Synthesis and Antibacterial Activity of 1β-Methyl-2-[5-(1,2-disubstituted ethyl)-pyrrolidin-3-ylthio]carbapenem Derivatives. Part III

Jung-Hyuck Cho, Soo-Hyun Ahn, Heechol Jeon, So Young Kim, and Chang-Hyun Oh*

Medicinal Chemistry Research Center, Korea Institute of Science and Technology, Seoul 130-650, Korea
**E-mail: choh@kist.re.kr*
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The synthesis of a new series of 1β-methylcarbapenems having 5-(1,2-disubstituted ethyl)pyrrolidine moiety are 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. Among them, compound (**IIIc**) having 1-methoxyimino-2-hydroxyethyl moiety showed the most potent antibacterial activity.

Key Words : 1β-Methylcarbapenem, Antibacterial activity, Substituent effect

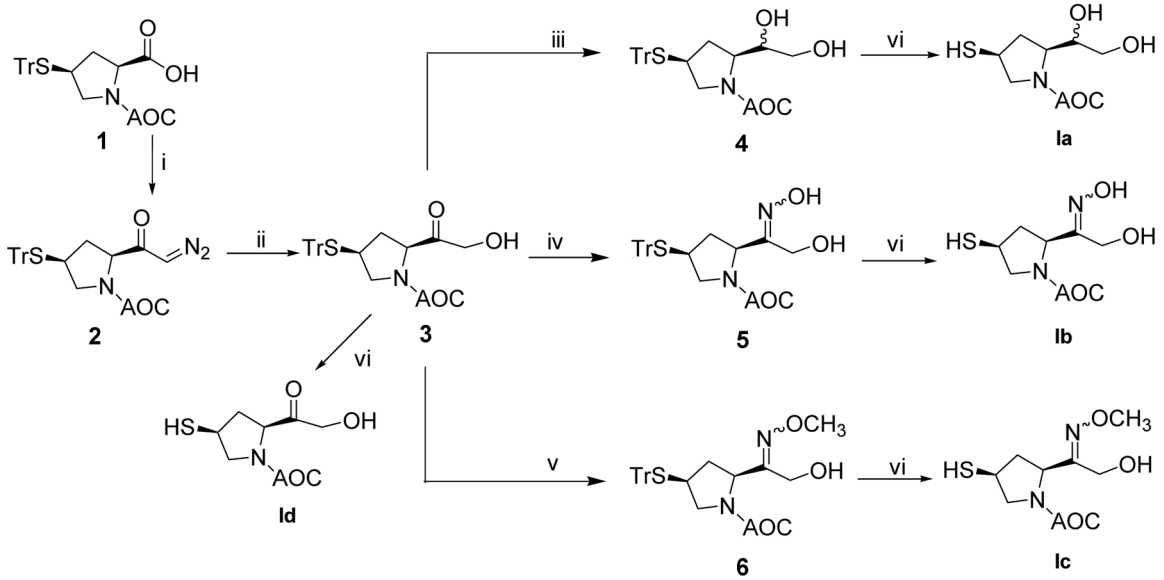
Introduction

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.

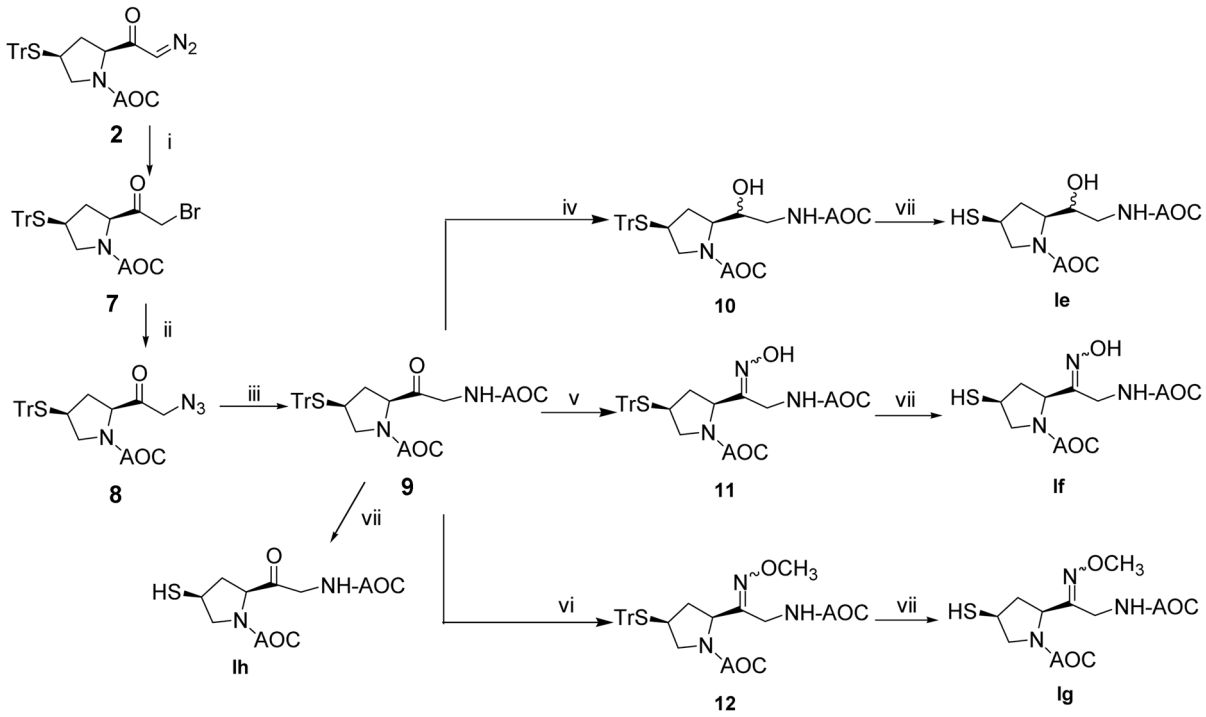
We also reported that the carbapenem compounds having a pyrrolidine-3-ylthio group at the C-2 position in the carbapenem skeleton are noted for their broad and potent antibacterial activity, and a large number of derivatives have been synthesized.[11-14] We conceived that the introduction of an additional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

