(2 mL) was then slowly added to the organic phase and the reaction mixture stirred at room temperature for 1 h. It was then diluted with EtOAc and worked up in the usual manner. The crude product (72% by GC) was used as such in the next step. An analytical sample of **25** was prepared by elution from basic alumina (activity III, 10 g) with C_6H_6 and crystallization from Et_2O: mp 160–163 °C (evacuated capillary); IR 1670 cm^{-1} (C=O); UV 227 nm (ϵ 9300); NMR δ 0.70 (s, 3, C-18), 2.22 (d, 3, J = 6 Hz, C-21), 3.74 (t, 1, J = 6 Hz, C-20), 5.98 (d, 1, J = 10 Hz, C-2), 7.10 (d, 1, J = 10 Hz, C-1). Anal. ($C_{20}H_{30}O_2$) m/e 302.225.

7(8→11α)abeo-19-Nor-10-isopregn-1-ene-3,20-dione (26). Following a literature procedure[5] for an analogous preparation, the crude alcohol **25** was oxidized to the 3,20-dione **26**. The crude product was purified by elution from a prepacked silica gel column (EM Merck, Size B) with 50% $CHCl_3$ in CCl_4 to give **26** (29% overall yield from **24**). An analytical sample of **26** was prepared by crystallization from Et_2O: mp 142–147 °C (evacuated capillary); IR 1700, 1675 cm^{-1} (C=O); UV 227 nm (ϵ 10 300); NMR δ 0.64 (s, 3, C-18), 2.09 (s, 3, C-21), 5.97 (d, 1, J = 10 Hz, C-2), 7.10 (d, 1, J = 10 Hz, C-1). Anal. ($C_{20}H_{28}O_2$) m/e 300.209.

Biological Procedures. Uterotropic–Antiuterotropic Activity. This assay for uterotropic (estrogenic) activity was carried out by NICHD. Immature, female rats, weighing 45–55 g, were treated daily for three consecutive days with 0.1 mL of the drug suspension (sesame oil). A vehicle control group treated with sesame oil alone was also run. On the day following treatment, the animals were sacrificed and the uteri were excised, cleaned, and weighed to the nearest 0.2 mg. Estradiol was used as a standard for sc administration and ethynylestradiol for oral administration. All values are expressed as percent activity relative to these two compounds.

Antiuterotropic activity was determined in an identical manner with the exception that estradiol and the test compound were administered together. The extent to which D-estradiol stimulated increase in uterine weight was inhibited by the test compound indicated its antiuterotropic activity.

Postcoital Antifertility. This assay was carried out by NICHD. Adult Sprague–Dawley rats were used as the experimental animal. The females were caged with males of proven fertility and checked the next morning for presence of sperm. The day sperm were found was considered day 0 of pregnancy. The test compounds were dissolved or suspended in sesame oil and were administered in a volume of 0.1 mL. The compounds were administered over a 5-day period, starting on day 0 of pregnancy. Autopsy was carried out on day 10 of presumptive pregnancy and the presence and number of normal and resorbing fetuses were determined. ED_{100} is defined as that dose (mg/kg/day) at which no implantation sites were found.

Progestational, Antiprogestational, and Antiandrogenic Activities. Progestational and antiprogestational activities were determined by measuring uterine stimulation in the immature rabbit (Clauberg). Antiandrogenic activity was determined in immature, castrated, male rats by evaluating the ability of the test compound to inhibit androgen stimulation of seminal vesicle, ventral prostate, and levator ani weight.

Relative Binding Activity. These assays were carried out by following previously reported procedures[10] with the following exceptions.

Receptor Source. For both the estrogen and progesterone receptor, the uteri from adult castrate rabbits which had been primed with estradiol were used as the tissue source. The uteri were homogenized in 4–8 vol (w/v) of ice-cold TE buffer (0.05 mM Tris–HCl, 1 mM EDTA, pH 7.4) and the cytosol was obtained by ultracentrifugation.

Competitive Binding Assay. The basic assay used a 0.6-mL incubation volume (0.1 mL of radiolabeled steroid, 0.1 mL of compound, 0.1 mL of cytosol, and 0.3 mL of TE buffer) and was carried out at 4 °C. The competitor concentration was varied from 0.1 nM to 10 mM and the radiolabel was held constant at 6000 cpm for [^{3}H]estradiol (110 Ci/mM) and 20 000 cpm of [^{3}H]progesterone (105 Ci/mM). A 24-h incubation was started by addition of the cytosol to the competitor and radiolabel. At the end of the incubation, the bound labeled steroid was isolated and analyzed as previously reported.[10] Standard competition curves for unlabeled estradiol or progesterone were included in the respective assays and the relative binding activity (RBA) was determined.

Acknowledgment. The financial support of this work by the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development, NIH, under Contract No. N01-HD-4-2830 and permission to use biological data obtained from the Contraceptive Development Branch are hereby acknowledged. The authors thank Dr. D. Rosenthal and Mr. F. Williams for mass spectral data (obtained from the Research Triangle Center for Mass Spectrometry, with support from the Biotechnology Resources Branch of the Division of Research Resources, NIH, Grant No. RR-330) and Brenda Hartwell for expert technical assistance.

References and Notes

(1) C. G. Pitt and R. W. Handy, *Tetrahedron*, **27**, 527 (1971).
(2) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3244 (1973).
(3) M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975).
(4) E. P. Oliveto in "Reactions in Steroid Chemistry", Vol. 2, J. Fried and J. A. Edwards, Ed., Van Nostrand–Reinhold, New York, N.Y., 1972, pp 127–236.
(5) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).
(6) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
(7) K. Kontula, O. Jänne, R. Vihko, E. de Jager, J. de Visser, and F. Zeelen, *Acta Endocrinol.*, **78**, 574 (1975).
(8) R. B. Miller and B. F. Smith, *Tetrahedron Lett.*, 5037 (1973).
(9) Although the configuration of H at C-10 in compounds **16**, **20**, **21**, **24**, **25**, and **26** is β, the 10-iso nomenclature is necessary because of the rotation about the 9–10 bond which is implicit in the 7(8→11α) nomenclature.
(10) M. C. Wani, D. H. Rector, H. D. Christensen, G. L. Kimmel, and C. E. Cook, *J. Med. Chem.*, **18**, 982 (1975).

Total Syntheses of (±)-1-Carbacefoxitin and -cefamandole and (±)-1-Oxacefamandole

Raymond A. Firestone,* John L. Fahey, Natalie S. Maciejewicz, Gool S. Patel, and B. G. Christensen

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065. *Received September 22, 1976*

The total syntheses of the (±)-1-carba analogues of cefoxitin (**11**), 7α-methoxydeacetylcephalothin (**5**) and cefamandole (**31**) and the (±)-1-oxa analogue of cefamandole (**43**) are described. Their bioactivity spectra against 14 typical organisms are similar to those of their natural 1-thia counterparts, with the 1-carba compounds somewhat less active and the 1-oxa compound more active than the natural ones.

