AN EFFICIENT SYNTHESIS OF (2S,4S)-2-SUBSTITUTED 4-MERCAPTOPYRROLIDINE DERIVATIVES

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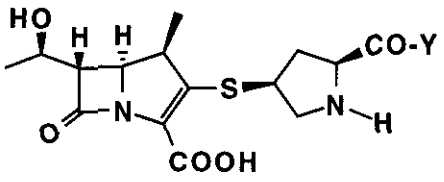
Abstract - An efficient synthesis of (2S,4S)-2-substituted 4-mercapto-1-*p*-nitrobenzyloxycarbonylpyrrolidine (**2**) was studied. Intramolecular cyclization of (2S,4R)-1-*p*-nitrobenzyloxycarbonyl-4-methanesulfonyloxy-2-pyrrolidine-thiocarboxylic acid (**8**), derived from *trans*-4-hydroxy-L-proline (**3**), afforded (1S,4S)-5-*p*-nitrobenzyloxycarbonyl-2-thia-5-azabicyclo[2.2.1]heptan-3-one (**7**). Reaction of **7** with primary amine, secondary amine and alkoxide afforded corresponding **2** in high yield.

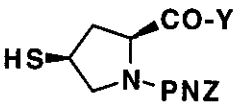
Meropenem is a 1β-methylcarbapenem antibiotic (**1**) which exhibits extremely potent antibacterial activities and broad spectra as well as enhanced metabolic stability toward renal dehydropeptidase-I.[1] Concerning the stereochemistry of pyrrolidine moiety at the carbapenem C-2 position, (3S,5S)-isomer showed the most effective antibacterial activities among the four stereoisomers.[1] Therefore, (2S,4S)-2-dimethyaminocarbonyl-4-mercaptopyrrolidine (**2a**) is an important intermediate and its stereoselective and facile synthetic method is necessary.

A synthesis of **2a** starting from *trans*-4-hydroxy-L-proline (**3**) was reported in our previous paper.[1] Subsequently we studied a practical route for the large-scale production of **2a** as shown in Scheme 1. In the transformation of *N*-protected 4-hydroxyproline (**4**) into **2a**, mesylation of hydroxyl group and activation of carboxyl group in **4** by using methanesulfonyl chloride (MsCl) and then the treatment of mesylate (**5**) with Me_2NH were carried out in one-pot procedure. **4** was treated with MsCl (2.3 eq.) and Et_3N (2.5 eq.) in CH_2Cl_2 at -15°C. After the completion of conversion to **5**, Me_2NH-HCl (2.5 eq.) and Et_3N (3 eq.) were added to the resulting mixture, followed by stirring at the same temperature to afford the amide (**6**), which was isolated by crystallization from isopropyl alcohol in 86%

Figure 1



1 (Y=NMe_2: Meropenem)



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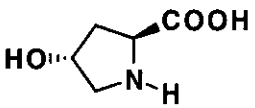
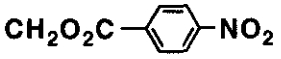
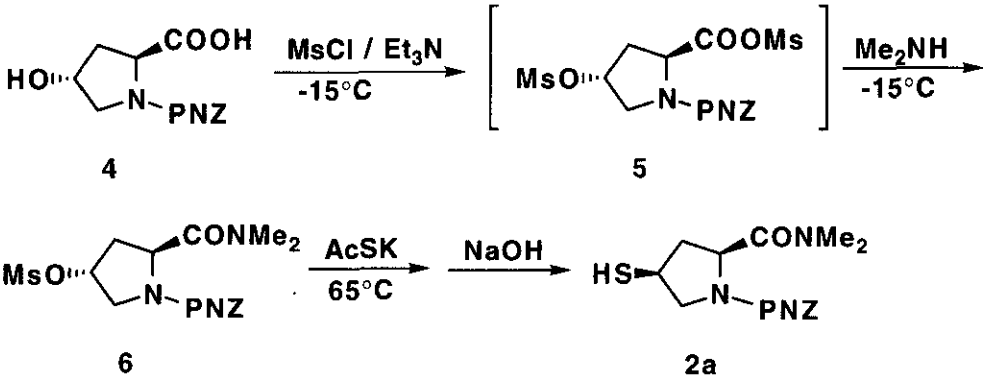


3

PNZ = 

Scheme 1



4 5

6 2a

yield. Conversion of **6** to the desired compound (**2a**) has been done as reported in 78% yield.[1]

Recently new 1β-methylcarbapenems having a pyrrolidinylthio group as a C-2 side chain have been synthesized and evaluated by several research groups.[2] With the aim of searching more efficient synthetic route leading to (2S,4S)-2-substituted 4-mercaptopyrrolidines (**2**) including **2a**, we continued to study another approach from **4**. We considered that thiollactone (**7**) would be a versatile intermediate for **2**, as thiollactone ring could be readily opened by aminolysis. The transformation of **3** into *N*-acetyl-thiollactone (**9**) has been published,[3] in which the synthesis of **9** was achieved by cyclization of *cis*-4-mercaptoproline (**10**) derived from **3**. However, there has been no report which utilizes **7** as an intermediate for preparing **2**. We planed the transformation of **4** into **7** using intramolecular cyclization of thiolcarboxylic acid (**8**) as a key step.

