SYNTHESIS AND *IN VITRO* ANTIBACTERIAL ACTIVITIES OF 3-THIAZOL-4-YL-1-CARBA-1-DETHIACEPHALOSPORINS

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The synthesis and microbiological evaluation of a new series of 3-thiazol-4-yl-carba-1-dethiacephalosporins is described. Structure activity relationship was achieved by changing substitution at the 2-position of the thiazole moiety. The result was a marked variance of microbiological activity in the C7 side-chain derivatives. ATMO derivatives possess potent activity against both Gram-positive and Gram-negative bacteria. For example, MICs (μg/ml) of LY215226 against representative organisms are as follows: *S. aureus* 0.25, *S. pneumoniae* 0.008, *H. influenzae* 0.008, *E. coli* 0.25, *K. pneumoniae* 0.008, *E. cloacae* 0.5, *S. typhi* 0.25, and *M. morganii* 0.25.

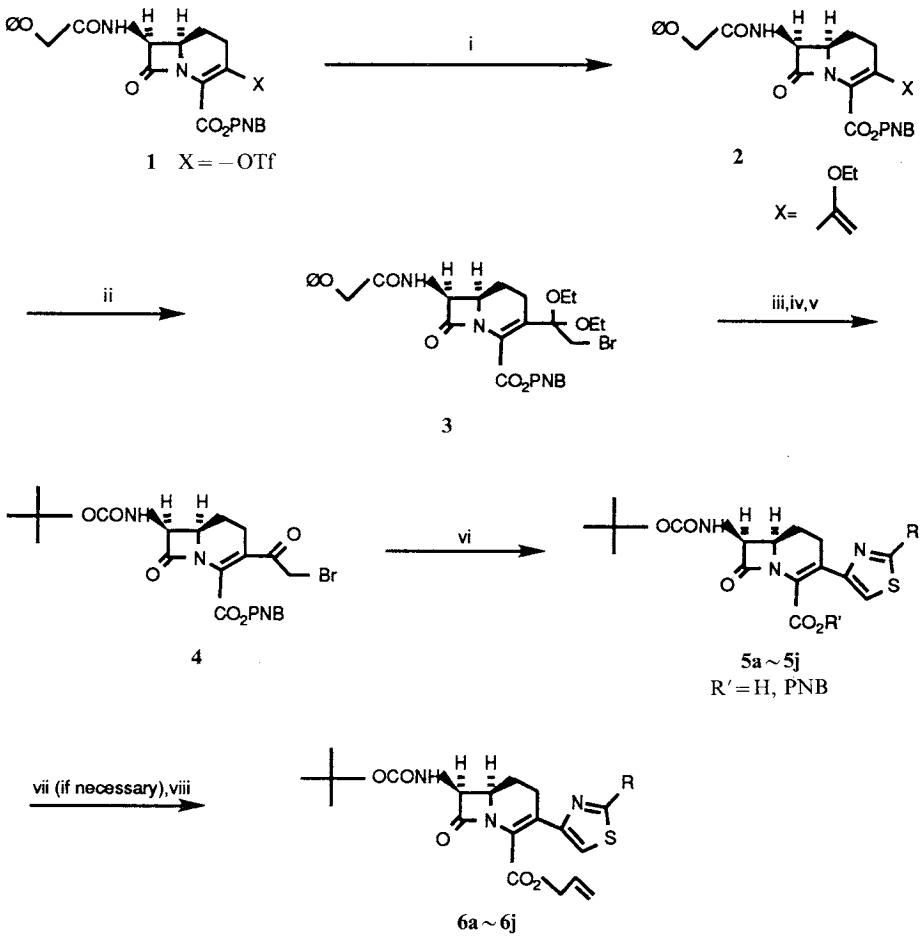
The 1-carba-1-dethiacephalosporins were first synthesized in 1974 by GUTHIKONDA *et al.*[1]. The recent revived interest in the 1-carbacephems[2], (Loracarbef[3]), has stimulated a wide range of structure activity relationships by substitution at the C3 position.[4~6] Much of the interest in this group has been facilitated by the readily accessible 1-carbacephem-3-enol triflate (**1**)[3,7,8] and the diverse chemical transformations that can be performed on this substrate.

One of our interest in this area has been development of methodology for conversion of the above mentioned enol triflate to substituted 3-thiazol-4-yl derivatives. This interest was supported by a report[9] that substituted 7-(3-aminothiazol-5-yl)-cephems exhibited potent antimicrobial activity. We wish now to report on the synthesis of these thiazol-4-yl carbacephem derivatives as well as the microbiological activity which they possess. The central feature of our synthetic strategy is the construction of a C3-bromomethyl ketone which could then be condensed with thioureas or thioamides limited only by the imagination of the medicinal chemist. Taking advantage of the previously described palladium catalyzed coupling of enol triflates with organostannanes[8] has provided us with a valuable intermediate (**2**) for this process.

Enol triflate **1**[3,7,8] was converted to the vinyl enol ether **2** under palladium catalysis in the presence of LiCl and trimethylethoxyvinylstannane[8]. In order to achieve a faster reaction time at lower temperatures (room temperature was ideal) the "ligandless" catalyst bis(acetonitrile)palladium(II) chloride[10~13] was used. Enol ether **2** was then dissolved in a 2 : 1 ethanol - methylene chloride solution containing 2,6-lutidine and treated with bromine to give the C3-bromoketal **3** in >99% crude yield. Compound **3** could be purified by flash chromatography, however, the crude was sufficiently pure to carry on to the proceeding transformations.

At this point we found it convenient to change the C7-amino protecting group (phenoxy-acetyl) to the acid labile *t*-butyloxycarbamate derivative. This was accomplished by first preparing the BOC imide of (**3**) by treatment with DMAP and di-*t*-butyldicarbonate and then removal of the phenoxyacetyl side-chain with base[14] (LiOH) to give a C7-*t*-butyloxycarbonylamino-3-(2-bromo-1,1-diethoxyethyl)-1-carbacephem. This compound was then hydrolyzed under mild acid catalysis (CH_3CN - AcOH - H_2O) to the C3-bromomethyl ketone **4** in quantitative yield.

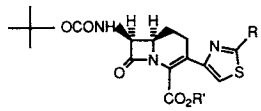
Scheme 1.



Reagents and conditions: **i**, LiCl, $(CH_3CN)_2PdCl_2$, $EtO(Me_3Sn)C{=}CH_2$; **ii**, 2,6-Lutidine, $EtOH\text{-}CH_2Cl_2$, $Br_2\text{-}CCl_4$; **iii**, $O[CO_2C(CH_3)]_2$, DMAP: **iv**, LiOH; **v**, $CH_3CN\text{-}AcOH\text{-}H_2O$; **vi**, 2,6-Lutidine, $RC{=}SNH_2$; **vii**, Zn, H^+; **viii**, $NaHCO_3$, Bu_4NHSO_4, $CH_2{=}CHCH_2Br$, NaI.

