Chem. Pharm. Bull. 28(5)1563—1577(1980)

Synthesis of 1-Carbacephem Derivatives[1]

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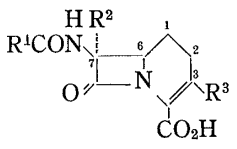
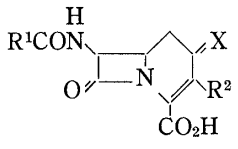
(Received November 24, 1979)

Total syntheses of several types of racemic 1-carbacephem derivatives, **30**, **32**, **35**, **37**, **39**, **45**, **46**, **50**, **56**, **57**, **58**, **65**, and preliminary biological results are described. Addition of azidoacetyl chloride to the Schiff base **10** in the presence of triethylamine gave *cis*-azetidinones **11a**, **b** which were converted to the racemic key intermediate **5**. By applying sequences of reactions developed in 1-oxacephem syntheses, various kinds of 1-carbacephems were prepared from **5**. Among twelve derivatives prepared, **50** showed the highest antibacterial activity.

Keywords——1-carbacephem; 1-carba-1-dethiacephalosporin; 1-oxacephem; β-lactam antibiotic; azetidinone; intramolecular Witting reaction; deprotection of 1-carbacephem; antibacterial activity

1-Carbacephalothin **1**, -cefamandole **2** and -cefoxitin **3** in which the sulfur atom of the corresponding cephalosporin antibiotics is replaced by carbon (methylene), have been synthesized as racemates, and the antibacterial activity of these compounds has been demonstrated to be at the same level as that of the cephem congeners.[3] Very recently, the preparation of 1-carbacephems functionalized at C_2 (**4**) and 3-methyl-1-carbacephem using an alternative approach has been reported.[4]





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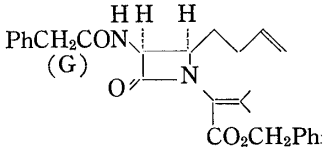
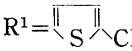
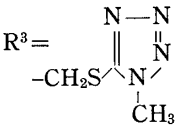


5

1: R^1=  , R^2=H, R^3=$-CH_2OAc$

2: R^1=PhCH(OH)–, R^2=H, R^3=  ($-CH_2STet$)

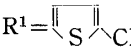
3: R^1=  . R^2=CH_3O–. R^3=$-CH_2OCONH_2$

Fig. 1

In connection with extensive studies on β-lactam antibiotics carried out in our laboratories, we have prepared several types of 1-carbacephem derivatives having an amide side-chain of current interest. We describe herein details of the synthesis and the preliminary biological results.

1) This work was presented at the 12th Congress of Heterocyclic Chemistry (Japan), Tokyo, Oct. 22, 1979, Abstract Papers, p. 51.
2) Location: *Fukushima-ku, Osaka 553, Japan.*
3) *a*) R.N. Guthikonda, L.D. Cama, and B.G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974); *b*) R.A. Firestone, J.L. Fahey, N.S. Maciejewicz, G.S. Patel, and B.G. Christensen, *J. Med. Chem.*, **20**, 551 (1977).
4) *a*) T.W. Doyle, T.T. Conway, G. Lim, and B.-Y. Luh, *Can. J. Chem.*, **57**, 227 (1979); *b*) A. Martel, T.W. Doyle, and B.-Y. Luh, *Can. J. Chem.*, **57**, 614 (1979).

1. Chemistry

In view of previous findings relating to 1-oxacephem syntheses in our laboratories,[5] azetidinone **5** appeared to be suitable as a common intermediate for synthesizing various types of 1-carbacephem antibiotics. Therefore, we first concentrated on the preparation of **5** having, if possible, the same absolute stereochemistry as penicillins and cephalosporins.

Preparation of the Intermediate 5——In order to obtain the chiral azetidinone **5**, we planned to use the D-amino acid benzyl ester **9**, which had been prepared from penicillin,[6] as a chiral template. Some modifications of the original procedure for large-scale operation allowed us to obtain sufficient material to carry out the synthesis. As shown in Chart 1, condensation of **9** with 4-pentenal[7] in methylene dichloride at room temperature provided the Schiff base **10** which, without isolation, was reacted with azidoacetyl chloride in the presence of triethylamine at low temperature, giving, after chromatographic separation, a mixture of *cis*-azetidinones **11a, b** in a ratio of approximately 1 to 1.[3,8] However, separation of this mixture by chromatography or crystallization into two optically active diastereoisomers at this or a later stage was unsuccessful. Following this failure to obtain a chiral intermediate, we converted the isopropenyl derivatives **11a, b** into a racemic isopropyridene derivative **12** by treatment with triethylamine. Reduction of **12** to the amine **13** with zinc and acetic acid followed by acylation with phenylacetyl chloride and pyridine gave the crystalline key intermediate **5** in 20—30% overall yield from the amino-acid ester **9**.

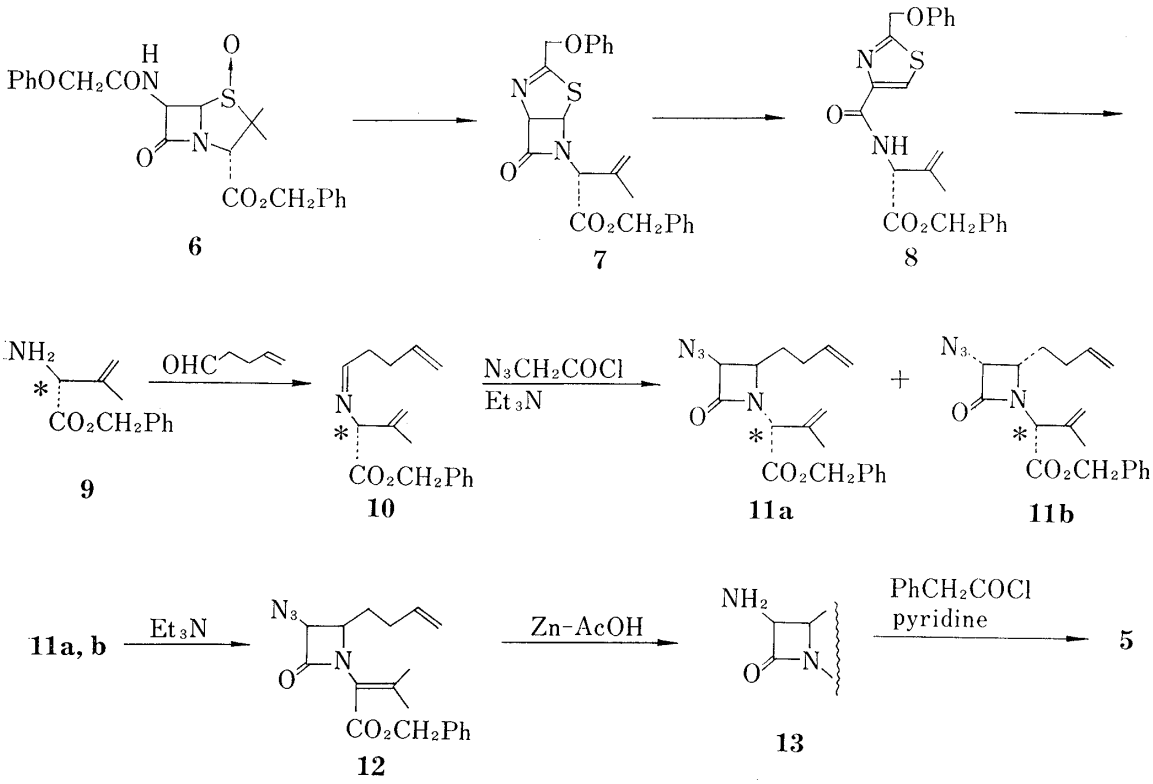


Chart 1

5) *a*) M. Narisada, H. Onoue, and W. Nagata, *Heterocycles*, **7**, 839 (1977); *b*) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, *J. Med. Chem.*, **22**, 757 (1979); *c*) S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikawa, Y. Ide, K. Nakano, and W. Nagata, *J. Am. Chem. Soc.*, **101**, 4403 (1979).
6) J.E. Baldwin, S.B. Haber, C. Hoskins, and L.I. Kruse, *J. Org. Chem.*, **42**, 1239 (1977).
7) A.I. Meyers, A. Nabeya, H.W. Adickes, I.R. Politzer, G.R. Malone, A.C. Kovelesky, R.L. Noleu, and R.C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
8) T.W. Doyle, B. Belleau, B.-L. Luh, C.F. Ferrari, and M.P. Cunnjngham, *Can. J. Chem.*, **55**, 468 (1977).

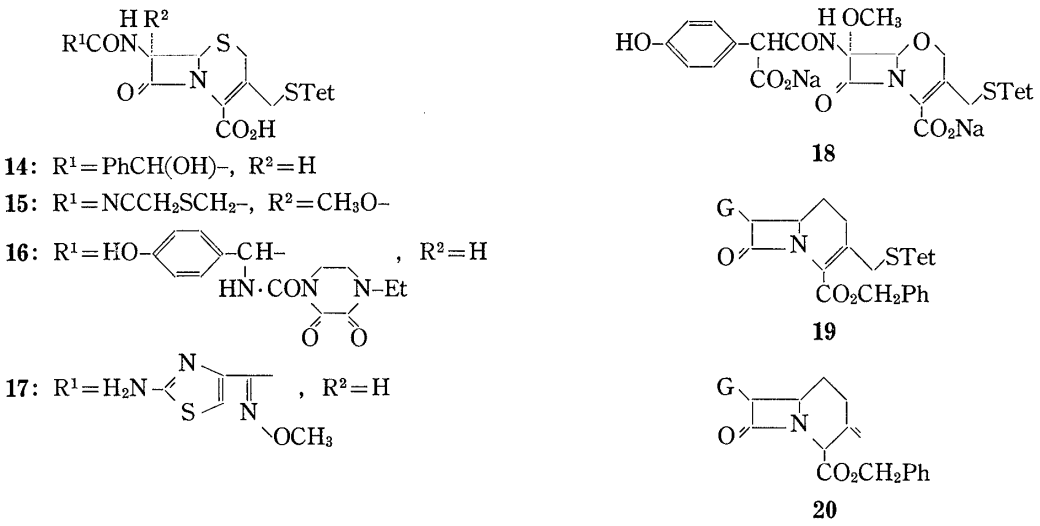


Fig. 2

3-Tetrazolylthiomethyl-1-carbacephems——It is well known that the 3-tetrazolylthiomethyl group constitutes an important part of cephalosporin antibiotics, as seen in cefamandole **14**,[9] cefmetazole **15**,[10] cefoperazone **16**[11] and SCE-1365 **17**[12] as well as in the 1-oxacephem antibiotic, 6059-S **18**.[5b] Moreover, 3-tetrazolylthiomethyl-1-carbacephem **19** could give, on reductive elimination of the tetrazolylthio group, an exomethylene compound, **20**, as a possible versatile intermediate for the synthesis of various 1-carbacephems, just as was the case with the 1-oxa counterpart.[13] Having the key intermediate **5** in hand, we therefore directed our attention to the preparation of **19** by applying a sequence of reactions developed in 1-oxacephem syntheses.

