extracts were dried, and the solvent was evaporated to yield 3.7 g of the tritylated acid.

HBT/DCC Procedure: Preparation of the Active Ester and Coupling to the 3-Chloro Nucleus.[7] To a solution of tritylated acid (3.68 g, 7.7 mmol) in 800 mL of THF were added 1.16 g of hydroxybenzotriazole and 1.86 g of dicyclohexylcarbodiimide. The mixture was stirred for 2 h at room temperature and concentrated under reduced pressure to approximately half the original volume, and the precipitated dicyclohexylurea was filtered off. The filtrate contained the activated ester ready for coupling.

The 3-chlorocephem nucleus[12] (1.69 g) was suspended in 35 mL of water and 17.5 mL of acetone, and the pH was adjusted to 7.5 with a 45% solution of K_3PO_4. To this mixture, the previously prepared active ester was added, and the pH was maintained at 7.5. The solution was stirred for 16 h at room temperature and then concentrated to remove the acetone and THF. The residue was diluted with water and EtOAc and then acidified to pH 2.5 with 1 N HCl. The EtOAc layer was separated and washed with a 5% $NaHCO_3$ solution. The combined aqueous solutions were acidified to pH 2.5 and extracted twice with EtOAc. After drying, the solvent was evaporated to give 2.52 g of a crude product. This material was chromatographed on a silica gel column, eluting first with $CHCl_3$ and then with 5% MeOH/95% $CHCl_3$. The yield of tritylated cephalosporin was 1.09 g (20%). This material was dissolved in 98% formic acid (14 mL) and 1.5 mL of water, and the solution was stirred at room temperature. The precipitated trityl alcohol was removed by filtration. The filtrate was evaporated under reduced pressure, and then ether was added to the residue, and the mixture was stirred for 30 min before the desired compound **28** was filtered off. Yield 420 mg (62%).

By following this general procedure, cephalosporin **31** was synthesized. The following data are for the trityl protected derivative of **31**: NMR (DMSO-d_6) δ 3.46 (s, 2 H), 3.62 and 3.96 (AB q, J = 18 Hz, 2 H), 5.12 (d, J = 5 Hz, 1 H), 5.62 (dd, J = 5 and 8 Hz, 1 H), 7.0–7.5 (m, 18 H), 8.9 (br s, 1 H), 9.04 (d, J = 8 Hz, 1 H); MS, m/e (667, M^+). Anal. ($C_{35}H_{27}N_4O_4S_2Cl$) C, H, N.

General Procedure for Preparation of Heterocyclic Thioacetamido Cephalosporins 32–34: Synthesis of 7-(Bromoacetyl)-3-chlorocephalosporanic Acid. A solution of 2.5 N NaOH was added dropwise to a suspension of 1.17 g (5.0 mmol) of 7-amino-3-chlorocephalosporanic acid in 25 mL of acetone and 25 mL of H_2O until the pH was 8. At this time the nucleus went into solution. The solution was cooled to −10 °C. Bromoacetyl bromide and 1 N NaOH were slowly added to the reaction alternately, with use of the 1 N NaOH to keep the pH between 8 and 9 so that the unreacted nucleus stayed in solution. Addition was continued until TLC showed no starting nucleus remained. Total addition of $BrCH_2COBr$ was 1.6 mL (18.3 mmol, 3.7 equiv). The acetone was evaporated, and the pH was adjusted to 2.2. The water was then evaporated until the product began to precipitate. After cooling, 829 mg (47%) of product was obtained in two crops: NMR (DMSO-d_6) δ 3.51 and 3.90 (AB q, J = 17.59 Hz, 2 H), 3.93 (s, 2 H), 5.12 (d, J = 4.95 Hz, 1 H), 5.58 (dd, J = 4.95 and 7.92 Hz, 1 H), 9.31 (d, J = 7.92 Hz, 1 H); MS, m/e (355, M^+); UV (EtOH) λ_{max} 264 nm (ϵ 7000); IR (KBr) 1771 cm^{-1} (C=O).