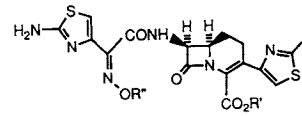
Compound **4** was then condensed with thiourea and a variety of thioamides which were commercially available or could be prepared from the corresponding nitrile by the method of BENNER[15] using diphenylphosphinodithioic acid[16]. This produced the desired C3-thiazoles in good yield. It is interesting to note that under these reaction conditions (see Scheme 1) deprotection of the C4-PNB ester concomitant with the desired thiazole formation sometimes occurred, in 70～90% yield (Table 1). Since removal of the PNB protecting group was desirable due to problems that standard deprotection (Zn, H^+) in the presence of the aminothiazolmethoximeacetyl (ATMO) side-chain present, this phenomena could have proved to be beneficial. Unfortunately, this transformation did not prove to be a general method, but dependent upon the thioamide substrate. In those cases where PNB deprotection did not occur, removal of the C4-PNB protecting group (Scheme 1) followed by reesterification of the tetrabutylammonium carboxylate with allyl iodide, afforded the desired allyl C7-*t*-butyloxycarbonylamino-3-(thiazol-4-yl)-1-carba-1-dethia-4-carboxylate nuclei (compounds **6a**～**6j**). The dihydroxy substituents of compound (**5j**) were silylated prior to conversion of PNB to allyl ester.

Table 1. Compounds **5a**~**5j**.



Compound	R	R′	% yield	Rx time (hours)
5a		H	82	2
5b		H	90	2
5c		H	31	16
5d		H	74	4
5e		H	98	4
5f		PNB	99	3
5g		PNB	97	1
5h		PNB	86	4
5i		PNB	70	2
5j		PNB	91	3

Table 2. Compounds **9a**~**9j**.



Compound	R	R′	R″
9a		Na	CH_3
9b		H	CH_3
9c (LY215226)		H	CH_3
9d		H	H
9e		Na	CH_3
9f		Na	CH_3
9g		H	CH_3
9h		H	CH_3
9i		Na	CH_3
9j		Na	CH_3

Deprotection of **6a**~**6j** (see Scheme 2), followed by acylation with typical cephalosporin side-chains by use of the 4,6-di-methoxy-1,3,5-triazine active ester[17] and final deprotection yielded compounds (**10**) and (**9a**~**9j**, Table 2). In some cases the C4-sodium-carboxylate was prepared from sodium bicarbonate.

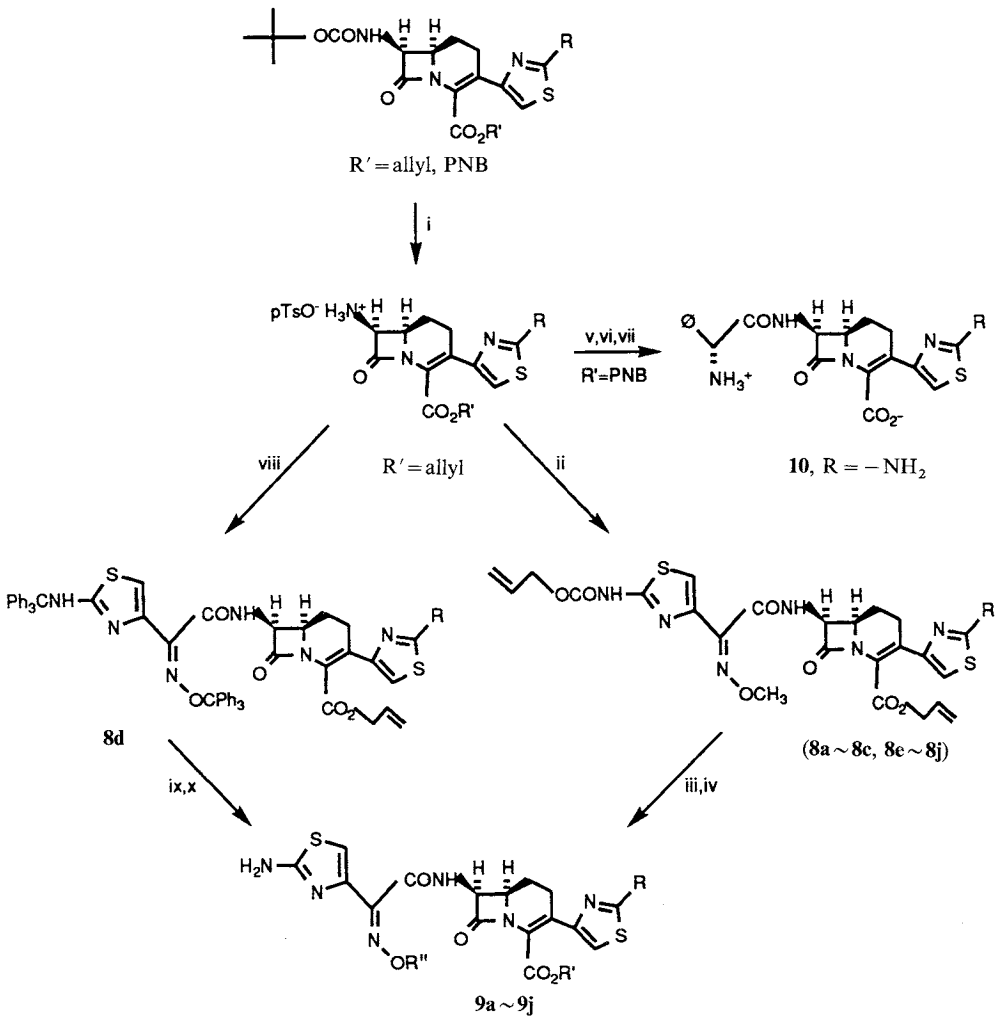
Biological Evaluation

Excellent Gram-positive and Gram-negative microbiological activity with directed emphasis on targeting specific organisms such as *P. aeruginosa*, *H. influenzae*, and *E. coli* was central to the design of these nuclei and their side-chain bearing derivatives. Thus, the rationale behind the synthesis of compounds (**9b** and **9i**) was due to the historically good activity of the ATMO-3′-quaternary ammonium salts, as well as the 3,4-dihydroxyphenyl derivatives, against *P. aeruginosa*.

As can be seen from the data (Table 3) compounds (**9a**~**9c**, **9g**, **9i**) all possessed good activity against a number of important organisms. However, the activity against *P. aeruginosa* was not sufficient to be considered practical in the clinical setting. The phenylglycyl derivative (**10**) did not possess significant activity against Gram-negative organisms.

The derivatives prepared herein showed potent Gram-positive and Gram-negative activity. Compound (**9c**) showed modest activity against resistant organisms [*i.e. E. cloacae* (265A: $\beta+$)] and may warrant modifications to improve upon this activity. If selected members of this SAR possess the appropriate pharmacological properties, they may provide an important utility to the antibiotic arena. These

Scheme 2.



Reagents and conditions: **i**, TsOH·H_2O; **ii**, Alloc-ATMO, 2-Cl-4,6(diMeO)C_3N_3, NMM; **iii**, $(Ph_3P)_2PdCl_2$, $(C_4H_9)_3SnH$; **iv**, $NaHCO_3$, H_2O-CH_3CN; **v**, Alloc-Phenylglycine, 2-Cl-4,6(diMeO)C_3N_3, NMM; **vi**, Zn, DMF-THF-AcOH; **vii**, Ph_3P, $Pd(OAc)_2$, $(C_4H_9)_3SnH$; **viii**, 2-triphenylmethylaminothiazol-4-yl-*Z*-triphenylmethoximinoacetic acid, 2-Cl-4,6(diMeO)C_3N_3, NMM; **ix**, Na-2-ethylhexanoate, Ph_3P, $(Ph_3P)_4Pd$; **x**, Aq. Formic acid.

modifications, and associated biological and pharmacological data, will be reported elsewhere.