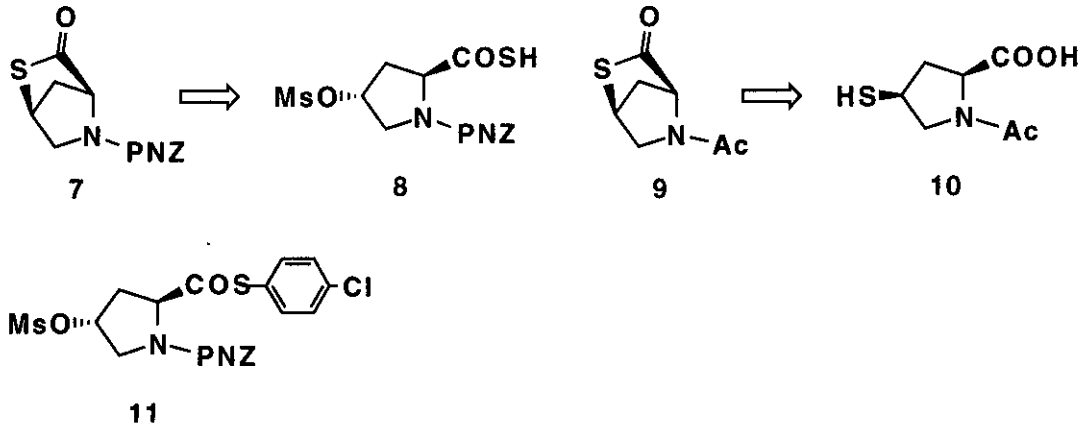
First, synthesis of **7** from **4** *via* the mesylate (**5**) was investigated as shown in Scheme 2. After **5** was prepared from **4** as described above, the reaction mixture was treated with excess H_2S in the presence of Et_3N at -25°C. When the balloon filled with H_2S is equipped to the flask, the rapid absorption of the gas and the rise of the temperature were observed. The workup of the reaction mixture afforded crude **8**, which was unstable against silica gel chromatography to give small amount of **7** and decomposed products. Therefore, **8** was used without purification in the next step. Conversion of **8** to **7** was readily achieved in 57% overall yield from **4** by refluxing with Et_3N in CH_2Cl_2. In this cyclization reaction, pyridine could also be used as the base to give **7** in the similar yield. **7** was stable solid, easy to handle, which could be purified by recrystallization from n-hexane and AcOEt. It seemed of interest to investigate the relative reactivity of **5** with amine and thiol. **5** was reacted with *p*-chlorothiophenol instead of Me_2NH, and we obtained thioester (**11**)[4] in 61% yield. When the active ester of naphthylacetic acid prepared by the reaction with MsCl was treated with *p*-chlorothiophenol, the yield of the corresponding thioester was 22%. From these results, we judged that the reactivity of **5** with SH group was lower than that with amine.

In order to improve the yield of **7**, another method was investigated as shown in Scheme 3. The reaction of acid anhydride with H_2S is generally known as a procedure for preparation of thiolcarboxylic acid from carboxylic acid.[5] We used isopropyl chloroformate for the formation of mixed anhydride and MsCl for the formation of mesylate. **4** was first treated with isopropyl chloroformate and then with MsCl at -25°C to give mixed anhydride (**12**). Subsequently, the treatment of **12** with H_2S in the presence of Et_3N afforded crude **8**, which was, without isolation, cyclized to **7**. Total yield of **7** from **4** was 84% after isolation by crystallization from isopropyl alcohol.

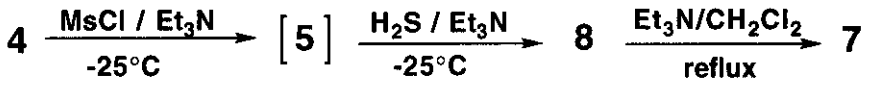
Then we examined the transformation of 4-hydroxyproline protected by allyloxycarbonyl (AOC) group (**4'**) into the corresponding thiollactone (**7'**) as shown in Scheme 4. AOC group is well used as an amino-protecting group, because of easy removal by palladium catalyst in mild condition.[6] According to the above described procedure *via* **12**, **7'** could be obtained as an oil in 69% yield from **4'** by silica gel chromatography.

