# Studies on the Synthesis and Structure–Activity Relationships of 2-(2-Functionalized Pyrrolidin-4-ylthio)-1β-methylcarbapenems

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**A series of new carbapenem derivatives, which have a pyrrolidin-4-ylthio group substituted with a hydroxyalkyl or carbamoyl group at the 2′ position as the C-2 side chain, have been prepared. The antibacterial activity and the stability to renal dehydropeptidase-I of these compounds were investigated, and the structure–activity relationships were studied. Among these new carbapenems, (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-hydroxy)ethylmercaptomethyl}pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid (1a) showed the most potent and well balanced activity and was selected as a candidate for further evaluation.**

**Key words** hydroxyethyl pyrrolidine; carbamoyl pyrrolidine; lyophilization; antibacterial activity; renal dehydropeptidase-I

The discovery of thienamycin I,[1,2] the first structurally elucidated carbapenem antibiotic, led to a search for more stable analogues with increased potency, the focused upon improving the chemical stability and also reducing the susceptibility to mammalian dehydropeptidase (DHP-I), which rapidly metabolizes thienamycin, rendering it inactive.[3] In an attempt to increase the potency against gram-negative organisms, especially *Pseudomonas aeruginosa*, the primary amino group of thienamycin was modified to obtain the nucleophilic *N*-formimidoyl derivative imipenem II.[4] This showed improved antibacterial potency and chemical stability, but not reduced susceptibility to DHP-I. Carbapenem compounds with a (4*S*)-pyrrolidin-4-ylthio group at the C-2 position in the carbapenem skeleton have a broad spectrum of activity.[5] Among these compounds, panipenem III was the first to be successfully launched in the market and clinical evaluations are in progress for meropenem IV, BO-2727 V and DX-8739 VI, which have enhanced metabolic stability to renal DHP-I because of the introduction of a 1β-methyl group into the carbapenem skeleton (Fig. 1).

Recently we reported[6,7] the synthesis and biological properties of new carbapenem compounds having 2′-aromatic heterocyclic carbamoyl pyrrolidine and 2′-substituted carbamoyl pyrrolidine as the C-2 side chain. As a continuation of this program, in order to obtain better antibacterial activities against *Pseudomonas aeruginosa* and greater stability to renal DHP-I, we focused our attention on the modification of the substituent on the pyrrolidine side chain. Some carbapenem derivatives with a 2′-hydroxyalkyl or substituted carbamoylalkyl pyrrolidin-4-ylthio group at the C-2 position have been reported in the literature.[8,9] Since we found that the compound **1a**, having a hydroxyethyl group at the C-2 position of pyrrolidine, showed good antibacterial activity, our subsequent research was focused on the biological properties of these compounds (Table 1). The results indicated that the hydroxyethylmercaptopyrrolidine group **1a** is the most appropriate substituent for both good antipseudomonal activity and improved stability against DHP-I.

## Chemistry

Treatment of enolphosphate[7] with freshly prepared thiol compound **6** afforded the 2-substituted carbapenem **7**. Deprotection of **1a** by hydrogenolysis over 10% Pd–C in the presence of 3-morpholinopropanesulfonic acid (MOPS) buffer (0.1, pH = 7.0) provided the target molecule (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2{(2-hydroxy)ethylmercaptomethyl}pyrrolidin-4-ylthio]-6-[(1*R*)-1-hydroxy-

