ORALLY ACTIVE CEPHALOSPORINS

II. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NEW 7β-[(Z)-2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-CEPHALOSPORINS WITH 1,2,3-TRIAZOLE IN C-3 SIDE CHAIN

MASAHARU KUME, TADATOSHI KUBOTA, YASUO KIMURA, HIROMU NAKASHIMIZU, KIYOSHI MOTOKAWA and MASAO NAKANO

Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu, Fukushima-ku, Osaka 553, Japan

(Received for publication August 19, 1992)

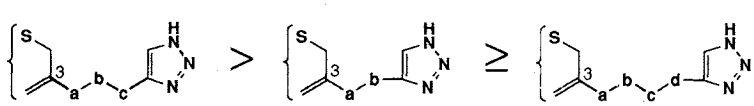
The synthesis, antibacterial activity and oral absorbability of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic acid (**1g**) and related compounds are described. Their oral absorbability was influenced by the spacer length between C-3 of a cephem nucleus and C-4′ of 1,2,3-triazole. The SCH_2S structure was also found to contribute to their good oral absorption. The quantitative relationship between the bioavailability and the spacer length of cephalosporins (**1a**～**1n**) is discussed.

Orally active cephalosporins bearing an aminothiazole moiety at the C-7 side chain, such as cefixime[1], ceftibuten[2] and cefdinir[3], have become a target of recent intensive research. Ceftibuten, which was found in our laboratories, has excellent oral bioavailability and potent activity against a broad range of Gram-negative bacteria. However ceftibuten shows only weak activity against most Gram-positive bacteria. For the improvement of this property, our effort was devoted to the synthesis of a new oral cephalosporin having good activity against both Gram-positive and Gram-negative bacteria.

In the previous paper[4] we described the synthesis and biological properties of 7-phenylglycyl cephalosporins with 1,2,3-triazole and other heteroaromatics in the C-3 side chain. Of these heteroaromatics, 1,2,3-triazole gave the best oral absorbability to these cephalosporins. The oral absorbability was also influenced by the spacer length between C-3 of a cephem nucleus and C-4′ of the 1,2,3-triazole. The spacer with the optimal length for good oral absorption was found to be a three-atom chain (Scheme 1).

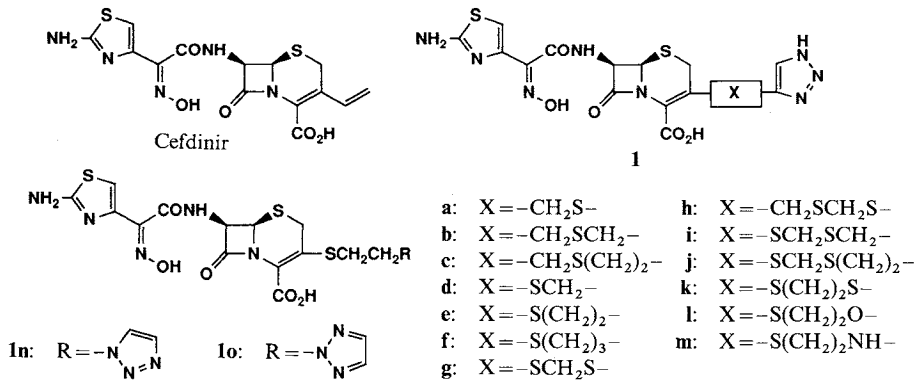
In this study, we applied this relationship between the spacer length and oral absorbability to the cephalosporins having the 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido group at the C-7 position; this C-7 side chain was expected to give these cephalosporins a broad antibacterial spectrum and some oral activity as shown in cefdinir. As a result of extensive syntheses of aminothiazole cephalosporins possessing a 1,2,3-triazole in the C-3 side chain (**1**) (Fig. 1), we ultimately obtained a novel orally active cephalosporin, 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic acid (**1g**), having both potent *in vitro* activity against a wide range of

Scheme 1. A spacer length for good oral absorbability in 7-phenylglycyl cephalosporins (**a**～**d**: C, O or S).

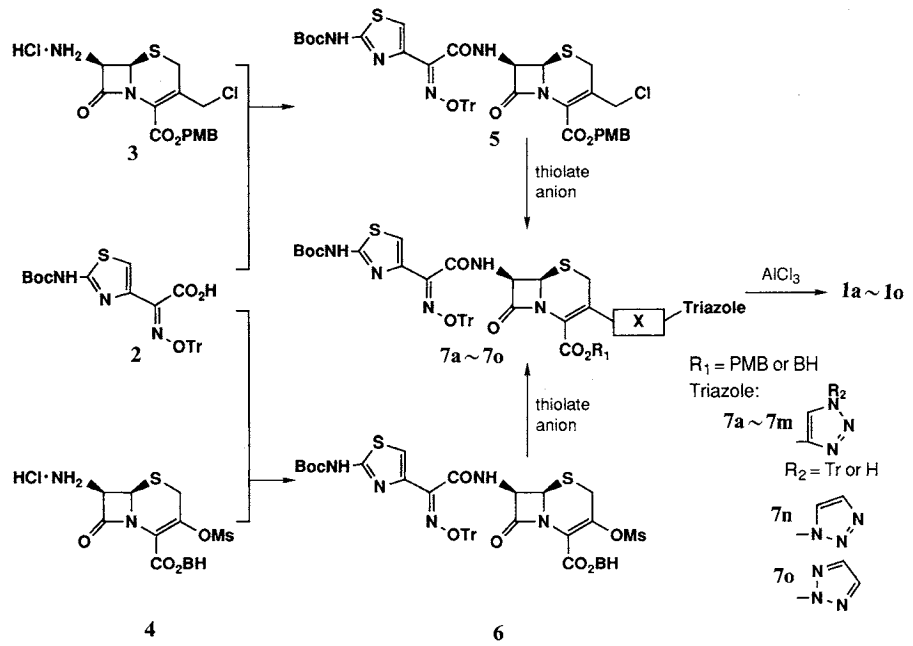


Oral absorbability in mice

Fig. 1. New cephalosporins with 1,2,3-triazole in the C-3 side chain.



Scheme 2.



Boc = *tert*-butoxycarbonyl, PMB = *p*-methoxybenzyl, BH = diphenylmethyl, Tr = triphenylmethyl.

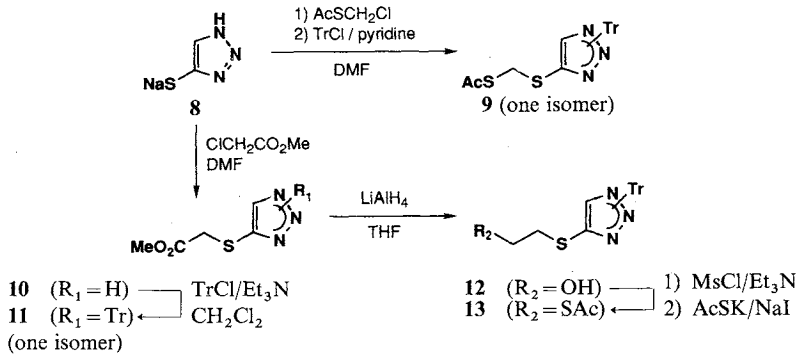
bacteria and excellent oral absorbability in mice and monkeys. This paper describes the synthesis and structure-activity relationships of the new cephalosporins (**1**).

Chemistry

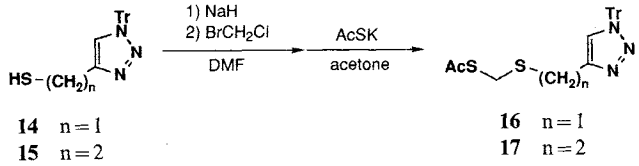
The new cephalosporins (**1a**~**1o**) were synthesized by the route outlined in Scheme 2.

p-Methoxybenzyl (PMB) [or diphenylmethyl(BH)] 7β-amino-3-chloromethyl(or 3-methanesulfonyloxy)-cephalosporin derivative (**3** or **4**) was coupled with the protected 2-aminothiazol-4-ylacetic acid derivative (**2**) to afford the 7β-acylaminocephalosporin derivative (**5** or **6**). Subsequently, the C-3 side chains were introduced into **5** or **6** by reaction with the corresponding thiolate anions to yield the protected 3-substituted

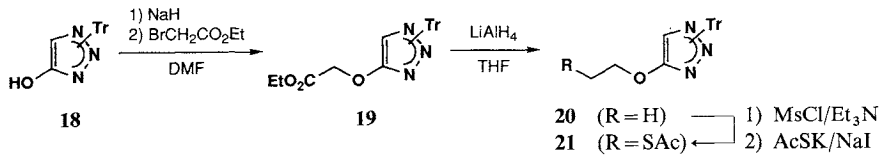
Scheme 3.



