Synthesis of 1-Oxa-2-oxocephalosporins

Matsuhiko Aratani, Daijiro Hagiwara, Hidekazu Takeno, Keiji Hemmi, and Masashi Hashimoto*

Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

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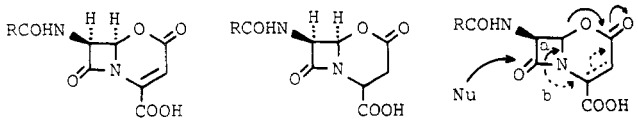
The first syntheses of 1-oxa-2-oxocephem (I) and 1-oxa-2-oxocepham (II) nuclei have been achieved by starting from penicillins. The oxazoline **8**, prepared in several steps from 1,2-secopenicillin (**1**), was converted, via reactions involving hydrolysis of the oxazoline ring of **8**, into the monocyclic β-lactam **10**, which was then transformed into the phosphorane **15** by a four-step sequence of reactions. Removal of the protective group of **15**, followed by oxidation with Me_2SO–Ac_2O afforded, via a spontaneous Wittig condensation, the type I 1-oxa-2-oxocephem **17**. Zinc dust reduction of **17** gave two epimeric cephams of type II (**19** and **20**). The β-lactam systems of the new cephem and cepham nuclei were found to be highly reactive. The corresponding free acids **23**, **26**, and **27** bearing the (*Z*)-2-(methoxyimino)-2-phenylacetyl side-chain have also been prepared for biological testing.

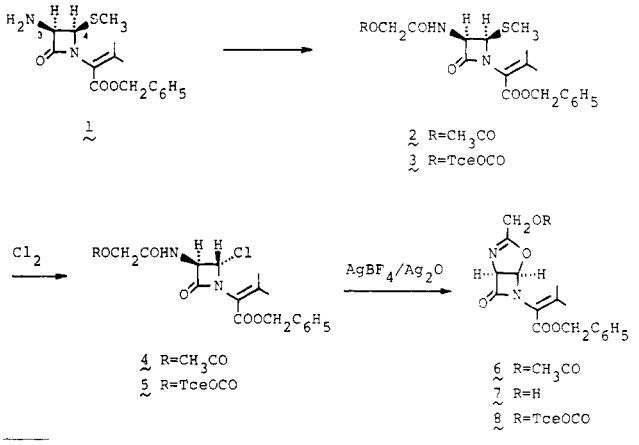
The biological action of penicillins and cephalosporins has been suggested by Strominger and his co-workers to occur by an irreversible reaction of the β-lactam carbonyl with the active sites of transpeptidase enzymes which mediate bacteria cell wall biosynthesis.[1] It has now been generally believed that the biological activity of the β-lactam antibiotics is correlated to the chemical reactivity of their β-lactam ring.[2] As part of our continuing research for unique and potent β-lactam antibiotics, we have had an interest in synthesizing novel β-lactam ring systems which may function more reactively than the penicillins and cephalosporins. We anticipated that introduction of the 1-oxa-2-oxo group to the cephem or cepham nuclei might modify the reactivity of the β-lactam ring in a different chemical sense from the parent compounds. Thus, the β-lactam C–N bond of these compounds may be cleaved via an ionic process (arrow a) as depicted in III, as well as via a conjugation with the unsaturated carbonyl in the case of the cephem (arrow b). In this paper we wish to report the syntheses of these 1-oxa-2-oxocephem (I) and 1-oxa-2-oxocepham (II) nuclei from penicillins.[3]



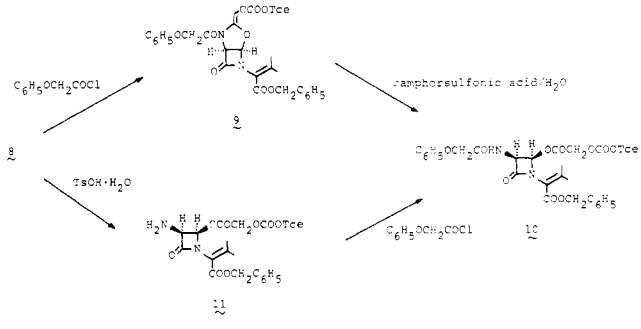
I II III

One of the most reliable methods for annelating new rings to the β-lactam group is the carbon–carbon bond formation utilizing an intramolecular Wittig reaction,[4] which we decided to adapt to the construction of our objective compounds. In order to accomplish this, we needed

Scheme I



Scheme II



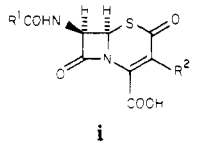
the stereoselective introduction of an oxycarbonyl function to the 4-position of the β-lactam ring with a cis relationship to the 3-acylamino group. For this purpose, we examined a route involving a ring-opening reaction of the oxazolines which could be readily obtained from the optically active penicillins.[5]

The starting material was 1,2-secopenicillin (**1**),[6] which was first acylated with acetylglycolyl chloride[7] to give the acyl derivative **2** (Scheme I). Chlorinolysis of **2** with Cl_2 in CH_2Cl_2 gave exclusively the trans chloride **4**, which in turn was treated with $AgBF_4/Ag_2O$ to give the oxazoline **6** in over 90% yield from the starting material. Since it was difficult to remove the acetyl protective group selectively after the oxazoline ring cleaved, the protective group was exchanged at this stage with the (trichloroethoxy)-

(1) See, e.g., J. L. Strominger, H. Amanuma, S. Curtis, G. Kleppe, J. Rasmussen, D. Waxman, and R. R. Yocum, "Advances in Pharmacology and Therapeutics of the International Congress of Pharmacology, 7th", Vol. 10, M. Adolfe, Ed., Pergamon Press, Oxford, 1979, pp 209–223, and references cited therein.

(2) See, e.g., M. Gorman and C. W. Ryan, "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, pp 536–539.

(3) Recently, the syntheses of several 2-oxocephalosporins (i), based on similar but somewhat different reasoning, have appeared: (a) C. U. Kim, P. F. Misco, and D. N. McGregor, *J. Med. Chem.*, **22**, 743 (1979); (b) C. F. Ebbinghaus, P. Morrissey, and R. L. Rosati, *J. Org. Chem.*, **44**, 4697 (1979); (c) I. Ernest, *Helv. Chim. Acta*, **62**, 2681 (1979).



i

(4) R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972).

