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Original article

Synthesis and antibacterial evaluation of 1β-methyl-2-[5-(1-methoxyimino-2-substituted sulfonamide ethyl)pyrrolidin-3-ylthio]carbapenems and their related compounds

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Abstract

The synthesis of a new series of 1β-methylcarbapenems having methoxyimine and substituted sulfonamide moieties is described. Their *in vitro* antibacterial activities against both Gram-positive and Gram-negative bacteria were tested and the effect of substituents on the pyrrolidine ring was investigated. A particular compound (**IIIc**) having methylaminosulfonamide moiety showed the most potent antibacterial activity.

Keywords: 1β-Methylcarbapenems; Antibacterial activity; DHP-I stability

1. Introduction

Carbapenems are one of the most potent types of antibacterial agents and are among those used as last resort against infections in the clinical field. Three carbapenems, imipenem [1–2], meropenem (**1**) [3], and ertapenem(**2**) [4] have been marketed so far. In particular, it was revealed that 1β-methylcarbapenems showed not only a broad antibacterial spectrum against both Gram-positive and Gram-negative bacteria but also high stability to human renal DHP-I [5–6]. The carbapenem compounds which have a (3*S*)-pyrrolidin-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity [7] and a large number of derivatives have been synthesized and investigated. At present, several carbapenem derivatives such as S-4661 (**3**) [8], BO-2727 [9] and E-1010 [10] are under clinical or preclinical studies since the launch of meropenem.

We were also reported that the carbapenem compounds having a pyrrolidin-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity, and a large number of derivatives have been synthesized [11–14]. We conceived that the introduction of additional methoxyimine and sulfonamide moieties into pyrrolidine side chain was responsible for the improvements of antibacterial activity, because the compounds having methoxyimine and sulfonamide moieties have shown to enhance drug activity in general. In this paper, we described the synthesis and structure–activity relationships of the 1β-methylcarbapenems having a 5′-(1-methoxyimino-2-substituted sulfonamide ethyl)pyrrolidin-3′-ylthio group as a C-2 side chain and our approach for improvement of antibacterial activity of the carbapenems was discussed.

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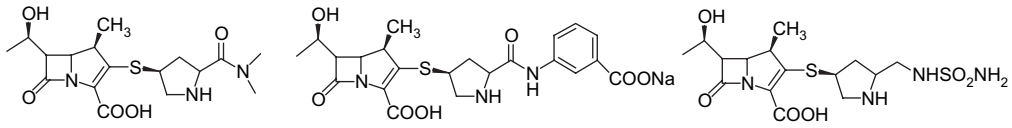


1, Meropenem **2, Ertapenem** **3, S-4661**

2. Results and discussion

2.1. Chemistry

Our general synthetic route leading to new carbapenems involved the preparation of appropriately protected thiols containing pyrrolidine ring as a side chain and subsequent coupling reaction with the carbapenem diphenylphosphate, followed by deprotection of the resulting protected carbapenems in a usual manner.

Acid **1** was treated with *N*,*N*′-carbonyldiimidazole and potassium salts of nitromethane, generated *in situ* from nitromethane and potassium *t*-butoxide in THF, to provide **2**, which was also successfully converted into **3** by treatment with methoxylamine. The key intermediate **4** was obtained by the reaction of **3** with indium wire in THF and subsequent treatment with methanesulfonyl chloride, ethanesulfonyl chloride, methylsulfamoyl, ethylsulfamoyl, dimethylsulfamoyl chloride, propylsulfamoyl and acetyl chloride afforded the corresponding *N*-acylated products, **5a**–**h**. Deprotection of the trityl group to mercaptans (**Ia**–**h**) was achieved by treatment of **5a**–**h** with trifluoroacetic acid in the presence of triethylsilane (Scheme 1).

Preparation of aminocarbamoyl compound (**5i**) was accomplished by treatment of compound **4** with trimethylsilylisothiocyanate reagent. Deprotection of the trityl group to mercaptan (**Ii**) was achieved by treatment of **5i** with trifluoroacetic acid in the presence of triethylsilane (Scheme 2).

Finally, the reaction of **6** [5] with thiols (**Ia**–**i**) in the presence of diisopropylethylamine provided the corresponding 2-substituted carbapenems (**IIa**–**i**). Deprotection of these compounds by treatment of tetrakis(triphenylphosphine)palladium(0) and tributyltin hydride gave the crude products, which were purified by HP-20 column to give the pure carbapenems (**IIIa**–**i**) (Scheme 3).

