Workup and chromatography (1:2 hexanes–ethyl acetate → ethyl acetate) afforded compound **24** as a white crystalline solid (5.1 mg, 65%). Recrystallization from ethanol provided an analytical sample, mp 261–263 °C. **24**: ^{1}H NMR (360 MHz) 1.42 (t, J = 7, 3 H), 2.25 (s, 3 H), 3.30 (t, J = 9, 2 H), 4.00 (s, 3 H), 4.20 (t, J = 9, 2 H), 4.42 (q, J = 7, 2 H), 7.07 (d, J = 2, 1 H), 8.05 (s, 1 H), 9.01 (br, 1 H); EI MS, m/z 302, 256, 214, 186.

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.26. Found: C, 63.65; H, 6.02; N, 9.20.

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Use of Bistrimethylsilylated Intermediates in the Preparation of Semisynthetic 7-Amino-3-substituted-cephems. Expedient Syntheses of a New 3-[(1-Methyl-1-pyrrolidinio)methyl]cephalosporin

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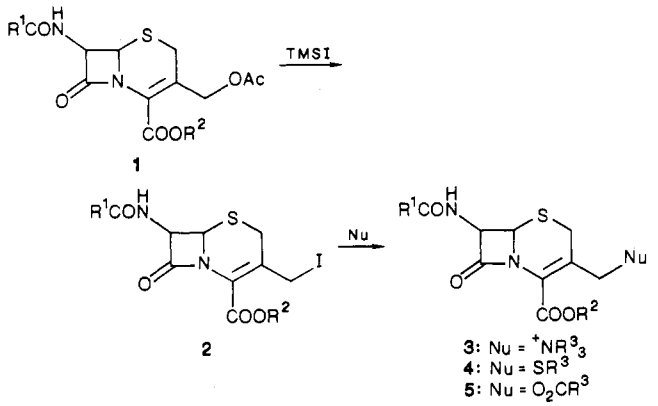
Several "one-pot" methods for conversion of 7-ACA (**6**) to a variety of 7-amino-3-(ammoniomethyl)- or 7-amino-3-[[(heteroaryl)thio]methyl]cephalosporin derivatives via bistrimethylsilylated intermediates are presented. For example, bistrimethylsilylation of 7-ACA (**6**) in 1,1,2-trichlorotrifluoroethane (Freon TF) using HMDS and 3 mol % TMSI, followed by treatment with 1.15 equiv of TMSI and subsequent reactions with tertiary alicyclic or heteroaromatic amines or heteroaromatic thiols, led to the desired products in good yields. Alternatively, novel reaction of the bistrimethylsilylated derivative **15** with amine/TMSI adducts in Freon TF at 35 °C provided an alternative approach to some 7-amino-3-(ammoniomethyl)cephalosporins. The solvent dependence of Δ^3/Δ^2 isomer ratios in quaternization reactions of **11** with *N*-methylpyrrolidine is presented. Hypotheses for the explanation of experimental results observed on reaction of **15** in Freon TF with amine/TMSI adducts are presented. Acylation of **17** (X = Cl, I) with **8** in aqueous THF provided **18** (BMY-28142) as its sulfate salt in overall yields of 18% and 43%, respectively, from 7-ACA (**6**).

During the past several years, the use of trimethylsilyl iodide (TMSI) in synthetic manipulations of various 3-(acetoxymethyl)cephalosporin nuclei, en route to compounds of medicinal interest (cf. **1** → **2** → **3–5**), has been

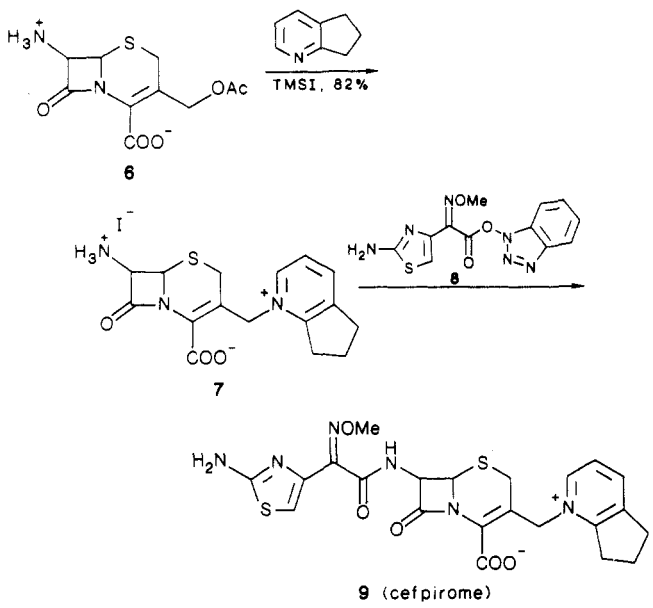


reported in the patent literature with increasing frequency. For example, quaternizations of **2** under anhydrous conditions with pyridines,[1-8] quinolines,[9] isoquinolines,[5,10] and various other heteroaromatic[4,11] and tertiary alicyclic[4,12-17] amines, and displacements using heteroaromatic thiols,[18,19] saccharin and related derivatives[20] and the trifluoroacetate anion[21] and other carboxylates[22] have been described. Furthermore, functionalization of 3-(acetoxymethyl)cephalosporins having a nonacylated 7-amino group [i.e., 7-ACA (**6**)] using TMSI-based chemistry has also been reported.[23-27] A prominent example in the literature was

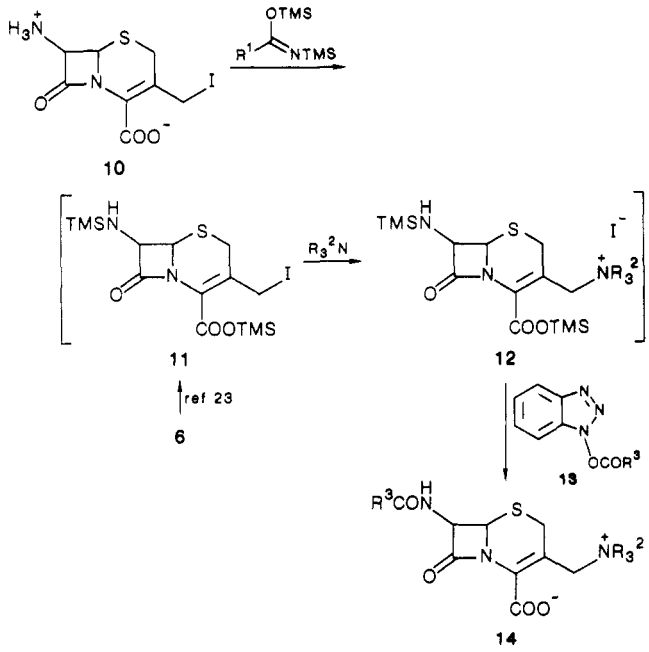
(1) Lunn, W. H. W.; Vasileff, R. T. U.S. Pat. 4577014, March 18, 1986.
(2) Miyake, A.; Kondo, M.; Fujino, M. Eur. *Pat.* Appl. 160969, Nov 13, 1985.
(3) Yamazaki, A.; Shibanuma, T.; Koda, A.; Nakano, K.; Maeda, T.; Nagano, N.; Murakami, Y.; Hara, R. Eur. Pat. Appl. 160546, June 11, 1985.
(4) Lattrell, R.; Blumbach, J.; Durckheimer, W.; Schwab, W.; Seeger, K. Eur. Pat. Appl. 137442, April 17, 1985.
(5) Lunn, W. H. W.; Vasileff, R. T. U.S. Pat. 4501739, Feb 26, 1985.
(6) Lunn, W. H. W.; Wheeler, W. J. U.S. Pat. 4379787, April 12, 1983.
(7) Lunn, W. H. W.; Shadle, J. K. U.S. Pat. 4336253, June 22, 1982.
(8) Yazawa, Y.; Ichihara, M.; Kagara, K.; Ogurado, T. Jpn. Tokkyo Koho 61010591, Jan 18, 1986 (Derwent 86-058977/09).
(9) Lunn, W. H. W.; Wheeler, W. J. U.S. Pat. 4382931, May 10, 1983.
(10) Lunn, W. H. W.; Wheeler, W. J. U.S. Pat. 4382932, May 10, 1983.
(11) Lattrell, R.; Blumbach, J.; Durckheimer, W.; Schwab, W.; Seibert, G. Eur. Pat. Appl. 137441, April 17, 1985.
(12) Fleischmann, K.; Durckheimer, W.; Lattrell, R.; Schwab, W.; Seeger, K. Eur. Pat. Appl. 137440, April 17, 1985.
(13) Yamauchi, H.; Sugiyama, I.; Saito, I.; Nomoto, S.; Kamiya, T.; Machida, Y.; Nemoto, S. Jpn. Tokkyo Koho 60197693, Oct 7, 1985 (Derwent 85-287157/46).
(14) (a) Angerbauer, R.; Boberg, M.; Metzger, K. G.; Zeiler, H.-J. U.S. Pat. 4632918, Dec 30, 1986. (b) Angerbauer, R.; Boberg, M.; Metzger, K. G.; Zeiler, H.-J. Ger. Pat. Appl. 3419012, Nov 28, 1985.
(15) Angerbauer, R.; Boberg, M.; Metzger, K.; Zeiler, H.-J.; Eur. Pat. Appl. 162394, Nov 27, 1985.
(16) Yamauchi, H.; Sugiyama, I.; Saito, I.; Nomoto, S.; Kamiya, T.; Machida, Y.; Nemoto, S. Jpn. Tokkyo Koho 61005085, Jan 10, 1986. (Derwent 86-051946/08).
(17) Yamauchi, H.; Sugiyama, I.; Saito, I.; Nomoto, S.; Kamiya, T.; Machida, Y.; Nemoto, S. Jpn. Tokkyo Koho 60258187, Dec 20, 1985. (Derwent 86-038638/06).
(18) (a) Bonjouklian, R.; Phillips, M. J. *Tetrahedron Lett.* **1981**, *22*, 3915. (b) Bonjouklian, R. U.S. Pat. 4266049, May 5, 1981.
(19) Wheeler, W. J.; Dieter, J. B.; Finley, D. R.; Kinnick, M. D.; Koehler, R.; Obsorne, H. E.; Ott, J. T.; Swartzendruber, J. K.; Wishka, D. G. *J. Antibiot.* **1986**, *39*, 111.
(20) Skotnicki, J. S.; Strike, D. P. *J. Antibiot.* **1986**, *39*, 380.
(21) Mobashery, S.; Johnston, M. *Tetrahedron Lett.* **1986**, *7*, 3333.
(22) Mobashery, S.; Lerner, S. A.; Johnston, M. *J. Am. Chem. Soc.* **1986**, *108*, 1685.
(23) (a) Ascher, G.; Thaler, H.; Ludescher, J. PCT Int. Appl. 8603204, June 5, 1986; (b) Ludescher, H.; Ascher, G. Austrian Pat. Appl. 8403716, Feb 15, 1986 (Derwent 86-075742/12).
(24) Lattrell, R.; Durckheimer, W.; Kirrstetter, R.; Schwab, W. Ger. Pat. Appl. 3316796, Aug 11, 1984.
(25) Kirrstetter, R.; Durckheimer, W.; Lattrell, R.; Schwab, W. Ger. Pat. Appl. 3316797, Aug 11, 1984.
(26) Blumbach, J.; Durckheimer, W.; Reden, J.; Seliger, H. Ger. Pat. Appl. 2758000, July 5, 1979.