(5) S. Wolfe, S.-L. Lee, J.-B. Ducep, G. Kannengiesser, and W. S. Lee, *Can. J. Chem.*, **53**, 497 (1975).

(6) E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, *J. Chem. Soc., Perkin Trans. 1*, 562 (1975).

(7) F. Benington and R. D. Morin, *J. Org. Chem.*, **26**, 194 (1961).

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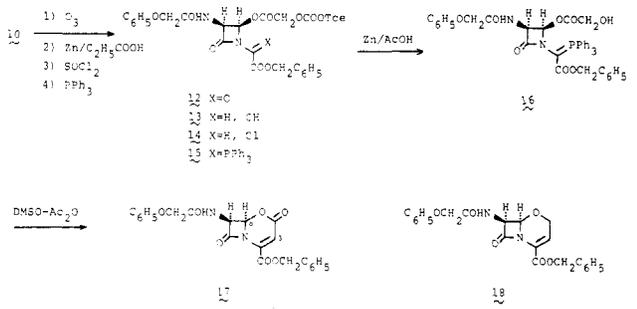
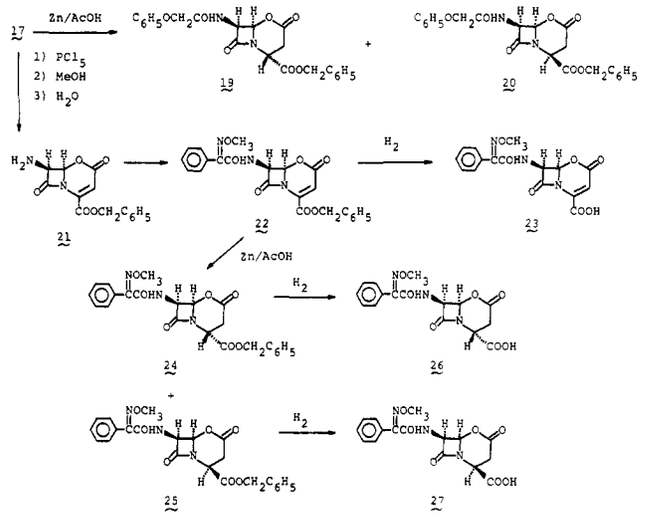
Scheme III



Scheme IV



carbonyl group. Thus, **6** was hydrolyzed with dilute aqueous NaOH to give in 36% yield the alcohol **7**, which was then acylated with (trichloroethoxy)carbonyl chloride to give **8** in 68% yield. A considerably improved overall yield (93%) of this compound was obtained by direct acylation of the starting material with [(trichloroethoxy)carbonyl]glycolyl chloride[8] (**1** → **3**) instead of acetylglycolyl chloride, followed by chlorinolysis and cyclization (**3** → **5** → **8**) in a similar manner.[9]

For effecting the oxazoline ring-opening reaction, **8** was first acylated with phenoxyacetyl chloride to give the oxazolidine **9** (Scheme II). The newly formed olefinic proton in **9** appeared at δ 7.67 as singlet in the NMR spectrum, indicating that there was one isomer, although the configuration was ambiguous. On treatment with camphorsulfonic acid in the presence of a small amount of H_2O, opening of the oxazolidine ring of **9** proceeded in the expected fashion to give the desired monocyclic β-lactam **10** in 82% yield from **8**. It was later found, however, that the reversed operation of the above two-step sequence with the oxazoline **8** could also be effectively carried out. Thus, treatment of **8** with $TsOH \cdot H_2O$ in CH_2Cl_2 gave the amino ester **11** (tosylate),[10] which was then acylated with phenoxyacetyl chloride to afford **10** in 87% yield.

For the transformation of **10** into the phosphorane **15**, a four-step sequence of reactions was carried out according to a known procedure.[11] The compound **10** was ozonized in AcOEt, and the crystalline oxalyl derivative **12** thus formed was then subjected to zinc-dust reduction, which was conducted by using a limited amount of zinc dust in the presence of propionic acid in CH_2Cl_2 at 0–13 °C to yield the epimeric alcohols **13** without damaging the (trichloroethoxy)carbonate group (Scheme III). Conversion of **13** into the corresponding chlorides **14** by treatment with $SOCl_2$ and, finally, treatment of the latter compound with PPh_3 gave the phosphorane **15**, after purification by silica gel chromatography, in 42% yield from **10**.

To remove the (trichloroethoxy)carbonyl group at this stage, **15** was again subjected to reduction with zinc dust, and by the use of a large excess of the reagent in the presence of AcOH in CH_2Cl_2 at 15 °C the alcohol **16** was obtained in 75% yield. Finally, **16** was oxidized by using Me_2SO–Ac_2O to afford, via a spontaneous cyclization of the resulting aldehyde, an 85% yield of the 1-oxa-2-oxocephem **17**.

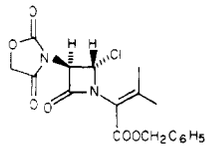
The UV spectrum of the 1-oxa-2-oxocephem **17** (λ_{max} 298 nm), as compared with that of the 1-oxacephem **18** (λ_{max} 263 nm) which we have recently prepared,[12] displayed a 35-nm bathochromic shift, reflecting the conjugation of the 2-oxo group to the Δ^3 double bond. The IR spectrum of **17** showed an extremely high wavenumber absorption of the β-lactam carbonyl at 1815 cm^{-1} instead of at 1795 cm^{-1} as for that of **18**, suggesting a very reactive β-lactam ring system in **17**.

It was of interest to inquire as to whether this unusual IR absorption would be reflected by a conjugative interaction of the lone-pair electrons on the nitrogen of the β-lactam with the α,β-unsaturated carbonyl function in competition with the β-lactam amide conjugation. In this connection, we examined the saturation of the Δ^3 double bond of **17**. When **17** was reduced with zinc dust in the presence of AcOH in CH_2Cl_2 at 15 °C a mixture of diastereoisomers, **19** and **20**, was obtained in a ratio of 7:2 (Scheme IV). Separation of **19** and **20** was readily achieved by chromatography on silica gel. The stereochemistry of these two products was assigned as follows. In the NMR spectrum of the minor product **20**, the newly introduced C-4 proton was long-range coupled to the 7α-proton, whereas that in the major product **19** was not. This five-bond coupling observed in **20** indicated that the C-4 proton of **20** is oriented in an α-axial configuration.[13] Consequently, the corresponding proton of the major product **19** was inevitably assigned to be β.