Experimental

^1H NMR spectra recorded at 300 MHz on a General Electric QE-300 spectrometer using TMS as an internal standard. MS was measured on a Varion-MAT 731 mass spectrometer. Infrared spectra were obtained on a Perkin-Elmer 281 instrument. For column chromatography, silica gel (Kieselgel 60, Merck) was used.

p-Nitrobenzyl 7β-Phenoxyacetylamido-1-carba(1-dethia)-3-trifluoromethanesulfonyloxy-3-cephem-4-carboxylate (1)

The title compound can be prepared according to the methods incorporated herein by reference.[3,7,8]

Table 3. Microbiological activity (MIC: μg/ml).

Organisms	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	10
S. aureus (X1.1)	1.0	1.0	0.25	0.06	0.5	2.0	4.0	1.0	4.0	8.0	4.0
S. aureus (V41: β+)	2.0	8.0	2.0	0.5	2.0	4.0	32.0	2.0	8.0	16.0	32.0
S. pyogenes (C203)	0.008	0.015	0.015	0.008	0.008	0.015	0.008	0.008	0.008	0.06	2.0
S. pneumoniae (PARK)	0.008	0.015	0.008	0.015	0.008	0.03	0.015	0.008	0.015	0.125	2.0
H. Influenzae (76: β+)	0.03	0.015	0.008	0.015	0.015	0.015	0.125	0.015	0.06	0.015	32.0
E. coli (N10)	2.0	0.03	0.25	2.0	1.0	1.0	8.0	2.0	1.0	0.125	128.0
E. coli (TEM: β+)	1.0	0.125	0.25	1.0	0.5	0.5	4.0	—	0.5	0.06	64.0
K. pneumoniae (X26)	0.015	0.008	0.008	0.015	0.008	0.008	0.125	0.008	0.015	0.015	16.0
E, cloacae (EB5)	1.0	0.125	1.0	1.0	1.0	2.0	8.0	2.0	2.0	0.25	128.0
E. cloacae (265A: β+)	64.0	4.0	0.5	16.0	16.0	128.0	128.0	128.0	128.0	64.0	128.0
S. typhi (X514)	2.0	0.015	0.25	0.5	1.0	1.0	4.0	0.5	1.0	0.03	128.0
P. aeruginosa (X528)	128.0	128.0	32.0	128.0	128.0	128.0	128.0	128.0	128.0	8.0	128.0
S. marcescens (X99)	4.0	0.06	1.0	2.0	4.0	2.0	8.0	4.0	1.0	0.25	128.0
M. morganii (PR15)	2.0	0.06	0.25	4.0	0.5	2.0	32.0	2.0	4.0	4.0	128.0
P. rettgeri (C24)	0.25	0.03	0.06	0.06	0.25	0.5	4.0	0.125	0.25	0.125	128.0

p-Nitrobenzyl 7β-Phenoxyacetylamino-1-carba(1-dethia)-3-(1-ethoxy-ethen-1-yl)-3-cephem-4-carboxylate (**2**)

A 1.0 g (1.77 mmol) sample of compound **1**, a 0.142 g (3.34 mmol) sample of lithium chloride, and a 0.043 g (0.167 mmol) sample of dichloropalladium (II) diacetonitrilate were dissolved in 3 ml of dimethylformamide and treated with 0.435 g (1.84 mmol) of trimethyl (1-ethoxy-ethen-1-yl)stannane. The reaction was then gently warmed with a hot air gun for about 10 seconds, and allowed to stir at room temperature for about one hour. The reaction mixture was poured into 100 ml 1:1 mixture of ethyl acetate - diethyl ether and 100 ml 10:1 mixture Brine - satd. $NaHCO_3$ solution. Organics were separated and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Resultant crude dark oil was then diluted with 2 ml CH_2Cl_2 and 5 ml diethyl ether and 20 ml of hexane. A dark oil again resulted. Supernatant was decanted and to it was added an additional 40 ml hexane. Desired precipitated as a solid which was filtered and washed with hexane and dried to give 87 mg of the desired compound. The dark oil was chromatographed on 50 g of silica gel using 15~25% ethyl acetate - CH_2Cl_2 as eluent. The resulting product fractions were concentrated *in vacuo* and treated with 20 ml Et_2O to provide 550 mg of **2** (total yield 637 mg, 74%): ^1H NMR: (300 MHz, $CDCl_3$) δ 8.20 (d, J=9 Hz, 2H), 7.60 (d, J=9 Hz, 2H), 7.35 (t, J=8 Hz, 2H), 7.10 (m, 2H), 6.90 (d, J=8 Hz, 2H), 5.45 (dd, J=5, 7 Hz, 1H), 5.37 (AB, 2H), 4.58 (s, 2H), 4.21 (d, J=3 Hz, 1H), 4.18 (d, J=3 Hz, 1H), 3.95 (m, 1H), 3.75 (m, 2H), 2.70 (dd, J=4, 18 Hz, 1H), 2.30 (m, 1H), 2.05 (m, 1H), 1.50 (m, 1H) and 1.25 (t, J=7 Hz, 3H); IR: ($CHCl_3$), 3028, 1772, 1734, 1691, 1524, 1496, 1389, 1299, 1277, and 1207 cm^{-1}: MS: *m/e* 521 (M^+); Analysis Calculated for $C_{27}H_{27}N_3O_8$: Calc.: C 62.18, H 5.22, N 8.06, Found: C 62.43, H 5.36, N 8.30.

p-Nitrobenzyl 7β-Phenoxyacetylamino-1-carba(1-dethia)-3-(2-bromo-1,1-diethoxyethyl)-3-cephem-4-carboxylate (**3**)

A 570 mg sample of **2** was dissolved in 4.5 ml of ethanol - 2 ml of CH_2Cl_2 and cooled to 0°C. The solution was then treated with 0.153 ml (1.312 mmol) of 2,6-lutidine and 1.1 ml (1.1 mmol) of a 1.0 M Br_2 - CCl_4 solution. The resulting mixture was then poured into a mixture of saturated sodium bicarbonate solution and 1:1 ethyl acetate - diethyl ether. The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide 621 mg (86%) of a yellow foam which was used directly in the next step.

A 25 mg sample of the above product was purified over a silica gel (2.5 g) column using 7% ethyl acetate - CH_2Cl_2 as eluent to provide 20 mg of the title compound: ^1H NMR: (300 MHz, $CDCl_3$) δ 8.23 (d, J=9 Hz, 2H), 7.60 (d, J=9 Hz, 2H), 7.35 (t, J=8 Hz, 2H), 7.10 (m, 2H), 6.95 (d, J=8 Hz, 2H), 5.35 (AB, 2H), 5.32 (dd, J=5, 7 Hz, 1H), 4.58 (s, 2H), 3.95 (m, 1H), 3.3~3.6 (2m, 4H), 2.48 (dd, J=2, 16 Hz, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 1.45 (m, 1H), 1.16 (t, J=4 Hz, 3H) and 1.10 (t, J=4 Hz, 3H); IR: ($CHCl_3$) 3019, 1772, 1751, 1749, 1695, 1349, 1290, 1206 and 1073 cm^{-1}; MS: *m/e* 646 (M^+ + 1); Analysis Calculated

for $C_{29}H_{32}N_3O_9Br$: Calc.: C 53.88, H 4.99, N 6.50; Found: C 53.59, H 4.75, N 6.77.

p-Nitrobenzyl 7β-Phenoxyacetyl-*t*-butyloxycarbonylamino-1-carba(1-dethia)-3-(2-bromo-1,1-diethoxy)-3-cephem-4-carboxylate (**3a**)