0022-3263/88/1953-0983$01.50/0

the preparation of 7, the precursor to the antibiotic candidate cefpirome 9.[24-27]

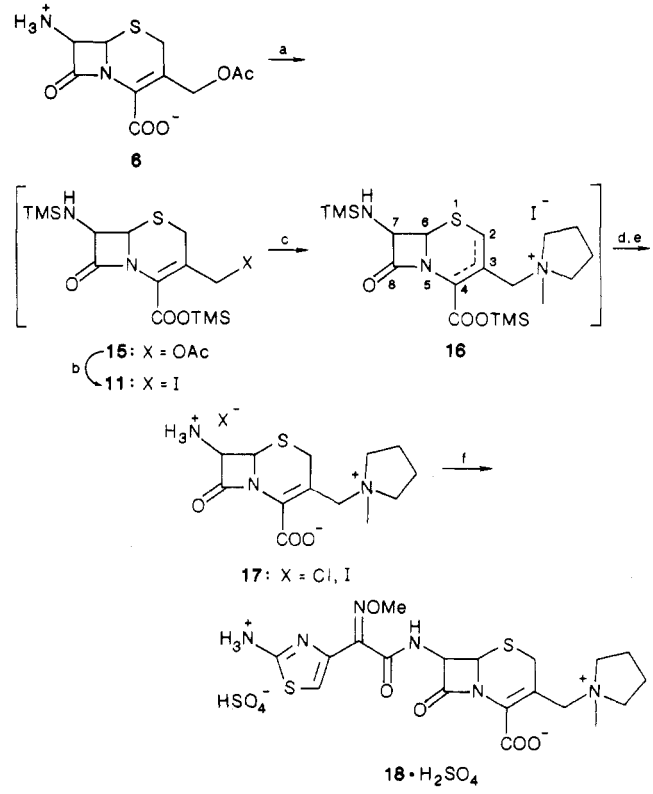


Related work based on quaternizations of the N,O-bistrimethylsilylated 3-(iodomethyl)cephalosporin 11 with pyridines,[4,23,28,29] other heteroaromatic amines,[4] and tertiary alicyclic amines,[4,12,23] followed by in situ acylation with HOBT active esters 13 in DMF to give antibiotics of general structure 14, has been the subject of other patent applications.



We now describe the results of our ongoing work in this area of silylation-based chemistry. In particular, the application of this technology toward the synthesis of 17, a key intermediate in the preparation of our antibiotic candidate BMY-28142[30] (18, cf. Scheme I), will be discussed.

Scheme I[a]



[a] (a) 1.2 equiv of HMDS, 3 mol % TMSI, Freon TF, reflux, 7–10 h; (b) 1.15 equiv of TMSI, 25–30 °C, 2 h; (c) 1.0 equiv of NMP, 0–5 °C, 15 min; (d) 3.35 equiv of MeOH, 0–5 °C, 15 min; (e) 3 N aqueous HCl, acetone, or 2-propanol, see ref 39; (f) (i) 1.0 equiv of 2 N aqueous NaOH, 8–10 °C; (ii) THF, 1.0 equiv of 2 N aqueous NaOH, 1.50 equiv of 8,[26,33] 0–5 °C → room temperature, 2–3 h; (iii) MIBK; (iv) 2.8 equiv of 4 N aqueous H_2SO_4.

Results and Discussion

Preparation of 17 (X = Cl) from 6 via N,O-Bistrimethylsilylated Intermediates. Of the known methods for the N,O-bistrimethylsilylation of 7-aminocephalosporins,[4,23,28,31] we found it most convenient to vigorously heat a slurry of 6, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and catalytic TMSI under reflux in 1,1,2-trichlorotrifluoroethane (Freon TF, Scheme I). The progress of the reaction was monitored by ^1H NMR spectroscopy and was found to reach >90% completion after 7–10 h. Smooth conversion of the resulting 15 to the (iodomethyl)cephem 11 was observed on treatment with a slight excess of TMSI. Within 1–2 h, the reaction was found to be >90% complete (NMR). The solution of 11 was quaternized with *N*-methylpyrrolidine to give a mixture of Δ^3/Δ^2-16 in Freon TF (HPLC area percent ratio Δ^3/Δ^2 = 14/1). The high preference for the desired Δ^3 isomer in this reaction was attributed to the extreme insolubility of 16 in Freon TF. Thus, 16 precipitated from solution as formed with minimal time allowed for prior in situ isomerization to the undesired Δ^2-16. After cleavage of the

(27) Lattrell, R.; Durckheimer, W.; Klesel, N.; Kirrstetter, R.; Seibert, G.; Wieduwilt, M. *HR 810, A New Parental Cephalosporin. I. Chemistry and Physical Properties*; 13th International Congress on Chemotherapy, Vienna Aug 28–Sept 2, 1983; PS 4.2/11.1

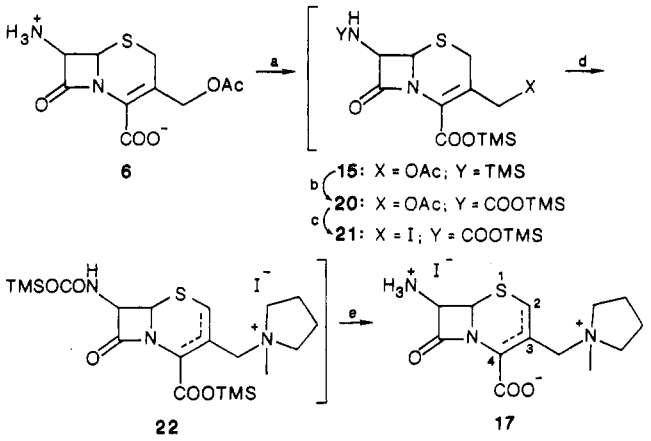
(28) Shibanuma, T.; Konano, K.; Nagano, N.; Murakami, Y.; Hara, R.; Koda, A.; Yamazaki, A. Eur. Pat. Appl. 154 417, Sept 11, 1985.

(29) Yamazaki, A.; Shibanuma, T.; Koda, A.; Nakano, K.; Maeda, T.; Nagano, N.; Murakami, Y.; Hara, R. Eur. Pat. Appl. 160 546, June 11, 1985.

(30) For a discussion of the microbiological activity profile of BMY-28142 (18) versus other cephalosporins, see: Tomatsu, K.; Ando, S.; Masuyoshi, S.; Hirano, M.; Miyaki, T.; Kawaguchi, H. *J. Antibiot.* **1986**, *39*, 1584 and references cited therein.

(31) (a) Walker, D.; Silvestri, H. H.; Sapino, C.; Johnson, D. A. U.S. Pat. 4 316 017, Feb 16, 1982. (b) Walker, D.; Silvestri, H. H.; Sapino, C.; Johnson, D. A. U.S. Pat. 4 223 135, Sept 16, 1980.

Scheme II[a]



[a] (a) 1.12 equiv of HMDS, 3 mol % TMSI, CH_2Cl_2, reflux, 5 h; (b) CO_2(g), room temperature, 12 h; (c) 1.15 equiv of TMSI, 25–30 °C, 1 h; (d) 1.0 equiv of NMP, 0–5 °C, 15 min; (e) equiv of MeOH, 0–5 °C, 15 min.

trimethylsilyl protecting groups by addition of excess methanol[32] and an aqueous acid workup, the desired Δ^3 cephem **17** was isolated by crystallization. Thus, **17** was easily and reproducibly prepared in a convenient "one pot" procedure from 7-ACA (**6**) in one day's time in overall yields of 35–40% (from aqueous acetone) or 45–47% (from aqueous 2-propanol). Subsequent acylation of the free base of **17** with **8**[26,33] gave high quality **18**·H_2SO_4 (BMY-28142-H_2SO_4) in 70–80% yields.

