Transformation of Penicillins into 3-Substituted Δ^3-Cephems through Addition/Cyclization of Allenecarboxylates

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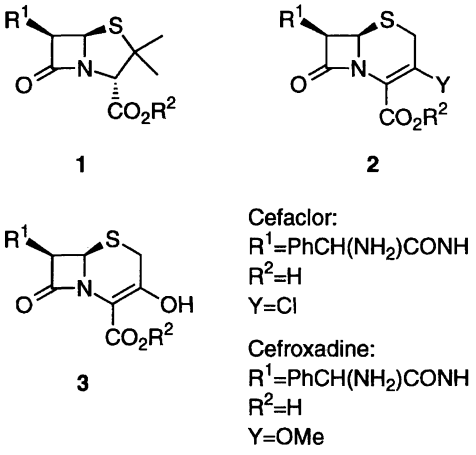
A straightforward synthesis of Δ^3-cephems **2** bearing heteroatom substituents directly attached to C(3)-position was performed successfully by a sequential addition/cyclization reaction of allenecarboxylate **4** derived from eithen penicillin **1**. Upon treatment of the allenecarboxylate **4** with morpholine, pyrrolidine, sodium azide, and 5-methyl-1,3,4-thiadiazole-2-thiol in DMF in the presence of calcium chloride, the addition/cyclization reaction proceeded smoothly to afford the corresponding 3-substituted Δ^3-cephems **2a**—**e**. Reaction of the allenecarboxylate **4** with lithium chloride in NMP (*N*-methyl-2-pyrrolidone) in the presence of aluminum chloride afforded 3-chloro-Δ^3-cephem **2f**, while without aluminum chloride, 3-phenylsulfonyl-Δ^3-cephem **2e** was mainly obtained. The 3-sulfenyl-Δ^3-cephems **12** were prepared by a similar addition/cyclization reaction of allenecarboxylates **10** with a catalytic amount of thiolates. The sulfenyl moieties attached at the sulfur atom of the C(4)-substituent of **10** were introduced at the C(3)-position of the cephem framework **2**.

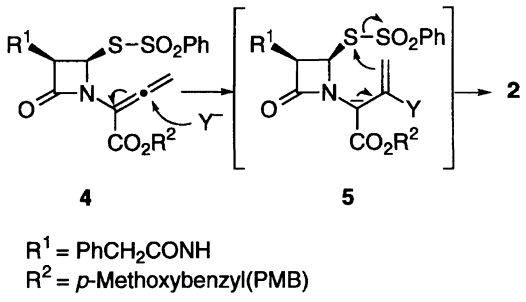
Δ^3-Cephems **2** bearing heteroatom substituents attached at the C(3)-position of the cephem framework are an important class of semisynthetic β-lactam antibiotics; they are used particularly as orally active drugs.[1] Indeed, 3-chloro- and 3-methoxy-Δ^3-cephems **2** (Y = Cl, OMe) are currently used in antibacterial chemotherapy (Scheme 1).[2] Many chemists have been interested in the development of more economical and straightforward synthetic approaches to these antibiotics starting from penicillins **1** which are readily available as fermentation products.[3,4]

Hitherto disclosed syntheses of the 3-substituted Δ^3-cephems **2** mainly rely on modification of the C(3)-hydroxy group of 3-hydroxy-Δ^3-cephems **3**, which are derived from either penicillins **1** or cephalosporins.[3—5] For instance, the synthesis of 3-chloro- and 3-methoxy-Δ^3-cephems **2** (Y=Cl, OMe) have been achieved by treatment of **3** with phosphorus trichloride and with diazomethane, respectively.[3] The introduction of other C(3)-substituents, e.g., sulfenyl and amino moieties, has been realized by transformation of the C(3)-hydroxy functional group of **3** into the corresponding mesylate, tosylate, or triflate, followed by displacement with appropriate heteroatom nucleophiles.[6] However, the methods involve a two-step procedure to prepare each derivative and/or undesired migration of the Δ^3-double bond of the cephem framework occurs, leading to the Δ^2-isomers.

In order to circumvent these problems, we investigated a conceptually new synthetic route to the 3-substituted Δ^3-cephems **2** starting from penicillin **1** through a sequential addition/cyclization with a central penultimate intermediate, the allenecarboxylate **4**, as illustrated in Scheme 2. Attack of heteroatom nucleophiles (Y^-) at the center carbon of the allene moiety of **4** affords anionic adducts **5** which undergo ring closure to form the Δ^3-cephem framework **2**. Consequently, the construction of the cephem framework as well as introduction of the heteroatom substituents (Y) at C(3)-po-



Scheme 1.



Scheme 2.

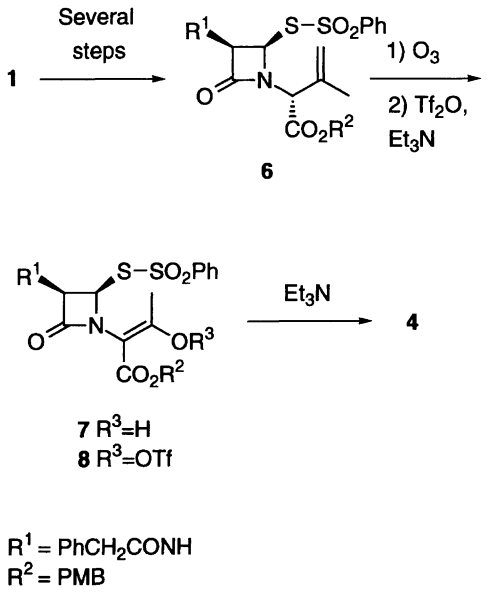
sition is achieved simultaneously by the one-pot operation.[7] The key intermediate **4** has been synthesized by our group and proved to be a useful intermediate for the synthesis of 2-*exo*-methylenepenams.[8]

After our preliminary report[7] on the new addition/cyclization reaction of the allenecarboxylate **4** leading to **2**, Kant and Farina[9] reported an analogous addition/cyclization reaction leading to Δ^3-cephems **2** bearing benzothiazolylsulfenyl or *N*-methyltetrazolylsulfenyl group at the C(3)-position. Both our[10] and their groups[11] have independently succeeded in the extension of the addition/cyclization methodology to synthesize 3-alkenyl-, 3-aryl-, 3-allyl-3-benzyl-Δ^3-cephems. Herein, we describe in detail the addition/cyclization methodology for the construction of the Δ^3-cephem framework bearing C(3)-heteroatom substituents e.g., amino, azido, and sulfenyl moieties as well as a new method for the synthesis of 3-chloro-Δ^3-cephem.[12]

Results and Discussion

The key intermediate, allenecarboxylate **4**, was prepared from azetidinone **6**,[13,14] in turn derived from penicillin **1** (Scheme 3). Thus, ozonolysis of the azetidinone **6** in a mixed solvent of methanol and dichloromethane at −78 °C afforded enol **7** in 81% yield. Treatment of the enol **7** with trifluoromethanesulfonic anhydride in dichloromethane containing triethylamine at −100 °C gave the corresponding triflate **8** in 82% yield. Subsequent β-elimination of the triflate **8** with triethylamine in DMF at −30 °C afforded the allenecarboxylate **4** in 98% yield.

