SYNTHESIS AND BIOLOGICAL ACTIVITY OF 7α-HYDROXYETHYL-
1-OXACEPHEM DERIVATIVES

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A series of 7α-hydroxyethyl-1-oxacephems (1) was synthesized. The main focus of this study was to investigate biological activity relationships between 1-oxacephems (1) and the corresponding cephems (2). Replacement of the sulfur atom of 2 by the oxygen atom caused an enhancement of antibacterial activity, although the antibacterial activity of 1 was not high enough. Additionally 1 showed β-lactamase inhibitory activity, especially against cephalosporinase. However, the potency was lower than that of 2.

Our recent work demonstrated the synthesis and biological activity of 7α-hydroxyethyl cephem derivatives (2). Cephems of type 2 have potent β-lactamase inhibitory activity against both of penicillinase and cephalosporinase, but exhibit poor antibacterial activity. Having been encouraged by the biological characteristics of 2, we were interested in studying on the properties of other nucleus analogue of 2.

It is well-known that the enhancement of antibacterial activity is induced by replacement of the sulfur atom of cephalosporin by the oxygen atom. Thus, the question has been raised as to whether or not 1 will have more potent biological activity than 2. Using CNDO/2 calculations, we investigated the influence of the 1 position atom on the β-lactam ring of model compounds 3 and 4 which have an electron-withdrawing group (EWG) at the 3 position as shown in Table 1.

The altitude of a pyramid (Dh) of 4 is higher than that of 3, and the atomic charge densities of the β-lactam show that the degree of amide resonance of 4 is lower than that of 3. These calculations suggest that 4 is more reactive than 3 and encouraged us to investigate 1-oxacephems (1).

Chemistry

1-Oxacephem (1) was synthesized according to the method of synthesis of 2. As shown in Scheme 1, azetidinone 5 was treated with allyl alcohol in the presence of zinc acetate to give 6. Oxidation of 6 with KMnO₄ in aqueous tert-butanol gave diol 7. 9 was afforded by selective protection of 7 followed by oxidation with DMSO-trifluoroacetic anhydride. Phosphorane 12 was obtained by the condensation of allyl glyoxylate with 9, conversion to the chloride with SOCl₂ and subsequent reaction with Ph₃P. An intramolecular Wittig reaction of 12 in the presence of hydroquinone gave
Table 1. CNDO/2 calculation*1 data of 7-hydroxyethyl cephem 3 and 1-oxacephem 4.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>X</th>
<th>$\Delta h^b$ (Å)</th>
<th>Charge density of $\beta$-lactam ring</th>
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<tr>
<td>3</td>
<td>S</td>
<td>0.23</td>
<td>N: -0.1812  C-8: 0.3495  O: -0.2810</td>
</tr>
<tr>
<td>4</td>
<td>O</td>
<td>0.29</td>
<td>N: -0.2009  C-8: 0.3509  O: -0.2786</td>
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* a Molecular geometries of structures 3 and 4 were calculated by minimizing the total energy with respect to all geometrical variables, using the MNDO method.

b $\Delta h$: The altitude of a pyramid, having N-5 as apex and C-4, C-6 and C-8 as base.

Scheme 1.

a) Allyl alcohol, Zn(OAc)$_2$, b) KMnO$_4$, NaOH, c) tert-BuMe$_2$SiCl, imidazole, d) DMSO, (CF$_3$CO)$_2$O, Et$_3$N, e) CH$_2$=CHCH$_2$OOCCHO·H$_2$O, f) SOCl$_2$, 2,6-lutidine, g) Ph$_3$P, KI, 2,6-lutidine, h) hydroquinone-toluene, i) 1 n HCl, j) pyridinium dichromate.