The IR spectra of the cephams **19** and **20** showed a somewhat lower β-lactam carbonyl absorption (1800 cm^{-1}) than that of the parent 1-oxa-2-oxocephem **17**, indicating the presence of an electron delocalization from the β-lactam nitrogen into the conjugated carbonyl in **17**. However, this absorption frequency is still higher than those of the 1-oxa-cephem **18** or most cephalosporins,[14] thus suggesting

(8) This reagent was prepared by a three-step reaction of benzyl glycolate: see the Experimental Section.

(9) An attempt to effect the cyclization of **5** to **8** under basic conditions (e.g., $NaHCO_3$/aqueous acetone) resulted in the clean formation of an undesired product, ii.



ii

(10) A similar ring-opening reaction of oxazolines was previously reported: see ref 5.

(11) See, e.g., (a) ref 4; (b) S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, *Heterocycles*, **8**, 283 (1977).

(12) D. Hagiwara, H. Takeno, M. Aratani, K. Hemmi, and M. Hashimoto, *J. Med. Chem.*, in press.

(13) There are some examples of cephalosporins in which the coupling between H-4α and H-7α was observed: see, e.g., (a) D. O. Spry, *Tetrahedron Lett.*, 165 (1973); (b) T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi, and T. Oku, *J. Am. Chem. Soc.*, **98**, 2343 (1976).

(14) In normal cephalosporins, the β-lactam carbonyl stretching frequency occurs in the range of 1792–1782 cm^{-1}; see P. V. Demarco and R. Nagarajan, ref 2, p 318.

a highly reactive β-lactam system even in the cepham nucleus. This might be, as we would have expected, due to an inductive effect of the 1-oxa-2-oxo function through the C_6–N σ bond.[15]

Our remaining task was to convert the cephem **17** and cephams **19** and **20** into the corresponding free acids with an appropriate 7-acyl side chain for biological testing. Cleavage of the phenoxyacetyl group of **17** was accomplished by the traditional imino chloride procedure, affording the key intermediate 7-amino-1-oxa-2-oxocephem **21** (HCl salt) in 51% yield. Reacylation of **21** with (*Z*)-2-(methoxyimino)-2-phenylacetic acid by a conventional acylating method (DMF–$POCl_3$) gave the compound **22**, which was finally subjected to hydrogenolysis over palladium black to yield the corresponding free acid **23**. Zinc dust reduction of **22** according to the method described above gave a 7:3 mixture of the cepham-4α-carboxylate **24** and its 4β isomer **25**, separable by chromatography on silica gel. Hydrogenolysis of both diastereoisomers over palladium black yielded the free acids **26** and **27**, respectively.

The new derivatives **23**, **26**, and **27** were tested in vitro against various gram-positive and gram-negative bacteria, but unfortunately these derivatives showed no significant antibacterial activity. This unexpected result may be due to the instability of these cephalosporin nuclei. The half-life of the 1-oxa-2-oxocepham **23** in a pH 7 buffer at room temperature was about 3 min when examined by TLC and UV spectroscopy. Although the cepham derivatives **26** and **27** had somewhat longer half-lifes, they were still unstable (half-life of about 10 min). Studies are continuing to attain more stable members of this class of compounds.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. IR spectra were taken on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a JEOL JNM-MH 100 NMR spectrometer. UV spectra were recorded on a Hitachi EPS-3T spectrophotometer. Mass spectra were measured with a Hitachi RMU-6M mass spectrometer. High-pressure LC separations were performed on a Waters Associates chromatograph equipped with a Model 6000 A pump, a Series 440 refractometer detector, and a μ-Porasil (30 cm × 4 mm) column.

3β-(Acetoxyacetamido)-1-[1-((benzyloxy)carbonyl)-2-methylprop-1-enyl]-4β-(methylthio)azetidin-2-one (2). A mixture of 1·TsOH (4.92 g, 10.0 mmol) and Et_3N (3.12 g, 30.8 mmol) in CH_2Cl_2 (20 mL) was cooled to −40 °C, and a solution of acetylglycolyl chloride (1.53 g, 11.2 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for 40 min, during which time the temperature was gradually raised to 0 °C. The reaction mixture was washed successively with 0.5 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give 4.35 g of **2** as an oil: IR (CH_2Cl_2) 3410, 1770, 1720, 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (s, 3 H), 1.99 (s, 3 H), 2.12 (s, 3 H), 2.24 (s, 3 H), 4.60 (s, 2 H), 5.04 (d, 1 H, J = 4.5 Hz), 5.18 (AB q, 2 H, J = 12 Hz), 5.47 (dd, 1 H, J = 4.5, 8 Hz), 7.03 (d, 1 H, J = 8 Hz), 7.37 (s, 5 H); mass spectrum, m/e 420 (M^+).

3β-(Acetoxyacetamido)-1-[1-((benzyloxy)carbonyl)-2-methylprop-1-enyl]-4α-chloroazetidin-2-one (4). A solution of **2** (crude oil; 4.35 g, ~10.0 mmol) in CH_2Cl_2 (50 mL) was cooled to −78 °C, and a solution of Cl_2 (1.50 g, 21.2 mmol) in CCl_4 (20 mL) was added. The mixture was stirred for 40 min at the same temperature and for 20 min at 0 °C. The reaction mixture was poured into cold, aqueous $NaHCO_3$ (50 mL of saturated $NaHCO_3$ plus ice). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to give 5.50 g of **4** as an oil: IR (CH_2Cl_2) 1780, 1755, 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.10 (s, 3 H), 2.27 (s, 3 H), 4.54 (s, 2 H), 5.04 (br d, 1 H, J = 8 Hz), 5.18 (s, 2 H), 5.76 (br s, 1 H), 7.24 (s, 5 H).