Addition/Cyclization of Allenecarboxylate with Heteroatom Nucleophiles. The direct transformation of the allenecarboxylate **4** into the 3-substituted Δ^3-cephems **2** was, at first, investigated by use of morpholine as a heteroatom nucleophile (Table 1). The reaction of **4** with morpholine in DMF in the presence of calcium chloride proceeded in an expected fashion to produce 3-morpholino-Δ^3-cephem **2a**



Scheme 3.

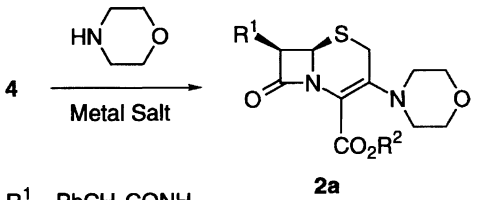
Table 1. Addition/Cyclization Reaction of Allenecarboxylate **4** with Morpholine[a]

Entry	Metal salts	Yield of **2a**/%[b]
1	$CaCl_2$	54(44)[c]
2	None	23[d]
3	$MnCl_2$	47
4	$CuCl_2$	24
5	$ZnCl_2$	11
6	$SnCl_2$	N.D.[e]

a) Carried out in DMF containing 9 molar amt. of metal salts. b) Determined by HPLC: column: YMC Pack® AM-312 ODS 6φ×150 mm, mobile phase: $CH_3CN/H_2O = 60/40$, flow rate: 1.0 ml min^{-1}. c) Isolated yield after column chromatography (SiO_2). d) Considerable amounts of decomposition products were formed without recovered **4**. e) Not detected.

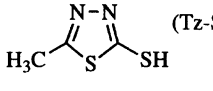
in 54% yield (Entry 1).[15] The presence of calcium chloride is indispensable, since the yield of **2a** was reduced to 23% yield without calcium chloride (Entry 2). Among thus far investigated metal salts, calcium chloride is the best choice for this purpose; indeed, the yields of **2a** decreased in the following order (Entries 3—6): manganese(II) chloride (47%) > copper(II) chloride (24%) > zinc chloride (11%) > tin(II) chloride (—).[7] Although the role of calcium chloride is still not clear, it is likely that intermediate **5** generated by the addition of **4** with morpholine would be trapped with calcium ion to promote the addition of the nucleophile and/or subsequent ring closure, leading to the 3-morpholino-Δ^3-cephem **2a** (Scheme 4).

The present addition/cyclization method was successfully applied to the syntheses of various 3-substituted Δ^3-cephems **2** (Table 2). The reaction of the allenecarboxylate **4** with pyrrolidine, sodium azide, and 5-methyl-1,3,4-thiadiazole-2-thiol in NMP in the presence of calcium chloride afforded the corresponding 3-substituted Δ^3-cephems **2b**—**d** in 39—63% yields (Entries 2—4). It is of interest to note that in the absence of the heteroatom nucleophile, 3-phenylsulfonyl-Δ^3-cephem **2e** (69%), was obtained together with 3-chloro-Δ^3-cephem **2f** (6%) (Entry 5). This result can be explained by assuming that in the initial stage of the reaction, chloride ion acts as a nucleophile to afford the corresponding adduct **5f** and subsequent ring closure of **5f** gives the 3-chloro-Δ^3-cephem **2f** together with benzenesulfinate ion ($PhSO_2^-$). The sulfinate ion thus formed would, in turn, work as a nucleophile to react with **4** to produce **2e** and additional benzenesulfinate ion, which reacts with **4** leading to the repeated formation of **2e** (Scheme 5).

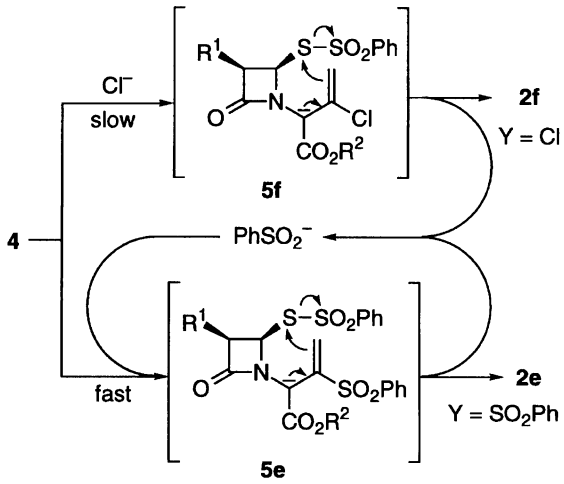


Scheme 4.

Table 2. Synthesis of 3-Substituted Δ^3-Cephems **2**[a]

Entry	Nucleophiles (Y)	Product (Yields/%)[b]
1	Morpholine	**2a** (44), (54)[c]
2	Pyrrolidine	**2b** (48)
3	Sodium azide	**2c** (37)
4	 (Tz-SH)	**2d** Y=Tz-S (63)
		2e Y=$PhSO_2$(19)
5	None	**2e** Y=$PhSO_2$(69)[c]
		2f Y=Cl (6)[c]

a) Carried out in DMF containing 9 molar amt. of calcium chloride. b) Isolated yield after column chromatography (SiO_2), unless otherwise noted. c) Determined by HPLC; see footnote (b) of Table 1.



R^1 = $PhCH_2CONH$
R^2 = PMB

Scheme 5.

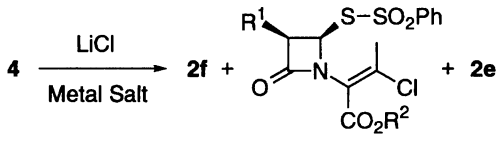
Synthesis of 3-Chloro-Δ^3-cephem via Addition/Cyclization of Allenecarboxylate. Next, our attention was focused on the synthesis of the 3-chloro-Δ^3-cephem **2f** which could not be obtained in good yield by the above procedure.[11] Chloride ion is less nucleophilic than the in situ generated benzenesulfinate ion which reacts with **4**, leading to the undesired 3-phenylsulfonyl-Δ^3-cephem **2e**.[16] A procedure which traps the nucleophilic benzenesulfinate ion was required for efficient formation of the 3-chloro-Δ^3-cephem **2f**.[12] After assaying various trapping reagents for the benzenesulfinate ion (as complied in Table 3), we found that aluminum chloride could completely suppress the formation of the 3-phenylsulfonyl-Δ^3-cephem **2e** (Entry 2). Thus, the reaction of the allenecarboxylate **4** with lithium chloride in NMP in the presence of aluminum chloride at room temperature afforded the 3-chloro-Δ^3-cephem **2f** (73%) together with a small amount of monochloro azetidinone **9** (6%) (Scheme 6).[17]

