Synthesis of 2-*exo*-Methylenepenam and 3-Chloro-Δ^3-cephem through a Sequential Reductive 1,2-Elimination/S−S Bond Fission or Chloride Ion-Addition/Cyclization of 3,4-Disubstituted 2-Butenoates in Metal Salt/Metal Combinations

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Synthesis of 2-*exo*-methylenepenam **1** through a sequential reductive 1,2-elimination/S−S bond fission/cyclization of **6** was performed by treatment with a $PbBr_2$/Al (or a $BiCl_3$/Al) combination in DMF, while that of 3-chloro-Δ^3-cephem **2** through reductive 1,2-elimination/chloride ion-addition/cyclization was attained by use of an $AlCl_3$/Al combination in *N*-methylpyrrolidone (NMP). The selective transformation of **6** to the allenecarboxylate **3** was also achieved by treatment with an $AlBr_3$/Al combination in NMP. Cyclic voltammograms of 3,4-disubstituted 2-[2-oxo-3-(phenylacetamido)-4-[(phenylsulfonyl)thio]azetidin-1-yl]-2-butenoates (**6**) exhibit two irreversible reduction peaks responsible for reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate moiety (at less negative potential) and for reductive S−S bond fission of the (phenylsulfonyl)thio moiety, suggesting that the reductive 1,2-elimination of **6** leading to allenecarboxylate **3** would occur prior to the reductive S−S bond cleavage.

Introduction

2-*exo*-Methylenepenam **1** may be regarded as a new candidate for potent broad spectrum antibiotics in its own right[1] and as a strategic intermediate for the synthesis of penam and penem families of β-lactam antibiotics through manipulation of the *exo*-methylene moiety.[2] The first synthesis of the 2-*exo*-methylenepenam **1** (R^1 = $PhOCH_2CONH$, R^2 = *p*-$NO_2C_6H_4CH_2$) was performed by Baldwin through decarboxylative Pummerer-type reaction of penicillin-2-carboxylic acid elaborated from penicillin V.[3] Recently, we developed an alternative access to **1** through reductive S−S bond fission of the (phenylsulfonyl)thio moiety of allenecarboxylate **3**, derived from penicillin, with a $BiCl_3$/Zn combination, producing a thiol (**4**) which underwent intramolecular Michael addition of the thiol moiety to the center carbon of the allene moiety (Scheme 1, path a).[2b,4]

On the other hand, 3-chloro-Δ^3-cephem **2** is currently used as an orally active drug in antibacterial chemotherapy.[5] Syntheses of the 3-chloro-Δ^3-cephem **2** explored so far mainly relied on the displacement of the C(3)-hydroxy group of 3-hydroxy-Δ^3-cephem.[6] Lately, we disclosed a conceptually new synthetic route to **2** through a sequential chloride ion-addition/cyclization of the allenecarboxylate **3** (Scheme 1, path b).[7]

Our methodologies for the synthesis of the 2-*exo*-methylenepenam **1** and the 3-chloro-Δ^3-cephem **2** (*vide supra)* are, however, not necessarily satisfactory for practical use because the key intermediate **3** is not always easy to handle owing to its lability.[8] We, therefore, sought a synthetic equivalent to the allenecarboxylate **3** that was readily available and stable under ambient conditions. As a result, we found that 3,4-disubstituted 2-[2-oxo-3-(phenylacetamido)-4-[(phenylsulfonyl)thio]azetidin-1-yl]-2-butenoates **6** (Y = Cl, OTf, and OTs) may behave as an alternative precursor of both the 2-*exo*-methylenepenam **1**[9] and the 3-chloro-Δ^3-cephem **2**. Herein, we describe the synthesis of the 2-*exo*-methylenepenam **1** through a sequential reductive 1,2-elimination/S−S bond fission/cyclization of the 3,4-disubstituted 2-butenoates **6** and the 3-chloro-Δ^3-cephem **2** through reductive 1,2-elimination/chloride ion-addition/cyclization of **6** (Scheme 2), both of which were performed by use of metal salt/aluminum redox systems.

Results and Discussion

Preparation of 3,4-Disubstituted 2-Butenoates. The 3,4-disubstituted 2-butenoates **6** were easily prepared starting from penicillin (Scheme 3). The transformation of the penicillin to enol **9** was performed by the reported procedures involving ene-type chlorination of azetidinone **7**,[10] derived from penicillin,[11] and subsequent oxidative cleavage of the terminal double bond of **8**.[12] The

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(1) The 2-*exo*-methylenepenam's framework represents a structural hybrid of those of penicillin and clavulanic acid, which displays a potent β-lactamase-inhibiting property.

(2) (a) Tanaka, H.; Kameyama, Y.; Sumida, S.; Torii, S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2253. (b) Tanaka, H.; Kameyama, Y.; Yamauchi, T.; Torii, S. *J. Chem. Soc., Chem. Commun*. **1992**, 1793.

(3) Baldwin, J. E.; Forrest, A. K.; Ko, S.; Sheppard, L. N. *J. Chem. Soc., Chem. Commun*. **1987**, 81.

(4) Tanaka, H.; Kameyama, Y.; Torii, S. *Synlett* **1992**, 878.

(5) Druckhemier, W.; Adam, F.; Fischer, G.; Kirrstetter, R. *Advances in Drug Research*; Druckhemier, W. Ed.; Academic Press: New York, 1988; Vol. 17, p 190.

(6) (a) Chauvette, R. R.; Pennington, P. A. *J. Am. Chem. Soc.* **1974**, *96*, 4986. (b) Scartazzini, R.; Bickel, H. *Helv. Chim. Acta* **1974**, *57*, 1919. (c) Chauvette, R. R.; Pennington, P. A. *J. Med. Chem*. **1975**, *18*, 403. (d) Kukolja, S.; Gleissner, M. R.; Ellis, A. I.; Dorman, D. E.; Paschal, J. W. *J. Org. Chem*. **1976**, *41*, 2276. (d) Scartazzini, R.; Bickel, H. *Heterocycles* **1977**, *7*, 1165. (e) Spry, D. O.; Bhala, A. R. *Heterocycles* **1986**, *24*, 1653. (f) Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem*. **1989**, *54*, 4962.

(7) (a) Tanaka, H.; Kikuchi, R.; Torii, S. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 1391. (b) Tanaka, H.; Sumida, S.; Kameyama, Y.; Sorajo, K.; Wada, I.; Torii, S. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 3651.

(8) The allenecarboxylates **3** can be stored in a refrigerator for several days without appreciable change but are gradually decomposed under ambient conditions, particularly in the presence of a trace amount of acid or base.

(9) Tanaka, H.; Nishioka, Y.; Kameyama, Y.; Sumida, S.; Matsuura, H.; Torii, S. *Chem. Lett.* **1995**, 709.