As shown in Chart 2, the conversion of the intermediate **5** into **19** was carried out in the same manner as in the "1-oxa" case, and **19** was obtained as a crystalline material. Thus, *meta*-chloroperbenzoic acid oxidation of **5** gave the epoxides **21** as a mixture of diastereoisomers, and these were treated with tetrazolethiol **22** in the presence of a catalytic amount of *n*-BuLi. The resulting alcohols were oxidized with Jones' reagent to the ketone **23**. Conversion of **23** into the phosphorane **26** was achieved by a three-step reaction sequence involving ozonization-reduction to the alcohols **24**, chlorination to the chlorides **25** and treatment with triphenylphosphine to give the ylide **26**. Finally, intramolecular Wittig reaction in refluxing dioxane gave the 1-carbacephem **19**. Side-chain cleavage by the usual method afforded the amine **27**. The synthesis of this compound by a different approach has previously been reported.[3] Acylation of **27** with the appropriately protected side-chain components **28** and **33** provided the amides **29** and **34** which in turn were deprotected with aluminum trichloride and anisole, giving the antibiotics **30** and **35** ((±)-1-carba SCE-1365), respectively, in good overall yields. This convenient deblocking technique developed recently in our laboratories[14] allowed us to use the otherwise inapplicable benzyl group for protection of the carboxylic acid. A ureido derivative **32** ((±)-1-carbadehydroxycefoperazone) was also prepared from **30** using **31**.

9) W.E. Wick and D.A. Preston, *Antimicrob. Agents. Chemother.*, **1**, 224 (1972).
10) B. Shimizu, M. Kaneko, M. Kimura, and S. Sugawara, *Chem. Pharm. Bull.*, **24**, 2629 (1976).
11) Toyama Chemical Co., U.S. Patent 4087424 (May 2, 1978).
12) M. Ochiai, O. Aoki, A. Morimoto, T. Okada, and Y. Matsushita, *Chem. Pharm. Bull.*, **25**, 3115 (1977).
13) Y. Hamashima, S. Yamamoto, T. Kubota, K. Tokura, K. Ishikura, K. Minami, F. Matsubara, M. Yamaguchi, I. Kikkawa, and W. Nagata, *Tetrahedron Lett.*, **1979**, 4947.
14) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, **1979**, 2793.

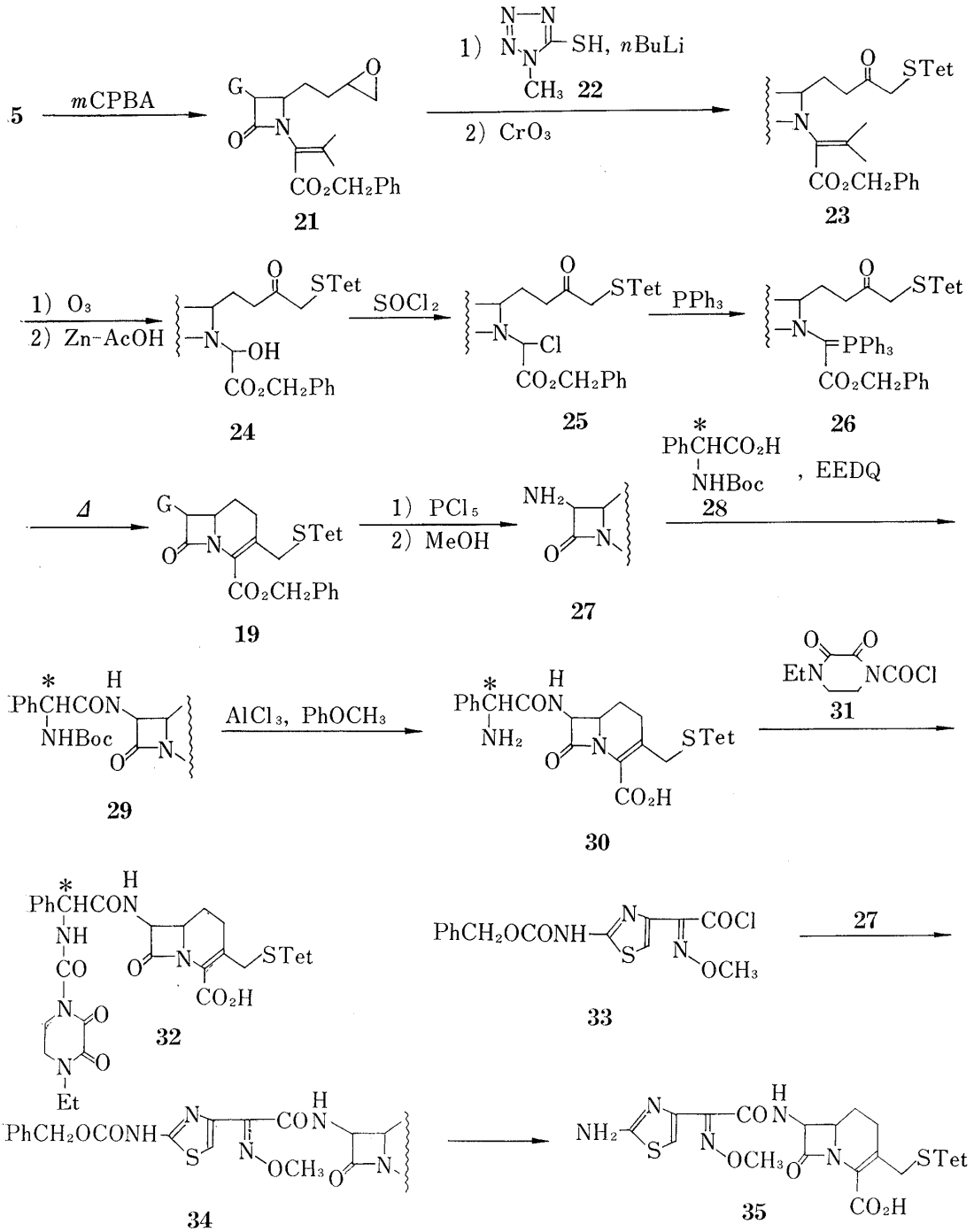


Chart 2

3-Methyl-1-carbacephems——On reduction with magnesium and acetic acid,[15] the 3-tetrazolylthiomethyl derivative **19** was successfully converted into the exomethylene compound **20**, which could be separated by crystallization from the contaminating 3-methyl-1-carbacephem **36**. On treatment with triethylamine, **20** was isomerized to **36**, which was deprotected to give the acid **37**. Removal of the phenylacetyl side-chain to give the amine **38** followed by acylation and deprotection afforded the antibiotic **39**. The amine **38** has been synthesized by a completely different approach.[4]

15) M. Narisada and F. Watanabe, unpublished result.

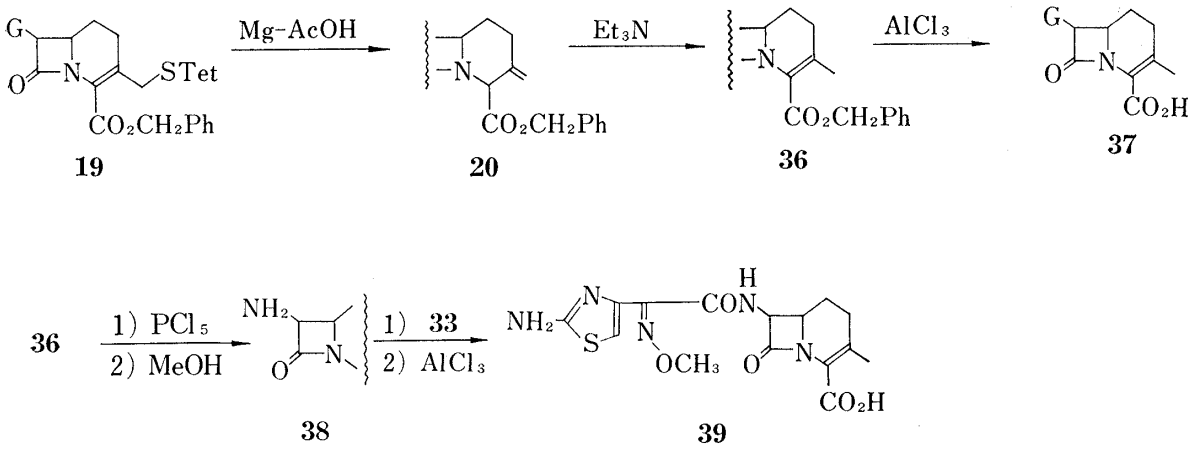


Chart 3

3-Methoxy-1-carbacephems——3′-Nor-type cephalosporins, in which C_3 of cephalosporins is unsubstituted or directly substituted with halogen, hydroxy, methoxy, *etc.*, as well as the corresponding 1-oxa congeners, have attracted much interest. Two orally active cephalosporins, cefachlor **40**[16] and CGP-9000 **41**,[17] are recent representatives of this family. As demonstrated in the cephem[18] and 1-oxacephem series,[13] it should be possible to obtain

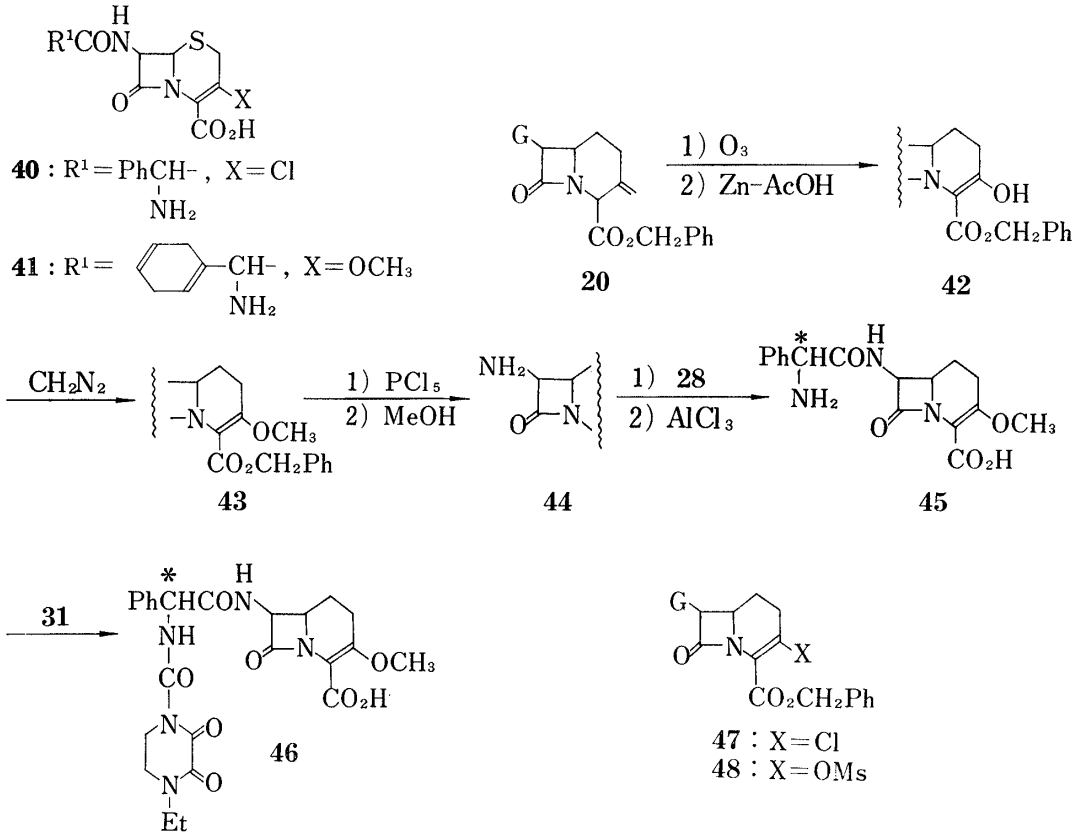


Chart 4

16) R.R. Chauvett and P.A. Pennington, *J. Med. Chem.*, **18**, 403 (1975).
17) *a*) R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, **57**, 1919 (1974); *b*) R. Scartazzini, P. Schneider, and H. Bickel, *ibid.*, **58**, 2437 (1975).
18) S. Kukolja, in "Recent Advances in the Chemistry of β-Lactam Antibiotics," ed. by J. Elks, The Chemical Society, 1977, p. 181.

