were concentrated in vacuo. The residue was dissolved in 200 mL of ethyl acetate and treated as described in the general procedure. Recrystallization from 2-propanol: yield 2.4 g (31%); mp 174–176 °C; R_f 0.43 (dichloromethane/methanol, 96/4); $[\alpha]^{20}_D$ 2.6° (c 1, DMF). Anal. ($C_{16}H_{21}N_3O_4Cl$) C, H, N.

N^α,N^ϵ-Bis(benzyloxycarbonyl)-L-lysine (2-chloroethyl)-amide: from N^α,N^ϵ-bis(benzyloxycarbonyl)-L-lysine N-hydroxysuccinimide ester;[16] recrystallized from a mixture of acetone and hexane: yield 88%; mp 123–125 °C; R_f 0.52 (ethyl acetate); $[\alpha]^{20}_D$ 4.2° (c 1, DMF). Anal. ($C_{24}H_{30}N_3O_5Cl$) C, H, N.

General Procedure for the Synthesis of [(2-Chloroethyl)nitrosocarbamoyl]amino Acid (2-Chloroethyl)amide. Method A. The N-(benzyloxycarbonyl)amino acid (2-chloroethyl)amide (0.01 mol) was hydrogenated in 100 mL of ethanol with an equivalent of a 10% HCl aqueous solution and 10% Pd/C as catalyst, at room temperature and under atmospheric pressure. The reaction was monitored by TLC.

The catalyst was removed by filtration and the filtrate concentrated in vacuo to give an oily residue, which was dried under reduced pressure.

To a cold solution of that compound in 20 mL of DMF was added DIEA (0.01 mol, 1.72 mL) and (2-chloroethyl)nitrosocarbamic acid 2,4,5-trichlorophenyl ester (0.012 mol, 3.98 g). The mixture was stirred for 3 h at room temperature and concentrated in vacuo. The residue was quickly chromatographed through a silica gel column and the compound was crystallized in the appropriate solvent (see Table II) or purified by chromatography on a silica gel column.

In the case of the lysine derivative, a twofold excess of reactants was used.

Method B. The N-(tert-butyloxycarbonyl)amino acid (2-chloroethyl)amide (0.01 mol) was dissolved in 5 mL of trifluoroacetic acid containing 2% of anisole or thioanisole under nitrogen and at room temperature. The reaction, monitored by TLC, was over in half an hour.

The solution was concentrated in vacuo at room temperature to give an oily residue, which was triturated in ether to give a white, amorphous solid, which was dried in a dessicator.

The subsequent operations were the same as those described for method A.

Antitumor Evaluation. The oncostatic activities and acute LD_{50} values were evaluated on L1210 leukemia. The method used for this evaluation is described: on day 0, adult F1 (DBA/2 × C57B1/6) mice were inoculated ip with 10^5 L1210 leukemia cells. A group of 8–10 mice was used for each concentration of every compound. On day 1, the mice received various doses of compound to be tested in olive oil (2–150 mg/kg). On days 5 and 9,

drug or solvent injections were repeated only in mice with no signs of toxicity. The mortality of mice was monitored daily and autopsies were performed to find out whether or not deaths were due to leukemia or to a toxic action of the drug. The acute LD_{50} of each compound was determined graphically (98% confidence limits). For each compound, the oncostatic index, $T/C \times 100$ (T = median survival time in the treated group of mice, C = median survival time in the control group) was calculated. This index expressed prolongation of survival. When this oncostatic index > 125 and the difference between treated and control groups was statistically significant according to the Wilcoxon nonparametric W test, the agent was considered active at the given dose. The value ∞ means that more than 50% of treated animals in the group had been cured. Antitumor activity evaluations were performed in Villejuif, France (ICIG, Dr. Maral and Chenu, Service of Professeur Mathe).

(16) Chillemi, F. *Gazz. Chim. Ital.* 1963, *93*, 1079.

Synthesis and Antibacterial Activity of 2-[(Methoxycarbonyl)methylene]cephalosporins

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The synthesis and in vitro activities of a series of 2-[(methoxycarbonyl)methylene]-3-cephem-4-carboxylic acids with methyl or acetoxymethyl at the 3-position are described. The key step in the synthesis includes the stereospecific formation of the 2-[(Z)-(methoxycarbonyl)methylene] group by Pummerer rearrangement of the sulfoxides **3a** and **3b**. It was also possible to isomerize photochemically the C-2 olefin of **4a** to its E isomer, **9**. The new derivatives exhibited significant in vitro Gram-positive antibacterial activity.

