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ELECTROOXIDATIVE DESULFURIZATION/CHLORINATION. A FACILE SYNTHESIS OF 4-CHLORO-2-AZETIDINONES, A POTENT INTERMEDIATE FOR CARBAPENEMS

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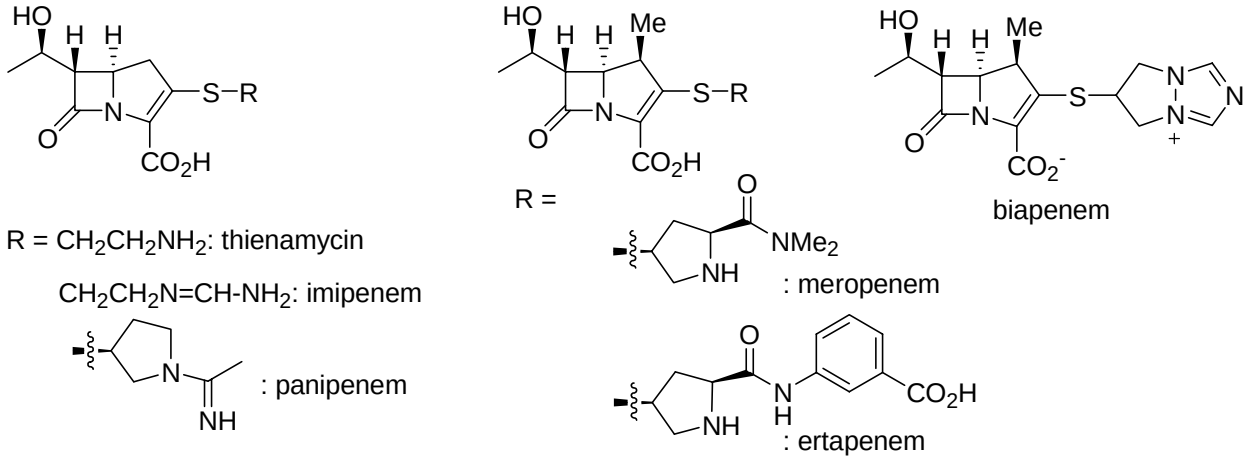
Dedicated to Prof. Noyori Ryoji on the occasion of his 70th Birthday

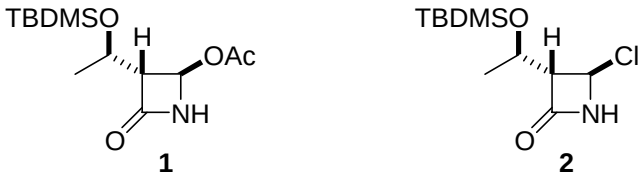
Abstract – (3*S*,4*R*)-3-(1'(*R*)-*tert*-Butyldimethylsilyloxyethyl)-4-chloro-2-azetidinone (**2**), a potent intermediate for the synthesis of carbapenem antibiotics, was synthesized by thermal ring opening/acylation of (3*S*,5*R*,6*S*)-6-(1'(*R*)-*tert*-butyldimethylsilyloxyethyl)penicillanate *S*-oxide (**8**) leading to 4-acylthio-2-azetidinone derivative **9** and subsequent removal of the *N*-substituent followed by electrooxidative desulfurization/chlorination of the C(4)-acylthio moiety.

Carbapenems have a broad spectrum against Gram-positive and Gram-negative bacteria and show high resistance to bacterial β-lactamases. Since thienamycin was discovered as the first member of carbapenems in 1976,[1] carbapenem derivatives such as imipenem,[2] panipenem,[3] meropenem,[4] ertapenem,[5] and biapenem[6] have been developed and marketed (Scheme 1).

Scheme 1. Carbapenem Antibiotics

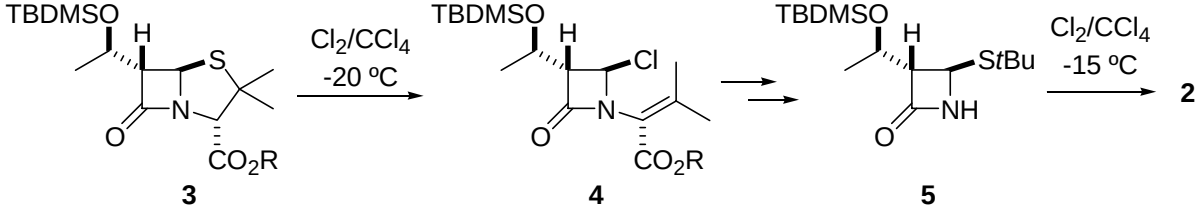


As a versatile intermediate for synthesis of the carbapenems, 4-acetoxy-2-azetidinone (**1**) has been widely used.[7] 4-Acetoxy-2-azetidinone (**1**) was prepared by oxidative acetoxylation of 2-azetidinones[8] and oxidative desulfurization/acetoxylation of penicillanate derivatives.[9] These methods, however, require toxic and hazardous reagents such as peracids, osmium(III) chloride, ruthenium(I) chloride, and/or mercury(II) acetate, and are not necessarily satisfactory from economical and/or environmental point of view. 4-Chloro-2-azetidinone (**2**) is a potent alternative of **1**, and has been used for synthesis of thienamycin,[10] 2-aryloxypenems,[11] and 5,6-*cis*-penems.[12]



