SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL 2-METHYL-1-OXACEPHALOSPORINS

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New 2-methyl-1-oxacephem compounds having 2-(2-aminothiazol-4-yl)-2-(alkoxyimino)acetamido substituents at C-7 and various C-3 side chains were synthesized starting from (3*R*,4*S*)-phenyloxazolinoazetidinone (**8**). Introduction of the 2β-methyl group into the 1-oxacephem nucleus increased the stability to β-lactamases. OCP-9-176 (**7b**) having the (1-methylpyridinium-4-yl)thiomethyl group at C-3 showed potent antibacterial activity and a broad spectrum.

In 1974, CAMA and CHRISTENSEN were successful in the synthesis of (±)-1-oxacephalothin[1] possessing comparable antibacterial activity with that of cephalothin, and (±)-1-oxacefamandole[2] was more active than the natural 1-thia counterpart. Since these findings, 1-oxacephem[†††] derivatives have been extensively studied by many research groups. Shionogi scientists synthesized a β-lactamase-stable analog, latamoxef by introduction of the 7α-methoxy group.[3,4] Fujisawa scientists[5] reported that the 2α-methyl analog of ceftizoxime (CZX) was more active than the 2β-methyl enantiomer, but less active than CZX. On the other hand, the 2β-methyl analog of cefmenoxime (CMX) having (1-methyl-1*H*-tetrazol-5-yl)thiomethyl substituent at C-3 was somewhat more active than the 2α-methyl analog.[6]

To examine the effect of the 2-methyl group of 1-oxacephems against β-lactamase-producing strains, we synthesized several 2α-methyl- and 2β-methyl-1-oxacephem compounds. Among these compounds, a 2β-methyl analog, (6*R*,7*S*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-2(*S*)-methyl-3-[(1-methylpyridinium-4-yl)thiomethyl]-1-oxacephem-4-carboxylate (OCP-9-176 and L-656,575) showed potent antibacterial activity with a broad spectrum,[7] and was selected for further biological evaluation.[8,9] In this paper, the synthesis of 2-methyl-1-oxacephem derivatives and their antibacterial activities are reported.

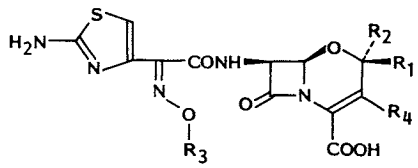
Chemistry

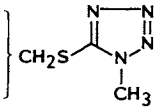
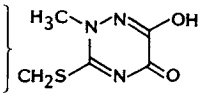
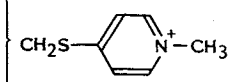
New 2α-methyl- and 2β-methyl-1-oxacephem compounds (series **a** and **b**) having 2-(2-aminothiazol-4-yl)-2-(alkoxyimino)acetamido substituents at C-7 and various C-3 side chains (compounds **1**~**7**, Fig. 1) were synthesized starting from (3*R*,4*S*)-phenyloxazolinoazetidinone[10] (**8**) through a useful key-intermediate, 3-hydroxy-2-methyl-1-oxacephem **15**.[11]

Compound **8** derived from 6-aminopenicillanic acid[10] was reacted with neat chiral alcohols **9a** and

[†††] In this paper, "1-oxacephem" is used for nomenclature of 1-oxa-1-dethia-3-cephem compounds.

Fig. 1. 2-Methyl-1-oxacephalosporins and their 2-non-methyl congeners.



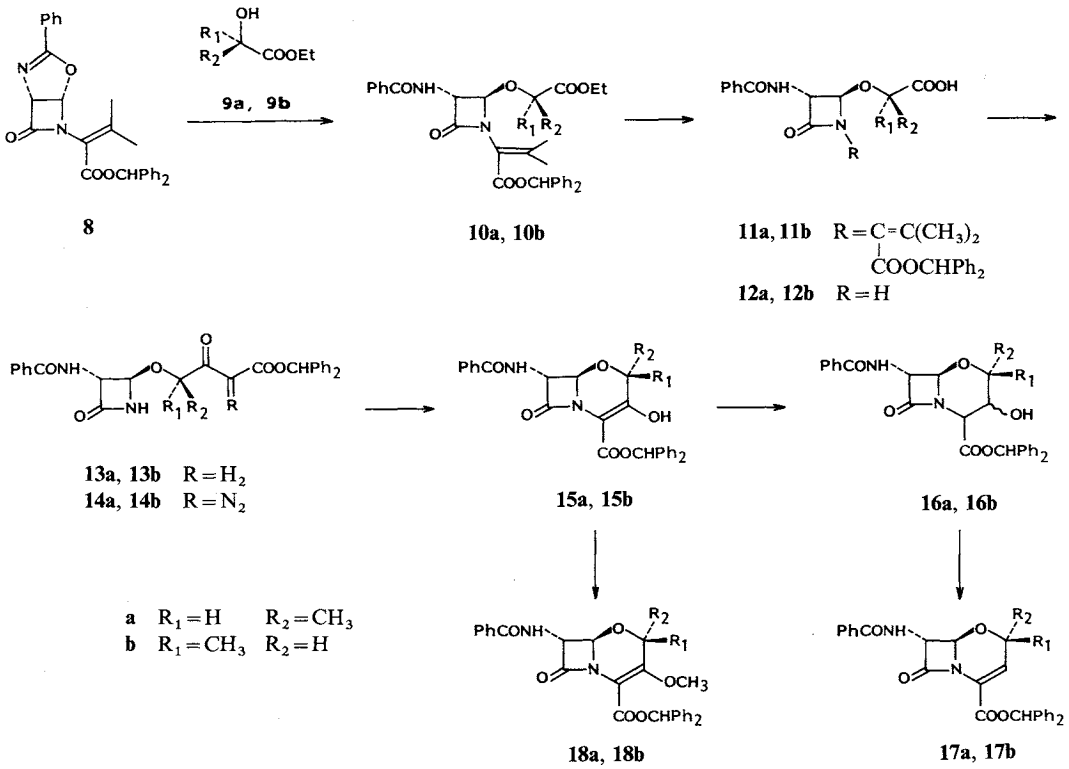
	R_1	R_2	R_3	R_4
1a	H	CH_3	CH_3	H
1b	CH_3	H	CH_3	
1c	H	H	CH_3	
2a	H	CH_3	CH_3	OCH_3
2b	CH_3	H	CH_3	
2c	H	H	CH_3	
3a	H	CH_3	CH_3	
3b	CH_3	H	CH_3	
3c	H	H	CH_3	
4b	CH_3	H	CH_3	
4c	H	H	CH_3	
5b	CH_3	H	CH_3	
5c	H	H	CH_3	
6b	CH_3	H	CH_2COOH	
6c	H	H	CH_2COOH	
7b	CH_3	H	$C(CH_3)_2COOH$	
7c	H	H	$C(CH_3)_2COOH$	

9b to give **10a** and **10b**, respectively.[12] Alkaline hydrolysis of **10**, followed by cleavage[13] of the substituent on the azetidinone nitrogen of **11** gave **12**. The reaction[14] of **12** with diphenylmethylmagnesium malonate, followed by diazotransfer reaction[15] of **13** with *p*-carboxybenzenesulfonyl azide yielded **14**. Cyclization *via* the intramolecular carbene insertion reaction[15] of **14** with a catalytic amount of rhodium (II) acetate gave unstable key-intermediate **15** (**b**: 6.7% yield from **8b**), which was treated with diazomethane to obtain stable 3-methoxyl **18**. Reduction of **15** with tetrabutylammonium borohydride gave **16**, which was treated with methanesulfonyl chloride to yield **17** (Scheme 1).

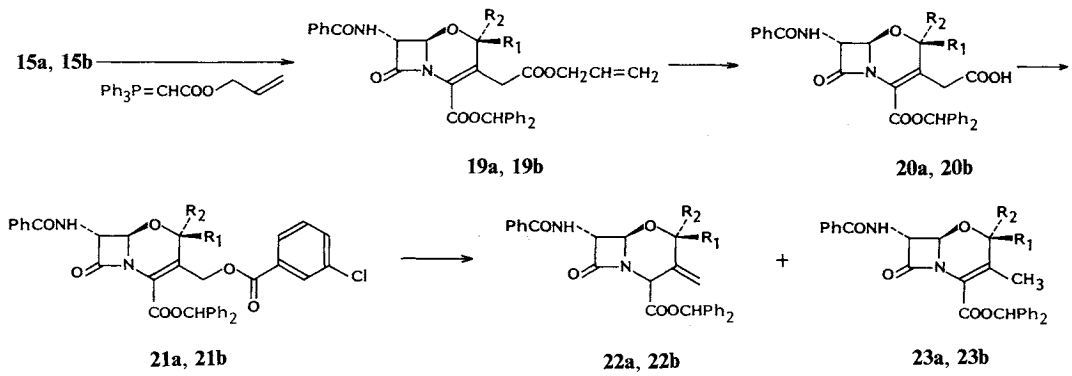
Treatment of **15a** and **15b** with allyl (triphenylphosphoranylidene)acetate, followed by 1,5-diazabicyclo[4.3.0]non-5-ene gave **19a** and **19b**, respectively. After removal of allyl ester, **20a** and **20b** were treated with 3-chloroperbenzoic acid to yield **21a** and **21b** (53% yield from **15b**), which were converted into 3-exomethylene **22a** and **22b** (64%) by reductive cleavage, together with 2,3-dimethyl **23a** and **23b** (18%), respectively (Scheme 2).