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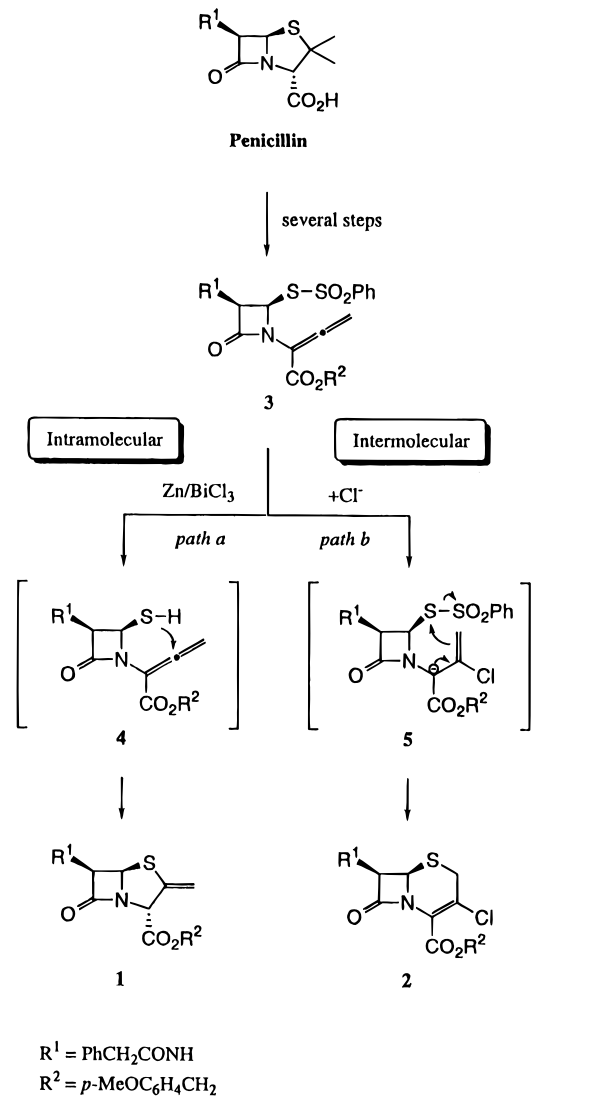
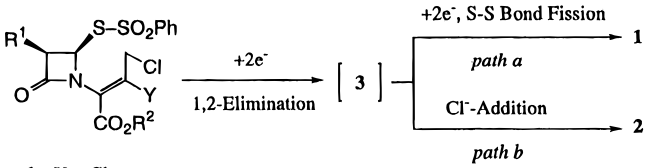
Scheme 1

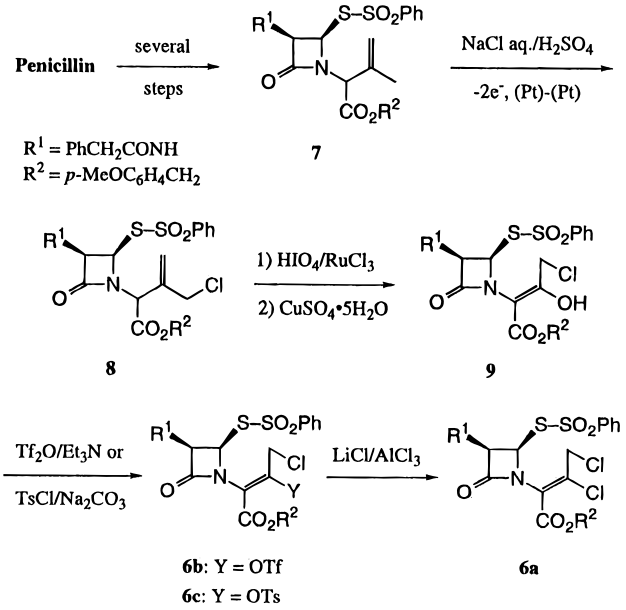


Scheme 2



enol **9** was then allowed to react with trifluoromethanesulfonic anhydride and triethylamine (1.5 molar equiv each) in dichloromethane at −78 °C for 1 h to afford 4-chloro-3-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate **6b** (Y = OTf) (95%). 4-Chloro-3-[[(*p*-methylphenyl)sulfonyl]-oxy]-2-butenoate **6c** (Y = OTs) (98%, *E*/*Z* = 9/1) was similarly prepared by treatment of the enol **9** with tosyl

Scheme 3



chloride (1.5 molar equiv) and sodium carbonate (3 molar equiv) in DMF at 0 °C for 2 h. Treatment of **6b** with lithium chloride (10 molar equiv) and aluminum(III) chloride (3 molar equiv) in *N*-methylpyrrolidone (NMP) at room temperature for 4 h gave 3,4-dichloro-2-butenoate (**6a**) (83%). All of the 3,4-disubstituted 2-butenoates **6** (Y = Cl, OTf, and OTs) obtained thus far are stable enough to survive under ambient conditions for several weeks without appreciable change.

Cyclic Voltammetry of 3,4-Disubstituted 2-Butenoates. The transformation of the 3,4-disubstituted 2-butenoates **6** to the 2-*exo*-methylenepenam **1** involves two two-electron reduction stages *via* the allene intermediate **3** (Scheme 2, path a). One is reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate moiety of **6**, affording the allenecarboxylate **3**, and the other is reductive S−S bond fission of (phenylsulfonyl)thio moiety of **3**, leading to the thiol **4**, which subsequently undergoes ring closure to give the final product **1**. On the other hand, the transformation of **6** to the 3-chloro-Δ^3-cephem **2** consists of the former two-electron reduction leading to **3**, followed by sequential chloride ion-addition and cyclization (Scheme 2, path b). In order to achieve both the conversions, the reductive 1,2-elimination of **6** must occur selectively or prior to the reductive S−S bond fission. As a preliminary experiment, we investigated cyclic voltammetry of the 3,4-disubstituted 2-butenoates **6** and the related compound **7** to know the reduction potentials of the 1,2-elimination and the S−S bond fission.

The cyclic voltammetry was performed in DMF containing Et_4NOTs with a platinum disk as a working electrode, a platinum wire as an auxiliary electrode, and an Ag/Ag^+ as a reference electrode at the potential sweep of 100 mV/s. Cyclic voltammograms of the 3,4-dichloro-2-butenoate **6a**, the triflate **6b**, and the tosylate **6c** exhibit two irreversible reduction peaks (E_{R1}, E_{R2}), respectively. E_{R1} values of the 3,4-disubstituted 2-butenoates **6** vary between −1.8 and −2.0 V, depending on the leaving group (Cl, OTf, or OTs), while all E_{R2} values are nearly constant at −2.2 V (Table 1, entries 1−3). On the other hand, a single reduction peak (E_{R2}) is observed in the cyclic voltammogram of the azetidinone **7** at −2.2 V (entry 4), which is identical to those of the second peaks

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Table 1. Reduction Potential[a]

entry	sub.	E_{R1} *vs* Ag/Ag^+, V	E_{R2} *vs* Ag/Ag^+, V
1	**6a**	−2.0	−2.1
2	**6b**	−1.8	−2.1
3	**6c**	−1.9	−2.2
4	**7**		−2.2

[a] All reactions were carried out in DMF containing Et_4NOTs with a platinum disk as a working electrode and a platinum wire as an auxilliary electrode at a potential sweep of 100 mV/s.

(E_{R2}) of the 3,4-disubstituted 2-butenoates **6**. The common electroactive functional group of **6** and **7** is the (phenylsulfonyl)thio moiety. It is, therefore, reasonable to assume that the second peak (E_{R2}) is the reduction peak for the S−S bond cleavage of the (phenylsulfonyl)-thio group and, accordingly, that the E_{R1} is ascribable to the reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate moieties.

Above all, the cyclic voltammograms, indicating that the reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate moiety occurs at less negative potential than the reductive S−S bond cleavage of the (phenylsulfonyl)-thio moiety, suggest the reductive 1,2-elimination of **6** leading to **3** takes place prior to the reductive S−S bond fission. It encouraged us to investigate the direct conversion of the 3,4-disubstituted 2-butenoates **6** to either the 2-*exo*-methylenepenam **1** or the 3-chloro-Δ^3-cephem **2**.

Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of 3,4-Disubstituted 2-Butenoates to 2-*exo*-Methylenepenam. The transformation of the 3,4-dichloro-2-butenoate **6a** to the 2-*exo*-methylenepenam **1** has been carried out in various metal salt/metal redox systems, in which the metal salt would work as an electron transfer catalyst and the metal would act as an electron pool (Table 2).[13] The reaction of **6a** with lead(II) bromide (1 molar equiv) and aluminum (5 molar equiv) in DMF at room temperature for 1 h afforded the 2-*exo*-methylenepenam **1** (82%) (entry 1). The presence of both lead(II) bromide and aluminum is indispensable for the formation of **1**, since in the absence of any of the components, no appreciable amount of **1** was obtained (entries 2 and 3). Other metal salt/aluminum combinations were also investigated (entries 4−9). Lead(II) chloride, tin(II) chloride, and bismuth(III) chloride could similarly effect the desired reaction though the yields of **1** were reduced to 40−65% (entries 4−6). Lead(II) acetate and titanium(IV) chloride were less effective (entries 7 and 8), and aluminum(III) chloride did not work at all (entry 9). In entries 10−12, zinc, tin, and magnesium were used in place of aluminum. Only zinc afforded the desired product **1** (59%) (entry 10), while tin and magnesium did not give **1**, resulting in the recovery of **6a** (94%) (entry 11) or the formation of a complex mixture of decomposition products (entry 12). Notably, a $BiCl_3$/Zn combination, which is an effective bimetal redox system for the transformation of the allenecarboxylate **3** to the 2-*exo*-methylenepenam **1**,[2b,4] gives **1** (43%) (entry 13), suggesting that the $BiCl_3$/Zn combination does not efficiently work for the reductive 1,2-elimination of **6a**.

Among the metal salt/metal combinations examined thus far, the $PbBr_2$/Al combination is the best choice for the conversion of **6a** to **1**. The yield of **1** was dependent on the amounts of metal salt and metal (entries 14 and 15). The reaction of **6a** with a catalytic amount of lead(II) bromide (0.1 molar equiv) and 5 molar equiv of aluminum afforded **1** in 76% yield (entry 14), while the increase of amounts of lead(II) bromide and aluminum to 1.8 and 25 molar equiv resulted in almost quantitative conversion of **6a** to **1** (entry 15).

A proper choice of the solvent was also important (Table 3). When NMP was employed instead of DMF, the yield of the desired penam **1** was reduced to 58% and a small amount of the 3-chloro-Δ^3-cephem **2** (1%) was formed (entry 2). In contrast, in methanol, dichloromethane, and THF, the desired reaction did not take place, resulting in the formation of a complex mixture of decomposition products (entry 3) or the recovery of most of the **6a** (entries 4 and 5).

The time course of the transformation of **6a** into **1** in the $PbBr_2$/Al redox system (Table 2, entry 15) was monitored by HPLC, showing that after a short induction period (2−3 min), the reaction proceeded smoothly and most of the **6a** was converted to **1** in 10 min (Figure 1). Notably, during the course of the reaction, the allenecarboxylate **3** was formed and finally disappeared. The result can be reasonably understood by assuming a sequential reaction involving the reductive 1,2-elimination of the vicinal dichloro group of **6a**, leading to **3**; subsequent reductive S−S bond fission of the (phenylsulfonyl)thio moiety of **3**, giving the thiol **4**; and cyclization of **4**, affording the desired product **1** (Scheme 2, path a). Although the role of lead(II) bromide and aluminum is not clear at present, lead(0) species, generated by reduction of lead(II) bromide with aluminum, probably works as a reductant for both the reductive 1,2-elimination and the S−S bond fission. The reaction of **6a** with commercially available lead metal, however, afforded no detectable amount of **1** (Table 2, entry 16). It is, therefore, likely that only freshly generated lead(0) on the aluminum surface could promote the conversion of **6a** to **1**.

In a similar manner, transformation of the triflate **6b** and the tosylate **6c** to the 2-*exo*-methylenepenam **1** has been achieved by use of adequate metal salt/metal combinations (Table 4). The reaction of the triflate **6b** with lead(II) bromide (1 molar equiv) and aluminum (5 molar equiv) in DMF at room temperature for 1 h afforded **1** in 74% yield (entry 1). Use of a catalytic amount of lead(II) bromide (0.1 molar equiv) also afforded **1** (73%) without significant change (entry 2), while excess amounts of lead(II) bromide (2.1 molar equiv) and aluminum (28.5 molar equiv) gave **1** in a quantitative yield (entry 3). Other metal salt/metal combinations, *e.g.*, $BiCl_3$/Al, $SnCl_2$/Al, and $PbBr_2$/Zn, also afforded the desired product **1** in 50−73% yields (entries 4−6).

The reaction of the tosylate **6c** with lead(II) bromide (1 molar equiv) and aluminum (5 molar equiv) proceeded in a similar fashion to afford 56% yield of **1** together with a small amount of 3-[[(*p*-methylphenyl)sulfonyl]oxy]-Δ^3-cephem **10c** (Y = OTs) (1%) and 3-norcephem **11** (2%) (entry 7) (Scheme 4).[14] The conversion of the tosylate

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(14) The formation of **10** can be rationalized by a sequential reaction involving a two-electron reduction of the chlorine atom of **6** leading to the corresponding anion and the nucleophilic attack of the terminal carbanion to the (phenylsulfonyl)thio group. The further reduction of C(3)-substituent (Z = OTs) of the cephem **10c** with the metal/metal salt combination would give the 3-norcephem **11**.

Table 2. Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of 6a to 2-*exo*-Methylenepenam 1[a]

entry	metal salt (molar equiv)	metal (molar equiv)	time, h	yield, %[b] 1	yield, %[b] 6a
1	$PbBr_2$ (1.0)	Al (5.0)	1.0	82	
2		Al (5.0)	4.2		quant
3	$PbBr_2$ (1.0)		4.0		42
4	$PbCl_2$ (1.0)	Al (5.0)	1.3	65	
5	$SnCl_2$ (1.0)	Al (5.0)	3.6	52	1
6	$BiCl_3$ (1.0)	Al (5.0)	2.5	40	5
7	$Pb(OAc)_2 \cdot 3H_2O$ (1.0)	Al (5.0)	8.1	25	
8	$TiCl_4$ (1.0)[c]	Al (5.0)	10	6	94
9	$AlCl_3$ (1.0)	Al (5.0)	3.9		56
10	$PbBr_2$ (1.0)	Zn (5.0)	1.5	59	
11	$PbBr_2$ (1.0)	Sn (5.0)	9.7		94
12[d]	$PbBr_2$ (1.0)	Mg (5.0)	1.0		
13	$BiCl_3$ (1.0)	Zn (5.0)	1.3	43	
14	$PbBr_2$ (0.1)	Al (5.0)	1.3	76	
15	$PbBr_2$ (1.8)	Al (25)	1.0	quant (57)[e]	
16		Pb (5.0)	4.0		43

[a] All reactions were carried out in DMF at room temperature. [b] Determined by HPLC; HPLC conditions: column, YMC-Pack AMC-312 ODS (6.0 $\phi \times$ 150 mm); mobile phase, CH_3CN/H_2O = 65/35; flow rate, 1.0 mL/min, detection UV at 254 nm. [c] 1.54 M solution in CH_2Cl_2 was used. [d] A complex mixture of decomposition products was formed. [e] Isolated yield after column chromatography (SiO_2).