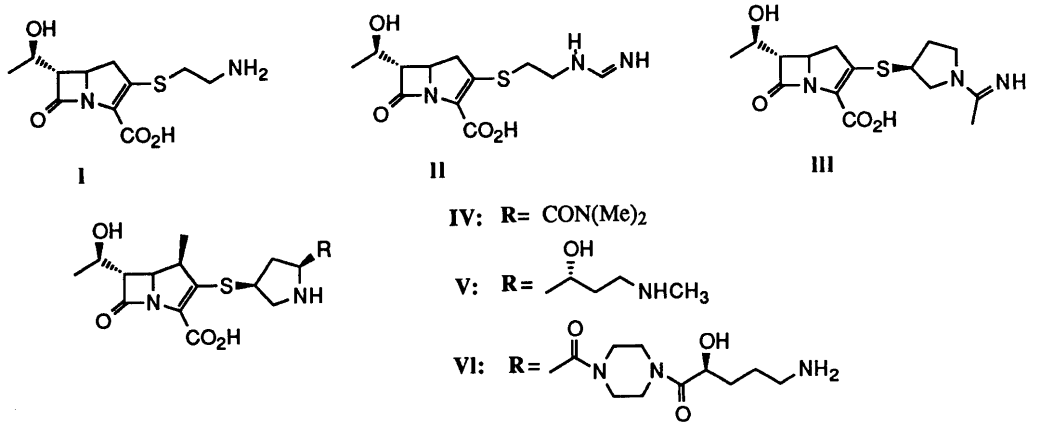


Fig. 1. Thienamycin, Imipenem and Carbapenem Antibiotics Having a (4*S*)-Pyrrolidin-4-ylthio Group at the C-2 Position

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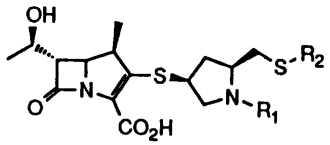
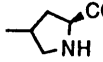
Table 1. Antibacterial Activity and DHP-I Stability of Carbapenems



