SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF CARBAPENEMS RELATED TO C-19393 H_2

HIDEAKI NATSUGARI, YOSHIHIRO MATSUSHITA, NORIKAZU TAMURA, KOUICHI YOSHIOKA, MASAHIRO KONDO, KENJI OKONOGI, MITSUZO KUNO and MICHIHIKO OCHIAI

Central Research Division, Takeda Chemical Industries, Ltd., Yodogawa-ku, Osaka 532, Japan

(Received for publication April 9, 1983)

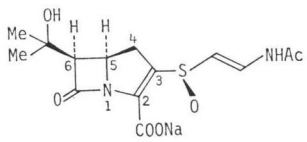
By applying the synthetic process reported in our previous paper, we synthesized new carbapenems having various (substituted) thio and alkoxy groups at the C(3) position and 1-hydroxy-1-methylethyl and analogous groups at the C(6) position with *cis*- and *trans*-stereochemistry; the *in vitro* antibacterial and β-lactamase inhibitory activities of these new carbapenems were examined.

Compared to C-19393 H_2, some of these compounds (*e.g.*, **11A-a-3**$\sim$**5**) showed improved *in vitro* antibacterial activity especially against *Pseudomonas aeruginosa*; they showed a strong β-lactamase inhibitory activity as well. Two noteworthy effects of substituent variation at the C(6) position on the activities were observed: 1) the *trans*-configuration caused a definite loss; and 2) introduction of 1-hydroxycyclobutyl and 1-hydroxy-1-methylpropyl groups in place of the 1-hydroxy-1-methylethyl group caused a diminution. The carbapenem (**13A-a-2**) with an alkoxy group at the C(3) position had a marked decrease in activity compared to the corresponding thio-substituted carbapenem (**11A-a-12**).

In a previous paper[1] we reported an efficient approach to *cis*-azetidinones and the first total synthesis of ($\pm$)-C-19393 H_2 and its several derivatives starting from the *cis*-azetidinones *via* a carbene insertion reaction.

The carbapenem antibiotic, C-19393 H_2,[2~4]* possesses not only highly potent broad-spectrum antibacterial activity, but also a strong β-lactamase inhibitory (BLI) activity. However, because of the low *in vitro* antibacterial activity against Pseudomonas strains with high β-lactamase activity and the poor protective effects in mice due to inactivation by renal peptidases,[7] further synthetic studies of carbapenem derivatives have been desired.

Fig. 1.



C-19393 H_2

In this paper, we report the synthesis of new carbapenems related to C-19393 H_2 by applying the synthetic process reported in our previous paper. The *in vitro* antibacterial activity and BLI activity of these new carbapenems are also described.

Chemistry

The new carbapenems** prepared in this study are those having various (substituted) thio and alkoxy groups at the C(3) position and 1-hydroxy-1-methylethyl group (type of C-19393 H_2) and its

* The same structure has been proposed for carpetimycin A.[5,6]

** All the β-lactams prepared in this study are racemic, but only one enantiomer is depicted for convenience.

analogous groups at the C(6) position with *cis*- and *trans*-stereochemistry.

Charts 1 and 2 show the synthetic route to the 3,7-dioxo-carbapenems (**9**), which are key intermediates for a variety of C(3) and C(6) substituted carbapenems. First, by applying the processes reported for the synthesis of **3A-a** from **1**,[1] the *cis*-azetidinones (**3A-b, c**) were prepared selectively by reductive desulfurization of **2b, c**, which were prepared by sulfenylation of **1** followed by aldol reaction with cyclobutanone and methyl ethyl ketone, respectively. The *trans*-isomers (**3B-a**～**c**) were obtained by direct aldol reaction of the enolate of **1** with acetone, cyclobutanone, and methyl ethyl ketone, respectively (Chart 1). The aldol products (**3A-c, 3B-c**) with 1-hydroxy-1-methylpropyl group were obtained as isomeric mixtures at the C(9) position; these mixtures were used in the subsequent reactions without separating the isomers.

Then, by analogy with the synthesis of **9A-a** from **3A-a**,[1] the 3,7-dioxo-carbapenems (**9A-b, c, 9B-a**～**c**) were prepared from the corresponding isomer of compound **3** as shown in Chart 2. Thus, protection of **3** with the methoxyethoxymethyl (MEM) group followed by JONES oxidation gave the acids (**5**) (Tables 4 and 5). The acids were transformed into the diazo keto-esters (**7**) *via* the keto-esters (**6**) (Tables 6 and 7). Removal of the MEM group was effected with titanium tetrachloride to

Chart 1.

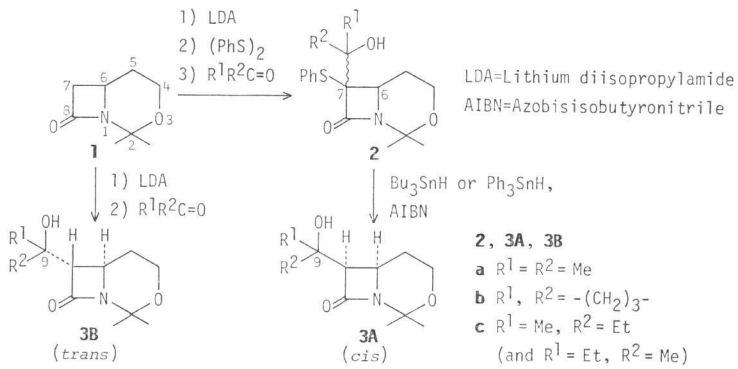
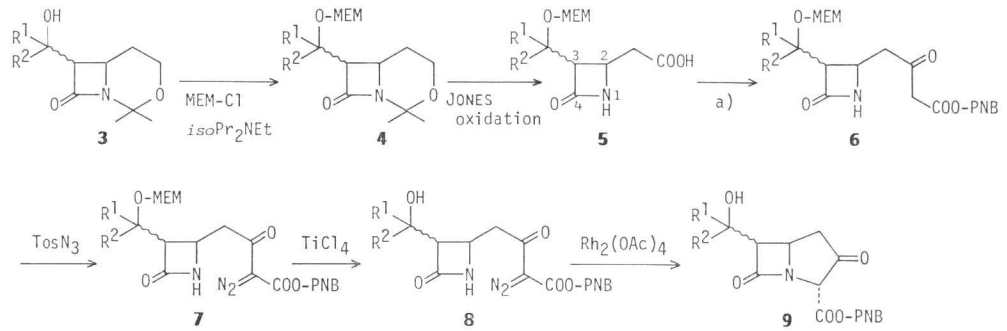


Chart 2.



form the cyclization precursors (**8**). Construction of the carbapenem ring was achieved by the rhodium catalyzed carbene insertion reaction.[8]

Chart 3 shows the synthetic route to 3-substituted carbapenems (**11, 13**) from **9**. Reaction of **9** with phosphoryl chloride followed by treatment with various thiol derivatives in the presence of a base gave the carbapenem esters (**10**) (Tables 8–1, 8–2). The *p*-nitrobenzyl group was removed by hydrogenolysis using 10% palladium-charcoal to give the carboxylic acids (or sodium salts) of the carbapenems **11** (Tables 9–1, 9–2). Among the carbapenems shown in the Tables, the formimidoyl derivatives(**11A-a-**3, 4) were prepared from the corresponding amino derivatives (**11A-a-**1, 2) by reaction with benzyl formimidate,[9,10] and the acetamido derivatives (**11A-a-**8, 9, **11B-a-**2*) were prepared by acetylation of the corresponding amino derivatives (**11A-a-**1, 2, **11B-a-**1) and/or by hydrogenolysis of the corresponding *p*-nitrobenzyl esters.

The 3-alkoxy carbapenems (**12**) were prepared by reaction of **9** with diazo-alkanes by an analogous procedure reported for the synthesis of alkoxy-penems.[12] The *p*-nitrobenzyl group of **12** was removed by hydrogenolysis to afford the sodium salts of the acids (**13**) (Tables 8–2, 9–2).

In addition, the carbapenem (**16**) with the MEM-oxy group at the C(8) position was synthesized from **7A-a** *via* the carbene insertion reaction as shown in Chart 4.

Chart 3.

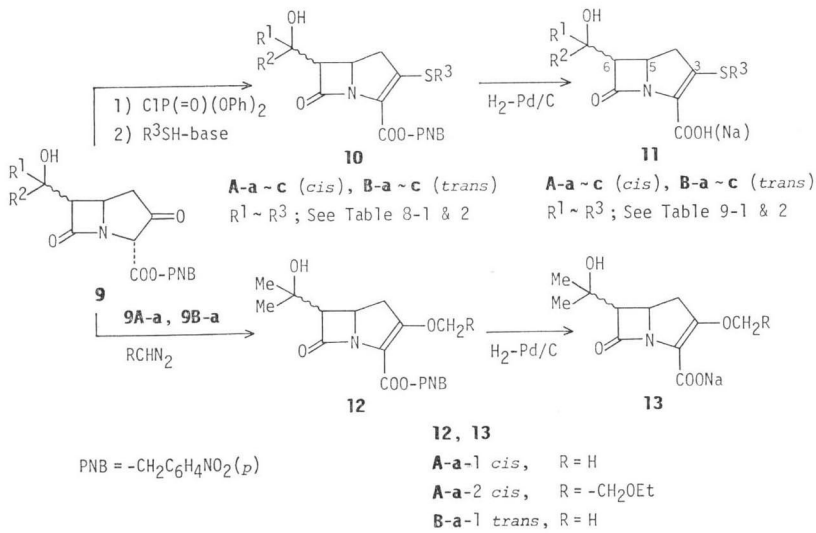
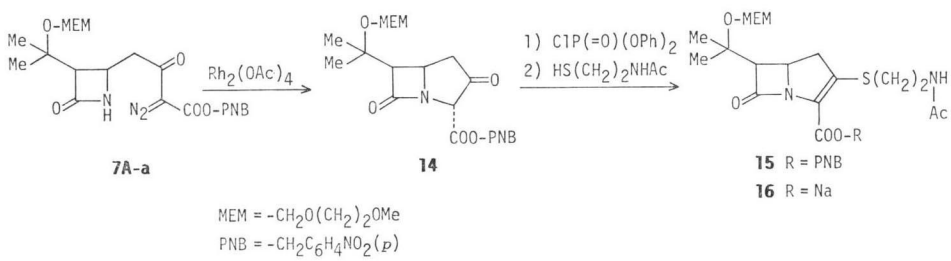
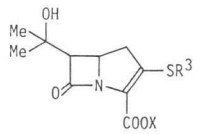


Chart 4.

