

A Synthesis of Cephamycins from Cephalosporins and Related Reactions¹⁾

TAKEO KOBAYASHI, KIMIO IINO, and TETSUO HIRAOKA

Central Research Laboratories, Sankyo Co., Ltd.²⁾

(Received April 16, 1979)

The sulfinamides **3** were transformed to sulfenimines **4** by treatment with thionyl chloride and a weak base such as quinoline (or triethylamine). The sulfenimines **4** were methoxylated with lithium methoxide to give 7 α -methoxysulfenamides **5**, which were directly acylated with an acyl chloride to furnish cephamycin derivatives **6**. There was a major difference between the acylation of 7 α -methoxysulfenamides **5** and that of the 7 α -H derivatives **7**. Reduction of the imines **4a** with metal hydrides gave 7 β -sulfenaminocephalosporins **12** together with a small amount of the 7 α -isomers **13**. The synthetic sequence **4a**→**12**→**14** provides a useful method for the isomerization of 7 α -aminocephalosporins **17** to the corresponding 7 β -isomers **18**.

Keywords—cephamycin; cephalosporin; sulfinamide; sulfenimine; methoxylation; oxidation; reduction

In the preceding paper³⁾ a synthesis of 7 α -methoxy-7 β -acylamidocephalosporins through 7-sulfenimino derivatives was reported. In view of the growing importance of 7 α -methoxycephalosporins (cephamycins) in the field of antibiotics, a more efficient method for methoxylation at the seven position of cephalosporins is desirable, even though several methods have been developed.⁴⁾ In this paper we describe another route to 7 α -methoxycephalosporins starting from 7 β -sulfinamide-cephalosporins.

Though the chemistry of a sulfoxide adjacent to carbon atoms has been extensively investigated⁵⁾ in connection with Pummerer-type reactions, the corresponding sulfinamides have been studied very little,⁶⁾ probably due to the unstable nature of sulfinic acids⁷⁾ which are the most suitable starting materials for sulfinamides. For example, aliphatic sulfinic acids are unstable and readily disproportionate to thiolsulfonates and sulfonic acids.⁷⁾ On the other hand, aromatic sulfinic acids seem to be sufficiently stable for utilization in synthesis. Thus we sought to develop a new synthetic route to 7-methoxylated cephalosporins using aromatic sulfinyl chlorides to form the sulfinamides.

Treatment of *tert*-butyl 7 β -amino-3-cephem-4-carboxylate (**2**) with *o*-nitrobenzenesulfinyl chloride gave the sulfinamide **3a**. *p*-Nitrobenzenesulfinamide **3b**, benzhydryl 3-acetoxymethyl-7 β -*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylate (**3c**), and 3-[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-7 β -*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylic acid (**3d**) were similarly prepared. The sulfinamides **3a**—**d** were mixtures of diastereomers due to chirality at the sulfinyl sulfur, but these diastereomers were smoothly converted into a single sulfenimine **4a**—**d** in the next reaction (*vide infra*). Treatment of the sulfinamide **3a** with thionyl chloride

- 1) A part of this work has been published in T. Kobayashi, K. Iino, and T. Hiraoka, *J. Am. Chem. Soc.*, **99**, 5505 (1977) as a preliminary communication.
- 2) Location: 1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.
- 3) T. Kobayashi and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **27**, 2718 (1979).
- 4) see T. Hiraoka, Y. Sugimura, T. Saito, and T. Kobayashi, *Heterocycles*, **8**, 719 (1977) and references cited therein.
- 5) S. Oae, "Organic Chemistry of Sulfur," Plenum Press, New York, 1977, p. 406.
- 6) M. Quaedyling, "Methoden der Organischen Chemie," Bd. IX, Houben-Weyl, Stuttgart, 1955, p. 297. therein.
- 7) S. Oae, "Organic Chemistry of Sulfur," Plenum Press, New York, 1977, p. 613.