Deacylation of **22b** with phosphorous pentachloride, followed by epimerization of the 7-amino group of **24b** by the use of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde[16] gave **27b** (43% yield) through **25b** and **26b**. After *N*-formylation of **27b**, treatment of **28b** with phenylselenyl chloride gave **29b**. The *N*-protecting group was then removed to give **30b** (62% yield). After acylation of **30b** with (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-(methoxyimino)acetic acid, -2-[(diphenylmethoxycarbonyl)methoxyimino]acetic acid and -2-[1-methyl-1-(diphenylmethoxycarbonyl)ethoxyimino]acetic acid, treatments with 5,6-dihydroxy-2-methyl-1,2,4-triazine-3-thione and 1-methylpyrid-4-thione, followed by deprotection[17] gave **4b**, **5b**, **6b** and **7b** (**7b**:

Scheme 1.



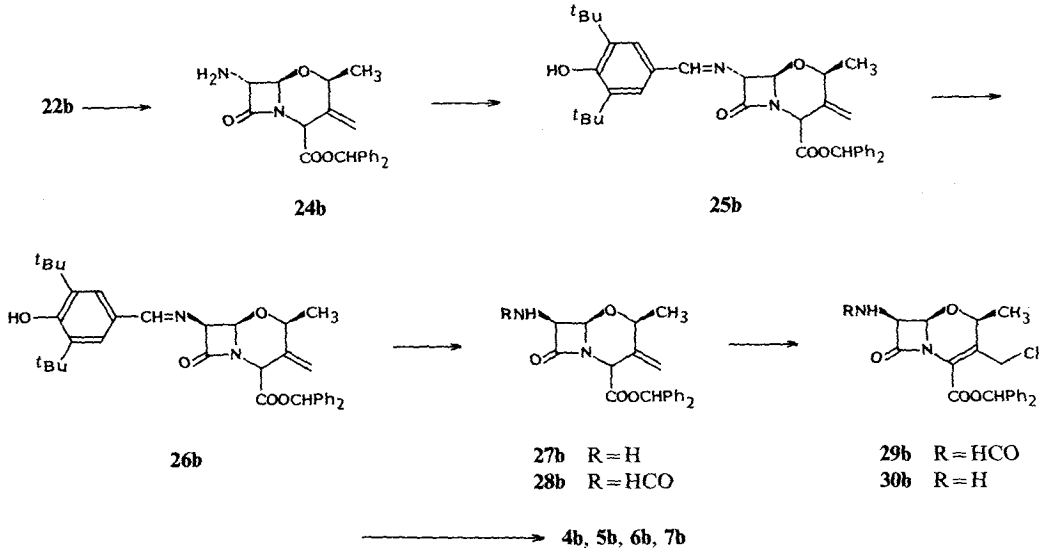
Scheme 2.



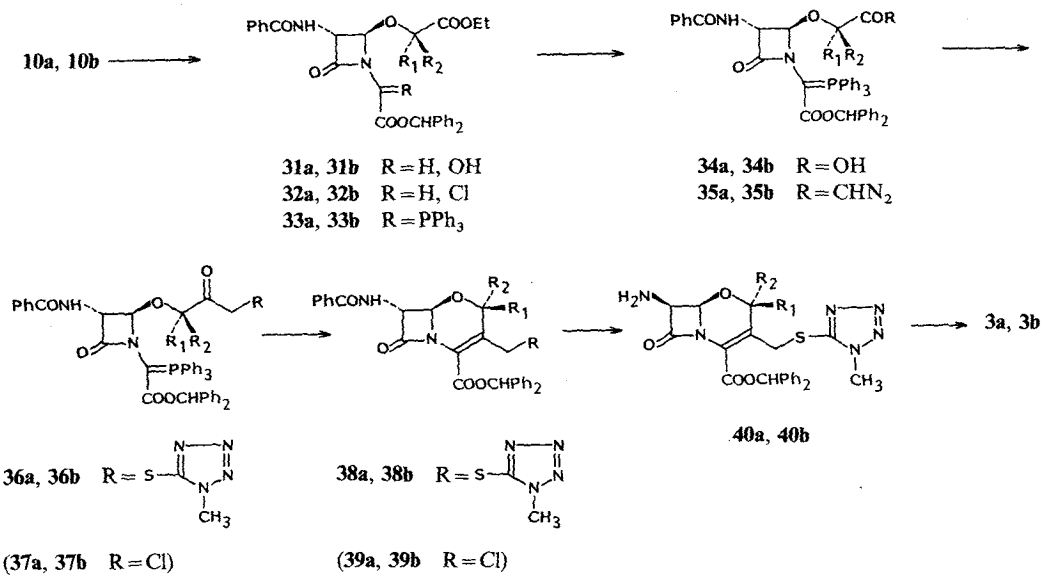
50% yield), respectively (Scheme 3).

For the direct synthesis of 3-substituted 2-methyl-1-oxacephems,[18] **36a** and **36b** (**b**: 26% yield) were prepared from **10a** and **10b**, respectively, through **31**~**35**, according to a known sequence.[19] Cyclization of **36a** and **36b** in toluene in the presence of hydroquinone gave **38a** and **38b** (84 and 81% yields), respectively. Epimerization of the 7-amino group of **38a** and **38b**, followed by acylation of **40a** and **40b** with (*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetic acid yielded **3a** and **3b** (24 and 16% yields), respectively (Scheme 4). Compound **37a** derived from **35a** by treatment with hydrochloric acid was easily

Scheme 3.



Scheme 4.



Scheme 5.

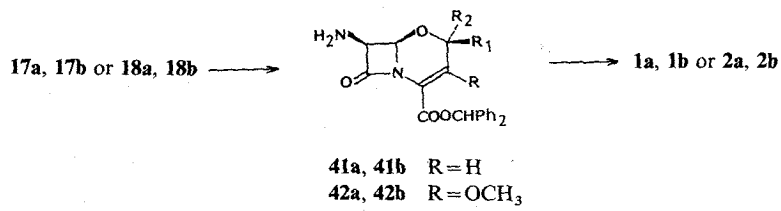


Table 1. Antibacterial activity (MIC, μg/ml).

Test organism	1a	1b	1c	2a	2b	2c	3a	3b	3c	CMX
Staphylococcus aureus FDA 209P JC-1	6.25	3.13	3.13	25	25	12.5	0.39	0.10	0.20	0.20
S. aureus 606[a]	25	6.25	12.5	50	50	50	1.56	0.39	0.78	0.78
S. epidermidis ATCC 14990	3.13	1.56	1.56	12.5	12.5	12.5	1.56	0.20	0.39	0.39
Bacillus subtilis ATCC 6633	12.5	6.25	12.5	25	12.5	12.5	0.78	0.20	0.39	12.5
Escherichia coli NIHJ JC-2	0.20	1.56	0.10	3.13	12.5	1.56	0.39	0.39	0.10	0.10
E. coli W3630 RGN14[a]	0.39	3.13	0.39	6.25	12.5	3.13	0.78	0.78	1.56	0.10
E. coli 255[b]	50	>100	50	>100	>100	>100	6.25	6.25	3.13	0.78
Klebsiella pneumoniae PCI 602	0.10	0.39	0.05	0.78	6.25	0.39	0.39	0.78	0.10	0.10
Proteus vulgaris GN76[b]	0.20	0.20	0.10	1.56	1.56	50	0.39	0.39	0.20	0.10
Morganella morganii 1510[b]	100	>100	100	>100	>100	>100	25	12.5	6.25	1.56
Citrobacter freundii GN346[b]	>100	>100	100	>100	>100	>100	100	25	25	12.5
Enterobacter cloacae G-0005[b]	0.78	6.25	0.78	6.25	50	12.5	1.56	1.56	3.13	0.39
Serratia marcescens GN629[b]	6.25	25	3.13	25	50	12.5	0.78	0.78	0.39	0.10
Pseudomonas aeruginosa M-0148[a]	>100	>100	>100	>100	>100	>100	>100	25	50	12.5
P. aeruginosa IAM-1007	>100	>100	>100	>100	>100	>100	>100	50	100	100

cyclized to **39a**, but **39b** was obtained from **37b** in a poor yield, together with a 7-membered ring compound.[20]

On the other hand, **38b** was converted into **22b** in 92% yield. Therefore, this route is also useful as an alternative synthesis of 2-methyl-1-oxacephem compounds.

Compounds **1** or **2** were synthesized from **17** or **18** through **41** or **42** by the method described above (Scheme 5).

The 2-non-methyl congeners (series **c**) were synthesized in a similar manner to the synthesis of 2-methyl-1-oxacephems. Compound **1c** is a known compound.[21]

Antibacterial Activity

Activities of several 2-methyl-1-oxacephem compounds were compared with those of the 2-non-methyl and the natural 1-thia counterparts, as shown in Table 1.

Among 2-methyl-3-nor-1-oxacephem compounds having a (*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamide substituent at C-7, the 2α-methyl analogs (**1a** and **2a**) were more active against Gram-negative bacteria than 2β-methyl enantiomers (**1b** and **2b**), but slightly less than 2-non-methyl analogs[21] (**1c** and **2c**), as similar to CZX analogs.[5] In the case of compounds having 3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl substituent, the 2α-methyl analog (**3a**) was less active than 2β-methyl enantiomer (**3b**), 2-non-methyl analog (**3c**) and CMX. Compound **4b** showed a similar or slightly less activity, compared to ceftriaxone (CTRX).

