Synthesis and Antibacterial Activities of New Carbapenems Having a Proline Reverse Amide Moiety at the C-2 Position

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Key Words *1-β-Methylcarbapenems; proline reverse amide moiety; antibacterial activities*

Summary

The synthesis of new 1β-methylcarbapenems (**1a–l**) having a proline reverse amide moiety at the C-2 position and their *in vitro* antibacterial activities are described. The compounds were evaluated by the Mueller-Hinton agar dilution method and compared with meropenem as control. Aliphatic amides (**1a–h**) are found to show greater antibacterial activity than aromatic amides (**1i–l**). Moreover, C-2 free amino compound (**1m**) reveals greater activity than any other amide compounds (**1a–l**).

Introduction

Since the discovery of thienamycin[1] and the appearance of bacteria resistant to penicillins and cephalosphorins, carbapenem antibiotics have become an important class of β-lactam antibiotics. In particular, 1-β-methylcarbapenem derivatives[2,3] exhibited an excellent spectrum of activity and strong stability against renal dehydropeptidase-I (DHP-I). Recently, Sumitomo developed a 1-β-methyl substituted carbapenem with 5′-dimethylaminocarbonyl pyrrolidine-3′-yl thio group at the C-2 side chain of the carbapenem ring system, meropenem, which showed a broad and balanced activity against Gram-positive and Gram-negative bacteria[4]. Thus, our early efforts[5] have been directed toward the synthesis of new 1-β-methylcarbapenems and the elucidation of structure activity relationships. Herein we wish to report the synthesis of the new carbapenems (**1a–l**) having a proline reverse amide moiety at the C-2 position and *in vitro* antibacterial activities of those compounds (Fig. 1).

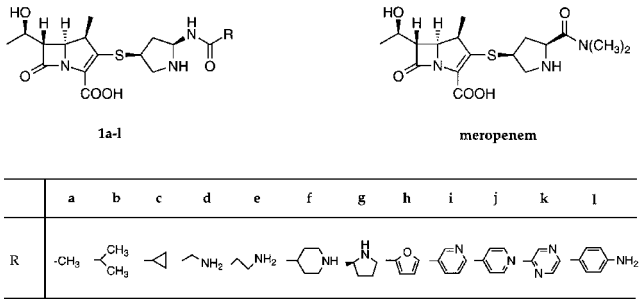
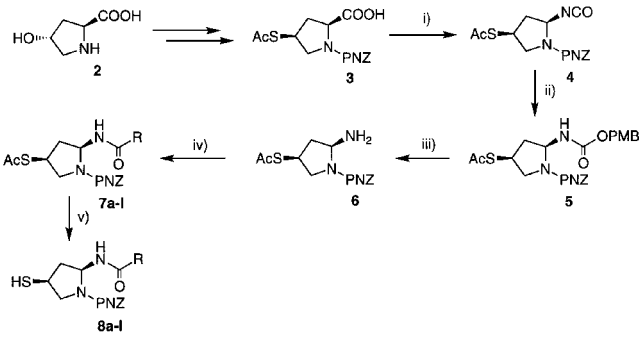


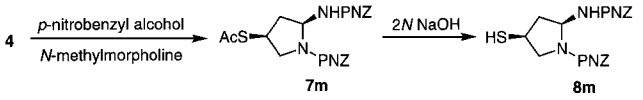
Fig. 1. New carbapenems having a proline reverse amide moiety.



Scheme 1. Synthesis of 4-mercapto proline reverse amide.
i) $(PhO)_2PON_3$, *N*-methylmorpholine; ii) *p*-methoxybenzyl alcohol, *N*-methylmorpholine; iii) CF_3CO_2H; iv) R-CO_2H, DCC, DMAP; v) 2N NaOH.

Synthesis

The synthesis of 4-mercaptoproline reverse amides (**8a–l**) is described in Scheme 1. *N*-*p*-Nitrobenzyloxycarbonyl protected 4-thioacetyl proline (**3**) was prepared from *trans*-4-hydroxy-*L*-proline by a known procedure reported by Sunagawa[4]. Isocyanate **4** was obtained by Curtius rearrangement[6] with retention of stereochemistry at the proline C-2 position of **3**, using diphenylphosphoryl azide and *N*-methylmorpholine in benzene at 80 °C in moderate yield (68%).