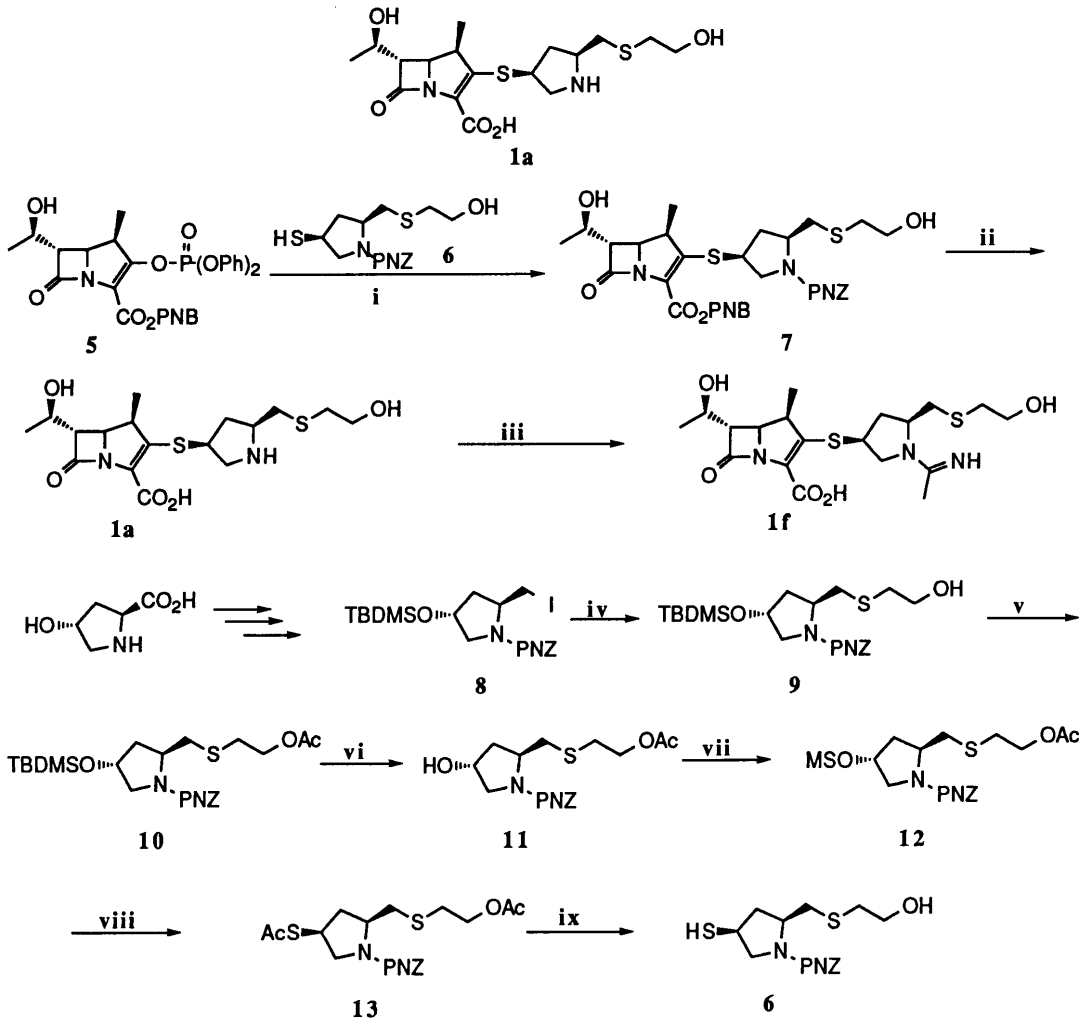
| Compound | $R_1$ | $R_2$ | MIC (μg/ml)[a] | | | | | | DHP-I[c] ($T_{1/2}$) min |
|---|---|---|---|---|---|---|---|---|---|
| | | | *S.a.*[b] | *S.p.* | *E.c.* | *P.a.* | *K.a.* | *En.c.* | |
| **1a** | H | $(CH_2)_2OH$ | 0.05 | 0.01 | 0.05 | 0.10 | 0.20 | 0.05 | 542 |
| **1b** | H | $CH_2CH(OH)CH_3$ | 0.05 | 0.01 | 0.10 | 0.20 | 0.20 | 0.05 | 486 |
| **1c** | H | $CH_2CH(OH)CH_2OH$ | 0.10 | 0.01 | 0.10 | 0.39 | 0.39 | 0.05 | 486 |
| **1d** | H | $(CH_2)_2OCONH_2$ | 0.05 | 0.01 | 0.05 | 0.20 | 0.20 | 0.05 | 516 |
| **1e** | H | $(CH_2)_2CONHCH(OH)$ $H_2NCO$ | 0.05 | 0.01 | 0.10 | 0.39 | 0.39 | 0.39 | 502 |
| **1f** | | $H_3C(=NH)(CH_2)_2OH$ | 0.39 | 0.01 | 1.56 | 6.25 | 0.39 | 0.39 | 520 |
| **1g** | | $H_3C(=NH)(CH_2)_2OCONH_2$ | 0.39 | 0.01 | 3.13 | 6.25 | 0.39 | 0.39 | 472 |
| **2a** | H | $CH_2CONH_2$ | 0.05 | 0.01 | 0.05 | 0.20 | 0.20 | 0.05 | 481 |
| **2b** | H | $CH_2CON(CH_3)_2$ | 0.05 | 0.01 | 0.05 | 0.39 | 0.20 | 0.10 | 463 |
| **2c** | H | $CH_2CONHCH_3$ | 0.05 | 0.01 | 0.10 | 0.78 | 0.20 | 0.05 | 405 |
| **2d** | H | $CH_2CONHEt$ | 0.39 | 0.01 | 0.39 | 1.56 | 0.20 | 0.05 | 385 |
| **2e** | H | $CH_2CONHCH_2CONH_2$ | 0.05 | 0.01 | 0.05 | 0.39 | 0.20 | 0.05 | 511 |
| **2f** | H | $CH_2CONHCH_2CN$ | 0.39 | 0.01 | 0.78 | 1.56 | 0.39 | 0.05 | 487 |
| **2g** | H | $CH_2CONH(CH_2)_2OH$ | 0.39 | 0.01 | 0.78 | 3.13 | 0.39 | 0.05 | 475 |
| **2h** | | $H_3C(=NH)CH_2CONH_2$ | 0.39 | 0.01 | 1.56 | 6.25 | 0.39 | 0.05 | 528 |
| **3** | H | $(CH_2)_2S(CH_2)_2CONH_2$ | 0.78 | 0.01 | 1.56 | 3.12 | 0.20 | 0.39 | 528 |
| **4** | H |  | 0.78 | 0.01 | 0.01 | 6.25 | 0.78 | 1.56 | 487 |
| Meropenem | | | 0.05 | 0.01 | 0.05 | 0.10 | 0.20 | 0.05 | 152 |
| Imipenem | | | 0.05 | 0.01 | 0.10 | 0.20 | 0.39 | 0.05 | 34 |