Displacement of Bromine by Heterocyclic Thiols. The bromoacetyl cephalosporin was dissolved in CH_3CN and H_2O (1:1), and the pH was adjusted to 7.5 with NaOH. The solution was cooled in an ice water bath, and the heterocyclic thiol (1.05 equiv) was added. The pH of the reaction mixture was maintained between 7.5 and 7.8 with 0.1 N NaOH. Stirring was continued in the ice bath for 2 h and then at room temperature for 2 h until TLC showed completion of the reaction. The pH was then adjusted to 2; the solid that precipitated was filtered and dried to give the desired product.

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Registry No. **1**, 115338-98-2; **1** (Ar = Br, R = Cl), 85690-93-3; **2**, 115338-99-3; **3**, 115339-00-9; **4**, 115339-01-0; **5**, 115339-02-1; **6**, 115339-03-2; **7**, 115339-04-3; **8**, 115339-05-4; **9**, 115339-06-5; **10**, 115339-07-6; **11**, 115339-08-7; **12**, 73426-29-6; **13**, 115339-09-8; **14**, 115339-10-1; **15**, 115339-11-2; **16**, 115339-12-3; **17**, 115339-13-4; **18**, 68506-27-4; **19**, 115339-14-5; **20**, 115339-15-6; **21**, 115339-16-7; **22**, 115339-17-8; **23**, 115339-18-9; **24**, 115339-19-0; **25**, 115339-20-3; **26**, 115339-21-4; **27**, 110425-20-2; **28**, 110425-19-9; **29**, 115339-22-5; **30**, 115339-23-6; **30** (trityl deriv), 115339-31-6; **31**, 115339-24-7; **31** (trityl deriv), 115339-32-7; **32**, 115339-25-8; **33**, 115339-26-9; **34**, 115339-27-0; $BrCH_2COBr$, 598-21-0; ethyl 2-aminobenzothiazole-5-acetate, 115339-33-8; ethyl 2-amino-5-phenylthiazole-4-acetate, 115339-28-1; ethyl 2-(tritylamino)-5-phenylthiazole-4-acetate, 115339-29-2; 2-(tritylamino)-5-phenyl-4-thiazole-4-acetic acid, 115339-30-5; 7-amino-3-chloro-3-cephem-4-carboxylic acid, 53994-69-7; 2-thiazolethiol, 5685-05-2; 4*H*-1,2,4-triazole-3-thiol, 3179-31-5; 5-amino-2*H*-1,2,4-triazole-3-thiole, 16691-43-3.

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Oral Absorption of Cephalosporin Antibiotics. 3. Synthesis and Biological Properties of 7α-Methoxy-7β-(arylacetamido)-3-chloro-3-cephem-4-carboxylic Acids[1]

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A series of 7α-methoxy-7β-amido-3-chloro-3-cephem-4-carboxylic acids was prepared and evaluated for biological activity. When compared with the parent 7-non-methoxy analogues, these new 7α-methoxy-3-chloro cephalosporins displayed diminished antimicrobial activity.

The cephalosporin class of antibiotics has proven to be very useful in clinical medicine due to its generally broad spectrum of antibacterial activity and relative lack of toxicity. Many structural variations of the original Cephalosporin C nucleus have been synthesized chemically.[2] Others have been discovered in microbiological fermentations—among these are the cephamycins.[3] Ce-

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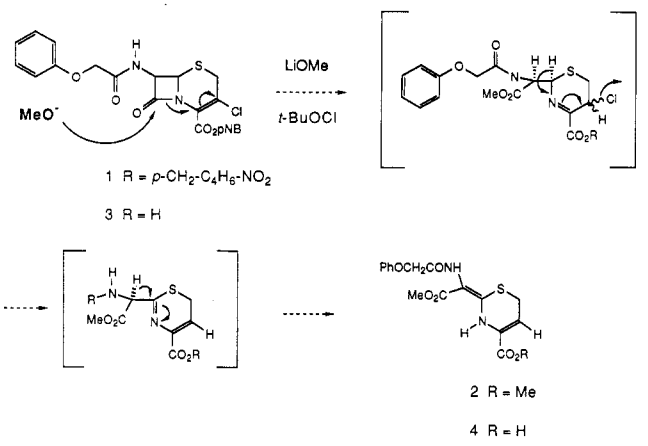
(2) For example, Nagata, W.; Narisada, M.; Yoshida, T. (Chapter 1), and Holden, K. G. (Chapter 2), *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2.

