SYNTHETIC STUDIES OF 1-β-METHYLCARBAPENEM ANTIBIOTICS

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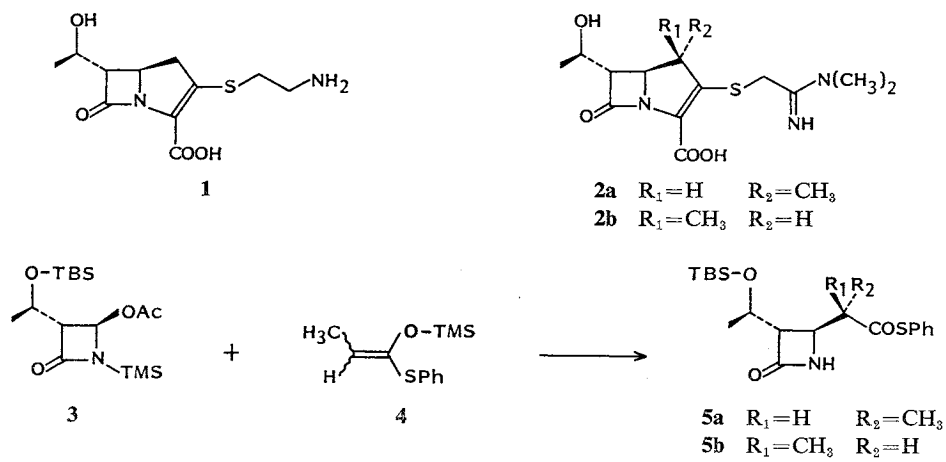
The diastereoselective synthesis of the 1-β-methylcarbapenems, (1*R*,5*R*,6*S*)-6-((*R*)-1-hydroxyethyl)-2-((*S*)-1-acetimidoylpyrrolidin-3-ylthio)-1-methyl-1-carbapen-2-em-3-carboxylic acid and sodium (1*R*,5*R*,6*S*)-6-((*R*)-1-hydroxyethyl)-2-(5-chloro-2-oxobenzoxazolin-3-yl)-1-methyl-1-carbapen-2-em-3-carboxylate has been achieved. The key step was an aldol reaction between the achiral boron enolate which was generated from dibutylboron triflate and 3-propionyl-2-oxobenzoxazoline, and (3*R*,4*R*)-4-acetoxy-3-((*R*)-1-hydroxyethyl)azetizin-2-one.

In order to improve the chemical and metabolical stability of thienamycin (**1**),[1] many carbapenem derivatives have been synthesized. The Merck group has reported that 1-β-methylcarbapenem (**2b**) has good chemical and metabolical stability and high antibacterial activity.[2] In contrast, 1-α-methylcarbapenem (**2a**) has relatively weak antibacterial activity.[2]

Therefore, a stereoselective synthesis of 1-β-methyl analogs is highly desirable. In a previous paper,[3] we reported the synthesis of 1-methylcarbapenems which involved, as a key step, the aldol reaction between acetoxyazetidinone (**3**) and silyl enol ether (**4**). In this method, however, the ratio of **5b** : **5a** is only 1.6. Recently, the Merck group reported a highly diastereoselective aldol reaction using the chiral boron enolate (the ratio of β-isomer : α-isomer was >99 : 1).[4] NAGAO *et al.*[5] and the Bristol-Myers group[6] also reported diastereoselective aldol reactions using chiral and achiral tin enolates, respectively (the ratios of β-isomer : α-isomer were 91 : 1 and 24 : 1, respectively). In this paper, we wish to report another highly diastereoselective aldol reaction between achiral boron enolate (**7**) and acetoxyazetidinone (**8**), which affords the key intermediate (**10**). We also report the syntheses of 1-β-methylcarbapenem (**13** and **25**) from **10**.

Chart 1.



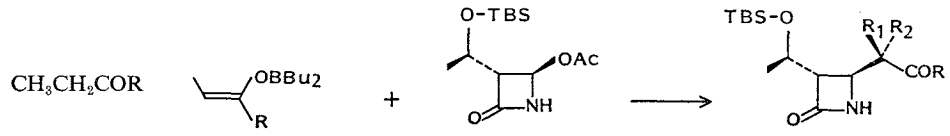
TBS=*tert*-Bu(CH$_3$)$_2$Si-, TMS=trimethylsilyl

Synthesis

Boron enolate (**7**) which was generated by treatment of propionamide (**6**) with dibutylboron triflate and diisopropylethylamine,[7] was reacted with **8** in methylene chloride at room temperature in the presence of a catalytic amount of $ZnBr_2$ to afford **9** and **10**. The results are summarized in Table 1. The ratio of **10** to **9** was determined by HPLC (column: μBondapack C_{18}, acetonitrile - water, 3 : 1). The stereochemistry of **10** was assigned by hydrolysis to compound **11**. In the case of entry **a**, the diastereoselectivity was low, however in entries **b**~**f** and especially entry **c**, high diastereoselectivity was obtained. These results indicated the lack of need for a chiral auxiliary on the boron enolate.

