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Short communication

Synthesis and in vitro activity of a series 1β-methylcarbapenem derivatives

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Abstract

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

Keywords: 1β-Methylcarbapenems; Antibacterial activity; Substituent effects

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 [3] and ertapenem [4] have been marketed so far. In particular, since 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 [8], BO-2727 [9] and E-1010 [10] are under clinical or preclinical studies since the launch of meropenem.

We were also interested in this pyrrolidin-3-ylthio group and reported that the carbapenem compounds which have 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 and investigated [11–15].

In this paper, we described the synthesis and structure–activity relationships of the 1 β-methylcarbapenems having 5′-piperidine and pyrrolidine derivatives substituted pyrrolidin-3′-ylthio group as C-2 side chain and our approach to improve the antibacterial activity of the carbapenems is discussed.

2. Results and discussions

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 diphenylphosphates, followed by deprotection of the resulting protected carbapenems in a usual manner.

The β-ketoester **3** was prepared in three steps from glycine ester and ethyl acrylate using Dieckmann condensation method [16]. The intermediate **4** was obtained from decarboxylation of **3** with 10% hydrochloric acid [17], which was deprotected by hydrogenation, respectively, in the presence of palladium carbon to provide the key compounds **5** and **6** (Scheme 1) [18].

The amides **8** and **9** were obtained by treatment of carboxylic acid **7** with β-keto ester amine **5** and **6** using oxalyl chloride. The amides **8** and **9** were converted to the hydroxy compounds **10** and **11** by treatment of sodium borohydride in THF. Preparation of the oximes **12** and **13,** and methoxyimino

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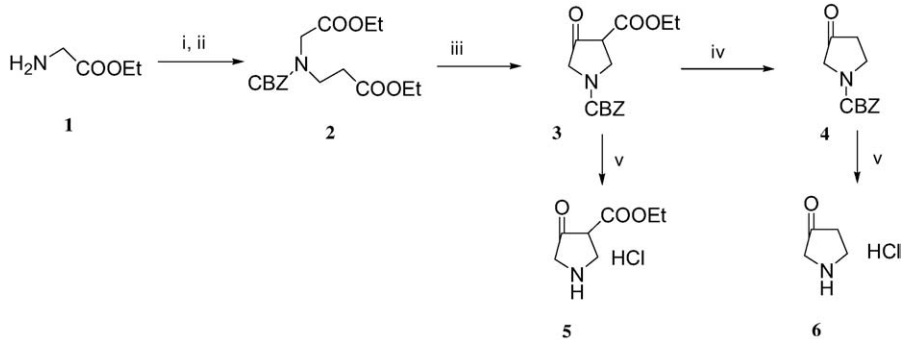
compounds **14** and **15** were accomplished by treatment of the amides **8** and **9** with hydroxyl and methoxyl amine. Deprotection of the trityl group to mercaptans **Ia**–**g** was achieved by treatment of **9**–**15** with trifluoroacetic acid in the presence of triethylsilane (Scheme 2).

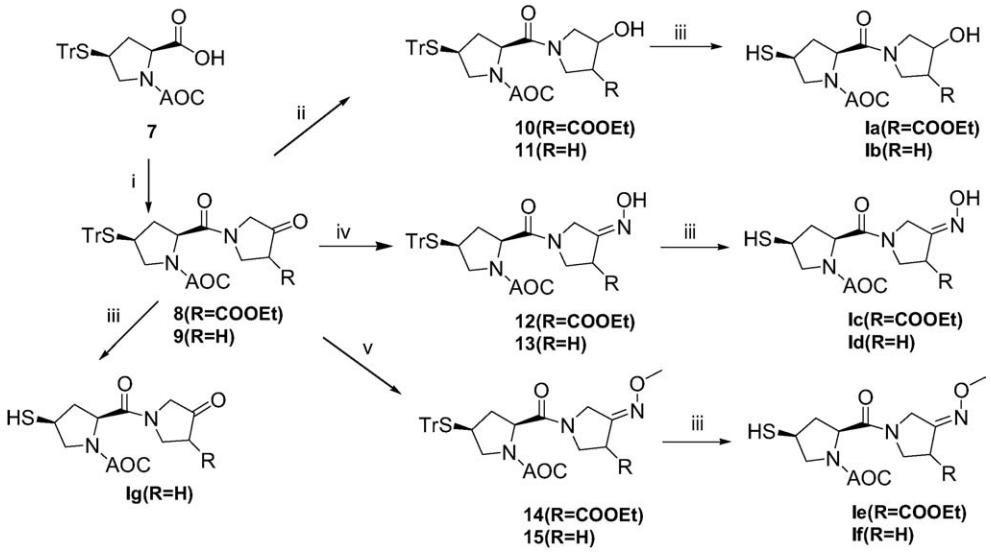
The reaction of benzylamine with excess of ethylacrylate in the presence of triethylamine gave **17** of bis-addition in excellent yield. Compound **17** was subjected to Dieckmann cyclization with sodium hydride to give ethyl-*N*-benzyl-4-oxo-piperidinecarboxylate (**18**) in moderate yield [19].

The compounds **20** and **21** were prepared from **18** and **19** by a similar manner as that described for the preparation of **5** and **6** (Scheme 3).

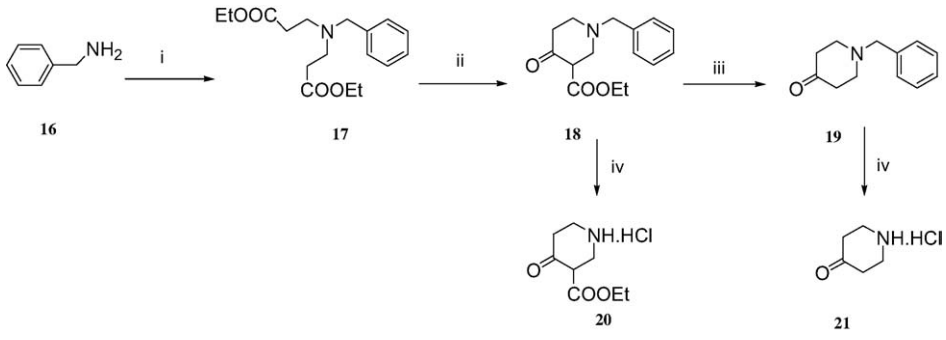
The treatment of the acid **7** with piperidine moiety **20** and **21** using oxalyl chloride gave the amides **22** and **23,** which were successfully converted into the derivatives **24**–**29,** using



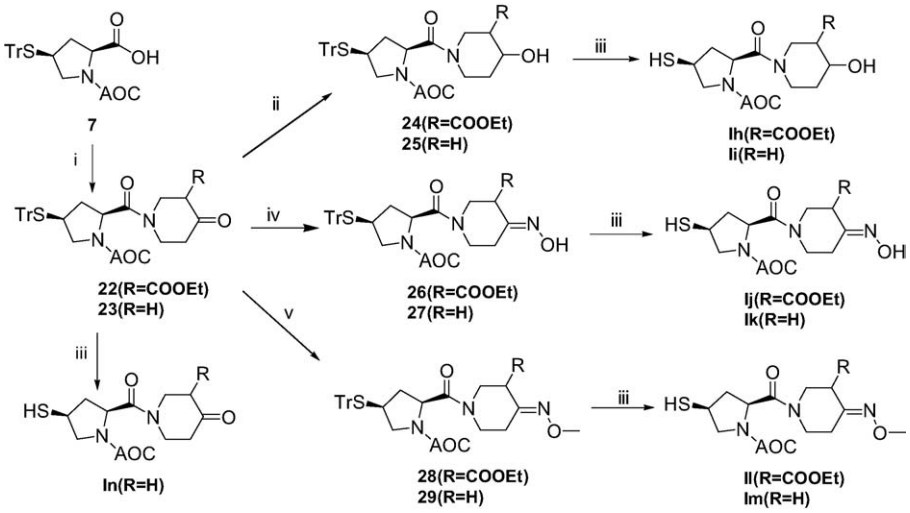
Scheme 1.