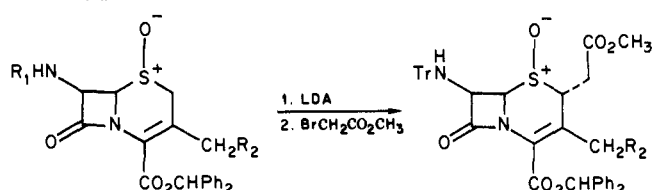The incorporation of substituents at the C-2 position of the cephalosporin nucleus has been of considerable interest in the search for cephalosporin analogues with interesting antibacterial activity.[1] Recently, a number of C-2 ethy-

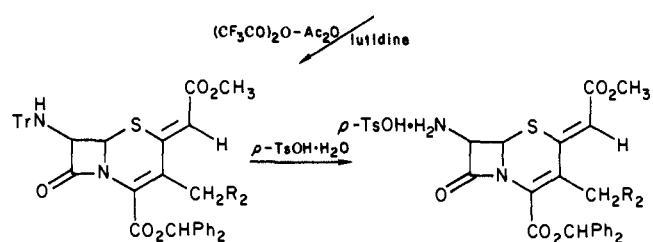Chart I. Structures of Some 2-Ethylidenecephalosporins
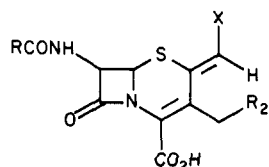
I, X = SR
II, X = H
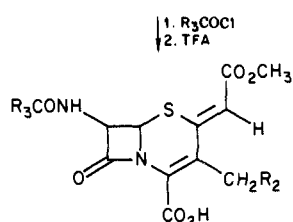III, X = alkyl or aryl; R_2 = H or OAc

Scheme I

1a, R_1 = R_2 = H
b, R_1 = H; R_2 = OAc
2a, R_1 = Ph$_3$C; R_2 = H
b, R_1 = Ph$_3$C; R_2 = OAc

3a, R_2 = H
b, R_2 = OAc

4a, R_2 = H
b, R_2 = OAc

5a, R_2 = H
b, R_2 = OAc

6a, R_2 = H
b, R_2 = OAc

Scheme II

7

8

→ 4a (4b)

Scheme III

4a

9

10

conjugation with the Δ^3-double bond and thereby enhance the antibacterial activity of this class of cephalosporin derivatives.[3]
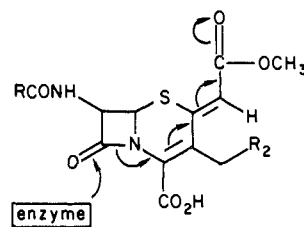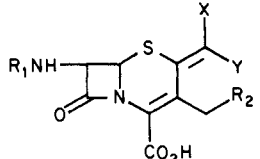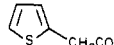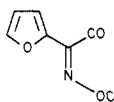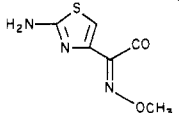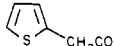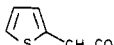
Chemistry. We have found that the sulfoxides **2a** and **2b** react rapidly with LDA at −25 °C to generate the C-2 anions cleanly. Alkylation of these anions with methyl bromoacetate yielded the 2-[(methoxycarbonyl)methyl]-cephems **3a** and **3b** in excellent yield (Scheme I). The compounds **3a** and **3b** are stereochemically single isomers at the C-2 position; to this we have assigned the α-configuration on the basis of the assumption that the alkylation of the C-2 anions will take place primarily from the sterically less crowded α-side to form the α-isomer only.
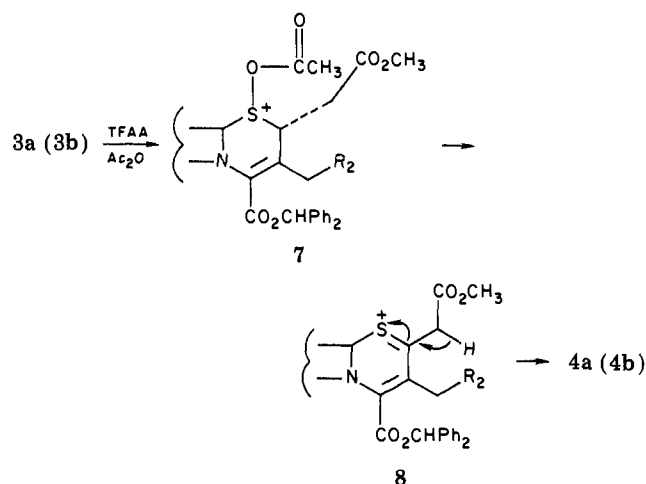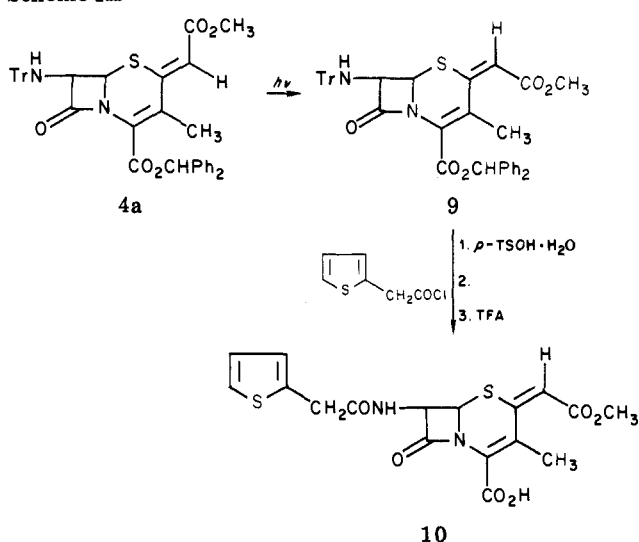
lidene cephalosporin derivatives (compounds I–III, Chart I) have been reported.[2] These compounds are characterized by the attachment of a hydrogen,[2a] a heteroatom,[2b] an alkyl group,[2c] or an aryl group[2c] to the C-2 ethylidene moiety.