1-oxacephem 13, from the following characteristics: Field desorption (FD)-MS $m/z$ 512 (M$^+$); IR (CHCl$_3$) cm$^{-1}$ 1770; the $R$ assignment of the 6 position was based upon the observed coupling constant ($J_{6,7}$=1 Hz) in the NMR spectrum. Selective desilylation of 13 was carried out with 1 n HCl in MeOH-THF and subsequent oxidation with PDC gave the key compound 14 (FD-MS $m/z$ 395 (M$^+$); $^1$H NMR (CDCl$_3$) $\delta$ 10.0 (1H, s, formyl)).
The introduction of EWG's at the 3 position was accomplished with key compound 14 and desired compounds were prepared as shown in Schemes 2 and 3. Desilylation of 14 and subsequent deprotection with palladium(0)-catalyzed exchange gave 3-formyl compound 16 (IR (Nujol) cm⁻¹ 1750; ¹H NMR (D₂O) δ 9.53 (1H, s, formyl)). 3-Hydroxyiminomethyl compound 18 (IR (Nujol) cm⁻¹ 1740; ¹H NMR (DMSO-d₆) δ 8.20 (1H, s, CH=NO)) was also obtained from 14 by the treatment with hydroxylamine hydrochloride in isopropyl alcohol and subsequent deprotection as in the preparation of 16. Compound 17 was dehydrated with SOCl₂ and then deprotected to give 20 (IR (Nujol) cm⁻¹ 2220, 1760).

As shown in Scheme 3, 3-substituted vinyl derivatives were synthesized by Wittig reaction. Compound 14 was treated with (triphenylphosphoranylidene)acetonitrile in CH₂Cl₂ to give (Z)-cyanovinyl compound 21 (IR (CH₂Cl₂) cm⁻¹ 2210, 1790; the assignment of Z configuration at the 3 position was based upon the observed coupling constant (Jₜₐₙₙ = 12 Hz)). Compound 22 was obtained by deprotection of 21 in the similar manner to that of 16. Then 14 was converted to 23 with 3-(1-triphenylphosphoranylideneacetyl)pyridine in 1,2-dichloroethane at reflux for 30 hours. The assignment of E configuration was determined by the observed coupling constant (Jₜₐₙₙₜₐₙₙ = 16 Hz). Compound 24 was prepared by the similar manner to that of 16.
Biological Activity and Discussion

The MICs of 1-oxacephem (16, 18, 20, 22 and 24) and cephem derivatives (25, 26 and 27) against four test organisms were shown in Table 2. 1-Oxacephem derivatives (20, 22 and 24) showed more potent antibacterial activity than the corresponding cephem derivatives (25, 26 and 27). The replacement of sulfur atom of cephem nuclei brought about 4 ~ 8-fold decrease of MIC values against Staphylococcus aureus 209P JC-1 in particular. But the antibacterial activity of 1-oxacephem derivatives was still low compared with a conventional cephem (cefaizolin). Compound 24 had the most potent antibacterial activity among these compounds and the structure-activity relationship concerning the side chain at the 3 position of 1-oxacephem derivatives seems to be common to that of cephem derivatives.

In contrast to the antibacterial activity, it was found that β-lactamase inhibitory activity against both penicilllnase and cephalosporinase of the 1-oxacephem derivatives was inferior to that of corresponding cephem derivatives, as shown in Table 3. For example, 1-oxacephem derivatives were shown to be ineffective against TEM PCase, and to have over 100-fold decreased β-lactamase inhibitory activity against Ic CSase compared with the corresponding cephem derivatives. Interestingly, of the 1-oxacephem derivatives, compound 20, which has the strongest EWG at the 3 position, had the most potent β-lactamase inhibitory activity, while compound 24, which had the most potent antibacterial activity, showed only poor β-lactamase inhibitory activity. The structure-activity relationships of 1-oxacephem derivatives seem to be in accord with those of the corresponding cephem derivatives.

It's not at all clear why the β-lactamase inhibitory activity of 1-oxacephem derivatives is inferior to that of cephem derivatives in contrast with the antibacterial activity, but it may relate to a difference in a stability of the complex formed between β-lactam and β-lactamase.
Table 2. MICs of 1-oxacephem and cephem derivatives.

<table>
<thead>
<tr>
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<tr>
<td>16</td>
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<td>O</td>
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<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>18</td>
<td>CH=NOH</td>
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<td>50</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<td>O</td>
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<tr>
<td>25</td>
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<td>S</td>
<td>50</td>
<td>100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
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<td>CH=CHCN</td>
<td>O</td>
<td>12.5</td>
<td>50</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<td>100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<tr>
<td>24</td>
<td>CH=CHCO-(\text{N})</td>
<td>O</td>
<td>6.25</td>
<td>6.25</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>27</td>
<td>CH=CHCO-(\text{N})</td>
<td>S</td>
<td>25</td>
<td>12.5</td>
<td>50</td>
<td>25</td>
</tr>
</tbody>
</table>

Cefazolin: 0.39 0.39 1.56 6.25

Abbreviations: S. a., Staphylococcus aureus 209P JC-1; B.s., Bacillus subtilis ATCC 6633; E.c., Escherichia coli 29; P.v., Proteus vulgaris IAM 1025.

a Mueller-Hinton agar 10⁻²: Stamp method; 37°C, 18 hours.