Table 3. Solvent Effect[a]

entry	solvent	time, h	yield %[b] 1	2	6a
1	DMF	1.0	82		
2	NMP	0.5	58	1	
3[c]	MeOH	4.2			2
4	CH_2Cl_2	8			quant
5	THF	7.8			quant

[a] All reactions were carried out with **6a** (0.15 mmol), $PbBr_2$ (1.0 molar equiv), and aluminum (5.0 molar equiv) in solvent (2 mL) at room temperature. [b] Determined by HPLC, see footnote *b* of Table 2. [c] A complex mixture of decomposition products was formed.

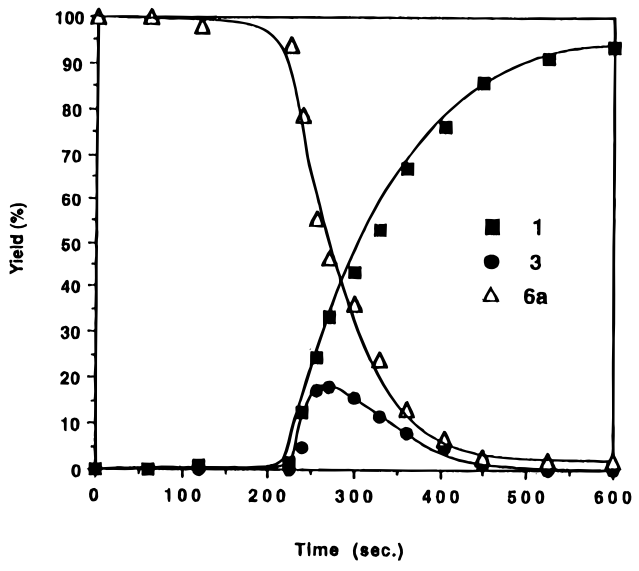


Figure 1. Time course of the transformation of **6a** to **1** in a $PbBr_2$/Al redox system (Table 2, entry 15).

6c into **1** was more efficiently performed by treatment with a $BiCl_3$/Al combination, affording **1** in 77% yield (entry 8). Other metal salt/metal combinations, *e.g.*, $SnCl_2$/Al, $BiCl_3$/Zn, and $BiCl_3$/Sn, were less effective (entries 9−11).

Reductive 1,2-Elimination/Chloride Ion-Addition/Cyclization of 3,4-Disubstituted 2-Butenoates to 3-Chloro-Δ^3-cephem. Next, the direct conversion of the 3,4-dichloro-2-butenoate **6a** to the 3-chloro-Δ^3-cephem **2** was investigated by use of various metal salt/metal redox systems (Table 5). Among the redox systems examined thus far, an $AlCl_3$/Al combination was the best choice for the present purpose; thus, the 3,4-dichloro-2-butenoate **6a** was allowed to react with aluminum(III) chloride (0.5 molar equiv) and aluminum (10 molar equiv) in NMP at room temperature for 8.8 h to afford 72% yield of the 3-chloro-Δ^3-cephem **2** together with a small amount of the 2-*exo*-methylenepenam **1** (1%) and monochloro azetidinone **12** (9%) (entry 1). The formation of the monochloro azetidinone **12** can be reasonably understood by assuming the protonation of an intermediate (**14**) generated from the chloride ion-addition of the allenecarboxylate **3** (Scheme 5). The presence of both aluminum(III) chloride and aluminum is apparently essential for the formation of **2** since most of the **6a** was recovered in the absence of any of the components (entries 2 and 3). In entries 4−8, other metal salts were examined with aluminum. Use of titanium(IV) chloride in combination with aluminum similarly promoted the reaction to afford **2** (41%) (entry 4). It is of interest to note that an $AlBr_3$/Al combination gave the allenecarboxylate **3** (91%) (entry 5). The result might be ascribed to the bulkiness of the bromide ion (or aluminum(III) bromide) which would suppress the nucleophilic attack to the allenecarboxylate **3**. Chromium(III) chloride, iron(III) chloride, and nickel(II) chloride could not effect the desired reaction, resulting in the recovery of most of the **6a** (entries 6−8).

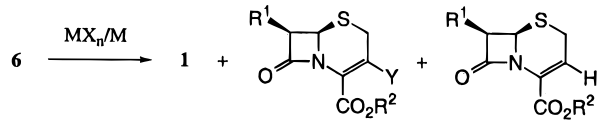
The choice of proper solvent is also important; thus, when DMF was used in place of NMP, the reaction of **6a** with the $AlCl_3$/Al combination did not afford the 3-chloro-Δ^3-cephem **2** at all (entry 9). In the presence of excess lithium chloride (10 molar equiv), the reaction was accelerated to some extent and completed in 4 h, but the yield of **2** slightly decreased (63%) (entry 10, cf. entry 1). Even with an excess amount of lithium chloride, the $PbBr_2$/Al redox system, however, afforded a mixture of **2** (14%) and the 2-*exo*-methylenepenam **1** (23%) (entry 11). The most efficient synthesis of the 3-chloro-Δ^3-cephem **2** has been attained by the reaction of **6a** with the $AlCl_3$/Al combination in NMP in the presence of 4A molecular sieves, affording up to 80% yield of **2** (entry 12). Although the role of the molecular sieves is not clear at present, it is likely that molecular sieves would trap a trace amount of water (or hydrogen chloride) in the reaction media to suppress the formation of **12** (entries 1 and 12).

Table 4. Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of 6b or 6c to 2-*exo*-Methylenepenam 1[a]

entry	sub.	metal salt (molar equiv)	metal (molar equiv)	time, h	yield, %[b] 1	10	11	3	6
1	**6b**	$PbBr_2$ (1.0)	Al (5.0)	1.0	74				
2	**6b**	$PbBr_2$ (0.1)	Al (5.0)	2.0	73				
3	**6b**	$PbBr_2$ (2.1)	Al (28.5)	1.2	quant (65)[c]				
4	**6b**	$BiCl_3$ (1.0)	Al (5.0)	2.3	68			1	
5	**6b**	$SnCl_2$ (1.0)	Al (5.0)	3.0	50				
6	**6b**	$PbBr_2$ (1.0)	Zn (5.0)	2.1	73	7			
7	**6c**	$PbBr_2$ (1.0)	Al (5.0)	0.9	56	1	2		1
8	**6c**	$BiCl_3$ (1.0)	Al (5.0)	1.5	77 (47)[c]		2		1
9	**6c**	$SnCl_2$ (1.0)	Al (5.0)	4.0	30	2		2	5
10	**6c**	$BiCl_3$ (1.0)	Zn (5.0)	2.1	58	3			
11	**6c**	$BiCl_3$ (1.0)	Sn (5.0)	5.8	10			7	25

[a] All reactions were carried out in DMF at room temperature. [b] Determined by HPLC; see footnote b of Table 2. [c] Isolated yield after column chromatography (SiO_2).

Scheme 4



10b: Y = OTf
10c: Y = OTs
11

The best combination, *i.e.*, $AlCl_3$/Al/4A molecular sieves/NMP, was applied successfully to the transformation of the triflate **6b** and the tosylate **6c** to the 3-chloro-Δ^3-cephem **2**. The reaction of either the triflate **6b** or the tosylate **6c** in the $AlCl_3$/Al/4A molecular sieves system proceed smoothly to afford the 3-chloro-Δ^3-cephem **2** in 69 and 76% yields, respectively (entries 13 and 14).