3-(Acetoxymethyl)-7-[1-((benzyloxy)carbonyl)-2-methylprop-1-enyl]-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (6). A solution of **4** (crude oil; 5.50 g, ~10.0 mmol) in THF (40 mL) was cooled to −30 °C, and Ag_2O (4.60 g, 19.8 mmol) and $AgBF_4$ (3.90 g, 20.0 mmol) were added. The mixture was stirred at about −15 °C for 2.5 h and at room temperature for 1 h. The reaction mixture was cooled to 0 °C, and benzene (100 mL), brine (20 mL) and saturated $NaHCO_3$ (20 mL) were added. After being stirred for 20 min at the same temperature, the mixture was filtered with the aid of Celite, and the organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to give an oil (5.40 g), which was chromatographed on silica gel (120 g, elution with CH_2Cl_2–MeOH) to give 3.35 g (90% from **1**) of **6** as an oil: IR (CH_2Cl_2) 1780, 1750, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.94 (s, 3 H), 2.12 (s, 3 H), 2.19 (s, 3 H), 4.69 (s, 2 H), 5.20 (d, 1 H, J = 3.5 Hz), 5.23 (s, 2 H), 6.01 (d, 1 H, J = 3.5 Hz), 7.38 (s, 5 H); mass spectrum, m/e 372 (M^+).

7-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-3-(hydroxymethyl)-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (7). To a solution of **6** (985 mg, 2.65 mmol) in acetone (15 mL) was added a solution of K_2CO_3 (440 mg, 3.18 mmol) in H_2O (7.5 mL), and the mixture was stirred at 55 °C for 3 h. The reaction mixture was concentrated, and AcOEt was added. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and evaporated to give an oil (800 mg), which was chromatographed on silica gel (30 g, elution with benzene–acetone) to give 322 mg (33%) of the starting material and 210 mg (36%) of **7** as an oil: IR (CH_2Cl_2) 1780, 1720, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3 H), 2.27 (s, 3 H), 3.90 (br s, 1 H), 4.24 (s, 2 H), 5.20 (d, 1 H, J = 3.5 Hz), 5.23 (s, 2 H), 6.03 (d, 1 H, J = 3.5 Hz), 7.39 (s, 5 H).

7-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-3-[[[(trichloroethoxy)carbonyl]oxy]methyl]-2-oxa-4,7-diazabicyclo[3.2.0]hept-3-en-6-one (8). Method 1. A mixture of **7** (210 mg, 0.64 mmol) and pyridine (64 μL, 0.79 mmol) in CH_2Cl_2 (4.5 mL) was cooled to −35 °C, and (trichloroethoxy)carbonyl chloride (96 μL, 0.70 mmol) was added. The mixture was stirred for 1 h, during which time the temperature was gradually raised to 0 °C. After being stirred for an additional 1 h at 0 °C, the reaction mixture was diluted with AcOEt and washed successively with dilute HCl, H_2O, dilute $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and evaporated to give an oil, which was chromatographed on silica gel (10 g, elution with CH_2Cl_2) to give 220 mg (68%) of **8** as an oil: IR (CH_2Cl_2) 1780, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.91 (s, 3 H), 2.25 (s, 3 H), 4.73 (s, 2 H), 4.75 (s, 2 H), 5.17 (AB q, 2 H, J = 13 Hz), ~5.2 (d, 1 H, J = 4 Hz), 5.98 (d, 1 H, J = 4 Hz), 7.32 (s, 5 H); mass spectrum, m/e 504 (M^+).

Method 2. A solution of **5** (9.30 g, ~15.6 mmol), obtained as a crude material as described below, in CH_2Cl_2 (120 mL) was cooled to −30 °C, and Ag_2O (2.55 g, 11.0 mmol) and $AgBF_4$ (4.32 g, 22.0 mmol) were added. After being stirred at −20 °C for 1.5 h, the mixture was allowed to warm to 0 °C, and benzene (120 mL), powdered NaCl (4 g), and saturated NaCl (12 mL) were added. The mixture was stirred for 25 min and then filtered with the aid of Celite. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to give a crude oil, which was purified in a way similar to that described above to give 7.59 g (96% from **3**) of **8**.

[[(Trichloroethoxy)carbonyl]oxy]acetyl Chloride. To a cooled (−30 to −35 °C) mixture of benzyl glycolate[16] (23.90 g, 143.8 mmol) and pyridine (13.95 mL, 172.5 mmol) in CH_2Cl_2 (120 mL) was added (trichloroethoxy)carbonyl chloride (33.60 g, 158.6 mmol) during a 15-min period. After the mixture was stirred for 30 min at the same temperature, the temperature was gradually raised to 0 °C, and the reaction mixture was poured into cold, dilute HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to leave 50.00 g of benzyl [[(trichloroethoxy)carbonyl]oxy]acetate as a crystalline mass: mp 49–51 °C; IR (Nujol) 1765, 1745 cm^{-1}; NMR ($CDCl_3$) δ 4.75 (s, 2 H), 4.82 (s, 2 H), 5.23 (s, 2 H), 7.40 (s, 5 H). Anal. Calcd for $C_{12}H_{11}O_5Cl_3$: C, 42.19; H, 3.25; Cl, 31.14. Found: C, 42.09; H, 3.12; Cl, 30.96.

(15) The electron-attracting effect of this 1-oxa-2-oxo group is also estimated from the fact that, in the NMR spectra of **17**, **19**, and **20**, the C-6 protons were considerably low-field shifted (ca. 0.70–0.87 ppm) from that of **18** (H-6, δ 5.06 in $CDCl_3$).[12]

(16) J.-C. Micheau and A. Lattes, *Bull. Soc. Chim. Fr.*, 4018 (1970).

The product (50.00 g, ~172.5 mmol) was dissolved in CH_2Cl_2 (120 mL), and anisole (55.60 g, 514.0 mmol) was added. This mixture was cooled to 0 °C, and a solution of $AlCl_3$ (28.75 g, 215.6 mmol) in $MeNO_2$ (50 mL) was added dropwise during a 30 min period. After being stirred for 15 min at the same temperature, the reaction mixture was poured into ice–water and acidified to pH 1 with 10% HCl. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, and evaporated to leave an oil, which was crystallized from petroleum ether to give 32.25 g of [[(trichloroethoxy)carbonyl]oxy]acetic acid as a crystalline solid: mp 85–88 °C; IR (Nujol) 1760, 1725 cm^{-1}; NMR ($CDCl_3$) δ 4.73 (s, 2 H), 4.80 (s, 2 H), 10.97 (s, 1 H). Anal. Calcd for $C_5H_5O_5Cl_3$: C, 28.88; H, 2.00; Cl, 42.30. Found: C, 28.80; H, 1.87; Cl, 42.27.

