

1-OXACEPHEMS WITH THE THIENAMYCIN-TYPE SIDE CHAIN (1).
SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7 α -[(1R)-1-HYDROXYETHYL]-1-OXACEPHEMS BEARING ELECTRON-WITHDRAWING GROUPS *1,*2

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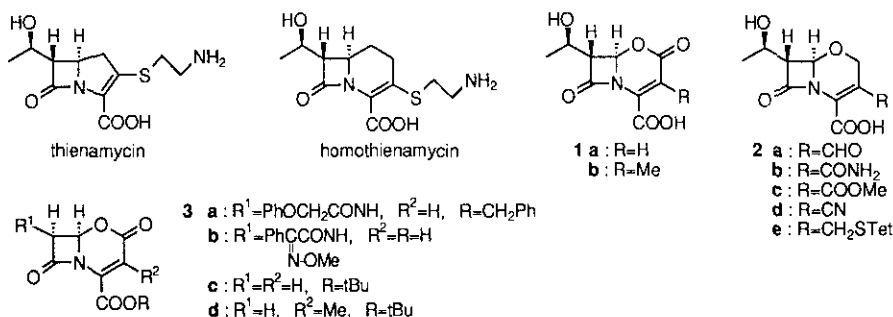
Abstract — 1-Oxacephem derivatives, 2a-d, bearing the hydroxyethyl group at C_{7 α} and some electron-withdrawing groups at C₃ were synthesized and tested for antibacterial activity. It was found that some of these compounds, in particular, 7 α -hydroxyethyl-3-cyano-1-oxacephem 2d, exhibited antibacterial activity, although the potency was low. Some 7 α -hydroxyethyl-2-oxo-1-oxacephems, 1a,b, were also prepared and found biologically inactive.

Elucidation of the hydroxyethyl structure and the α -configuration of the thienamycin side chain has brought about an innovation in the concept regarding the structure-activity relationships of β -lactam antibiotics. Thus, the well-established concept that the side chain should be an acylamide with β -configuration on the β -lactam ring was upset, and, as a rational consequence, a question arose whether or not the hydroxyethyl group could be valid for the nuclei of the conventional β -lactam antibiotics. In order to examine this point, homothienamycin was synthesized by the Merck group² and tested for biological activity. Surprisingly it turned out that this compound was virtually inactive in marked contrast with the parent compound. From the viewpoint of structure-activity relationships, this fact was quite intriguing and led us to investigate the basis of this marked difference. It is well accepted that two structural factors operate in determining the biological activity of a β -lactam nucleus. The first is the chemical reactivity of the β -lactam ring to acylate the target enzymes and the second is the shape of the β -lactam molecule which determines the fitness to the enzyme active site. Thienamycin and homothienamycin differ markedly in

*1 This work is contributed to the memory of the late Professor Emeritus (Tohoku University) Tetsuji Kametani, the former Chief Editor of this Journal.

*2 An account of this work was presented by W.N. at the 16th International Conference on Chemistry of Natural Product (IUPAC), Kyoto, May 29-June 3, 1988.¹ Details of this work were also presented by M. M. at the 55th Symposium of Synthetic Organic Chemistry, Tokyo, June 1-2, 1989.

these two characteristics. While the thienamycin molecule is greatly folded and its reactivity is high, homothienamycin is shaped rather flat and has low reactivity. We suspected that the low reactivity might be a primary reason for the loss of activity in homothienamycin, as the Merck chemists initially suggested.² On the basis of this view we planned synthesis and biological evaluation of certain 1-oxacephems **1** and **2** bearing 7 α -hydroxyethyl and electron-withdrawing groups which were expected to enhance the chemical reactivity and, in turn, impart antibacterial activity to the molecules.*³

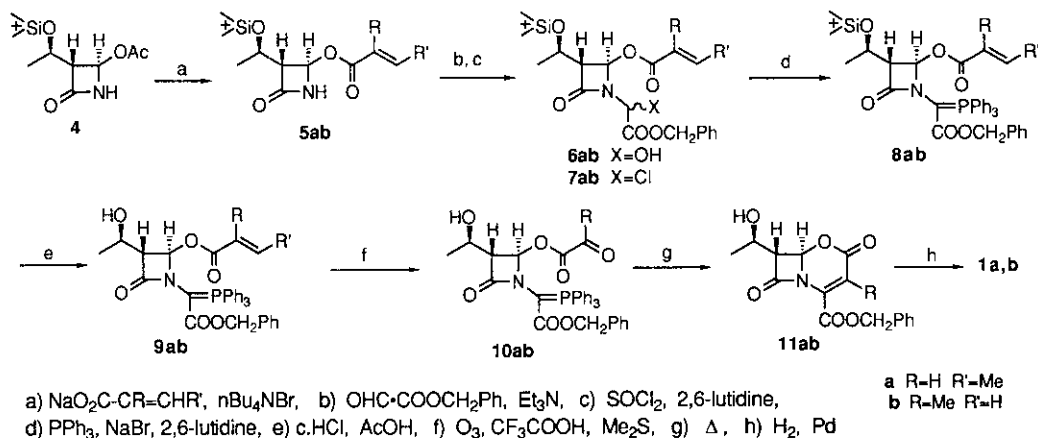


Synthesis of 7 α -Hydroxyethyl-2-oxo-1-oxacephem Derivatives

Synthesis of certain 2-oxo-1-oxacephem derivatives **3a-d** was already documented in the literature⁴ and the compounds were reported to be generally unstable. Thus, half-life ($t_{1/2}$) of compound **3b**, the only compound obtained in the free acid form, was reported to be about 3 min in a pH 7 buffer at room temperature. We thought that the instability was mainly due to either complete exposure of the β -lactam ring to nucleophiles for unsubstituted derivatives **3c-d**, or the presence of an acylamino group at 7 β for **3a-b**, in which the acylamide could internally participate in β -lactam ring opening. Substitution of the hydroxyethyl group at 7 α could eliminate these destabilizing factors and, thus, the target 1-oxacephems **1** would have increased stability.

Synthesis of **1** was carried out principally in a similar way to that reported for the synthesis of **3c-d**.^{4b} Commercially available, chiral azetidinone **45** was reacted with either sodium crotonate or sodium methacrylate in a two-phase system to give **5a** or **5b** in 67% or 74% yield, respectively. Compounds **5a** and **5b** were then converted into phosphoranes **8a** and **8b** in 78% and 80% yields, respectively, by application of the well-used Woodward process⁶ as shown in Scheme 1. Desilylation of **8a** and **8b** with hydrochloric acid followed by ozonolysis in the presence of trifluoroacetic acid gave α -oxo esters **10a** and **10b** which, respectively, spontaneously or on warming for a short time, were cyclized to the benzyl esters of the target compounds **11a** and **11b** in 54% and 81% yields from **8a** and **8b**, respectively. Catalytic hydrogenation of

*³ After our work was completed and published^{1,2} a similar work³ was reported very recently without citation of our work.