Table 3. β-Lactamase inhibitory activity of 1-oxacephem and cephem derivatives.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>X</th>
<th>TEM PCase</th>
<th>Ia CSase</th>
<th>Ib CSase</th>
<th>Ic CSase</th>
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<tr>
<td>16</td>
<td>CHO</td>
<td>O</td>
<td>&gt;500</td>
<td>4.5</td>
<td>17</td>
<td>36</td>
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<tr>
<td>18</td>
<td>CH=NOH</td>
<td>O</td>
<td>&gt;500</td>
<td>6.5</td>
<td>11.5</td>
<td>&gt;500</td>
</tr>
<tr>
<td>20</td>
<td>CN</td>
<td>O</td>
<td>&gt;500</td>
<td>0.66</td>
<td>6.5</td>
<td>&gt;500</td>
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<tr>
<td>25</td>
<td>CN</td>
<td>S</td>
<td>17</td>
<td>&lt;0.03</td>
<td>&lt;0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>22</td>
<td>CH=CHCN</td>
<td>O</td>
<td>&gt;500</td>
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<tr>
<td>26</td>
<td>CH=CHCN</td>
<td>S</td>
<td>&gt;500</td>
<td>0.78</td>
<td>14</td>
<td>&lt;7.8</td>
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<tr>
<td>24</td>
<td>CH=CHCO-(\text{N})</td>
<td>O</td>
<td>&gt;500</td>
<td>300</td>
<td>&gt;500</td>
<td>100</td>
</tr>
<tr>
<td>27</td>
<td>CH=CHCO-(\text{N})</td>
<td>S</td>
<td>30</td>
<td>33</td>
<td>450</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Sulbactam: 1.2 42 14 <0.5
Clavulanic acid: 1.0 12 7.8 0.6


a Serial dilution of a β-lactamase inhibitor were incubated with enzyme solution for 10 minutes at 37°C. Residual β-lactamase activity was determined spectrophotometrically using the chromogenic substrate nitrocefin (50 μg/ml) at 482 nm. ID₅₀ was calculated as the concentration inhibiting 50% of activity.
Experimental

MP's were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIF-140 automatic polarimeter. IR spectra were recorded with a Hitachi 260-10 spectrometer. $^1$H NMR were recorded using a Hitachi R-90H. Chemical shifts ($\delta$) are reported in ppm from sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) (in D$_2$O) or TMS (in CDCl$_3$ and DMSO-d$_6$) as internal standard. Secondary ion (SI)-MS were recorded with a Hitachi M-80 mass spectrometer and FD-MS were recorded with a Jeol D-300 mass spectrometer.

(3R,4R)-4-Allyloxy-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidine-2-one (6)

To a solution of (3R,4R)-4-acetoxy-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]azetidine-2-one (5) (30 g) and allyl alcohol (35.5 ml) in benzene (210 ml) was added zinc acetate dihydrate (11.5 g). The mixture was refluxed for 3 hours, cooled and poured into cold aqueous solution of NaHCO$_3$. The organic layer was separated, washed with saturated aqueous solution of NaHCO$_3$ and brine, dried over MgSO$_4$ and evaporated to give 6 as colorless powder (26.9 g, 90%): $[\alpha]_D^2$ -7.0° (c 1, CHCl$_3$); IR (CHCl$_3$) cm$^{-1}$ 1760, 1665; $^1$H NMR (CDCl$_3$) $\delta$ 0.13 (6H, s), 0.93 (9H, s), 1.30 (3H, d, $J=6$ Hz), 3.07 (1H, m), 4.00~4.40 (3H, m), 5.00~5.45 (3H, m), 5.70~6.20 (1H, m), 6.63 (1H, br s); FD-MS m/z 286 (M$^+$).

Anal Calcd for C$_{14}$H$_{27}$NO$_3$Si: C 58.95, H 9.54, N 4.91.
Found: C 58.66, H 9.97, N 4.89.