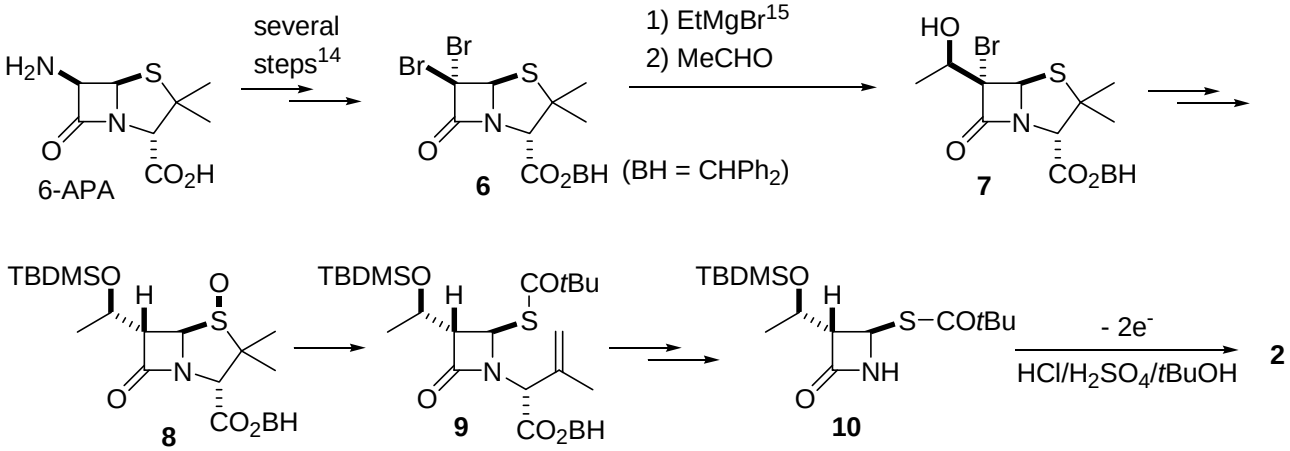
Endo reported synthesis of 4-chloro-2-azetidinone (**2**)[13a] starting from penicillanate derivative **3**[14] through several steps of conversions as outlined in Scheme 2.[13b] The final stage of the transformation was desulfurization/chlorination of 4-*tert*-butylthio-2-azetidinone (**5**), which was performed by treatment with two-molar equivalents of chlorine at -15 ºC. Although several different routes to **2** have been reported so far,[13,15] there still remains a significant demand for an improved process in a practical sense.

Scheme 2. Endo's Route to 4-Chloro-2-azetidinone (**2**).



6,6-Dibromopenicillanates are potent intermediates for various penem and carbapenem antibiotics[16] as well as some β-lactamase inhibitors,[17] and currently prepared on an industrial scale from 6-aminopenicillanic acid (6-APA). In a previous paper, we reported stereoselective "Reformatsky-type coupling" of diphenylmethyl 6,6-dibromopenicillanate (**6**) with acetaldehyde to give the corresponding diphenylmethyl (3*S*,5*R*,6*S*)-6-bromo-6-[1'(*R*)-hydroxyethyl]penicillanate (**7**).[18] In our continuing study, we developed a new synthetic route to **2** starting from **7**. Herein, we describe the transformation involving thermal ring opening/*S*-acylation of penicillanate *S*-oxide (**8**) and removal of the *N*-substituent followed by electrooxidative desulfurization/chlorination of 4-acylthio-2-azetidinone (**10**), as outlined in Scheme 3.

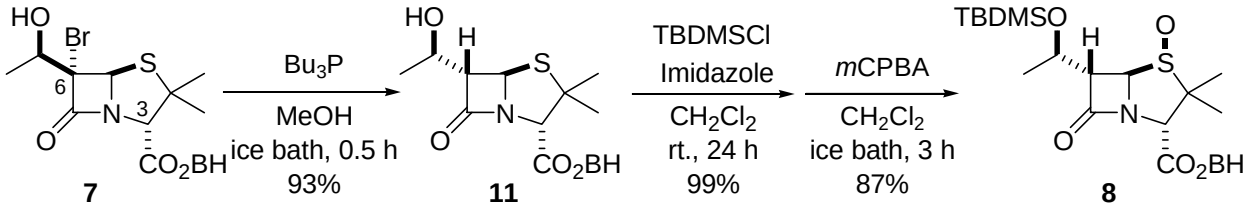
Scheme 3. Synthesis of 4-Chloro-2-azetidinone (**2**)



RESULTS AND DISCUSSION

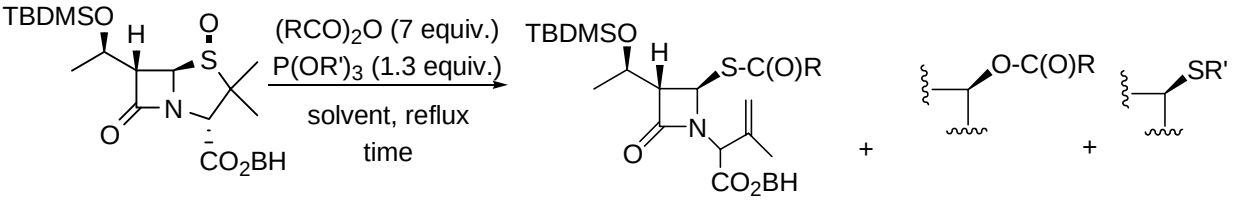
The conversion of bromopenicillanate (**7**) to penicillanate *S*-oxide (**8**) was successfully performed as shown in Scheme 4. Reduction of **7** with Bu_3P in methanol at 0 ºC for 0.5 h afforded the corresponding debrominated compound **11** in 93% yield.[19] The stereochemistry at C6-position was totally inverted and that at C3-position was retained. After protection of the hydroxyl group of **11** with *tert*-butyldimethylsilyl chloride/imidazole,[9b] oxidation of the sulfide moiety was performed by treatment with *m*CPBA in CH_2Cl_2 at 0 ºC for 3 h to afford the penicillanate *S*-oxide **8** in 87% yield.[20]

Scheme 4. Synthesis of Penicillanate *S*-Oxide (**8**).



Next, the ring opening/acylation of the penicillanate *S*-oxide (**8**) leading to the corresponding 4-acylthio-2-azetidinone (**9**) was investigated.[21] The results are summarized in Table 1. First, the *S*-oxide **8** was treated with acetic anhydride and trimethyl phosphite in refluxing benzene to give the desired 4-acetylthio-2-azetidinone (**9a**, R = Me) in 36% yield together with 4-acetoxy-2-azetidinone (**14a**, R = Me) and 4-methylthio-2-azetidinone (**15a**, R' = Me) in 27% and 23% yields, respectively (Entry 1). The formation of undesired **15a** was completely suppressed when triethyl phosphite or triisopropyl phosphite was used in place of trimethyl phosphite (Entries 2 and 3). Triphenyl phosphite could not promote any desired ring-opening/acylation reaction, resulting in the recovery of the starting material **8** (Entry 4).

