A Novel 1β-Methylcarbapenem Antibiotic, S-4661

Synthesis and Structure-activity Relationships of 2-(5-Substituted Pyrrolidin-3-ylthio)-1β-methylcarbapenems

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The synthesis and biological activity of (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-substituted pyrrolidin-3-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acids are described. These compounds exhibit potent antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. Of these new carbapenems, (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-5-sulfamoylaminomethyl pyrrolidin-3-ylthio]-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid (S-4661) showed the most potent and well balanced activity and was selected as a candidate for further evaluation.

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[1], and a large number of derivatives have been synthesized and investigated with enthusiasm. Among those compounds, panipenem[2] was the first to be successfully launched in the market and clinical evaluations are in progress for meropenem[3], BO-2727[4] and DX-8739[5] which have enhanced metabolic stability to renal dehydropeptidase-1 (DHP-1) because of the introduction of a 1β-methyl group to the carbapenem skeleton for high antibacterial potency (Fig. 1). We were also interested in this pyrrolidin-3-ylthio group and focused on the substituted group at the C-5′ position of pyrrolidine.

As we found that the compound (**1a**) which had an aminomethyl group at the C-5′ position of pyrrolidine showed relatively good antibacterial activity, our subsequent research on the correlation of biological properties was aimed at the substituent connected to this amino group. A series of aminomethyl derivatives variously *N*-substituted at C-5′, which could be classified into five categories as shown in Fig. 2, were synthesized and investigated, and as a result, the sulfamoylamino group was found to be the most appropriate substituent for optimal biological properties.

Chemistry

The common intermediates, 2-methanesulfonyloxymethyl pyrrolidine derivative (**7**) and 2-aminomethyl pyrrolidine derivative (**9**), for the preparation of a series of 2-*N*-substituted aminomethyl 4-mercaptopyrrolidine derivatives (**11a**～**11q**) were synthesized as shown in Scheme 1. trans-4-Hydroxy-L-proline (**2**) was esterified by FISCHER's method and *N*-protected by *S*-*p*-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine

Fig. 1. Carbapenem antibiotics having (3*S*)-pyrrolidin-3-ylthio group at C-2 position.

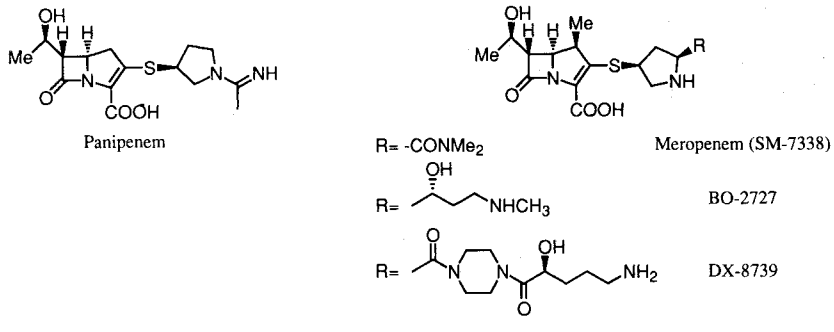
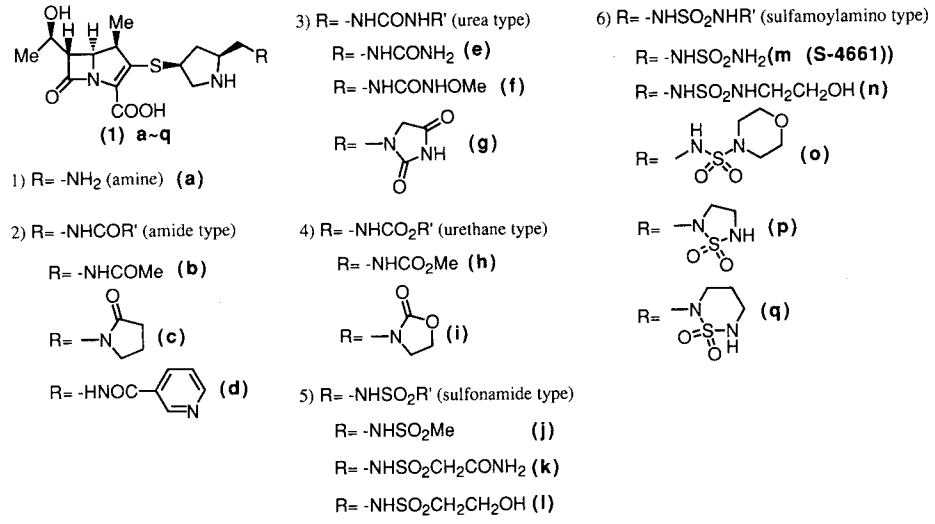
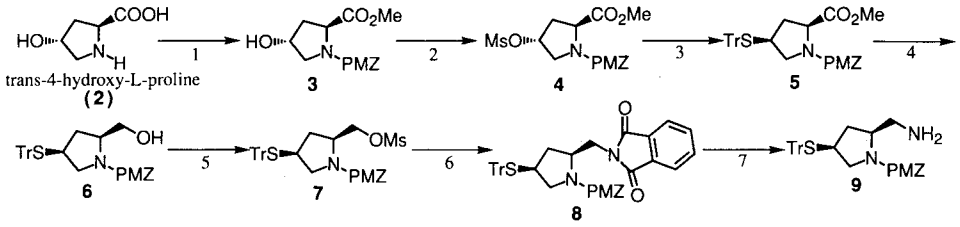


Fig. 2. Categories of substituents at C-5′ position of pyrrolidine and prepared compounds.



Scheme 1.



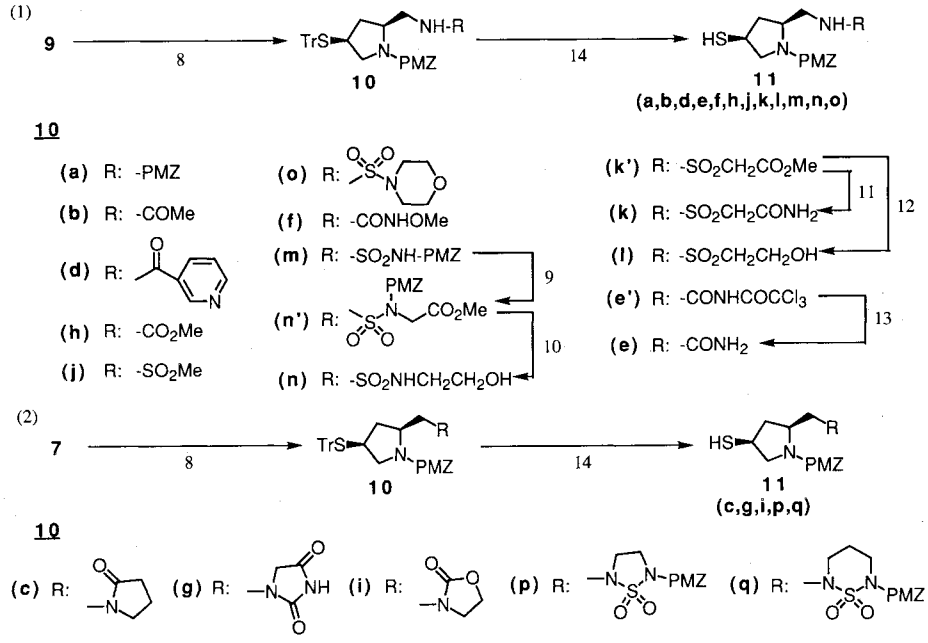
1,(¡) HCl-MeOH, (¡¡) S-p-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine(MZ-SDP), NEt_3; 2, mesyl chloride, NEt_3; 3, TrSNa; 4, $LiBH_4$; 5, mesyl chloride, NEt_3; 6, potassium phthalimide; 7, $H_2NNH_2 \cdot H_2O$

(MZ-SDP) to give **3**, which was *O*-mesylated and subsequently treated with sodium triphenylmethylthioate, which was generated *in situ* from triphenylmethylmercaptan and sodium hydride in DMF, to provide **5** with inversion of the C-4 configuration. **5** was reduced with lithium borohydride in THF and subsequently mesylated to give **7**, which was successfully converted into amine (**9**) *via* phthalimide derivative (**8**) by the usual method.