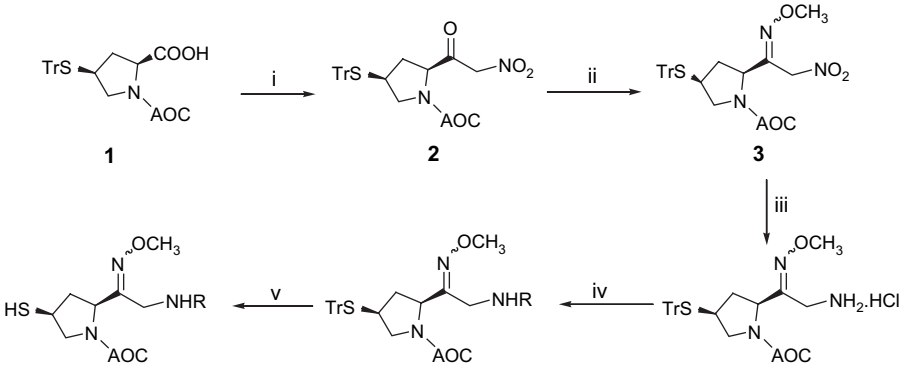
2.2. Biological activity

2.2.1. Measurement of in vitro antibacterial activity

The MICs were determined by the agar dilution method using test agar. An overnight culture of bacteria in tryptosoy broth was diluted to about 10^6 cells/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 MICs of a compound were defined as the lowest concentration that visibly inhibited growth.

2.2.2. Antibacterial activity studies

The *in vitro* antibacterial activities of the new carbapenems (**IIIa**–**i**) prepared above against both Gram-positive and Gram-negative bacteria are listed in Table 1. For comparison, the MIC values of imipenem and meropenem are also listed. All the compounds displayed superior or similar antibacterial activities against Gram-positive to meropenem, and against Gram-negative bacteria except *Pseudomonas aeruginosa* to imipenem.

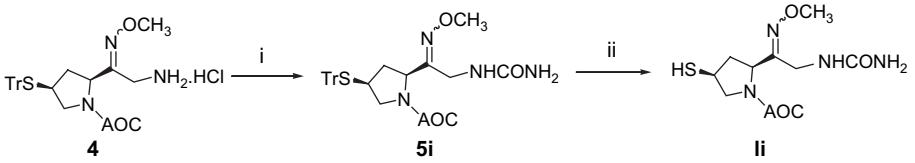


1 **2** **3** **4** **Ia-h** **5a-h**

R:a=SO_2CH_3, b=$SO_2C_2H_5$ c=SO_2NHCH_3, d=$SO_2NHC_2H_5$ e=$SO_2N(CH_3)_2$, f=$SO_2NHC_3H_7$ g=$COCH_3$, h=H

(i) 1. *N*,*N*-Carbonyldiimidazole 2. Potassium *tert*-butoxide, nitromethane, THF (ii) Methoxylamine hydrochloride, pyidine (iii) indiumwire, HCl, H_2O, THF (iv) a=Mesyl chloride b=Ethanesulfonyl chloride c=Methylsulfamoyl chloride d=ethylsulfamoyl chloride e=Dimethylsulfamoyl chloride f=propylsulfamoyl chloride g=Acetyl chloride h=Allylchloroformate (v) Trifluoroacetic acid, triethylsilane, CH_2Cl_2

Scheme 1.



(i) Trimetylsilylisocyanate, CH_2Cl_2 (ii) Trifluoroacetic acid, triethylsilane, CH_2Cl_2

Scheme 2.

As to the substituents on the pyrrolidine chain, the compounds **IIIc–f** having alkylaminosulfonamide moieties were generally more potent than the alkylsulfonamide compounds **IIIa–b**. In alkylaminosulfonamide compounds **IIIc–f**, it also shows that the larger the size of the alkyl substituents, the lower the activity against Gram-positive and Gram-negative bacteria. As expected, methylaminosulfonamide compound **IIIc** with small alkyl group exhibited the most potent and well balanced activity. Also we observed that acetyl amide substituted compound **IIIg** is more potent than aminocarbamoyl **IIIi** against all bacteria.

The stability to DHP-I of most compounds was tested and all the tested compounds were more stable than meropenem. In particular, the compounds **IIIa** and **IIIc** exhibited the most stability (Table 2).

Comparative *in vitro* activities of **IIIc**, meropenem, and imipenem against 40 bacterial strains were summarized in Table 3. The selected carbapenem **IIIc** possessed excellent *in vitro* activity against 40 target pathogens except *P. aeruginosa*, and superior or similar antibacterial activities against Gram-positive to meropenem, and against Gram-negative bacteria to imipenem. Against *Klebsiella pneumonise*, *Escherichia coil* and *Enterobacter cloacae* **IIIc** was 2–4 times more active than the compared meropenem and imipenem.

3. Experimental

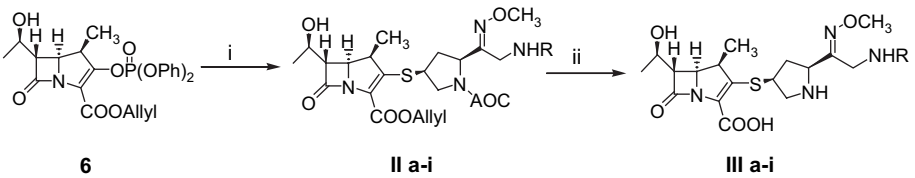
Melting point (mp): Thomas Hoover apparatus, uncorrected. UV spectra: Hewlett Packard 8451A UV–vis spectrophotometer. IR spectra: Perkin–Elmer 16F-PC FT-IR. NMR spectra: Varian Gemini 300 spectrometer, tetramethylsilane (TMS) as an internal standard. The mass spectrometry system was based on a HP5989A MS Engine (Palo Alto, CA, USA) mass spectrometer with a HP Model 59987A.