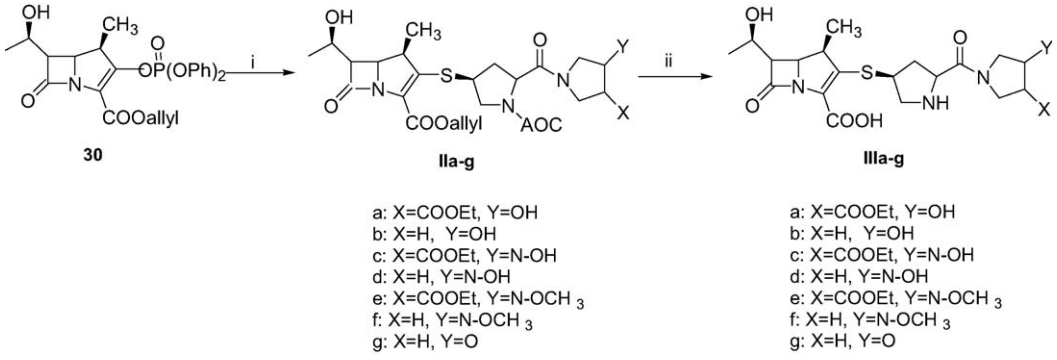
Scheme 2.



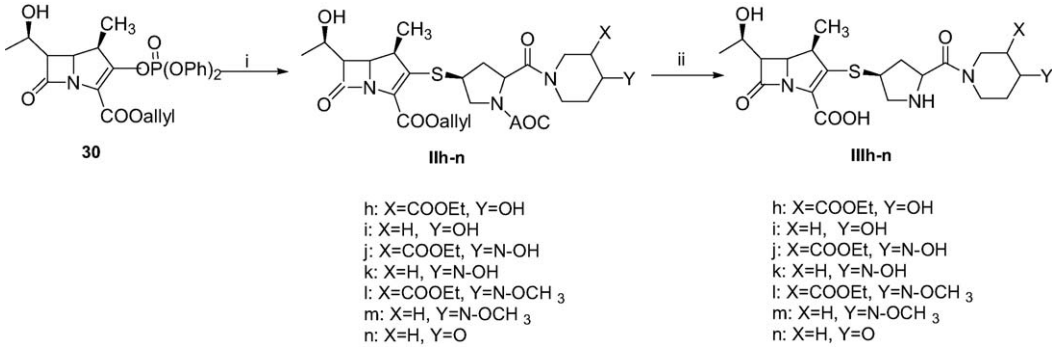
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

the same procedure as described for the preparation of **10**–**15** (Scheme 4).

Finally, the reaction of **30** with thiols (**Ia**–**n**) in the presence of diisopropylethylamine gave the corresponding 2-substituted carbapenems (**IIa**–**n**). 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**–**n**) (Schemes 5 and 6).

2.2. Biological studies

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^{-1} 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 hours. The MICs of a compound were defined as the lowest concentration that visibly inhibited growth.

The in vitro antibacterial activities of the new carbapenems (**IIIa**–**n**) prepared above against Gram-positive and -negative bacteria are listed in Tables 1 and 2. For comparison, the MIC values of imipenem and meropenem are also listed. All compounds displayed superior or similar antibacterial activities against Gram-positive to meropenem, and Gram-negative bacteria to imipenem.

As to the substituent of the C-5 on the pyrrolidine side chain, pyrrolidine moieties (**IIIa**–**g**) were generally more potent than the piperidine moieties (**IIIh**–**n**). Introduction of ester group (**IIIa, IIIc, IIIe, IIIh, IIIj** and **IIIl**) led to significantly lowered antibacterial activity against Gram-positive and Gram-negative bacteria compared to non-ester group (**IIIb, IIId, IIIf, IIIi, IIIk** and **IIIm**). The effects of substituent on the pyrrolidine and piperidine ring were investigated. The compounds (**IIIa**, **IIIb, IIIh and IIIi)** having the hydroxy group were generally more potent than the oxime and methoxy imine groups. As a result, among them, compound **IIIb** having hydroxypyrrolidine moiety showed the most potent antibacterial activity.

Comparative in vitro activities of **IIIb**, meropenem, and imipenem against 40 bacterial strains are summarized in Table 3. The selected carbapenem **IIIb** 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 *Staphylococcus aureus*, *Escherchia coil, Klebsiella pneumonise, Enterobacter cloacae* and *Serratia marcescens,* **IIIb** was 2–5 times more active than the compared meropenem and imipenem.

3. Experimental

Melting point (m.p.): 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-[(4-oxo-3-ethoxycarbonypyrrolidinyl) carbonyl]-4-tritylthio-1-(allyloxycarbon yl)pyrrolidine (**8**)*

To a solution of **7** (2.0 g, 4.2 mmol) in dry CH_2Cl_2 (20 ml) was added drop-wise oxalyl chloride (3.8 ml, 42.0 mmol) and

Table 1
In vitro antibacterial activity(MIC, μg ml^{-1}) of the carbapenem derivatives(**IIIa**–**g**)

Strains	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg	MPM[a]	IPM[b]
Staphylococcus aureus 121	1.56	0.20	12.5	12.5	6.25	12.5	12.5	6.25	1.56
Coagulasen staphylococci	0.20	0.20	0.80	0.20	0.80	0.80	0.80	0.10	0.02
Enterococcus faecalis 234	6.25	6.25	25.0	12.5	12.5	12.5	12.5	12.5	1.56
Streptococcus pyogenes 98	0.01	< 0.01	0.04	0.02	0.04	0.02	0.04	0.01	< 0.01
Streptococcus agalaciae 32	0.01	0.01	0.20	0.10	0.04	0.04	0.10	0.04	0.01
Streptococcus pneumoniae	0.02	< 0.01	0.04	0.04	0.02	0.01	0.04	0.01	< 0.01
Haemophilus influenzae 12	6.25	3.12	12.5	3.12	12.5	6.25	12.5	3.12	6.25
Escherichia coli 04	0.01	0.01	0.10	0.02	0.10	0.10	0.10	0.04	0.20
Klebsiella pneumoniae 52	0.02	0.01	0.10	0.10	0.20	0.10	0.10	0.02	0.80
Citrobacter freundii 323	0.02	0.05	0.20	0.04	0.20	0.10	0.10	0.02	0.40
Enterobacter cloacae 34	0.01	0.01	0.20	0.04	0.10	0.10	0.05	0.02	0.80
Serratia marcescens 3349	0.02	0.01	0.20	0.10	0.20	0.10	0.10	0.04	0.80
Acinetobacter baumannii 2	12.5	6.25	50.0	12.5	50.0	50.0	12.5	6.25	12.5
Pseudomonas aeruginosa 5	25.0	3.12	50.0	3.12	25.0	25.0	6.25	3.12	3.12

[a] Meropenem.
[b] Imipenem.