Each 2-*N*-substituted aminomethyl 4-mercaptopyrrolidine derivative (**11a**~**11q**) was prepared by the sequence of reactions shown in Scheme 2. Treatment of **9** with MZ-SDP, acetyl chloride, nicotinoyl chloride and methyl chloroformate afforded the corresponding *N*-acylated products, **10a**, **10b**, **10d** and **10h**, respectively. Carbamoylation of amine (**9**) was carried out by a conventional method using trichloroacetyl isocyanate to give **10e**. Amine (**9**) was reacted with 1,1′-carbonyldiimidazole, then with methoxylamine to furnish **10f**. Sulfonylation of amine with mesylchloride and methyl (chlorosulfonyl)-acetate proceeded smoothly to afford **10j** and **10k′**, respectively. **10k′** was further converted into **10k** and **10l** by aminolysis with aqueous ammonia in MeOH and by reduction with lithium borohydride, respectively. Reaction of amine (**9**) with *p*-methoxybenzyloxycarbonyl sulfamoyl chloride, generated *in situ* from chlorosulfonyl isocyanate and *p*-methoxybenzyl alcohol below $-10°C$, was carried out at $-60°C$ to give **10m**. Mitsunobu reaction of **10m** with methyl glycolate provided **10n′**, which was reduced with lithium borohydride in THF to afford **10n**. Sulfonylation of **9** with 4-morpholinesulfonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine as a catalyst in DMF proceeded slowly affording **10o**.

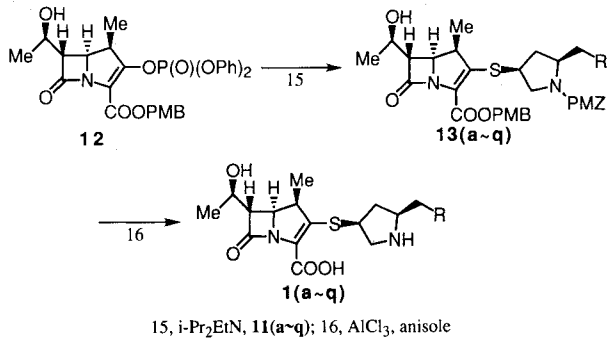
Cyclic aminomethyl derivatives (**10c**, **10g**, **10i**, **10p**, **10q**) were conveniently prepared by the reaction of mesylate (**7**) and sodium salt of the corresponding cyclic amino derivatives in DMF. 1,1-Dioxo-(1,2,5)-thiadiazolidine-2-carboxylic acid *p*-methoxybenzyl ester and 1,1-dioxo-(1,2,6)-thiadiazinane-2-carboxylic acid *p*-methoxybenzyl ester were obtained by treatment of *p*-methoxy-

Scheme 2.



8(a), MZ-SDP, CH_2Cl_2, room temperature, 1 hour; **8(b)**, acetyl chloride, NEt_3, CH_2Cl_2, −30°C, 20 minutes; **8(d)**, nicotinoyl chloride hydrochloride, NEt_3, CH_2Cl_2, 0°C, 1 hour; **8(h)**, methyl chloroformate, NEt_3, CH_2Cl_2, −30°C, 20 minutes; **8(j)**, mesyl chloride, NEt_3, CH_2Cl_2, −30°C, 10 minutes; **8(o)**, 4-morpholinesulfonyl chloride, NEt_3, 4-dimethylaminopyridine, CH_2Cl_2, −10°C, 15 hours; **8(f)**, (i), 1,1'-carbonyldiimidazole, THF, room temperature, 1 hour, (ii) methoxyl amine, THF, room temperature, 18 hours; **8(m)**, *p*-methoxybenzyloxycarbonyl sulfamoyl chloride, NEt_3, CH_2Cl_2, −30°C, 20 minutes; **9**, methyl glycolate, diethyl azodicarboxylate, PPh_3, THF, room temperature, 40 minutes; **10**, $LiBH_4$, THF, room temperature, 30 minutes; **8(k')**, methyl (chlorosulfonyl)acetate, NEt_3, CH_2Cl_2, −20°C, 25 minutes; **11**, NH_3 aq., MeOH, room temperature, 3 days; **12**, $LiBH_4$, THF, room temperature, 10 minutes; **8(e')**, trichloroacetyl isocyanate, CH_2Cl_2, −30°C, 5 minutes; 13, NaOH, MeOH/CH_2Cl_2, room temperature, 2 hours; **8(c)**, 2-pyrrolidone, NaH, DMF, 80°C, 3 hours; **8(g)**, hydantoin, NaH, DMF, 80°C, 3 hours; **8(i)**, 2-oxazolidone, NaH, DMF, 80°C, 3 hours; **8(p)**, 1,1-dioxo-(1,2,5)-thiadiazolidine-2-carboxylic acid *p*-methoxybenzyl ester, NaH, DMF, 80°C, 3 hours; **8(q)**, 1,1-dioxo-(1,2,5)-thiadiazinane-2-carboxylic acid *p*-methoxybenzyl ester, NaH, DMF, 80°C, 3 hours; **14**, (i) $AgNO_3$, pyridine, MeOH/CH_2Cl_2, room temperature, 10 minutes, (ii) H_2S.

Scheme 3.



15, i-Pr_2EtN, **11(a~q)**; 16, $AlCl_3$, anisole

benzyloxycarbonyl sulfamoyl chloride, which was prepared with chlorosulfonyl isocyanate and *p*-methoxybenzyl alcohol, and the corresponding amino alcohols (ethanolamine or 3-amino-1-propanol) in the presence of triethylamine and the following Mitsunobu reaction. Deprotection[6] of the trityl group to mercaptan (**11** (**a**~**q**)) was achieved by aqueous $AgNO_3$ and pyridine in CH_2Cl_2/MeOH and subsequent treatment with H_2S.

Each 2-substituted 4-mercaptopyrrolidine derivative freshly prepared as above (**11** (**a**~**q**)) was treated with enol phosphate[7] (**12**) in the presence of diisopropylethylamine to provide the protected 1β-methylcarbapenem (**13** (**a**~**q**)). The final deprotection step of **13** (**a**~**q**) was performed by treatment with $AlCl_3$ in the presence of anisole[8] to give the corresponding deprotected 1β-methylcarbapenem (**1** (**a**~**q**)), which was purified by Diaion HP-20AG column chromatography. (Scheme 3)

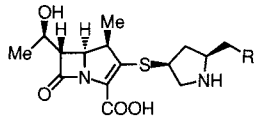
Biological Evaluation

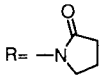
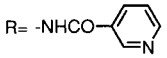
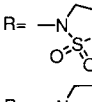
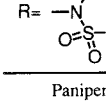
The *in vitro* antibacterial activities of the new carbapenems (**1a**~**1q**) prepared as above against Gram-positive and Gram-negative bacteria are listed in Table 1. For comparison, the MIC values of panipenem and meropenem are also listed. As expected, the antibacterial activity against all tested bacteria was found to be greatly enhanced by acylation or sulfonylation of the amino moiety of **1a**. Comparing the compounds (**1b**~**1i**)

having amide, urea or urethane type side chain at C-5′ showed little difference in the antibacterial activities for Gram-positive and Gram-negative bacteria, but reduced activity against *Pseudomonas aeruginosa* was observed with compounds **1d** and **1g**. Among these compounds, **1i** having a 2-oxazolidone side chain had better antibacterial activity including that against *Pseudomonas aeruginosa*. The compounds (**1j**, **1m**) having a sulfonamide type or sulfamoylamino type side chain at C-5′ had the tendency to exhibit better antibacterial activity especially against Gram-negative bacteria including *P. aeruginosa* than the corresponding carbonyl analogue **1b** or **1e**. Further introduction of the hydroxy or carbamoyl group to the end of the side chain (**1k**, **1l**, **1n**, **1o**) did not enhance the antibacterial activity. On the whole, the compounds (**1c**, **1i**, **1p**) having a cyclic side chain showed better antibacterial activity especially against Gram-negative bacteria than the corresponding acyclic analogues (**1b**, **1h**, **1m**).

Among these compounds, **1m** and **1p** possessed the most favorable biological profile and also exhibited better antibacterial activity than panipenem in general, and

Table 1. Antibacterial activity (MIC, μg/ml) of carbapenem compounds having a 5′-substituted pyrrolidinylthio side chain.



