STUDIES ON β-LACTAM ANTIBIOTICS

XI.† SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF NEW 3-(2,2-DIHALOVINYL)CEPHALOSPORINS

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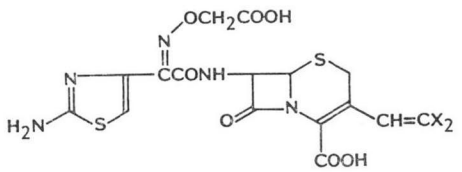
The synthesis and *in vitro* antibacterial activity of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]-3-(2,2-dihalovinyl)cephalosporins (**1**) are described. 3-(2,2-Dihalovinyl)cephalosporins (**1c** and **1d**) exhibited excellent antimicrobial activity against both Gram-positive and Gram-negative bacteria, especially showed higher activity against *Staphylococcus aureus* than the corresponding 3-vinylcephalosporin (**1a**; FK027).

In a previous paper[1] we reported on the antibacterial activity and oral absorption of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]cephalosporins having various substituents at the 3-position. Among these, the 3-vinylcephalosporin[2,3] (**1a**; FK027)†† exhibited the highest activity against most of the Gram-negative bacteria and showed also better recovery after oral administration to rats. However, the less potent activity of FK027 (**1a**) against *Staphylococcus aureus* as compared with cephalexin[4] and cefaclor[5] prompted us to search for a new orally active cephalosporin having higher activity against not only Gram-negative bacteria but also *S. aureus* by chemical modification of FK027 (**1a**). Therefore, we made an effort to modify the vinyl group at the 3-position, because the (*Z*)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetyl side chain seems to be essential for both high activity against Gram-negative bacteria and better oral absorptivity[6,7].

In the first approach to a new substituent at the 3-position of the cephem nucleus, we assumed that introduction of more lipophilic functions such as *gem*-dihalovinyl groups (X=F, Cl, Br) could enhance activity against *S. aureus* (Fig. 1).

In this paper we report the synthesis and structure-activity relationships of 7β-[(*Z*)-2-(2-amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]-3-(2,2-dihalovinyl)-3-cephem-4-carboxylic acids (**1**).

Fig. 1. Structure of FK027 and its related compounds.