This compound (32.25 g, 128.3 mmol) was dissolved in benzene (40 mL), and $SOCl_2$ (45.25 g, 380.3 mmol) was added. The mixture was refluxed for 2 h and then concentrated. The residue was distilled under reduced pressure to give 32.65 g (84%) of [[(trichloroethoxy)carbonyl]oxy]acetyl chloride: bp 77–79 °C (0.2 torr); IR (film) 1800, 1760 cm^{-1}; NMR ($CDCl_3$) δ 4.87 (s, 2 H), 5.03 (s, 2 H).

1-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-4β-(methylthio)-3β-[[[(trichloroethoxy)carbonyl]oxy]acetamido]azetidin-2-one (3). A mixture of **1**·TsOH (15.00 g, 30.5 mmol) and Et_3N (9.3 mL, 66.7 mmol) in CH_2Cl_2 (100 mL) was cooled to −40 °C and stirred, and a solution of [[(trichloroethoxy)carbonyl]oxy]acetyl chloride (11.42 g, 42.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise during a period of 30 min. After being stirred for an additional 30 min, during which time the temperature was allowed to warm to 0 °C, the mixture was washed successively with 1 N HCl, H_2O, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give an oil, which was chromatographed on silica gel (100 g, elution with benzene–AcOEt) to give 16.46 g (97%) of **3** as an oil: IR (CH_2Cl_2) 3400, 1770, 1710 (sh), 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.02 (s, 3 H), 2.27 (s, 3 H), 4.76 (s, 2 H), 4.82 (s, 2 H), 5.44 (dd, 1 H, J = 4.5, 8 Hz), 5.04–5.32 (m, 3 H), 7.13 (d, 1 H, J = 8 Hz), 7.38 (s, 5 H).

1-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-4α-chloro-3β-[[[(trichloroethoxy)carbonyl]oxy]acetamido]azetidin-2-one (5). A solution of **3** (8.66 g, 15.6 mmol) in CH_2Cl_2 (45 mL) was cooled to −78 °C, and a solution of Cl_2 (1.35 g, 19.0 mmol) in CCl_4 (15.6 mL) was added. The mixture was stirred for 30 min at the same temperature and then allowed to warm to 0 °C (30 min). The reaction mixture was purged with N_2 and then concentrated to give 9.30 g of **5** as a crude oil: IR (CH_2Cl_2) 3400, 1780, 1710 (sh), 1695 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.34 (s, 3 H), 4.73 (s, 2 H), 4.84 (s, 2 H), 5.15 (dd, 1 H, J = 2, 8 Hz), 5.20 (br s, 2 H), 5.80 (d, 1 H, J = 2 Hz), 7.30 (d, 1 H, J = 8 Hz), 7.40 (s, 5 H).

7-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-4-(phenoxyacetyl)-3-[[[(trichloroethoxy)carbonyl]oxy]methylene]-2-oxa-4,7-diazabicyclo[3.2.0]heptan-6-one (9). A solution of **8** (680 mg, 1.34 mmol) in THF (5 mL) was cooled to −78 °C, and pyridine (0.15 mL, 1.86 mmol) and phenoxyacetyl chloride (0.21 mL, 1.52 mmol) were added. The mixture was stirred for 1.5 h, during which time the temperature was gradually raised to room temperature. After evaporation of the solvent, the residue was dissolved in AcOEt and washed successively with dilute HCl, brine, dilute $NaHCO_3$, and brine. Drying over $MgSO_4$ and evaporation gave 880 mg of **9** as an oil: IR (CH_2Cl_2) 1785, 1725, 1700, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.32 (s, 3 H), 4.82 (s, 2 H), 4.92 (AB q, 2 H, J = 13 Hz), 5.22 (AB q, 2 H, J = 12 Hz), 5.58 (d, 1 H, J = 4 Hz), 6.15 (d, 1 H, J = 4 Hz), 6.8–7.6 (m, 10 H), 7.67 (s, 1 H).

1-[1-((Benzyloxy)carbonyl)-2-methylprop-1-enyl]-3β-(phenoxyacetamido)-4β-[[[(trichloroethoxy)carbonyl]oxy]acetoxy]azetidin-2-one (10). Method 1. To a solution of **9** (880 mg, ~1.34 mmol), obtained as described above, in CH_2Cl_2 (10 mL) saturated with H_2O was added camphorsulfonic acid (16 mg, 0.07 mmol), and the mixture was stirred for 35 min at room temperature. The reaction mixture was diluted with AcOEt and washed with dilute $NaHCO_3$ and H_2O. Drying over $MgSO_4$ and evaporation gave an oil (930 mg), which was chromatographed on silica gel (15 g, elution with CH_2Cl_2) to give 730 mg (82% from **8**) of **10** as an oil: IR (CH_2Cl_2) 1780, 1765, 1720 (sh), 1695 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (s, 3 H), 2.30 (s, 3 H), 4.5–4.9 (m, 6 H), 5.23 (s, 2 H), 5.38 (dd, 1 H, J = 4, 8 Hz), 6.38 (d, 1 H, J = 4 Hz), 6.8–7.6 (m, ~11 H); mass spectrum, m/e 656 (M^+).

Method 2. To a suspension of **11**·TsOH (4.00 g, 5.75 mmol) in CH_2Cl_2 (20 mL) was added phenoxyacetyl chloride (1.03 mL, 7.47 mmol) with ice-bath cooling. This mixture was stirred, and a solution of pyridine (1.10 mL, 13.60 mmol) in CH_2Cl_2 (4 mL) was added during a period of 30 min. After being stirred for an additional 30 min, the mixture was concentrated, and the residue was dissolved in AcOEt, washed successively with dilute HCl, H_2O, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give a crude oil (4.10 g), which was purified in a similar manner as that described above to give 3.59 g (95%) of **10**.