Compound	MIC (μg/ml)									
	S.a.	*S.a.*(R)	*E.c.*	*K.p.*	*E.cl.*	*P.m.*	*P.v.*	*S.m.*	*P.a.*1	*P.a.*2
R= -NH_2 (**1a**)	0.2	3.1	0.1	0.1	0.4	0.1	0.1	0.8	12.5	3.1
R= -NHCOMe (**1b**)	0.05	0.8	0.05	0.05	0.2	0.2	0.2	0.2	3.1	0.4
R=  (**1c**)	0.05	0.4	0.02	0.05	0.1	0.1	0.1	0.1	3.1	0.4
R=  (**1d**)	0.05	0.4	0.05	0.05	0.1	0.1	0.1	0.1	12.5	3.1
R= -$NHCONH_2$ (**1e**)	0.02	0.2	0.05	0.05	0.1	0.4	0.2	0.2	1.6	0.8
R= -NHCONHOMe (**1f**)	0.05	0.4	0.05	0.05	0.1	0.2	0.2	0.2	3.1	1.6
R=  (**1g**)	0.05	0.8	0.02	0.05	0.1	0.1	0.1	0.1	12.5	6.3
R= -$NHCO_2Me$ (**1h**)	0.05	0.4	0.05	0.1	0.1	0.2	0.2	0.1	3.1	0.8
R=  (**1i**)	0.05	0.8	0.02	0.05	0.05	0.05	0.1	0.1	1.6	0.2
R= -$NHSO_2Me$ (**1j**)	0.05	0.2	0.02	0.05	0.05	0.1	0.1	0.1	1.6	0.2
R= -$NHSO_2CH_2CONH_2$ (**1k**)	0.05	0.4	0.02	0.05	0.1	0.2	0.1	0.1	1.6	0.2
R= -$NHSO_2CH_2CH_2OH$ (**1l**)	0.05	0.4	0.02	0.05	0.05	0.2	0.1	0.2	1.6	0.4
R= -$NHSO_2NH_2$(**1m (S-4661)**)	0.02	0.2	0.02	0.05	0.05	0.1	0.1	0.1	0.4	0.1
R= -$NHSO_2NHCH_2CH_2OH$(**1n**)	0.05	0.4	0.05	0.05	0.1	0.2	0.1	0.1	1.6	0.4
R=  (**1o**)	0.05	0.4	0.05	0.05	0.2	0.2	0.2	0.2	25	6.3
R=  (**1p**)	0.05	0.2	0.02	0.02	0.05	0.1	0.1	0.05	0.4	0.1
R=  (**1q**)	0.02	0.4	0.02	0.05	0.05	0.1	0.1	0.1	0.4	0.2
Panipenem	0.02	0.2	0.1	0.2	0.2	0.4	0.4	0.4	6.3	3.1
Meropenem	0.1	0.8	0.02	0.02	0.05	0.05	0.05	0.05	0.8	0.1

S.a., *Staphylococcus aureus* FDA 209P JC-1; *S.a.*(R), *Staphylococcus aureus* SR3131; *E.c.*, *Escherichia coli* NIHJ JC-2; *K.p.*, *Klebsiella pneumoniae* SR1: *E.cl.*, *Enterobacter cloacae* SR233; *P.m.*, *Proteus mirabilis* PR-4; *P.v.*, *Proteus vulgaris* CN-329; *S.m.*, *Serratia marcescens* ATCC 13880; *P.a.*1, *Pseudomonas aeruginosa* SR1012; *P.a.*2, *Pseudomonas aeruginosa* SR24.

better than that of meropenem against Gram-positive bacteria including methicillin-resistant *S. aureus* SR3131 as shown in Table 1. Taking the overall biological and physical properties into account, **1m** was selected for further evaluation and designated as S-4661.

Experimental

Chemistry

MP was determined with a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were taken on a Jasco IR-700 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR-200 NMR spectrometer using TMS or sodium 2,2-dimethyl-2-silapentan-5-sulfonate (in D_2O) as an internal standard. All reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in a nitrogen atmosphere.

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 hours. The MIC of a compound was defined as the lowest concentration that visibly inhibited growth.

(2*S*,4*R*)-1-*p*-Methoxybenzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic Acid Methyl Ester (3)

trans-4-Hydroxy-L-proline (**2**) (25 g, 0.19 mol) was added to a methanol solution of HCl gas (10.4 g, 0.285 mol in 450 ml MeOH) under ice cooling. After being stirred at room temperature for 1 hour, the reaction mixture was evaporated *in vacuo* completely to dryness. To a solution of above residue in MeOH (500 ml) under ice cooling, *S*-*p*-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine (MZ-SDP) (63.46 g, 0.209 mol) and triethylamine (34.43 ml, 0.247 mol) were added and the reaction mixture was stirred for 20 minutes. After the mixture was evaporated, the residue was dissolved in EtOAc and the solid was filtered off. The filtrate was washed with dilute HCl, aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (toluene-EtOAc = 1 : 1) to give **3** (32.48 g, 55%): IR ($CHCl_3$) cm^{-1} 3389, 1752, 1706, 1617; ^{1}H NMR ($CDCl_3$) δ 2.02~2.17 (m, 1H), 2.23~2.35 (m, 1H), 3.54 (s, 3H), 3.65~3.67 (m, 1H), 3.76 (s, 1H), 3.80 (s, 3H), 4.42~4.56 (m, 2H), 5.03, 5.11 (ABq, J=12 Hz, 2H), 6.87 (dd, J=2.4, 8.8 Hz, 2H), 7.23~7.32 (m, 2H).

(2*S*,4*R*)-1-*p*-Methoxybenzyloxycarbonyl-4-methanesulfonyloxypyrrolidine-2-carboxylic Acid Methyl Ester (4)

To a stirred solution of **3** (227.2 g, 0.735 mol) in CH_2Cl_2 (1.3 liters) containing triethylamine (112.5 ml, 0.809 mol), methanesulfonyl chloride (56.8 ml, 0.735 mol) was slowly added at −30°C. After being stirred at the same temperature for 15 minutes, the reaction mixture was successively washed with dilute HCl and water, dried over $MgSO_4$, and concentrated *in vacuo* to give **4** (280.1 g, 98%): IR ($CHCl_3$) cm^{-1} 1755, 1709, 1620; ^{1}H NMR ($CDCl_3$) δ 2.01~2.35 (m, 1H), 2.55~2.74 (m, 1H), 3.02, 3.04 (2×s, 3H), 3.56, 3.78 (2×s, 3H), 3.81 (s, 3H), 4.42~4.58 (m, 1H), 4.98, 5.08 (ABq, J=12 Hz, 2H), 5.23~5.30 (m, 1H), 6.88 (dd, J=2, 8.6 Hz, 2H), 7.23~7.33 (m, 2H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-4-tritylthiopyrrolidine-2-carboxylic Acid Methyl Ester (5)

To a solution of triphenylmethylmercaptan (107.02 g, 0.387 mol) in DMF (350 ml), sodium hydride (*ca.*, 60% oil suspension, 13.42 g, 0.335 mol) was added portion wise at 0°C and the reaction mixture was stirred at room temperature for 1 hour. The resultant solution of sodium triphenylmethylthioate was added to **4** (100 g, 0.258 mol) dissolved in DMF (70 ml) with stirring at 0°C. After being stirred at 60°C for 30 minutes, the mixture was poured into cold dilute HCl and extracted with EtOAc. The extract was successively washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (toluene-EtOAc = 5 : 1) to give **5** (127.1 g, 87%): IR ($CHCl_3$) cm^{-1} 1750, 1700, 1618; ^{1}H NMR ($CDCl_3$) δ 1.65~2.23 (m, 2H), 2.76~3.23 (m, 3H), 3.50, 3.71 (2×s, 3H), 3.78, 3.84 (2×s, 3H), 3.93~4.12 (m, 1H), 4.87, 5.13 (ABq, J=12 Hz, 2H), 6.86 (dd, J=2, 8.6 Hz, 2H), 7.15~7.45 (m, 17H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-hydroxymethyl-4-tritylthiopyrrolidine (6)

To a solution of **5** (127.1 g, 0.224 mol) in THF (1 liter), lithium borohydride (4.88 g, 0.224 mol) was added portion wise with stirring at room temperature. After being stirred at 60°C for 30 minutes, the reaction mixture was cooled to room temperature and water (100 ml) was slowly added dropwise. The resulting precipitates were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2, dried over $MgSO_4$, and evaporated to give a solid residue, which was crystallized from ether to give **6** as white crystals (82.3 g, 68%): IR ($CHCl_3$) cm^{-1} 3400, 1668, 1610; ^{1}H NMR ($CDCl_3$) δ 1.32~1.40 (m, 1H), 1.92~1.99 (m, 1H), 2.66~2.80 (m, 2H), 2.88~2.91 (m, 1H), 2.92~3.60 (m, 2H), 3.70~2.75 (m, 1H), 3.84 (s, 3H), 4.93, 4.99 (ABq, J=12 Hz, 2H), 6.93 (d, J=8.4 Hz, 2H), 7.17 (d, J=7.2 Hz, 2H), 7.13~7.44 (m, 15H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-methanesulfonyloxymethyl-4-tritylthiopyrrolidine (7)