In our studies on C-2 modified cephalosporins, particular attention has been paid to incorporating the methoxycarbonyl group on the C-2 ethylidene moiety in an attempt to obtain broad-spectrum cephalosporins. We hoped that the introduction of an electron-withdrawing group might increase the acylating power of the β-lactam carbonyl via

(1) (a) For a summary of 2-substituted cephalosporin derivatives, see "Cephalosporins and Penicillins: Chemistry and Biology", Flynn, E. H., Ed., Academic Press, New York, 1972, Chapter 4; (b) "Topics in Antibiotic Chemistry", P. Sammes, Ed., Ellis Horwood Limited, 1980, Vol. 4, Chapter 4.

(2) (a) I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, *J. Med. Chem.*, 14, 420 (1971); (b) G. V. Kaiser, C. W. Ashbrook, T. Goodson, I. G. Wright, and E. M. Van Heyningen, *ibid.*, 14, 426 (1971). (C) R. B. Woodward, K. Heusler, I. Ernest, K. Burri, R. J. Friary, F. Haviv, W. Oppolzer, R. Paioni, K. Syhora, R. Wenger, and J. K. Whitesell, *Nouv. J. Chem.*, 1, 85 (1977).

(3) For a review on theoretical and physicochemical studies on β-lactam antibiotics, see "Chemistry and Biology of β-Lactam Antibiotics", R. B. Morin and M. Gorman, Ed., Academic Press, New York, 1982, Vol. 1, chapter 5.

Table I

compd	R_1	R_2	X	Y	UV[g], max, nm (ϵ)	formula	anal.
6a₁	(thienyl-CH₂CO)	H	CO_2CH_3	H	345 (18 360)	$C_{17}H_{16}N_2O_6S_2$	C, H, N
6a₂ (TFA salt)	$PhCH(NH_2)CO$[a]	H	CO_2CH_3	H	336 (15 505)	$C_{21}F_3H_{20}N_3O_8S$	e
6a₃	$PhCH(OH)CO$[b]	H	CO_2CH_3	H	336 (12 100)	$C_{19}H_{18}N_2O_7S$	C, H, N
6a₄	(furyl/methoximino)[c]	H	CO_2CH_3	H	342 (11 300)	$C_{18}H_{17}N_3O_8S$	C, H, N[f]
6a₅ (TFA salt)	(aminothiazole/methoximino)[d]	H	CO_2CH_3	H	340 (14 100)	$C_{19}F_3H_{18}N_5O_9S_2$	C, H, N
6b	(thienyl-CH₂CO)	OAc	CO_2CH_3	H	340 (16 900)	$C_{19}H_{18}N_2O_8S_2$	e
10	(thienyl-CH₂CO)	H	H	CO_2CH_3	314 (9384)	$C_{17}H_{16}N_2O_6S_2$	C, H, N

[a] For preparation, see ref 7a. [b] Reference 7b. [c] Reference 7d. [d] Reference 7c. [e] Isolated as gum. [f] C: calcd, 49.65; found, 51.48. H: calcd, 3.93; found, 4.38. N: calcd, 9.65; found, 8.39. [g] In ethanol.

