Articles

A Stereoselective Synthesis of 1β-Aminocarbapenems

Kyung Jae Seo, Tae Ho Lee, and Youn Young Lee*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, Korea
Received February 13, 2001

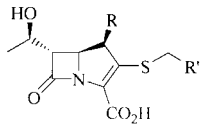
A stereoselective synthesis of 1β-aminocarbapenems (**11a-c**) starting from 4-acetoxy-2-azetidinone derivative **4** is described. 4-Acetoxy-2-azetidinone derivative (**4**) was reacted with the lithium enolate of benzophenone imine of glycine phenyl ester (**5f**) to give alkylated product (***R***)-**6f** in good yield with high diastereoselectivity. The alkylated product (***R***)-**6f** was transformed to thioesters (**7a-c**) by transesterification with thiols. Thioesters (**7a-c**) were converted to their oxalimides (**8a-c**), followed by the phosphite-mediated reductive cyclization to give carbapenems (**9a-c**). Removal of all protecting groups of carbapenems (**9a-c**) afforded 1β-aminocarbapenems (**11a-c**).

Keywords : Carbapenems, Phosphite-mediated reductive cyclization, Benzophenone imines of glycine esters.

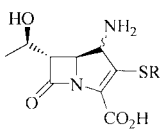
Introduction

Since the discovery of thienamycin (**1**),[1] extensive efforts have been devoted to the development of new carbapenem antibiotics. Shih *et al.* at Merck developed 1β-methylcarbapenem (**2**) which possesses fairly strong stability against renal dehydropeptidase-I and chemical stability.[2] In addition, they reported the synthesis of 1-heteroatom-substituted carbapenems, including 1-aminocarbapenems (**3**), which are effective against Gram-positive and Gram-negative bacteria.[3] Their approach to the synthesis of 1-aminocarbapenems (**3**) involves introduction of the amino group at the C-4 side chain of (3*S*,4*S*)-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-4-methoxycarbonylmethyl-2-azetidinone by bromination, substitution with azide, and reduction in sequence and cyclization *via* the Merck carbene insertion reaction.

We have been interested in a short route to a stereoselective synthesis of 1-aminocarbapenems by alkylation at the C-4 position of 4-acetoxy-2-azetidinone derivative (**4**) with lithium enolate of *N*-protected glycine ester followed by cyclization. We have shown that the alkylation of **4** with the lithium enolates of benzophenone imines of glycine esters (**5**) gave alkylation products (**6**) in high yields.[4] Especially the alkylation of **4** with that of glycine phenyl ester (**5f**) was found to be highly diastereoselective. The present study deals with synthesis of 1β-aminocarbapenems from the alkylation

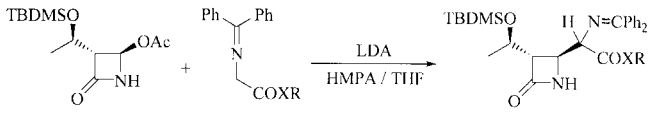


1. R = H, R' = CH_2NH_2
2. R = CH_3, R' = $C(=NH_2)N(CH_3)_2$



3. R = Alkyl, Aryl

Figure 1



4 **5** **6**

a XR = OMe
b XR = OEt
c XR = OAllyl
d XR = OBn
e XR = OPNB
f XR = OPh
g XR = SEt

Scheme 1

product (***R***)-**6f** by the phosphite-mediated reductive cyclization method.[5]

Results and Discussion

The lithium enolate of *N*-(diphenylmethylene)glycine phenyl ester (**5f**), generated with LDA in THF at -78 °C, was reacted with 4-acetoxy-2-azetidinone derivative (**4**) in THF containing a small amount of HMPA at room temperature for 1 h to give a diastereomeric mixture of C-4 alkylated 2-azetidinones (**6f**) in 81% yield. The ratio of the two diastereomers, (***R***)-**6f** and (***S***)-**6f**, was 93 : 7. Pure (***R***)-**6f** was isolated in 75% yield from the diastereomeric mixture by chromatography on a silica gel column with hexane-dichloromethane-ethyl acetate (15 : 4 : 1).

The stereochemistry of the newly formed chiral center at C-4 side chain of the two diastereomers was tentatively assigned by their 2D NOESY spectra on the basis of conformational preference due to hydrogen bonding of the amide NH with the ester carbonyl group.[6] The NOESY spectrum of (***R***)-**6f** showed that a NOE was observed between the α-hydrogen (δ 4.40 ppm) at the side chain and C-4 hydrogen (δ 4.47 ppm) of β-lactam moiety, whereas that of (***S***)-**6f** showed that a NOE was observed between the α-hydrogen

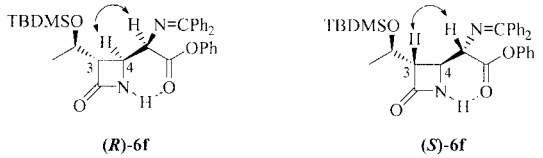
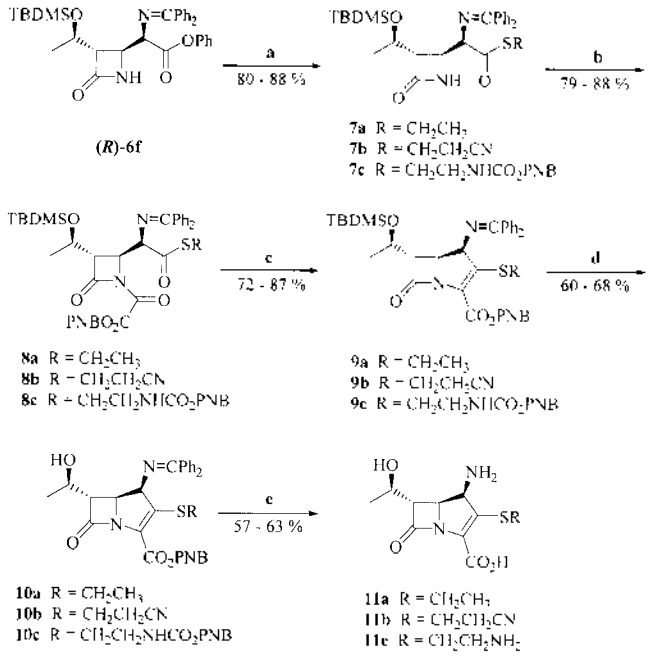


Figure 2

(δ 4.48 ppm) at the side chain and C-3 hydrogen (δ 3.04 ppm) of β-lactam moiety.