Results and Discussion

Chemistry. Our general synthetic route leading to new



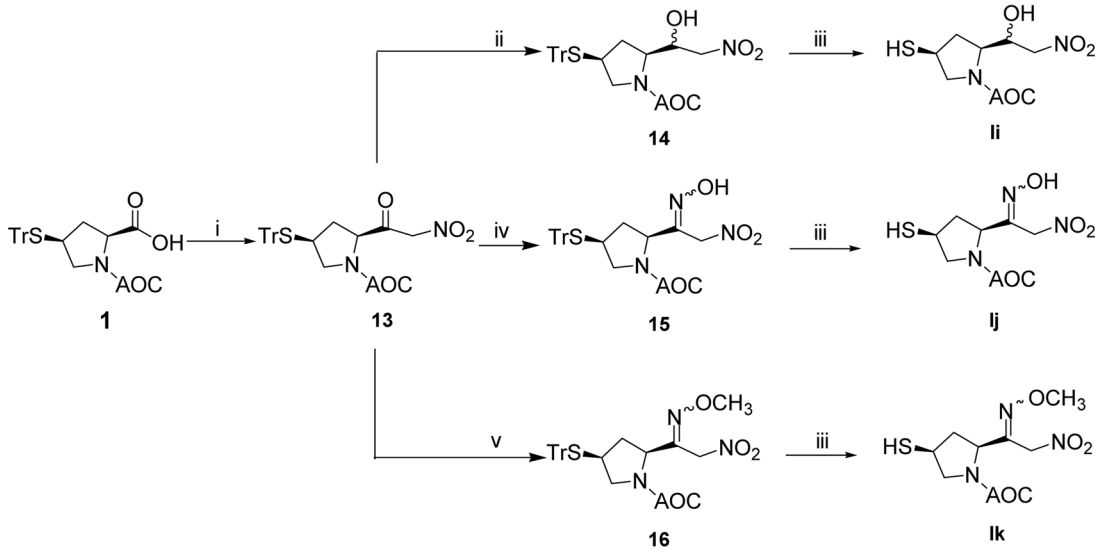
Scheme 1. (i) 1. Ethyl chloroformate, TEA, THF 2. Diazomethane (ii) 0.25 M H_2SO_4, THF (iii) $NaBH_4$, THF (iv) Hydroxyl amine, EtOH (v) Methoxylamine hydrochloride, pyridine (vi) Trifluoroacetic acid, triethylsilane, CH_2Cl_2.



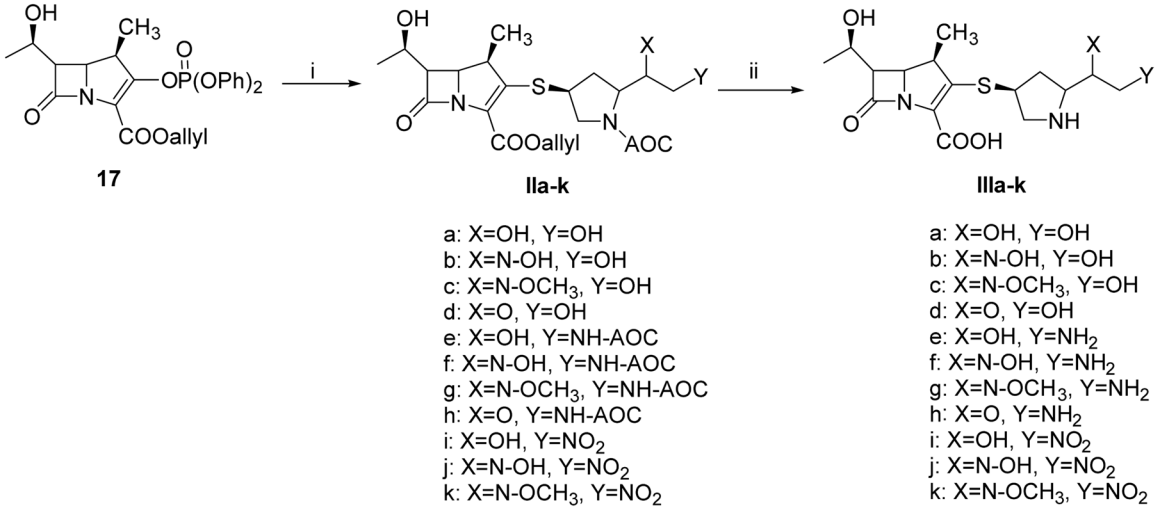
Scheme 2. (i) 40% HBr (ii) NaN_3, DMF (iii) 1. PPh_3, H_2O, THF 2. allyl chloroformate, TEA, CH_2Cl_2 (iv) $NaBH_4$, THF (v) Hydroxyl amine, EtOH (vi) Methoxylamine hydrochloride, pyridine (vii) Trifluoroacetic acid, triethylsilane, CH_2Cl_2.

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. 5-(1,2-Disubstituted ethyl)pyrrolidinethiol derivatives (**Ia-k**) were prepared by the sequence shown in Scheme 1-3. The carboxylic acid **1**[15] can be converted to the diazomethyl ketone **2** by formation of the mixed anhydride with ethyl chloroformate followed by trapping with diazomethane. The key intermediate **3** was obtained by reaction of diazoketone **2** with dilute acid in THF and subsequently treated with sodium borohydride to provide dihydroxy compound **4**. Preparation of the oxime **5** and methoxyimino compound **6** was accomplished by treatment of the hydroxy compound **3** with hydroxyl and methoxyl amines (Scheme 1).