Scheme 2. Synthesis of 4-mercapto proline amine.

As any attempts to obtain the key intermediate, amine **6**, from isocyanate **4** directly failed, isocyanate **4** was treated with *p*-methoxybenzyl alcohol to afford the *p*-methoxybenzyl carbamate **5** as a protected amine compound, which was further transformed to the amine trifluoroacetic acid by the treatment with trifluoroacetic acid. Amidation of amine **6** with various aliphatic and aromatic acids in DCC and DMAP gave 4-thioacetyl reverse amides; subsequent saponification with aqueous 2*N* NaOH in MeOH gave 4-mercapto proline reverse amides (**8a–l**). 4-Mercapto proline amine (**8m**) for the synthesis of C-2 free amino carbapenem (**1m**) was prepared from isocyanate **4** according to Scheme 2.

  0365-6233/98/0404/0139 $17.50 +.50/0

Table 1. *In vitro* antibacterial activities of carbapenems **1a–m** (MIC, μg/ml).

Organism	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
S. p. 77A	0.02	0.01	0.01	0.2	0.1	0.1	0.8
S. f. MD8b	12.5	12.5	12.5	50	25	25	50
S. a. SG511	0.2	0.2	0.1	1.5	0.4	0.4	6.2
S. a. 285	0.4	0.2	0.2	1.5	0.8	0.2	6.2
E. c. O55	0.1	0.05	0.05	1.5	0.8	0.4	6.2
E. c. DC2	0.2	0.1	0.1	1.5	0.8	0.8	3.1
E. c. TEM	0.1	0.1	0.1	3.1	1.5	0.8	6.2
P. a. 9027	12.5	50	12.5	100	12.5	25	100
P. a. 1771	6.2	12.5	6.2	100	6.2	6.2	100
S. t.	0.4	0.2	0.2	3.1	1.5	1.5	12.5
K. o. 1082E	0.2	0.2	0.4	6.2	1.5	1.5	25
E. c. P99	0.4	0.2	0.2	6.2	0.8	0.4	12.5
E. c. 1321E	0.1	0.05	0.05	1.5	0.8	0.4	6.2

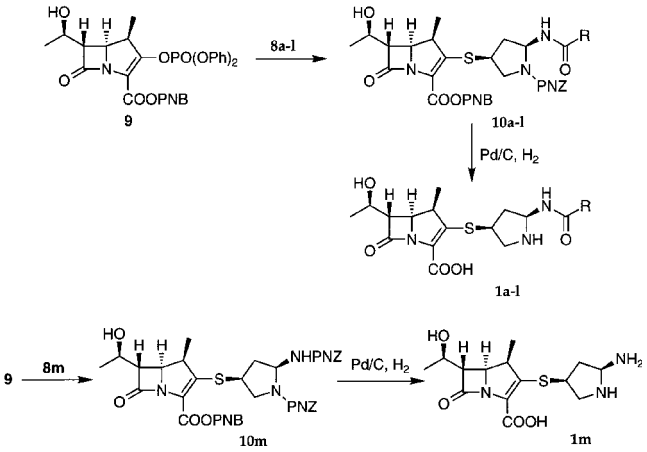
Organism	**1h**	**1i**	**1j**	**1k**	**1l**	**1m**	**MPM**
S. p. 77A	0.2	0.1	0.2	0.4	0.05	0.01	<0.002
S. f. MD8b	50	50	50	50	12.5	12.5	12.5
S. a. SG511	1.5	0.8	1.5	0.8	0.4	0.1	0.1
S. a. 285	1.5	0.8	1.5	1.5	0.4	0.1	0.2
E. c. O55	1.5	0.8	1.5	1.5	0.4	0.1	0.01
E. c. DC2	0.8	1.5	1.5	1.5	0.8	0.2	0.03
E. c. TEM	3.1	0.8	1.5	3.1	0.4	0.1	0.03
P. a. 9027	100	50	100	100	12.5	1.5	0.2
P. a. 1771	100	50	100	100	12.5	3.1	0.2
S. t.	3.1	1.5	3.1	3.1	0.8	0.2	0.03
K. o. 1082E	6.2	3.1	6.2	12.5	0.8	0.4	0.05
E. c. P99	3.1	1.5	3.1	6.2	0.8	0.1	0.03
E. c. 1321E	1.5	0.8	1.5	1.5	0.4	0.1	0.03