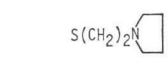


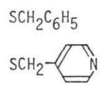
* Isolation of the natural form of this compound (**11B-a-**2), designated as KA-6643-G, has recently been reported in the patent literature.[11]

Table 1. *In vitro* antibacterial activity and β-lactamase inhibitory activity (1). 3-Substituted-thio-5,6-*cis*-6-(1-hydroxy-1-methylethyl)carbapenems (**11A-a**).



11A-a

Compound (**11A-a**)	SR^3	X	MIC (μg/ml); 10^8 CFU* Organism							ID_{50} (μg/ml)** Source of enzyme			
			S. a[a]	*E. c*(S)[b]	*E. c*[c]	*E. cl*[d]	*S. mar*[e]	*P. vul*[f]	*P. ae*[g]	*S. a*[h]	*E. c*[i]	*E. cl*[j]	*P. vul*[k]
C-19393 H_2	*R* S(O)CH=CHNHAc (dl)	Na^l	3.13	≦0.1	1.56	1.56	0.78	6.25	100	0.070	0.0080	0.055	0.0012
	〃 *S* (natural)	Na^m	1.56	≦0.1	1.56	0.78	0.78	3.13	50	0.043	0.0030	0.034	0.00060
iso-C-19393 H_2	S(O)CH=CHNHAc (dl)	Na^l	6.25	1.56	25	50	12.5	12.5	>100	1.6	0.080	0.0070	0.0047
C-19393 H_2-M1	SCH=CHNHAc (dl)	Na^l	3.13	0.2	3.13	3.13	1.56	3.13	>100	1.9	0.025	0.015	0.0090
11A-a-1	$S(CH_2)_2NH_2$	H	1.56	0.39	1.56	12.5	12.5	50	25	0.70	0.028	0.042	0.026
2	$S(CH_2)_3NH_2$	H	0.78	0.39	0.78	6.25	6.25	50	50	0.80	0.031	0.028	0.040
3	$S(CH_2)_2NHCH=NH$	H	0.78	0.39	0.78	6.25	3.13	25	6.25	0.85	0.019	0.053	0.031
4	$S(CH_2)_3NHCH=NH$	H	0.78	0.39	0.78	6.25	3.13	25	12.5	0.54	0.0085	0.037	0.024
5	$SCH_2C(=NH)NH_2$	H	0.78	0.78	0.78	6.25	6.25	50	6.25	0.49	0.032	0.062	0.035
6	$S(CH_2)_2NMe_2$	H	0.78	0.39	0.78	6.25	6.25	50	50	1.1	0.065	0.070	0.080
7		H	0.78	0.39	0.78	12.5	6.25	100	50	0.060	0.0055	0.0090	0.0034
8	$S(CH_2)_2NHAc$	Na^l	3.13	0.2	0.78	1.56	0.78	6.25	>100	0.80	0.0070	0.011	0.025
9	$S(CH_2)_3NHAc$	Na	3.13	0.39	1.56	3.13	1.56	3.13	>100	1.2	0.0086	0.013	0.019
10	SEt	Na	1.56	0.2	0.39	1.56	1.56	3.13	>100	1.3	0.015	0.013	0.011
11	$S(CH_2)_2OH$	Na	3.13	0.2	0.39	1.56	1.56	6.25	>100	2.0	0.011	0.013	0.020
12	$S(CH_2)_2OEt$	Na	1.56	<0.1	0.78	3.13	3.13	3.13	>100	0.055	0.00042	0.0011	0.0025
13	$SCH_2CONHMe$	Na	6.25	0.78	1.56	3.13	3.13	12.5	>100	>5	0.31	0.29	0.32
14	SC_6H_5	Na	1.56	12.5	50	50	100	25	>100	1.3	0.0019	0.0038	0.011

15		Na	3.13	1.56	25	12.5	6.25	6.25	>100	1.2	0.060	0.046	0.0065
16		Na	1.56	0.78	6.25	>100	3.13	3.13	>100	2.1	0.060	0.0080	0.020
17		Na	3.13	12.5	100	25	50	12.5	>100	1.4	0.038	0.022	0.035
18		Na	0.78	0.2	3.13	1.56	1.56	3.13	>100	1.6	0.012	0.013	0.0046
19	$SCH_2C_6H_5$	Na	0.78	3.13	25	25	50	6.25	>100	0.36	0.0011	0.0032	0.017
20		Na	0.78	0.39	1.56	1.56	3.13	1.56	>100	0.31	0.0030	0.0056	0.0020

* The MICs were determined by a standard dilution method in Trypticase soy agar (BBL).[16]

** The ID_{50}s (concentrations required to cause 50% inhibition) were determined by micro iodometric method.[17]

[a] *Staphylococcus aureus* 1840 ($PCase^+$), [b] *Escherichia coli* O-111, [c] *Escherichia coli* T-7 ($PCase^+$), [d] *Enterobacter cloacae* IFO 12937 ($CSase^+$), [e] *Serratia marcescens* IFO 12648 ($CSase^+$), [f] *Proteus vulgaris* IFO 3988 ($CSase^+$), [g] *Pseudomonas aeruginosa* U 31 ($CSase^+$), [h] *Staphylococcus aureus* 1840 (PCase), [i] *Escherichia coli* TN 713 (PCase), [j] *Enterobacter cloacae* TN 1282 (CSase), [k] *Proteus vulgaris* GN 4413 (CSase).

[l] Synthesis of these compounds; see reference 1, [m] reference 2~4.

In Vitro Antibacterial Activity and BLI Activity

The *in vitro* antibacterial activity of these new carbapenems against several bacteria and their BLI activity are shown in Tables 1 ~ 3.* All the bacteria shown in the Tables are β-lactamase producing strains except *Escherichia coli* O-111.

The effects of the substituent variation at C(3)-thio groups of the 5,6-*cis*-6-(1-hydroxy-1-methylethyl)carbapenems (type of C-19393 H_2) are shown in Table 1. Racemic C-19393 H_2[1] showed, as expected, about half the activities of the natural compound.[2~4] Most of the compounds with (substituted)-alkylthio group (**11A-a**-1 ~ 13) showed good to excellent antibacterial activity as well as strong BLI activity. The compounds having an amidine moiety in the side chain (**11A-a**-3 ~ 5) showed excellent antibacterial activity including activity against *Pseudomonas aeruginosa*. The compound **11A-a**-3, which has the same type of substituent at the C(3) position as MK 0787,[9,10] exhibited particularly good antibacterial activity, and possesses strong BLI activity as well. Although the carbapenems (**11A-a**-8 ~ 13), when compared to **11A-a**-3, showed a slightly improved activity against *Proteus vulgaris*, they did not show anti-Pseudomonas activity.

The aryl- and aralkylthio substituted carbapenems (**11A-a**-14 ~ 20), especially those with heterocyclic groups, showed excellent activities. Their activity profile is similar to that of **11A-a**-8 ~ 13.

Table 2 shows the effects of the substituent variation including the alteration of the configuration at the C(6) position. Contrary to our expectation, the *trans*-isomers (**11B-a**-1, 2), which have the homologous structure of thienamycins,[14] exhibited no significant antibacterial activity against most bacteria. Their BLI activity is also far less potent than that of the corresponding *cis*-isomers. Introduction of 1-hydroxycyclobutyl and 1-hydroxy-1-methylpropyl groups into the C(6) position in place of the 1-hydroxy-1-methylethyl group caused a decrease of the activities. The *trans*-isomers (**11B-b**, **c**) again showed a definite loss of the activities. Replacement of the hydroxyl group by MEM-oxy group caused a decrease in the antibacterial activity, although the BLI activity still remained strong.

Table 3 shows the activities of 3-alkoxy carbapenems (**13**). Compared to the corresponding 3-alkylthio carbapenems (**11A-a**-12), the oxy-analogue (**13A-a**-2) showed a marked decrease in the activities. The chemical instability of **13A-a**-2 may be one of the reasons of this decrease; when **13A-a**-2 was stored at 37°C for 12 hours in aqueous solution, the residual rate was about 50% as determined by UV measurement, whereas that of **11A-a**-12 was over 90%.

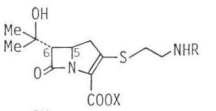
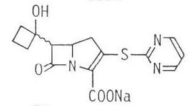
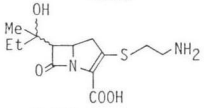
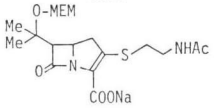
The *in vivo* protective effects of some of these compounds and the relationship between the effects and stability in mouse kidney homogenate will be reported in a separate paper.[15]

Experimental

Mp was determined using a Yanagimoto mp apparatus and are uncorrected. IR spectra were measured with a Hitachi 215 spectrophotometer. ^{1}H NMR spectra were taken on a Varian T-60 (60 MHz), a Varian EM-390 (90 MHz), or a Varian XL-100 (100 MHz) spectrometer with Me_4Si as a standard. UV spectra were taken with a Perkin-Elmer 450 or a Hitachi EPS-3T spectrophotometer. Chemical shifts in the NMR spectra are given with proton numbers, absorption patterns, and coupling constants (Hz) in parentheses. The abbreviations used are as follows: s, singlet; d, doublet, t, triplet; q, quartet; dd, doublet of doublet; dt, doublet of triplets; m, multiplet; b, broad. Extracted solutions were dried over sodium sulfate. All the β-lactams prepared are racemic. The MICs were determined by a standard dilution method in Trypticase soy agar (BBL) as described previously.[16] The BLI

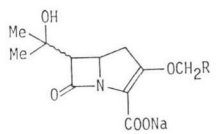
* All the carbapenems are tested as the racemic form.

Table 2. *In vitro* antibacterial activity and β-lactamase inhibitory activity (2). Effects of substituent at C(6) position on activities.