The alkylation product **(*R*)-6f** was readily converted to thioesters without deprotection of the *N*-diphenylmethylene group by reaction with thiols in the presence of a base. In the first place, we examined the transesterification of **(*R*)-6f** with ethanethiol in the presence of various bases such as pyridine, triethylamine, CsF, and DBU, and found that DBU was the most efficient. Thus, **(*R*)-6f** was reacted with ethanethiol, 3-mercaptopropionitrile, and 2-(*p*-nitrobenzyloxycarbonylamino)ethanethiol[7] in the presence of DBU at room temperature to give thioesters (**7a-c**) in 80-88% yields.

We then obtained oxalimides (**8a-c**) in 79-88% yields by acylation of the amino group of **7a-c** with *p*-nitrobenzyloxalyl chloride[8] in the presence of triethylamine at room temperature. The reaction should be carried out under anhydrous conditions by using excess triethylamine, because the *N*-diphenylmethylene group is easily deprotected under acidic conditions. In the next step these oxalimides were smoothly cyclized to carbapenems by the phosphite-mediated reductive cyclization method. Thus oxalimides (**8a-c**) were reacted with 7 equiv. of triethyl phosphite for 4 h at 80 °C, followed by reaction with a catalytic amount of hydroquinone for 48 h at 105 °C to give carbapenems (**9a-c**) in 72-87% yields.



Scheme 2. Reagents and conditions: (a) RSH, DBU, CH_2Cl_2, rt, 8 h. (b) $ClCOCO_2PNB$, NEt_3, CH_2Cl_2, rt, 5 h. (c) $P(OEt)_3$, cat. hydroquinone, toluene, 105 °C, 48 h. (d) NH_4F-HF, NMP-DMF, rt, 72 h. (e) H_2, 5% Pd/C, MeOH, rt, 2 h.

Previously we assigned the configuration at the chiral center at the C-4 side chain of **(*R*)-6f** to be *R* according to 2D NOESY study. The configuration at the C-1 position of carbapenem **9a**, which is the same chiral center as the C-4 side chain of **(*R*)-6f**, was again assigned through 2D NOESY study. The NOESY spectrum of **9a** showed that a NOE was observed between C-1 hydrogen (δ 5.03 ppm) and C-5 hydrogen (δ 4.12 ppm) of carbapenem **9a**. Consequently, the configuration at the C-1 position of **9a** was unambiguously determined to be *R*.

The TBDMS, diphenylmethylene and *p*-nitrobenzyl groups of **9a-c** were successfully deprotected to afford the desired product, 1-amino-2-carbapenem-3-carboxylates (**11a-c**). The deprotection of the TBDMS group of **9a-c** was accomplished by treatment with 6 equiv. of ammonium bifluoride at room temperature for 72 h to give **10a-c** in 60-68% yields.[9] The diphenylmethylene and *p*-nitrobenzyl groups of **10a-c** were removed simultaneously by catalytic hydrogenolysis. Compounds **10a-c** were dissolved in methanol and hydrogenolyzed in the presence of 5% Pd-C under hydrogen gas for 2 h at room temperature to give 1β-aminocarbapenems (**11a-c**) in 57-63% yields.

Experimental Section

Melting points were measured on a Electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a 300, a 400 or a 500 MHz instrument in $CDCl_3$ or CD_3OD as solvent. ^{13}C NMR spectra were obtained on a 75, a 100 or a 125 MHz instrument in $CDCl_3$ or CD_3OD as solvent. The spectral data were given in δ (ppm) units downfield from TMS. IR spectra were recorded on a Bruker IFS-48 FT-IR spectrophotometer. Mass spectra were recorded on a Bruker Data System Winchester 24 spectrometer. THF and Et_2O were distilled in the presence of sodium and benzophenone. Dichloromethane was distilled over calcium hydride. Other solvents are first grade and distilled before use. All the chemicals were purchased from Aldrich Chemical Co. or Merck Co..

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(diphenylmethylideneamino)(phenoxycarbonyl)methyl]-2-azetidinone (6f). To a solution of *N*-(diphenylmethylene)-glycine phenyl ester (**5f**, 1.45 g, 4.59 mmol) in THF (25 mL) at -78 °C was added an 2.0 *M* solution of LDA in THF (2.60 mL, 5.20 mmol) with stirring under nitrogen atmosphere. The mixture was stirred at -78 °C for 10 min. After addition of HMPA (1.30 mL, 7.40 mmol) and a solution of (3*R*,4*R*)-4-acetoxy-3-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**4**, 1.37 g, 4.76 mmol) in THF (12 mL), the mixture was stirred at -78 °C for 10 min and at room temperature for 1 h. The reaction was then quenched with saturated NH_4Cl solution (6 mL) and the mixture was extracted with Et_2O (50 mL × 2). The Et_2O solution was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated to give an oily residue. Column chromatography of the residue

