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Synthesis of 3-Hydroxycephems from Penicillin G through Cyclization of Chlorinated 4-(Phenylsulfonylthio)-2-azetidinones Promoted by a $BiCl_3/Sn$ or $TiCl_4/Sn$ Bimetal Redox System

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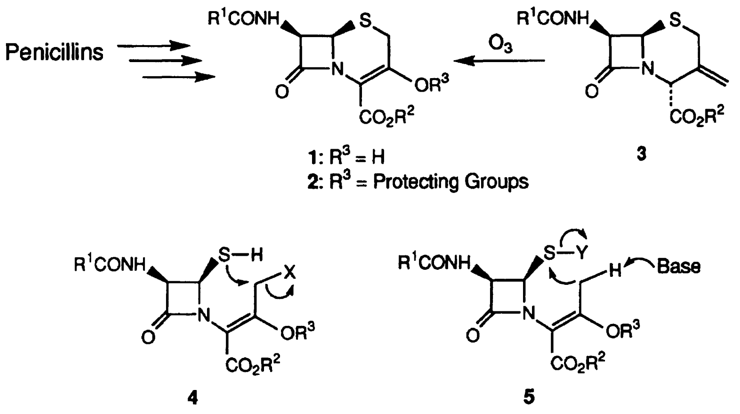
A novel access to 3-hydroxycephems was attained from penicillin G via the C=C bond cleavage of 1-(1-alkoxycarbonyl-2-chloromethyl-2-propenyl)-4-(phenylsulfonylthio)-2-azetidinones by successive treatment with $RuCl_3/HIO_4$ and $HIO_4/CuSO_4$ and reductive cyclization of 1-(1-alkoxycarbonyl-3-chloro-2-hydroxy-1-propenyl)-4-(phenylsulfonylthio)-2-azetidinones on treatment with a newly devised $BiCl_3/Sn$ or $TiCl_4/Sn$ bimetal redox couple in DMF containing pyridine.

3-Hydroxycephems **1** have been focused as a key intermediate for the synthesis of various orally active cephalosporin antibiotics having hydrogen or hetero atom substituents, such as chloro and methoxyl groups, attached directly to the C(3)-position of the Δ^3-cephem skeleton,[1)] and many synthetic approaches to **1** have been reported. Early trials involved ozonolysis of 3-*exo*-methylenecephams **3** derived either from cephalosporanic acid derivatives by reductive manipulation of the C(3)-acetoxymethyl group[2)] or from penicillins by ring expansion of the thiazolidine ring.[3)] The ozonolysis of the exocyclic double bond of **3** leading to **1** was, however, often accompanied with undesired oxidation on the sulfur atom.[4)]

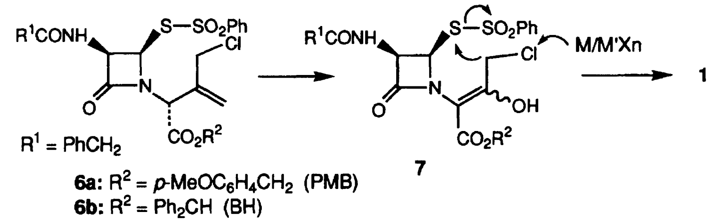
Other attempts which circumvented the above problem have been made starting from penicillins via intermediates equivalent to azetidinones **4** or **5** as illustrated in Scheme 1. The intermediary azetidinones **4** and **5** have been prepared through ring opening of thiazolidine ring of penicillin and subsequent ozonolysis.[5—9)] The cyclization of the intermediates **4** and **5** to 3-hydroxycephems **1** disclosed so far can be classified into two categories of reactions depending upon the direction of the electron flow. Thus, one includes nucleophilic substitution of a terminal halogen atom with a thiol group[5,7,8)] and the other relies on nucleophilic attack of carbanion generated at a terminal carbon to sulfide functions (S-Y).[6,9)] In the previous papers,[10)] we have reported a straightforward access to chlorinated 4-(phenylsulfonylthio)-2-azetidinones **6** from penicillin G, which are subsequently converted to 3-chloromethylcephems, versatile intermediates for the synthesis of cephalosporin antibiotics. We have now envisioned that the C=C bond fission of the azetidinones **6** followed by reductive cyclization in a newly devised $BiCl_3/Sn$ or $TiCl_4/Sn$ bimetal redox system may open a new shortcut route to the 3-hydroxycephems **1** from penicillins as illustrated in Scheme 2.[11)]

Results and Discussion

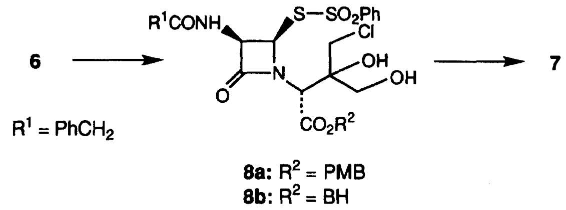
C=C Bond Fission of Azetidinones 6. Ozonolysis is a generally accepted method for the C=C bond cleavage, but it is often obliged to make an effort to avoid the procedure because of its explosive nature, in particular when the large scale reaction is required. Accordingly, we investigated other mode of oxidative cleavage of the C=C bond of **6** without use of ozone.[12)] The desired C=C bond fission of **6a** (R^2=PMB) was performed by employing periodic acid and a catalytic amount of ruthenium(IV) dioxide combination (Method A). Thus, oxidation of **6a** with periodic acid (5.8 molar amounts) and ruthenium(IV) dioxide (0.05 molar amount) in aqueous dioxane containing copper(II) sulfate (4 molar amounts) at 14 °C for 2 h afforded the enol **7a** in 59% yield. Several efforts for improvement of the yield of **7a** faced some difficulties.[13)]



Scheme 1.



