SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1β-METHYL-CARBAPENEMS WITH *N*-METHYLPYRROLIDINYLTHIO GROUP AT C-2 POSITION

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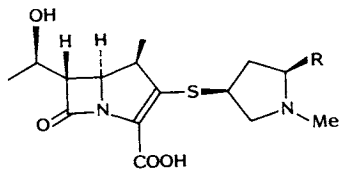
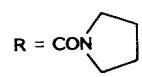
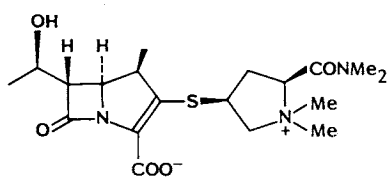
A series of 1β-methylcarbapenem compounds, which have a 5'-substituted-*N*-methylpyrrolidin-3'-ylthio group as a C-2 side chain, have been prepared and their biological properties were investigated. Substitution with a methyl group on the nitrogen atom in the C-2 side chain effectively enhanced stability to renal dehydropeptidase-I as well as introduction of methylene spacer between the aminocarbonyl group and the pyrrolidine ring of the 5'-aminocarbonylpyrrolidin-3'-ylthio group.

We previously reported that the introduction of a methylene spacer at the C-5' position of carbapenem antibiotics bearing 5'-aminocarbonylpyrrolidin-3'-ylthio group as a C-2 side chain enhances the stability to renal dehydropeptidase-I (DHP-I)[1]. In this study, the effect on DHP-I stability by introduction of methyl group on the nitrogen atom of the pyrrolidine ring was investigated. It was found that the *N*-methylation effectively increased the stability beyond our expectations. The present paper describes the antibacterial activity and the stability to DHP-I of 1β-methylcarbapenems with *N*-methylated pyrrolidinylthio side chain (**1** and **2**).

Fig. 1. 1β-Methylcarbapenem compounds.



1a R=$CONMe_2$ **1d** R = 
1b R=CONHMe
1c R=$CONH_2$ **1e** R=$CH_2CONHMe$
1f R=$CH_2CH_2CONHMe$



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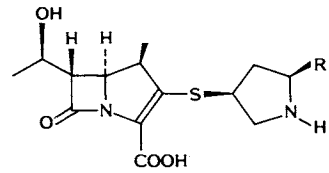


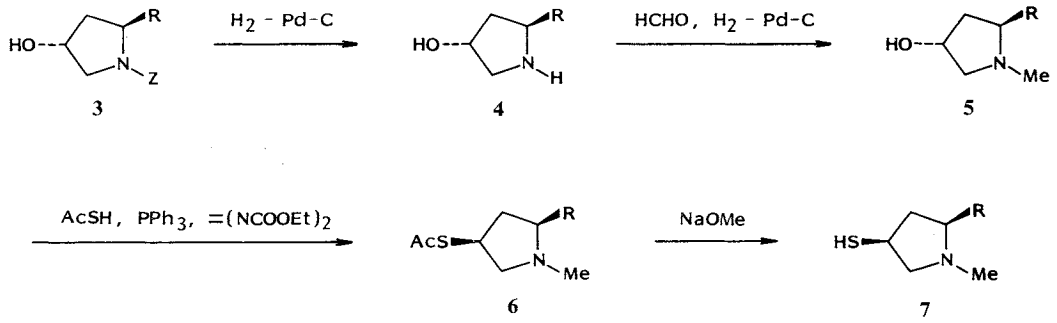
Meropenem (**10**) R=$CONMe_2$
11 R=$CH_2CONHMe$

Chemistry

The title compounds were synthesized as shown in Schemes 1 and 2. The mercaptans (**7a**~**7f**) used in this work were prepared as follows. *N*-Protected pyrrolidine (**3**) was derived from *trans*-4-hydroxy-L-proline according to the reported procedure[1,2]. Removal of the benzyloxycarbonyl group of **3** was carried out by hydrogenolysis over 10% Pd-C to give 4-hydroxypyrrolidine (**4**). Reductive *N*-methylation of **4** was accomplished by treatment with formaldehyde over 10% Pd-C in a hydrogen atmosphere to give *N*-methylpyrrolidine (**5**). The hydroxyl group of **5** was transformed by a modified MITSUNOBU reaction[3], using triphenyl phosphine, diethyl azodicarboxylate and thioacetic acid, into the acetylthio group with inversion of C-4 configuration. Thioacetate (**6**) was treated with sodium methoxide to provide mercaptan (**7**).