To a solution of **6** (22.33 g, 41.37 mmol) and triethylamine (6.92 ml, 49.6 mmol) in CH_2Cl_2 (300 ml), methanesulfonylchloride (3.52 ml, 45.51 mmol) was ad-

ded at −30°C. After being stirred for 20 minutes at the same temperature, the reaction mixture was successively washed with dilute HCl and water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (toluene - EtOAc = 8 : 1) to give **7** (22.31 g, 87.4%): IR ($CHCl_3$) cm^{-1} 1691, 1613; ^1H NMR ($CDCl_3$) δ 1.76~1.80 (m, 1H), 2.05~2.12 (m, 1H), 2.73~2.88 (m,3H), 2.90 (s, 3H), 3.79~3.86 (m, 1H), 3.84 (s, 3H), 4.15~4.41 (m, 2H), 4.90, 4.97 (ABq, J=12 Hz, 2H), 6.91 (d, J=9 Hz, 2H), 7.17~7.45 (m, 17H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-phthalimidomethyl-4-tritylthiopyrrolidine (**8**)

A mixture of **7** (22.31 g, 36.11 mmol) and potassium phthalimide (13.38 g, 72.2 mmol) in DMF (290 ml) was heated at 100°C for 1 hour. The reaction mixture was poured into ice water and extracted with EtOAc. The extract was successively washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (toluene - EtOAc = 8 : 1) to give **8** (18.86 g, 78.1%): IR ($CHCl_3$) cm^{-1} 1770, 1712, 1693, 1611; ^1H NMR ($CDCl_3$) δ 1.32~1.36 (m, 1H), 1.88~1.93 (m, 1H), 2.65~2.77 (m, 2H), 2.87~2.94 (m, 1H), 3.65~4.13 (m, 3H), 3.78, 3.84 (2×s, 3H), 4.65~5.00 (m, 2H), 6.76 (d, J=8.1 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 7.10~7.83 (m, 21H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-aminomethyl-4-tritylthiopyrrolidine (**9**)

To a solution of **8** (752 mg, 1.124 mmol) in a mixture of CH_2Cl_2 (3 ml) and MeOH (12 ml), hydrazine hydrate (109 μl, 2.248 mmol) was added. After being heated at 60°C for 5 hours, the reaction mixture was evaporated *in vacuo* to dryness. The residue was dissolved in CH_2Cl_2 and the resulting precipitates were filtered off. The filtrate was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from a mixture of CH_2Cl_2 and MeOH to give **9** (471 mg, 78%): MP 165~167°C; IR ($CHCl_3$) cm^{-1} 1683, 1610; ^1H NMR ($CDCl_3$) δ 1.54~1.59 (m, 1H), 1.92~2.13 (m, 1H), 2.68~2.88 (m, 4H), 3.39~3.64 (m, 2H), 3.84 (s, 3H), 4.86, 4.97 (ABq, J=12 Hz, 2H), 6.85~6.94 (m, 2H), 7.13~7.48 (m, 17H).

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-*p*-methoxybenzyloxycarbonyl aminomethyl-4-tritylthiopyrrolidine (**10a**)

To a solution of **9** (390 mg, 0.724 mmol) in CH_2Cl_2 (8 ml), *S*-*p*-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopyrimidine (MZ-SDP) (220 mg, 0.724 mmol) was added. After being stirred at room temperature for 1 hour, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in toluene and the resulting precipitates were filtered off. The filtrate was evaporated and the residue was purified by silica gel column chromatography (toluene - EtOAc = 8 : 1) to give **10a**.

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-acetylaminomethyl-4-tritylthiopyrrolidine (**10b**)

To a solution of **9** (250 mg, 0.464 mmol) and triethylamine (77.6 μl, 0.557 mmol) in CH_2Cl_2 (5 ml), acetyl chloride (36.3 μl, 0.51 mmol) was added at −30°C. After being stirred for 20 minutes at the same temperature, the reaction mixture was successively washed with dilute HCl and water, dried over $MgSO_4$, and filtrated. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (toluene - EtOAc = 4 : 1) to give **10b**.

10d, **10h**, **10j**, **10o**, **10m**, **10k'** were also prepared as described for the preparation of **10b** using the corresponding carbonyl chlorides or sulfonyl chlorides instead of acetyl chloride.

N-(2*S*,4*S*)-1-*p*-Methoxybenzyloxy carbonyl-2-(methoxyaminocarbonyl)aminomethyl-4-tritylthiopyrrolidine (**10f**)

To a solution of 1,1'-carbonyldiimidazole (301.6 mg, 1.86 mmol) in THF (5 ml), **9** (1 g, 1.86 mmol) in THF (10 ml) was added dropwise and the mixture was stirred at room temperature for 1 hour. After addition of methoxylamine (350 mg, 7.44 mmol), the resulting mixture was stirred for further 18 hours at the same temperature. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in EtOAc. After the usual work up, **10f** was obtained as a colorless foam.

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-(*N*-*p*-methoxybenzyloxycarbonyl-*N*-methoxycarbonylmethylsulfamoyl)aminomethyl-4-tritylthiopyrrolidine (**10n'**)

To a solution of **10m** (782 mg, 1 mmol) in THF (8 ml), methyl glycolate (93 μl, 1.2 mmol), triphenylphosphine (315 mg, 1.2 mmol) and diethyl azodicarboxylate (189 μl, 1.2 mmol) were successively added under ice cooling. After being stirred for 40 minutes at the same temperature, the reaction mixture was diluted with toluene and the resulting precipitates were filtered off. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (toluene - EtOAc = 6 : 1) to give **10n'**.

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-(2-hydroxyethylsulfamoyl)aminomethyl-4-tritylthiopyrrolidine (**10n**)

To a solution of **10n'** (627 mg, 0.73 mmol) in THF (3 ml), lithium borohydride (20 mg, 0.73 mmol) was added with stirring at room temperature. The mixture was stirred at the same temperature for 30 minutes and water (0.3 ml) was added dropwise with stirring. The resulting precipitates were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (toluene - EtOAc = 1 : 1) to give **10n**.

10l was also prepared as described for the preparation of **10n**.

Table 2. Yields, IR and ^{1}H NMR spectral data (**10a**～**10e**).