over silica gel with hexane-dichloromethane-ethyl acetate (15 : 4 : 1) as an eluent gave **(*R*)-6f** (1.86 g, 74.9%) and **(*S*)-6f** (140 mg, 5.6%). **(*R*)-6f**: $[\alpha]_D^{18}$ -105.0° (c 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.88 (s, 9H, *t*-Bu), 1.19 (d, J = 6.3 Hz, 3H, $CHCH_3$), 2.89 (t, J = 2.0 Hz, 1H, H-3), 4.26 (dd, J = 2.5, 6.3 Hz, 1H, $CHCH_3$), 4.40 (d, J = 7.9 Hz, 1H, $NCHCO_2$), 4.47 (dd, J = 2.1, 7.9 Hz, 1H, H-4), 5.95 (s, 1H, NH), 7.06-7.70 (m, 15H, 3 Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.17, -4.52, 17.82, 22.76, 25.64, 50.75, 62.14, 64.14, 68.42, 121.17, 125.97, 127.58, 127.97, 128.74, 128.89, 128.98, 129.28, 130.74, 135.63, 138.52, 150.26, 168.08, 168.79, 172.48; IR (neat) 3237, 2956, 2857, 1758, 1624, 1486, 1251, 1186 cm^{-1}; MS (CI, CH_4) m/z 543 ($[M+H]^-$, 100), 527 (30), 485 (32), 421 (12), 182 (15), 95 (27); HRMS (CI, CH_4) Calcd for $C_{32}H_{39}N_2O_4Si$ $(M+H)^-$: 543.2680, Found: 543.2675. **(*S*)-6f**: $[\alpha]_D^{18}$ +108.3° (c 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.15 (d, J = 6.4 Hz, 3H, $CHCH_3$), 3.04 (d, J = 1.6 Hz, 1H, H-3), 4.24 (m, 1H, $CHCH_3$), 4.34 (dd, J = 2.1, 5.4 Hz, 1H, H-4), 4.48 (d, J = 5.4 Hz, 1H, $NCHCO_2$), 6.00 (s, 1H, NH), 7.03-7.71 (m, 15H, 3 Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.08, -4.36, 17.89, 22.70, 25.71, 51.59, 61.04, 64.93, 67.25, 121.23, 126.15, 127.68 128.20, 128.82, 129.02, 129.09, 129.47, 131.02, 135.76, 138.80, 150.26, 168.04, 168.51, 173.73; IR (neat) 3238, 2935, 2858, 1761, 1623, 1486, 1251, 1190 cm^{-1}; MS (CI, CH_4) m/z 543 ($[M+H]^-$, 100), 527 (26), 485 (19), 421 (8), 182 (15), 95 (32); HRMS (CI, CH_4) Calcd for $C_{32}H_{39}N_2O_4Si$ $(M+H)^+$: 543.2680, Found: 543.2673.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-(diphenylmethylideneamino)(ethylthiocarbonyl)methyl]-2-azetidinone (7a). (3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-(diphenylmethylideneamino)(phenoxycarbonyl)methyl]-2-azetidinone (**(*R*)-6f**; 1.40 g, 2.58 mmol) was dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. Ethanethiol (0.60 mL, 7.86 mmol) and DBU (0.06 mL, 0.397 mmol) were added with stirring. The mixture was stirred for 30 min at the same temperature and for 8 h at room temperature. Evaporation of the solvent and excess ethanethiol gave an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (9 : 1) as an eluent to afford 1.16 g (88.1%) of **7a** as a colorless oil. $[\alpha]_D^{18}$ +43.85° (c 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.09 (d, J = 6.4 Hz, 3H, $CHCH_3$), 1.26 (t, J = 7.5 Hz, 3H, SCH_2CH_3), 2.87 (q, J = 7.5 Hz, 2H, SCH_2CH_3), 3.14 (m, 1H, H-3), 4.18 (dd, J = 2.0, 6.1 Hz, 1H, H-4), 4.21 (m, 1H, $CHCH_3$), 4.22 (d, J = 6.1 Hz, 1H, NCHCO), 5.78 (s, 1H, NH), 7.14-7.73 (m, 10H, 2 Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.19 -4.53, 14.13, 17.81, 22.45, 22.87, 25.64, 51.89, 61.16, 63.95, 73.50, 127.36, 128.06, 128.76, 128.96, 130.86, 135.23, 138.52, 167.96, 172.41, 200.66; IR (neat) 3232, 2936, 2859, 1761, 1674, 1623, 1455, 1256 cm^{-1}; MS (CI, CH_4) m/z 511 ($[M+H]^+$, 100), 495 (31), 453 (27), 421 (12) 182 (7), 85 (12); HRMS (CI, CH_4) Calcd for $C_{28}H_{39}N_2O_3SiS$ $(M+H)^-$: 511.2451, Found: 511.2451.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-(diphenylmethylideneamino)(2-cyanoethylthiocarbonyl)methyl]-2-azetidinone (7b). Compound **(*R*)-6f** (501 mg, 0.922 mmol) was reacted with 3-mercaptopropionitrile (261 mg, 3.00 mmol) and DBU (0.03 mL, 0.199 mmol) by the same procedure as described for the preparation of **7a**. After evaporation of the solvent, the oily residue was purified by chromatography on silica gel with hexane-ethyl acetate (6 : 1) as an eluent to afford 406 mg (82.2%) of **7b** as a colorless oil. $[\alpha]_D^{19}$ +59.25° (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, *t*-Bu), 1.07 (d, J = 6.4 Hz, 3H, $CHCH_3$), 2.65 (m, 2H, SCH_2CH_2CN), 3.09 (m, 2H, SCH_2CH_2CN), 3.16 (d, J = 2.2 Hz, 1H, H-3), 4.15 (dd, J = 2.2, 5.6 Hz, 1H, H-4), 4.21 (dd, J = 2.4, 6.4 Hz, 1H, $CHCH_3$), 4.28 (d, J = 5.6 Hz, 1H, NCHCO), 5.92 (s, 1H, NH), 7.13-7.73 (m, 10H, 2 Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.17 -4.44, 17.88, 18.18, 22.55, 24.21, 25.68, 51.83, 61.27, 63.84, 73.17, 117.78, 127.35, 128.14, 128.25, 128.95, 129.02, 129.10, 129.23, 131.29, 134.94, 138.21 167.73, 173.30, 200.30; IR (neat) 3230, 2216, 1765, 1681, 1650, 1540, 1458 cm^{-1}; MS (CI, CH_4) m/z 536 ($[M+H]^+$, 100), 520 (15), 478 (14), 423 (10) 182 (14); HRMS (CI, CH_4) Calcd for $C_{29}H_{38}N_3O_3SiS$ $(M+H)^+$: 536.2404, Found: 536.2403.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-{(*R*)-(diphenylmethylideneamino)[2-(*p*-nitrobenzyloxycarbonylamino)ethylthiocarbonyl]methyl}-2-azetidinone (7c). Compound **(*R*)-6f** (300 mg, 0.554 mmol) was reacted with 2-(*p*-nitrobenzyloxycarbonylamino)ethanethiol (304 mg, 1.19 mmol) and DBU (0.02 mL, 0.132 mmol) by the same procedure as described for the preparation of **7a**. After evaporation of the solvent, the residue was purified by chromatography on silica gel with hexane-ethyl acetate (4 : 1) as an eluent to afford 311 mg (79.8%) of **7c** as a colorless oil. $[\alpha]_D^{24}$ +31.16° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.83 (s, 9H, *t*-Bu), 1.06 (d, J = 6.3 Hz, 3H, $CHCH_3$), 3.01 (m, 2H, SCH_2CH_2NH), 3.06 (m, 1H, H-3), 3.37 (m, 2H, SCH_2CH_2NH), 4.16 (dd, J = 1.7, 6.3 Hz, 1H, H-4), 4.21 (m, 1H, $CHCH_3$), 4.23 (d, J = 6.3 Hz, 1H, NCHCO), 5.16 (s, 2H, CO_2CH_2), 5.61 (s, 1H, SCH_2CH_2NH), 6.33 (s, 1H, $NHCO_2$), 7.12-7.48 (m, 10H, 2 Ph) 7.70 (d, J = 8.6 Hz, 2H, $C_6H_4NO_2$), 8.15 (d, J = 8.6 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.52, -3.78, 18.53, 23.23, 26.32, 29.20, 41.15, 52.47, 62.23, 64.54, 65.53, 74.48, 124.28, 128.02, 128.67, 128.88, 129.61, 129.70, 129.83, 131.84, 135.72, 138.98, 144.59, 156.52, 168.82, 173.46, 201.65; IR (neat) 3248, 2938, 2360, 1754, 1735, 1673, 1624, 1531, 1449 cm^{-1}; MS (CI, CH_4) m/z 705 ($[M+H]^+$, 100), 689 (29), 647 (21), 615 (15); HRMS (CI, CH_4) Calcd for $C_{36}H_{45}N_4O_7SiS$ $(M+H)^-$: 705.2778, Found: 705.2776.