3′-nor-type 1-carbacephem from the exomethylene compound **20**. However, we could prepare only the methoxy derivative **43** *via* this intermediate **20** because of the unexpected instability of 3-hydroxy-1-carbacephem **42**. Ozonolysis of the exomethylene compound **20** followed by zinc-acetic acid reduction gave a very unstable 3-hydroxy derivative **42** which could be isolated on trapping with diazomethane as the methyl ether **43**. Attempted conversion of **42** into the chloride **47** or mesylate **48** under various conditions was unsuccessful. From the 3-methoxy derivative **43**, compounds **45** and **46** were prepared as described for the preparation of **30** and **32**.

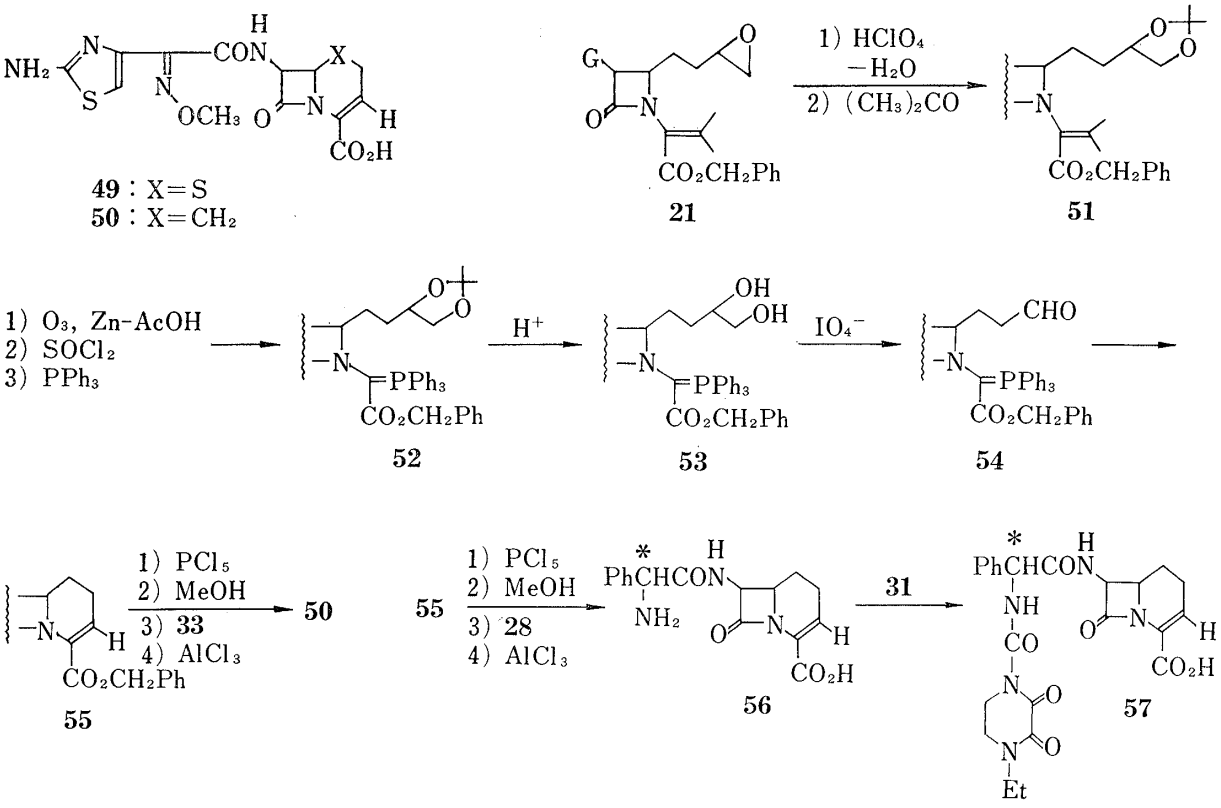


Chart 5

3-Hydrogen-1-carbacephems——The recent development of ceftizoxime **49**[19] led us to prepare its 1-carba congener **50**. Since the 3-chloro or 3-mesyloxy derivatives **47** or **48** were not available we had to apply a different approach[13,20] to the preparation of **50** starting from the epoxides **21**, as shown in Chart 5. The epoxides **21** were transformed to glycol-acetonides **51** and then to phosphoranes **52**. Acidic hydrolysis of the acetonide and subsequent glycol cleavage with metaperiodic acid gave the aldehyde **54** which cyclized spontaneously at room temperature while washing the reaction mixture with aqueous sodium bicarbonate solution, giving 1-carbacephem **55**. (±)-1-Carba ceftizoxime **50** was prepared from **55** in three steps. The phenylglycine derivatives **56** and **57** were also prepared.

7α-Methoxy-1-carbacephems——The 7α-methoxy-1-oxacephem antibiotic 6059-S **20**, discovered recently in our laboratories, has been shown to possess potent antibacterial activity against Gram-negative microorganisms, including resistant strains and *Pseudomonas* species.[4,21]

19) Fujisawa Pharmaceutical Co., Japan Patent Kokai 78-137988.
20) H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, **1979**, 3867.
21) H.C. Neu, N. Aswapokee, K.P. Fu, and P. Aswapokee, *Antimicrob. Agents Chemother.*, **16**, 141 (1979).

In connection with this antibiotic, the preparation of (±)-1-carba 6059-S **58** was clearly of interest, and was carried out as follows. The 7β-amino derivative **27** was first converted into the 7α-methoxy-7β-amino derivative **62** by means of a sequence of reactions developed by the Sankyo group.[22] Thus the amine **27** was treated with the aldehyde **59** and the resulting imine was oxidized with nickel peroxide[23] to give **60** which, on addition of methanol, was transformed into the methoxy derivative **61**. Mild hydrolysis with Girard's "T" reagent afforded the methoxy-amine **62**. Acylation with **63** in the presence of phosphorous oxychloride to give **64** followed by deprotection afforded the desired compound **58**.

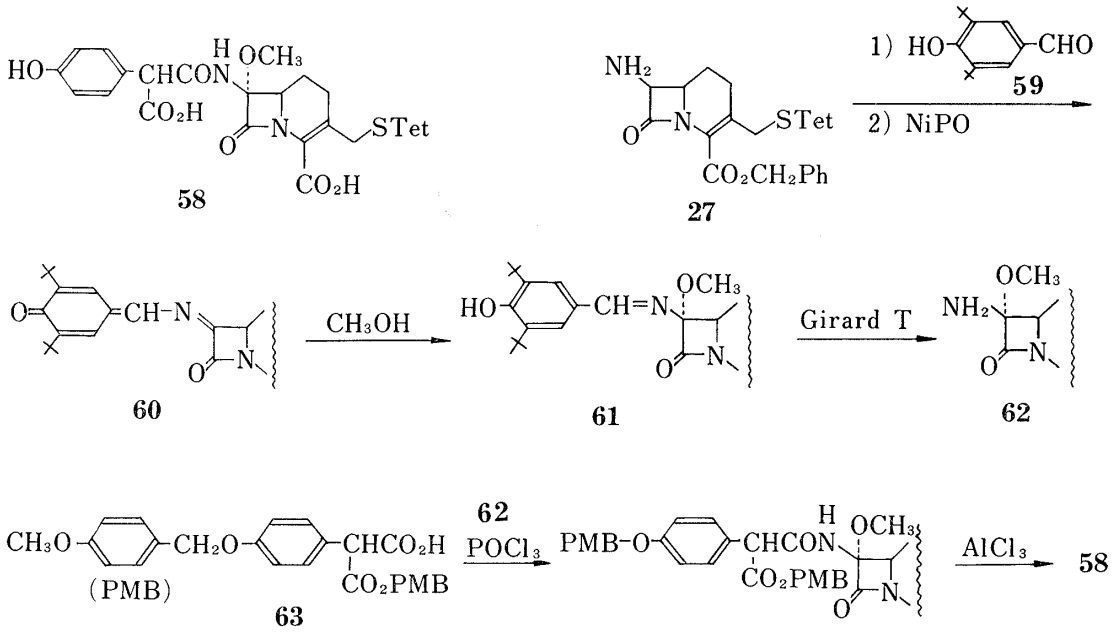
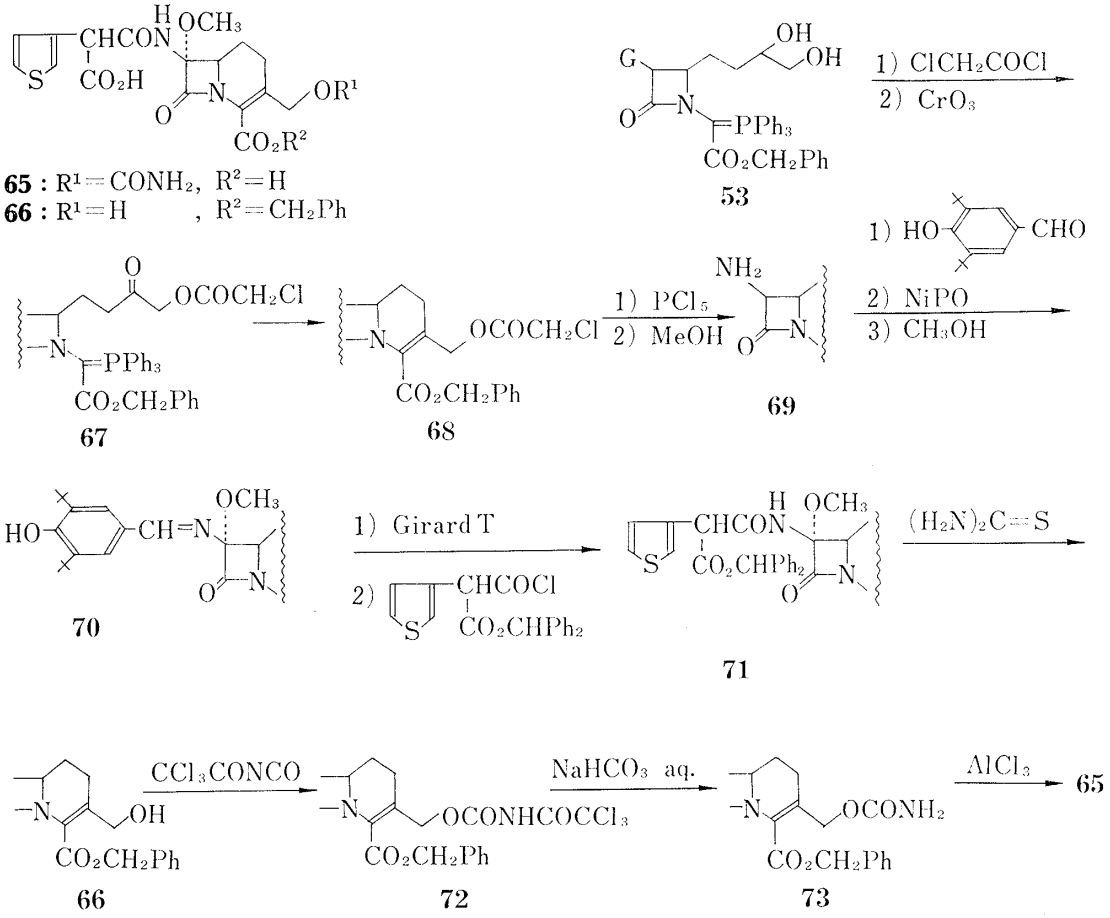