Table II. Antibacterial Activities of 2-[(Methoxycarbonyl)methylene]cephalosporin Derivatives[a]

organism	strain no.	cephal-othin	6a₁	6a₂	6a₃	6a₄	6a₅	6b	10
Streptococcus pneumoniae	9585	0.03	0.25	0.13	0.25	0.25	0.016	0.13	0.5
Streptococcus pyogenes	9604	0.06	2	0.025	0.25	0.25	0.016	0.5	2
Staphylococcus aureus	9537	0.06	0.13	1	0.5	2	2	2	0.06
Staphylococcus aureus + 50% serum	9537	2	63	32	32	63	125	63	63
Staphylococcus aureus (Pen-Res)	9606	0.5	2	>125	>125	4	4	2	1
Streptococcus faecalis	20688	32	2	63	16	32	63	4	8
Escherichia coli	15119	16	63	>125	>125	16	2	125	125
Escherichia coli	20341	32	125	>125	>125	63	2	>125	125
Klebsiella pneumoniae	15130	16	125	>125	>125	16	16	>125	>125
Klebsiella pneumoniae	20468	>125	>125	>125	>125	>125	32	63	>125
Proteus mirabilis	9900	1	16	>125	63	4	2	125	32
Proteus mirabilis	9716	8	32	>125	>125	4	16	125	4
M. morganii	15153	>125	125	>125	>125	63	>125	>125	16
P. rettgeri	21203	63	63	>125	>125	32	32	>125	4
Serratia marcescens	20019	>125	>125	>125	>125	>125	>125	>125	4
Enterobacter cloacae	9659	>125	>125	>125	>125	>125	>125	>125	>125
Enterobacter cloacae	9656	>125	>125	>125	>125	63	>125	>125	>125

[a] Determined by serial twofold dilution of compound in Mueller-Hinton agar and inoculation of the agar surface or broth with an appropriately diluted 18–24-h broth culture. Agar plates and tubes of broth were incubated at 37 °C for 17 h, and the lowest concentration causing inhibition of visible growth was considered to be the minimal inhibitory concentration.

Exposure of **3a** and **3b** to TFAA (trifluoroacetic anhydride)–Ac₂O–lutidine[4] produced the 2-[(Z)-(methoxycarbonyl)methylene]cephems **4a** and **4b** in good yield. This Pummerer rearrangement probably proceeds as shown in Scheme II. The reaction pathway from **3a** (**3b**) to **4a** (**4b**) might involve a stepwise sequence through the intermediate **8**, followed by the migration of the double bond to furnish the thermodynamically more stable isomers.

The Pummerer rearrangement products **4a** and **4b** were obtained as single isomers in each case. Nuclear Overhauser effects (NOE) were used to determine the configuration of compound **4a**. When the 3-methyl of compound **4a** is irradiated, an approximately 30% signal increase for the vinyl proton was observed, indicating the close proximity of those two groups. This strongly suggests the Z sterochemical arrangement. Compound **4a** exhibited an extended UV absorption at λ_{max} 348 nm (ϵ 11 000) for the trans diene diester chromophore (Table I). In 2-unsubstituted cephems, UV absorption is observed in the range of λ_{max} 265–275 nm.

As shown in Scheme III, it was possible to photochemically isomerize compound **4a** to a 35:65 mixture of **4a** and its isomer, **9**,[5] from which **9** could be crystallized out in 43% yield. In an NOE study of **9**, no signal increase of the C-2 vinyl proton was observed by irradiating the C-3 methyl, confirming the stereochemical arrangement as

(4) R. Tanikaga, Y. Yabuki, N. Ono, and A. Kaji, *Tetrahedron Lett.*, 2257 (1976). Also, see C. U. Kim, P. F. Misco, and D. N. McGregor, *J. Org. Chem.*, **47**, 170 (1982).

(5) For a review of photochemical cis–trans isomerizations of olefins, see "Modern Molecular Photochemistry", N. J. Turro, Ed., The Benjamin Cummings Publishing Co. Inc., Menlo Park, CA, 1978, Chapter 12.

depicted. The cis diene diester grouping of 9 showed UV absorption at λ_{max} 320 nm (ϵ 7250), a little shorter wavelength than the corresponding trans isomer, 4a.

Following removal of the trityl blocking group, the new cephem nuclei 5a and 5b were acylated and then deesterified to give a series of 7-(acylamino)-2-[(Z)-(methoxycarbonylmethylene]cephalosporinic acids 6a and 6b. Similarly, compound 9 was converted to 10.