(3R,4R)-3-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-4-(2,3-dihydroxypropane-1-oxy)azetidine-2-one (7)

To a mixture of 7 (25 g) and imidazole (19 g) in DMF (125 ml) was added tert/-butyldimethylsilyl chloride (13.3 g) at 0°C. The mixture was stirred at room temperature for 1 hour and poured into a mixture of EtOAc and 1 n HCl. The residue was chromatographed on silica gel column (elucent; CHCl$_3$ - MeOH (20:1)), and evaporated to give 21.2 g (63 %) of 8 as colorless oil: IR (CHCl$_3$) cm$^{-1}$ 1770, 1670, 1460; $^1$H NMR (CDCl$_3$) $\delta$ 0.15 (6H, s), 0.93 (9H, s), 1.30 (3H, d, $J=6$ Hz), 2.43 (2H, br s), 3.05 (1H, m), 5.10 (1H, m), 6.73 (1H, br s); SI-MS m/z 320 (M$^+$).

Anal Calcd for C$_{14}$H$_{29}$NO$_5$Si$_2$H$_2$O: C 51.19, H 9.21, N 4.26.
Found: C 51.05, H 9.02, N 4.09.

To a mixture of DMSO (6.63 ml) and CH$_2$Cl$_2$ (100 ml) was added trifluoroacetic anhydride (9.87 ml) at -60°C. The mixture was stirred for 30 minutes maintaining the temperature at -60°C, treated with 8 (20.2 g) and stirred for another 30 minutes, after triethylamine (18.7 ml) was added, the mixture was warmed to room temperature and poured into ice-cooled water. The organic layer was separated, washed with water, 0.5 n HCl, aqueous solution of NaHCO$_3$ and then brine, dried over MgSO$_4$, and evaporated. The residue was purified by column chromatography on silica gel (elucent; CH$_2$Cl$_2$ -
acetone, 20:1), and crystallized from ether to give 13 g (65%) of 9: MP 58°C; [α]D —14° (c 1, CHCl3); IR (CHCl3) cm⁻¹ 1770, 1735; ¹H NMR (CDCl3) δ 0.10 (12H, s), 0.88—0.92 (18H, m), 1.25 (3H, d, J=6 Hz), 3.03 (1H, m), 4.00—4.20 (1H, m), 4.26 (2H, s), 4.42 (2H, s), 5.03 (1H, m), 6.57 (1H, s); FD-MS m/z 432 (M⁺).

Anal Calcd for C20H41NO5Si2·H2O: C 54.50, H 9.61, N 3.17. Found: C 54.71, H 9.30, N 2.84.

(3R,4R)-1-(1-Allyloxycarbonyl-1-hydroxymethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-(3-tert-butyldimethylsilyloxy-2-oxopropane-1-oxo)azetidine-2-one (10)

A mixture of 9 (13 g), allyl glyoxylate monohydrate (12 g) in toluene (1.3 liters) was stirred and heated under reflux in a Dean Stark apparatus for 3 hours in an atmosphere of nitrogen. After cooling, the mixture was evaporated. The residue was purified by column chromatography on silica gel (eluent; CH₂Cl₂ - acetone, 20:1) to give a colorless oil of 10 (14.5 g, 88%): IR (CH₂Cl₂) cm⁻¹ 1770, 1735; ¹H NMR (CDCl₃) δ 0.12 (12H, s), 0.91—0.98 (18H, m), 1.30 (3H, d, J=6 Hz), 3.10 (1H, m), 4.00—5.00 (8H, m), 5.15—5.55 (3H, m), 5.70—6.20 (1H, m); FD-MS m/z 545 (M⁺).

(3R,4R)-1-(1-Allyloxycarbonyl-1-chloromethyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-(3-tert-butyldimethylsilyloxy-2-oxopropane-1-oxo)azetidine-2-one (11)

To a solution of 10 (14.3 g) in THF (350 ml) was added 2,6-lutidine (5.64 ml) at -20°C. A mixture of thionyl chloride (3.53 ml) and THF (80 ml) was added dropwise to the mixture at -15°C. After 40 minutes, the mixture was poured into dry benzene (500 ml). A precipitate was removed by filtration. The filtrate was evaporated. The residue was chromatographed on silica gel (eluent; CH₂Cl₂ - acetone, 40:1) to give colorless oil of 11 (10.3 g, 70%): IR (CH₂Cl₂) cm⁻¹ 1785, 1760; ¹H NMR (CDCl₃) δ 0.10 (12H, m), 0.90—1.10 (18H, m), 1.30 (3H, d, J=6 Hz), 3.10—3.30 (1H, m), 4.00—4.80 (8H, m), 5.20—5.50 (2H, m), 5.60—6.10 (2H, m); FD-MS m/z 563 (M⁺).