Scheme 2.



Scheme 3.

As an alternative approach to the enols **7**, a two step oxidation (Method B) has been attempted, which involves preparation of diols **8** and subsequent C–C bond cleavage of the 1,2-diol moieties (Scheme 3). The isolation of the diols **8** was achieved successfully by employing ruthenium(III) chloride as a catalyst. Thus, treatment of **6a** with periodic acid (2.3 molar amounts) and ruthenium(III) chloride (0.04 molar amount) in dioxane/water (2/1) afforded **8a** in quantitative yield. With the combination of ruthenium(IV) dioxide and periodic acid, the oxidation was hardly stopped at the diol stage and even with reduced amounts of periodic acid a mixture of the olefin **6a**, the diol **8a**, and the enol **7a** was obtained.

The subsequent oxidation of the isolated diol **8a** to the enol **7a** was achieved by treatment with periodic acid (2.1 molar amounts) and copper(II) sulfate (2.7 molar amounts) in acetone/water (5/2) at room temperature for 2.5 h affording **7a** in 80% yield. The presence of copper(II) sulfate seems to prevent decomposition of the product **7a** under the reaction condition, because in the absence of copper(II) sulfate, the yield of the desired **7a** decreased to less than half of that obtained in the presence of copper(II) sulfate. Conversion of **6b** (R^2=BH) to the enol **7b** through the diol **8b** was similarly performed by the two step oxidation.

The ^{1}H NMR spectrum of the enols **7** in chloroform-*d* did not exhibit any signals due to the methine proton α to the ester carbonyl group (keto form) but showed signals at 11.86 and 11.69 ppm assigned to be the enol protons of **7a** and **7b**, respectively. The ^{1}H NMR spectrum of **7** also revealed the presence of only one of the *E*- and *Z*-isomers but the stereochemistry could not yet be determined.

Cyclization of Enols 7 to 3-Hydroxycephems 1. Next, reductive cyclization of the enols **7** to the 3-hydroxycephems **1** in a bimetal redox system comprising a metal salt and a metal was investigated. The first combination we examined was a $PbCl_2$/Al bimetal redox system, a powerful reducing system which we had developed for many reductive transformations.[14] Thus, the enol **7a** was treated with lead(II) chloride (1.3 molar amounts) and aluminium powder (30 molar amounts) in *N*,*N*-dimethylformamide (DMF) at room temperature. The HPLC analysis of the reaction mixture showed the presence of a trace amount of the desired **1a** but the major was a complex mixture of untractable decomposition products. We then screened various bimetal redox combinations. The results of the reductive cyclization of the enol **7a** with various bimetal systems are summarized in Table 1. Apparently, bismuth(III) chloride and tin metal combination is the best choice for the reductive cyclization of **7a** to **1a**. In fact, a mixture of **7a**, bismuth(III) chloride, and tin powder (1 : 0.1 : 2.5 molar ratio) in DMF containing pyridine (20 vol/vol %) was stirred at room temperature to afford the desired 3-hydroxycephem **1a** in 85% yield (Entry 2). In place

Table 1. Cyclization of Chlorinated Azetidinone **7a** in Bimetal Redox Systems[a)]

Entry	Metal salt (molar amounts)	Metal (molar amounts)	Additive	Time h	Yield %
1	$PbCl_2$ (1.3)	Al (30)	None	2	Trace[b)]
2	$BiCl_3$ (0.1)	Sn (2.5)	Pyridine	1	85[c)]
3	$TiCl_4$ (0.1)	Sn (2.5)	Pyridine	2	80[c)]
4	$SbCl_3$ (0.1)	Sn (2.5)	Pyridine	1	28[b)]
5	$BiCl_3$ (0.1)	Al (2.5)	Pyridine	1	13[b)]
6	$BiCl_3$ (0.1)	Zn (2.5)	Pyridine	1	15[b)]
7	$BiCl_3$ (0.1)	Mg (2.5)	Pyridine	2	4[b)]
8	None	Sn (2.5)	Pyridine	1	—
9	None	Bi (2.5)	Pyridine	1	—
10	$BiCl_3$ (0.1)	Sn (2.5)	None	3	31[b)]

a) A DMF solution of **7a** (100 mg/1 ml) containing additive (0.2 ml) was treated with metal salt and metal combinations at ambient temperature. b) Determined by HPLC with an external standard. The HPLC conditions were as follows, column: YMC-Pack® AM-312 ODS (6.0Φ×150 mm); mobile phase: $CH_3CN/H_2O=40/60$ with 0.005 M PIC®-A; flow rate: 2 ml min^{-1}; detection wavelength: 254 nm. c) Isolated yield.