Finally, conversion of **7** to (2S,4S)-2-substituted 4-mercaptopyrrolidine (**2**) with some types of nucleophile was investigated. The result was listed in Table I. In this reaction, common organic solvents such as MeCN, THF and CH_2Cl_2 could be used. In the case of primary and secondary alkylamines, the reaction smoothly proceeded at room temperature to afford the amide (**2b-2d**) in good yield. Amine salt, instead of free amine, also reacted with **7** in the presence of tertiary amine. The reaction with aromatic amine was somewhat slow at room temperature but

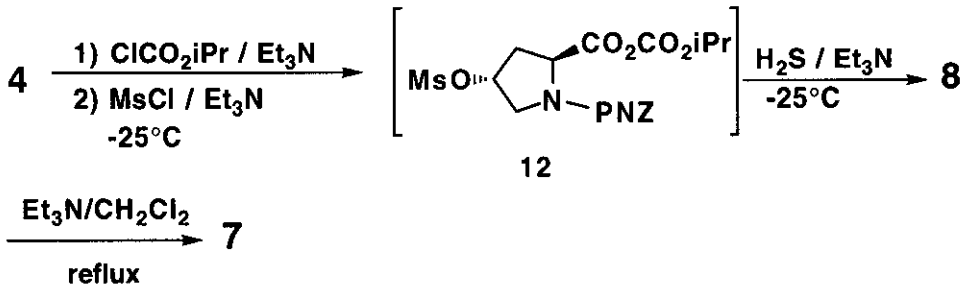
Figure 2



Scheme 2



Scheme 3



Scheme 4

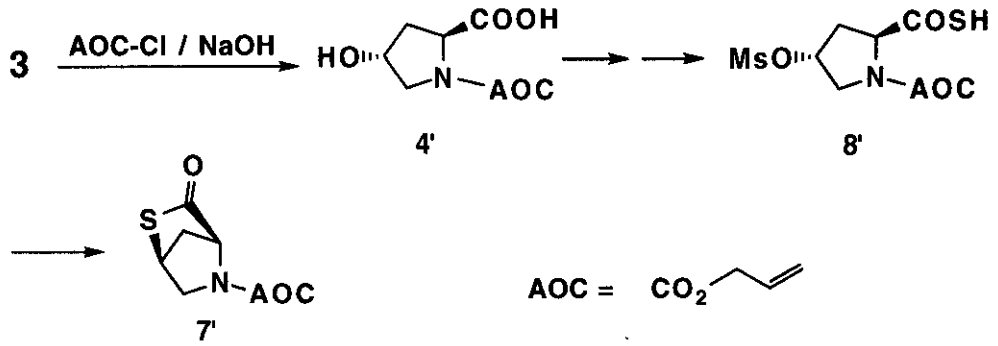
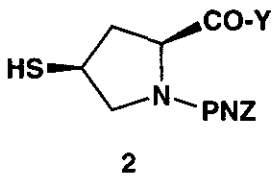


Table 1. Reaction of thiollactone (**7**) with nucleophiles.



2

a: Y=-NMe_2

b: Y=-$NHCH_2CH_2Ph$

c: Y= -N

d: Y= -N N-Me

e: Y= -NH-Me

f: Y=-OMe

g: Y=-OCH_2Ph

h: Y= COOMe / COOMe

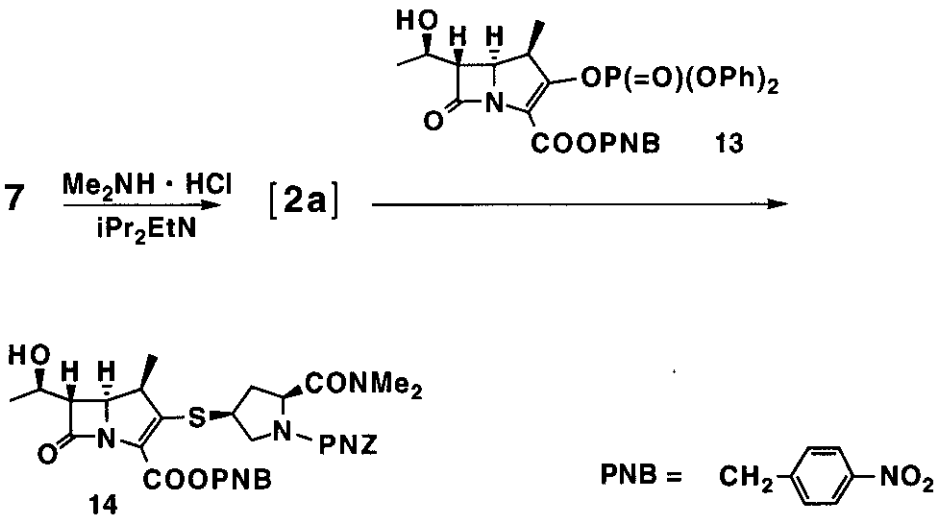
run	nucleophile	solvent	condition[a)]	product (isolated yield, %)
1	2-Phenylethylamine	THF	room temperature, 4 h	**2b** (90%)
2	Pyrrolidine	THF	room temperature, 2 h	**2c** (91%)
3	*N*-Methylpiperazine	CH_2Cl_2	room temperature, 10 h	**2d** (90%)
4	$Me_2NH{\cdot}HCl + Et_3N$	THF	room temperature, 5 h	**2a** (92%)
5	$Me_2NH{\cdot}HCl + iPr_2EtN$	MeCN	room temperature, 1 h	**2a** (75%)
6	*p*-Toluidine	THF	50°C, 3 h	**2e** (72%)
7	NaOMe	MeCN / MeOH	0 °C, 30 min	**2f** (96%)
8	$LiOCH_2Ph$	THF	0 °C , 5 min	**2g** (45%)
9	Na^+ COOMe / COOMe	THF	room temperature, Overnight	**2h** (69%)

a) usual conditions: solvent (1-2 ml) per thiollactone (**7**) (1 mmol) under nitrogen atmosphere

proceeded smoothly at elevated temperature. Ring cleavage of **7** with other nucleophile such as alkoxide ion and carbanion was also attempted. Alkolysis of **7** was carried out with ice-cooling to give the ester (**2f** and **2g**). The reaction with malonate at room temperature afforded the ketoester (**2h**) in a moderate yield.