Chart 6

Finally, a 7α-methoxy-3-carbamoyloxymethyl derivative **65** was synthesized, although by a rather lengthy route, as outlined in Chart 7. A synthesis of this compound **65** has been filed in a patent,[24] but neither experimental details nor characterizing data for identification were described. Some difficulties were anticipated in preparing the 3-carbamoyloxymethyl derivative **65**, because a 3-hydroxymethyl derivative **66**, the preferred intermediate, was presumed to be very unstable; it should be generated from its protected form under very mild conditions, otherwise lactone formation or double bond migration to Δ^2 would be expected. With this limitation in mind, we selected the chloroacetyl protective group for this purpose, because this protective group seemed to remain intact through the sequence of reactions but still could be removed on mild treatment with thiourea. In fact, as shown in Chart 7, the desired hydroxymethyl derivative **66** was prepared as planned starting from the glycol-ylides **53**. Partial chloroacetylation of **53** followed by Jones' oxidation yielded the keto-ylide **67** which was cyclized to the 1-carbacephem **68** on heating. The corresponding 7β-amine **69** was converted into the 7α-methoxy derivative **70** and then into a 3-thienylmalonyl derivative **71**. Removal of the chloroacetyl group with thiourea in methanol worked well, giving the hydroxymethyl derivative **66**. Carbamoylation was successfully carried out by a two-step sequence involving treatment with trichloroacetyl isocyanate to give **72** and subsequent partial hydrolysis to provide the carbamoyloxy derivative **73**. The remaining two ester groups were then removed to give **65**.

22) H. Yanagisawa, M. Fukushima, A. Ando, and H. Nakano, *Tetrahedron Lett.*, **1975**, 2705.
23) See Ref. 5*b* footnote 14.
24) Merck and Co., Japan Patent Kokai, 73-133594.



53 67 68 69 70 71 66 72 73 65

Chart 7

TABLE I. Antibacterial Activities of 1-Carbacephem Derivatives

Structure R¹	R²	R³		Minimum inhibitory concentrations (μg/ml)[a] *Staph. aureus* 209P JC-1	*Strep. pyogenes* C-203	*E. coli* NIHJ JC-2	*Kreb. pneumoniae* SRL-1	*Proteus mirabilis* PR-4	*Proteus vulgaris* CN-329
PhCH(NH₂)–	-H	-CH_2STet	**30**	6.3	0.8	1.6	1.6	6.3	12.5
		-OCH_3	**45**	50	25	50	50	100	>100
		-H	**56**	25	3.1	25	12.5	25	100
PhCH(HNCONNEt(=O)=O)–	-H	-CH_2STet	**32**	12.5	0.8	0.8	0.8	12.5	12.5
		-OCH_3	**46**	25	25	6.3	1.6	6.3	12.5
		-H	**57**	12.5	1.6	3.1	0.8	6.3	12.5
H_2N-(2-thiazolyl)-C(=N-OCH_3)–	-H	-CH_2STet	**35**	12.5	0.4	0.05	0.05	0.1	0.2
		-CH_3	**39**	>100	3.1	6.3	6.3	6.3	12.5
		-H	**50**	25	0.05	0.05	0.01	0.02	0.05
$PhCH_2$–	-H	-CH_3	**37**	6.3	3.1	>100	100	>100	>100
HO-(4-hydroxyphenyl)-CH(-CO_2H)–	-OCH_3	-CH_2STet	**58**	>100	>50	6.3	3.1	6.3	6.3
(2-thienyl)-CH(-CO_2H)–	-OCH_3	-CH_2OCONH_2	**65**	>100	>50	25	25	50	50
Cefazolin				0.1	0.1	1.6	1.6	3.1	100.0

a) Minimum inhibitory concentrations were determined by the agar dilution method.

2. Biological Results

The above 1-carbacephem derivatives were tested *in vitro* against several strains of Gram-positive and Gram-negative bacteria, and the results are shown in the table. Among twelve derivatives tested, **50** showed the highest antibacterial activity; however, its activity was less than that of the 1-thia congener **49**. In conclusion, no 1-carbacephems prepared here surpassed the 1-thia and 1-oxa congeners in biological activity.

Experimental

All reactions were carried out under a nitrogen atmosphere using dry solvents under anhydrous conditions unless otherwise stated. Melting points were determined on a Yanagimoto apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Hitachi EPI-G3 instrument in $CHCl_3$ unless otherwise noted. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60A spectrometer for proton NMR and a Varian NV-14 spectrometer for ^{13}C NMR in $CDCl_3$, with TMS as an internal standard. Rotations were determined on a Perkin-Elmer 141 spectrometer in $CHCl_3$. Mass spectra (MS) were obtained on Hitachi RUM8-GN and 6-E spectrometers. Medium pressure liquid chromatographies were performed on Merck "Lobar ®" pre-packed columns packed with LiChroprep® Si 60; size A (240—10 mm, 40—63 μm), size B (310—25 mm, 40—63 μm) and size C (440—37 mm, 63—125 μm).

(−)-Isodehydrovaline Benzyl Ester (9) Hydrochloride——A solution of penicillin-V β-sulfoxide benzyl ester (107 g) and trimethylphosphite (95 ml) in 500 ml of toluene was refluxed for 2 hr with a Dean-Stark trap filled with molecular sieves. After cooling, the solution was washed with water, dried ($MgSO_4$) and concentrated to give the crude thiazoline **7** (131 g) which was used directly for the next step.

A solution of crude **7** (*ca.* 50 g) in 300 ml of MeOH containing 15 ml of 0.5 N hydrochloric acid was refluxed for 15 min and poured into ice-water. The product was extracted with CH_2Cl_2, washed with brine and dried ($MgSO_4$). Removal of the solvent, first with a rotary evaporator and then with a vacuum pump, gave the crude oily product **8** (*ca.* 48 g), NMR δ: 1.83 (3H, d, J=*ca.* 1 Hz), 5.1—5.2 (3H, m, $-NHC\underline{H}(CO_2-)-$ and olefinics), 5.27 (2H, s, $CO_2C\underline{H}_2Ph$), 5.37 (2H, s, $C\underline{H}_2OPh$), 6.9—7.5 (10H, m, aromatics), 8.07 (1H, br d, J=*ca.* 8 Hz), 8.17 (1H, s, $C{=}C\underline{H}{-}S$).

PCl_5 (45 g) was added in portions to a solution of the above crude product **8** in 300 ml of CH_2Cl_2 at room temperature, and the mixture was stirred for 2 hr. The dark-red solution was cooled to *ca.* −40°, and added dropwise with vigorous stirring into 300 ml of MeOH cooled in a dry ice-acetone bath. The mixture was stirred for 2 hr at room temperature and poured into ice-water. After vigorous shaking, the aqueous phase was separated, washed with CH_2Cl_2 and concentrated to give a crystalline residue. The crystalline material was collected and washed with CH_2Cl_2–ether mixture to afford **9**·HCl (*ca.* 10 g) as white crystals, mp 160—167°; this material was used for the next reaction. Recrystallization from CH_2Cl_2–MeOH gave a pure sample, mp 166—168° (dec.); $[\alpha]_D^{25}$ −44.0±0.8 (c=1.052, MeOH). IR (KBr): 3440 (br w), 3000—2830 (br s), 2700 (m), 2630 (m), 1748 (s), 1585 (m), 1510 (br m), 1500 (m) cm^{-1}. NMR (CD_3OD) δ: 1.82 (3H, d, J=*ca.* 1 Hz), 4.68 (1H, s, $NC\underline{H}(CO_2-)-$), 4.4—5.6 (7H, m), 7.08 (5H, s, aromatics). *Anal.* Calcd for $C_{12}H_{16}ClO_2N\cdot 1/4H_2O$ (246.22): C, 58.54; H, 6.75; N, 5.69. Found: C, 58.77; H, 6.71; N, 5.90.

Benzyl 2-(3β-Phenylacetylamino-4β-but-3-enyl)-2-oxoazetidin-1-yl-3-methylbut-2-enoate (5)——(−)-Isodehydrovaline benzyl ester hydrochloride (7.26 g, 0.03 mol) was dissolved in a minimal amount of water. The solution was made basic with saturated aqueous $NaHCO_3$, and the free amine **9** was extracted three times with 150 ml each of CH_2Cl_2. To the combined CH_2Cl_2 solution were added 4-pentenal (3.1 ml, 0.0315 mol) and anhydrous $MgSO_4$ (10 g), and the mixture was stirred at room temperature for 15 min then filtered. Molecular sieves (4A) (10 g) were added to the filtrate and the mixture was stirred for 30 min in an ice-bath and cooled to −78° in a dry ice-acetone bath. Et_3N (7.1 ml, 1.7 eq) was added, then a solution of azidoacetyl chloride (4.8 ml, 1.5 equiv) in 15 ml of CH_2Cl_2 was added dropwise over a period of 30 min. The reaction mixture was allowed to stand overnight under ice-cooling, giving the crude azidoazetidinones **11a, b**. The mixture was treated with Et_3N (8.4 ml) at room temperature for 2 hr and filtered to remove molecular sieves and some insoluble material. The filtrate was washed with water (300 ml×3) and brine, dried ($MgSO_4$) and concentrated. The residue was dissolved in 500 ml of ether and treated with 20 g of charcoal. Removal of the ether by evaporation left crude **12** (10 g) as a red-brown oil. IR: 2110 (s), 1765 (s), 1750 (sh, s) cm^{-1}.

A solution of the above crude azidoazetidinone **12** (6.1 g, 16.4 mmol) in 60 ml of CH_2Cl_2 was added to a mixture of Zn powder (8.5 g) and acetic acid (8.5 ml) in 100 ml of CH_2Cl_2 with vigorous agitation under ice-cooling, and the mixture was stirred until no further evolution of gas could be seen (30 min). The reaction mixture was filtered, washed with water (100 ml×3), dried ($MgSO_4$) and filtered, giving a solution of the amine **13**.

Pyridine (1.98 ml, 1.5 eq) and phenylacetylchloride (2.63 ml, 1.2 eq) were added to the filtrate with stirring under ice-cooling. After 10 min of stirring, the mixture was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on 200 g of silica gel (Merck) with benzene and benzene–EtOAc mixtures as eluting solvents. The desired compound **5** (2.3 g, 28% overall

from **9**) was obtained by eluting the column with benzene–EtOAc (1: 1) and crystallizing the product from ether. Recrystallization from ether gave a pure material, mp 140—142°; $[\alpha]_D^{26}$ −2.2±0.4 (c=1.015%); IR: 1775 (s), 1720 (s), 1680 (s) cm^{-1}. NMR δ: 0.7—2.0 (4H, br m), 1.92 (3H, s), 2.22 (3H, s), 3.55 (2H, s, PhC$\underline{H}_2$CONH–), 3.97 (1H, br q, J=5 Hz, β-lactam), 4.6—6.0 (3H, m, olefinics), 5.11 (1H, dd, J=5 and 8 Hz, β-lactam), 5.18 (2H, s, –$CO_2C\underline{H}_2$Ph), 6.55 (1H, br d, J=8 Hz, –CON$\underline{H}$–), 7.28 and 7.35 (10H, two s, aromatics); ^{13}C NMR δ: 21.7 and 23.6 (isopropyridene $CH_3\times2$), 28.3 and 29.2 (butenyl $CH_2\times2$), 43.2 (amide CH_2), 57.7 and 60.5 (β-lactam CH×2), 66.9 (ester CH_2), 115.4 (butenyl=CH_2), 120.4 (quaternary, α-position to ester), 127.3, 128.4, 128.7, 128.9, and 129.2 (aromatic tertiary), 134.7 and 135.5 (aromatic quaternary), 137.0 (butenyl CH=), 153.9 (isopropyridene quaternary), 163.1 (amide C=O), 166.7 (ester C=O), 171.6 (β-lactam C=O) ppm. *Anal.* Calcd for $C_{27}H_{30}N_2O_4$ (446.56): C, 72.62; H, 6.77; O, 14.33; N, 6.27. Found: C, 72.63; H, 6.80; O, 14.63; N, 6.37.