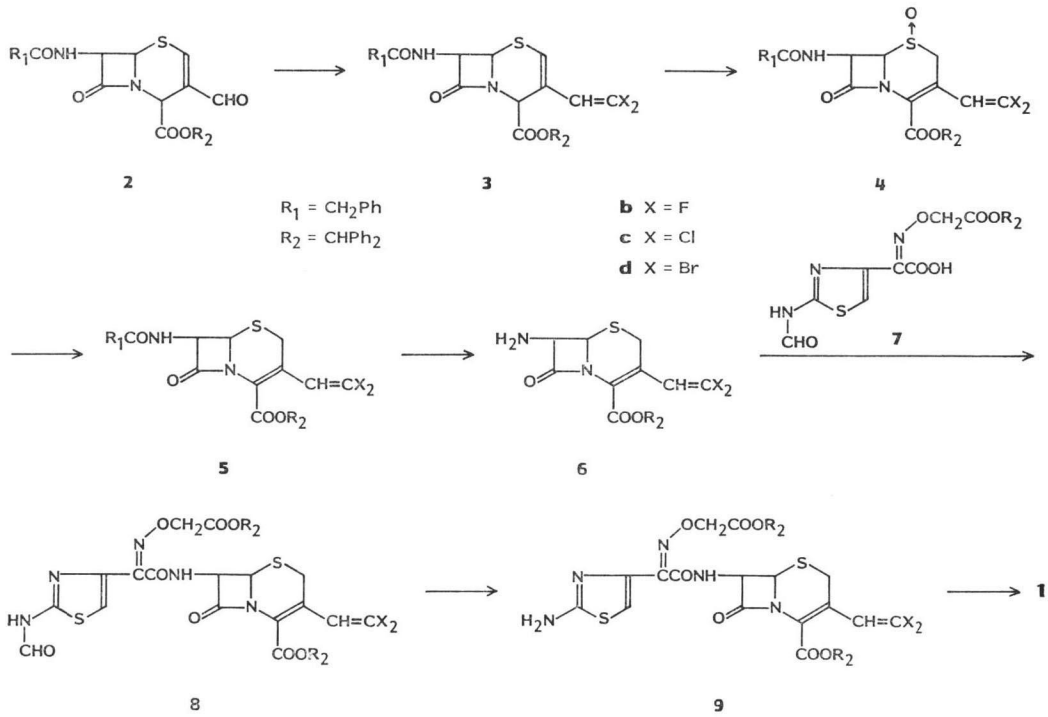
1a X=H (FK027)
1b X=F
1c X=Cl
1d X=Br

Chemistry

New cephalosporins with 2,2-dihalovinyl groups at the 3-position were prepared by the route outlined in Scheme 1. Both 3-(2,2-dichlorovinyl)-2-cephem (**3c**) and 3-(2,2-dibromovinyl)-2-cephem (**3d**) were successfully synthesized by WITTIG-like reaction of 3-formyl-2-cephem (**2**)[8] with the corresponding carbontetrahalide, triphenylphosphine and zinc powder[9~11]. 3-(2,2-Dihalovinyl)-2-cephems (**3c** and

† Paper X. See ref 1).
†† Generic name: Cefixime.

Scheme 1.

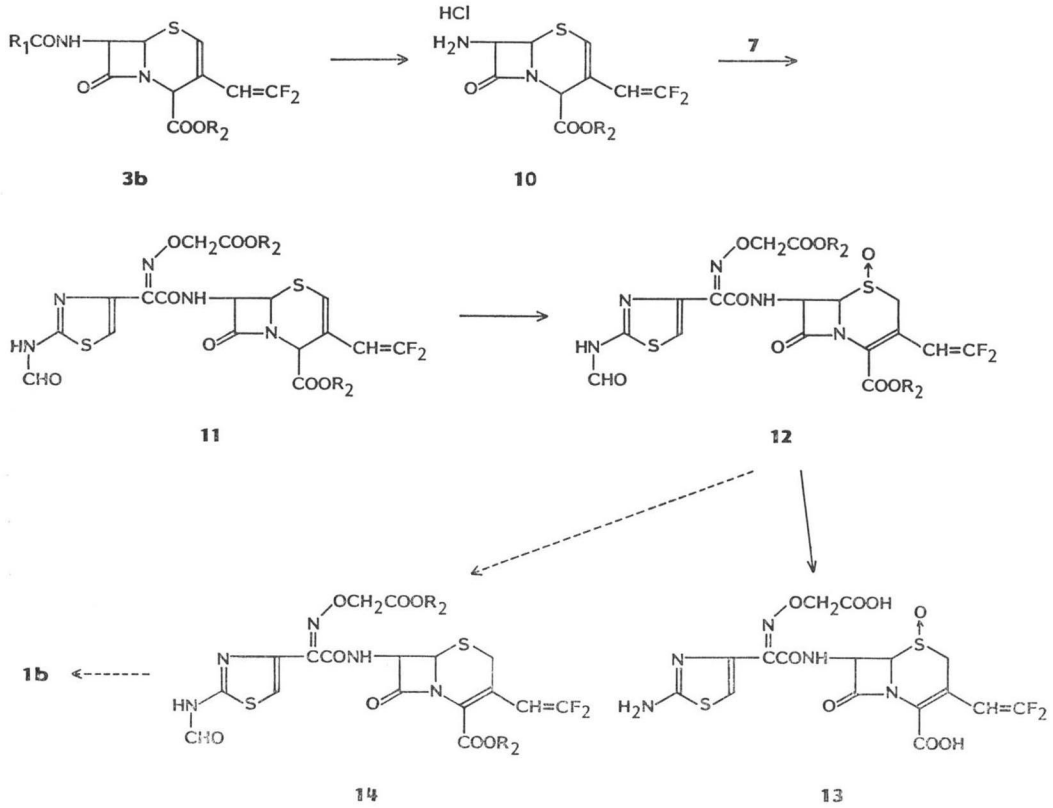


3d) were converted to the corresponding 3-cephems (**5c** and **5d**) by utilizing the oxidative-reductive process (**3**→**4**→**5**) for isomerization of the double bond.