Scheme 1

11a and 11b gave crystalline free acids 1a, mp 173-175°C and 1b, mp 171-173°C in 73% and 80% yields, respectively. Compounds 1a and 1b show ir absorption at 1800 cm^{-1} and 1792 cm^{-1} (KBr), respectively, suggesting enhanced reactivity of the β -lactam carbonyl. In accord with this high-frequency ir absorption, half lives of 1a and 1b were only 40 min and 73 min, respectively, in pH 7.0 buffer at 37°C, showing, however, that the compounds were, as expected, of higher stability as compared with the 7 β -acylamido analog 3b. Unfortunately, however, each compound was shown biologically inactive, suggesting that the stability was not high enough for exhibiting antibacterial activity.

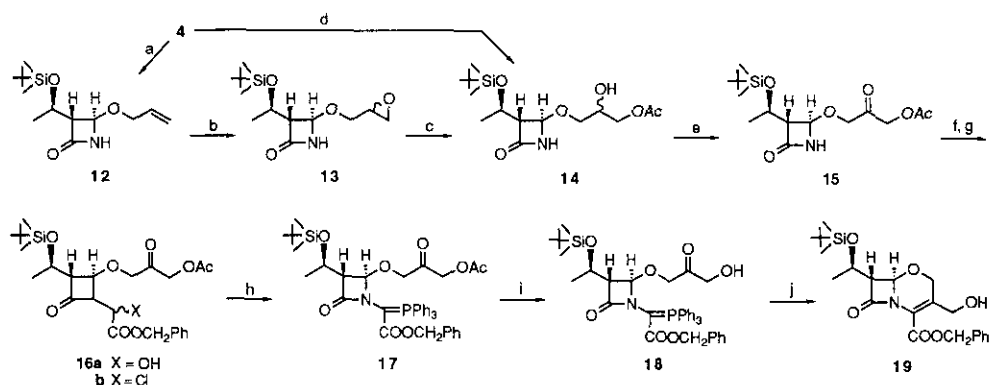
Synthesis and Antibacterial Activity of 7 α -Hydroxyethyl-1-oxacephem Derivatives Bearing Electron-Withdrawing Groups at C₃

Our next target was to synthesize compound 2, another type of 7 α -hydroxyethyl-1-oxacephems with enhanced chemical reactivity. In these molecules, enhancement was expected to be attained by substitution with certain electron-withdrawing groups at C₃. The synthesis was carried out again according to the same strategy as that used for the synthesis of 1.

Refluxing of a benzene solution of azetidinone 4 with allyl alcohol in the presence of a catalytic amount of zinc acetate gave a single allyloxyazetidinone 12 which was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to an inseparable epoxide mixture 13 in 91% overall yield from 4. Assignment of (R)-stereochemistry at C₄ in the allyloxyazetidinone 12 and hence in the epoxides 13 was based upon the nmr data (see Experimental). The epoxide ring in 13 was then opened at the terminal carbon with acetic acid and a catalytic amount of titanium tetraisopropoxide to give a 1:1 stereo mixture of diol monoacetate 14 in 77% yield. The same mixture was directly obtained in 86% yield by reaction of 4 with glycerol 1-acetate in refluxing benzene in the presence of zinc acetate catalyst, demonstrating that acetalization at C₄ took place

preferentially with the primary hydroxy group in glycerol monoacetate. The mixture was then oxidized by Swern oxidation to a single ketol acetate **15** in around 50% yield.

Ketol acetate **15** was then converted into the acetoxy phosphorane **17** in 60% overall yield by the well-established three-step process shown in Scheme 2. Selective hydrolysis was effected by cautious treatment of **17** with sodium methoxide in methanol at -40°C to give **18** in 60% yield. In compound **17** the azetidinone and ester carbonyls are deactivated by the phosphorane group and thus remained intact on this treatment. Heating of a toluene solution of **18** at 100°C for 3.5 h now gave a key intermediate **19** in 87% yield.

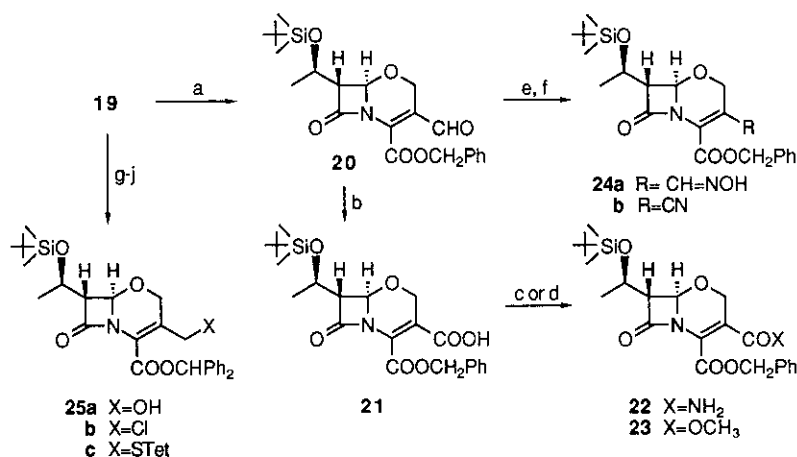


a) allyl alcohol, $\text{Zn}(\text{OAc})_2$, b) *m*-CPBA, NaHCO_3 , c) AcOH , $\text{Ti}(\text{O}i\text{Pr})_4$, d) $\text{HOCH}_2\text{CHOH} \cdot \text{CH}_2\text{OAc}$, $\text{Zn}(\text{OAc})_2$, e) $\text{DMSO} \cdot (\text{COCl})_2$, Et_3N , f) $\text{OHC} \cdot \text{COOCH}_2\text{Ph}$, Et_3N , g) SOCl_2 , 2,6-lutidine, h) PPh_3 , i) NaOMe , MeOH , j) Δ

Scheme 2

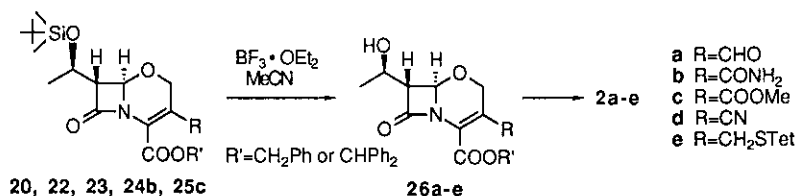
Compound **19** was first oxidized by Swern oxidation to aldehyde **20** in a quantitative yield. This aldehyde was further oxidized to the corresponding carboxylic acid **21** by treatment with NaClO_2 in NaH_2PO_4 buffer in the presence of 2-methyl-2-butene for trapping chlorine which was generated during the oxidation.⁷ Acid amide **22** and methyl ester **23** were easily derived from **21** by reaction with ammonia and phenyl dichlorophosphate, and with diazomethane, respectively. On the other hand the aldehyde **20** was converted into nitrile **24b** in quantitative yield by dehydration of the corresponding aldoxime **24a**. Finally 3'-*N*-methyltetrazolylthio derivative **25c** was prepared as a reference compound by a sequence of reactions as shown in Scheme 3. First, the benzyloxycarbonyl group in **19** was changed into the easily deprotectable benzhydryloxycarbonyl group. The resulting benzhydryl ester was then transformed to **25c** by chlorination and subsequent substitution with sodium *N*-methyltetrazolyl thiolate.