*3.1. (2S,4S)-2-[(1-Oxo-2-nitro)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**2**)*

A mixture of acid **1** (4.0 g, 8.5 mmol) and *N,N′*-carbonyldiimidazole (1.6 g, 10.2 mmol) suspended in dry THF (100 mL) was stirred under nitrogen until the solution was clear (*ca*. 1 h). To an ice-cold solution of potassium *t*-butoxide (1.1 g, 10.2 mmol) in dry THF (20 mL) was slowly added nitromethane (2.3 g, 42.5 mmol) at 0 °C, and the mixture stirred for 30 min at room temperature. The prepared above solution of the imidazolide of **1** was transferred rapidly under a nitrogen stream directly to the nitronate salt suspension which was stirred vigorously at 0–5 °C for 30 min. After stirring for 17 h at room temperature, the mixture was neutralized with 1 N HCl, and then was diluted with H_2O (50 mL) and ethyl acetate (100 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by silica gel column chromatography (EtOAc:hexane = 1:4) to give **2** (2.8 g, 55%). ^{1}H NMR ($CDCl_3$) δ 1.98–2.16 (m, 2H), 2.97 (q, 1H, $J = 4.3$ Hz), 3.14–3.20 (m, 2H), 4.23 (bs, 1H), 4.59 (bs, 2H), 5.26–5.32 (m, 4H), 5.84–5.89 (m, 1H), 7.23–7.36 (m, 9H), 7.50 (d, 6H, $J = 5.4$ Hz).

*3.2. (2S,4S)-2-[(1-Methoxyimino-2-nitro)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**3**)*

To a solution of **2** (1.0 g, 2.0 mmol) in dry pyridine (20 mL) was added dropwise methoxylamine hydrochloride (0.41 mL, 2.4 mmol, 35%) and was stirred for 10 h at 50 °C. The mixture was evaporated under reduced pressure. The residue was dissolved with ethyl acetate and washed with 1 N HCl, 10% $NaHCO_3$ and brine. The organic layer was concentrated *in vacuo* to give a residue, which was purified by silica gel column chromatography (EtOAc:hexane = 1:1) to give **3** (0.75 g,



R:a=SO_2CH_3, b=$SO_2C_2H_5$ c=SO_2NHCH_3, d=$SO_2NHC_2H_5$
e=$SO_2N(CH_3)_2$, f=$SO_2NHC_3H_7$, g=$COCH_3$, h=H, i=$CONH_2$

(i) *N,N*-Diisopropylethyl amine, **Ia-h** (ii) n-Bu_3SnH, cat. $(PPh_3)_4Pd(0)$, CH_2Cl_2

Scheme 3.

Table 1
In vitro antibacterial activity (MIC, μg/mL) of carbapenem derivatives **IIIa–i**

Strains	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	IIIh	IIIi	IPM[a]	MPM[b]
Streptococcus pyogenes 308A	0.098	0.195	<0.01	<0.01	0.025	0.049	<0.01	<0.01	<0.01	<0.01	0.013
Streptococcus pyogenes 77A	0.098	0.098	<0.01	<0.01	0.013	0.025	<0.01	<0.01	0.013	<0.01	<0.01
Staphylococcus aureus SG511	0.195	0.195	0.049	0.049	0.195	0.195	0.049	0.098	0.098	0.013	0.098
Staphylococcus aureus 285	0.391	0.781	0.098	0.098	0.195	0.195	0.098	0.195	0.195	0.013	0.098
Escherichia coli DC2	0.195	0.391	0.013	0.013	0.098	0.098	0.025	0.049	0.049	0.391	0.025
Escherichia coli TEM	0.195	0.195	0.025	0.049	0.098	0.195	0.025	0.195	0.049	0.195	0.025
Pseudomonas aeruginosa 9027	12.5	12.5	1.56	3.12	6.25	12.5	1.56	3.12	1.56	0.781	0.195
Salmonella typhimurium	0.781	1.56	0.025	0.025	0.195	0.098	0.049	0.098	0.098	0.781	0.025
Klebsiella aerogenes 1522E	0.781	0.781	0.025	0.049	0.391	0.195	0.049	0.195	0.195	0.098	0.049
Enterobactor cloacae 1321E	0.391	0.781	0.013	0.025	0.195	0.195	0.013	0.098	0.049	0.098	0.025

[a] Imipenem.
[b] Meropenem.

71%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.19–1.96 (m, 2H), 2.06 (bs, 1H), 2.48–2.54 (m, 1H), 2.82 (bs, 1H), 2.94 (bs, 1H), 3.94 (d, 3H, $J = 4.6$ Hz), 4.60 (d, 2H, $J = 9.4$ Hz), 5.07–5.13 (m, 2H), 5.23–5.28 (m, 2H), 5.84–5.89 (m, 1H), 7.23–7.35 (m, 9H), 7.51 (d, 6H, $J = 4.4$ Hz).