Table 2
In vitro antibacterial activity (MIC, μg ml^{-1}) of the carbapenem derivatives(**IIIh**–**n**)

Strains	IIIh	IIIi	IIIj	IIIk	IIIl	IIIm	IIIn	MPM	IPM
Staphylococcus aureus 121	3.12	3.12	12.5	6.25	6.25	6.25	12.5	6.25	1.56
Coagulasen staphylococci	0.20	0.10	0.80	0.40	0.10	0.10	0.20	0.10	0.02
Enterococcus faecalis 234	6.25	6.25	25.0	12.5	6.25	6.25	12.5	12.5	1.56
Streptococcus pyogenes 98	0.02	0.01	0.04	0.02	0.01	0.01	0.02	0.01	< 0.01
Streptococcus agalaciae 32	0.02	0.01	0.04	0.02	0.02	0.02	0.04	0.04	0.01
Streptococcus pneumoniae	0.02	0.01	0.04	0.04	< 0.01	< 0.01	0.01	0.01	< 0.01
Haemophilus influenzae 12	3.12	3.12	12.5	6.25	6.25	3.12	3.12	3.12	6.25
Escherichia coli 04	0.02	0.01	0.04	0.02	0.20	0.10	0.04	0.04	0.20
Klebsiella pneumoniae 52	0.10	0.05	0.10	0.10	0.20	0.10	0.04	0.02	0.80
Citrobacter freundii 323	0.02	0.02	0.10	0.04	0.10	0.10	0.04	0.02	0.40
Enterobacter cloacae 34	0.04	0.02	0.04	0.04	0.10	0.10	0.04	0.02	0.80
Serratia marcescens 3349	0.02	0.02	0.10	0.04	0.40	0.10	0.10	0.04	0.80
Acinetobacter baumannii 2	12.5	6.25	25.0	12.5	50.0	50.0	25.0	6.25	12.5
Pseudomonas aeruginosa 5	25.0	12.5	25.0	12.5	25.0	12.5	3.12	3.12	3.12

Table 3
comparative in vitro antibacterial activity of **IIIb**, meropenem and imipenem against 40 strains (MIC, μg ml^{-1})

Organism	**IIIb**	IPM	MPM	Organism	**IIIb**	IPM	MPM
Staphylococcus aureus giorgio	0.01	0.01	0.10	*Salmonella paratyphi A*	0.10	0.10	0.02
Staphylococcus aureus 209P	0.01	0.01	0.10	*Salmonella typhimurium*	0.20	0.40	0.04
Staphylococcus aureus 503	0.01	< 0.01	0.04	*Salmonella oranienberg*	0.20	0.40	0.04
Micrococcus luteus ATCC 9341	0.01	0.01	0.04	*Salmonella typhi*	0.03	0.04	0.01
Streptococcus facium 77A	< 0.01	< 0.01	0.01	*Salmonella orion*	0.10	0.20	0.10
Streptococcus agalctiae B	0.02	0.01	0.04	*Salmonella give*	0.10	0.20	0.02
Streptococcus durans D	0.10	0.10	0.80	*Klebsiella pneumoniae 477*	0.02	0.20	0.04
Bacillus subtilis ATCC 6633	0.02	0.02	0.04	*Enterobacter cloacae*	0.02	0.10	0.04
Bacillus megatherium	0.04	0.02	0.04	*Enterobacter cloacae 417*	0.01	0.20	0.02
Pseudomonas aeruginosa 9027	1.56	0.80	0.40	*Serratia marcescens 370*	0.02	0.20	0.04
Pseudomonas aeruginosa 77/2	0.80	0.80	0.80	*Serratia marcescens 6093*	0.02	0.40	0.04
Pseudomonas aeruginosa 110/2	0.80	0.80	0.40	*Serratia marcescens 14273*	0.10	0.80	0.20
Pseudomonas aeruginosa 880/2	0.80	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 coli 086	0.02	0.10	0.04	*Proteus vulgaris 868*	0.40	0.10	0.10
Escherichia coli 0114	0.02	0.10	0.02	*Proteus rettgeri 936*	0.40	0.20	0.10
Escherichia coli 0126	0.04	0.10	0.04	*Proteus rettgeri 937*	0.40	0.20	0.04
Escherichia coli V6311/65	0.02	0.04	0.02	*Pasteurella multocida*	0.05	<0.01	0.04
Escherichia coli TEM	0.04	0.20	0.04	*Corynebacterium diphtheriae*	0.01	0.02	0.04
Escherichia coli 1507	0.02	0.10	0.04	*Corynebacterium pyogenes*	0.01	<0.01	0.02

was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure. To an ice-cold solution of **5** (0.75 g, 4.2 mmol) and triethylamine (1.4 ml, 10.6 mmol) in dry CH_2Cl_2 (20 ml) was slowly added to the above solution at 0 °C and mixture was stirred for 30 min at room temperature. The mixture was diluted with H_2O (50 ml) and CH_2Cl_2 (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 = 1:3) to give **8** (2.1 g, 82.5%). ^{1}H NMR ($CDCl_3$): δ 1.27–1.36 (m, 3H), 1.45 (bs, 1H), 1.78–1.90 (m, 1H), 1.97–2.06 (m, 1H), 2.41–2.65 (m, 2H), 3.05–3.31 (m, 2H), 3.70–3.82 (m, 2H), 4.12–4.31 (m, 3H), 4.41–4.53 (m, 3H), 5.20–5.31 (m, 2H), 5.82–5.90 (m, 1H), 7.23–7.37 (m, 9H), 7.46 (d, 6H, J = 7.2 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.2, 29.4, 29.6, 31.9, 36.2, 37.2, 51.3, 57.5, 60.6, 62.4, 67.3, 117.2, 126.9, 128.1, 129.5, 132.7, 144.6, 153.2, 170.2, 171.6, 206.2.

The synthesis of compound **9** was carried out by the same procedure as described for the preparation of **8** using compound **6**.

9: ^{1}H NMR ($CDCl_3$): δ 1.76–2.03 (m, 2H), 2.52–2.67 (m, 2H), 2.70–2.82 (m, 1H), 3.13 (d, 2H, J = 9.0 Hz), 3.60–3.74 (m, 1H), 3.77–3.87 (m, 1H), 3.91–4.04 (m, 2H), 4.07–4.14 (m, 1H), 4.40–4.60 (m, 2H), 5.11–5.26 (m, 2H), 5.71–5.93 (m, 1H), 7.20–7.32 (m, 9H), 7.46 (d, 6H, J = 7.5 Hz).

^{13}C NMR (300 MHz, $CDCl_3$): δ 35.7, 36.2, 37.2, 43.3, 52.4, 53.5, 55.7, 66.0, 67.3, 117.3, 127.0, 128.0, 129.5, 132.6, 144.6, 153.1, 170.8, 209.8.

*3.2. (2S,4S)-2-[(4-hydroxy-3-ethoxycarbonypyrrolidinyl) carbonyl]-4-tritylthio-1-(allyloxycar bonyl)pyrrolidine (**10**)*

To a solution of **8** (1.5 g, 2.5 mmol) in THF (30 ml) was added slowly $NaBH_4$ (0.18 g, 4.9 mmol) at 0 °C and was stirred for 2 h at room temperature. The reaction mixture was poured into cold ice water, acidified to pH 4–5 with acetic acid, and then extracted with ethyl acetate. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography (EtOAc/hexane = 1:2) to give **10** (1.2 g, 78.0%) as a pale yellow oil.