In a similar manner, the reaction of the allenecarboxylate **4** with lithium chloride in the presence of other trapping reagents was carried out (Entries 3—10). Aluminum bromide worked as the trapping reagent to afford the 3-chloro-Δ^3-cephem **2f** in 46% yield (Entry 3), whereas aluminum isopropoxide was less effective and mainly produced the undesired 3-phenylsulfonyl-Δ^3-cephem **2e** in 71% yield (Entry 4). Trimethylsilyl chloride, dichlorodimethylsilane, and tin(IV) chloride were effective trapping reagents to remove the benzenesulfinate ion in the medium (Entries 5—7). Copper(I) chloride, zinc bromide, and silver(I) nitrate were not effective (Entries 8—10). Above all, aluminum chloride is the best choice for trapping the in situ generated benzenesulfinate to suppress the formation of **2e**.

Table 3. Synthesis of 3-Chloro-Δ^3-cephem **2f** in the Presence of Absence of Metal Salts[a]

Entry	Metal salts (equiv)	Yield/%[b]		
		2f	**9**	**2e**
1	None	2	—	81
2	$AlCl_3$ (2)	73	6	—
3	$AlBr_3$ (2)	46	8	—
4	Al(O*i*-Pr)$_3$ (2)	11	—	71
5	TMSCl (6)	46	19	—
6	Me_2SiCl_2 (2)	56	19	—
7	$SiCl_4$ (2)	36	22	—
8	CuCl (6)	1	—	77
9	$ZnBr_2$ (3)	1	—	69
10	$AgNO_3$ (6)	3	—	45

a) Carried out in NMP containing 10 molar amt. of lithium chloride. b) Isolated yield after column chromatography (SiO_2).



R^1 = $PhCH_2CONH$
R^2 = PMB

Scheme 6.

Further application of the present method to the synthesis of the corresponding 3-fluoro, 3-bromo-, and 3-iodo-Δ^3-cephems **2** (Y = F, Br, and I) was also investigated (Table 4). The reaction of the allenecarboxylate **4** with various combinations of appropriate halide salts and aluminum halides did not give any detectable amount of the corresponding 3-fluoro-, 3-bromo-, and 3-iodo-Δ^3-cephems **2** (Y = F, Br, and

Table 4. The Reaction of Allenecarboxylate **4** with Metal Salts[a]

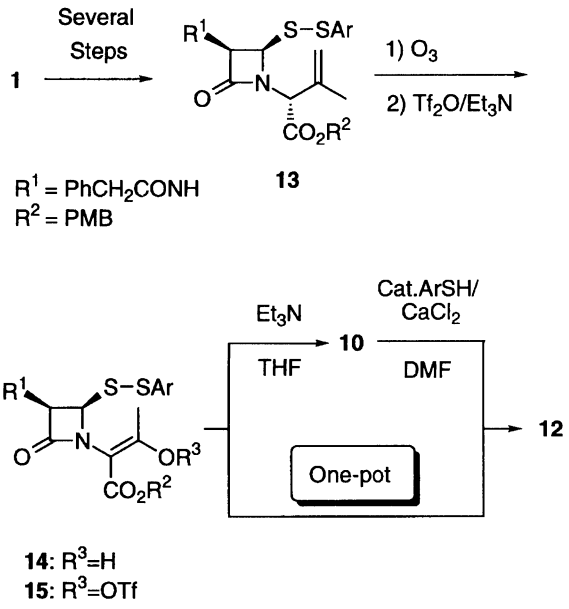
Entry	$MX/M'X'_n$	Yield/%[b]		
		2f	**2e**	**4**
1	CsF/AlF_3	—	20	66
2	$CsF/AlBr_3$	—	—	70
3	$LiBr/AlBr_3$	—	—	73
4	LiI/AlI_3	—	—	—

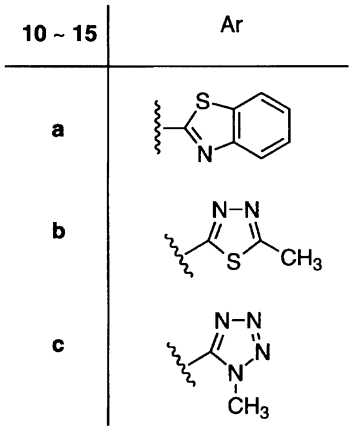
a) Carried out in NMP containing 9 molar amt. of MX and 2 molar amt. of $M'X'_n$. b) Isolated yield after column chromatography (SiO_2).

I). The disappointing result might be ascribed to the poor nucleophilic nature of fluoride ion or to the bulkiness of a bromide or iodide ion.[18]

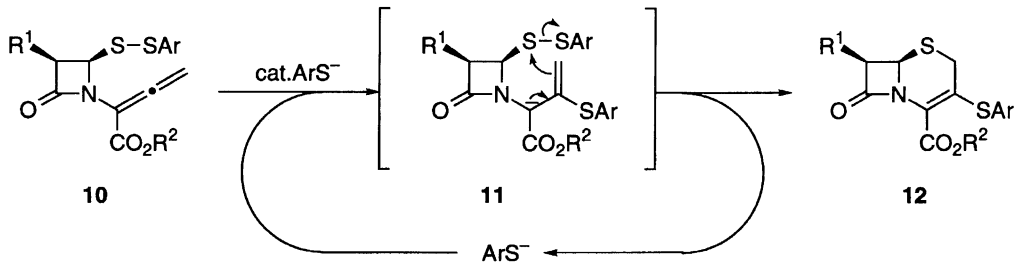
Synthesis of 3-Sulfenyl-Δ^3-cephems via Thiolate-Catalyzed Addition/Cyclization of Allenecarboxylate. As described previously, the addition/cyclization reaction of the allenecarboxylate **4** without a heteroatom nucleophile afforded 3-phenylsulfonyl-Δ^3-cephem **2e** (Table 2, Entry 5). The phenylsulfonyl moiety attached at sulfur atom of C(4)-position of **4** works as a leaving group in the cyclization step and the resulting benzenesulfinate ion acts as a nucleophile in the addition step. This fact prompted us to investigate an alternative synthesis of 3-sulfenyl-Δ^3-cephems **12** as illustrated in Scheme 7. Farina and his co-workers have reported a similar addition/cyclization of a allenecarboxylate (R^1 = $PhOCH_2CONH$, $PhCH_2CONH$, $R^2 = p-NO_2C_6H_4CH_2$, Ph_2CH) involving a chloride ion induced S–S bond fission of disulfide moiety at the C(4) position of the allenecarboxylate.[9,11b,11c] Our strategy involves the addition/cyclization reaction of **10**. The reaction is initiated by the attack of a catalytic amount of the thiolate (ArS^-) on the central carbon of the allene moiety, affording the anionic adducts **11**. Subsequent cyclization to the 3-sulfenyl-Δ^3-cephems **12** also affords the thiolate (ArS^-), which is used repeatedly to complete the addition/cyclization reaction.

