypenem acids **13g** and **13h**, respectively, as sodium salts.

The monohydroxy penem ester **8g** provides a useful intermediate for manipulation of the C-2 side chain, as demonstrated in our previous paper.4b) The alcohol **8g** was treated with hydrogen azide in the presence of triphenylphosphine and diethyl azodicarboxylate to give the azido penem **11i** in quantitative yield. Removal of the silyl group in **11i** followed by hydrogenolysis afforded 2-(3-aminopropylthio)penem acid **13c**, already described above.

The diastereomeric pair of 8*R* and 8*S* 2-(ethoxyethylthio)penem acids, **13i** and **13j**, and the *cis* 8*R* isomer **14i** were also obtained by the standard procedure as described above, starting from the azetidinones **3** and **4** and 2-ethoxyethanethiol.

Antibaceterial activities of the 6-(hydroxyethyl)-2-(alkylthio)penem-3-carboxylic acids thus obtained are shown in Table I. In general, the introduction of the 6α-hydroxyethyl group into the penem increased the activity against β-lactamase- producing strains. The 8*R* *trans* diastereomers **13a**, **e**, **g**, **i**, which have the same configuration as thienamycin, showed far more potent activity than the corresponding 8*S* *trans* diastereomers **13b**, **f**, **h**, **j**.11) Compared to the racemic 6-unsubstituted parent penems,6) the 8*R* hydroxyethylpenem acids had markedly increased activity against gram-positive bacteria; and in particular, the anti-*Pseudomonas* activity of the 8*R* penems **13a**, **c**, **d**, having the amino function in the side chain, was outstanding. It is interesting to note that the difference of the side chain length did not result in any significant difference in antibacterial activity, as observed with the 8*R* amino acids **13a**, **c**, **d**. The *cis* penems **14a**, **c**, **d**, **i** with the unnatural C-5 configuration of thienamycin exhibited no significant activity against most micro-organisms.

The biological stability of these compounds seemed to be substantially improved considering that the urinary recovery of the (hydroxyethyl)penem acid **13i** parenterally administrated to mice was 44.6% during 0—24 hours, which is much higher than the 5.8% urinary recovery of the corresponding 6-unsubstituted penem acid.6)

Experimental

Melting points are uncorrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer and ultraviolet spectra (UV) on a Cary 14 CM-50 (Serial 1258) spectrometer. Proton magnetic resonance spectra (NMR) were obtained on a Varian A-60 or a Hitachi-Perkin-Elmer R-24 spectrometer unless otherwise specified, or on a Varian XL 100A-15 spectrometer, using, unless otherwise specified, tetramethylsilane as an internal standard. Rotations were determined on a Perkin-Elmer 141 spectrometer at 25°C. Thin-layer chromatography (TLC) was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 0.25 mm (E. Merck) and spots were made visible by UV irradiation or by spraying with vanadic acid-sulfuric acid followed by heating, or by iodine treatment. Chromatography columns were prepared with Wakogel C-200 (Wako Pure Chemical Industries, Ltd.) and preparative TLC was carried out on plates of Silica gel $60F_{254}$ (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; dq, doublet of quartets; qd, quartet of doublets; m, multiplet; br., broad; sh., shoulder.

Mercaptans——2-Ethoxyethanethiol[12] was prepared from 2-ethoxyethyl bromide. 3-(*tert*-Butyldimethylsilyloxy)propanethiol (bp_8 85—87°C) was provided in 90% yield by silylation of 3-mercaptopropanol with *tert*-butyldimethylchlorosilane (1.1 equiv.) and imidazole in N,N-dimethylformamide (DMF). 2-[[(*p*-Nitrobenzyl)oxycarbonyl]amino]ethanethiol[13] (mp 67—68°C) was derived from 2-aminoethanethiol and *p*-nitrobenzyl chloroformate. 3-[[(*p*-Nitrobenzyl)oxycarbonyl]amino]propanethiol (mp 68—69°C) was synthesized from 3-aminopropanol by a reaction sequence involving N-protection with a (*p*-nitrobenzyl)-oxycarbonyl group, mesylation and subsequent displacement reaction with disodium trithiocarbonate[14] in aqueous MeOH, followed by acidification. 4-[[(*p*-Nitrobenzyl)oxycarbonyl]amino]butanethiol (mp 43—44°C) was synthesized as follows; γ-[[(*p*-nitrobenzyl)oxycarbonyl]amino]butyric acid was treated with *i*-butyl chloroformate and triethylamine in THF to give *in situ* the mixed anhydride, which was then reduced with $NaBH_4$ to the corresponding alcohol whose mesylation and subsequent displacement with disodium trithiocarbonate as described above afforded the desired N-protected 4-aminobutanethiol.

(3*S*,4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[(*R* or *S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinones (5a—f, j, k)——As a typical example, the preparation of the 4-[[2-[[(*p*-nitrobenzyl)oxycarbonyl]amino]-ethylthio]thiocarbonyl]thio derivative **5a** is described. 2-[[(*p*-Nitrobenzyl)oxycarbonyl]amino]ethanethiol (712 mg, 2.78 mmol) was added to an ice-cold sodium methoxide solution, prepared by dissolving sodium metal (60.9 mg, 2.64 mmol) in MeOH (6 ml), and after 5 min, carbon disulfide (211 mg, 2.78 mmol) was added. The mixture was stirred for 20 min, then cooled to −10°C and **3** (758 mg, 2.64 mmol) was added. Stirring was continued for 40 min at the same temperature. One drop of acetic acid was added and the mixture was diluted with AcOEt, washed with brine and dried. The solvent was evaporated off *in vacuo* and the residue was chromatographed (25 g, benzene–acetone, 10: 1) to give **5a** (1.37 g, 87%) as a yellow oil.

The other trithiocarbonates (**5b—f, j, k**) were similarly prepared. The products were purified by column or preparative TLC over silica gel using benzene–AcOEt solvent systems. Appearance, elementary analysis data and yields are given in Table II and spectral data in Table III.

TABLE II. (3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinones (5)

Compd.	R[a]	Stereochemistry[b]	Appearance[c] mp, °C	Formula	Analysis, (%) Calcd (Found) C	H	N	S	Yield (%)
5a	$(CH_2)_2NHPNZ$	*R*	Oil	$C_{22}H_{33}N_3O_6S_3Si$	47.20 (47.97	5.94 5.89	7.51 7.39	17.18 17.10)	87
5b	$(CH_2)_2NHPNZ$	*S*	Oil	$C_{22}H_{33}N_3O_6S_3Si$	47.20 (47.88	5.94 5.71	7.51 7.36	17.18 16.89)	67
5c	$(CH_2)_3NHPNZ$	*R*	Powder 127—128 (B–H)	$C_{23}H_{35}N_3O_6S_3Si$	48.14 (48.10	6.15 6.24	7.32 7.20	16.76 16.76)	71
5d	$(CH_2)_4NHPNZ$	*R*	Powder 101—103 (MeOH)	$C_{24}H_{37}N_3O_6S_3Si$	49.04 (49.23	6.34 6.38	7.15 7.11	16.36 16.35)	85
5e	$(CH_2)_3OTBDMS$	*R*	Prisms 115—117 (MeOH)	$C_{21}H_{43}NO_3S_3Si_2$	49.46 (49.35	8.50 8.53	2.75 2.72	18.87 19.17)	70
5f	$(CH_2)_3OTBDMS$	*S*	Fine needles 56—61 (MeOH)	$C_{21}H_{43}NO_3S_3Si_2$	49.46 (49.66	8.50 8.68	2.75 2.64	18.87 18.92)	64
5j	$(CH_2)_2OC_2H_5$	*R*	Fine needles 69—71 (H)	$C_{16}H_{31}NO_3S_3Si$	46.90 (46.88	7.63 7.61	3.42 3.26	23.48 23.48)	78
5k	$(CH_2)_2OC_2H_5$	*S*	Oil	$C_{16}H_{31}NO_3S_3Si$	46.90 (46.83	7.63 7.59	3.42 3.35	23.48 23.38)	75

a) PNZ, (*p*-nitrobenzyl)oxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.
b) Configuration at the carbon bearing the *tert*-butyldimethylsilyloxy group in the side chain.
c) Yellow-colored. Recrystallization solvents in parentheses: B, benzene; H, hexane.