The synthesis of 3-(2,2-difluorovinyl)-2-cephem (**3b**) was accomplished by WITTIG-like reaction of 3-formyl-2-cephem (**2**) with dibromodifluoromethane, hexamethylphosphorous triamide and zinc powder in *N*,*N*-dimethylacetamide (DMAc)[12], although **3b** could not be obtained by similar treatment of **2** with triphenylphosphine instead of hexamethylphosphorous triamide. 3-(2,2-Difluorovinyl)-2-cephem (**3b**) was oxidized with *m*-chloroperbenzoic acid to afford the corresponding sulfoxide (**4b**). However, reduction of the sulfoxide (**4b**) with phosphorus trichloride (PCl_3) or acetylbromide-amylene did not give the desired 3-(2,2-difluorovinyl)-3-cephem (**5b**) but many unknown compounds. Therefore, we investigated the alternative route outlined in Scheme 2 in order to obtain the 7-acylcephalosporin (**1b**). The 7-phenylacetyl side chain of 3-(2,2-difluorovinyl)-2-cephem (**3b**) was removed with phosphorus pentachloride (PCl_5) to yield the 7-amino-3-(2,2-difluorovinyl)-2-cephem (**10**), which was acylated to give the 7-acylcephem (**11**) by reaction with an activated acid prepared by treatment of the acid (**7**) with Vilsmeier reagent (phosphoryl chloride and *N*,*N*-dimethylformamide). Oxidation of the 7-acylcephem (**11**) with *m*-chloroperbenzoic acid gave the corresponding sulfoxide (**12**), however, its reduction with PCl_3 or acetylbromide-amylene to afford the corresponding 3-(2,2-difluorovinyl)-3-cephem (**14**) could not be achieved. This result suggested that 3-(2,2-difluorovinyl)-3-cephems (**5b** and **14**) might be unstable under these conditions. Therefore, the *N*-formylsulfoxide (**12**) was deformylated by treatment with concentrated hydrochloric acid in methanol, followed by deprotection of the diphenylmethyl group with trifluoroacetic acid (TFA) and anisole to yield the corresponding 3-(2,2-difluorovinyl)-3-cephem-4-carboxylic acid 1-oxide (**13**).

Cleavage of the 7-phenylacetyl side chain of 3-(2,2-dichlorovinyl)cephem (**5c**) and 3-(2,2-dibromo-

Scheme 2.



vinyl)cephem (**5d**) with PCl_5 gave the corresponding 7-amino-3-(2,2-dihalovinyl)cephems (**6c** and **6d**), respectively. Cephalosporins (**1c** and **1d**) were obtained by coupling **6c** and **6d**, respectively, with the activated acid of **7**, followed by removal of the formyl and diphenylmethyl groups.

Antibacterial Activity and Urinary Recovery

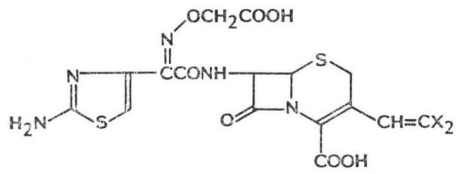
The antibacterial activity of the tested cephalosporins (**1**) and their urinary recovery after oral administration (100 mg/kg) to rats are shown in Tables 1 and 2, respectively. For comparison, the MIC values and urinary recovery of FK027 (**1a**) are listed at the top of the Tables.

3-(2,2-Dihalovinyl)cephalosporins (**1c** and **1d**) were more active against *S. aureus* 209P JC-1 than FK027 (**1a**). Particularly, 3-(2,2-dibromovinyl)cephalosporin (**1d**) exhibited excellent activity against *S. aureus* (0.78 μg/ml).