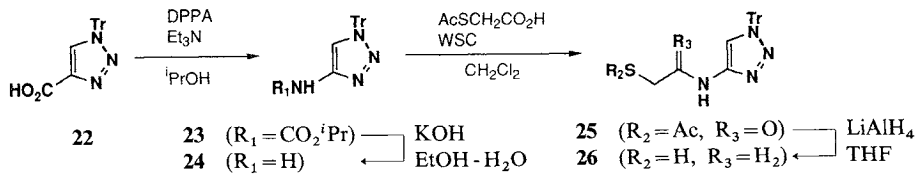
Scheme 4.



Scheme 5.



Scheme 6.



WSC = water soluble carbodiimide, DPPA = diphenyl phosphoryl azide.

Scheme 7.

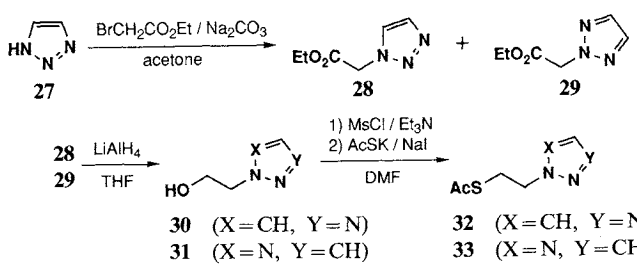


Table 1. *In vitro* antibacterial activity of cephem derivatives (**1a**~**1o**).

Organism	MIC (μg/ml)							
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
Staphylococcus aureus FDA 209P JC-1	0.2	0.2	0.1	0.2	0.1	0.1	0.2	0.1
S. aureus Smith	0.4	0.4	0.2	0.4	0.2	0.2	0.2	0.2
S. aureus SR3131	6.3	50	6.3	12.5	12.5	12.5	12.5	50
S. epidermidis ATCC 14990	0.2	0.2	0.1	0.1	0.2	0.1	0.2	0.1
Streptococcus pyogenes C-203	0.02	0.01	0.01	0.006	<0.003	<0.003	0.006	0.006
S. pneumoniae Type 1	0.05	0.1	0.05	0.02	0.02	0.02	0.02	0.02
S. faecalis SR 700	N.T.	25	12.5	3.1	3.1	3.1	3.1	12.5
Escherichia coli H	0.02	0.2	0.4	0.02	0.05	0.05	0.05	0.2
E. coli NIHJ JC-2	0.1	1.6	3.1	0.1	0.2	0.4	0.2	1.6
E. coli EC-14	0.05	0.8	0.8	0.05	0.1	0.1	0.1	0.4
E. coli SR377	0.4	6.3	6.3	0.4	1.6	0.8	1.6	3.1
Klebsiella pneumoniae SR1	0.02	0.4	0.8	0.05	0.05	0.1	0.1	0.4
Proteus mirabilis PR-4	0.05	0.2	0.4	0.05	0.05	0.05	0.05	0.1
P. vulgaris CN-329	0.05	0.4	0.2	0.8	0.4	0.1	0.2	0.1
Morganella morganii SR9	0.05	0.4	0.4	0.4	0.2	0.1	0.1	0.2
Enterobacter cloacae SR233	0.2	3.1	3.1	0.4	1.6	0.8	0.8	1.6
Serratia marcescens ATCC 13880	0.4	6.3	6.3	0.8	3.1	1.6	3.1	6.3
Pseudomonas aeruginosa ATCC 25619	100	>100	>100	>100	>100	>100	>100	>100

Organism	MIC (μg/ml)						
	1i	**1j**	**1k**	**1l**	**1m**	**1n**	**1o**
Staphylococcus aureus FDA 209P JC-1	0.1	0.1	0.1	0.2	0.2	0.2	0.2
S. aureus Smith	0.2	0.2	0.4	0.2	0.4	0.2	0.4
S. aureus SR3131	12.5	3.1	12.5	12.5	50	12.5	25
S. epidermidis ATCC 14990	0.1	0.1	0.1	0.2	0.2	0.2	0.2
Streptococcus pyogenes C-203	0.006	0.006	0.006	<0.003	0.006	0.006	0.006
S. pneumoniae Type 1	0.02	0.02	0.01	0.01	0.02	0.02	0.02
S. faecalis SR700	3.1	N.T.	6.3	3.1	6.3	6.3	6.3
Escherichia coli H	0.05	0.2	0.1	0.05	0.1	0.1	0.2
E. coli NIHJ JC-2	0.4	1.6	0.8	0.4	0.4	0.2	0.8
E. coli EC-14	0.2	0.4	0.4	0.2	0.2	0.1	0.4
E. coli SR377	1.6	1.6	1.6	1.6	3.1	0.8	1.6
Klebsiella pneumoniae SR1	0.1	0.4	0.2	0.1	0.1	0.1	0.4
Proteus mirabilis PR-4	0.1	0.2	0.05	0.05	0.1	0.1	0.2
P. vulgaris CN-329	0.1	0.2	0.2	0.2	0.2	0.2	0.8
Morganella morganii SR9	0.1	0.4	0.2	0.2	0.4	0.4	0.8
Enterobacter cloacae SR233	0.8	1.6	1.6	1.6	1.6	1.6	1.6
Serratia marcescens ATCC 13880	3.1	6.3	6.3	3.1	12.5	1.6	6.3
Pseudomonas aeruginosa ATCC 25619	>100	>100	>100	>100	>100	>100	>100

N.T.: Not tested.

cephalosporins (**7a**～**7o**). Each thiolate anion was prepared by methanolysis of the corresponding thioacetate with sodium methoxide or deprotonation of the corresponding thiol with sodium hydride. The preparation of several thiols used here have been reported in a previous paper[4]. The other thiols and thioacetates were synthesized by the method shown in Schemes 3～7. Finally, the protecting groups in **7a**～**7o** were removed by a conventional method using aluminum trichloride ($AlCl_3$) to obtain the desired cephalosporin derivatives (**1a**～**1o**).

Antibacterial Activity and Oral Absorption

The *in vitro* antibacterial activity of the new cephalosporins (**1**) against selected Gram-positive and Gram-negative bacteria is shown in Table 1. Their plasma levels and urinary recovery after oral administration (40 mg/kg) to mice are summarized in Table 2. Also shown is their relative bioavailability which was calculated according to the following equation, and we used this bioavailability as a measure of gastrointestinal absorption.

$$\text{Bioavailability (BA\%)} = \frac{\text{Urinary recovery after p.o. dosage}}{\text{Urinary recovery after s.c. dosage}} \times 100$$

Most of the new cephalosporins exhibited potent activity against the Gram-positive and Gram-negative bacteria except *Pseudomonas aeruginosa* ATCC 25619, irrespective of the spacer moiety. The derivatives with the sulfur atom directly attached to the C-3 position of the cephem nucleus (**1d**～**1g** and **1i**～**1o**) showed the higher activity against *Streptococcus pyogenes* C-203 and *Streptococcus faecalis* SR700 than the others. The comparison of the activity of **1e** with that of **1n** and **1o** showed that attachment of a 1,2,3-triazole to the spacer carbon at its nitrogen atom, especially at the N-2′ position, lowered the activity against both Gram-positive and Gram-negative bacteria.

Compounds (**1b**, **1e** and **1g**), which have three atoms as a spacer in the C-3 side chain, showed good oral absorbability in mice as expected from the correlation between the spacer length and the oral absorbability of 7-phenylglycyl cephalosporins in our previous paper[4]. Also, very high plasma levels were observed in compound **1g**. Furthermore, it is noteworthy that compounds (**1i** and **1m**) exhibited high oral absorbability although they have four atoms as a spacer in the C-3 side chain. All of the other compounds showed only a limited absorption. The compounds (**1n** and **1o**), the triazole moiety of

Table 2. Plasma levels, urinary recovery and oral bioavailability of cephem derivatives (**1a**～**1o**) in mice after oral administration of 40 mg/kg.

Compound	Plasma level (μg/ml)		Urinary recovery (%)	Bio-availability (%)
	15 minutes	120 minutes		
1a	1.26	1.15	1.3	6.3
1b	3.9	3.0	2.7	22
1c	1.45	0.77	1.6	7.0
1d	3.41	2.93	4.5	16
1e	6.06	3.35	6.9	24
1f	4.95	2.19	5.7	14
1g	29.6	51.3	5.5	36
1h	4.99	6.66	1.0	6.3
1i	12.1	4.31	7.6	50
1j	4.87	2.30	0.8	6.1
1k	2.05	1.86	1.2	4.5
1l	1.87	0.65	3.1	9.6
1m	11.4	4.00	6.5	53
1n	0.88	<0.73	2.2	5.3
1o	1.73	0.9	2.6	7.8

Mice: ICR-strain, 6-week-old male, n=5.