Biological Results. Table II summarizes the Grampositive and Gram-negative activity for selected 2-[(methoxycarbonyl)methylene]cephalosporins. The new cephalosporins were all active against gram-positive organisms (*Streptococcus pneumoniae, Streptococcus pyogenes,* and *Staphylococcus aureus*), but no significant Gram-negative activities were noted. There is, however, a general trend toward increasing activity against Gramnegative organisms in compounds $6a_4$ and $6a_5$ in which the α-methoxyimino functional group is present in the 7-(acylamino) side chains. Contrary to the general trend in cephalosporin structure–activity relationships,[6] the incorporation of an acetoxymethyl group at the C-3 position of the 2-[(methoxycarbonyl)methylene]cephem nucleus did not lead to enhanced antibacterial activity relative to the corresponding C-3 methyl (6a₁ vs. 6b). The reduced activity against *S. aureus* in the presence of 50% human serum indicates a significant serum inactivation of these compounds. The cis derivative 10 showed surprisingly good overall Gram-positive and Gram-negative activity compared to its trans isomer 6a₁, an indication that the structure–activity relationships of these new cephems are significantly influenced by the stereochemical configuration of the C-2 double bond.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The UV spectra were run in EtOH; IR spectra were recorded on a Beckman 5240 spectrophotometer using KBr pellets; NMR spectra were obtained on a Varian HA-100 spectrometer using Me₄Si as an internal standard. All solid compounds were characterized by UV, IR, NMR, and elemental analyses (C, H, N.). Unless stated otherwise, these analyses were within ±0.4% of the theoretical value.

Diphenylmethyl 7β-(Tritylamino)-3-methyl-3-cephem-4-carboxylate 1-Oxide (2a). To a cooled (5 °C) suspension of 16.0 g (75 mmol) of 7β-amino-3-methyl-3-cephem-4-carboxylic acid (7-ADCA) in 200 mL of CH₂Cl₂ was added 10.4 mL (75 mmol) of triethylamine and 38 mL (300 mmol) of dimethylaniline under a N₂ atmosphere. After 10 min of stirring, 9.0 mL (83 mmol) of trimethylsilyl chloride was added over a 5-min period, the ice bath was removed, and the reaction mixture was stirred for 45 min at room temperature and then 23.8 g (85 mmol) of trityl chloride was added in one portion. After stirring for 3 h at room temperature, the mixture was filtered and 400 mL of EtOAc was added to the filtrate. The organic solution was washed with 20% H₃PO₄ (3 × 50 mL) and brine, dried over MgSO₄, filtered, and evaporated to give a crude oil, which was chromatographed on SiO₂. Elution with CH₂Cl₂ gave 19.6 g (58% yield) of 7β-(tritylamino)-3-methyl-3-cephem-4-carboxylic acid as a white amorphous powder: IR (KBr) 1765 and 1720 (br) cm⁻¹; NMR (CDCl₃) δ 2.05 (s, 3 H), 3.0 (br s, 2 H), 4.10 (d, J = 5.8 Hz, 1 H), 4.55 (d, J = 5.8 Hz, 1

(6) "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, 1972, Chapter 12.
(7) (a) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, 12, 310 (1969); (b) R. A. Firestone, J. L. Fahey, N. S. Maciejewicz, G. S. Patel, and B. G. Christensen, *J. Med. Chem.*, 20, 551 (1977). (c) P. C. Cheny, M. C. Cook, M. W. Foxton, M. Gregson, G. I. Gregory, and G. B. Webb, "Recent Advances in the Chemistry of the β-lactam Antibiotics", The Chemical Society, London, 1977, pp 145–152; (d) R. Reiner, U. Weiss, U. Brombacher, P. Lanz, M. Montaron, A. Furlenmeier, P. Angehrn, and P. J. Probst, *J. Antibiot.*, 33, 783 (1980).

H), 6.9–7.6 (m, 15 H). Anal. (C₂₇H₂₄N₂O₃S) C, H, N.

A 15.6-g (34 mmol) sample of the 7β-tritylamino compound was treated with a slight excess of Ph₂CN₂ in CH₂Cl₂ for 60 min. After washing with 10% aqueous HCl, the organic solution was dried (MgSO₄), filtered, and evaporated to a slightly yellow oil, which was purified by SiO₂ column chromatography. Elution of the column with CH₂Cl₂ gave 16.0 g (76% yield) of the desired diphenylmethyl 7β-(tritylamino)-3-methyl-3-cephem-4-carboxylate as a white amorphous powder: IR (KBr) 1770, 1720 cm⁻¹; NMR (CDCl₃) δ 2.0 (s, 3 H), 3.1 (br s, 2 H), 4.15 (d, J = 6.0 Hz, 1 H), 4.72 (q, J = 6.0, 11.5 Hz, 1 H), 6.90 (s, 1 H), 7.0–7.6 (m, 15 H).

A 6.2-g (10 mmol) sample of the ester in 60 mL of CH₂Cl₂ was treated with 2.2 g (11 mmol) of 85% μ-chloroperbenzoic acid at 5 °C for 60 min. The reaction was washed with 5% aqueous NaOH, dried over MgSO₄, filtered, and evaporated in vacuo to a yellow oil, which was purified by chromatography on SiO₂. Elution of the column with 10% EtOAc in CH₂Cl₂ gave 6.0 g (94% yield) of the sulfoxide 2a as a white amorphous powder: IR (KBr) 1785, 1735, 1640 cm⁻¹; NMR (CDCl₃) δ 2.0 (s, 3 H), (AB q, J = 19.5 Hz, 1 H each), 2.82 and 3.25–3.60 (d, J = 5.5 Hz, 1 H), 3.75 (d, J = 12.6 Hz, 1 H), 4.82 (q, J = 5.5, 12.6 Hz, 1 H), 6.92 (s, 1 H), 7.0–7.7 (m, 25 H). Anal. (C₄₀H₃₄N₂O₄S) C, H, N.