The allenecarboxylates **10** bearing the appropriate substituents at the sulfur atom of C(4)-position of the azetidinone framework were prepared from penicillin **1** (Scheme 8). Ozonolysis of the azetidinones **13**,[13] in acetone at −78 °C afforded enols **14** in 84—85% yields. Treatment of the enols **14** with trifluoromethanesulfonic anhydride in dichloromethane containing triethylamine at −78 °C gave the corresponding triflates **15** in 56—84% yields. Treatment of the triflate **15a** (Ar=benzothiazol-2-yl) with triethylamine in THF at 20 °C afforded the corresponding allenecarboxylate **10a**. The allenecarboxylate **10a** was allowed to react with a catalytic amount of 2-benzothiazolethiol in DMF in the presence of calcium chloride. The thiolate-catalyzed addition/cyclization reaction proceeded in an expected fashion to afford 3-(benzothiazol-2-ylsulfenyl)-Δ^3-cephem **12a** in 83% yield (Table 5, Entry 1). One-pot transformation of the triflate **15a** into the 3-(benzothiazol-2-ylsulfenyl)-Δ^3-cephem **12a** was also examined. The triflate **15a** was allowed to react with triethylamine in THF at 20 °C for 2 h, and then, a solution of a catalytic amount of 2-benzothiazolethiol and calcium chloride in DMF was added at −40 °C and the mixture was stirred for an additional 0.5 h to obtain **12a** in 84% overall yield (Entry 2). The presence of a catalytic amount of 2-benzothiazolethiol is needed to start the reaction smoothly;





Scheme 8.



Scheme 7.

Table 5. Transformation of Triflate **15** into 3-Sulfenyl-Δ^3-cephems **12** by Thiol-Catalyzed Cyclization of Allenecarboxylate **10**

Entry	Substrate	Method	Product (Yields/%)[a]
1	**15a**	Step-by-step	**12a** (83)
2	**15a**	One-pot	**12a** (84)
3	**15b**	One-pot	**12b** (76)
4	**15c**	One-pot	**12c** (40)

a) Isolated yield after column chromatography (SiO_2).

indeed, in the absence of 2-benzothiazolethiol, the reaction was hard to start and more than 7 h were required to complete the conversion.

In a similar manner, transformation of the triflates **15b** (Ar = 5-methyl-1,3,4-thiadiazol-2-yl) and **15c** (Ar = 1-methyl-1,2,3,4-tetrazol-5-yl) into 3-sulfenyl-Δ^3-cephems **12b** and **12c** in a one-pot reaction was performed in 76 and 40% yields, respectively (Entries 3 and 4).

Conclusion

Synthesis of the Δ^3-cephems **2** bearing heteroatom substituents directly attached to the C(3)-position was performed by a sequential addition/cyclization reaction of the allenecarboxylate **4** with heteroatom nucleophiles e.g., morpholine, pyrrolidine, sodium azide, and 5-methyl-1,3,4-thiadiazole-2-thiol in the presence of calcium chloride. Without the heteroatom nucleophiles, 3-phenylsulfonyl-Δ^3-cephem **2e** was mainly formed, together with a small amount of 3-chloro-Δ^3-cephem **2f**. The selective synthesis of the 3-chloro-Δ^3-cephem **2f** was attained by the presence of aluminum chloride in the reaction media. The transformation of the allenecarboxylates **10** into 3-sulfenyl-Δ^3-cephems **12a** was performed by the aid of a catalytic amount of the 2-benzothiazolethiol. One-pot transformation of the triflates **15** into 3-sulfenyl-Δ^3-cephems **12** was also achieved by successive treatment of **15** with triethylamine and a catalytic amount of thiols.

Experimental

All solvents were dried by the standard methods. Starting materials **6** and **13** were prepared from penicillin **1** ($R^1 = PhCH_2CONH$, $R^2 = p$-$MeOC_6H_4CH_2$) according to the reported procedures.[13,14] High-performance liquid chromatography (HPLC) was executed with a Waters HPLC instrument equipped with a 510 LC pump, a 440 UV detector, and a Hitachi D-2500 integrator. All other reagents were used as supplied without further purification, unless otherwise noted. Infrared spectra (IR) were recorded with JASCO FT/IR-5000 spectrometer in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were determined in chloroform-*d* with a Varian VXR-200 (200 MHz for ^1H and 50 MHz for ^{13}C) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) down field from tetramethylsilane. Elemental analyses were obtained with Perkin–Elmer PE 2400 Series II CHNS/O Analyzer.

1-[2-Hydroxy-1-(*p*-methoxybenzyloxycarbonyl)-1-propenyl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (7). Into a solution of **6** (3.41 g, 5.74 mmol) in dichloromethane (10 ml) and methanol (5 ml) was bubbled ozone at −78 °C. After **6** was almost consumed (1 h), argon gas was bubbled for a few minutes and then dimethyl sulfide (0.42 ml, 5.74 mmol) was added. The cooling bath was removed and the mixture was stirred at room temperature for additional 3 h. After evaporation of the solvent in vacuo, the residue was extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 3/1—1/1), affording enol **7** (2.78 g, 81%): IR (KBr) 3424, 3316, 1779, 1667, 1330, 1145 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.02 (s, 3H, CH_3), 3.64 (s, 2H, $PhCH_2$), 3.80 (s, 3H, OCH_3), 4.72 (dd, J = 5.5, 6.9 Hz, 1H, NCH), 5.11 (ABq, J = 12.0 Hz, 2H, CO_2CH_2), 5.69 (d, J = 5.5 Hz, 1H, SCH), 5.99 (d, J = 6.9 Hz, 1H, NH), 6.88—7.63 (m, 14H, Ar), 11.91 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 18.2, 42.9, 55.3, 61.8, 67.1, 72.0, 98.5, 114.2, 126.2, 126.9, 127.8, 129.3, 129.4, 129.6, 130.4, 133.4, 134.0, 145.3, 160.0, 165.0, 168.7, 172.8, 178.9. Found: C, 58.40; H, 4.52; N, 4.52%. Calcd for $C_{29}H_{28}N_2O_8S_2$: C, 58.38; H, 4.73; N, 4.69%.