of the $BiCl_3$/Sn combination, $TiCl_4$/Sn could be used without significant change, affording **1a** in 80% yield (Entry 3). Other metal salt/metal combinations investigated so far are less effective (Entries 4—7). The presence of the metal salts is indispensable for this reaction since in the absence of the metal salts, no appreciable amount of **1a** was obtained (Entries 8 and 9). Although the role of the metal salts is still ambiguous, it is likely that low valent bismuth or titanium generated in situ by reduction of Bi(III) or Ti(IV) with tin metal works as a promoter of the cyclization reaction. The addition of pyridine was also effective, presumably due to its buffering effect; indeed, without pyridine, the yield of **1a** was reduced significantly (Entry 10).

Cyclization of Protected Enols 9. In order to examine the influence of the acidic proton of the enols **7** upon the cyclization reaction, we attempted the protection of **7** as diphenylmethyl ethers and cyclization of the protected enols **9** (Scheme 4). The protection was readily achieved on treatment of **7** with diphenyldiazomethane (2.0 molar amounts) in dioxane to give **9** as a mixture of *E* and *Z* isomers. The ratio of the *E* and *Z* isomers was 2/1 for **9a** and 7/3 for **9b**. Although there still remains ambiguity on the assignment of the *E* and *Z* stereochemistry for each isomer based on their ^{1}H NMR spectrum, the results obtained by the subsequent cyclization reactions suggest that the major isomers are in an *E* form and the minor isomers in a *Z* form.

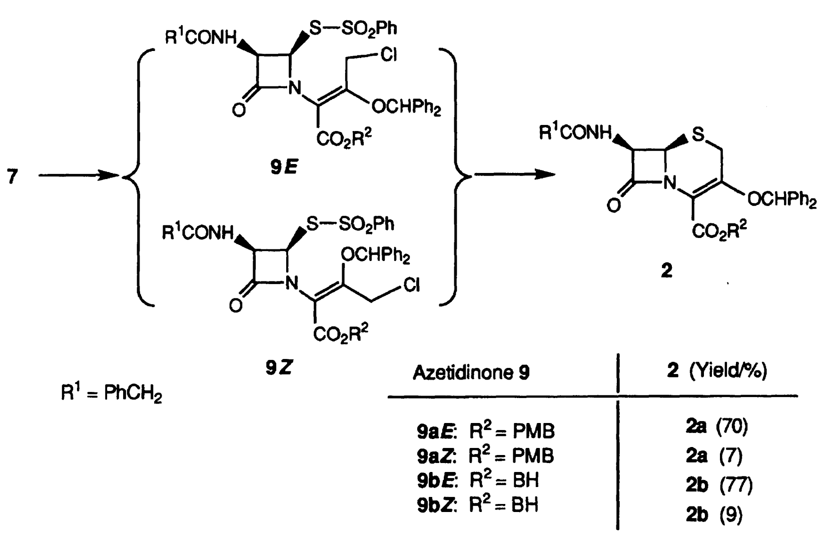
The *E*- and *Z*-isomers of **9** were separated by silica gel column chromatography and subjected to the cyclization reaction. In contrast to the cyclization of the enols **7** (vide supra), the cyclization of the *E*-isomers **9*E*** proceeded smoothly in a $PbBr_2$/Al system;[15)] thus, the *E*-isomers **9*E*** were treated with lead(II) bromide and aluminium powder in DMF at room temperature to give the cyclized products **2** in 70—77% yields. On the other hand, the *Z*-isomers **9*Z*** gave only 7—9% yields of **2**. These results are well in accordance with the fact that only the *E*-isomers **9*E*** may satisfy the requirement for the intramolecular cyclization.

Removal of the diphenylmethyl ether moiety of **2** was easily performed by treatment with trifluoroacetic acid (6 molar amounts) in acetic acid at room temperature. Under the conditions the ether moiety of **2** was selectively cleaved and the ester groups were remained intact to give **1a** (91%) and **1b** (79%), respectively.

Mechanism of Reductive Cyclization of Enols 7. The bimetal redox-promoted intramolecular cyclization of the enols **7** to the 3-hydroxycephems **1** can be understood by assuming the nucleophilic substitution of the phenylsulfonyl group with the terminal carbanion generated in situ by a two-electron reduction of the chloride moiety (Scheme 2). At present, however, one cannot exclude another pathway through reduction of the thiosulfonate moiety of **7** in the bimetal system, generating thiol **11** (X=Cl) which undergoes cyclization reaction to **1** (Scheme 5). In this connection, Yoshioka et al. have reported that the hydrolysis of thiazoline ring of enamine **10a** (X=Br) affords thiol **11a** which, in turn, undergoes intramolecular cyclization leading to **1b** in 74% yield (Scheme 5).[8)] This spurred us to attempt a similar hydrolytic cyclization of a chlorinated analog **10b** (X=Cl) through thiol **11b**. The cyclization reaction of **10b** was, indeed, observed but the yield of **1b** was only 15%. This suggests that the cyclization reaction of **7** in bimetal redox systems would proceed mainly through the reduction of the terminal chloro group rather than the reduction of the thiosulfonate moiety.