*a*) Agar dilution method, *b*) *S.a.*, *Staphylococcus aureus SG51*; *S.p.*, *Streptococcus pyrogenes A77*; *E.c.*, *Escherichia coli O55*; *P.a.*, *Pseudomonas aeruginosa 1771M*; *K.a.*, *Klebsiella aerogenes 1522E*; *En.c.*, *Enterobacter cloacae 1321E*, *c*) DHP-I; dehydropeptidase-I (Sigma Chemical Co.; kidney acetone powder-porcine, type II).

ethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid (**1a**). Column purification of the crude product on Diaion HP-20 gave the hydroxyethyl pyrrolidinyl carbapenem derivative **1a** as an amorphous solid. *N*-Methylimidoylation of compound **1a** with methyl acetimidate hydrochloride in 10% $K_2CO_3$ solution provided **1f**. The common intermediate, the 4′-*tert*-butyldimethylsilyl 2′-iodomethyl pyrrolidine derivative **8**, was synthesized by a known method[6,7] using *trans*-4-hydroxy-L-proline as a starting material. Reaction of the iodomethylpyrrolidine compound **8** with 3-hydroxyethanethiol in dimethyl formamide (DMF) afforded the hydroxyethyl mercaptomethyl pyrrolidine compound **9**. Protection of compound **9** was carried out with acetic anhydride in dichloromethane to give the acetylalkylmercaptopyrrolidine compound **10**. Desilyation of compound **10** carried out with 6 N HCl in methanol gave the hydroxypyrrolidine compound **11**. After mesylation of compound **11**, the mesylated acetyloxyethyl pyrrolidine compound **12** was converted into the acetylthio-acetyloxyethyl pyrrolidine compound **13** with potassium thioacetate in DMF, and the acetyl protecting group was readily hydrolyzed with 4 N NaOH solution to give the new thiol pyrrolidine compound **6**. Thus, the thiol compound **6** was obtained in nine steps with the high overall yield of 36.5%.

## Results and Discussion

The minimum inhibitory concentrations (MICs) of the novel carbapenems for gram-positive and gram-negative bacteria and stability data ($T_{1/2}$) with DHP-I are listed in Table 1, along with the values for imipenem and meropenem, for comparison. The nonheterocyclic pyrrolidinyl carbapenem derivatives **1a**—**2h**, except for compound **3**, exhibited enhanced antibacterial activity against *P. aeruginosa* compared to the heterocyclic pyrrolidinyl carbapenem **4**. It is interesting that compounds with *N*-acetimidolylated pyrrolidine at the C-2 side chain, **1f**, **1a** and **2h**, did not show high activity against *P. aeruginosa*. The novel compounds **1a**, **1d**, **2a** exhibited enhanced or similar antibacterial activity to meropenem and imipenem against *P. aeruginosa*. As the extent of functionalization in the carbamoyl group increased, antibacterial activity was generally decreased against gram-negative bacteria, as shown by compound **1a** which exhibited higher activity against *P. aeruginosa* than compounds **1c**—**1e**, **2a**—**2g**. There was no significant difference between the activity of meropenem and that of the **1a**. The hydroxyalkyl pyrrolidine compound **1a** exhibited higher antibacterial activity than the carbamoyl oxyalkyl pyrrolidine compound **1d**, especially against *P. aeruginosa*. It is very interesting that the terminal monohydroxyethyl pyrrolidine **1a** showed superior antibacterial activity to the



Reagents and conditions: i) iso-$Pr_2NEt$, $CH_3CN$, −20 °C, 2 h; ii) $H_2$, 10% Pd–C, MOPS–THF, 55 psi, 4 h; iii) methyl acetimidate–HCl, 10% $K_2CO_3$, 0 °C, 2 h; iv) 2-mercaptoethanol, NaH, DMF, 55—60 °C, 1 h; v) $Ac_2O$, $Et_3N$, $CHCl_3$, r.t., 3 h; vi) 6 N HCl, MeOH, r.t., 2 h; vii) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 1 h; viii) KSAc, DMF, 60—70 °C, 2 h; ix) 4 N NaOH, MeOH, 0 °C, 2 h, acidify.

