extracted with chloroform (3 × 5 mL). The combined organic extracts were evaporated to yield a light yellow solid. The NMR spectra of the products indicated that they were exclusively **9c** in yields ranging from 72 to 138 mg.

Competition Experiment of Benzaldehyde (16) and Benzylidenemethylamine (8c) for Reaction with Homophthalic Anhydride (5). Homophthalic anhydride (5; 0.76 g, 4.7 mmol) was added at room temperature to a mixture of benzaldehyde (16; 0.50 g, 4.7 mmol) and *N*-benzylidenemethylamine (8c; 0.56 g, 4.7 mmol) in chloroform (15 mL) containing triethylamine (1 mL). An immediate exothermic reaction occurred upon addition of the anhydride. The reaction mixture was stirred at room temperature for 1 h. The product obtained after evaporation of the solvent was subjected to NMR analysis, which indicated that the ratio of the imine-derived product 7 to the aldehyde-derived product 17 was 3:1.

The Reaction of Metal Fluorides with *unsym*-Azetidinone Disulfides and 2β-(Halomethyl)penams. The 3β-Fluoro-3α-methylcephams

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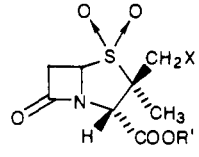
Fluorination studies on *unsym*-azetidinone disulfides and 2β-[halo(Cl- and Br-)methyl]penams with metal fluorides are described. The *unsym*-azetidinone disulfides with AgF, in CH_2Cl_2, produce the 3β-fluoro-3α-methylcephams in low yields. The reaction of the 2β-[halo(Cl- and Br-)methyl]penams with AgF or HgF_2 gave the 3β-fluoro-3α-methylcepham as the only identifiable fluorine-containing compound; the reaction was dependent on the solvent, time, temerature, and the 2β-[halo(Cl- or Br-)methyl]penam used. The ^{19}F, ^{13}C, and ^1H NMR spectral data of the 3β-fluoro-3α-methylcepham and its sulfoxide and sulfone are reported.

During the course of our previous studies on the very potent YTR class of β-lactamase inhibitors **1a**,[1-4] we had occasion to synthesize and study the 6,6-dihydro-2β-(chloro-, 6,6-dihydro-2β-(bromo-, and 6,6-dihydro-2β-(azidomethyl)penam 1,1-dioxides **1b** (X = Cl, Br, N_3).[2] Gottstein and co-workers and we independently found that these compouds also possessed good β-lactamase inhibitory activity.[5-8] In continuation of this work we have been investigating methods for the synthesis of 2β-(fluoromethyl)penam 1,1-dioxides **1c** (X = F), since the fluoromethyl substituent in organic molecules can function as an irreversible enzyme inhibitor.[9]



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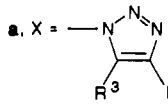
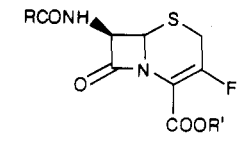
a, X =  **b**, X = Cl, Br, N_3 **c**, X = F

Reagents such as diethylaminosulfur trifluoride (DAST),[10] 2-chloro-1,1,2-trifluorotriethylamine (CTT),[11] or piperidinosulfur trifluoride (PST)[12] have been extensively used for the conversion of hydroxyl to fluoro groups. Utilizing such reagents, 3-fluorocephems **2**, 3-(fluoromethyl)cephems **3**, and 3-(difluoromethyl)cephems **4** have been made by Muller and co-workers,[13] and 6-(fluoroisopropyl)carbapenem **5** has been made by Mak and Wagner.[14] We found that the reaction of 2β-(hydroxymethyl)penams[15] with DAST under reflux in methylene chloride gave mainly the starting compound with small amounts of a new product identified as 3β-fluoro-3α-methylcephams **7** (X = F, *n* = 0).