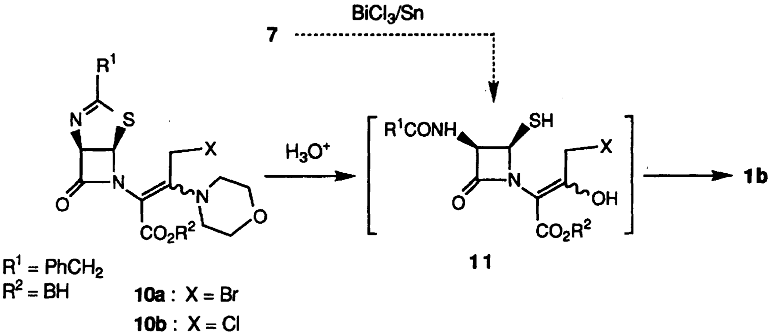
Experimental

IR spectra were obtained on a JEOL RFX-3002 grating infrared spectrophotometer. ^{1}H NMR spectra were recorded



Azetidinone 9	2 (Yield/%)
9a*E*: R^2 = PMB	2a (70)
9a*Z*: R^2 = PMB	2a (7)
9b*E*: R^2 = BH	2b (77)
9b*Z*: R^2 = BH	2b (9)

Scheme 4.



Scheme 5.

with a Varian VXR-300S (300 MHz) spectrometer or a Varian FT-80 (80 MHz) spectrometer and chemical shifts are reported in part per million (δ) relative to tetramethylsilane (δ=0.0 ppm) as an internal standard in a CDCl$_3$ solution. Mass spectra were obtained on a Hitachi M-80 spectrometer. Chloro-substituted 4-(phenylsulfonylthio)-2-azetidinones **6** were prepared from penicillin G according to the method described in the previous paper.[10]

1-[3-Chloro-2-hydroxy-1-(*p*-methoxybenzyloxycarbonyl)-1-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (7a). Method A. To a solution of 1-[2-chloromethyl-1-(*p*-methoxybenzyloxycarbonyl)-2-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (**6a**) (9.5 g, 15.1 mmol) in dioxane (200 ml) was added copper(II) sulfate pentahydrate (10 g, 62.7 mmol) with stirring. To this mixture was added periodic acid (20 g, 87.7 mmol), water (100 ml), and ruthenium(IV) dioxide (0.1 g, 0.8 mmol) in this order. The mixture was then stirred at 13 °C for 2 h and was extracted with ethyl acetate. The extracts were washed with aqueous sodium thiosulfate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with benzene/ethyl acetate (3/2) to afford **7a** (5.6 g, 59%) as colorless solids: IR (KBr) 3400, 1794, 1679, 1647, 1627, 1525 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.64 (d, J=16.8 Hz, 1H), 3.71 (d, J=16.8 Hz, 1H), 3.81 (s, 3H), 4.17 (d, J=12.6 Hz, 1H), 4.35 (d, J=12.6 Hz, 1H), 4.71 (dd, J=5.4, 7.2 Hz, 1H), 5.06 (d, J=11.7 Hz, 1H), 5.18 (d, J=11.7 Hz, 1H), 5.71 (d, J=5.4 Hz, 1H), 5.89 (d, J=7.2 Hz, 1H), 6.90—7.65 (m, 14H), 11.86 (s, 1H); MS (FD) m/z 630 (M$^+$). Anal. Found: C, 55.13; H, 4.31; N, 4.24%. Calcd for $C_{29}H_{27}N_2O_8S_2Cl$: C, 55.19; H, 4.31; N, 4.44%.

Method B. To a solution of **6a** (4.3 g, 6.8 mmol) in dioxane (100 ml) were added water (50 ml), periodic acid (3.6 g, 15.8 mmol), and ruthenium(III) chloride (0.05 g, 0.24 mmol) in this order and the mixture was stirred at room temperature for 1 h. The mixture was diluted with brine (300 ml) and extracted with ethyl acetate. The extracts were washed with aqueous sodium thiosulfate and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with methanol/dichloromethane (5/95) to afford 1-[3-chloro-2-hydroxy-2-hydroxymethyl-1-(*p*-methoxybenzyloxycarbonyl)-1-propyl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (**8a**) (4.5 g, quantitative yield) as colorless solids: IR (KBr) 3367, 1775, 1679, 1627, 1531 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=1.75 (bs, 2H), 3.56 (s, 2H), 3.66 (d, J=12.3 Hz, 1H), 3.70 (s, 2H), 3.81 (d, J=12.3 Hz, 1H), 3.81 (s, 3H), 4.44 (s, 1H), 5.10 (d, J=5.4 Hz, 1H), 5.12 (d, J=5.4 Hz, 1H), 5.14 (dd, J=4.8, 7.5 Hz, 1H), 5.71 (d, J=4.8 Hz, 1H), 6.08 (d, J=7.5 Hz, 1H), 6.80—7.90 (m, 14H).