Alkaline hydrolysis of **10c** followed by the chain extension sequence (i; carbonyldiimidazole, ii; magnesium *p*-nitrobenzyl malonate) gave **12**.[2] Compound **12** was also obtained directly from **10c** by reaction with magnesium *p*-nitrobenzyl malonate. Synthesis of **13** from **12** has already been reported.[3] Desilylation of **10c** with boron trifluoride etherate followed by trimethylsilylation of **14** (i; chlorotrimethylsilane and triethylamine, ii; silica gel) gave **15**. Compound **15** was reacted readily with mercaptan (**16**) in the presence of triethylamine, under mild conditions (room temperature, 1 hour), to give the thioester (**17**). Treatment of **17** with *p*-nitrobenzyloxyoxalyl chloride and triethylamine gave **18**. Cyclization of **18** in refluxing xylene, in the presence of triethyl phosphite and a catalytic amount of hydroquinone, gave **19**. Compared to the 1-H carbapenem analog, a higher temperature was necessary for this cyclization reaction. Desilylation of **19** with potassium fluoride and acetic acid gave **20**. Hydrogenolysis of **20** with 10% Pd-C catalyst, and subsequent amidination with acetimidoethyl ether hydrochloride afforded the desired carbapenem **13**, which has good biostability (urinary recovery by sc in mice is 90%) and very strong antimicrobial activity (the detailed data will be reported elsewhere).

Table 1. Aldol condensation of boron enolate (**7**) with acetoxyazetidinone (**8**).



6 **7** **8** **9** R_1=H R_2=CH_3; **10** R_1=CH_3 R_2=H

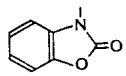
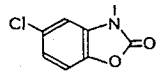
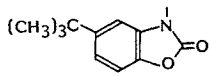
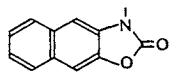
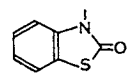
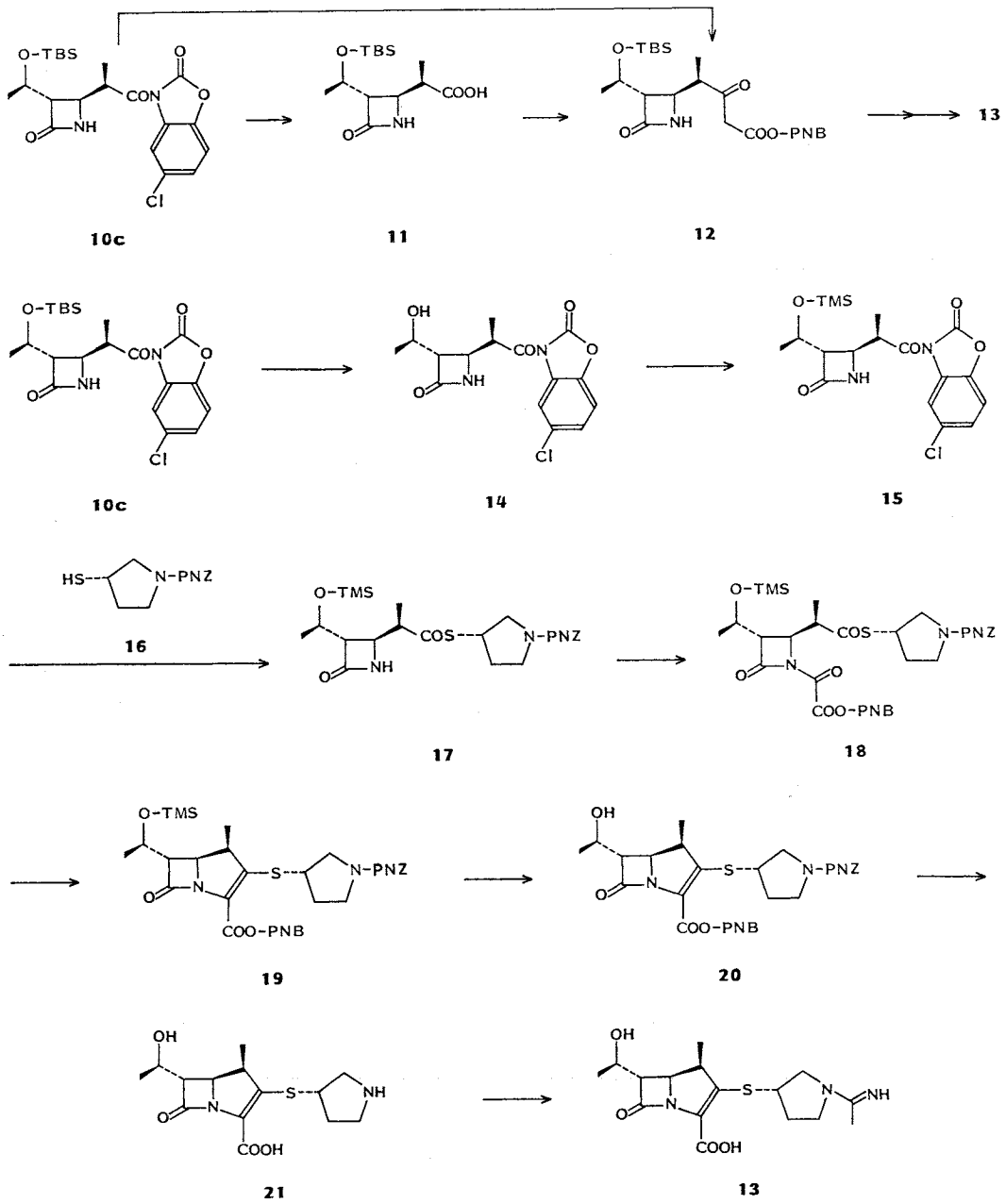
Entry	R	Yield (%)	10/9
a	SPh	18	1.4
b		56	15
c		75	60
d		81	10
e		55	38
f		72	20