Table 1. Ring Opening and *S*-Acylation of Penicillanate *S*-Oxide (**8**)



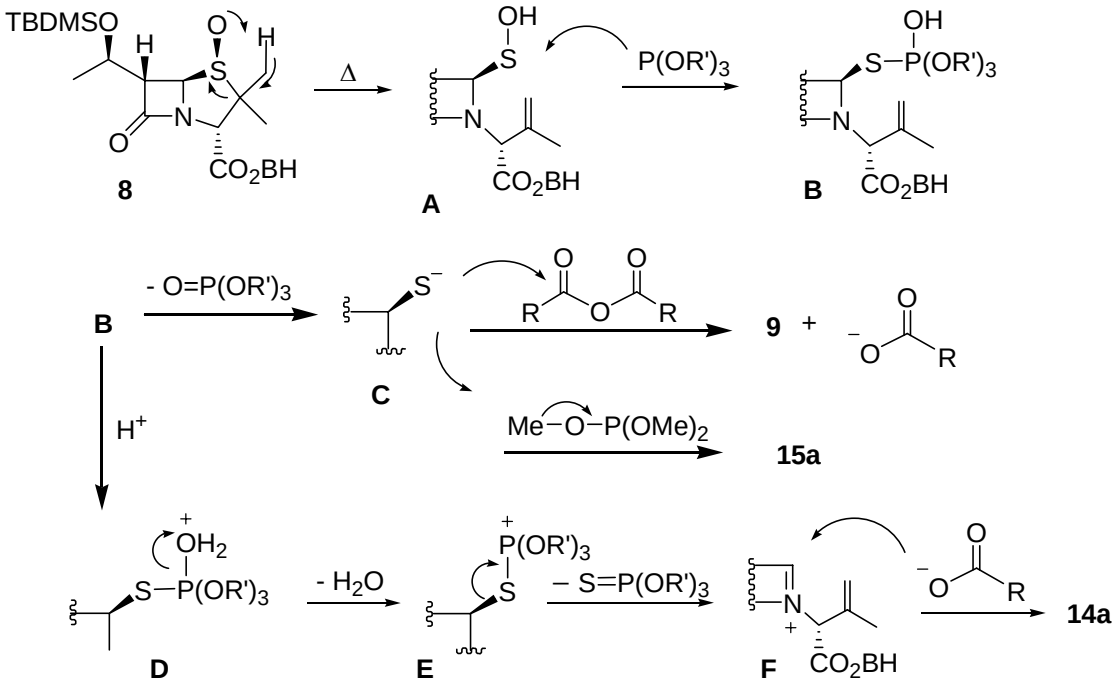
8 **9** **14** **15**

Entry	R	R'	Solvent	Temp[a]	Time/h	Yield/%[b]				
						9	**14**	**9/14**	**15**	**8**
1	Me	Me	benzene	reflux (80 ºC)	50	36	27	1.3	23	n.d.
2	Me	Et	benzene	reflux	24	62	25	2.5	n.d.	n.d.
3	Me	iPr	benzene	reflux	24	56	32	1.7	n.d.	n.d.
4	Me	Ph	benzene	reflux	24	n.d.	n.d.	-	n.d.	90[c]
5	*t*Bu	Et	benzene	reflux	24	67	18	3.7	n.d.	n.d.
6	Ph	Et	benzene	reflux	24	17	63	0.3	n.d.	n.d.
7	CF_3	Et	benzene	reflux	6	n.d.	n.d.	-	n.d.	n.d.
8	*t*Bu	Et	1,2-dichloroethane	reflux (82 ºC)	30	72	6	12.0	n.d.	n.d.
9	*t*Bu	Et	1,2-dichloropropane	reflux (97 ºC)	24	71	9	7.9	n.d.	n.d.
10	*t*Bu	Et	chlorobenzene	70 ºC	24	61	14	4.4	n.d.	19[c]
11	*t*Bu	Et	chlorobenzene	105 ºC	20	68	16	4.3	n.d.	n.d.
12	*t*Bu	Et	chlorobenzene	reflux (132 ºC)	2.5	55	18	3.0	n.d.	n.d.
13	*t*Bu	Et	cyclohexane	reflux (81 ºC)	24	51	37	1.4	n.d.	n.d.
14	*t*Bu	Et	acetonitrile	reflux (82 ºC)	24	n.d.	n.d.	-	n.d.	n.d.

[a]Boiling points of each solvent are shown in the parenthesis. [b]Determined by ^{1}H NMR. n.d. = not detected. [c]Isolated yield.

A plausible mechanism of the formation of **9**, **14a**, and **15a** is shown in Scheme 5.[22] Thermal ring opening of *S*-oxide **8** would give the corresponding sulfenic acid derivatives **A**. Trialkyl phosphite would react with **A** to give intermediate **B**. Cleavage of S-P bond in **B** would give thiolate intermediate **C**. Acylation of **C** with acid anhydride would give the corresponding 4-acylthio-2-azetidinone (**9**), whereas alkylation of **C** with trimethyl phosphite would partly occur to give the methylthio-substituted compound **15a**. On the other hand, acid-catalyzed dehydration of **B** followed by elimination of thiophosphate would afford iminium intermediate **F**, which would subsequently react with carboxylate to give the acyloxyl-substituted product **14a**.

