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 LY21 5226
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-carbacephems2), (Loracarbef3)), 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 report9)
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 carbasephem 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 organostannanes9) has provided us with a valuable intermediate (2) for this process.

Enol triflate 13'7,8) was converted to the vinyl enol ether 2 under palladium catalysis in the presence
of LiCl and trimethylthoxyvinylstannane6). In order to achieve a faster reaction time at lower temperatures
(room temperature was ideal) the “ligandless” catalyst bis(acetonitrile)palladium(II) chloride10~13) 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-butyloxy carbamate 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 phenoxyacetil
side-chain with base14) (LiOH) to give a C7-t-butyloxy carbonylamino-3-(2-bromo-1,1-diethoxyethyl)-1-
carbacephem. This compound was then hydrolyzed under mild acid catalysis (CH₃CN - AcOH - H₂O) to
the C3-bromomethyl ketone 4 in quantitative yield.
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\textsuperscript{15) using diphenylphosphinodithioic acid\textsuperscript{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\textsuperscript{+}) in the presence of the aminothiazolmethoximeacetyle (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-r-butylxycarbonylamino-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.
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: β+)] 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

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R’</th>
<th>% yield</th>
<th>Rx time (hours)</th>
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<td>-</td>
<td>H</td>
<td>82</td>
<td>2</td>
</tr>
<tr>
<td>5b</td>
<td>-</td>
<td>H</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td>5c</td>
<td>-</td>
<td>H</td>
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<td>16</td>
</tr>
<tr>
<td>5d</td>
<td>-</td>
<td>H</td>
<td>74</td>
<td>4</td>
</tr>
<tr>
<td>5e</td>
<td>-</td>
<td>H</td>
<td>98</td>
<td>4</td>
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<tr>
<td>5f</td>
<td>-</td>
<td>PNB</td>
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<td>3</td>
</tr>
<tr>
<td>5g</td>
<td>-</td>
<td>PNB</td>
<td>97</td>
<td>1</td>
</tr>
<tr>
<td>5h</td>
<td>-</td>
<td>PNB</td>
<td>86</td>
<td>4</td>
</tr>
<tr>
<td>5i</td>
<td>-</td>
<td>PNB</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>5j</td>
<td>-</td>
<td>PNB</td>
<td>91</td>
<td>3</td>
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### Table 2. Compounds 9a~9j.

<table>
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<tr>
<th>Compound</th>
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<th>R”</th>
</tr>
</thead>
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<tr>
<td>9a</td>
<td>-</td>
<td>Na</td>
<td>CH₃</td>
</tr>
<tr>
<td>9b</td>
<td>-</td>
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<td>CH₃</td>
</tr>
<tr>
<td>9c</td>
<td>(LY215226)</td>
<td>H</td>
<td>CH₃</td>
</tr>
<tr>
<td>9d</td>
<td>-</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>9e</td>
<td>-</td>
<td>Na</td>
<td>CH₃</td>
</tr>
<tr>
<td>9f</td>
<td>-</td>
<td>Na</td>
<td>CH₃</td>
</tr>
<tr>
<td>9g</td>
<td>-</td>
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<td>CH₃</td>
</tr>
<tr>
<td>9j</td>
<td>-</td>
<td>Na</td>
<td>CH₃</td>
</tr>
</tbody>
</table>
Reagents and conditions: i, TsOH·H₂O; ii, Alloc-ATMO, 2-Cl-4,6(diMeO)C₃N₃, NMM; iii, (Ph₃P)₂PdCl₂, (C₄H₉)₃SnH; iv, NaHCO₃, H₂O - CH₃CN; v, Alloc-Phenylglycine, 2-Cl-4,6(diMeO)C₃N₃, NMM; vi, Zn, DMF-THF-AcOH; vii, Ph₃P, Pd(OAc)₂, (C₆H₆)₃SnH; viii, 2-triphenylmethylaminothiazol-4-yl-Z-triphenylmethoximinoacetic acid, 2-Cl-4,6(diMeO)C₃N₃, NMM; ix, Na-2-ethylhexanoate, Ph₃P, (Ph₃P)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-trifluromethanesulfonyloxy-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)