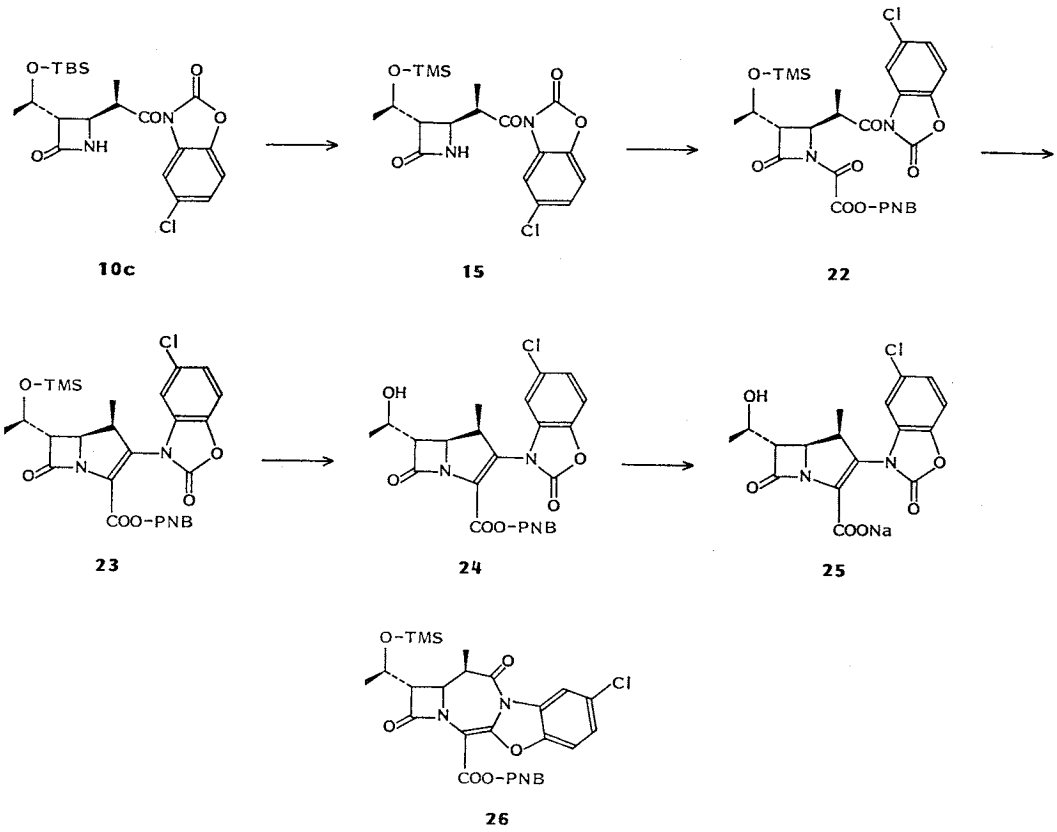
Chart 2.



PNB=*p*-Nitrobenzyl, PNZ=*p*-nitrobenzyloxycarbonyl

By the method shown in Chart 3, 1-β-methylcarbapenem (**25**) was also synthesized. Exchange of the alcohol protecting group of **10c** followed by oxalylation of **15** gave the ester-amide **22**. Cyclization of **22** afforded the carbapenem **23** accompanied by a small amount of by-product. This by-product had NMR and mass spectra similar to **23**. However, disappearance of the peak *m/z* 168 (5-chloro-2-oxobenzoxazole moiety) in negative chemical ionization (CI)-MS and negative fast atom bombardment (FAB)-MS suggested the structure of this by-product to be **26**. Deprotection of **23** afforded the carbapenem **25**, which showed fairly good antimicrobial activity against Gram-positive bacteria

Chart 3.



(MIC (μg/ml) of **25**: *Staphylococcus aureus* 209P; 0.1, *S. aureus* 56; 6.2, *Escherichia coli* NIHJ; 6.2, *E. coli* 609; 12.5, *Salmonella enteritidis*; 1.5, *Klebsiella pneumoniae* 806; 6.2, *Serratia marcescens* 1184; 6.2, *Proteus vulgaris* 1420; 1.5, *Morganella morganii* 1510; 6.2).