All compounds (**5**, **6** and **7**) having a (1-methylpyridinium-4-yl)thiomethyl group at C-3 showed

Table 1. (Continued)

Test organism	4b	4c	CTRX	5b	5c	6b	6c	7b	7c	CAZ
Staphylococcus aureus FDA 209P JC-1	0.78	0.78	0.39	0.10	0.10	0.78	1.56	1.56	1.56	3.13
S. aureus 606[a]	1.56	3.13	0.78	0.20	0.78	1.56	3.13	3.13	3.13	6.25
S. epidermidis ATCC 14990	0.20	0.78	0.39	0.10	0.20	0.78	1.56	0.78	1.56	3.13
Bacillus subtilis ATCC 6633	0.20	0.78	0.20	0.10	0.39	1.56	6.25	1.56	6.25	3.13
Escherichia coli NIHJ JC-2	0.10	0.10	0.10	0.05	<0.025	<0.025	<0.025	0.20	0.10	0.20
E. coli W3630 RGN14[a]	0.20	1.56	0.10	0.20	0.10	0.20	0.05	0.39	0.10	0.20
E. coli 255[b]	25	12.5	3.13	0.20	0.20	0.39	0.78	0.39	6.25	12.5
Klebsiella pneumoniae PCI 602	0.20	0.05	0.05	0.05	<0.025	0.05	—	0.20	0.10	0.20
Proteus vulgaris GN76[b]	0.10	0.10	0.05	0.39	0.20	0.05	0.05	0.10	<0.025	0.05
Morganella morganii 1510[b]	6.25	12.5	6.25	0.39	1.56	0.20	1.56	0.39	3.13	12.5
Citrobacter freundii GN346[b]	50	>50	12.5	1.56	1.56	1.56	6.25	0.78	50	25
Enterobacter cloacae G-0005[b]	0.20	12.5	0.39	0.10	0.20	<0.025	0.05	0.20	0.10	0.10
Serratia marcescens GN629[a]	0.39	1.56	0.20	0.20	0.05	0.05	0.05	0.78	0.20	0.20
Pseudomonas aeruginosa M-0148[a]	25	>50	12.5	12.5	50	6.25	12.5	1.56	3.13	1.56
P. aeruginosa IAM-1007	12.5	>50	25	6.25	12.5	1.56	3.13	0.78	1.56	0.78

[a] Penicillinase producer.
[b] Cephalosporinase producer.

excellent antibacterial activity. Methoxime analog **5b** showed strong activity against Gram-positive and Gram-negative bacteria, but the activity against *Pseudomonas aeruginosa* was lower than that of ceftazidime (CAZ). The introduction of carboxylic acid group into the alkoxime moiety clearly increased the anti-pseudomonal activity. Compound **7b** showed the best anti-pseudomonal activity which was comparable to that of CAZ. The 2-non-methyl analogs (**6c** and **7c**) showed lower activity against cephalosporinase producing strains including *Morganella morganii* and *Citrobacter freundii*. The introduction of a 2β-methyl group into 1-oxacephems having substituted thiomethyl groups at C-3 not only increased the intrinsic activity, but also the activity against β-lactamase producing strains. Among these derivatives, **7b** (OCP-9-176) was selected for further evaluations as a broad-spectrum cephalosporin.[8,9]

Experimental

General Method

MP's were determined with a Yamato MP-21 melting point apparatus and uncorrected. IR spectra were measured on a Hitachi 260-10 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol JNM-GX400 (400 MHz) and a Hitachi R-90 (90 MHz) spectrometers. Mass spectra were obtained on a Hitachi M-80B mass spectrometer. Antibacterial activities (MIC) were determined in Sensitivity Disk Agar (Nissui) by the serial 2-fold dilution method after incubation at 37°C for 18 hours, according to the method of Japan Society of Chemotherapy.

Compound **10b**

To a soln of **8** (10.0 g, 22.1 mmol) in ethyl (*S*)-lactate (**9b**, 35 ml) was added trifluoromethanesulfonic acid (0.5 ml). The mixture was stirred at room temperature for 1.5 hours and poured into dil $NaHCO_3$ aq soln and extracted with EtOAc. The extract was washed with NaCl-satd aq soln and water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel eluted with toluene - EtOAc (7 : 1) to give an oil which was crystallized from ether (6.68 g, 53%): MP 104~106°C; $[\alpha]_D$ −75° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1763, 1738, 1661; ^1H NMR (90 MHz, $CDCl_3$) δ 1.12 (3H, t, J=7.2 Hz, CH_2CH_3), 1.42 (3H, d, J=7.0 Hz, $CHCH_3$), 2.06 and 2.23 (6H, each s, CCH_3), 3.97 (2H, q, J=7.2 Hz, CH_2), 4.40 (1H, q, J=7.0 Hz, CH), 4.79 (1H, dd, J=6.7 and 1.1 Hz, 3-H), 5.07 (1H, d, J=1.1 Hz, 4-H), 6.67 (1H, d, J=6.7 Hz, CONH), 6.85 (1H, s, $CHPh_2$), 7.00~7.60 (15H, m, Ph).

Anal Calcd for $C_{33}H_{34}N_2O_7$: C 69.46, H 6.01, N 4.91.
Found: C 69.43, H 6.01, N 4.88.

Compound **10a**

This was prepared from **8** and ethyl (*R*)-lactate (**9a**) as described for **10b**: MP 133~135°C; $[\alpha]_D$ −2.1° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1768, 1735, 1668; ^1H NMR (90 MHz, $CDCl_3$) δ 1.19 (3H, t, J=7.2 Hz, CH_2CH_3), 1.25 (3H, d, J=7.0 Hz, $CHCH_3$), 2.08 and 2.27 (6H, each s, CCH_3), 4.03 (1H, q, J=7.0 Hz, CH), 4.10 (2H, q, J=7.2 Hz, CH_2), 4.89 (1H, dd, J=6.7 and 1.1 Hz, 3-H), 5.30 (1H, d, J=1.1 Hz, 4-H), 6.55 (1H, d, J=6.7 Hz, CONH), 6.92 (1H, s, $CHPh_2$), 7.00~7.70 (15H, m, Ph).

Anal Calcd for $C_{33}H_{34}N_2O_7$: C 69.46, H 6.01, N 4.91.
Found: C 69.53, H 6.04, N 4.86.

Compound **12b**

To a soln of **10b** (6.10 g, 10.7 mmol) in acetone (70 ml) at 0°C was added 0.4 M NaOH (30 ml). After stirring at 0°C for 1 hour and room temperature for a further 1 hour, acetone was removed by evaporation. The resultant aq soln was acidified to pH 2.0 and extracted with EtOAc. The extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from ether to give **11b** (5.3 g, 91%): MP 163~166°C (dec); IR ($CHCl_3$) cm^{-1} 1765, 1725, 1660.

Into a soln of **11b** (3.3 g, 6.08 mmol) in MeOH (60 ml), O_3 gas was passed for 20 minutes at −60°C and then N_2 gas was bubbled to remove excess O_3. After dilution with EtOAc (180 ml), $NaHSO_3$-satd aq soln was added and the mixture was stirred at 0°C for 30 minutes. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The acetone soln (30 ml) of the residue was poured into 2% aq MeOH (500 ml) containing $NaHCO_3$ (511 mg). After stirring for 30 minutes at 5°C, concentration of the mixture followed by trituration with acetone gave **12b** as the Na salt (1.70 g, 93%): MP 140~142°C (dec); IR (Nujol) cm^{-1} 1765, 1642, 1605; ^1H NMR (90 MHz, DMSO-d_6) δ 1.18 (3H, d, J=6.8 Hz, CH_3), 3.75 (1H, q, J=6.8 Hz, CH), 4.49 (1H, dd, J=7.9 and 0.9 Hz, 3-H), 5.11 (1H, d, J=0.9 Hz, 4-H), 7.10~7.90 (5H, m, Ph), 8.68 (1H, s, 1-H), 9.15 (1H, d, J=7.9 Hz, CONH).

Compound **12a**

This was prepared from **10a** as described for **12b**: MP 69~71°C (dec); IR (Nujol) cm^{-1} 1760, 1650, 1600; ^1H NMR (90 MHz, DMSO-d_6) δ 1.20 (3H, d, J=6.8 Hz, CH_3), 3.75 (1H, q, J=6.8 Hz, CH), 4.61 (1H, dd, J=8.1 and 1.3 Hz, 3-H), 5.32 (1H, d, J=1.3 Hz, 4-H), 7.20~7.80 (5H, m, Ph), 8.90 (1H, s, 1-H), 9.19 (1H, d, J=8.1 Hz, CONH).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-3-hydroxy-2-methyl-1-oxacephem-4-carboxylate (**15b**)

To a suspension of **12b** (1.66 g, 5.53 mmol) in THF (80 ml) at 0°C were added 1 M HCl in dioxane (5.5 ml) and *N*,*N*'-carbonyldiimidazole (893 mg, 5.51 mmol). The mixture was stirred at 0°C for 15 minutes and at room temperature for further 30 minutes. After cooling to 0°C, diphenylmethylmagnesium malonate (3.10 g, 5.53 mmol) was added. The mixture was stirred at 5°C overnight and evaporated under reduced pressure. The residue was dissolved in EtOAc and washed with acidic water (pH 2.0), $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave an oil which was chromatographed on a column of silica gel eluted with toluene - EtOAc (1 : 1) to afford **13b** (617 mg, 23%): FD-MS *m*/*z* 486 (M^+); IR ($CHCl_3$) cm^{-1} 1775, 1718, 1655; ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, d, J=7.0 Hz, CH_3),

3.51 and 3.77 (2H, ABq, J=15.6 Hz, CH_2), 4.38 (1H, q, J=7.0 Hz, CH), 4.61 (1H, dd, J=6.2 and 0.9 Hz, 3-H), 4.90 (1H, d, J=0.9 Hz, 4-H), 6.44 (1H, s, 1-H), 6.83 (1H, s, C*H*Ph_2), 7.20~7.80 (16H, m, Ph, CONH).