As mentioned above, the synthesis of **2** from crystalline **7** can be achieved cleanly in good yield. This seems to be one of effective points for the synthesis of 1β-methylcarbapenem compound (**1**). After completion of the reaction, the reaction mixture containing **2** can be used without isolation in the next introduction of thiol substituent at the C-2 position of **13**. (Scheme 5). Thus **7** was shown as a convenient key intermediate to synthesize various types of carbapenem including 1β-methylcarbapenem.

Scheme 5



In summary, the efficient synthesis of 4-mercaptopyrrolidine (**2**) was accomplished starting from **3** *via* thiollactone (**7**), which could be obtained without purification by chromatography. **7** was converted to **2** by cleavage of thiollactone ring. This synthetic route has some advantages; (a) various amides, esters and ketones can be produced in the final step; (b) the obtained **2** can be used without purification in the next step; (c) all reactions are performed in mild conditions; and (d) the necessary reagents are easily available in large amounts. Consequently the present process is practicable for large-scale production of **2**.

EXPERIMENTAL

Melting point was determined with a Thomas-Hoover capillary melting points apparatus without correction. Ir spectra were recorded on a Perkin Elmer 1600 infrared spectrophotometer. ^{1}H-Nmr spectra were measured with a JEOL GX-270 FT spectrometer using tetramethylsilane as an internal reference. Optical rotations were determined with a JASCO DIP-181 digital polarimeter. Column chromatography was conducted with silica gel 60 (70-230 mesh, E. Merck).

(2S,4R)-2-Dimethylaminocarbonyl-4-methanesulfonyloxy-1-*p*-nitrobenzyloxy-carbonylpyrrolidine (6)

To a solution of (2S,4R)-4-hydroxy-1-*p*-nitrobenzyloxycarbonyl-2-pyrrolidine-carboxylic acid (**4**) (8.06 g, 26 mmol)[1] and Et_3N (6.57 g, 65 mmol) in CH_2Cl_2 (100 ml) was added MsCl (6.87 g, 60 mmol) dropwise at -15°C and stirred for 1 h. Me_2NH-HCl (4.25 g, 52 mmol) and Et_3N (7.88 g, 78 mmol) were added successively, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was washed with 1N HCl, 5% $NaHCO_3$ and brine. Drying over $MgSO_4$ and evaporation gave a crude crystal which was recrystallized from isopropyl alcohol to afford **6** (9.28 g, 86%) as a colorless crystal. mp 113.0-114.0 °C. The ir and ^{1}H-nmr spectral data were identical with those reported.[1]

(2S,4R)-1-*p*-Nitrobenzyloxycarbonyl-4-methanesulfonyloxy-2-pyrrolidinethiocarboxylic acid (8)

To the solution of **4** (1.27 g, 4.09 mmol) and Et_3N (1.24 g, 12.3 mmol) in CH_2Cl_2 (15 ml) was added MsCl (1.17 g, 10.2 mmol) at -25°C and stirred for 30 min. After addition of Et_3N (1.24 g, 12.3 mmol), a balloon filled with H_2S was equipped to the flask and the mixture was stirred for 1 h, during which the temperature was gradually raised to 0 °C. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and washed with 1N HCl (10 ml). The organic layer was evaporated and the residue was dissolved in toluene (10 ml). After twice extraction with 1N NaOH (6 ml and 4 ml), the combined aqueous layer was acidifed with 1N HCl (15 ml) and extracted with CH_2Cl_2 (15 ml). The extract was dried over $MgSO_4$ and concentrated in vacuo to give oily **8** (1.61 g, apparently 4.32 mmol), which was used for the next reaction without further purification. Ir (neat) 1700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.36 (1H, ddd, J = 5.0, 8.2 and 14.5 Hz) 2.72 (1H, m), 3.07 (3H, s), 3.81 (1H, m), 4.07 (1H, m), 4.64 (1H, m), 5.15-5.40 (3H, m), 7.53 (2H, m), 8.23 (2H, d, J = 8.3 Hz).