The azoketone **2** was reacted with HBr and subsequently treated with sodium azide in DMSO to give the azide compound **8**. The azide **8** was converted to amine using triphenylphosphine and H_2O, followed by treatment with



Scheme 3. (i) Potassium-tert butoxide, nitromethane, THF (ii) $NaBH_4$, THF (iii) Trifluoroacetic acid, triethylsilane, CH_2Cl_2 (iv) Hydroxyl amine, EtOH (v) Methoxylamine hydrochloride, pyridine.



Scheme 4. (i) *N,N'*-Diisopropylethyl amine, **1a-h** (ii) Tetrakis(triphenylphosphine)palladium, tributyltin hydride, CH_2Cl_2.

allyl chloroformate to provide protected amine **9**. The syntheses of compounds **10-12** were carried out by the same procedure as described for the preparation of **4-6** (Scheme 2).

The acid **1** was treated with 1,1'-carbonyldiimidazole and potassium salts of nitromethane generated *in situ* from nitromethane and potassium *t*-butoxide in THF to provide **13**, which was also successfully converted into the **14**, **15** and **16** using the same procedure as described for the preparation of **3**, **4** and **5** respectively. Deprotection of the trityl group into mercaptans (**Ia-k**) was achieved by treatment of **3-16** with trifluoroacetic acid in the presence of triethylsilane (Scheme 3).

Finally, the reaction of **17** with thiols (**Ia-k**) in the presence of diisopropylethylamine provided the 2-substituted carbapenem (**IIa-k**). Deprotection of these compounds by treatment with tetrakis(triphenylphosphine)palladium and tributyltin hydride gave the crude products, which were purified by HP-20 column to give the pure carbapenems (**IIIa-k**) (Scheme 4).

Biological assay.

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 twofold dilutions of the test compounds. Organisms were incubated at 37 °C for 18-20 h. The MICs of a compound was defined as the lowest concentration that visibly inhibited growth.

Determination of susceptibility to renal dehydropeptidase-I (DHP-I): The relative hydrolysis rate of carbapenems by porcine renal DHP-I was determined, taking the initial hydrolysis rate of imipenem as 1.0. Partially purified porcine DHP-I (final concentration, 0.3 U/mL) was incubated with 50 μM carbapenem at 35 °C in 50 mM MOPS buffer pH 7.0. The initial hydrolysis rate was monitored by the spectrophotometric method. One unit of activity was defined as the amount of enzyme hydrolyzing 1 μM of glycyldehydrophenylalanine per min when the substrate (50 μM) was incubated at 35 °C in 50 mM MOPS buffer, pH 7.0.

Antibacterial activity studies: The *in vitro* antibacterial activities of the new carbapenems (**IIIa-k**) prepared above against Gram-positive and negative bacteria are listed in Table 1. For comparison, the MIC values of Imipenem, Meropenem are also listed. Among these compounds, **IIIc** showed superior or similiar antibacterial activity against Gram-positive bacteria to Meropenem, and exhibited improved antibacterial activity against Gram-negative bacteria than Imipenem.

As to the substituents of the 1,2-disubstituted ethyl side chain, the compounds **IIIa-IIId** having hydroxy group were generally more potent than the amine and nitro groups.

The existence of a nitro group (**IIIi-IIIk**) significantly lowered the antibacterial activity compared to compounds with hydroxy and amine groups.

Also, the introduction of methoxyimine group (**IIIc**, **IIIg** and **IIIk**) led to the significantly enhanced antibacterial activity against Gram-negative bacteria compared to hydroxy (**IIIa**, **IIIe** and **IIIi) a**nd oxime group (**IIIb**, **IIIf** and **IIIj**). As a result, the compound **IIIc** having methoxyimine and hydroxy group exhibited the most potent and well balanced activity.

Comparative *in vitro* activities of **IIIc**, meropenem, and imipenem against 40 bacterial strains were summarized in Table 2. 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 *Enterobacter cloacae* and *Corynebacterium diphtheriae*, **IIIc** was 2-3 fold more active than meropenem and imipenem.

The stability to DHP-I of a potent compounds was tested and all the compounds were more stable than Meropenem. In particular, the compounds **IIIg** exhibited the most stability.

Table 1. *In vitro* antibacterial activity (MIC, μg/mL) of the carbapenem derivatives

STRAINS	**IIIa**	**IIIb**	**IIIc**	**IIId**	**IIIe**	**IIIf**	**IIIg**	**IIIh**	**IIIi**	**IIIj**	**IIIk**	**IPM**[a]	**MPM**[b]
Staphylococcus aureus 1218	3.125	6.25	3.125	6.25	3.125	12.5	3.125	12.5	3.125	25	25.0	1.560	6.250
Coagulasenegative staphylococci	0.098	0.198	0.098	0.195	0.195	0.098	0.195	0.781	3.125	3.125	1.563	0.025	0.098
Enterococcus faecalis 2347	6.25	6.25	3.125	6.25	6.25	12.500	3.125	25	3.125	25	25	1.563	12.500
Streptococcus pyogenes 9889	< 0.01	0.013	< 0.01	0.013	0.025	0.025	0.025	0.013	0.049	0.049	0.013	< 0.01	0.013
Streptococcus agalaciae 32	0.025	0.049	0.013	0.049	0.049	0.025	0.013	0.098	0.049	0.098	0.049	0.013	0.049
Streptococcus pneumoniae 0025	< 0.01	0.013	< 0.01	0.013	< 0.01	0.013	0.013	0.013	0.195	0.098	0.025	< 0.01	0.01
Haemophilus influenzae 1210	6.25	12.500	6.25	12.500	25	6.250	12.500	25	25	12.500	3.125	6.250	3.125
Escherichia coil 04	0.049	0.098	0.025	0.049	0.098	0.195	0.098	0.195	0.049	0.098	0.049	0.195	0.049
Klebsiella peneumoniae 523	0.098	0.391	0.049	0.198	0.195	0.391	0.198	0.781	1.563	0.781	0.781	0.781	0.025
Citrobacter freundii 323	0.098	0.195	0.049	0.198	0.195	0.195	0.195	0.781	0.781	0.781	0.391	0.391	0.025
Enterobactor cloacae 34	0.098	0.198	0.049	0.098	0.098	0.195	0.195	0.781	0.195	0.781	0.098	0.781	0.025
Serratia marcescens 3349	0.198	0.198	0.049	0.198	0.098	0.098	0.098	0.391	0.098	0.098	0.098	0.781	0.049
Acinetobacter baumannii 2289	25.0	50	12.5	50	25	12.5	12.5	25	12.5	25	12.500	12.500	12.5
Psudemonas aeruginosa 5455	3.125	12.5	3.125	25	12.500	3.125	6.25	12.5	12.5	12.5	3.125	3.125	3.125