To a soln of **13b** (850 mg, 1.74 mmol) in acetonitrile (70 ml) were added *p*-carboxybenzenesulfonyl azide (474 mg, 2.09 mmol) and triethylamine (615 mg, 6.09 mmol), and the mixture was stirred at room temperature for 2 hours. After evaporation of acetonitrile, the residue was dissolved in EtOAc and the insoluble matter was removed by filtration. The filtrate was evaporated and the residue was chromatographed on a column of silica gel eluted with toluene-EtOAc (1:1) to give **14b** (756 mg, 85%): FD-MS m/z 513 (M^+); IR ($CHCl_3$) cm^{-1} 2140, 1775, 1715, 1658; ^1H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.6 Hz, CH_3), 4.61 (1H, dd, J=6.6 and 1.1 Hz, 3-H), 5.09 (1H, d, J=1.1 Hz, 4-H), 5.18 (1H, q, J=6.6 Hz, CH), 6.61 (1H, s, 1-H), 6.95 (1H, s, C*H*Ph_2), 7.10 (1H, d, J=6.6 Hz, CONH), 7.20~7.80 (15H, m, Ph).

To a soln of **14b** (563 mg, 1.10 mmol) in EtOAc (100 ml) was added rhodium(II) acetate dimer (10 mg) under N_2 atmosphere and the mixture was heated to 60°C for 30 minutes. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was evaporated to give an oil. Crystallization from acetonitrile afforded **15b** (404 mg, 76%): MP 175~177°C (dec); FD-MS m/z 484 (M^+); IR ($CHCl_3$) cm^{-1} 1775, 1740, 1665; ^1H NMR (90 MHz, $CDCl_3$) δ 1.41 (3H, d, J=6.8 Hz, CH_3), 4.54 (1H, q, J=6.8 Hz, 2-H), 5.02 (1H, dd, J=6.6 and 0.7 Hz, 7-H), 5.20 (1H, d, J=0.7 Hz, 6-H), 6.89 (1H, d, J=6.6 Hz, CONH), 6.93 (1H, s, C*H*Ph_2), 7.10~7.80 (15H, m, Ph).

Compound **15a**

This was prepared from **12a** as described for **15b**: MP 111~112°C (dec); FD-MS m/z 484 (M^+); IR ($CHCl_3$) cm^{-1} 1779, 1740, 1664; ^1H NMR (90 MHz, $CDCl_3$) δ 1.51 (3H, d, J=6.9 Hz, CH_3), 4.56 (1H, q, J=6.9 Hz, 2-H), 5.02 (1H, dd, J=7.4 and 0.6 Hz, 7-H), 5.20 (1H, d, J=0.6 Hz, 6-H), 6.78 (1H, d, J=7.4 Hz, CONH), 6.98 (1H, s, C*H*Ph_2), 7.10~7.80 (15H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-2-methyl-1-oxacephem-4-carboxylate (**17b**)

To a soln of **15b** (2.80 g, 5.78 mmol) in methylene chloride (40 ml) at −20°C was added a soln of tetrabutylammonium borohydride (0.41 g, 2.85 mmol) and the mixture was stirred at 0°C for 10 minutes. The reaction mixture was poured into ice-water (50 ml) and adjusted to pH 3.0. The organic layer was washed with water and dried over $MgSO_4$. Evaporation gave an oil which was crystallized from EtOAc to afford **16b** (2.20 g, 78%): MP 105~108°C (dec); FD-MS m/z 486 (M^+); IR ($CHCl_3$) cm^{-1} 1763, 1724, 1650; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, J=6.2 Hz, CH_3), 3.63 (1H, dd, J=9.2 and 6.9 Hz, 3-H), 3.85 (1H, dq, J=9.2 and 6.2 Hz, 2-H), 4.90 (1H, d, J=6.9 Hz, 4-H), 4.91 (1H, dd, J=6.7 and 0.8 Hz, 7-H), 5.25 (1H, d, J=0.8 Hz, 6-H), 6.74 (1H, d, J=6.7 Hz, CONH), 6.92 (1H, s, C*H*Ph_2), 7.20~7.80 (15H, m, Ph).

To an ice-cold soln of **16b** (2.20 g, 4.52 mmol) and triethylamine (1.13 g, 11.2 mmol) in methylene chloride (35 ml) was added methanesulfonyl chloride (0.62 g, 5.41 mmol) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was washed with NaCl-satd aq soln, $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave an oil which was chromatographed on a column of silica gel eluted with toluene-EtOAc (5:1) to afford **17b** (2.07 g, 98%): FD-MS m/z 468 (M^+); IR ($CHCl_3$) cm^{-1} 1781, 1727, 1665; ^1H NMR (90 MHz, $CDCl_3$) δ 1.39 (3H, d, J=7.0 Hz, CH_3), 4.50 (1H, dq, J=7.0 and 1.7 Hz, 2-H), 5.03 (1H, d, J=1.0 Hz, 6-H), 5.07 (1H, dd, J=7.9 and 1.0 Hz, 7-H), 6.21 (1H, d, J=1.7 Hz, 3-H), 6.92 (1H, s, C*H*Ph_2), 7.10~7.90 (16H, m, Ph, CONH).

Compound **17a**

This was prepared from **15a** as described for **17b**: FD-MS m/z 468 (M^+); IR ($CHCl_3$) cm^{-1} 1782, 1725, 1664; ^1H NMR (90 MHz, $CDCl_3$) δ 1.33 (3H, d, J=6.9 Hz, CH_3), 4.69 (1H, dq, J=6.9 and 3.7 Hz, 2-H), 5.06 (1H, d, J=0.7 Hz, 6-H), 5.06 (1H, dd, J=6.8 and 0.7 Hz, 7-H), 6.44 (1H, d, J=3.7 Hz, 3-H), 6.97 (1H, s, C*H*Ph_2), 7.10~7.80 (16H, m, Ph, CONH).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-3-methoxy-2-methyl-1-oxacephem-4-carboxylate (**18b**)

To a soln of **15b** (1.83 g, 3.78 mmol) in EtOAc (20 ml) was added an ether soln of diazomethane (5 mmol) dropwise and the mixture was stirred at room temperature for 30 minutes. After addition of

acetic acid (0.1 ml) and stirring for 1 hour at room temperature, the mixture was washed with $NaHCO_3$-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave an oil which was chromatographed on a column of silica gel eluted with toluene - EtOAc (8 : 1) to afford **18b** (1.77 g, 94%): FD-MS *m/z* 498 (M^+); IR ($CHCl_3$) cm^{-1} 1770, 1715, 1663; ^1H NMR (90 MHz, $CDCl_3$) δ 1.43 (3H, d, J=6.7 Hz, CH_3), 3.57 (3H, s, OCH_3), 4.47 (1H, q, J=6.7 Hz, 2-H), 4.90 (1H, d, J=0.7 Hz, 6-H), 5.04 (1H, dd, J=7.7 and 0.7 Hz, 7-H), 6.91 (1H, s, C*H*Ph_2), 7.10~7.80 (16H, m, Ph, CONH).

Compound **18a**

This was prepared from **15a** as described for **18b**: FD-MS *m/z* 498 (M^+); IR ($CHCl_3$) cm^{-1} 1780, 1720, 1670; ^1H NMR (90 MHz, $CDCl_3$) δ 1.42 (3H, d, J=7.0 Hz, CH_3), 3.67 (3H, s, OCH_3), 4.63 (1H, q, J=7.0 Hz, 2-H), 5.06 (1H, dd, J=7.0 and 0.9 Hz, 7-H), 5.11 (1H, d, J=0.9 Hz, 6-H), 6.95 (1H, s, C*H*Ph_2), 7.10~7.80 (16H, m, Ph, CONH).