TABLE III. IR and NMR Data for (3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinones (**5**)

Compd.	IR, cm^{-1} (state)	NMR, $\delta^{a)}$ ($CDCl_3$)
5a	3400 (br.), 1770, 1720 (KBr)	0.05 (6H, s), 0.90 (9H, s), 1.20 (3H, d, 6), 3.23 (1H, dd, 4, 2.5), 3.55 (4H, br s), 4.20 (1H, m), 5.13 (2H, s), 5.59 (1H, d, 2.5), 7.15 (1H, br s), 7.50 (2H, d, 9), 8.16 (2H, d, 9)
5b	3460, 3430, 1775, 1725 ($CHCl_3$)	0.08 (6H, s), 0.85 (9H, s), 1.27 (3H, d, 6), 3.23 (1H, t, 2.5), 3.45 (4H, m), 4.15 (1H, m), 5.11 (2H, s), 5.43 (1H, d, 2.5), 6.55 (1H, br s), 7.42 (2H, d, 9), 8.16 (2H, d, 9)
5c	3400 (br.), 3300, 1760, 1700 (KBr)	0.08 (6H, s), 0.88 (9H, s), 1.21 (3H, d, 6), 1.98 (2H, m), 3.30 (5H, m), 4.20 (1H, qd, 6, 2), 5.16 (2H, s), 5.63 (1H, d, 2.5), 7.44 (2H, d, 9), 8.14 (2H, d, 9)
5d	3425, 1780, 1725 (KBr)	0.10 (6H, s), 0.85 (9H, s), 1.15 (3H, d, 6), 1.60 (4H, m), 3.10 (5H, m), 4.12 (1H, qd, 6, 2.5), 5.05 (2H, s), 5.50 (1H, d, 3), 7.33 (2H, d, 9), 8.02 (2H, d, 9)
5e	3140 (sh.), 3080, 1773, 1731 (Nujol)	0.10 (12H, s), 0.90 (18H, s), 1.20 (3H, d, 6.5), 1.95 (2H, m), 3.26 (1H, dd, 4.5, 2.5), 3.52 (2H, t, 7), 3.78 (2H, t, 6), 4.35 (1H, m), 5.80 (1H, d, 2.5), 6.7 (1H, br)
5f	3420, 1779 ($CHCl_3$)	0.08 (6H, s), 0.10 (6H, s), 0.90 (18H, s), 1.33 (3H, d, 6), 1.95 (2H, m), 3.33 (1H, m), 3.52 (2H, t, 7), 3.75 (2H, t, 6), 4.35 (1H, m), 5.67 (1H, d, 2.5), 6.7 (1H, br)
5j	3425, 1779 ($CHCl_3$)	0.08 (6H, s), 0.88 (9H, s), 1.20 (3H, t, 6.5), 1.22 (3H, d, 6.5), 3.22 (1H, dd, 4, 2.5), 3.55 (2H, q, 6.5), 3.66 (4H, br. s), 4.3 (1H, m), 5.73 (1H, d, 2.5), 6.80 (1H, br s)
5k	3425, 1780 ($CHCl_3$)	0.08 (6H, s), 0.88 (9H, s), 1.20 (3H, t, 6.5), 1.34 (3H, d, 6.5), 3.25 (1H, m). 3.55 (2H, q, 6.5), 3.66 (4H, br s), 4.3 (1H, m), 5.59 (1H, d, 2.5), 6.8 (1H, br s)

a) Chemical shifts are given with porton numbers, absorption patterns and coupling constants in Hz in parentheses.

TABLE IV. *p*-Nitrobenzyl 2-[(3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxo-1-azetidinyl]-2-hydroxyacetates (**6**)

Compd.	R$^{a)}$	Stereo-chemistry$^{b)}$	Formula	Analysis, (%) Calcd (Found)				Yield (%)	Reaction Time (h)
				C	H	N	S		
6a	$(CH_2)_2NHPNZ$	*R*	$C_{31}H_{40}N_4O_{11}S_3Si$	48.42 (48.42	5.24 5.95	7.29 7.66	12.51 12.28)	78	5
6b	$(CH_2)_2NHPNZ$	*S*	$C_{31}H_{40}N_4O_{11}S_3Si$	48.42 (48.26	5.24 5.48	7.29 7.50	12.51 12.22)	64	16
6c	$(CH_2)_3NHPNZ$	*R*	$C_{32}H_{42}N_4O_{11}S_3Si$	49.09 (49.27	5.41 5.36	7.16 7.08	12.28 12.34)	88	16
6d	$(CH_2)_4NHPNZ$	*R*	$C_{33}H_{44}N_4O_{11}S_3Si$	49.73 (49.46	5.56 5.98	7.03 6.84	12.07 12.23)	78	22
6e	$(CH_2)_3OTBDMS$	*R*	$C_{30}H_{50}N_2O_8S_3Si_2$	50.10 (50.30	7.01 7.36	3.90 3.76	13.38 13.66)	97	13
6f	$(CH_2)_3OTBDMS$	*S*	$C_{30}H_{50}N_2O_8S_3Si_2$	50.10 (50.33	7.01 7.27	3.90 3.65	13.38 13.29)	97	8
6j	$(CH_2)_2OC_2H_5$	*R*	$C_{25}H_{38}N_2O_8S_3Si$	48.52 (48.48	6.19 6.03	4.53 4.88	15.54 15.54)	100	10
6k	$(CH_2)_2OC_2H_5$	*S*	$C_{25}H_{38}N_2O_8S_3Si$	48.52 (48.59	6.19 6.01	4.53 4.44	15.54 15.57)	96	8

a) PNZ, (*p*-nitrobenzyl)oxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.
b) Configuration at the carbon bearing the *tert*-butyldimethylsilyloxy group in the side chain.

***p*-Nitrobenzyl 2-[(3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[(*R* or *S*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-oxo-1-azetidinyl]-2-hydroxyacetates (6a—f, j, k)**——As a typical example, the preparation of **6a** is described. A solution of **5a** (1.00 g, 1.78 mmol) and *p*-nitrobenzyl glyoxylate (hydrate, 404 mg, 1.78 mmol) in benzene (10 ml) was refluxed for 5 h. The mixture was evaporated to dryness *in vacuo* and the residue was chromatographed (15 g, hexane–acetone, 3: 1) to provide **6a** (1.08 g, 78%) as a yellow oil. The other glyoxylate adducts were prepared in a similar manner. Elementary analysis, yields and spectral data are given in Tables IV and V.