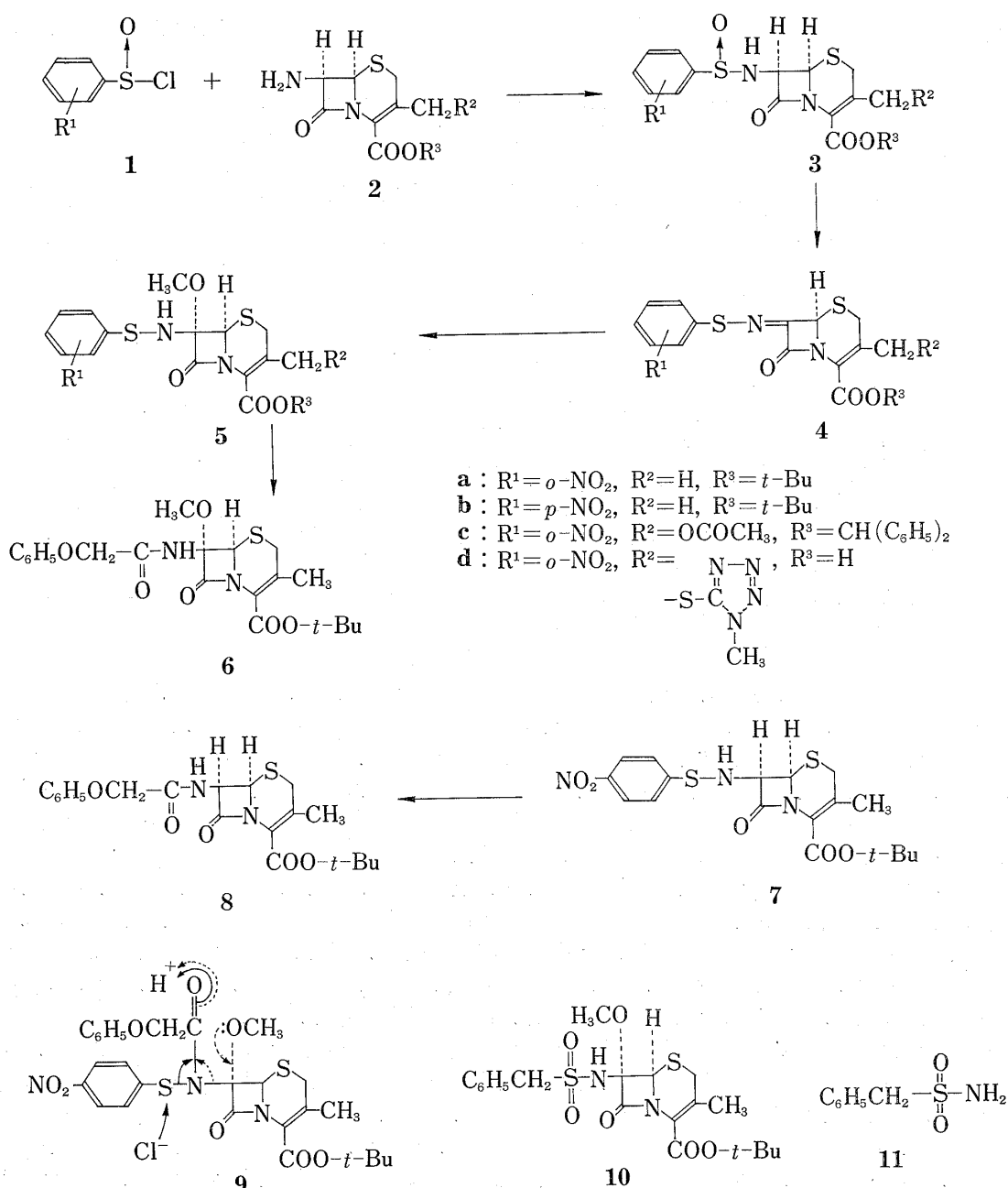


Chart 1

in the presence of quinoline gave the desired sulfenimine **4a** in 53.6% yield. To our knowledge, this is the first example of a Pummerer-type reaction of a sulfenamide. Curiously, the reaction of **3a** with trifluoroacetic anhydride and triethylamine or with acetyl chloride and quinoline afforded a mixture of the desired sulfenimine **4a** and the reduction product, *tert*-butyl 3-methyl-7 β -*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**12**). Reduction of a sulfoxide with an acylating reagent in the presence of an alkali metal iodide is well known,⁸⁾ but in our case reduction occurred with a combination of an acylating reagent and an organic base. The mechanism of this reduction is not clear, but it was not further investigated in the present work. Analogously, the sulfenamides **3b**, **c** were converted into the sulfenimines **4b**, **c** by treatment with thionyl chloride and quinoline (or triethylamine). Methoxylation

8) G.V. Kaiser, R.D.G. Cooper, R.E. Koehler, C.F. Murphy, J.A. Webber, I.G. Wright, and E.M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).

of the imines **4a—c** was achieved by reaction with lithium methoxide in methanol as described in the preceding paper⁹⁾ to give the 7 α -methoxy-7 β -sulfenamides **5a—c** in good yields. In the case of the free carboxylic acid **3d**, the carboxylic group was protected as the trimethylsilyl ester, using trimethylsilyl chloride and triethylamine in chloroform. The resulting sulfenamide trimethylsilyl ester was treated with thionyl chloride and quinoline at -40° to afford the sulfenimino trimethylsilyl ester **4d** ($R^3=SiMe_3$), which was reacted with lithium methoxide in methanol without isolation to furnish 7 α -methoxysulfenamide **5d** in 19.5% overall yield from **3d**.

We next investigated direct acylation of the sulfenamides **5**, since the process of conversion of **5** to an unstable 7 α -methoxy-7 β -amino derivative and subsequent acylation is likely to be less efficient than direct acylation of **5** in a single step. A model experiment using *tert*-butyl 3-methyl-7 β -*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate **7** was encouraging. Namely, treatment of **7** with phenoxyacetyl chloride in the absence of a base afforded the acylated product **8** in 96.3% yield. This reaction was applied to the 7 α -methoxy-7 β -*p*-nitrobenzenesulfenamide **5b**, using the same reaction conditions, to give the acyl-derivative **6** in only 5.1% yield. This acylation reaction was repeated many times under various conditions, but the yield could not be improved. The reason for this may be steric crowding and instability of the intermediate 7 α -methoxy-*N*-benzenesulfonyl-*N*-acylaminocephalosporin **9** in the presence of hydrochloric acid liberated in the reaction. In the postulated intermediate shown in formula **9**, chloride ion would attack the sulfur atom with protonation of the carbonyl adjacent to the nitrogen to produce the desired amide **6** (shown by solid arrows), while protonation of the carbonyl oxygen with the assistance of lone pair electrons of the methoxy oxygen would cleave the 7 β -nitrogen group to afford a decomposed product (shown by dotted arrows). A similar decomposition was observed in the case of the 7 β -methoxysulfonamide **10**,⁹⁾ which gradually decomposed during chromatography on silica gel or alumina with the liberation of benzylsulfonamide **11**; no cephalosporin compound was isolated.