Experimental

IR spectra were recorded on a Jasco A-102 spectrometer and UV spectra were obtained on a Cary 14 CM-50 (Serial 1258) spectrometer. ^{1}H NMR spectra were recorded on a Jeol JNM GX-270 or Varian EM 360L spectrometer. Chemical shifts are reported in ppm using, unless otherwise specified, TMS as an internal standard.

General Procedure to Prepare **9a**~**9c**, **9f** and **10a**~**10f**

To a solution of **6a**~**6f** (1 mmol) in methylene chloride (3 ml) were added dibutylboron triflate (2.2 ml, 1 M solution in methylene chloride) and diisopropylethylamine (0.42 ml) successively at 0°C. The mixture was stirred for 30 minutes at the same temperature, and then a solution of **8** (587 mg) in methylene chloride (2 ml) and zinc bromide (50 mg) were added successively at 0°C. After being stirred at room temperature for 1 day, the mixture was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with hexane - ethyl acetate (2 : 1) to give **9a**~**9c**, **9f** and **10a**~**10f**.

9a: ^{1}H NMR (270 MHz) δ 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.25 (3H, d, J=6 Hz), 1.37 (3H, d, J=7 Hz), 2.81 (1H, dd, J=6 and 2 Hz), 2.87 (1H, dq, J=10 and 7 Hz), 3.78 (1H, dd, J=10 and 2 Hz), 4.20 (1H, quintet, J=6 Hz), 5.97 (1H, br s), 7.3~7.5 (5H, m).

10a: ^{1}H NMR (270 MHz) δ 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.19 (3H, d, J=6 Hz), 1.33

(3H, d, J=7 Hz), 3.00 (1H, dq, J=7 and 6 Hz), 3.04 (1H, dd, J=5 and 2 Hz), 3.95 (1H, dd, J=6 and 2 Hz), 4.21 (1H, dq, J=6 and 5 Hz), 5.83 (1H, br s), 7.3~7.5 (5H, m).

9b: ^{1}H NMR (270 MHz) δ 0.08 (6H, s), 0.89 (9H, s), 1.24 (3H, d, J=7 Hz), 1.37 (3H, d, J=7 Hz), 2.87 (1H, dd, J=6 and 2 Hz), 3.8~4.5 (3H, m), 6.2 (1H, br s), 7.1~7.4 (3H, m), 7.9~8.2 (1H, m).

10b: ^{1}H NMR (270 MHz) δ 0.08 (6H, s), 0.89 (9H, s), 1.24 (3H, d, J=7 Hz), 1.35 (3H, d, J=7 Hz), 3.06 (1H, dd, J=4 and 2 Hz), 3.9~4.5 (3H, m), 6.1 (1H, br s), 7.1~7.4 (3H, m), 7.9~8.2 (1H, m).

9c: ^{1}H NMR (270 MHz) δ 0.09 (6H, s), 0.88 (9H, s), 1.24 (3H, d, J=7 Hz), 1.35 (3H, d, J=7 Hz), 2.86 (1H, dd, J=5 and 2 Hz), 3.8~4.4 (3H, m), 6.5 (1H, br s), 7.0~7.4 (2H, m), 8.0~8.2 (1H, m).

10c: ^{1}H NMR (270 MHz) δ 0.07 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.21 (3H, d, J=6 Hz), 1.35 (3H, d, J=7 Hz), 3.08 (1H, dd, J=4 and 2 Hz), 4.08 (1H, dd, J=4 and 2 Hz), 4.2~4.3 (2H, m), 5.97 (1H, br s), 7.17 (1H, d, J=9 Hz), 7.28 (1H, dd, J=9 and 2 Hz), 8.11 (1H, d, J=2 Hz).

10d: ^{1}H NMR (270 MHz) δ 0.07 (6H, s), 0.87 (9H, s), 1.24 (3H, d, J=7 Hz), 1.32 (9H, s), 1.35 (3H, d, J=6 Hz), 3.06 (1H, dd, J=4 and 2 Hz), 3.9~4.5 (3H, m), 6.6 (1H, br s), 7.08 (1H, d, J=9 Hz), 7.30 (1H, dd, J=9 and 2 Hz), 8.14 (1H, d, J=2 Hz); IR ($CHCl_3$) cm^{-1} 3430, 1795, 1765, 1720.

10e: ^{1}H NMR (270 MHz) δ 0.08 (3H, s), 0.09 (3H, s), 0.89 (9H, s), 1.25 (3H, d, J=6 Hz), 1.40 (3H, d, J=7 Hz), 3.12 (1H, dd, J=4 and 2 Hz), 4.12 (1H, dd, J=4 and 2 Hz), 4.25 (1H, dq, J=6 and 4 Hz), 4.32 (1H, dq, J=7 and 4 Hz), 6.01 (1H, br s), 7.5~7.6 (2H, m), 7.61 (1H, s), 7.8~8.0 (2H, m), 8.51 (1H, s); IR ($CHCl_3$) cm^{-1} 3400, 1790, 1760.