(1S,4S)-5-*p*-Nitrobenzyloxycarbonyl-2-thia-5-azabicyclo[2.2.1]heptan-3-one (7)

Method A (Scheme 2). A solution of above crude **8** (1.61 g, apparently 4.32 mmol) and Et_3N (656 mg, 6.48 mmol) in CH_2Cl_2 (12 ml) was stirred for 4 h under reflux. The reaction mixture was diluted with CH_2Cl_2 (12 ml) and washed successively with 1N HCl (10 ml), sat. $NaHCO_3$ (10 ml) and 1N HCl (10 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a residue, which was purified by silica gel chromatography to afford **7** (719 mg, 2.33 mmol, 57% from **4**) as a pale yellow crystal. Analytically pure sample was obtained by recrystallization from hexane-AcOEt. mp 103-104°C. $[\alpha]_D^{22}$= -108° (c=0.052, $CHCl_3$). Ir (KBr) 1747, 1704 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.11-2.27 (2H, m), 3.67-3.72 (1H, m), 3.85-3.90 (1H, m), 4.15-4.19 (1H, m), 4.62-4.70 (1H, m), 5.21 (1H, d, J = 13.7 Hz), 5.31 (1H, d, J = 13.7 Hz), 7.54 (2H, d, J = 8.6 Hz), 8.23 (2H, d, J = 8.6 Hz). Anal. Calcd for $C_{13}H_{12}N_2O_5S$: C,50.64; H,3.92; N,9.09; S,10.40. Found: C,50.59; H,3.88; N,9.08; S,10.46.

Method B (Scheme 3). A solution of **4** (3.78 g, 12.2 mmol) and Et_3N (1.60 g, 15.9 mmol) in CH_2Cl_2 (50 ml) was added to a solution of isopropyl chloroformate (1.72 g, 14.0 mmol) in CH_2Cl_2 (20 ml) at -25 °C. After stirrig for 1 h, Et_3N (1.98 g, 19.5 mmol) and MsCl (1.96 g, 17.1 mmol) were added successively and the solution was stirred for another 1 h at the same temperature. After addition of Et_3N (3.09 g, 30.5 mmol), a balloon filled with H_2S was equipped to the flask and the reaction mixture was stirred for 1 h. The excess H_2S was removed by nitrogen bubbling and the reaction mixture was washed with 10% H_2SO_4 (25 ml). The organic layer was separated and stirred with Et_3N (1.30 g, 12.8 mmol) under reflux for 4 h. The reaction mixture was washed with 10% H_2SO_4 (25 ml), water (25 ml), 4% $NaHCO_3$ (25 ml), and water (25 ml) successively. After addition of isopropyl alcohol (60 ml), the organic layer was evaporated in vacuo and the precipitate was filtered and washed with isopropyl alcohol (25 ml) to give **7** (3.2 g, 84% from **4**) as a pale yellow crystal.

(2S,4R)-1-Allyloxycarbonyl-4-hydroxy-2-pyrrolidinecarboxylic acid (4')

A solution of allyl chloroformate (3.63 g, 30 mmol) in CH_2Cl_2 (25 ml) was added dropwise to a solution of **3** (3.59 g, 27 mmol) and NaOH (2.4 g, 60 mmol) in water (30 ml) with ice-water cooling. After stirring for 2 h, the aqeuous layer was separated from the reaction mixture, washed with CH_2Cl_2, and then acidified with conc. H_2SO_4 below 30°C. After adding NaCl, the aqueous solution was extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated in vacuo to give crude crystaline **4'** (5.61 g, 97%), mp 93-94°C. Ir (KBr) 3345, 1744, 1686, 1648 cm^{-1}. ^{1}H-Nmr (10% $CD_3OD/CDCl_3$) δ 2.09 (1H, m), 2.25 (1H, m), 3.45-3.63 (2H, m),

4.40 (2H, m), 4.53 (2H, m), 5.10-5.30 (2H, m), 5.86 (1H, m). Anal. Calcd for $C_9H_{13}NO_5$: C 50.23; H 6.09; N 6.51. Found C 50.25; H 6.10; N 6.50.

(2S,4R)-1-Allyloxycarbonyl-4-methanesulfonyloxy-2-pyrrolidinethiocarboxylic acid (8')

A solution of **4'** (3.0 g, 13.9 mmol) and Et_3N (1.69 g, 16.7 mmol) in CH_2Cl_2 (25 ml) was added to a solution of isopropyl chloroformate (1.88 g, 15.3 mmol) in CH_2Cl_2 (30 g) at -20 °C and the solution was stirred for 30 min. Et_3N (2.26 g, 22.3 mmol) and MsCl (2.23 g, 19.5 mmol) were added, and the mixture was stirred at -20 °C for 30 min. After addition of Et_3N (3.53 g, 34.8 mmol), an excessive amount of H_2S was passed through the mixture for 30 min. Excess H_2S was removed by nitrogen bubbling and 1N HCl (55.6 ml) was added. The organic layer was separated and extracted with 7% $NaHCO_3$ (50 ml). The water layer was acidified with 36% HCl (5.63 g, 55.6 mmol), and extracted with CH_2Cl_2 (34 ml). The extract was dried over $MgSO_4$. Evaporation in vacuo gave oily crude **8'** (4.11 g, apparently 13.3 mmol), which was used in the next step without further purification. Ir (neat) 1700 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ 2.35 (1H, m), 2.70 (1H, m), 3.06 (3H, m), 3.77 (1H, m), 4.00 (1H, m), 4.50-4.73 (3H, m), 5.14-5.39 (3H, m), 5.90 (1H, m).