TABLE V. IR and NMR Data for *p*-Nitrobenzyl 2-[(3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]-thio]-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxo-1-azetidinyl]-2-hydroxyacetates (**6**)

Compd.	IR, cm^{-1} (state)	NMR, $\delta^{a)}$ ($CDCl_3$)
6a	3350, 1770, 1720 (liq.)	0.04 (3H, s), 0.06 (3H, s), 0.82 (9H, s), 1.13 and 1.15 (1: 1, 3H, d, 6), 3.30 (1H, m), 3.50 (4H, br s), 3.90—4.3 (3H, m), 5.18 (2H, s), 5.24 and 5.33 (1: 1, 2H, s), 5.55 (1/2H, d, 9), 6.18 and 6.26 (1: 1, 1H, d, 3)
6b	3520, 3470, 1784, 1765 (sh.), 1735 ($CHCl_3$)	0.10 (6H, s), 0.84 (9H, s), 1.23 and 1.27 (1: 1, 3H, d, 6), 3.35 (1H, m), 3.5 (4H, br.), 3.9—4.5 (3H, m), 5.15 (2H, s), 5.25 and 5.30 (2H, s), 5.5 (2H, m), 6.02 and 6.07 (1: 1, 1H, d, 3)
6c	3375, 1780, 1730 (liq.)	0.04 and 0.06 (6H, s), 0.95 (9H, s), 1.26 and 1.28 (3H, d, 6), 1.95 (2H, m), 3.0—3.35 (4H, m), 3.7—4.3 (2H, m), 5.05 (2H, s), 5.11 and 5.20 (2H, s), 5.41 (1/2H, d, 9.5), 6.05 and 6.10 (1H, d, 3)
6d	3400 (br.), 1780, 1725 (liq.)	0.04 and 0.05 (6H, s), 0.83 (9H, s), 1.16 (3H, d, 6), 1.60 (4H, m), 2.9—3.3 (5H, m), 4.00 (1H, m), 5.06 (2H, s), 5.15 and 5.23 (2H, s), 6.03 and 6.09 (1H, d, 3)
6e	3470, 3390, 1770 (br) (Nujol)	0.06 (12H, s), 0.88 (18H, s), 1.23 (3H, d, 6.5), 1.90 (2H, m), 3.32 (1H, dd, 4.5, 2.5), 3.48 (2H, t, 7), 3.70 (2H, t, 6.5), 4.25 (1H, m), 5.30 and 5.38 (1: 3, 2H, s), 5.25 and 5.62 (1:3, 1H, d), 6.26 and 6.30 (3: 1, 1H, d, 2.5)
6f	3430, 1775, 1750 (sh.) (liq.)	0.08 (12H, s), 0.88 (18H, s), 2.32 (3H, d, 6), 3.4 (1H, m), 3.47 (2H, t, 7), 3.70 (2H, t, 6), 4.3 (1H, m), 5.31 and 5.37 (1: 1, 1H, d, 8.5), 6.07 (1H, m)
6j	3430, 1775, 1750 (sh.) (liq.)	0.06 (6H, s), 0.85 (9H, s), 1.15 (3H, t, 6.5), 1.21 (3H, d, 6.5), 3.45 (2H, q, 6.5), 3.56 (4H, br), 4.1 (1H, m), —5.3 (3H, m), 6.19 and 6.23 (1: 1, 1H, d, 2.5)
6k	3430, 1775, 1750 (liq.)	0.06 (6H, s), 0.85 (9H, s), 1.15 (3H, t, 6.5), 1.26 and 1.30 (1: 1, 3H, d, 6), 3.45 (2H, q, 6.5), 3.56 (4H, s), 4.1 (1H, m),—5.3 (3H, m), 5.98 and 6.02 (1: 1, 1H, d, 2.5)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons of the *p*-nitrobenzyl group at δ 7.5—8.3 are not given in the table.

***p*-Nitrobenzyl 2-[(3*S*, 4*R*)-4-[[(Alkylthio)thiocarbonyl]thio]-3-[(*R* or *S*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetates (7a—f, j, k)**——A typical procedure is as follows. Thionyl chloride (146 mg, 1.23 mmol) was added dropwise to a solution of **6a** (865 mg, 1.12 mmol) and 2,6-lutidine (132 mg, 1.23 mmol) in THF (32 ml) at −15°C with stirring. The mixture was stirred for 15 min and then triphenylphosphine (590 mg, 2.24 mmol) and 2,6-lutidine (241 mg, 2.24 mmol) were added. The whole was stirred for 42 h at 75°C (bath temperature) under an N_2 atmosphere, then diluted with AcOEt, washed successively with water, dil. HCl and dil. $NaHCO_3$, and dried. The product obtained by removal of the solvent was chromatographed (25 g, $CHCl_3$–AcOEt, 20: 1) to give **7a** (705 mg, 62%) as a yellow viscous oil. The other phosphoranes were similarly synthesized. IR data, elementary analysis data and yields are given in Table VI.

Intramolecular Wittig Reaction of the Phosphoranes (7a—f, j, k)——A typical procedure is described for the cyclization of **7a**. A solution of **7a** (1.33 g) and hydroquinone (92 mg) in xylene (130 ml) was heated at 125—130°C for 15 h with stirring under an N_2 atmosphere. The reaction mixture was evaporated to dryness *in vacuo* and the residue was chromatogrophed (20 g, benzene) to afford the *trans* isomer **8a** (717 mg, 76%) and the *cis* isomer **9a** (158 mg, 17%) as oils; **9a** was eluted first. UV λ_{max}^{THF} nm (ε) for **8a**: 263 (25600), 340 (10800); for **9a**: 263 (25700), 338 (10900). The other penem esters (**8b—f, j, k** and **9c—e, j**) were analogously obtained. Reaction time, products and yields are shown in Table VII. Optical rotations, elementary analysis and spectroscopic data are given in Tables VIII and IX. *Cis* and *trans* isomers were easily separated

TABLE VI. *p*-Nitrobenzyl 2-[(3*S*, 4*R*)-4-[[(Alkylthio) thiocarbonyl]thio]-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-oxo-1-azetidinyl]-2-(triphenylphosphoranylidene)acetates (**7**)

Compd.	R[a)]	Stereochemistry[b)]	Formula	Analysis, (%) Calcd (Found) C	H	N	P	S	Yield[c)] (%)
7a	$(CH_2)_2NHPNZ$	*R*	$C_{49}H_{53}N_4O_{10}PS_3Si$	58.08 (58.29	5.27 5.31	5.53 5.66	—	9.49 9.65)	62
7b	$(CH_2)_2NHPNZ$	*S*	$C_{49}H_{53}N_4O_{10}PS_3Si$	58.08 (57.18	5.27 5.30	5.53 5.91	3.09 2.97)	—	44
7c	$(CH_2)_3NHPNZ$	*R*	$C_{50}H_{55}N_4O_{10}PS_3Si$	58.46 (58.60	5.40 5.65	5.45 5.25	—	9.36 9.65)	55
7d	$(CH_2)_4NHPNZ$	*R*	$C_{51}H_{57}N_4O_{10}PS_3Si$	58.83 (58.94	5.52 5.10	5.38 4.99	—	9.24 9.35)	59
7e	$(CH_2)_3OTBDMS$	*R*	$C_{48}H_{63}N_2O_7PS_3Si_2$	59.84 (59.71	6.59 6.65	2.91 2.93	3.21 3.17)	—	57
7f	$(CH_2)_3OTBDMS$	*S*	$C_{48}H_{63}N_2O_7PS_3Si_2$	59.84 (59.69	6.59 6.53	2.91 2.98	3.21 3.04)	—	72
7j	$(CH_2)_2OC_2H_5$	*R*	$C_{43}H_{51}N_2O_7PS_3Si$	59.83 (59.85	5.96 5.93	3.25 3.33	3.59 3.32)	—	64
7k	$(CH_2)_2OC_2H_5$	*S*	$C_{43}H_{51}N_2O_7PS_3Si$	59.83 (59.57	5.96 5.84	3.25 3.16	3.59 3.20)	—	56

a) PNZ, (*p*-nitrobenzyl)oxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.
b) Configuration at the carbon bearing the *tert*-butyldimethylsilyloxy group in the side chain.
c) All compounds were obtained as yellow-colored viscous oils.

TABLE VII. Transformation of the Phosphoranes **7** into the Penem Esters **8** and **9**.