Abbreviations: *S. p. Streptococcus pyogenes, S. f. Streptococcus faecium, S. a. Staphylococcus aureus, E. c. Escherichia coli, P. a. Pseudomonas aeruginosa, S. t. Salmonella typhimurium, K. o. Klebsiella oxytoca, E. c. Enterobacter cloacae,* MPM meropenem

Coupling of thiols **8a–l** and the carbapenem nucleus and deprotection of *p*-nitrobenzyloxycarbonyl and *p*-nitrobenzyl groups were carried out in the usual manner[4] to obtain the target carbapenem analogs **1a–l** (Scheme 3).

Antibacterial Activity

In vitro antibacterial activities of new carbapenems having a proline reverse amide are shown in Table 1. The minimal inhibitory concentrations (MICs) of these compounds were determined by the Mueller-Hinton agar dilution method and compared with meropenem as a control.



Scheme 3. Synthesis of new carbapenems.

There was a tendency toward greater antibacterial activity of aliphatic amides (**1a–h**) than those of aromatic amides (**1i–l**) and the bulkier the size of amide, the lower the activity against Gram-positive and Gram-negative bacteria. Interestingly, C-2 free amino compound (**1m**) showed greater activity than any other amide compounds (**1a–l**). However, all the compounds synthesized showed poor activities against both Gram-positive and Gram-negative bacteria compared with meropenem, particularly against *Pseudomonas aeruginosa*. Thus we could infer from the above results that the introduction of reverse amide to the proline C-2 position instead of carboxamides was not desirable for improving the antibacterial activities.

Acknowledgments

We are grateful to the Ministry of Science and Technology (MOST) of Korea for financial support, and wish also to thank Il-Dong Pharm. Co. for its donation of Chair Fund to KIST.

Experimental Section

Melting points Thomas-Hoover apparatus (uncorrected).– UV spectra Hewlett Packard 8451A UV-VIS spectrophotometer.– IR spectra Perkin-Elmer 1710 spectrophotometer, KBr discs.– ^{1}H NMR spectra Varian Gemini 300 spectrometer, TMS int. standard.– MS data Hewlett Packard 59987A electrospray-5989A mass spectrometer.

*(2S,4S)-4-Acetylthio-1-p-nitrobenzyloxycarbonylpyrrolidin-2-isocyanate (**4**)*

N-Methylmorpholine (51.8 g, 513 mmol) and diphenylphosphorazidate (140 g, 513 mmol) were added to a solution of compound **3** (63.0 g, 171 mmol) in dried benzene (450 ml) and stirred at 50–60 °C for 10 h. After cooling, removal of the solvent gave an oily residue, which was chromatographed on silica gel using ethyl acetate/*n*-hexane (1:2) to give **4**, yield 31.5 g (50.0%).– mp 71–73 °C (dec.).– IR (KBr) ν= 1682 cm^{-1} (C=O), 2148 (NCO).– ^{1}H NMR ($CDCl_3$) δ= 2.03–2.36 (m, 1H, H_a3), 2.35 (s, 3H, COCH_3), 2.60–2.79 (m, 1H, H_b3), 3.49–3.54 (m, 1H, H4), 3.90–4.02 (m, 2H, H5), 5.17–5.23 (m, 2H, CH_2-aromatic), 6.63–6.71 (m, 1H, H2), 7.52 (d, *J* = 9.0 Hz, 2H, PNZ H), 8.22 (d, *J*=9.0 Hz, 2H, PNZ H).

*(2S,4S)-4-Acetylthio-1-p-nitrobenzyloxycarbonyl-2-p-methoxybenzyloxycarboaminopyrrolidine (**5**)*