9f: ^{1}H NMR (270 MHz) δ 0.09 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.27 (3H, d, J=6 Hz), 1.37 (3H, d, J=6 Hz), 2.88 (1H, dd, J=5 and 1 Hz), 3.8~4.3 (3H, m), 5.99 (1H, br s), 7.1~7.6 (3H, m), 8.1~8.3 (1H, m).

10f: ^{1}H NMR (270 MHz) δ 0.06 (3H, s), 0.07 (3H, s), 0.87 (9H, s), 1.23 (3H, d, J=7 Hz), 1.33 (3H, d, J=7 Hz), 3.10 (1H, dd, J=5 and 2 Hz), 4.0~4.3 (3H, m), 5.99 (1H, br s), 7.1~7.6 (3H, m), 8.1~8.3 (1H, m); IR ($CHCl_3$) cm^{-1} 3450, 1760, 1695.

(*R*)-2-((3*S*,4*S*)-3-((*R*)-1-*tert*-Butyldimethylsilyloxyethyl)-2-oxoazetidin-4-yl)propionic Acid (**11**)

A solution of **10b** (300 mg) in methanol (3 ml) was treated with 1 N NaOH (3 ml) at room temperature for 16 hours. The reaction mixture was neutralized to pH 9 with dil HCl, washed with ethyl acetate, acidified with dil HCl and then extracted with ethyl acetate. The extract was dried over $MgSO_4$ and evaporated under reduced pressure to give **11** (165 mg). Yield 83%.

MP 138~141°C (dec); ^{1}H NMR (CD_3OD, 270 MHz) δ 0.07 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 1.18 (3H, d, J=6 Hz), 1.21 (3H, d, J=7 Hz), 2.58 (1H, quintet, J=7 Hz), 3.00 (1H, t, J=2 Hz), 3.80 (1H, dd, J=7 and 2 Hz), 4.22 (1H, dq, J=6 and 2 Hz); IR (KBr) cm^{-1} 3450, 3300, 1720.

Anal Calcd for $C_{14}H_{27}NO_4Si$: C 55.78, H 9.03, N 4.65.
Found: C 55.55, H 9.06, N 4.71.

3-((*S*)-2-((3*S*,4*R*)-3-((*R*)-1-Hydroxyethyl)-2-oxoazetidin-4-yl)propionyl)-5-chloro-2-oxobenzoxazoline (**14**)

A solution of **10c** (2.00 g) in acetonitrile (20 ml) was treated with boron trifluoride etherate (1.12 ml) at room temperature for 1 hour. The reaction mixture was neutralized with 1 N NaOH, extracted with ethyl acetate, washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel eluting with ethyl acetate - hexane (10 : 1) to give **14** (1.01 g). Yield 67%.

MP 160~162°C; ^{1}H NMR (CD_3OD, 60 MHz) δ 1.20 (3H, d, J=7 Hz), 1.32 (3H, d, J=7 Hz), 3.03 (1H, dd, J=6 and 2 Hz), 3.7~4.3 (3H, m), 7.0~7.4 (2H, m), 0.8~8.1 (1H, m); IR ($CHCl_3$) cm^{-1} 3400, 3250, 1830, 1800, 1765, 1730.

3-((*S*)-2-((3*S*,4*R*)-3-((*R*)-1-Trimethylsilyloxyethyl)-2-oxoazetidin-4-yl)propionyl)-5-chloro-2-oxobenzoxazoline (**15**)

To a solution of **14** (1.35 g) in methylene chloride (10 ml) were added chlorotrimethylsilane (1.6

ml) and triethylamine (1.7 ml) successively. After being stirred at room temperature for 2 hours, the mixture was evaporated under reduced pressure. The residue was extracted with ether and insoluble matter was removed by filtration. The filtrate was evaporated under reduced pressure, and the residue obtained was extracted with ethyl acetate (10 ml) and methanol (10 ml). And silica gel (5 g) was added to the mixture. After being stirred at room temperature for 3 hours, the silica gel was removed by filtration. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel eluting with hexane - ethyl acetate (2 : 1) to give **15** (1.12 g). Yield 68%.

^{1}H NMR (60 MHz) δ 0.10 (9H, s), 1.22 (3H, d, J=6 Hz), 1.33 (3H, d, J=7 Hz), 3.04 (1H, dd, J=6 and 2 Hz), 3.8~4.5 (3H, m), 6.75 (1H, br s), 7.08 (1H, d, J=10 Hz), 7.24 (1H, dd, J=10 and 2 Hz), 8.06 (1H, d, J=2 Hz).