Deprotection in compounds **20**, **22**, **23**, and **24b** was smoothly effected by treatment with BF_3 etherate in acetonitrile followed by catalytic hydrogenation to give the corresponding free acids **2a**, **2b**, **2c**, and **2d**, respectively. Similarly free acid **2e** was obtained by treatment of **25c** first with BF_3 etherate and then with trifluoroacetic acid and anisole in dichromethane.



a) DMSO-(COCl)₂, Et₃N, b) NaClO₂, NaH₂PO₄, 2-butyl-2-butene, c) NH₃, PhOPCl₂, Et₃N, d) CH₂N₂, e) NH₂OH·HCl, f) SOCl₂, pyridine, g) H₂, Pd, h) Ph₂CN₂, i) SOCl₂, 2,6-lutidine, j) NaSTet.

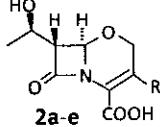
Scheme 3



Scheme 4

Compounds 2a-e were tested for antibacterial activity and the results are listed in Table I. As can be seen from this table, compounds 2b-d actually showed antibacterial activity and, in particular, activity of the nitrile 2d was notable. However, the potency was unfortunately very low against our expectation, suggesting that in addition to chemical reactivity another factor, *i.e.* the shape of the molecule, should also be taken into account for effecting the biological activity.

Table I. In Vitro Activity of 7α-Hydroxyethyl-3-substituted 1-Oxacephems MIC (μg/ml)

 2a-e	a	b	c	d	e
	R: CHO	CONH ₂	COOMe	CN	CH ₂ STet
<i>S. aureus</i> JC-1	>100	25	50	12.5	>100
<i>S. pyogenes</i> C-203	>100	100	50	12.5	>100
<i>S. pneumoniae</i> 1	>100	25	6.3	6.3	12.5
<i>E. coli</i> JC-2	>100	>100	50	50	>100
<i>K. pneum.</i> SRL-1	>100	>100	50	50	>100

EXPERIMENTAL

Melting points were determined on a Yanagimoto apparatus and were uncorrected. Ir spectra were obtained on a Hitachi 260-10 spectrophotometer. ^1H Nmr spectra were recorded on Varian EM-390 and VXR-200 spectrometers using TMS as an internal standard. Uv spectra were obtained on a Hitachi 320 spectrometer. Unless otherwise stated, ir, ^1H nmr, and uv spectra were recorded respectively on CHCl_3 , CDCl_3 , and EtOH solutions. All reactions were done under nitrogen atmosphere and extracts were dried over anhydrous sodium sulfate. Column chromatography was performed on Merck Lobar column using various toluene and ethyl acetate mixtures as eluants.

(3R,4R)-4-(2-Butenoyloxy)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidin-2-one (5a) To a cold stirred solution of crotonic acid (7.75 g) in 4 N NaOH solution (23.6 ml) were added a solution of 4-acetoxyazetidinone 4 (4.311 g) in CH_2Cl_2 (40 ml) and tetrabutylammonium bromide (97 mg). After being stirred for 1 h at room temperature, the reaction mixture was poured into cold 5% aqueous NaHCO_3 solution, and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give **5a** (3.83 g, 67%) as a colorless solid, nmr δ : 0.87 (9H, s), 1.26 (3H, d, $J = 6.3$ Hz), 1.91 (3H, m), 3.20 (1H, m), 4.25 (1H, m), 5.83 (1H, m), 5.90 (1H, s), 6.61 (1H, br s), 7.05 (1H, m); ir cm^{-1} : 3415, 1778, 1716, 1627.

(3R,4R)-1-(Benzyloxycarbonyl-1-hydroxymethyl)-4-(2-butenoyloxy)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidin-2-one (6a) A mixture of **5a** (400 mg), benzyl glyoxylate (272 mg), triethylamine (0.05 ml) and THF (1.5 ml) was stirred overnight at room temperature. The reaction mixture was poured into ice-water, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give crude **6a** (760 mg) as a mixture of two possible stereoisomers, nmr δ : 0.83 (9H, s), 1.24 (3H, d, $J = 7$ Hz), 1.85 (3H, m), 3.23 (1H, m), 3.83 (1H, d, $J = 8$ Hz), 4.22 (1H, m), 5.1-6.2 (5H, m), 7.03 (1H, m), 7.3-7.4 (5H, m); ir cm^{-1} : 3450, 1778, 1740, 1720.

(3R,4R)-1-(Benzyloxycarbonyl-1-chloromethyl)-4-(2-butenoyloxy)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidin-2-one (7a) To a cold solution of crude hydroxy derivative **6a** (760 mg) in THF (10 ml) were added 2,6-lutidine (0.37 ml) and thionyl chloride (0.20 ml) at -30°C . After being stirred for 30 min at -30°C , the reaction mixture was poured into cold 1 N aqueous HCl solution, and extracted with EtOAc. The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure to give crude chloride **7a** (748 mg), nmr δ : 0.84 (9H, s), 1.26 (3H, d, $J = 6$ Hz), 1.86 (3H, m), 3.27 (1H, m), 4.23 (1H, m), 4.9-6.3 (4H, m), 6.54 (1H, m), 7.04 (1H, m), 6.3-6.4 (5H, m); ir cm^{-1} : 1780, 1750, 1722, 1650.

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-4-(2-butenoyloxy)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidin-2-one (8a) To a solution of crude chloride **7a** (748 mg) in dioxane (14

ml) were added 2,6-lutidine (0.22 ml), sodium bromide (329 mg) and triphenylphosphine (670 mg) and the mixture was stirred overnight at 40°C. The reaction mixture was poured into cold 1 N aqueous HCl and extracted with EtOAc. The organic layer was washed with cold 5% aqueous NaHCO₃ solution, brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give ylide 8a (721 mg, 78% from 5a) as a colorless foam, nmr δ : 0.74 (9H, s), 1.16 (3H, d, $J = 6$ Hz), 1.75 (3H, d, $J = 7$ Hz), 2.95 (1H, m), 4.7-7.1 (6H, m), 7.2-7.8 (20H, m); ir cm⁻¹: 1754, 1720, 1655, 1612.