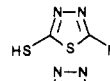
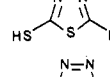
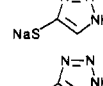
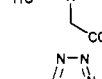
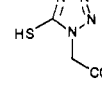
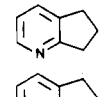
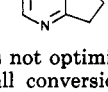
A comment regarding the choice of solvent for the preparation of **17** is in order. Table I lists selected experimental results showing the dependency of the Δ^3/Δ^2 HPLC area percent ratio in **17** (X = I) and yield as a function of the reaction solvent. The data showed that optimal Δ^3/Δ^2 ratios and yields were obtained with use of low boiling (<50 °C), perhalogenated, fluorine-containing solvents (Freon TF, Cl_3CCF_3). Use of these solvents therefore provided the best yields for conversion of **6** to isolated Δ^3-**17** (cf. Scheme I) while minimizing in situ formation of Δ^2-**16** and 7-*epi*-Δ^3-**16** (α-face amino group). These results were an important aspect of this synthetic sequence, since isomerically pure Δ^3-**17** could be acylated to afford Δ^3-**18** (BMY-28142) *only*. Thus, separation of Δ^3-**18** from the undesired and nonefficacious drug Δ^2-**18**[34] by chromatography, or use of known oxidation/reduction techniques to chemically convert a Δ^3/Δ^2 mixture to the Δ^3 isomer only,[35] was avoided. These latter approaches are commonly employed when Δ^3/Δ^2 mixtures of intermediates are encountered. These results and the addi-

Table I. Selected Results for the Quaternization of 11 with *N*-Methylpyrrolidine in Various Organic Solvents at 0–5 °C

entry	solvent (bp, °C)	Δ^3-/Δ^2-17[a]	7-*epi*-Δ^3-17[b,c]	% yield[d]
1	CH_2Cl_2 (40)	42/35	0	22
2	Freon TF (48)	70/5	1	32
3	Cl_3CCF_3 (50)	76/9	0	29
4	CH_3CHCl_2 (57)	36/36	1	18
5	$CHCl_3$ (61)	33/31	0	10
6	CH_3CCl_3 (74)	45/17	1	18
7	CCl_4 (77)	37/42	0	17
8	CH_3CN (82)	47/12	0	16
9	$ClCH_2CH_2Cl$ (83)	52/14	6	22
10	$Cl_2C{=}CHCl$ (87)	27/51	0	17
11	$PhCH_3$ (111)	43/17	5	24
12	Cl_2CHCH_2Cl (114)	44/22	5	20
13	$Cl_2C{=}CCl_2$ (120)	42/2	4	15
14	PhCl (132)	17/1	22	7

[a] HPLC area percents of Δ^3-17 and Δ^2-17 in the chromatogram of the isolated mixture of HI salts. [b] HPLC area percent of 7-*epi*-Δ^3-17 in the chromatogram of the isolated mixture of HI salts. [c] In addition to this material, each chromatogram showed 5–13 area % iodide ion as the only other identifiable peak. The remaining peaks (totaling 6–47 area %) observed in the chromatogram were of unknown structure. [d] This number was obtained by HPLC quantitation of the isolated salt mixture versus a reference standard of Δ^3-17·HCl and is, therefore, a yield for Δ^3-17 *only*.

Table II. Experimental Results for Reactions of 11 and 21 with Various Nucleophiles[a]

substrate	Nu	compd	yield[b]	purity[c]	cephalosporin nucleus for
11		**19a**	43	98	cefamandole, cefmenoxime
21		**19a**	63	86	cefamandole, cefmenoxime
11		**19b**	50	91	cefazolin, cefazedone
21		**19b**	60	89	cefazolin, cefazedone
11		**19c**	49	93	cefatrizine
21		**19c**	56	84	cefatrizine
11		**19d**	37	92	ceforanide
21		**19d**	54	80	ceforanide
11		**19e**	>100[d]	72[e]	ceftazidime, GR 32620[f]
21		**19e**	96[d]	80	ceftazidime, GR 32620[f]
11		**19f**	93[d]	84[g]	cefpirome
21		**19f**	94[d]	78	cefpirome

[a] Yields not optimized. [b] Weight yields reported were based on the overall conversion of **6** to **19a–f**. [c] Reported purities were HPLC chromatogram area percents. [d] Isolated as an HI salt (see ref 28, 36). [e] Major HPLC contaminant was 18 area % pyridine. [f] See ref 37. [g] Major HPLC contaminant was 4 area % 2,3-cyclopentenopyridine.

(32) The use of 3.35 equiv (based on **6**) of methanol was found to be most convenient for this purpose and served to convert Δ^3/Δ^2-**16** to Δ^3/Δ^2-17·HI. Use of lesser amounts of methanol (or none at all) resulted in poorer organic/aqueous phase separations after the subsequent treatment with 3 N aqueous HI.

(33) (a) Schwab, W.; Durckheimer, W.; Kirrstetter, R.; Latrell, R. Ger. Pat. Appl. 3316798, Aug 11, 1984. (b) Kim, W. J.; Lee, C. H.; Kim, B. J.; Lee, G. S. Brit. Pat. Appl. 2158432, April 27, 1984. (c) Jackson, B. G.; Nezich, D. A. U.S. Pat 4252951, Feb 24, 1981.

(34) In general, Δ^2 cephalosporins have little or no microbiological activity relative to their Δ^3 isomer counterparts. See: (a) Holden, K. G. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 2 (Nontraditional β-Lactam Antibiotics), pp 100 and 155; (b) Boyd, D. B. In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1 (Penicillins and Cephalosporins), p 446.

(35) Numerous examples of this chemical transformation can be found in *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vol. 1 (Penicillins and Cephalosporins), pp 83–87, 125, 164–166, 177, 179–80, 183–86, and 187–90. For a recent example from the patent literature specifically related to **18** (BMY-28142), see: Looker, B. E. Brit. UK Pat. Appl. 2165245, April 9, 1986 (Derwent 86-096026/15).

(36) Smith, G. C. D. Eur. Pat. Appl. 70706, Jan 26, 1983.

Table III. Selected Results for the Preparation of 17 in Freon TF from 15 and 23

entry	method[a]	mole ratio 15/NMP/TMSI[b]	temp, °C/time, days	Δ^3-/Δ^2-16 area %'s[c]	% yield Δ^3-17[d,e]
1	A	1:1.4:1.5	25/7	79/12	43
2	A	1:1.4:1.65	25/8	83/5	48
3	A	1:1.4:1.8	25/8	82/4	58
4	A	1:1.8:1.8	25/7	66/3	35
5	B	1:1.4:1.5	25/6	60/27	41
6	B	1:1.4:1.8	25/7	83/5	57
7	B	1:1.4:1.8	31/3	82/4	62
8	B	1:1.4:1.8	35/2	77/13	63
9	B	1:1.4:2.4	35/2	77/8	49
10	B	1:1.4:1.8	35/2	72/15	55[f]

[a] This refers to the order of addition of the reagents. Method A: 15 in Freon TF added to a slurry of 23 in Freon TF at 0–5 °C. Method B: *N*-methylpyrrolidine and then TMSI were added to a solution of 15 in Freon TF at 0–5 °C. [b] The mole ratios were based on the amount of 7-ACA (6). [c] This refers to the final HPLC area percents of Δ^3-16 and Δ^2-16 in the chromatogram of the reaction mixture after the indicated reaction time. [d] Calculated from 6 by HPLC quantitation versus a reference standard of Δ^3-17·HCl. [e] Unless indicated otherwise, a mixture of HI and HCl salts was obtained, by use of 3 N aqueous HCl workup, with the HI salt form predominating.[39] [f] Isolated as a pure monohydroiodide salt by addition of 3 N aqueous HI instead of 3 N aqueous HCl after the methanol quench.

tional factors of commercial availability, low toxicity and cost, nonflammability, negligible water solubility, and ease of recycling made Freon TF the solvent of choice for large scale preparations of Δ^3-17 from 6.

During the course of this investigation, experimental details for the "one-pot" preparation of 7 from 6 in dichloromethane appeared in the literature.[24-26] Attempts to apply this technology to the preparation of 16 in dichloromethane, Freon TF, or mixtures thereof under a variety of reaction conditions failed to produce 17 in any significant isolated yield. These results clearly pointed out the reactivity differences of 2,3-cyclopentenopyridine versus *N*-methylpyrrolidine under these conditions.[24-26]

Additional synthetic utility of solutions of 11 was demonstrated in displacement reactions employing various heterocyclic thiols, pyridine, and 2,3-cyclopentenopyridine. The results of these studies are summarized in Table II.

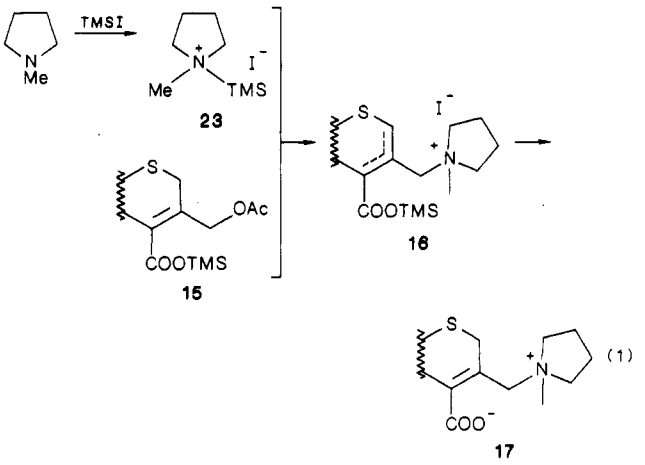
Preparation of 17 (X = I) from 6 via a Trimethylsilyl Carbamate. As an alternative to relying on the insolubility of 16 in Freon TF to control the Δ^3/Δ^2 isomer ratio during the preparation of 17, the use of a different, easily removable amine blocking group, the trimethylsilyl carbamate, was investigated (Scheme II).