0022-2623/88/1831-1997$01.50/0

Scheme I



phamycins (7α-methoxy cephalosporins) have been shown to be more stable to β-lactamase deactivation than their non-methoxy analogues and as a result possess enhanced antibacterial activity.[4] Recently we observed that certain cephalosporins having a non-glycyl aromatic acetic acid side chain are orally absorbed.[5] We decided to investigate the effect that introducing a 7-methoxy group onto the 3-chloro-3-cephem-4-carboxylic acid nucleus would have upon the biological activity and pharmacokinetics of these non-glycyl arylacetyl cephalosporins.

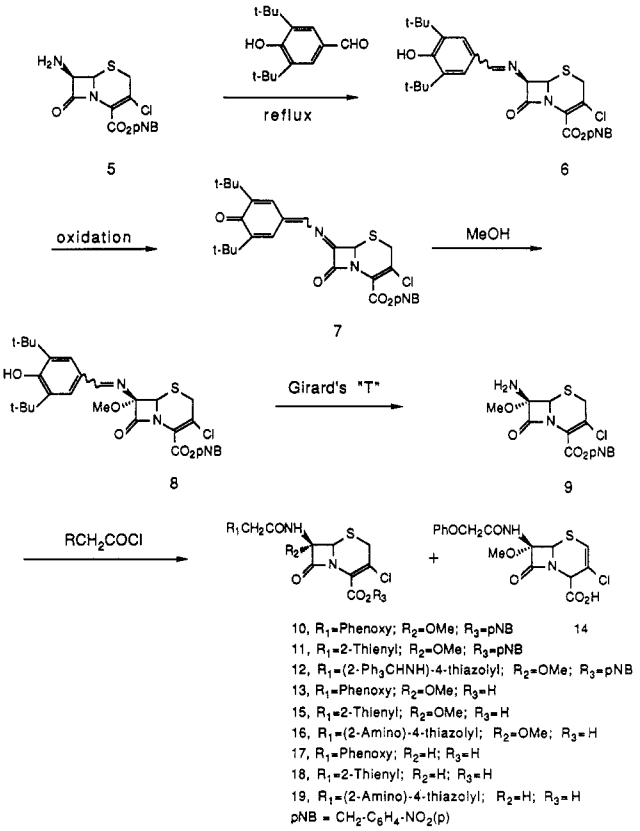
Chemistry

A number of methods have been reported for introducing the 7-methoxy group onto cephalosporins.[6] Koppel and Koehler reported the 7-methoxylation of various β-lactams by treating the non-methoxy acyl substrate with lithium methoxide followed by *tert*-butyl hypochlorite.[7] We repeated their procedure, using the *p*NB ester of 7-(phenoxyacetamido)-3-chloro-3-cephem-4-carboxylic acid **1** as the starting material, but isolated only the non-β-lactam product **2**. In addition to opening of the β-lactam and loss of chlorine, transesterification also took place. This structure is similar to one reported by Indelicato et al. in 1977.[8] Our adaptation of their mechanism is shown in Scheme I.

Feyen and Schrock reported a similar methoxylation procedure for β-lactams.[9] They chose free acids, not esters, of penicillins and cephalosporins as starting materials. Application of their procedure to **3** led only to the non-β-lactam acid **4**.

Trying to determine the reason for these problems, we repeated the reaction, quenching before completion. Careful isolation of the products yielded only unchanged starting material and **4**. We recovered none of the 7α-methoxy-β-lactam, indicating that this desired product either was not formed or that it wasn't stable to reaction

Scheme II



conditions and thus decomposed before isolation. In light of these unsuccessful reactions, we decided to pursue a different approach.

Yanagisawa et al. solved the 7-methoxylation problem in a different way, utilizing a quinoidal imine intermediate.[10] We applied their method to our substrate **5** as shown in Scheme II. Formation of the Schiff base **6** from 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde and 7-amino-3-chloro-3-cephem-4-carboxylic acid *p*NB ester **5** was accomplished easily by refluxing in benzene for 90 min. According to NMR spectrometry, the yield was almost quantitative. Oxidation of the Schiff base **6** with nickel peroxide gave the quinoidal imine **7** in variable yields ranging from 20 to 90%. However, when DDQ was used for oxidation, consistently high and reproducible yields of 80–90% were achieved. Methanol addition to the quinoidal imine bond in **7** yielded the 7α-methoxy Schiff base **8** in good yields (50–90%). The time required for complete methanol addition varied from 1 h to overnight and was monitored by NMR spectroscopy. Compound **8** was purified by silica gel chromatography and isolated as a yellow amorphous solid. Girard's "T" reagent was used to remove the benzalidene side chain. The desired 7α-methoxy-β-amino nucleus **9** thus obtained was used immediately without purification for acylation with various substituted acetyl chlorides.