Table 3. Plasma levels and urinary recovery of **1g**, **1i** and **1m** in monkeys after oral administration of 10 mg/kg.

Compound	AUC (μg·hour/ml)	Cmax (μg/ml)	Urinary recovery (%)
1g	24.2±8.9	8.7±2.2	10.7±4.7
1i	1.9±0.7	1.2±0.3	6.0±2.3
1m	1.6±0.3	1.1±0.2	8.2±4.9

AUC: The area under the concentration curve. Monkeys: Cynomolgus, female, n=3 (for **1i** and **1m**) or 6 (for **1g**).

Fig. 2. Correlation between log BA and D value.

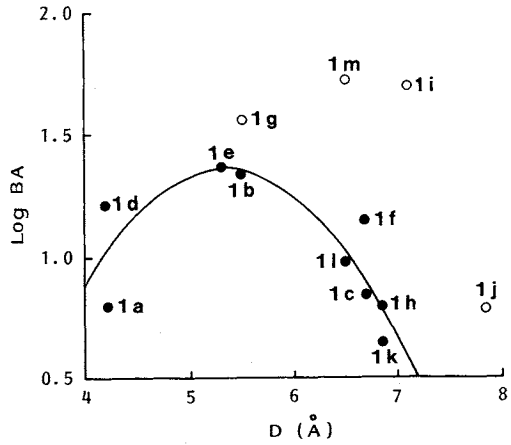
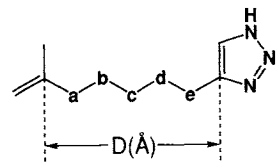


Fig. 3. Model structure.



which was different from the others in its substitution site, showed poor oral absorbability, even though their spacers consisted of three atoms.

The representative compounds (**1g**, **1i** and **1m**) possessing high oral absorbability in mice, were further tested for their oral absorbability in monkeys. As shown in Table 3, compound **1g** exhibited the best oral absorption and the highest plasma level among all of the test compounds.

These preliminary data demonstrate the high *in vitro* antibacterial activity and the excellent oral absorption of **1g**, which was selected for further evaluation.

Relationship between Spacer-length and Oral Absorbability

In order to investigate a correlation of the structure of the spacer moiety in the C-3 side chain with the oral absorbability of the cephalosporins, the common logarithms of their bioavailability (log BA) were plotted against the spacer length (Fig. 2). We used the D value, the meaning of which is explained in Fig. 3, as an indicator of the spacer length. Fig. 3 shows a model structure, in which all atoms were placed on the same plane with the spacer moiety zigzagged, and the geometry of which was optimized using a MAXIMIN2 program (SYBYL; Tripos Associates, Inc., St. Louis, MO: The calculation was carried out on VAX6320.). Compounds **1n** and **1o** were omitted from the plot because of a difference in the substitution site on 1,2,3-triazole. As can be seen in Fig. 2, the D value shows a fairly good parabolic correlation with the log BA of the compounds except **1g**, **1i**, **1j** and **1m**, and the following equation was obtained by least square analysis.

$$\log BA = -0.26\,D^2 + 2.8\,D - 6.2$$
$$(0.21) \quad (2.3) \quad (6.2)$$
$$(n=9,\ r=0.82,\ s=0.17)$$

Where n is the sample number, r is the multiple correlation coefficient and s is the standard deviation. The 95% confidence intervals are given in parentheses. The deviation of the compounds (**1g**, **1i**, **1j** and **1m**) can be attributed to the SCH_2S structure directly attached to the C-3 position of cephem nucleus and the amino group in the spacer moiety. Therefore, assigning an indicator variable (I) to the SCH_2S structure directly attached to the C-3 position, the following equation was obtained.

$$\log BA = -0.16\,D^2 + 1.7\,D + 0.60\,I - 3.4$$
$$(0.14) \quad (1.6) \quad (0.40) \quad (4.6)$$
$$(n=12,\ r=0.82,\ s=0.23)$$

These equations indicate that the optimal D value is 5.3~5.4 Å and that the SCH_2S structure directly

attached to the C-3 position of the cephem nucleus has contributed much to the improvement of oral absorbability. Compound **1m** was omitted from the regression because no other compounds possessing the same type of spacer with that of **1m** were available.

In conclusion we found that there were at least three factors affecting the oral absorbability. One was the spacer length and the others were factors derived from the SCH_2S group directly attached to the C-3 position of the cephem nulceus and the amino group in the spacer moiety. Considering that the aminothiazole-type cephalosporins such as cefixime, ceftibuten and cefdinir were reported to be absorbed through a carrier-mediated transport system in small intestine[5~7], we speculate that the cephalosporins prepared in this study are absorbed in a similar manner and that the highest oral absorbability is obtained when the 1,2,3-triazole is placed at the position most favorable for the interaction with the carrier.

Experimental

MP was determined with a Yanagimoto micro melting point apparatus and uncorrected. IR spectra were taken on a Jasco IR-700 spectrometer. ^1H 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. MS was measured on a Hitachi M-68 mass spectrometer. The following abbreviations are used; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sep, septet; m, multiplet; br, broad; ABq, AB quartet. All reactions under anhydrous conditions were carried out using anhydrous solvents dried over Molecular Sieves type 4A in a nitrogen atmosphere.

Determination of Antibacterial Activity

All the *in vitro* antibacterial activities are given as MIC in μg/ml required to prevent growth of bacterial culture. MICs were determined by the serial agar dilution method (Sensitivity Disk Agar-N) after incubation at 37°C for 18~20 hours with an inoculum size of about 10^6 cells/ml.

Oral Absorption Study

Male ICR-strain mice aged 6 weeks weighing 24~30 g were used in groups of 5 and female cynomolgus monkeys weighing 2.1 to 3.1 kg were used in groups of 3 or 6. The antibiotics were given to mice orally in a single dose of 40 mg/kg or subcutaneously in 20 mg/kg as a solution in dilute aqueous sodium bicarbonate. Monkeys were orally dosed with 10 mg/kg of the test compounds as a suspension in 0.5% of methyl cellulose. For mice, plasma samples were collected at 0.25 and 2 hours respectively after dosing and urine specimens were collected over a period of 2 hours after dosing. For monkeys, plasma samples were obtained at 0.25, 0.50, 1, 2, 3, 4, 6 and 8 hour(s) after administration and urine specimens were collected at 0~24 hours after administration. The concentrations of the test compounds were determined by the band culture method using *Escherichia coli* 7437 as a test organism and Trypto-soy agar as the test medium.

(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetic Acid (**2**)

To a suspension of ethyl (*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate (86 g, 0.40 mol) in methylene chloride (1,200 ml) were added 4-dimethylaminopyridine (9.6 g, 79 mmol) and di-*tert*-butyl dicarbonate (240 ml, 1.04 mol) and the mixture was stirred at room temperature for 19 hours. Next, 500 ml of 0.5 N HCl was added to the mixture. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. To the resulting residue 200 ml of EtOH was added and the solution was concentrated. Again the residue was dissolved in EtOH (300 ml) and to the solution was added aqueous NaOH solution (NaOH 64 g, 1.6 mol; H_2O 300 ml) dropwise under ice-cooling. After being stirred at ice-bath temperature for 30 minutes, the mixture was stirred at room temperature for 19 hours. Next, conc HCl (140 ml) and ice-water (1,000 ml) were added to the mixture, which was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The resulting solid was washed with water, dried and washed with ether to give (*Z*)-2-(2-*tert*-butoxycarbonylaminothiazol-4-

yl)-2-hydroxyiminoacetic acid (86.3 g, 75%) as white crystals: mp 170~173°C; ^{1}H NMR ($CDCl_3$ - DMSO-d_6) δ 7.38 (1H, s), 1.55 (9H, s); IR (Nujol) cm^{-1} 3640, 3510, 3125, 2520 (br), 1730, 1635, 1600, 1530; MS *m/z* 287 (M^+).

Anal Calcd for $C_{10}H_{13}N_3O_5S \cdot \frac{1}{5}H_2O$: C 41.29, H 4.64, N 14.44, S 11.02.
Found: C 41.38, H 4.72, N 14.68, S 10.94.

To a solution of the above crystals (86.3 g, 0.30 mol) in *N*,*N*-dimethylformamide (DMF) (600 ml) were added potassium carbonate (92 g, 0.67 mol) and trityl chloride (100 g, 0.36 mol) and the mixture was stirred at room temperature for 3 days. The mixture was then poured into conc HCl (111 ml) and ice water (1,500 ml) and extracted with EtOAc. The extract was washed successively with water, 5% aq $NaHCO_3$, 2% HCl and brine, then dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from methylene chloride to yield 114 g (91%) of **2** as white crystals: mp 157~158°C; ^{1}H NMR ($CDCl_3$ - DMSO-d_6) δ 7.2~7.4 (15H, m), 7.04 (1H, s), 1.50 (9H, s); IR (Nujol) cm^{-1} 3200, 1726, 1697, 1563.