(3R,4R)-1-(1-Allyloxycarbonyl-1-triphenylphosphoranylidene)methyl)-3-[(1R)-1-tert-butyldimethylsilyloxyethyl]-4-(3-tert-butyldimethylsilyloxy-2-oxopropane-1-oxo)azetidine-2-one (12)

11 (10.1 g) was dissolved in DMF (150 ml). To the solution of KI (3.66 g), 2,6-lutidine (2.57 ml) and triphenylphosphine (5.78 g) was added at room temperature. The mixture was stirred for 1 hour at room temperature and poured into a mixture of EtOAc and water. The extract was washed with ice-water, dried over MgSO₄ and evaporated. The residue was purified by column chromatography on silica gel (eluent; CH₂Cl₂ - MeOH, 10:1). Evaporation gave colorless oil of 12 (12.6 g, 89%): IR (CHCl₃) cm⁻¹ 1750, 1620, 1440; ¹H NMR (CDCl₃) δ 0.05—0.15 (12H, m), 0.90—1.00 (18H, m), 1.30 (3H, d, J=6 Hz), 3.10—3.30 (1H, m), 4.00—5.50 (14H, m), 5.60—6.20 (1H, m), 7.30—7.90 (15H, m); FD-MS m/z 790 (M⁺).

Allyl 7α-[(1R)-1-tert-butyldimethylsilyloxyethyl]-3-tert-butyldimethylsilyloxymethyl-1-oxa-3-cephem-4-carboxylate (13)

A mixture of 12 (11.0 g) and hydroquinone (110 mg) in toluene (1.1 liters) was stirred and heated under reflux for 4 hours in an atmosphere of nitrogen. After cooling, the mixture was evaporated. The residue was purified by column chromatography on silica gel with CH₂Cl₂. Evaporation gave 13 as colorless powder (4.6 g, 62%): [α]D +17° (c 1, CHCl₃); IR (CHCl₃) cm⁻¹ 1770, 1715; ¹H NMR (CDCl₃) δ 0.07 (12H, s), 0.87 (18H, s), 1.27 (3H, d, J=6 Hz), 3.00 (1H, dd, J=1 and 3 Hz), 4.22 (1H, m), 4.55 (2H, m), 4.70—4.80 (4H, m), 4.95 (1H, s), 5.15—5.50 (2H, m), 5.65—6.20 (1H, m); FD-MS m/z 512 (M⁺).

Anal Calcd for C₂₅H₄₅NO₆Si₂: C 58.67, H 8.86, N 2.74. Found: C 58.48, H 8.46, N 2.75.

Allyl 7α-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylate (14)

To a solution of 13 (3.40 g) in MeOH - THF (5:1, 82 ml) was added 1 N HCl (6.6 ml). The mixture was stirred at room temperature for 2 hours, neutralized with aqueous solution of NaHCO₃, and extracted with EtOAc. The extract was dried over MgSO₄ and evaporated. The residue was dissolved in CH₂Cl₂ (102 ml) and treated with pyridinium dichromate (3.75 g) for 3 hours at room temperature. A precipitate was removed by filtration. The filtrate was evaporated. The residue was purified by
column chromatography on silica gel with CH₂Cl₂. Evaporation gave 14 as colorless oil (1.54 g, 59%): IR (CH₂Cl₂) cm⁻¹ 1800, 1730, 1665, 1610; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.87~0.90 (9H, m), 1.33 (3H, d, J=6 Hz), 3.20 (1H, dd, J=1.5 and 4.0 Hz), 4.25~4.40 (1H, m), 4.33 and 4.93 (2H, ABq, J=16 Hz), 4.80~4.90 (2H, m), 5.08 (1H, d, J=1.5 Hz), 5.20~5.55 (2H, m), 5.80~6.25 (1H, m), 10.0 (1H, s); FD-MS m/z 395 (M⁺).

Allyl 7α-[(1R)-1-Hydroxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylate (15)

To a solution of 14 (13.3 mg) in MeOH (0.4 ml) was added 2 n HCl (0.13 ml) at 0°C. The mixture was stirred at room temperature for 3 hours, poured into phosphate buffer (pH 7.0) and extracted with EtOAc. The extract was dried over MgSO₄ and evaporated to give 15 as colorless oil (11.3 mg); IR (CH₂Cl₂) cm⁻¹ 1795, 1730, 1665, 1610; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.90 (9H, s), 1.38 (3H, d, J=6 Hz), 1.85 (1H, m), 3.20~3.40 (1H, m), 4.20~4.65 (2H, m), 4.65~5.10 (4H, m), 5.10~5.50 (2H, m), 5.70~6.20 (1H, m).