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-4-(2-butenyloxy)-3-[(1R)-1-hydroxyethyl]azetidin-2-one (9a) To a solution of ylide 8a (216 mg) in acetonitrile (3 ml) were added acetic acid (0.3 ml) and conc. HCl (0.24 ml) at ice cooling. After being stirred for 1 h, the reaction mixture was poured into cold 5% aqueous NaHCO₃ solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give crude ylide 9a as a foam, nmr δ : 0.89 (9H, s), 1.20 (3H, m), 1.78 (3H, d, $J = 7$ Hz), 4.7-7.2 (6H, m), 7.2-7.8 (20H, m); ir cm⁻¹: 3450, 1760, 1700, 1617.

Benzyl 7 α -[(1R)-1-Hydroxyethyl]-2-oxo-1-oxa-3-cephem-4-carboxylate (11a) To a solution of crude ylide 9a (193 mg) in CH₂Cl₂ (4 ml) was added CF₃COOH (0.23 ml), and the mixture was cooled to -78°C. Into this solution ozone was bubbled until the solution was colored blue. Dimethyl sulfide (0.22 ml) was added, and the solution was further stirred for 30 min at room temperature, then poured into cold 5% aqueous NaHCO₃ solution and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-oxacephem derivative 11a (51 mg, 54% from 8a) as a crystalline solid, mp 111-113°C (from CH₂Cl₂-Et₂O), nmr δ : 1.33 (3H, d, $J = 6$ Hz), 2.86 (1H, br s), 3.55 (1H, m), 4.27 (1H, m), 5.31 (2H, s), 5.82 (1H, s), 6.26 (1H, s), 7.41 (5H, s); ir cm⁻¹: 3616, 1809, 1744, 1611; uv: 295 nm ($\epsilon = 7200$).

7 α -[(1R)-1-Hydroxyethyl]-2-oxo-1-oxa-3-cephem-4-carboxylic Acid (1a) A solution of benzyl ester 11a (94 mg) in EtOAc (2 ml) and EtOH (2 ml), and Pd black (40 mg) was stirred in a hydrogen atmosphere for 20 min at room temperature. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting precipitate was collected to give acid 1a (49 mg, 73%) as a crystalline solid from methanol-ether, mp 173-175°C, nmr (CD₃OD) δ : 1.32 (3H, d, $J = 7$ Hz), 3.60 (1H, d, $J = 5.4$ Hz), 4.17 (1H, m), 5.89 (1H, s), 6.20 (1H, s); ir (KBr) cm⁻¹: 3572, 3440, 1800, 1758, 1723, 1610; uv: 295 nm ($\epsilon = 7400$).

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-methacryloyloxy-azetidin-2-one (5b) To a solution of methacrylic acid (2.15 g) in 4 N NaOH solution (6.25 ml) were added 4-acetoxiazetidinone 4 (1.437 g) in CH₂Cl₂ (12 ml) and tetrabutylammonium bromide (48 mg). After being stirred for 2 h at room temperature, the reaction mixture was poured into cold 5% aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to give 5b (1.15 g, 74%) as a crystalline solid, mp

116-117.5°C (from CH₂Cl₂-hexane), nmr δ : 0.87 (9H, s), 1.27 (3H, d, J = 6.3 Hz), 1.95 (3H, s), 3.23 (1H, d, J = 3.6 Hz), 4.23 (1H, m), 5.65 (1H, s), 5.90 (1H, s), 6.16 (1H, s), 6.58 (1H, br); ir cm⁻¹: 3400, 1778, 1715, 1630.

(3R,4R)-1-(Benzyloxycarbonyl-1-hydroxymethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-methacryloyloxy-azetidin-2-one (6b) A solution of **5b** (1.13 g), benzyl glyoxylate (770 mg), and triethylamine (0.15 ml) in THF (7 ml) was stirred for 2 h under ice cooling. The reaction mixture was poured into ice-water, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give crude hydroxy derivative **6b** (2.02 g), nmr δ : 0.84 (9H, s), 1.26 (3H, d, J = 6.3 Hz), 1.89 (3H, d, J = 4.5 Hz), 3.24 (1H, m), 4.17 (1H, m), 5.1-6.2 (6H, m), 7.3-7.4 (5H, m); ir cm⁻¹: 3500, 1780, 1742, 1720, 1630.

(3R,4R)-1-(Benzyloxycarbonyl-1-chloromethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-methacryloyloxyazetidin-2-one (7b) To a cold solution of crude hydroxy derivative **6b** (2.02 g) in THF (20 ml) were added 2,6-lutidine (1.05 ml) and thionyl chloride (0.63 ml) at -35°C, and the solution was stirred for 20 min at -35°C. The mixture was poured into cold 1 N aqueous HCl solution, and extracted with EtOAc. The organic layer was washed with 5% aqueous NaHCO₃ solution, brine, dried, and evaporated under reduced pressure to give crude chloride **7b** (2.10 g); ir cm⁻¹: 1782, 1756, 1723, 1637.

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-methacryloyloxyazetidin-2-one (8b) To a solution of crude chloride **7b** (2.10 g) in dioxane (42 ml) were added 2,6-lutidine (0.62 ml), sodium bromide (932 mg) and triphenylphosphine (1.899 g). After being stirred overnight at 40°C, the reaction mixture was poured into cold 1 N aqueous HCl solution, and extracted with EtOAc. The organic layer was washed with cold 5% aqueous NaHCO₃ solution, brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give ylide **8b** (2.09 g, 80% from **5b**) as a colorless foam, nmr δ : 0.73 (9H, s), 1.17 (3H, d, J = 7.2 Hz), 1.69 (3H, s), 2.97 (1H, m), 3.83 (1H, m), 4.7-7.1 (5H, m), 7.2-7.9 (20H, m); ir cm⁻¹: 1758, 1718, 1612.

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-3-[(1R)-1-hydroxyethyl]-4-methacryloyloxyazetidin-2-one (9b) To a solution of ylide **8b** (1.22 g) in acetonitrile (12 ml) were added acetic acid (1.2 ml) and conc. HCl (1.0 ml) under ice cooling. After being stirred for 5 min, the reaction mixture was poured into cold 5% aqueous NaHCO₃ solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give crude ylide **9b** (1.14 g); ir cm⁻¹: 3460, 1762, 1705, 1620.

