

STUDIES ON ORALLY ACTIVE CEPHALOSPORINS

I. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NEW 3-SUBSTITUTED CARBAMOYLOXYMETHYL CEPHALOSPORINS

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The synthesis and antibacterial activities of 7 β -[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylic acid (E1100) and its analogs are described, as well as oral absorbability and *in vivo* activities of the 1-(isopropoxycarbonyloxy)ethyl ester (E1101) and its analogous esters. The introduction of acyclic and cyclic lower alkyl groups at the *N*-position of 3-carbamoyloxymethyl cepheems influences antibacterial activities, especially against *H. influenzae*, and oral absorbability of their prodrug esters. The structure-activity relationships are also discussed.

Since the discovery of ceftoram pivoxil¹⁾ and cefixime²⁾, a number of orally active cephalosporins^{3~9)} bearing an aminothiazole moiety at the C-7 side chain have been reported and developed, such as cefpodoxime proxetil³⁾ (CPDX-PR) (Fig. 1) and cefdinir⁴⁾ (CFDN) (Fig. 2). Compared with first generation oral cephalosporins like cephalixin and cefaclor (CCL), these newly developed compounds show a wider antibacterial spectrum and high stability against various β -lactamases, and consequently, have made a great contribution to the treatment of infectious diseases. Much effort in this field has been made to find

a more well-balanced and more active compound with better oral bioavailability⁹⁾. In the course of our research program, we have found that 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-cephalosporins modified with a variety of *N*-substituted carbamoyloxymethyl groups at the C-3 position and their prodrug esters at the C-4 position, represented as **I** in Fig. 3, show potent antibacterial

Fig. 1.

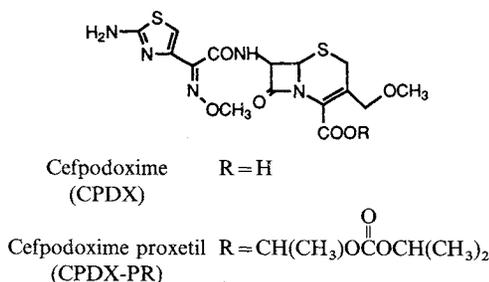


Fig. 2.

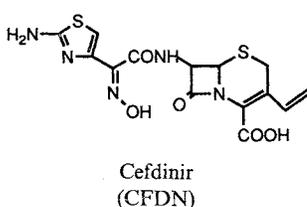
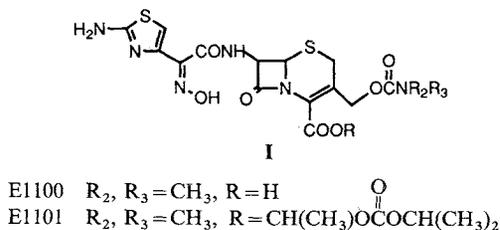


Fig. 3. Structure of *N*-substituted carbamoyloxymethyl cepheems.



activity against both Gram-positive and Gram-negative bacteria as well as good oral absorption.

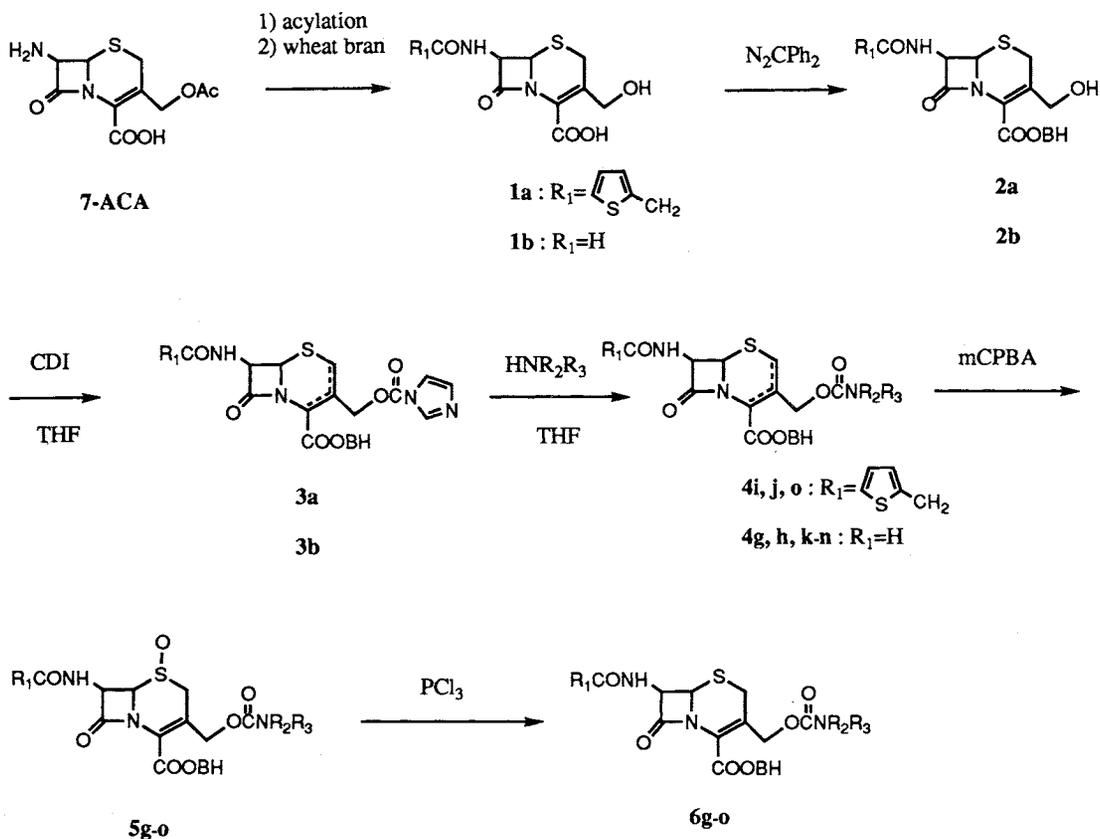
This report describes the synthesis and structure-activity relationships of the new cephalosporins and their *in vivo* efficacy.

Chemistry

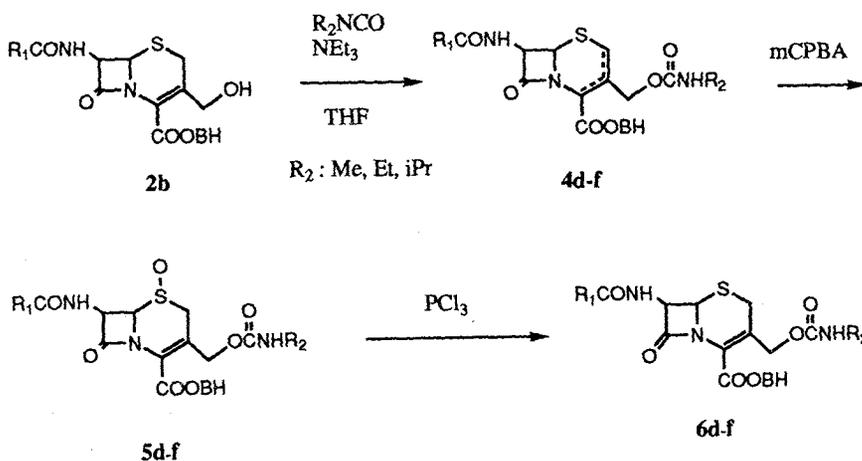
New cephalosporins with *N*-substituted carbamoyloxymethyl at the C-3 position were prepared by the routes shown in Scheme 1~5. Scheme 1 and Scheme 2 show two general methods for modification of 3-hydroxymethyl cepheems (**1a**, **1b**) to 7-protected 3-substituted carbamoyloxy cepheems. One is the *N,N'*-carbonyldiimidazole method¹¹⁾ (Method a) and another is the isocyanate method (Method b). Scheme 3 illustrates the general route from 7-protected 3-substituted carbamoyloxy cepheems to aminothiazolyl cephem carboxylic acids and their prodrug esters. Scheme 4 describes the synthetic route for *N*-methylpiperazine cepheems, because they were synthesized from 3-hydroxymethyl cephem oxide (**13**). Scheme 5 shows the route for *anti* hydroxyimino cephem (**9v**).

In Scheme 1 (Method a), benzhydryl 3-hydroxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate (**2a**) or 7-formamido-3-hydroxymethyl cephem (**2b**) was synthesized by acylation at the C-7 position of 7-ACA with (2-thienyl)acetyl chloride or formic acid-acetic anhydride, hydrolysis of acetoxy substituent at the C-3 position with bran-enzyme and esterification of the C-4 carboxylic acid with diphenyldiazomethane, following the procedure reported in a previous paper¹⁰⁾. The hydroxymethyl group was converted with

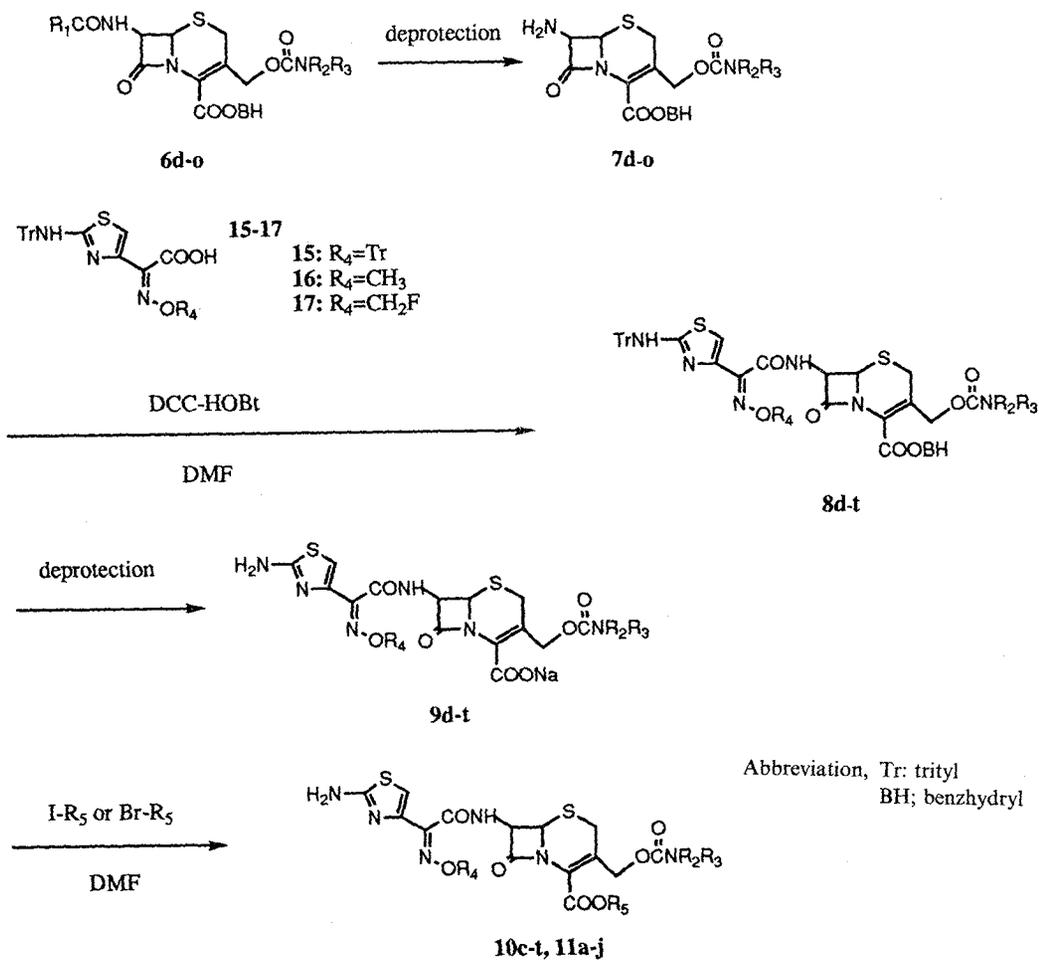
Scheme 1.