Sodium 7α-[(1R)-1-Hydroxyethyl]-3-formyl-1-oxa-3-cephem-4-carboxylate (16)

To a solution of 15 (52 mg), triphenylphosphine (4.8 mg), sodium 2-ethylhexanoate (30.8 mg) in EtOAc (1.5 ml) was added tetrakis(triphenylphosphine)palladium(0) (4.3 mg) at 0°C under an atmosphere of nitrogen. The mixture was stirred for 1 hour at room temperature and poured into water (20 ml). The aqueous layer was separated, washed with EtOAc and lyophilized. The powder (47.2 mg) was purified by column chromatography (non-ionic adsorption resin Diaion HP-20 (10 ml), eluent; isopropyl alcohol - water (5 : 95)). Freeze drying of the product fractions gave 27 mg (55%) of 16: IR (Nujol) cm⁻¹ 1750, 1600; ¹H NMR (90MHz, D₂O) δ 1.30 (3H, d, J=6 Hz), 3.47 (1H, dd, J=1.5 and 4 Hz), 4.10~4.40 (1H, m), 4.43 and 4.83 (2H, ABq, J=16 Hz), 5.20 (1H, d, J=1.5 Hz), 9.53 (1H, s).

Allyl 7α-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-hydroxyiminomethyl-1-oxa-3-cephem-4-carboxylate (17)

A mixture of 14 (50 mg), hydroxylamine hydrochloride (17.6 mg) and isopropyl alcohol (5 ml) was stirred, heated at 50°C for 30 minutes, and evaporated. The residue was purified by preparative TLC on silica gel (eluent; CHCl₃) to give 17 as colorless powder (35 mg, 69%); IR (CHCl₃) cm⁻¹ 1780, 1720, 1610, 1590; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.90 (9H, s), 1.30 (3H, d, J=6 Hz), 3.15 (1H, dd, J=1.5 and 3 Hz), 4.10~4.40 (1H, m), 4.40 and 4.90 (2H, ABq, J=18 Hz), 4.70~4.80 (2H, m), 5.00 (1H, d, J=1.5 Hz), 5.10~5.50 (2H, m), 5.70~6.20 (1H, m), 8.10 (1H, s), 8.47 (1H, s); FD-MS m/z 410 (M⁺).

Allyl 7α-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate (19)

To a solution of 17 (500 mg) in CHCl₃ (228 ml) was added thionyl chloride (11.4 ml). The mixture was heated at reflux for 2 hours, poured into ice-cooled aqueous solution of NaHCO₃ and extracted. The extract was washed with brine, dried with MgSO₄ and evaporated. The residue was purified by column chromatography on silica gel with CHCl₃ to give 19 as oil (229 mg, 48%); IR (CHCl₃) cm⁻¹ 2220, 1790, 1730, 1605; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.90 (9H, s), 1.30 (3H, d, J=6 Hz), 3.25 (1H, dd, J=1.5 and 3 Hz), 4.30 (1H, m), 4.53 (2H, m), 4.83 (2H, m), 5.05 (1H, d, J=1.5 Hz), 5.20~5.60 (2H, m), 5.70~6.20 (1H, m); FD-MS m/z 393 (M⁺).

Allyl 7α-[(1R)-1-tert-Butyldimethylsilyloxyethyl]-3-cyano-1-oxa-3-cephem-4-carboxylate (21)

To a solution of 14 (100 mg) in CH₂Cl₂ (2 ml) was added (triphenylphosphoranylidene)acetonitrile (80 mg) at 0°C. The mixture was stirred at room temperature for 3 hours, and purified by preparative TLC on silica gel (eluent; CH₂Cl₂) to give 21 as oil (84 mg, 79%): [α]D° -30° (c 1, CHCl₃); IR (CH₂Cl₂) cm⁻¹ 2210, 1790, 1720, 1600, 1565; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.90 (9H, s), 1.25 (3H, d, J=6 Hz), 3.17 (1H, dd, J=1.5 and 3 Hz), 4.15~4.45 (1H, m), 4.65~4.90 (3H, m), 5.00~5.50 (5H, m), 5.70~6.20 (1H, m), 7.50 (1H, d, J=12 Hz); FD-MS m/z 418 (M⁺).
Allyl 7α-[{(1R)-1-tert-Butyldimethylsilyloxyethyl}-3-[(E)-3-(3-pyridyl)-3-oxo-1-propene-1-yl]-1-oxa-3-cephem-4-carboxylate (23)