Benzyl 7a-[(1R)-1-Hydroxyethyl]-2-oxo-3-methyl-1-oxa-3-cephem-4-carboxylate (11b) To a solution of crude ylide **9b** (1.14 g) in CH₂Cl₂ (25 ml) was added CF₃COOH (1.31 ml), and the solution was cooled to -78°C. Into this solution ozone was bubbled until the solution colored blue. Dimethyl sulfide (0.73 ml) was added, and the reaction mixture was stirred for 15 min at room temperature, poured into cold 5% aqueous NaHCO₃ solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and

evaporated under reduced pressure to give crude keto ester 10b. The crude keto ester 10b was dissolved in CH_2Cl_2 (10 ml) and the solution was refluxed for 70 min. The reaction mixture was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography followed by crystallization from CH_2Cl_2 -hexane to give 1-oxacephem derivative 11b (450 mg, 81% from 8b) as a crystalline solid, mp 156.0-157.5°C, nmr δ : 1.33 (3H, d, $J = 7.2$ Hz), 1.90 (1H, br s), 2.18 (3H, s), 3.49 (1H, d, $J = 4.5$ Hz), 4.22 (1H, m), 5.33 (2H, s), 5.77 (1H, s), 7.40 (5H, s); ir cm^{-1} : 3616, 1803, 1737, 1616, 1500; uv: 295 nm ($\epsilon = 7700$).

7 α -(1R)-1-Hydroxyethyl]-2-oxo-3-methyl-1-oxa-3-cephem-4-carboxylic Acid (1b) A solution of benzyl ester 11b (105 mg) in EtOAc (2.1 ml) and EtOH (2.1 ml) and Pd black (30 mg) was stirred in a hydrogen atmosphere for 15 min at room temperature. The catalyst was filtered off and the filtrate was concentrated under reduced pressure, and the residue was crystallized from EtOAc-Et₂O to give acid 1b (61 mg, 80%), mp 175-177°C, nmr (CD_3OD) δ : 1.31 (3H, d, $J = 6.3$ Hz), 2.13 (3H, s), 3.51 (1H, d, $J = 6.3$ Hz), 4.13 (1H, m), 5.83 (s, 1H); ir (KBr) cm^{-1} : 3432, 1792, 1735, 1733, 1714, 1623; uv: 295 nm ($\epsilon = 8200$).

(3R,4R)-4-Allyloxy-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidin-2-one (12) To a solution of 4-acetoxyazetidinone 4 (12 g) in benzene (80 ml) were added allyl alcohol (40 ml) and anhydrous zinc acetate (13.6 g). The mixture was heated overnight under reflux in the presence of molecular sieves in a Dean Stark apparatus. After being cooled, the mixture was poured into ice cold water and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography to give allyl ether 12 (11.96 g, 100%) as a colorless foam, nmr δ : 0.88 (9H, s), 1.26 (3H, d, $J = 7.2$ Hz), 3.03 (1H, d, $J = 4$ Hz), 4.0-4.1 (2H, m), 4.15 (1H, m), 5.0-5.4 (3H, m), 5.7-6.2 (1H, m), 6.67 (1H, br).

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-(2,3-epoxypropyloxy)azetidin-2-one (13) To a solution of allyl ether 12 (5.70 g) in CH_2Cl_2 (50 ml) were added 70% m-chloroperbenzoic acid (6.37 g) and NaHCO_3 (2.18 g). After being stirred overnight at room temperature, the reaction suspension was poured into ice cold water, and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give epoxide mixture 13 (5.46 g, 91%) as a white foam, nmr δ : 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.26 (3H, d, $J = 6.2$ Hz), 2.6-2.9 (2H, m), 3.05 (1H, br s), 3.17-3.2 (2H, m), 3.5-3.9 (1H, m), 4.14 (1H, m), 5.07 (1H, d, $J = 8.8$ Hz), 6.51 (1H, s), 6.62 (1H, s); ir cm^{-1} : 3250, 1770.

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-(3-acetoxy-2-hydroxypropane-1-oxy)azetidin-2-one (14) (1) From 13 To a solution of epoxide mixture 13 (6.06 g) in acetic acid (19 ml) was added $\text{Ti}(\text{iOPr})_4$ (3.43 g). After being stirred for 6 h at room temperature, the reaction mixture was poured into cold 1 N aqueous HCl solution and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give acetate mixture 14 (5.57 g, 77%), nmr δ : 0.06 (3H, s), 0.08 (3H, s),

0.87 (9H, s), 1.26 (3H, d, $J = 6.2$ Hz), 2.11 (3H, s), 3.04 (1H, m), 3.5-3.8 (2H, m), 4.03 (1H, m), 4.1-4.2 (3H, m), 5.10 (1H, s), 6.62 (1H, br); ir cm^{-1} : 3420, 3250, 1740.

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-(3-acetoxy-2-hydroxypropane-1-oxy)azetidin-2-one (14) (2) **From 4** To a solution of 4-acetoxyazetidinone 4 (1.0 g) in benzene (20 ml) were added ($\pm$)-glycerol-1-acetate (700 mg) and anhydrous zinc acetate (1.5 g). The mixture was heated for 8.5 h under reflux in the presence of molecular sieves in a Dean Stark apparatus. The reaction mixture was poured into ice water, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography to give acetate 14 as a mixture (1.09 g, 86%).

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-(3-acetoxy-2-oxopropane-1-oxy)azetidine-2-one (15) Oxalyl chloride (1.61 ml) was added dropwise to a cold solution of DMSO (2.89 g) in CH_2Cl_2 (14 ml) at -50°C and the mixture was kept at the same temperature for 20 min under stirring. To this mixture was added a solution of alcohol 14 (5.57 g) in CH_2Cl_2 (14 ml). After 15 min, triethylamine (4.62 g) was added and the mixture was kept at -50°C for 1 h under stirring. The reaction mixture was poured into cold 1 N aqueous HCl solution and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give ketone 15 (4.86 g, 49%), nmr δ : 0.06 (3H, s), 0.08 (3H, s), 0.87 (9H, s), 1.27 (3H, d, $J = 6.2$ Hz), 2.18 (3H, s), 3.09 (1H, m), 4.05 (1H, m), 4.22 and 4.30 (2H, ABq, $J = 16.8$ Hz), 4.61 and 4.85 (2H, ABq, $J = 17.8$ Hz), 5.14 (1H, s), 6.51 (1H, s).