Chart 1

secondary or branched dihydroxy alkyl pyrrolidine compounds **1b** and **1c** against gram-positive and gram-negative bacteria. Introduction of a heterocyclic carbamoyl pyrrolidine group **4** significantly lowered the antibacterial activity against gram-negative bacteria, especially against *P. aeruginosa*, but afforded good stability to DHP-I. Hydroxy or carbamoylalkyl pyrrolidine compounds **1a**—**4**, showed high stability to renal DHP-I. Also, on the whole, the novel carbapenem derivatives showed enhanced or similar antibacterial activity to imipenem against gram-positive and gram-negative bacteria, except *P. aeruginosa*. Based on the overall biological and physical properties, the novel compound **1a** was selected for further evaluation and is presently under biological evaluation.

## Experimental

**Chemical Reactions** All reactions were conducted under anhydrous conditions in solvents dried over molecular sieves type 4 A in a nitrogen atmosphere. Melting points were determined with a Buchi capillary apparatus and are uncorrected. IR spectra were taken on a Nicolet FT-IR 205 spectrometer. $^1$H-NMR spectra were recorded at 400 HMz on a Bruker spectrometer using TMS or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (in $D_2O$) as an internal standrad. The coupling constants ($J$) are reported in Hz. The mass spectra were measured on VG Trio 2000. For thin-layer chromatography (TLC) analysis, Merck precoated plates (Silica gel $60F_{254}$, 0.25 mm) were used. Silica gel 60 (9385, 230—400 mesh) from Merck was used for column chromatography. The yields reported are for chromatographically pure isolated products.

**Measurement of *in Vitro* Antibacterial Activity** The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in Mueller Hinton broth was diluted to about $10^6$ cell/ml with the same broth and inoculated with an inoculating device onto agar containing serial two fold dilutions of the test compounds. Organisms were incubated at 37 °C for 18—20 h. The MIC of a compound was defined as the lowest concentration that visibly inhibited growth.

**4-Nitrobenzyl(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-1-(*p*-nitrobenzyloxycarbonyl)-2-{(2-hydroxy)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(1*R*)-1-hydroxylethyl]-1-methyl-1-carbapen-2-em-carboxylate (7). General Procedure for the Preparation of Compound 1a** A solution of *p*-nitrobenzyl (1*R*,5*S*,6*S*)-6-[(*R*)-1-hydroxyethyl)-1-methyl-2-oxo carbapenem-3-carboxylate (1.5 g, 4.3 mmol) in acetonitrile (20 ml) was cooled at 0 °C under nitrogen atmosphere, and diisopropylamine (0.56 g, 4.3 mmol) and diphenylchlorophosphate (1.15 g, 4.3 mmol) were added. The resulting solution was stirred at 0 °C for 1 h to give *p*-nitrobenzyl (1*R*,5*S*,6*S*)-3-(diphenylphosphoryloxy)-6-[(1*R*)-1-hydroxyethyl-1-methyl-1-carbapen-2-em-3-carboxylate (**5**). To this solution was added diisopropylethylamine (0.56 g, 4.3 mmol) followed by dropwise addition of a solution of **6** (1.9 g, 5.1 ml) in acetonitrile (10 ml). The mixture was stirred for 2 h, then evaporated *in vacuo* to obtain a crude residue, which was purified by silica gel column chromatography to obtain **7** as a yellow oil (47.5%). $^1$H-NMR ($CDCl_3$) $\delta$: 1.25 (d, 3H, $J$=7.0 Hz), 1.32 (d, 3H,