The time course of the transformation of **6a** into **2** in the $AlCl_3$/Al/4A molecular sieves system (Table 5, entry 12) was monitored by HPLC (Figure 2). In the initial stage of the reaction, the reductive 1,2-elimination of the dichloro moiety of **6a** predominantly occurred and most of **6a** was converted to the allenecarboxylate **3** in 1 h. The subsequent addition/cyclization reaction of **3** leading to **2** gradually proceeded and, even after 5 h, ca. 10% of the intermediate **3** still remained.

It is evident that aluminum(III) chloride plays an important role in the reductive 1,2-elimination of the 3,4-disubstituted 2-butenoate moiety of **6**, since in the absence of aluminum(III) chloride, no appreciable reaction occurred (cf. Table 5, entry 3). The fact might be ascribed to the activation of terminal chlorine atom and/or the 3-substituent (X) of **6** by coordination with aluminum(III) chloride so as to realize the reductive 1,2-elimination (step 1 in Scheme 5). In the next stage (step 2), thus formed aluminum complex [$AlCl_3X^-$ (X = Cl, OTf, or OTs)] or NMP complex **16**, generated from aluminum(III) chloride and NMP, would act as a nucleophile (Cl^-) for promoting the subsequent addition reaction. In the final stage (step 3) of the reaction, the 3-chloro-Δ^3-cephem **2** was formed together with benzenesulfinate anion, which would work as a nucleophile (more nucleophilic than chloride ion), resulting in the formation of 3-(phenylsulfonyl)-Δ^3-cephem **13**. Namely, the reaction of the benzenesulfinate ion with **3** would afford **13** with regeneration of the benzenesulfinate ion, which would again react with **3**, leading to **13**.[7] Aluminum(III) chloride also plays an important role in removing the *in situ* generated benzenesulfinate anion to suppress the formation of **13**.

Conclusion

We developed new synthetic schemes of both the 2-*exo*-methylenepenam **1** and the 3-chloro-Δ^3-cephem **2** based on sequential reductive 1,2-elimination/S−S bond fission/cyclization and reductive 1,2-elimination/chloride ion-addition/cyclization of the 3,4-disubstituted 2-butenoates **6**. The direct transformation of **6** to **1** was successfully achieved in the $PbBr_2$/Al/DMF (or the $BiCl_3$/Al/DMF) system, while synthesis of **2** was performed by treatment of **6** with the $AlCl_3$/Al combination in NMP. Stepwise transformations of **6** to **3**, **3** to **1**, and **3** to **2** were also performed by the proper choice of metal salt/metal combination and solvent (Scheme 6).

Experimental Section

IR spectra were obtained on a Japan Spectroscopic Co., Ltd. JASCO FT/IR-5000 spectrometer. ^1H NMR spectra were recorded with a Varian Gemini 200 (200 MHz) and a Varian VXR-500 (500 MHz) spectrometer. ^{13}C NMR spectra were obtained on a Varian Gemini 200 (50 MHz) spectrometer. HPLC was executed with a Waters HPLC instrument equipped with a 600 E system controller, a Waters 486 tunable absorbance detector, and a Hitachi D-2500 chromatointegrator. Elemental analyses were performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer. Cyclic voltammetry was carried out with BAS 100B/W & CV-50W.

DMF and NMP were distilled over calcium hydride under reduced pressure and stored over 4A molecular sieves. Methanol, dichloromethane, and THF were distilled over magnesium, phosphorus pentoxide, and sodium/benzophenone ketyl, respectively. All other reagents were purchased from commercial source and used without further purification.

Cyclic Voltammetry of 3,4-Dichloro-2-butenoate 6a. A typical three-electrode cell fitted with a platinum disk as a working electrode, a platinum wire as an auxiliary electrode, and an Ag/Ag^+ couple as a reference electrode was used. The working electrode was polished with alumina before use. Cyclic voltammetry was carried out in a solution of **6a** (10.0 mg, 0.02 mmol) in DMF (4 mL) containing Et_4NOTs (12.0 mg, 0.04 mmol). The potential was swept at the rate of 100 mV/s until the electrode current was limited (+0.4 to −2.5 V).

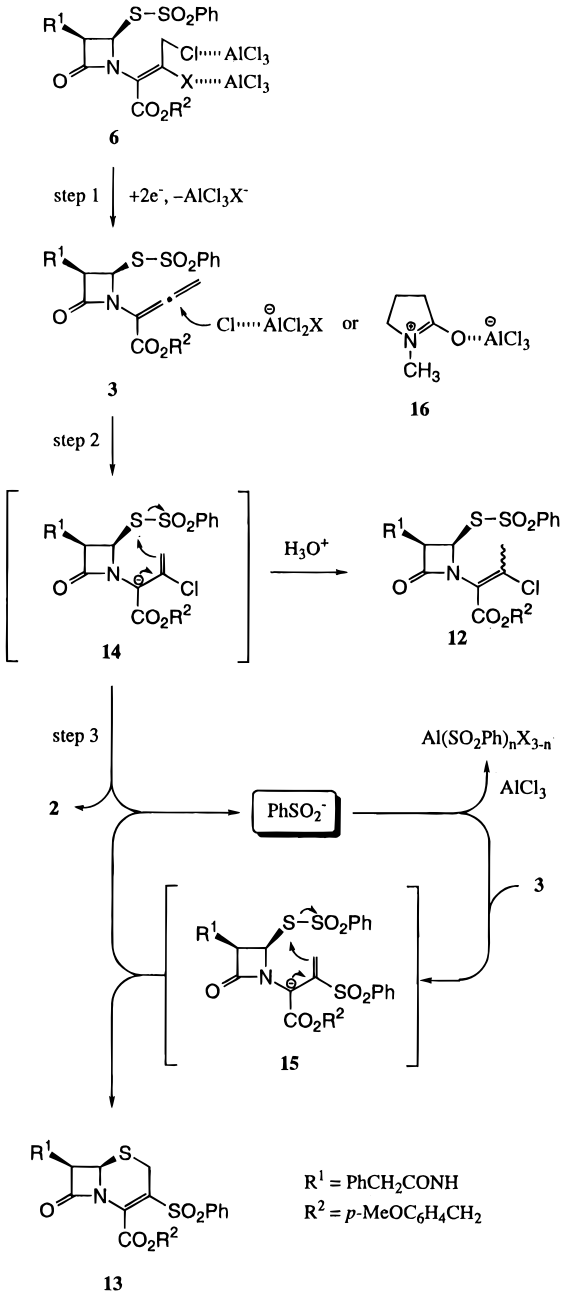
***p*-Methoxybenzyl (*E*)-3,4-Dichloro-2-[2-oxo-3-(phenylacetamido)-4-[(phenylsulfonyl)thio]azetidin-1-yl]-2-butenoate (6a).** A mixture of lithium chloride (2.8 g, 65.52 mmol) and aluminum(III) chloride (2.6 g, 19.66 mmol) in NMP (100 mL) was stirred for 5 min at room temperature. To the mixture was added a solution of triflate **6b** (5.0 g, 6.55 mmol) in NMP (25 mL) over a 1 h period at this temperature under stirring. After being stirred for additional 4 h, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. The combined extracts were washed twice with water and successively with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 5/1) to afford **6a** (3.53 g, 83%) as a white solid: IR (KBr) 3280, 1790, 1680, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.51 (s, 2H), 3.68 (s, 3H), 4.20 (d, J = 12.9 Hz, 1H), 4.59 (d, J = 12.9 Hz, 1H), 4.64 (dd, J = 5.5, 7.0 Hz, 1H), 5.01 (d, J =