(3R,4R)-1-(Benzyloxycarbonyl-1-hydroxymethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-(3-acetoxy-2-oxopropane-1-oxy)azetidin-2-one (16a) A solution of ketone 15 (3.74 g), benzyl glyoxylate (1.8 g), triethylamine (0.72 ml) in THF (28 ml) was stirred for 3 h at room temperature, then poured into cold 1 N aqueous HCl solution, and extracted with EtOAc. The organic layer was washed with 5% aqueous NaHCO_3 solution, brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give a mixture of hydroxy derivative 16a (6.63 g), nmr δ : 0.04 (3H, s), 0.06 (3H, s), 0.86 (9H, s), 2.16 and 2.17 (3H, each s), 3.05 (1H, m), 4.13 (1H, m), 4.2 (2H, br s), 4.74 (2H, br s), 5.1-5.5 (4H, m), 7.3-7.4 (5H, m); ir cm^{-1} : 3500, 1770, 1740.

(3R,4R)-1-(Benzyloxycarbonyl-1-chloromethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-(3-acetoxy-2-oxopropane-1-oxy)azetidin-2-one (16b) To a cold solution of crude mixture 16a (6.63 g) in CH_2Cl_2 (60 ml) were added 2,6-lutidine (3.17 ml) and thionyl chloride (1.01 ml) at -40°C . After being stirred for 45 min, the reaction mixture was poured into cold 1 N aqueous HCl solution and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure to give crude chloride 16b, nmr δ : 0.78 and 0.86 (9H, each s), 1.25 (3H, m), 2.18 (3H, s), 3.18 (1H, m), 4.18 (1H, m), 4.3-4.9 (5H, m), 5.1-5.4 (3H, m), 6.12 (1H, m), 7.3-7.4 (5H, m).

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-3-[(1R)-1-tert-butyldimethylsilyloxy-ethyl]-4-(3-acetoxy-2-oxopropane-1-oxy)azetidin-2-one (17) A solution of crude chloride 16b (11.5 g) and triphenylphosphine (4.65 g) in CH_2Cl_2 (60 ml) was stirred overnight at room temperature. The reaction mixture was poured into cold 5% aqueous NaHCO_3 solution and extracted with CH_2Cl_2 . The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give ylide 17 (4.76 g, 60% from 15), nmr δ : 0.10 (6H, m), 0.95 (9H, m), 1.1-1.3 (3H, m), 2.25 (3H, s), 3.7-5.4 (9H, m), 6.9-7.8 (20H, m); ir cm^{-1} : 3470, 1743, 1618.

(3R,4R)-1-(Benzyloxycarbonyl-1-triphenylphosphoranylidene-methyl)-3-[(1R)-1-tert-butyldimethylsilyloxy-ethyl]-4-(3-hydroxy-2-oxopropane-1-oxy)azetidin-2-one (18) To a cold solution of ylide 17 (4.76 g) in MeOH (20 ml) was added 5.18 M solution of NaOMe in MeOH (1.37 ml) at -40°C and the solution was kept at the same temperature for 2.5 h under stirring. The reaction mixture was poured into cold 1 N aqueous HCl solution and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give ylide 18 (2.68 g, 60%), nmr δ : 0.10 (6H, m), 0.95 (9H, m), 1.2-1.3 (3H, m), 3.7-5.4 (9H, m), 6.9-7.8 (20H, m); ir cm^{-1} : 3430, 1745, 1608.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-hydroxymethyl-1-oxa-3-cephem-4-carboxylate (19) A solution of ylide 18 (2.66 g) in toluene (30 ml) was heated at 100°C for 3.5 h and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 1-oxacephem derivative 19 (1.43 g, 87%) as a colorless foam, nmr δ : 0.05 (3H, s), 0.08 (3H, s), 0.83 (9H, s), 1.31 (3H, d, $J = 6.4$ Hz), 2.88 (1H, m), 3.12 (1H, br s), 4.0-4.4 (2H, m), 4.30 (1H, m), 4.43 and 4.61 (2H, ABq, $J = 18.4$ Hz), 5.00 (1H, s), 5.32 and 5.35 (2H, ABq, $J = 12.2$ Hz), 7.3-7.6 (5H, m); ir cm^{-1} : 3500, 1780, 1706, 1632.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylate (20) Oxalyl chloride (190 mg) was added to a cold solution of DMSO (257 mg) in CH_2Cl_2 (4 ml) at -40°C and the mixture was kept at the same temperature for further 15 min under stirring. To this mixture was added a solution of alcohol 19 (447 mg) in CH_2Cl_2 (5 ml). After 20 min, triethylamine (333 mg) was added and the mixture was stirred for 1 h at -40°C . The reaction mixture was poured into cold 1 N aqueous HCl solution and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution, and then brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 3-formyl derivative 20 (443 mg, 99%) as a colorless foam, nmr δ : 0.07 (6H, s), 0.82 (9H, s), 1.29 (3H, d, $J = 6.4$ Hz), 3.27 (1H, br s), 4.32 (1H, m), 4.38 and 4.93 (2H, ABq, $J = 17.7$ Hz), 5.09 (1H, s), 5.36 and 5.41 (2H, ABq, $J = 11.9$ Hz), 7.25-7.5 (5H, m), 10.02 (1H, s); ir cm^{-1} : 1790, 1721, 1660, 1601.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-carboxyl-1-oxa-3-cephem-4-carboxylate (21) A mixture of aldehyde 20 (430 mg) in THF (8 ml), 2-methyl-2-butene (2 ml), water (2.5 ml), sodium chlorite (350 mg) and sodium dihydrogenphosphate (452 mg) was stirred for 3.5 h at room temperature. The

reaction mixture was poured into cold sodium sulfite solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give crude acid **21**, nmr δ : 0.02 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 1.27 (3H, d, $J = 6.2$ Hz), 3.28 (1H, br s), 4.28 (1H, m), 4.39 and 4.74 (2H, ABq, $J = 16.8$ Hz), 5.07 (1H, s), 5.29 and 5.35 (2H, ABq, $J = 12.4$ Hz), 7.3-7.45 (5H, m).