a = Imipenem, b = Meropenem

Table 2. Comparative *in vitro* antibacterial activity of **IIIc**, meropenem and imipenem against 40 strains (MIC, μg/mL)

Organism	IIIc	IPM	MPM	Organism	IIIc	IPM	MPM
Staphylococcus aureus giorgio	0.01	0.01	0.10	*Salmonella paratyphi A*	0.10	0.10	0.03
Staphylococcus aureus 209P	0.03	0.01	0.10	*Salmonella typhimurium*	0.10	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*	0.20	0.20	0.05
Bacillus subtilts ATCC 6633	0.03	0.03	0.05	*Enterobacter cloacae*	0.03	0.10	0.05
Bacillus megatherium	0.03	0.03	0.05	*Enterobacter cloacae 417*	0.01	0.10	0.03
Pseudomonas aeruginosa 9027	1.56	0.80	0.40	*Serratia marcescens 370*	0.20	0.20	0.05
Pseudomonas aeruginosa 77/2	0.80	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	0.40	*Proteus mirabilis 112/3*	0.20	0.20	0.10
Pseudomonas cepacia	0.10	0.80	0.40	*Proteus mirabilis 174/3*	0.20	0.10	0.10
Escherchia coil 086	0.05	0.10	0.03	*Proteus vulgaris 868*	0.20	0.10	0.10
Escherchia coil 0114	0.05	0.10	0.01	*Proteus rettgeri 936*	0.20	0.20	0.10
Escherchia coil 0126	0.05	0.10	0.03	*Proteus rettgeri 937*	0.40	0.20	0.05
Escherchia coil V6311/65	0.05	0.05	0.01	*Pasteurella multocida*	0.05	< 0.01	0.05
Escherchia coil TEM	0.05	0.20	0.05	*Corynebacterium diphtheriae*	0.01	0.03	0.05
Escherchia coil 1507	0.10	0.10	0.05	*Corynebacterium pyogenes*	0.01	< 0.01	0.03

Table 3. DHP-I stablity of **IIIa**, **IIIc** and **IIIg**

	IIIa	**IIIc**	**IIIg**	Meropenem	Imipenem
DHP-1	1.47	1.12	1.60	1.00	0.20

Experimental Section

-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.

(2*S*,4*S*)-2-[(1-Oxo-2-diazo)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (2). A solution of **1** (44.5 g, 94.0 mmol) and triethylamine (31.4 mL, 188.0 mmol) in dry THF (500 mL) was cooled to −20 °C under nitrogen and treated with ethyl chloroformate (10.8 mL, 112.9 mmol). After 30 min, a solution of CH_2N_2 in ether was added at −20 °C until the pale yellow color persisted and was stirred for 3 h at room temperature. The excess of CH_2N_2 was destroyed with acetic acid (25 mL), and washed with 10% $NaHCO_3$ and brine. 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 : *n*-Hexane = 1 : 3) to give **2** (40.1 g, 86%) as a pale

yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.77-2.01 (brs, 2H), 2.76-2.83 (m, 1H), 2.94-3.09 (m, 2H), 4.05 (brs, 1H), 4.02-4.50 (m, 2H), 5.15-5.25 (m, 2H), 5.33-5.35 (m, 1H), 5.83-5.86 (m, 1H), 7.21 -7.33 (m, 9H), 7.47 (d, 6H, J = 7.2 Hz).

(2*S*,4*S*)-2-[(1-Oxo-2-hydroxy)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (3). To a solution of **2** (10.0 g, 20.0 mmol) in dioxane (70 mL) was added slowly 0.25 *M* sulphuric acid (160 mL) and was stirred for 48 h at water bath. The solution was then cooled in an ice bath, neutralized with solid $NaHCO_3$, and extracted with chloroform (3 × 100 mL). The organic extracts were washed successively with 10% $NaHCO_3$, brine, and 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 : 2) to give **3** (7.0 g, 72%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.71- 2.00 (m, 2H), 2.83 (brs, 1H), 3.01-3.18 (m, 2H), 4.10-4.28 (m, 2H), 4.38 (brs, 1H), 4.50 (brs, 2H), 5.16-5.29 (m, 2H), 5.83-5.88 (m, 1H), 7.24-7.34 (m, 9H), 7.48 (d, 6H, J = 6.9 Hz).

(2*S*,4*S*)-2-[(1-Hydroxy-2-hydroxy)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrololidine (4). To a solution of **3** (1.0 g, 2.0 mmol) in THF (30 mL) was added slowly $NaBH_4$ (0.15 g, 4.0 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 **4** (0.78 g, 78%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.88-1.91 (m, 2H), 2.64-2.76 (m, 1H), 3.39 (brs, 1H), 3.46 (brs, 2H), 3.57-3.62 (m, 2H), 3.76-3.78 (m, 1H), 4.48 (d, 2H, J = 6.1 Hz), 5.21-5.28 (m, 2H), 5.83-5.89 (m, 1H), 7.20-7.33 (m, 9H), 7.69 (d, 6H, J = 7.1 Hz).