Anal Calcd for $C_{29}H_{27}N_3O_5S \cdot \frac{1}{2}$EtOAc: C 64.91, H 5.45, N 7.32, S 5.59.
Found: C 65.13, H 5.53, N 7.50, S 5.36.

p-Methoxybenzyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (**5**)

To a suspension of **3** (2.43 g, 6.0 mmol) in methylene chloride (50 ml), was added 5% aq $NaHCO_3$ (20 ml) and the mixture was stirred at room temperature for an hour. Next, the organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated. To a solution of the residue in methylene chloride (40 ml), were added **2** (3.17 g, 6.0 mmol) and *N*,*N'*-dicyclohexylcarbodiimide (1.24 g, 6.0 mmol), and the mixture was stirred at room temperature for 2.5 hours. This mixture was filtered and evaporated. The residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 10 : 1), and triturated with hexane - ether to afford 3.38 g (64%) of **5** as a white powder: ^{1}H NMR ($CDCl_3$) δ 8.45~8.25 (1H, br s), 7.45~7.20 (18H, m), 7.03 (1H, s), 6.95~6.85 (2H, m), 5.98 (1H, dd, J=5.0, 8.8 Hz), 5.25 and 5.20 (2H, ABq, J=11.9 Hz), 5.02 (1H, d, J=5.0 Hz), 4.54 and 4.40 (2H, ABq, J=12.0 Hz), 3.82 (3H, s), 3.57 and 3.35 (2H, ABq, J=18.4 Hz), 1.50 (9H, s); IR ($CHCl_3$) cm^{-1} 3400, 1785, 1720, 1680, 1540, 1510, 1445, 1365.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamino]-3-methanesulfonyloxy-3-cephem-4-carboxylate (**6**)

To a suspension of **2** (45.6 g, 86 mmol) and **4** (37.3 g, 75 mmol) in methylene chloride was added *N*-methylmorpholine (27.2 ml, 0.25 mol) at -30°C and the mixture was stirred at -30°C for a few minutes. After phenylphosphoryl dichloride (12.3 ml, 82 mmol) was added to the mixture, the mixture was stirred at the same temperature for 3 hours. 10% HCl (40 ml) was added to the mixture, which was diluted with water and extracted with EtOAc. The extract was washed successively with water, aq $NaHCO_3$, diluted HCl and water, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was dissolved in hot *iso*-propanol (2,000 ml). After the solution was cooled to ice-bath temperature, **6** was precipitated. The mother liquor was concentrated to a volume of *ca.* 1,000 ml, cooled to the ice-bath temperature and the precipitate was collected. Combining the precipitates gave 67 g (92%) of **6** as a white powder: ^{1}H NMR ($CDCl_3$) δ 9.0~8.8 (1H, br s), 7.5~7.2 (26H, m), 7.02 (1H, s), 6.96 (1H, s), 6.06 (1H, dd, J=5.0, 8.9 Hz), 5.13 (1H, d, J=5.0 Hz), 3.77 and 3.45 (2H, ABq, J=19.4 Hz), 2.78 (3H, s), 1.50 (9H, s); IR ($CHCl_3$) cm^{-1} 3400, 1793, 1724, 1690, 1543, 1513, 1493, 1445, 1368, 1157.

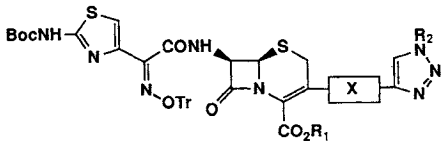
Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-[1(or 2)-triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]thiomethylthio-3-cephem-4-carboxylate (**7g**)

To a solution of **9** (25.0 g, 58.0 mmol) in THF (100 ml) and DMF (300 ml), at -78°C, was added a solution of sodium methoxide in MeOH (1.35 M, 37.8 ml) and the mixture was stirred at -78°C for 15 minutes. To the above mixture was added a solution of **6** (45.0 g, 46.3 mmol) in THF (45 ml) and DMF (120 ml), which was cooled to -78°C before the addition, over 5 minutes. During the period of the addition, the reaction temperature was maintained below -75°C. After being stirred at the same temperature for an hour, the mixture was neutralized with 10% HCl, diluted with water and extracted with EtOAc.

The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by column chromatography on silica gel (eluent; toluene-EtOAc, 15:1→10:1) and triturated with hexane-ether to yield 49.1 g (84%) of **7g** as a white powder.

Compounds **7a**~**7c** and **7h**~**7o** were similarly prepared from **5** or **6** with the corresponding thiols or thioacetates according to the procedure described for **7g**.

Table 4. Spectral data.



7

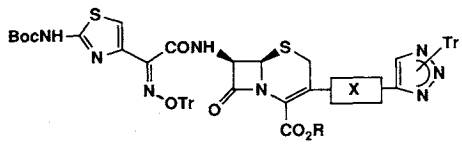
Compound No.	X R_1, R_2	IR ($CHCl_3$) cm^{-1} (C=O)	^1H NMR (δ)	Solvent[a]
7a	$-CH_2S-$ BH, H	1790, 1721, 1685	10.0~8.5 (1H, br s), 7.52 (1H, d, J=8.6 Hz), 7.45~7.10 (26H, m), 7.02 (1H, s), 6.91 (1H, s), 5.99 (1H, dd, J=4.8, 8.6 Hz), 4.95 (1H, d, J=4.8 Hz), 4.01 and 3.83 (2H, ABq, J=13.2 Hz), 3.52 and 3.33 (2H, ABq, J=17.8 Hz), 1.50 (9H, s)	a
7b	$-CH_2SCH_2-$ PMB, Tr	1780, 1715, 1690	8.3~8.1 (1H, br s), 7.40 (1H, s), 7.4~7.05 (33H, m), 7.03 (1H, s), 6.9~6.8 (2H, m), 5.93 (1H, dd, J=5.0, 8.8 Hz), 5.08 (2H, s), 4.98 (1H, d, J=5.0 Hz), 3.79 (3H, s), 3.75 (2H, s), 3.72 and 3.62 (2H, ABq, J=13.8 Hz), 3.54 and 3.35 (2H, ABq, J=18.2 Hz), 1.50 (9H, s)	a
7c	$-CH_2S(CH_2)_2-$ PMB, Tr	1785, 1720, 1685	8.3~8.1 (1H, br s), 7.45~7.05 (34H, m), 7.01 (1H, s), 6.95~6.8 (2H, m), 5.97 (1H, dd, J=4.8, 9.0 Hz), 5.13 and 5.09 (2H, ABq, J=11.9 Hz), 5.02 (1H, d, J=4.8 Hz), 3.79 (3H, s), 3.77 and 3.42 (2H, ABq, J=13.2 Hz), 3.46 (2H, s), 3.0~2.9 and 2.85~2.75 (4H, A_2B_2), 1.50 (9H, s)	a
7d	$-SCH_2-$ BH, H	1784, 1718, 1687	11.9~11.6 (1H, br s), 9.99 (1H, d, J=8.8 Hz), 7.6~7.25 (26H, m), 7.22 (1H, s), 6.87 (1H, s), 5.99 (1H, dd, J=4.6, 8.8 Hz), 5.32 (1H, d, J=4.6 Hz), 4.31 (2H, s), 3.95 (2H, s), 1.45 (9H, s)	b
7e	$-S(CH_2)_2-$ BH, H	1783, 1715, 1684	14.65 (1H, br s), 11.79 (1H, s), 9.99 (1H, d, J=8.6 Hz), 7.6~7.2 (26H, m), 7.24 (1H, s), 6.90 (1H, s), 5.99 (1H, dd, J=4.6, 8.6 Hz), 5.34 (1H, d, J=4.6 Hz), 3.87 (2H, s), 3.25~3.15 and 2.95~2.8 (4H, A_2B_2), 1.44 (9H, s)	b
7f	$-S(CH_2)_3-$ BH, H	1780, 1710, 1690	7.55~7.2 (26H, m), 7.09 (1H, s), 6.97 (1H, s), 5.89 (1H, d, J=4.5 Hz), 5.15 (1H, d, J=4.5 Hz), 3.47 and 3.36 (2H, ABq, J=17.6 Hz), 2.77 (2H, t, J=7.2 Hz), 2.74 (2H, t, J=7.2 Hz), 1.93 (2H, quin, J=7.2 Hz), 1.53 (9H, s)	c
7i	$-SCH_2SCH_2-$ BH, Tr	1784, 1717, 1686	8.65 (1H, br s), 7.60~7.05 (42H, m), 7.02 (1H, s), 6.89 (1H, s), 5.89 (1H, dd, J=4.6, 8.4 Hz), 5.04 (1H, d, J=4.6 Hz), 3.77 (4H, s), 3.51 and 3.35 (2H, ABq, J=17.0 Hz), 1.50 (9H, s)	a
7j	$-SCH_2S(CH_2)_2-$ BH, Tr	1784, 1717, 1686	11.23 (1H, br s), 9.73 (1H, d, J=8.4 Hz), 7.58 (1H, s), 7.5~7.05 (41H, m), 6.89 (1H, s), 5.88 (1H, dd, J=4.6, 8.4 Hz), 5.12 (1H, d, J=4.6 Hz), 3.87 and 3.83 (2H, ABq, J=12.0 Hz), 3.74 and 3.67 (2H, ABq, J=16.8 Hz), 3.05~2.85 (4H, m), 1.51 (9H, s)	d
7m	$-S(CH_2)_2NH-$ BH, Tr	1784, 1717, 1686	7.7~7.5 (1H, br s), 7.45~7.05 (42H, m), 6.95 (1H, s), 6.80 (1H, s), 6.61 (1H, s), 5.75~5.60 (1H, m), 5.03 (1H, d, J=4.5 Hz), 3.25~3.15 (2H, m), 3.15~2.95 (2H, m), 2.85~2.55 (2H, m), 1.49 (9H, s)	a