Scheme 5. A Plausible Mechanism for Formation of 4-Acylthio-2-azetidinone (**9**), 4-Acyloxy-2-azetidinone (**14a**), and 4-Methylthio-2-azetidinone (**15a**)

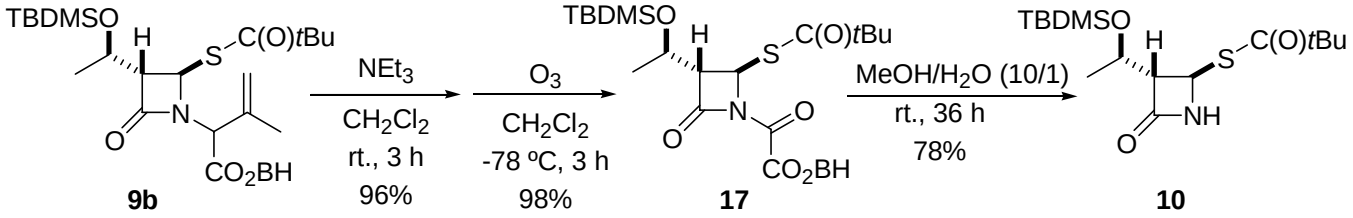


The ratio of **9**/**14** was significantly changed depending on the choice of the acylating reagents. With pivalic anhydride, the ratio was improved up to 3.7 (Entry 5), whereas with benzoic anhydride, undesired product **14** was formed predominantly (**9**/**14** = 0.3, R = Ph, Entry 6). Trifluoroacetic anhydride was useless affording only a complex mixture of unidentified compounds (Entry 7). The selectivity (**9b**/**14b**) was also highly dependent on the solvents (Entries 8-14). When the reaction was carried out in refluxing 1,2-dichloroethane and 1,2-dichloropropane, the ratio **9b**/**14b** increased up to 12.0 and 7.9, respectively, affording **9b** in *ca*. 70% yield (Entries 8 and 9). Chlorobenzene was another proper choice of the solvent; indeed, **9b** was obtained in 55 – 68% yields, depending on the reaction temperature; temperature (yield): 70 ºC (61%), 105 ºC (68%), and reflux (55%) (Entries 10-12). Cyclohexane was

not a suitable solvent, in which compounds **9b** and **14b** were obtained in 51% and 37% yields, respectively (**9b**/**14b** = 1.4, Entry 13). In acetonitrile, a complex mixture was formed without any detectable amount of **9b** (Entry 14). Above all, a combination of pivalic anhydride and triethyl phosphite in refluxing 1,2-dichloroethane or 1,2-dichloropropane is the most desirable for practical preparation of **9b**.

Elimination of the substituent ($CH(CO_2BH)C(Me)=CH_2$) on nitrogen atom of **9b** was performed by conventional procedures as illustrated in Scheme 6. Isomerization of compound **9b** with NEt_3 followed by ozonolysis gave the corresponding *N*-acyl-4-pivaloylthio-2-azetidinone (**17**) in good yield.[22] Deacylation of **17** in aq. MeOH at room temperature for 36 h afforded 4-pivaloylthio-2-azetidinone (**10**) in 78% yield.[23]

Scheme 6. Synthesis of 4-Acylthioazetidinone (**10**)

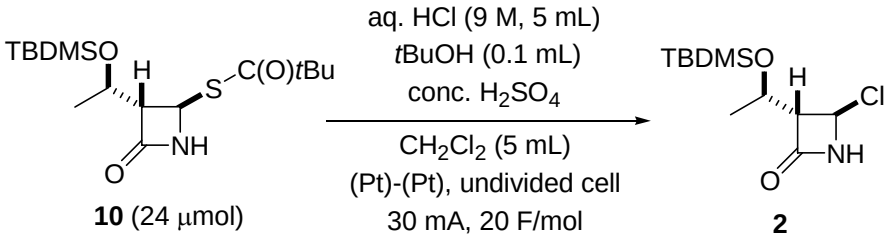


The final stage of the synthesis of 4-chloro-2-azetidinone (**2**) is desulfurization/chlorination which was achieved successfully by the aid of electrochemically generated [Cl^+] species. The electrooxidative desulfurization/chlorination of **10** was carried out in a beaker-type undivided cell fitted with two Pt electrodes. Into the cell were placed aq. HCl (9 M, 5 mL), H_2SO_4 (16 μL), *t*BuOH (0.1 mL), and a CH_2Cl_2 (5 mL) solution of **10** (8.4 mg, 0.024 mmol). Regulated current (30 mA) was passed through the solution at 0 ºC. After 25 min.(20 F/mol), most of **10** disappeared. Extractive work-up afforded compound **2** in 97% yield (Table 2, Entry 2). The yield of **2** gradually decreased when the electrolysis was carried out at elevated temperature; indeed, at room temperature (18 – 20 ºC), the yield of **2** decreased to 78% (Entry 3). The presence of a small amount of sulfuric acid is indispensable, thus, in the absence of H_2SO_4, a complex mixture involving lactam-ring cleaved products was formed (Entry 4).

A plausible mechanism of the electrooxidative desulfurization/chlorination is illustrated in Scheme 7. Electrooxidation of hydrochloric acid in the presence of *t*BuOH would give cationic chlorine species [Cl^+], such as Cl_2, HO-Cl, and *t*BuO-Cl, etc.[24] The presence of sulfuric acid[25] would enhance the electrophilic properties of these chlorine species. The activated [Cl^+] would, in turn, react with **10** to give sulfonium intermediate **A**. Subsequently, elimination of *t*BuC(O)SCl followed by addition of

chloride ion would proceed smoothly to give the desired 4-chloro-2-azetidinone **2**. In the absence of H_2SO_4, the electrogenerated chlorine species [Cl^+] would not be sufficient for C-S bond fission, and undesired reactions would mainly occur to give a complex mixture

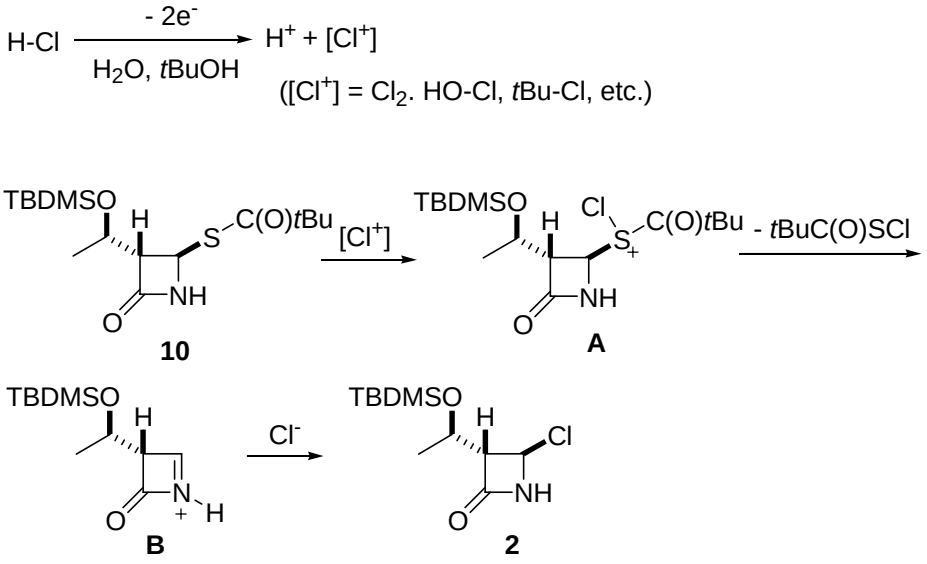
Table 2. Electrooxidative Desulfurization/Chlorination of Compound **10**



