STUDIES ON ORALLY ACTIVE CEPHALOSPORINS

II. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONS OF NEW [(*E*) OR (*Z*) 3-SUBSTITUTED CARBAMOYLOXY]-1-PROPENYL CEPHALOSPORINS

SHIGETO NEGI, MANABU SASHO, MOTOSUKE YAMANAKA, ISAO SUGIYAMA, YUKI KOMATSU, AKIHIKO TSURUOKA, ATSUSHI KAMADA, ITARU TSUKADA, RYOICHI HIRUMA, KANEMASA KATSU and YOSHIMASA MACHIDA

Tsukuba Research Laboratories, Eisai Co., Ltd.,
5-1-3 Tokodai, Tsukuba, Ibaraki 300-26, Japan

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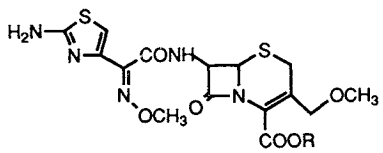
In an effort to find a new oral cephalosporin with well-balanced antibacterial spectrum, good oral absorbability and long plasma half-life, a series of oxyimino aminothiazolyl 3-[(*E*)- or (*Z*)-*N*-substituted carbamoyloxy]propenyl cephems was synthesized and evaluated for antibacterial activity and oral absorbability. The substituents of the carbamoyloxy group affected their *in vitro* activity and bioavailability after oral administration of their pivaloyloxymethyl esters at the C-4 position. The compound possessing an *N*,*N*-dimethylcarbamoyloxy moiety at the C-3 position showed good oral absorption and well-balanced antibacterial activity. In this report, the structure-activity relationships and the structure-oral absorbability relationships of 3-(*N*-substituted carbamoyloxy)-propenyl cephems are described.

Since the discovery of so-called third generation oral cephalosporins, such as cefteram pivoxil[1] and cefixime,[2] a number of aminothiazole cephalosporins have been developed to obtain a compound with more potent antibacterial activity, wider spectrum and better oral absorbability,[3~6] for example cefpodoxime proxetil (CPDX-PR) (Fig. 1) and cefdinir (CFDN) (Fig. 2). In a previous paper, we reported the synthesis and structure-activity and structure-oral absorption relationships of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyimino]-3-(*N*-substituted carbamoyloxy)methyl cephem carboxylic acids and their prodrug esters (**I**), shown in Fig. 3.[7] On the other hand, we have reported that modification of the substituent at the C-3 position from (quarternary ammonio)methyl cephems to 3-[(*E*)-(quarternary ammonio)propenyl] cephems such as E1077 results in an increase of antibacterial activity against Gram-positive bacteria, especially *S. aureus* while maintaining almost the same activity against Gram-negative species.[8] Thus, we were prompted to investigate the antibacterial activity and the oral

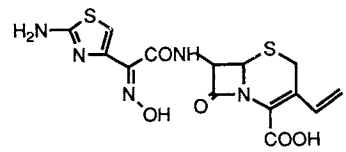
Fig. 1.



Cefpodoxime (CPDX) R=H

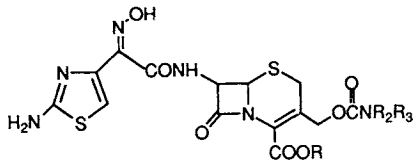
Cefpodoxime proxetil (CPDX-PR) R=CH(CH$_3$)OCOCH(CH$_3$)$_2$

Fig. 2.

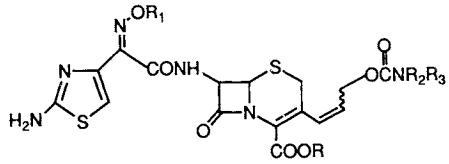


Cefdinir (CFDN)

Fig. 3. Structures of methyl cephem (I) and propenyl cephem (II).



I methyl cephem type
Ia R=H, R_2, R_3=H
Ib R=H, R_2, R_3=CH_3(E1100)
R=$CH(CH_3)OCOCH(CH_3)_2$ (E1101)



II propenyl cephem type

absorption of the "propenyl cephem" compounds (**II**) with insertion of vinyl moiety at the C-3 position of E1101 and its analogs.

In this report, we describe the synthesis and structure-activity relationships of 3-[(*E*)- or (*Z*)- carbamoyloxypropenyl]cephems and oral absorbability of their prodrug type esters represented by the general structure (**II**). The comparative data of antibacterial activity and pharmacokinetics of an E1100 ester and its propenyl derivative are also discussed.

Chemistry

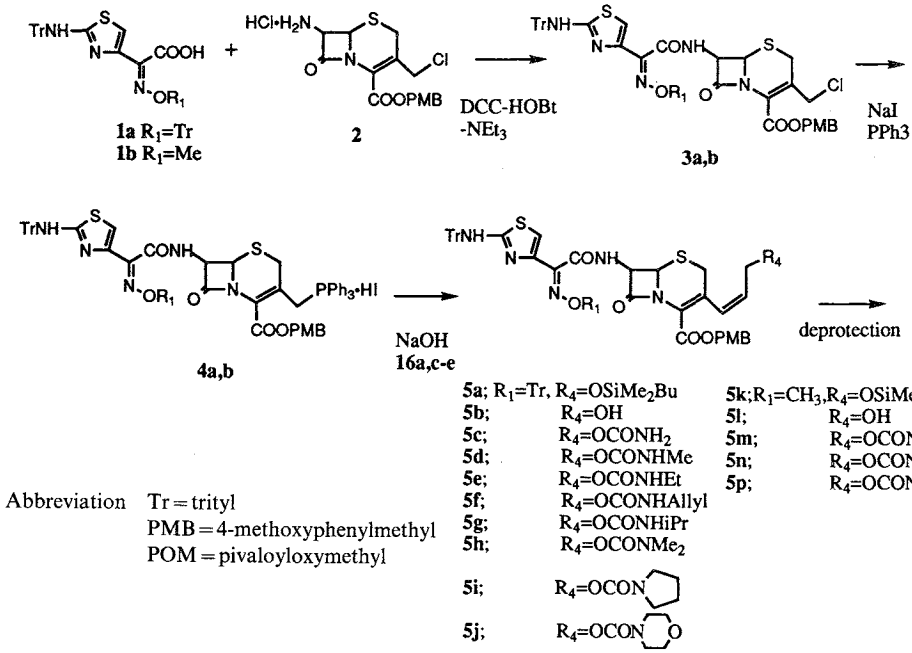
The new cephalosporins (**6**, **7**) with [(*E*)- or (*Z*)-substituted carbamoyloxy]propenyl at the C-3 position were prepared by the routes shown in Scheme 1~3.

In Scheme 1, the 2-(2-tritylaminothiazol-4-yl)-2-acetic acids (**1a**,[9] **1b**) were condensed with *p*-methoxybenzyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate (**2**) in DMF in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenztriazole (HOBt) to give *p*-methoxybenzyl 7-[(*Z*)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyimino or 2-(methoxyimino)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (**3a**, **3b**). After treatment of **3a**, **3b** with sodium iodide, triphenylphosphine was reacted with the resultant iodomethyl cephems to afford the phosphonium salts (**4a**, **4b**).[10] The ylides which were obtained by treatment of **4a** or **4b** with aqueous sodium hydroxide were treated with the various 2-substituted acetaldehydes (**16a**, **16c**~**16e**), which were prepared according to the general method outlined in Scheme 2, to give exclusively (*Z*)-propenyl cephems (**5a**~**5p**).