[a] a, $CDCl_3$; b, DMSO-d_6; c, $CDCl_3$-CD_3OD; d, $CDCl_3$-DMSO-d_6.

Diphenylmethyl 7β-[(*Z*)-2-(2-*tert*-Butoxycarbonylaminothiazol-4-yl)-2-triphenylmethoxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)methylthio-3-cephem-4-carboxylate (**7d**)

To a solution of **14**[4] (327 mg, 0.92 mmol) in DMF (5 ml), 36 mg (0.90 mmol) of sodium hydride (60% in oil) was added and the mixture was stirred at room temperature for 10 minutes. Next, the mixture was added to a solution of **6** (970 mg, 1.00 mmol) in DMF (5 ml) at −65°C. After being stirred at the same temperature for 30 minutes, the mixture was neutralized with 10% HCl, diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. To a solution of the residue in acetone (8 ml), was added 380 mg (2.00 mmol) of *p*-toluenesulfonic acid monohydrate under ice-cooling. After being stirred at the ice-bath temperature for an hour, the mixture

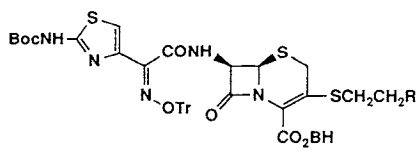
Table 5. Spectral data.



7

Compound No.	X R	IR ($CHCl_3$) cm^{-1} (C=O)	^1H NMR ($CDCl_3$, δ)
7g	$-SCH_2S-$ BH	1783, 1718, 1685	8.7~8.4 (1H, br s), 7.45 (1H, s), 7.4~7.05 (41H, m), 7.02 (1H, s), 6.86 (1H, s), 5.84 (1H, dd, *J*=4.8, 8.7 Hz), 4.97 (1H, d, *J*=4.8 Hz), 4.05 (2H, s), 3.56 and 3.31 (2H, ABq, *J*=16.9 Hz), 1.50 (9H, s)
7h	$-CH_2SCH_2S-$ PMB	1784, 1718, 1686	8.35 (1H, br s), 7.51 (1H, s), 7.4~7.05 (33H, m), 7.03 (1H, s), 6.95~6.85 (2H, m), 5.96 (1H, dd, *J*=4.9, 8.9 Hz), 5.19 and 5.15 (2H, ABq, *J*=11.6 Hz), 5.00 (1H, d, *J*=4.9 Hz), 4.01 and 3.93 (2H, ABq, *J*=13.5 Hz), 3.80 (3H, s), 3.75 and 3.70 (2H, ABq, *J*=13.2 Hz), 3.50 and 3.37 (2H, ABq, *J*=18.0 Hz), 1.50 (9H, s)
7k	$-S(CH_2)_2S-$ BH	1780, 1715, 1684	8.7~8.4 (1H, br s), 7.5~7.05 (42H, m), 7.03 (1H, s), 6.91 (1H, s), 5.82 (1H, dd, *J*=4.6, 8.2 Hz), 5.05 (1H, d, *J*=4.6 Hz), 3.42 and 3.16 (2H, ABq, *J*=17.4 Hz), 3.05~2.90 (4H, m), 1.50 (9H, s)
7l	$-S(CH_2)_2O-$ BH	1779, 1714, 1683	8.80 (1H, br s), 7.6~7.05 (42H, m), 6.99 (1H, s), 6.85 (1H, s), 5.8~5.7 (1H, m), 5.04 (1H, d, *J*=4.5 Hz), 4.27 (2H, t, *J*=6.4 Hz), 3.32 and 3.15 (2H, ABq, *J*=16.0 Hz), 3.05~2.9 (2H, m), 1.50 (9H, s)

Table 6. Spectral data.



7n~7o

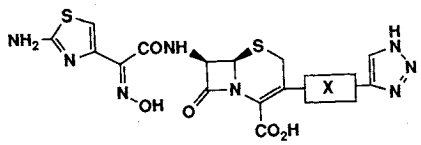
Compound No.	R	IR ($CHCl_3$) cm^{-1} (C=O)	^1H NMR ($CDCl_3$, δ)
7n		1782, 1715, 1682	9.87 (1H, br s), 8.12 (1H, d, *J*=9.4 Hz), 7.56 (1H, s), 7.45~7.15 (26H, m), 6.96 (1H, s), 6.94 (1H, s), 5.95 (1H, dd, *J*=4.8, 9.4 Hz), 5.01 (1H, d, *J*=4.8 Hz), 4.46 (2H, t, *J*=5.9 Hz), 3.4~3.0 (4H, m), 1.48 (9H, s)
7o		1783, 1717, 1685	8.95~8.7 (1H, br s), 7.57 (2H, s), 7.55~7.15 (26H, m), 7.02 (1H, s), 6.93 (1H, s), 5.83 (1H, dd, *J*=4.5, 7.7 Hz), 5.06 (1H, d, *J*=4.5 Hz), 4.46 (2H, t, *J*=7.0 Hz), 3.24 and 3.14 (2H, ABq, *J*=16.4 Hz), 3.08 (2H, t, *J*=7.0 Hz), 1.51 (9H, s)

was diluted with water and extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 1 : 1) and gave 572 mg (58%) of **7d** as a colorless froth.

The preparation of **7e** and **7f** was carried out by a method similar to that described for **7d**.

The spectral data of various derivatives **7a**～**7o** are listed in Tables 4, 5 and 6.

Table 7. Spectral data of **1a**～**1m**.