N-Methylmorpholine (16.6 g, 164 mmol) and *p*-methoxybenzyl alcohol (12.5 g, 82.0 mmol) were added to a solution of compound **4** (30.0 g, 82.0 mmol) in dried benzene (350 ml) and stirred at 60–70 °C for 10 h. After

cooling, removal of the solvent gave an oily residue, which was chromatographed on silica gel using ethyl acetate/*n*-hexane (1:2) to give **4**, yield 18.5 g (45.0%).– mp 126–128 °C (dec.).– IR (KBr) ν= 1682 cm^{-1} (C=O).– ^{1}H NMR ($CDCl_3$) δ= 2.16–2.18 (m, 1H, H_a3), 2.34 (s, 3H, CO*CH*$_3$), 2.62–2.70 (m, 1H, H_b3), 3.48–3.53 (m, 1H, H4), 3.79 (s, 3H, O*CH*$_3$), 3.89–4.05 (m, 2H, H5), 5.19–5.27 (m, 2H, *CH*$_2$-aromatic), 5.60–5.71 (m, 1H, H2), 6.85, 7.24 (each-d, 4H, PMB H), 7.52, 8.23 (each-d, 4H, PNZ H).

*(2S,4S)-4-Acetylthio-1-p-nitrobenzyloxycarbonyl-2-aminopyrrolidine (***6***)*

Trifluoroacetic acid (4.5 ml, 57.9 mmol) was added to a solution of compound **5** (634 mg, 1.28 mmol) in dichloromethane (10 ml) and stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* to give an oily residue. The resulting residue was alkalized with satd. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave a crude compound **6** as an oil, yield 355 mg (83.0%), which was used to the next step without purification.

*(2S,4S)-4-Acetylthio-1-p-nitrobenzyloxycarbonyl-2-nicotylaminopyrrolidine (***7i***)*

1,3-Dicyclohexylcarbodiimide (DCC) (390 mg, 1.89 mmol) and *N*,*N*′-dimethylaminopyridine (DMAP) (10 mg) were added to a solution of nicotic acid (233 mg, 1.89 mmol) in THF (10 ml) and stirred at room temperature for 30 min. To this solution was added compound **6** (355 mg, 1.05 mmol). After stirring for 6 h, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give an oily residue. The resulting residue was chromatographed on silica gel using ethyl acetate/*n*-hexane (3:1) to give **7i** as an oil, yield 200 mg (36.0%).– ^{1}H NMR ($CDCl_3$) δ= 1.91–1.99 (m, 1H, H_a3), 2.34 (s, 3H, CO*CH*$_3$), 2.54–2.75 (m, 1H, H_b3), 3.28–3.34 (m, 1H, H4), 3.91–4.12 (m, 2H, H5), 5.09–5.21 (m, 2H, *CH*$_2$-aromatic), 6.08–6.14 (m, 1H, H2), 7.26–7.39 (m, 3H, PNZ 2H and nicotyl 1H), 8.00–8.15 (m, 3H, PNZ 2H and nicotyl 1H), 8.62 (d, 1H, nicotyl H), 8.88 (s, 1H, nicotyl H).

*(2S,4S)-4-Acetylthio-1-p-nitrobenzyloxycarbonyl-2-p-nitrobenzylaminopyrrolidine (***7m***)*

N-Methylmorpholine (552 mg, 5.46 mmol) and *p*-nitrobenzyl alcohol (417 mg, 2.73 mmol) were added to a solution of compound **4** (1.0 g, 2.73 mmol) in dried benzene (20 ml) and stirred at 60–70 °C for 10 h. After cooling, removal of the solvent gave an oily residue, which was chromatographed on silica gel using ethyl acetate/*n*-hexane (1:2) to give **7m**, yield 640 mg (45.0 %).– ^{1}H NMR ($CDCl_3$) δ = 2.10–2.15 (m, 1H, H_a3), 2.36 (s, 3H, CO*CH*$_3$), 2.69–2.73 (m, 1H, H_b3), 3.51–3.55 (m, 1H, H4), 3.92–3.93 (m, 1H, H5), 3.98–4.02 (m, 1H, H5), 5.17–5.21 (m, 4H, *CH*$_2$x2-aromatic), 5.72–5.74 (m, 1H, H2), 7.49–7.51 (m, 4H, PNZ H), 8.17–8.19 (m, 4H, PNZ H).

General procedure for preparation of compounds **8a–m**

The solution of 2*N* NaOH (0.3 ml) was added dropwise to a solution of appropriate alkylthio compound **7** (0.45 mmol) in methanol (10 ml) at 0 °C and stirred for 30 min at the same temperature. After addition of 1*N* HCl (0.6 ml), the reaction mixture was concentrated *in vacuo* to give an oil residue and extracted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave a crude compound **8** , which was used to the next step without purification.