$J$=6.0 Hz), 3.10—4.83 (m, 3H), 4.81 (br, 2H), 5.24 (s, 2H), 5.38 (dd, $J$=18 Hz), 7.56—7.68 (dd, 4H, $J$=9 Hz), 8.24 (d, 4H, $J$=8 Hz). IR (Nujol) $cm^{-1}$: 3400, 1770—1740, 1710—1680, 1605.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-Hydroxy)ethylmercaptomethyl}pyrrolidine-4-yl]-thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1a). General Procedure for Deprotection of 1a** Compound **7** (1.8 g, 3.2 mmol) and 10% palladium on charcoal (1.8 g) were suspended in THF–MOPS buffer (pH=7.0, 30 ml). The mixture was hydrogenated at 55 psi for 4 h. This mixture was filtered through Celite. The filtrate was washed with chloroform (2×20 ml) and lyophilized to give a white powder, which was purified on HP-20 resin with 5% THF in water as the eluent. Fractions having a UV absorption at 297.5 nm were collected and lyophilized again to give the title compound **1a** as a powder (36.5%). $^1$H-NMR ($D_2O$) $\delta$: 1.21 (d, 3H, $J$=8 Hz), 1.28 (d, 3H, $J$=9 Hz), 1.52—1.89 (m, 1H), 2.40—2.91 (m, 1H), 3.28—3.45 (m, 5H), 3.61—3.78 (m, 1H), 3.91—4.06 (m, 2H), 4.20—4.30 (m, 2H). IR (KBr) $cm^{-1}$: 3400, 1745, 1710, 1680, 1605. mp 168—173.5 °C (dec.). SI-MS ($m/z$) 403 $(M+H)^+$. UV $\lambda_{max}^{H_2O}$: 297.5 nm

**4-Methylimidoyl (1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-hydroxy)ethylmercaptomethyl}pyrrolidin-4-yl]-thio-6-[(1*R*)-1-hydroxylethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1f)** Methylacetimidate hydrochloride (0.25 g, 2.7 mmol) was added to a solution of compound **1a** (1.2 g, 2.5 mmol) in water (15 ml) at 0 °C. The resulting solution was adjusted to pH 8.4 by adding 10% $K_2CO_3$ solution at the same temperature. When the reaction was completed, the reaction mixture was adjusted to pH 6.5 by adding 1 N HCl, and then washed with EtOAc (50 ml). The organic layer was removed and the aqueous layer was lyophilized to obtain the title compound **1f** (80%). $^1$H-NMR ($D_2O$) $\delta$: 1.21 (d, 3H, $J$=7.0 Hz), 1.27 (d, 3H, $J$=7.4 Hz), 1.60—1.85 (m, 1H), 2.39 (s, 3H), 2.63—2.82 (m, 1H), 3.25—4.05 (m, 8H). IR (KBr) $cm^{-1}$: 3400—3100, 1750—1725, 1580. mp 180—185 °C (dec.). SI-MS ($m/z$) 444 $(M+H)^+$.

General procedure for the preparation of the **1b—4** all derivatives, **1b—4**, were prepared in the same manner as described above for **1a—1f**.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2-Hydroxy)propylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1b)** Yield: 28.4%, $^1$H-NMR ($D_2O$) $\delta$: 1.19 (d, 3H, $J$=8 Hz), 1.28 (d, 3H, $J$=8 Hz), 2.61—2.88 (m, 1H), 3.23—3.69 (m, 4H), 3.85—4.04 (m, 4H). IR (KBr) $cm^{-1}$: 1750—1745, 1590—1560. mp 175—180 °C (dec.). UV $\lambda_{max}^{H_2O}$: 297.3 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2,3-Dihydroxy)propylmercaptomethyl}-pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1c)** Yield: 32.5%, $^1$H-NMR ($D_2O$) $\delta$: 1.22 (d, 3H, $J$=8 Hz), 1.27 (d, 3H, $J$=7.5 Hz), 1.70—1.86 (m, 1H), 2.58—2.88 (m, 1H), 3.32—3.76 (m, 6H), 3.82—3.93 (m, 1H). IR (KBr) $cm^{-1}$: 1755, 1740, 1585, 1560. mp 168—174 °C (dec.). UV $\lambda_{max}^{H_2O}$: 296.1 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2-Carbamoyloxy)ethylmercaptomethyl}-pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1d)** Yield: 38.6%, $^1$H-NMR ($D_2O$) $\delta$: 1.22 (d, 3H, $J$=7 Hz), 1.28 (d, 3H, $J$=6 Hz), 1.6—1.9 (m, 1H), 2.65—2.95 (m, 1H), 3.27—3.63 (m, 6H). IR (KBr) $cm^{-1}$: 1750, 1725, 1705, 1580. mp 148—155 °C (dec.). SI-MS ($m/z$) 446 $(M+H)^+$. UV $\lambda_{max}^{H_2O}$: 295.5 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2-Carbamoyloxy(hydroxy)methylcarbamoyl)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1e)** Yield: 17.5%, $^1$H-NMR ($D_2O$) $\delta$: 1.21 (d, 3H, $J$=9 Hz), 1.27 (d, 3H, $J$=6 Hz), 1.64—1.80 (m, 1H), 2.58—2.74 (m, 1H), 3.28—3.68 (m, 4H), 3.85—4.05 (m, 4H). IR (KBr) $cm^{-1}$: 1755, 1650, 1580. mp >168 °C (dec.). UV $\lambda_{max}^{H_2O}$: 298.9 nm.