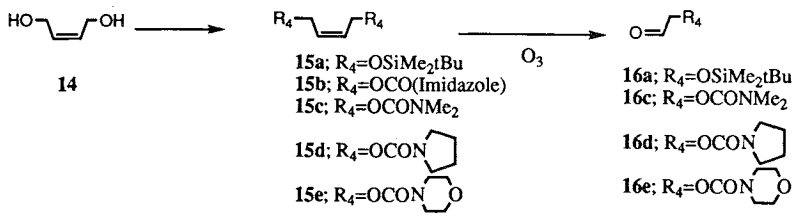
Scheme 2 describes the general synthetic method for 2-substituted acetaldehydes (**16a**, **16c**~**16e**). *tert*-Butyldimethylsilyloxyacetadehyde (**16a**)[11] was synthesized from *cis*-2-buten-1,4-diol (**14**), silylated with *tert*-butyldimethylsilylchloride in the presence of imidazole, and treated with ozone to give aldehyde (**16a**). As another possible synthetic route for **5c**~**5d**, ozonolysis of 1,4-bis(carbamoyloxy)-2-butene and 1,4-bis(*N*-mono substituted carbamoyl)-2-butene was tried, but this route was found to be unpromising because these butens were fragile to ozone to be decomposed during the reaction. *N*,*N*-Disubstituted carbamoyloxy acetaldehydes (**16c**~**e**) were able to be prepared from the same starting material (**14**). The hydroxy group of **14** was transformed with *N*,*N'*-carbonyldiimidazole to activated ester (**15b**), which was reacted with the appropriate secondary amines to afford 1,4-bis(*N*,*N*-disubstituted carbamoyloxy)-2-butenes (**15c**~**15e**). Unlike carbamoyloxy or *N*-monosubstituted carbamoyloxy butenes, the double bond of these butens (**15c**~**15e**) were successfully cleaved with ozone to yield aldehydes (**16c**~**16e**).

Consequently, (*Z*)-carbamoyloxy propenyl cephems (**5a**~**5p**) were obtained by two routes, one for

Scheme 1.

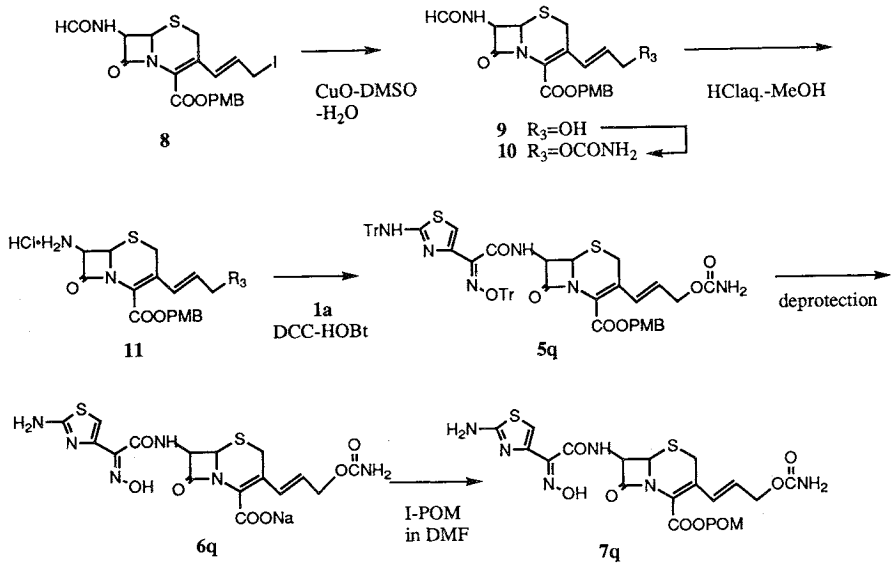


Scheme 2.



unsubstituted.(**5c**, **5m**) and mono-substituted carbamoyloxy cephems (**5d**~**5g**, **5n**), and another for disubstituted carbamoyloxy cephems (**5h**~**5j**, **5p**). In the former route, the ylides were coupled with the aldehyde (**16a**) to give *tert*-butyldimethylsilyloxypropenyl cephems (**5a**, **5k**). After deprotection of the *tert*-butyldimethylsilyl substituent of **5a**, **5k** with hydrochloric acid in aqueous acetone, the resultant (*Z*)-3-hydroxy-1-propenyl cephems (**5b**, **5l**) were transformed with chlorosulfonylisocyanate to afford 3-carbamoyloxy propenyl cephems (**5c**, **5m**) or treated with alkylisocyanates in the presence of triethylamine

Scheme 3.



to afford 3-(mono substituted carbamoyloxy)propenyl cephems (**5d**~**5g**, **5n**). In the latter route, (*N*,*N*-disubstituted carbamoyloxy)propenyl cephems (**5h**~**5j**, **5p**) were directly manufactured through the Wittig reaction of ylides with aldehydes (**16c**~**16e**).

These protected cephems were treated with trifluoroacetic acid-anisole, and subsequently with formic acid to give crude materials, and purified by ODS-chromatography to afford cephem sodium salts (**6c**~**6p**). These new cephalosporins (**6c**~**6p**) were esterified with pivaloyloxymethyl iodide to give their prodrug esters (**7c**~**7p**) in good yields.

Scheme 3 shows the synthetic route for (*E*)-carbamoyloxypropenyl cephem. *p*-Methoxybenzyl 7-formamido-3-[(*E*)-3-iodo-1-propenyl]-cephem-4-carboxylate (**8**) prepared by the method reported in our previous paper[10] was treated with H_2O-dimethylsulfoxide in the presence of cuprous oxide and subsequently reacted with chlorosulfonylisocyanate to afford the carbamoyl cephem (**10**). The cleavage of 7-formamido was accomplished with concentrated hydrochloric acid to give the amino cephem (**11**), which was coupled with **1a** using DCC and HOBt to afford the protected carbamoyloxypropenyl cephem (**5q**). After similar treatments to those described above in the case of **5c** and **6c**, (*E*)-carbamoyloxypropenyl cephem (**6q**) and its pivaloyloxymethyl (POM) ester (**7q**) were prepared.

Antibacterial Activity and Oral Absorption

Table 1 shows the *in vitro* antibacterial activity of the new cephalosporins and reference compounds, such as cefaclor (CCL), cefpodoxime (CPDX) and CFDN against Gram-positive and Gram-negative bacteria. Table 2 shows the urinary recovery (%) after oral administration of POM esters (20 mg/kg as the parent compound) and the relative bioavailability (%) calculated according to the following equation.

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

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 comparison between

Table 1. *In vitro* antibacterial activity of 3-substituted carbamoyloxy propenyl cephems.

Compound	**6c**	**6q**	**6d**	**6e**	**6f**	**6g**
R_1	H					
R_2	H	H	H	H	H	H
R_3	H	H(*E*)	CH_3	C_2H_5	allyl	*i*Pr
S. aureus 209P	0.1	0.1	0.1	0.1	0.2	0.2
S. aureus JS1 (MRSA)	1.56	1.56	1.56	1.56	1.56	1.56
S. pneumoniae IID552	0.05	0.012	0.05	—	0.05	0.05
E. feacalis E22018	6.25	6.25	3.13	12.5	12.5	6.25
E. coli NIHJ JC-2	0.025	0.1	0.025	0.05	0.1	0.2
K. pneumoniae IID875	0.012	0.1	0.012	0.05	0.05	0.2
M. morganii E06071[a]	1.56	0.8	0.8	0.2	0.2	0.4
C. freundii GN346[a]	0.8	0.4	0.4	0.2	0.2	0.4
E. cloacae GN7471[a]	6.25	6.25	3.13	1.56	3.13	3.13
S. marcescens IID620	0.025	0.1	0.025	0.05	0.05	0.05
H. influenzae IID1638	0.05	—	0.1	0.1	0.05	—
P. aeruginosa PA01	>100	>100	>100	>100	>100	>100