Diphenylmethyl (2*S*,6*R*,7*R*)-3-Allyloxycarbonylmethyl-7-benzamido-2-methyl-1-oxacephem-4-carboxylate (**19b**)

To a soln of **15b** (2.00 g, 4.12 mmol) in benzene (60 ml) was added allyl(triphenylphosphoranylidene)acetate (2.23 g, 6.18 mmol) and the mixture was stirred at 60°C for 3 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on silica gel (toluene - EtOAc, 5 : 1) to afford a mixture (2.33 g) of **19b** and its 3,3'-olefin isomer. The mixture was dissolved in methylene chloride (40 ml) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene (255 mg, 2.06 mmol) at 0°C for 15 minutes. The reaction mixture was washed with acidic water (pH 2.5), $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave **19b** (2.01 g, 86%): FD-MS *m/z* 567 (M^+); IR ($CHCl_3$) cm^{-1} 1779, 1722, 1668; ^1H NMR (90 MHz, $CDCl_3$) δ 1.39 (3H, d, J=6.8 Hz, 2-CH_3), 3.27 and 3.68 (2H, ABq, J=17.1 Hz, 3'-H_2), 4.35~4.49 (2H, m, CO_2CH_2), 4.50 (1H, q, J=6.8 Hz, 2-H), 4.96 (1H, dd, J=7.3 and 0.9 Hz, 7-H), 5.04 (1H, d, J=0.9 Hz, 6-H), 5.05~5.30 (2H, m, CH=C*H*$_2$), 5.50~6.00 (1H, m, C*H*=CH_2), 6.89 (1H, s, C*H*Ph_2), 7.00 (1H, d, J=7.3 Hz, CONH), 7.10~7.80 (15H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-3-carboxymethyl-2-methyl-1-oxacephem-4-carboxylate (**20b**)

To a soln of **19b** (2.00 g, 3.53 mmol) in methylene chloride (20 ml) were added triphenylphosphine (37 mg, 0.14 mmol) and $Pd(Ph_3P)_4$ (82 mg, 0.07 mmol) under N_2 atmosphere. After stirring at room temperature for 10 minutes, a soln of potassium 2-ethylhexanoate (706 mg, 3.88 mmol) in EtOAc (40 ml) was added and the mixture was stirred for further 30 minutes to yield **20b** as the ppt of K salt. The ppt was partitioned between EtOAc (20 ml) and water (20 ml) adjusted to pH 2.0. The organic layer was separated, dried over $MgSO_4$ and evaporated to give **20b** (1.60 g, 86%): FD-MS *m/z* 526 (M^+); IR ($CHCl_3$) cm^{-1} 1780, 1720, 1664; ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (3H, d, J=6.6 Hz, 2-CH_3), 3.23 and 3.61 (2H, ABq, J=18 Hz, 3'-H_2), 4.45 (1H, q, J=6.6 Hz, 2-H), 4.93 (1H, d, J=7.4 Hz, 7-H), 5.02 (1H, s, 6-H), 6.87 (1H, s, C*H*Ph_2), 7.10~7.80 (16H, m, Ph, CONH).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-3-(3-chlorobenzoyloxy)methyl-2-methyl-1-oxacephem-4-carboxylate (**21b**)

To a soln of **20b** (1.40 g, 2.66 mmol) and 3-chloroperoxybenzoic acid (549 mg, 3.19 mmol) in methylene chloride (27 ml) at −20°C was added dicyclohexylcarbodiimide (712 mg, 3.46 mmol) and the mixture was stirred at −20°C for 2 hours and 5°C overnight. After removal of dicyclohexylurea by filtration, the filtrate was evaporated and purified by column chromatography (toluene - EtOAc, 10 : 1) to give **21b** (1.20 g, 72%): FD-MS *m/z* 637 (M^+); IR ($CHCl_3$) cm^{-1} 1785, 1720, 1668; ^1H NMR (90 MHz, $CDCl_3$) δ 1.49 (3H, d, J=6.6 Hz, 2-CH_3), 4.63 (1H, q, J=6.6 Hz, 2-H), 4.87 and 5.35 (2H, ABq, J=13 Hz, 3'-H_2), 4.99 (1H, d, J=7.3 Hz, 7-H), 5.05 (1H, s, 6-H), 6.87 (1H, d, J=7.3 Hz, CONH), 6.91 (1H, s, C*H*Ph_2), 7.10~7.80 (19H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-2-methyl-3-methylene-1-oxacepham-4-carboxylate (**22b**)

To a soln of **21b** (1.10 g, 1.75 mmol) in DMF (88 ml) and water (18 ml) were added zinc chloride

(3.58 g), ammonium chloride (7.50 g) and zinc powder (9.12 g), and the mixture was stirred at 50°C for 3.5 hours. The reaction mixture was poured into EtOAc (220 ml) and NaCl-satd aq soln (220 ml). The organic layer was separated, washed with NaCl-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave a mixture of **22b** and **23b** which were separated by column chromatography on silica gel (toluene - EtOAc, 10 : 1) to afford **22b** (543 mg, 64%) and **23b** (153 mg, 18%). **22b**: FD-MS *m/z* 482 (M^+); IR ($CHCl_3$) cm^{-1} 1766, 1738, 1664; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, d, J=6.1 Hz, 2-CH_3), 4.19 (1H, q, J=6.1 Hz, 2-H), 5.01 (1H, dd, J=7.4 and 1.5 Hz, 7-H), 5.19 and 5.38 (2H, each s, =CH_2), 5.32 (1H, d, J=1.5 Hz, 6-H), 5.36 (1H, s, 4-H), 6.83 (1H, d, J=7.4 Hz, CONH), 6.84 (1H, s, C*H*Ph_2), 7.20~7.50 (15H, m, Ph). **23b**: IR ($CHCl_3$) cm^{-1} 1776, 1720, 1664; ^1H NMR (90 MHz, $CDCl_3$) δ 1.39 (3H, d, J=6.6 Hz, 2-CH_3), 1.92 (3H, s, 3-CH_3), 4.34 (1H, q, J=6.6 Hz, 2-H), 4.94 (1H, s, 6-H), 5.00 (1H, d, J=7.6 Hz, 7-H), 6.90 (1H, s, C*H*Ph_2), 7.10~7.80 (16H, m, Ph, CONH).

Compound **22a**

This was prepared from **15a** by the method used for **22b**. **22a**: FD-MS *m/z* 482 (M^+); IR ($CHCl_3$) cm^{-1} 1770, 1743, 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, J=7 Hz, 2-CH_3), 4.58 (1H, q, J=7 Hz, 2-H), 5.09 (1H, dd, J=7.8 and 1.1 Hz, 7-H), 5.20 and 5.23 (2H, each s, =CH_2), 5.31 (1H, d, J=1.1 Hz, 6-H), 5.38 (1H, s, 4-H), 6.89 (1H, s, C*H*Ph_2), 6.91 (1H, d, J=7.8 Hz, CONH), 7.20~7.80 (15H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*S*)-7-Amino-2-methyl-3-methylene-1-oxacepham-4-carboxylate (**27b**)

To a soln of **22b** (6.11 g, 12.7 mmol) in methylene chloride (50 ml) at −40°C were added pyridine (3.01 g, 38.1 mmol) and phosphorous pentachloride (5.02 g, 25.4 mmol). The mixture was stirred at 5°C for 30 minutes and at 20°C for further 30 minutes. After addition of MeOH (100 ml) at −40°C, the reaction mixture was stirred at 0°C for 1 hour. After addition of water (50 ml), the mixture was stirred at 0°C for 30 minutes and then concentrated. The concentrate was poured into a mixture of water (5 ml), EtOAc (50 ml) and diisopropyl ether (100 ml). The aq layer was adjusted to pH 3.0 and extracted with EtOAc. The extract was washed with $NaHCO_3$-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave an oil which was chromatographed on a column of silica gel eluted with toluene - EtOAc (1 : 1) to obtain **24b** (3.67 g, 76%): FD-MS *m/z* 378 (M^+); IR ($CHCl_3$) cm^{-1} 1764, 1745; ^1H NMR (90 MHz, $CDCl_3$) δ 1.32 (3H, d, J=6.4 Hz, CH_3), 1.62 (2H, s, NH_2), 3.96 (1H, s, 7-H), 4.17 (1H, q, J=6.4 Hz, 2-H), 5.07 (1H, s, 6-H), 5.11 (1H, s, 4-H), 5.24 and 5.30 (2H, each s, =CH_2), 6.82 (1H, s, C*H*Ph_2), 7.10~7.50 (10H, m, Ph).

To a soln of **24b** (3.67 g, 9.70 mmol) in methylene chloride (50 ml) was added 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (2.27 g, 9.70 mmol) and the mixture was refluxed for 2 hours in a Dean-Stark apparatus. The reaction mixture was evaporated to afford **25b** as an oil (5.80 g): FD-MS *m/z* 594 (M^+); IR ($CHCl_3$) cm^{-1} 1764, 1740; ^1H NMR (90 MHz, $CDCl_3$) δ 1.36 (3H, d, J=6.3 Hz, CH_3), 1.44 (18H, s, *tert*-butyl), 4.26 (1H, q, J=6.3 Hz, 2-H), 4.65 (1H, br, 7-H), 5.19 (1H, s, 4-H), 5.27 (1H, d, J=1.1 Hz, 6-H), 5.33 (1H, s, OH), 5.46 and 5.50 (2H, each s, =CH_2), 6.84 (1H, s, C*H*Ph_2), 7.10~7.40 (10H, m, Ph), 7.57 (2H, s, Ph), 8.33 (1H, d, J=1.1 Hz, C*H*=N).

To a soln of **25b** (5.80 g, 9.75 mmol) in methylene chloride (46 ml) at 0°C was added nickel peroxide (3.88 g) and the mixture was stirred at 0°C for 20 minutes. The reaction mixture was filtered and the filtrate was treated with a soln of tetraethylammonium borohydride (314 mg, 2.18 mmol) at −50°C for 5 minutes. After addition of 6 M HCl in dioxane (0.44 ml), the reaction mixture was washed with water and dried over $MgSO_4$. Evaporation gave **26b** as an oil (5.60 g).