**4-Methylimidoyl(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2-(hydroxy)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1f)** Yield: 65.3%, $^1$H-NMR ($D_2O$) $\delta$: 1.18 (d, 3H, $J$=7 Hz), 1.27 (d, 3H, $J$=6 Hz), 1.67—1.82 (m, 1H), 2.68—2.88 (m, 1H), 2.68—2.88 (m, 1H), 3.31—3.72 (m, 6H), 3.82—4.06 (m, 2H). IR (KBr) $cm^{-1}$: 1755, 1750, 1580, 1560. mp >183 °C (dec.). UV $\lambda_{max}^{H_2O}$: 296.4 nm.

**4-Methylimidoyl(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-(2-(carbamoyl)ethylmercaptomethyl}pyrrolidin-4yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (1g)** Yield: 37.4%, $^1$H-NMR ($D_2O$) $\delta$: 1.17 (d, 3H, $J$=8Hz), 1.27 (d, 3H, $J$=7 Hz), 1.66—1.81 (m, 1H), 2.58 (s, 3H), 3.65—3.75 (m, 2H), 3.87—4.07 (m, 2H). IR (KBr) $cm^{-1}$: 1755, 1750, 1580, 1560. mp 176—182 °C (dec.). UV $\lambda_{max}^{H_2O}$: 296.5 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{2-Carbamoyl)methyl}mercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2a)** Yield: 28.4%, $^1$H-NMR ($D_2O$) $\delta$: 1.21 (d, 3H, $J$ =7 Hz), 1.27 (d, 3H, $J$=7 Hz), 1.65—1.80 (m, 1H), 2.71—2.85 (m, 1H), 3.28—4.12 (m, 10H). IR (KBr) $cm^{-1}$: 1750, 1670, 1580, 1150. mp 171—174 °C (dec.). UV $\lambda_{max}^{H_2O}$: 297.3 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{*N*,*N*-Dimethylcarbamoyl}methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2b)** Yield: 31.5%, $^1$H-NMR ($D_2O$) $\delta$: 1.19 (d, 3H, $J$=7.5 Hz), 1.27 (d, 3H, $J$=6.5 Hz), 1.66—1.82 (m, 1H), 2.63—2.78 (m, 1H), 3.30—3.72 (m, 6H), 3.82—4.06 (m, 2H). IR (KBr) $cm^{-1}$: 1755, 1680, 1610. mp >177 °C (dec.). UV $\lambda_{max}^{H_2O}$: 298.5 nm.