^{1}H NMR ($CDCl_3$): δ 1.24–1.32 (m, 3H), 1.82–2.08 (m, 2H), 2.74–2.79 (m, 1H), 2.95–3.08 (m, 2H), 3.15–3.19 (m, 1H), 3.54–3.66 (m, 2H), 3.75–3.82 (m, 1H), 3.83–4.07 (m, 1H), 4.14–4.21 (m, 3H), 4.39–4.55 (m, 3H), 5.14–5.26 (m, 2H), 5.79–5.89 (m, 1H), 7.20–7.33 (m, 9H), 7.46 (d, 6H, J = 7.5 Hz).

The synthesis of compound **11** was carried out by the same procedure as described for the preparation of **10** using compound **9**.

11: ^{1}H NMR ($CDCl_3$): δ 1.67–1.78 (m, 1H), 1.90–1.98 (m, 1H), 2.31–2.51 (m, 3H), 2.59–2.98 (m, 2H), 3.13–3.28 (m, 2H), 3.49–3.64 (m, 2H), 4.05–4.14 (m, 1H), 4.39–4.57 (m, 3H), 5.10–5.23 (m, 2H), 5.83–5.93 (m, 1H), 7.20–7.33 (m, 9H), 7.47 (d, 6H, J = 7.8 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 29.6, 32.6, 34.1, 41.7, 52.2, 53.5, 54.3, 57.0, 67.2, 69.0, 117.4, 126.9, 128.1, 130.0, 132.6, 114.6, 153.4, 171.2.

*3.3. (2S,4S)-2-[(4-hydroxyimino-3-ethoxycarbonypyrrolidinyl) carbonyl]-4-tritylthio-1-(allyl oxycarbonyl)pyrrolidine (**12**)*

To a stirred solution of **8** (1.5 g, 2.5 mmol) in EtOH (20 ml) was added drop-wise 50% aqueous hydroxylamine (0.18 ml, 2.9 mmol) and was stirred for 7 h at 50 °C. The reaction mixture was diluted with ethyl acetate (50 ml) and water (50 ml), and then the organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave a crude residue, which was purified by silica gel column chromatography (EtOAc/hexane = 1:1) to give **12** (1.3 g, 81.2%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.22–1.31 (m, 4H), 1.73–1.94 (m, 1H), 2.74–2.86 (m, 1H), 2.99–3.11 (m, 2H), 3.72–4.05 (m, 3H), 4.10–4.27 (m, 4H), 4.47–4.61 (m, 3H), 5.11–5.23 (m, 2H), 5.71–5.93 (m, 1H), 7.20–7.33 (m, 9H), 7.47 (d, 6H,

J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 21.1, 36.0, 44.8, 47.9, 52.2, 53.5, 56.4, 60.5, 61.9, 67.3, 117.3, 127.0, 128.1, 129.5, 132.6, 144.6, 154.4, 169.4, 170.0, 170.2.

The synthesis of compound **13** was carried out by the same procedure as described for the preparation of **12** using compound **9**.

13: ^{1}H NMR ($CDCl_3$): δ 1.75–1.86 (m, 1H), 1.98–2.05 (m, 1H), 2.65 (t, 1H, J = 7.2 Hz), 2.75–2.79 (m, 2H), 3.10–3.14 (m, 1H), 3.19–3.53 (m, 1H), 3.60–3.64 (m, 1H), 3.84–4.05 (m, 1H), 4.14–4.30 (m, 2H), 4.37–4.53 (m, 3H), 5.10–5.27 (m, 2H), 5.70–5.93 (m, 1H), 7.03–7.32 (m, 9H), 7.47 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 27.1, 29.0, 36.0, 45.8, 52.2, 53.5, 56.5, 57.1, 67.3, 117.3, 127.0, 128.1, 129.5, 132.5, 114.6, 154.4, 158.7, 170.4.

*3.4. (2S,4S)-2-[(4-methoxyimino-3-ethoxycarbonypyrrolidinyl) carbonyl]-4-tritylthio-1-(allyl oxycarbonyl)pyrrolidine (**14**)*

To a solution of **8** (1.0 g, 1.6 mmol) in dry pyridine (20 ml) was added drop-wise methoxylamine hydrochloride (0.52 ml, 2.9 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 **14** (0.78 g, 76.2%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.25–1.34 (m, 4H), 1.73–1.88 (m, 2H), 2.00–2.09 (m, 1H), 2.71–2.80 (m, 1H), 3.06–3.13 (m, 1H), 3.71–3.82 (m, 1H), 3.89–3.95 (m, 4H), 4.11–4.27 (m, 5H), 4.45–4.51 (m, 2H), 5.10–5.22 (m, 1H), 5.27 (d, 1H, J = 6.8 Hz), 5.80–5.91 (m, 1H), 7.20–7.32 (m, 9H), 7.46 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 36.1, 37.1, 44.8, 47.7, 52.2, 53.5, 57.0, 62.0, 65.8, 67.3, 117.1, 126.9, 128.1, 129.5, 132.6, 144.6, 155.4, 164.6, 172.0, 173.2.

The synthesis of compound **15** was carried out by the same procedure as described for the preparation of **14** using compound **9**.

15: ^{1}H NMR ($CDCl_3$): δ 1.84 (t, 1H, J = 10.5 Hz), 1.90–2.05 (m, 1H), 2.67–2.79 (m, 3H), 3.12 (d, 1H, J = 8.1 Hz), 3.29–3.58 (m, 1H), 3.64–3.68 (m, 1H), 3.88 (s, 3H), 3.95–4.00 (m, 1H), 4.07–4.22 (m, 2H), 4.38–4.54 (m, 3H), 5.11–5.28 (m, 2H), 5.71–5.93 (m, 1H), 7.20–7.32 (m, 9H), 7.46 (d, 6H, J = 6.9 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 26.5, 27.2, 36.1, 41.7, 44.4, 46.1, 47.8, 52.0, 62.1, 67.3, 117.2, 126.9, 128.1, 129.5, 132.7, 144.6, 154.1, 165.3, 173.2.

*3.5. (2S,4S)-2-[(4-oxo-3-ethoxycarbonypiperidinyl)carbonyl]-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (**22**)*

To a solution of **7** (2.0 g, 4.2 mmol) in dry CH_2Cl_2 (20 ml) was added drop-wise oxalyl chloride (3.8 ml, 42.0 mmol) and was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure. To an ice-cold solution of **20** (0.72 g, 4.2 mmol) and triethylamine (1.4 ml, 10.5 mmol) in dry CH_2Cl_2 (20 ml) was slowly added the prepared above solution at 0 °C and was the mixture stirred for 30 min at room temperature. The mixture was diluted with H_2O (50 ml) and CH_2Cl_2 (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 = 1:3) to give **22** (2.2 g, 82.5%). ^{1}H NMR ($CDCl_3$): δ 1.21–1.37 (m, 4H), 1.43–2.01 (m, 2H), 2.33–2.34 (d, 2H, J = 4.5 Hz), 2.80–2.86 (m, 1H), 3.14–3.25 (m, 2H), 3.49–3.53 (m, 2H), 4.15–4.30 (m, 4H), 4.38–4.50 (m, 3H), 5.06–5.30 (m, 2H), 5.80–5.91 (m, 1H), 7.20–7.38 (m, 9H), 7.45 (d, 6H, J = 7.6 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 36.7, 37.8, 41.7, 44.2, 55.0, 53.5, 55.4, 67.2, 117.2, 126.9, 128.0, 129.5, 132.7, 144.6, 154.1, 170.5, 206.8.