(2*S*,4*S*)-2-[(1-Hydroxyimino-2-hydroxy)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (5). To a stirred solution of **3** (1.0 g, 2.0 mmol) in EtOH (20 mL) was added dropwise 50% aqueous hydroxylamine (0.15 mL, 2.2 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 **5** (0.6 g, 60%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.75-1.79 (m, 1H), 2.48-2.52 (m, 1H), 2.64-2.78 (m, 2H), 2.90 (brs, 1H), 4.12 (s, 2H), 4.42-4.56 (m, 2H), 4.73-4.78 (m, 1H), 5.22-5.29 (m, 2H), 5.84-5.88 (m, 1H), 7.21-7.33 (m, 9H), 7.49 (d, 6H, J = 6.9 Hz).

(2*S*,4*S*)-2-[(1-Methoxyimino-2-hydroxy)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (6). To a solution of **3** (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 1N-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 **6** (0.75 g, 71%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.89-2.06 (m, 2H), 2.73-2.76 (m, 1H), 2.86-2.92 (m, 2H), 3.34-3.38 (m, 1H), 3.90 (s, 3H), 4.17 (brs, 2H), 4.35-4.48 (m, 2H), 5.22-5.30 (m, 2H), 5.86 (brs, 1H), 7.21-7.33 (m, 9H), 7.48 (d, 6H, J = 7.6 Hz).

(2*S*,4*S*)-2-[(1-Oxo-2-bromo)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (7). To a solution of **2** (12.9 g, 25.9 mmol) in THF (100 mL) was added slowly aq. 48% HBr (4.86 mL, 28.8 mmol) at −10 °C and was stirred for 1 h at same temperature . The solution was then neutralized with 10% $NaHCO_3$, and extracted with ethyl acetate (2 × 100 mL). The organic extracts were washed successively with 10% $NaHCO_3$, brine, and 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 : 3) to give **7** (10.0 g, 70%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.89-2.09 (m, 2H), 2.84-2.87 (m, 1H), 3.08-3.12 (m, 2H), 3.92 (s, 1H), 4.10 (s, 1H), 4.29-4.35 (m, 1H), 4.46-4.52 (m, 2H), 5.17-5.29 (m, 2H), 5.83-5.87 (m, 1H), 7.22-7.34 (m, 9H), 7.49 (d, 6H, J = 5.4 Hz).

(2*S*,4*S*)-2-[(1-Oxo-2-azido)ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (8). A mixture of **7** (8.0 g, 14.5 mol) and sodium azide (2.8 g, 43.5 mmol) in DMSO (100 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into ice water and extracted with ethyl acetate (100 mL × 2). The organic layer was successively washed with water (100 mL × 2), brine and 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 : *n*-Hexane = 1 : 5) to give **8** (5.9 g, 79.4%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 1.61-1.68 (m, 1H), 2.04-2.06 (m, 1H), 2.85-2.88 (m, 1H), 3.05-3.18 (m, 2H), 3.94 (brs, 1H), 4.12-4.22 (m, 2H), 4.46-4.53 (m, 2H), 5.19-5.30 (m, 2H), 5.84-5.91 (m, 1H), 7.22-7.34 (m, 9H), 7.47 (d, 6H, J = 6.7 Hz).

(2*S*,4*S*)-2-[(1-Oxo-2-(*N*-allyloxycarbonyl)amino)ethyl]-4-tritylthio-1-(allyloxycarbonyl) pyrrolidine (9). A mixture of **8** (7.7 g, 15.0 mmol), triphenylphosphine (5.36 g, 20.0 mmol) and H_2O (0.36 mL, 20.0 mmol) in THF (30 mL) was heated at 40 °C for 4 h. After cooling, the reaction mixture was diluted with H_2O (30 mL) and ethyl acetate (30 mL). The organic layer was successively washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave a crude residue. To above solution and triethylamine (1.9 mL, 13.8 mmol) in dry CH_2Cl_2 (100 mL) was added slowly allyl chloroformate (1.7 g, 13.8 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 **9** (4.8 g, 56%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ 2.05-2.11 (m, 2H), 2.83 (brs, 1H), 3.04-3.16 (m, 2H), 4.10 (brs, 1H), 4.14-4.18 (m, 2H), 4.49-4.55 (m, 4H), 5.23-5.40 (m, 4H), 5.88-5.96 (m, 2H), 7.21-7.24 (m, 9H), 7.26-7.46 (m,

6H).

(2*S*,4*S*)-2-[(1-Hydroxy-2-(*N*-allyloxycarbonyl)amino)-ethyl]-4-tritylthio-1-(allyloxycarbonyl)pyrrolidine (10). The synthesis of the compound **10** was carried out by the same procedure as described for the preparation of **4** using compound **3**. Yield: 83%. ^{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), 3.57-3.62 (m, 2H), 3.76-3.78 (m, 1H), 4.09 (brs, 1H), 4.33-4.59 (m, 4H), 5.26-5.39 (m, 4H), 5.84-5.96 (m, 2H), 7.23-7.36 (m, 9H), 7.50 (d, 6H, J = 5.4 Hz).

(2*S*,4*S*)-2-[(1-Hydroxyimino-2-(*N*-allyloxycarbonyl)-amino)ethyl]-4-tritylthio-1-(allyloxy carbonyl)pyrrolidine (11). The synthesis of the compound **11** was carried out by the same procedure as described for the preparation of **5** using compound **3**. Yield: 80%. ^{1}H-NMR ($CDCl_3$) δ 1.90-1.97 (m, 2H), 2.73-2.88 (m, 2H), 3.10-3.15 (m, 1H), 3.58 (d, 2H, J = 4.2 Hz), 3.72 (d, 1H, J = 5.2 Hz), 4.29-4.52 (m, 4H), 5.23-5.39 (m, 4H), 5.91-6.01 (m, 2H), 7.23-7.45 (m, 9H), 7.48 (d, 6H, J = 7.5 Hz).