Compound	No.	Stereo-chemistry at C(5) & C(6)	MIC (μg/ml); 10^8 CFU* Organism							ID$_{50}$ (μg/ml)** Source of enzyme			
			S. a[a]	*E. c*(S)[b]	*E. c*[c]	*E. cl*[d]	*S. mar*[e]	*P. vul*[f]	*P. ae*[g]	*S. a*[h]	*E. c*[i]	*E. cl*[j]	*P. vul*[k]
	**11B-a-1** (R=H, X=H)	*trans*	3.13	>100	>100	>100	>100	>100	>100	>5	5.0	1.5	4.9
	11B-a-2 (R=Ac, X=Na)	*trans*	25	>100	>100	>100	>100	>100	>100	>5	1.80	0.65	1.40
	**11A-b**	*cis*	1.56	3.13	50	25	12.5	3.13	>100	0.070	0.055	0.20	0.022
	11B-b	*trans*	12.5	>100	>100	>100	>100	>100	>100	>5	3.9	3.0	2.7
	**11A-c**	*cis*	1.56	3.13	6.25	50	25	100	50	1.1	0.19	0.082	0.090
	11B-c	*trans*	12.5	>100	>100	>100	>100	>100	>100	>5	>5	4.9	>5
	**16**	*cis*	100	25	100	>100	>100	>100	>100	0.69	0.01	0.0060	0.0023

*, **, [a~k] See the corresponding footnotes in Table 1.

Table 3. *In vitro* antibacterial activity and β-lactamase inhibitory activity (3). 3-Alkoxy-6-(1-hydroxy-1-methylethyl)carbapenems (**13**).



13

Compound (**13**)	OCH_2R (stereo-chemistry at C(5) and C(6))	MIC (μg/ml); 10^8 CFU* Organism							ID$_{50}$ (μg/ml)** Source of enzyme			
		S. a[a]	*E. c*(S)[b]	*E. c*[c]	*E. cl*[d]	*S. mar*[e]	*P. vul*[f]	*P. ae*[g]	*S. a*[h]	*E. c*[i]	*E. cl*[j]	*P. vul*[k]
A-a-1	OCH_3 (*cis*)	25	3.13	3.13	12.5	12.5	50	>100	3.4	0.30	0.36	0.11
B-a-1	OCH_3 (*trans*)	>100	>100	>100	>100	>100	>100	>100	>5	>5	>5	>5
A-a-2	$O(CH_2)_2OEt$ (*cis*)	25	1.56	3.13	50	25	100	>100	0.55	0.032	0.21	0.090

*, **, [a~k] See the corresponding footnotes in Table 1.

activities were determined as described previously[17] and expressed in terms of ID_{50}, the concentration required to inhibit β-lactamase activity by 50%.

(7*R*)- and (7*S*)-7-Hydroxyalkyl-2,2-dimethyl-7-phenylthio-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (**2**)

According to the procedure reported for the synthesis of **2a** from **1**,[1] the compounds (**2b, c**) were prepared by sulfenylation of the lithium enolate of **1** with diphenyl disulfide in dry tetrahydrofuran (THF) at −78°C followed by the addition of cyclobutanone and methyl ethyl ketone, respectively. The stereochemistry at the C(7) (and C(9)) position(s) has not been determined. The properties of **2b** and **2c** are as follows.

2b: A colorless oil. Yield 94%. IR ν_{max}^{liquid} cm^{-1} 1740: NMR ($CDCl_3$) δ 1.40, 1.68 (each 3H, s), 1.7~2.8 (8H, m), 3.1 (1H, b), 3.5~4.1 (3H, m), 7.2~8.0 (5H, m).

2c: Colorless prisms. Mp 77~78°C. Yield 70%. IR ν_{max}^{KBr} cm^{-1} 1750: NMR ($CDCl_3$) δ 0.99 (3H, t, 7), 1.29, 1.40, 1.48 (each 3H, s), 1.62 (2H, m), 1.72~2.0 (2H, m), 3.0 (1H, b), 3.7~4.1 (3H, m), 7.01~7.50 (5H, m).

Anal. Calcd. for $C_{15}H_{25}NO_3S$: C 64.65, H 7.51, N 4.18.
Found: C 64.61, H 7.42, N 4.27.

7-Hydroxyalkyl-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (**3**)

Method A. Desulfurization of **2**: According to the procedure reported for the desulfurization of **2a**,[1] the compound **2b** was desulfurized with triphenyltin hydride (2 equiv.) in the presence of azobisisobutyronitrile (AIBN, 0.2 equiv.) in acetone under reflux for 14 hours to give the *cis*-azetidinone (**3A-b**) stereoselectively.

3A-b: A colorless oil. Yield 89%. IR ν_{max}^{liquid} cm^{-1} 1740: NMR ($CDCl_3$) δ 1.37, 1.72 (each 3H, s), 1.4~2.7 (8H, m), 3.0 (1H, b), 3.42 (1H, d, 6), 3.5~4.0 (3H, m).

Analogously, the compound **2c** was desulfurized with tri-*n*-butyltin hydride (3 equiv.) in the presence of AIBN (0.2 equiv.) in acetone under reflux for 24 hours to give the *cis*-azetidinone (**3A-c**) (69%) and the *trans*-azetidinone (**3B-c**) (20%).

3A-c: Colorless prisms. Mp 84~86°C: IR ν_{max}^{KBr} cm^{-1} 1730: NMR ($CDCl_3$) δ 0.84 (2.1H, t, 7), 0.90 (0.9H, t, 7), 1.34, 1.39, 1.72 (each 3H, s), 1.62 (2H, m), 1.80 (2H, m), 3.0 (1H, b), 3.19 (1H, d, 6), 3.8~3.9 (3H, m).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16.
Found: C 63.70, H 9.15, N 6.15.

3B-c: Colorless prisms. Mp 64~65°C. IR ν_{max}^{KBr} cm^{-1} 1720: NMR ($CDCl_3$) δ 0.94 (3H, t, 7), 1.17, 1.77 (each 3H, s), 1.28 (0.9H, s), 1.40 (2.1H, s), 1.62 (2H, m), 1.85 (2H, m), 2.8 (1H, b), 2.86 (1H, d, 2), 3.4~3.9 (3H, m).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16.
Found: C 63.51, H 9.34, N 6.21.

The compounds **3A-c** and **3B-c** were obtained as the isomeric mixtures at the C(9) position (*ca.* 5: 2 ratio as indicated by NMR) whose stereochemistry has not been determined.

Method B. Direct Aldol Reaction of **2** (Preparation of the *trans*-Azetidinones): As a typical example, the preparation of **3B-a** is described. A solution of the compound **1** (2.33 g, 15 mmol) in dry THF (15 ml) was added at −78°C to a solution of lithium diisopropylamide, prepared from *n*-butyllithium (15 ml of 15% hexane solution, 24 mmol) and diisopropylamine (3.16 ml, 23 mmol) in dry THF (60 ml) under nitrogen. The mixture was stirred for 10 minutes, and dry acetone (3 ml) was added to this enolate solution. After being stirred for 15 minutes at −78°C, the mixture was poured into ice-cooled saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel with hexane - ethyl acetate (1: 1, v/v) as eluant to give the *trans*-azetidinone (**3B-a**) (2.44 g, 80%) as colorless prisms. The IR and NMR spectra and mp were identical with those of the compound obtained as the minor product in the desulfurization of **2a**.[1] The formation of a trace of the *cis*-isomer (**3A-a**)[1] was detected by thin-layer chromatography, but isolation failed.

By a similar procedure, the *trans*-azetidinones (**3B-b, c**) were prepared, stereo-selectively. Their properties are as follows.

3B-b: Colorless prisms. Mp 99~101°C. Yield 82%. IR ν_{max}^{KBr} cm^{-1} 1740: NMR ($CDCl_3$) δ 1.43, 1.76 (each 3H, s), 1.8~2.6 (9H, m), 3.06 (1H, d, 3), 3.60 (1H, m), 3.89 (2H, m).

Anal. Calcd. for $C_{12}H_{19}NO_3$: C 63.98, H 8.50, N 6.22.
Found: C 64.10, H 8.40, N 6.01.

3B-c: Colorless prisms. Mp 56~61°C. IR ν_{max}^{KBr} cm^{-1} 1720: NMR ($CDCl_3$) δ 0.94 (3H, t, 7), 1.17, 1.77 (each 3H, s), 1.28 (0.5H, s), 1.40 (2.5H, s), 1.62 (2H, m), 1.85 (2H, m), 2.8 (1H, b), 2.86 (1H, d, z), 3.4~3.9 (3H, m).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16.
Found: C 63.05, H 9.30, N 6.05.

The ratio of the isomers (**3B-c**) was estimated as 5: 1 by NMR and this material was used in the subsequent reactions.

7-(2-Methoxyethoxymethoxyalkyl)-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (**4**)

According to the procedure reported for the synthesis of **4A-a** from **3A-a**,[1] protection of the hydroxyl group of **3** with the MEM group was carried out by reaction of the aldol products (**3A-b, c, 3B-a~c**) with MEM chloride (*ca.* 3 equiv.) in the presence of diisopropylethylamine (*ca.* 3 equiv.) in methylene dichloride at room temperature. The results are summarized in Table 4.

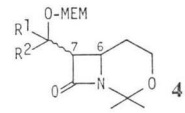
3-(2-Methoxyethoxymethoxyalkyl)-4-oxoazetidine-2-acetic Acids (**5**)

According to the procedure reported for the synthesis of **5A-a** from **3A-a**,[1] the protected-azetidinones (**4A-b, c, 4B-a~c**) were oxidized with excess JONES reagent in acetone at 0°C to give the acids (**5A-b, c, 5B-a~c**) as oily substances. The results are summarized in Table 5.

p-Nitrobenzyl 4-[3-(2-Methoxyethoxymethoxyalkyl)-4-oxoazetidin-2-yl]-3-oxobutanoates (**6**)

According to the procedure reported for the synthesis of **6A-a** from **5A-a**[1], the keto-esters (**6A-b, c, 6B-a~c**) were prepared by successive treatment of the corresponding acids (**5**) with *N,N'*-carbonyldiimidazole (1.3 equiv.) and the magnesium salt of the mono-*p*-nitrobenzyl ester of malonic acid (1.1 equiv.) in dry THF at room temperature. The results are summarized in Table 6.