We next considered reduction of the sulfenimines **4**, since this kind of reduction might be useful for the epimerization of 7 α -aminocephalosporins **17** to the 7 β -isomers **18** (Chart 2). Such epimerization is necessary in the total synthesis of cephalosporins or penicillins obtained by (2+2) cycloaddition as *trans* isomers at the 6, 7 (5, 6)-position.¹⁰⁾ Christensen *et al.* have carried out this transformation at the seven position of cephalosporins by proton abstraction from the corresponding Schiff base with a strong base.¹²⁾ However, the procedure is not efficient unless repeated several times, since protonation of the anion at the seven position gives a mixture of 7 α - and 7 β -isomers. If the reduction of sulfenimines **4** could be done stereospecifically, isomerization of the 7 α -amino derivative **17** to the β -isomer **18** might be useful to complete a total synthesis of cephalosporins. We found that treatment of **4a** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at 0° for 2 hr gave the 7 β -sulfenamide **12** (50.4%) together with a fair amount of the α -isomer **13** (27.7%) and the starting material (12.7%). This disappointing result led us to investigate other reduction reagents and reaction conditions. Thus, reduction of **4a** with sodium borohydride in a mixture of THF and DMSO at 0° for 10 min produced the desired 7 β -sulfenamide **12** (52.0%) in addition to some 7 α -isomer **13** (5.6%). Other reduction conditions were also examined and the results

9) *tert*-Butyl 7 β -benzylsulfonylamino-7 α -methoxy-3-methyl-3-cephem-4-carboxylate (**10**) was prepared by the *tert*-butyl hypochlorite method¹¹⁾ starting from *tert*-butyl 7 β -benzylsulfonylamino-3-methyl-3-cephem-4-carboxylate. The NMR spectrum of the crude compound **10** showed peaks consistent with the structure **10**.

10) a) A.K. Bose, G. Spiegelman, and M.S. Manhas, *J. Am. Chem. Soc.*, **90**, 4506 (1968); b) R.W. Ratcliffe and B.G. Christensen, *Tetrahedron Lett.*, **1973**, 4645, 4649, 4653.

11) a) J.E. Baldwin, F.J. Urban, R.D.G. Cooper, and F.L. Jose, *J. Am. Chem. Soc.*, **95**, 2401 (1973); b) G.A. Koopel and R.E. Koehler, *ibid.*, **95**, 2403 (1973).

12) R.A. Firestone, N.S. Maciejewicz, R.W. Ratcliffe, and B.G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

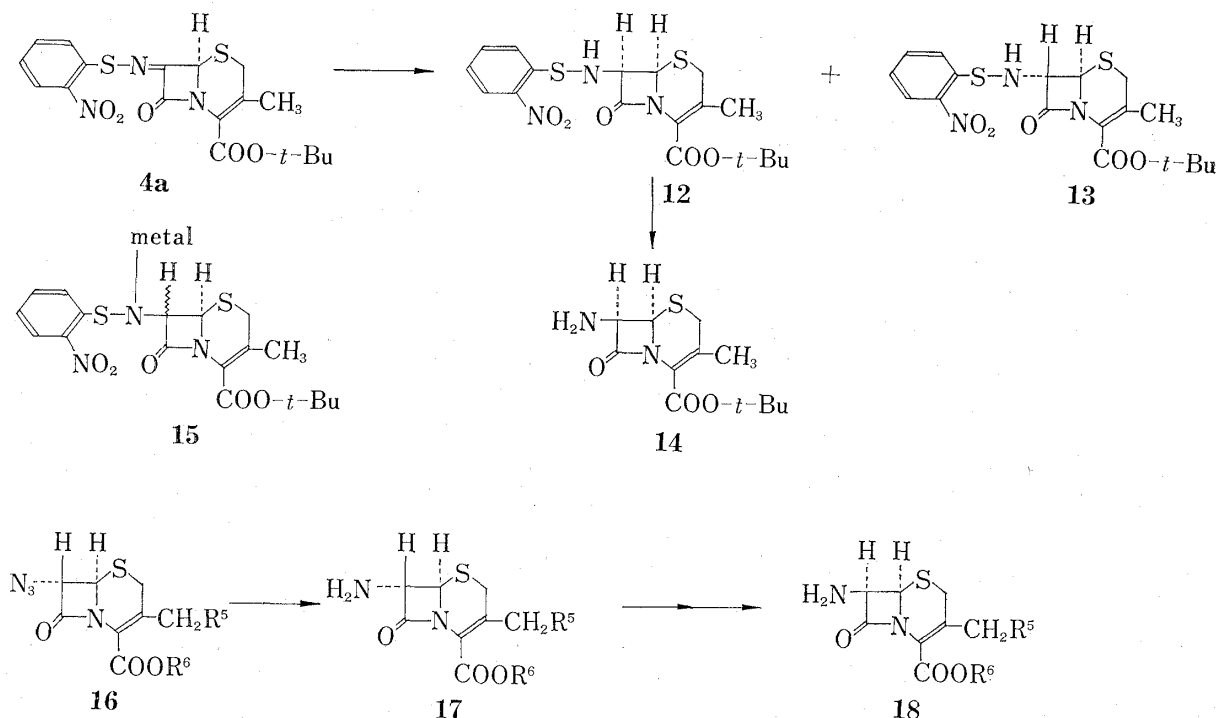


Chart 2

are summarized in Table I. It should be noted that the product ratio α/β given in Table I does not indicate the exact ratio of attack of the reagent from the α and β sides, since equilibration between α - and β -isomers is probable after reduction is completed, judging from the larger α/β ratios at longer reaction times. Namely, before quenching the reaction, the nitrogen of the reduction product is bonded by the metal species as depicted in formula **15**, and this kind of compound without hydrogen at the nitrogen atom is known to equilibrate easily between 7 α - and 7 β -isomers on treatment with a base.¹³⁾