To a mixture of **8a** (41.8 g, 63 mmol) and copper(II) sulfate pentahydrate (42 g, 168 mmol) in acetone (420 ml) with stirring was added water (168 ml) and periodic acid (30.1 g, 132 mmol). The mixture was stirred at room temperature for 2.5 h and extracted with ethyl acetate. The extracts were washed with aqueous sodium thiosulfate, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with benzene/ethyl acetate (3/2) to afford **7a** (31.8 g, 80%) whose IR and ^{1}H NMR spectra are identical with those described above.

1-[3-Chloro-1-(diphenylmethyloxycarbonyl)-2-hydroxy-1-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (7b). The oxidative cleavage of the terminal olefin of 1-[2-chloromethyl-1-(diphenylmethyloxycarbonyl)-2-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (**6b**) (1 g, 1.5 mmol) was carried out in a similar manner to those described above to afford **7b** (Method A: 0.5 g, 50%; Method B: 0.76 g, 76%) through **8b**.

7b: IR (KBr) 3400, 1789, 1670, 1627, 1523 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.66 (d, J=16.8 Hz, 1H), 3.73 (d, J=16.8 Hz, 1H), 4.20 (d, J=12.9 Hz, 1H), 4.30 (d, J=12.9 Hz, 1H), 4.83 (dd, J=5.4, 6.9 Hz, 1H), 5.77 (d, J=5.4 Hz, 1H), 6.07 (d, J=6.9 Hz, 1H), 6.88 (s, 1H), 7.15—7.55 (m, 20H), 11.69 (s, 1H); MS (FD) m/z 676 (M$^+$). Anal. Found: C, 60.02; H, 4.39; N, 3.84%. Calcd for $C_{34}H_{29}N_2O_7S_2Cl$: C, 60.30; H, 4.32; N, 4.14%.

8b: IR (KBr) 3412, 1775, 1679, 1531, 1502 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=1.80 (bs, 2H), 3.54 (s, 2H), 3.65 (d, J=11.1 Hz, 1H), 3.68 (d, J=11.1 Hz, 1H), 3.73 (d, J=17.1 Hz, 1H), 3.89 (d, J=17.1 Hz, 1H), 4.58 (s, 1H), 5.11 (dd, J=4.2, 7.5 Hz, 1H), 5.69 (d, J=4.2 Hz, 1H), 6.02 (d, J=7.5 Hz, 1H), 6.86 (s, 1H), 7.10—7.80 (m, 20H). Anal. Found: C, 59.06; H, 4.75; N, 3.81%. Calcd for $C_{35}H_{33}N_2O_8S_2Cl$: C, 59.27; H, 4.69; N, 3.95%.

***p*-Methoxybenzyl 3-Hydroxy-7-(phenylacetamido)-3-cephem-4-carboxylate (1a).** A mixture of **7a** (100 mg, 0.16 mmol), tin powder (47 mg, 0.4 mmol), bismuth(III) chloride (5 mg, 0.016 mmol), and pyridine (0.2 ml) in DMF (1 ml) was stirred at room temperature for 1 h. The mixture was poured into aqueous 1 M HCl (1 M=1 mol dm^{-3}) and extracted with ethyl acetate. The extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with methanol/dichloromethane (1/100) to afford **1a** (61 mg, 85%) as colorless solids: Mp 128 °C; IR (KBr) 3300, 1789, 1672, 1627, 1537, 1521 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.19 (d, J=17.1 Hz, 1H), 3.42 (d, J=17.1 Hz, 1H), 3.61 (d, J=16.2 Hz, 1H), 3.68 (d, J=16.2 Hz, 1H), 3.80 (s, 3H), 4.96 (d, J=4.5 Hz, 1H), 5.21 (s, 2H), 5.59 (dd, J=4.5, 9.0 Hz, 1H), 6.04 (d, J=9.0 Hz, 1H), 6.88 (d, J=8.4 Hz, 2H), 7.25—7.40 (m, 7H), 11.67 (s, 1H); MS (FD) m/z 454 (M$^+$). Anal. Found: C, 60.55; H, 4.73; N, 6.09%. Calcd for $C_{23}H_{22}N_2O_6S$: C, 60.78; H, 4.88; N, 6.16%.

Diphenylmethyl 3-Hydroxy-7-(phenylacetamido)-3-cephem-4-carboxylate (1b). Cyclization of **7b** (100 mg, 0.15 mmol) was carried out in a similar manner to that described above to afford **1b** (46 mg, 61%) as colorless solids: Mp 139 °C; IR (KBr) 3290, 1789, 1679, 1624, 1560, 1502 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.22 (d, J=17.4 Hz, 1H), 3.46 (d, J=17.4 Hz, 1H), 3.64 (d, J=15.9 Hz, 1H), 3.70 (d, J=15.9 Hz, 1H), 4.99 (d, J=4.8 Hz, 1H), 5.71 (dd, J=4.8, 9.0 Hz, 1H), 6.11 (d, J=9.0 Hz, 1H), 6.87 (s, 1H), 7.26—7.55 (m, 15H), 11.65 (s, 1H); MS (FD) m/z 500 (M$^+$). Anal. Found: C, 66.96; H, 4.73; N, 5.53%. Calcd for $C_{28}H_{24}N_2O_5S$: C, 67.13; H, 4.83; N, 5.60%.