Against Gram-negative bacteria, 3-(2,2-dihalovinyl)cephalosporins (**1c** and **1d**) showed almost the same activity as FK027 (**1a**). The order of activity against *Escherichia coli* NIHJ JC-2 was 3-vinylcephalosporin (**1a**) > 3-(2,2-dichlorovinyl)cephalosporin (**1c**) > 3-(2,2-dibromovinyl)cephalosporin (**1d**). The increasing lipophilicity of the 3-substituent on the cephem nucleus enhanced the activity against *S. aureus* but slightly reduced the activity against *E. coli*.

The urinary recovery of **1c** and **1d** after oral administration (100 mg/kg) to rats was 5.7% and 3.0%, respectively, whereas 34.0% of FK027 (**1a**) was excreted in the urine. The attachment of the larger geminal atom (X) to the β-carbon in the 3-vinyl group resulted in decreasing oral absorptivity.

Table 1. Antibacterial activity of cephalosporins with various vinyl groups at the 3-position (**1a**, **1c** and **1d**).



Inoculum size 10^6 cfu/ml

Compound	X	MIC (μg/ml)		
		Staphylococcus aureus 209P JC-1	*Escherichia coli* NIHJ JC-2	*Proteus vulgaris* 1
1a	H	25	0.2	≦0.025
1c	Cl	6.25	0.39	≦0.025
1d	Br	0.78	0.78	≦0.025

Table 2. 24-Hour urinary recovery (%) of cephalosporins (**1a**, **1c** and **1d**) after oral administration (100 mg/kg) to rats.

Compound	X	Urinary recovery (%)
1a	H	34.0
1c	Cl	5.7
1d	Br	3.0

As a result of our investigations, we succeeded in finding new substituents at the 3-position such as the 2,2-dihalovinyl groups which have excellent activity against both Gram-negative organisms and *S. aureus*. Unfortunately, their urinary excretion turned out to be poor.

Our further studies on structure-activity relationships and oral absorptivity of a new substituent at the 3-position of the cephem nucleus will be presented in the subsequent paper.

Experimental

MP were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a Jeol-MH 100 NMR spectrometer using Me_4Si as an internal standard. IR spectra were taken on a Hitachi 260-10 spectrophotometer or a Shimadzu IR-420 spectrophotometer.

Antibiotic Susceptibility

All *in vitro* antibacterial activity data are given as the minimum inhibitory concentration (MIC) in μg/ml. MICs were determined by the agar dilution method using heart infusion agar (Difco) after incubation at 37°C for 20 hours with an inoculum size of about 10^6 cfu/ml.

Urinary Recovery

Sprague Dawley rats were fasted overnight and orally dosed with 100 mg/kg of the test drugs. Urine samples were collected for 24 hours after dosing. The samples were assayed by a disc-agar diffusion method using *E. coli* NIHJ JC-2 or *E. coli* ATCC 33546 as the test organism and nutrient agar (Difco) as the test medium.

(*Z*)-2-Diphenylmethoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)acetic Acid (7)

N-Diphenylmethoxycarbonylmethoxyphthalimide: To a soln of bromoacetic acid (10.45 g, 0.075 mol) in MeOH (30 ml) was added diphenyldiazomethane (14.55 g, 0.075 mol) in EtOAc (100 ml) at 45°C and the mixture was stirred at the same temp for 1 hour. The resultant soln was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* and the residue was dissolved in DMF (60 ml). To the DMF soln was added *N*-hydroxyphthalimide (11.7 g, 0.072 mol) and triethylamine (15.1 ml, 0.11 mol), and the reaction mixture was stirred at room

Table 3. Yields of **3**, **4**, **5**, **6**, **8**, **9** and **1**.

Compound	X	Yields (%)						
		WITTIG reaction **3**	Oxidation **4**	Reduction **5**	Cleavage **6**	*N*-Acylation **8**	Deformylation **9**	Deesterification **1**
b	F	9.8	54.2	—	—	—	—	—
c	Cl	13.2	42.4	87.9	100.0	87.5	87.5	66.0
d	Br	33.0	53.5	83.2	82.9	68.4	89.1	64.2

Table 4. Yields of **10**, **11**, **12** and **13**.