A 700 mg sample of **3** was dissolved in 10 ml of CH_2Cl_2 at room temperature and treated with 0.256 ml (1.126 mmol) of di-*t*-butyldicarbonate, followed by 132 mg (1.08 mmol) of 4-dimethylaminopyridine and stirring for 30 minutes. An additional 50 μl of di-*t*-butyldicarbonate was added and the reaction stirred for about 30 minutes. The reaction mixture was chromatographed directly over a silica gel column (40 g) using 20~30% ethyl acetate-CH_2Cl_2 as eluent to provide 730 mg (91%) of **3a**: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.23 (d, J=9 Hz, 2H), 7.62 (d, J=9 Hz, 2H), 7.30 (t, J=8 Hz, 2H), 7.0 (m, 2H), 6.95 (d, J=8 Hz, 2H), 5.70 (d, J=4 Hz, 1H), 5.35 (AB, 2H), 5.18 (d, J=3 Hz, 2H), 3.86 (m, 1H), 3.35~3.7 (m, 4H), 2.5 (dd, J=2, 18 Hz, 1H), 2.18 (m, 1H), 1.85 (m, 1H), 1.55 (s, 9H), 1.50 (m, 1H), 1.16 (t, J=4 Hz, 3H) and 1.10 (t, J=4 Hz, 3H); IR: ($CHCl_3$) 3019, 1791, 1747, 1349, 1226, 1205 and 1145 cm^{-1}; MS: *m/e* 672 ($M^+ - OC_4H_9$); Analysis Calculated for $C_{34}H_{40}N_3O_{11}Br$: Calc.: C 54.70, H 5.40, N 5.63; Found: C 53.55, H 4.48, N 6.42.

p-Nitrobenzyl 7β-*t*-Butyloxycarbonylamino-1-carba(1-dethia)-3-(2-bromo-1,1-diethoxyethyl-3-cephem-4-carboxylate (**3b**)

A 750 mg (0.957 mmol) sample of **3a** was dissolved in 8 ml of tetrahydrofuran, treated with 0.85 ml (0.85 mmol) of 1.0 M lithium hydroxide soln. and sonicated. A further 0.155 ml portion of lithium hydroxide was added and sonication continued for 30 minutes. The reaction mixture was then poured into 50 ml of saturated sodium bicarbonate-75 ml ethyl acetate solution. The organic phase was separated and dired over anhydrous Na_2SO_4, filtered, and concentrated to provide 410 mg of the product as a foam after column chromatography over silica gel (8% ethyl acetate-CH_2Cl_2).

The above chromatography provided 176 mg of starting material which was re-submitted to the above conditions to obtain an additional 102 mg of **3b**. Total yield = 512 mg (87%). ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.23 (d, J=9 Hz, 2H), 7.61 (d, J=9 Hz, 2H), 5.35 (AB, 2H), 5.01 (m, 1H), 5.09 (m, 1H), 3.85 (m, 1H), 3.3~3.6 (m, 4H), 2.47 (dd, J=2, 16 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.43 (s, 9H), 1.12 (t, J=4 Hz, 3H) and 1.08 (t, J=4 Hz, 3H); IR: ($CHCl_3$) 1769, 1741, 1716, 1524, 1349, 1224, 1207 and 1160 cm^{-1}; MS: 611 (M^+); Analysis Calculated for $C_{26}H_{34}N_3O_9Br$: Calc.: C 50.99, H 5.60, N 6.86; Found: C 51.99, H 5.16, N 7.67.

p-Nitrobenzyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-bromomethylcarbonyl)-3-cephem-4-carboxylate (**4**)

A 125 mg (0.204 mmol) sample of **3b** was dissolved in 1.2 ml of acetonitrile-0.25 ml of acetic acid-0.05 ml H_2O and stirred for about 2 hours. The reaction mixture was then poured into (50 ml) saturated sodium bicarbonate solution-(100 ml) 1:1 ethyl acetate-diethyl ether solution. The organic phase was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated to provide 111 mg (about 100%) of **4** as a white solid: ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.20 (d, J=9 Hz, 2H), 7.62 (d, J=9 Hz, 2H), 5.33 (AB, 2H), 5.28 (dd, J=4, 7 Hz, 1H), 5.25 (d, J=4 Hz, 1H), 4.03 (AB, 2H), 3.87 (m, 1H), 2.80 (dd, J=4, 18 Hz, 1H), 2.45 (m, 1H), 2.13 (m, 1H), 1.57 (m, 1H) and 1.4 (s, 9H); IR: ($CDCl_3$) 3019, 1782, 1718, 1525, 1369, 1291 and 1159 cm^{-1}; MS: *m/e* 480 ($M^+ - C_4H_9$); Analysis Calculated for $C_{22}H_{24}N_3O_8Br$: Calc.: C 49.08, H 4.49, N 7.81; Found: C 49.29, H 4.64, N 7.62.

The following is a general preparation for the formation of the C3-substituted thiazoles. Compound **5a** demonstrates the unexpected result of PNB ester deprotection coinciding with thiazole formation.

7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-phenylthiazolo)-3-cephem-4-carboxylic acid (**5a**)

A 75 mg (0.140 mmol) sample of *p*-nitrobenzyl 7β-*t*-butoxycarbonylamino-1-carba(1-dethia)-3-bromomethylcarbonyl)-3-cephem-4-carboxylate **4** was dissolved in 1.5 ml of isopropanol and 1 ml of 1,1,2-trichloroethane, followed by the addition of 20 mg (0.146 mmol) of phenylthiocarbamate. The reaction mixture was then heated to about 65°C for 1.5 hours. The reaction mixture was concentrated *in vacuo* and treated with 3 ml of diethyl ether-4 ml hexane. The resulting solid was dried to provide 52 mg (85% yield) of **5a**.

Compounds **5b**, **5c**, **5d**, **5e**, and **5f**, were also converted to their free 4-carboxylates during thiazole formation. These compounds were then converted to their 4-allyl-carboxylates in an analogous manner to that of example **6a** to give compounds **6b**, **6c**, **6d**, **6e** and **6f**.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-phenylthiazol-4-yl)-3-cephem-4-carboxylate (**6a**)