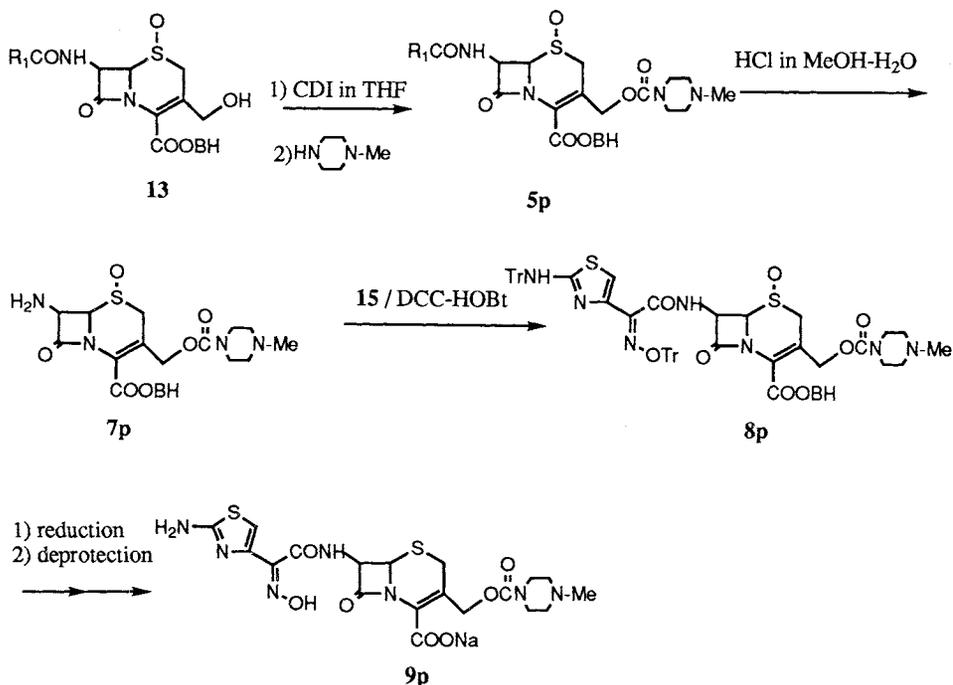
Scheme 2.



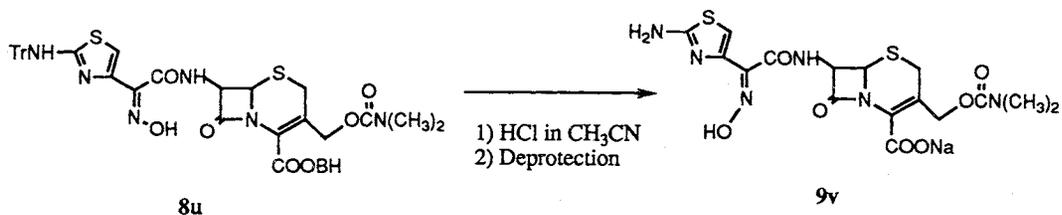
Scheme 3.



Scheme 4.



Scheme 5.



N,N'-carbonyldiimidazole to activated ester (**3a**, **3b**) and was successively reacted with various amines to afford substituted carbamoyloxymethyl cephem (**4g**~**4o**). As the double bond of the cephem nucleus was isomerized from Δ^3 to Δ^2 in the course of the reactions, these mixtures (**4g**~**4o**) were oxidized with *m*-chloroperoxybenzoic acid and treated with phosphorus trichloride to provide the desired Δ^3 derivatives (**6g**~**6o**).

Scheme 2 (Method b) illustrates another procedure for preparing 3-monosubstituted carbamoyloxymethyl cephem (**4d**~**4f**). The hydroxymethyl group of **2a** was acylated with several alkylisocyanates in the presence of triethylamine. The double bond of the cephem was again partially isomerized to Δ^2 , so the mixture was converted through the oxidation-reduction sequence described above to afford benzhydryl 7-formamido-3-monosubstituted carbamoyloxymethyl-3-cephem-4-carboxylate (**6d**~**6f**).

As shown in Scheme 3, the 7-protected carbamoyloxy cephem (**6d**~**6o**), which were prepared in Scheme 1 and Scheme 2, were transformed to aminothiazolyoxyimino cephem acids (**9d**~**9t**) and their prodrugs (**10c**~**10t**, **11a**~**11j**) in several steps. First, the 7-acyl side chains of **6d**~**6o** were cleaved to give 7-amino-cepheps. The thienylacetamido moiety of **6i**, **6j**, **6o** was removed by the PCl_5 imino-chloride

method. On the other hand, the formamido group of **6** was cleaved by 12 M hydrochloric acid in methanol to yield 7-amino-3-substituted carbamoyl cepheams (**7d** ~ **7o**). Second, 7-amino cepheams (**7d** ~ **7o**) were coupled with (*Z*)-2-(2-tritylaminothiazol-4-yl)-trityloxyimino acid (**15**)¹² or alkoxyiminoacetic acids such as (**16**) and (**17**)¹³ in the presence of 1-hydroxybenztriazole and *N,N'*-dicyclohexylcarbodiimide to give the acylated compounds (**8d** ~ **8t**). Third, protected aminothiazolyl cepheams (**8d** ~ **8t**) were treated with trifluoroacetic acid and anisole, successively treated with formic acid in the case of trityl-protected hydroxyimino cepheams, and purified by ODS chromatography to yield 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyimino or alkoxyimino acetamido]-3-substituted carbamoyloxymethyl-3-cephem-4-carboxylic acids (**9d** ~ **9t**). Finally, these sodium salts (**9d** ~ **9t**) were esterified with appropriate iodo or bromo ester reagents (I or Br-*R*₅) in *N,N*-dimethylformamide to give the corresponding prodrug-type esters (**10c** ~ **10t**, **11a** ~ **11j**).

Scheme 4 depicts the route for *N*-methylpiperazine derivative (**8p**). This compound couldn't be obtained by the Method a, because the double bond of the cephem nucleus of the intermediates was found to be isomerized due to the basicity of *N*-methylpiperazine. In order to avoid this annoying isomerization, the 3-hydroxymethyl cephem sulfoxide (**13**) was chosen as the starting material and converted to benzhydryl 7-formamido-3-(4-methylpiperazinyl)carbonyloxymethyl-3-cephem-4-carboxylate-1-oxide (**5p**) by a similar method (Method a) to that described in Scheme 1. Cephem oxide (**5p**) was transformed through acyl cleavage and acylation at the C-7 side chain to protected thiazolyl cephem (**8p**), which was converted by reduction with PCl_3 , deprotection with trifluoroacetic acid-anisole and formic acid and purification to 3-(4-methylpiperazinyl)carbonyloxymethyl-3-cephem (**9p**).

Scheme 5 illustrates the synthetic route for the *anti* counterpart of E1100. The protected compound (**8u**) was treated with 12 M hydrochloric acid in acetonitrile to afford the mixture of the isomerized (*E*)-hydroxyimino compound (**8v**) and the (*Z*) isomer (**8u**). The isolated (*E*)-isomer by chromatography was converted through deprotection and purification by a similar manner to that described in Scheme 3 to 7-[(*E*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-cephem (**9v**).

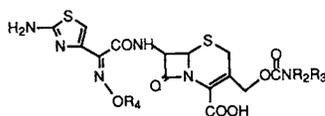
Antibacterial Activity and Oral Absorption

The *in vitro* antibacterial activity of the new cephalosporins (**9c** ~ **9v**) against selected Gram-positive and Gram-negative bacteria is shown in Table 1 compared with that of CCL, cefpodoxime (CPDX), and CFDN. Table 2 shows that the urinary recovery (%) after oral administration of their pivaloyloxymethyl (POM) esters (**10c** ~ **10s**) (20 mg/kg as the parent compound) to mice and the relative bioavailability (%) calculated according to the following equation.

$$\text{Relative Bioavailability (BA\%)} = \frac{(\text{Urinary recovery (\%)} \text{ after po dosage})}{(\text{Urinary recovery (\%)} \text{ after iv dosage})} \times 100$$

Most of the new tested compounds showed potent activity against Gram-positive and Gram-negative bacteria including β -lactamase producing strains except for *P. aeruginosa* PAO1. In general, the antibacterial activities of hydroxyimino derivatives (**9c** ~ **9p**) against Gram-positive bacteria especially *S. aureus* were higher than those of methoxy and other alkoxy derivatives (**9q** ~ **9t**). The hydroxyimino cepheams (**9c** ~ **9p**) exhibited as potent against *S. aureus* as CFDN, and more potent than CPDX, while they showed more potent against Gram-negative bacteria than both CFDN and CPDX.

In the series of hydroxyimino derivatives, the modification with a more lipophilic substituent at the C-3 position of the nucleus resulted in slight reduction in activity but still maintenance in strong potency

Table 1. *In vitro* antibacterial activity of 3-substituted carbamoyloxymethyl cepems (**9c**~**v**).