*3.3. (2S,4S)-2-[(1-Methoxyimino-2-methanesulfonylamino)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**5a**)*

To a solution of **3** (1.3 g, 2.4 mmol) and indium wire (2.0 g) in THF (20 mL) were added H_2O (2.0 mL) and concentrated HCl (1.5 mL), and stirred at room temperature for 4 h. Evaporation of the solvent *in vacuo* gave a crude residue **4**. To above residue and triethylamine (1.0 mL, 7.1 mmol) in dry CH_2Cl_2 (50 mL) was added slowly mesyl chloride (0.4 g, 4.7 mmol) at 0 °C and was stirred for 1 h at same temperature. The mixture was diluted with H_2O (100 mL), CH_2Cl_2 (100 mL) and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the resulting residue was purified by silica gel column chromatography to give **5a** (0.9 g, 60%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.01–2.09 (bs, 1H), 2.22–2.28 (m, 1H), 2.75–2.86 (m, 1H), 2.92 (s, 3H), 3.01–3.48 (m, 2H), 3.85 (d, 3H, $J = 5.4$ Hz), 4.41–4.62 (m, 3H), 5.25 (d, 2H, $J = 18.3$ Hz), 5.82–5.93 (m, 1H), 7.21–7.33 (m, 9H), 7.46 (d, 6H, $J = 7.5$ Hz).

The synthesis of compounds **5b–h** was carried out by the same procedure as described for the preparation of **5a**.

Compound **5b**: Yield 68%. ^{1}H NMR ($CDCl_3$) δ 1.24–1.36 (t, 3H, $J = 4.2$ Hz), 1.92–2.20 (m, 2H), 2.77–2.82 (m, 1H), 2.92–3.10 (m, 3H), 3.63–3.78 (m, 3H), 3.85 (d, 3H, $J = 5.1$ Hz), 4.43–4.55 (m, 3H), 5.21–5.28 (m, 2H), 5.79–5.90 (m, 1H), 7.21–7.33 (m, 9H), 7.46 (d, 6H, $J = 3.6$ Hz).

Compound **5c**: Yield 55%. ^{1}H NMR ($CDCl_3$) δ 1.86–1.97 (m, 2H), 2.84 (d, 3H, $J = 5.4$ Hz), 3.57–3.72 (m, 3H), 3.85 (d, 3H, $J = 6.0$ Hz), 4.10–4.17 (m, 2H), 4.43–4.59 (m, 3H), 5.21–5.27 (m, 2H), 5.81–5.90 (m, 1H), 7.24–7.34 (m, 9H), 7.44–7.47 (m, 6H).

Compound **5d**: Yield 61%. ^{1}H NMR ($CDCl_3$) δ 1.20–1.22 (t, 3H, $J = 6.3$ Hz), 1.87–1.93 (m, 1H), 2.13–2.28 (m, 1H), 3.09 (q, 2H, $J = 6.3$ Hz), 3.23–3.29 (m, 2H), 3.70–3.88 (m, 5H), 4.44–4.52 (m, 4H), 5.20 (d, 2H, $J = 11.4$ Hz), 5.78–5.91 (m, 1H), 7.25–7.37 (m, 9H), 7.46 (d, 6H, $J = 7.5$ Hz).

Compound **5e**: Yield 46%. ^{1}H NMR ($CDCl_3$) δ 1.85–1.89 (m, 1H), 2.11–2.27 (bs, 1H), 2.77 (s, 3H), 2.89 (s, 3H), 3.48–3.66 (m, 2H), 3.72–3.80 (bs, 2H), 3.82–3.86 (d, 3H, $J = 6.0$ Hz), 4.31–4.50 (m, 3H), 5.23 (d, 2H, $J = 9.0$ Hz), 5.85–5.90 (m, 1H), 7.24–7.33 (m, 9H), 7.46 (d, 6H, $J = 7.2$ Hz).

Compound **5d**: Yield 43%. ^{1}H NMR ($CDCl_3$) δ 1.20–1.22 (t, 3H, $J = 6.0$ Hz), 1.67–1.75 (m, 2H), 1.89–1.95 (m, 1H), 2.19–2.38 (bs, 1H), 3.02 (q, 2H, $J = 6.1$ Hz), 3.25–3.33 (m, 2H), 3.71–3.92 (m, 5H), 4.41–4.51 (m, 4H), 5.20 (d, 2H, $J = 9.7$ Hz), 5.78–5.91 (m, 1H), 7.25–7.37 (m, 9H), 7.46 (d, 6H, $J = 7.5$ Hz).

Compound **5g**: Yield 55%. ^{1}H NMR ($CDCl_3$) δ 1.86–1.96 (m, 2H), 2.05 (s, 3H), 2.11–2.17 (m, 1H), 2.73–2.82 (m, 1H), 2.91–3.02 (m, 2H), 3.83 (d, 3H, $J = 3.9$ Hz), 4.39–4.53 (m, 4H), 5.21–5.28 (m, 2H), 5.82–5.91 (m, 1H), 7.20–7.32 (m, 9H), 7.42 (d, 6H, $J = 7.5$ Hz).