Table 4. 7-(2-Methoxyethoxymethoxyalkyl)-2,2-dimethyl-3-oxa-1-azabicyclo[4.2.0]octan-8-ones (**4**).



4

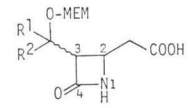
Compound[a] (**4**)	R^1	R^2	Stereochemistry at C(6) and C(7)	IR (liquid) (cm^{-1})	NMR, δ ($CDCl_3$)
A-a[b]	Me	Me	*cis*		
B-a	Me	Me	*trans*	1750	1.33 (6H, s), 1.42, 1.75 (each 3H, s), 1.90 (2H, m), 2.95 (1H, d, 3), 3.37 (3H, s), 3.4~4.0 (7H, m), 4.81 (2H, s)
A-b	$-(CH_2)_3-$		*cis*	1745	1.39, 1.72 (each 3H, s), 1.4~2.7 (8H, m), 3.36 (3H, s), 3.4~4.0 (8H, m), 4.79 (2H, s)
B-b	$-(CH_2)_3-$		*trans*	1750	1.40, 1.79 (each 3H, s), 1.8~2.6 (8H, m), 3.13 (1H, d, 3), 3.36 (3H, s), 3.4~4.0 (7H, m), 4.76 (2H, s)
A-c	Me (Et)	Et (Me)	*cis*	1750	0.87 (3H, t, 7), 1.32, 1.44, 1.75 (each 3H, s), 1.62 (2H, m), 1.90 (2H, m), 3.20 (1H, d, 6), 3.36 (3H, s), 3.36~3.90 (6H, m), 4.80 (0.6H, s), 4.85 (1.4H, s)
B-c[c]	Me (Et)	Et (Me)	*trans*	1750	0.90 (3H, t, 7), 1.32, 1.43, 1.77 (each 3H, s), 1.72 (2H, m), 1.90 (2H, m), 3.0 (1H, d, 2), 3.37 (3H, s), 3.49~3.90 (6H, m), 4.82 (2H, s)

[a] All the compounds were obtained as oily substances, and the crude materials were used for the subsequent reactions.

[b] For the properties; see reference 1.

[c] Prepared from the compound (**3B-c**) obtained by direct aldol reaction of the enolate of **1**.

Table 5. 3-(2-Methoxyethoxymethoxyalkyl)-4-oxoazetidine-2-acetic acids (**5**).

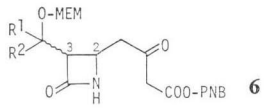


5

Compound (**5**)	R^1	R^2	Stereochemistry at C(2) and C(3)	Yield (%)	IR (liquid) (cm^{-1})	NMR, δ ($CDCl_3$)
A-a[a]	Me	Me	*cis*			
B-a	Me	Me	*trans*	—[b]	1740	—[c]
A-b	$-(CH_2)_3-$		*cis*	65	1735	1.4~2.7 (6H, m), 2.8 (2H, m), 3.35 (3H, s), 3.4~4.0 (6H, m), 4.78 (2H, s), 7.0 (1H, b), 8.1 (1H, b)
B-b	$-(CH_2)_3-$		*trans*	—[b]	1740	—[c]
A-c	Me (Et)	Et (Me)	*cis*	61	1750	0.88 (3H, t, 7), 1.46 (3H, s), 1.61 (2H, m), 2.91~3.4 (3H, m), 3.37 (3H, s), 3.40~3.80 (4H, m), 4.0 (1H, m), 4.81 (2H, s), 7.2 (1H, b), 8.3 (1H, b)
B-c	Me (Et)	Et (Me)	*trans*	79	1750	0.89 (3H, t, 7), 1.22 (3H, s), 1.62 (2H, m), 2.50~3.10 (3H, m), 3.35 (3H, s), 3.40~3.83 (4H, m), 3.90 (1H, m), 4.80 (2H, s), 5.81 (1H, b), 8.3 (1H, b)

[a] For the properties; see reference 1.
[b] Crude products were used for the subsequent reactions without purification.
[c] Not measured.

Table 6. *p*-Nitrobenzyl 4-[3-(2-methoxyethoxymethoxyalkyl)-4-oxoazetidin-2-yl]-3-oxobutanoates (**6**).



6

Compound[a] (**6**)	R^1	R^2	Stereochemistry at C(2) and C(3)	Yield (%)	IR (liquid) (cm^{-1})	NMR, δ ($CDCl_3$)[b]
A-a[c]	Me	Me	*cis*			
B-a	Me	Me	*trans*	51[d]	1750	1.33, 1.35 (each 3H, s), 2.9~3.2 (3H, m), 3.0 (3H, s), 3.3~4.0 (7H, m), 4.77 (2H, s), 5.27 (2H, s), 6.90 (1H, s)
A-b	$-(CH_2)_3-$		*cis*	57[e]	1750	1.6~2.6 (6H, m), 3.26 (3H, s), 3.56 (2H, s), 3.4~3.9 (5H, m), 4.1 (1H, m), 4.75 (2H, s), 5.23 (2H, s), 6.43 (1H, b)
B-b	$-(CH_2)_3-$		*trans*	64[d]	1750	1.6~2.8 (6H, m), 3.0~3.2 (3H, m), 3.36 (3H, s), 3.4~4.2 (7H, m), 4.73 (2H, s), 5.26 (2H, s), 6.36 (1H, b)
A-c	Me (Et)	Et (Me)	*cis*	62[e]	1750	0.87 (3H, t, 7), 1.49 (3H, s), 1.74 (2H, m), 3.34 (3H, s), 3.59 (2H, s), 3.20~4.71 (3H, m), 4.09 (1H, m), 4.79 (0.6H, s), 4.85 (1.4H, s), 5.28 (2H, s), 6.1 (1H, b)
B-c	Me (Et)	Et (Me)	*trans*	40[e]	1750	0.88 (3H, t, 7), 1.25 (2.5H, s), 1.32 (0.5H, s), 1.72 (2H, m), 3.34 (3H, s), 3.56 (2H, s), 3.00 (1H, d, 2), 3.50~4.71 (3H, m), 4.80 (2H, s), 5.29 (2H, s), 6.1 (1H, b)

[a] All the compounds were obtained as oily substances.
[b] Absorptions of aromatic protons of *p*-nitrobenzyl group are not given in Table for convenience.
[c] For the properties; see reference 1.
[d] Based on the corresponding **4** after purification by chromatography (SiO_2).
[e] Based on the corresponding **5** after purification by chromatography (SiO_2).

p-Nitrobenzyl 2-Diazo-4-[3-(2-methoxyethoxymethoxyalkyl)-4-oxoazetidin-2-yl]-3-oxobutanoates (7)

According to the procedure reported for the synthesis of **7A-a** from **6A-a**, the protected diazo-esters (**7A-b, c, 7B-a~c**) were prepared by reaction of the corresponding keto-esters (**6**) with toluene-*p*-sulfonyl azide (1.3 equiv.) in the presence of triethylamine (3.6 equiv.) in dry acetonitrile at 0~25°C. The results are summarized in Table 7.

p-Nitrobenzyl 2-Diazo-4-[3-(hydroxyalkyl)-4-oxoazetidin-2-yl]-3-oxobutanoates (8)

According to the procedure reported for the synthesis of **8A-a** from **7A-a**,[1] cleavage of the MEM group of the protected diazo-esters (**7A-b, c, 7B-a~c**) was carried out by reaction with titanium tetrachloride (5~7 equiv.) in dichloromethane at 0°C. After conventional work-up,[1] the diazo-esters (**8A-b, c, 8B-a~c**) were obtained as oily substances. The properties of **8B-a** and **8B-b** are as follows.

8B-a: Yield quantitative. IR ν_{max}^{liquid} cm^{-1} 2140, 1750, 1720: NMR ($CDCl_3$) δ 1.28, 1.37 (each 3H, s), 1.9 (1H, b), 2.93 (1H, d, 2), 3.0~4.2 (3H, m), 5.35 (2H, s), 6.4 (1H, b), 7.53, 8.23 (each 2H, d, 9).

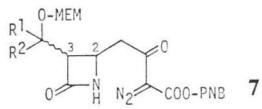
8B-b: Yield 93%. IR ν_{max}^{liquid} cm^{-1} 2140, 1750, 1720: NMR ($CDCl_3$) δ 1.6~2.7 (7H, m), 3.1~4.4 (4H, m), 5.33 (2H, s), 6.5 (1H, b), 7.48, 8.17 (each 2H, d, 9).

The other compounds (**8A-b, c, 8B-c**) were used in the subsequent reactions without characterization.

p-Nitrobenzyl 6-Hydroxyalkyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylates (9)

According to the procedure reported for the synthesis of **9A-a** from **8A-a**,[1] the dioxo-carbapenems (**9A-b, c, 9B-a~c**) were prepared from the corresponding diazoazetidinones (**8**) by reaction with a catalytic amount of rhodium (II) diacetate (*ca.* 0.05 equiv.) in benzene [or a mixture of benzene and

Table 7. *p*-Nitrobenzyl 2-diazo-4-[3-(2-methoxyethoxymethoxyalkyl)-4-oxoazetidin-2-yl]-3-oxobutanoates (7).