Compound	9c	9d	9e	9f	9g	9h
R ₄	H	H	H	H	H	H
R ₂	H	H	H	H	H	H
R ₃	H	CH ₃	C ₂ H ₅	CH(CH ₃) ₂	CH ₂ CH ₂ F	CH ₂ CF ₃
<i>S. aureus</i> 209P	0.1	0.1	0.1	0.2	0.2	0.4
<i>S. aureus</i> JS1 (MRSA)	1.56	1.56	1.56	1.56	1.56	6.25
<i>S. pneumoniae</i> E33023	0.1	0.05	—	0.05	0.05	0.05
<i>E. faecalis</i> E22018	25	12.5	12.5	12.5	6.25	12.5
<i>E. coli</i> NIHJ JC-2	0.05	0.025	0.05	0.1	0.05	0.1
<i>K. pneumoniae</i> IID875	0.025	0.025	0.05	0.05	0.05	0.1
<i>M. morgani</i> E06071 ^a	1.56	0.4	0.2	0.2	1.56	3.13
<i>C. freundii</i> GN346 ^a	0.2	0.2	0.2	0.2	0.8	0.8
<i>E. cloacae</i> GN7471 ^a	3.13	6.25	1.56	3.13	3.13	6.25
<i>S. marcescens</i> IID620	0.05	0.05	0.05	0.05	0.1	0.1
<i>H. influenzae</i> IID1638	0.4	0.2	0.1	0.05	0.2	0.4
<i>P. aeruginosa</i> PA01	> 100	> 100	> 100	> 100	> 100	> 100

Compound	9i	9j	9k	9l	9m	9n
R ₄	H	H	H	H	H	H
R ₂	CH ₃	CH ₃	CH ₃			
R ₃	CH ₃	C ₂ H ₅	CH ₂ CH ₂ OH			
<i>S. aureus</i> 209P	0.1	0.2	0.1	0.2	0.1	0.2
<i>S. aureus</i> JS1 (MRSA)	1.56	3.13	1.56	1.56	1.56	3.13
<i>S. pneumoniae</i> E33023	0.1	0.1	0.1	0.1	0.1	0.05
<i>E. faecalis</i> E22018	100	50	100	50	25	50
<i>E. coli</i> NIHJ JC-2	0.1	0.4	0.05	0.1	0.4	1.56
<i>K. pneumoniae</i> IID875	0.05	0.2	0.05	0.1	0.2	0.8
<i>M. morgani</i> E06071 ^a	0.8	—	0.8	0.8	0.8	1.56
<i>C. freundii</i> GN346 ^a	0.2	0.8	0.4	0.4	0.8	1.56
<i>E. cloacae</i> GN7471 ^a	1.56	3.13	3.13	3.13	3.13	3.13
<i>S. marcescens</i> IID620	0.05	0.2	0.05	0.05	0.1	0.8
<i>H. influenzae</i> IID1638	0.1	0.05	0.1	0.1	0.1	0.1
<i>P. aeruginosa</i> PA01	> 100	> 100	> 100	> 100	> 100	> 100

against most members of the Enterobacteriaceae. Like **9p**, which was acylated with a basic amine such as *N*-methylpiperazine, the introduction of basic amines at the C-3 position led to significant reduction in potency against both Gram-positive bacteria and Gram-negative bacteria. Therefore, the modification of the carbamoyloxy substituent seemed to be rather disappointing with respect to *in vitro* antibacterial activities. However, as for the activity against *H. influenzae*, which is a very important pathogen in respiratory tract infection, the disubstituted analogues (**9i**~**9o**) generally were more potent than monosubstituted (**9d**~**9h**) and non-substituted (**9c**)¹³ carbamoyloxymethyl cepems. Among methyl derivatives such as non-substituted (**9c**), monomethyl (**9d**) and dimethyl derivatives (**9i**), this tendency was confirmed in the activity against clinical isolates of *H. influenzae*, which is depicted in Fig. 4. Therefore, dimethyl cepem (**9i**) was regarded as one of the most well-balanced compounds.

Fluoromethoxyimino cepem (**9t**) showed very similar activity to methoxyimino cepem (**9s**), in spite of the report¹⁷) that fluoromethoxyimino derivatives are more potent than their counterparts of methoxyimino derivatives. The *anti*-hydroxyimino isomer (**9u**) was found to be less active than **9i**, which

Table 1. (Continued)

Compound	9o	9p			
R ₄	H	H	Cefaclor	Cefdinir	Cefpodoxime
R ₂					
R ₃					
<i>S. aureus</i> 209P	0.4	0.2	0.4	0.1	1.56
<i>S. aureus</i> JS1 (MRSA)	1.56	3.13	50	3.13	50
<i>S. pneumoniae</i> IID552	0.1	0.2	0.4	0.1	0.05
<i>E. faecalis</i> E22018	50	12.5	50	12.5	100
<i>E. coli</i> NIHJ JC-2	0.2	0.05	1.56	0.4	0.4
<i>K. pneumoniae</i> IID875	0.1	0.05	0.8	0.2	0.05
<i>M. morgani</i> E06071 ^a	3.13	1.56	> 100	> 100	100
<i>C. freundii</i> GN346 ^a	1.56	0.8	25	12.5	25
<i>E. cloacae</i> GN7471 ^a	6.25	12.5	100	> 100	> 100
<i>S. marcescens</i> IID620	0.1	0.4	50	6.25	0.1
<i>H. influenzae</i> IID1638	0.1	0.8	1.56	0.4	0.1
<i>P. aeruginosa</i> PA01	> 100	> 100	> 100	> 100	> 100

Compound	9q	9r	9s	9t	9v
R ₄	CH ₃	CH ₃	CH ₃	CH ₂ F	H (Anti)
R ₂	H	H	CH ₃	CH ₃	CH ₃
R ₃	H	CH ₃	CH ₃	CH ₃	CH ₃
<i>S. aureus</i> 209P	1.56	0.8	0.8	0.8	3.13
<i>S. aureus</i> JS1 (MRSA)	0.8	6.25	3.13	3.13	25
<i>S. pneumoniae</i> IID552	0.025	0.025	0.012	0.025	6.25
<i>E. faecalis</i> E22018	—	100	> 100	> 100	> 100
<i>E. coli</i> NIHJ JC-2	0.05	0.1	0.2	0.2	3.13
<i>K. pneumoniae</i> IID 875	0.012	0.025	0.1	0.2	1.56
<i>M. morgani</i> E06071 ^a	1.56	0.8	0.8	3.13	6.25
<i>C. freundii</i> GN346 ^a	0.4	0.4	0.8	1.56	6.25
<i>E. cloacae</i> GN7471 ^a	6.25	3.13	3.13	3.13	25
<i>S. marcescens</i> IID620	0.012	0.006	0.025	0.025	0.8
<i>H. influenzae</i> IID1638	0.025	0.025	0.012	0.012	6.25
<i>P. aeruginosa</i> PA01	12.5	12.5	25	25	> 100

^a High cephalosporinase producing strain.

Table 2. Urinary recovery (U.R.) and bioavailability (B.A.) after oral administration of their pivaloyloxymethyl (POM) esters to mice (20 mg/kg).

Compound	R ₄	R ₂ , R ₃	U.R. (%) (po)	B.A. (%)
10c	H	H, H	11	17
10d		H, CH ₃	6	9
10i		CH ₃ , CH ₃	18	36
10j		CH ₃ , CH ₂ CH ₃	20	39
10k		CH ₃ , CH ₂ CH ₂ OH	2	3
10l			9	23
10m			3	7
10n			6	26
10o			7	15
10q	CH ₃	H, H	10	18
10r		H, CH ₃	15	19
10s		CH ₃ , CH ₃	20	34
10t	CH ₂ F	CH ₃ , CH ₃	10	23

Fig. 4. Antibacterial activity of carbamoyloxymethyl cepheems (9c, 9d, 9i) against clinical isolates of *H. influenzae* (20 strains).

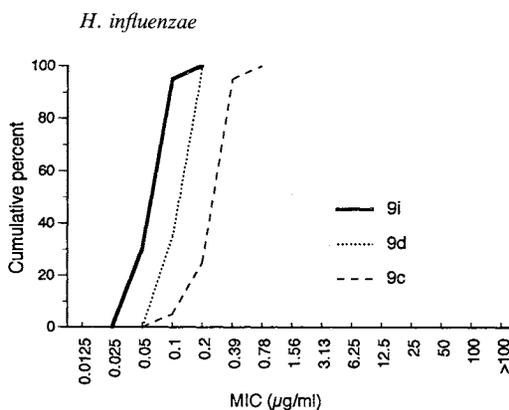
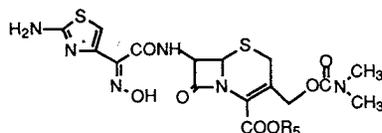


Table 3. Urinary recovery (U.R.) and bioavailability (B.A.) in mice (20 mg/kg, n=5) and protective effects (ED₅₀) against systemic infection in mice (n=8) after oral administration of various prodrugs of **9i**.



Compound	R ₅	U.R. (%) (po)	B.A. (%)	ED ₅₀ mg/kg	
				<i>S. aureus</i> E312908 ^a	<i>E. coli</i> E01125 ^a
9i	Na	3	6		
11a		6	12	22.2	0.57
10i		18	36	9	0.58
11b		24	48	10.8	0.58
11c		19	38		
11d		19	38		
11e		13	26		
11f		9	18	19.1	0.57
11g		7	14		
11h (E1101)		22	44	10.1	0.33
11i		22	44	23.5	0.95
11j		2	4		

^a MICs of **9i** are 0.8 µg/ml against *S. aureus* E31290 and 0.05 µg/ml against *E. coli* E01125.

means that the (*Z*)-configuration of oxyimino substituent is very important for potent antibacterial activity.

As shown in Table 2, the POM esters (**10c**~**10s**) showed modest and good bioavailability. Among the derivatives, *N,N*-dimethyl (**10i**, **10s**) and *N*-ethyl-*N*-methyl cephems (**10j**) showed good urinary recovery. In general, *N,N*-disubstituted carbamoyloxy cepheps esters showed better bioavailability than non-substituted (**10c**, **10q**) and mono-substituted esters (**10d**, **10r**), except for pyrrolidine cephem (**10m**), *N*-hydroxyethyl-*N*-methyl (**10k**) and morpholine (**10o**). The reason why the latter two derivatives exhibited poor oral absorbability was considered to be due to their polar substituents. It is interesting that both *N,N*-dimethyl derivatives (**10i**, **10s**) of the series of the hydroxyimino cepheps and the methoxyimino cepheps exhibited good oral absorbability, which prompted us to conclude that *N,N*-dimethylcabmoyloxymethyl group at the C-3 position worked as the key substituents for good oral absorption of cephem

prodrugs. However, fluoromethoxyimino cephem (**10t**) showed less bioavailability. Therefore, it was difficult to anticipate the oral absorption of cephem prodrugs simply from their chemical structures.

Since hydroxyimino *N,N*-dimethylcarbamoyloxy cephem (**10i**) showed well-balanced antibacterial activity and good oral absorbability, a series of other prodrug esters were synthesized and evaluated. Table 3 shows the bioavailability of various types of prodrug esters (**11b~11j**). Among the series of *N,N*-dimethylcarbamoyloxy cepheims (**10i, 11a~11j**), the POM ester (**10i**), 2-ethylbutyryloxymethyl ester (**11b**), 1-(isopropoxycarbonyloxy)ethyl ester (**11h**) and 1-(cyclohexyloxycarbonyloxy)ethyl esters (**11i**) exhibited good bioavailability. On the other hand, less lipophilic esters like **11a, 11f, 11g, 11j** showed poor bioavailability. These results mean that the lipophilicity of the prodrugs deeply affected their oral absorbability. Consequently, as shown in Table 3, the modification of cephem carboxylic acid (**9i**) to prodrug type esters such as **11b, 11h, 11i** resulted in about 7-fold increase in oral absorbability, while **9i** showed only 6% bioavailability after oral administration.

Since some *N,N*-dimethylcarbamoyloxy cepheims exhibited good oral absorbability, several prodrugs (**10i** and **11a, 11b, 11f, 11h, 11i**) were evaluated further for their *in vivo* activity. As shown in Table 3, the POM ester (**10i**) and the 1-(isopropoxycarbonyloxy)ethyl ester (**11h**) were found to be effective against *S. aureus* E31290 and *E. coli* E01125. It is still not clear why the cyclohexyl compound (**11i**) was not effective *in vivo*, even though **11i** showed good oral absorbability. Now, we assume that this discrepancy happened due to the difference in absorption between non-infected mice and infected mice.