To a solution of 14 (500 mg) in 1,2-dichloroethane (15 ml) was added 3-(1-triphenylphosphoranylideneacetyl)pyridine (506 mg) at room temperature. The mixture was heated at reflux for 30 hours and evaporated. The residue was purified by column chromatography on silica gel (eluent; CH₂Cl₂ - acetone, 20 : 1). Evaporation gave 23 as powder (268 mg, 43%): IR (CH₂Cl₂) cm⁻¹ 1785, 1720, 1665, 1640, 1590; ¹H NMR (CDCl₃) δ 0.10 (6H, s), 0.90 (9H, s), 1.30 (3H, d, J=6 Hz), 3.20 (1H, dd, J=1.5 and 4 Hz), 4.20~4.40 (1H, m), 4.53 and 4.77 (2H, ABq, J=16 Hz), 4.75 (2H, m), 5.05 (1H, m), 5.15~5.50 (2H, m), 5.70~6.20 (1H, m), 6.72 (1H, d, J=15 Hz), 7.30~7.50 (1H, m), 8.05 (1H, d, J=15 Hz), 8.10~8.30 (1H, m), 8.75 (1H, dd, J=2 and 6 Hz), 9.05 (1H, d, J=2 Hz); FD-MS m/z 498 (M⁺).

Preparation of 18, 20, 22 and 24

These compounds were prepared as described for 16 from 14 in 2 steps.

Sodium 7α-[{(1R)-1-Hydroxyethyl}-3-hydroxyiminomethyl-1-oxa-3-cephem-4-carboxylate (18)

IR (Nujol) cm⁻¹ 1740, 1600; ¹H NMR (D₂O) δ 1.32 (3H, d, J=6 Hz), 3.35 (1H, d, J=6 Hz), 3.50 (1H, dd, J=1.5 and 4 Hz), 4.00~4.40 (2H, m), 5.12 (1H, m), 8.20 (1H, s).

Sodium 7α-[{(1R)-1-Hydroxyethyl}-3-cyano-1-oxa-3-cephem-4-carboxylate (20)

IR (Nujol) cm⁻¹ 2220, 1760; ¹H NMR (DMSO-d₆) δ 1.17 (3H, d, J=6 Hz), 3.95 (1H, m), 4.27 and 4.47 (2H, ABq, J=15 Hz), 4.95 (1H, d, J=1.5 Hz), 5.10 (1H, m).

Sodium 7α-[{(1R)-1-Hydroxyethyl}-3-[{(Z)-2-cyano-1-vinyl]-1-oxa-3-cephem-4-carboxylate (22)

IR (Nujol) cm⁻¹ 2200, 1750, 1600; ¹H NMR (D₂O) δ 1.33 (3H, d, J=6 Hz), 3.40 (1H, dd, J=1.5 and 4 Hz), 4.00~4.40 (1H, m), 4.80 and 5.15 (2H, ABq, J=17 Hz), 5.15 (1H, d, J=15 Hz), 5.40 (1H, d, J=12 Hz), 7.15 (1H, d, J=12 Hz); SI-MS m/z 263 (M⁺—Na).

Sodium 7α-[{(1R)-1-Hydroxyethyl}-3-[(E)-3-(3-pyridyl)-3-oxo-1-propene-1-yl]-1-oxa-3-cephem-4-carboxylate (24)

IR (Nujol) cm⁻¹ 1760, 1650, 1610, 1585; ¹H NMR (D₂O) δ 1.35 (3H, d, J=6 Hz), 3.40 (1H, dd, J=1.5 and 6 Hz), 4.25 (1H, m), 4.60 and 4.90 (2H, ABq, J=15 Hz), 5.15 (1H, d, J=1.5 Hz), 6.83 (1H, d, J=15 Hz), 7.55 (1H, dd, J=6 and 9 Hz), 7.80 (1H, d, J=15 Hz), 8.25 (1H, dt, J=1.5 and 9 Hz), 8.65 (1H, m), 8.95 (1H, m); SI-MS m/z 366 (M⁺).

References