Gentle bubbling of dry carbon dioxide gas into a dichloromethane solution of 15 afforded 20 after 12 h (NMR).[31] Alternatively, 20 was prepared by introducing carbon dioxide gas into a Freon TF solution of 15 containing 10 mol % of freshly prepared pyridine hydrochloride. Under these conditions, an 85% yield of 20 was isolated as an extremely moisture sensitive solid. However, due to the insolubility of 20 in Freon TF, use of this procedure for further synthetic manipulations of 20 was severely limited.

Treatment of 20 in dichloromethane with TMSI gave 21 after 1 h (NMR). The resulting solution was cooled and treated with *N*-methylpyrrolidine. Following removal of the protecting groups, 17 was isolated as an HI salt. Disappointingly, the HPLC chromatogram of 17 showed a Δ^3/Δ^2 area percent ratio of 1/6. Thus, the use of the *N*-trimethylsilyl carbamate protecting group in the conversion of 6 to 17 in dichloromethane was clearly inferior to the use of the *N*-trimethylsilyl derivative 11 in Freon TF.

Dichloromethane solutions of 21 were useful, however, in the preparation of 19a–f. The results for this series of reactions are also summarized in Table II.

Preparation of 17 (X = I) from 15 via the Use of an NMP–TMSI Adduct. A study was made to determine the efficiency of converting 15 directly to 17 in Freon TF using the *N*-methylpyrrolidine–trimethylsilyl iodide adduct 23[38] (eq 1). The rate of this reaction, the final Δ^3/Δ^2-16 isomer ratio, and the yield of 17 were found to be dependent on the order of addition of the reactants, reactant stoichiometries, and reaction temperatures. Table III lists the results of these experiments.



Entries 1–3 in Table III demonstrate the affects of TMSI stoichiometry on the final Δ^3/Δ^2-16 isomer ratio and the yield of Δ^3-17 in reactions employing preformed adduct 23 (method A). Increasing the number of equivalents of TMSI from 1.5 to 1.8 lead to a marginally more selective formation of Δ^3-16 with concomitant suppression of undesired side reactions. Thus, higher yields of Δ^3-17 were observed. Further increases in the *N*-methylpyrrolidine stoichiometry to 1.8 equiv, for example (entry 4), reversed this affect for reactions run under these conditions. Lower yields of Δ^3-17 and lower total Δ^3/Δ^2-16 area percents were observed.

A second process (method B) called for in situ preparation of adduct 23 in a Freon TF solution of 15 at 0–5 °C. Interestingly, no significant isomerization to Δ^2-15 occurred upon addition of the *N*-methylpyrrolidine to Δ^3-15 (NMR).

(37) Newall, C. E. In *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Brown, A. G.; Roberts, S. M., Eds.; The Royal Society of Chemistry: London, 1985; Special Publication No. 52, pp 1–17.

(38) Reports of 1/1 adducts of tertiary amines with TMSI have been communicated in the literature. For example, see: (a) Bassindale, A. R.; Stout, T. *Tetrahedron Lett.* **1985**, *26*, 3403. (b) Campbell-Ferguson, H. J.; Ebsworth, E. A. V. *J. Chem. Soc.* **1967**, 705. (c) Campbell-Ferguson, H. J.; Ebsworth, E. A. V. *Ibid.* **1966**, 1508. (d) Beattie, I. R.; Parret, F. W. *Ibid.* **1966**, 1784.

Table IV. Selected Results for the Reaction of 15 with Various R_3N–TMSI Adducts in Freon TF at 35 °C

R_3N	cephalosporin nucleus for	compd	reaction time, h	Δ^3/Δ^2 area %'s[a]	% yield[b] (purity[c])
	BMY-28142	17	48	73/8	57[d] (97)
	ceftazidime, GR 32620[f]	19e	51	68/3	95 (65[e])
	cefpirome	19f	52	75/0	76 (89)
	BMY-28220	24	8	58/25	41[d] (>95)

[a] This refers to the final HPLC area percents of the Δ^3 and Δ^2 isomers in the chromatogram of the reaction mixture after the indicated reaction time. [b] Crude yield of HI salt obtained after the methanol quench unless otherwise indicated. [c] HPLC area percents of the desired compound in the chromatogram of the crude HI salt. [d] Yield of crystalline HI salt by precipitation from aqueous 2-propanol. [e] The major HPLC contaminant was 13 area % pyridine. [f] See ref 37.

Entries 5 and 6 of Table III list the results for variation of the TMSI stoichiometry with use of in situ prepared **23** (method B). As in entries 1–4, these results showed the sensitivity of the Δ^3/Δ^2 ratio to the *N*-methylpyrrolidine and TMSI stoichiometries. Increasing the amount of TMSI from 1.5 to 1.8 equiv resulted in improvement in the Δ^3/Δ^2-**16** ratio from 60/27 to 83/5. Optimal *N*-methylpyrrolidine and TMSI stoichiometries for reactions run under these conditions proved to be 1.4 equiv and 1.8 equiv, respectively, per equivalent of **6**.

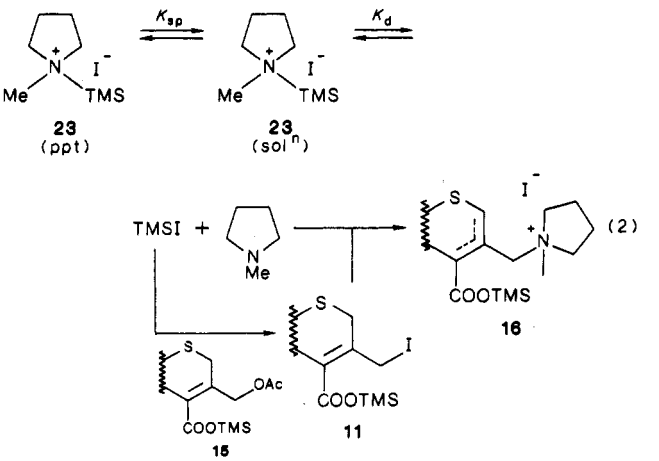
Entries 7 and 8 of Table III clearly showed the affect of temperature. With use of method B conditions, increasing the temperature to 31 °C (entry 7) or to 35 °C (entry 8) led to significant rate enhancements. However, higher reaction temperatures (35 °C and higher) also produced increased amounts of the undesired Δ^2-**16** isomer. Further increases in the TMSI stoichimetry to 2.4 equiv (entry 9) for reactions run at 35 °C were detrimental, as lower yields of Δ^3-**17** were obtained.

The conditions of entry 10 consistently gave high quality Δ^3-**17**·HI in yields of 55–57% from 7-ACA (**6**). Subsequent acylation of this material provided **18**·H_2SO_4 (BMY-28142-H_2SO_4) from **6** in an overall yield of 43%.

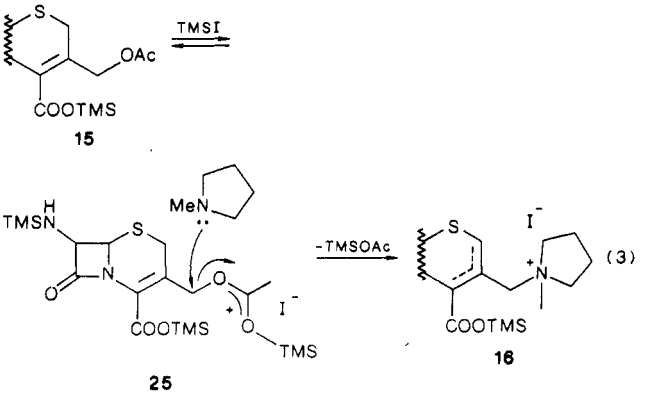
Further demonstration of the synthetic utility of this process is shown below in the data of Table IV. This data summarizes the results for the conversion of **15** to some selected 3-substituted cephalosporin nuclei with use of the conditions of entry 10, Table III.

Reaction Rate and Mechanism Implications. Although a specific mechanism(s) for conversion of **15** to **17**, **19e,f**, and **24**, by the reaction of in situ generated TMSI adducts with the appropriate amine, is(are) not fully understood, some general observations of factors affecting reaction rates provided some insights. The ensuing discussion focuses on the preparation of **17** from **15** and **23**, since this system was most thoroughly studied. The hypotheses presented, however, are also applicable to the systems represented by the examples in Table IV.

It seemed reasonable that the threefold rate increase observed by elevating the reaction temperature from 25 to 35 °C (cf. Table III, entries 6 and 8) involved changes in the solubility product (K_{sp}) and dissociation constant (K_d) of **23** (eq 2). Specifically, higher temperatures were presumed to shift both of these equilibria to the right, thus providing higher concentrations of TMSI and *N*-methylpyrrolidine for conversion of **15** to **11** and **16**, respectively.



An alternative mechanism for formation of **16** is shown in eq 3. Direct displacement of trimethylsilyl acetate from **25** by *N*-methylpyrrolidine would yield **16** directly. A



360-MHz ^1H NMR spectrum of a MeOH-d_4/D_2O quenched reaction aliquot showed, in addition to major peaks for **6** and Δ^3/Δ^2-**17**, minor peaks attributed to trimethylsilyl deblocked **11**. Also, replacement of the TMSI with trimethylsilyl triflate in the conversion of **15** to **16** resulted in formation of only trace amounts of Δ^3/Δ^2-**16** after 24 h at 35 °C (HPLC). While these observations did not rule out the mechanism involving **25**, they did lend support to the mechanism involving the intermediacy of **11**.