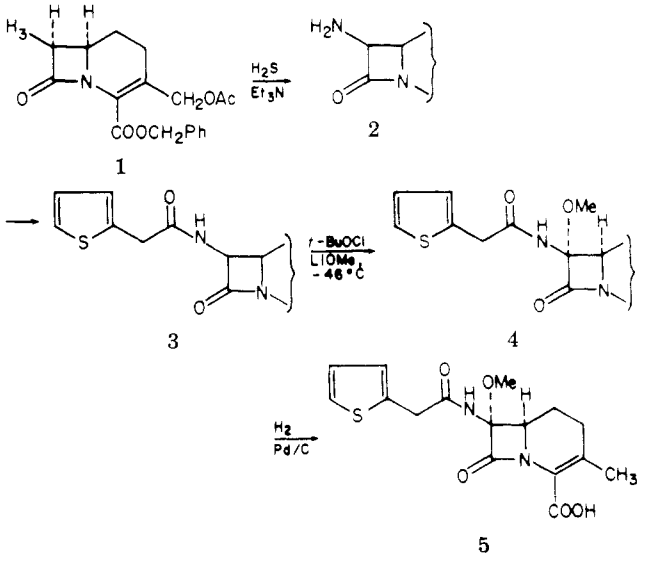
Replacement of the sulfur atom at position 1 of the cephalosporin nucleus with oxygen or carbon has been found not to eliminate the antibiotic activity. In fact, (±)-1-carbacephalothin[1] and (±)-1-oxacephalothin,[2] first

Table I. Bioassays, MIC,[a] μg/mL

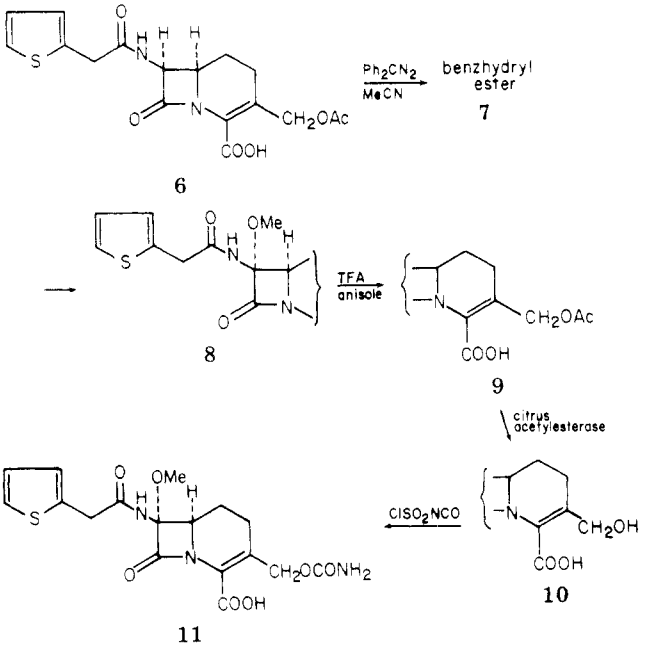
	Medium[b]	Cefoxitin	11	Cefamandole	31	43
S. aureus 2865	M	1.56	6.25	<0.39	1.56	<0.39
S. pyogenes 3124	M	0.78	6.25	<0.39	3.12	<0.39
Enterococcus 2862	M	>100	>100	50	>100	25
Klebsiella 2882	M	3.12	6.25	1.56	1.56	0.78
E. coli 2884	M	1.56	12.5	<0.39	1.56	<0.39
Enterobacter 2902	T	>100	>100	50	>100	12.5
Serratia 2852	N	25	50	>100	>100	>100
Aerobacter 2826	M	0.78	12.5	<0.39	1.56	<0.39
Aerobacter 2828	N	>100	>100	50	>100	25
Pseudomonas	N, H	>100	>100	>100	>100	>100
Providencia 2851	H	1.56	6.25	3.12	6.25	2.56
P. vulgaris 2829	H	<0.39	6.25	1.56	6.25	1.28
P. Morganii 2834	H	6.25	6.25	6.25	6.25	1.28
P. mirabilis 2830	H	1.56	12.5	6.25	25	100

[a] Kindly determined by Dr. Elizabeth Thiele by the agar dilution method, screened against human and/or animal pathogens. [b] M = Mueller-Hinton; N = nutrient; H = nutrient + horse serum; T = trypticase soy.

Scheme I



Scheme II



prepared in these laboratories, are comparable in bioactivity to their natural 1-thia counterparts. It therefore seemed worthwhile to prepare more analogues, in both the 1-carba and 1-oxa series, of especially broad spectrum or otherwise efficacious cephalosporins. In this article are described the total syntheses of the (±)-1-carba analogues of cefoxitin (**11**), 7α-methoxydeacetylcephalothin (**5**), and cefamandole (**31**) and the (±)-1-oxa analogue of cefamandole (**43**), following the general approach used in the original syntheses of (±)-1-carba- and (±)-oxacephalothin.

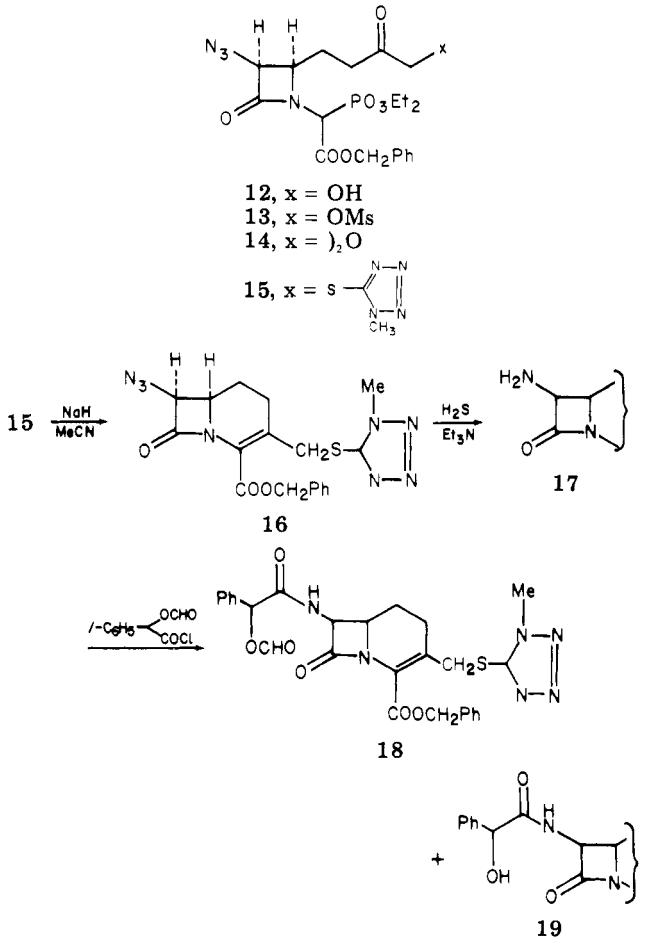
Our first approach to (±)-1-carbacefoxitin (**11**) is shown in Scheme I. In order to retain the ester function (needed for the methoxylation step) while reducing the azide, reduction of **1** was carried out with H_2S–Et_3N rather than catalytically as it was done originally.[1] Thienylacetylation, followed by 7-methoxylation with LiOMe–*t*-BuOCl,[3] afforded the 7α-methoxycephalothin ester **4**. Yields in this reaction were better at −46 °C than at −78 °C, but even so they were not as good as on normal cephalothin esters. This sequence was also carried out on the 7α-amino series, obtained by chromatographic separation of the cis and trans isomers of **1**. Yields in the trans series were equal to or better than those in the cis series, probably because the trans isomers are less crowded at the 7 position. Both series gave the same 7α-methoxy derivative **4**, since the stereochemistry in the methoxylation step is determined by steric approach control to the planar C-7 of an *N*-acylimine.