Entry	Temp/°C	conc. H_2SO_4/μL	Yield of **2**/%[a]
1	-20	16	93
2	0	16	97
3	rt.	16	78
4	rt.	0	n.d.[b]

[a]Isolated yield. [b]A complex mixture including ring-opening compounds was obtained.

Scheme 7. A Plausible Mechanism of Electrooxidative Desulfurization/chlorination of Compound **10**



In conclusion, (3*S*,4*R*)-3-(1'(*R*)-*tert*-butyldimethylsilyloxyethyl)-4-chloroazetidinone (**2**), a potent intermediate of carbapenem antibiotics, was synthesized from (3*S*,5*R*,6*S*)-3-(1'(*R*)-*tert*-butyldimethylsilyloxyethyl)penicillanate *S*-oxide (**8**) derived from penicillanic acid. Thermal ring

opening/acylation of the thiazol ring of **8** and subsequent removal of the *N*-substituent by the conventional method and finally electrooxidative desulfurization/chlorination of the 4-pivaloylthio moiety afforded the desired 4-chloro-2-azetidinone (**2**).

EXPERIMENTAL

^{1}H NMR spectra were determined with a Varian Gemini-200 (200 MHz) instrument or Varian VXR-600 (600 MHz) instrument. ^{13}C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) or Varian VXR-600 (150 MHz). IR spectra were obtained with a JASCO FT/IR-4100 spectrometer. Elemental analyses were carried out with Perkin Elmer PE 2400 Series II CHNS/O Analyzer. Unless otherwise noted, materials were obtained from commercial suppliers and reagent grade materials were used without further purification. Reaction solvents were distilled just before use, unless otherwise specified. Diphenylmethyl (3*S*,5*R*)-6,6-dibromopenicillanate (**6**) was donated from Otsuka Chemical Co., Ltd. Diphenylmethyl (3*S*,5*R*,6*S*)-6-bromo-6-[1'(*R*)-hydroxyethyl]penicillanate (**7**) was prepared according to the procedure reported in the previous paper.[16]

Reductive debromination of diphenylmethyl (3*S*,5*R*,6*S*)-6-bromo-6-[1'(*R*)- hydroxyethyl]-penicillanate (7):[19] To a MeOH (20 mL) solution of diphenylmethyl (3*S*,5*R*,6*S*)-6-bromo-6-[1'(*R*)-hydroxyethyl]penicillanate (**7**) (493 mg, 1.0 mmol) was added Bu_3P (344 mg, 1.7 mmol) in one portion at 0 ºC. After being stirred at 0 ºC for 30 min, the mixture was concentrated under reduced pressure. The residue was chromatographed (SiO_2, toluene/AcOEt = 2/1) to give the debrominated penicillanate **11** (386 mg, 0.93 mmol, 93%) and its isomer **12** (30 mg, 0.07 mmol, 7%), respectively.

Diphenylmethyl (3*S*,5*R*,6*S*)-6-[1'(*R*)-hydroxyethyl]penicillanate (**11**): colorless solids; R_f = 0.51 (toluene/AcOEt: 2/1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.61 (s, 3H), 2.43 (br, 1H), 3.32 (dd, *J* = 1.8, 6.0 Hz, 1H), 4.21 (m, 1H), 4.56 (s, 1H), 5.31 (d, *J* = 1.8 Hz, 1H), 6.93 (s, 1H), 7.27-7.37 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.61, 26.00, 32.52, 63.61, 65.20, 65.50, 68.29, 69.63, 78.20, 126.91, 127.51, 128.07, 128.28, 128.50, 128.53, 139.08, 139.17, 166.99, 172.42; **IR** (KBr) 3467, 3064, 3033, 2969, 2930, 2871, 1774, 1455, 1258, 1177, 1030, 745, 700 cm^{-1}; **Anal**. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.14; N, 3.46. Found: C, 66.45; H, 6.14; N, 3.49.

Diphenylmethyl (3*S*,5*R*,6*R*)-6-[1'(*R*)-hydroxyethyl]penicillanate (**12**): colorless solids; R_f = 0.51 (toluene/AcOEt: 2/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.66 (s, 3H), 2.67 (br, 1H), 3.47 (dd, *J* = 4.6, 8.8 Hz, 1H), 4.27 (m, 1H), 4.53 (s, 1H), 5.41 (d, *J* = 4.6 Hz, 1H), 6.94 (s, 1H), 7.32-7.36 (m, 10H); **IR** (KBr) 3451, 3065, 3033, 2967, 2926, 2849, 1771, 1455, 1259, 1180, 1083, 757, 700 cm^{-1}.