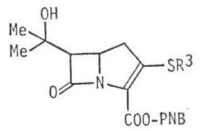


7

Compound (7)	R^1	R^2	Stereochemistry at C(2) and C(3)	Yield (%)	IR (state) (cm^{-1})	NMR, δ ($CDCl_3$)[a]
A-a[b]	Me	Me	*cis*			
B-a[c]	Me	Me	*trans*	73	2140, 1750, 1720 (Nujol)	1.33, 1.40 (each 3H, s), 2.93 (1H, d, 2), 3.37 (3H, s), 3.0~4.0 (7H, m), 4.83 (2H, s), 5.39 (2H, s), 6.1 (1H, s)
A-b[d]	$-(CH_2)_3-$		*cis*	89	2130, 1750, 1720 (liquid)	1.7~2.7 (6H, m), 3.34 (3H, s), 3.3~3.9 (7H, m), 4.1 (1H, m), 4.79 (2H, s), 5.34 (2H, s), 6.2 (1H, b)
B-b[d]	$-(CH_2)_3-$		*trans*	91	2140, 1760, 1720 (liquid)	1.7~2.8 (6H, m), 3.0~3.4 (3H, m), 3.36 (3H, s), 3.3~4.2 (5H, m), 4.83 (2H, s), 5.33 (2H, s), 6.40 (1H, b)
A-c[d]	Me (Et)	Et (Me)	*cis*	79	2140, 1760, 1720 (liquid)	0.78 (3H, t, 7), 1.49 (3H, s), 1.75 (2H, m), 3.32 (3H, s), 3.3~3.8 (7H, m), 4.1 (1H, m), 4.81 (0.6H, s), 4.85 (1.4H, s), 5.34 (2H, s), 6.12 (1H, b)
B-c[d]	Me (Et)	Et (Me)	*trans*	95	2140, 1760, 1720 (liquid)	0.88 (3H, t, 7), 1.25 (2.5H, s), 1.32 (0.5H, s), 1.73 (2H, m), 3.05 (1H, d, 2), 3.34 (3H, s), 3.4~3.8 (6H, m), 4.0 (1H, m), 4.80 (2H, s), 5.35 (2H, s), 6.1 (1H, b)

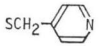
[a] Absorptions of aromatic protons of *p*-nitrobenzyl group are not given in Table for convenience.
[b] For the properties; see reference 1.
[c] Colorless prisms, mp 98~100°C, *Anal.* Calcd. for $C_{21}H_{26}N_4O_9$: C 52.71, H 5.48, N 11.71. Found: C 52.65, H 5.39, N 11.70.
[d] Oily substances.

Table 8–1. *p*-Nitrobenzyl 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (1). 3-(Substituted)thio-5,6-*cis*-6-(1-hydroxy-1-methylethyl) derivatives (**10A-a**).



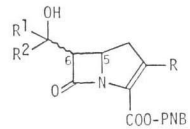
10A-a

Compound (**10A-a**)	SR^3	Yield[a] (%)	Mp (°C)	IR (KBr) (cm^{-1})	UV, nm[b] ($E^{1\%}_{1cm}$)	NMR, δ[c]	Analysis[d]
1	$S(CH_2)_2NH$ | CO_2PNB	53	120~123	1770	264 (303), 313 (165)	1.28, 1.52 (each 3H, s), 3.02 (3H, m), 3.60 (1H, d, 6), 4.0~4.4 (2H, m), 5.18 (2H, s), 5.36 (2H, ABq, 29, 14)	$C_{27}H_{28}N_4O_{10}S$
2	$S(CH_2)_3NH$ | CO_2PNB	42	—[e]	1770	264 (280), 318 (164)	1.29, 1.51 (each 3H, s), 1.8~2.0 (2H, m), 2.7~3.4 (5H, m), 3.59 (1H, d, 6), 4.0~4.5 (2H, m), 5.18 (2H, s), 5.31 (2H, ABq, 24, 15)	—[f]
5	$SCH_2C(=NH)NH_2$[g]				265 (—), 315 (—)		
6	$S(CH_2)_2NMe_2$	40	148~150	1770	266 (265), 317.5 (291)	1.27, 1.52 (each 3H, s), 2.26 (6H, s), 2.2~3.3 (5H, m), 3.57 (1H, d, 6), 4.0~4.4 (2H, m), 5.33 (2H, ABq, 23, 14)	$C_{21}H_{23}N_3O_6S$
7		35	172~174	1760	264 (243), 318 (272)	1.29, 1.52 (each 3H, s), 1.7~3.2 (13H, m), 3.59 (1H, d, 6), 4.05~4.32 (2H, m), 5.37 (2H, ABq, 24, 15)	$C_{23}H_{29}N_3O_6S$
8[h]	$S(CH_2)_2NHAc$						
10	SEt	50	133~135	1770	262 (247), 317.5 (244)	1.27, 1.47 (each 3H, s), 1.30 (3H, t, 7), 2.87 (2H, q, 7), 2.8~3.2 (1H, m), 3.57 (1H, d, 6), 3.9~4.4 (2H, m), 5.30 (2H, ABq, 22, 14)	$C_{19}H_{22}N_2O_6S \cdot H_2O$
11	$S(CH_2)_2OH$	29	129~133	1770	265 (262), 318 (280)	1.27, 1.49 (each 3H, s), 2.9~3.1 (3H, m), 3.55 (1H, d, 6), 3.6~4.3 (4H, m), 5.32 (2H, ABq, 24, 15)	$C_{19}H_{22}N_2O_7S$

12	$S(CH_2)_2OEt$	44	150~151	1760	263 (250), 315 (279)	1.12 (3H, t, 7), 1.28, 1.52 (each 3H, s), 2.82~3.61 (8H, m), 3.80~4.23 (2H, m), 5.20 (2H, ABq, 24, 15)	$C_{21}H_{26}N_2O_7S$
13	$SCH_2CONHMe$	37	187~188	1755	266 (251), 315 (279)	1.20, 1.38 (each 3H, s), 2.63 (3H, d, 4), 2.98~4.28 (4H, m), 3.57 (2H, s), 5.35 (2H, ABq, 24, 15)	$C_{20}H_{22}N_3O_7S$
14	SC_6H_5	55	165~167	1770	265 (282), 315 (333)	1.12, 1.48 (each 3H, s), 2.39 (1H, dd, 16, 8), 3.53 (1H, d, 6), 3.4~4.4 (2H, m), 5.41 (2H, ABq, 22, 14)	$C_{23}H_{22}N_2O_6S$
15		42	159~160	1770	263 (293), 320 (332)	1.25, 1.53 (each 3H, s), 3.09 (1H, dd, 17, 9), 3.58 (1H, d, 6), 3.95 (1H, dd, 17, 8), 4.31 (1H, m), 5.37 (2H, ABq, 24, 15)	$C_{22}H_{21}N_3O_6S$
16		55	160~162	1775	262 (164), 315 (165)	1.24, 1.50 (each 3H, s), 3.5~3.8 (1H, m), 3.63 (1H, d, 6), 4.0~4.5 (2H, m), 5.39 (2H, ABq, 25, 14)	$C_{21}H_{20}N_4O_6S$
17		48	164~166	1780	263 (154), 320 (162)	1.27, 1.51 (each 3H, s), 2.43 (6H, s), 3.4~3.8 (1H, m), 3.65 (1H, d, 6), 4.2~4.5 (2H, m), 5.40 (2H, ABq, 25, 14)	$C_{23}H_{24}N_4O_6S$
18		48	159~160	1750	264 (274),[i] 310 (222)	—[j]	$C_{21}H_{20}N_4O_6S$
19	$SCH_2C_6H_5$	41	180~181	1760	265 (255), 320 (312)	1.20, 1.49 (each 3H, s), 2.96 (1H, dd, 17, 9), 3.58 (1H, d, 6), 4.13 (2H, s), 3.9~4.3 (2H, m), 5.36 (2H, ABq, 24, 15)	$C_{24}H_{24}N_2O_6S$
20		45	181~182	1770	262 (291), 315 (293)	1.13, 1.20 (each 3H, s), 3.0~3.29 (1H, m), 3.57 (1H, d, 6), 3.94~4.37 (2H, m), 4.17 (2H, s), 5.31 (2H, ABq, 21, 15)[k]	$C_{23}H_{23}N_3O_6S$

[a] Based on **8A-a**. [b] Measured in EtOH unless otherwise stated. [c] Measured in $CDCl_3$ unless otherwise stated. Absorptions of aromatic protons and protons of NH and OH groups are not given for convenience. [d] All the compounds given the formula were analyzed for C, H and N; analytical results obtained for these elements were within ± 0.4 % of calculated values. [e] A pale yellow foam. [f] Not analyzed. [g] Crude product was used for the subsequent reaction without characterization; only UV spectrum was measured qualitatively. [h] For the properties; see reference 1. [i] Measured in MeOH. [j] Not measured. [k] Measured in DMSO-d_6.

Table 8–2. *p*-Nitrobenzyl 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (2).



10, 12

Compound No.	R^1	R^2	R	Stereochemistry at C(5) and C(6)	Yield (%)	Mp (°C)	IR (KBr) (cm^{-1})	UV (EtOH) nm ($E^{1\%}_{1cm}$)	NMR, δ ($CDCl_3$)[a]	Analysis[b]
10B-a-1	Me	Me	$S(CH_2)_2NH$ | CO_2PNB	*trans*	49[c]	—[d]	1765	265 (316), 315 (187)	1.32, 1.40 (each 3H, s), 2.8~3.7 (7H, m), 4.21 (1H, dt, 9, 3), 5.17 (2H, s), 5.34 (2H, ABq, 27, 14)	—[e]
10A-b	$-(CH_2)_3-$			*cis*	21[f]	—[d]	1760	270 (—),[g] 320 (—)	1.5~2.8 (6H, m), 3.6 (1H, m), 3.97 (1H, d, 6), 4.0~4.6 (2H, m), 5.43 (2H, ABq, 25, 14)	—[e]
10B-b	$-(CH_2)_3-$			*trans*	37[c]	—[d]	1760	260 (—),[g] 322 (—)	1.7~2.6 (6H, m), 3.26 (1H, d, 3), 3.4 (2H, m), 4.1 (1H, m), 5.33 (2H, ABq, 25, 14)	—[e]
10A-c	Me (Et)	Et (Me)	$S(CH_2)_2NH$ | CO_2PNB	*cis*	28[f]	115~120	1775	264 (290), 310 (162)	0.8~1.8 (5H, m), 1.23 (0.9H, s), 1.48 (2.1H, s), 3.02 (3H, m), 3.46 (2H, m), 3.60 (1H, d, 6), 4.0~4.4 (2H, m), 5.20 (2H, s), 5.36 (2H, ABq, 24, 15)	$C_{28}H_{30}N_4O_{10}S$
10B-c	Me (Et)	Et (Me)	$S(CH_2)_2NH$ | CO_2PNB	*trans*	33[f]	—[d]	1775	264 (342), 315 (184)	0.9~1.7 (5H, m), 1.22 (3H, s), 3.01 (4H, m), 3.35 (2H, m), 3.95~4.30 (2H, m), 5.10 (2H, s), 5.38 (2H, ABq, 24, 15)	—[e]
12A-a-1	Me	Me	OMe	*cis*	43[c]	147~149	1760	274 (400)	1.25, 1.50 (each 3H, s), 2.81 (1H, dd, 20, 12), 3.57 (1H, d, 6), 3.3~4.3 (2H, m), 3.93 (3H, s), 5.32 (2H, ABq, 20, 14)	$C_{18}H_{20}N_2O_7$
12A-a-2	Me	Me	$O(CH_2)_2OEt$	*cis*	38[c]	143~145	1760	274 (355)	1.07 (3H, t, 7), 1.27, 1.50 (each 3H, s), 2.90 (1H, dd, 20, 13), 3.4~4.4 (9H, m), 5.32 (2H, ABq, 20, 14)	$C_{21}H_{26}N_2O_8$
12B-a-1	Me	Me	OMe	*trans*	35[c]	158~160	1760	268 (388)	1.35, 1.40 (each 3H, s), 3.0~3.4 (2H, m), 3.90 (3H, s), 4.1 (1H, m), 5.30 (2H, ABq, 20, 14)	$C_{18}H_{20}N_2O_7$