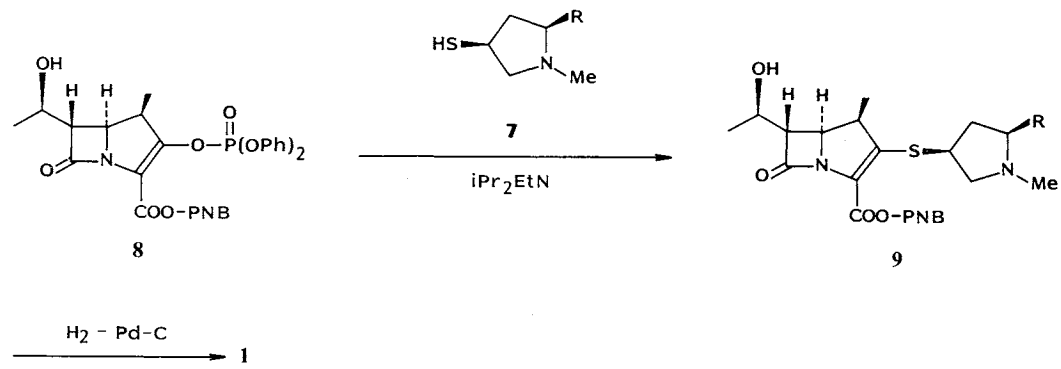
Protected 1β-methylcarbapenem (**9**) was obtained by treatment of enol phosphate (**8**)[4] with the freshly prepared mercaptan (**7**) in the presence of diisopropylethylamine. The *p*-nitrobenzyl group of **9** was removed by hydrogenolysis over 10% Pd-C in the presence of 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (pH 7.0) to afford the target 1β-methylcarbapenem (**1**), after purification by column chromatography on Diaion CHP-20P. With the aim of studying further of *N*-methylation, the *N*,*N*-dimethylpyrrolidine derivative (**2**)[5] was prepared by treatment of **9a** with methyl iodide followed by removal of the protecting group.

Scheme 1.



Z: Benzyloxycarbonyl.

Scheme 2.



PNB: *p*-Nitrobenzyl.

Biological Properties and Discussion

The stability to DHP-I and the MICs of the new series of 1β-methylcarbapenems are listed in Table 1 with those of the reference compounds **10**[2] and **11**[1].

The 1β-methylcarbapenems substituted with methyl group on the nitrogen atom of the pyrrolidine ring exhibited potent antibacterial activities against Gram-positive and Gram-negative bacteria. However, comparing with the *N*-unsubstituted compounds, these compounds showed slightly lower activities against Gram-negative bacteria and their activities against *Pseudomonas aeruginosa* were significantly decreased. Comparison of **1a** and **2** demonstrated that further *N*-methylation did not affected anti-pseudomonal activity but resulted in reduced activities against other bacteria. It is interestingly to note that dimethylaminocarbonyl derivatives (**1a** and **2**) are more active compounds against *P. aeruginosa* compared with other 5'-aminocarbonyl derivatives (**1b**, **1c** and **1d**).

As for the stability to DHP-I, *N*-methyl substitution resulted in a 5~7-fold increased stability when compared with the *N*-unsubstituted derivatives. The stabilizing effect was comparable to that of the introduction of a methylene spacer $(CH_2)_n$ at the C-5' position of the pyrrolidine ring. *N,N*-dimethylpyrrolidine derivative (**2**) was 2-fold more stable than **1a**. The 1β-methylcarbapenems (**1e** and **1f**) having both *N*-methyl group and methylene spacer exhibited excellent stability to DHP-I. This suggests that the introduction of a methylene spacer in the series of *N*-methylated compounds enhances the DHP-I stability synergetically.

It is possible that the highly improved stability is related to basicity and steric crowding of the amino group of pyrrolidinylthio side chain. That is, the introduction of methylene spacer at the C-5' position increases the basicity of the nitrogen atom of the pyrrolidine ring and the *N*-substitution with a methyl group enhances the steric crowding of the amino group. Hence, the basicity and steric factor on the nitrogen atom of the pyrrolidinylthio side chain are likely to be important for the stabilization toward DHP-I as well as the orientation of methyl group at the C-1 position[2,6].

Table 1. Antibacterial activity and DHP-1 stability of 1β-methylcarbapenem compounds having *N*-methylpyrrolidine side chain at C-2 position.