Compound	X	Yields (%)			
		Cleavage **10**	*N*-Acylation **11**	Oxidation **12**	Deprotection **13**
b	F	97.8	100.0	19.1	28.0

temp for 1 hour. The mixture was poured into brine (500 ml). The resultant precipitate was collected by filtration and washed with H_2O. The precipitate was dissolved in dichloromethane (700 ml), and the soln was washed with brine, dried ($MgSO_4$), and evaporated to give 20.4 g (70.0%) of *N*-diphenylmethoxycarbonylmethoxyphthalimide: mp 173~175°C; IR (Nujol) 1754, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (4H, s), 7.30 (10H, s), 7.00 (1H, s), 4.93 (2H, s).

(*Z*)-2-Diphenylmethoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)acetic Acid (**7**): To a soln of *N*-diphenylmethoxycarbonylmethoxyphtalimide (10 g, 0.026 mol) in dichloromethane (100 ml) was added a soln of 100% hydrazine hydrate (6.08 g, 0.124 mol) in MeOH (7 ml). The reaction mixture was stirred at room temp for 1 hour. The precipitate was filtered off, and the filtrate was adjusted to pH 7 with 10% HCl. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was dissolved in THF (40 ml) and added to a suspension of 2-(2-formamido-4-thiazolyl)glyoxalic acid[13] (6.0 g, 0.03 mol) in H_2O (60 ml). The reaction mixture was stirred at room temp for 3 hours. To the resultant soln was added EtOAc (200 ml), the organic layer was washed with 5% HCl and brine, and dried ($MgSO_4$). The soln was evaporated to afford 13.0 g (88.7%) of **7**: mp 143~151°C; IR (Nujol) 3150, 1733, 1692 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.77 (1H, br s), 8.60 (1H, s), 7.56 (1H, s), 7.40 (10H, m), 6.97 (1H, s), 5.00 (2H, br s).

Diphenylmethyl 7β-Phenylacetamido-3-(2,2-difluorovinyl)-2-cephem-4-carboxylate (**3b**)

Hexamethylphosphorous triamide (55.7 ml, 0.31 mol) was added to a suspension of diphenylmethyl 7β-phenylacetamido-3-formyl-2-cephem-4-carboxylate (**2**) (66.7 g, 0.13 mol), zinc powder (16.99 g, 0.26 mol) and dibromodifluoromethane (23.8 ml, 0.26 mol) under ice-cooling. The resultant mixture was stirred at the same temp for 30 minutes and allowed to warm to 35°C for 2 hours. The reaction mixture was added to brine and the resulting precipitate was collected by filtration. The precipitate was purified by column chromatography on silica gel, eluting with dichloromethane - EtOAc (10: 1) to give 9.0 g (9.8%) of **3b**: mp 147~152°C; IR (Nujol) 3620, 1775, 1725, 1645 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.12 (1H, d, J=8 Hz), 7.50~7.17 (15H, m), 6.83 (1H, s), 6.66 (1H, s), 5.57 (1H, dd, J=5, 8 Hz), 5.36 (1H, s), 5.25 (1H, dd, J=4, 12 Hz), 5.05 (1H, d, J=5 Hz), 3.56 (2H, s).

Anal Calcd for $C_{30}H_{24}N_2O_4SF_2$: C 65.92, H 4.42, N 5.13, S 5.87, F 6.95.
Found: C 65.90, H 4.58, N 5.11, S 6.00, F 6.88.

Diphenylmethyl 7β-Phenylacetamido-3-(2,2-dichlorovinyl)-2-cephem-4-carboxylate (**3c**)

Zinc powder (78.4 g, 1.2 mol) was added to a soln of **2** (102.4 g, 0.2 mol) and triphenylphosphine (367.2 g, 1.4 mol) in a mixture of carbon tetrachloride (800 ml) and DMAc (200 ml) at room temp, and the reaction mixture was stirred at 60°C for 30 minutes. The resulting mixture was poured into EtOAc, and the precipitate was filtered off. The filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel, eluting with dichloromethane - EtOAc (10: 1) to

Table 5. ^{1}H NMR and IR spectral data of **4b**~**d** and **5c**, **d**.