In summary, *N,N*-dimethylcarbamoyloxy cephem (**9i**, E1100) showed potent and well-balanced antibacterial activity and its prodrug esters exhibited good oral absorption and excellent *in vivo* efficacy. Considering the safety of the ester moiety, the 1-(isopropoxycarbonyloxy)ethyl prodrug (**11h**, E1101) was chosen as a candidate for further evaluation.

Experimental

¹H NMR spectra were recorded on a Varian UNITY 400 spectrometer. IR spectra were measured on a Hitachi 260-30 or a Nicolet 205 FT-IR spectrometer. Melting points were taken on a Yamato MP21.

Determination of Antibacterial Activities

All the *in vitro* antibacterial activities are given as MIC in $\mu\text{g/ml}$ required to prevent growth of bacterial culture. MICs were determined by the serial agar dilution method 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 4 weeks weighing 24~30 g were used in groups of 4. The antibiotics were given to mice orally as a single dose of 20 mg/kg in a suspension of 0.5% CMC and intravenously at 20 mg/kg as a solution. Urine was collected over 6 hours after dosing.

Benzhydryl 7-(2-Thienylacetamido)-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate-1-oxide (**5i**) (Method a)

To a solution of benzhydryl 7-(2-thienylacetamido)-3-hydroxymethyl-3-cephem-4-carboxylate¹⁰⁾ (**1a**; 30 g, 0.058 mol) in tetrahydrofuran (600 ml) was added *N,N'*-carbonyldiimidazole (11.25 g, 0.069 mol) under ice cooling, and the mixture was stirred at the same temperature for 3 hours. The mixture was diluted with ethyl acetate (1 liter), and the organic layer was washed with water (0.4 liter). To the extract was added a solution of 50% aqueous dimethylamine (12 g, 0.075 mol) under ice cooling, and the reaction mixture was stirred for 1 hour. The mixture was washed with brine, dried over anhydrous MgSO_4 and concentrated

under reduced pressure to give a mixture of benzhydryl 7-(2-thienylacetamido)-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate and benzhydryl 7-(2-thienylacetamido)-3-*N,N*-dimethylcarbamoyloxymethyl-2-cephem-4-carboxylate (24 g).

To a solution of the compounds obtained above in tetrahydrofuran (400 ml) under ice cooling was added a solution of *m*-chloroperoxybenzoic acid (20 g, 0.116 mol) in tetrahydrofuran (100 ml), and the mixture was stirred at the same temperature for 30 minutes. The mixture was concentrated under reduced pressure, and the residue was washed with ethyl ether. The residue was purified by silica gel column chromatography (eluent; *n*-hexane-ethyl acetate, 3:1). The fractions containing the desired compound were collected and evaporated under reduced pressure to give 7.5 g of **5i** (21%). MP 174~176°C (dec), ¹H NMR (CDCl₃) δ 2.84 (3H, s), 2.92 (3H, s), 3.23 and 3.88 (2H, ABq, *J*=18 Hz), 3.88 (2H, s), 4.48 (2H, d, *J*=4 Hz), 4.78 and 5.34 (2H, ABq, *J*=8 Hz), 6.15 (1H, dd, *J*=4, 8 Hz), 6.90~7.10 (2H, m), 6.97 (1H, s), 7.20~7.60 (11H, m).

Benzhydryl 7-(2-Thienylacetamido)-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**6i**)

To a solution of **5i** (5 g, 8.2 mmol) in *N,N*-dimethylformamide (50 ml) under ice cooling was added phosphorus trichloride (2.5 g, 18 mmol), and the mixture was stirred at the same temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate (500 ml), and the organic layer was washed with water and then with brine, and dried over anhydrous MgSO₄. The filtrate was concentrated under reduced pressure, and to the residue was added a solution of acetone-diisopropyl ether, and the precipitate was collected by filtration to give 3.8 g of **6i** (79%). MP 62~68°C (dec), ¹H NMR (CDCl₃) δ 2.82 (3H, s), 2.90 (3H, s), 3.40 and 3.55 (2H, ABq, *J*=18 Hz), 3.84 (2H, s), 4.81 and 5.06 (1H, ABq, *J*=12 Hz), 4.98 (1H, d, *J*=4 Hz), 5.84 (1H, dd, *J*=4, 8 Hz), 6.27 (1H, d, *J*=8 Hz), 6.94 (1H, s), 6.98~7.02 (2H, m), 7.25~7.43 (11H, m).

Preparation of **6k**, **6o** was carried out by a method similar to that described for **6i**.

Benzhydryl 7-Amino-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate hydrochloride (**7i**)

To a solution of phosphorous pentachloride (2.8 g, 13 mmol) and pyridine (1.04 g, 13 mmol) in dichloromethane (80 ml) at -10°C was added **6i** (1.6 g, 2.7 mmol), and the mixture was stirred at the same temperature for 1 hour. 1,3-Propanediol (1 ml) was added to the reaction mixture at -20°C. After stirring for 1 hour, methanol (10 ml) was added to the mixture and the resulting mixture was heated to room temperature. The mixture was diluted with water (50 ml), and the organic layer was washed with water and dried over anhydrous MgSO₄. The extract was evaporated *in vacuo*, and the residue was crystallized from ethyl ether and diisopropyl ether to give 1.0 g of **7i** (74%). MP 140~143°C (dec), ¹H NMR (CDCl₃) δ 2.83 (3H, s), 2.90 (3H, s), 3.43 and 3.58 (2H, ABq, *J*=18 Hz), 4.80 and 5.06 (2H, ABq, *J*=12 Hz), 4.80~5.00 (1H, m), 4.97 (1H, d, *J*=4 Hz), 6.98 (1H, s), 7.25~7.50 (10H, m).

Benzhydryl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**8i**)

To a solution of (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetic acid (**15**; 1.9 g, 2.8 mmol) and 1-hydroxybenztriazole (0.4 g, 2.9 mmol) in *N,N*-dimethylformamide (20 ml), *N,N'*-dicyclohexylcarbodiimide (0.6 g, 2.9 mmol) was added and the mixture was stirred for 30 minutes. To the resulting mixture were added **7i** (1.3 g, 2.8 mmol) and triethylamine (2.8 g, 2.8 mmol), and the mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate (300 ml). After being filtered off, the filtrate was washed with water and brine, and dried over anhydrous MgSO₄. The filtrate was evaporated under reduced pressure, and the residue was chromatographed on a column of silica gel (Wako C-200, 50 g). The column was eluted with *n*-hexane-ethyl acetate (2:1). The fractions containing the desired product were collected and evaporated. The residue was solidified with diisopropyl ether to give 1.4 g of **8i** as an amorphous powder (45%).

Preparation of **8k**, **8o** was carried out by a method similar to that described for **8i**.

The spectral data for **8i**, **8k**, **8o** are listed in Table 4.

Benzhydryl 7-Formamido-3-hydroxymethyl-3-cephem-4-carboxylate (**1b**)¹⁰⁾

A mixture of 99% formic acid (17 g, 370 mmol) and acetic anhydride (7.5 g, 73.5 mmol) was stirred

Table 4. Spectral data of protected cepheps **8d**~**t**.

Compound	¹ H NMR (δ)	Solvent ^a
8d	2.73 (1.5H, s), 2.75 (1.5H, s), 3.39, 3.49 (2H, ABq, $J=19$ Hz), 4.40~4.48 (1H, m), 4.75, 5.04 (2H, ABq, $J=14$ Hz), 5.04 (1H, d, $J=5$ Hz), 6.10 (1H, dd, $J=9, 5$ Hz), 6.43 (1H, s), 6.97 (1H, s), 7.18~7.48 (42H, m)	A
8e	0.98 (3H, t, $J=6$ Hz), 2.97 (2H, m), 3.40~3.70 (2H, m), 4.62, 4.81 (2H, ABq, $J=14$ Hz), 5.24 (1H, d, $J=5$ Hz), 5.92 (1H, dd, $J=5, 9$ Hz), 6.59 (1H, s), 6.93 (1H, s), 7.10~7.80 (40H, m), 8.78 (1H, s), 9.88 (1H, d, $J=9$ Hz)	B
8f	0.91 (3H, t, $J=7$ Hz), 1.42~1.58 (2H, m), 3.09 (2H, q, $J=7$ Hz), 3.24, 3.49 (2H, ABq, $J=19$ Hz), 4.50~4.58 (1H, m), 4.76, 5.03 (2H, ABq, $J=14$ Hz), 5.04 (1H, d, $J=5$ Hz), 6.09 (1H, dd, $J=5, 8$ Hz), 6.43 (1H, s), 6.96 (1H, s), 7.10~7.50 (41H, m)	A
8g	3.18, 3.37 (2H, ABq, $J=18$ Hz), 3.10~3.40 (2H, m), 4.20~4.40 (2H, m), 4.70, 4.99 (2H, ABq, $J=14$ Hz), 4.92 (1H, d, $J=5$ Hz), 6.04 (1H, dd, $J=5, 9$ Hz), 6.44 (1H, s), 6.84 (1H, s), 6.95 (1H, s), 7.10~7.50 (41H, m)	A
8h	3.05, 3.33 (2H, ABq, $J=19$ Hz), 3.50~3.65 (2H, m), 4.72, 5.01 (2H, ABq, $J=14$ Hz), 4.91 (1H, d, $J=5$ Hz), 6.03 (1H, dd, $J=5, 8$ Hz), 6.45 (1H, s), 6.83 (1H, s), 6.95 (1H, s), 7.13~7.47 (41H, m)	A
8i	2.82 (3H, s), 2.91 (3H, s), 3.36, 3.48 (2H, ABq, $J=18$ Hz), 4.81, 5.14 (2H, ABq, $J=12$ Hz), 5.05 (1H, d, $J=4$ Hz), 6.08 (1H, dd, $J=4, 8$ Hz), 6.43 (1H, s), 6.80 (1H, s), 6.97 (1H, s), 7.18~7.50 (42H, m)	A
8k	2.94~2.97 (3H, m), 3.24~3.30 (2H, m), 3.43~3.52 (2H, m), 4.80~4.83 (1H, m), 5.06 (1H, d, $J=5$ Hz), 5.10~5.15 (1H, m), 6.11 (1H, dd, $J=5, 9$ Hz), 6.44 (1H, s), 6.96 (1H, s), 7.20~7.40 (42H, m)	A
8j	1.10~1.20 (3H, m), 2.79 (1.5H, s), 2.87 (1.5H, s), 3.18~3.35 (3H, m), 3.48, 3.48 (1H, ABq, $J=18$ Hz), 4.82 (1H, d, $J=12$ Hz), 5.06 (1H, d, $J=5$ Hz), 5.07~5.15 (1H, m), 6.07 (1H, dd, $J=5, 8$ Hz), 6.43 (1H, s); 6.83 (1H, s), 6.95 (1H, s), 7.10~7.40 (40H, m), 7.47 (1H, d, $J=8$ Hz)	A
8l	2.15~2.27 (2H, m), 3.26, 3.50 (2H, ABq, $J=19$ Hz), 3.85~4.10 (4H, m), 4.82, 5.08 (2H, ABq, $J=14$ Hz), 5.05 (1H, d, $J=5$ Hz), 6.11 (1H, dd, $J=5, 9$ Hz), 6.47 (1H, s), 6.99 (1H, s), 7.15~7.53 (42H, m)	A
8m	1.80~1.90 (4H, m), 3.20~3.40 (4H, m), 3.29, 3.50 (2H, ABq, $J=14$ Hz), 5.07 (1H, d, $J=5$ Hz), 6.09 (1H, dd, $J=5, 9$ Hz), 6.43 (1H, s), 6.96 (1H, s), 7.15~7.50 (42H, m)	A
8n	1.42~1.64 (6H, m), 3.25~3.43 (4H, m), 3.26, 3.48 (2H, ABq, $J=19$ Hz), 4.82, 5.12 (2H, ABq, $J=14$ Hz), 5.05 (1H, d, $J=5$ Hz), 6.05~6.12 (1H, m), 6.44 (1H, s), 6.96 (1H, s), 7.15~7.43 (41H, m)	A
8o	3.26, 3.50 (2H, ABq, $J=19$ Hz), 3.30~3.70 (8H, m), 4.82, 5.11 (2H, ABq, $J=13$ Hz), 5.05 (1H, d, $J=5$ Hz), 6.20 (1H, dd, $J=5, 8$ Hz), 6.44 (1H, s), 6.85 (1H, brs), 6.96 (1H, s), 7.15~7.50 (41H, m)	A
8p	2.08 (3H, s), 2.30~2.90 (4H, m), 3.26, 3.51 (2H, ABq, $J=18$ Hz), 3.40~3.80 (4H, m), 4.82, 5.04 (2H, ABq, $J=12$ Hz), 5.03 (1H, d, $J=5$ Hz), 6.09 (1H, dd, $J=5, 10$ Hz), 6.45 (1H, s), 6.96 (1H, s), 7.10~7.50 (42H, m)	A
8r	2.74 (1.5H, s), 2.75 (1.5H, s), 3.39, 3.56 (2H, ABq, $J=19$ Hz), 4.07 (3H, s), 4.45~4.53 (1H, m), 4.77, 5.04 (2H, ABq, $J=14$ Hz), 5.04 (1H, d, $J=5$ Hz), 5.95 (1H, dd, $J=5, 9$ Hz), 6.73 (1H, s), 6.88 (1H, d, $J=9$ Hz), 6.95 (1H, s), 7.03 (1H, s), 7.24~7.44 (25H, m)	A
8s	2.83 (3H, s), 2.89 (3H, s), 3.36, 3.50 (2H, ABq, $J=19$ Hz), 4.04 (3H, s), 4.84, 5.10 (2H, ABq, $J=14$ Hz), 5.04 (1H, d, $J=5$ Hz), 5.92~5.96 (1H, m), 6.76 (1H, s), 6.94 (1H, s), 7.20~7.45 (25H, m)	A
8t	2.82 (3H, s), 2.86 (3H, s), 3.42, 3.56 (2H, ABq, $J=19$ Hz), 4.82, 5.09 (2H, ABq, $J=14$ Hz), 5.05 (1H, d, $J=5$ Hz), 5.72, 5.86 (2H, ABq, d, $J=4, 55$ Hz), 5.94 (1H, dd, $J=5, 8$ Hz), 6.81 (1H, s), 6.93 (1H, s), 7.03 (1H, d, $J=8$ Hz), 7.28~7.45 (25H, m)	A