Compound No.	yield (%)	IR ($CHCl_3$) cm^{-1}	^{1}H NMR ($CDCl_3$, δ)
10a	98	3436, 1687, 1612	1.47~1.52 (m, 1H), 2.08~2.18 (m, 1H), 2.63~2.69 (m, 2H), 2.82~2.85, (m, 1H), 3.20~3.23 (m, 1H), 3.43~3.50 (m, 1H), 3.65~3.70 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 4.84~5.00 (m, 4H), 5.83 (br, 1H), 6.85~6.94 (m, 4H), 7.12~7.45 (m, 19H)
10b	78	3352, 1672, 1613	1.42~1.46 (m, 1H), 1.93 (s, 3H), 2.12~2.19 (m, 1H), 2.66~2.72 (m, 2H), 2.89~2.91 (m, 1H), 3.03~3.10 (m, 1H), 3.54~3.60 (m, 1H), 3.69~3.74 (m, 1H), 3.85 (s, 3H), 4.90, 4.97 (ABq, J = 12 Hz, 2H), 5.53 (br, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.11~7.47 (m, 17H)
10d	70	3318, 1665, 1612	1.46~1.50 (m, 1H), 2.17~2.23 (m, 1H), 2.71~2.77 (m, 2H), 2.97~3.00 (m, 1H), 3.20~3.26 (m, 1H), 3.75~3.91 (m, 2H), 3.83 (s, 3H), 4.95, 5.00 (ABq, J = 12 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 7.14~7.44 (m, 18H), 8.11 (d, J = 8.1 Hz, 1H), 8.62~8.65 (m, 1H), 8.70 (dd, J = 1.8 Hz, J = 5.1 Hz, 1H), 9.06~9.07 (m, 1H)
10h	79	3450, 1687, 1612	1.43~1.52 (m, 1H), 2.05~2.17 (m, 1H), 2.65~2.71 (m, 2H), 2.84~2.87 (m, 1H), 3.18~3.50 (m, 2H), 3.63 (s, 3H), 3.65~3.72 (m, 1H), 3.84 (s, 3H), 4.89, 4.98 (ABq, J = 12 Hz, 2H), 5.90 (br, 1H), 6.92 (d, J = 8.1 Hz, 2H), 7.12~7.43 (m, 17H)
10j	100	3248, 1680, 1612	1.47~1.57 (m, 1H), 2.09~2.17 (m, 1H), 2.67~2.78 (m, 2H), 2.83~2.92 (m, 1H), 2.87 (s, 3H), 3.09~3.15 (m, 1H), 3.30~3.36 (m, 1H), 3.72~3.79 (m, 1H), 3.84 (s, 3H), 4.90, 4.97 (ABq, J = 12 Hz, 2H), 5.88 (br, 1H), 6.92 (d, J = 7.5 Hz, 2H), 7.14~7.43 (m, 17H)
10o	33	3220, 1680, 1612	1.32~1.55 (m, 1H), 2.03~2.20 (m, 1H), 2.60~3.31 (m, 10H), 3.54~3.80 (m, 4H), 3.84 (s, 3H), 4.93 (br, 3H), 6.10 (m, 1H), 6.93 (d, J = 8.2 Hz, 2H), 7.07~7.49 (m, 17H)
10f	100	3338, 1681, 1612	1.47~1.55 (m, 1H), 2.13~2.20 (m, 1H), 2.65~2.77 (m, 2H), 2.84~2.93 (m, 1H), 3.14~3.55 (m, 2H), 3.78~3.86 (m, 1H), 3.84 (s, 3H), 4.91, 4.97 (ABq, J = 12 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.15~7.44 (m, 17H)
10m	41	3393, 1683, 1614	1.48~1.52 (m, 1H), 2.07~2.16 (m, 1H), 2.65~2.70 (m, 2H), 2.83~2.87 (m, 1H), 3.06~3.17 (m, 1H), 3.23~3.38 (m, 1H), 3.58~3.63 (m, 1H), 3.78 (s, 3H), 3.81, 3.83 (2×s, 3H), 4.85~5.04 (m, 4H), 6.59 (br, 1H), 6.84~6.93 (m, 4H), 7.14~7.43 (m, 19H)
10n'	73	1685, 1616	1.42~1.50 (m, 1H), 2.07~2.18 (m, 1H), 2.63~2.70 (m, 2H), 2.80~2.86 (m, 1H), 3.15~3.21 (m, 1H), 3.26~3.38 (m, 1H), 3.63~3.68 (m, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 4.41 (s, 2H), 4.86, 4.97 (ABq, J = 12 Hz, 2H), 5.08, 5.17 (ABq, J = 12 Hz, 2H), 6.81~7.44 (m, 23H), 7.00 (br, 1H)
10n	77	3396, 1678, 1612	1.44~1.56 (m, 1H), 2.08~2.21 (m, 1H), 2.67~2.79 (m, 2H), 2.82~2.88 (m, 1H), 3.20~3.45 (m, 4H), 3.65~3.81 (m, 3H), 3.84 (s, 3H), 4.87~5.06 (m, 2H), 6.93 (d, J = 8.2 Hz, 2H), 7.26~7.44 (m, 17H)
10k'	82	3450, 1736 1680, 1605	1.42~1.63 (m, 1H), 2.02~2.32 (m, 1H), 2.60~3.45 (m, 6H), 3.76 (s, 3H), 3.84 (s, 3H), 3.96 (s, 2H), 4.88, 4.95 (ABq, J = 10 Hz, 2H), 6.33 (br, 1H), 6.93 (d, J = 8.6 Hz, 2H), 7.09~7.36 (m, 10H), 7.44 (d, J = 8.6 Hz, 2H), 7.36~7.48 (m, 5H)
10k	77	3443, 3387, 1688, 1610	1.42~1.54 (m, 1H), 2.08~2.22 (m, 1H), 2.65~2.78 (m, 2H), 2.82~2.92 (m, 1H), 3.14~3.36 (m, 2H), 3.71~3.90 (m, 3H), 3.84 (s, 3H), 4.89, 4.97 (ABq, J = 12Hz, 2H), 5.59 (br, 1H), 6.55 (br, 1H), 6.72 (br, 1H), 6.92 (d, J = 8.2 Hz, 2H), 7.16~7.44 (m, 17H)
10l	100	3387, 1680, 1613	1.43~1.53 (m, 1H), 2.04~2.17 (m, 1H), 2.67~2.77 (m, 2H), 2.81~2.91 (m, 1H), 3.10~3.21 (m, 3H), 3.23~3.35 (m, 1H), 3.73~3.82 (m, 1H), 3.84 (s, 3H), 3.92~4.01 (m, 2H), 4.89, 4.97 (ABq, J = 12 Hz, 2H), 6.11 (br, 1H), 6.92 (d, J = 8.0 Hz, 2H), 7.15~7.44 (m, 17H)
10e'	100	3400, 3350, 1738, 1694, 1614	1.48~1.55 (m, 1H), 2.06~2.17 (m, 1H), 2.68~2.80 (m, 2H), 2.83~2.92 (m, 1H), 3.42~3.53 (m, 1H), 3.56~3.63 (m, 1H), 3.75~3.82 (m, 1H), 3.83 (s, 3H), 4.94, 5.05 (ABq, J = 12 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H), 7.22~7.44 (m, 17H), 8.20 (br, 1H), 8.38 (br,1H)
10e	100	3349, 1679, 1616	1.43~1.57 (m, 1H), 2.15~2.42 (m, 3H), 2.59~2.75 (m, 3H), 2.94~3.05 (m, 1H), 3.34~3.47 (m, 1H), 3.64~3.77 (m, 1H), 3.81 (s, 3H), 4.82, 4.92 (ABq, 12 Hz, 2H), 6.06 (br, 1H), 6.89 (d, J = 8.0 Hz, 2H), 7.10~7.43 (m, 17H)

Table 3. Yields, IR and ^{1}H NMR spectral data (**10g**～**10q**).

Compound No.	yield (%)	IR ($CHCl_3$) cm^{-1}	^{1}H NMR ($CDCl_3$, δ)
10c	81	1678, 1612	1.84~1.98 (m, 3H), 2.11~2.19 (m, 1H), 2.29~2.36 (m, 2H), 2.61~2.76 (m, 3H), 3.03~3.61 (m, 4H), 3.77~3.84 (m, 1H), 3.84 (s, 3H), 4.87, 4.96 (ABq, J = 12 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 7.14~7.44 (m, 17H)
10g	51	1777, 1714, 1612	1.38~1.45 (m, 1H), 2.08~2.18 (m, 1H), 2.65~3.00 (m, 3H), 3.38~3.52 (m, 2H), 3.62~3.82 (m, 2H), 3.83 (s, 3H), 4.03~4.16 (m, 1H), 4.85, 5.00 (ABq, J = 12 Hz, 2H), 5.23 (br, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.15~7.44 (m, 17H)
10i	51	1743, 1683, 1610	1.59~1.72 (m, 1H), 2.08~2.20 (m, 1H), 2.64~2.81 (m, 3H), 3.18~3.55 (m, 4H), 3.77~3.82 (m, 1H), 3.83 (s, 3H), 4.10~4.25 (m, 2H), 4.84, 4.93 (ABq, J = 12 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 7.14~7.50 (m, 17H)
10p	41	1733, 1688, 1613	1.73~1.86 (m, 1H), 2.17~2.28 (m, 1H), 2.63~2.80 (m, 2H), 3.02~3.31 (m, 4H), 3.59~3.79 (m, 4H), 3.80 (s, 3H), 3.81 (s, 3H), 4.86, 4.93 (ABq, J = 12 Hz, 2H), 5.23 (s, 2H), 6.89 (d, J = 8.8 Hz, 4H), 7.19~7.45 (m, 19H)
10q	62	1718, 1690, 1615	1.38~1.46 (m, 1H), 1.74~1.86 (m, 2H), 2.17~2.28 (m, 1H), 2.63~2.75 (m, 3H), 3.14~3.95 (m, 7H), 3.78 (s, 3H), 3.83 (s, 3H), 4.83, 4.95 (ABq, J = 12 Hz, 2H), 5.18 (s, 2H), 6.87 (d, J = 8.4 Hz, 4H), 7.18~7.45 (m, 19H)

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-(aminocarbonylmethylsulfonyl)aminomethyl-4-tritylthiopyrrolidine (**10k**)

To a solution of **10k'** (680 mg, 1.01 mmol) in MeOH (40 ml), 28%-NH_4OH (1.3 ml, 10.1 mmol) was added. After being stirred at room temperature for 3 days, the reaction mixture was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (toluene-EtOAc = 1 : 2) to give **10k**.

N-(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-(trichloroacetylcarbamoyl)aminomethyl-4-tritylthiopyrrolidine (**10e'**)

To a solution of **9** (730 mg, 1.36 mmol) in CH_2Cl_2 (20 ml), trichloroacetyl isocyanate (178 μl, 1.47 mmol) was added with stirring at $-30°C$. The mixture was stirred at the same temperature for 5 minutes and evaporated *in vacuo* to give **10e'** as a colorless foam.