To a soln of **26b** (5.60 g, 9.42 mmol) in EtOAc (87 ml) was added a soln of GIRARD's reagent T (2.42 g, 14.5 mmol) in MeOH (100 ml) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was evaporated and the residue was dissolved in EtOAc. The soln was washed with water and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene - EtOAc, 1 : 1) to obtain **27b** (2.09 g, 57% from **24b**): MP 116~119°C (dec); FD-MS *m/z* 378 (M^+); IR ($CHCl_3$) cm^{-1} 1764, 1740; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, d, J=6.1 Hz, CH_3), 1.65 (2H, s, NH_2), 4.31 (1H, q, J=6.1 Hz, 2-H), 4.34 (1H, d, J=3.6 Hz, 7-H), 5.12 (1H, s, 4-H), 5.28 and 5.35 (2H, each s, =CH_2), 5.34 (1H, d, J=3.6 Hz, 6-H), 6.84 (1H, s, C*H*Ph_2), 7.20~7.40 (10H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*S*)-7-Amino-3-chloromethyl-2-methyl-1-oxacephem-4-carboxylate (**30b**)

To a soln of **27b** (2.09 g, 5.52 mmol) in methylene chloride (30 ml) was added 2,4,5-trichlorophenyl formate (1.51 g, 6.62 mmol) and the mixture was stirred at room temperature for 15 hours. The mixture was washed with $NaHCO_3$-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene - EtOAc, 3 : 1) to afford **28b** (1.81 g, 81%): FD-MS *m/z* 407 (M^+); IR ($CHCl_3$) cm^{-1} 3420, 1780, 1740, 1690; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, d, J=6.1 Hz, CH_3), 4.33 (1H, q, J=6.1 Hz, 2-H), 5.14 (1H, s, 4-H), 5.30 and 5.38 (2H, each s, $=CH_2$), 5.44 (1H, d, J=3.3 Hz, 6-H), 5.63 (1H, dd, J=9.8 and 3.3 Hz, 7-H), 6.16 (1H, d, J=9.8 Hz, CONH), 6.85 (1H, s, C*H*Ph_2), 7.20~7.40 (10H, m, Ph), 8.21 (1H, s, HCO).

To a soln of **28b** (600 mg, 1.48 mmol) in methylene chloride (16 ml) was added phenylselenyl chloride (566 mg, 2.96 mmol) and the mixture was stirred at room temperature for 1 hour. After addition of 40% peracetic acid (639 mg), the mixture was stirred at room temperature for 30 minutes. The reaction mixture was washed with $NaHCO_3$-satd aq soln, $Na_2S_2O_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene - EtOAc, 3 : 1) to afford **29b** (502 mg, 77%): FD-MS *m/z* 440 (M^+); IR ($CHCl_3$) cm^{-1} 1795, 1720, 1690; ^1H NMR (90 MHz, $CDCl_3$) δ 1.51 (3H, d, J=6.6 Hz, CH_3), 4.11 and 5.16 (2H, ABq, J=12.5 Hz, 3′-H_2), 4.78 (1H, q, J=6.6 Hz, 2-H), 5.12 (1H, d, J=3.7 Hz, 6-H), 5.77 (1H, dd, J=9.8 and 3.7 Hz, 7-H), 6.28 (1H, d, J=9.8 Hz, CONH), 6.90 (1H, s, C*H*Ph_2), 7.10~7.50 (10H, m, Ph), 8.25 (1H, s, HCO).

To a soln of **29b** (400 mg, 0.91 mmol) in MeOH (4 ml) was added 6 M HCl in dioxane (0.46 ml) and the mixture was stirred at room temperature for 30 minutes. Evaporation followed by trituration with ether gave **30b** as the hydrochloride (400 mg, quantitative): FD-MS *m/z* 413 (M^+); IR ($CHCl_3$) cm^{-1} 1783, 1720; ^1H NMR (90 MHz, $CDCl_3$) δ 1.51 (3H, d, J=6.6 Hz, CH_3), 1.73 (2H, s, NH_2), 4.08 and 5.13 (2H, ABq, J=12.3 Hz, 3′-H_2), 4.47 (1H, d, J=4.1 Hz, 7-H), 4.76 (1H, q, J=6.6 Hz, 2-H), 5.02 (1H, d, J=4.1 Hz, 6-H), 6.88 (1H, s, C*H*Ph_2), 7.10~7.50 (10H, m, Ph).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-carboxy-1-methylethoxyimino)acetamido]-2(*S*)-methyl-3-[(1-methylpyridinium-4-yl)thiomethyl]-1-oxacephem-4-carboxylate (**7b**)

To a soln of (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-[1-methyl-1-(diphenylmethoxycarbonyl)ethoxyimino]-acetic acid[17] (1.28 g, 1.88 mmol) and **30b** (770 mg, 1.71 mmol) in methylene chloride (20 ml) were added pyridine (675 mg, 8.55 mmol) and phosphoryl chloride (366 mg, 2.39 mmol) at −20°C and the mixture was stirred at 0°C for 30 minutes. The mixture was washed with NaCl-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene - EtOAc, 5 : 1) to afford an amide (1.31 g).

To a soln of the amide (1.31 g, 1.22 mmol) in DMF (13 ml) were added NaI (360 mg, 2.44 mmol) and 1-methylpyrid-4-thione (163 mg, 1.30 mmol) and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with a mixture of $CHCl_3$ (20 ml) and EtOAc (10 ml), washed with water, and dried over $MgSO_4$. Evaporation gave an oil (1.45 g).

The oil was dissolved in anisole (3 ml) and TFA (14 ml) at 0°C. After stirring for 30 minutes, diisopropyl ether was added to the mixture and the resulting ppt was collected by filtration. The ppt (825 mg) was dissolved in water (8.0 ml) containing $NaHCO_3$ (340 mg, 4.04 mmol) and purified by column chromatography on Diaion HP-20 (83 ml). After washing the column with water, elution with 50% aq MeOH (300 ml) gave **7b** as the sodium salt (520 mg, 50% from **30b**): MP 175~180°C (dec); $[\alpha]_D^{25}$ −48.7° (*c* 1.88, H_2O); IR (KBr) cm^{-1} 1775, 1730, 1650; ^1H NMR (400 MHz, D_2O) δ 1.45 and 1.47 (6H, each s, $C(CH_3)_2$), 1.49 (3H, d, J=7.0 Hz, CH_3), 3.80 and 4.80 (2H, ABq, J=17.0 Hz, 3′-H_2), 4.19 (3H, s, NCH_3), 4.73 (1H, q, J=7.0 Hz, 2-H), 5.17 (1H, d, J=3.5 Hz, 6-H), 5.58 (1H, d, J=3.5 Hz, 7-H), 7.00 (1H, s, thiazole), 7.70 and 8.40 (4H, ABq, J=6.2 Hz, pyridine).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2(*S*)-methyl-3-(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thiomethyl-1-oxacephem-4-carboxylate (**4b**)

This was prepared from **30b**, (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-(methoxyimino)acetic acid and 1,2,5,6-tetrahydro-3-mercapto-2-methyl-1,2,4-triazine-5,6-dione, as described for **7b**. **4b** (2Na salt): IR (KBr) cm^{-1} 1765, 1600; ^1H NMR (400 MHz, D_2O) δ 1.45 (3H, d, J=6.6 Hz, CH_3), 3.65 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 3.96 and 4.47 (2H, ABq, J=13.9 Hz, 3′-H), 4.85 (1H, q, J=6.6 Hz, 2-H), 5.25 (1H,

d, J=3.4 Hz, 6-H), 5.52 (1H, d, J=3.4 Hz, 7-H), 7.06 (1H, s, thiazole).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2(*S*)-methyl-3-[(1-methylpyridinium-4-yl)thiomethyl]-1-oxacephem-4-carboxylate (**5b**)

This was prepared from **30b**, (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-(methoxyimino)acetic acid and 1-methylpyrid-4-thione, as described for **7b**. **5b** (Na salt): IR (KBr) cm^{-1} 1770, 1659; ^1H NMR (400 MHz, D_2O) δ 1.48 (3H, d, J=6.3 Hz, 2-CH_3), 3.89 and 4.83 (2H, ABq, J=14 Hz, 3'-H_2), 3.97 (3H, s, OCH_3), 4.19 (3H, s, NCH_3), 4.76 (1H, q, J=6.3 Hz, 2-H), 5.17 (1H, d, J=3.6 Hz, 6-H), 5.51 (1H, d, J=3.6 Hz, 7-H), 7.03 (1H, s, thiazole), 7.70 and 8.40 (4H, ABq, J=6.6 Hz, pyridine).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-2(*S*)-methyl-3-[(1-methylpyridinium-4-yl)thiomethyl]-1-oxacephem-4-carboxylate (**6b**)

This was prepared from **30b**, (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-[(diphenylmethoxycarbonyl)methoxyimino]acetic acid and 1-methylpyrid-4-thione, as described for **7b**. **6b** (Na salt): IR (KBr) cm^{-1} 1763, 1660; ^1H NMR (400 MHz, D_2O) δ 1.46 (3H, d, J=6.6 Hz, CH_3). 3.89 and 4.83 (2H, ABq, J=14.1 Hz, 3'-H_2), 4.19 (3H, s, NCH_3), 4.55 (2H, s, CH_2CO), 5.17 (1H, d, J=3.6 Hz, 6-H), 5.55 (1H, d, J=3.6 Hz, 7-H), 7.05 (1H, s, thiazole), 7.70 and 8.39 (4H, ABq, J=8.4 Hz, pyridine).