<table>
<thead>
<tr>
<th>Organisms</th>
<th>9a</th>
<th>9b</th>
<th>9c</th>
<th>9d</th>
<th>9e</th>
<th>9f</th>
<th>9g</th>
<th>9h</th>
<th>9i</th>
<th>9j</th>
<th>10</th>
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<td>1.0</td>
<td>0.25</td>
<td>0.06</td>
<td>0.5</td>
<td>2.0</td>
<td>4.0</td>
<td>1.0</td>
<td>4.0</td>
<td>8.0</td>
<td>4.0</td>
</tr>
<tr>
<td><em>S. aureus</em> (V41: β +)</td>
<td>2.0</td>
<td>8.0</td>
<td>8.0</td>
<td>2.0</td>
<td>2.0</td>
<td>4.0</td>
<td>32.0</td>
<td>2.0</td>
<td>2.0</td>
<td>8.0</td>
<td>16.0</td>
</tr>
<tr>
<td><em>S. pyogenes</em> (C203)</td>
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<td>0.015</td>
<td>0.015</td>
<td>0.008</td>
<td>0.008</td>
<td>0.015</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.006</td>
<td>2.0</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> (PARK)</td>
<td>0.008</td>
<td>0.015</td>
<td>0.008</td>
<td>0.015</td>
<td>0.008</td>
<td>0.03</td>
<td>0.015</td>
<td>0.008</td>
<td>0.015</td>
<td>0.125</td>
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<tr>
<td><em>H. Influenzae</em> (76: β +)</td>
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<td>0.015</td>
<td>0.008</td>
<td>0.015</td>
<td>0.015</td>
<td>0.125</td>
<td>0.015</td>
<td>0.06</td>
<td>0.015</td>
<td>32.0</td>
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<tr>
<td><em>E. coli</em> (N10)</td>
<td>2.0</td>
<td>0.03</td>
<td>0.25</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>8.0</td>
<td>2.0</td>
<td>1.0</td>
<td>0.125</td>
<td>128.0</td>
</tr>
<tr>
<td><em>E. coli</em> (TEM: β +)</td>
<td>1.0</td>
<td>0.125</td>
<td>0.25</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
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<td>—</td>
<td>0.5</td>
<td>0.06</td>
<td>64.0</td>
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<tr>
<td><em>K. pneumoniae</em> (X26)</td>
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<td>0.008</td>
<td>0.008</td>
<td>0.015</td>
<td>0.008</td>
<td>0.008</td>
<td>0.125</td>
<td>0.008</td>
<td>0.015</td>
<td>0.015</td>
<td>16.0</td>
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<tr>
<td><em>E. cloacae</em> (EB5)</td>
<td>1.0</td>
<td>0.125</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>8.0</td>
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<td>2.0</td>
<td>0.25</td>
<td>128.0</td>
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<tr>
<td><em>E. cloacae</em> (26SA: β +)</td>
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<td>128.0</td>
<td>128.0</td>
<td>128.0</td>
<td>128.0</td>
<td>64.0</td>
<td>128.0</td>
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<tr>
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<td>0.25</td>
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<td>0.03</td>
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<td>128.0</td>
<td>32.0</td>
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<td>128.0</td>
<td>128.0</td>
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<td><em>M. morganii</em> (PR15)</td>
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</tr>
<tr>
<td><em>P. rettgeri</em> (C24)</td>
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<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
<td>0.25</td>
<td>0.5</td>
<td>4.0</td>
<td>0.125</td>
<td>0.25</td>
<td>0.125</td>
<td>128.0</td>
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</table>

*p*-Nitrobenzyl 7β-Phenoxyacetamidino-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 dichloror paddium (II) diacetonitril 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. NaHCO3 solution. Organics were separated and dried over Na2SO4, filtered, and concentrated in vacuo. Resultant crude dark oil was then diluted with 2 ml CH2Cl2 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 - CH2Cl2 as eluent. The resulting product fractions were concentrated in vacuo and treated with 20 ml Et2O to provide 550 mg of 2 (total yield 637 mg, 74%).

1H NMR: (300 MHz, CDCl3) 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), 5.92 (d, J = 8 Hz, 2H), 5.25 (dd, J = 5, 7 Hz, 1H), 5.37 (AB, 2H), 4.58 (s, 2H), 4.21 (d, J = 3 Hz, XH), 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: (CHCl3), 3028, 1772, 1751, 1749, 1695, 1524, 1507, 1349, 1290, 1206 and 1073 cm⁻¹; MS: m/e 646 (M⁺ + 1); Analysis Calculated for C27H27N3O8: Calc: C 64.0, H 4.9, N 8.0.