Starting material	R[a)]	Stereochemistry[b)]	Reaction time (h)	Products (yield, %) *trans* isomer	*cis* isomer	Recovery of starting material (%)
7a	$(CH_2)_2NHPNZ$	*R*	15	**8a** (76)	**9a** (17)	—
7b	$(CH_2)_2NHPNZ$	*S*	10	**8b** (65)	trace	8
7c	$(CH_2)_3NHPNZ$	*R*	15	**8c** (57)	**9c** (20)	—
7d	$(CH_2)_4NHPNZ$	*R*	16	**8d** (58)	**9d** (20)	6
7e	$(CH_2)_3OTBDMS$	*R*	12	**8e** + **9e** (4:1, 66)[c)]		17
7f	$(CH_2)_3OTBDMS$	*S*	8	**8f** (51)	—	28
7j	$(CH_2)_2OC_2H_5$	*R*	10	**8j** (53)	**9j** (17)	8
7k	$(CH_2)_2OC_2H_5$	*S*	10	**8k** (77)	trace	6

a) PNZ, (*p*-nitrobenzyl)oxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.
b) Configuration at the carbon bearing the *tert*-butyldimethylsilyloxy group in the side chain.
c) The ratio was determined by NMR analysis.

by column chromatography or preparative TLC except for the mixture of **8e** and **9e**, which was inseparable and whose separation was achieved after desilylation to **8g** and **9g** as described later.

Interconversion of the *trans* Penem Esters 8 and the *cis* Esters 9——i) A solution of **8a** (50 mg) and hydroquinone (5 mg) in xylene (8 ml) was heated at 125°C for 7 h under an N_2 atmosphere. Xylene was evaporated off *in vacuo*. Separation of the products by preparative TLC (benzene–AcOEt, 3: 1) afforded the *trans* isomer **8a** (37 mg, 74%) and the less polar *cis* isomer **9a** (9 mg, 18%) as oils. IR, NMR and TLC properties of **9a** thus obtained were identical with those of the sample described above.

ii) A solution of **9a** (35 mg) and hydroquinone (3 mg) in xylene (5 ml) was heated at 130°C for 7 h under an N_2 atmosphere. Separation of the product as described above gave **8a** (25 mg) and **9a** (7 mg).

iii) A solution of **8j** (45 mg) and hydroquinone (4 mg) in xylene (7 ml) was heated at 135°C for 7 h under an N_2 atmosphere. Removal of the solvent under reduced pressure and preparative TLC of the residue (benzene–AcOEt, 7: 1) gave the *trans* isomer **8j** (31 mg) and the less polar *cis* isomer **9j** (10 mg). IR, NMR and TLC properties of **9j** thus obtained were identical with those of the *cis* isomer obtained in the cyclization reaction of the phosphorane **7j**. Heating **8j** without hydroquinone resulted in some decomposition, but the formation of **9j** was similarly observed.

Table VIII. *p*-Nitrobenzyl (6*S*)-2-(Alkylthio)-6-[1-(*tert*-butyldimethylsilyloxy)ethyl]penem-3-carboxylates (**8** and **9**)

Compd.	R[a]	Stereochemistry[b]	Appearance, mp,[c] optical rotation	Formula	Analysis, (%) Calcd (Found)			
					C	H	N	S
8a	$(CH_2)_2NHPNZ$	8*R trans*	Oil	$C_{31}H_{38}N_4O_{10}S_2Si$	51.79 (51.68	5.33 5.30	7.79 7.71	8.92 9.20)
9a	$(CH_2)_2NHPNZ$	8*R cis*	Oil	$C_{31}H_{38}N_4O_{10}S_2Si$	51.79 (51.78	5.33 5.42	7.79 7.91	8.92 9.10)
8b	$(CH_2)_2NHPNZ$	8*S trans*	Needles mp 165—166°C (E.A) $[\alpha]_D$ +77° (c=0.52, $CHCl_3$)	$C_{31}H_{38}N_4O_{10}S_2Si$	51.79 (51.77	5.33 5.29	7.79 7.93	8.92 9.22)
8c	$(CH_2)_3NHPNZ$	8*R trans*	Oil	$C_{32}H_{40}N_4O_{10}S_2Si$	52.44 (52.18	5.50 5.46	7.65 7.81	8.75 8.96)
9c	$(CH_2)_3NHPNZ$	8*R cis*	Oil	$C_{32}H_{40}N_4O_{10}S_2Si$	—	—	—	—
8d	$(CH_2)_4NHPNZ$	8*R trans*	Needles mp 164—165°C (B) $[\alpha]_D$ +57° (c=0.50, $CHCl_3$)	$C_{33}H_{42}N_4O_{10}S_2Si$	53.06 (53.01	5.67 5.69	7.50 7.58	8.58 8.59)
9d	$(CH_2)_4NHPNZ$	8*R cis*	Oil, $[\alpha]_D$ −64° (c=2.25, $CHCl_3$)	$C_{33}H_{42}N_4O_{10}S_2Si$	53.06 (53.20	5.67 5.56	7.50 7.62	8.58 8.56)
8e[d]	$(CH_2)_3OTBDMS$	8*R* (*trans*)	Oil	$C_{30}H_{48}N_2O_7S_2Si_2$	53.36 (53.81	7.23 7.25	4.19 4.24	9.59 9.63)
8f	$(CH_2)_3OTBDMS$	8*S trans*	Oil	$C_{30}H_{48}N_2O_7S_2Si_2$	53.36 (53.55	7.23 7.36	4.19 4.31	9.59 9.74)
8g	$(CH_2)_3OH$	8*R trans*	Needles mp 100—101°C (B–H) $[\alpha]_D$ +96° (c=0.91, $CHCl_3$)	$C_{24}H_{34}N_2O_7S_2Si$	51.96 (51.68	6.18 6.24	5.05 4.85	11.56 11.46)
9g	$(CH_2)_3OH$	8*R cis*	Oil, $[\alpha]_D$ −64° (c=1.10, $CHCl_3$)	$C_{24}H_{34}N_2O_7S_2Si$	—	—	—	—
8i	$(CH_2)_3N_3$	8*R trans*	Needles mp 92.5—93.5°C (B–H) $[\alpha]_D$ +79° (c=0.93, $CHCl_3$)	$C_{24}H_{33}N_5O_6S_2Si$	49.72 (49.68	5.74 5.71	12.08 12.02	11.06 11.15)
8j	$(CH_2)_2OC_2H_5$	8*R trans*	Oil, $[\alpha]_D$ +83° (c=0.98, $CHCl_3$)	$C_{25}H_{36}N_2O_7S_2Si$	52.79 (53.08	6.38 6.64	4.93 4.65	11.28 11.42)
9j	$(CH_2)_2OC_2H_5$	8*R cis*	Oil, $[\alpha]_D$ −97° (c=1.22, $CHCl_3$)	$C_{25}H_{36}N_2O_7S_2Si$	52.79 (53.11	6.38 6.27	4.93 4.73	11.28 11.56)
8k	$(CH_2)_2OC_2H_5$	8*S trans*	Oil, $[\alpha]_D$ +64° (c=1.08, $CHCl_3$)	$C_{25}H_{36}N_2O_7S_2Si$	52.79 (53.04	6.38 6.56	4.93 4.81	11.28 11.02)

[a] PNZ, (*p*-nitrobenzyl)oxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.
[b] *trans*, 5*R*, 6*S*; *cis*, 5*S*, 6*S*.
[c] Recrystallization solvents in parentheses: E.A, ethyl acetate; B, benzene; H, hexane.
[d] A 4: 1 mixture of **8e** and **9e**.

iv) Heating **9j** in the same manner as described above afforded a mixture of **8j** and **9j** in approximately a **3**: 1 ratio.