However, **4** could not be carried through to **11** because hydrogenolysis of the benzyl ester was exceedingly sluggish, and meanwhile the hydrogenolysis of the 3-acetoxymethyl group to methyl, which normally is a minor side reaction, took place at an equal or greater rate, so that the major product was **5** rather than the desired 3-acetoxymethyl acid **9**.

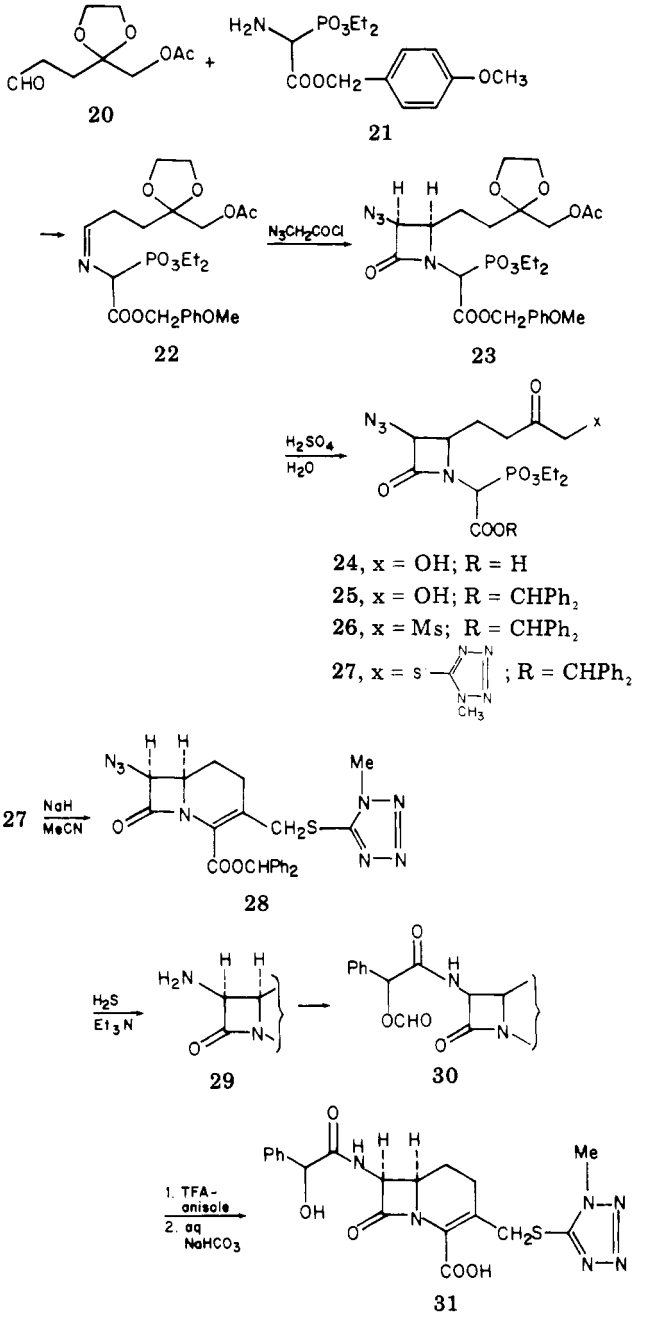
To circumvent this problem, we switched to an ester that could be removed chemically rather than hydrogenolytically (Scheme II). Compound **6**, (±)-1-carbacephalothin, was esterified with diphenyldiazomethane in acetonitrile,[4] methoxylated as before, and then deesterified with trifluoroacetic acid–anisole, affording **9**. Hydrolysis of the acetyl group with citrus acetylesterase[5] to **10**, followed by carbamoylation with chlorosulfonyl isocyanate,[6,7] afforded (±)-1-carbacefoxitin (**11**). Its bioactivity is almost equal to that of cefoxitin itself (Table I).

For the preparation of (±)-1-carbacefamandole (**31**), we branched off the original synthetic scheme at an earlier point (Scheme III). Here, too, the first approach was frustrated by poor hydrogenolysis of a benzyl ester. The monocyclic β-lactam **12**[1] was mesylated to **13** with mesyl chloride–triethylamine. During this step, reaction of **12** with **13** to form the dimeric ether **14** could not be prevented; however, at 0 °C as opposed to 25 °C, this side

Scheme III



Scheme IV



reaction was slow enough so that **13** became the major product. Displacement of the mesylate with the sodium salt of 1-methyl-1,2,3,4-tetrazole-5-thiol, followed by intramolecular Wittig–Horner cyclization in acetonitrile, gave the 1-carbacephem **16**. This was reduced to the 7β-amino compound **17** with H_2S–Et_3N and acylated with *l-O*-formylmandeloyl chloride to **18**, accompanied by some deformylated compound **19**; **18** and **19** were separable by PLC. Neither of these compounds could be catalytically debenzylated, however, nor could their precursor **16**.