*p-Nitrobenzyl-(1R,5S,6S)-6-[(1R)-1-hydroxyethyl]-2-[(3S,5S)-(5-nicotylamino-1-p-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (***10i***)*

To a solution of *p*-nitrobenzyl-(*1R,5S,6S*)-3-diphenylphosphoryloxy-6-[(*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylate **9** (prepared from 0.68 mmol of diazo keto ester) and *N*,*N*-diisopropylethylamine (106 mg, 0.82 mmol) in acetonitrile (10 ml) was added diphenylchlorophosphate (213 mg, 0.82 mmol) at 0 °C under N_2. After stirring for 3 h, the reaction mixture was cooled to –30 °C.

N,*N*-Diisopropylethylamine (106 mg, 0.82 mmol) and compound **8i** was added to this mixture, and then stirred at room temperature for 8 h. The reaction mixture was diluted with ethyl acetate, washed with water and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was chromatographed on silica gel using ethyl acetate/methanol (10:1) to give **10i** as an oil, yield 75 mg (20.0%).– ^{1}H NMR ($CDCl_3$) δ = 1.28 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.33 (d, *J* = 7.2 Hz, 3H, *CH*$_3$CHOH), 2.00–2.18 (m, 1H, H_a4′), 2.89–2.95 (m, 1H, H_b4′), 3.28–3.36 (m, 2H, H2′), 3.69–3.78 (m, 1H, H6), 3.85–3.94 (m, 2H, H3′ and H5), 4.24–4.38 (m, 2H, CH_3*CH*OH, H1), 5.09–5.24 (m, 4H, *CH*$_2$x2-aromatic), 6.34–6.42 (m, 1H, H5′), 7.34–7.52 (m, 5H, PNB 2H, PNZ 2H and nicotyl 1H), 7.62–7.65 (m, 2H, PNB 2H), 7.93–8.03 (m, 1H, nicotyl 1H), 8.14–8.16 (m, 2H, PNZ 2H), 8.70–8.82 (m, 1H, nicotyl H), 8.94–9.03 (m, 1H, nicotyl H).

General procedure for the preparation of carbapenems **1a–m**

The appropriate compound **10** (0.10 mmol) and 10% Pd/C (35.0 mg) were dissolved in THF/phosphate buffer (pH=7) (1:1, 10 ml each). The mixture was hydrogenated at 50–60 psi at room temperature for 3h. The solution was filtered through celite and washed with water. The filtrate and washings were diluted with ethyl acetate. The separated aqueous layer was lyophilized to give a residue, which was purified on a Diaion HP-20 column by eluting with 1% THF in water. Fractions having a UV absorption at 298 nm were collected and lyophilized again to give the title compound **1** as a white powder.

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-acetylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1a***)*

Yield 37.2%.– ^{1}H NMR (D_2O) δ = 1.26 (d, *J* = 7.3 Hz, 3H, 1-CH_3), 1.33 (d, *J* = 6.2 Hz, 3H, *CH*$_3$CHOH), 2.03-2.10 (s and m, 4H, NHCO*CH*$_3$ and H_a4′), 2.93–2.98 (m, 1H, H_b4′), 3.41–3.54 (m, 3H, H2′ and H6), 3.72–3.78 (m, 1H, H3′), 4.08–4.10 (m, 1H, H5), 4.27–4.31 (m, 2H, CH_3*CH*OH, H1), 5.53–5.59 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-isopropionylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1b***)*

Yield 35.1%.– ^{1}H NMR (D_2O) δ = 1.13 [d, *J* = 6.6 Hz, 6H, COCH *(CH*$_3$*)*$_2$], 1.24 (d, *J* = 7.1 Hz, 3H, 1-CH_3), 1.30 (d, *J* = 6.3 Hz, 3H, *CH*$_3$CHOH), 2.02–2.10 (m, 1H, H_a4′), 2.57–2.63 [m, 1H, CO*CH*$(CH_3)_2$], 2.89–2.94 (m, 1H, H_b4′), 3.40–3.50 (m, 3H, H2′ and H6), 3.67–3.73 (m, 1H, H3′), 4.01–4.05 (m, 1H, H5), 4.24–4.28 (m, 2H, CH_3*CH*OH, H1), 5.49–5.55 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-cyclopropionylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1c***)*