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

A 570 mg sample of 2 was dissolved in 4.5 ml of ethanol - 2 ml of CH2Cl2 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 Br2 - CCl4 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 Na2SO4, 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 - CH2Cl2 as eluent to provide 20 mg of the title compound: 1H NMR: (300 MHz, CDCl3) 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: (CHCl3), 3019, 1772, 1751, 1749, 1695, 1349, 1290, 1260 and 1073 cm⁻¹; MS: m/e 646 (M⁺ + 1); Analysis Calculated...
p-Nitrobenzyl 7β-Phenoxyacetyl-β-butyloxy carbonylamino-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 CH₂Cl₂ at room temperature and treated with 0.256 ml (1.126 mmol) of di-tert-butyldicarbonate, followed by 132 mg (1.08 mmol) of 4-dimethylaminopyridine and stirring for 30 minutes. An additional 50 μl of di-tert-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-CH₂Cl₂ as eluent to provide 730 mg (91%) of 3a: *H NMR: (300 MHz, CDCl₃) 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: (CHCl₃) 3019, 1791, 1747, 1349, 1226, 1205 and 1145 cm⁻¹; MS: m/e 672 (M+ -OC₄H₉); Analysis Calculated for C₃₄H₄₀N₃O₁₁Br: Calc: C 54.70, H 5.40, N 5.63; Found: C 53.55, H 4.48, N 6.42.

p-Nitrobenzyl 7β-Phenylthio carbonylamino-1-carba(1-dethia)-3-(2-bromomethylcarbonyl)-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, dried over anhydrous Na₂SO₄, filtered, and concentrated to provide 410 mg of the product as a foam after column chromatography over silica gel (8% ethyl acetate-CH₂Cl₂). 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%). *H NMR: (300 MHz, CDCl₃) 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: (CDCl₃) 1769, 1741, 1716, 1524, 1369, 1291 and 1159 cm⁻¹; MS: m/e 611 (M⁺); Analysis Calculated for C₂₆H₃₄N₃O₉Br: 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 H₂O and stirred for about 2 hours. The reaction mixture was then poured into (50 ml) saturated sodium bicarbonate-75 ml ethyl acetate solution. The organic phase was separated, dried over anhydrous Na₂SO₄, filtered, and concentrated to provide 111 mg (about 100%) of 4 as a white solid: *H NMR: (300 MHz, CDCl₃) δ 8.23 (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: (CDCl₃) 1769, 1741, 1716, 1524, 1349, 1224, 1207 and 1160 cm⁻¹; MS: m/e 480 (M⁺ -C₄H₉); Analysis Calculated for C₂₂H₂₄N₃O₈Br: Calc: C 49.08, H 4.49, N 7.67; 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.

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

A 75 mg (0.140 mmol) sample of p-nitrobenzyl 7β-t-butyloxy carbonylamino-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 NaHCO₃ 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 an 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 NaHCO₃ solution and 50 ml of ethyl acetate. The organic phase was separated and washed (2 x 30 ml) with 0.5 N HCl solution, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to provide (6a) (100 mg, 89%, isolated as a solid from diethyl ether-hexane): ¹H NMR: (300 MHz, CDCl₃) 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), 2.50 (m, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: (CHCl₃) 1769, 1718, 1506, 1369, 1248 and 1161 cm⁻¹; MS: m/e 482 (M⁺ + 1); Analysis Calculated for C₂₅H₂₇N₃O₅S: 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)**

¹H NMR: (300 MHz, CDCl₃) 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, 1H), 4.70 (ABX, 2H), 3.95 (m, 1H), 3.0 (dd, J = 4 Hz, 1H), 2.20 (m, 1H), 1.70 (m, 1H) and 1.48 (s, 9H); IR: (CHCl₃) 1769, 1718, 1506, 1246 and 1162 cm⁻¹; MS: m/e 482 (M⁺); Analysis Calculated for C₂₄H₂₆N₄O₅S: 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)**