(1S,4S)-5-Allyloxycarbonyl-2-thia-5-azabicyclo[2.2.1]heptan-3-one (7')

To a solution of above **8'** (1.23 g, apparently 3.96 mmol) in CH_2Cl_2 (12 g), was added Et_3N (802 mg, 7.93 mmol) and the solution was stirred under reflux for 5 h. After addition of 1N HCl (8 ml), the organic layer was separated and dried over $MgSO_4$. Evaporation in vacuo gave an oily residue, which was purified by silica gel chromatography to afford **7'** (611 mg, 2.87 mmol, 69 % from **4'**) as an oil. $[\alpha]_D^{22}$= -115° (c=0.35, $CHCl_3$). Ir (neat): 1716cm^{-1}. ^1H-Nmr ($CDCl_3$) δ 2.18 (2H, m), 3.65 (1H, m), 3.85 (1H, dd, J = 3.0 and 10.2 Hz), 4.14 (1H, m), 4.63 (2H, d, J = 5.0 Hz), 4.67 (1H, m), 5.22 (1H, d, J = 10.6 Hz), 5.32 (1H, d, J = 17.2 Hz), 5.92 (1H, tdd, J = 5.0, 10.6 and 17.2 Hz).

(2S,4S)-*N*-Phenylethyl-4-mercapto-1-*p*-nitrobenzyloxycarbonyl-2-pyrrolidinecarboxamide (2b)

2-Phenylethylamine (133 mg, 1.1 mmol) was added to a solution of **7** (308 mg, 1.0 mmol) in THF (2 ml). After stirring for 2 h at room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with 1N HCl and dried over $MgSO_4$. Evaporation in vacuo gave an oily residue, which was purified by silica gel chromatography to afford **2b** (387 mg, 90%), mp 174-175°C (AcOEt-toluene). $[\alpha]_D^{22}$=-27.6° (c=0.10, $CHCl_3$). Ir (KBr) 1715, 1655 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ 2.26 (1H, m), 2.56 (1H, m), 2.80 (2H, m), 3.34 (2H, m), 3.54 (2H, m), 4.02 (1H, br), 4.25

(1H, dd, J = 6.8, 8.4 Hz), 5.17 (2H, br), 7.15-7.32 (5H, m), 7.47 (2H, br), 8.22 (2H, d, J = 7.9 Hz).

(2S,4S)-4-Mercapto-1-*p*-nitrobenzyloxycarbonyl-2-(1-pyrroridinyl-carbonyl)pyrrolidine (2c)

Treatment of **7** (154 mg, 0.5 mmol) and pyrrolidine (43 mg, 0.6 mmol) in the similar manner as described for the preparation of **2b** gave **2c** (173 mg, 91 %) as an oil. $[\alpha]_D^{22}$=+12.1°(c=0.62, $CHCl_3$). Ir (neat) 1700, 1650 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.60-2.05 (6H, m), 2.65 (1H, m), 3.10-3.70 (6H, m), 4.02 (1H, m), 4.45 (1H, m), 4.97 (1H × 1/3, d, J = 13.5 Hz), 5.12 (1H × 2/3, d, J = 13.9 Hz), 5.18 (1H × 2/3, d, J = 13.9 Hz), 5.25 (1H × 1/3, d, J = 13.5 Hz), 7.37 (2H × 1/3, d, J = 8.9 Hz), 7.44 (2H × 2/3, d, J = 8.9 Hz), 8.13 (2H, m).

1-[(2S,4S)-4-Mercapto-1-*p*-nitrobenzyloxycarbonyl-2-pyrrolidine-carbonyl]-4-methylpiperadine (2d).

N-Methylpiperazine (110 mg, 1.1 mmol) was added to a solution of **7** (308 mg, 1 mmol) in CH_2Cl_2 (2.0 ml). After stirring for 10 h at room temperature, the reaction mixture was concentrated in vacuo to give a solid residue, which was recrystallized from hexane-CH_2Cl_2 to afford **2d** (368 mg, 90 %), mp 137.0-138.0°C. $[\alpha]_D^{22}$=-0.6° (c=0.16, $CHCl_3$). Ir (KBr) 1711, 1657 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.88 (2H, m), 2.20-2.50 (3H, m), 2.25 (3H × 1/3, s), 2.31 (3H × 2/3, s), 2.49 (1H, m), 2.72 (1H, m), 3.25 (1H, m), 3.35-3.70 (5H, m), 4.11 (1H, m), 4.67 (1H, m), 5.06 (3H × 1/3, d, J = 13.5 Hz), 5.19 (3H × 2/3, d, J = 13.5 Hz), 5.26 (3H × 2/3, d, J = 13.5 Hz), 5.31 (3H × 1/3, d, J = 13.5 Hz), 7.44 (2H × 1/3, d, J = 8.9 Hz), 7.51 (2H × 2/3, d, J = 8.9 Hz), 8.20 (2H × 1/3, d, J = 8.9 Hz), 8.22 (2H × 2/3, d, J = 8.9 Hz).