***p*-Nitrobenzyl (5*R*, 6*S*)-6-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-2-[(3-hydroxypropyl)thio]penem-3-carboxylate (8g) and Its 5*S* Isomer (9g)**——Acetic acid (402 mg, 6.7 mmol) and tetrabutylammonium fluoride (350 mg, 1.34 mmol) were added to a solution of the 4: 1 mixture of **8e** and **9e** (450 mg, 0.67 mmol), obtained by cyclization of the phosphorane **7e**, in THF (20 ml). The mixture was allowed to stand at room temperature for 3 h, and then diluted with AcOEt, washed with water and dried. Removal of the solvent *in vacuo* and preparative TLC of the residue (benzene–AcOEt, 3: 1) gave the *trans* isomer **8g** (160 mg, 43%) and the less polar *cis* isomer **9g** (46 mg, 12%) as oils along with a mixture of dihydroxyesters **11g** and **12g** (35 mg, 12%) and the starting material (107 mg, 24%). Analytical and spectral data are given in Tables VIII and IX.

***p*-Nitrobenzyl (5*R*, 6*S*)-2-[(3-Azidopropyl)thio]-6-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]penem-3-carboxylate (8i)**——Triphenylphosphine (73 mg, 0.28 mmol), a 1.1 M solution of hydrogen azide in benzene (0.28 ml, 0.31 mmol) and diethyl azodicarboxylate (49 mg, 0.28 mmol) were successively added to an ice-cold solution of **8g** (77 mg, 0.14 mmol) in THF (2.5 ml) with stirring. The mixture was then stirred at room

TABLE IX. Spectral Data for *p*-Nitrobenzyl (6*S*)-2-(Alkylthio)-6-[1-(*tert*-butyldimethylsilyloxy)ethyl]penem-3-carboxylates (**8** and **9**)

Compd.	IR, cm^{-1} (state)	NMR, $\delta^{a)}$ (CDCl$_3$)
8a	3400, 1780, 1720, 1670 (Nujol)	0.03 (3H, s), 0.07 (3H, s), 0.80 (9H, s), 1.20 (3H, d, 6), 3.04 (2H, m), 3.42 (2H, q, 5), 3.66 (2H, dd, 4, 2), 4.12 (1H, m), 5.04 and 5.37 (1H each, ABq, 14), 5.10 (2H, s), 5.57 (1H, d, 2)
9a	3350, 1780, 1730, 1690 (Nujol)	0.10 (6H, s), 0.81 (9H, s), 1.32 (3H, d, 6), 3.01 (2H, m), 3.36 (2H, t, 5), 3.74 (1H, dd, 10, 4), 4.22 (1H, dq, 10, 6), 5.01 and 5.40 (1H each, ABq, 14), 5 05 (2H, s), 5.58 (1H, d, 4)
8b	3360, 1790, 1725, 1679 (Nujol)	0.08 (6H, s), 0.83 (9H, s), 1.29 (3H, d, 6), 3.01 (2H, m), 3.41 (2H, m), 3.69 (1H, dd, 3, 1.5), 4.1 (1H, m), 5.13 (2H, s), 5.15 and 5.36 (1H each, ABq, 14), 5.46 (1H, d, 1.5)
8c	3350 (br.), 1780, 1720, 1690 (sh.) (liq.)	0.05 and 0.08 (3H each, s), 0.80 (9H, s), 1.20 (3H, d, 6), 1.86 (2H, m), 2.92 (2H, t, 7), 3.28 (2H, q, 7), 3.63 (1H, dd, 4, 1.5), 4.10 (1H, qd, 6, 4), 5.12 and 5.42 (1H each ,ABq, 14), 5.15 (2H, s), 5.60 (1H, d, 1.5)
9c	3400, 1790, 1730 (br) 1700 (sh.) (liq.)	0.14 (6H, s), 0.85 (9H, s), 1.40 (2H, d, 6), 1.92 (2H, m), 3.00 (2H, t, 6.5), 3.30 (2H, q, 6.5), 3.83 (1H, dd, 10, 4.5), 4.3 (1H, m), 5.15 and 5.52 (1H each, ABq, 14.5), 5.20 (2H, s), 5.69 (1H, d, 4.5)
8d	3400 (br.), 1790, 1725, 1695 (KBr)	0.05 and 0.07 (3H each, s), 0.80 (9H, s), 1.21 (3H, d, 6), 1.52 (4H, m), 2.83—3.4 (4H, m), 3.78 (1H, dd, 5, 2), 4.1 (1H, m), 5.14 and 5.48 (1H each, ABq, 14), 5.20 (2H, s), 5.65 (1H, 2)
9d	3400, 1795, 1735, 1700 (sh.) (liq.)	0.15 (6H, s), 0.86 (9H, s), 1.38 (3H, d, 6), 1.68 (4H, m), 2.8—3.3 (4H, m), 3.85 (1H, dd, 10, 4), 4.35 (1H, m), 5.12 and 5.49 (1H each ,ABq, 14), 5.20 (2H, s), 5.72 (1H, d, 4)
8e	1790, 1690 (CHCl$_3$)	0.05 (12H, s), 0.87 (9H, s), 0.92 (9H, s), 1.26 (3H, d, 6), 1.90 (2H, m), 3.00 (2H, m), 3.66 (1H, dd, 4, 1.5), 3.67 (2H, t, 6), 4.25 (1H, m), 5.17 and 5.44 (1H each, ABq, 14), 5.62 (1H, d, 1.5)
9e		1.42 (3H, d, 6), 5.69 (1H, d, 4)$^{b)}$
8f	1785, 1688 (CHCl$_3$)	0.05 and 0.10 (6H each, s), 0.87 (18H, s), 1.35 (3H, d, 6), 1.90 (2H, m), 3.00 (2H, m), 3.67 (2H, t, 6), 3.79 (1H, dd, 3.5, 1.5), 4.2 (1H, m), 5.17 and 5.44 (1H each, ABq, 14), 5.50 (1H, d, 1.5)
8g	3360, 1782, 1671 (Nujol)	0.08 (6H, s), 0.80 (9H, s), 1.20 (3H, d, 6), 1.90 (2H, m), 3.04 (2H, m), 3.68 (1H, dd, 3.5, 1.5), 3.73 (2H, t, 6), 4.25 (1H, m), 5.16 and 5.44 (1H each ,ABq, 14), 5.63 (1H, d, 1.5)
9g	3400, 1790, 1692 (CHCl$_3$)	0.11 (6H, s), 0.83 (9H, s), 1.36 (3H, d, 6), 1.90 (2H, m), 3.07 (2H, m), 3.74 (2H, t, 6), 3.84 (1H, dd, 10.5, 4), 4.37 (1H, m), 5.17 and 5.48 (1H each, ABq, 14), 5.68 (1H, d, 4)
8i	2110, 1791, 1695 (CHCl$_3$)	0.06 (6H, s), 0.80 (9H, s), 1.20 (3H, d, 6), 1.90 (2H, m), 2.97 (2H, m), 3.39 (2H, t, 6.5), 3.65 (1H, dd, 4, 1.5), 4.2 (1H, m), 5.13 and 5.43 (1H each, ABq, 14), 5.63 (1H, d, 1.5)
8j	1790, 1691 (CHCl$_3$)	0.04 and 0.06 (3H each, s), 0.80 (9H, s), 1.16 (3H, t, 7), 1.22 (3H, d, 6.5), 3.2 (2H, m), 3.7 (2H, m), 3.55 (2H, q, 7), 3.75 (1H, dd, 4, 1.5), 4.3 (1H, m), 5.23 and 5.50 (1H each, ABq, 14), 5.70 (1H, d, 1.5)
9j	1790, 1691 (CHCl$_3$)	0.12 (6H, s), 0.84 (9H, s), 1.16 (3H, t, 7), 1.40 (3H, d, 6.5), 3.2 (2H, m), 3.7 (2H, m), 3.55 (2H, q, 7), 3.90 (1H, dd, 10, 4), 4.4 (1H, m), 5.21 and 5.56 (1H each, ABq, 14), 5.76 (1H, d, 4)
8k	1790, 1692 (CHCl$_3$)	0.08 (6H, s), 0.80 (9H, s), 1.11 (3H, t, 7), 1.26 (3H, d, 6), 3.1 (2H, m), 3.7 (2H, m), 3.50 (2H, q, 7), 3.81 (1H, dd, 3.5, 1.5), 4.2 (1H, m), 5.20 and 5.47 (1H each, ABq, 14), 5.53 (1H, d, 1.5)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons of the *p*-nitrobenzyl group(s) at δ 7.5—8.3 are not given in the table.