Penicillin reduction of methyl 6 β -*o*-nitrobenzenesulfenimino-penicillanate (**19**)³⁾ with sodium borohydride gave only 7 β -sulfenamide **20**. The 7 α -isomer was not detected by thin-

TABLE I. Reduction of **4a**

Reagent	Conditions	<i>cis</i> (12)	<i>trans</i> (13)	(4a)	α (13)/ β (12)
LiAl(OBu ^t) ₃	THF -78°, 2 hr	32.7%	10.1%	41.0%	0.309
LiAl(OBu ^t) ₃	THF -78°, 10 min 0°, 2 hr	50.4%	27.7%	12.7%	0.550
NaBH ₄	THF-DMSO 0°, 10 min	52.0%	5.6%	Trace	0.108

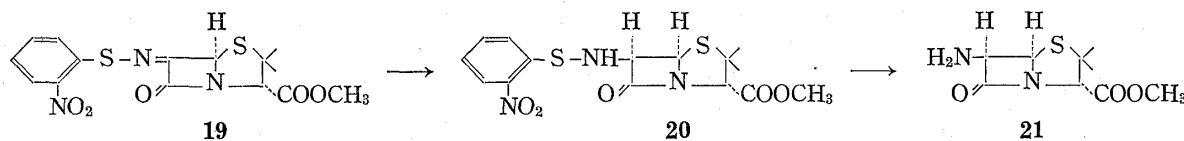


Chart 3

13) S. Wolfe and W.S. Lee, *J. Chem. Soc., Chem. Commun.*, 1968, 242.

layer chromatography, in striking contrast to the case with the cephalosporin series. The sulfur-nitrogen bond of the amide **12** or **20** was cleaved by treatment with potassium iodide in methanol-acetic acid at 0° to afford the desired amine **14** or **21**.

The isomerization method at the seven position of cephalosporins described above (**17**→**18**) was successfully applied by Miyadera *et al.*¹⁴⁾ in our laboratories for a total synthesis of 3-trifluoromethylcephalosporin, in which they used diborane as a reducing reagent with very satisfactory results.

In conclusion, a novel conversion of cephalosporins to cephamycins using sulfenamides has been established, together with a method for the isomerization of 7 α -aminocephalosporins to the 7 β -amino isomer.

Experimental¹⁵⁾

tert-Butyl 3-Methyl-7 β -*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (3a)—*o*-Nitrobenzenesulfinyl chloride (590 mg, 2.8 mmol) in dry THF (3 ml) was added to a stirred solution of *tert*-butyl 7 β -amino-3-methyl-3-cephem-4-carboxylate (540 mg, 2.0 mmol) and triethylamine (253 mg, 2.5 mmol) in dry THF (7 ml) at 0°. The resulting suspension was further stirred at 0° for 2 hr. The solution was diluted with EtOAc, then washed with water, NaHCO₃ solution and saturated NaCl solution. After drying over Na₂SO₄ the solvents were evaporated off under reduced pressure to afford an oil. This crude product was purified by chromatography on silica gel to give *o*-nitrobenzenesulfenamide **3a** (739 mg, 84.2%). The sulfenamide **3a** was a mixture of diastereoisomers due to the sulfinyl group in the 7 β -side chain, and was used without further separation in the next reaction. **3a**: NMR (CDCl₃) δ =1.45 and 1.48 (9H, two kinds of s), 2.02 and 2.05 (3H, two kinds of s), 3.06 and 3.25; 3.17 and 3.43 (2H, two kinds of ABq, J =18 Hz), 4.33 (2/3H, d, J =4.5 Hz), 4.82—5.03 (2/3H, m), 5.27 (2/3H, dd, J =4.5 and 9 Hz), 5.60 (1H, bd, J =9 Hz), 7.58—8.43 (4H, m).

tert-Butyl 3-Methyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4a)—Quinoline (93 mg, 0.72 mmol) was added to a cold solution of *o*-nitrobenzenesulfenamide **3a** (70 mg, 0.16 mmol) in dry CHCl₃ (2.5 ml) and dry THF (1 ml), followed by addition of thionyl chloride (29 mg, 0.24 mmol) in dry CHCl₃ (0.2 ml). The mixture was stirred at -30° for 1 hr and at 0° for 1 hr. Further quinoline (93 mg, 0.72 mmol) in dry CHCl₃ (0.4 ml) and thionyl chloride (29 mg, 0.24 mmol) in dry CHCl₃ (0.2 ml) were added to this mixture and the reaction was continued overnight at 0°. The mixture was diluted with EtOAc, washed with aqueous NaHCO₃ and water, then dried over MgSO₄. The solvents were removed *in vacuo* to give a solid, which was purified by silica gel chromatography (solvent: benzene-EtOAc 10:1) to furnish *o*-nitrobenzenesulfenimine **4a** (36 mg, 53.6%). **4a**: mp 183—184° (isopropyl ether-CHCl₃); IR $\nu_{\text{max}}^{\text{solid}}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.60 (9H, s), 2.16 (3H, s), 3.27 and 3.58 (2H, ABq, J =19 Hz), 5.47 (1H, s), 7.33—8.62 (4H, m).