Protection of the hydroxyl group of diphenylmethyl (3*S*,5*R*,6*S*)-6-[1'(*R*)-hydroxyethyl]penicillanate (11) To a mixture of the alcohol **11** (227 mg, 0.55 mmol) and imidazole (113 mg, 1.7 mmol) in CH_2Cl_2 (3.0 mL) was added a CH_2Cl_2 (2.0 mL) solution of TBDMSCl (257 mg, 1.7 mmol) in one portion at 0 ºC. The mixture was stirred at 0 ºC for 30 min and at rt. for 24 h, and the resulting mixture was poured into water and extracted with CH_2Cl_2. The combined extracts were washed with brine, and concentrated under reduced pressure. The residue was chromatographed (SiO_2, toluene/AcOEt = 30/1) to afford *O*-silylated penicillanate **13** (288 mg, 0.55 mmol, 99%): colorless liquid; $\boldsymbol{R_f}$ = 0.67 (toluene/AcOEt: 5/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 1.25 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.60 (s, 3H), 3.28 (dd, *J* = 2.0, 5.6 Hz, 1H), 4.17-4.29 (m, 1H), 4.55 (s, 1H), 5.30 (d, *J* = 1.6 Hz, 1H), 6.93 (s, 1H), 7.31-7.37 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ -5.05, -4.41, 17.80, 22.34, 25.57, 25.77, 33.03, 63.47, 65.23, 65.30, 69.45, 69.60, 78.04, 126.95, 127.43, 127.97, 128.15, 128.40, 128.48, 139.19, 139.21, 166.78, 172.48; **IR** (neat) 3064, 3033, 2956, 2929, 2856, 1778, 1744, 1495, 1373, 1252, 1176 cm^{-1}; **Anal**. Calcd for $C_{29}H_{39}NO_4SSi$: C, 66.25; H, 7.48; N, 3.66. Found: C, 65.98; H, 7.48; N, 2.73.

Diphenylmethyl (3*S*,5*R*,6*S*)-6-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]penicillanate 1β-sulfoxide (8). To a CH_2Cl_2 (3 mL) solution of penicillanate **13** (210 mg, 0.4 mmol) was added a CH_2Cl_2 (3 mL) solution of *m*CPBA (92 mg, 0.4 mg) at 0 - 5 ºC. After being stirred for 3 h at the same temperature, the mixture was filtered, and the solids were washed with aq. sat. Na_2SO_3 solution and aq. sat. $NaHCO_3$ solution, successively. The aqueous washings were extracted with CH_2Cl_2. The organic filtrate and the extracts were combined, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed (SiO_2, toluene/AcOEt = 10/1) to afford the corresponding sulfoxide **8** (184 mg, 0.34 mmol, 87%): colorless solids; $\boldsymbol{R_f}$ = 0.20 (toluene/AcOEt: 10/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 0.96 (s, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 1.67 (s, 3H), 3.59 (dd, *J* = 2.0, 4.0 Hz, 1H), 4.38 (m, 1H), 4.59 (d, *J* = 2.0 Hz, 1H), 7.00 (s, 1H), 7.29-7.38 (m, 10H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ -4.86, -4.55, 17.93, 18.28, 20.08, 22.81, 25.69, 57.39, 63.98, 64.86, 72.83, 74.12, 78.29, 126.81, 127.67, 128.06, 128.35, 128.48, 128.5, 138.80, 139.16, 167.02, 171.08; **IR** (KBr) 3547, 3032, 2954, 2929, 2856, 1783, 1496, 1461, 1254, 1061, 837 cm^{-1}; **Anal**. Calcd for $C_{29}H_{39}NO_5SSi$: C, 64.29; H, 7.26; N, 2.54. Found: C, 64.29; H, 8.04; N, 2.59.

(3*S*,4*R*)-4-(Acetylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)-oxycarbonyl-2-propenyl]-2-azetidinone (9a) (Table 1, Entry 1). A mixture of sulfoxide **8** (174 mg, 0.32 mmol), trimethyl phosphite (0.05 mL, 0.42 mmol), and acetic anhydride (0.20 mL, 2.1 mmol) in benzene (12 mL) was heated to reflux for 50 h under argon atmosphere. The mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed

(SiO_2, toluene/AcOEt = 15/1) to give a mixture of (3*S*,4*R*)-4-(acetylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[{2-methyl-1-(diphenylmethyl)oxycarbonyl}-2-propenyl]-2-azetidinone (**9a**, 65.4 mg, 0.12 mmol, 36%), (3*S*,4*R*)-4-(acetoxy)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-2-propenyl]-2-azetidinone (**14a**, 47.5 mg, 0.09 mmol, 27%) and (3*S*,4*R*)-4-Methylthio-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-2-propenyl]-2-azetidinone (**15a,** 40.0 mg, 0.07 mmol, 23%). The ratio of **9a**, **14a** and **15a** was determined by ^{1}H NMR.

(3*S*,4*R*)-4-(acetylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[{2-methyl-1-(diphenylmethyl)oxycarbonyl}-2-propenyl]-2-azetidinone (**9a**): colorless liquid; R_f = 0.70 (toluene/AcOEt: 10/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.84 (s, 3H), 2.23 (s, 3H), 3.18 (dd, *J* = 2.6, 5.2 Hz, 1H), 4.14-4.24 (m, 1H), 4.57 (s, 1H), 4.89 (s, 1H), 5.00 (s, 1H), 5.65 (d, *J* = 2.6 Hz,1H), 6.95 (s, 1H), 7.28-7.38 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -4.90, -4.54, 17.82, 21.09, 22.21, 25.64, 30.63, 57.49, 61.29, 64.61, 65.22, 78.07, 117.39, 127.14, 127.35, 128.03, 128.40, 128.46, 128.50, 137.39, 139.48, 139.50, 165.86, 167.47, 194.20; IR (neat) 3064, 3032, 2955, 2929, 2886, 2856, 1772, 1702, 1471, 1454, 1375, 1253, 1169, 1127, 955, 836, 777, 699 cm^{-1}; **Anal**. Calcd for $C_{31}H_{41}NO_5SSi$: C, 65.57; H, 7.28; N, 2.47. Found: C, 65.67; H, ;7.41, N, 2.51.