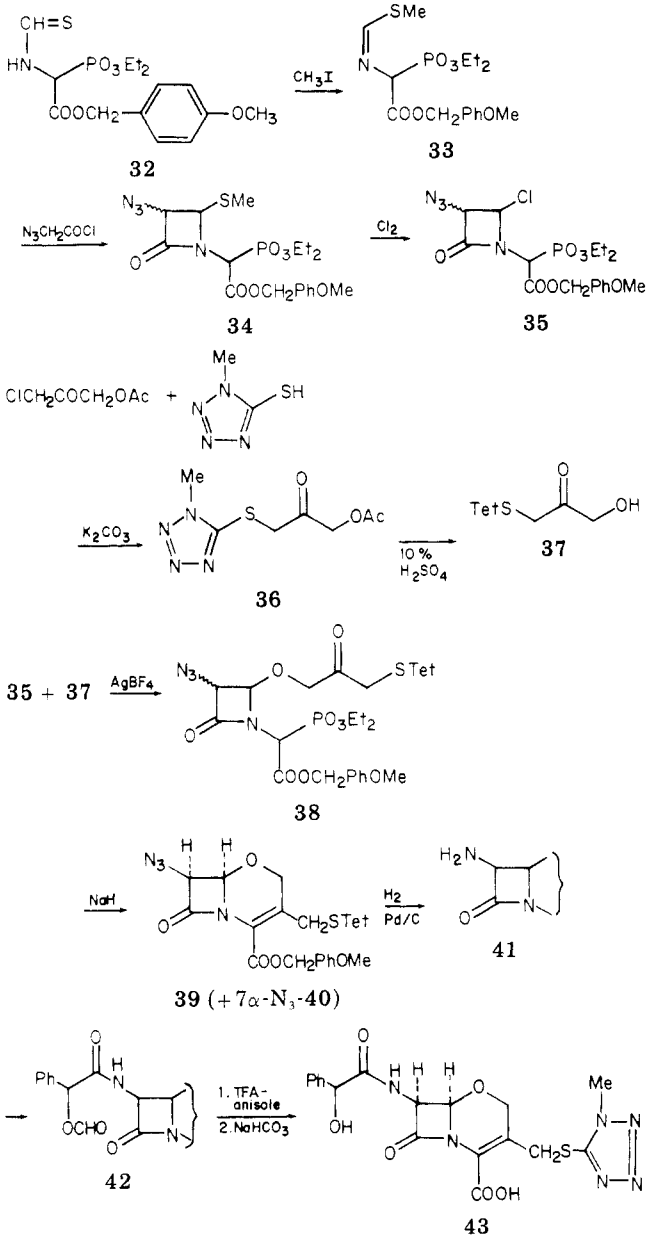
Once again an acid-labile ester was indicated, but this time it was necessary to go further back in the synthetic sequence (Scheme IV). Condensation of the aldehyde **20** with the anisyl ester **21** of α-aminophosphonoacetate[8] instead of the benzyl ester gave the Schiff base **22**, which afforded β-lactam **23** with azidoacetyl chloride. Hydrolysis of the ketal required such vigorous acidic conditions that both the anisyl and acetate esters came off at the same time, producing the hydroxy free acid **24**. Reesterification with diphenyldiazomethane gave **25**, which was mesylated to **26**, converted to the tetrazole derivative **27**, cyclized to **28**, reduced to **29**, and acylated to **30** by the same sequence used for **18** in Scheme III. The benzhydryl ester was smoothly removed with TFA–anisole, and without isolation the formate ester was saponified with aqueous bicarbonate to provide the final product **31**. Its bioactivity is similar to that of cefamandole, but slightly lower (Table I).

In the synthesis of (±)-1-oxacefamandole (**43**), the original general scheme[2] was followed. However, because **43** bears a heteroatom at the 3′ position, the TFA-removable *p*-methoxybenzyl ester was employed instead of benzyl, owing to the difficulty we had experienced with hydrogenolysis of the 3′-acetoxy group during deesterification of 7α-methoxy-1-carbacephalothin (**4**). It was anticipated that this problem might be even more severe in the 1-oxa series.

For the preparation of **43**, then (Scheme V), the *p*-methoxybenzyl ester of α-thioformamidophosphonoacetic acid (**32**)[8] was methylated to **33** and cycloadded with azidoacetyl chloride to the monocyclic β-lactam **34**, and the thiomethyl group was replaced with chlorine, forming **35** as a mixture of isomers.

It was considered best to introduce the thiotetrazole group as early in the sequence as possible, and so the synthon **37** for the cephem atoms at positions 1, 2, 3, and 3′ was used in place of 1-hydroxy-3-acetoxyacetone.[2] It was prepared by alkylation of 1-methyl-1,2,3,4-tetrazole-5-thiol with 1-chloro-3-acetoxyacetone, followed by hydrolysis of the acetate ester of **36** with 10% H_2SO_4. Saponification of **36** with base seemed like a poor idea for preparing the delicate **37**, and 10% H_2SO_4 had already been proven efficient at hydrolyzing α-acetoxy ketones in

Scheme V



the 1-carbacephem syntheses.

Silver-mediated condensation of **37** with chloroazetidinone (**35**) provided **38** as a mixture of isomers. These had to be carefully purified before the intramolecular Wittig–Horner cyclization or else no cephem could be obtained; however, separation of cis from trans was not made until after cyclization, when the desired cis-cephem **39** could be easily separated from trans-cephem **40** by chromatography. The NaH reaction was best done in glyme and went much more poorly in benzene or acetonitrile. Reduction of the azide in **39** with H_2S–Et_3N was not successful, and hydrogenation with Pt in benzene was so slow that hydrogenolysis of the thiotetrazole group to the 3-methyl occurred concomitantly. Finally, hydrogenation with Pd/C in dioxane or EtOAc afforded the amine **41**, with minimal 3-methyl compound if the reaction was not carried too far. It was acylated to **42** with *l*-*O*-formylmandeloyl chloride, and the two esters were deblocked by successive treatment with TFA–anisole and aqueous $NaHCO_3$, providing (±)-1-oxacefamandole (**43**). Its bioactivity compares very favorably with that of cefamandole itself (Table I).

Experimental Section

Reduction of 1 to 2. To 38 mg of **1** in ca. 0.9 mL of $CHCl_3$, degassed by bubbling N_2 through, was added 50 μL of Et_3N. H_2S was bubbled through for 6 min, followed by N_2. The solution was evaporated and flushed three times with benzene, leaving 39 mg of **2**, suitable for the next step without purification: NMR ($CDCl_3$) δ 1.9–2.4 (m, CH_2CH_2), 2.02 (s, Ac), 3.65 (m, 6-H), 4.47 (d, J = 5 Hz, 7-H), 4.83 and 4.99 (2 d, J = 14 Hz, CH_2OAc), 5.26 (s, CH_2Ph), 7.37 (s, C_6H_5); IR (film) 2.9, 5.65, 5.74 μ.

Acylation of 2 to 3. To 39 mg of **2**, prepared above, was added successively 2 mL of CH_2Cl_2, 13 μL of Et_3N, and 19 mg of 2-thienylacetyl chloride. After 25 min at room temperature, the mixture was evaporated, flushed with benzene, taken up in benzene, washed successively with water, pH 3 aqueous phosphate, water, pH 8 aqueous phosphate, and brine, dried with $MgSO_4$, filtered, and evaporated, affording 50 mg of crude **3**. This was purified by PLC on silica gel (500 μ), developing with 4:1 $CHCl_3$–EtOAc, yielding 27 mg of pure **3**: R_f ~0.3; yield 56% based on **1**; NMR ($CDCl_3$) δ 1.9–2.4 (m, CH_2CH_2), 2.02 (s, Ac), 3.76 (s, CH_2CO), 3.7 (m, 6-H), 4.8 and 5.1 (2 d, J = 14 Hz, CH_2OAc), 5.21 (s, CH_2Ph), 5.31 (d of d, J = 7, 5 Hz, 7-H), 6.9–7.3 (m, thienyl), 7.37 (s, C_6H_5); IR (film) 3.0, 5.65, 5.73, 5.95 μ.