Evidence that the concentration of **23** in solution and its dissociation into free *N*-methylpyrrolidine and TMSI were important in the overall reaction rate was provided by preparation of **16** from **11** and **23**. For example, addition of **11** in Freon TF to adduct **23** (from 1.4 equiv of *N*-methylpyrrolidine and 1.42 equiv of TMSI) in Freon TF at 0–5 °C and subsequent heating of the resulting slurry at 35 °C resulted in complete conversion to Δ^3-**16** after 48 h (HPLC). A 41% yield of Δ^3-**17** was isolated as a mixture of HI and HCl salt forms.[39] Interestingly, HPLC profiles of this reaction showed only trace amounts of the undesired Δ^2-**16** were produced under these conditions. This suggested that under standard reaction conditions intermediates such as **15**, **16**, or **25** were more susceptible to isomerization to Δ^2 compounds due to *N*-methylpyrrolidine acting as a base rather than solely as a nucleophile. These results also further supported the reaction mechanism involving the intermediacy of **11**.

The increase in the HPLC area percent of Δ^2-**16** associated with increasing the reaction temperature from 25

(39) The amounts of HI and HCl salt in the mixture were determined by analysis of the samples for iodide and chloride ion content with use of the Dionex ion chromatography system.

to 35 °C was attributed, in part, to greater solubility of Δ^3-16. This would allow more contact time with *N*-methylpyrrolidine in solution prior to complete consumption of 15. Alternatively, as suggested above, the elevated temperature may have permitted isomerization of 15 and/or 25 to Δ^2 isomers to become more competitive processes. Presumably, these Δ^2 isomers would then be converted to Δ^2-16 under the reaction conditions. In order to qualitatively test this latter hypothesis, 15 was reacted with 1.0 equiv of *N*-methylpyrrolidine in Freon TF at 0–5 °C and in a second experiment at 35 °C. The progress of the isomerization at each temperature was monitored by ^{1}H NMR spectroscopy. Each reaction proceeded to give a 2/3 mixture of Δ^3/Δ^2-15, with the rate of isomerization of the 35 °C reaction being two-to threefold greater than the 0–5 °C reaction.

Given the differences in *N*-methylpyrrolidine levels in these pilot reactions versus an actual conversion of 6 → 16, these results supported the hypothesis that Δ^3-15 was more prone to isomerization at higher temperatures.

Thus, arguments for the higher Δ^2-16 content observed in these reactions based on *N*-methylpyrrolidine isomerizing (a) Δ^3-16 due to its greater solubility at 35 °C in Freon TF and (b) Δ^3-15 due to a higher reaction temperature seemed reasonable.

Summary

The synthetic manipulation of 7-ACA (6) to produce 7-amino-3-substituted-cephalosporins, through application of a bistrimethylsilylation/iodination/quaternization or displacement technology in Freon TF or dichloromethane, was found to be an efficient means for preparing these compounds. Thus, treatment of the N,O-bistrimethylsilylated derivative 15 with TMSI gave the iodomethyl compound 11. Subsequently, quaternizations with *N*-methylpyrrolidine, pyridine, and 2,3-cyclopentenopyridine in dichloromethane, Freon TF, or mixtures thereof, or displacements using various heterocyclic thiols in Freon TF/dichloromethane solutions, provided a convenient route to these desired 7-amino-3-substituted-cephalosporins in reasonable yields.

Alternatively, novel reactions of the 3-acetoxymethyl group in 15 with in situ prepared adducts of TMSI with various tertiary amines (particularly *N*-methylpyrrolidine and *N*-methylmorpholine) in Freon TF at 35 °C followed by silyl group deprotection, aqueous workup, and crystallization gave the corresponding quaternized materials in a "one-pot" operation in acceptable yields.

In addition to these methods, the synthetic utility of dichloromethane solutions of the 7-(trimethylsilyl carbamate) 20 was demonstrated in its conversion to 21 followed by reactions with pyridine, 2,3-cyclopentenopyridine, and a variety of heteroaromatic thiols.

With the exception of the 7-(trimethylsilyl carbamate) route, these processes have been successfully scaled to provide kilogram quantities of needed intermediates such as Δ^3-17. Subsequent conversion of Δ^3-17·HI to 18·H_2SO_4 (BMY-28142-H_2SO_4) proceeded in an overall yield of 43% from 6. In addition to being scalable, this technology[40] nicely complements other existing anhydrous methods for the synthesis of 18[41] and, in general, for 3-position substitutions in 7-amino- or 7-(acylamino)-3-(acetoxymethyl)cephalosporins with use of various amines and thiols in a "one-pot" fashion via trimethylsilyl-protected intermediates.

Experimental Section

Infrared spectra were recorded on a Nicolet Model 5DX FT-IR spectrophotometer and data are given in reciprocal centimeters. ^{1}H NMR spectra were obtained at 80 MHz on a Varian FT-80 spectrometer or at 360 MHz on a Bruker AM 360 spectrometer. Chemical shifts are reported on the δ scale in parts per million downfield from either tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate (TSP) as reference standard. Iodide and chloride ion analyses were performed on a Dionex 2010i ion chromatograph. Elemental analyses were performed by the Analytical Research Department at Bristol-Myers. HPLC analyses were done at 254 nm on a Waters 840 HPLC system equipped with a Waters WISP injection system and a Waters μ Bondpak C_{18} reverse-phase column (part number 27324). Solvents were dried overnight over molecular sieves prior to use. Pyridine was dried over KOH prior to use.

Synthesis of 15 from 6 in Freon TF. An oven-dried flask and Friedrich condenser were cooled to ambient temperature under a stream of dry nitrogen. The flask was charged with 50.0 g (184 mmol) of 7-ACA (Bristol) and 400 mL of dry 1,1,2-trichlorotrifluoroethane (Aldrich) under a blanket of dry nitrogen. To the resulting slurry were added 46.5 mL (222 mmol, 1.2 equiv) of 98% 1,1,1,3,3,3-hexamethyldisilazane (HMDS, Aldrich) and 0.78 mL (5.5 mmol, 0.03 equiv) of iodotrimethylsilane (TMSI, Aldrich) by syringe. The slurry was vigorously heated under reflux with protection from moisture for 7–10 h, after which time it was cooled to ambient temperature under a blanket of dry nitrogen. A ^{1}H NMR spectrum of an aliquot of the slightly hazy yellow/orange reaction mixture showed >95% conversion to 15: NMR (CD_2Cl_2, 360 MHz) δ 0.23 (s, 9 H, *N*-Si(CH_3)$_3$), 0.38 (s, 9 H, COOSi(CH_3)$_3$), 1.51 (d, 1 H, J = 13.6 Hz, NH), 2.09 (s, 3 H, $COCH_3$), 3.41, 3.61 (AB q, 2 H, J = 18.3 Hz, SCH_2), 4.80 (dd, 1 H, J = 4.5, 13.6 Hz, C-7 β-lactam), 4.83, 5.11 (AB q, 2 H, J = 13.2 Hz, CH_2OAc), 4.91 (d, 1 H, J = 4.5 Hz, C-6 β-lactam).

The same result (≥95% conversion of 6 to 15) was obtained after 5 h under reflux with CH_2Cl_2 as solvent.

Synthesis of (Iodomethyl)cephem 11 in Freon TF. A total of 30 mL (210 mmol, 1.15 equiv) of TMSI (Aldrich) was added in a slow stream over 2–3 min by syringe to a slightly hazy solution of 15 [from 50.0 g (184 mmol) of 7-ACA] in Freon TF at 25 °C with good stirring under a blanket of dry nitrogen. An exotherm to 30 °C was noted. The progress of the reaction was monitored by ^{1}H NMR spectroscopy (acetate methyl region). After 1–2 h, the resulting slurry was cooled to 0–5 °C in an ice water bath for 15–20 min. Undissolved solids were removed by filtration of the reaction mixture through a Schlenk funnel under nitrogen pressure. The filtrate was collected in a precooled receiver flask (ice water). The filtercake was washed with Freon TF (100 mL). An aliquot of the clear red/orange filtrate gave the following ^{1}H NMR spectrum in support of 11: NMR (CD_2Cl_2, 360 MHz) δ 0.16 (s, 9 H, NHSi(CH_3)$_3$), 0.40 (s, 9 H, COOSi(CH_3)$_3$), 1.51 (d, 1 H, J = 13.4 Hz, NH), 3.54, 3.80 (AB q, 2 H, J = 17.9 Hz, SCH_2), 4.37, 4.49 (AB q, 2 H, J = 9.2 Hz, CH_2I), 4.75 (dd, 1 H, J = 4.6, 13.4 Hz, C-7 β-lactam), 4.89 (d, 1 H, J = 4.6 Hz, C-6 β-lactam).

The same result (≥95% conversion of 15 to 11) was obtained after 1–2 h with CH_2Cl_2 as solvent. In contrast to the synthesis of 11 in Freon TF, however, this reaction remained a solution throughout the course of the conversion.

Preparation of 17 (X = Cl) from (Iodomethyl)cephem 11. To a solution of 11 in Freon TF at 0–5 °C under a blanket of dry nitrogen was added 19.1 mL (184 mmol, 1.0 equiv) of sieve-dried 97% *N*-methylpyrrolidine (Aldrich) dropwise with good stirring over 5–10 min while a reaction temperature of <10 °C was maintained. Following the addition, the slurry was stirred vigorously at 0–5 °C for an additional 5 min. After this time, an additional amount of Freon TF was added (100 mL), and stirring was continued at 0–5 °C for 10 min. Next, 25 mL (615 mmol, 3.35 equiv) of methanol (Fisher) was added dropwise over 10 min while a reaction temperature of <10 °C[32] was maintained. The resulting slurry of Δ^3/Δ^2-17·HI in Freon TF was vigorously stirred

(40) Brundidge, S. P.; Brodfuehrer, P. R.; Sapino, C.; Shih, K. M.; Walker, D. G. PCT Int. Appl. 8701116, Feb 26, 1987 (Derwent 87-064842/09).