(3*S*,4*R*)-4-(acetoxy)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-2-propenyl]-2-azetidinone (**14a**)**:** colorless liquid; R_f = 0.63 (toluene/AcOEt: 10/1); **^{1}H NMR** δ 0.02 (s, 3H), 0.07 (s, 3H), 0.83 (s, 9H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.78 (s, 3H), 2.02 (s, 3H), 3.36 (dd, *J* = 3.8, 8.4 Hz, 1H), 4.27-4.35 (m, 1H), 4.88 (s, 1H), 4.90 (s, 1H), 5.08 (s, 1H), 6.26 (d, *J* = 4.6 Hz, 1H), 6.89 (s, 1H), 7.27-7.35 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -4.76, -3.77, 17.80, 20.74, 21.08, 22.37, 25.64, 61.31, 61.88, 64.06, 78.22, 117.55, 127.13, 127.17, 127.46, 128.06, 128.47, 128.51, 137.45, 139.33, 139.46, 166.82, 167.24, 170.68; IR (neat) 3065, 3033, 2955, 2929, 2888, 2856, 2361, 1775, 1749, 1455, 1375, 1212, 1170, 916, 836, 776, 699 cm^{-1}; **Anal**. Calcd for $C_{31}H_{41}NO_6Si$: C, 67.48; H, 7.49; N, 2.54. Found: C, 67.35; H, 7.62; N, 2.62.

(3*S*,4*R*)-4-Methylthio-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-2-propenyl]-2-azetidinone (**15a**): yellow liquid; R_f = 0.70 (toluene/AcOEt: 10/1); **^{1}H NMR** δ 0.01 (s, 3H), 0.05 (s, 3H), 0.81 (s, 9H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.88 (s, 3H), 2.01 (s, 3H), 3.01-3.11 (m, 1H), 4.17-4.28 (m, 1H), 4.83 (s, 1H), 4.87 (s, 1H), 5.02 (s, 1H), 5.04 (d, *J* = 4.4 Hz, 1H), 6.92 (s, 1H), 7.29-7.37 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -4.77, -4.58, 12.26, 17.84, 20.81, 22.32, 25.65, 59.33, 60.52, 63.79, 65.04, 78.18, 116.59, 127.10, 127.36, 128.00, 128.10, 128.45, 128.47, 138.92, 139.38, 166.53, 167.56; **IR** (neat) 3083, 3068, 3032, 2928, 2856, 1764, 1651, 1455, 1375, 1251, 1065, 835, 778, 699 cm^{-1}; **Anal**. Calcd for $C_{30}H_{41}NO_4SSi$: C, 66.75; H, 7.66; N, 2.59. Found: C, 66.98; H, 7.96; N, 2.65.

(3*S*,4*R*)-4-(Pivaloylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)-oxycarbonyl-2-propenyl]-2-azetidinone (9b) (Table 1, Entry 8). A mixture of sulfoxide **8** (141.7 mg, 0.26 mmol), triethyl phosphite (0.06 mL, 0.34 mmol), and pivaloyl anhydride (0.36 mL, 1.82 mmol) in 1,2-dichloroethane (2.5 mL) was heated to reflux for 30 h under argon atmosphere. The mixture was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed (SiO_2, toluene/AcOEt = 15/1) to give a mixture of (3*S*,4*R*)-4-(pivaloylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[{2-methyl-1-(diphenylmethyl)oxycarbonyl}-2-propenyl]-2-azetidinone (**9b**, 113.9 mg, 0.19 mmol, 72%) and (3*S*,4*R*)-4-(pivaloyloxy)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-2-propenyl]-2-azetidinone (**14b**, 8.6 mg, 0.014 mmol, 6%). The ratio of **9b** and **14b** was determined by ^{1}H NMR.

(3*S*,4*R*)-4-(pivaloylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxy-carbonyl-2-propenyl]-2-azetidinone (**9b**): colorless liquid; R_f = 0.70 (toluene/AcOEt: 10/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 3H), 0.81 (s, 9H), 1.14 (s, 9H), 1.22 (d, *J* = 6.0 Hz、3H), 1.85 (s, 3H), 3.20 (dd, *J* = 2.6, 5.8 Hz, 1H), 4.13-4.25 (m, 1H), 4.57 (s, 1H), 4.88 (s, 1H), 4.97 (s, 1H), 5.62 (d, *J* = 2.6 Hz, 1H), 6.96 (s, 1H), 7.26-7.38 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -5.03, -4.50, 17.77, 21.17, 22.26, 25.63, 26.99, 46.73, 57.35, 60.97, 64.50, 65.66, 77.96, 117.41, 127.01, 127.35, 127.85, 127.96, 128.34, 128.40, 137.11, 139.45, 139.49, 166.12, 167.49; **IR** (neat) 3092, 3064, 3032, 2958, 2930, 2888, 2857, 1769, 1688, 1473, 1455, 1375, 1252, 1169, 1139, 938, 836, 778, 699 cm^{-1}; **Anal**. Calcd for $C_{34}H_{47}NO_5SSi$: C, 66.96; H, 7.77; N, 2.30. Found: C, 67.14; H, 7.74; N, 2.36.

(3*S*,4*R*)-4-(pivaloyloxy)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxy-carbonyl-2-propenyl]-2-azetidinone (**14b**)**:** yellow liquid; R_f = 0.63 (toluene/AcOEt: 10/1); **^{1}H NMR** δ 0.02 (s, 3H), 0.05 (s, 3H), 0.81 (s, 9H), 1.14 (s, 9H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.79 (s, 3H), 3.38 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.27-4.33 (m, 1H), 4.77 (s, 1H), 4.90 (s, 1H), 5.05 (s, 1H), 6.18 (d, *J* = 4.6 Hz, 1H), 6.89 (s, 1H), 7.27-7.35 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -4.65, -3.97, 17.90, 20.59, 21.55, 25.68, 25.73, 26.90, 38.86, 61.56, 62.20, 64.19, 77.21, 77.92, 78.25, 117.46, 127.06, 127.18, 127.93, 128.02, 128.40, 128.41, 137.73, 139.35, 139.41, 166.47, 167.09, 178.38; **IR** (neat) 3344, 3065, 3032, 2955, 2930, 2893, 2857, 1739, 1753, 1496, 1455, 1372, 1280, 1254, 1157, 1092, 835, 777, 699 cm^{-1}; **Anal**. Calcd for $C_{34}H_{47}NO_6Si$: C, 68.77; H, 7.98; N, 2.36. Found: C, 68.61; H, 8.06; N, 2.40.