1-[1-(*p*-Methoxybenzyloxycarbonyl)-2-(trifluoromethylsulfonyloxy)-1-propenyl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (8). Into a solution of the enol **7** (1.92 g, 3.21 mmol) in dichloromethane (5 ml) were successively added triethylamine (0.67 ml, 4.82 mmol) and trifluoromethanesulfonic anhydride (0.81 ml, 8.03 mmol) at −100 °C. After being stirred for 1 h, the mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 2/1—1/1) and afforded triflate **8** (1.93 g, 82%): IR (KBr) 3282, 1792, 1721, 1669, 1330, 1145 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.32 (s, 3H, CH_3), 3.61 (s, 2H, $PHCH_2$), 3.78 (s, 3H, OCH_3), 4.79 (dd, J = 5.5, 7.1 Hz, 1H, NCH), 5.17 (ABq, J = 12.0 Hz, 2H, CO_2CH_2), 5.93 (d, J = 5.5 Hz, 1H, SCH), 6.19 (d, J = 7.1 Hz, 1H, NH), 6.85—7.76 (m, 14H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 18.5, 42.8, 55.2, 62.6, 68.2, 70.0, 114.0, 117.9, 126.5, 126.7, 127.8, 129.2, 129.5, 130.9, 133.2, 134.2, 144.4, 156.8, 160.0, 162.9, 173.1. Found: C, 49.31; H, 3.73; N, 3.90%. Calcd for $C_{30}H_{27}F_3N_2O_{10}S_3$: C, 49.45; H, 3.73; N, 3.84%.

1-[1-(*p*-Methoxybenzyloxycarbonyl)-1,2-propadien-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (4). Into a solution of the triflate **8** (145 mg, 0.20 mmol) in DMF (2.5 ml) was added triethylamine (0.07 ml, 0.50 mmol) at −25 °C. After being stirred for 1 h, the mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography (SiO_2, benzene/ethyl acetate: 9/1—3/1) and afforded allenecarboxylate **4** (113 mg, 98%): IR (KBr) 3308, 1968, 1667, 1783, 1721, 1678, 1330, 1147 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 3.60 (s, 2H, $PhCH_2$), 3.80 (s, 3H, OCH_3), 5.10 (ABq, J = 12.1 Hz, 2H, C=C=CH_2), 5.33 (dd, J = 5.0, 8.2 Hz, 1H, NCH), 5.55 (ABq, J = 15.0 Hz, 2H, CO_2CH_2), 5.87 (d, J = 5.0 Hz, 1H, SCH), 6.05 (d, J = 8.2 Hz, 1H, NH), 6.85—7.85 (m, 14H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 42.4, 55.1, 61.9, 67.2, 70.6, 86.0, 98.2, 113.8, 126.7, 127.0, 127.2, 128.1, 128.7, 129.2, 129.3, 129.5, 129.9, 130.1, 133.7, 133.8, 144.6, 159.6, 162.5, 163.7, 172.4, 212.0.

Addition/Cyclization Reactions of Allenecarboxylate with Heteroatom Nucleophiles. *p*-Methoxybenzyl 3-Morpholino-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (2a). Into a mixture of the allenecarboxylate **4** (102 mg, 0.18 mmol) and calcium chloride (188 mg, 1.69 mmol) in DMF (2 ml) was added morpho-

line (46 ml, 0.53 mmol) at room temperature for 1 h. An aliquot of the reaction mixture was analyzed by HPLC, showing the presence of 3-morpholino-Δ^3-cephem **2a** (54%). After evaporation of the solvents, the residue was poured into water and extracted with ethyl acetate. The extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, benzene/ethyl acetate: 3/2—1/2) to afford **2a** (33 mg, 44%): IR (KBr) 1754, 1673, 1547 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.88 (d, J = 14.0 Hz, 1H, SCH_2), 2.96 (dt, J = 4.7, 14.0 Hz, 2H, NCH_2), 3.03 (d, J = 14.0 Hz, 1H, SCH_2), 3.26 (dt, J = 4.7, 14.0 Hz, 2H, NCH_2), 3.40—3.72 (m, 4H, CH_2OCH_2), 3.65 (s, 2H, $PhCH_2$), 3.78 (s, 3H, OCH_3), 5.00 (ABq, J = 12.0 Hz, 2H, CO_2CH_2), 4.99 (d, J = 3.7 Hz, 1H, SCH), 5.33 (dd, J = 3.7, 8.3 Hz, 1H, NCH), 6.78—7.44 (m, 9H, Ar), 7.72 (d, J = 8.3 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 27.9, 43.7, 52.1, 55.3, 60.3, 64.4, 65.5, 66.8, 113.5, 127.2, 128.9, 129.4, 130.5, 134.5, 159.3, 159.4, 161.2, 168.1, 171.4. Found: C, 61.71; H, 5.39; N, 7.85%. Calcd for $C_{27}H_{29}N_3O_6S$: C, 61.93; H, 5.58; N, 8.03%.

In a similar manner, the following 3-substituted Δ^3-cephems **2b—e** were obtained. The reaction conditions and results are complied in Table 2.

***p*-Methoxybenzyl 7-(Phenylacetamido)-3-(1-pyrrolidinyl)-Δ^3-cephem-4-carboxylate (2b).** IR (KBr) 3316, 1748, 1667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.60—1.78 (m, 4H, CH_2CH_2), 2.56 (d, J = 14.0 Hz, 1H, SCH_2), 3.20 (d, J = 14.0 Hz, 1H, SCH_2), 3.22—3.56 (m, 4H, CH_2NCH_2), 3.64 (s, 2H, $PhCH_2$), 3.76 (s, 3H, OCH_3), 5.04 (ABq, J = 12.0 Hz, 2H, CO_2CH_2), 5.00 (d, J = 3.7 Hz, 1H, SCH), 5.34 (dd, J = 3.7, 8.3 Hz, 1H, NCH), 6.80—7.37 (m, 9H, Ar), 7.83 (d, J = 8.3 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 25.6, 27.9, 43.4, 52.4, 55.1, 60.2, 64.1, 65.2, 95.6, 113.5, 113.9, 126.9, 128.5, 129.0, 129.2, 129.7, 134.7, 155.9, 159.0, 161.5, 168.3, 171.4. Found: C, 64.00; H, 5.65; N 8.29%. Calcd for $C_{27}H_{29}N_3O_5S$: C, 63.89; H, 5.76; N, 8.28%.

***p*-Methoxybenzyl 3-Azido-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (2c).** IR (KBr) 2112, 1771, 1676, 1613 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 3.40 (d, J = 17.0 Hz, 1H, SCH_2), 3.54 (d, J = 17.0 Hz, 1H, SCH_2), 3.61 (s, 2H, $PhCH_2$), 3.78 (s, 3H, OCH_3), 4.92 (d, J = 4.7 Hz, 1H, SCH), 5.18 (ABq, J = 12.0 Hz, 2H, CO_2CH_2), 5.74 (dd, J = 4.7, 9.0 Hz, 1H, NCH), 6.63 (d, J = 9.0 Hz, 1H, NH), 6.82—7.40 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 25.5, 43.3, 55.3, 57.9, 58.8, 67.7, 113.9, 126.9, 127.6, 129.0, 129.3, 130.6, 132.4, 133.9, 159.9, 160.2, 165.0, 171.3. Found: C, 57.43; H, 4.62; N, 14.41%. Calcd for $C_{23}H_{21}N_5O_5S$: C, 57.61; H, 4.41; H, 14.61%.