Methoxylation of 3 to 4. To 8 mL of THF at 0 °C under N_2 was added 0.38 mL of 2.3 M PhLi, followed by 0.8 mL of MeOH. The mixture was aged 2 min at 0 °C and then cooled to −46 °C. To this was added 88.5 mg of **3** (0.189 mmol) in 3 mL of THF and, after 1 min, 28 μL of *t*-BuOCl. After 2 min a mixture of 0.8 mL of AcOH and 0.8 mL of THF was added. The reaction mixture was allowed to warm to room temperature, diluted with benzene, evaporated, taken up in benzene, washed successively with water, aqueous $NaHSO_3$, pH 8 aqueous phosphate, and brine, dried with $MgSO_4$, filtered, and evaporated, leaving 91 mg of crude **4**. After PLC on 1000-μ silica gel with 3:1 benzene–EtOAc, this afforded 22 mg of pure **4**, R_f 0.3 (23% yield), and 18 mg of recovered **3**, R_f 0.2 (20%): NMR of **4** ($CDCl_3$) δ 2.0–2.4 (m, CH_2CH_2), 2.02 (s, Ac), 3.41 (s, OMe), 3.80 (s, CH_2CO), 3.8 (m, 6-H), 4.80 and 4.95 (2 d, J = 14 Hz, CH_2OAc), 5.24 (s, CH_2Ph), 6.9–7.3 (m, thienyl), 7.33 (s, C_6H_5); IR (film) 3.0, 5.65, 5.77, 5.9 μ; MS 499 (w), 438, 408, 288.

Hydrogenation of 4 to 5. Compound **4**, 35 mg, was hydrogenated 1 h at 45 psi in 3 mL of dioxane and 1 mL of water with 35 mg of 10% Pd/C and 8 mg of $NaHCO_3$. The mixture was filtered, evaporated, and partitioned between water and CH_2Cl_2. The CH_2Cl_2 contained 25 mg of crude recovered **4**. The aqueous portion was washed with EtOAc, acidified to pH 2 with H_3PO_4, and extracted twice with EtOAc. The EtOAc was washed with brine, dried with $MgSO_4$, filtered, and evaporated, leaving 3 mg of **5**: IR (film) 3.0, 3.8 (br) 5.62, 5.92 μ; NMR (Na salt, D_2O) δ 2.0–2.5 (m, CH_2CH_2), 1.97 (s, 3-CH_3), 3.67 (s, OCH_3), 4.11 (s, CH_2CO), 4.85 (s, HDO), 7.2–7.6 (m, thienyl); MS of ester (from CH_2N_2) 364, 210, 154; UV (Na salt, H_2O) E 218, 167 at 235, 258 nm, respectively.

Benzhydryl Ester of (±)-1-Carbacephalothin (7). (±)-1-Carbacephalothin (**6**), 870 mg, was treated in 60 mL of MeCN with 485 mg of Ph_2CN_2. After 1 h the excess diazo compound was destroyed with glacial AcOH and the solvent evaporated. The residue was taken up in 40 mL of benzene, washed with aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, evaporated, and chromatographed on silica gel, eluting with 3:1 benzene–EtOAc, affording 642 mg of pure **7**: NMR ($CDCl_3$) δ 1.99 (s, Ac), 1.9–2.3 (m, CH_2CH_2), 3.74 (s, CH_2CO), 3.7 (m, 6-H), 4.75 and 5.10 (2 d, J = 13 Hz, CH_2OAc), 5.40 (d of d, J = 7, 5, Hz, 7-H), 6.9–7.4 (m, $CHPh_2$ and thienyl), 7.31 (s, C_6H_5); IR (film) 3.0, 5.63, 5.72, 5.95 μ; MS 544, 484, 377, 167.

Methoxylation of 7 to 8. Compound **7**, 578 mg, was added at −46 °C to a solution of LiOMe in 26 mL of THF (prepared from 2.07 mL of 2.3 M PhLi and 4.2 mL of MeOH). After 1 min, 154 μL of *t*-BuOCl was added and, after another 3 min, a solution of 4.2 mL of AcOH in 4.2 mL of THF. The mixture was allowed to warm to room temperature, diluted with benzene, stripped partially in vacuo, diluted with benzene, and washed successively with water, aqueous Na_2SO_3, aqueous pH 8 phosphate, and brine. After drying with $MgSO_4$, filtration, evaporation, and chromatography on silica gel, eluting with 3:1 benzene–EtOAc, pure **8** was obtained: 166 mg (27%); NMR ($CDCl_3$) δ 1.99 (s, Ac), 2.0–2.4

(m, CH_2CH_2), 3.47 (s, OMe), 3.78 (s, CH_2CO), 3.98 (d of d, J = 11, 3 Hz, 6-H), 4.82 and 4.95 (2 d, J = 14 Hz, CH_2OAc), 6.9–7.4 (m, $CHPh_2$ and thienyl), 7.34 (s, C_6H_5); IR (film) 3.0, 5.63, 5.72, 5.9 μ; MS 574, 514, 407.

(±)-7α-Methoxy-1-carbacephalothin (9). Compound **8**, 230 mg, was dissolved in 1.0 mL of anisole and treated with 5.0 mL of TFA at 0 °C for 2.0 min. The TFA was pumped off in the cold and then the anisole at 30 °C. More anisole was added and pumped off. The residue was treated with 10 mL of water and 42 mg of $NaHCO_3$, washed twice with CH_2Cl_2, and lyophilized, affording 168 mg of **9** as the Na salt: NMR (D_2O) δ 2.40 (s, Ac), 2.3–2.6 (m, CH_2CH_2); 3.78 (s, OMe), 4.24 (s, CH_2CO), 4.2 (m, 6-H), 4.99 (s, HDO), 4.93 and 5.30 (d, J = 17 Hz, CH_2OAc), 7.3 (d, J = 3 Hz), 7.65 (m, thienyl); MS of Me ester (from CH_2N_2 on the free acid) 363, 212, 210.

Deacetylation of 9 to 10. Compound **9**, 168 mg, was dissolved in 7 mL of citrus acetylesterase solution and maintained on a pH-stat at pH 6.7 overnight at 31 °C. The solution was cooled to 0 °C, saturated with NaCl, layered with EtOAc, and its pH brought to 2 with H_3PO_4. It was extracted five times with EtOAc. The combined EtOAc extracts were reextracted with water containing 66 mg of $NaHCO_3$. The aqueous extracts were lyophilized, affording 161 mg of **10** as the Na salt admixed with NaOAc: NMR (D_2O) δ 2.0–2.4 (m, CH_2CH_2), 3.40 (s, OMe, 3.83 (s, CH_2CO), 3.8 (m, 6-H), 4.09 (s, CH_2OH), 4.60 (s, HDO), 6.94 (d, J = 3 Hz), 7.25 (m, thienyl).