***p*-Toluenesulfonate of 3β-Amino-1-[1-((benzyloxy)carbonyl)-2-methylprop-1-enyl]-4β-[[[(trichloroethoxy)carbonyl]oxy]acetoxy]azetidin-2-one (11).** To a solution of **8** (5.00 g, 9.87 mmol) in acetone (35 mL) was added TsOH·H_2O (1.94 g, 10.20 mmol), and the mixture was stirred for 20 min at 18 °C. The solvent was then removed by evaporation to leave a semisolid, which was triturated with ether and washed with petroleum ether to give 6.33 g (92%) of **11** (tosylate) as a crystalline solid: mp 109–113 °C dec; IR (CH_2Cl_2) 1785, 1770, 1725 cm^{-1}; NMR (Me_2SO-d_6) δ 2.00 (s, 3 H), 2.18 (s, 3 H), 2.33 (s, 3 H), 4.8–5.1 (m, 3 H), 5.01 (s, 2 H), 5.25 (s, 2 H), 6.47 (d, 1 H, J = 4 Hz), 7.17 (d, 2 H, J = 8 Hz), 7.42 (s, 5 H), 7.55 (d, 2 H, J = 8 Hz). Anal. Calcd for $C_{20}H_{21}N_2O_8Cl_3$: C, 46.59; H, 4.20; N, 4.03; S, 4.61; Cl, 15.28. Found: C, 46.35; H, 4.11; N, 3.96; S, 4.78; Cl, 15.44.

1-[Oxo((benzyloxy)carbonyl)methyl]-3β-(phenoxyacetamido)-4β-[[[(trichloroethoxy)carbonyl]oxy]acetoxy]azetidin-2-one (12). A solution of **10** (3.38 g, 5.14 mmol) in AcOEt (60 mL) was cooled to −78 °C, and O_3 was bubbled through it until the starting material disappeared, by TLC. The reaction mixture was purged with N_2 and poured into a solution of $NaHSO_3$ (10 g, 96.1 mmol) and Na_2SO_3 (2.5 g, 19.8 mmol) in H_2O (100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crystalline solid, which was washed with ether to give 2.60 g (80%) of **12**: mp 122–126 °C dec; IR (CH_2Cl_2) 1835, 1765, 1715, 1705 cm^{-1}; NMR ($CDCl_3$) δ 4.49 (s, 4 H), 4.57 (s, 2 H), 5.26 (s, 2 H), 5.47 (dd, 1 H, J = 5, 9 Hz), 6.70 (d, 1 H, J = 5 Hz), 6.6–7.5 (m, ~11 H). Anal. Calcd for $C_{25}H_{21}N_2O_{11}Cl_3$: C, 47.52; H, 3.35; N, 4.43; Cl, 16.84. Found: C, 47.35; H, 3.26; N, 4.33; Cl, 16.66.

1-[((Benzyloxy)carbonyl)(triphenylphosphoranylidene)methyl]-3β-(phenoxyacetamido)-4β-[[[(trichloroethyl)carbonyl]oxy]acetoxy]azetidine-2-one (15). A solution of **12** (1.58 g, 2.50 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, and propionic acid (1.2 mL, 16.1 mmol) and Zn dust (0.60 g, 9.2 mmol) were added. The mixture was stirred for 30 min, during which time the temperature was gradually raised to 13 °C and, after 30 min, again cooled to 0 °C. The reaction mixture was diluted with cold AcOEt and filtered with the aid of Celite. The filtrate was washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give 1.49 g of the epimeric alcohols **13** (oil): IR (CH_2Cl_2) 1795, 1765 (br), 1695 cm^{-1}.

A mixture of **13** (1.26 g, 2.00 mmol) and 2,6-lutidine (0.35 mL, 3.00 mmol) in CH_2Cl_2 (15 mL) was cooled to −30 °C, and $SOCl_2$ (0.22 mL, 3.00 mmol) was added. The mixture was stirred for 20 min, during which time the temperature was allowed to warm to 0 °C. After being stirred for an additional 1.5 h, the mixture was poured into chilled brine and extracted with AcOEt. The extract was washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated to give 1.31 g of the epimeric chlorides **14** (oil): IR (CH_2Cl_2) 1805, 1765, 1730 (sh), 1700 cm^{-1}.

To a solution of **14** (1.31 g, ~2.00 mmol) in CH_2Cl_2 (10 mL) was added PPh_3 (1.05 g, 4.00 mmol), and the mixture was left at room temperature for 12 h and then heated to reflux for 4.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed with dilute $NaHCO_3$. Drying over $MgSO_4$ and evaporation gave an oil, which was chromatographed on silica gel (12 g, elution with benzene–AcOEt) to give 0.99 g (53% from **12**) of **15** as an amorphous solid: IR (CH_2Cl_2) 1765, 1690, 1620 cm^{-1}.

1-[((Benzyloxy)carbonyl)(triphenylphosphoranylidene)methyl]-4β-(hydroxyacetoxy)-3β-(phenoxyacetamido)azetidin-2-one (16). To a solution of **15** (915 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) were added acetic acid (0.5 mL, 8.7 mmol) and Zn dust (900 mg, 13.7 mmol), and the mixture was stirred at 15 °C for 5 h. The reaction mixture was filtered with the aid of Celite, and the filtrate was washed successively with saturated

$NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and evaporated to give an oil (780 mg), which was chromatographed on silica gel (elution with benzene–AcOEt) to give 550 mg (75%) of **16** as an oil: IR (CH_2Cl_2) 1780, 1755, 1690, 1620 cm^{-1}.

Benzyl 7-(Phenoxyacetamido)-1-oxa-2-oxocephem-4-carboxylate (17). To a solution of **16** (288 mg, 0.41 mmol) in Me_2SO (1.4 mL) was added Ac_2O (1.4 mL), and the mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated in vacuo, and the concentrate was dissolved in a mixture of benzene and AcOEt (1:2) and washed successively with dilute $NaHCO_3$, H_2O, and brine. Drying over $MgSO_4$ and evaporation gave an oil (280 mg), which was chromatographed on silica gel (5 g, elution with benzene–acetone) to give 147 mg (85%) of **17** as a foam: IR (CH_2Cl_2) 1815, 1745, 1700 cm^{-1}; NMR ($CDCl_3$) δ 4.53 (s, 2 H), 5.33 (s, 2 H), 5.6–5.8 (m, 2 H), 6.38 (s, 1 H), 6.7–7.7 (m, ~11 H); UV (dioxane) λ_{max} 270 nm (ϵ 5000), 278 (5300), 298 (5700); mass spectrum, *m/e* 422 (M^+). Anal. Calcd for $C_{22}H_{18}N_2O_7$: C, 62.56; H, 4.30; N, 6.63. Found: C, 62.28; H, 4.52; N, 6.37.