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-carbamoyl-1-oxa-3-cephem-4-carboxylate (22) To a cold solution of crude acid **21** (120 mg) in CH_2Cl_2 (3 ml) were added phenyl dichlorophosphate (71 mg) and triethylamine (57 mg). After being stirred for 5 min, 1.6 M ammonia solution in DMF (0.2 ml) was added and the mixture was stirred for further 30 min at -25°C . The mixture was poured into cold 1N aqueous HCl solution, and extracted with CH_2Cl_2 . The organic layer was washed with 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give carbamoyl **22** (48 mg, 40%), nmr δ : 0.04 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.32 (3H, d, $J = 6.4$ Hz), 3.22 (1H, br s), 4.33 (1H, m), 4.65 and 4.71 (2H, ABq, $J = 17.9$ Hz), 5.10 (1H, s), 5.31 and 5.41 (2H, ABq, $J = 12.0$ Hz), 7.4-7.5 (5H, m); ir cm^{-1} : 3450, 1781, 1717, 1660, 1580.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-methoxycarbonyl-1-oxa-3-cephem-4-carboxylate (23) To a solution of crude acid **21** (125 mg) in CH_2Cl_2 (2 ml) was added an ethereal solution of diazomethane. The solution was chromatographed on a silica gel column to give methyl ester **23** (86 mg, 90%), nmr δ : 0.03 (3H, s), 0.06 (3H, s), 0.84 (9H, s), 1.26 (3H, d, $J = 6.4$ Hz), 3.25 (1H, br s), 3.57 (3H, s), 4.28 (1H, m), 4.36 and 4.76 (2H, ABq, d, $J = 16.8$ Hz), 5.04 (1H, s), 5.31 and 5.35 (2H, ABq, $J = 11$ Hz), 7.3-7.5 (5H, m); ir cm^{-1} : 1782, 1728, 1700, 1620.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-hydroxyiminomethyl-1-oxa-3-cephem-4-carboxylate (24a) To a solution of aldehyde **20** (270 mg) in THF (6 ml) was added hydroxylamine hydrochloride (63 mg) in water (2 ml) and the solution was stirred for 2 h at room temperature. The reaction mixture was poured into cold 5% aqueous NaHCO_3 solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The residue was purified by silica gel column chromatography to give oxime **24a** (290 mg, 100%), nmr δ : 0.08 (6H, s), 0.83 (9H, s), 3.19 (1H, br s), 4.31 (1H, m), 4.48 and 4.93 (2H, ABq, $J = 17.6$ Hz), 5.07 (1H, s), 5.30 and 5.37 (2H, ABq, $J = 12.2$ Hz), 7.2-7.5 (5H, m), 8.58 (1H, s); ir cm^{-1} : 3550, 1778, 1710, 1598.

Benzyl 7 α -[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate (24b) To a solution of oxime **24a** (290 mg) in CH_2Cl_2 (3 ml) were added pyridine (373 mg) and thionyl chloride (187 mg) and the solution was stirred for 2 h at room temperature. The reaction mixture was poured into cold 1 N aqueous HCl solution, and extracted with CH_2Cl_2 . The organic layer was washed with cold 5% aqueous NaHCO_3 solution and brine, dried, and evaporated. The residue was purified by silica gel column chromatography to give nitrile **24b** (290 mg, 100%), nmr δ : 0.07 (6H, s), 0.82 (9H, s), 1.28 (3H, d, $J = 6.4$

Hz), 3.27 (1H, br s), 4.33 (1H, m), 4.52 and 4.59 (2H, ABq, $J = 17.2$ Hz), 5.06 (1H, s), 5.38 (2H, s), 7.3-7.55 (5H, m); ir cm^{-1} : 2205, 1792, 1722, 1601.

Benzhydryl 7a-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-hydroxymethyl-1-oxa-3-cephem-4-carboxylate (25a) A solution of benzyl ester 19 (300 mg) in EtOAc (12 ml) was mixed with Pd black (80 mg) and the mixture was stirred in a hydrogen atmosphere for 15 min. The catalyst was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in MeOH. To this solution, diphenyldiazomethane was added and the mixture was stirred for 1 h at room temperature. The solution was concentrated under reduced pressure and the residue was purified by silica gel column chromatography to give benzhydryl ester 25a (260 mg, 86%), nmr δ : 0.06 (3H, s), 0.10 (3H, s), 0.83 (9H, s), 1.34 (3H, d, $J = 6.4$ Hz), 1.63 (1H, s), 3.15 (1H, br s), 3.9-4.5 (3H, m), 4.46 and 4.61 (2H, ABq, $J = 18$ Hz), 5.03 (1H, s), 7.00 (1H, s), 7.2-7.7 (10H, m); ir cm^{-1} : 3500, 1780, 1705, 1623.

Benzhydryl 7a-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-chlormethyl-1-oxa-3-cephem-4-carboxylate (25b) To a cold solution of alcohol 25a (180 mg) in CH_2Cl_2 (2 ml) were added 2,6-lutidine (0.09 ml) and thionyl chloride (0.03 ml) at -30°C and the mixture was stirred for 40 min. The reaction mixture was poured into cold 1 N aqueous HCl solution, and extracted with CH_2Cl_2 . The organic layer was washed with cold 5% aqueous NaHCO_3 solution and brine, dried, and evaporated under reduced pressure to give crude chloride 25b (190 mg), nmr δ : 0.09 (6H, s), 0.83 (9H, s), 1.32 (3H, d, $J = 6.2$ Hz), 3.16 (1H, br s), 4.29 (1H, m), 4.50 (2H, s), 4.52 and 4.58 (2H, ABq, $J = 13.4$ Hz), 5.06 (1H, s), 7.03 (1H, s), 7.2-7.6 (10H, m); ir cm^{-1} : 1782, 1718, 1623, 1600.

Benzhydryl 7a-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-tetrazolthiomethyl-1-oxa-3-cephem-4-carboxylate (25c) To a solution of crude chloride 25b (190 mg) in DMF (3 ml) was added sodium 1-methyl-tetrazolthiolate (96 mg) and the solution was stirred for 40 min at room temperature. The reaction mixture was poured into cold 1 N aqueous HCl solution, and extracted with EtOAc. The organic layer was washed with cold 5% aqueous NaHCO_3 solution and then brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give tetrazole 25c (93 mg, 43.5% from 20a), nmr δ : 0.10 (6H, s), 0.84 (9H, s), 1.33 (3H, d, $J = 6.0$ Hz), 3.15 (1H, d, $J = 3.4$ Hz), 3.90 (3H, s), 4.27 and 4.35 (2H, ABq, $J = 13.5$ Hz), 4.57 and 4.69 (2H, ABq, $J = 19.6$ Hz), 5.07 (1H, s), 7.04 (1H, s), 7.3-7.7 (10H, m).

Desilylation of 3-Substituted 1-Oxacephem Derivatives 24b, 20, 22, 23, and 25c. Benzyl 7a-[(1R)-1-Hydroxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate (26d) To a cold solution of nitrile 24b (210 mg) in acetonitrile (3 ml) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (101 mg, 1.5 eq.) at -40°C and the reaction mixture was stirred for 2 h, and then poured into cold 5% aqueous NaHCO_3 solution, and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give hydroxy derivative 26d (155 mg, 99%), nmr δ : 1.36 (3H, d, $J = 6.4$ Hz),

3.29 (1H, d, $J = 5.2$ Hz), 4.33 (1H, m), 4.50 and 4.58 (2H, ABq, $J = 17.2$ Hz), 5.05 (1H, s), 5.40 (2H, s), 7.35-7.55 (5H, m); ir cm^{-1} : 3400, 2202, 1792, 1727, 1600.