(2S,4S)-*N,N*-Dimethyl-4-mercapto-1-*p*-nitrobenzyloxycarbonyl-2-pyrrolidinecarboxamide (2a).

(a) Me_2NH-HCl (26.9 mg, 0.33 mmol) and Et_3N (45.5 mg, 0.45 mmol) were added to a solution of **7** (92.5 mg, 0.3 mmol) in THF (0.6 ml). After stirring for 5 h at room temperature, the reaction mixture was concentrated in vacuo to give an oily residue, which was purified by silica gel chromatography to afford **2a** (97.5 mg, 92 %). $[\alpha]_D^{22}$=+9.8° (c=0.25, $CHCl_3$). The ir and ^{1}H-nmr spectral data were identical with the reported data.[1] Anal. Calcd for $C_{15}H_{19}N_3O_5S$: C,50.98; H,5.42; N,11.89; S,9.07. Found; C,50.86; H,5.44; N,11.89; S,8.95.

(b) Me_2NH-HCl (56.9 mg, 0.698 mmol) and diisopropylethylamine (123 mg, 0.951 mmol) were added to a solution of **7** (196 mg, 0.634 mmol) in MeCN (1.5 ml). After stirring for 1 h at room temperature, the reaction mixture was worked up in the same manner as described above to afford **2a** (168 mg, 75%).

(2S,4S)-*N*-(*p*-Tolyl)-1-*p*-nitrobenzyloxycarbonyl-4-mercapto-2-pyrrolidinecarboxamide (2e)

p-Toluidine (35.4 mg, 0.33 mmol) was added to a solution of **7** (92.5 mg, 0.30 mmol) in THF (0.6 ml). After stirring for 3 h at 50°C, the reaction mixture was worked up in the same manner as described for the preparation of **2a** to afford **2e** (90 mg, 72 %), mp 185-188°C (AcOEt-toluene). $[\alpha]_D^{22}$=-52.9° (c=0.11, $CHCl_3$). Ir (KBr) 1714, 1666 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.93 (1H, m), 2.32 (3H, s), 2.60-2.90 (2H, m), 3.43 (2H, m), 4.09 (1H, m), 4.44 (1H, m), 5.05-5.45 (2H, m), 7.05-7.75 (6H, m), 7.80-8.30 (2H, m).

(2S,4S)-1-*p*-Nitrobenzyloxycarbonyl-2-methoxycarbonyl-4-mercapto-2-pyrrolidine (2f)

5% MeOH solution of sodium methoxide (600 mg, 0.56 mmol) was added to a solution of **7** (162 mg, 0.53 mmol) in MeCN (3 ml) with ice-water cooling. After stirring for 30 min, the reaction mixture was diluted with AcOEt, washed with 1N HCl and dried over $MgSO_4$. Evaporation in vacuo gave an oily residue, which was purified by silica gel chromatography to afford **2f** (172 mg, 96%) as an oil. $[\alpha]_D^{24}$=-29.0° (c=0.99, $CHCl_3$). Ir (neat) 1700 cm^{-1}. ^{1}H-Nmr δ ($CDCl_3$) 1.84 (1H, d, J = 5.6 Hz), 2.03 (1H, m), 2.77 (1H, m), 3.40 (1.5H, m), 3.69 (3H × 1/2, s), 3.78 (3H × 1/2, s), 4.06 (1/2H, dd, J = 4.0, 5.3 Hz), 4.12 (1H, dd, J = 7.3, 14.2 Hz), 4.40 (1H, t, J = 7.8 Hz), 5.11 (1/2H, AB, J = 13.5 Hz), 5.24 (2 × 1/2H, s), 5.31 (1/2H, AB, J = 13.5 Hz), 7.46 (1H, d, J = 8.9 Hz), 7.52 (1H, d, J = 8.9 Hz), 8.21 (1H, d, J = 8.9 Hz), 8.23 (1H, d, J = 8.9 Hz).

(2S,4S)-1-*p*-Nitrobenzyloxycarbonyl-2-benzyloxycarbonyl-4-mercapto-2-pyrrolidine (2g)

1M THF solution of lithium benzyl alkoxide (0.66 ml, prepared from benzyl alcohol and n-BuLi) was added to a solution of **7** (202 mg, 0.656 mmol) in THF (1.5 ml) at 0°C. After stirring for 5 min, the reaction mixture was worked up in the same manner as described for the preparation of **2f** to afford **2g** (123 mg, 45 %) as an oil. $[\alpha]_D^{22}$=-24.0° (c=0.21, $CHCl_3$). Ir (neat) 1700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 1.80 (1H, m), 2.01 (1H, m), 2.78 (1H, m), 3.38 (2H, m), 4.05 (1H, m), 4.44 (1H × 1/2, dd, J = 8.5, 15.7 Hz), 4.70 (1H × 1/2, br), 5.06-5.28 (4H, m), 7.25-7.40 (5H + 2H × 1/2, m), 7.49 (2H × 1/2, d, J = 8.8 Hz), 8.10 (2H × 1/2, d, J = 8.8 Hz), 8.20 (2H × 1/2, d, J = 8.8 Hz).