[a] Absorptions of aromatic protons and protons of NH and OH groups are not given in Table for convenience. [b] All the compounds given the formula were analyzed for C, H and N; analytical results obtained for these elements were within ±0.4% of calculated values. [c] Based on the corresponding **8**. [d] Pale yellow forms. [e] Not analyzed. [f] Based on the corresponding **7**. [g] Not determined.

THF (1: 1)] at 78°C for 30 minutes under nitrogen. Evaporation of the solvent gave **9**.

9B-a: Yield quantitative (oil). IR ν_{max}^{liquid} cm^{-1} 1720~1780: NMR ($CDCl_3$) δ 1.33, 1.43 (each 3H, s), 2.1~4.3 (4H, m), 3.30 (3H, d, 2), 4.80 (1H, s), 5.27 (2H, s), 7.50, 8.17 (each 2H, d, 9).

The other compounds (**9A-b**, **c**, **9B-b**, **c**) were used in the subsequent reactions without characterization.

p-Nitrobenzyl 3-(Substituted)thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (**10**)

As a typical example, the preparation of **10A-a**-1 from **9A-a** is described. To a stirred, cooled (0°C) solution of 3-oxocarbapenem (**9A-a**),[1] prepared from the compound **8A-a** (250 mg, 0.52 mmol), in dry acetonitrile (20 ml) under nitrogen were added diisopropylethylamine (0.12 ml, 0.7 mmol) and diphenyl chlorophosphate (0.14 ml, 0.7 mmol). The mixture was stirred for 1.5 hours at 0°C and then diisopropylethylamine (0.2 ml, 1.1 mmol) and *N*-(*p*-nitrobenzyloxycarbonyl)cysteamine (250 mg, 1.0 mmol) were added. After being stirred for 2 hours at 0°C and kept at −20°C for 16 hours, the mixture was diluted with ethyl acetate, washed with water, dried and evaporated to dryness. The residue was subjected to chromatography on Florisil using acetone - hexane (1: 1, v/v) as eluant to give **10A-a**-1 (170 mg) as pale yellow prisms. The other compounds (**10**) listed in Tables 8–1 and 8–2, except **10A-a**-13, 15~18, **10A-b** and **10B-b**, were similarly prepared by reacting with the corresponding thiol derivatives (*vide infra*) in place of *N*-(*p*-nitrobenzyloxycarbonyl)cysteamine. The compounds, **10A-a**-15~18, **10A-b** and **10B-b** were prepared using lithium salts of the corresponding thiol derivatives and **10A-a**-13 was prepared using silver salt of the thiol derivative.

p-Nitrobenzyl 3-Alkoxy-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylates (**12**)

As a typical example, the preparation of **12A-a**-1 is described. To a stirred solution of the 3-oxocarbapenems (**9A-a**),[1] prepared from the compound **8A-a** (234 mg, 0.5 mmol), in dichloromethane (20 ml) was added excess diazomethane (*ca.* 5 mmol) in ether (20 ml) and the mixture was stirred for 1 hour at 25°C. A trace of rhodium (II) diacetate was added to decompose excess diazomethane. The mixture was filtered through Celite and the solvent was evaporated to dryness. The residue was subjected to chromatography on Florisil using hexane - ethyl acetate (1: 2, v/v) as eluant to give **12A-a**-1 as colorless crystals (80 mg). Similarly, **12B-a**-1 was prepared from **9B-a** and diazomethane, and **12A-a**-2 was prepared from **9A-a** and 2-ethoxydiazoethane.[12,13] The results are summarized in Table 8–2.

p-Nitrobenzyl 5,6-*cis*-6-[1-(2-Methoxyethoxymethoxy)-1-methylethyl]-3,7-dioxo-1-azabicyclo[3.2.0]-heptane-2-carboxylate (**14**)

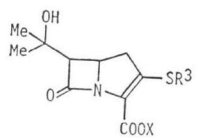
A suspension of the diazoazetidinone (**7A-a**) (320 mg, 0.67 mmol) and a catalytic amount of rhodium (II) diacetate (16 mg) in dry benzene was heated at 78°C for 45 minutes under nitrogen. After being cooled to room temperature the mixture was filtered through Celite and the filtrate was evaporated to dryness to give **14** (0.30 g, quantitative) as a pale yellow oil, which was used without further purification for the subsequent reactions. IR ν_{max}^{liquid} cm^{-1} 1740~1780: NMR ($CDCl_3$) δ 1.30, 1.51 (each 3H, s), 2.60 (1H, dd, 8, 7), 3.8~4.4 (2H, m), 4.65 (1H, s), 4.71 (2H, s), 5.20 (2H, s), 7.42, 8.10 (each 2H, d, 9).

p-Nitrobenzyl 5,6-*cis*-3-(2-Acetamidoethylthio)-6-[1-(2-methoxyethoxymethoxy)-1-methylethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**15**)

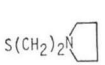
To a stirred, cooled (0°C) solution of the 3-oxocarbapenem (**14**) (0.30 g, 0.67 mmol) in dry acetonitrile (25 ml) under nitrogen were added diisopropylethylamine (0.145 ml, 0.83 mmol) and diphenyl chlorophosphate (0.172 ml, 0.83 mmol). The mixture was stirred for 75 minutes at 0°C and then diisopropylethylamine (0.17 ml, 1 mmol) and *N*-acetylcysteamine (120 mg, 1 mmol) were added. After being stirred for 2 hours at 0°C, the mixture was treated with further quantities of diisopropylethylamine (0.17 ml, 1 mmol) and *N*-acetylcysteamine (120 mg, 1 mmol), and then stirred for 17 hours at 0°C. The mixture was diluted with ethyl acetate, washed with water, dried, and evaporated to dryness. The residue was subjected to chromatography on silica gel using ethyl acetate - methanol (95 : 5, v/v) as eluant to give **15** (270 mg, 73%) as colorless crystals.

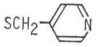
Mp 128~130°C. IR ν_{max}^{Nujol} cm^{-1} 1775, 1700, 1650: UV λ_{max}^{EtOH} nm ($E_{1cm}^{1\%}$) 265 (209), 315 (239):

Table 9–1. 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acids (1). 3-(Substituted)thio-5,6-*cis*-6-(1-hydroxy-1-methylethyl) derivatives (**11A-a**).



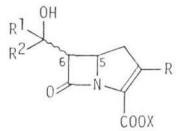
11A-a

Compound (**11A-a**)	SR^3	X	IR (KBr) (cm^{-1})	UV (H_2O) nm ($E^{1\%}_{1cm}$)	NMR, δ (D_2O)	Yield[b] (%)
1	$S(CH_2)_2NH_2$	H	1750	295 (219)	1.32, 1.45 (each 3H, s), 2.9~3.3 (5H, m), 3.76 (1H, d, 6), 3.9 (1H, m), 4.4 (1H, m)	45
2	$S(CH_2)_3NH_2$	H	1740	298 (246)	1.44, 1.57 (each 3H, s), 1.9~2.3 (2H, m), 2.9~3.4 (5H, m), 3.86 (1H, d, 6), 3.8~4.2 (1H, m), 4.3~4.6 (1H, m)	43
3	$S(CH_2)_2NHCH{=}NH$	H	1750, 1715	296 (230)	1.43, 1.56 (each 3H, s), 3.0~3.4 (3H, m), 3.6~4.2 (3H, m), 3.87 (1H, d, 6), 4.4 (1H, m), 8.00 (1H, s)	70[c]
4	$S(CH_2)_3NHCH{=}NH$	H	1750, 1715	298 (261)	1.41, 1.58 (each 3H, s), 1.9~2.3 (2H, m), 2.9~3.4 (5H, m), 3.85 (1H, d, 6), 3.5~4.1 (1H, m), 7.95 (1H, s)	77[c]
5	$SCH_2C(=NH)NH_2$	H	1750	292 (221)	1.49, 1.62 (each 3H, s), 3.14 (1H, dd, 17, 10), 3.89~4.76 (5H, m)	29[d]
6	$S(CH_2)_2NMe_2$	H	1750	294 (177)	1.42, 1.55 (each 3H, s), 2.75 (6H, s), 3.19 (4H, s), 3.2 (1H, m), 3.85 (1H, d, 6), 3.7~4.2 (1H, m), 4.45 (1H, m)	32
7		H	1750	292 (197)	1.49, 1.62 (each 3H, s), 2.13~2.34 (4H, m), 2.93~3.62 (9H, m), 3.90 (1H, d, 6), 3.87~4.15 (1H, m), 4.51 (1H, m)	60
8[e]	$S(CH_2)_2NHAc$	Na				57 (82)[f]
9	$S(CH_2)_3NHAc$	Na	1750, 1635	299 (248)	1.33 (3H×2, s), 1.7~2.0 (2H, m), 2.02 (3H, s), 2.8~4.0 (6H, m), 3.74 (1H, d 6), 4.3 (1H, m)	42[f]
10	SEt	Na	1750	297 (268)	1.38 (3H, t, 7), 1.43, 1.53 (each 3H, s), 2.98 (2H, q, 7), 3.23 (1H, dd, 17, 10), 3.83 (1H, d, 6), 3.98 (1H, dd, 17, 9), 4.4 (1H, m)	44
11	$S(CH_2)_2OH$	Na	1750	298 (248)	1.45, 1.60 (each 3H, s), 3.11 (2H, t, 9), 3.20 (1H, dd, 17, 10), 3.88 (1H, d, 6), 3.8~4.1 (3H, m), 4.45 (1H, m)	50