Compound	**6h**	**6i**	**6j**		
R_1	H				
R_2	CH_3			**Ia**	**Ib** E1100
R_3	CH_3				
S. aureus 209P	0.2	0.2	0.2	0.1	0.1
S. aureus JS1 (MRSA)	1.56	1.56	1.56	1.56	1.56
S. pneumoniae IID552	0.05	0.025	0.05	0.1	0.1
E. feacalis E22018	6.25	6.25	—	25	100
E. coli NIHJ JC-2	0.2	0.8	0.2	0.05	0.1
K. pneumoniae IID875	0.2	0.4	0.1	0.025	0.05
M. morganii E06071[a]	0.4	0.8	0.8	1.56	0.8
C. freundii GN346[a]	0.4	0.8	0.8	0.2	0.2
E. cloacae GN7471[a]	3.13	3.13	6.25	3.13	1.56
S. marcescens IID620	0.05	0.2	0.05	0.05	0.05
H. influenzae IID1638	0.05	0.05	—	0.4	0.1
P. aeruginosa PA01	>100	>100	>100	>100	>100

Compound	**6m**	**6n**	**6p**			
R_1	CH_3					
R_2	H	H	CH_3	Cefdinir	Cefpodoxime	Cefaclor
R_3	H	CH_3	CH_3			
S. aureus 209P	0.8	0.8	0.8	0.1	1.56	0.4
S. aureus JS1 (MRSA)	6.25	50	6.25	3.13	50	50
S. pneumoniae IID552	0.025	—	0.012	0.1	0.05	0.4
E. feacalis E22018	>100	>100	>100	12.5	100	50
E. coli NIHJ JC-2	0.2	0.2	0.4	0.4	0.4	1.56
K. pneumoniae IID875	0.025	0.05	0.1	0.2	0.05	0.8
M. morganii E06071[a]	3.13	1.56	0.8	>100	>100	>100
C. freundii GN346[a]	0.8	0.8	0.8	12.5	25	25
E. cloacae GN7471[a]	12.5	12.5	3.13	>100	>100	100
S. marcescens IID620	0.025	0.05	0.05	6.25	0.1	50
H. influenzae IID1638	0.025	0.05	0.025	0.4	0.1	1.56
P. aeruginosa PA01	12.5	50	50	>100	>100	>100

[a] High cephalosoporinase producing strain.

(*Z*)-carbamoyloxypropenyl cephem (**6q**) and its (*E*)-counterpart (**6c**), the (*Z*)-isomer was found to be less active against Gram-negative bacteria while it showed almost the same activity against Gram-positive bacteria. In addition, the (*E*)-isomer's activity was a little stronger than that of carbamoyloxymethyl

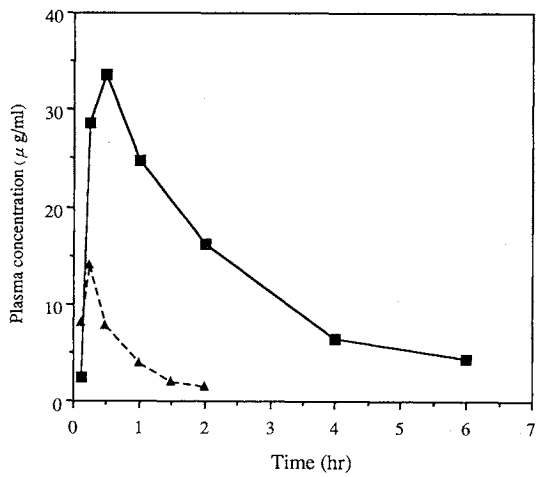
Table 2. Urinary recovery (U.R.) and bioavailability (B.A.) after oral administration of the pivaloyloxymethyl (POM) esters to mice (20 mg/kg).

Compound	R_1	R_2, R_3	U.R. (%) (7) (po)	B.A. (%)
7c	H	H, H	13	20
7q[a]		H, H(*E*)	5	9
7d		H, CH_3	5	7
7e		H, C_2H_5	7	14
7f		H, $CH_2CH=CH_2$	5	25
7g		H, $CH(CH_3)_2$	7	25
7h		CH_3, CH_3	14	38
7i			2	12
7j			6	27
7m	CH_3	H, H	12	21
7n		H, CH_3	15	23
7p		CH_3, CH_3	13	33
E1100-POM			18	36

[a] 3-(*E*)-propenyl cephalosporin.

Fig. 4. Plasma concentration of **7h** and E1100-POM after po single administration (20 mg/kg) to mice.

■ E1100-POM, ▲ **7h**.



cephems (**Ia**[12], **Ib**). Therefore, the substituents at the *N* position of 3-[(*E*)-3-carbamoyloxypropenyl]-cephems were modified with a variety of functional groups.

As for the mono-substituted derivatives (**6d**～**6g**), modification with a more hydrophobic substituent led to reduction in potency against Gram-negative bacteria including *H. influenzae*, which is one of the most important pathogens in respiratory tract infection. *N*,*N*-Disubstituted carbamoyloxy analogues (**6h**～**6j**) showed similar reduction in activity against Gram-negative bacteria as well as some Gram-positive bacteria. On the contrary, the activity against *H. influenzae* of *N*,*N*-disubstituted carbamoyloxy derivatives was found to be maintained. However, unlike the carbamoyloxymethyl type cephems (**I**)[7], substitution at the *N*-position of carbamoyloxy group did not result in increase on potency against *H. influenzae*.

Generally, the methoxyimino derivatives (**6m**[13]～**6p**) were significantly less active against *S. aureus* and had almost the same potency against Gram-negative bacteria as hydroxyimino cephems (**6c**～**6j**). The methoxyimino derivatives exhibited a similar tendency to that of the hydroxyimino series, that is, modification with lipophilic substituents at the C-3 carbamoyloxy group led to reduction of activity against Gram-negative bacteria.

Over all, most of the hydroxyimino (*Z*)-carbamoyloxypropenyl cephems showed similar activity against *S. aureus* and stronger activity against Gram-negative species including *H. influenzae* than CFDN, and they exhibited stronger potency against almost all the Gram-positive and negative bacteria than CPDX, while they possessed similar activity against *H. influenzae* to that of CPDX.

The POM esters (**7**) showed moderate or good oral absorbability, as shown in Table 2. As rather high oral absorption of (*Z*)-carbamoyloxy cephem (**7c**) was observed compared with (*E*)-isomer (**7q**), (*Z*)-carbamoyl propenyl cephems were synthesized and evaluated more extensively. Among them, compounds bearing more lipophilic substituents such as **7f**, **7g**, **7h**, **7j**, **7p** showed good oral absorption. In particular, *N*,*N*-dimethylcarbamoyl derivatives (**7h**, **7p**) showed the best absorbability. It is interesting that both *N*,*N*-dimethyl derivatives exhibited the best oral absorbability in the series of (*E*)-carbamoyloxypropenyl cephems (**II**) and carbamoyloxymethyl cephems (**I**). However, we have not been

able to obtain quantitative interpretation for this finding in spite of several physical chemistry studies.

Among a number of compounds, **7h** was found to be a compound with well-balanced antibacterial activity and good oral absorption, so we did the pharmacokinetic studies between two types. In Fig. 4, the plasma concentration curves after oral administration of both E1100 POM ester and its counterpart ester (**7h**) are depicted. Since E1100-POM showed long-lasting activity and a high C_{max} in plasma compared with **7h**, E1100 and its proxetil ester (E1101) were chosen as candidates for further evaluation.

Experimental

^{1}H NMR spectra were recorded on a JEOL 90Q or a Varian UNITY 400 spectrometer. IR spectra were measured on a Hitachi 260-30 or a Nicolet 205 FT-IR spectrometer. Mass spectra were measured on JEOL JMS HX100. Melting points were taken on a Yamato MP21.