Compound **5h**: Yield 57%. ^{1}H NMR ($CDCl_3$) δ 1.87–2.05 (m, 2H), 2.73 (bs, 1H), 2.83–2.89 (bs, 2H), 2.94–2.97 (m, 1H), 3.45–3.49 (m, 2H), 3.88 (d, 3H, $J = 3.3$ Hz), 4.40–4.59 (m, 5H), 5.16–5.28 (m, 4H), 5.79–5.82 (m, 2H), 7.22–7.33 (m, 9H), 7.47 (d, 6H, $J = 7.6$ Hz).

Table 2
DHP-I stability of **IIIa**, **IIIc**, **IIId** and **IIIi**

	IIIa	IIIc	IIId	IIIi	Meropenem	Imipenem
DHP-I	1.40	1.32	1.18	1.09	1.00	0.14

*3.4. (2S,4S)-2-[(1-Methoxyimino-2-aminocarbamoyl)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (**5i**)*

To the above residue (**4**, 2.0 g, 3.6 mmol) and triethylamine (0.8 mL, 5.4 mmol) in dry CH_2Cl_2 (20 mL) was added slowly trimethylsilyl isocyanate (0.7 mL, 5.4 mmol) at 0 °C and was stirred for 7 h at same temperature. The mixture was diluted with H_2O (30 mL), CH_2Cl_2 (40 mL) and washed with brine. After drying (Na_2SO_4), the filtrate was concentrated under

Table 3
Comparative *in vitro* antibacterial activity of **IIIc**, meropenem and imipenem against 40 strains (MIC, μg/mL)

Organism	**IIIc**	IPM	MPM	Organism	**IIIc**	IPM[a]	MPM[b]
Staphylococcus aureus giorgio	0.03	0.01	0.10	*Salmonella paratyphi* A	0.10	0.10	0.03
Staphylococcus aureus 209P	0.03	0.01	0.10	*Salmonella typhimurium*	0.20	0.40	0.05
Staphylococcus aureus 503	0.03	<0.01	0.05	*Salmonella oranienberg*	0.20	0.40	0.05
Micrococcus luteus ATCC 9341	0.01	0.01	0.05	*Salmonella typhi*	0.03	0.05	0.01
Streptococcus facium 77A	<0.01	<0.01	0.01	*Salmonella orion*	0.10	0.20	0.10
Streptococcus agalctiae B	0.03	0.01	0.05	*Salmonella give*	0.10	0.20	0.03
Streptococcus durans D	0.10	0.10	0.80	*Klebsiella pneumonise* 477	0.03	0.20	0.05
Bacillus subtilts ATCC 6633	0.03	0.03	0.05	*Enterobacter cloacae*	0.01	0.10	0.03
Bacillus megatherium	0.05	0.03	0.05	*Enterobacter cloacae* 417	0.05	0.10	0.01
Pseudomonas aeruginosa 9027	1.56	0.80	0.40	*Serratia marcescens* 370	0.20	0.20	0.05
Pseudomonas aeruginosa 77/2	1.56	0.80	0.80	*Serratia marcescens* 6093	0.20	0.40	0.05
Pseudomonas aeruginosa 110/2	0.80	0.80	0.40	*Serratia marcescens* 14273	0.40	0.80	0.20
Pseudomonas aeruginosa 880/2	0.40	0.80	0.20	*Proteus mirabilis* 112/3	0.20	0.20	0.10
Pseudomonas cepacia	0.40	0.80	0.40	*Proteus mirabilis* 174/3	0.20	0.10	0.10
Escherichia coil 086	0.03	0.20	0.05	*Proteus vulgaris* 868	0.40	0.10	0.10
Escherichia coil 0114	0.03	0.20	0.03	*Proteus rettgeri* 936	0.40	0.20	0.10
Escherichia coil 0126	0.03	0.10	0.05	*Proteus rettgeri* 937	0.40	0.20	0.05
Escherichia coil V6311/65	0.05	0.05	0.01	*Pasteurella multocida*	0.05	<0.01	0.05
Escherichia coil TEM	0.03	0.20	0.03	*Corynebacterium diphtheriae*	0.01	0.01	0.05
Escherichia coil 1507	0.05	0.10	0.03	*Corynebacterium pyogenes*	0.01	<0.01	0.03

[a] Imipenem.
[b] Meropenem.

reduced pressure, and the resulting residue was purified by silica gel column chromatography to give **5i** (0.6 g, 31%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.89–2.06 (m, 2H), 2.74–2.99 (m, 1H), 3.05–3.26 (bs, 1H), 3.45–3.49 (bs, 2H), 3.82 (d, 3H, $J = 2.7$ Hz), 4.39–4.57 (m, 4H), 5.20–5.30 (m, 2H), 5.84–5.85 (m, 1H), 7.15–7.33 (m, 9H), 7.45 (d, 6H, $J = 7.2$ Hz).