The acid chlorides we employed for these acylations were phenoxyacetyl, thiopheneyl-2-acetyl, and 2-[[(triphenylmethyl)amino]thiazol-4-yl]acetyl. The desired products **10–12** were isolated. After hydrogenation of **10** to remove the *p*NB protective group, the NMR spectrum of the crude

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Table I. Agar Dilution Minimum Inhibitory Concentrations (μg/mL) against Representative Organisms[a]

compd	*S. aureus* (Pen G suscept)	*S. pyogenes*	*S. pneumoniae*	*H. influenzae* (β-lactamase(−))	*H. influenzae* (β-lactamase(+))	*E. coli*
17[b]	0.25	0.125	0.25	2	2	64
13	>[c]	128	128	>	>	>
18[b]	0.5	0.125	0.125	1	1	4
15	>	128	128	>	>	>
19[b]	1	0.125	0.5	1	1	1
16	16	1	0.5	16	16	8
cefaclor	1	0.25	0.5	1	2	1

[a] Determined by agar dilution as described in ref 12. [b] Kukolja, S. et al. *J. Med. Chem.* 2nd paper previous, this issue. [c] > denotes an MIC of greater than 128 μg/mL.

product indicated a mixture of 3-cephem and 2-cephem acids **13** and **14** in a 3:1 ratio. These isomers were separated on silica gel, and the 2-cephem acid **14** was crystallized from $CHCl_3$. The 3-cephem-4-carboxylic acid **13** was isolated as an amorphous solid. Apparently isomerization was caused by the amine formed during hydrogenation. In order to prevent this form occurring in the next experiments, 1 equiv of 1 N HCl was added to the reaction solution before hydrogenation. Consequently, when the *p*NB group was removed from the 7-thiophene-2-acetamido ester **11**, only the 3-cephem-4-carboxylic acid **15** was isolated. The 2-amino-4-thiazolyl derivative **16** was similarly prepared and characterized. It can be seen that this method affords the possibility of preparing numerous 7-methoxy-3-chloro cephalosporins and is limited only by the success of the final acylation.

Biological Results and Discussion

The 7α-methoxy acids described above were submitted for agar dilution antimicrobial testing. These results, and comparison with the corresponding non-methoxy cephalosporins, are shown in Table I. When compared with their non-methoxy analogues, the 7α-methoxy cephalosporins show significantly less antimicrobial activity. The phenoxyacetyl and thiopheneylacetyl derivatives **13** and **15** showed MIC's of greater than 128 μcg/mL for most organisms tested. Only the aminothiazolyl compound **16** showed moderate activity. UV studies on all three compounds showed no significant loss of absorption after 24 h at pH 7 and 8, so apparently the lack of activity is not due to instability at the pH of the agar. We conclude that addition of a 7-methoxy group to these arylacetamido cephalosporins decreases rather than increases their antimicrobial activity.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on Nicolet FT-IR Model 10-DX instruments. UV spectra were recorded on a Cary Model 219 spectrometer in 95% EtOH. NMR spectra were determined on JEOL FX-90Q, Brucher WM270, and GE QE-300 instruments. Merck silica gel plates were used for TLC. Temperatures are reported in degrees Centigrade. Solvents were dried over molecular sieves unless noted otherwise. Elemental analyses were performed by the microanalytical group of the Lilly Research Laboratories. Analytical results indicated by symbols of the elements were within ±0.4%.