Table 5. Reductive 1,2-Elimination/Chloride Ion-Addition/Cyclization of 6 to 3-chloro-Δ^3-cephem 2[a]

entry	sub.	metal salt (molar equiv)	metal (molar equiv)	additive	time, h	yield, %[b] 2	3	1	12	13
1	**6a**	$AlCl_3$ (0.5)	Al (10)		8.8	72	3	1	9	
2[c]	**6a**	$AlCl_3$ (1.0)			2.6					
3[c]	**6a**		Al (10)		6.6					
4	**6a**	$TiCl_4$ (0.5)[d]	Al (10)		6.5	41	2	3	21	1
5	**6a**	$AlBr_3$ (0.5)	Al (10)		2.0	4	91	1	2	1
6[c]	**6a**	$CrCl_3$ (0.5)	Al (10)		4.5					
7[c]	**6a**	$FeCl_3$ (0.5)	Al (10)		4.5					
8[c]	**6a**	$NiCl_3$ (0.5)	Al (10)		6.2					
9[e,f]	**6a**	$AlCl_3$ (1.0)	Al (5.0)		3.9				5	
10	**6a**	$AlCl_3$ (0.5)	Al (10)	LiCl (10 molar equiv)	3.9	63	5		13	2
11	**6a**	$PbBr_2$ (1.0)	Al (0.5)	LiCl (10 molar equiv)	3.0	14		23		
12	**6a**	$AlCl_3$ (0.5)	Al (10)	MS-4A (25 mg)	7.6	80 (77)[g]	4	2	3	1
13	**6b**	$AlCl_3$ (0.5)	Al (10)	MS-4A (25 mg)	10	69	6	1	20	
14	**6c**	$AlCl_3$ (0.5)	Al (10)	MS-4A (25 mg)	7.6	76	3	1	7	

[a] All reactions were carried out with **6** (100 mg) in NMP at room temperature unless otherwise noted. [b] Determined by HPLC; see footnote *b* in Table 2. [c] Most of the **6a** was recovered. [d] 1.54 M solution of CH_2Cl_2 was used. [e] **6a** was recovered in 56% field. [f] The reaction was carried out in DMF. [g] Isolated yield after column chromatography (SiO_2).

Scheme 5



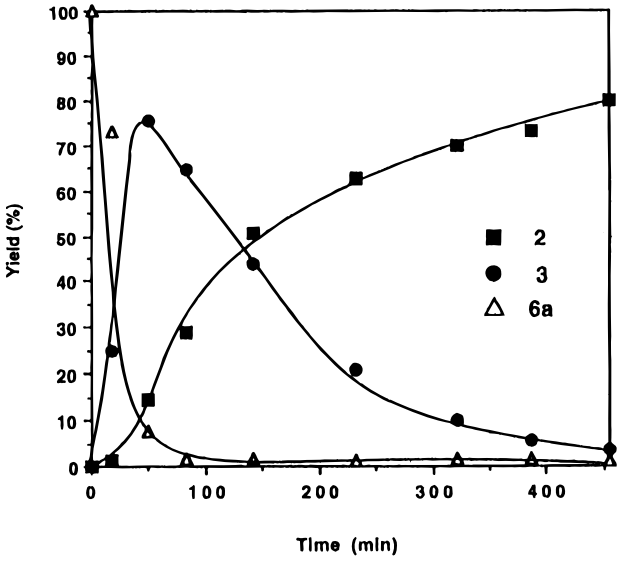
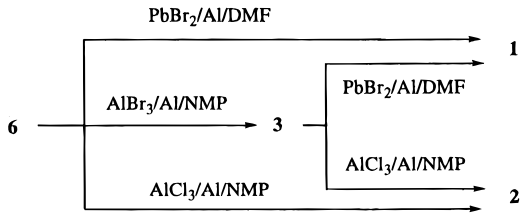


Figure 2. Time course of the transformation of **6a** to **2** in an $AlCl_3$/Al/4A molecular sieves system (Table 5, entry 12).

Scheme 6



11.9 Hz, 1H), 5.10 (d, J = 11.9 Hz, 1H), 5.80 (d, J = 5.5 Hz, 1H), 6.30 (d, J = 7.0 Hz, 1H), 6.83 (d, J = 8.7 Hz, 2H), 7.09−7.63 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.8, 44.7, 55.2, 62.5, 68.1, 70.9, 114.1, 121.1, 126.5, 126.6, 127.9, 128.3, 129.3 129.5, 129.5, 130.5, 133.2, 134.3, 144.5, 146.4, 160.0, 160.3, 163.8, 173.3. Anal. Calcd for $C_{29}H_{26}Cl_2N_2O_7S_2$: C, 53.62; H, 4.03; N, 4.31. Found: C, 53.82; H, 4.24; N, 4.07.

***p*-Methoxybenzyl (*E*)-3-Chloro-2-[2-oxo-3-(phenylacetamido)-4-[(phenylsulfonyl)thio]azetidin-1-yl]-4-[[(trifluoromethyl)sulfonyl]oxy]-2-butenoate (6b).** To a solution of enol **9**[12] (500 mg, 0.79 mmol) in dichloromethane (5 mL) were successively added triethylamine (166 μL, 1.19 mmol) and trifluoromethanesulfonic anhydride (200 μL, 1.19 mmol) at −78 °C. After being stirred for 1 h, the reaction mixture was poured into ice-cold aqueous 5% HCl and extracted with dichloromethane. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 8/1) to afford triflate **6b** (574 mg, 95%) as yellow foam: IR (KBr) 3290, 1770, 1685, 1650, 1330, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ

3.66 (s, 2H), 3.80 (s, 3H), 4.35 (d, J = 14.1 Hz, 1H), 4.74 (d, J = 14.1 Hz, 1H), 4.83 (dd, J = 5.5, 7.1 Hz, 1H), 5.17 (d, J = 11.7 Hz, 1H), 5.22 (d, J = 11.7 Hz, 1H), 5.96 (d, J = 7.1 Hz, 1H), 6.00 (d, J = 5.5 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H) 7.21−7.77 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.8, 43.4, 55.9, 63.7, 69.4, 70.5, 114.6, 119.8, 126.6, 127.5, 128.6, 128.9, 130.0, 130.2, 131.8, 133.7, 134.9, 144.7, 152.1, 160.2, 160.7, 163.5, 163.6, 173.9. Anal. Calcd for $C_{30}H_{26}ClF_3N_2O_{10}S_3$: C, 47.21; H, 3.43; N, 3.67. Found: C, 47.47; H, 3.49; N, 3.63.

***p*-Methoxybenzyl 3-Chloro-4-[[(*p*-methylphenyl)sulfonyl]oxy]-2-[2-oxo-3-(phenylacetamido)-4-((phenylsulfonyl)thio)azetidin-1-yl]-2-butenoate (6c).** A mixture of enol **9**[12] (500 mg, 0.79 mmol), tosyl chloride (227 mg, 1.19 mmol), and sodium carbonate (252 mg, 2.34 mmol) in DMF (5 mL) was stirred at 0 °C for 2 h. The reaction mixture was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 15/1) to afford tosylates ***E*-6c** (554 mg, 89%) and ***Z*-6c** (54 mg, 9%) as yellow foam.