The synthesis of compound **23** was carried out by the same procedure as described for the preparation of **22** using compound **21**.

23: ^{1}H NMR ($CDCl_3$): δ 1.62–1.77 (m, 2H), 1.88–1.94 (m, 1H), 2.31–2.49 (m, 3H), 2.78–2.84 (m, 2H), 3.12–3.27 (m, 2H), 3.49–3.63 (m, 2H), 3.81–3.95 (m, 1H), 4.38–4.52 (m, 3H), 5.09–5.30 (m, 2H), 5.83–5.92 (m, 1H), 7.20–7.36 (m, 9H), 7.46 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 36.7, 37.8, 41.7, 44.2, 55.0, 53.5, 55.4, 67.2, 117.2, 126.9, 128.0, 129.5, 132.7, 144.6, 154.1, 170.5, 206.8.

The synthesis of compounds **24** and **25** was carried out by the same procedure as described for the preparation of **10** using compounds **20** and **21**.

24: ^{1}H NMR ($CDCl_3$): δ 1.22–1.37 (m, 6H), 1.49–1.61 (m, 1H), 1.72–1.97 (m, 2H), 2.73–2.81 (m, 1H), 3.07–3.27 (m, 2H), 3.41–3.52 (m, 1H), 3.41–3.52 (m, 1H), 3.54–3.69 (m, 1H), 4.08–4.26 (m, 2H), 4.42–4.52 (m, 4H), 5.10–5.27 (m, 2H), 5.81–5.92 (m, 1H), 7.20–7.32 (m, 9H), 7.45 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 21.1, 22.7, 29.7, 31.5, 31.7, 37.5, 45.6, 52.4, 55.5, 60.4, 61.5, 67.2, 117.0, 126.9, 128.1, 129.5, 132.8, 144.6, 154.0, 169.5, 172.1.

25: ^{1}H NMR ($CDCl_3$): δ 1.42–1.52 (m, 1H), 1.55–1.66 (m, 2H), 1.75–1.98 (m, 4H), 2.75–2.81 (m, 1H), 3.07–3.27 (m, 3H), 3.54–3.59 (m, 2H), 3.92–4.00 (m, 2H), 4.33–4.58 (m, 2H), 5.12–5.27 (m, 2H), 5.82–5.93 (m, 1H), 7.20–7.33 (m, 9H), 7.46 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.4, 29.7, 33.8, 36.6, 42.4, 52.0, 53.4, 55.8, 65.8, 67.2, 117.1, 126.9, 128.1, 129.5, 132.8, 144.6, 154.0, 176.4.

The synthesis of compounds **26** and **27** was carried out by the same procedure as described for the preparation of **12** using compounds **20** and **21**.

26: ^{1}H NMR ($CDCl_3$): δ 1.23–1.39 (m, 6H), 1.53–1.65 (m, 1H), 1.72–1.99 (m, 2H), 2.73–2.81 (m, 1H), 3.07–3.27 (m, 2H), 3.41–3.52 (m, 1H), 3.41–3.52 (m, 1H), 3.54–3.69 (m, 1H), 4.08–4.26 (m, 1H), 4.42–4.52 (m, 4H), 5.10–5.27 (m, 2H), 5.81–5.92 (m, 1H), 7.20–7.32 (m, 9H), 7.45 (d, 6H, J = 7.5 Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.1, 21.1, 22.7, 29.7, 31.5, 31.7, 37.5, 45.6, 52.4, 60.4, 61.5, 67.2, 117.0, 126.9, 128.1, 129.5, 132.8, 144.6, 154.0, 169.5, 172.1.

27: ^{1}H NMR ($CDCl_3$): δ 1.65 (s, 4H), 2.32 (d, 1H, J = 6.0 Hz), 2.47–2.69 (m, 2H), 2.73–2.85 (m, 1H), 3.10–3.29 (m, 2H), 3.32–3.47 (m, 1H), 3.55–3.60 (m, 2H), 3.72–

3.87 (m, 1H), 4.32–4.57 (m, 2H), 5.19–5.30 (m, 2H), 5.83–5.92 (m, 1H), 7.20–7.32 (m, 9H), 7.45 (d, 6H, $J = 7.5$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 25.2, 25.8, 30.6, 31.4, 36.7, 45.1, 52.0, 52.3, 61.4, 67.2, 117.1, 126.9, 128.0, 129.5, 132.8, 114.6, 153.3, 169.9, 171.3.

The synthesis of compounds **28** and **29** was carried out by the same procedure as described for the preparation of **14** using compounds **20** and **21**.

28: ^{1}H NMR ($CDCl_3$): δ 1.22 (m, 3H), 1.62 (s, 3H), 1.86–2.08 (m, 1H), 2.38–2.56 (m, 2H), 3.02–3.42 (m, 3H), 3.45–3.55 (m, 1H), 3.88 (d, 3H, $J = 11.1$ Hz), 4.08–4.22 (m, 3H), 4.25–4.42 (m, 2H), 4.46–4.55 (m, 2H), 5.11–5.29 (m, 2H), 5.79–5.87 (m, 1H), 7.19–7.32 (m, 9H), 7.44 (d, 6H, $J = 7.5$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.2, 24.0, 25.6, 29.6, 29.7, 44.4, 46.2, 51.9, 52.2, 55.7, 56.0, 61.7, 61.8, 67.2, 117.0, 126.9, 128.1, 132.7, 154.0, 170.2, 171.4.

29: ^{1}H NMR ($CDCl_3$): δ 1.60–1.70 (m, 5H), 2.32–2.35 (m, 1H), 2.71–2.88 (m, 1H), 3.14–3.25 (m, 2H), 3.51–3.65 (m, 5H), 3.85 (d, 3H, $J = 3.3$ Hz), 4.39–4.53 (m, 2H), 5.10–5.23 (m, 2H), 5.82–5.93 (m, 1H), 7.21–7.33 (m, 9H), 7.47 (d, 6H, $J = 7.5$ Hz). ^{13}C NMR (300 MHz, $CDCl_3$): δ 25.2, 25.8, 30.6, 31.4, 36.7, 45.1, 52.0, 52.3, 55.7, 61.4, 67.2, 117.1, 126.9, 128.0, 129.5, 132.8, 114.6, 153.3, 169.9, 171.3.

*3.6. Allyl(1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[5-(4-hydroxyimino-3-ethoxycarbonypyrrolidinyl)carbonyl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (**IIa**)*

To a solution of **10** (0.61 g, 1.0 mmol) in CH_2Cl_2 (3 ml) was added drop-wise triethylsilane (0.20 ml, 1.2 mmol) at 5 °C, and then TFA (1.2 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% $NaHCO_3$, 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-methylcarbapen-2-em-3-carb-oxylate (**30**, 0.60 g, 1.2 mmol) in CH_3CN (10 ml) was cooled to 0 °C under N_2. To this solution was added diisopropylethyl amine (0.13 g, 1.0 mmol) and a solution of the mercapto compound **Ia** in CH_3CN (5 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** (0.20 g, 33.3%) as a yellow amorphous solid. ^{1}H NMR ($CDCl_3$): δ 1.25–1.31 (m, 6H), 1.36 (d, 3H, $J = 4.3$ Hz), 1.95–2.05 (m, 1H), 2.60–2.65 (bs, 1H), 2.95–3.06 (m, 1H), 3.24–3.28 (bs, 1H), 3.48–3.65 (m, 3H), 3.69–3.78 (m, 2H), 3.88–4.02 (m, 2H), 4.12–4.25 (m, 5H), 4.46–4.58 (m, 4H), 4.70 (dd, 1H, $J = 5.7$ and 5.8 Hz), 4.82 (dd, 1H, $J = 5.4$ and 5.5 Hz), 5.19–5.34 (m, 3H), 5.42 and 5.47 (2s, 1H), 5.87–6.04 (m, 2H).