tert-Butyl 3-Methyl-7 β -*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (3b)—A solution of *p*-nitrobenzenesulfinyl chloride (4.11 g, 20 mmol) in dry THF (25 ml) was added to a solution of *tert*-butyl 7 β -amino-3-cephem-4-carboxylate (4.5 g, 16.6 mmol) and triethylamine (2.79 ml, 20.0 mmol) in dry THF (90 ml) at 0°. The resulting suspension was stirred for 2 hr at 0° then at room temperature for 3 hr. The mixture was then diluted with EtOAc, washed with water, and dried over MgSO₄. The solvents were removed *in vacuo* and the residue was purified by chromatography on silica gel (solvent: benzene-EtOAc 2:1) to give *p*-nitrobenzenesulfenamide **3b** (6.9 g, 95.2%). The sulfenamide **3b** was a mixture of diastereoisomers due to the sulfinyl group in the 7 β -side chain, and was used without further separation in the next step. **3b**: NMR (CDCl₃) δ : 1.43 (9H, s), 2.02 (3H, s), 3.06 and 3.37; 3.15 and 3.45 (2H, two kinds of ABq, J =18 Hz), 4.52 (1H, d, J =5 Hz), 4.78 and 5.06 (1H, two kinds of dd, J =5 and 9 Hz), 6.25 (1H, d, J =9 Hz), 7.77—8.48 (4H, m).

tert-Butyl 3-Methyl-7-*p*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4b)—Triethylamine (0.20 ml, 1.43 mmol) and thionyl chloride (0.10 ml, 1.38 mmol) were added to a solution of *p*-nitrobenzenesulfenamide **3b** (200 mg, 0.455 mmol) in dry CH₂Cl₂ (5 ml) at -78° under vigorous stirring. The solution was maintained at -78° for 1.5 hr, then methylene chloride was added. The mixture was washed with saturated NaHCO₃ solution and water, dried over MgSO₄, and evaporated down *in vacuo*. The resulting solid was

14) a) T. Hashimoto, T. Watanabe, Y. Kawano, T. Tanaka, and T. Miyadera, *Heterocycles*, **11**, 207 (1978);
b) T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, and T. Miyadera, *Chem. Pharm. Bull.* (Tokyo), accepted.

15) All melting points are uncorrected. IR spectra were recorded on a JASCO A-2 spectrometer. NMR spectra were measured on Hitachi R-24 spectrometer using tetramethylsilane as an internal standard. The abbreviations in the NMR spectra are as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet.

chromatographed on silica gel using benzene-EtOAc (10:1) to yield *p*-nitrobenzenesulfenimine **4b** (77 mg, 44%). **4b**: mp 169–170° (isopropyl ether-EtOAc); IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 1790; NMR (CDCl₃) δ : 1.58 (9H, s), 2.15 (3H, s), 3.23 and 3.57 (2H, ABq, *J*=18 Hz), 5.37 (1H, s), 7.55–8.40 (4H, m).

Benzhydryl 3-Acetoxyethyl-7 β -*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (3c)—A solution of 7 β -amino-3-methyl-3-cephem-4-carboxylic acid (3.41 g, 12.5 mmol) and triethylamine (7.0 ml, 50 mmol) in dry CH₂Cl₂ (50 ml) was stirred and cooled to 0°. *o*-Nitrobenzenesulfinyl chloride (3.85 g, 18.7 mmol) in dry CH₂Cl₂ (25 ml) was added and the mixture was stirred overnight at room temperature. Cold phosphate buffer solution (pH 7.8, 100 ml) was added to the mixture and stirred well. The solid precipitate was removed by filtration, then the aqueous layer was separated, washed with a small amount of CH₂Cl₂, and adjusted to pH 2.6 (15% HCl). Repeated extraction with EtOAc gave combined extracts, which were dried (Na₂SO₄) and evaporated down to a yellow foam. This foam was dissolved in EtOAc (300 ml). A small amount of insoluble substance was filtered off, and the filtrate was again evaporated down to give a foam (3.35 g). This was taken up in THF (25 ml), an excess of diphenyldiazomethane in THF (15 ml) was added, and the solution was left overnight at room temperature. After removal of the solvent, the residue was triturated with *n*-hexane and the resulting solid was purified by chromatography using silica gel (solvent: benzene-EtOAc 4:1) to give *o*-nitrobenzenesulfenamide **3c** (1.17 g, 15.3%). The sulfenamide **3c** was a mixture of diastereoisomers due to the sulfinyl group in the 7 β -side chain, and was used without further separation. **3c**: NMR (CDCl₃) δ : 1.92 (3H, s), 3.27 (6/5H, bs), 3.30 and 3.53 (4/5H, ABq, *J*=18 Hz), 4.32 (4/5H, d, *J*=4.5 Hz), 4.25–5.52 (21/5H, m), 6.95 (1H, s), 7.17–8.48 (14H, m).