b) Absorptions distinguishable in the spectrum of a 4: 1 mixture of **8e** and **9e**.

temperature for 10 min, diluted with AcOEt, washed with water, dried and evaporated to dryness *in vacuo*. Preparative TLC of the residue (hexane–acetone, 3: 1) gave **8i** (81 mg, 100%), which was recrystallized from benzene–hexane to afford analytical samples, mp 92—93.5°C, as needles. Analytical and spectral data are given in Tables VIII and IX.

***p*-Nitrobenzyl 2-(Alkylthio)-6-(1-hydroxyethyl)penem-3-carboxylates (11a—d, g—k and 12a, c, d, j)**—— As a typical example, the preparation of **11a** is described. A solution of **8a** (200 mg, 0.278 mmol), acetic acid (167 mg, 2.78 mmol) and tetrabutylammonium fluoride (218 mg, 0.835 mmol) in THF (5 ml) was allowed to stand at room temperature for 14 h. The mixture was diluted with AcOEt, washed successively with water and dil. $NaHCO_3$ and dried. Removal of the solvent by evaporation afforded a crystalline mass which was recrystallized from benzene–MeOH to provide the alcohol **11a** (156 mg, 92%), mp 189—190°C, as prisms The other 6-(hydroxyethyl)penem esters were similarly prepared by desilylation of **8** and **9**. The disilyl-

Table X. *p*-Nitrobenzyl (6*S*)-2-(Alkylthio)-6-(1-hydroxyethyl)penem-3-carboxylates (11 and 12)

Compd.	R[a]	Stereochemistry[b]	Appearance, mp,[c] optical rotation	Formula	Analysis (%) Calcd (Found)				Yield (%)
					C	H	N	S	
11a	$(CH_2)_2NHPNZ$	8*R* *trans*	Powder mp 189—190°C (B–M) [α]D +71° (*c*=0.63, DMF)	$C_{25}H_{24}N_4O_{10}S_2$	49.66 (49.84	4.00 4.02	9.27 9.30	10.61 10.48)	92
12a	$(CH_2)_2NHPNZ$	8*R* *cis*	Oil, [α]D −87° (*c*=0.98, DMF)	$C_{25}H_{24}N_4O_{10}S_2$	49.66 (49.78	4.00 3.89	9.27 9.12	10.61 10.60)	87
11b	$(CH_2)_2NHPNZ$	8*S* *trans*	Prisms mp 151—152.5°C (E.A) [α]D +76° (*c*=0.34, THF)	$C_{25}H_{24}N_4O_{10}S_2$	49.66 (49.72	4.00 3.95	9.27 9.24	10.61 10.55)	89
11c	$(CH_2)_3NHPNZ$	8*R* *trans*	Powder mp 157—158°C (B–M) [α]D +78° (*c*=0.68, 10% DMF–acetone)	$C_{26}H_{26}N_4O_{10}S_2$	50.48 (50.44	4.24 4.18	9.06 9.01	10.37 10.29)	90
12c	$(CH_2)_3NHPNZ$	8*R* *cis*	Oil, [α]D −77° (*c*=0.65, 10% DMF–acetone)	$C_{26}H_{26}N_4O_{10}S_2$	—	—	—	—	91
11d	$(CH_2)_4NHPNZ$	8*R* *trans*	Powder mp 171—172°C (B–M)	$C_{27}H_{28}N_4O_{10}S_2$	51.26 (51.32	4.46 4.45	8.86 8.78	10.14 10.08)	92
12d	$(CH_2)_4NHPNZ$	8*R* *cis*	Oil	$C_{27}H_{28}N_4O_{10}S_2$	51.26 (51.35	4.46 4.12	8.86 8.58	10.14 9.98)	84
11g	$(CH_2)_3OH$	8*R* *trans*	Needles mp 177—179°C (E.A–M) [α]D +98° (*c*=0.52, THF)	$C_{18}H_{20}N_2O_7S_2$	49.08 (49.22	4.58 4.77	6.36 6.14	14.56 14.79)	88
11h	$(CH_2)_3OH$	8*S* *trans*	Prisms mp 175—178°C (E.A.–M) [α]D +109° (*c*=0.49, THF)	$C_{18}H_{20}N_2O_7S_2$	49.08 (49.13	4.58 4.66	6.36 6.29	14.56 14.68)	84
11i	$(CH_2)_3N_3$	8*R* *trans*	Needles mp 161—162°C [α]D +94° (*c*=0.96, THF)	$C_{18}H_{19}N_5O_6S_2$	46.44 (46.31	4.11 4.37	15.05 15.22	13.78 13.59)	94
11j	$(CH_2)_2OC_2H_5$	8*R* *trans*	Leaflets mp 174—175.5°C (E.A) [α]D +99° (*c*=0.42, THF)	$C_{19}H_{22}N_2O_7S_2$	50.20 (49.67	4.88 4.95	6.16 5.83	14.11 14.20)	89
12j	$(CH_2)_2OC_2H_5$	8*R* *cis*	Prisms mp 126—127°C (B) [α]D −127° (*c*=0.93, $CHCl_3$)	$C_{19}H_{22}N_2O_7S_2$	50.20 (50.07	4.88 4.77	6.16 5.97	14.11 14.30)	81
11k	$(CH_2)_2OC_2H_5$	8*S* *trans*	Oil, [α]D+90° (*c*=0.93, $CHCl_3$)	$C_{19}H_{22}N_2O_7S_2$	50.20 (49.87	4.88 4.93	6.16 6.31	14.11 14.08)	85

a) PNZ, (*p*-nitrobenzyl)oxycarbonyl.
b) *trans*, 5*R*, 6*S*; *cis*, 5*S*, 6*S*.
c) Recrystallization solvents in parentheses: B, benzene; M, methanol; E.A, ethyl acetate.

penem ester **8f** was fully desilylated to **11h** under the same reaction conditions described as above. Analytical and spectral data are given in Tables X and XI.

2-(Alkylthio)-6-(1-hydroxyethyl)penem-3-carboxylic Acids (13a—j and 14a, c, d, i)——As a typical procedure, the preparation of the amino acid **13a** is described. A solution of **11a** (1.20 g) in a mixture of THF (120 ml) and 0.1 M phosphate buffer solution (pH 7.1, 120 ml) was shaken with 10% palladium-charcoal (2.10 g) under an H_2 atmosphere for 9 h. The catalyst was filtered off using Celite and washed with the same buffer solution (20 ml). The filtrate and washings were washed with AcOEt, concentrated *in vacuo* at room temperature to half the initial volume and chromatographed on Diaion HP20AG (Mitsubishi Chemical Industries, Ltd., 40 ml). Fractions eluted with 2—5% acetone–water were collected and lyophilized to give the amino acid **13a** (345 mg, 60%) as a powder. Proceeding exactly as described above, the amino acids **13b—d** and **14a, c, d** were obtained from the protected penem esters **11b—d** and **12a, c, d**, respectively. **13c** was alternatively obtained, under the same reaction conditions, from the azido ester **11i** in 43% yield.