12	$S(CH_2)_2OEt$	Na	1755	297 (269)	1.30 (3H, t, 7), 1.42, 1.56 (each 3H, s), 3.17~3.46 (3H, m), 3.37~4.26 (5H, m), 4.48~4.72 (2H, m)	27
13	$SCH_2CONHMe$	Na	1750	296 (186)	1.48, 1.57 (each 3H, s), 3.07~4.30 (4H, m), 3.03 (3H, s), 3.88 (2H, s)	67
14	SC_6H_5	Na	1750	300 (329)	1.25, 1.50 (each 3H, s), 2.53 (1H, q, 17, 10), 3.60 (1H, q, 17, 9), 3.75 (1H, d, 6), 4.25 (1H, m), 7.6 (5H, m)	45
15		Na	1750	304 (353)	1.20, 1.42 (each 3H, s), 2.70 (1H, dd, 17, 10), 3.58 (1H, dd, 17, 9), 3.71 (1H, d, 6), 4.30 (1H,m), 7.4~8.5 (4H, m)	51
16		Na	1750	295 (336)	1.26, 1.42 (each 3H, s), 3.19 (1H, dd, 17, 10), 3.68 (1H, dd, 17, 9), 3.78 (1H, d, 6), 4.40 (1H, m), 7.34 (1H, t, 5), 8.66 (2H, d, 5)	72
17		Na[g]	1750	300 (338)	1.25, 1.42 (each 3H, s), 2.45 (6H, s), 3.15 (1H, dd, 17, 10), 3.68 (1H, dd, 17, 9), 3.76 (1H, d, 6), 4.4 (1H, m), 7.12 (1H, s)	62
18		Na	1750	296 (276)	1.32, 1.53 (each 3H, s), 2.90 (1H, dd, 17, 10), 3.71 (1H, dd, 17, 9), 3.86 (1H, d, 6), 4.47 (1H, m), 7.76~9.26 (3H, m)	45
19	$SCH_2C_6H_5$	Na	1740	300 (275)	1.39, 1.51 (each 3H, s), 3.17 (1H, dd, 17, 10), 3.78 (1H, d, 6), 3.80~4.43 (2H, m), 4.28 (2H, s), 7.60 (5H, s)	44
20		Na[h]	1750	262 (144), 298 (252)	1.35, 1.49 (each 3H, s), 3.07 (1H, dd, 17, 10), 3.75 (1H, dd, 17, 9), 3.76 (1H, d, 6), 4.25 (2H, s), 4.30 (1H, m), 7.62 (1H, d, 6), 8.61 (1H, d, 6)	41

[a] All the compounds were obtained as colorless powders. [b] By hydrogenolysis of the corresponding *p*-nitrobenzyl esters unless otherwise stated, and yields were calculated on the anhydrous basis. [c] By reaction of the corresponding amino derivatives (**11A-a**-1, 2) with benzyl formimidate. [d] Overall yield from **8A-a**. [e] For the properties; see reference 1. [f] By acetylation of the corresponding amino derivatives (**11A-a**-1, 2). [g] *Anal.* Calcd. for $C_{16}H_{18}N_3NaO_4S \cdot 2H_2O$: C 47.17, H 5.44, N 10.31, Na 5.64. Found: C 46.82, H 5.39, N 10.09, Na 5.60. [h] *Anal.* Calcd. for $C_{16}H_{17}N_2NaO_4S \cdot 3H_2O$: Na 5.60. Found: Na 5.40.

Table 9–2. 7-Oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acids (2).



11, 13

Compound[a] No.	R^1	R^2	R	X	Stereochemistry at C(5) and C(6)	IR (KBr) (cm^{-1})	UV (H_2O) nm ($E^{1\%}_{1cm}$)	NMR, δ (D_2O)	Yield[b] (%)
11B-a-1	Me	Me	$S(CH_2)_2NH_2$	H	*trans*	1755	296 (260)	1.33, 1.38 (each 3H, s), 3.1~3.3 (6H, m), 3.48 (1H, d, 2), 4.25 (1H, m)	46
11B-a-2	Me	Me	$S(CH_2)_2NHAc$	Na	*trans*	1750, 1640	300 (239)	1.43, 1.47 (each 3H, s), 2.12 (3H, s), 2.8~3.7 (7H, m), 4.31 (1H, dt, 9, 3)	91[c]
11A-b	$-(CH_2)_3-$			Na	*cis*	1750	295 (239)	1.7~2.6 (6H, m), 3.3 (2H, m), 4.15 (1H, d, 6), 4.50 (1H, m), 7.50 (1H, t, 5), 8.84 (2H, d, 5)	25
11B-b	$-(CH_2)_3-$			Na	*trans*	1760	295 (242)	1.7~2.6 (6H, m), 3.4 (2H, m), 3.93 (1H, d, 3), 4.5 (1H, m), 7.56 (1H, t, 5), 8.90 (2H, d, 5)	51
11A-c	Me (Et)	Et (Me)	$S(CH_2)_2NH_2$	H	*cis*	1755	294 (205)	1.10 (3H, t, 7), 1.41 (0.9H, s), 1.59 (2.1H, s), 1.82 (2H, m), 2.8~3.43 (5H, m), 3.94 (1H, d, 6), 3.97 (1H, m), 4.50 (1H, m)	18
11B-c	Me (Et)	Et (Me)	$S(CH_2)_2NH_2$	H	*trans*	1755	295 (217)	1.11 (3H, t, 7), 1.42 (2.5H, s), 1.52 (0.5H, s), 1.84 (2H, m), 3.13~3.54 (5H, m), 3.74 (1H, d, 2), 4.09~4.61 (2H, m)	23
13A-a-1	Me	Me	OMe	Na	*cis*	1760	272 (216)	1.43, 1.55 (each 3H, s), 3.10 (1H, dd, 17, 9), 3.81 (1H, d, 6), 3.8~4.5 (2H, m), 3.90 (3H, s)	57
13A-a-2	Me	Me	$O(CH_2)_2OEt$	Na	*cis*	1755	274 (200)	1.22 (3H, t, 7), 1.34, 1.46 (each 3H, s), 3.02 (1H, ABq, 17, 9), 3.67 (2H, q, 7), 3.75~4.3(3H, m)	68
13B-a-1	Me	Me	OMe	Na	*trans*	1755	274 (195)	1.43, 1.47 (each 3H, s), 3.27 (2H, d, 9), 3.50 (1H, d, 3), 3.92 (3H, s), 4.20 (1H, dt, 9, 3)	55

[a], [b] See the corresponding footnotes in Table 9–1. [c] By acetylation of **11B-a-1**.

NMR ($CDCl_3$) δ 1.35, 1.52 (each 3H, s), 1.96 (3H, s), 2.8~3.7 (10H, m), 3.33 (3H, s), 3.9~4.4 (2H, m), 4.77 (2H, s), 5.35 (2H, ABq, 20, 14), 6.2 (1H, b), 7.61, 8.20 (each 2H, d, 9).

Anal. Calcd. for $C_{25}H_{33}N_3O_9S$: C 54.44, H 6.03, N 7.61.
Found: C 54.40, H 5.78, N 7.61.

Deprotection of the *p*-Nitrobenzyl Group of the Carbapenem Esters (**10**, **12**, **15**) by Hydrogenolysis

As a typical example, the preparation of **11A-a**-1 from **10A-a**-1 is described. A mixture of **10A-a**-1 (140 mg, 0.23 mmol) and 10% palladium-charcoal (140 mg) in THF (28 ml), pH 7.0 phosphate buffer (14 ml) and water (14 ml) was stirred under hydrogen at room temperature for 2 hours. After a further quantity of 10% palladium-charcoal (140 mg) had been added, the mixture was stirred for another 3.5 hours under hydrogen. The catalyst was filtered off and washed with water. The filtrate was evaporated to remove THF, washed with ethyl acetate, and concentrated under reduced pressure to *ca.* 5 ml. The concentrate was subjected to chromatography on Amberlite XAD-2 with water and 5% (v/v) aqueous EtOH as eluants. The fractions eluted with 5% aqueous EtOH were collected and lyophilized to give **11A-a**-1 (30 mg) as a colorless powder. The compounds (**11**, **13**) listed in Tables 9–1 and 9–2, except **11A-a**-3, 4, 9 and **11B-a**-2, were similarly prepared from the corresponding carbapenem esters. The compound **16** was also prepared from **15** by a similar manner. The properties of **16** are as follows:

Yield 87% (a colorless powder). IR ν_{max}^{KBr} cm^{-1} 1740, 1640: UV λ_{max}^{EtOH} nm ($E_{1cm}^{1\%}$) 298 (212): NMR (D_2O) δ 1.36, 1.46 (each 3H, s), 2.01 (3H, s), 2.8~3.9 (11H, m), 3.33 (3H, s), 4.30 (1H, m), 4.83 (2H, s).