Compound **33b**

Into a soln of **10b** (5.50 g, 9.65 mmol) in methylene chloride (150 ml) was passed O_3 gas at $-60°C$ for 20 minutes and then N_2 gas was bubbled into the soln to remove excess O_3. Acetic acid (11 ml) and zinc powder (10 g) were added to the soln at $-60°C$ and the mixture was stirred at 0°C for 30 minutes. The mixture was filtered and the filtrate was washed with $NaHCO_3$-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave **31b** (4.73 g): IR ($CHCl_3$) cm^{-1} 1771, 1727, 1660; ^1H NMR (90 MHz, $CDCl_3$) δ 1.17 and 1.20 (3H, t, CH_2CH_3), 1.20 and 1.47 (3H, d, $CHCH_3$), 4.03 and 4.12 (2H, q, CH_2), 4.32 and 4.43 (1H, q, CH), 4.75 and 4.80 (1H, dd, 3-H), 4.90 and 4.99 (1H, d, 4-H), 5.05 and 5.41 (1H, s, $CHOH$), 6.87 and 6.92 (1H, s, $CHPh_2$), 7.10~7.80 (16H, m, Ph, CONH).

To an ice-cooled soln of **31b** (4.58 g, 8.39 mmol) and pyridine (1.38 g, 17.4 mmol) in methylene chloride (50 ml) was added thionyl chloride (2.07 g, 17.4 mmol) and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was poured into ice-water and extracted with methylene chloride. The extract was washed with water and dried over $MgSO_4$. Evaporation gave **32b** (4.50 g): IR ($CHCl_3$) cm^{-1} 1785, 1738, 1667; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (3H, t, CH_2CH_3), 1.36 and 1.47 (3H, d, $CHCH_3$), 4.12 (2H, q, CH_2), 4.43 and 4.52 (1H, q, CH), 4.72 and 4.73 (1H, dd, 3-H), 5.32 and 5.38 (1H, d, 4-H), 6.17 and 6.22 (1H, s, CHCl), 6.88 and 6.93 (1H, s, $CHPh_2$), 7.10~7.89 (16H, m, Ph, CONH).

To a soln of **32b** (4.50 g, 7.97 mmol) and triethylamine (0.97 g, 9.56 mmol) in chloroform (50 ml) was added triphenylphosphine (4.17 g, 15.9 mmol) and the mixture was stirred at room temperature for 15 hours. The reaction mixture was washed with water, $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene-EtOAc, 3:1) to afford **33b** (4.65 g, 61% from **10b**): FD-MS m/z 790 (M^+); IR ($CHCl_3$) cm^{-1} 1760, 1740, 1650.

Compound **36b**

To a soln of **33b** (4.50 g, 5.70 mmol) in 30% aq acetone (70 ml) was added 1 M NaOH (5.7 ml) and the mixture was stirred at room temperature for 2 hours. After addition of 1 M NaOH (2.8 ml), the mixture was stirred for further 30 minutes, and then adjusted to pH 3.0. After removal of acetone by evaporation, the concentrate was extracted with EtOAc and the extract was dried over $MgSO_4$. Evaporation gave an oil which was crystallized from MeOH to afford **34b** (3.60 g, 83%): MP 139~141°C (dec); FD-MS m/z 763 (M^+); IR ($CHCl_3$) cm^{-1} 1765, 1730, 1658.

To a soln of **34b** (3.29 g, 4.32 mmol) and 4-methylmorphorine (0.52 g, 5.18 mmol) in methylene chloride (40 ml) at $-10°C$ was added ethyl chloroformate (0.51 g, 4.75 mmol) and the mixture was stirred for 30 minutes. An ether soln of diazomethane (6 mmol) was added to the soln dropwise and the mixture was stirred at 0°C for 30 minutes. After addition of AcOH (0.23 ml), the reaction mixture was washed with water, $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. Evaporation gave an oil

which was purified by column chromatography on silica gel (toluene - EtOAc, 3 : 1) to afford **35b** (2.91 g, 86%): FD-MS *m/z* 786 (M^+); IR ($CHCl_3$) cm^{-1} 2110, 1765, 1730, 1657.

To a soln of **35b** (1.45 g, 1.84 mmol) in benzene (30 ml) were added 5-mercapto-1-methyl-1*H*-tetrazole (428 mg, 3.69 mmol) and $Rh_2(OAc)_4$ (10 mg), and the mixture was stirred at 50°C for 1.5 hours under N_2 atmosphere. The reaction mixture was washed with $NaHCO_3$-satd aq soln, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene - EtOAc, 2 : 1) to afford **36b** (970 mg, 60%): FD-MS *m/z* 875 (M^+); IR ($CHCl_3$) cm^{-1} 1765, 1735, 1658.

Compound **37b**

To an ice-cooled soln of **35b** (2.91 g, 3.69 mmol) in methylene chloride (40 ml) was added 6 M HCl in dioxane (1.23 ml) dropwise and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was washed with $NaHCO_3$-satd aq soln and water, and dried over $MgSO_4$. Evaporation gave **37b** (2.73 g, 93%): FD-MS *m/z* 786 (M^+); IR ($CHCl_3$) cm^{-1} 1763, 1735, 1658.

Diphenylmethyl (2*S*,6*R*,7*R*)-7-Benzamido-2-methyl-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-oxacephem-4-carboxylate (**38b**)

A soln of **36b** (2.70 g, 3.09 mmol) and hydroquinone (0.18 g) in toluene (270 ml) was refluxed for 20 hours under N_2 atmosphere. The reaction mixture was washed with $NaHCO_3$-satd aq soln, and dried over $MgSO_4$. After evaporation, **38b** was crystallized from EtOAc by addition of DMF (0.48 ml) as the 1 : 1 DMF solvate (1.67 g, 81%): MP 157~158°C (dec); FD-MS *m/z* 597 (M^+); IR ($CHCl_3$) cm^{-1} 1782, 1720, 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, d, J=6.7 Hz, CH_3), 3.80 (3H, s, NCH_3), 4.06 and 4.67 (2H, ABq, J=13.3 Hz, 3'-H_2), 4.81 (1H, q, J=6.7 Hz, 2-H), 4.91 (1H, dd, J=7.2 and 1.0 Hz, 7-H), 5.12 (1H, d, J=1.0 Hz, 6-H), 6.94 (1H, s, C*H*Ph_2), 7.20~7.80 (16H, m, Ph, CONH).

Compounds **35a**, **36a**, **37a** and **38a**

These compounds were obtained from **10a** by the similar method described above.

35a: FD-MS *m/z* 786 (M^+); IR ($CHCl_3$) cm^{-1} 2110, 1765, 1655. **36a**: FD-MS *m/z* 875 (M^+); IR ($CHCl_3$) cm^{-1} 1765, 1730, 1655. **37a**: FD-MS *m/z* 796 (M^+); IR ($CHCl_3$) cm^{-1} 1765, 1740, 1650. **38a**: MP 155~158°C (dec); FD-MS *m/z* 596 (M^+); IR ($CHCl_3$) cm^{-1} 1788, 1718, 1670; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (3H, d, J=6.9 Hz, CH_3), 3.81 (3H, s, NCH_3), 4.21 and 4.39 (2H, ABq, J=13.3 Hz, 3'-H_2), 4.82 (1H, dd, J=7.2 and 1.0 Hz, 7-H), 4.83 (1H, q, J=6.9 Hz, 2-H), 5.30 (1H, d, J=1.0 Hz, 6-H), 6.95 (1H, s, C*H*Ph_2), 7.05 (1H, d, J=7.2 Hz, CONH), 7.20~7.80 (15H, m, Ph).

Diphenylmethyl (2*S*,6*R*,7*S*)-7-Amino-2-methyl-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-oxacephem-4-carboxylate (**40b**)

Compound **40b** was prepared from **38b** in 26% yield by the method used for **27b** from **22b**: MP 149~151°C (dec); IR ($CHCl_3$) cm^{-1} 1796, 1716; ^1H NMR (90 MHz, $CDCl_3$) δ 1.53 (3H, d, J=6.8 Hz, 2-CH_3), 2.12 (2H, s, NH_2), 3.78 (3H, s, NCH_3), 4.02 and 4.67 (2H, ABq, J=14 Hz, 3'-H_2), 4.45 (1H, d, J=5.0 Hz, 7-H), 4.80 (1H, q, J=6.8 Hz, 2-H), 4.98 (1H, d, J=5.0 Hz, 6-H), 6.87 (1H, s, C*H*Ph_2), 7.10~7.60 (10H, m, Ph).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2(*S*)-methyl-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-oxacephem-4-carboxylic Acid (**3b**)

To a soln of (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-(methoxyimino)acetic acid (173 mg, 0.39 mmol) and **40b** (160 mg, 0.325 mmol) in methylene chloride (6 ml) at −20°C were added pyridine (103 mg, 1.30 mmol) and phosphoryl chloride (70 mg, 0.455 mmol) and the mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted with EtOAc (12 ml) and washed with NaCl-satd aq soln, $NaHCO_3$-satd aq soln and water successively, and dried over $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (toluene - EtOAc, 5 : 1) to afford an amide (241 mg, 81%): IR ($CHCl_3$) cm^{-1} 1795, 1717, 1684; ^1H NMR (90 MHz, $CDCl_3$) δ 1.48 (3H, d, J=6.6 Hz, 2-CH_3), 3.81 (3H, s, NCH_3), 4.07 (3H, s, OCH_3), 4.03 and 4.72 (2H, ABq, J=14 Hz, 3'-H_2), 4.87 (1H, q, J=6.6 Hz, 2-H), 5.13 (1H, d, J=3.8 Hz, 6-H), 5.76 (1H, dd, J=8.9 and 3.8 Hz, 7-H), 6.77 (1H, s, thiazole), 6.87 (1H, s, C*H*Ph_2), 6.94

(1H, d, J=8.9 Hz, CONH), 7.10~7.80 (25H, m, Ph).