Cyclization of 7a with TiCl$_4$/Sn. A mixture of **7a** (100 mg, 0.16 mmol), tin powder (47 mg, 0.4 mmol), titanium(IV) chloride (3 mg, 0.016 mmol), and pyridine (0.2 ml) in DMF (1 ml) was stirred at room temperature for 2 h. The mixture was poured into aqueous 1 M hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with methanol/dichloromethane (1/100) to afford **1a** (58 mg, 80%) whose IR and ^{1}H NMR spectra are identical with those described above.

1-[3-Chloro-1-(*p*-methoxybenzyloxycarbonyl)-2-(diphenylmethyloxy)-1-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (9a). A mixture of **7a** (1 g, 1.6 mmol) and diphenyldiazomethane (1 g, 5.1 mmol) in dioxane (1 ml) was stirred at 40 °C for 1.5 h and concentrated in vacuo. The residue was chromatographed on a silica gel column with benzene/ethyl acetate (8/1) to afford **9a** as a mixture of E and Z isomers (1.1 g, 85%, major/minor=2/1).

The major and minor isomers of **9a** were separated by preparative thin-layer chromatography by developing with benzene/ethyl acetate (2/1).

Major Isomer (9a*E*): IR (KBr) 1791, 1692, 1618, 1521, 1502 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.59 (d, J=16.8 Hz, 1H), 3.66 (d, J=16.8 Hz, 1H), 3.79 (s, 3H), 4.09 (d, J=13.2 Hz, 1H), 4.61 (d, J=13.2 Hz, 1H), 4.68 (dd, J=5.1, 7.2 Hz, 1H), 5.10 (d, J=11.7 Hz, 1H), 5.18 (d, J=11.7 Hz, 1H), 5.85 (d, J=5.1 Hz, 1H), 5.94 (d, J=7.2 Hz, 1H), 6.53 (s, 1H), 6.80—7.80 (m, 24H). Anal. Found: C, 63.03; H, 4.74; N, 3.43%. Calcd for $C_{42}H_{37}N_2O_8S_2Cl$: C, 63.27; H, 4.68; N, 3.51%.

Minor Isomer (9a*Z*): IR (KBr) 1801, 1692, 1627, 1531, 1502 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.44 (s, 2H), 3.81 (s, 3H), 4.63 (d, J=12.3 Hz, 1H), 4.70 (d, J=12.3 Hz, 1H), 5.04 (d, J=11.7 Hz, 1H), 5.10 (d, J=11.7 Hz, 1H), 5.32 (dd, J=4.8, 8.4 Hz, 1H), 5.59 (d, J=4.8 Hz, 1H), 5.62 (d, J=8.4 Hz, 1H), 6.60 (s, 1H), 6.80—7.60 (m, 24H). Anal. Found: C, 63.03; H, 4.72; N, 3.39%. Calcd for $C_{42}H_{37}N_2O_8S_2Cl$: C, 63.27; H, 4.68; N, 3.51%.

1-[3-Chloro-2-(diphenylmethyloxy)-1-(diphenylmethyloxycarbonyl)-1-propen-1-yl]-3-(phenylacetamido)-4-(phenylsulfonylthio)-2-azetidinone (9b). Protection of **7b** (1 g, 1.5 mmol) was carried out in a similar manner to that described above to afford **9b** as a mixture of E and Z isomers (1.1 g, 88%, major/minor=7/3). The major and minor isomers of **9b** were separated by preparative thin-layer chromatography by developing with benzene/ethyl acetate (2/1).

Major Isomer (9b*E*): IR (KBr) 1801, 1711, 1621, 1525, 1505 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.59 (d, J=16.8 Hz, 1H), 3.67 (d, J=16.8 Hz, 1H), 4.18 (d, J=13.5 Hz, 1H), 4.62 (d, J=13.5 Hz, 1H), 4.74 (dd, J=5.4, 7.2 Hz, 1H), 5.85 (d, J=5.4 Hz, 1H), 5.94 (d, J=7.2 Hz, 1H), 6.65 (s, 1H), 6.99 (s, 1H), 7.00—7.60 (m, 30H). Anal. Found: C, 67.06; H, 4.75; N, 3.17%. Calcd for $C_{47}H_{39}N_2O_7S_2Cl$: C, 66.93; H, 4.66; N, 3.32%.