2-[1-(Phenoxyacetamido)-2-methoxy-2-oxoethylidene]-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylic Acid Methyl Ester (2). To 160 mL of THF was added 184 mg of lithium (26.4 mmol) under positive N_2 pressure. MeOH (30 mL) was added dropwise over ~15 min with magnetic stirring. After the lithium had completely reacted, the solution was cooled with a dry ice/acetone bath and (phenoxyacetyl)-3-chloro-3-cephem-4-carboxylic acid *p*-nitrobenzyl ester **1** (4.02 g, 8.0 mmol) in 50 mL of THF was added in a slow stream over 4 min with rapid stirring. After stirring 3 min more, *tert*-butyl hypochlorite (1.14 mL, 10.1 mmol) was added. After stirring at dry ice/acetone temperature for 30 min, $P(OMe)_3$ (0.24 mL) and HOAc (2 mL) were added to quench the reaction. The dry ice/acetone bath was removed, and the reaction mixture was allowed to warm to room temperature for 1 h. The THF was evaporated in vacuo, and the residue was dissolved in EtOAc/5% HCl. The organic layer was washed successively with 5% HCl (2×), 5% $NaHCO_3$ (2×), and saturated NaCl (1×). The organic layer was dried over $MgSO_4$, filtered, and evaporated in vacuo to give 4.22 g of a dark brown oil. The oil was chromatographed over silica gel, eluting with a gradient composed of toluene and 60% EtOAc/toluene to give 1.40 g (46%) of **2** as a colorless gum: ^1H NMR (DMSO-d_6, ppm) 3.52 (d, J = 5.7, 2 H), 3.61 (s, 3 H), 3.81 (s, 3 H), 4.55 (s, 2 H), 6.18 (d of t, J = 5.7, <1, 1 H, collapses to t upon addition of D_2O), 6.8–7.4 (m, 5 H), 9.00 (br s, 1 H, exchangeable), 11.18 (br s, 1 H, exchangeable); ^{13}C (DMSO-d_6, ppm) 22.47, 51.08, 52.85, 66.67, 94.94, 108.01, 114.72, 121.09, 129.08, 129.33, 155.02, 157.69, 162.17, 166.44, 168.30; UV (EtOH) λ_{max} 335 (ε 13 800), 275 (ε 6400), 269 nm (ε 6100); IR (KBr) 1723, 1693, 1670, 1569 cm^{-1}; MS, m/e 378 (M^+).

2-[1-(Phenoxyacetamido)-2-methoxy-2-oxoethylidene]-3,6-dihydro-2*H*-1,3-thiazine-4-carboxylic Acid (4). (Phenoxyacetyl)-3-chloro-3-cephem-4-carboxylic acid *p*-nitrobenzyl ester **3** (1.84 g, 5.0 mmol) was dissolved in 55 mL of THF and, under positive N_2 pressure, cooled with a dry ice/acetone bath. A solution of lithium (104 mg, 15 mmol) in MeOH (8.4 mL) was added dropwise over ~15 min so that the temperature of the reaction mixture did not rise above −55 °C. The reaction mixture became very thick, and 75 mL of THF was added slowly to facilitate stirring and dissolution. After 4 h at ~−78 °C, *tert*-butyl hypochlorite (0.73 mL, 6.5 mmol) in 2 mL of CH_2Cl_2 was added to the reaction mixture. The reaction mixture was allowed to warm to −55 °C and was stirred for 30 min. The reaction solution was poured into a solution of NH_4Cl and Na_2SO_3 in H_2O, and the pH of the solution was adjusted to 7.0 with 1 N HCl. The THF was evaporated in vacuo, and the water layer was washed with EtOAc (2 × 50 mL). Fresh EtOAc was added to the water layer; the pH was adjusted to 2.0. The layers were separated, and the water layer was washed with additional EtOAc. The combined EtOAc washes at pH 2 were dried over $MgSO_4$, filtered, and evaporated in vacuo to give 929 mg (51%) of **4** as a yellow solid: ^1H NMR (DMSO-d_6, ppm) 3.54 (d, J = 5.7, 2 H), 3.62 (s, 3 H), 4.58 (s, 2 H), 6.14 (d of t, J = 5.7, ~1, 1 H, collapses to t upon addition of D_2O), 6.9–7.4 (m, 5 H), 9.01 (br s, 1 H, exchangeable), 11.18 (br s, 1 H, exchangeable); ^{13}C (DMSO-d_6, ppm) 22.03, 50.49, 66.19, 94.09, 106.53, 114.23, 120.61, 128.85, 129.31, 154.67, 157.21, 162.76, 165.85, 167.85; UV (EtOH) λ_{max} 335 (ε 15 200), 275 (ε 5000), 269 nm (ε 5100); IR (KBr) 1710, 1687, 1670, 1655, 1574 cm^{-1}; MS, m/e 364 (M^+). Anal. ($C_{16}H_{16}N_2O_6S$) C, H, N.