Benzyl 7-(Phenoxyacetamido)-1-oxa-2-oxocepham-4α-carboxylate (19) and Its 4β Isomer 20. To a solution of **17** (580 mg, 1.37 mmol) in CH_2Cl_2 (10 mL) were added AcOH (0.85 mL, 14.8 mmol) and Zn dust (670 mg, 10.2 mmol), and the mixture was stirred for 25 min at room temperature. The reaction mixture was diluted with AcOEt and filtered with the aid of Celite. The filtrate was washed successively with H_2O, dilute $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated to give an amorphous solid (**19** and **20**, 7:2 on high-pressure LC), which was crystallized from benzene–CH_2Cl_2 to give 387 mg of **19**: mp 137–138.5 °C; IR (CH_2Cl_2) 3400, 1800, 1770, 1750, 1695 cm^{-1}; NMR ($CDCl_3$) δ 2.91 (AB part of an ABX spectrum, 2 H, J = 8, 10, 16 Hz), 4.50 (s, 2 H), 4.75 (X part of an ABX spectrum, 1 H, J = 8, 10 Hz), 5.20 (s, 2 H), 5.57 (dd, 1 H, J = 3.5, 9 Hz), 5.76 (d, 1 H, J = 3.5 Hz), 6.8–7.4 (m, 10 H), 7.50 (d, 1 H, J = 9 Hz). Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.36; H, 4.67; N, 6.57.

The mother liquor was concentrated and chromatographed on silica gel (6 g, elution with benzene–AcOEt) to give 8 mg of **19** and 38 mg of **20** (crystalline solid): mp 114–115.5 °C; IR (CH_2Cl_2) 3400, 1800, 1745, 1695 cm^{-1}; NMR ($CDCl_3$) δ 2.90 (d, 2 H, J = 5 Hz), 4.44 (dt, 1 H, J = 1.5, 5 Hz), 4.50 (s, 2 H), 5.20 (s, 2 H), 5.62 (ddd, 1 H, J = 1.5, 3.5, 9 Hz), 5.71 (d, 1 H, J = 3.5 Hz), 6.8–7.4 (m, ~11 H) 7.95 (br d, 1 H, J = 9 Hz). Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 61.94; H, 4.61; N, 6.53.

Benzyl 7-Amino-1-oxa-2-oxocephem-4-carboxylate (21) Hydrochloride. A solution of **17** (379 mg, 0.90 mmol) in CH_2Cl_2 (10 mL) was cooled to −40 °C, and *N,N*-dimethylaniline (218 mg, 1.72 mmol) and PCl_5 (373 mg, 1.80 mmol) were added. After being stirred for 50 min at the same temperature, the mixture was cooled to −60 °C, and MeOH (0.6 mL, 14.8 mmol) was added dropwise. The mixture was further stirred for 1 h, during which time the temperature was gradually raised to 0 °C, and H_2O (0.3 mL, 16.7 mmol) was added. Stirring was continued for an additional 30 min, and the resulting crystalline mass was filtered and washed with dimethoxyethane to give 149 mg (51%) of **21** (HCl salt): mp 75–82 °C dec; IR (Nujol) 1815, 1725 cm^{-1}; NMR (CD_3OD) δ 5.24 (d, 1 H, J = 4 Hz), 5.33 (s, 2 H), 6.15 (d, 1 H, J = 4 Hz), 6.46 (s, 1 H), 7.2–7.8 (m, 5 H). Anal. Calcd for $C_{14}H_{13}N_2O_5Cl$: C, 51.78; H, 4.03; N, 8.63. Found: C, 51.43; H, 4.12; N, 8.35.

Benzyl 7-[(*Z*)-2-(Methoxyimino)-2-phenylacetamido]-1-oxa-2-oxocephem-4-carboxylate (22). To a solution of DMF (440 mg, 6.02 mmol) in CH_2Cl_2 (10 mL) was added $POCl_3$ (540 mg, 3.52 mmol) at 0 °C, and the mixture was stirred for 70 min at the same temperature. To this mixture was added (*Z*)-2-(methoxyimino)-2-phenylacetic acid (540 mg, 3.01 mmol), and the mixture was stirred for 1 h at the same temperature. This mixture was then added to a cooled (−45 °C) suspension of **21**·HCl (460 mg, 1.42 mmol) in CH_2Cl_2 (15 mL), and pyridine (660 mg, 8.34 mmol) was added. The mixture was stirred for 1 h, during which time the temperature was gradually raised to −10 °C. The reaction mixture was diluted with AcOEt and washed successively with H_2O, dilute $NaHCO_3$, dilute HCl, and brine. Drying over $MgSO_4$ and evaporation gave an oil (~600 mg), which was chromatographed on silica gel (20 g, elution with benzene–AcOEt) to give 352 mg of **22** as an amorphous solid: IR (CH_2Cl_2) 3390, 1815, 1740, 1690 cm^{-1}; NMR (acetone-d_6) δ 3.95 (s, 3 H), 5.40 (s, 2 H), 6.03 (dd, 1 H, J = 4, 8 Hz), 6.23 (d, 1 H, J = 4 Hz), 6.33 (s, 1 H), 7.3–7.8 (m, 10 H), 8.50 (br d, 1 H, J = 8 Hz). Anal. Calcd for $C_{23}H_{19}N_3O_7$: C, 61.47; H, 4.26; N, 9.35. Found: C, 61.18; H, 4.45; N, 9.08.

7-[(*Z*)-2-(Methoxyimino)-2-phenylacetamido]-1-oxa-2-oxocephem-4-carboxylic Acid (23). To a solution of **22** (200 mg, 0.45 mmol) in a mixture of AcOEt (5 mL) and EtOH (5 mL) was added palladium black (130 mg), and the mixture was stirred for 20 min under an atmospheric pressure of H_2. After removal of the catalyst by filtration, the filtrate was concentrated, and the residue was triturated with ether and isopropyl ether to give 120 mg of **23** as an amorphous solid: IR (Nujol) 3370, 1815, 1740, 1680 cm^{-1}; NMR (Me_2SO-d_6) δ 3.95 (s, 3 H), 5.75 (dd, 1 H, J = 4, 8 Hz), 6.11 (d, 1 H, J = 4 Hz), 6.19 (s, 1 H), 7.4–7.8 (m, 5 H), 9.61 (d, 1 H, J = 8 Hz).