Compound	X	^{1}H NMR (DMSO-d_6, δ)								IR (Nujol, cm^{-1})		
		CONH (1H, d, J=8 Hz)	Ph×3 (15H, m)	CH=CX$_2$ (1H)	Ph$_2$CH (1H, s)	C(7)-H (1H, dd, J=5, 8 Hz)	C(6)-H (1H, d, J=5 Hz)	PhCH_2 (2H, s)	C(2)-CH$_2$ (2H, br s)	β-Lactam	Ester	CONH
4b	F	8.42	7.75~7.08	5.80 (dd, J=4 Hz, 12 Hz)	6.95	5.97	4.97	3.67	3.94	1770	1715	1640
4c	Cl	8.42	7.73~7.10	6.88 (s)	6.95	5.92	4.98	3.62	3.85	1780	1725	1645
4d	Br	8.90	7.70~7.10 (16H, m)		6.98	6.15	5.45	3.65	3.90	1770	1720	1680
5c	Cl	9.02	7.57~7.08	6.80 (s)	6.83	5.72	5.12	3.60	3.56	1760	1720	1640
5d	Br	9.23	7.80~7.28 (16H, m)		7.00	5.82	5.23	3.60	3.70	1780	1720	1650

Table 6. ^{1}H NMR and IR spectral data of **6c** and **6d**.

Compound	X	^{1}H NMR (DMSO-d_6, δ)				IR (Nujol, cm^{-1})
		Ph×2 (10H, m)	CH=CX$_2$ (1H)	C(7)-H and C(6)-H (2H, s)	C(2)-CH$_2$ (2H, br s)	β-Lactam
6c	Cl	7.67~7.17	7.00 (s)	5.30	3.82	1780
6d	Br	7.80~7.20 (11H, m)		5.28	3.78	1770

afford 15.26 g (13.2%) of **3c**: IR (Nujol) 1765, 1720, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.15 (1H, d, J=8 Hz), 7.83~7.06 (15H, m), 7.05 (1H, s), 6.83 (1H, s), 6.78 (1H, s), 5.60 (1H, s), 5.45 (1H, dd, J=5, 8 Hz), 5.08 (1H, d, J=5 Hz), 3.56 (2H, s).

Diphenylmethyl 7β-Phenylacetamido-3-(2,2-dibromovinyl)-2-cephem-4-carboxylate (**3d**)

Carbon tetrabromide (45 g, 0.136 mol) was added to a mixture of zinc powder (8.5 g, 0.13 mol), triphenylphosphine (40.7 g, 0.156 mol) and **2** (10.0 g, 0.0195 mol) in dichloromethane (250 ml) under ice-cooling. The reaction mixture was stirred at the same temp for 30 minutes. The resultant mixture was poured into EtOAc (200 ml), and the precipitate was filtered off. The filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel, eluting with dichloromethane - EtOAc (10: 1) to afford 4.4 g (33.0%) of **3d**: IR (Nujol) 1790, 1730, 1650 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.20 (1H, d, J=8 Hz), 7.70~7.20 (16H, m), 7.10 (1H, s), 6.90 (1H, s), 5.65 (1H, s), 5.45 (1H, dd, J=5, 8 Hz), 5.13 (1H, d, J=5 Hz), 3.55 (2H, s).

General Preparation of Diphenylmethyl 7β-Phenylacetamido-3-(2,2-dihalovinyl)-3-cephem-4-carboxylate 1-Oxide (**4**)

To a soln of **3** (10 mmol) in EtOAc (20 ml) was added a soln of *m*-chloroperbenzoic acid (12 mmol) in EtOAc (10 ml) under ice-cooling, and the resulting mixture was stirred at the same temp for 1 hour. The resultant precipitate was collected by filtration to give the sulfoxide (**4**).