(±)-1-Carbacefoxitin (11). The product of the previous experiment was dissolved in 5 mL of brine, layered with EtOAc at 0 °C, and brought to pH 2 with H_3PO_4. It was extracted five times with EtOAc, and the combined extracts were dried at 0 °C with $MgSO_4$, filtered, and evaporated, providing **10** as the free acid. This was dissolved in 7.3 mL of THF and treated at −40 °C under N_2 for 4 h with 36 μL of chlorosulfonyl isocyanate. Then 0.62 mL of 0.1 M pH 7 phosphate was added. The solvent was stripped in vacuo in the cold and the residue treated with 4.15 mL of 0.1 M pH 7 aqueous phosphate and 4 mL of EtOAc, stirring 1 h at 25 °C. The pH was adjusted to 8 with alkali, the EtOAc layer was separated and washed once with 4 mL of 0.1 M pH 7 phosphate, and the combined aqueous portions were saturated with NaCl, adjusted to pH 2, and extracted five times with EtOAc. The combined EtOAc extracts were dried with $MgSO_4$, filtered, evaporated, and pumped 2.5 h at 0.050 Torr, leaving 62 mg of **11**: 38% yield from **8**: NMR (acetone-d_6) δ 2.0–2.3 (m, CH_2CH_2), 3.30 (s, OMe), 3.81 (s, CH_2CO), 3.8 (m, 6-H), 4.70 and 4.83 (2 d, J = 14 Hz, CH_2OCONH_2), 5.95 (m, NH), 6.83 (d, J = 3 Hz), 7.14 (m, thienyl), 8.0 (m, NH_2, COOH); IR (film) 3.0 (br), 5.65, 5.8–5.9 μ; UV (Na salt, H_2O) E 218, 175 at 234, 256 nm, respectively.

Mesylation of 12 to 13. Compound **12**, 463 mg (0.961 mmol), was stirred under N_2 at 0 °C in 50 mL of CH_2Cl_2 while mesyl chloride, 117 μL (1.52 mmol), was added. After 5 min, Et_3N, 214 μL (1.52 mmol), was added. After 15 min at 0 °C [$CHCl_3$–acetone (10:3), silica gel], TLC showed almost complete conversion to **13**, R_f 0.55; dimer **14** has R_f 0.7. Chromatography on silica gel with the same eluent gave pure **13**: IR (film) 4.72, 5.63, 5.73 μ; NMR ($CDCl_3$) δ 1.25 (m, OCH_2CH_3), 2.0–2.7 (m, CH_2CH_2), 3.16 (s, OMe), 4.1 (m, OCH_2CH_3), 4.75 (s, $COCH_2O$), 5.10 (s, CH_2Ph), 7.34 (s, C_6H_5).

Sequence 13 → 15 → 16. Compound **13**, 88 mg (0.157 mmol), was stirred under N_2 at 35 °C for 60 min with 20.2 mg of 1-methyl-1,2,3,4-tetrazole-5- thiol (0.175 mmol) and 20 mg of NaH (57% oil dispersion, 0.47 mmol) in 6 mL of MeCN. Within 10 min, TLC (silica gel, 10:1 $CHCl_3$–EtOAc) showed complete consumption of the tetrazole and a new spot at R_f 0.16, presumably **15**. After 60 min a new spot, R_f 0.7, appeared, and after another 90 min at 40 °C reaction was complete. Compound **16** was isolated by PLC: 27 mg, 40% yield from **13**: IR (film) 4.72, 5.62 5.80, 6.13 μ; NMR ($CDCl_3$) δ 1.7–2.7 (m, CH_2CH_2), 3.88 (s, CH_3), 3.8 (m, 6-H), 4.2 and 4.4 (2 d, J = 13 Hz, CH_2S), 4.92 (d, J = 5 Hz, 7-H), 5.26 (s, CH_2Ph), 7.40 (s, C_6H_5); MS 426, 398, 343, 311.

Reduction of 16 to 17. To 34.2 mg of **16** (0.080 mmol) in 5 mL of $CHCl_3$ was added 45 μL of Et_3N (0.32 mmol), and then H_2S was bubbled through for 35 min. Evaporation of the solvent left **17**, which was carried forward without purification: IR (film) 2.95, 5.65, 5.80, 6.12 μ.

Acylation of 17 to 18 and 19. Compound **17**, prepared above, was treated in 5 mL of $CHCl_3$ with 12 μL (0.088 mmol) of *l*-*O*-formylmandeloyl chloride and 13 μL (0.092 mmol) of Et_3N at 0 °C for 5 min. The solvent was removed and the product purified by PLC on silica gel with 10:1 $CHCl_3$–acetone, affording 25.6 mg of **18** (57%), R_f 0.33, and 6.5 mg of **19** (15%), R_f 0.19: IR of **18** (film) 3.0, 5.65, 5.77, 5.9 μ; NMR of **18** ($CDCl_3$) δ 1.7–2.7 (m, CH_2CH_2), 3.86 (s, CH_3), 3.8 (m, 6-H), 4.2 (m, CH_2S), 5.17 (s, CH_2Ph), 5.98 and 6.08 (2 s, $CHOCHO$, *d* and *l*), 7.27 (s, C_6H_5), 7.97 (s, CHO). The IR of **19** was like that of **18**.

Formation of Schiff Base 22 from 20 and 21. A mixture of 490 mg of **20** and 893 mg of **21** was stirred 2 h in 70 mL of CH_2Cl_2 and then an additional hour with 300 mg of $MgSO_4$. After filtration and evaporation of solvent, 1.442 g of **22** was obtained: NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, OCH_2CH_3), 2.12 (s, Ac), 3.88 (s, OCH_3), 4.0–4.4 (m, OCH_2CH_2O and CH_2CH_3), 4.52 (d, J = 20 Hz, CHP), 5.23 (s, CH_2Ar), 6.95 and 7.40 (2 d, J = 9 Hz, C_6H_4), 7.88 (m, CH=N); IR (film) 5.75, 6.02 μ.

Preparation of 23 from 22. Compound **22**, 1.442 g, was flushed four times with dry benzene and taken up in 27 mL of benzene and 27 mL of cyclohexane. Et_3N, 0.751 mL, was added and then over 1 h a solution of 0.471 mL of azidoacetyl chloride in 55 mL of cyclohexane. The mixture was diluted with benzene, washed with aqueous pH 3 phosphate, water, aqueous pH 8 phosphate, and brine, dried with $MgSO_4$, filtered, and evaporated, affording 1.667 g of crude **23**. Purification by chromatography on silica gel, eluting with 2:1 cyclohexane–isopropyl alcohol, gave 0.558 g of pure **23**, R_f 0.4 on TLC. PLC of mixed fractions gave additional **23** for a total of 0.787 g, 54% from **20**: IR (film) 4.74, 5.65, 5.73 μ; MS 598, 570; NMR ($CDCl_3$) δ 1.25 (m, OCH_2CH_3), 1.75 (m, CH_2CH_2), 2.10 (s, Ac), 3.81 (s, OCH_3), 4.02 (s, OCH_2CH_2O), 4.1 (m, OCH_2CH_3), 4.52 (d, J = 19 Hz, CHP), 4.7 (m, CHN_3), 5.18 (s, OCH_2Ar), 6.90 and 7.31 (2 d, J = 9 Hz, C_6H_4).

Hydrolysis of 23 to 24. To 0.677 g of **23** in 6.4 mL of AcOH was added 51.3 mL of 10% aqueous H_2SO_4. The mixture was vigorously stirred 2.5 h at 50 °C, cooled, treated with 10 g of Na_2SO_4, and extracted ten times with CH_2Cl_2. The extracts were dried with $MgSO_4$, filtered, and evaporated to provide 450 mg of **24** admixed with anisyl alcohol: IR (film) 2.85 (br), 4.72, 5.65, 5.75 μ; NMR ($CDCl_3$) δ 4.22 (s, $COCH_2OH$), other peaks correct.