(3*S*,4*S*)-4-((*R*)-1-(((*S*)-1-*p*-Nitrobenzyloxycarbonylpyrrolidin-3-ylthio)carbonyl)ethyl)-3-((*R*)-1-trimethylsilyloxyethyl)azetidin-2-one (**17**)

To a solution of **15** (1.81 g) in methylene chloride (10 ml) were added **16** (1.23 g) and triethylamine (0.68 ml) successively at 0°C. After being stirred at room temperature for 1 hour, the mixture washed with water, dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel eluting with hexane - ethyl acetate (1 : 4) to give **17** (1.53 g) as a colorless oil. Yield 67%.

^{1}H NMR (60 MHz) δ 0.10 (9H, s), 1.18 (3H, d, J=7 Hz), 1.22 (3H, d, J=7 Hz), 1.7~2.4 (2H, m), 2.6~3.1 (2H, m), 3.2~4.3 (7H, m), 5.18 (2H, s), 6.1 (1H, br s), 7.47 (2H, d, J=8 Hz), 8.18 (2H, d, J=8 Hz); IR ($CHCl_3$) cm^{-1} 3430, 1760, 1695.

p-Nitrobenzyl 2-Oxo-2-((3*S*,4*S*)-4-((*R*)-1-(((*S*)-1-*p*-nitrobenzyloxycarbonylpyrrolidin-3-ylthio)-carbonyl)ethyl)-3-((*R*)-1-trimethylsilyloxyethyl)-2-oxoazetidin-1-yl)acetate (**18**)

A solution of **17** (984 mg) in THF (10 ml) was treated with triethylamine (615 μl) and *p*-nitrobenzyloxalyl chloride (911 mg) at room temperature for 1 hour. The reaction mixture was extracted with ethyl acetate, washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel eluting with ethyl acetate - cyclohexane (1 : 2) to give **18** (769 mg) as a colorless oil. Yield 56%.

^{1}H NMR (60 MHz) δ 0.10 (9H, s), 1.24 (3H, d, J=6 Hz), 1.31 (3H, d, J=7 Hz), 1.7~2.3 (2H, m), 3.2~4.5 (9H, m), 5.20 (2H, s), 5.38 (2H, s), 7.47 (2H, d, J=9 Hz), 7.54 (2H, d, J=9 Hz), 8.21 (4H, d, J=9 Hz); IR ($CHCl_3$) cm^{-1} 1805, 1730, 1710.

p-Nitrobenzyl (1*R*,5*R*,6*S*)-1-Methyl-2-((*S*)-1-*p*-nitrobenzyloxycarbonylpyrrolidin-3-ylthio)-6-((*R*)-1-trimethylsilyloxyethyl)-1-carbapen-2-em-2-carboxylate (**19**)

To a solution of **18** (746 mg) in xylene (80 ml) were added triethylamine (0.98 ml) and hydroquinone (10 mg). The mixture was refluxed for 1 day under a nitrogen atmosphere. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel eluting with cyclohexane - ethyl acetate (1 : 2) to give **19** (415 mg) as a colorless oil. Yield 58%.

^{1}H NMR (60 MHz) δ 0.10 (9H, s), 1.25 (6H, d, J=6 Hz), 1.7~2.4 (2H, m), 3.1~4.4 (9H, m), 5.11 (1H, d, J=14 Hz), 5.15 (2H, s), 5.24 (1H, d, J=14 Hz), 7.43 (2H, d, J=9 Hz), 7.57 (2H, d, J=9 Hz), 8.14 (4H, d, J=9 Hz); IR ($CHCl_3$) cm^{-1} 1765, 1700.

p-Nitrobenzyl (1*R*,5*R*,6*S*)-6-((*R*)-1-Hydroxyethyl)-1-methyl-2-((*S*)-1-*p*-nitrobenzyloxycarbonylpyrrolidin-3-ylthio)-1-carbapen-2-em-2-carboxylate (**20**)

To a solution of **19** (279 mg) in acetonitrile (3 ml) were added a solution of potassium fluoride (65 mg) in water (1 ml) and acetic acid (0.13 ml). After being stirred at room temperature for 1 hour, the mixture was extracted with ethyl acetate, washed with water, dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue obtained was shortly chromatographed on silica gel eluting with ethyl acetate - methanol (10 : 1) to give **20** (237 mg) as a colorless oil. Yield 95%.

^{1}H NMR (60 MHz) δ 1.30 (3H, d, J=6 Hz), 1.38 (3H, d, J=6 Hz), 1.6~2.5 (2H, m), 3.1~4.4 (10H, m), 5.20 (2H, s), 5.29 (1H, d, J=15 Hz), 5.40 (1H, d, J=15 Hz), 7.47 (2H, d, J=9 Hz), 7.62

(2H, d, J=9 Hz), 8.20 (4H, d, J=9 Hz); IR (KBr) cm^{-1} 3400, 1770, 1705.