Organism	MIC (μg/ml)								
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**2**	**10**[3]	**11**[1]
S.a. FDA 209P	0.10	0.20	0.10	0.20	0.10	0.10	0.20	<0.013	<0.013
S.p. Cook	<0.013	<0.013	<0.013	0.025	<0.013	<0.013	0.10	<0.013	<0.013
E.c. NIHJ JC-2	0.025	<0.013	0.025	0.05	0.05	0.05	0.20	<0.013	0.025
K.p. ATCC 10031	<0.013	<0.013	<0.013	0.025	0.025	0.025	0.10	<0.013	<0.013
P.m. GN 2425	0.05	0.05	0.05	0.10	0.10	0.10	0.20	<0.013	0.10
P.a. IFO 3451	1.56	12.5	12.5	12.5	6.25	3.13	1.56	0.10	0.78
S.m. X 100	0.05	0.05	0.025	0.05	0.05	0.05	0.39	<0.013	0.025
E.c. ML 1410/RP4[a]	0.05	0.05	0.05	0.10	0.10	0.10	0.39	<0.013	0.05
E.c. GN 5482[a]	0.025	0.025	0.025	0.05	0.05	0.025	N.D.	<0.013	<0.013
P.v. GN 7919[a]	0.10	0.20	0.10	0.20	0.20	0.20	0.78	<0.013	0.05
S.m. GN 6473[a]	0.10	0.39	0.20	0.20	0.20	0.10	0.39	<0.013	0.025
DHP-I stability[b]	7.3	5.5	5.9	6.8	34.5	43.2	15.5	1.0	3.9

[a] β-Lactamase producing strain.

[b] DHP-I stability[7] is given relative to compound **10**.

Abbreviations: *S.a.*, *Staphylococcus aureus*; *S.p.*, *Streptococcus pyogenes*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *P.m.*, *Proteus mirabilis*; *P.a.*, *Pseudomonas aeruginosa*; *S.m.*, *Serratia marcescens*; *P.v.*, *Proteus vulgaris*; N.D., not determined.

Experimental

IR spectra were recorded on a Hitachi 260-10 IR spectrophotometer. ^{1}H NMR spectra were taken with Jeol FX-90Q (90 MHz) or JNM-GX270 (270 MHz) FT spectrometers using tetramethylsilane or residual HOD (δ 4.80) as an internal reference. UV spectra were recorded on a Hitachi 330 UV-VIS spectrophotometer. Mass spectra were obtained on a Hitachi M-80B spectrometer. Optical rotations were determined on a Jasco DIP-181 digital polarimeter. TLC was performed on Kieselgel 60 F_{254} (E. Merck).

MIC determination and DHP-I stability test were carried out in the same manner as previously described[2].

(2*S*,4*R*)-2-Dimethylaminocarbonyl-4-hydroxypyrrolidine (**4a**)

A mixture of (2*R*,4*R*)-4-hydroxy-2-dimethylaminocarbonyl-1-benzyloxycarbonylpyrrolidine (**3a**) (2.92 g, 10.0 mmol), which was prepared in a similar manner to that for the preparation of the *p*-nitrobenzyloxycarbonyl derivative described in ref 2, and 10% Pd-C (0.3 g) in EtOH (30 ml) was stirred under hydrogen atmosphere for 3 hours at room temperature. The catalyst was filtered off and washed with EtOH, and the combined filtrate and washings were evaporated *in vacuo* to give **4a** (1.60 g, quantitative): $[\alpha]_D^{30}$ −45.3° (*c* 0.41, MeOH); IR (KBr) cm^{-1} 1640; ^{1}H NMR ($CDCl_3$-CD_3OD, 4:1) δ 1.81 (1H, m), 2.25 (1H, dd, J=7.4 and 13.5 Hz), 2.97 (3H, s), 3.05 (3H, s), 3.26 (1H, dd, J=4.5 and 11.5 Hz), 4.28 (1H, t, J=8.0 Hz), 4.46 (1H, m); FD-MS *m/z* 159 $(M+H)^+$.