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

IIb: Yield 24.8%. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H, $J = 8.1$ Hz), 1.36 (d, 3H, $J = 5.9$ Hz), 1.63 (bs, 2H), 2.19 (bs, 1H), 2.65 (bs, 1H), 3.25–3.28 (m, 1H), 3.32–3.55 (m, 4H), 3.58–3.63 (m, 2H), 3.77 (d, 1H, $J = 12.3$ Hz), 3.89–4.10 (m, 1H), 4.23–4.27 (m, 2H), 4.49–4.59 (m, 4H), 4.72 (dd, 1H, $J = 5.4$ and 5.8 Hz), 4.82 (dd, 1H, $J = 5.7$ and 5.8 Hz), 5.22–5.34 (m, 3H), 5.43 and 5.48 (2s, 1H), 5.92–6.03 (m, 2H).

IIc: Yield 29.3%. ^{1}H NMR ($CDCl_3$): δ 1.27–1.34 (m, 6H), 1.36 (d, 3H, $J = 4.3$ Hz), 2.02–2.06 (m, 2H), 2.34–2.39 (m, 1H), 2.48–2.80 (m, 2H), 3.32–3.52 (m, 2H), 3.96–4.12 (m, 2H), 4.24–4.46 (m, 5H), 4.59 (bs, 4H), 4.72 (dd, 1H, $J = 5.8$ and 5.3 Hz), 4.81 (dd, 1H, $J = 5.8$ and 5.3 Hz), 5.23–5.35 (m, 4H), 5.43 and 5.49 (2s, 1H), 5.89–6.02 (m, 2H).

IId: Yield 33.8%. ^{1}H NMR ($CDCl_3$): δ 1.26 (d, 3H, $J = 7.5$ Hz), 1.37 (d, 3H, $J = 6.2$ Hz), 2.00–2.18 (m, 2H), 2.54–2.66 (m, 1H), 2.73–2.85 (m, 1H), 2.96–3.08 (m, 1H), 3.25 (d, 1H $J = 5.1$ Hz), 3.34–3.40 (m, 1H), 3.45–3.51 (m, 2H), 3.52–3.75 (m, 2H), 3.73 (s, 1H), 4.14–4.30 (m, 2H), 4.58 (bs, 4H), 4.70 (dd, 1H, $J = 5.7$ and 6.0 Hz), 4.82 (dd, 1H, $J = 5.4$ and 5.8 Hz), 5.22–5.29 (m, 3H), 5.42 and 5.48 (2s, 1H), 5.89–6.01 (m, 2H).

IIe: Yield 26.9%. ^{1}H NMR ($CDCl_3$): δ 1.25–1.33 (m, 6H), 1.37 (d, 3H, $J = 6.2$ Hz), 1.67 (bs, 2H), 2.00–2.09 (m, 2H), 2.65 (m, 1H), 3.29–3.39 (m, 1H), 3.41–3.53 (m, 1H), 3.55–2.72 (m, 1H), 3.91 (m, 4H), 4.11–4.38 (m, 6H), 4.39–4.66 (m, 4H), 4.66–4.71 (m, 1H), 4.81 (dd, 1H, $J = 3.3$ and 10.2 Hz), 5.17–5.32 (m, 3H), 5.42 and 5.46 (2s, 1H), 5.88–5.99 (m, 2H).

IIf: Yield 32.1%. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, $J = 7.2$ Hz), 1.36 (d, 3H, $J = 5.8$ Hz), 1.82 (bs, 2H), 2.58–2.67 (m, 1H), 2.72–2.81 (m, 1H), 2.86–2.94 (m, 1H), 3.25–3.29 (m, 1H), 3.37–3.50 (m, 2H), 3.64–3.82 (m, 2H), 3.88–3.90 (m, 3H), 4.15–4.25 (m, 4H), 4.39–4.57 (m, 4H), 4.70 (dd, 1H, $J = 5.4$ and 5.2 Hz), 4.82 (dd, 1H, $J = 5.2$ and 5.3 Hz), 5.17–5.29 (m, 3H), 5.42 and 5.48 (2s, 1H), 5.88–5.98 (m, 2H).

IIg: Yield 29.6%. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H, $J = 6.1$ Hz), 1.37 (d, 3H, $J = 4.5$ Hz), 2.07–2.17 (m, 2H), 2.62 (bs, 2H), 2.72 (bs, 1H), 3.36 (t, 1H, $J = 5.7$ Hz), 3.48 (t, 1H, $J = 7.8$ Hz), 3.64 (bs, 1H), 3.78–3.96 (m, 2H), 3.98–4.09 (m, 2H), 4.24–4.31 (m, 2H), 4.49–4.67 (m, 4H), 4.70 (dd, 1H, $J = 5.2$ and, 5.0 Hz), 4.82 (dd, 1H, $J = 5.1$ and 5.2 Hz), 5.19–5.23 (m, 3H), 5.43 and 5.47 (2s, 1H), 5.90–6.00 (m, 2H).

IIh: Yield 34.2%. ^{1}H NMR ($CDCl_3$): δ 1.25–1.33 (m, 6H), 1.36 (d, 3H, $J = 5.6$ Hz), 2.00–2.19 (m, 2H), 2.61–2.74 (m, 3H), 3.10–3.30 (m, 3H), 3.32–3.49 (m, 4H), 3.55–3.66 (m, 2H), 4.16–4.27 (m, 3H), 4.35 (s, 1H), 4.38–4.60 (m, 4H), 4.72 (dd, 1H, $J = 5.1$ and 5.1 Hz), 4.83 (dd, 1H, $J = 5.7$ and 5.5 Hz), 5.21–5.35 (m, 3H), 5.42 and 5.48 (2s, 1H), 5.88–5.98 (m, 2H).

IIi: Yield 33.0%. ^{1}H NMR ($CDCl_3$): δ 1.17 (d, 3H, $J = 5.0$ Hz), 1.26 (d, 3H, $J = 6.3$ Hz), 1.90 (bs, 4H), 2.69 (bs, 1H), 3.25 (d, 2H, $J = 6.9$ Hz), 3.33–3.48 (m, 3H), 3.56–3.85 (m, 2H), 3.98–4.16 (m, 3H), 4.23–4.26 (m, 2H), 4.58 (d, 4H, $J = 5.1$ Hz), 4.70 (dd, 1H, $J = 5.1$ and 5.0 Hz), 4.82 (dd, 1H,

J = 4.2 and 4.1 Hz), 5.21–5.35 (m, 3H), 5.42 and 5.47 (2s, 1H), 5.87–6.03 (m, 2H).