General Preparation of Diphenylmethyl 7β-Phenylacetamido-3-(2,2-dihalovinyl)-3-cephem-4-carboxylate (**5**)

To a soln of **4** (10 mmol) in DMF (100 ml) was added PCl_3 (2.75 g, 20 mmol) at $-30°C$ and the reaction mixture was stirred at -30~$-20°C$ for 30 minutes. The resulting mixture was poured into a mixture of EtOAc and H_2O. The separated organic layer was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The soln was evaporated *in vacuo* to afford **5**.

General Preparation of Diphenylmethyl 7β-Amino-3-(2,2-dihalovinyl)-3-cephem-4-carboxylate (**6**)

To a suspension of PCl_5 (2.5 g, 12 mmol) in dichloromethane (30 ml) was added pyridine (0.95 g, 12 mmol) at $-10°C$, and the mixture was stirred at the same temp for 30 minutes. **5** (10 mmol) was added to the above mixture at $-10°C$ and the reaction mixture was stirred under ice-cooling for 1~2 hours. Then, methyl cellosolve (7.6 g, 100 mmol) was added to the reaction mixture at $-20°C$, the resulting soln was stirred at -20~$-15°C$ for 1~2 hours and H_2O (10 ml) was added under ice-cooling.

6c and **6d** were obtained by the following methods A and B, respectively.

A) The resultant precipitate was collected by filtration to afford **6c** as its hydrochloride.

B) The soln was adjusted to pH 7.5 with satd sodium bicarbonate soln, and extracted with EtOAc. The separated organic layer was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was triturated with diisopropyl ether to afford **6d** as a powder.

General Preparation of Diphenylmethyl 7β-[(*Z*)-2-Diphenylmethoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)acetamido]-3-(2,2-dihalovinyl)-3-cephem-4-carboxylate (**8**)

To a soln of DMF (0.21 g, 2.88 mmol) in THF (3 ml) was added phosphoryl chloride (0.44 g, 2.88 mmol) under ice-cooling, and the mixture was stirred at the same temp for 30 minutes to prepare the Vilsmeier reagent. To the above mixture was added *N*-formyl acid (**7**) (2.4 mmol) under ice-cooling,

Table 7. ^{1}H NMR and IR spectral data of **8**, **9** and **1**.

Compound	X	^{1}H NMR (DMSO-d_6, δ)									IR (Nujol, cm^{-1})	
		CONH (1H, d, J=8 Hz)	C(7)-H (1H, dd, J=5, 8 Hz)	C(6)-H (1H, d, J=5 Hz)	CH_2COO (2H, s)	C(2)-CH_2 (2H, br s)	Ph_2CH×2	HCO (1H, s)	Ph×4 (20H)	CH=CX_2 (1H)	Thiazole C(5)-H (1H, s)	β-Lactam	CONH
8c	Cl	9.82	6.05	5.35	4.95	3.53	6.97 (1H, s), 6.93 (1H, s)	8.57	7.78~7.12 (22H, m)			1780	1680
8d	Br	9.78	6.00	5.28	4.95	3.67	6.92 (2H, s)	8.53	7.73~7.10 (22H, m)			1780	1680
9c	Cl	9.67	5.98	5.20	4.83	3.53	6.93 (1H, s), 6.90 (1H, s)	—	7.80~7.02 (21H, m)		6.80	1770	1680
9d	Br	9.67	5.95	5.25	4.85	3.62	6.90 (2H, s)	—	7.67~6.95 (21H, m)		6.78	1770	1680
1c	Cl	9.55	5.93	5.30	4.67	3.77	—	—	—	7.03 (s)	6.87	1775	1670
1d	Br	9.49	5.83	5.17	4.85	3.67	—	—	—	7.42 (s)	6.77	1770	1640

and the resultant mixture was stirred at the same temp for 30 minutes to produce an activated acid soln of **7**. To a soln of the 7β-amino-3-(2,2-dihalovinyl)cephem (**6**) (2.0 mmol) and *N*-(trimethylsilyl)-acetamide (1.05 g, 8 mmol) in EtOAc (10 ml) was added the above activated acid soln at −30°C, and the reaction mixture was stirred at −20~−10°C for 30 minutes. The reaction mixture was poured into a soln of EtOAc and H_2O. The separated organic layer was washed with satd sodium bicarbonate soln and brine, and dried ($MgSO_4$). The solvent was evaporated to afford **8**.