Benzyl 2-[3β-Phenylacetylamino-4β-(3,4-epoxy)butyl]-2-oxoazetidin-1-yl-3-methylbut-2-enoate (21)——A mixture of **5** (12.82 g, 28.7 mmol) and mCPBA (85% purity, 9.3 g, 1.5 eq) in 290 ml of CH_2Cl_2 was allowed to stand overnight at room temperature. The reaction mixture was washed with aqueous $NaHCO_3$ (several times) and brine, then dried ($MgSO_4$). Removal of the solvent by evaporation afforded the crude epoxides **21** (14 g). A small portion of the epoxides was chromatographed on a Lobar column (size A, benzene–EtOAc, 1: 1) and crystallized from CCl_4 to give a crystalline diastereoisomeric mixture (*ca.* 1: 1), mp 130—139°. IR: 3415 (w), 1755 (s), 1717 (s), 1682 (s) cm^{-1}. NMR δ: 0.6—3.0 (7H, m), 1.93 (3H, s), 2.20 (3H, s), 3.54 (2H, s, PhC$\underline{H}_2$CONH–), 3.7—4.2 (1H, m, β-lactam), 4.9—5.3 (1H, m, β-lactam), 5.18 (2H, s), 6.82 and 6.95 (1H, two br d, J=8 Hz, –CON$\underline{H}$–), 7.30 and 7.35 (10H, two s, aromatics). *Anal.* Calcd for $C_{27}H_{30}N_2O_5$ (462.56): C, 70.11; H, 6.56; O, 17.30; N, 6.06. Found: C, 69.90; H, 6.53; O, 17.27; N, 6.12.

Benzyl 2-{3β-Phenylacetylamino-4β-[4-(1-methyl-1*H*-tetrazol-5-yl)thio]-3-oxobutyl}-2-oxoazetidin-1-yl-3-methylbut-2-enoate (23)——A mixture of the crude epoxides **21** (13 g) and 1-methyl-1*H*-tetrazol-5-yl-thiol (**22**) (3.67 g, 1.1 eq) in 250 ml of THF was treated with 14.4 ml (0.3 eq) of a solution of *n*-BuLi in hexane (0.6 N), and the whole was stirred for 6 hr at room temperature. The mixture was concentrated under reduced pressure, extracted with EtOAc, washed with water and dried ($MgSO_4$). Removal of the solvent gave the crude hydroxy-esters (17.4 g) which were dissolved in 170 ml of acetone and treated with 26 ml of Jones' reagent (2.5 M solution) for 15 min at room temperature and then the excess reagent was quenched with 30 ml of MeOH. The product was taken up in EtOAc, washed with water, aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$). Removal of the solvent by evaporation and chromatography of the residue on a Lobar column (size C, benzene–EtOAc, 1: 2) gave **23** (11.8 g, 67% from **5**) as an amorphous solid, IR: 3420 (w), 1755 (s), 1700 (s), 1678 (s) cm^{-1}. NMR δ: 1.2—3.1 (4H, m), 1.92 (3H, s), 2.20 (3H, s), 3.56 (2H, s, PhC$\underline{H}_2$CONH–), 3.95 (3H, s, N–C$\underline{H}_3$), 3.9—4.4 (3H, m, β-lactam and –COC$\underline{H}_2$S–), 5.09 (1H, dd, J=5 and 7 Hz, β-lactam), 5.20 (2H, s, $CO_2C\underline{H}_2$Ph), 7.00 (1H, br d, J=7 Hz, CON$\underline{H}$), 7.28 and 7.36 (10H, two s).

Benzyl 7β-Phenylacetylamino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-carba-1-dethia-3-cephem-4-carboxylate (19)——Excess ozone was passed through a solution of **23** (11.08 g, 19.2 mmol) in 192 ml of CH_2Cl_2 cooled in a dry ice-acetone bath until the solution became blue. After removing excess ozone by passing dry nitrogen, the ozonization mixture was allowed to reach −20° and stirred vigorously with Zn powder (134 g) and 192 ml of acetic acid for 40 min while maintaining the reaction temperature between −25° and −15°. The reaction mixture was diluted with CH_2Cl_2, filtered, washed with water (×3) and brine, then dried ($MgSO_4$). Removal of the solvent gave the hydroxy esters **24** (10.89 g) having no absorption at 1825 cm^{-1} (characteristic α-keto-ester absorption) in the IR.

A solution of the above crude product **24** in 390 ml of CH_2Cl_2 was treated with $SOCl_2$ (2.09 ml, 1.5 eq) and pyridine (2.32 ml, 1.5 eq) under ice-cooling. After stirring for 30 min, the mixture was poured into ice-water and the product was extracted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated to approximately one-half the original volume.

Ph_3P (7.55 g, 1.5 equiv) was added to this solution containing the crude chlorides **25** and the mixture was refluxed for 1 hr. Removal of the solvent and chromatography of the residue on 250 g of silica gel (Merck, deactivated with 10% w/w H_2O) with benzene–EtOAc mixture (1: 1) as an eluting solvent gave the phosphorane **26** (8.81 g, 58% overall from **23**).

A solution of the above ylide **26** in 89 ml of dioxane was refluxed for 10 hr. Removal of the solvent by evaporation and chromatography of the residue on a Lobar column (size C, benzene–EtOAc, 1: 2) gave the 1-carbacephem **19** (3.45 g, 60%) as crystals. Recrystallization from CH_2Cl_2–ether gave pure material, mp 153—154°; $[\alpha]_D^{27}$ 0 (c=1.054%). IR: 3410 (w), 3320 (br w), 3100—2900 (br w), 1775 (sh s), 1770 (s), 1720 (m), 1680 (m) cm^{-1}. NMR δ: 1.0—2.7 (4H, m) 3.56, (2H, s, PhC$\underline{H}_2$CONH–), 3.87 (3H, s), 3.4—3.9 (1H, m, β-lactam), 4.13 and 4.58 (2H, AB-q, J=13.5 Hz, –C$\underline{H}_2$S–), 5.32 (1H, dd, J=5 and 7 Hz), 6.86 (1H, br d, J=7Hz, β-lactam), 7.1—7.6 (10H, m, aromatics). MS: 518 (M^+), 427 [M^+−91 (PhCH·)], 403 [M^+−115 (·S-Tet)], 402 [M^+−116 (HS-Tet)]. *Anal.* Calcd for $C_{26}H_{26}N_6O_4S$ (518.61): C, 60.22; H, 5.05; N, 16.21; S, 6.18. Found: C, 60.33; H, 4.93; N, 16.12; S, 6.34.

Benzyl 7β-[2-(2-Benzyloxycarbonylamino)thiazole-4-yl-2-(Z)-methoxyimino]acetylamino-3-(1-methyl-1*H*-tetrazole-5-yl)thiomethyl-1-carba-1-dethia-3-cephem-4-carboxylate (34)——A stirred solution of the amide **19** (1.56 g, 3 mmol) in 30 ml of CH_2Cl_2 was treated with PCl_5 (1.25 g, 2 eq) and pyridine (0.73 ml, 3 eq) at −25°. The mixture was allowed to reach room temperature over 30 min while the PCl_5 dissolved

completely. The solution was then cooled to −30° and 15 ml of MeOH was added with vigorous stirring. Stirring was continued for 20 min at the same temperature and for a few min at room temperature. The reaction mixture was cooled to −20° and 15 ml of water was added. After stirring for 10 min at −20° then for 30 min at room temperature, organic solvents were removed on a rotary evaporator, keeping the temperature below 10°. The product was extracted with CH_2Cl_2 (×3), washed with aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent afforded an oily residue which was triturated with ether to give almost pure amine **27** (1.2 g) as a pale yellow powder, NMR δ: 1.0—2.7 (4H, m), 3.80 (3H, s), 4.28 (2H, AB-q, J=13 Hz, $-C\underline{H}_2S-$), 5.22 (2H, br s, $CO_2C\underline{H}_2Ph$), 7.0—7.7 (10H, m).

A solution of PCl_5 (33 mg, 1.5 eq) in 0.5 ml of CH_2Cl_2 and pyridine (27 μl, 3 eq) were added to a solution of 2-(2-benzyloxycarbonylamino)thiazol-4-yl-2-(Z)-methoxyiminoacetic acid (56.4 mg, 1.5 eq) in 1 ml of THF under ice-cooling, and stirring was continued for 1 hr. The mixture was evaporated to dryness, 2 ml of benzene was added to the residue, and the whole was again evaporated to dryness. This procedure was repeated twice.

The acid chloride **33** thus obtained was dissolved in a mixture of 1 ml of THF and 0.5 ml of CH_2Cl_2 and added to a solution of the amine **27** (45 mg, 0.11 mmol) in 0.5 ml of CH_2Cl_2 at 0°. After stirring for 35 min at 0°, the reaction mixture was poured into ice-water. The product was extracted with CH_2Cl_2, washed successively with diluted hydrochloric acid, water, aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size A, benzene–EtOAc, 1: 2) gave the amide **34** (62 mg, 77%) as an amorphous solid, NMR δ: 1.0—2.8 (4H, m), 3.85 (6H, s, $N-C\underline{H}_3$ and $O-C\underline{H}_3$), 3.9—4.7 (3H, m, $-CH_2S-$ and β-lactam) 5.0—5.5 (4H, m, two $PhC\underline{H}_2O-$), 5.68 (1H, dd, J=5 and 8 Hz, β-lactam), 7.00 (1H, s, $-S-C\underline{H}=$), 7.35 (10H, s), 8.37 (1H, br d, J=8 Hz).

7β-[2-(2-Amino)thiazol-4-yl-2-(*Z*)-methoxyimino]acetylamino-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-carba-1-dethia-3-cephem-4-carboxylic Acid (35)——A solution of the amide **34** (62 mg, 0.086 mmol) in 1.5 ml of anisole was treated with $AlCl_3$ (115 mg, 10 eq) at 0° and the mixture was stirred for 1.5 hr at 0°. A solution of $NaHCO_3$ (0.45 g) in 5 ml of water and 10 ml of EtOAc were added to the reaction mixture and the whole was stirred vigorously at room temperature then filtered to remove some insoluble material. The aqueous layer of the filtrate was acidified with 10% hydrochloric acid to pH 1, and the product was extracted once with EtOAc and three times with methyl ethyl ketone. The methyl ethyl ketone extracts were dried ($MgSO_4$) and concentrated to give the target compound **35** (32 mg 76%) as a light yellow powder, IR (KBr): 3650—2700 (br s), 1755 (s), 1720 (sh s), 1670 (s), 1630 (s) cm^{-1}. **35** does not dissolve in NMR solvents sufficiently to show measurable signals.