Esterification of 24 to 25. To 450 mg of **24** in 36 mL of MeCN was added 220 mg of diphenyldiazomethane in portions. After 0.5 h, AcOH was added dropwise to kill excess diazo compound, the solvent was evaporated, and the residue was chromatographed on 21 g of silica gel, eluting with EtOAc, affording 251 mg of **25**: IR (film) 2.85, 4.73, 5.64, 5.73 μ; MS (silylated) 602 ($M^+ - N_2$); NMR ($CDCl_3$) δ 6.96 (s, $CHPh_2$), 7.38 (s, C_6H_5), other peaks correct.

Mesylation of 25 to 26. Compound **25**, 251 mg, was treated at 0 °C under N_2 in 22 mL of CH_2Cl_2 with 56 μL of mesyl chloride for 5 min, and then 100 μL of Et_3N was added. After 2 min more at 0 °C and 30 min at 25 °C, the solvent was evaporated and the product was chromatographed by PLC, using 10:3 $CHCl_3$–acetone, affording 197 mg of **26**. The IR and NMR were like those of **13** except for the different ester groups.

Sequence 26 → 27 → 28. Compound **26**, 179 mg, was stirred overnight in 11 mL of MeCN with 36 mg of 1-methyl-1,2,3,4-tetrazole-5-thiol and 36 mg of 57% NaH dispersion. The reaction mixture was then heated 1.5 h at 41 °C, evaporated, treated with brine, and extracted four times with CH_2Cl_2. The organic extracts were dried with $MgSO_4$, filtered, evaporated, and chromatographed by PLC on silica gel with 10:1 $CHCl_3$–acetone, giving 69 mg of pure **28** (49%), R_f 0.6. The IR and NMR were like those of **16** except for δ 6.92 (s, $CHPh_2$ instead of the CH_2Ph): MS 474, 419.

Reduction of 28 to 29. Compound **28**, 351 mg, was treated with 512 μL of Et_3N in 9.6 mL of $CHCl_3$. First N_2 and then H_2S for 15 min were bubbled through. The solvent was evaporated and the residue flushed three times with benzene, providing **29** pure enough for the next step: IR like that of **17**; NMR ($CDCl_3$) δ 4.48 (d, J = 5 Hz, 7-H), other peaks correct.

Acylation of 29 to 30. To the crude **29** above in 30 mL of CH_2Cl_2 was added 0.5 mL of pyridine and then, over 0.5 min, 0.236 mL of *l*-*O*-formylmandeloyl chloride. After 30 min, the reaction mixture was evaporated, taken up in 30 mL of benzene, washed successively with water, pH 3 aqueous phosphate, water, pH 8 aqueous phosphate, and brine, dried with $MgSO_4$, filtered, evaporated, and chromatographed by PLC on silica gel with 10:1

$CHCl_3$–acetone, affording 215 mg **30** (48%), R_f 0.3, and 84 mg of deformylated **30** (20%), R_f 0.2: IR of **30** (film) 3.0, 5.65, 5.78, 5.9 μ; NMR of **30** ($CDCl_3$) δ 1.4–2.6 (m, CH_2CH_2), 3.8 (m, 6-H), 3.83 (s, CH_3), 4.2 (m, CH_2S), 5.35 (m, 7-H), 6.15 (m, PhC*H*), 6.89 (s, C*H*Ph_2), 7.4 (s, C_6H_5), 8.10 (s, OCHO). Deformylated **30** lacked the δ 8.10 peak and showed PhC*H* as singlet at δ 5.19.

(±)-1-Carbacefamandole (31). Compound **30**, 215 mg, was dissolved in 0.5 mL of anisole, cooled to 0 °C, and treated with 2.5 mL of TFA for 2.0 min. The TFA was pumped off at 0.1 Torr and then the anisole at 30 °C. More anisole was added and pumped off. The residue was treated with 15 mL of water and 200 mg of $NaHO_3$, washed twice with CH_2Cl_2, and kept 3 h at room temperature to saponify the formate ester. It was then acidified to pH 2 with H_3PO_4, saturated with NaCl, and extracted five times with EtOAc. The extracts were dried with $MgSO_4$, filtered, and evaporated at 0.1 Torr to provide 133 mg of **31**: NMR (acetone-d_6) δ 1.7–2.8 (m, CH_2CH_2), 3.9 (m, 6-H), 3.95 (s, CH_3), 4.32 (s, CH_2S), 5.12 (s, C*H*Ph), 5.45 (d of d, J = 8, 5 Hz, 7-H), 7.38 (m, C_6H_5), 8.27 (d, J = 8 Hz, NH), 8.87 (m, OH); IR (film) 3.0 (br), 5.64, 5.76, 5.95 μ; MS of Me ester (CH_2N_2) 458; UV of Na salt (H_2O) E 234 at 267 nm.

Methylation of 32 to 33. A mixture of 375 mg of **32**, 152 mg of powdered K_2CO_3, 75 μL of CH_3I and 9 mL of acetone was stirred overnight under N_2, filtered, and evaporated to afford 411 mg of **33**: NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, OCH_2CH_3), 2.45 (s, SCH_3), 3.85 (s, OCH_3), 4.20 (m, OCH_2CH_3), 4.74 (d, J = 20 Hz, CHP), 5.23 (s, OCH_2Ar), 6.97 and 7.37 (2 d, J = 9 Hz, C_6H_4), 8.50 (d, J = 4 Hz, CH=N).

Cycloaddition of Azidoacetyl Chloride to 33. Compound 34. To 411 mg of crude **33** (prepared above) in 6.5 mL of CH_2Cl_2 at 0 °C under N_2 was added 0.131 mL of azidoacetyl chloride and then, over 40 min, a solution of 0.208 mL of Et_3N in 3 mL of CH_2Cl_2. The mixture was stirred 30 min at 25 °C and then 3 min with 5 mL of 1 M aqueous K_2HPO_4. The organic layer was separated, dried with $MgSO_4$, filtered, and chromatographed on silica gel with 10:1 $CHCl_3$–acetone to obtain 375 mg of **34**: NMR ($CDCl_3$) δ 2.10 (s, SCH_3), 4.5–4.9 (m, CHCH and CHP), other peaks correct; IR (film) 4.72, 5.60, 5.73 μ.

Chlorination of 34 to 35. To 375 mg of **34** in 1.9 mL of CCl_4 at 0 °C was added 1.0 mL of a solution of 0.46 mL of liquefied Cl_2 in 10 mL of CCl_4. The mixture was stirred 2 min at 0 °C and 2 min at 25 °C, evaporated, and flushed twice with benzene to provide 405 mg of **35**: NMR ($CDCl_3$) δ 4.5–5.1 (m, CHN_3 and CHP), 5.6–6.3 (m, CHCl), other peaks correct; IR (film) 4.72, 5.56, 5.72 μ.