Sodium 5,6-*trans*-3-(2-Acetamidoethylthio)-6-(1-hydroxy-1-methylethyl)-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (**11B-a**-2)

A solution of **11B-a**-1 (20 mg, 0.07 mmol) in water (5 ml) and THF (5 ml) was treated at 0°C with a solution of sodium hydrogen carbonate (17 mg) in water (5 ml) and then with a solution of acetic anhydride (10 mg) in THF (2 ml). After the mixture was stirred for 30 minutes, the solution was concentrated under reduced pressure and the concentrate was subjected to chromatography on Amberlite XAD-2 with water and 5% (v/v) aqueous EtOH as eluants. The fractions eluted with 5% aqueous EtOH were collected and lyophilized to give **11B-a**-2 (23 mg) as a colorless powder. Similarly, the compounds (**11A-a**-8, 9) were prepared by acetylation of the corresponding amino derivatives (**11A-a**-1, 2). The IR, NMR, and UV spectra of **11A-a**-8 thus prepared were identical with those of the compound obtained by the hydrogenolysis of **10A-a**-8.[1]

5,6-*cis*-3-(2-Formimidolylaminoethylthio)-6-(1-hydroxy-1-methylethyl)-7-oxo-1-azabicyclo [3.2.0]-hept-2-ene-2-carboxylic Acid (**11A-a**-3)

A solution of **11A-a**-1 (44 mg, 0.15 mmol) in pH 7.0 phosphate buffer (11 ml) was treated with 2 N NaOH to adjust the pH to be 8.5 with ice-cooling. Benzyl formimidate (190 mg, 1.1 mmol) was added portion-wise to the mixture over 5 minutes and the pH of the mixture was maintained to be 8.5 by adding 2 N NaOH. The mixture was stirred for 5 minutes, treated with 1 N HCl to adjust the pH to be 7.0 and washed with ethyl acetate. The aqueous layer was concentrated under reduced pressure and the concentrate was subjected to chromatography on Diaion HP-20 using water and 3% (v/v) aqueous acetone as eluants. The fractions eluted with 3% aqueous acetone are combined and lyophilized to give **11A-a**-3 (32 mg) as a colorless powder. Similarly, **11A-a**-4 was prepared from **11A-a**-2. The properties of **11A-a**-3 and 4 are listed in Table 9–1.

Thiol Derivatives

The thiol derivatives used for the synthesis of **10** and **15** were obtained as follows. 2-(*p*-Nitrobenzyloxycarbonylamino)ethanethiol,[18] and 3-(*p*-nitrobenzyloxycarbonylamino)propanethiol,[19,20] were prepared from the corresponding amino derivatives and *p*-nitrobenzyl chloroformate. Mercaptoacetamidine,[21,22] *N*-acetylcysteamine,[23] and 3-pyridazinethiol[24] were prepared according to the reported procedures, respectively. 2-(1-Pyrrolidinyl)ethanethiol,[25] 2-ethoxyethanethiol,[26] 2-pyrimidinethiol,[27] 2-(4,5-dimethyl)pyrimidinethiol,[27] and 4-pyridinemethanethiol[28] were derived from the corresponding chloro derivatives by substitution reaction with NaSH in the presence of NaOH. 2-Mercapto-

N-methylacetamide silver salt was obtained from 2-triphenylmethylthio-*N*-methylacetamide (mp 222~224°C), which was prepared from 2-chloro-*N*-methylacetamide and triphenylmethanethiol, by treatment with silver nitrate in pyridine. The other thiol derivatives are those commercially available.

Acknowledgments

The authors thank Dr. K. MORITA of this division for encouragement throughout this work. Thanks are also due to Misses Y. NOJI and E. SAGA for their skillful assistance.

References

1) NATSUGARI, H.; Y. MATSUSHITA, N. TAMURA, K. YOSHIOKA & M. OCHIAI: Synthesis of *cis*-carbapenems related to C-19393 H_2. J. Chem. Soc., Perkin I, 1983: 403~411, 1983
2) IMADA, A.; Y. NOZAKI, K. KINTAKA, K. OKONOGI, K. KITANO & S. HARADA: C-19393 S_2 and N_2, new carbapenem antibiotics. I. Taxonomy of the producing strain, fermentation and antibacterial properties. J. Antibiotics 33: 1417~1424, 1980
3) HARADA, S.; S. SHINAGAWA, Y. NOZAKI, M. ASAI & T. KISHI: C-19393 S_2 and H_2, new carbapenem antibiotics. II. Isolation and structures. J. Antibiotics 33: 1425~1429, 1980
4) HARADA, S.; S. TSUBOTANI, S. SHINAGAWA & M. ASAI: Stereo-chemical studies on the sulfoxide of 5,6-*cis*-carbapenem antibiotics, C-19393 components. Tetrahedron 39: 75~82, 1983
5) NAKAYAMA, M.; A. IWASAKI, S. KIMURA, T. MIZOGUCHI, S. TANABE, A. MURAKAMI, M. OKUCHI, H. ITOH, Y. SAINO, F. KOBAYASHI & T. MORI: Carpetimycins A and B, new β-lactam antibiotics. J. Antibiotics 33: 1388~1389, 1980
6) NAKAYAMA, M.; S. KIMURA, S. TANABE, T. MIZOGUCHI, I. WATANABE, T. MORI, K. MIYAHARA & T. KAWASAKI: Structures and absolute configurations of carpetimycins A and B. J. Antibiotics 34: 818~823, 1981
7) HARADA, S.; S. TSUBOTANI, M. ASAI, K. OKONOGI & M. KONDO: Synthesis and biological activities of Z isomers of carbapenem antibiotics. J. Med. Chem. 26: 271~275, 1983
8) RATCLIFFE, R. W.; T. N. SALZMANN & B. G. CHRISTENSEN: A novel synthesis of the carbapen-2-em ring system. Tetrahedron Lett. 21: 31~34, 1980
9) LEANZA, W. J.; K. J. WILDONGER, T. W. MILLER & B. G. CHRISTENSEN: *N*-Acetimidoyl- and *N*-formimidoylthienamycin derivatives: Antipseudomonal β-lactam antibiotics. J. Med. Chem. 22: 1435~1436, 1979
10) KROPP, H.; J. G. SUNDELOF, J. S. KAHAN, F. M. KAHAN & J. BIRNBAUM: MK 0787 (*N*-formimidoyl thienamycin): Evaluation of *in vitro* and *in vivo* activities. Antimicrob. Agents Chemother. 17: 993~1000, 1980
11) OKUCHI, M.; M. NAKAYAMA, A. IWASAKI, S. KIMURA, T. MIZOGUCHI, S. TANABE, A. MURAKAMI, H. ITOH & T. MORI: Antibiotics and method for the preparation. Japanese Published Unexamined Patent Application 58-18,384, Feb. 2, 1983
12) SHIMIZU, B.; A. SAITO, T. NISHIMURA & M. NAKAHARA: Penicillin derivatives and method for the preparation. Japanese Published Unexamined Patent Application 54-103,885, Aug. 15, 1979
13) SHIMIZU, B.; A. SAITO, S. SUGAWARA & K. HIRAI: Azetidinone derivatives and method for the preparation. Japanese Published Unexamined Patent Application 56-115,788, Sept. 11, 1981
14) ALBERS-SCHÖNBERG, G.; B. H. ARISON, O. D. HENSENS, J. HIRSHFIELD, K. HOOGSTEEN, E. A. KACZKA, R. E. RHODES, J. S. KAHAN, F. M. KAHAN, R. W. RATCLIFFE, E. WALTON, L. J. RUSWINKLE, R. B. MORIN & B. G. CHRISTENSEN: Structure and absolute configuration of thienamycin. J. Am. Chem. Soc. 100: 6491~6499, 1978
15) OKONOGI, K.; M. KONDO & M. KUNO: The stabilities of β-lactam antibiotics to the mouse renal enzymes and their *in vitro* and *in vivo* antibacterial activities. In preparation
16) TSUCHIYA, K.; M. KIDA, M. KONDO, H. ONO, M. TAKEUCHI & T. NISHI: SCE-963, a new broad-spectrum cephalosporin: *In vitro* and *in vivo* antibacterial activities. Antimicrob. Agents Chemother. 14: 557~568, 1978
17) OKONOGI, K.; Y. NOZAKI, A. IMADA & M. KUNO: C-19393 S_2 and H_2, new carbapenem antibiotics. IV. Inhibitory activity against β-lactamases. J. Antibiotics 34: 212~217, 1981
18) CHRISTENSEN, B. G.; D. B. R. JOHNSTON & S. M. SCHMIDT: 3,6-Disubstituted-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acids. Japanese Published Unexamined Patent Application 54-66,697, May 29, 1979

19) BERGMANN, E. D. & A. KALUSZYNER: Reaction products of primary β-hydroxyamines with carbonyl compounds. XV. Condensation of carbonyl compounds with 3-mercaptopropylamine. Rec. Trav. Chim. 78: 327~330, 1959
20) CHRISTENSEN, B. G.; D. B. R. JOHNSTON & S. M. SCHMIDT: 3-Substituted-6-(1'-hydroxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acids. Japanese Published Unexamined Patent Application 54-66,696, May 29, 1979
21) CONWAY, T. T.; A. SHOEB & L. BAUER: Synthesis of α-mercaptoamidinium chlorides *via* the corresponding phosphorothioates. J. Pharm. Sci. 57: 455~459, 1968
22) CHRISTENSEN, B. G.; D. B. R. JOHNSTON & S. M. SCHMIDT: 2-Carbamimidoyl-6-substituted-1-carbadethiapen-2-em-3-carboxylic acids derivatives. Japanese Published Unexamined Patent Application 57-95,989, June 15, 1982
23) KUHN, R. & G. QUADBECK: Darstellung und Wirkungen von Acetylderivaten des Cysteamins. Chem. Ber. 84: 844~847, 1951
24) DUFFIN, G. F. & J. D. KENDALL: The structure and reactivity of pyridazine quaternary salts. J. Chem. Soc. 1959: 3789~3799, 1959
25) HAEFELE, J. W. & R. W. BROGE: Synthesis and properties of mercaptans having different degrees of acidity of the sulfhydryl group. Proc. Sci. Sect. Toilet Goods Assoc. 32: 52~59, 1959 (Chem. Abstr. 54: 17234, 1960)
26) SWALLEN, L. C. & C. E. BOORD: The synthesis of beta-bromoalkyl ethers and their use in further synthesis. J. Am. Chem. Soc. 52: 651~660, 1930
27) HUNT, R. R.; J. F. W. MCOMIE & E. R. SAYER: Pyrimidines. X. Pyrimidine, 4,6-dimethylpyrimidine and their 1-oxides. J. Chem. Soc. 1959: 525~530, 1959
28) NISHIMURA, H. & H. TAKAMATSU: Synthesis of aminothiol derivatives. Yakugaku Zasshi 84: 944~955, 1964