Determination of Antibacterial Activities

All *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 with 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. For the purpose of calculating the relative bioavailability, the parent anitbiotics were given intravenously at a single dose of 20 mg/kg in solution. Urine was collected over 6 hours after dosing.

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (**3a**)

To a solution of (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetic acid[1] (**1a**; 1.3 g, 1.9 mmol) in *N*,*N*-dimethylformamide (10 ml), were added 1-hydroxybenztriazole (0.27 g, 2 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (0.4 g, 2 mmol), and the reaction mixture was stirred for 1 hour. To the reaction mixture were added a solution of 4-methoxyphenylmethyl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride (**2**; 0.8 g, 2 mmol) and triethylamine (0.2 g, 2 mmol) in *N*,*N*-dimethylformamide (4 ml), and the mixture was stirred for 18 hours. After the insoluble urea was filtered off, the mixture was diluted with ethyl acetate. The organic layer was washed with water and then brine and dried over anhydrous $MgSO_4$ and the filtrate was evaporated. The residue was chromatographed on a column of silica gel (Wako C-200, 20 g, eluent; *n*-hexane - ethyl acetate, 3 : 1). The fractions containing **3a** were collected and evaporated under reduced pressure. The residue was solidified from diisopropyl ether to give 1.08 g of **3a** (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 and 3.56 (2H, ABq, J=18 Hz), 3.81 (3H, s), 4.40 and 4.53 (2H, ABq, J=12 Hz), 5.03 (1H, d, J=5 Hz), 5.25 (2H, s), 6.05 (1H, dd, J=5, 9 Hz), 6.42 (1H, s), 6.77 (1H, s), 6.91 (2H, d, J=8 Hz), 7.20~7.40 (32H, m); IR (nujol) cm^{-1} 1791, 1726, 1687.

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloromethyl-3-cephem-4-carboxylate (**3b**)

Praparation of **3b** was carried out by a similar method to that described for **3a** (59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 and 3.65 (2H, ABq, J=18 Hz), 3.81 (3H, s), 4.07 (3H, s), 4.44 and 4.53 (2H, ABq, J=11 Hz), 5.04 (1H, d, J=5 Hz), 5.23 (2H, s), 5.93 (1H, dd, J=5, 9 Hz), 6.73 (1H, s), 6.79 (1H, d, J=9 Hz), 6.89 (2H, d, J=9 Hz), 7.25~7.38 (18H, m); IR (nujol) cm^{-1} 1783, 1725, 1680.

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-(triphenylphosphonium)methyl-3-cephem-4-carboxylate iodide (**4a**)

To a solution of sodium iodide (67 g, 0.45 mol) in acetone (400 ml) was added **3a** (83 g, 0.08 mol), and the mixture was stirred for 1 hour. The reaction mixture was concentrated *in vacuo* and diluted with

water (300 ml). The suspension was extracted with ethyl acetate (600 ml) and the extract was washed with 10% sodium hydrosulfite aqueous solution (200 ml), water (300 ml), and then brine (300 ml) and dried over anhydrous $MgSO_4$. To the filtrate was added triphenylphosphine (34 g, 0.13 mol), and the mixture was stirred for 4 hours. The resulting mixture was evaporated under reduced pressure. To the residue, diisopropyl ether (2 liters) was added and the precipitate was filtered off to give 110 g of **3a** (97%).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(triphenylphosphonium)methyl-3-cephem-4-carboxylate iodide (**4b**)

Praparation of **4b** was carried out by a similar method to that described for **4a** (95%).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*Z*)-3-*tert*-butyldimethylsilyloxy-1-propenyl]-3-cephem-4-carboxylate (**5a**)

To a solution of **4a** (9.07 g, 7.27 mmol) in dichloromethane (40 ml) was added 1 M sodium hydroxide solution (10 ml), and the mixture was stirred for 20 minutes. The organic layer was separated and washed with brine, and dried over anhydrous $MgSO_4$. To the resulting solution was added *tert*-butyl dimethylsilyloxyacetaldehyde[11] (**16a**; 1.8 g, 10.34 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and the residue was chromatographed on a column of silica gel (Wako C-200, 200 g). The column was eluted with *n*-hexane - ethyl acetate (5 : 2). The fractions containing the desired compound were evaporated to give 4.99 g of **5a** as an amorphous powder (60%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.20 (6H, br s), 1.04 (9H, br s), 3.40~3.60 (2H, m), 3.88 (3H, s), 4.20~4.40 (2H, m), 5.00~6.40 (3H, m), 6.56 (1H, s), 6.90~7.80 (34H, m).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*Z*)-3-hydroxy-1-propenyl]-3-cephem-4-carboxylate (**5b**)

To a solution of **5a** (4.99 g, 4.36 mmol) in acetone (50 ml) was added 1 M hydrochloric acid (10 ml) at room temperature, and the mixture was stirred for 2 hours. After the mixture was concentrated under reduced pressure, water (200 ml) was added and the mixture was extracted with ethyl acetate (200 ml). The extracted organic layer was washed with water and then brine, and dried over anhydrous $MgSO_4$ and evaporated. The resulting solid was purified by chromatography on a column of silica gel (eluent; *n*-hexane - ethyl acetate, 2 : 1) to yield 2.2 g of **5b** (49 %). ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.08 and 3.38 (2H, ABq, J=18 Hz), 3.80 (3H, s), 3.90~4.10 (2H, m), 5.02 (1H, d, J=5 Hz), 5.16 (2H, s), 5.60~6.00 (2H, m), 6.14 (1H, d, J=12 Hz), 6.42 (1H, s), 6.80~7.70 (34H, m).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*Z*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**5c**)

To a solution of **5b** (386 mg, 0.375 mmol) in tetrahydrofuran (15 ml) at −50°C was added chlorosulfonylisocyanate (0.08 ml, 0.919 mmol) dropwise and the mixture was stirred at −20°C for 1 hour. The mixture was added to a phosphate buffer solution (pH 7, 15 ml) and extracted with ethyl acetate (150 ml). The extract was washed with brine and dried over anhydrous $MgSO_4$ and evaporated. The residue was solidified from *n*-hexane to yield 400 mg of **5c** as an amorphous powder (99%). The spectral data for **5c** are listed in Table 3.

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*Z*)-3-(*N*-methylcarbamoyloxy)-1-propenyl]-3-cephem-4-carboxylate (**5d**)

To a solution of **5b** (2 g, 1.944 mmol) and triethylamine (40 mg, 0.4 mmol) in tetrahydrofuran (40 ml) was added methyl isocyanate (887 mg, 15.5 mmol), and the mixture was stirred at 60°C for 4 hours. After evaporation, the mixture was purified by chromatography on a column of silica gel (Wako gel C-200, 40 g, eluent; dichloromethane - acetone, 19 : 1) and triturated with *n*-hexane - diisopropyl ether to yield 1 g of **5d** as white powder (47%).

Preparation of **5e**~**5g** was carried out by a method similar to that described for **5d**.

The spectral data for derivatives **5d**~**5g** are listed in Table 3.

1,4-Bis[(1-imidazolyl)carbonyloxy]-*cis*-2-butene (**15b**)

To a solution of *cis*-2-buten-1,4-diol (**14**; 500 mg, 5.7 mmol) in tetrahydrofuran (10 ml) at room

Table 3. Spectral data of protected cephems **5c**~**r**.