7β-[(2*R*)-2-Phenyl-2-amino]acetylamino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylic Acid (30)——A mixture of the amine **27** (149 mg, 0.289 mmol), N-Boc-phenylglycine (110 mg, 2 equiv) and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (107 mg, 2 eq) in 3 ml of THF was allowed to stand overnight. Removal of the solvent and chromatography of the residue on a Lobar column (size A, benzene–EtOAc, 1: 1) gave the amido-ester **29** (171 mg, 93% from 27) as an amorphous solid. IR: 3425 (w), 1780 (s), 1770 (s), 1724 (s), 1712 (s), 1695 (s), 1685 (sh s) cm^{-1}. NMR δ: 1.1—2.6 (4H, m), 1.38 (9H, s, $-C_4H_9$), 3.5—3.9 (1H, m, β-lactam), 3.84 (3H, s, $-NCH_3$), 4.06 and 4.64 (4H, AB-q, J=13 Hz, $-CH_2S-$), 4.9—5.4 (1H, m, β-lactam), 5.22 (br s, $CO_2C\underline{H}_2Ph$), 5.73 (1H, br d, J=7 Hz, $PhC\underline{H}(NH-)CO-$), 7.22 (5H, s, aromatics), 7.33 (5H, br s, aromatics), 7.54 (1H, br d, J=8 Hz, $-NH-$). MS: 518 [M^+ (633) −115 (·STet)], 461 [M^+-172 ($-STet+\cdot C_4H_9$)], 417 [M^+-216 ($\cdot STet+\cdot CO_2C_4H_9$)]. *Anal.* Calcd for $C_{31}H_{35}N_7O_6S$ (633.74): C, 58.75; H, 5.57; N, 15.47; S, 5.06. Found: C, 58.76; H, 5.54; N, 15.14; S, 5.29.

A mixture of the amido-ester **29** (380 mg, 0.60 mmol) and $AlCl_3$ (0.80 g, 10 eq) in 6 ml of anisole and 1 ml of nitromethane was stirred for 3.5 hr under ice-cooling. To the resulting mixture, 15 ml of 10% hydrochloric acid and 15 ml of CH_2Cl_2 were added. The aqueous phase was separated after vigorous stirring, washed with CH_2Cl_2 (×2) and passed through a column packed with 6 g of HP-20 (highly porous polymer, Mitsubishi Daiya-ion HP-20). Elution with MeOH–H_2O (1: 1) and removal of the solvent *in vacuo* gave the target compound **30** (234 mg, 88%) as a light yellow powder. IR (KBr): 3420 (br s), 3040 (br m), 2940 (br m), 1760 (s), 1690 (m) cm^{-1}; NMR (DMSO-d_6/D_2O) δ: 1.0—2.8 (4H, m), 3.48 and 3.73 (1H, assigned to a part of the AB-quartet due to $-CH_2S-$, J=15 Hz), 3.96 (3H, s, $N-CH_3$), 5.03 (1H, br s, $PhC\underline{H}(NH_2)CO-$), 5.19 (1H, d, J=5 Hz, β-lactam), 7.51 (5H, s, aromatics).

7β-[2(*R*)-2-Phenyl-2-(4-ethyl-2,3-dioxopiperazin-1-yl-carbonyl)amino]acetylamino-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-carba-1-dethia-3-cephem-4-carboxylic Acid (32)——A mixture of 4-ethyl-2,3-dioxopiperazin-1-yl-carbonyl chloride **31** (102 mg, 2 eq), the amino-acid **30** (111 mg, 0.25 mmol), 1 ml of propylene oxide and 0.5 ml of bistrimethylsilylacetamide (BSA) in 2.5 ml of acetonitrile was stirred for 25 min under ice-cooling. The solvent and the excess reagents were evaporated off, and the residue was rinsed with EtOAc to give the target compound **32** (137 mg, 90%) as a pale yellow solid, NMR (CD_3OD) δ: 1.15 (3H, br t, J=7 Hz, $C\underline{H}_3CH_2-$), 1.5—2.8 (4H, m), 3.3—4.4 (9H, m, $-C\underline{H}_2-S-$, β-lactam, $-NCH_2CH_2-N-$, and $-C\underline{H}_2CH_3$), 3.64 (3H, s, $N-CH_3$), 5.23 (1H, br d, J=5 Hz, β-lactam), 5.46 (1H, br s, $PhC\underline{H}(NH-)CO-$), 7.4 (5H, br s).

Benzyl 7β-Phenylacetylamino-3-methyl-1-carba-1-dethia-3-cephem-4-carboxylate (36)——Mg powder (322 mg, 15 eq) was added in portions to a stirred solution of **19** (450 mg, 0.868 mmol) in 8.7 ml of CH_2Cl_2 and 5 ml of acetic acid during a period of 5 hr while the reaction temperature was maintained between 10°

and 20°. The resulting mixture was diluted with 50 ml of EtOAc, washed with aqueous $NaHCO_3$ (×2), water and brine, and then dried ($MgSO_4$). Removal of the solvent gave 363 mg of a solid which was crystallized from CH_2Cl_2–ether to afford 3-exomethylene **20** (135 mg). Recrystallization from the same solvent mixture gave pure **20**, mp 144—145°; IR: 3430 (w), 3310 (w), 1760 (br s), 1680 (s) cm^{-1}. NMR δ: 1.0—2.5 (4H, m), 3.58 (2H, s, $PhC\underline{H}_2CONH$–), 3.8—4.3 (1H, m, β-lactam), 4.9—5.3 (5H, m, $C{=}C\underline{H}_2$, $CO_2C\underline{H}_2Ph$ and β-lactam), 7.29 and 7.38 (10H, two s). NMR of the mother liquid showed the presence of **20** and the 3-methyl derivative **36**.

A solution of the mother liquid residue (210 mg) in 0.6 ml of $CDCl_3$ and 0.2 ml of Et_3N was placed in an NMR tube. The isomerization reaction (**20** to **36**) was monitored by taking NMR spectra. After standing for approximately 2.5 hr at room temperature, the solvent was evaporated off and the residue was chromatographed on a Lobar column (size A, benzene–EtOAc, 2: 1) to give **36** (159 mg). Recrystallization from CH_2Cl_2–ether mixture gave the pure material, mp 180—182°; IR: 1760 (s), 1720 (s), 1673 (s) cm^{-1}. NMR ($CDCl_3$–CD_3OD, 3: 1) δ: 1.2—2.5 (4H, m), 1.88 (3H, s), 3.58 (2H, s, $PhC\underline{H}_2CONH$–), 3.6—4.0 (1H, m, β-lactam), 5.25 (2H, s, $-CO_2C\underline{H}_2Ph$), 5.33 (1H, d, J=4.5 Hz, β-jactam), 7.30 and 7.35 (11H, two s, aromatics and $-CON\underline{H}$–); MS: 404 (M^+), 313 [M^+−91 ($PhCH_2\cdot$)], 285 [M^+−119 ($PhCH_2CO\cdot$)], 241 [M^+−163 ($PhCH_2CO_2\cdot$+CO)], 230 [M^++1—175 ($PhCH_2CONHCH{=}CO$)]. *Anal.* Calcd for $C_{24}H_{24}N_2O_4$ (404.48): C, 71.27; H, 5.98; N, 6.93. Found: C, 71.47; H, 5.93; N, 6.97.

7β-[2-(2-Amino)thiazol-4-yl-2-(*Z*)-methoxyimino]acetylamino-3-methyl-1-carba-1-dethia-3-cephem-4-carboxylic Acid (31)——Using a procedure similar to that described for **27**, the amide **36** (175 mg, 0.432 mmol) was converted into the amine **38** (110 mg, 89%). NMR δ: 1.1—2.5 (4H, m), 2.00 (3H, s), 3.4—3.9 (1H, m, β-lactam), 4.1—4.7 (1H, m, β-lactam), 5.20 (2H, s, $-CO_2C\underline{H}_2Ph$), 7.28 (5H, s, aromatics).

The amine **38** (110 mg, 0.384 mmol) was acylated with **33** and the product was purified by chromatography on a Lobar column (size A, benzene–EtOAc, 1: 1) to give the amino-ester (153 mg, 80%) as a pale yellow powder. IR: 1760 (s), 1730 (s), 1680 (s) cm^{-1}; NMR δ: 1.5—2.6 (4H, m), 2.06 (3H, s), 3.7—4.2 (1H, m, β-lactam), 3.95 (3H, s, $=NOCH_3$), 5.08 and 5.22 (2H, AB-q, J=13 Hz, $PhC\underline{H}_2OCO$–), 5.30 (2H, br s, $CH_2C\underline{H}_2Ph$), 7.30 (10H, s), 8.53 (1H, d, J=8.5 Hz, CONH–); MS: 496 (M^+ (603) −107 ($PhCH_2O\cdot$)], 464, 404 [M^+−199 ($PhCH_2OH+PhCH_2\cdot$)].

Treatment of the amido-ester (150 mg, 0.249 mmol) with $AlCl_3$ in anisole as described for **30** gave the target compound **39** (56 mg, 59%) as an amorphous solid, IR (KBr): 3700—2700 (br s), 1753 (s), 1647 (br s) cm^{-1}. NMR (CD_3OD) δ: 0.8—2.7 (4H, m), 2.05 (3H, s), 3.97 (3H, s, $=NOC\underline{H}_3$, overlapped with a peak assigned to a β-lactam proton), 5.50 (1H, br d, J=4 Hz, β-lactam), 6.86 (1H, s, S–C$\underline{H}$=).

Benzyl 7β-Phenylacetylamino-3-methoxy-1-carba-1-dethia-3-cephem-4-carboxylate (43)——Excess ozone was passed through a solution of crude **20** (357 mg, contaminated with approximately 33% of **36**) in 7 ml of CH_2Cl_2 and 3 ml of MeOH at −78° until a blue color persisted. After removing excess ozone with dry nitrogen, the ozonide in the same solvent was treated with Zn powder (0.5 g) and 5 ml of acetic acid at 0° for 10 min. The filtered reaction mixture was concentrated *in vacuo* and the residue was diluted with a mixture of EtOAc and CH_2Cl_2 (1: 1), washed with water (×2) and brine, then dried ($MgSO_4$). Excess diazomethane in ether was added under ice-cooling and the mixture was allowed to stand at room temperature for 3 hr. Removal of the solvent and crystallization of the residue from CH_2Cl_2–ether afforded the methoxy derivative **43** (188 mg), mp 175—180° (dec.); NMR δ: 1.2—2.6 (4H, m), 3.5—4.0 (1H, m, β-lactam), 3.57 (2H, s, $PhC\underline{H}_2CONH$–), 3.73 (3H, s, $OC\underline{H}_3$), 5.18 (2H, s, $-CO_2C\underline{H}_2Ph$), 5.30 (1H, dd, J=5 and 8.5 Hz β-lactam), 7.10 (1H, br d, J=8.5 Hz, $-CON\underline{H}$–), 7.27 (5H, s, aromatics), centered at 7.3 (5H, aromatics); MS: 420 (M^+), 329 [M^+−91 ($PhCH_2\cdot$)], 301 [M^+−119 ($PhCH_2CO\cdot$)], 285 [M^+−135 ($PhCH_2CO_2\cdot$)], 257 [M^+−163 ($PhCH_2CO_2\cdot$+CO)], 246 [M^++1—157 ($PhCH_2CONHCH{=}CO$)].