TABLE XI. Spectral Data for *p*-Nitrobenzyl (6*S*)-2-(Alkylthio)-6-(1-hydroxyethyl)penem-3-carboxylates (11 and 12)

Compd.	IR, cm^{-1} (state)	NMR, δ[a] (d_7-DMF)
11a	3425, 3275, 1785, 1720 (sh.), 1690 (KBr)	1.21 (3H, d, 6), 3.3 (4H, br), 3.79 (1H, dd, 6, 2), 4.0 (1H, m), 5.18 (2H, s), 5.20 and 5.54 (1H each, ABq, 14), 5.80 (1H, d, 2)
12a	3400 (br), 1780, 1730, 1700 (br) (liq.)	1.35 (3H, d, 6), 3.10 (2H, m), 3.45 (2H, t-like), 3.82 (1H, dd, 10, 4), 4.24 (1H, m), 5.14 and 5.48 (1H each, ABq, 14), 5.17 (2H, s), 5.72 (1H, d, 4)[b]
11b	3540, 3380, 1785, 1705, 1684 (Nujol)	1.25 (3H, d, 6), 2.9—3.6 (4H, m), 3.88 (1H, dd, 3.5, 1.5), 4.1 (1H, m), 5.18 (2H, s), 5.20 and 5.50 (1H each, ABq, 14.5), 5.71 (1H, d, 1.5)
11c	3400, 3300, 1770, 1720 (sh.), 1690 (KBr)	1.21 (3H, d, 6), 2.02 (2H, m), 3.2 (4H, m), 3.80 (1H, dd, 6, 1.5), 5.29 (2H, s), 5.33 and 5.63 (1H each, ABq, 14.5), 5.82 (1H, d, 1.5)
12c	3350 (br), 1790, 1730, 1705 (liq.)	1.30 (3H, d, 5.5), 1.88 (2H, m), 3.12 (2H, t, 7.5), 3.23 (2H, t, 6), 4.0 (2H, m), 5.22 (2H, s), 5.22 and 5.54 (1H each, ABq, 14.5), 5.87 (1H, d, 4)[b]
11d	3425 (br), 3300, 1780, 1720, 1690 (KBr)	1.21 (3H, d, 6), 1.65 (4H, m), 3.1 (4H, m), 3.82 (1H, dd, 6.5, 1.5), 4.13 (1H, m), 5.23 (2H, s), 5.25 and 5.56 (1H each, ABq, 14), 5.83 (1H, d, 1.5)
12d	3400 (br), 1785, 1730 (sh.), 1700 (br.), (liq.)	1.36 (3H, d, 6), 1.64 (4H, m), 2.8—3.3 (4H, m), 3.82 (1H, dd, 10, 4), 4.24 (1H, m), 5.14 and 5.49 (1H each, ABq, 14), 5.17 (2H, s), 5.73 (1H, d, 4)[b]
11g	3430, 1770, 1692 (Nujol)	1.21 (3H, d, 6), 1.80 (2H, m), 2.88 (2H, m), 3.40 (2H, q, 6), 3.74 (1H, dd, 7, 1.5), 4.00 (1H, m), 4.52 (1H, t, 5.5), 5.21 (1H, d, 6), 5.17 and 5.45 (1H each, ABq, 14), 5.72 (1H, d, 1.5)
11h	3480 (br), 1766, 1690 (KBr)	1.25 (3H, d, 6), 1.80 (2H, m), 2.98 (2H, m), 3.46 (2H, q, 5.5), 3.83 (1H, dd, 3.5, 1.5), 4.0 (1H, m), 4.54 (1H, t, 5.5), 5.21 (1H, d, 6), 5.16 and 5.45 (1H each, ABq, 14), 5.71 (1H, d, 1.5)
11i	3460, 2110, 1772, 1687 (Nujol)	1.21 (3H, d, 6), 1.90 (2H, m), 3.00 (2H, m), 3.42 (2H, t, 6.5), 3.78 (1H, dd, 6, 1.5), 4.0 (1H, m), 5.19 and 5.47 (1H each, ABq, 14), 5.77 (1H, d, 1.5)
11j	3440, 1773, 1689 (Nujol)	1.12 (3H, t, 7), 1.27 (3H, d, 6), 3.25 (2H, m), 3.7 (2H, m), 3.53 (2H, q, 7), 3.91 (1H, dd, 8, 1.5), 5.15 (1H, m), 5.35 (1H, d, 4), 5.34 and 5.65 (1H each, ABq, 14.5), 5.90 (1H, d, 1.5)
12j	3410, 1796, 1788, 1690, 1681 (Nujol)	1.12 (3H, t, 7), 1.41 (3H, d, 6), 2.05 (1H, br s), 3.22 (2H, m), 3.72 (2H, m), 3.55 (2H, q, 7), 3.88 (1H, dd, 10, 4.5), 4.4 (1H, m), 5.22 and 5.55 (1H each, ABq, 14), 5.78 (1H, d, 4.5)[b]
11k	3350, 1793, 1698 ($CHCl_3$)	1.15 (3H, t, 7), 1.35 (3H, d, 6.5), 2.65 (1H, br s), 3.15 (2H, m), 3.65 (2H, m), 3.51 (2H, q, 7), 3.85 (1H, dd, 4.5, 1.5), 4.3 (1H, m), 5.18 and 5.51 (1H each, ABq, 14), 5.67 (1H, d, 1.5)[b]

UV λ_{max}^{EtOH} nm (ε): **11b**, 263(25500), 340(10800); **11j**, 263(17600), 342(11900); **12j**, 262(16900), 337(11400); **11k**, 263(16400), 341(11300).

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons of the *p*-nitrobenzyl group(s) at δ 7.5—8.3 are not given in the table.

b) $CDCl_3$ was used as a solvent.

TABLE XII. (6*S*)-2-(Alkylthio)-6-(hydroxyethyl)penem-3-carboxylic Acids (**13** and **14**)