IIj: Yield 30.8%. ^{1}H NMR ($CDCl_3$): δ 1.25–1.33 (m, 6H), 1.36 (d, 3H, J = 5.6 Hz), 1.90–2.10 (m, 2H), 2.18–2.30 (m, 1H), 2.54–2.81 (m, 1H), 2.83–3.15 (m, 1H), 3.17–3.28 (m, 1H), 3.41–3.51 (m, 5H), 3.87 (d, 5H, J = 6.6 Hz), 4.14–4.29 (m, 4H), 4.54 (d, 4H, J = 17.1 Hz), 4.69 (dd, 1H, J = 5.7 and 5.8 Hz), 4.83 (m, 1H, J = 5.4 and 5.1 Hz), 5.20–5.34 (m, 3H), 5.42 and 5.48 (2s, 1H), 5.86–6.00 (m, 2H).

IIk: Yield 34.3%. ^{1}H NMR ($CDCl_3$): δ 1.17 (d, 3H, J = 6.0 Hz), 1.29(d, 3H, J = 6.1 Hz), 1.56–1.79 (bs, 3H), 2.31–2.41 (m, 1H), 2.43–2.58 (m, 1H), 2.97–3.16 (m, 2H), 3.27 (s, 1H), 3.35–3.59 (m, 4H), 3.66–3.74 (m, 3H), 4.25 (d, 1H, J = 4.2 Hz), 4.60–4.62 (m, 4H), 4.68–4.74 (m, 1H), 4.84 (dd, 1H, J = 5.1 and 5.5 Hz), 5.20–5.31 (m, 3H), 5.43 and 5.49 (2s, 1H), 5.88–6.00 (m, 2H).

IIl: Yield 31.3%. ^{1}H NMR ($CDCl_3$): δ 1.18–1.27 (m, 6H), 1.33 (d, 3H, J = 5.6 Hz), 1.90–2.10 (m, 2H), 2.18–2.30 (m, 1H), 2.54–2.81 (m, 1H), 2.83–3.15 (m, 1H), 3.17–3.28 (m, 1H), 3.41–3.51 (m, 5H), 3.87 (d, 5H, J = 6.6 Hz), 4.14–4.29 (m, 4H), 4.54 (d, 4H, J = 17.1 Hz), 4.69 (dd, 1H, J = 5.7 and 5.8 Hz), 4.83 (m, 1H, J = 5.4 and 5.1 Hz), 5.20–5.34 (m, 3H), 5.42 and 5.48 (2s, 1H), 5.86–6.00 (m, 2H).

IIm: Yield 31.5%. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H, J = 4.2 Hz), 1.35 (d, 3H, J = 7.5 Hz), 1.91–2.04 (m, 2H), 2.40 (d, 3H, J = 4.2 Hz), 2.60–2.71 (m, 3H), 3.19–3.37 (m, 1H), 3.44–3.62 (m, 5H), 3.85 (d, 3H, J = 3.7 Hz), 3.92–4.19 (m, 2H), 4.49–4.60 (m, 4H), 4.73 (dd, 1H, J = 4.9 and 13.2 Hz), 4.80 (m, 1H, J = 3.8 and 12.1 Hz), 5.21–5.33 (m, 3H), 5.42 and 5.46 (2s, 1H), 5.92–6.00 (m, 2H).

IIn: Yield 37.7%. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H, J = 6.2 Hz), 1.36 (d, 3H, J = 6.2 Hz), 1.71 (bs, 2H), 1.97–2.13 (m, 2H), 3.25–3.27 (m, 1H), 3.29–3.53 (m, 3H), 3.60–3.79 (m, 3H), 4.04–4.14 (m, 3H), 4.16–4.27 (m, 2H), 4.56 (dd, 3H, J = 5.4 and 14.4 Hz), 4.65–4.73 (m, 1H), 4.80 (dd, 2H, J = 7.8 and 14.6 Hz), 4.86–5.35 (m, 3H), 5.42 and 5.47 (2s, 1H), 5.89–6.00 (m, 2H).

*3.7. (1R,5S,6S)-6-[(1R)-hydroxyethyl]-2-[[5-(4-hydroxyimino-3-ethoxycarbonypyrrolidinyl)car bonyl]pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylic acid (**IIIa**)*

To a stirred solution of **IIa** (0.1 g, 0.2 mmol) and $Pd(PPh_3)_4$ (30 mg) in CH_2Cl_2 (10 ml) was added drop-wise *n*-tributylin hydride (0.1 ml, 0.25 mmol) at 0 °C and was stirred for 1 h at same temperature. To the resulting solution was diluted with water (10 ml) and the organic layers was 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 27.5%. UV λ_{max}: 298 nm. m.p.: 102–110 °C (dec.). ^{1}H NMR (D_2O): δ 1.09–1.19 (m, 9H), 1.90–1.98 (m, 2H), 2.96–3.00 (m, 1H), 3.18–3.30 (m, 1H), 3.36–3.40 (m, 3H), 3.63–3.70 (m, 2H), 3.72–3.84 (m, 2H), 3.93–3.97 (m, 1H), 4.07–4.16 (m, 4H), 4.47–4.52 (m, 2H). IR (KBr): 3480, 1720, 1690, 1670 cm^{-1}. HRMS (FAB) Calcd. for $C_{22}H_{31}N_3O_8S$ 497.1832, Found 497.1830.

The synthesis of compounds **IIIb-n** were carried out by the same procedure as described for the preparation of **IIIa**.

IIIb: Yield 24.2%. UV λ_{max}: 298 nm. m.p.: 115–122 °C (dec.). ^{1}H NMR (D_2O): δ 1.10 (d, 3H, J = 7.2 Hz), 1.18 (d, 3H, J = 6.3 Hz), 1.80–2.12 (m, 4H), 2.95 (bs, 1H), 3.23–3.37 (m, 4H), 3.41–3.68 (m, 5H), 3.94 (t, 1H, J = 6.0 Hz), 4.12–4.16 (m, 2H). IR (KBr): 3460, 1710, 1650 cm^{-1}. HRMS (FAB) Calcd. for $C_{19}H_{27}N_3O_6S$ 425.1621, Found 425.1621.

IIIc: Yield 23.9%. UV λ_{max}: 298 nm. m.p.: 120–125 °C (dec.). ^{1}H NMR (D_2O): δ 1.13–1.23 (m, 6H), 1.32 (d, 3H, J = 5.5 Hz), 1.91 (bs, 1H), 2.99 (bs, 1H), 3.18–3.38 (m, 3H), 3.56–3.73 (m, 1H), 3.74–3.88 (m, 1H), 3.90–4.07 (m, 1H), 4.08–4.34 (m, 4H), 4.35–4.54 (m, 2H), 4.55–4.61 (m, 1H), 5.39–5.45 (m, 2H). IR (KBr): 3460, 1740, 1710, 1660, 1610 cm^{-1}. HRMS (FAB) Calcd. for $C_{22}H_{30}N_4O_8S$ 510.1784, Found 510.1780.

IIId: Yield 24.0%. UV λ_{max}: 298 nm. m.p.: 128–134 °C (dec.). ^{1}H NMR (D_2O): 1.09 (d, 3H, J = 5.4 Hz), 1.17 (d, 3H, J = 4.5 Hz), 1.79–1.99 (m, 1H), 2.66–2.70 (m, 1H), 2.74–2.78 (m, 1H), 2.95–2.99 (m, 1H), 3.23–3.29 (m, 1H), 3.31–3.47 (m, 2H), 3.49–3.56 (m, 1H), 3.58–3.72 (m, 3H), 3.73–3.84 (m, 2H), 3.95 (m, 1H), 4.07–4.17 (m, 2H). IR (KBr): 3490, 1710, 1670, 1610 cm^{-1}. HRMS (FAB) Calcd. for $C_{19}H_{26}N_4O_6S$ 438.1573, Found 438.1577.