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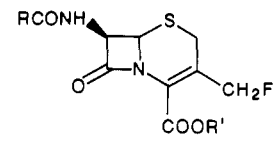

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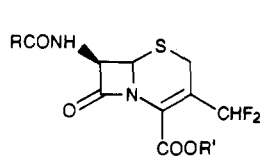

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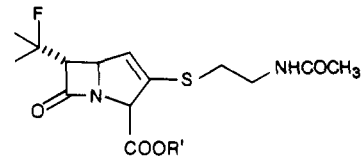

5

A very recent abstract by von Daehne and co-workers reports the formation of a mixture of 6β-bromo-2β-(fluoromethyl)penam **6** (R = Br, X = F), 7β-bromo-3β-fluorocepham **7** (R = Br, X = F, *n* = 0), and 7β-bromocephem **8** (R = Br, *n* = 0), by the nucleophilic substitution of

(1) Hall, T. W.; Maiti, S. N.; Micetich, R. G.; Spevak, P.; Yamabe, S.; Ishida, N.; Kajitani, M.; Tanaka, M.; Yamasaki, T. *Recent Advances in Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Chemical Society: London, 1985; p 242.
(2) Micetich, R. G.; Maiti, S. N.; Spevak, P.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *Synthesis* **1986**, 292.
(3) Taiho Pharm. Co. Ltd. Japan Kokai JP 5 804 788 1983; *Chem. Abstr.* **1983**, *98*, 197889z.
(4) Micetich, R. G.; Hall, T. W.; Maiti, S. N.; Spevak, P.; Yamabe, S.; Ishida, N.; Ogawa, K.; Tanaka, M.; Yamasaki, T.; Nakai, A. *Recent Advances in Chemotherapy, Antimicrobial Section*; Ishigami, J., Ed.; University of Tokyo: Tokyo, 1985; p 249.
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(14) Mak, C. P.; Wagner, K. *Recent Advances in Chemistry of β-Lactam Antibiotics*; Brown, A. G., Roberts, S. M., Eds.; The Chemical Society: London, 1985; p 242.
(15) Spry, D. O. *J. Org. Chem.* **1979**, *44*, 3084.

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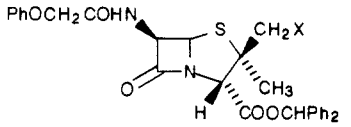
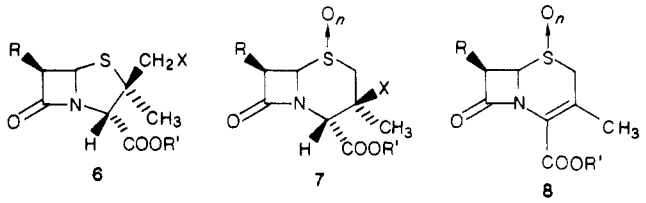
Table I. Reaction of 6a,b with Metal Fluorides



6a, X = Br
b, X = Cl

substr	reacn conditions: metal fluoride	reacn time	reacn temp, °C	product yield, %: start material	3β-fluorocepham 7 (X = F, n = 0)	3β-bromocepham 7 (X = Br, n = 0)
6a	NaF	1–2 days	25	100		
6a	KF	1–2 days	25	100		
6a	FeF_3	1–2 days	25	100		
6a	CoF_2	1–2 days	25	100		
6a	CuF_2	1–2 days	25	100		
6a	HgF_2	2 h	25	50	50	
6a	AgF	1 h	0	50	50	
6a	AgF	2 h	0	25	75	
6a	AgF	4 h	0		100	
6a	AgF	2 h	25		100	
6a	AgF	2 h	reflux		67	33
6b	AgF	48 h	25		95	

6β-bromo-2β-(bromomethyl)penam **6** (R = X = Br), although no details of this reaction are provided.[16]



6 **7** **8**

The 2β-(halomethyl)penams **6** (X = Cl, Br, and I) have been extensively studied by various groups[17-21] and are conveniently prepared by reaction of the *unsym*-azetidinone disulfides **9** with metal halides ($CuCl_2$ or $CuBr_2$ for example) or halogenating agents such as Cl_2 or SO_2Cl_2 for the 2β-(chloromethyl)penams **6** (X = Cl), Br_2 for the 2β-(bromomethyl)penams **6** (X = Br), and I_2 for the 2β-(iodomethyl)penams **6** (X = I).