Minor Isomer (9b*Z*): IR (KBr) 1801, 1698, 1615, 1525, 1505 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ=3.48 (s, 2H), 4.57 (d, J=12.6 Hz, 1H), 4.65 (d, J=12.6 Hz, 1H), 5.34 (dd, J=5.1, 8.2 Hz, 1H), 5.59 (d, J=5.1 Hz, 1H), 5.64 (d, J=8.2 Hz, 1H), 6.61 (s, 1H), 6.81 (s, 1H), 7.10—7.60 (m, 30H). Anal. Found: C, 67.23; H, 4.70; N, 3.23%. Calcd for $C_{47}H_{39}N_2O_7S_2Cl$: C, 66.93; H, 4.66; N, 3.32%.

Cyclization of Protected Enol 9a*E*. A mixture of **9a*E*** (200 mg, 0.25 mmol), lead(II) bromide (200 mg, 0.54 mmol), and aluminium powder (200 mg, 7.4 mmol) in anhydrous DMF (2 ml) was stirred at room temperature for 2 h. The mixture was taken up with ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with benzene/ethyl acetate (5/1) to afford **2a** as colorless solids (109 mg, 70%): ^{1}H NMR (80 MHz, $CDCl_3$) δ=3.20 (s, 2H), 3.57 (s, 2H), 3.77 (s, 3H), 4.72 (d, J=5.2 Hz, 1H), 5.15 (s, 2H), 5.51 (dd, J=5.2, 8.3 Hz, 1H), 6.00 (s, 1H), 6.31 (d, J=8.3 Hz, 1H), 6.74—7.50 (m, 19H).

Into a solution of **2a** (300 mg, 0.48 mmol) in acetic acid (3 ml) was added trifluoroacetic acid (0.25 ml, 3 mmol). After being stirred for 5 h at room temperature the mixture was poured into water and extracted with ethyl acetate. The extracts were washed with aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on a silica gel column with methanol/dichloromethane (1/100) to afford **1a** (199 mg, 91%).

Cyclization of Protected Enol 9a*Z*. Cyclization of **9a*Z*** (200 mg, 0.25 mmol) was carried out in a similar manner to that described above to afford **2a** (11 mg, 7%).

Cyclization of Protected Enol 9b*E*. Cyclization of **9b*E*** (200 mg, 0.24 mmol) was carried out in a similar manner to that described above to afford **2b** as colorless solids (123 mg, 77%): ^{1}H NMR (80 MHz, $CDCl_3$) δ=3.17 (s, 2H), 3.53 (s, 2H), 4.20 (d, J=5.0 Hz, 1H), 5.48 (dd, J=5.0, 9.2 Hz, 1H), 6.03 (s, 1H), 6.47 (d, J=9.2 Hz, 1H), 6.99 (s, 1H), 7.00—7.60 (m, 25H), which (100 mg, 0.15 mmol) was subsequently deprotected in a similar manner to that described above to afford **1b** (59 mg, 79%).

Cyclization of Protected Enol 9b*Z*. Cyclization of **9b*Z*** (200 mg, 0.24 mmol) was carried out in a similar manner to that described above to afford **2b** (14 mg, 9%).

Diphenylmethyl 2-(3-Benzyl-6-oxo-2-thia-4,7-diazabicyclo[3.2.0]hept-3-en-7-yl)-4-chloro-3-morpholino-2-butenoate (10b). Into a solution of diphenylmethyl 2-(3-benzyl-6-oxo-2-thia-4,7-diazabicyclo[3.2.0]hept-3-en-7-yl)-3-chloromethyl-3-butenoate[16] (12.4 g, 24 mmol) in dichloromethane (400 ml) and methanol (800 ml) was bubbled ozone (22 mmol h^{-1}) and −60 °C for 1 h. After addition of trimethyl phosphite (5.7 ml, 48 mmol) at −60 °C, the mixture was stirred at room temperature for 2 h and concentrated in vacuo. The residue was chromatographed on a silica gel column with benzene/ethyl acetate (10/1) to afford diphenylmethyl 2-(3-benzyl-6-oxo-2-thia-4,7-diazabicyclo[3.2.0]hept-3-en-7-yl)-4-chloro-3-hydroxy-2-butenoate (7.5 g, 60%) as pale yellow solids: IR (KBr) 3457, 1780, 1764, 1680, 1623, 1606, 1499 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.76 (d, J=14.7 Hz, 1H), 3.79 (d, J=12.6 Hz, 1H), 3.84 (d, J=14.7 Hz, 1H), 3.92 (d, J=12.6 Hz, 1H), 5.68 (d, J=4.2 Hz, 1H), 6.04 (d, J=4.2 Hz, 1H), 6.90 (s, 1H), 7.20—7.40 (m, 15H), 12.17 (s, 1H), which (1.0 g, 2 mmol) was treated with N-methylmorpholine (0.88 ml, 8 mmol) in tetrahydrofuran (15 ml) containing p-toluenesulfonic anhydride (0.8 g, 2.4 mmol) for 1 h at −50 °C. Into the mixture was added morpholine (0.26 ml, 3 mmol) at −50 °C and the mixture was stirred for 2.5 h at 0 °C and for 1 h at room temperature. To the mixture was added benzene (15 ml) and the precipitates formed were separated by suction filtration. The filtrate was concentrated in vacuo and the residue was chromatographed on a silica gel column with benzene/ethyl acetate (8/1) to afford a mixture of E and Z isomers of **10b** (0.97 g, 82%; major/minor=65/35) as pale yellow solids: IR (KBr) 1775, 1698, 1688, 1560 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.96—3.34 (m, 4H), 3.46—3.74 (m, 4H), 3.80 (d, J=14.1 Hz, 1H), 3.86 (d, J=14.1 Hz, 1H), 3.92 (d, J=13.8 Hz, 0.35H), 4.06 (d, J=13.8 Hz, 0.35H), 4.55 (d, J=13.5 Hz, 0.65H), 4.76 (d, J=13.5 Hz, 0.65H), 5.60 (d, J=4.2 Hz, 0.35H), 5.68 (d, J=4.5 Hz, 0.65H), 5.88 (d, J=4.5 Hz, 0.65H), 5.91 (d, J=4.2 Hz, 0.35H), 6.83 (s, 0.35H), 6.87 (s, 0.65H), 7.20—7.40 (m, 15H); MS m/z 587 (M^+).