IIIe: Yield 24.2%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.09 (d, 3H, J = 5.3 Hz), 1.17 (d, 3H, J = 4.6 Hz), 1.80–1.97 (m, 1H), 2.86–3.09 (m, 2H), 1.25–1.32 (m, 3H), 3.19–3.42 (m, 2H), 3.47–3.60 (m, 1H), 3.61–3.72 (m, 2H), 3.78 (s, 1H), 3.83 (s, 3H), 3.92–4.01 (m, 2H), 4.08–4.14 (m, 6H). IR (KBr): 3540, 1720, 1705, 1670, 1620 cm^{-1}. HRMS (FAB) Calcd. for $C_{23}H_{32}N_4O_8S$ 524.1941, Found 524.1930.

IIIf: Yield 23.5%. UV λ_{max}: 298 nm. m.p.: 128–134 °C (dec.). ^{1}H NMR (D_2O): δ 1.08 (d, 3H, J = 6.2 Hz), 1.17 (d, 3H, J = 4.8 Hz), 1.79–1.90 (m, 1H), 2.58–2.73 (m, 2H), 2.79–2.89 (m, 1H), 3.26–3.35 (m, 2H), 3.52–3.67 (m, 2H), 3.75–3.76 (m, 6H), 3.90–3.93 (m, 1H), 4.04–4.20 (m, 4H). IR (KBr): 3510, 1730, 1710, 1630 cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{28}N_4O_6S$ 452.1730, Found 452.1734.

IIIg: Yield 18.2%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): 1.09 (d, 3H, J = 6.1 Hz), 1.17 (d, 3H, J = 4.7 Hz), 1.91–1.98 (m, 1H), 2.06–2.12 (m, 1H), 2.63–2.67 (m, 1H), 2.70–2.74 (m, 1H), 2.92–3.00 (m, 1H), 3.34–3.40 (m, 2H), 3.44–3.54 (m, 1H), 3.60–3.70 (m, 1H), 3.75–4.07 (m, 5H), 4.11–4.15 (m, 2H). IR (KBr): 3440, 1710, 1690, 1670, 1630 cm^{-1}. HRMS (FAB) Calcd. for $C_{19}H_{25}N_3O_6S$ 423.1464, Found 423.1464.

IIIh: Yield 33.2%. UV λ_{max}: 298 nm. m.p.: 125–130 °C (dec.). ^{1}H NMR (D_2O): δ 1.08–1.17 (m, 6H), 1.23 (d, 3H, J = 4.5 Hz), 174–2.00 (m, 2H), 2.11 (s, 1H), 2.38–2.79 (m, 2H), 3.12–3.27 (m, 4H), 3.33–3.43 (m, 2H), 3.60 (s, 2H), 3.84 (S, 1H), 4.10–4.13 (m, 4H), 4.21–4.39 (m, 2H). IR (KBr): 3490, 1710, 1690, 1670 cm^{-1}. HRMS (FAB) Calcd. for $C_{23}H_{33}N_3O_8S$ 511.1988, Found 511.1987.

IIIi: Yield 14.0%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.11 (d, 3H, J = 7.8 Hz), 1.17 (d, 3H, J = 4.7 Hz), 1.30–1.47 (m, 2H), 1.81–1.91 (m, 2H), 2.11 (s, 1H), 3.19–3.27 (m, 3H), 3.35–3.39 (m, 3H), 3.57–3.68 (m, 3H), 3.86–3.95 (m, 3H), 4.12–4.15 (m, 2H). IR (KBr): 3440, 1710, 1670 cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{29}N_3O_6S$ 439.1777, Found 439.1770.

IIIj: Yield 10.5%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O) δ 1.10–1.17 (m, 6H), 1.20 (d, 3H J = 6.4 Hz), 1.65–1.72 (m, 1H), 1.82–1.87 (bs, 2H), 2.13 (m, 1H), 2.53 (bs, 1H), 2.83–3.05 (m, 2H), 3.19–3.49 (m, 3H), 3.53–3.60 (m, 3H), 3.76–3.81 (m, 3H), 3.92 (bs, 1H), 4.32–4.40 (m, 2H). IR (KBr): 3490, 1720, 1690, 1670, 1610 cm^{-1}. HRMS (FAB) Calcd. for $C_{23}H_{32}N_4O_8S$ 524.1941, Found 524.1939.

IIIk: Yield 18.4%. UV λ_{max}: 298 nm. m.p.: 127–131 °C (dec.). ^{1}H NMR (D_2O): δ 1.10 (d, 3H, J = 7.2 Hz), 1.18 (d, 3H, J = 6.3 Hz), 1.81–1.93 (m, 1H), 2.12 (s, 1H), 2.58 (bs, 3H), 2.89–3.11 (m, 2H), 3.36–3.43 (m, 3H), 3.55–3.78 (m, 6H), 4.12–4.19 (m, 2H). IR (KBr): 3460, 1710, 1680, 1590 cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{28}N_4O_6S$ 452.1730, Found 452.1730.

IIIl: Yield 13.5%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.10–1.16 (m, 6H), 1.19 (d, 3H J = 6.9 Hz), 1.65–1.72 (m, 1H), 1.82–1.89 (m, 2H), 2.13 (s, 1H), 2.53 (bs, 1H), 2.67–3.07 (m, 2H), 3.16–3.47 (m, 6H), 3.53–3.63 (m, 3H), 3.76–3.81 (m, 3H), 3.92 (s, 1H), 4.02–4.19 (m, 2H). IR (KBr): 3490, 1710, 1695, 1670, 1580 cm^{-1}. HRMS (FAB) Calcd. for $C_{24}H_{34}N_4O_8S$ 538.2097, Found 538.2090.

IIIm: Yield 19.4%. UV λ_{max}: 298 nm. ^{1}H NMR (D_2O): δ 1.12 (d, 3H, J = 7.2 Hz), 1.19 (d, 3H, J = 6.3 Hz), 1.81–1.90 (m, 2H), 2.91–2.96 (m, 2H), 2.57–2.65 (m, 2H), 3.25–3.38 (m, 3H), 3.54–3.68 (m, 6H), 3.75 (s, 3H), 3.79–4.10 (m, 1H), 4.12–4.15 (m, 2H). IR (KBr): 3490, 1710, 1670, 1570 cm^{-1}. HRMS (FAB) Calcd. for $C_{21}H_{30}N_4O_6S$ 466.1886, Found 466.1897.

IIIn: Yield 10%. UV λ_{max}: 298 nm. m.p.: 129–134 °C (dec.). ^{1}H NMR (D_2O): δ 1.12 (d, 3H, J = 7.2 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.75–1.82 (m, 2H), 2.51–2.56 (m, 4H), 2.92–3.00 (m, 1H), 3.38 (d, 2H, J = 3.6 Hz), 3.45–3.72 (m, 2H), 3.79–3.82 (m, 4H), 3.92–4.11 (m, 1H), 4.14 (d, 2H, J = 6.6 Hz). IR (KBr): 3490, 1710, 1690, 1660 cm^{-1}. HRMS (FAB) Calcd. for $C_{20}H_{27}N_3O_6S$ 437.1621, Found 437.1630.

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