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-carbamoylaminomethyl-4-tritylthiopyrrolidine (**10e**)

To a solution of crude **10e'** (1.04 g, 1.43 mmol) in MeOH (10 ml) and CH_2Cl_2 (3 ml), 1 N-NaOH aq. (1.4 ml, 1.4 mmol) was added. After being stirred at room temperature for 2 hours, the reaction mixture was evaporated *in vacuo*. After the residue was dissolved in CH_2Cl_2 (30 ml), the usual work up gave **10e**.

Table 4-1. Yields, IR and ^1H NMR spectral data (**13a**~**13q**).

Compound No.	yield (%)	IR ($CHCl_3$) cm^{-1}	^1H NMR ($CDCl_3$, δ)
13a	55	3438, 1770, 1698, 1612	1.22 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.71~1.78 (m, 1H), 2.41~2.50 (m, 2H), 3.14~3.30 (m, 2H), 3.22 (dd, J = 2.8 Hz, J = 6.8 Hz, 1H), 3.33~3.51 (m, 3H), 3.78 (s, 3H), 3.80 (s, 6H), 3.92~4.04 (m, 2H), 4.15~4.25 (m, 2H), 5.04 (s, 4H), 5.17, 5.26 (ABq, J = 12 Hz, 2H), 5.73 (br, 1H), 6.85~6.90 (m, 6H), 7.16~7.41 (m, 6H)
13b	76	3442, 1773, 1679, 1613	1.23 (d, J = 7.4 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.70~1.78 (m, 1H), 1.95 (s, 3H), 2.45~2.57 (m, 1H), 3.14~3.32 (m, 4H), 3.22 (dd, J = 2.8 Hz, J = 6.8 Hz, 1H), 3.43~3.54 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.95~4.05 (m, 2H), 4.14~4.26 (m, 2H), 5.07 (s, 2H), 5.14, 5.26 (ABq, J = 12 Hz, 2H), 6.86 (d, J = 4.6 Hz, 2H), 6.91 (d, J = 4.6 Hz, 2H), 7.02 (br, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H)
13c	72	3398, 1768, 1685, 1612	1.22 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.78~1.89 (m, 3H), 2.28~2.44 (m, 1H), 3.11~3.65 (m, 8H), 3.22 (dd, J = 2.6 Hz, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.86~3.99 (m, 1H), 4.07~4.23 (m, 4H), 5.05 (s, 2H), 5.17, 5.26 (ABq, J = 12 Hz, 2H), 6.86 (d, J = 2.6 Hz, 2H), 6.90 (d, J = 2.6 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H)
13d	52	3350, 1768, 1726, 1678, 1612	1.23 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.68~1.81 (m, 1H), 2.51~2.63 (m, 1H), 3.20~3.65 (m, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 3.93~4.25 (m, 4H), 5.10 (s, 2H), 5.16, 5.26 (ABq, J = 12 Hz, 2H), 6.87 (d, J = 8.6 Hz, 4H), 7.15 (br, 1H), 7.34 (d, J = 6.8 Hz, 2H), 7.38 (d, J = 6.8 Hz, 2H), 8.15~8.22 (m, 1H), 8.53~8.61 (m, 1H), 8.68~8.75 (m, 1H), 9.07~9.13 (m, 1H)
13e	60	3499, 3400, 1775, 1679, 1611	1.22 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.68~1.82 (m, 1H), 2.44~2.60 (m, 1H), 3.23 (dd, J = 2.8 Hz, J = 7.0 Hz, 1H), 3.24~3.60 (m, 5H), 3.79 (s, 3H), 3.81 (s, 3H), 3.94~4.03 (m, 2H), 4.16~4.26 (m, 2H), 5.02, 5.10 (ABq, J = 12 Hz, 2H), 5.16, 5.26 (ABq, J = 12 Hz, 2H), 5.65 (br, 1H), 6.86 (d, J = 4.8 Hz, 2H), 6.91 (d, J = 4.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H)
13f	59	3430, 3349, 1771, 1686, 1612	1.23 (d, J = 7.0 Hz, 3H), 1.35 (d, J = 6.4 Hz, 3H), 1.68~1.80 (m, 1H), 2.40~2.54 (m, 1H), 3.16~3.63 (m, 5H), 3.22 (dd, J = 2.2 Hz, J = 7.0 Hz, 1H), 3.68 (s, 3H), 3.80 (s, 3H), 3.81 (s, 3H), 3.96~4.24 (m, 4H), 4.59 (br, 1H), 5.08 (s, 2H), 5.17, 5.26 (ABq, J = 12 Hz, 2H), 6.87 (d, J = 3.6 Hz, 2H), 6.91 (d, J = 3.6 Hz, 2H), 6.98 (br, 1H), 7.28 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H)
13g	48	3452, 1769, 1713, 1608	1.22 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.80~1.94 (m, 1H), 2.45~2.63 (m, 1H), 3.18~3.32 (m, 3H), 3.23 (dd, J = 2.4 Hz, J = 7.0 Hz, 1H), 3.53~3.83 (m, 5H), 3.79 (s, 3H), 3.81 (s, 3H), 4.14~4.39 (m, 3H), 5.03 (s, 2H), 5.16, 5.26 (ABq, J = 12 Hz, 2H), 5.24 (br, 1H), 6.86 (d, J = 3.2 Hz, 2H), 6.90 (d, J = 3.2 Hz, 2H), 7.39~7.40 (m, 4H)
13h	81	3446, 3368, 1768, 1690, 1613	1.22 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.68~1.81 (m, 1H), 2.41~2.52 (m, 1H), 3.14~3.55 (m, 6H), 3.66 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.94~4.06 (m, 2H), 4.14~4.26 (m, 2H), 5.06 (s, 2H), 5.17, 5.27 (ABq, J = 12 Hz, 2H), 5.75 (br, 1H), 6.86 (d, J = 4.0 Hz, 2H), 6.91 (d, J = 4.0 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H)
13i	57	3460, 1746, 1690, 1610	1.23 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.76~1.92 (m, 1H), 2.40~2.53 (m, 1H), 3.14~3.61 (m, 8H), 3.23 (dd, J = 2.8 Hz, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.08~4.28 (m, 5H), 5.05 (s, 2H), 5.17, 5.27 (ABq, J = 12 Hz, 2H), 6.86 (d, J = 2.8 Hz, 2H), 6.90 (d, J = 2.8 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H)
13j	48	3528, 3390, 1771, 1690, 1612	1.23 (d, J = 7.0 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.67~1.81 (m, 1H), 2.48~2.57 (m, 1H), 2.78~2.89 (m, 1H), 2.91 (s, 3H), 3.21~3.33 (m, 4H), 3.47~3.59 (m, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 3.88~3.95 (m, 1H), 4.02~4.10 (m, 1H), 4.17~4.25 (m, 2H), 5.06 (s, 2H), 5.19, 5.25 (ABq, J = 12 Hz, 2H), 5.81 (br, 1H), 6.88 (d, J = 6.2 Hz, 2H), 6.90 (d, J = 6.2 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H)
13k	24	3489, 3381, 1773, 1698, 1617	1.21 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 6.4 Hz, 3H), 1.82~1.92 (m, 1H), 2.46~2.56 (m, 1H), 3.18~3.61 (m, 8H), 3.78 (s, 3H), 3.80 (s, 3H), 3.87~3.96 (m, 2H), 4.00~4.11 (m, 1H), 4.15~4.23 (m, 1H), 5.05 (s, 2H), 5.15, 5.25 (ABq, J = 12 Hz, 2H), 6.03 (br, 1H), 6.55 (br, 1H), 6.68 (br, 1H), 6.86 (d, J = 3.4 Hz, 2H), 6.90 (d, J = 3.4 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H)

Table 4-2. Yields, IR and ^{1}H NMR spectral data (**13a**~**13q**).