(41) (a) Aburaki, S.; Narita, Y.; Okumura, J.; Naito, T.; Walker, D. G. U.S. Pat. 4659812, April 21, 1987. (b) Naito, T.; Aburaki, S.; Kamachi, H.; Narita, Y.; Okumura, J.; Kawaguchi, H. *J. Antibiot.* **1986**, *39*, 1092. (c) Aburaki, S.; Kamachi, H.; Narita, Y.; Okumura, J.; Naito, T. U.S. Pat. 4406899, Sept 27, 1983.

at 0–5 °C for 15 min. The cooling bath was removed, and 125 mL of 3 N HCl was added in one portion. The addition was accompanied by an exotherm to 12–15 °C. A warm water bath was used to quickly (<1 min) warm the reaction mixture to 20–25 °C. Vigorous stirring of the two phase system was continued for an additional 15 min. The phases containing **17** were separated, and the organic phase was back extracted with water (50 mL). The combined aqueous phases containing Δ^3/Δ^2-**17** were stirred for 30 min at room temperature with 10 g of Darco KB. The decolorizing carbon was removed by filtration of the slurry through a 10.0-g pad of Celite. The pad was washed with water (50 mL) and was partially dried under suction for 5 min. The product was crystallized from the solution by dropwise addition of acetone (5 volumes). The slurry thus obtained was cooled to 0–5 °C in an ice water bath and was maintained at this temperature for 1 h. The slurry was vacuum filtered, washed with cold (0–5 °C) 5/1 acetone/water (v/v, 2 × 50 mL) and acetone (2 × 50 mL). The filtercake was partially dried under suction for 15 min. Further drying in vacuo afforded 23.3 g (38%) of Δ^3-**17** as a snow white, crystalline HCl salt: NMR (360 MHz, D_2O with solvent suppression) δ 2.14–2.32 (envelope, 4 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$), 3.00 (s, 3 H, $^+NCH_3$), 3.46–3.67 (m, 5 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$, SCH_2), 3.96 (one leg of AB q, 1 H, J = 16.9 Hz, SCH_2), 4.09, 4.73 (AB q, 2 H, J = 13.9 Hz, $-CH_2{}^+N(CH_3)CH_2CH_2CH_2CH_2$), 5.21 (d, 1 H, J = 5.1 Hz, C-7 β-lactam), 5.41 (d, 1 H, J = 5.1 Hz, C-6 β-lactam); HPLC potency, 96.3% versus a standard lot of Δ^3-**17**·HCl.

An analytical sample of Δ^3-**17**·HCl was prepared by carbon treatment of a portion of the above lot in 1 N HCl followed by crystallization with use of 3.5 volumes of 2-propanol. Anal. Calcd for $C_{13}H_{20}ClN_3O_3S$: C, 46.77; H, 6.04; N, 12.59; S, 9.61. Found (corrected for KF (percent H_2O) of 1.31): C, 46.70; H, 6.08; N, 12.56; S, 9.94.

Preparation of 17 (X = I) from (Acetoxymethyl)cephem 15. To a solution of **15** in Freon TF [from 10.0 g (36.7 mmol) 7-ACA] at 0–5 °C under a blanket of dry nitrogen was added 5.35 mL (51.4 mmol, 1.4 equiv) of 97% *N*-methylpyrroldine (Aldrich, sieve-dried) dropwise over 1–2 min with good stirring. Next, 9.40 mL (66.1 mmol, 1.8 equiv) of TMSI (Aldrich) was added by syringe over about 5 min with continued good stirring. The reaction temperature was kept below 10 °C during the addition. The resulting slurry was stirred at 0–5 °C for an additional 30 min. After this time, the slurry was placed into an oil bath carefully maintained at 35–36 °C. The progress of the reaction was monitored by HPLC. After 45–48 h, the reaction was complete [<2 area % 7-ACA (**6**)], and the mixture was cooled to 0–5 °C under a blanket of dry nitrogen. A total of 5.0 mL (123 mmol, 3.35 equiv) of methanol was added dropwise with good stirring.[32] The reaction temperature was maintained at <10 °C during the addition. The resulting slurry of Δ^3/Δ^2-**17**·HI was stirred at 0–5 °C for an additional 15 min. Next, 25 mL (75 mmol, 2.0 equiv) of 3 N aqueous HI solution was added in one portion. Following the addition, the cooling bath was removed, and the two phase mixture was rapidly warmed to 20–25 °C. Vigorous stirring was continued for 15 min. The phases were separated, and the organic phase was back-extracted with water (10 mL). This back wash was saved for later use.

The main aqueous phase containing Δ^3/Δ^2-**17**·HI was stirred at 20–25 °C for 10 min with 0.5 g of Celite. The slurry was filtered through 1.5 g of Celite (prewashed with 50 mL water). The pad was washed with the aqueous back wash from above and then with water (5 mL). The cake was partially dried under suction for 5 min. A total of 2.0 g of Darco KB was added, and the slurry was stirred at 20–25 °C for 30 min. After this time, 0.5 g of Celite was added, and stirring was continued for an additional 5 min. The slurry was filtered through 1.5 g of Celite (prewashed with 50 mL of water), and the pad was washed with water (5 mL). The Celite pad was partially dried under suction for 5 min. The filtrate was polish filtered through a 5-μm Millipore filter.

Precipitation of Δ^3-**17**·HI was achieved by dropwise addition of 3.5 volumes of 2-propanol to the clear, amber-colored aqueous phase at 20–25 °C. The resulting slurry was cooled to 0–5 °C and was stirred for 1 h. The slurry was filtered and washed with cold (0–5 °C) 4/1 2-propanol/water (v/v, 2 × 20 mL) and acetone (2 × 20 mL). The cake was partially dried under suction for 5 min. Further drying in vacuo at 20–25 °C to a constant weight afforded 8.94 g (57%) of white, crystalline Δ^3-**17** as an HI salt. The HPLC chromatogram showed the salt to be 97 area % pure: NMR (D_2O with solvent suppression, 360 MHz) δ 2.14–2.32 (envelope, 4 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$), 3.00 (s, 3 H, $^+NCH_3$), 3.46–3.67 (m, 5 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$, SCH_2), 3.96 (one leg of AB q, 1 H, J = 16.9 Hz, SCH_2), 4.09, 4.73 (AB q, 2 H, J = 13.9 Hz, $CH_2{}^+N(CH_3)CH_2CH_2CH_2CH_2$), 5.21 (d, 1 H, J = 5.1 Hz, C-7 β-lactam), 5.41 (d, 1 H, J = 5.1, C-6 β-lactam). Anal. Calcd $C_{13}H_{19}N_3O_3S$·HI: C, 36.71; H, 4.74; N, 9.88; S, 7.54. Found: C, 36.47; H, 4.82; N, 9.83; S, 7.19.

Synthesis of 18 (BMY-28142) from 17 (X = Cl). A total of 21.7 g (61.2 mmol) of recrystallized Δ^3-**17**·HCl was dissolved in 190 mL of water at 25 °C with good stirring. The solution was cooled to 8–10 °C, and the pH was adjusted to 5.8 by dropwise addition of 30.5 mL (61 mmol, ~1.0 equiv) of 2 N sodium hydroxide solution. Next, 555 mL of THF was added, and the pH of the resulting solution was increased to 6.8 at 8–10 °C by dropwise addition of 2.0 mL (4 mmol, 0.07 equiv) of 2 N sodium hydroxide solution. The cooling bath was removed, and 29.5 g (92.7 mmol, 1.5 equiv) of **8**[26,33] was added in two equal portions of 14.75 g each over 30 min. Following each addition, the pH was readjusted to 6.5 every 5–10 min by dropwise addition of 2 N sodium hydroxide solution. In the remaining reaction time, the pH was readjusted to 6.5 by addition of 2 N sodium hydroxide solution every 15 min (total 2 N NaOH 29.5 mL, 60 mmol, 1.0 equiv). The completion of the reaction was determined by HPLC analysis.

The yellow/orange solution containing **18** (BMY-28142) was poured into 790 mL of methyl isobutyl ketone, and after phase separation, the upper organic phase was back-extracted with water (64 mL). The combined aqueous phases were stirred 10 min at ambient temperature with 5.1 g of Dicalite. The insoluble materials were removed by suction filtration, and the filtercake was washed with water (2 × 5 mL). The pH of the resulting clear orange filtrate was lowered to 3.7 by dropwise addition of 14.5 mL of 4 N sulfuric acid. At this point, crystallization of **18**·H_2SO_4 was allowed to proceed for 15 min. The pH was lowered to 3.0 by dropwise addition of 7.5 mL of 4 N sulfuric acid. The slurry was cooled to 0–5 °C, and additional 4 N sulfuric acid (63.5 mL) was added dropwise over 30 min with continued good stirring. The slurry was stirred for 1 h at 0–5 °C.