Benzyl 7-[(*Z*)-2-(Methoxyimino)-2-phenylacetamido]-1-oxa-2-oxocepham-4α-carboxylate (24) and Its 4β Isomer 25. To a solution of **22** (270 mg, 0.60 mmol) in CH_2Cl_2 (8 mL) were added AcOH (0.9 mL, 15.7 mmol) and Zn dust (540 mg, 8.26 mmol), and the mixture was stirred for 20 min at room temperature. The reaction mixture was diluted with AcOEt and filtered with the aid of Celite. The filtrate was washed successively with H_2O, dilute $NaHCO_o$, and brine, dried over $MgSO_4$, and evaporated to give a crude foam (**24** and **25**, 7:3, on high-pressure LC). Chromatography on silica gel (8 g, elution with benzene–AcOEt) gave 102 mg of **24** (foam) and 68 mg of **25** (foam). For **24**: IR (CH_2Cl_2) 3370, 1790, 1760, 1740, 1680 cm^{-1}; NMR (acetone-d_6) δ 3.12 (d, 2 H, J = 5 Hz), 3.93 (s, 3 H), 4.87 (t, 1 H, J = 5 Hz), 5.23 (s, 2 H), 5.68 (dd, 1 H, J = 3.5, 9 Hz), 6.03 (d, 1 H, J = 3.5 Hz), 7.3–7.8 (m, 10 H), 8.45 (d, 1 H, J = 9 Hz). Anal. Calcd for $C_{23}H_{21}N_3O_7$: C, 61.19; H, 4.69; N, 9.31. Found: C, 61.38; H, 4.66; N, 8.95. For **25**: IR (CH_2Cl_2) 3370, 1795, 1770, 1740, 1680 cm^{-1}; NMR (acetone-d_6) δ 3.04 (AB part of an ABX spectrum, 2 H, J = 4, 8, 16 Hz), 3.94 (s, 3 H), 4.65 (m, X part of an ABX spectrum which is long-range coupled to the proton at δ 5.71, 1 H), 5.19 (s, 2 H), 5.71 (ddd, 1 H, J = 1.5, 3.5, 8.5 Hz), 5.99 (d, 1 H, J = 3.5 Hz), 7.2–7.8 (m, 10 H), 8.15 (d, 1 H, J = 8.5 Hz). Anal. Calcd for $C_{23}H_{21}N_3O_7$: C, 61.19; H, 4.69; N, 9.31. Found: C, 60.83; H, 4.58; N, 9.15.

7-[(*Z*)-2-(Methoxyimino)-2-phenylacetamido]-1-oxa-2-oxocepham-4α-carboxylic Acid (26). To a solution of **24** (173 mg, 0.83 mmol) in a mixture of AcOEt (3 mL) and EtOH (3 mL) was added palladium black (75 mg), and the mixture was stirred for 15 min under an atmospheric pressure of H_2. After removal of the catalyst by filtration, the filtrate was concentrated, and the residue was triturated with isopropyl ether to give 125 mg of **26** as an amorphous solid: IR (Nujol) 1790, 1730, 1650 cm^{-1}; NMR (Me_2SO-d_6) δ 2.97 (d, 2 H, J = 8 Hz), 3.92 (s, 3 H), 4.68 (t, 1 H, J = 8 Hz), 5.48 (dd, 1 H, J = 3.5, 8 Hz), 5.93 (d, 1 H, J= 3.5 Hz), 7.3–7.8 (m, 5 H), 9.47 (d, 1 H, J = 8 Hz).

7-[(*Z*)-2-(Methoxyimino)-2-phenylacetamido]-1-oxa-2-oxocepham-4β-carboxylic Acid (27). Hydrogenolysis of **25** (110 mg, 0.24 mmol) was carried out in a way similar to that described for preparation of **26**, giving 74 mg of **27** as an amorphous solid: IR (Nujol) 1800, 1770, 1680 cm^{-1}; NMR (Me_2SO-d_6) δ 2.90 (a pair of dd, 2 H, J = 4, 16 Hz and 8, 16 Hz), 3.93 (s, 3 H), 4.44 (m, 1 H), 5.53 (ddd, 1 H, J = 1.5, 4, 8 Hz), 5.88 (d, 1 H, J = 4 Hz), 7.4–7.7 (m, 5 H), 9.67 (d, 1 H, J = 8 Hz).

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Registry No. 1·TSOH, 74280-93-6; **2**, 74280-94-7; **3**, 74280-95-8; **4**, 74280-96-9; **5**, 74280-97-0; **6**, 74280-98-1; **7**, 74310-18-2; **8**, 74280-99-2; **9**, 74281-00-8; **10**, 74281-01-9; **11**·TSOH, 74281-03-1; **12**, 74281-04-2; **13** epimer 1, 74281-05-3; **13** epimer 2, 74281-06-4; **14** epimer 1, 74281-07-5; **14** epimer 2, 74281-08-6; **15**, 74281-09-7; **16**, 74281-10-0; **17**, 74310-19-3; **19**, 74310-20-6; **20**, 74310-21-7; **21**·HCl, 74281-11-1; **22**, 74281-12-2; **23**, 74310-22-8; **24**, 74281-13-3; **25**, 74281-14-4; **26**, 74281-15-5; **27**, 74281-16-6; acetylglycolyl chloride, 13831-31-7; (trichloroethoxy)carbonyl chloride, 17341-93-4; [[(trichloroethoxy)carbonyl]oxy]acetyl chloride, 73884-79-4; benzyl glycolate, 30379-58-9; benzyl[[(trichloroethoxy)carbonyl]oxy]acetate, 74231-20-2; [[(trichloroethoxy)carbonyl]oxy]acetic acid, 74231-21-3; phenoxyacetyl chloride, 701-99-5; triphenylphosphine, 603-35-0; (*Z*)-2-(methoxyimino)-2-phenylacetic acid, 38113-96-1.