^a A; CDCl₃, B; d₆-DMSO.

at 40°C for 30 minutes. To the reaction mixture was added 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (10 g, 37 mmol) in several portions at room temperature, and the mixture was stirred for 2 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved in methanol (40 ml). To the mixture was added sodium acetate (4.5 g, 55 mmol), and the mixture was stirred for 20 minutes. To the resulting mixture was added diisopropyl ether (160 ml), and the crystals were collected on a filter and

washed with diisopropyl ether to give 11 g of sodium 7-formamido-3-acetoxymethyl-3-cephem-4-carboxylate (93%).

To a solution of phosphate buffer (pH 6.5, 200 ml) were added sodium 7-formamido-3-acetoxymethyl-3-cephem-4-carboxylate (5 g, 15.5 mmol) and wheat bran (32 g), and the mixture was stirred for 18 hours. After being filtered off, a solution of diphenyldiazomethane (4 g, 55 mmol) in dichloromethane (8 ml) was added to the filtrate. The pH of the mixture was adjusted to 2.8 by adding of 1 M hydrochloric acid, and the mixture was stirred for 14 hours at 20°C. The organic layer was washed with water and then brine, and dried over anhydrous MgSO₄. The filtrate was evaporated to dryness, and the residue was crystallized from diisopropyl ether to give 1.15 g of **1b** (16%). MP 150~152°C (dec), ¹H NMR (DMSO-*d*₆) δ 3.58 and 3.64 (2H, ABq, *J* = 18 Hz), 3.96 and 4.42 (2H, ABq, *J* = 13 Hz), 4.97 (1H, d, *J* = 5 Hz), 5.98 (1H, dd, *J* = 5, 8 Hz), 6.49 (1H, d, *J* = 8 Hz), 6.94 (1H, s), 7.20~7.50 (10H, m), 8.23 (1H, s).

Benzhydryl 7-Formamido-3-(1-piperidinyl)carbonyloxymethyl-3-cephem-4-carboxylate-1-oxide (**5n**) (Method a)

To a solution of **1b** (4.24 g, 10 mmol) in tetrahydrofuran (80 ml) under ice cooling was added *N,N'*-carbonyldiimidazole (1.62 g, 10 mmol), and the mixture was stirred for 2 hours. To the reaction mixture, piperidine (1.02 g, 12 mmol) was added and the mixture was stirred for 18 hours at the same temperature. The mixture was evaporated *in vacuo*, and the residue was dissolved in ethyl acetate (200 ml). The organic layer was washed with water and then with brine, and dried over anhydrous MgSO₄. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on a column of silica gel (Wako C-200, 100 g). The column was eluted with *n*-hexane-ethyl acetate (2:1), and the fractions containing the desired product were collected and evaporated to give 2.3 g of benzhydryl 7-formamido-3-(1-piperidinyl)carbonyloxymethyl-2-cephem-4-carboxylate as an amorphous powder (43%). MP 185~188°C (dec), ¹H NMR (CDCl₃) δ 1.20~1.40 (6H, m), 3.30~3.40 (4H, m), 4.57 and 4.66 (2H, ABq, *J* = 13 Hz), 5.13 (1H, s), 5.22 (1H, d, *J* = 4 Hz), 5.70~5.75 (1H, m), 6.44 (1H, s), 6.89 (1H, s), 7.25~7.40 (10H, m), 8.23 (1H, s)

To a solution of benzhydryl 7-formamido-3-(1-piperidinyl)carbonyloxymethyl-2-cephem-4-carboxylate (3.4 g, 6.3 mmol) in ethyl acetate (20 ml) was added *m*-chloroperoxybenzoic acid (1.53 g, 8.9 mmol) under ice cooling, and the mixture was stirred at the same temperature for 35 minutes. The reaction mixture was evaporated under reduced pressure, and the residue was chromatographed on a column of silica gel (Wako C-200, 100 g). The column was eluted with dichloromethane-ethyl acetate (4:1). The fractions containing the desired product were collected and evaporated. The residue was crystallized from diisopropyl ether to give 1.53 g of **5n** (44%). MP 185~188°C (dec), ¹H NMR (DMSO-*d*₆) δ 1.35~1.55 (6H, m), 3.23~3.30 (4H, m), 3.65 and 4.01 (2H, ABq, *J* = 19 Hz), 4.58 and 5.11 (2H, ABq, *J* = 14 Hz), 4.98 (1H, d, *J* = 4 Hz), 6.05 (1H, m), 6.93 (1H, s), 7.25~7.55 (10H, m), 8.15 (1H, s), 8.43 (1H, d, *J* = 9 Hz).

Benzhydryl 7-Formamido-3-(1-piperidinyl)carbonyloxymethyl-3-cephem-4-carboxylate (**6n**)

To a solution of **5n** (2.07 g, 3.9 mmol) in *N,N*-dimethylformamide (25 ml) at -20°C was added phosphorous trichloride (1 ml, 11 mmol), and the reaction mixture was stirred at the same temperature for 35 minutes. The mixture was diluted with ethyl acetate (300 ml), and organic layer was washed with water and then brine, and dried over anhydrous MgSO₄. The filtrate was evaporated under reduced pressure, and the residue was purified by chromatography on a silica gel (Wako C-200, 50 g; eluent; *n*-hexane-ethylacetate, 3:1). The fractions containing the desired compound were collected and evaporated. The residue was crystallized from diisopropyl ether to give 1.87 g of **6n** as crystals (93%). MP 130~132°C (dec), ¹H NMR (CDCl₃) δ 1.35~1.55 (6H, m), 3.20~3.35 (4H, m), 3.35 and 3.46 (2H, ABq, *J* = 19 Hz), 4.76 and 5.03 (2H, ABq, *J* = 14 Hz), 4.90 (1H, d, *J* = 4 Hz), 5.80~5.85 (1H, m), 6.86 (1H, s), 7.14~7.40 (10H, m), 7.84 (1H, d, *J* = 9 Hz), 8.15 (1H, s).

Preparation of **6g**, **6h**, **6j**, **6l**, **6m** was carried out by a method similar to that described for **6n**.

Benzhydryl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-(1-piperidinyl)carbonyloxymethyl-3-cephem-4-carboxylate (**8n**)

To a solution of **6n** (1.87 g, 35 mmol) in tetrahydrofuran (10 ml) and methanol (10 ml) was added 12 M hydrochloric acid (3 ml, 36 mmol), and the mixture was stirred at room temperature for 2 hours. After

evaporation, the mixture was added to a solution of ethyl acetate and water. The organic layer was washed with water and then brine, and dried over anhydrous MgSO_4 . After being distilled off, the crude product of 7-amino cephem (**7n**) was obtained.

To a solution of **15** (2.35 g, 3.5 mmol) and 1-hydroxybenztriazole (0.56 g, 4.1 mmol) in *N,N*-dimethylformamide (18 ml) was added *N,N'*-dicyclohexylcarbodiimide (0.79 g, 3.8 mmol), and the mixture was stirred for 1 hour. To the resulting mixture was added **7n** (1.3 g, 2.8 mmol), and the mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate (300 ml) and after the precipitate was filtered off, the filtrate was washed with water and then brine, and dried over anhydrous MgSO_4 . The filtrate was evaporated under reduced pressure, and the residue was chromatographed on a column of silica gel (Wako C-200, 50 g). The column was eluted with *n*-hexane-ethyl acetate (2:1). The fractions containing the desired product were collected and evaporated. The residue was solidified from diisopropyl ether to give 1.4 g of **8n** as an amorphous powder (34%).

Preparation of **8d**~**8h**, **8j**, **8l**, **8m** was carried out by a method similar to that described for **8n**. The spectral data for **8d**~**8h**, **8j**, **8l**~**8n** are listed in Table 4.