A 103 mg (0.234 mmol) sample of **5a**, was dissolved in a small amount of *N*,*N*-dimethylformamide, treated with 60 mg (0.70 mmol) of $NaHCO_3$ and stirred for 10 minutes. The reaction mixture was then treated with 83 mg (0.246 mmol) of tetra-*n*-butylammonium hydrogen sulfate, allowed to stir for 10 minutes, followed by treatment with 26 μl (0.294 mmol) of allyl bromide (followed by a additional 10 μl) and 109 mg (0.725 mmol) of NaI. After stirring at room temperature overnight, the reaction mixture was poured into 30 ml of saturated $NaHCO_3$ solution and 50 ml of ethyl acetate. The organic phase was separated and washed (2×30 ml) with 0.5 N HCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide (**6a**) (100 mg, 89%, isolated as a solid from diethyl ether - hexane): ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.40 (m, 3H), 7.15 (s, 1H), 5.78 (m, 1H), 5.10 (m, 4H), 4.65 (ABX, 2H), 3.90 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 1769, 1718, 1506, 1369, 1248 and 1161 cm^{-1}; MS: *m/e* 482 (M^++1); Analysis Calculated for $C_{25}H_{27}N_{30}O_5S$: Calc.: C 62.35, H 5.65, N 8.73; Found: C 64.23, H 5.81. N 8.93.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(3-pyridyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6b**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.1 (d, J=2 Hz, 1H), 8.65 (d, J=4 Hz, 1H), 8.18 (m, 1H), 7.38 (m, 1H), 7.22 (s, 1H), 5.80 (m, 1H), 5.2 (m, 4H), 4.70 (ABX, 2H), 3.95 (m, 1H), 3.0 (dd, J=4, 18 Hz, 1H), 2.52 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.48 (s, 9H); IR: ($CHCl_3$) 3025, 1771, 1717, 1602, 1246 and 1162 cm^{-1}: MS: *m/e* 482 (M^+); Analysis Calculated for $C_{24}H_{26}N_4O_5S$: Calc.: C 59.74, H 5.43, N 11.61; Found: C 59.90, H 5.62, N 11.63.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(5-nitrothiazol-2-yl)thiazol-4-yl]-3-cephem-4-carboxylate (**6c**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.43 (s, 1H), 5.85 (m, 1H), 5.25 (m, 3H), 5.10 (m, 1H), 4.75 (ABX, 2H), 4.95 (m, 1H), 2.98 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.23 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 2976, 1772, 1719, 1390, 1351, 1251 and 1159 cm^{-1}; MS: *m/e* 534 (M^++1); Analysis Calculated for $C_{22}H_{23}N_5O_7S_2$: Calc.: C 49.52, H 4.35, N 13.13; Found: C 50.90, H 4.33 N 13.23.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(3-methyl-4-nitroimidazol-2-yl)thiazol-4-yl]-3-cephem-4-carboxylate (**6d**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.40 (s, 1H), 5.62 (m, 1H), 5.25 (m, 3H), 5.08 (d, J=8 Hz, 1H), 4.70 (d, J=6 Hz, 2H), 4.48 (s, 3H), 3.95 (m, 1H), 3.0 (dd, J=4, 18 Hz, 1H), 2.58 (m, 1H), 2.25 (m, 1H), 1.75 (m, 1H) and 1.48 (s, 9H); IR: ($CHCl_3$) 3018, 1772, 1719, 1530, 1472, 1365, 1270 and 1161 cm^{-1}; MS: *m/e* 530 (M^+).

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(*p*-nitrophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6e**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.30 (d, J=9 Hz, 2H), 8.05 (d, J=9 Hz, 2H), 7.30 (s, 1H), 5.80 (m, 1H), 5.20 (m, 4H), 4.68 (ABX, 2H), 3.95 (m, 1H), 3.0 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.25 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 3020, 1771, 1719, 1525, 1348, 1248 and 1161 cm^{-1}; MS: *m/e* 527 (M^++1); Analysis Calculated for $C_{25}H_{26}N_4O_7S$: Calc.: C 57.03, H 4.98, N 10.64; Found: C 57.48, H 4.82, N 11.33.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(2-furenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6f**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.48 (d, J=2 Hz, 1H), 7.10 (s, 1H), 6.95 (m, 1H), 6.5 (m, 1H), 5.80 (m, 1H), 5.15 (m, 4H), 4.68 (ABX, 2H), 3.90 (m, 1H), 2.95 (dd, J=4, 8 Hz, 1H), 2.50 (m, 1H), 2.20 (m,

1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 3019, 1770, 1718, 1502, 1393, 1249 and 1160 cm^{-1}; MS: *m/e* 472 ($M^+ - 1$); Analysis Calculated for $C_{23}H_{25}N_3O_6S$: Calc.: C 58.59, H 5.34, N 8.91; Found: C 59.83, H 5.27, N 8.41.

Compounds **5g**, **5h**, **5i** and **5j**, were prepared in a manner analogous to that of **5a** (without deesterification) utilizing the appropriate thiocarbamate. Yields and reaction times are listed in Table 1.

p-Nitrobenzyl 7*β*-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-(phenyl)(2-pyridyl)methylthiazol-4-yl)-3-cephem-4-carboxylate (**5g**)

^1H NMR: (300 MHz, $CDCl_3$) δ 8.60 (dd, J=4, 9 Hz, 1H), 8.05 (d, J=9 Hz, 2H), 7.60 (m, 9H), 5.83 (d, J=4 Hz, 1H), 5.15 (m, 3H), 4.70 (m, 1H), 3.90 (m, 1H), 2.92 (dd, J=4, 18 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.48 (s, 9H).

p-Nitrobenzyl 7*β*-*t*-butoxycarbonylamino-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**5h**)

^1H NMR: (300 MHz, $CDCl_3$) δ 8.20 (d, J=9 Hz, 2H), 7.90 (m, 2H), 7.60 (d, J=9 Hz, 2H), 7.19 (s, 1H), 7.12 (m, 2H), 5.15 (m, 2H), 3.90 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H).

p-Nitrobenzyl 7*β*-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(allyloxycarbonylamino)thiazol-4-yl]-3-cephem-4-carboxylate (**5i**)

^1H NMR: (300 MHz, $CDCl_3$) δ 8.22 (m, 2H), 6.90 (m, 1H), 6.58 (m, 1H), 6.10 (s, 2H), 5.90 (m, 1H), 5.35 (m, 3H), 5.25 (m, 2H), 4.70 (m, 2H), 3.85 (m, 1H), 2.85 (m, 1H), 2.58 (m, 1H), 2.40 (m, 1H), 1.80 (m, 1H) and 1.45 (s, 9H).

p-Nitrobenzyl 7*β*-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-(2,3-dihydroxyphenyl)thiazol-4-yl)-3-cephem-4-carboxylate (**5j**)

^1H NMR: (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.40 (m, 1H), 7.12 (m, 3H), 6.98 (s, 1H), 6.84 (m, 1H), 5.20 (m, 4H), 4.05 (m, 1H), 2.84 (dd, J=4, 18 Hz, 1H), 2.35 (m, 1H), 2.15 (m, 1H), 1.75 (m, 1H) and 1.45 (s, 9H).

The catechol **5j** was silylated prior to conversion to **6j**.

Allyl 7*β*-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(3,4-(*t*-butyldimethylsilyloxy)phenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6j**)

A. Silylation

A 370 mg sample of (**5j**) was dissolved in 4 ml of dimethylformamide and treated with 184 mg of *t*-butyldimethylsilylchloride and 85 mg of imidazole and stirred for about 24 hours. An additional 180 mg of *t*-butyldimethylsilyl chloride and 90 mg of imidazole were added and the solution stirred an additional 24 hours. The reaction mixture was then diluted with 100 ml of ethyl acetate and 100 ml of H_2O. The organic phase was separated and washed with 100 ml of saturated $NaHCO_3$ solution. The organic phase was then dried over anhydrous Na_2SO_4 and purified over (50 g) silica gel using ethyl acetate as eluent. Further chromatography over silica gel (25% ethyl acetate-hexane) provided 320 mg of *p*-nitrobenzyl 7*β*-butoxycarbonylamino-1-carba(1-dethia)-3-(3,4-di(*t*-butyldimethylsilyloxy)phenylthiazol-4-yl-3-cephem-4-carboxylate: ^1H NMR: (300 MHz, $CDCl_3$) δ 8.0 (d, J=9 Hz, 2H), 7.32 (m, 2H), 7.22 (d, J=9 Hz, 2H), 7.05 (s, 1H), 6.80 (m, 1H), 5.28 (AB, 2H), 5.22 (m, 1H), 5.05 (m, 1H), 3.95 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H), 1.42 (s, 9H), 1.0 (s, 9H), 0.97 (s, 9H), 0.23 (s, 6H) and 0.20 (s, 6H).