General Preparation of Diphenylmethyl 7β-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-diphenylmethoxycarbonylmethoxyiminoacetamido]-3-(2,2-dihalovinyl)-3-cephem-4-carboxylate (**9**)

To a soln of **8** (1.5 mmol) in MeOH (8 ml) was added concd HCl (0.42 g, 4 mmol) at room temp, and the reaction mixture was stirred at the same temp for 2~4 hours. The reaction mixture was poured into a mixture of EtOAc and H_2O, and the mixture was adjusted to pH 7 with satd sodium bicarbonate soln. The separated organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford **9**.

General Preparation of 7β-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]-3-(2,2-dihalovinyl)-3-cephem-4-carboxylic Acid (**1**)

TFA (2 ml) was added to a soln of **9** (1 mmol) and anisole (1 ml) in dichloromethane (3 ml) under ice-cooling, and the reaction mixture was stirred at the same temp for 30~60 minutes. The resultant mixture was poured into diisopropyl ether, and the precipitate was collected by filtration. The precipitate was added to a mixture of EtOAc and H_2O, and the mixture was adjusted to pH 7 with satd sodium bicarbonate soln. The separated aq soln was evaporated *in vacuo* to remove the organic solvent, and then acidified to pH 3 with 10% HCl under ice-cooling. The precipitate was collected by filtration, and dried (P_2O_5) to afford **1**.

Diphenylmethyl 7β-Amino-3-(2,2-difluorovinyl)-2-cephem-4-carboxylate Hydrochloride (**10**)

10 was obtained from **3b** by a similar procedure as described for the prepn of **6c**: IR (Nujol) 1782, 1738 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67~7.17 (10H, m), 6.87 (1H, s), 6.68 (1H, s), 5.83~5.50 (1H, m), 5.40 (1H, s), 5.20 (1H, d, J=5 Hz), 5.03 (1H, d, J=5 Hz).

Diphenylmethyl 7β-[(*Z*)-2-Diphenylmethoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)-acetamido]-3-(2,2-difluorovinyl)-2-cephem-4-carboxylate (**11**)

11 was obtained from the 7-amino-3-(2,2-difluorovinyl)-2-cephem (**10**) and the *N*-formyl acid (**7**) by a similar procedure as described for the prepn of **8**: IR (Nujol) 1775, 1720 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.80 (1H, d, J=8 Hz), 8.53 (1H, s), 7.61~7.05 (21H, m), 6.90 (2H, s), 6.63 (1H, s), 5.70 (1H, dd, J=5, 8 Hz), 5.83~5.50 (1H, m), 5.35 (1H, s), 5.20 (1H, d, J=5 Hz), 4.90 (2H, s).

Diphenylmethyl 7β-[(*Z*)-2-Diphenylmethoxycarbonylmethoxyimino-2-(2-formamido-4-thiazolyl)-acetamido]-3-(2,2-difluorovinyl)-3-cephem-4-carboxylate 1-Oxide (**12**)

12 was obtained from **11** by a similar procedure as described for the prepn of **4**: IR (Nujol) 1795, 1685 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.08 (1H, d, J=8 Hz), 8.53 (1H, s), 7.60~7.20 (21H, m), 6.92 (2H, s), 6.13 (1H, dd, J=5, 8 Hz), 5.60~5.30 (1H, m), 5.17 (1H, d, J=5 Hz), 4.93 (2H, s), 3.45 (2H, br s).

7β-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-carboxymethoxyiminoacetamido]-3-(2,2-difluorovinyl)-3-cephem-4-carboxylic Acid 1-Oxide (**13**)

13 was obtained from **12** by a similar procedure as described for the prepn of **1**: IR (Nujol) 1770, 1660 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.07 (1H, d, J=8 Hz), 6.55 (1H, s), 6.03 (1H, dd, J=5, 8 Hz), 5.70~5.34 (1H, m), 5.08 (1H, d, J=5 Hz), 4.68 (2H, s), 3.74 (2H, m).

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