Benzhydryl 7-Formamido-3-*N*-methylcarbamoyloxymethyl-3-cephem-4-carboxylate-1-oxide (**5d**) (Method b)

To a solution of **1b** (10 g, 24 mmol) in tetrahydrofuran (70 ml) were added methylisocyanate (13.9 ml, 240 mmol) and triethylamine (0.33 ml, 0.24 mmol), and the mixture was stirred at 50°C for 8 hours in a sealed bottle. The mixture was diluted with ethyl acetate (500 ml), and the organic layer was washed with water and then brine, and dried over anhydrous MgSO_4 . The filtrate was evaporated and purified by column chromatography of silica gel (Wako C-200 200 g; eluent; dichloromethane-ethyl acetate, 2:1) and the fractions containing the desired product were collected and evaporated to give 9.34 g of benzhydryl 7-formamido-3-*N*-methylcarbamoyloxymethyl-2-cephem-4-carboxylate (38%). ^1H NMR (CDCl_3) δ 2.55 (1.5H, s), 2.56 (1.5H, s), 4.44 and 4.52 (2H, ABq, $J=13$ Hz), 5.06 (1H, s), 5.10~5.20 (1H, m), 5.13 (1H, d, $J=4$ Hz), 5.55 (1H, dd, $J=4, 9$ Hz), 6.33 (1H, s), 6.81 (1H, s), 7.20~7.28 (10H, m), 7.62 (1H, d, $J=9$ Hz), 8.10 (1H, s).

To a solution of the Δ^2 -cephem obtained above (9.3 g, 19.3 mmol) in a solution of ethyl acetate (100 ml) and tetrahydrofuran (50 ml) under ice cooling was added *m*-chloroperoxybenzoic acid (4.76 g, 19 mmol), and the mixture was stirred for 30 minutes. To the mixture was added ethyl ether (400 ml), and the precipitate was collected to give 5.9 g of **5d** (62%). MP 192~194°C (dec), ^1H NMR (CDCl_3) δ 2.68 (3H, s), 2.69 (3H, s), 3.21 and 3.83 (2H, ABq, $J=18$ Hz), 4.46 (1H, d, $J=4$ Hz), 4.43~4.55 (1H, m), 4.66 and 5.20 (2H, ABq, $J=15$ Hz), 6.09 (1H, dd, $J=4, 9$ Hz), 6.79 (1H, d, $J=9$ Hz), 6.90 (1H, s), 7.19~7.44 (10H, m), 8.02 (1H, s).

Benzhydryl 7-Formamido-3-*N*-methylcarbamoyloxymethyl-3-cephem-4-carboxylate (**6d**)

Preparation of **6d** was carried out by a method similar to that described for **6n**. MP 174~175°C (dec), ^1H NMR (CDCl_3) δ 2.74 (1.5H, s), 2.75 (1.5H, s), 3.41 and 3.56 (2H, ABq, $J=19$ Hz), 4.57~4.61 (1H, m), 4.79 and 5.04 (2H, ABq, $J=15$ Hz), 4.98 (1H, d, $J=5$ Hz), 5.93 (1H, dd, $J=5, 9$ Hz), 6.44 (1H, d, $J=9$ Hz), 6.95 (1H, s), 7.26~7.43 (10H, m), 8.24 (1H, s).

Preparation of **6e**~**6f** was carried out by a method similar to that described for **6d**.

Sodium 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**9i**)

To a solution of anisole (2 ml) and trifluoroacetic acid (3 ml) under ice-cooling was added the compound **8i** (1.4 g, 1.3 mmol), and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the residue was triturated with diisopropyl ether (100 ml). The precipitate was collected by filtration and was added to a solution of 90% formic acid (10 ml). After being stirred at room temperature for 3 hours, the mixture was concentrated, and the residue was triturated with diisopropyl ether. The crystals were collected by filtration and mixed with sodium acetate (262 mg, 3.2 mmol) in methanol (10 ml). The mixture was evaporated to dryness, and the residue was triturated with 2-propanol. The precipitate was collected by filtration to give a crude product of **9i**. The solid was chromatographed on a column of C_{18} Silica Gel (YMC A-343, eluent; 5% methanol). The fractions containing the desired compound were

concentrated under reduced pressure, and the residue was freeze-dried to give 240 mg of **9i** (39%).

Preparation of **9d**~**9p** was carried out by a method similar to that described for **9i**.

The spectral data of various derivatives **9d**~**9p** are listed in Table 5.

Benzhydryl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-N,N-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**8s**)

Preparation of **8s**, **8r**, **8t**, was carried out by a method similar to that described for **8i**, using **16**, **17**¹³⁾ instead of **15**.

The spectral data for various derivatives **8r**~**8t** are listed in Table 4.

Sodium 7-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-N,N-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**9s**)

To a solution of anisole (10 ml) and trifluoroacetic acid (20 ml) under ice-cooling was added **8s** (1.46 g, 1.6 mmol), and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo*, and the residue was triturated with diisopropylether (100 ml). The precipitate collected by filtration was mixed with sodium acetate (600 mg, 7.3 mmol) in methanol (15 ml). The mixture was evaporated to dryness, and the residue was solidified from 2-propanol. The precipitate was collected by filtration to give a crude product of **9s**. The solid was purified by chromatography on a column of C₁₈ Silica Gel (YMC A-343, eluent; 5% methanol). The fractions containing the desired compound were concentrated under reduced pressure and the residue was freeze-dried to give 71 mg of **9s** (8.5%).

Preparation of **9r**, **9t** was carried out by a method similar to that described for **9s**.

The spectral data for derivatives **9r**~**9t** are listed in Table 5.

Pivaloyloxymethyl 7-[(Z)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-N,N-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**10i**)

To a solution of **9i** (80 mg, 0.16 mmol) in *N,N*-dimethylformamide (2 ml) was added iodomethyl pivalate (37 mg, 0.16 mmol) dropwise under ice cooling. The mixture was stirred at the same temperature for 30 minutes and diluted with ethyl acetate. The reaction mixture was washed with water and then brine, and dried over anhydrous MgSO₄. The filtrate was concentrated *in vacuo*, and the residue was triturated with diisopropyl ether (50 ml) to yield 21 mg of **10i** as an amorphous powder (23%).

Preparation of **10c**~**10t**, **11a**~**11j** was carried out by a method similar to that described for **10i**.

The spectral data of various derivatives **10c**~**10t**, **11a**~**11j** are listed in Table 6 and Table 7.

Benzhydryl 7-Formamido-3-(4-methyl-1-piperazinyl)carbonyloxymethyl-3-cephem-4-carboxylate-1-oxide (**5p**)

To a solution of benzhydryl 7-formamido-3-hydroxymethyl-3-cephem-4-carboxylate-1-oxide (**13**; 22 g, 0.05 mol) in tetrahydrofuran (200 ml) under ice cooling was added *N,N*-carbonyldiimidazole (8.8 g, 0.055 mol), and the reaction mixture was stirred at the same temperature for 1 hour. To the reaction mixture were added *N*-methylpiperazine (10.25 g, 0.125 mol) and water (10 ml), and the mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate (500 ml). The mixture was washed with water and then brine, dried over MgSO₄ and concentrated under reduced pressure to give the crude desired product. The residue was purified by silica gel column chromatography (eluent; dichloromethane - methanol, 80 : 20) to afford 2.3 g of **5p** (8%). ¹H NMR (CDCl₃) δ 2.30 (3H, s), 2.25~2.60 (4H, m), 3.25 and 3.88 (2H, ABq, *J*=19 Hz), 3.30~3.50 (4H, m), 4.52 (1H, d, *J*=5 Hz), 4.76 and 5.33 (2H, ABq, *J*=15 Hz), 6.14 (1H, dd, *J*=5, 10 Hz), 6.95 (1H, s), 7.00~7.50 (11H, m), 8.24 (1H, s).

Benzhydryl 7-[(Z)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-(4-methyl-1-piperazinyl)carbonyloxymethyl-3-cephem-4-carboxylate-1-oxide hydrochloride (**8p**)

To a solution of **5p** (10.6 g, 18.7 mol) in tetrahydrofuran (100 ml) and methanol (50 ml) was added 1 M hydrochloric acid (10 ml), and the mixture was stirred at room temperature for 6 hours. After being evaporated, ethyl ether (300 ml) was added to the residue and the resulting precipitate was collected by filtration to give 10.3 g of 7-amino cephem (**7p**) (90%).

To a solution of **7p** (9.25 g, 15.2 mol) in *N,N*-dimethylformamide (18 ml) and triethylamine (2.3 ml,

Table 5. Spectral data and yields of cepheids 9d~t.