Isomerization of compound 9b: A mixture of β,γ-unsaturated ester **9b** (77.7 mg, 0.12 mmol), triethylamine (0.02 mL, 0.12 mmol) in CH_2Cl_2 (2 mL) was stirred at rt. for 3 h under argon atmosphere. The resultant mixture was poured into aq. sat. NH_4Cl solution, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was chromatographed (SiO_2, toluene/AcOEt = 15/1) to give (3*S*,4*R*)-4-(pivaloylthio)-3-

[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[2-methyl-1-(diphenylmethyl)oxycarbonyl-1-propenyl]-2-azetidinone (**16**) (74.4 mg, 0.12 mmol, 96%): colorless liquid; $\boldsymbol{R_f}$ = 0.70 (toluene/AcOEt: 10/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.12 (s, 9H), 1.25 (d, *J* = 6.2 Hz, 3H), 2.04 (s, 3H), 2.20 (s, 3H), 3.23 (dd, *J* = 2.6, 6.2 Hz, 1H), 4.15-4.21 (m, 1H), 5.60 (d, *J* = 2.8 Hz, 1H), 6.92 (s, 1H), 7.28-7.46 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -4.89, -4.58, 17.90, 21.71, 22.22, 23.96, 25.70, 26.92, 46.70, 58.92, 63.47, 66.00, 77.96, 119.69, 127.19, 127.46, 127.75, 127.78, 128.32, 128.44, 139.88, 140.17, 162.54, 165.65, 204.72; **IR** (neat) 3088, 3064, 3032, 2930, 2857, 1770, 1725, 1694, 1632, 1455, 1363, 1253, 1216, 1078, 939, 831, 778, 699 cm^{-1}; **Anal**. Calcd for $C_{34}H_{47}NO_5SSi$: C, 66.96; H, 7.77; N, 2.30. Found: C, 66.71; H, 7.99; N, 2.32.

Ozonolysis of compound 16. A CH_2Cl_2 (3 mL) solution of compound **16** (16.8 mg, 0.028 mmol) was treated with ozone (bubbling) at -78 ºC for 3 h. The excess O_3 was removed by passing a stream of nitrogen gas, and the resultant mixture was washed with cold aq. sat. Na_2SO_3 and brine, successively, dried over Na_2SO_4, and concentrated *in vacuo.* The residue was chromatographed (SiO_2, toluene/AcOEt = 10/1) to give the corresponding imide **17** (15.7 mg, 0.027 mmol, 98%).
(3*S*,4*R*)-4-(Pivaloylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-*N*-[(diphenylmethyl)oxycarbonyloxo]-2-azetidinone (**17**): colorless solids; $\boldsymbol{R_f}$ = 0.80 (toluene/AcOEt: 15/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.81 (s, 9H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.26 (s, 9H), 3.47 (dd, *J* = 3.2, 3.2 Hz, 1H), 4.29-4.40 (m, 1H), 6.00 (d, *J* = 3.6 Hz, 1H), 7.04 (s, 1H), 7.28-7.42 (m, 10H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -5.41, -4.34, 17.67, 21.64, 25.52, 26.87, 47.03, 53.37, 64.59, 65.92, 79.61, 127.17, 127.51, 128.26, 128.32, 128.50, 138.30, 138.37, 154.34, 158.66, 163.45, 202.17; **IR** (KBr) 3395, 3034, 2956, 2930, 2857, 1814, 1752, 1712, 1369, 1232, 1202, 1139, 1066, 936, 838, 779, 698 cm^{-1}; **Anal**. Calcd for $C_{31}H_{41}NO_6SSi$: C, 63.78; H, 7.08; N, 2.40. Found: C, 63.55; H, 7.29; N, 2.42.

Hydrolysis of Imide 17: An aq. MeOH (6 mL, H_2O/MeOH = 10/1) solution of compound **17** (60.3 mg, 0.103 mmol) was stirred at rt. for 36 h. The mixture was concentrated in vacuo, and the residue was chromatographed (SiO_2, toluene/AcOEt = 15/1) to give (3*S*,4*R*)-4-(pivaloylthio)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-2-azetidinone **10** (28.7 mg, 0.080 mmol, 78%): colorless solids $\boldsymbol{R_f}$ = 0.23 (toluene/AcOEt: 15/1); **^{1}H NMR** (200 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.24 (s, 9H), 3.16-3.19 (m, 1H), 4.23-4.28 (m, 1H), 5.21 (d, *J* = 2.4 Hz, 1H), 6.35 (br, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ -5.21, -4.27, 17.90, 22.29, 25.65, 27.11, 46.68, 51.66, 64.59, 64.70, 166.50, 207.55; **IR** (KBr) 3163, 3096, 2968, 2928, 2904, 2857, 1772, 1732, 1683, 1237, 1143, 1132, 1063, 950, 928, 829, 808, 776 cm^{-1}; **Anal**. Calcd for $C_{16}H_{31}NO_3SSi$: C, 55.61; H, 9.04; N, 4.05. Found: C, 55.48; H, 8.93; N, 3.92.

Electrooxidative desulfurization/chlorination of compound 10: Into an undivided cell fitted with two Pt electrodes (1.5 x 1.0 cm^2) were placed aq. HCl (9 M, 5 mL), H_2SO_4 (16 μL), *t*BuOH (0.1 mL), and a CH_2Cl_2 (5 mL) solution of **10** (8.8 mg, 0.025 mmol). The mixture was electrolyzed under constant current conditions (30 mA, 20 F/mol) with vigorous stirring at 0 ºC. The resultant was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give (3*S*,4*R*)-3-[(1'(*R*)-*tert*-butyldimethylsiloxy)ethyl]-4-chloro-2-azetidinone (**2**, 6.6 mg, 0.024 mmol, 97%): colorless solids; R_f = 0.80 (benzene/AcOEt: 4/1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.83 (s, 9H), 1.26 (d, *J* = 6.4 Hz, 3H), 3.44 (m, 1H), 4.22 (m, 1H), 5.71 (s, 1H), 6.43 (br, 1H); **IR** (KBr) 3415, 3343, 2957, 2929, 2896, 2857, 1774, 1686, 1259, 1104, 836 cm^{-1}.

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