Compound No.	yield (%)	IR ($CHCl_3$) cm^{-1}	^{1}H NMR ($CDCl_3$, δ)
13l	40	3515, 1785, 1691, 1614	1.22 (d, J = 7.2 Hz, 3H), 1.33 (d, J = 6.2 Hz, 3H), 1.80~1.91 (m, 1H), 2.44~2.58 (m, 1H), 3.20~3.45 (m, 8H), 3.22 (dd, J = 2.8 Hz, J = 7.0 Hz, 1H), 3.47~3.63 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 3.95~4.06 (m, 2H), 4.12~4.25 (m, 2H), 5.05 (s, 2H), 5.17, 5.26 (ABq, J = 12 Hz, 2H), 5.94 (br, 1H), 6.87 (d, J = 4.4 Hz, 2H), 6.91 (d, J = 4.4 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H)
13m	50	3392, 1770, 1693, 1613	1.20 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.0 Hz, 3H), 1.81~1.91 (m, 1H), 2.37~2.48 (m, 1H), 3.15~3.61 (m, 6H), 3.79 (s, 9H), 4.00~4.28 (m, 4H), 5.03~5.13 (m, 4H), 5.14, 5.24 (ABq, J = 12 Hz, 2H), 5.53 (br, 1H), 6.55 (br, 1H), 6.85 (d, J = 1.8 Hz, 3H), 6.90 (d, J = 1.8 Hz, 3H), 7.26~7.38 (m, 6H)
13n	26	3400, 1775, 1690, 1618	1.22 (d, J = 7.0 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.79~1.90 (m, 1H), 2.44~2.58 (m, 1H), 3.13~3.31 (m, 8H), 3.54~3.71 (m, 4H), 3.79 (s, 3H), 3.80 (s, 3H), 4.10~4.25 (m, 2H), 5.05 (s, 2H), 5.17, 5.24 (ABq, J = 12 Hz, 2H), 5.76 (br, 1H), 6.86 (d, J = 2.8 Hz, 2H), 6.91 (d, J = 2.8 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H)
13o	78	3373, 1762, 1680, 1605	1.23 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 6.0 Hz, 3H), 1.65~1.77 (m, 1H), 2.46~2.61 (m, 1H), 3.14~3.31 (m, 8H), 3.50~3.63 (m, 1H), 3.68~3.74 (m, 6H), 3.79 (s, 3H), 3.81 (s, 3H), 3.93~4.04 (m, 1H), 4.08~4.25 (m, 2H), 5.06 (s, 2H), 5.17, 5.26 (ABq, J = 12 Hz, 2H), 6.04 (br, 1H), 6.87 (d, J = 3.8 Hz, 2H), 6.91 (d, J = 3.8 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H)
13p	72	3527, 1773, 1699, 1618	1.22 (d, J = 7.4 Hz, 3H), 1.34 (d, J = 6.2 Hz, 3H), 1.92~2.10 (m, 1H), 2.43~2.57 (m, 1H), 3.36~3.44 (m, 8H), 3.53~3.67 (m, 1H), 3.72~3.82 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 3.90~4.10 (m, 2H), 4.14~4.24 (m, 2H), 5.04 (s, 2H), 5.18, 5.24 (ABq, J = 12 Hz, 2H), 6.85~6.91 (m, 6H), 7.32~7.41 (m, 6H)
13q	64	3531, 1773, 1698, 1615	1.22 (d, J = 7.4 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 1.46~1.55 (m, 1H), 1.74~1.82 (m, 1H), 1.96~2.07 (m, 1H), 2.39~2.52 (m, 1H), 3.16~3.62 (m, 8H), 3.22 (dd, J = 2.4 Hz, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.87~3.99 (m, 3H), 4.13~4.24 (m, 2H), 5.05 (s, 2H), 5.17, 5.25 (ABq, J = 12 Hz, 2H), 6.87 (d, J = 8.6 Hz, 6H), 7.34 (d, J = 7.0 Hz, 3H), 7.39 (d, J = 7.0 Hz, 3H)

(2*S*,4*S*)-1-*p*-Methoxybenzyloxycarbonyl-2-(2-pyrrolidon-1-yl)methyl-4-tritylthiopyrrolidine (**10c**)

To a solution of 2-pyrrolidone (54 μl, 0.704 mmol) in DMF (5 ml), sodium hydride (*ca.* 60% oil suspension, 28 mg, 0.704 mmol) was added and the mixture was stirred at room temperature for 10 minutes, then a solution of **7** (290 mg, 0.47 mmol) in DMF (5 ml) was added. After being stirred at 80°C for 3 hours, the mixture was partitioned between dilute HCl and EtOAc. After the usual work up of the organic layer, the residue was purified by silica gel column chromatography (toluene-EtOAc = 1 : 1) to give **10c**.

10g, **10i**, **10p** and **10q** were also prepared as described for the preparation of **10c** using hydantoin, 2-oxazolidone, 1,1-dioxo-(1,2,5)-thiadiazolidine-2-carboxylic acid *p*-methoxybenzyl ester or 1,1-dioxo-(1,2,6)-thiadiazinane-2-carboxylic acid *p*-methoxybenzyl ester, respectively instead of 2-pyrrolidone.

General procedure for the preparation of compounds **11**:

To a solution of **10** (0.724 mmol) and pyridine (86 μl, 1.09 mmol) in MeOH (10 ml)/CH_2Cl_2 (2 ml), $AgNO_3$ (184 mg, 1.09 mmol) in water (0.1 ml) was added under ice cooling. After being stirred for 10 minutes at room temperature, the mixture was poured into water and extracted with CH_2Cl_2. After the extract was dried over $MgSO_4$ and filtered, H_2S gas was passed through the filtrate and resulting precipitates were filtered off. The filtrate was evaporated *in vacuo* to give crude **11**, which was immediately used for the next coupling reaction with enol phosphate (**12**) without characterization.

General procedure for the preparation of compounds **13**:

To a solution of (1*R*,5*S*,6*S*)-2-diphenoxy-phosphonyloxy-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid *p*-methoxybenzyl ester (**12**) (350 mg, 0.6 mmol) in MeCN (7 ml), crude **11** (0.724 mmol) and diisopropylethylamine (0.126 ml, 0.724 mmol) were added under ice cooling. After being stirred for 4.5 hours, the mixture was partitioned between dilute HCl and EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, evaporated *in vacuo*, and the residue was purified by silica gel column chromatography (toluene-EtOAc = 1 : 1) to give **13**.

General procedure for deprotection of **13**:

A solution of $AlCl_3$ (352 mg, 2.64 mmol) in anisole (0.29 ml, 2.64 mmol)/CH_2Cl_2 (2.64 ml) was added to a solution of **13** (0.33 mmol) in anhydrous CH_2Cl_2 (1.3 ml) at −40°C. After being vigorously stirred at −30°C for 1.5 hours, the reaction mixture was partitioned between NaOAc (650 mg, 7.92 mmol)/water (6 ml) and ether (6 ml). The aqueous layer was washed with ether, concentrated *in vacuo* to remove remaining organic solvent, and subjected to Diaion HP-20AG column chromatography. The fraction eluting with MeOH-water (including acetic acid in the case of **1a**) was lyophilized to give **1** as colorless foam.

1a: 57%; IR (KBr) cm^{-1} 3392, 1748, 1632; ^{1}H NMR (D_2O) δ 1.23 (d, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.71~1.86 (m, 1H), 1.94 (s, 3H), 2.74~2.91 (m, 1H), 3.33~3.51 (m, 5H), 3.63~3.78 (m, 1H), 3.91~4.06 (m, 2H), 4.20~4.30 (m, 2H).

1b: 53%; IR (KBr) cm^{-1} 3389, 1756, 1650; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.66~1.82 (m, 1H), 2.04 (s, 3H), 2.63~2.78 (m, 1H), 3.31~3.72 (m, 6H), 3.82~4.06 (m, 2H), 4.18~4.28 (m, 2H).

Anal Calcd for $C_{17}H_{25}N_3O_5S \cdot 2.1H_2O$:
C 48.47, H 6.99, N 9.97, S 7.61.
Found:
C 48.49, H 6.98, N 10.09, S 7.53.

1c: 47%; IR (KBr) cm^{-1} 3397, 1773, 1662; ^1H NMR (D_2O) δ 1.21 (d, $J=7.3$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.67~1.82 (m, 1H), 2.03~2.16 (m, 2H), 2.41~2.51 (m, 2H), 2.66~2.82 (m, 1H), 3.32~3.80 (m, 8H), 3.89~4.06 (m, 2H), 4.19~4.27 (m, 2H).

Anal Calcd for $C_{19}H_{27}N_3O_5S \cdot 1.0H_2O$:
C 53.38, H 6.84, N 9.83, S 7.50.
Found:
C 53.49, H 6.77, N 9.81, S 7.49.

1d: 13%; IR (KBr) cm^{-1} 3399, 1754, 1650; ^1H NMR (D_2O) δ 1.20 (d, $J=7.0$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.74~1.90 (m, 1H), 2.69~2.86 (m, 1H), 3.29~3.48 (m, 3H), 3.66~3.85 (m, 3H), 3.95~4.10 (m, 2H), 4.18~4.27 (m, 2H) 7.57~7.67 (m, 1H), 8.25 (d, $J=6.4$ Hz, 1H), 8.70~9.99 (m, 2H). SI-MS (m/z) 447 $(M+H)^+$.