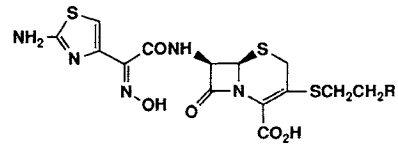


1a～**1m**

Compound No.	X	IR (KBr) cm^{-1} (C=O)	^1H NMR (δ)	Solvent[a]
1a	$-CH_2S-$	1760, 1650	7.95 (1H, s), 6.99 (1H, s), 5.75 (1H, d, J=4.5 Hz), 5.15 (1H, d, J=4.5 Hz), 4.22 and 3.55 (2H, ABq, J=13.5 Hz), 3.84 and 3.38 (2H, ABq, J=17.7 Hz)	a
1b	$-CH_2SCH_2-$	1762, 1650	7.69 (1H, s), 6.81 (1H, s), 5.82 (1H, d, J=4.8 Hz), 5.14 (1H, d, J=4.8 Hz), 3.89 and 3.61 (2H, ABq, J=13.5 Hz), 3.88 (2H, s), 3.62 and 3.57 (2H, ABq, J=17.8 Hz)	b
1c	$-CH_2S(CH_2)_2-$	1763, 1650	7.64 (1H, s), 6.71 (1H, s), 5.72 (1H, d, J=5.1 Hz), 5.18 (1H, d, J=5.1 Hz), 3.77 and 3.56 (2H, ABq, J=13.4 Hz), 3.60 (2H, s), 3.0～2.7 (4H, A_2B_2)	c
1d	$-SCH_2-$	1760, 1650	7.88 (1H, s), 7.04 (1H, s), 5.73 (1H, d, J=4.6 Hz), 5.17 (1H, d, J=4.6 Hz), 4.17 and 4.14 (2H, ABq, J=15.3 Hz), 3.69 and 3.45 (2H, ABq, J=17.2 Hz)	c
1e	$-S(CH_2)_2-$	1765, 1660	7.80 (1H, s), 7.05 (1H, s), 5.74 (1H, d, J=4.7 Hz), 5.21 (1H, d, J=4.7 Hz), 3.73 and 3.53 (2H, ABq, J=17.0 Hz), 3.2～3.0 (4H, m)	c
1f	$-S(CH_2)_3-$	1760, 1660	7.71 (1H, s), 6.99 (1H, s), 5.80 (1H, d, J=4.8 Hz), 5.24 (1H, d, J=4.8 Hz), 3.72 and 3.46 (2H, ABq, J=17.3 Hz), 2.87 (2H, t, J=7.3 Hz), 2.8～2.65 and 2.0～1.85 (4H, ABX_2)	a
1g	$-SCH_2S-$	1760, 1650	8.07 (1H, s), 6.99 (1H, s), 5.84 (1H, d, J=4.7 Hz), 5.21 (1H, d, J=4.7 Hz), 4.25 and 4.14 (2H, ABq, J=13.9 Hz), 3.75 and 3.51 (2H, ABq, J=17.2 Hz)	a
1h	$-CH_2SCH_2S-$	1760, 1650	7.97 (1H, s), 7.00 (1H, s), 5.80 (1H, d, J=4.7 Hz), 5.22 (1H, d, J=4.7 Hz), 3.97 and 3.93 (2H, ABq, J=13.7 Hz), 3.94 and 3.41 (2H, ABq, J=13.7 Hz), 3.71 and 3.36 (2H, ABq, J=17.7 Hz)	a
1i	$-SCH_2SCH_2-$	1760, 1655	7.88 (1H, s), 6.99 (1H, s), 5.83 (1H, d, J=4.6 Hz), 5.26 (1H, d, J=4.6 Hz), 4.03 and 4.00 (2H, ABq, J=14.8 Hz), 3.87 and 3.77 (2H, ABq, J=13.8 Hz), 3.79 and 3.53 (2H, ABq, J=17.4 Hz)	a
1j	$-SCH_2S(CH_2)_2-$	1765, 1655	7.78 (1H, s), 6.99 (1H, s), 5.83 (1H, d, J=4.6 Hz), 5.24 (1H, d, J=4.6 Hz), 3.93 and 3.86 (2H, ABq, J=13.8 Hz), 3.79 and 3.52 (2H, ABq, J=17.3 Hz), 3.12～2.99 (4H, m)	a
1k	$-S(CH_2)_2S-$	1755, 1660	8.02 (1H, s), 6.96 (1H, s), 5.70 (1H, d, J=4.5 Hz), 5.18 (1H, d, J=4.5 Hz), 3.60 and 3.43 (2H, ABq, J=18.0 Hz), 3.15～2.85 (4H, m)	c
1l	$-S(CH_2)_2O-$	1765, 1665	7.41 (1H, s), 6.98 (1H, s), 5.81 (1H, d, J=5.1 Hz), 5.25 (1H, d, J=5.1 Hz), 4.35 (2H, t, J=6.4 Hz), 3.83 and 3.55 (2H, ABq, J=17.6 Hz), 3.14 (2H, t, J=6.4 Hz)	a
1m	$-S(CH_2)_2NH-$	1760, 1660	7.25 (1H, s), 6.95 (1H, s), 5.74 (1H, d, J=4.7 Hz), 5.18 (1H, d, J=4.7 Hz), 3.67 and 3.46 (2H, ABq, J=17.4 Hz), 3.40～3.25 (2H, m), 3.10～2.80 (2H, m)	c

[a] a, D_2O - $NaHCO_3$; b, CD_3OD - DMSO-d_6; c, D_2O - DMSO-d_6.

Table 8. Spectral data of **1n**~**1o**.



1n~**1o**

Compound No.	R	IR (KBr) cm^{-1} (C=O)	^1H NMR (D_2O-DMSO-d_6, δ)
1n		1765, 1660	8.05 (1H, s), 7.80 (1H, s), 7.02 (1H, s), 5.76 (1H, d, J=4.5 Hz), 5.16 (1H, d, J=4.5 Hz), 4.69~4.61 (2H, X_2 part of ABX_2), 3.64 and 3.44 (2H, ABq, J=17.4 Hz), 3.37~3.18 (2H, AB part of ABX_2, J_{AB}=6.3 Hz)
1o		1765, 1660	7.80 (1H, s), 6.95 (1H, s), 5.71 (1H, d, J=4.6 Hz), 5.16 (1H, d, J=4.6 Hz), 4.8~4.5 (2H, overlapping with D_2O), 3.67 and 3.47 (2H, ABq, J=17.3 Hz), 3.36 and 3.31 (2H, ABq, J=6.1 Hz)

Deprotection of **7**: General Procedure Illustrated with the Preparation of 7β-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-3-cephem-4-carboxylic Acid (**1g**)

To a solution of **7g** (29.0 g, 22.9 mmol) in anisole (50 ml) and nitromethane (200 ml), a solution of $AlCl_3$ (20.7 g, 0.156 mol) in anisole (50 ml) was added dropwise at -30~-20°C. After the reaction mixture had been stirred at the same temperature for an hour, 200 ml of 1 N HCl, water and EtOAc were added to the reaction mixture. The aqueous layer was separated and the organic layer was re-extracted with water. The combined aqueous layer was chromatographed on a Diaion HP-20 column (eluent; methanol-water 4:1). After the concentration, the resulting precipitate was collected by filtration, washed with EtOAc and dried *in vacuo* to give 8.07 g (68%) of **1g** as a pale yellow powder.

The spectral data of various derivatives **1a**~**1o** are listed in Tables 7 and 8.

[1(or 2)-Triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]thiomethyl Thioacetate (**9**)

To a suspension of **8** (107 g, 0.87 mol) in DMF (300 ml), chloromethyl thioacetate[8] (109 g, 0.87 mol) was added dropwise at -30~-20°C and the mixture was stirred at room temperature for 2 hours. To the reaction mixture, under ice-cooling, were added trityl chloride (292 g, 1.05 mol) and pyridine (84.6 ml, 1.05 mol). After being stirred at room temperature for 18 hours, the mixture was diluted with methylene chloride, washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from ether to yield 183 g (49%) of **9** as white crystals: mp 115~116°C; ^1H NMR ($CDCl_3$) δ 7.47 (1H, s), 7.4~7.3 (9H, m), 7.15~7.05 (6H, m), 4.34 (2H, s), 2.29 (3H, s); IR ($CHCl_3$) cm^{-1} 1688, 1488, 1442; MS *m/z* 431 (M^+).

Anal Calcd for $C_{24}H_{21}N_3OS_2$: C 66.79, H 4.90, N 9.74, S 14.86.
Found: C 66.77, H 5.00, N 9.74, S 15.10.

2-[1(or 2)-Triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]thioethyl Thioacetate (**13**)

To a suspension of **8** (1.23 g, 10.0 mmol) in DMF (5 ml), under ice-cooling, methyl chloroacetate (0.88 ml, 10.0 mmol) was added. After being stirred at ice-bath temperature for 30 minutes, the mixture was diluted with water, extracted with EtOAc, washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; toluene-EtOAc, 1:2) to afford 1.22 g (70%) of **10** as white crystals: mp 137°C; ^1H NMR ($CDCl_3$) δ 11.46 (1H, s), 7.76 (1H, s), 3.76 (3H, s), 3.71 (2H, s); IR ($CHCl_3$) cm^{-1} 3150 (br), 1730, 1432.

HRMS Calcd for $C_5H_7N_3O_2S$(M^+): 173.0259.
Found: *m/z* 173.0283 (M^+).

To a solution of **10** (1.13 g, 6.53 mmol) in methylene chloride (10 ml), were added trityl chloride (2.19 g, 7.86 mmol) and triethylamine (1.09 ml, 7.82 mmol). After being stirred at room temperature for 20 minutes, the mixture was diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated.

The residue was crystallized from ether to give 2.13 g (79%) of **11** as white crystals: mp 126~127°C; ^{1}H NMR ($CDCl_3$) δ 7.48 (1H, s), 7.4~7.3 (9H, m), 7.15~7.05 (6H, m), 3.68 (2H, s), 3.66 (3H, s); IR ($CHCl_3$) cm^{-1} 1731, 1487, 1441; MS *m/z* 415 (M^+).

Anal Calcd for $C_{24}H_{21}N_3O_2S$: C 69.38, H 5.09, N 10.11, S 7.72.
Found: C 69.61, H 5.13, N 9.83, S 7.44.