Compound	^{1}H NMR (δ)	Solvent[a]
5c	3.10, 3.41 (2H, ABq, J=18 Hz), 3.78 (3H, s), 4.25~4.50 (2H, m), 4.80 (2H, br s), 5.00 (1H, d, J=5 Hz), 5.16 (2H, s), 5.50~5.70 (1H, m), 5.96 (1H, dd, J=5, 8 Hz), 6.24 (1H, d, J=13 Hz), 6.46 (1H, s), 6.80~7.70 (34H, m)	A
5d	2.66 (3H, d, J=4 Hz), 3.14, 3.70 (2H, ABq, J=18 Hz), 3.74 (3H, s), 4.30~4.70 (2H, m), 5.02 (1H, d, J=5 Hz), 5.10 (2H, s), 5.55~5.80 (1H, m), 5.96 (1H, dd, J=5, 8 Hz), 6.18 (1H, d, J=12 Hz), 6.40 (1H, s), 6.80~7.60 (34H, m)	A
5e	1.00 (3H, t, J=7 Hz), 3.05~3.15 (2H, m), 3.20~3.60 (2H, m), 3.77 (3H, s), 4.40~4.80 (2H, m), 5.07 (1H, d, J=5 Hz), 5.14 (2H, s), 5.55~6.00 (2H, m), 6.22 (1H, d, J=12 Hz), 6.39 (1H, s), 6.80~7.60 (34H, m)	A
5g	1.12 (6H, t, J=6 Hz), 3.13, 3.46 (2H, ABq, J=18 Hz), 3.60~3.80 (1H, m), 3.76 (3H, s), 4.25~4.60 (2H, m), 5.04 (1H, d, J=5 Hz), 5.14 (2H, s), 5.50~5.80 (1H, m), 5.98 (1H, dd, J=5, 8 Hz), 6.26 (1H, d, J=12 Hz), 6.40 (1H, s), 6.70~7.40 (34H, m)	A
5h	2.84 (6H, s), 3.26, 3.48 (2H, ABq, J=18 Hz), 3.78 (3H, s), 4.30~4.70 (2H, m), 5.06 (1H, d, J=5 Hz), 5.16 (2H, br s), 5.50~6.10 (2H, m), 6.26 (1H, d, J=12 Hz), 6.40~7.50 (35H, m)	A
5i	1.80~2.00 (4H, m), 3.20~3.50 (6H, m), 3.80 (3H, s), 4.30~4.38 (1H, m), 4.50~4.63 (1H, m), 5.08 (1H, d, J=5 Hz), 5.18 (2H, s), 5.65~5.76 (1H, m), 6.02 (1H, dd, J=5, 8 Hz), 6.18 (1H, d, J=12 Hz), 6.44 (1H, s), 6.85~7.40 (35H, m)	A
5j	3.20~3.70 (10H, m), 3.79 (3H, s), 5.00~5.40 (2H, m), 5.30~5.70 (2H, m), 5.17 (2H, s), 6.00 (1H, dd, J=5, 9 Hz), 6.25 (1H, d, J=12 Hz), 6.41 (1H, s), 6.70~7.50 (34H, m)	A
5q	3.20~3.50 (2H, m), 3.73 (3H, s), 4.43 (2H, d, J=6 Hz), 4.80 (2H br s), 4.90 (1H, d, J=5 Hz), 5.16 (2H, s), 5.60~6.00 (2H, m), 6.40 (1H, s), 6.70~7.50 (35H, m)	A
5m	3.20~3.50 (2H, m), 3.72 (3H, s), 3.98 (3H, s), 4.30~4.60 (2H, m), 4.84 (2H, br s), 5.00 (1H, d, J=5 Hz), 5.08 (2H, s), 5.50~5.95 (2H, m), 6.17 (1H, d, J=12 Hz), 6.54 (1H, s), 6.70~7.40 (20H, m)	A
5n	2.78 (1.5H, s), 2.79 (1.5H, s), 3.37, 3.58 (2H, ABq, J=18 Hz), 3.82 (3H, br s), 4.09 (3H, s), 4.30~4.70 (2H, m), 5.09 (1H, d, J=5 Hz), 5.09 (2H, s), 5.50~5.98 (2H, m), 6.17 (1H, d, J=12 Hz), 6.74 (1H, s), 6.80~7.40 (20H, m)	A
5p	2.87 (6H, br s), 3.37, 3.59 (2H, ABq, J=18 Hz), 3.80 (3H, s), 4.07 (3H, s), 4.11, 4.12 (2H, ABq, J=6 Hz), 4.30~4.40 (1H, m), 4.55~4.62 (1H, m), 5.09 (1H, d, J=5 Hz), 5.65~5.72 (1H, m), 5.91 (1H, dd, J=5, 8 Hz), 6.28 (1H, d, J=12 Hz), 6.73 (1H, s), 6.85~7.50 (20H, m)	A

[a] A; $CDCl_3$.

temperature was added *N,N'*-carbonyldiimidazole (2.3 g, 15 mmol) and the mixture was stirred for 24 hours and evaporated under reduced pressure. The resulting residue was diluted with ethyl acetate and the organic layer was washed with water and then brine and dried over anhydrous $MgSO_4$. The filtrate was evaporated under reduced pressure and the residue was crystallized from diisopropyl ether to give 1.22 g of **15b** as white crystals (85%). The analytical sample was recrystallized from ethyl acetate to give **15b** as white crystals (70%): MP 110~111°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (4H, d, J=4 Hz), 6.01 (2H, t, J=4 Hz), 7.09 (2H, s), 7.43 (2H, s), 8.15 (2H, s); IR (nujol) cm^{-1} 1742; MS m/z 277 (MH^+).

Anal Calcd for $C_{12}H_{12}N_4O_4$: C 52.17, H 4.38, N 20.28
Found: C 52.27, H. 4.38, N 20.01

1,4-Bis(*N,N*-dimethylcarbamoyloxy)-*cis*-2-butene (**15c**)

To a solution of **15b** (1 g, 3.9 mmol) in tetrahydrofuran (10 ml) was added a solution of dimethylamine (0.36 g, 8 mmol) in tetrahydrofuran (1.6 ml), and the mixture was stirred for 5 hours. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure to give 0.9 g of **15c** as a colorless liquid (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (12H, s), 4.66 (4H, d, J=5 Hz), 5.72 (2H, t, J=5 Hz); IR (nujol) cm^{-1} 1716; MS m/z 231 (MH^+).

Preparation of **15d** and **15e** was carried out by a method similar to that described for **15c**.

The spectral data for derivatives **15d**, **15e** are as follows.

15d; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80~1.98 (8H, m), 3.30~3.50 (8H, m), 4.71 (4H, d, J=5 Hz), 5.75 (2H, t, J=5 Hz); IR (nujol) cm^{-1} 1713; MS m/z 283 (MH^+).

15e; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46~3.48 (8H, m), 3.60~3.72 (8H, m), 4.72 (4H, d, J=5 Hz), 5.76 (2H, t, J=5 Hz); IR (nujol) cm^{-1} 1710; MS m/z 315 (MH^+).

N,N-Dimethylcarbamoyloxyacetaldehyde (**16c**)

To a solution of **15c** (6.33 g, 27.5 mmol) in methanol (80 ml) at −78 °C, ozone gas was bubbled at the same temperature for 30 minutes. To the reaction mixture was added dimethylsulfide (6 ml) and the mixture was stirred at room temperature for 1 hour. After evaporation, the residue was diluted with ethyl ether. The organic layer was washed with water and then brine, and dried over anhydrous $MgSO_4$. The filtrate was evaporated and the residue was chromatographed on a column of silica gel (Wako C-200, 120 g). The column was eluted with *n*-hexane-ethyl acetate (2:1) and the fractions containing the product were evaporated to give 4 g of **16c** as a colorless oil (56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (3H, s), 3.00 (3H, s), 4.62 (2H, s), 9.63 (1H, s).

Preparation of **16d** and **16e** was carried out by a method similar to that described for **16c**.

The spectral data for derivatives **16d**, **16e** are as follows.