Dimethyl 2-[(2S,4S)-1-*p*-Nitrobenzyloxycarbonyl-4-mercapto-pyrrolidinyl]carbonylmalonate (2h)

A solution of **7** (460 mg, 1.493 mmol) in THF (2.0 ml) was added to a suspension of sodium salt of dimethyl malonate, which was prepared from dimethyl malonate (267 mg, 2.02 mmol) and NaH (60%, 120 mg, 3.0 mmol), in THF (5.0 ml) under ice-water cooling. After stirring overnight at room temperature, the reaction mixture was worked up in the same manner as described for the preparation of **2f** to afford **2h** (353 mg, 69 %) as an oil and then **7** (103 mg) was recovered. Ir (neat) 1716, 1700 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.00 (1H, m), 2.84 (1H, m), 3.32 (1H, m), 3.76 (3H, s), 3.82 (3H, s), 3.93 (1H, m), 4.13 (1H, m), 4.62-4.97 (1H, m), 5.17 (2H × 1/2, ABq, 13.5 Hz), 5.22 (2H × 1/2, s), 7.42 (2H × 1/2, d, J = 8.6 Hz), 7.50 (2H × 1/2, d, J = 8.6 Hz), 8.16 (2H × 1/2, d, J = 8.6 Hz), 8.22 (2H × 1/2, d, J = 8.6 Hz).

(4R,5S,6S)-*p*-Nitrobenzyl 3-[(3S,5S)-(5-Dimethylaminocarbonyl-1-*p*-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (14)

A solution of **7** (200 mg, 0.65 mmol), Me_2NH-HCl (59 mg, 0.72 mmol) and diisopropylethylamine (186 mg, 1.44 mmol) in MeCN (3 ml) was stirred with ice-water cooling for 1.5 h. The reaction mixture was added to a solution of enol phosphate (**13**) (387 mg, 0.65 mmol) in MeCN (3 ml) at -30°C. After stirring for 2.5 h, the reaction mixture was diluted with AcOEt, washed with water and dried over $MgSO_4$. Evaporation in vacuo gave an oily residue, which was purified by silica gel chromatography to afford **14** (315mg, 69%) as a pale yellow powder. The ir and ^{1}H-nmr spectral data were identical with those reported.[1]

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REFERENCES AND NOTES

1 M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, and M. Kato, *J. Antibiotics*, 1990, **43**, 519.

2 a: I. Kawano, R. Endo, T. Tanaka, and M. Iwata, Japan Patent 1990, 02003687 [*Chem. Abstr.*, 1990, **113**, 40335v]; b: M. Murata, H. Tsutsumi, K. Matsuda, K. Hattori, and T. Nakajima, *Japan Patent* 1990, 02042081 [*Chem. Abstr.*, 1990, **113**, 131870h]; c: M. Sunagawa, A. Sasaki, H. Yamaga, M. Fukasawa, and H. Nouda, *Eur. Patent* 1991, 442497 [*Chem. Abstr.*, 1991, **116**, 59080t]; d: I. Kawano, M. Miyauchi, E. Nakayama, R. Endo, and S. Ohya, *Eur. Patent* 1991, 443883 [*Chem. Abstr.*, 1991, **116**, 151432g]; e: Y. Ishida, M. Takemura, and T. Hayano, *Japan Patent* 1991, 03275685 [*Chem. Abstr.*, 1991, **116**, 214237v]; f: T. Nishi, M. Takemura, T. Saito, Y. Ishida, K. Sugita, M. Houmura, H. Ishi, K. Sato, I. Hayakawa, and T. Hayano, Abstracts of Papers, 32th Interscience

Conference on Antimicrobial Agents and Chemotherapy, p. 132, No.131, Anaheim, Oct. 11-14, 1992.

3 a: Y. Murakami, K. Koga, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, 1972, **20**, 543; b: V. Eswarakrishnan and L. Field, *J. Org. Chem.*, 1981, **46**, 4182.

4 (2S,4R)-2-*p*-Chlorophenylthiocarbonyl-4-mesyloxy-1-*p*-nitrobenzyloxycarbonylpyrrolidine (**11**): Ir (neat) 1712 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ 2.42 (1H, m), 2.66-2.88 (1H, m), 3.07 (3H, s), 3.86 (1H, m), 4.10 (1H, t, J = 12 Hz), 4.79 (1H, q, J= 8.2 Hz), 5.30 (2H×1/2, ABq, J = 13.5 Hz), 5.31 (2H×1/2, s), 7.33 (2H×1/2, d, J = 8.6 Hz), 7.51 (2H×1/2, d, J = 8.3 Hz), 7.54 (2H×1/2, d, J = 8.3 Hz), 8.20 (2H×1/2, d, J = 8.3 Hz), 8.23 (2H×1/2, d, J = 8.3 Hz).

5 E. K. Ellingboe, *Org. Synth.*, 1963, **IV**, 928.

6 P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, 1982, **47**, 589.

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