Benzhydryl 3-Acetoxyethyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4c)—Quinoline (233 mg, 1.8 mmol) in dry CHCl₃ (0.5 ml) was added to a solution of *o*-nitrobenzenesulfenamide **3c** (122 mg, 0.2 mmol) in dry CHCl₃ (3 ml), followed by the addition of thionyl chloride (72 mg, 0.6 mmol) in CHCl₃ (1 ml) under ice-water cooling. The mixture was stirred at 0° for 1.5 hr. The solution was treated with EtOAc-aqueous NaHCO₃ solution, and the organic layer was washed twice with water. After drying over Na₂SO₄ the solvents were evaporated off *in vacuo* to afford a residue. Purification by chromatography on silica gel using benzene-EtOAc (4:1) gave *o*-nitrobenzenesulfenimine **4c** (18.5 mg, 15.6%) and benzhydryl 3-acetoxyethyl-7-*o*-nitrobenzenesulfenimino-2-cephem-4-carboxylate (18.5 mg, 15.6%). **4c**: mp 134–135° (*n*-hexane-EtOAc); IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 2.01 (3H, s), 3.39 and 3.65 (2H, ABq, *J*=19 Hz), 4.85 and 5.08 (2H, ABq, *J*=14 Hz), 5.47 (1H, s), 7.08 (1H, s), 7.25–8.60 (14H, m).

3-[[1-(1-Methyl-1H-tetrazol-5-yl)thio]methyl]-7 β -*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylic Acid (3d)—Trimethylchlorosilane (0.5 ml, 3.9 mmol) was added to a cold solution of 7 β -amino-3-[[1-(1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-cephem-4-carboxylic acid (986 mg, 3 mmol) and triethylamine (0.5 ml, 3.6 mmol) in CH₂Cl₂ (15 ml), and the mixture was stirred for 1 hr at room temperature. After cooling the solution to -40°, dimethylaniline (0.57 ml, 4.5 mmol) was added, followed by the addition of *o*-nitrobenzenesulfinyl chloride (920 mg, 4.5 mmol) in dry CH₂Cl₂ (5 ml) with vigorous stirring. The mixture was stirred for 30 min at -40° then for 2 hr at 0°. A cold phosphate buffer solution (pH 7.8, 50 ml) was added to the mixture and well stirred. The aqueous layer was separated and adjusted to pH 2.7 (15% HCl). Repeated extraction with EtOAc gave combined extracts, which were washed with NaCl solution, dried (MgSO₄) and evaporated down to give a solid. The solid was triturated with ether to give *o*-nitrobenzenesulfenamide **3d** (531 mg, 35.0%). This *o*-nitrobenzenesulfenamide **3d** was a mixture of two diastereoisomers due to the 7 β -sulfinyl group. The structures of the two isomers were confirmed by conversion to the corresponding benzhydryl esters, which were chromatographed on silica gel using benzene-EtOAc (1:1) to give a more polar isomer (*R*_f=0.53) and a less polar isomer (*R*_f=0.61). *R*_f=0.53 compound: IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 1790; NMR (DMF-*d*₇) δ : 3.80 (2H, s), 3.95 (3H, s), 4.31 and 4.42 (2H, ABq, *J*=14 Hz), 5.13–5.50 (2H, m), 6.95 (1H, s), 7.25–8.51 (14H, m). *R*_f=0.61 compound: IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 1785; NMR (DMF-*d*₇) δ : 3.66 (2H, s), 3.92 (3H, s), 4.25 and 4.41 (2H, ABq, *J*=14 Hz), 4.53 (1H, d, *J*=4.5 Hz), 5.50 (1H, dd, *J*=4.5 and 9 Hz), 6.98 (1H, s), 7.25–8.50 (14H, m).

Benzhydryl 7 α -Methoxy-3-[[1-(1-methyl-1H-tetrazol-5-yl)thio]methyl]-7 β -*o*-nitrobenzenesulfenamino-3-cephem-4-carboxylate (5d)—Trimethylchlorosilane (52 mg, 0.48 mmol) was added to a stirred suspension of *o*-nitrobenzenesulfenamide **3d** (200 mg, 0.4 mmol) (a mixture of two isomers) and triethylamine (44.4 mg, 0.44 mmol) in dry CHCl₃ (5 ml) and the mixture was stirred for 30 min at room temperature. The solution was cooled to -40°, then quinoline (310 mg, 2.4 mmol) in dry CHCl₃ (1 ml) was added, followed by the addition of thionyl chloride (119 mg, 1.0 mmol) with vigorous stirring. The mixture was stirred for 2 hr at -30°. The solution was then cooled to -78° and lithium methoxide (prepared from 36 mg (5.2 mmol) of lithium) in dry MeOH (2 ml) was added. After reaction for 2 hr at -78°, glacial AcOH was added. Cold phosphate buffer solution (pH 7.8) was added to the mixture and stirred well. The aqueous phase was separated and acidified to pH 3.0 with 15% HCl. The aqueous layer was saturated with NaCl and extracted twice with EtOAc. The combined extracts were washed with saturated NaCl and dried over MgSO₄. Excess diphenyldiazomethane (194 mg, 1 mmol) was added and the solution was allowed to stand at room temperature overnight. After removal of the solvent, the residue was purified by silica gel preparative TLC (solvent: benzene-EtOAc 4:1) to give 7 α -methoxy-*o*-nitrobenzenesulfenamide **5d** (58 mg, 19.5%). **5d**: IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹): 1785; NMR (CDCl₃) δ : 3.50 (3H, s), 3.60 (2H, s), 3.76 (3H, s), 4.20 and 4.46 (2H, ABq, *J*=14 Hz), 4.40 (1H, s), 4.92 (1H, s), 6.90 (1H, s), 7.05–8.36 (14H, m).