1-Pyrrolidinylcarbonyloxyacetaldehyde (**16d**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85~1.96 (4H, m), 3.37~3.50 (4H, m), 4.63 (2H, s), 9.64 (1H, s).

1-Morpholinylcarbonyloxyacetaldehyde (**16e**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55~3.80 (8H, m), 4.67 (2H, s), 9.58 (1H, s).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*Z*)-3-(*N,N*-dimethylcarbamoyloxy)-1-propenyl]-3-cephem-4-carboxylate (**5h**)

To a solution of **4a** (34.5 g, 27.6 mmol) in dichloromethane (150 ml) was added 1 M aqueous sodium hydroxide (40 ml), and the mixture was stirred for 20 minutes. The organic layer was separated and washed with brine, and dried over anhydrous $MgSO_4$. To the resulting solution was added *N,N*-dimethylcarbamoyloxyacetaldehyde (**16c**; 4 g, 30.5 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and the residue was chromatographed on a column of silica gel (Wako C-200, 200 g). The column was eluted with *n*-hexane-ethyl acetate (1:1). The fractions containing the desired compound were evaporated to give 11.3 g of **5h** as an amorphous powder (37%).

Preparation of **5i** and **5j** was carried out by a method similar to that described for **5h**.

The spectral data for derivatives **5h**~**5j** are listed in Table 3.

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(*Z*)-3-*tert*-butyldimethylsilyloxy-1-propenyl]-3-cephem-4-carboxylate (**5k**)

To a solution of **4b** (10.5 g, 10.3 mmol) in dichloromethane (100 ml) was added 1 M aqueous sodium hydroxide solution (15 ml) and the mixture was stirred for 20 minutes. The organic layer was separated and washed with brine and dried over anhydrous $MgSO_4$. To the resulting solution was added **16a** (2.6 g, 14.8 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and the residue was chromatographed on a column of silica gel (Wako C-200, 200 g). The column was eluted with *n*-hexane-ethyl acetate (5:2). The fraction containing the desired compound was collected and evaporated to give 4.30 g of **5k** as an amorphous powder (46%). ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.20 (6H, br s), 1.04 (9H, br s), 3.55~3.80 (2H, m), 3.92 (3H, s), 4.10 (3H, s), 4.10~4.30 (2H, m), 5.10~5.30 (3H, m), 5.70~6.40 (3H, m), 6.60~7.60 (20H, m).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(*Z*)-3-hydroxy-1-propenyl]-3-cephem-4-carboxylate (**5l**)

Preparation of **5l** was carried out by a method similar to that described for **5b** (55%).

^{1}H NMR (90 MHz, $CDCl_3$) δ 3.25 and 3.70 (2H, ABq, J=18 Hz), 3.72 (3H, s), 4.00 (3H, s), 3.85~4.15 (2H, m), 5.00 (1H, d, J=5 Hz), 5.08 (2H, s), 5.55~5.95 (2H, m), 6.10 (1H, d, J=12 Hz), 6.56 (1H, s), 6.70~7.40 (19H, m).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(*Z*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**5m**)

Preparation of **5m** and **5n** was carried out by a method similar to that described for **5c** and **5d**, rsrespectively (63% and 60%).

Preparation of **5p** was carried out by a method similar to that described for **5h**.

The spectral data for **5m**~**5p** are listed in Table 3.

Sodium 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(*Z*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**6c**)

To a solution of anisole (8 ml) and trifluoroacetic acid (10 ml) under ice-cooling was added **5c** (1.1 g, 1.1 mmol), and the mixture was stirred at room temperature for 2 hours. After the solvent was evaporated *in vacuo* and the residue was triturated with diisopropyl ether (20 ml) and *n*-hexane (80 ml). The precipitate formed 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 crystallized with 2-propanol. The precipitate was collected by filtration to give a crude product of **6c**. The solid was purified by chromatography on a column of C_{18} Silica Gel (YMC A-343, eluent; 5% methanol). The fractions containing the desired compound were concentrated under pressure and the residue was freeze-dried to give 208 mg of **6c** (40%).

Preparation of **6d**~**6j**, **6q**, **6r** was carried out by a method similar to that described for **6c**.

The spectral data for derivatives **6c**~**6j**, **6q**, **6r** are listed in Table 4.

Sodium 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(*Z*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**6m**)[14]

To a solution of anisole (8 ml) and trifluoroacetic acid (10 ml) was added **5m** (0.96 g, 1.1 mmol) under ice cooling, and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the residue was triturated with diisoprpyl ether (20 ml) and *n*-hexane (80 ml). The precipitate was collected by filtration. The crystals were mixed with sodium acetate (262 mg, 3.2 mmol) in methanol (10 ml). The mixture were evaporated to dryness and the residue was crystallized with 2-propanol. The precipitate was collected by filtration to give a crude product of **6m**. The solid was purified by chromatography on a column of C_{18} Silica Gel (YMC A-343, elluent; 5% methanol). The fractions containing the desired compound were concentrated under pressure and the residue was freeze-dried to give 138 mg of **6m** (24%).

Preparation of **6n**~**6p** was carried out by a method similar to that described for **6m**.

The spectral data for derivatives **6m**~**6p** are listed in Table 4.

Pivaloyloxymethyl 7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-[(*Z*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**7c**)

To a solution of **6c** (137 mg, 0.34 mmol) in *N*,*N*-dimethylformamide (3 ml) was added iodomethyl pivalate (83 mg, 0.34 mmol) dropwise under ice cooling and 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 $MgSO_4$. The filtrate was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel (Wako C-200, 20 g). The column was eluted with ethyl acetate-methanol (25:1). The fractions containing the desired product were combined and concentrated under reduced pressure. The residue was triturated with diisopropyl ether (50 ml) to yield 56 mg of **7c** as an amorphous powder (28%).

Preparation of **7d**~**7r** was carried out by a method similar to that described for **7c**.

The spectral data for derivatives **7c**~**7r** are listed in Table 5.

4-Methoxyphenylmethyl 7-Formamido-3-[(*E*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**10**)

To a solution of 4-methoxyphenylmethyl 7-formamido-3-[(*E*)-3-iodo-1-propenyl]-3-cephem-4-

Table 4. Spectral data and yields of propenyl cephems **6c**～**p**.