7β-[(2*R*)-2-Phenyl-2-amino]acetylamino-3-methoxy-1-carba-1-dethia-3-cephem-4-carboxylic Acid (45)——Removal of the phenylacetyl moiety from the 3-methoxy derivative **43** (172 mg, 0.409 mmol) in the manner described for **27** gave **44** (114 mg, 92%) which, on acylation as described for **29**, afforded the 3-methoxy amido-ester (180 mg, 90%). NMR δ: 1.0—2.6 (4H, m), 1.43 (9H, s, *tert*-Bu), 3.63 and 3.73 (3H, two s, $-OC\underline{H}_3$), 5.0—5.6 (3H, m), 5.76 (1H, br d, J=7 Hz, $-N\underline{H}$–), 7.1—7.6 (11H, m, aromatics and $-N\underline{H}$–).

Deprotection of the amido-ester as described for **30** gave, after purification by HP-20 column chromatography, the target compound **45** (44 mg, 38%). IR (KBr): 3400 (br s), 3200 (br s), 3000 (br s), 2620 (m), 1745 (s), 1685 (s) cm^{-1}.

7β-[(2*R*)-2-Phenyl-2-(4-ethyl-2,3-dioxopiperazin-1-yl-carbonyl)amino]acetylamino-3-methoxy-1-carba-1-dethia-3-cephem-4-carboxylic Acid (46)——Treatment of the amino acid **45** (25 mg) with **31** as described for **32** gave the crude product (45 mg), which was rinsed with EtOAc and then with EtOAc–acetone to give the target compound **46** (15 mg) as a pale yellow powder. IR (KBr): 3325 (br s), 2975 (br s), 1750 (sh), 1720 (s), 1675 (br s) cm^{-1}.

Benzyl 2-{3β-Phenylacetylamino-4β-[2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]}-2-oxoazetidin-1-yl-3-methylbut-2-enoate (51)——A mixture of the crude epoxides **21** (2.10 g), 20 ml of acetone, 4.9 ml of water and 7.2 ml of 30% perchloric acid was stirred for 2.5 hr at room temperature. The product was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated to give crude diols (2.29 g), which were dissolved in 15 ml of acetone and stirred with 50 mg of *p*-toluenesulfonic acid at room temperature for 1 hr. The resulting mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, and then dried ($MgSO_4$). Removal

of the solvent and chromatography of the residue on a Lobar column (size B, benzene–EtOAc, 1: 2) afforded the acetonides **51** (1.99 g, 86% from **21**). IR: 1755 (s), 1717 (s), 1682 (s) cm^{-1}. NMR δ: 0.8—2.3 (4H, m), 1.33 (6H, s, acetonide methyls), 1.93 (3H, s), 2.21 (3H, s), 3.2—4.2 (4H, m), 3.52 and 3.55 (2H, two s, PhC$\underline{H}_2$-CONH–), 5.11 (1H, dd, J=5 and 8 Hz), 5.17 (2H, s, –$O_2C\underline{H}_2$Ph), 6.74 and 6.96 (1H, two br d, –CON$\underline{H}$–).

Benzyl 7β-Phenylacetylamino-1-carba-1-dethia-3-cephem-4-carboxylate (55)——The phosphorane **52** was prepared from **51** using the procedure described for **26**. Ozonolysis of the acetonides **51** (1.81 g, 3.47 mmol) in 35 ml of CH_2Cl_2 was followed by reduction with Zn (22.8 g) and acetic acid (35 ml), chlorination with $SOCl_2$ (0.36 ml) and pyridine (0.40 ml) in 70 ml of CH_2Cl_2 and phosphorane formation with Ph_3P (1.3 g), giving after chromatography on a Lobar column (size B, benzene–EtOAc, 1: 3 and EtOAc) the ylide **52** (1.58 g, 60% from **51**) as an amorphous solid. IR: 1750 (s), 1670 (s), 1620 (s) cm^{-1}. NMR δ: 1.32 (6H, br s, $CH_3\times2$), 3.51 (2H, br s, PhC$\underline{H}_2$CO–), 4.76 and 5.09 (2H, two br s, $CO_2C\underline{H}_2$Ph), 6.64 and 6.86 (1H, two br d, J=8 Hz and 6 Hz, CON$\underline{H}$–).

A stirred solution of the ylide **52** (978 mg, 1.29 mmol) in 21 ml of MeOH was treated with 3.9 ml of 10% hydrochloric acid at room temperature. After stirring for 1 hr, the reaction mixture was extracted with EtOAc, dried ($MgSO_4$) and concentrated to give the diols **53** (956 mg). A solution of $NaIO_4$ (329 mg) in 15.4 ml of 1 N H_2SO_4 was added to a solution of the above compounds **53** in 26 ml of THF under ice-cooling, and the mixture was allowed to reach room temperature over a period of 1 hr. The mixture was extracted with EtOAc, washed with cold water, aqueous $NaHCO_3$ and brine, and then dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size B, benzene–EtOAc, 1: 2) gave the target compound **55** (375 mg, 75% from **52**) as white crystals. Recrystallization from ether gave a pure sample, mp 147—150°; IR: 3420 (w), 3630 (w), 1770 (s), 1725 (m), 1680 (m) cm^{-1}. NMR δ: 0.9—2.2 (4H, m), 3.58 (2H, s), 3.5—4.0 (1H, m, β-lactam), 5.23 (2H, s, –$CO_2C\underline{H}_2$Ph), 5.38 (1H, dd, J=5 and 7 Hz), 6.43 (1H, br t, J=4 Hz, =C$\underline{H}$–CH_2–), 6.95 (1H, br d, J=7 Hz, –CON$\underline{H}$–), 7.31 and 7.38 (10H, two s, aromatics). MS: 390 (M^+), 362 [M^+-28 (CO)], 299 [M^+-91 ($PhCH_2\cdot$)], 271 [M^+-119 ($PhCH_2CO\cdot$)].

7β-[2-(2-Amino)thiazol-4-yl-2-(*Z*)-methoxyimino]acetylamino-1-carba-1-dethia-3-cephem-4-carboxylic Acid (50)——The target compound was prepared using a procedure similar to that described for **34** and **39**.

The amido-ester **55** (794 mg 2.03 mmol) afforded the crude amine (648 mg) which provided, on acylation with **33**, the amidoester (1.03 g 86% from **55**). Amorphous solid, NMR δ: 0.8—2.6 (4H, m), 3.90 (3H, s), 5.21 and 5.28 (4H, two s, PhC$\underline{H}_2$OCONH– and –$CO_2C\underline{H}_2$Ph), 5.73 (1H, dd, J=5 and 8 Hz, β-lactam), 6.53 (1H, br t, J=4 Hz, =C$\underline{H}$–CH_2–), 7.01 (1H, s, S–C$\underline{H}$=), 7.37 (10H, br s, aromatics), 8.42 (1H, br d, J=8 Hz, –C(=N–)CON$\underline{H}$–).

Treatment of the above amido-ester with $AlCl_3$ in anisole gave, after purification by HP-20 column chromatography, the target compound **50** (316 mg, 50%) as an amorphous solid. IR (KBr): 3700—2800 (br m), 1775 (s) cm^{-1}.

7β-[(2*R*)-2-Phenyl-2-amino]acetylamino-1-carba-1-dethia-3-cephem-4-carboxylic Acid (56)——The amine (132 mg, 0.484 mmol) prepared from **55** was converted to the amide (224 mg, 92%) as described for **29**. Amorphous solid, NMR δ: 1.1—2.5 (4H, m), 1.32 (9H, s, *tert*-Bu), 3.5—3.9 (1H, m, β-lactam), 5.10 (1H, dd, J=5 and 7 Hz, β-lactam), 5.18 (2H, br s, –$CO_2C\underline{H}_2$Ph), 5.78 (1H, d, J=7 Hz, PhC$\underline{H}$(NH–)CO–), 6.37 (1H, br t, J=3 Hz, =C$\underline{H}$–CH_2–), 7.22 and 7.29 (10H, two s, aromatics), 7.56 (1H, br d, J=7 Hz, –N$\underline{H}$–$CO_2C_4H_9$). MS: 448 [M^+ (505) -57 (C_4H_9)], 405 [$M^+ +1-101$ ($CO_2C_4H_9$)], 388 [$M^+ +1-117$ ($NHCO_2C_4H_9$)], 358 [$M^+ +1-147$ ($\cdot CH_2Ph+C_4H_9$)].

The amide (310 mg, 0.613 mmol) gave, after purification by HP-20 column chromatography, the target compound **56** (127 mg, 66%). Amorphous solid, NMR (CD_3OD) δ: 1.0—2.7 (4H, m), 3.6—4.1 (1H, m, β-lactam), 5.11 (1H, br s, PhC$\underline{H}$(NH_2)–), 5.33 (1H, br d, J=5 Hz, β-lactam), 6.48 (1H, br t, J=4 Hz, =C$\underline{H}$–CH_2–), 7.5 (5H, s, aromatics).

7β-[(2*R*)-2-Phenyl-2-(4-ethyl-2,3-dioxopiperazine-1-yl-carbonyl)amino]acetylamino-1-carba-1-dethia-3-cephem-4-carboxylic Acid (57)——The target compound **57** (61 mg, 93%) was obtained from the amino acid **56** (43 mg) after rinsing the crude product with EtOAc. Amorphous solid, NMR (acetone-d_6) δ: 1.2 (3H, t, J=7 Hz, –$CH_2C\underline{H}_3$), 1.5—2.6 (4H, m), 3.3—4.2 (7H, m, β-lactam, N$C\underline{H}_2C\underline{H}_2$N, –$C\underline{H}_2CH_3$), 5.42 (1H, br d, J=5 Hz, β-lactam), 5.45 (1H, br s, PhC$\underline{H}$(–NH–)CO–), 6.47 (1H, br t, J=4 Hz, =C$\underline{H}$–CH_2–), 7.4 (5H, br s, aromatic).

7β-[2-(4-Hydroxy)phenyl-2-carboxy]acetylamino-7α-methoxy-3-(1-methyl-1*H*-tetrazol-5-yl)thiomethyl-1-carba-1-dethia-3-cephem-4-carboxylic Acid (58)——A solution of the 7β-amino derivative **27** (419 mg, 1.01 mmol) and 3,4-di-*tert*-butyl-4-hydroxybenzaldehyde (262 mg, 1.1 eq) in 15 ml of CH_2Cl_2 was refluxed for 1 hr. Nickel peroxide (2.7 mg atm/g, 0.56 g, 1.5 eq) was then added with stirring at $-20°$ and stirring was continued for 50 min while the reaction mixture was allowed to reach 0°. After stirring for an additional 1 hr at 0°, the mixture was filtered to remove insoluble material. To this filtrate containing the quinone **60**, 12 ml of MeOH was added and the solution was left overnight under ice-cooling then for 4 hr at room temperature. The solvent was evaporated off and the residue was chromatographed (40 g of silica gel, deactivated with 10% w/w H_2O, benzene–EtOAc, 9: 1) to give the 7α-methoxy derivative **61** (388 mg, 59% from **27**). The above **61** (388 mg, 0.598 mmol) in 9 ml of MeOH was stirred with Girard's T reagent (151 mg, 1.5 eq) for 5 hr at room temperature and then allowed to stand overnight under ice-cooling. The mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$) and concentrated to afford crude 7α-methoxy-

amine **62** (340 mg). A stirred mixture of the above **62**, *p*-methoxybenzyl *p*-(*p*-methoxybenzyl)oxyphenylmalonic acid (279 mg, 1.07 eq) and pyridine (193 μl, 4 eq) in 6 ml of CH_2Cl_2 was treated with $POCl_3$ (61 μl, 1.1 eq) at −25° and the whole was stirred for 15 min under ice-cooling. The reaction mixture was diluted with EtOAc, washed with water and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size A, benzene–EtOAc, 2: 1) gave the diester **64** (200 mg, 39% from **61**) as an amorphous solid. IR: 3720 (w), 1776 (s), 1768 (s), 1728 (sh s), 1724 (s), 1715 (m) cm^{-1}. NMR δ: 1.1—2.7 (4H, m), 3.30 (3H, s, $OC\underline{H}_3$), 3.75, 3.78, and 3.82 (9H, three s, two $C\underline{H}_3O$–C_6H_4–, N–$C\underline{H}_3$), 3.8—4.1 (1H, m, β-lactam), 4.15 and 4.38 (2H, AB-q, J=13 Hz, –$C\underline{H}_2$–S–), 4.57 (1H, s, –$C\underline{H}(CO_2$–)CONH–), 4.94, 5.11 and 5.26 (6H, three s, two –O–$C_6H_4C\underline{H}_2$–, –$CO_2C\underline{H}_2$Ph), 6.7—7.7 (18H, m, aromatics, –CON<u>H</u>–). *Anal.* Calcd for $C_{44}H_{44}N_6O_{10}S$ (848.95): C, 62.25; H, 5.22; N, 9.90; S, 3.78. Found: C, 62.42; H, 5.19; N, 9.86; S, 3.89.