Schiff Base 6. The *p*NB ester of 3-chloro-3-cephem-4-carboxylic acid **5**[11] (777 mg, 2.1 mmol) and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (470 mg, 2.0 mmol) were heated to reflux in benzene (80 mL) for 2 h. Approximately 20 mL of benzene was collected in a Dean–Stark trap during this time. After filtration, the benzene was evaporated to give the desired product as a gum, which was immediately oxidized: ^1H NMR ($CDCl_3$, ppm) 1.45 (s, 18 H), 3.47, 3.81 (AB q, J = 18.5, 2 H), 5.20 (d, J = 4.8, 1 H), 5.40 (br s, 3 H), 5.58 (s, 1 H), 7.57, 8.19 (AB q, J = 8.6, 4 H), 7.61 (s, 2 H), 8.47 (d, J = 1.8, 1 H).

Quinoidal Imine 7 by Nickel Peroxide Oxidation. The Schiff base **6** prepared above was dissolved in 60 mL of CH_2Cl_2 and cooled in an ice water bath. $MgSO_4$ (1.25 g) and nickel peroxide (1.25 g) were added. The reaction mixture was stirred at ice bath temperature, and the progress of the reaction was monitored by NMR spectroscopy. At 5 h, the NMR spectrum indicated ~90% conversion to the quinoidal compound **7**: ^1H

NMR ($CDCl_3$, ppm) 1.31, 1.32 (2 s, 18 H), 3.59, 3.90 (AB q, J = 18.5, 2 H), 5.40 (br s, 1 H), 5.46 (br s, 2 H), 6.97 (d, J = 2.0, 1 H), 7.59, 8.21 (AB q, J = 8.8, 4 H), 7.87 (d, J = 2.0, 1 H). This product was not isolated, but was used immediately in the following reaction.

The CH_2Cl_2 suspension from the previous reaction was filtered through Celite and cooled in an ice water bath. MeOH (50 mL) was added, and stirring was continued for 1 h at ice bath temperature. The solvents were evaporated to give 900 mg of the 7-OMe Schiff base **8** as a gum. Chromatography over silica gel, eluting with a 9:1 mixture of toluene/hexanes gave 300 mg of the desired product: ^{1}H NMR ($CDCl_3$, ppm) 1.46 (s, 18 H), 3.41, 3.77 (AB q, J = 18.2, 2 H), 5.12 (s, 1 H), 5.43 (s, 2 H), 5.66 (s, 2 H), 7.60, 8.20 (AB q, J = 8.8, 4 H), 7.68 (s, 2 H), 8.51 (s, 1 H); UV (EtOH) λ_{max} 284 (ϵ 26 500), 228 nm (ϵ 24 200); IR ($CHCl_3$) 1772, 1743 cm^{-1}; MS, m/e 616 (M^+). Anal. ($C_{30}H_{34}N_3ClO_7S$) C, H, N.

Quinoidal Imine 7 by DDQ Oxidation. To a benzene solution (200 mL) of the Schiff base **6** prepared as described above from 1.88 g (8.0 mmol) of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde at room temperature was added 2.45 g (10.7 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The dark solution was stirred at room temperature for 1 h. An aliquot was removed and evaporated. The NMR analysis showed complete oxidation to the desired quinoidal imine **7** described above. After filtration, MeOH (50 mL) was added for conversion to the 7-methoxy product **8** described above.

7α-Methoxy-7β-amino-3-chloro-3-cephem-4-carboxylic Acid *p*-Nitrobenzyl Ester (9). The Schiff base **8** (308 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (12 mL). Girard's "T" reagent (176 mg, 1 mmol) was dissolved in MeOH (8 mL) and added to the CH_2Cl_2 solution. The reaction mixture was stirred 2.5 h at room temperature and then evaporated in vacuo to dryness. The residue was dissolved in CH_2Cl_2 (25 mL), washed with 2 × 10 mL of H_2O, dried over $MgSO_4$, and filtered. This solution was used for acylation as described below.