Compound	Yield (%)	MP (°C)	IR (Nujol) cm^{-1} (C=O)	^1H NMR (δ)	Solvent[a]
6c	40	145～156 (dec)	1766, 1703, 1667	3.36, 3.67 (2H, ABq, J=16 Hz), 4.50～4.70 (2H, m), 5.04 (1H, d, J=5 Hz), 5.20～5.30 (1H, m), 5.59 (1H, dd, J=8, 5 Hz), 6.45 (2H, br s), 6.64 (1H, d, J=12 Hz), 6.66 (1H, s), 7.09 (2H, s), 9.40 (1H, d, J=8 Hz), 11.00 (1H, br s)	B
6d	54	154～156 (dec)	1764, 1671, 1601	2.56 (3H, d, J=4 Hz), 3.37, 3.67 (2H, ABq, J=16 Hz), 4.50～4.70 (2H, m), 5.03 (1H, d, J=5 Hz), 5.20～5.30 (1H, m), 5.58 (1H, dd, J=8, 5 Hz), 6.63 (1H, d, J=12 Hz), 6.65 (1H, s), 6.99 (1H, d, J=4 Hz), 7.09 (2H, s), 9.38 (1H, d, J=8 Hz), 11.20 (1H, br s)	B
6e	41	157～159 (dec)	1764, 1673, 1614	1.00 (3H, t, J=7 Hz), 2.99 (2H, dq, J=12, 7 Hz), 3.41, 3.67 (2H, ABq, J=17 Hz), 4.55, 4.66 (2H, d, ABq, J=6, 14 Hz), 5.04 (1H, d, J=5 Hz), 5.20～5.30 (1H, m), 5.50～5.65 (1H, m), 6.61 (1H, d, J=12 Hz), 6.65 (1H, s), 7.00 (1H, t, J=7 Hz), 7.09 (2H, s), 9.42 (1H, d, J=8 Hz)	B
6f	17	157～159 (dec)	1770, 1670, 1602	3.51, 3.73 (2H, ABq, J=17 Hz), 3.84 (2H, d, J=5 Hz), 4.55～4.85 (2H, m), 4.80, 4.94 (2H, ABq, J=18 Hz), 5.25 (1H, dd, J=2, 10 Hz), 5.30 (1H, dd, J=2, 17 Hz), 5.42 (1H, d, J=5 Hz), 5.78～5.87 (1H, m), 5.92～6.03 (1H, m), 5.97 (1H, d, J=5 Hz), 6.32 (1H, d, J=12 Hz), 7.12 (1H, s)	D
6g	44	154～157 (dec)	1764, 1676, 1598	1.04 (6H, d, J=7 Hz), 3.39, 3.67 (2H, ABq, J=17 Hz), 3.55～3.65 (1H, m), 4.50～4.70 (2H, m), 5.05 (1H, m), 5.25～6.35 (1H, m), 5.65～5.65 (1H, m), 6.64 (1H, d, J=12 Hz), 6.66 (1H, s), 7.00～7.11 (1H, m), 7.10 (2H, s), 9.44 (1H, d, J=8 Hz)	B
6h	20	157～159 (dec)	1767, 1671, 1593	2.83 (6H, s), 3.55, 3.65 (2H, ABq, J=18 Hz), 4.55～4.75 (2H, m), 5.02 (1H, d, J=5 Hz), 5.15～5.20 (1H, m), 5.57 (1H, dd, J=5, 8 Hz), 6.62 (1H, d, J=12 Hz), 6.65 (1H, s), 7.09 (2H, s), 9.37 (1H, d, J=8 Hz)	B
6i	20	157～159 (dec)	1767, 1671, 1603	1.60～1.76 (4H, m), 3.10～3.20 (4H, m), 3.24, 3.44 (2H, ABq, J=17 Hz), 4.28～4.35 (1H, m), 4.50～4.57 (1H, m), 5.12 (1H, d, J=5 Hz), 5.52～5.60 (1H, m), 5.68 (1H, d, J=5 Hz), 6.05 (1H, d, J=11 Hz), 6.80 (1H, s)	D
6j	20	167～168 (dec)	1767, 1674, 1600	3.10～3.20 (4H, m), 3.40～3.60 (4H, m), 3.40, 3.65 (2H, ABq, J=18 Hz), 4.60～4.75 (2H, m), 5.06 (1H, d, J=5 Hz), 5.30～5.35 (1H, m), 5.62 (1H, dd, J=8, 5 Hz), 6.62 (1H, d, J=10 Hz), 6.63 (1H, s), 7.14 (2H, s), 9.44 (1H, d, J=8 Hz)	B
6q	40	158～160 (dec)	1762, 1662, 1606	3.20～3.80 (2H, m), 4.42 (2H, d, J=7 Hz), 5.00 (1H, d, J=5 Hz), 5.50～5.70 (2H, m), 6.45 (2H, br s), 6.65 (1H, s), 6.98 (1H, d, J=16 Hz), 7.09 (2H, s), 9.41 (1H, d, J=8 Hz)	B
6m	40	124～127 (dec)	1766, 1670, 1630	3.38, 3.68 (2H, ABq, J=17 Hz), 3.84 (3H, s), 4.50～4.70 (2H, m), 5.04 (1H, d, J=5 Hz), 5.20～5.30 (1H, m), 5.57 (1H, dd, J=5, 8 Hz), 6.50 (2H, br s), 6.63 (1H, d, J=13 Hz), 6.74 (1H, s), 7.20 (2H, s), 9.52 (1H, d, J=8 Hz)	B
6n	38	174～176 (dec)	1737, 1660, 1610	2.56 (3H, d, J=4 Hz), 3.37, 3.68 (2H, ABq, J=16 Hz), 3.84 (3H, s), 4.50～4.70 (2H, m), 5.03 (1H, d, J=5 Hz), 5.20～5.30 (1H, m), 5.55 (1H, dd, J=5, 8 Hz), 6.62 (1H, d, J=12 Hz), 6.74 (1H, s), 7.00 (1H, d, J=4 Hz), 7.19 (2H, s), 9.51 (1H, d, J=8 Hz)	B
6p	25	109～111 (dec)	1766, 1681, 1604	2.73 (6H, br s), 3.24, 3.45 (2H, ABq, J=18 Hz), 3.84 (3H, s), 4.25～4.35 (1H, m), 4.50～4.70 (1H, m), 5.12 (1H, d, J=5 Hz), 5.52～5.11 (1H, m), 5.66 (1H, d, J=5 Hz), 6.04 (1H, d, J=12 Hz), 6.85 (1H, s)	D

[a] B; d_6-DMSO, D; D_2O.

Table 5. Spectral data and yields of POM esters **7c**~**p**.