***p*-Methoxybenzyl 3-[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (2d).** IR (KBr) 3258, 1787, 1707, 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.75 (s, 3H, CH_3), 3.43 (d, J = 18.5 Hz, 1H, CH_2S), 3.73 (d, J = 18.5 Hz, 1H, CH_2S), 3.63 (s, 2H, $PhCH_2$), 3.80 (s, 3H, OCH_3), 4.98 (d, J = 5.0 Hz, 1H, SCH), 5.30 (s, 2H, CO_2CH_2), 5.85 (dd, J = 5.0, 9.3 Hz, 1H, NCH), 6.27 (d, J = 9.3 Hz, 1H, NH), 6.86—7.37 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 15.8, 29.6, 43.2, 55.3, 57.9, 59.5, 68.5, 113.9, 120.3, 126.4, 127.7, 129.2, 129.4, 130.8, 133.6, 160.0, 161.0, 164.1, 168.5, 171.1. Found: C, 55.09; H, 4.30; N, 9.62%. Calcd for $C_{26}H_{24}N_4O_5S_3$: C, 54.91; H, 4.25; N, 9.85%.

***p*-Methoxybenzyl 7-(Phenylacetamido)-3-(phenylsulfonyl)-Δ^3-cephem-4-carboxylate (2e).** IR (KBr) 3310, 1800, 1740, 1682, 1661, 1325, 1151 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 3.32 (d, J = 18.0 Hz, 1H, SCH_2), 3.51 (d, J = 18.0 Hz, 1H, SCH_2), 3.61 (ABq, J=15.0 Hz, 2H, $PhCH_2$), 3.82 (s, 3H, OCH_3), 4.92 (d, J = 5.2 Hz, 1H, SCH), 5.35 (s, 2H, CO_2CH_2), 5.86 (dd, J = 5.2, 9.1 Hz, 1H, NCH), 6.01 (d, J = 9.1 Hz, 1H, NH), 6.80—8.00 (m, 14H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 24.2, 43.2, 55.3, 59.1, 60.2, 69.4, 113.9, 114.0, 118.7, 126.1, 127.8, 128.2, 129.2, 129.2, 129.3, 129.4, 130.6, 131.1, 133.3, 133.9, 134.0, 138.6, 160.1, 161.0, 163.9, 171.0. Found: C, 59.94; H, 4.65; N, 4.72%. Calcd for $C_{29}H_{26}N_2O_7S_2$: C, 60.19; H, 4.53; N, 4.84%.

Synthesis of 3-Chloro-Δ^3-cephem by Addition/Cyclization of Allenecarboxylate with Lithium Chloride in the Presence of Aluminum Chloride. Into a mixture of $AlCl_3$ (30.7 mg, 0.23 mmol) and LiCl (51.5 mg, 1.2 mmol) in NMP (1.0 ml) was added a solution of the allenecarboxylate **4** (66.7 mg, 0.12 mmol) in NMP (1.0 ml) at room temperature. After being stirred for 2.5 h, the mixture was poured into water and extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, benzene/ethyl acetate: 8/1), affording **2f** (38.7 mg, 71%) and azetidinone **9** (4.2 mg, 6%).

***p*-Methoxybenzyl 3-Chloro-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (2f).** IR (KBr) 3348, 1789, 1732, 1689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 3.43 (d, J = 18.4 Hz, 1H, SCH_2), 3.61 (s, 2H, $PhCH_2$), 3.72 (d, J = 18.4 Hz, 1H, SCH_2), 3.79 (s, 3H, OCH_3), 4.95 (d, J = 4.8 Hz, 1H, SCH), 5.21 (s, 2H, CO_2CH_2), 5.81 (dd, J = 4.8, 9.0 Hz, 1H, NCH), 6.16 (d, J = 9.0 Hz, 1H, NH), 6.85—7.40 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 31.5, 43.6, 55.8, 57.8, 59.4, 68.7, 114.5, 124.7, 125.7, 127.1, 128.0, 129.5, 129.8, 131.2, 134.5, 160.4, 160.6, 165.3, 172.0. Found: C, 58.25; H, 4.50; N, 5.84%. Calcd for $C_{23}H_{21}ClN_2O_5S$: C, 58.41; H, 4.48; N, 5.92%.

1-[2-Chloro-1-(*p*-methoxybenzyloxycarbonyl)-1-propenyl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (9). IR (KBr) 3300, 1786, 1724, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.50 (s, 3H, CH_3), 3.55 (s, 2H, $PhCH_2$), 3.80 (s, 3H, OCH_3), 5.13 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.19 (dd, J = 5.1, 7.9 Hz, 1H, NCH), 5.53 (d, J = 5.1 Hz, 1H, SCH), 6.15 (d, J = 7.9 Hz, 1H, NH), 6.85—7.40 (m, 14H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 25.2, 43.4, 55.8, 61.5, 68.3, 71.3, 114.7, 121.3, 127.2, 127.3, 128.2, 129.6, 129.8, 130.0, 131.1, 134.1, 134.6, 145.4, 154.1, 160.5, 161.8, 164.0, 172.2. Found: C, 56.42; H, 4.41; N, 4.42%. Calcd for $C_{29}H_{27}ClN_2O_7S_2$: C, 56.63; H, 4.42; N, 4.55%.

4-[(Benzothiazol-2-yl)dithio]-1-[2-hydroxy-1-(*p*-methoxybenzyloxycarbonyl)-1-propenyl]-3-(phenylacetamido)-2-azetidinone (14a). Into a solution of **13a** (0.66 g, 1.07 mmol) in acetone (50 ml) was bubbled ozone at −78 °C. After **13a** was almost consumed (1 h), argon gas was bubbled for a few minutes and, then, dimethyl sulfide (0.39 ml, 5.33 mmol) was added. The cooling bath was removed and the mixture was stirred at room temperature for an additional 3 h. After evaporation of the solvent in vacuo, the residue was extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 3/1—1/1), affording enol **14a** (0.56 g, 84%): IR (KBr) 3294, 1775, 1663 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.31 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.71 (s, 2H, $PhCH_2$), 4.80 (dd, J = 5.1, 7.4 Hz, 1H, NCH), 4.97 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.28 (d, J = 5.1 Hz, 1H, SCH), 6.09 (d, J = 7.4 Hz, 1H, NH), 6.66—7.92 (m, 13H, Ar), 12.31 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 18.7, 43.1, 55.1, 61.5, 67.0, 79.6, 98.8, 113.9, 121.1, 122.3, 125.0, 126.5, 126.6, 127.8, 129.1, 129.7, 130.0, 133.7, 133.8, 154.5, 159.7, 164.8, 168.8, 172.5, 178.3. Found: C, 57.86; H, 4.49; N, 6.65%. Calcd for $C_{30}H_{27}N_3O_6S_3$: C, 57.95; H, 4.38; N, 6.76%.