¹H NMR: (300 MHz, CDCl₃) δ 8.55 (s, 1H), 7.23 (s, 1H), 5.85 (m, 1H), 5.25 (m, 1H), 5.10 (m, 1H), 4.75 (ABX, 2H), 4.95 (s, 1H), 2.98 (dd, J = 4 Hz, 1H), 2.55 (m, 1H), 2.23 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H); IR: (CHCl₃) 2976, 1772, 1719, 1530, 1472, 1365, 1270 and 1161 cm⁻¹; MS: m/e 534 (M⁺ + 1); Analysis Calculated for C₂₂H₂₃N₅O₇S₂: 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)**

¹H NMR: (300 MHz, CDCl₃) δ 8.10 (s, 1H), 7.40 (s, 1H), 5.62 (m, 1H), 5.25 (m, 1H), 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 Hz, 1H), 2.58 (m, 1H), 2.25 (m, 1H), 1.75 (m, 1H) and 1.48 (s, 9H); IR: (CHCl₃) 3018, 1772, 1719, 1530, 1472, 1365, 1270 and 1161 cm⁻¹; MS: m/e 530 (M⁺); Analysis Calculated for C₂₅H₂₆N₄O₇S: 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-(p-nitrophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (6e)**

¹H NMR: (300 MHz, CDCl₃) δ 7.80 (d, J = 9 Hz, 2H), 8.05 (d, J = 9 Hz, 2H), 7.40 (s, 1H), 5.80 (m, 1H), 5.20 (m, 4H), 4.68 (ABX, 2H), 3.95 (m, 1H), 3.0 (dd, J = 4 Hz, 1H), 2.55 (m, 1H), 2.25 (m, 1H), 1.75 (m, 1H) and 1.45 (s, 9H); IR: (CHCl₃) 3020, 1771, 1719, 1525, 1348, 1248 and 1161 cm⁻¹; MS: m/e 527 (M⁺ + 1); Analysis Calculated for C₂₅H₂₆N₄O₇S: 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-furyl)thiazol-4-yl]-3-cephem-4-carboxylate (6f)**

¹H NMR: (300 MHz, CDCl₃) 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 Hz, 1H), 2.50 (m, 1H), 2.20 (m,
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.

\[ \text{p-Nitrobenzyl 7\(\beta\)-\(\tau\)-Butoxycarbonylamino-1-carba(1-dethia)-3-(2-(phenyl)(2-pyridyl)methylthiazol-4-yl)-3-cephem-4-carboxylate (5g)} \]
\[ \text{\(\text{\(\text{\textbf{H NMR: (300 MHz, CDCl}_3\)}}\text{\(\text{\delta}\) 8.60 (dd, \(J=4, 9\text{ Hz, 1H)}\), 7.60 (m, 9H), 5.15 (m, 3H), 4.70 (m, 1H), 3.90 (m, 1H), 2.92 (dd, \(J=4, 18\text{ Hz, 1H)}\), 2.20 (m, 1H), 1.70 (m, 1H) and 1.48 (s, 9H).} \]

\[ \text{p-Nitrobenzyl 7\(\beta\)-\(\tau\)-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (5h)} \]
\[ \text{\(\text{\(\text{\textbf{H NMR: (300 MHz, CDCl}_3\)}}\text{\(\text{\delta}\) 8.20 (d, \(J=9\text{ Hz, 2H)}\), 7.90 (m, 2H), 7.60 (d, \(J=9\text{ Hz, 2H)}\), 7.19 (s, 1H), 7.12 (m, 2H), 5.15 (m, 2H), 3.90 (m, 1H), 2.95 (dd, \(J=4, 18\text{ Hz, 1H)}\), 2.20 (m, 1H), 1.70 (m, 1H) and 1.45 (s, 9H).} \]

\[ \text{p-Nitrobenzyl 7\(\beta\)-\(\tau\)-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(allyloxycarbonylamino)thiazol-4-yl]-3-cephem-4-carboxylate (5i)} \]
\[ \text{\(\text{\(\text{\textbf{H NMR: (300 MHz, CDCl}_3\)}}\text{\(\text{\delta}\) 8.22 (m, 2H), 6.90 (m, 1H), 6.58 (m, 1H), 6.10 (s, 2H), 5.90 (m, 1H), 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).} \]

\[ \text{The catechol 5j was silylated prior to conversion to 6j.} \]

\[ \text{Allyl 7\(\beta\)-\(\tau\)-Butoxycarbonylamino-1-carba(1-dethia)-3-[2-(3,4-(\(\text{-}\)-butyldimethylsilyloxy)phenyl)thiazol-4-yl]-3-cephem-4-carboxylate (6j)} \]
\[ \text{\(\text{\(\text{\textbf{H NMR: (300 MHz, CDCl}_3\)}}\text{\(\text{\delta}\) 8.0 (d, \(J=9\text{ Hz, 2H)}\), 7.32 (m, 2H), 7.22 (d, \(J=9\text{ Hz, 2H)}\), 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, \(J=4, 18\text{ Hz, 1H)}\), 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).} \]