*3.5. Allyl (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[[5-(1-methoxyimino-2-methanesulfonylamino) ethyl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (**IIa**)*

To a solution of **5a** (0.4 g, 0.7 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise triethylsilane (0.3 mL, 1.5 mmol) at 5 °C, and then TFA (1.5 mL). After stirring for 30 min at room temperature, the mixture was evaporated under reduced pressure. The residue was dissolved with ethyl acetate and washed with 10% $NaHCO_3$ and brine. The organic layer was concentrated *in vacuo* to give a residue **Ia**, which was used without further purification. A solution of allyl (1*R*,5*S*,6*S*)-2-(diphenylphosphoryloxy)-6-[(*R*)-1-hydroxyethyl]-1-methyl carbapen-2-em-3-carb-oxylate (**6**, 0.6 g, 1.2 mmol) in CH_3CN (10 mL) was cooled to 0 °C under N_2. To this solution was added diisopropylethylamine (0.1 g, 1.0 mmol) and a solution of the mercapto compound **Ia** in CH_3CN (5.0 mL). After stirring for 5 h, the mixture was diluted with ethyl acetate, washed with 10% $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. Evaporation *in vacuo* gave a foam, which was purified by silica gel chromatography (EtOAc:*n*-hexane = 3:1) to give **IIa** (0.3 g, 36%) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.24–1.29 (m, 3H), 1.40 (d, 3H, $J = 14.6$ Hz), 2.05 (bs, 2H), 2.16 (d, 2H, $J = 11.0$ Hz), 2.27–2.35 (m, 1H), 2.57 (bs, 1H), 2.98 (s, 3H), 3.37–3.42 (m, 1H), 3.35–3.69 (m, 1H), 3.90 (bs, 6H), 4.25 (d, 1H, $J = 6.3$ Hz), 4.59 (bs, 1H), 4.70 (dd, 1H, $J = 4.5$ and 12.6 Hz), 4.83 (dd, 1H, $J = 4.5$ and 12.6 Hz), 5.26–5.34 (m, 4H), 5.43 and 5.49 (2s, 1H), 5.94–6.02 (m, 2H).

The synthesis of compounds **IIb–h** was carried out by the same procedure as described for the preparation of **IIa**.

Compound **IIb**: Yield 44%. ^{1}H NMR ($CDCl_3$) δ 1.34–1.39 (m, 6H), 1.46 (d, 3H, $J = 6.3$ Hz), 3.02–3.09 (m, 3H), 3.26 (d, 1H, $J = 5.4$ Hz), 3.34–3.41 (m, 1H), 3.41–3.68 (m, 3H), 3.89–3.96 (bs, 5H), 4.25 (d, 2H, $J = 6.9$ Hz), 4.58 (bs, 3H), 4.70 (dd, 1H, $J = 5.1$ and 13.5 Hz), 4.83 (dd, 1H, $J = 5.1$ and 13.5 Hz), 5.25–5.33 (m, 4H), 5.42 and 5.48 (2s, 1H), 5.91–6.00 (m, 2H).

Compound **IIc**: Yield 32%. ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3H, $J = 6.4$ Hz), 1.34 (d, 3H, $J = 6.6$ Hz), 2.18 (bs, 2H), 2.72–2.81 (bs, 4H), 3.26–3.34 (m, 1H), 3.73–3.85 (m, 2H), 3.90 (bs, 4H), 4.27 (d, 2H, $J = 6.3$ Hz), 4.60 (d, 3H, $J = 7.5$ Hz), 4.70 (dd, 1H, $J = 5.7$ and 12.0 Hz), 4.83 (dd, 1H, $J = 5.4$ and 11.4 Hz), 5.11 (m, 1H), 5.29 (d, 4H, $J = 11.1$ Hz), 5.44 and 5.50 (2s, 1H), 5.9.2–6.01 (m, 2H).

Compound **IId**: Yield 52%. ^{1}H NMR ($CDCl_3$) δ 1.18–1.39 (m, 6H), 1.48 (d, 3H, $J = 6.4$ Hz), 2.05 (bs, 2H), 3.08–3.12 (m, 2H), 3.35–3.42 (m, 1H), 3.65–3.79 (m, 3H), 3.83–3.89 (m, 5H), 4.24–4.33 (bs, 2H), 4.49–4.54 (bs, 3H), 4.72 (dd, 1H, $J = 5.4$ and 11.0 Hz), 5.24 (dd, 1H, $J = 5.4$ and 11.0 Hz), 5.25–5.33 (m, 4H), 5.48 and 5.42 (2s, 1H), 5.92–6.01 (m, 2H).

Compound **IIe**: Yield 54%. ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 3H), 1.40 (d, 3H, $J = 6.2$ Hz), 1.88 (m, 2H), 2.06–2.15 (bs, 2H), 2.82–2.98 (bs, 5H), 3.01 (bs, 1H), 3.60–3.77 (m, 3H), 3.89 (s, 3H), 4.11–4.25 (m, 3H), 4.50 (d, 3H, $J = 3.0$ Hz), 4.60 (bs, 1H), 4.70 (dd, 1H, $J = 6$ and 15.0 Hz), 4.82 (dd, 1H, $J = 5.4$ and 16.0 Hz), 5.28 (d, 3H, $J = 13.2$ Hz), 5.43 and 5.49 (2s, 1H), 5.92–5.97 (m, 2H).