***E*-6c**: IR (KBr) 3295, 1770, 1680, 1645, 1325 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.53 (s, 2H), 3.83 (s, 3H), 4.41 (d, J = 13.1 Hz, 1H), 4.73 (d, J = 13.1 Hz, 1H), 5.19 (s, 2H), 5.40 (dd, J = 4.8, 9.1 Hz, 1H), 5.81 (d, J = 4.8 Hz, 1H), 6.07 (d, J = 9.1 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.15−7.81 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 26.8, 42.9, 55.2, 57.5, 58.4, 67.9, 113.8, 121.9, 126.3, 127.3, 128.3, 128.8, 129.0, 129.2, 129.3, 130.0, 130.2, 130.3, 131.9, 133.9, 139.2, 146.1, 159.1, 159.7, 165.5, 171.2. Anal. Calcd for $C_{36}H_{33}ClN_2O_{10}S_3$: C, 55.06; H, 4.24; N, 3.57. Found: C, 54.95; H, 4.48; N, 3.38.

***Z*-6c**: IR (KBr) 3300, 1770, 1680, 1640, 1325 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.63 (d, J = 9.2 Hz, 1H), 3.65 (d, J = 9.2 Hz, 1H), 3.81 (s, 3H), 3.93 (d, J = 13.3 Hz, 1H), 4.54 (d, J = 13.3 Hz, 1H), 4.84 (dd, J = 5.5, 7.0 Hz, 1H), 5.02 (s, 2H), 5.90 (d, J = 5.5 Hz, 1H), 5.98 (d, J = 7.0 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 7.29−7.81 (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 26.8, 42.9, 55.2, 57.5, 58.4, 67.9, 113.8, 121.9, 126.3, 127.3, 128.3, 128.8, 129.0, 129.2, 129.3, 130.0, 130.2, 130.3, 131.9, 133.9, 139.2, 146.1, 159.1, 159.7, 165.5, 171.2. Anal. Calcd for $C_{36}H_{33}ClN_2O_{10}S_3$: C, 55.06; H, 4.24; N, 3.57. Found: C, 55.00; H, 4.53; N, 3.50.

Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of 3,4-Dichloro-2-butenoate 6a to 2-*exo*-Methylenepenam 1 by Use of the $PbBr_2$/Al Redox System (Table 2, entry 15). A mixture of lead(II) bromide (100 mg, 0.27 mmol) and aluminum (100 mg, 3.71 mmol) in DMF (2 mL) was stirred for 3 min at room temperature. To the mixture was added 3,4-dichloro-2-butenoate **6a** (100 mg, 0.15 mmol) under stirring. After being stirred for 1 h at room temperature, the reaction mixture, whose HPLC (conditions: column, YMC-Pack AM-312 ODS (6.0 ϕ × 150 mm); mobile phase, CH_3CN/H_2O = 65/35; flow rate, 1.0 mL/min) analysis showed the formation of **1** (quantitative) based on an external reference, was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 5/1) to afford **1** (38.5 mg, 57%) as a white solid.

***p*-Methoxybenzyl 2-*exo*-methylene-6-(phenylacetamido)penam-3-carboxylate (1):** IR (KBr) 3309, 1801, 1743, 1666, 1627, 1531 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.63 (s, 2H), 3.82 (s, 3H), 5.12 (s, 2H), 5.18 (dd, J = 1.5, 1.7 Hz, 1H), 5.24 (dd, J = 1.5, 2.2 Hz, 1H), 5.35 (dd, J = 1.7, 2.2 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.75 (dd, J = 4.0, 9.3 Hz, 1H), 6.13 (d, J = 9.3 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.21−7.41 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.3, 55.3, 60.0, 64.5, 67.8, 69.5, 108.0, 114.1, 126.8, 127.7, 129.1, 129.4, 130.2, 133.6, 146.1, 159.9, 166.9, 170.4, 172.4. Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 63.08; H, 4.94; N, 6.32.

Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of Triflate 6b to 2-*exo*-Methylenepenam 1 by Use of $PbBr_2$/Al Redox System (Table 4, entry 3). A mixture of lead(II) bromide (100 mg, 0.27 mmol) and aluminum (100 mg, 3.71 mmol) in DMF (2 mL) was stirred for 3 min at room temperature. To the mixture was added triflate **6b** (100 mg, 0.13 mmol) under stirring. After being stirred for 1 h at room temperature, the reaction mixture, whose HPLC (conditions: column, YMC-Pack AM-312 ODS (6.0 ϕ × 150 mm); mobile phase, CH_3CN/H_2O = 65/35; flow rate, 1.0 mL/min) analysis showed the formation of **1** (quantitative) based on an external reference, was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 5/1) to afford **1** (37.4 mg, 65%) as a white solid.

***p*-Methoxybenzyl 7-(Phenylacetamido)-3-[[(trifluoromethyl)sulfonyl]oxy]-Δ^3-cephem-4-carboxylate (10b):** IR (KBr) 3300, 1770, 1725, 1657, 1300 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31 (d, J = 18.5 Hz, 1H), 3.59 (d, J = 18.5 Hz, 1H), 3.54 (s, 2H), 3.73 (s, 3H), 4.90 (d, J = 5.1 Hz, 1H), 5.08 (d, J = 11.7 Hz, 1H), 5.26 (d, J = 11.7 Hz, 1H), 5.80 (dd, J = 5.1, 9.1 Hz, 1H), 6.41 (d, J = 9.1 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.15−7.33 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.30, 42.48, 54.60, 56.94, 58.14, 68.05, 113.28, 120.71, 122.52, 125.33, 127.05, 128.46, 128.66, 130.34, 132.96, 138.67, 157.95, 159.41, 164.56, 170.58.

Reductive 1,2-Elimination/S−S Bond Fission/Cyclization of Tosylate 9c to 2-*exo*-Methylenepenam 1 by Use of $BiCl_3$/Al Redox System (Table 4, entry 8). A mixture of bismuth(III) chloride (40.2 mg, 0.13 mmol) and aluminum (17.2 mg, 0.64 mmol) in DMF (2 mL) was stirred for 3 min at room temperature. To the mixture was added tosylate **6c** (a mixture of *E*- and *Z*-isomer, 100 mg, 0.13 mmol) with stirring. After being stirred for 1.5 h at room temperature, the reaction mixture, whose HPLC (conditions: column, YMC-Pack AM-312 ODS (6.0 ϕ × 150 mm); mobile phase, CH_3CN/H_2O = 65/35; flow rate, 1.0 mL/min) analysis showed the formation of **1** (77%), **12** (2%), and recovered **6c** (1%) based on external references, was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 5/1) to afford **1** (26.2 mg, 47%) as a white solid.

***p*-Methoxybenzyl 3-[[(*p*-methylphenyl)sulfonyl]oxy]-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (10c):** IR (KBr) 3350, 1776, 1675, 1650, 1325 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.31 (d, J = 18.7 Hz, 1H), 3.51 (d, J = 18.7 Hz, 1H), 3.57 (s, 2H), 3.78 (s, 3H), 4.95 (d, J = 4.9 Hz, 1H), 5.00 (s, 2H), 5.79 (dd, J = 4.9, 9.1 Hz, 1H), 6.00 (d, J = 9.1 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.19−7.36 (m, 9H), 7.73 (d, J = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1, 26.3, 42.5, 54.6, 56.9, 57.9, 67.3, 113.2, 121.3, 125.7, 126.9, 127.8, 128.4, 128.7, 129.4, 129.8, 131.3, 133.1, 138.4, 145.6, 158.5, 159.2, 164.6, 170.5. Anal. Calcd for $C_{30}H_{28}N_2O_8S_2$: C, 59.20; H, 4.64; N, 4.60. Found: C, 59.15; H, 4.62; N, 4.54.