(2*S*,4*R*)-2-Dimethylaminocarbonyl-4-hydroxy-1-methylpyrrolidine (**5a**)

To a solution of **4a** (0.89 g, 5.63 mmol) and 37% aqueous formaldehyde (0.55 g, 6.78 mmol) in AcOH (4.5 ml) and water (4.0 ml) was added 10% Pd-C (0.45 g). The mixture was stirred under hydrogen atmosphere for 3 hours at room temperature. The catalyst was filtered off and washed with EtOH, and the combined filtrate and washings were evaporated *in vacuo*. The oily residue was dissolved in CH_2Cl_2 (50 ml) and then stirred with $MgSO_4$ (2.0 g) and K_2CO_3 (2.0 g) for 1 hour at room temperature. The insoluble salts were removed by filtration and the filtrate was concentrated *in vacuo* to give crude **5a** as a pale yellow oil (775 mg, 80%): $[\alpha]_D^{28}$ −66.8° (*c* 0.50, $CHCl_3$); IR (neat) cm^{-1} 1630; ^{1}H NMR ($CDCl_3$) δ 2.0~2.23 (2H, m), 2.37 (3H, s), 2.97 (3H, s), 3.08 (3H, s), 3.56 (2H, m), 4.52 (1H, m); FD-MS *m/z* 172 $(M)^+$.

(2*S*,4*S*)-4-Acetylthio-2-dimethylaminocarbonyl-1-methylpyrrolidine (**6a**)

To a solution of **5a** (430 mg, 2.5 mmol) and triphenylphosphine (1.18 g, 4.5 mmol) in THF (5 ml) was added dropwise diethyl azodicarboxylate (0.7 ml, 4.5 mmol) at 0~5°C under nitrogen atmosphere and stirred for 30 minutes at the same temperature. Thioacetic acid (685 mg, 9.0 mmol) was added dropwise to the mixture and followed by stirring for 30 minutes at 0~5°C and then overnight at room temperature. The reaction mixture was concentrated *in vacuo* to give an oily residue which was purified by column chromatography on silica gel using toluene-EtOAc, EtOAc and EtOAc-Me_2CO. The fractions eluted with EtOAc-Me_2CO (3:1 and 1:1) were concentrated *in vacuo* to give **6a** as a colorless oil (291 mg, 50%): $[\alpha]_D^{26}$ −56.3° (*c* 0.50, MeOH); IR (neat) cm^{-1} 1685, 1640; ^{1}H NMR ($CDCl_3$) δ 1.88 (1H, m), 2.30 (3H, s), 2.36 (3H, s), 2.65 (1H, m), 2.82 (1H, dd, J=7.5 and 10.0 Hz), 2.97 (3H, s), 3.08 (3H, s), 3.27 (1H, t, J=8.0 Hz), 3.99 (1H, m); SI-MS *m/z* 231 $(M+H)^+$.

The following compounds (**6b~6f**) were prepared in a similar manner to that described above.

6b: IR (neat) cm^{-1} 1678, 1648; ^{1}H NMR ($CDCl_3$) δ 1.87 (1H, br d, J=14.0 Hz), 2.30 (3H, s), 2.38 (3H, s), 2.73~3.04 (5H, m), 3.97 (1H, m).

6c: IR (Nujol) cm^{-1} 1680, 1647; ^{1}H NMR ($CDCl_3$) δ 1.97 (1H, m), 2.31 (3H, s), 2.41 (3H, s), 2.65~3.16 (4H, m), 3.98 (1H, m), 5.10 (1H, br s), 6.04 (1H, br s).

6d: IR (neat) cm^{-1} 1682, 1637; ^{1}H NMR ($CDCl_3$) δ 1.65~2.10 (6H, m), 2.29 (3H, s), 2.36 (3H, s), 3.51 (4H, t, J=6.5 Hz), 3.95 (1H, m).

6e: IR (Nujol) cm^{-1} 1675, 1635; ^{1}H NMR ($CDCl_3$) δ 1.68 (3H, m), 2.31 (3H, s), 2.33 (3H, s), 2.72 (1H, dd, J=6.5 and 11.0 Hz), 2.82 (3H, d, J=5.0 Hz), 3.03 (1H, d, J=11.0 Hz), 3.90 (1H, m).

6f: IR (neat) cm^{-1} 1682, 1640; ^{1}H NMR ($CDCl_3$) δ 1.47 (1H, m), 1.66 (1H, m), 2.16~2.27 (3H, m), 2.30 (6H, s), 2.69 (1H, dd, J=7.0 and 10.5 Hz), 2.80 (3H, d, J=5.0 Hz), 2.98 (1H, dd, J=1.5 and 10.5 Hz), 3.86 (1H, m).