1e: 63%; IR (KBr) cm^{-1} 3363, 1752, 1658; ^1H NMR (D_2O) δ 1.23 (d, $J=7.4$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.67~1.82 (m, 1H), 2.60~2.75 (m, 1H), 3.32~3.72 (m, 6H), 3.81~3.92 (m, 1H), 3.93~4.06 (m, 1H), 4.16~4.25 (m, 2H).

Anal Calcd for $C_{16}H_{24}N_4O_5S \cdot 2.8H_2O$:
C 44.19, H 6.86, N 12.88, S 7.37.
Found:
C 44.18, H 6.66, N 12.86, S 7.59.

1f: 58%; IR (KBr) cm^{-1} 3389, 1753; ^1H NMR (D_2O) δ 1.17 (d, $J=7.2$ Hz, 3H), 1.24 (d, $J=6.2$ Hz, 3H), 1.64~1.80 (m, 1H), 2.58~2.74 (m, 1H), 3.27~3.63 (m, 6H), 3.66 (s, 3H), 3.79~3.89 (m, 1H), 3.92~4.03 (m, 1H), 4.14~4.24 (m, 2H).

Anal Calcd for $C_{17}H_{26}N_4O_6S \cdot 3.6H_2O$:
C 42.60, H 6.98, N 11.69, S 6.69.
Found:
C 42.58, H 6.87, N 11.86, S 6.70.

1g: 58%; IR (KBr) cm^{-1} 3400, 1750, 1698; ^1H NMR (D_2O) δ 1.20 (d, $J=7.2$ Hz, 3H), 1.27 (d, $J=6.4$ Hz, 3H), 1.68~1.83 (m, 3H), 2.70~2.85 (m, 1H), 3.28~3.47 (m, 3H), 3.68 (dd, $J=7.4$, 12.6 Hz, 1H), 3.85~4.05 (m, 4H), 4.12 (s, 2H), 4.17~4.27 (m, 2H).

Anal Calcd for $C_{18}H_{24}N_4O_6S \cdot 2.0H_2O$:
C 46.95, H 6.13, N 12.17, S 6.96.
Found:
C 46.91, H 6.16, N 12.39, S 6.82.

1h: 49%; IR (KBr) cm^{-1} 3392, 1753, 1715; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.66~1.82 (m, 1H), 2.63~2.78 (m, 1H), 3.32~3.72 (m, 6H), 3.68 (s, 3H), 3.78~3.92 (m, 1H), 3.96~4.08 (m, 1H), 4.18~4.27 (m, 2H).

Anal Calcd for $C_{17}H_{25}N_3O_6S \cdot 1.7H_2O$:
C 47.48, H 6.66, N 9.77, S 7.46.
Found:
C 47.37, H 6.67, N 9.86, S 7.45.

1i: 61%; IR (KBr) cm^{-1} 3410, 1774, 1722, 1633; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.4$Hz, 3H), 1.68~1.83 (m, 1H), 2.69~2.85 (m, 1H), 3.32~3.47 (m, 3H), 3.63~3.82 (m, 5H), 3.92~4.11 (m, 2H), 4.20~4.31 (m, 2H), 4.40~4.48 (m, 2H).

Anal Calcd for $C_{18}H_{25}N_3O_6S \cdot 3.2H_2O$:
C 46.09, H 6.75, N 8.96, S 6.83.
Found:
C 46.02, H 6.64, N 9.09, S 7.02.

1j: 52%; IR (KBr) cm^{-1} 3402, 1752; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.6$ Hz, 3H), 1.62~1.77 (m, 1H), 2.62~2.76 (m, 1H), 3.11 (s, 3H), 3.31~3.53 (m, 5H), 3.65 (dd, $J=7.0$, 12.4 Hz, 1H), 3.74~3.89 (m, 1H), 3.94~4.04 (m, 1H), 4.17~4.25 (m, 2H).

Anal Calcd for $C_{16}H_{25}N_3O_6S_2 \cdot 2.6H_2O$:
C 41.21, H 6.53, N 9.01, S 13.75.
Found:
C 41.03, H 6.41, N 9.21, S 13.71.

1k: 48%; IR (KBr) cm^{-1} 3394, 3195, 1750, 1681; ^1H NMR (D_2O) δ 1.21 (d, $J=7.4$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.67~1.82 (m, 1H), 2.66~2.81 (m, 1H), 3.32~3.76 (m, 8H), 3.82~3.93 (m, 1H), 3.97~4.12 (m, 1H), 4.19~4.27 (m, 2H). SI-MS (m/z) 463 $(M+H)^+$.

1l: 67%; IR (KBr) cm^{-1} 3380, 1750; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.67~1.81 (m, 1H), 2.65~2.81 (m, 1H), 3.32~3.76 (m, 8H), 3.82~3.93 (m, 1H), 3.96~4.06 (m, 3H), 4.18~4.26 (m, 2H).

Anal Calcd for $C_{17}H_{27}N_3O_7S_2 \cdot 1.7H_2O$:
C 42.52, H 6.38, N 8.75, S 13.36.
Found:
C 42.69, H 6.40, N 8.77, S 13.19.

1m: 72%; IR (KBr) cm^{-1} 3400, 1750; ^1H NMR (D_2O) δ 1.22 (d, $J=7.2$ Hz, 3H), 1.27 (d, $J=6.3$ Hz, 3H), 1.64~1.82 (m, 1H), 2.62~2.80 (m, 1H), 3.26~3.59 (m, 5H), 3.69 (dd, $J=7.0$, 12.4 Hz, 1H), 3.84~4.10 (m, 2H), 4.16~4.29 (m, 2H).

Anal Calcd for $C_{15}H_{24}N_4O_6S_2 \cdot 1.0H_2O$:
C 41.08, H 5.98, N 12.78, S 14.62.
Found:
C 40.83, H 5.97, N 13.06, S 14.58.

1n: 46%; IR (KBr) cm^{-1} 3394, 1747; ^1H NMR (D_2O) δ 1.21 (d, $J=7.2$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H), 1.66~1.81 (m, 1H), 2.66~2.81 (m, 1H), 3.15 (t, $J=5.6$ Hz, 2H), 3.32~3.54 (m, 5H), 3.65~3.75 (m, 3H), 3.87~4.07 (m, 2H), 4.18~4.27 (m, 2H).
SI-MS (m/z) 465 $(M+H)^+$.

1o: 80%; IR (KBr) cm^{-1} 3397, 1757; ^1H NMR (D_2O) δ 1.21 (d, $J=7.0$ Hz, 3H), 1.28 (d, $J=6.4$ Hz, 3H),

1.65~1.80 (m, 1H), 2.66~2.81 (m, 1H), 3.23 (t, J=4.8 Hz, 4H), 3.32~3.53 (m, 5H), 3.66~3.92 (m, 2H), 3.80 (t, J=4.8 Hz, 4H), 3.97~4.06 (m, 1H), 4.18~4.27 (m, 2H).

Anal Calcd for $C_{19}H_{30}N_4O_7S_2 \cdot 2.1H_2O$:
C 43.19, H 6.52, N 10.60, S 12.14.
Found:
C 43.13, H 6.47, N 10.68, S 12.06.

1p: 72%; IR (KBr) cm^{-1} 3408, 1753; ^1H NMR (D_2O) δ 1.21 (d, J=7.4 Hz, 3H), 1.28 (d, J=6.4 Hz, 3H), 1.68~1.84 (m, 1H), 2.71~2.85 (m, 1H), 3.28~3.77 (m, 10H), 3.94~4.12 (m, 2H), 4.17~4.31 (m, 2H).

Anal Calcd for $C_{17}H_{26}N_4O_6S_2 \cdot 2.3H_2O$:
C 41.84, H 6.32, N 11.48, S 13.14.
Found:
C 41.85, H 6.25, N 11.48, S 13.22.

1q: 63%; IR (KBr) cm^{-1} 3398, 1749; ^1H NMR (D_2O) δ 1.20 (d, J=7.2 Hz, 3H), 1.27 (d, J=6.4 Hz, 3H), 1.65~1.80 (m, 3H), 2.65~2.80 (m, 1H), 3.27~3.56 (m, 9H), 3.69 (dd, J=7.2, 12.8 Hz, 1H), 3.91~4.10 (m, 2H), 4.15~4.30 (m, 2H).

Anal Calcd for $C_{18}H_{28}N_4O_6S_2 \cdot 2.2H_2O$:
C 43.22, H 6.53, N 11.20, S 12.82.
Found:
C 43.11, H 6.50, N 11.33, S 12.68.

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