**(1R,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{*N*-Methylcarbamoyl}methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2c)** Yield: 35.7%, $^1$H-NMR ($D_2O$) $\delta$: 1.18 (d, 3H, $J$=7 Hz), 1.28 (d, 3H, $J$=7 Hz), 1.71—1.86 (m, 1H), 2.74—2.91 (m, 1H), 3.25—4.11 (m, 8H). IR (KBr) $cm^{-1}$: 1750, 1710, 1610, 1580. mp 168—174 °C (dec.). UV $\lambda_{max}^{H_2O}$: 295.5 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{*N*-Ethylcarbamoyl}methylmercaptomethyl}-pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2d)** Yield: 30.8%, $^1$H-NMR ($D_2O$) $\delta$: 1.20 (d, 3H, $J$=8 Hz), 1.29 (d, 3H, $J$=8 Hz), 1.74—1.85 (m, 1H), 2.58—2.74 (m, 1H), 3.52—4.28 (m, 8H). IR (KBr) $cm^{-1}$: 1755, 1745, 1680, 1590. mp 180—185 °C (dec.). UV $\lambda_{max}^{H_2O}$: 299.4 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-Carbamoylmethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2e)** Yield: 19.3%, $^1$H-NMR ($D_2O$) $\delta$: 1.22 (d, 3H, $J$=7 Hz), 1.28 (d, 3H, $J$=6 Hz), 1.64—1.82 (m, 1H), 2.62—2.80 (m, 1H), 3.26—3.39 (m, 5H), 3.84—4.10 (m, 2H), 4.16—4.29 (m, 2H). IR (KBr) $cm^{-1}$: 1760, 1750, 1590, 1580, 1150. mp >178 °C (dec.). UV $\lambda_{max}^{H_2O}$: 298.2 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-Cyanomethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2f)** Yield: 27.3%, $^1$H-NMR ($D_2O$) $\delta$: 1.21 (d, 3H, $J$=9 Hz), 1.27 (d, 3H, $J$=7.5 Hz), 1.58—1.74 (m, 1H), 2.72—2.84 (m, 1H), 3.55—4.05 (m, 12H). IR (KBr) $cm^{-1}$: 1755, 1690, 1580. mp >180 °C (dec.). UV $\lambda_{max}^{H_2O}$: 297.8 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4S)-2-{(2-Hydroxyethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2g)** Yield: 25.4%, $^1$H-NMR ($D_2O$) $\delta$: 1.20 (d, 3H, $J$=7.5 Hz), 1.28 (d, 3H, $J$=6.5 Hz), 1.61—1.84 (m, 1H), 3.32—3.54 (m, 5H), 3.65—3.84 (m, 6H). IR (KBr) $cm^{-1}$: 1760, 1755, 1745. mp 174—177 °C (dec.). UV $\lambda_{max}^{H_2O}$: 296.6 nm.

**4-Methyl(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-Carbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2h)** Yield: 74.3%, $^1$H-NMR ($D_2O$) $\delta$: 1.19 (d, 3H, $J$=7.0 Hz), 1.28 (d, 3H, $J$=6 Hz), 1.68—1.84 (m, 1H), 2.39 (s, 3H), 2.64—2.88 (m, 1H), 3.35—3.80 (m, 8H). IR (KBr) $cm^{-1}$: 1750, 1730, 1580. mp >187 °C (dec.). UV $\lambda_{max}^{H_2O}$: 298.2 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(2-Carbamoylethylmercapto)ethylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (3)** Yield: 41.3%, $^1$H-NMR ($D_2O$) $\delta$: 1.20 (d, 3H, $J$=7.0 Hz), 1.28 (d, 3H, $J$=6 Hz), 1.82 (m, 1H), 3.31—3.55 (m, 4H), 3.65 (m, 1H), 3.94—4.04 (m, 2H). UV $\lambda_{max}^{H_2O}$: 297.1 nm.

**(1*R*,5*S*,6*S*)-2-[(2*S*,4*S*)-2-{(*N*-Dimethylcarbamoyl)methylmercaptomethyl}pyrrolidin-4-yl]thio-6-[(1*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic Acid (2g)** Yield: 15.7%, $^1$H-NMR ($D_2O$) $\delta$: 1.19 (d, 3H, $J$=7 Hz), 1.27 (d, 3H, $J$=7 Hz), 1.72—1.85 (m, 1H), 2.68—2.92 (m, 1H), 2.85—4.85 (m, 14H). IR (KBr) $cm^{-1}$: 1750, 1582, 1290, 1260. mp >200 °C (dec.). UV $\lambda_{max}^{H_2O}$: 296.8 nm.

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