To a suspension of lithium aluminum hydride (288 mg, 7.59 mmol) in THF (100 ml) under ice-cooling, 2.10 g (5.06 mmol) of **11** was added and the mixture was stirred at room temperature for 30 minutes. Next, the reaction mixture was cooled to ice-bath temperature, quenched with aq THF and neutralized with 10% HCl. The precipitate was filtered off, the filtrate was diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was crystallized from ether to yield 1.62 g (83%) of **12** as white crystals: mp 158°C; ^{1}H NMR ($CDCl_3$) δ 7.44 (1H, s), 7.4~7.3 (9H, m), 7.15~7.05 (6H, m), 3.89 (2H, t, J=5.4 Hz), 3.09 (2H, t, J=5.4 Hz), 2.05 (1H, br s); IR ($CHCl_3$) cm^{-1} 3350 (br), 1487, 1441.

HRMS Calcd for $C_{23}H_{21}N_3OS$ (M^+): 387.1405.
Found: *m/z* 387.1423 (M^+).

To a solution of **12** (1.61 g, 4.16 mmol) in DMF (20 ml), were added triethylamine (0.70 ml, 5.02 mmol) and methanesulfonyl chloride (0.39 ml, 5.04 mmol) at −40~−30°C. The mixture was stirred at the same temperature. Next, potassium thioacetate (950 mg, 8.32 mmol) and sodium iodide (1.24 g, 8.33 mmol) were added to the mixture. After being stirred at room temperature for 3 days, the mixture was diluted with water, extracted with EtOAc, washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 10 : 1) to give 1.53 g (83%) of **13** as white crystals: mp 138°C; ^{1}H NMR ($CDCl_3$) δ 7.46 (1H, s), 7.4~7.3 (9H, m), 7.15~7.05 (6H, m), 3.20~3.12 and 3.10~3.02 (4H, A_2B_2), 2.32 (3H, s); IR ($CHCl_3$) cm^{-1} 1684, 1488, 1441; MS *m/z* 445 (M^+).

Anal Calcd for $C_{25}H_{23}N_3OS_2$: C 67.39, H 5.20, N 9.43, S 14.39.
Found: C 67.47, H 5.31, N 9.11, S 14.37.

(1-Triphenylmethyl-1*H*-1,2,3-triazol-4-yl)methylthiomethyl Thioacetate (**16**)

To a solution of **14**[4] (3.00 g, 8.40 mmol) in DMF (10 ml), sodium hydride (60% in oil) (370 mg, 9.25 mmol) was added and the mixture was stirred at room temperature for 5 minutes. The reaction mixture was poured into a mixture of bromochloromethane (15 ml) and DMF (15 ml) at −30°C. After being stirred at −30~−20°C for 30 minutes, the reaction mixture was diluted with water, extracted with EtOAc, washed with brine four times, dried over anhydrous Na_2SO_4, and evaporated. To a solution of the resulting residue in acetone (30 ml), potassium thioacetate (1.92 g, 16.8 mmol) was added. After being stirred at room temperature for an hour, the mixture was diluted with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; toluene - EtOAc, 10 : 1) and crystallized from ether to yield 2.65 g (71%) of **16** as white crystals: mp 106°C; ^{1}H NMR ($CDCl_3$) δ 7.39 (1H, s), 7.4~7.3 (9H, m), 7.2~7.1 (6H, m), 4.04 (2H, s), 3.89 (2H, s), 2.32 (3H, s); IR ($CHCl_3$) cm^{-1} 1690, 1491, 1444; MS *m/z* 445 (M^+).

Anal Calcd for $C_{25}H_{23}N_3OS_2$: C 67.39, H 5.20, N 9.43, S 14.39.
Found: C 67.61, H 5.09, N 9.46, S 14.28.

2-(1-Triphenylmethyl-1*H*-1,2,3-triazol-4-yl)ethylthiomethyl Thioacetate (**17**)

The compound **17** was prepared as described for the preparation of **16**. MP 87°C; ^{1}H NMR ($CDCl_3$) δ 7.4~7.3 (9H, m), 7.25 (1H, s), 7.15~7.10 (6H, m), 4.02 (2H, s), 3.10~2.85 (4H, A_2B_2), 2.33 (3H, s); IR ($CHCl_3$) cm^{-1} 1688, 1491, 1444; MS *m/z* 459 (M^+).

Anal Calcd for $C_{26}H_{25}N_3OS_2$: C 67.94, H 5.48, N 9.14, S 13.95.
Found: C 67.81, H 5.61, N 9.39, S 14.22.

2-[1(or 2)-Triphenylmethyl-1(or 2)*H*-1,2,3-triazol-4-yl]oxyethyl Thioacetate (**21**)

To a solution of **18**[4] (4.00 g, 12.2 mmol) in DMF (50 ml), sodium hydride (60% in oil) (538 mg, 13.5 mmol) was added and the mixture was stirred at room temperature for 15 minutes. Next, ethyl bromoacetate (1.5 ml, 13.5 mmol) was added to the mixture, which was stirred at room temperature for

40 minutes. After being stirred at 40°C for an additional 20 minutes, the mixture was neutralized with 10% HCl, diluted with water and extracted with EtOAc. The extract was washed with brine four times, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; methylene chloride) and the resulting crystals were rinsed with ether to yield 3.55 g (70%) of **19** as white crystals: mp 162~163°C; ^{1}H NMR ($CDCl_3$) δ 7.4~7.3 (9H, m), 7.2~7.1 (6H, m), 6.98 (1H, s), 4.92 (2H, s), 4.25 (2H, q, J=7.2 Hz), 1.28 (3H, t, J=7.2 Hz); IR ($CHCl_3$) cm^{-1} 1751, 1568, 1491, 1443, 1342; MS m/z 413 (M^+).

Anal Calcd for $C_{25}H_{23}N_3O_3$: C 72.62, H 5.61, N 10.16.
Found: C 72.22, H 5.61, N 10.09.

The reduction of **19**, the subsequent mesylation and acetylthiolation were carried out by a method similar to that described for the preparation of **13**. The spectral data of **20** and **21** are described below.

20: mp 151~152°C; ^{1}H NMR ($CDCl_3$) δ 7.4~7.3 (9H, m), 7.2~7.1 (6H, m), 6.91 (1H, s), 4.38~4.34 and 3.97~3.92 (4H, A_2B_2); IR ($CHCl_3$) cm^{-1} 3370 (br), 1560, 1491, 1444, 1337, 1325; MS m/z 371 (M^+).

Anal Calcd for $C_{23}H_{21}N_3O_2$: C 74.37, H 5.70, N 11.31.
Found: C 74.28, H 5.64, N 11.16.

21: mp 125~126°C; ^{1}H NMR ($CDCl_3$) δ 7.4~7.3 (9H, m), 7.2~7.1 (6H, m), 6.90 (1H, s), 4.35 (2H, t, J=6.4 Hz), 3.28 (2H, t, J=6.4 Hz), 2.34 (3H, s); IR ($CHCl_3$) cm^{-1} 1689, 1565, 1491, 1444, 1338; MS m/z 429 (M^+).

Anal Calcd for $C_{25}H_{23}N_3O_2S$: C 69.91, H 5.40, N 9.78, S 7.46.
Found: C 69.82, H 5.58, N 9.94, S 7.49.

2-(1-Triphenylmethyl-1*H*-1,2,3-triazol-4-yl)aminoethan-1-thiol (**26**)

To a suspension of **22** (9.50 g, 26.8 mmol) in *iso*-propanol (80 ml) were added triethylamine (4.10 ml, 29.4 mmol) and diphenylphosphoryl azide (6.34 ml, 29.4 mmol), and the mixture was refluxed for 3 hours and then concentrated. The residue was crystallized from ether containing a small amount of EtOAc to give **23**. The mother liquor was concentrated and purified by column chromatography on silica gel (eluent; toluene - EtOAc, 10 : 1). The resulting crystals were rinsed with ether and combined with the above crystal to yield 7.07 g (64%) of **23** as white crystals: mp 169~170°C; ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, s), 7.43 (1H, br s), 7.4~7.3 (9H, m), 7.2~7.1 (6H, m), 4.93 (1H, sep, J=6.2 Hz), 1.26 (6H, d, J=6.2 Hz); IR ($CHCl_3$) cm^{-1} 3422, 1716, 1580, 1522, 1488, 1442, 1384, 1312.

HRMS Calcd for $C_{25}H_{24}N_4O_2$ (M^+): 412.1899.
Found: m/z 412.1880 (M^+).

Potassium hydroxide (86%) (3.32 g, 51.0 mmol) was dissolved in 30 ml of water and this solution was added to a suspension of **23** (7.00 g, 17.0 mmol) in ethanol (30 ml). The mixture was refluxed for 24 hours. After being cooled to room temperature, the mixture was diluted with water and the crystalline precipitate was collected by filtration to give 5.29 g (95%) of **24** as white crystals: mp 235~240°C (dec); ^{1}H NMR (DMSO-d_6) δ 7.5~7.35 (9H, m), 7.1~7.6 (6H, m), 6.66 (1H, s), 4.80 (2H, s); IR (KBr) cm^{-1} 3410, 3280, 3180, 1631, 1575, 1492, 1444, 1348.