Compound	Yield (%)	MP (°C)	$[\alpha]_D^{24}$ in H ₂ O	IR (Nujol) cm ⁻¹ (C=O)	¹ H NMR (δ)	Solvent ^a
9d	14	145~148 (dec)	46 (c 0.5)	1767, 1694, 1663	2.54 (3H, s), 3.21, 3.51 (2H, ABq, <i>J</i> =18 Hz), 4.60, 4.70 (2H, ABq, <i>J</i> =18 Hz), 5.06 (1H, d, <i>J</i> =5 Hz), 5.69 (1H, d, <i>J</i> =5 Hz), 6.83 (1H, s)	D
9e	18	146~148 (dec)	50 (c 0.5)	1767, 1667, 1607	1.09 (3H, t, <i>J</i> =7 Hz), 3.10 (2H, q, <i>J</i> =7 Hz), 3.30, 3.57 (2H, ABq, <i>J</i> =18 Hz), 4.79, 4.92 (2H, ABq, <i>J</i> =12 Hz), 5.09 (1H, d, <i>J</i> =5 Hz), 5.81 (1H, d, <i>J</i> =5 Hz), 6.77 (1H, s)	D
9f	36	139~141 (dec)	41 (c 1.0)	1773, 1664, 1600	0.90 (3H, t, <i>J</i> =8 Hz), 1.48 (2H, tq, <i>J</i> =7, 8 Hz), 3.04 (2H, t, <i>J</i> =7 Hz), 3.32, 3.58 (2H, ABq, <i>J</i> =18 Hz), 4.80, 4.95 (2H, ABq, <i>J</i> =13 Hz), 5.09 (1H, d, <i>J</i> =5 Hz), 5.81 (1H, d, <i>J</i> =5 Hz), 6.77 (1H, s)	C
9g	14	138~141 (dec)	40 (c 0.5)	1772, 1670, 1605	3.30~3.70 (4H, m), 4.34~4.48 (2H, m), 4.80~5.00 (2H, m), 5.10 (1H, d, <i>J</i> =5 Hz), 5.82 (1H, d, <i>J</i> =5 Hz), 6.79 (1H, s)	C
9h	16	124~126 (dec)	26 (c 0.5)	1766, 1717, 1654	3.51, 3.61 (2H, ABq, <i>J</i> =18 Hz), 3.70~3.80 (2H, m), 4.80, 5.03 (2H, ABq, <i>J</i> =13 Hz), 5.10 (1H, d, <i>J</i> =5 Hz), 5.81 (1H, d, <i>J</i> =5 Hz), 6.78 (1H, s)	C
9i	39	138~142 (dec)	68 (c 1.0)	1770, 1687, 1592	2.70 (6H, brs), 3.42, 3.69 (2H, ABq, <i>J</i> =19 Hz), 4.67, 4.91 (2H, ABq, <i>J</i> =13 Hz), 5.22 (1H, d, <i>J</i> =5 Hz), 5.85 (1H, d, <i>J</i> =5 Hz), 7.00 (1H, s)	D
9j	15	148~150 (dec)	41 (c 0.5)	1767, 1677, 1611	1.05~1.15 (2.7H, m), 1.25~1.35 (0.3H, m), 2.72 (0.3H, brs), 2.90 (2.7H, brs), 3.05 (0.2H, m), 3.25~3.40 (1.8H, m), 3.40~3.50 (1H, m), 3.70~3.78 (1H, m), 4.70~4.78 (1H, m), 4.90~5.00 (1H, m), 5.24~5.27 (1H, m), 5.85~5.90 (1H, m), 7.02 (1H, s)	D
9k	8.8	142~144 (dec)	60 (c 0.5)	1770, 1679, 1597	2.79~2.82 (3H, m), 3.28~3.30 (3H, m), 3.56~3.58 (3H, m), 3.57~4.75 (2H, m), 5.09 (1H, d, <i>J</i> =5 Hz), 5.73 (1H, d, <i>J</i> =5 Hz), 6.84 (1H, s)	D
9l	25	121~122 (dec)	47 (c 1.0)	1767, 1668, 1605	2.00~2.10 (2H, m), 3.21, 3.47 (2H, ABq, <i>J</i> =1.8 Hz), 3.75~3.87 (4H, m), 4.51, 4.70 (2H, ABq, <i>J</i> =18 Hz), 5.05 (1H, d, <i>J</i> =5 Hz), 5.68 (1H, d, <i>J</i> =5 Hz), 6.78 (1H, s)	D
9m	22	137~139 (dec)	43 (c 1.0)	1766, 1687, 1600	1.84~1.94 (4H, m), 3.25~3.60 (4H, m), 3.56, 3.66 (2H, ABq, <i>J</i> =18 Hz), 4.82, 5.02 (2H, ABq, <i>J</i> =13 Hz), 5.11 (1H, d, <i>J</i> =5 Hz), 5.81 (1H, d, <i>J</i> =5 Hz), 6.77 (1H, s)	C
9n	28	139~142 (dec)	45 (c 1.0)	1769, 1687, 1621	1.27~1.47 (6H, m), 3.17~3.29 (4H, m), 3.25, 3.51 (2H, ABq, <i>J</i> =18 Hz), 4.55, 4.78 (2H, ABq, <i>J</i> =13 Hz), 5.07 (1H, d, <i>J</i> =5 Hz), 5.70 (1H, d, <i>J</i> =5 Hz), 6.82 (1H, s)	D
9o	15	147~149 (dec)	42 (c 0.5)	1764, 1674, 1605	3.42, 3.72 (2H, ABq, <i>J</i> =18 Hz), 3.45~3.60 (4H, m), 3.70~3.80 (4H, m), 4.75, 4.95 (2H, ABq, <i>J</i> =13 Hz), 5.23 (1H, d, <i>J</i> =5 Hz), 5.86 (1H, d, <i>J</i> =5 Hz), 7.01 (1H, s)	D
9p	8	—	—	1789, 1713, 1694	2.79 (3H, s), 2.89~3.20 (4H, m), 3.26, 3.56 (2H, ABq, <i>J</i> =18 Hz), 3.31~3.44 (2H, m), 4.02~4.18 (2H, m), 4.57, 4.81 (2H, ABq, <i>J</i> =13 Hz), 5.08 (1H, d, <i>J</i> =5 Hz), 5.70 (1H, d, <i>J</i> =5 Hz), 6.89 (1H, s)	D
9r	38	145~148 (dec)	34 (c 0.5)	1769, 1667, 1613	2.55 (3H, s), 3.27, 3.52 (2H, ABq, <i>J</i> =18 Hz), 3.84 (3H, s), 4.53, 4.74 (2H, ABq, <i>J</i> =12 Hz), 5.06 (1H, d, <i>J</i> =5 Hz), 5.67 (1H, d, <i>J</i> =5 Hz), 6.86 (1H, s)	D
9s	9	138~140 (dec)	32 (c 0.5)	1770, 1680, 1616	2.65~2.80 (6H, m), 3.26, 3.48 (2H, ABq, <i>J</i> =18 Hz), 3.83 (3H, s), 4.52, 4.75 (2H, ABq, <i>J</i> =12 Hz), 5.05 (1H, d, <i>J</i> =5 Hz), 5.66 (1H, d, <i>J</i> =5 Hz), 6.85 (1H, s)	D
9t	10	134~136 (dec)	40 (c 0.5)	1763, 1695, 1604	2.62~2.73 (6H, m), 3.22, 3.48 (2H, ABq, <i>J</i> =18 Hz), 4.49, 4.72 (2H, ABq, <i>J</i> =13 Hz), 5.02~5.04 (1H, m), 5.63~5.66 (1H, m), 5.61 (2H, d, <i>J</i> =55 Hz), 6.95 (1H, s)	D

^a C; CD₃OD, B; D₂O.

Table 6. Spectral data and yields of POM cephem esters **10c**~**s**.

Compound	Yield (%)	MP (°C)	IR (Nujol) cm^{-1} (C=O)	^1H NMR (δ)	Solvent ^a
10c	58	116~118 (dec)	1788, 1748, 1714	1.21 (9H, s), 3.53, 3.69 (2H, ABq, $J=19$ Hz), 4.78, 5.08 (2H, ABq, $J=14$ Hz), 5.19 (1H, d, $J=5$ Hz), 5.83 (1H, d, $J=5$ Hz), 5.91~5.94 (2H, m), 6.76 (1H, s)	C
10d	20	118~120 (dec)	1787, 1751, 1677	1.14 (9H, s), 2.70 (3H, s), 3.42~3.59 (2H, m), 4.72~4.76 (1H, m), 4.95~5.05 (2H, m), 5.78~5.81 (1H, m), 5.81~5.89 (2H, m), 6.93 (1H, s)	A
10i	23	90~92 (dec)	1791, 1752, 1689	1.24 (9H, s), 2.92 (6H, br s), 3.50, 3.61 (2H, ABq, $J=19$ Hz), 4.89, 5.17 (2H, ABq, $J=13$ Hz), 5.07 (1H, d, $J=5$ Hz), 5.85, 5.97 (2H, ABq, $J=6$ Hz), 5.93 (1H, dd, $J=5, 8$ Hz), 7.08 (1H, s), 7.26 (2H, s)	A
10j	57	199~122 (dec)	1786, 1752, 1679	1.21~1.25 (9H, m), 2.97 (3H, s), 3.41~3.45 (2H, m), 3.46~3.60 (2H, m), 3.71~3.77 (2H, m), 4.82~4.95 (2H, m), 5.05~5.08 (1H, m), 5.86, 5.95 (2H, ABq, $J=6$ Hz), 5.88~5.91 (1H, m), 7.00 (1H, s)	A
10k	34	100~103 (dec)	1788, 1753, 1685	1.12 (3H, t, $J=7$ Hz), 1.24 (9H, s), 2.89 (2H, s), 2.90 (1H, s), 3.25~3.35 (2H, m), 3.47, 3.61 (1H, ABq, $J=18$ Hz), 3.48, 3.61 (1H, ABq, $J=18$ Hz), 4.89 (1H, d, $J=13$ Hz), 5.06 (1H, d, $J=5$ Hz), 5.10~5.20 (1H, m), 5.82, 5.97 (1H, ABq, $J=5$ Hz), 5.92 (1H, dd, $J=5, 8$ Hz), 7.07 (1H, s)	A
10l	54	118~122 (dec)	1787, 1752, 1685	1.12 (9H, m), 2.24~2.30 (2H, m), 3.47, 3.60 (2H, ABq, $J=18$ Hz), 3.95~4.10 (4H, m), 4.87, 5.12 (2H, ABq, $J=14$ Hz), 5.06 (1H, d, $J=5$ Hz), 5.87, 5.95 (2H, ABq, $J=6$ Hz), 5.90~5.93 (1H, m), 7.07 (1H, s)	A
10m	28	119~121 (dec)	1790, 1755, 1683	1.22 (9H, s), 1.84~1.95 (4H, m), 3.35~3.40 (4H, m), 3.56, 3.71 (2H, ABq, $J=19$ Hz), 4.78, 5.14 (2H, ABq, $J=13$ Hz), 5.20 (1H, d, $J=5$ Hz), 5.84 (1H, d, $J=5$ Hz), 5.94~5.98 (2H, m), 6.78 (1H, s)	C
10n	59	119~122 (dec)	1789, 1753, 1678	1.13 (9H, s), 1.48~1.66 (6H, m), 3.37~3.46 (4H, m), 3.54, 3.69 (2H, ABq, $J=18$ Hz), 4.77, 5.13 (2H, ABq, $J=13$ Hz), 5.20 (1H, d, $J=5$ Hz), 5.84, 5.93 (2H, ABq, $J=6$ Hz), 5.92 (1H, d, $J=5$ Hz), 6.76 (1H, s)	C
10o	24	124~126 (dec)	1789, 1752, 1682	1.12 (9H, s), 3.45~3.50 (5H, m), 3.58~3.70 (5H, m), 4.89, 5.18 (2H, ABq, $J=12$ Hz), 5.07 (1H, d, $J=5$ Hz), 5.84, 5.97 (2H, ABq, $J=5$ Hz), 5.93 (1H, dd, $J=5, 8$ Hz), 7.08 (1H, s)	A
10q	86	137~139 (dec)	1789, 1745, 1681	1.23 (9H, s), 3.48, 3.61 (2H, ABq, $J=19$ Hz), 4.07 (3H, s), 4.72, 5.11 (2H, ABq, $J=14$ Hz), 5.08 (1H, d, $J=5$ Hz), 5.24 (2H, br s), 5.87, 5.95 (2H, ABq, $J=6$ Hz), 6.01 (1H, d, $J=5$ Hz), 6.91 (1H, s)	A
10r	57	118~120 (dec)	1789, 1747, 1681	1.14 (9H, s), 2.70 (3H, s), 3.42~3.59 (2H, m), 4.00 (3H, s), 4.72~4.76 (1H, m), 4.95~5.05 (2H, m), 5.78~5.81 (1H, m), 5.81~5.89 (2H, m), 6.93 (1H, s)	A
10s	65	120~122 (dec)	1788, 1752, 1681	1.23 (9H, s), 2.92 (6H, s), 3.50, 3.60 (2H, ABq, $J=19$ Hz), 4.09 (3H, s), 4.84, 5.16 (2H, ABq, $J=14$ Hz), 5.09 (1H, d, $J=5$ Hz), 5.85~5.95 (2H, m), 5.99~6.03 (1H, m), 6.92 (1H, s), 7.49 (1H, d, $J=8$ Hz)	A

^a A; CDCl_3 , C; CD_3OD .