Hydrolysis of 10b. To a mixture of E and Z isomers of **10b** (59 mg, 0.1 mmol), tetrahydrofuran (0.6 ml), and methanol (0.6 ml) was added 5% sulfuric acid (0.28 ml, 0.5 mmol) and the mixture was stirred for 1.5 h at room temperature. The HPLC analysis of the reaction mixture showed the formation of 15% yield of **1b**. For the HPLC conditions, see the footnote of Table 1.

References

1) S. Kukolja and R. R. Chauvette, "Chemistry and Biology of β-Lactam Antibiotics," ed by R. B. Morin and M. Gorman, Academic Press, New York (1982), Vol. 1, p. 93; H. Yamanaka, H. Takasugi, T. Masugi, H. Kochi, K. Miyai, and T. Takaya, *J. Antibiot.*, **38**, 1068 (1985); Y. Hamashima, "Recent Advances in Chemistry of β-Lactam Antibiotics," ed by P. H. Bentley and R. Southgate, Royal Society of Chemistry, London (1989), p. 77, and references cited therein.

2) R. R. Cauvette and P. A. Pennington, *J. Org. Chem.*, **38**, 2994 (1973); M. Ochiai, O. Aki, A. Morimoto, T. Okada, and K. Morita, *Tetrahedron*, **31**, 115 (1975).

3) R. D. G. Cooper and G. A. Koppel, "Chemistry and Biology of β-Lactam Antibiotics," ed by R. B. Morin and M. Gorman, Academic Press, New York (1982), Vol. 1, p. 1, and references cited therein.

4) R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, **57**, 1919 (1979).

5) S. Kukolja, M. R. Gleissner, A. I. Ellis, D. E. Dorman, and J. W. Paschal, *J. Org. Chem.*, **41**, 2276 (1976).

6) Y. Hamashima, T. Kubota, K. Ishikura, K. Minami, K. Tokura, and W. Nagata, *Heterocycles*, **5**, 419 (1976).

7) S. Uyeo, T. Aoki, H. Itani, T. Tsuji, and W. Nagata, *Heterocycles*, **10**, 99 (1978).

8) M. Yoshioka, *Pure Appl. Chem.*, **59**, 1041 (1987).

9) J. Gosteli, *Chimia*, **30**, 13 (1976); H. R. Pfaendler, P. A. Rossy, J. Gosteli, and R. B. Woodward, *Heterocycles*, **5**, 293 (1976).

10) S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, *Tetrahedron Lett.*, **23**, 2187 (1982); S. Torii, H. Tanaka, N. Tada, S. Nagao, and M. Sasaoka, *Chem. Lett.*, **1984**, 877.

11) Preliminary results on the transformation of **6** to **1** have recently been reported: H. Tanaka, M. Taniguchi, Y.

Kameyama, M. Monnin, M. Sasaoka, T. Shiroi, S. Nagao, and S. Torii, *Chem. Lett.*, **1990**, 1867.

12) Recently, C=C bond cleavage of non-chlorinated analogues of **6** has been attained by employing an OsO_4(cat.)/$NaIO_4$ combination: J. Thomas and J. Kant, *Synthesis*, **1993**, 293.

13) Upon treatment of **6a** with RuO_2(cat.)/$NaIO_4$ in aqueous acetone the starting material **6a** was recovered intact.

14) H. Tanaka, S. Yamashita, M. Yamanoue, and S. Torii, *J. Org. Chem.*, **54**, 444 (1989); H. Dhimane, H. Tanaka, and S. Torii, *Bull. Soc. Chim. Fr.*, **127**, 238 (1990), and references cited therein.

15) Reaction of **9a*E*** with $BiCl_3$/Sn or $TiCl_4$/Sn in DMF containing pyridine did not afford a detectable amount of the cyclized product **2a** but resulted in the formation of a complex mixture containing less than 5% of the starting material **9a*E***.

16) Prepared by the reported method: S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, *Tetrahedron Lett.*, **22**, 3193 (1981).