In this paper we describe our studies on the fluorination of *unsym*-azetidinone disulfides **9** and the displacement of 2β-(halomethyl)penams **6** (X = Cl, Br) with metal fluorides.

When the *unsym*-azetidinone disulfide **9** (R = $PhOCH_2CONH$, $R^1 = CHPh_2$) dissolved in methylene chloride was stirred with AgF or AgF_2 at room temperature for 5 days, a difficult-to-separate mixture of products containing large amounts of starting material **9** was obtained. Oxidation of the crude reaction product with *m*-chloroperbenzoic acid gave the 3β-fluorocepham 1-oxide **7** (X = F, *n* = 1) and the ceph-3-em 1-oxide **8** (*n* = 1). The structures of these compounds were confirmed by ^{19}F and ^1H NMR spectroscopy. In case of compound **7** (X = F, *n* = 1), the ^{19}F NMR spectrum showed a fluorine multiplet at δ 16.22, while **8** (n = 1) showed no absorptions in the ^{19}F NMR spectrum but was identical in its ^1H NMR spectrum with that of an authentic sample.

The *unsym*-azetidinone disulfide **9** (R = $PhOCH_2CONH$, $R^1 = CHPh_2$) in methylene chloride reacts with $CuCl_2$ in 4 h to give the 2β-(chloromethyl)penam **6** (X = Cl), the reaction being complete. With CuF_2 or ZnF_2 under otherwise identical conditions, there is no reaction; even after 5 days, only starting material is recovered.

The results of our studies on the displacement reaction of the 2β-(halomethyl)penams **6** (X = Cl or Br) with various metal fluorides are summarized in Table I. In methylene chloride as solvent only AgF and HgF_2 react, whereas NaF, KF, FeF_3, CoF_2, and CuF_2 are inert. In these reactions with AgF, the 2β-(chloromethyl)penams **6** (X = Cl) react more slowly than the 2β-(bromomethyl)penams **6** (X = Br). The solvent is also an important factor in this reaction. The reaction proceeds in acetonitrile at a slower rate than in methylene chloride, while there is no observable reaction in DMF. Table I also summarizes the effect of the temperature on the reaction rate of **6** (X = Br) with AgF. As expected, at 25 °C the reaction is complete in 2 h, while at 0 °C only 75% of the reaction occurs in this time. At reflux in methylene chloride, after 2 h, a 67% yield of the 3β-fluorocepham **7** (X = F, *n* = 0) results along with a 33% yield of the 3β-bromocepham **7** (X = Br, *n* = 0). It would appear that under reflux the 2β-(bromomethyl)penam **6** (X = Br) converts fairly rapidly to the 3β-bromocepham **7** (X = Br, *n* = 0) via the episulfonium ion **11** and that this compound **7** (X = Br, *n* = 0) is relatively stable and unreactive to AgF.

Scheme I summarizes the suggested mechanism of these reactions. The *unsym*-azetidinone disulfides **9** are converted to the azetidinone sulfenyl halides **10**, which transform to the thiiranium halides **11**. In the case of nucleophilic displacement reactions of 2β-(halomethyl)-penams **6** (X = Cl, Br), the same intermediate thiiranium ion **11** is involved. These reactive (unisolated) thiiranium compounds **11** can then follow one of the rearrangement pathways—attack of the cation at the tertiary carbon leading to the thermodynamically stable 3β-substituted cepham **7** (*n* = 0) or attack of the cation at the primary carbon producing the kinetic product, the methyl-substituted 2β-methylpenam **6**. We have found that with the halides (X = Cl, Br, or I) the products formed in this reaction are dependent on the experimental conditions. Thus, particularly in the case of the iodo and the bromo compounds, the formation of the 2β-(halomethyl)penams **6** (X = I and Br) are favored by short reaction times and