Diphenylmethyl 7β-(Tritylamino)-3-(acetoxymethyl)-3-cephem-4-carboxylate 1-Oxide (2b). This compound was prepared in the same manner as that described in detail for 2a, starting from 7-aminocephalosporanic acid (7-ACA): IR (KBr) 1785, 1730, 1715 cm⁻¹; NMR (CDCl₃) δ 1.95 (s, 3 H), 2.85 and 3.55 (AB q, J = 17.0 Hz, 1 H each), 3.49 (d, J = 6.5 Hz, 1 H), 4.57 and 5.18 (AB q, J = 14.0 Hz, 1 H each), 4.88 (q, J = 6.5, 12.0 Hz, 1 H), 6.90 (s, 1 H), 7.0–7.80 (m, 25 H).

Diphenylmethyl 7β-(Tritylamino)-2α-[(methoxycarbonyl)methyl]-3-methyl-3-cephem-4-carboxylate 1-Oxide (3a). To a solution of 222 mg (2.2 mmol) of diisopropylamine in 7 mL of dry THF was added at 5 °C 1.3 mL (2.1 mmol) of 1.6 M n-BuLi in hexane, and the resulting solution was stirred for 10 min under a N₂ atmosphere. The above solution was cooled to −23 °C and then a solution of 1.27 g (2.0 mmol) of the sulfoxide 2a in 10 mL of THF–HMPA (5:1) was added dropwise over a 5-min period followed by 320 mg (2.1 mmol) of methyl bromoacetate in 0.5 mL of THF. The reaction mixture was allowed to stir at −25 °C for 3 h and then poured into EtOAc–10% H₃PO₄ (50 mL each). The organic layer was washed with water and brine, dried (MgSO₄), filtered, and evaporated to an orange oil. The crude product was purified by SiO₂ column chromatography and elution of the column with 5% EtOAc in CH₂Cl₂ gave 950 mg (67% yield) of 3a as a slightly yellow amorphous powder: IR (KBr) 1790, 1730, 1710 cm⁻¹; NMR (CDCl₃) δ 1.68 (q, J = 8.5, 16.0 Hz, 1 H), 1.95 (s, 3 H), 2.40 (q, J = 5.0, 16.0 Hz, 1 H), 3.35 (d, J = 6.0 Hz, 1 H), 3.45 (d, J = 12.0 Hz, 1 H), 3.5–3.8 (m, 1 H), 3.70 (s, 3 H), 4.85 (q, J = 6.0, 12.0 Hz, 1 H), 6.90 (s, 1 H), 7.0–7.7 (m, 25 H). Anal. (C₄₃H₃₈N₂O₆S) C, H, N.

Diphenylmethyl 7β-(Tritylamino)-2α-[(methoxycarbonyl)methyl]-3-(acetoxymethyl)-3-cephem-4-carboxylate 1-Oxide (3b). This compound was prepared in 72% yield from 2b, in a manner similar to that used for the preparation of 3a: UV λ_{max} (EtOH) 354 nm (ϵ 9550); IR (KBr) 1785, 1730, 1710 cm⁻¹; NMR (CDCl₃) δ 1.60 (q, J = 8.0, 16.0 Hz, 1 H), 1.78 (s, 3 H), 2.45 (q, J = 5.5, 16.0 Hz, 1 H), 3.30 (d, J = 5.4 Hz, 1 H), 3.61 (s, 3 H), 3.5–3.8 (m, 2 H), 4.50 and 4.89 (AB q, J = 15.0 Hz, 1 H each), 4.90 (q, J = 5.4, 12.0 Hz, 1 H), 6.90 (s, 1 H), 7.0–7.6 (m, 25 H). Anal. (C₄₅H₄₀N₂O₈S) C, H, N.