Compd.	R	Stereo-chemistry[a]	$[\alpha]_D$ (c, H_2O)	UV, $\lambda^{H_2O}_{max}$ nm (ε)	IR, cm^{-1} (KBr)	NMR δ[b] (D_2O)	Yield (%)
13a	$(CH_2)_2NH_2$	8*R* *trans*	+175°(0.44)	253(4790) 321(6130)	3400(br), 1770, 1575	1.34 (3H, d, 6.5), 3.32 (4H, m), 3.90 (1H, dd, 6, 1.5), 4.26 (1H, m), 5.75 (1H, d, 1.5)	60
14a	$(CH_2)_2NH_2$	8*R* *cis*	−205°(0.62)	252(5010) 318(6480)	3400, 1760, 1570	1.40 (3H, d, 6), 3.33 (4H, m), 3.98 (1H, dd, 10, 4), 4.30 (1H, m), 5.80 (1H, d, 4)	51
13b	$(CH_2)_2NH_2$	8*S* *trans*	+198°(0.57)	252(4700) 320(5700)	3400, 1762, 1561	1.34 (3H, d, 6.5), 2.9—3.5 (4H, m), 4.02 (1H, dd, 4, 1.5), 4.25 (1H, m), 5.70 (1H, d, 1.5)[c]	36
13c	$(CH_2)_3NH_2$	8*R* *trans*	+199°(0.49)	254(5020) 322(6620)	3400, 1767, 1572	1.32 (3H, d, 6), 2.05 (2H, m), 3.01 (2H, m), 3.14 (2H, t, 7), 3.94 (1H, dd, 6, 1.5), 4.30 (1H, m), 5.75 (1H, d, 1.5)[c]	49
14c	$(CH_2)_3NH_2$	8*R* *cis*	−212°(0.18)	—	3400(br), 1770, 1570	1.39 (3H, d, 6), 2.08 (2H, m), 2.8—3.3 (4H, m), 3.98 (1H, dd, 10, 4), 4.30 (1H, m), 5.80 (1H, d, 4)[c]	53
13d	$(CH_2)_4NH_2$	8*R* *trans*	+210°(0.39)	254(5030) 322(6680)	3500, 1780, 1570	1.30 (3H, d, 6), 1.78 (4H, m), 3.02 (4H, m), 3.90 (1H, dd, 6, 1.5), 4.26 (1H, m), 5.68 (1H, d, 1.5)[c]	62
14d	$(CH_2)_4NH_2$	8*R* *cis*	−190°(0.43)	252(5190) 318(6760)	3500, 1760, 1560	1.41 (3H, d, 6), 1.80 (4H, m), 3.04 (4H, m), 3.98 (1H, dd, 10, 4), 4.30 (1H, m), 5.80 (1H, d, 4)[c]	58
13e	$(CH_2)_2NHCOCH_3$ Na salt	8*R* *trans*	+127°(0.49)	255(4020) 322(5190)	3400(br), 1760, 1635, 1580	1.25 (3H, d, 6.5), 2.00 (3H, s), 3.11 (2H, t, 6), 3.50 (2H, t), 3.91 (1H, dd, 6, 1.5), 4.25 (1H, m), 5.68 (1H, d, 1.5)[c]	90
13f	$(CH_2)_2NHCOCH_3$ Na salt	8*S* *trans*	+168°(0.29)	—	3400, 1760, 1640, 1585	1.33 (3H, d, 6), 1.99 (3H, s), 3.10 (2H, m), 3.48 (2H, m), 3.96 (1H, dd, 4, 1.5), 4.24 (1H, m), 5.64 (1H, d, 1.5)[c]	67
13g	$(CH_2)_3OH$ Na salt	8*R* *trans*	+195°(0.38)	254(5190) 323(6810)	3400, 1760, 1583	1.30 (3H, d, 6), 1.92 (2H, m), 2.99 (2H, m), 3.70 (2H, t, 6), 3.88 (1H, dd, 6, 1.5), 4.25 (1H, m), 5.68 (1H, d, 1.5)[c]	48
13h	$(CH_2)_3OH$ Na salt	8*S* *trans*	+167°(0.26)	—	3400, 1760, 1582	1.33 (3H, d, 6.5), 1.92 (2H, m), 2.99 (2H, m), 3.70 (2H, t, 6), 3.96 (1H, dd, 4, 1.5), 4.23 (1H, m), 5.64 (1H, d, 1.5)[c]	37
13i	$(CH_2)_2OC_2H_5$ Na salt	8*R* *trans*	+183°(0.57)	254(5520) 322(7220)	3350, 1770, 1590	1.20 (3H, t, 6.5), 1.33 (3H, d, 7), 3.15 (2H, m), 3.70 (2H, q, 6.5), 3.9 (2H, m), 4.00 (1H, dd, 6, 1.5), 4.4 (1H, m), 5.81 (1H, d, 1.5)	66
14i	$(CH_2)_2OC_2H_5$ Na salt	8*R* *cis*	−192°(0.53)	252(5660) 319(7620)	3380, 1764, 1588	1.27 (3H, t, 7), 1.47 (3H, d, 6), 3.3 (2H, m), 3.72 (2H, q, 7), 3.9 (2H, m), 4.03 (1H, dd, 10, 4), 4.4 (1H, m) 5.88 (1H, d, 4)	83
13j	$(CH_2)_2OC_2H_5$ Na salt	8*S* *trans*	+112°(0.38)	255(5580) 322(7290)	3340, 1769, 1587	1.24 (3H, t, 7), 1.39 (3H, d, 6.5), 3.25 (2H, m), 3.73 (2H, q, 7), 3.85 (2H, m), 4.05 (1H, dd, 4.5, 1.5), 4.35 (1H, m), 5.78 (1H, d, 1.5)	87

[a] *trans*, 5*R*, 6*S*; *cis*, 5*S*, 6*S*.

[b] Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Tetramethylsilane was used as an external standard.

[c] 100 MHz data.

The penem acids **13g**—**j** and **14i** were obtained as sodium salts from the corresponding esters in the same manner, the reactions being completed in shorter times (2.5—3 h). Optical rotations and spectral data are given in Table XII.

(5*R*, 6*S*)-2-[(2-Acetamidoethyl)thio]-6-[(*R* and *S*)-1-hydroxyethyl]penem-3-carboxylic Acids (13e and 13f)——$NaHCO_3$ (0.7 mg, 0.068 mmol) and acetic anhydride (4.5 mg, 0.044 mmol) were added to a stirred solution of **13a** (10 mg, 0.034 mmol) in a mixture of water (1 ml) and THF (0.5 ml) at 0°C. After being stirred for 30 min, the mixture was diluted with 0.1 M phosphate buffer solution (3 ml) and washed with AcOEt. The aqueous layer was concentrated to *ca.* 2 ml, and charged on Diaion HP20AG (8 ml). The eluate with 1% acetone–water was lyophilized to give the 8*R* acetamido acid **13e** as its sodium salt (11 mg, 90%).

Similarly, acetylation of **13b** afforded the 8*S* acetamido acid **13f** (sodium salt) in 67% yield.

Spectral data for **13e** and **13f** are given in Table XII.

References and Notes

1) Part IV: A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **29**, 2899 (1981).
2) G. Albers-Shönberg, B.H. Arison, O.D. Hensens, J. Hirshfield, K. Hoogsteen, E.A. Kaczka, R.E. Rhodes, J.S. Kahan, F.M. Kahan, R.W. Ratcliffe, E. Walton, L.J. Ruswinkel, R.B. Morin, and B.G. Christensen, *J. Am. Chem. Soc.*, **100**, 6491 (1978).
3) H. Kropp, J.S. Kahan, F.M. Kahan, J. Sundelof, G. Darland, and J. Birnbaum, 16th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill., 1976, Abstr. p. 228.
4) *a*) S, Oida. A. Yoshida, T. Hayashi, N. Takeda, and E. Ohki, *Chem. Pharm. Bull.*, **28**, 3232 (1980). *b*) *Idem*, *ibid.*, 3258 (1980). Also see M. Lang, K. Prasad, J. Gosteli, and R. B. Woodward, *Helv. Chim. Acta*, **63**, 1093 (1980).
5) A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **29**, 1854 (1981).
6) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, *J. Antibiotics*, **33**, 107 (1980).
7) Numbering is that of the corresponding atoms in "1-thiathienamycin".
8) R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R.B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972).
9) A similar betaine intermediate was supposed to be involved in racemization and ring cleavage of the oxapenem compound derived from natural clavulanic acid: P.C. Cherry, C.E. Newall, and N.S. Watson, *J.C.S. Chem. Comm.*, **1978**, 469.
10) G. Just and T.J. Liak, *Can. J. Chem.*, **56**, 211 (1978).
11) The same trend, *i.e.*, that the 8*R* isomer shows much higher activity than the 8*S* isomer, was also observed in the 2-unsubstituted 6-(hydroxyethyl)penem-3-carboxylic acid system: H.R. Pfaendler, J. Gosteli, and R.B. Woodward, *J. Am. Chem. Soc.*, **102**, 2039 (1980).
12) C.A. Rojahn and G. Lemme, *Archiv der Pharmazie*, **1925**, 612.
13) I. Shinkai, T. Liu, R. Reamer, and M. Sletzinger, *Synthesis*, **1980**, 924.
14) D.J. Martin and C.C. Greco, *J. Org. Chem.*, **33**, 1275 (1968).