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-(diphenylmethylideneamino)(ethylthiocarbonyl)methyl]-1-(*p*-nitrobenzyloxalyl)-2-azetidinone (8a). Compound **7a** (1.01 g, 1.98 mmol) was dissolved in CH_2Cl_2 (25 mL) at 0 °C. After addition of triethylamine (0.95 mL, 6.75 mmol) and *p*-nitrobenzyloxalyl chloride (1.45 g, 5.91 mmol), the mixture was stirred 30 min at the same temperature and for 5

h at room temperature, and diluted with CH_2Cl_2 (50 mL). The CH_2Cl_2 solution was washed with aqueous NaCl solution and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (15 : 1) as an eluent to afford 1.25 g (88.0%) of **8a** as a colorless oil. $[\alpha]_D^{22}$ -66.94° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.03 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.78 (s, 9H, *t*-Bu), 1.12 (d, J = 6.4 Hz, 3H, $CHCH_3$), 1.24 (t, J = 7.4 Hz, 3H SCH_2CH_3), 2.87 (q, J = 7.4 Hz, 2H, SCH_2CH_3), 4.17 (m, 1H, H-3), 4.39 (m, 1H, $CHCH_3$), 4.79 (m, 1H, H-4), 4.90 (d, J = 2.5 Hz, 1H, NCHCO), 5.30 (s, 2H, CO_2CH_2), 7.05-7.42 (m, 10H, 2 Ph), 7.58 (d, J = 8.3 Hz, 2H, $C_6H_4NO_2$), 8.02 (d, J = 8.3 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.93, -3.92, 14.71, 18.14, 22.11, 23.59, 25.98, 53.91, 59.86, 64.67, 66.92, 69.57, 124.16, 127.89, 128.67, 129.05, 129.22, 129.56, 129.67, 131.70, 135.26, 139.10, 141.42, 148.25, 155.02, 159.94, 166.09, 175.90, 199.48; IR (neat) 2939, 2862, 1808, 1756, 1698, 1675, 1619, 1451, 1383 cm^{-1}; MS (CI, CH_4) m/z 718 ([M+H]$^+$, 100), 702 (27), 660 (29), 628 (23) 586 (7), 379 (5).