Preparation of 36. A mixture of 58 mg of 1-methyl-1,2,3,4-tetrazole-5-thiol, 76 mg of 1-chloro-3-acetoxyacetone, 73 mg powdered K_2CO_3 and 5 mL of acetone was stirred overnight at 25 °C under N_2, filtered, and chromatographed on silica gel with 4% AcOH in $CHCl_3$, affording 77 mg of pure **36**: mp 92 °C; NMR ($CDCl_3$) δ 2.12 (s, Ac), 3.96 (s, NCH_3), 4.31 (s, CH_2S), 4.89 (s, CH_2O); MS 230, 188, 157, 130, 116. Anal. Calcd for $C_7H_{10}N_4O_3S$: C, 36.5; H, 4.38; N, 24.3; S, 13.9. Found: C, 36.5; H, 4.40; N, 24.2; S, 14.3.

Hydrolysis of 36 to 37. Compound **36**, 5.52 g, was heated in 410 mL of 10% H_2SO_4 at 50 °C for 1.5 h, cooled, treated with 88 g of Na_2SO_4, and extracted eight times with CH_2Cl_2. The extracts were dried with $MgSO_4$, filtered, and evaporated to yield 1.7 g of **37**: NMR ($CDCl_3$) δ 3.95 (s, NCH_3), 4.32 (s, CH_2S), 4.46 (s, CH_2O). This compound decomposed on standing and was prepared fresh daily.

Preparation of 38 from 35 + 37. To 230 mg (0.5 mmol) of **35** and 474 mg (2.5 mmol) of **37** in 1 mL of MeCN at 0 °C were added 58 mg of Ag_2O (0.25 mmol) and 130 mg of $AgBF_4$ (0.67 mmol) with vigorous stirring. The mixture foamed and evolved heat. After 1 min the ice bath was removed and the mixture stirred 30 min at room temperature. It was diluted with CH_2Cl_2, filtered, washed with aqueous K_2HPO_4, dried with $MgSO_4$, filtered, and subjected twice to PLC on silica gel, first on 2000 μ with 1:1 benzene–EtOAc (R_f 0.15) and then on 1000 μ with EtOAc (R_f 0.3), affording 34 mg of pure **38**: NMR ($CDCl_3$) δ 3.92 (s, NCH_3), 4.6 (m, OCH_2CO, CHN_3, and CHP), 5.3–5.8 (m, CHO), other peaks correct; IR (film) 4.74, 5.59, 5.74 μ; MS 496 (M^+ – STet), 116 (STet).

Cyclization of 38 to 39 and 40. A mixture of 57 mg of **38**, 5.0 mg of 50% NaH dispersion, and 1 ml of glyme was stirred overnight at room temperature under N_2. The mixture was diluted with CH_2Cl_2 and washed with brine, which in turn was washed three times with CH_2Cl_2. The combined organic portions were dried, filtered, evaporated, and chromatographed on silica gel with 10:1 $CHCl_3$–acetone, affording 6 mg (14%) of pure **39**, R_f 0.55, and 7 mg of **40** (16%), R_f 0.7: IR of **39** (film) 4.72, 5.58, 5.81 μ; NMR ($CDCl_3$) δ 4.21 and 4.28 (d, J = 12 Hz, CH_2S), 4.5–4.6 (m, OCH_2 and CHN_3), 5.00 (d, J = 4 Hz, 6-H), 5.16 (s, OCH_2Ar), other peaks correct; MS 458, 430.

Reduction of 39 to 41. Compound **39**, 30 mg, was hydrogenated at 45 psi in 3 mL of dioxane for 6 h with 40 mg of 10% Pd/C, filtered, and evaporated, affording 29 mg of **41**: IR (film) 3.0, 5.69, 5.80 μ. Some 3-methylcephem is also formed and is separated after the next step.

Acylation of 41 to 42. To 82 mg of crude **41** in 2 mL of CH_2Cl_2 was added 30 μL of *l*-*O*-formylmandeloyl chloride and then 20 μL of pyridine. After 2 min of stirring, 1 mL of water was added and, after another 0.5 min, 0.75 mL of 1 M aqueous pH 2 phosphate. Benzene was added and the organic layer was separated, washed with water, aqueous pH 8 phosphate, and brine, dried with $MgSO_4$, filtered, and chromatographed by PLC on 1000 μ of silica gel with 10:3 $CHCl_3$–acetone to provide 24 mg of pure **42** (25% from **39**) at R_f 0.35 and 30 mg of unreduced **39** mixed with 3-methylcephem at R_f 0.5: IR of **42** (film) 3.05, 5.59, 5.80, 5.90 μ; NMR ($CDCl_3$) δ 3.80 (s, OCH_3), 3.90 (s, NCH_3), 4.30 (s, CH_2S), 4.62 (m, OCH_2), 5.04 (d, J = 4 Hz, 6-H), 5.24 (s, OCH_2Ar), 5.60 (d of d, J = 4, 9 Hz, 7-H), 6.27 (s, PhC*H*OCHO), 6.92 and 7.30 (2, d, J = 9 Hz, C_6H_4), 7.41 (s, C_6H_5), 8.13 (s, PhCHOC*H*O); MS 594, 478, 473, 376, 357, 121, 116.

(±)-1-Oxacafamandole (43). Compound **42**, 8 mg, was dissolved in 0.1 mL of anisole and, at 0 °C, treated for 2.0 min with 0.5 mL of TFA. The mixture was pumped to 35 °C at 0.1 Torr and flushed with anisole at 0.1 Torr. Water, 1 mL, and 8 mg of $NaHCO_3$ were added, and the aqueous portion was washed with CH_2Cl_2. It was kept 3 h at 25 °C, acidified to pH 2 with H_3PO_4, saturated with NaCl, and extracted six times with EtOAc. The extracts were dried with $MgSO_4$, filtered, and evaporated to give 5 mg of **43**: IR (film) 3.0 (br), 5.57, 5.85, 5.93 μ; NMR (acetone-d_6) δ 3.99 (s, NCH_3), 4.37 (s, CH_2S), 4.73 (m, OCH_2), 5.21 (s and d, J = 4 Hz, PhC*H*OH and 6-H), 5.67 (d of d, J = 4, 9 Hz, 7-H), 7.36 (m, C_6H_5), 7.8 (m, OH and NH). The acid was converted to the Na salt by adding water and 2.5 mg of $NaHCO_3$ and lyophilizing: yield 6 mg; UV (H_2O) E 183 at 264 nm.

References and Notes

(1) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7584 (1974).
(2) L. D. Cama and B. G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974).
(3) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973).
(4) N. B. Chapman, M. R. J. Dack, D. J. Newman, J. Shorter, and R. Wilkinson, *J. Chem. Soc., Perkin Trans. 2*, 962 (1974), report large solvent effects in the esterification of benzoic acid with diphenyldiazomethane. In accord with their results, we found acetonitrile > ethyl acetate > dioxane as solvents for esterification of cephalothin with diphenyldiazomethane.
(5) J. D'A. Jeffrey, E. P. Abraham, and G. G. F. Newton, *Biochem. J.*, **81**, 591 (1961).
(6) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4653 (1973).
(7) R. Graf, *Chem. Ber.*, **96**, 56 (1963).
(8) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645 (1973).