B. Removal of *p*-nitrobenzyl ester

A 320 mg (0.382 mmol) silylated (**5j**) from above was dissolved in 2.5 ml of dimethylformamide-3 ml of tetrahydrofuran and 2.5 ml of acetic acid, treated with 100 mg (1.53 mmol) of Zn dust and stirred for 20 minutes. The reaction mixture was then treated with an additional 1 ml of acetic acid and 100 mg of Zn. After 1 hour, the reaction mixture was filtered, diluted with ethyl acetate and washed with water. The organic phase was then dried and concentrated *in vacuo* azeotroping any remaining dimethylformamide

away with toluene (5 times) to provide the 4-carboxylic acid as a foam (220 mg, 82%).

C. Formation of allyl ester

A 215 mg (0.306 mmol) sample of the product from part B above was treated, as in example **5a** to **6a**, with allyl bromide in dimethylformamide in the presence of tetra-*n*-butylammonium hydrogen sulfate, sodium bicarbonate and sodium iodide to provide 188 mg (83%) of (**6j**): ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.05 (s, 1H), 6.85 (d, J=9 Hz, 1H), 5.75 (m, 1H), 5.15 (m, 4H), 4.65 (ABX, 2H), 3.90 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.48 (m, 1H), 2.18 (m, 1H), 1.70 (m, 1H), 1.45 (s, 9H), 1.02 (s, 9H), 1.0 (s, 9H), 0.24 (s, 6H) and 0.21 (s, 6H); IR: ($CHCl_3$) 2931, 1768, 1718, 1520, 1472, 1392, 1297, 1254 and 1161 cm^{-1}; MS: *m/e* 742 (M^++1); Analysis Calculated for $C_{37}H_{55}N_3O_7SSi_2$: Calc.: C 59.89, H 7.47, N 5.66; Found: C 62.22, H 7.57, N 5.65.

Compounds **5g**, **5h** and **5i** were converted to **6g**, **6h** and **6i** in similar fashion as part B and C above.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(1,1-(2-pyridyl)(phenyl)methyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6g**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.60 (d, J=4 Hz, 1H), 7.63 (t, J=9 Hz, 1H), 7.30 (m, 5H), 7.18 (m, 2H), 7.13 (s, 1H), 7.11 (s, 1H), 5.86 (s, 1H), 5.85 (s, 1H), 5.65 (m, 1H), 5.10 (m, 4H), 4.53 (d, J=6 Hz, 1H), 4.47 (d, J=6 Hz, 1H), 4.28 (dd, J=5, 15 Hz, 1H), 4.20 (dd, J=5, 15 Hz, 1H), 3.88 (m, 1H), 2.90 (m, 1H), 2.45 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 3019, 1769, 1718, 1496, 1393, 1369, 1247 and 1160 cm^{-1}; MS: *m/e* 572 (M^+); Analysis Calculated for $C_{31}H_{32}N_4O_5S$: Calc.: C 65.02, H 5.63, N 9.78; Found: C 65.01, H 5.60, N 9.52.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6h**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.19 (s, 1H), 7.12 (m, 2H), 5.8 (m, 1H), 5.15 (m, 4H), 4.70 (ABX, 2H), 3.90 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: (KBr) 3019, 2977, 1770, 1719, 1393, 1336 and 1157 cm^{-1}; MS: *m/e* 499 (M^+); Analysis Calculated for $C_{25}H_{26}N_3O_5SF$: Calc.: C 60.10, H 5.25, N 8.41; Found: C 62.52, H 5.57, N 8.42.

Allyl 7β-*t*-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(allyloxycarbonylamino)thiazol-4-yl]-3-cephem-4-carboxylate (**6i**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 5.90 (m, 2H), 5.30 (m, 6H), 4.72 (d, J=6 Hz, 2H), 4.55 (d, J=6 Hz, 2H), 4.90 (m, 1H), 3.85 (dd, J=4, 18 Hz, 1H), 2.38 (m, 1H), 2.10 (m, 1H) and 1.45 (s, 9H); IR: ($CHCl_3$) 3018, 1769, 1722, 1549, 1237 and 1207 cm^{-1}; MS: *m/e* 504 (M^+); Analysis Calculated for $C_{23}H_{28}N_4O_7S$: Calc.: C 54.75, H 5.59, N 11.10; Found: C 54.93, H 5.31, N 11.94.

A general procedure for the deprotection of compounds (**6a**~**6j**), as well as a typical acylation with the protected ATMO sidechain, follows. All compounds except **6d** were acylated with (2-allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximino acetic acid to give **8a**~**8c**, **8e**~**8j**. **6d** was acylated after deprotection using (2-triphenylmethyl-aminothiazol-4-yl)-*Z*-triphenylmethoximino acetic acid to afford (**8d**).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**8h**)

A. Deprotection

An 80 mg (0.16 mmol) sample of allyl 7β-*t*-butoxycarbonylamino-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**6h**) was dissolved in 1 ml of CH_2Cl_2 and 1 ml of trifluoroacetic acid. The solution was stirred for 1 hour at 23°C and concentrated *in vacuo* concentrated out of acetonitrile to provide a foam. The resulting foam was recrystallized from (CH_2Cl_2 - diethyl ether - hexane; 1 : 3 : 3) to afford a tan solid which was used without further purification.

B. Acylation

In another container, a 46 mg (0.16 mmol) sample of (2-allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximino acetic acid was dissolved in 1 ml of CH_2Cl_2 and treated with 28 mg (0.16 mmol) of 2-chloro-4,6-dimethoxytriazene and cooled to 0 °C. The reaction mixture was then diluted with an additional 1 ml of CH_2Cl_2 and treated with 19 μl (0.168 mmol) of *N*-methylmorpholine and stirred for about 40 minutes.

An additional 19 μl of *N*-methylmorpholine was added, followed by addition of the product from Part A, above, using about 2 ml of CH_2Cl_2 as wash. After 2 hours, the reaction mixture was concentrated *in vacuo* and purified by column chromatography (silica gel, 30~40% ethyl acetate-CH_2Cl_2) to provide 42 mg of (**8h**), (38%, 2 steps): ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.90 (m, 2H), 7.20 (s, 1H), 7.12 (m, 2H), 5.85 (m, 3H), 5.25 (m, 4H), 4.70 (m, 4H), 4.10 (m, 1H), 4.05 (s, 3H), 3.05 (dd, J=4, 18 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H) and 1.95 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[(2-phenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**8a**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.40 (s, 1H), 7.90 (m, 3H), 7.40 (m, 2H), 7.20 (s, 1H), 7.10 (s, 1H), 5.95 (m, 1H), 5.80 (m, 1H), 5.60 (m, 1H), 5.20 (m, 4H), 4.70 (m, 4H), 4.10 (m, 1H), 4.05 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H) and 1.95 (m, 1H).

Allyl 7β-[2-(Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[(pyridyl)thiazol-4-yl]-3-cephem-4-carboxylate (**8b**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 9.10 (s, 1H), 8.65 (d, J=6 Hz, 1H), 8.20 (d, J=9 Hz, 1H), 8.05 (s, 1H), 7.38 (m, 1H), 7.30 (s, 1H), 7.10 (s, 1H), 5.95 (m, 1H), 5.80 (m, 1H), 5.75 (m, 1H), 5.25 (m, 4H), 4.70 (m, 4H), 4.10 (m, 1H), 4.05 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H) and 1.95 (m, 1H).