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(18) Kamiya et al. U.S. Patent 3 954 732, 1976.
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(20) Micetich, R. G.; Morin, R. B. *Tetrahedron Lett.* **1976**, *13*, 979.
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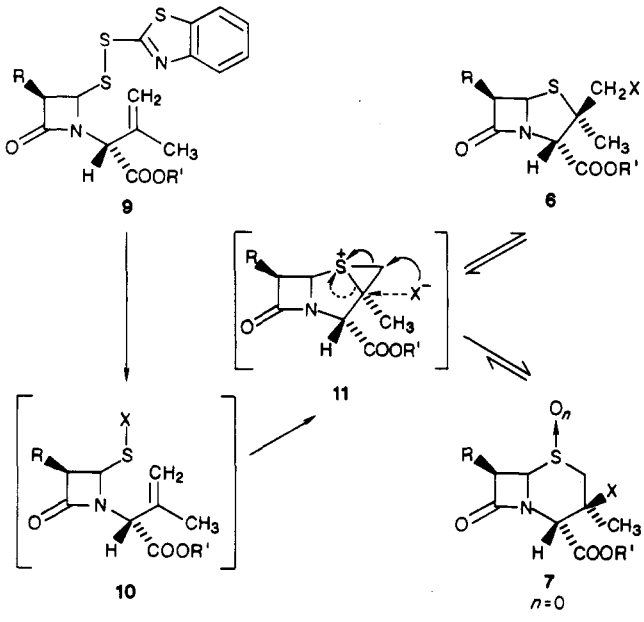
Table II. Physical Constants and Spectroscopic Data of 3β-Fluoro-3α-cepham 7 (X = F)[a]

7						
R	R′	n	mp, °C	yield, %	^{19}F, δ	^{1}H NMR chemical shifts, δ
$C_6H_5OCH_2CONH$	$CHPh_2$	0	103	100	16.55	1.26 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 2.76 (1 H, dd, [ABF], J_{H-H} = 15.4 Hz, J_{H-F} = 6.8 Hz, C_2-CH_2), 3.38 (1 H, dd, [ABF], J_{H-F} = 33.5 Hz, J_{H-H} = 15.4 Hz, C_2-CH_2), 4.84 (1 H, d, J_{H-F} = 12.9 Hz, C_4-*H*), 5.3 (1 H, d, J_{H-H} = 4.7 Hz, C_6-*H*), 5.78 (1 H, dd, J_{N-H} = 10.98 Hz, J_{H-H} = 4.7 Hz, C_7-*H*), 7.54 (1 H, d, J_{N-H} = 10.98 Hz, N*H*)
$C_6H_5OCH_2CONH$	$CHPh_2$	1	96	80	23.07	1.34 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 3.28 (1 H, dd, [ABF], J_{H-F} = 37.7 Hz, J_{H-H} = 12.56 Hz, C_2-CH_2), 3.54 (1 H, d, J_{H-H} = 12.56 Hz, C_2-CH_2), 4.72 (1 H, d, J_{H-F} = 13.8 Hz, C_4-*H*), 4.92 (1 H, d, J_{H-H} = 4.32 Hz, C_6-*H*), 5.78 (1 H, dd, J_{N-H} = 8.65 Hz, J_{H-H} = 4.32 Hz, C_7-*H*), 8.66 (1 H, d, J_{N-H} = 8.65 Hz, N*H*)
$C_6H_5OCH_2CONH$	$CHPh_2$	2	185	68	16.22	1.32 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 3.28 (1 H, dd, [ABF], J_{H-H} = 14.7 Hz, J_{H-F} = 3.9 Hz, C_2-CH_2), 3.52 (1 H, dd, [ABF], J_{H-F} = 32.5 Hz, J_{H-H} = 14.7 Hz, C_2-CH_2), 4.9 (1 H, d, J_{H-F} = 12.6 Hz, C_4-*H*), 5.1 (1 H, d, J_{H-H} = 3.95 Hz, C_6-*H*, 6.16 (1 H, dd, J_{N-H} = 9.49 Hz, J_{H-H} = 3.95 Hz, C_7-*H*), 8.36 (1 H, d, J_{N-H} = 9.49 Hz, N*H*).
H	$CH_2C_6H_4$-4-NO_2	0	127	90	15.67	1.42 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 2.8 (1 H, dd, [ABF], J_{H-H} = 15.1 Hz, J_{H-F} = 4.2 Hz, C_2-CH_2), 3.42 (1 H, dd, [ABF], J_{H-F} = 31 Hz, J_{H-H} = 15.1 Hz, C_2-CH_2), 4.76 (1 H, d, J_{H-F}) = 12.4 Hz, C_4-*H*), 5.04 (1 H, d, J_{H-H} = 5.47 Hz, C_6-*H*), 2.98 (1 H, dd, J_{H-H} = 15.12 Hz, J_{H-H} = 1.8 Hz, α C_7-*H*); 3.42 (1 H, dd, J_{H-H} = 15.12 Hz, J_{H-H} = 5.4 Hz, β C_7-*H*)
H	$CHPh_2$	0	121	90	16.19	1.26 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 2.7 (1 H, dd, [ABF], J_{H-H} = 14.9 Hz, J_{H-F} = 4.7 Hz, C_2-CH_2), 3.36 (1 H, dd, [ABF], J_{H-F} = 31.9 Hz, J_{H-H} = 14.9 Hz, C_2-CH_2), 4.82 (1 H, d, J_{H-F} = 11.53 Hz, C_4-*H*), 5.0 (1 H, d, J_{H-H} = 3.95 Hz, C_6-*H*), 2.96 (1 H, dd, J_{H-H} = 14.9 Hz, J_{H-H} = 1.86 Hz, α C_7-*H*), 3.36 (1 H, dd, J_{H-H} = 14.9 Hz, J_{H-H} = 4.53 Hz, β C_7-*H*)
H	$CH_2C_6H_4$-4-NO_2	2	220	75	3.0[b]	1.56 (3 H, d, J_{H-F} = 21 Hz, C_3-CH_3), 3.56 (1 H, dd, [ABF], J_{H-F} = 57 Hz, J_{H-H} = 4.57 Hz, C_2-CH_2), 3.8 (1 H, dd, [ABF], J_{H-F} = 26.3 Hz, J_{H-H} = 14.8 Hz, C_2-CH_2), 5.04 (1 H, d, J_{H-F} = 13.72 Hz, C_4-*H*), 5.14 (1 H, d, J_{H-H} = 3.43 Hz, C_6-*H*), 3.64 (1 H, dd, J_{H-H} = 10.29 Hz, J_{H-H} = 5.14 Hz, α C_7-*H*), 4.1 (1 H, dd, J_{H-H} = 16.01 Hz, J_{H-H} = 5.7 Hz, β C_7-*H*)