***p*-Methoxybenzyl 7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (11):** IR (KBr) 3250, 1776, 1731, 1657 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.33 (dd, J = 6.2, 19.3 Hz, 1H), 3.55 (dd, J = 2.6, 19.3 Hz, 1H), 3.64 (d, J = 16.2 Hz, 1H), 3.67 (d, J = 16.2 Hz, 1H), 3.80 (s, 3H), 4.91 (d, J = 4.9 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 5.21 (d, J = 12.0 Hz, 1H), 5.87 (dd, J = 4.9, 9.2 Hz, 1H), 6.07 (d, J = 9.2 Hz, 1H), 6.50 (dd, J = 2.6, 6.2 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.22−7.41 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.7, 43.9, 55.9, 57.5, 60.2, 68.2, 114.6, 120.4, 127.7, 128.3, 128.6, 129.8, 130.1, 131.0, 134.3, 160.1, 162.0, 165.0, 171.8; Anal. Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.81; H, 4.99; N, 6.29%.

Reductive 1,2-Elimination/Chloride Ion-Addition/Cyclization of 3,4-Dichloro-2-butenoate 6a into 3-Chloro-Δ^3-cephem 2 by Use of $AlCl_3$/Al Redox System (Table 5, entry 12). In a 10 mL two-necked flask fitted with a three-way stopcock were placed aluminum(III) chloride (10.3 mg, 0.08 mmol), aluminum (41.5 mg, 1.54 mmol), and 4A molecular sieves (25 mg). The flask was purged with argon and to the mixture was added NMP (0.5 mL) under stirring. After being stirred for 15 min at room temperature, a solution of the 3,4-dichloro-2-butenoate **6a** (100 mg, 0.15 mmol) in NMP (1.5 mL)

was added under stirring. After being stirred for additional 7.6 h at room temperature, HPLC (conditions: column, YMC-Pack AM-312 ODS (6.0 $\phi \times$ 150 mm); mobile phase, CH_3CN/H_2O = 65/35; flow rate, 1.0 mL/min) analysis of the reaction mixture showed the formation of **2** (80%), **3** (4%), **1** (2%), **12** (3%), and **13** (1%) based on external references. The mixture was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 8/1) to afford **2** (56 mg, 77%) as white solids.

***p*-Methoxybenzyl 3-chloro-7-(phenylacetamido)-Δ^3-cephem-4-carboxylate (2):** IR (KBr) 3352, 1776, 1727, 1665, 1517, 1248, 1223, 1176 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.45 (d, J = 18.8 Hz, 1H), 3.70 (d, J = 18.8 Hz, 1H), 3.60 (s, 2H), 3.78 (s, 3H), 4.94 (d, J = 4.8 Hz, 1H), 5.20 (s, 2H), 5.81 (dd, J = 4.8, 9.2 Hz, 1H), 6.62 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.20−7.40 (m, 7H); ^{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. Anal. Calcd for $C_{23}H_{21}ClN_2O_5S$: C, 58.41; H, 4.48; N, 5.92. Found: C, 58.25; H, 4.50; N, 5.84.

***p*-Methoxybenzyl 3-Chloro-2-[2-oxo-3-(phenylacetamido)-4-[(phenylsulfonyl)thio]azetidin-1-yl]-2-butenoate (12). *E*-12:** IR ($CHCl_3$) 3300, 1786, 1724, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.57 (s, 2H), 3.81 (s, 3H), 5.10 (d, J = 11.8 Hz, 1H), 5.16 (d, J = 11.8 Hz, 1H), 5.21 (dd, J = 5.1, 8.0 Hz, 1H), 5.77 (d, J = 5.1 Hz, 1H), 5.96 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 7.19−7.79 (m, 12H); ^{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. Anal. Calcd for $C_{29}H_{27}ClN_2O_7S_2$: C, 56.63; H, 4.42; N, 4.55. Found: C, 56.61; H, 4.41; N, 4.40.

***Z*-12:** IR ($CHCl_3$) 3300, 1786, 1724, 1670 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.64 (s, 2H), 3.80 (s, 3H), 4.70 (dd, J = 5.5, 7.2 Hz, 1H), 5.08, (d, J = 11.8 Hz, 1H), 5.17 (d, J = 11.8 Hz, 1H), 5.83 (d, J = 5.5 Hz, 1H), 5.97 (d, J = 7.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.11−7.71 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.1, 43.4, 55.9, 61.3, 68.2, 71.2, 114.4, 121.3, 127.2, 127.4, 128.2, 129.6, 129.8, 130.0, 131.1, 134.1, 134.6, 145.4, 154.1, 161.0, 161.8, 164.0, 172.3. Anal. Calcd for $C_{29}H_{27}ClN_2O_7S_2$: C, 56.63; H, 4.42; N, 4.55. Found: C, 56.52; H, 4.66; N, 4.39.

***p*-Methoxybenzyl 7-(phenylacetamido)-3-(phenylsulfonyl)-Δ^3-cephem-4-carboxylate (13):** IR (KBr) 3310, 1800, 1740, 1682, 1661, 1325, 1151 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.34 (d, J = 17.7 Hz, 1H), 3.48 (d, J = 17.7 Hz, 1H), 3.59 (d, J = 15.1 Hz, 1H), 3.62 (d, J = 15.1 Hz, 1H), 3.82 (s, 3H), 4.92 (d, J = 5.2 Hz, 1H), 5.35 (s, 2H), 5.86 (dd, J = 5.2, 9.1 Hz, 1H), 6.01 (d, J = 9.1 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.19−7.68 (m, 10H), 7.93 (d, J = 7.5 Hz, 2H); ^{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, 129.1, 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. Anal. Calcd for $C_{29}H_{26}N_2O_7S_2$: C, 60.19; H, 4.53; N, 4.84. Found: C, 59.94; H, 4.65; N, 4.72.

Reductive S−S Bond Fission/Cyclization of Allenecarboxylate 3 to 2-*exo*-Methylenepenam 1 by Use of Al/$PbBr_2$/DMF System. A mixture of lead(II) bromide (26 mg, 0.07 mmol) and aluminum (12.5 mg, 0.46 mmol) in DMF (0.8 mL) was stirred for 3 min at room temperature. To the mixture was added allenecarboxylate **3** (35 mg, 0.06 mmol) under stirring. After being stirred for 1.3 h at room temperature, the reaction mixture was poured into ice-cold aqueous 5% HCl and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, benzene/ethyl acetate = 5/1) to afford **1** (10.8 mg, 41%) and **3** (3.4 mg, 10%).

Synthesis of 3-Chloro-Δ^3-cephem 2 through Chloride Ion-Addition/Cyclization of Allenecarboxylate 3 with Lithium Chloride in the Presence of Aluminum Chloride. Into a mixture of aluminum(III) chloride (30.7 mg, 0.23 mmol) and lithium chloride (51.5 mg, 1.2 mmol) in NMP (1.0 mL) was added a solution of the allenecarboxylate **3** (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 under reduced pressure. The crude product was purified by column chromatography (SiO_2, benzene/ethyl acetate = 8/1) to afford **2** (38.7 mg, 71%) and **12** (4.2 mg, 6%).

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