(2*S*,4*S*)-2-[(1-Methoxyimino-2-(*N*-allyloxycarbonyl)-amino)ethyl]-4-tritylthio-1-(allyloxy carbonyl)pyrrolidine (12). The synthesis of the compound **12** was carried out by the same procedure as described for the preparation of **6** using compound **3**. Yield: 62%. ^{1}H-NMR ($CDCl_3$) δ 1.87-2.05 (m, 2H), 2.73 (brs, 1H), 2.83-2.89 (brs, 2H), 2.94-2.97 (m, 1H), 3.45-3.49 (t, 2H, J = 5.0 Hz), 3.88 (d, 3H, J = 3.3 Hz), 4.45-4.49 (m, 4H), 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).

(2S,4S)-2-[(1-Oxo-2-nitro)ethyl]-4-tritylthio-1-(allyloxy-carbonyl)pyrrolidine (13). A mixture of acid **1** (4.0 g, 8.5 mmol) and 1,1'-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 was 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 vigorously stirred 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, and concentrated, and the resulting residue was purified by silica gel column chromatography (EtOAc : hexane = 1 : 4) to give **13** (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 (brs, 1H), 4.59 (brs, 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).

The synthesis of the compounds **11**, **12** and **13** were carried out by the same procedure as described for the preparation of **4**, **5** and **6** using compound **13**.

14: Yield: 83%. ^{1}H-NMR ($CDCl_3$) δ 1.90-1.97 (m, 2H), 2.73-2.88 (m, 2H), 3.10-3.15 (m, 1H), 3.58 (d, 2H, J = 4.2 Hz), 3.72 (d, 1H, J = 5.2 Hz), 4.49-4.52 (m, 3H), 5.23-5.30 (m, 2H), 5.91-5.98 (m, 1H), 7.23-7.45 (m, 9H), 7.48 (d, 6H, J = 7.5 Hz).

15: Yield: 70%. ^{1}H-NMR ($CDCl_3$) δ 2.07 (brs, 2H), 2.80 (q, 1H, J = 6.5 Hz), 2.93 (brs, 2H), 4.01 (brs, 1H), 4.41-4.47 (m, 2H), 4.49-4.52 (m, 2H), 5.31 (d, 2H, J = 8.4 Hz), 5.79-5.87 (m, 1H), 7.22-7.36 (m, 9H), 7.46 (d, 6H, J = 7.4 Hz).

16: Yield: 86%. ^{1}H-NMR ($CDCl_3$) δ 1.19-1.96 (m, 2H), 2.06 (brs, 1H), 2.48-2.54 (m, 1H), 2.82 (brs, 1H), 2.94 (brs, 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).

Allyl (1*R*,5*S*,6*S*)-6-[(1*R*)-hydroxyethyl]-2-[[5-(1-hydr-oxy-2-hydroxy)ethyl]-1-(allyloxycarbonyl)pyrrolidin-3-ylthio]-1-methylcarbapen-2-em-3-carboxylate (IIa). To a solution of **4** (0.70 g, 1.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise triethylsilane (0.25 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% $NaHCO_3$, 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-carboxylate (**17**, 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 7 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** (0.21 g, 32%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 6.2 Hz), 1.34 (d, 3H, J = 5.7 Hz), 2.04 (brs, 1H), 2.50 (m, 1H), 3.24-3.26 (m, 2H), 3.58-3.72 (m, 3H), 3.81-4.18 (m, 4H), 4.42-4.58 (m, 4H), 4.67 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.25-5.41 (m, 4H), 5.83-5.98 (m, 2H).

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

IIb: Yield 32%. ^{1}H-NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 5.3 Hz), 1.34 (d, 3H, J = 5.9 Hz), 2.04 (brs, 1H), 2.75 (brs, 1H), 3.25 (brs, 1H), 3.32 (brs, 2H), 3.37 (brs, 1H), 3.95 (brs, 1H), 4.05-4.20 (brs, 2H), 4.56-4.61 (m, 4H), 4.69 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.02 (brs, 1H), 5.21-5.27 (m, 4H), 5.89-5.94 (m, 2H), 9.95-9.77 (brs, 1H).

IIc: Yield 27%. ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 5.6 Hz), 1.31 (d, 3H, J = 5.8 Hz), 1.97 (brs, 1H), 2.46 (brs, 1H), 2.66 (brs, 1H), 3.10 (brs, 1H), 3.27 (t, 2H, J = 7.6 Hz), 3.51 (brs, 1H), 3.88 (s, 3H), 4.05 (m, 1H), 4.17-4.29 (m, 2H), 4.31-4.44 (brs, 4H), 4.67 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.21-5.39 (m, 4H), 5.89-5.95 (m, 2H).

IId: Yield 38%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 5.3 Hz), 1.34 (d, 3H, J = 6.0 Hz), 2.05-2.14 (m, 1H), 2.45 (brs, 1H), 2.69 (brs, 1H), 3.27 (brs, 1H), 3.39-3.45 (m, 2H), 3.84-3.94 (brs, 1H), 3.98-4.04 (brs, 2H), 4.13 (brs, 1H), 4.31-4.44 (brs, 4H), 4.64 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.25-5.33 (m, 4H), 5.90-5.97 (m, 2H).