The colorless, crystalline precipitate of Δ^3-**18**·H_2SO_4 was filtered under suction, washed with 0.5 N sulfuric acid (63.5 mL), and partially dried under suction for 15 min. The filtercake was washed with acetone (2 × 100 mL) and was again partially dried under suction for 15 min. The filtercake was slurried for 1 h at ambient temperature in 400 mL of acetone with good stirring. The slurry was filtered, washed with acetone (2 × 100 mL), and dried in vacuo at 40 °C to a constant weight. A total of 28.8 g (81%) of **18**·H_2SO_4 (BMY-28142-H_2SO_4) was obtained as a colorless, highly crystalline salt: NMR (360 MHz, D_2O with solvent suppression) δ 2.16–2.33 (envelope, 4 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$), 3.01 (s, 3 H, $^+NCH_3$), 3.45–3.64 (m, 5 H, $^+N(CH_3)CH_2CH_2CH_2CH_2$, SCH_2), 3.95 (one leg of AB q, 1 H, J = 17 Hz, SCH_2), 4.04, 4.75 (AB q, 2 H, J = 14 Hz, $CH_2{}^+N(CH_3)CH_2CH_2CH_2CH_2$), 4.08 (s, 3 H, OCH_3), 5.37 (d, 1 H, J = 5 Hz, C-6 β-lactam), 5.86 (d, 1 H, J = 5 Hz, C-7 β-lactam), 7.16 (s, 1 H, C-5 thiazole).

The same result (75–80% **18**·H_2SO_4) was achieved by substituting an equimolar amount of **17** (X = I) for the recrystallized **17** (X = Cl) described in the above experiment.

An analytical sample of **18**·H_2SO_4 (BMY-28142-H_2SO_4) was prepared by carbon treatment of a resin-neutralized aqueous solution followed by crystallization by addition of 4 N sulfuric acid. Anal. Calcd for $C_{19}H_{26}N_6O_9S_3$: C, 39.43; H, 4.53; N, 14.53; S, 16.63. Found: C, 39.28; H, 4.50; N, 14.43; S, 17.03.

Synthesis of 19a–d from (Iodomethyl)cephem 11. General Procedure. To a well-stirred solution of **11** in Freon TF [from 2.50 g (9.2 mmol) of 7-ACA] under a blanket of dry nitrogen at 0–5 °C was added a solution or slurry of the thiol (9.2 mmol, 1.0 equiv) and 0.74 mL (9.2 mmol, 1.0 equiv) of dry pyridine in 20

mL of dry dichloromethane dropwise over 10 min. The progress of the displacement reaction was monitored by ^{1}H NMR (CH_2I region). After 30 min, 1.5 mL (37 mmol, 4.0 equiv) of methanol was added dropwise over 10 min while a reaction temperature of <10 °C was maintained. Following the addition, the slurry was stirred at 0–5 °C for an additional 10 min. The solids were collected by suction filtration, washed with fresh Freon TF (2 × 10 mL), and dried to constant weight in vacuo to yield crude mixtures of **19a–d**.

The crude material was slurried in 10 mL of water and was cooled to 0–5 °C. The pH was lowered to 0.30 by the dropwise addition of concentrated HCl solution (**19b,d**) or to 0.50 by the dropwise addition of 4 N HCl solution (**19a,c**). To the resulting slightly cloudy solution was added Darco KB (10% by weight of crude **19a–d**), and stirring was continued at 0–5 °C for 15 min. The charcoal slurry was filtered through a pad of Celite, and the pH of the resulting clear yellow filtrate was raised to either 3.0 (**19b,d**) or 4.0 (**19a,c**) by dropwise addition of 6 N NaOH solution at 0–5 °C. The resulting slurry was stirred at 0–5 °C for 1 h. Filtration of the slurry followed by washing with cold (0–5 °C) water (2 × 5 mL) and drying to a constant weight in vacuo yielded the desired compound.

3-[[(1*H*-1-Methyltetrazol-5-yl)thio]methyl]cephem (19a): 43% yield; the IR and 360-MHz ^{1}H NMR spectra and the HPLC chromatogram (98 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[42]

3-[[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]methyl]cephem (19b): 50% yield; the IR and 360-MHz ^{1}H NMR spectra and the HPLC chromatogram (91 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[42b]

3-[(1*H*-1,2,3-Triazol-4-ylthio)methyl]cephem (19c): 49% yield; the IR and 360-MHz ^{1}H NMR spectra and the HPLC chromatogram (93 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[43]

3-[[[1*H*-1-(Carboxymethyl)tetrazol-5-yl]thio]methyl]cephem (19d): 37% yield; the IR and 360-MHz ^{1}H NMR spectra and the HPLC chromatogram (92 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[44]

Synthesis of 3-[(1-Pyridinio)methyl]cephem (19e) from (Iodomethyl)cephem 11. To a well-stirred solution of **11** in dichloromethane [from 10.0 g (36.7 mmol) of 7-ACA] at 0–5 °C under a blanket of dry nitrogen was added a solution of 6.0 mL (73.5 mmol, 2.0 equiv) of dry pyridine in 20 mL of dichloromethane dropwise over 5 min. The progress of the reaction was monitored by HPLC. After 3.5 h 5.0 mL (123 mmol, 3.35 equiv) of methanol as a solution in 50 mL of dichloromethane was added dropwise with good stirring while a reaction temperature of <10 °C was maintained. The resulting slurry was stirred at 0–5 °C for 10 min and filtered, and the collected solid was washed with CH_2Cl_2 (2 × 50 mL). Drying in vacuo to a constant weight gave 16.52 g (>100%) of crude **19e** as an HI salt. The 360-MHz ^{1}H NMR spectrum and HPLC chromatogram (72 area % purity plus 18 area % pyridine as an HI salt) were consistent with an authentic sample prepared according to the literature.[28,36]

3-[[1-(2,3-Cyclopenteno)pyridinio]methyl]cephem (19f) from (Iodomethyl)cephem 11. This material (15.72 g) was prepared in 93% yield as an HI salt from a solution of **11** in CH_2Cl_2 (from 10.0 g of 7-ACA) exactly as described for cephem **19e**, except that 8.6 mL (73.5 mmol, 2.0 equiv) of 2,3-cyclopentenopyridine (Aldrich) was substituted for the pyridine. The 360-MHz ^{1}H NMR spectrum and HPLC chromatogram (84 area % purity plus 4 area % 2,3-cyclopentenopyridine as an HI salt) were consistent with an authentic sample prepared according to the literature.[24–28]

Preparation of 24 from (Acetoxymethyl)cephem 15. This material was prepared from a solution of **15** in Freon TF [from 50.0 g (184 mmol) 7-ACA] exactly as described for the preparation of **17** from **15**, except that (a) 28.3 mL (257 mmol, 1.4 equiv) of 4-methylmorpholine (sieve-dried, Aldrich) was substituted for the *N*-methylpyrrolidine, (*b*) the reaction was heated at 35–36 °C for 7–8 h, and (c) the reaction was worked up with 5 times the amounts of materials due to the increased reaction scale. A total of 36.0 g (41%) of slightly off-white, crystalline **24** was isolated as an HI salt. The HPLC chromatogram showed the salt to be >95 area % pure: NMR (D_2O with solvent suppression, 360 MHz) δ 3.30 (s, 3 H, $^+NCH_3$), 3.60 (m, 4 H, $^+N(CH_3)CH_2CH_2OCH_2CH_2$), 3.68, 4.04 (AB q, 2 H, J = 10 Hz, SCH_2), 4.20 (m, 4 H, $^+N(CH_3)CH_2CH_2OCH_2CH_2$), 4.25, 4.93 (AB q, 2 H, J = 14 Hz, $CH_2{}^+N(CH_3)CH_2CH_2OCH_2CH_2$), 5.30 (d, 1 H, J = 5 Hz, C-7 β-lactam), 5.53 (d, 1 H, J = 5 Hz, C-6 β-lactam). Anal. Calcd for $C_{13}H_{19}N_3O_4S$·HI: C, 35.40; H, 4.34; N, 9.53. Found: C, 34.99; H, 4.38; N, 9.35.

Preparation of 19e from (Acetoxymethyl)cephem 15. This material was prepared from a solution of **15** in Freon TF [from 10.0 g (36.7 mmol) 7-ACA] exactly as described for the preparation of **17** from **15** except that 4.2 mL (51.4 mmol, 1.4 equiv) of dry pyridine was substituted for the *N*-methylpyrrolidine. The progress of the reaction was monitored by HPLC and was found to be complete after 51 h at 35–36 °C. The slurry was cooled to 20–25 °C under a blanket of dry nitrogen. The solid was removed by filtration through a Schlenk funnel under nitrogen pressure. The collected solid was washed with Freon TF (2 × 100 mL). The filtercake was quickly added to 50 mL of dry dichloromethane, which was precooled to 0–5 °C in an ice bath. To the resulting dark solution was added 5.0 mL (123 mmol, 3.35 equiv) of methanol dropwise with good stirring and with a reaction temperature of <10 °C. The resulting slurry was stirred at 0–5 °C for an additional 15 min. The solid was collected by filtration and was washed with fresh CH_2Cl_2 (2 × 50 mL). The filtercake was reslurried in 150 mL CH_2Cl_2 for 1 h. The solid was filtered, washed with CH_2Cl_2 (2 × 50 mL), and dried in vacuo at 20–25 °C to a constant weight to afford 14.7 g (95%) of crude **19e** as an HI salt. The 360-MHz ^{1}H NMR spectrum and HPLC chromatogram (65 area % purity plus 13 area % pyridine as an HI salt) of this material were consistent with an authentic sample prepared according to the literature.[28,36]

Preparation of 19f from (Acetoxymethyl)cephem 15. This material was prepared from a solution of **15** in Freon TF [from 10.0 g (36.7 mmol) 7-ACA] exactly as described for the preparation of **19e** from **15**, except that 6.02 mL (51.4 mmol, 1.4 equiv) of 2,3-cyclopentenopyridine (sieve-dried, Aldrich) was substituted for the pyridine. After 52 h, the reaction was worked up to yield 13.2 g (78%) of crude **19f** as an HI salt. The 360-MHz ^{1}H NMR spectrum and HPLC chromatogram (89 area % purity) of this material was consistent with an authentic sample prepared according to the literature.[24–28]