Allyl 7β-[2-(Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[(2-(1-methyl-pyrid-3-yl)thiazol-4-yl]-3-cephem-4-carboxylate Iodide (**8bb**)

A 58 mg sample of (**8b**) was dissolved in 0.9 ml of *N*,*N*-dimethylformamide and treated with 17 μl (0.278 mmol) of methyliodide. Crystallization by addition of diethyl ether-hexane to the reaction mixture provided 50 mg (95% yield) of (**8bb**): ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.80 (d, J=9 Hz, 1H), 8.70 (d, J=6 Hz, 1H), 8.10 (m, 1H), 7.70 (s, 1H), 7.60 (d, J=9 Hz, 1H), 7.25 (s, 1H), 5.95 (m, 1H), 5.75 (m, 1H), 5.55 (m, 1H), 5.25 (m, 4H), 4.65 (m, 4H), 4.35 (s, 3H), 4.05 (m, 1H), 3.95 (s, 1H), 3.05 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.10 (m, 1H) and 1.85 (m, 1H).

Allyl 7β-[2-(Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-[5-nitrothiazol-4-yl]thiazol-4-yl]-3-cephem-4-carboxylate (**8c**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.55 (s, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.15 (s, 1H), 5.90 (m, 2H), 5.70 (m, 1H), 5.30 (m, 4H), 4.70 (m, 4H), 4.10 (m, 1H), 4.05 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.60 (m, 1H) and 1.90 (m, 1H).

Allyl 7β-[(2-Triphenylmethylaminothiazol-4-yl)-*Z*-triphenylmethoximinoacetylamino]-1-carba(1-dethia)-3-[2-[4-nitro-3-methylimidiazol-2-yl]thiazol-4-yl-3-cephem-4-carboxylate (**8d**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.25 (m, 30H), 6.62 (s, 1H), 6.58 (d, J=6 Hz, 1H), 6.43 (s, 1H), 5.85 (m, 1H), 5.45 (m, 1H), 5.20 (m, 2H), 4.70 (m, 2H), 4.43 (s, 3H), 4.0 (m, 1H), 2.58 (dd, J=4, 18 Hz, 1H), 2.35 (m, 1H), 2.10 (m, 1H) and 1.45 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(4-nitrophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**8e**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.25 (d, J=8 Hz, 2H), 8.18 (s, 1H), 8.05 (d, J=8Hz, 2H), 7.35 (s, 1H), 7.05 (s, 1H), 5.90 (m, 3H), 5.25 (m, 4H), 4.70 (m, 4H), 4.15 (m, 1H), 4.05 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.60 (m, 1H), 2.30 (m, 1H) and 1.95 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(2-furyl)thiazol-4-yl]-3-cephem-4-carboxylate (**8f**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 8.05 (s, 1H), 7.48 (s, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 6.95 (m, 1H), 6.52 (m, 1H), 5.85 (m, 3H), 5.25 (m, 4H), 4.70 (m, 4H), 4.10 (m, 1H), 4.02 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.25 (m, 1H) and 1.95 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl]-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-[(phenyl)(2-pyridyl)methyl]thiazol-4-yl]-3-cephem-4-carboxylate (**8g**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.60 (d, J=4 Hz, 1H), 8.05 (s, 1H), 7.60 (m, 1H), 7.25 (m, 5H), 7.20 (m, 1H), 7.12 (s, 1H), 7.0 (s, 1H), 5.80 (m, 3H), 5.20 (m, 4H), 4.50 (m, 4H), 4.10 (m, 1H), 4.0 (s, 3H), 2.90 (m, 1H), 2.50 (m, 1H), 2.20 (m, 1H) and 1.90 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl]-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-allyloxycarbonylaminothiazol-4-yl]-3-cephem-4-carboxylate (**8i**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.60 (s, 1H), 8.52 (s, 1H), 8.10 (s, 1H), 7.02 (s, 1H), 6.80 (s, 1H), 5.90 (m, 3H), 5.70 (m, 1H), 5.25 (m, 6H), 4.70 (m, 6H), 4.05 (m, 1H), 4.0 (s, 3H), 2.88 (dd, J=4, 18 Hz, 1H), 2.43 (m, 1H), 2.20 (m, 1H) and 1.90 (m, 1H).

Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl]-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(3,4-(*t*-butyldimethylsilyl)oxy)phenylthiazol-4-yl]-3-cephem-4-carboxylate (**8j**)

^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.95 (s, 1H), 7.35 (m, 2H), 7.12 (s, 1H), 6.84 (m, 1H), 5.95 (m, 1H), 5.75 (m, 2H), 5.25 (m, 4H), 4.65 (m, 4H), 4.10 (m, 1H), 4.02 (s, 3H), 3.0 (dd, J=4, 18 Hz, 1H), 2.55 (m, 1H), 2.25 (m, 1H), 1.90 (m, 1H), 1.0 (s, 9H), 0.97 (s, 9H), 0.23 (s, 6H) and 0.18 (s, 6H).

This compound was subsequently treated with trifluoroacetic acid - dichloromethane (1 : 1, rt, 1 hour) to give the unprotected 3,4-dihydroxy derivative, which was deprotected by the procedure below to give (**9a**).

The following is a general procedure for the deprotection of compounds (**8a**～**8c**, **8e**～**8j**), and the subsequent preparation of the sodium salts of compounds (**9a**, **9e**, **9f**, **9i**, **9j**).

Sodium 7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(phenyl)-thiazol-4-yl]-3-cephem-4-carboxylate (**9a**)

A 217 mg (0.3351 mmol) sample of **8a** was dissolved in 10 ml of CH_2Cl_2, treated with 10.54 mg (0.0104 mmol) of bistriphenylphosphine Pd(II) dichloride and 48 μl (0.596 mmol) of tri-*n*-butyltinhydride and stirred for 10 minutes. The reaction mixture was then treated with an additional 40 μl of tri-*n*-butyltinhydride. After 10 minutes, the reaction mixture was quenched with a solution of 80 μl concentrated HCl in 3.0 ml of CH_3CN. The resultant mixture was treated with 60 ml of diethyl ether and 60 ml hexane and centrifuged (2×). The resulting solid was dried under vacuum to provide 130 mg (74%) of the free acid of **9a** (93% pure by HPLC).

A 130 mg (0.248 mmol) of the above was suspended in 7 ml H_2O and 2 ml CH_3CN. A solution of 25 mg (0.297 mmol) of $NaHCO_3$ in 1.5 ml of H_2O was prepared and added. The resulting solution was sonicated and passed through an HP20SS column eluting with 8% CH_3CN - 18% CH_3CN - H_2O. The desired fractions were concentrated and the resulting solid was washed with diethyl ether - hexane to provide 125 mg of (**9a**) (99.8% pure by isocratic HPLC): ^{1}H NMR: (300 MHz, DMSO-d_6) δ 9.2 (d, J=9 Hz, 2H), 7.85 (m, 2H), 7.65 (s, 1H), 7.40 (m, 3H), 7.15 (s, 2H), 6.70 (s, 1H), 5.25 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.35 (m, 1H), 1.90 (m, 1H) and 1.70 (m, 1H); IR: (KBr) 3500～3100, 1733, 1648, 1591, 1557, 1539, 1405 and 1376 cm^{-1}; MS: *m/e* 547 (M^++1); Analysis calculated for $C_{23}H_{19}N_6O_5S_2Na$: Calc.: C 50.54, H 3.50, N 15.38; Found: C 50.33, H 3.76, N 15.17.