Treatment of the diester **64** (150 mg, 0.176 mmol) with $AlCl_3$ in anisole and extraction of the product with methyl ethyl ketone afforded 106 mg of crude product, which was rinsed with CH_2Cl_2 to give the target compound **58** (83 mg) as an amorphous solid. IR (KBr): 3600—2800 (br s), 1780—1680 (br s). NMR (acetone-d_6) δ: 0.9—2.9 (4H, m), 3.26 and 3.47 (3H, two s, –$OC\underline{H}_3$), 3.96 and 3.98 (3H, two s, N–$C\underline{H}_3$), 3.7—4.0 (1H, m, β-lactam), 4.30 (2H, br s, –$C\underline{H}_2$S–), 4.81 (1H, s, –$C\underline{H}(CO_2H)$CONH–), 6.0—7.4 (3H, m, two –$CO_2\underline{H}$, –CON<u>H</u>), 6.78 and 7.30 (4H, A_2B_2-q, J=9 Hz, aromatics), 8.40 (1H, br s, <u>H</u>O–C_6H_4).

Benzyl 2-[3β-Phenylacetylamino-4β- (4-chloroacetoxy-3- oxobutyl) -2- oxoazetidin -1- yl]-2-triphenylphosphorane-diylethanoate (67)——A solution of monochloroacetyl chloride (0.48 ml, 1 eq) in 65 ml of CH_2Cl_2 was added dropwise to a stirred solution of the diol-phosphoranes **53** (4.33 g, 6.0 mmol) and pyridine (0.73 ml, 1.5 eq) in 300 ml of CH_2Cl_2 under dry ice-acetone cooling over a period of 2 hr. The resulting mixture was poured into 50 ml of water and the organic phase was washed with brine, dried ($MgSO_4$) and concentrated to leave an oily residue (5,12 g), which was dissolved in 56 ml of acetone and treated with 5.6 ml of Jones' reagent (2.5 M) under ice-cooling. The mixture was allowed to reach room temperature over a period of 45 min. The excess reagent was quenched with MeOH and the product was extracted with EtOAc, washed with water and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size C, $CHCl_3$–EtOAc, 3: 1 and 1: 1, EtOAc) gave **67** (2.9 g, 60% from **53**) as an amorphous solid. IR: 1750 (s), 1745 (sh), 1735 (sh), 1670 (s), 1620 (m) cm^{-1}. NMR δ: 3.50 (2H, br s, PhC<u>H</u>$_2$CONH–), 3.86 (2H, s, –OCOC<u>H</u>$_2$Cl), 6.8—7.9 (m, aromatics), (other peaks, not clearly assigned).

Benzyl 7β-Phenylacetylamino-3-chloroacetoxymethyl-1-carba-1-dethia-3-cephem-4-carboxylate (68)——A solution of the phosphorane **67** (2.9 g, 3.63 mmol) in 75 ml of dioxane was refluxed for 24 hr. Removal of the solvent and chromatography of the residue on a Lobar column (size B, benzene–EtOAc, 2: 1) gave the target compound **68** (1.09 g, 60%). Recrystallization from ether gave a pure material, mp 138—139°. IR: 1775 (sh s), 1765 (s), 1730 (m), 1680 (m) cm^{-1}. NMR δ: 1.0—2.5 (4H, m), 3.57 (2H, s, PhC<u>H</u>$_2$CONH–), 3.6—4.0 (1H, m, β-lactam), 4.01 (2H, s, OCOC<u>H</u>$_2$Cl), 4.89 and 5.25 (2H, AB-q, J=13 Hz, –CH_2OCO–), 5.23 (2H, s, –$CO_2C\underline{H}_2$Ph), 5.34 (1H, dd, J=5 and 7 Hz, β-lactam), 6.71 (1H, br d, J=7 Hz, –CON<u>H</u>–), 7.27 and 7.36 (10H, two s, aromatics). MS: 402 [M^+ (496) −94 ($ClCH_2CO_2H$)], 374 [M^+−122 ($ClCH_2CO_2H$+CO)], 311 [M^+−185 ($ClCH_2CO_2H$+$PhCh_2$·)], 283 [M^+−213 ($ClCH_2CO_2H$+$PhCH_2CO$·)]. *Anal.* Calcd for $C_{26}H_{25}ClN_2O_6 \cdot 1/4H_2O$ (501.46): C, 62.27; H, 5.13; N, 5.59. Found: C, 62.45; H, 5.06; N, 5.60.

Benzyl 7β-(2-Thien-3-yl-2-diphenylmethoxycarbonyl)acetylamino-7α-methoxy-3-chloroacetoxymethyl-1-carba-1-dethia-3-cephem-4-carboxylate (71)——The target compound **71** was prepared in a manner similar to that described for **64**. The phenylacetoamide **68** (514 mg, 1.03 mmol) was converted into the amine **69** (286 mg, 73%), which was then treated with 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (195 mg, 1.1 equiv). The resulting imine was oxidized with nickel peroxide (2.7 mg atm/g, 0.5 g, 1.8 eq) and then treated with MeOH to afford the methoxy derivative **70** (160 mg, 26% from **68**). NMR δ: 0.9—2.6 (4H, m), 1.48 (18H, s, di-*tert*-Bu), 3.55 (3H, s, $OC\underline{H}_3$), 3.94 (1H, br dd, J=4 and 11 Hz, β-lactam), 3.98 (2H, s, –OCOC<u>H</u>$_2$Cl), 4.87 and 5.12 (2H, AB-q, J=13 Hz, –$C\underline{H}_2$–OCO–), 5.33 (2H, s, –$CO_2C\underline{H}_2$Ph), 5.63 (1H, s, –C<u>H</u>=N–).

The above product **70** (160 mg, 0.256 mmol) was treated with Girard's T reagent (120 mg, 2.8 mmol) in 3 ml of MeOH and 1 ml of CH_2Cl_2, and the resulting methoxy-amine (156 mg) was acylated in CH_2Cl_2 with pyridine (62 μl, 2 eq) and an acid chloride prepared in the following manner. A mixture of 3-thienylmalonic acid diphenylmethyl half-ester (270 mg, 2 eq), oxalyl chloride (59 μl, 1.8 eq) and pyridine (62 μl, 2 eq) in 7.3 ml of benzene containing 0.9 ml of CH_2Cl_2 and one drop of DMF was stirred at 0° to room temperature until no further evolution of gas could be seen (*ca.* 30 min), and the mixture was used as such. Usual work-up and chromatography on a Lobar column (size B, benzene–EtOAc, 9: 1) gave the amide **71** (109 mg, 57% from **70**) as an amorphous solid. IR: 1768 (s), 1728 (s), 1700 (sh m) cm^{-1}. NMR δ: 0.9—2.5 (4H, m), 3.24 and 3.28 (3H, two s, O–$C\underline{H}_3$), 3.90 (1H, br d, J=11 Hz, β-lactam), 3.95 (2H, s, –COC<u>H</u>$_2$Cl), 4.85 and 5.08 (AB-q, 2H, J=13 Hz, –$C\underline{H}_2$OCO–), 4.93 (1H, s, –$C\underline{H}(CO_2$–)CONH–), 5.24 (2H, br s, –$CO_2C\underline{H}_2$Ph), 6.92 (1H, s, –$CO_2C\underline{H}Ph_2$), 7.0—8.1 (19H, m, aromatics and –CON<u>H</u>–).

7β -(2-Thien -3- yl -2- carboxy)acetylamino-7α-methoxy -3- aminoformyloxymethyl -1 -carba-1-dethia-3-cephem-4-carboxylic Acid (65)——A solution of the chloroacetate **71** (107 mg, 0.144 mmol) and thiourea (55 mg, 5 eq) in 3 ml of MeOH and 0.5 ml of EtOAc was stirred overnight at room temperature. The mixture was diluted with EtOAc, washed with water (×5) and brine, and dried ($MgSO_4$). Removal of the solvent afforded the 3-hydroxymethyl derivative **66** (95 mg) which, without purification, was treated with trichloroacetyl isocyanate (50 μl, 2 eq) in 1.5 ml of CH_2Cl_2 under ice-cooling for 40 min. The reaction

mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and concentrated to give the crude trichloroacetylcarbamoyloxy derivative **72** (159 mg). A solution of this compound **72** (155 mg) in 2 ml of MeOH and 0.5 ml of 5% aqueous $NaHCO_3$ was stirred for 50 min at room temperature. The product was taken up in CH_2Cl_2, washed with water and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size A, benzene–EtOAc, 2: 1) gave the 3-carbamoyloxymethyl derivative **73** (71 mg, 70% from **71**) as an amorphous solid. IR: 3530 (w), 3420 (w), 1768 (s), 1730 (s), 1700 (sh m) cm^{-1}. NMR δ: 0.8—2.5 (4H, m), 3.29 (3H, br s, $-OC\underline{H}_3$), 3.88 (1H, br d, $J=11$ Hz, β-lactam), 4.6—5.2 (5H, m, $-C\underline{H}(-CO_2-)CONH-$, $-C\underline{H}_2OCONH_2$), 6.91 (1H, s, $-CO_2C\underline{H}Ph_2$), 7.0—8.1 (19H, m, aromatics, $-CON\underline{H}-$).

The diester **73** (71 mg, 0.1 mmol) was treated with $AlCl_3$ in anisole and the product was extracted with methyl ethyl ketone and rinsed with CH_2Cl_2 to give the target compound **65** (35 mg, 77%). Amorphous solid, IR (KBr): 3600—2800 (br m), 1770—1680 (br s). NMR (acetone-d_6) δ: 0.9—2.6 (4H, m), 3.29 and 3.47 (3H, two s, $O-C\underline{H}_3$), 3.7—4.1 (1H, m, β-lactam), 4.6—5.3 (2H, m, $-C\underline{H}_2OCONH_2$), 6.0 (1H, br s, $-C\underline{H}(CO_2H)-CONH-$), 6.8—8.0 (3H, m, aromatics).

Acknowledgement The authors thank Dr. Wataru Nagata, Director, Division of Chemical Research, and members of the β-lactam antibiotics research group for valuable discussions and advice. The authors are grateful to Dr. Tadashi Yoshida and his associates for the microbiological assay.