[a] All NMR spectra were taken in $CDCl_3$. [b] Me_2SO used as solvent for NMR spectra.

Scheme I



low temperatures. In the case of the compound **6** (R = H, X = Br), we found that when compound **9** (R = H) was reacted with $CuBr_2$ in methylene chloride at room temperature for 4 h, an about 1:1 mixture of **6** (R = H, X = Br) and **7** (R = H, X = Br, *n* = 0) was formed, while the same reaction run at 0 °C gave only **6** (R = H, X = Br) as the product.[1]

The 2β-(halomethyl)penams **6** (X = Cl, Br, and I) are also readily converted to the 3β-halocephams **7** (X = Cl, Br, and I, *n* = 0) via the same thiiranium intermediate **11**. In the case of **6** (X = Br or I), conversions to **7** (X = Br or I, *n* = 0) occur with time even in the solid state.[19,20]

Thus, the ease of preparation of the 2β-(halomethyl)-penams **6** (X = Cl, Br, or I) follows the sequence Cl > Br > I, paralleling the increase in the ionic character of the C–X bond from C–Cl to C–I. Fluorine is an atypical halogen and forms essentially convalent bonds with carbon. It would appear that the difference in character favors a preferential attack of F^- at the tertiary carbon, resulting in the formation of the 3β–fluoro-3α-methylcepham **7** (X = F, *n* = 0). Thus, with $CuBr_2$ or I_2, reaction with **9** for a short reaction time or at low temperature results in the preferential formation of the methyl-substituted 2β-methylpenams **6** (X = Br or I), whereas these factors have no effect on the reaction of **6** (X = Cl or Br) or **9** with AgF, only the 3β-fluoro-3α-methylcepham **7** (X = F, *n* = 0) being detected in these reactions.