Compound	Yield (%)	MP (°C)	IR (Nujol) cm^{-1} (C=O)	^1H NMR (δ)	Solvent[a]
7c	28	108~109 (dec)	1781, 1750, 1671, 1617	1.16 (9H, s), 3.55, 3.66 (2H, ABq, J=18 Hz), 4.30~4.50 (2H, m), 5.24 (1H, d, J=5 Hz), 5.60~5.70 (1H, m), 5.75~5.85 (3H, m), 6.27 (1H, d, J=12 Hz), 6.52 (2H, br s), 6.66 (1H, s), 7.10 (2H, s), 9.47 (1H, d, J=8 Hz), 11.28 (1H, s)	B
7d	66	136~138 (dec)	1789, 1754, 1681, 1633	1.16 (9H, s), 2.55 (3H, d, J=4 Hz), 3.55, 3.66 (2H, ABq, J=18 Hz), 4.35~4.55 (2H, m), 5.24 (1H, d, J=5 Hz), 5.60~5.70 (1H, m), 5.75~5.85 (3H, m), 6.27 (1H, d, J=12 Hz), 6.66 (1H, s), 6.98 (1H, d, J=4 Hz), 7.12 (2H, s), 9.47 (1H, d, J=8 Hz), 11.30 (1H, s)	B
7e	65	113~115 (dec)	1785, 1754, 1681, 1633	1.00 (3H, t, J=7 Hz), 1.15 (9H, s), 2.98 (2H, dq, J=3, 7 Hz), 3.55, 3.72 (2H, ABq, J=18 Hz), 4.35~4.60 (2H, m), 5.28 (1H, d, J=5 Hz), 5.60~5.75 (1H, m), 5.80 (1H, dd, J=5, 8 Hz), 5.81 (2H, s), 6.27 (1H, d, J=12 Hz), 6.83 (1H, s), 7.15 (1H, t, J=3 Hz), 9.68 (1H, d, J=8 Hz)	B
7f	61	102~104 (dec)	1766, 1713, 1667	1.15 (9H, s), 3.55~3.77 (4H, m), 4.35~4.65 (2H, m), 5.04 (1H, dd, J=1, 10 Hz), 5.10 (1H, dd, J=1, 17 Hz), 5.25 (1H, d, J=5 Hz), 5.60~5.70 (1H, m), 5.70~5.90 (4H, m), 6.27 (1H, d, J=12 Hz), 6.67 (1H, s)	B
7g	60	139~140 (dec)	1795, 1754, 1689, 1667	1.04 (6H, d, J=7 Hz), 1.15 (9H, s), 3.55~3.65 (1H, m), 3.55, 3.66 (2H, ABq, J=18 Hz), 4.35~4.55 (2H, m), 5.25 (1H, d, J=5 Hz), 5.60~5.70 (1H, m), 5.75~5.85 (3H, m), 6.27 (1H, d, J=12 Hz), 6.66 (1H, s), 7.05 (1H, d, J=8 Hz), 7.12 (2H, br s), 9.47 (1H, d, J=8 Hz)	B
7h	69	157~159 (dec)	1786, 1752, 1677	1.15 (9H, s), 2.81 (6H, s), 3.55, 3.66 (2H, ABq, J=18 Hz), 4.40~4.60 (2H, m), 5.24 (1H, d, J=5 Hz), 5.65~5.70 (1H, m), 5.76, 5.83 (2H, ABq, J=6 Hz), 5.80~5.85 (1H, m), 6.28 (1H, d, J=12 Hz), 6.66 (1H, s), 7.11 (2H, s), 9.46 (1H, d, J=8 Hz), 11.30 (1H, s)	B
7i	60	109~110 (dec)	1787, 1754, 1678	1.20 (9H, s), 1.80~2.00 (4H, m), 3.30~3.50 (4H, m), 3.52, 3.70 (2H, ABq, J=18 Hz), 4.45~4.55 (1H, m), 4.62~4.70 (1H, m), 5.24 (1H, d, J=5 Hz), 5.65~5.95 (4H, m), 6.25 (1H, d, J=12 Hz), 6.80 (1H, s)	C
7j	60	109~110 (dec)	1786, 1752, 1683	1.21 (9H, s), 3.20~3.30 (4H, m), 3.50, 3.69 (2H, ABq, J=18 Hz), 3.58~3.70 (4H, m), 4.50~4.58 (1H, m), 4.65~4.70 (1H, m), 5.26 (1H, d, J=5 Hz), 5.72~5.80 (1H, m), 5.81, 5.86 (2H, ABq, J=6 Hz), 5.91 (1H, d, J=5 Hz), 6.34 (1H, d, J=12 Hz), 6.77 (1H, s)	C
7q	50	119~121 (dec)	1770, 1750, 1672 1614	1.22 (9H, s), 3.67 and 3.83 (2H, ABq, J=18 Hz), 4.64 (2H, ABq, J=4 Hz), 5.22 (1H, d, J=5 Hz), 5.92 (1H, d, J=5 Hz), 6.22 (1H, dd, J=4, 16 Hz), 6.77 (1H, s), 7.04 (1H, d, J=16 Hz)	C
7m	67	116~118 (dec)	1779, 1754, 1715, 1669	1.17 (9H, s), 3.56, 3.67 (2H, ABq, J=18 Hz), 3.84 (3H, s), 4.30~4.50 (2H, m), 5.25 (1H, d, J=5 Hz), 5.60 ~5.70 (1H, m), 5.75~5.85 (3H, m), 6.27 (1H, d, J=11 Hz), 6.50 (2H, br s), 6.75 (1H, s), 7.22 (2H, br s), 9.61 (1H, d, J=8 Hz)	B
7n	57	162~164 (dec)	1782, 1752, 1713, 1678	1.16 (9H, s), 2.55 (3H, d, J=4 Hz), 3.56, 3.67 (2H, ABq, J=18 Hz), 3.84 (3H, s), 4.35~4.55 (2H, m), 5.25 (1H, d, J=5 Hz), 5.60~5.70 (1H, m), 5.75~5.85 (3H, m), 6.27 (1H, d, J=12 Hz), 6.75 (1H, s), 6.95~7.05 (1H, m), 7.20 (2H, s), 9.61 (1H, d, J=8 Hz)	B
7p	60	105~107 (dec)	1766, 1681, 1662	1.13 (9H, s), 2.89 (6H, s), 3.46, 3.63 (2H, ABq, J=18 Hz), 4.06 (3H, s), 4.22~4.50 (1H, m), 4.58~4.67 (1H, m), 5.14 (1H, d, J=5 Hz), 5.70~5.82 (1H, m), 5.83, 5.90 (2H, ABq, J=6 Hz), 6.04 (1H, dd, J=4, 8 Hz), 6.32 (1H, d, J=12 Hz), 6.86 (1H, s), 7.56 (1H, d, J=8 Hz)	A

[a] A; $CDCl_3$, B; d_6-DMSO, C; CD_3OD.

carboxylate[8] (**8**; 69 g, 0.13 mol) in dimethylsulfoxide (690 ml) and water (210 ml) was added cuprous oxide (17.9 g, 0.23 mol) and the mixture was stirred for 30 minutes at 50°C. The reaction mixture was cooled in an ice bath and the insoluble matter was filtered off. The filtrate was extracted with ethyl acetate and the organic layer was washed with water and then brine, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and crystallized from ethyl ether and ethyl acetate to yield crude 4-methoxyphenylmethyl 7-formamido-3-[(*E*)-3-hydroxy-1-propenyl]-3-cephem-4-carboxylate (**9**; 7.4 g, 14%).

To a solution of **9** (7.4 g, 18.3 mmol) in tetrahydrofuran (185 ml) at −50°C was added chlorosulfonyl isocyanate (3.5 ml, 40 mmol), and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was added to a phosphate buffer solution (pH 7, 300 ml) at 0°C and extracted with ethyl acetate. The extracts were washed with water and then brine, and dried over anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was chromatographed on a column of silica gel (Wako C-200, 200 g). The fractions containing the desired compound were evaporated to give 530 mg of **10** as an amorphous powder (6%). ^{1}H NMR (90 MHz, DMSO-d_6) δ 3.75 (3H, s), 4.48 (2H, d, J=6 Hz), 5.15 (1H, d, J=5 Hz), 5.17 (2H, s), 5.76 (1H, dd, J=8, 5 Hz), 6.00~6.30 (1H, m), 6.51 (2H, br s), 6.73 (1H, d, J=15 Hz), 6.90 (2H, d, J=9 Hz), 7.33 (2H, d, J=9 Hz), 8.10 (1H, s), 9.05 (1H, d, J=8 Hz).

4-Methoxyphenylmethyl 7-[(*Z*)-2-(2-Tritylaminothiazol-4-yl)-2-trityloxyiminoacetamido]-3-[(*E*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**5q**)

To a suspension of **10** (530 mg, 1.1 mmol) in tetrahydrofuran (15 ml) and methanol (15 ml) was added concentrated hydrochloric acid (0.53 ml), and the mixture was stirred for 4 hours. The mixture was diluted with ethyl acetate (200 ml) and was adjusted to pH 6 with 5% aqueous sodium carbonate solution. The organic layer was washed with water and then brine and dried over anhydrous $MgSO_4$. The filtrate was evaporated to yield 480 mg of 4-methoxyphenymethyl 7-amino-3-[(*E*)-3-carbamoyloxy-1-propenyl]-3-cephem-4-carboxylate (**11**) as an amorphous powder (quantitative).

To a solution of **11** (480 mg, 1.1 mmol) in *N*,*N*-dimethylformamide (10 ml) was added **1a** (706 mg, 1.2 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (244 mg, 1.2 mmol), 1-hydroxybenztriazole (173 mg, 1.3 mmol), and the mixture was stirred for 4 hours. After the insoluble urea was filtered off, the mixture was diluted with ethyl acetate. The organic layer was washed with water and then brine and dried over anhydrous $MgSO_4$ and the the filtrate was evaporated. The residue was chromatographed on a column of silica gel (Wako C-200, 20 g, eluent; dichloromethane-ethyl acetate, 9:1). The fractions containing the desired product were collected and evaporated under reduced pressure to give 620 mg of **5q** as an amorphous powder (53%).

The spectral data for **5q** are listed in Table 3.

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