IIe: Yield 26%. ^{1}H-NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 6.2 Hz), 1.30 (d, 3H, J = 5.9 Hz), 2.04 (brs, 1H), 2.45 (m, 1H), 2.80-2.91 (m, 1H), 3.24-3.36 (m, 2H), 3.58-3.62 (m, 2H), 3.81-3.93 (brs, 2H), 4.15-4.18 (m, 2H), 4.42-4.58 (m, 4H), 4.65(dd, 1H, J = 6.2 an 7.1 Hz), 4.70 (dd, 1H, J = 6.2 an 7.1 Hz), 5.25-5.41 (m, 4H), 5.83-5.98 (m, 2H).

IIf: Yield 33%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 6.7 Hz), 1.35 (d, 3H, J = 6.2 Hz), 1.95 (brs, 1H), 2.30 (brs, 1H), 2.66 (brs, 1H), 3.05 (brs, 1H), 3.26-3.40 (m, 2H), 3.51 (brs, 1H), 4.05 (brs, 1H), 4.25 (d, 2H, J = 5.5 Hz), 4.44-4.55 (bs, 4H), 4.64 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.18-5.35 (m, 4H), 5.88-6.02 (m, 2H).

IIg: Yield 29%. ^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H, J = 6.7 Hz), 1.35 (d, 3H, J = 6.2 Hz), 1.97 (brs, 1H), 2.35 (brs, 1H), 2.60 (brs, 1H), 3.05 (brs, 1H), 3.26-3.40 (m, 2H), 3.51 (brs, 1H), 3.91 (s, 3H), 4.05 (brs, 1H), 4.25 (d, 2H, J = 5.5 Hz), 4.44-4.55 (brs, 4H), 4.64 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.19-5.32 (m, 4H), 5.88-5.97 (m, 2H).

IIh: Yield 39%. ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 5.7 Hz), 1.35 (d, 3H, J = 6.2 Hz), 2.02 (brs, 1H), 2.35 (brs, 1H), 2.60 (brs, 1H), 3.26 (brs, 1H), 3.45 (brs, 1H), 3.77 (brs, 1H), 3.87 (brs, 1H), 4.05 (brs, 1H), 4.23 (brs, 2H), 4.44-4.51 (brs, 4H), 4.64 (dd, 1H, J = 6.2 an 7.1 Hz), 4.71 (dd, 1H, J = 6.2 an 7.1 Hz), 5.20-5.34 (m, 4H), 5.87-5.96 (m, 2H).

IIi: Yield 33%. ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, 3H, J = 7.1 Hz), 1.34 (d, 3H, J = 6.3 Hz), 1.79 (brs, 1H), 3.24-3.33 (m, 3H), 3.68-3.72 (m, 2H), 4.04 (brs, 3H), 4.18-4.20 (m, 2H), 4.60 (d, 4H, J = 4.2 Hz), 4.77-4.78 (m, 1H), 4.82-4.84 (m, 1H), 5.22-5.31 (m, 4H), 5.88-5.94 (m, 2H).

IIj: Yield 17%. ^{1}H-NMR ($CDCl_3$) δ 1.19-1.32 (m, 6H), 2.41-2.46 (m, 4H), 3.67 (s, 2H), 3.74-3.78 (m, 2H), 4.07-4.10 (m, 2H), 4.20-4.22 (m, 2H), 4.62-4.67 (m, 4H), 5.19-5.35 (m, 4H), 5.87-5.93 (m, 2H).

IIk: Yield 34%. ^{1}H-NMR ($CDCl_3$) δ 1.27 (d, 3H, J = 4.8 Hz), 1.33 (d, 3H, J = 6.2 Hz), 2.03 (brs, 1H), 3.12-3.25 (m, 3H), 3.51-3.56 (m, 2H), 3.91 (s, 3H), 4.23 (t, 2H, J = 6.7 Hz), 4.54-4.55 (m, 4H), 4.69-4.70 (m, 1H), 4.72-4.74 (m, 1H), 5.11 (brs, 2H), 5.44-5.46 (m, 4H), 5.89-5.94 (m, 2H).

(1*R*,5*S*,6*S*)-6-[(1*R*)-Hydroxyethyl]-2-[[5-(1-hydroxy-2-hydroxy)ethyl]pyrrolidin-3-yl thio]-1-methylcarbapen-2-em-3-carboxylic acid (IIIa). To a stirred solution of **IIa** (0.2 g, 0.4 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. 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 amorphorus solid. Yield 24%. -UV λ_{max}: 298 nm. -^{1}H-NMR (D_2O) δ 1.12 (d, 3H, J = 5.9 Hz), 1.18 (d, 3H, J = 6.3 Hz), 1.68-1.72 (m, 1H), 2.45-2.58 (m, 2H), 3.20-3.26 (m, 2H), 3.47-3.53 (brs, 3H), 3.57-3.64 (m, 1H), 3.88-3.99 (m, 3H), 4.11-4.15 (m, 1H). -IR (KBr): 3480, 1720, 1670 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{24}N_2O_6S$ 372.1355, Found 372.1311.

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

IIIb: Yield 27%. -UV λ_{max} : 298nm. -^{1}H-NMR (D_2O) δ 1.11 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 7.4 Hz), 1.95-2.10 (m, 2H), 2.73-2.76 (m, 1H), 3.24-3.34 (m, 3H), 3.59-3.65 (m, 3H), 3.93 (brs, 1H). 4.10-4.14 (m, 2H). -IR (KBr): 3460, 1730, 1710, 1650 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{23}N_3O_6S$ 385.1308, Found 385.1309.

IIIc: Yield 23%. -UV λ_{max} : 298 nm. -^{1}H-NMR (D_2O) δ 1.09 (d, 3H, J = 6.1 Hz), 1.16 (d, 3H, J = 6.3 Hz), 1.97-2.02 (m, 1H), 2.70-2.74 (m, 1H), 3.22-3.29 (m, 3H), 3.53 (m, 1H), 3.84 (s, 3H), 3.90-4.09 (m, 3H), 4.18 (s, 2H), 4.44 (t, 1H, J = 7.1 Hz). -IR (KBr): 3460, 1740, 1710, 1660 cm^{-1}. -HRMS (FAB) Calcd. for $C_{17}H_{25}N_3O_6S$ 399.1464, Found 399.1460.