1-[2-Hydroxy-1-(*p*-methoxybenzyloxycarbonyl)-1-propenyl]-4-[(5-methyl-1,3,4-thiadiazol-2-yl)dithio]-3-(phenylacetamido)-2-azetidinone (14b). **14b** was obtained in 84% yield from **13b**

(0.50 g, 5.74 mmol): IR (KBr) 3282, 1775, 1661 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.45 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.64 (s, 2H, $PhCH_2$), 3.78 (s, 3H, OCH_3), 4.75 (dd, J = 4.9, 7.3 Hz, 1H, NCH), 5.05 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.35 (d, J = 4.9 Hz, 1H, SCH), 6.41 (d, J = 7.3 Hz, 1H, NH), 6.83—7.36 (m, 9H, Ar), 12.33 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 15.8, 18.6, 43.0, 55.2, 61.6, 67.2, 80.0, 98.8, 114.0, 126.7, 127.6, 129.1, 129.5, 130.4, 133.7, 159.8, 164.6, 167.9, 168.8, 172.6, 178.2. Found: C, 53.45; H, 4.77; N, 9.36%. Calcd for $C_{26}H_{26}N_4O_6S_3$: C, 53.23; H, 4.47; N, 9.55%.

4-[(Benzothiazol-2-yl)dithio]-1-[1-(*p*-methoxybenzyloxycarbonyl)-2-(trifluoromethylsulfonyloxy)-1-propenyl]-3-(phenylacetamido)-2-azetidinone (15a). Into a solution of **14a** (174 mg, 0.28 mmol) in dichloromethane (1.8 ml) were successively added triethylamine (0.13 ml, 0.95 mmol) and trifluoromethanesulfonic anhydride (84 ml, 0.48 mmol) at −78 °C. After being stirred for 1 h, the mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 4/1), affording **15a** (158 mg, 75%): IR (KBr) 3300, 1789, 1717, 1669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.48 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.78 (s, 2H, $PhCH_2$), 4.80 (dd, J = 5.2, 7.1 Hz, 1H, NCH), 4.87 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.57 (d, J = 5.2 Hz, 1H, SCH), 6.19 (d, J = 7.1 Hz, 1H, NH), 6.69—7.83 (m, 13H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 20.0, 44.2, 56.1, 63.7, 68.9, 80.2, 114.9, 114.9, 119.8, 122.5, 123.3, 126.1, 127.4, 127.6, 130.3, 130.7, 131.8, 131.8, 134.6, 136.8, 155.8, 157.0, 160.9, 161.0, 164.1, 171.2, 174.3. Found: C, 49.20; H, 3.69; N, 5.38%. Calcd for $C_{31}H_{26}F_3N_3O_8S_4$: C, 49.39; H, 3.48; N, 5.57%.

1-[1-(*p*-Methoxybenzyloxycarbonyl)-2-(trifluoromethylsulfonyloxy)-1-propenyl]-4-[(5-methyl-1,3,4-thiadiazol-2-yl)dithio]-3-(phenylacetamido)-2-azetidinone (15b). **15b** was obtained in 62% yield from **14b** (221 mg, 0.38 mmol). IR (KBr) 3224, 1789, 1723, 1667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.43 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.78 (s, 2H, $PhCH_2$), 4.81 (dd, J = 5.2, 7.0 Hz, 1H, NCH), 5.10 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.60 (d, J = 5.2 Hz, 1H, SCH), 6.54 (d, J = 7.0 Hz, 1H, NH), 6.83—7.35 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 15.8, 18.9, 43.0, 55.2, 62.6, 68.1, 78.7, 114.0, 118.5, 126.4, 127.7, 129.2, 129.5, 131.0, 133.5, 155.8, 159.7, 160.0, 162.8, 167.8, 173.1. Found: C, 45.06; H, 3.57; N, 7.67%. Calcd for $C_{27}H_{25}F_3N_4O_8S_4$: C, 45.12; H, 3.51; N, 7.79%.

1-[1-(*p*-Methoxybenzyloxycarbonyl)-2-(trifluoromethylsulfonyloxy)-1-propenyl]-4-[(1-methyl-1,2,3,4-tetrazol-5-yl)dithio]-3-(phenylacetamido)-2-azetidinone (15c). Into a solution of **13c** (0.66 g, 1.07 mmol) in acetone (50 ml) was bubbled ozone at −78 °C. After **13c** was almost consumed (45 min), argon gas was bubbled for a few minutes and, then, dimethyl sulfide (0.39 ml, 5.33 mmol) was added. The mixture was stirred at room temperature for an additional 1 h. After evaporation of the solvent, the residue was extracted with ethyl acetate. The extracts were washed twice with brine, dried over Na_2SO_4, and concentrated in vacuo. Into a solution of the residue (457 mg) in dichloromethane (4.5 ml) were successively added triethylamine (0.21 ml, 1.50 mmol) and trifluoromethanesulfonic anhydride (0.13 ml, 0.74 mmol) at −78 °C. After being stirred for 1 h, the mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 10/1—4/1), affording **15c** (439 mg, 55%): IR (KBr) 3284, 1789, 1725, 1667 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.43 (s, 3H, CH_3), 3.60 (s, 2H, $PhCH_2$), 3.75 (s, 3H, OCH_3), 3.95 (s, 3H, CH_3), 4.85 (dd, J = 5.3, 7.1 Hz, 1H, NCH), 5.23 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.78 (d, J = 5.3 Hz, 1H, SCH), 6.62 (d, J = 7.1 Hz, 1H, NH), 6.80—7.40 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 18.9, 34.2, 42.9, 55.2, 62.7, 68.0, 77.9, 113.8, 118.5, 126.7, 127.6, 129.1, 129.4, 131.1, 133.5, 153.4, 155.4, 159.8, 156.6, 162.6, 173.2. Found: C, 44.29; H, 3.70; N, 12.03%. Calcd for $C_{26}H_{25}F_3N_6O_8S_3$: C, 44.44; H, 3.59; N, 11.96%.