(2*S*,4*S*)-2-Dimethylaminocarbonyl-4-mercapto-1-methylpyrrolidine (**7a**)

To a solution of **6a** (0.66 g, 2.87 mmol) in MeOH (6.6 ml) was added 28% MeOH solution of sodium methoxide (575 mg, 1.04 mmol) at 0~5°C and stirred for 15 minutes at the same temperature. After addition of 6 N HCl (1.05 ml), the reaction mixture was concentrated *in vacuo* to give an oily residue which was dissolved in $CHCl_3$-MeOH (4:1). The solution was dried over Na_2SO_4 and evaporated *in vacuo* to give **7a** as a hydrochloric acid salt, which was used in the next step without purification: IR (neat) cm^{-1} 1655.

p-Nitrobenzyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-(5-Dimethylaminocarbonyl-1-methyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**9a**)

A solution of mercaptan (**7a**) (74 mg, 0.33 mmol) in CH_3CN (1.0 ml) was added to a solution of *p*-nitrobenzyl (1*R*,5*R*,6*S*)-2-diphenylphosphoro-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**8**) (160 mg, 0.27 mmol) and diisopropylethylamine (86 mg, 0.66 mmol) in CH_3CN (1.5 ml) at −30~−40°C under nitrogen atmosphere and followed by stirring for 1 hour at the same temperature. The reaction mixture was diluted with EtOAc, washed with brine and dried over $MgSO_4$. Evaporation of the solvents *in vacuo* gave an oily residue which was purified by preparative TLC using EtOAc-Me_2CO-MeOH (9:9:2) to give **9a** (208 mg, 83%) as a pale yellow powder: IR (neat) cm^{-1} 1760, 1702, 1635; ^1H NMR ($CDCl_3$) δ 1.27 (3H, d, J=7.5 Hz), 1.37 (3H, d, J=6.5 Hz), 2.34 (3H, s), 2.98 (3H, s), 3.16 (3H, s), 5.25 (1H, d, J=14.0 Hz), 5.48 (1H, d, J=14.0 Hz), 7.66 (2H, d, J=9.0 Hz), 8.20 (2H, d, J=9.0 Hz).

The following compounds (**9b**~**9f**) were prepared in a similar manner to that described above.

9b: IR (neat) cm^{-1} 1760, 1705, 1660; ^1H NMR ($CDCl_3$) δ 1.27 (3H, d, J=7.5 Hz), 1.35 (3H, d, J=7.0 Hz), 2.36 (3H, s), 2.83 (3H, d, J=5.0 Hz), 5.23 (1H, d, J=14.0 Hz), 5.49 (1H, d, J=14.0 Hz), 7.66 (2H, d, J=8.5 Hz), 8.20 (2H, d, J=8.5 Hz).

9c: IR (neat) cm^{-1} 1765, 1705 (sh), 1680; ^1H NMR ($CDCl_3$) δ 1.28 (3H, d, J=7.0 Hz), 1.35 (3H, d, J=6.0 Hz), 2.39 (3H, s), 5.23 (1H, d, J=14.0 Hz), 5.49 (1H, d, J=14.0 Hz), 6.04 (1H, br s), 7.13 (1H, br s), 8.20 (2H, d, J=8.5 Hz).

9d: IR (neat) cm^{-1} 1760, 1702, 1630; ^1H NMR ($CDCl_3$) δ 1.26 (3H, d, J=7.0 Hz), 1.34 (3H, d, J=7.0 Hz), 2.33 (3H, s), 5.26 (1H, d, J=14.0 Hz), 5.45 (1H, d, J=14.0 Hz), 7.67 (2H, d, J=9.0 Hz), 8.20 (2H, d, J=9.0 Hz).

9e: IR (neat) cm^{-1} 1760, 1705, 1643; ^1H NMR ($CDCl_3$) δ 1.27 (3H, d, J=7.0 Hz), 1.35 (3H, d, J=7.5 Hz), 2.32 (3H, s), 2.81 (3H, d, J=5.0 Hz), 3.71 (1H, q, J=7.0 Hz), 4.26 (2H, m), 5.24 (1H, d, J=14.0 Hz), 5.48 (1H, d, J=14.0 Hz), 7.66 (2H, d, J=9.0 Hz), 8.21 (2H, d, J=9.0 Hz).

9f: IR (neat) cm^{-1} 1760, 1705, 1650; ^1H NMR ($CDCl_3$) δ 1.26 (3H, d, J=7.0 Hz), 1.35 (3H, d, J=6.5 Hz), 2.26 (3H, s), 2.77 (3H, s), 5.23 (1H, d, J=14.0 Hz), 5.47 (1H, d, J=14.0 Hz), 7.66 (2H, d, J=9.0 Hz), 8.19 (2H, d, J=9.0 Hz).