tert-Butyl 3-Methyl-7 β -phenoxyacetamido-3-cephem-4-carboxylate (8)—A stirred solution of *tert*-butyl 3-methyl-7 β -*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate **7** (102 mg, 0.24 mmol) in dry methylene chloride (10 ml) was cooled to 0°, and phenoxyacetyl chloride (0.12 ml, 0.72 mmol) was added with vigorous stirring. The mixture was stirred for 1.5 hr at room temperature. Removal of the solvent *in vacuo* left a residue, which was purified by preparative chromatography on silica gel to give 7 β -phenoxyacetamide **8** (93.8 mg, 96.3%) using benzene–EtOAc (5:1). **8**: oil; IR $\nu_{\max}^{\text{CHCl}_3}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.53 (9H, s), 2.10 (3H, s), 3.15 and 3.50 (2H, ABq, $J=19$ Hz), 4.57 (2H, s), 5.01 (1H, d, $J=4.5$ Hz), 5.85 (1H, dd, $J=4.5$ and 10 Hz), 6.83–7.80 (6H, m).

tert-Butyl 7 α -Methoxy-3-methyl-7 β -phenoxyacetamido-3-cephem-4-carboxylate (6)—Phenoxyacetyl chloride (0.10 ml, 0.6 mmol) was added to a solution of 7 α -methoxy-*p*-nitrobenzenesulfenamide **5b** (101 mg, 0.22 mmol) in dry acetonitrile (5 ml) at 0°, and the mixture was stirred for 30 min at 0°. After dilution with EtOAc, the solution was washed with saturated NaHCO₃ solution and saturated NaCl solution. Concentration of the dried solution (over MgSO₄) *in vacuo* left a residue, which was subjected to preparative TLC on silica gel (benzene–EtOAc 5:1) to give 7 α -methoxy-7 β -phenoxyacetamide **6** (4.8 mg, 5.1%). **6**: oil; IR $\nu_{\max}^{\text{CHCl}_3}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.53 (9H, s), 2.12 (3H, s), 3.08 and 3.33 (2H, ABq, $J=18$ Hz), 3.55 (3H, s), 4.60 (2H, s), 5.07 (1H, s), 6.80–7.53 (5H, m).

tert-Butyl 3-Methyl-7 β -*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (12)—(a) Reduction with Lithium Tri-*tert*-butoxyaluminum Hydride at -10°: Lithium tri-*tert*-butoxyaluminum hydride (205 mg, 0.81 mmol) in dry THF (2 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (98.8 mg, 0.23 mmol) in dry THF (4 ml) at -78° with vigorous stirring. The solution was stirred at -78° for 10 min, then the reaction was continued at -10° for 1 hr. The mixture was diluted with CHCl₃, and phosphate buffer (pH 4.01) was added. The precipitate was removed by filtration, and the organic layer was separated and washed with water. The solution was dried over MgSO₄ and concentrated *in vacuo* to give a residue, which was purified by preparative TLC using benzene–EtOAc (10:1) to afford *o*-nitrobenzenesulfenimine **4a** ($R_f=0.78$, 40.8 mg, 41.0%), 7 β -*o*-nitrobenzenesulfenamide **12** ($R_f=0.62$, 32.5 mg, 32.7%), and 7 α -*o*-nitrobenzenesulfenamide **13** ($R_f=0.45$, 10.0 mg, 10.1%). 7 β -*o*-Nitrobenzenesulfenamide **12**: mp 171–172° (isopropyl ether–CHCl₃); IR $\nu_{\max}^{\text{NaIO}_4}$ (cm⁻¹): 1775; NMR (CDCl₃) δ : 1.50 (9H, s), 2.08 (3H, s), 3.22 and 3.60 (2H, ABq, $J=18$ Hz), 3.67 (1H, d, $J=9$ Hz), 4.73 (1H, dd, $J=9$ and 5 Hz), 4.99 (1H, d, $J=5$ Hz), 7.17–8.37 (4H, m). 7 α -*o*-Nitrobenzenesulfenamide **13**: yellow oil; IR $\nu_{\max}^{\text{CHCl}_3}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.45 (9H, s), 2.01 (3H, s), 3.15 and 3.43 (2H, s, $J=18$ Hz), 3.73 (1H, d, $J=7$ Hz), 4.38 (1H, dd, $J=7$ and 2 Hz), 4.68 (1H, d, $J=2$ Hz), 7.12–8.35 (4H, m).

(b) Reduction with Lithium Tri-*tert*-butoxyaluminum Hydride at 0°: Lithium tri-*tert*-butoxyaluminum hydride (327 mg, 1.29 mmol) in dry THF (4 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (101 mg, 0.24 mmol) in dry THF (4 ml) at -78°. The solution was stirred at -78° for 10 min and then at 0° for 2 hr. The mixture was then diluted with CHCl₃, followed immediately by the addition of phosphate buffer solution (pH 4.01) with vigorous stirring. The organic layer was separated, washed with water, and dried over MgSO₄. Removal of organic solvents and preparative TLC of the residue on silica gel (solvent benzene–EtOAc 10:1) gave *o*-nitrobenzenesulfenimine **4a** ($R_f=0.78$, 12.8 mg, 12.7%), 7 β -*o*-nitrobenzenesulfenamide **12** ($R_f=0.62$, 51.0 mg, 50.4%), and 7 α -*o*-nitrobenzenesulfenamide **13** ($R_f=0.45$, 28.0 mg, 26.7%).