The catechol 5j was silylated prior to conversion to 6j.
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): ^H NMR: (300 MHz, CDCl3) 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: (CHCl3) 2931, 1768, 1718, 1520, 1472, 1392, 1297, 1254 and 1161 cm⁻¹; MS: m/e 742 (M⁺ + 1); Analysis Calculated for C37H55N3O7SSi2: 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-Butoxycarbonylamo-1-carba(1-dethia)-3-[2-(1,1-(2-pyridyl)(phenyl)methyl)thiazol-4-yl]-3-cephem-4-carboxylate (6g)

^H NMR: (300 MHz, CDCl3) 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) and 1.45 (s, 9H); IR: (KBr) 3019, 2977, 1770, 1719, 1393, 1336 and 1157 cm⁻¹; MS: m/e 572 (M⁺); Analysis Calculated for C31H32N4O5S: 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)

^H NMR: (300 MHz, CDCl3) 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: (CHCl3) 3018, 1769, 1719, 1549, 1237 and 1207 cm⁻¹; MS: m/e 504 (M⁺); Analysis Calculated for C23H28N4O7S: 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-methoximinoacylamino]-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-butoxycarbonylamo-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (6h) was dissolved in 1 ml of CH₂Cl₂ 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 (CH₂Cl₂ - 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 CH₂Cl₂ 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 CH₂Cl₂ 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 CH₂Cl₂ as wash. After 2 hours, the reaction mixture was concentrated in vacuo and purified by column chromatography (silica gel, 30~40% ethyl acetate - CH₂Cl₂) to provide 42mg of (8b), (38%, 2 steps): ¹H NMR: (300 MHz, CDCl₃) 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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(2-phenylthiazol-4-yl)-3-cephem-4-carboxylate (8a)

¹H NMR: (300 MHz, CDCl₃) 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), 5.75 (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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(pyridyl)thiazol-4-yl]-3-cephem-4-carboxylate (8b)

¹H NMR: (300 MHz, CDCl₃) 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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(2-(1-methylpyrid-3-yl)thiazol-4-yl]-3-cephem-4-carboxylate Iodide (8bb)

A 58mg sample of (8b) was dissolved in 0.9ml of N,N-dimethylformamide and treated with 17μl (0.278 mmol) of methyl iodide. Crystallization by addition of diethyl ether - hexane to the reaction mixture provided 50mg (95% yield) of (8bb): ¹H NMR: (300 MHz, CDCl₃) 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), 4.55 (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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(2-(4-nitrophenyl)thiazol-4-yl]-3-cephem-4-carboxylate (8c)

¹H NMR: (300 MHz, CDCl₃) δ 9.30 (s, 1H), 8.55 (s, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 5.90 (m, 3H), 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) and 1.90 (m, 1H).

Allyl β-[(2-Triphenylmethylaminothiazol-4-yl)-Z-triphenylmethoximinoacetylamino]-1-carba(l-dethia)-3-[(2-[5-nitrothiazol-4-yl]thiazol-4-yl)-3-cephem-4-carboxylate Iodide (8d)

A 58mg sample of (8d) was dissolved in 0.9ml of N,N-dimethylformamide and treated with 17μl (0.278 mmol) of methyl iodide. Crystallization by addition of diethyl ether - hexane to the reaction mixture provided 50mg (95% yield) of (8d): ¹H NMR: (300 MHz, CDCl₃) 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, 4H), 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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(2-[4-nitro-3-methylimidiazol-2-yl]thiazol-4-yl)-3-cephem-4-carboxylate (8e)

¹H NMR: (300 MHz, CDCl₃) δ 9.60 (s, 1H), 8.25 (d, J = 8 Hz, 2H), 8.18 (s, 1H), 8.05 (d, J = 8 Hz, 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 β-[(2-Allyloxycarbonylaminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(l-dethia)-3-[(2-4-furyl)thiazol-4-yl]-3-cephem-4-carboxylate (8f)