In the reaction of AgF and AgF_2 with *unsym*-azetidinone disulfides **9** or AgF and HgF_2 with 2β-(halomethyl)penams **6** (X = Cl and Br), only one identifiable fluorine-containing product was isolated, which has been assigned the 3β-fluorocepham **7** (X = F, *n* = 0) structure from the data obtained so far. The ^{19}F NMR spectrum shows a complex multiplet at δ 16.55, expected of the 3β-fluorocepham **7** (X = F, *n* = 0), rather than the 2β-(fluoromethyl)penam **6** (X = F). The ^{1}H NMR spectrum (see Table II) shows a methyl doublet at δ 1.36. Although the position is more in keeping with the C_2-CH_3 of a penicillin, the fluorine splitting of this methyl is 21 Hz, which is characteristic of a CH_3CF group.[22] In addition the splitting pattern of the CH_2 group in the δ 2.76 and 3.38 region is also that

(22) Silverstein, R. M.; Bassler, G. C.; Morril, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974; p 227.

Table III. ^{13}C Chemical Shift Data (δ) for the 2β-(Halomethyl)penams 6 (X = Cl, Br) and 3β-Halo-3α-methylcephams 7 (X = Br, F; n = 0, 1, 2)

	penams 6	
C	X = Cl	X = Br
2	69.29	68.83
3	68.14	68.31
5	65.14	65.80
6	59.48	59.56
2-CH_3	21.70	22.75
2-CH_2X	52.69	42.33

	cephams 7			
C	X = Br, n = 0	X = F, n = 0	X = F, n = 1	X = F, n = 2
2	37.44	32.03	54.78	56.65
		32.34	55.07	56.96
3	58.39	83.60	122.81	92.98
		85.75	123.44	95.52
4	54.07	57.89	56.70	56.36
		58.24	57.05	56.65
6	58.84	53.59	73.63	67.95
7	61.75	58.61	59.64	59.09
3-CH_3	30.22	23.78	23.74	23.58
		24.09	24.04	23.89

[a] The characterization of the methyl, methylene, methine, and tertiary carbons is on the basis of J (Mod) experiments. [b] All spectra were run in $CDCl_3$ as solvent and Me_4Si as internal standard. [c] Only the carbon atoms affected by the halogens are listed.

expected of the C_2-CH_2 of 7 (X = F, n = 0) rather than the C_2-CH_2F of 6 (X = F). The ^{19}F NMR and ^1H NMR spectra of the sulfoxide 7 (X = F, n = 1) and the sulfone 7 (X = F, n = 2) (see Table II) follow the same pattern as that of the sulfide 7 (X = F, n = 0).

Table III summarizes the ^{13}C NMR data on the 2β-(halomethyl)penams 6 (X = Cl, Br) and the isomeric 3β-halo-3α-methylcephams 7 (X = Br, F, n = 0). The C_2-methylene signal of the penams 6 appears at δ 52.69 (X = Cl) and 42.23 (X = Br), whereas in the cephams 7, the C_2-methylene is found at δ 37.44 (X = Br, n = 0), and in the case of the fluoro compound this C_2-methylene occurs as a doublet at δ 32.03 and 32.34. In addition the tertiary C_3 carbon occurs as a doublet at δ 83.60 and 85.75, the tertiary C_4 carbon as a doublet at δ 57.89 and 58.24, and the C_3-methyl carbon as a doublet at δ 23.78 and 24.09. In the case of the 3β-bromo-3α-methylcepham 7 (X = Br, n = 0), these signals are found as singlets at δ 58.39 for the tertiary C_3 carbon, δ 54.07 for the tertiary C_4 carbon, and δ 30.22 for the C_3-methyl carbon.