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-[(*R*)-(diphenylmethylideneamino)(2-cyanoethylthiocarbonyl)-methyl]-1-(*p*-nitrobenzyloxalyl)-2-azetidinone (8b). The same procedure as described for the preparation of **8a** was employed with **7b** (349 mg, 0.651 mmol), *p*-nitrobenzyloxalyl chloride (533 mg, 2.19 mmol) and triethylamine (0.35 mL, 2.49 mmol) to give an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (9 : 1) as an eluent to afford 384 mg (79.4%) of **8b** as a colorless oil. $[\alpha]_D^{17}$ +38.59° (c 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.79 (s, 9H, *t*-Bu), 1.10 (d, J = 6.4 Hz, 3H, $CHCH_3$), 2.64 (m, 2H, SCH_2CH_2CN), 3.06 (m, 2H, SCH_2CH_2CN), 4.06 (t, J = 2.7 Hz, 1H, H-3), 4.36 (m, 1H, $CHCH_3$), 4.76 (m, 1H, H-4), 4.93 (d, 1H, J = 2.5 Hz, NCHCO), 5.21 (s, 2H, CO_2CH_2), 7.10-7.67 (m, 12H, 2 Ph, $C_6H_4NO_2$), 8.12 (d, J = 8.5 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.42, -4.50, 17.61, 17.87, 21.67, 24.38, 25.47, 54.01, 59.21, 64.01, 67.05, 69.09, 117.59, 124.19, 127.35, 128.17, 128.68, 129.15, 129.22, 129.64, 130.18, 131.36, 134.51, 138.30, 140.24, 147.85, 152.55, 159.71, 164.50, 176.29, 198.70; IR (neat) 2910, 2850, 2250, 1810, 1755, 1705, 1690, 1620, 1445, 1385 cm^{-1}; MS (CI, CH_4) m/z 743 ([M+H]$^+$, 100), 727 (10), 685 (11), 404 (13), 182 (17).

(3*S*,4*S*)-3-[(*R*)-1-(*t*-Butyldimethylsilyloxy)ethyl]-4-{(*R*)-(diphenylmethylideneamino)[2-(*p*-nitobenzyloxycarbonyl-amino)ethylthiocarbonyl]methyl}-1-(*p*-nitrobenzyloxalyl)-2-azetidinone (8c). The same procedure as described for the preparation of **8a** was employed with **7c** (276 mg, 0.391 mmol), *p*-nitrobenzyloxalyl chloride (320 mg, 1.31 mmol) and triethylamine (0.25 mL, 1.78 mmol) to give an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (3 : 1) as an eluent to afford 280 mg (78.5%) of **8c** as a colorless oil. $[\alpha]_D^{24}$ -43.94° (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.77 (s, 9H, *t*-Bu), 1.08 (d, J = 6.3 Hz, 3H, $CHCH_3$), 3.03 (m, 2H, SCH_2CH_2NH), 3.37 (m, 2H, SCH_2CH_2NH), 4.07 (d, J = 3.2 Hz, 1H, H-3), 4.35 (m, 1H, $CHCH_3$), 4.74 (m, 1H, H-4), 4.83 (s, 2H, CO_2CH_2), 4.90 (d, J = 2.6 Hz, 1H, NCHCO), 5.18 (s, 2H, CO_2CH_2), 5.31 (s, 1H, SCH_2CH_2NH), 7.04-7.49 (m, 10H, 2 Ph), 7.53-8.22 (m, 8H, 2 $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.72, -3.74, 18.33, 22.37, 26.17, 29.25, 30.34, 32.56, 41.15, 64.56, 64.80, 65.92, 124.34, 124.40, 127.60, 128.07, 128.78, 128.96, 129.37, 129.49, 129.81, 130.00, 132.15, 135.31, 139.10, 141.56, 144.38, 148.50, 148.96, 156.39, 176.41, 199.81; IR (neat) 3350, 2911, 2358, 1807, 1751, 1740-1660, 1617, 1522, 1388 cm^{-1}; MS (CI, CH_4) m/z 912 ([M+H]$^+$, 100), 786 (13), 744 (25), 533 (16), 182 (35).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-(*t*-butyldimethylsilyloxy)-ethyl]-1-diphenylmethylideneamino-2-ethylthio-2-carba-penem-3-carboxylate (9a)**. Compound **8a** (783 mg, 1.09 mmol) was dissolved in toluene (40 mL) under nitrogen gas. After addition of triethyl phosphite (1.25 mL, 7.14 mmol) the mixture was stirred for 4 h at 80 °C. Then hydroquinone (15 mg) was added and the mixture was stirred for 48 h at 105 °C. Evaporation of the solvent gave an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (12 : 1) as an eluent to afford 648 mg (86.7%) of **9a** as a pale yellow oil. $[\alpha]_D^{23}$ +1.02° (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05 (s, 3H, $SiCH_3$), 0.04 (s, 3H, $SiCH_3$), 0.73 (s, 9H, *t*-Bu), 1.13 (t, J = 7.4 Hz, 3H, SCH_2CH_3), 1.32 (d, J = 6.3 Hz, 3H, $CHCH_3$), 2.58-2.90 (m, 2H, SCH_2CH_3), 3.14 (dd, J = 2.3, 8.2 Hz, 1H, H-6), 4.12 (dd, J = 2.3, 7.1 Hz, 1H, H-5), 4.21 (m, 1H, $CHCH_3$), 5.03 (d, J = 7.1 Hz, 1H, H-1), 5.24 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 5.48 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 7.30-7.62 (m, 12H, 2 Ph, $C_6H_4NO_2$), 8.16 (d, J = 8.7 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.26, -3.97, 15.04, 18.34, 23.70, 26.14, 61.15, 64.49, 65.57, 68.05, 75.05, 124.08, 125.74, 126.29, 128.49, 128.67, 128.94, 129.38, 129.43, 130.05, 131.39, 135.82, 139.11, 143.65, 147.95, 151.34, 160.97, 171.79, 175.05; IR (neat) 2936, 2860, 2359, 1782, 1710, 1611, 1551, 1448 cm^{-1}; MS (EI) m/z 685 (M$^+$, 23), 628 (22), 527 (33), 485 (23), 466 (21), 391 (19), 347 (12), 286 (15), 208 (9), 180 (82), 159 (52), 73 (100); HRMS (CI, CH_4) Calcd for $C_{37}H_{44}N_3O_6SiS$ (M+H)$^+$: 686.2720, Found: 686.2720.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-(*t*-butyldimethylsilyl-oxy)ethyl]-2-(2-cyanoethylthio)-1-diphenylmethylidene-amino-2-carbapenem-3-carboxylate (9b)**. The same procedure as described for the preparation of **9a** was employed with **8b** (291 mg, 0.392 mmol), triethyl phosphite (0.50 mL, 2.86 mmol) and hydroquinone (18 mg) to give an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (7 : 1) as an eluent to afford 216 mg (77.6%) of **9b** as a pale yellow oil. $[\alpha]_D^{19}$ +4.97° (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.78 (s, 9H, *t*-Bu), 1.29 (d, J = 6.1 Hz, 3H, $CHCH_3$), 2.59 (m, 2H, SCH_2CH_2CN), 2.82 (m, 1H, $SCH_aH_bCH_2CN$), 3.03 (dd, J = 2.4, 7.6 Hz, 1H, H-6), 3.28 (m, 1H, $SCH_aH_bCH_2CN$), 4.11 (dd, J = 2.4, 7.3 Hz, 1H, H-5), 4.17 (m, 1H, $CHCH_3$), 5.02 (d, J = 7.3 Hz, 1H, H-1), 5.28