IIId: Yield 25%. -UV λ_{max} : 298nm. -^{1}H-NMR (D_2O) δ 1.10 (d, 3H, J = 7.0 Hz), 1.17 (d, 3H, J = 6.2 Hz), 1.97-2.12 (m, 2H), 2.70-2.74 (m, 1H), 3.26-3.36 (m, 3H), 3.60- 3.67 (m, 2H), 3.89-3.99 (m, 2H). 4.10-4.18 (m, 2H). -IR (KBr): 3490, 1735, 1710, 1670 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{22}N_2O_6S$ 370.1199, Found 370.1196.

IIIe: Yield 24%. -UV λ_{max} : 298nm. -^{1}H-NMR (D_2O) δ 1.13 (d, 3H, J = 6.8 Hz), 1.21 (d, 3H, J = 6.3 Hz), 1.79 (brs, 1H), 2.02-2.05 (m, 1H), 2.75-2.87 (m, 2H), 3.28-3.30 (m, 1H), 3.30-3.35(m, 2H), 3.57 (brs, 1H), 3.83-3.99 (brs, 3H), 4.10-4.16 (m, 2H). -IR (KBr): 3540, 1720, 1670 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{25}N_3O_5S$ 371.1515, Found 371.1513.

IIIf: Yield 24%. -UV λ_{max} : 298 nm. -^{1}H-NMR (D_2O) δ 1.13 (d, 3H, J = 6.8 Hz), 1.20 (d, 3H, J = 6.3 Hz), 1.84 (brs, 1H), 2.04-2.08 (m, 1H), 2.75-2.82 (m, 2H), 3.28-3.30 (m, 1H), 3.30-3.35(m, 2H), 3.50 (brs, 1H), 3.83 (m, 1H), 3.99 (brs, 1H), 4.12- 4.16 (m, 2H). -IR (KBr): 3510, 1730, 1710, 1660 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{24}N_4O_5S$ 384.1467, Found 384.1464.

IIIg: Yield 18%. -UV λ_{max} : 298 nm. -^{1}H-NMR (D_2O) δ 1.16 (d, 3H, J = 6.8 Hz), 1.25 (d, 3H, J = 6.3 Hz), 1.86 (brs, 1H), 2.07-2.09 (m, 1H), 2.85-2.92 (m, 2H), 3.28-3.33 (m, 1H), 3.34-3.37 (m, 2H), 3.56 (brs, 1H), 3.79 (m, 1H), 3.86-3.88 (s, 3H), 3.96 (brs, 1H), 4.12-4.16 (m, 2H). -IR (KBr): 3440, 1710, 1690, 1630 cm^{-1}. -HRMS (FAB) Calcd. for $C_{17}H_{26}N_4O_5S$ 398.1624, Found 398.1625.

IIIh: Yield 33%. -UV λ_{max} : 298 nm. -^{1}H-NMR (D_2O) δ 1.13 (d, 3H, J = 6.4 Hz), 1.26 (d, 3H, J = 6.8 Hz), 1.89 (brs, 1H), 2.07-2.09 (m, 1H), 2.80-2.97 (m, 2H), 3.25-3.28 (m, 1H), 3.34-3.40 (m, 2H), 3.56 (brs, 1H), 3.80-3.91 (brs, 2H), 4.10-4.19 (m, 2H). -IR (KBr): 3490, 1710, 1690, 1660 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{23}N_3O_5S$ 369.1358, Found 369.1356.

IIIi: Yield 14%. -UV λ_{max} : 298 nm. -mp: 162-170 °C (dec.) -^{1}H-NMR (D_2O) δ 1.14 (d, 3H, J = 4.1 Hz), 1.55 (d, 3H, J = 3.9 Hz), 1.54-1.57 (m, 2H), 2.45-2.49 (m, 2H), 3.33-3.35 (m, 2H), 3.46-3.48 (m, 2H), 3.69-3.74 (m, 3H), 4.10-4.14 (m, 2H). -IR (KBr): 3440, 1710, 1670, 1550 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{23}N_3O_7S$ 401.1257, Found

401.1255.

IIIj: Yield 10%. -UV λ_{max} : 298 nm. -mp: 160-163 °C (dec.). -^{1}H-NMR (D_2O) δ 0.96-1.26 (m, 6H), 2.32-2.43 (m, 4H), 3.43-3.49 (m, 2H), 3.71-3.79 (m, 4H), 5.01 (d, 2H, J = 4.5 Hz). -IR (KBr): 3490, 1710, 1670, 1570 cm^{-1}. -HRMS (FAB) Calcd. for $C_{16}H_{22}N_4O_7S$ 414.1209, Found 414.1203.

IIIk: Yield: 18%. -UV λ_{max} : 298 nm. -mp: 158-162 °C (dec.). -^{1}H-NMR (D_2O) δ 1.11 (d, 3H, J = 6.9 Hz), 1.18 (d, 3H, J = 6.3 Hz), 1.23 (d, 1H, J = 6.7 Hz), 2.01-2.03 (m, 1H), 2.79-2.84 (m, 1H), 3.31-3.36 (m, 2H), 3.49-3.51 (m, 2H), 3.81 (s, 3H), 4.07-4.11 (m, 2H), 4.15 (t, 2H, J = 6.1 Hz), 4.60-4.62 (m, 1H). -IR (KBr): 3460, 1710, 1680, 1570 cm^{-1}. -HRMS (FAB) Calcd. for $C_{17}H_{24}N_4O_7S$ 428.1366, Found 428.1362.

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