Synthesis of Carbamate 20 from 15. Method A. To a slightly hazy solution of **15** in Freon TF [from 10.0 g (36.7 mmol) of 7-ACA] at ambient temperature under a blanket of dry nitrogen was added 410 mg (3.5 mmol, 0.10 equiv) of freshly prepared pyridine hydrochloride with good stirring. Next, dry carbon dioxide gas (passed through Drierite) was gently bubbled into the reaction through a drawn out capillary pipet for 24 h with continued good stirring. After this time, the resulting slurry was filtered through a tared Schlenk funnel under nitrogen pressure, and the collected solid was washed with dry Freon TF (2 × 25 mL). The filtercake was partially dried with a stream of nitrogen. Further drying at ambient temperature at 0.05 mmHg for 5 h gave 13.3 g (85%) of light yellow, extremely moisture sensitive **20**: IR (CH_2Cl_2) 1790, 1743, 1709, 1511, 1250, 1232 cm^{-1}; NMR (CD_2Cl_2, 360 MHz) δ 0.31 (s, 9 H, $NHCOOSi(CH_3)_3$), 0.36 (s, 9 H, $COOSi(CH_3)_3$), 2.08 (s, 3 H, $COCH_3$), 3.44, 3.63 (AB q, 2 H, J = 18.6 Hz, SCH_2), 4.85, 5.11 (AB q, 2 H, J = 13.4 Hz, CH_2OAc), 5.02 (d, 1 H, J = 5.1 Hz, C-6 β-lactam), 5.54 (d, 1 H, J = 9.7 Hz, NH), 5.63 (dd, 1 H, J = 5.1, 9.7 Hz, C-7 β-lactam).

Method B. Dry carbon dioxide gas (passed through Drierite) was gently bubbled into a dichloromethane solution of **15** [from 5.0 g (18.4 mmol) of 7-ACA] through a drawn out capillary pipet with good stirring and with protection from moisture for 12 h. A 360-MHz ^{1}H NMR spectrum of an aliquot of the solution showed >95% conversion to **20**.

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Synthesis of (Iodomethyl)cephem 21 in CH_2Cl_2. To a solution of **20** in dichloromethane [from 5.0 g (18.4 mmol) of 7-ACA] under a blanket of dry nitrogen at ambient temperature was added 3.0 mL (21.1 mmol, 1.15 equiv) of TMSI (Aldrich) in a slow stream over 2–3 min with good stirring. After 1–2 h, the 360-MHz ^1H NMR spectrum (acetate methyl region) of an aliquot of the solution showed >95% conversion to **21**: NMR (CD_2Cl_2/CH_2Cl_2, 360 MHz) δ 0.27 (br s, 9 H, $NHCOOSi(CH_3)_3$), 0.37 (s, 9 H, $COOSi(CH_3)_3$), 3.57, 3.80 (AB q, 2 H, J = 18.1 Hz, SCH_2), 4.34, 4.51 (AB q, 2 H, J = 9.2 Hz, CH_2I), 5.00 (d, 1 H, J = 4.6 Hz, C-6 β-lactam), the remainder of the spectrum was obliterated by protonic dichloromethane.

Synthesis of 19a–d from Carbamate 21. General Procedure. To a stirred solution of **21** in dichloromethane [from 5.0 g (18.4 mmol) of 7-ACA] under a blanket of dry nitrogen at 0–5 °C was added a solution or slurry of the thiol (18.4 mmol, 1.0 equiv) and 1.49 mL (18.4 mmol, 1.0 equiv) of dry pyridine in 20 mL of dry dichloromethane dropwise over 5 min. The progress of the displacement reaction was monitored by ^1H NMR (CH_2I region). After the appropriate time (1.5–4.5 h), 2.50 mL (61.5 mmol, 3.35 equiv) of methanol was added dropwise over 2–3 min (evolution of carbon dioxide noted). Following the addition, the slurry was stirred at 0–5 °C for an additional 15 min. The solids were collected by suction filtration, washed with dichloromethane (2 × 20 mL), and dried in vacuo at ambient temperature to a constant weight.

The crude material was slurried in 40 mL of water, and the pH was lowered to 0.50 by the dropwise addition of 4 N HCl solution with good stirring. Darco KB was added (10% by weight of crude), and the slurry was stirred at ambient temperature for 15 min. The charcoal was removed by filtration through a pad of Celite (2.0 g), and the pad was washed with water (5 mL).

The filtrate was colled to 0–5 °C in an ice water bath, and the pH was raised to 4.0 by dropwise addition of 6 N NaOH solution. After the resulting slurry was stirred at 0–5 °C for an additional 90 min, the solid was filtered, washed with cold (0–5 °C) water (10 mL), and dried in vacuo at ambient temperature to a constant weight.

3-[[(1-Methyl-1*H*-tetrazol-5-yl)thio]methyl]cephem 19a: 63% yield; the IR and 360-MHz ^1H NMR spectra and the HPLC chromatogram (86 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[42]

3-[[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]methyl]cephem 19b: 60% yield; the IR and 360-MHz ^1H NMR spectra and HPLC chromatogram (89 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[42b]

3-[(1*H*-1,2,3-Triazol-4-ylthio)methyl]cephem 19c: 56% yield; the IR and 360-MHz ^1H NMR spectra and HPLC chromatogram (84 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[43]

3-[[[1-(Carboxymethyl)-1*H*-tetrazol-5-yl]thio]methyl]cephem 19d: 54% yield; the IR and 360-MHz ^1H NMR spectra and HPLC chromatogram (80 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[44]

Synthesis of 3-[(1-Pyridinio)methyl]cephem 19e from Carbamate 21. To a solution of **21** [from 5.0 g (18.4 mmol) 7-ACA] in CH_2Cl_2 at 0–5 °C under a blanket of dry nitrogen was added a solution of 3.0 mL (36.7 mmol, 2.0 equiv) of dry pyridine in 20 mL of CH_2Cl_2 dropwise over 5 min. The progress of the reaction was monitored by ^1H NMR spectroscopy (CH_2I region). After 90 min, 2.5 mL (61.5 mmol, 3.35) equiv of methanol was added dropwise to the solution while a reaction temperature of <10 °C was maintained (CO_2 evolution noted). The slurry was stirred at 0–5 °C for an additional 15 min. The solid was filtered under suction, washed with fresh CH_2Cl_2 (2 × 20 mL), and dried in vacuo at ambient temperature to constant weight to afford 7.41 g (96%) of **19e** as an HI salt. The 360-MHz ^1H NMR spectrum and the HPLC chromatogram (80 area % purity) of this material were consistent with an authentic sample prepared according to the literature.[28,36]

Synthesis of 3-[[1-(2,3-Cyclopenteno)pyridinio]methyl]cephem 19f from Carbamate 21. This material (15.82 g) was prepared in 94% yield as an HI salt from a solution of **21** in CH_2Cl_2 [from 10.0 g (36.7 mmol) 7-ACA] exactly as described for cephem **19e**, except that 8.6 mL (73.5 mmol, 2.0 equiv) of 2,3-cyclopentenopyridine (Aldrich) was substituted for the pyridine, and the total reaction time was extended to 3.75 h. The 360-MHz ^1H NMR spectrum and HPLC chromatogram (78 area % purity) were consistent with an authentic sample prepared according to the literature.[24-28]

Preparation and Characterization of 23. An oven-dried flask was cooled to ambient temperature under a stream of nitrogen. The flask was charged with 25 mL of dry Freon TF and 1.42 mL (10.0 mmol) of TMSI (Aldrich). The resulting solution was cooled to 0–5 °C under a blanket of dry nitrogen. A total of 1.04 mL (10.0 mmol, 1.0 equiv) of dry 97% *N*-methylpyrrolidine (from sieves; Aldrich) was added dropwise while maintaining a temperature of <10 °C. The resulting slurry was stirred at 0–5 °C for 30 min. The slurry was filtered under positive nitrogen pressure through a tared Schlenk funnel via a cannula, and the collected solid was washed with dry Freon TF (2 × 25 mL). Drying at ambient temperature in vacuo at 0.05 mmHg afforded 2.51 g (89%) of **23** as a colorless, *extremely* air sensitive solid: $C_8H_{20}INSi$ requires 44.49% iodide; found, 44.40% iodide (iodide ion chromatography analysis).

In a separate experiment, a total of 0.40 mL (10.0 mmol, 1.0 equiv) of methanol was added dropwise to the slurry of **23** in Freon TF at 0–5 °C. The resulting slurry was stirred at 0–5 °C under a blanket of dry nitrogen for 30 min. The slurry was filtered via cannulation through a tared Schlenk funnel under positive nitrogen pressure. The filtercake was washed with fresh Freon TF (2 × 25 mL) and was dried at ambient temperature in vacuo at 0.05 mmHg. The isolated solid (1.93 g, 91%) was identified as *N*-methylpyrrolidinium iodide, mp 80–82 °C. An authentic sample of this salt was prepared independently by gently bubbling hydrogen iodide gas into a solution of *N*-methylpyrrolidine in Freon TF. The isolated solid had mp 83.5–85.5 °C. The 360-MHz ^1H NMR (D_2O) spectrum of this material was consistent with the spectrum observed for the salt isolated from the methanol-quenched reaction.

The 360-MHz ^1H NMR spectrum of the filtrate from the methanol quenched reaction showed, as the major components, methoxytrimethylsilane and methyl iodide (integration ratio 17/1, respectively), as well as a small amount of hexamethyldisiloxane.

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