Yield 35.3%.– ^{1}H NMR (D_2O) δ = 0.77–0.80 (m, 2H, *CH*$_2$-cyclopropyl), 0.98–1.08 (m, 2H, *CH*$_2$-cyclopropyl), 1.42–1.46 (m, 1H, CO*CH*-cyclopropyl), 1.26 (d, *J* = 7.3 Hz, 3H, 1-CH_3), 1.32 (d, *J* = 7.2 Hz, 3H, *CH*$_3$CHOH), 2.02–2.16 (m, 1H, H_a4′), 2.89–2.96 (m, 1H, H_b4′), 3.40–3.49 (m, 3H, H2′ and H6), 3.92–4.08 (m, 2H, H3′ and H5), 4.26–4.40 (m, 2H, CH_3*CH*OH, H1), 5.51–5.57 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-aminoacetylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1d***)*

Yield 74.2%.– ^{1}H NMR (D_2O) δ = 1.26 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, *CH*$_3$CHOH), 1.96–2.12 (m, 1H, H_a4′), 2.90–3.02 (m, 1H, H_b4′), 3.34–3.53 (m, 5H, H6, H2′ and CO*CH*$_2$NH$_2$), 3.65–3.81 (m, 1H, H3′), 4.01–4.11 (m, 1H, H5), 4.23–4.30 (m, 2H, CH_3*CH*OH and H1), 5.61–5.69 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-aminopropionylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1e***)*

Yield 79.0%.– ^{1}H NMR (D_2O) δ = 1.28 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, *CH*$_3$CHOH), 1.99–2.22 (m, 1H, H_a4′), 2.81 (t, 2H, COCH$_2$*CH*$_2$NH$_2$), 2.90–3.01 (m, 1H, H_b4′), 3.32 (t, 2H, CO*CH*$_2$CH$_2$NH$_2$), 3.39–3.50 (m, 3H, H6 and H2′), 3.70–3.78 (m, 1H, H3′), 4.02–4.11 (m, 1H, H5), 4.21–4.29 (m, 2H, CH_3*CH*OH and H1), 5.50–5.57 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-isonipecotylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1f***)*

Yield 49.4%.– ^{1}H NMR (D_2O) δ = 1.24 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, *CH_3*CHOH), 1.72–1.81 (m, 1H, H_a4′), 1.84–1.92, 2.03–2.15 (each m, 4H, *CH_2*x2-nipecotyl), 2.67–2.72 (m, 1H, CO*CH*-nipecotyl), 2.98–3.09 (m, 1H, H_b4′), 3.11–3.16 (m, 2H, *CH_2*-nipecotyl), 3.38–3.54 (m, 5H, *CH_2*-nipecotyl, H6 and H2′), 3.78–3.81 (m, 1H, H3′), 4.04–4.12 (m, 1H, H5), 4.24–4.29 (m, 2H, CH_3*CH*OH and H1), 5.22–5.27 (m, 1H, H5′).– MS *m/z* 438 (M^-).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-(2-pyrrolidinyl)-carbonylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1g***)*

Yield 33.7%.– ^{1}H NMR (D_2O) δ = 1.25 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.35 (d, *J* = 6.2 Hz, 3H, *CH_3*CHOH), 1.87–2.05 (m, 4H, NH*CH_2CH_2*-pyrrolidinyl), 2.04–2.08 (m, 1H, H_a4′), 2.82–2.92 (m, 1H, H_b4′), 3.38–3.41 (m, 2H, H2′), 3.42–3.62 (m, 3H, NHCH*CH_2*-pyrrolidinyl and H6), 3.72–3.78 (m, 2H, H3′ and H5), 4.23–4.28 (m, 3H, NH*CH*CH_2-pyrrolidinyl, CH_3*CH*OH and H1), 5.65–5.71 (m, 1H, H5′).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-(2-furanyl)-carbonylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1h***)*

Yield 27.2%.– ^{1}H NMR (D_2O) δ = 1.25 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.34 (d, *J* = 6.2 Hz, 3H, *CH_3*CHOH), 2.02–2.14 (m, 1H, H_a4′), 2.86–2.96 (m, 1H, H_b4′), 3.30–3.42 (m, 2H, H2′), 3.58–3.68 (m, 1H, H6), 3.74–3.78 (m, 2H, H3′ and H5), 4.06–4.12 (m, 2H, CH_3*CH*OH and H1), 5.59–5.65 (m, 1H, H5′), 6.52 (s, 1H, furanyl H), 7.02–7.10 (d, *J* = 7.4 Hz, 1H, furanyl H), 8.02–8.10 (d, *J* = 7.8 Hz, 1H, furanyl H).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-nicotylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1i***)*