(c) Reduction with Sodium Borohydride: A solution of sodium borohydride (110 mg, 2.9 mmol) in dry DMSO (4 ml) and dry THF (4 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (284 mg, 0.67 mmol) in dry THF (28 ml) and dry DMSO (4 ml) at 0° over a period of 10 min. The mixture was stirred at 0° for 10 min and quenched with AcOH (1.2 ml). The solution was diluted with EtOAc and washed successively with water, NaHCO₃ solution, and saturated NaCl solution. After drying over Na₂SO₄, the solvent was evaporated off *in vacuo* to give a yellow oil (crude product: 300 mg). Preparative TLC of the crude product (solvent: benzene–EtOAc 10:1) gave 7 β -*o*-nitrobenzenesulfenamide **12** ($R_f=0.62$, 148 mg, 52.0%) and 7 α -*o*-nitrobenzenesulfenamide **13** ($R_f=0.45$, 15.9 mg, 5.6%).

tert-Butyl 7 β -Amino-3-methyl-3-cephem-4-carboxylate (14)—The reduction of *o*-nitrobenzenesulfenimine **4a** (284 mg, 0.67 mmol) with sodium borohydride was repeated as described above. The resulting crude 7 β -*o*-nitrobenzenesulfenamide **12** (300 mg) was dissolved in CH₂Cl₂ (4.5 ml), and a solution of potassium iodide (1.18 g, 7.1 mmol) in a mixture of MeOH (15 ml) and AcOH (2.2 ml) was added under ice-water cooling, followed by the addition of 1 M Na₂S₂O₃ solution (1.5 ml). The reaction mixture, containing precipitates, was stirred at room temperature for 2 hr. Ethyl acetate and NaHCO₃ solution were added to the mixture, and the organic layer was separated. The organic phase was washed with NaHCO₃ solution and saturated NaCl solution, dried over Na₂SO₄ and evaporated down to furnish a yellow solid (231 mg). This crude product was dissolved in a small amount of EtOAc (insoluble material was filtered off) and applied to a preparative TLC plate, developed with benzene–EtOAc (1:1). The usual work-up gave 7 β -amino-cephalosporin **14** (90 mg, 49.4% from **4a**). **14**: amorphous solid; IR $\nu_{\max}^{\text{CHCl}_3}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.48 (9H, s), 2.02 (3H, s), 2.05 (2H, bs), 3.15 and 3.53 (2H, ABq, $J=18$ Hz), 4.72 (1H, d, $J=5$ Hz), 4.90 (1H, d, $J=5$ Hz).

Methyl 6 β -*o*-Nitrobenzenesulfenamido-penicillanate (20)—Sodium borohydride (167 mg, 4.4 mmol) in dry THF (6 ml) and dry DMSO (6 ml) was added to a solution of methyl 6-*o*-nitrobenzenesulfenimino-penicillanate **19**³⁾ (380 mg, 1.0 mmol) in dry THF (32 ml) and dry DMSO (6 ml) at 0° with vigorous stirring.

The mixture was stirred at 0° for 15 min, then the solution was quenched with AcOH (1.8 ml), diluted with EtOAc, and washed successively with water, NaHCO₃ solution, and saturated NaCl solution. The organic solution was dried over MgSO₄ and evaporated down *in vacuo* to afford a residue, which was purified by preparative TLC (solvent: benzene–EtOAc 5:1) to give 6β-*o*-nitrobenzenesulfenamide **20** (200 mg, 52.2%). **20**: yellow oil; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹): 1790; NMR (CDCl₃) δ : 1.54 (3H, s), 1.70 (3H, s), 3.70 (1H, d, $J=10$ Hz), 3.80 (1H, s), 4.51 (1H, s), 4.67 (1H, dd, $J=4.5$ and 10 Hz), 5.67 (1H, d, $J=4.5$ Hz), 7.22–8.48 (4H, m).

Methyl 6β-Amino-penicillanate (21)—6β-*o*-Nitrobenzenesulfenamide **20** (298 mg, 0.78 mmol) in CH₂Cl₂ (4.5 ml) was added to a solution of potassium iodide (1.20 g, 7.2 mmol) in a mixture of MeOH (15 ml) and AcOH (2.2 ml) at 0°, followed by the addition of 1 M Na₂S₂O₃ solution (1.5 ml). The mixture was stirred for 2 hr at room temperature. EtOAc and NaHCO₃ solution were added to the mixture and the organic phase was washed with saturated NaHCO₃ solution then saturated NaCl solution. The organic solution was dried over MgSO₄ and concentrated *in vacuo* to give a crude substance, which was purified by silica gel chromatography using benzene–EtOAc (1:4) to furnish 6β-amino-penicillin **21** (59.7 mg, 33.4%). **21**: oil; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ (cm⁻¹): 1780; NMR (CDCl₃) δ : 1.48 (3H, s), 1.64 (3H, s), 2.15 (2H, bs), 3.78 (3H, s), 4.41 (1H, s), 4.56 (1H, d, $J=5$ Hz), 5.55 (1H, d, $J=5$ Hz).

Acknowledgement We are grateful to Dr. Y. Kishida, Director of Chemical Research, for his encouragement throughout this work.