(d, J = 13.6 Hz, 1H, $CO_2CH_aH_b$), 5.51 (d, J = 13.6 Hz, 1H, $CO_2CH_aH_b$), 7.26-7.66 (m, 12H, 2 Ph, $C_6H_4NO_2$), 8.19 (d, J = 8.7 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.80, -4.40, 17.91, 18.99, 23.03, 25.68, 28.16, 60.16, 64.58, 65.98, 67.04, 75.85, 117.52, 128.09, 128.33, 128.72, 128.89, 129.48, 130.85, 131.13, 131.35, 135.32, 138.27, 142.84, 143.95, 148.05, 151.34, 160.27, 172.09, 173.83; IR (neat) 2920, 2850, 2250, 1785, 1725, 1620, 1460, 1380 cm^{-1}; MS (EI) m/z 710 (M^+, 1), 630 (2), 495 (2), 480 (20), 377 (38), 316 (36), 208 (60), 136 (79), 75 (100); HRMS (CI, CH_4) Calcd for $C_{38}H_{43}N_4O_6SiS$ $(M+H)^+$: 711.2673, Found: 711.2670.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-(*t*-butyldimethylsilyloxy)ethyl]-1-diphenylmethylideneamino-2-[2-(*p*-nitrobenzyloxycarbonylamino)ethylthio]-2-carbapenem-3-carboxylate (9c)**. The same procedure as described for the preparation of **9a** was employed with **8c** (212 mg, 0.232 mmol), triethyl phosphite (0.30 mL, 1.72 mmol) and hydroquinone (15 mg) to give an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (3 : 1) as an eluent to afford 148 mg (72.3%) of **9c** as a pale yellow oil. $[\alpha]_D^{16}$ +55.75° (c 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.78 (s, 9H, *t*-Bu), 1.29 (d, J = 6.1 Hz, 3H, $CHCH_3$), 2.76 (m, 1H, $SCH_aH_bCH_2NH$), 3.00 (m, 2H, $SCH_aH_bCH_2NH$, H-6), 3.24 (m, 2H, SCH_2CH_2NH), 4.11 (dd, J = 2.4, 7.3 Hz, 1H, H-5), 4.16 (m, 1H, $CHCH_3$), 4.83 (s, 2H, CO_2CH_2), 4.95 (d, J = 7.3 Hz, 1H, H-1), 5.21 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 5.28 (s, 1H, SCH_2CH_2NH), 5.44 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 7.26-8.23 (m, 18H, 2 Ph, 2 $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.80, -4.44, 17.85, 23.01, 25.64, 32.94, 40.74, 60.32, 64.26, 65.46, 65.82, 67.24, 75.11, 124.46, 124.98, 128.08, 128.23, 128.58, 128.86, 129.38, 130.37, 130.95, 131.40, 132.84, 135.40, 138.42, 139.10, 141.56, 144.84, 155.96, 160.35, 171.74, 173.71; IR (neat) 3980, 3381, 2937, 1782, 1720, 1636, 1519, 1438 cm^{-1}; MS (EI) m/z 880 ([M^++1], 2), 822 (2), 669 (6), 566 (4), 457 (2), 309 (4), 180 (39), 75 (100); HRMS (CI, CH_4) Calcd for $C_{45}H_{50}N_5O_{10}SiS$ $(M+H)^+$: 880.3048, Found: 880.3024.