Table 7. Spectral data and yields of various type esters **11a**~**j**.

Compound	Yield (%)	MP (°C)	IR (Nujol) cm ⁻¹ (C=O)	¹ H NMR (δ)	Solvent ^a
11a	14	123~126 (dec)	1784, 1768, 1682	1.55~1.58 (3H, m), 2.11 (3H; d, <i>J</i> =5 Hz), 2.94 (6H, br s), 3.47~3.65 (2H, m), 4.83~5.24 (3H, m), 5.83~5.94 (1H, m), 6.98~7.15 (2H, m)	A
11b	63	102~104 (dec)	1789, 1754, 1682	0.90 (6H, t, <i>J</i> =7 Hz), 1.50~1.70 (4H, m), 2.25~2.34 (1H, m), 2.93 (6H, br s), 3.49, 3.60 (2H, ABq, <i>J</i> =18 Hz), 4.91, 5.15 (2H, ABq, <i>J</i> =14 Hz), 5.07 (1H, d, <i>J</i> =5 Hz), 5.84~5.95 (3H, m), 7.07 (1H, s)	A
11c	10	104~106 (dec)	1786, 1752, 1685	1.18 (6H, t, <i>J</i> =7 Hz), 1.56 (3H, d, <i>J</i> =6 Hz), 2.55~2.65 (1H, m), 2.92 (6H, s), 3.50, 3.61 (1H, ABq, <i>J</i> =18 Hz), 3.51, 3.62 (1H, ABq, <i>J</i> =18 Hz), 4.90, 5.12 (1H, ABq, <i>J</i> =14 Hz), 4.95, 5.18 (1H, ABq, <i>J</i> =14 Hz), 5.05 (0.5H, d, <i>J</i> =5 Hz), 5.07 (0.5H, d, <i>J</i> =5 Hz), 5.88~5.95 (1H, m), 7.00 (0.5H, q, <i>J</i> =6 Hz), 7.10 (0.5H, q, <i>J</i> =6 Hz), 7.09 (1H, s)	A
11d	15	97~100 (dec)	1788, 1749, 1683	0.90 (3H, t, <i>J</i> =7 Hz), 0.91 (3H, t, <i>J</i> =7 Hz), 1.50~1.75 (7H, m), 2.20~2.30 (1H, m), 2.92 (6H, s), 3.48, 3.60 (1H, ABq, <i>J</i> =18 Hz), 3.53, 3.61 (1H, ABq, <i>J</i> =18 Hz), 4.90, 5.14 (1H, ABq, <i>J</i> =14 Hz), 4.97, 5.15 (1H, ABq, <i>J</i> =14 Hz), 5.07 (1H, d, <i>J</i> =5 Hz), 5.88~5.95 (1H, m), 7.00~7.10 (1H, m), 7.08 (1H, s)	A
11e	4.5	99~100 (dec)	1787, 1751, 1683	1.09 (9H, s), 1.56 (3H, d, <i>J</i> =6 Hz), 2.20~2.30 (2H, m), 2.93 (6H, s), 3.48, 3.60 (1H, ABq, <i>J</i> =18 Hz), 3.50, 3.61 (1H, ABq, <i>J</i> =18 Hz), 4.91, 5.12 (1H, ABq, <i>J</i> =12 Hz), 4.98, 5.17 (1H, ABq, <i>J</i> =12 Hz), 5.03~5.10 (1H, m), 5.86~5.93 (1H, m), 6.97~7.12 (1H, m), 7.12 (1H, s)	A
11f	10	122~126 (dec)	1789, 1763, 1683	1.33 (3H, t, <i>J</i> =7 Hz), 1.58~1.63 (3H, m), 2.94 (6H, br s), 3.51, 3.61 (1H, ABq, <i>J</i> =18 Hz), 3.51, 3.62 (1H, ABq, <i>J</i> =18 Hz), 4.20~4.32 (2H, m), 4.91, 5.17 (1H, ABq, <i>J</i> =14 Hz), 4.99, 5.22 (1H, ABq, <i>J</i> =14 Hz), 5.05 (0.5H, d, <i>J</i> =5 Hz), 5.10 (0.5H, d, <i>J</i> =5 Hz), 5.90~5.98 (1H, m), 6.92 (0.5H, q, <i>J</i> =6 Hz), 7.04 (0.5H, q, <i>J</i> =6 Hz), 7.08 (1H, s)	A
11g	51	114~116 (dec)	1789, 1761, 1683	1.26 (6H, m), 2.90 (3H, s), 2.92 (3H, s), 3.55, 3.71 (2H, ABq, <i>J</i> =18 Hz), 4.78, 5.13 (2H, ABq, <i>J</i> =14 Hz), 5.20 (1H, d, <i>J</i> =5 Hz), 5.80 (1H, d, <i>J</i> =5 Hz), 5.90~5.97 (1H, m), 6.84 (1H, s)	C
11h	30	118~121 (dec)	1793, 1760, 1687	1.27 (3H, d, <i>J</i> =6 Hz), 1.28 (3H, d, <i>J</i> =6 Hz), 1.54 (3H, d, <i>J</i> =6 Hz), 2.91 (3H, s), 2.93 (3H, s), 2.56, 3.70 (2H, ABq, <i>J</i> =19 Hz), 4.80~5.06 (3H, m), 5.20 (1H, d, <i>J</i> =5 Hz), 6.75 (1H, s), 6.85 (0.5H, q, <i>J</i> =6 Hz), 6.94 (0.5H, q, <i>J</i> =6 Hz)	C
11i	19	99~100 (dec)	1789, 1759, 1682	1.10~1.60 (6H, m), 1.58~1.63 (3H, m), 1.66~2.00 (4H, m), 2.93 (6H, s), 3.52, 3.40 (2H, ABq, <i>J</i> =18 Hz), 4.60~4.70 (1H, m), 4.89 (0.5H, d, <i>J</i> =12 Hz), 4.97 (0.5H, d, <i>J</i> =12 Hz), 6.83~6.94 (1H, m), 6.89 (0.5H, q, <i>J</i> =6 Hz), 6.89 (0.5H, q, <i>J</i> =6 Hz), 7.15 (1H, s)	A
11j	49	121~123 (dec)	1821, 1795, 1738, 1681	2.20 (3H, s), 2.87 (3H, s), 2.92 (3H, s), 3.52, 3.69 (2H, ABq, <i>J</i> =18 Hz), 4.80~5.18 (4H, m), 5.20 (1H, d, <i>J</i> =5 Hz), 5.92 (1H, d, <i>J</i> =5 Hz), 6.76 (1H, s)	C

^a A; CDCl₃, C; CD₃OD.

16.9 mol), **15** (10.2 g, 15.2 mol) were added *N,N'*-dicyclohexylcarbodiimide (3.13 g, 15.2 mol) and 1-hydroxybenztriazole (2.05 g, 15.2 mol), and the mixture was stirred at room temperature for 2 hours. The precipitate was removed by filtration and the filtrate was diluted with *n*-hexane (700 ml). The oily product was collected by decantation and the residue was purified by silica gel column chromatography (eluent; dichloromethane - methanol, 98:2) to give 3.1 g of **8p** (17%). ¹H NMR (CDCl₃) δ 2.47 (3H, s), 2.40~2.75 (4H, m), 3.02 and 3.65 (2H, ABq, *J*=18 Hz), 3.42~3.70 (4H, m), 4.47 (1H, d, *J*=5 Hz), 4.74 and 5.27 (2H, ABq, *J*=14 Hz), 6.36 (1H, dd, *J*=5, 10 Hz), 6.43 (1H, s), 6.96 (1H, s), 7.20~7.60 (41H, m), 7.72 (1H, d, *J*=10 Hz).

7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(4-methyl-1-piperazinyl)carbonyloxy-methyl-3-cephem-4-carboxylic acid ditrifluoroacetate (**9p**)

To a solution of **8p** (4.0 g, 3.4 mmol) in dichloromethane (24 ml) under ice cooling was added phosphorus trichloride (2.3 g, 16.8 mmol), and the mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added *n*-hexane (500 ml), and the precipitate was collected by filtration. The residue was added to a solution of anisole (25 ml) and trifluoroacetic acid (33 ml), and the mixture was stirred for 1 hour and diluted with diisopropyl ether (200 ml). The precipitate was collected through filtration and was added to a solution of 90% formic acid (25 ml). After being stirred for 2 hours, the reaction mixture was diluted with a solution of ethyl acetate (100 ml) and diisopropyl ether (100 ml), and the precipitate was filtered off to give crude **9p**, which was chromatographed on a column of C₁₈ Silica Gel (YMC A-343; eluent; 1~10% methanol-0.1% trifluoroacetic acid). The fractions containing the desired compound were concentrated under reduced pressure, and the residue was freeze-dried to provide 200 mg of **9p** (8%).

The spectral data of **9p** are listed in Table 5.

Benzhydryl 7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-*N,N*-dimethylcarbamoyl oxyymethyl-3-cephem-4-carboxylate (**8v**)

To a solution of **8u** (6.05 g, 6.9 mmol) in acetonitrile (70 ml) was added 12 M hydrochloric acid (1.97 ml), and the mixture was stirred for 20 hours at room temperature and adjusted to pH 6 with sodium bicarbonate solution. To the mixture were added ethyl acetate (250 ml) and water (200 ml), and the organic layer was separated. The organic layer was evaporated to dryness and the residue was chromatographed on a column of silica gel (Wako C-200 200 g; eluent; benzene - acetone, 4:1). The fractions containing the desired product were collected and evaporated to give 1.03 g of **8v** (17%). ¹H NMR (CDCl₃) δ 2.84 (3H, s), 2.89 (3H, s), 3.45 and 3.57 (2H, ABq, *J*=19 Hz), 4.84 and 5.11 (2H, ABq, *J*=14 Hz), 5.04 (1H, d, *J*=5 Hz), 5.29 (2H, s), 5.90~6.00 (1H, m), 6.97 (1H, s), 7.26~7.42 (10H, m), 7.44 (1H, s).

Sodium 7-[(*E*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-*N,N*-dimethylcarbamoyloxymethyl-3-cephem-4-carboxylate (**9v**)

To a solution of **8v** (1.03 g, 1.2 mmol) in dichloromethane (22 ml) were added trifluoroacetic acid (1 ml) and anisole (0.5 ml), and the mixture was stirred at room temperature for 40 minutes. To the mixture was added diisopropyl ether (50 ml), and the resulting precipitate was collected by filtration. The crude material was purified by C₁₈ silica gel chromatography, and the desired fractions were collected and concentrated under reduced pressure. The residue was freeze-dried to give 220 mg of **9v** (37%). MP 154~157°C, [α]_D 61 (24°C, *c* 0.5, H₂O), ¹H NMR (D₂O) δ 2.9 (6H, br s), 3.43 and 3.69 (2H, ABq, *J*=18 Hz), 4.69 and 4.92 (2H, ABq, *J*=13 Hz), 5.20 (1H, d, *J*=5 Hz), 5.82 (1H, d, *J*=5 Hz), 7.56 (1H, s), IR (nujol) cm⁻¹; 1765, 1681, 1606.

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