We also found that when the sulfoxide 7 (X = F, n = 1) was treated with pyridine for 30 min at room temperature the ceph-3-em 1-oxide 8 (n = 1), was obtained in 35% yield. This product could only have arisen by dehydrofluorination of the 3β-fluorocepham 1-oxide 7 (X = F, n = 1). It is also not possible for the 2β-(fluoromethyl)penam 1-oxide to isomerize to the 3β-fluorocepham 1-oxide 7 (X = F, n = 1) under these conditions. The data would thus indicate that the fluorine-containing product isolated in all our reactions is the 3β-fluoro-3α-methylcepham 7 (X = F, n = 0).

Experimental Section

^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer, and chemical shifts are recorded as δ values relative to tetramethylsilane and hexafluorobenzene, respectively, as internal standard. IR spectra were recorded on a Nicolet DX-FTIR spectrophotometer. Satisfactory microanalysis (C,H, and N) data (with ±0.4% of calculated values) were obtained on all compounds reported. Representative experiments are described.

Reaction of Benzhydryl 2-([2-Oxo-3β-(phenoxyacetamido)-4-(benzothiazol-2-yldithio)azetidine-1-yl]-2-isopropenylacetate (9) with Silver Fluoride. To a solution of the *unsym*-azetidinone disulfide (1.7025 g, 2.5 mmol) 9, in CH_2Cl_2 (50 mL) in a flask, wrapped with aluminum foil, was added AgF (0.635 g, 5 mmol) and the mixture stirred at room temperature for 5 days. The reaction mixture was filtered through Celite, and the clear, dark reddish brown filtrate was concentrated and dried to yield 1.0762 g of crude product. The TLC and ^1H NMR of the crude product showed a complex mixture, which was difficult to purify by usual chromatographic techniques.

Oxidation of the Above Crude Reaction Mixture with *m*-Chloroperbenzoic Acid. To a cooled (0 °C) solution of the crude product (1.0762 g) in CH_2Cl_2 (15 mL) was added dropwise *m*-chloroperbenzoic acid (0.345 g, 2 mmol) in CH_2Cl_2 (15 mL) and the mixture stirred at the same temperature for 1.5 h. The reaction mixture was filtered and the filtrate washed sequentially with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield a yellow foam (750 mg), which was purified by gradient flash chromatography using ethyl acetate/hexane as eluants, to give 7 (X = F, n = 1; 160 mg, 21%) and 8 (n = 1; 180 mg, 24%).

Benzhydryl 7β-(Phenoxyacetamido)-3β-fluoro-3α-methylcepham (7, R = $PhOCH_2CONH$, R′ = $CHPh_2$, X = F, n = 0). To a solution of benzhydryl 6β-(phenoxyacetamido)-2β-(halomethyl)penicillinate 6 (X = Br; 0.534 g, 1 mmol) in distilled CH_2Cl_2 (20 mL), in a flask wrapped with aluminum foil, was added silver fluoride (0.254 g, 2 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated, the residue taken up in ethyl acetate, decolorized by stirring with adsorbent charcoal, and filtered through Celite, and the filtrate was concentrated and dried to a white foam. Crystallization of the foam with ethyl acetate–hexane gave 7 (X = F, n = 0), the spectral data and physical constants of which are listed in Table II.

Benzhydryl 7β-(Phenoxyacetamido)-3β-fluoro-3α-methylcepham 1,1-Dioxide (7, R = $PhOCH_2CONH$, R′ = $CHPh_2$, X = F, n = 2). To a cooled solution of benzhydryl 7β-(phenoxyacetamido)-3β-fluoro-3α-methylcepham 7 (X = F, n = 0; 0.35 g, 0.65 mmol) in glacial acetic acid (6.54 mL) and water (0.85 mL) was added portionwise $KMnO_4$ (0.237 g, 1.3 mmol) over a period of 1 h. The reaction mixture was stirred at room temperature for 3.5 h and a 30% solution of H_2O_2 added dropwise until decolorization was complete. The resulting solution was poured into ice–water (15 mL) and the solid collected by filtration, taken up in CH_2Cl_2, washed sequentially with saturated $NaHCO_3$ solution, distilled water, and brine, dried over anhydrous Na_2SO_4, and concentrated to a white foam, which weighed 250 mg.