***p*-Methoxybenzyl 3-[(Benzothiazol-2-yl)thio]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (12a). A Step by Step Method:** Into a solution of **15a** (92 mg, 0.12 mmol) in THF (2 ml) was added triethylamine (25 ml, 0.18 mmol) at 0 °C. The mixture was stirred at this temperature for 30 min and then at room temperature for additional 1.5 h. The mixture was poured into ice-cold 5% HCl and extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford **10a** (83 mg) as pale brown solids: ^1H NMR (200 MHz, $CDCl_3$) δ = 3.68 (ABq, J = 16.0 Hz, 2H, $PhCH_2$), 3.79 (s, 3H, OCH_3), 5.02 (s, 2H, CO_2CH_2), 5.31 (ABq, J = 15.6 Hz, 2H, C=C=CH_2), 5.49 (dd, J = 4.8, 8.1 Hz, 1H, NCH), 5.76 (d, J = 4.8 Hz, 1H, SCH), 6.37 (d, J = 8.1 Hz, 1H, NH), 6.83—7.82 (m, 13H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 44.1, 56.3, 56.4, 68.4, 100.4, 114.9, 115.0, 122.3, 123.3, 126.0, 127.5, 128.2, 128.5, 130.0, 130.4, 131.2, 135.2, 136.9, 154.4, 155.4, 160.8, 163.5, 164.8, 172.1, 173.2, 211.6. Into a solution of crude product **10a** in DMF (1.8 ml) were successively added calcium chloride (15 mg, 0.135 mmol) and 2-benzothiazolethiol (3 mg, 0.019 mmol) at room temperature. After being stirred for 2 h, the mixture was poured into water and extracted with ethyl acetate. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, hexane/ethyl acetate: 10/1—4/1), affording **12a** (61 mg, 83%): IR (KBr) 3258, 1787, 1707, 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 3.48 (d, J = 16.2 Hz, 1H, CH_2S), 3.65 (ABq, J = 15.4 Hz, 2H, $PhCH_2$), 3.75 (s, 3H, OCH_3), 3.88 (d, J = 16.2 Hz, 1H, CH_2S), 5.04 (d, J = 5.0 Hz, 1H, SCH), 5.22 (s, 2H, CH_2CO_2), 5.88 (dd, J = 5.0, 9.0 Hz, 1H, NCH), 6.13 (d, J = 9.0 Hz, 1H, NH), 6.78 (m, 13H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 30.0, 43.3, 55.2, 58.0, 59.5, 68.4, 113.8, 119.5, 121.2, 122.7, 123.4, 126.4, 126.5, 127.7, 129.2, 129.4, 130.7, 133.5, 136.5, 153.4, 159.8, 161.0, 164.0, 171.1. Found: C, 59.39; H, 4.15; N, 6.87%. Calcd for $C_{30}H_{25}N_3O_5S_3$: C, 59.68; H, 4.17; N, 6.96%.

A One-Pot Method: Into a solution of **15a** (60 mg, 0.08 mmol) in THF (1.2 ml) was added triethylamine (16 ml, 0.115 mmol) at −40 °C. The mixture was stirred at this temperature for 30 min and, then, at room temperature for an additional 2 h. After the reaction mixture was cooled again at −40 °C, a mixture of 2-benzothiazolethiol (2 mg, 0.013 mmol) and calcium chloride (33 mg, 0.3 mmol) in DMF (1.5 ml) was added. After being stirred at −40 °C for 30 min, the mixture was extracted with ethyl acetate. The extracts were washed three times with water and once with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/ethyl acetate: 50/1), affording **12a** (40 mg, 84%) whose IR, ^1H NMR, and ^{13}C NMR spectra are identical with those described above.

In a similar manner (one-pot method), the following compounds **12b** and **12c** were obtained in 76 and 40% yields, respectively (Table 5).

***p*-Methoxybenzyl 3-[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (12b).** IR (KBr) 3258, 1787, 1707, 1659 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.75 (s, 3H, CH_3), 3.43 (d, J = 18.5 Hz, 1H, CH_2S), 3.73 (d, J = 18.5

Hz, 1H, CH_2S), 3.63 (s, 2H, $PhCH_2$), 3.80 (s, 3H, OCH_3), 4.98 (d, J = 5.0 Hz, 1H, SCH), 5.30 (s, 2H, CO_2CH_2), 5.85 (dd, J = 5.0, 9.3 Hz, 1H, NCH), 6.27 (d, J = 9.3 Hz, 1H, NH), 6.86—7.37 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 15.8, 29.6, 43.2, 55.3, 57.9, 59.5, 68.5, 113.9, 120.3, 126.4, 127.7, 129.2, 129.4, 130.8, 133.6, 156.0, 161.0, 164.1, 168.5, 171.1. Found: C, 55.09; H, 4.30; N, 9.62%. Calcd for $C_{26}H_{24}N_4O_5S_3$: C, 54.91; H, 4.25; N, 9.85%.

***p*-Methoxybenzyl 3-[(1-Methyl-1,2,3,4-tetrazol-5-yl)thio]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (12c).** IR (KBr) 3284, 1789, 1729, 1657 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 3.38 (d, J = 18.0 Hz, 1H, CH_2S), 3.83 (d, J = 18.0 Hz, 1H, CH_2S), 3.65 (ABq, J = 15.2 Hz, 2H, $PhCH_2$), 3.81 (s, 3H, OCH_3), 3.96 (s, 3H, CH_3), 5.00 (d, J = 4.9 Hz, 1H, SCH), 5.23 (ABq, J = 11.7 Hz, 2H, CO_2CH_2), 5.89 (dd, J = 4.9, 9.3 Hz, 1H, NCH), 6.06 (d, J = 9.3 Hz, 1H, NH), 6.87—7.40 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 29.7, 34.2, 43.3, 55.3, 57.9, 59.5, 68.6, 114.0, 117.3, 126.2, 127.8, 129.2, 129.4, 130.8, 133.8, 150.0, 155.5, 160.9, 164.1, 171.0. Found: C, 54.68; H, 4.36; N, 15.14%. Calcd for $C_{25}H_{24}N_6O_5S_2$: C, 54.34; H, 4.38; N, 15.21%.

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15) Farina's group used LiCl as alternative salt for transformation of allenecarboxylates **10** (R^1 = $PhOCH_2CONH$, R^2 = *p*-nitrobenzyl, Ar = benzothiazolyl etc.) into 3-sulfenyl-Δ^3-cephems **12**; see Refs. 9 and 11.

16) The 3-phenylsulfonyl-Δ^3-cephem **2e** was produced more efficiently when the same reaction was carried out in NMP; see Entry 1 in Table 3.

17) The formation of a small amount of monochloro azetidinone **9** can be ascribed to protonation of the intermediate **5f**, presumably with a trace amount of water contaminated in the solution. When the reaction was carried out in the presence of *N,O*-bis(trimethylsilyl)-acetamide for removing the trace amount of water, the side product **9** was not detected. However, the yield of **2f** did not significantly change.

18) Synthesis of 3-chloro-, 3-bromo-, and 3-iodo-Δ^3-cephems has been performed by an addition/elimination reaction of 3-trifluoromethylsulfonyloxy-Δ^3-cephem with the corresponding lithium halides; see Ref. 6b.