General Acylation Procedure for Compounds 10–12. To an ice bath cooled CH_2Cl_2 solution of the 7α-methoxy-7β-amino-3-chloro-3-cephem-4-carboxylic acid *p*NB ester **9**, prepared as described above, was added 1 equiv of quinoline and then a solution of 1 equiv of the appropriate acid chloride in CH_2Cl_2 (25 mL). The reaction mixture was stirred at ice bath temperature for 45–90 min. The solution was then washed successively with saturated $NaHCO_3$, H_2O, 1 N HCl, and H_2O, dried over $MgSO_4$, filtered, and evaporated in vacuo. This residue was chromatographed over silica gel, eluting with a gradient composed of 1 L of toluene and 1 L of EtOAc.

7α-Methoxy-7β-(phenoxyacetamido)-3-chloro-3-cephem-4-carboxylic Acid *p*-Nitrobenzyl Ester (10). With ~0.5 mmol of **9** as the starting material, 71 mg (~27%) of **10** was obtained: ^{1}H NMR ($CDCl_3$, ppm) 3.41, 3.63 (AB q, J = 17.4, 2 H), 3.47 (s, 3 H), 4.53 (s, 2 H), 5.11 (s, 1 H), 5.35 (s, 2 H), 6.7–8.2 (m, 10 H).

7α-Methoxy-7β-(thiopheneyl-2-acetamido)-3-chloro-3-cephem-4-carboxylic Acid *p*-Nitrobenzyl Ester (11). With ~4.5 mmol of **9** as the starting material, 470 mg (~20%) of **11** was obtained: ^{1}H NMR ($CDCl_3$, ppm) 3.45, 3.69 (AB q, J = 18.0, 2 H), 3.46 (s, 3 H), 3.89 (s, 2 H), 5.12 (s, 1 H), 5.38 (s, 2 H), 6.65 (s, 1 H), 6.9–7.4 (m, 3 H), 7.4, 8.2 (AB q, J = 8.8, 4 H).

7α-Methoxy-7β-[[2-[(triphenylmethyl)amino]thiazol-4-yl]acetamido]-3-chloro-3-cephem-4-carboxylic Acid *p*-Nitrobenzyl Ester (12). With ~4.7 mmol of **9** as the starting material, 750 mg (~20%) of **12** was obtained: ^{1}H NMR ($CDCl_3$, ppm) 3.48, 3.70 (AB q, J = 18, 2 H), 3.44 (s, 3 H), 5.10 (s, 1 H), 5.20 (s, 2 H), 6.14 (s, 1 H), 6.68 (br s, 1 H), 7.18 (s, 15 H), 7.4–8.4 (m, 5 H).

General Hydrogenation Procedure for Compounds 13–15 and Trityl-Protected 16. Five percent Pd/C (using a weight equivalent to cephalosporin starting material) was prereduced in "2B" EtOH (5 mL) at 60 psi of H_2 for 30 min. A solution of the cephalosporin *p*NB ester in THF (2–5 mL, enough to dissolve the compound) and MeOH (30–100 mL) was added to the prereduced catalyst. Except in the case of **10**, 1 equiv of 1 N HCl was also added. This solution was hydrogenated at 60 psi for 50 min. The reaction was filtered, and the catalyst washed with a solution of 5 mL of 1 N HCl in 20 mL MeOH and then 15 mL of MeOH. The combined filtrates were evaporated in vacuo to a volume of ~5 mL and then added to a slurry of EtOAc and H_2O (30 mL each). The pH was adjusted to 7.5 with 1 N NaOH. To the water layer was added fresh EtOAc (50 mL), and the pH was adjusted to 2.3 with 1 N HCl. The acidic H_2O was washed with additional EtOAc, and the combined EtOAc layers were dried over MgSO4, filtered, and evaporated in vacuo to give the product.