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-1-diphenylmethylideneamino-2-ethylthio-6-[(*R*)-1-hydroxyethyl]-2-carbapenem-3-carboxylate (10a)**. Compound **9a** (42 mg, 0.062 mmol) was dissolved in DMF (2.5 mL) under nitrogen gas. After addition of *N*-methylpyrrolidine (1.0 mL) and NH_4F-HF (22 mg, 0.37 mmol), the mixture was stirred for 72 h at room temperature and diluted with ethyl acetate (25 mL). The ethyl acetate solution was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave an oily residue which was purified by chromatography on silica gel with hexane-ethyl acetate (5 : 2) as an eluent to afford 24 mg (68%) of **10a** as a yellow oil. $[\alpha]_D^{20}$ +240.7° (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17-1.25 (m, 6H, SCH_2CH_3, $CHCH_3$), 1.72 (br s, 1H, OH), 2.61-2.80 (m, 2H, SCH_2CH_3), 3.25 (dd, J = 2.5, 6.1 Hz, 1H, H-6), 4.11-4.16 (m, 2H, H-5, $CHCH_3$), 5.12 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 5.14 (d, J = 3.0 Hz, 1H, H-1), 5.28 (d, J = 13.9 Hz, 1H, $CO_2CH_aH_b$), 7.26-7.82 (m, 12H, 2 Ph, $C_6H_4NO_2$), 8.22 (d, J = 8.8 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.45, 22.35, 26.71, 61.93, 66.10, 66.58, 66.92, 124.46, 128.84, 128.95, 129.34, 130.23, 143.35, 148.37, 151.53, 168.64, 171.62, 178.36; IR ($CHCl_3$) 3475, 2961, 2932, 1773, 1746, 1626, 1447, 1373 cm^{-1}; MS (EI) m/z 571 (M^+, 100), 538 (27), 452 (38), 391 (41), 347 (62), 286 (37), 213 (18), 165 (74), 105 (16), 77 (26).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-1-diphenylmethylideneamino-2-(2-cyanoethylthio)-6-[(*R*)-1-hydroxyethyl]-2-carbapenem-3-carboxylate (10b)**. Compound **9b** (86 mg, 0.12 mmol) was reacted with NH_4F-HF (44 mg, 0.73 mmol) by the same procedure as described for the preparation of **10a**. The residue was purified by chromatography on silica gel with hexane-ethyl acetate (3 : 1) as an eluent to afford 43 mg (60%) of **10b** as a yellow oil. $[\alpha]_D^{18}$ +229.7° (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 6.3 Hz, 3H, $CHCH_3$), 2.03 (br s, 1H, OH), 2.60 (m, 2H, SCH_2CH_2CN), 2.80-3.20 (m, 2H, SCH_2CH_2CN), 3.13 (dd, J = 2.4, 6.1 Hz, 1H, H-6), 4.06 (m, 1H, $CHCH_3$), 4.20 (m, 1H, H-5), 5.01 (d, J = 3.2 Hz, 1H, H-1), 5.14 (d, J = 13.7 Hz, 1H, $CO_2CH_aH_b$), 5.29 (d, J = 13.7 Hz, $CO_2CH_aH_b$), 7.27-7.86 (m, 12H, 2 Ph, $C_6H_4NO_2$), 8.19 (d, J = 8.8 Hz, 2H, $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.67, 21.53, 26.89, 61.37, 64.80, 65.80, 66.07, 66.48, 117.75, 128.34, 131.35, 131.36, 142.67, 146.54, 153.39, 167.75, 170.95, 177.49; IR (neat) 3478, 2969, 2250, 1774, 1746, 1628, 1447 cm^{-1}; MS (FAB) *m/z* 597 ([M+1]$^+$, 2), 539 (8), 511 (17), 477 (26), 349 (28), 239 (25), 165 (100), 136 (78), 77 (83).

***p*-Nitrobenzyl (1*R*,5*S*,6*S*)-1-diphenylmethylideneamino-6-[(*R*)-1-hydroxyethyl]-2-[2-(*p*-nitrobenzyloxycarbonylamino)ethylthio]-2-carbapenem-3-carboxylate (10c)**. Compound **9c** (69 mg, 0.078 mmol) was reacted with NH_4F-HF (29 mg, 0.48 mmol) by the same procedure as described for the preparation of **10a**. The residue was purified by chromatography on silica gel with hexane-ethyl acetate (1 : 1) as an eluent to afford 32 mg (62%) of **10c** as a yellow oil. $[\alpha]_D^{16}$ +252.2° (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J = 6.4 Hz, 3H, $CHCH_3$), 2.27 (br s, 1H, OH), 2.63-2.93 (m, 2H, SCH_2CH_2NH), 3.15 (m, 1H, H-6), 3.29 (m, 2H, SCH_2CH_2NH), 4.05 (m, 2H, $CHCH_3$, H-5), 4.89 (s, 2H, CO_2CH_2), 5.02 (d, J = 3.2 Hz, 1H, H-1), 5.16 (d, J = 13.4 Hz, 1H, $CO_2CH_aH_b$), 5.26 (s, 1H, SCH_2CH_2NH), 5.31 (d, J = 13.4 Hz, 1H, $CO_2CH_aH_b$), 7.27-8.20 (m, 18H, 2 Ph, 2 $C_6H_4NO_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.46, 32.26, 40.22, 60.70, 64.70, 65.47, 65.73, 65.92, 66.39, 124.61, 124.98, 128.34, 129.58, 130.18, 131.46, 132.92, 135.95, 137.91, 143.56, 144.10, 156.07, 167.90, 171.41, 177.47; IR (neat) 3382, 2935, 1773, 1711, 1624, 1522, 1448 cm^{-1}; MS (FAB) *m/z* 766 ([M+1]$^+$, 1), 705 (1), 641 (2), 461 (3), 401 (4), 327 (8), 281 (7), 207 (10), 165 (14), 136 (81), 73 (100).