(1*R*,5*R*,6*S*)-6-((*R*)-1-Hydroxyethyl)-1-methyl-2-((*S*)-pyrrolidin-3-ylthio)-1-carbapen-2-em-2-carboxylic Acid (**21**)

A solution of **20** (80 mg) in THF (10 ml) and water (10 ml) was shaken with 10% Pd-C (80 mg) for 1.5 hours under a hydrogen atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to a half volume, washed with ethyl acetate, and chromatographed on Diaion CHP-20P eluting with 3% acetone - water to give **21** (25 mg) as a white powder. Yield 63%.

UV λ_{max} (ε) nm 297 (8,460); IR (KBr) cm^{-1} 3400, 1760, 1590; ^1H NMR (D_2O, TSP, 270 MHz) δ 1.03 (3H, d, J=7 Hz), 1.10 (3H, d, J=6 Hz), 1.7~1.9 (1H, m), 2.2~2.4 (1H, m), 3.0~4.1 (9H, m).

(1*R*,5*R*,6*S*)-2-((*S*)-1-Acetimidoylpyrrolidin-3-ylthio)-6-((*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-2-carboxylic Acid (**13**)

To a solution of **21** (100 mg) in phosphate buffer (pH 7.1, 12 ml) was added 1 N NaOH to adjust to pH 8.5. To the resulting mixture was added acetimido ethyl ether hydrochloride (200 mg) and 1 N NaOH to maintain pH 8.5. After being stirred at 5°C for 30 minutes, the mixture was neutralized to pH 7.0 with dil HCl and chromatographed on Diaion CHP-20P eluting with 3% acetone - water to give **13** (102 mg) as a white powder. Yield 90%.

UV λ_{max} (ε) nm 297 (8,700); IR (KBr) cm^{-1} 3400, 1755, 1680, 1635, 1590; ^1H NMR (D_2O, TSP, 270 MHz) δ 1.04 (3H, d, J=7 Hz), 1.10 (3H, d, J=6 Hz), 1.85~2.05 (1H, m), 2.05 and 2.09 (each 1.5H, s), 2.25~2.4 (1H, m), 3.15~3.95 (7H, m), 4.0~4.15 (2H, m).

p-Nitrobenzyl 2-Oxo-2-((3*S*,4*R*)-4-((*R*)-1-(5-chloro-2-oxobenzoxazolin-3-ylcarbonyl)ethyl-3-((*R*)-1-trimethylsilyloxyethyl)-2-oxoazetidin-1-yl)acetate (**22**)

Compound **15** (491 mg) was treated with triethylamine (340 μl) and *p*-nitrobenzyloxalyl chloride (495 mg), and worked up as described in the case of **18** to give **22** (610 mg) as a colorless oil. Yield 83%.

^1H NMR (60 MHz) δ 0.08 (9H, s), 1.13 (3H, d, J=7 Hz), 1.44 (3H, d, J=7 Hz), 3.57 (1H, dd, J=4 and 3 Hz), 4.30 (1H, dq, J=7 and 3 Hz), 4.4~4.8 (2H, m), 5.36 (2H, s), 7.0~7.4 (2H, m), 7.55 (2H, d, J=9 Hz), 8.0~8.1 (1H, m), 8.22 (2H, d, J=9 Hz); IR ($CHCl_3$) cm^{-1} 1800, 1760, 1725, 1700, 1530, 1480.

p-Nitrobenzyl (1*R*,5*R*,6*S*)-2-(5-Chloro-2-oxobenzoxazolin-3-yl)-1-methyl-6-((*R*)-1-trimethylsilyloxyethyl)-1-carbapen-2-em-2-carboxylate (**23**)

To a solution of **22** (565 mg) of xylene (60 ml) were added triethyl phosphite (0.88 ml) and hydroquinone (10 mg). The mixture was refluxed for 1 day under a nitrogen atmosphere. The solvent was evaporated under reduced pressure, the residue obtained was chromatographed on silica gel eluting with hexane - ethyl acetate (2 : 1) to give **23** (383 mg, yield 71%) and **26** (53 mg, yield 10%).

23: IR ($CHCl_3$) cm^{-1} 1780, 1725; ^1H NMR (270 MHz) δ 0.16 (9H, s), 1.14 (3H, d, J=7 Hz), 1.28 (3H, d, J=6 Hz), 3.47 (1H, dd, J=6 and 3 Hz), 3.85 (1H, dq, J=10 and 7 Hz), 4.31 (1H, quintet, J=6 Hz), 4.44 (1H, dd, J=10 and 3 Hz), 5.22 (1H, d, J=14 Hz), 5.30 (1H, d, J=14 Hz), 6.73 (1H, s), 7.10 (2H, s), 7.47 (2H, d, J=9 Hz), 8.17 (2H, d, J=9 Hz).