The following desilylated compounds **26a**, **26b**, **26c**, and **26e** were obtained from **20**, **22**, **23**, and **25c**, respectively, by a similar procedure to that described above.

Benzyl 7 α -[(1R)-1-Hydroxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylate (**26a**) Nmr δ : 1.31 (3H, d, $J = 6.3$ Hz), 3.25 (1H, m), 4.23 (1H, m), 4.29 and 4.84 (2H, ABq, $J = 17.6$ Hz), 5.03 (1H, s), 7.2-7.5 (5H, m), 9.98 (1H, s); ir cm^{-1} : 3450, 1790, 1726, 1660, 1603.

Benzyl 7 α -[(1R)-1-Hydroxyethyl]-3-carbamoyl-1-oxa-3-cephem-4-carboxylate (**26b**) Nmr (d_6 -acetone) δ : 1.29 (3H, d, $J = 6.4$ Hz), 3.18 (1H, d, $J = 6$ Hz), 4.18 (1H, m), 4.56 and 4.75 (2H, ABq, $J = 17.3$ Hz), 5.12 (1H, s), 5.20 and 5.31 (2H, ABq, $J = 12.6$ Hz), 7.3-7.5 (5H, m).

Benzyl 7 α -[(1R)-1-Hydroxyethyl]-3-metoxycarbonyl-1-oxa-3-cephem-4-carboxylate (**26c**) Nmr δ : 1.35 (3H, d, $J = 6.4$ Hz), 3.30 (1H, d, $J = 6$ Hz), 3.56 (3H, s), 4.28 (1H, m), 4.36 and 4.76 (2H, ABq, $J = 16.8$ Hz), 5.06 (1H, s), 5.30 and 5.38 (2H, ABq, $J = 12.1$ Hz), 7.3-7.5 (5H, m); ir cm^{-1} : 1782, 1730, 1703, 1622.

Benzhydryl 7 α -[(1R)-1-Hydroxyethyl]-3-tetrazolylthiomethyl-1-oxa-3-cephem-4-carboxylate (**26e**) Nmr δ : 1.38 (3H, d, $J = 6.2$ Hz), 3.16 (1H, d, $J = 5.6$ Hz), 3.83 (3H, s), 4.28 (2H, s), 4.56 and 4.64 (2H, ABq, $J = 18.7$ Hz), 4.98 (1H, s), 6.93 (1H, s), 7.2-7.6 (10H, m).

Deprotection of Benzylester

Sodium Salt of 7 α -[(1R)-1-Hydroxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylic Acid (**2d**) A solution of benzylester of nitrile **26d** (180 mg) was mixed with Pd black (80 mg) and the mixture was stirred in a hydrogen atmosphere for 20 min. The catalyst was filtered off and the filtrate was washed with aqueous NaHCO_3 solution. The washing was chromatographed on Diaion HP-20 (non-ionic adsorption resin). Lyophilization of the product fractions (monitored by tlc) gave **2d** (126 mg, 88%), nmr (D_2O) δ : 1.31 (3H, d, $J = 6.4$ Hz), 3.46 (1H, d, $J = 6.0$ Hz), 4.28 (1H, m), 4.60 (2H, s), 5.05 (1H, s), 5.19 (1H, s), 5.40 (2H, s), 7.35-7.55 (5H, m); ir (KBr) cm^{-1} : 3400, 2205, 1784, 1653, 1592.

A similar procedure was applied to **26a**, **26b**, and **26c** to give **2a**, **2b**, and **2c**, respectively.

Sodium Salt of 7 α -[(1R)-1-Hydroxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylic Acid (**2a**) Nmr (D_2O) δ : 1.32 (3H, d, $J = 6.4$ Hz), 3.54 (1H, d, $J = 5.4$ Hz), 4.28 (1H, m), 4.46 and 4.55 (2H, ABq, $J = 14.4$ Hz), 5.23 (1H, s), 9.64 (1H, s); ir (KBr) cm^{-1} : 3375, 1744, 1640, 1600; uv: 298 nm ($\epsilon = 11230$).

7 α -[(1R)-1-Hydroxyethyl]-3-carbamoyl-1-oxa-3-cephem-4-carboxylic Acid (**2b**) MP $> 300^\circ\text{C}$ (from acetone-ether), nmr (D_2O - NaHCO_3) δ : 1.32 (3H, d, $J = 6.4$ Hz), 3.40 (1H, d, $J = 4.4$ Hz), 4.30 (1H, m), 4.53 and 4.68 (2H, ABq, $J = 16.7$ Hz), 5.15 (1H, s), 7.3-7.5 (5H, m); ir (KBr): 3536, 3416, 3212, 1789, 1697, 1654, 1593; uv: 275 nm ($\epsilon = 9730$).

7 α -[(1R)-1-Hydroxyethyl]-3-methoxycarbonyl-1-oxa-3-cephem-4-carboxylic Acid (2c) Nmr (acetone) δ : 1.30 (3H, d, $J = 6.4$ Hz), 3.30 (1H, d, $J = 6.0$ Hz), 3.71 (3H, s), 4.20 (1H, m), 4.48 and 4.72 (2H, ABq, $J = 16.6$ Hz), 5.18 (1H, s).

Sodium Salt of 7 α -[(1R)-1-Hydroxyethyl]-3-tetrazolthiomethyl-1-oxa-3-cephem-4-carboxylic Acid (2e) To a solution of benzhydryl ester of tetrazole derivatives **26e** (108 mg) and anisole (0.2 ml) in CH_2Cl_2 (1.5 ml) was added CF_3COOH (0.2 ml) at 0°C . After being stirred for 1 h, the mixture was evaporated under reduced pressure. The residue was triturated with ether and the resulting precipitate was collected and dissolved in aqueous NaHCO_3 solution. This solution was subject to chromatography through HP-20 column using aqueous acetone as an eluant. Lyophilization of the product fractions gave **2e**, nmr (D_2O). δ : 1.30 (3H, d, $J = 6.4$ Hz), 3.24 (1H, d, $J = 4.6$ Hz), 3.98 and 4.25 (2H, ABq, $J = 13.5$ Hz), 4.04 (3H, s), 4.23 (1H, m), 4.52 and 4.62 (2H, ABq, $J = 20.8$ Hz), 5.07 (1H, s); ir (KBr), cm^{-1} : 3400, 1745, 1597; uv: 265 nm ($\epsilon = 13140$).

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Received, 30th August, 1989