To a soln of the amide (230 mg, 0.25 mmol) in anisole (0.5 ml) was added TFA (2.5 ml) dropwise at 0°C and the mixture was stirred for 30 minutes. After addition of diisopropyl ether, the resulting ppt was collected by filtration and washed with diisopropyl ether to give **3b** as the TFA salt (93 mg, 80%): IR (Nujol) cm^{-1} 1787, 1670; ^1H NMR (90 MHz, DMSO-d_6) δ 1.40 (3H, d, J=6.7 Hz, 2-CH_3), 3.86 (3H, s, OCH_3), 3.93 (3H, s, NCH_3), 4.05 and 4.67 (2H, ABq, J=13 Hz, 3'-H_2), 4.78 (1H, q, J=6.7 Hz, 2-H), 5.14 (1H, d, J=3.8 Hz, 6-H), 5.34 (1H, dd, J=8.7 and 3.8 Hz, 7-H), 6.83 (1H, s, thiazole), 9.35 (1H, d, J=8.7 Hz, CONH).

Compounds **40a** and **3a**

These compounds were obtained from **38a** by the method described for **40b** and **3b**.

40a: IR ($CHCl_3$) cm^{-1} 1785, 1720; ^1H NMR (90 MHz, $CDCl_3$) δ 1.57 (3H, d, J=6.8 Hz, 2-CH_3), 2.08 (2H, s, NH_2), 3.82 (3H, s, NCH_3), 4.23 and 4.46 (2H, ABq, J=13 Hz, 3'-H_2), 4.56 (1H, d, J=4.1 Hz, 7-H), 4.86 (1H, q, J=6.8 Hz, 2-H), 5.16 (1H, d, J=4.1 Hz, 6-H), 6.93 (1H, s, C*H*Ph_2), 7.10~7.60 (10H, m, Ph). **3a** (TFA salt): IR (Nujol) cm^{-1} 1790, 1670; ^1H NMR (90 MHz, DMSO-d_6) δ 1.51 (3H, d, J=6.9 Hz, 2-CH_3), 3.86 (3H, s, OCH_3), 3.92 (3H, s, NCH_3), 4.07 and 4.42 (2H, ABq, J=13.5 Hz, 3'-H_2), 4.87 (1H, q, J=6.9 Hz, 2-H), 5.37 (1H, d, J=3.9 Hz, 6-H), 5.62 (1H, dd, J=8.4 and 3.9 Hz, 7-H), 6.76 (1H, s, thiazole), 9.40 (1H, d, J=8.4 Hz, CONH).

Compound **22b** from **38b**

To a mixture of **38b** (24.0 g, 40.0 mmol), ammonium chloride (24.0 g, 417 mmol) and thiourea (12.0 g, 157 mmol) in DMF was added zinc powder (26.4 g) at 0°C. The mixture was stirred for 1 hour and then filtered. The filtrate was poured into NaCl-satd aq soln (480 ml) and extracted with EtOAc. The extract was washed with acidic water (pH 2.0) and water, and dried over $MgSO_4$. Evaporation gave an oil which was purified by column chromatography on silica gel (toluene-EtOAc, 7:1) to afford **22b** (17.7 g, 92%).

Diphenylmethyl (2*S*,6*R*,7*S*)-7-Amino-2-methyl-3-methoxy-1-oxacephem-4-carboxylate (**42b**)

This was prepared from **18b** by the similar method for **27b** from **22b**: IR ($CHCl_3$) cm^{-1} 1782, 1717; ^1H NMR (90 MHz, $CDCl_3$) δ 1.45 (3H, d, J=6.7 Hz, CH_3), 1.84 (2H, s, NH_2), 3.69 (3H, s, OCH_3), 4.42 (1H, d, J=3.9 Hz, 7-H), 4.52 (1H, q, J=6.7 Hz, 2-H), 5.01 (1H, d, J=3.9 Hz, 6-H), 6.93 (1H, s, C*H*Ph_2), 7.10~7.60 (10H, m, Ph).

(6*R*,7*S*)-7-[(*Z*)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-methoxy-2(*S*)-methyl-3-methoxy-1-oxacephem-4-carboxylic acid (**2b**)

Compound **2b** was obtained as the TFA salt from **42b** in 49% yield by the method used for **3b** from **40b**: IR (Nujol) cm^{-1} 1780, 1670; ^1H NMR (90 MHz, DMSO-d_6) δ 1.33 (3H, d, J=6.7 Hz, CH_3), 3.75 (3H, s, 3-OCH_3), 3.86 (3H, s, oxime-CH_3), 4.66 (1H, q, J=6.7 Hz, 2-H), 5.21 (1H, d, J=3.7 Hz, 6-H), 5.43 (1H, dd, J=8.4 and 3.7 Hz, 7-H), 6.83 (1H, s, thiazole), 9.35 (1H, d, J=8.4 Hz, CONH).

Compounds **42a** and **2a**

These compounds were obtained from **18a** by the similar method described for **42b** and **2b**.

42a: IR ($CHCl_3$) cm^{-1} 1780, 1720; ^1H NMR (90 MHz, $CDCl_3$) δ 1.49 (3H, d, J=6.9 Hz, CH_3), 1.80 (2H, s, NH_2), 3.70 (3H, s, 3-OCH_3), 4.47 (1H, d, J=3.8 Hz, 7-H), 4.64 (1H, q, J=6.9 Hz, 2-H), 5.14 (1H, d, J=3.8 Hz, 6-H), 6.95 (1H, s, C*H*Ph_2), 7.10~7.60 (15H, m, Ph). **2a** (TFA salt): IR (Nujol) cm^{-1} 1785, 1670; ^1H NMR (90 MHz, DMSO-d_6) δ 1.43 (3H, d, J=6.9 Hz, CH_3), 3.72 (3H, s, 3-OCH_3), 3.85 (3H, s, oxime-CH_3), 4.77 (1H, q, J=6.9 Hz, 2-H), 5.34 (1H, d, J=4.2 Hz, 6-H), 5.48 (1H, dd, J=8.3 and 4.2 Hz, 7-H), 6.77 (1H, s, thiazole), 9.33 (1H, d, J=8.3 Hz, CONH).

Compounds **41a**, **41b**, **1a** and **1b**

These compounds were obtained from **17a** and **17b**, respectively, as described for **42b** and **2b**.

41a: IR ($CHCl_3$) cm^{-1} 1784, 1724; ^1H NMR (90 MHz, $CDCl_3$) δ 1.38 (3H, d, J=7.0 Hz, CH_3), 1.74 (2H, s, NH_2), 4.53 (1H, d, J=4.0 Hz, 7-H), 4.70 (1H, dq, J=7.0 and 3.5 Hz, 2-H), 5.04 (1H, d, J=4.0 Hz, 6-H), 6.51 (1H, d, J=3.5 Hz, 3-H), 6.96 (1H, s, C*H*Ph_2), 7.10~7.60 (10H, m, Ph). **41b**: IR ($CHCl_3$) cm^{-1}

1785, 1712; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.9 Hz, CH_3), 1.87 (2H, s, NH_2), 4.45 (1H, d, J=4.0 Hz, 7-H), 4.58 (1H, dq, J=6.9 and 1.8 Hz, 2-H), 5.03 (1H, d, J=4.0 Hz, 6-H), 6.35 (1H, d, J=1.8 Hz, 3-H), 6.95 (1H, s, C*H*Ph_2), 7.10~7.60 (10H, m, Ph). **1a** (TFA salt): IR (Nujol) cm^{-1} 1780, 1660; ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.33 (3H, d, J=7.2 Hz, CH_3), 3.86 (3H, s, OCH_3), 4.72 (1H, dq, J=7.2 and 3.6 Hz, 2-H), 5.22 (1H, d, J=3.5 Hz, 6-H), 5.53 (1H, dd, J=8.5 and 3.5 Hz, 7-H), 6.50 (1H, d, J=3.6 Hz, 3-H), 6.78 (1H, s, thiazole), 9.34 (1H, d, J=8.5 Hz, CONH). **1b** (TFA salt): IR (Nujol) cm^{-1} 1780, 1665; ^{1}H NMR (90 MHz, DMSO-d_6) δ 1.32 (3H, d, J=7.0 Hz, CH_3), 3.87 (3H, s, OCH_3), 4.65 (1H, dq, J=7.0 and 1.8 Hz, 2-H), 5.25 (1H, d, J=3.9 Hz, 6-H), 5.46 (1H, dd, J=7.9 and 3.9 Hz, 7-H), 6.34 (1H, d, J=1.8 Hz, 3-H), 6.86 (1H, s, thiazole), 9.37 (1H, d, J=7.9 Hz, CONH).

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