(1*R*,5*S*,6*S*)-1-Amino-2-ethylthio-6-[(*R*)-1-hydroxyethyl]-2-carbapenem-3-carboxylic acid (11a). Compound **10a** (18 mg, 0.031 mmol) was dissolved in methanol (2.0 mL) and 5% Pd-C (16.5 mg) was added to the solution. The mixture was stirred for 2 h at room temperature under hydrogen gas. The reaction mixture was filtered through Celite and the filtrate was evaporated to give an oily residue. The residue was chromatographed on dianion HP 20 with 5% *aq*. THF

solution as an eluent and lyophilized to give 5.0 mg (59%) of **11a** as a brown solid. mp 161 (dec.); $[\alpha]_D^{18}$ +224.0° (c 0.2, H_2O); ^1H NMR (300 MHz, CD_3OD) δ 1.20 (d, J = 6.3 Hz, 3H, $CHCH_3$), 1.23 (t, J = 7.4 Hz, 3H, SCH_2CH_3), 2.60 (dd, J = 2.3, 7.1 Hz, 1H, H-6), 2.71-2.89 (m, 2H, SCH_2CH_3), 4.02 (m, 1H, H-5), 4.37 (m, 1H, $CHCH_3$), 4.85 (d, J=3.3 Hz, 1H, H-1); ^{13}C NMR (75 MHz, CD_3OD) 15.77, 22.06, 26.76, 31.09, 63.12, 66.47, 71.64, 121.70, 129.21, 171.38, 180.79; IR (KBr) 3387, 3063, 2967, 2926, 1761, 1607, 1386, 1318, 1123, 868 cm^{-1}; MS (FAB) m/z 273 ($[M+1]^+$, 4), 245 (5), 213 (4), 176 (38), 154 (100), 136 (83), 89 (33).

(1*R*,5*S*,6*S*)-1-Amino-2-(2-cyanoethylthio)-6-[(*R*)-1-hydroxyethyl]-2-carbapenem-3-carboxylic acid (11b). The same procedure as described for the preparation of **11a** was employed with **10b** (14 mg, 0.023 mmol), 5% Pd-C (21.0 mg) and hydrogen gas to give an oily residue. The residue was chromatographed on dianion HP 20 with 10% *aq*. THF solution as an eluent and lyophilized to give 4.0 mg (57%) of **11b** as an yellow solid. mp 165 (dec.); $[\alpha]_D^{21}$ +277.6° (*c* 0.1, H_2O); ^1H NMR (300 MHz, CD_3OD) δ 1.11 (d, J = 6.0 Hz, 3H, $CHCH_3$), 2.49 (m, 2H, SCH_2CH_2CN), 2.68 (m, 1H, $SCH_aH_bCH_2CN$), 2.83 (m, 1H, H-6), 2.92 (m, 1H, $SCH_aH_bCH_2CN$), 3.89 (m, 1H, $CHCH_3$), 4.30 (m, 1H, H-5), 4.84 (s, 1H, H-1); ^{13}C NMR (75 MHz, CD_3OD) δ 18.07, 22.86, 27.23, 61.21, 64.62, 67.74, 70.59, 117.62, 124.37, 128.62, 171.86, 178.54; IR (KBr) 3425, 3064, 2968, 2928, 2215, 1766, 1616, 1395, 1318, 1128 cm^{-1}; MS (FAB) m/z 298 ($[M+1]^+$, 1), 257 (4), 192 (21), 165 (21), 154 (100), 136 (81), 89 (29).

(1*R*,5*S*,6*S*)-1-Amino-2-(2-aminoethylthio)-6-[(*R*)-1-hydroxyethyl]-2-carbapenem-3-carboxylic acid (11c). The same procedure as described for the preparation of **11a** was employed with **10c** (21 mg, 0.027 mmol), 5% Pd-C (29.5 mg) and hydrogen gas to give an oily residue. The residue was chromatographed on dianion HP 20 with 1% *aq*. THF solution as an eluent and lyophilized to give 5.0 mg (63%) of **11c** as an yellow solid. mp 163 (dec.); $[\alpha]_D^{15}$ +125.6° (*c* 0.3, H_2O); ^1H NMR (300 MHz, CD_3OD) δ 1.11 (d, J = 6.4 Hz, 3H, $CHCH_3$), 2.84 (m, 2H, $SCH_aH_bCH_2NH_2$, H-6), 3.05 (m, 1H, $SCH_aH_bCH_2NH_2$), 3.59 (m, 2H, $SCH_2CH_2NH_2$), 4.17 (m, 1H, H-5), 4.41 (m, 1H, $CHCH_3$), 4.84 (m, 1H, H-1); ^{13}C NMR (75 MHz, CD_3OD) δ 18.62, 24.18, 32.60, 40.53, 61.28, 65.39, 66.54, 123.29, 128.94, 171.32, 178.68; IR (KBr) 3409, 3059, 2965, 2929, 1761, 1614, 1516, 1393, 1319, 1133 cm^{-1}; MS (FAB) m/z 288 ($[M+1]^+$, 10), 209 (3), 154 (100), 136 (79), 107 (28), 89 (27).

Acknowledgment. This work was supported by the Brain Korea 21 program, Ministry of Education.

References

1. (a) Albers-Schonberg, G.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491. (b) Kahan, J. S.; Kahan, F. M.; Goegelman, R.; Currie, S. A.; Jackson, M.; Stapley, E. O.; Miller, T. W.; Miller, A. K.; Hendlin, D.; Mochales, S.; Hernandez, S.; Woodruff, H. B.; Birnbaum, J. *J. Antibiotics* **1979**, *32*, 1.
2. Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29.
3. (a) Cama, L. D.; Christensen, B. G.; Shih, D. H. *US Appl. 603005*; 23 Apr., 1984; p 254. (b) Cama, L. D.; Christensen, B. G.; Shih, D. H. *Eur. Pat. Appl. EP 160,876* (cl. C07D487/04); 13 Nov., 1985.
4. Seo, K. J.; Lim, M. H.; Moon, J. M.; Goo, Y. M.; Lee, Y. Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 767.
5. Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH Publishers: New York, U. S. A., 1993; pp 149-156.
6. Fuentes, L. M.; King, S. A.; Purick, R.; Reamer, R. A.; Schmit, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563.
7. Shinkai, I.; Liu, T.; Reamer, R.; Sletzinger, M. *Synthesis* **1980**, 924.
8. Toogo, H.; Fujii, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 57.
9. Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, Y. *Synlett* **1995**, 609.