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-(5-Dimethylaminocarbonyl-1-methyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic Acid (**1a**)

A mixture of **9a** (64 mg, 0.12 mmol) and 10% Pd-C (52 mg) in THF (3.5 ml) and 0.6 M MOPS buffer (3.5 ml) was stirred under hydrogen atmosphere for 5 hours at room temperature. The catalyst was filtered off and THF was evaporated *in vacuo* from the filtrate. The residual solution was washed with CH_2Cl_2. The separated aqueous layer was concentrated briefly to remove any residual organic solvents *in vacuo* and then subjected to column chromatography on Diaion CHP-20P. The fractions eluted with water containing 1% of THF were combined and lyophilized to give **1a** (30 mg, 63%) as a colorless powder: IR (KBr) cm^{-1} 1755, 1640; ^1H NMR (D_2O) δ 1.20 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz), 2.51 (3H, s), 2.97 (3H, s), 3.07 (3H, s); UV $\lambda_{max}^{H_2O}$ nm 301; SI-MS m/z 420 $(M+Na)^+$, 398 $(M+H)$.

The following compounds (**1b**~**1f**) were prepared in a similar manner to that described above.

1b: IR (KBr) cm^{-1} 1750, 1650; ^1H NMR (D_2O) δ 1.17 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz), 2.32 (3H, s), 2.79 (3H, s), 3.42 (1H, dd, J=2.5 and 6.0 Hz), 4.19 (1H, dd, J=2.5 and 9.0 Hz); UV $\lambda_{max}^{H_2O}$ nm 301.

1c: IR (KBr) cm^{-1} 1750, 1675; ^1H NMR (D_2O) δ 1.20 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz), 2.35 (3H, s), 3.42 (1H, dd, J=2.0 and 6.0 Hz), 4.19 (1H, dd, J=2.0 and 9.0 Hz); UV $\lambda_{max}^{H_2O}$ nm 301.

1d: IR (KBr) cm^{-1} 1755, 1610; ^1H NMR (D_2O) δ 1.20 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz), 2.34 (3H, s), 4.19 (1H, dd, J=2.0 and 9.0 Hz); UV $\lambda_{max}^{H_2O}$ nm 301.

1e: IR (KBr) cm^{-1} 1745, 1640; ^1H NMR (D_2O) δ 1.21 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz),

1.78 (1H, m), 2.76 (3H, s), 2.94 (3H, s), 3.34 (1H, m), 3.48 (1H, dd, J=2.5 and 6.0 Hz); UV $\lambda_{max}^{H_2O}$ nm 298.

1f: IR (KBr) cm^{-1} 1756, 1645; ^1H NMR (D_2O) δ 1.21 (3H, d, J=7.5 Hz), 1.29 (3H, d, J=6.5 Hz), 2.73 (3H, s), 2.74 (3H, s); UV $\lambda_{max}^{H_2O}$ nm 298.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-(5-Dimethylaminocarbonyl-1,1-dimethyl)pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate (**2**)

To a solution of **9a** (104 mg, 0.2 mmol) in Me_2CO (1.5 ml) was added methyl iodide (0.25 ml) and stirred for 1 day at room temperature. The reaction mixture was concentrated *in vacuo* to give a residue which was suspended in EtOAc. The suspension was extracted with 5% $NaHCO_3$ (10 ml × 2). The combined $NaHCO_3$ extracts was neutralized to pH 7.5 with 0.1 M phosphate buffer. To the aqueous solution was added 10% Pd-C (200 mg) and stirred under hydrogen atmosphere for 1 hour at room temperature. Catalyst was filtered off and the filtrate was subjected to column chromatography on Diaion CHP-20P. The fractions eluted with water containing 2% of THF were combined and lyophilized to give **2** (4.8 mg, 6%) as a colorless powder: IR (KBr) cm^{-1} 1740, 1635; ^1H NMR (D_2O) δ 1.20 (3H, d, J=7.0 Hz), 1.28 (3H, d, J=6.5 Hz), 2.37 (1H, m), 3.01 (3H, s), 3.18 (3H, s), 3.28 (3H, s), 3.29 (3H, s), 3.47 (1H, m), 4.00 (1H, m), 4.24 (2H, m), 4.93 (1H, t, J=7.5 Hz); UV $\lambda_{max}^{H_2O}$ nm 298.

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