HRMS Calcd for $C_{21}H_{18}N_4$ (M^+): 326.1531.
Found: m/z 326.1530 (M^+).

Acetylthioacetic acid (1.31 g, 9.78 mmol), which was readily prepared from bromoacetic acid and potassium thioacetate, was mixed with **24** (3.18 g, 9.75 mmol), *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide (water soluble) (1.87 g, 9.75 mmol) and methylene chloride (10 ml). After being stirred at room temperature for 2 hours, the mixture was diluted with methylene chloride. This solution was washed successively with diluted HCl, diluted aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (eluent; methylene chloride - EtOAc, 10 : 1) and the resulting crystals were washed with ether to obtain 3.49 g (81%) of **25** as white crystals: mp 217°C; ^{1}H NMR ($CDCl_3$) δ 9.54 (1H, s), 7.91 (1H, s), 7.4~7.25 (9H, m), 7.15~7.05 (6H, m), 3.72 (2H, s), 2.40 (3H, s); IR ($CHCl_3$) cm^{-1} 3375, 3200, 1687, 1572, 1530, 1489, 1441, 1386; MS m/z 442 (M^+).

Anal Calcd for $C_{25}H_{22}N_4O_2S$: C 67.85, H 5.01, N 12.66, S 7.25.
Found: C 67.92, H 5.04, N 12.55, S 6.98.

To a suspension of lithium aluminum hydride (808 mg, 21.3 mmol) in THF (70 ml), under ice-cooling, 3.14 g (7.10 mmol) of **25** was added and the mixture was heated at 60~65°C for 50 minutes. After being cooled to ice-bath temperature, the reaction mixture was quenched with aq THF and neutralized with 10% HCl. The precipitate was filtered off through Hyflo Super Cel. The filtrate was diluted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The crystalline residue was washed with hexane - ether to afford 2.31 g (84%) of **26** as white crystals: mp 175°C; ^{1}H NMR ($CDCl_3$) δ 7.4~7.25 (9H, m), 7.2~7.05 (6H, m), 6.69 (1H, s), 3.5~2.9 (1H, br s), 3.28 (2H, t, J=6.4 Hz), 2.73 (2H, dt, J=6.4, 8.4 Hz), 1.43 (1H, t, J=8.4 Hz); IR ($CHCl_3$) cm^{-1} 3350, 1577, 1488, 1441; MS m/z 386 (M^+).

Anal Calcd for $C_{23}H_{22}N_4S$: C 71.47, H 5.74, N 14.50, S 8.30.
Found: C 71.57, H 5.68, N 14.39, S 8.01.

2-(1*H*-1,2,3-Triazol-1-yl)ethyl Thioacetate (**32**), 2-(2*H*-1,2,3-Triazol-2-yl)ethyl Thioacetate (**33**)

To a solution of 1,2,3-triazole (13.8 g, 0.20 mol) in acetone (200 ml) were added ethyl bromoacetate (33.4 g, 0.20 mol) and sodium carbonate (30.0 g, 0.28 mol). After being stirred at 30°C for 5 days, the mixture was filtered and evaporated. The residue was chromatographed on silica gel (eluent; toluene - EtOAc, 10:1→2:1→1:1) to yield 20.3 g (65%) of **28** and 7.99 g (26%) of **29**, as white crystals. The reduction of **28** and **29**, the subsequent mesylation and acetylthiolation were carried out by a method similar to that described for the preparation of **13**. The spectral data of **28**~**33** are described below.

28: mp 44°C; ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, s), 7.73 (1H, s), 5.21 (2H, s), 4.28 (2H, q, J=7.2 Hz), 1.31 (3H, t, J=7.2 Hz); IR ($CHCl_3$) cm^{-1} 1748, 1463, 1372.

HRMS Calcd for $C_6H_9N_3O_2$ (M^+): 155.0695.
Found: m/z 155.0702 (M^+).

29: mp 34~35°C; ^{1}H NMR ($CDCl_3$) δ 7.70 (2H, s), 5.25 (2H, s), 4.25 (2H, q, J=7.2 Hz), 1.28 (3H, t, J=7.2 Hz); IR ($CHCl_3$) cm^{-1} 1749, 1408, 1385, 1368, 1343.

HRMS Calcd for $C_6H_9N_3O_2$ (M^+): 155.0695.
Found: m/z 155.0677 (M^+).

30: ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, d, J=0.9 Hz), 7.62 (1H, d, J=0.9 Hz), 4.53~4.48 and 4.08~4.03 (4H, A_2B_2), 3.65 (1H, s); IR ($CHCl_3$) cm^{-1} 3314, 1461, 1428, 1358.

HRMS Calcd for $C_4H_7N_3O$ (M^+): 113.0589.
Found: m/z 113.0595 (M^+).

31: ^{1}H NMR ($CDCl_3$) δ 7.64 (2H, s), 4.62~4.57 and 4.14~4.09 (4H, A_2B_2), 2.82 (1H, br s); IR ($CHCl_3$) cm^{-1} 3412, 1415, 1374, 1341.

HRMS Calcd for $C_4H_7N_3O$ (M^+): 113.0589.
Found: m/z 113.0589 (M^+).

32: ^{1}H NMR ($CDCl_3$) δ 7.72 (1H, d, J=0.8 Hz), 7.62 (1H, d, J=0.8 Hz), 4.57 (2H, t, J=6.8 Hz), 3.37 (2H, t, J=6.8 Hz), 2.37 (3H, s); IR ($CHCl_3$) cm^{-1} 1687, 1490, 1457, 1435, 1400, 1353.

HRMS Calcd for $C_6H_{10}N_3OS$ (MH^+): 172.0545.
Found: m/z 172.0543 (MH^+).

33: ^{1}H NMR ($CDCl_3$) δ 7.62 (2H, s), 4.63 (2H, t, J=6.6 Hz), 3.44 (2H, t, J=6.6 Hz), 2.35 (3H, s); IR ($CHCl_3$) cm^{-1} 1686, 1437, 1413, 1372, 1353.

HRMS Calcd for $C_6H_9N_3OS$ (M^+): 171.0466.
Found: m/z 171.0477 (M^+).

References

1) YAMANAKA, H.; T. CHIBA, K. KAWABATA, H. TAKASUGI, T. MASUGI & T. TAKAYA: Studies on β-lactam antibiotics. IX. Synthesis and biological activity of a new orally active cephalosporin, cefixime (FK027). J. Antibiotics 38: 1738~1751, 1985

2) HAMASHIMA, Y.; T. KUBOTA, K. MINAMI, K. ISHIKURA, T. KONOIKE, M. YOSHIOKA, T. YOSHIDA, H. NAKASHIMIZU & K. MOTOKAWA: Synthesis and biological properties of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid (7432-S), a new oral cephem antibiotic. J. Antibiotics 40: 1468~1470, 1987

3) INAMOTO, Y.; T. CHIBA, T. KAMIMURA & T. TAKAYA: FK 482, a new orally active cephalsporin. Synthesis and biological properties. J. Antibiotics 41: 828~830, 1988

4) KUME, M.; T. KUBOTA, Y. KIMURA, H. NAKASHIMIZU & K. MOTOKAWA: Orally active cephalosporins. I. Synthesis and structure-activity relationships of 7β-[2-(*R*)-amino-2-phenylacetamido]-3-(1*H*-1,2,3-triazol-4-yl)alkylthiomethyl-3-cephem-4-carboxylic acid and related compounds. Yakugaku Zasshi (Japanese) 112: 622～637, 1992
5) TSUJI, A.; T. TERASAKI, I. TAMAI & H. HIROOKA: H^+ Gradient-dependent and carrier-mediated transport of cefixime, a new cephalosporin antibiotic, across brush-border membrane vesicles from rat small intesine. J. Pharmacol. Exp. Ther. 241: 594～601, 1987
6) MURANUSHI, N.; T. YOSHIKAWA, M. YOSHIDA, T. OGUMA, K. HIRANO & H. YAMADA: Transport characteristics of ceftibuten, a new oral cephem, in rat intestinal brush-border membrane vesicles: Relationship to oligopeptide and amino β-lactam transport. Pharm. Res. 6: 308～312, 1989
7) MAKANISHI, M.; I. TAMAI, T. TERASAKI & A. TSUJI: Intestinal absorption mechanism of cefdinir, a new oral cephalosporin. Xenobio. Metabol. and Dispos. (Japanese) 5: 141, 1990
8) BÖHME, VON H.; H. BEZZENBERGER, M. CLEMENT, A. DICK, E. NÜRNBERG & W. SCHLEPHACK: Über α-Hydroxyalkyl-acyl-sulfide und α-Halogenalkyl-acyl-sulfide. Liebigs Ann. Chem. 623: 92～102, 1959