26: IR ($CHCl_3$) cm^{-1} 1760, 1705, 1640, 1605; ^1H NMR (270 MHz) δ 0.10 (9H, s), 1.27 (3H, d, J=6 Hz), 1.28 (3H, d, J=6 Hz), 3.12 (1H, dd, J=6 and 2 Hz), 3.54 (1H, quintet, J=6 Hz), 4.26 (1H, quintet, J=6 Hz), 4.44 (1H, dd, J=6 and 2 Hz), 5.33 (1H, d, J=14 Hz), 5.44 (1H, d, J=14 Hz), 7.22 (1H, s), 7.23 (1H, d, J=2 Hz), 7.60 (2H, d, J=9 Hz), 7.93 (1H, d, J=2 Hz), 8.23 (2H, d, J=9 Hz).

p-Nitrobenzyl (1*R*,5*R*,6*S*)-2-(5-Chloro-2-oxobenzoxazolin-3-yl)-6-((*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-2-carboxylate (**24**)

To a solution of **23** (200 mg) in acetonitrile (2 ml) were added a solution of potassium fluoride (56 mg) in water (1 ml) and acetic acid (0.11 ml). After being stirred at room temperature for 1 hour, the mixture was extracted with ethyl acetate, washed with water, dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue obtained was chromatographed on silica gel

eluting with ethyl acetate to give **24** (158 mg) as a colorless oil. Yield 98%.

IR ($CHCl_3$) cm^{-1} 1785, 1735; ^1H NMR (270 MHz) δ 1.16 (3H, d, J=7 Hz), 1.38 (3H, d, J=6 Hz), 1.8 (1H, m), 3.52 (1H, dd, J=6 and 3 Hz), 3.87 (1H, dq, J=10 and 7 Hz), 4.3~4.4 (1H, m), 4.48 (1H, dd, J=10 and 3 Hz), 5.21 (1H, d, J=13 Hz), 5.31 (1H, d, J=13 Hz), 6.73 (1H, d, J=1 Hz), 7.09 (1H, d, J=1 Hz), 7.10 (1H, s), 7.46 (2H, d, J=9 Hz), 8.16 (2H, d, J=9 Hz).

Sodium (1*R*,5*R*,6*S*)-2-(5-Chloro-2-oxobenzoxazolin-3-yl)-1-methyl-6-((*R*)-1-hydroxyethyl)-1-methyl-1-carbapen-2-em-2-carboxylate (**25**)

A solution of **24** (158 mg) in THF (5 ml) and phosphate buffer (pH 7.0, 2.5 ml) was shaken with 10% Pd-C (280 mg) for 2 hours under a hydrogen atmosphere. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to a half volume, washed with ethyl acetate, and chromatographed on Diaion CHP-20P eluting with 3% acetone - water to give **25** (20 mg) as a white powder. Yield 17%.

^1H NMR (D_2O, TSP, 270 MHz) δ 0.91 (3H, d, J=7 Hz), 1.13 (3H, d, J=6 Hz), 3.46 (1H, dd, J=6 and 3 Hz), 3.51 (1H, dq, J=10 and 7 Hz), 4.12 (1H, quintet, J=6 Hz), 4.22 (1H, dd, J=10 and 3 Hz), 6.9~7.2 (3H, m); IR (KBr) cm^{-1} 3440, 1770, 1610, 1480.

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References

1) KROPP, H.; J. S. KAHAN, F. M. KAHAN, J. SUNDELOF, G. DARLAND & J. BIRNBAUM: Thienamycin. A new β-lactam antibiotic. II. *In vitro* and *in vivo* evaluation. Program and Abstracts of the 16th Intersci. Conf. on Antimicrob. Agents Chemother., No. 228, Chicago, Oct. 27~29, 1976
2) SIH, D. H.; F. BAKER, L. CAMA & B. G. CHRISTENSEN: Synthetic carbapenem antibiotics. I. 1-β-Methylcarbapenem. Heterocycles 21: 29~40, 1984
3) SHIBATA, T.; K. IINO, T. TANAKA, T. HASHIMOTO, Y. KAMEYAMA & Y. SUGIMURA: Synthetic study of 1-substituted carbapenem antibiotics. Tetrahedron Lett. 26: 4739~4742, 1985
4) FUENTES, L. M.; I. SHINKAI & T. N. SALZMANN: Lewis acid mediated condensation of chiral imide enolates. A general approach to the synthesis of chiral carbapenem precursors. J. Am. Chem. Soc. 108: 4675~4676, 1986
5) NAGAO, Y.; T. KUMAGAI, S. TAMAI, T. ABE, Y. KURAMOTO, T. TAGA, S. AOYAGI, Y. NAGASE, M. OCHIAI, Y. INOUE & E. FUJITA: Highly diastereoselective alkylation onto 4-acetoxy-2-azetidinones employing tin(II) enolates of C4-chiral 3-acyl-1,3-thiazolidine-2-thiones. J. Am. Chem. Soc. 108: 4673~4675, 1986
6) DÉZIEL, R. & D. FAVREAU: Simple and highly diastereoselective synthesis of a 1β-methylcarbapenem key intermediate involving divalent tin enolates. Tetrahedron Lett. 27: 5687~5690, 1986
7) EVANS, D. A.; J. V. NELSON, E. VOGEL & T. R. TABER: Stereoselective aldol condensations via boron enolates. J. Am. Chem. Soc. 103: 3099~3111, 1981