7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(1-methyl-3-pyridyl)thiazol-4-yl]-3-cephem-4-carboxylic Acid (**9b**)

^{1}H NMR: (300 MHz, D_2O) δ 9.30 (s, 1H), 8.90 (d, J=8 Hz, 1H), 8.78 (d, J=6 Hz, 1H), 8.10 (m, 1H), 7.65 (s, 1H), 6.95 (s, 1H), 5.50 (d, J=6 Hz, 1H), 4.45 (s, 3H), 4.10 (m, 1H), 4.0 (s, 3H), 3.95 (m, 1H), 2.58 (m, 1H), 2.20 (m, 1H) and 1.80 (m, 1H); IR: (KBr) 3200, 1758, 1674, 1532, 1384, 1203 and 1168 cm^{-1}; MS: *m/e* 540 (M+1).

7β-(2-Aminothiazol-4-yl)-4-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(5-nitrothiazol-2-yl)-thiazol-4-yl]-3-cephem-4-carboxylic Acid (**9c**)

^{1}H NMR: (300 MHz, DMSO-d_6) δ 9.35 (d, J=9 Hz, 1H), 8.90 (s, 1H), 8.02 (s, 1H), 7.40 (s, 2H), 6.78 (s, 1H), 5.45 (m, 1H), 3.90 (m, 1H), 3.80 (s, 3H), 2.95 (dd, J=4, 18 Hz, 1H), 2.40 (m, 1H), 2.0 (m, 1H)

and 1.70 (m, 1H); IR: (KBr) 3419, 1764, 1629, 1524 and 1350 cm^{-1}; MS: *m/e* 532 ($M^+ - CO_2$).

7β-[(2-Aminothiazol-4-yl)-*Z*-hydroxyiminoacetylamino-1-carba(1-dethia)-3-[2-(4-nitro-3-methylimidazol-2-yl)thiazol-4-yl]-3-cephem-4-carboxylic acid (**9d**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.15 (d, J=9 Hz, 1H), 8.15 (s, 1H), 7.88 (s, 1H), 7.08 (s, 2H), 6.65 (s, 1H), 5.40 (m, 1H), 4.30 (s, 3H), 3.80 (m, 1H), 3.90 (dd, J=4, 18 Hz, 1H), 2.38 (m, 1H), 1.95 (m, 1H) and 1.75 (m, 1H); IR: (KBr) 3500~3100, 1754, 1617, 1528, 1397, 1365, 1339, 1268 and 1209 cm^{-1}; HRFAB-MS: Calcd. for $C_{20}H_{18}N_9O_7S_2$: 560.0771, Found: 560.0784.

Sodium 7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(4-nitrophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**9e**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.25 (d, J=9 Hz, 1H), 8.25 (d, J=9 Hz, 2H), 8.15 (d, J=9 Hz, 2H), 7.85 (s, 1H), 7.15 (s, 2H), 6.72 (s, 1H), 5.25 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 2.95 (dd, J=4, 18 Hz, 1H), 2.40 (m, 1H), 1.90 (m, 1H) and 1.70 (m, 1H); IR: (KBr) 3400~3200, 1733, 1649, 1594, 1521, 1402, 1345, 1050 and 851 cm^{-1}; MS: *m/e* 592 ($M^+ + 1$).

Sodium 7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(2-furyl)-thiazol-4-yl]-3-cephem-4-carboxylate (**9f**)

^1H NMR; (300 MHz, DMSO-d_6) δ 9.25 (d, J=9 Hz, H), 7.80 (s, 1H), 7.65 (s, 1H), 7.20 (s, 2H), 6.95 (m, 1H), 6.70 (s, 1H), 6.60 (m, 1H), 5.25 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.85 (dd, J=4, 18 Hz, 1H), 2.32 (m, 1H), 1.85 (m, 1H) and 1.65 (m, 1H); IR: (KBr) 3500~3200, 1744, 1647, 1595, 1538, 1104, 1383 and 1035 cm^{-1}; HRFAB-MS: Calcd. for $C_{21}H_{18}N_6O_6S_2Na$: 537.0627, Found: 537.0645.

7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(phenyl)(2-pyridyl)-methyl)thiazol-4-yl]-3-cephem-4-carboxylic Acid (**9g**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.28 (d, J=9 Hz, 1H), 8.50 (d, J=4 Hz, 1H), 7.70 (m, 1H), 7.50 (s, 1H), 7.45 (m, 1H), 7.25 (m, 8H), 6.72 (s, 1H), 5.90 (s, 1H), 5.40 (m, 1H), 3.80 (s, 3H), 2.85 (dd, J=4, 18 Hz, 1H), 2.30 (m, 1H), 1.90 (m, 1H) and 1.65 (m, 1H); IR: (KBr) 3400~3000, 1758, 1671, 1619, 1589, 1532 and 1379 cm^{-1}; MS: *m/e* 616 ($M^+ + 1$).

7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(4-fluorophenyl)-thiazol-4-yl]-3-cephem-4-carboxylic Acid (**9h**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.45 (d, J=9 Hz, 1H), 7.95 (m, 2H), 7.65 (s, 1H), 7.35 (m, 2H), 6.83 (s, 1H), 5.50 (m, 1H), 3.95 (m, 1H), 3.90 (s, 3H), 2.95 (m, 1H), 2.40 (m, 1H), 2.0 (m, 1H) and 1.75 (m, 1H); IR: (KBr) 3400~3000, 1762, 1673, 1631, 1517, 1389, 1234 and 1046 cm^{-1}; HRFAB-MS: Calcd for $C_{23}H_{20}N_6O_5S_2F$: 543.0921, Found: 543.0949.

Sodium 7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino-1-carba(1-dethia)-3-(2-aminothiazol-4-yl)-3-cephem-4-carboxylate (**9i**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.20 (d, J=9 Hz, 1H), 7.15 (s, 2H), 6.70 (s, 1H), 6.60 (s, 2H), 6.55 (s, 1H), 5.20 (m, 1H), 3.78 (s, 3H), 3.62 (s, 1H), 2.64 (dd, J=4, 18 Hz, 1H), 2.15 (m, 1H), 1.75 (m, 1H) and 1.60 (m, 1H); IR: (KBr) 3500~3100, 1744, 1661, 1607, 1591, 1527, 1382, 1350 and 1034 cm^{-1}; MS: *m/e* 485 (M^+).

Sodium 7β-[(2-Aminothiazol-4-yl)-*Z*-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(3,4-dihydroxyphenyl)thiazol-4-yl]-3-cephem-4-carboxylate (**9j**)

^1H NMR: (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 9.25 (d, J=9 Hz, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 7.15 (m, 3H), 6.75 (d, J=8 Hz, 1H), 6.70 (s, 1H), 5.25 (m, 1H), 3.80 (s, 3H), 3.72 (m, 1H), 2.90 (dd, J=4, 18 Hz, 1H), 2.35 (m, 1H), 1.88 (m, 1H) and 1.65 (m, 1H); IR: (KBr) 3341, 3226, 2223, 1648, 1628, 1600, 1587, 1365, 1253 and 1159 cm^{-1}; HRFAB-MS: Calcd. for $C_{23}H_{20}N_6O_7S_2Na$: 579.0733, Found: 579.0744.

7β-(D-Phenylglycylamino)-1-carba(1-dethia)-3-(2-aminothiazol-4-yl)-3-cephem-4-carboxylic Acid (**10**)

^1H NMR: (300 MHz, D_2O) δ 7.60 (m, 5H), 6.60 (s, 1H), 5.50 (d, J=4 Hz, 1H), 5.22 (s, 1H), 4.0 (m,

1H), 2.70 (dd, J=4, 18 Hz, 1H), 2.35 (m, 1H), 1.78 (m, 1H) and 1.35 (m, 1H).

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