Diphenylmethyl 7β-(Tritylamino)-2-[(Z)-(methoxycarbonyl)methylene]-3-methyl-3-cephem-4-carboxylate (4a). To 3 mL of acetic anhydride was added 1.8 mL of trifluoroacetic anhydride, and the solution was stirred for 4 h at room temperature under N₂ atmosphere. To the above solution at 5 °C was added a solution of 3.5 g (5.0 mmol) of 3a and 1.1 g (10 mmol) of 2,6-lutidine in 15 mL of CH₂Cl₂. The orange reaction solution was allowed to stir for 15 h at room temperature and then diluted with 300 mL of EtOAc. The organic solution was washed with aqueous saturated NaHCO₃, 20% H₃PO₄, and brine and dried over MgSO₄. Evaporation of the dried solvents gave an orange oil, which was column chromatographed on SiO₂; elution of the column with CH₂Cl₂ gave 2.05 g (58% yield) of 4a as a colorless foam: UV λ_{max} (EtOH) 348 nm (ϵ 11 000); IR (KBr) 1770, 1720, 1700 cm⁻¹; NMR (CDCl₃) δ 2.10 (s, 3 H), 3.15 (d, J = 11.0 Hz,

1 H), 3.72 (s, 3 H), 4.15 (d, J = 5.0 Hz, 1 H), 4.80 (q, J = 5.0, 11.0 Hz), 6.10 (s, 1 H), 6.85 (s, 1 H), 7.0–7.5 (m, 25 H). Anal. (C_{43}-$H_{36}N_2O_5S$) C, H, N.

Photoisomerization of 4a to 9. In a Rayonet photochemical reactor, a solution of 207 mg (0.3 mmol) of 4a in 30 mL of ether was irradiated in a quartz tube with a Hanover UV lamp for 60 min. The reaction solution was concentrated to about 15 mL of volume and kept at 5 °C for 15 h to obtain 89 mg (43% yield) of 9 as white needles: mp 162–164 °C; UV λ_{max} (EtOH) 320 nm (ϵ 7250); IR (KBr) 1790, 1700–1725 (br) cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3 H), 3.20 (d, J = 9.5 Hz, 1 H), 3.52 (s, 3 H), 4.15 (d, J = 6.0 Hz, 1 H), 4.70 (q, J = 6.0, 9.5 Hz, 1 H), 6.05 (s, 1 H), 6.90 (s, 1 H), 7.0–7.8 (m, 25 H). Anal. ($C_{43}H_{34}N_2O_5S$) C, H, N.

Diphenylmethyl 7β-(Tritylamino)-2-[(Z)-(methoxycarbonyl)methylene]-3-(acetoxymethyl)-3-cephem-4-carboxylate (4b). This compound was prepared in 49% yield from 3b in a similar manner as that described in detail for 4a: UV λ_{max} (EtOH) 354 nm (ϵ 9550); IR (KBr) 1780, 1730, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3 H), 3.20 (d, J = 10.0 Hz, 1 H), 3.82 (s, 3 H), 4.25 (d, J = 5.8 Hz, 1 H), 4.7–5.1 (m, 3 H), 6.15 (s, 1 H), 6.90 (s, 1 H), 790–7.9 (m, 26 H).

Diphenylmethyl 7β-Amino-2-[(Z)-(methoxycarbonyl)-methylene]-3-methyl-3-cephem-4-carboxylate p-Toluenesulfonic Acid Salt (5a). To a cooled (5 °C) solution of 1.8 g (2.5 mmol) of 4a in 20 mL of acetone was added 570 mg (3.0 mmol) of p-toluenesulfonic acid monohydrate, and the solution was allowed to stand for 3 h at 5 °C. Acetone was removed in vacuo and the residue was triturated with ice-cold ether. The white solid was collected, washed with ice cold ether, and vacuum dried to give 1.2 g (73% yield) of 5a as a white amorphous solid: UV λ_{max} (EtOH) 350 nm (ϵ 11200); IR (KBr) 3400, 1780, 1710, 1090 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 2.04 (s, 3 H), 2.20 (s, 3 H), 3.57 (s, 3 H), 5.0 (d, J = 6.0 Hz, 1 H), 5.29 (d, J = 6.0 Hz, 1 H), 5.95 (s, 1 H), 6.90 (s, 1 H), 7.0–7.80 (m, 14 H). Anal. ($C_{31}H_{30}N_2O_8S_2$) C, H, N.

Diphenylmethyl 7β-Amino-2-[(Z)-(methoxycarbonyl)-methylene]-3-(acetoxymethyl)-3-cephem-4-carboxylate p-Toluenesulfonic Acid Salt (5b). This compound was obtained as white powder in 68% yield from 4b in the same manner as that described for preparation of 5a: UV λ_{max} (EtOH) 345 nm (ϵ 10100); IR (KBr) 1780, 1720, 1700, 1090 cm^{-1}; NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.15 (s, 3 H), 3.45 (s, 3 H), 4.3–5.2 (m, 2 H), 5.90 (s, 1 H), 6.7–7.8 (m, 15 H), 8.2–8.6 (br s, 3 H). Anal. ($C_{33}H_{32}$-$N_2O_{10}S_2$) C, H, N.