7α-Methoxy-7β-(phenoxyacetamido)-3-chloro-3-cephem-4-carboxylic Acid (13). With 0.75 mmol of **10** as the starting material, 216 mg of a mixture of the title compound **13** and the corresponding Δ-2 isomer **14** were obtained. This mixture was chromatographed over silica gel, eluting with a gradient composed of 500 mL of $CHCl_3$ and 500 mL of 20% MeOH in $CHCl_3$: yields **13**, 81 mg (27%); **14**, 58 mg (19%). **13**: ^{1}H NMR ($CDCl_3$, ppm) 3.48, 3.65 (AB q, J = 18, 2 H), 3.55 (s, 3 H), 4.62 (s, 2 H), 5.19 (s, 1 H), 6.20 (v br s, 1 H), 6.9–7.6 (m, 6 H); UV (EtOH) λ_{max} 268 nm (ϵ 8005); IR (KBr) 1778 cm^{-1}. Anal. ($C_{16}H_{15}N_2ClO_6S$) C, H, N. **14**: ^{1}H NMR ($CDCl_3$, ppm) 3.53 (s, 3 H), 4.60 (s, 2 H), 5.00 (d, J = 1.3, 1 H), 5.46 (s, 1 H), 6.33 (d, J = 1.3, 1 H), 6.8–7.8 (m, 7 H); UV (EtOH) λ_{max} 238 nm (ϵ 7586); IR 1789 cm^{-1}; MS, m/e 398 (M^+). Anal. ($C_{16}H_{15}N_2ClO_6S$) C, H, N.

7α-Methoxy-7β-(thiophene-2-ylacetamido)-3-chloro-3-cephem-4-carboxylic Acid (15). With 0.71 mmol of **11** as the starting material, 189 mg (69%) of **15** was obtained, which was crystallized from a small amount of $CHCl_3$: ^{1}H NMR ($CDCl_3$, ppm) 3.49, 3.69 (AB q, J = 17.6, 2 H), 3.50 (s, 3 H), 3.91 (s, 2 H), 5.14 (s, 1 H), 6.50 (br s, 1 H), 6.9–7.4 (m, 3 H); UV (EtOH) λ_{max} 268 nm (ϵ 8661); IR (KBr) 1775 cm^{-1}; MS, m/e 388 (M^+). Anal. ($C_{14}H_{13}N_2ClO_5S_2$) C, H, N.

7α-Methoxy-7β-[[2-[(triphenylmethyl)amino]thiazol-4-yl]acetamido]-3-chloro-3-cephem-4-carboxylic Acid. With 0.58 mmol of **12** as the starting material, 178 mg (48%) of the title compound was obtained: ^{1}H NMR ($CDCl_3$, ppm) 3.2–3.9 (m, 2 H), 3.44 (s, 3 H), 3.63 (s, 2 H), 5.07 (s, 1 H), 6.27 (s, 1 H), 7.22 (s, 15 H), 8.34 (br s, 1 H).

7α-Methoxy-7β-[(2-aminothiazol-4-yl)acetamido]-3-chloro-3-cephem-4-carboxylic Acid (16). 7α-methoxy-7β-[[2-[(triphenylmethyl)amino]thiazo-4-ylacetamido]-3-chloro-3-cephem-4-carboxylic acid (150 mg, 0.23 mmol) was dissolved in HCO_2H (98%, 4.0 ml) at room temperature. H_2O (0.4 mL) was added, and stirring was continued. TLC at 3 h (20% HOAc in EtOAc) showed no starting material. A white solid that had precipitated was filtered, and the volume was reduced to ~2 mL. More solid precipitated and was filtered. The filtrate was evaporated in vacuo, and the resulting residue was sonicated with ~10 mL of Et_2O for 30 min. The resulting brown solid was filtered and dried overnight in vacuo to give 78 mg of the desired product **16**: ^{1}H NMR (DMSO-d_6, ppm), 1.08 (t, J = 7.0, 3 H), 3.37 (q, J = 7.0, 2 H), 3.36 (s, 2 H), 3.38 (s, 3 H), 3.53, 3.89 (AB q, J = 18.0, 2 H), 5.24 (s, 1 H), 6.30 (s, 1 H), 7.03 (br s, 2 H), 9.33 (br s, 1 H); IR (KBr) 1772 cm^{-1}; UV (EtOH) λ_{max} 258 nm (ϵ 5556); MS, m/e 405 (M^+ + 1). Anal. ($C_{13}H_{13}N_4ClO_5S_2$) C, H, N.

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Supplementary Material Available: Assignments of ^{1}H and ^{13}C NMR spectra and description of two-dimensional NMR experiments for product **2** (1 page). Ordering information is given on any current masthead page.