Compound **IIf**: Yield 52%. ^{1}H NMR ($CDCl_3$) δ 1.18–1.39 (m, 6H), 1.48 (d, 3H, $J = 6.4$ Hz), 1.77–1.89 (bs, 2H), 2.05–2.11 (bs, 2H), 3.08–3.12 (m, 2H), 3.34–3.46 (m, 1H), 3.68–3.76 (m, 3H), 3.83–3.89 (m, 5H), 4.24–4.33 (bs, 2H), 4.59–4.654 (bs, 3H), 4.70 (dd, 1H, $J = 5.4$ and 11.0 Hz), 5.22 (dd, 1H, $J = 5.4$ and 11.0 Hz), 5.25–5.33 (m, 4H), 5.48 and 5.42 (2s, 1H), 5.92–6.01 (m, 2H).

Compound **IIg**: Yield 49%. ^{1}H NMR ($CDCl_3$) δ 1.25–1.29 (m, 3H), 1.38 (d, 3H, $J = 6.0$ Hz), 1.81–1.90 (m, 1H), 2.04 (s, 3H), 2.50–2.74 (m, 1H), 3.25–3.37 (m, 3H), 3.61 (bs, 1H), 3.89 (s, 3H), 4.03–4.15 (m, 3H), 4.23–4.24 (m, 2H), 4.59 (d, 3H, $J = 5.4$ Hz), 4.71 (dd, 1H, $J = 6.9$ and 12.9 Hz), 4.85 (dd, 1H, $J = 7.8$ and 17.4 Hz), 5.26–5.34 (m, 4H), 5.43 and 4.48 (2s, 1H), 5.92–6.01 (m, 2H).

Compound **IIh**: Yield 31%. ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3H, $J = 6.6$ Hz), 1.34 (d, 3H, $J = 6.3$ Hz), 2.04–2.12 (bs, 2H), 3.24 (bs, 1H, $J = 5.7$ Hz), 3.31–3.45 (m, 2H), 3.87–3.97 (bs, 5H), 4.24 (d, 2H, $J = 7.5$ Hz), 4.50–4.56 (m, 6H), 4.68 (dd, 1H, $J = 5.7$ and 13.2 Hz), 4.81 (dd, 1H, $J = 5.4$ and 13.5 Hz), 5.20–5.32 (m, 6H), 5.41 and 5.47 (2s, 1H), 5.92–6.03 (m, 3H).

Compound **IIi**: Yield 42%. ^{1}H NMR ($CDCl_3$) δ 1.26 (m, 3H), 1.38 (d, 3H, $J = 6.0$ Hz), 2.20–2.15 (bs, 2H), 2.98–3.09 (m, 2H), 3.26–3.41 (m, 1H), 3.87–3.95 (bs, 6H), 4.10–4.16 (m, 1H), 4.25–4.30 (d, 1H, $J = 6.0$ Hz), 4.38–4.55 (bs, 4H), 4.69 (dd, 1H, $J = 4.2$ and 9.0 Hz), 4.80 (dd, 1H, $J = 4.2$ and 9.0 Hz), 5.29–5.35 (m, 3H), 5.47 and 5.52 (2s, 1H), 5.92–5.97 (m, 2H).

*3.6. (1R,5S,6S)-6-[(1R)-Hydroxyethyl]-2-[[5-(1-methoxyimino-2-methanesulfonylamino)ethyl] pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (**IIIa**)*

To a stirred solution of **IIa** (0.1 g, 0.2 mol) and $Pd(PPh_3)_4$ (30 mg) in CH_2Cl_2 (10 mL) was added dropwise *n*-tributyltin hydride (0.2 mL, 0.5 mmol) at 0 °C and was stirred for 1 h at same temperature. The resulting solution was diluted with water (10 mL) and the organic layers were washed with water (2×10 mL). The combined aqueous layers were washed with ethyl ether (2×10 mL) and lyophilized to give a yellow powder which was purified on a Diaion HP-20 column, eluting with 2% THF in water. Fractions having UV absorption at 298 nm were collected and lyophilized again to give the title compound **IIIa** as an amorphous solid. Yield 24%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.12 (d, 3H, $J = 7.2$ Hz), 1.19 (d, 3H, $J = 6.6$ Hz), 1.84–1.95 (m, 1H), 3.03–3.15 (m, 4H), 3.30–3.46 (m, 3H), 3.56–3.72 (m, 2H), 3.85–3.97 (m, 5H), 4.13–4.20 (m, 3H). IR (KBr): 3480, 1720, 1670, 1630, 1320 cm^{-1}. –HRMS (FAB) Calcd. for $C_{18}H_{28}N_4O_7S_2$ 476.1399, found 476.1396.

The synthesis of compounds **IIIb–i** was carried out by the same procedure as described for the preparation of **IIIa**.

Compound **IIIb**: Yield 27%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.12 (d, 3H, $J = 7.1$ Hz), 1.19–1.29 (m, 6H), 3.10–3.18 (m, 3H), 3.25–3.37 (m, 3H), 3.55–3.57 (m, 1H), 3.63 (bs, 2H), 3.65–3.71 (m, 1H), 3.84 (s, 3H), 3.87–3.89 (m, 2H), 4.13–4.17 (m, 2H). IR (KBr): 3460, 1730, 1710, 1650, 1310 cm^{-1}. –HRMS (FAB) Calcd. for $C_{19}H_{30}N_4O_7S_2$ 490.1556, found 490.15555.