7β-[(2-Thienyl)acetamido]-2-[(Z)-(methoxycarbonyl)-methylene]-3-methyl-3-cephem-4-carboxylic Acid (6a₁). To a cooled (5 °C) solution of 312 mg (0.5 mmol) of 5a in 10 mL of CH_2Cl_2 were added 40 mg (1.1 mmol of dimethylaniline and 88 mg (0.55 mmol) of 2-thienylacetyl chloride followed by 55 mg (0.55 mmol) of triethylamine. After 2 h of stirring at 5 °C, the reaction was diluted with 30 mL of EtOAc and washed with saturated aqueous $NaHCO_3$, 10% H_3PO_4, and brine. Evaporation of the dried ($MgSO_4$) solvents gave a yellow oil, which was column chromatographed on SiO_2. Elution of the column with 10% EtOAc in CH_2Cl gave 310 mg (73% yield) of the acylated product

as a white foam: UV λ_{max} (EtOH) 345 nm (ϵ 10906); IR (KBr) 1780, 1720, 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 2 H), 5.05 (d, J = 5.8 Hz, 1 H), 5.94 (q, J = 5.8, 8.5 Hz, 1 H), 6.30 (s, 1 H), 6.55 (d, J = 8.5 Hz, 1 H), 7.0–7.6 (m, 14 H).

A solution of 170 mg (0.3 mmol) of this material in 2.5 mL of TFA and 0.5 mL of anisole was allowed to stand at 5 °C for 5 min. The reaction mixture was evaporated to dryness and the residue was triturated with ether–n-pentane (1:1) to give 100 mg (82% yield) of 6a₁ as a white solid: IR (KBr) 1785, 1730, 1700, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.72 (s, 3 H), 3.80 (s, 2 H), 5.05 (d, J = 5.8 Hz, 1 H), 5.09 (q, J = 5.8, 8.0 Hz, 1 H), 6.42 (s, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 7.0–7.25 (m, 3 H).

In a similar manner 6a₂, 6a₃, 6a₄, 6a₅, 6b, 10 were prepared, and the spectroscopic data are as follows.

6a₂: IR (KBr) 1785, 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.82 (s, 3 H), 3.92 (s, 2 H), 5.08 (d, J = 4.5 Hz, 1 H), 5.90 (q, J = 4.5, 9.0 Hz, 1 H), 6.41 (s, 1 H, 6.80 (d, J = 9.0 Hz, 1 H), 7.0–7.3 (m, 3 H).

6a₃: IR (KBr) 1770, 1700, 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.70 (s, 3 H), 5.19 (d, J = 4.4 Hz, 1 H), 5.32 (s, 1 H), 5.60 (q, J = 4.4, 9.0 Hz, 1 H), 6.32 (s, 1 H), 7.52 (s, 5 H).

6a₄: IR (KBr) 1790, 1730, 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 2.17 (s, 3 H), 3.71 (s, 3 H), 4.00 (s, 3 H), 5.25 (d, J = 5.0 Hz, 1 H), 5.82 (q, J = 5.0, 9.0 Hz, 1 H), 6.39 (s, 1 H), 6.65 (q, J = 1.0, 3.0 Hz, 1 H), 7.30 (d, J = 3.0 Hz, 1 H), 7.85 (d, J = 1.0 Hz, 1 H).

6a₅: IR (KBr) 1780, 1680, 1640 cm^{-1}; NMR (Me_2SO-d_6) δ 2.10 (s, 3 H), 3.72 (s, 3 H), 3.98 (s, 3 H), 5.22 (d, J = 4.0 Hz, 1 H), 5.79 (q, J = 4.0, 10.0 Hz, 1 H), 6.35 (s, 1 H), 6.90 (s, 1 H).

6b: IR (KBr) 1780, 1730, 1700, 1680 cm^{-1}; NMR (Me_2SO-d_6) 1.95 (s, 3 H), 3.65 (s, 3 H), 3.70 (s, 2 H), 4.85 (d, J = 14.0 Hz, 1 H), 5.10 (d, J = 14.0 Hz, 1 H), 5.15 (d, J = 4.0 Hz, 1 H), 5.72 (q, J = 4.0, 9.0 Hz, 1 H), 6.32 (s, 1 H), 6.8–7.3 (m, 3 H).

10: IR (KBr) 1785, 1730, 1700, 1660 cm^{-1}; NMR (Me_2SO-d_6) δ 2.20 (s, 3 H), 3.68 (s, 3 H), 3.82 (s, 2 H), 5.26 (d, J = 4.0 Hz, 1 H), 5.55 (q, J = 4.0, 9.0 Hz, 1 H), 6.18 (s, 1 H), 6.8–7.2 (m, 3 H).