¹H NMR: (300 MHz, CDCl₃) δ 9.55 (s, 1H), 8.05 (s, 1H), 7.48 (s, 1H), 7.15 (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-Allyloxycarbamoyl)-thiazol-4-yl]-Z-methoximino-3-carba(1-dethia)-3-cephem-4-carboxylate (8g)

\[ \text{Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)]-Z-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-[(phenyl)(2-pyridyl)methyl]thiazol-4-yl]-3-cephem-4-carboxylate (8i) } \]

\[ \text{Allyl 7β-[(2-Allyloxycarbonylaminothiazol-4-yl)]-Z-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(3,4-(/-butyldimethylsilyl)oxy)phenylthiazol-4-yl]-3-cephem-4-carboxylate (8j) } \]

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-(3,4-(/-butyldimethylsilyl)oxy)phenylthiazol-4-yl]-3-cephem-4-carboxylate (9a)

\[ \text{Allyl 7β-[(2-Aminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(phenyl)-thiazol-4-yl]-3-cephem-4-carboxylate (8k) } \]

\[ \text{Allyl 7β-[(2-Aminothiazol-4-yl)-Z-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(5-nitrothiazol-2-yl)-thiazol-4-yl]-3-cephem-4-carboxylic Acid (9c) } \]

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

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

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

\[ \text{Allyl 7β-[(2-Aminothiazol-4-yl)-4-methoximinoacetylamino]-1-carba(1-dethia)-3-[2-(5-nitrothiazol-2-yl)-thiazol-4-yl]-3-cephem-4-carboxylic Acid (9c) } \]
and 1.70 (m, 1H); IR: (KBr) 3419, 1764, 1629 and 1350 cm⁻¹; MS: m/e 532 (M⁺ - CO₂).

7β-[(2-Aminothiazol-4-yl)-Z-hydroxyiminoacetamido]-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-d₆) δ 9.15 (d, J = 9 Hz, 1H), 8.15 (d, J = 9 Hz, 2H), 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 C₂₀H₁₈N₉O₇S₂: 560.0771, Found: 560.0784.

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

1H NMR: (300 MHz, DMSO-d₆) 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), 2.30 (m, 1H), 1.85 (m, 1H) and 1.65 (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-methoximinoacetamido]-1-carba(1-dethia)-3-[2-(2-furyl)thiazol-4-yl]-3-cephem-4-carboxylate (9f)

1H NMR: (300 MHz, DMSO-d₆) δ 9.25 (d, J = 9 Hz, 1H), 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), 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 C₂₁H₁₈N₆O₆S₂Na: 537.0627, Found: 537.0645.

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

1H NMR: (300 MHz, DMSO-d₆) 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 (s, 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-methoximinoacetamido]-1-carba(1-dethia)-3-[2-(4-fluorophenyl)thiazol-4-yl]-3-cephem-4-carboxylic Acid (9h)

1H NMR: (300 MHz, DMSO-d₆) 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) 3400-3200, 1762, 1673, 1631, 1517, 1389, 1234 and 1046 cm⁻¹; HRFAB-MS: Calcd. for C₂₃H₂₀N₆O₅S₂F: 543.0921, Found: 543.0949.

Sodium 7β-[(2-Aminothiazol-4-yl)-Z-methoximinoacetamido]-1-carba(1-dethia)-3-[2-(2-furyl)methyl)thiazol-4-yl]-3-cephem-4-carboxylate (9i)

1H NMR: (300 MHz, DMSO-d₆) 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) 3400-3100, 1744, 1661, 1607, 1591, 1527, 1382, 1350 and 1034 cm⁻¹; MS: m/e 485 (M⁺).

7β-[(2-Aminothiazol-4-yl)-Z-methoximinoacetamido]-1-carba(1-dethia)-3-[2-(3,4-dihydroxyphenyl)thiazol-4-yl]-3-cephem-4-carboxylic Acid (9j)

1H NMR: (300 MHz, DMSO-d₆) δ 9.50 (s, 1H), 9.25 (d, J = 9 Hz, 1H), 7.48 (m, 1H), 7.28 (m, 1H), 7.15 (m, 1H), 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 C₂₃H₂₀N₆O₆S₂Na: 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, D₂O) 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).

References