Yield 85.0%.– ^{1}H NMR (D_2O) δ = 1.28 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.33 (d, *J* = 6.3 Hz, 3H, *CH_3*CHOH), 2.26–2.28 (m, 1H, H_a4′), 3.01–3.06 (m, 1H, H_b4′), 3.42–3.53 (m, 3H, H2′ and H6), 3.77–3.83 (m, 1H, H3′), 4.09–4.13 (m, 1H, H5), 4.29–4.31 (m, 2H, CH_3*CH*OH and H1), 5.78–5.80 (m, 1H, H5′), 7.64–7.69 (m, 1H, pyridyl H), 8.30 (d, *J* = 8.7 Hz, 1H, pyridyl H), 8.79 (s, 1H, pyridyl H), 8.99 (s, 1H, pyridyl H).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-isonicotylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1j***)*

Yield 75.7%.– ^{1}H NMR (D_2O) δ = 1.27 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.31 (d, *J* = 6.3 Hz, 3H, *CH_3*CHOH), 2.22–2.31 (m, 1H, H_a4′), 2.98–3.07 (m, 1H, H_b4′), 3.40–3.45 (m, 3H, H2′ and H6), 3.76–3.83 (m, 1H, H3′), 4.08–4.14 (m, 1H, H5), 4.29–4.31 (m, 2H, CH_3*CH*OH and H1), 5.78–5.79 (m, 1H, H5′), 7.85 (d, *J* = 5.7 Hz, 2H, pyridyl H), 8.30 (d, *J* = 5.7 Hz, 2H, pyridyl H).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-nipecotylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1k***)*

Yield 68.4%.– ^{1}H NMR (D_2O) δ = 1.27 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.32 (d, *J* = 6.3 Hz, 3H, *CH_3*CHOH), 2.26–2.36 (m, 1H, H_a4′), 3.00–3.08 (m, 1H, H_b4′), 3.42–3.47 (m, 3H, H2′ and H6), 3.73–3.82 (m, 1H, H3′), 4.08–4.12 (m, 1H, H5), 4.29–4.31 (m, 2H, CH_3*CH*OH and H1), 5.80–5.91 (m, 1H, H5′), 8.81, 8.90, 9.23 (each-s, 3H, nipecotyl H), $^-$ MS *m/z* 433 (M^-).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-(4-amino)-benzoylaminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1l***)*

Yield 41.1%.– ^{1}H NMR (D_2O) δ = 1.28 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.33 (d, *J* = 6.3 Hz, 3H, *CH_3*CHOH), 2.20–2.29 (m, 1H, H_a4′), 2.95–3.04 (m, 1H, H_b4′), 3.40–3.44 (m, 3H, H2′ and H6), 3.74–3.83 (m, 1H, H3′), 4.03–4.12 (m, 1H, H5), 4.23–4.30 (m, 2H, CH_3*CH*OH and H1), 5.71–5.80 (m, 1H, H5′), 7.15 (d, *J* = 8.2 Hz, 2H, aromatic H), 7.84 (d, *J* = 8.2 Hz, 2H, aromatic H).

*(1R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-2-[(3S,5S)-5-aminopyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (***1m***)*

Yield 8.8%.– ^{1}H NMR (D_2O) δ = 1.28 (d, *J* = 7.2 Hz, 3H, 1-CH_3), 1.34 (d, *J* = 6.2 Hz, 3H, *CH_3*CHOH), 2.08–2.11 (m, 1H, H_a4′), 2.51–2.56 (m, 1H, H_b4′), 3.32–3.49 (m, 2H, H2′), 3.52–3.59 (m, 1H, H6), 3.61–3.70 (m, 1H, H3′), 4.04–4.18 (m, 1H, H5), 4.24–4.32 (m, 2H, CH_3*CH*OH and H1), 5.72–5.81 (m, 1H, H5′).

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Received: January 12, 1998 [FP273]