Compound **IIIc**: Yield 23%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.11 (d, 3H, $J = 7.2$ Hz), 1.18 (d, 3H, $J = 6.3$ Hz), 2.06–2.17 (m, 1H), 2.55 (bs, 3H), 2.70–2.801 (m, 1H), 3.23–3.37 (m, 3H), 3.57–3.64 (m, 1H), 3.77 (bs, 2H), 3.88 (bs, 4H), 4.12–4.16 (m, 2H), 4.41 (t, 1H, $J = 9.3$ Hz). IR (KBr): 3460, 1740, 1710, 1630 1320 cm^{-1}. –HRMS (FAB) Calcd. for $C_{18}H_{29}N_5O_7S_2$ 491.1508, found 491.1500.

Compound **IIId**: Yield 25%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.07 (d, 3H, $J = 7.1$ Hz), 1.13 (d, 3H, $J = 8.1$ Hz), 1.20 (t, 3H, $J = 6.0$ Hz), 1.85–2.04 (m, 1H), 2.08–2.21 (m, 1H), 2.96–3.00 (m, 2H), 3.18–3.25 (m, 1H), 3.30–3.39 (m, 4H), 3.71–3.81 (m, 2H), 3.85–3.90 (m, 4H), 4.13–4.18 (m, 2H). IR (KBr): 3490, 1735, 1710, 1640, 1290 cm^{-1}. –HRMS (FAB) Calcd. for $C_{19}H_{31}N_5O_7S_2$ 505.1665, found 505.1663.

Compound **IIIe**: Yield 21%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.10–1.21 (m, 6H), 1.86–1.94 (m, 1H), 2.71 (s, 6H), 2.92–3.05 (m, 2H), 3.24–3.38 (m, 3H), 3.52–3.73 (m, 4H), 3.83 (s, 3H), 4.04–4.16 (m, 2H). IR (KBr): 3540, 1720, 1670, 1620, 1310 cm^{-1}. –HRMS (FAB) Calcd. for $C_{18}H_{28}N_4O_7S_2$ 476.1399, found 476.1396.

Compound **IIIf**: Yield 22%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.07 (d, 3H, $J = 7.1$ Hz), 1.13 (d, 3H, $J = 8.1$ Hz), 1.20 (t, 3H, $J = 6.0$ Hz), 1.65–1.77 (m, 2H), 1.89–2.01 (m, 1H), 2.08–2.25 (m, 1H), 2.90–3.03 (m, 2H), 3.22–3.29 (m, 1H), 3.30–3.39 (m, 4H), 3.71–3.85 (m, 2H), 3.85–3.90 (m, 4H), 4.13–4.20 (m, 2H). IR (KBr): 3490, 1735, 1710, 1650, 1300 cm^{-1}. –HRMS (FAB) Calcd. for $C_{20}H_{33}N_5O_7S_2$ 519.1821, found 519.1820.

Compound **IIIg**: Yield 24%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.11 (d, 3H, $J = 7.2$ Hz), 1.20 (d, 3H, $J = 6.3$ Hz), 1.93–2.02 (bs, 4H), 2.66–2.77 (m, 1H), 3.23–3.31 (m, 2H), 3.35–3.41 (m, 1H), 3.56–3.67 (m, 2H), 3.86 (s, 3H), 3.94 (bs, 2H), 4.10–4.15 (m, 2H), 4.33–4.37 (m, 1H). IR (KBr): 3510, 1730, 1710, 1670, 1620 cm^{-1}. HRMS (FAB) Calcd. for $C_{19}H_{28}N_4O_6S$ 440.1730, found 440.1730.

Compound **IIIh**: Yield 19%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.11 (d, 3H, $J = 7.2$ Hz), 1.20 (d, 3H, $J = 6.3$ Hz), 1.90–1.98 (bs, 1H), 2.06–2.18 (m, 1H), 2.66–2.77 (m, 1H), 3.24–3.57 (m, 4H), 3.70–3.94 (m, 5H), 4.08–4.15 (m, 2H), 4.36–4.50 (m, 1H). IR (KBr): 3440, 1710, 1690, 1630 cm^{-1}. –HRMS (FAB) Calcd. for $C_{17}H_{26}N_4O_5S$ 398.1624, found 398.1620.

Compound **IIIi**: Yield 22%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.12 (d, 3H, $J = 7.1$ Hz), 1.19 (d, 3H, $J = 6.3$ Hz), 2.12 (bs, 1H), 2.69–2.76 (m, 1H), 3.25–3.37 (m, 2H), 3.50–3.59 (m, 2H), 3.63–3.74 (m, 2H), 3.79–3.86 (m, 1H), 3.91 (s, 3H), 4.06–4.17 (m, 2H), 4.36–4.50 (m, 1H). IR (KBr) 3490, 1710, 1690, 1670, 1620 cm^{-1}. –HRMS (FAB) Calcd. for $C_{18}H_{27}N_5O_6S$ 441.1682, found 441.1680.

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